The Synthesis of Functionalised Sulfonamides

A thesis submitted in partial fulfilment of the requirements for the degree

of

DOCTOR OF PHILOSOPHY

At the Chemistry Department of University College London

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DECLARATION

The work described in this thesis is the work of the author and has not previously been submitted to this or any other university for any other degree.

Bei Lin Mok

April 2008

ACKNOWLEDGEMENTS

I would like to first thank my supervisor Prof. Steve Caddick for taking me on this exciting project, and for his continual enthusiasm, motivation, and support during my PhD. I am also especially grateful to Steve for finding me the necessary funds to continue my studies and complete this PhD.

A special thanks to everyone in the Caddick group past and present for making my time at UCL an enjoyable experience and for all the help I have received. In particular, Lynsey Geldeard, Jack Lee, Mark Cawley, Olivier Thominet, Mirella Verdecchia and Nick Callan for their friendship and laughs throughout the years.
I am truly indebted to Richard Fitzmaurice and Alex Sinclair for proofreading this thesis and for the excellent advice they have given me. In addition, I would also like to thank Jon Wilden, Alex Lewis, and Jamie Baker for the help and assistance they have offered me all the way through my PhD.

A big thank you must go to Dr. Abil Aliev for his invaluable help and advice with NMR analysis of my samples, and additionally Lisa Harris for her time and patience in running my endless mass spectrometry samples.

Finally, I am forever indebted to my family for their love and support throughout my studies.

ABSTRACT

Sulfonamides are important therapeutic agents and have a diverse array of biological functions in biology and medicine. Their means of synthesis has often involved the use of unstable sulfonyl chloride species; however, recent research has established pentafluorophenyl (PFP) sulfonate esters as a useful stable alternative to such species.

This thesis describes the use of PFP vinyl sulfonate in a [3+2] cycloaddition with a variety of *N*-methyl nitrones, providing access to the corresponding 4C-substituted isoxazolidine in a regio- and diastereoselective manner. Aminolysis of the resultant PFP sulfonate ester then provides functionalised sulfonamides of potential biological utility. In addition, the [3+2] cycloaddition reaction of several vinyl sulfonamides with *N*-methyl nitrones is reported. Regiospecificity of the reaction is poor, nevertheless a diverse collection of heterocyclic sulfonamide structures have been isolated. Further attempts to further diversify the isoxazolidine products generated from [3+2] cycloaddition chemistry were carried out. The synthesis of isoxazoles from isoxazolidines was explored, and in the process a novel tertiary amine catalysed 'cycloaddition' has been discovered.

The resulting isoxazolidine products were assessed as potential biological probes against various enzymes/diseases, and as a result a collection of products were submitted for biological evaluation against the enzymes dimethylarginine dimethylamino hydrolase (DDAH) and arginine deiminase (ADI). Several compounds displayed μM inhibition against DDAH and ADI; and in addition, these currently represent the first known inhibitors of ADI.

During the course of our investigation, it was also revealed that a small assortment of our heterocyclic sulfonamides possess good anti-HIV activity at concentrations of 75-100μM. Attempts to isolate the cellular target, through modifications to our drug candidates for the purpose of affinity chromatography have also been explored.

CONTENTS

ABBREVIATIONS

AcOH – Acetic acid

ADI – Arginine deiminase

ADMA - Asymmetric dimethylated L-arginine

ADP - Adenosine diphosphate

AIBN – 2,2'-azobisisobutyronitrile

AIDS – Acquired immunodeficiency syndrome

ALDH1 - Aldehyde dehydrogenase 1

ATP – Adenosine triphosphate

BH_4 - Tetrahydrobiopterin

Boc – *tert*-Butoxycarbonyl

Bu_4NOAc – Ammonium acetate

CA – Carbonic anhydrase

$CDCl_3$ – Deuterated chloroform

cGMP – Cyclic guanosine monophosphate

CDDO - 2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid

$CHCl_3$ – Chloroform

CI – Chemical ionisation

CK – Carbamate kinase

CK1 - Casein kinase 1

Cl_3CCN – Trichloro-acetonitrile

cNOS - Constitutive nitric oxide synthase

COX – Cyclooxygenase

DABCO – 1,4-Diazabicyclo[2.2.2]octane

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM – Dichloromethane

DDAH – Dimethylarginine dimethylamino hydrolase

DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

de – Diastereomeric excess

DEAD – Diethyl azodicarboxylate

DIPEA – *N,N'*-Diisopropylethylamine

DMAP – Dimethylaminopyridine

DMF – Dimethylformamide

DMSO – Dimethyl sulfoxide

DNA – Deoxyribose nucleic acid

dNTP - Deoxynucleotide triphosphate

DOS – Diversity orientated synthesis

EDC – 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide

ee – Enantiomeric excess

EI – Electron ionisation

eNOS – Endothelial nitric oxide synthase

ES – Electrospray

Et_2O – Diethyl ether

EtOAc – Ethyl acetate

EtOH – Ethanol

FAB – Fast atom bombardment

FACS – Fluorescent activated cell sorting

FAD - Flavin adenine dinucleotide

FMN - Flavin mononucleotide

FMO – Frontier molecular orbital

GAK - Cyclin G-associated kinase

HAART – Highly active anti-retroviral therapy

HCl – Hydrochloric acid

HIV – Human immunodeficiency virus

H_2O_2 – Hydrogen peroxide

HOBt – 1-Hydroxybenzotriazole

HOMO – Highest occupied molecular orbital

HRMS – High resolution mass spectrum

Hz – Hertz

IN – Integrase

iNOS – Inducible nitric oxide synthase

IR – Infra-red

k_{ass} – Association equilibrium constant

K_d – Dissociation equilibrium constant

K_i – Inhibitory equilibrium constant

k_{inact} – Inactivation rate constant

$KMnO_4$ – Potassium permanganate

KOH – Potassium hydroxide

L-NMMA – Monomethylated L-arginine

LUMO – Lowest unoccupied molecular orbital

MA – Matrix protein

***m*-CPBA** – *meta*-Chloroperoxybenzoic acid

MeCN – Acetonitrile

MeOH – Methanol

$MgSO_4$ – Magnesium sulphate

µM – Micromolar

MMPP – Magnesium monoperoxyphthalate

$Mo(CO)_6$ – Molybdenum hexacarbonyl

mp – Melting point

mRNA – Messenger ribonucleic acid

MS – Molecular sieves

MW – Microwave

$NaBH_3CN$ – Sodium cyanoborohydride

NaCl – Sodium chloride

NADPH - Nicotinamide adenine dinucleotide phosphate

NaH – Sodium hydride

$NaHCO_3$ – Sodium hydrogen carbonate

NaOEt – Sodium ethoxide

NCS – *N*-chlorosuccinimide

NEt_3 – Triethylamine

NH_4Cl – Ammonium chloride

NLS – Nuclear localisation signal

nM – Nanomolar

NMP – *N*-Methylpyrrolidone

NMR – Nuclear magnetic resonance

nNOS – Neuronal nitric oxide synthase

NNRTI - Non-nucleoside reverse-transcriptase inhibitor

NO – Nitric oxide

NOE – Nuclear overhauser effect

NRTI – Nucleoside reverse-transcriptase inhibitor

NSAID – Non-steroidal anti-inflammatory drug

OTC - Ornithine transcarbamylase

Pa - *Pseudomonas aeruginosa*

PABA – *para*-Aminobenzoic acid

pfCAI – *Plasmodium falciparum* carbonic anhydrase I

PFP – Pentafluorophenyl

PFPOH – Pentafluorophenol

PhMe – Toluene

PIC – Pre-integration complex

PMB – *para*-Methoxy-benzyl

PPh_3 – Triphenylphosphine

ppm – Parts per million

PRMT - Protein arginine methyltransferase

PyBOP – Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate

QR2 - Quinone reductase 2

RICK - Rip-like interacting caspase-like apoptosis-regulatory protein kinase

RNA – Rbonucleic acid

RT – Room temperature

RT – Reverse transcriptase

RTCs - Reverse-transcription complexes

SAR – Structure-activity relationships

SDMA - Symmetric dimethylated L-arginine

sGC - Soluble guanylate cyclase

SO_2 – Sulfur dioxide

$SOCl_2$ – Thionyl chloride

SPS – Solid phase synthesis

TBAC – *tetra*-Butylammonium chloride

TBAF – *tetra*-Butylammonium fluoride

TBDMS –*tert*-Butyldimethylsilyl

TBDPS – *tert*-Butyldiphenylsilyl

TCCA – Trichloroisocyanuric acid

TCP – 2,4,6-Trichlorophenyl

TFAA – Trifluoroacetic acid

THF – Tetrahydrofuran

TLC – Thin layer chromatography

TMS – Trimethylsilyl

UV – Ultra violet

vDNA – Viral deoxyribose nucleic acid

Vpr – Viral protein R

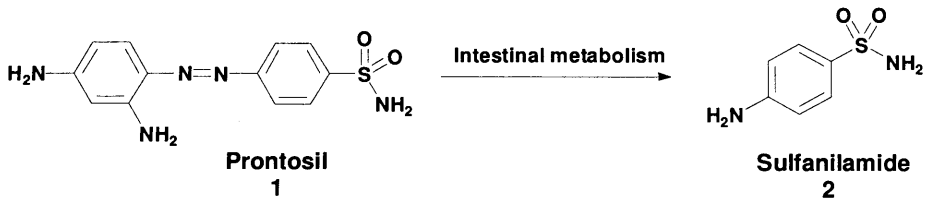
CHAPTER 1: Introduction

This thesis presents research directed towards the synthesis of a structurally diverse range of sulfonamides through the development of new methods, and by applying this discovery to new biological probes and potential therapeutics.

1.1. Introduction to sulfonamides

Sulfonamides are an important class of synthetic bacteriostatic antibiotics still used today for the treatment of bacterial infections and those caused by other microorganisms. They are also known as sulfa drugs and were the main source of therapy against bacterial infections before the introduction of penicillin in 1941.[1, 2] Although sulfonamides have for the most part been replaced by other agents, they still maintain considerable action in certain types of infection, for example in the urinary tract, eye and ear, and bronchitis.[3]

One of the first sulfonamides identified by Domagk *et al.* in 1935 was the red azo dye known as Prontosil **1**. It was active against streptococcal infection *in vivo*, but not *in vitro*. This observation was finally clarified when it was discovered that Prontosil **1** was metabolised by bacteria in the intestines into sulfanilamide **2**, the active metabolite (Scheme 1).[1,4]



Prontosil **1**

Sulfanilamide **2**

Scheme 1

Having determined that sulfanilamide **2** was the antibacterial agent this led to its synthesis in 1936.[4] Since then there have been many analogues of sulfanilamide **2** developed as pharmacological agents that display a wide range of biological activities (Figure 1). For example, Glibenclamide **3** has found use as a hypoglycaemic agent, E7070 **4** as an anticancer agent, Amprenavir **5** is used in HIV therapy, Furosemide **6** as a diuretic, Acetazolamide **7** as a carbonic anhydrase inhibitor, and Sulfathiazole **8** as an antibacterial agent.[5]

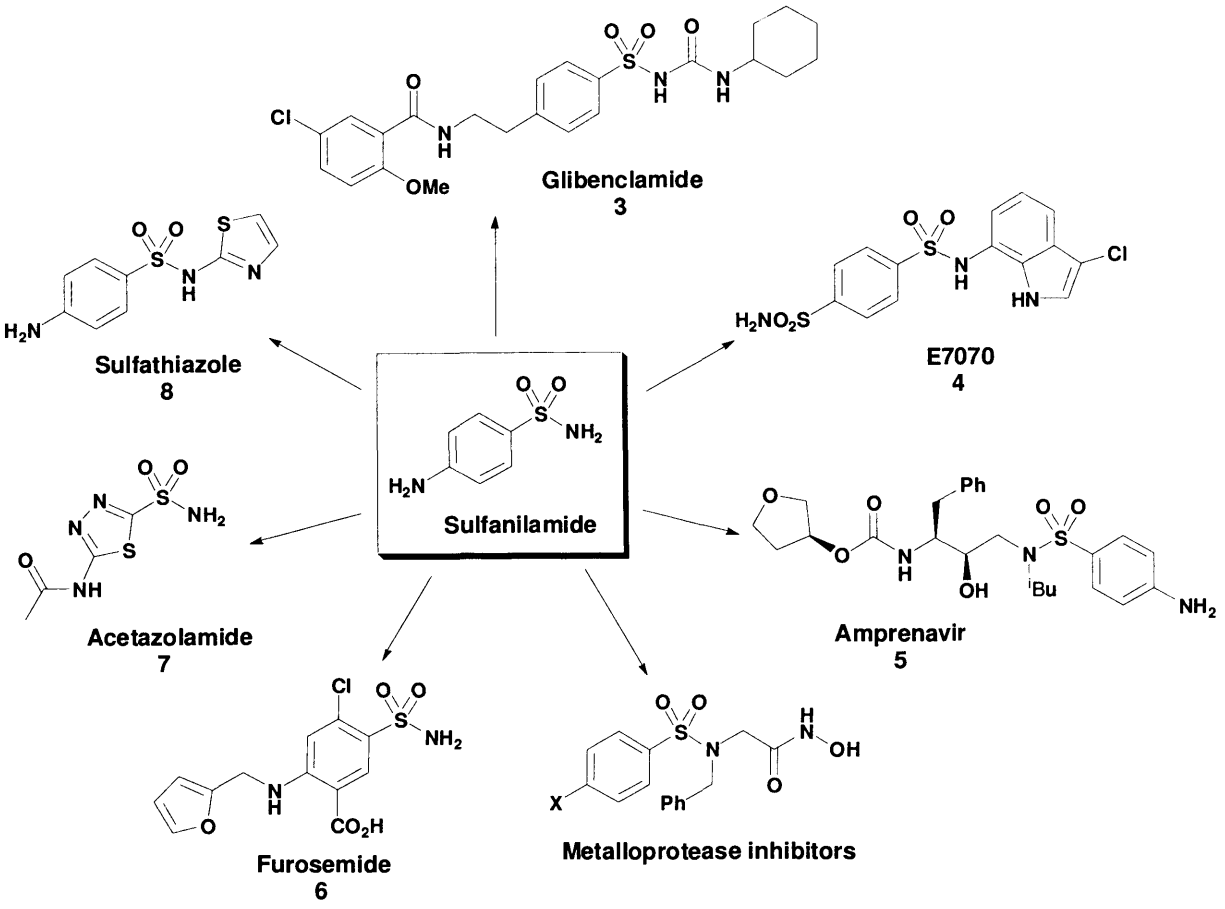
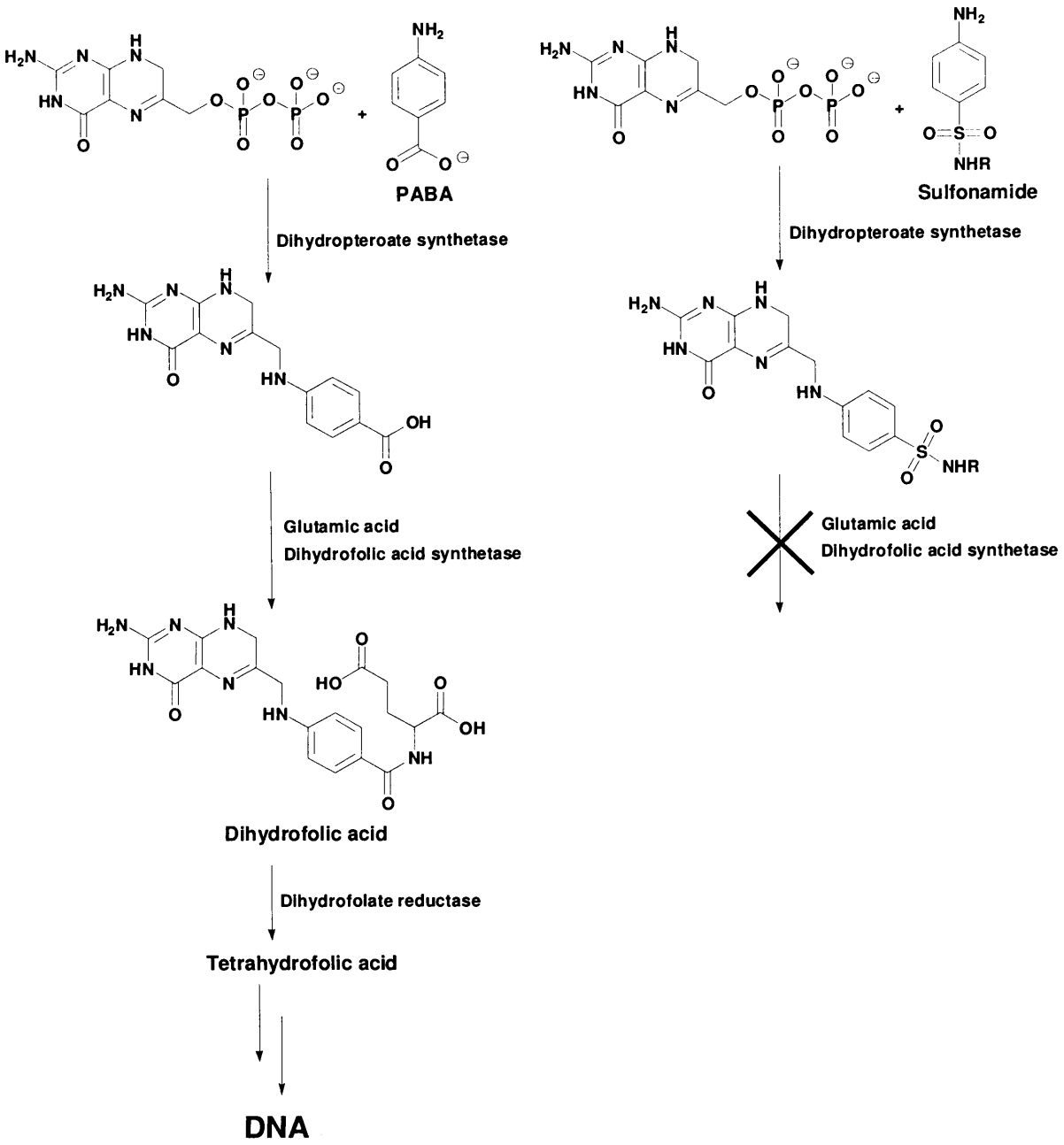


Figure 1

1.1.1. Action of sulfonamides

The majority of sulfonamides prevent bacterial reproduction by acting as an antimetabolite to *para*-aminobenzoic acid (PABA), where PABA is a vital component in the biosynthesis of tetrahydrofolic acid.[1, 6] Competitive inhibition of PABA processing enzymes by sulfonamides ultimately blocks the action of dihydrofolic acid synthetase, and therefore prevents dihydrofolic acid formation (Scheme 2). As bacteria are unable to take up tetrahydrofolic acid from their surroundings, inhibition of dihydrofolic acid synthetase will starve the bacteria of thymidine and uridine. These two nucleosides are required for DNA replication and transcription, therefore cell growth and division is disrupted, and thus provides enough time for the body's own immune system to eliminate the bacterial threat.[1,6]

Often sulfonamides are employed in conjunction with trimethoprim which inhibits dihydrofolate reductase. This approach of sequential blocking in treatment permits the inhibition of two enzymes in the same biosynthetic route and allows the dose of each drug to be reduced.[6,7]



Scheme 2

1.1.2. Value of sulfonamides as therapeutic agents

Sulfonamides were primarily developed as antibacterial agents, with sulfanilamide **2** the first recognized sulfonamide antibacterial. Since then many other effective antibacterials derived from sulfonamides have been discovered and utilised in medicine. For example, other common sulfonamide antibacterials still in circulation are Sulfathiazole **8**, Sulfaquinoxaline **9**, silver Sulfadiazine (Silvadene®) **10**, Sulfasalazine (Azulfidine®) **11**, and Sulfamethoxazole (Gantanol®) **12** (Figure 2).[8]

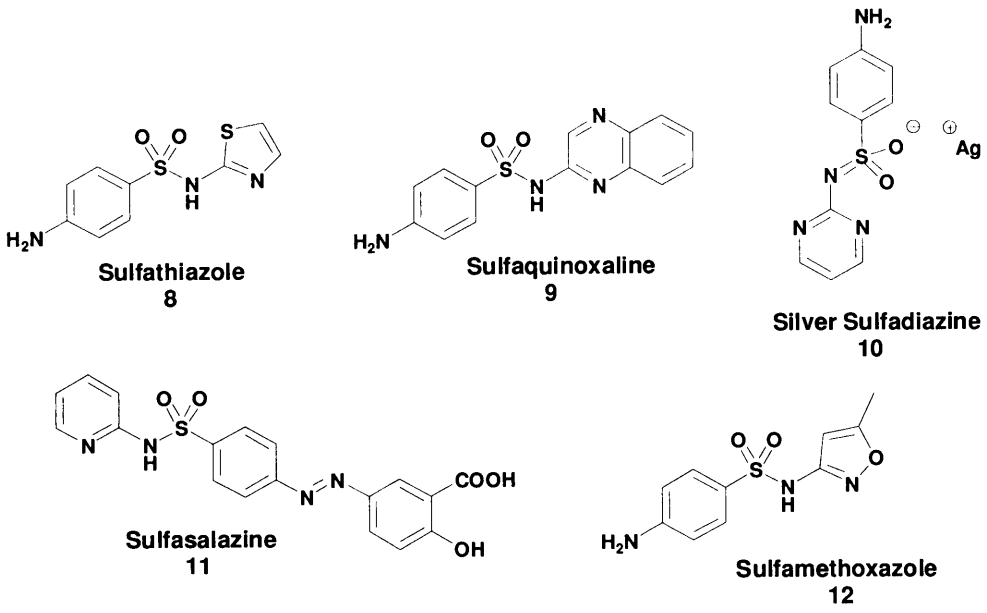


Figure 2

Of these sulfamethoxazole **12** and sulfasalazine **11** are antibiotics utilised in alleviating the symptoms of malaria, urinary tract infections, and Crohn's disease.[2] Silver sulfadiazine **10** is used as a topical treatment for severe burns,[9] and has more recently been discovered to prevent relapses of toxoplasmic encephalitis in HIV-infected patients. [10] Sulfathiazole **8** has found use as an anti-microbial agent, [11] and sulfaquinoxaline **9** is an antiprotozoal agent used to combat coccidial infections.[12]

The development of bacterial resistance to some sulfonamides has seen their use as antibacterials restricted in modern therapy. However, in recent years sulfonamides have been identified as inhibitors of other classes of enzymes which control important physiological processes in the human body. Consequently, the effects of these sulfonamides have been extended to uncovering treatments for certain diseases, some of which are discussed below.

1.1.3. Sulfonamides with anti-carbonic anhydrase activity

Sulfonamides are also known to inhibit the enzyme carbonic anhydrase (CA), an enzyme present in red blood cells and kidneys that catalyses the hydration of carbon dioxide and the dehydration of bicarbonate at physiological pH, ($CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$).[13] The formation of bicarbonate is essential as it is involved in the carboxylation step of key metabolic pathways in gluconeogenesis, lipogenesis, ureagenesis, as well as the biosynthesis of amino acids and pyrimidines.[14] CA controls the release of CO_2 from the body *via* its transfer from tissue to blood and blood to the lungs. CA is also responsible for the secretion of electrolytes in tissues and organs as

well as homeostasis, and because of its ubiquitous nature has been the target for inhibitors in the clinical treatment of a variety of diseases.[13,15]

The discovery that sulfonamides inhibit CA has led to them being used for more than 50 years as agents to reduce blood pressure, in the treatment of conditions such as heart failure, glaucoma, epilepsy, and now potentially cancer. Acetazolamide **7**, methazolamide **13**, ethoxzolamide **14**, and dichlorophenamide **15**, are four such sulfonamides that have been in clinical use as systemic CA inhibitors since the 1950's (Figure 3). In addition, dorzolamide **16**, and brinzolamide **17**, have been launched as topically acting antiglaucoma pharmacological agents since the 1990's (Figure 3).[15,16]

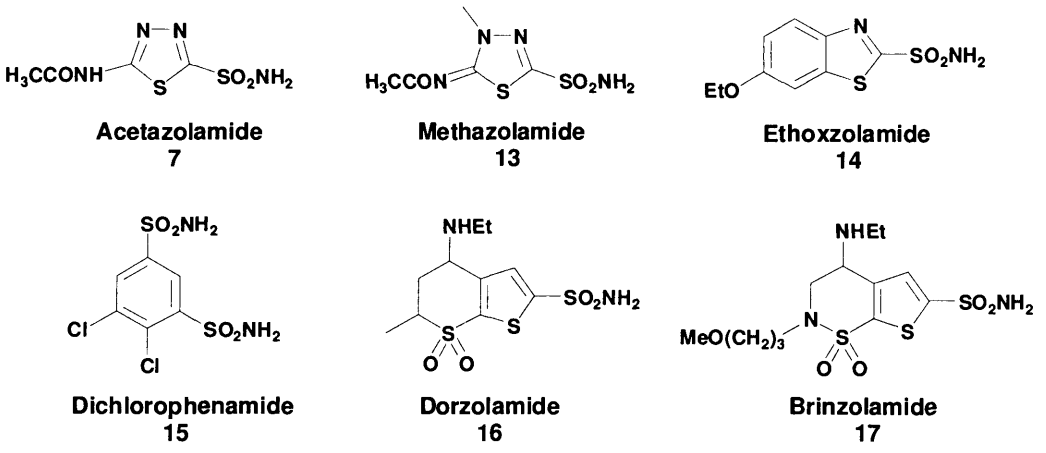


Figure 3

In humans there are 14 different CA isozymes each with a specific cellular location or tissue distribution. CA I, II, III, and VII are found in the cytosol of cells, CA IV, IX, XII, and XIV are membrane bound, CA V is located in the mitochondria, and CA VI is secreted in saliva.[15] Little is known about the outstanding CA isozymes and their cellular locations have yet to be revealed. Each isozyme possesses a distinct biological function within the body and hence through the design of isozyme specific CA inhibitors, any side effects that result from non-specific inhibition will be reduced. In addition, specific isoform inhibition may further enhance our understanding of each physiological and physiopathological role displayed by each CA isozyme.

It has been revealed in recent years that CA IX and CA XII are over-expressed in cancer cells, and that membrane bound CA IX is associated with the development of tumours in kidney, lung, oesophagus, breast, colon, and cervical carcinomas by instigating hypoxia. CA IX expression is strongly related to intra-tumoural hypoxia, as CA IX is thought to be crucial in the acidification of extracellular surroundings thus assisting

tumour invasion. Therefore, *via* the selective inhibition of CA IX and/or CA XII there is a potential for the development of anticancer agents.[15, 17]

This has led to the discovery of several aromatic and heterocyclic sulfonamides by Supuran *et al.* that display inhibition against CA IX in the region of 14-285nM. However, these sulfonamides are not completely selective for CA IX as inhibition against CA I, II, and IV was also achieved, although of the 32 sulfonamides evaluated 5 of these (**19-23**) showed promising levels of CA IX selectivity over the rest (Figure 4). The strongest CA IX inhibitor was the ethoxzolamide phenol **18** with a K_i of 14nM, however this lacked any selectivity. These sulfonamides on the other hand constitute the first sulfonamide inhibitors of CA IX studied.[15]

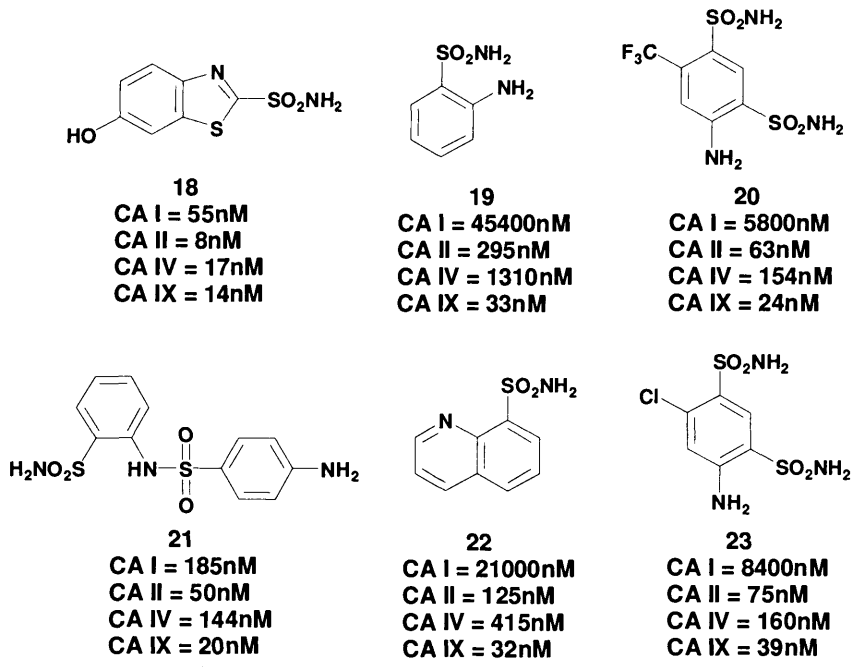


Figure 4

In the search for more potent inhibitors of CA IX, Supuran *et al.* revealed another class of sulfonamides incorporating a thiadiazole moiety that exhibited improved levels of inhibition. Each analogue displayed nM inhibition of between 3.2-23nM for CA IX, however with all compounds surveyed there was no selectivity between the CA isozymes I, II, and IX. In fact, inhibition levels were far greater for CA I (0.6-62nM) and CA II (0.5-1.7nM), a few of the most promising sulfonamides are shown in Figure 5.[17]

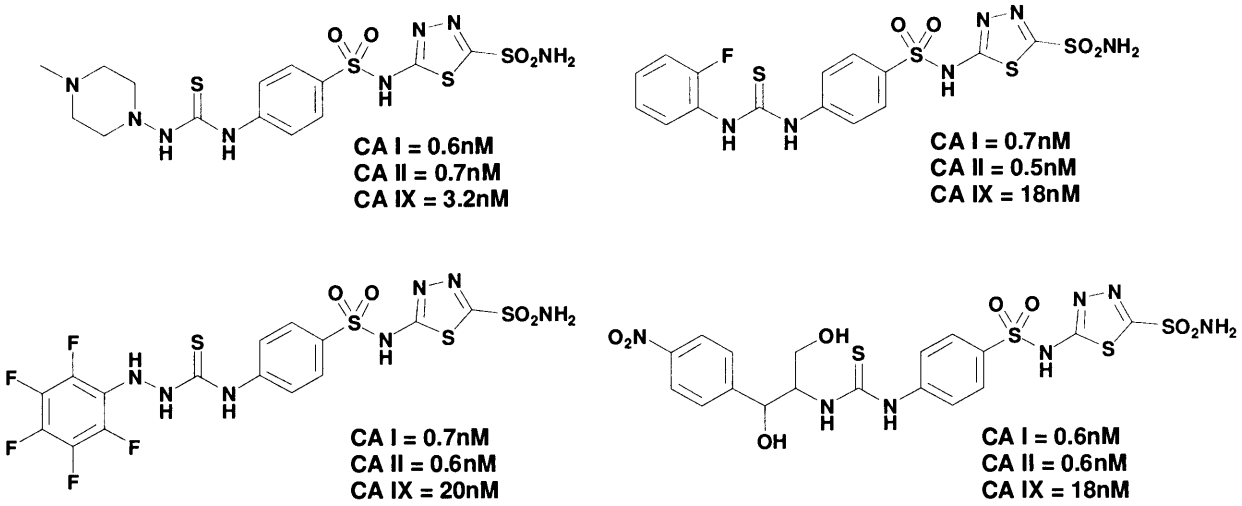


Figure 5

CA inhibitors have been utilised in the treatment of glaucoma and macular edema which results from over-activity of two CA isozymes (namely CA II and IV). It has been shown by Maren *et al.* that the topical application of sulfonamides such as dorzolamide **16** and brinzolamide **17** (Figure 3) can alleviate symptoms of glaucoma and macular edema, by reducing intraocular pressure through the suppression of bicarbonate formation and hence aqueous humor secretion. Unfortunately these two sulfonamides are secondary amines, and to apply them as efficient topical agents requires their usage as the hydrochloride salt in order to achieve water solubility. However, such a conversion produces problematic side effects namely stinging of the eye, blurred vision, and pruritus.[16]

Subsequently, Scozzafava *et al.* identified a solution to this problem and set about correcting it with the design of CA sulfonamide inhibitors with increased water solubility. They recognized during their investigation that the perfluoroalkyl- or aryl moiety exhibited good water solubility, and set about synthesizing a range of sulfonamide derivatives. A total of 150 perfluoro-sulfonamides were produced and assayed against CA II and IV, the isozymes connected to glaucoma. The most active inhibitors are shown (Figure 6).[16]

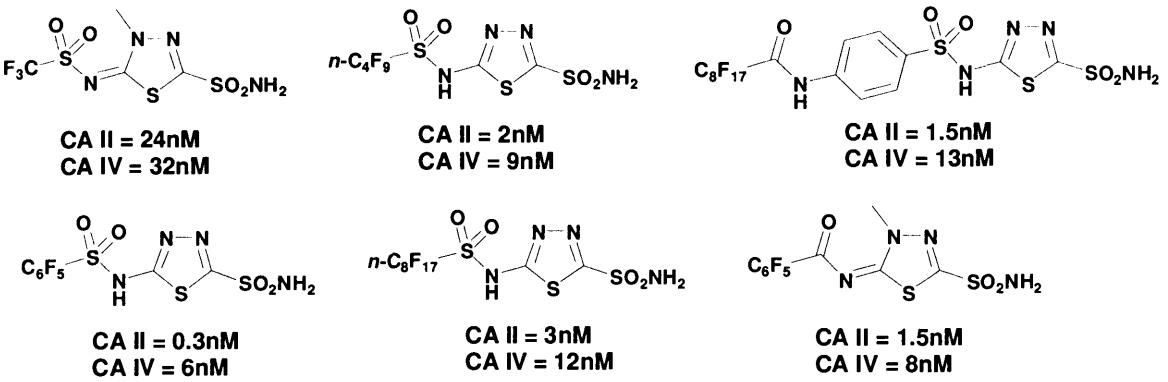
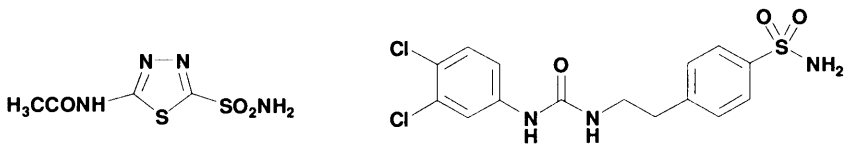


Figure 6

They also examined the *in vivo* effect of the most effective CA sulfonamide inhibitors on glaucomatous rabbits, and observed a significant drop in intraocular pressure. The best result obtained saw a drop from 31.9±3.0mmHg to 6.8±0.3mmHg, and as testing was carried out under neutral pH eye irritation was avoided.[16,18]

CA inhibition has also generated interest as a target for malaria chemotherapy, by targeting an enzyme fundamental to the life cycle of the parasite. *Plasmodium falciparum* is responsible for 2.5 million deaths annually, and it has been established that infected individuals display high levels of CA in human red cells. In 2004 this CA was isolated and characterised as CA I by Krungkrai *et al.* Malarial parasites require the synthesis of pyrimidines for DNA/RNA replication, and as bicarbonate is essential to this process, inhibition of CA I may be targeted as a means for the design of new anti-malarials.[19,20] This revelation has opened the possibility for sulfonamide based inhibition of CA I as a method for malarial treatment, which potentially does not suffer from the toxicity and drug-resistance shown by current anti-malarials.

Krungkrai *et al.* having cloned and expressed the *P. falciparum* CA I (pfCAI) gene in *E. coli*, subjected this to testing *in vitro* by acetazolamide **7** and sulfanilamide **2**. They report that it was possible to achieve a 50% inhibition on *P. falciparum* growth at a concentration of 100μM. In extension of this work Krungkrai *et al.* identified another sulfonamide **24** with an inhibition constant of 80nM (Figure 7), four times more potent than acetazolamide **7** (315nM).[20]



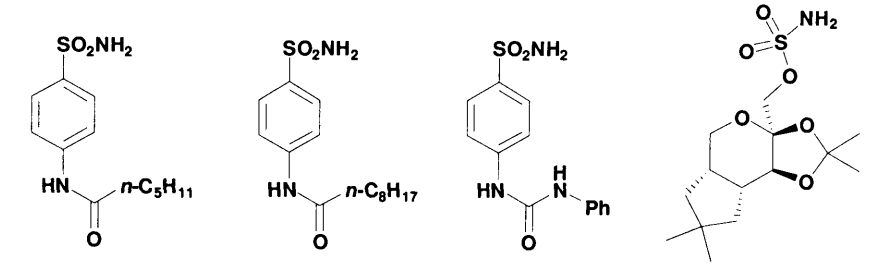
Acetazolamide (7)
pfCAI = 315nM
IC_{50} = 20μM

24
pfCAI = 80nM
IC_{50} = 2μM

Figure 7

Selective inhibition of the mitochondrial prevalent CA V has been investigated as a tool in the development of novel anti-obesity drugs based on sulfonamides. This hypothesis is derived from the knowledge that CA V is responsible for important biosynthetic pathways namely ureagenesis, gluconeogenesis, and more importantly lipogenesis. In lipogenesis, bicarbonate ions are required by the enzymes pyruvate carboxylase (in the mitochondria) and acetyl CoA carboxylase (in the cytosol) in the eventual synthesis of fatty acids, therefore by inhibition of CA V and CA II there exists a possibility to prevent obesity. This in fact was demonstrated when obese epileptic patients were supplied with the anti-epileptic drug topiramate **25**, which also displays a potent CA II and good CA V inhibitory effect. Such patients recorded a 10-15% reduction in body weight, and **25** was consequently patented as an anti-obesity drug (Figure 8).[21]

Supuran *et al.* explored the possibility of obtaining selective CA V inhibition over CA I, II, and IV using a large collection of sulfonamides with interesting results. They found that while all sulfonamides inhibited each CA isozyme to some degree; it was possible to get selective nM inhibition of CA V over the other CA isozymes (Figure 8). Moreover, the sulfonamides (**26-28**) highlighted by Supuran *et al.* showed increased potency for CA V over topiramate **25**.[21]



26
CA I = 14200nM
CA II = 63nM
CA IV = 980nM
CA V = 18nM

27
CA I = 1400nM
CA II = 66nM
CA IV = 850nM
CA V = 13nM

28
CA I = 1200nM
CA II = 240nM
CA IV = 460nM
CA V = 21nM

Topiramate (25)
CA I = 250nM
CA II = 5nM
CA IV = 54nM
CA V = 63nM

Figure 8

1.1.4. Sulfonamides with anticancer activity

Apart from the examples above where anti-tumour activity is gained by the inhibition of CA (see Section 1.1.3.), other structurally related sulfonamides have also generated interest as potential anti-cancer agents. Chloroquinoxaline **29** is one such sulfanilamide derivative that has progressed to Phase II clinical trials (Figure 9).[12, 22] Chloroquinoxaline **29** inhibited the formation of solid tumours in breast, lung, ovarian, and skin cancer, and whilst its mode of action is unclear, it is understood that folate metabolism remains unaffected, hence deviating from the usual distinctive nature of sulfonamide action. However, the lack of success during phase II clinical trials in non-small cell lung cancer meant its development as a clinical drug candidate was suspended.[14]

In 1992 Yoshino *et al.* discovered sulfonamide **30** displays weak *in vitro* activity (IC_{50} = 1.2μM/mL) in tumour-bearing mice (Figure 9).[23] This encouraging result led to the design of derivatives of sulfonamide **30** with the aim of finding improved anti-tumour activity. Thus, Yoshino *et al.* reported sulfonamide E7010 **31** as a suitable candidate which displayed pleasing levels of tumour growth inhibition (IC_{50} = 0.06-0.8μM/mL) against 26 human tumour cell lines (Figure 9). In rodent colon tumour models it was possible to reach a 60-99% inhibition of tumour growth at a dosage of 25-100mg/kg daily over an eight day period. E7010 **31** has been clinically assessed in phase I and II trials, and is currently being developed as an anti-tumour agent.[14, 24] Ueda *et al.* in 1995 developed a second generation sulfonamide ER-34410 **32** based on the structure of E7010 that exhibited double the potency of the parent compound (Figure 9). It was effective *in vitro* against human tumour cell lines, and could be administered at a lower dose (50mg/kg) compared with E7010 **31** (400mg/kg).[14]

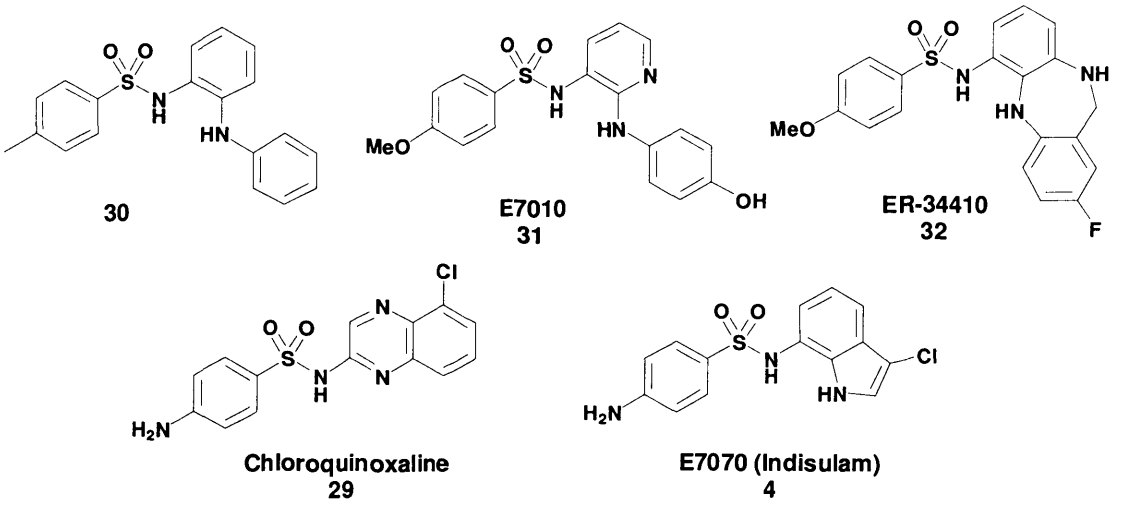


Figure 9

More recently, studies by Ozawa *et al.* have disclosed a series of *N*-7-indolyl-benzenesulfonamides of which E7070 **4** is revealed to be the most potent anti-tumour sulfonamide known (Figure 9). E7070 **4** is effective *in vitro* (IC_{50} = 0.11μM/mL) and *in vivo* (IC_{50} < 0.5μM/mL) against human colon carcinoma, and exhibited tumour growth suppression. This was evident in its ability to exert complete tumour regression in lung and colon carcinomas at a daily intravenous dose of 25mg/kg over 8 days. [14, 25] E7070 **4** more commonly known as indisulam is currently in phase II clinical trials, and is awaiting approval to be used as an anticancer drug.[26]

1.1.5. Sulfonamides with protease inhibitory activity (cysteine and HIV)

In recent years, sulfonamides have been investigated as inhibitors of cysteine protease, a ubiquitous group of enzymes that hold important roles in mammalian cell turnover, apoptosis, and the life cycles of several parasitic protozoa. Therefore, sulfonamide inhibitors could potentially have therapeutic uses in the treatment of Alzheimer's, arthritis, cancer, and osteoporosis.[27, 28] The potential to treat such high profile diseases means that the synthesis of sulfonamides is highly desirable, and in an early example by Roush *et al.*, work was directed towards the synthesis of vinyl sulfonates and sulfonamides which targeted *Trypanosoma cruzi*, the parasite responsible for Chaga's disease. Chaga's disease is prevalent in South America and is the main cause of heart disease, to which current therapy is limited due to toxicity of drugs. Cruzain has been identified as the cysteine protease of *T. cruzi*, and hence it was envisaged that inhibition of cruzain holds the key to treatment of Chaga's disease. This was demonstrated by Brömme *et al.* and McKerrow *et al.* through *in vivo* experiments with vinyl sulfone compounds **33**, k_{inact} 16400 s^{-1} M^{-1} (Figure 10); however these sulfones are not especially potent at therapeutic doses and displays poor selectivity for cruzain over other cysteine proteases.[29] In search of more potent inhibitors of cruzain Roush and co-workers examined vinyl sulfonamides **34** and **35**.[28] These compounds screened were moderately potent **34** (k_{ass} = 9700 s^{-1} M^{-1}) and **35** (k_{ass} = 289000 s^{-1} M^{-1}), however, they were able to further enhance potency with the synthesis of second generation inhibitors. Thus, by utilising the vinyl sulfone scaffold developed by Brömme *et al.*, Roush *et al.* synthesized the two *N*–benzyloxysulfonamides **36** and **37** which displayed much improved inhibition compared to **34** and **35** (Figure 10).[30]

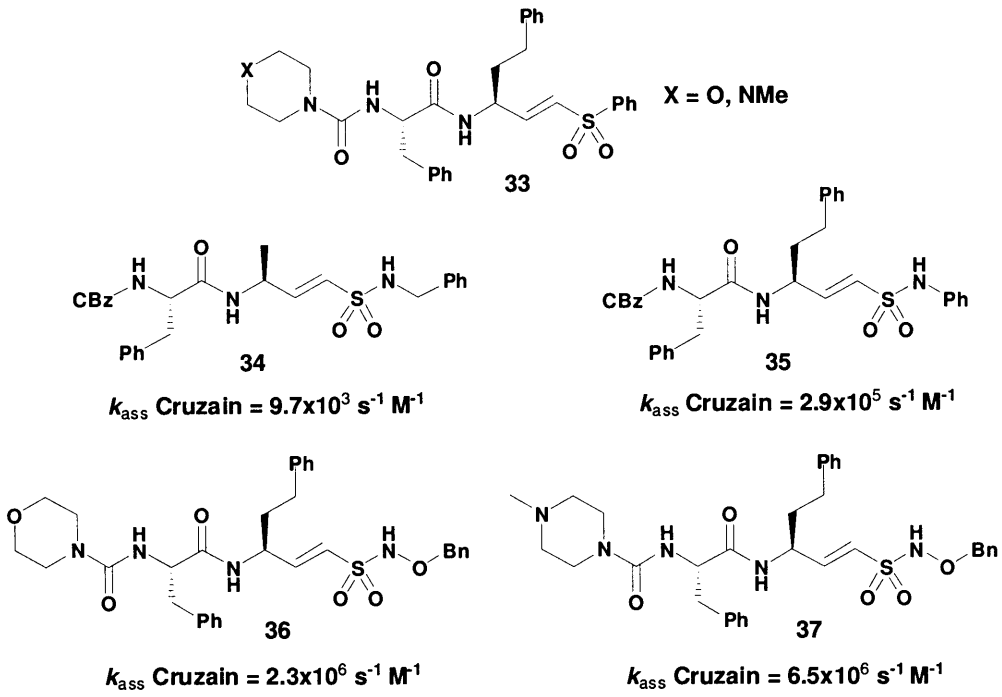


Figure 10

Another benefit derived from the inhibition of cysteine proteases is in the potential treatment of *P. falciparum* (malaria). *P. falciparum* contains falcipain, a member of the papain family of cysteine proteases responsible for hydrolysing haemoglobin, and thus providing amino acids for parasite replication. Shenai *et al.* using an SAR based approach discovered that their peptidyl vinyl sulfonamides provided low nM inhibition against falcipain-2, and therefore demonstrating the potential for sulfonamides as anti-malarial cysteine protease inhibitors (Figure 11).[31]

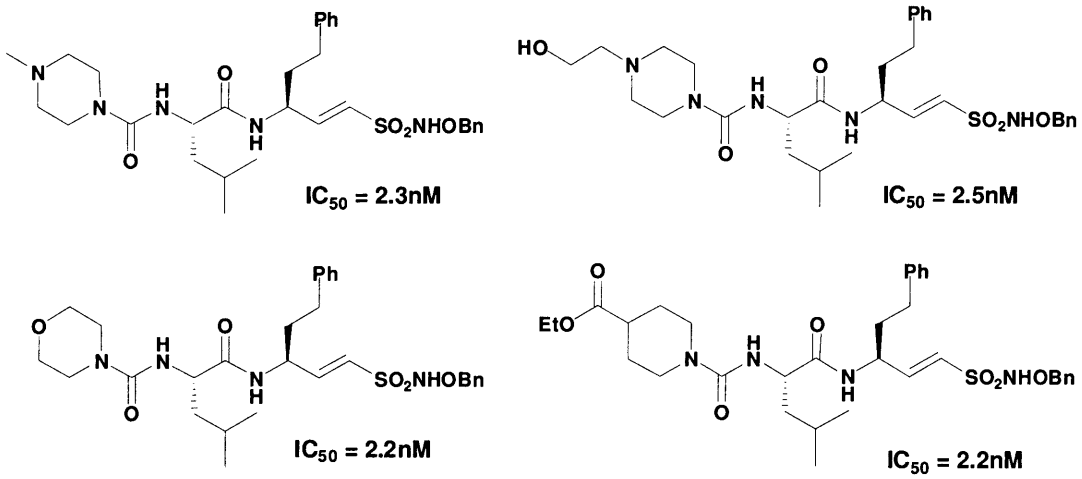
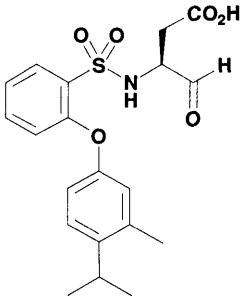


Figure 11

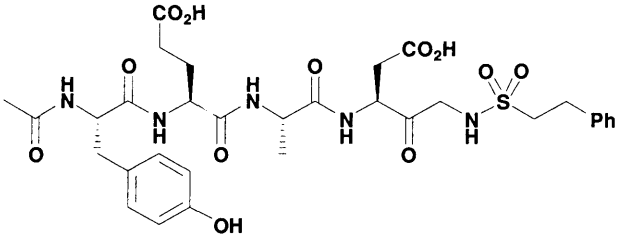
Caspase-1 belongs to the family of cysteine proteases and is responsible for controlling interleukin-1β. Interleukin-1β is a cytokine and therefore responsible for peripheral

inflammatory disorders and apoptosis; such diseases that are concerned with a raised interleukin-1β level are arthritis, Alzheimer's disease, and septic shock. As a result the control of interleukin-1β *via* the modulation of caspase-1 has been explored as a target for sulfonamide inhibition.[32]

A biphenyl ether sulfonamide **38** synthesised by Shahripour and co-workers displayed good μM inhibition against caspase-1, which also exhibited good potential against apoptosis in cell studies performed *in vitro* (Figure 12).[32, 33] However, the more illustrious nM potency was finally reached through efforts by Harter *et al.* in 2004, through their design and synthesis of rigidified sulfonamides. By examining the crystal structure of the enzyme, they rationalised that enhanced potency could be gained upon the addition of rigidity to the molecule through intramolecular H-bonding. Consequently, a variety of conformationally locked sulfonamides were screened against caspase-1 and the best inhibitor **39** is shown in Figure 12.[34]



38, *Ki* = 0.11μM

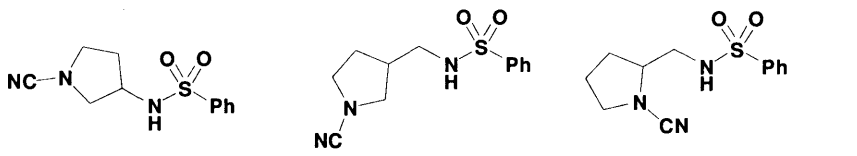


39, *Ki* = 4nM

Figure 12

Another related class of cysteine protease enzymes known as cathepsins has also been the target for sulfonamide action. Cathepsins are functionally important lysosomal enzymes involved in intracellular proteolysis, and have been implicated in diseases such as osteoporosis, cancer, muscular dystrophy, Alzheimer's, and multiple sclerosis. There are eleven types of human cysteinyl cathepsin (B, C, F, H, K, L, O, S, V, W, and X), of which sulfonamide inhibition has been examined with two forms (K and L).[35] Oballa *et al.* reported the synthesis of non-peptidic inhibitors of cathepsin K and L based on a 1-cyanopyrrolidinyl ring. *In vitro* testing determined sulfonamides **40** and **41** have low μM levels of inhibition, and that substitution at the 3-position of the cyanopyrrolidine ring is essential for maintaining an inhibitory effect (Figure 13). During their studies it was also revealed that it was possible to gain some degree of selectivity for cathepsin K and L over cathepsin B, with sulfonamide **40** the most selective. Cathepsin K is

expressed in bone-resorbing osteoclasts it is thus a target in osteoporosis. The most potent sulfonamide **40** was tested against cathepsin K in a bone resorption assay (IC_{50} = 0.75μM), earmarking this as a potential starting-point in the development of a novel anti-osteoporosis drug.[35, 36]



40

IC_{50}
Cathepsin K = 0.05μM
Cathepsin L = 0.08μM
Cathepsin B = 1.4μM

41

IC_{50}
Cathepsin K = 0.2μM
Cathepsin L = 0.35μM
Cathepsin B = 1.5μM

42

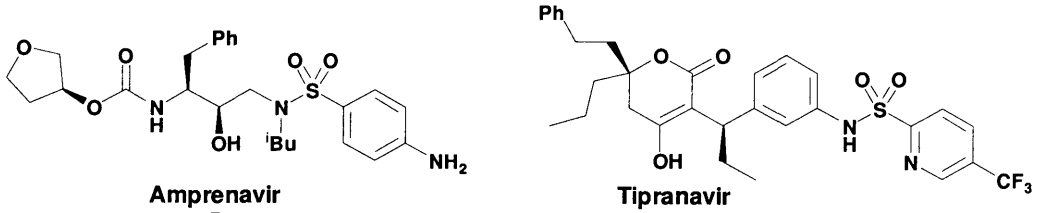
IC_{50}
Cathepsin K = 12.1μM
Cathepsin L = 11.5μM

Figure 13

Sulfonamides display a wide range of actions against cysteine proteases. However, there has also been literature precedent for the use of sulfonamides in the inhibition of another class of protease enzyme belonging to the HIV family, namely HIV protease.

Inhibitors of HIV protease are able to prevent formation of mature viral particles and consequently, hinder or inhibit the infectious process. Since 1996 HIV protease inhibitors have been used with some success in conjunction with reverse transcriptase inhibitors to treat AIDS patients through highly active anti-retroviral therapy (HAART).[36] However, the development of drug resistant strains of virus means that the continual development of new protease candidates is of utmost importance.

Currently there are several sulfonamide-derived HIV protease inhibitors employed clinically, such as amprenavir **5** and tipranavir **43** (Figure 14). Amprenavir **5** is a potent protease inhibitor with a K_i of 0.6nM against the wild type enzyme, whilst tipranavir **43** exhibits a K_i < 1nM. The emergence of these sulfonamide HIV protease inhibitors has resulted in much research into derivatizing these aforementioned clinical compounds, in the search for more potent inhibitors. For instance various analogues of amprenavir have been reported since its acceptance as HIV protease inhibitor.[36]



Amprenavir
5

Tipranavir
43

Figure 14

Fosamprenavir **44** has recently been disclosed as a bioequivalent prodrug of amprenavir **5**, has also exhibited promising results during phase I and II clinical trials. In addition, as the sodium salt of amprenavir it is more water soluble, and as a prodrug it provides the opportunity for single daily dosing. Other sulfonamides possessing structural similarities to amprenavir **5** include DPC-681 **45**, which is undergoing phase I clinical trials, and also TMC-126 **46** and TMC-114 **47**, which exhibit sub-nM inhibition and are being evaluated in human clinical trials (Figure 15). Examples of tipranavir derived analogues (PNU-103017 **48** and **49**) with low nM affinity for HIV protease are also shown in Figure 15.[36]

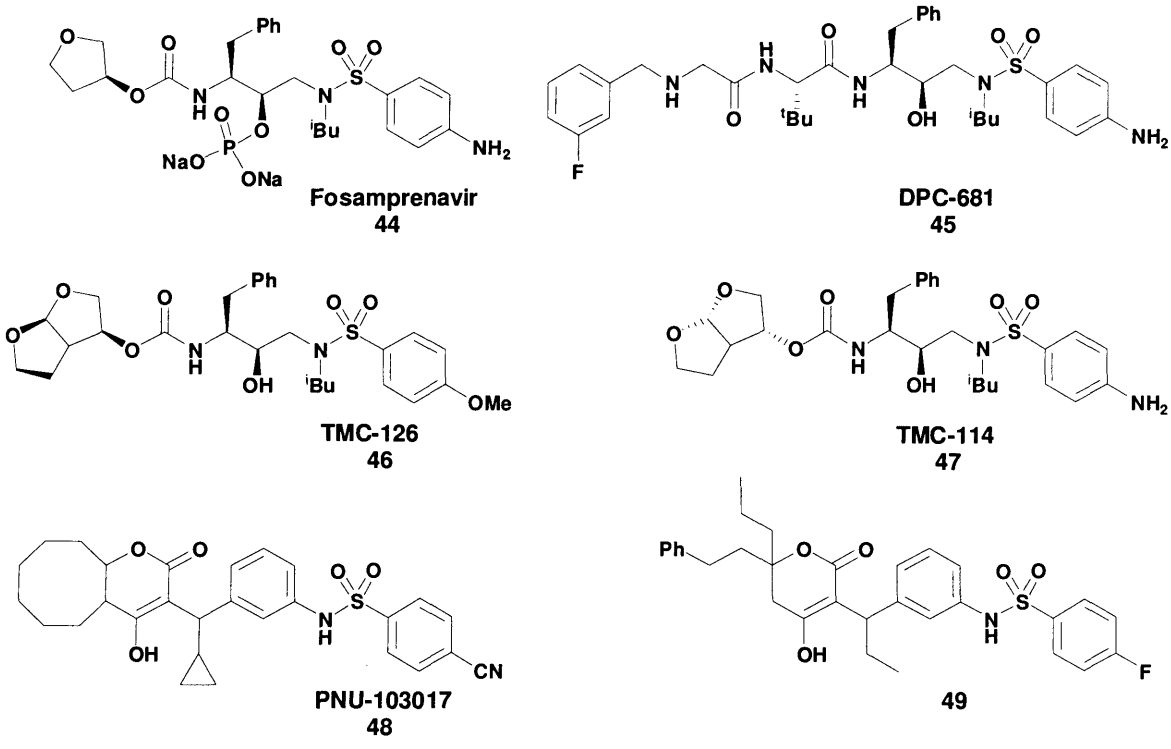


Figure 15

Hallberg *et al.* reported a range of sulfonamides distinct from the clinically used drugs. Their symmetrical cyclic sulfamides were able to inhibit HIV protease within the range of 3-84nM, and the most potent compound **50** exhibited a K_i of 3.1nM (Figure 16).[37] In a related study by Stranix *et al.*, they synthesized a range of sulfonamides incorporating a lysine backbone that displayed highly potent nM inhibition of the wild type HIV protease. Compound **51** was the most active (K_i = 1.7nM) from a selection of alkyl, and aryl lysine sulfonamide derivatives (Figure 16); the authors speculated that increased potency was gained from the additional ability of the dioxolane oxygens to H-bond to the enzyme active site.[38]

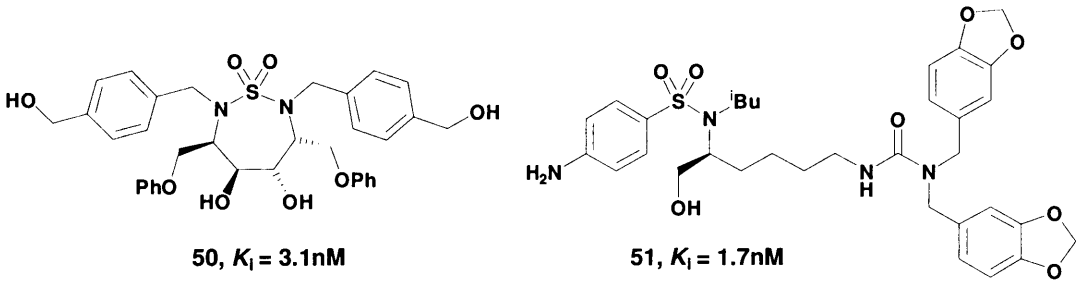


Figure 16

1.1.6. COX inhibition by sulfonamides

Since 1999 sulfonamides have been used extensively as selective COX-II inhibitors. COX enzymes are responsible for catalysing the conversion of arachidonic acid to prostaglandins, which in turn is responsible for many biological functions such as platelet aggregation, normal renal function, and vasodilation, but most notably the perception of pain.[39,40] The COX family is further subdivided into COX-I and COX-II, of which COX-II is the key contributor in induced inflammatory responses. Hence, ever since COX-II was identified in 1991, it has become a target for inhibition as a means to control pain resulting from rheumatoid and osteo- arthritis. This has led to the discovery of aryl sulfonamides celecoxib **52** and more recently vadecoxib **53** in 2002 as selective COX-II inhibitors (Figure 17).[40] Both are used clinically in the management of pain and inflammation, and as selective COX-II inhibitors they do not exhibit the side effects displayed through non-selective COX inhibition most commonly seen with non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin. In human whole blood assays IC_{50} values for COX-II inhibition was 0.65μM/L for valdecoxib **53**, and 0.54μM/L for celecoxib **52**.[41]

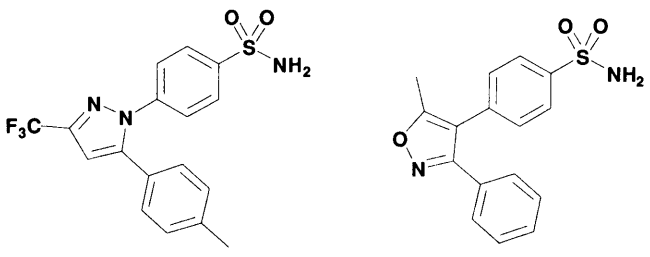


Figure 17

Celecoxib **52** and valdecoxib **53** have also been identified as potent carbonic anhydrase inhibitors, specifically for CA II (IC_{50} 21-43nM) and CA IX (IC_{50} 16-27nM). It has

been previously described that CA II is implicated in glaucoma and CA IX with various carcinomas; therefore, these two COX-II inhibitors also possess the potential to treat these disorders *via* CA inhibition. Klebe *et al.* showed that celecoxib and valdecoxib compared favourably with other clinically used CA inhibitors (see Figure 3), and additionally the authors report that celecoxib **52** (IC_{50} = 16nM) is one of the most potent CA IX inhibitors known to date.[42]

1.1.7. Other applications for sulfonamides

Several other sulfonamides have been clinically accepted and are currently employed in the treatment of various diseases (Figure 18). Furosemide **6** and torsemide **54** are two such sulfonamides that have found value as diuretics which relieve hypertension in patients with chronic systolic heart failure,[43] whilst glibenclamide **55** is a sulfonamide that is prescribed for treatment of type II diabetes. Glibenclamide **55** is a potent and selective ATP-sensitive potassium ion channel blocker, which applies a glucose lowering effect by stimulating calcium influx and thus insulin production in the β cells of the pancreas.[44] Finally amongst the most topical of current sulfonamide drugs is sildenafil **56**. Sildenafil was launched in 1998 as an anti-impotence drug and is responsible for inhibiting the degradation of cyclic guanosine monophosphate (cGMP), as a result the effects of nitric oxide are prolonged and thus vasodilation occurs.[45]

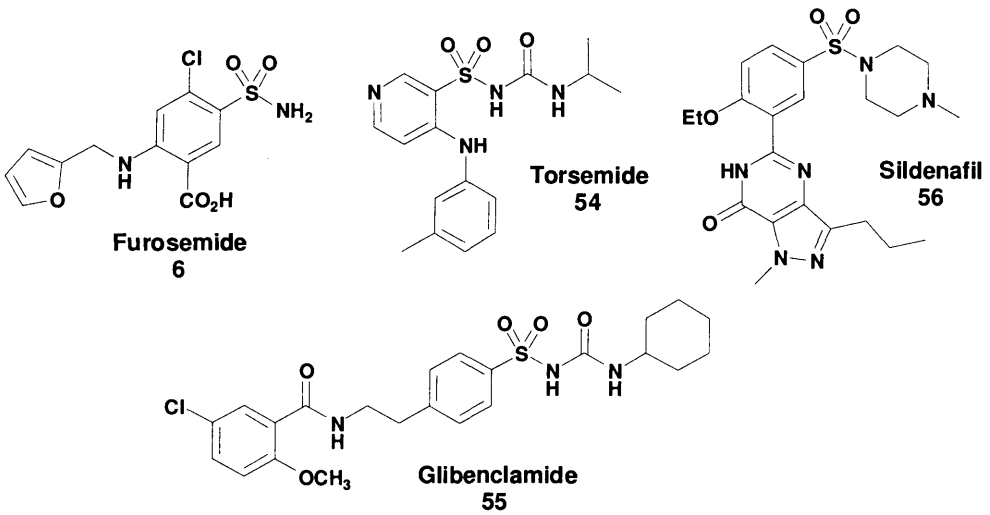


Figure 18

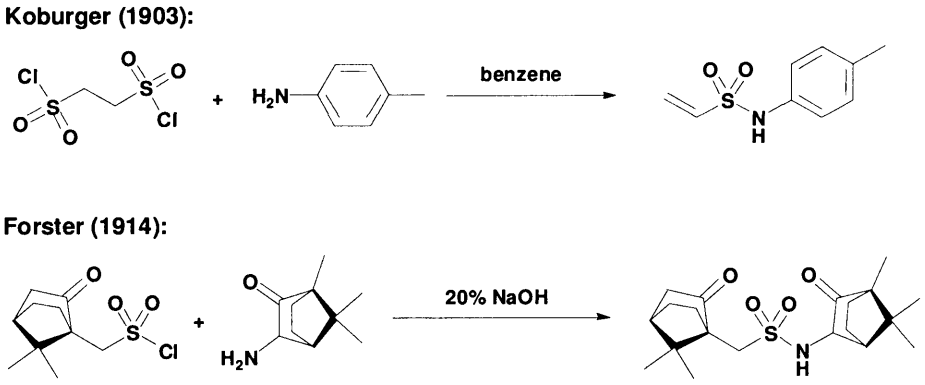
In conclusion, it has been shown that sulfonamides have a number of biological applications in the treatment of a wide range of ailments. Their key importance as motifs in an array of therapeutic agents seems certain to continue.

1.2. Synthesis of sulfonamides

As this investigation concerns the synthesis of functionalised sulfonamides, it would be noteworthy here to provide a brief overview of the key methods for their synthesis.

1.2.1. Sulfonamides from sulfonyl chlorides

Traditionally sulfonamides are synthesized by the reaction of a sulfonyl chloride with a primary or secondary amine. Sulfonyl chlorides in turn are most commonly synthesized by oxidation of the required thiol by bubbling chlorine gas into the reaction.[46] Some of the earliest examples of sulfonamide synthesis date back to 1903 and involved utilising simple alkyl sulfonyl chlorides (Scheme 3).[47]



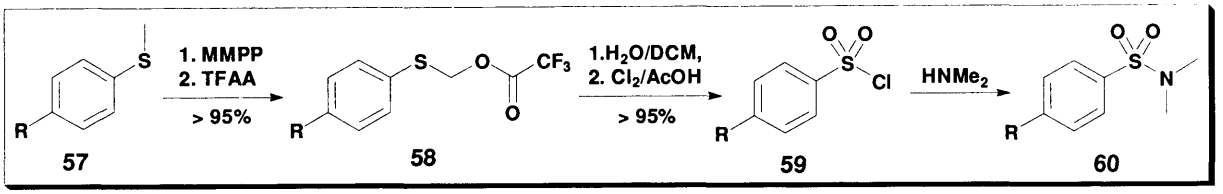
Scheme 3

Yields were not reported however Koburger showed that it was possible to obtain reactions with the normally non-nucleophilic anilines, whilst Forster *et al.* provided an interesting example in the synthesis of a camphor-derived sulfonamide.[48]

Since these early examples, the formation of sulfonamides from sulfonyl chlorides has often involved the use of more complex reagents containing sensitive functional groups, and/or the use of novel conditions to generate the corresponding sulfonyl chloride required for aminolysis.

An example of sulfonamide synthesis from sulfonyl chlorides that are derived from thioanisoles *via* a Pummerer reaction is described by Gauthier *et al.* Thioanisoles are readily available stable reagents and as a result were chosen by Gauthier as suitable precursors to sulfonyl chlorides. Their synthetic route involves the oxidation of the desired thioanisole **57** to the analogous sulfoxide by means of magnesium monoperoxyphthalate (MMPP). This is followed by a Pummerer reaction to provide the corresponding sulfide derivative **58**. Chlorine oxidation furnishes the sulfonyl chloride

59, which when treated with dimethylamine gives sulfonamide **60**. Some high yielding examples are shown in Scheme 4.[49]



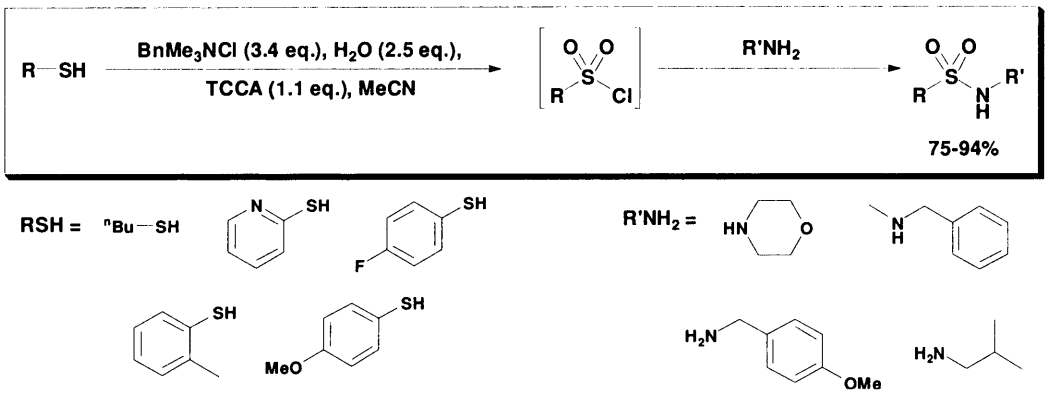
R =	H	Br	BnO	TBDPSO	MeO_2C
	59 = 95% 60 = 85%	59 = 91% 60 = 90%	59 = 95% 60 = 86%	59 = 85% 60 = 72%	59 = 88% 60 = 74%

Scheme 4

Although this entails a long synthetic sequence into sulfonamides, yields throughout are high and can tolerate a broad range of substrates that contain a variety of common functional groups. Typical R groups used include saturated hydrocarbons, halogens, carbonyls, alcohols, ethers, and heterocycles.[49]

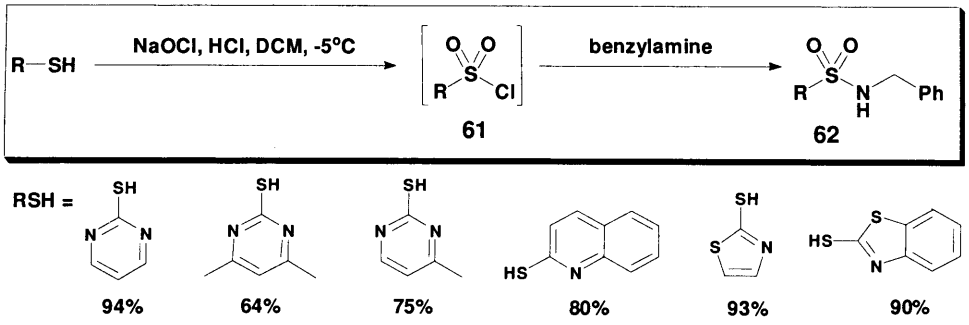
The use of chlorine gas to affect the oxidation of thiols/sulfides to sulfonyl chlorides has been widely exploited to carry out this transformation. However, the use of excess oxidant and/or aqueous acid during reaction conditions could be potentially unfavourable in the case of sensitive substrates, and thus has led to the development of novel methods to furnish sulfonyl chlorides in preparation for sulfonamide synthesis.

Bonk *et al.* in 2007 reported the synthesis of sulfonamides *via* a mild and general protocol, which limited the amount of oxidant and aqueous component used in the oxidation of thiols to sulfonyl chlorides. They recognized that it was possible to release a controlled quantity of chlorine into aprotic organic solvents, by the addition of benzyltrimethylammonium chloride to trichloroisocyanuric acid (TCCA) in acetonitrile. Two equivalents of water are also required to complete the oxidation and so this was employed in a slight excess. A selection of alkyl and aryl thiols were subjected to these conditions and provided sulfonamides in excellent yields, by entrapment of the '*in-situ*' produced sulfonyl chloride (Scheme 5). Unsuccessful reactions were observed with heteroaromatic thiols of pyrimidine and benzothiazole.[46]



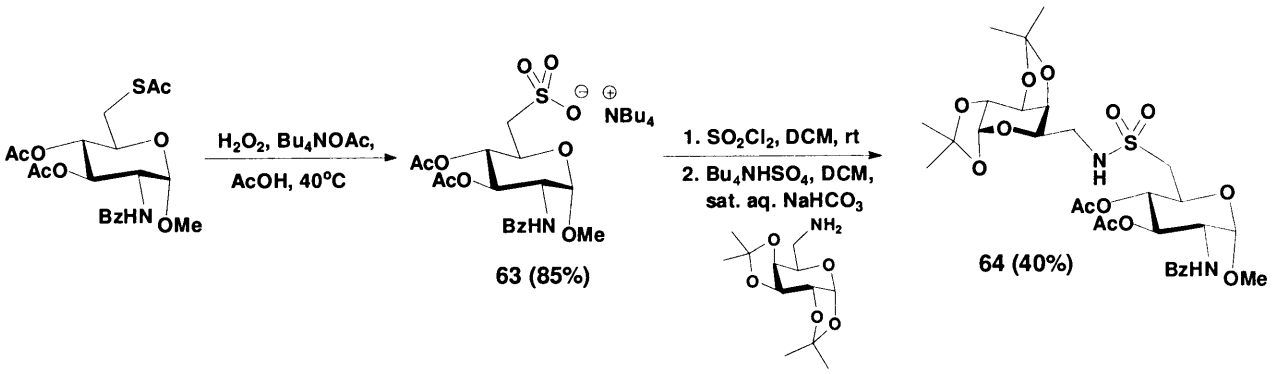
Scheme 5

In addition, Wright *et al.* showed that by using commercial bleach (NaOCl) it was possible to produce sulfonamides from heteroaromatic thiols *via* formation of an '*in-situ*' sulfonyl chloride. Wright *et al.* reasoned that bleach was a safer and more convenient reagent to chlorine gas and allowed control of the stoichiometry of the oxidant added; therefore, yields could be enhanced due to minimised decomposition of the sulfonyl chloride from excess oxidant. This work also highlights their success with mercapto-pyrimidines which have been reported in the literature as providing poor yields or unsuccessful reactions. The unstable sulfonyl chloride **61** generated is subsequently trapped with benzylamine, providing in some cases near quantitative yields of the heteroaryl sulfonamide **62** (Scheme 6).[50]



Scheme 6

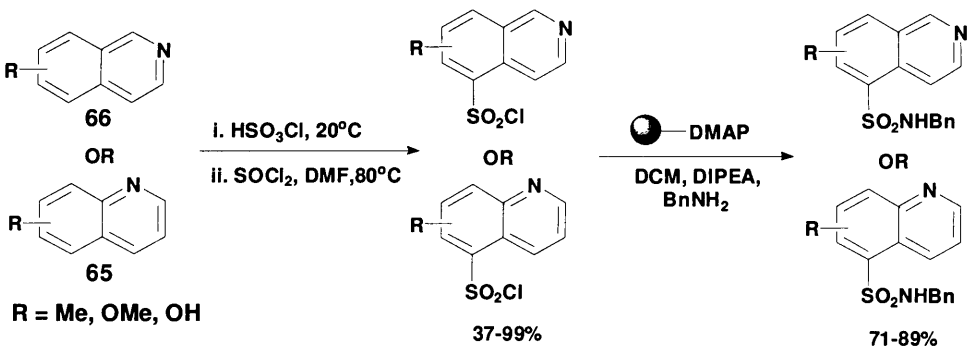
Less frequently seen is the synthesis of carbohydrate-derived sulfonamides, in which a phosphate linkage is replaced with a sulfonamido internucleoside linkage. Bolaños *et al.* report the synthesis of an *N*-alkyl sugar sulfonamide **64** from its sulfonyl chloride precursor, by coupling with an amine under phase-transfer conditions (Scheme 7).[51]



Scheme 7

Oxidation of the 6-thiosugar to its corresponding sulfonic acid salt **63** is achieved with hydrogen peroxide in an 85% yield, which is followed by chlorination to the sulfonyl chloride with sulfuryl chloride. Finally, synthesis of the sulfonamide-linked pseudo-disaccharide **64** is completed in a 40% yield upon reaction with an aminosugar.[51]

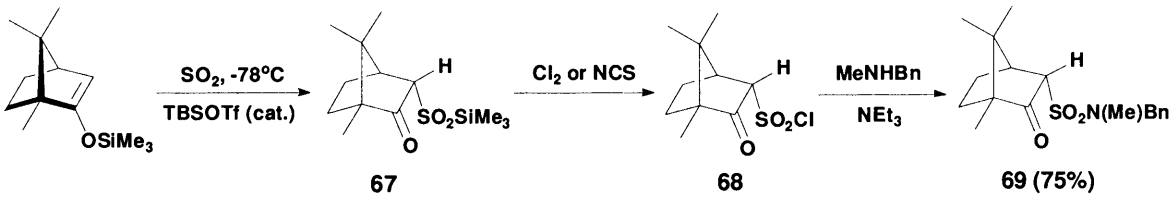
In the development of novel sulfonamides derived from substituted quinolines **65** and isoquinolines **66**, Lai *et al.* explored chlorosulfonylation as a route into sulfonyl chlorides (Scheme 8). These sulfonyl chlorides are subsequently converted to sulfonamides in good yields, through the actions of solid phase DMAP and benzylamine in a process termed 'resin-capture and release' (Scheme 8).[52]



Scheme 8

Vogel *et al.* have recently reported a one-pot, three component synthesis of sulfonamides, which incorporates an ene reaction between a silyl enol ether and sulfur dioxide (SO_2) as a key step into compounds that can contain keto β-alkoxyketone, allylic ether, or alkenyl ester moieties. The ene reaction of a silyl enol ether with SO_2 promoted by a Lewis acid generates sulfinate **67**, which is oxidised by treatment with chlorine or *N*-chlorosuccinimide (NCS) to furnish the corresponding sulfonyl chloride

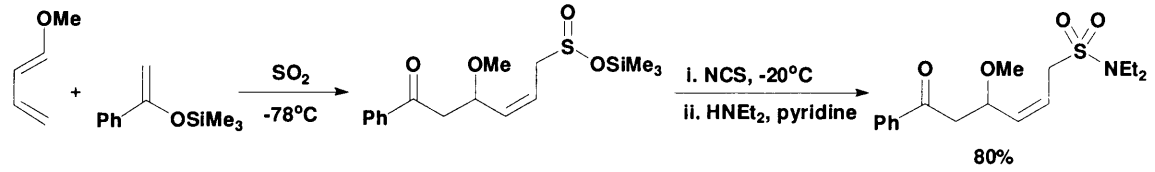
68. This is followed by the simple addition of a primary or secondary amine to the crude material, thus providing the sulfonamide **69** in a good yield; an example is presented in Scheme 9.[53]



67 68 69 (75%)

Scheme 9

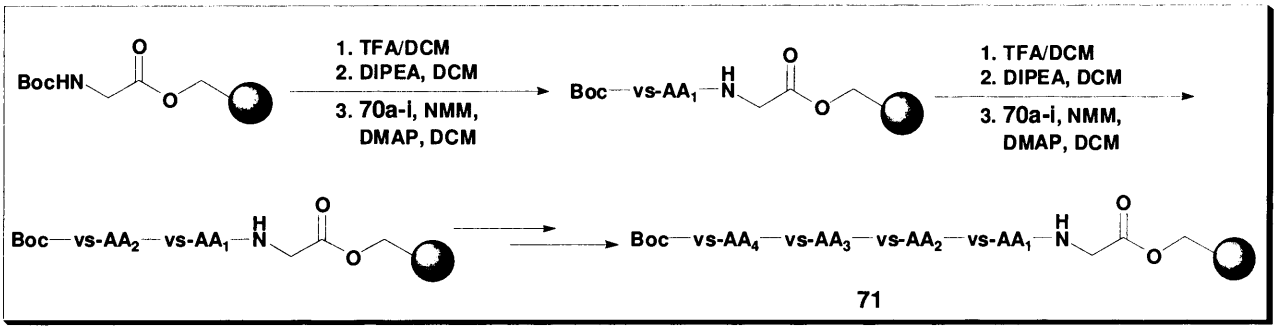
They also disclose a four component synthesis of sulfonamides in which an additional hetero-Diels-Alder reaction is added to the sequence in order to introduce another level of molecular diversity to the product (Scheme 10).[53]



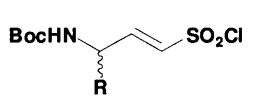
80%

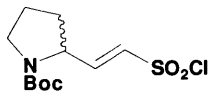
Scheme 10

Sulfonamides have more recently been investigated as potential peptidomimetics in the field of drug discovery. The replacement of a peptidyl amide bond with a sulfonamido bond holds several advantages due to their increased resistance to metabolic catabolism, their structural similarity to the analogous amides in enzymatic hydrolysis, and its more acidic hydrogen giving rise to the possibility of a stronger H-bond.[54] This idea was explored by Gennari *et al.* through the solid phase synthesis (SPS) of vinylogous sulfonamidopeptides. Vinylogous amino-sulfonyl chlorides **70a-i** were consecutively coupled together to form an extended peptide chain, which is covalently attached to a TentaGel-OH resin *via* a glycine linkage (Scheme 11). Gennari *et al.* demonstrated the generality of their SPS approach by successfully synthesizing a library of vinylogous sulfonamido-tetrapeptides **71**. Cleavage from solid support was achieved by direct ester methanolysis to afford the corresponding glycine methyl ester derivative.[54, 55] In addition, further functionalisation of the vinylogous sulfonamidopeptides is possible by *N*-alkylation of the sulfonamide nitrogen, or Michael addition of stabilised enolates to the vinyl component.[55]



vs-AA =



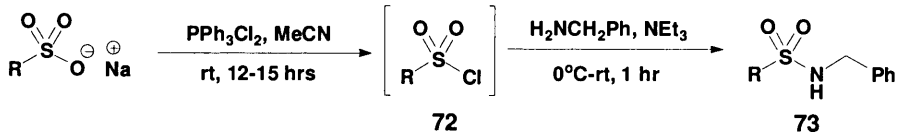


70a: (*S*)-*N*-Boc-vsAla-Cl, R = Me
70b: (*S*)-*N*-Boc-vsVal-Cl, R = *i*Pr
70c: (*S*)-*N*-Boc-vsLeu-Cl, R = *i*Bu
70d: (*S*)-*N*-Boc-vsPhe-Cl, R = Bn
70e: (*R*)-*N*-Boc-vsPhe-Cl, R = Bn
70f: (*S*)-*N*-Boc-vsSer-Cl, R = $CH_2OTBDPS$
70g: (*S*)-*N*-Boc-vsTyr-Cl, R = $CH_2C_6H_4OTBDPS$

70h: (*S*)-*N*-Boc-vsPro-Cl
70i: (*R*)-*N*-Boc-vsPro-Cl

Scheme 11

As shown previously, the corresponding sulfonyl chlorides required for sulfonamide synthesis can be accessed from sulfonic acid species. The most common method for this functional group interconversion is through the action of phosphorus pentachloride, phosphoryl chloride, or thionyl chloride. However, these chlorinating reagents are fairly harsh and produce toxic and corrosive by-products; therefore, there existed a need for milder reagents to effect this conversion. Kataoka *et al.* reported the transformation of sodium sulfonate salts into sulfonyl chlorides under mild neutral conditions. They envisaged that triphenylphosphine dichloride would be a suitable chlorinating agent, with the generation of neutral triphenylphosphine oxide as the by-product. A variety of alkyl and aromatic sulfonic acid salts were subjected to their conditions, with the ensuing aminolysis of sulfonyl chloride **72** to provide excellent yields of sulfonamide **73** (Scheme 12).[56]



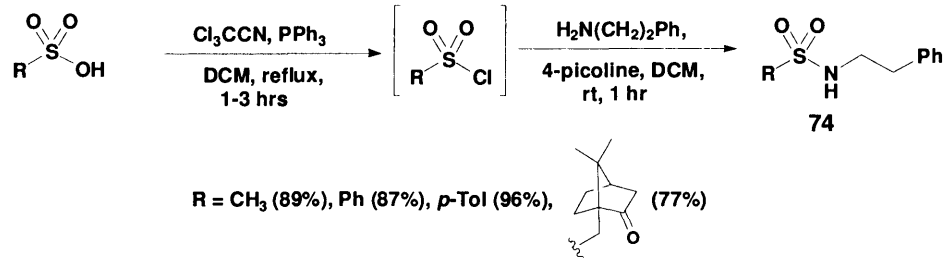
72 **73**

R = Ph (64%), 1-Naphthyl (84%), 2-Naphthyl (94%),
p-Tol (85%), Pr (93%), Bu (92%), *i*-Bu (89%)

Scheme 12

In a related study by Jang *et al.*, they developed a set of mild conditions that allows access into sulfonamides from sulfonic acids *via* a reactive sulfonyl chloride

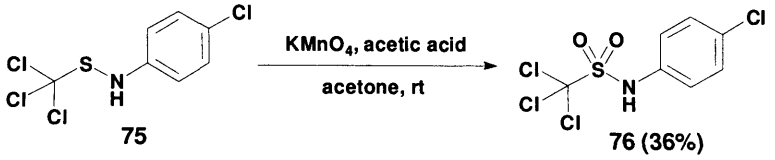
intermediate. Having established the successful conversion of carboxylic acids to acid chlorides with PPh_3 and Cl_3CCN, they applied this methodology to the analogous sulfonic acids. Accordingly, a selection of alkyl and aryl sulfonic acids were surveyed and gave good yields of sulfonamide **74** (Scheme 13). The scope of amines used was also explored, and it was reported that primary and secondary amines, as well as aryl amines produced pleasing yields (71-100%).[57]



Scheme 13

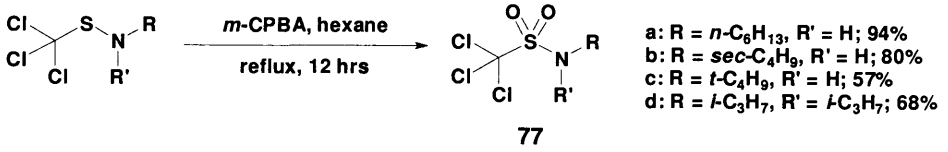
1.2.2. Sulfonamides from sulfenamides and methyl sulfones

As the reduced form of sulfonamides, sulfenamides may also be regarded as useful intermediates towards the synthesis of sulfonamides. In 1960, Farrar was one of the first to apply oxidative conditions to sulfenamide **75** in order to furnish sulfonamide **76** in a modest 36% yield (Scheme 14).[58]



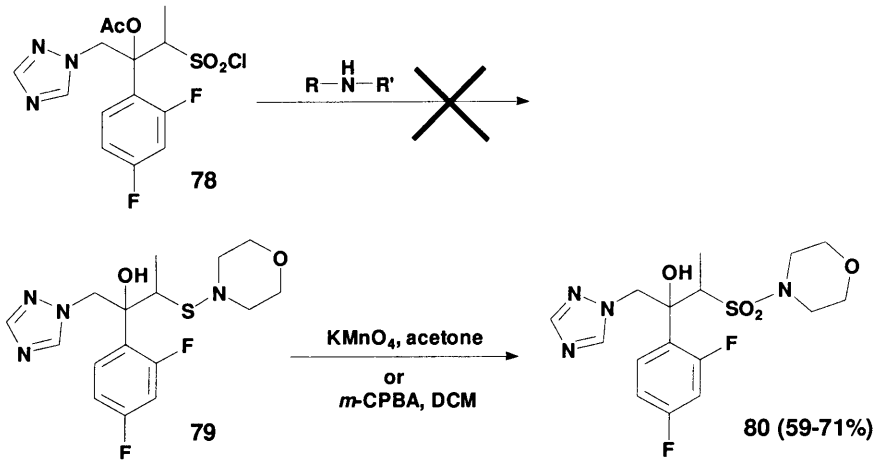
Scheme 14

Glass *et al.* also investigated the oxidation of trichloromethyl-sulfenamides as a route into sulfonamides. However, unlike with Farrar's endeavours with $KMnO_4$, Glass discovered that *m*-CPBA was a far better oxidant and provided aliphatic sulfonamides **77a-d** in much improved yields (Scheme 15).[59]



Scheme 15

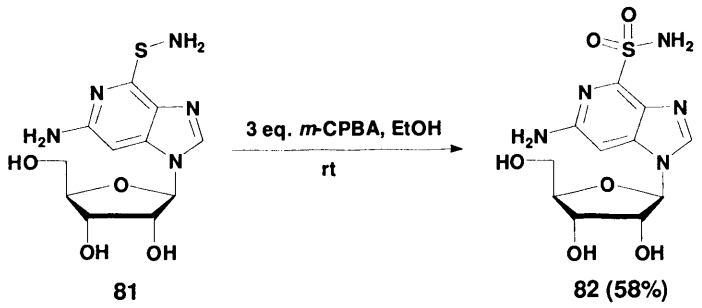
In their attempts to generate potent anti-fungal agents, Tasaka and co-workers required the oxidation of triazole sulfenamide **79** to afford triazole sulfonamide **80**. Oxidation of **79** was preferred over aminolysis of the analogous sulfonyl chloride **78**, as this route failed to provide the desired product due to an additional competing elimination reaction (Scheme 16).[60]



Scheme 16

$KMnO_4$ oxidation of **79** provided a 59% isolated yield of sulfonamide **80** along with 17% of the mono-oxygenated sulfinamide. Nevertheless, removal of this unwanted by-product was resolved by changing the oxidant to *m*-CPBA, with the resultant product **80** furnished exclusively in a 71% yield. The authors report that other primary and secondary amino-sulfenamides have been successfully oxidised to sulfonamides and thus demonstrating the practicality of their protocol.[60]

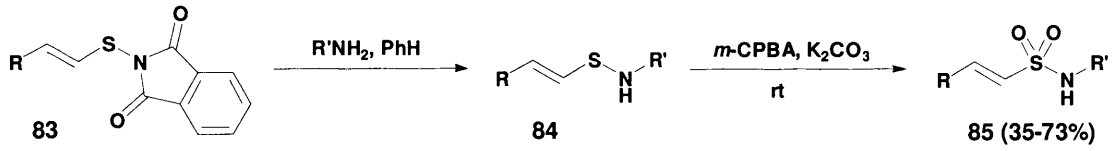
So far oxidation of alkane-sulfenamides has been presented. Revankar *et al.*, in their pursuit of pyrimidine-4-sulfonamides as potential anticancer agents, utilise an oxidation protocol to achieve the synthesis of aromatic sulfonamides from aromatic sulfenamides. Oxidation of sulfenamide **81** with one-equivalent of *m*-CPBA resulted in a 48% yield of the corresponding sulfinamide, the desired sulfonamide **82** was eventually realised in a 58% yield with three equivalents of *m*-CPBA (Scheme 17).[61]



81 82 (58%)

Scheme 17

Alkenyl-sulfenamides are less well studied, with Schwan *et al.* being one group to have accomplished their synthesis as well as studied their conversion to sulfonamides. Transamination of their *N*-(1-alkenylthio) phthalimides **83** with the desired amine was first conducted to provide the necessary crude sulfenamide **84**. *m*-CPBA oxidation is then performed to afford the sulfonamide **85** in variable yields (Scheme 18). Schwan *et al.* reported that yields were generally good except with aniline, which was explained by observation of a sluggish transamination step.[62]



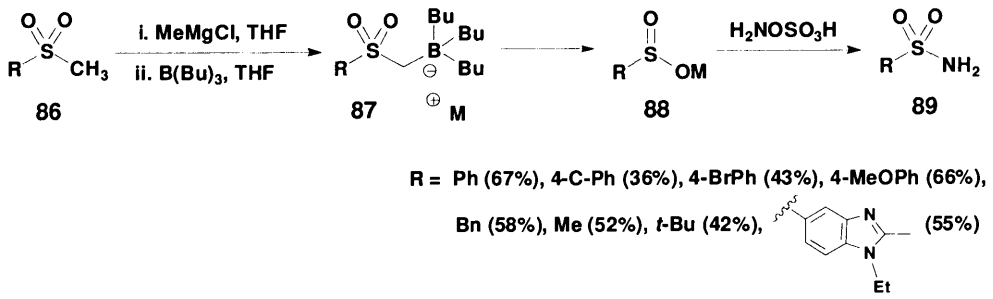
83 84 85 (35-73%)

R = *n*-Bu or $(CH_2)_2Ph$

$R'NH_2$ = benzylamine, *N*-methyl benzylamine, allyl amine, *N*-allylaniline, morpholine

Scheme 18

Other unique and atypical methods towards the synthesis of sulfonamides also deserve a mention. A one-pot conversion of methyl sulfones to sulfonamides was reported by Huang *et al.* in 1994. They rationalised that the known formation of 'ate' complexes from the treatment of trialkylboranes with lithiated organosulfur compounds, could potentially be extended to sulfonamide synthesis *via* rearrangement of the 'ate' complex **87** to a sulfinic acid salt **88** (Scheme 19). A selection of methyl sulfones **86** was subjected to methylmagnesium chloride followed by tributylborane; the resultant sulfinic acid **88** is subsequently treated with hydroxylamine-*O*-sulfonic acid to afford sulfonamide **89**.[63]



Scheme 19

This protocol although moderately yielding, provides the opportunity to conduct multiple reactions on a readily accessible methyl sulfone as a 'masked' sulfonamide during a total synthesis, since they possess the ability to withstand harsher chemical transformations over the analogous sulfonamide.[63]

To conclude, this literature survey has revealed that the synthesis of sulfonamides relies heavily on the use of sulfonyl chlorides or a sulfonyl chloride intermediate which can be trapped by an amine. Lesser known procedures are used in cases where the sulfonyl chloride is not accessible; however, these are not especially high yielding, tedious, and often involve numerous chemical steps to obtain the sulfonamide precursor.

1.3. Sulfonate esters as sulfonamide precursors

The value of sulfonamides in medicine and chemistry has become increasingly important with time, and so they are often in high demand as potential therapeutic agents. Their conventional means of synthesis has often involved the use of sulfonyl chlorides which are often unstable species which are not amenable to long term storage. Furthermore, the lack of availability of sulfonyl chlorides and difficulty in preparation adds to the disadvantages.

This has led to the discovery and introduction of pentafluorophenyl (PFP) sulfonate esters within the Caddick group, as a shelf stable alternative to sulfonyl chlorides.[64] They postulated that the resultant PFP sulfonate esters would be crystalline solids and so provide ease of handling. In addition, due to the electron-withdrawing nature of the PFP group, the sulfur centre would be susceptible to nucleophilic attack especially by amines, to make sulfonamides (Scheme 20). Furthermore, the PFPOH regenerated upon exposure to an amine can easily be removed with a basic work up.

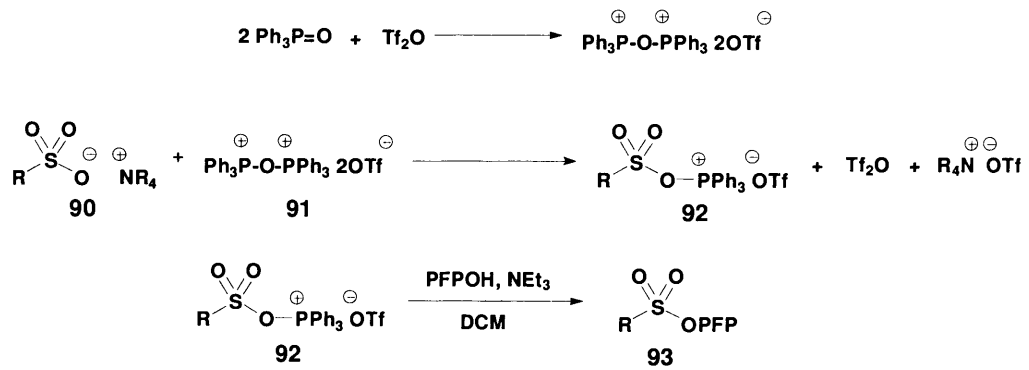
Where R, R' = akyl or aryl groups

Scheme 20

To date work within the Caddick group has established that PFP sulfonate esters have the added advantage over sulfonyl chlorides of being stable to a variety of conditions, such as acidic and basic work-ups, column chromatography, and ability to be employed under aqueous conditions.[65] They have identified that to get a successful aminolysis reaction a base is required, and those used include NEt_3 and DBU. Solvents typically used are THF, NMP, and toluene, although choice of solvent depends on how harshly one wants to heat the reaction. Studies have also shown that aminolysis is possible for primary, secondary, and a selection of sterically hindered amines. Herein the results of previous group studies into sulfonamide synthesis *via* PFP sulfonate esters are presented.

1.3.1. PFP sulfonate esters in the synthesis of sulfonamides

In order to obtain PFP sulfonate esters, a novel method for their synthesis avoiding the use of sulfonyl chlorides was desired. By analogy with the amide bond formation through the coupling of a carboxylic acid with an amine, Caddick *et al.* devised a strategy that utilised the same principle to make sulfonamides *via* activation of a sulfonic acid (Scheme 21).[64]



Scheme 21

They rationalised that nucleophilic attack by the PFP anion to an activated intermediate such as **92** would be a facile process, because the generation of a strong P=O double bond would provide the necessary driving force for this reaction to proceed. To make this activated intermediate **92**, triphenylphosphine ditriflate **91** was treated with a

sulfonic acid salt **90** (Scheme 21). The pyridine or triethylamine sulfonic acid salt were used in their studies principally due to their solubility in organic solvents.[64]

Once **92** has been prepared treatment with PFPOH then provided the PFP sulfonate esters **93** in good yields, and these were carried out on a number of alkyl, aryl and heteroaromatic intermediates, demonstrating that a number of different functionalities are tolerated by this new protocol (Figure 19).

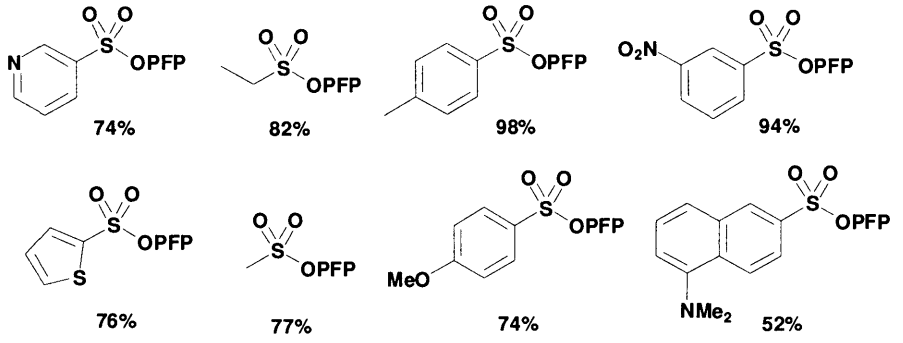


Figure 19

These PFP esters can be treated with an amine to transform them into sulfonamides. However, Caddick *et al.* also revealed that intermediate **92** could potentially be converted directly to the sulfonamide therefore waiving the need for PFP sulfonate esters. To test this theory they treated **92** with a variety of primary and secondary amines and were happy to report successful reactions for all (Figure 20), and in general providing the first literature example for the transformation of a sulfonic acid or its salt directly into a sulfonamide.[64]

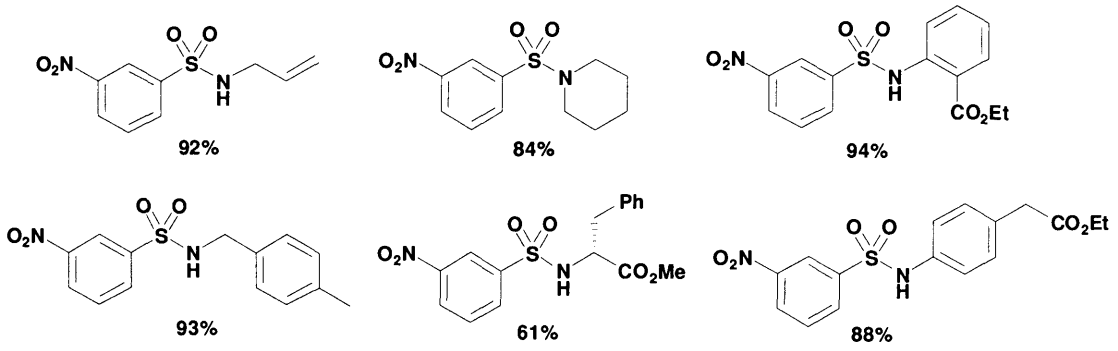


Figure 20

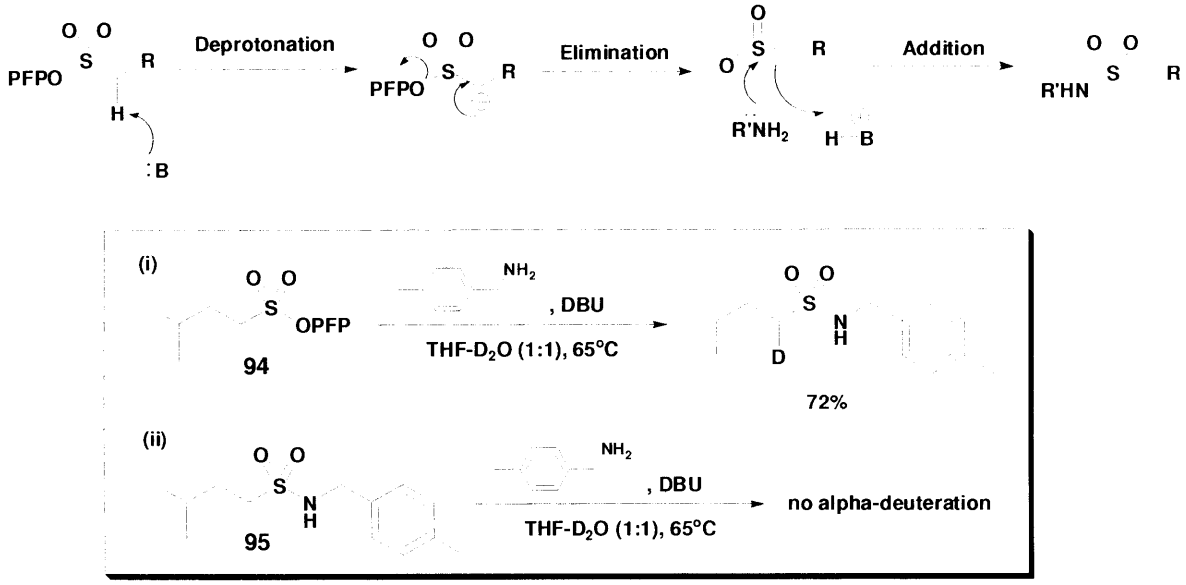
Often it is more convenient to prepare the PFP sulfonate ester first and then transform it to sulfonamides at a later date. PFP sulfonate esters are very stable species and suitable

for long term storage in comparison to sulfonic acid salts, which are often hygroscopic species and not tolerant to a range of chemistries.

Having established that PFP sulfonate esters react well with amines thermally under refluxing conditions, the effects of microwave irradiation on the aminolysis of various alkyl and aryl PFP sulfonate esters were investigated.[66]

Alkyl and aryl PFP sulfonate esters have been investigated due to their difference in reactivity with amines. Alkyl PFP sulfonate esters require much milder conditions for aminolysis due to the presence of an α-sulfonyl CH_2 group, which in theory provides an alternative elimination pathway *via* the reactive sulfene intermediate (Scheme 22). This postulation was confirmed by experimental methods in the aminolysis of PFP sulfonate **94** with 4-methyl-benzylamine in the presence of THF-D_2O. A trapping of a single deuterium atom at the α-sulfonyl position accordingly provides persuasive evidence for a sulfene intermediate (Scheme 22 (i)). To verify that the capture of deuterium was not occuring post-product formation, a solution of sulfonamide **95** was treated to the same conditions with no deuterium inclusion being observed (Scheme 22 (ii)).[67] Aryl PFP esters do not possess this α-sulfonyl CH_2 group, and so need harsher conditions and longer reaction times, as aminolysis presumably proceeds by direct displacement of the leaving group. The reactivity of aryl PFP esters is further governed by what functional groups are on the arene ring, with electron-withdrawing groups tending to give faster reaction times than those with electron-donating groups.[66]

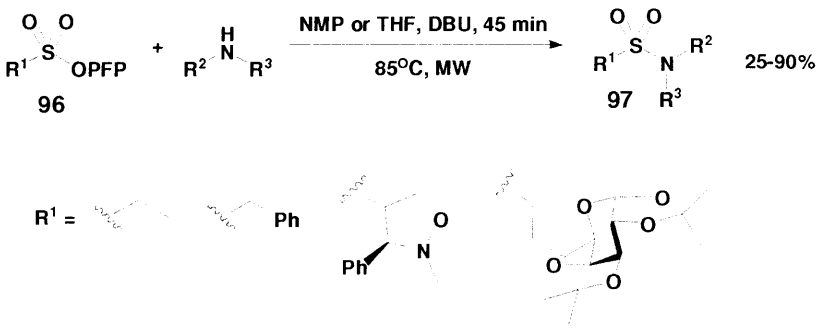
ALKYL PFP ESTERS:



ARYL PFP ESTERS:

Scheme 22

The alkyl PFP sulfonate esters were the first to be considered. A range possessing an aryl group, a heterocycle, and a sugar derivative were subjected to optimum conditions of 85°C heating for up to 45 minutes, using NMP or THF as solvent, one equivalent of the amine and two equivalents of base (Scheme 23).[66]

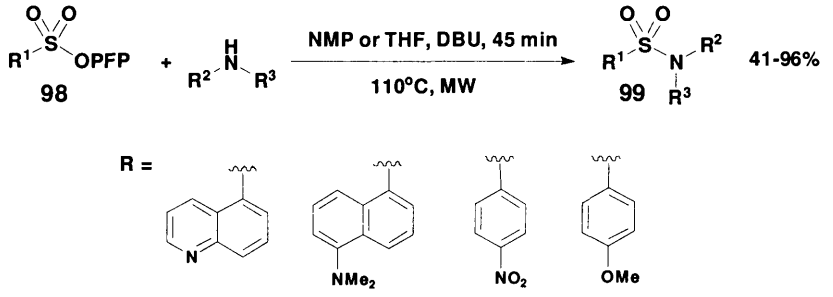


Scheme 23

Each alkyl PFP sulfonate ester **96** was treated with a variety of secondary amines and successfully produced a diverse array of aliphatic sulfonamides **97**. Yields reported were generally good for the simple alkyl PFP esters (76-90%) and average with the heterocyclic and sugar-derived PFP esters (25-70%). With the sterically encumbered *N*-

methyl-*tert*-butyl amine the yields were low as a result of the high steric demands forced upon the corresponding product, especially when reacted with the heterocyclic and sugar-derived PFP sulfonate ester (25% and 38% respectively).[66]

Aryl PFP sulfonate esters **98** were treated with an analogous series of amines; however, because of the reduced reactivity of aryl PFP sulfonate esters, elevated temperatures were applied to drive reactions to completion (Scheme 24).[66]



Scheme 24

As expected, aminolysis with an assortment of primary and secondary amines provided excellent yields of the corresponding sulfonamide **99**. Lower yields were again obtained when the sterically hindered *N*-methyl-*tert*-butyl amine was employed (41-58%), although this may be due to decomposition resulting from an increased reaction time and elevated temperature.[66]

The difficulty in achieving a high yielding and fast aminolysis reaction between PFP sulfonate esters with a sterically demanding amine was resolved by Wilden *et al.* They envisaged that if *tetra*-butylammonium chloride (TBAC) was added to the reaction, an '*in-situ*' sulfonyl chloride would be produced which is more susceptible to nucleophilic attacked by an amine. This hypothesis was confirmed when TBAC was added to the reaction of an electron-rich aryl PFP sulfonate ester with a selection of bulky amines, and presented a marked increased rate of reaction as well as yield in some examples (Table 1).[68]

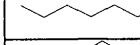
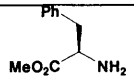
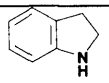
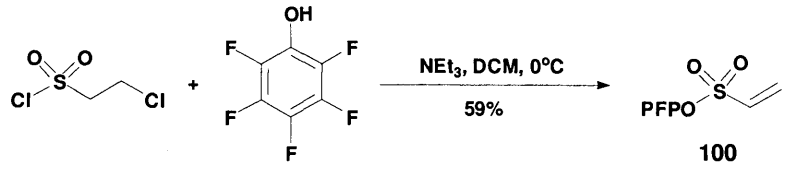
Amine	Time (no TBAC)	Time (1.5 eq. TBAC)	Yield (no TBAC)	Yield (1.5 eq. TBAC)
	> 7 days	7.5 hrs	67%	89%
	45 mins	5 mins	91%	96%
	55 mins	10 mins	88%	85%
	1.5 hrs	25 mins	77%	75%
	> 7 days	13 hrs	38%	84%

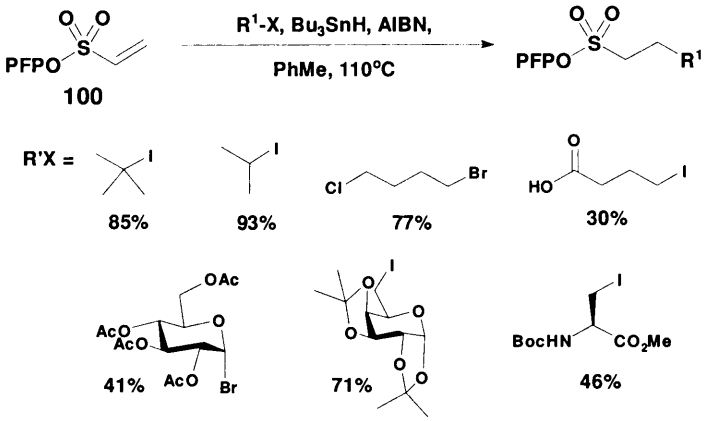
Table 1

Continued studies on the chemistry of PFP sulfonate esters centred around PFP-vinyl sulfonate **100** (Scheme 25). PFP-vinyl sulfonate was chosen because it is a bifunctional acceptor, and so susceptible to attack from both radical and nucleophilic species. It was proposed that the olefinic region of PFP-vinyl sulfonate could act as a template, upon which a wide range of reactions could be carried out before aminolysis to sulfonamides is performed.[65, 69]



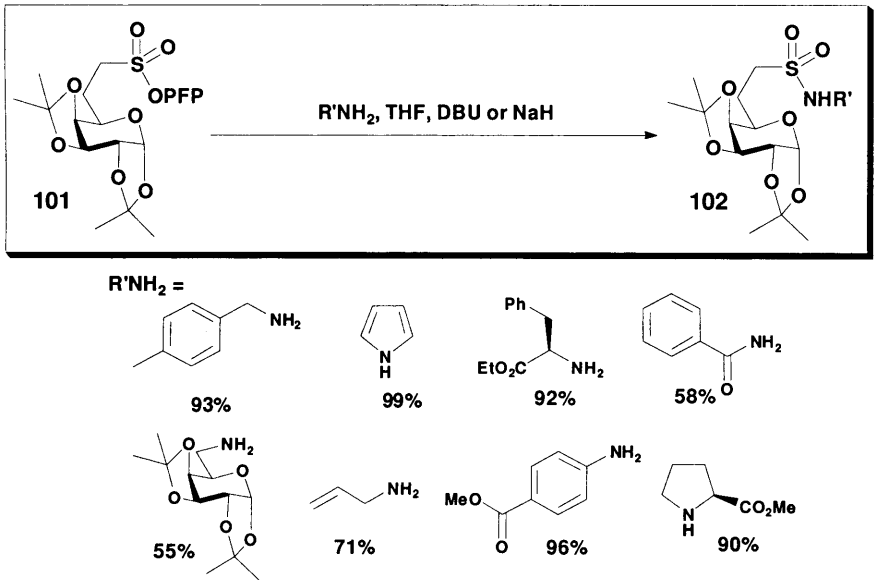
Scheme 25

Intermolecular tin-mediated radical addition of a variety of organo-halide compounds to **100** has been reported utilising AIBN as the radical initiator (Scheme 26). The reaction was successful with a variety of primary, secondary and tertiary alkyl halides with moderate to good yields.[65]



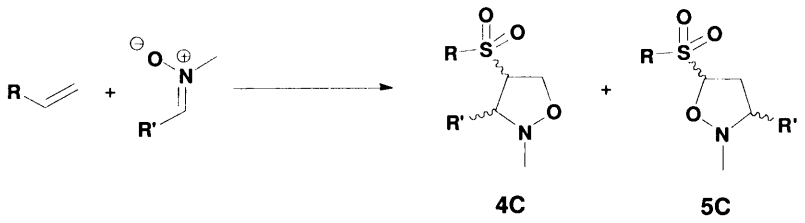
Scheme 26

The authors report that the reaction was not restricted to simple alkyl radicals or those that are stabilised, but that it was also possible using sugar and amino acid analogues. They then proceeded to test the aminolysis reaction on a sugar-derived alkyl PFP sulfonate ester **101** (Scheme 27). A wide variety of amines were used to give a selection of derivatised sulfonamides **102**, and the yields reported were near quantitative except when an amide or a bulky sugar molecule was involved.[65]



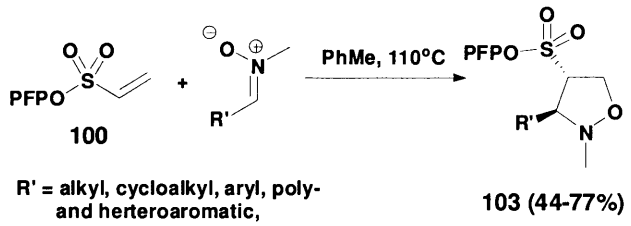
Scheme 27

PFP-vinyl sulfonate **100** was also examined as a potential dipolarophile in the 1,3-dipolar cycloaddition with nitrones. Cycloaddition of nitrones to monosubstituted alkenes can provide a mixture of products, the 5C-substituted and 4C-substituted products (Scheme 28).[69]



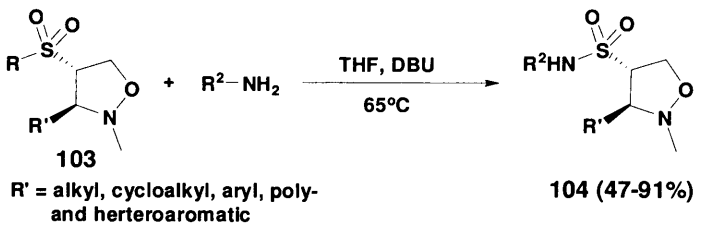
Scheme 28

It is widely accepted in literature that the 5C cycloadduct is usually given, but when increasingly electron-deficient dipolarophiles are used the 'reversed' 4C cycloadduct is formed. This literature observation was supported when Caddick *et al.* reported that cycloaddition of PFP-vinyl sulfonate **100** with a large assortment of *C*-alkyl and *C*-aryl-*N*-methyl nitrones proceeded with complete regio- and diastereo- control for the 4C-*anti* cycloadduct **103** (Scheme 29).[69]



Scheme 29

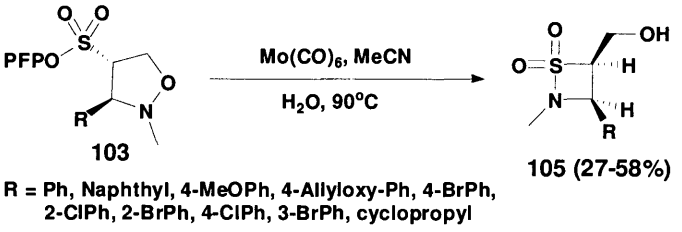
All cycloadditions were successful and produced 4C-*anti* isoxazolidines **103** containing alkyl groups, aryl groups (with electron-withdrawing and electron-donating functionalities), and heteroaromatic groups. Yields obtained were moderate and dependant on the stability of the nitrone under elevated temperatures. Caddick group research then continued with the facile aminolysis of each of these shelf-stable PFP isoxazolidines, and they report that aminolysis proceeds with clean retention of stereochemistry (Scheme 30).[69]



Scheme 30

Amines explored included the primary amines 4-methylbenzylamine and allylamine, and yields reported were generally good; where the more hindered phenylalanine ethyl ester was employed this was reflected with a slight drop in yield. A further contributing factor towards a decrease in the isolated yield, results from the presence of a polar functional R′ group (i.e. *p*-NO_2Ph). In all it has been shown that by utilising a 1,3-dipolar cycloaddition it has been possible to synthesise a diverse array of biologically interesting acyclic sulfonamides **104** *via* PFP-isoxazolidines.[69]

Furthermore, PFP isoxazolidines **103** synthesised within the Caddick group have been identified as intermediates towards the synthesis of β-sultams. β-Sultams are cyclic sulfonamides, and are potential serine β-lactamase inhibitors which have been implicated in the treatment of penicillin resistance. It was reported that an N-O bond cleavage of a PFP-isoxazolidine **103**, followed by an intramolecular nucleophilic displacement of pentafluorophenol provided β-sultam **105** (Scheme 31).[70]



103 **105 (27-58%)**

R = Ph, Naphthyl, 4-MeOPh, 4-Allyloxy-Ph, 4-BrPh, 2-ClPh, 2-BrPh, 4-ClPh, 3-BrPh, cyclopropyl

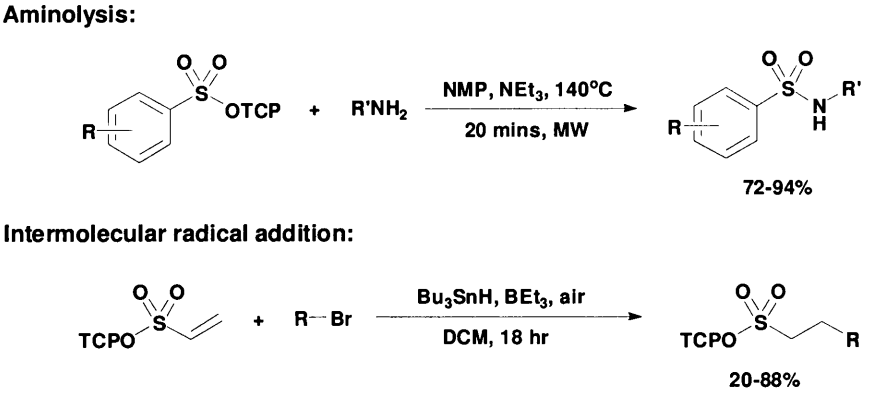
Scheme 31

This functional group interconversion was achieved with $Mo(CO)_6$ in a one-pot procedure to furnish a selection of predominantly aromatic β-sultams. Although yields were low this protocol represented a new route towards the synthesis of β-sultams and further demonstrates the synthetic utility of PFP sulfonate esters in organic chemistry.[70]

1.3.2. TCP sulfonate esters in the synthesis of sulfonamides

Due to the perceived toxicity of polyfluorinated aromatic compounds and relatively high cost of PFPOH, a cheaper and less-toxic alternative was sought. Trichlorophenol is a known cheap household antiseptic which fulfils these requirements, and has been found to be a good leaving group in the aminolysis reaction. This supposition has prompted the introduction of trichlorophenyl (TCP) sulfonate esters as a suitable replacement for PFP sulfonate esters, and hence sulfonyl chlorides in the eventual synthesis of sulfonamides. Present Caddick group research has focused on optimising

the aminolysis reactions of TCP sulfonate esters with a variety of amines and in addition, radical experiments on the analogous TCP vinyl sulfonate have been explored (Scheme 32).[71]



Scheme 32

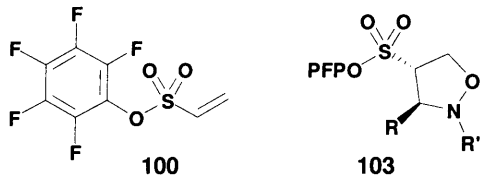
Although TCP sulfonate esters are less toxic, their reactivity versus PFP sulfonate esters is noticeably reduced, and reactions normally require increased reaction times and more forcing conditions. Therefore, TCP sulfonate esters are complementary to PFP sulfonate esters and they both hold great promise as future intermediates towards sulfonamide formation.

In conclusion, Caddick *et al.* have shown from their comprehensive work that PFP and more recently TCP sulfonate esters, whether alkyl or aryl, are excellent alternatives to sulfonyl chlorides, and provide a new route towards the synthesis of highly desirable sulfonamides.

CHAPTER 2: R&D - Studies on cycloaddition reactions of vinyl sulfonates and sulfonamides

2.1. Aim

The aim of this work is to explore the scope of cycloaddition reactions of pentafluorophenyl (PFP) vinyl sulfonate **100** (Figure 21). It has previously been found that this species can act as an effective dipolarophile, and the present investigation is a continuation of work previously conducted within the group on 1,3-dipolar-cycloaddition chemistry involving nitrones and vinyl sulfonates (see Section 1.3.1.).



100 103

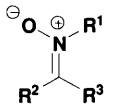
Figure 21

The [3+2] cycloaddition of 1,3-dipoles to olefins has been a widely studied topic since the 1880's, and is still one of the best ways of synthesizing heterocyclic compounds. PFP vinyl sulfonate **100** contains an extremely electron-deficient olefin making it very reactive, and therefore can readily participate in cycloaddition reactions. It has been shown that cycloaddition of PFP-vinyl sulfonate **100** with nitrones occurs in a regioselective and diastereoselective manner furnishing isoxazolidine products **103** (Figure 21). Aminolysis of these PFP isoxazolidines can then generate heterocyclic sulfonamides.[69]

2.2. Introduction

The 1,3-dipolar cycloaddition addition reaction dates back to 1883 when Buchner performed the reaction of a diazoacetic ester with an α,β-unsaturated ester.[72] It is still one of the best and easiest ways of synthesizing heterocyclic compounds, and the reaction is highly attractive because of its use for the synthesis of 5-membered rings with multiple stereocentres in one step.

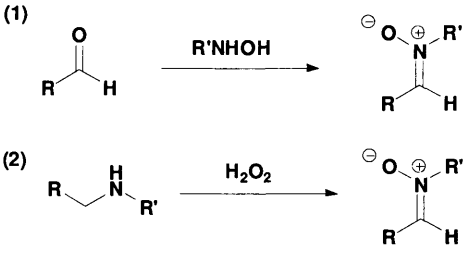
Many 1,3-dipoles have been used in 1,3-dipolar cycloadditions: nitrile ylides, nitrile imines, diazoalkanes, nitrous oxide, azomethine ylides, azomethine imines, nitrones, and azides are just a few examples.



Where R^1, R^2, R^3 = H, alkyl aryl, alkenyl

Figure 22

Nitrones (or azomethine oxides) were first discovered in the 1880's by Beckmann (Figure 22).[72, 73] They are a commonly studied class of 1,3-dipole with over a thousand papers describing their use since their discovery. They are mostly synthesized by two reported methods; the first and most common method is the condensation of a monosubstituted hydroxylamine with an aldehyde, and the second method is the oxidation of secondary amines by hydrogen peroxide (Scheme 33).[74]

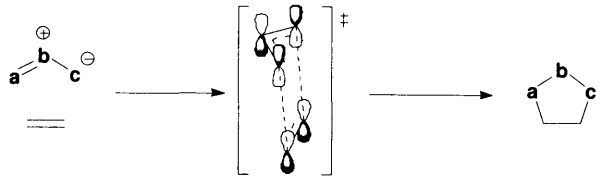


where R, R' = alkyl, aryl

Scheme 33

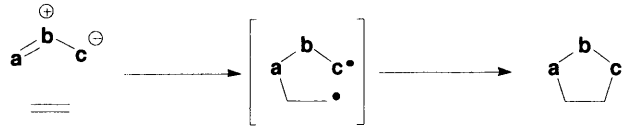
2.2.1. Mechanism of 1,3-dipolar cycloaddition

The 1,3-dipolar cycloaddition reaction involves the 2π electrons of the alkene and the 4π electrons of the nitrone. It was first proposed to be a concerted mechanism by Huisgen; this means that the three p_z orbitals of the nitrone and the two p_z orbitals of the alkene combine suprafacially in a single step to generate two stronger σ bonds (Scheme 34).[72, 75]



Scheme 34

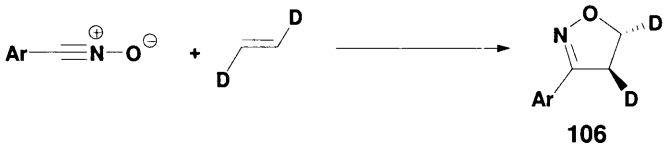
However, in the 1960's Firestone challenged this mechanism by suggesting that it in fact proceeds *via* a two-step spin-paired diradical intermediate (Scheme 35).[72, 76]



Scheme 35

Methods for differentiating between a concerted and a two-step reaction involve: (1) Study of the stereoselectivity and regioselectivity observed in product formation, (2) Exploration of the influence of solvent polarity on rate, (3) Trapping of intermediates, and (4) Study of substituent effects.[76]

The mechanism was eventually confirmed as concerted, by a study of the stereochemical outcome of the reaction of benzonitrile oxide with *trans* deuterated ethene. The product obtained from this reaction was exclusively the *trans* isoxazoline **106**, and so thereby confirming a concerted mechanism (Scheme 36).[72, 77]

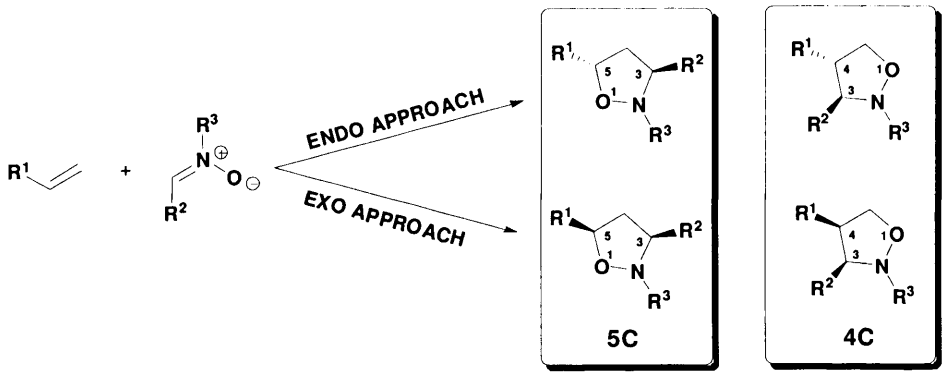


106

Scheme 36

2.2.2. Selectivity in nitrone 1,3-dipolar cycloaddition with monosubstituted alkenes

1,3-Dipolar cycloadditions can give rise to four potential isomeric products, which can be grouped into two categories: the 5C-substituted isoxazolidine, or the 4C-substituted isoxazolidine, depending on the orientation that the nitrone approaches the double bond (Scheme 37).[78]



Scheme 37

In the past, work conducted on the cycloaddition of mono-substituted alkenes was presumed to be unidirectional, furnishing only the 5C cycloadducts.[79] However, through the early work of Houk *et al.* it has become clear that the 4C cycloadduct is also formed depending on the nature of the olefin substituents.

The application of FMO theory by Sustman has led to the categorisation of 1,3-dipolar cycloaddition reactions into 3 classes (Figure 23).[72, 76, 80]

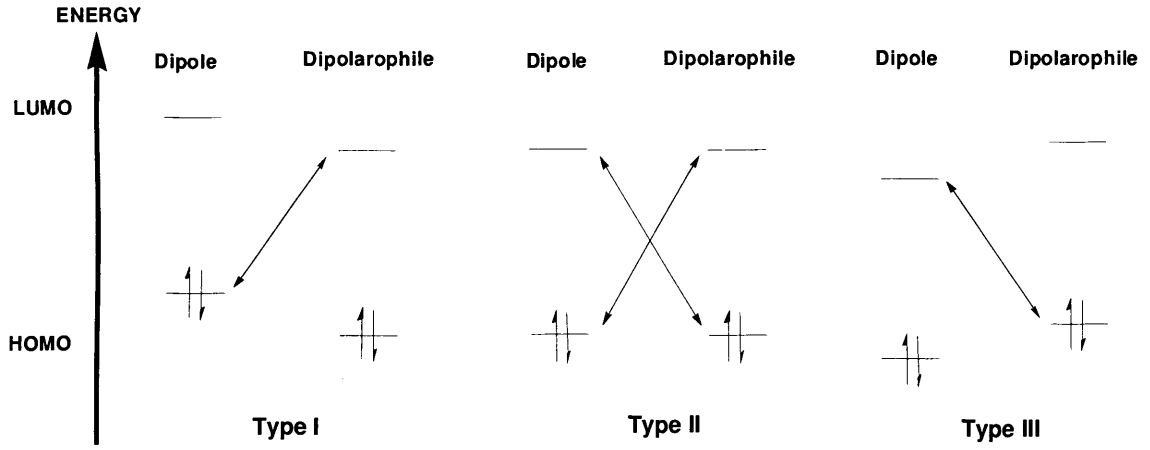


Figure 23

In type I reactions the dominant FMO interaction is between that of the $HOMO_{dipole}$ and the $LUMO_{dipolarophile}$, for type III it is between the $LUMO_{dipole}$ and the $HOMO_{dipolarophile}$. Finally, for type II cycloaddition reactions the similarity in energies between the HOMO and LUMO of each dipole and dipolarophile, means that the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ and the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interactions are both just as important in determining the regiochemistry and reactivity. In general, substituents that raise the $HOMO_{dipole}$ or lower the $LUMO_{dipolarophile}$ energy will accelerate Type I cycloadditions; whilst substituents that raise the $LUMO_{dipole}$ or raise the $HOMO_{dipolarophile}$ energy will accelerate Type III cycloaddition reactions.[78, 80]

For example, comparing *C*-phenyl-*N*-methyl nitrone with a range of dipolarophiles with different substituents generates the following FMO's (Figure 24).[76]

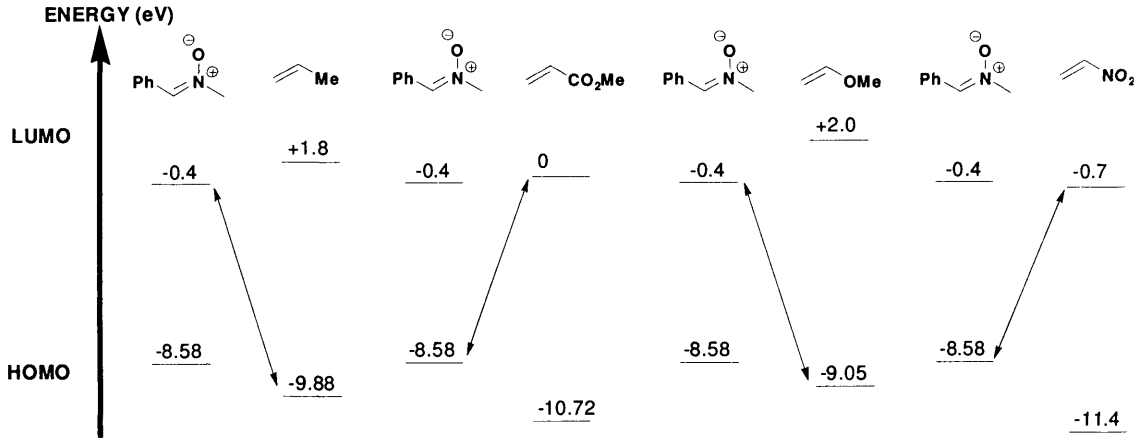
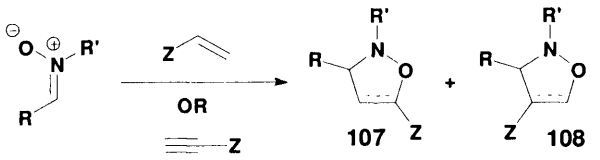


Figure 24

From the orbital diagrams a general pattern can be observed, electron-rich alkenes tend to give dominant $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interactions (Type I), and electron-deficient alkenes give dominant $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interactions (Type III). It was also noted that the 4C-substituted cycloadduct involves a transition state with an interaction between the $HOMO_{dipole}$-$LUMO_{dipolarophile}$, and *vice versa* for the 5C-substituted cycloadduct. However, it was reported that if the alkene is weakly electron-deficient, then regio-isomeric mixtures of the cycloadducts will be obtained.[76]

2.2.3. 1,3-dipolar cycloaddition with electron deficient dipolarophiles

Having established that electron deficient dipolarophiles tend to give the 4C-substituted product, a few examples are shown. Houk and co-workers were one of the first groups interested in exploring the reversal of regioselectivity in nitrone cycloaddition with electron-deficient dipolarophiles. The results of their investigation are shown in Table 2.[81]



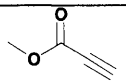
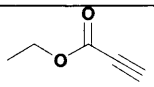
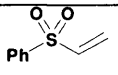
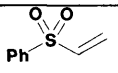
Entry	Nitrone	Dipolarophile	Ratio 107 : 108	
a	R= Ph, R′= Me		42	58
b	R= H, R′= *t*-Bu		70	30
c	R= Ph, R′= Me		0	100
d	R= H, R′= *t*-Bu		50	50
e	R= Ph, R′= Me		0	100
f	R= H, R′= *t*-Bu		100	0
g	R= Ph, R′= Me		32	68
h	R= H, R′= *t*-Bu		70	30

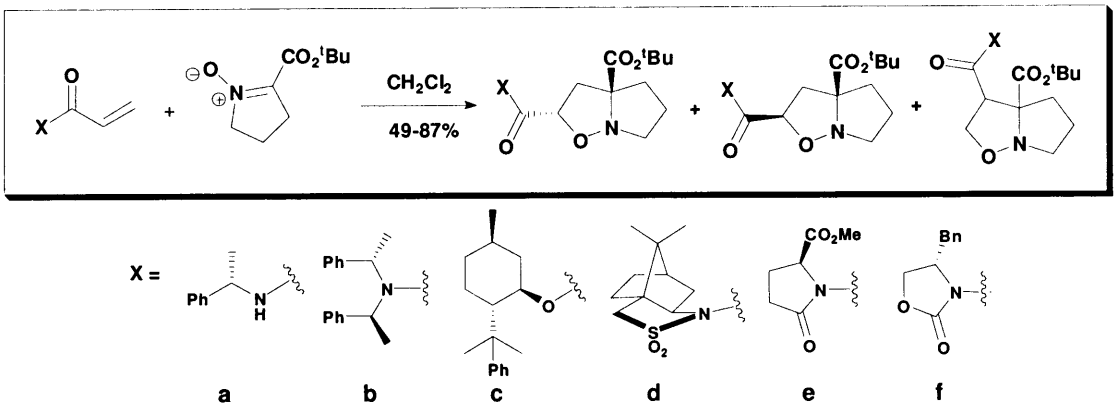
Table 2

Houk *et al.* observed that cycloaddition of *C*-phenyl-*N*-methyl nitrone with mildly electron-deficient dipolarophiles (entry a and g) produced a mixture of products **107** and **108**. More electron-deficient dipolarophiles such as cyanoacetylene (entry c) and nitroethylene (entry e) exhibited complete regioselectivity for the 4C cycloadduct **108**. They also investigated the effect of increasing steric bulk of the nitrone nitrogen (entries b, d, f, and h). Their endeavours showed that it is possible to greatly reduce the amount of the reverse 4C product formed no matter how electron-deficient the dipolarophile is; this effect was seen greatest with nitroethylene (entry f) which saw a complete switch in regioselectivity for the 5C-cycloadduct **107**.[81]

In 1984 Padwa *et al.* also explored the 1,3-dipolar cycloaddition of nitroethylene and methyl acrylate with *C*-phenyl-*N*-methyl nitrone, and they also reported the presence of the 4C-substituted product in both cases.[79] Arbuzov has also shown that vinyl phosphonates and *C,N*-diphenyl nitrone show regioselective behaviour furnishing the 4C-cycloadduct exclusively.[76]

Brandi *et al.* exploit the [3+2] cycloaddition reaction involving chiral acrylates/acrylamides with a cyclic nitrone, as a synthetic tool towards the synthesis of

pyrrolizidinone derivatives which are capable of imitating the two central residues of a β-turn (Scheme 38).[82]

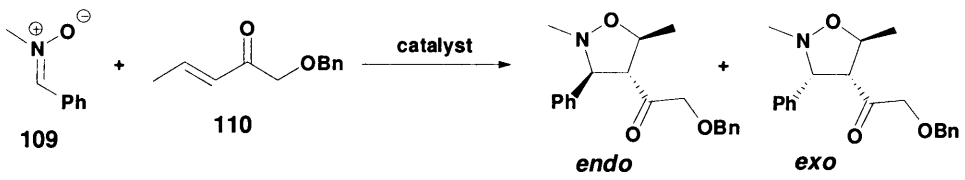


Scheme 38

The combined effect of an electron deficient dipolarophile with an electron deficient nitrone led to a 3:2 ratio of the 5C-cycloadducts versus the 4C-cycloadduct. However, there was no asymmetric induction from the chiral auxiliaries, and the products were isolated as racemates for each cycloadduct.[82]

Recent work on the enantioselective 1,3-dipolar cycloaddition between a nitrone and a dipolarophile often involves the use of a transition metal catalyst to control the enantioselectivity of the reaction. Not only are they able to offer control in the *endo*/*exo* selectivity of each diastereoisomer but also the regioselectivity. Lewis acid catalysts exert their effect on the dipolarophile or dipole by lowering the energy of the LUMO, thus with a smaller energy difference between the HOMO and LUMO of the reacting partners, increased reactivity is achieved.[83]

Kanemasa *et al.* was one group that explored this phenomenon in the racemic series in 1992, with the use of $ZnCl_2$, $TiCl(O\textit{i}\text{-}Pr)_3$, or $TiCl_2(O\textit{i}\text{-}Pr)_2$ in the 1,3-dipolar cycloaddition between nitrone **109** and enone **110** (Scheme 39).[72, 84]

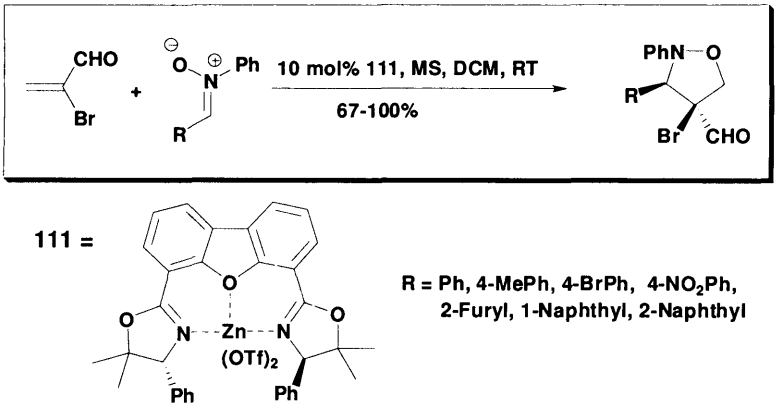


Uncatalysed: 30%, *endo*:*exo* = 40:60
Catalysed [$TiCl_2(O\textit{i}\text{-}Pr)_2$]: 50%, *endo*:*exo* = >99:1

Scheme 39

Although yields were moderate (35-77%) the use of these Lewis acids in stoichiometric amounts did provide excellent *endo* selectivity, especially when promoted with $TiCl_2(Oi\text{-}Pr)_2$ (*endo*:*exo*, >99:1). In the absence of this promoter the reaction gave a product *endo*:*exo* ratio of 40:60.[84]

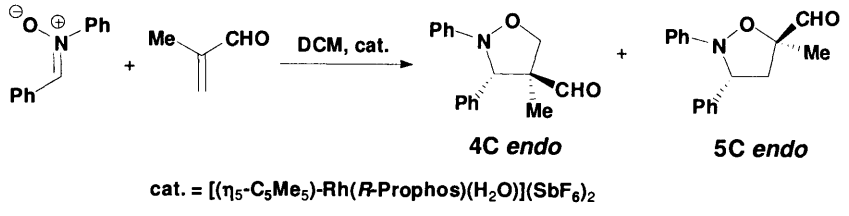
While Kanemasa's work showed excellent regioselectivity and diastereoselectivity, their reactions produced a racemic mixture of products. In more recent years it has also been possible to gain excellent enantioselectivities through transition metal complexation with chiral catalysts.



Scheme 40

This was demonstrated by Kanemasa *et al.* in their utilisation of a DBFOX/Ph-$Zn(OTf)_2$ catalyst **111** in the cycloaddition of α,β-unsaturated aldehydes with acyclic nitrones (Scheme 40). The authors report that this catalyst promotes an entirely *endo*-4C selective reaction with enantioselectivities greater than 94% ee.[85]

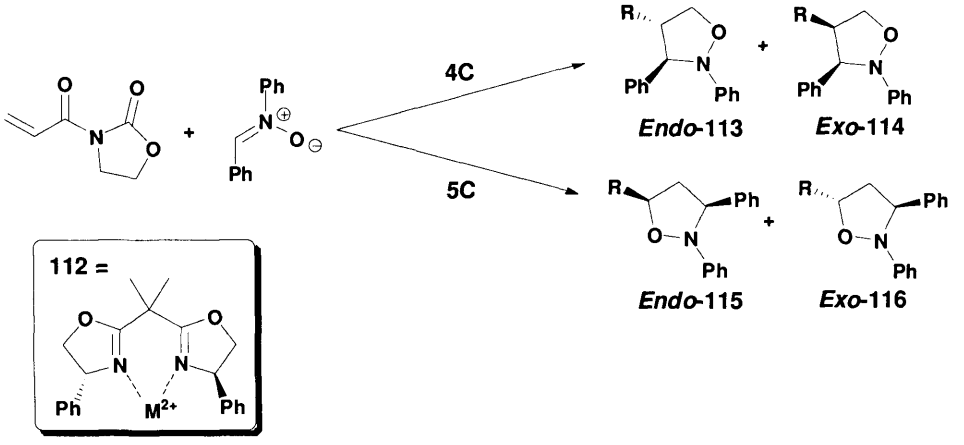
Carmona and co-workers utilised a rhodium-SbF_6 complex to catalyse the cycloaddition of *C*,*N*-diphenyl nitrone with the mildly electron-deficient methacrolein (Scheme 41).[86]



Scheme 41

In the absence of catalyst at room temperature they observe exclusively the 5C cycloadduct in a 63% yield. However using 5 mol% of catalyst under various temperatures (-45°C to 5°C) quantitative yields were obtained, with a switch in regioselectivity in favour of the 4C cycloadduct (approx. 6:4 ratio of 4C:5C). It was also reported that ee's of up to 92% were obtained and with 100% *endo* selectivity.[86]

In 2005 Desimoni and Faita described the use of various transition metals catalysts based on (4*R*)-phenyl-bis(oxazolines) **112**, as a way to obtain either *endo* or *exo* selective products by careful manipulation of reaction conditions. They report that their catalysts provided excellent regio- and stereoselectivity in the reaction between acryloyloxazolidinone and *C,N*-diphenyl nitrone (Table 3).[87]

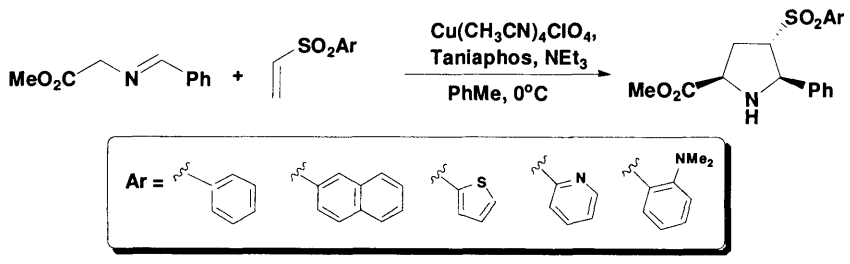


Entry	Cation	Anion	Temp (°C)	Additive	Ratio [113+114]/[115+116]	Ratio 113:114
a	Mg^{II}	ClO_4	-15	-	>98:<2	95:5
b	Co^{II}	ClO_4	-15	-	95:5	90:10
c	Mn^{II}	ClO_4	-15	-	95:5	93:7
d	Ni^{II}	ClO_4	-15	-	>98:<2	98:2
e	Zn^{II}	ClO_4	-15	-	decomposition	-
f	Co^{II}	ClO_4	-15	4Å MS	>98:<2	24:76
g	Zn^{II}	ClO_4	-15	4Å MS	>98:<2	27:73
h	Mg^{II}	ClO_4	-15	4Å MS	>98:<2	70:30
i	Ni^{II}	ClO_4	-15	4Å MS	88:12	72:28
j	Mn^{II}	ClO_4	-15	4Å MS	78:22	48:52

Table 3

It was reported that quantitative yields were obtained for all reactions, with the 4C-substituted cycloadducts **113** and **114** preferentially formed. The reactions were also *endo*- selective irrespective of the metal counterion used (entries a-d), except for Zn(II) (entry e) which failed to offer any appreciable product formation. Surprisingly, upon addition of 4Å molecular sieves to the Co(II) and Zn(II) catalysts (entries f and g) *exo*-selectivity was favoured with ee's of up to 84%. However, this effect was less prominent when Mg(II), Mn(II), and Ni(II) were utilised (entries h-j), due to a reported change in the conformation of the transition state.[87]

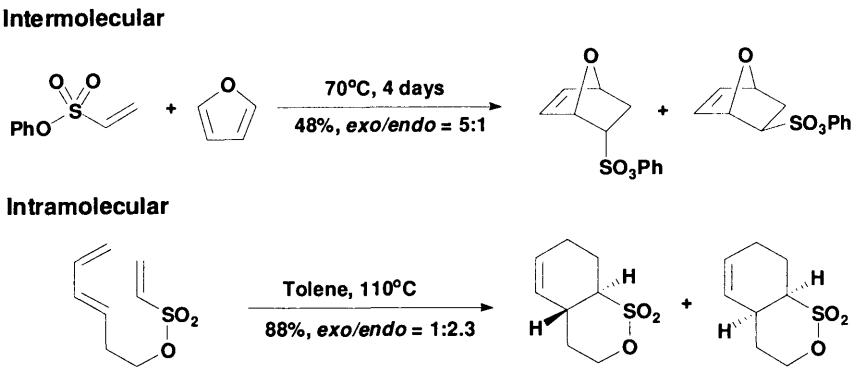
More recently Carretero *et al.* have achieved complete regioselectivity and diastereoselectivity in a 1,3-dipolar cycloaddition with the related azomethine ylides. Catalysis was attributed to the Cu(I)-Taniaphos system they employed in their [3+2] cycloaddition with a variety of aryl vinyl sulfones (Scheme 42).[88]



Scheme 42

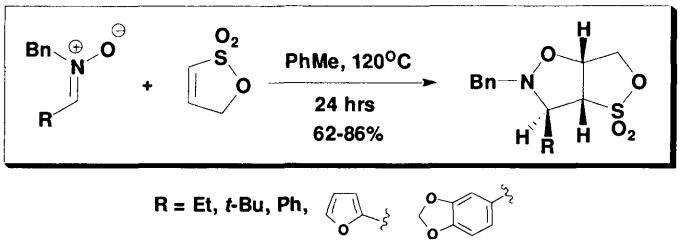
Yields of the single product obtained were over 70% and ee's of up to 83% were observed where Ar was phenyl or thiophenyl. Desulfonylation of their products with Na(Hg) then transformed their products into enantiopure 2,5-disubstituted pyrrolidines, which are synthetically useful building blocks for many natural products.[88]

Much less well studied are cycloaddition reactions of vinyl sulfonates. Unfortunately, it appears that there is very little precedent in the literature on 1,3-dipolar cycloadditions to vinyl sulfonates, with only Chan and co-workers having explored its potential.[89] [4+2] Diels-Alder cycloaddition with vinyl sulfonates is more commonly seen, and a few examples are shown in Scheme 43.[90, 91]



Scheme 43

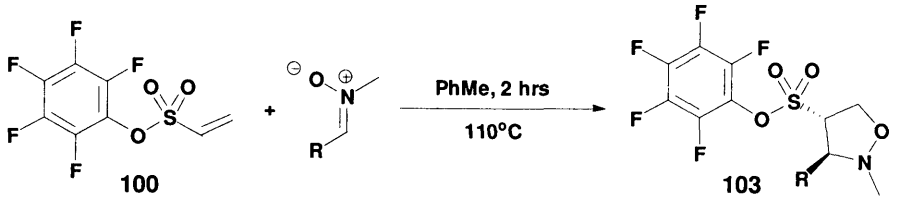
Chan and co-workers, having already shown that vinyl sulfonates are effective dienophiles in Diels-Alder reactions, also demonstrated its ability to act as a useful dipolarophile (Scheme 44).[89]



Scheme 44

They tried a variety of simple and bulky nitrones and the yields obtained were moderate to good, affording a reaction that is diastereo- and regioselective for only the 4C-substituted product.[89]

In addition, Caddick group research into the [3+2] cycloaddition between PFP-vinyl sulfonate **100** with a selection of *N*-methyl nitrones has been reported (Scheme 45, see Section 1.3.1.).[69]

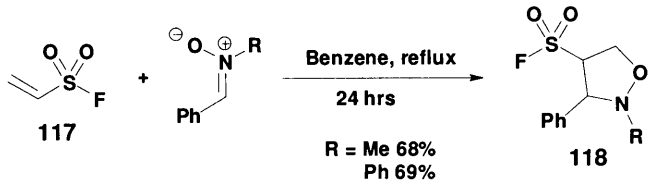


Scheme 45

Various alkyl, aromatic, and heterocyclic R groups were utilised, with yields between 44-77%. Moreover, with this electron deficient dipolarophile it was reported that

regioselectivity and complete diastereoselectivity for the 4C *anti*-cycloadduct **103** was obtained.[69]

Vessiére *et al.* has shown that a related dipolarophile akin to that of PFP-vinyl sulfonate **100**, the very electron-deficient vinyl sulfone **117** underwent a regioselective [3+2] cycloaddition with 2 different nitrones to furnish only the 4C-substituted isoxazolidine **118** exclusively in gratifying yields, although the stereochemistry of the final product is not reported (Scheme 46).[92]



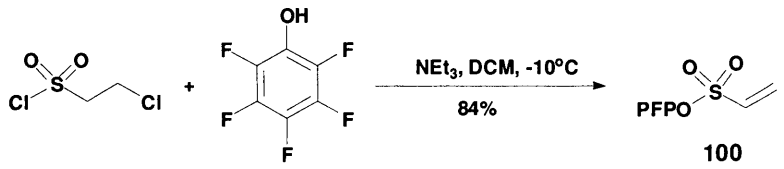
Scheme 46

In conclusion, it has been possible to show through pioneering work by Houk *et al.* that electron-deficient olefins exhibit a preference in regiochemistry for the 4C cycloadducts. Therefore through this, it is possible to predict that the [3+2] cycloaddition between the extremely electron poor PFP-vinyl sulfonate and a nitrone should furnish solely the 4C-substituted product, and this was confirmed through previous work in the group. However, whilst the literature displays numerous nitrone cycloadditions with a variety of electron-deficient olefins, few reported cases with a vinyl sulfonate are known. While the aforementioned examples show excellent regioselectivity, a current limitation on nitrone cycloadditions with vinyl sulfonates is that little is known about the diastereoselectivity of the reaction. Through the following work it is hoped a better understanding of cycloadditions with vinyl sulfonates and related dipolarophiles will be gained. The use of microwave chemistry in organic synthesis has risen in the past 10 years, and so the effect of microwave heating will also be explored. Furthermore, as the transformation of PFP sulfonate esters to sulfonamides is known, further studies were proposed, involving the application of any methodology to the synthesis of sulfonamides, containing a diverse array of functional groups.

2.3. Studies on [3+2] cycloaddition reactions of vinyl sulfonates and related dipolarophiles

2.3.1. Synthesis of PFP vinyl sulfonate (100)

To initiate the study, work commenced with the synthesis of PFP vinyl sulfonate **100**, through a slight modification to Distler's procedure for vinyl sulfonate synthesis.[93] Commercially available 2-chloroethane-1-sulfonyl chloride was treated with a suspension of pentafluorophenol and NEt_3 (Scheme 47).

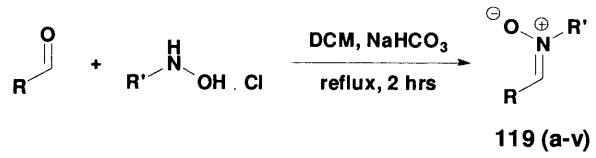


Scheme 47

The reaction is particularly temperature sensitive and requires that the internal reaction temperature is maintained below -10°C to avoid significant decomposition. Nevertheless, the reaction proceeds in high yields and was reproducible on up to a 20g scale.

2.3.2. Synthesis of nitrones

Nitrones can be easily prepared from the condensation reaction of an aldehyde with an *N*-substituted hydroxylamine (Scheme 48).[69] R and R′ can be aryl or alkyl groups, but our initial studies utilised R′ = Me with variations in the aldehyde component. R groups included alkyl, cyclic, heterocyclic, and aryl groups (incorporating electron-withdrawing, electron-donating, and halogen substituents) (Table 4).



Scheme 48

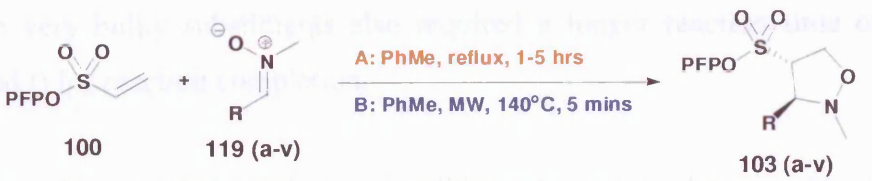
Entry (119)	R	Yield (%)
a	Ph	74
b	*p*-MeOPh	93
c	*p*-Allyloxy-Ph	88
d	*p*-NO_2Ph	56
e	*p*-ClPh	91
f	*p*-BrPh	96
g	*m*-ClPh	96
h	*m*-BrPh	99
i	*o*-FPh	96
j	*o*-ClPh	97
k	*o*-BrPh	83
l	Naphthyl	99
m	Terephthyl	17
n	Furyl	98
o	2-Br-furyl	98
p	Cyclopropyl	99
q	Cyclohexyl	95
r	Valeryl (C_5H_{11})	61
s	2,6-Dimethylphenyl	85
t	Pentamethylphenyl	59
u	*o*-IPh	98
v	*m*-IPh	89

Table 4

The reactions proceed very smoothly to give product **119** in good to excellent yields. Often the reaction proceeds sufficiently well such that the product is isolated in high purity without the need for purification. If necessary, recrystallisation can be used to give the product as readily handled crystalline solids. However, yields for entries d and m are appreciably lower because they contained polar substituents which made isolation of the product non-trivial due to its insolubility in organic solvents. The reaction time was generally 2 hours; however, entries s-v required a prolonged reflux presumably due to the extra bulk of its substituents.

2.3.3. Formation of PFP isoxazolidines

Previous work within the group has presented us with a procedure for carrying out the 1,3-dipolar cycloaddition of nitrones with PFP vinyl sulfonate **100** in a regio- and diastereoselective manner by refluxing in toluene.[69, 94] This protocol was followed to synthesize a library of isoxazolidines with varied R groups (Table 5). In addition, microwave heating was also investigated and it was found that this enabled us to carry out the reactions with a significantly reduced reaction time (Table 5).



100 119 (a-v) 103 (a-v)

Entry (103)	R	Yield A (%)	Yield B (%)
a	Ph	65	74
b	*p*-MeOPh	71	64
c	*p*-Allyloxy-Ph	81	78
d	*p*-NO_2Ph	43	73
e	*p*-ClPh	77	83
f	*p*-BrPh	73	79
g	*m*-ClPh	65	76
h	*m*-BrPh	66	79
i	*o*-FPh	47	60
j	*o*-ClPh	56	59
k	*o*-BrPh	51	53
l	Naphthyl	72	80
m	Terephthyl	35	-
n	2-Furyl	70	74
o	2-Br-furyl	44	69
p	Cyclopropyl	62	44
q	Cyclohexyl	53	46
r	Valeryl (C_5H_{11})	18	-
s	2,6-Dimethylphenyl	61	-
t	Pentamethylphenyl	57	-
u	*o*-IPh	-	33
v	*m*-IPh	-	36

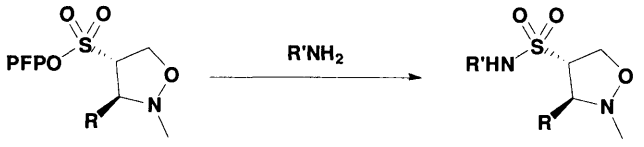
Table 5

Apart from the benefits of reduced reaction times microwave heating also generally produced higher yields than using conventional heating. There is no obvious general trend between the nitrone used and the yield obtained. However, some aryl groups with electron-donating substituents seem to give excellent yields (entries c and l), while hydrophilic nitrones (entries d and m) are less efficiently converted into isoxazolidines **103d** and **103m** respectively. Aryl groups with halogen functionality tended to give moderate to good yields, but when microwave assisted gave enhanced yields. Aromatic groups with very bulky substituents also required a longer reaction time of 5 hours (entries s and t) for reaction completion.

Most of the yields reported employing conditions A compared favourably with those obtained previously within the group. One particularly pleasing result was the success of the *p*-halogeno aryl nitrones (entries e and f), since these have been reported as giving unsuccessful reactions in the past.[94] In these cases it was found that the product and PFP-vinyl sulfonate **100** exhibited the same R_f, and so it became clear why previous attempts were mistaken for an unsuccessful reaction. For all examples the presence of exclusively the 4C *anti* cycloadduct was confirmed by NMR comparisons with literature examples.[69]

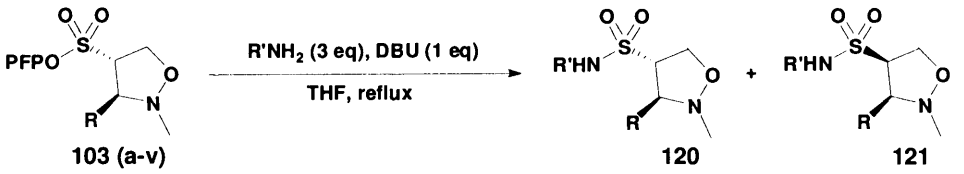
2.3.4. Aminolysis of PFP isoxazolidine cycloadducts

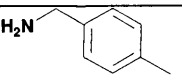
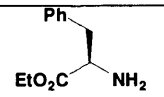
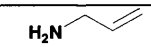
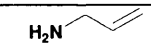
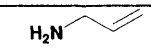
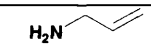
Now in possession of a selection of isoxazolidines, the aminolysis reaction of these products was attempted (Scheme 49).



Scheme 49

It has been reported that aminolysis of these substrates proceed with no loss of stereochemistry during the transformation.[69, 94] Accordingly, a selection of simple amines was subjected to aminolysis conditions (Table 6).



Entry (120/121)	R	R'NH$_2$	Time	Product ratio (120 : 121)	Yield (%)
a	Ph		30 mins	4 : 1	70
b	Ph		1 hr	3 : 1	84
c	Ph		2 hrs	1 : 1*	65
d	*p*-MeOPh		1 hr	3 : 1*	63
e	2-Br-furyl		1 hr	4 : 1	78
f	*p*-NO$_2$Ph		1 hr	3 : 1	63
g	Cyclopropyl		30 mins	3 : 1*	92

* = products not separated **Table 6**

It soon became clear by TLC analysis that, in general, the reactions were generating a mixture of products, which were difficult to separate by column chromatography. Fortunately, separation of each product (entries a, b, e, and f) was achieved and NMR analysis confirmed that both the *anti* and *syn* diastereoisomers were synthesized. Further NMR analyses, including NOE analysis, combined with molecular modelling have confirmed that the major product is the *anti* cycloadduct **120**, and the minor product the *syn* cycloadduct **121**. An example of this is shown in Figure 25. There are marked differences between the two ^{1}H NMR spectrum of **120a** and **121a**, which is evident by comparing the positions of protons 1 and 2, and how clearly the peak resolves. In particular, the amino proton 1 of the 4C *anti* cycloadduct **120a** shows a clear triplet at 4.75 ppm; however, in the 4C *syn* cycloadduct **121a** this proton shifts up-field and its multiplicity less well defined. In addition, molecular modelling suggests that the dihedral angle between protons 2 and 3 in **120a** is approximately 145°, whilst that for **121a** is 23°. These dihedral angles correspond to calculated coupling constants of approximately 7Hz and 8Hz respectively, and this agrees favourably with measured coupling constants of 7.3Hz (**120a**) and 8.4Hz (**121a**). NOE was also used to confirm that sulfonamides **120a** and **121a** were indeed the *anti* and *syn* diastereoisomers respectively. In the *anti* diastereoisomer no apparent NOE between protons 2 and 3 is visible, whilst an NOE is clearly evident between that of proton 2 and those of the phenyl ring of 4. In stark contrast to the *syn* diastereoisomer, an obvious NOE signal is

visible between protons 2 and 3, whilst that of protons 2 and 4 is absent (Supplementary data graphs 1 and 2). Using these guidelines the *syn* and *anti* products for the other aminolysis reactions were identified accordingly.

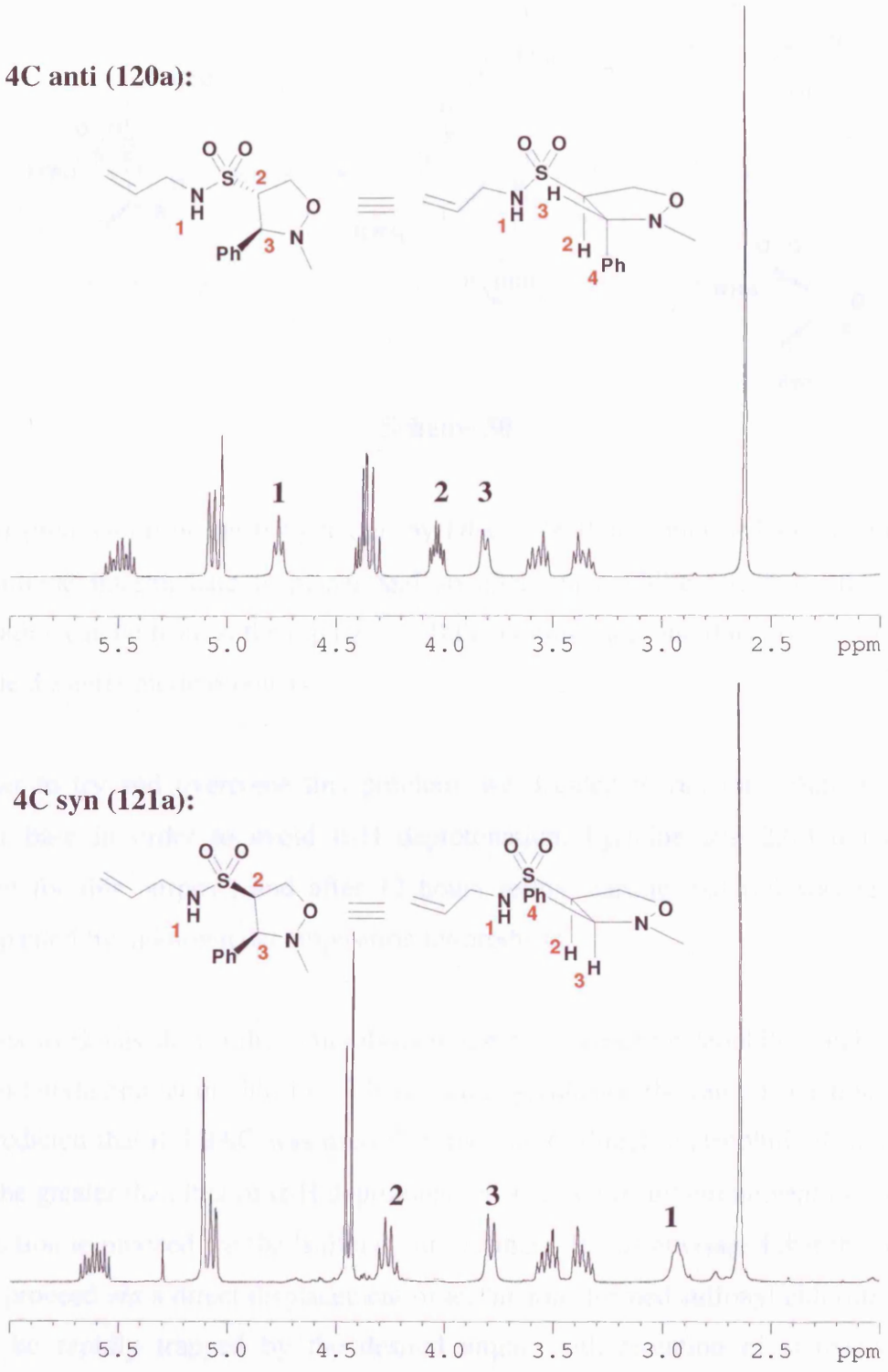
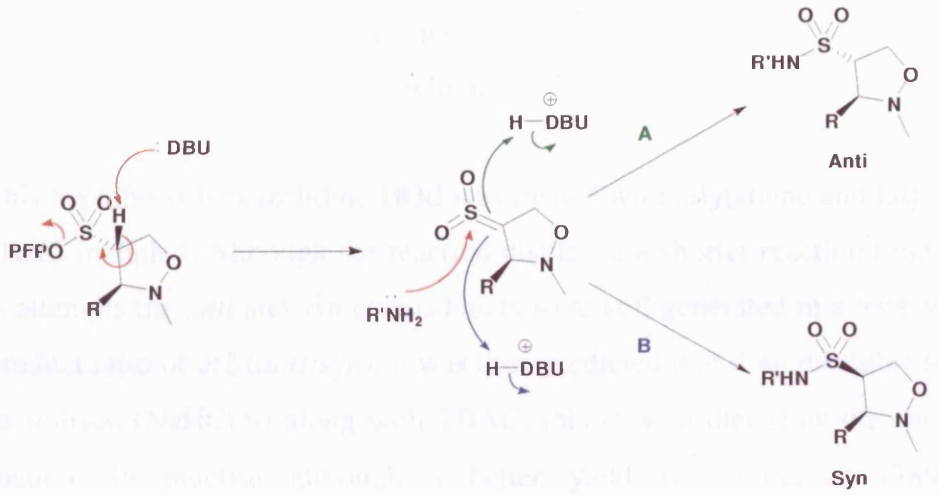


Figure 25

After numerous attempts at the aminolysis reaction, it was possible to conclude that aminolysis does not proceed with exclusive retention of stereochemistry, but is in fact a

diastereoselective reaction. A possible mechanistic explanation is that aminolysis proceeds through a 'sulfene' intermediate (Scheme 50).[67]

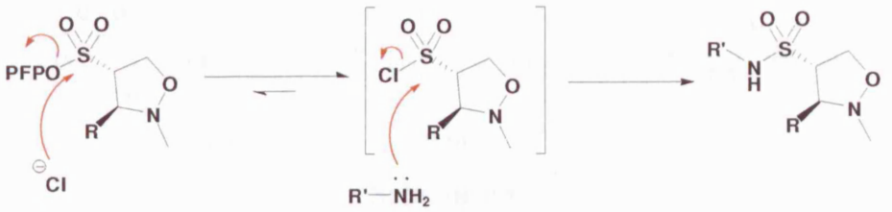


Scheme 50

After deprotonation of the α hydrogen by DBU a 'sulfene' intermediate is generated. This sulfene intermediate is planar and so after nucleophilic attack by the amine, protonation can be from A the top face, or B the bottom face, and thus giving rise to two possible diastereomeric products.

In order to try and overcome this problem, we decided to run the reaction using a weaker base in order to avoid α-H deprotonation. Pyridine and 2,6-lutidine were selected for this purpose, and after 12 hours reflux starting material was recovered accompanied by unknown decomposition by-products.

Previous work has shown that aminolysis in the presence of nucleophilic catalysts such as *tetra*-butylammonium chloride (TBAC) greatly enhance the rate of reaction.[68] So it was predicted that if TBAC was used then the rate of direct nucleophilic displacement might be greater than that of α-H deprotonation, and as a result circumvent the need for the reaction to proceed *via* the 'sulfene' intermediate. It was envisaged that the reaction would proceed *via* a direct displacement of an '*in situ*' formed sulfonyl chloride, which would be rapidly trapped by the desired amine with retention of stereochemistry (Scheme 51).



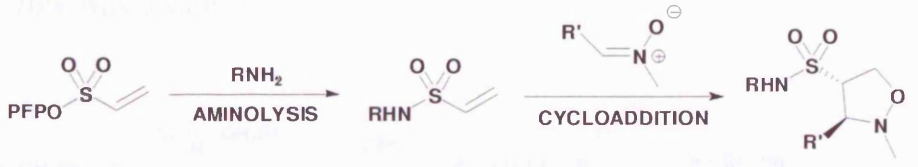
Scheme 51

To test this hypothesis isoxazolidine **103d** was treated with allylamine and DBU, with 1 eq. of TBAC included. Although the reaction displayed a shorter reaction time, as with previous attempts the *anti* and *syn* cycloadducts were still generated in a 58% yield and with a product ratio of 3:2 (*anti:syn*). It was then predicted that if an insoluble source of base was utilised ($NaHCO_3$) along with TBAC, this may further slow the rate of α-H deprotonation. In practise although a better yield was observed (78%) both diastereoisomers were still generated (5:2 *anti:syn*), therefore suggesting aminolysis possibly prefers to proceed *via* the 'sulfene' intermediate.

By this stage, it became clear that we were not going to easily be able to suppress this undesirable isomerisation, and we therefore sought a new solution.

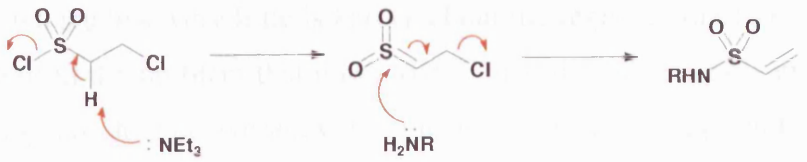
2.3.5. 1,3-Dipolar cycloaddition of vinyl sulfonamides

Having established that cycloaddition is both regio- and diastereospecific, it was decided to change the synthetic sequence. For example, if aminolysis is carried out before 1,3-dipolar cycloaddition we felt that it might be possible to isolate the products with improved diastereoselectivity (Scheme 52).



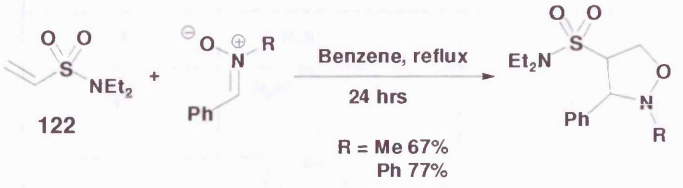
Scheme 52

An additional advantage was that vinyl sulfonamides can be synthesized directly from 2-chloroethane-1-sulfonyl chloride using an existing protocol (Scheme 53).[69, 93]



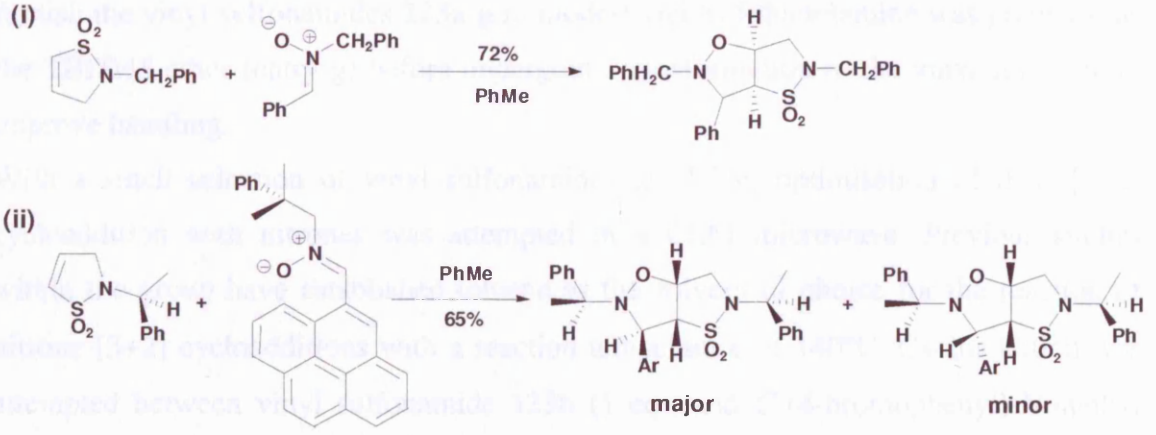
Scheme 53

1,3-Dipolar cycloaddition of nitrones to vinyl sulfonamides is not well described in literature, with Vessière *et al.* and Chan and co-workers being two groups who have reported brief studies. An early example from Vessière in 1987 reported the regioselective [3+2] cycloaddition between a mono-substituted vinyl sulfonamide **122** with two nitrones (Scheme 54). The authors also report that the reaction is diastereoselective, however the stereochemical outcome was not reported.[92]



Scheme 54

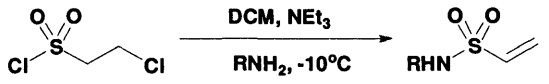
Chan's reported examples are shown in Scheme 55. Although they utilise a di-substituted olefin they do not report formation of the 5C-substituted cycloadduct, so the reaction appears to be proceed with excellent regioselectivity (Scheme 55 (i)).[95] Further work from this group described a double asymmetric induction between a chiral α,β-unsaturated-γ-sultam with a chiral nitrone (Scheme 55 (ii)). The reaction was regioselective with respect to the 4C-substituted cycloadduct, and a diastereomeric excess of 76% was obtained.[83]



Scheme 55

Despite these two studies, very little is known about the regio- or diastereoselectivity of the reaction. Indeed the problem that now exists is that the sulfonamide group does not exhibit as strong an electron withdrawing effect as the PFP group, and consequently might have an effect on the reactivity of the double bond. It has been mentioned earlier that if a dipolarophile is weakly electron-deficient then a regioisomeric mixture of cycloadducts will be obtained.

In order to perform a study into the reactivity of vinyl sulfonamides, a range were synthesized using a variety of primary and secondary amines (Table 7).



123 (a-g)

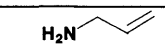
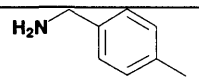
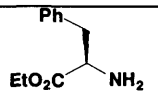
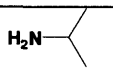
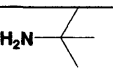
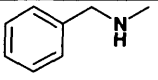
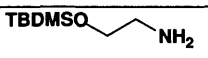
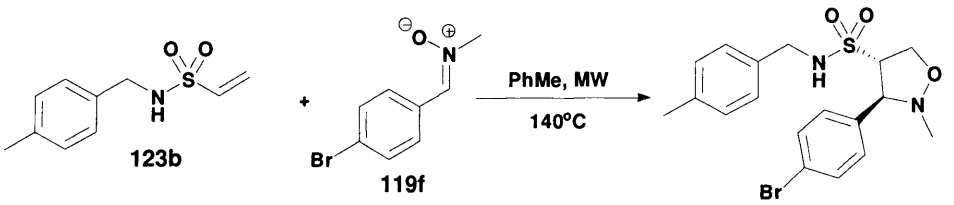
Entry (123)	Amine	Yield (%)
a		65
b		76
c		56
d		55
e		64
f		67
g		65

Table 7

All the reactions were non-trivial and required purification by flash chromatography to furnish the vinyl sulfonamides **123a-g** in modest yields. Ethanolamine was protected as the TBDMS ether (entry g) before undergoing transformation to the vinyl sulfonate to improve handling.

With a small selection of vinyl sulfonamides available, optimisation of their [3+2] cycloaddition with nitrones was attempted in a CEM microwave. Previous studies within the group have established toluene as the solvent of choice for the reaction of nitrone [3+2] cycloadditions with a reaction temperature of 140°C. Cycloaddition was attempted between vinyl sulfonamide **123b** (1 eq.) and *C*-(4-bromophenyl)-*N*-methyl nitrone (1.5 eq.) **119f** initially (Table 8, entry 1) for 10 minutes; however the presence

of vinyl peaks in the ^{1}H NMR suggested the reaction was incomplete after this time. Reaction times of 30 and 60 minutes (entry 2 and 3) produced a similar result. Rather than increase the reaction time it was suggested that degradation of the nitrone under intense MW heating was responsible for the inability of the reaction to proceed to completion. Hence, the amount of nitrone used was increased (3 eq.) to drive the reaction to completion. Accordingly, various reaction times were screened and the ^{1}H NMR of the crude material recorded to determine the extent of conversion (entries 4-13). Optimum conditions were eventually found to be 3 eq. of nitrone with a reaction time of 30 minutes (entry 11).

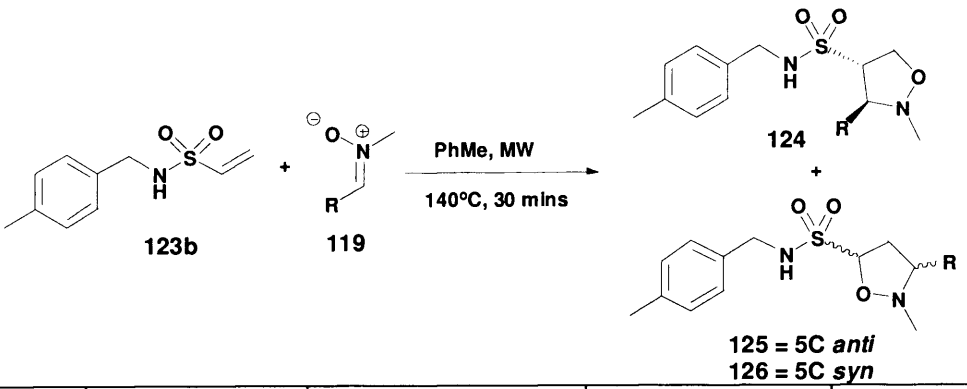


Entry	Nitrone	Time (mins)	Outcome
1	1.5 eq.	10	Approximately 40% conversion
2	1.5 eq.	30	Approximately 70% conversion
3	1.5 eq.	60	Approximately 85% conversion
4	3 eq.	1	Approximately 10% conversion
5	3 eq.	2	Approximately 15% conversion
6	3 eq.	5	Approximately 40% conversion
7	3 eq.	10	Approximately 65% conversion
8	3 eq.	15	Approximately 75% conversion
9	3 eq.	20	Approximately 80% conversion
10	3 eq.	25	Approximately 95% conversion
11	3 eq.	30	100% conversion
12	3 eq.	40	100% conversion
13	3 eq.	50	100% conversion

Table 8

This new protocol was repeated on vinyl sulfonamide **123b** and nitrone **119f** (Table 9, entry a); however upon purification it was observed that there was no regiocontrol, and that the 5C-substituted isoxazolidines (**125a** and **126a**) were also produced. No evidence for the formation of the 4C *syn* diastereoisomer was observed, and the 4C *anti*

124a could be easily separated from the 5C diastereoisomers. The remaining nitrones were also examined and the results shown (Table 9).



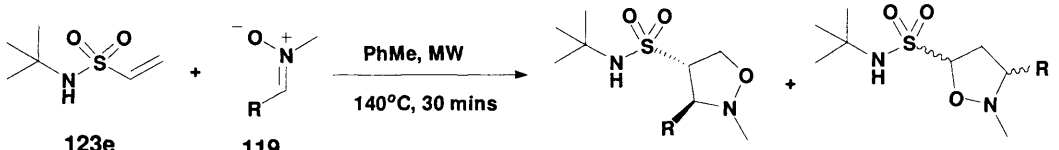
Entry	R	Product ratio (124 : [125/126])	Product ratio 125 : 126	Overall Yield (%)
a	*p*-BrPh	3 : 2	3 : 1	72
b	*o*-ClPh	2 : 3	2 : 1	78
c	Ph	5 : 1	2 : 1	81
d	*o*-BrPh	2 : 3	2 : 1	83
e	*o*-FPh	6 : 7	5 : 2	89
f	*p*-MeOPh	7 : 3	2 : 1	73
g	*p*-NO_2Ph	7 : 2	2 : 5	67
h	*p*-ClPh	5 : 2	3 : 1	78
i	Naphthyl	5 : 2	2 : 1	57
j	*m*-BrPh	5 : 1	1 : 0	57
k	*m*-ClPh	3 : 1	1 : 0	62
l	2-Br-furyl	1 : 0	-	20
m	2-Furyl	4 : 9	6 : 3	63
n	*p*-Allyloxy-Ph	1 : 0	-	24
o	*o*-IPh	2 : 1	0 : 1	32
p	*m*-IPh	5 : 2	1 : 0	61

Table 9

As with entry a, the majority of other nitrones also furnished mixtures of the 4C *anti* diastereoisomer **124**, as well as the 5C diastereoisomers **125** and **126** often as an inseparable mixture. Yields were generally good, however for the less stable nitrones (entries l and o) poor yields were obtained and this was visible by a severe darkening of the reaction vial after MW irradiation. A poor yield for entry n can also be explained by

possible complications resulting from the presence of another olefin on the nitrone available for cycloaddition. An unexpected result from this study was the disappearance of the 5C *syn* cycloadduct **126** when *meta*-substituted phenyl nitrones (entries j, k, and p) were used, although it is not obvious how this phenomenon occurs.

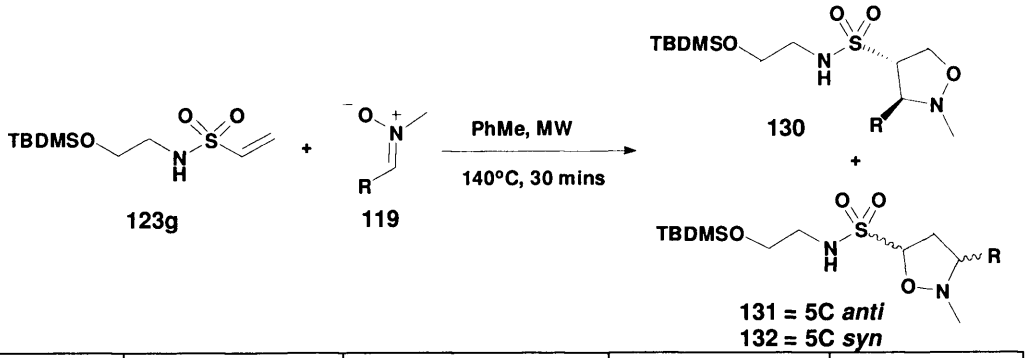
Although there was not perfect regiocontrol in nitrone [3+2] cycloadditions with vinyl sulfonamides, the ease with which the 5C-substituted products can be separated from the desired 4C *anti* diastereoisomer was advantageous. Overall this may be preferred over the approach utilising aminolysis of PFP isoxazolidines **103a-v** (Section 2.3.4.). Furthermore, as there is little known about the 1,3-dipolar cycloaddition between vinyl sulfonamides and nitrones, this study does provide some useful information about such cycloaddition reactions. We therefore utilised this route to prepare a selection of heterocyclic sulfonamides from vinyl sulfonamides **123e** and **123g**, and the results shown in Tables 10 and 11.



123e 119 127 128 = 5C *anti* 129 = 5C *syn*

Entry	R	Product ratio (127 : [128/129])	Product ratio 128 : 129	Overall Yield (%)
a	*p*-BrPh	10 : 3	2 : 1	59
b	*o*-ClPh	1 : 1	3 : 2	58
c	Ph	3 : 1	2 : 1	55
d	*o*-BrPh	2 : 1	3 : 2	43
e	*o*-FPh	7 : 6	4 : 2	57
f	*p*-MeOPh	5 : 1	3 : 2	39
g	*p*-NO_2Ph	8 : 1	1 : 0	47
h	*p*-ClPh	13 : 4	2 : 2	59
i	Naphthyl	7 : 1	1 : 1	49
j	*m*-BrPh	2 : 1	2 : 1	57
k	*m*-ClPh	12 : 3	2 : 1	52
l	2-Br-furyl	1 : 0	-	37
m	2-Furyl	2 : 3	2 : 1	72
n	Cyclopropyl	3 : 7	9 : 5	43

Table 10



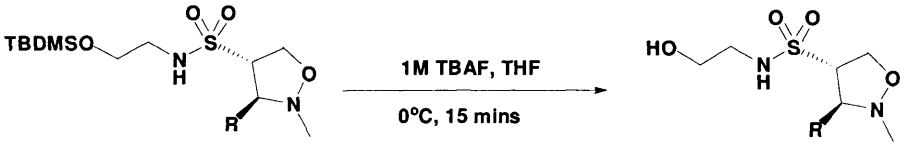
Entry	R	Product ratio (130 : [131/132])	Product ratio 131 : 132	Overall Yield (%)
a	*p*-BrPh	5 : 1	4 : 1	70
b	*o*-ClPh	1 : 1	5 : 3	82
c	Ph	3 : 1	3 : 2	55
d	*o*-BrPh	1 : 1	3 : 2	57
e	*o*-FPh	1 : 1	1 : 1	76
f	*p*-MeOPh	11 : 3	1 : 2	66
g	*p*-NO_2Ph	11 : 2	2 : 0	60
h	*p*-ClPh	11 : 2	2 : 0	62
i	Naphthyl	3 : 1	3 : 2	75
j	*m*-BrPh	6 : 1	1 : 0	63
k	*m*-ClPh	5 : 1	1 : 0	66
l	2-Br-furyl	1 : 0	-	12
m	2-Furyl	5 : 6	4 : 2	71
n	*p*-Allyloxy-Ph	6 : 5	3 : 2	58
o	Cyclopropyl	6 : 21	13 : 9	64

Table 11

With vinyl sulfonamide **123e**, the yields were not as encouraging as those previously described in Table 9, although better yields were obtained with the less sterically congested vinyl sulfonamide **123g**. It was interesting to note that there was normally a greater preference for the 4C *anti* cycloadduct over the 5C cycloadducts irrespective of the nature of the vinyl sulfonamide. A few exceptions arose when furyl or cyclopropyl nitrone was used (Tables 9-11), and in these cases we observed a reversal in product selectivity, although additional work would be required to investigate this inconsistency.

Likewise when 2-bromofuryl nitrone was used, yields were consistently low with only the 4C substituted diastereoisomer obtained from a mixture of decomposition products (Tables 9-11, entry l). A pattern that also re-emerges is the loss of the 5C *syn* products when *meta*-substituted phenyl nitrones were used (Table 11, entries j and k), however this outcome was not observed in cycloadditions with **123e**, thus adding further confusion over how to predict the diastereoselectivity of the 5C regioisomers when *meta*-substituted phenyl nitrones are involved.

The simple and clean removal of the TBDMS protecting group from isoxazolidines **130a-n** was achieved in excellent yields after purification (Table 12) to provide another collection of interesting sulfonamides which, as can be seen later, have some potential application in chemical biology (see Chapter 3).



130a-n 133a-n

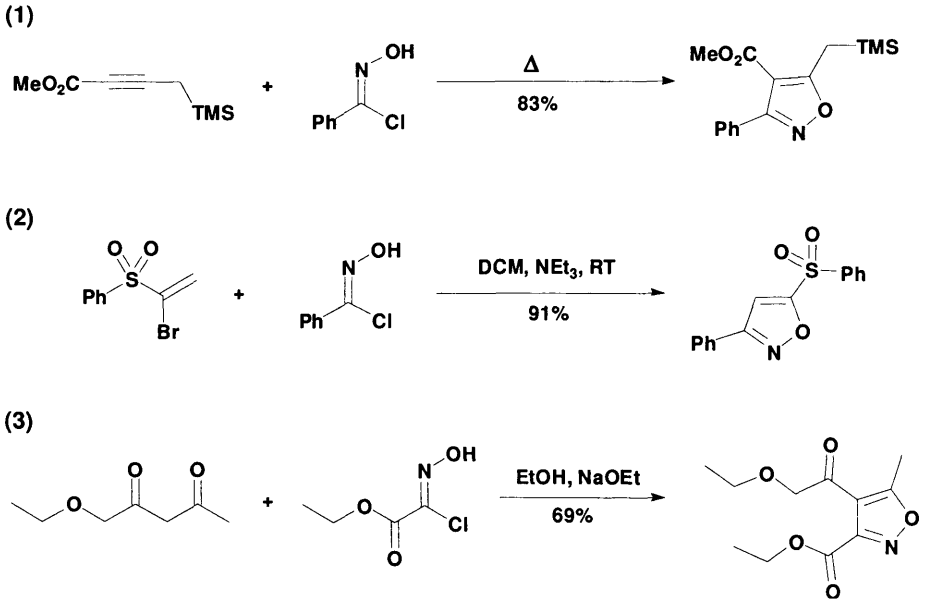
Entry (133)	R	Yield (%)
a	*p*-BrPh	86
b	*o*-ClPh	91
c	Ph	92
d	*o*-BrPh	85
e	*o*-FPh	78
f	*p*-MeOPh	83
g	*p*-NO_2Ph	50
h	*p*-ClPh	85
i	Naphthyl	97
j	*m*-BrPh	82
k	*m*-ClPh	70
l	2-Br-furyl	70
m	2-Furyl	69
n	*p*-Allyloxy-Ph	92

Table 12

2.4. Isoxazole synthesis from vinyl sulfonates

We were interested in developing the cycloaddition chemistry further such that we could apply this to the synthesis of isoxazoles. The most obvious way to achieve this is by utilising PFP-alkynylsulfonate; however, previous researchers in the group had shown that this was a difficult compound to prepare. In this section we describe a range of attempts to find a means towards synthesizing isoxazole species.

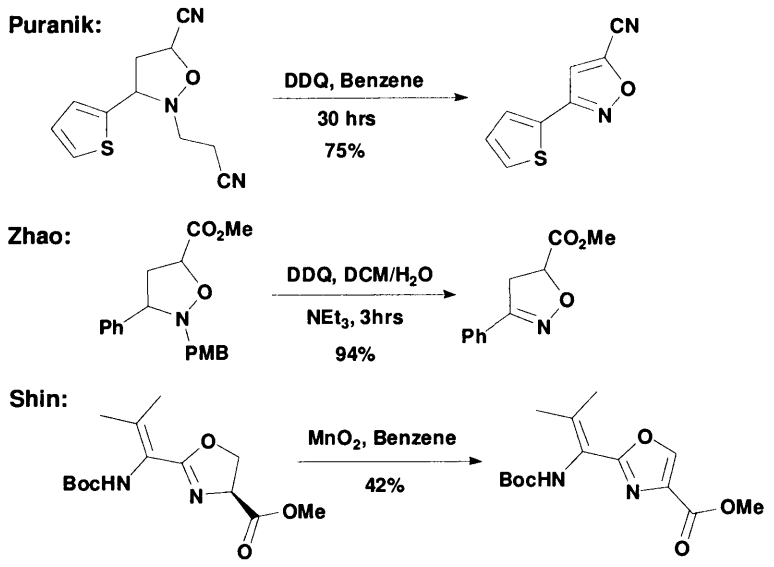
Common literature preparations for the synthesis of isoxazoles often involve the use of an alkyne (1),[96] an alkyne equivalent (2),[97] or a 1,3-dicarbonyl (3)[98] as shown in Scheme 56.



Scheme 56

There is, however, much less precedent for the direct oxidation of isoxazolidines as a route into isoxazoles; hence work will be focused on this particular pathway.

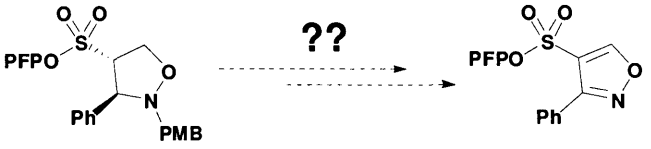
A literature search reveals a limited number of examples for the oxidation of isoxazolidine rings (Scheme 57). Puranik and Zhao both utilise DDQ as the oxidant of choice to carry out an *N*-deprotection followed by oxidation, and while Puranik *et al.* obtained the aromatic product with their protocol Zhao *et al.*, obtained the partially oxidised isoxazoline.[99,100] Whilst it may be difficult to predict how our 4C-substituted isoxazolidines may preferentially oxidise, there is also literature precedent as demonstrated by Shin *et al.* that the oxidation of oxazolines to oxazoles is available as an option should our 4C-cycloadducts fail to aromatise (Scheme 57).[101]



Scheme 57

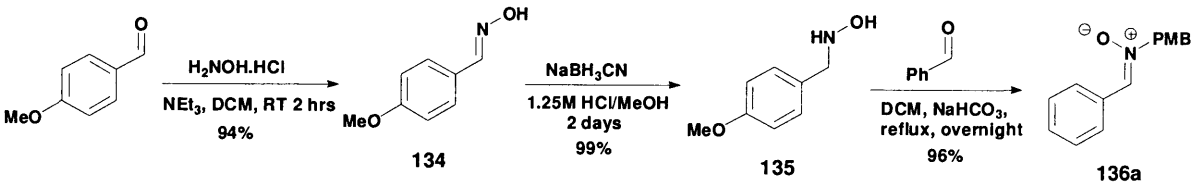
2.4.1. Oxidation of isoxazolidines

The initial focus of this work was to develop the key reaction where an isoxazolidine possessing a PFP sulfonate group might be fully oxidised to the analogous isoxazole with preservation of the PFP functionality (Scheme 58). It was anticipated that the PMB group could be removed and then the free isoxazolidine subjected to oxidation conditions to give the desired isoxazole (Scheme 58).



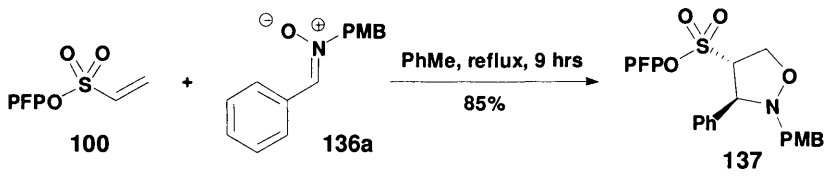
Scheme 58

For the initial optimisation study, a phenyl-substituted isoxazolidine was selected as a suitable substrate, with an *N*-PMB substituent. As with previous cycloaddition strategies we have examined, it would be possible to vary the R group in the initial cycloaddition for the purposes of introduction of diversity. Hence, nitrone **136a** was synthesized *via* the following route (Scheme 59).



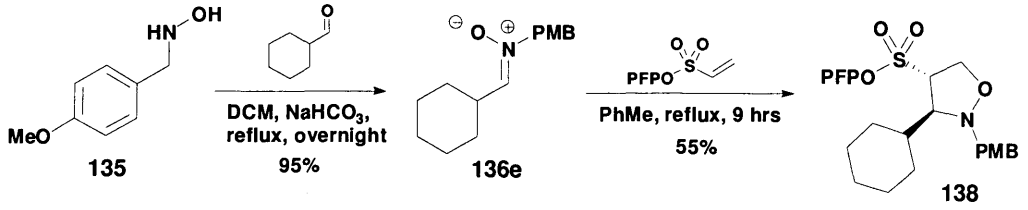
Scheme 59

Using known literature procedures the required nitrone **136a** was easily prepared in excellent yield through a series of simple reactions. Condensation of hydroxylamine with anisaldehyde provided oxime **134** in a 94% yield.[102] Compound **134** was reduced with $NaBH_3CN$ in a near quantitative yield, and a final condensation of hydroxylamine **135** with benzaldehyde produced the required nitrone in a yield of 96%.[69, 102, 103] 1,3-Dipolar cycloaddition with PFP vinyl sulfonate **100** subsequently furnished the PFP isoxazolidine **137** in a entirely regioselective and diastereoselective manner (see Section 2.3.3), in an 85% yield (Scheme 60).



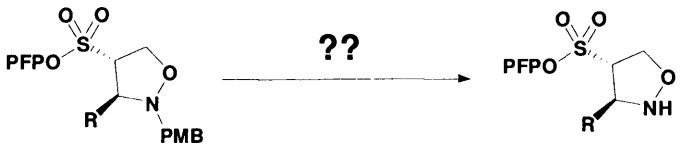
Scheme 60

The cyclohexyl-substituted variant **138** was also prepared in a slightly more modest 55% yield *via* the condensation of hydroxylamine **135** with cyclohexanecarbaldehyde, followed by a [3+2] cycloaddition of the resulting nitrone **136e** with PFP vinyl sulfonate **100** (Scheme 61).



Scheme 61

With the *N*-protected isoxazolidines in hand, removal of the PMB group was attempted using various typical literature conditions. The results of these trials are shown in Table 13.



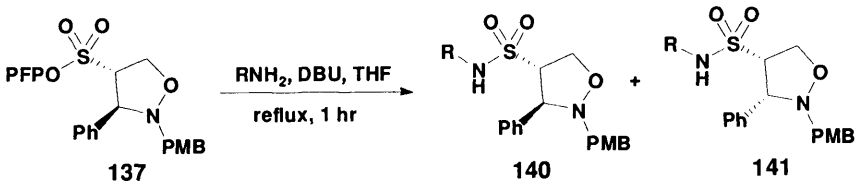
139

Entry	Conditions	R	Yield (%)
a	Pd/H_2, RT, MeOH, 24 hrs	Cyclohexyl	Failed
b	Pd/H_2, reflux, MeOH, 7 hrs	Cyclohexyl	34%
c	Pd/H_2, reflux, EtOAc, 16 hrs	Cyclohexyl	Failed
d	1-chloroethylchloroformate, reflux	Phenyl	Failed
e	DDQ, DCM/H_2O, RT, 16 hrs	Phenyl	Failed
f	DDQ, DCM/H_2O, reflux, 16 hrs	Phenyl	Failed
g	DDQ, dioxane, reflux, 6 hrs	Phenyl	Failed

Table 13

With the more common hydrogenation conditions the reaction was unsuccessful at room temperature,[104] no reaction was taking place and instead recovery of starting material was obtained as the major result (entry a). Heat was applied to the reaction with some degree of success (entry b), however the product **139** generated proved to be difficult to isolate *via* silica gel chromatography. Nevertheless, the problem associated with this protocol was the generation of PFPOH, and consequently suggesting degradation of starting material **138** or the resultant product. Changing the solvent from MeOH to the less polar EtOAc stopped the reaction altogether (entry c), as starting material was recovered. 1-Chloroethyl chloroformate was attempted as a means of trapping the product isoxazolidine as the HCl salt (entry d);[105] however, failure of this method was again verified by the recovery of starting material. Endeavours with DDQ (entries e-f) led to the decomposition of starting material or product, although this was possibly down to hydrolysis of the PFP group by water.[106, 107] Removal of water (entry g) provided no appreciable product formation so studies were directed elsewhere.

Due to the labile nature of the PFPOH group it was decided that aminolysis should be carried out first to make a more stable S-N bond, which would also be more likely to survive the harsher deprotection and oxidation conditions (Table 14).



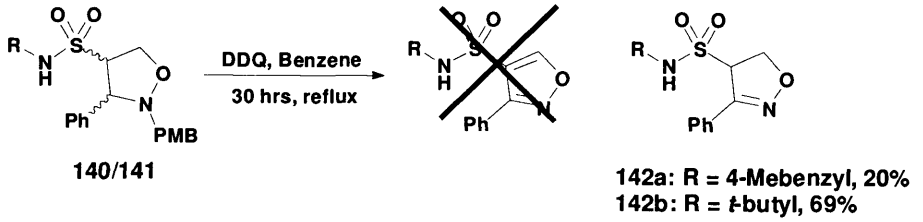
Entry	Amine	Yield (%)	Product ratio (140 : 141)
a	4-methylbenzylamine	95	7 : 2 *
b	4-methylbenzylamine	90	3 : 1
c	*tert*-butylamine	85	2 : 1

* = separated

Table 14

4-Methylbenzylamine and *tert*-butylamine sulfonamides **140/141a-c** were prepared in excellent yield; however, as with previous attempts at aminolysis (see Section 2.3.4.) the reactions proceeded with little diastereocontrol (Table 14). This was not a concern however, as upon oxidation to the isoxazole both diastereoisomers should furnish the same final product. Therefore, after the first reaction with 4-methylbenzyl amine, we did not attempt to separate the product isomers, but simply continued using the mixture of products (entries b and c).

Due to the difficulties associated with the isolation of the free isoxazolidine **139**, the one-step deprotection-oxidation process reported by Puranik *et al.* (Scheme 57) was examined, as this would remove the need for a separate PMB deprotection step (and the resulting necessary purification).[99] This process utilised DDQ to carry out an '*in situ*' *N*-deprotection followed by isoxazolidine oxidation to the isoxazole. Investigation of this procedure met with limited success (Scheme 62).



Scheme 62

With 4-methylbenzylamine the reaction was not trivial, and the only characterisable product obtained from a complex mixture of decomposition products was the partially oxidised isoxazoline **142a** in a 12-20% yield. In addition, the reaction was left for a longer period of 48 hours to determine whether complete conversion to the aromatic

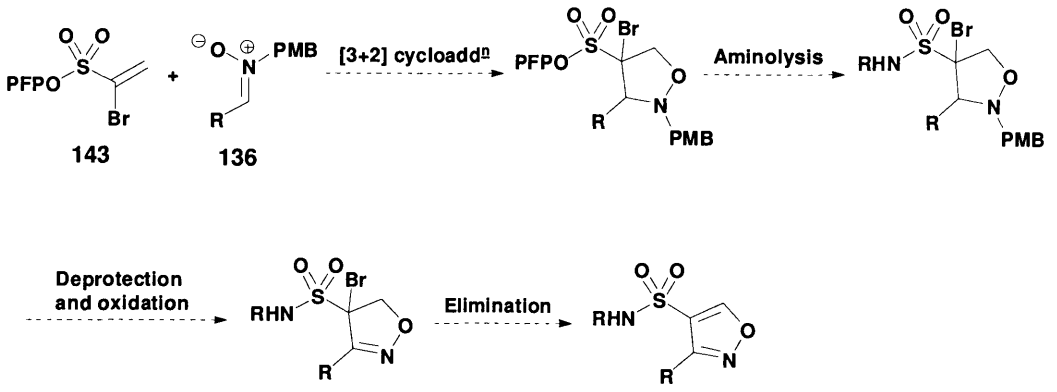
isoxazole could be achieved. However, disappointingly the product was reluctant to undergo aromatisation and degradation is observed which further diminished the poor yield. Further attempts at optimisation were unsuccessful. As it was envisaged that there was a possibility that the DDQ could also be reacting with the 4-methylbenzylamine moiety, this was subsequently exchanged for *tert*-butylamine (Table 14, entry c).

The DDQ deprotection/oxidation reaction was repeated on the *tert*-butylamine analogue **140/141c** furnishing the isoxazoline **142b** in a gratifying 69% yield (Scheme 62). Repeated attempts produced similar yields and consequently demonstrated that the choice of amine was an important factor. Again it was noticeable that the isoxazoline **142b** was resistant to aromatisation as there was no evidence of the isoxazole, even with prolonged heating.

2.4.2. Cycloaddition studies on α-bromo-PFP-vinyl sulfonate

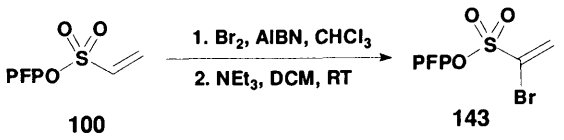
Following these difficulties in the preparation of the isoxazole, a modification to the synthetic route was sought. Due to the lack of success in mediating aromatisation of isoxazolidines, it was envisaged a PFP-alkynyl-sulfonate equivalent might enable us to circumvent these problems. Hence, it was decided to study the reactions of a novel 1,3-dipolarophile, α-bromo-PFP-vinyl sulfonate **143**.

The use of α-bromo-PFP-vinyl sulfonate **143** as an alkyne equivalent is well established within the group, thus it was conceived that as a direct replacement for PFP-vinyl sulfonate **100** in the previously described cycloaddition chemistry (see Section 2.3.3.) aromatisation could be accomplished later in the synthesis. Accordingly, a new synthetic plan is shown, Scheme 63.



Scheme 63

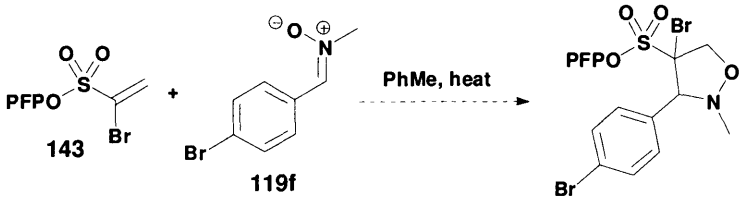
Following a known procedure α-bromo-PFP-vinyl sulfonate **143** was synthesised in 75% yield through a radical mediated process (Scheme 64).[108]



100 143

Scheme 64

A [3+2] cycloaddition with **143** as the dipolarophile was first performed using a simple model nitrone **119f**, to determine optimal conditions for this novel transformation (Scheme 65).

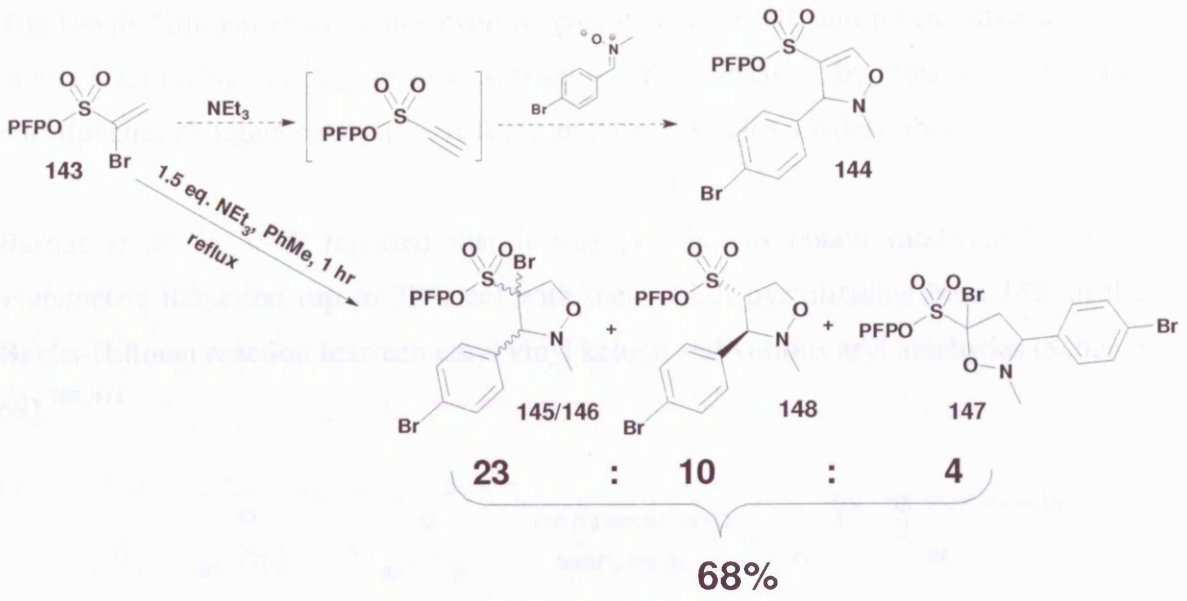


143 119f

Scheme 65

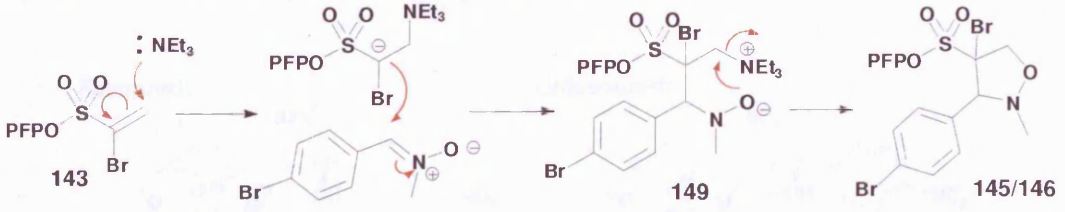
However, when subjected to the previously optimised cycloaddition conditions (1.5 eq. nitrone and 1 eq. of dipolarophile in refluxing toluene), no product was visible after 20 hours, instead partial recovery of α-bromo-PFP-vinyl sulfonate **143** was the main outcome. Similarly no product was obtained when the reaction mixture was heated in a microwave oven at 140°C for 2 hours. It was assumed that the olefin was too hindered and even prolonged heating at an elevated temperature was insufficient to drive the reaction forward. It was noticed that under MW heating PFPOH was liberated, indicative of degradation of the α-bromo-PFP-vinyl sulfonate prior to cycloaddition.

It was then decided to examine the potential beneficial effect of base in the reaction. It was conceived that if a base was added to the reaction, '*in situ*' elimination of HBr could be effected and the nitrone could then undergo cycloaddition, with the much less sterically encumbered alkyne. Hence, the reaction was repeated with 1.5 eq. of NEt_3 and after purification 3 products were obtained (Scheme 66). Surprisingly none of the expected eliminated cycloadduct **144** was obtained. However, more remarkable was the presence of the brominated cycloadduct **145/146** as the major product. Also eluted from the column were the de-brominated product **148** and the other regioisomer **147** as a minor product. Additionally, **145/146** was obtained as a diastereomeric mixture of the 4C regioisomer, whilst **148** and **147** were furnished as single diastereoisomers.



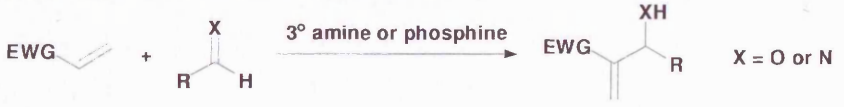
Scheme 66

Isoxazolidine **145/146** could be the result of several different reaction pathways. Previous work from the group had shown that amines tend to undergo conjugate addition to PFP-vinyl sulfonate.[94] Hence it is possible that apparent cycloaddition is in fact proceeding *via* a stepwise process bearing some similarity to the Baylis-Hillman reaction. Thus under such a scheme, triethylamine undergoes conjugate addition to the vinyl sulfonate, the resulting anion **149** undergoes addition to the nitrone, and finally a cyclisation leads to the product (Scheme 67).



Scheme 67

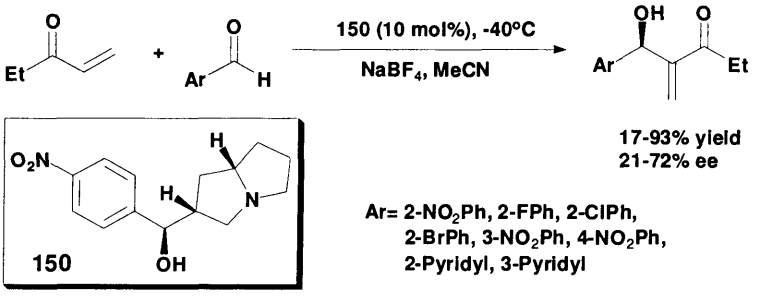
The Baylis-Hillman reaction is an atom economic reaction that involves the condensation of an electron-deficient olefin with an aldehyde catalysed by a tertiary amine or phosphine, to produce an α-methylene-β-hydroxy-carbonyl (Scheme 68).[109]



Scheme 68

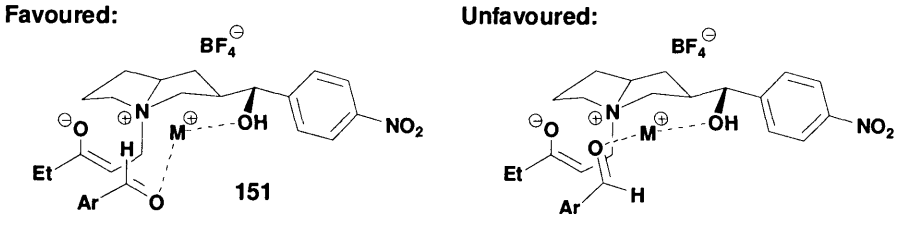
The Baylis-Hillman reaction has evolved greatly since 1998, and recent advancements involve achieving an asymmetric version of this reaction by means of a chiral multifunctional organocatalyst.[110] A few literature examples are described.

Barrett *et al.* in 1998 reported that it was possible to obtain moderate levels of asymmetric induction (up to 72% ee) with their chiral pyrrolizidine base **150**, in the Baylis-Hillman reaction between ethyl vinyl ketone and various aryl aldehydes (Scheme 69).[109, 111]



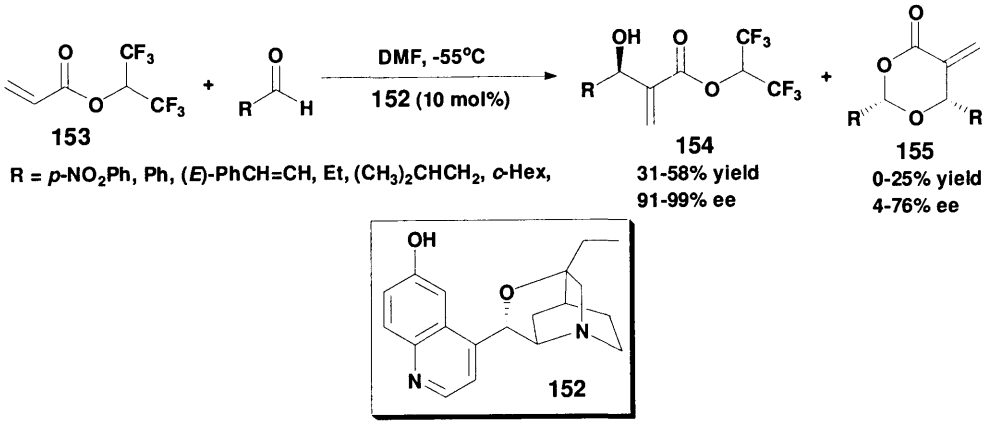
Scheme 69

Since the formation of the *R*-configuration of the alcohol was observed it was postulated that the aldol step proceeded *via* the least sterically hindered intermediate **151** (Scheme 70). In addition, rate enhancement was explained by the ability of the hydroxyl group of the catalyst to tether to the aldehyde through a metal-oxygen bond thus increasing the susceptibility of the aldehyde to nucleophilic attack.[111]



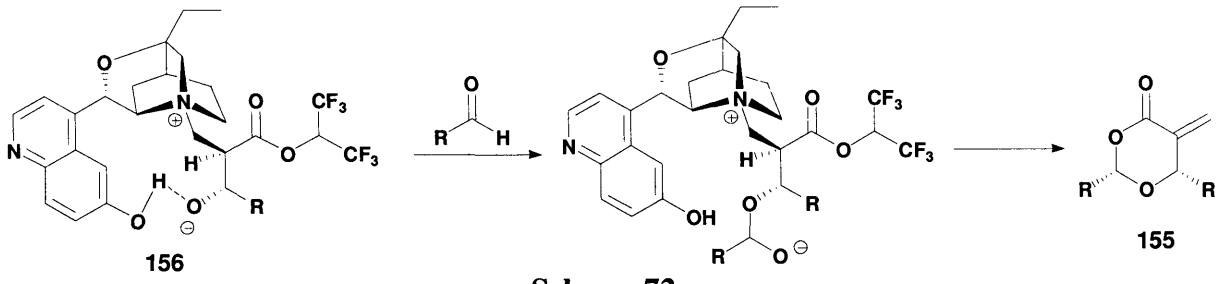
Scheme 70

In 1999, work by Hatakeyama *et al.* produced one of the first examples of an enantioselective Baylis-Hillman reaction catalysed by a rigid tricyclic chiral amine **152** derived from the *Cinchona* alkaloids (Scheme 71).[110, 112]



Scheme 71

The reaction of 1,1,1,3,3,3-hexafluoroisopropyl acrylate **153** with a selection of aromatic and aliphatic aldehydes provided moderate yields of the corresponding α-methylene-β-hydroxy esters **154**, albeit with excellent enantioselectivity (> 91% ee). The modest yields obtained were as a consequence of the formation of a secondary product, the dioxanone **155**, which is formed *via* the addition of a second molecule of aldehyde to the zwitterionic species **156** (Scheme 72).[112]

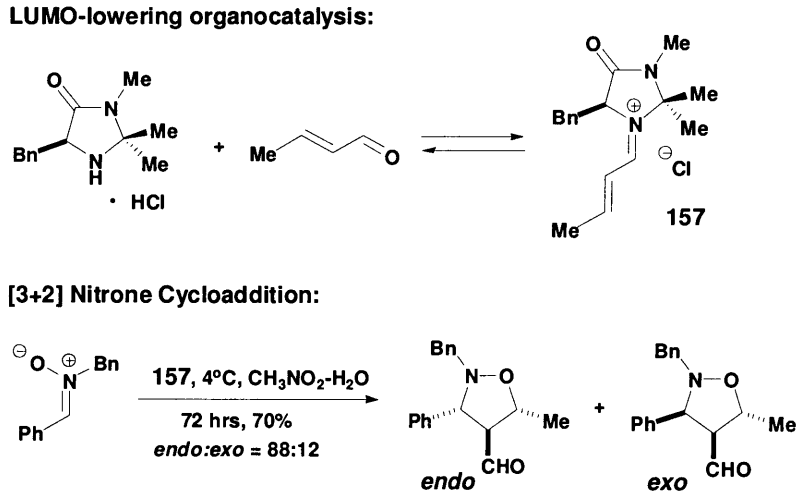


Scheme 72

Interestingly upon exchanging the hexafluoroisopropyl moiety for a methyl group enantioselectivity is lost (8% ee) along with reaction rate enhancement (14 hours compared to 1 hour). Therefore, Hatakeyama concluded that not only did their catalyst control enantioselectivity and rate of reaction, but these were also dependent on the nature of their activated alkene.[112]

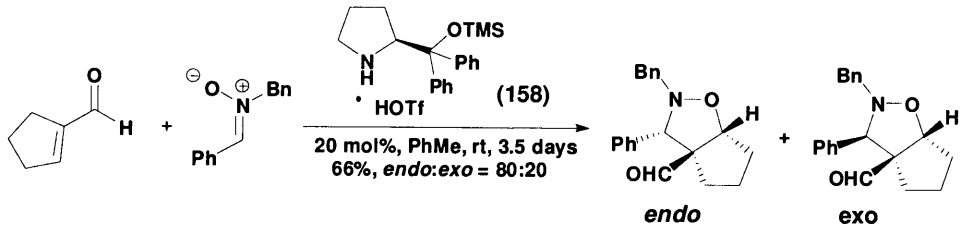
This brief survey of the literature has shown that while tertiary amines are widely used to mediate reactions involving a conjugate addition step, there are few instances of an amine promoted/catalysed [3+2] cycloaddition reaction. Consequently, a search of the literature reveals that although amines have been used to mediate 1,3-dipolar cycloadditions, this has been limited to secondary amines and there does not currently

appear to be a [3+2] cycloaddition mediated by a tertiary amine.[83] Secondary amine activation of [3+2] cycloadditions has been intensely explored by MacMillan *et al.* and involves a LUMO-lowering activation of α,β-unsaturated aldehydes (Scheme 73).[113] Iminium ion formation is reversible and utilises no more than 20 mol% of the chiral imidazolidinones **157** to provide improved enantioselectivities of up to 93% ee for the *endo* cycloadduct. Overall the amine catalyses the process by generating a covalently bound and activated iminium species and this approach has become known as organocatalysis.[113]



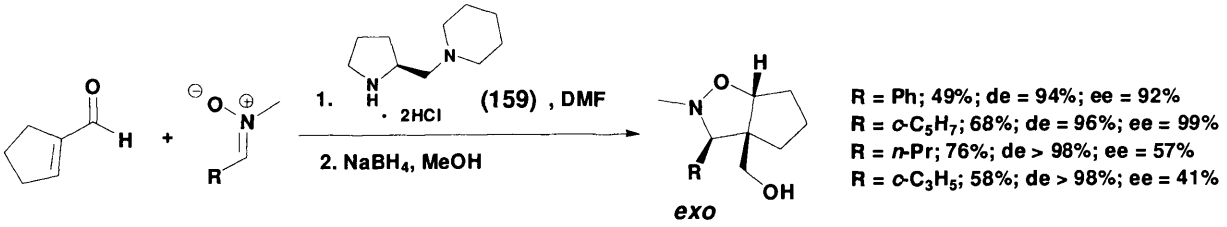
Scheme 73

More recently in 2007, Nevalainen *et al.* have developed a prolinol catalyst **158** which was employed for [3+2] cycloaddition with mono-substituted and di-substituted α,β-unsaturated aldehydes, giving comparable statistics to MacMillan's catalyst (Scheme 74). The advantage of this catalyst over Macmillan's catalyst was that it was synthesized in one step from commercially available diphenyl-(*S*)-prolinol, whereas MacMillan's catalyst requires multiple steps from phenylalanine methyl ester.[114]



Scheme 74

Karlsson *et al.* have also studied an enantioselective [3+2] cycloaddition between cyclic α,β-unsaturated aldehydes and nitrones using their chiral pyrrolidinium salt **159** as catalyst, providing the *exo*-isoxazolidine as the major product in high diastereo- and enantioselectivity (Scheme 75).[115]



Scheme 75

Given that there appears at present no precedent for tertiary amine-catalysed [3+2] cycloadditions, further investigation into this area is necessary to understand more about this promising reaction.

As it appeared that NEt_3 was promoting the previously unsuccessful reaction, it became desirable to optimise conditions and to try to eliminate/minimise the two other undesirable side products. It is logical to assume that if the reaction does proceed through a Baylis-Hillman type pathway then the reaction should also work with catalytic NEt_3. This was examined (Table 15), and it was pleasing to observe that the reaction works with a sub-stoichiometric amount (10%) of NEt_3 in a 76% yield, and also that the amount of de-brominated product **148** was also reduced (Table 15, entry 2). It was then desirable to test the reaction at room temperature and it was repeated with both 1.5 eq. of NEt_3 (entry 3) or catalytic quantities (0.1 eq.) of NEt_3 (entry 4). The yields obtained were excellent and it was evident that performing the reaction at room temperature leads to an approximately 10% increase in the yield of **145/146**. As a result it was decided that further investigation should be carried out at room temperature.

Entry	Temp.	NEt_3	Nitrone	Time	Yield/Ratio (145/146 : 148 : 147)
1	110°C	1.5 eq.	1.5 eq.	1 hour	68% / 6 : 2.5 : 1
2	110°C	0.1 eq.	1.5 eq.	1 hour	76% / 6 : 1 : 1
3	RT	1.5 eq.	1.5 eq.	3 days	79% / 14 : 1 : 1
4	RT	0.1 eq.	3 eq.	3 days	92% / 20 : 2 : 1

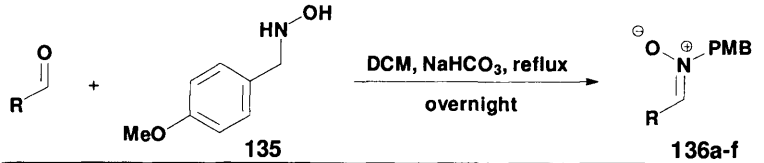
Table 15

Due to the impractical length of the reaction (3 days), other base/catalysts were explored. It is well known that DABCO has been used in Baylis-Hillman reactions, therefore this was examined as an alternative to NEt_3 (Table 16, entry 1 and 2). With 1.5 eq. of DABCO the α-bromo-PFP-vinyl sulfonate **143** underwent slow decomposition, but when a catalytic amount was used the reaction worked extremely well, and provided the desired product **145/146** in an excellent yield with a significantly reduced reaction time. The other regioisomer **147** was still obtained as a minor product, but even more pleasing was the disappearance of the de-brominated isoxazolidine **148**. In addition, one could also use 2,6-lutidine as the base in catalytic amounts, however DABCO was preferred as it was an easy-to-handle solid and provided a slightly better product ratio.

Entry	Base/Catalyst	Time	Temp.	Yield	Product ratio (145/146 : 148 : 147)
1	DABCO (1.5 eq.)	3 days	RT	-	-
2	DABCO (0.1 eq.)	18 hours	RT	89%	23:0:1
3	2,6-Lutidine (0.1 eq.)	18 hours	RT	93%	19:0:1

Table 16

Although a larger variety of tertiary amines ought to have been screened, we felt it was more beneficial to further explore the scope with efforts concentrated on synthesizing a range of isoxazoles. Work continued with the synthesis of a larger selection of PMB-nitrones, all in excellent yields, through the simple condensation reaction of hydroxylamine **135** with the desired aldehyde (Table 17).

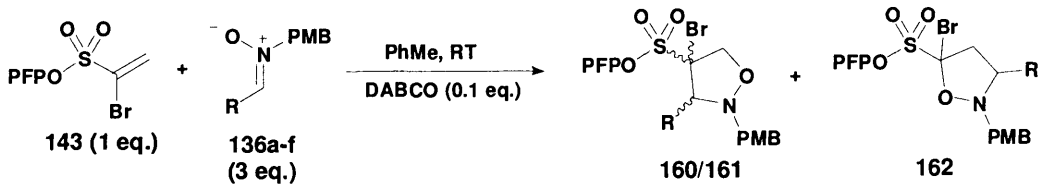


135 136a-f

Entry (136)	R	Yield (%)
a	Phenyl	96
b	4-Bromophenyl	80
c	4-Methoxyphenyl	92
d	4-Chlorophenyl	90
e	Cyclohexyl	95
f	Naphthyl	92

Table 17

Having established a set of optimum conditions of 1 eq. alkene, 3 eq. nitrone, and 0.1 eq. of DABCO in toluene at RT, this protocol was employed in the formal 1,3-dipolar cycloaddition to synthesize substituted isoxazolidines (Table 18).



143 (1 eq.) 136a-f (3 eq.) 160/161 162

Entry	R	Time	Yield (%)	Product ratio 160/161 : 162	Product ratio 160/161
a	Ph	18 hours	84	34 : 1	2 : 1
b	4-Methoxyphenyl	18 hours	94	65 : 1	4 : 1
c	4-Chlorophenyl	48 hours *	74	18 : 1	3 : 1
d	4-Bromophenyl	48 hours *	57	11 : 1	5 : 2
e	Naphthyl	48 hours *	85	19 : 1	2 : 1
f	Cyclohexyl	18 hours	68	4 : 1	-

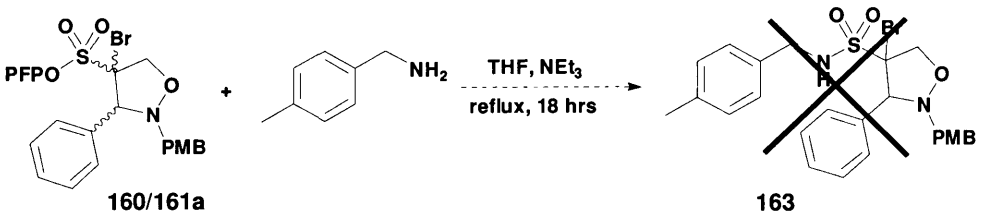
* = DCM added after 24 hours

Table 18

The reaction worked very well and furnished two isolable regioisomeric products which significantly favoured formation of **160/161** over **162**, in particular entry b. The 4C cycloadduct is obtained as an inseparable mixture of diastereoisomers, whilst the 5C cycloadduct is formed solely one diastereomer. The only exception was when cyclohexyl nitrone **136e** (entry f) was employed in the reaction; rather peculiarly the 4C cycloadduct was obtained as a single diastereoisomer. It is not understood how this happens, but further investigation is needed in order to establish whether this pattern occurs with other alkyl R groups. Yields in general were good but it can be seen that electron-donating aryl groups furnished slightly higher yields. A slightly prolonged reaction time was required for entries c, d, and e; this was presumably due to the reluctance of those particular nitrones to dissolve in toluene at room temperature, so DCM was added to aid dissolution. Consequently, this suggests that the reaction time reported is not a true reflection of rate of reaction and so more work is needed in screening for a more suitable solvent in the future.

Meanwhile aminolysis was attempted on isoxazolidine **160/161a**. It was anticipated that the reaction would require a greater length of time as aminolysis would not be occurring *via* the 'sulfene' intermediate, but instead through the direct displacement of a leaving

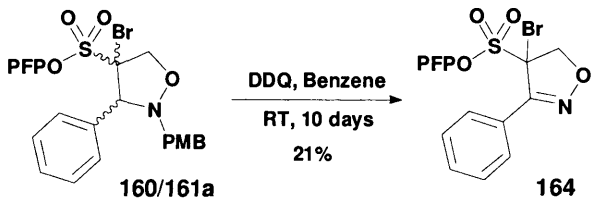
group. Nevertheless, each attempt has failed to yield the desired sulfonamide **163**, as the reaction generates a complex mixture of products which do not correspond to sulfonamide **163** (Scheme 76). The use of TBAC to aid the reaction through formation of an '*in situ*' sulfonyl chloride was also unsuccessful.[68]



Scheme 76

It appeared that the very bulky Br substituent was hindering the aminolysis reaction, and so DBU was added to remove HBr and install the first double bond of the isoxazole. However, rapid decomposition of starting material resulted on addition of DBU to the isoxazole.

As there does not seem to be a way of accessing the sulfonamide **163** for oxidation studies at present, oxidation was attempted on isoxazolidine **160/161a**. Hence, isoxazolidine **160/161a** was refluxed with DDQ in benzene,[99] and upon NMR analysis of the recovered product it was evident that isoxazoline **164** was generated along with α-bromo-PFP-vinyl sulfonate **143** through cycloreversion of the starting material. To minimise the cycloreversion a room temperature protocol was followed; this produced very similar results although we noted a slight improvement in the yield of isoxazoline **164** after purification (Scheme 77).



Scheme 77

2.5. Conclusion on Chapter 2

This study has established that PFP vinyl sulfonate is indeed a good dipolarophile towards 1,3-dipoles such as nitrones, which was shown by the relative ease by which a library of PFP isoxazolidines could be synthesized.

Aminolysis of these isoxazolidines, however, has been troublesome and progress in this area has been slow. The realisation that aminolysis proceeds with loss of stereochemical integrity at the α-sulfonyl carbon to give two often inseparable diastereoisomers has led to a new approach, which has so far proved to be quite successful in acquiring the required 4C *anti* cycloadduct. However, this new synthetic route also produces the 5C cycloadducts, and though this doesn't interfere with isolation of the 4C *anti* product, the yield will never be especially high because of these unwanted products. So after all, it seems the real solution is still to accomplish aminolysis of PFP isoxazolidines with retention of stereochemistry. Therefore, further work is required in this area.
Nonetheless, it has been demonstrated that this approach can be used to rapidly produce interesting functionalised isoxazolidine compounds.

More recently studies directed towards the synthesis of isoxazoles has met with limited success. Direct oxidation studies were generally unsuccessful since the isoxazoline obtained was reluctant to aromatise. When a leaving group (Br) is attached to the isoxazolidine ring to aid aromatisation, it appears not only to hinder the aminolysis reaction but also makes it more difficult to oxidise. Although this new route seems more promising, it does require further work on identifying conditions for effective aminolysis of the resultant PFP isoxazolidines.

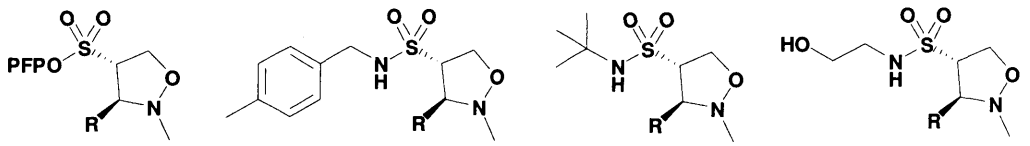
Our investigation did, however, uncover a novel tertiary amine catalysed [3+2] cycloaddition which still requires further investigation. Solvents, catalysts and mechanistic studies need to be explored, to further provide optimal conditions and fully understand how this reaction works. General applicability of this methodology to other electron-deficient olefins also remains to be explored. Overall the reaction remains in its infancy and has the potential to be an asset to the field of organocatalysis.

CHAPTER 3: R&D - Development of new small molecule inhibitors of DDAH, ADI, and HIV

The use of small molecules to probe a range of diseases by means of high-throughput screening is a concept widely used today in the identification of a lead-compound. Once a hit/target has been identified, further SAR is carried out in an attempt to improve activity and hence the effectiveness of the tools, through the design of compounds with enhanced molecular interactions and/or biological activity. This field of organic chemistry has been utilised efficiently in dissecting biological mechanisms of action, and of course underpins medicinal chemistry. Moreover, the small molecule approach has much merit because, where appropriate, it can provide a basis for the development of small molecule therapeutics. In this chapter our efforts toward developing generic small molecule tools for biological studies are presented.

3.1. Aim

Our investigations have thus far been directed towards the [3+2] cycloaddition of vinyl sulfonates and sulfonamides with nitrones (see Section 2.3.). This comprehensive study has been used to synthesise a range of heavily functionalised and structurally diverse small molecules, many of which may possibly possess biological activity (Figure 26).



103 124 127 133

where R = aryl, alkyl

Figure 26

In order to explore their potential in chemical biology these small molecules need to be screened against a multitude of enzymes. The main focus of this chapter in which we intend to apply to: (a) the arginine processing enzymes; dimethylarginine dimethylamino hydrolase (DDAH) and arginine deiminase (ADI), and (b) HIV-inhibition, in the hope of uncovering a novel series of small molecule inhibitors.

Dimethylarginine dimethylamino hydrolase (DDAH) and arginine deiminase (ADI) have a similar catalytic triad in their active sites as cysteine protease (see Section 3.2.5.),[116] and there has been some literature precedent on the inhibition of cysteine protease with sulfonates and sulfonamides by Roush *et al.* (Figure 27).[28, 30]

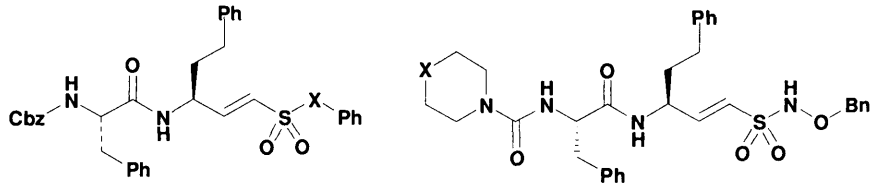


Figure 27

Given this precedent it was believed that there was some merit in screening some sulfonates and sulfonamides against these arginine processing enzymes. There are currently very few known inhibitors of DDAH and those are based primarily on analogues of arginine (see Section 3.2.3.). Moreover, there are no known inhibitors of ADI.

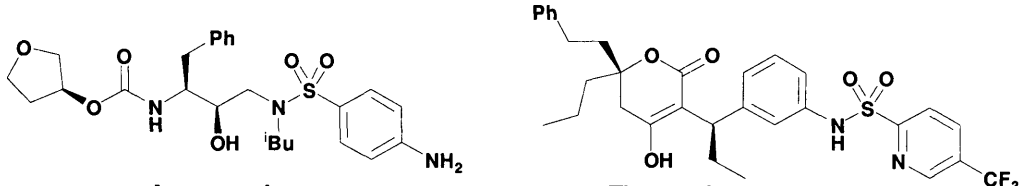


Figure 28

In addition, sulfonamide structures have found use in HIV therapy (Figure 28), in which for example amprenavir **5** and tipranavir **43** display an inhibitory effect on HIV protease.[36] Furthermore, HIV protease has been the target in the design of more potent sulfonamide inhibitors through the efforts of Hallberg *et al.*, and Stranix *et al.* (see Section 1.1.5.).[37, 38] Therefore, through a collaborative effort our compounds will also be evaluated against HIV, and herein the results of this investigation are presented.

3.2. Introduction: Control of arginine processing enzymes

DDAH and ADI are both important biological enzymes which are involved in processing arginine or arginine analogues into citrulline. Furthermore, citrulline plays an essential role in the nitric oxide (NO) cycle and in the production of adenosine triphosphate (ATP).[117, 118] Thus, it would be appropriate here to discuss the roles of DDAH and ADI in these biological processes (NO synthesis and ATP production respectively).

3.2.1 NO synthesis and control

Nitric oxide (NO) is an important biological messenger that is involved in cardiovascular, gastrointestinal, respiratory, and nervous system signalling. It is also known to regulate a variety of physiological processes such as vascular tone and immune system response. NO is biosynthesised endogenously from L-arginine *via* a family of enzymes known as nitric oxide synthase (NOS).[119] The reaction requires the action of several co-factors, specifically nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), calmodulin, tetrahydrobiopterin (BH_4) and oxygen to catalyse the formation of NO along with citrulline through the intermediate *N*-hydroxyl-L-arginine (Figure 29).[120, 121]

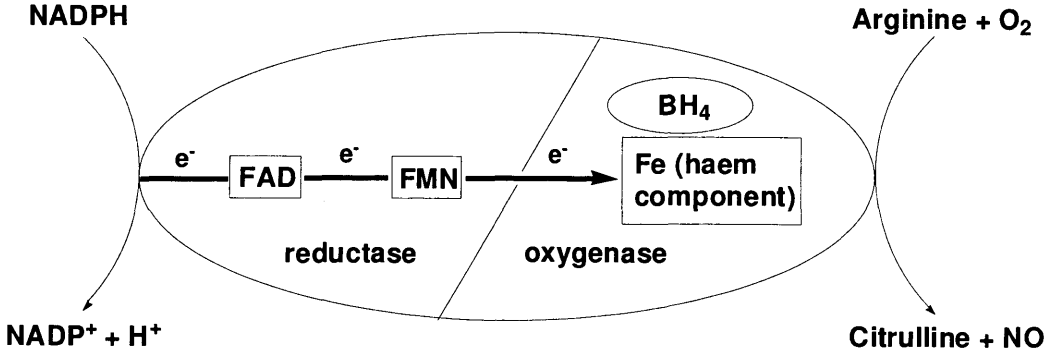


Figure 29

There are two main isoforms of NOS, an inducible Ca^{2+}/calmodulin-independent form (iNOS) and a constitutive Ca^{2+}/calmodulin-dependent type (cNOS), which can be further sub-divided into endothelial (eNOS) and neuronal (nNOS) isoforms. iNOS is present in activated macrophages and is only induced as a response to inflammatory mediators and bacterial endotoxins. eNOS is found in vascular endothelial cells and is responsible for smooth muscle relaxation, blood pressure, and platelet aggregation, whilst nNOS is located in neural tissue and plays a key role in neurotransmission. All 3

isoforms share a 50% sequence homology but display differences in their structure, their mode of action, and regulatory aspects.[125, 122] Associated with all isoforms is a Ca^{2+} binding protein (calmodulin), and when Ca^{2+} levels are high the Ca^{2+}/calmodulin complex binds to and activates eNOS/nNOS, which in turn initiates NO synthesis. iNOS is insensitive to Ca^{2+} levels as it already contains a Ca^{2+}/calmodulin complex bound to the enzyme, and as a result enables it to produce large quantities of NO when 'induced'.[121]

The formation of NO starts with the binding of acetylcholine to receptors on the endothelial cell membrane, which in turn opens a Ca^{2+} channel allowing extracellular Ca^{2+} to enter the cell (Figure 30). As Ca^{2+} levels rise, NO is produced through arginine by activation of NOS, and since NO is a gas it can permeate the plasma membrane and rapidly diffuse into neighbouring cells. NO's mechanism of action involves binding to the heme moiety of the enzyme soluble guanylate cyclase (sGC) and stimulating cyclic guanosine monophosphate (cGMP) synthesis. As cGMP levels rise, a cascade of reactions subsequently leads to muscle relaxation and therefore increased blood flow.[121, 123]

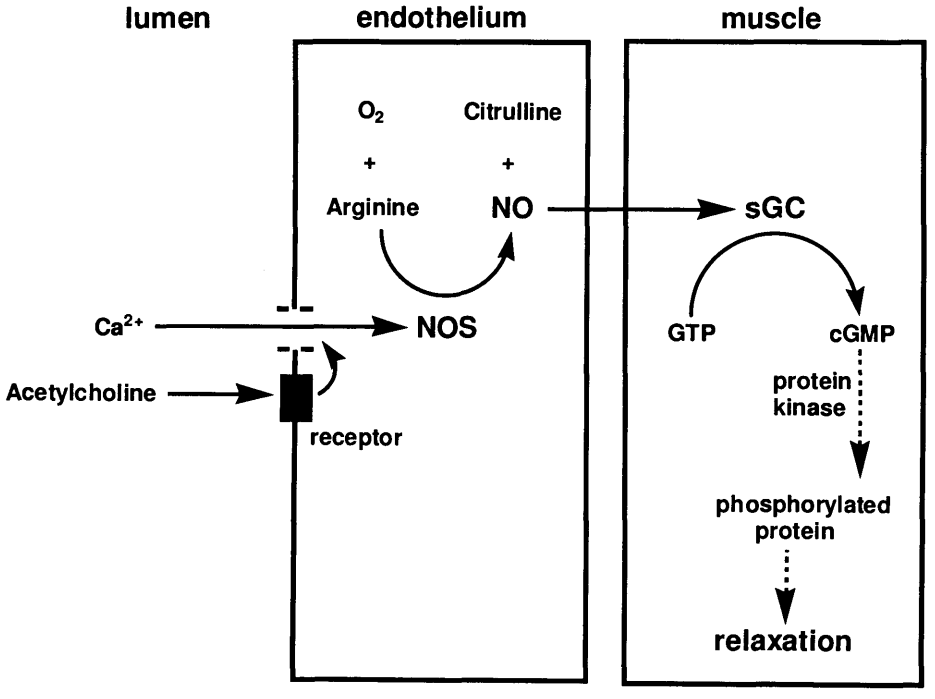


Figure 30

Although NO synthesis is important in biological systems, overproduction of NO has been linked to various diseases and conditions. Specifically, overproduction of NO by

iNOS is connected to septic shock, nociception, arthritis, asthma, ischaemia, and cerebral inflammation. nNOS over-activity is related to neurodegeneration during stroke, migraines, Parkinson's and Alzheimer's disease, while increased activity of eNOS is associated with acute inflammation in various tissues and diabetes.[123] Therefore, there is an obvious advantage for preventing or minimising NO production through the inhibition of NOS. Moreover, as each isoform of NOS possesses a different regulatory role, selective inhibition of each isoform is highly desirable.

The first NOS inhibitor identified was monomethylated L-arginine (L-NMMA) **165**, a naturally occurring amino acid that is present in cell cytosol, tissue, and plasma. Two other analogues of L-NMMA that are also present in submicromolar concentrations were named asymmetric dimethylated L-arginine (ADMA) **166** and symmetric dimethylated L-arginine (SDMA) **167** (Figure 31).[124, 125]

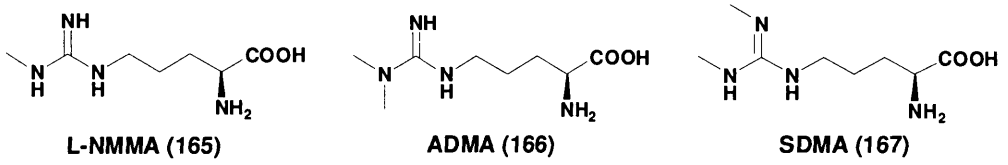


Figure 31

All 3 methylated arginine derivatives are synthesised endogenously by the action of the enzyme protein arginine methyltransferases (PRMTs) on arginine residues in proteins. The number of methyl groups that are transferred to the guanidine nitrogens of arginine, determines whether an asymmetric (type 1) or symmetric (type 2) methyl arginine is formed.[124, 125] However, only L-NMMA and ADMA are competitive inhibitors of NOS whilst SDMA is inactive; and furthermore, as mammalian concentrations of ADMA are ten times higher than L-NMMA, it is presumed this plays a greater role in NOS inhibition. Although since L-NMMA and ADMA inhibit all 3 isoforms of NOS, there is a greater need for inhibitors which are able to discriminate between each isoform.[125] A few examples of other NOS inhibitors that have been evaluated are shown in Figure 32.[123]

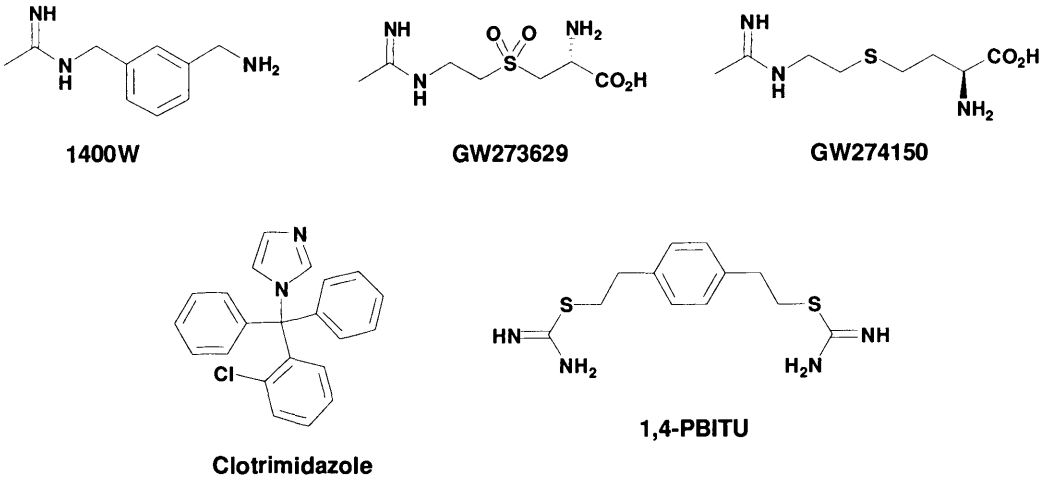


Figure 32

The substrate based inhibitor 1400W has shown great selectivity for iNOS over eNOS (10000 fold), and iNOS over nNOS (30 fold); however due to toxicity problems it has not been developed as a drug candidate. Toxicity of GW273629, GW274150, and the *bis*-isothiourea 1,4-PBITU also prevented their development as selective NOS inhibitors. Clotrimidazole does not exhibit toxicity, but there are issues with its NOS isoform selectivity *in vivo*, hence limiting its therapeutic potential.[123]

As there appear to be very few potent and selective clinically viable NOS inhibitors available, new strategies for NO inhibition need to be investigated. Recently it has been discovered that control of NO levels could be possible through regulation of the endogenous methylarginines L-NMMA and ADMA.[124]

3.2.2. Control of NO *via* the ADMA/DDAH pathway

It is well known that NO generation can be competitively inhibited by the endogenous methyl arginines L-NMMA and ADMA. Therefore, control of L-NMMA and ADMA levels could provide an indirect route for the modulation of NO levels. L-NMMA and ADMA concentrations are further governed by the enzyme dimethylarginine dimethylamino hydrolase (DDAH), which catalyses their catabolism into citrulline and monomethyl or dimethylamine respectively (Figure 33). SDMA is unaffected by DDAH and is cleared from our system by urinary excretion.[123-125]

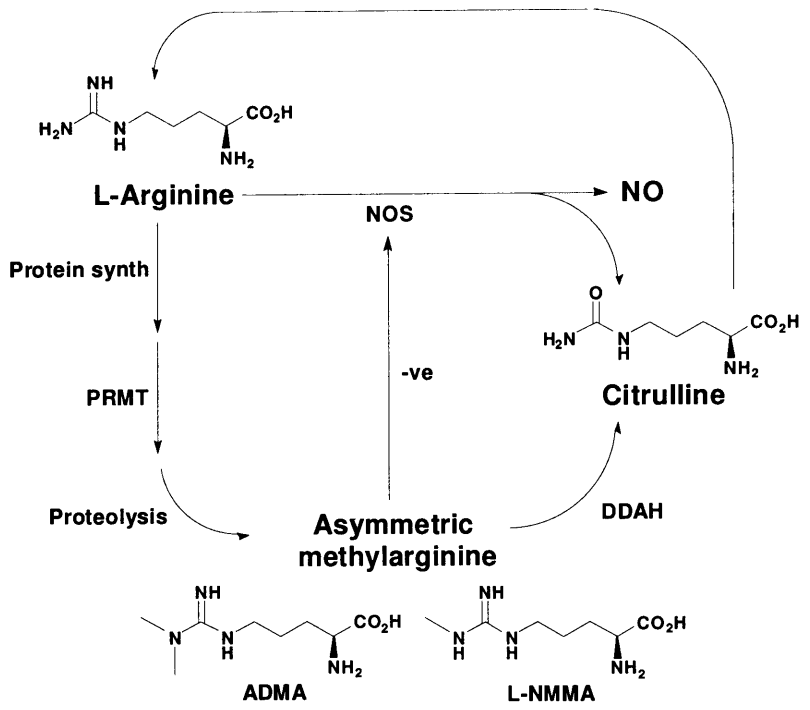


Figure 33

As a result, through the inhibition of DDAH the resultant rise in ADMA and L-NMMA levels will exert a negative effect on NOS. Hence, pathological levels of NO will be reduced, alleviating the symptoms of NO overproduction. Leiper *et al.* discovered in 1999 that there are two isoforms of mammalian DDAH: DDAH 1 and DDAH 2. The authors report that DDAH 1 shares 62% homology with DDAH 2 through their amino acid sequence, and both isoforms inhibit L-NMMA and ADMA but not SDMA. DDAH 1 is present primarily in the brain, liver, kidney, skeletal muscle, and pancreas, organs which are generally associated with nNOS. DDAH 2 is expressed predominantly in highly vascularised tissues such as the heart, placenta, and kidney, indicative of cells governed by eNOS.[126, 127, 128] Hence, it could be assumed that through the selective inhibition of one isoform of DDAH over the other, selective inhibition between NOS isoforms could also be achieved. This indirect method for controlling excess NO levels over a more direct NOS inhibitor also offers an added advantage whereby NO production will not be completely blocked, as it is generally accepted that ADMA and L-NMMA inhibition of NOS is not likely to exceed 30%.[123] The danger associated with complete NO inhibition is that decreased levels of NO are also linked to renal failure, cardiovascular and neurological diseases.[125] Thus, a controlled level of NO inhibition without disrupting NO-mediated processes is highly desirable and this is more likely *via* DDAH inhibition.

3.2.3. Inhibitors of DDAH

Apart from the endogenous inhibitors of DDAH which comprise L-citrulline, L-homocysteine, *S*-nitroso-L-homocysteine, and Zn^{2+}, there are very few known literature examples of synthetic inhibitors for DDAH (Figure 34).[128] Vallance *et al.* discovered the first selective but non-potent inhibitor, 4124W, with an IC_{50} of 1.5mM in 1996 (Figure 34).[125]

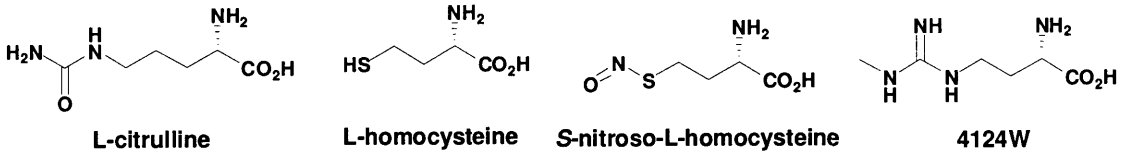


Figure 34

4124W, a chain shortened L-NMMA analogue, was able to inhibit DDAH with no direct affect on NOS. However, this substrate was not capable of discriminating between each isoform of DDAH, and this, coupled with its low potency, limited its usage as an indirect NO inhibitor. Conversely, it did provide a good lead molecule from which further substrate based inhibitors could be designed.[125, 129]

More recently in 2005, Rossiter *et al.* developed secondary analogues of 4124W as more potent inhibitors for DDAH. It was from their library of compounds synthesized that 3 good inhibitors of DDAH with IC_{50} values < 30μM were identified (Figure 35).[129]

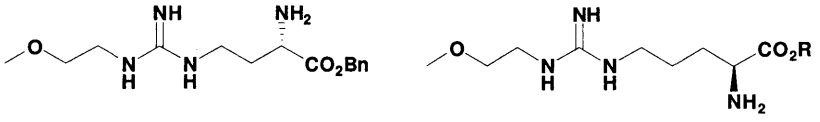
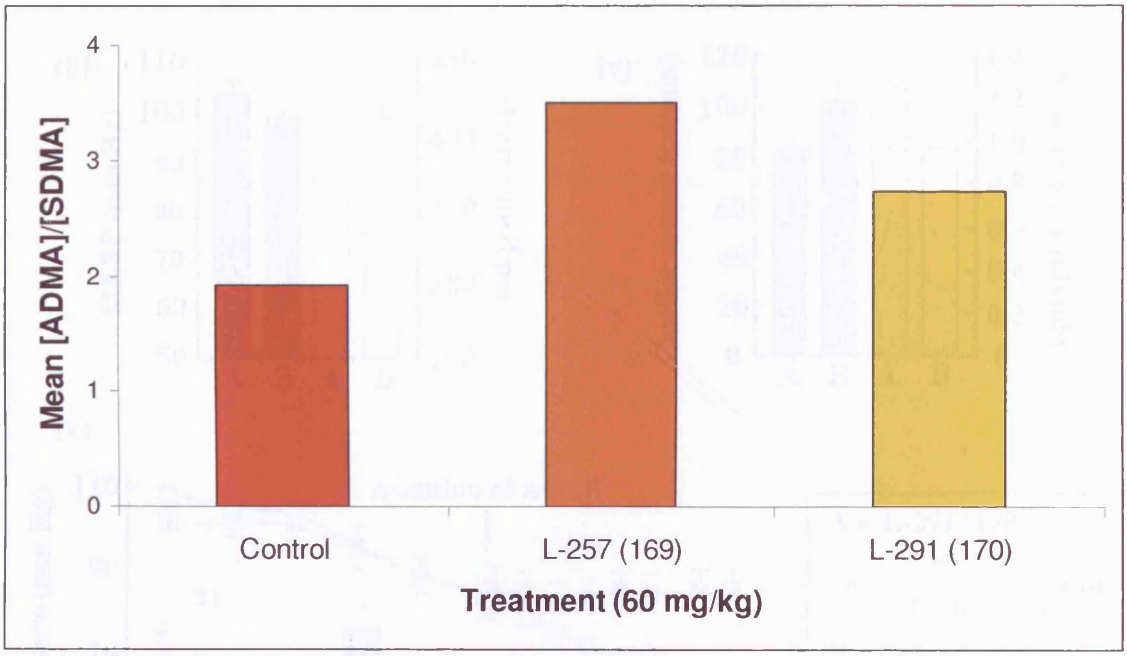


Figure 35

Common to all three inhibitors was the presence of a 2-methoxyethyl group on the terminal guanidine nitrogen. However, whilst *ex vivo* testing reveals that all 3 inhibitors are selective for DDAH over each NOS isoform, these compounds lack DDAH isoform specificity. Hence, it has not been possible to establish the relative importance of DDAH 1 and 2 in the regulation of L-NMMA and ADMA levels.[129] Nonetheless, the most promising inhibitors identified (**169** and **170**), were used to determine if DDAH inhibition was retained *in vivo*.[130]

As inhibition of DDAH should give rise to an elevated concentration of ADMA, a preliminary study was conducted and involved giving rats a 60mg/kg intravenous injection of each inhibitor. The efficiency of DDAH activity after 4 hours (i.e. the mean ADMA/SDMA ratio) was recorded and in comparison to saline treated rats, it was shown that both inhibitors were well tolerated and gave rise to raised blood ADMA levels (Table 19). A more in-depth time course study was conducted with inhibitor **170**, and revealed that after a 60mg/kg intravenous dose of **170** the ADMA concentration was significantly raised after 30 mins peaking at around 2 hours (approx. 1.5μM), this was followed by a steady decrease in ADMA concentration (approx. 1.1μM at 5 hours).[129, 130]



Experiment (4 hours)	[ADMA], μM	[SDMA], μM	Mean [ADMA]/[SDMA]
Control	0.665 ± 0.023	0.350 ± 0.026	1.93
L-257 (**169**)	1.292 ± 0.124	0.374 ± 0.036	3.50
L-291 (**170**)	0.870 ± 0.092	0.318 ± 0.013	2.73

Table 19

Having shown that inhibition of DDAH occurred *in vivo* and that it was a key regulator of ADMA concentrations, the functional relevance of DDAH *in vivo* was probed with methyl ester **170** (Figure 36). As DDAH is an indirect modulator of NO synthesis and effectively vasodilation and vasoconstriction, the effect of 100μM L-291 (170) on mouse aortic rings was examined in the presence of phenylephrine and acetylcholine

(Figure 36 i and ii). The authors report that the respective blood vessel contraction and relaxation in response to increased concentrations of stimuli is indicative of reduced levels of endogenous endothelial NO.[130]

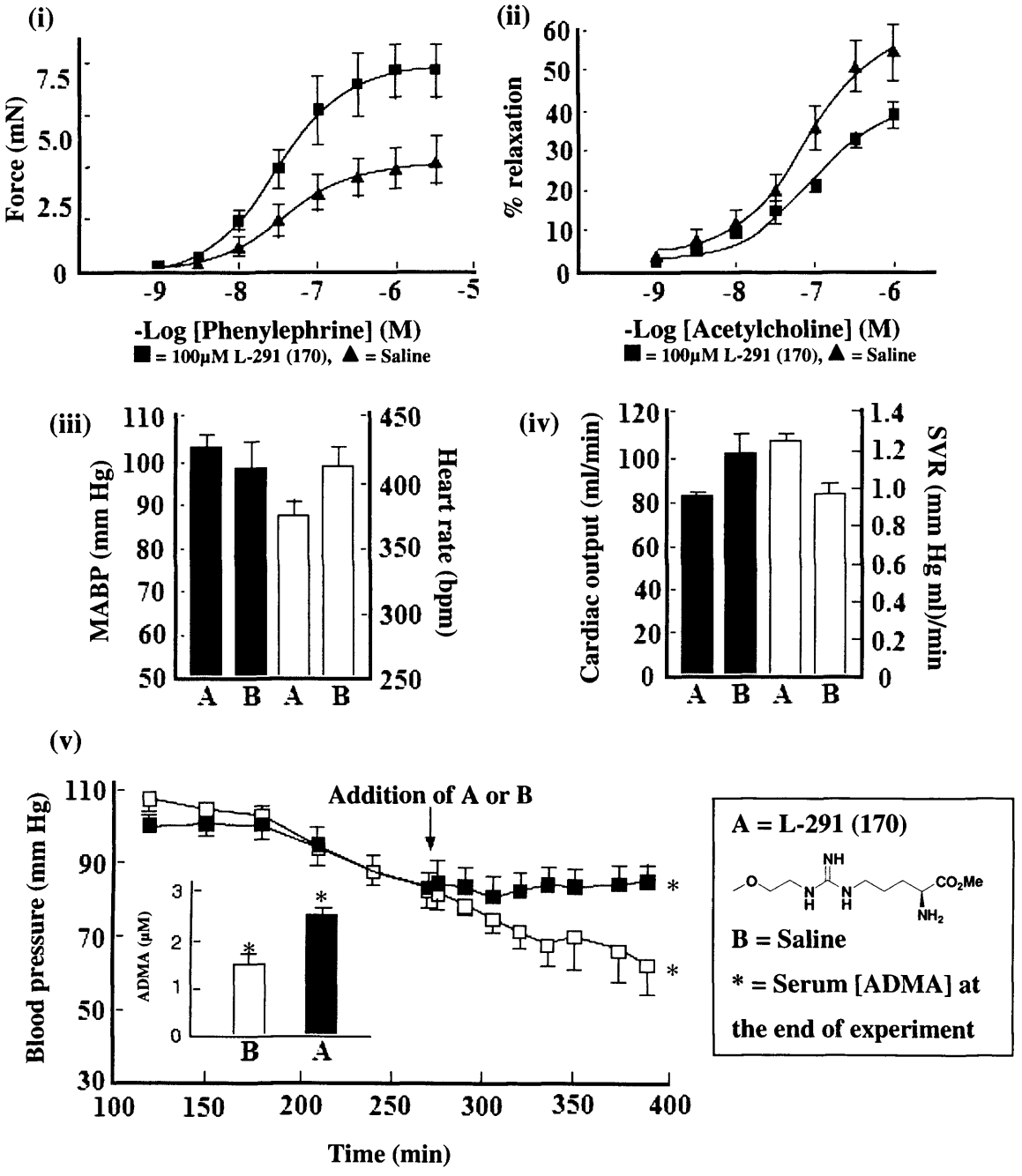


Figure 36

In addition, the hemodynamic effects resulting from chemical DDAH inhibition *in vivo* was explored (Figure 36 iii and iv). A 30mg/kg injection of **170** was administered to rats, and after 2.5 hours a resulting rise in systemic vascular resistance and mean arterial blood pressure, and decreased heart rate and cardiac output was observed. Finally, when iNOS expression was induced in rats, the rapid onset of hypotension brought about

through increased NO production, was directly alleviated upon treatment with a DDAH inhibitor **170** (Figure 36 v). Therefore, as a result of these *in vivo* studies the authors have been able to demonstrate, that a loss in DDAH activity or raised ADMA level is associated with an increased cardiovascular risk and endothelial dysfunction.[130]

In 2005 Stone and co-workers developed an irreversible small molecule inhibitor of DDAH (Figure 37). 2-Chloroacetamidine **171** was reported to exhibit a K_i of 3.1 ± 0.8mM, however activity was not limited to DDAH, as peptidylarginine deiminase was also inactivated (K_i = 20 ± 5mM).[131] More recently, virtual screening has been employed by Selwood *et al.* as an investigative tool in the discovery of DDAH inhibitors without the need for high throughput screening. By utilising the crystal structure of DDAH, a series of computer aided processes were applied (namely physicochemical filtering, virtual screening, and hit analysis) to a database of 308,000 compounds.[132] Compounds with the indolylthiobarbituric acid skeleton were identified as potential inhibitors, and subsequently a variety of commercially available analogues were tested for activity. Of these, **172** and **173** displayed good activity against DDAH, with **173** the most potent DDAH inhibitor known to date (Figure 37). The authors also reported that synthesis of the most active compounds **172** and **173** was carried out, and that they maintained biological activity, and thus confirming their results.[132]

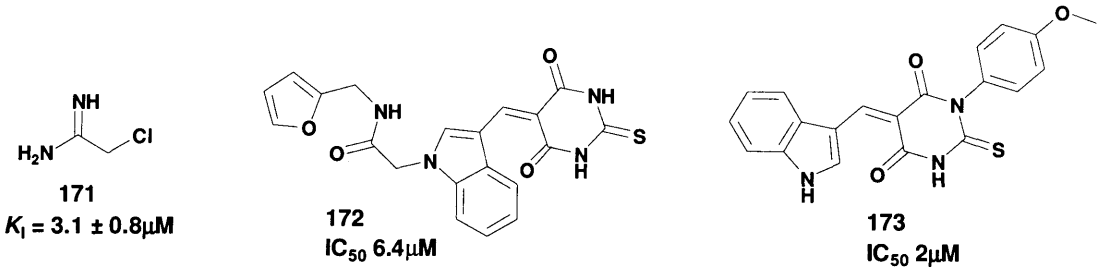
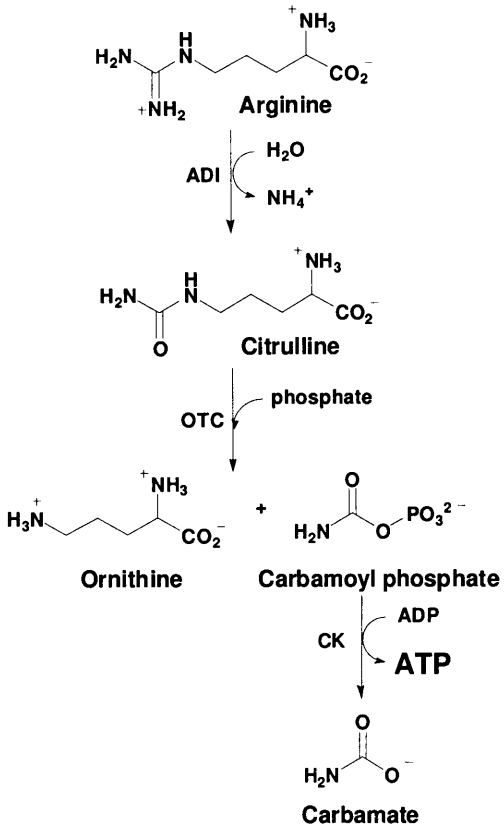


Figure 37

3.2.4. ADI

ADI belongs to the amidotransferase family of enzymes and is ultimately responsible for the irreversible catabolism of arginine to citrulline and ammonia.[132, 133] This key reaction is the first step of the arginine dihydrolase pathway, which plays a fundamental role in the generation of ATP under anaerobic conditions (Scheme 78). The citrulline by-product from arginine hydrolysis undergoes further degradation into ornithine and carbamoyl phosphate, in a reaction catalysed by ornithine transcarbamylase (OTC). The

final step involved in ATP production is the carbamate kinase (CK) catalysed phosphorylation of adenosine diphosphate (ADP) by carbamoyl phosphate.[134]



Scheme 78

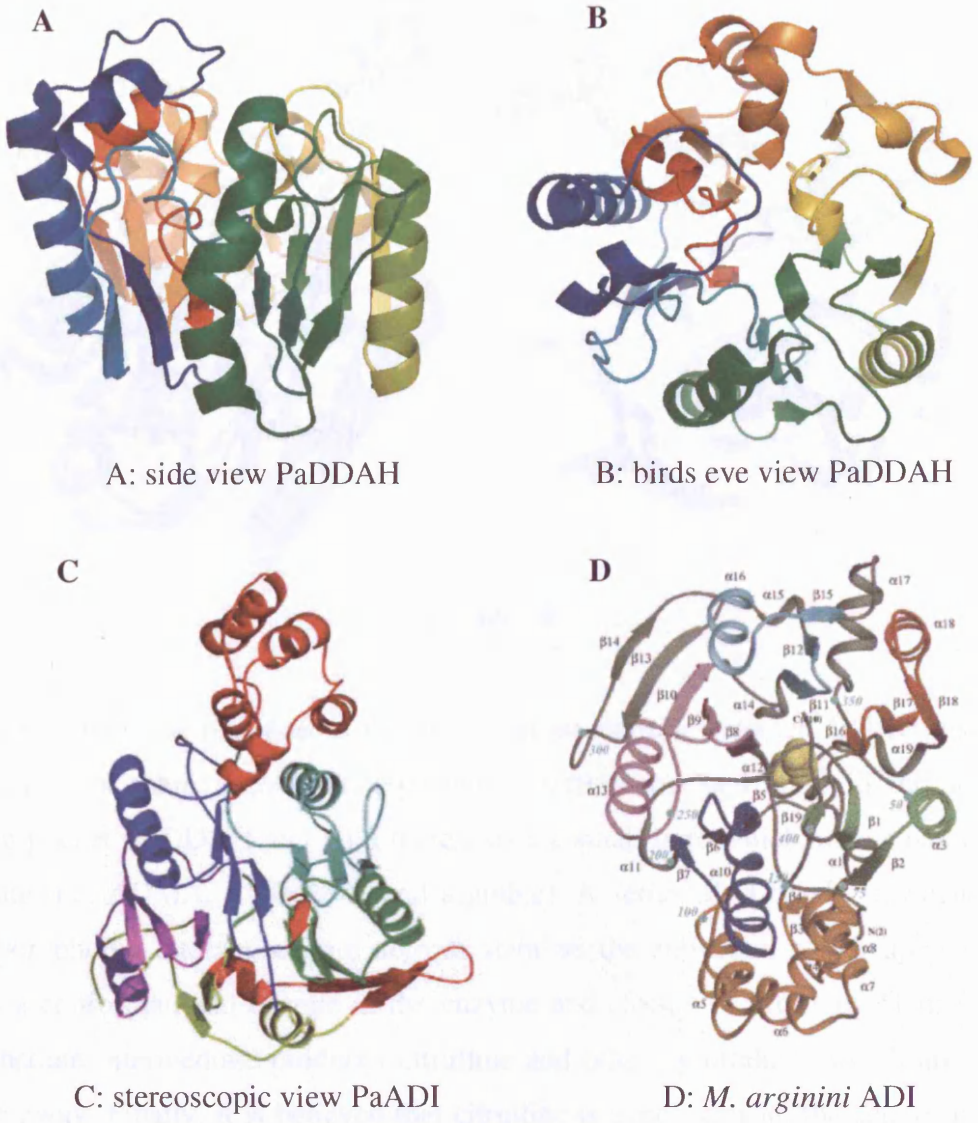
ADI is found only in prokaryotes and the primitive eukaryote *Giardia intestinalis*, thus is largely responsible for supplying these organisms with a source of energy (ATP).[135] For this reason, inhibition of ADI presents itself as a possible antibacterial/anti-protozoal drug target for treatment against various pathogens. *Giardia intestinalis* in particular is a prevalent intestinal pathogen that causes symptoms of giardiasis, vomiting, and diarrhoea. The rising emergence in drug resistant strains of *Giardia intestinalis* means that current treatments are of limited expediency, and consequently ADI represents an attractive target for chemotherapeutic intervention in the treatment of giardial infection.[135] More recently it has been reported that ADI may also play a part in apoptosis,[136] angiogenesis,[137] and act as a tumour growth inhibitor.[138] In addition, ADI processing of intestinal arginine can have a negative effect on NO production, due to competition for endogenous arginine between ADI and NOS. Therefore, the action of NOS and NO mediated processes may be blocked, and Thomas *et al.* suggested that this can be advantageous in neutralising the toxic effects of tumour necrosis factor-α (TNF-α) and endotoxins.[133, 139]

Although inhibition/control of ADI exhibits the potential to be of enormous benefit in the treatment of various diseases, there are currently no known inhibitors of ADI. Therefore, there exists a pressing need for the development of ADI inhibitors, so that the role of ADI (and consequently arginine catabolism) in various disease states could be better understood.

3.2.5. Structural and mechanistic insight into DDAH and ADI

DDAH and ADI are both very similar enzymes that catalyse the hydrolysis of arginine by the breaking of the same equivalent guanidino C-N bond. Leiper *et al.* identified that there were considerable similarities between the protein sequences of DDAH I/II and ADI. They report that ADI derived from *Pseudomonas putida* shared 48% homology with human DDAH I and 31% to DDAH II. Additionally, a 70% level of homology with each DDAH isoform could be observed by considering a 72-residue domain within the protein sequence (residues 123-194 DDAH I and 121-192 DDAH II).[126]

Comparisons of the X-ray crystal structures of both enzymes reveal that there are further similarities between DDAH and ADI. The crystal structure of DDAH from *Pseudomonas aeruginosa* (Pa) was first elucidated by McDonald *et al.* in 2001;[140] those of ADI from *Pseudomonas aeruginosa* and *Mycoplasma arginine* followed simultaneously in 2004 by Herzberg *et al.*[134] and Das *et al.*[133] respectively (Figure 38).



A: side view PaDDAH

B: birds eve view PaDDAH

C: stereoscopic view PaADI

D: *M. arginini* ADI

Figure 38

From these crystal structures it was revealed that the core structure of both enzymes is made up of 5 repeats of a ββαβ motif, presenting a barrel-shaped structure that encloses the active site. Furthermore, it has been revealed that the active site of both enzymes contains a similar catalytic triad comprising a cysteine-histidine-glutamine/asparagine unit, which can be seen by superimposition of their active site residues (Figure 39 B).[125, 133, 134, 140]

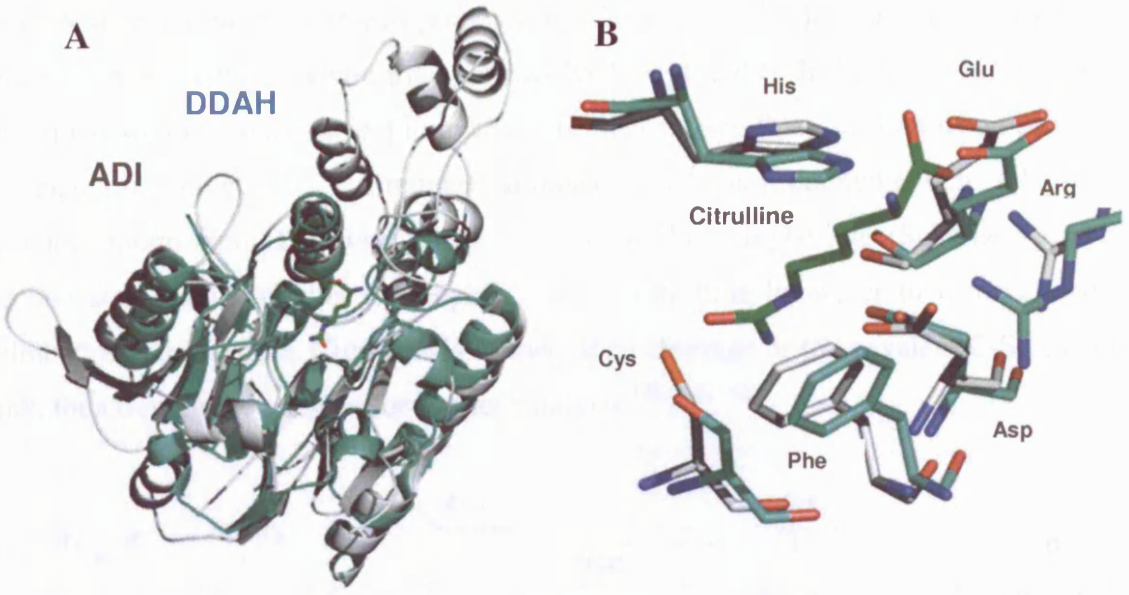


Figure 39

It has been reported that due to the structural similarities between DDAH and ADI, these enzymes share a common enzymatic reaction mechanism.[128] In the substrate binding pocket of DDAH and ADI there exists a small pore which allows entry of the substrate (i.e. ADMA, L-NMMA, and arginine). A series of H-bonds, covalent links, and hydrophobic interactions are able to stabilise the substrate, which upon binding causes a conformational change in the enzyme and closure of the pore. Hydrolysis of the substrate intermediate produces citrulline and other by-products which are able to diffuse away. Finally, it is believed that citrulline is expelled from the active site upon another conformational change of the enzyme from a closed to an open state.[125, 133]

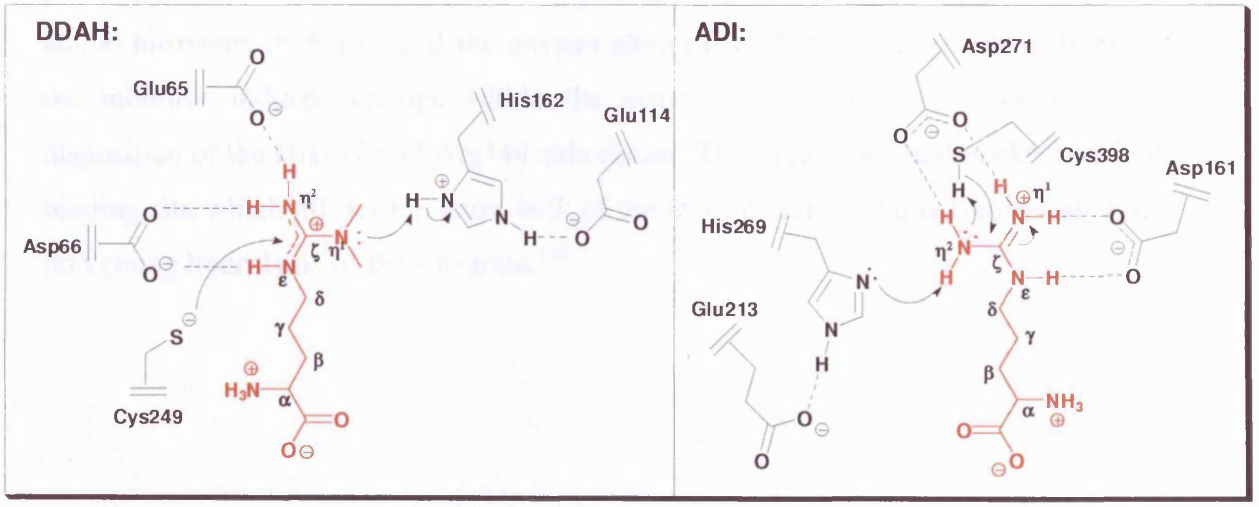
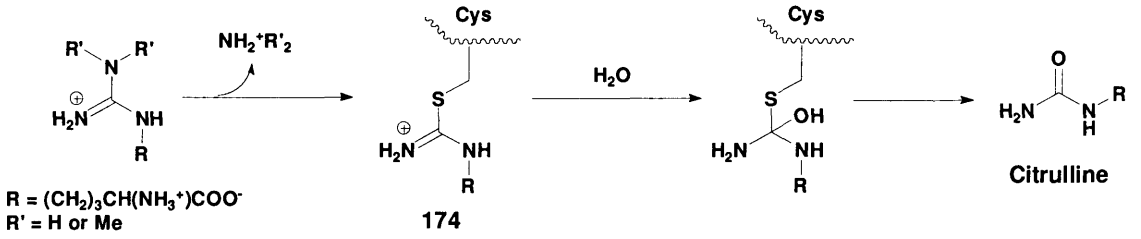


Figure 40

A more detailed mechanism was proposed by Vallance *et al.* and Das *et al.*, whereby all three residues of the catalytic triad are involved (Figure 40). In both DDAH and ADI, the initial step involves nucleophilic attack of the cysteine thiol on the carbon centre of the guanidino moiety.[133, 140] A tetrahedral transition state is generated which collapses to provide thiouronium **174** with release of ammonia or alkylamine (Scheme 79). The second step entails another nucleophilic attack, this time by water to form a second tetrahedral intermediate. Citrulline is formed upon cleavage of the covalent C-S cysteine link, thus freeing the enzyme for further catalysis.[125, 141, 142]



Scheme 79

More recently, the crystal structures of the DDAH inhibitor L-257 **169** and citrulline bound to active site of DDAH-1 have been resolved by McDonald *et al.* (Figure 41).[130] Diagram A represents the experimental electron density that **169** occupies inside the human DDAH-1 active site, and also reveals that a water molecule is co-bound within the cavity. Diagram B highlights the ability of both L-257 **169** (cyan) and citrulline (yellow) to anchor to the DDAH active by an H-bonding interaction with Asp78. In addition, it shows that the aliphatic backbones of both compounds are in close proximity to Phe75, and that an additional H-bonding interaction is present between the amino-nitrogens to Asp72 and the oxygen atom of residue 29. A notable difference is the inhibitor induced change within the active site, as shown by the change in disposition of the His172 and Arg144 side chains. This creates a small pocket within the binding site which allows the extra bulk of the ether moiety to be accommodated, thus preventing hydrolysis of the substrate.[130]

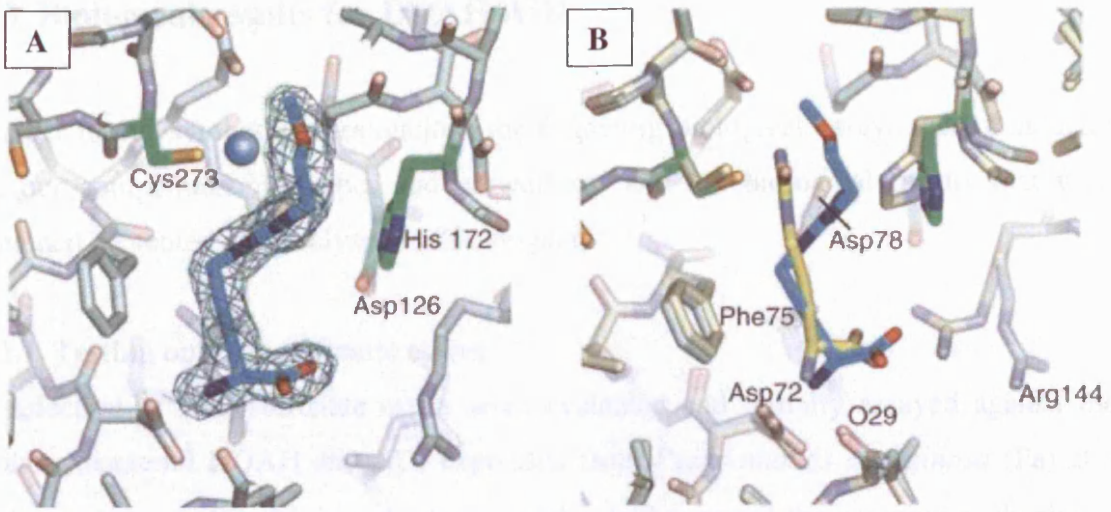


Figure 41

It has been reported that cysteine proteases, such as those belonging to the papain family, contain a three residue catalytic triad in their active sites comprising of cysteine-histidine-asparagine.[125, 143, 144] This displays analogy with the catalytic triad observed with DDAH and ADI (cysteine-histidine-glutamine/asparagine), which means cysteine protease could potentially exhibit a comparable enzymatic reaction mechanism. In fact, it is known that cysteine proteases catalyse the hydrolysis of peptide (amide, ester and thiol ester) bonds *via* the action of a nucleophilic cysteine thiolate. Two tetrahedral transition states are generated *en route* to the product with concomitant release of the enzyme, which suggest that this mechanistic pathway is much akin to that displayed by ADI and DDAH.[144]

As sulfonates and sulfonamides have been successfully utilised by Roush *et al.* in the inhibition of cysteine protease (see Section 1.1.5.),[28, 30] it was envisaged that the related sulfonates and sulfonamides synthesised previously (see Section 2.3.3. and 2.3.5.) could be of potential interest as DDAH/ADI inhibitors. Accordingly, a range of products was biologically evaluated against the aforementioned enzymes and the results of these endeavours presented.

3.3. Biological results for DDAH/ADI

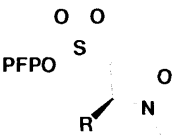
Further to our synthetic investigations the following biological assays were conducted on our compounds by Leiper and co-workers, and the biological results that were obtained presented and analysed in this chapter.

3.3.1. Testing on PFP sulfonate esters

A selection of PFP sulfonate esters were evaluated and initially assayed against the isolated bacterial DDAH and ADI expressed from *Pseudomonas aeruginosa* (Pa) at a concentration of 500 μM, in order to establish whether or not the compounds displayed any activity.

The assays run by Leiper *et al.* were performed by incubating our compounds with the required enzyme for a period of 5 minutes, thus allowing sufficient time for the inhibitor to bind to the enzyme. The substrate (ADMA for DDAH and L-arginine for ADI) is then added, and a measure of their conversion into citrulline is recorded with the aid of colour developers (see Supplementary data). If the compound is a good inhibitor less citrulline is produced, and as a result the intensity of the colour displayed is reduced. The colour displayed is then compared against that of a control experiment (i.e. no inhibitor) and recorded as a percentage.

It was pleasing to see that at a concentration of 500 μM all compounds showed greater than 40% inhibition, with a small selection reaching 90%. The compounds were subjected to further testing at a much lower concentration of 50 μM and the results are shown in Table 20.



		% inhibition at 50 μM	
Entry	**R**	**DDAH**	**ADI**
1	Ph	30	14
2	*p*-NO_2Ph	**76**	**35**
3	*p*-Allyloxy-Ph	44	14
4	*p*-MeOPh	19	-
5	*o*-FPh	10	-
6	*m*-ClPh	36	-
7	*p*-ClPh	28	-
8	*o*-BrPh	1	9
9	*m*-BrPh	**58**	27
10	Naphthyl	**56**	33
11	2-Furyl	**63**	27
12	2-Br-Furyl	**65**	**38**
13	Cyclohexyl	40	26
14	Cyclopropyl	41	15

- = compounds not tested

Table 20

It was encouraging to see that a handful of PFP sulfonate esters retained a good level of inhibition, with a greater effect seen against DDAH over ADI at this concentration. There is no clear SAR, although it was noticed that *ortho* substituted aromatics (entries 5 and 8) gave poor results while furyl R groups (entries 11 and 12) showed good levels of inhibition. The most active compounds, entries 2, 9, 10, 11, and 12 were taken and further evaluated to provide IC_{50} values (Table 21).

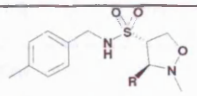
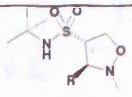
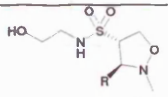
Entry	**R**	**IC_{50} μM (DDAH)**	**IC_{50} μM (ADI)**
2	*p*-NO_2Ph	21	74
9	*m*-BrPh	58	-
10	Naphthyl	32	167
11	2-Furyl	34	246
12	2-Br-Furyl	16	103

Table 21

IC_{50} values show that entries 2, 9, 10, 11, and 12 still retained good activity against DDAH, while entries 2 and 12 show moderate activity against ADI. However, as the first inhibitors of ADI identified, this will provide a platform on which further design of more potent small molecule inhibitors of ADI will be based.

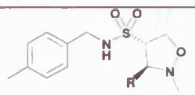
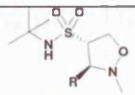
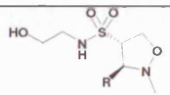
3.3.2. Testing on sulfonamides

Having revealed that PFP sulfonate esters exhibit an inhibitory effect on DDAH and ADI, an analogous study on sulfonamides was conducted. As previously, all compounds' inhibitory effects were initially evaluated at 500 μM and then further scrutinised at 50 μM. It soon became apparent that sulfonamides showed a comparable level of inhibition at 500 μM with PFP sulfonate esters. However, the level of inhibition at 50 μM was not maintained, except for in a few examples (Table 22 and 23).

	DDAH % inhibition at 50 μM					
						
R	Entry	DDAH	Entry	DDAH	Entry	DDAH
Ph	1	**46**	14	15	27	23
p-NO_2Ph	2	16	15	21	28	**50**
p-MeOPh	3	14	16	0	29	21
o-FPh	4	15	17	1	30	**33**
o-ClPh	5	7	18	12	31	-
m-ClPh	6	18	19	0	32	-
p-ClPh	7	10	20	1	33	23
o-BrPh	8	3	21	9	34	**38**
m-BrPh	9	18	22	21	35	25
p-BrPh	10	2	23	25	36	-
Naphthyl	11	22	24	-	37	-
2-Furyl	12	26	25	-	38	-
2-Br-furyl	13	**38**	26	**32**	39	-

- = compounds not tested

Table 22

	ADI % inhibition at 50 μM					
						
R	**Entry**	**ADI**	**Entry**	**ADI**	**Entry**	**ADI**
Ph	1	24	14	10	27	9
p-NO_2Ph	2	8	15	9	28	23
p-MeOPh	3	5	16	0	29	10
o-FPh	4	26	17	10	30	22
o-ClPh	5	0	18	15	31	-
m-ClPh	6	35	19	13	32	-
p-ClPh	7	28	20	9	33	2
o-BrPh	8	9	21	0	34	**35**
m-BrPh	9	**62**	22	23	35	13
p-BrPh	10	16	23	0	36	-
Naphthyl	11	**65**	24	-	37	-
2-Furyl	12	9	25	-	38	-
2-Br-furyl	13	6	26	17	39	-

- = compounds not tested

Table 23

Overall, it seemed that while PFP sulfonate esters produced better results against DDAH, sulfonamides showed better promise against ADI. Additional patterns did emerge from within the 3 sets of sulfonamides tested, in that sulfonamides possessing the 4-methylbenzylamine moiety provided better results with ADI especially entries 9 and 11 (Table 23), while sulfonamides processing the ethanolamine moiety gave better inhibition against DDAH, entries 28 and 34 (Table 22). Furthermore, sulfonamides with the *tert*-butyl amine moiety were generally poor for both ADI and DDAH, possibly resulting from the restricted conformation of the compound due to the bulk of *tert*-butyl group; thus suggesting that this group would not be suitable in further inhibitor design. Other general patterns that could be spotted were the poor levels of inhibition observed for the 4-methylbenzyl and *tert*-butyl sulfonamides containing *ortho* functionalised R groups. Interestingly, this effect was not observed with the ethanolamine sulfonamides. The *p*-MeOPh, *p*-ClPh, and *p*-BrPh groups also exhibited very modest inhibitory effects regardless of the amine moiety present, and therefore would be excluded from future SAR studies.

IC_{50} values were determined for some of the most active sulfonamides, with entry 2 showing the greatest potency against DDAH and entry 1 with ADI (Table 24).

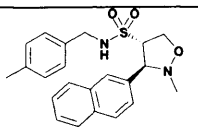
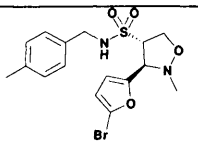
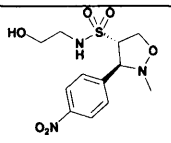
Entry	R	IC_{50} μM (DDAH)	IC_{50} μM (ADI)
1		-	69
2		11	-
3		35	-

Table 24

Through examination of the IC_{50} values (Table 21 and 24), it is possible to infer that retention of the 2-bromofuryl and *p*-NO_2Ph R groups might be appropriate for the future design of inhibitors for DDAH. This conclusion is drawn from the observation that both PFP sulfonate esters and sulfonamides which incorporate these two groups have the shown the most promising IC_{50} values of < 35μM.

3.3.3. Nature of DDAH inhibition

Having identified a novel series of active PFP sulfonate esters and sulfonamides, the nature of the inhibition against DDAH was investigated by considering the reversibility and time-dependence.

In supplementary experiments it was shown that the inhibitory effect of PFP sulfonate ester **103o** could be somewhat reversed upon increasing the concentration of ADMA, and therefore indicating that our compounds exert their effect through competitive inhibition (Figure 42 A). The great excess needed to reverse inhibition suggests that the inhibitor has a greater binding affinity for the active site than ADMA. In a time-dependent experiment, isoxazolidine **103d** maintained a near constant level of inhibition over a period of 80 minutes at a concentration of 10μM (Figure 42 B). This confirms that these inhibitors do not bind irreversibly to the active site *via* a covalent interaction, as an increase in the time-dependent inhibition is normally seen as the inhibitor becomes increasingly irreversibly bound over time.

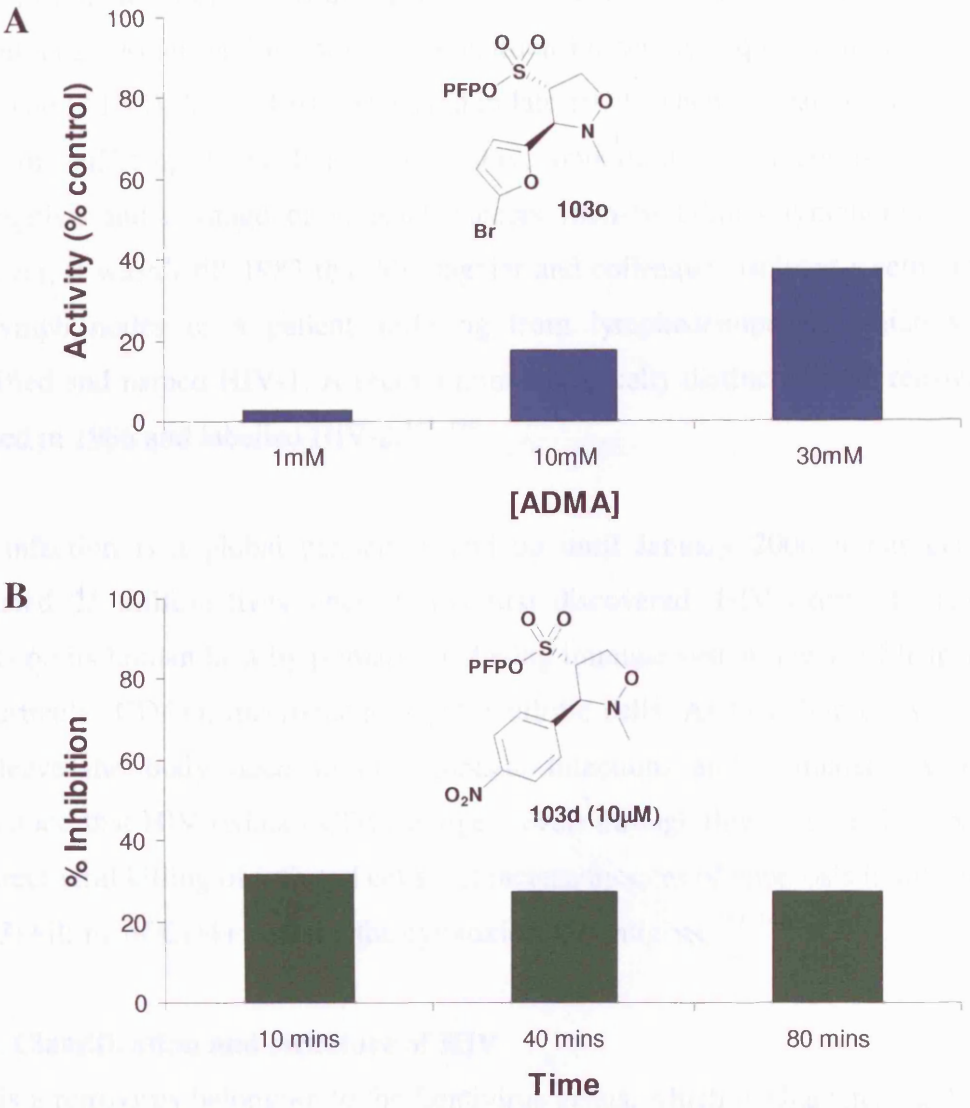


Figure 42

In conclusion, a new class of small molecule inhibitors of DDAH and ADI have been revealed which bind reversibly to the active site. However, there still remains a lot to discover about their mode of action, and how these compounds sit in the enzyme active site. Therefore, future work involves identifying compounds with increased potency *via* a combination of SAR, molecular modelling and X-ray crystallography.

Biological investigations of our PFP sulfonate esters and sulfonamides were continued with their evaluation against HIV.

3.4. Introduction: HIV

Human immunodeficiency virus (HIV) is a prevalent retrovirus that leads to failure of the immune system, and eventually a condition known as acquired immunodeficiency syndrome (AIDS). It was first discovered in late 1970s when the patients displaying the signs of suffering from lymphadenopathy, opportunistic infections (i.e. retinitis, meningitis), and a range of unusual cancers (non-Hodgkin's lymphoma) appeared. However, it wasn't till 1983 that Montagnier and colleagues isolated a retrovirus from the lymph nodes of a patient suffering from lymphadenopathy, which was later identified and named HIV-1. A second immunologically distinct human retrovirus was isolated in 1986 and labelled HIV-2.[145, 146]

HIV infection is a global pandemic, and up until January 2006 it has claimed an estimated 25 million lives since it was first discovered. HIV exerts its detrimental effects on its human host by primarily reducing immune system levels of helper T cells (in particular CD4+), macrophages, and dendritic cells. As host immunity is lowered this leave the body open to opportunistic infections and ultimately AIDS. It is understood that HIV reduces CD4+ antigen levels through three mechanistic pathways: (1) direct viral killing of infected cells, (2) increasing rates of apoptosis in infected cells, and (3) killing of CD4+ cells by the cytotoxic CD8 antigens.[147, 148]

3.4.1. Classification and structure of HIV

HIV is a retrovirus belonging to the Lentivirus genus, which is characterised by a slow unremitting disease that targets hematopoietic cells (lymphocytes and macrophages). Lentiviruses are RNA-containing viruses that convert its RNA into doubly stranded DNA by means of a virally-encoded reverse transcriptase enzyme after infection. This enables the viral genome to become integrated into the hosts DNA and replicated by the host, spreading the infection to healthy cells. It is also possible that following infection the virus remains in a latent state, and normal cellular function is maintained until it becomes active.[146, 148]

There are two known types of HIV infection, HIV-1 and HIV-2. HIV-1 is the more virulent form with a higher rate of transmissibility, whilst HIV-2 displays a lower level of virulence. In addition, HIV-2 causes a slower decline in CD4+ T-lymphocyte levels compared to HIV-1, and exhibits a prolonged period of asymptomatic infection with a considerably lower mortality rate.[145]

The structure of HIV is approximately 120nm in diameter and is generally spherical in nature (Figure 43). It comprises a viral protein core surrounded by a matrix whose purpose is to maintain the integrity of the viral particle. This is all encased in a viral envelope constructed from two phospholipid layers, and embedded in this is a series of proteins known as envelope glycoproteins (*env*). These *env* glycoproteins exist on the particle surface as gp41/gp120 trimers, which form complexes that enable binding and attachment of the virion particle to the target cell.[147, 149]

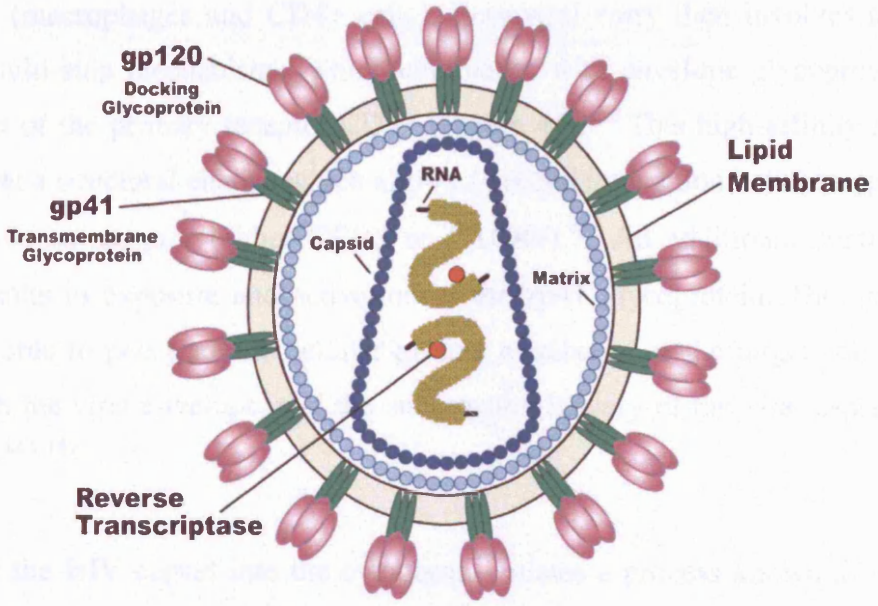


Figure 43

The viral protein core is composed of a shell of capsid protein which encompasses two single strands of RNA in close association with nucleocapsid proteins and a string of viral-encoded enzymes (reverse transcriptase, integrase, protease, and ribonuclease). The RNA genome is responsible for coding the HIV's nine genes required for infectivity.[147] Of these nine genes, three of these HIV encoded proteins include *pol*, and the two structural proteins *gag*, and *env*. *Pol* is responsible for coding the enzymes reverse transcriptase, integrase, and protease; while *Gag* codes for the polyproteins that form the matrix, capsid and nucleocapsid. The *Env* gene codes for gp160, a protein that is eventually broken down to give gp120 and gp41, the glycoproteins that comprise the envelope polyproteins. In addition, there remain six other genes that collectively make up the accessory proteins, and these are *tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu* (*vpx* in HIV-2). These regulatory proteins are responsible for promoting the HIV infection of cells, facilitating replication, and the ability to cause disease.[145, 147]

3.4.2. HIV-1 replication cycle

The rise in HIV research over the last 25 years has led to a better understanding of the HIV-1 life cycle. Although there still remains a lot to discover about each fundamental process involved in HIV-1 replication, its mode of action can be divided into 3 distinct stages: (1) binding and entry into cell, (2) replication and transcription, and (3) assembly and release (Figure 44).[157]

The life cycle of HIV-1 begins with adsorption of the virus particle to the surface of a target cell (macrophages and CD4+ cells). Retroviral entry then involves a series of intricate multi-step mechanisms, which commence with envelope glycoprotein gp120 recognition of the primary receptor CD4+ (Figure 44).[150] This high-affinity interaction brings about a structural change which allows a second interaction between gp120 and a β-chemokine co-receptor (either CCR5 or CXCR4).[151] An additional conformational change results in exposure and activation of the gp41 glycoprotein. The gp41 fusion peptide is able to penetrate the cellular plasma membrane of the target cell triggering fusion with the viral envelope, and the subsequent delivery of the viral capsid into the cytoplasm.[149, 152]

Release of the HIV capsid into the cytoplasm initiates a process known as uncoating, whereby the viral core undergoes a partial and progressive disassembly generating reverse-transcription complexes (RTCs). It is here that the enzyme reverse transcriptase catalyses the formation of a reverse transcribed doubly stranded viral DNA intermediate (vDNA). This vDNA in close association with the viral proteins: reverse transcriptase (RT), matrix protein (MA), integrase (IN), and viral protein R (Vpr) form a pre-integration complex (PIC) that travels across the cytoplasm to the cell nucleus.[149, 153]

The mechanism of PIC nuclear import or how it is regulated is not well understood; however, there have been several postulations which involve the viral proteins MA, IN, and Vpr. The most widely accepted mechanism however, is that the PIC and its components are karyophilic, recruiting the necessary cellular transport proteins required to cross the nuclear pore. It is believed MA, IN, and Vpr all contain nuclear localisation signals (NLS) that interact with importin, an important nucleocytoplasmic shuttling receptor that has been implicated in HIV-1 PIC nuclear import.[149, 154]

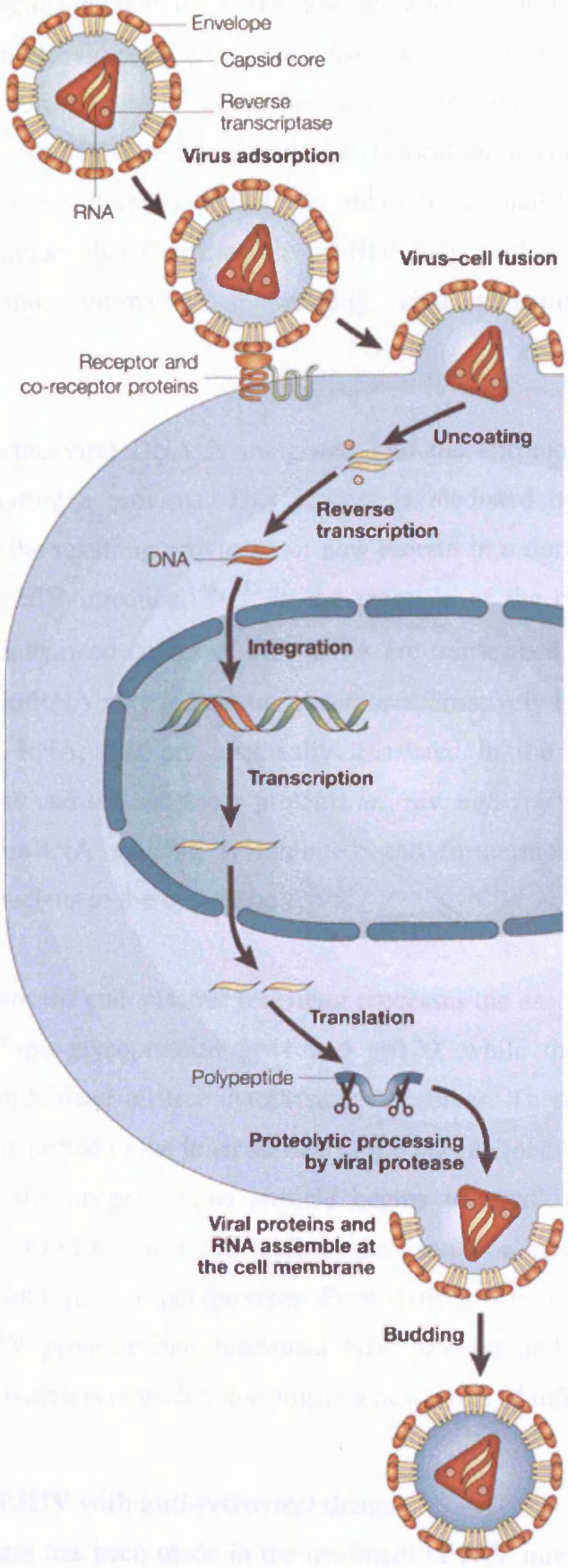

Envelope
Capsid core
Reverse transcriptase
Virus adsorption
RNA
Virus–cell fusion
Receptor and co-receptor proteins
Uncoating
Reverse transcription
DNA
Integration
Transcription
Translation
Polypeptide
Proteolytic processing by viral protease
Viral proteins and RNA assemble at the cell membrane
Budding

Figure 44

An additional distinguishing feature of HIV is its remarkable ability to replicate in non-dividing cells. Most retroviruses (i.e. gamma-retroviruses) gain entry into the nucleus of proliferating cells during mitosis when the nuclear membrane breaks and divides. However, HIV can also utilise an active nuclear translocation mechanism to gain access to the nucleus of non-proliferating cells. Given that only a small number of T-cells in the human body divide, this characteristic of HIV may explain why it has a high replication rate, thus ultimately, maintaining viral transmission and disease pathogenesis.[155]

Inside the nucleus the viral DNA is integrated into the chromosomal DNA of the infected cell generating a provirus. This process is mediated by the viral enzyme integrase (IN), and the resulting provirus can now remain in a dormant stage or go on actively promoting HIV infection.[149, 153] In the presence of the cellular transcription factor NF-κB, the integrated copies of HIV DNA are transcribed to mRNA by RNA polymerise II. This mRNA may remain unspliced or alternatively be spliced to provide smaller strands of RNA, that are eventually translated in the cytoplasm into the structural protein *env* and the accessory proteins *tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu*. As *rev* levels accumulate mRNA splicing is inhibited, and furthermore mediates mRNA transport from the nucleus to the cytoplasm.[145, 156]

Here in the cytoplasm the endoplasmic reticulum processes the *env* polyprotein (gp160) into the two envelope glycoproteins gp41 and gp120, while the *gag* and *gag-pol* polyproteins are synthesised on free cytoplasmic ribosomes. These glycoproteins and polyproteins are transported to the inner surface of the plasma membrane along with the viral RNA, where the progeny virus particle begins to 'bud' from the host cell. Complete 'budding' from the host cell leads to the formation of an immature virion, containing the *gag* and *gag-pol* polyproteins. Proteolytic processing of these enclosed polyproteins by HIV protease into functional HIV proteins and enzymes creates a mature HIV virion, which is now able to instigate a new cycle of infection.[145, 147]

3.4.3. Treatment of HIV with anti-retroviral drugs

Considerable progress has been made in the treatment of HIV infection in the last ten years, however there remains at present no cure or vaccine for HIV. Current HIV chemotherapy known as highly active anti-retroviral therapy (HAART) involves using anti-retrovirals agents to delay the onset of HIV by suppressing/inhibiting its replication

cycle.[147, 157] However, treatment needs to be continued life-long, and once treatment is interrupted viral replication restarts and the symptoms of HIV infection resume. The problems associated with current anti-retroviral drugs are the toxic side effects they exhibit from long-term usage; for example rash, nausea, and severe suppression of hematopoesis.[158] Furthermore, due to its extremely high mutation rate, the ability of the virus to develop drug resistance to these agents is a major issue, and additionally the virus is able to penetrate the brain, a site not readily accessible to drugs.[159] Therefore, there is a continual need for the improvement and development of new highly specific non-toxic anti-retroviral drugs.

Potential biological targets for therapeutic intervention during key stages of the HIV replication cycle comprise inhibition of virus fusion, the co-receptor (CXCR4 or CCR5), reverse transcriptase, integrase, and protease. However, it is primarily a combination of reverse transcriptase inhibitors (nucleoside reverse-transcriptase inhibitor (NRTI) and non-nucleoside reverse-transcriptase inhibitor (NNRTI)) and protease inhibitors that form the basis of HAART.[157, 160] The recommended course of therapy includes a minimum of three active drugs, which constitute two NRTIs in combination with either a NNRTI or a protease inhibitor. Its ultimate goal is to suppress viral genome replication at the earliest point of its life cycle, by using a combination of as many antiviral drugs as a patient can tolerate, ideally targeting different stages of viral replication. This strategy's success is based on the idea that if a mutation were to occur and rendering one drug ineffective, then the other two will still be able to suppress replication. HAART was first introduced in 1996, and its success has seen a massive decline in the morbidity and mortality of HIV-infected patients.[157, 161, 162]

The first anti-HIV drugs developed were reverse transcriptase inhibitors, of which two different classes exist; the nucleoside reverse-transcriptase inhibitors (NRTIs) and non-nucleoside reverse-transcriptase inhibitor (NNRTIs).[163]

The NRTIs inhibit transcription of viral RNA into DNA by preventing chain elongation of viral DNA, and therefore no viral DNA is inserted into the host cell DNA and virus replication stops (Figure 45).[157] To successfully synthesise viral DNA the naturally occurring deoxynucleoside building blocks must first be converted into their active metabolite deoxynucleotide triphosphate (dNTP), *via* three consecutive phosphorylation reactions. These phosphorylated metabolites are then incorporated into DNA by RT, and subsequently chain elongation is permitted upon the addition of further dNTP

metabolites.[145, 157] NRTIs are essentially nucleotide mimetics that lack the necessary 3'-OH group, which is required to synthesise a 5'-3' phosphodiester bond with the next deoxynucleotide in order for DNA chain elongation to continue. They act as competitive inhibitors for the natural substrate dNTP which once incorporated into DNA, ultimately leads to chain termination and inhibition of viral DNA synthesis.[157, 164]

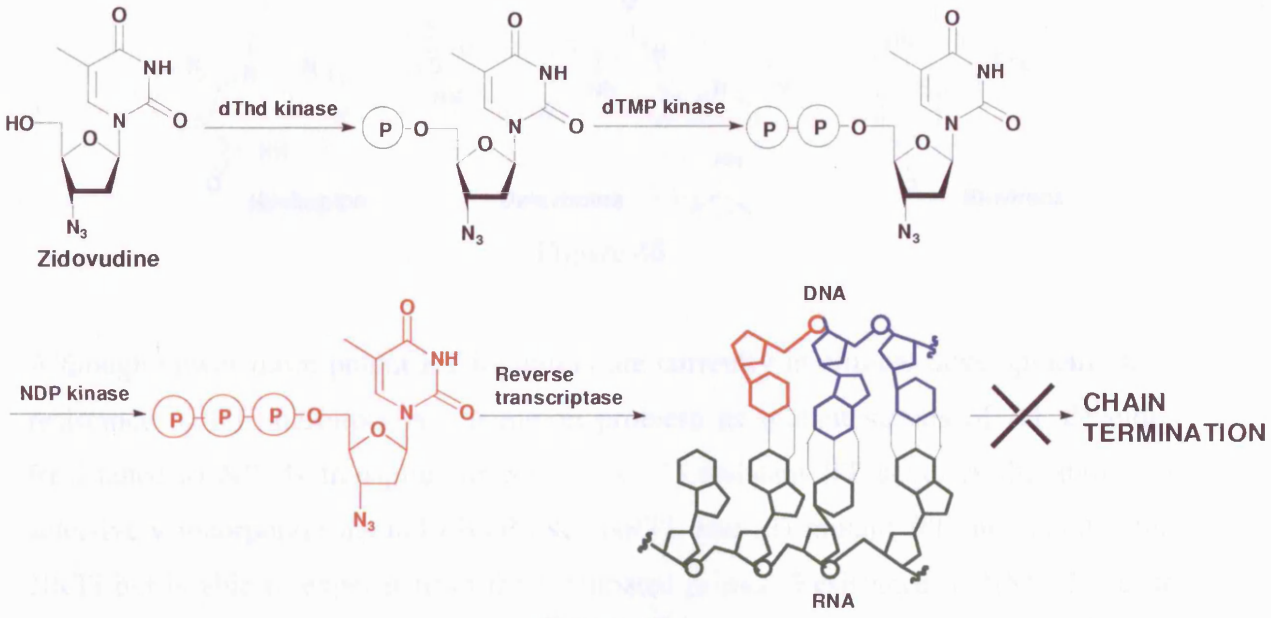


Figure 45

There are currently seven such NRTIs that have been effectively employed in the treatment of HIV (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine); a few of these are shown in Figure 46.[161]

NNRTIs were first discovered in 1990 and are classified as non-competitive inhibitors. They inhibit DNA polymerisation by binding to a hydrophobic allosteric binding pocket near the RT active site, and inducing a conformational change in the enzyme that blocks DNA synthesis. There are at present 3 such NNRTIs that have been approved for the treatment of HIV: nevirapine, delavirdine, and efavirenz (Figure 46).[157, 165]

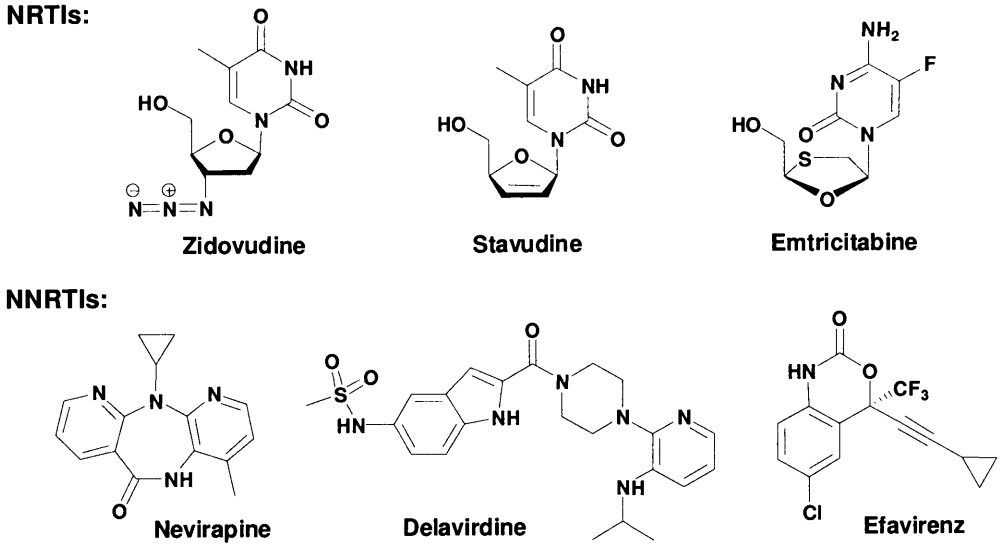


Figure 46

Although newer more potent RT inhibitors are currently in clinical development, drug resistance to RT inhibitors is a common problem as mutant strains of RT develop. Resistance to NRTIs transpires in two ways: (1) resistant RT acquires the ability to selectively incorporate natural dNTP over NRTI, and (2) mutant RT incorporates the NRTI but is able to expel it from the terminated primer. Resistance to NNRTIs occur when mutations in RT impede binding of the inhibitor to its allosteric active site.[145, 162]

The other constituent of highly active anti-retroviral therapy (HAART) involves the use of HIV protease inhibitors. These agents attack HIV later in its life cycle, by targeting a protease used by HIV to proteolytically cleave polyproteins into smaller structural or functional viral proteins, which mature and assemble into new infectious virions. In particular, *gag* and *gag-pol* polyproteins are cleaved to produce the structural capsid proteins, nucleocapsid, and the retroviral enzymes (RT, protease, and IN).[157, 166]
In total there are ten different protease inhibitors currently available for the treatment of HIV (saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir, and darunavir), and of these all are considered peptidomimetics except for tipranavir (examples shown in Figure 47). This is because within the structure of each protease inhibitor is a non-scissile hydroxyethylene moiety, which is able to mimic the readily hydrolysable peptide bond cleaved by HIV protease. Thus, the inhibitor competes with the *gag-pol* polyproteins for the protease active site, and as a result of its binding renders the enzyme inactive, thereby preventing the maturation and assembly of infectious viral particles.[157, 166]

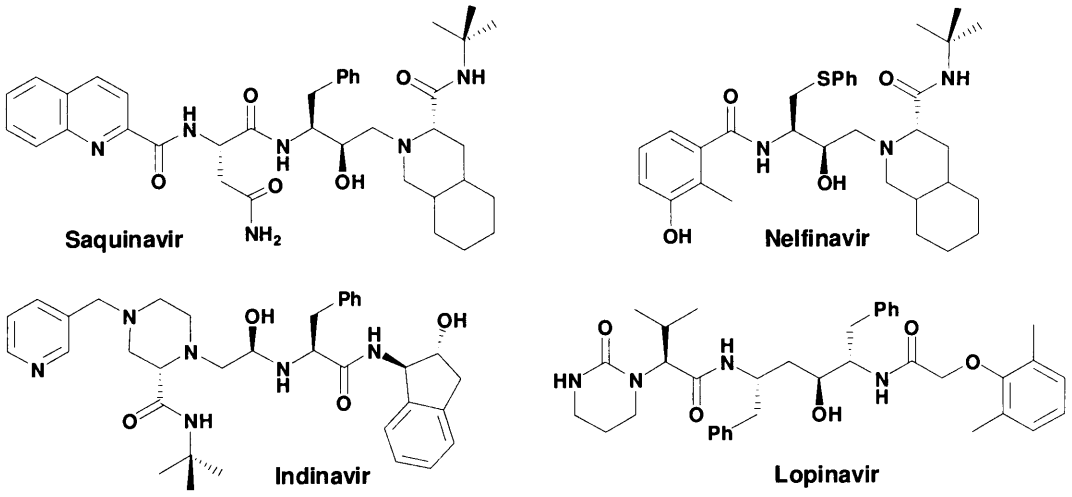


Figure 47

HIV cell entry has also been considered as a prime target for HIV inhibition, especially at the stages of cell fusion and co-receptor binding. The recently registered HIV fusion inhibitor enfuvirtide, is a 38 amino acid peptide that binds to and inhibits gp41, the glycoprotein responsible for mediating fusion of the viral envelope with the plasma membrane.[164, 167] Additionally, in 2007 a drug candidate that targeted the CCR5 chemokine co-receptor was also approved. Maraviroc was launched as a selective antagonist that bound to CCR5 preventing the HIV infection of target cells (Figure 48).[157, 161] These cell entry inhibitors, while not the basis of first-line therapy, provided additional benefits when supplemented with HAART, especially in patients developing drug resistance to existing anti-retrovirals.

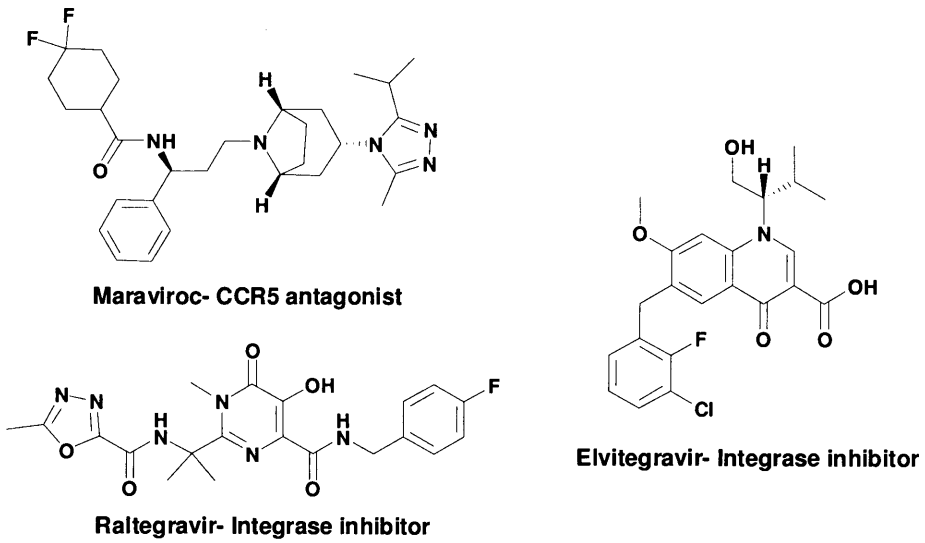


Figure 48

Integration of viral DNA into the host genome is another fundamental process during the HIV replication cycle, which has drawn much interest in recent years as an attractive target for HIV chemotherapy. Consequently, the integrase enzyme that mediates such a process has been explored as a novel target for inhibition. Accordingly, as a result of drug discovery and development this has seen the advent of two HIV integrase inhibitors, raltegravir and elvitegravir (Figure 48).[157, 168]

In conclusion HIV is a deadly and lethal infection which was previously thought of as untreatable, but through a better understanding of the viral life cycle and the introduction of HAART, HIV can now be regarded as a chronic infection that can be carefully controlled. Although a vaccine is considered the most promising cure for HIV it still remains elusive, and the continual design and development of more potent less toxic HIV inhibitors is essential for the incessant management of HIV infection. Having revealed that sulfonamides play a role in HIV chemotherapy (see Section 1.1.5.), it is of interest to see if our sulfonamides and their PFP sulfonate precursors display any biological activity against HIV.

3.5. Biological results for HIV

3.5.1. Testing on PFP sulfonate esters and sulfonamides

Through a collaborative study with Fassati *et al.* a small collection of PFP sulfonate esters and sulfonamides were randomly selected and evaluated against HIV, using a screening protocol based on the infection of human T-cell lines with HIV-1 vectors. Their biological evaluation of our compounds has led to the discovery of a previously uncharacterised family of small molecules that show anti-HIV activity.

In order to determine whether our compounds were able to reduce HIV infection; Fassati *et al.* incubated lymphocytic T-cells with our PFP sulfonate esters and sulfonamides for 6 hours, and then infected them with HIV-1. After 24 hours a measure of the HIV-1 infection reduction displayed against untreated HIV-1 cells was recorded as a percentage, by detecting GFP (green fluorescent protein) expression with the aid of fluorescent activated cell sorting (FACS) analysis. The higher the percentage exhibited by each compound the better its ability to act as an antiviral. Their preliminary results

are shown in Figure 49. A total of 24 compounds were screened against the HIV-1 vector pCSGW at an initial concentration of 250μM.

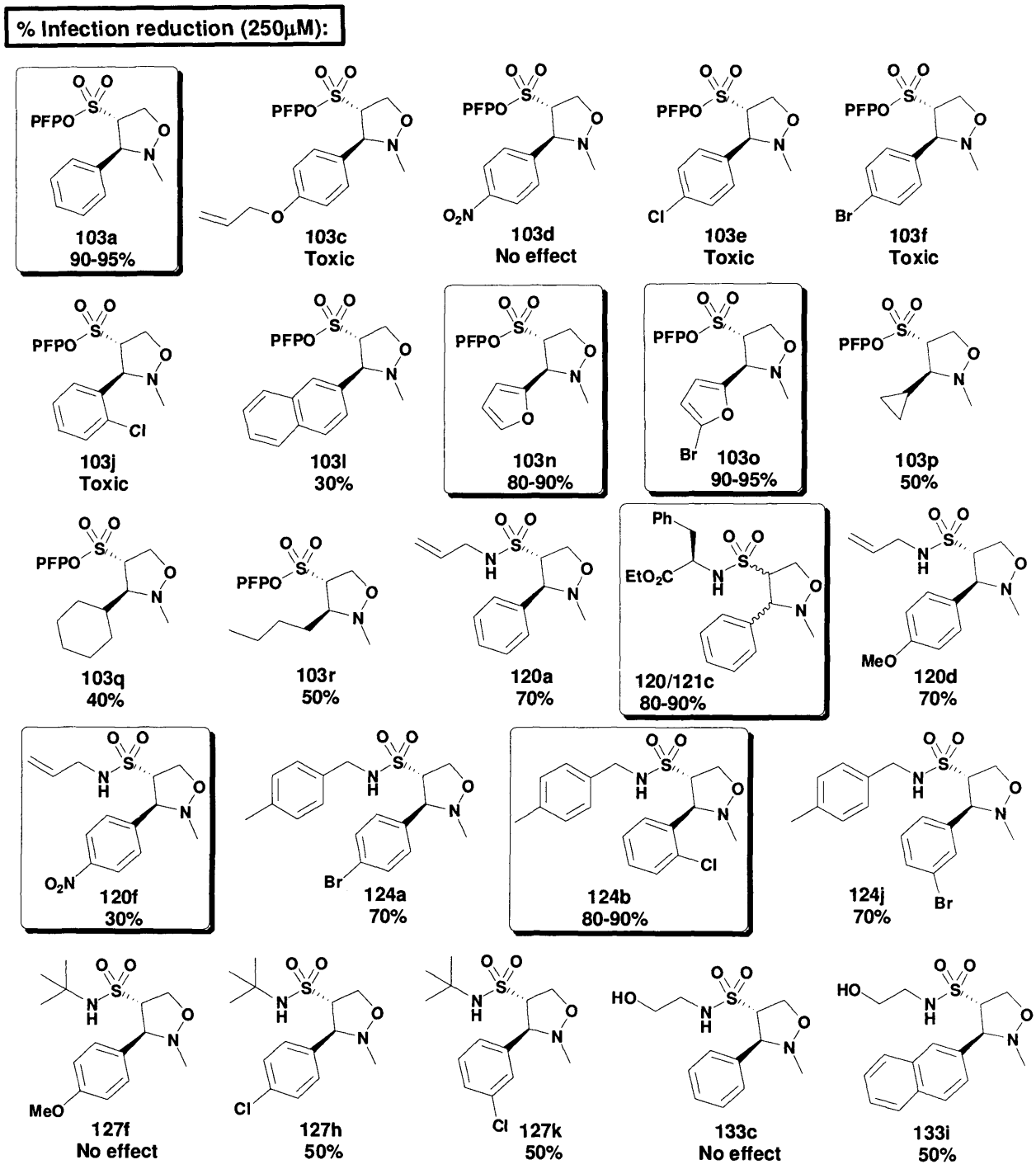


Figure 49

Their initial screen highlighted 5 potential inhibitors which exhibited almost complete reduction in infection at μM concentrations (**103a**, **103n**, **103o**, **120/121c**, and **124b**). Several PFP sulfonate esters did show antiviral activity, however, there were a few examples where the compounds were ineffective because of the toxic effect they exerted

on the cells. The sulfonamides were essentially non-toxic, and generally better tolerated by the T-cells, with only two out of twelve sulfonamides displaying no antiviral activity. The 5 most promising compounds were identified (Figure 49) and it was decided that these would be the focus for further testing. Compound **120f** was also identified as a suitable negative control to use during testing as it exhibited essentially no activity and was fundamentally non-toxic.

Re-evaluation of the compounds (Figure 50) by examining the % reduction in infection with respect to cells infected with the HIV-1 vector pCSGW (chart 2), established that **124b** provided the best result. It showed close to complete reduction of infection at 150μM. For example, **124b** reduces HIV infection from 4.53% to 0.41%, close to the percentage seen for non-infected T-cells (chart 1, 0.16%). Another sulfonamide (**120/121c**) showed a similar degree of activity at a higher concentration (200μM). It is noticeable that PFP sulfonate esters were not as effective as sulfonamides, and higher concentrations (250μM) were needed to provide good antiviral activity (**103n** and **103o**). The role of **120f** as the negative control was also confirmed by its inability to reduce infection in HIV infected cells

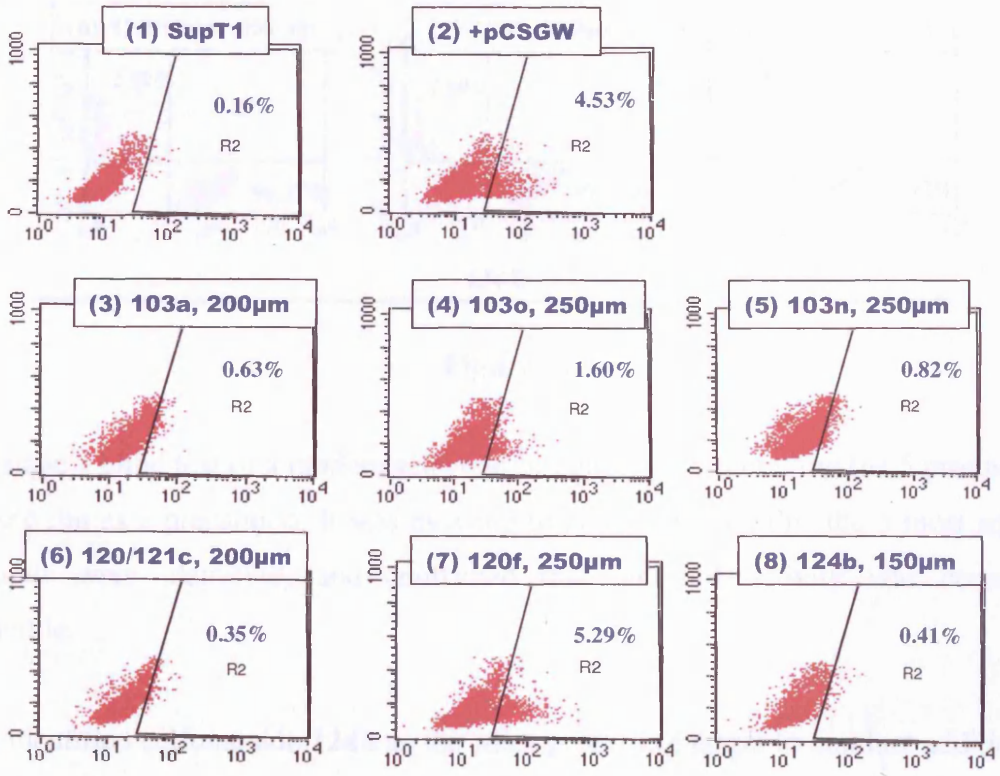


Figure 50

With the 5 most encouraging compounds identified, toxicity tests at the working dose in the presence of SupT1 cells were performed by Fassati *et al.*, to determine whether they displayed any toxicity to the cells (Figure 51). In SupT1 it could be seen that 97.48% of cells present are alive, but when treated with digitonin (a membrane solubilising non-ionic detergent) 98.8% of all cells died. The live/dead cell assay determined that our compounds showed low toxicity, as greater than 94% of cells survived incubation with the each candidate, except with **103a**. Nonetheless, at least 4 compounds remain suitable for continual testing.

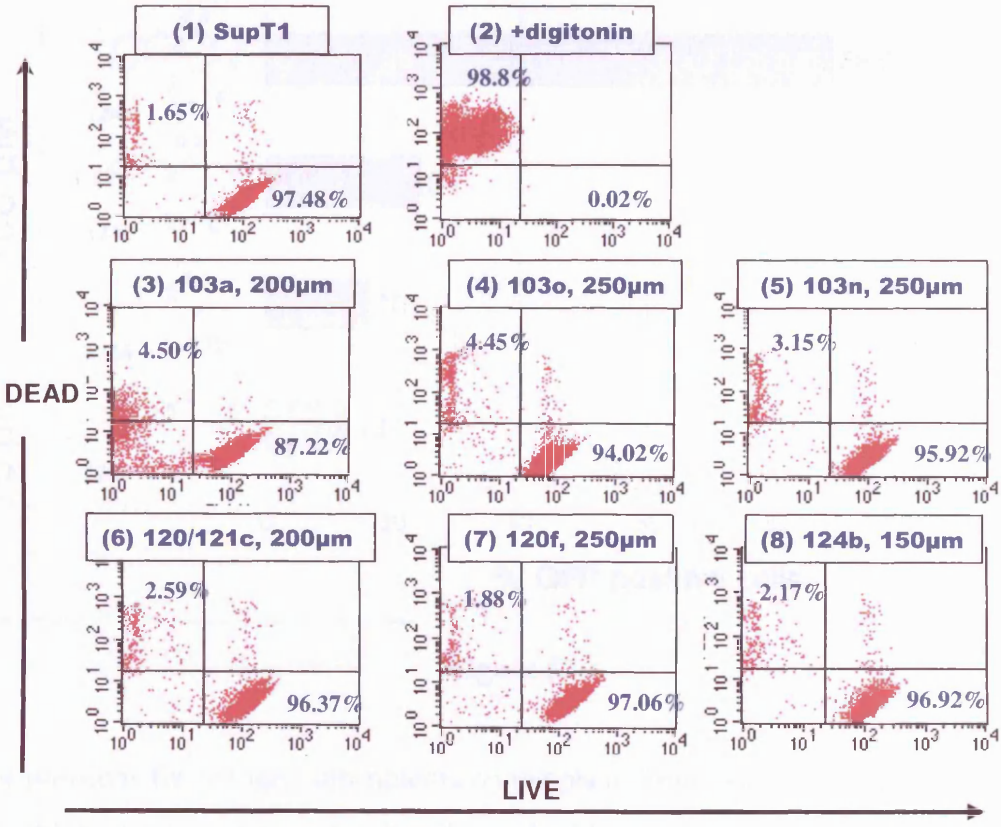


Figure 51

At this stage a blind test of a random selection of compounds including the 5 promising ones were run as a precaution. It was pleasing to note that from this the 5 most active compounds were identified, and confirmed that antiviral activity was certainly reproducible.

Having identified sulfonamide **124b** as the most promising target to conduct additional studies, further structural changes were introduced to see if potency could be improved. A survey of a range of *ortho*-functionalised aromatic rings quickly establishes that an increase in bulk at the *ortho* position greatly influences the anti-viral potency (Figure

52). With an increase in potency it was also possible to lower the dose down from 150μM to 75μM, especially with the iodo analogue **124o** which resulted in a >80% reduction in HIV infection. Whilst an anti-viral concentration of 75μM is an excellent start point, it is still relatively high and further SAR is required to lower the working dose into the more desirable nM region.

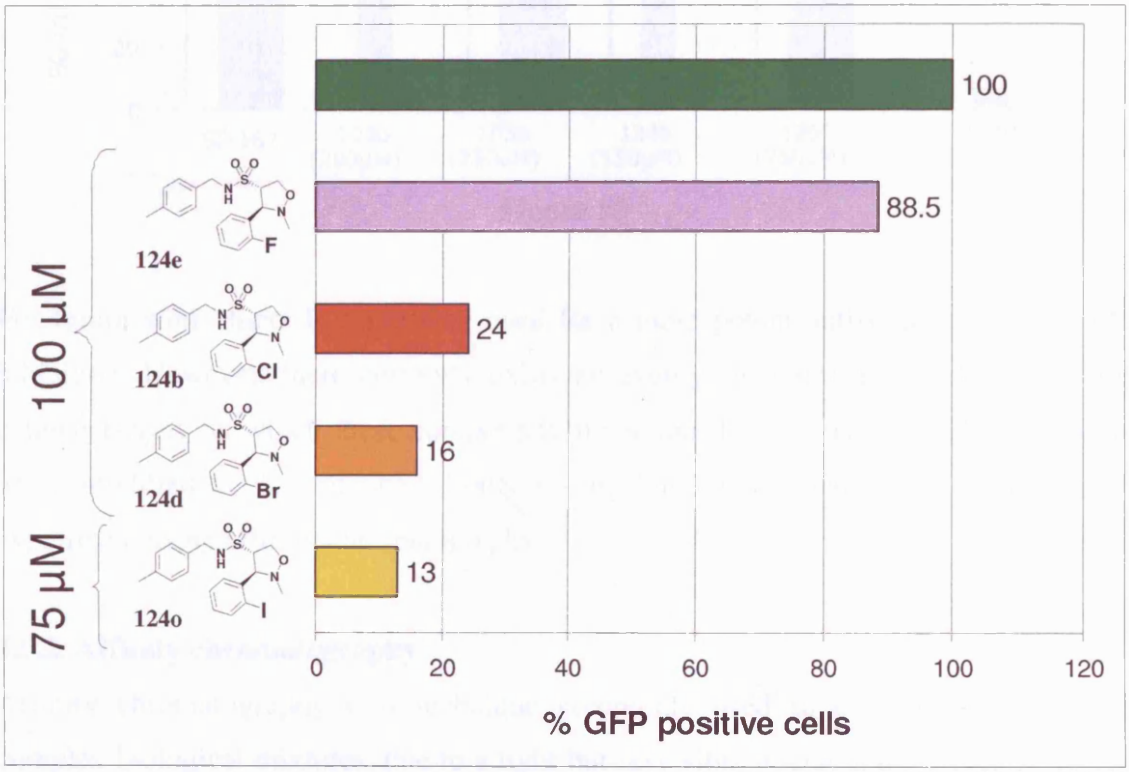


Figure 52

Other positions for halogen substituents on the phenyl ring were investigated (*meta* and *para* chlorophenyl, and bromophenyl), and although they too displayed anti-viral activity, the results were not as good or consistent to those obtained with *ortho* substituents.

In separate tests by Fassati *et al.*, the ability to inhibit replication of a primary HIV-1 isolate in lymphocytes obtained from healthy human donors was also assessed with interesting results (Figure 53). Donor 2 was not sensitive to any of the 3 drugs (**103o**, **103n**, and **124b**), while donors 1 and 3 responded well to **103o**. Rather pleasing to see was the potent inhibition displayed by **124d** in all three donors.

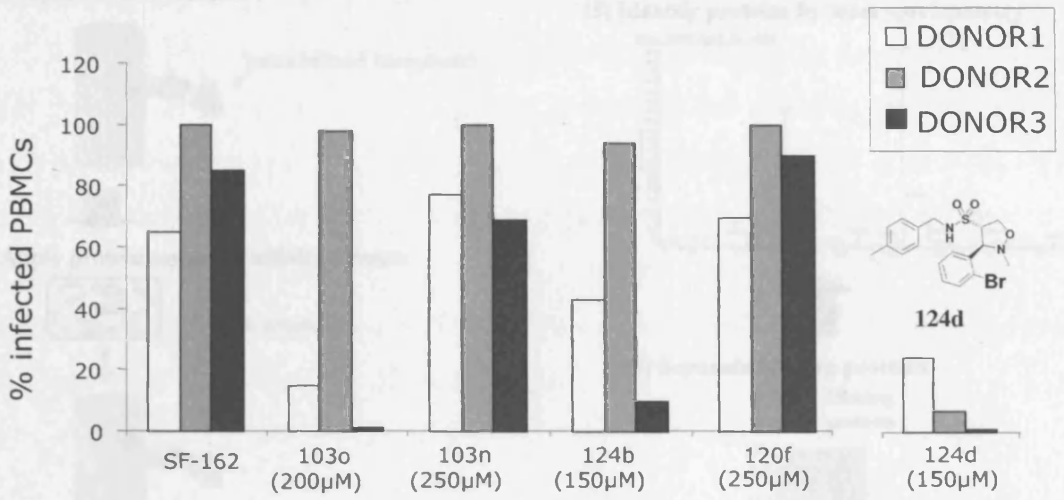
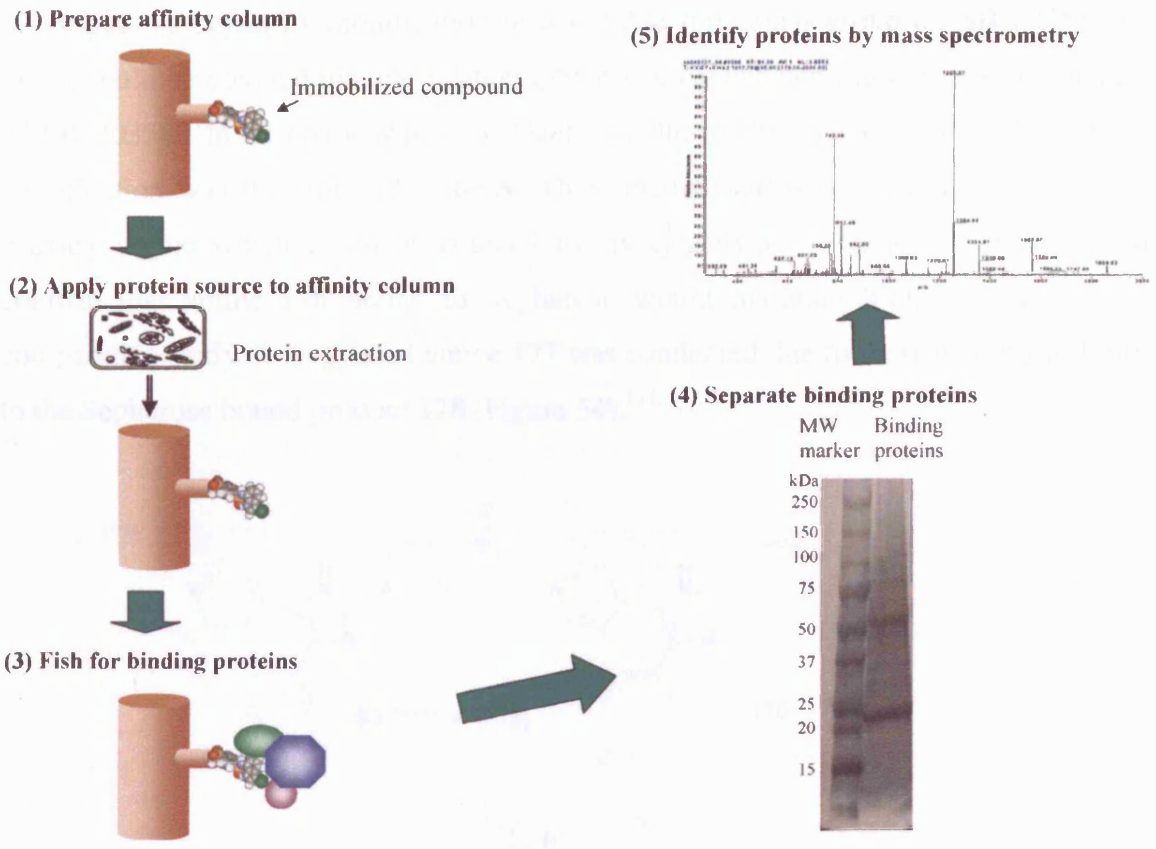


Figure 53

For future work, there is a pressing need for a more potent anti-viral possessing nM inhibition. However, there currently exists an even greater desire for identifying the cellular targets on which these compounds are acting. It was envisaged that we could use a modified version of one of our existing inhibitors to carry out a 'pull-down' experiment using affinity chromatography.

3.5.2. Affinity chromatography

Affinity chromatography is a technique commonly used to capture proteins from complex biological mixtures, due to a tight but reversible interaction (k_D ideally 10^{-4} M to 10^{-8} M) of a target molecule for a specific ligand coupled to a chromatography matrix. This interaction is either an electrostatic, hydrophobic, van der Waal's, or H-bonding interaction. The target is then released from the affinity matrix, often by changing the pH, polarity, ionic strength, or by addition of a competitive ligand so that the reversible interaction is broken.[169] Mass spectrometric evaluation is then applied to identify the protein/s which was bound to the immobilised candidate, in an overall process known as chemical proteomics (Scheme 80). Chemical proteomics is a well established practice that can aid in the discovery of (1) unknown protein functions, (2) identifying the molecular mechanisms of drug action, and (3) help in the optimisation of lead compounds. However, for this process to be viable the protein must bind specifically to the target molecule, and this can often be difficult to predict if chemical modifications have been made to the target molecule in order to accommodate ligand attachment/binding.[170]



Scheme 80

A few examples of small molecules tethered to affinity beads and used to 'pull-down' biological targets will be discussed. Most commonly affinity chromatography is carried out by biotinylation of a target molecule, or *via* direct attachment of the target molecule to solid supported beads (i.e. Sepharose).

Immobilisation of a drug candidate onto chromatographic beads intended for affinity chromatography has been commonly used to determine the selectivity of synthesised protein kinase inhibitors.[171] The design of selective protein kinase inhibitors is complicated due to the relatively well conserved ATP-binding site amongst protein kinases, meaning cross-over inhibition is frequently observed. In an example by Daub *et al.* they immobilised the anti-inflammatory drug SB 203580 (**175**), a pyridinyl imidazole which was designed as a mitogen-activated protein kinase p38 inhibitor (Figure 54). Initially, *in vitro* assays of SB 203580 against a variety of protein kinases deemed it to be relatively selective for p38 kinase. However, as there are over 500 human protein kinases and other protein targets to consider (i.e. other cellular enzymes), the knowledge of SB 203580's true selectivity for p38 kinase is not entirely accurate. Thus, a proteome-wide assessment of SB 203580 selectivity is required, and this was reported by Daub and co-workers.[172]

Investigations began by modification of a suitable functional group on SB 203580 so that it could be coupled to a chromatography resin. By considering the crystal structure of SB 203580 in complex with p38, Daub concluded that the best possible site for modification was the sulfoxide moiety. Thus, methyl sulfoxide was substituted for a primary amine which could be coupled to epoxy-activated Sepharose. However, to confirm that amine **176** bound to Sepharose would maintain biological activity, a comparative study on pegylated amine **177** was conducted due to its structure similarity to the Sepharose bound product **178** (Figure 54).[171, 172]

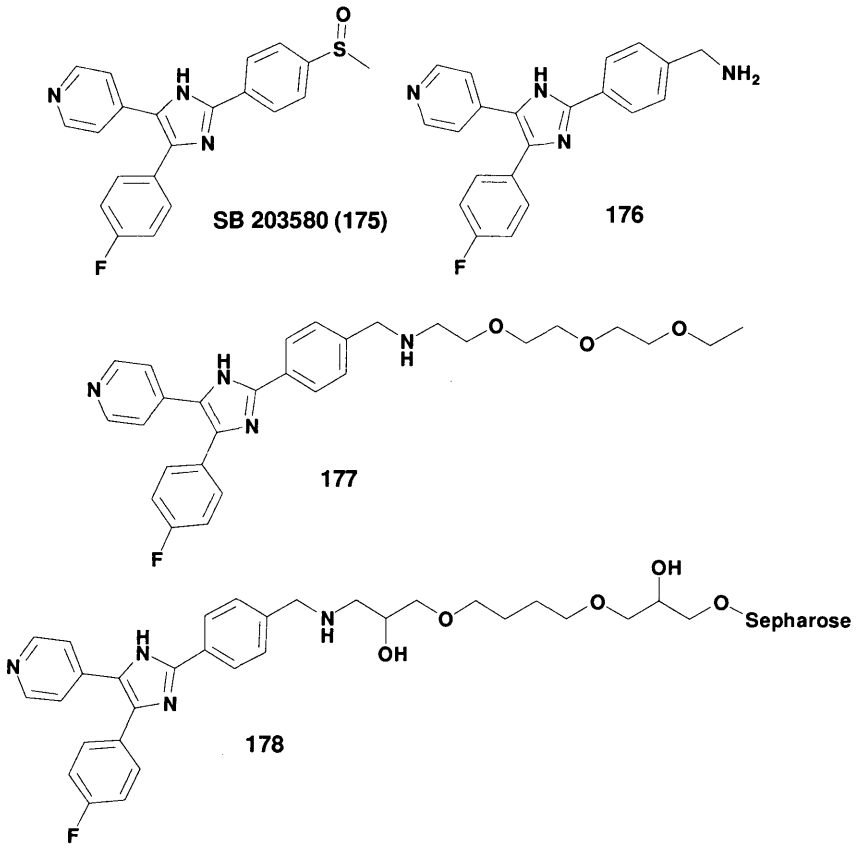
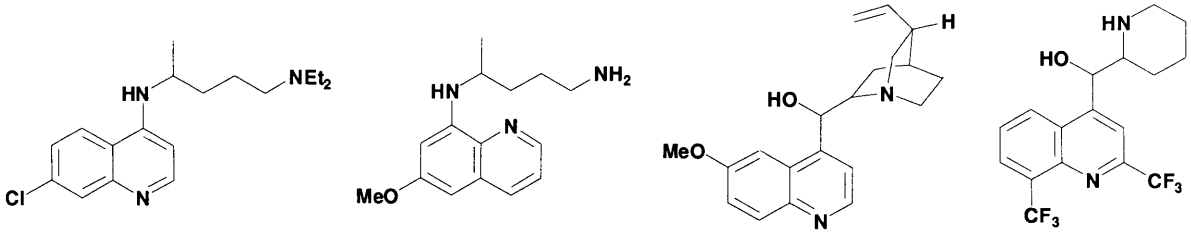


Figure 54

Consequently, **176** and **177** were biologically evaluated against p38 kinase, and displayed IC_{50} values of 4nM and 40nM respectively. Although pegylation reduced the inhibitory potency of **176** its IC_{50} value compared favourably with **175** ($IC_{50} \approx 40nM$); therefore, Daub *et al.* deduced that **178** should still retain activity and was subjected to affinity chromatography. The binding and separation of p38 inhibitor targets was successfully performed, with gel electrophoresis and mass spectral analysis confirming that in addition to p38, a variety of other previously unknown protein kinases were identified. These unknown protein kinases also potently inhibited by SB 203580 were

identified as Rip-like interacting caspase-like apoptosis-regulatory protein kinase (RICK), cyclin G-associated kinase (GAK), and casein kinase 1 (CK1). As a result of this work by Daub *et al.*, it was shown that SB 203580 is not as selective for p38 kinase as previously reported. This suggests that SB 203580 possesses a more complicated mechanism of action, and has potentially provided further insight into the role of p38 kinases in cellular signal transduction and as anti-inflammatory drugs.[172]

Additionally, affinity chromatography has been employed to discover the primary targets of clinically-used drugs whose mode of action has not been established. The amino-quinolines (Chloroquine and Primaquine) and the quinolinemethanols (Quinine and Mefloquine) are used primarily in the treatment of malaria (Figure 55); however, there is no known mechanism and its mode of action is unclear. The accepted hypothesis for their mode of action, as suggested by Foley and Tilley is that these anti-malarials exert their therapeutic effect by interfering with red blood cell heme detoxification.[173]



Chloroquine Primaquine Quinine Mefloquine

Figure 55

In order to better understand the precise mechanism of these quinoline drugs, Graves *et al.* used displacement affinity chromatography to first identify all quinoline-interacting proteins in a cell. They hypothesised that the structurally related ATP may be immobilised onto sepharose and used to capture quinoline binding proteomes from cell lysates. The bound proteins are then displaced from the affinity matrix with one of the quinoline drugs, eluted and identified by mass spectrometry. Graves *et al.* successfully performed displacement affinity chromatography with chloroquine, primaquine, and mefloquine to identify the two proteins: aldehyde dehydrogenase 1 (ALDH1) and quinone reductase 2 (QR2). To confirm their findings hydroxychloroquine and primaquine were immobilised onto sepharose for 'pull-down' studies, and the authors report that isolation of ALDH1 and QR2 was observed. Consequently, in good agreement with their displacement affinity chromatography work, Graves and co-

workers effectively identified the cellular targets of the quinoline drugs (ALDH1 and QR2), thus providing additional information on their mode of action.[173]

Whereas drug candidates can be directly coupled to the chromatography matrix in the case of sepharose, they may also be indirectly coupled *via* a biotin-streptavidin system. This provides an alternative technique for affinity chromatography which first involves the covalent attachment of candidates to biotin, for which then exhibits an extremely strong binding affinity for the streptavidin matrix.

In studies by Honda *et al.,* they wanted to identify the protein targets of their synthesised anti-inflammatory/anti-carcinogenic agent 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) **179** and its analogues. CDDO **179** and its analogues (CDDO-Me **180** and CDDO-Im **181**) displayed inhibitory activity against NO production, and were also able to inhibit proliferation of leukaemia and carcinoma cell lines (Figure 56).[174]

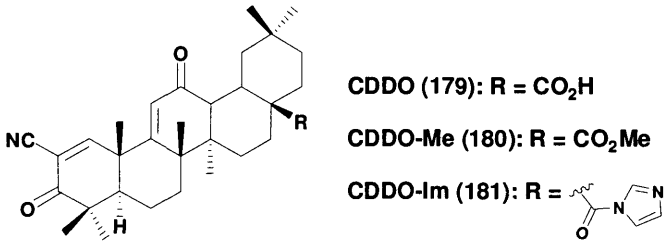


Figure 56

However, its mechanism of action remains unexplored, and clarification of this may aid in its eventual development as a valuable clinical candidate. To facilitate this study, Honda *et al.* set out to use the well established biotin-streptavidin methodology in order to capture cellular proteins. Biotinylation was achieved to provide 3 functionalised CDDO analogues, with a suitable spacer to avoid steric hindrance between protein and bead. Two analogues of CDDO were biotinylated at C-17 whilst the remaining analogue was derivatised at C-23 (Figure 57). To confirm that these biotinylated conjugates retained biological activity, they were evaluated against the proliferation of MCF-7 breast cancer cells. The authors report that reduced potency of **182**, **183**, and **184** compared to CDDO **179** and CDDO-Me **180** (IC_{50} = 0.16μM and 0.056μM respectively) was seen (Figure 57).[174] However, with their most active compound (**184**) they were able to carry out successful affinity chromatography, identifying IκB kinase β as the biological target of CDDO and its analogues. IκB kinase β is responsible for

regulating nuclear factor-κB, a transcription factor that is activated in numerous carcinomas.

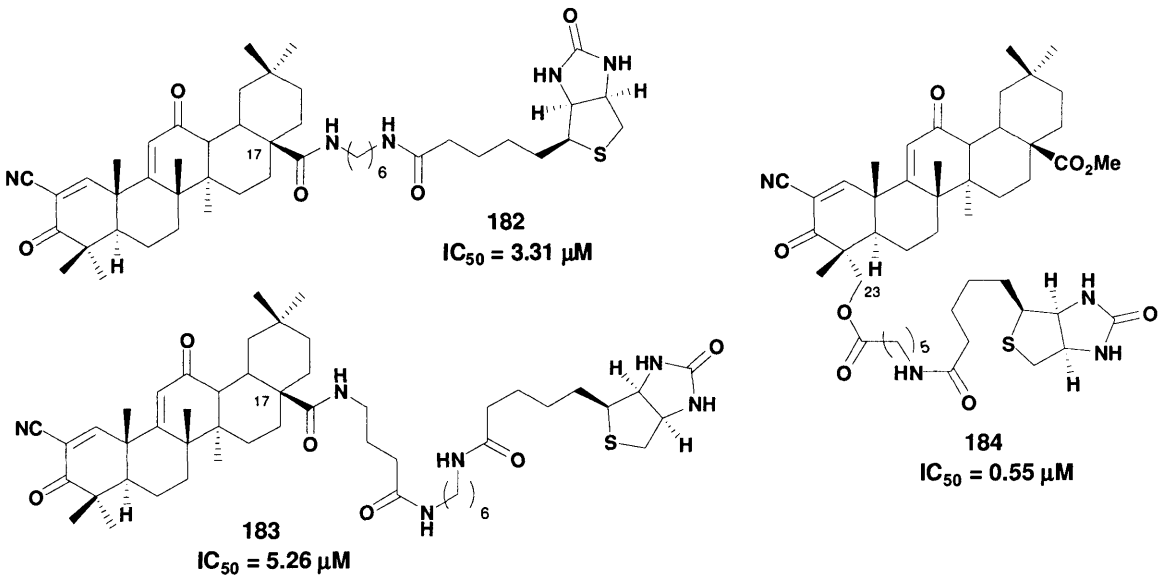


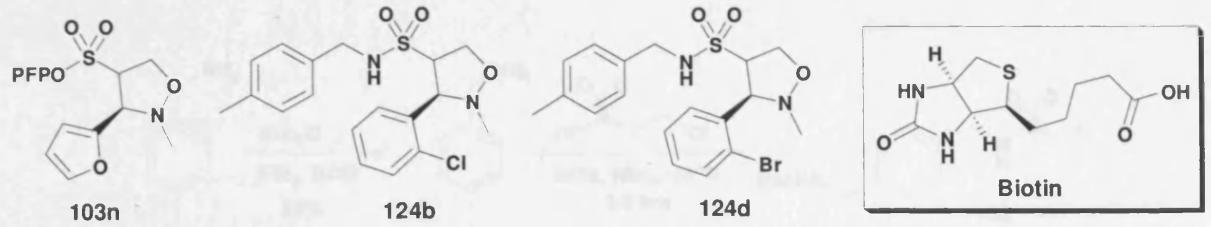
Figure 57

Hence, having established CDDO and its analogue directly inhibit IκB kinase β, this has led to their progression into phase I clinical trials for the treatment of leukaemia and solid tumours.[175]

3.5.3. Preparation of immobilised inhibitors/ligands for pull down experiments

3.5.3.1. Synthesis of modified sulfonates and sulfonamides for immobilisation onto an affinity matrix

Through the testing of PFP sulfonate esters and sulfonamides against HIV; PFP sulfonate ester **103n** and sulfonamides **124b** and **124d** have been identified as the most suitable candidates for affinity chromatography (Figure 58). For affinity chromatography to work a segment of our inhibitor will have to be modified so that it can be covalently attached to a ligand, or directly to a polymer support or affinity matrix. In this study the commonly used biotin-streptavidin system will be used for the detection of biomolecules. The biotin-streptavidin system was chosen due to the extremely strong interaction between these two species ($K_A \sim 10^{14}$ M^{-1}), and also from the ease at which biotin may be attached to the inhibitor.[176] Biotin is a vitamin from the vitamin B complex and contains a carboxylic acid unit to which drug molecules can be coupled (Figure 58).[177]



103n 124b 124d

Figure 58

We considered that the best position for attachment of biotin would be the amino portion of the sulfonamide or on the PFP group of the PFP sulfonate ester (Scheme 81).

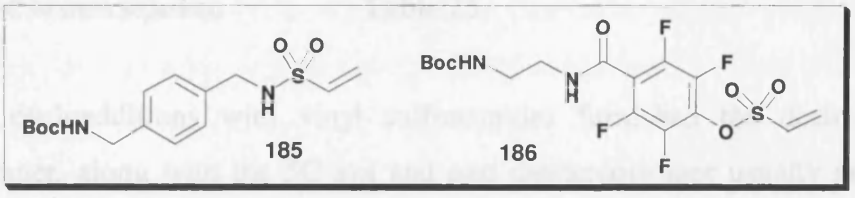
SULFONAMIDES:

PFP SULFONATE ESTER:

Scheme 81

3.5.3.2. Modification of the amine component

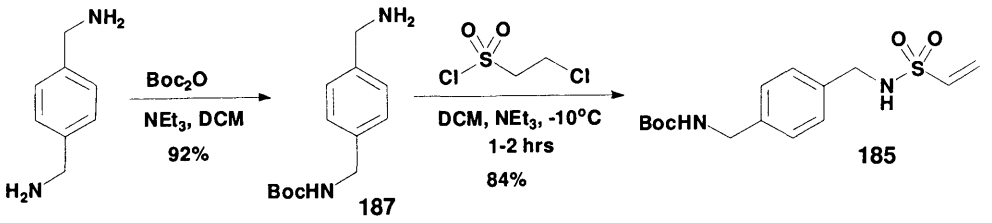
A simple retrosynthetic analysis of both target molecules established the two dipolarophiles **185** and **186** as good [3+2] cycloaddition precursors (Figure 59).



185 186

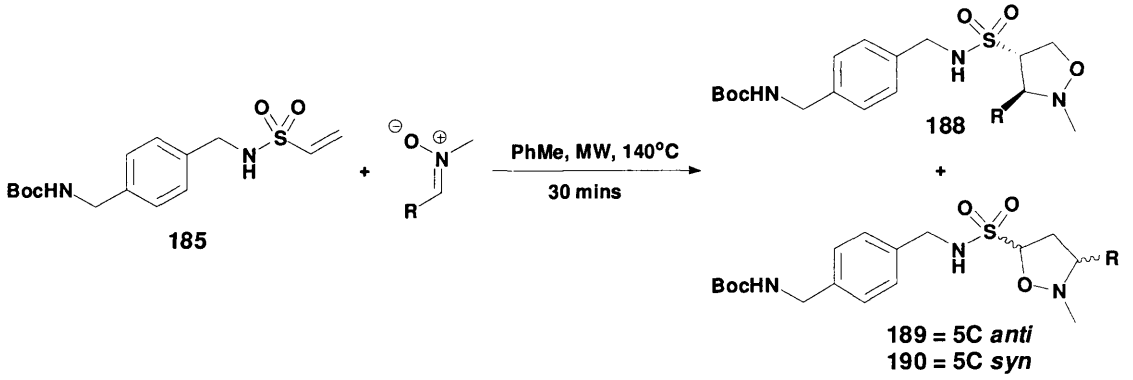
Figure 59

The proposed synthesis of **185** (Scheme 82) would start with the mono-protection of *p*-xylylenediamine,[178] followed by vinyl sulfonamide synthesis using existing procedures (see Section 2.3.5.).



Scheme 82

185 was eventually synthesized with excellent yields and then subjected to a [3+2] cycloaddition with the required nitrone. As conditions had already been set up for this type of cycloaddition (see Section 2.3.5.), these were employed here with a small collection of nitrones (Table 25).

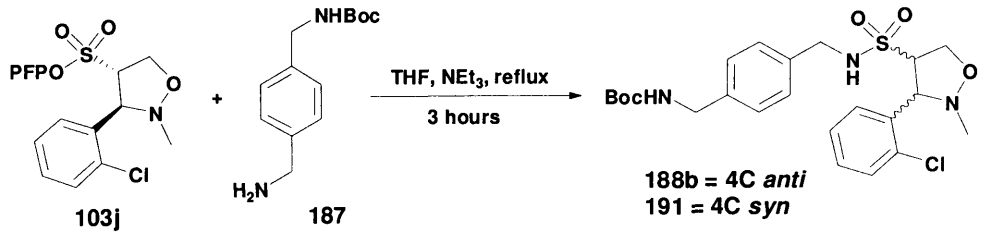


Entry	R	Yield (%)	Product ratio (188 : [189/190])	Product ratio 189 : 190
a	*o*-FPh	67	5 : 6 *	2 : 1
b	*o*-ClPh	53	1 : 1 *	3 : 2
c	*o*-BrPh	46	5 : 4 *	1 : 1
d	*p*-ClPh	79	3 : 2	3 : 2
e	*p*-BrPh	67	3 : 1	1 : 1

* = 5C isomers separated

Table 25

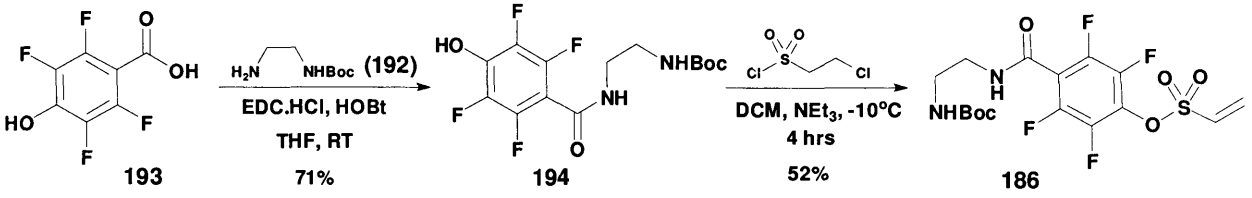
Previously cycloadditions with vinyl sulfonamides furnished the desired 4C *anti* diastereoisomer, along with the 5C *syn* and *anti* diastereoisomer usually as a mixture (see Section 2.3.5.). In all examples shown in Table 25 the same results were observed with moderate to good yields. It was disappointing to see that the desired pre-biotinylation precursors (entries b and c) required for testing showed the lowest yields. As a result, aminolysis of PFP sulfonate ester **103j** with **187** was examined as a way to improve the yield (Scheme 83).



Scheme 83

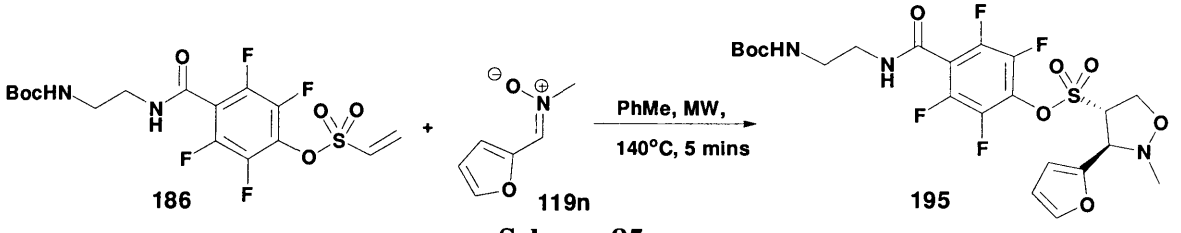
Although the reaction does indeed provide a much improved yield of 90%, separation of the diastereomeric mixture (*anti:syn* = 5:2) proved a lot more troublesome and time consuming so this alternative route was avoided. With two of three pre-biotinylated testing precursors synthesized (**188b** and **188c**); the TFP sulfonate ester was the next endeavour.

Synthesis of **186** involved a similar synthetic sequence to that used for the synthesis of **185** (Scheme 82), but with an additional EDC coupling step of Boc-ethylene diamine **192** to 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid **193** (Scheme 84).



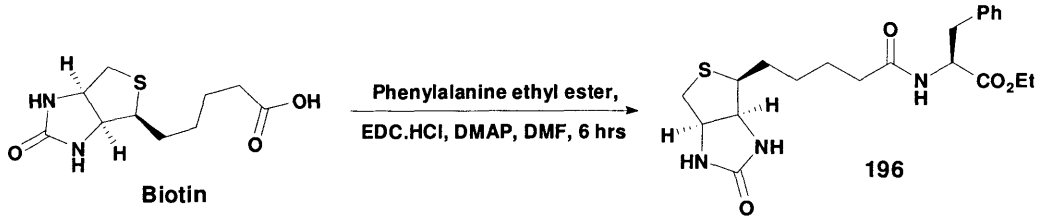
Scheme 84

Mono-protection of ethylene diamine furnished a 78% yield of the desired product **192**,[179] which was then utilized for amide coupling to give **194**,[180] and finally vinyl sulfonamide **186** synthesis was achieved in a modest yield of 52%. The [3+2] cycloaddition with 2-furyl nitrone **119n** was performed to give cycloadduct **195** in a regioselective and diastereoselective fashion, albeit in a poor yield, 38% (Scheme 85).



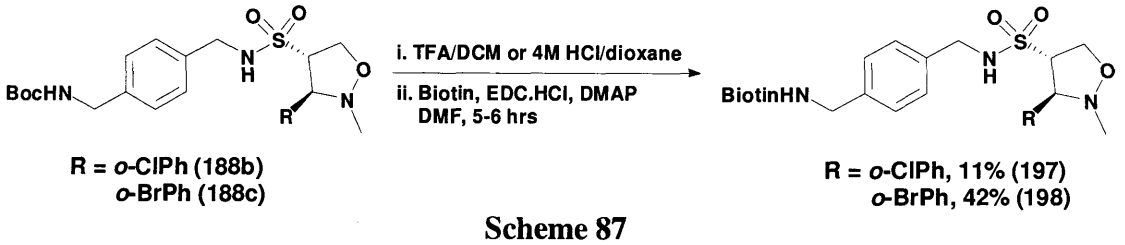
Scheme 85

With our more valuable biotin containing precursors synthesized it was considered more appropriate to first test the coupling reaction of biotin with a standard amine using a set of conditions obtained from literature. Thus, *L*-phenylalanine ethyl ester.HCl in DMF was coupled to biotin using a procedure set out by Kim *et al.* (Scheme 86).[181] The reaction worked extremely well furnishing a 64% yield of the desired product **196**.



Scheme 86

Having established that the reaction was successful, the amine was finally liberated as the TFA or HCl salt and then subjected to Kim's conditions for coupling (Scheme 87). Disappointingly the isolated yields of **197** and **198** obtained were poor, but furnished sufficient material for biological testing. Accordingly, if encouraging biological results are obtained then further optimisation will be required to improve these disappointing yields.



Scheme 87

With the two biotinylated inhibitors synthesized it was now vitally important that these molecules retained activity against HIV for affinity chromatography to be successful. However, preliminary tests deemed these biotinylated compounds to be devoid of any activity. To determine whether biotin was the problem the non-biotinylated precursors **188b** and **188c** were also tested as the free amine and Boc protected species; however, evaluation of these also displayed no antiviral activity.

To check the importance of the amine moiety, sulfonamide **124g** was also assayed against HIV, and effectively this revealed that the 4-methylbenzylamine region is essential and not suitable for modification. In support of this, Fassati *et al.* noted that the allyl sulfonamide **120f** exhibited no anti-viral activity but the 4-methylbenzylamine sulfonamide **124g** possessed a good level of inhibition at 100 μM (Figure 60). This loss

of activity associated with biotinylation, along with the known problem associated with protein purification when associated with biotin,[176, 182] led to the development of a new strategy.

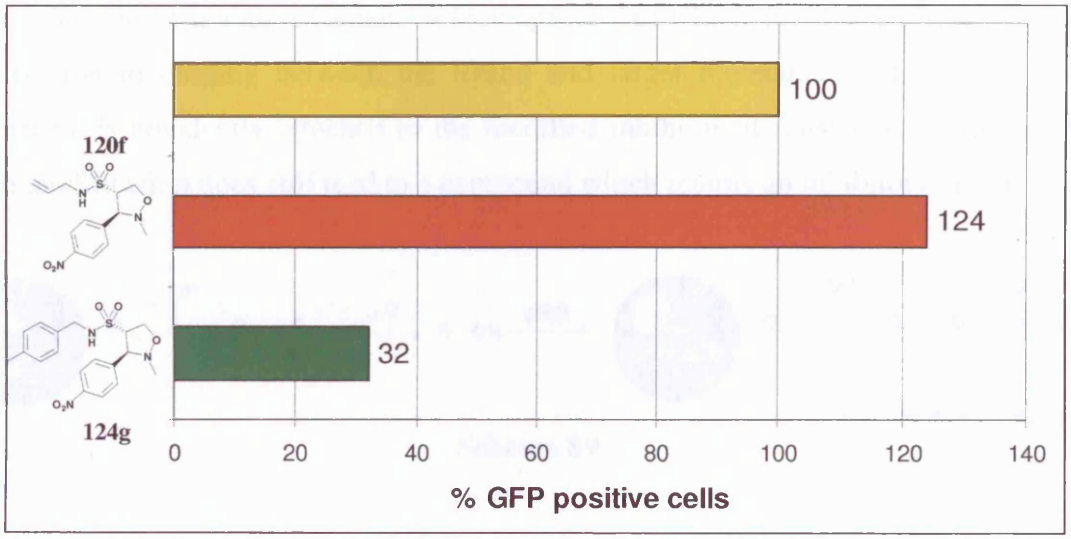
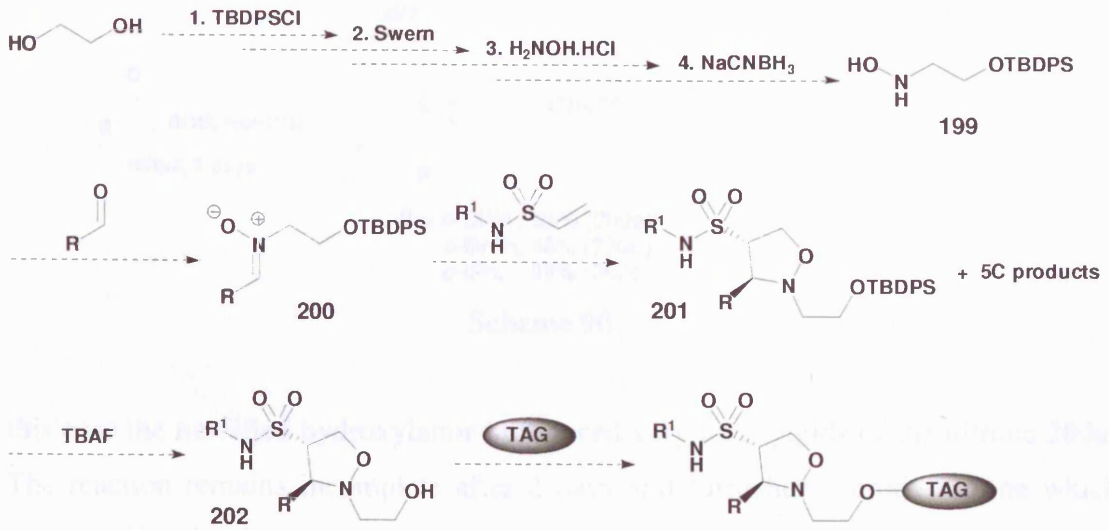


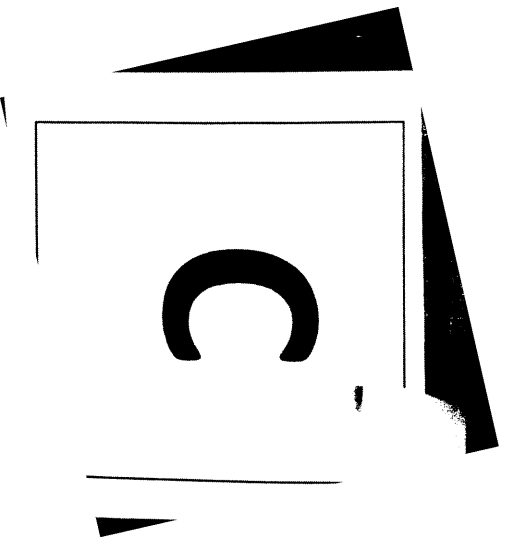
Figure 60

3.5.3.3. Modification of the *N*-terminus

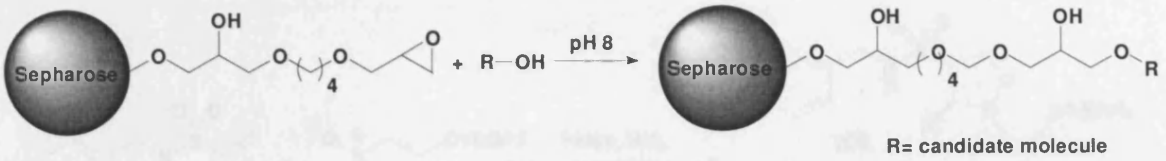
We needed to determine an appropriate position for attachment of the tag, and the options were limited by the requirement to retain the amine moiety and R group of the isoxazolidine ring for anti-viral activity. It was therefore decided that the nitrogen of the isoxazolidine ring would be utilised as a point of attachment. Hence, a new synthetic plan was devised in which a hydroxyl group would provide a suitable linker at the end of isoxazolidine **202**, and to which a suitable tag for affinity chromatography would be appended (Scheme 88).



Scheme 88

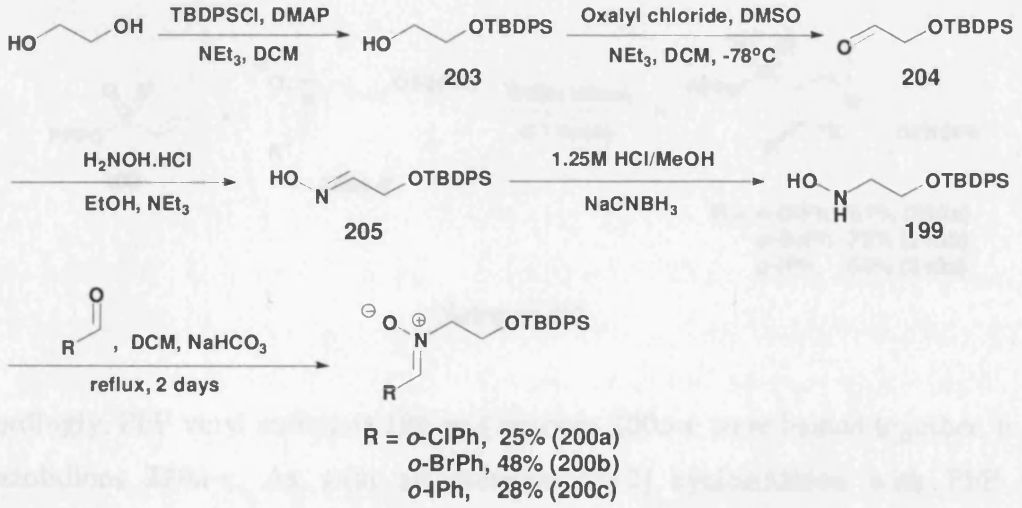


As biotin also raised some potential problems in protein purification it was decided to modify the approach so that the ligand would be attached to the affinity matrix, not by biotin, but *via* epoxy-activated Sepharose 6B (Scheme 89). The advantage of using epoxy-Sepharose is that it contains a long spacer arm which should help minimise any obstruction to binding between the ligand and target molecule.[169] However, before sepharose is covalently attached to the modified inhibitor, it must first be shown that such modification does still lead to a compound which retains an inhibitory affect.



Scheme 89

The synthesis began with the mono-silylation of ethylene glycol to give a 91% yield of **203**.[183] Swern oxidation furnished aldehyde **204** in a 95% yield[184] which was condensed with hydroxylamine to give oxime **205** (95%) as a mixture of geometrical isomers.[185] Finally, reduction with $NaBH_3CN$ provided hydroxylamine **199** in a 92% yield.[186] All 4 steps, although simple and tedious, were near quantitative and set up nitrone formation (Scheme 90).

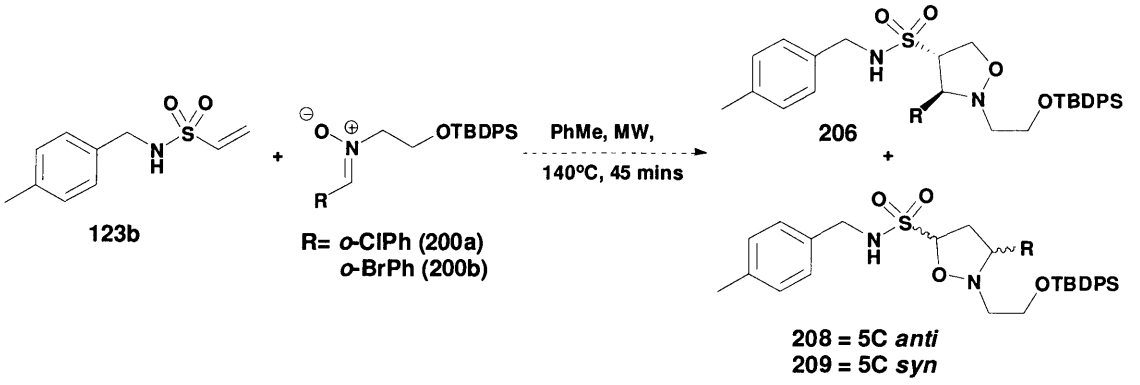


Scheme 90

In this case the modified hydroxylamine produced very poor yields of the nitrone **200a-c**. The reaction remains incomplete after 2 days and furnishes a crude nitrone which requires purification by column chromatography. Longer reaction times do not improve

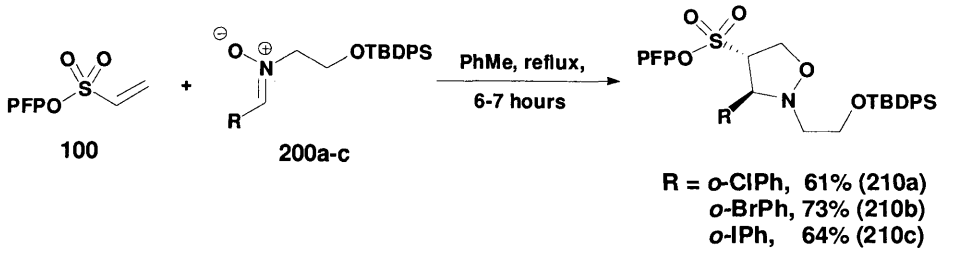
the isolated yield, so it was suspected that the low yields observed are as a result of the polar nitrone adhering to or decomposing on silica during purification.

However despite this, it is possible to prepare sufficient quantities of material for further studies and the [3+2] cycloaddition with vinyl sulfonamide **123b** was attempted. Reagents were heated in a microwave at 140°C for 45 minutes, but disappointingly no appreciable amount of product was generated (Scheme 91). The reaction was very messy and TLC analysis showed decomposition of nitrone as the major result.



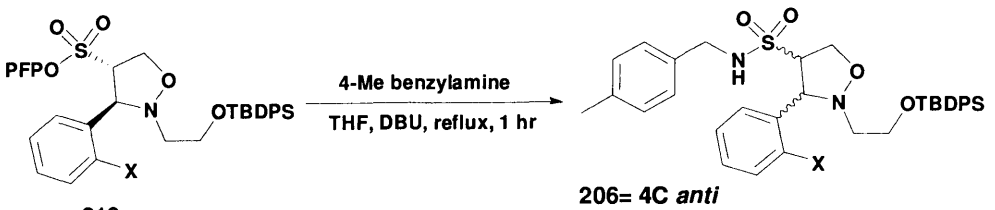
Scheme 91

Therefore, as the alternative route available, it was decided to proceed through the PFP sulfonate ester pathway (Scheme 92).



Scheme 92

Accordingly, PFP vinyl sulfonate **100** and nitrones **200a-c** were heated together, to give isoxazolidines **210a-c**. As with all previous [3+2] cycloaddition with PFP vinyl sulfonate, the reactions produced the *anti* diastereoisomer cleanly and with satisfactory yields (see Section 2.3.3.). Isoxazolidines **210a-c** were unfortunately rapidly epimerised upon aminolysis with 4-methylbenzylamine (Table 26).



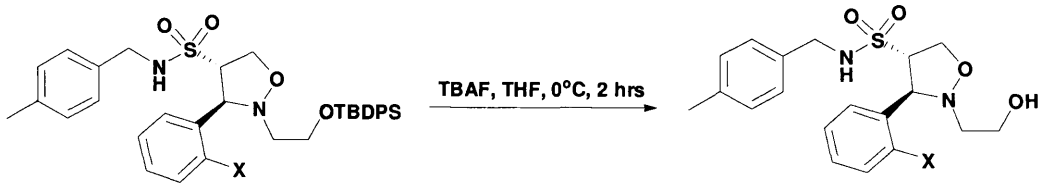
210a-c

206= 4C *anti*
207 = 4C *syn*

Entry	X	Yield (%)	Product ratio [206 : 207]
a	Cl	78	10 : 3
b	Br	69	7 : 3
c	I	63	5 : 2

Table 26

Repeated column chromatography of the diastereomeric mixture was eventually successful in enabling the separation of both the *syn* and *anti* diastereoisomers with a minor reduction in yield. Yet again the preferred *anti* diastereoisomer **206** was produced in a greater quantity, and this was taken and subjected to desilylation using 1 M TBAF in THF[187] to deliver near quantitative yields of the alcohols **211a-c** for biological screening in a HIV assay (Scheme 93).



206a-c

R = Cl, 98% (211a)
Br, 93% (211b)
I, 97% (211c)

Scheme 93

Our 3 compounds are currently being assayed against HIV to assess if anti-viral activity has been retained. Preliminary screening has revealed that alcohols **211a-c** have no anti-HIV activity, however further in-depth testing is required to corroborate these initial results. This did lead to further uncertainty as to whether the *N*-position of the isoxazolidine ring is also not suitable for modification, and or whether the free OH is complicating testing. There is a possibility of an internal H-bond between the free alcohol and the O of the isoxazolidine ring causing a small conformational change in the structure, and therefore changing the activity of the candidate. As a test, the silylated alcohol **206b** was also examined by Fassati *et al.*, but initial tests suggest this compound is toxic at the working doses, and at present does not possess anti-viral activity.

3.6. Conclusion on Chapter 3

In conclusion a new class of small molecule inhibitors for the enzymes DDAH, ADI and HIV has been discovered, demonstrating the general role of our sulfonamides and PFP sulfonate esters as potential chemical agents to aid in biological and potentially medicinal studies.

In the DDAH/ADI study a selection of PFP sulfonate esters and sulfonamides tested showed encouraging levels of inhibition at a concentration of 50μM, and a more accurate determination of their potency has been carried out. Generally PFP sulfonate esters exhibited greater levels of inhibition against DDAH, whilst sulfonamides showed most promise against ADI. It was also evident that isoxazolidines containing the naphthyl, 2-bromofuryl, *p*-NO_2Ph, or *m*-bromoaryl groups tended to give good inhibition against ADI and DDAH, irrespective of whether they are PFP sulfonate esters or sulfonamides (Tables 20, 22 and 23). Pleasingly this study has identified the first known inhibitor of ADI, and moreover revealed the first example of a non-substrate based inhibitor for DDAH. Inhibition has provided promising levels of activity in the μM range; however, further SAR is required to obtain a potent inhibitor displaying nM inhibition, which will be important for fundamental biological studies and/or clinical studies. Future work also entails a more detailed investigation into the molecular interactions of our active compounds within the DDAH and ADI binding pocket. Once this has been achieved the next objective would then be to design inhibitors with DDAH isoform selectivity.

In the HIV study, a selection of PFP sulfonate esters and sulfonamides that exhibit anti-HIV activity have been identified, and through further evaluation it has been possible to identify inhibitors with anti-viral activity at around 75-100μM. Although nM activity is more desirable we have established an excellent foundation on which further SAR and drug design will be used to target this.

Attempts to identify the cellular component which our compounds are acting on were unsuccessful, due to loss of anti-viral activity from modifications to our active compounds for tag attachment. It was discovered that a change to the amine component of our sulfonamide was detrimental to anti-HIV activity, and so a new position was investigated. However, tag attachment to the nitrogen of the isoxazolidine ring has also given negative preliminary results and additional tests are currently being investigated.

Conceptually isoxazolidine *N*-tagging still offers the most robust position for drug modification, so future work would entail exploring alternative linkers and spacers that could be used in biological evaluation. If biological results ultimately suggest that isoxazolidine *N*-tagging removes anti-viral activity, then future work entails exploring another position on the sulfonamide motif for tag attachment. The most feasible remaining position for this is the CH_2 of the isoxazolidine ring, and this would ideally be the next endeavour.

Finally, it is also notable that biological activity of the PFP group is totally unexplored, so could be potentially valuable in the future identification of other enzyme inhibitors. Consequently, screening against a wider range of enzymes would also be desirable.

CHAPTER 4: Experimental section

4.1. General methods and experimentation

All the starting materials including solvents were used as received without further purification, unless otherwise stated. Where necessary, reactions were carried out under argon unless otherwise stated. Specially dried (anhydrous) solvents were used when necessary. Reactions were monitored by TLC analysis carried out on SIL G/UV_{254} silica plates purchased from VWR, and were visualised under a UV lamp operating at short and long wavelength ranges. Visualisation was aided by dipping plates into an alkaline potassium permanganate solution. Flash column chromatography was carried out with Kieselgel 60M 0.04/0.063mm (230-400 mesh) silica gel. All yields quoted are isolated yields, and when multiple products are obtained data are presented in terms of order isolated.

Microwave reactions utilized a CEM Discover instrument. ^{1}H NMR spectra were recorded on a Bruker AMX 300 (300 MHz) instrument operating at ambient probe temperature, unless otherwise stated. Deuterated chloroform $CDCl_3$, CD_3OD, D_2O, and DMSO were used as the deuterated solvents for all the spectra run. Peaks are reported as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), appears (app), some combinations of these, or multiplet (m). All chemical shifts are reported in parts per million (ppm) relative to residual protiated signals of the solvent, and coupling constants (*J*) in hertz (Hz). ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AMX 300 unless otherwise stated. Standard abbreviations used were singlet (s), doublet (d), triplet (t), and quartet (q). C-F aromatic peaks not observed due to ^{19}F coupling.

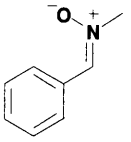
Mass spectra were obtained from a VG70-SE or a MAT 900 XP spectrometer, and infra red spectra were run on a Shimadzu FTIR 8700 spectrophotometer using KBr discs or using a Perkin Elmer Spectrum 100. IR's were run as thin films using DCM as a solvent or neat. Melting points were measured, where appropriate, with a Gallenkamp apparatus and are uncorrected. Elemental analysis was performed at the Department of Chemistry, University College London.

4.2. Nitrone procedures

General protocol [69, 94]

To *N*-methylhydroxylamine hydrochloride (1.2 eq.) in dry DCM (50 mL) was added aldehyde (10 g, 1 eq.) and $NaHCO_3$ (3 eq.). The mixture was heated at reflux (40 °C) for 2 hours, then the resulting suspension was filtered and the remaining residue washed thoroughly with DCM (4 × 40 mL). The combined organic fractions were concentrated *in vacuo* to yield a solid that was recrystallised (hexane/EtOAc) to give the title compound.

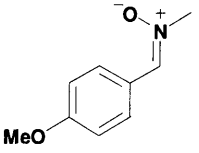
C-(Phenyl)-*N*-methyl nitrone (119a) [69, 94]



General protocol was followed using 3.2 g of benzaldehyde. Recrystallisation from hexane/EtOAc, gave the product as white crystals (3.0 g, 74%).

R_f 0.26 (9:1 DCM/MeOH); mp 89-91 °C; υ_{max} (film)/cm^{-1} 3410, 3003, 1591, 1416, 1163, 937; δ_H (300 MHz, $CDCl_3$) 8.17-8.23 (m, 2 H, Ar*H*), 7.37-7.44 (m, 3 H, Ar*H*), 7.35 (s, 1 H, C*H*N), 3.85 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 135.2 (d), 130.5 (s), 130.4 (d), 128.5 (d), 128.4 (d), 54.4 (q); *m/z* (EI) 271 (24), 135 (M^+, 99), 134 (100), 118 (57), 107 (42), 89 (57); HRMS (EI): calcd for C_8H_9NO (M^+) 135.0684, found 135.0682.

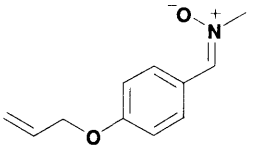
C-(4-Methoxyphenyl)-*N*-methyl nitrone (119b) [69, 94]



General protocol was followed using 10 g of 4-methoxybenzaldehyde. Recrystallisation from hexane/EtOAc, gave the product as white crystals (11.3 g, 93%).

R_f 0.40 (9:1 DCM/MeOH); mp 80-82 °C; υ_{max} (film)/cm^{-1} 3389, 3051, 2976, 1601, 1506, 1456, 1418, 1167, 1030, 945; δ_H (300 MHz, $CDCl_3$) 8.20 (d, J = 9.0 Hz, 2 H, Ar*H*), 7.29 (s, 1 H, C*H*N), 6.93 (d, J = 9.0 Hz, 2 H, Ar*H*), 3.84 (s, 6 H, OCH_3 and NCH_3); δ_C (75 MHz, $CDCl_3$) 161.1 (s), 134.9 (d), 130.4 (d), 123.5 (s), 113.8 (d), 55.3 (q), 53.9 (q); *m/z* (EI) 165 (M^+, 100), 135 (51); HRMS (EI): calcd for $C_9H_{11}NO_2$ (M^+) 165.0790, found 165.0791.

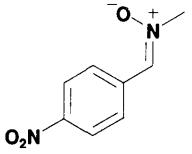
***C*-(4-Allyloxyphenyl)-*N*-methyl nitrone (119c)** [69, 94]



General protocol was followed using 1.9 g of 4-allyloxybenzaldehyde. Recrystallisation from hexane/EtOAc, gave the product as light yellow crystals (2.0 g, 88%).

R_f 0.37 (9:1 DCM/MeOH); mp 89-91 °C; υ_{max} (film)/cm^{-1} 3404, 3084, 2986, 1655, 1564, 1502, 1418, 1308, 1252, 1163, 991; δ_H (300 MHz, $CDCl_3$) 8.17 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 7.26 (s, 1 H, C*H*N), 6.91 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 6.02 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1 H, OCH_2CHCH_2), 5.38 (app. dq, *J* = 17.3, 1.5 Hz, 1 H, CHC*H*H), 5.27 (app. dq, *J* = 10.5, 1.5 Hz, 1 H, CHCH*H*), 4.54 (app. dt, *J* = 5.3, 1.5 Hz, 2 H, OCH_2), 3.81 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 160.0 (s), 134.8 (d), 132.7 (d), 130.4 (d), 123.6 (s), 118.0 (t), 114.6 (d), 68.8 (t), 54.0 (q); *m/z* (EI) 191 (M^+, 100), 150 (29) 122 (18); HRMS (EI): calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0947.

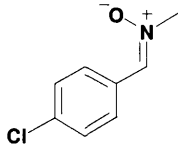
***C*-(4-Nitrophenyl)-*N*-methyl nitrone (119d)** [69, 94]



General protocol was followed using 10 g of 4-nitrobenzaldehyde. Recrystallisation from EtOAc gave the product as orange-yellow crystals (6.7 g, 56%).

R_f 0.48 (9:1 DCM/MeOH); mp 218-220 °C; υ_{max} (film)/cm^{-1} 3055, 2986, 1597, 1518, 1423, 1342, 1175, 897; δ_H (300 MHz, $CDCl_3$) 8.44 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 8.27 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 8.10 (s, 1 H, C*H*N), 3.85 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 146.9 (s), 136.7 (s), 132.7 (d), 128.3 (d), 123.7 (d), 54.7 (q); *m/z* (EI) 180 (M^+, 100), 179 (100), 163 (21), 133 (97), 105 (63), 89 (33); HRMS (EI): calcd for $C_8H_8N_2O_3$ (M^+) 180.0535, found 180.0526.

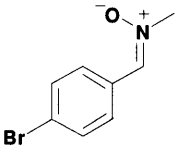
***C*-(4-Chlorophenyl)-*N*-methyl nitrone (119e)** [188, 189]



General protocol was followed using 5 g of 4-chlorobenzaldehyde. Recrystallisation from hexane/EtOAc, gave the required product as white crystals (5.5 g, 91%).

R_f 0.44 (9:1 DCM/MeOH); mp 135-136 °C; υ_{max} (film)/cm^{-1} 3007, 2951, 1558, 1423, 1310, 1173, 947, 854, 739; δ_H (300 MHz, $CDCl_3$) 8.16 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.37 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.34 (s, 1 H, C*H*N), 3.86 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 135.8 (s), 134.1 (d), 129.6 (d), 128.9 (s), 128.8 (d), 54.5 (q); *m/z* (EI) 171 (M^+, ^{37}Cl, 100), 170 (100), 169 (M^+, ^{35}Cl, 99), 168 (98), 152 (34), 139 (75), 125 (31), 111 (43), 99 (32), 89 (93); HRMS (EI): calcd for $C_8H_8{}^{35}ClNO$ (M^+) 169.0294, found 169.0296.

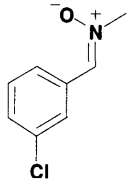
C-(4-Bromophenyl)-*N*-methyl nitrone (119f) [2]



General protocol was followed using 10 g of 4-bromobenzaldehyde. Recrystallisation from hexane/EtOAc, gave the product as white crystals (11.2 g, 96%).

R_f 0.46 (9:1 DCM/MeOH); mp 130-131 °C; υ_{max} (film)/cm^{-1} 3427, 3078, 3003, 1551, 1423, 1310, 1171, 945, 821; δ_H (300 MHz, $CDCl_3$) 8.07 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.51 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.31 (s, 1 H, C*H*N), 3.84 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 134.1 (d), 131.7 (d), 129.7 (d), 129.3 (s), 124.2 (s), 54.6 (q); *m/z* (EI) 215 (M^+, ^{81}Br, 88), 214 (100), 213 (M^+, ^{79}Br, 89), 212 (99), 185 (23), 89 (37); HRMS (EI): calcd for $C_8H_8{}^{79}BrNO$ (M^+) 212.9789, found 212.9784.

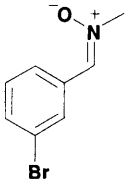
C-(3-Chlorophenyl)-*N*-methyl nitrone (119g) [69, 94]



General protocol was followed using 10 g of 3-chlorobenzaldehyde. Recrystallisation from hexane/EtOAc provided the product as a white solid (11.6 g, 96%).

R_f 0.33 (9:1 DCM/MeOH); mp 57-58 °C; υ_{max} (film)/cm^{-1} 3410, 3096, 1560, 1470, 1418, 1273, 1171, 1090, 947, 787; δ_H (300 MHz, $CDCl_3$) 8.33 (s, 1 H, Ar*H*) 7.89 (d, *J* = 7.1 Hz, 1 H, Ar*H*), 7.26-7.33 (m, 3 H, C*H*N and Ar*H*), 3.82 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 134.4 (s), 133.9 (d), 132.0 (s), 130.3 (d), 129.7 (d), 127.8 (d), 126.5 (d), 54.6 (q); *m/z* (EI) 171 (M^+, ^{37}Cl, 32), 170 (42), 169 (M^+, ^{35}Cl, 100), 168 (96), 89 (53); HRMS (EI): calcd for $C_8H_8{}^{35}ClNO$ (M^+) 169.0294, found 169.0297.

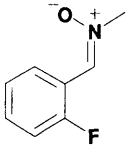
***C*-(3-Bromophenyl)-*N*-methyl nitrone (119h)** [69, 94]



General protocol was followed using 10 g of 3-bromobenzaldehyde. Recrystallisation from hexane/EtOAc, gave the product as a white solid (11.5 g, 99%).

R_f 0.36 (9:1 DCM/MeOH); mp 59-60 °C; υ_{max} (film)/cm^{-1} 3418, 3053, 2986, 1636, 1589, 1420, 1173, 1076, 991, 894, 748; δ_H (300 MHz, $CDCl_3$) 8.47 (s, 1 H, Ar*H*), 8.04 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.52 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.32 (s, 1 H, C*H*N), 7.24-7.30 (m, 1 H, Ar*H*), 3.88 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 133.7 (d), 133.2 (d), 132.3 (s), 130.7 (d), 129.9 (d), 126.9 (d), 122.6 (s), 54.6 (q); *m/z* (EI) 215 (M^+, ^{81}Br, 100), 214 (99), 213 (M^+, ^{79}Br, 95), 212 (90), 196 (100), 185 (88), 171 (33), 157 (43), 134 (87), 119 (78), 106 (95); HRMS (EI): calcd for $C_8H_8{}^{79}BrNO$ (M^+) 212.9789, found 212.9790.

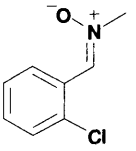
***C*-(2-Fluorophenyl)-*N*-methyl nitrone (119i)** [69, 94]



General protocol was followed using 5 g of 2-fluorobenzaldehyde. Recrystallisation from hexane/EtOAc, gave the product as a light orange solid (5.9 g, 96%).

R_f 0.70 (9:1 DCM/MeOH); mp 58-59 °C; υ_{max} (film)/cm^{-1} 3412, 3111, 2941, 1643, 1597, 1410, 1308, 1167, 1103, 1031, 947, 772; δ_H (300 MHz, $CDCl_3$) 9.20 (app. t, *J* = 7.7 Hz, 1 H, Ar*H*), 7.65 (s, 1 H, C*H*N), 7.34-7.44 (m, 1 H, Ar*H*), 7.20 (app t, *J* = 7.6 Hz, 1 H, Ar*H*), 7.02-7.09 (m, 1 H, Ar*H*), 3.89 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 159.8 (s, J_{CF} = 252.8 Hz), 131.6 (d, J_{CF} = 8.7 Hz), 128.6 (d, J_{CF} = 1.1 Hz), 127.4 (d, J_{CF} = 8.8 Hz), 124.3 (d, J_{CF} = 3.7 Hz), 118.9 (s, J_{CF} = 8.9 Hz), 114.6 (d, J_{CF} = 21.2 Hz), 54.9 (q); *m/z* (EI) 153 (M^+, 100), 123 (49), 107 (18); HRMS (EI): calcd for C_8H_8FNO (M^+) 153.0590, found 153.0597.

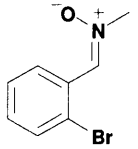
***C*-(2-Chlorophenyl)-*N*-methyl nitrone (119j)**



General protocol was followed using 10 g of 2-chlorobenzaldehyde. Recrystallisation from hexane/EtOAc gave the product as a white solid (11.7 g, 97%).

R_f 0.34 (9:1 DCM/MeOH); mp 79-81 °C; υ_{max} (film)/cm^{-1} 3418, 3055, 2986, 1583, 1423, 1265, 1175, 1043, 897, 745; δ_H (300 MHz, $CDCl_3$) 9.26 (dd, J = 7.2, 2.7 Hz, 1 H, Ar*H*), 7.82 (s, 1 H, C*H*N), 7.24-7.38 (m, 3 H, Ar*H*), 3.89 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 132.7 (s), 131.0 (d), 129.4 (d), 129.0 (d), 128.1 (s), 127.1 (d), 113.0 (d), 55.3 (q); *m/z* (EI) 171 (M^+, ^{37}Cl, 47), 170 (100), 169 (M^+, ^{35}Cl, 50), 152 (22), 107 (33), 89 (27); HRMS (EI): calcd for $C_8H_8{}^{35}ClNO$ (M^+) 169.0294, found 169.0295.

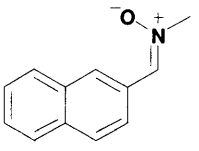
C-(2-Bromophenyl)-N-methyl nitrone (119k)



General protocol was followed using 10 g of 2-bromobenzaldehyde. Recrystallisation from hexane/EtOAc, gave the product as white crystals (9.6 g, 83%).

R_f 0.49 (9:1 DCM/MeOH); mp 88-89 °C; υ_{max} (film)/cm^{-1} 3412, 3090, 2937, 1636, 1578, 1420, 1171, 1096, 1018, 947, 754; δ_H (300 MHz, $CDCl_3$) 9.26 (dd, J = 8.0, 1.9 Hz, 1 H, Ar*H*), 7.82 (s, 1 H, C*H*N), 7.59 (dd, J = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.37 (app. dt, J = 7.8, 1.3 Hz, 1 H, Ar*H*), 7.22 (app. dt, J = 7.8, 1.9 Hz, 1 H, Ar*H*), 3.91 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 133.6 (d), 132.8 (d), 131.4 (d), 129.5 (s), 129.3 (d), 127.7 (d), 123.1 (s), 55.3 (q); *m/z* (EI) 215 (M^+, ^{81}Br, 82), 213 (M^+, ^{79}Br, 85), 183 (16), 134 (100), 119 (78), 107 (95), 91 (58); HRMS (EI): calcd for $C_8H_8{}^{79}BrNO$ (M^+) 212.9789, found 212.9791.

C-(Naphthyl)-N-methyl nitrone (119l) [69, 94]

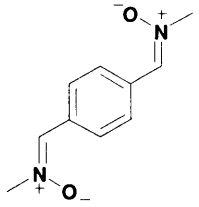


General protocol was followed using 10 g of 2-Naphthaldehyde. Recrystallisation from hexane/EtOAc provided the product as cream crystals (11.8 g, 99%).

R_f 0.11 (20:1 Et_2O/AcOH); mp 126-128 °C; υ_{max} (film)/cm^{-1} 3416, 3090, 2941, 1574, 1415, 1366, 1128, 957, 842; δ_H (300 MHz, $CDCl_3$) 9.18 (s, 1 H, C*H*N), 7.79-7.93 (m, 4 H, Ar*H*), 7.48-7.52 (m, 3 H, Ar*H*), 3.90 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 135.3 (d), 134.1 (s), 133.1 (s), 129.2 (d), 128.4 (d), 128.0 (d), 127.8 (s), 127.6 (d), 127.4 (d), 126.5

(d), 125.7 (d), 54.5 (q); *m/z* (EI) 185 (M^+, 100), 184 (57), 139 (20), 127 (16), 115 (36); HRMS (EI): calcd for $C_{12}H_{11}NO$ (M^+) 185.0841, found 185.0844.

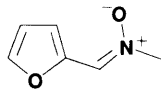
_N,N'_-Dimethyl-_p_-phenylene dinitrone (119m) [190]



General protocol was followed using 5 g of terephthaldehyde, gave the product as yellow crystals (1.2 g, 17%).

R_f 0.29 (9:1 DCM/MeOH); mp 248-250 °C; υ_{max} (film)/cm^{-1} 3319, 3055, 2986, 1580, 1416, 1310, 1265, 1169, 937; δ_H (300 MHz, $CDCl_3$) 8.24 (s, 4 H, Ar*H*), 7.40 (s, 2 H, C*H*N), 3.88 (s, 6 H, CH_3); δ_C (75 MHz, DMSO) 133.4 (d), 131.8 (s), 127.5 (d), 54.1 (q); *m/z* (EI) 219 (70), 192 (M^+, 57), 184 (54), 175 (22), 155 (24), 136 (24), 115 (23), 91 (55), 85 (46); HRMS (EI): calcd for $C_{10}H_{12}N_2O_2$ (M^+) 192.0899, found 192.0894.

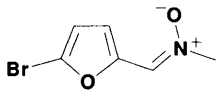
_C_-(2-Furyl)-_N_-methyl nitrone (119n) [69, 94]



General protocol was followed using 10 g of 2-furaldehyde. Recrystallisation from hexane/EtOAc, gave the product as orange crystals (12.8 g, 98%).

R_f 0.36 (9:1 DCM/MeOH); mp 96-98 °C; υ_{max} (film)/cm^{-1} 3369, 3105, 1678, 1612, 1479, 1402, 1229, 1146, 1011, 939; δ_H (300 MHz, $CDCl_3$) 7.69 (d, J = 3.5 Hz, 1 H, C*H*O), 7.50 (s, 1 H, C*H*N), 7.42 (d, J = 1.4 Hz, 1 H, C*H*CO), 6.49 (ddd, J = 3.5, 1.8, 0.6 Hz, 1 H, OCHC*H*CH), 3.77 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 146.7 (s), 143.6 (d), 123.6 (d), 115.2 (d), 112.3 (d), 52.7 (q); *m/z* (EI) 126 (98), 125 (M^+, 98), 125 (98), 124 (24), 108 (100); HRMS (EI): calcd for $C_6H_7NO_2$ (M^+) 125.0477, found 125.0479.

_C_-(5-Bromofuryl)-_N_-methyl nitrone (119o) [69, 94]

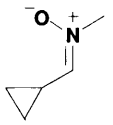


General protocol was followed using 5 g of 5-bromo-2-furaldehyde. Recrystallisation from hexane/EtOAc, gave the product as off white crystals (5.7 g, 98%).

R_f 0.40 (9:1 DCM/MeOH); mp 142-143 °C; υ_{max} (film)/cm^{-1} 3396, 3053, 2984, 1599, 1479, 1396, 1225, 1136, 1009, 912; δ_H (300 MHz, $CDCl_3$) 7.64 (d, J = 3.5 Hz, 1 H,

C*H*CO), 7.46 (s, 1 H, C*H*N), 6.42 (d, *J* = 3.5 Hz, 1 H, C*H*CBr), 3.77 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 148.7 (s), 125.2 (d), 124.2 (s), 117.3 (d), 114.1 (d), 52.8 (q); *m/z* (EI) 205 (M^+, ^{81}Br, 98), 203 (M^+, ^{79}Br, 100), 79 (97); HRMS (EI): calcd for $C_6H_6{}^{79}BrNO_2$ (M^+) 202.9582, found 202.9589.

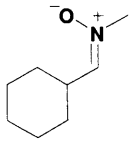
C-(Cyclopropyl)-N-methyl nitrone (119p) [69, 94]



General protocol was followed using 5 g of cyclopropane carboxaldehyde, to give the product as a yellow oil (7.0 g, 99%).

R_f 0.24 (9:1 DCM/MeOH); υ_{max} (neat)/cm^{-1} 3387, 3005, 2945, 1616, 1408, 1319, 1227, 1138, 970; δ_H (300 MHz, $CDCl_3$) 6.07 (d, *J* = 8.5 Hz, 1 H, C*H*N), 3.56 (s, 3 H, CH_3), 2.18-2.30 (m, 1 H, $CH(CH_2)_2$), 0.92-0.99 (m, 2 H, CH_2CH), 0.57-0.60 (m, 2 H, CH_2CH); δ_C (75 MHz, $CDCl_3$) 143.2 (d), 51.8 (q), 9.3 (d), 6.9 (t), 6.6 (t); *m/z* (EI) 99 (M^+, 68), 86 (34), 84 (100); HRMS (EI): calcd for C_5H_9NO (M^+) 99.0684, found 99.0690.

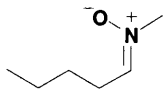
C-(Cyclohexyl)-N-methyl nitrone (119q) [69, 94]



General protocol was followed using 5 g of cyclohexancarboxaldehyde. Gave the product as a white solid (6.0 g, 95%).

R_f 0.49 (9:1 DCM/MeOH); mp 51-52 °C; υ_{max} (film)/cm^{-1} 3395, 2928, 2855, 1616, 1447, 1356, 1171, 972, 941, 889; δ_H (300 MHz, $CDCl_3$) 6.42 (d, *J* = 7.5 Hz, 1 H, C*H*N), 3.57 (s, 3 H, CH_3), 2.85-2.93 (m, 1 H, CH_2CHCH_2), 1.76-1.81 (m, 2 H, CH_2), 1.60-1.65 (m, 3 H, CH_2 and C(*H*)HCH_2), 1.23-1.31 (m, 2 H, CH_2), 1.01-1.14 (m, 3 H, CH_2 and C(H)HCH_2); δ_C (75 MHz, $CDCl_3$) 144.2 (d), 52.6 (q), 44.2 (d), 28.7 (t), 25.8 (t), 25.1 (t); *m/z* (EI) 141 (M^+, 97), 124 (25), 111 (29), 95 (100), 83 (45); HRMS (EI): calcd for $C_8H_{15}NO$ (M^+) 141.1154, found 141.1160.

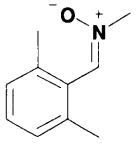
C-(Pentyl)-N-methyl nitrone (119r) [69, 94]



General protocol was followed using 10 g of valeraldehyde. Purified by flash chromatography (98:2 DCM/MeOH), to give the product as a light yellow solid (8.1 g, 61%).

R_f 0.34 (9:1 DCM/MeOH); mp 62-64 °C; υ_{max} (film)/cm^{-1} 3246, 2955, 2864, 1636, 1456, 1375, 1126, 1086, 947; δ_H (300 MHz, $CDCl_3$) 6.61 (t, J = 5.9 Hz, 1 H, C*H*N), 3.61 (s, 3 H, NCH_3), 2.40 (app. q, J = 7.0 Hz, 2 H, CH_2CHN), 1.24-1.48 (m, 4 H, CH_3(CH_2)$_2$CH_2), 0.85 (t, J = 7.2 Hz, 3 H, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 140.5 (d), 52.3 (q), 27.5 (t), 26.5 (t), 22.5 (t), 13.7 (q); *m/z* (EI) 115 (M^+, 100), 86 (18); HRMS (EI): calcd for $C_6H_{13}NO$ (M^+) 115.0997, found 115.0997.

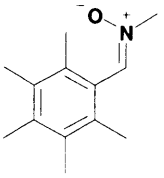
C-(2,6-Dimethylphenyl)-N-methyl nitrone (119s) [191]



General protocol was followed using 4 g of 2,6-dimethylbenzaldehyde, and refluxed for 18 hours. Recrystallisation from hexane/EtOAc provided the product as white crystals (4.1 g, 85%).

R_f 0.41 (9:1 DCM/MeOH); mp 156-159 °C; υ_{max} (neat)/cm^{-1} 3040, 2913, 1590, 1460, 1431, 1395, 1176, 1042, 954; δ_H (300 MHz, $CDCl_3$) 7.56 (br s, 1 H, C*H*N), 7.19 (dd, J = 8.0, 7.2 Hz, 1 H, Ar*H*), 7.05 (d, J = 7.8 Hz, 2 H, Ar*H*), 3.90 (s, 3 H, NCH_3), 2.29 (s, 6 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.6 (s), 137.2 (s), 135.4 (d), 129.5 (d), 128.5 (s), 128.1 (d), 127.6 (d), 53.4 (q), 19.9 (q); *m/z* (CI) 164 (MH^+,100); HRMS (CI): calcd for $C_{10}H_{14}NO$ (MH^+) 164.1075, found 164.1068.

C-(2,3,4,5,6-Pentamethylphenyl)-N-methyl nitrone (119t) [191]

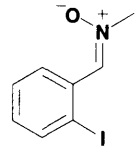


General protocol was followed using 2 g of pentamethylbenzaldehyde, and refluxed for 18 hours. Recrystallisation from hexane/EtOAc provided the product as white crystals (1.4 g, 59%).

R_f 0.44 (9:1 DCM/MeOH); mp 206-209 °C; υ_{max} (neat)/cm^{-1} 3037, 2916, 1585, 1417, 1389, 1182, 952; δ_H (500 MHz, $CDCl_3$) 7.61 (s, 1 H, C*H*N), 3.90 (s, 3 H, NCH_3), 2.23 (s, 3 H, Ar(CH_3)$_5$), 2.20 (s, 6 H, Ar(CH_3)$_5$), 2.18 (s, 6 H, Ar(CH_3)$_5$); δ_C (125 MHz,

$CDCl_3$) 137.2 (d), 136.8 (s), 132.9 (s), 132.3 (s), 126.5 (s), 53.0 (q), 17.3 (q), 17.0 (q), 16.4 (q); *m/z* (EI) 205 (M^+, 26), 190 (97), 175 (100), 159 (34), 149 (18); HRMS (EI): calcd for $C_{13}H_{19}NO$ (M^+) 205.1461, found 205.1470.

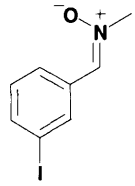
_C_-(2-Iodophenyl)-_N_-methyl nitrone (119u)



General protocol was followed using 0.5 g of 2-iodobenzaldehyde, and refluxed for 18 hours. Recrystallised from hexane/EtOAc, gave the product as white crystals (0.6 g, 98%).

R_f 0.59 (9:1 DCM/MeOH); mp 122-124 °C; υ_{max} (neat)/cm^{-1} 3086, 2924, 1573, 1405, 1164, 1011, 946; δ_H (300 MHz, $CDCl_3$) 9.18 (dd, *J* = 8.0, 1.6 Hz, 1 H, Ar*H*), 7.89 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.70 (s, 1 H, C*H*N), 7.38-7.44 (m, 1 H, Ar*H*), 7.06 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 3.91 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 139.7 (d), 138.6 (d), 132.3 (s), 131.6 (d), 129.2 (d), 128.5 (d), 99.0 (s), 55.2 (q); *m/z* (EI) 261 (M^+, 100), 245 (33), 134 (52), 119 (49), 107 (99), 89 (66), 77 (98), 63 (64); HRMS (EI): calcd for C_8H_8INO (M^+) 260.9645, found 260.9635.

_C_-(3-Iodophenyl)-_N_-methyl nitrone (119v)



General protocol was followed using 0.5 g of 3-iodobenzaldehyde, and refluxed for 18 hours. Recrystallised from hexane/EtOAc, gave the product as white crystals (0.5 g, 89%).

R_f 0.58 (9:1 DCM/MeOH); mp 110-113 °C; υ_{max} (neat)/cm^{-1} 3078, 1575, 1468, 1392, 1159, 1064, 948; δ_H (300 MHz, $CDCl_3$) 8.60 (s, 1 H, Ar*H*), 8.11 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.71 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.28 (s, 1 H, C*H*N), 7.12 (app. t, *J* = 8.0 Hz, 1 H, Ar*H*), 3.86 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 139.2 (d), 136.7 (d), 133.6 (d), 132.3 (s), 130.1 (d), 127.4 (d), 94.2 (s), 54.7 (q); *m/z* (EI) 261 (M^+, 100); HRMS (EI): calcd for C_8H_8INO (M^+) 260.9645, found 260.9645.

4.3. Cycloaddition with pentafluorophenyl-vinyl sulfonate procedures

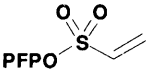
Method A:

To pentafluorophenyl vinyl sulfonate **100** (1 eq.) in dry toluene was added nitrone (1.2-2 eq.), and the mixture was heated at reflux for 1-5 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 petroleum ether 40-60°C /Et_2O) to give the title compound.

Method B:

To pentafluorophenyl vinyl sulfonate **100** (1 eq.) in dry toluene was added nitrone (1.5 eq.), and the mixture was heated in a CEM microwave at 140 °C for 10 mins. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 9:1 petroleum ether 40-60°C/Et_2O) to give the title compound

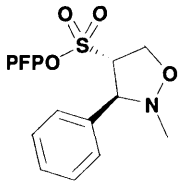
Pentafluorophenyl-vinyl sulfonate (100) [69, 94]



NEt_3 (11.2 g, 110.4 mmol) was carefully added to a stirring suspension of pentafluorophenol (8.1 g, 44.2 mmol) in DCM (20 mL). 2-Chloroethane-1-sulfonyl chloride (6.0 g, 36.8 mmol) in DCM (60 mL) was then treated slowly with the PFP solution while stirring in an ice-MeOH bath, keeping the internal temperature below 10 °C. The reaction was allowed to stir for a further 10 minutes after addition, warmed up to RT, and then diluted with DCM (ca. 50 mL). The DCM layer was washed consecutively with 2M HCl (3 x 50 mL), sat. $NaHCO_3$ (3 x 50 mL), H_2O (1 x 50 mL), dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to leave a crude oil, which was purified by flash chromatography (9:1 hexane/Et_2O) to give a grey solid (8.5 g, 84%).

R_f 0.45 (1:1 hexane/Et_2O); mp 24-26 °C; υ_{max} (neat)/cm^{-1} 3123, 3080, 1649, 1522, 1393, 1144, 997; δ_H (300 MHz, $CDCl_3$) 6.80 (dd, J = 16.5, 9.8 Hz, 1 H, C*H*CH_2), 6.54 (d, J = 16.5 Hz, 1 H, CHC*H*H), 6.34 (d, J = 9.8 Hz, 1 H, CHCH*H*); δ_C (75 MHz, $CDCl_3$) 133.2 (t), 131.8 (d); *m/z* (EI) 274 (M^+, 54), 211 (49), 184 (100), 155 (63), 136 (37), 117 (28), 91 (79); HRMS (EI): calcd for $C_8H_3F_5O_3S$ (M^+) 273.9723, found 273.9727.

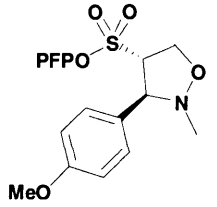
(3*S, 4*S**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103a)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (5.0 g, 18.2 mmol) in dry toluene (50 mL) was added *C*-phenyl-*N*-methyl nitrone **119a** (6.2 g, 45.6 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (4.9 g, 65%) as a grey white solid.

R_f 0.28 (3:1 hexane/Et_2O); mp 69-71 °C; υ_{max} (film)/cm^{-1} 2970, 2880, 1522, 1464, 1391, 1142, 997, 746; δ_H (300 MHz, $CDCl_3$) 7.36-7.49 (m, 5 H, Ar*H*), 4.61 (dd, *J* = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.49 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.33 (app. td, *J* = 7.1, 3.2 Hz, 1 H, SC*H*), 4.06 (d, *J* = 7.1 Hz, 1 H, NC*H*), 2.70 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 135.6 (s), 129.2 (d), 129.1 (d), 128.0 (d), 74.1 (d), 73.9 (d), 66.8 (t), 42.7 (q); *m/z* (EI) 410 (100), 409 (M^+, 100), 332 (33), 183 (76), 161 (100), 119 (100); HRMS (EI): calcd for $C_{16}H_{12}F_5NO_4S$ (M^+) 409.0407, found 409.0418; Anal. calcd for $C_{16}H_{12}F_5NO_4S$: C 46.95, H 2.95, N 3.42, found C 46.87, H 2.92, N 3.27.

(3*S, 4*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103b)** [69, 94]

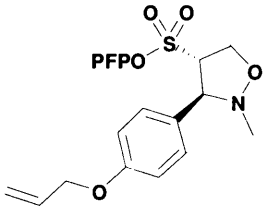


Using Method A. To pentafluorophenyl vinyl sulfonate **100** (4.4 g, 16.1 mmol) in dry toluene (50 mL) was added *C*-(4-methoxyphenyl)-*N*-methyl nitrone **119b** (4.0 g, 24.2 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (5.0 g, 71%) as a yellow solid.

R_f 0.22 (2:1 petroleum ether 40-60°C/Et_2O); mp 79-81 °C; υ_{max} (film)/cm^{-1} 2934, 1612, 1520, 1466, 1389, 1252, 1182, 995; δ_H (300 MHz, $CDCl_3$) 7.37 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.90 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.58 (dd, *J* = 10.2, 3.1 Hz, 1 H, SCHC*H*H), 4.47 (dd, *J* = 10.2, 8.1 Hz, 1 H, SCHCH*H*), 4.29 (app. td, *J* = 7.8, 3.1 Hz, 1 H, SC*H*), 3.99 (d,

J = 7.1 Hz, 1 H, NC*H*), 3.80 (s, 3 H, OCH_3), 2.67 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 160.2 (s), 129.2 (d), 127.2 (s), 114.5 (d), 73.7 (d), 66.7 (t), 55.3 (q), 42.5 (q), 1 x d not observed; *m/z* (EI) 439 (M^+, 57), 184 (19), 165 (100), 147 (55), 86 (55); HRMS (EI): calcd for $C_{17}H_{14}F_5NO_5S$ (M^+) 439.0513, found 439.0501; Anal. calcd for $C_{17}H_{14}F_5NO_5S$: C 46.47, H 3.21, N 3.19, found C 46.40, H 3.11, N 3.16.

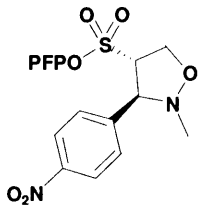
(3*S, 4*S**)-3-(4-Allyloxyphenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103c)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (4.0 g, 14.6 mmol) in dry toluene (50 mL) was added *C*-(4-allyloxyphenyl)-*N*-methyl nitrone **119c** (3.5 g, 18.2 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 petroleum ether 40-60°C/Et_2O) to give the title compound (5.5 g, 81%) as a yellow solid.

R_f 0.38 (2:1 petroleum ether 40-60°C/Et_2O); mp 58-60 °C; υ_{max} (film)/cm^{-1} 2970, 2878, 1611, 1520, 1429, 1389, 1246, 1144, 997, 932, 777; δ_H (300 MHz, $CDCl_3$) 7.37 (d, J = 8.8 Hz, 2 H, Ar*H*), 6.92 (d, J = 8.8 Hz, 2 H, Ar*H*), 6.04 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H, OCH_2CHCH_2), 5.41 (app. dq, J = 17.2, 1.5 Hz, 1 H, OCH_2CHCHH), 5.29 (app dq, J = 10.5, 1.5 Hz, 1 H, OCH_2CHCHH), 4.58 (dd, J = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.53 (app. dt, J = 5.3, 1.5 Hz, 2 H, OCH_2CHCH_2), 4.46 (dd, J = 10.2, 8.0 Hz, 1 H, SCHC*H*H), 4.29 (app. td, J = 7.6, 3.2 Hz, 1 H, SC*H*), 3.99 (d, J = 7.2 Hz, 1 H, NC*H*), 2.63 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 159.2 (s), 133.0 (d), 129.2 (d), 127.4 (s), 117.9 (t), 115.2 (d), 73.8 (d), 68.8 (t), 66.7 (t), 42.6 (q); *m/z* (EI) 465 (M^+, 71), 218 (25), 191 (100), 136 (37); HRMS (EI): calcd for $C_{19}H_{16}F_5NO_5S$ (M^+) 465.0669, found 465.0665.

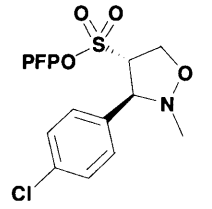
(3*S, 4*S**)-2-Methyl-3-(4-nitro-phenyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester (103d)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (5.0 g, 18.2 mmol) in dry toluene (50 mL) was added *C*-(4-nitrophenyl)-*N*-methyl nitrone **119d** (4.9 g, 27.4 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 petroleum ether 40-60°C/Et_2O) to give the title compound (3.6 g, 43%) as a white solid.

R_f 0.35 (2:1 petroleum ether 40-60°C/Et_2O); mp 127-129 °C; υ_{max} (film)/cm^{-1} 3078, 2856, 1601, 1518, 1389, 1105, 993, 779; δ_H (300 MHz, $CDCl_3$) 8.26 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.70 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 4.62 (dd, *J* = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.50 (dd, *J* = 10.2, 7.8 Hz, 1 H, SCHCH*H*), 4.27 (app. td, *J* = 7.2, 3.2 Hz, 1 H, SC*H*), 4.20 (d, *J* = 7.0 Hz, 1 H, NC*H*), 2.73 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 148.4 (s), 143.1 (s), 129.0 (d), 124.3 (d), 73.8 (d), 72.9 (d), 66.9 (t), 42.9 (q); *m/z* (EI) 454 (M^+, 97), 207 (67), 191 (88), 164 (45), 131 (24), 116 (100); HRMS (EI): calcd for $C_{16}H_{11}F_5N_2O_6S$ (M^+) 454.0258, found 454.0265; Anal. calcd for $C_{16}H_{11}F_5N_2O_6S$: C 42.30, H 2.44, N 6.17, found C 42.41, H 2.43, N 6.05.

(3*S, 4*S**)-3-(4-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103e)**

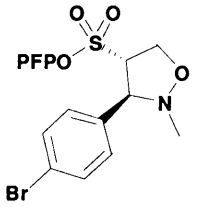


Using Method A. To pentafluorophenyl vinyl sulfonate **100** (3.2 g, 11.8 mmol) in dry toluene (30 mL) was added *C*-(4-chlorophenyl)-*N*-methyl nitrone **119e** (3.0 g, 17.7 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (4.0 g, 77%) as light yellow solid.

R_f 0.46 (2:1 hexane/Et_2O); mp 99-102 °C; υ_{max} (film)/cm^{-1} 2968, 2882, 1522, 1466, 1389, 1184, 1096, 997, 777; δ_H (300 MHz, $CDCl_3$) 7.42 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.36 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.59 (dd, *J* = 10.2, 3.1 Hz, 1 H, SCHC*H*H), 4.47 (dd, *J* =

10.2, 8.1 Hz, 1 H, SCHCH*H*), 4.26 (app. td, *J* = 7.4, 3.1 Hz, 1 H, SC*H*), 4.03 (d, *J* = 7.1 Hz, 1 H, NC*H*), 2.69 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 135.2 (s), 134.1 (s), 129.4 (d), 129.3 (d), 73.8 (d), 73.4 (d), 66.8 (t), 42.7 (q); *m/z* (EI) 445 (M^+, ^{37}Cl, 26), 443 (M^+, ^{35}Cl, 100), 196 (72), 151 (80), 115 (66), 89 (24); HRMS (EI): calcd for $C_{16}H_{11}{}^{35}ClF_5NO_4S$ (M^+) 443.0018, found 443.0019; Anal. calcd for $C_{16}H_{11}ClF_5NO_4S$: C 43.30, H 2.50, N 3.16, found C 43.40, H 2.47, N 2.97.

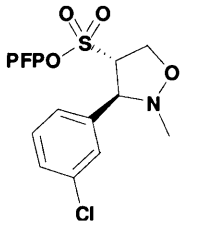
(3*S, 4*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103f)**



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (3.0 g, 10.9 mmol) in dry toluene (30 mL) was added *C*-(4-bromophenyl)-*N*-methyl nitrone **119f** (3.5 g, 16.4 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 petroleum ether 40-60°C/Et_2O) to give the title compound (5.9 g, 66%) as a yellow solid.

R_f 0.33 (2:1 petroleum ether 40-60°C/Et_2O); mp 112-114 °C; υ_{max} (film)/cm^{-1} 2885, 1589, 1518, 1477, 1379, 1171, 993, 783; δ_H (300 MHz, $CDCl_3$) 7.52 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.35 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.59 (dd, *J* = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.46 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.25 (app. td, *J* = 7.4, 3.2 Hz, 1 H, SC*H*), 4.02 (d, *J* = 7.2 Hz, 1 H, NC*H*), 2.69 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 134.7 (s), 132.3 (d), 129.6 (d), 123.3 (s), 73.8 (d), 73.4 (d), 66.8 (t), 42.7 (q); *m/z* (EI) 489 (M^+, ^{81}Br, 50), 487 (M^+, ^{79}Br, 48), 240 (28), 213 (22), 197 (18), 116 (100); HRMS (EI): calcd for $C_{16}H_{11}{}^{79}BrF_5NO_4S$ (M^+) 486.9512, found 486.9506; Anal. calcd for $C_{16}H_{11}BrF_5NO_4S$: C 39.36, H 2.27, N 2.87, found C 39.40, H 2.22, N 2.75.

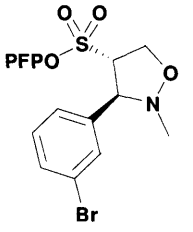
(3*S, 4*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103g)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (5.0 g, 18.2 mmol) in dry toluene (50 mL) was added *C*-(3-chlorophenyl)-*N*-methyl nitrone **119g** (4.6 g, 27.4 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (5.3 g, 65%) as a yellow solid.

R_f 0.37 (3:1 hexane/Et_2O); mp 78-81 °C; υ_{max} (neat)/cm^{-1} 3080, 2970, 1576, 1516, 1472, 1394, 1267, 1142, 993, 791; δ_H (300 MHz, $CDCl_3$) 7.49 (s, 1 H, Ar*H*), 7.29-7.38 (m, 3 H, Ar*H*), 4.59 (dd, *J* = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.47 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.28 (app. td, *J* = 7.2, 3.2 Hz, 1 H, SC*H*), 4.04 (d, *J* = 7.0 Hz, 1 H, NC*H*), 2.71 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 135.0 (s), 130.4 (d), 129.4 (d), 127.9 (d), 126.4 (d), 73.8 (d), 73.3 (d), 66.8 (t), 42.7 (q); *m/z* (EI) 445 (M^+, ^{37}Cl, 26), 443 (M^+, ^{35}Cl, 72), 196 (32), 151 (34), 101 (100); HRMS (EI): calcd for $C_{16}H_{11}{}^{35}ClF_5NO_4S$ (M^+) 443.0018, found 443.0019; Anal. calcd for $C_{16}H_{11}ClF_5NO_4S$: C 43.30, H 2.50, N 3.16, found C 43.66, H 2.41, N 3.10.

(3*S, 4*S**)-3-(3-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103h)** [69, 94]

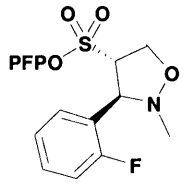


Using Method A. To pentafluorophenyl vinyl sulfonate **100** (5.0 g, 18.2 mmol) in dry toluene (50 mL) was added *C*-(3-bromophenyl)-*N*-methyl nitrone **119h** (5.9 g, 27.4 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (5.9 g, 66%) as a light brown solid.

R_f 0.26 (3:1 hexane/Et_2O); mp 86-88 °C; υ_{max} (film)/cm^{-1} 3090, 2968, 2881, 1570, 1522, 1431, 1391, 1267, 1142, 997, 791; δ_H (300 MHz, $CDCl_3$) 7.65 (s, 1 H, Ar*H*), 7.48-7.52 (m, 1 H Ar*H*), 7.40 (br d, *J* = 7.7 Hz, 1 H, Ar*H*), 7.26 (app. t, *J* = 7.7 Hz, 1 H, Ar*H*), 4.59 (dd, *J* = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.46 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.28 (app. td, *J* = 7.1, 3.2 Hz, 1 H, SC*H*), 4.02 (d, *J* = 7.0 Hz, 1 H, NC*H*), 2.71 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 138.1 (s), 132.4 (d), 130.7 (d), 130.6 (d), 126.9 (d), 123.2 (s), 73.8 (d), 73.2 (d), 66.8 (t), 42.8 (q); *m/z* (EI) 488 (M^+, ^{81}Br, 64), 486 (M^+, ^{79}Br, 63), 332 (54), 274 (20), 241 (73), 155 (72), 117 (68), 89 (100); HRMS (EI): calcd for

$C_{16}H_{11}{}^{79}BrF_5NO_4S$ (M^+) 486.9512, found 486.9506; Anal. calcd for $C_{16}H_{11}BrF_5NO_4S$: C 39.36, H 2.27, N 2.87, found C 39.09, H 2.24, N 2.64.

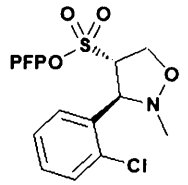
(3*S, 4*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103i)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (4.0 g, 14.6 mmol) in dry toluene (50 mL) was added *C*-(2-fluorophenyl)-*N*-methyl nitrone **119i** (3.4 g, 21.9 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (2.9 g, 47%) as a yellow oil.

R_f 0.28 (2:1 hexane/Et_2O); υ_{max} (neat)/cm^{-1} 2970, 2883, 1618, 1587, 1522, 1462, 1394, 1184, 1105, 995, 779; δ_H (300 MHz, $CDCl_3$) 7.47 (ddd, J = 9.0, 7.4, 1.5 Hz, 1 H, Ar*H*), 7.34-7.41 (m, 1 H, Ar*H*), 7.09-7.23 (m, 2 H, Ar*H*), 4.63 (dd, J = 14.1, 7.4 Hz, 1 H, SCHC*H*H), 4.49-4.56 (m, 2 H, SC*H* and SCHCH*H*), 4.33 (br d, J = 4.8 Hz, 1 H, NC*H*), 2.70 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 161.2 (s, J_{CF} = 248.4 Hz), 131.0 (d, J_{CF} = 8.6 Hz), 129.9 (d, J_{CF} = 3.3 Hz), 124.9 (d, J_{CF} = 3.6 Hz), 122.1 (s, J_{CF} = 11.6 Hz), 116.3 (d, J_{CF} = 21.6 Hz), 72.3 (d), 68.6 (d), 66.9 (t), 42.8 (q); *m/z* (EI) 427 (M^+, 100), 180 (99), 133 (98); HRMS (EI): calcd for $C_{16}H_{11}F_6NO_4S$ (M^+) 427.0313, found 427.0335; Anal. calcd for $C_{16}H_{11}F_6NO_4S$: C 44.97, H 2.59, N 3.28, found C 45.48, H 2.71, N 2.88.

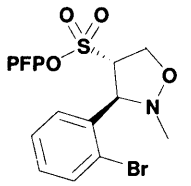
(3*S, 4*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103j)**



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (3.0 g, 10.9 mmol) in dry toluene (30 mL) was added *C*-(2-chlorophenyl)-*N*-methyl nitrone **119j** (2.8 g, 16.4 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (2.7 g, 56%) as an orange solid.

R_f 0.23 (2:1 petroleum ether 40-60°C/Et_2O); mp 72-73 °C; υ_{max} (film)/cm^{-1} 2968, 2883, 1580, 1522, 1472, 1393, 1186, 998, 783; δ_H (300 MHz, $CDCl_3$) 7.52-7.56 (m, 1 H, Ar*H*), 7.41-7.44 (m, 1 H, Ar*H*), 7.30-7.35 (m, 2 H, Ar*H*), 4.71 (br d, *J* = 6.9 Hz, 1 H, NC*H*), 4.65 (dd, *J* = 10.1, 3.2 Hz, 1 H, SCHC*H*H), 4.56 (dd, *J* = 10.1, 7.9 Hz, 1 H, SCHCH*H*), 4.45 (app. td, *J* = 7.3, 3.2 Hz, 1 H, SC*H*), 2.70 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 134.6 (s), 132.7 (s), 130.4 (d), 130.3 (d), 129.8 (d), 127.6 (d), 73.0 (d), 70.1 (d), 67.1 (t), 42.6 (q); *m/z* (EI) 445 (M^+, ^{37}Cl, 38), 443 (M^+, ^{35}Cl, 100), 196 (88), 151 (63), 134 (66), 115 (44); HRMS (EI): calcd for $C_{16}H_{11}ClF_5NO_4S$ (M^+) 443.0018, found 443.0023; Anal. calcd for $C_{16}H_{11}{}^{35}ClF_5NO_4S$: C 43.30, H 2.50, N 3.16, found C 43.45, H 2.57, N 2.87.

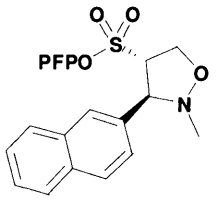
(3*S, 4*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103k)**



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (3.5 g, 12.8 mmol) in dry toluene (40 mL) was added *C*-(2-bromophenyl)-*N*-methyl nitrone **119k** (4.1 g, 19.2 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (3.2 g, 51%) as a light brown solid.

R_f 0.26 (2:1 petroleum ether 40-60°C/Et_2O); mp 76-78 °C; υ_{max} (film)/cm^{-1} 2967, 2919, 1515, 1475, 1386, 1179, 992, 778; δ_H (300 MHz, $CDCl_3$) 7.61 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.52 (dd, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.34 (app. dt, *J* = 7.5, 1.3 Hz, 1 H, Ar*H*), 7.23 (app. dt, *J* = 7.8, 1.9 Hz, 1 H, Ar*H*), 4.75 (br d, *J* = 6.8 Hz, 1 H, NC*H*), 4.64 (dd, *J* = 10.2, 3.3 Hz, 1 H, SCHC*H*H), 4.55 (dd, *J* = 10.2, 7.9 Hz, 1 H, SCHCH*H*), 4.42 (app. td, *J* = 7.6, 3.3 Hz, 1 H, SC*H*), 2.71 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 134.4 (s), 133.7 (d), 130.5 (d), 129.9 (d), 128.2 (d), 124.8 (s), 73.2 (d), 72.1 (d), 67.2 (t), 42.5 (q); *m/z* (EI) 489 (M^+, ^{81}Br, 20), 487 (M^+, ^{79}Br, 20), 244 (70), 240 (43), 198 (16), 183 (23), 155 (24), 134 (57), 116 (100); HRMS (EI): calcd for $C_{16}H_{11}{}^{79}BrF_5NO_4S$ (M^+) 486.9507, found 486.9499.

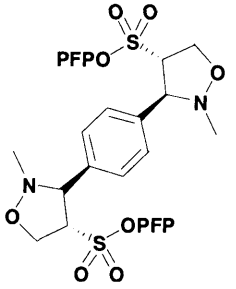
(3*S, 4*S**)-2-Methyl-3-naphthalen-2-ylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103l)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (4.0 g, 14.6 mmol) in dry toluene (50 mL) was added *C*-(2-naphthyl)-*N*-methyl nitrone **119l** (4.1 g, 21.9 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (starting 16:1 hexane/Et_2O) to give the title compound (4.8 g, 72%) as a yellow solid.

R_f 0.27 (3:1 hexane/Et_2O); mp 111-114 °C; υ_{max} (film)/cm^{-1} 3059, 2968, 2880, 1520, 1466, 1389, 1184, 995, 822, 746; δ_H (300 MHz, $CDCl_3$) 7.96 (s, 1 H, Ar*H*), 7.84-7.91 (m, 3 H, Ar*H*), 7.58 (dd, *J* = 8.5, 1.5 Hz, 1 H, Ar*H*), 7.50-7.55 (m, 2 H, Ar*H*), 4.67 (dd, *J* = 10.2, 3.1 Hz, 1 H, SCHC*H*H), 4.56 (dd, *J* = 10.2, 7.9 Hz, 1 H, SCHCH*H*), 4.44 (app. td, *J* = 7.3, 3.1 Hz, 1 H, SC*H*), 4.14 (d, *J* = 7.4 Hz, 1 H, NC*H*), 2.75 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 133.6 (s), 133.2 (s), 132.9 (s), 129.2 (d), 128.1 (d), 128.0 (d), 127.8 (d), 126.8 (d), 126.7 (d), 124.7 (d), 74.3 (d), 73.4 (d), 67.0 (t), 42.8 (q); *m/z* (EI) 459 (M^+, 35), 185 (26), 167 (100), 152 (41), 128 (34); HRMS (EI): calcd for $C_{20}H_{14}F_5NO_4S$ (M^+) 459.0564, found 459.0572; Anal. calcd for $C_{20}H_{14}F_5NO_4S$: C 52.29, H 3.07, N 3.05, found C 52.11, H 2.98, N 2.96.

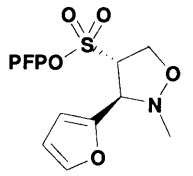
(3*S, 4*S**)-Terephthyl PFP bis-isoxazolidine (103m)**



Using Method A with 1.4 eq. of **100**. To pentafluorophenyl vinyl sulfonate **100** (1.0 g, 3.7 mmol) in dry toluene (10 mL) was added *C*-(terephthyl)-*N*-methyl bis nitrone **119m** (0.5 g, 2.7 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 petroleum ether 40-60°C/Et_2O) to give the title compound (0.9 g, 35%) as a white solid.

R_f 0.09 (2:1 petroleum ether 40-60°C/Et_2O); mp 66-68 °C; υ_{max} (film)/cm^{-1} 2882, 1522, 1466, 1389, 1184, 997; δ_H (300 MHz, $CDCl_3$) 7.51 (br s, 4 H, Ar*H*), 4.59 (dd, *J* = 10.2, 2.9 Hz, 2 H, SCHC*H*H), 4.47 (app. t, *J* = 9.1 Hz, 2 H, SCHCH*H*), 4.29 (app. td, *J* = 7.5, 2.9 Hz, 2 H, SC*H*), 4.08 (app. t, *J* = 6.4 Hz, 2 H, NC*H*), 2.70 (s, 6 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 136.9 (s), 136.8 (s), 128.7 (d), 128.2 (d), 73.9 (d), 73.8 (d), 73.5 (d), 66.9 (t), 66.8 (t), 42.9 (q), 42.7 (q); *m/z* (FAB^+) 740 (MH^+, 7), 307 (19), 154 (100); HRMS (FAB^+): calcd for $C_{26}H_{19}F_{10}N_2O_8S_2$ (MH^+) 741.0423, found 741.0410; Anal. calcd for $C_{26}H_{18}F_{10}N_2O_8S_2$: C 42.17, H 2.45, N 3.78, found C 42.40, H 2.49, N 3.62.

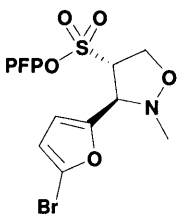
(3*S, 4*S**)-3-Furan-2-yl-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103n)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (5.0 g, 18.2 mmol) in dry toluene (50 mL) was added *C*-(2-furyl)-*N*-methyl nitrone **119n** (4.6 g, 36.5 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (5.1 g, 70%) as a brown oil.

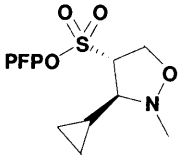
R_f 0.28 (2:1 hexane/Et_2O); υ_{max} (neat)/cm^{-1} 3126, 2972, 2883, 1520, 1468, 1344, 1246, 1145, 1107, 999, 750; δ_H (300 MHz, $CDCl_3$) 7.46-7.48 (m, 1 H, OC*H*CHCH), 6.48 (d, *J* = 3.2 Hz, 1 H, OCC*H*CH), 6.38 (dd, *J* = 3.2, 1.9 Hz, 1 H, OCHC*H*CH), 4.69 (app. td, *J* = 7.8, 3.2 Hz, 1 H, SC*H*), 4.59 (dd, *J* = 10.3, 3.2 Hz, 1 H, SCHC*H*H), 4.45-4.51 (m, 1 H, SCHCH*H*), 4.17 (br s, 1 H, NC*H*), 2.76 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 146.7 (s), 144.0 (d), 111.1 (d), 110.8 (d), 69.7 (d), 67.5 (d), 66.7 (t), 42.8 (q); *m/z* (EI) 399 (M^+, 100); HRMS (EI): calcd for $C_{14}H_{10}F_5NO_5S$ (M^+) 399.0200, found 399.0185.

(3*S, 4*S**)-3-(5-Bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103o)** [69, 94]



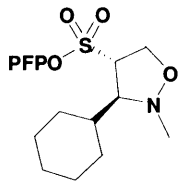
Using Method A. To pentafluorophenyl vinyl sulfonate **100** (5.6 g, 20.4 mmol) in dry toluene (50 mL) was added *C*-(5-bromo-2-furyl)-*N*-methyl nitrone **119o** (5.0 g, 24.5 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 petroleum ether 40-60°C/Et_2O) to give the title compound (4.3 g, 44%) as a yellow oil.
R_f 0.59 (1:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 3138, 2972, 1649, 1520, 1468, 1321, 1184, 1130, 997, 791; δ_H (300 MHz, $CDCl_3$) 6.47 (d, *J* = 3.3 Hz, 1 H, C*H*CO), 6.31 (d, *J* = 3.3 Hz, 1 H, C*H*CBr), 4.66 (app. td, *J* = 7.3, 3.0 Hz, 1 H, SC*H*), 4.57 (dd, *J* = 10.2, 3.0 Hz, 1 H, SCHC*H*H), 4.47 (dd, *J* = 10.2, 8.2 Hz, 1 H, SCHCH*H*), 4.11 (br s, 1 H, NC*H*), 2.75 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 148.7 (s), 123.8 (s), 113.8 (d), 112.6 (d), 69.6 (d), 67.5 (d), 66.7 (t), 42.9 (q); *m/z* (EI) 479 (M^+, ^{81}Br, 67), 477 (M^+, ^{79}Br, 63), 433 (37), 230 (25), 205 (100), 159 (41), 106 (42); HRMS (EI): calcd for $C_{14}H_9{}^{79}BrF_5NO_5S$ (M^+) 476.9305, found 476.9307; Anal. calcd for $C_{14}H_9BrF_5NO_5S$: C 35.16, H 1.90, N 2.93, found C 34.90, H 1.89, N 2.53.

(3*S, 4*S**)-3-Cyclopropyl-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103p)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (4.0 g, 14.6 mmol) in dry toluene (50 mL) was added *C*-(cyclopropyl)-*N*-methyl nitrone **119p** (1.8 g, 18.2 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (3.4 g, 62%) as an orange/yellow solid.
R_f 0.16 (2:1 hexane/Et_2O); mp 60-62 °C; υ_{max} (film)/cm^{-1} 3088, 2930, 2880, 1522, 1468, 1387, 1184, 1144, 997, 910, 773, 715; δ_H (300 MHz, $CDCl_3$) 4.46 (app. d, *J* = 7.0 Hz, 1 H, SCHC*H*H), 4.22-4.32 (m, 2 H, SC*H* and SCHCH*H*), 2.83 (s, 3 H, NCH_3), 2.49 (br s, 1 H, NC*H*), 0.94-1.06 (m, 1 H, CH_2CH_2CH), 0.54-0.76 (m, 3 H, $(CH_2)_2CH$), 0.37-0.45 (m, 1 H, $(CH_2)_2CH$); δ_C (75 MHz, $CDCl_3$) 74.1 (d), 71.7 (d), 66.4 (t), 43.9 (q), 12.8 (d), 4.6 (t), 1.9 (t); *m/z* (EI) 373 (M^+, 100), 332 (100), 183 (89), 155 (90), 124 (93); HRMS (EI): calcd for $C_{13}H_{12}F_5NO_4S$ (M^+) 373.0407, found 373.0423; Anal. calcd for $C_{13}H_{12}F_5NO_4S$: C 41.83, H 3.24, N 3.75, found C 41.14, H 3.25, N 3.72.

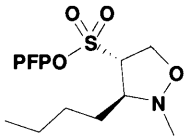
(3*S, 4*S**)-3-Cyclohexyl-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103q)** [69, 94]



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (5.0 g, 18.2 mmol) in dry toluene (50 mL) was added *C*-(cyclohexyl)-*N*-methyl nitrone **119q** (5.2 g, 36.5 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 hexane/Et_2O) to give the title compound (4.0 g, 53%) as a yellow oil.

R_f 0.40 (2:1 hexane/Et_2O); υ_{max} (neat)/cm^{-1} 2930, 2858, 1672, 1521, 1450, 1387, 1142, 997, 721; δ_H (300 MHz, $CDCl_3$) 4.57 (dd, *J* = 9.6, 4.9 Hz, 1 H, SCHC*H*H), 4.18-4.31 (m, 2 H, SC*H* and SCHCH*H*), 3.21 (dd, *J* = 5.8, 4.2 Hz, 1 H, NC*H*), 2.81 (s, 3 H, NCH_3), 1.48-1.86 (m, 6 H, cyclohexyl-*H*), 1.01-1.31 (m, 5 H, cyclohexyl-*H*); δ_C (75 MHz, $CDCl_3$) 73.8 (d), 68.7 (d), 66.5 (t), 44.9 (q), 41.6 (d), 29.6 (t), 29.3 (t), 26.2 (t), 26.0 (2 x t); *m/z* (EI) 416 (34), 415 (M^+, 31), 332 (68), 142 (30), 85 (100); HRMS (EI): calcd for $C_{16}H_{18}F_5NO_4S$ (M^+) 415.0877, found 415.0882.

(3*S, 4*S**)-3-Butyl-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103r)** [69, 94]

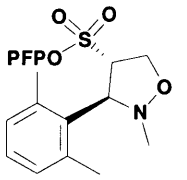


Using Method A. To pentafluorophenyl vinyl sulfonate **100** (4.0 g, 14.6 mmol) in dry toluene (40 mL) was added *C*-(pentyl)-*N*-methyl nitrone **119r** (2.5 g, 21.9 mmol) and the mixture was heated at reflux for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 16:1 petroleum ether 40-60°C/Et_2O) to give the title compound (1.0 g, 18%) as a brown oil.

R_f 0.11 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2961, 2870, 1647, 1522, 1466, 1389, 1142, 997, 754; δ_H (300 MHz, $CDCl_3$) 4.50 (dd, *J* = 10.2, 4.4 Hz, 1 H, SCHC*H*H), 4.27 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.04-4.10 (m, 1 H, SC*H*), 3.27 (br s, 1 H, NC*H*), 2.79 (s, 3 H, NCH_3), 1.62-1.82 (m, 2 H, $NCHCH_2CH_2$), 1.32-1.47 (m, 4 H, $CH_2(CH_2)_2CH_3$), 0.92 (t, *J* = 7.0 Hz, 3 H, $(CH_2)_3CH_3$); δ_C (75 MHz, $CDCl_3$) 70.8 (d), 69.3 (d), 66.1 (t), 43.7 (q), 32.6 (t), 27.6 (t), 22.6 (t), 13.8 (q); *m/z* (EI) 390 (42), 389

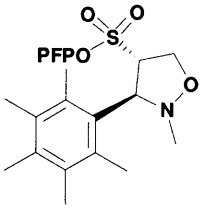
(M^+, 32), 332 (100), 184 (45), 155 (58), 142 (72); HRMS (EI): calcd for $C_{14}H_{16}F_5NO_4S$ (M^+) 389.0720, found 389.0722; Anal. calcd for $C_{14}H_{16}F_5NO_4S$: C 43.19, H 4.14, N 3.60, found C 44.73, H 4.57, N 2.77.

(3*S, 4*S**)-3-(2,6-Dimethylphenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103s)**



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (4.0 g, 14.6 mmol) in dry toluene (40 mL) was added *C*-(2,6-dimethylphenyl)-*N*-methyl nitrone **119s** (3.6 g, 21.9 mmol) and the mixture was heated at reflux for 4 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 8:1 petroleum ether 40-60°C/Et_2O) to give the title compound (3.9 g, 61%) as a white solid. R_f 0.51 (2:1 petroleum ether 40-60°C/Et_2O); mp 114-117 °C; υ_{max} (neat)/cm^{-1} 2929, 1515, 1467, 1366, 1169, 990, 776; δ_H (300 MHz, $CDCl_3$) 7.14 (app. dd, J = 8.0, 6.7 Hz, 1 H, Ar*H*), 7.04 (d, J = 7.5 Hz, 2 H, Ar*H*), 4.52-4.68 (m, 4 H, SC*H*, SCHCH_2, and NC*H*), 2.66 (s, 3 H, NCH_3), 2.53 (br s, 6 H, Ar(CH_3)$_2$; δ_C (75 MHz, $CDCl_3$) 129.5 (s), 128.8 (d), 70.2 (d), 69.7 (d), 66.9 (t), 42.8 (q), 21.1 (q), 1 x s and 1 x d not observed; *m/z* (EI) 437 (M^+, 47), 244 (100), 190 (40), 183 (21), 155 (20), 148 (91), 130 (34), 115 (39), 105 (17), 91 (24); HRMS (EI): calcd for $C_{18}H_{16}F_5NO_4S$ (M^+) 437.0715, found 437.0707.

(3*S, 4*S**)-2-Methyl-3-pentamethylphenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103t)**



Using Method A. To pentafluorophenyl vinyl sulfonate **100** (1.0 g, 3.7 mmol) in dry toluene (10 mL) was added *C*-(2,3,4,5,6-pentamethylphenyl)-*N*-methyl nitrone **119t** (1.1 g, 5.5 mmol) and the mixture was heated at reflux for 5 hours. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography

(starting 16:1 petroleum ether 40-60°C/Et_2O) to give the title compound (1.0 g, 57%) as a white solid.

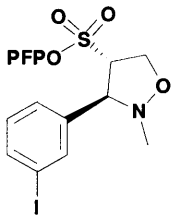
R_f 0.66 (2:1 petroleum ether 40-60°C/Et_2O); mp 153-155 °C; υ_{max} (neat)/cm^{-1} 2962, 1520, 1472, 1391, 1187, 994, 778; δ_H (300 MHz, $CDCl_3$) 4.76 (d, *J* = 8.0, 4.0 Hz, 1 H, SCHC*H*H), 4.62-4.69 (m, 3 H, SC*H*, SCHCH*H*, and NC*H*), 2.69 (s, 3 H, NCH_3), 2.50 (br s, 3 H, ArCH_3), 2.42 (br s, 3 H, ArCH_3), 2.25 (s, 3 H, ArCH_3), 2.23 (s, 6 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 136.2 (s), 134.3 (s), 133.0 (s), 126.6 (s), 71.1 (d), 70.2 (d), 67.1 (t), 42.9 (q), 17.4 (q), 16.9 (q), 16.7 (q); *m/z* (FAB$^+$) 479 (MH^+, 4), 307 (28), 289 (16), 154 (100); HRMS (FAB$^+$): calcd for $C_{21}H_{23}F_5NO_4S$ (MH^+) 480.1268, found 480.1278.

(3*S, 4*S**)-3-(2-Iodophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103u)**

Using Method B. To pentafluorophenyl vinyl sulfonate **100** (100 mg, 0.43 mmol) in dry toluene (4 mL) was added *C*-(2-iodophenyl)-*N*-methyl nitrone **119u** (170 mg, 0.65 mmol) and the mixture was heated in a CEM microwave at 140 °C for 10 mins. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 9:1 petroleum ether 40-60°C/Et_2O) to give the title compound (75 mg, 33%) as a brown oil.

R_f 0.57 (1:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2927, 2882, 1516, 1471, 1392, 1181, 991, 779, 720; δ_H (300 MHz, $CDCl_3$) 7.89 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.46 (dd, *J* = 8.0, 1.9 Hz, 1 H, Ar*H*), 7.39-7.44 (m, 1 H, Ar*H*), 7.06 (app. dt, *J* = 8.0, 1.9 Hz, 1 H, Ar*H*), 4.62-4.66 (m, 2 H, SCHC*H*H, and NC*H*), 4.55 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.35 (app. td, *J* = 7.5, 3.2 Hz, 1 H, SC*H*), 2.71 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 140.4 (d), 137.5 (s), 130.8 (d), 129.5 (d), 129.1 (d), 100.5 (s), 76.3 (d), 73.6 (d), 67.3 (t), 42.3 (q); *m/z* (EI) 535 (M^+, 100), 286 (16), 183 (53), 155 (48), 134 (61), 116 (74), 102 (24), 77 (36); HRMS (EI): calcd for $C_{16}H_{11}F_5INO_4S$ (M^+) 534.9368, found 534.9377.

(3*S, 4*S**)-3-(3-Iodophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (103v)**

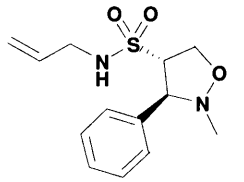


Using Method B. To pentafluorophenyl vinyl sulfonate **100** (100 mg, 0.43 mmol) in dry toluene (4 mL) was added *C*-(3-iodophenyl)-*N*-methyl nitrone **119v** (170 mg, 0.65 mmol) and the mixture was heated in a CEM microwave at 140 °C for 10 mins. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/Et_2O) to give the title compound (82 mg, 36%) as a brown oil.

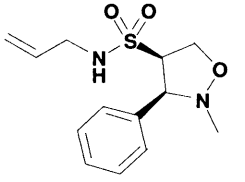
R_f 0.58 (1:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2925, 2882, 1516, 1472, 1381, 1182, 991, 790, 716; δ_H (300 MHz, $CDCl_3$) 7.84 (s, 1 H, Ar*H*), 7.69-7.72 (m, 1 H, Ar*H*), 7.43 (app. dt, *J* = 7.8, 1.1 Hz, 1 H, Ar*H*), 7.12 (app. t, *J* = 7.8 Hz, 1 H, Ar*H*), 4.59 (dd, *J* = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.46 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.27 (app. td, *J* = 8.0, 3.2 Hz, 1 H, SC*H*), 3.99 (d, *J* = 7.0 Hz, 1 H, NC*H*), 2.70 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 138.3 (d), 138.1 (s), 136.6 (d), 130.8 (d), 127.6 (d), 94.8 (s), 73.8 (d), 73.1 (d), 66.8 (t), 42.8 (q); *m/z* (EI) 535 (M^+, 100), 288 (23), 260 (33), 207 (38), 184 (26), 155 (22), 116 (64); HRMS (EI): calcd for $C_{16}H_{11}F_5INO_4S$ (M^+) 534.9368, found 534.9353.

4.4. Isoxazolidine sulfonamides (thermal procedures)

(3*S, 4*S**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid allylamide (120a), and (3*S**, 4*R**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid allylamide (121a)** [69, 94]



120a



121a

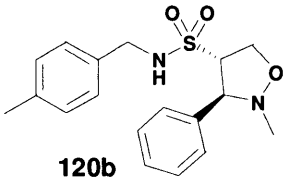
To a stirring solution of (3*S**, 4*S**)-2-methyl-3-phenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **103a** (300 mg, 0.73 mmol) in dry THF (5 mL), was added allyl amine (130 mg, 2.20 mmol) followed by DBU (170 mg, 1.10 mmol). The mixture was refluxed for 30 minutes. The reaction was diluted with DCM (20 mL) and washed with 2M HCl (2 x 20 mL), sat. $NaHCO_3$ (2 x 20 mL), and water (1 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/EtOAc) to give the *anti* product **120a** (115 mg, 56%) as a white solid and the *syn* product **121a** (30 mg, 14%) as a yellow oil- overall yield (70%, **120a**:**121a** = 4:1).

Data for **120a**: R_f 0.17 (2:1 petroleum ether 40-60°C/EtOAc); mp 88-91 °C; υ_{max} (film)/cm^{-1} 3281, 3047, 2926, 1636, 1597, 1454, 1313, 1150, 1040, 986; δ_H (300 MHz, $CDCl_3$) 7.34-7.47 (m, 5 H, Ar*H*), 5.49 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1 H, CH_2=C*H*), 5.05 (app. dq, *J* = 17.1, 1.3 Hz, 1 H, C*H*H=CH), 5.04 (app. dq, *J* = 10.3, 1.2 Hz, 1 H, CH*H*=CH), 4.75 (t, *J* = 6.7 Hz, 1 H, CH_2N*H*), 4.39 (dd, *J* = 9.8, 4.2 Hz, 1 H, SCHC*H*H), 4.33 (dd, *J* = 9.8, 8.1 Hz, 1 H, SCHCH*H*), 4.03 (app. td, *J* = 7.7, 4.2 Hz, 1 H, SC*H*), 3.81 (d, *J* = 7.3 Hz, 1 H, NC*H*), 3.52-3.62 (m, 1 H, NHC*H*H), 3.31-3.41 (m, 1 H, NHCH*H*), 2.62 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 136.8 (s), 133.0 (d), 129.0 (d), 128.9 (d), 128.3 (d), 118.1 (t), 74.6 (d), 73.3 (d), 66.8 (t), 45.8 (t), 42.8 (q); *m/z* (EI) 282 (M^+, 38), 161 (100), 134 (57), 117 (88), 103 (18); HRMS (EI): calcd for $C_{13}H_{18}N_2O_3S$ (M^+) 282.1038, found 282.1035.

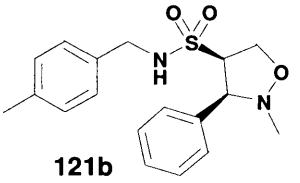
Data for **121a**: R_f 0.12 (2:1 petroleum ether 40-60°C/EtOAc); υ_{max} (neat)/cm^{-1} 3309, 2923, 1455, 1329, 1150, 997; δ_H (300 MHz, $CDCl_3$) 7.51-7.54 (m, 2 H, Ar*H*), 7.37-7.43 (m, 3 H. Ar*H*), 5.61 (ddt, *J* = 16.5, 10.6, 6.0 Hz, 1 H, CH_2=C*H*), 5.04-5.12 (m, 2 H, CH_2=CH), 4.44 (app. d, *J* = 8.0 Hz, 2 H, SCHCH_2), 4.25 (app. q, *J* = 8.3 Hz, 1 H, SC*H*), 3.78 (d, *J* = 8.4 Hz, 1 H, NC*H*), 3.48-3.58 (m, 1 H, NHC*H*H), 3.31-3.41 (m, 1 H, NHCH*H*), 2.93 (t, *J* = 5.8 Hz, 1 H, N*H*CH_2), 2.65 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$)

133.0 (s and d), 129.3 (d), 129.1 (d), 128.6 (d), 117.9 (t), 74.3 (d), 68.2 (d), 66.6 (t), 45.7 (t), 43.3 (q); *m/z* (EI) 282 (M^+, 32), 160 (20), 146 (17), 134 (100), 117 (74), 91 (37); HRMS (EI): calcd for $C_{13}H_{18}N_2O_3S$ (M^+) 282.1038, found 282.1040.

(3*S, 4*S**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (120b), and (3*S**, 4*R**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (121b)** [69, 94]



120b



121b

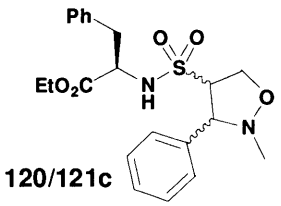
To a stirring solution of (3*S**, 4*S**)-2-methyl-3-phenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **103a** (300 mg, 0.73 mmol) in dry THF (10 mL), was added 4-methyl-benzyl amine (270 mg, 2.20 mmol) followed by DBU (170 mg, 1.10 mmol). The mixture was refluxed for 1 hour. The reaction was diluted with DCM (20 mL) and washed with 2M HCl (2 x 20 mL), sat. $NaHCO_3$ (2 x 20 mL), and water (1 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/EtOAc) to give the *anti* product **120b** (159 mg, 63%) as a yellow solid and the *syn* product **121b** (53 mg, 21%) as a yellow oil- overall yield (84%, **120b**:**121b** = 3:1).

Data for **120b**: R_f 0.34 (2:1 hexane/EtOAc); mp 84-86 °C; υ_{max} (film)/cm^{-1} 3290, 3034, 2924, 1611, 1448, 1323, 1146, 1043; δ_H (300 MHz, $CDCl_3$) 7.36-7.44 (m, 5 H, Ar*H*), 7.05 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.93 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.89 (app. t, *J* = 5.8 Hz, 1 H, CH_2NH), 4.34 (dd, *J* = 9.8, 3.8 Hz, 1 H, SCHC*H*H), 4.23 (dd, *J* = 9.8, 8.4 Hz, 1 H, SCHCH*H*), 4.08 (dd, *J* = 13.7, 6.4 Hz, 1 H, NHC*H*H), 3.93 (app. td, *J* = 8.0, 3.8 Hz, 1 H, SC*H*), 3.80-3.86 (m, 2 H, NC*H* and NHCH*H*), 2.58 (s, 3 H, NCH_3), 2.31 (s, 3 H, $ArCH_3$); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 136.8 (s), 133.2 (s), 129.4 (d), 129.0 (d), 128.8 (d), 128.3 (d), 128.0 (d), 74.5 (d), 73.2 (d), 66.9 (t), 47.0 (t), 42.7 (q), 21.1 (q); *m/z* (EI) 346 (M^+, 10), 160 (100), 105 (83); HRMS (EI): calcd for $C_{18}H_{22}N_2O_3S$ (M^+) 346.1351, found 346.1359; Anal. calcd for $C_{18}H_{22}N_2O_3S$: C 62.40, H 6.40, N 8.09, found C 61.94, H 6.47, N 7.71.

Data for **121b**: R_f 0.29 (2:1 hexane/EtOAc); υ_{max} (film)/cm^{-1} 3296, 2923, 2876, 1506, 1448, 1327, 1150, 1051, 833; δ_H (300 MHz, $CDCl_3$) 7.39-7.48 (m, 2 H, Ar*H*), 7.30-7.35 (m, 3 H, Ar*H*), 7.12 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.02 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.36-4.47

(m, 2 H, SCHCH_2), 4.10-4.23 (m, 1 H, SC*H*), 4.03 (dd, *J* = 13.8, 6.9 Hz, 1 H, NHC*H*H), 3.89 (dd, *J* = 13.8, 5.3 Hz, 1 H, NHCH*H*), 3.71 (d, *J* = 8.4 Hz, 1 H, NC*H*), 3.28 (app. t, *J* = 8.7 Hz, 1 H, CH_2N*H*), 2.62 (s, 3 H, NCH_3), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.9 (s), 133.4 (s), 133.2 (s), 129.4 (d), 129.3 (d), 129.0 (d), 128.8 (d), 128.5 (d), 128.3 (d), 128.0 (d), 74.2 (d), 68.5 (d), 66.7 (t), 46.9 (t), 43.3 (q), 21.1 (q); *m/z* (EI) 346 (M^+, 14), 134 (100), 120 (72); HRMS (EI): calcd for $C_{18}H_{22}N_2O_3S$ (M^+) 346.1351, found 346.1367.

(3*S, 4*S**) and (3*S**, 4*R**)-2-(2-Methyl-3-phenylisoxazolidine-4-sulfonylamino)-3-phenylpropionic acid ethyl ester (120/121c)** [69, 94]



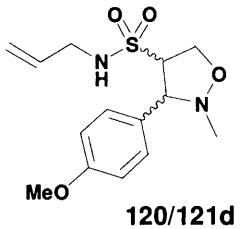
120/121c

To a stirring solution of (3*S**, 4*S**)-2-methyl-3-phenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **103a** (200 mg, 0.49 mmol) in dry toluene (10 mL), was added phenylalanine ethyl ester (280 mg, 1.47 mmol) followed by DBU (110 mg, 0.73 mmol). The mixture was refluxed for 2 hours. The reaction was diluted with DCM (30 mL) and washed with 2M HCl (2 x 20 mL), sat. $NaHCO_3$ (2 x 20 mL), and water (1 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/EtOAc) to give the product (145 mg, 71%, **120c** and **121c** = 1:1 major:minor) as a mixture of diastereoisomers.

R_f 0.24 (2:1 petroleum ether 40-60°C/EtOAc); υ_{max} (neat)/cm^{-1} 3277, 3031, 2927, 1734, 1496, 1455, 1334, 1215, 1149, 1031, 948, 853; δ_H (300 MHz, $CDCl_3$) 7.22-7.46 (m, 8 H, Ar*H*), 7.02-7.11 (m, 2 H, Ar*H*), 4.92 (d, *J* = 9.1 Hz, 1 H_{minor}, N*H*), 4.84 (d, *J* = 9.6 Hz, 1 H_{major}, N*H*), 4.08-4.29 (m, 4 H, $CO_2CH_2CH_3$, NHC*H*, and SCHC*H*H), 3.83-3.93 (m, 3 H, NCH_{minor}, SCH_{major}, and SCHCH*H*), 3.74 (br d, *J* = 7.0 Hz, 1 H_{major}, NC*H*), 3.37 (app. td, *J* = 7.8, 3.5 Hz, 1 H_{minor}, SC*H*), 3.06 (dd, *J* = 13.9, 5.1 Hz, 1 H_{minor}, C*H*HPh), 2.87-2.98 (m, 2 H, CH_2Ph), 2.83 (dd, *J* = 13.9, 8.0 Hz, 1 H_{minor}, CH*H*Ph), 2.62 (s, 3 H_{minor}, NCH_3), 2.58 (s, 3 H_{major}, NCH_3), 1.23 (t, *J* = 7.2 Hz, 3 H_{major}, $CO_2CH_2CH_3$), 1.18 (t, *J* = 7.2 Hz, 3 H_{minor}, $CO_2CH_2CH_3$); δ_C (75 MHz, $CDCl_3$) 171.3 (s), 171.1 (s), 137.2 (s), 137.0 (s), 135.7 (s), 135.0 (s), 129.9 (d), 129.5 (d), 129.3 (d), 128.9 (d), 128.8 (d), 128.7 (d), 128.6 (d), 128.5 (d), 128.2 (d), 128.1 (d), 127.5 (d), 127.4 (d), 74.3 (d), 74.1 (d), 74.0 (d), 73.8 (d), 67.2 (t), 67.1 (t), 62.0 (t), 61.9 (t), 57.6 (d), 57.2 (d), 43.2

(q), 42.7 (q), 39.5 (t), 39.4 (t), 14.0 (q), 33 out of 34 expected signals observed; *m/z* (EI) 418 (M^+, 22), 160 (100), 115 (100), 91 (98); HRMS (EI): calcd for $C_{21}H_{26}N_2O_5S$ (M^+) 418.1562, found 418.1570.

(3*S, 4*S**) and (3*S**, 4*R**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-4-sulfonic acid allylamide (120/121d)** [69, 94]



120/121d

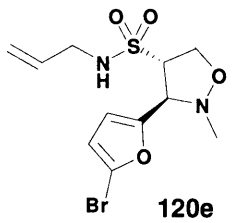
To a stirring solution of (3*S**, 4*S**)-3-(4-methoxyphenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **103b** (500 mg, 1.14 mmol) in dry THF (10 mL), was added allyl amine (190 mg, 3.41 mmol) followed by DBU (260 mg, 1.71 mmol). The mixture was refluxed for 1 hour. The reaction was diluted with DCM (30 mL) and washed with 2M HCl (2 x 20 mL), sat. $NaHCO_3$ (2 x 20 mL), and water (1 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/EtOAc) to give *anti* product **120d** (35 mg, 10%) as a yellow solid, and the remaining as a mixture of diastereoisomers (191 mg, 53%)- overall yield (63%, **120d** and **121d** = 3:1 major:minor).

Data for **120d**: R_f 0.32 (1:1 petroleum ether 40-60°C/EtOAc); mp 85-87 °C; υ_{max} (film)/cm^{-1} 3292, 3082, 2924, 1612, 1514, 1439, 1319, 1250, 1146, 1034, 839; δ_H (300 MHz, $CDCl_3$) 7.36 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 5.52 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1 H, CH_2=C*H*), 5.03-5.11 (m, 2 H, CH_2=CH), 4.76 (t, *J* = 6.0 Hz, 1 H, CH_2N*H*), 4.28-4.39 (m, 2 H, SCHCH_2), 3.99 (app. td, *J* = 7.7, 4.2 Hz, 1 H, SC*H*), 3.80 (s, 3 H, OCH_3), 3.74 (br d, *J* = 7.1 Hz, 1 H, NC*H*), 3.52-3.62 (m, 1 H, NHC*H*H), 3.32-3.41 (m, 1 H, NHCH*H*) 2.59 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 160.0 (s), 133.1 (d), 129.4 (d), 128.4 (s), 118.0 (t), 114.4 (d), 74.1 (d), 73.1 (d), 66.7 (t), 55.3 (q), 45.8 (t), 42.6 (q); *m/z* (EI) 312 (M^+, 18), 190 (100), 165 (75), 147 (100), 121 (43), 91 (89); HRMS (EI): calcd for $C_{14}H_{20}N_2O_3S$ (M^+) 312.1144, found 312.1138.

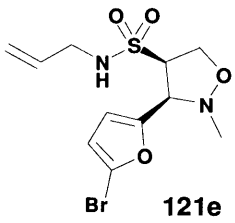
Data for **120d/121d**: R_f 0.30 (1:1 petroleum ether 40-60°C/EtOAc); δ_H (300 MHz, $CDCl_3$) 7.42 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 7.35 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 6.90 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 6.89 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 5.45-5.69 (m, 1 H, C*H*=CH_2), 5.02-5.13 (m, 2 H, CH=CH_2), 4.77 (br t, *J* = 6.2 Hz, 1 H_{major}, N*H*), 4.39 (app.

d, J = 8.3 Hz, 2 H_{major}, SCHCH_2), 4.33 (dd, J = 9.6, 5.4 Hz, 1 H_{minor}, SCHCHH), 4.30 (dd, J = 9.6, 8.0 Hz, 1 H_{minor}, SCHCHH), 4.16-4.25 (m, 1 H_{minor}, SCH), 3.98 (app. td, J = 7.8, 4.0 Hz, 1 H_{major}, SCH), 3.79 (s, 3 H, OCH_3), 3.72 (br d, J = 8.3 Hz, 1 H, NCH), 3.47-3.61 (m, 1 H, NHCHH), 3.32-3.44 (m, 1 H, NHCHH), 3.26 (br t, J = 5.9 Hz, 1 H_{minor}, NH), 2.60 (s, 3 H_{major}, NCH_3), 2,59 (s, 3 H_{minor}, NCH_3); δ_C (75 MHz, $CDCl_3$) 160.0 (s), 159.9 (s), 133.2 (d), 130.5 (d), 129.4 (d), 128.5 (s), 124.7 (s), 117.9 (t), 117.8 (t), 114.4 (d), 114.0 (d), 74.1 (d), 73.7 (d), 73.1 (d), 67.9 (d), 66.7 (t), 66.6 (t), 55.3 (q), 55.2 (q), 45.7 (t), 45.6 (t), 43.2 (q), 42.6 (q), 23 out of 24 expected signals observed.

(3*S, 4*S**)-3-(5-Bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid allylamide (120e), and (3*S**, 4*R**)-3-(5-Bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid allylamide (121e)** [69, 94]



120e



121e

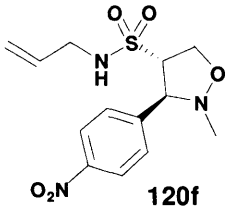
To a stirring solution of (3*S**, 4*S**)-3-(5-bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **103o** (500 mg, 1.05 mmol) in dry THF (10 mL), was added allyl amine (180 mg, 3.14 mmol) followed by DBU (240 mg, 1.57 mmol). The mixture was refluxed for 1 hour. The reaction was diluted with DCM (30 mL) and washed with 2M HCl (2 x 20 mL), sat. $NaHCO_3$ (2 x 20 mL), and water (1 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/EtOAc) to give the *anti* product as a brown solid **120e** (226 mg, 62%) and the *syn* product **121e** (60 mg, 16%) as a brown oil- overall yield (78%, **120e**:**121e** = 4:1).

Data for **120e**: R_f 0.14 (2:1 petroleum ether 40-60°C/EtOAc); mp 88-90 °C; υ_{max} (film)/cm^{-1} 3292, 3134, 2930, 1672, 1636, 1502, 1423, 1306, 1142, 1067, 930; δ_H (500 MHz, $CDCl_3$) 6.38 (d, J = 3.3 Hz, 1 H, CHCO), 6.26 (d, J = 3.3 Hz, 1 H, CHCBr), 5.66 (ddt, J = 17.1, 10.6, 5.7 Hz, 1 H, CH_2=CH), 5.10-5.19 (m, 2 H, CH_2=CH), 4.77 (t, J = 5.7 Hz, 1 H, CH_2NH), 4.21-4.32 (m, 3 H, SCH and SCHCH_2), 3.94 (br s, 1 H, NCH), 3.55-3.65 (m, 2 H, CH_2NH), 2.65 (s, 3 H, NCH_3); δ_C (300 MHz, $CDCl_3$) 150.6 (s), 133.1 (d), 122.9 (s), 118.2 (t), 113.1 (d), 112.6 (d), 69.3 (d), 67.5 (d), 66.8 (t), 45.8 (t), 42.9 (q); *m/z* (EI) 352 (M^+, ^{81}Br, 24), 350 (M^+, ^{79}Br, 23), 230 (100), 203 (44), 187 (50),

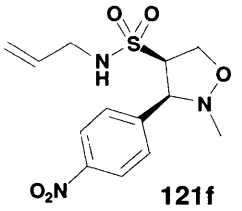
159 (20), 106 (18); HRMS (EI): calcd for $C_{11}H_{15}{}^{79}BrN_2O_4S$ (M^+) 349.9936, found 349.9928.

Data for **121e**: R_f 0.09 (2:1 petroleum ether 40-60°C/EtOAc); υ_{max} (neat)/cm^{-1} 3306, 3138, 2926, 2883, 1636, 1499, 1433, 1325, 1148, 1049, 928; δ_H (500 MHz, $CDCl_3$) 6.48 (d, *J* = 3.3 Hz, 1 H, C*H*CO), 6.34 (d, *J* = 3.3 Hz, 1 H, C*H*CBr), 5.79 (ddt, *J* = 17.1, 10.3, 5.9 Hz, 1 H, CH_2=C*H*), 5.24 (app. dq, *J* = 17.1, 1.3 Hz, 1 H, C*H*H=CH), 5.18 (app. dq, *J* = 10.3, 1.3 Hz, 1 H, CH*H*=CH), 4.29-4.38 (m, 2 H, SCHCH_2), 4.24 (app. q, *J* = 8.1 Hz, 1 H, SC*H*), 3.92 (br d, *J* = 7.3 Hz, 1 H, NC*H*), 3.84 (br t, *J* = 5.4 Hz, 1 H, N*H*), 3.65-3.69 (m, 2 H, NHCH_2), 2.65 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 149.0 (s), 133.3 (d), 122.0 (s), 118.2 (t), 113.5 (d), 113.0 (d), 67.7 (d), 67.3 (d), 66.7 (t), 45.9 (t), 43.8 (q); *m/z* (EI) 352 (M^+, ^{81}Br, 26), 350 (M^+, ^{79}Br, 25), 230 (100), 203 (68), 185 (59), 159 (25), 106 (28); HRMS (EI): calcd for $C_{11}H_{15}{}^{79}BrN_2O_4S$ (M^+) 349.9936, found 349.9928.

(3*S, 4*S**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-4-sulfonic acid allylamide (120f), and (3*S**, 4*R**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-4-sulfonic acid allylamide (121f)** [69, 94]



120f



121f

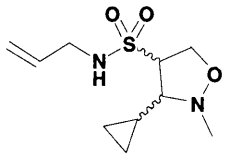
To a stirring solution of (3*S**, 4*S**)-2-methyl-3-(4-nitrophenyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester **103d** (500 mg, 1.10 mmol) in dry THF (10 mL), was added allyl amine (190 mg, 3.30 mmol) followed by DBU (250 mg, 1.65 mmol). The mixture was refluxed for 1 hour. The reaction was diluted with DCM (30 mL) and washed with 2M HCl (2 x 20 mL), sat. $NaHCO_3$ (2 x 20 mL), and water (1 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/EtOAc) to give the *anti* product as a yellow solid **120f** (166 mg, 46%) and the *syn* product **121f** (61 mg, 17%) as an orange solid- overall yield (63%, **120f**:**121f** = 3:1).

Data for **120f**: R_f 0.13 (2:1 petroleum ether 40-60°C/EtOAc); mp 159-162 °C; υ_{max} (film)/cm^{-1} 3263, 3055, 2986, 1620, 1522, 1423, 1265, 1150, 1038, 893; δ_H (400 MHz, DMSO) 8.20 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.75 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.39 (t, *J* = 5.7 Hz, 1 H, N*H*), 5.70 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1 H, CH_2=C*H*), 5.16 (app. dq, *J* = 17.2, 1.6 Hz, 1 H, C*H*H=CH), 5.05 (app. dq, *J* = 10.3, 1.6 Hz, 1 H, CH*H*=CH), 4.27 (d, *J* =

6.4 Hz, 2 H, SCHCH_2), 4.17 (app.td, J = 6.5, 5.9 Hz, 1 H, SCH), 4.08 (d, J = 6.6 Hz, 1 H, NCH), 3.49-3.63 (m, 2 H, NHCH_2), 2.59 (s, 3 H, NCH_3); δ_C (100 MHz, DMSO) 147.1 (s), 145.4 (s), 134.2 (d), 129.0 (d), 122.9 (d), 115.9 (t), 72.3 (d), 71.8 (d), 66.2 (t), 44.3 (t), 42.0 (q); *m/z* (EI) 327 (M^+, 7), 205 (100), 116 (55); HRMS (EI): calcd for $C_{13}H_{17}N_3O_5S$ (M^+) 327.0889, found 327.0885.

Data for **121f**: R_f 0.06 (2:1 petroleum ether 40-60°C/EtOAc); mp 119-122 °C; υ_{max} (film)/cm^{-1} 3265, 3082, 2922, 1601, 1518, 1429, 1339, 1153, 1047, 924; δ_H (300 MHz, $CDCl_3$) 8.21 (d, J = 8.8 Hz, 2 H, ArH), 7.69 (d, J = 8.8 Hz, 2 H, ArH), 5.72 (ddt, J = 17.1, 10.1, 5.9 Hz, 1 H, CH_2=CH), 5.16-5.22 (m, 2 H, CH_2=CH), 4.31-4.47 (m, 3 H, SCHCH_2 and SCH), 3.92-3.99 (m, 2 H, NCH and NHCH$_2$), 3.58 (app. t, J = 6.0 Hz, 2 H, NHCH_2), 2.64 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 148.0 (s), 141.2 (s), 133.2 (d), 130.7 (d), 123.2 (d), 118.2 (t), 73.1 (d), 69.3 (d), 67.2 (t), 45.7 (t), 43.3 (q); *m/z* (EI) 327 (M^+, 34), 179 (100), 163 (36), 133 (56), 116 (85); HRMS (EI): calcd for $C_{13}H_{17}N_3O_5S$ (M^+) 327.0889, found 327.0883.

(3*S, 4*S**) and (3*S**, 4*R**)-3-Cyclopropyl-2-methylisoxazolidine-4-sulfonic acid allylamide (120/121g)** [69, 94]



120/121g

To a stirring solution of (3*S**, 4*S**)-3-cyclopropyl-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **103p** (300 mg, 0.80 mmol) in dry THF (5 mL), was added allyl amine (180 μL, 2.41 mmol) followed by DBU (180 μL, 1.21 mmol). The mixture was refluxed for 30 minutes then diluted with DCM (30 mL) and washed with 2M HCl (2 x 20 mL), sat. $NaHCO_3$ (2 x 20 mL), and water (1 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 3:1 petroleum ether 40-60°C/EtOAc) to give the product as a mixture of diastereoisomers (182 mg, 92%, **120g** and **121g** = 3:1 major:minor).

R_f 0.17 (1:1 petroleum ether 40-60°C/EtOAc); υ_{max} (neat)/cm^{-1} 3584, 3289, 2874, 1437, 1315, 1144, 1046, 921, 830; δ_H (300 MHz, $CDCl_3$) 5.82 (ddt, J = 16.1, 10.2, 5.9 Hz, 1 H, CH=CH$_2$), 5.21-5.29 (m, 1 H, CH=CHH), 5.13-5.19 (m, 1 H, CH=CHH), 5.12 (br t, J = 5.9 Hz, 1 H_{major}, NH), 5.00 (br t, J = 6.2 Hz, 1 H_{minor}, NH), 3.97-4.23 (m, 3 H, SCHCH_2 and SCH_{minor}), 3.82-3.89 (m, 1 H_{major}, SCH), 3.71-3.77 (m, 2 H, NHCH_2), 2.74

(s, 3 H_{major}, NCH_3), 2.69 (s, 3 H_{minor}, NCH_3), 2.33 (br s, 1 H_{major}, NC*H*), 1.84 (br s, 1 H_{minor}, NC*H*), 1.15-1.29 (m, 1 H_{minor}, NCHC*H*), 0.86-0.99 (m, 1 H_{major}, NCHC*H*), 0.71 (dd, J = 8.0, 1.1 Hz, 1 H_{minor}, cyclopropyl-*H*), 0.49-0.63 (m, 2 H + 1H_{major}, cyclopropyl-*H*), 0.24-0.38 (m, 2 H, cyclopropyl-*H*); δ_C (75 MHz, $CDCl_3$) 133.7 (d), 117.9 (t), 117.8 (t), 73.5 (d), 71.9 (d), 67.3 (d), 66.6 (t), 66.4 (t), 46.0 (t), 45.8 (t), 44.3 (q), 13.6 (d), 5.9 (t), 4.4 (t), 3.4 (t), 2.0 (t), 16 out of 20 expected signals observed; *m/z* (EI) 246 (M^+, 13), 124 (86), 99 (35), 84 (100), 68 (28), 56 (22); HRMS (EI): calcd for $C_{10}H_{18}N_2O_3S$ (M^+) 246.1033, found 246.1035.

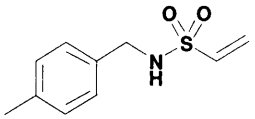
4.5. Isoxazolidine sulfonamides (MW procedures)

General protocol for [3+2] MW cycloaddition (Sections 4.5.1. to 4.5.3.)

To a solution of vinyl sulfonamide (1 eq.) in dry toluene (5 mL), nitrone (3 eq.) was added. The reaction mixture was heated in a CEM microwave for 30 minutes at 140 °C. When complete the reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the desired products.

4.5.1. Cycloadditions with ethenesulfonic acid 4-methylbenzylamide (123b)

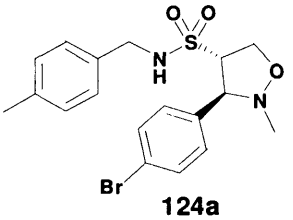
Ethenesulfonic acid 4-methylbenzylamide (123b)



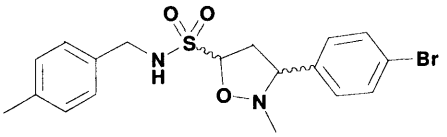
A premixed suspension of 4-methylbenzylamine (8.2 g, 67.5 mmol) and NEt_3 (12.4 g, 122.7 mmol) in DCM (25 mL) was added dropwise to a stirring solution of 2-chloroethane-1-sulfonyl chloride (10.0 g, 61.3 mmol) in DCM (100 mL), while keeping the temperature at -10 °C. The reaction mixture was stirred for a further 30 minutes after addition, and then warmed to RT. The reaction was diluted with DCM (60 mL) and washed with 2M HCl (3 x 80 mL), H_2O (1 x 80 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* to give the crude which was purified by flash chromatography (starting 3:1 petroleum ether 40-60°C/Et_2O) to furnish the desired product (11.7 g, 90%) as white crystals.

R_f 0.14 (1:1 hexane/Et_2O); mp 86-88 °C; υ_{max} (film)/cm^{-1} 3227, 3036, 2835, 1510, 1421, 1356, 1144, 1045, 976, 812; δ_H (300 MHz, $CDCl_3$) 7.13-7.26 (m, 4 H, Ar*H*), 6.46 (dd, *J* = 16.5, 9.8 Hz, 1 H, SC*H*CH_2), 6.22 (d, *J* = 16.5 Hz, 1 H, SCHC(*H*)H), 5.90 (d, *J* = 9.8 Hz, 1 H, SCHCH*H*), 4.83 (br s, 1 H, N*H*), 4.14 (d, *J* = 6.1 Hz, 2 H, NHCH_2), 2.33 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 136.1 (d), 133.5 (s), 129.4 (d), 128.0 (d), 126.7 (t), 46.8 (t), 21.1 (q); *m/z* (EI) 211 (M^+, 33), 203 (49), 160 (35), 146 (50), 118 (100), 105 (72), 91 (80); HRMS (EI): calcd for $C_{10}H_{13}NO_2S$ (M^+) 211.0667, found 211.0663.

(3*S, 4*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124a), (3*R**, 5*S**) and (3*S**, 5*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125/126a)**



124a



125/126a

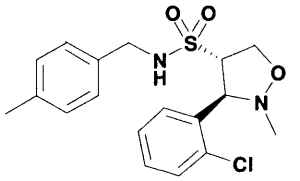
General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **125/126a** (58 mg, 29%) as a mixture, and **124a** (85 mg, 43%) as a brown solid- overall yield (72%, **124a**:**125/126a** = 3:2, **125a** and **126a** = 3:1 major:minor).

Data for **125/126a**: R_f 0.37 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 2921, 1487, 1327, 1147, 1071, 1010, 729; δ_H (300 MHz, $CDCl_3$) 7.48 (d, *J* = 8.3 Hz, 2 H_{major}, Ar*H*), 7.46 (d, *J* = 8.3 Hz, 2 H_{minor}, ArH), 7.28 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.23 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.16 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 5.00 (dd, *J* = 8.6, 5.6 Hz, 1 H_{minor}, SC*H*), 4.94 (dd, *J* = 8.6, 2.4 Hz, 1 H_{major}, SC*H*), 4.88 (br t, *J* = 5.9 Hz, 1 H_{minor}, N*H*), 4.77 (br t, *J* = 5.9 Hz, 1 H_{major}, N*H*), 4.43 (dd, *J* = 14.2, 6.4 Hz, 1 H_{minor}, NHC*H*H), 4.36-4.41 (m, 1 H_{minor}, NHCH*H*), 4.34-4.39 (m, 1 H_{major}, NHC*H*H), 4.30 (dd, *J* = 14.2, 5.9 Hz, 1 H_{major}, NHCH*H*), 4.02 (br dd, *J* = 8.6, 5.9 Hz, 1 H_{major}, NC*H*), 3.53 (br dd, *J* = 9.6, 7.5 Hz, 1 H_{minor}, NC*H*), 2.96-3.08 (m, 1 H, SCHC*H*H), 2.84 (ddd, *J* = 13.7, 10.2, 5.6 Hz, 1 H_{minor}, SCHCH*H*), 2.73 (s, 3 H_{major}, NCH_3), 2.70 (ddd, *J* = 13.7, 10.2, 8.6 Hz, 1 H_{major}, SCHCH*H*), 2.60 (s, 3 H_{minor}, NCH_3), 2.34 (s, 3 H, ArCH_3); δ_C (125 MHz, $CDCl_3$) 139.0 (s), 137.1 (s), 136.7 (s), 135.2 (s), 134.8 (s), 133.2 (d), 130.8 (d), 130.6 (d), 130.4 (d), 129.8 (d), 129.1 (d), 123.7 (s), 123.4 (s), 90.2 (d), 71.3 (d), 48.7 (t), 45.4 (q), 44.3 (q), 42.6 (t), 42.2 (t), 22.3 (q), 21 out of 28 expected signals observed; *m/z* (FAB$^+$) 427 (MH^+, ^{81}Br, 21), 425 (MH^+, ^{79}Br, 22), 338 (94), 240 (37), 219 (100), 203 (36), 163 (45); HRMS (FAB$^+$): calcd for $C_{18}H_{22}{}^{79}BrN_2O_3S$ (MH^+) 425.0534, found 425.0522.

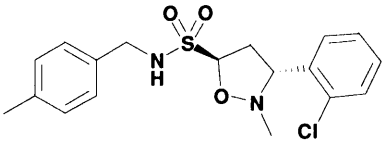
Data for **124a**: R_f 0.29 (2:1 Et_2O/petroleum ether 40-60°C); mp 96-98 °C; υ_{max} (film)/cm^{-1} 3300, 2922, 2856, 1589, 1456, 1414, 1319, 1144, 1034, 856; δ_H (300 MHz, $CDCl_3$) 7.48 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.27 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.08 (d, *J* = 7.7 Hz, 2 H, Ar*H*), 6.96 (d, *J* = 7.7 Hz, 2 H, Ar*H*), 4.91 (br t, *J* =5.6 Hz, 1 H, N*H*), 4.29-4.33 (m, 1 H, SCHC*H*H), 4.09-4.21 (m, 2 H, SCHCH*H* and NHC*H*H), 3.98 (dd, *J* = 13.9, 5.6 Hz, 1 H, NHCH*H*), 3.76-3.82 (m, 2 H, SC*H* and NC*H*), 2.58 (s, 3 H, NCH_3),

2.33 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 138.0 (s), 136.1 (s), 133.1 (s), 132.1 (d), 129.8 (d), 129.5 (d), 128.0 (d), 122.8 (s), 73.6 (d), 73.5 (d), 66.9 (t), 47.1 (t), 42.7 (q), 21.2 (q); *m/z* (EI) 426 (M^+, ^{81}Br, 6), 424 (M^+, ^{79}Br, 8), 240 (63), 197 (28), 120 (100); HRMS (EI): calcd for $C_{18}H_{21}{}^{79}BrN_2O_3S$ (M^+) 424.0456, found 424.0450.

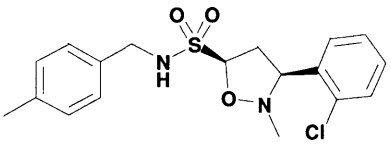
(3*S, 4*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124b), (3*R**, 5*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125b), and (3*S**, 5*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (126b)**



124b



125b



126b

General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the three separable products **124b** (58 mg, 32%), **125b** (55 mg, 31%), and **126b** (27 mg, 15%)- overall yield (78%, **124b**:**125b**:**126b** = 2:2:1).

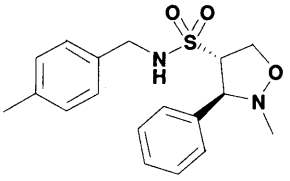
Data for **126b**: R_f 0.43 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (film)/cm^{-1} 3379, 3294, 3055, 2986, 1514, 1429, 1329, 1265, 1151, 1059, 897, 741; δ_H (300 MHz, $CDCl_3$) 7.64 (dd, *J* = 7.4, 2.1 Hz, 1 H, Ar*H*), 7.22-7.38 (m, 5 H, Ar*H*), 7.17 (d, *J* = 2.1 Hz, 2 H, Ar*H*), 5.04 (dd, *J* = 8.7, 5.6 Hz, 1 H, SC*H*), 4.72 (app. t, *J* = 6.0 Hz, 1 H, N*H*), 4.43 (dd, *J* = 14.0, 6.4 Hz, 1 H, NHC*H*H), 4.38 (dd, *J* = 14.0, 6.1 Hz, 1 H, NHCH*H*), 4.20 (dd, *J* = 9.8, 7.4 Hz, 1 H, NC*H*), 3.18 (ddd, *J* = 13.5, 8.7, 7.4 Hz, 1 H, SCHC*H*H), 2.66-2.75 (m, 4 H, SCHCH*H* and NCH_3), 2.35 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 134.7 (s), 134.1 (s), 133.7 (s), 129.6 (d), 129.5 (d), 129.2 (d), 128.4 (d), 128.0 (d), 127.7 (d), 89.3 (d), 68.5 (d), 47.6 (t), 43.5 (q), 39.6 (t), 21.2 (q); *m/z* (EI) 382 (M^+, ^{37}Cl, 1), 380 (M^+, ^{35}Cl, 3), 272 (35), 270 (100), 167 (32), 149 (50), 141 (75), 125 (8), 86 (36), 77 (30); HRMS (EI): calcd for $C_{18}H_{21}{}^{35}ClN_2O_3S$ (M^+) 380.0961, found 380.0952.

Data for **125b**: R_f 0.36 (2:1 Et_2O/petroleum ether 40-60°C); mp 70-75 °C; υ_{max} (film)/cm^{-1} 3290, 3061, 2922, 1516, 1439, 1331, 1148, 1059, 847, 756; δ_H (300 MHz, $CDCl_3$) 7.54 (dd, *J* = 7.4, 2.1 Hz, 1 H, Ar*H*), 7.38 (dd, *J* = 7.4, 1.9 Hz, 1 H, Ar*H*), 7.21-7.26 (m, 4 H, Ar*H*), 7.17 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 4.89 (dd, *J* = 8.3, 4.2 Hz, 1 H, SC*H*), 4.69 (app. t, *J* = 6.0 Hz, 1 H, N*H*), 4.60 (app. t, *J* = 7.4 Hz, 1 H, NC*H*), 4.39 (dd, *J* = 13.9, 6.1 Hz, 1 H, NHC*H*H), 4.34 (dd, *J* = 13.9, 5.9 Hz, 1 H, NHCH*H*), 3.28 (ddd, *J*

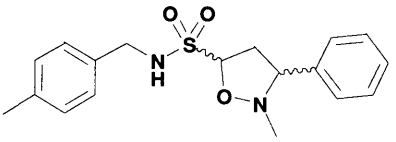
= 13.4, 6.6, 4.2 Hz, 1 H, SCHC*H*H), 2.85 (s, 3 H, NCH_3), 2.62 (dt, *J* = 13.4, 8.3 Hz, 1 H, SCHCH*H*), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.9 (s), 135.8 (s), 133.7 (s), 133.5 (s), 129.7 (d), 129.5 (d), 129.0 (d), 128.0 (d), 127.6 (d), 127.3 (d), 89.8 (d), 67.0 (d), 47.7 (t), 45.6 (q), 38.9 (t), 21.1 (q); *m/z* (EI) 382 (M^+, ^{37}Cl, 1), 380 (M^+, ^{35}Cl, 2), 196 (17), 168 (67), 154 (48), 138 (26), 118 (38), 105 (100), 91 (52); HRMS (EI): calcd for $C_{18}H_{21}{}^{35}ClN_2O_3S$ (M^+) 380.0961, found 380.0952.

Data for **124b**: R_f 0.23 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3294, 3020, 2926, 1514, 1439, 1327, 1207, 1148, 1045, 835, 760; δ_H (300 MHz, $CDCl_3$) 7.28-7.51 (m, 4 H, Ar*H*), 7.03 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.90 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.70 (app. t, *J* = 5.6 Hz, 1 H, N*H*), 4.49 (br d, *J* = 7.6 Hz, 1 H, NC*H*), 4.44 (dd, *J* = 9.9, 3.8 Hz, 1 H, SCHC*H*H), 4.34 (dd, *J* = 9.9, 8.4 Hz, 1 H, SCHCH*H*), 4.13 (dd, *J* = 13.6, 6.6 Hz, 1 H, NHC*H*H), 3.97 (app. td, *J* = 7.6, 3.8 Hz, 1 H, SC*H*), 3.82 (dd, *J* = 13.6, 5.0 Hz, 1 H, NHCH*H*), 2.62 (s, 3 H, NCH_3), 2.31 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 134.3 (s), 134.2 (s), 133.0 (s), 130.1 (d), 129.9 (d), 129.8 (d), 129.4 (d), 127.9 (d), 127.8 (d), 72.9 (d), 70.1 (d), 67.1 (t), 47.2 (t), 42.7 (q), 21.1 (q); *m/z* (EI) 382 (M^+, ^{37}Cl, 3), 380 (M^+, ^{35}Cl, 9), 194 (100), 151 (49), 134 (23), 120 (53), 105 (71), 91 (33); HRMS (EI): calcd for $C_{18}H_{21}{}^{35}ClN_2O_3S$ (M^+) 380.0961, found 380.0955.

(3*S, 4*S**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (124c),** [69, 94] **(3*R**, 5*S**) and (3*S**, 5*S**)-2-Methyl-3-phenylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125/126c)**



124c



125/126c

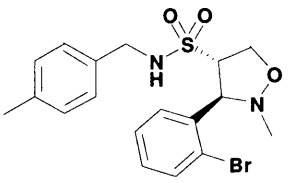
General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **125/126c** (22 mg, 13%) as a mixture, and **124c** (110 mg, 68%)- overall yield (81%, **124c**:**125/126c** = 5:1, **125c** and **126c** = 2:1 major:minor).

Data for **125/126c**: R_f 0.37 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 2922, 1455, 1327, 1147, 1037; δ_H (300 MHz, $CDCl_3$) 7.27-7.43 (m, 7 H, Ar*H*), 7.17 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 5.03 (dd, *J* = 8.6, 5.9 Hz, 1 H_{minor}, SC*H*), 4.98 (dd, *J* = 8.6, 2.4 Hz, 1 H_{major}, SC*H*), 4.82 (app. t, *J* = 5.9 Hz, 1 H_{minor}, N*H*), 4.73 (app. t, *J* = 5.9 Hz, 1 H_{major}, N*H*), 4.46 (dd, *J* = 13.9, 6.4 Hz, 1 H_{minor}, NHC*H*H), 4.38-4.43 (m, 1 H_{minor}, NHCH*H*),

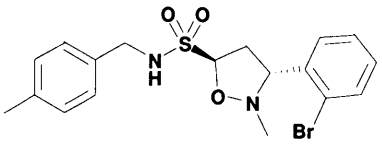
4.35-4.40 (m, 1 H_{major}, NHC*H*H), 4.31 (dd, *J* = 13.9, 5.9 Hz, 1 H_{major}, NHCH*H*), 4.06 (br s, 1 H_{major}, NC*H*), 3.58 (br dd, *J* = 9.9, 7.8 Hz, 1 H_{minor}, NC*H*), 3.07 (ddd, *J* = 13.7, 6.2, 2.4 Hz, 1 H, SCHC*H*H), 2.77-2.99 (m, 1 H, SCHCH*H*), 2.75 (s, 3 H_{major}, NCH_3), 2.62 (s, 3 H_{minor}, NCH_3), 2.35 (s, 3 H, $ArCH_3$); δ_C (125 MHz, $CDCl_3$) 139.4 (s), 139.0 (s), 137.9 (s), 137.5 (s), 135.3 (s), 134.9 (s), 130.9 (d), 130.5 (d), 130.4 (d), 130.0 (d), 129.8 (d), 129.5 (d), 129.1 (d), 128.7 (d), 128.5 (d), 90.3 (d), 72.0 (d), 48.7 (t), 45.5 (q), 44.3 (q), 42.6 (t), 42.3 (t), 22.3 (q), 23 out of 28 expected signals observed; *m/z* (EI) 346 (M^+, 50), 282 (38), 236 (86), 209 (74), 162 (52), 147 (35), 134 (70), 120 (48), 105 (100); HRMS (EI): calcd for $C_{18}H_{22}N_2O_3S$ (M^+) 346.1296, found 346.1301.

Data for **124c**: R_f 0.29 (2:1 Et_2O/petroleum ether 40-60°C); mp 84-86 °C; υ_{max} (film)/cm^{-1} 3290, 3034, 2924, 1611, 1448, 1323, 1146, 1043; δ_H (300 MHz, $CDCl_3$) 7.36-7.44 (m, 5 H, Ar*H*), 7.05 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.93 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.89 (app. t, *J* = 5.8 Hz, 1 H, CH_2NH), 4.34 (dd, *J* = 9.8, 3.7 Hz, 1 H, SCHC*H*H), 4.23 (dd, *J* = 9.8, 8.4 Hz, 1 H, SCHCH*H*), 4.08 (dd, *J* = 13.7, 6.4 Hz, 1 H, NHC*H*H), 3.93 (app. td, *J* = 8.0, 3.7 Hz, 1 H, SC*H*), 3.80-3.86 (m, 2 H, SCHC*H*N and NHCH*H*), 2.58 (s, 3 H, NCH_3), 2.31 (s, 3 H, $ArCH_3$); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 136.8 (s), 133.2 (s), 129.4 (d), 129.0 (d), 128.8 (d), 128.3 (d), 128.0 (d), 74.5 (d), 73.2 (d), 66.9 (t), 47.0 (t), 42.7 (q), 21.1 (q); *m/z* (EI) 346 (M^+, 10), 160 (100), 105 (83); HRMS (EI): calcd for $C_{18}H_{22}N_2O_3S$ (M^+) 346.1351, found 346.1359; Anal. calcd for $C_{18}H_{22}N_2O_3S$: C 62.40, H 6.40, N 8.09, found C 61.94, H 6.47, N 7.71.

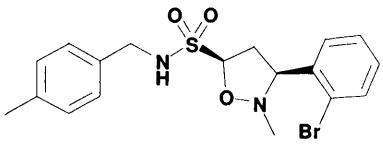
(3*S, 4*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124d), (3*R**, 5*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125d), and (3*S**, 5*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (126d)**



124d



125d



126d

General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the three separable products **124d** (61 mg, 31%), **125d** (72 mg, 36%), and **126d** (33 mg, 16%)- overall yield (83%, **124d**:**125d**:**126d** = 2:2:1).

Data for **126d**: R_f 0.40 (2:1 Et_2O/petroleum ether 40-60°C); mp 107-109 °C; υ_{max} (neat)/cm^{-1} 3295, 2918, 1515, 1424, 1332, 1155, 1023, 958, 765; δ_H (300 MHz, $CDCl_3$)

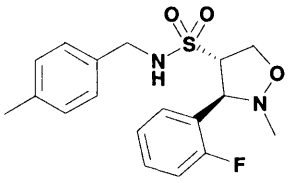
7.63 (dd, *J* = 7.8, 1.7 Hz, 1 H, Ar*H*), 7.55 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar*H*), 7.28-7.34 (m, 1 H, Ar*H*), 7.27 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.13-7.18 (m, 3 H, Ar*H*), 5.04 (dd, *J* = 8.6, 5.6 Hz, 1 H, SC*H*), 4.80 (app. t, *J* = 6.0 Hz, 1 H, N*H*), 4.43 (dd, *J* = 14.2, 6.4 Hz, 1 H, NHC*H*H), 4.38 (dd, *J* = 14.2, 5.8 Hz, 1 H, NHCH*H*), 4.17 (dd, *J* = 9.8, 7.5 Hz, 1 H, NC*H*), 3.18 (ddd, *J* = 13.4, 8.6, 7.5 Hz, 1 H, SCHC*H*H), 2.65-2.76 (m, 4 H, SCHCH*H* and NCH_3), 2.35 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 136.4 (s), 134.1 (s), 132.9 (d), 129.6 (d), 129.5 (d), 128.7 (d), 128.3 (d), 128.0 (d), 123.9 (s), 89.3 (d), 71.0 (d), 47.6 (t), 43.4 (q), 39.7 (t), 21.1 (q); *m/z* (EI) 426 (M^+, ^{81}Br, 4), 424 (M^+, ^{79}Br, 4), 316 (64), 244 (28), 224 (31), 222 (35), 198 (28), 180 (19), 165 (34), 149 (76), 140 (100), 129 (26), 125 (44), 121 (89), 112 (74), 105 (56); HRMS (EI): calcd for $C_{18}H_{21}{}^{79}BrN_2O_3S$ (M^+) 424.0456, found 424.0459.

Data for **125d**: R_f 0.35 (2:1 Et_2O/petroleum ether 40-60°C); mp 89-94 °C; υ_{max} (neat)/cm^{-1} 3250, 2919, 1516, 1432, 1291, 1152, 1027, 890, 756; δ_H (300 MHz, $CDCl_3$) 7.55 (app. dt, *J* = 8.0, 1.3 Hz, 2 H, Ar*H*), 7.32 (app. dt, *J* = 7.8, 1.1 Hz, 1 H Ar*H*), 7.26-7.28 (m, 2 H, Ar*H*), 7.13-7.19 (m, 3 H, Ar*H*), 4.88 (dd, *J* = 8.2, 4.2 Hz, 1 H, SC*H*), 4.72 (app. t, *J* = 6.0 Hz, 1 H, N*H*), 4.57 (app. t, *J* = 7.2 Hz, 1 H, NC*H*), 4.40 (dd, *J* = 14.0, 6.0 Hz, 1 H, NHC*H*H), 4.33 (dd, *J* = 14.0, 5.8 Hz, 1 H, NHCH*H*), 3.28 (ddd, *J* = 13.5, 6.6, 4.2 Hz, 1 H, SCHC*H*H), 2.8 (s, 3 H, NCH_3), 2.59 (app. dt, *J* = 13.5, 8.2 Hz, 1 H, SCHCH*H*), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.9 (s), 137.4 (s), 133.8 (s), 133.1 (d), 129.5 (d), 129.3 (d), 128.0 (2 x d), 127.9 (d), 123.7 (s), 89.8 (d), 69.4 (d), 47.7 (t), 45.2 (q), 39.1 (t), 21.1 (q); *m/z* (EI) 426 (M^+, ^{81}Br, 3), 424 (M^+, ^{79}Br, 3), 314 (66), 244 (54), 234 (20), 214 (59), 198 (77), 184 (33), 167 (54), 147 (59), 132 (65), 120 (85), 105 (97), 92 (70), 84 (100); HRMS (EI): calcd for $C_{18}H_{21}{}^{79}BrN_2O_3S$ (M^+) 424.0456, found 424.0459.

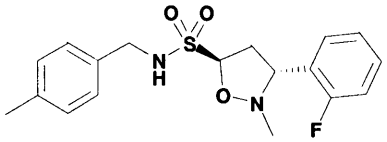
Data for **124d**: R_f 0.22 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3289, 2921, 1516, 1433, 1325, 1146, 1028, 828, 749; δ_H (300 MHz, $CDCl_3$) 7.59 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.48 (dd, *J* = 7.8, 1.3 Hz, 1 H, Ar*H*), 7.38 (app. dt, *J* = 7.5, 1.3 Hz, 1 H, Ar*H*), 7.21-7.27 (m, 1 H, Ar*H*), 7.02 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 4.76 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.51 (br d, *J* = 6.7 Hz, 1 H, NC*H*), 4.44 (dd, *J* = 9.8, 3.8 Hz, 1 H, SCHC*H*H), 4.34 (dd, *J* = 9.8, 8.4 Hz, 1 H, SCHCH*H*), 4.12 (dd, *J* = 13.7, 6.6 Hz, 1 H, NHC*H*H), 3.95 (app. td, *J* = 8.0, 3.8 Hz, 1 H, SC*H*), 3.79 (dd, *J* = 13.7, 4.8 Hz, 1 H, NHCH*H*), 2.63 (s, 3 H, NCH_3), 2.30 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 136.0 (s), 133.3 (s), 133.0 (d), 130.1 (d), 130.0 (d), 129.4 (d), 128.4 (d), 127.9 (d), 124.8 (s), 73.1 (d), 72.3 (d), 67.2 (t), 47.2 (t), 42.6 (q), 21.1 (q); *m/z* (EI) 426 (M^+, ^{81}Br, 9), 424 (M^+, ^{79}Br, 9), 240 (88), 197 (54), 134 (26), 120 (87), 116 (70),

105 (79), 97 (47), 91 (38), 84 (100); HRMS (EI): calcd for $C_{18}H_{21}{}^{79}BrN_2O_3S$ (M^+) 424.0456, found 424.0450.

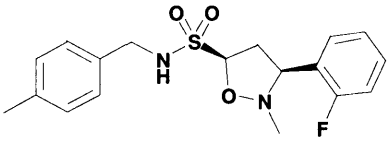
(3*S, 4*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124e),** [69, 94] **(3*R**, 5*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125e), and (3*S**, 5*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (126e)**



124e



125e



126e

General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the three separable products **124e** (73 mg, 43%), **125e** (56 mg, 33%), and **126e** (23 mg, 13%)- overall yield (89%, **124e**:**125e**:**126e** = 6:5:2).

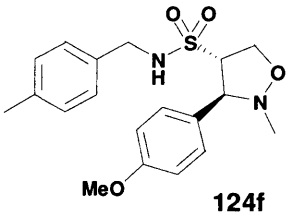
Data for **126e**: R_f 0.45 (2:1 Et_2O/petroleum ether 40-60°C); mp 96-99 °C; υ_{max} (neat)/cm^{-1} 3276, 2920, 1489, 1453, 1319, 1232, 1155, 1053, 956, 764; δ_H (300 MHz, $CDCl_3$) 7.57 (app. dt, *J* = 7.5, 1.6 Hz, 1 H, Ar*H*), 7.26-7.30 (m, 3 H, Ar*H*), 7.13-7.18 (m, 3 H, Ar*H*), 7.05 (ddd, *J* = 10.3, 8.2, 1.2 Hz, 1 H, Ar*H*), 5.05 (dd, *J* = 8.6, 5.6 Hz, 1 H, SC*H*), 4.74 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.45 (dd, *J* = 13.9, 6.2 Hz, 1 H, NHC*H*H), 4.38 (dd, *J* = 13.9, 5.7 Hz, 1 H, NHCH*H*), 4.01 (br dd, *J* = 10.0, 7.6 Hz, 1 H, NC*H*), 3.07 (ddd, *J* = 13.5, 8.6, 7.6 Hz, 1 H, SCHC*H*H), 2.85 (ddd, *J* = 13.5, 10.0, 5.6 Hz, 1 H, SCHCH*H*), 2.67 (s, 3 H, NCH_3), 2.35 (s, 3 H, $ArCH_3$); δ_C (75 MHz, $CDCl_3$) 160.9 (s, J_{CF} = 247.1 Hz), 137.8 (s), 134.1 (s), 129.8 (d, J_{CF} = 8.5 Hz), 128.0 (d), 128.7 (d, J_{CF} = 3.8 Hz), 128.0 (d), 124.9 (d, J_{CF} = 3.5 Hz), 123.5 (s, J_{CF} = 11.4 Hz), 115.6 (d, J_{CF} = 21.7 Hz), 89.4 (d), 65.1 (d), 47.6 (t), 43.4 (q), 39.6 (t), 21.1 (q); *m/z* (FAB^+) 365 (MH^+, 3), 307 (35), 289 (16), 154 (100); HRMS (FAB^+): calcd for $C_{18}H_{22}FN_2O_3S$ (MH^+) 365.1335, found 365.1324.

Data for **125e**: R_f 0.35 (2:1 Et_2O/petroleum ether 40-60°C); mp 112-115 °C; υ_{max} (neat)/cm^{-1} 3269, 2920, 1596, 1490, 1312, 1218, 1134, 1082, 1053, 892, 763; δ_H (300 MHz, $CDCl_3$) 7.25-7.41 (m, 4 H, Ar*H*), 7.03-7.17 (m, 4 H, Ar*H*), 4.93 (dd, *J* = 8.4, 3.4 Hz, 1 H, SC*H*), 4.85 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.43-4.46 (m, 1 H, NC*H*), 4.38 (dd, *J* = 14.1, 6.1 Hz, 1 H, NHC*H*H), 4.31 (dd, *J* = 14.1, 6.1 Hz, 1 H, NHCH*H*), 3.13 (ddd, *J* = 13.5, 6.5, 3.4 Hz, 1 H, SCHC*H*H), 2.67-2.79 (m, 4 H, NCH_3 and SCHCH*H*), 2.33 (s, 3

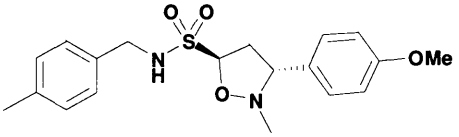
H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 160.8 (s, J_{CF} = 247.7 Hz), 137.9 (s), 133.8 (s), 129.6 (d, J_{CF} = 8.5 Hz), 129.5 (d), 128.2 (d), 128.0 (d), 124.5 (d, J_{CF} = 3.5 Hz), 115.7 (d, J_{CF} = 21.7 Hz), 89.7 (d), 63.9 (d), 47.6 (t), 44.9 (q), 39.1 (t), 21.1 (q), 1 x s not observed; *m/z* (EI) 364 (M^+, 2), 254 (32), 152 (100), 137 (44), 120 (22), 109 (16), 105 (55), 91 (19); HRMS (EI): calcd for $C_{18}H_{21}FN_2O_3S$ (M^+) 364.1251, found 364.1238.

Data for **124e:** R_f 0.22 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3280, 2918, 1494, 1456, 1327, 1234, 1146, 1037, 804, 759; δ_H (300 MHz, $CDCl_3$) 7.35-7.45 (m, 2 H, Ar*H*), 7.19 (app. t, *J* = 7.5 Hz, 1 H, Ar*H*), 7.03-7.11 (m, 3 H, Ar*H*), 6.95 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 4.79 (app. t, *J* = 5.4 Hz, 1 H, N*H*), 4.39 (dd, *J* = 9.8, 3.5 Hz, 1 H, SCHC*H*H), 4.29 (dd, *J* = 9.8, 8.2 Hz, 1 H, SCHCH*H*), 4.14 (m, 2 H, NC*H* and NHC*H*H), 4.02 (app. td, *J* = 7.7, 3.5 Hz, 1 H, SC*H*), 3.93 (dd, *J* = 13.8, 5.2 Hz, 1 H, NHCH*H*), 2.62 (s, 3 H, NCH_3), 2.31 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 161.0 (s, J_{CF} = 248.0 Hz), 137.9 (s), 133.2 (s), 130.4 (d, J_{CF} = 8.5 Hz), 129.9 (d, J_{CF} = 3.8 Hz), 129.5 (d), 127.9 (d), 124.9 (d, J_{CF} = 3.5 Hz), 123.7 (s, J_{CF} = 11.4 Hz), 116.1 (d, J_{CF} = 22.0 Hz), 72.2 (d), 68.0 (d), 67.0 (t), 47.2 (t), 42.8 (q), 21.1 (q); *m/z* (EI) 364 (M^+, 2), 178 (100), 135 (44), 120 (19), 105 (19); HRMS (EI): calcd for $C_{18}H_{21}FN_2O_3S$ (M^+) 364.1251, found 364.1252.

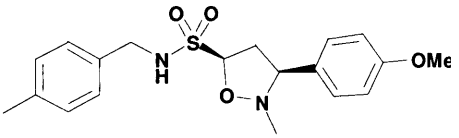
(3*S, 4*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124f),**[69, 94] **(3*R**, 5*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125f), and (3*S**, 5*S**)-3-(4-Methoxyphenyl)-2-methyl isoxazolidine-5-sulfonic acid 4-methylbenzylamide (126f)**



124f



125f



126f

General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the three separable products **124f** (94 mg, 53%), **125f** (23 mg, 13%), and **126f** (13 mg, 7%)- overall yield (73%, **124f**:**125f**:**126f** = 7:2:1).

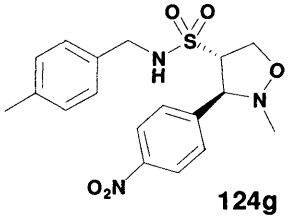
Data for **126f**: R_f 0.26 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3289, 2921, 1612, 1514, 1456, 1327, 1247, 1151, 1034; δ_H (300 MHz, $CDCl_3$) 7.33 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.29 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.17 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.87 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 5.02 (dd, *J* = 8.5, 5.9 Hz, 1 H, SC*H*), 4.72 (app. t, *J* = 6.0 Hz, 1 H, N*H*), 4.46 (dd, *J* = 13.9, 6.4 Hz, 1 H, NHC*H*H), 4.39 (dd, *J* = 13.9, 5.9 Hz, 1 H, NHCH*H*),

3.80 (s, 3 H, OCH_3), 3.54 (br dd, J = 9.6, 7.5 Hz, 1 H, NCH), 2.84-3.05 (m, 2 H, SCHCH_2), 2.60 (s, 3 H, NCH_3), 2.35 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 160.0 (s), 137.8 (s), 134.2 (s), 129.5 (d), 129.2 (d), 128.2 (s), 128.0 (d), 114.3 (d), 89.3 (d), 67.8 (d), 55.3 (q), 47.6 (t), 43.4 (q), 41.4 (t), 21.1 (q); *m/z* (EI) 376 (M^+, 3), 266 (24), 192 (71), 164 (58), 149 (100), 135 (36), 119 (25), 105 (87), 91 (41), 77 (24); HRMS (EI): calcd for $C_{19}H_{24}N_2O_4S$ (M^+) 376.1451, found 376.1444.

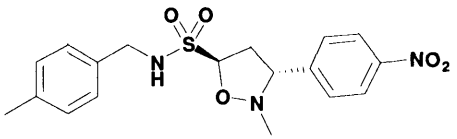
Data for **125f**: R_f 0.21 (2:1 Et_2O/petroleum ether 40-60°C); mp 132-135 °C; υ_{max} (neat)/cm^{-1} 3295, 2918, 1613, 1458, 1421, 1326, 1243, 1145, 1063, 1022; δ_H (300 MHz, $CDCl_3$) 7.27 (m, 4 H, ArH), 7.17 (d, J = 7.9 Hz, 2 H, ArH), 6.88 (d, J = 8.7 Hz, 2 H, ArH), 4.98 (dd, J = 8.6, 2.1 Hz, 1 H, SCH), 4.70 (app. t, J = 5.4 Hz, 1 H, NH), 4.38 (dd, J = 14.0, 6.2 Hz, 1 H, NHCHH), 4.31 (dd, J = 14.0, 5.7 Hz, 1 H, NHCHH), 3.99 (br s, 1 H, NCH), 3.81 (s, 3 H, OCH_3), 3.02 (ddd, J = 13.7, 6.0, 2.1 Hz, 1 H, SCHCHH), 2.72-2.82 (m, 4 H, SCHCHH and NCH_3), 2.35 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 159.7 (s), 137.9 (s), 133.8 (s), 129.5 (d), 128.8 (d), 128.3 (s), 128.0 (d), 114.3 (d), 89.1 (d), 67.6 (d), 55.3 (q), 47.6 (t), 44.5 (q), 41.1 (t), 21.1 (q); *m/z* (EI) 376 (M^+, 5), 264 (100), 148 (16), 105 (47); HRMS (EI): calcd for $C_{19}H_{24}N_2O_4S$ (M^+) 376.1402, found 376.1408.

Data for **124f**: R_f 0.16 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3332, 2959, 1612, 1514, 1464, 1422, 1315, 1251, 1137, 1058, 1028; δ_H (300 MHz, $CDCl_3$) 7.32 (d, J = 8.8 Hz, 2 H, ArH), 7.08 (d, J = 8.0 Hz, 2 H, ArH), 6.95 (d, J = 8.0 Hz, 2 H, ArH), 6.90 (d, J = 8.8 Hz, 2 H, ArH), 4.85 (app. t, J = 5.7 Hz, 1 H, NH), 4.33 (dd, J = 9.9, 3.5 Hz, 1 H, SCHCHH), 4.23 (dd, J = 9.9, 8.3 Hz, 1 H, SCHCHH), 4.09 (dd, J = 13.7, 6.4 Hz, 1 H, NHCHH), 3.91 (app. td, J = 7.8, 3.5 Hz, 1 H, SCH), 3.80-3.88 (m, 1 H, NHCHH), 3.82 (s, 3 H, OCH_3), 3.75 (d, J = 6.4 Hz, 1 H, NCH), 2.57 (s, 3 H, NCH_3), 2.32 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 160.0 (s), 137.8 (s), 133.3 (s), 129.4 (d), 128.8 (d), 128.4 (s), 128.0 (d), 114.4 (d), 74.1 (d), 73.0 (d), 66.7 (t), 55.3 (q), 47.0 (t), 42.5 (q), 21.1 (q); *m/z* (EI) 376 (M^+, 6), 216 (71), 190 (100), 174 (26), 164 (34), 147 (93), 134 (45), 120 (46), 105 (53), 91 (42), 77 (28); HRMS (EI): calcd for $C_{19}H_{24}N_2O_4S$ (M^+) 376.1451, found 376.1460.

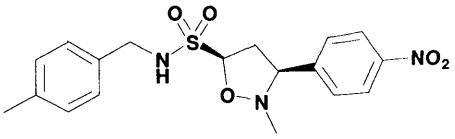
(3*S, 4*S**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-4-sulfonic acid 4-methyl benzylamide (124g),** [69, 94] **(3*R**, 5*S**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-5-sulfonic acid 4-methylbenzylamide (125g), and (3*S**, 5*S**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-5-sulfonic acid 4-methylbenzylamide (126g)**



124g



125g



126g

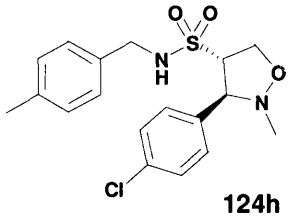
General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **124g** (96 mg, 52%), **125g** (8 mg, 4%), and **126g** (19 mg, 10%)- overall yield (67%, **124g**:**125g**:**126g** = 24:2:5).

Data for **126g**: R_f 0.23 (2:1 Et_2O/petroleum ether 40-60°C); mp 135-139 °C; υ_{max} (neat)/cm^{-1} 3279, 2922, 1737, 1599, 1518, 1440, 1329, 1143, 1060, 850; δ_H (300 MHz, $CDCl_3$) 8.22 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.56 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.26 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.18 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.93 (dd, *J* = 8.5, 2.6 Hz, 1 H, SC*H*), 4.70 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.39 (dd, *J* = 13.9, 6.2 Hz, 1 H, NHC*H*H), 4.32 (dd, *J* = 13.9, 5.9 Hz, 1 H, NHCH*H*), 4.22 (dd, *J* = 9.7, 6.3 Hz, 1 H, NC*H*), 3.13 (ddd, *J* = 13.7, 6.3, 2.6 Hz, 1 H, SCHC*H*H), 2.78 (s, 3 H, NCH_3), 2.68-2.77 (m, 1 H, SCHCH*H*), 2.35 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 147.9 (s), 144.8 (s), 138.0 (s), 133.6 (s), 129.6 (d), 128.4 (d), 128.0 (d), 124.1 (d), 89.3 (d), 69.9 (d), 47.6 (t), 44.9 (q), 39.6 (t), 21.1 (q); *m/z* (CI) 392 (MH^+, 71), 225 (66), 207 (58), 191 (30), 177 (78), 122 (100); HRMS (ES^+): calcd for $C_{18}H_{22}N_3O_5S$ (MH^+) 392.1275, found 392.1279.

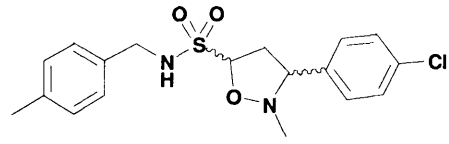
Data for **125g**: R_f 0.15 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3280, 2923, 1737, 1520, 1435, 1348, 1149, 1054, 855; δ_H (300 MHz, $CDCl_3$) 8.20 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.63 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.28 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.18 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 5.02 (dd, *J* = 8.8, 5.4 Hz, 1 H, SC*H*), 4.73 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.45 (dd, *J* = 14.2, 6.2 Hz, 1 H, NHC*H*H), 4.38 (dd, *J* = 14.2, 6.2 Hz, 1 H, NHCH*H*), 3.70 (dd, *J* = 9.8, 7.6 Hz, 1 H, NC*H*), 3.10 (ddd, *J* = 13.7, 8.8, 7.6 Hz, 1 H, SCHC*H*H), 2.87 (ddd, *J* = 13.7, 9.8, 5.4 Hz, 1 H, SCHCH*H*), 2.64 (s, 3 H, NCH_3), 2.36 (s, 3 H, ArCH_3); δ_C (125 MHz, $CDCl_3$) 148.2 (s), 144.3 (s), 138.0 (s), 133.9 (s), 129.6 (d), 129.0 (d), 128.0 (d), 124.2 (d), 89.2 (d), 72.6 (d), 47.6 (t), 43.4 (q), 41.3 (t), 21.2 (q); *m/z* (CI) 392 (MH^+, 5), 281 (27), 251 (21), 225 (34), 207 (74), 165 (80), 148 (70), 135 (46), 120 (77), 105 (100); HRMS (CI): calcd for $C_{18}H_{22}N_3O_5S$ (MH^+) 392.1280, found 392.1272.

Data for **124g**: R_f 0.19 (2:1 Et_2O/petroleum ether 40-60°C); mp 146-149 °C; υ_{max} (neat)/cm^{-1} 3281, 2870, 1737, 1522, 1447, 1348, 1309, 1148, 1061, 861; δ_H (300 MHz, $CDCl_3$) 8.21 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.59 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.07 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.02 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 4.91 (br s, 1 H, N*H*), 4.32 (dd, *J* = 9.8, 3.9 Hz, 1 H, SCHC*H*H), 4.09-4.22 (m, 3 H, SCHCH*H* and NHCH_2), 3.98 (br d, *J* = 6.8 Hz, 1 H, NC*H*), 3.73 (ddd, *J* = 10.8, 7.0, 3.9 Hz, 1 H, SC*H*), 2.64 (s, 3 H, NCH_3), 2.31 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 148.0 (s), 144.8 (s), 138.2 (s), 133.1 (s), 129.6 (d), 129.0 (d), 128.0 (d), 124.0 (d), 74.1 (d), 72.9 (d), 67.2 (t), 47.3 (t), 42.9 (q), 21.1 (q); *m/z* (EI) 391 (M^+, 2), 205 (100), 120 (56), 116 (27), 105 (44); HRMS (EI): calcd for $C_{18}H_{21}N_3O_5S$ (M^+) 391.1196, found 391.1208.

(3*S, 4*S**)-3-(4-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124h), (3*R**, 5*S**) and (3*S**, 5*S**)-3-(4-Chlorophenyl)-2-methyl isoxazolidine-5-sulfonic acid 4-methylbenzylamide (125/126h)**



124h



125/126h

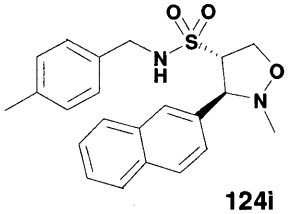
General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **125/126h** (41 mg, 23%) as a mixture, and **124h** (98 mg, 55%) as a yellow solid- overall yield (78%, **124h**:**125/126h** = 5:2, **125h** and **126h** = 3:1 major:minor).

Data for **125/126h**: R_f 0.35 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3274, 2922, 1490, 1329, 1298, 1144, 1058, 807; δ_H (300 MHz, $CDCl_3$) 7.28-7.37 (m, 4 H, Ar*H*), 7.26 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.17 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 5.00 (dd, *J* = 8.6, 5.6 Hz, 1 H_{minor}, SC*H*), 4.95 (dd, *J* = 8.6, 2.4 Hz, 1 H_{major}, SC*H*), 4.83 (app. t, *J* = 5.9 Hz, 1 H_{minor}, N*H*), 4.73 (app. t, *J* = 5.9 Hz, 1 H_{major}, N*H*), 4.44 (dd, *J* = 13.9, 6.2 Hz, 1 H_{minor}, NHC*H*H), 4.37-4.42 (m, 1 H_{minor}, NHCH*H*), 4.36 (dd, *J* = 13.9, 6.2 Hz, 1 H_{major}, NHC*H*H), 4.31 (dd, *J* = 13.9, 5.9 Hz, 1 H_{major}, NHCH*H*), 4.04 (br dd, *J* = 8.6, 6.2 Hz, 1 H_{major}, NC*H*), 3.55 (br dd, *J* = 9.9, 7.5 Hz, 1 H_{minor}, NC*H*), 3.05 (ddd, *J* = 13.7, 6.2, 2.4 Hz, 1 H_{major}, SCHC*H*H), 3.01 (ddd, *J* = 13.7, 8.6, 7.5 Hz, 1 H_{minor}, SCHC*H*H), 2.85 (ddd, *J* = 13.7, 9.9, 5.6 Hz, 1 H_{minor}, SCHCH*H*), 2.73 (s, 3 H_{major}, NCH_3), 2.71 (ddd, *J* = 13.7, 10.2, 8.6 Hz, 1 H_{major}, SCHCH*H*), 2.60 (s, 3 H_{minor}, NCH_3), 2.35 (s, 3 H, ArCH_3); δ_C (125 MHz, $CDCl_3$) 139.0 (s), 138.0 (s), 136.5 (s), 135.9 (s), 134.8 (s), 133.6 (s),

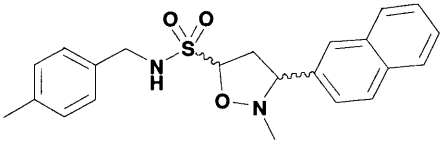
130.6 (d), 130.1 (d), 129.6 (d), 129.5 (d), 129.1 (d), 129.0 (d), 90.2 (d), 89.1 (d), 71.2 (t), 48.6 (t), 45.4 (q), 45.3 (q), 42.5 (t), 22.2 (q), 20 out of 28 expected signals observed; *m/z* (FAB^+) 383 (MH^+, ^{37}Cl, 10), 381 (MH^+, ^{35}Cl, 22), 338 (63), 307 (96), 289 (60), 273 (28), 196 (34), 155 (100); HRMS (FAB^+): calcd for $C_{18}H_{22}{}^{35}ClN_2O_3S$ (MH^+) 381.1040, found 381.1046.

Data for **124h**: R_f 0.27 (2:1 Et_2O/petroleum ether 40-60°C); mp 101-105 °C; υ_{max} (neat)/cm^{-1} 3347, 2879, 1492, 1328, 1305, 1136, 1032, 750; δ_H (300 MHz, $CDCl_3$) 7.33 (s, 4 H, Ar*H*), 7.07 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.96 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.93 (app. t, *J* = 5.4 Hz, 1 H, N*H*), 4.30-4.34 (m, 1 H, SCHC*H*H), 4.16-4.23 (m, 1 H, SCHCH*H*), 4.12 (dd, *J* = 13.9, 6.2 Hz, 1 H, NHC*H*H), 3.98 (dd, *J* = 13.9, 5.6 Hz, 1 H, NHCH*H*), 3.76-3.83 (m, 2 H, SC*H* and NC*H*), 2.58 (s, 3 H, NCH_3), 2.32 (s, 3 H, $ArCH_3$); δ_C (75 MHz, $CDCl_3$) 138.0 (s), 135.5 (s), 134.6 (s), 133.1 (s), 129.6 (d), 129.5 (d), 129.2 (d), 128.0 (d), 73.5 (d), 66.9 (t), 47.1 (t), 42.7 (q), 21.1 (q), 1 x d not observed; *m/z* (EI) 382 (M^+, ^{37}Cl, 2), 380 (M^+, ^{35}Cl, 5), 196 (33), 194 (100), 120 (83); HRMS (EI): calcd for $C_{18}H_{21}{}^{35}ClN_2O_3S$ (M^+) 380.0956, found 380.0949.

(3*S, 4*S**)-2-Methyl-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid 4-methyl benzylamide (124i), (3*R**, 5*S**) and (3*S**, 5*S**)-2-Methyl-3-naphthalen-2-yl-isoxazolidine-5-sulfonic acid 4-methylbenzylamide (125/126i)**



124i



125/126i

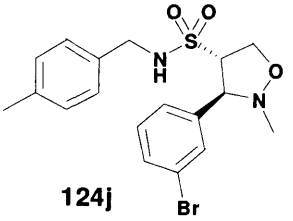
General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **125/126i** (30 mg, 16%) as a mixture, and **124i** (77 mg, 41%) as a yellow solid- overall yield (57%, **124i**:**125/126i** = 5:2, **125i** and **126i** = 2:1 major:minor).

Data for **125/126i**: R_f 0.34 (2:1 Et_2O/petroleum ether 40-60°C); mp 118-120 °C; υ_{max} (neat)/cm^{-1} 3227, 2924, 1515, 1437, 1320, 1286, 1153, 1048, 889; δ_H (300 MHz, $CDCl_3$) 7.79-7.87 (m, 4 H, Ar*H*), 7.60 (dd, *J* = 8.3, 1.3 Hz, 1 H, Ar*H*), 7.46-7.53 (m, 2 H, Ar*H*), 7.25-7.32 (m, 2 H, Ar*H*), 7.17 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 5.08 (dd, *J* = 8.3, 6.2 Hz, 1 H_{minor}, SC*H*), 5.03 (dd, *J* = 8.3, 2.4 Hz, 1 H_{major}, SC*H*), 4.90 (app. t, *J* = 5.9 Hz, 1 H_{minor}, N*H*), 4.80 (app. t, *J* = 5.9 Hz, 1 H_{major}, N*H*), 4.48 (dd, *J* = 13.9, 6.2 Hz, 1 H_{minor}, NHC*H*H), 4.41-4.46 (m, 1 H_{minor}, NHCH*H*), 4.41 (dd, *J* = 13.9, 6.2 Hz, 1 H_{major},

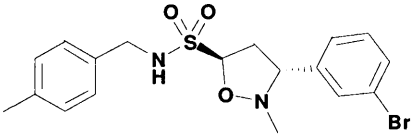
NHC*H*H), 4.34 (dd, *J* = 13.9, 5.9 Hz, 1 H_{major}, NHCH*H*), 4.25 (br s, 1 H_{major}, NC*H*), 3.75 (br dd, *J* = 9.4, 8.3 Hz, 1 H_{minor}, NC*H*), 2.99-3.18 (m, 1 H, SCHC*H*H), 2.82-2.98 (m, 1 H, SCHCH*H*), 2.80 (s, 3 H_{major}, NCH_3), 2.66 (s, 3 H_{minor}, NCH_3), 2.35 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.9 (s), 134.1 (s), 133.8 (s), 133.3 (s), 129.5 (d), 129.4 (d), 128.9 (d), 128.7 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.7 (d), 127.5 (d), 126.4 (d), 126.3 (d), 126.2 (d), 125.1 (s), 124.7 (s), 89.3 (d), 74.3 (d), 47.6 (t), 43.3 (q), 39.7 (t), 21.1 (q), 25 out of 34 expected signals observed; *m/z* (FAB^+) 397 (MH^+, 15), 219 (100), 203 (43), 187 (22), 163 (68); HRMS (FAB^+): calcd for $C_{22}H_{25}N_2O_3S$ (MH^+) 397.1586, found 397.1591.

Data for **124i**: R_f 0.28 (2:1 Et_2O/petroleum ether 40-60°C); mp 116-118 °C; υ_{max} (neat)/cm^{-1} 3278, 2959, 2874, 1508, 1457, 1412, 1308, 1152, 1038, 918; δ_H (300 MHz, $CDCl_3$) 7.79-7.89 (m, 4 H, Ar*H*), 7.49-7.57 (m, 3 H, Ar*H*), 6.86 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.75 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.85 (app. t, *J* = 5.1 Hz, 1 H, N*H*), 4.43 (dd, *J* = 9.6, 3.5 Hz, 1 H, SCHC*H*H), 4.32 (dd, *J* = 9.6, 7.8 Hz, 1 H, SCHCH*H*), 4.01-4.09 (m, 3 H, NC*H* and SC*H* and NHC*H*H), 3.81 (dd, *J* = 13.9, 5.4 Hz, 1 H, NHCH*H*), 2.64 (s, 3 H, NCH_3), 2.24 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 134.1 (s), 133.5 (s), 133.4 (s), 132.9 (s), 129.3 (d), 129.0 (d), 128.1 (d), 127.9 (2 x d), 127.8 (d), 126.6 (d), 126.5 (d), 125.1 (d), 74.7 (d), 73.1 (d), 67.0 (t), 47.1 (t), 42.8 (q), 21.1 (q); *m/z* (EI) 396 (M^+, 36), 244 (43), 205 (61), 118 (57), 104 (33), 91 (45), 84 (100); HRMS (EI): calcd for $C_{22}H_{24}N_2O_3S$ (M^+) 396.1502, found 396.1497.

(3*S, 4*S**)-3-(3-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124j),[69, 94] and (3*R**, 5*S**)-3-(3-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125j)**



124j



125j

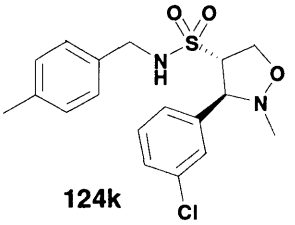
General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the two products **124j** (94 mg, 47%) and **125j** (20 mg, 10%)- overall yield (57%, **124j**:**125j** = 5:1).

Data for **125j**: R_f 0.43 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3259, 2918, 1594, 1460, 1430, 1322, 1295, 1144, 1044, 779; δ_H (300 MHz, $CDCl_3$) 7.54 (br s, 1 H Ar*H*), 7.45 (app. dt, *J* = 7.5, 1.6 Hz, 1 H, Ar*H*), 7.25-7.30 (m, 2 H, Ar*H*), 7.24 (d, *J* =

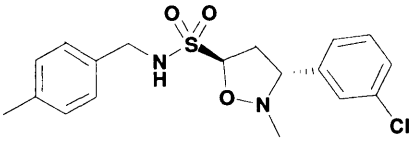
8.0 Hz, 2 H, Ar*H*), 7.17 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.95 (dd, *J* = 8.6, 2.4 Hz, 1 H, SC*H*), 4.69 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.39 (dd, *J* = 13.9, 6.4 Hz, 1 H, NHC*H*H), 4.31 (dd, *J* = 13.9, 5.6 Hz, 1 H, NHCH*H*), 4.05 (br dd, *J* = 9.1, 6.2 Hz, 1 H, NC*H*), 3.07 (ddd, *J* = 13.7, 6.2, 2.4 Hz, 1 H, SCHC*H*H), 2.76 (s, 3 H, NCH_3), 2.73 (ddd, *J* = 13.7, 10.2, 8.6 Hz, 1 H, SCHCH*H*), 2.35 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 139.2 (s), 138.0 (s), 133.7 (s), 131.5 (d), 130.4 (d), 129.6 (d), 128.9 (d), 128.0 (d), 126.3 (d), 123.0 (s), 89.2 (d), 70.0 (d), 47.6 (t), 44.5 (q), 41.8 (t), 21.2 (q); *m/z* (FAB$^+$) 427 (MH$^+$, ^{81}Br, 4), 425 (MH$^+$, ^{79}Br, 4), 338 (19), 154 (100); HRMS (FAB$^+$): calcd for $C_{18}H_{22}{}^{79}BrN_2O_3S$ (MH$^+$) 425.0534, found 425.0518.

Data for **124j**: R_f 0.35 (2:1 Et_2O/petroleum ether 40-60°C); mp 97-100 °C; υ_{max} (neat)/cm^{-1} 3145, 2920, 1570, 1464, 1325, 1140, 1020, 817; δ_H (300 MHz, $CDCl_3$) 7.55 (s, 1 H, Ar*H*), 7.47-7.50 (m, 1 H, Ar*H*), 7.34 (app. dt, *J* = 7.8, 1.3 Hz, 1 H, Ar*H*), 7.22 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.08 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.99 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.95 (app. t, *J* = 5.1 Hz, 1 H, N*H*), 4.32 (dd, *J* = 9.9, 3.5 Hz, 1 H, SCHC*H*H), 4.18 (dd, *J* = 9.9, 7.8 Hz, 1 H, SCHCH*H*), 4.13 (dd, *J* = 13.9, 5.9 Hz, 1 H, NHC*H*H), 4.00 (dd, *J* = 13.9, 5.4 Hz, 1 H, NHCH*H*), 3.74-3.79 (m, 2 H, NC*H* and SC*H*), 2.60 (s, 3 H, NCH_3), 2.32 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 139.5 (s), 138.0 (s), 133.1 (s), 131.8 (d), 130.9 (d), 130.5 (d), 129.6 (d), 128.0 (d), 127.1 (d), 123.0 (s), 73.6 (d), 73.4 (d), 67.0 (t), 47.2 (t), 42.8 (q), 21.2 (q); *m/z* (EI) 426 (M$^+$, ^{81}Br, 2), 424 (M$^+$, ^{79}Br, 2), 240 (100), 238 (94), 120 (68), 105 (68), 91 (27); HRMS (EI): calcd for $C_{18}H_{21}{}^{79}BrN_2O_3S$ (M$^+$) 424.0451, found 424.0432.

(3*S, 4*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124k),[69, 94] and (3*R**, 5*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine -5-sulfonic acid 4-methylbenzylamide (125k)**



124k



125k

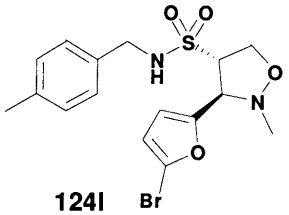
General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the two products **124k** (84 mg, 47%) and **125k** (27 mg, 15%)- overall yield (62%, **124k**:**125k** = 3:1).

Data for **125k**: R_f 0.42 (2:1 Et_2O/petroleum ether 40-60°C); mp 72-75 °C; υ_{max} (neat)/cm^{-1} 3260, 2919, 1597, 1431, 1327, 1296, 1144, 1063, 782; δ_H (300 MHz, $CDCl_3$)

7.38 (s, 1 H, Ar*H*), 7.21-7.30 (m, 5 H, Ar*H*), 7.17 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.95 (dd, *J* = 8.6, 2.7 Hz, 1 H, SC*H*), 4.74 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.39 (dd, *J* = 13.9, 6.2 Hz, 1 H, NHC*H*H), 4.31 (dd, *J* = 13.9, 5.6 Hz, 1 H, NHCH*H*), 4.05 (br dd, *J* = 9.9, 5.9 Hz, 1 H, NC*H*), 3.07 (ddd, *J* = 13.7, 6.2, 2.7 Hz, 1 H, SCHC*H*H), 2.75 (s, 3 H, NCH_3), 2.73 (ddd, *J* = 13.9, 10.2, 8.6 Hz, 1 H, SCHCH*H*), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 139.1 (s), 137.9 (s), 134.8 (s), 133.7 (s), 130.1 (d), 129.5 (d), 128.6 (d), 128.0 (d), 127.6 (d), 125.8 (d), 89.2 (d), 70.3 (d), 47.6 (t), 44.6 (q), 41.2 (t), 21.1 (q); *m/z* (CI) 383 (MH^+, ^{37}Cl, 6), 381 (MH^+, ^{35}Cl, 16), 270 (35), 198 (31), 196 (100), 105 (46); HRMS (CI): calcd for $C_{18}H_{22}{}^{35}ClN_2O_3S$ (MH^+) 381.1034, found 381.1029.

Data for **124k**: R_f 0.34 (2:1 Et_2O/petroleum ether 40-60°C); mp 88-92 °C; υ_{max} (neat)/cm^{-1} 3159, 2920, 1516, 1432, 1327, 1141, 1021, 904, 791; δ_H (300 MHz, $CDCl_3$) 7.39 (s, 1 H, Ar*H*), 7.28-7.35 (m, 3 H, Ar*H*), 7.08 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.99 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 5.01 (app. t, *J* = 5.4 Hz, 1 H, N*H*), 4.32 (dd, *J* = 10.2, 3.5 Hz, 1 H, SCHC*H*H), 4.18 (dd, *J* = 10.2, 7.8 Hz, 1 H, SCHCH*H*), 4.13 (dd, *J* = 13.9, 5.9 Hz, 1 H, NHC*H*H), 4.00 (dd, *J* = 13.9, 5.6 Hz, 1 H, NHCH*H*), 3.74-3.82 (m, 2 H, SC*H* and NC*H*), 2.59 (s, 3 H, NCH_3), 2.32 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 139.3 (s), 138.0 (s), 134.9 (s), 133.1 (s), 130.2 (d), 129.5 (d), 128.9 (d), 128.1 (d), 128.0 (d), 126.6 (d), 73.6 (2 x d), 67.0 (t), 47.1 (t), 42.7 (q), 21.1 (q); *m/z* (CI) 383 (MH^+, ^{37}Cl, 13), 381 (MH^+, ^{35}Cl, 31), 252 (100), 237 (28), 193 (41), 145 (18); HRMS (CI): calcd for $C_{18}H_{22}{}^{35}ClN_2O_3S$ (MH^+) 381.1034, found 381.1018.

(3*S, 4*S**)-3-(5-Bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124l)**



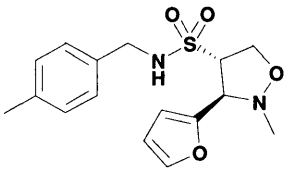
124l

General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **124l** (39 mg, 20%) as a brown oil.

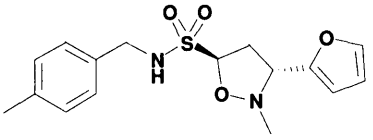
Data for **124l**: R_f 0.27 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3142, 2919, 1441, 1320, 1141, 1020, 901, 793; δ_H (300 MHz, $CDCl_3$) 7.14 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.08 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.37 (d, *J* = 3.5 Hz, 1 H, BrCC*H*), 6.31 (d, *J* = 3.5 Hz, 1 H, OCC*H*), 4.81 (br s, 1 H, N*H*), 4.33 (dd, *J* = 9.1, 3.2 Hz, 1 H, SCHC*H*H), 4.05-4.24

(m, 4 H, SCHCH*H* and NHCH_2 and SC*H*), 3.89 (br s, 1 H, NC*H*), 2.67 (s, 3 H, NCH_3), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 150.6 (s), 138.1 (s), 133.1 (s), 129.6 (d), 128.0 (d), 123.0 (s), 113.8 (d), 112.6 (d), 69.4 (d), 67.5 (d), 66.8 (t), 47.2 (t), 42.8 (q), 21.2 (q); *m/z* (EI) 416 (M^+, ^{81}Br, 7), 414 (M^+, ^{79}Br, 7), 230 (100), 187 (52), 159 (22), 120 (95); HRMS (EI): calcd for $C_{16}H_{19}{}^{79}BrN_2O_4S$ (M^+) 414.0194, found 414.0206.

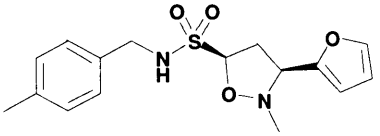
(3*S, 4*S**)-3-Furan-2-yl-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzyl amide (124m),** [69, 94] **(3*R**, 5*S**)-3-Furan-2-yl-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125m), and (3*S**, 5*S**)-3-Furan-2-yl-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (126m)**



124m



125m



126m

General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the three products **124m** (30 mg, 19%), **125m** (46 mg, 29%), and **126m** (23 mg, 15%)- overall yield (63%, **124m**:**125m**:**126m** = 4:6:3).

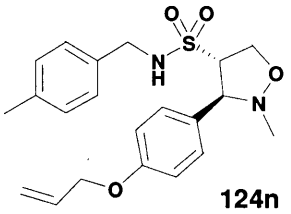
Data for **126m**: R_f 0.40 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3279, 2921, 1516, 1436, 1325, 1144, 1054, 951; δ_H (300 MHz, $CDCl_3$) 7.40-7.41 (m, 1 H, OC*H*CHCH), 7.25 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.14 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.39 (d, *J* = 3.2 Hz, 1 H, OCHCHC*H*), 6.36 (dd, *J* = 3.2, 1.6 Hz, 1 H, OCHC*H*CH), 5.06 (dd, *J* = 8.6, 5.6 Hz, 1 H, SC*H*), 4.76 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.45 (dd, *J* = 13.9, 6.4 Hz, 1 H, NHC*H*H), 4.38 (dd, *J* = 13.9, 5.9 Hz, 1 H, NHCH*H*), 3.72 (br dd, *J* = 10.2, 7.7 Hz, 1 H, NC*H*), 3.15 (ddd, *J* = 13.7, 10.2, 5.6 Hz, 1 H, SCHC*H*H), 2.97 (ddd, *J* = 13.7, 8.6, 7.7 Hz, 1 H, SCHCH*H*), 2.74 (s, 3 H, NCH_3), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 148.5 (s), 143.2 (d), 137.6 (s), 134.3 (s), 129.4 (d), 128.0 (d), 110.6 (d), 109.5 (d), 89.6 (d), 66.1 (d), 47.7 (t), 43.6 (q), 36.8 (t), 21.1 (q); *m/z* (FAB$^+$) 337 (MH^+, 52), 210 (20), 165 (31), 154 (100); HRMS (FAB$^+$): calcd for $C_{16}H_{21}N_2O_4S$ (MH^+) 337.1222, found 337.1226.

Data for **125m**: R_f 0.36 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3288, 2917, 1505, 1426, 1335, 1294, 1134, 1071, 999; δ_H (300 MHz, $CDCl_3$) 7.41 (dd, *J* = 1.9, 0.8 Hz, 1 H, OC*H*CHCH), 7.25 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.15 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.35 (dd, *J* = 3.2, 1.9 Hz, 1 H, OCHC*H*CH), 6.30 (app. d, *J* = 3.2 Hz, 1 H,

OCHCHC*H*), 4.98 (br s, 1 H, SC*H*), 4.82 (app. t, *J* = 5.6 Hz, 1 H, N*H*), 4.37 (dd, *J* = 13.9, 6.4 Hz, 1 H, NHC*H*H), 4.30 (dd, *J* = 13.9, 5.9 Hz, 1 H, NHCH*H*), 4.17 (br s, 1 H, NC*H*), 3.00 (br s, 2 H, SCHCH_2), 2.82 (br s, 3 H, NCH_3), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 149.1 (s), 143.1 (d), 137.9 (s), 133.8 (s), 129.5 (d), 128.0 (d), 110.5 (d), 109.3 (d), 89.4 (d), 64.7 (d), 47.6 (t), 45.0 (q), 37.1 (t), 21.1 (q); *m/z* (CI) 337 (MH^+, 5), 252 (20), 169 (59), 152 (100), 148 (23), 124 (42), 109 (36), 105 (41); HRMS (CI): calcd for $C_{16}H_{21}N_2O_4S$ (MH^+) 337.1217, found 337.1220.

Data for **124m**: R_f 0.30 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3280, 2919, 1516, 1436, 1322, 1146, 1039; δ_H (500 MHz, $CDCl_3$) 7.45 (br t, *J* = 1.3 Hz, 1 H, OC*H*CHCH), 7.12 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.06 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.41 (app. d, *J* = 1.3 Hz, 2 H, OCHCHC*H* and OCHC*H*CH), 4.34-4.43 (m, 2 H, SC*H* and N*H*), 4.25-4.31 (m, 2 H, SCHCH_2), 4.18 (dd, *J* = 13.6, 6.5 Hz, 1 H, NHC*H*H), 3.98 (br dd, *J* = 13.6, 4.6 Hz, 1 H, NHCH*H*), 3.93 (br s, 1 H, NC*H*), 2.70 (br s, 3 H, NCH_3), 2.33 (s, 3 H, ArCH_3); δ_C (125 MHz, $CDCl_3$) 148.6 (s), 143.5 (d), 138.1 (s), 133.1 (s), 129.6 (d), 128.1 (d), 110.9 (d), 110.2 (d), 69.4 (d), 67.9 (d), 66.8 (t), 47.3 (t), 42.8 (q), 21.2 (q); *m/z* (CI) 336 (M^+, 9), 150 (100), 120 (24), 105 (22), 91 (19), 84 (93); HRMS (CI): calcd for $C_{16}H_{20}N_2O_4S$ (M^+) 336.1138, found 336.1125.

(3*S, 4*S**)-3-(4-Allyloxyphenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (124n)** [69, 94]



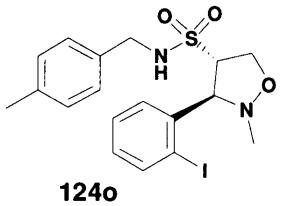
124n

General protocol was followed using 100 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **124n** (92 mg, 24%) as a brown oil.

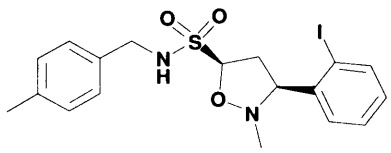
Data for **124n**: $R_{f\ (4C\ anti)}$ 0.24 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3287, 2923, 1611, 1511, 1425, 1326, 1306, 1242, 1146, 1021; δ_H (300 MHz, $CDCl_3$) 7.30 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.06 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 6.89-6.95 (m, 4 H, Ar*H*), 6.06 (ddt, *J* = 17.4, 10.4, 5.4 Hz, 1 H, C*H*=CH_2), 5.43 (app. dq, *J* = 17.4, 1.6 Hz, 1 H, CH=C*H*H), 5.31 (app. dq, *J* = 10.4, 1.6 Hz, 1 H, CH=CH*H*), 4.80 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.54 (app. dt, *J* = 5.4, 1.6 Hz, 2 H, OCH_2CH=), 4.33 (dd, *J* = 9.6, 3.8 Hz, 1 H, SCHC*H*H), 4.23 (dd, *J* = 9.6, 8.3 Hz, 1 H, SCHCH*H*), 4.08 (dd, *J* = 13.7, 6.4 Hz, 1 H,

NHC*H*H), 3.91 (app. td, *J* = 8.0, 3.8 Hz, 1 H, SC*H*), 3.84 (dd, *J* = 13.7, 5.1 Hz, 1 H, NHCH*H*), 3.74 (br d, *J* = 7.2 Hz, 1 H, NC*H*), 2.56 (s, 3 H, NCH_3), 2.31 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 159.0 (s), 137.8 (s), 133.2 (s), 133.1 (d), 129.4 (d), 128.6 (s), 128.0 (d), 117.9 (t), 115.2 (d), 114.7 (d), 74.1 (d), 73.0 (d), 68.9 (t), 66.7 (t), 47.0 (t), 42.6 (q), 21.1 (q); *m/z* (EI) 402 (M^+, 41), 353 (21), 217 (80), 191 (66), 173 (100), 150 (25), 120 (60), 105 (56), 91 (36); HRMS (EI): calcd for $C_{21}H_{26}N_2O_4S$ (M^+) 402.1613, found 402.1614.

(3*S, 4*S**)-3-(2-Iodophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzyl amide (124o), and (3*S**, 5*S**)-3-(2-Iodophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (126o)**



124o



126o

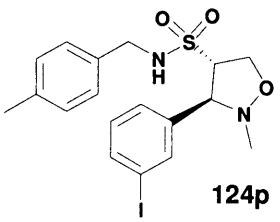
General protocol was followed using 110 mg of **123b**. Crude residue purified by flash chromatography (starting 9:1 petroleum ether 40-60°C/Et_2O) to give **124o** (48 mg, 20%) and **126o** (27 mg, 11%) as a brown oils- overall yield (32%, **124o**:**126o** = 2:1).

Data for **126o**: R_f 0.56 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 2918, 1520, 1495, 1319, 1234, 1142, 991, 808, 752; δ_H (300 MHz, $CDCl_3$) 7.83 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.59 (dd, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.35 (app. dt, *J* = 7.8, 1.1 Hz, 1 H, Ar*H*), 7.27 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 7.16 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 7.00 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 5.04 (dd, *J* = 8.8, 5.6 Hz, 1 H, SC*H*), 4.91 (app. t, *J* = 5.1 Hz, 1 H, N*H*), 4.43 (dd, *J* = 14.5, 5.9 Hz, 1 H, NHC*H*H), 4.37 (dd, *J* = 14.5, 5.4 Hz, 1 H, NHCH*H*), 4.05 (dd, *J* = 9.9, 7.5 Hz, 1 H, NC*H*), 3.16-3.25 (m, 1 H, SCHC*H*H), 2.69 (s, 3 H, NCH_3), 2.65 (ddd, *J* = 13.7, 9.9, 5.6 Hz, 1 H, SCHCH*H*), 2.35 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 139.6 (d), 139.0 (s), 138.2 (s), 134.0 (s), 130.0 (d), 129.5 (d), 129.2 (d), 128.6 (d), 127.9 (d), 93.6 (s), 89.1 (d), 76.2 (d), 47.5 (t), 43.3 (q), 39.8 (t), 21.2 (q); *m/z* (CI) 473 (MH^+, 27), 362 (100), 288 (63), 260 (27), 212 (20), 168 (26), 151 (34), 105 (60); HRMS (CI): calcd for $C_{18}H_{22}IN_2O_3S$ (MH^+) 473.0396, found 473.0386.

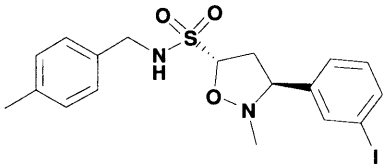
Data for **124o**: R_f 0.35 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3287, 2920, 1516, 1469, 1432, 1324, 1145, 1038, 807, 749; δ_H (300 MHz, $CDCl_3$) 7.87 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.38-7.42 (m, 2 H, Ar*H*), 7.05-7.11 (m, 1 H, Ar*H*), 7.01 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.72 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.45 (dd, *J* = 9.9, 3.8 Hz, 1 H, SCHC*H*H), 4.38 (br d, *J* = 6.4 Hz, 1 H, NC*H*), 4.34 (dd, *J* = 9.9, 8.3

Hz, 1 H, SCHCH*H*), 4.13 (dd, *J* = 13.7, 6.7 Hz, 1 H, NHC*H*H), 3.88-3.94 (m, 1 H, SC*H*), 3.78 (dd, *J* = 13.7, 4.8 Hz, 1 H, NHCH*H*), 2.64 (s, 3 H, NCH_3), 2.30 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 140.0 (d), 139.1 (s), 137.8 (s), 132.9 (s), 130.4 (d), 129.7 (d), 129.4 (d), 129.2 (d), 128.0 (d), 101.1 (s), 77.3 (d), 73.4 (d), 67.2 (t), 47.2 (t), 42.5 (q), 21.2 (q); *m/z* (CI) 473 (MH^+, 100), 287 (52), 151 (21), 105 (17); HRMS (CI): calcd for $C_{18}H_{22}IN_2O_3S$ (MH^+) 473.0396, found 473.0388.

(3*S, 4*S**)-3-(3-Iodophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzyl amide (124p), and (3*R**, 5*S**)-3-(3-Iodophenyl)-2-methylisoxazolidine-5-sulfonic acid 4-methylbenzylamide (125p)**



124p



125p

General protocol was followed using 150 mg of **123b**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **125p** (57 mg, 17%) as a light brown solid, and **124p** (146 mg, 44%) as a yellow oil- overall yield (61%, **124p**:**125p** = 5:2).

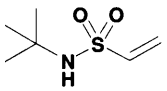
Data for **125p**: R_f 0.50 (2:1 Et_2O/petroleum ether 40-60°C); mp 100-102 °C; υ_{max} (neat)/cm^{-1} 3260, 3000, 2917, 1516, 1433, 1321, 1143, 1042, 879, 778; δ_H (300 MHz, $CDCl_3$) 7.73 (s, 1 H, Ar*H*), 7.65 (dd, *J* = 7.8, 1.1 Hz, 1 H, Ar*H*), 7.31 (app. d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.26 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.16 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.08 (app. t, *J* = 7.8 Hz, 1 H, Ar*H*), 4.93 (dd, *J* = 8.6, 2.4 Hz, 1 H, SC*H*), 4.76 (br t, *J* = 5.9 Hz, 1 H, N*H*), 4.38 (dd, *J* = 14.2, 5.9 Hz, 1 H, NHC*H*H), 4.30 (dd, *J* = 14.2, 5.9 Hz, 1 H, NHCH*H*), 4.00 (app. t, *J* = 7.5 Hz, 1 H, NC*H*), 3.04 (ddd, *J* = 13.9, 6.2, 2.4 Hz, 1 H, SCHC*H*H), 2.65-2.76 (m, 4 H, SCHCH*H* and NCH_3), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 139.4 (s), 137.9 (s), 137.5 (d), 136.4 (d), 133.7 (s), 130.6 (d), 129.5 (d), 128.0 (d), 126.9 (d), 94.7 (s), 89.2 (d), 70.2 (d), 47.6 (t), 44.6 (q), 42.1 (t), 21.2 (q); *m/z* (EI) 472 (M^+, 11), 562 (43), 288 (24), 260 (42), 246 (37), 149 (75), 120 (59), 105 (98), 91 (68), 55 (100); HRMS (CI): calcd for $C_{18}H_{21}IN_2O_3S$ (M^+) 472.0312, found 472.0328.

Data for **124p**: R_f 0.43 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3296, 2865, 1514, 1423, 1323, 1138, 1043, 832, 784; δ_H (300 MHz, $CDCl_3$) 7.75 (s, 1 H, Ar*H*), 7.66-7.71 (m, 1 H, Ar*H*), 7.37 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.10 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.08 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.98 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 5.09 (app. t, *J* =

5.9 Hz, 1 H, N*H*), 4.27-4.34 (m, 1 H, SCHC*H*H), 4.16 (dd, *J* = 8.0, 4.3 Hz, 1 H, SCHCH*H*), 4.11 (dd, *J* = 13.9, 6.2 Hz, 1 H, NHC*H*H), 3.98 (dd, *J* = 13.9, 5.6 Hz, 1 H, NHCH*H*), 3.73-3.80 (m, 2 H, SC*H* and NC*H*), 2.58 (s, 3 H, NCH_3), 2.33 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 139.6 (s), 137.9 (s), 137.8 (d), 136.8 (d), 133.2 (s), 130.6 (d), 129.6 (d), 128.1 (d), 127.8 (d), 94.8 (s), 73.6 (d), 73.3 (d), 67.0 (t), 47.1 (t), 42.8 (q), 21.2 (q); *m/z* (CI) 473 (MH^+, 57), 287 (100), 151 (25), 120 (31), 105 (21); HRMS (CI): calcd for $C_{18}H_{22}IN_2O_3S$ (MH^+) 473.0396, found 473.0393.

4.5.2. Cycloadditions with ethenesulfonic acid *tert*-butylamide (123e)

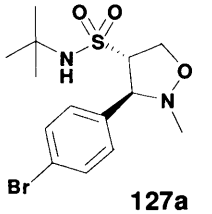
Ethenesulfonic acid *tert*-butylamide (123e)



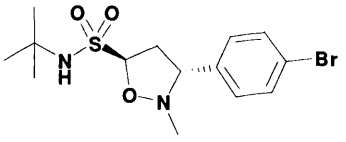
A premixed suspension of *tert*-butyl amine (7.4 g, 101.2 mmol) and NEt_3 (27.9 g, 276.0 mmol) in DCM (40 mL) was added dropwise to a stirring solution of 2-chloroethane-1-sulfonyl chloride (15.0 g, 92.0 mmol) in DCM (150 mL) at -10 °C. The reaction mixture was stirred for a further 30 minutes after addition, and then warmed to RT. The reaction was diluted with DCM (60 mL) and washed with 2M HCl (3 x 80 mL), H_2O (80 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* and purification by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) furnished the desired product (9.5 g, 64%) as a yellow solid.

R_f 0.16 (1:1 petroleum ether 40-60°C/Et_2O); mp 66-68 °C; υ_{max} (neat)/cm^{-1} 3296, 3101, 3053, 2980, 1618, 1468, 1425, 1377, 1313, 1136, 1011, 870; δ_H (300 MHz, $CDCl_3$) 6.59 (dd, *J* = 16.6, 9.9 Hz, 1 H, SC*H*), 6.20 (d, *J* = 16.6 Hz, 1 H, SCHC*H*H), 5.81 (d, *J* = 9.9 Hz, 1 H, SCHCH*H*), 4.65 (br s, 1 H, N*H*), 1.32 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 139.6 (d), 124.4 (t), 54.7 (s), 30.3 (q); *m/z* (CI) 164 (MH^+, 54), 147 (71), 135 (23), 124 (28), 119 (40), 107 (63); HRMS (CI): calcd for $C_6H_{14}NO_2S$ (MH^+) 164.0749, found 164.0751.

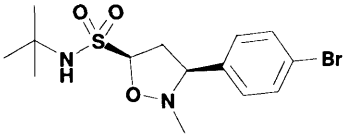
(3*S, 4*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butyl amide (127a), (3*R**, 5*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128a), and (3*S**, 5*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (129a)**



127a



128a



129a

General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **127a** (107 mg, 46%), **128a** (18 mg, 8%), and **129a** (11 mg, 5%)- overall yield (59%, **127a**:**128a**:**129a** = 10:2:1).

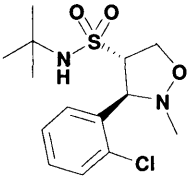
Data for **128a**: R_f 0.31 (2:1 Et_2O/petroleum ether 40-60°C); mp 122-125 °C; υ_{max} (neat)/cm^{-1} 3295, 2970, 1489, 1431, 1390, 1323, 1286, 1141, 1067, 1007, 971, 826; δ_H (300 MHz, $CDCl_3$) 7.47 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.24 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.93 (dd, *J* = 8.6, 2.0 Hz, 1 H, SC*H*), 4.28 (br s, 1 H, N*H*), 4.00 (br dd, *J* = 9.2, 6.2 Hz, 1 H, NC*H*), 3.05 (ddd, *J* = 13.6, 6.2, 2.0 Hz, 1 H, SCHC*H*H), 2.63-2.76 (m, 4 H, SCHCH*H* and NCH_3), 1.40 (s, 9 H $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 136.9 (s), 132.0 (d), 129.2 (d), 122.2 (s), 90.2 (d), 67.7 (d), 55.1 (s), 44.7 (q), 38.1 (t), 30.6 (q); *m/z* (EI) 378 (M^+, ^{81}Br, 17), 376 (M^+, ^{79}Br, 17), 266 (32), 240 (77), 212 (100), 199 (57), 167 (23), 149 (60), 132 (48), 117 (27); HRMS (EI): calcd for $C_{14}H_{21}{}^{79}BrN_2O_3S$ (M^+) 376.0456, found 376.0459.

Data for **129a**: R_f 0.27 (2:1 Et_2O/petroleum ether 40-60°C); mp 130-134 °C; υ_{max} (neat)/cm^{-1} 3266, 2957, 1486, 1428, 1394, 1312, 1290, 1144, 1009, 956, 824; δ_H (300 MHz, $CDCl_3$) 7.48 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.32 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.94 (dd, *J* = 8.6, 5.6 Hz, 1 H, SC*H*), 4.37 (br s, 1 H, N*H*), 3.53 (br dd, *J* = 9.9, 7.8 Hz, 1 H, NC*H*), 3.03 (ddd, *J* = 13.7, 8.6, 7.8 Hz, 1 H, SCHC*H*H), 2.88 (ddd, *J* = 13.4, 9.9, 5.6 Hz, 1 H, SCHCH*H*), 2.59 (s, 3 H, NCH_3), 1.42 (s, 9 H $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 136.8 (s), 132.0 (d), 129.8 (d), 122.6 (s), 90.1 (d), 67.4 (d), 55.1 (s), 43.9 (q), 37.8 (t), 30.7 (q); *m/z* (EI) 378 (M^+, ^{81}Br, 21), 376 (M^+, ^{79}Br, 20), 266 (36), 240 (76), 212 (100), 197 (54), 149 (29), 132 (38), 117 (22), 99 (97); HRMS (EI): calcd for $C_{14}H_{21}{}^{79}BrN_2O_3S$ (M^+) 376.0456, found 376.0452.

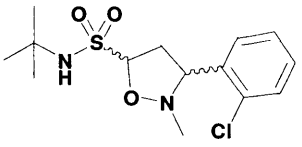
Data for **127a**: R_f 0.22 (2:1 Et_2O/petroleum ether 40-60°C); mp 173-178 °C; υ_{max} (neat)/cm^{-1} 3268, 2959, 2859, 1489, 1427, 1393, 1306, 1141, 1009, 837, 814; δ_H (300 MHz, $CDCl_3$) 7.51 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.36 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.81 (s, 1

H, N*H*), 4.40 (dd, *J* = 9.9, 3.7 Hz, 1 H, SCHC*H*H), 4.30 (dd, *J* = 9.9, 8.3 Hz, 1 H, SCHCH*H*), 3.92 (app. td, *J* = 8.0, 3.7 Hz, 1 H, SC*H*), 3.77 (br d, *J* = 7.3 Hz, 1 H, NC*H*), 2.61 (s, 3 H, NCH_3), 1.12 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 136.6 (s), 132.0 (d), 130.1 (d), 122.7 (s), 75.6 (d), 74.1 (d), 67.2 (t), 55.1 (s), 42.7 (q), 30.0 (q); *m/z* (EI) 378 (M^+, ^{81}Br, 21), 376 (M^+, ^{79}Br, 19), 238 (93), 213 (37), 149 (35), 116 (100); HRMS (ESI): calcd for $C_{14}H_{21}{}^{79}BrN_2O_3S$ (M^+) 376.0456, found 376.0452.

(3*S, 4*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butyl amide (127b), (3*R**, 5*S**) and (3*S**, 5*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128/129b)**



127b



128/129b

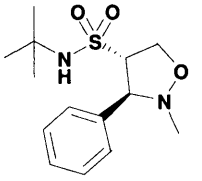
General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **128/129b** (56 mg, 28%) as a mixture, and **127b** (62 mg, 30%) as a light brown solid- overall yield (58%, **127b**:**128/129b** = 1:1, **128b** and **129b** = 3:2 major:minor).

Data for **128/129b**: R_f 0.37 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3279, 2971, 1474, 1438, 1319, 1231, 1142, 997, 752; δ_H (300 MHz, $CDCl_3$) 7.70 (dd, *J* = 7.8, 1.9 Hz, 1 H_{minor}, Ar*H*), 7.56 (dd, *J* = 7.8, 1.9 Hz, 1 H_{major}, Ar*H*), 7.18-7.38 (m, 3 H, Ar*H*), 4.99 (dd, *J* = 8.6, 5.6 Hz, 1 H_{minor}, SC*H*), 4.88 (dd, *J* = 8.3, 4.3 Hz, 1 H_{major}, SC*H*), 4.55 (app. br t, *J* = 7.5 Hz, 1 H_{major}, NC*H*), 4.46 (br s, 1 H_{minor}, N*H*), 4.41 (br s, 1 H_{major}, N*H*), 4.20 (br dd, *J* = 9.9, 7.5 Hz, 1 H_{minor}, NC*H*), 3.26 (ddd, *J* = 13.4, 6.7, 4.3 Hz, 1 H_{major}, SCHC*H*H), 3.16 (ddd, *J* = 13.4, 8.6, 7.5 Hz, 1 H_{minor}, SCHC*H*H), 2.83 (s, 3 H_{major}, NCH_3), 2.74 (ddd, *J* = 13.4, 9.9, 5.6 Hz, 1 H_{minor}, SCHCH*H*), 2.66 (s, 3 H_{minor}, NCH_3), 2.61 (app. dt, *J* = 13.4, 8.3 Hz, 1 H_{major}, SCHCH*H*), 1.41 (s, 9 H_{minor}, C(CH_3)$_3$), 1.40 (s, 9 H_{major}, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 135.9 (s), 134.8 (s), 133.6 (s), 133.5 (s), 129.7 (d), 129.4 (d), 129.1 (d), 128.9 (d), 128.7 (d), 127.6 (d), 127.3 (d), 90.9 (d), 90.1 (d), 68.5 (d), 67.1 (d), 55.1 (s), 55.0 (s), 45.1 (q), 43.5 (q), 39.7 (t), 39.2 (t), 30.6 (q), 29.7 (q), 23 out of 24 expected signals observed; *m/z* (FAB^+) 335 (MH^+, ^{37}Cl, 14), 333 (MH^+, ^{35}Cl, 36), 222 (27), 196 (100), 168 (59); HRMS (FAB^+): calcd for $C_{14}H_{22}{}^{35}ClN_2O_3S$ (MH^+) 333.1040, found 333.1036.

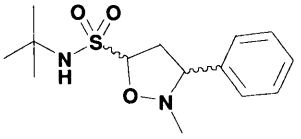
Data for **127b**: R_f 0.25 (2:1 Et_2O/petroleum ether 40-60°C); mp 190-194 °C; υ_{max} (neat)/cm^{-1} 3287, 2962, 2920, 1478, 1439, 1306, 1201, 1137, 1036, 870, 774; δ_H (300

MHz, $CDCl_3$) 7.57 (dd, *J* = 7.7, 1.6 Hz, 1 H, Ar*H*), 7.42 (dd, *J* = 7.7, 1.6 Hz, 1 H, Ar*H*), 7.29-7.37 (m, 2 H, Ar*H*), 4.37-4.48 (m, 4 H, N*H* and NC*H* and SCHCH_2), 4.03 (app. td, *J* = 8.2, 3.9 Hz, 1 H, SC*H*), 2.62 (s, 3 H, NCH_3), 1.01 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 134.8 (s), 134.6 (s), 129.9 (d), 129.8 (d), 127.8 (d), 75.2 (d), 70.5 (d), 67.2 (t), 54.9 (s), 42.6 (q), 29.8 (q), 1 x d not observed; *m/z* (EI) 334 (M^+, ^{37}Cl, 7), 332 (M^+, ^{35}Cl, 29), 194 (100), 148 (43) 134 (87), 115 (98); HRMS (EI): calcd for $C_{14}H_{21}{}^{35}ClN_2O_3S$ (M^+) 332.0961, found 332.0968.

(3*S, 4*S**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid *tert*-butylamide (127c), (3*R**, 5*S**) and (3*S**, 5*S**)-2-Methyl-3-phenylisoxazolidine-5-sulfonic acid *tert*-butylamide (128c/129c)**



127c



128/129c

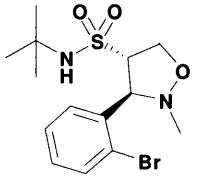
General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60 °C/Et_2O) to give **128/129c** (25 mg, 14%) as a mixture, and **127c** (75 mg, 41%) as an orange/brown solid- overall yield (55%, **127c**:**128/129c** = 3:1, **128c** and **129c** = 2:1 major:minor).

Data for **128/129c**: R_f 0.33 (2:1 Et_2O/petroleum ether 40-60°C); mp 102-104 °C; υ_{max} (neat)/cm^{-1} 3287, 2983, 2871, 1495, 1430, 1316, 1289, 1141, 866; δ_H (300 MHz, $CDCl_3$) 7.28-7.45 (m, 5 H, Ar*H*), 4.94-4.99 (m, 1 H, SC*H*), 4.44 (br s, 1 H_{minor}, N*H*), 4.32 (br s, 1 H_{major}, N*H*), 4.02 (app. br t, *J* = 7.5 Hz, 1 H_{major}, NC*H*), 3.56 (br dd, *J* = 9.6, 7.8 Hz, 1 H_{minor}, NC*H*), 2.97-3.11 (m, 1 H, SCHC*H*H), 2.95 (ddd, *J* = 13.7, 10.2, 5.9 Hz, 1 H_{minor}, SCHCH*H*), 2.78 (ddd, *J* = 13.7, 10.2, 8.8 Hz, 1 H_{major}, SCHCH*H*), 2.74 (s, 3 H_{major}, NCH_3), 2,60 (s, 3 H_{minor}, NCH_3), 1.42 (s, 9 H_{minor}, C(CH_3)$_3$), 1.41 (s, 9 H_{major}, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 137.0 (s), 136.5 (s), 128.8 (d), 128.6 (d), 128.3 (d), 128.1 (d), 127.6 (d), 90.3 (d), 90.1 (d), 70.9 (d), 55.0 (s), 43.7 (q), 43.3 (q), 38.8 (t), 30.7 (q), 30.6 (q), 16 out of 20 expected signals observed; *m/z* (EI) 298 (M^+, 27), 188 (23), 162 (64), 134 (100), 118 (33); HRMS (EI): calcd for $C_{14}H_{22}N_2O_3S$ (M^+) 298.1351, found 298.1354.

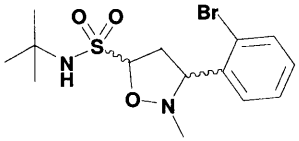
Data for **127c**: R_f 0.25 (2:1 Et_2O/petroleum ether 40-60°C); mp 160-163 °C; υ_{max} (neat)/cm^{-1} 3272, 2966, 2870, 1494, 1454, 1393, 1264, 1137, 1010, 870; δ_H (300 MHz, $CDCl_3$) 7.32-7.47 (m, 5 H, Ar*H*), 4.60 (s, 1 H, N*H*), 4.45 (dd, *J* = 9.7, 3.8 Hz, 1 H,

SCHC*H*H), 4.34 (br dd, *J* = 9.7, 8.6 Hz, 1 H, SCHCH*H*), 4.01 (app. td, *J* = 8.0, 3.8 Hz, 1 H, SC*H*), 3.77 (br d, *J* = 7.6 Hz, 1 H, NC*H*), 2.62 (s, 3 H, NCH_3), 1.05 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 137.2 (s), 128.9 (d), 128.8 (d), 128.6 (d), 75.5 (d), 75.1 (d), 67.1 (t), 55.0 (s), 42.7 (q), 29.9 (q); *m/z* (EI) 298 (M^+, 20), 160 (100), 134 (21), 117 (38), 91 (28); HRMS (EI): calcd for $C_{14}H_{22}N_2O_3S$ (M^+) 298.1351, found 298.1352.

(3*S, 4*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butyl amide (127d), (3*R**, 5*S**) and (3*S**, 5*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128/129d)**



127d



128/129d

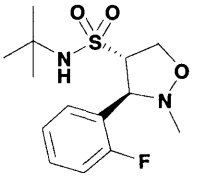
General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **128/129d** (34 mg, 15%) as a mixture, and **127d** (66 mg, 28%) as a brown solid- overall yield (43%, **127d**:**128/129d** = 2:1, **128d** and **129d** = 3:2 major:minor).

Data for **128/129d**: R_f 0.36 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3279, 2962, 1469, 1434, 1319, 1142, 997, 862, 754; δ_H (300 MHz, $CDCl_3$) 7.69 (dd, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.51-7.57 (m, 1 H, Ar*H*), 7.29-7.36 (m, 1 H, Ar*H*), 7.11-7.18 (m, 1 H, Ar*H*), 4.99 (dd, *J* = 8.6, 5.6 Hz, 1 H_{major}, SC*H*), 4.88 (dd, *J* = 8.3, 4.1 Hz, 1 H_{minor}, SC*H*), 4.53 (app. t, *J* = 7.5 Hz, 1 H_{minor}, NC*H*), 4.40 (br s, 1 H_{major}, N*H*), 4.34 (br s, 1 H_{minor}, N*H*), 4.18 (dd, *J* = 9.6, 7.5 Hz, 1 H_{major}, NC*H*), 3.29 (ddd, *J* = 13.4, 6.7, 4.1 Hz, 1 H_{minor}, SCHC*H*H), 3.18 (ddd, *J* = 13.4, 8.6, 7.5 Hz, 1 H_{major}, SCHC*H*H), 2.83 (s, 3 H_{minor}, NCH_3), 2.71 (ddd, *J* = 13.4, 9.6, 5.6 Hz, 1 H_{major}, SCHCH*H*), 2.67 (s, 3 H_{major}, NCH_3), 2.59 (app. dt, *J* = 13.4, 8.3 Hz, 1 H_{minor}, SCHCH*H*), 1.41 (s, 9 H_{major}, C(CH_3)$_3$), 1.40 (s, 9 H_{minor}, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 137.6 (s), 136.5 (s), 133.0 (d), 132.7 (d), 129.5 (d), 129.3 (d), 129.0 (d), 128.3 (d), 127.9 (d), 127.8 (d), 123.9 (s), 123.7 (s), 90.8 (d), 90.1 (d), 71.1 (d), 69.4 (d), 55.2 (s), 55.0 (s), 45.1 (q), 43.5 (q), 39.8 (t), 39.3 (t), 30.7 (q), 30.4 (q); *m/z* (FAB$^+$) 379 (MH^+, ^{81}Br, 50), 377 (MH^+, ^{79}Br, 52), 307 (33), 240 (48), 154 (100); HRMS (EI): calcd for $C_{14}H_{22}{}^{79}BrN_2O_3S$ (MH^+) 377.0534, found 377.0538.

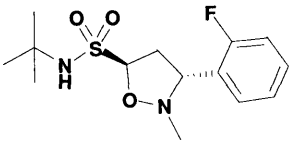
Data for **127d**: R_f 0.24 (2:1 Et_2O/petroleum ether 40-60°C); mp 202-206 °C; υ_{max} (neat)/cm^{-1} 3282, 2920, 1595, 1474, 1435, 1323, 1302, 1135, 998, 826, 763; δ_H (300

MHz, $CDCl_3$) 7.61 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.56 (dd, *J* = 8.0, 1.6 Hz, 1 H, Ar*H*), 7.40 (app. dt, *J* = 7.8, 1.1 Hz, 1 H, Ar*H*), 7.22 (app dt, *J* = 8.0, 1.6 Hz, 1 H, Ar*H*), 4.35-4.48 (m, 4 H, SCHCH_2 and N*H* and NC*H*), 4.01 (app. td, *J* = 8.2, 3.9 Hz, 1 H, SC*H*), 2.63 (s, 3 H, NCH_3), 1.01 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 136.5 (s), 133.2 (d), 130.2 (d), 130.1 (d), 128.4 (d), 125.3 (s), 75.4 (d), 72.9 (d), 67.2 (t), 54.9 (s), 42.5 (q), 30.1 (q); *m/z* (EI) 378 (M^+, ^{81}Br, 23), 376 (M^+, ^{79}Br, 22), 240 (100), 198 (26), 160 (25), 134 (74), 116 (78); HRMS (EI): calcd for $C_{14}H_{21}{}^{79}BrN_2O_3S$ (M^+) 376.0456, found 376.0459.

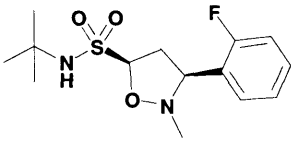
(3*S, 4*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butyl amide (127e), (3*R**, 5*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128e), and (3*S**, 5*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (129e)**



127e



128e



129e

General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **127e** (58 mg, 30%), **128e** (35 mg, 18%), and **129e** (17 mg, 9%)- overall yield (57%, **127e**:**128e**:**129e** = 7:4:2).

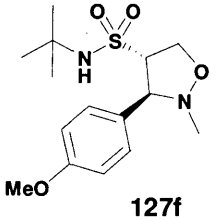
Data for **129e**: R_f 0.36 (2:1 Et_2O/petroleum ether 40-60°C); mp 78-82 °C; υ_{max} (neat)/cm^{-1} 3302, 2967, 1495, 1428, 1320, 1233, 1143, 1095, 998, 760; δ_H (300 MHz, $CDCl_3$) 7.65 (app. dt, *J* = 7.2, 1.6 Hz, 1 H, Ar*H*), 7.23-7.31 (m, 1 H, Ar*H*), 7.16 (app. dt, *J* = 7.5, 1.1 Hz, 1 H, Ar*H*), 7.04 (ddd, *J* = 10.2, 8.3, 1.1 Hz, 1 H, Ar*H*), 4.99 (dd, *J* = 8.5, 5.7 Hz, 1 H, SC*H*), 4.39 (br s, 1 H, N*H*), 4.03 (br dd, *J* = 10.0, 7.8 Hz, 1 H, NC*H*), 3.07 (ddd, *J* = 13.4, 8.5, 7.8 Hz, 1 H, SCHC*H*H), 2.88 (ddd, *J* = 13.5, 10.0, 5.7 Hz, 1 H, SCHCH*H*) 2.65 (s, 3 H, NCH_3), 1.41 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 161.0 (s, J_{CF} = 247.1 Hz), 129.7 (d, J_{CF} = 8.5 Hz), 128.8 (d, J_{CF} = 3.8 Hz), 124.9 (d, J_{CF} = 3.5 Hz), 118.4 (s), 115.3 (d, J_{CF} = 22.0 Hz), 90.1 (d), 64.9 (d), 55.0 (s), 43.5 (q), 39.8 (t), 30.7 (q); *m/z* (EI) 316 (M^+, 25), 206 (24), 180 (31), 152 (100), 137 (45), 122 (23), 109 (28); HRMS (EI): calcd for $C_{14}H_{21}FN_2O_3S$ (M^+) 316.1257, found 316.1259.

Data for **128e**: R_f 0.32 (2:1 Et_2O/petroleum ether 40-60°C); mp 115-118 °C; υ_{max} (neat)/cm^{-1} 3243, 2986, 2919, 1589, 1494, 1327, 1233, 1145, 1008, 868, 765; δ_H (300

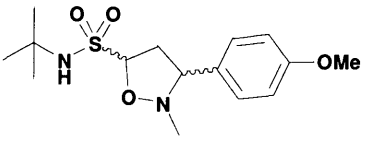
MHz, $CDCl_3$) 7.46 (app. t, J = 7.5 Hz, 1 H, Ar*H*), 7.24-7.32 (m, 1 H, Ar*H*), 7.14 (app. t, J = 7.5 Hz, 1 H, Ar*H*), 7.05 (ddd, J = 10.2, 8.3, 1.1 Hz, 1 H, Ar*H*), 4.93 (dd, J = 8.5, 3.5 Hz, 1 H, SC*H*), 4.37-4.42 (m, 2 H, N*H* and NC*H*), 3.14 (ddd, J = 13.5, 6.6, 3.5 Hz, 1 H, SCHC*H*H), 2.71-2.79 (m, 4 H, SCHCH*H* and NCH_3), 1.40 (s, 9 H $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 161.0 (s, J_{CF} = 248.0 Hz), 129.6 (d, J_{CF} = 8.2 Hz), 128.2 (d), 124.5 (d, J_{CF} = 3.7 Hz), 116.6 (s), 115.4 (d, J_{CF} = 21.6 Hz), 90.7 (d), 64.0 (d), 55.1 (s), 44.9 (q), 39.3 (t), 30.6 (q); *m/z* (EI) 316 (M^+, 19), 180 (34), 152 (76), 137 (37), 84 (25); HRMS (EI): calcd for $C_{14}H_{21}FN_2O_3S$ (M^+) 316.1257, found 316.1261.

Data for **127e**: R_f 0.24 (2:1 Et_2O/petroleum ether 40-60°C); mp 160-164 °C; υ_{max} (neat)/cm^{-1} 3275, 2872, 1590, 1493, 1453, 1305, 1230, 1138, 1042, 1005, 869, 765; δ_H (300 MHz, $CDCl_3$) 7.50 (app. dt, J = 7.5, 1.6 Hz, 1 H, Ar*H*), 7.31-7.39 (m, 1 H, Ar*H*), 7.21 (app. dt, J = 7.5, 0.8 Hz, 1 H, Ar*H*), 7.11 (ddd, J = 10.2, 8.0, 0.8 Hz, 1 H, Ar*H*), 4.31-4.47 (m, 3 H, SCHCH_2 and N*H*), 4.05-4.10 (m, 2 H, SC*H* and NC*H*), 2.64 (s, 3 H, NCH_3), 1.05 (s, 9 H $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 160.9 (s, J_{CF} = 247.7 Hz), 130.4 (d, J_{CF} = 8.5 Hz), 129.9 (d, J_{CF} = 3.5 Hz), 125.0 (d, J_{CF} = 3.5 Hz), 119.6 (s), 116.0 (d, J_{CF} = 22.0 Hz), 74.4 (d), 68.4 (d), 67.0 (t), 54.9 (s), 42.8 (q), 29.9 (q); *m/z* (EI) 316 (M^+, 13), 178 (100), 135 (22); HRMS (EI): calcd for $C_{14}H_{21}FN_2O_3S$ (M^+) 316.1257, found 316.1253.

(3*S, 4*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butylamide (127f), (3*R**, 5*S**) and (3*S**, 5*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128/129f)**



127f



128/129f

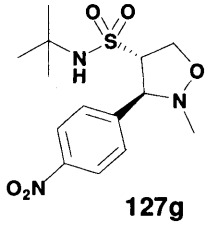
General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **128/129f** (13 mg, 7%) as a mixture, and **127f** (65 mg, 32%) as an orange/brown solid- overall yield (39%, **127f**:**128/129f** = 5:1, **128f** and **129f** = 3:2 major:minor).

Data for **128/129f**: R_f 0.27 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3235, 2971, 1612, 1514, 1427, 1327, 1244, 1140, 1006, 843; δ_H (300 MHz, $CDCl_3$) 7.35 (d, J = 8.8 Hz, 2 H_{minor}, ArH), 7.28 (d, J = 8.8 Hz, 2 H_{major}, Ar*H*), 6.88 (d, J = 8.8 Hz, 2 H, Ar*H*), 4.92-4.97 (m, 1 H, SC*H*), 4.40 (br s, 1 H_{minor}, N*H*), 4.28 (br s, 1 H_{major}, N*H*), 3.95

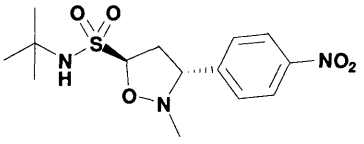
(app. br s, 1 H_{major}, NC*H*), 3.80 (s, 3 H, OCH_3), 3.52 (br dd, *J* = 9.9, 7.8 Hz, 1 H_{minor}, NC*H*), 2.87-3.06 (m, 2 H, SHC*H*H and SHCHH_{minor}), 2.75 (ddd, *J* = 13.7, 10.4, 9.9 Hz, 1 H_{major}, SHCH*H*), 2.71 (s, 3 H_{major}, NCH_3), 2.58 (s, 3 H_{minor}, NCH_3), 1.42 (s, 9 H_{minor}, C(CH_3)$_3$), 1.40 (s, 9 H_{major}, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 159.9 (s), 159.7 (s), 129.3 (d), 128.9 (d), 128.7 (s), 128.3 (s), 114.4 (d), 114.3 (d), 90.2 (d), 90.1 (d), 73.4 (d), 70.6 (d), 55.4 (q), 55.1 (s), 44.1 (q), 43.3 (q), 41.7 (t), 41.0 (t), 30.8 (q), 30.4 (q), 20 out of 22 expected signals observed; *m/z* (FAB^+) 329 (MH^+, 31), 307 (32), 192 (63), 154 (100); HRMS (FAB^+): calcd for $C_{15}H_{25}N_2O_4S$ (MH^+) 329.1535, found 329.1543.

Data for **127f**: R_f 0.18 (2:1 Et_2O/petroleum ether 40-60°C); mp 133-137 °C; υ_{max} (neat)/cm^{-1} 3280, 2961, 1614, 1516, 1435, 1305, 1252, 1138, 1010, 867; δ_H (300 MHz, $CDCl_3$) 7.37 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.91 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.57 (s, 1 H, N*H*), 4.41 (dd, *J* = 9.7, 3.8 Hz, 1 H, SCHC*H*H), 4.32 (dd, *J* = 9.7, 8.6 Hz, 1 H, SCHCH*H*), 3.97 (app. td, *J* = 8.0, 3.8 Hz, 1 H, SC*H*), 3.81 (s, 3 H, OCH_3), 3.72 (br d, *J* = 7.5 Hz, 1 H, NC*H*), 2.60 (s, 3 H, NCH_3), 1.08 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 159.9 (s), 129.7 (d), 129.0 (s), 114.3 (d), 75.2 (d), 74.6 (d), 67.0 (t), 55.3 (q), 55.0 (s), 42.6 (q), 30.0 (q); *m/z* (EI) 328 (M^+, 21), 190 (100), 147 (32); HRMS (EI): calcd for $C_{15}H_{24}N_2O_4S$ (M^+) 328.1457, found 328.1449.

(3*S, 4*S**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-4-sulfonic acid *tert*-butylamide (127g), and (3*R**, 5*S**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-5-sulfonic acid *tert*-butylamide (128g)**



127g



128g

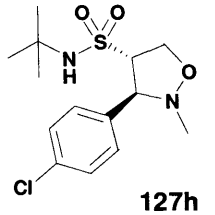
General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **128g** (11 mg, 5%), and **127g** (87 mg, 42%)- overall yield (47%, **127g**:**128g** = 8:1).

Data for **128g**: R_f 0.27 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3281, 2922, 1601, 1520, 1463, 1325, 1141, 997, 855; δ_H (300 MHz, $CDCl_3$) 8.22 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.57 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 4.94 (dd, *J* = 8.6, 2.4 Hz, 1 H, SC*H*), 4.28 (br s, 1 H, N*H*), 4.19 (br dd, *J* = 9.9, 6.4 Hz, 1 H, NC*H*), 3.14 (ddd, *J* = 13.7, 6.4, 2.4 Hz, 1 H, SHC*H*H), 2.77 (s, 3 H, NCH_3), 2.72 (ddd, *J* = 13.7, 9.9, 8.6 Hz, 1 H, SCHCH*H*), 1.41 (s, 9 H, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 147.8 (s), 144.7 (s), 129.5 (d), 125.2 (d), 91.4

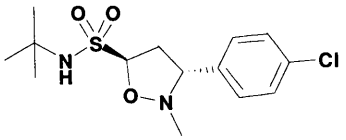
(d), 70.3 (d), 56.3 (s), 45.2 (q), 42.8 (t), 31.7 (q); *m/z* (FAB$^+$) 344 (MH$^+$, 69), 299 (90), 233 (30), 219 (21), 207 (98), 179 (28), 161 (66), 149 (100); HRMS (FAB$^+$): calcd for $C_{14}H_{22}N_3O_5S$ (MH$^+$) 344.1280, found 344.1271.

Data for **127g**: R_f 0.19 (2:1 Et_2O/petroleum ether 40-60°C); mp 176-180 °C; υ_{max} (neat)/cm^{-1} 3271, 2968, 2921, 1607, 1519, 1430, 1347, 1142, 1040, 859, 821; δ_H (300 MHz, $CDCl_3$) 8.25 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.70 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.76 (s, 1 H, N*H*), 4.41 (dd, *J* = 9.6, 3.9 Hz, 1 H, SCHC*H*H), 4.32 (br dd, *J* = 9.6, 8.3 Hz, 1 H, SCHCH*H*), 4.01 (d, *J* = 7.0 Hz, 1 H, NC*H*), 3.93 (app. td, *J* = 7.5, 3.9 Hz, 1 H, SC*H*), 2.66 (s, 3 H, NCH_3), 1.17 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 148.0 (s), 145.4 (s), 129.2 (d), 124.0 (d), 75.9 (d), 73.4 (d), 67.4 (t), 55.4 (s), 43.0 (q), 30.1 (q); *m/z* (EI) 343 (M$^+$, 10), 205 (100), 116 (21); HRMS (EI): calcd for $C_{14}H_{21}N_3O_5S$ (M$^+$) 343.1202, found 343.1202.

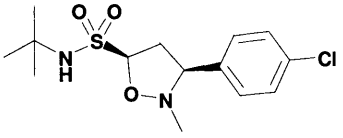
(3*S, 4*S**)-3-(4-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butyl amide (127h), (3*R**, 5*S**)-3-(4-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128h), and (3*S**, 5*S**)-3-(4-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (129h)**



127h



128h



129h

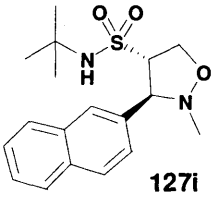
General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **127h** (90 mg, 44%), **128h** (15 mg, 8%), and **129h** (14 mg, 7%)- overall yield (59%, **127h**:**128h**:**129h** = 13:2:2).

Data for **128h**: R_f 0.35 (2:1 Et_2O/petroleum ether 40-60°C); mp 122-125 °C; υ_{max} (neat)/cm^{-1} 3295, 2972, 1491, 1431, 1389, 1323, 1286, 1141, 1087, 1001, 829; δ_H (300 MHz, $CDCl_3$) 7.32 (app. s, 4 H, Ar*H*), 4.93 (dd, *J* = 8.6, 2.5 Hz, 1 H, SC*H*), 4.28 (s, 1 H, N*H*), 4.01 (br dd, *J* = 9.4, 6.4 Hz, 1 H, NC*H*), 3.05 (ddd, *J* = 13.6, 6.4, 2.5 Hz, 1 H, SCHC*H*H), 2.63-2.77 (m, 4 H, SCHCH*H* and NCH_3), 1.40 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 136.0 (s), 134.1 (s), 129.1 (d), 128.9 (d), 90.2 (d), 66.7 (d), 55.1 (s), 44.3 (q), 38.9 (t), 30.6 (q); *m/z* (EI) 334 (M$^+$, ^{37}Cl, 8), 332 (M$^+$, ^{35}Cl, 21), 222 (27), 196 (66), 168 (100), 153 (56), 99 (29); HRMS (EI): calcd for $C_{14}H_{21}{}^{35}ClN_2O_3S$ (M$^+$) 332.0961, found 332.0971.

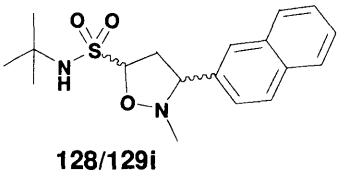
Data for **129h**: R_f 0.30 (2:1 Et_2O/petroleum ether 40-60°C); mp 134-137 °C; υ_{max} (neat)/cm^{-1} 3263, 2919, 1491, 1428, 1311, 1289, 1145, 1089, 1013, 956, 826; δ_H (300 MHz, $CDCl_3$) 7.28-7.40 (m, 4 H, Ar*H*), 4.95 (dd, *J* = 8.4, 5.5 Hz, 1 H, SC*H*), 4.38 (s, 1 H, N*H*), 3.53 (br dd, *J* = 9.4, 7.4 Hz, 1 H, NC*H*), 3.03 (ddd, *J* = 13.5, 8.4, 7.4 Hz, 1 H, SCHC*H*H), 2.89 (ddd, *J* = 13.5, 10.0, 5.5 Hz, 1 H, SCHCH*H*), 2.59 (s, 3 H, NCH_3), 1.42 (s, 9 H $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 135.1 (s), 134.4 (s), 129.5 (d), 129.1 (d), 90.2 (d), 72.2 (d), 55.1 (s), 43.3 (q), 40.0 (t), 30.6 (q); *m/z* (EI) 334 (M^+, ^{37}Cl, 19), 332 (M^+, ^{35}Cl, 43), 222 (29), 196 (75), 168 (100), 153 (53), 138 (26), 103 (38); HRMS (EI): calcd for $C_{14}H_{21}{}^{35}ClN_2O_3S$ (M^+) 332.0961, found 332.0974.

Data for **127h**: R_f 0.24 (2:1 Et_2O/petroleum ether 40-60°C); mp 164-168 °C; υ_{max} (neat)/cm^{-1} 3267, 2921, 1493, 1307, 1141, 1091, 1012, 816; δ_H (300 MHz, $CDCl_3$) 7.42 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.36 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 4.85 (s, 1 H, N*H*), 4.40 (dd, *J* = 9.7, 3.7 Hz, 1 H, SCHC*H*H), 4.31 (dd, *J* = 9.7, 8.3 Hz, 1 H, SCHCH*H*), 3.93 (app. td, *J* = 7.9, 3.7 Hz, 1 H, SC*H*), 3.78 (br d, *J* = 7.3 Hz, 1 H, NC*H*), 2.61 (s, 3 H, NCH_3), 1.12 (s, 9 H $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 136.0 (s), 134.5 (s), 129.8 (d), 129.1 (d), 75.6 (d), 74.1 (d), 67.1 (t), 55.1 (s), 42.7 (q), 30.0 (q); *m/z* (EI) 334 (M^+, ^{37}Cl, 10), 332 (M^+, ^{35}Cl, 27), 194 (100), 174 (39), 151 (26), 115 (33); HRMS (EI): calcd for $C_{14}H_{21}{}^{35}ClN_2O_3S$ (M^+) 332.0961, found 332.0976.

(3*S, 4*S**)-2-Methyl-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid *tert*-butylamide (127i), (3*R**, 5*S**) and (3*S**, 5*S**)-2-Methyl-3-naphthalen-2-yl-isoxazolidine-5-sulfonic acid *tert*-butylamide (128/129i)**



127i



128/129i

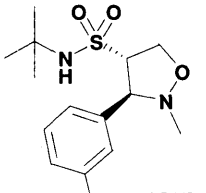
General protocol was followed using 200 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C /Et_2O) to give **128/129i** (26 mg, 6%) as a mixture, and **127i** (182 mg, 43%) as a brown solid- overall yield (49%, **127i**:**128/129i** = 7:1, **128** and **129i** = 1:1 major:minor).

Data for **128/129i**: R_f 0.38 (2:1 Et_2O/petroleum ether 40-60°C) ; υ_{max} (neat)/cm^{-1} 2918, 1545, 1376, 1317, 1229, 1136, 1040, 860; δ_H (500 MHz, $CDCl_3$) 7.79-7.86 (m, 4 H, Ar*H*), 7.45-7.52 (m, 3 H, Ar*H*), 5.01 (br t, *J* = 7.2 Hz, 1 H, SC*H*), 4.68 (br s, 1 H_{major}, N*H*), 4.44 (br s, 1 H_{minor}, N*H*), 4.16-4.24 (m, 1 H_{major}, NC*H*), 3.74 (br t, *J* = 8.6 Hz, 1 H_{minor}, NC*H*), 3.05-3.16 (m, 1 H, SCHC*H*H), 2.84-2.92 (m, 1 H SCHCH*H*), 2.79 (s, 3

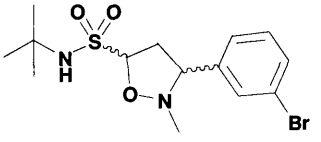
H_{minor}, NCH_3), 2.65 (s, 3 H_{major}, NCH_3), 1.45 (s, 9 H_{minor}, C(CH_3)$_3$), 1.43 (s, 9 H_{major}, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 138.2 (s), 133.6 (s), 133.4 (3 x s), 128.9 (d), 128.8 (d), 127.9 (2 x d), 127.8 (2 x d), 127.6 (d), 127.1 (d), 126.4 (2 x d), 126.3 (d), 90.4 (d), 74.1 (d), 55.1 (s), 43.5 (q), 41.7 (t), 41.2 (t), 30.7 (q), 23 out of 26 expected signals observed; *m/z* (FAB$^+$) 349 (MH$^+$, 6), 307 (26), 154 (100); HRMS (FAB$^+$): calcd for $C_{18}H_{25}N_2O_3S$ (MH$^+$) 349.1586, found 349.1591.

Data for **127i**: R_f 0.26 (2:1 Et_2O/petroleum ether 40-60°C); mp 147-150 °C; υ_{max} (neat)/cm^{-1} 3303, 2990, 2867, 1506, 1422, 1311, 1137, 1044, 863; δ_H (300 MHz, $CDCl_3$) 7.99 (s, 1 H, Ar*H*), 7.84-7.92 (m, 3 H, Ar*H*), 7.62 (dd, *J* = 8.5, 1.6 Hz, 1 H, Ar*H*), 7.50-7.53 (m, 2 H, Ar*H*), 5.06 (s, 1 H, N*H*), 4.53 (dd, *J* = 9.7, 3.6 Hz, 1 H, SCHC*H*H), 4.43 (dd, *J* = 9.7, 8.3 Hz, 1 H, SCHCH*H*), 4.13 (app. td, *J* = 8.1, 3.6 Hz, 1 H, SC*H*), 4.02 (br d, *J* = 7.4 Hz, 1 H, NC*H*), 2.68 (s, 3 H, NCH_3), 1.01 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 134.6 (s), 133.4 (s), 133.2 (s), 128.9 (d), 128.5 (d), 128.0 (d), 127.8 (d), 126.6 (d), 126.5 (d), 125.2 (d), 75.3 (d), 75.2 (d), 67.3 (t), 55.0 (s), 42.8 (q), 29.9 (q); *m/z* (EI) 348 (M$^+$, 43), 210 (100), 184 (25), 167 (38), 152 (20); HRMS (EI): calcd for $C_{18}H_{24}N_2O_3S$ (M$^+$) 348.1508, found 348.1498.

(3*S, 4*S**)-3-(3-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butylamide (127j), (3*R**, 5*S**) and (3*S**, 5*S**)-3-(3-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128/129j)**



127j



128/129j

General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **128/129j** (43 mg, 19%) as a mixture, and **127j** (88 mg, 38%) as a light brown solid- overall yield (57%, **127j**:**128/129j** = 2:1, **128j** and **129j** = 2:1 major:minor).

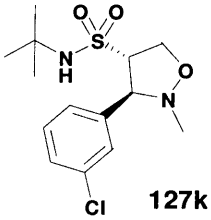
Data for **128j**: R_f 0.37 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3274, 2919, 1475, 1431, 1329, 1142, 1066, 863, 787; δ_H (300 MHz, $CDCl_3$) 7.55 (s, 1 H, Ar*H*), 7.44 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.19-7.30 (m, 2 H, Ar*H*), 4.93 (dd, *J* = 8.6, 2.4 Hz, 1 H, SC*H*), 4.28 (s, 1 H, N*H*), 4.00 (br dd, *J* = 9.1, 6.5 Hz, 1 H, NC*H*), 3.06 (ddd, *J* = 13.6, 6.5, 2.4 Hz, 1 H, SCHC*H*H), 2.65-2.78 (m, 4 H, SCHC*H*H and NCH_3), 1.40 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 139.9 (s), 131.5 (d), 130.5 (d), 130.4 (d), 126.3 (d),

122.9 (s), 90.2 (d), 67.6 (d), 55.1 (s), 44.7 (q), 41.9 (t), 30.6 (q); *m/z* (EI) 378 (M^+, ^{81}Br, 12), 376 (M^+, ^{79}Br, 11), 268 (30), 240 (50), 212 (100), 198 (38), 132 (36); HRMS (EI): calcd for $C_{14}H_{21}{}^{79}BrN_2O_3S$ (M^+) 376.0456, found 376.0462.

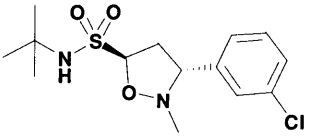
Data for **129j**: R_f 0.34 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$, picking diagnostic peaks from **128/129j** mixture) 7.62 (dd, *J* = 1.9, 1.6 Hz, 1 H, Ar*H*), 7.37-7.50 (m, 2 H, Ar*H*), 7.18-7.29 (m, 1 H, Ar*H*), 4.95 (dd, *J* = 8.3, 5.6 Hz, 1 H, SC*H*), 4.48 (br s, 1 H, N*H*), 3.53 (br dd, *J* = 9.6, 7.5 Hz, 1 H, NC*H*), 3.04 (ddd, *J* = 13.7, 8.3, 7.5 Hz, 1 H, SCHC*H*H), 2.89 (ddd, *J* = 13.7, 9.6, 5.6 Hz, 1 H, SCHCH*H*), 2.61 (s, 3 H, NCH_3), 1.42 (s, 9 H, $C(CH_3)_3$).

Data for **127j**: R_f 0.28 (2:1 Et_2O/petroleum ether 40-60°C); mp 117-120 °C; υ_{max} (neat)/cm^{-1} 3319, 2963, 2849, 1477, 1419, 1390, 1313, 1132, 1039, 984, 794; δ_H (300 MHz, $CDCl_3$) 7.64 (s, 1 H, Ar*H*), 7.41-7.49 (m, 2 H, Ar*H*), 7.23-7.29 (m, 1 H, Ar*H*), 4.78 (br s, 1 H, N*H*), 4.41 (dd, *J* = 9.7, 3.8 Hz, 1 H, SCHC*H*H), 4.30 (dd, *J* = 9.7, 8.3 Hz, 1 H, SCHCH*H*), 3.93 (app. td, *J* = 8.1, 3.8 Hz, 1 H, SC*H*), 3.78 (br d, *J* = 7.3 Hz, 1 H, NC*H*), 2.63 (s, 3 H, NCH_3), 1.12 (s, 9 H $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 140.0 (s), 131.8 (d), 131.4 (d), 130.5 (d), 127.1 (d), 122.9 (s), 75.6 (d), 74.1 (d), 67.1 (t), 55.2 (s), 42.8 (q), 30.0 (q); *m/z* (EI) 378 (M^+, ^{81}Br, 21), 376 (M^+, ^{79}Br, 20), 240 (100), 116 (49); HRMS (EI): calcd for $C_{14}H_{21}{}^{79}BrN_2O_3S$ (M^+) 376.0456, found 376.0459.

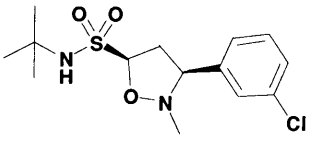
(3*S, 4*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butyl amide (127k), (3*R**, 5*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128k), and (3*S**, 5*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (129k)**



127k



128k



129k

General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **127k** (84 mg, 41%), **128k** (15 mg, 7%), and **129k** (7 mg, 4%)- overall yield (52%, **127k**:**128k**:**129k** = 12:2:1).

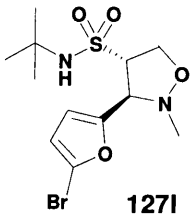
Data for **128k**: R_f 0.35 (2:1 Et_2O/petroleum ether 40-60°C); mp 76-80 °C; υ_{max} (neat)/cm^{-1} 3292, 2918, 1577, 1469, 1432, 1321, 1212, 1142, 1014, 872, 784; δ_H (300 MHz, $CDCl_3$) 7.39 (br s, 1 H, Ar*H*), 7.22-7.29 (m, 3H, Ar*H*), 4.93 (dd, *J* = 8.6, 2.5 Hz,

1 H, SC*H*), 4.27 (br s, 1 H, N*H*), 4.01 (br dd, *J* = 9.6, 6.2 Hz, 1 H, NC*H*), 3.07 (ddd, *J* = 13.6, 6.2, 2.5 Hz, 1 H, SCHC*H*H), 2.67-2.78 (m, 4 H, SCHCH*H* and NCH_3), 1.40 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 139.1 (s), 134.8 (s), 130.1 (d), 128.5 (d), 127.6 (d), 125.8 (d), 90.2 (d), 70.8 (d), 55.1 (s), 44.6 (q), 41.8 (t), 30.6 (q); *m/z* (EI) 334 (M^+, ^{37}Cl, 4), 332 (M^+, ^{35}Cl, 8), 196 (21), 168 (100), 152 (60), 125 (27), 103 (40); HRMS (EI): calcd for $C_{14}H_{21}{}^{35}ClN_2O_3S$ (M^+) 332.0961, found 332.0971.

Data for **129k**: R_f 0.31 (2:1 Et_2O/petroleum ether 40-60°C); mp 120-133 °C; υ_{max} (neat)/cm^{-1} 3300, 2975, 2918, 1578, 1479, 1426, 1318, 1207, 1143, 1094, 996, 879, 793; δ_H (300 MHz, $CDCl_3$) 7.43 (br s, 1 H, Ar*H*), 7.28-7.37 (m, 3 H, Ar*H*), 4.95 (dd, *J* = 8.5, 5.5 Hz, 1 H, SC*H*), 4.37 (br s, 1 H, N*H*), 3.53 (br dd, *J* = 9.4, 7.8 Hz, 1 H, NC*H*), 3.04 (ddd, *J* = 13.5, 8.5, 7.2 Hz, 1 H, SCHC*H*H), 2.90 (ddd, *J* = 13.5, 10.0, 5.5 Hz, 1 H, SCHC(H)*H*), 2.61 (s, 3 H, NCH_3), 1.42 (s, 9 H C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 131.3 (s), 129.9 (s), 129.3 (d), 127.3 (d), 91.0 (d), 74.2 (d), 52.3 (s), 44.5 (q), 42.3 (t), 31.8 (q); *m/z* (EI) 334 (M^+, ^{37}Cl, 6), 332 (M^+, ^{35}Cl, 12), 222 (22), 196 (26), 168 (100), 153 (32), 103 (32); HRMS (EI): calcd for $C_{14}H_{21}{}^{35}ClN_2O_3S$ (M^+) 332.0961, found 332.0981.

Data for **127k**: R_f 0.27 (2:1 Et_2O/petroleum ether 40-60°C); mp 117-119 °C; υ_{max} (neat)/cm^{-1} 3322, 2963, 2873, 1575, 1479, 1426, 1316, 1133, 1040, 986, 833, 797; δ_H (300 MHz, $CDCl_3$) 7.49 (s, 1 H, Ar*H*), 7.31-7.39 (m, 3 H, Ar*H*), 4.73 (s, 1 H, N*H*), 4.41 (dd, *J* = 9.7, 3.7 Hz, 1 H, SCHC*H*H), 4.31 (dd, *J* = 9.7, 8.4 Hz, 1 H, SCHCH*H*), 3.94 (app. td, *J* = 8.1, 3.7 Hz, 1 H, SC*H*), 3.79 (d, *J* = 7.3 Hz, 1 H, NC*H*), 2.64 (s, 3 H, NCH_3), 1.12 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 139.8 (s), 134.7 (s), 130.2 (d), 128.9 (d), 128.5 (d), 126.7 (d), 75.6 (d), 74.1 (d), 67.1 (t), 55.2 (s), 42.8 (q), 30.0 (q); *m/z* (EI) 334 (M^+, ^{37}Cl, 4), 332 (M^+, ^{35}Cl, 12), 194 (100), 115 (25); HRMS (EI): calcd for $C_{14}H_{21}{}^{35}ClN_2O_3S$ (M^+) 332.0961, found 332.0974.

(3*S, 4*S**)-3-(5-Bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid *tert*-butyl amide (127l)**

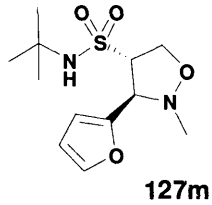


127l

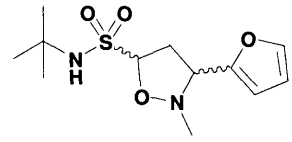
General protocol was followed using 100 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **127l** as a brown solid (84 mg, 37%).

Data for **127l**: R_f 0.21 (2:1 Et_2O/petroleum ether 40-60°C); mp 104-110 °C; υ_{max} (neat)/cm^{-1} 3305, 2973, 2919, 1645, 1507, 1472, 1390, 1306, 1180, 1135, 954, 784; δ_H (300 MHz, $CDCl_3$) 6.43 (d, *J* = 3.2 Hz, 1 H, BrCC*H*), 6.31 (d, *J* = 3.2 Hz, 1 H, BrCCHC*H*), 4.64 (s, 1 H, N*H*), 4.26-4.40 (m, 3 H, SCHCH_2 and SC*H*), 3.84 (br s, 1 H, NC*H*), 2.65 (s, 3 H, NCH_3), 1.20 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 150.9 (s), 122.7 (s), 114.1 (d), 112.5 (d), 71.3 (d), 68.3 (d), 66.9 (t), 55.2 (s), 43.5 (q), 30.3 (q), 30.0 (q), 29.7 (q); *m/z* (EI) 368 (M^+, ^{81}Br, 17), 366 (M^+, ^{79}Br, 16), 230 (100), 205 (27); HRMS (EI): calcd for $C_{12}H_{19}{}^{79}BrN_2O_4S$ (M^+) 366.0249, found 366.0245.

(3*S, 4*S**)-3-Furan-2-yl-2-methylisoxazolidine-4-sulfonic acid *tert*-butylamide (127m), (3*R**, 5*S**) and (3*S**, 5*S**)-3-Furan-2-yl-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (128/129m)**



127m



128/129m

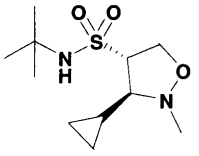
General protocol was followed using 200 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **128/129m** (149 mg, 42%) as a mixture, and **127m** (106 mg, 30%) as a brown solid- overall yield (72%, **127m**:**128/129m** = 2:3, **128m** and **129m** = 2:1 major:minor).

Data for **128/129m**: R_f 0.21 (2:1 Et_2O/petroleum ether 40-60°C); mp 83-85 °C; υ_{max} (neat)/cm^{-1} 3293, 3122, 2972, 1507, 1435, 1316, 1202, 1134, 1058, 990; δ_H (300 MHz, $CDCl_3$) 7.37-7.39 (m, 1 H, OC*H*CHCH), 6.37 (d, *J* = 3.2 Hz, 1 H_{minor}, OCHCHC*H*), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1 H, OCHC*H*CH), 6.29 (d, *J* = 3.2 Hz, 1 H_{major}, OCHCHC*H*), 4.94 (dd, *J* = 8.3, 5.9 Hz, 1 H, SC*H*), 4.63 (br s, 1 H_{minor}, N*H*), 4.52 (br s, 1 H_{major}, N*H*), 4.10 (br s, 1 H_{major}, NC*H*), 3.69 (br dd, *J* = 9.9, 7.5 Hz, 1 H_{minor}, NC*H*), 3.16 (ddd, *J* = 13.4, 10.4, 5.9 Hz, 1 H_{minor}, SCHC*H*H), 2.86-3.08 (m, 2 H, SCHC*H*H_{major} and SCHCH*H*), 2.79 (br s, 3 H_{major}, NCH_3), 2.69 (s, 3 H_{minor}, NCH_3), 1.37 (s, 9 H_{minor}, C(CH_3)$_3$), 1.36 (s, 9 H_{major}, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 149.4 (s), 148.8 (s), 143.1 (d), 143.0 (d), 110.5 (d), 110.4 (d), 109.1 (d), 108.8 (d), 90.5 (d), 89.9 (d), 66.2 (d), 64.3 (d), 55.1 (s), 55.0 (s), 44.7 (q), 43.7 (q), 36.7 (t), 30.6 (q), 29.7 (q), 19 out of 20 expected signals observed; *m/z* (FAB^+) 307 (26), 289 (MH^+, 100), 154 (77); HRMS (FAB^+): calcd for $C_{12}H_{21}N_2O_4S$ (MH^+) 289.1222, found 288.1228.

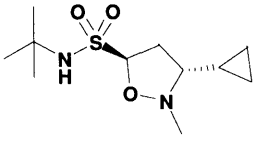
Data for **127m**: R_f 0.16 (2:1 Et_2O/petroleum ether 40-60°C); mp 148-152 °C; υ_{max} (neat)/cm^{-1} 3279, 2921, 1505, 1431, 1314, 1235, 1142, 1010; δ_H (300 MHz, $CDCl_3$)

7.45 (dd, J = 1.9, 0.8 Hz, 1 H, OC*H*CHCH), 6.47 (dd, J = 3.2, 0.8 Hz, 1 H, OCHCHC*H*), 6.38 (dd, J = 3.2, 1.9 Hz, 1 H, OCHC*H*CH), 4.72 (s, 1 H, N*H*), 4.26-4.42 (m, 3 H, SCHCH_2 and SC*H*), 3.88 (br s, 1 H, NC*H*), 2.67 (s, 3 H, NCH_3), 1.14 (s, 9 H C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 148.6 (s), 143.3 (d), 110.8 (2 x d), 71.3 (d), 68.4 (d), 66.9 (t), 55.0 (s), 42.8 (q), 29.9 (q); *m/z* (EI) 288 (M^+, 5), 151 (48), 150 (100), 118 (26), 91 (30); HRMS (EI): calcd for $C_{12}H_{20}N_2O_4S$ (M^+) 288.1138, found 288.1131.

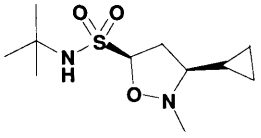
(3*S, 4*S**)-3-Cyclopropyl-2-methylisoxazolidine-4-sulfonic acid *tert*-butylamide (127n), (3*R**, 5*S**)-3-Cyclopropyl-2-methylisoxazolidine-5-sulfonic acid *tert*-butyl amide (128n), and (3*S**, 5*S**)-3-Cyclopropyl-2-methylisoxazolidine-5-sulfonic acid *tert*-butylamide (129n)**



127n



128n



129n

General protocol was followed using 200 mg of **123e**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **127n** (41 mg, 12%), **128n** (64 mg, 20%), and **129n** (35 mg, 11%)- overall yield (43%, **127n**:**128n**:**129n** = 6:9:5).

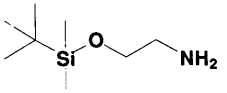
Data for **129n**: R_f 0.41 (2:1 Et_2O/petroleum ether 40-60°C); mp 113-117 °C; υ_{max} (neat)/cm^{-1} 3304, 2983, 2918, 1474, 1427, 1316, 1232, 1141, 1056, 863; δ_H (300 MHz, $CDCl_3$) 4.79 (t, J = 7.2 Hz, 1 H, SC*H*), 4.39 (br s, 1 H, N*H*), 2.66-2.76 (m, 5 H, NCH_3 and SCHCH_2), 1.85 (br q, J = 7.8 Hz, 1 H, NC*H*), 1.37 (s, 9 H C(CH_3)$_3$), 0.82-0.95 (m, 1 H, CH_2C*H*CH_2), 0.51-0.60 (m, 2 H, cyclopropyl-*H*), 0.15-0.28 (m, 2 H, cyclopropyl-*H*); δ_C (75 MHz, $CDCl_3$) 89.5 (d), 74.2 (d), 54.9 (s), 44.3 (q), 37.9 (t), 30.6 (q), 11.2 (d), 4.2 (t), 1.0 (t); *m/z* (EI) 262 (M^+, 81), 152 (100), 126 (72), 98 (54); HRMS (EI): calcd for $C_{11}H_{22}N_2O_3S$ (M^+) 262.1351, found 262.1352.

Data for **128n**: R_f 0.36 (2:1 Et_2O/petroleum ether 40-60°C); mp 92-95 °C; υ_{max} (neat)/cm^{-1} 3288, 2969, 2921, 1459, 1429, 1316, 1289, 1142, 1067, 863; δ_H (300 MHz, $CDCl_3$) 4.80 (br dd, J = 6.7, 2.9 Hz, 1 H, SC*H*), 4.31 (br s, 1 H, N*H*), 2.76-2.89 (m, 4 H, NCH_3 and SCHC*H*H), 2.52-2.60 (m, 1 H, SCHCH*H*), 2.25 (br s, 1 H, NC*H*), 1.35 (s, 9 H C(CH_3)$_3$), 0.65-0.76 (m, 1 H, CH_2C*H*CH_2), 0.47-0.61 (m, 2 H, cyclopropyl-*H*), 0.17-0.30 (m, 2 H, cyclopropyl-*H*); δ_C (75 MHz, $CDCl_3$) 90.0 (d), 71.6 (d), 54.9 (s), 45.2 (q), 38.7 (t), 30.3 (q), 11.5 (d), 4.1 (t), 1.1 (t); *m/z* (EI) 262 (M^+, 32), 152 (100), 126 (78), 96 (48); HRMS (EI): calcd for $C_{11}H_{22}N_2O_3S$ (M^+) 262.1351, found 262.1348.

Data for **127n**: R_f 0.22 (2:1 Et_2O/petroleum ether 40-60°C); mp 62-66 °C; υ_{max} (neat)/cm^{-1} 3286, 2964, 1464, 1428, 1306, 1232, 1136, 1041, 867; δ_H (300 MHz, $CDCl_3$) 4.45 (s, 1 H, N*H*), 4.23 (br dd, *J* = 9.6, 4.8 Hz, 1 H, SCHC*H*H), 4.12 (app. br t, *J* = 8.9 Hz, 1 H, SCHCH*H*), 3.88 (app. td, *J* = 7.9, 5.6 Hz, 1 H, SC*H*), 2.79 (s, 3 H, NCH_3), 2.41 (app. s, 1 H, NC*H*), 1.39 (s, 9 H C(CH_3)$_3$), 0.81-1.03 (m, 1 H, CH_2CHCH_2), 0.55-0.78 (m, 3 H, cyclopropyl-*H*), 0.17-0.30 (m, 1 H, cyclopropyl-*H*); δ_C (75 MHz, $CDCl_3$) 74.2 (d), 73.4 (d), 66.9 (t), 55.3 (s), 43.8 (q), 30.3 (q), 13.8 (d), 4.7 (t), 2.3 (t); *m/z* (EI) 262 (M^+, 15), 124 (100), 99 (67); HRMS (EI): calcd for $C_{11}H_{22}N_2O_3S$ (M^+) 262.1351, found 262.1348.

4.5.3. Cycloadditions with ethenesulfonic acid [2-(*tert*-butyldimethyl silanyloxy)ethyl]amide (123g)

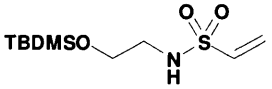
2-(*tert*-Butyldimethylsilanyloxy)ethylamine [192]



Ethanolamine (5.0 g, 81.8 mmol) was dissolved in DCM (125 mL), then NEt_3 (12.6 mL, 90.0 mmol) and TBDMSCl (13.6 g, 90.0 mmol) added to the stirring suspension. DMAP (1.0 g, 8.2 mmol) was added and the reaction allowed to stir at RT for 16 hours. The reaction mixture was washed with H_2O (2 x 40 mL), followed by brine (1 x 40 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the product (13.2 g, 92%) as a yellow oil. Data agrees with literature.

R_f 0.20 (4:1 DCM/MeOH); δ_H (300 MHz, $CDCl_3$) 3.55 (t, *J* = 5.3 Hz, 2 H, OCH_2CH_2), 2.70 (t, *J* = 5.3 Hz, 2 H, CH_2CH_2N), 1.39 (br s, 2 H, NH_2), 0.83 (s, 9 H, C(CH_3)$_3$), 0.07 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 65.3 (t), 44.3 (t), 25.8 (q), 18.3 (s), -5.0 (q).

Ethenesulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (123g)

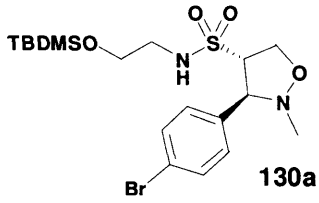


A premixed suspension of 2-(*tert*-butyldimethylsilanyloxy)ethylamine (11.7 g, 44.2 mmol) and NEt_3 (7.5 g, 73.6 mmol) in DCM was dropwise added to a stirring solution of 2-chloroethane-1-sulfonyl chloride (6.0 g, 36.8 mmol) in DCM (100 mL), while keeping the temperature at -10 °C. The reaction mixture was left to stir for a further 3 hours after addition, then warmed to RT. The reaction was diluted with DCM (60 mL)

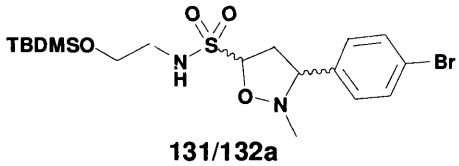
and washed with 2M HCl (3 x 80 mL), H_2O (80 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* to give the crude residue which was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to furnish the desired product (6.3 g, 65%) as a white solid.

R_f 0.24 (1:1 petroleum ether 40-60°C/Et_2O); mp 48-50 °C; υ_{max} (neat)/cm^{-1} 3297, 2930, 1472, 1327, 1254, 1152, 1084, 967, 834, 776; δ_H (300 MHz, $CDCl_3$) 6.52 (dd, *J* = 16.6, 9.9 Hz, 1 H, SC*H*), 6.25 (d, *J* = 16.6 Hz, 1 H, SCHC*H*H), 5.94 (d, *J* = 9.9 Hz, 1 H, SCHCH*H*), 4.64 (br s, 1 H, N*H*), 3.71 (t, *J* = 5.2 Hz, 2 H, OCH_2CH_2N), 3.14 (app. q, *J* = 5.4 Hz, 2 H, OCH_2CH_2N), 0.88 (s, 9 H, C(CH_3)$_3$), 0.05 (s, 6 H, Si(CH_3)$_2$; δ_C (75 MHz, $CDCl_3$) 136.0 (d), 126.4 (t), 61.8 (t), 45.1 (t), 26.0 (q), 18.2 (s), -5.4 (q); *m/z* (CI) 266 (MH^+, 100), 250 (28), 208 (34), 134 (31); HRMS (CI): calcd for $C_{10}H_{24}NO_3SSi$ (MH^+) 266.1246, found 266.1247.

(3*S, 4*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (130a), (3*R**, 5*S**) and (3*S**, 5*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethyl silanyloxy)ethyl]amide (131/132a)**



130a



131/132a

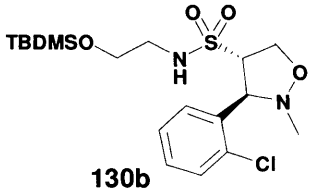
General protocol was followed using 200 mg of **123g**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **131/132a** (40 mg, 11%) as a mixture, and **130a** (213 mg, 59%) as a brown oil- overall yield (70%, **130a**:**131/132a** = 5:1, **131** and **132a** = 4:1 major:minor).

Data for **131/132a**: R_f 0.44 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.48 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.25 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 5.04 (dd, *J* = 8.6, 5.6 Hz, 1 H_{minor}, SC*H*), 5.01 (dd, *J* = 8.6, 2.5 Hz, 1 H_{major}, SC*H*), 4.87 (br t, *J* = 5.9 Hz, 1 H_{minor}, N*H*), 4.79 (br t, *J* = 5.8 Hz, 1 H_{major}, N*H*), 4.02 (br dd, *J* = 9.4, 6.3 Hz, 1 H_{major}, NC*H*), 3.75 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.54 (br dd, *J* = 10.1, 7.5 Hz, 1 H_{minor}, NC*H*), 3.34-3.40 (m, 2 H_{minor}, OCH_2CH_2N), 3.27-3.34 (m, 2 H_{major}, OCH_2CH_2N), 3.07-3.16 (m, 1 H_{minor}, SCHC*H*H), 3.05 (ddd, *J* = 13.7, 6.3, 2.5 Hz, 1 H_{major}, SCHC*H*H), 2.84 (ddd, *J* = 13.6, 10.1, 5.6 Hz, 1 H_{minor}, SCHCH*H*), 2.74 (ddd, *J* = 13.7, 10.2, 8.6 Hz, 1 H_{major}, SCHCH*H*), 2.72 (s, 3 H_{major}, NCH_3), 2.59 (s, 3 H_{minor}, NCH_3), 0.90 (s, 9 H, C(CH_3)$_3$), 0.07 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 136.0 (s), 135.6 (s), 132.1 (d), 132.0 (d),

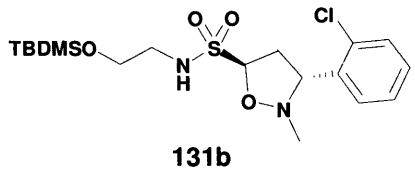
129.7 (d), 129.2 (d), 122.6 (s), 122.3 (s), 88.8 (d), 67.6 (d), 62.5 (t), 62.2 (t), 45.9 (t), 44.6 (q), 41.9 (t), 25.9 (q), 18.3 (s), -5.4 (q), 18 out of 26 expected signals observed.

Data for **130a**: R_f 0.36 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.49 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.34 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.81 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.34 (dd, *J* = 9.9, 4.2 Hz, 1 H, SCHC*H*H), 4.28 (dd, *J* = 9.9, 8.0 Hz, 1 H, SCHCH*H*), 3.97 (app. td, *J* = 7.5, 4.2 Hz, 1 H, SC*H*), 3.81 (br d, *J* = 7.1 Hz, 1 H, NC*H*), 3.48-3.60 (m, 2 H, OCH_2CH_2N), 3.10 (ddt, *J* = 12.8, 6.2, 4.4 Hz, 1 H, OCH_2CHHN), 2.95 (ddt, *J* = 11.8, 6.0, 4.4 Hz, 1 H, OCH_2CHHN), 2.62 (s, 3 H, NCH_3), 0.86 (s, 9 H, $C(CH_3)_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 136.3 (s), 132.1 (d), 129.8 (d), 122.7 (s), 73.6 (d), 73.3 (d), 67.0 (t), 62.1 (t), 45.4 (t), 42.8 (q), 25.9 (q), 18.3 (s), -5.4 (q).

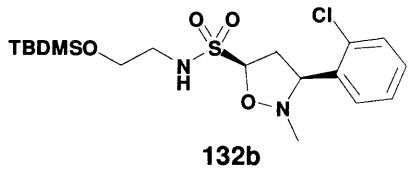
(3*S, 4*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130b), (3*R**, 5*S**)-3-(2-Chlorophenyl)-2-methyl isoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131b), and (3*S**, 5*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (132b)**



130b



131b



132b

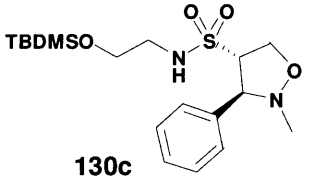
General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the three separable products **130b** (134 mg, 41%), **131b** (85 mg, 26%), and **132b** (49 mg, 15%)-overall yield (82%, **130b**:**131b**:**132b** = 8:5:3).

Data for **132b**: R_f 0.50 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.66 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.36 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.19-7.31 (m, 2 H, Ar*H*), 5.09 (dd, *J* = 8.6, 5.7 Hz, 1 H, SC*H*), 4.86 (br t, *J* = 5.7 Hz, 1 H, N*H*), 4.19 (br dd, *J* = 9.3, 8.0 Hz, 1 H, NC*H*), 3.77 (t, *J* = 4.9 Hz, 2 H, OCH_2CH_2N), 3.37 (app. q, *J* = 5.4 Hz, 2 H, OCH_2CH_2N), 3.14-3.24 (m, 1 H, SCHC*H*H), 2.67-2.80 (m, 4 H, SCHCH*H* and NCH_3), 0.91 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 134.7 (s), 133.7 (s), 129.6 (d), 129.2 (d), 128.4 (d), 127.7 (d), 88.9 (d), 68.5 (d), 62.6 (t), 46.0 (t), 43.4 (q), 39.7 (t), 25.9 (q), 18.3 (s), -5.3 (q).

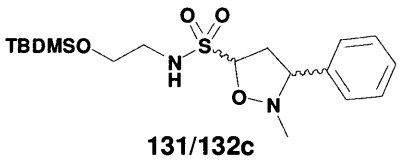
Data for **131b**: R_f 0.44 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.55 (dd, *J* = 7.5, 1.8 Hz, 1 H, Ar*H*), 7.36 (dd, *J* = 7.5, 1.7 Hz, 1 H, Ar*H*), 7.22-7.30 (m, 2 H, Ar*H*), 4.96 (dd, *J* = 8.4, 4.0 Hz, 1 H, SC*H*), 4.81 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.57 (br t, *J* = 7.2 Hz, 1 H, NC*H*), 3.76 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.28-3.36 (m, 2 H, OCH_2CH_2N), 3.26 (ddd, *J* = 13.5, 6.7, 4.0 Hz, 1 H, SCHC*H*H), 2.83 (s, 3 H, NCH_3), 2.63 (app. dt, *J* = 13.5, 8.4 Hz, 1 H, SCHCH*H*), 0.90 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 135.8 (s), 133.5 (s), 129.7 (d), 129.0 (d), 127.6 (d), 127.3 (d), 89.5 (d), 67.0 (d), 62.3 (t), 46.0 (t), 45.1 (q), 39.0 (t), 25.9 (q), 18.3 (s), -5.4 (q).

Data for **130b**: R_f 0.28 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.54 (dd, *J* = 7.5, 1.8 Hz, 1 H, Ar*H*), 7.39 (dd, *J* = 7.7, 1.7 Hz, 1 H, Ar*H*), 7.25-7.34 (m, 2 H, Ar*H*), 4.78 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.48 (br d, *J* = 7.4 Hz, 1 H, NC*H*), 4.43 (dd, *J* = 9.9, 4.6 Hz, 1 H, SCHC*H*H), 4.38 (dd, *J* = 9.9, 7.8 Hz, 1 H, SCHCH*H*), 4.11 (app. td, *J* = 7.8, 4.6 Hz, 1 H, SC*H*), 3.39-3.56 (m, 2 H, OCH_2CH_2N), 3.07-3.15 (m, 1 H, OCH_2CHHN), 2.73-2.82 (m, 1 H, OCH_2CHHN), 2.63 (s, 3 H, NCH_3), 0.86 (s, 9 H, $C(CH_3)_3$), 0.02 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 134.4 (s), 134.3 (s), 130.0 (d), 129.8 (d), 129.7 (d), 127.7 (d), 72.7 (d), 70.1 (d), 67.1 (t), 62.1 (t), 45.3 (t), 42.7 (q), 25.9 (q), 18.3 (s), -5.4 (q).

(3*S, 4*S**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid [2-(*tert*-butyldimethyl silanyloxy)ethyl]amide (130c), (3*R**, 5*S**) and (3*S**, 5*S**)-2-Methyl-3-phenylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131/132c)**



130c



131/132c

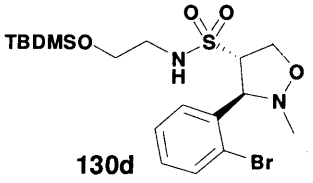
General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **131/132c** (43 mg, 14%) as a mixture, and **130c** (123 mg, 41%) as a brown oil- overall yield (55%, **130c**:**131/132c** = 3:1, **131c** and **132c** = 3:2 major:minor).

Data for **131/132c**: R_f 0.46 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.40-7.44 (m, 2 H, Ar*H*), 7.30-7.38 (m, 3 H, Ar*H*), 5.07 (dd, *J* = 8.6, 5.9 Hz, 1 H_{major}, SC*H*), 5.01-5.05 (m, 1 H_{minor}, SC*H*), 4.88 (br t, *J* = 5.9 Hz, 1 H_{major}, N*H*), 4.79 (br t, *J* = 5.9 Hz, 1 H_{minor}, N*H*), 4.03 (app. br s , 1 H_{minor}, NC*H*), 3.77 (app. q, *J* = 5.4 Hz, 2 H,

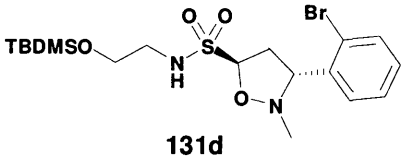
OCH_2CH_2N), 3.57 (br dd, J = 9.9, 7.5 Hz, 1 H_{major}, NC*H*), 3.39 (app. q, J = 5.4 Hz, 2 H_{major}, OCH_2CH_2N), 3.28-3.36 (m, 2 H_{minor}, OCH_2CH_2N), 3.00-3.14 (m, 1 H, SCHC*H*H), 2.77-2.95 (m, 1 H, SCHCH*H*), 2.73 (br s, 3 H_{minor}, NCH_3), 2.61 (s, 3 H_{major}, NCH_3), 0.91 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 136.4 (s), 128.9 (d), 128.8 (d), 128.6 (d), 128.4 (d), 128.0 (d), 127.6 (d), 88.9 (d), 88.8 (d), 73.7 (d), 62.6 (t), 62.3 (t), 45.9 (t), 43.2 (q), 41.2 (t), 25.9 (q), 25.8 (q), 18.3 (s), -5.4 (q), 19 out of 26 expected signals observed.

Data for **130c**: R_f 0.39 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.32-7.45 (m, 5 H, Ar*H*), 4.72 (br t, J = 5.7 Hz, 1 H, N*H*), 4.30-4.39 (m, 2 H, $SCHCH_2$), 4.05 (app. td, J = 7.5, 4.4 Hz, 1 H, SC*H*), 3.82 (br d, J = 7.1 Hz, 1 H, NC*H*), 3.43-3.56 (m, 2 H, OCH_2CH_2N), 3.02-3.12 (m, 1 H, OCH_2CHHN), 2.81-2.91 (m, 1 H, OCH_2CHHN), 2.63 (s, 3 H, NCH_3), 0.86 (s, 9 H, $C(CH_3)_3$), 0.02 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 137.0 (s), 129.0 (d), 128.7 (d), 128.2 (d), 74.5 (d), 73.2 (d), 66.9 (t), 62.0 (t), 45.3 (t), 42.8 (q), 25.9 (q), 18.3 (s), -5.4 (q).

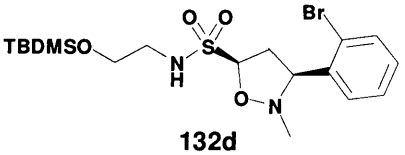
(3*S, 4*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130d), (3*R**, 5*S**)-3-(2-Bromophenyl)-2-methyl isoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131d), and (3*S**, 5*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (132d)**



130d



131d



132d

General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **130d** (100 mg, 28%), **131d** (62 mg, 17%), and **132d** (43 mg, 12%)-overall yield (57%, **130d**:**131d**:**132d** = 5:3:2).

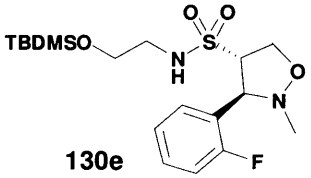
Data for **132d**: R_f 0.52 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.65 (dd, J = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.54 (dd, J = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.30-7.35 (m, 1 H, Ar*H*), 7.15 (ddd, J = 8.0, 7.4, 1.6 Hz, 1 H, Ar*H*), 5.08 (dd, J = 8.6, 5.6 Hz, 1 H, SC*H*), 4.87 (br t, J = 5.8 Hz, 1 H, N*H*), 4.16 (dd, J = 9.8, 7.4 Hz, 1 H, NC*H*), 3.77 (t, J = 5.1 Hz, 2 H, OCH_2CH_2N), 3.37 (app. q, J = 5.4 Hz, 2 H, OCH_2CH_2N), 3.21 (ddd, J = 13.5, 8.6, 7.4 Hz, 1 H, SCHC*H*H), 2.63-2.72 (m, 4 H, SCHCH*H* and NCH_3), 0.91 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 136.4 (s), 132.8 (d), 129.5 (d),

128.7 (d), 128.3 (d), 123.9 (s), 88.9 (d), 71.1 (d), 62.6 (t), 46.0 (t), 43.4 (q), 39.7 (t), 25.9 (q), 18.3 (s), -5.3 (q).

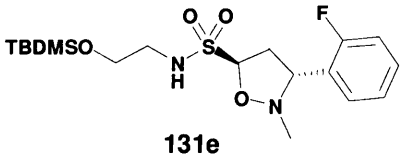
Data for **131d**: R_f 0.47 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.52-7.59 (m, 2 H, Ar*H*), 7.32 (app. dt, *J* = 7.4, 1.1 Hz, 1 H, Ar*H*), 7.15 (app. dt, *J* = 8.0, 1.7 Hz, 1 H, Ar*H*), 4.96 (dd, *J* = 8.4, 4.1 Hz, 1 H, SC*H*), 4.81 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.54 (app. t, *J* = 7.3 Hz, 1 H, NC*H*), 3.76 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.24-3.36 (m, 2 H, OCH_2CH_2N), 3.28 (ddd, *J* = 13.7, 6.6, 4.1 Hz, 1 H, SCHC*H*H), 2.83 (s, 3 H, NCH_3), 2.58-2.68 (m, 1 H, SCHCH*H*), 0.90 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 137.4 (s), 133.0 (d), 129.3 (d), 128.0 (d), 127.9 (d), 123.6 (s), 89.5 (d), 69.4 (d), 62.3 (t), 46.0 (t), 45.1 (q), 39.2 (t), 25.9 (q), 18.3 (s), -5.4 (q).

Data for **130d**: R_f 0.29 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.58 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar*H*), 7.52 (dd, *J* = 7.8, 1.7 Hz, 1 H, Ar*H*), 7.36 (app. dt, *J* = 7.8, 1.2 Hz, 1 H, Ar*H*), 7.19 (app. dt, *J* = 8.0, 1.7 Hz, 1 H, Ar*H*), 4.80 (br t, *J* = 6.0 Hz, 1 H, N*H*), 4.50 (br d, *J* = 7.4 Hz, 1 H, NC*H*), 4.35-4.44 (m, 2 H, $SCHCH_2$), 4.09 (app. br td, *J* = 7.8, 4.7 Hz, 1 H, SC*H*), 3.38-3.52 (m, 2 H, OCH_2CH_2N), 3.06-3.15 (m, 1 H, OCH_2CHHN), 2.70-2.80 (m, 1 H, OCH_2CHHN), 2.64 (s, 3 H, NCH_3), 0.86 (s, 9 H, $C(CH_3)_3$), 0.02 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 135.9 (s), 133.3 (d), 130.1 (d), 129.9 (d), 128.3 (d), 124.9 (s), 72.9 (d), 72.4 (d), 67.1 (t), 62.1 (t), 45.3 (t), 42.6 (q), 25.9 (q), 18.3 (s), -5.4 (q).

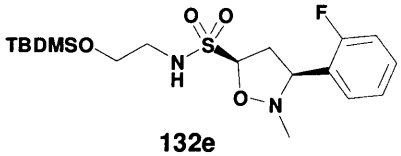
(3*S, 4*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130e), (3*R**, 5*S**)-3-(2-Fluorophenyl)-2-methyl isoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131e), and (3*S**, 5*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (132e)**



130e



131e



132e

General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **130e** (113 mg, 36%), **131e** (68 mg, 22%), and **132e** (58 mg, 18%)-overall yield (76%, **130e**:**131e**:**132e** = 2:1:1).

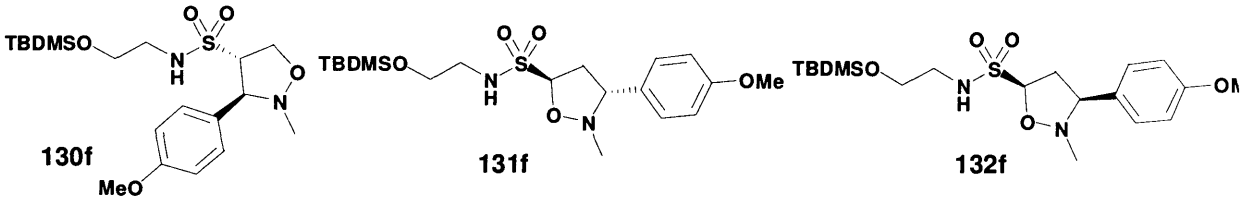
Data for **132e**: R_f 0.47 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.60 (app. td, *J* = 7.5, 1.9 Hz, 1 H, Ar*H*), 7.24-7.32 (m, 1 H, Ar*H*), 7.16 (app. td, *J* = 7.8, 1.1 Hz, 1 H, Ar*H*), 7.05 (ddd, *J* = 10.2, 8.2, 1.1 Hz, 1 H, Ar*H*), 5.09 (dd, *J* = 8.4, 5.6 Hz, 1

H, SC*H*), 4.88 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.02 (dd, *J* = 10.2, 7.4 Hz, 1 H, NC*H*), 3.77 (t, *J* = 5.1 Hz, 2 H, OCH_2CH$_2$N), 3.38 (app. q, *J* = 5.4 Hz, 2 H, OCH$_2$CH_2N), 3.09 (ddd, *J* = 13.5, 8.4, 7.4 Hz, 1 H, SCHC*H*H), 2.84 (ddd, *J* = 13.5, 10.2, 5.6 Hz, 1 H, SCHCH*H*), 2.65 (s, 3 H, NCH_3), 0.89 (s, 9 H, C(CH_3)$_3$), 0.08 (s, 6 H, Si(CH$_3$)$_2$); δ_C (75 MHz, CDCl$_3$) 161.1 (s, J_{CF} = 246.8 Hz), 129.7 (d, J_{CF} = 8.5 Hz), 128.6 (d, J_{CF} = 3.5 Hz), 124.9 (d, J_{CF} = 3.8 Hz), 123.5 (s, J_{CF} = 12.3 Hz), 115.5 (d, J_{CF} = 22.0 Hz), 89.0 (d), 65.0 (d), 62.6 (t), 46.0 (t), 43.4 (q), 39.7 (t), 25.9 (q), 18.3 (s), -5.4 (q).

Data for **131e**: R_f 0.41 (2:1 Et$_2$O/petroleum ether 40-60°C); δ_H (300 MHz, CDCl$_3$) 7.45 (app. br t, *J* = 7.2 Hz, 1 H, Ar*H*), 7.24-7.29 (m, 1 H, Ar*H*), 7.14 (app. td, *J* = 7.6, 1.1 Hz, 1 H, Ar*H*), 7.05 (ddd, *J* = 10.3, 8.2, 1.1 Hz, 1 H, Ar*H*), 5.01 (dd, *J* = 8.4, 3.5 Hz, 1 H, SC*H*), 4.82 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.37-4.45 (m, 1 H, NC*H*), 3.75 (t, *J* = 5.1 Hz, 2 H, OCH_2CH$_2$N), 3.29-3.35 (m, 2 H, OCH$_2$CH_2N), 3.14 (ddd, *J* = 13.5, 6.5, 3.5 Hz, 1 H, SCHC*H*H), 3.72-3.83 (m, 4 H, SCHCH*H* and NCH_3), 0.90 (s, 9 H, C(CH_3)$_3$), 0.08 (s, 6 H, Si(CH$_3$)$_2$); δ_C (75 MHz, CDCl$_3$) 161.0 (s, J_{CF} = 247.7 Hz), 129.6 (d, J_{CF} = 8.5 Hz), 128.2 (d, J_{CF} = 3.5 Hz), 124.5 (d, J_{CF} = 3.5 Hz), 124.4 (s), 115.7 (d, J_{CF} = 21.7 Hz), 89.3 (d), 63.9 (d), 62.3 (t), 45.9 (t), 44.7 (q), 39.2 (t), 25.9 (q), 18.3 (s), -5.4 (q).

Data for **130e**: R_f 0.30 (2:1 Et$_2$O/petroleum ether 40-60°C); δ_H (300 MHz, CDCl$_3$) 7.07-7.46 (m, 4 H, Ar*H*), 4.75 (br t, *J* = 5.9 Hz, 1 H, N*H*), 4.32-4.42 (m, 2 H, SCHCH_2), 4.12-4.19 (m, 2 H, SC*H* and NC*H*), 3.45-3.54 (m, 2 H, OCH_2CH$_2$N), 3.11 (ddt, *J* = 12.7, 6.0, 4.3 Hz, 1 H, OCH$_2$C*H*HN), 2.84-2.95 (m, 1 H, OCH$_2$CH*H*N), 2.63 (s, 3 H, NCH_3), 0.86 (s, 9 H, C(CH_3)$_3$), 0.02 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, CDCl$_3$) 160.8 (s, J_{CF} = 248.0 Hz), 130.4 (d, J_{CF} = 8.5 Hz), 129.7 (d, J_{CF} = 3.5 Hz), 124.9 (d, J_{CF} = 3.5 Hz), 123.7 (s, J_{CF} = 11.7 Hz), 116.0 (d, J_{CF} = 22.0 Hz), 72.1 (d), 68.0 (d), 67.0 (t), 62.1 (t), 45.4 (t), 42.8 (q), 25.8 (q), 18.3 (s), -5.4 (q).

(3*S, 4*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (130f), (3*R**, 5*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]-amide (131f), and (3*S**, 5*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (132f)**



General protocol was followed using 200 mg of **123g**. Crude residue purified by flash

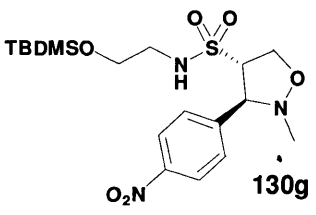
chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **130f** (171 mg, 53%), **131f** (16 mg, 5%), and **132f** (27 mg, 8%)- overall yield (66%, **130f**:**131f**:**132f** = 11:1:2).

Data for **132f**: R_f 0.33 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.34 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 5.05 (dd, *J* = 8.5, 5.8 Hz, 1 H, SC*H*), 4.87 (br t, *J* = 5.8 Hz, 1 H, N*H*), 3.80 (s, 3 H, OCH_3), 3.78 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.52 (br dd, *J* = 9.6, 7.8 Hz, 1 H, NC*H*), 3.39 (app. q, *J* = 5.3 Hz, 2 H, OCH_2CH_2N), 3.01 (ddd, *J* = 13.6, 8.5, 7.2 Hz, 1 H, SCHC*H*H), 2.88 (ddd, *J* = 13.6, 10.2, 5.8 Hz, 1 H, SCHCH*H*), 2.58 (s, 3 H, NCH_3), 0.91 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 159.8 (s), 129.2 (d), 127.9 (s), 114.3 (d), 88.9 (d), 67.8 (d), 62.6 (t), 55.3 (q), 45.9 (t), 43.1 (q), 29.7 (t), 25.9 (q), 18.3 (s), -5.4 (q).

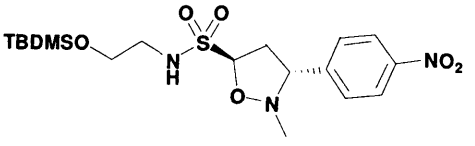
Data for **131f**: R_f 0.33 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.28 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 5.01-5.05 (m, 1 H, SC*H*), 4.77 (br t, *J* = 5.8 Hz, 1 H, N*H*), 3.98 (br s, 1 H, NC*H*), 3.80 (s, 3 H, OCH_3), 3.76 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.26-3.38 (m, 2 H, OCH_2CH_2N), 3.02 (ddd, *J* = 13.6, 6.0, 2.3 Hz, 1 H, SCHC*H*H), 2.78 (ddd, *J* = 13.6, 10.4, 8.8 Hz, 1 H, SCHCH*H*), 2.71 (s, 3 H, NCH_3), 0.91 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 159.7 (s), 129.1 (d), 127.5 (s), 114.3 (d), 89.1 (d), 67.7 (d), 62.3 (t), 55.3 (q), 45.9 (t), 43.9 (q), 29.7 (t), 25.9 (q), 18.5 (s), -5.4 (q).

Data for **130f**: R_f 0.27 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.34 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.69 (app. t, *J* = 5.9 Hz, 1 H, NH), 4.27-4.36 (m, 2 H, $SCHCH_2$), 4.01 (app. td, *J* = 7.6, 4.3 Hz, 1 H, SC*H*), 3.79 (s, 3 H, OCH_3), 3.75 (br d, *J* = 6.9 Hz, 1 H, NC*H*), 3.44-3.56 (m, 2 H, OCH_2CH_2N), 3.06 (ddt, *J* = 12.5, 6.2, 4.6 Hz, 1 H, OCH_2CHHN), 2.87 (ddt, *J* = 12.5, 5.5, 4.6 Hz, 1 H, OCH_2CHHN), 2.60 (s, 3 H, NCH_3), 0.86 (s, 9 H, $C(CH_3)_3$), 0.02 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 159.9 (s), 129.3 (d), 128.6 (s), 114.3 (d), 74.1 (d), 73.0 (d), 66.8 (t), 62.1 (t), 55.2 (q), 45.3 (t), 42.6 (q), 25.9 (q), 18.3 (s), -5.4 (q).

(3*S, 4*S**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130g), and (3*R**, 5*S**)-2-Methyl-3-(4-nitrophenyl) isoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131g)**



130g



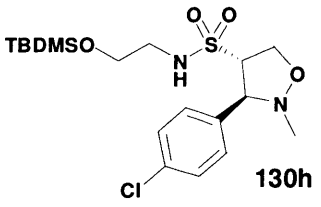
131g

General protocol was followed using 200 mg of **123g**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give two separable products **130g** (168 mg, 50%) and **131g** (31 mg, 10%)- overall yield (60%, **130g**:**131g** = 11:2).

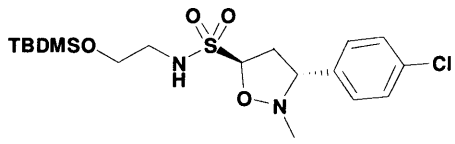
Data for **131g**: R_f 0.35 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 8.22 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.56 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 5.02 (dd, *J* = 8.5, 2.6 Hz, 1 H, SC*H*), 4.82 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.21 (br dd, *J* = 9.9, 6.3 Hz, 1 H, NC*H*), 3.76 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.30-3.37 (m, 2 H, OCH_2CH_2N), 3.13 (ddd, *J* = 13.6, 6.3, 2.6 Hz, 1 H, SCHC*H*H), 2.72-2.80 (m, 4 H, SCHCH*H* and NCH_3), 0.90 (s, 9 H, C(CH_3)$_3$), 0.09 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 147.9 (s), 144.8 (s), 128.4 (d), 124.1 (d), 88.9 (d), 69.9 (d), 62.2 (t), 45.9 (t), 44.5 (q), 29.7 (t), 25.9 (q), 18.3 (s), -5.4 (q).

Data for **130g**: R_f 0.29 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 8.20 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.68 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.92 (br t, *J* = 5.9 Hz, 1 H, N*H*), 4.35 (dd, *J* = 9.9, 4.3 Hz, 1 H, SCHC*H*H), 4.30 (dd, *J* = 9.9, 7.5 Hz, 1 H, SCHCH*H*), 4.03 (d, *J* = 6.7 Hz, 1 H, NC*H*), 3.98 (app. td, *J* = 7.0, 4.3 Hz, 1 H, SC*H*), 3.55-3.66 (m, 2 H, OCH_2CH_2N), 3.02-3.21 (m, 2 H, OCH_2CH_2N), 2.67 (s, 3 H, NCH_3), 0.85 (s, 9 H, C(CH_3)$_3$), 0.03 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 147.9 (s), 145.3 (s), 128.9 (d), 124.0 (d), 73.7 (d), 72.9 (d), 67.2 (t), 62.2 (t), 45.6 (t), 43.1 (q), 25.8 (q), 18.3 (s), -5.4 (q).

(3*S, 4*S**)-3-(4-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130h), and (3*R**, 5*S**)-3-(4-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131h)**



130h



131h

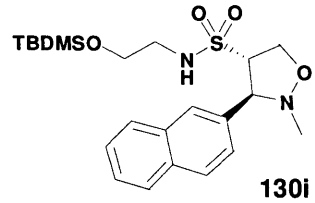
General protocol was followed using 200 mg of **123g**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the two products **130h** (172 mg, 53%) and **131h** (31 mg, 9%)- overall yield (62%, **130h**:**131h** = 11:2).

Data for **131h**: R_f 0.49 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.30-7.39 (m, 4 H, Ar*H*), 5.01 (dd, *J* = 8.6, 2.3 Hz, 1 H, SC*H*), 4.79 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.03 (br dd, *J* = 9.8, 6.4 Hz, 1 H, NC*H*), 3.76 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N),

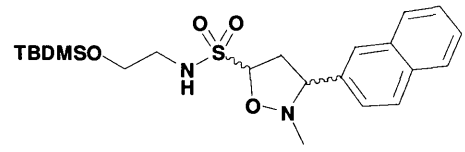
3.24-3.40 (m, 2 H, OCH_2CH_2N), 3.05 (ddd, J = 13.7, 6.4, 2.3 Hz, 1 H, SCHC*H*H), 2.74 (ddd, J = 13.7, 10.2, 8.6 Hz, 1 H, SCHCH*H*), 2.71 (s, 3 H, NCH_3), 0.90 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 135.5 (s), 134.2 (s), 129.1 (d), 128.9 (d), 88.8 (d), 67.3 (d), 62.2 (t), 45.9 (t), 44.5 (q), 29.7 (t), 25.9 (q), 18.3 (s), -5.4 (q).

Data for **130h**: R_f 0.40 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.40 (d, J = 8.5 Hz, 2 H, Ar*H*), 7.33 (d, J = 8.5 Hz, 2 H, Ar*H*), 4.78 (app. t, J = 5.9 Hz, 1 H, N*H*), 4.26-4.36 (m, 2 H, $SCHCH_2$), 3.97 (app. td, J = 7.5, 4.2 Hz, 1 H, SC*H*), 3.82 (br d, J = 7.2 Hz, 1 H, NC*H*), 3.48-3.61 (m, 2 H, OCH_2CH_2N), 3.10 (ddt, J = 12.8, 6.1, 4.4 Hz, 1 H, OCH_2CHHN), 2.95 (ddt, J = 11.9, 6.0, 4.4 Hz, 1 H, OCH_2CHHN), 2.62 (s, 3 H, NCH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 135.8 (s), 134.5 (s), 129.4 (d), 129.1 (d), 73.5 (d), 73.4 (d), 67.0 (t), 62.1 (t), 45.4 (t), 42.8 (q), 25.9 (q), 18.3 (s), -5.4 (q).

(3*S, 4*S**)-2-Methyl-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130i), (3*R**, 5*S**) and (3*S**, 5*S**)-2-Methyl-3-naphthalen-2-yl-isoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy) ethyl]amide (131/132i)**



130i



131/132i

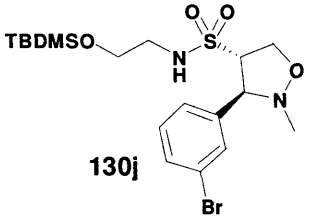
General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **131/132i** (60 mg, 18%) as a mixture, and **130i** (192 mg, 57%) as a yellow oil- overall yield (75%, **130i**:**131/132i** = 3:1, **131i** and **132i** = 3:2 major:minor).

Data for **131/132i**: R_f 0.41 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.79-7.87 (m, 4 H, Ar*H*), 7.46-7.52 (m, 3 H, Ar*H*), 5.11 (dd, J = 8.3, 5.9 Hz, 1 H_{major}, SC*H*), 5.09 (dd, J = 8.3, 2.1 Hz, 1 H_{minor}, SC*H*), 4.93 (br t, J = 5.9 Hz, 1 H_{major}, N*H*), 4.83 (br t, J = 5.9 Hz, 1 H_{minor}, N*H*), 4.22 (br s, 1 H_{major}, NC*H*), 3.76-3.82 (m, 2 H, OCH_2CH_2N), 3.71-3.75 (m, 1 H_{minor}, NC*H*), 3.41 (app. q, J = 5.6 Hz, 2 H_{major}, OCH_2CH_2N), 3.31-3.38 (m, 2 H_{minor}, OCH_2CH_2N), 3.04-3.17 (m, 1 H, SCHC*H*H), 3.02 (ddd, J = 13.7, 10.2, 5.9 Hz, 1 H_{minor}, SCHCH*H*), 2.91 (ddd, J = 13.7, 10.2, 8.3 Hz, 1 H_{major}, SCHCH*H*), 2.78 (br s, 3 H_{minor}, NCH_3), 2.65 (s, 3 H_{major}, NCH_3), 0.92 (s, 9 H, $C(CH_3)_3$), 0.11 (s, 6 H, $Si(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 135.3 (s), 134.9 (s), 134.6 (s),

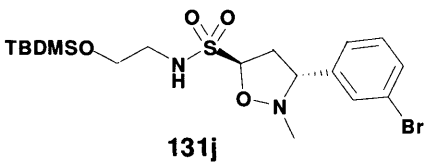
134.4 (s), 130.0 (d), 129.9 (d), 128.9 (d), 128.7 (d), 128.2 (d), 127.5 (d), 126.2 (d), 125.9 (s), 90.0 (d), 75.0 (d), 72.2 (d), 63.7 (t), 63.4 (t), 45.5 (t), 44.4 (q), 42.6 (t), 42.1 (t), 27.2 (q), 27.0 (q), 19.4 (s), -4.2 (q), 25 out of 32 expected signals observed.

Data for **130i**: R_f 0.34 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.92 (s, 1 H, Ar*H*), 7.81-7.88 (m, 3 H, Ar*H*), 7.57 (dd, *J* = 8.5, 1.6 Hz, 1 H, Ar*H*), 7.47-7.54 (m, 2 H, Ar*H*), 4.81 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.37-4.46 (m, 2 H, SCHCH_2), 4.16 (app. td, *J* = 7.5, 4.6 Hz, 1 H, SC*H*), 4.02 (br d, *J* = 7.2 Hz, 1 H, NC*H*), 3.37-3.50 (m, 2 H, OCH_2CH_2N), 3.06 (ddt, *J* = 12.9, 6.2, 4.4 Hz, 1 H, OCH$_2$C*H*HN), 2.88 (ddt, *J* = 12.2, 5.9, 4.4 Hz, 1 H, OCH$_2$CH*H*N), 2.68 (s, 3 H, NCH_3), 0.82 (s, 9 H, C(CH_3)$_3$), -0.04 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 134.4 (s), 133.4 (s), 133.3 (s), 128.9 (d), 128.0 (d), 127.9 (d), 127.8 (d), 126.5 (d), 125.1 (d), 74.6 (d), 73.2 (d), 67.1 (t), 62.0 (t), 45.4 (t), 42.9 (q), 25.8 (q), 18.2 (s), -5.4 (q).

(3*S, 4*S**)-3-(3-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130j), and (3*R**, 5*S**)-3-(3-Bromophenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131j)**



130j



131j

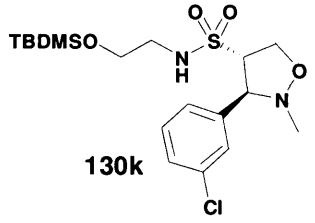
General protocol was followed using 200 mg of **123g**. Crude residue purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the two products **130j** (196 mg, 54%) and **131j** (32 mg, 9%)- overall yield (63%, **130j**:**131j** = 6:1).

Data for **131j**: R_f 0.51 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.55 (s, 1 H, Ar*H*), 7.44 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.19-7.30 (m, 2 H, Ar*H*), 5.01 (dd, *J* = 8.5, 2.5 Hz, 1 H, SC*H*), 4.79 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.03 (br dd, *J* = 9.6, 6.2 Hz, 1 H, NC*H*), 3.76 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.23-3.41 (m, 2 H, OCH$_2$CH_2N), 3.06 (ddd, *J* = 13.7, 6.2, 2.5 Hz, 1 H, SCHC*H*H), 2.70-2.80 (m, 4 H, SCHCH*H* and NCH_3), 0.91 (s, 9 H, C(CH_3)$_3$), 0.09 (s, 6 H, Si(CH$_3$)$_2$); δ_C (75 MHz, $CDCl_3$) 139.5 (s), 131.5 (d), 130.5 (d), 130.4 (d), 126.3 (d), 123.0 (s), 88.8 (d), 70.0 (d), 62.3 (t), 45.9 (t), 41.2 (q), 29.7 (t), 25.9 (q), 18.3 (s), -5.4 (q).

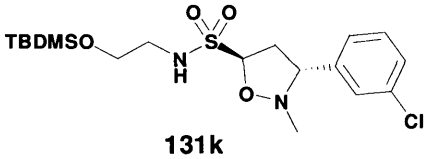
Data for **130j**: R_f 0.46 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.64 (s, 1 H, Ar*H*), 7.43-7.48 (m, 1 H, Ar*H*), 7.39 (app. dt, *J* = 7.8, 1.2 Hz, 1 H, Ar*H*), 7.20-

7.27 (m, 1 H, Ar*H*), 4.74 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.36 (dd, *J* = 9.9, 4.2 Hz, 1 H, SCHC*H*H), 4.30 (dd, *J* = 9.9, 7.9 Hz, 1 H, SCHCH*H*), 3.99 (app. td, *J* = 7.5, 4.2 Hz, 1 H, SC*H*), 3.83 (br d, *J* = 7.0 Hz, 1 H, NC*H*), 3.56-3.60 (m, 2 H, OCH_2CH_2N), 3.13 (ddt, *J* = 12.1, 5.8, 4.5 Hz, 1 H, OCH$_2$C*H*HN), 3.00 (ddt, *J* = 11.7, 5.8, 4.5 Hz, 1 H, OCH$_2$CH*H*N), 2.66 (s, 3 H, NCH_3), 0.87 (s, 9 H, C(CH_3)$_3$), 0.04 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 139.8 (s), 131.8 (d), 130.8 (d), 130.4 (d), 126.9 (d), 123.0 (s), 73.5 (d), 67.0 (t), 62.1 (t), 45.5 (t), 42.9 (q), 25.9 (q), 18.3 (s), -5.4 (q), 1 x d not observed.

(3*S, 4*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130k), and (3*R**, 5*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131k)**



130k



131k

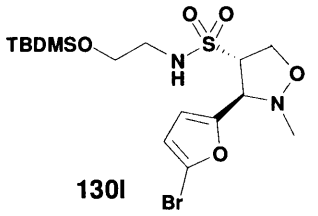
General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the two products **130k** (179 mg, 55%) and **131k** (35 mg, 11%)- overall yield (66%, **130k**:**131k** = 5:1).

Data for **131k**: R_f 0.46 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.39 (s, 1 H, Ar*H*), 7.21-7.33 (m, 3 H, Ar*H*), 5.01 (dd, *J* = 8.8, 2.9 Hz, 1 H, SC*H*), 4.79 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.04 (br dd, *J* = 10.0, 6.4 Hz, 1 H, NC*H*), 3.76 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.26-3.39 (m, 2 H, OCH$_2$CH_2N), 3.07 (ddd, *J* = 13.9, 6.4, 2.9 Hz, 1 H, SCHC*H*H), 2.76 (ddd, *J* = 13.9, 10.0, 8.8 Hz, 1 H, SCHCH*H*), 2.74 (s, 3 H, NCH_3), 0.90 (s, 9 H, C(CH_3)$_3$), 0.09 (s, 6 H, Si(CH$_3$)$_2$); δ_C (75 MHz, $CDCl_3$) 139.2 (s), 134.8 (s), 130.1 (d), 128.6 (d), 127.6 (d), 125.8 (d), 88.8 (d), 70.1 (d), 62.3 (t), 45.9 (t), 44.5 (q), 41.9 (t), 25.9 (q), 18.3 (s), -5.4 (q).

Data for **130k**: R_f 0.39 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.47 (s, 1 H, Ar*H*), 7.27-7.36 (m, 3 H, Ar*H*), 4.86 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.35 (dd, *J* = 9.9, 4.0 Hz, 1 H, SCHC*H*H), 4.29 (dd, *J* = 9.9, 7.8 Hz, 1 H, SCHCH*H*), 3.99 (app. td, *J* = 7.5, 4.0 Hz, 1 H, SC*H*), 3.83 (br d, *J* = 7.0 Hz, 1 H, NC*H*), 3.50-3.61 (m, 2 H, OCH_2CH_2N), 3.12 (ddt, *J* = 12.2, 5.9, 4.8 Hz, 1 H, OCH$_2$C*H*HN), 2.98 (ddt, *J* = 11.7, 5.9, 4.5 Hz, 1 H, OCH$_2$CH*H*N), 2.64 (s, 3 H, NCH_3), 0.86 (s, 9 H, C(CH_3)$_3$), 0.03 (s, 6

H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 139.6 (s), 134.8 (s), 130.2 (d), 128.8 (d), 128.0 (d), 126.5 (d), 73.5 (d), 73.4 (d), 67.0 (t), 62.1 (t), 45.5 (t), 42.9 (q), 25.9 (q), 18.3 (s), -5.4 (q).

(3*S, 4*S**)-3-(5-Bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (130l)**

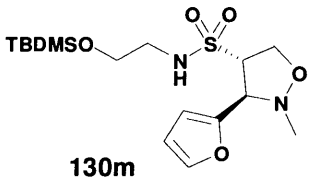


130l

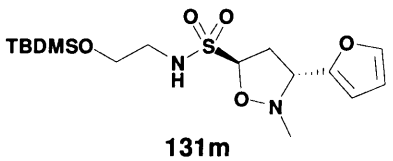
General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **130l** as a brown oil (41 mg, 12%).

Data for **130l**: R_f 0.31 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 6.41 (d, *J* = 3.2 Hz, 1 H, BrCC*H*), 6.30 (d, *J* = 3.2 Hz, 1 H, BrCCHC*H*), 4.68 (br s, 1 H, N*H*), 4.29-4.38 (m, 3 H, SCHCH_2 and SC*H*), 3.90 (br s, 1 H, NC*H*), 3.56-3.68 (m, 2 H, OCH_2CH_2N), 3.18 (ddt, *J* = 12.9, 5.9, 4.3 Hz, 1 H, OCH$_2$C*H*HN), 3.07 (ddt, *J* = 12.2, 5.9, 4.3 Hz, 1 H, OCH$_2$CH*H*N), 2.71 (br s, 3 H, NCH_3), 0.88 (s, 9 H, C(CH_3)$_3$), 0.05 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 150.6 (s), 123.8 (s), 112.9 (d), 112.5 (d), 69.1 (d), 67.9 (d), 66.8 (t), 62.1 (t), 45.5 (t), 42.8 (q), 25.9 (q), 18.3 (s), -5.4 (q).

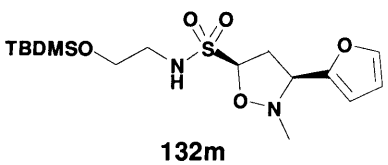
(3*S, 4*S**)-3-Furan-2-yl-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130m), (3*R**, 5*S**)-3-Furan-2-yl-2-methyl isoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131m), and (3*S**, 5*S**)-3-Furan-2-yl-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (131/132m)**



130m



131m



132m

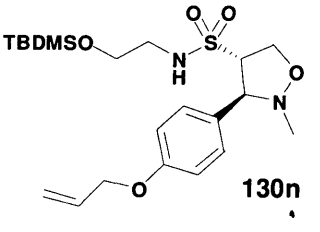
General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give three separable products **130m** (99 mg, 34%), **131m** (71 mg, 24%), and **132m** (38 mg, 13%)-overall yield (71%, **130m**:**131m**:**132m** = 5:4:2).

Data for **132m**: R_f 0.38 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.40 (dd, *J* = 1.9, 0.8 Hz, 1 H, OC*H*CHCH), 6.38 (d, *J* = 3.2 Hz, 1 H, OCHCHC*H*), 6.35 (dd, *J* = 3.2, 1.9 Hz, 1 H, OCHC*H*CH), 5.07 (dd, *J* = 8.6, 5.7 Hz, 1 H, SC*H*), 4.87 (app. t, *J* = 5.8 Hz, 1 H, N*H*), 3.74 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.69 (br dd, *J* = 10.0, 7.6 Hz, 1 H, NC*H*), 3.37 (app. q, *J* = 5.5 Hz, 2 H, OCH_2CH_2N), 3.13 (ddd, *J* = 13.7, 10.0, 5.7 Hz, 1 H, SCHC*H*H), 2.96 (ddd, *J* = 13.7, 8.6, 7.6 Hz, 1 H, SCHCH*H*), 2.71 (s, 3 H, NCH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 148.6 (s), 143.2 (d), 110.6 (d), 109.3 (d), 89.2 (d), 66.2 (d), 62.6 (t), 46.0 (t), 43.6 (q), 36.8 (t), 25.9 (q), 18.3 (s), -5.4 (q).

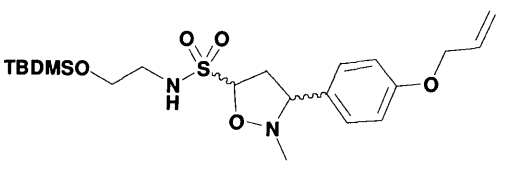
Data for **131m**: R_f 0.33 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.40 (dd, *J* = 1.6, 0.8 Hz, 1 H, OC*H*CHCH), 6.34 (dd, *J* = 3.2, 1.6 Hz, 1 H, OCHC*H*CH), 6.31 (d, *J* = 3.2 Hz, 1 H, OCC*H*CH), 5.06 (br dd, *J* = 8.5, 5.8 Hz, 1 H, SC*H*), 4.82 (br t, *J* = 5.5 Hz, 1 H, N*H*), 4.15 (app. br s, 1 H, NC*H*), 3.73 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.24-3.37 (m, 2 H, OCH_2CH_2N), 2.93-3.12 (m, 2 H, $SCHCH_2$), 2.81 (br s, 3 H, NCH_3), 0.89 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 149.1 (s), 143.1 (d), 110.4 (d), 109.2 (d), 89.1 (d), 67.4 (d), 62.3 (t), 45.9 (t), 44.9 (q), 36.8 (t), 25.9 (q), 18.3 (s), -5.4 (q).

Data for **130m**: R_f 0.28 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.42 (dd, *J* = 1.8, 0.8 Hz, 1 H, OC*H*CHCH), 6.41 (d, *J* = 3.2 Hz, 1 H, OCHCHC*H*), 6.36 (dd, *J* = 3.2, 1.8 Hz, 1 H, OCHC*H*CH), 4.78 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.30-4.37 (m, 3 H, $SCHCH_2$ and SC*H*), 3.92 (app. br s, 1 H, NC*H*), 3.49-3.63 (m, 2 H, OCH_2CH_2N), 3.11 (ddt, *J* = 12.3, 6.3, 4.4 Hz, 1 H, OCH_2CHHN), 2.90-2.99 (m, 1 H, OCH_2CHHN), 2.69 (br s, 3 H, NCH_3), 0.86 (s, 9 H, $C(CH_3)_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 148.5 (s), 143.4 (d), 110.8 (d), 110.1 (d), 69.0 (d), 66.7 (t), 62.1 (t), 45.3 (t), 43.9 (q), 25.9 (q), 18.3 (s), -5.4 (q).

(3*S, 4*S**)-3-(4-Allyloxyphenyl)-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130n), (3*R**, 5*S**) and (3*S**, 5*S**)-3-(4-Allyloxy phenyl)-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy) ethyl]amide (131/132n)**



130n



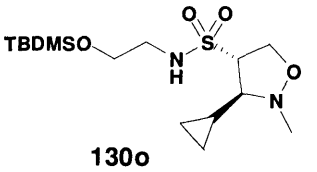
131/132n

General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give **131/132n** (90 mg, 26%) as a mixture, and **130n** (109 mg, 32%) as a yellow oil- overall yield (58%, **130n**:**131/132n** = 6:5, **131n** and **132n** = 3:2 major:minor).

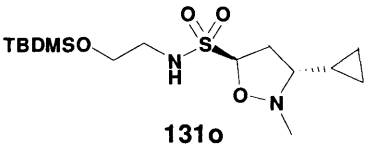
Data for **131/132n**: R_f 0.40 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.32 (d, *J* = 8.8 Hz, 2 H_{major}, Ar*H*), 7.07 (d, *J* = 8.8 Hz, 2 H_{minor}, Ar*H*), 6.87-6.91 (m, 2 H, Ar*H*), 5.97-6.11 (m, 1 H, C*H*=CH_2), 5.40 (app. dq, *J* = 17.4, 1.6 Hz, 1 H, CH=C*H*H), 5.28 (app. dq, *J* = 10.4, 1.6 Hz, 1 H, CH=CH*H*), 5.01-5.07 (m, 1 H, SC*H*), 4.90 (app. t, *J* = 5.9 Hz, 1 H_{minor}, N*H*), 4.82 (app. t, *J* = 5.9 Hz, 1 H_{major}, N*H*), 4.50-4.55 (m, 2 H, OCH_2CH=), 4.39 (dd, *J* = 9.9, 7.8 Hz, 1 H_{minor}, NC*H*), 4.00 (br dd, *J* = 9.9, 4.0 Hz, 1 H_{major}, NC*H*), 3.76 (app. q, *J* = 5.4 Hz, 2 H, OCH_2CH_2N), 3.28-3.44 (m, 2 H, OCH_2CH_2N), 2.74-3.06 (m, 2 H, SCHCH_2), 2.70 (br s, 3 H_{minor}, NCH_3), 2.57 (s, 3 H_{major}, NCH_3), 0.90 (s, 9 H, C(CH_3)$_3$), 0.08 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 158.8 (s), 158.7 (s), 133.2 (d), 133.1 (d), 131.9 (d), 128.8 (d), 128.7 (d), 128.3 (s), 117.8 (t), 115.1 (d), 115.0 (d), 88.8 (d), 88.7 (d), 74.6 (d), 68.8 (t), 62.6 (t), 62.3 (t), 45.9 (t), 43.1 (q), 42.8 (q), 40.9 (t), 40.6 (t), 25.9 (q), 18.3 (s), -5.4 (q), 25 out of 32 expected signals observed.

Data for **130n**: R_f 0.29 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 7.34 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.90 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.03 (ddt, *J* = 17.4, 10.7, 5.3 Hz, 1 H C*H*=CH_2), 5.40 (app. dq, *J* = 17.4, 1.6 Hz, 1 H, CH=C*H*H), 5.28 (app. dq, *J* = 10.7, 1.6 Hz, 1 H, CH=CH*H*), 4.68 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.52 (app. dt, *J* = 5.3, 1.6 Hz, 2 H, OCH_2CH=), 4.29-4.38 (m, 2 H, SCHCH_2), 4.01 (app. td, *J* = 7.8, 4.6 Hz, 1 H, SC*H*), 3.76 (br d, *J* = 7.0 Hz, 1 H, NC*H*), 3.43-3.57 (m, 2 H, OCH_2CH_2N), 3.07 (ddt, *J* = 12.6, 5.9, 4.3 Hz, 1 H, OCH_2C*H*HN), 2.87 (ddt, *J* = 12.1, 5.9, 4.3 Hz, 1 H, OCH_2CH*H*N), 2.61 (s, 3 H, NCH_3), 0.85 (s, 9 H, C(CH_3)$_3$), 0.02 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 158.9 (s), 133.0 (d), 129.3 (d), 128.8 (s), 117.8 (t), 115.1 (d), 74.1 (d), 73.0 (d), 68.8 (t), 66.8 (t), 62.1 (t), 45.3 (t), 42.6 (q), 25.9 (q), 18.3 (s), -5.4 (q).

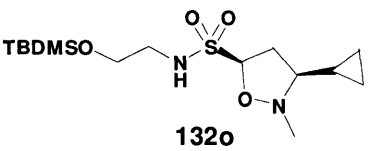
(3*S, 4*S**)-3-Cyclopropyl-2-methylisoxazolidine-4-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (130o), (3*R**, 5*S**)-3-Cyclopropyl-2-methyl isoxazolidine-5-sulfonic acid [2-(*tert*-butyldimethylsilanyloxy)ethyl]amide (131o), and (3*S**, 5*S**)-3-Cyclopropyl-2-methylisoxazolidine-5-sulfonic acid [2-(*tert*-butyl dimethylsilanyloxy)ethyl]amide (132o)**



130o



131o



132o

General protocol was followed using 200 mg of **123g**. Crude residue was purified by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) to give the three separable products **130o** (37 mg, 14%), **131o** (80 mg, 29%), and **132o** (57 mg, 21%)-overall yield (64%, **130o**:**131o**:**132o** = 6:13:9).

Data for **132o**: R_f 0.26 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 4.89 (dd, *J* = 8.4, 6.0 Hz, 1 H, SC*H*), 4.80 (br t, *J* = 5.8 Hz, 1 H, N*H*), 3.73 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.33 (app. q, *J* = 5.4 Hz, 2 H, OCH_2CH_2N), 2.63-2.82 (m, 5 H, SCHCH_2 and NCH_3), 1.84 (br dd, *J* = 16.6, 8.6 Hz, 1 H, NC*H*), 0.89 (s, 9 H, C(CH_3)$_3$), 0.82-0.89 (m, 1 H, CH_2CHCH_2), 0.51-0.63 (m, 2 H, CH_2CH_2), 0.16-0.28 (m, 2 H, CH_2CH_2), 0.07 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 88.5 (d), 74.0 (d), 62.5 (t), 45.9 (t), 44.2 (q), 38.0 (t), 25.9 (q), 18.3 (s), 11.2 (d), 4.2 (t), 0.9 (t), -5.4 (q).

Data for **131o**: R_f 0.17 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 4.88 (app. br d, *J* = 7.2 Hz, 1 H, SC*H*), 4.76 (br t, *J* = 5.5 Hz, 1 H, N*H*), 3.71 (t, *J* = 5.2 Hz, 2 H, OCH_2CH_2N), 3.19-3.33 (m, 2 H, OCH_2CH_2N), 2.78-2.86 (m, 4 H, NCH_3 and SCHC*H*H), 2.57-2.67 (m, 1 H, SCHCH*H*), 2.23-2.32 (m, 1 H, NC*H*), 0.88 (s, 9 H, C(CH_3)$_3$), 0.67-0.79 (m, 1 H, CH_2CHCH_2), 0.50-0.62 (m, 2 H, CH_2CH_2), 0.19-0.30 (m, 2 H, CH_2CH_2), 0.05 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 88.5 (d), 71.6 (d), 62.3 (t), 45.8 (t), 45.2 (q), 38.6 (t), 25.9 (q), 18.2 (s), 11.5 (d), 4.0 (t), 1.2 (t), -5.4 (q).

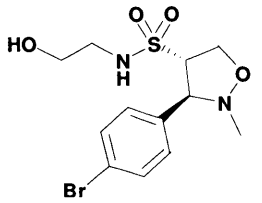
Data for **130o**: R_f 0.13 (2:1 Et_2O/petroleum ether 40-60°C); δ_H (300 MHz, $CDCl_3$) 4.70 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.21 (dd, *J* = 9.9, 4.2 Hz, 1 H, SCHC*H*H), 4.13 (dd, *J* = 9.9, 8.0 Hz, 1 H, SCHCH*H*), 3.90-3.94 (m, 1 H, SC*H*), 3.73 (t, *J* = 5.1 Hz, 2 H, OCH_2CH_2N), 3.25 (app. q, *J* = 5.6 Hz, 2 H, OCH_2CH_2N), 2.79 (s, 3 H, NCH_3), 2.34-2.41 (m, 1 H, NC*H*), 0.89-1.01 (m, 1 H, CH_2CHCH_2), 0.89 (s, 9 H, C(CH_3)$_3$), 0.54-0.68 (m, 3 H, CH(CH_2)$_2$), 0.33-0.40 (m, 1 H, CH(CH_2)$_2$), 0.06 (s, 6 H, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 74.1 (d), 71.7 (d), 66.7 (t), 62.3 (t), 45.7 (t), 44.5 (q), 25.9 (q), 18.3 (s), 13.9 (d), 4.8 (t), 2.0 (t), -5.4 (q).

4.6. Procedures for TBAF deprotection of 130a-n

General protocol [187]

A solution of **130a-n** (1 eq.) in THF (5 mL) was treated with TBAF (1 M solution in THF, 1.5 eq.) while stirring at 0 °C. The suspension was allowed to stir for a further 15 minutes and then diluted with DCM (25 mL). The organic layer was washed with sat. aq. NH_4Cl (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography to give products **133a-n** as appropriate.

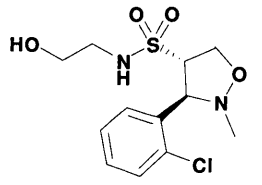
(3*S, 4*S**)-3-(4-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133a)**



General protocol was followed using 210 mg of **130a**. The crude residue was purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/EtOAc) to give **133a** (138 mg, 86%) as a yellow solid.

R_f 0.24 (4:1 EtOAc/petroleum ether 40-60°C); mp 66-68 °C; υ_{max} (neat)/cm^{-1} 3457, 3220, 2878, 1488, 1456, 1320, 1274, 1142, 1101, 1040, 947, 836, 751; δ_H (300 MHz, $CDCl_3$) 7.49 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.34 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 5.73 (br t, *J* = 6.0 Hz, 1 H, N*H*), 4.34 (dd, *J* = 10.0, 4.0 Hz, 1 H, SCHC*H*H), 4.29 (dd, *J* = 10.0, 7.6 Hz, 1 H, SCHCH*H*), 4.00 (app. td, *J* = 7.2, 4.0 Hz, 1 H, SC*H*), 3.80 (br d, *J* = 6.0 Hz, 1 H, NC*H*), 3.51-3.62 (m, 2 H, OCH_2CH_2N), 2.95-3.17 (m, 3 H, OCH_2CH_2N and O*H*), 2.61 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 136.1 (s), 132.1 (d), 129.9 (d), 122.8 (s), 73.5 (d), 73.2 (d), 67.0 (t), 61.6 (t), 45.5 (t), 42.7 (q); *m/z* (EI) 366 (M^+, ^{81}Br, 12), 364 (M^+, ^{79}Br, 12), 240 (100), 160 (82), 116 (87), 102 (20); HRMS (EI): calcd for $C_{12}H_{17}{}^{79}BrN_2O_4S$ (M^+) 364.0092, found 364.0080.

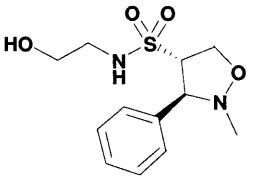
(3*S, 4*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133b)**



General protocol was followed using 134 mg of **130b**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133b** (90 mg, 91%) as a light brown oil.

R_f 0.28 (9:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 3476, 3309, 2879, 1478, 1438, 1314, 1135, 1038, 939, 749; δ_H (300 MHz, $CDCl_3$) 7.53 (dd, *J* = 7.6, 1.6 Hz, 1 H, Ar*H*), 7.41 (dd, *J* = 7.4, 1.9 Hz, 1 H, Ar*H*), 7.24-7.35 (m, 2 H, Ar*H*), 5.31 (br t, *J* = 6.0 Hz, 1 H, N*H*), 4.39-4.48 (m, 3 H, NC*H* and SCHCH_2), 4.18 (app. td, *J* = 7.0, 5.5 Hz, 1 H, SC*H*), 3.43-3.55 (m, 2 H, OCH_2CH_2N), 3.12 (ddt, *J* = 12.1, 6.0, 4.3 Hz, 1 H, OCH_2C*H*HN), 2.89-2.99 (m, 1 H, OCH_2CH*H*N), 2.62 (s, 3 H, NCH_3), 2.53 (br s, 1 H, O*H*); δ_C (75 MHz, $CDCl_3$) 134.4 (s), 134.1 (s), 130.1 (d), 130.0 (d), 129.9 (d), 127.7 (d), 72.6 (d), 70.1 (d), 67.2 (t), 61.7 (t), 45.5 (t), 42.6 (q); *m/z* (EI) 322 (M^+, ^{37}Cl, 6), 320 (M^+, ^{35}Cl, 16), 194 (100), 151 (25), 134 (30); HRMS (EI): calcd for $C_{12}H_{17}{}^{35}ClN_2O_4S$ (M^+) 320.0598, found 320.0598.

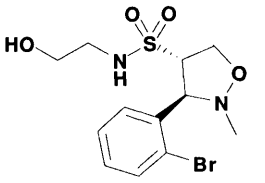
(3*S, 4*S**)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid (2-hydroxyethyl)amide (133c)**



General protocol was followed using 122 mg of **130c**. The crude residue was purified by flash chromatography (starting 4:1 petroleum ether 40-60°C/EtOAc) to give **133c** (79 mg, 92%) as a brown oil.

R_f 0.15 (2:1 EtOAc/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3480, 3279, 2921, 1456, 1311, 1144, 1039, 934, 887; δ_H (300 MHz, $CDCl_3$) 7.33-7.47 (m, 5 H, Ar*H*), 5.53 (t, *J* = 6.2 Hz, 1 H, N*H*), 4.38 (dd, *J* = 9.9, 4.3 Hz, 1 H, SCHC*H*H), 4.43 (dd, *J* = 9.9, 7.8 Hz, 1 H, SCHCH*H*), 4.08 (app. td, *J* = 7.4, 4.3 Hz, 1 H, SC*H*), 3.82 (br d, *J* = 6.4 Hz, 1 H, NC*H*), 3.43-3.56 (m, 2 H, OCH_2CH_2N), 3.08 (ddt, *J* = 12.6, 6.2, 3.9 Hz, 1 H, OCH_2C*H*HN), 2.84-2.96 (m, 1 H, OCH_2CH*H*N), 2.69 (br s, 1 H, O*H*), 2.62 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 136.8 (s), 129.0 (d), 128.8 (d), 128.3 (d), 74.4 (d), 73.1 (d), 67.0 (t), 61.6 (t), 45.4 (t), 42.7 (q); *m/z* (EI) 286 (M^+, 11), 160 (100), 117 (48); HRMS (EI): calcd for $C_{12}H_{18}N_2O_4S$ (M^+) 286.0987, found 286.0981.

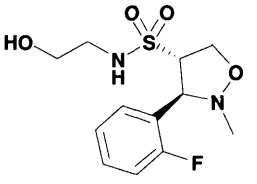
(3*S, 4*S**)-3-(2-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)-amide (133d)**



General protocol was followed using 100 mg of **130d**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133d** (65 mg, 85%) as a light brown solid.

R_f 0.26 (9:1 $CHCl_3$/MeOH); mp 98-100 °C; υ_{max} (neat)/cm^{-1} 3403, 3308, 2876, 1473, 1431, 1301, 1132, 1038, 938, 826, 748; δ_H (300 MHz, $CDCl_3$) 7.60 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.53 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.38 (app. dt, *J* = 7.5, 1.3 Hz, 1 H, Ar*H*), 7.21 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1 H, Ar*H*), 5.16 (br t, *J* = 6.1 Hz, 1 H, N*H*), 4.50 (br d, *J* = 5.6 Hz, 1 H, NC*H*), 4.37-4.46 (m, 2 H, SCHCH_2), 4.15 (app. td, *J* = 7.2, 5.2 Hz, 1 H, SC*H*), 3.42-3.55 (m, 2 H, OC$H_2$$CH_2$N), 3.12 (ddt, *J* = 12.2, 6.1, 4.2 Hz, 1 H, OCH_2C*H*HN), 2.87-2.97 (m, 1 H, OCH_2CH*H*N), 2.64 (s, 3 H, NCH_3), 2.28 (br s, 1 H, O*H*); δ_C (75 MHz, $CDCl_3$) 135.8 (s), 133.3 (d), 130.3 (d), 130.1 (d), 128.4 (d), 124.8 (s), 72.9 (d), 72.3 (d), 67.2 (t), 61.7 (t), 45.4 (t), 42.5 (q); *m/z* (EI) 366 (M^+, ^{81}Br, 12), 364 (M^+, ^{79}Br, 12), 240 (94), 116 (100), 102 (18); HRMS (EI): calcd for $C_{12}H_{17}{}^{79}BrN_2O_4S$ (M^+) 364.0092, found 364.0100.

(3*S, 4*S**)-3-(2-Fluorophenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133e)**

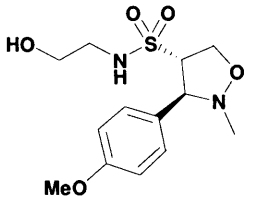


General protocol was followed using 108 mg of **130e**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133e** (62 mg, 78%) as a yellow solid.

R_f 0.36 (9:1 $CHCl_3$/MeOH); mp 108-111 °C; υ_{max} (neat)/cm^{-1} 3247, 2975, 2891, 1586, 1446, 1317, 1233, 1143, 1038, 934, 893, 773; δ_H (300 MHz, $CDCl_3$) 7.46 (t, *J* = 7.3 Hz, 1 H, Ar*H*), 7.29-7.37 (m, 1 H, Ar*H*), 7.18 (app. dt, *J* = 7.4, 1.1 Hz, 1 H, Ar*H*), 7.09 (ddd, *J* = 10.4, 8.2, 1.1 Hz, 1 H, Ar*H*), 5.59 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.32-4.42 (m, 2 H, SCHCH_2), 4.21 (app. td, *J* = 7.0, 4.8 Hz, 1 H, SC*H*), 4.11 (br s, 1 H, NC*H*), 3.46-3.58 (m, 2 H, OC$H_2$$CH_2$N), 3.08-3.18 (m, 1 H, OCH_2C*H*HN), 2.95-3.05 (m, 1 H,

OCH_2CHHN), 2.70 (br s, 1 H, O*H*), 2.62 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 160.9 (s, J_{CF} = 248.3 Hz), 130.6 (d, J_{CF} = 8.8 Hz), 130.0 (d, J_{CF} = 3.8 Hz), 124.9 (d, J_{CF} = 3.8 Hz), 123.5 (s, J_{CF} = 11.7 Hz), 116.1 (d, J_{CF} = 22.0 Hz), 71.9 (d), 68.1 (d), 67.1 (t), 61.7 (t), 45.5 (t), 42.8 (q); *m/z* (EI) 304 (M^+, 8), 228 (20), 178 (100), 135 (39), 109 (27); HRMS (EI): calcd for $C_{12}H_{17}FN_2O_4S$ (M^+) 304.0893, found 304.0886.

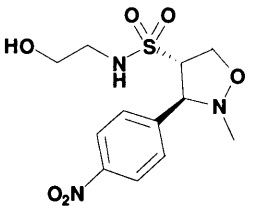
(3*S, 4*S**)-3-(4-Methoxyphenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133f)**



General protocol was followed using 138 mg of **130f**. The crude residue was purified by flash chromatography (starting 4:1 petroleum ether 40-60°C/EtOAc) to give **133f** (84 mg, 83%) as a yellow solid.

R_f 0.18 (4:1 EtOAc/petroleum ether 40-60°C); mp 105-108 °C; υ_{max} (neat)/cm^{-1} 3503, 3152, 2966, 1613, 1516, 1456, 1319, 1253, 1148, 1040, 839; δ_H (300 MHz, $CDCl_3$) 7.36 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 5.50 (br t, *J* = 6.0 Hz, 1 H, N*H*), 4.36 (dd, *J* = 9.9, 4.3 Hz, 1 H, SCHC*H*H), 4.31 (dd, *J* = 9.9, 7.4 Hz, 1 H, SCHCH*H*), 4.04 (app. td, *J* = 7.4, 4.3 Hz, 1 H, SC*H*), 3.75-3.81 (m, 4 H, OCH_3 and NC*H*), 3.45-3.58 (m, 2 H, OCH_2CH_2N), 3.03-3.13 (m, 1 H, OCH_2CHHN), 2.87-2.97 (m, 1 H, OCH_2CHHN), 2.69 (br s, 1 H, O*H*), 2.60 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 159.9 (s), 129.4 (d), 128.4 (s), 114.4 (d), 74.0 (d), 72.9 (d), 66.9 (t), 61.6 (t), 55.3 (q), 45.4 (t), 42.6 (q); *m/z* (EI) 316 (M^+, 39), 190 (100), 165 (53), 147 (47); HRMS (EI): calcd for $C_{13}H_{20}N_2O_5S$ (M^+) 316.1093, found 316.1098.

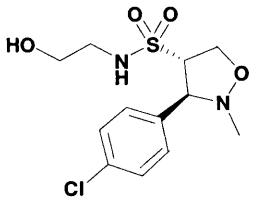
(3*S, 4*S**)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133g)**



General protocol was followed using 175 mg of **130g**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133g** (41 mg, 50%) as a yellow solid.

R_f 0.26 (9:1 $CHCl_3$/MeOH); mp 122-125 °C; υ_{max} (neat)/cm^{-1} 3497, 2926, 1597, 1508, 1403, 1349, 1307, 1270, 1071, 959; δ_H (300 MHz, CD_3OD) 8.24 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.75 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 4.23-4.36 (m, 3 H, SCHCH_2 and SC*H*), 4.03 (br d, *J* = 6.4 Hz, 1 H, NC*H*), 3.47 (t, *J* = 5.9 Hz, 2 H, OCH_2CH_2N), 2.92-3.13 (m, 2 H, OCH_2CH_2N), 2.63 (s, 3 H, NCH_3); δ_C (75 MHz, CD_3OD) 149.4 (s), 146.9 (s), 130.7 (d), 124.7 (d), 74.5 (d), 74.3 (d), 68.4 (t), 62.3 (t), 46.3 (t), 43.2 (q); *m/z* (EI) 331 (M^+, 10), 205 (100); HRMS (EI): calcd for $C_{12}H_{17}N_3O_6S$ (M^+) 331.0838, found 331.0829.

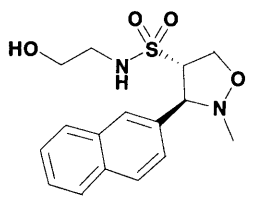
(3*S, 4*S**)-3-(4-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133h)**



General protocol was followed using 179 mg of **130h**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133h** (112 mg, 85%) as a light yellow solid.

R_f 0.38 (9:1 $CHCl_3$/MeOH); mp 97-100 °C; υ_{max} (neat)/cm^{-1} 3453, 3231, 2874, 1486, 1433, 1306, 1134, 1039, 935, 841, 816; δ_H (300 MHz, $CDCl_3$) 7.41 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.33 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.74 (br s, 1 H, N*H*), 4.35 (dd, *J* = 10.0, 4.0 Hz, 1 H, SCHC*H*H), 4.29 (dd, *J* = 10.0, 7.8 Hz, 1 H, SCHCH*H*), 4.00 (app. td, *J* = 7.8, 4.0 Hz, 1 H, SC*H*), 3.82 (br d, *J* = 6.6 Hz, 1 H, NC*H*), 3.50-3.62 (m, 2 H, OCH_2CH_2N), 2.96-3.16 (m, 3 H, O*H* and OCH_2CH_2N), 2.61 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 135.6 (s), 134.6 (s), 129.6 (d), 129.2 (d), 73.4 (d), 73.3 (d), 67.0 (t), 61.6 (t), 45.5 (t), 42.7 (q); *m/z* (EI) 322 (M^+, ^{37}Cl, 7), 320 (M^+, ^{35}Cl, 17), 194 (100); HRMS (EI): calcd for $C_{12}H_{17}{}^{35}ClN_2O_4S$ (M^+) 320.0598, found 320.0593.

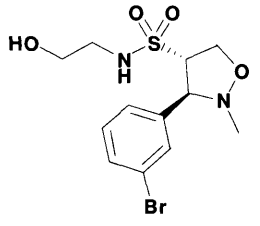
(3*S, 4*S**)-2-Methyl-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133i)**



General protocol was followed using 181 mg of **130i**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133i** (130 mg, 97%) as a light brown oil.

R_f 0.33 (9:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 3457, 3284, 2923, 1509, 1435, 1314, 1144, 1040, 955; δ_H (300 MHz, $CDCl_3$) 7.93 (s, 1 H, Ar*H*), 7.81-7.87 (m, 3 H, Ar*H*), 7.57 (dd, *J* = 8.6, 1.5 Hz, 1 H, Ar*H*), 7.49 (app. dt, *J* = 9.5, 3.6 Hz, 2 H, Ar*H*), 5.69 (br t, *J* = 5.8 Hz, 1 H, N*H*), 4.43 (dd, *J* = 10.0, 4.0 Hz, 1 H, SCHC*H*H), 4.38 (dd, *J* = 10.0, 7.6 Hz, 1 H, SCHCH*H*), 4.17 (app. td, *J* = 7.6, 4.0 Hz, 1 H, SC*H*), 4.02 (br d, *J* = 6.6 Hz, 1 H, NC*H*), 3.36-3.49 (m, 2 H, OCH_2CH_2N), 2.82-3.08 (m, 3 H, OCH_2CH_2N and O*H*), 2.65 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 134.2 (s), 133.4 (s), 133.2 (s), 128.9 (d), 128.0 (2 x d), 127.8 (d), 126.6 (2 x d), 125.1 (d), 74.5 (d), 73.1 (d), 67.1 (t), 61.5 (t), 45.4 (t), 42.8 (q); *m/z* (EI) 336 (M^+, 24), 210 (100), 184 (23), 167 (58), 152 (33), 127 (20); HRMS (EI): calcd for $C_{16}H_{20}N_2O_4S$ (M^+) 336.1144, found 336.1138.

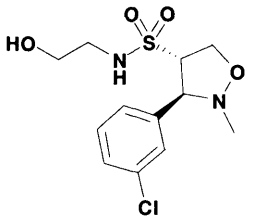
(3*S, 4*S**)-3-(3-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133j)**



General protocol was followed using 198 mg of **130j**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133j** (123 mg, 82%) as a light brown oil.

R_f 0.51 (4:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 3468, 3279, 2924, 1475, 1430, 1317, 1144, 1039, 936, 882, 787; δ_H (300 MHz, $CDCl_3$) 7.63 (s, 1 H, Ar*H*), 7.43-7.48 (m, 1 H, Ar*H*), 7.40 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.24 (app. t, *J* = 7.8 Hz, 1 H, Ar*H*), 5.67 (br t, *J* = 5.9 Hz, 1 H, N*H*), 4.35 (dd, *J* = 10.0, 4.0 Hz, 1 H, SCHC*H*H), 4.30 (dd, *J* = 10.0, 7.5 Hz, 1 H, SCHCH*H*), 4.02 (app. td, *J* = 7.5, 4.0 Hz, 1 H, SC*H*), 3.82 (br d, *J* = 6.4 Hz, 1 H, NC*H*), 3.52-3.64 (m, 2 H, OCH_2CH_2N), 3.10-3.20 (m, 1 H, OCH_2C*H*HN), 2.97-3.07 (m, 1 H, OCH_2CH*H*N), 2.92 (br s, 1 H, O*H*), 2.63 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 139.6 (s), 131.9 (d), 131.0 (d), 130.5 (d), 127.0 (d), 122.9 (s), 73.3 (d), 67.1 (t), 61.7 (t), 45.5 (t), 42.8 (q) 1 x d not observed; *m/z* (EI) 366 (M^+, ^{81}Br, 5), 364 (M^+, ^{79}Br, 5), 240 (32), 120 (70); HRMS (EI): calcd for $C_{12}H_{17}{}^{79}BrN_2O_4S$ (M^+) 364.0092, found 364.0083.

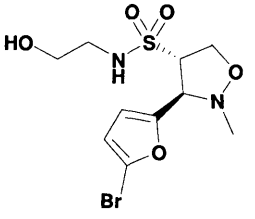
(3*S, 4*S**)-3-(3-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133k)**



General protocol was followed using 159 mg of **130k**. The crude residue was purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/EtOAc) to give **133k** (83 mg, 70%) as a brown oil.

R_f 0.28 (4:1 EtOAc/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3480, 3283, 2877, 1575, 1433, 1318, 1144, 1040, 935, 882, 788; δ_H (300 MHz, $CDCl_3$) 7.48 (s, 1 H, Ar*H*), 7.29-7.37 (m, 3 H, Ar*H*), 5.69 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.36 (dd, *J* = 9.8, 4.0 Hz, 1 H, SCHC*H*H), 4.30 (dd, *J* = 9.8, 7.7 Hz, 1 H, SCHCH*H*), 4.02 (app. td, *J* = 7.7, 4.0 Hz, 1 H, SC*H*), 3.83 (br d, *J* = 6.7 Hz, 1 H, NC*H*), 3.52-3.65 (m, 2 H, OCH_2CH_2N), 3.15 (ddt, *J* = 11.9, 6.2, 4.0 Hz, 1 H, OCH$_2$C*H*HN), 3.03 (ddt, *J* = 11.9, 5.6, 4.0 Hz, 1 H, OCH$_2$CH*H*N), 2.89 (br s, 1 H, O*H*), 2.63 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 139.3 (s), 134.8 (s), 130.3 (d), 128.9 (d), 128.1 (d), 126.5 (d), 73.5 (d), 73.3 (d), 67.1 (t), 61.7 (t), 45.5 (t), 42.8 (q); *m/z* (EI) 322 (M^+, ^{37}Cl, 5), 320 (M^+, ^{35}Cl, 13), 194 (100), 151 (23); HRMS (EI): calcd for $C_{12}H_{17}{}^{35}ClN_2O_4S$ (M^+) 320.0598, found 320.0598.

(3*S, 4*S**)-3-(5-Bromofuran-2-yl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133l)**

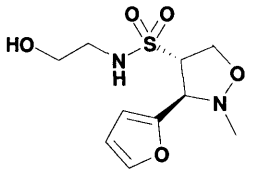


General protocol was followed using 29 mg of **130l**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133l** (15 mg, 70%) as a brown oil.

R_f 0.32 (9:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 3489, 3281, 2924, 1503, 1457, 1316, 1148, 1041, 955, 798; δ_H (300 MHz, $CDCl_3$) 6.43 (d, *J* = 3.3 Hz, 1 H, BrCC*H*), 6.31 (d, *J* = 3.3 Hz, 1 H, OCC*H*), 5.19 (br t, *J* = 6.0 Hz, 1 H, N*H*), 4.31-4.38 (m, 3 H, SCHCH_2 and NC*H*), 3.90 (br s, 1 H, SC*H*), 3.60-3.72 (m, 2 H, OCH_2CH_2N), 3.09-3.29 (m, 2 H, OCH$_2$CH_2), 2.71 (s, 3 H, NCH_3), 2.12 (br s, 1 H, O*H*); δ_C (75 MHz, $CDCl_3$) 150.8 (s),

123.9 (s), 112.9 (d), 112.6 (d), 69.2 (d), 67.2 (d), 66.9 (t), 61.7 (t), 45.5 (t), 42.7 (q); *m/z* (EI) 356 (M^+, ^{81}Br, 21), 354 (M^+, ^{79}Br, 21), 230 (100), 203 (33), 187 (28); HRMS (EI): calcd for $C_{10}H_{15}{}^{79}BrN_2O_5S$ (M^+) 353.9885, found 353.9889.

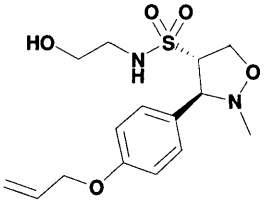
(3*S, 4*S**)-3-Furan-2-yl-2-methylisoxazolidine-4-sulfonic acid (2-hydroxyethyl) amide (133m)**



General protocol was followed using 97 mg of **130m**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133m** (48 mg, 69%) as a brown oil.

R_f 0.22 (9:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 3459, 3281, 2878, 1505, 1437, 1318, 1145, 1038, 950; δ_H (300 MHz, $CDCl_3$) 7.44 (d, *J* = 1.9 Hz, 1 H, OC*H*CHCH), 6.46 (d, *J* = 3.2 Hz, 1 H, OCHCHC*H*), 6.38 (dd, *J* = 3.2, 1.9 Hz, 1 H, OCHC*H*CH), 5.53 (br s, 1 H, N*H*), 4.27-4.40 (m, 3 H, SC*H* and SCHCH_2), 3.94 (br s, 1 H, NC*H*), 3.51-3.64 (m, 2 H, OCH_2CH_2N), 3.09-3.21 (m, 1 H, OCH_2C*H*HN), 2.95-3.07 (m, 1 H, OCH_2CH*H*N), 2.82 (br s, 1 H, O*H*), 2.70 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 148.4 (s), 143.5 (d), 110.9 (d), 110.4 (d), 69.0 (d), 67.7 (d), 66.8 (t), 61.7 (t), 45.4 (t), 42.8 (q); *m/z* (EI) 276 (M^+, 13), 150 (100), 125 (24), 107 (37); HRMS (EI): calcd for $C_{10}H_{16}N_2O_5S$ (M^+) 276.0780, found 276.0785.

(3*S, 4*S**)-3-(4-Allyloxyphenyl)-2-methylisoxazolidine-4-sulfonic acid (2-hydroxy ethyl)amide (133n)**



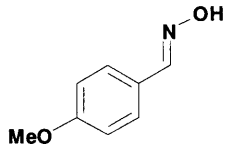
General protocol was followed using 109 mg of **130n**. The crude residue was purified by flash chromatography (starting 99:1 $CHCl_3$/MeOH) to give **133n** (76 mg, 92%) as a yellow oil.

R_f 0.38 (9:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 2918, 2850, 1611, 1512, 1463, 1308, 1242, 1145, 1038, 928; δ_H (300 MHz, $CDCl_3$) 7.35 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.91 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.04 (ddt, *J* = 17.3, 10.5, 5.4 Hz, 1 H, C*H*=CH_2), 5.37-5.45 (m, 2 H,

CH=C*H*H and N*H*), 5.28 (app. dq, *J* = 10.5, 1.4 Hz, 1 H, CH=CH*H*), 4.52 (app. dt, *J* = 5.4, 1.4 Hz, 2 H, OCH_2CH=), 4.37 (dd, *J* = 9.9, 4.0 Hz, 1 H, SCHC*H*H), 4.32 (dd, *J* = 9.9, 7.6 Hz, 1 H, SCHCH*H*), 4.04 (app. td, *J* = 7.6, 4.0 Hz, 1 H, SC*H*), 3.76 (br s, 1 H, NC*H*), 3.45-3.58 (m, 2 H, OCH_2CH_2N), 3.03-3.13 (m, 1 H, OCH_2C*H*HN), 2.87-2.96 (m, 1 H, OCH_2CH*H*N), 2.70 (s, 1 H, O*H*), 2.60 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 159.0 (s), 133.0 (d), 129.4 (d), 128.6 (s), 117.9 (t), 115.2 (d), 74.0 (d), 72.9 (d), 68.9 (t), 66.9 (t), 61.6 (t), 45.4 (t), 42.6 (q); *m/z* (EI) 342 (M^+, 6), 217 (54), 216 (100), 191 (17), 173 (14), 150 (19), 118 (23), 91 (52), 86 (62); HRMS (EI): calcd for $C_{15}H_{22}N_2O_5S$ (M^+) 342.1244, found 342.1239.

4.7. Procedures for isoxazole studies

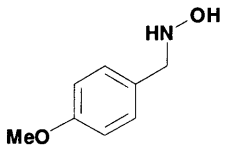
4-Methoxybenzaldehyde oxime (134) [102]



To a stirring suspension of 4-methoxybenzaldehyde (20.0 g, 0.15 mol) in DCM (500 mL) was added to it hydroxylamine hydrochloride (17.9 g, 0.26 mol), and NEt_3 (70 mL, 0.5 mol). The reaction mixture was allowed to stir at RT for 2 hours then quenched with sat. $NaHCO_3$ (200 mL) at 0 °C and extracted with DCM (2 x 200 mL). The combined DCM layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude which was purified by flash chromatography (starting 7:1 petroleum ether 40-60°C/EtOAc) to give the desired product (20.8 g, 94%).

R_f 0.48 (2:1 petroleum ether 40-60°C/EtOAc); mp 72-74 °C; υ_{max} (neat)/cm^{-1} 3174, 3007, 2839, 1607, 1512, 1441, 1307, 1250, 1168, 1025, 953, 824; δ_H (300 MHz, $CDCl_3$) 9.22 (br s, 1 H, O*H*), 8.13 (s, 1 H, C*H*N), 7.52 (d, J = 8.7 Hz, 2 H, Ar*H*), 6.91 (d, J = 8.7 Hz, 2 H, Ar*H*), 3.82 (s, 3 H, OCH_3); δ_C (75 MHz, $CDCl_3$) 161.1 (s), 150.0 (d), 128.6 (d), 124.6 (s), 114.3 (d), 55.4 (q); *m/z* (CI) 152 (MH^+, 100); HRMS (CI): calcd for $C_8H_{10}NO_2$ (MH^+) 152.0712, found 152.0708.

N-(4-Methoxybenzyl)-hydroxylamine (135) [102, 103]

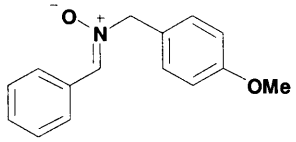


4-Methoxybenzaldehyde oxime **134** (9.6 g, 63.5 mmol) was dissolved in 1.25M HCl in MeOH (350 mL) and treated slowly with $NaBH_3CN$ (8.0 g, 127.0 mmol). The reaction was stirred at RT for 5 days and then solvents were removed *in vacuo*. The remaining solid suspended in H_2O was basified to pH >9 using 6M KOH. The aqueous layer was then saturated with NaCl and extracted with $CHCl_3$ (4 x 200 mL). The combined $CHCl_3$ layers were dried with $MgSO_4$ from which the solvent was evaporated to give the product as an off white solid (9.6 g, 99%).

mp 80-82 °C; υ_{max} (neat)/cm^{-1} 3227, 3004, 2836, 1610, 1510, 1301, 1246, 1175, 1031, 810; δ_H (300 MHz, $CDCl_3$) 7.23 (d, J = 8.6 Hz, 2 H, Ar*H*), 6.86 (d, J = 8.6 Hz, 2 H, Ar*H*), 6.12 (br s, 1 H, N*H*), 3.91 (s, 2 H, CH_2NH), 3.78 (s, 3 H, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.2 (s), 130.5 (d), 128.9 (s), 113.9 (d), 57.6 (t), 55.3 (q); *m/z* (EI) 153 (M^+,

24), 151 (100), 134 (33), 122 (57), 108 (78), 91 (46), 77 (98), 63 (36); HRMS (EI): calcd for $C_8H_{11}NO_2$ (M^+) 153.0784, found 153.0795.

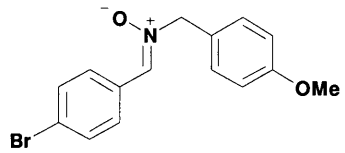
C-(Phenyl)-*N*-(4-methoxybenzyl) nitrone (136a) [193]



To *N*-(4-methoxybenzyl)-hydroxylamine **135** (4.8 g, 31.4 mmol) in dry DCM (50 mL) was added benzaldehyde (2.9 mL, 28.6 mmol) and $NaHCO_3$ (7.2 g, 85.7 mmol). The mixture was refluxed at 40 °C overnight, then the resulting suspension was filtered and the remaining residue washed thoroughly with DCM (4 × 50 mL). The combined organic fractions were concentrated *in vacuo* to yield a white solid that was recrystallised (hexane/EtOAc) to give the title compound as white crystals (6.6 g, 96%).

R_f 0.13 (2:1 petroleum ether 40-60°C/EtOAc); mp 96-99 °C; υ_{max} (neat)/cm^{-1} 3051, 2934, 1610, 1514, 1250, 1146, 1026, 919, 812; δ_H (300 MHz, $CDCl_3$) 8.18-8.21 (m, 2 H, Ar*H*), 7.38-7.42 (m, 5 H, Ar*H*), 7.33 (s, 1 H, C*H*N), 6.93 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.99 (s, 2 H, CH_2N), 3.82 (s, 3 H, OCH_3); δ_C (75 MHz, $CDCl_3$) 160.2 (s), 133.8 (d), 130.9 (d), 130.5 (s), 130.4 (d), 128.6 (d), 128.4 (d), 125.3 (s), 114.4 (d), 70.7 (t), 55.4 (q); *m/z* (FAB^+) 264 (MNa^+, 48), 199 (63), 173 (100); HRMS (FAB^+): calcd for $C_{15}H_{15}NO_2Na$ (MNa^+) 264.1000, found 264.1004.

C-(4-Bromophenyl)-*N*-(4-methoxybenzyl) nitrone (136b)

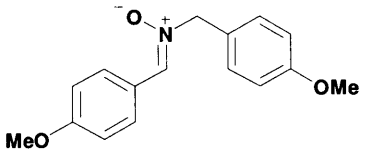


To *N*-(4-methoxybenzyl)-hydroxylamine **135** (2.6 g, 17.0 mmol) in dry DCM (25 mL) was added 4-bromobenzaldehyde (2.6 g, 14.2 mmol) and $NaHCO_3$ (3.6 g, 42.6 mmol). The mixture was refluxed at 40 °C overnight, then the resulting suspension was filtered and the remaining residue washed thoroughly with DCM (4 × 30 mL). The combined organic fractions were concentrated *in vacuo*, and the crude product was recrystallised (hexane/EtOAc) to give the title compound as a light brown solid (4.0 g, 87%).

R_f 0.14 (2:1 petroleum ether 40-60°C/EtOAc); mp 153-155 °C; υ_{max} (neat)/cm^{-1} 3062, 2965, 1611, 1512, 1452, 1238, 1142, 1031, 928, 834, 771; δ_H (300 MHz, $CDCl_3$) 8.07 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.50 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.38 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.29 (s, 1 H, C*H*N), 6.92 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.96 (s, 2 H, NCH_2Ar), 3.81

(s, 3 H, OCH_3); δ_C (75 MHz, $CDCl_3$) 160.3 (s), 132.7 (d), 131.7 (d), 131.0 (d), 129.9 (d), 129.3 (s), 124.9 (s), 124.2 (s), 114.4 (d), 70.8 (t), 55.4 (q); *m/z* (EI) 321 (M^+, ^{81}Br, 22), 319 (M^+, ^{79}Br, 21), 121 (100), 89 (62), 78 (67), 63 (45); HRMS (EI): calcd for $C_{15}H_{14}{}^{79}BrNO_2$ (M^+) 319.0202, found 319.0197.

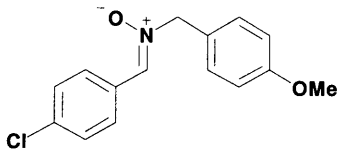
C-(4-Methoxyphenyl)-N-(4-methoxybenzyl) nitrone (136c) [194]



To *N*-(4-methoxybenzyl)-hydroxylamine **135** (3 g, 19.6 mmol) in dry DCM (30 mL) was added 4-methoxybenzaldehyde (2.0 mL, 16.3 mmol) and $NaHCO_3$ (4.1 g, 49.0 mmol). The mixture was refluxed at 40 °C overnight, then the resulting suspension was filtered and the remaining residue washed thoroughly with DCM (4 × 40 mL). The combined organic fractions were concentrated *in vacuo*, and the crude product was recrystallised (hexane/EtOAc) to give the title compound as a light yellow solid (4.1 g, 92%).

R_f 0.15 (2:1 petroleum ether 40-60°C/EtOAc); mp 127-129 °C; υ_{max} (neat)/cm^{-1} 3007, 2839, 1603, 1507, 1455, 1303, 1239, 1143, 1025, 936; δ_H (300 MHz, $CDCl_3$) 8.18 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 7.37 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.25 (s, 1 H, C*H*N), 6.90 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 4.92 (s, 2 H, NCH_2Ar), 3.80 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3); δ_C (75 MHz, $CDCl_3$) 161.1 (s), 160.1 (s), 133.6 (d), 130.9 (d), 130.6 (d), 125.5 (s), 123.5 (s), 114.3 (d), 113.7 (d), 70.1 (t), 55.3 (q), 55.2 (q); *m/z* (EI) 271 (M^+, 12), 121 (100), 91 (31), 77 (53); HRMS (EI): calcd for $C_{16}H_{17}NO_3$ (M^+) 271.1203, found 271.1208.

C-(4-Chlorophenyl)-N-(4-methoxybenzyl) nitrone (136d)

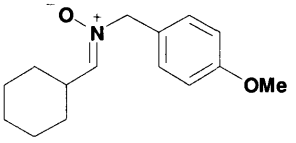


To *N*-(4-methoxybenzyl)-hydroxylamine **135** (3 g, 19.6 mmol) in dry DCM (30 mL) was added 4-chlorobenzaldehyde (2.3 g, 16.3 mmol) and $NaHCO_3$ (4.1 g, 49.0 mmol). The mixture was refluxed at 40 °C overnight, then the resulting suspension was filtered and the remaining residue washed thoroughly with DCM (4 × 40 mL). The combined

organic fractions were concentrated *in vacuo*, and the crude product was recrystallised (hexane/EtOAc) to give the title compound as a light yellow solid (4.0 g, 90%).

R_f 0.17 (2:1 petroleum ether 40-60°C/EtOAc); mp 142-145 °C; υ_{max} (neat)/cm^{-1} 3006, 2964, 1612, 1513, 1456, 1238, 1142, 1031, 928, 836, 770; δ_H (300 MHz, $CDCl_3$) 8.14 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.38 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.33 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.31 (s, 1 H, C*H*N), 6.92 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.96 (s, 2 H, NCH_2Ar), 3.80 (s, 3 H, OCH_3); δ_C (75 MHz, $CDCl_3$) 160.3 (s), 135.8 (s), 132.7 (d), 131.0 (d), 129.8 (d), 129.0 (s), 128.7 (d), 125.0 (s), 114.4 (d), 70.7 (t), 55.4 (q); *m/z* (EI) 277 (M^+, ^{37}Cl, 4), 275 (M^+, ^{35}Cl, 12), 121 (100), 89 (41), 78 (47), 63 (19); HRMS (EI): calcd for $C_{15}H_{14}{}^{35}ClNO_2$ (M^+) 275.0708, found 275.0711.

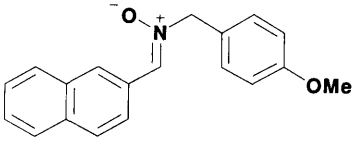
C-(Cyclohexyl)-N-(4-methoxybenzyl) nitrone (136e)



To *N*-(4-methoxybenzyl)-hydroxylamine **135** (2 g, 13.1 mmol) in dry DCM (25 mL) was added cyclohexanecarbaldehyde (1.3 mL, 10.9 mmol) and $NaHCO_3$ (2.7 g, 32.6 mmol). The mixture was refluxed at 40 °C overnight, then the resulting suspension was filtered and the remaining residue washed thoroughly with DCM (4 × 30 mL). The combined organic fractions were concentrated *in vacuo*, and the crude product was recrystallised (hexane/EtOAc) to give the title compound as an orange solid (2.6 g, 95%).

R_f 0.45 (9:1 DCM/MeOH); mp 92-95 °C; υ_{max} (neat)/cm^{-1} 3063, 2924, 1612, 1513, 1448, 1302, 1249, 1172, 1031, 823; δ_H (300 MHz, $CDCl_3$) 7.29 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.38 (d, *J* = 7.2 Hz, 1 H, C*H*N), 4.77 (s, 2 H, NCH_2Ar), 3.79 (s, 3 H, OCH_3), 2.88-3.01 (m, 1 H, C*H*CHN), 1.76-1.86 (m, 2 H, cyclohexyl-*H*), 1.58-1.70 (m, 3 H, cyclohexyl-*H*), 1.01-1.41 (m, 5 H, cyclohexyl-*H*); δ_C (75 MHz, $CDCl_3$) 160.0 (s), 142.8 (d), 130.7 (d), 125.2 (s), 114.3 (d), 68.7 (t), 55.3 (q), 35.0 (d), 28.8 (t), 25.9 (t), 25.2 (t); *m/z* (EI) 247 (M^+, 8), 230 (16), 122 (100), 91 (33); HRMS (EI): calcd for $C_{15}H_{21}NO_2$ (M^+) 247.1567, found 247.1561.

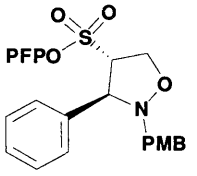
C-(Naphthyl)-N-(4-methoxybenzyl) nitrone (136f)



To *N*-(4-methoxybenzyl)-hydroxylamine **135** (2 g, 13.1 mmol) in dry DCM (25 mL) was added 2-naphthaldehyde (1.7 g, 10.9 mmol) and $NaHCO_3$ (2.7 g, 32.6 mmol). The mixture was refluxed at 40 °C overnight, then the resulting suspension was filtered and the remaining residue washed thoroughly with DCM (4 × 30 mL). The combined organic fractions were concentrated *in vacuo*, and the crude product was recrystallised (hexane/EtOAc) to give the title compound as a cream solid (2.9 g, 92%).

R_f 0.17 (2:1 petroleum ether 40-60°C/EtOAc); mp 155-158 °C; υ_{max} (neat)/cm^{-1} 3053, 2932, 1610, 1514, 1445, 1305, 1249, 1178, 1028, 945; δ_H (300 MHz, $CDCl_3$) 9.22 (s, 1 H, C*H*N), 7.78-7.91 (m, 4 H, Ar*H*), 7.47-7.51 (m, 3 H, Ar*H*), 7.44 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.95 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.03 (s, 2 H, NCH_2Ar), 3.82 (s, 3 H, OCH_3); δ_C (75 MHz, $CDCl_3$) 160.2 (s), 134.1 (d), 133.9 (s), 133.1 (s), 131.0 (d), 129.2 (d), 128.6 (d), 127.9 (d), 127.7 (s), 127.5 (d), 127.3 (d), 126.5 (d), 125.9 (d), 125.3 (s), 114.4 (d), 70.7 (t), 55.4 (q); *m/z* (EI) 291 (M^+, 38), 275 (15), 156 (20), 139 (40), 121 (100), 97 (44); HRMS (EI): calcd for $C_{19}H_{17}NO_2$ (M^+) 291.1254, found 291.1260.

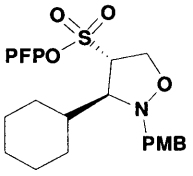
(3*S, 4*S**)-2-(4-Methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (137)**



To pentafluorophenyl vinyl sulfonate **100** (0.5 g, 1.8 mmol) in dry toluene (10 mL) was added *C*-(phenyl)-*N*-(4-methoxybenzyl) nitrone **136a** (0.5 g, 2.2 mmol) and the mixture was heated to reflux for 9 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash chromatography (starting 8:1 petroleum ether 40-60°C/EtOAc) to give the title compound (850 mg, 85%) as a yellow solid.

R_f 0.60 (2:1 petroleum ether 40-60°C/EtOAc); mp 88-92 °C; υ_{max} (neat)/cm^{-1} 2957, 1511, 1468, 1392, 1249, 1184, 1020, 993, 786; δ_H (300 MHz, $CDCl_3$) 7.52-7.56 (m, 2 H, Ar*H*), 7.36-7.45 (m, 3 H, Ar*H*), 7.23 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.61 (dd, *J* = 10.4, 2.4 Hz, 1 H, SCHC*H*H), 4.42-4.49 (m, 1 H, SCHCH*H*), 4.29-4.36 (m, 2 H, SC*H* and NC*H*), 3.97 (d, *J* = 14.2 Hz, 1 H, NC*H*HAr), 3.82 (d, *J* = 14.2 Hz, 1 H, NCH*H*Ar), 3.78 (s, 3 H, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.1 (s), 136.2 (s), 130.2 (d), 129.1 (d), 128.5 (s), 128.1 (2 x d), 113.7 (d), 73.6 (d), 71.4 (d), 66.9 (t), 58.8 (t), 55.2 (q); *m/z* (FAB^+) 516 (MH^+, 10), 154 (100); HRMS (FAB^+): calcd for $C_{23}H_{19}F_5NO_5S$ (MH^+) 516.0904, found 516.0900.

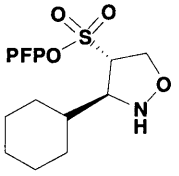
(3*S, 4*S**)-3-Cyclohexyl-2-(4-methoxybenzyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester (138)**



To pentafluorophenyl vinyl sulfonate **100** (1.0 g, 3.7 mmol) in dry toluene (20 mL) was added *C*-(cyclohexyl)-*N*-PMB nitrone **136e** (1.4 g, 5.5 mmol) and the mixture was heated to reflux for 17 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/EtOAc) to give the title compound (1.0 g, 55%) as a yellow solid.

R_f 0.72 (2:1 petroleum ether 40-60°C/EtOAc); mp 120-123 °C; υ_{max} (neat)/cm^{-1} 2917, 1519, 1378, 1245, 1181, 991, 817, 731; δ_H (300 MHz, $CDCl_3$) 7.31 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 6.87 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 4.63 (dd, *J* = 9.9, 7.0 Hz, 1 H, SCHC*H*H), 4.42 (dd, *J* = 9.9, 8.3 Hz, 1 H, SCHCH*H*), 4.28 (app. td, *J* = 7.0, 3.8 Hz, 1 H, SC*H*), 4.11 (d, *J* = 12.3 Hz, 1 H, NC*H*HAr), 4.00 (d, *J* = 12.3 Hz, 1 H, NCH*H*Ar), 3.80 (s, 3 H, OCH_3), 3.47 (dd, *J* = 6.7, 3.8 Hz, 1 H, NC*H*), 1.58-1.84 (m, 5 H, cyclohexyl-*H*), 1.36-1.48 (m, 1 H, cyclohexyl-*H*), 1.06-1.28 (m, 3 H, cyclohexyl-*H*), 0.82-1.02 (m, 2 H, cyclohexyl-*H*); δ_C (75 MHz, $CDCl_3$) 159.2 (s), 130.8 (d), 128.2 (s), 113.8 (d), 70.4 (d), 68.6 (d), 67.0 (t), 59.5 (t), 55.3 (q), 42.2 (d), 29.5 (t), 29.4 (t), 26.1 (t), 26.0 (t), 25.9 (t); *m/z* (FAB$^+$) 522 (MH$^+$, 12), 176 (22), 154 (100); HRMS (FAB$^+$): calcd for $C_{23}H_{25}F_5NO_5S$ (MH$^+$) 522.1374, found 522.1337.

(3*S, 4*S**)-3-Cyclohexylisoxazolidine-4-sulfonic acid pentafluorophenyl ester (139)**

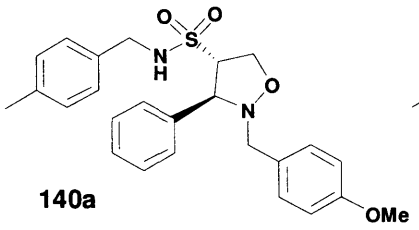


PFP ester **138** (100 mg, 0.19 mmol) in MeOH (10 mL) was treated with 10% Pd/C (10 mg). The round bottom flask was evacuated and cycled with Ar three times, and finally flushed with H_2. The reaction was heated at reflux for 7 hours then the reaction mixture filtered through a pad of Celite®, and the filtrate concentrated *in vacuo*. The crude was purified by flash chromatography (starting 95:5 DCM/MeOH) to yield the product (26 mg, 34%) as a white solid.

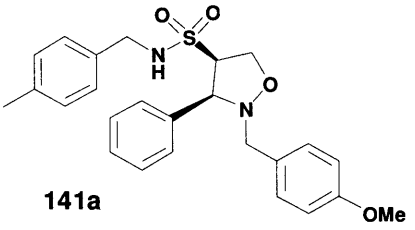
R_f 0.08 (9:1 DCM/MeOH); mp 287-291 °C; υ_{max} (neat)/cm^{-1} 3414, 3097, 2921, 1520, 1244, 1138, 1041, 892, 722; δ_H (300 MHz, $(CD_3)_2SO$) 7.84 (br s, 1 H, N*H*), 3.87 (dd, *J*

= 12.1, 4.6 Hz, 1 H, SCHC*H*H), 3.77 (dd, *J* = 12.1, 5.9 Hz, 1 H, SCHCH*H*), 3.30 (dd, *J* = 9.9, 2.2 Hz, 1 H, NC*H*), 2.84 (app. td, *J* = 5.9, 2.2 Hz, 1 H, SC*H*), 1.56-1.91 (m, 6 H, cyclohexyl-*H*), 1.08-1.21 (m, 3 H, cyclohexyl-*H*), 0.78-0.97 (m, 2 H, cyclohexyl-*H*); δ_C (75 MHz, $(CD_3)_2SO$) 57.5 (d), 57.0 (t), 55.3 (d), 37.1 (d), 29.1 (t), 28.7 (t), 25.5 (t), 25.1 (t), 25.0 (t).

(3*S, 4*S**)-2-(4-Methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid 4-methyl benzylamide (140a) and (3*S**, 4*R**)-2-(4-Methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (141a)**



140a



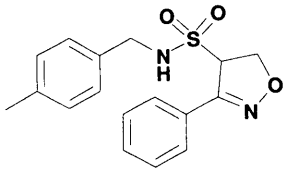
141a

4-Methylbenzylamine (0.6 mL, 4.66 mmol) was added to a stirring solution of (3*S**, 4*S**)-2-(4-methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **137** (800 mg, 1.55 mmol) in dry THF (20 mL), followed by DBU (0.4 mL, 2.33 mmol). The mixture was refluxed for 1 hour then diluted with DCM (50 mL) and washed with 2M HCl (2 x 25 mL), sat. $NaHCO_3$ (2 x 25 mL), and water (1 x 25 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 4:1 petroleum ether 40-60°C/Et_2O) to give **140a** (516 mg, 74%) as a white solid and the **141a** (150 mg, 21%) as a yellow solid- overall yield (95%, **140a**:**141a** = 7:2).

Data for **140a**: R_f 0.40 (2:1 Et_2O/petroleum ether 40-60°C); mp 152-154 °C; υ_{max} (neat)/cm^{-1} 3317, 3284, 2921, 1513, 1420, 1320, 1243, 1156, 1028, 850; δ_H (300 MHz, $CDCl_3$) 7.38-7.50 (m, 5 H, Ar*H*), 7.19 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.07 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 6.96 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 6.81 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.46 (app. t, 5.9 Hz, 1 H, N*H*), 4.35 (dd, *J* = 9.9, 4.0 Hz, 1 H, SCHC*H*H), 4.24 (dd, *J* = 9.9, 8.3 Hz, 1 H, SCHCH*H*), 4.11 (dd, *J* = 13.7, 6.4 Hz, 1 H, NHC*H*HAr), 4.08 (d, *J* = 7.2 Hz, 1 H, NC*H*), 3.83-3.98 (m, 3 H, SC*H*, NHCH*H*Ar, and NC*H*HAr), 3.71-3.78 (m, 4 H, NCH*H*Ar and OCH_3), 2.32 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 159.0 (s), 137.8 (s), 137.5 (s), 133.4 (s), 130.2 (d), 129.5 (d), 129.0 (d), 128.7 (d), 128.3 (d), 128.0 (d), 113.7 (d), 73.2 (d), 71.6 (d), 67.0 (t), 58.8 (t), 55.2 (q), 47.1 (t), 21.2 (q), 1 x s not observed; *m/z* (CI) 454 (27), 453 (MH^+, 100), 345 (75); HRMS (CI): calcd for $C_{25}H_{29}N_2O_4S$ (MH^+) 453.1848, found 453.1833.

Data for **141a**: R_f 0.30 (2:1 Et_2O/petroleum ether 40-60°C); mp 146-149 °C; υ_{max} (neat)/cm^{-1} 3334, 3002, 2926, 1513, 1402, 1326, 1244, 1153, 1026, 809; δ_H (300 MHz, $CDCl_3$) 7.55 (dd, *J* = 7.8, 2.1 Hz, 2 H, Ar*H*), 7.31-7.38 (m, 3 H, Ar*H*), 7.23 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.13 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 7.04 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.33-4.44 (m, 2 H, SCHCH_2), 4.18 (app. q, *J* = 8.3 Hz, 1 H, SC*H*), 3.89-4.08 (m, 4 H, NC*H*HAr, NHCH_2Ar, and NC*H*), 3.80 (s, 3 H, OCH_3), 3.60 (d, *J* = 14.2 Hz, 1 H, NCH*H*Ar), 3.29 (br t, *J* = 5.9 Hz, 1 H, N*H*), 2.34 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 159.0 (s), 137.9 (s), 133.4 (2 x s), 130.2 (d), 129.6 (d), 129.4 (d), 129.0 (d), 128.5 (d), 128.4 (s), 128.0 (d), 113.7 (d), 70.8 (d), 68.1 (d), 66.7 (t), 58.8 (t), 55.3 (q), 46.9 (t), 21.2 (q); *m/z* (FAB^+) 453 (MH^+, 5), 154 (100); HRMS (FAB^+): calcd for $C_{25}H_{29}N_2O_4S$ (MH^+) 453.1848, found 453.1836.

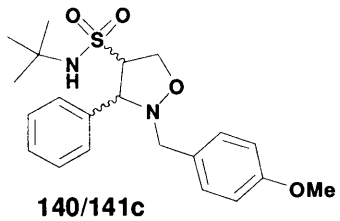
3-Phenyl-4,5-dihydroisoxazole-4-sulfonic acid 4-methylbenzylamide (142a)



(3*S**, 4*S**) and (3*S**, 4*R**)-2-(4-Methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid 4-methylbenzylamide **140/141a** (139 mg, 0.31 mmol) in toluene (10 mL) was treated with DDQ (280 mg, 1.23 mmol) and refluxed for 30 hours. Solvents were removed *in vacuo* and residue dissolved in DCM (20 mL). The organic phase was washed with sat. $NaHCO_3$ (15 mL), and then the aqueous layer further extracted with DCM (3 x 15 mL). The combined DCM layers were dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the crude oil by flash chromatography (starting 4:1 petroleum ether 40-60°C/Et_2O) yielded the product (20 mg, 20%) as a pink solid.

R_f 0.34 (2:1 Et_2O/petroleum ether 40-60°C); mp 129-131 °C; υ_{max} (neat)/cm^{-1} 3316, 2920, 3021, 2920, 1515, 1434, 1327, 1129, 1053, 939, 892; δ_H (300 MHz, $CDCl_3$) 7.86-7.89 (m. 2 H, Ar*H*), 7.41-7.47 (m, 3 H, Ar*H*), 7.11-7.13 (m, 4 H, Ar*H*), 5.14 (dd, *J* = 10.7, 2.7 Hz, 1 H, SCHC*H*H), 5.05 (dd, *J* = 9.6, 2.7 Hz, 1 H, SCHCH*H*), 4.63 (dd, *J* = 10.7, 9.6 Hz, 1 H, SC*H*), 4.46 (app. t, *J* = 5.6 Hz, 1 H, N*H*), 4.13 (dd, *J* = 13.6, 5.9 Hz, 1 H, NC*H*HAr), 4.06 (dd, *J* = 13.6, 5.9 Hz, 1 H, NCH*H*Ar), 2.32 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 153.2 (s), 138.1 (s), 133.3 (s), 131.0 (d), 129.5 (d), 128.9 (d), 128.0 (d), 127.8 (d), 127.3 (s), 73.3 (t), 70.3 (d), 48.0 (t), 21.1 (q); *m/z* (FAB^+) 353 (MNa^+, 22), 329 (20), 176 (100), 154 (42); HRMS (FAB^+): calcd for $C_{17}H_{18}N_2NaO_3S$ (MNa^+) 353.0936, found 353.0926.

(3*S, 4*S**) and (3*S**, 4*R**)-2-(4-Methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid *tert*-butylamide (140/141c)**

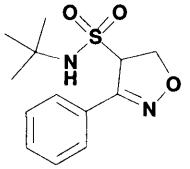


140/141c

tert-Butylamine (120 μL, 1.16 mmol) was added to a stirring solution of (3*S**, 4*S**)-2-(4-methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **137** (200 mg, 0.39 mmol) in dry THF (6 mL), followed by DBU (90 μL, 0.58 mmol). The mixture was refluxed for 1 hour then diluted with DCM (20 mL) and washed with 2M HCl (2 x 20 mL), sat. $NaHCO_3$ (2 x 20 mL), and water (1 x 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 3:1 Petroleum ether 40-60°C/Et_2O) to give the product (134 mg, 85%) as an inseparable mixture of diastereoisomers (**140** and **141c** = 2:1 major:minor).

Data for **140/141c**: R_f 0.43 (2:1 Et_2O/petroleum ether 40-60°C); mp 177-179 °C; υ_{max} (neat)/cm^{-1} 3300, 2933, 1513, 1389, 1251, 1143, 1038, 996, 832; δ_H (300 MHz, $CDCl_3$) 7.58-7.63 (m, 2 H_{minor}, Ar*H*), 7.50-7.55 (m, 2 H_{major}, Ar*H*), 7.33-7.45 (m, 3 H, Ar*H*), 7.22 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 7.19 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 6.80 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 4.49 (s, 1 H_{major}, N*H*), 4.38-4.46 (m, 2 H, SCHC*H*H and SCHCH*H*$_{minor}$), 4.31 (dd, *J* = 9.4, 8.0 Hz, 1 H_{major}, SCHCH*H*), 4.21 (app. q, *J* = 8.3 Hz, 1 H_{minor}, SC*H*), 3.96-4.08 (m, 3 H, NC*H*, NC*H*HAr$_{minor}$, and SC*H*$_{major}$), 3.87 (d, *J* = 13.9 Hz, 1 H_{major}, NC*H*HAr), 3.78 (s, 3 H_{minor}, OCH_3), 3.76 (s, 3 H_{major}, OCH_3), 3.73-3.79 (m, 1 H_{major}, NCH*H*Ar), 3.60 (d, *J* = 14.2 Hz, 1 H_{minor}, NCH*H*Ar), 3.08 (br s, 1 H_{minor}, N*H*), 1.15 (s, 9 H_{minor}, C(CH_3)$_3$), 1.08 (s, 9 H_{major}, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 159.0 (s), 158.9 (s), 137.8 (s), 133.8 (s), 130.3 (d), 130.1 (d), 129.2 (s), 128.9 (d), 128.8 (d), 128.7 (d), 128.6 (d), 128.3 (s), 75.1 (d), 72.6 (d), 71.2 (d), 70.8 (d), 67.3 (t), 67.1 (t), 58.9 (t), 58.6 (t), 55.2 (q), 55.0 (s), 54.7 (s), 30.3 (q), 29.9 (q), 25 out of 30 expected signals observed; *m/z* (ES^+) 468 (35), 427 (MNa^+, 100), 405 (91), 180 (38); HRMS (ES^+): calcd for $C_{21}H_{28}N_2NaO_4S$ (MNa^+) 427.1658, found 427.1667.

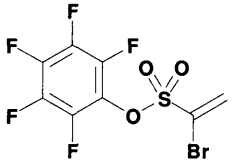
3-Phenyl-4,5-dihydroisoxazole-4-sulfonic acid *tert*-butylamide (142b)



DDQ (300 mg, 1.33 mmol) was added to a stirring suspension of (3*S**, 4*S**) and (3*S**, 4*R**)-2-(4-methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid *tert*-butylamide **140/141c** (134 mg, 0.33 mmol) in benzene (6 mL), and the mixture heated at reflux for 48 hours. The reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (starting 4:1 petroleum ether 40-60°C/Et_2O) to give the product (64 mg, 69%) as a white solid.

R_f 0.25 (2:1 Et_2O/petroleum ether 40-60°C); mp 180-183 °C; υ_{max} (neat)/cm^{-1} 3301, 2979, 1513, 1422, 1389, 1240, 1138, 1021, 906; δ_H (300 MHz, $CDCl_3$) 7.82-7.86 (m, 2 H, Ar*H*), 7.41-7.46 (m, 3 H, Ar*H*), 5.11 (dd, *J* = 10.7, 3.5 Hz, 1 H, SCHC*H*H), 5.04 (dd, *J* = 10.2, 3.5 Hz, 1 H, SCHCH*H*), 4.66 (app. t, *J* = 10.2 Hz, 1 H, SC*H*), 4.22 (br s, 1 H, N*H*), 1.29 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 153.0 (s), 130.7 (d), 128.7 (d), 128.0 (d), 127.7 (s), 73.0 (t), 71.9 (d), 56.2 (s), 30.2 (q); *m/z* (CI) 283 (MH^+, 29), 265 (38), 227 (36), 165 (21), 146 (100), 125 (34), 111 (48), 97 (82), 89 (23); HRMS (CI): calcd for $C_{13}H_{19}N_2O_3S$ (MH^+) 283.1116, found 283.1109.

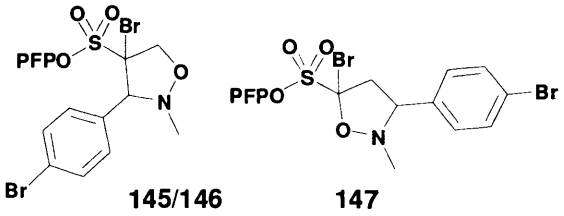
α-Bromo-pentafluorophenyl vinyl sulfonate (143)



Bromine (4.5 mL, 87.5 mmol) in $CHCl_3$ (30 mL) was added dropwise over a period of 10 minutes to a stirring suspension of PFP vinyl sulfonate **100** (12.0 g, 43.8 mmol) and AIBN (0.5 g) in $CHCl_3$ (150 mL). After addition, AIBN was added (0.5 g) and the reaction mixture heated to reflux for 4 hours, followed by 40 hours at RT. The solvent was removed *in vacuo* and the crude oil remaining re-suspended in DCM (100 mL). To this stirring solution was added NEt_3 (9.2 mL, 65.7 mmol) and the reaction stirred at RT for 3 hrs. The reaction mixture was washed with 2M HCl (2 x 50 mL), the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether 40-60°C/Et_2O) to give the desired product as a yellow solid (14.0 g, 91%).

R_f 0.52 (5:1 petroleum ether 40-60°C /Et_2O); mp 36-38 °C; υ_{max} (neat)/cm^{-1} 3118, 1513, 1354, 1188, 990, 788, 722; δ_H (300 MHz, $CDCl_3$) 7.05 (d, *J* = 3.5 Hz, 1 H, SCC*H*H), 6.54 (d, *J* = 3.5 Hz, 1 H, SCCH*H*); δ_C (75 MHz, $CDCl_3$) 133. 8 (t), 122.0 (s); *m/z* (EI) 512 (27), 354 (M^+, ^{81}Br, 6), 352 (M^+, ^{79}Br, 4), 184 (100), 155 (47), 117 (53), 69 (37); HRMS (EI): calcd for $C_8H_2{}^{79}BrF_5O_3S$ (M^+) 351.8823, found 351.8827.

4-Bromo-3-(4-bromophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluoro phenyl ester (145/146), and 5-Bromo-3-(4-bromophenyl)-2-methylisoxazolidine-5-sulfonic acid pentafluorophenyl ester (147)



145/146 **147**

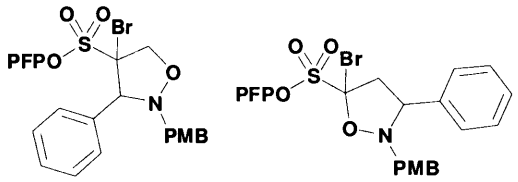
α-Bromo PFP vinyl sulfonate **143** (300 mg, 0.85 mmol) and DABCO (10 mg, 0.08 mmol) was dissolved in PhMe (5 mL) and stirred at RT for 5 mins, then treated with *C*-(4-bromophenyl)-*N*-methyl nitrone **119f** (550 mg, 2.55 mmol). The resulting suspension was stirred at RT for 18 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (starting 30:1 petroleum ether 40-60°C/Et_2O) to give **145/146** (411 mg, 85%) as a mixture of diastereoisomers and **147** (18 mg, 4%) as a single product- overall yield (89%, **145/146**:**147** = 23:1, **145** and **146** = 5:2 major:minor).

Data for **145/146**: R_f 0.67 (2:1 petroleum ether 40-60°C/Et_2O); mp 86-88 °C; υ_{max} (neat)/cm^{-1} 2995, 2879, 1513, 1401, 1194, 988, 823, 731; δ_H (300 MHz, $CDCl_3$) 7.55 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 7.53 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 7.42 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 7.33 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 5.10 (d, *J* = 11.0 Hz, 1 H_{major}, SCBrC*H*H), 5.08 (d, *J* = 11.0 Hz, 1 H_{minor}, SCBrC*H*H), 4.62 (d, *J* = 11.0 Hz, 1 H_{minor}, SCBrCH*H*), 4.58 (d, *J* = 11.0 Hz, 1 H_{major}, SCBrCH*H*), 4.42 (s, 1 H_{minor}, NC*H*), 4.36 (s, 1 H_{major}, NC*H*), 2.76 (s, 3 H_{major}, NCH_3), 2.74 (s, 3 H_{minor}, NCH_3); δ_C (75 MHz, $CDCl_3$) 132.6 (s), 132.5 (s), 131.8 (d), 131.7 (d), 131.6 (d), 131.4 (d), 124.3 (s), 123.9 (s), 83.0 (s), 80.9 (s), 78.0 (t), 77.2 (t), 77.0 (2 x d), 43.1 (q), 42.9 (q); *m/z* (FAB$^+$) 570 (MH^+, $^{81}Br^{81}Br$, 2), 568 (MH^+, $^{79}Br^{81}Br$, 4), 566 (MH^+, $^{79}Br^{79}Br$, 2), 329 (28), 176 (100); HRMS (FAB$^+$): calcd for $C_{16}H_{11}{}^{79}Br_2F_5NO_4S$ (MH^+) 565.8696, found 565.8699.

Data for **147**: R_f 0.21 (2:1 petroleum ether 40-60°C/Et_2O); mp 102-104 °C; υ_{max} (neat)/cm^{-1} 2918, 1518, 1404, 1321, 1230, 1165, 991, 894, 653; δ_H (300 MHz, $CDCl_3$)

7.52 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.30 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.07 (br dd, *J* = 11.2, 7.8 Hz, 1 H, NC*H*), 3.01 (dd, *J* = 16.9, 7.8 Hz, 1 H, SCBrC*H*H), 2.93 (dd, *J* = 16.9, 11.2 Hz, 1 H, SCBrCH*H*), 2.80 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 172.3 (s), 134.9 (s), 132.3 (d), 129.1 (d), 123.1 (s), 72.6 (d), 44.5 (q), 40.5 (t); *m/z* (EI) 569 (M^+, $^{81}Br^{81}Br$, 1), 567 (M^+, $^{79}Br^{81}Br$, 2), 565 (M^+, $^{79}Br^{79}Br$, 1), 512 (23), 257 (94), 184 (98), 149 (71), 102 (100); HRMS (EI): calcd for $C_{16}H_{10}{}^{79}Br_2F_5NO_4S$ (M^+) 564.8612, found 564.8596.

4-Bromo-2-(4-methoxybenzyl)-3-phenylisoxazolidine-4-sulfonic acid pentafluoro phenyl ester (160/161a), and 5-Bromo-2-(4-methoxybenzyl)-3-phenylisoxazolidine-5-sulfonic acid pentafluorophenyl ester (162a)



160/161a **162a**

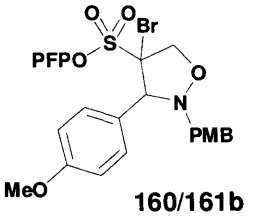
α-Bromo-PFP-vinyl sulfonate **143** (300 mg, 0.85 mmol) and DABCO (10 mg, 0.08 mmol) was dissolved in PhMe (5 mL) and stirred at RT for 5 mins, then treated with *C*-(phenyl)-*N*-(4-methoxybenzyl) nitrone **136a** (410 mg, 1.70 mmol). The resulting suspension was stirred at RT for 18 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (starting 30:1 petroleum ether 40-60°C/Et_2O) to give **160/161a** (410 mg, 81%) as a mixture of diastereoisomers and **162a** (12 mg, 3%) as a single product- overall yield (84%, **160/161a**:**162a** = 34:1, **160** and **161a** = 2:1 major:minor).

Data for **160/161a**: R_f 0.72 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2918, 1514, 1456, 1384, 1246, 1190, 994, 793; δ_H (300 MHz, $CDCl_3$) 7.50-7.56 (m, 2 H, Ar*H*), 7.40-7.47 (m, 3 H, Ar*H*), 7.23 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.8 Hz, 2 H_{minor}, Ar*H*), 6.84 (d, *J* = 8.8 Hz, 2 H_{major}, Ar*H*), 5.08 (d, *J* = 11.0 Hz, 1 H_{major}, SCBrC*H*H), 5.06 (d, *J* = 11.0 Hz, 1 H_{minor}, SCBrC*H*H), 4.67 (s, 1 H_{minor}, NC*H*), 4.65 (s, 1 H_{major}, NC*H*), 4.55 (d, *J* = 11.0 Hz, 1 H, SCBrCH*H*), 4.15 (d, *J* = 14.5 Hz, 1 H_{minor}, NC*H*HAr), 4.09 (d, *J* = 14.5 Hz, 1 H_{major}, NC*H*HAr), 3.81 (s, 3 H_{minor}, OCH_3), 3.79 (d, *J* = 14.5 Hz, 1 H_{major}, NCH*H*Ar), 3.79 (s, 3 H_{major}, OCH_3), 3.71 (d, *J* = 14.5 Hz, 1 H_{minor}, NCH*H*Ar); δ_C (75 MHz, $CDCl_3$) 159.2 (s), 133.8 (s), 130.4 (d), 130.2 (d), 130.1 (d), 130.0 (d), 129.8 (d), 129.6 (d), 129.5 (d), 129.0 (s), 128.5 (d), 127.8 (s), 127.7 (s), 113.8 (d), 113.7 (d), 83.1 (s), 81.1 (s), 77.9 (t), 77.5 (t), 74.9 (d), 59.0 (t), 58.6 (t), 55.3 (q), 55.2 (q), 24 out of 26 expected signals observed; *m/z* (FAB$^+$) 618 (MNa^+, ^{81}Br, 11), 616

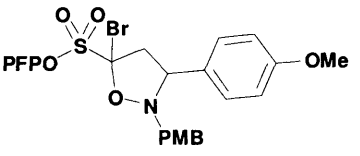
(MNa$^+$, ^{79}Br, 11), 314 (26), 176 (100); HRMS (FAB$^+$): calcd for $C_{23}H_{17}{}^{79}BrF_5NNaO_5S$ (MNa$^+$) 615.9829, found 615.9817.

Data for **162a**: R_f 0.31 (2:1 petroleum ether 40-60°C/Et_2O); mp 83-86 °C; υ_{max} (neat)/cm^{-1} 3009, 2896, 1772, 1612, 1514, 1463, 1364, 1238, 1115, 1028, 803; δ_H (300 MHz, $CDCl_3$) 7.35-7.48 (m, 5 H, Ar*H*), 7.21 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.58 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.32 (br t, *J* = 9.6 Hz, 1 H, NC*H*), 4.12 (d, *J* = 14.4 Hz, 1 H, NC*H*HAr), 3.88 (d, *J* = 14.4 Hz, 1 H, NCH*H*Ar), 3.79 (s, 3 H, OCH_3), 2.97 (d, *J* = 9.6 Hz, 2 H, SCBrCH_2); δ_C (75 MHz, $CDCl_3$) 172.9 (s), 159.3 (s), 136.2 (s), 130.6 (d), 129.2 (d), 129.0 (d), 127.6 (d), 127.2 (s), 113.9 (d), 69.8 (d), 60.2 (t), 55.3 (q), 40.4 (t); *m/z* (CI) 596 (MH$^+$, ^{81}Br, 2), 594 (MH$^+$, ^{79}Br, 2), 567 (51), 404 (32), 284 (66), 226 (45), 176 (44), 121 (100).

4-Bromo-2-(4-methoxybenzyl)-3-(4-methoxyphenyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester (160/161b), and 5-Bromo-2-(4-methoxybenzyl)-3-(4-methoxyphenyl)isoxazolidine-5-sulfonic acid pentafluorophenyl ester (162b)



160/161b



162b

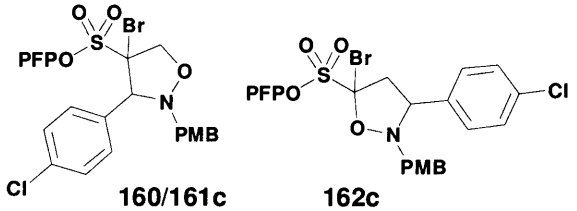
α-Bromo-PFP-vinyl sulfonate **143** (2.0 g, 5.7 mmol) and DABCO (60 mg, 0.6 mmol) was dissolved in PhMe (30 mL) and stirred at RT for 5 mins, then treated with *C*-(4-methoxyphenyl)-*N*-(4-methoxybenzyl) nitrone **136c** (2.3 g, 8.5 mmol). The resulting suspension was stirred at RT for 18 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (starting 30:1 petroleum ether 40-60°C/Et_2O) to give **160/161b** (3.3 g, 93%) as a mixture of diastereoisomers and **162b** (0.05 g, 1%) as a single product- overall yield (94%, **160/161b**:**162b** = 65:1, **160** and **161b** = 4:1 major:minor).

Data for **160/161b**: R_f 0.59 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2938, 2839, 1612, 1512, 1467, 1304, 1246, 1190, 993, 830, 730; δ_H (300 MHz, $CDCl_3$) 7.47 (br d, *J* = 8.6 Hz, 2 H, Ar*H*), 7.25 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.99 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 5.08 (d, *J* = 11.0 Hz, 1 H_{major}, SCBrC*H*H), 5.07 (d, *J* = 11.0 Hz, 1 H_{minor}, SCBrC*H*H), 4.65 (s, 1 H_{minor}, NC*H*), 4.63 (s, 1 H_{major}, NC*H*), 4.57 (d, *J* = 11.0 Hz, 1 H, SCBrCH*H*), 4.11 (d, *J* = 14.5 Hz, 1 H, NC*H*HAr), 3.85 (s, 3 H, OCH_3), 3.83 (s, 3 H_{minor}, OCH_3), 3.80 (s, 3

H_{major}, OCH_3), 3.79 (d, J = 14.5 Hz, 1 H_{major}, NCH*H*Ar), 3.71 (d, J = 14.5 Hz, 1 H_{minor}, NCH*H*Ar); δ_C (75 MHz, $CDCl_3$) 160.8 (s), 160.5 (s), 131.2 (d), 130.4 (d), 130.2 (d), 127.9 (s), 127.8 (s), 125.6 (s), 114.1 (d), 113.9 (d), 113.8 (d), 113.7 (d), 83.6 (s), 81.2 (s), 77.8 (t), 77.3 (t), 74.6 (d), 58.9 (t), 58.5 (t), 55.3 (q), 55.2 (q), 21 out of 28 expected signals observed; *m/z* (FAB$^+$) 648 (MNa$^+$, ^{81}Br, 6), 646 (MNa$^+$, ^{79}Br, 6), 329 (17), 176 (100); HRMS (FAB$^+$): calcd for $C_{24}H_{19}{}^{79}BrF_5NNaO_6S$ (MNa$^+$) 645.9934, found 645.9942.

Data for **162b**: R_f 0.05 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2933, 2838, 1773, 1612, 1512, 1464, 1301, 1241, 1173, 1029, 825; δ_H (300 MHz, $CDCl_3$) 7.38 (d, J = 8.6 Hz, 2 H, Ar*H*), 7.20 (d, J = 8.6 Hz, 2 H, Ar*H*), 6.94 (d, J = 8.6 Hz, 2 H, Ar*H*), 6.85 (d, J = 8.6 Hz, 2 H, Ar*H*), 4.27 (t, J = 9.6 Hz, 1 H, NC*H*), 4.11 (d, J = 14.7 Hz, 1 H, NC*H*HAr), 3.84 (d, J = 14.7 Hz, 1 H, NCH*H*Ar), 3.83 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 2.94 (d, J = 10.4 Hz, 2 H, SCBrCH_2); δ_C (75 MHz, $CDCl_3$) 172.6 (s), 160.1 (s), 159.3 (s), 130.6 (d), 128.9 (d), 127.9 (s), 127.3 (s), 114.5 (d), 113.8 (d), 69.4 (d), 59.9 (t), 55.4 (q), 55.3 (q), 40.3 (t); *m/z* (CI) 626 (MH$^+$, ^{81}Br, 2), 624 (MH$^+$, ^{79}Br, 2), 434 (27), 390 (51), 314 (50), 269 (64), 206 (59), 179 (70), 121 (100); HRMS (CI): calcd for $C_{24}H_{20}{}^{79}BrF_5NO_6S$ (MH$^+$) 624.01148, found 624.01234.

4-Bromo-3-(4-chlorophenyl)-2-(4-methoxybenzyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester (160/161c), and 5-Bromo-3-(4-chlorophenyl)-2-(4-methoxybenzyl)isoxazolidine-5-sulfonic acid pentafluorophenyl ester (162c)

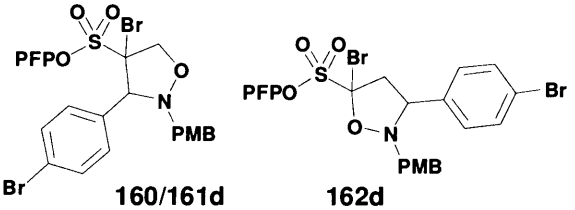


α-Bromo PFP vinyl sulfonate **143** (2.0 g, 5.7 mmol) and DABCO (60 mg, 0.6 mmol) was dissolved in PhMe (45 mL) and stirred at RT for 5 mins, then treated with *C*-(4-chlorophenyl)-*N*-(4-methoxybenzyl) nitrone **136d** (2.3 g, 8.5 mmol). After 24 hours stirring enough DCM (10 mL) was added to aid dissolution of the nitrone and the resulting suspension was stirred for a further 1 day at RT. Solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (starting 30:1 petroleum ether 40-60°C/Et_2O) giving products **160/161c** (2.5 g, 70%) as a mixture of diastereoisomers and **162c** (0.14 g, 4%) as a single product- overall yield (74%, **160/161c**:**162c** = 18:1, **160** and **161c** = 3:1 major:minor).

Data for **160/161c**: R_f 0.80 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2936, 1514, 1386, 1247, 1191, 1092, 993, 826, 723; δ_H (300 MHz, $CDCl_3$) 7.38-7.50 (m, 4 H, Ar*H*), 7.21 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 5.07 (d, *J* = 11.2 Hz, 1 H, SCBrC*H*H), 4.63 (s, 1 H_{minor}, NC*H*), 4.61 (s, 1 H_{major}, NC*H*), 4.55 (d, *J* = 11.2 Hz, 1 H, SCBrCH*H*), 4.11 (d, *J* = 14.2 Hz, 1 H_{minor}, NC*H*HAr), 4.08 (d, *J* = 14.2 Hz, 1 H_{major}, NC*H*HAr), 3.82 (s, 3 H_{minor}, OCH_3), 3.81 (d, *J* = 14.2 Hz, 1 H_{major}, NCH*H*Ar), 3.79 (s, 3 H_{major}, OCH_3), 3.72 (d, *J* = 14.2 Hz, 1 H_{minor}, NCH*H*Ar); δ_C (75 MHz, $CDCl_3$) 159.3 (s), 135.6 (s), 133.7 (s), 132.3 (s), 131.2 (d), 130.5 (d), 130.3 (d), 128.8 (d), 127.3 (s), 113.8 (d), 113.7 (d), 83.1 (s), 82.8 (s), 77.8 (t), 77.2 (t), 74.1 (d), 58.9 (t), 55.2 (q), 18 out of 26 expected signals observed; *m/z* (FAB^+) 654 (MNa^+, $^{37}Cl^{81}Br$, 1), 652 (MNa^+, $^{37}Cl^{79}Br$ and $^{35}Cl^{81}Br$, 5), 650 (MNa^+, $^{35}Cl^{79}Br$, 4), 176 (100); HRMS (FAB^+): calcd for $C_{23}H_{16}{}^{79}Br^{35}ClF_5NNaO_5S$ (MNa^+) 649.9439, found 649.9441.

Data for **162c**: R_f 0.26 (2:1 petroleum ether 40-60°C/Et_2O); mp 109-112 °C; υ_{max} (neat)/cm^{-1} 3002, 2935, 1773, 1612, 1513, 1420, 1306, 1236, 1149, 1010, 836, 799; δ_H (500 MHz, $CDCl_3$) 7.36-7.41 (m, 4 H, Ar*H*), 7.19 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.30 (br dd, *J* = 11.8, 7.1 Hz, 1 H, NC*H*), 4.09 (d, *J* = 14.3 Hz, 1 H, NC*H*HAr), 3.90 (d, *J* = 14.3 Hz, 1 H, NCH*H*Ar), 3.79 (s, 3 H, OCH_3), 2.97 (dd, *J* = 17.0, 7.1 Hz, 1 H, SCBrC*H*H), 2.89 (dd, *J* = 17.0, 11.8 Hz, 1 H, SCBrCH*H*); δ_C (125 MHz, $CDCl_3$) 172.1 (s), 159.4 (s), 134.9 (s), 134.7 (s), 130.6 (d), 129.3 (d), 128.8 (d), 126.8 (s), 113.8 (d), 68.8 (d), 60.2 (t), 55.3 (q), 40.2 (t).

4-Bromo-3-(4-bromophenyl)-2-(4-methoxybenzyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester (160/161d), and 5-Bromo-3-(4-bromophenyl)-2-(4-methoxybenzyl)isoxazolidine-5-sulfonic acid pentafluorophenyl ester (162d)



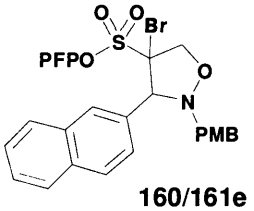
α-Bromo PFP vinyl sulfonate **143** (2.0 g, 5.7 mmol) and DABCO (60 mg, 0.6 mmol) was dissolved in PhMe (40 mL) and stirred at RT for 5 mins, then treated with *C*-(4-bromophenyl)-*N*-(4-methoxybenzyl) nitrone **136b** (2.7 g, 8.5 mmol). After 24 hours stirring enough DCM (10 mL) was added to aid dissolution of the nitrone and the resulting suspension was stirred for a further 1 day at RT. Solvent was removed *in*

vacuo and the crude residue was purified by flash chromatography (starting 30:1 petroleum ether 40-60°C/Et_2O) giving products **160/161d** (2.0 g, 52%) as a mixture of diastereoisomers and **162d** (0.18 g, 5%) as a single product- overall yield (57%, **160/161d**:**162d** = 11:1, **160** and **161d** = 5:2 major:minor).

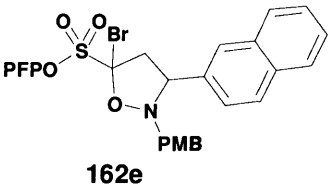
Data for **160/161d**: R_f 0.70 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2935, 1589, 1384, 1246, 1190, 1067, 994, 819, 722; δ_H (300 MHz, $CDCl_3$) 7.58 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.40 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.20 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 6.83 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 5.07 (d, *J* = 11.0 Hz, 1 H_{major}, SCBrC*H*H), 5.03 (d, *J* = 11.0 Hz, 1 H_{minor}, SCBrC*H*H), 4.61 (s, 1 H_{minor}, NC*H*), 4.59 (s, 1 H_{major}, NC*H*), 4.54 (d, *J* = 11.0 Hz, 1 H, SCBrCH*H*), 4.11 (d, *J* = 14.5 Hz, 1 H_{minor}, NC*H*HAr), 4.07 (d, *J* = 14.5 Hz, 1 H_{major}, NC*H*HAr), 3.82 (d, *J* = 14.5 Hz, 1 H_{major}, NCH*H*Ar), 3.81 (s, 3 H_{minor}, OCH_3), 3.79 (s, 3 H_{major}, OCH_3), 3.71 (d, *J* = 14.5 Hz, 1 H_{minor}, NCH*H*Ar); δ_C (75 MHz, $CDCl_3$) 159.3 (s), 132.9 (s), 132.5 (d), 131.8 (d), 131.5 (d), 131.0 (d), 130.5 (d), 130.3 (d), 127.3 (s), 123.9 (s), 113.8 (d), 113.7 (d), 82.7 (s), 77.8 (t), 74.2 (d), 59.0 (t), 58.7 (t), 55.2 (q), 18 out of 26 expected signals observed; *m/z* (FAB^+) 698 (MNa^+, $^{81}Br^{81}Br$, 1), 696 (MNa^+, $^{79}Br^{81}Br$, 3), 694 (MNa^+, $^{79}Br^{79}Br$, 1), 176 (100); HRMS (FAB^+): calcd for $C_{23}H_{16}{}^{79}Br_2F_5NNaO_5S$ (MNa^+) 693.8934, found 693.8924.

Data for **162d**: R_f 0.18 (2:1 petroleum ether 40-60°C/Et_2O); mp 116-118 °C; υ_{max} (neat)/cm^{-1} 3000, 2840, 1788, 1611, 1511, 1461, 1305, 1236, 1105, 1026, 827; δ_H (300 MHz, $CDCl_3$) 7.54 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.23 (d, *J* = 8.3 Hz, 1 H, Ar*H*), 7.19 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.29 (br dd, *J* = 11.5, 7.5 Hz, 1 H, NC*H*), 4.09 (d, *J* = 14.5 Hz, 1 H, NC*H*HAr), 3.89 (d, *J* = 14.5 Hz, 1 H, NCH*H*Ar), 3.79 (s, 3 H, OCH_3), 2.98 (dd, *J* = 16.9, 7.5 Hz, 1 H, SCBrC*H*H), 2.88 (dd, *J* = 16.9, 11.5 Hz, 1 H, SCBrCH*H*); δ_C (75 MHz, $CDCl_3$) 172.1 (s), 159.4 (s), 135.5 (s), 132.3 (d), 130.7 (d), 129.2 (d), 126.8 (s), 122.9 (s), 113.9 (d), 68.9 (d), 60.3 (t), 55.3 (q), 40.2 (t).

4-Bromo-2-(4-methoxybenzyl)-3-naphthalen-2-yl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester (160/161e), and 5-Bromo-2-(4-methoxybenzyl)-3-naphthalen-2-yl-isoxazolidine-5-sulfonic acid pentafluorophenyl ester (162e)



160/161e



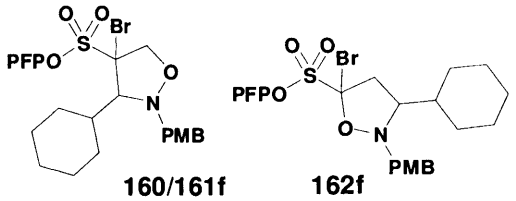
162e

α-Bromo PFP vinyl sulfonate **143** (2.0 g, 5.7 mmol) and DABCO (60 mg, 0.6 mmol) was dissolved in PhMe (40 mL) and stirred at RT for 5 mins, then treated with *C*-(2-naphthyl)-*N*-(4-methoxybenzyl) nitrone **136f** (2.5 g, 8.5 mmol). After 24 hours stirring enough DCM (10 mL) was added to aid dissolution of the nitrone and the resulting suspension was stirred for a further 1 day at RT. Solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (starting 30:1 petroleum ether 40-60°C/Et_2O) giving products **160/161e** (2.9 g, 81%) as a mixture of diastereoisomers and **162e** (0.15 g, 4%) as a single product- overall yield (85%, **160/161e**:**162e** = 19:1, **160** and **161e** = 2:1 major:minor).

Data for **160/161e**: R_f 0.60 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2936, 2837, 1514, 1468, 1384, 1246, 1190, 994, 820, 739; δ_H (300 MHz, $CDCl_3$) 8.02 (br s, 1 H, Ar*H*), 7.84-7.97 (m, 3 H, Ar*H*), 7.50-7.69 (m, 3 H, Ar*H*), 7.25 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.6 Hz, 2 H_{minor}, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2 H_{major}, Ar*H*), 5.13 (d, *J* = 11.0 Hz, 1 H, SCBrC*H*H), 4.84 (s, 1 H_{minor}, NC*H*), 4.83 (s, 1 H_{major}, NC*H*), 4.66 (d, *J* = 11.0 Hz, 1 H_{minor}, SCBrCH*H*), 4.64 (d, *J* = 11.0 Hz, 1 H_{major}, SCBrCH*H*), 4.15 (d, *J* = 14.2 Hz, 1 H, NC*H*HAr), 3.86 (d, *J* = 14.2 Hz, 1 H, NCH*H*Ar), 3.82 (s, 3 H_{minor}, OCH_3), 3.79 (s, 3 H_{major}, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.3 (s), 133.9 (s), 133.0 (s), 131.3 (s), 130.5 (d), 130.3 (d), 129.1 (s), 128.4 (d), 128.2 (d), 127.8 (d), 127.7 (d), 127.1 (d), 127.0 (d), 126.5 (d), 113.8 (d), 113.7 (d), 83.0 (s), 77.9 (t), 77.2 (t), 74.9 (d), 59.1 (t), 58.7 (t), 55.2 (q), 23 out of 32 expected signals observed; *m/z* (FAB^+) 668 (MNa^+, ^{81}Br, 9), 666 (MNa^+, ^{79}Br, 9), 644 (20), 245 (19), 166 (100); HRMS (FAB^+): calcd for $C_{27}H_{19}{}^{79}BrF_5NNaO_5S$ (MNa^+) 665.9985, found 665.9971.

Data for **162e**: R_f 0.20 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2934, 2836, 1773, 1612, 1513, 1302, 1242, 1173, 1031, 904, 820, 728; δ_H (300 MHz, $CDCl_3$) 7.84-7.94 (m, 4 H, Ar*H*), 7.61 (dd, *J* = 8.6, 1.6 Hz, 1 H, Ar*H*), 7.52-7.57 (m, 2 H, Ar*H*), 7.22 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.50 (br dd, *J* = 11.0, 8.0 Hz, 1 H, NC*H*), 4.17 (d, *J* = 14.2 Hz, 1 H, NC*H*HAr), 3.94 (d, *J* = 14.2 Hz, 1 H, NCH*H*Ar), 3.78 (s, 3 H, OCH_3), 3.09 (dd, *J* = 16.9, 11.0 Hz, 1 H, SCBrC*H*H), 3.02 (dd, *J* = 16.9, 8.0 Hz, 1 H, SCBrCH*H*); δ_C (75 MHz, $CDCl_3$) 172.5 (s), 159.4 (s), 133.6 (s), 133.5 (s), 133.3 (s), 130.7 (d), 129.2 (d), 127.9 (d), 127.8 (d), 127.3 (d), 127.2 (s), 126.7 (d), 124.4 (d), 113.9 (d), 69.9 (d), 60.3 (t), 55.3 (q), 40.3 (t), 1 x d not observed; *m/z* (CI) 646 (MH^+, ^{81}Br, 1), 644 (MH^+, ^{79}Br, 1), 410 (31), 334 (48), 290 (70), 199 (74), 121 (100).

4-Bromo-3-cyclohexyl-2-(4-methoxybenzyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester (160/161f), and 5-Bromo-3-cyclohexyl-2-(4-methoxy benzyl)isoxazolidine-5-sulfonic acid pentafluorophenyl ester (162f)



160/161f **162f**

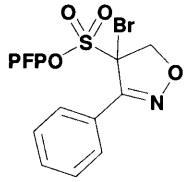
α-Bromo-PFP-vinyl sulfonate **143** (1.4 g, 4.0 mmol) and DABCO (50 mg, 0.4 mmol) was dissolved in PhMe (30 mL) and stirred at RT for 5 mins, then treated with *C*-(cyclohexyl)-*N*-(4-methoxybenzyl) nitrone **136e** (1.5 g, 6.1 mmol). The resulting suspension was stirred at RT for 18 hours. Solvent was removed *in vacuo* and the crude residue purified by flash chromatography (starting 30:1 petroleum ether 40-60°C/Et_2O) to give **160/161f** (1.3 g, 54%) and **162f** (0.34 g, 14%) as a single products- overall yield (68%, **160/161f**:**162f** = 4:1).

Data for **160/161f**: R_f 0.72 (2:1 petroleum ether 40-60°C/Et_2O); mp 112-114 °C; υ_{max} (neat)/cm^{-1} 2973, 2937, 1613, 1514, 1391, 1257, 1133, 994, 816; δ_H (300 MHz, $CDCl_3$) 7.32 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.06 (d, *J* = 11.0 Hz, 1 H, SCBrC*H*H), 4.49 (d, *J* = 11.0 Hz, 1 H, SCBrCH*H*), 4.11 (d, *J* = 13.7 Hz, 1 H, NC*H*HAr), 4.01 (d, *J* = 13.7 Hz, 1 H, NCH*H*Ar), 3.80 (s, 3 H, OCH_3), 3.46 (br d, *J* = 5.6 Hz, 1 H, NC*H*), 2.15 (app. br d, *J* = 12.6 Hz, 1 H, cyclohexyl-*H*), 1.97-2.09 (m, 1 H, cyclohexyl-*H*), 1.91 (app. br d, *J* = 12.6 Hz, 1 H, cyclohexyl-*H*), 1.66-1.85 (m, 3 H, cyclohexyl-*H*), 1.32 (app. br t, *J* = 12.6 Hz, 2 H, cyclohexyl-*H*), 1.07-1.25 (m, 3 H, cyclohexyl-*H*); δ_C (75 MHz, $CDCl_3$) 159.2 (s), 130.2 (d), 128.5 (s), 113.8 (d), 83.4 (s), 77.3 (t), 73.8 (d), 60.5 (t), 55.2 (q), 42.0 (d), 32.4 (t), 29.6 (t), 26.3 (t), 26.2 (t), 26.1 (t); *m/z* (FAB^+) 624 (MNa^+, ^{81}Br, 12), 622 (MNa^+, ^{79}Br, 12), 270 (20), 176 (100); HRMS (FAB^+): calcd for $C_{23}H_{23}{}^{79}BrF_5NNaO_5S$ (MNa^+) 622.0298, found 622.0301.

Data for **162f**: R_f 0.27 (2:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 2926, 2852, 1772, 1612, 1513, 1450, 1246, 1171, 1032, 910, 802; δ_H (500 MHz, $CDCl_3$) 7.27 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 4.11 (d, *J* = 13.7 Hz, 1 H, NC*H*HAr), 4.03 (d, *J* = 13.7 Hz, 1 H, NCH*H*Ar), 3.80 (s, 3 H, OCH_3), 3.20 (app. dt, *J* = 7.7, 5.9 Hz, 1 H, NC*H*), 2.64 (dd, *J* = 17.5, 8.0 Hz, 1 H, SCBrC*H*H), 2.57 (dd, *J* = 17.5, 8.3 Hz, 1 H, SCBrCH*H*), 1.62-1.78 (m, 5 H, cyclohexyl-*H*), 1.46-1.53 (m, 1 H, C*H*CHN), 1.10-1.26 (m, 3 H, cyclohexyl-*H*), 1.01 (ddd, *J* = 15.6, 12.5, 3.2 Hz, 1 H, cyclohexyl-*H*), 0.86-0.95 (m, 1 H, cyclohexyl-*H*); δ_C (125 MHz, $CDCl_3$) 175.6 (s), 159.4 (s), 130.7 (d), 127.1 (s), 113.9 (d), 68.0 (d), 62.4 (t), 55.3 (q), 40.4 (d), 31.9 (t), 29.9 (t), 28.0 (t), 26.3

(t), 26.1 (t), 25.8 (t); *m/z* (CI) 602 (MH^+, ^{81}Br, 1), 600 (MH^+, ^{79}Br, 1), 577 (21), 410 (37), 290 (87), 230 (31), 208 (43), 182 (80), 121 (100).

4-Bromo-3-phenyl-4,5-dihydroisoxazole-4-sulfonic acid pentafluorophenyl ester (164)

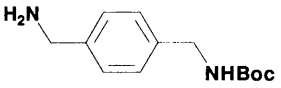


To a stirring suspension of isoxazolidine **160/161a** (100 mg, 0.17 mmol) in benzene (4 mL) DDQ (150 mg, 0.67 mmol) was added. The reaction was stirred at RT for 10 days. Removal of solvent followed by column chromatography (starting 15:1 petroleum ether 40-60°C/Et_2O) yielded the desired product **164** (17 mg, 21%) as a yellow solid.

R_f 0.65 (4:1 petroleum ether 40-60°C/Et_2O); mp 105-108 °C; υ_{max} (neat)/cm^{-1} 3063, 2920, 1519, 1447, 1189, 920, 762; δ_H (300 MHz, $CDCl_3$) 7.94-7.99 (m, 2 H, Ar*H*), 7.41-7.54 (m, 3 H, Ar*H*), 5.58 (d, *J* = 12.3 Hz, 1 H, SCBrC*H*H), 5.26 (d, *J* = 12.3 Hz, 1 H, SCBrCH*H*); δ_C (75 MHz, $CDCl_3$) 152.1 (s), 131.5 (d), 128.7 (d), 128.6 (d), 124.9 (s), 82.9 (t), 75.9 (s); *m/z* (EI) 473 (M^+, ^{81}Br, 1), 471 (M^+, ^{79}Br, 1), 392 (34), 225 (32), 208 (67), 184 (64), 144 (100), 89 (63); HRMS (EI): calcd for $C_{15}H_7{}^{79}BrF_5NO_4S$ (M^+) 470.9194, found 470.9203.

4.8. Procedures from HIV studies

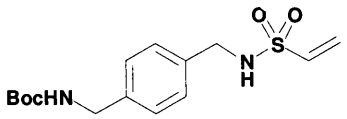
(4-Aminomethylbenzyl)carbamic acid *tert*-butyl ester (187) [178]



p-Xylyldiamine (3.1 g, 22.9 mmol) in DCM (20 mL) at 0 °C was treated with NEt_3 (7.7 mL, 55.0 mmol). To this ice-cold suspension was added dropwise over 3 hours a solution of Boc_2O (2.0 g, 9.2 mmol) in DCM (25 mL) whilst maintaining the temperature at 0 °C. The reaction mixture was allowed to stir at RT overnight then concentrated *in vacuo*. The residue was redissolved in DCM (30 mL) and washed consecutively with sat. $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the product (2.0 g, 92%) as a white solid. Data agrees with literature.

mp 146-148 °C; δ_H (300 MHz, $CDCl_3$) 7.25 (m, 4 H, Ar*H*), 4.88 (br s, 1 H, N*H*), 4.28 (br d, *J* = 4.9 Hz, 2 H, C*H*$_2$NHBoc), 3.84 (s, 2 H, C*H*$_2$NH$_2$), 1.45 (s, 9 H, C(C*H*$_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 156.0 (s), 142.2 (s), 137.6 (s), 127.6 (d), 127.2 (d), 79.2 (s), 46.1 (t), 44.3 (t), 28.4 (q).

[4-(Ethenesulfonylaminomethyl)benzyl]carbamic acid *tert*-butyl ester (185)

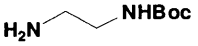


A premixed suspension of (4-aminomethylbenzyl)carbamic acid *tert*-butyl ester **187** (1.9 g, 8.0 mmol) and NEt_3 (2.8 mL, 20.1 mmol) in DCM (10 mL) was added dropwise to a stirring solution of 2-chloroethane-1-sulfonyl chloride (1.1 g, 6.7 mmol) in DCM (10 mL) at -10 °C. The reaction mixture was stirred for a further 1 hour after addition and then warmed to RT. The reaction was diluted with DCM (20 mL) and washed with H_2O (1 x 25 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* to give the crude which was purified by flash chromatography (starting 1:1 petroleum ether 40-60°C/Et_2O) to furnish the desired product (1.8 g, 84%) as white solid.

R_f 0.16 (1:2 petroleum ether 40-60°C/Et_2O); mp 141-142 °C; υ_{max} (neat)/cm^{-1} 3369, 3207, 2976, 1687, 1509, 1427, 1330, 1248, 1154, 1051, 960; δ_H (300 MHz, $CDCl_3$) 6.48 (dd, *J* = 16.6, 9.6 Hz, 1 H, SC*H*=), 6.25 (d, *J* = 16.6 Hz, 1 H, SCH=C*H*H), 5.92 (d, *J* = 9.6 Hz, 1 H, SCH=CH*H*), 4.87 (br s, 1 H, BocN*H*), 4.68 (br s, 1 H, N*H*), 4.28 (br d, *J* = 5.9 Hz, 2 H, BocNHC*H*$_2$), 4.18 (d, *J* = 6.2 Hz, 2 H, NHC*H*$_2$), 1.45 (s, 9 H, C(C*H*$_3$)$_3$); δ_C

(75 MHz, $CDCl_3$) 155.9 (s), 139.0 (s), 136.1 (d), 135.6 (s), 128.2 (d), 127.8 (d), 126.7 (t), 46.7 (t), 44.2 (t), 28.4 (q); *m/z* (ES^+) 365 (38), 349 (MNa^+, 100), 293 (19), 180 (40); HRMS (ES^+): calcd for $C_{15}H_{22}N_2NaO_4S$ (MNa^+) 349.1207, found 349.1198.

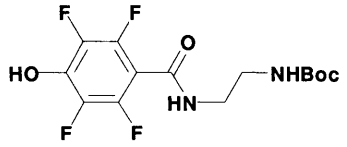
(2-Aminoethyl)carbamic acid *tert*-butyl ester (192) [179]



Ethylenediamine (33.5 mL, 500.0 mmol) in DCM (300 mL) was added dropwise over 3 hours to a solution of Boc_2O (11.5 mL, 50.0 mmol) in DCM (50 mL), whilst stirring at 0 °C. After addition the reaction mixture was allowed to stir at RT overnight. The suspension was washed with H_2O (3 x 60 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the product (6.2 g, 78%) as a white gel. Data agrees with literature.

δ_H (300 MHz, $CDCl_3$) 5.01 (br s, 1 H, N*H*), 3.12 (app. q, J = 5.9 Hz, 2 H, NCH_2), 2.75 (t, J = 5.9 Hz, 2 H, CH_2N), 1.40 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 156.2 (s), 79.1 (s), 43.4 (t), 41.9 (t), 28.4 (q).

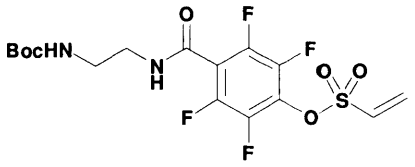
[2-(2,3,5,6-Tetrafluoro-4-hydroxybenzoylamino)ethyl]carbamic acid *tert*-butyl ester (194)



HOBt (1.3 g, 9.6 mmol) and EDC.HCl (2.9 g, 15.3 mmol) was added to a suspension of 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid hydrate (2.0 g, 8.8 mmol) in THF (80 mL) and left to stir at RT for 10 minutes. (2-Aminoethyl)carbamic acid *tert*-butyl ester **192** (1.4 g, 8.8 mmol) was added and stirred overnight at RT. Brine (40 mL) was added and the reaction mixture extracted with EtOAc (3 x 80 mL). The combined EtOAc layers was washed with brine, dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. Purification by flash chromatography (starting 3:1 petroleum ether 40-60°C/EtOAc) furnished the desired product (2.2 g, 71%) as a white solid.

R_f 0.18 (2:1 EtOAc/petroleum ether 40-60°C); mp 151-154 °C; υ_{max} (neat)/cm^{-1} 3395, 3327, 2983, 1652, 1542, 1489, 1329, 1238, 1160, 969, 746; δ_H (300 MHz, CD_3OD) 3.43 (t, J = 6.4 Hz, 2 H, NCH_2), 3.24 (t, J = 6.4 Hz, 2 H, NCH_2), 1.42 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, CD_3OD) 161.5 (s), 80.3 (s), 41.0 (t), 40.6 (t), 28.7 (q); *m/z* (FAB^+) 375 (MNa^+, 31), 297 (28), 154 (100); HRMS (FAB^+): calcd for $C_{14}H_{16}F_4N_2NaO_4$ (MNa^+) 375.0944, found 375.0950.

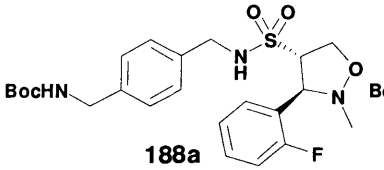
Ethenesulfonic acid 4-(2-*tert*-butoxycarbonylaminoethylcarbamoyl)-2,3,5,6-tetra fluorophenyl ester (186)



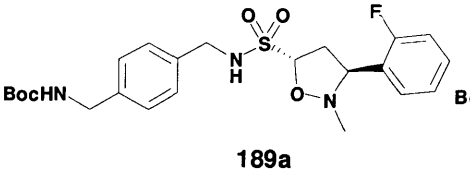
A premixed suspension of [2-(2,3,5,6-tetrafluoro-4-hydroxybenzoylamino)ethyl] carbamic acid *tert*-butyl ester **194** (1.0 g, 2.8 mmol) and NEt_3 (1.1 mL, 8.1 mmol) in DCM (20 mL) was added dropwise to a stirring solution of 2-chloroethane-1-sulfonyl chloride (440 mg, 2.7 mmol) in DCM (15 mL) at -10 °C. The reaction mixture was stirred for a further 1 hour after addition, followed by 3 hours at RT. The reaction was diluted with DCM (20 mL) and washed with H_2O (1 x 25 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* to give a crude product which was purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/Et_2O) to furnish the desired product (0.6 g, 52%) as a white solid.

R_f 0.13 (2:1 Et_2O/petroleum ether 40-60°C); mp 149-152 °C; υ_{max} (neat)/cm^{-1} 3364, 3322, 3083, 2949, 1686, 1653, 1427, 1375, 1250, 1177, 986, 709; δ_H (300 MHz, $CDCl_3$) 7.23 (br s, 1 H, N*H*), 6.80 (dd, *J* = 16.6, 9.6 Hz, 1 H, SC*H*=), 6.54 (d, *J* = 16.6 Hz, 1 H, SCH=C*H*H), 6.33 (d, *J* = 9.6 Hz, 1 H, SCH=CH*H*), 4.96 (br t, *J* = 5.6 Hz, 1 H, N*H*), 3.57 (app. q, *J* = 5.4 Hz, 2 H, NCH_2), 3.38 (app q, *J* = 5.6 Hz, 2 H, NCH_2), 1.41 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, CD_3OD) 159.6 (s), 134.6 (t), 133.3 (d), 80.3 (s), 41.0 (t), 40.6 (t), 28.7 (q); *m/z* (ES^+) 506 (100), 465 (MNa^+, 84), 180 (53); HRMS (ES^+): calcd for $C_{16}H_{18}F_4N_2NaO_6S$ (MNa^+) 465.0700, found 465.0719.

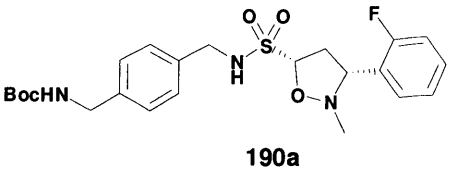
(3*S, 4*S**)-(4-{[3-(2-Fluorophenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl} benzyl)carbamic acid *tert*-butyl ester (188a), (3*R**, 5*S**)-(4-{[3-(2-Fluorophenyl)-2-methylisoxazolidine-5-sulfonylamino]methyl}benzyl)carbamic acid *tert*-butyl ester (189a), and (3*S**, 5*S**)-(4-{[3-(2-Fluorophenyl)-2-methylisoxazolidine-5-sulfonyl amino]methyl}benzyl)carbamic acid *tert*-butyl ester (190a)**



188a



189a



190a

To a solution of [4-(ethenesulfonylaminomethyl)benzyl]carbamic acid *tert*-butyl ester **185** (200 mg, 0.6 mmol) in dry toluene (5 mL), *C*-(2-fluorophenyl)-*N*-methyl nitrone **119i** (280 mg, 1.8 mmol) was added. The reaction mixture was heated in a CEM

microwave for 30 minutes at 140 °C. When complete the reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/Et_2O) to give the three products **188a** (90 mg, 31%), **189a** (75 mg, 26%), and **190a** (32 mg, 11%) as light brown solids- overall yield (67%, **188a**:**189a**:**190a** = 3:2:1).

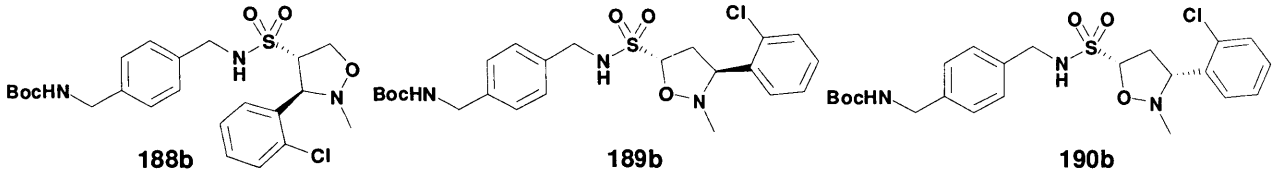
Data for **190a**: R_f 0.25 (2:1 Et_2O/petroleum ether 40-60°C); mp 122-124 °C; υ_{max} (neat)/cm^{-1} 3393, 3291, 2926, 1687, 1513, 1427, 1362, 1299, 1145, 1051, 927, 812, 754; δ_H (300 MHz, $CDCl_3$) 7.57 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.34 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.24-7.30 (m, 3 H, Ar*H*), 7.15 (app. dt. *J* = 7.8, 1.1 Hz, 1 H, Ar*H*), 7.02-7.09 (m, 1 H, Ar*H*), 5.05 (dd, *J* = 8.6, 5.6 Hz, 1 H, SC*H*), 4.84-4.90 (m, 2 H, SN*H* and BocN*H*), 4.44 (d, *J* = 6.2 Hz, 1 H, SNHC*H*H), 4.43 (d, *J* = 5.9 Hz, 1 H, SNHCH*H*), 4.30 (br d, *J* = 5.6 Hz, 2 H, BocNHCH_2), 4.01 (dd, *J* = 10.2, 7.8 Hz, 1 H, NC*H*), 3.07 (ddd, *J* = 13.7, 8.6, 7.8 Hz, 1 H, SCHC*H*H), 2.85 (ddd, *J* = 13.7, 10.2, 5.6 Hz, 1 H, SCHCH*H*), 2.66 (s, 3 H, NCH_3), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 159.6 (s), 155.9 (s), 138.8 (s), 136.3 (s), 129.8 (d, J_{CF} = 8.8 Hz), 128.7 (d, J_{CF} = 3.5 Hz), 128.2 (d), 127.8 (d), 124.9 (d, J_{CF} = 3.8 Hz), 123.5 (s, J_{CF} = 12.6 Hz), 115.6 (d, J_{CF} = 22.0 Hz), 89.5 (d), 79.6 (s), 65.2 (d), 47.5 (t), 44.3 (t), 43.4 (q), 39.6 (t), 28.4 (q); *m/z* (ES^+) 480 (MH^+, 100), 424 (25), 263 (18), 101 (26); HRMS (ES^+): calcd for $C_{23}H_{31}FN_3O_5S$ (MH^+) 480.1963, found 480.1965.

Data for **189a**: R_f 0.18 (2:1 Et_2O/petroleum ether 40-60°C); mp 86-88 °C; υ_{max} (neat)/cm^{-1} 3363, 3239, 2919, 1696, 1512, 1454, 1363, 1248, 1151, 1050, 875, 831, 753; δ_H (300 MHz, $CDCl_3$) 7.43 (app. br t, *J* = 6.7 Hz, 1 H, Ar*H*), 7.32 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.25-7.30 (m, 1 H, Ar*H*), 7.24 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.14 (app. br t, *J* = 7.2 Hz, 1 H, Ar*H*), 7.02-7.09 (m, 1 H, Ar*H*), 5.12 (br t, *J* = 5.6 Hz, 1 H, BocN*H*), 4.89-4.96 (m, 2 H, SN*H* and SC*H*), 4.34-4.44 (m, 3 H, NC*H* and SNHCH_2), 4.27 (br d, *J* = 5.4 Hz, 2 H, BocNHCH_2), 3.12 (ddd, *J* = 13.4, 6.4, 3.8 Hz, 1 H, SCHC*H*H), 2.72-2.81 (m, 4 H, NCH_3 and SCHCH*H*), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 160.8 (s, J_{CF} = 247.4 Hz), 156.0 (s), 138.9 (s), 136.1 (s), 129.6 (d, J_{CF} = 8.8 Hz), 128.2 (d), 127.8 (d), 124.6 (d, J_{CF} = 3.5 Hz), 124.4 (s), 115.7 (d, J_{CF} = 21.7 Hz), 89.7 (d), 79.6 (s), 63.9 (d), 47.5 (t), 44.8 (q), 44.3 (t), 28.4 (q), 1 x d not observed; *m/z* (ES^+) 480 (MH^+, 100), 424 (25), 129 (21), 101 (33); HRMS (ES^+): calcd for $C_{23}H_{31}FN_3O_5S$ (MH^+) 480.1963, found 480.1959.

Data for **188a**: R_f 0.12 (2:1 Et_2O/petroleum ether 40-60°C); mp 107-110 °C; υ_{max} (neat)/cm^{-1} 3379, 3181, 2918, 1685, 1537, 1455, 1367, 1281, 1145, 1046, 857, 762; δ_H

(300 MHz, $CDCl_3$) 7.41 (app. br t, J = 7.2 Hz, 1 H, Ar*H*), 7.34 (app. dt, J = 7.8, 1.9 Hz, 1 H, Ar*H*), 7.13 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.10-7.21 (m, 1 H, Ar*H*), 7.03 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.01-7.08 (m, 1 H, Ar*H*), 5.12 (br s, 1 H, SN*H*), 4.94 (br t, J = 5.6 Hz, 1 H, BocN*H*), 4.37 (dd, J = 9.9, 3.5 Hz, 1 H, SCHC*H*H), 4.15-4.20 (m, 4 H, SCHCH*H*, NHCH_2, and BocNHC*H*H), 4.12 (br d, J = 6.4 Hz, 1 H, NC*H*), 3.93-4.03 (m, 2 H, BocNHCH*H* and SC*H*), 2.60 (s, 3 H, NCH_3), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 161.1 (s, J_{CF} = 248.3 Hz), 156.0 (s), 138.9 (s), 135.4 (s), 130.5 (d, J_{CF} = 8.8 Hz), 129.9 (d, J_{CF} = 3.2 Hz), 128.2 (d), 127.8 (d), 125.0 (d, J_{CF} = 3.5 Hz), 123.7 (s, J_{CF} = 11.7 Hz), 116.1 (d, J_{CF} = 22.0 Hz), 79.6 (s), 72.3 (d), 68.0 (d), 67.0 (t), 47.0 (t), 44.2 (t), 42.8 (q), 28.4 (q); *m/z* (ES^+) 518 (37), 502 (MNa^+, 100), 454 (20); HRMS (ES^+): calcd for $C_{23}H_{30}FN_3NaO_5S$ (MNa^+) 502.1795, found 502.1788.

(3*S, 4*S**)-(4-{[3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl} benzyl)carbamic acid *tert*-butyl ester (188b), (3*R**, 5*S**)-(4-{[3-(2-Chlorophenyl)-2-methylisoxazolidine-5-sulfonylamino]methyl}benzyl)carbamic acid *tert*-butyl ester (189b), and (3*S**, 5*S**)-(4-{[3-(2-Chlorophenyl)-2-methylisoxazolidine-5-sulfonyl amino]methyl}benzyl)carbamic acid *tert*-butyl ester (190b)**



To a solution of [4-(ethenesulfonylaminomethyl)benzyl]carbamic acid *tert*-butyl ester **185** (250 mg, 0.8 mmol) in dry toluene (5 mL), *C*-(2-chlorophenyl)-*N*-methyl nitrone **119j** (390 mg, 2.3 mmol) was added. The reaction mixture was heated in a CEM microwave for 30 minutes at 140 °C. When complete the reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/Et_2O) to give the three products **188b** (98 mg, 25%), **189b** (65 mg, 17%), and **190b** (41 mg, 11%)- overall yield (53%, **188b**:**189b**:**190b** = 5:3:2).

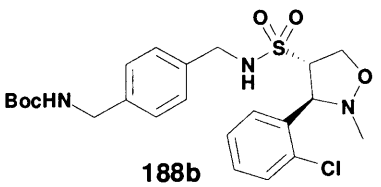
Data for **190b**: R_f 0.30 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3312, 2917, 1689, 1514, 1440, 1366, 1249, 1149, 1051, 861, 755; δ_H (300 MHz, $CDCl_3$) 7.64 (dd, J = 7.2, 2.1 Hz, 1 H, Ar*H*), 7.34 (d, J = 8.3 Hz, 2 H, Ar*H*), 7.15-7.38 (m, 5 H, Ar*H*), 5.04 (dd, J = 8.8, 5.6 Hz, 1 H, SC*H*), 4.84-4.96 (m, 2 H, BocN*H* and SN*H*), 4.42 (d, J = 5.9 Hz, 2 H, SNHCH_2), 4.29 (br d, J = 5.6 Hz, 2 H, BocNHCH_2), 4.19 (dd, J = 9.9, 7.8 Hz, 1 H, NC*H*), 3.17 (ddd, J = 13.7, 8.8, 7.8 Hz, 1 H, SCHC*H*H), 2.65-2.74 (m, 4 H, SCHCH*H* and NCH_3), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 155.9 (s), 138.9 (s), 136.3 (s), 134.7 (s), 133.7 (s), 129.6 (d), 129.2 (d), 128.4 (d), 128.2 (d), 127.8 (d), 127.7

(d), 89.4 (d), 79.6 (s), 68.5 (d), 47.5 (t), 44.3 (t), 43.5 (q), 39.6 (t), 28.4 (q); *m/z* (EI) 497 (M^+, ^{37}Cl, 2), 495 (M^+, ^{35}Cl, 6), 385 (60), 225 (45), 164 (79), 106 (61), 57 (100); HRMS (EI): calcd for $C_{23}H_{30}{}^{35}ClN_3O_5S$ (M^+) 495.1589, found 495.1584.

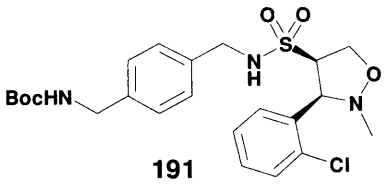
Data for **189b**: R_f 0.22 (2:1 Et_2O/petroleum ether 40-60°C); mp 116-119 °C; υ_{max} (neat)/cm^{-1} 3393, 3290, 2925, 1687, 1512, 1428, 1363, 1271, 1145, 1051, 927, 813, 750; δ_H (300 MHz, $CDCl_3$) 7.53 (dd, *J* = 7.8, 1.9 Hz, 1 H, Ar*H*), 7.20-7.38 (m, 7 H, Ar*H*), 5.04 (app. t, *J* = 5.6 Hz, 1 H, BocN*H*), 4.91 (br s, 1 H, SN*H*), 4.87 (dd, *J* = 8.3, 4.0 Hz, 1 H, SC*H*), 4.58 (br t, *J* = 7.2 Hz, 1 H, NC*H*), 4.37 (d, *J* = 5.9 Hz, 1 H, NHC*H*H), 4.36 (d, *J* = 5.9 Hz, 1 H, NHCH*H*), 4.27 (br d, *J* = 5.6 Hz, 2 H, BocNHCH_2), 3.26 (ddd, *J* = 13.4, 6.7, 4.0 Hz, 1 H, SCHC*H*H), 2.83 (s, 3 H, NCH_3), 2.55-2.67 (m, 1 H, SCHCH*H*), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 155.9 (s), 138.9 (s), 136.0 (s), 135.7 (s), 133.5 (s), 129.7 (d), 129.0 (d), 128.2 (d), 127.8 (d), 127.6 (d), 127.4 (d), 89.9 (d), 79.6 (s), 67.0 (d), 47.5 (t), 45.1 (q), 44.3 (t), 39.0 (t), 28.4 (q); *m/z* (EI) 497 (M^+, ^{37}Cl, 7), 495 (M^+, ^{35}Cl, 17), 385 (72), 225 (42), 154 (87), 106 (75), 57 (100); HRMS (EI): calcd for $C_{23}H_{30}{}^{35}ClN_3O_5S$ (M^+) 495.1589, found 495.1590.

Data for **188b**: R_f 0.09 (2:1 Et_2O/petroleum ether 40-60°C); mp 138-141 °C; υ_{max} (neat)/cm^{-1} 3376, 3209, 2919, 1685, 1538, 1439, 1326, 1280, 1144, 1044, 931, 862, 766; δ_H (300 MHz, $CDCl_3$) 7.47 (dd, *J* = 7.0, 2.1 Hz, 1 H, Ar*H*), 7.29-7.40 (m, 3 H, Ar*H*), 7.11 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.97 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.95 (app. t, *J* = 5.6 Hz, 1 H, BocN*H*), 4.90 (br t, *J* = 5.9 Hz, 2 H, SN*H*), 4.46 (br d, *J* = 7.0 Hz, 1 H, NC*H*), 4.41 (dd, *J* = 9.9, 4.0 Hz, 1 H, SCHC*H*H), 4.31 (dd, *J* = 9.9, 8.6 Hz, 1 H, SCHCH*H*), 4.24 (br d, *J* = 5.9 Hz, 2 H, SNHCH_2), 4.13 (dd, *J* = 13.9, 6.4 Hz, 1 H, BocNHC*H*H), 3.96 (app. td, *J* = 8.0, 4.0 Hz, 1 H, SC*H*), 3.85 (dd, *J* = 13.9, 5.0 Hz, 1 H, BocNHCH*H*), 2.60 (s, 3 H, NCH_3), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 155.9 (s), 138.9 (s), 135.2 (s), 134.3 (s), 134.2 (s), 130.1 (d), 129.9 (d), 129.8 (d), 128.2 (d), 127.8 (d), 79.6 (s), 72.9 (d), 70.1 (d), 67.1 (t), 47.0 (t), 44.2 (t), 42.7 (q), 28.4 (q), 1 x d not observed; *m/z* (ES^+) 498 (MH^+, ^{37}Cl, 42), 496 (MH^+, ^{35}Cl, 100), 440 (22); HRMS (ES^+): calcd for $C_{23}H_{31}{}^{35}ClN_3O_5S$ (MH^+) 496.1667, found 496.1664.

(3*S, 4*S**)-(4-{[3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl} benzyl)carbamic acid *tert*-butyl ester (188b), and (3*S**, 4*R**)-(4-{[3-(2-Chloro phenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl}benzyl)carbamic acid *tert*-butyl ester (191)**



188b



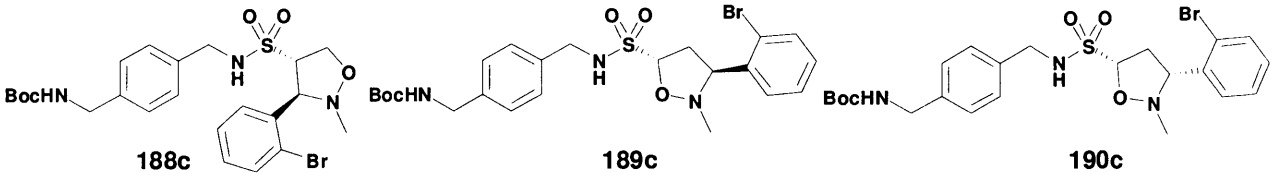
191

(3*S**,4*S**)-3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid pentafluorophenyl ester **103j** (200 mg, 0.5 mmol) in THF (5 mL) was treated with (4-aminomethylbenzyl) carbamic acid *tert*-butyl ester **187** (160 mg, 0.7 mmol) followed by NEt_3 (0.2 mL, 1.4 mmol), and the reaction refluxed for 3 hours. The reaction mixture was concentrated *in vacuo* and the resulting crude residue purified by flash chromatography (starting 8:1 petroleum ether 40-60°C/EtOAc) to give **188b** (144 mg, 64%) and **191** (58 mg, 26%)- overall yield (90%, **188b**:**191** = 5:2).

Data for **188b**: R_f 0.18 (2:1 petroleum ether 40-60°C/EtOAc); Data as for above.

Data for **191**: R_f 0.23 (2:1 petroleum ether 40-60°C/EtOAc); υ_{max} (neat)/cm^{-1} 3341, 2965, 1688, 1515, 1440, 1331, 1256, 1148, 1032, 862, 763; δ_H (300 MHz, $CDCl_3$) 7.65 (dd, *J* = 7.5, 1.6 Hz, 1 H, Ar*H*), 7.35 (dd, *J* = 7.5, 1.6 Hz, 1 H, Ar*H*), 7.13-7.31 (m, 6 H, Ar*H*), 4.92 (br s, 1 H, SN*H*), 4.35-4.42 (m, 3 H, SCHCH_2 and SC*H*), 4.26 (br d, *J* = 5.6 Hz, BocNHCH_2), 4.13 (d, *J* = 7.2 Hz, 1 H, NC*H*), 4.11 (dd, *J* = 14.2, 7.0 Hz, 1 H, SNHC*H*H), 3.99 (dd, *J* = 14.2, 4.8 Hz, 1 H, SNHCH*H*), 3.67 (br t, *J* = 5.4 Hz, 1 H, BocN*H*), 2.65 (s, 3 H, NCH_3), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 156.0 (s), 138.9 (s), 135.7 (s), 134.7 (s), 131.2 (s), 130.6 (d), 129.7 (d), 129.1 (d), 128.1 (d), 127.7 (d), 127.1 (d), 79.7 (s), 70.8 (d), 66.8 (t), 66.5 (d), 46.9 (t), 44.2 (t), 43.3 (q), 28.4 (q); *m/z* (EI) 497 (M^+, ^{37}Cl, 4), 495 (M^+, ^{35}Cl, 10), 235 (27), 154 (53), 134 (100), 91 (23); HRMS (EI): calcd for $C_{23}H_{30}{}^{35}ClN_3O_5S$ (M^+) 495.1589, found 495.1597.

(3*S, 4*S**)-(4-{[3-(2-Bromophenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl} benzyl)carbamic acid *tert*-butyl ester (188c), (3*R**, 5*S**)-(4-{[3-(2-Bromophenyl)-2-methylisoxazolidine-5-sulfonylamino]methyl}benzyl)carbamic acid *tert*-butyl ester (189c), and (3*S**, 5*S**)-(4-{[3-(2-Bromophenyl)-2-methylisoxazolidine-5-sulfonyl amino]methyl}benzyl)carbamic acid *tert*-butyl ester (190c)**



188c 189c 190c

To a solution of [4-(ethenesulfonylaminomethyl)benzyl]carbamic acid *tert*-butyl ester **185** (250 mg, 0.8 mmol) in dry toluene (5 mL), *C*-(2-bromophenyl)-*N*-methyl nitrone **119k** (490 mg, 2.3 mmol) was added. The reaction mixture was heated in a CEM microwave for 30 minutes at 140 °C. When complete the reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/Et_2O) to give the three products **188c** (105 mg, 25%), **189c** (45 mg, 11%), and **190c** (40 mg, 10%)- overall yield (46%, **188c**:**189c**:**190c** = 5:2:2).

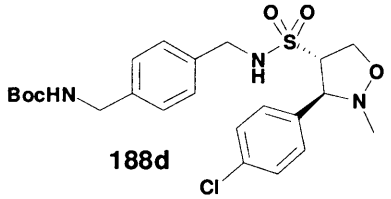
Data for **190c**: R_f 0.24 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3310, 2964, 2918, 1688, 1513, 1434, 1327, 1250, 1152, 1021, 860, 755; δ_H (300 MHz, $CDCl_3$) 7.63 (dd, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.55 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.24-7.36 (m, 5 H, Ar*H*), 7.15 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 5.04 (dd, *J* = 8.6, 5.6 Hz, 1 H, SC*H*), 4.83-4.89 (m, 2 H, SN*H* and BocN*H*), 4.42 (d, *J* = 6.2 Hz, 2 H, SNHCH_2), 4.30 (br d, *J* = 5.6 Hz, 2 H, BocNHCH_2), 4.17 (dd, *J* = 9.6, 7.5 Hz, 1 H, NC*H*), 3.19 (ddd, *J* = 13.6, 8.6, 7.5 Hz, 1 H, SCHC*H*H), 2.68 (s, 3 H, NCH_3), 2.63-2.72 (m, 1 H, SCHCH*H*), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 155.9 (s), 138.9 (s), 136.3 (2 x s), 132.9 (d), 129.6 (d), 128.7 (d), 128.3 (d), 128.2 (d), 127.8 (d), 123.9 (s), 89.4 (d), 79.6 (s), 71.0 (d), 47.5 (t), 44.3 (t), 43.4 (q), 39.7 (t), 28.4 (q); *m/z* (FAB$^+$) 564 (MNa$^+$, ^{81}Br, 9), 562 (MNa$^+$, ^{79}Br, 9), 554 (100), 531 (72), 361 (72), 339 (28), 219 (39), 176 (39); HRMS (FAB$^+$): calcd for $C_{23}H_{30}{}^{79}BrN_3NaO_5S$ (MNa$^+$) 562.0987, found 562.0972.

Data for **189c**: R_f 0.17 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3306, 2918, 2850, 1687, 1513, 1436, 1330, 1249, 1148, 1022, 861, 754; δ_H (300 MHz, $CDCl_3$) 7.55 (dd, *J* = 8.0, 1.3 Hz, 2 H, Ar*H*), 7.25-7.36 (m, 5 H, Ar*H*), 7.16 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 4.90 (dd, *J* = 8.3, 4.0 Hz, 1 H, SC*H*), 4.83-4.89 (m, 1 H, BocN*H*), 4.76 (br t, *J* = 5.9 Hz, 1 H, SN*H*), 4.57 (br t, *J* = 7.2 Hz, 1 H, NC*H*), 4.40 (d, *J* = 5.6 Hz, 1 H, BocNHC*H*H), 4.38 (d, *J* = 5.6 Hz, 1 H, BocNHCH*H*), 4.30 (br d, *J* = 5.9 Hz, 2 H, SNHCH_2), 3.30 (ddd, *J* = 13.4, 6.4, 4.0 Hz, 1 H, SCHC*H*H), 2.85 (s, 3 H, NCH_3), 2.56-

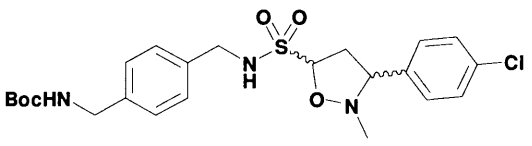
2.66 (m, 1 H, SCHCH*H*), 1.46 (s, 9 H, C(C*H*$_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 155.9 (s), 139.0 (s), 137.4 (s), 136.0 (s), 133.1 (d), 129.4 (d), 128.2 (d), 128.0 (d), 127.9 (2 x d), 123.6 (s), 89.9 (d), 79.7 (s), 69.4 (d), 47.5 (t), 45.2 (q), 44.3 (t), 39.1 (t), 28.4 (q); *m/z* (EI) 541 (M^+, ^{81}Br, 14), 539 (M^+, ^{79}Br, 14), 431 (76), 373 (24), 240 (34), 225 (80), 163 (100); HRMS (EI): calcd for $C_{23}H_{30}{}^{79}BrN_3O_5S$ (M^+) 539.1084, found 539.1083.

Data for **188c**: R_f 0.08 (2:1 Et_2O/petroleum ether 40-60°C); mp 83-86 °C; υ_{max} (neat)/cm^{-1} 3319, 2971, 1688, 1513, 1433, 1326, 1250, 1146, 1027, 863, 761; δ_H (300 MHz, $CDCl_3$) 7.57 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.46 (br d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.34-7.41 (m, 1 H, Ar*H*), 7.20-7.27 (m, 1 H, Ar*H*), 7.11 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.96 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.97 (app. t, *J* = 5.6 Hz, 1 H, BocN*H*), 4.90 (br t, *J* = 5.9 Hz, 1 H, SN*H*), 4.48 (br d, *J* = 7.0 Hz, 1 H, NC*H*), 4.42 (dd, *J* = 9.9, 3.8 Hz, 1 H, SCHC*H*H), 4.32 (dd, *J* = 9.9, 8.3 Hz, 1 H, SCHCH*H*), 4.24 (br d, *J* = 5.9 Hz, 2 H, SNHCH_2), 4.13 (dd, *J* = 13.9, 6.7 Hz, 1 H, BocNHC*H*H), 3.93 (app. td, *J* = 8.0, 3.8 Hz, 1 H, SC*H*), 3.82 (dd, *J* = 13.9, 5.6 Hz, 1 H, BocNHCH*H*), 2.61 (s, 3 H, NCH_3), 1.45 (s, 9 H, C(C*H*$_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 155.9 (s), 138.9 (s), 136.0 (s), 135.2 (s), 133.3 (d), 130.2 (d), 130.1 (d), 128.4 (d), 128.2 (d), 127.8 (d), 124.7 (s), 79.6 (s), 73.1 (d), 72.3 (d), 67.1 (t), 47.1 (t), 44.2 (t), 42.6 (q), 28.4 (q); *m/z* (ES^+) 542 (MH^+, ^{81}Br, 100), 540 (MH^+, ^{79}Br, 95), 105 (27); HRMS (ES^+): calcd for $C_{23}H_{31}{}^{79}BrN_3O_5S$ (MH^+) 540.1162, found 540.1160.

(3*S, 4*S**)-(4-{[3-(4-Chlorophenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl} benzyl)carbamic acid *tert*-butyl ester (188d), (3*R**, 5*S**) and (3*S**, 5*S**)-(4-{[3-(4-Chlorophenyl)-2-methylisoxazolidine-5-sulfonylamino]methyl}benzyl)carbamic acid *tert*-butyl ester (189/190d)**



188d



189/190d

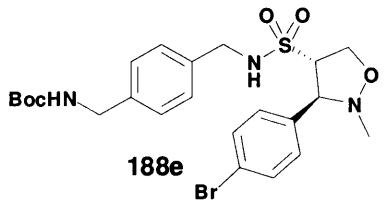
To a solution of [4-(ethenesulfonylaminomethyl)benzyl]carbamic acid *tert*-butyl ester **185** (100 mg, 0.3 mmol) in dry toluene (5 mL), *C*-(4-chlorophenyl)-*N*-methyl nitrone **119e** (160 mg, 0.9 mmol) was added. The reaction mixture was heated in a CEM microwave for 30 minutes at 140 °C. When complete the reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/Et_2O) to give **189/190d** (51 mg, 33%) as a mixture, and

188d (70 mg, 46%)- overall yield (79%, **188d**:**189/190d** = 3:2, **189d** and **190d** = 3:2 major:minor).

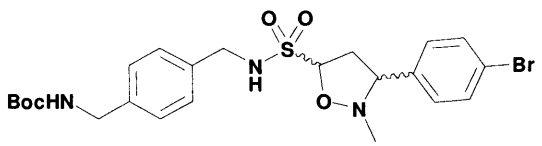
Data for **189/190d**: R_f 0.16 (2:1 Et_2O/petroleum ether 40-60°C); mp 109-112 °C; υ_{max} (neat)/cm^{-1} 3364, 3235, 2925, 1694, 1511, 1326, 1248, 1150, 1050, 875, 830; δ_H (500 MHz, $CDCl_3$) 7.26-7.38 (m, 8 H, Ar*H*), 5.00 (dd, *J* = 8.4, 5.4 Hz, 1 H_{minor}, SC*H*), 4.78-4.96 (m, 3 H, SCH_{major}, N*H* and BocN*H*), 4.13-4.47 (m, 4 H, $NHCH_2$ and $BocNCH_2$), 3.99-4.06 (m, 1 H_{major}, NC*H*), 3.55 (br dd, *J* = 9.8, 7.6 Hz, 1 H_{minor}, NC*H*), 3.05 (ddd, *J* = 13.8, 6.2, 2.4 Hz, 1 H_{major}, SCHC*H*H), 3.02 (ddd, *J* = 13.8, 8.4, 7.6 Hz, 1 H_{minor}, SCHC*H*H), 2.85 (ddd, *J* = 13.8, 9.8, 5.4 Hz, 1 H_{minor}, SCHCH*H*), 2.69-2.77 (m, 4 H, NCH_{3major} and $SCHCHH_{major}$), 2.60 (s, 3 H_{minor}, NCH_3), 1.46 (s, 9 H, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 156.0 (s), 139.1 (s), 139.0 (s), 136.3 (s), 135.9 (s), 134.5 (s), 134.3 (s), 129.6 (d), 129.4 (d), 129.3 (d), 129.2 (2 x d), 129.0 (d), 128.3 (d), 127.9 (d), 89.3 (d), 79.7 (s), 73.6 (d), 72.9 (d), 47.6 (t), 47.2 (t), 44.3 (t), 43.2 (q), 43.2 (t), 28.5 (q), 25 out of 34 expected signals observed; *m/z* (ES^+) 498 (MH^+, ^{37}Cl, 42), 496 (MH^+, ^{35}Cl, 100), 271 (20), 101 (19); HRMS (ES^+): calcd for $C_{23}H_{31}{}^{35}ClN_3O_5S$ (MH^+) 496.1667, found 496.1669.

Data for **188d**: R_f 0.12 (2:1 Et_2O/petroleum ether 40-60°C); mp 146-149 °C; υ_{max} (neat)/cm^{-1} 3394, 3334, 2926, 1683, 1522, 1312, 1268, 1164, 1061, 859, 828; δ_H (300 MHz, $CDCl_3$) 7.31-7.34 (m, 4 H, Ar*H*), 7.16 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.04 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 5.24 (br t, *J* = 5.4 Hz, 1 H, BocN*H*), 4.94 (br t, 5.9 Hz, 1 H, SN*H*), 4.16-4.32 (m, 4 H, $BocNHCH_2$ and $SCHCH_2$), 4.13 (dd, *J* = 14.2, 5.9 Hz, 1 H, SNHC*H*H), 3.99 (dd, *J* = 14.2, 5.9 Hz, 1 H, SNHCH*H*), 3.76-3.86 (m, 2 H, SC*H* and NC*H*), 2.57 (s, 3 H, NCH_3), 1.44 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 156.0 (s), 139.1 (s), 135.6 (s), 135.4 (s), 134.6 (s), 129.5 (d), 129.2 (d), 128.2 (d), 127.8 (d), 79.7 (s), 73.6 (d), 66.9 (t), 47.0 (t), 44.2 (t), 42.7 (q), 28.4 (q), 1 x d not observed; *m/z* (ES^+) 498 (MH^+, ^{37}Cl, 41), 496 (MH^+, ^{35}Cl, 100), 440 (24), 105 (22); HRMS (ES^+): calcd for $C_{23}H_{31}{}^{35}ClN_3O_5S$ (MH^+) 496.1667, found 496.1667.

(3*S, 4*S**)-(4-{[3-(4-Bromophenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl} benzyl)carbamic acid *tert*-butyl ester (188e), (3*R**, 5*S**) and (3*S**, 5*S**)-(4-{[3-(4-Bromophenyl)-2-methylisoxazolidine-5-sulfonylamino]methyl}benzyl)carbamic acid *tert*-butyl ester (189/190e)**



188e



189/190e

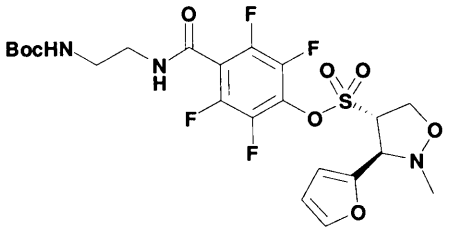
To a solution of [4-(ethenesulfonylaminomethyl)benzyl]carbamic acid *tert*-butyl ester **185** (250 mg, 0.8 mmol) in dry toluene (5 mL), *C*-(4-bromophenyl)-*N*-methyl nitrone **119f** (490 mg, 2.3 mmol) was added. The reaction mixture was heated in a CEM microwave for 30 minutes at 140 °C. When complete the reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/Et_2O) to give **189/190e** (67 mg, 16%) as a mixture, and **188e** (213 mg, 51%)- overall yield (67%, **188e**:**189/190e** = 3:1, **189e** and **190e** = 3:2 major:minor).

Data for **189/190e**: R_f 0.20 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3287, 2928, 1690, 1514, 1327, 1249, 1148, 1070, 831, 731; δ_H (500 MHz, $CDCl_3$) 7.44-7.49 (m, 2 H, Ar*H*), 7.21-7.35 (m, 6 H, Ar*H*), 4.86-5.02 (m, 3 H, N*H*, BocN*H*, and SC*H*), 4.12-4.43 (m, 4 H, NHCH_2 and BocNCH_2), 3.98-4.04 (m, 1 H_{major}, NC*H*), 3.53 (br dd, *J* = 9.3, 7.6 Hz, 1 H_{minor}, NC*H*), 2.96-3.07 (m, 1 H, SCHC*H*H), 2.80-2.87 (m, 1 H_{minor}, SCHCH*H*), 2.68-2.75 (m, 4 H, SCHCHH_{major} and NCH_{3minor}), 2.59 (s, 3 H_{major}, NCH_3), 1.45 (s, 9 H, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 156.0 (s), 139.0 (s), 138.9 (s), 136.3 (s), 136.0 (s), 135.9 (s), 135.6 (s), 132.2 (d), 132.1 (d), 129.9 (d), 129.8 (d), 129.3 (d), 128.2 (d), 127.9 (d), 122.6 (s), 122.4 (s), 89.3 (d), 79.7 (s), 73.6 (d), 72.9 (d), 47.5 (t), 47.1 (t), 44.3 (t), 43.2 (q), 41.1 (t), 28.5 (q), 26 out of 34 expected signals observed; *m/z* (ES^+) 542 (MH^+, ^{81}Br, 100), 540 (MH^+, ^{79}Br, 93), 214 (36); HRMS (ES^+): calcd for $C_{23}H_{31}{}^{79}BrN_3O_5S$ (MH^+) 540.1162, found 540.1164.

Data for **188e**: R_f 0.15 (2:1 Et_2O/petroleum ether 40-60°C); mp 156-157 °C; υ_{max} (neat)/cm^{-1} 3215, 2929, 1697, 1534, 1458, 1199, 1031, 860, 697; δ_H (400 MHz, $CDCl_3$) 7.46 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.27 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.15 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 7.04 (d, *J* = 7.9 Hz, 2 H, Ar*H*), 5.39 (app. t, *J* = 5.4 Hz, 1 H, BocN*H*), 4.97 (br t, *J* = 5.7 Hz, 1 H, SN*H*), 4.28 (dd, *J* = 10.2, 3.1 Hz, 1 H, SCHC*H*H), 4.23 (br d, *J* = 5.7 Hz, 2 H, SNHCH_2), 4.16 (dd, *J* = 10.2, 7.8 Hz, 1 H, SCHCH*H*), 4.11 (dd, *J* = 14.2, 6.0 Hz, 1 H, BocNHC*H*H), 3.98 (dd, *J* = 14.2, 5.4 Hz, 1 H, BocNHCH*H*), 3.75-3.83 (m, 2 H,

SC*H* and NC*H*), 2.56 (s, 3 H, NCH_3), 1.44 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 155.0 (s), 139.0 (s), 136.2 (s), 135.5 (s), 132.1 (d), 129.9 (d), 128.2 (d), 127.7 (d), 122.7 (s), 79.7 (s), 73.5 (d), 66.9 (t), 46.9 (t), 44.2 (t), 42.7 (q), 28.4 (q), 1 x d not observed; *m/z* (ES^+) 564 (20), 542 (MH^+, ^{81}Br, 100), 540 (MH^+, ^{79}Br, 90), 279 (27), 217 (31), 199 (29), 163 (32), 105 (62); HRMS (ES^+): calcd for $C_{23}H_{31}{}^{79}BrN_3O_5S$ (MH^+) 540.1162, found 540.1157.

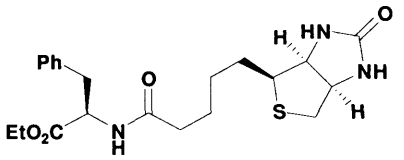
(3*S, 4*S**)-3-Furan-2-yl-2-methylisoxazolidine-4-sulfonic acid 4-(2-*tert*-butoxy carbonylaminoethylcarbamoyl) -2,3,5,6-tetrafluorophenyl ester (195)**



To a solution of ethenesulfonic acid 4-(2-*tert*-butoxycarbonylaminoethylcarbamoyl)-2,3,5,6-tetrafluorophenyl ester **186** (100 mg, 0.23 mmol) in dry toluene (5 mL), *C*-(2-furyl)-*N*-methyl nitrone **119n** (80 mg, 0.68 mmol) was added. The reaction mixture was heated in a CEM microwave for 5 minutes at 140 °C. When complete the reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (starting 2:1 petroleum ether 40-60°C/Et_2O) to give the product (49 mg, 38%) as a brown oil.

R_f 0.13 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 3284, 3073, 2918, 1665, 1548, 1489, 1383, 1254, 1178, 1099, 924, 748; δ_H (300 MHz, $CDCl_3$) 7.46 (d, *J* = 1.6 Hz, 1 H, OC*H*CH), 7.35 (br s, 1 H, N*H*), 6.47 (d, *J* = 3.2 Hz, 1 H, OCHCHC*H*), 6.37 (dd, *J* = 3.2, 1.6 Hz, 1 H, OCHC*H*), 4.99-5.05 (m, 1 H, SN*H*), 4.69 (app. td, *J* = 8.0, 3.2 Hz, 1 H, SC*H*), 4.58 (dd, *J* = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.47 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.16 (br s, 1 H, NC*H*), 3.53 (br q, *J* = 5.4 Hz, 2 H, BocNHCH_2), 3.35 (br q, *J* = 5.9 Hz, 2 H, SNCH_2), 2.75 (br s, 3 H, NCH_3), 1.39 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 156.8 (s), 146.7 (s), 144.0 (d), 111.1 (d), 110.8 (d), 80.3 (s), 70.0 (d), 67.5 (d), 66.7 (t), 42.8 (q), 42.1 (t), 39.6 (t), 28.2 (q); *m/z* (ES^+) 631 (100), 590 (MNa^+, 88), 526 (23), 454 (20), 375 (20), 180 (32); HRMS (ES^+): calcd for $C_{22}H_{25}F_4N_3NaO_8S$ (MNa^+) 590.1195, found 590.1196.

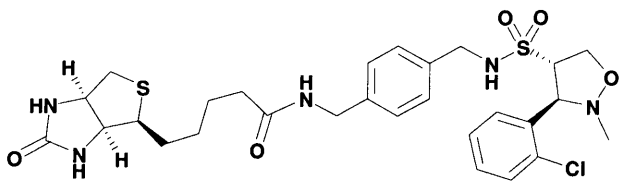
2-[5-(2-Oxohexahydrothieno[3,4-*d*]imidazol-6-yl)pentanoylamino]-3-phenyl propionic acid ethyl ester (196)



To D-Biotin (200 mg, 1.0 mmol), EDC.HCl (200 mg, 1.0 mmol), and DMAP (100 mg, 1.0 mmol) in DMF (25 mL) was added *L*-Phenylalanine ethyl ester.HCl (200 mg, 1.0 mmol). This was allowed to stir at RT for 6 hours, then poured onto H_2O (15 mL). The aqueous suspension was extracted with $CHCl_3$ (2 x 40 mL), and the combined $CHCl_3$ layers dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant crude material was purified by flash chromatography (starting 100% DCM) to give **196** (270 mg, 64%) as a white solid.

R_f 0.44 (9:1 DCM/MeOH); mp 127-130 °C; υ_{max} (neat)/cm^{-1} 3212, 2928, 1731, 1697, 1645, 1535, 1455, 1265, 1199, 1029, 860; δ_H (500 MHz, $CDCl_3$) 7.18-7.27 (m, 3 H, Ar*H*), 7.14 (d, *J* = 7.2 Hz, 2 H, Ar*H*), 7.10 (d, *J* = 7.8 Hz, 1 H, N*H*), 6.89 (s, 1 H, N*H*), 6.27 (s, 1 H, N*H*), 4.80 (dt, *J* = 7.8, 6.1 Hz, 1 H, $PhCH_2CH$), 4.45 (br dd, *J* = 7.7, 5.0 Hz, 1 H, biotinyl-C*H*), 4.25 (br dd, *J* = 7.7, 4.7 Hz, 1 H, biotinyl-C*H*), 4.12 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.12 (dd, *J* = 14.0, 6.1 Hz, 1 H, PhC*H*H), 3.08 (dt, *J* = 7.2, 4.7 Hz, 1 H, biotinyl-C*H*), 3.02 (dd, *J* = 14.0, 7.8 Hz, 1 H, PhCH*H*), 2.79 (dd, *J* = 12.9, 5.0 Hz, 1 H, biotinyl-CH_2), 2.55 (d, *J* = 12.9 Hz, 1 H, biotinyl-CH_2), 2.12-2.19 (m, 2 H, biotinyl-CH_2), 1.52-1.72 (m, 4 H, biotinyl-CH_2), 1.32-1.40 (m, 2 H, biotinyl-CH_2), 1.19 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 173.4 (s), 172.9 (s), 164.7 (s), 136.5 (s), 129.3 (d), 128.5 (d), 127.0 (d), 62.0 (d), 61.5 (t), 60.3 (d), 56.1 (d), 53.3 (d), 40.5 (t), 37.8 (t), 35.8 (t), 28.6 (t), 28.0 (t), 25.5 (t), 14.1 (q); *m/z* (EI) 419 (7), 359 (45), 227 (57), 194 (43), 166 (53), 120 (100), 91 (40); HRMS (EI): calcd for $C_{21}H_{29}N_3O_4S$ (M^+) 419.1873, found 419.1878.

5-(2-Oxohexahydrothieno[3,4-*d*]imidazol-6-yl)pentanoic acid (3*S, 4*S**)-4-{[3-(2-chlorophenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl}benzylamide (197)**

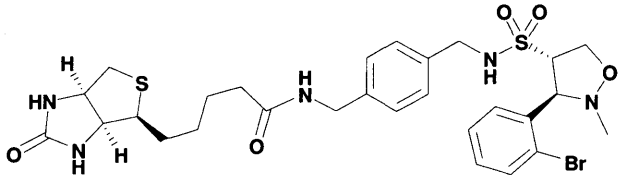


Boc-isoxazolidine **188b** (139 mg, 0.28 mmol) was stirred in a solution of 1:1 DCM/TFA (2 mL) at RT for 5 hours, after which PhMe (1 mL) was added and then

volatiles removed *in vacuo*. The resultant TFA salt, D-Biotin (60 mg, 0.23 mmol), HOBt (37 mg, 0.28 mmol), and EDC.HCl (50 mg, 0.28 mmol) was dissolved in DMF (1.5 mL), treated with NEt_3 (60 μL, 0.46 mmol), and stirred overnight at RT. DMF was removed *in vacuo* and the crude oil purified by flash chromatography (starting 100% DCM) to give the desired product (16 mg, 11%) as a white solid.

R_f 0.39 (9:1 DCM/MeOH); mp 125-128 °C; υ_{max} (neat)/cm^{-1} 3284, 2919, 1699, 1645, 1539, 1461, 1323, 1144, 1037; δ_H (500 MHz, $CDCl_3$) 7.50 (d, *J* = 7.0 Hz, 1 H, Ar*H*), 7.40 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.28-7.36 (m, 2 H, Ar*H*), 7.17 (d, *J* = 7.4 Hz, 2 H, Ar*H*), 7.05-7.10 (m, 2 H, Ar*H*), 6.55 (br s, 1 H, N*H*), 6.18 (br s, 1 H, N*H*), 5.80 (br s, 1 H, N*H*), 5.39 (br s, 1 H, N*H*), 4.47 (br s, 1 H, NC*H*), 4.26-4.44 (m, 5 H, SCHCH_2, NHCH_2, and biotinyl-C*H*), 3.95-4.22 (m, 4 H, SC*H*, biotinyl-C*H*, and BocNCH_2), 3.07-3.14 (m, 1 H, biotinyl-C*H*), 2.87 (dd, *J* = 12.9, 4.9 Hz, 1 H, biotinyl-CH_2), 2.59-2.69 (m, 4 H, NCH_3 and biotinyl-CH_2), 2.19-2.26 (m, 2 H, biotinyl-CH_2), 1.56-1.76 (m, 4 H, biotinyl-CH_2), 1.37-1.45 (m, 2 H, biotinyl-CH_2); δ_C (125 MHz, $CDCl_3$) 173.0 (s), 163.8 (s), 138.4 (s), 135.8 (s), 134.5 (s), 134.3 (s), 130.2 (d), 129.9 (d), 128.2 (d), 127.8 (d), 73.0 (d), 72.2 (d), 67.4 (t), 61.9 (d), 60.2 (d), 55.6 (d), 47.1 (t), 43.1 (t), 42.8 (q), 40.7 (t), 35.6 (t), 29.8 (t), 27.9 (t), 25.3 (t), 2 x d not observed; *m/z* (ES^+) 624 (MH^+, ^{37}Cl, 48), 622 (MH^+, ^{35}Cl, 100), 149 (43), 119 (55), 91 (48); HRMS (ES^+): calcd for $C_{28}H_{37}{}^{35}ClN_5O_5S_2$ (MH^+) 622.1919, found 622.1926.

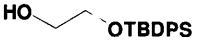
5-(2-Oxohexahydrothieno[3,4-*d*]imidazol-6-yl)pentanoic acid (3*S, 4*S**)-4-{[3-(2-bromophenyl)-2-methylisoxazolidine-4-sulfonylamino]methyl}benzylamide (198)**



Boc-isoxazolidine **188c** (50 mg, 0.09 mmol) was stirred in 4M HCl/Dioxane (4 mL) for 1 hour at RT, after which solvents were removed *in vacuo*. The resultant HCl salt was dissolved in DMF (3 mL) and treated with consecutively D-Biotin (23 mg, 0.09 mmol), EDC.HCl (18 mg, 0.09 mmol), and DMAP (11 mg, 0.09 mmol). Reaction was stirred at RT for 5 hours then poured onto H_2O (4 mL), and extracted with $CHCl_3$ (2 x 10 mL). The $CHCl_3$ layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude product which was further purified by flash chromatography (starting 95:5 DCM/MeOH) to give the biotinylated product **198** (25 mg, 42%) as a white solid.

R_f 0.35 (9:1 DCM/MeOH); mp 136-139 °C; υ_{max} (neat)/cm^{-1} 3266, 2920, 1687, 1537, 1432, 1322, 1144, 1024; δ_H (500 MHz, $CDCl_3$) 7.59 (app. dt, J = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.48 (br d, J = 7.6 Hz, 1 H, Ar*H*), 7.35-7.39 (m, 1 H, Ar*H*), 7.20-7.24 (m, 1 H, Ar*H*), 7.15 (d, J = 7.5 Hz, 2 H, Ar*H*), 7.07 (br dd, J = 7.7, 4.6 Hz, 2 H, Ar*H*), 6.74 (br s, 1 H, N*H*), 6.27 (br s, 1 H, N*H*), 6.05 (br s, 1 H, N*H*), 5.53 (br s, 1 H, N*H*), 4.49 (br s, 1 H, NC*H*), 4.25-4.43 (m, 5 H, SCHCH_2, NHCH_2, and biotinyl-C*H*), 3.83-4.20 (m, 4 H, SC*H*, biotinyl-C*H*, and BocNCH_2), 3.06-3.11 (m, 1 H, biotinyl-C*H*), 2.85 (dd, J = 13.0, 5.0 Hz, 1 H, biotinyl-CH_2), 2.61-2.67 (m, 4 H, NCH_3 and biotinyl-CH_2), 2.21 (br t, J = 7.0 Hz, 2 H, biotinyl-CH_2), 1.55-1.75 (m, 4 H, biotinyl-CH_2), 1.35-1.45 (m, 2 H, biotinyl-CH_2); δ_C (125 MHz, $CDCl_3$) 173.2 (s), 164.0 (s), 138.5 (s), 135.9 (s), 135.8 (s), 133.4 (d), 130.3 (2 x d), 128.4 (d), 128.2 (2 x d), 124.9 (s), 73.3 (d), 72.4 (d), 67.4 (t), 61.9 (d), 60.2 (d), 55.7 (d), 47.1 (t), 43.1 (t), 42.7 (q), 40.7 (t), 35.6 (t), 29.8 (t), 28.0 (t), 25.4 (t); *m/z* (ES^+) 668 (MH^+, ^{81}Br, 62), 666 (MH^+, ^{79}Br, 56), 241 (27), 148 (56), 119 (100), 91 (79); HRMS (ES^+): calcd for $C_{28}H_{37}{}^{79}BrN_5O_5S_2$ (MH^+) 666.1414, found 666.1419.

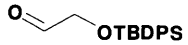
2-(*tert*-Butyldiphenylsilanyloxy)ethanol (203) [183]



TBDPSCl (10 mL, 38.4 mmol) was added dropwise over 5 minutes to a stirring suspension of ethylene glycol (10.7 mL, 192.0 mmol), NEt_3 (29.5 mL, 211.0 mmol), and DMAP (0.47 g, 3.8 mmol) in DCM (200 mL) at 0 °C. Stirring was continued overnight at RT. The reaction mixture was washed with 10% HCl, sat. $NaHCO_3$, and brine. Organic layer was dried ($MgSO_4$), filtered, and filtrate concentrated *in vacuo* to give crude which was purified by flash chromatography (starting 6:1 petroleum ether 40-60°C/EtOAc) to give the product (9.9 g, 91%) as a white solid. Data agrees with literature.

R_f 0.54 (2:1 petroleum ether 40-60°C/EtOAc); mp 42-44 °C; δ_H (300 MHz, $CDCl_3$) 7.70-7.75 (m, 4 H, Ar*H*), 7.39-7.49 (m, 6 H, Ar*H*), 3.78-3.82 (m, 2 H, OCH_2), 3.70-3.74 (m, 2 H, OCH_2), 2.32 (br s, 1 H, O*H*), 1.12 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 135.6 (d), 133.4 (s), 129.9 (d), 127.8 (d), 65.1 (t), 63.8 (t), 26.9 (q), 19.3 (s).

(*tert*-Butyldiphenylsilanyloxy)acetaldehyde (204) [184]

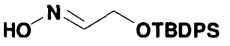


To 2M oxalyl chloride in DCM (4.2 mL, 8.4 mmol) in DCM (25 mL) at -78 °C was added slowly DMSO (2.4 mL, 33.8 mmol). This was followed by dropwise addition of

2-(*tert*-butyldiphenylsilanyloxy)ethanol **203** (2.0 g, 7.0 mmol) in DCM (5 mL) then 20 minutes stirring at -78 °C. NEt_3 (5 mL) was added carefully then the reaction was allowed to warm slowly to RT. Solvents were removed *in vacuo* and the residue remaining triturated with 4:1 hexane/EtOAc (100 mL) before filtering through a small silica pad. The filtrate was concentrated *in vacuo* and the crude purified by flash chromatography (starting 12:1 petroleum ether 40-60°C/EtOAc) to give product (1.9 g, 95%) as a clear oil. Data agrees with literature.

R_f 0.18 (12:1 petroleum ether 40-60°C/EtOAc); υ_{max} (neat)/cm^{-1} 3072, 2931, 1738, 1472, 1105, 822, 739; δ_H (300 MHz, $CDCl_3$) 9.74 (s, 1 H, C*H*O), 7.66-7.71 (m, 4 H, Ar*H*), 7.38-7.49 (m, 6 H, Ar*H*), 4.23 (s, 2 H, CH_2), 1.13 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 201.6 (d), 135.5 (d), 132.6 (s), 130.1 (d), 128.0 (d), 70.0 (t), 26.8 (q), 19.3 (s); *m/z* (ES^-) 317 (50), 297 (M-H, 28), 265 (48), 255 (100), 225 (28); HRMS (ES^-): calcd for $C_{18}H_{21}O_2Si$ (M-H) 297.1313, found 297.1311.

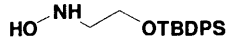
(*tert*-Butyldiphenylsilanyloxy)acetaldehyde oxime (205) [185]



(*tert*-Butyldiphenylsilanyloxy)acetaldehyde **204** (1.5 g, 5.3 mmol) was dissolved in EtOH (18 mL) and treated with hydroxylamine.HCl (1.2 g, 17.0 mmol) followed by NEt_3 (2.5 mL, 17.5 mmol). The suspension was stirred at RT for 4 hours, then diluted with H_2O (50 mL) and the reaction mixture extracted with EtOAc (3 x 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. Flash chromatography (starting 12:1 petroleum ether 40-60°C/EtOAc) of the crude material gave the desired product (1.6 g, 95%). Data agrees with literature.

R_f 0.40 (12:1 petroleum ether 40-60°C/EtOAc); mp 56-58 °C; υ_{max} (neat)/cm^{-1} 3203, 3071, 2857, 1426, 1104, 934, 821, 737; δ_H (300 MHz, $CDCl_3$) 7.64-7.69 (m, 4 H, Ar*H*), 7.49 (app. t, *J* = 5.4 Hz, 1 H, C*H*N), 7.36-7.47 (m, 6 H, Ar*H*), 4.55 (d, *J* = 3.2 Hz, 1 H, OC*H*H), 4.26 (d, *J* = 5.4 Hz, 1 H, OCH*H*), 1.07 (s, 4.5 H, C(CH_3)$_3$), 1.05 (s, 4.5 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 150.2 (d), 135.6 (d), 133.0 (s), 129.9 (d), 127.9 (d), 61.4 (t), 26.7 (q), 19.2 (s); *m/z* (FAB^+) 314 (MH^+, 17), 256 (100), 236 (84), 199 (96); HRMS (FAB^+): calcd for $C_{18}H_{24}NO_2Si$ (MH^+) 314.1576, found 314.1571.

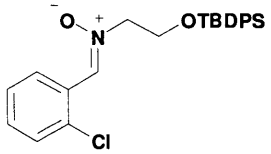
N-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl] hydroxylamine (199) [186]



A solution of (*tert*-butyldiphenylsilanyloxy)acetaldehyde oxime **205** (5.0 g, 16.0 mmol), in 1.25M HCl in MeOH (100 mL) was treated with $NaBH_3CN$ (2.0 g, 31.9 mmol) and the reaction stirred at RT for 5 hours. Solvent was removed *in vacuo*, then the white residue suspended in H_2O (150 mL) and basified to pH >9 with 6N KOH. The aqueous layer was then saturated with NaCl and extracted with $CHCl_3$ (4 x 70 mL). The organic layer was dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo* to give the product (4.6 g, 92%). Data agrees with literature.

R_f 0.05 (5:1 petroleum ether 40-60°C/EtOAc); υ_{max} (neat)/cm^{-1} 3071, 2931, 2857, 1471, 1427, 1111; δ_H (300 MHz, $CDCl_3$) 7.65-7.75 (m, 4 H, Ar*H*), 7.34-7.46 (m, 6 H, Ar*H*), 4.37-4.45 (br m, 2 H, O*H* and N*H*), 3.83 (br t, J = 5.1 Hz, 2 H, OCH_2), 3.07 (br t, J = 5.1 Hz, 2 H, NCH_2), 1.08 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 135.5 (d), 133.0 (s), 129.6 (d), 127.9 (d), 60.8 (t), 53.3 (t), 26.6 (q), 19.1 (s).

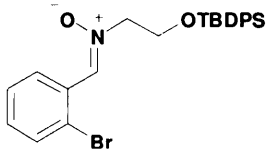
C-(2-Chlorophenyl)-*N*-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl] nitrone (200a)



To *N*-[2-(*tert*-butyldiphenylsilanyloxy)ethyl] hydroxylamine **199** (3.0 g, 9.5 mmol) in DCM (30 mL) was added 2-chlorobenzaldehyde (1.0 mL, 8.6 mmol) and $NaHCO_3$ (2.2 g, 25.9 mmol). The mixture was refluxed at 40 °C for 40 hours, then the resulting suspension was filtered and the residue washed thoroughly with DCM (4 × 40 mL). The combined organic fractions were concentrated *in vacuo* and the product purified by flash chromatography (starting 7:1 petroleum ether 40-60°C/EtOAc) to give the title compound (0.9 g, 25%) as an orange solid.

R_f 0.29 (5:1 petroleum ether 40-60°C/EtOAc); mp 89-92 °C; υ_{max} (neat)/cm^{-1} 2964, 2854, 1568, 1427, 1268, 1103, 941, 821, 751; δ_H (300 MHz, $CDCl_3$) 9.44 (dd, J = 7.8, 2.1 Hz, 1 H, Ar*H*), 8.01 (s, 1 H, C*H*N), 7.64-7.68 (m, 4 H, Ar*H*), 7.31-7.45 (m, 9 H, Ar*H*), 4.16-4.21 (m, 2 H, OCH_2), 4.03-4.08 (m, 2 H, NCH_2), 1.03 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 135.5 (d), 133.1 (s), 132.9 (s), 131.4 (d), 131.0 (d), 129.9 (d), 129.4 (d), 129.2 (d), 128.2 (s), 127.8 (d), 127.1 (d), 70.5 (t), 60.4 (t), 26.8 (q), 19.2 (s); *m/z* (FAB$^+$) 440 (MH^+, ^{37}Cl, 3), 438 (MH^+, ^{35}Cl, 9), 329 (18), 176 (86), 154 (100); HRMS (FAB$^+$): calcd for $C_{25}H_{29}{}^{35}ClNO_2Si$ (MH^+) 438.1656, found 438.1661.

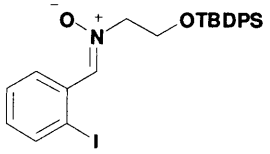
***C*-(2-Bromophenyl)-*N*-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl] nitrone (200b)**



To *N*-[2-(*tert*-butyldiphenylsilanyloxy)ethyl] hydroxylamine **199** (1.0 g, 3.2 mmol) in DCM (15 mL) was added 2-bromobenzaldehyde (0.3 mL, 2.9 mmol) and $NaHCO_3$ (0.7 g, 8.6 mmol). The mixture was refluxed at 40 °C for 40 hours, then the resulting suspension was filtered and the residue washed thoroughly with DCM (4 × 25 mL). The combined organic fractions were concentrated *in vacuo* and the product purified by flash chromatography (starting 7:1 petroleum ether 40-60°C/EtOAc) to give the title compound (0.7 g, 48%) as a cream solid.

R_f 0.20 (5:1 petroleum ether 40-60°C/EtOAc); mp 79-81 °C; υ_{max} (neat)/cm^{-1} 3072, 2855, 1564, 1427, 1269, 1104, 941, 822, 734; δ_H (300 MHz, $CDCl_3$) 9.40 (dd, J = 8.0, 1.9 Hz, 1 H, Ar*H*), 7.97 (s, 1 H, C*H*N), 7.61-7.66 (m, 5 H, Ar*H*), 7.32-7.44 (m, 7 H, Ar*H*), 7.25 (app. dt, J = 7.8, 1.9 Hz, 1 H, Ar*H*), 4.15-4.19 (m, 2 H, OCH_2), 4.02-4.06 (m, 2 H, NCH_2), 1.01 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 135.5 (d), 134.1 (s), 133.1 (s), 132.8 (d), 131.3 (d), 129.9 (d), 129.6 (d), 129.5 (d), 127.8 (d), 127.7 (d), 123.3 (s), 70.5 (t), 60.3 (t), 26.8 (q), 19.2 (s); *m/z* (FAB$^+$) 506 (MNa^+, ^{81}Br, 23), 504 (MNa^+, ^{79}Br, 22), 329 (19), 199 (23), 176 (100); HRMS (FAB$^+$): calcd for $C_{25}H_{28}{}^{79}BrNNaO_2Si$ (MNa^+) 504.0970, found 504.0965.

***C*-(2-Iodophenyl)-*N*-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl] nitrone (200c)**

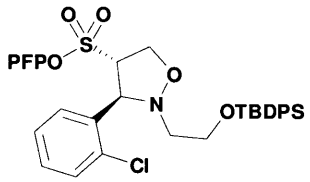


To *N*-[2-(*tert*-butyldiphenylsilanyloxy)ethyl] hydroxylamine **199** (1.8 g, 5.7 mmol) in DCM (25 mL) was added 2-iodobenzaldehyde (1.2 g, 5.2 mmol) and $NaHCO_3$ (1.3 g, 15.4 mmol). The mixture was refluxed at 40 °C for 40 hours, then the resulting suspension was filtered and the residue washed thoroughly with DCM (4 × 40 mL). The combined organic fractions were concentrated *in vacuo* and the product purified by flash chromatography (starting 7:1 petroleum ether 40-60°C/EtOAc) to give the title compound (0.8 g, 28%) as a clear oil.

R_f 0.57 (2:1 petroleum ether 40-60°C/EtOAc); υ_{max} (neat)/cm^{-1} 3067, 2930, 1551, 1427, 1207, 1156, 1105, 1000, 941, 821, 736; δ_H (300 MHz, $CDCl_3$) 9.34 (dd, J = 8.3, 1.6 Hz,

1 H, Ar*H*), 7.93 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.85 (s, 1 H, C*H*N), 7.62-7.68 (m, 4 H, Ar*H*), 7.32-7.48 (m, 7 H, Ar*H*), 7.09 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 4.15-4.20 (m, 2 H, OCH_2), 4.02-4.06 (m, 2 H, NCH_2), 1.03 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 139.8 (d), 139.0 (d), 135.5 (d), 133.1 (s), 132.4 (s), 131.5 (d), 129.8 (d), 129.3 (d), 128.4 (d), 127.8 (d), 99.1 (s), 70.4 (t), 60.3 (t), 26.9 (q), 19.3 (s); *m/z* (FAB$^+$) 552 (MNa$^+$, 52), 452 (20), 199 (31), 176 (100); HRMS (FAB$^+$): calcd for $C_{25}H_{28}INNaO_2Si$ (MNa$^+$) 552.0832, found 552.0834.

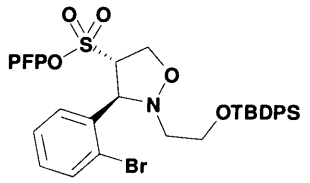
(3*S, 4*S**)-2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-3-(2-chlorophenyl) isoxazolidine-4-sulfonic acid pentafluorophenyl ester (210a)**



To pentafluorophenyl vinyl sulfonate **100** (430 mg, 1.56 mmol) in dry toluene (10 mL) was added *C*-(2-chlorophenyl)-*N*-[2-(*tert*-butyldiphenylsilanyloxy)ethyl] nitrone **200a** (819 mg, 1.87 mmol) and the mixture was heated to reflux for 7 hours. The reaction was concentrated *in vacuo*, and the crude residue purified by flash chromatography (starting 14:1 petroleum ether 40-60°C/Et_2O) to give the title compound (680 mg, 61%) as a brown oil.

R_f 0.61 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 2932, 1517, 1473, 1391, 1112, 993, 823, 737; δ_H (300 MHz, $CDCl_3$) 7.57-7.69 (m, 5 H, Ar*H*), 7.30-7.46 (m, 9 H, Ar*H*), 4.87 (d, *J* = 6.7 Hz, 1 H, NC*H*) 4.62 (dd, *J* = 9.9, 2.9 Hz, 1 H, SCHC*H*H), 4.48 (dd, *J* = 9.9, 8.0 Hz, 1 H, SCHCH*H*), 4.41 (app. td, *J* = 8.0, 2.9 Hz, 1 H, SC*H*), 3.80-3.96 (m, 2 H, OCH_2), 2.88-3.08 (m, 2 H, NCH_2), 1.03 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 135.6 (d), 134.6 (s), 133.7 (s), 133.1 (s), 130.3 (d), 130.2 (d), 130.0 (d), 129.6 (d), 127.6 (d), 127.5 (d), 72.9 (d), 68.4 (d), 67.1 (t), 61.5 (t), 57.7 (t), 26.8 (q), 19.2 (s); *m/z* (FAB$^+$) 736 (MNa$^+$, ^{37}Cl, 25), 734 (MNa$^+$, ^{35}Cl, 54), 301 (100), 241 (25), 199 (48); HRMS (FAB$^+$): calcd for $C_{33}H_{31}{}^{35}ClF_5NNaO_5SSi$ (MNa$^+$) 734.1199, found 734.1183.

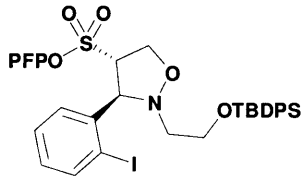
(3*S, 4*S**)-3-(2-Bromophenyl)-2-[2-(*tert*-butyldiphenylsilanyloxy)ethyl] isoxazolidine-4-sulfonic acid pentafluorophenyl ester (210b)**



To pentafluorophenyl vinyl sulfonate **100** (1.1 g, 3.9 mmol) in dry toluene (25 mL) was added *C*-(2-bromophenyl)-*N*-[2-(*tert*-butyldiphenylsilanyloxy)ethyl] nitrone **200b** (2.2 g, 4.6 mmol) and the mixture was heated to reflux for 6 hours. The reaction was concentrated *in vacuo*, and the crude residue purified by flash chromatography (starting 14:1 petroleum ether 40-60°C/Et_2O) to give the title compound (2.1 g, 73%) as a brown oil.

R_f 0.63 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 2932, 1517, 1472, 1392, 1185, 994, 823, 737; δ_H (300 MHz, $CDCl_3$) 7.56-7.64 (m, 5 H, Ar*H*), 7.53 (dd, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.30-7.42 (m, 7 H, Ar*H*), 7.22 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 4.83 (d, *J* = 7.0 Hz, 1 H, NC*H*), 4.58 (dd, *J* = 10.2, 2.9 Hz, 1 H, SCHC*H*H), 4.44 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.33 (app. td, *J* = 7.8, 2.9 Hz, 1 H, SC*H*), 3.74-3.90 (m, 2 H, OCH_2), 3.00 (ddd, *J* = 13.1, 5.4, 4.0 Hz, 1 H, NC*H*HCH_2), 2.82-2.92 (m, 1 H, NCH*H*CH_2), 0.99 (s, 9 H, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 135.6 (d), 134.8 (s), 133.7 (d), 133.6 (s), 130.4 (d), 130.2 (d), 129.6 (d), 128.2 (d), 127.6 (d), 124.8 (s), 73.1 (d), 70.5 (d), 67.2 (t), 61.4 (t), 57.6 (t), 26.8 (q), 19.2 (s); *m/z* (FAB^+) 780 (MNa^+, ^{81}Br, 21), 778 (MNa^+, ^{79}Br, 18), 225 (23), 176 (100); HRMS (FAB^+): calcd for $C_{33}H_{31}{}^{79}BrF_5NNaO_5SSi$ (MNa^+) 778.0693, found 778.0706.

(3*S, 4*S**)-2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-3-(2-iodophenyl)isoxazolidine-4-sulfonic acid pentafluorophenyl ester (210c)**

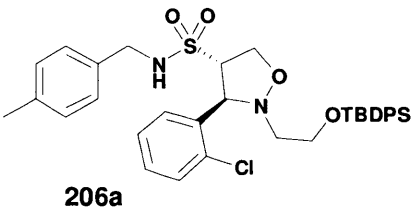


To pentafluorophenyl vinyl sulfonate **100** (350 mg, 1.28 mmol) in dry toluene (8 mL) was added *C*-(2-iodophenyl)-*N*-[2-(*tert*-butyldiphenylsilanyloxy)ethyl] nitrone **200c** (745 mg, 1.41 mmol) and the mixture was heated to reflux for 7 hours. The reaction was concentrated *in vacuo*, and the crude residue purified by flash chromatography (starting 14:1 petroleum ether 40-60°C/Et_2O) to give the title compound (663 mg, 64%) as a brown oil.

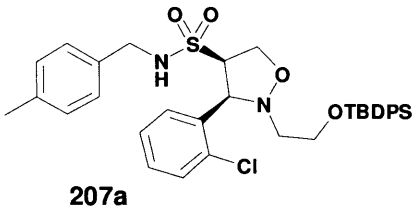
R_f 0.59 (2:1 Et_2O/petroleum ether 40-60°C); υ_{max} (neat)/cm^{-1} 2932, 1517, 1471, 1392, 1112, 994, 823, 738; δ_H (300 MHz, $CDCl_3$) 7.90 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.57-7.66 (m, 4 H, Ar*H*), 7.48 (dd, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 7.32-7.44 (m, 7 H, Ar*H*), 7.07 (app. dt, *J* = 8.0, 1.9 Hz, 1 H, Ar*H*), 4.78 (d, *J* = 7.2 Hz, NC*H*), 4.59 (dd, *J* = 10.2, 3.2 Hz, 1 H, SCHC*H*H), 4.46 (dd, *J* = 10.2, 8.0 Hz, 1 H, SCHCH*H*), 4.30 (app. td, *J* = 8.0,

3.2 Hz, 1 H, SC*H*), 3.77-3.92 (m, 2 H, OCH_2), 3.04 (ddd, *J* = 13.1, 5.1, 4.0 Hz, 1 H, NC*H*HCH$_2$), 2.83-2.92 (m, 1 H, NCH*H*CH$_2$), 1.01 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 140.3 (d), 137.7 (s), 135.6 (d), 133.7 (s), 130.7 (d), 129.8 (d), 129.6 (d), 129.0 (d), 127.6 (d), 100.7 (s), 74.9 (d), 73.4 (d), 67.2 (t), 61.4 (t), 57.4 (t), 26.8 (q), 19.2 (s); *m/z* (FAB$^+$) 826 (MNa$^+$, 28), 323 (30), 176 (100); HRMS (FAB$^+$): calcd for $C_{33}H_{31}F_5INNaO_5SSi$ (MNa$^+$) 826.0555, found 826.0533.

(3*S, 4*S**)-2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-3-(2-chlorophenyl) isoxazolidine-4-sulfonic acid 4-methylbenzylamide (206a), and (3*S**, 4*R**)-2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-3-(2-chlorophenyl)isoxazolidine-4-sulfonic acid 4-methylbenzylamide (207a)**



206a



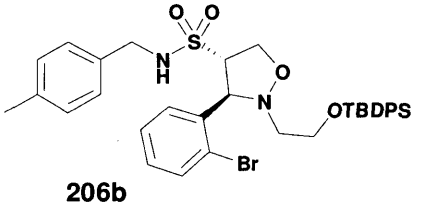
207a

To a stirring solution of PFP ester **210a** (440 mg, 0.62 mmol) in dry THF (10 mL), 4-methylbenzylamine (240 µL, 1.85 mmol) was added followed by DBU (140 µL, 0.93 mmol). The mixture was refluxed for 1 hour and then concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 8:1 petroleum ether 40-60°C/EtOAc) to yield the two products **206a** (243 mg, 60%) and **207a** (73 mg, 18%) as yellow solids- overall yield (78%, **206a**:**207a** = 10:3).

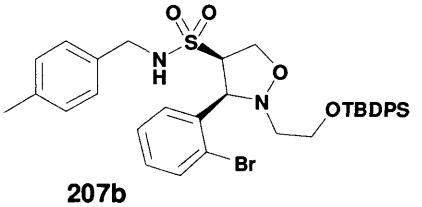
Data for **207a**: R_f 0.24 (2:1 petroleum ether 40-60°C/Et_2O); mp 135-137 °C; υ_{max} (neat)/cm^{-1} 3276, 3049, 2929, 1516, 1426, 1335, 1112, 1084, 955, 805, 760; δ_H (300 MHz, $CDCl_3$) 7.79-7.84 (m, 1 H, Ar*H*), 7.47-7.76 (m, 4 H, Ar*H*), 7.34-7.46 (m, 7 H, Ar*H*), 7.23-7.28 (m, 2 H, Ar*H*), 7.11 (s, 4 H, Ar*H*), 4.29-4.42 (m, 4 H, SCHCH_2, NC*H*, and SC*H*), 4.13 (dd, *J* = 13.7, 6.7 Hz, 1 H, NHC*H*H), 4.04 (dd, *J* = 13.7, 4.8 Hz, 1 H, NHCH*H*), 3.96-4.03 (m, 1 H, OC*H*HCH$_2$N), 3.87 (ddd, *J* = 10.4, 6.2, 4.2 Hz, 1 H, OCH*H*CH$_2$N), 3.48 (dd, *J* = 6.7, 4.8 Hz, 1 H, N*H*), 3.05 (ddd, *J* = 13.4, 7.5, 6.2 Hz, 1 H, NC*H*HCH$_2$), 2.70 (ddd, *J* = 13.4, 5.1, 4.2 Hz, 1 H, NCH*H*CH$_2$), 2.33 (s, 3 H, ArCH_3), 1.07 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 135.7 (d), 134.8 (s), 133.8 (s), 133.6 (s), 131.5 (s), 131.2 (d), 129.6 (d), 129.4 (d), 129.0 (d), 127.8 (d), 127.7 (d), 127.6 (d), 127.0 (d), 68.8 (d), 66.9 (d), 66.2 (t), 61.6 (t), 58.5 (t), 47.1 (t), 26.9 (q), 21.1 (q), 19.2 (s); *m/z* (ESI) 673 (MNa$^+$, ^{37}Cl, 17), 671 (MNa$^+$, ^{35}Cl, 50), 338 (45), 319 (100), 178 (19); HRMS (ESI): calcd for $C_{35}H_{41}{}^{35}ClN_2NaO_4SSi$ (MNa$^+$) 671.2143, found 671.2139.

Data for **206a**: R_f 0.19 (2:1 petroleum ether 40-60°C/Et_2O); mp 127-129 °C; υ_{max} (neat)/cm^{-1} 3349, 3073, 2855, 1519, 1428, 1316, 1115, 1088, 955, 822, 746; δ_H (300 MHz, $CDCl_3$) 7.58-7.66 (m, 4 H, Ar*H*), 7.51-7.55 (m, 1 H, Ar*H*), 7.29-7.44 (m, 9 H, Ar*H*), 7.04 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.92 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.74 (dd, *J* = 6.5, 5.1 Hz, 1 H, N*H*), 4.60 (d, *J* = 7.2 Hz, 1 H, NC*H*), 4.40 (dd, *J* = 9.9, 4.0 Hz, 1 H, SCHC*H*H), 4.27 (dd, *J* = 9.9, 8.6 Hz, 1 H, SCHCH*H*), 4.14 (dd, *J* = 13.7, 6.5 Hz, 1 H, NHC*H*H), 3.93 (dt, *J* = 8.0, 4.1 Hz, 1 H, OC*H*HCH$_2$N), 3.82 (dd, *J* = 13.7, 5.1 Hz, 1 H, NHCH*H*), 3.74-3.82 (m, 2 H, SC*H* and OCH*H*CH$_2$N), 2.97 (ddd, *J* = 13.1, 5.6, 4.1 Hz, 1 H, NC*H*HCH$_2$), 2.77-2.87 (m, 1 H, NCH*H*CH$_2$), 2.32 (s, 3 H, ArCH_3), 1.01 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 135.5 (d), 134.7 (s), 134.2 (s), 133.8 (s), 133.1 (s), 130.2 (d), 130.0 (d), 129.7 (d), 129.6 (d), 129.5 (d), 129.4 (d), 127.9 (d), 127.8 (d), 127.6 (d), 127.5 (d), 72.7 (d), 68.4 (d), 67.1 (t), 61.6 (t), 57.8 (t), 47.2 (t), 26.8 (q), 21.1 (q), 19.2 (s); *m/z* (FAB^+) 673 (MNa^+, ^{37}Cl, 5), 671 (MNa^+, ^{35}Cl, 12), 329 (20), 176 (100), 154 (39); HRMS (FAB^+): calcd for $C_{35}H_{41}{}^{35}ClN_2NaO_4SSi$ (MNa^+) 671.2143, found 671.2126.

(3*S, 4*S**)-3-(2-Bromophenyl)-2-[2-(*tert*-butyldiphenylsilanyloxy)ethyl] isoxazolidine-4-sulfonic acid 4-methylbenzylamide (206b) and (3*S**, 4*R**)-3-(2-Bromophenyl)-2-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]isoxazolidine-4-sulfonic acid 4-methylbenzylamide (207b)**



206b



207b

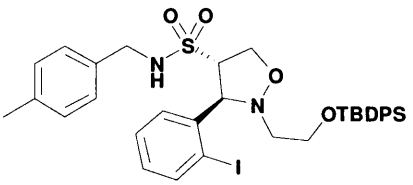
To a stirring solution of PFP ester **210b** (1.4 g, 1.9 mmol) in dry THF (30 mL), 4-methylbenzylamine (0.7 mL, 5.6 mmol) was added followed by DBU (0.4 mL, 2.8 mmol). The mixture was refluxed for 2 hours and then concentrated *in vacuo*. The crude residue remaining was purified by flash chromatography (starting 8:1 petroleum ether 40-60°C/EtOAc) to yield the two products **206b** (625 mg, 48%) and **207b** (264 mg, 20%) as yellow solids- overall yield (69%, **206b**:**207c** = 7:3).

Data for **207b**: R_f 0.18 (2:1 petroleum ether 40-60°C/Et_2O); mp 73-75 °C; υ_{max} (neat)/cm^{-1} 3289, 2928, 1516, 1428, 1332, 1111, 1022, 950, 823, 735; δ_H (500 MHz, $CDCl_3$) 7.79 (dd, *J* = 8.0, 1.7 Hz, 1 H, Ar*H*), 7.71-7.74 (m, 2 H, Ar*H*), 7.67-7.69 (m, 2 H, Ar*H*), 7.55 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.35-7.44 (m, 6 H, Ar*H*), 7.27 (app. dt, *J* = 7.8, 1.3 Hz, 1 H, Ar*H*), 7.17 (app. dt, *J* = 7.8, 1.7 Hz, 1 H, Ar*H*), 7.10 (s, 4 H, Ar*H*),

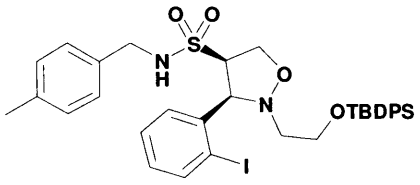
4.36-4.43 (m, 3 H, SCHCH_2 and SC*H*), 4.26 (d, *J* = 7.4 Hz, 1 H, NC*H*), 4.12 (dd, *J* = 13.7, 7.0 Hz, 1 H, NHC*H*H), 4.04 (dd, *J* = 13.7, 4.7 Hz, 1 H, NHCH*H*), 3.98 (ddd, *J* = 10.6, 7.7, 5.3 Hz, 1 H, OC*H*HCH$_2$), 3.85 (ddd, *J* = 10.6, 6.2, 3.9 Hz, 1 H, OCH*H*CH$_2$), 3.38 (dd, *J* = 7.0, 4.7 Hz, 1 H, N*H*), 3.03 (ddd, *J* = 13.4, 7.7, 6.2 Hz, 1 H, NC*H*HCH$_2$O), 2.69 (ddd, *J* = 13.4, 5.3, 3.9 Hz, 1 H, NCH*H*CH$_2$O), 2.32 (s, 3 H, ArCH_3), 1.05 (s, 9 H, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 137.9 (s), 135.8 (d), 135.7 (d), 133.8 (s), 133.7 (s), 133.1 (s), 132.4 (d), 131.9 (d), 130.1 (d), 129.7 (d), 129.5 (d), 128.0 (d), 127.8 (d), 127.7 (d), 127.6 (d), 125.5 (s), 71.4 (d), 67.0 (d), 66.2 (t), 61.7 (t), 58.5 (t), 47.3 (t), 27.0 (q), 21.2 (q), 19.3 (s); *m/z* (ESI) 717 (MNa^+, ^{81}Br, 100), 715 (MNa^+, ^{79}Br, 96), 454 (36), 299 (84); HRMS (ESI): calcd for $C_{35}H_{41}{}^{79}BrN_2NaO_4SSi$ (MNa^+) 715.1637, found 715.1631.

Data for **206b**: R_f 0.13 (2:1 petroleum ether 40-60°C/Et_2O); mp 131-133 °C; υ_{max} (neat)/cm^{-1} 3333, 2929, 1518, 1428, 1314, 1114, 1089, 955, 822, 746; δ_H (500 MHz, $CDCl_3$) 7.59-7.62 (m, 2 H, Ar*H*), 7.55-7.58 (m, 3 H, Ar*H*), 7.50 (dd, *J* = 7.8, 1.7 Hz, 1 H, Ar*H*), 7.36-7.40 (m, 2 H, Ar*H*), 7.29-7.34 (m, 5 H, Ar*H*), 7.25 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1 H, Ar*H*), 7.02 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 6.87 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 4.71 (dd, *J* = 6.8, 5.0 Hz, 1 H, N*H*), 4.59 (d, *J* = 7.3 Hz, 1 H, NC*H*), 4.40 (dd, *J* = 9.9, 3.7 Hz, 1 H, SCHC*H*H), 4.28 (dd, *J* = 9.9, 8.5 Hz, 1 H, SCHCH*H*), 4.13 (dd, *J* = 13.6, 6.8 Hz, 1 H, NHC*H*H), 3.90 (ddd, *J* = 8.5, 7.3, 3.7 Hz, 1 H, SC*H*), 3.83 (ddd, *J* = 10.6, 7.7, 5.8 Hz, 1 H, OC*H*HCH$_2$N), 3.76 (ddd, *J* = 10.6, 6.6, 4.2 Hz, 1 H, OCH*H*CH$_2$N), 3.75 (dd, *J* = 13.6, 5.0 Hz, 1 H, NHCH*H*), 2.97 (ddd, *J* = 13.2, 5.8, 4.2 Hz, 1 H, NC*H*HCH$_2$), 2.81 (ddd, *J* = 13.2, 7.7, 6.6 Hz, 1 H, NCH*H*CH$_2$), 2.29 (s, 3 H, ArCH_3), 0.97 (s, 9 H, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 137.9 (s), 136.4 (s), 135.7 (d), 135.6 (d), 133.9 (s), 133.8 (s), 133.3 (d), 133.0 (s), 130.5 (d), 130.1 (d), 129.7 (d), 129.6 (d), 129.5 (d), 128.5 (d), 128.0 (d), 127.7 (d), 127.6 (d), 124.8 (s), 72.9 (d), 70.9 (d), 67.1 (t), 61.6 (t), 57.7 (t), 47.2 (t), 26.8 (q), 21.1 (q), 19.2 (s); *m/z* (ESI) 717 (MNa^+, ^{81}Br, 100), 715 (MNa^+, ^{79}Br, 96), 504 (28); HRMS (ESI): calcd for $C_{35}H_{41}{}^{79}BrN_2NaO_4SSi$ (MNa^+) 715.1637, found 715.1642.

(3*S, 4*S**)-2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-3-(2-iodophenyl)isoxazolidine-4-sulfonic acid 4-methylbenzylamide (206c) and (3*S**, 4*R**)-2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-3-(2-iodophenyl)isoxazolidine-4-sulfonic acid 4-methylbenzylamide (207c)**



206c



207c

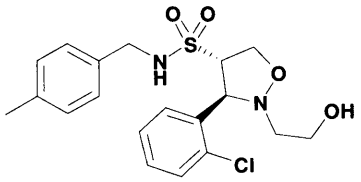
To a stirring solution of PFP ester **210c** (570 mg, 0.72 mmol) in dry THF (10 mL), 4-methylbenzylamine (270 μL, 2.15 mmol) was added followed by DBU (160 μL, 1.08 mmol). The mixture was refluxed for 1 hour and then concentrated *in vacuo*. The crude residue remaining was purified by flash chromatography (starting 8:1 petroleum ether 40-60°C/Et_2O) to yield the two products **206c** (246 mg, 46%) and **207c** (92 mg, 17%) as yellow solids- overall yield (63%, **206c**:**207c** = 5:2).

Data for **207c**: R_f 0.22 (2:1 petroleum ether 40-60°C/Et_2O); mp 86-88 °C; υ_{max} (neat)/cm^{-1} 3323, 2930, 1516, 1428, 1332, 1111, 951, 820, 736; δ_H (300 MHz, $CDCl_3$) 7.84 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.68-7.78 (m, 5 H, Ar*H*), 7.35-7.46 (m, 6 H, Ar*H*), 7.31 (app. dt, *J* = 7.8, 1.1 Hz, 1 H, Ar*H*), 7.11 (s, 4 H, Ar*H*), 7.03 (app. dt, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 4.36-4.45 (m, 3 H, SCHCH_2 and SC*H*), 4.15 (d, *J* = 7.2 Hz, 1 H, NC*H*), 4.10 (d, *J* = 6.7 Hz, 1 H, NHC*H*H), 4.07 (d, *J* = 5.1 Hz, 1 H, NHCH*H*), 4.00 (ddd, *J* = 10.2, 7.5, 5.1 Hz, 1 H, OC*H*HCH_2N), 3.85 (ddd, *J* = 10.2, 6.4, 4.3 Hz, 1 H, OCH*H*CH_2N), 3.47 (dd, *J* = 6.7, 5.1 Hz, 1 H, N*H*), 3.03 (ddd, *J* = 13.4, 7.5, 6.4 Hz, 1 H, NC*H*HCH_2), 2.70 (ddd, *J* = 13.4, 5.1, 4.3 Hz, 1 H, NCH*H*CH_2), 2.33 (s, 3 H, ArCH_3), 1.07 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 138.9 (d), 137.8 (s), 136.0 (s), 135.7 (d), 135.6 (d), 133.8 (s), 133.7 (s), 131.8 (d), 130.4 (d), 129.6 (d), 129.4 (d), 128.3 (d), 127.9 (d), 127.7 (d), 127.6 (d), 101.8 (s), 76.1 (d), 66.9 (d), 66.1 (t), 61.6 (t), 58.3 (t), 47.2 (t), 26.9 (q), 21.1 (q), 19.2 (s); *m/z* (ES^+) 764 (44), 763 (MNa^+, 100), 741 (17); HRMS (ES^+): calcd for $C_{35}H_{41}IN_2NaO_4SSi$ (MNa^+) 763.1487, found 763.1499.

Data for **206c**: R_f 0.15 (2:1 petroleum ether 40-60°C/Et_2O); mp 124-126 °C; υ_{max} (neat)/cm^{-1} 3310, 2929, 1517, 1428, 1311, 1112, 956, 862, 745; δ_H (300 MHz, $CDCl_3$) 7.89 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar*H*), 7.59-7.67 (m, 4 H, Ar*H*), 7.32-7.46 (m, 8 H, Ar*H*), 7.10 (app. dt, *J* = 8.0, 1.9 Hz, 1 H, Ar*H*), 7.04 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.92 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.84 (dd, *J* = 6.7, 5.4 Hz, 1 H, N*H*), 4.48 (d, *J* = 7.2 Hz, 1 H, NC*H*), 4.41 (dd, *J* = 9.9, 3.8 Hz, 1 H, SCHC*H*H), 4.28 (dd, *J* = 9.9, 8.6 Hz, 1 H, SCHCH*H*), 4.15 (dd, *J* = 13.7, 6.7 Hz, 1 H, NHC*H*H), 3.82-3.93 (m, 3 H, SC*H* and OCH_2CH_2), 3.80 (dd,

J = 13.7, 5.4 Hz, 1 H, NHCH*H*), 3.02 (ddd, J = 13.1, 5.4, 4.3 Hz, 1 H, NC*H*HCH$_2$), 2.78-2.88 (m, 1 H, NCH*H*CH$_2$), 2.33 (s, 3 H, ArCH_3), 1.02 (s, 9 H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 139.9 (d), 139.3 (s), 137.8 (s), 135.6 (d), 135.5 (d), 133.9 (s), 133.8 (s), 133.0 (s), 130.4 (d), 130.2 (d), 129.6 (d), 129.5 (d), 129.4 (d), 129.2 (d), 128.0 (d), 127.6 (d), 127.5 (d), 101.2 (s), 75.4 (d), 73.1 (d), 67.1 (t), 61.6 (t), 57.5 (t), 47.2 (t), 26.9 (q), 21.2 (q), 19.2 (s); *m/z* (ESI) 763 (MNa^+, 28), 327 (38), 300 (86), 255 (46), 241 (66), 185 (53), 173 (100); HRMS (ESI): calcd for $C_{35}H_{41}IN_2NaO_4SSi$ (MNa^+) 763.1499, found 763.1491.

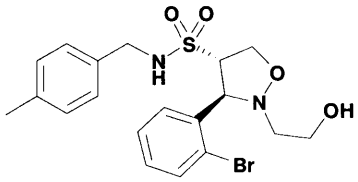
(3*S, 4*S**)-3-(2-Chlorophenyl)-2-(2-hydroxyethyl)isoxazolidine-4-sulfonic acid 4-methylbenzylamide (211a)**



To a stirring solution of **206a** (173 mg, 0.27 mmol) in THF (4 mL) at 0 °C was added TBAF (1M in THF, 400 μL, 0.40 mmol). After 2 hours at 0 °C the reaction mixture was concentrated *in vacuo*, and the residue purified by flash chromatography (starting 100% $CHCl_3$) to give the product (109 mg, 98%) as a yellow oil.

R_f 0.57 (9:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 3476, 3295, 2923, 1515, 1438, 1323, 1144, 1038, 807, 752; δ_H (300 MHz, $CDCl_3$) 7.46-7.50 (m, 1 H, Ar*H*), 7.38-7.42 (m, 1 H, Ar*H*), 7.31-7.38 (m, 2 H, Ar*H*), 7.02 (d, J = 7.8 Hz, 2 H, Ar*H*), 6.89 (d, J = 7.8 Hz, 2 H, Ar*H*), 4.68 (d, J = 7.4 Hz, 1 H, NC*H*), 4.58 (app. t, J = 5.8 Hz, 1 H, N*H*), 4.48 (dd, J = 9.9, 3.9 Hz, 1 H, SCHC*H*H), 4.36 (dd, J = 9.9, 8.4 Hz, 1 H, SCHCH*H*), 4.14 (dd, J = 13.7, 6.6 Hz, 1 H, NHC*H*H), 3.96 (ddd, J = 8.4, 7.4, 3.9 Hz, 1 H, SC*H*), 3.83 (dd, J = 13.7, 5.1 Hz, 1 H, NHCH*H*), 3.78 (app. dt, J = 8.3, 2.9 Hz, 1 H, OC*H*HCH$_2$), 3.62 (app. dt, J = 11.4, 4.0 Hz, 1 H, OCH*H*CH$_2$), 2.99 (ddd, J = 13.4, 5.0, 2.9 Hz, 1 H, NC*H*HCH$_2$), 2.80 (ddd, J = 13.4, 8.0, 4.0 Hz, 1 H, NCH*H*CH$_2$), 2.31 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 134.2 (2 x s), 133.1 (s), 130.2 (d), 130.0 (d), 129.9 (d), 129.4 (d), 127.9 (d), 127.7 (d), 72.2 (d), 68.5 (d), 67.4 (t), 60.5 (t), 57.3 (t), 47.1 (t), 21.1 (q); *m/z* (ESI) 435 (MNa^+, ^{37}Cl, 35), 433 (MNa^+, ^{35}Cl, 100), 222 (42); HRMS (ESI): calcd for $C_{19}H_{23}{}^{35}ClN_2NaO_4S$ (MNa^+) 433.0965, found 433.0959.

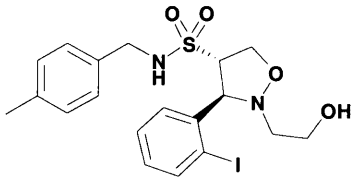
(3*S, 4*S**)-3-(2-Bromophenyl)-2-(2-hydroxyethyl)isoxazolidine-4-sulfonic acid 4-methylbenzylamide (211b)**



To a stirring solution of **206b** (330 mg, 0.48 mmol) in THF (6 mL) at 0 °C was added TBAF (1M in THF, 710 μL, 0.71 mmol). After 2 hours at 0 °C the reaction mixture was concentrated *in vacuo*, and the residue purified by flash chromatography (starting 100% $CHCl_3$) to give the product (204 mg, 93%) as a yellow oil.

R_f 0.61 (9:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 3498, 3290, 2879, 1515, 1434, 1323, 1203, 1144, 1044, 806, 751; δ_H (300 MHz, $CDCl_3$) 7.59 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar*H*), 7.47 (dd, *J* = 7.8, 1.9 Hz, 1 H, Ar*H*), 7.38 (app. td *J* = 7.8, 1.2 Hz, 1 H, Ar*H*), 7.25 (app. td, *J* = 7.8, 1.9 Hz, 1 H, Ar*H*), 7.01 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.69 (d, *J* = 7.1 Hz, 1 H, NC*H*), 4.63 (app. t, *J* = 5.9 Hz, 1 H, N*H*), 4.49 (dd, *J* = 9.9, 3.9 Hz, 1 H, SCHC*H*H), 4.37 (dd, *J* = 9.9, 8.4 Hz, 1 H, SCHCH*H*), 4.14 (dd, *J* = 13.5, 6.7 Hz, 1 H, NHC*H*H), 3.94 (ddd, *J* = 8.4, 7.1, 3.9 Hz, 1 H, SC*H*), 3.81 (dd, *J* = 13.5, 5.0 Hz, 1 H, NHCH*H*), 3.75-3.80 (m, 1 H, OC*H*HCH$_2$N), 3.62 (dt, *J* = 11.6, 4.1 Hz, 1 H, OCH*H*CH$_2$N), 3.01 (ddd, *J* = 13.4, 5.0, 2.8 Hz, 1 H, NC*H*HCH$_2$), 2.81 (ddd, *J* = 13.4, 8.0, 4.1 Hz, 1 H, NCH*H*CH$_2$), 2.30 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 137.8 (s), 135.8 (s), 133.4 (d), 133.0 (s), 130.2 (d), 129.4 (d), 128.5 (d), 127.9 (d), 127.7 (d), 124.6 (s), 72.4 (d), 70.8 (d), 67.4 (t), 60.5 (t), 57.3 (t), 47.2 (t), 21.1 (q); *m/z* (FAB$^+$) 457 (MH$^+$, ^{81}Br, 10), 455 (MH$^+$, ^{79}Br, 10), 329 (97), 307 (24), 176 (90), 154 (100); HRMS (FAB$^+$): calcd for $C_{19}H_{24}{}^{79}BrN_2O_4S$ (MH$^+$) 455.0640, found 455.0631.

(3*S, 4*S**)-2-(2-Hydroxyethyl)-3-(2-iodophenyl)isoxazolidine-4-sulfonic acid 4-methylbenzylamide (211c)**

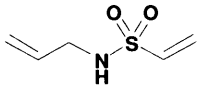


To a stirring solution of **206c** (184 mg, 0.25 mmol) in THF (4 mL) at 0 °C was added TBAF (1M in THF, 370 μL, 0.37 mmol). After 2 hours at 0 °C the reaction mixture was concentrated *in vacuo*, and the residue purified by flash chromatography (starting 100% $CHCl_3$) to give the product (122 mg, 97%) as a yellow oil.

R_f 0.61 (9:1 $CHCl_3$/MeOH); υ_{max} (neat)/cm^{-1} 3531, 3288, 2882, 1516, 1435, 1323, 1144, 1042, 807, 749; δ_H (300 MHz, $CDCl_3$) 7.87 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.37-7.42 (m, 2 H, Ar*H*), 7.05-7.11 (m, 1 H, Ar*H*), 7.01 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.76 (app t, *J* = 5.9 Hz, 1 H, N*H*), 4.55 (d, *J* = 7.2 Hz, 1 H, NC*H*), 4.47 (dd, *J* = 9.9, 3.8 Hz, 1 H, SCHC*H*H), 4.35 (dd, *J* = 9.9, 8.6 Hz, 1 H, SCHCH*H*), 4.13 (dd, *J* = 13.7, 6.4 Hz, 1 H, NHC*H*H), 3.91 (app. td, *J* = 8.0, 3.8 Hz, 1 H, SC*H*), 3.81 (dd, *J* = 13.7, 5.1 Hz, 1 H, NHCH*H*), 3.73-3.80 (m, 1 H, OC*H*HCH_2N), 3.60 (app. dt, *J* = 11.8, 4.3 Hz, 1 H, OCH*H*CH_2N), 3.03 (ddd, *J* = 13.4, 5.1, 3.2 Hz, 1 H, NC*H*HCH_2), 2.80 (ddd, *J* = 13.4, 8.0, 3.8 Hz, 1 H, NCH*H*CH_2), 2.30 (s, 3 H, ArCH_3); δ_C (75 MHz, $CDCl_3$) 140.2 (d), 138.8 (s), 137.9 (s), 132.8 (s), 130.6 (d), 129.9 (d), 129.5 (d), 129.3 (d), 128.0 (d), 100.9 (s), 75.2 (d), 72.7 (d), 67.5 (t), 60.5 (t), 57.2 (t), 47.2 (t), 21.1 (q); *m/z* (FAB^+) 503 (MH^+, 60), 289 (77), 212 (28), 176 (40), 152 (100); HRMS (FAB^+): calcd for $C_{19}H_{24}IN_2O_4S$ (MH^+) 503.0502, found 505.0490.

4.9. Miscellaneous products

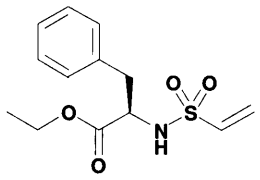
Ethenesulfonic acid allylamide (123a)



A premixed suspension of allylamine (3.9 g, 67.5 mmol) and NEt_3 (12.4 g, 122.7 mmol) in DCM (25 mL) was added dropwise to a stirring solution of 2-chloroethane-1-sulfonyl chloride (10.0 g, 61.3 mmol) in DCM (100 mL) at -10 °C. The reaction mixture was stirred for a further 30 minutes after addition, and then warmed to RT. The reaction was diluted with DCM (60 mL) and washed with 2M HCl (3 x 80 mL), H_2O (80 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* and purification by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) furnished the desired product (5.9 g, 65%) as a yellow oil.

R_f 0.14 (1:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 3288, 3063, 2860, 1645, 1427, 1393, 1256, 1150, 1065, 928; δ_H (300 MHz, $CDCl_3$) 6.52 (dd, *J* = 16.6, 9.9 Hz, 1 H, SC*H*), 6.23 (d, *J* = 16.6 Hz, 1 H, SCHC*H*H), 5.94 (d, *J* = 9.9 Hz, SCHCH*H*), 5.82 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1 H, CH_2=C*H*), 5.25 (app. dq, *J* = 17.1, 1.3 Hz, 1 H, CH=C*H*H), 5.17 (app. dq, *J* = 10.2, 1.3 Hz, 1 H, CH=CH*H*), 4.73 (br s, 1 H, N*H*), 3.61-3.67 (m, 2 H, NCH_2); δ_C (75 MHz, $CDCl_3$) 136.1 (d), 133.2 (d), 126.7 (t), 117.8 (t), 45.5 (t); *m/z* (EI) 147 (M^+, 100), 91 (39), 82 (26); HRMS (ESI): calcd for $C_5H_9NO_2S$ (M^+) 147.0354, found 147.0351.

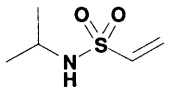
2-Ethenesulfonylamino-3-phenylpropionic acid ethyl ester (123c)



A premixed suspension of phenylalanine ethyl ester (1.3 g, 6.8 mmol) and NEt_3 (0.6 g, 6.1 mmol) in DCM (5 mL) was added dropwise to a stirring solution of 2-chloroethane-1-sulfonyl chloride (1.0 g, 6.1 mmol) in DCM (10 mL) at -10 °C. The reaction mixture was stirred for a further 30 minutes after addition, and then warmed to RT. The reaction was diluted with DCM (20 mL) and washed with 2M HCl (3 x 80 mL), H_2O (80 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* and purification by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) furnished the desired product (968 mg, 56%) as a white solid.

R_f 0.27 (1:1 hexane/Et_2O); mp 88-90 °C; υ_{max} (film)/cm^{-1} 3310, 3010, 2870, 1720, 1609, 1433, 1321, 1263, 1103, 1022; δ_H (300 MHz, $CDCl_3$) 7.15-7.33 (m, 5 H, Ar*H*), 6.28 (dd, *J* = 16.5, 9.5 Hz, 1 H, SC*H*), 6.14 (d, *J* = 16.5 Hz, 1 H, SCHC*H*H), 5.78 (d, *J* = 9.5 Hz, 1 H, SCHCH*H*), 5.01 (d, *J* = 9.1 Hz, 1 H, N*H*), 4.12-4.22 (m, 3 H, CH_3CH_2O and NHC*H*), 3.07-3.10 (m, 2 H, $PhCH_2CH$), 1.23 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 171.2 (s), 136.0 (d), 135.2 (s), 129.6 (d), 128.6 (d), 127.4 (d), 126.5 (t), 61.9 (t), 56.7 (d), 39.5 (t), 14.1 (q); *m/z* (EI) 284 (M^+, 3), 215 (98), 192 (100), 176 (100), 164 (26), 146 (27), 118 (56), 109 (31), 91 (90); HRMS (ESI): calcd for $C_{13}H_{17}NO_4S$ (M^+) 283.0878, found 283.0879.

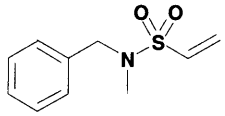
Ethenesulfonic acid isopropylamide (123d)



A premixed suspension of isopropyl amine (6.0 g, 101.2 mmol) and NEt_3 (27.9 g, 276.0 mmol) in DCM (40 mL) was added dropwise to a stirring solution of 2-chloroethane-1-sulfonyl chloride (15.0 g, 92.0 mmol) in DCM (150 mL) at -10 °C. The reaction mixture was stirred for a further 30 minutes after addition, and then warmed to RT. The reaction was diluted with DCM (60 mL) and washed with 2M HCl (3 x 80 mL), H_2O (80 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* and purification by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) furnished the desired product (7.5 g, 55%) as a yellow oil.

R_f 0.15 (1:1 petroleum ether 40-60°C/Et_2O); υ_{max} (neat)/cm^{-1} 3294, 3059, 2880, 1620, 1464, 1425, 1327, 1134, 1007; δ_H (300 MHz, $CDCl_3$) 6.53 (dd, *J* = 16.3, 9.9 Hz, 1 H, SC*H*), 6.22 (d, *J* = 16.3 Hz, 1 H, SCHC*H*H), 5.89 (d, *J* = 9.9 Hz, 1 H, SCHCH*H*), 4.51 (br d, *J* = 6.2 Hz, 1 H, N*H*), 3.49 (app. octet, *J* = 6.7 Hz, 1 H, $NCH(CH_3)_2$), 1.19 (d, *J* = 6.7 Hz, 6 H, $CH(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 137.1 (d), 125.8 (t), 46.1 (d), 24.0 (q); *m/z* (CI) 150 (MH^+, 67), 134 (76), 122 (65), 108 (100); HRMS (CI): calcd for $C_5H_{12}NO_2S$ (MH^+) 150.0589, found 150.0586.

Ethenesulfonic acid benzylmethyl amide (123f)



A premixed suspension of *N*-benzylmethyl amine (12.3 g, 101.2 mmol) and NEt_3 (27.9 g, 276.0 mmol) in DCM (40 mL) was added to a stirring solution of 2-chloroethane-1-

sulfonyl chloride (15.0 g, 92.0 mmol) in DCM (150 mL) at -10 °C. The reaction mixture was stirred for a further 30 minutes after addition, and then warmed to RT. The reaction was diluted with DCM (60 mL) and washed with 2M HCl (3 x 80 mL), H_2O (80 mL), dried ($MgSO_4$), and filtered. The filtrate was collected and concentrated *in vacuo* and purification by flash chromatography (starting 5:1 petroleum ether 40-60°C/Et_2O) furnished the desired product (13.1 g, 67%) as light yellow solid.

R_f 0.24 (1:1 petroleum ether 40-60°C/Et_2O); mp 23-25 °C; υ_{max} (neat)/cm^{-1} 3033, 2918, 1455, 1334, 1148, 936; δ_H (300 MHz, $CDCl_3$) 7.28-7.40 (m, 5 H, Ar*H*), 6.45 (dd, *J* = 16.6, 9.8 Hz, 1 H, SC*H*), 6.26 (d, *J* = 16.6 Hz, 1 H, SCHC*H*H), 6.01 (d, *J* = 9.8 Hz, 1 H, SCHCH*H*), 4.25 (s, 2 H, NCH_2Ph), 2.60 (s, 3 H, NCH_3); δ_C (75 MHz, $CDCl_3$) 135.6 (s), 133.3 (d), 128.7 (d), 128.4 (d), 128.0 (d), 127.7 (t), 53.8 (t), 34.1 (q); *m/z* (EI) 211 (M^+, 9), 118 (98), 91 (100), 77 (29), 65 (42), 51 (23); HRMS (EI): calcd for $C_{10}H_{13}NO_2S$ (M^+) 211.0662, found 211.0657.

CHAPTER 5: References

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CHAPTER 6: Supplementary data

The following biological assays were conducted by Leiper *et al.* at the Centre for Clinical Pharmacology, UCL, Rayne Building, 5 University Street, London WC1E 6JF:

6.1. DDAH activity assay (from *Pseudomonas aeruginosa*)

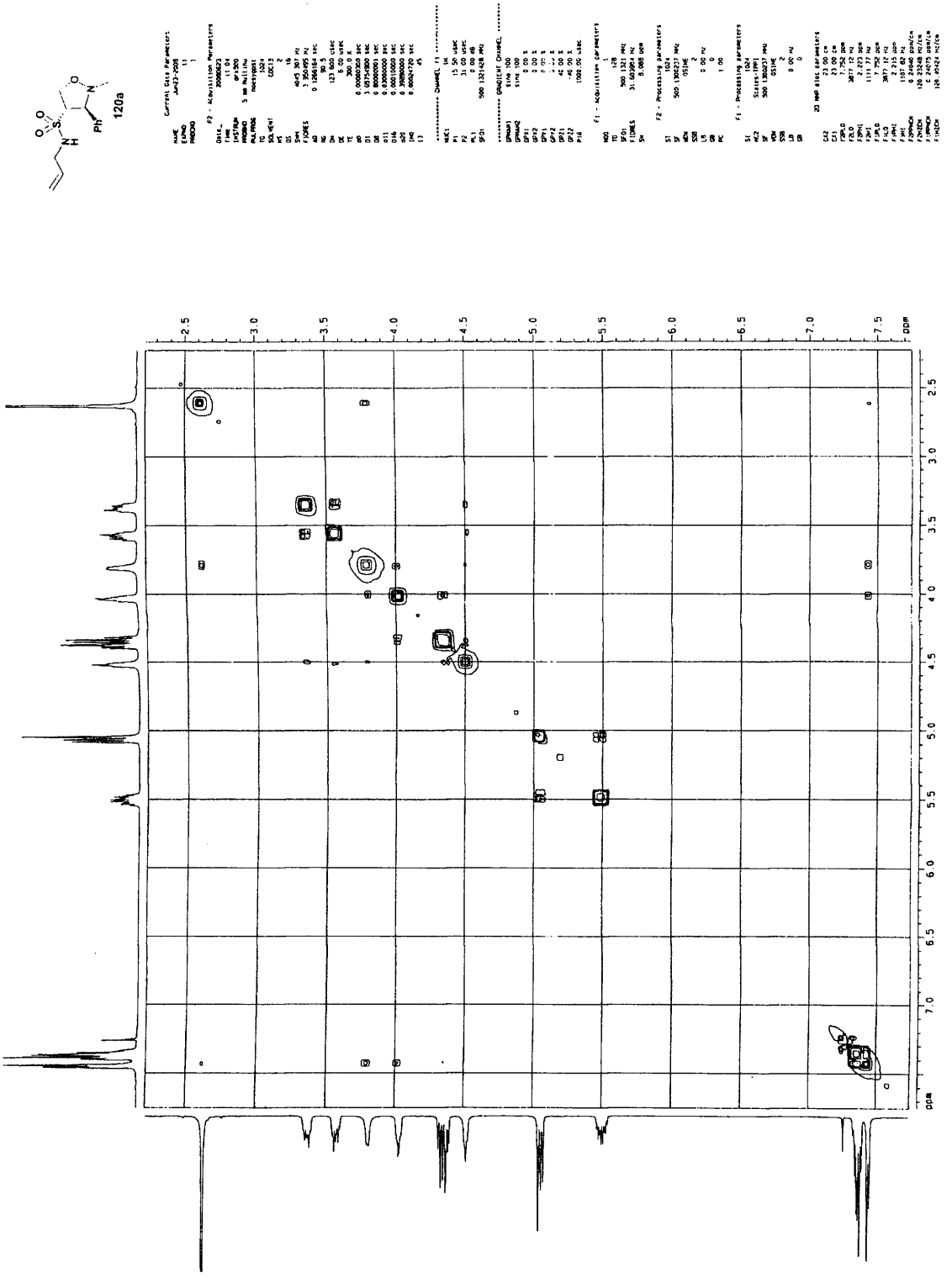
1. Require 12.5 μM working stock of PaDDAH.
2. Buffer used is 90 mM sodium phosphate ph 7.4.
3. Take 2 μL of working stock PaDDAH and add 97 μL of 90mM sodium phosphate buffer ph 7.4, (if adding inhibitors alter amount of buffer accordingly to aquire final volume of 100 μL).
4. Incubate for 5 minutes at 37°C.
5. Add 1 mM of ADMA to start the reaction.
6. Stop the reaction after 10 minutes with 200 μL of colour developer. To make the colour developer add 1 part of diacetylmonoxime (0.2 g diacetylmonoxime in 23.8 mL of H_2O and 1.2 mL of acetic acid) to 2 parts of anti-pyrine (125 mg of anti-pyrine in 12.5 mL H_2O and 12.5 mL sulphuric acid) prior to stopping the reaction.
7. Heat samples at 94°C for 30 minutes to allow the colour to develop.
8. Read on a spectrophotometer at wavelength 450 nm.

6.2. ADI activity assay (from *Pseudomonas aeruginosa*)

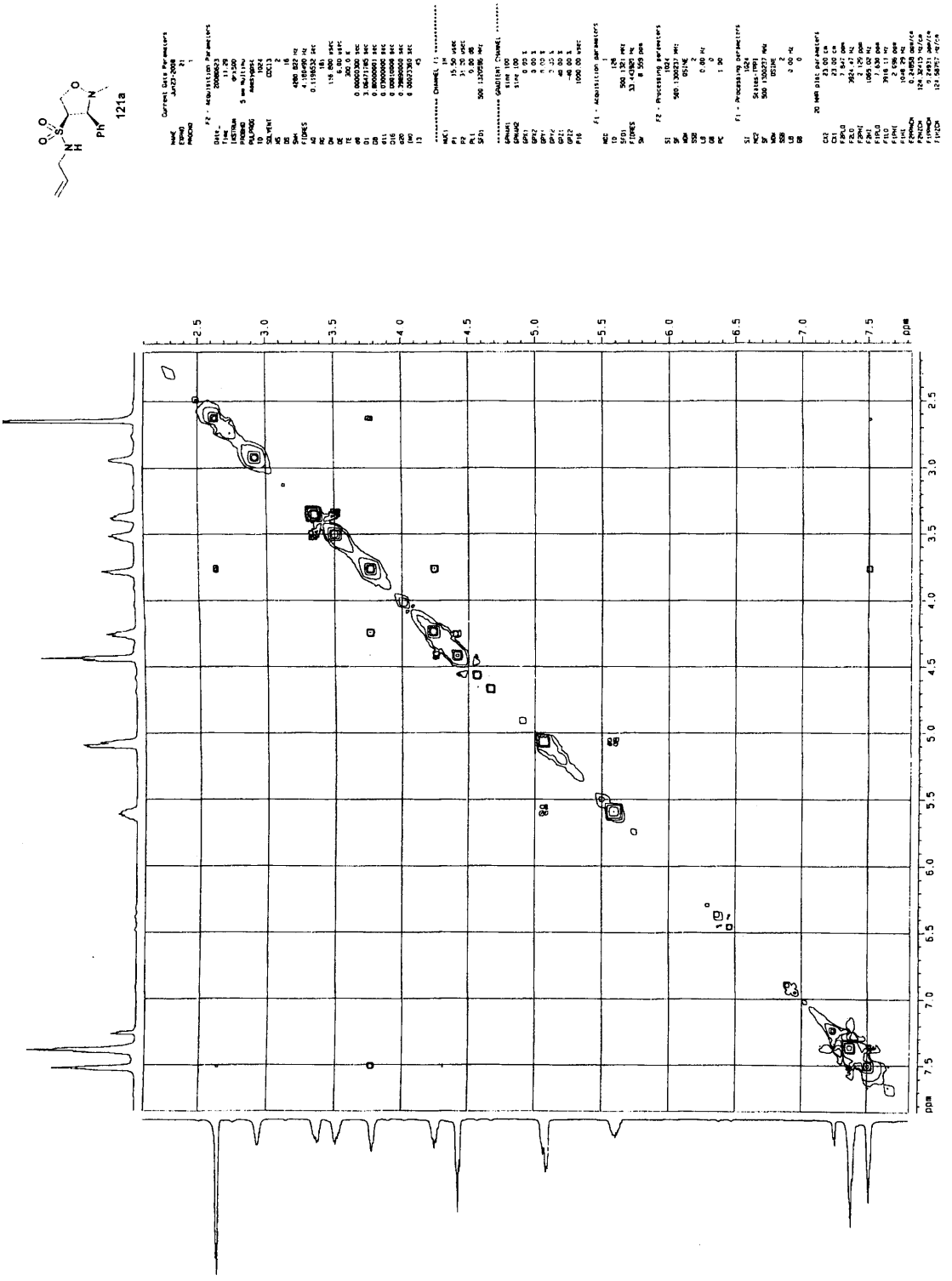
1. Require 1 μM working stock of PaADI.
2. Buffer used is 50 mM Mes (2-(*N*-morpholino)ethanesulfonic acid), 20 mM $MgCl_2$ at ph 5.6 (Buffer A).
3. Take 1 μL of working stock PaADI and add 98 μL of Buffer A, (if adding inhibitors alter amount of buffer accordingly to aquire final volume of 100 μL).
4. Incubate for 5 minutes at 37°C.
5. Start the reaction with 1 μL of Buffer B (50 mM Mes, 20 mM $MgCl_2$ at pH 5.6 with 100 mM L-Arginine) and mix well with a pipette.
6. Incubate the reaction for a further 10 minutes at 37°C.
7. Stop the reaction with 100 μL of colour developer just before the end of the reaction (to make the colour developer see section 6.1)
8. Heat samples at 94°C for 30 minutes to allow the colour to develop.
9. Read on a spectrophotometer at wavelength 450 nm.

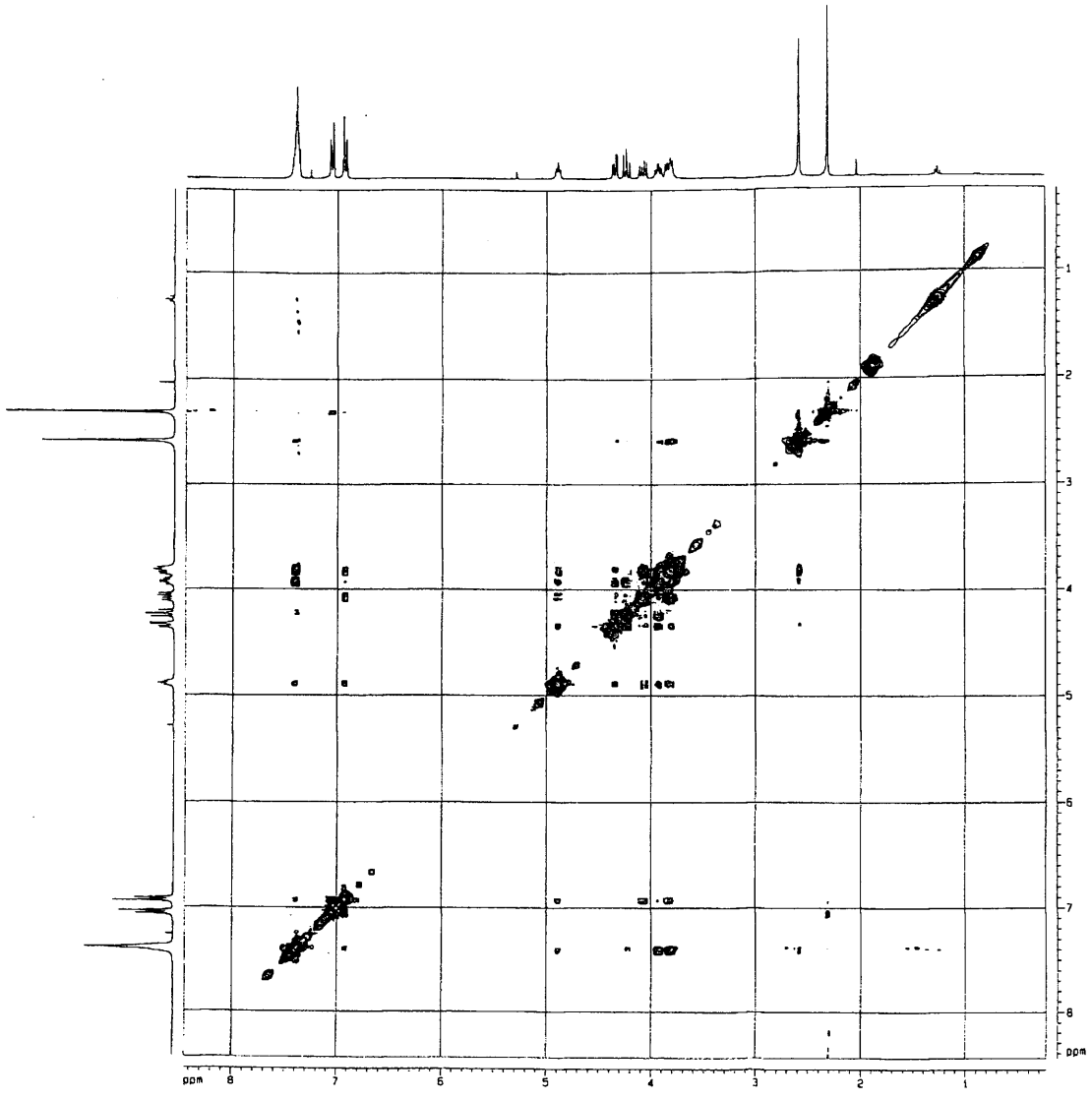
6.3. NOE data

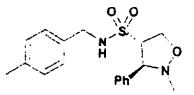
Graph 1



Graph 2







120b

Current Data Parameters
NAME Feb24-2005
EXPNO 32
PROCNO 1

F2 - Acquisition Parameters
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Time 15.22
INSTRUM spect300
PROBHD 5 mm DNP 1H
PULPROG noesytp
TD 1024
SOLVENT CDCl3
RG 0
NS 8
DS 0
SWH 2463.054 Hz
FIDRES 2.405326 Hz
AQ 0.2079220 sec
RG 128
DW 203.000 usec
DE 232.86 usec
TE 300.0 K
D1 1.95903695 sec
P1 6.80 usec
D0 0.00000300 sec
D8 0.60000002 sec
SFO1 299.8740954 MHz
NUCLEUS 1H
INO 0.00020300 sec

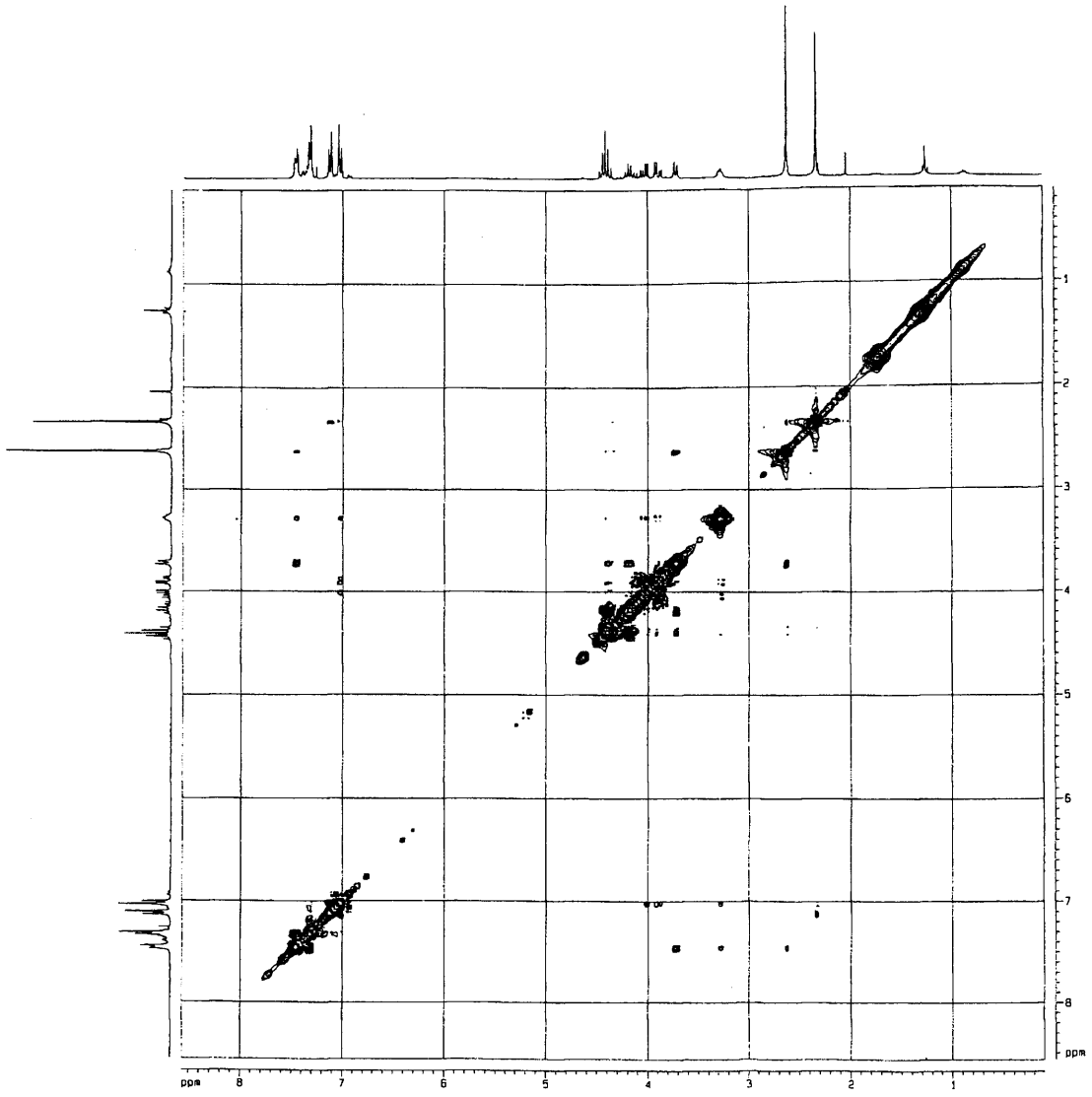
F1 - Acquisition parameters
NDO 2
TD 128
SFO1 299.8741 MHz
FIDRES 19.242611 Hz
SW 8.214 ppm

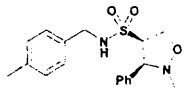
F2 - Processing parameters
SI 1024
SF 299.8727940 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.00
SR 2794.00 Hz

F1 - Processing parameters
SI 1024
MC2 TPPI
SF 299.8727940 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0

2D NMR plot parameters
CX2 22.50 cm
CX1 22.50 cm
F2PLO 9.447 ppm
F2LO 2532.95 Hz
F2PHI 0.233 ppm
F2HI 69.91 Hz
F1PLO 8.447 ppm
F1LO 2532.95 Hz
F1PHI 0.233 ppm
F1HI 69.91 Hz
F2PPMCM 0.36505 ppm/cm
F2HZCM 109.46861 Hz/cm
F1PPMCM 0.36505 ppm/cm
F1HZCM 109.46861 Hz/cm

Graph 3





121b

Current Data Parameters

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EXPNO	42
PROCNO	1

F2 - Acquisition Parameters

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PROBHD	5 mm QNP 1H
PULPROG	noesytp
TD	1024
SOLVENT	CDCl3
NS	8
DS	8
RD	0
SWH	2538.071 Hz
FIDRES	2.478585 Hz
AQ	0.2017780 sec
RG	256
DW	197.000 usec
DE	232.86 usec
TE	300.0 K
NL1	1 GB
D1	1.96518099 sec
P1	6.80 usec
D0	0.00000300 sec
D8	0.60000002 sec
SFO1	299.8740946 MHz
NUCLEUS	1H
IN0	0.00019700 sec

F1 - Acquisition parameters

NDO	2
TD	128
SFO1	299.874! MHz
FIDRES	19.828680 Hz
SW	8.464 ppm

F2 - Processing parameters

SI	1024
SF	299.8727940 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00
SR	2794.00 Hz

F1 - Processing parameters

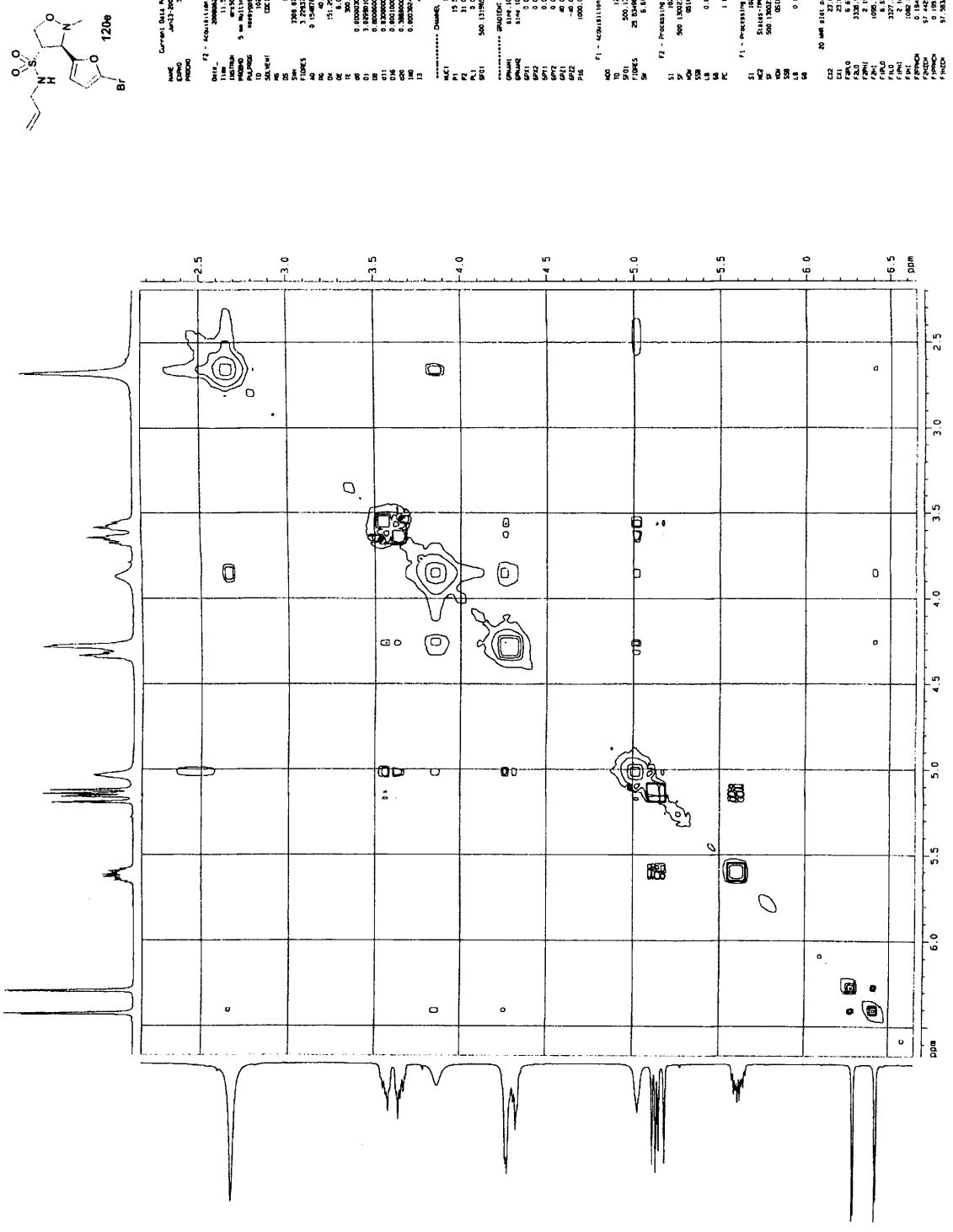
SI	1024
MC2	TPPI
SF	299.8727940 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

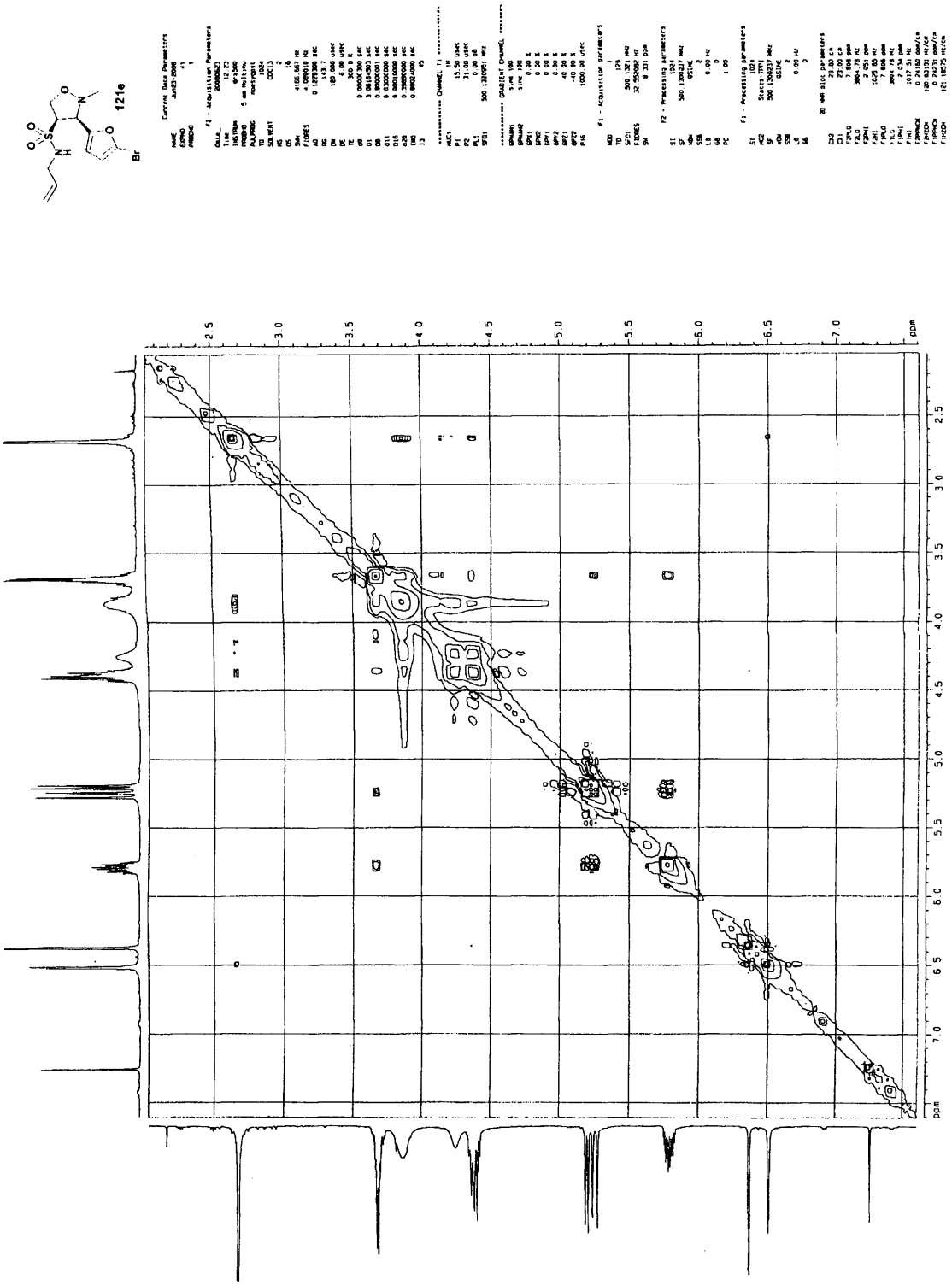
CX2	22.50 cm
CX1	22.50 cm
F2PLO	8.569 ppm
F2LO	2569.65 Hz
F2PHI	0.105 ppm
F2HI	31.59 Hz
F1PLO	8.569 ppm
F1LO	2569.65 Hz
F1PHI	0.105 ppm
F1HI	31.59 Hz
F2PPMCM	0.37617 ppm/cm
F2HZCM	112.80267 Hz/cm
F1PPMCM	0.37617 ppm/cm
F1HZCM	112.80267 Hz/cm

Graph 4

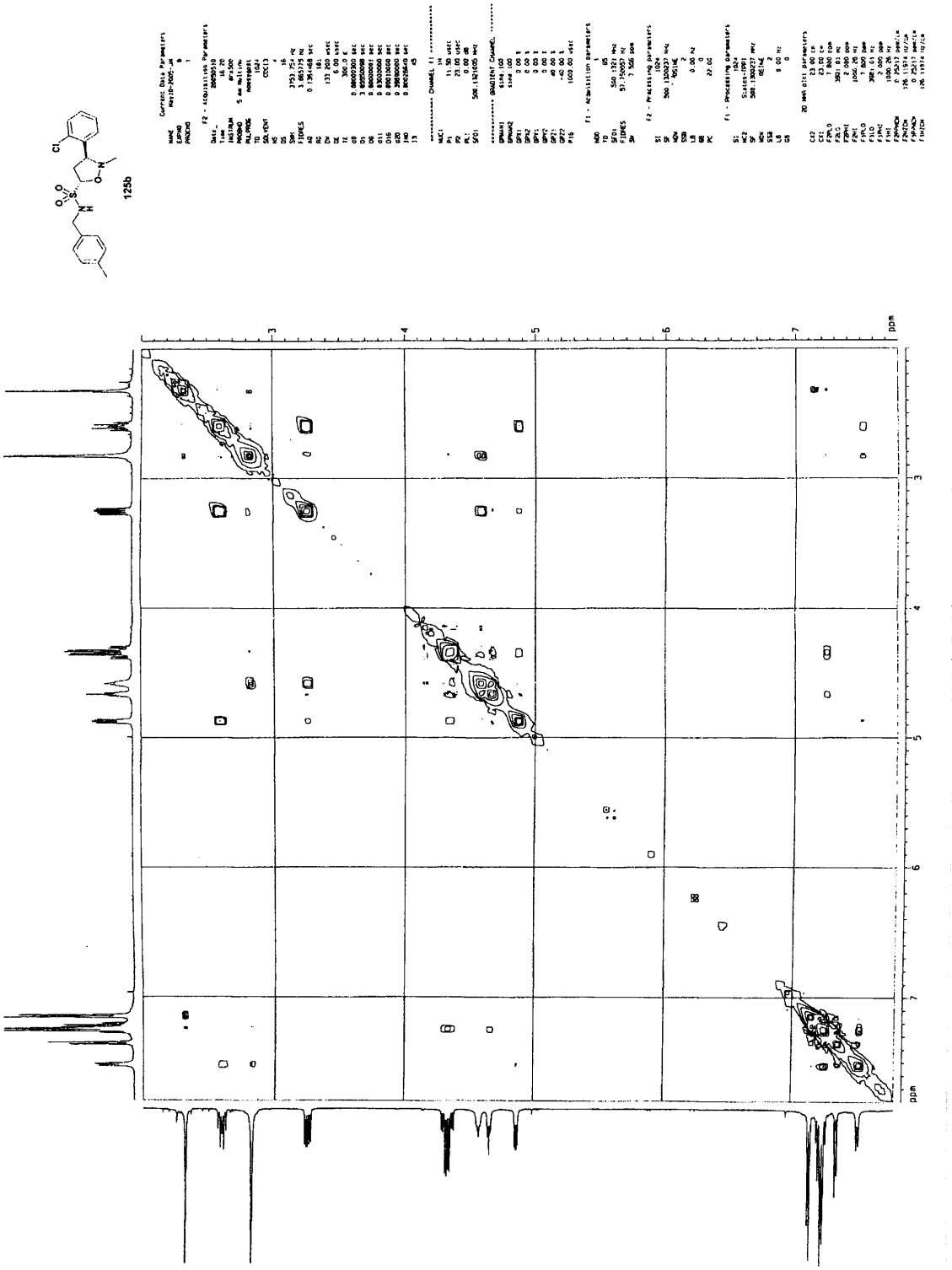
Graph 5



Graph 6



Graph 7



Graph 8