Synthetic approaches to biologically active sulfonates and sulfonamides

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Declaration

I, Chieh-Chien Lee confirm that the work presented in this thesis is my own. Where information has been derived from other sources, and I confirm that this has been indicated appropiately.

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Abstract

This research describes the scope of 1,3-dipolar cycloaddition between selected 1,3-dipoles (nitrile oxide/nitrone) and dipolarophiles (PFP ethenesulfonate/PFP-1-bromoethenesulfonate). Nitrile oxide cycloaddition with PFP-1-bromoethenesulfonate furnished 3,5-isoxazoles in a regiospecific fashion; where solvent polarity, reaction temperature and the amount of base are the determining factors for efficient cycloaddition. Subsequent aminolysis with various amines were also carried out. Aminolysis with secondary and aromatic amines produced low yields, nevertheless a wide range of the corresponding sulfonamides were synthesized.

A collection of the isoxazolidinyl PFP sulfonate esters, and the corresponding sulfonamides, were found to exhibit anti HIV-1 activity in micromolar scale. Synthesis of the isoxazolidinyl sulfonamides was also diversified in order to investigate the structure-activity relationships. Furthermore, synthesis of the candidate for immobilized medium for affinity chromatography was established, *via* a multi-step reaction sequence.

Biological testing of the synthesized isoxazolidinyl PFP sulfonate esters, and sulfonamides show that the candidate molecules act on the host factors required for viral infection, rather than the virus itself. Furthermore, they show specific activity toward viral targets and do not exhibit toxicity toward live cells.

Table of Contents

Abbreviations

ADI	Arginine deiminase
ADP	Adenosine diphosphate
AIBN	Azobisisobutylonitrile
AIDS	Aquired immodeficiency syndrome
ATP	Adenosine triphosphate
bp.	Boiling point
CA	Carbonic anhydrase
CI	Chemical ionisation
COX	Cyclooxygensae
DBU	1,8-diazobicyclo [5.4.0] undec-7-ene
DCM	Dichloromethane
DDAH	Dimethylarginine dimethylamino hydrolase
DDQ	Dichloro dicyanide benzoquinone
de	Diastereomeric excess
DHF	DiHydrofolic acid
DHODH	Dihydroorotate dehydrogenase
DMAP	Dimethyl-amino-pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribose nucleic acid
dNTP	Deoxynucleotide triphosphate
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EI	Electron ionization
ES	Electrospray
FAB	Fast atom bombardment
FMO	Frontier molecular orbital
g	grams
gp	Glycoprotein
HAART	Highly active anti-retroviral therapy
HIV	Human Immunodefficiency Virus
HOBt	1-Hydroxybenzotriazole

HRV	Human Rhinovirus
HSV	Herpes Simplex Virus
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrum
Hz	Hertz
IN	Integrase
IR	Infrared
KBr	Potassium bromide
K_i	Inhibitory equilibrium constant
LRMS	Low resolution mass spectroscopy
LUMO	Lowest unoccupied molecular orbital
M	Molar
MA	Matrix protein
m-**CPBA**	*meta*-Chloroperoxybenzoic acid
MHz	Megahertz
μM	Micromolar
mg	Milligrams
mL	Millilitre
mmol	Millimoles
mp	Melting point
mRNA	Messenger ribonucleic acid
NCS	*N*-chlorosuccinamide
NLS	Nuclear localisation signal
nM	Nanomolar
NMR	Nuclear magnetic resonance
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
NOE	Nuclear overhauser effect
NRTI	Nucleoside reverse-transcriptase inhibitor
NSAID	Non-steroidal anti-inflammatory drug
p-**ABA**	*para*-aminobenzoic acid
PFP	Pentafluorophenyl
PFPOH	Pentafluorophenol
Petrol	Petroleum ether (bp. 40-60°C)
PG	Protecting group

PIC	Pre-integration complex
PMB	*p*-methoxybenzyl
ppm	Parts per million
RNA	Ribonucleic acid
RT	Room temperature
RT	Reverse transcriptase
RTCs	Reverse-transcription complexes
SAR	Structure-activity relationships
SMX	Sulfamethoxazole
TBAC	*tetra*-Butyl-ammonium chloride
TBAF	*tetra*-Butyl-ammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TCCA	Trichloroisocyanuric acid
TCP	2,4,6-Trichlorophenyl
TFAA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMP	Trimethoprim
TMS	Trimethylsilyl
UV	Ultra violet
vDNA	Viral deoxyribose nucleic acid
Vpr	Viral protein R

1   Introduction

1.1   Introduction to sulfonamides

Sulfonamides have been used as therapeutic agents for over fifty years. They were first used as antibacterial/antibiotic agents, but their applications have been extended to treat other diseases since. In 1935, Sulfonilamide was identified by Domagk *et al.* as the active metabolite of the red azo dye known as Prontosil **1**. Prontosil **1** does not possess any activity *in vitro*; however it metabolizes *in vivo* to give the active agent sulfanilamide **2**; where it can interfere with the process of bacterial DNA synthesis and act as potent antibacterial agent.[1]
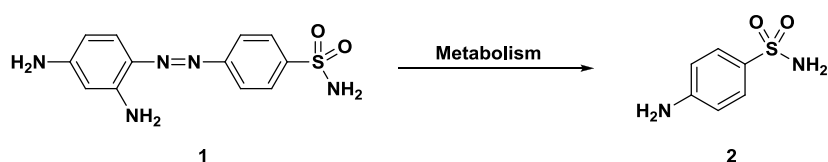
Scheme 1 *In vivo* metabolism of Prontosil

Apart from the commercialized application as antibacterial/antibiotic agents, various sulfonamides are also known to inhibit several enzymes such as carbonic anhydrase, cysteine protease, HIV protease and cyclooxygenase.[2] Moreover, the widespread potential value of sulfonamides, have led to the discovery of various other therapeutic applications, in cancer chemotherapy, diuretics, hypoglyceamia and the anti-impotence agent Viagra.[3]

Due to the inability of bacteria to acquire dihydrofolic acid from their environment, as part of bacteria's DNA biosynthesis, inhibition of dihydrofolic acid synthase poses a desirable target for bacteriostatic agents (Scheme 2).[4] Inhibition of these enzymes has been achieved with early sulfonamides such as sulfanilamide **2**. The formation of dihydrofolic acid is initiated by coupling pteridine diphosphate **3** with para-aminobenzoic acid **4**, which can then undergo amide coupling with glutamic acid to form dihydrofolic acid **5**. Sulfonilamide **2** displays similar core structure to that of *p*-aminobenzoic acid **4** and act as a competitive inhibitor. Dihydrofolic acid formation is interrupted during the second step; due to a lack of acidic terminal available to couple with glutamic acid, hence dihydrofolic acid **5** formation is interrupted.[4]
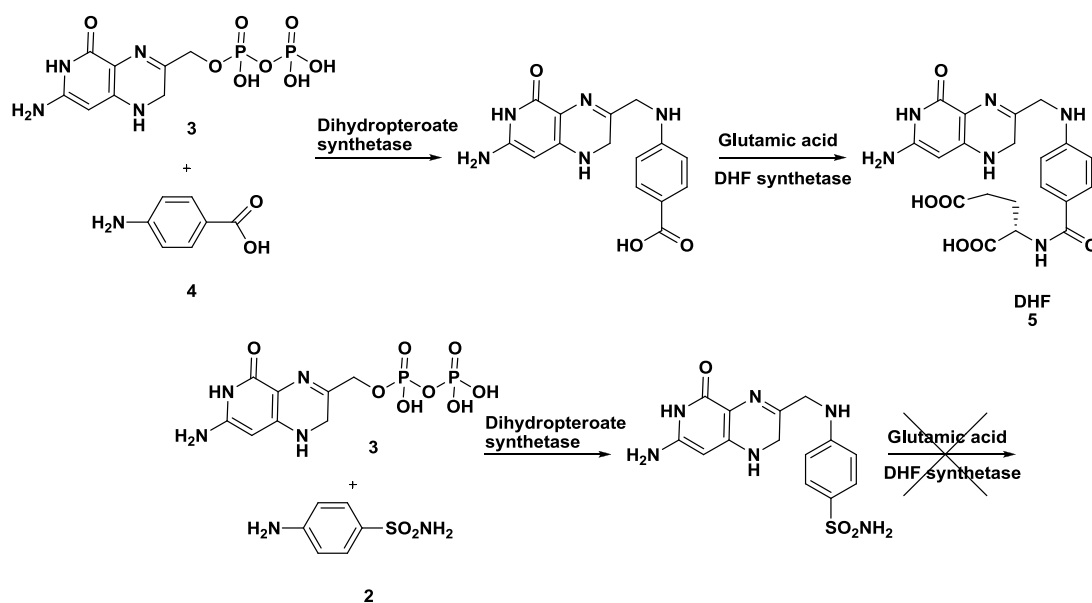
Scheme 2 Inhibition of DHF formation by sulfanilamide

Later steps involve reduction to tetrahydrofolic acid using dihydrofolate reductase; however this step can also be inhibited using methotrexate **6** or trimethoprim **7** to enhance antibacterial activity, and it is commonly taken in conjunction to increase inhibitory activity and reduced dosage.
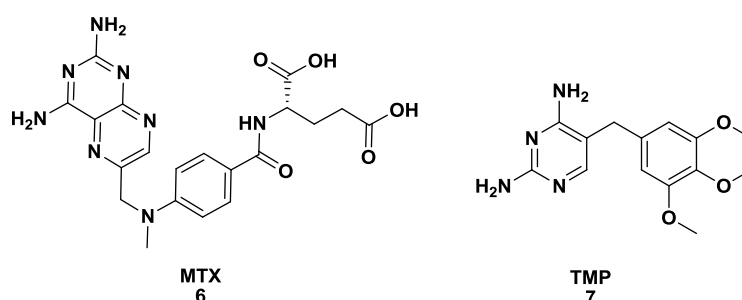
Figure 1 Structures of methotrexate and trimethoprim

1.1.1 <u>Sulfonamides as therapeutic agents</u>

1.1.1.1 <u>Sulfonamides as cysteine protease inhibitors</u>

Cysteine proteases are a class of biologically important enzymes, which are involved in inflammation, cell apoptosis and protein degradation.[5-7] These enzymes are also implicated in several disease states such as arthritis, osteoporosis, Alzheimer's disease, cancer and malaria.

Examples of cysteine protease enzymes include caspase, a cysteine protease which cleaves at the Ala-Asp residue (hence caspase), and is strongly associated with

apoptosis, necrosis and inflammation. There are 11 caspases now know, namely caspase 1-10 and 13. Not all caspases are directly involved in apoptosis; where the initiator caspases (CASP-2, CASP-8 and CASP-9) are responsible for activating the effector (executioner) caspases (CASP-3, CASP-6 and CASP-7) before the apoptosis. Therefore, apoptosis occurs through a network cascade of caspases instead of an individual enzymatic reaction.[5, 7]

Another example is the interleukins illustrated by interleukin-1β (IL-1β), a cytokine implicated in various neurodegenerative diseases such as Alzheimer's disease. However, IL-1β is normally present in its inactive pro-form and needs to be converted into the active cytokine by an IL-1β converting enzyme (ICE), now known as caspase-1. Early studies from various groups have found that deficiency of caspase-1 on animal model (transgenic mice) were associated with decreased neuronal apoptosis, suggesting an indirect association of caspase-1 with neuronal cell death. Therefore if caspase-1 level can be moderated, this will then be possible to treat Alzheimer's disease. [8-10]

It is clear that inhibition/interference with caspases offers a number of therapeutic opportunities and this motivated Shahripour *et al.* to develop an approach toward a library of diphenyl ether sulfonamides **8** and these were shown to exhibit micromolar inhibition against caspase-1.[11] However an SAR study by Harter *et al.* suggested that, by increasing the number of H-bonding on a known peptide-based caspase-1 inhibitor **9**, increases the rigidity of the molecule as well as potency (Figure 2). In addition, K_I and IC_{50} are further decreased by introducing a sulfonamide group and a C_2H_4Ph side arm in **10** and **11**.[12] Thus improvements in potency can be achieved rendering sulfonamides potentially therapeutically useful.
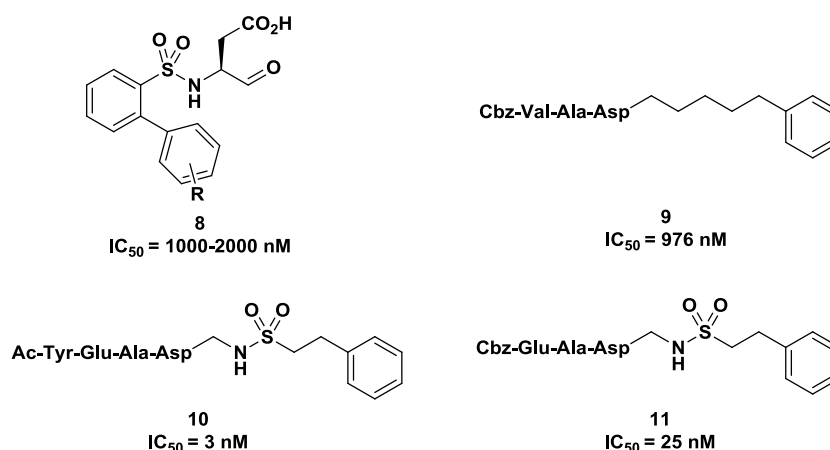
Figure 2 Structures and biological activity of Caspase-1 inhibitors

A high-throughput screen at GSK identified two 5-nitroisatin based compounds **12** and **13** as potent caspase-3 inhibitor (Figure 3). Caspase-3 is an effector caspase that directly linked to apoptosis. Lee *et al.* have synthesized several analogues with different substituents on the 5-*C* position, and found that replacing a nitro group with a sulfonamide group can improve the potency to low-nanomolar range, for example the pyrrolidine sulfonamide **14** exhibited potent caspase-3 and caspase-7 inhibition.[13, 14]
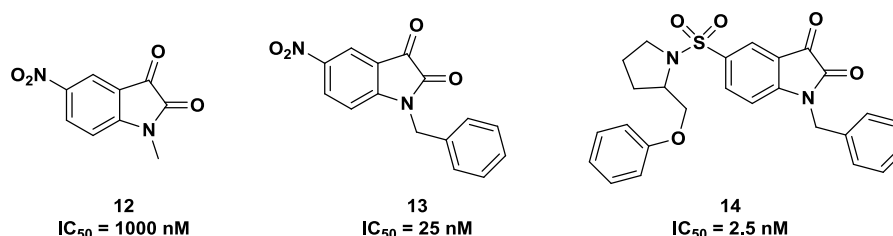
Figure 3 Structures and biological activity of Caspase-3 inhibitors

Cysteine proteases are also important to the life cycle of pathogenic protozoa such as *Trypanosoma Curzi*, which was found to be the cause of Chagas' disease in South America. Cruzain, a form of cysteine protease in *T. Cruzi*, was found to be a potential therapeutic target for treatment of Chagas' disease. Roush *et al.* have synthesized several vinyl sulfones, sulfonates and sulfonamides and these were screened against Cruzain. It was found that several of these compounds were very potent inhibitors (Figure 4),[15] especially vinyl sulfonamide **15** and vinyl sulfonate **16**. Furthermore, the second generation of the vinylsulfonamides **17** and **18** are found to be active *in vitro* and *in vivo*.[16]
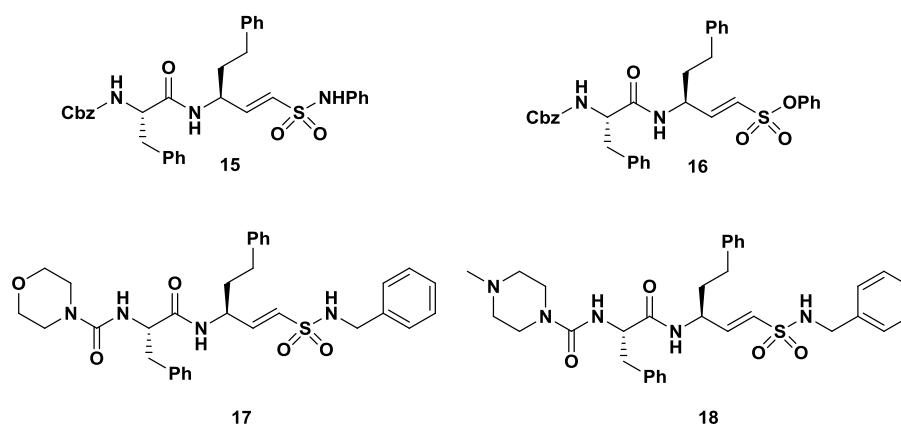
Figure 4 Structures of Cruzain inhibitiors

1.1.1.2 Sulfonamides as HIV inhibitors

Sulfonamides also possess activity against HIV proteases. HIV protease consists of a homodimer with aspartyl active sites (Asp^{25} and Asp^{125}), which have the ability to cleave difficult bonds, such as Tyr-Pro and Phe-Pro[2]. Thus far, several HIV protease inhibitors are clinically available, and are often used in conjunction with reverse transcriptase inhibitors to deliver the multi-drug treatment known as the Highly Active Anti-Retroviral Therapy (HAART, see section 2.3.3). It was found that non-peptidic protease inhibitors display higher bioavailability as well as slower excretion rate compared to the conventional peptide-base protease inhibitors. Among those protease inhibitors Amprenavir **19** and Tipranavir **20** are sulfonamide derived drugs.[2, 17, 18]
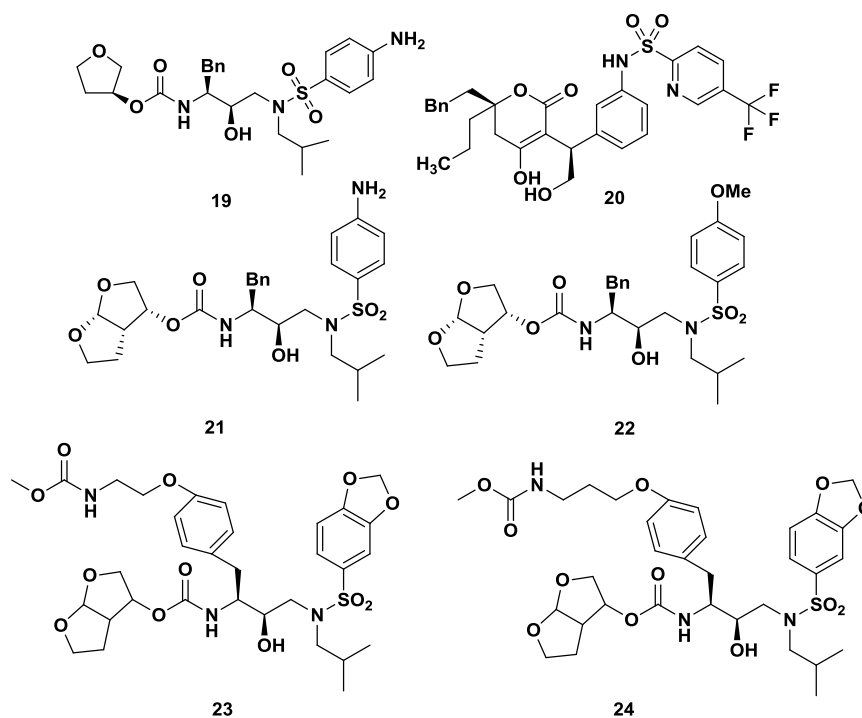
Figure 5 Structures of HIV protease inhibitors

Most drugs achieved their high potency due to their ability to bind rigidly and optimally into an active site. However, high mutation rates within HIV viral particles renders many anti HIV drugs inactive, furthermore it poses tremendous challenge on antiretroviral therapy. A more recent idea of overcoming this problem is to synthesize a drug that, instead of binding tightly to the protease active site, binds tightly with the protein backbone since the protein backbone are only minimally deformed during mutation.[19] An example of this approach can be seen in the investigations of derivatives of Amprenavir **19** which are currently being investigated; these include TMC-114 (a.k.a Darunavir) **21** and TMC-126 **22** (Figure 5). X-ray crystallography of TMC-114 **21** bound to HIV protease showed that the bis-THF moiety of TMC-114 **21** forms strong H-bonds with Asp[29] and Asp[30] amides within the protein backbone, and showed 10-fold higher potency than Amprenavir **19** and Tipranavir **20**.[2, 19] Ohtaka *et al.* also showed that TMC-126 **22** displays 13-fold higher potency than that for Amprenavir **19**.[2, 20] Meanwhile, another class of arylsulfonamide **23** and **24**, which are structurally related to TMC-114 **21** and TMC-126 **22**, also display low nanomolar concentration during a QSAR study.[21]

Apart from the numerous studies as HIV protease inhibitors, sulfonamides in recent years, are also found to inhibit HIV reverse transcriptase[22] and cell entry.[23] Tucker *et*

al. have modified a previously known viral fusion inhibitor BMS806[24, 25] **25** by replacing the α-ketoamide with a sulfonamide and a biaryl moiety **26** to further improve the potency (Figure 6).[23]

25
IC_{50} = 930 nM

26
IC_{50} = 215 nM
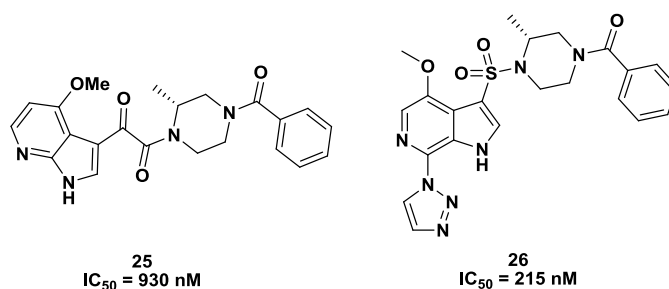
Figure 6 Structures and biological activity of HIV cell entry inhibitors

1.1.1.3 Sulfonamides as carbonic anhydrase inhibitors

Carbonic anhydrases catalyze the interconversion of carbon dioxide and bicarbonate. The active site of the enzymes consist of a zinc ion coordinating to 3 histidine (His^{94}, His^{96} and His^{119}) side chains, with the fourth site occupied by a water molecule. The water molecule is deprotonated by the fourth histidine imidazole before attacking carbon dioxide to form bicarbonate molecule. The main function of carbonic anhydrases is to modulate physiological pH, respiration, CO_2 transport, electrolyte excretion, regulation and homeostasis. Sixteen CA isozymes have been identified in humans, CA I to CA XV, with different sub-cellular localization.[26-28]

Carbonic anhydrase IX and XII (as secondary tumor related CA) are found to be over-expressed in cervical, breast, bladder and non-small cell lung cancers by instigating hypoxia, causing acidification in the extracellular region, which leads to metastatic spread of these tumor cells. Furthermore, the acidification can render classical cancer treatments ineffective, particularly those utilizing basic antitumor drugs and radiotherapy. It is therefore believed that inhibition of CA IX/CA XII could be an attractive alternative option for anticancer therapy. Supuran *et al.* have reported that a range of sulfonamides **27**-**30** have anti-carbonic anhydrase activity in nanomolar concentration (Figure 7).[26, 28] However, due to their low selectivity, these CA inhibitors show good inhibitory activity against several isozymes including CA I, CA II, CA IX, and to some extent, CA XII.

27
IC$_{50}$ = 16 nM

28
IC$_{50}$ = 14 nM

29
IC$_{50}$ = 21 nM

30
IC$_{50}$ = 22 nM
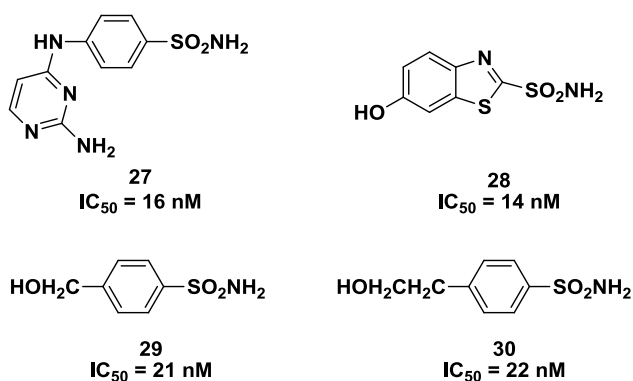
Figure 7 Structures and biological activity of CA I/CA II/CA IX inhibitors

Supuran *et al.* later synthesized another class of sulfonamides **31-33** and carried out an investigation of their potency against CA I, CA II and CA IX. It was found that even though the compounds were ineffective against CA I they were very effective against both CA II and CA IX (Figure 8). Furthermore, a docking study of **33** within CA II and CA IX, by the same group, indicates that the binding pockets of the two isozymes (CA II and CA IX) are very similar; if this is the case then it will make it difficult to target one isozyme over the other. [29]

31
CA I = 8386 nM
CA II = 49 nM
CA IX = 27 nM

32
CA I = 62 nM
CA II = 1.4 nM
CA IX = 2.3 nM

33
CA I = 707 nM
CA II = 17 nM
CA IX = 1.8 nM
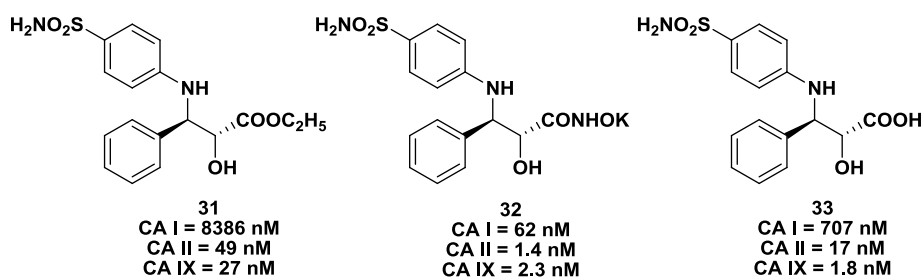
Figure 8 Non-selective inhibition of CA I/CA II/CA IX

Supuran *et al.* more recently reported that, by introducing a pyridinium moiety to the CA II/CA IX inhibitor **34**, tumor acidification can be reduced by specifically inhibiting CA IX. **35** were reported and display good inhibition of CA IX over CA II.[30]

34

35
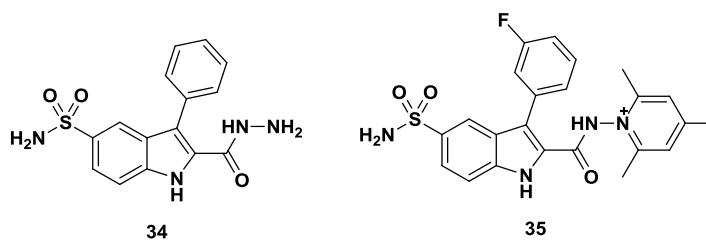
Figure 9 Specific inhibitors for CA IX

Acetazolamide **36** (AZA, anti-glaucoma), Zonisamide **37** (ZNS, anti-convulsant) and

Topiramate **38** (TPM, anti-convulsant) are known for their ability to inhibit CAs, and their X-ray crystal structures have been determined,[31, 32] which show tight binding of the inhibitors to CA II, CA VA and CA VB. Interestingly it has been noted that, during clinical studies, obese patients experienced dramatic weight loss as a side effect.[33] Therefore inhibiting CA II, VA and VB can reduce the rate of lypogenesis, and in turn, can be used as anti-obesity drugs.[33, 34]
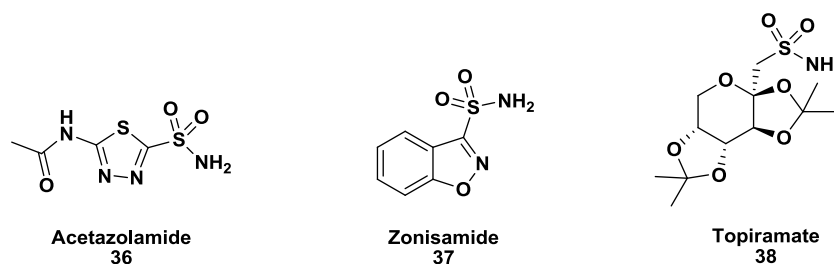
Figure 10 Commercially available inhibitors of CA V

Supuran *et al.* and Vullo *et al.,* have synthesized a wide range of sulfonamides such as **39** and **40** for anti-CA V activity, and it was found that several aminobenzolamides display low-nanomolar potency compare to registered CA inhibitors (Figure 11).[33-35]
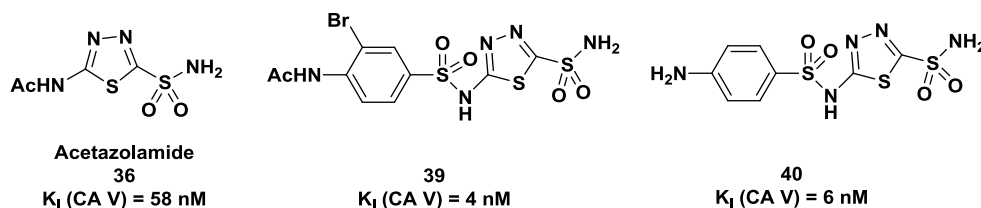
Figure 11 Structures and biological activity of CA V inhibitors

1.1.1.4   Sulfonamides as COX-II specific inhibitors

Cyclooxygenase (COX) is involved in the synthesis of prostaglandins and thromboxane from arachidonic acid. Cyclooxygenase exist in three isoforms: COX(I-III). Cyclooxygenase-I is expressed in platelet aggregation and mucosal protection by prostaglandin production, thus an undesirable side effect of COX-I inhibition can be gastric damage. Cyclooxygenase-II is induced and expressed during inflammation, cell proliferation and oncogenesis. Cyclooxygenase-III is identified as a COX-I variant, and it's known to be inhibited by paracetamol.[36-38]

Traditional COX inhibitors such as ibuprofen are known to have low selectivity and hence may induce ulcer, bleeding and gastroduodenal erosion. However, COX-II specific inhibitors can relieve symptoms such as pain, caused by inflammation, but

without the undesirable side effects of traditional COX inhibitors.[39] Celecoxib **41** and Valdecoxib **42** (Figure 12) have been developed by Pfizer as COX-II specific inhibitors for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA).[40, 41]
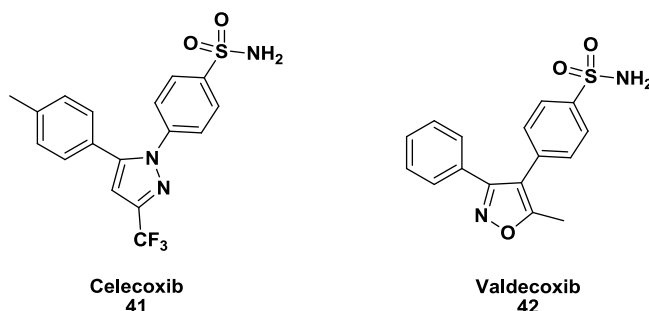
Figure 12 Commercially available COX-II inhibitors

Normally, prostacyclin (PGI_2) and thromboxane (TxA_2) are both produced, but the traditional COX-II specific inhibitors may disrupt the optimum balance of the two species and an increase in the amount of thromboxane, can elevate the risk of cardiovascular disease, heart attack and stroke; which it is the case for Valdecoxib **42**. Recently a new approach has been to utilize an inhibitor which is mainly COX-II selective but with mild COX-I inhibitory properties. Yang *et al.* have synthesized a range of iminium benzenesulfonamides **43** (Figure 13), based on the natural product Resveratrol **44**, that have 7-80 fold selectivity for COX-II over COX-I.[42]
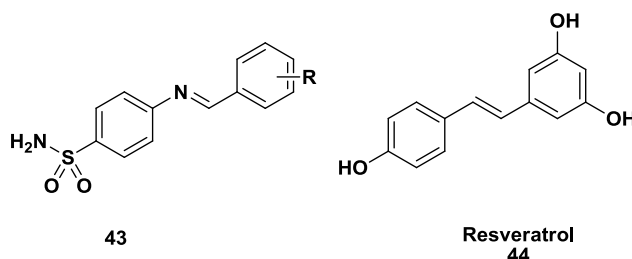
Figure 13 COX-II selective inhibitors with mild COX-I inhibitory properties

1.1.1.5 Other applications of sulfonamides

A large number of sulfonamides have been used for therapeutic intervention and more recently a very well known example is that of as Sildenafil **45** (Viagra®, Figure 14) for the treatment of erectile dysfunction. Erection is caused by binding of nitric oxide NO (released from the brain) to guanylate cyclase, causing the build-up of cyclic guanosine monophosphate (cGMP) resulting in smooth muscle relaxation and increase blood flow to the male organ. Viagra works by inhibiting phosphodiesterase-5; which is responsible for metabolizing cGMP, resulting in prolonged erection.[43]
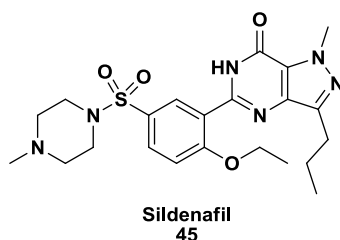
Sildenafil
45

Figure 14 Commercially available anti-impotence agent Sildenafil

1.1.1.6 PFP sulfonate esters as bacterial DDAH and ADI inhibitors

Nitric oxide (NO) is an endogenous signaling agonist, which may be implicated in several disease states upon a rise in NO levels;[44] therefore partial inhibition of enzymes responsible for NO production can be useful in developing effective therapeutic agents. An indirect approach has been described which involves the inhibition of dimethylarginine dimethylamino hydrolase (DDAH) which is responsible for controlling levels of N-methyl-L-arginine (MMA) and asymmetric N-,N-dimethyl-L-arginine (ADMA) which are both inhibitors of nitric oxide synthase (NOS). Recent studies reported by the groups of Vallance and Caddick have shown that small molecules such as functionalized PFP sulfonates display activity against DDAH and, the structural related arginine deiminase (ADI). Various heterocyclic PFP sulfonates were screened against DDAH and ADI, and it was reported that **46** and **47** have significant activity against DDAH and ADI (Figure 15).[45]

46
K_I (DDAH) = 35 µM
K_I (ADI) = 74 µM

47
K_I (DDAH) = 38 µM
K_I (ADI) = 103 µM
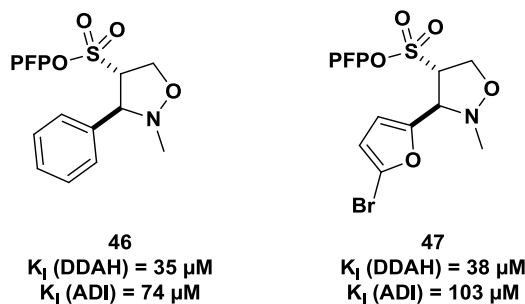
Figure 15 Isoxazolidines as modulators of nitric oxide synthesis via inhibition of DDAH and ADI

1.2 Isoxazoles as therapeutic agents

Although there are numerous active heterocyclic aromatic compounds, there are reatively few drugs that contain the isoxazole moiety, however it would appear that there is a growing interest in the development of biologically active compounds based on isoxazoles.[46]

An example is Sulfamethoxazole **48**, an antibacterial agent which contains both isoxazole and sulfonamide moiety (Figure 16). The mode of action is the same as described in Section 1.1 Sulfamethoxazole **48** has mainly been used in conjunction with trimethoprim for treatment in many bacterial-linked diseases such as urinary tract infection and *E.Coli*-induced sickness.

Sulfamethoxazole
48
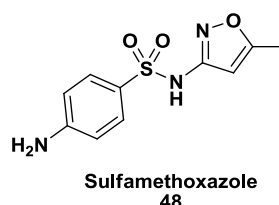
Figure 16 Structure of sulfamethoxazole

1.2.1 Isoxazoles as enzyme inhibitors

1.2.1.1 Isoxazoles as anti-inflammatory agents

Dihydroorotate dehydrogenase (DHODH) is an enzyme catalyzing the conversion from dihydroorotate **49** to orotate **50** which is required for pyrimidine synthesis (Scheme 3). The proliferative and inflammatory effects of DHODH suggest that it could be implicated in rheumatoid arthritis and hence a potential target for therapeutic intervention. The enzyme consist of 2 domains- a large *C*-terminal and a smaller *N*-terminal domain, with the smaller *N*-terminal domain containing a binding site for the cofactor ubiquinone.[47]

49   **50**
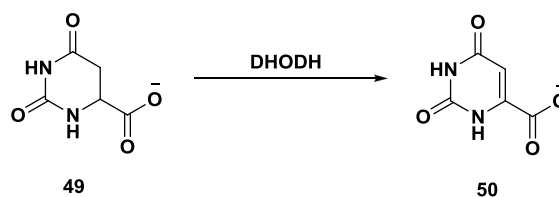
Scheme 3 Formation of orotate **50** from dihydroorotate **49**

Leflunomide **51**, developed by Sanofi-Aventis, is used in the treatment for rheumatoid arthritis. The isoxazole moiety of leflunomide is quickly converted to an enol-nitrile active metabolite A771726 **52** *in vivo* (Figure 17) and acts as a competitive inhibitor of ubiquinone. Albert *et al.* have reported that lefluonomide **51**, its active metabolite **52**, and its thioamide analogue display micromolar inhibition against DHODH.[48, 49]
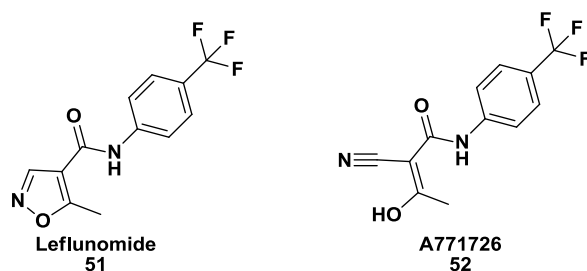
Figure 17 Structures of leflunomide and its active metabolite

Another example of an isoxazole containing drug is valdecoxib **42** , which is a COX-II inhibitor for treatment of osteoarthritis (OA) and rheumatoid arthritis (RA).[50-52] In a recent study it was shown that the specific COX-II selectivity of Valdecoxib **42** is due to the presence of *p*-phenylsulfonamide moiety. The removal of the sulfonamide moiety is associated with reversal of COX-II selectivity.[40]

1.2.1.2   Isoxazoles as anti-convulsion agents

Epilepsy is caused by a sudden excitation of neurons in the brain, which is found to be associated with high abundance of carbonic anhydrase (described in 1.1.1.3) isoform II, VII and XIV within the neuron cells, in such CA inhibitors can be used as anti-convulsant.[32, 53, 54] Recently, the anti-epileptic agent Zonisamide **53** (ZNS, Figure 18) was reported as a weak CA II and CA V inhibitor with micromolar inhibition. However in contrast, Supuran *et al.* reported that a long period of *in vitro* incubation, of Zonisamide **53** led to very potent inhibition of CA II ($K_I =$ 35.2 nM).[32] As follow up Uno *et al.* described the synthesis and biological activity of a range of Zonisamide analogues and explored the SAR where they observed that the presence of a halide in the 5- position increases potency as anti-convulsant.[55]
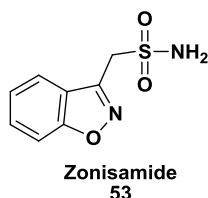
Figure 18 Structure of Zonisamide

1.2.1.3   Isoxazoles as antiviral agents

Human rhinovirus (HRV) is one of the most common infectious viral diseases, which is responsible for 50% of all human fevers. Its capsid consists of 4 types of proteins (VP1-VP4).[56, 57] Two extensively studied HRV inhibitors WIN51711 **54** (Figure 19)

and WIN52084 **55** contain one oxazoline and one isoxazole ring. They inhibit HRV by binding to the VP1 Asn[219] residue on the nitrogen atom of the oxazoline ring, which results in a conformational change in the VP1 protein. The seven-carbon chain and the isoxazole ring is extended into the binding site's side pocket ensuring tight binding, and subsequently inhibit the function of the viral capsid.[58]

54 WIN51711 R=H
55 WIN52084 R=Me

Figure 19 Structures of HRV inhibitors

Other anti-viral agents based on sulfonamides include Amprenavir **19** and Tipranavir **20** which are active against human immunodeficiency viruses (HIV). However, isoxazole-containing anti HIV agents are considerably less common than sulfonamides. A range of isoxazole based nucleosides **56** and **57**, synthesized by Kim *et al.* were found to have anti-poliovirus activity (Figure 20) and were also tested against HIV and HSV.[59]

56   **57**

Figure 20 Potential anti-poliovirus agents

1.2.1.4 Isoxazoles as anti cancer agents

Cancer is defined as an uncontrolled cell growth, which has deregulated from normal cell apoptosis. Several anti-tumor agents operate purely through latent cytotoxicity; however the induced side effects are normally irreversible. Other agents have been focused on the inhibitory activity during cancer cell cycle, i.e cell phosphorylation and angiogenesis.[4, 60]

Combretastatin A-4 **58** is a natural product isolated from the South African willow tree, which shows an ability to shut down cancer cell vasculature and successfully inhibit cancer cell angiogenesis. To successfully replicate the *cis*-diaryl moieties and the effect of Combretastatin A-4 **58**, several derivatives have been synthesized by Carrez *et al.*, where the rigid olefin linker has been replaced by a five-membered

heterocyclic ring.[61, 62] Several isoxazoline and isoxazole derivatives show antitubulin activity, and **59** shows higher antitubulin activity than Combretastatin A-4 **58** (Figure 21)[61] Another diaryl isoxazole compound **60**, developed by Oh *et al.* displays nanomolar inhibition against cancer metastasis and angiogenesis (Figure 21).[63]

58   **59**   **60**

Figure 21 Anti cancer agents derived from combretastatin A-4

1.3   Synthetic approaches to sulfonamides

Due to the broad applicability of sulfonamides, it is desirable to find general and effective methods for their synthesis. Although a comprehensive review of this is not provided the following section provides several of the most common and recent methods of sulfonamide synthesis.

1.3.1   Sulfonamides from sulfonyl chlorides and sulfonic acids

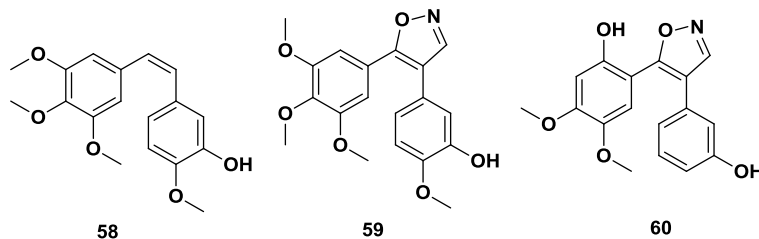The traditional and general method for preparing sulfonamides **62** is *via* coupling of sulfonyl chloride **61** with primary or secondary amine (Scheme 4). The sulfonyl chloride is normally prepared from the corresponding sulfonic/sulfinic acid with $SOCl_2$, PCl_5 or $POCl_3$,[64-67] or from bubbling chlorine gas through thiols in aqueous acid.[68] However, this method requires excess oxidant and aqueous acid, and is not compatable with acid sensitive substrates.[69]
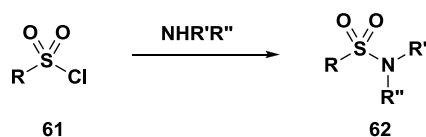
Scheme 4 Formation of sulfonamides from sulfonyl chlorides

Wright *et al.* reported a method for the formation of sulfonamides from thiols, requiring the *in situ* synthesis of a sulfonyl chloride using sodium hypochlorite (commercial bleach) mediated oxidation of thiol. This methodology introduces several advantages, such as readily availability of the reagents as well as controlled amount of the oxidant used. The resulting sulfonyl chlorides **63** were then trapped with benzylamine in the subsequent reaction to produce sulfonamides **64** up to 98%

yield (Scheme 5).[68]
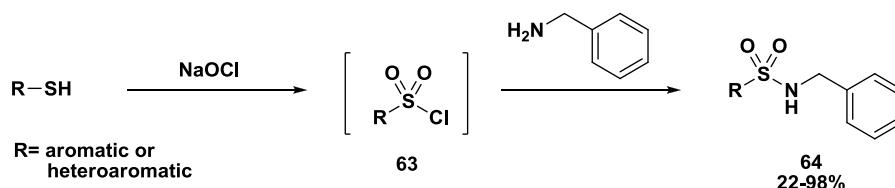
Scheme 5 Formation of sulfonyl chloride using sodium hypochlorite

Bonk *et al.* have developed a methodology of using trichlorocyanuric acid (TCCA) and benzyltrimethyl ammonium chloride in water to generate a controlled amount of chlorine into aprotic solvent (MeCN). The use of TCCA introduces the advantage of high-purity chlorine production compare to that of hypochlorite. In order to optimize the reaction conditions, the group then further modified the methodology by adding the subsequent amine into a one-pot reaction, generating sulfonyl chloride **65** *in situ*, and furnishing sulfonamides **66** under 1 hour (Scheme 6).[70]
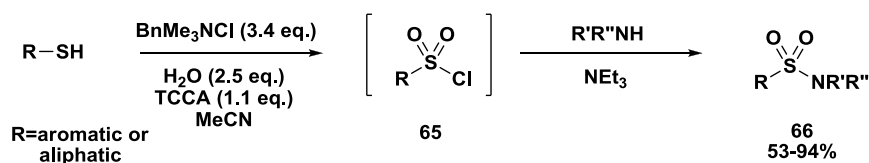
Scheme 6 Formation of sulfonyl chlorides using trichlorocyanuric acid

Even though a wide variety of sulfonamides can be generated from these procedures, several steps are required. Furthermore, the conditions are fairly harsh and therefore restrict the functional group compatibility. In an alternative, Barrett *et al.* reported the use of Grignard reagent **67** to increase diversity on sulfur in a one-pot sulfonamide synthesis (Scheme 7). Aromatic halides are mixed with magnesium to form Grignard reagent **67**, which can then attack sulfur dioxide to form sulfinic acid salt **68**. Subsequent chlorination using sulfuryl chloride generates sulfonyl chloride, and aminolysis furnishes sulfonamides **69** in one-pot. A wide range of organohalides were studied, but only aromatic and heteroaromatic halides produced desirable results.[71]
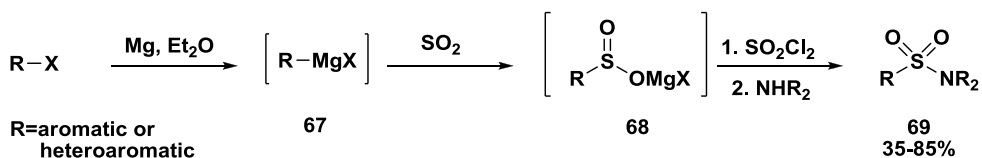
Scheme 7 Sulfonamides formation via Grignard reagents

It would appear that some general limitations to sulfonamide synthesis exist

including (1): excessive amount of highly toxic chlorinating agents (SO_2Cl_2, PCl_5 and $POCl_3$) and (2): organolithium and Grignard reagents are incompatible with several functional groups (-OH, -SH and -COOH)

Charasiri *et al.* reported the use of trichloroacetonitrile-triphenylphosphine complex (Cl_3CCN/PPh_3) for sulfonamide formation. It was found that the optimal yield is reached when 3:3:1 (Cl_3CCN:PPh_3:sulfonic acid) ratio and dichloromethane are used, however the yields are not reproducible in other solvents and ratios (Scheme 8), One of the notable advantages of this methodology is that it is not limited to aromatic sulfonyl chlorides, and can be applied to heterocyclic and aliphatic sulfonyl chlorides.[72]
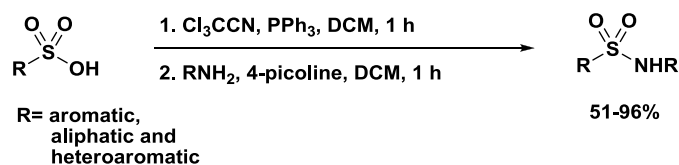
Scheme 8 Sulfonamide formation from sulfonic acids using Cl_3CCN:PPh_3

Shaabani *et al.* recently developed a novel approach to sulfonamide synthesis utilizing sulfonic acids and isonitriles under aqueous conditions (Scheme 9). Their preliminary study showed that aromatic and camphor sulfonic acids **70** were converted into sulfonamides **71** in high yield (86-93%). Even though the mechanism has not yet been verified experimentally, a working model has been suggested and is given in Scheme 10.[73]
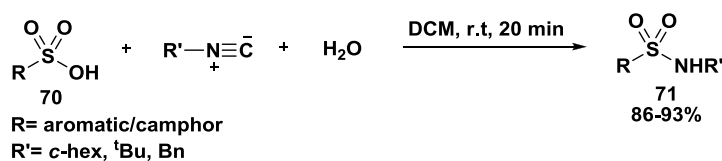
Scheme 9 Sulfonamides formation from sulfonic acids using isonitrile
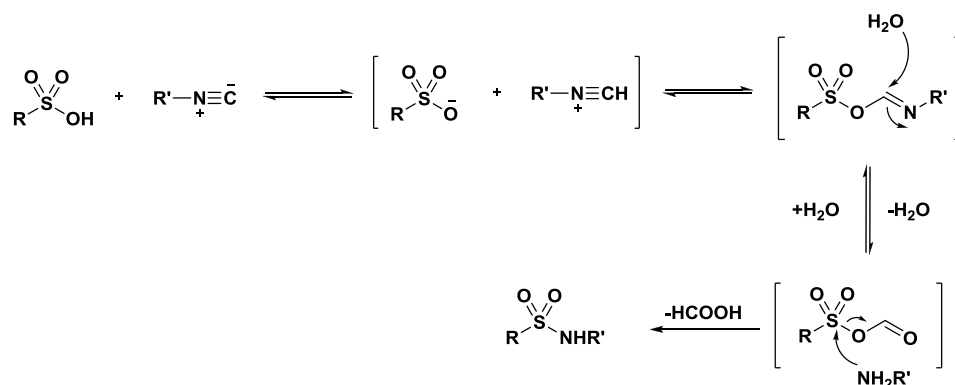
Scheme 10 Postulated mechanism by Shaabani[73]

1.3.2 Sulfonamides from sulfenamides

Another innovative example of sulfonamides synthesis is illustrated in the synthesis of 6-uracilsulfonamide (an antagonist of orotic acid) by Greenbaum *et al.* In this approach the sulfonamide is reasonably effectively oxidized from 6-uracilsulfenamide using $KMnO_4$ with 64% yield.[74] Schwam *et al.* also used similar methodology for the synthesis of 6-hydroxybenzothiazole-2-sulfonamide **72** as a potential carbonic anhydrase inhibitor in 80% yield (Scheme 11).[75]
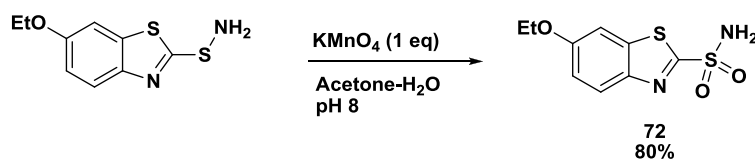
Scheme 11 $KMnO_4$ oxidation of sulfonamide to sulfonamide

Alternative mild and selective oxidants have also been used for the conversion of sulfenamides into sulfonamides.[76] For example Revankar *et al.* reported that, during their synthesis of pyrimidine-4-sulfonamide **73** as potential antitumor drug, oxidation of sulfenamide **74** using one equivalent of m-CPBA produced 48% of the corresponding sulfonamide **73**, this could be increased to 58% using four equivalents of m-CPBA in ethanol (Scheme 12).[77-79]
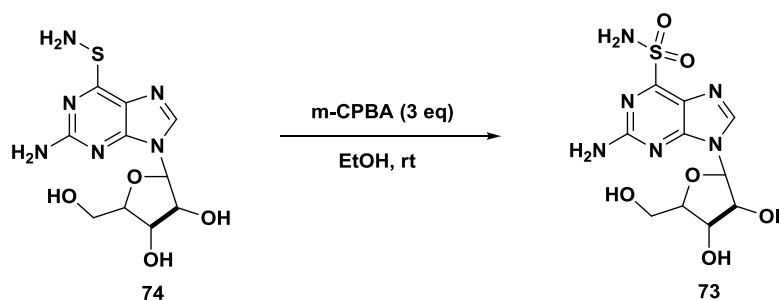
Scheme 12 m-CPBA oxidation of sulfenamide to sulfonamide

1.3.3   Sulfonamides from *N*-arylation

The aforementioned methods do have some limitations in as much as they do not allow diversification of substituents on sulfur or nitrogen. An alternative approach is to carry out synthetic modification of a primary sulfonamide.[80] Transition-metal catalyzed *C-N* bond formation has been studied extensively, where the most well-known, palladium catalyzed *N*-arylation is the Buchwald-Hartwig reaction.[81-83] However there are few reports of *N*-arylation on sulfonamides. The first example used cupric acetate and arylboronic acid to give *N*-arylsulfonamide. Lam *et al.* described an effective protocol using 0.1 equivalent of copper(II) acetate in air, to give near-quantitative yield (Scheme 13).[84, 85]
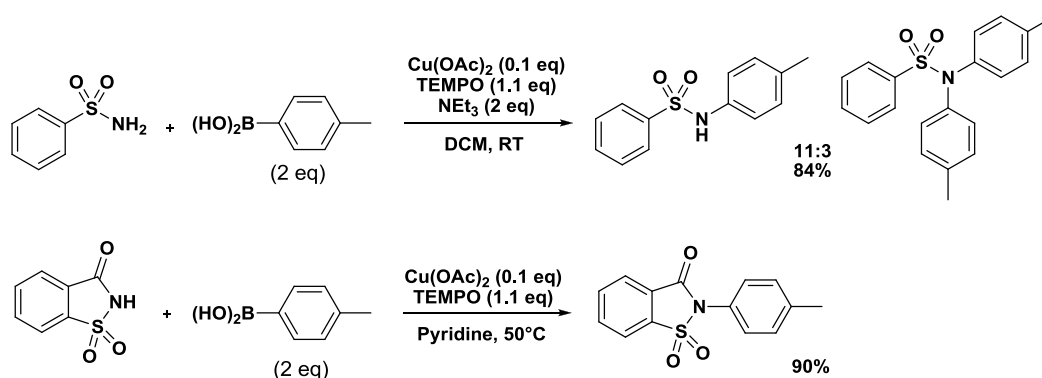
Scheme 13 *N*-arylation of sulfonamides using Chan-Lam reaction

More recently, Guo *et al.* have synthesized a range of sulfonamides using copper (I) catalysed coupling using aryl bromide/iodide (Scheme 14). During the optimization process, they found that using an amino acid as a ligand introduces several advantages such as easy removal after the reaction. After screening several amino acids, they found that *N*-methylglycine and *N, N*-dimethylglycine are the most effective with Cu(I). Together with K_3PO_4 as base, and DMF as the solvent, all desired *N*-arylsulfonamides **75**-**78** can be generated in up to 99% yield (Figure 22).[86]
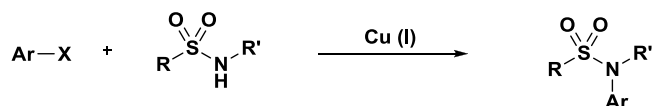
Scheme 14 Copper mediated *N*-arylation using amino acids as ligand
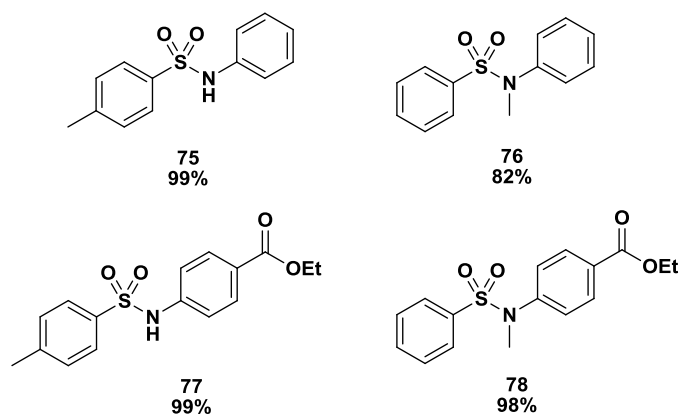
Figure 22 Isolated yield obtained from copper catalyzed *N*-arylation

Despite the advances in transition metal catalysis, few applications have been reported for sulfonamide synthesis,[87, 88] and even fewer under microwave heating.[89] Cao *et al.* reported the palladium catalysed *N*-arylation of sulfonamides under microwave irradiation. In their report they describe the effect of modifying the ligands, bases and solvents, and identified optimal reaction conditions under microwave heating at 180 °C for 10 minutes (Scheme 15). Unfortunately this method led to only modest yield of *N*-arylsulfonamides.[80]
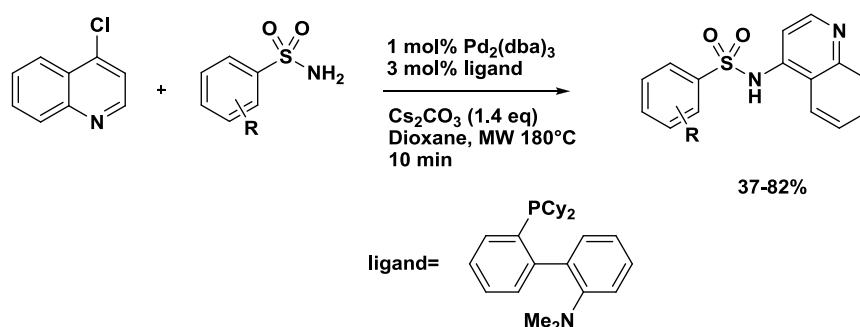
Scheme 15 Palladium mediated *N*-arylation of sulfonamides under microwave conditions

1.3.4 Sulfonamides from sulfonate esters

Pentafluorophenyl (PFP) sulfonate esters have been recently introduced to replace sulfonyl chlorides for sulfonamide preparation. The use of PFP sulfonate esters **79** may introduce several advantages such as reduced toxicity, enhanced shelf stability, makes them desirable as precursors.[69] Caddick *et al.* have reported that the aminolysis of sulfonates in refluxing THF can be used as an effective method for the synthesis of sulfonamides **80** in good to excellent yield. It was further shown that a range of amines (primary, secondary, aromatic, and aliphatic) could undergo reaction

with PFP sulfonate esters **79** to produce a wide range of sulfonamides (Scheme 16).[90, 91]
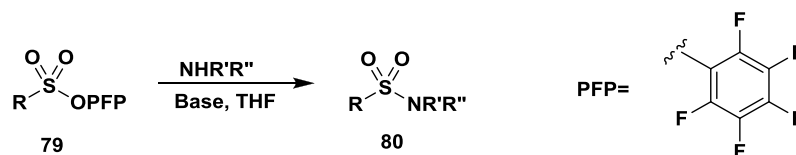
Scheme 16 Aminolysis of pentafluorophenyl sulfonate esters to generate sulfonamides

Caddick *et al.* have postulated a sulfene mechanism for amine substitution for alkyl PFP sulfonates based on deuterium incorporation (Scheme 17).[90-92] However, aryl PFP sulfonates do not have α-proton available for deprotonation therefore aminolysis proceed through the classic direct displacement, resulting in a slower reaction rate than that for alkyl sulfonates.
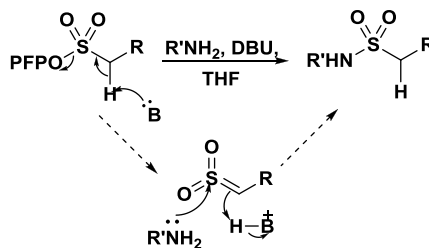
Scheme 17 Postulated sulfene mechanism by Caddick[90-92]

Caddick *et al.* have also reported the relative stability/reactivity of PFP sulfonate esters in comparison to sulfonyl chlorides. Thus *p*-tolylpentafluorophenyl sulfonate **81** is mixed with benzenesulfonyl chloride **82** and subjected to aminolysis with 4-methylbenzylamine **83** at 0 °C. In the product mixture, 90% of the *p*-tolylpentafluorophenyl sulfonate ester **81** was recovered, thereby showing that PFP sulfonates are not as reactive as sulfonyl chlorides (Scheme 18). Another advantage of PFP sulfonate esters over sulfonyl chlorides is that they can readily be employed under aqueous conditions.[90]
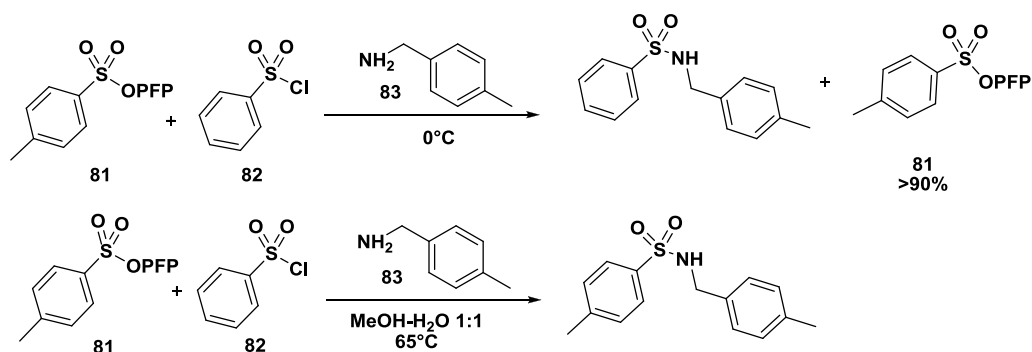
Scheme 18 Reactivity between PFP sulfonate esters and sulfonyl chlorides

Caddick *et al.* have also reported aminolysis of PFP sulfonate esters with various amines under microwave heating. All desired sulfonamides were generated in moderate to high yield (Figure 23) while the reaction times were significantly reduced (5 min).[69, 93]
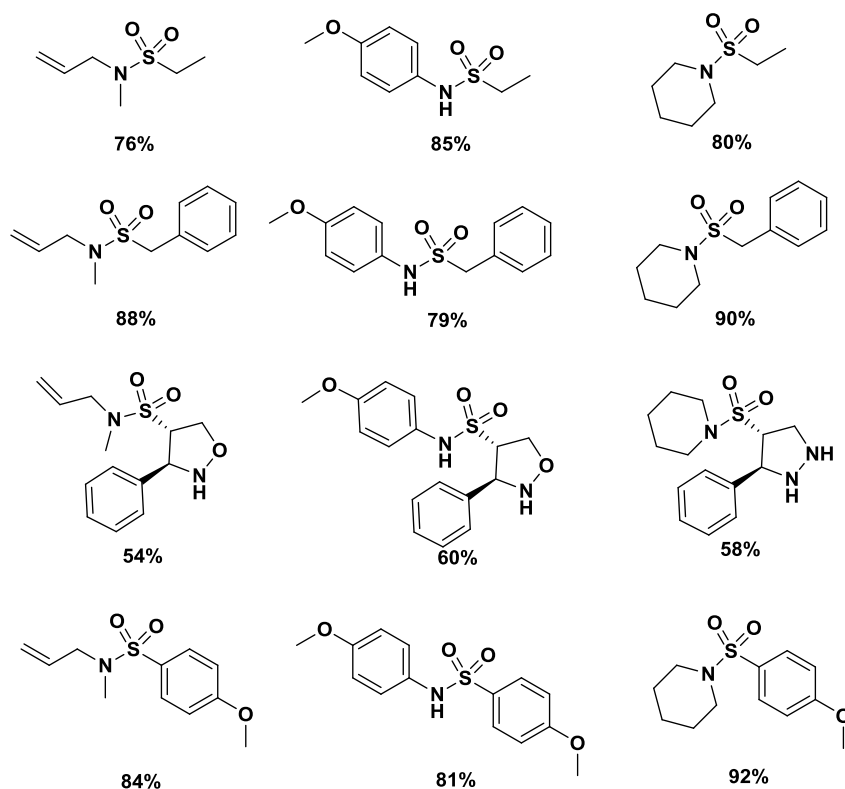
Figure 23 Yield reported from aminolysis under microwave irradiation

So far, all the above examples are focused on intermolecular aminolysis; however an intramolecular aminolysis was also reported by Caddick *et al.* in the formation of β-sultams **84** (cyclic sulfonamides), which are potential serine lactamase inhibitors in bacterial developed resistance to penicillin. Caddick *et al.* reported the use of $Mo(CO)_6$ to catalyse *N-O* bond cleavage in isoxazolidine PFP sulfonate esters **85** (Scheme 19), this was then followed by direct displacement of PFP by the

intramolecular amine to give pure *cis β*-sultams, which were characterized by x-ray crystallography.[94]
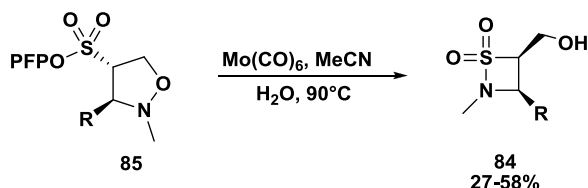
Scheme 19 Formation of *β*-sultams via *N-O* bond cleavage using MO(CO)$_6$

Due to the high cost of pentafluorophenol, a cheaper and even less toxic alternative was sought. Trichlorophenol (TCPOH), a household antiseptic, was employed in the formation of sulfonate esters, and found to be a good leaving group during subsequent aminolysis. Aminolysis of TCP sulfonate esters **86** later furnished sulfonamides **87** in up to 94% yield. However due to high stability of TCP, the reactivity is noticeably reduced in comparison with that of PFP, therefore an increase in reaction time is needed as well as more forcing condition (Scheme 20).[95]
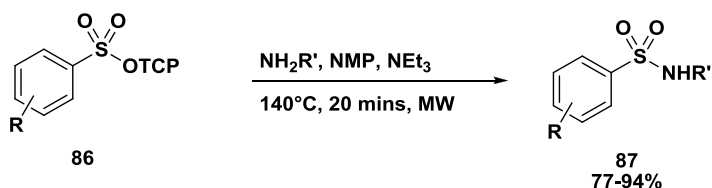
Scheme 20 Aminolysis from TCP sulfonate esters

1.4 Introduction to 1,3-dipolar cycloaddition

The history of 1,3-dipolar cycloaddition dates back to 1888, when Buchner studied the reaction between diazoacetic ester and *α,β*-unsaturated esters.[96] However, the potential value of cycloadditions were not realized until the discovery of the Diels-Alder reaction in 1928.[97] Since then 1,3-dipolar cycloadditions have evolved and become more widely utilized due to thier applicability to synthesize various heterocycles, while generating up to three stereocenters in a single step (Scheme 21).[98]
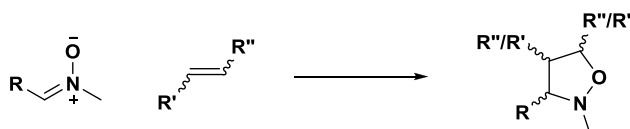
Scheme 21 Generation of three stereo-centers from cycloaddition

Mechanism of 1,3-Dipolar cycloaddition involves overlap between three p$_z$ orbitals of a dipole and two p$_z$ orbitals of a dipolarophile e.g. alkenes, alkynes or carbon-

heteroatom multiple bonds. That suggests the cycloaddition could proceed *via* a concerted process (Scheme 22) or a step-wise procedure. However the concerted mechanism is generally accepted because the reaction retains the relative stereochemistry of the dipolarophile. In the cycloaddition between benzonitrile oxide and *trans*-dideuterated ethene, the product isolated was exclusively the *trans*-dideuterated isoxazoline (Scheme 23).[98, 99]
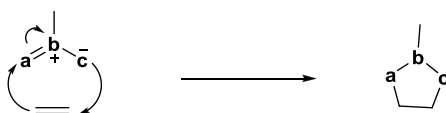
Scheme 22 Cycloaddition *via* a concerted process
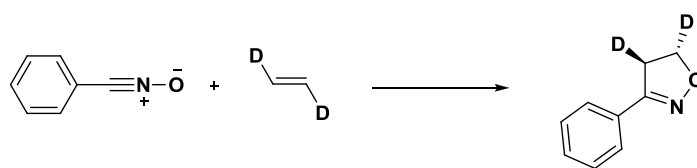
Scheme 23 Concerted reaction between benzonitrile oxide and *trans*-dideuterated ethene

There are two principal types of 1,3-dipoles: the allyl anion type and the propargyl anion type. The allyl anion type dipoles are characterized by a bent structure, where the central atom can be nitrogen, oxygen or sulfur e.g. nitrones, azomethine imines, azomethine ylides, carbonyl ylides, thiocarbonyl ylides, carbonyl imines and carbonyl oxides. The propargyl anion type dipoles are linear, and the central atom can only be nitrogen e.g. nitrile oxides, nitrile imines, diazoalkanes and azides (Figure 24).[98, 100]

Allyl anion type

nitrones   azomethine imines   azomethine ylides

carbonyl ylides   carbonyl imines   carbonyl oxides

Propargyl anion type

nitrile oxides   nitrile imines   diazoalkanes   azides
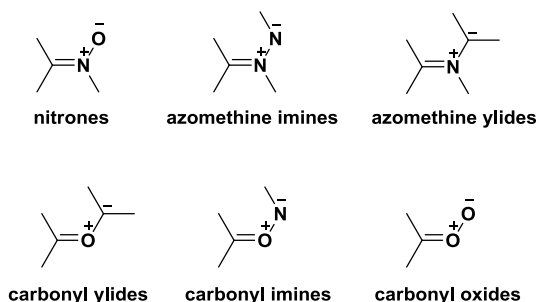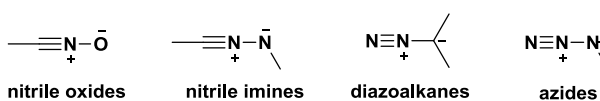
Figure 24 Structure of various allyl and propargyl anion dipoles

1.4.1 Properties of 1,3 dipoles

This thesis is concerned principally with the reactivity of 1,3-dipoles in cycloaddition reactions. The widely-studied 1,3-dipoles nitrones and nitrile oxides have become the species of interest, therefore only the chemical properties, preparations and reactions of these dipoles are discussed.

1.4.1.1 Preparation and reaction of nitrile oxides

The first nitrile oxide, fuminic acid (R = H, Scheme 25) was discovered in early 1800s, and one of its most used analogues benzonitrile oxide, was first generated in 1886.[101] Despite of the long history of nitrile oxides, their chemical and physical properties are little understood due to their inherent instablity.[102] At ambient temperature, most nitrile oxides **88** readily dimerize to furoxan-2-oxides **89** in the absence of a dipolarophiles. However with bulky nitrile oxides, dimerization is less likely and rearrangement to isocyanates **90** predominates at elevated temperature.[102] Dimerization to 1,2,4-oxadiazole-4-oxides **91** in the presence of triethylamine and 1,4,2,5-dioxadiazines **92** in the presence of excess BF_3 has also been reported (Scheme 24).[103]
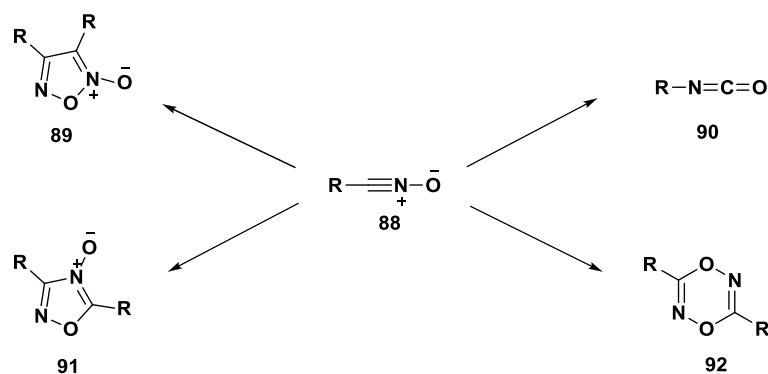
Scheme 24 Decomposition of nitrile oxides

The most common literature preparations of nitrile oxides are:

(1) dehydrohalogenation of hydroximoyl chlorides **93** using triethylamine in a biphasic solution, Scheme 25 (i),[104, 105] where the preparation of the hydroximoyl chloride from oxime have been reported using DMF/*N*-chlorosuccinimide,[102, 104] DMF/HCl/ozone[106] or trichlorocyanuric acid/pyridine/dichloromethane;[102, 105]

(2) dehydration of nitroalkane **94** using phenylisocyanate in the presence of triethylamine, Scheme 25 (ii),[107] (nitrile oxides generated from primary nitroalkanes are usually unstable, and are normally employed in a one-pot 1,3-dipolar cycloaddition);[102] and

(3) cycloreversion from furoxan-2-oxide **95**, Scheme 25 (iii), where dimerization of nitrile oxide becomes reversible at elevated temperature,[102] the latter procedure is far less common than (i) and (ii).
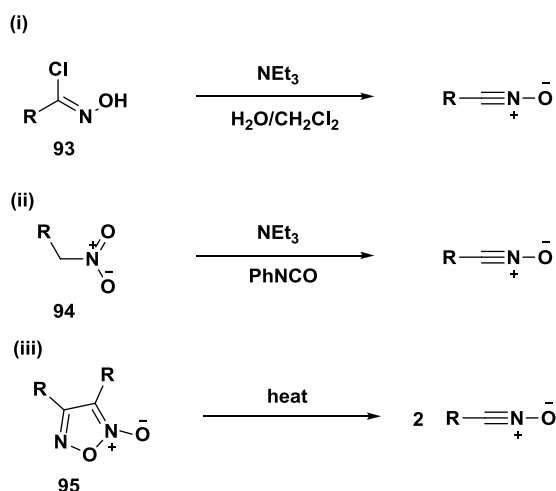
Scheme 25 Preparation of nitrile oxide from (i) hydroximoyl chloride, (ii) nitroalkane, and (iii) cycloreversion from from furoxan-2-oxide

In the presence of other reagents, nitrile oxides can undergo a range of reactions including deoxygenation, condensation with an appropriate nucleophile and 1,3-

dipolar cycloaddition. Synthetically, the most important reaction of nitrile oxide is the 1,3-dipolar cycloaddition; where cycloaddition with an alkene, alkyne or oxime generates an isoxazoline **96**, an isoxazole **97** or an oxadiazoline-oxide **98** (Scheme 26).[102, 108]
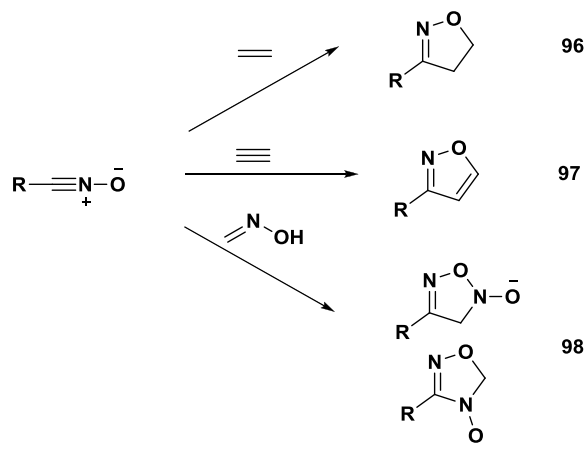
Scheme 26 1,3-Dipolar cycloadditions of nitrile oxide

Sandhu *et al.* for example have reported that when chromone-3-carbonitrile oxide **99** underwent cycloaddition with a terminal alkene such as allyl bromide, a single isomer of isoxazoline **100** was formed. If the same nitrile oxide underwent cycloaddition with phenylacetylene, the fully oxidized ring, isoxazole **101**, was formed (Scheme 27).[109]
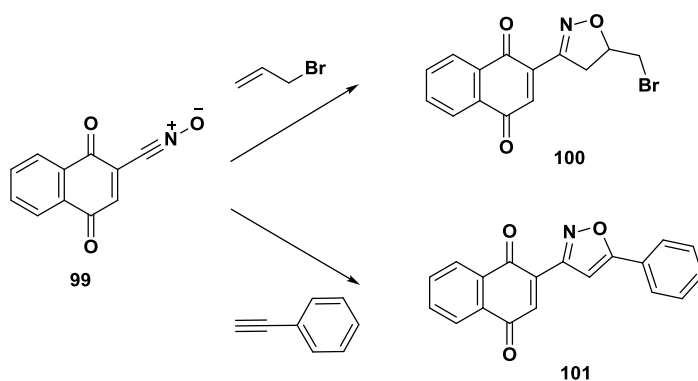
Scheme 27 Nitrile oxide cycloaddition with an alkene and an alkyne

1.4.1.2   Preparations and reactions of nitrones

Nitrones were first discovered by Beckmann in 1890.[98] Since then nitrones have been extensively studied due to their relative stability compared to nitrile oxides.[102] Preparation of nitrones are generally divided into two categories: oxidative and non-oxidative methods. Oxidative methods include:

(1) oxidation of imines using peracid or H_2O_2 to generate oxaziridines, which can

then rearrange to nitrones, Scheme 28 (i);[110]

(2) oxidation of amines using various oxidants such as peracids,[111] H_2O_2 or DMDO,[112] Scheme 28 (ii). (oxidation of primary amines leads to a mixture of nitro-, nitroso- and oxime compounds, whereas direct oxidation of secondary amines furnishes nitrones as a sole product[102]); and

(3) oxidation of secondary hydroxylamines (with an α-proton) using peracid, H_2O_2 or various metal oxides, provides mild condition for generating the corresponding nitrones, Scheme 28 (iii). Non-oxidative methods include condensation of mono-substituted hydroxylamine with a carbonyl group, which proceeds under mild condition, Scheme 28 (iv); this is compatible with various functional groups that are sensitive to oxidation, and thus used extensively in nitrone preparation.[102]
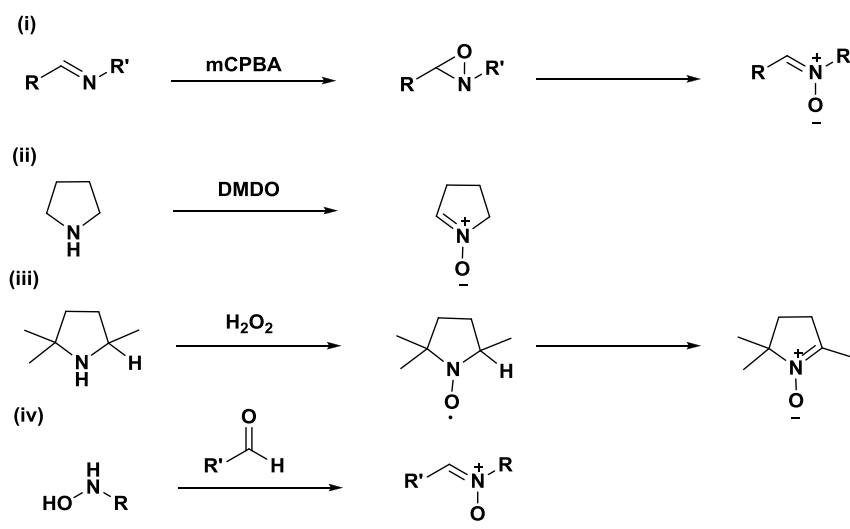
Scheme 28 Nitrone formation through oxidative (i-iii) and non-oxidative (iv) methods

Nitrones can undergo a range of reactions include rearrangement, oxidation, reduction, nucleophilic/electrophilic substitution and 1,3-dipolar cycloaddition. Nitrone cycloaddition with alkenes and alkynes have been extensively studied, and have been shown to generate isoxazolidines and isoxazolines in good regio- and diastereocontrol. In addition, nitriles, isocyanates, ketenes and porphyrins have also been reported as dipolarophiles.[102] However, only cycloadditions with alkenes are discussed here due to the relevance to our work.

1.4.2 Selectivity in 1,3-dipolar cycloadditions

The outcome of 1,3-Dipolar cycloaddition is influenced by frontier orbital

interactions, which can be approximated using Frontier Molecular Orbital (FMO) theory. Sustman has categorized 1,3-dipolar cycloaddition into three types (Figure 25). In type I, $HOMO_{dipole}$-$LUMO_{dipolarophile}$ predominates. In type III, $LUMO_{dipole}$-$HOMO_{dipolarophile}$ predominates; however in type II, the HOMO and LUMO energy of dipole and dipolarophile are similar, therefore $HOMO_{dipole}$-$LUMO_{dipolarophile}$ and $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interactions are equally possible. Substituents that raise the $HOMO_{dipole}$ or lower the $LUMO_{dipolarophile}$ favour type I interaction, whereas substituents that raise the $HOMO_{dipolarophile}$ or lower the $LUMO_{dipole}$ favour type III interaction.[98, 113]
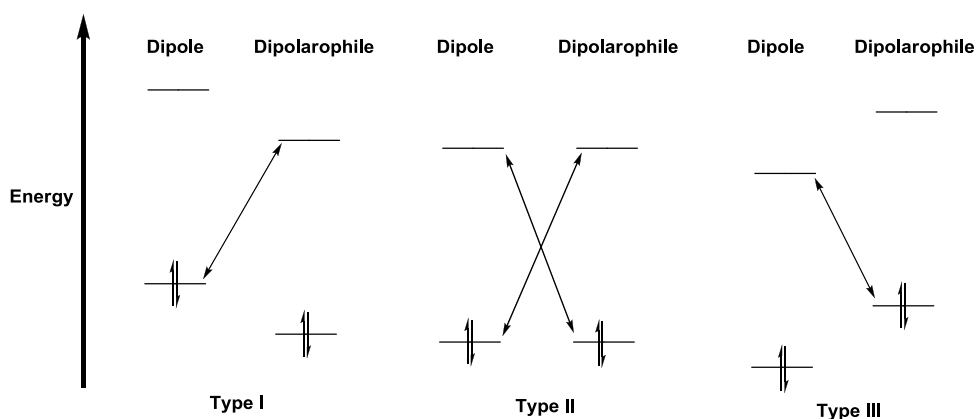
Figure 25 Classification of 1,3-dipolar cycloaddition using FMO theory

Nitrones are normally classified as type II; whereas nitrile oxides are at the border line of type II and type III, due to their low lying HOMO. The characterized low-lying HOMO of nitrile oxides make $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction less likely, which in turn bias towards $LUMO_{dipole}$-$HOMO_{dipolarophiles}$ interaction. In addition, energy overlap of each counterparts to generate isoxazol(in)es are essentially regiospecific, forming the 3,5-isoxazol(in)es (Figure 26). However, reversal of regiochemistry in nitrile oxide cycloaddition has been reported when highly electron deficient dipolarophile is used (Scheme 29),[114] or substituents on both nitrile oxides and alkenes are sterically demanding.[115,116]
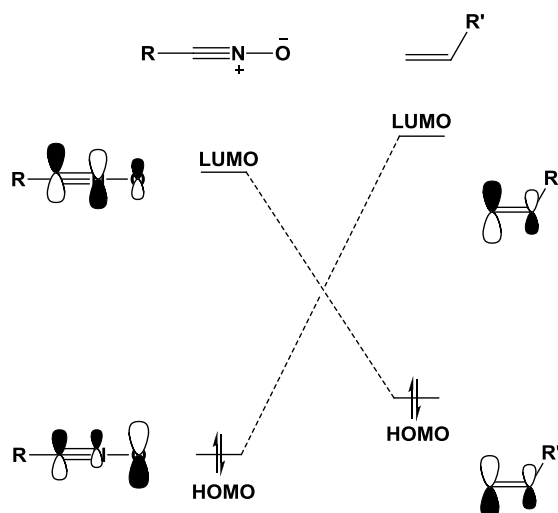
Figure 26 Type III interaction between nitrile oxides and monosubstituted alkenes
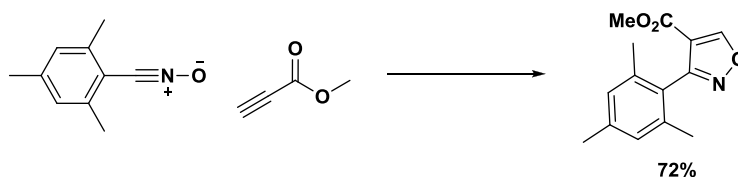
Scheme 29 Generation of 4-substituted isoxazole using electron deficient dipolarophile

1.4.2.1 Regioselectivity in nitrone cycloadditions

Nitrone cycloaddition are generally categorized as type II; they could be bias towards either type I or type III interaction depending on the electronic and steric factors of nitrone or alkene.[98, 113]

In early studies, cycloaddition of nitrones with alkenes was considered to be dominated by the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interaction (type III) generating the 3,5-isoxazolidine; however Houk *et al.* reported the use of strong electron deficient dipolarophiles to generate predominantly the 3,4-substituted isoxazoli(di)ne **102** (entries 1, 3 & 5) as the major regioisomer (Table 1). However, as the steric bulk of the nitrone increases (entries 2, 4 & 6), the 3,5-substituted isoxazoli(di)ne **103** increases inspite even with these highly electron deficient dipolarophiles.[117,118] Such electron deficient alkenes possess a low-lying LUMO, and favors $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction (type I) leading to the 3,4-isoxazolidines. However, the steric factors will overwrite the orbital overlap consider when either nitrone and alkene become sterically demanding.[117, 119]

Table 1 Cycloaddition using highly electron deficient dipolarophiles
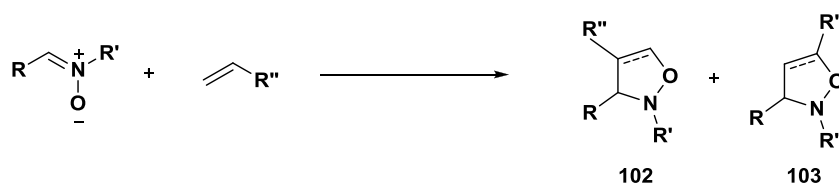
Entry	R=	R'=	Dipolarophile	102	103
1	Ph	Me	≡—CN	100	0
2	H	^{t}Bu	≡—CN	50	50
3	Ph	Me	⁼—NO₂	100	0
4	H	^{t}Bu	⁼—NO₂	0	100
5	Ph	Me	CH₂=CH–S(O)₂Ph	68	32
6	H	^{t}Bu	CH₂=CH–S(O)₂Ph	30	70

1.4.2.2 Diastereoselectivity in nitrone cycloadditions

A nitrone can interact with an alkene in either an endo- or an exo- orientation, where endo- orientation is characterized by secondary π interaction during the transition state (Figure 27). The favourability of each transition state is dependent on three factors: (1) orientation of alkene, (2) orientation of nitrone, and (3) geometry of nitrone. Therefore upon cycloaddition, these factors determine the ratio of the regio- and distereoisomers amongst all possible outcomes (Scheme 30). Therefore stereoselectivity and enantioselectivity have become the major issue in 1,3-dipolar cycloaddition.[98, 100]

Exo

Endo
(secondary overlap)
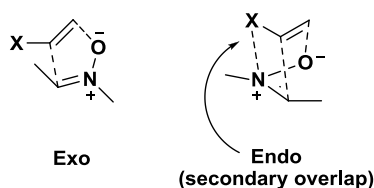
Figure 27 Endo- and exo- orientation in nitrone-alkene cycloaddition
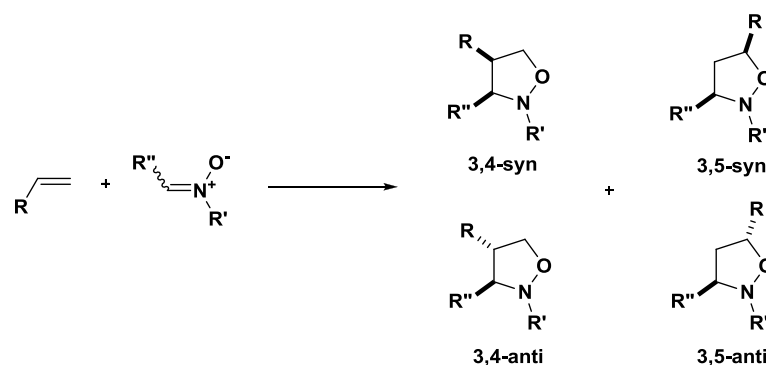
Scheme 30 Regio- and stereo-chemical outcomes of nitrone cycloaddition to an alkene

In order to achieve enantioselectivity, either chiral alkenes or chiral nitrones could be used. Saito *et al.* developed a chiral nitrone **104** based on tartaric acid which undergoes cycloaddition with methyl crotonate **105**. The transition state is formed from a unidirectional endo- approach of the chiral nitrone **104**, generating the 3,4-anti isoxazolidine **106** in 95% de.[120] The same group also developed a tartaric acid derived chiral alkene **107** which undergoes cycloaddition with cyclic nitrone **108**. The endo- approach furnishes the 3,4-anti isoxazolidine **109** in high de (Scheme 31).[121]
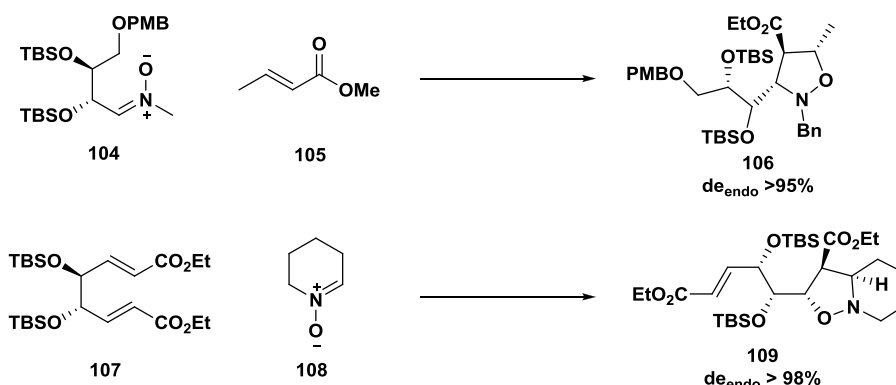
Scheme 31 Asymmetric 1,3-dipolar cycloaddition with chiral nitrone/alkene

In conclusion, through early work of Houk *et al.* it is apparent that the regioselectivity is influenced by the energy levels of the reacting orbitals of the dipolarophile. Diastereoselectivity and enantioselectivity have also been achieved through the usage of chiral nitrones, chiral alkenes and catalysts such as $TiCl(O^iPr)_3$ and $ZnCl_2$. However, cycloadditions with vinyl sulfonates and vinyl sulfonamides are less common.[122] Therefore, guided by previous work conducted within the group, the present studies were directed toward expanding the scope of cycloaddition with vinyl sulfonates and vinyl sulfonamides.

2 Results and Discussion

2.1 Aim

The aim of this research was to study the 1,3-dipolar cycloaddition reactions of PFP ethenesulfonate with dipoles such as nitrones and nitrile oxides. The concept of 1,3-dipolar cycloadditions have been introduced since 1950s. However PFP ethenesulfonate has only been introduced recently as a dipolarophile. Therefore an in-depth study of cycloaddition reaction with PFP ethenesulfonate is of great interest in expanding this area.[113, 122]

Formation of isoxazolyl PFP sulfonates and isoxazolyl sulfonamides have been the focus of this project as isoxazolidines made in previous work showed biological activity against DDAH, ADI and HIV-1, and hence being able to synthesize a collection of related compounds is of interest as well as the potential opportunities for using isoxazoles as a reasonably new class of biologically active agent for drug discovery.[123]

Cycloaddition between nitrile oxides and an alkyne equivalent furnished a collection of isoxazoles in mild conditions (2.5 eq NEt_3, RT, 1 h, Figure 28). Isoxazolyl PFP sulfonates were then able to undergo subsequent aminolysis to produce isoxazolyl sulfonamides that can be screened against HIV-1.
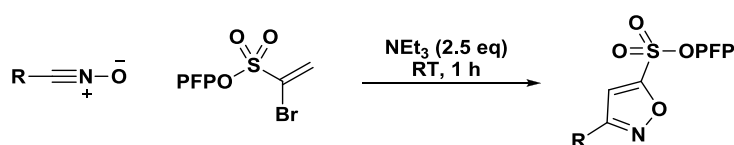
Figure 28 1,3-dipolar cycloaddition between a nitrile oxide and an alkyne equivalent

As a continuation to the previous work within the group,[113] isoxazolidinyl PFP sulfonates and sulfonamides were also synthesized *via* 1,3-dipolar cycloaddition to provide suitable candidates for testing against HIV-1. Further study is required in order to investigate the structure–activity relationship of the isoxazolidinyl PFP sulfonates and sulfonamides. At the same time, diastereoselectivity of aminolysis also needed to be addressed in order to synthesize each diastereomer of sulfonamide more efficiently (Scheme 32).
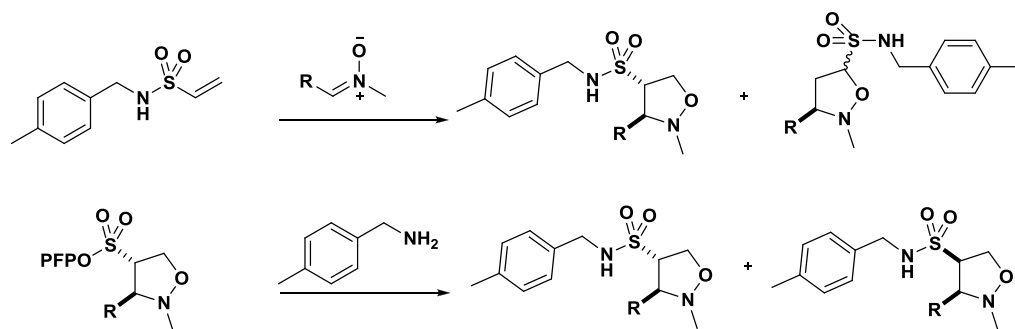
Scheme 32 Various outcomes of nitrone cycloaddition and aminolysis

2.2   Synthesis of isoxazoles

Preparation of isoxazoles described in the literature often involve the use of alkynes,[76] bromoalkenes[124] and 1,3 dicarbonyls (Scheme 33).[82] However, we envisaged an alternative based on the oxidation of the isoxazolidine PFP sulfonates.
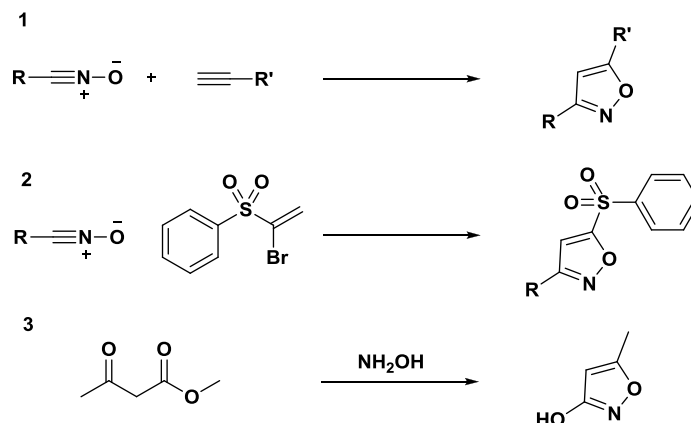
Scheme 33 Literature preparation of isoxazoles

2.2.1   Preparation of pentafluorophenyl (PFP) ethenesulfonate

Pentafluorophenyl ethenesulfonate **110** was prepared using a procedure developed by Wilden from 2-chloroethane-1-sulfonyl chloride **111** (Scheme 34)[125] Due to the exothermic reaction upon addition of pentafluorophenoxide to 2-chloroethane-1-sulfonyl chloride **111**, the reaction temperature must be kept below 0 °C to minimize decomposition. Furthermore, by introducing a dry ice-acetone bath to the reaction, this allows faster addition of pentafluorophenoxide solution to the reaction mixture.
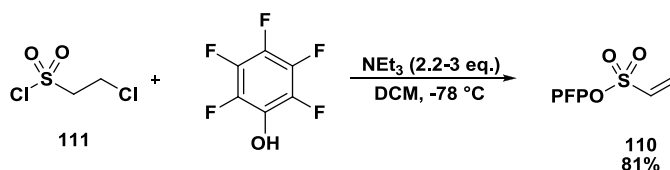
Scheme 34 Preparation of PFP ethenesulfonate

2.2.2 Nitrone cycloaddition and isoxazolidine oxidation

Preparation of nitrones reported in the literature include oxidation of imines[110] or more commonly condensation of a hydroxylamine with an aldehyde.[126] With our desired dipolarophile **110** in hand, the required nitrone had to be synthesized. *N*-^{t}butyl-*C*-phenyl was initially chosen due to its acid labile nature of the ^{t}butyl group which can be easily removed. To synthesize the desired nitrone, ^{t}butyl hydroxylamine **112** was condensed with benzaldehyde to generate the desired nitrone **113**; which then underwent cycloaddition with PFP ethenesulfonate **110** to form isoxazolidine **114** in moderate yield (Scheme 35). The structure of the 3,4-substituted isoxazolidine was determined by NMR, which compared favourably with the literature.[92] With isoxazolidine **114** in hand, we envisaged the removal of the *N*-protecting group followed by ring oxidation to give the corresponding isoxazole (Scheme 36).
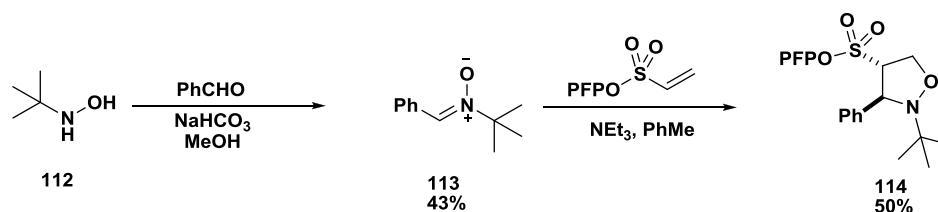
Scheme 35 Synthesis of *N*-^{t}butyl isoxazolidine

However, after 48 hours of refluxing **114** in TFA, 65% of the starting material **114** was recovered with no evidence of desired isoxazoline and isoxazole formation. Therefore it was suspected that prolonged heating was required in order to partially oxidize the heterocycle to isoxazoline, and subsequent DDQ oxidation would furnish our desired isoxazoles. However upon reluxing for 5 days in TFA, only 24% of the starting material **114** was recovered, and the rest of the reagents were decomposed.
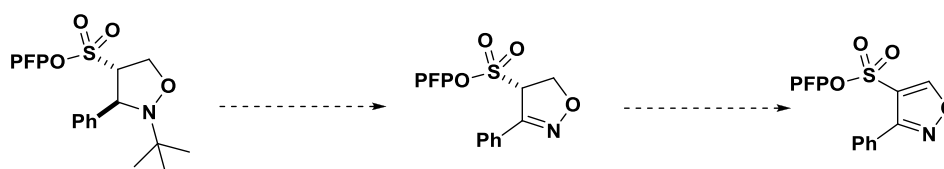
Scheme 36 Initial proposed route to form isoxazole

Due to the lack of success in ring oxidation *via* ^{t}butyl deprotection, this approach was disgarded, and an alternative approach to isoxazolyl PFP sulfonate synthesis was sought.

2.2.3 1,3-Dipolar cycloaddition of nitrile oxide with PFP-1-bromoethenesulfonate

The classical approach to isoxazoles is the condensation of hydroxylamine with a 1,3 dicarbonyl compounds.[82] Our next route towards isoxazole synthesis involves the 1,3-dipolar cycloaddition of nitrile oxide with an alkyne (Scheme 37).[76, 127]
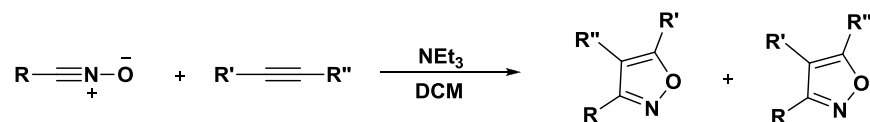
Scheme 37 Cycloaddition between nitrile oxide and alkyne

In order to incorporate the PFP sulfonyl moiety into this cycloaddition, it was proposed to use the acetylenic PFP sulfonate ester as dipolarophile (Scheme 38).
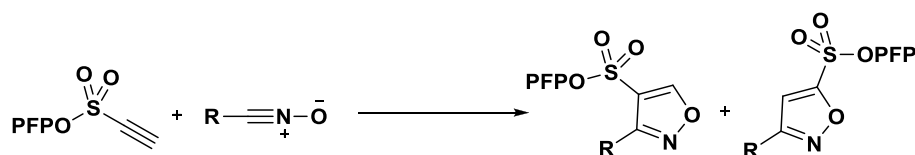
Scheme 38 Cycloaddition between nitrile oxide and acetylenic PFP sulfonate ester

Acetylenic sulfonate ester synthesis has only been seldom reported,[128, 129] and with several unsuccessful attempts (pyridine/NEt$_3$/LDA + AgOTf, Scheme 39) within the group, this problem still remains to be overcome. However, a synthon to the acetylenic sulfonate ester-, the 1-bromo ethenesulfonate ester, has been successful synthesized using radical chemistry,[130] and this dipolarophile was used in place of acetylenic sulfonate ester in our synthesis. Pentafluorophenyl-1-bromoethenesulfonate **115** was readily generated by radical bromination of PFP ethenesulfonate **110** followed by dehydrobromination to furnish the PFP-1-bromoethenesulfonate **115** in excellent yield, 97%, over two steps (Scheme 39).[130]
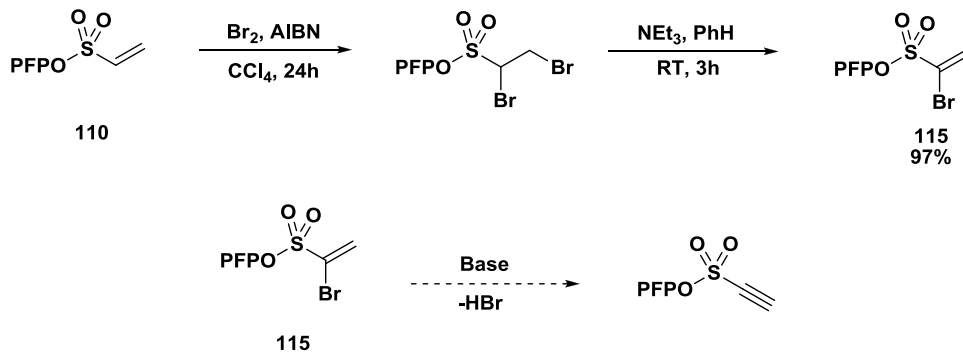
Scheme 39 Preparation of PFP-1-bromoethenesulfonate

2.2.3.1 Preparation of nitrile oxide

Nitrile oxides, as described in 1.4.1.1, are very reactive 1,3-dipoles, and can readily dimerize to form furoxan,[131] thus *in-situ* formation from hydroximoyl chloride is required, nitrile oxide is then rapidly trapped by a suitable dipolarophile in a one-pot cycloaddition. Preparation of hydroximoyl chlorides **116a-p** was easily achieved by chlorination of oximes **117a-p** using *N*-chlorosuccinimide (Scheme 40).[104] In order to obtain uniformly high yield it was crucial to keep the temperature below 40 °C. Most of the desired hydroximoyl chlorides were then obtained in moderate to high yield, with the exception of **116n**. It was observed that **116n** chlorinated on the furyl ring instead of on the oxime α-carbon, to give a mixture of chlorinated compounds that were inseparable by flash chromatography. Therefore furyl substrates were not a suitable for this methodology.
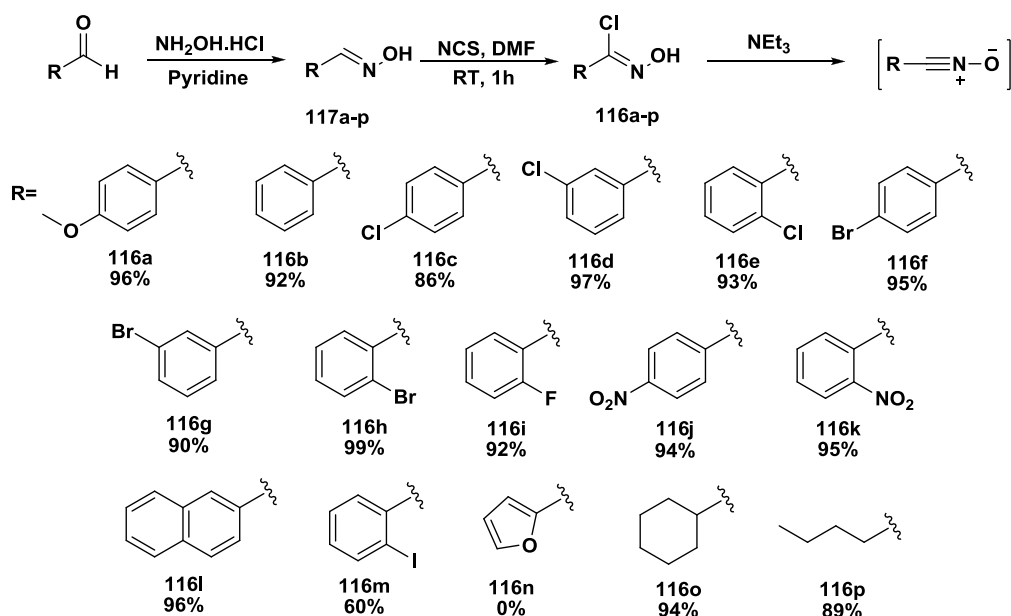
Scheme 40 Preparation and yield of hydroximoyl chlorides from oximes using *N*-chlorosuccinimide

2.2.3.2 Cycloaddition of hydroxymoyl chlorides with PFP-1-bromoethenesulfonate

With both hydroximoyl chlorides **116a-p** and PFP-1-bromoethenesulfonate **115** in hand, cycloadditions were carried out in dichloromethane using Touaux's method.[127] The reaction was refluxed in dichloromethane for 15 hours. However, poor yields were obtained upon purification (Table 2). Therefore it was suspected that the nitrile oxides could have dimerized readily to produce furoxan-2-oxide (as described earlier) as a competing reaction to cycloaddition, resulting in the poor yield obtained.
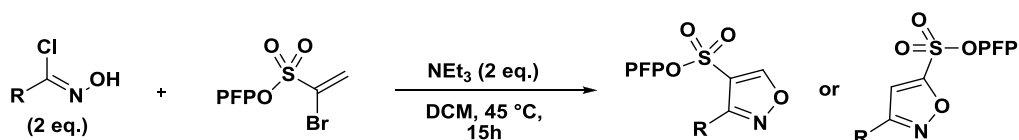
Entry	R	Yield/ %
a	4-methoxyphenyl	24%
b	Ph	42%
c	4-chlorophenyl	0%
d	2-chlorophenyl	44%
e	4-bromophenyl	0%
f	4-nitrophenyl	0%
g	2-nitrophenyl	0%

Table 2 Isoxazolyl PFP sulfonates obtained using Touaux's method

2.2.3.3 NMR study and structure determination

Selectivity in nitrile oxide cycloaddition, as discussed in 1.4.2, suggest that most nitrile oxides cycloaddition with monosubstituted alkenes should be regiospecific, forming the 3,5-substituted isoxazole. However, in a few cases, highly electron deficient dipolarophiles were used and the reverse regioisomer was observed.

The structure of the product isoxazoles was confirmed to be 3,5 substituted by NMR experiments and X-Ray crystallography. Proton, carbon and fluorine NMR spectra were consistent with the structure in Figure 29. In addition, ^1J C-H coupling on the isoxazole 4-C position has a value of 189 Hz; which is consistent with the literature data; whereas ^1J C-H coupling on the isoxazole 5-C position would have a value of >200 Hz.[132] Therefore the structural analysis confirmed that the 3,5-substituted isoxazole is formed despite of the electron deficient nature of the dipolarophile. This led to the conclusion that even though the dipolarophile contains an electron deficient PFP sulfonyl group, this does not overwrite the steric factors of both

counterparts. Therefore steric factors still remain the determining issue of this regio-outcome.
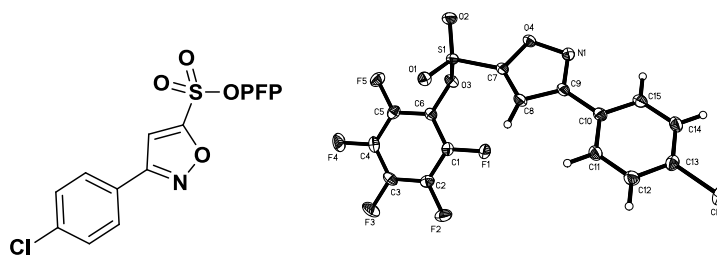
Figure 29 Structure of cycloadduct determined by NMR and X-ray crystallography

2.2.3.4 Optimization of reaction condition

As discussed in 2.2.3.2, cycloaddition using Touaux's conditions (2 eq NEt$_3$, DCM, 45 °C) resulted in low yields. However, Hamme *et al.* reported that most of their cycloadducts were isolated in high yield (Scheme 41), using only slightly different condition.[124]
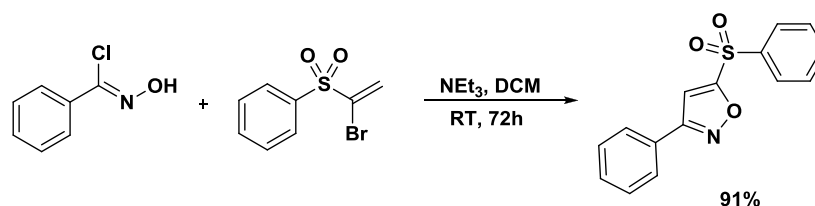
Scheme 41 Hamme's cycloaddition using 1-bromophenylvinylsulfone

Hamme's conditions (1.2 eq NEt$_3$, DCM, RT) were then employed for our cycloaddition (Table 3 entry b). However it was found that the majority of PFP-1-bromoethenesulfonate **115** was still present by TLC (not isolated) even after 72 hours and no product was produced; which suggests that Hamme's conditions were not optimal for our cycloaddition.

During optimization, varying temperature (Table 3 entry c) and solvent (Table 3 entry d) were also investigated with no success. However, with an increase in the amount of triethylamine, the reaction time was observed to be significantly reduced (Table 3 entry e). It is believed that an excess amount of triethylamine may be catalyzing the reaction by either addition to the dipolarophile in a Baylis-Hillman fashion,[82] which triggers cycloaddition with the nitrile oxide; or by addition to the nitrile oxide to form amidoxime.[102] Therefore a mechanistic study was required, which is discussed at the end of this section.
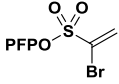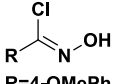
Entry	PFPO–S(O)(O)–C(=CH2)Br / eq.	Cl–C(R)=N–OH, R=4-OMePh / eq.	NEt$_3$/ eq.	Solvent	Temp/ °C	Time/ h	Yield/ %
a	1	2	2	DCM	45	15	30%
b	1	1	1.2	DCM	21	72	0%
c	1	1	1.2	DCM	45	12	0%
d	1	1	1.2	Toluene	110	12	<5%
e	1	1.5	2.5	Toluene	110	1	60%

Table 3 Initial optimization of nitrile oxide cycloaddition

The initial optimized conditions (Table 3 entry e) were then applied to synthesize a collection of isoxazolyl PFP sulfonates and was pleasing to observe significantly improved yields (Table 4).

Due to the recent advances in microwave chemistry, microwave assisted cycloadditions were also attempted. In an initial attempt using a microwave conditions developed by Mok,[113] all starting materials were decomposed, therefore reaction conditions were modified to be less forcing. The reaction time and the temperature were varied, and it was found that the optimal condition for cycloaddition was 100 °C, 4 minutes. Even though the reaction time was significantly reduced compared to conventional thermal heating, the product obtained from conventional thermal heating was much cleaner (Table 4).

Only aromatic hydroximoyl chlorides were employed, because cycloaddition with aliphatic hydroximoyl chlorides appeared to be unsuccessful, this is believed due to that aliphatic hydroximoyl chlorides are unstable upon addition of triethylamine, and were prone to be deprotonated at the α-proton instead of forming nitrile oxide.
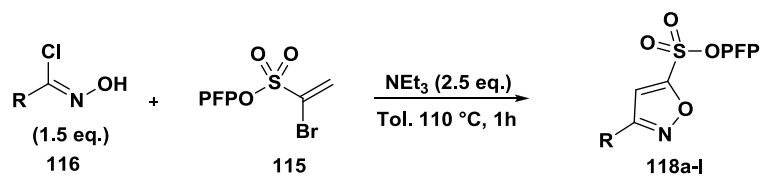
Compound	R	Yield/% (Δ)	Yield/% (MW)
118a		92%	85%
118b	Ph	86%	54%
118c		88%	52%
118d		75%	24%
118e		87%	84%
118f		87%	75%
118g		69%	63%
118h		86%	61%
118i		90%	70%
118j		52%	30%
118k		82%	46%
118l		50%	---

Table 4 Comparison between thermal and microwave irradiation conditions in nitrile oxide cycloaddition

It was observed that all electron rich isoxazoles (**118a**, **118c**, **118e**, **118f** and **118h**) were generated in higher yield than the electron poor isoxazoles (**118j**), and was observed that halides on ortho- and para- position (**118c**, **118e**, **118f** and **118h**)

produces higher yield than on meta-position (**118d** and **118g**), which is in congruent with the aromatic mesomeric affect. The iodo- compound **118l** was isolated in moderate yield, and was believed that this is due to the steric demand of iodide; contrastingly the fluoro- compound **118i** was isolated in high yield. Therefore it is concluded that the electron donating effect of the aryl group and the steric hinderance are directly related to the yield.

Several new conditions were also investigated for these cycloaddition. Temperature, quantity of triethylamine and solvent were varied in order to compare with our previously best condition (Table 5 entry a). It was observed that an increase in the amount of triethylamine had led to an increase in the rate of reaction, and on the reaction with 2.5 eq NEt_3 performing at room temperature (Table 5 entries b, c, f and g) it was found that all reactions reached completion within 2 hours. This suggests that triethylamine could be catalyzing the reaction. Furthermore, an investigation of the solvent effect between toluene and DCM has also been carried out, and it was found that the reaction proceed faster in less polar solvent (toluene) than in more polar solvent (DCM), as well as in higher yield. DMF (Table 5 entry h) was also introduced to investigate whether increasing solvent polarity would affect the rate of reaction, but it was found that the reaction in DMF led to low yields.[123]
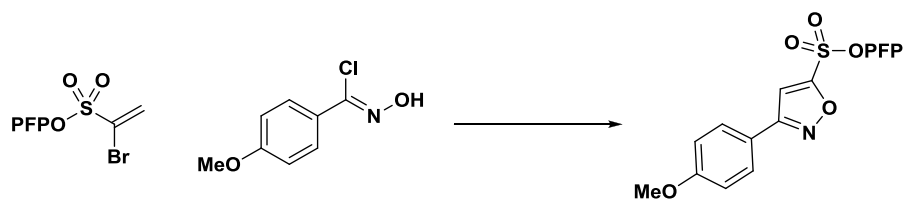
Entry	$\begin{array}{c}R=4\text{-OMePh}\\ \text{/ eq.}\end{array}$	NEt_3 / eq.	Solvent	Temp/ °C	Time/ min	Yield/ %
a*	1.5	2.5	Toluene	110	30	60%
b	1.5	2.5	DCM	21	120	52%
c	1.5	2.5	Toluene	21	100	87%
d*	1.5	5	DCM	45	20	50%
e*	1.5	5	Toluene	110	10	81%
f	1.5	5	DCM	21	90	48%
g	1.5	5	Toluene	21	60	92%
h	1.5	5	DMF	21	20	43%

Table 5 Optimization of nitrile oxide cycloaddition. * = reflux

With the optimized conditions in hand (Table 5 entries c and g), our interest was to study the mechanistic pathway of this cycloaddition. In entries b, c and d, reactions were monitored by TLC every 10 minutes, and all showed that the immediate consumption of hydroximoyl chloride after the addition of triethylamine, suggesting as expected that the cycloaddition does not proceed *via* hydroximoyl chloride, but through an intermediate nitrile oxide. On the other hand, excess triethylamine seems to catalyze the reaction (comparing entries c and g), suggesting that excess triethylamine participated in our cycloaddition. It has been reported that nitrile oxide is susceptible to nucleophilic attack by amine to form amidoxime.[102, 133] Therefore we suspect that the excess triethylamine underwent nucleophilic attack on the nitrile oxide prior to cycloaddition, and subsequent dehydrobromination to furnish the 3,5 isoxazolyl PFP sulfonate as a sole product (Scheme 42).
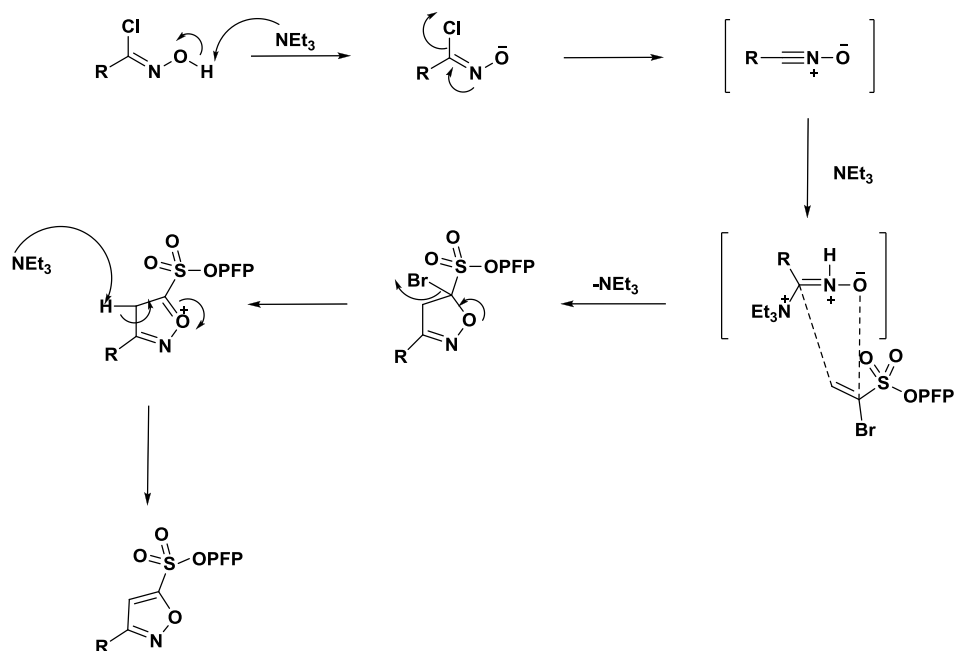
Scheme 42 Proposed mechanism of nitrile oxide cycloaddition

2.2.4 Aminolysis of isoxazolyl PFP sulfonate

With the desired isoxazolyl PFP sulfonates in hand, subsequent aminolysis was then carried out using 4-methylbenzylamine and allylamine to generate isoxazolyl sulfonamides **119a-120k**. Displacement of the pentafluorophenol with an amine generated isoxazolyl sulfonamides in good yield. However, this reaction (1-3 h) did not proceed as fast as the analogous aminolysis of isoxazolidinyl PFP sulfonate (1 h) that had previously been reported by the group. Aminolysis of alkyl sulfonates generally proceeds *via* the sulfene intermediate, however, isoxazolyl PFP sulfonate does not contain an α-proton available for deprotonation; therefore direct displacement has to occur, resulting in prolonged reaction time. Despite the longer reaction time required for aminolysis, all isoxazolyl sulfonamides were isolated in high yield, and no general trend in yield was observed relating to the electronics of the isoxazolyl PFP sulfonates (Table 6). Therefore it was believed that all the isoxazolyl PFP sulfonates are sufficiently electron deficient to be susceptible to substitution by primary amines.
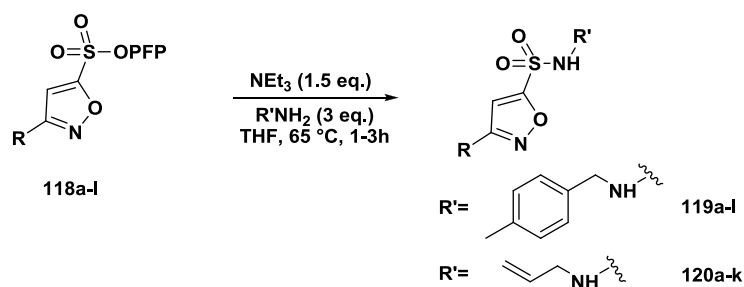
Compound	R	Yield/%	Compound	R	Yield/%
119a	4-methoxyphenyl	71%	**120a**	4-methoxyphenyl	66%
119b	Ph	95%	**120b**	Ph	64%
119c	4-chlorophenyl	83%	**120c**	4-chlorophenyl	60%
119d	3-chlorophenyl	72%	**120d**	3-chlorophenyl	53%
119e	2-chlorophenyl	82%	**120e**	2-chlorophenyl	64%
119f	4-bromophenyl	73%	**120f**	4-bromophenyl	67%
119g	3-bromophenyl	84%	**120g**	3-bromophenyl	67%
119h	2-bromophenyl	90%	**120h**	2-bromophenyl	68%
119i	2-fluorophenyl	84%	**120i**	2-fluorophenyl	77%
119j	4-nitrophenyl	72%	**120j**	4-nitrophenyl	69%
119k	naphthyl	83%	**120k**	naphthyl	69%
119l	2-iodophenyl	71%			

Table 6 Aminolysis of isoxazolyl PFP sulfonate using 4-methylbenzylamine or allylamine

Other primary amines were also chosen for this reaction, namely *tert*-butylamine and isopropylamine. However, due to their bulky nature, aminolysis did not proceed efficiently as detailed in Table 6 (Scheme 43) and therefore tetrabutylammonium

chloride (TBAC) was then introduced as a nucleophilic catalyst. The primary action of TBAC is to generate sulfonyl chloride *in-situ* from the PFP sulfonate ester in order to enhance reactivity for aminolysis.[134] It was found that the reaction time was significantly reduced, from 24 hours to 3 hours upon TBAC addition, along with an increase in yield. Again, there was no general trend of the yield that corresponded to the electronic nature of substituent, however, *tert*-butylsulfonamides **121a-121k** were isolated in lower yield than isopropylsulfonamides **122a-122k** due to the increased steric demand of the *tert*-butylamine.

Scheme 43 Aminolysis using t-butylamine and isopropylamine

The scope of aminolysis was also extended to secondary and aromatic amines. Initially, when the previous aminolysis conditions (Table 7 entry a) were applied, sulfonamides were isolated in poor yield, therefore in order to optimize this reaction, temperature, amount of triethylamine and TBAC were then varied. It was observed that a lower yield was obtained when using LHMDS (Table 7 entries d and e), and it was suspected that LHMDS was too harsh a base. Optimal conditions were identfied that prolonged heating of the reaction mixture was required (Table 7 entry c), where upon yields obtained were markedly improved (Scheme 44).

Entry	/ eq.	Base	Heating	Temp/ °C	Time/ min	Yield/ %
a	3 With TBAC	NEt$_3$	Δ	65	180	47%
b	3 With TBAC	NEt$_3$	MW	100	5	44%
c	3 With TBAC	NEt$_3$	Δ	65	24 h	62%
d	3	LHMDS	Δ	65	240	0%
e	3 With TBAC	LHMDS	Δ	65	240	37%

Table 7 Optimization of aminolysis using *N*-methylbenzylamine
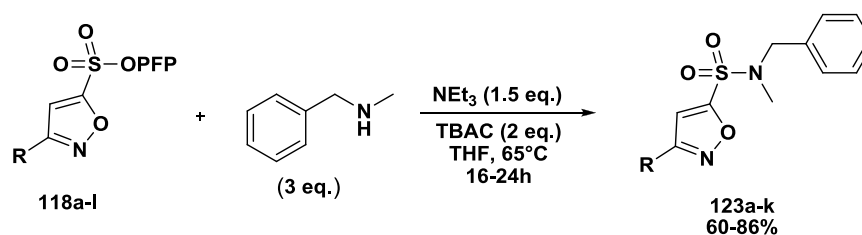
Scheme 44 Optimized condition from Table 7 entry c

Next, aminolysis with an aromatic amine, aniline was studied. Due to the participation of the nitrogen lone pair within the aromatic system, it is known to be less nucleophilic compared to other amines. Previous aminolysis conditions (Table 7 entry c) were then employed for the following reactions. However, sulfonamides were only obtained in up to 50% yield. It was suspected that the aniline used was slowly oxidized; therefore aniline was distilled prior to aminolysis to investigate whether the purity of aniline affects the yield (Table 8). It was observed that upon using freshly distilled aniline, yields improved slightly by about 10-15%; therefore concluding that the purity of aniline does affect the yield.

Over the course of consecutive aminolyses, yields decreased dramatically (Table 8). Aniline was then suspected to oxidize steadily to produce lower yield, therefore all reactions were then repeated in carousel using a batch of freshly distilled aniline. No distinctive pattern was shown on the Carousel reactions. However, with para-

substituted electron donating ligands (**124a**, **124c** and **124f**) the yields tend to be higher.
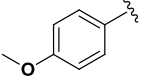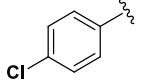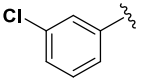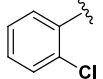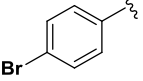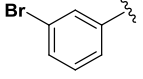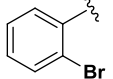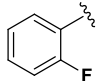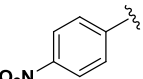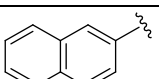
Compound	R	Yield/ %	Yield/ % (carousel)
124a		60 %	93 %
124b	Ph	68 %	46 %
124c		67 %	68 %
124d		50 %	62 %
124e		43 %	42 %
124f		46 %	80 %
124g		42 %	32 %
124h		37 %	47 %
124i		17 %	10%
124j		9 %	44 %
124k		6 %	46 %

Table 8 Comparison in yields between consecutive aminolysis and carousel

2.3   Introduction to HIV

Human immunodeficiency virus (HIV) is a lentivirus (a class of retrovirus) that causes the delayed onset immune system failure in human, and eventually leads to the Acquired Immunodeficiency Syndrome (AIDS) and opportunistic diseases such as meningitis, bronchitis, eruption of Herpes Simplex virus (HSV) and Hodgkin's lymphoma.[135]

The origin of HIV is believed to be the cross-species variant of the Simian Immunodeficiency Virus in chimpanzees (SIVcpz), after various minor mutations, the modern HIV virion was born.[136, 137] It was first discovered in 1970s when a patient displays the signs of lymphadenopathy, but remain un-named until it was isolated from lymph nodes of a patient suffering lymphadenopthy in 1983.[138]

HIV infects cells in the immune system such as the $CD4^+$ helper T-cells, macrophages and dendritic cells. It reduces $CD4^+$ count through three mechanisms: (1) direct killing of the infected cells by the virus, (2) increased apoptosis of infected cells and (3) recognition and killing of the infected $CD4^+$ T_h-cells by the CD8 cytotoxic T-cells. Reduced level of $CD4^+$ count leads to immunedysfunction, and increases the risk of contracting opportunistic diseases.[138]

2.3.1   Structure and genomic organization of HIV

The structure of HIV is approximately 120nm in diameter; which consists of a core capsid, viral matrix and protein membrane (Figure 30). The core capsid comprises of two single stranded RNA molecules, which are in close association with reverse transcriptase, integrase, protease, ribonuclease and nucleocapsid proteins. The surrounding matrix maintains and ensures the integrity of the viral structure; which is all encased in a viral envelope constructed from two phospholipid layers. There are two embedded surface proteins: gp120, a cap trimer that is responsible for initial binding to $CD4^+$ T_h-cell, and the transmembrane gp41, which consists of homodimeric trimer helix (total six helix) that support the extracellular nature of gp120. [139, 140]

There are two types of HIV: HIV-1 and HIV-2. HIV-1 is more virulent and possesses

higher transmissibility and mortality rate than HIV-2. While HIV-1 is globalized, HIV-2 is localized within West Africa. Both subtypes of HIVs contain the same genome (apart from *Vpr* and *Vpx*), but are different in their genome mapping, where HIV-2 is closer resembled to SIVcpz than HIV-1.[141]
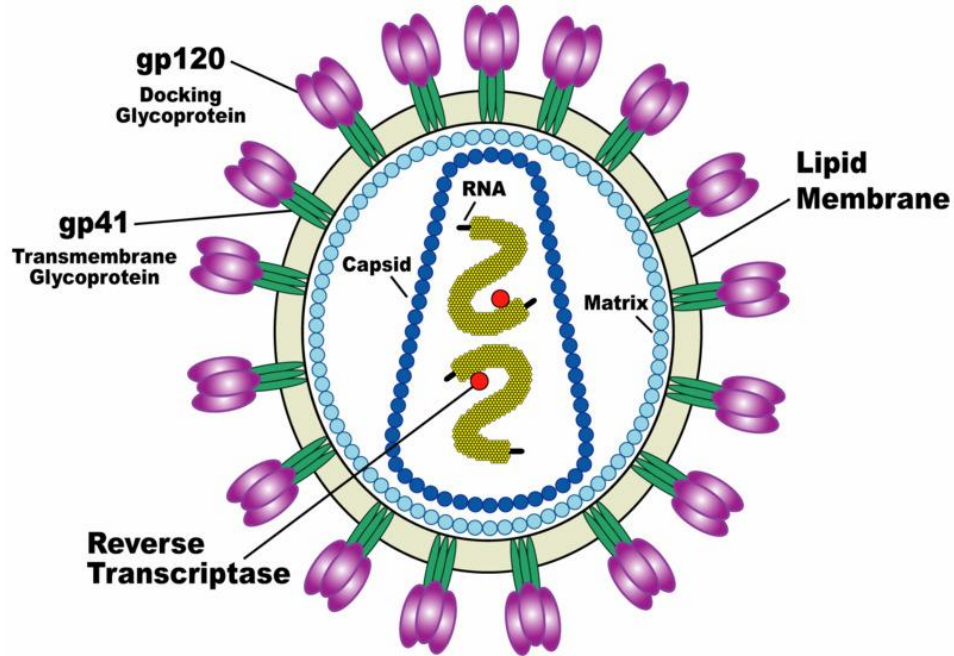
Figure 30 Schematic of HIV virion from Behera[142]

Each viral RNA encodes for nine genes within the HIV viral particle (*Gag*, *Pol*, *Env*, *Vif*, *Vpr/Vpx*, *Rev*, *Tat*, *Vpu* and *Nef*), five of the genes (*Gag*, *Pol* and *Env, Tat* and *Rev*) encode for proteins that are vital to infection and life cycle: *Gag* codes for the structural matrix protein, capsid protein and nucleocapsid proteins; *Pol* codes for enzymes within the capsid, such as protease, reverse transcriptase, and integrase; *Env* (envelope protein) codes for the gp160 glycoprotein, which is later broken down to gp41 and gp120; *Tat* and *Rev* are essential during the viral transcription as they are the transcription activator and RNA transporter/stabilizer. Absence or mutation of *Tat* and *Rev* genes inactivate the virus.[143, 144] The remaining four genes regulate the viral replication cycle. The start/end region of the HIV genome is occupied by a structural landmark called viral Long Terminal Repeats (LTRs), which contain sequences that repeat up to several hundred times. After the viral RNA is reverse-transcribed into a double helix vDNA, LTR is used for mediating insertion of vDNA into host DNA during integration. LTRs are specific to retrovirus, therefore it can be used to determined the degree of HIV infection by counting the number of LTRs.[140, 141]

2.3.2 **HIV life cycle**

The life cycle of HIV can be divided into 3 stages: (1) cell entry, (2) replication and transcription, and (3) resemble and release.

2.3.2.1 Cell entry

The life cycle of HIV begins with binding of the gp120 glycoprotein with the CD4$^+$ receptors and macrophages; which allows a structural change in the gp120, exposing a secondary binding ligand. The secondary binding ligand is then able to interact with the chemokine co-receptors on the host cell surface (α-chemokine receptor CCR5 or β-chemokine receptor CXCR4). Secondary interaction between gp120 and chemokine co-receptor ensures further conformational changes within the viral particle, and allows exposure of gp41 glycoprotein to penetrate into the hydrophobic cell membrane. The HR1 domain of the gp41 stabilizes cell penetration, and the HR2 domain begins to coil up, bringing viral particle closer to the cell membrane, known as the "HR2 zipping". This triggers fusion between viral phospholipid layers and host cell membrane, and subsequent delivery of the viral capsid into the cell (Figure 31).[139, 145]

2.3.2.2 Replication and transcription

The uncoated viral RNA is reverse transcribed into single stranded complementary DNA, then into the double stranded vDNA by its reverse transcriptase. vDNA is now in close association with reverse transcriptase, matrix protein, integrase and *Tat* protein, forming a pre-integration complex (PIC), which can then be imported into the nucleus with the aid of viral protein R (*Vpr*).[141, 145, 146] It is believed that matrix protein and *Vpr* contains nuclear localization signal that can interact with Importin (a nucleocytoplasmic shuttling receptor) in order to achieve nuclear import.[147, 148]

Within the nucleus, vDNA is integrated into the chromosomal DNA, generating a provirus. This provirus DNA can lay dormant, or become active when *Tat* (HIV transcription transactivator) protein activates the host transcription factor NF-kB, and the cellular transcription then copies the integrated DNA into mRNA by RNA polymerase.[144, 149, 150] It has been reported that the transcription factor NF-kB could be activated in the infected cell, and that this has antiapoptotic property. This antiapoptotic property acts as a defence mechanism to limit replication, and leads to direct cytotoxic killing (by other cytotoxic cells) of the infected cells.[151] HIV exploit

the antiapoptotic property of NF-kB by triggering cytotoxic killing of the infected T_h-cell, or conversely by increasing apoptosis to increase viral spread.[151, 152] Post transcription, mRNA is exported to cytoplasm (by *Rev* protein), where it can be spliced into smaller fragments of mRNA to provide essential structural proteins during translation. As *Rev* level increases, RNA splicing is inhibited, furthermore it provides stabilization of the RNA in cytosplam.[141]
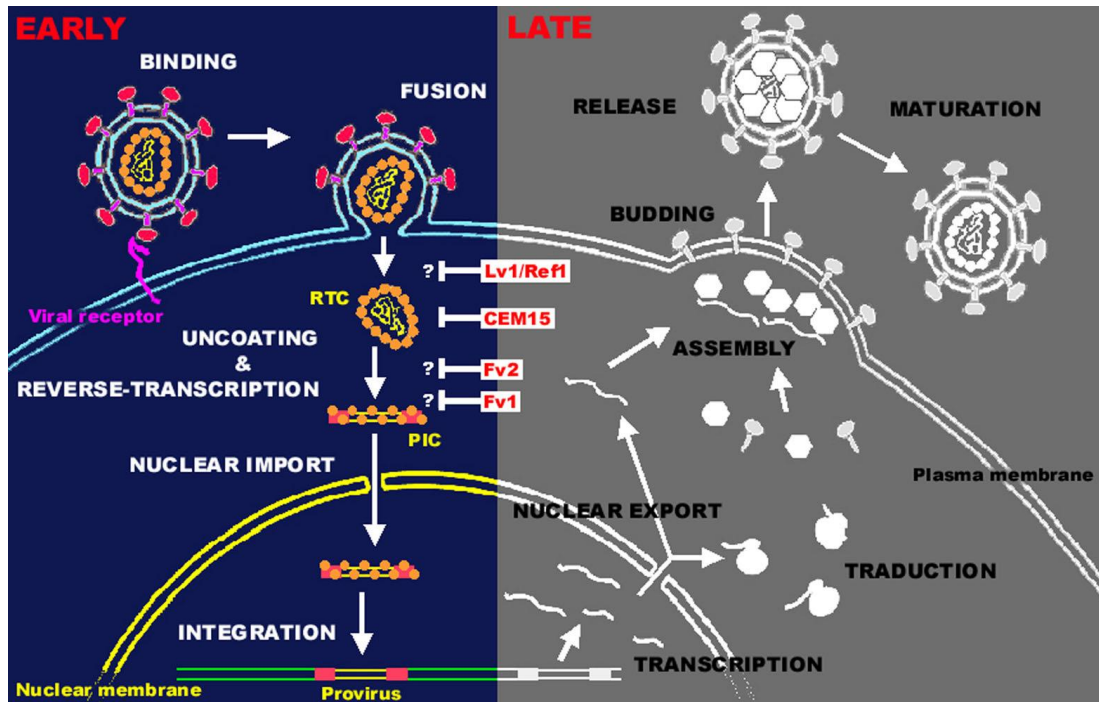
Figure 31 HIV replication cycle from Nisole[145]

2.3.2.3 Assembly and release

During translation, glycoprotein gp160 is produced, which is further broken down to provide surface glycoproteins gp41 and gp120. At the same time, *gag* and *gag-pol* polyproteins are synthesized in the cytoplasm, and then transported to the cell membrane. The immature virus starts to bud from the host cell, but maturation only occurs when protease cleaves the polyproteins into smaller essential and regulatory proteins. The mature viral particle can then be released from the infected host cell, which can then proceed to infect more cells.[141]

2.3.3 Treatment of HIV

Through a better understanding of the HIV replication cycle, it has been possible to develop various anti-retroviral agents. Each of them had been synthesized to

specifically target different enzymes during the replication cycle. Key stages include reverse transcriptase, protease, integrase and viral fusion. However, due to the error-prone nature of the reverse transcriptase, viral RNA is can mutate rapidly; and results in mutated viral proteins, renders most antiretroviral agents inactive. Highly Active Anti-Retroviral Therapy (HAART) is a multi-drug treatment that was first introduced in 1996, which comprises of three or more antiretroviral agents working in conjunction with one another. Clinical success of HAART is due to the simultaneous inhibition during different stages of replication cycle, and has significantly reduced the mortality rate of viral infection. However, life-long treatment is required to suppress viral spread, where disruption or termination of treatment may resume viral activity.[153]

2.3.3.1   Reverse transcriptase inhibitors

The first identified target for anti HIV treatment is reverse transcriptase. There are two known types of reverse transcriptase inhibtors: nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Reverse transcriptase comprises of two enzymes: nuclease and polymerase, where the initial reverse transcription occurs at the polymerase. In order for the polymerase to form the complementary single stranded DNA, it requires deoxynucleotide triphosphate (dNTP) as a building blocks and these must be phosphorylated into a triphosphate to allow subsequent chain elongation to occur.[139] Nucleotide reverse transcriptase inhibitors (NRTIs) resemble the structure of the building block, and act as competitive inhibitors. However, NRTIs lack 3'-OH group, which is required for chain elongation. Once the NRTI is incorporated into the cDNA, there is no 3'-OH available for chain elongation. Therefore chain elongation terminates and viral replication ceased (Scheme 45).[139]

Scheme 45 Inhibition of reverse transcription using NRTIs

Another class of reverse transcriptase inhibitor NNRTI: do not competitively bind to the polymerase active sites; instead they interacts with the hydrophobic allosteric binding pocket near the active site, creating a conformational change within the active site of the reverse transcriptase and this in turns leads to lost of function of reverse transcriptase.[139, 154] Current available reverse transcriptase inhibitors include Zidovudine **125**, Stavudine **126** and Lamivudine **127** as NRTIs; Enfavirenz **128**, Delavirdine **129**, Nevirapine **130** and TIBO **131** as NNRTIs (Figure 32).[139, 154]

NRTIs

| Zidovudine 125 | Stavudine 126 | Lamivudine 127 |

NNRTIs

| Enfavirenz 128 | Delavirdine 129 | Nevirapine 130 | TIBO 131 |

Figure 32 Commercially available NRTIs and NNRTIs

2.3.3.2 Protease inhibitors

Another type of HIV inhibitor, also a constituent part of HAART, is the HIV protease

inhibitors. HIV protease inhibitors act on the later stage of the replication cycle, where the *Gag* and *Gag-Pol* polyproteins are being processed into essential viral proteins by the enzyme protease. HIV protease is a homodimeric enzyme that consists of two active sites (Asp^{25} and Asp^{125}). Both aspartic residues work in conjunction, using water as nucleophile to hydrolyze the peptide bond.[155, 156]

HIV protease inhibitors mimic the structure of a natural substrate (biomimetics), therefore acting as a competitive inhibitor; however most of them contain a non-hydrolysable hydroxyethylamine moiety in place of a peptide bond (Figure 33). Therefore, subsequent binding of HIVPIs terminates the action of protease, and protease function is lost.[156] Several HIVPIs are currently available, such as Amprenavir **19**, Atazanavir **132**, Tipranavir, Indinavir, Ritonavir and Darunavir; however some are more active than another due to development of drug resistance within the protease.

Atazanavir
132

Amprenavir
19
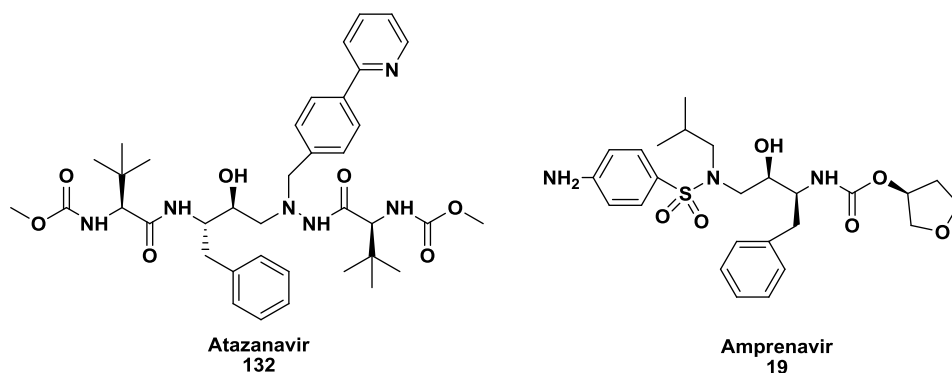
Figure 33 Commercially available HIV protease inhibitors

2.3.3.3   Fusion inhibitors

HIV entry inhibition has also been a subject of interest; where if HIV fusion can be inhibited, subsequent HAART treatment could pose a significant advantage in combating HIV. There are several fusion inhibitors available, such as Enfuvirtide (gp41 inhibitor)[157]and the recombinant protein CD4-IgG2 (gp120 inhibitor), which acts on HIV virion.[158] However, several other inhibitors are designed to act on the host cell instead, such as AD101 **133**, PSC-RANTES and Maraviroc **134** (CCR5 inhibitors).[159, 160]

It has been reported that with 50% of HIV infected people, the virus switches its entry pathway from CCR5 predominant pathway to CXCR4 predominant pathway. These strains are known as the syncytium-inducing virus.[161, 162] Therefore it is

desirable to develop an inhibitor that acts on both CCR5 and CXCR4. Schols *et al.* have developed a dual CCR5/CXCR4 antagonist AMD3451,that block R5 (HIV that uses only CCR5), X4 (HIV that uses only CXCR4) and R5/X4 HIV.[163]
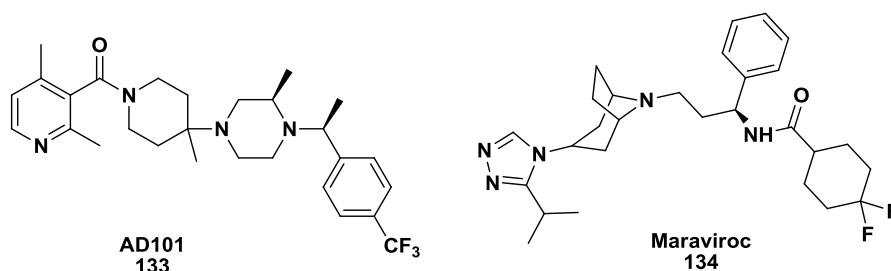
Figure 34 Entry inhibitors

Through a better understanding of the structure and replication cycle of HIV, various treatments have been employed to significantly reduce the threat of viral infection. Although there still remains no cure, numerous more potent, less toxic anti-HIV drugs are being developed at the meantime, including several sulfonamide-based drugs, therefore our synthesized sulfonamides and PFP sulfonates are potential interest for activity against HIV.

2.4   Synthesis of isoxazolidines

Previous work conducted within the group has been focused on 1,3-dipolar cycloadditions of PFP ethenesulfonate and nitrones to generate 3,4-anti isoxazolidines as the products (Scheme 46).[113, 122] In addition, several of the isoxazolidinyl PFP sulfonates prepared and the corresponding isoxazolidinyl sulfonamides have been evaluated for their inhibitory activity against HIV-1. Therefore, as a continuation of this work, the following studies were conducted (1) synthesis of different analogues of isoxazolidinyl sulfonamide for SAR study, and (2) development of reagents for the target identification.
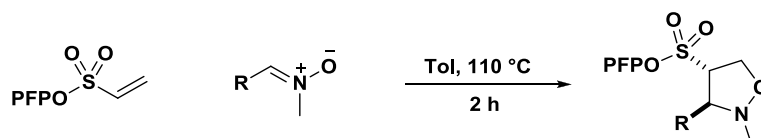
Scheme 46 Formation of isoxazolidine *via* nitrone cycloaddition

2.4.1   Initial screening and SAR study

Previous work by Mok examined the cycloaddition of nitrones with PFP ethenesulfonate and *N*-(4-methylbenzyl)ethenesulfonamide.[113] This library of

isoxazolidines was then screened against HIV-1 vector. It was found that several small molecules **135**-**139** exhibit micromolar inhibition against HIV, furthermore, sulfonamides **138** and **139** appeared to exhibit the highest potency. Therefore several sulfonamides were then synthesized in order to try and establish some structure-activity relationship.[113]

135
80-90%
250μM

136
90-95%
250μM

137
90-95%
250μM

138
80-90%
150μM

139
80-90%
150μM
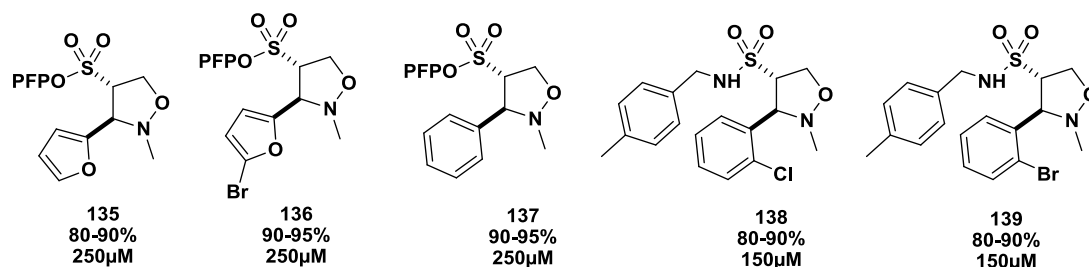
Figure 35 Percentage of HIV inhibition at 150-250 μM concentration

From the initial screening it was observed that the potency is determined on several factors: The 4-methylbenzyl sulfonamide group is essential for HIV inhibition. Substitution to other sulfonamide leads to loss in potency (Figure 36).

Toxic

30%

40%

70%

90%

70%

90%

30%

70%

70%

90%
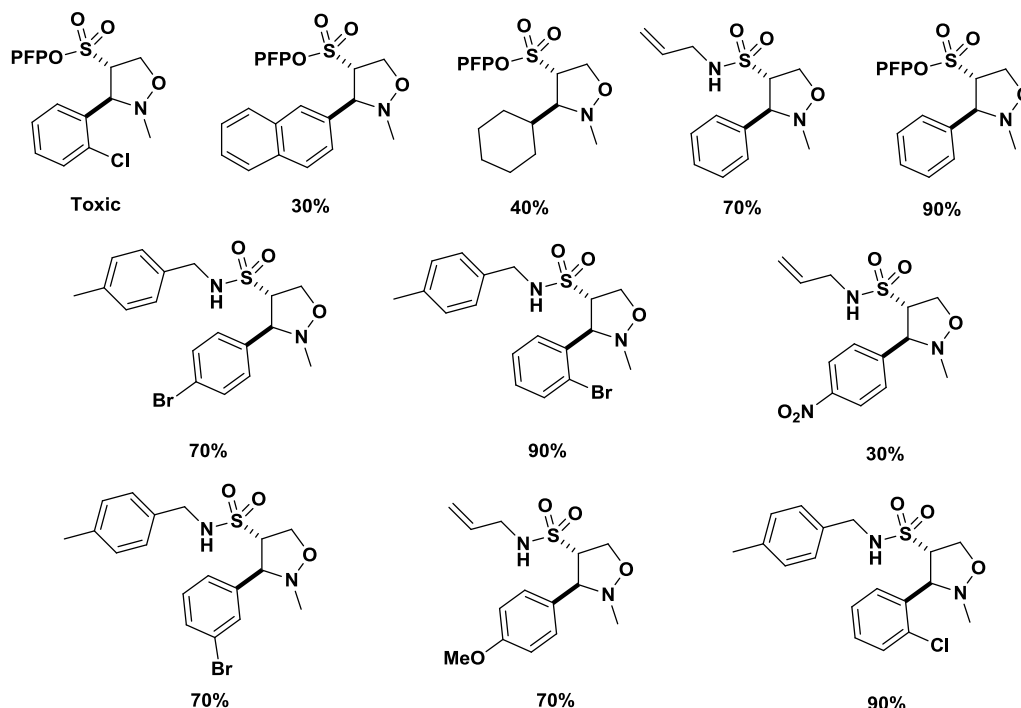
Figure 36 A selected initial screening at 150-250 μM

Substituents on the phenyl ring also shows fluctuation in inhibition activity. The *o*-halide compounds were found to be the most potent, and potency was closely followed by the *p*-halide compounds. Thus the *o*-halide appears crucial for high potency. In addition, it was discovered that as the size of the halogen increases,

potency increases (e.g. activity I>Br>Cl>F).[113]

Methyl substitution on nitrogen in the isoxazolidine ring also appears important. For example with the *N*-methyl substituted isoxazolidines, the optimal concentration for target inhibition is 150-250 μM. However when it is changed to *N*-hydroxyethyl moiety the optimal concentration was then increased to 400-500 μM in order to obtain the same level of inhibition. Thus it would appear that the *N*-methyl moiety is neccessary. From the SAR study it was concluded that 2-methyl-3-(2-halo)phenyl isoxazolidine-4-(4-methylbenzyl)sulfonamides display the highest potency (Figure 37).[113]
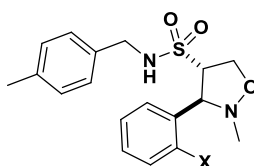
Figure 37 Structure of the most potent compound where it contains a 4-methylbenzylsulfonamide, an *o*-halophenyl and an *N*-methyl group

2.4.2 Synthesis of isoxazolidinyl sulfoanimdes and optimization of stereoselectivity

In order to synthesize a collection of isoxazolidinyl sulfonamides for further testing against HIV, nitrones **140** were selected to undergo cycloaddition with *N*-(4-methylbenzyl)ethenesulfonamide **141** (Scheme 47). It was observed that the reaction generated the 3,4-anti, 3,5-anti and 3,5-syn isoxazolidinyl sulfonamides under microwave irradiation. The 3,4-anti isoxazolidinyl sulfonamide **142** appeared to be the major product, and the 3,5-anti/syn mixture were detected as the minor products. Several purifications were required to isolate the major product resulting in reduced yield, in addition the 3,5-anti/syn mixture is unable to be isolated therefore the yield reported is for the 3,4-anti isoxazolidinyl sulfonamide (Scheme 47).
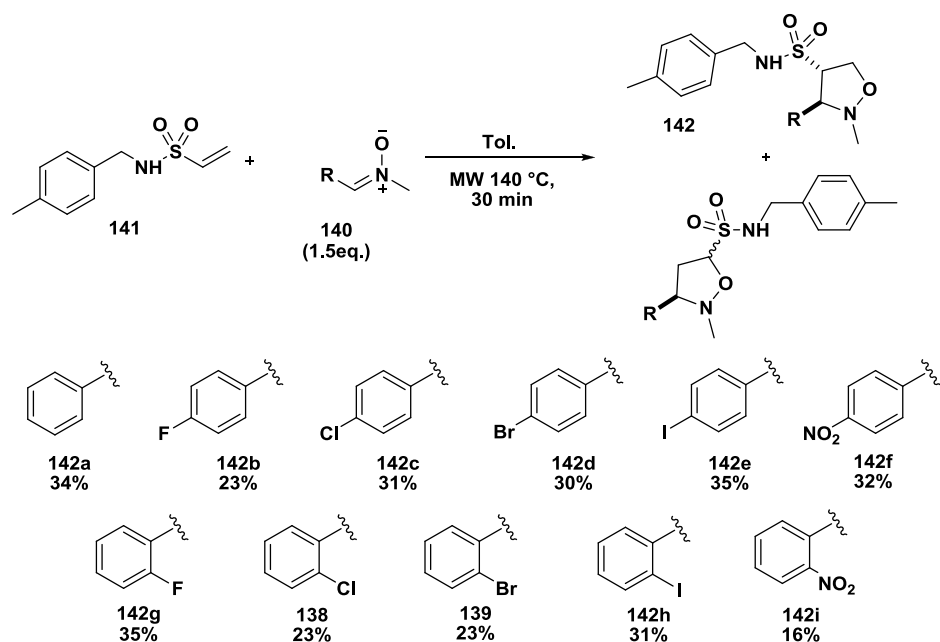
Scheme 47 Collection of the isoxazolidinyl sulfonamides

2.4.2.1 Stereochemical implications of aminolysis reactions of isoxazolidinyl sulfonates

To date the synthesis of isoxazolidinyl sulfonamides has been carried out *via* two different approaches: (1) the classical aminolysis *via* isoxazolidinyl PFP sulfonate esters, and (2) 1,3-dipolar cycloaddition of ethenesulfonamide with nitrones (Scheme 48). Both approaches present potential problems such as regio-, stereoselectivity and difficulties in compound isolation. Such problems decrease the efficiency of the route; therefore this section describes an investigation of the stereochemical outcome of the aminolysis reactions.
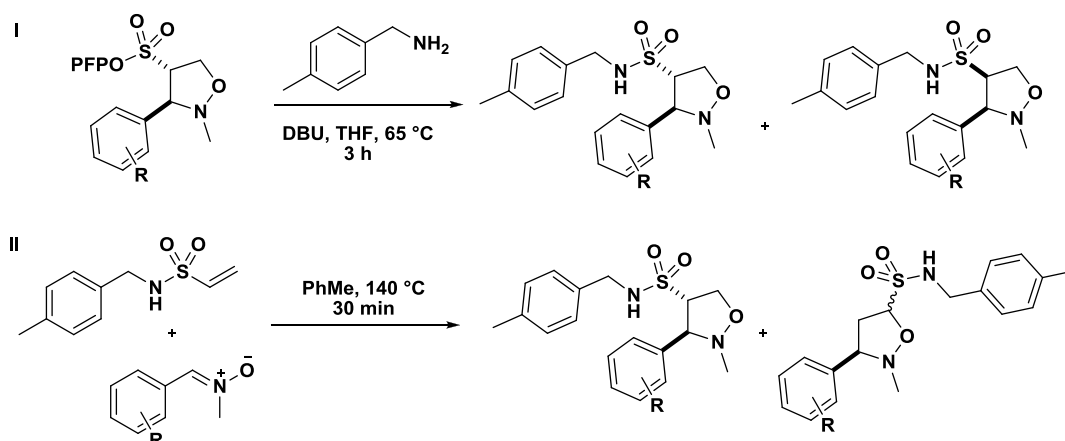
Scheme 48 Synthesis of isoxazolidinyl sulfonamides *via* (1) aminolysis and (2) 1,3-dipolar cycloaddition

As mentioned in 1.3.4, aminolysis proceeds through a sulfene intermediate with the

presence of an α-H. During amine addition, a carbanion is formed, which can then be re-protonated from either faces of the molecule to form two diastereomers (Scheme 49.).
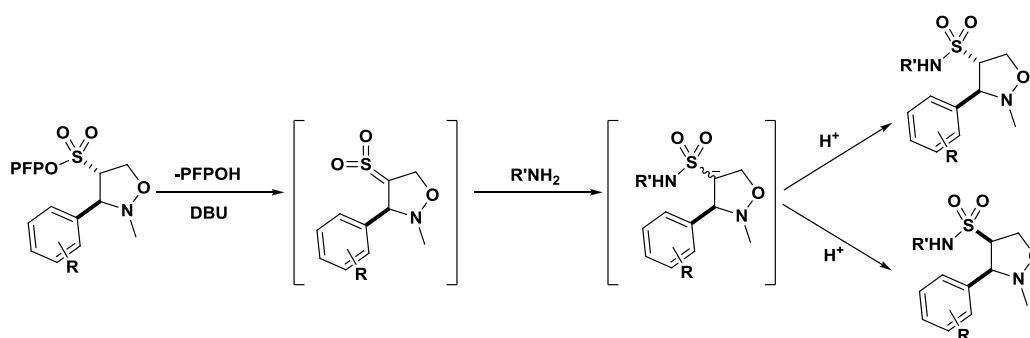
Scheme 49 Formation of diastereomeric sulfonamides from aminolysis

Prior to the optimization, it is of our interest to investigate which diastereomer possesses more thermodynamic stability. With the original aminolysis condition as a reference point (3 eq. amine, DBU, THF reflux for 3 hours) a representative 3,4-syn isoxazolidinyl sulfonamide **143a** was selected for epimerization studies in the presence of DBU, DMF at higher temperatures (Table 9 entry a&b). However, only the starting material was recovered, therefore a stronger/bulkier base and proton source was introduced in order to enhance the rate of epimerization (entry c-e). However, from the NMR analysis it appeared that no epimerization has occurred.

143a = (structure) 143b = (structure)
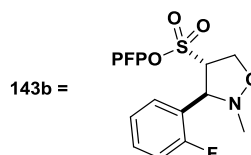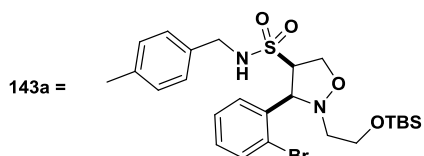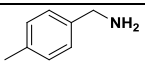
Entry	Substrate	(amine structure) NH₂	Base/ H⁺ source	Solvent	Temperature /Time	Ratio anti:syn
a	**143a**	---	DBU (1.2 eq)	DMF	153 °C/ 3 h	0:1
b	**143a**	---	DBU (1.2 eq)	DMF	153 °C/ 24 h	0:1
c	**143a**	---	^{t}BuOK (1.2 eq) /^{t}BuOH (1.2 eq)	THF	66 °C/ 3 h	0:1
d	**143a**	---	^{t}BuOK (1.2 eq) /^{t}BuOH (1.2 eq)	THF	66 °C/ 24 h	0:1
e	**143a**	---	^{t}BuOK (1.2 eq) /^{t}BuOH (1.2 eq)	THF	66 °C/ 48 h	0:1
f	**143a**	---	^{t}BuOK (1.2 eq) /^{t}BuOH (1.2 eq)	Dioxane	101 °C/ 48 h	1:6 76%[a]
g	**143a**	---	^{t}BuOK (1.2 eq) /^{t}BuOH (1.2 eq)	DMF	153 °C/ 48 h	1:1* 35%[a]
h	**143b**	3 eq	^{t}BuOK (1.2 eq) /^{t}BuOH (1.2 eq)	DMF	153 °C/ 3 h	1:1 69%[b]

Table 9 Epimerization and optimization of diastereoselectivity. Reaction using forcing conditions (^tBuOH, ^tBuOK, DMF) generates 1:1 anti/syn mixture. * Contain trace amount of decomposition. [a] Starting material recovery. [b] Overall yields.

It was noted that when solvents are changed to allow for higher reaction temperature, epimerization was observed (entry f&g). Therefore it was observed that at high temperature using strong base and a bulky proton source, the 3,4-anti isoxazolidinyl sulfonamide is generated slowly over time.

Applying these conditions to the aminolysis (entry h) it was observed that the diastereomeric ratio again stays at 1:1, and further reaction modification (prolonging the reaction period and varying the amount of ^tBuOH) did not improve the diastereo-mixture beyond 1:1.

In conclusion, at higher temperature, thermodynamic mixture of 1:1 anti/syn was achieved inspite of using bulkier proton source. On the other hand, our original aminolysis condition (3 eq. amine, DBU and THF reflux for 3 hours) promotes 3:1 to 4:1 ratio in favour of the anti protuct, therefore it was disappointed to observe that a reduction in diastereomeric ratio when the reaction conditions were modified to enhance the diastereoselectivity.

2.4.3   Affinity chromatography

Affinity chromatography is a technique used for capturing protein from biological mixture. Affinity chromatography works by tightly binding the target protein to the ligand-tagged immobilized matrix *via* either electrostatic, hydrophobic, van der Waal's or H-bonding. The target protein is then released from the column by means of changing the pH, polarity, ionic strength or counter ion exchange. The released protein is then identified by mass spectrometry.[164] To perform an affinity chromatography, the active compound has to first bind covalently to the immobilized bead (ie. biotin complex or sepharose) to form the solid support. A mixture of the biological proteins is then introduced into the column; where only the target protein will interact with the molecule of interest. The remaining unattached protein complexes can be eluted, followed by releasing of the target protein by changing pH,

ionic strength or ion exchange (Figure 38).
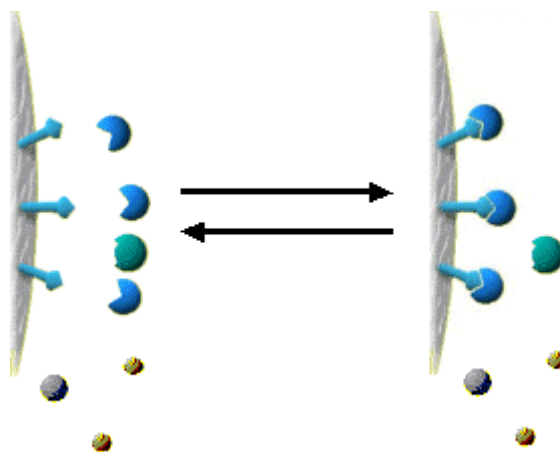
Figure 38 Affinity chromatography[164]

2.4.3.1   Preparation of candidate substrates for affinity matrix attachment

Through the testing of several PFP sulfonates and sulfonamides for activity against HIV, sulfonamide **139** is identified as the most promising candidate for the pull-down study. Together with **139**, the *o*-fluorinated analogue **142g** (Figure 39).
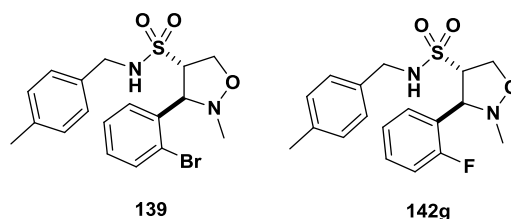
Figure 39 Candidate sulfonamides selected for affinity chromatography

Previous work by Mok attempted to link biotin onto the active compound *via* the sulfonamide moiety, however attempts were unsuccessful in identification of the target protein, and it was suspected that the sulfonamide moiety is crucial for interacting with the target protein, therefore it is not a suitable attachment position.[113] It was decided that the nitrogen atom on the isoxazolidine ring could potentially be another point of attachment. Therefore a novel strategy was proposed based on a hydroxyl group; which provides suitable attachment for the candidate substrates to an affinity matrix (Scheme 50).
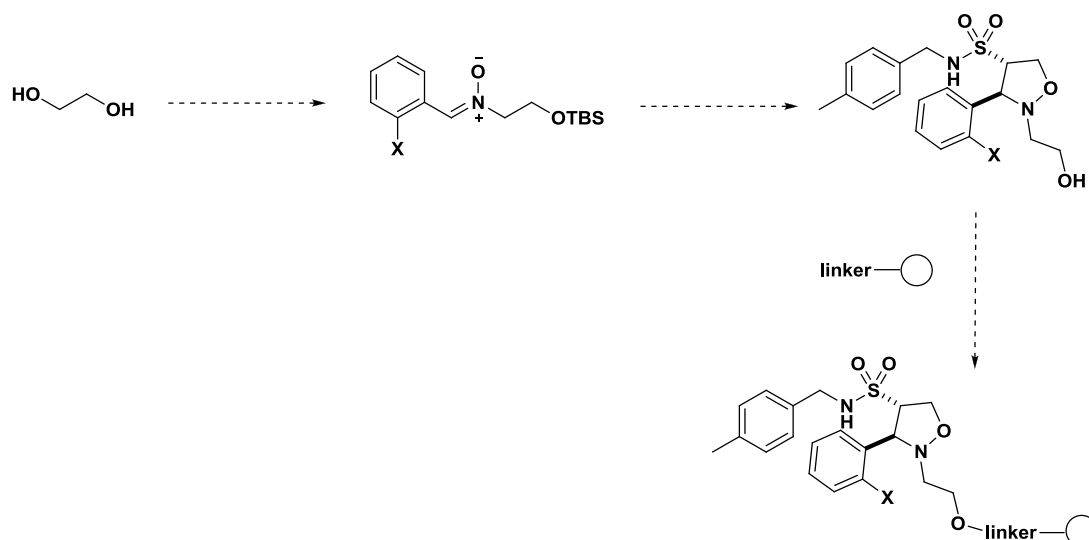
Scheme 50 Alternative route for attachment *via* nitrogen on isoxazolidine

Due to the previous attempt in affinity chromatography, where the loss of potency was associated with the attachment of biotin onto the sulfonamide moiety, it was also of interest to change the affinity matrix to epoxy-activated sepharose 6B. The advantage of using epoxy-activated sepharose is that it contains a 13-atom spacer which is able to link directly to the active compound for the affinity chromatography (Scheme 51); whereas biotin requires an additional protein-ligand interaction to the affinity matrix (avidin).
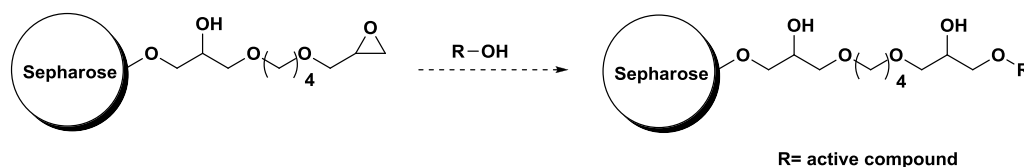
Scheme 51 Attachment of epoxy-activated sepharose 6B with an alcohol

The multi-step synthesis started from mono protection of ethylene glycol to give 72% of **144** (Scheme 52); Swern oxidation furnished aldehyde **145** in 53% yields. It then underwent condensation with hydroxylamine hydrochloride to produce a mixture of geometric isomers of oxime **146** in 91% yields. Subsequent reductive amination using NaBH$_3$CN furnished hydroxylamine **147** in 87% yields, which was followed by secondary condensation to furnish nitrone **148** in near quantitative yield. Cycloaddition between nitrone and PFP ethenesulfonate **110** gave the 3,4-anti isoxazolidine **149** as the sole product.

Subsequent aminolysis with 4-methylbenzylamine generated the syn and anti

diastereoisomers **150** and **151** in a 4:1 ratio. Repeated flash chromatography was required in order to separate the two diastereomers with some loss in yield, and the major product **150** (3,4-anti isoxazolidinyl sulfonamides) then underwent silyl deprotection using TBAF at 0 °C to produce alcohol **152** in 79% yield. This was then ready to couple to epoxy-activated sepharose 6B.
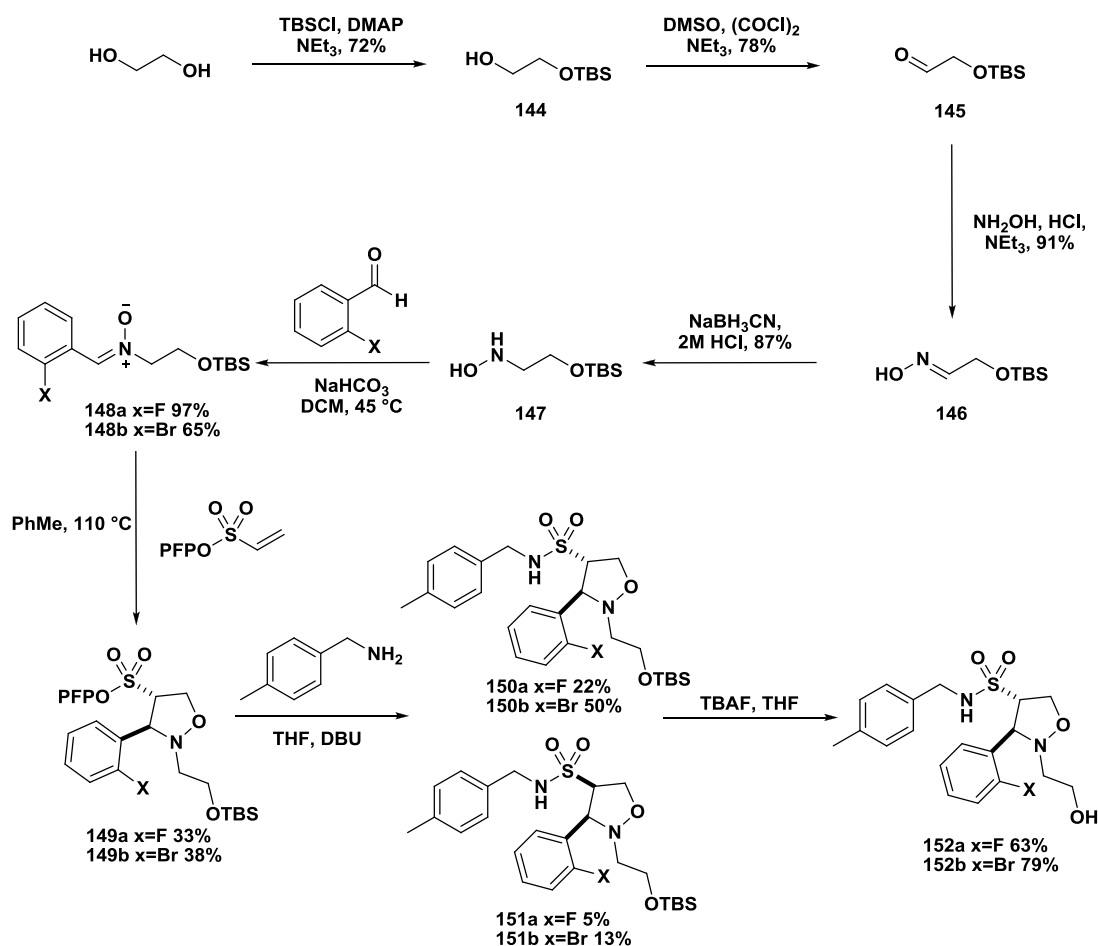
Scheme 52 Stepwise synthesis towards candidate substrate for affinity matrix

2.4.3.2   Preparation of the immobilized ligands for affinity chromatography

In order to successfully attach the alcohol **152** onto the epoxy-activated sepharose, an optimization of the reaction condition was required. However, because of the multi-step process required to synthesize the valuable candidate compounds, as well as the higher cost of the affinity matrix, a model substrate was selected for the optimization.

Due to the sensitivity of the epoxy-activated sepharose, the reaction conditions are limited due to the following factors:

• The affinity matrix may denature at elevated temperature, and

• The magnetic stirrer may disrupt the affinity matrix

Therefore in order to investigate the optimal reaction conditions it was envisaged that, the model substrates must react at room temperature (or below 40 °C) using a shaking water bath (Table 10).
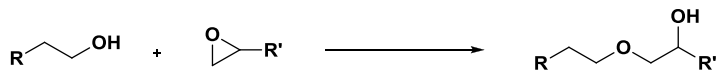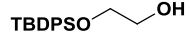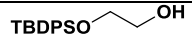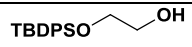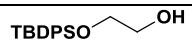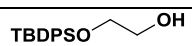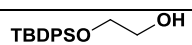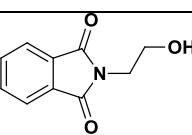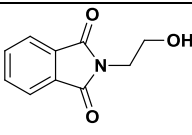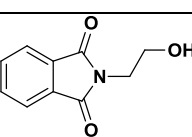
Entry	Alcohol	Epoxide	Reagent/ catalyst	Solvent/ Temperature	Time/ h	Yield
a	TBDPSO—OH	Ph 1 eq	TFA 0.01 eq	THF 25 °C	3	N/A
b	TBDPSO—OH	Ph 1 eq	TFA 0.01 eq	DCM 25 °C	3	N/A
c	TBDPSO—OH	Ph 10 eq	TFA 0.01 eq	THF 25 °C	3	N/A
d	TBDPSO—OH	Ph 10 eq	$SnCl_4$ 0.01 eq	DCM 25 °C	3	N/A
e	TBDPSO—OH	Ph 10 eq	Na_2CO_3	DMF 25 °C	16	N/A
f	TBDPSO—OH	Ph 10eq	Na_2CO_3	DMF/H_2O 25 °C	16	N/A
g	phthalimido—OH	Ph 10 eq	Na_2CO_3	$DMSO/H_2O$ 25 °C	16	N/A
h	phthalimido—OH	Epoxy-activated sepharose	Na_2CO_3	DMF 25 °C	16	N/A
i	phthalimido—OH	Epoxy-activated sepharose	Na_2CO_3	DMF/H_2O 25 °C	16	N/A

Table 10 Optimization for attaching candidate substrate onto the affinity matrix

Under the initial reaction conditions, TFA (and later $SnCl_4$) was chosen as the lewis acid; and the solvent and the amount of styrene oxide were varied (Table 10 entry a,

b, c and d). However, the NMR spectra indicated a mixture with no evidence of the desired product or starting material.

Fortunately, an appropriate coupling method had been developed by the sepharose distributor. This coupling method suggested a requirement for pre-washing of the affinity matrix prior to the coupling, and the dissolution of candidate ligand in buffer solution (up to 50% DMF/H$_2$O) at pH 9-10 (Table 10 entry e-i). The reaction must be shaken at room temperature for 16 hours before blocking the excess epoxy-activated sepharose with ethanolamine.[164] However, it became clear that monitoring the reaction was going to be problematic because of the inability to use NMR or MS for analysis of the resin bound products. We therefore abandoned this approach and re-assessed the possibility of using biotin and considered that past failures might be associated with the position of attachment and hence embarked upon a new approach in which the position of attachment was modified.

In order to form a stable (amide) bond between the candidate substrate and *D*-biotin, it was necessary to change the functional group on the candidate substrate from a hydroxyethyl to ethylamine group. This functional group transformation incorporated three simple steps: mesylation, azide addition and hygrogenation as it was carried out in succession.[165] The amine was now available to couple to *D*-biotin (Scheme 53).[113]
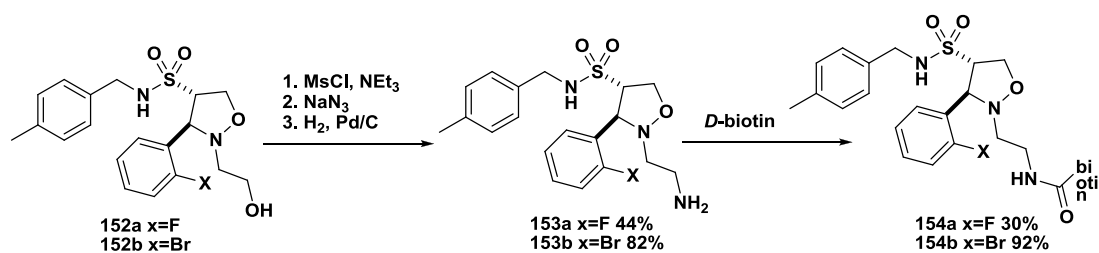
Scheme 53 Functional group modification and coupling of *D*-biotin

Upon coupling to the enantiomerically pure *D*-biotin we saw that the biotinylated 3,4-anti isoxazolidine **154** was a mixture of two diastereoisomers which could not be separated. They were sent off to our collaborator for pull-down study as a mixture.

2.4.4   Further biological evaluation of heterocyclic sulfonates and sulfonamides

2.4.4.1   Testing results of the compound efficacy

All biological testings were carried out by Fassati and coworkers, and from screening a collection of synthesized isoxazolidines, four of the active compounds **135**, **136,**

138 and **139** were selected for effect on healthy cells growth, cycle, viability and the effect on HIV life cycle (Figure 40).
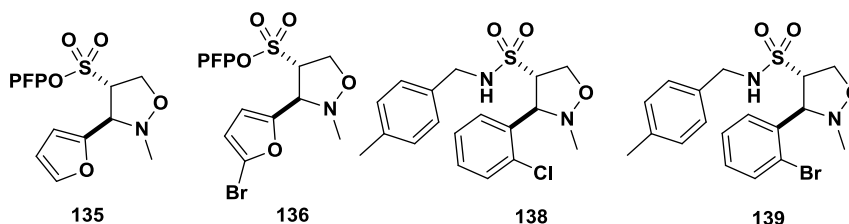
Figure 40 Structure of the lead compounds

Active compounds **135**, **136, 138** and **139** were also tested on HeLa cell (cervical cancer) and embryonic fibroblastic cell 293T. It was found that HIV activity was inhibited to varying degrees in different cell lines. In addition, healthy cells were incubated with the active compounds, and infected with Murine Leukaemia Virus (MLV, another retrovirus). It was found that the Murine Leukaemia Virus activity was also inhibited. Therefore suggesting that the active compounds **135**, **136, 138** and **139** may not act on the virus itself, but thay are probably acting on the host factors required for viral infection.[166]

2.4.4.2 Effect of active compounds on SupT1 cell growth

This experiment investigated the effect of the active compounds **135**, **136, 138** and **139** on SupT1 (healthy T cell) cell growth. Compounds were incubated with SupT1 cell for 48 hours at various concentrations and the amount of viable cells were counted every 24 hours (Figure 41 & Figure 42). It was observed that **138** and **139** do not significantly alter cell growth at 100-150 μM compare to the untreated healthy T-cells (in DMSO). However it was observed that both compounds **138** and **139** slow down cell growth at 200-300 μM concentration, and eventually leads to termination of cell growth at 48 hours. In addition, at 100-125 μM concentration of **135** and **136**, cell growth is intact compare to the untreated healthy T-cells. However, at higher concentration of **135** and **136** (400-500 μM), the viable cell count shows initial increase of cell growth up to 24 hours, but the cell growth slow down after 24 hours, and eventually leads to termination of cell growth at 48 hours. This suggested that the active compounds **135**, **136, 138** and **139** appear to show minimal alteration in cell growth at 100-150 μM concentration within 24 hour period compare to the healthy T-cells; however, termination of cell growth occurs at higher concentration or prolong exposure.[166]
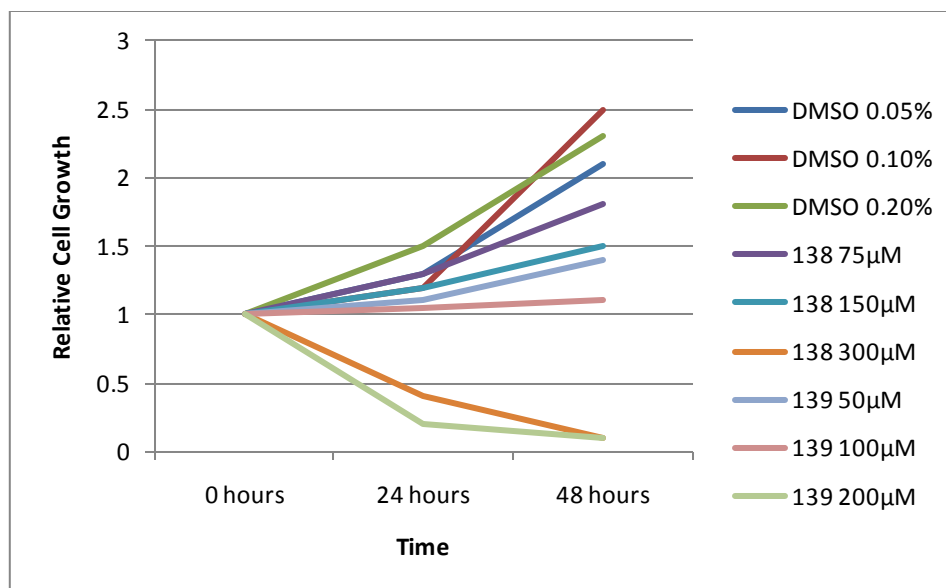
Figure 41 SupT1 growth rate upon exposure to sulfonamides
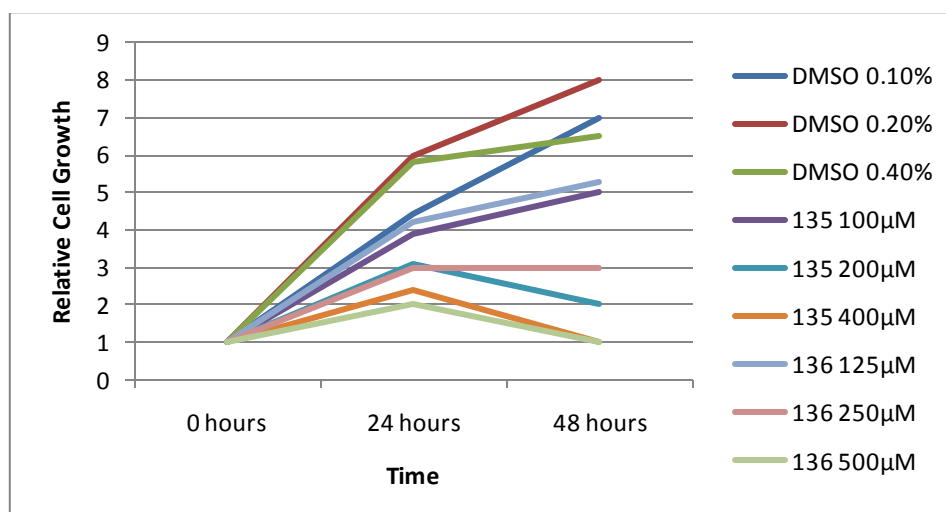
Figure 42 SupT1 growth rate upon exposure to PFP sulfonate esters

2.4.4.3 <u>Toxicity of active compounds on SupT1 cells</u>

SupT1 cells were incubated with the active compounds **135**, **136, 138** and **139** at IC_{90} and $IC_{90}/2$ concentration for 30 hours, and the ratio of live/dead cell was determined (Figure 43). Digitonin (a detergent that ensure cell death) was used as negative control to ensure cell arrest at 30 hours. It showed that **135**, **138** and **139** did not display cell toxicity unless at IC_{90} concentration, and surprisingly **136** did not show cell toxicity even at IC_{90} concentration.
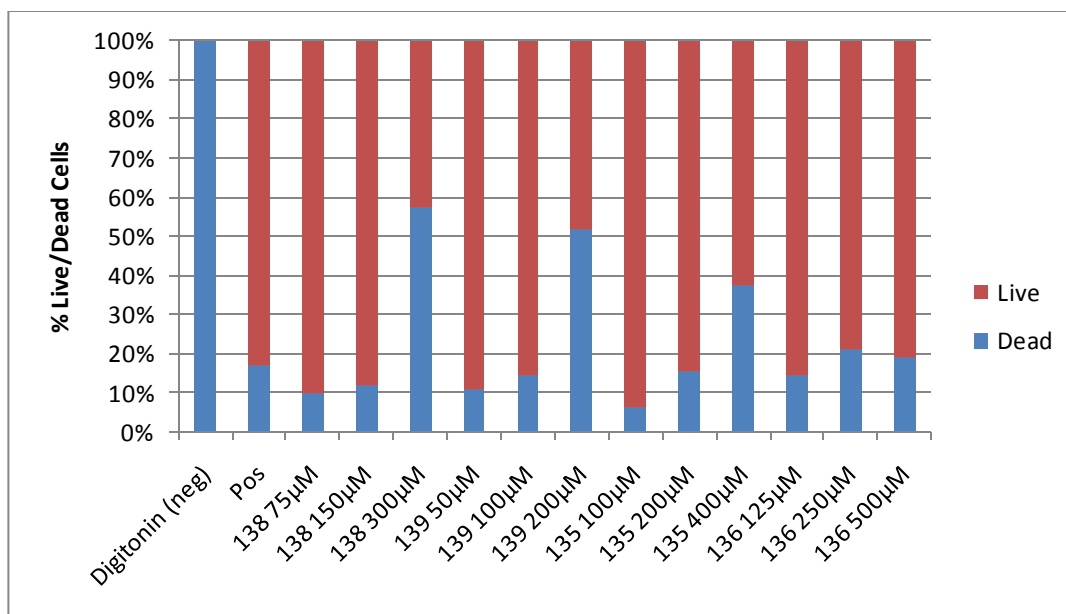
Figure 43 SupT1 cell toxicity upon exposure to PFP sulfonates and sulfonamides

2.4.4.4   Effect of active compounds on HeLa cell cycle

HeLa cell (an immortal cell line derived from cervical cancer. The purpose of choosing HeLa is due to its distinctive phase-transition in the cell cycle; which makes HeLa an ideal candidate for evaluation of cell cycle alteration) was exposed to the active compounds **135**, **136, 138** and **139** at IC_{90} concentration. Aphidicholine (DNA polymerase inhibitor) was used as positive control ensuring cell arrest at the G1 phase, and HeLa DNA was stained with propidium iodide at 30 hours to determine the percentage of each phases. From the graph it did not show any significant effect of the active compounds to the HeLa cell cycle. This indicated that the active compounds retain cell progression and are non-toxic (Figure 44).[166]
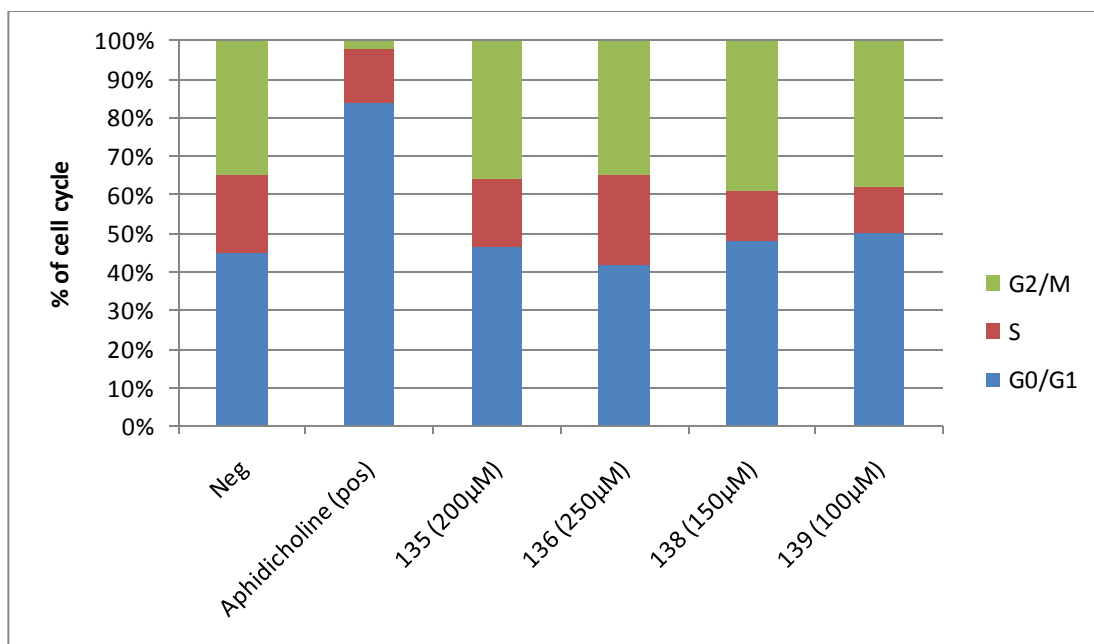
Figure 44 Effect of PFP sulfonate esters and sulfonamides on HeLa cell cycle

2.4.4.5   Compound effect on HIV life cycle

Compound inhibition of the HIV life cycle was also investigated. Distinctive stages such as cell entry, reverse transcription, nuclear import/export, integration, transcription, translation and budding were systematically considered. SupT1 cell line was incubated with the active compounds **135**, **136, 138** and **139**, and infected with pCSGW pseudoviral vector for 24 hours. Prior to the infection, the viral vector was encoded with green fluorescent protein (GFP), therefore as the viral life cycle progressed, GFP would be expressed. If the viral life cycle is blocked, GFP expression would be impaired. Therefore the amount of viral inhibition is determined by the amount of GFP expressed.[166]

In the initial experiment, one portion was infected with single cycle pseudoviral vector (viral vector unable to bud), and the other portion infected with wild type HIV-1. Both experiments show similar GFP expression (data not shown), and this suggests that the active compounds do not inhibit viral budding.

Effect of the active compounds on cell entry was also considered. CD4^{+} T-cells were incubated with the active compounds **135**, **136, 138** and **139**, and infected with pan-tropic HIV vector and wild type HIV-1 in parallel experiments. It was found that both experiments presented similar viral infection, where the pan-tropic viral vector (with

wider choice of cell entry) displays similar viral infection to the wild type HIV-1 infection. Therefore it suggested that cell entry is not the target for compound activity.[166]

In order to assess the ability of the active compounds to inhibit reverse transcription, viral DNA count was analysed by flow cytometry. However, the viral DNA count does not corresponds with the trend in reduced GFP expression at the presence of the active compounds. Therefore this indicated that the reverse transcription was not impaired by the active compounds **135**, **136, 138** and **139** (Figure 45).[166]
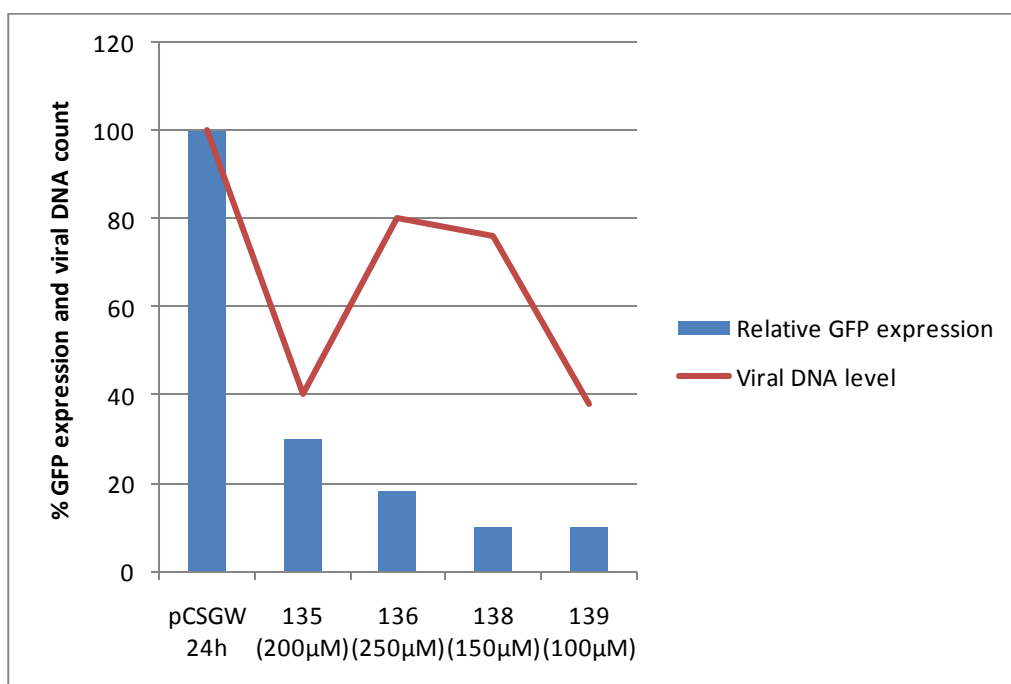
Figure 45 Percentage GFP expression and viral DNA count compare to the system where the healthy cells were infected with the viral vector pCSGW at the absence of active compounds.

When viral DNA is imported into the nucleus, viral DNA curls up in a circular arrangement; where the 3' LTR (Long Terminal Repeats, described in 2.3.1) is connected to the 5' LTR, called the 2LTRs. By counting the number of 2LTRs in relation to the total amount of viral DNA, the level of nuclear import can be determined. From the experiment of counting 2LTRs it was observed that the number of 2LTRs is not significantly reduced compare to the viral vector alone, suggesting that nuclear import is not greatly inhibited (Figure 46).[166]
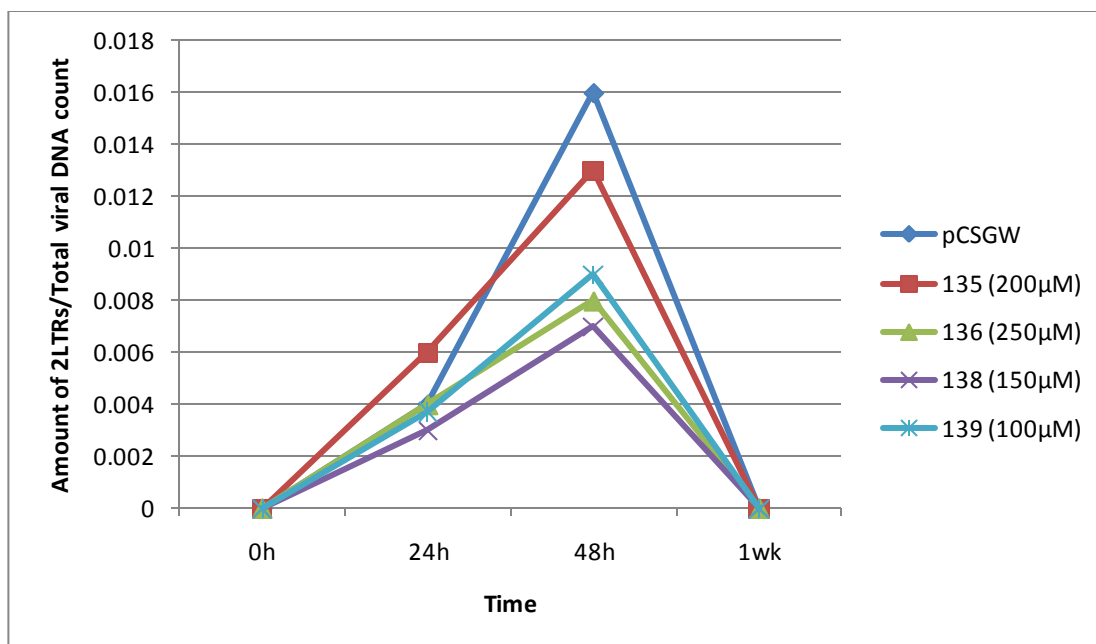
Figure 46 Amount of 2LTRs/total viral DNA count plotted against time. Comparing to the pCSGW viral vector, the active compounds do not impaired nuclear import

In order to determine whether the compounds block viral DNA integration, healthy cells were incubated with the active compounds **135**, **136, 138** and **139**, and infected with pCSGW vector for 1 week. The unintegrated DNA was gradually lost through dilution and degradation. On a parallel experiment, healthy cells were infected with pCSGW viral vector, and treated with an integrase inhibitor Raltegravir before Raltegravir could be washed out after 24 hours. Infected cells that were treated with Raltegravir had significantly reduced DNA count, whereas the system with active compounds **135**, **136, 138** and **139** shows minimal reduction in integrated DNA count, suggesting that compounds **135, 136, 138** and **139** do not block integration.[166]

In a separate experiment, cells were pre-treated with active compounds **135**, **136, 138** and **139**, and transfected with HIV-1 vector that has a deleted *env* gene and encoded GFP. Gene expression was measured by flow cytometry 24 hours later and it was found that GFP level was dramatically reduced, suggesting inhibition in transcription (Figure 47).[166]

An untreated SupT1 cells was transfected with pCSGW viral vector, and then the active compounds **135**, **136, 138** and **139** were introduced for 48 hours. Result shows no sign of reduction in viral mRNA count and viral protein level, suggesting that

viral mRNA nuclear export and translation were not affected (data not shown).[166]

Relative GFP expression
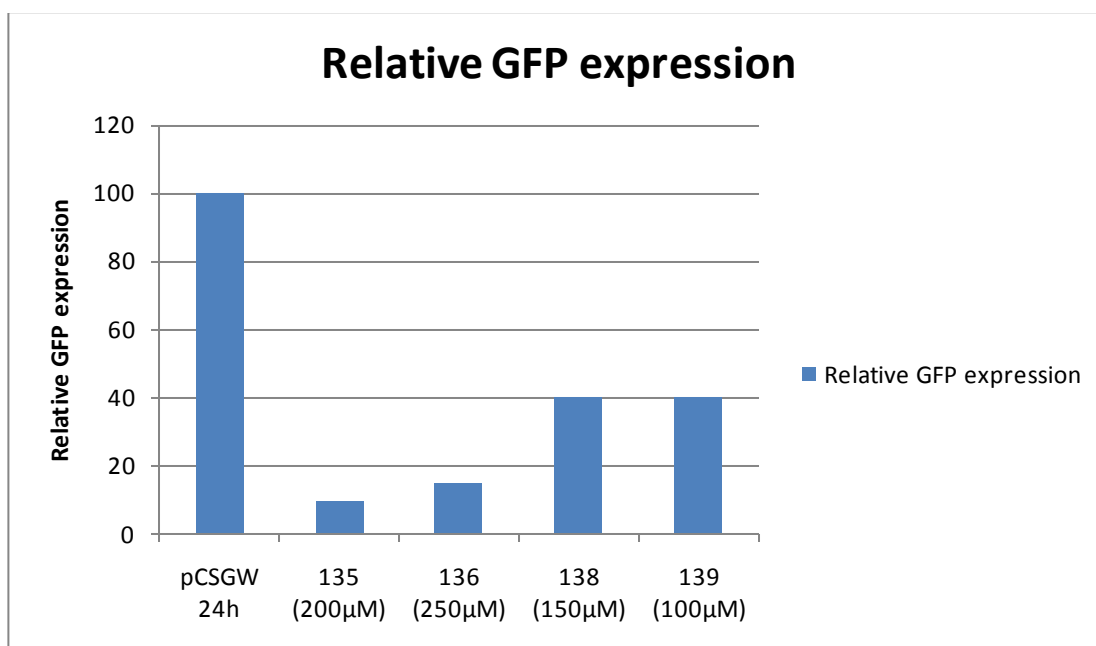
Figure 47 Relative GFP expression was plotted against infected SupT1 cells that are pre-treated with the active compounds **135, 136**, **138** and **139**

Based on the data presented above, it was suggested that nuclear import, integration, reverse transcription, cell entry and budding are mildly impaired. Viral gene expression/transcription on the other hand, was significantly impaired, indicating that the viral transcription is the most likely target for the candidate compounds.

3   Conclusion

In conclusion we have synthesized a library of isoxazolyl and isoxazolidinyl sulfonates and sulfonamides in a regio- and stereoselective fashion; which a selection of them were found to display anti-HIV activity, and demonstrated the general application of PFP sulfonates and sulfonamides as potential therapeutic agents.

Cycloaddition between PFP-1-bromoethenesulfonate **115** and nitrile oxides furnished a collection of isoxazoles in a regiospecific fashion, forming the the 3,5-substituted isoxazole PFP sulfonate esters as verified by NMR and x-ray crystallography. While all nitrile oxide cycloadditions proceed under mild conditions (2.5 eq NEt_3, Toluene, RT, 1 h), cycloadducts containing electron donating groups (*p*-OMePh, p-ClPh, *p*-BrPh, *o*-ClPh and *o*-BrPh) were obtained in higher yields than those containing electron withdrawing groups (*p*-NO$_2$Ph). It was also evident that the reaction proceeded *via* nitrile oxides rather than hydroximoyl chlorides, and the rate of the cycloaddition is directly influenced by the amount of NEt_3 used. Subsequent aminolysis were also proceeded smoothly under THF reflux and good yields were obtained; however, aminolysis using secondary amine and aromatic amine generated relatively poor yields, therefore tetrabutylammonium chloride (TBAC) was introduced to act as a nucleophilic catalyst, and reaction period was prolonged in order to obtain sulfonamides in moderate yields. Nontheless, diversity oriented synthesis of sulfonates and sulfonamides were achieved.

In the HIV study, a selection of isoxazolidinyl PFP sulfonate esters and sulfonamides display excellent anti HIV-1 activity at 100-250 μM concentration. In addition, healthy cell growth rate, cell viability and life cycle were also preserved, leading to a specific candidate for viral target. During SAR study, molecules containing 4-methylbenzylsulfonamide group and 2-halophenyl group appeared to exhibit the highest potency; where upon modification on the sulfonamides moiety for target identification, the anti-HIV activity was lost, therefore suggesting that the sulfonamide group is crucial in exhibiting anti-HIV activity. Later it was envisaged that tagging of an immobilized bead on the isoxazolidine nitrogen would provide a suitable alternative in target identification. Upon synthesis of the immobilized medium for target identification, epoxy-activated sepharose 6B posed a challenging

task; however this problem was resolved by incorporating *D*-biotin in place of epoxy-activated sepharose 6B, and target identification is currently being investigated.

If the target identification suggests that isoxazolidine nitrogen linkage remove anti-HIV activity, future work would entail linking the immobilized bead onto the 5-*C* position on the isoxazolidine ring. However, if the target enzyme/protein can be successfully identified, a suggestion for future work would be to study the binding mechanism of the target, and subsequent structure-modification of our molecules to enhance binding, in order to achieve higher potency.

4   Experimental

4.1   General experimental

All the reagents and solvents were used as received without further purification, unless otherwise stated. Reactions were carried out under argon and anhydrous solvents unless otherwise stated. Reactions were monitored by TLC on SIL G/UV$_{254}$ silica plates purchased from VWR, and were visualized under UV lamp operating at short and long wavelength ranges with alkaline potassium permanganate solution. Flash column chromatography was carried out with Kieselgel 60M 0.04/0.063 nm (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 were carried out in the CEM Discover™ system. Proton (^{1}H) NMR spectra were recorded at 300 MHz and 500 MHz on a Bruker AMX300 or Bruker AMX500 MHz spectrometer operating at ambient temperature using an internal deuterium lock and chemical shifts are reported in parts per million. Coupling constants are reported in Hertz (Hz). Carbon (^{13}C) NMR spectra were recorded at 75 MHz on a Bruker AMX300 and 125 MHz on a Bruker AMX500 MHz spectrometer and are reported in ppm using CDCl$_3$ as an internal standard. Carbon-fluorine (^{13}C-^{19}F) coupling is also observed and recorded at 282 MHz on a Bruker AMX300 MHz spectrometer; however it is not quoted for pentafluorophenyl group due to its complex plitting pattern. Mass spectra (EI, CI and FAB) were obtained from VG70-SE or a MAT 900 XP spectrometer. Infrared Spectra were recorded on a Shimadzu FTIR-8700 spectrophotometer using KBr disc or using a Perkin Elmer Spectrum 100 operating in ATR mode. Infrared spectra were run as thin film 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   Experimental procedure for Chapter 2.2

Preparation of pentafluoropenyl ethenesulfonate (110)[92, 113]
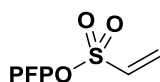
2-Chloroethane sulfonyl chloride **111** (10.1 g, 62.5 mmol) in dichloromethane (100 mL) was cooled to -78 °C. To the cooled solution was added a premixed solution of pentafluorophenol (11.5 g, 62.5 mmol) and NEt_3 (19.1 mL, 137 mmol, 2.2 eq.) in dichloromethane (20 mL) dropwise over 1 h. The reaction was allowed to warm to RT and diluted with dichloromethane (100 mL) and washed with water (100 mL), 2M HCl (100 mL) and saturate $NaHCO_3$ (2 x 100 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography (10% Et_2O/ petroleum ether) to give the title compound as a white solid (13.9 g, 50.6 mmol, 81%).

R_f 0.55 (10% Et_2O/ petroleum ether); **mp** 23-25 °C (lit.[113] **mp** 25 °C); v_{max} (thin film, cm^{-1}) 2963, 1650, 1625, 1340, 1158.; δ_H (CDCl$_3$, 300 MHz) 6.79 (1 H, dd, J = 16.4, 9.8 Hz, C*H*), 6.53 (1 H, dd, J = 16.5, 0.7 Hz, CH*H*trans), 6.34 (1 H, dd, J = 9.8, 0.7 Hz, C*H*Hcis); δ_C (CDCl$_3$, 75 MHz) 133.2 (t), 131.6 (d); **LRMS** (ES$^+$) 274 (M$^+$, 46), 184 (47), 136 (17), 91 (100).

Preparation of α-bromo pentafluoropenyl ethenesulfonate (115)[113]
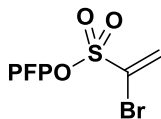
Bromine (6.15 mL, 120 mmol, 2 eq.) was dissolved in CHCl$_3$ (30 mL) and was added dropwise to the premixed solution of pentafluorophenyl ethenesulfonate **110** (16.4 g, 60.0 mmol) and AIBN (0.60 g) in chloroform (200 mL) at 70 °C. Additional AIBN was added after the addition of the bromine solution and reaction was refluxed for 4 h followed by 48 h stirring at RT. The solvent was removed *in vacuo* and the residue was dissolved in toluene (200 mL). A premixed solution of NEt_3 (6.06 g, 60.0 mmol) in toluene (30 mL) was added to the reation solution and stirred at RT for 3 h. The reaction mixture was washed with water and brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (10% Et_2O/petroleum ether) to give the title compound as a white solid (20 g, 57 mmol, 94%).

R_f 0.51 (20% Et_2O/petroleum ether); **mp** 37-39 °C (lit.[113] **mp** 37 °C); v_{max} (thin film, cm^{-1}) 3120, 3032, 1651, 1606, 1510, 1355, 1140; δ_H (CDCl$_3$, 300 MHz) 7.05 (1 H, d, J = 3.5 Hz, C*H$_2$*), 6.54 (1 H, d, J = 3.5 Hz, C*H$_2$*); δ_C (CDCl$_3$, 75 MHz) 133.7 (t), 121.7 (s); **LRMS** (CI$^+$) 355 (M$^+$, ^{81}Br, 91), 353 (M$^+$, ^{79}Br, 91), 352 (33), 184 (100),

155 (36); **HRMS** (CI$^+$) calcd for $C_8H_2BrF_5O_3S$ (M$^+$) 352.8906, observed 352.8902

4.2.1 Preparation of oximes

General Procedure 1

Aldehyde (50 mmol), Hydroxylamine.HCl (100 mmol) and NEt$_3$ (150 mmol) were mixed in dichloromethane (2.4 mL/mmol) and stirred at RT for 2 h. The mixture was added NaHCO$_3$ at 0 °C and was extracted with dichloromethane (50 mL). The organic layer was dried, filtered and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (10-20% EtOAc/ petroleum ether) and all products were isolated as a single diastereoisomers as judged by NMR unless otherwise stated.[124]

4-Methoxybenzoxime (117a)[113, 167]
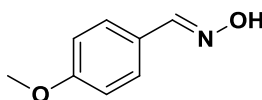
According to general procedure 1 to give the title compound as a white solid and as a 16:1 diastereo-mixture (6.1 g, 40 mmol, 80%).

R$_f$ 0.30 (20% EtOAc/petroleum ether); **mp** 66-67 °C (lit.[167] **mp** 64 °C); **ν$_{max}$** (thin film, cm^{-1}) 3072, 2922, 1608, 1516; **δ$_H$**(CDCl$_3$, 300 MHz) 8.93 (1 H, br s, O*H*), 8.11 (1 H, s, C*H*N) 7.53 (2 H, d, *J* = 9.5 Hz, Ar*H*), 6.89 (2 H, d, *J* = 9.5 Hz, Ar*H*), 3.82 (3 H, s, OC*H$_3$*); **δ$_C$** (CDCl$_3$, 75 MHz) 161.1 (s), 149.9 (d), 128.5 (d), 124.5 (s), 114.2 (d), 55.3 (q); **LRMS** (EI) 151 (M$^{+\bullet}$, 100), 108 (14); **HRMS** (EI) calcd for $C_8H_9NO_2$ (M$^{+\bullet}$) 151.0627, observed 151.0629

Benzoxime (117b)[168]
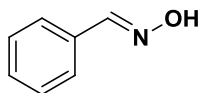
According to general procedure 1 to give the title compound as a white solid (3.9 g, 32 mmol, 66%).

R$_f$ 0.67 (20% EtOAc/petroleum ether); **mp** 34-35 °C(lit.[169] **mp** 35 °C); **ν$_{max}$** (thin film, cm^{-1}) 3242, 3062, 2983, 1630; **δ$_H$** (CDCl$_3$, 300 MHz) 9.14 (1 H, br s, O*H*), 8.11 (1 H, s, C*H*N), 7.60 (2 H, t, *J* = 6.4 Hz, Ar*H*), 7.39-7.41 (3 H, m, Ar*H*); **δ$_C$** (CDCl$_3$, 75 MHz) 150.4 (d), 131.9 (s), 130.1 (d), 128.8 (d), 127.1 (d); **LRMS** (EI) 121 (M$^{+\bullet}$,

100%), 103 (33), 94 (51); **HRMS** (EI) calcd for $C_7H_7NO(M^{+\bullet})$ 121.0522, observed 121.0518

4-Chlorobenzoxime (117c)[168]
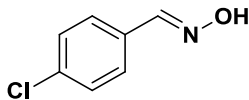
According to general procedure 1 to give the title compound as a white solid (6.8 g, 44 mmol, 87%).

R_f 0.53 (20% EtOAc/petroleum ether); **mp** 112-114 °C (lit.[170] **mp** 111 °C); ν_{max} (thin film, cm^{-1}) 3311, 3311, 2997, 1595; δ_H (CDCl$_3$, 300 MHz) 8.32 (1 H, br s, O*H*), 8.11 (1 H, s, C*H*N), 7.51 (2 H, d, J = 8.4 Hz, Ar*H*), 7.36 (2 H, d, J = 8.3 Hz, Ar*H*); δ_C (CDCl$_3$, 75 MHz) 149.3 (d), 135 9 (s), 130.4 (s), 129.1 (d), 128.2 (d); **LRMS** (EI) 157 (M$^{+\bullet}$, ^{37}Cl, 30), 155, (M+, ^{35}Cl, 100), 112 (75); **HRMS** (EI) calcd for C_7H_6ClNO (M$^{+\bullet}$) 155.0132, observed 155.0129

3-Chlorobenzoxime (117d)[171, 172]

According to general procedure 1 to give the title compound as a white solid and as a 21:1 diastereo-mixture (7.2 g, 46 mmol, 93%).

R_f 0.22 (10% EtOAc/petroleum ether); **mp** 69-71 °C (lit.[173] **mp** 72 °C); ν_{max} (thin film, cm^{-1}) 3558, 3319, 3053, 2985, 1598; δ_H (CDCl$_3$, 300 MHz) 8.29 (1 H, br s, O*H*), 8.10 (1 H, s, C*H*N), 7.59 (1 H, s, Ar*H*), 7.44 (1 H, d, J = 7.1 Hz, Ar*H*), 7.29-7.39 (2 H, m, Ar*H*); δ_C (CDCl$_3$, 75 MHz) 149.2 (d), 134.9 (s), 133.8 (s), 130.0 (d), 127.1 (d), 126.8 (d), 125.3 (d); **LRMS** (EI) 157 (M$^{+\bullet}$, ^{37}Cl, 28), 155 (M$^+$, ^{35}Cl, 100), 128 (39), 112 (32), 111 (29), 75 (38); **HRMS** (EI) calcd for C_7H_6ClNO (M$^{+\bullet}$) 155.0132, observed 155.0139

2-Chlorobenzoxime (117e)[172]

According to general procedure 1 to give the title compound as a white solid (6.8 g,

44 mmol, 87%).

R_f 0.53 (20% EtOAc/petroleum ether); **mp:** 74-75 °C (lit.[174] **mp** 75 °C); ν_{max} (thin film, cm^{-1}) 3562, 3319, 3053, 2985; δ_H(CDCl$_3$, 300 MHz) 8.75 (1 H, br s, O*H*), 8.51 (1 H, s, C*H*N), 7.80~7.83 (1 H, m, Ar*H*), 7.26~7.40 (3 H, m, Ar*H*); δ_C(CDCl$_3$, 75 MHz) 147.6 (d), 134.0 (s), 131.1 (d), 130.0 (s), 129.7 (d), 127.2 (d), 127.1 (d); **LRMS** (CI$^+$) 157 (M$^+$, ^{37}Cl, 37), 155 (M$^+$, ^{35}Cl, 100), 138 (50), 112 (31), 91 (28); **HRMS** (CI$^+$) calcd for C$_7$H$_6$ClNO(MH$^+$) 156.0216, observed 156.0210

4-Bromobenzoxime (117f)
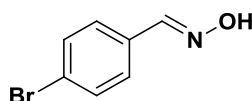
According to general procedure 1 to give the title compound as a white solid (9.6 g, 48 mmol, 96%).

R_f 0.64 (20% EtOAc/petroleum ether); **mp** 114-118 °C; ν_{max} (thin film, cm^{-1}) 3562, 3315, 3053, 2987, 1595; δ_H (CDCl$_3$, 300 MHz) 8.64 (1 H, br s, O*H*), 8.11 (1 H, s, C*H*N), 7.53 (2 H, d, J = 8.5 Hz, Ar*H*), 7.44 (2 H, d, J = 8.5 Hz, Ar*H*) ; δ_C (CDCl$_3$, 75 MHz) 149.4 (d), 132.1 (d), 130.8 (s), 128.5 (d), 124.3 (s); **LRMS** (EI) 201 (M$^{+\bullet}$, ^{81}Br, 98), 199 (M$^+$, ^{79}Br, 100), 156 (45), 102 (37), 75 (43); **HRMS** (EI) calcd for C$_7$H$_6$BrNO (M$^{+\bullet}$) 198.9627, observed 198.9622

3-Bromobenzoxime (117g)
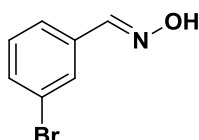
According to general procedure 1 to give the title compound as a white solid (8.6 g, 43 mmol, 86%).

R_f 0.24 (10% EtOAc/petroleum ether); **mp** 70-72 °C; ν_{max} (thin film, cm^{-1}) 3562, 3319, 3053, 2985; δ_H (CDCl$_3$, 300 MHz) 8.09 (1 H, s, C*H*N), 7.40 (1 H, s, Ar*H*), 7.50 (2 H, d, J = 7.9 Hz, Ar*H*), 7.26 (1 H, t, J = 7.9 Hz, Ar*H*); δ_C (CDCl$_3$, 75 MHz) 133.9 (s), 132.6 (d), 132.5 (d), 129.9 (d), 128.9 (d), 125.1 (d), 123.1 (s); **LRMS** (EI) 201 (M$^{+\bullet}$, ^{81}Br, 7), 199 (M$^{+\bullet}$, ^{79}Br, 7), 183 (46), 181 (44), 102 (50); **HRMS** (EI) calcd for C$_7$H$_6$BrNO (M$^{+\bullet}$) 198.9627, observed 198.9621

2-Bromobenzoxime (117h)
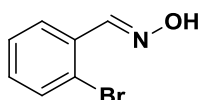
According to general procedure 1 to give the title compound as a white solid and as a 19:1 diastereo-mixture (9.4 g, 47 mmol, 95%).

R_f 0.14 (10% EtOAc/petroleum ether); **mp** 100-103 °C; ν_{max} (thin film, cm^{-1}) 3562, 3298, 3053, 2985; δ_H (CDCl$_3$, 300 MHz) 8.68 (1 H, br s, O*H*), 8.55 (1 H, s, C*H*N), 7.80 (1 H, dd, J = 7.7, 1.7 Hz, Ar*H*), 7.58 (1 H, dd, J = 7.7, 1.6 Hz, Ar*H*), 7.32 (1 H, t, J = 7.5 Hz, Ar*H*), 7.24 (1 H, td, J = 7.6, 1.6 Hz, Ar*H*); δ_C (CDCl$_3$, 75 MHz) 149.8 (d), 133.2 (d), 131.3 (d), 127.6 (d), 127.5 (s), 127.5 (d), 123.9 (s); **LRMS** (EI) 201 (M$^{+\bullet}$, ^{81}Br, 56), 199 (M$^{+\bullet}$, ^{79}Br, 58), 120 (100), 102 (60), 92 (26), 76 (36), 75 (42), 65 (42); **HRMS** (EI) calcd for C$_7$H$_6$BrNO (M$^{+\bullet}$) 198.9627, observed 198.9622

2-Fluorobenzoxime (117i)[175]
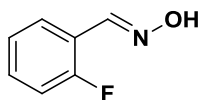
According to general procedure 1 to give the title compound as a white solid (5.9 g, 42 mmol, 86%).

R_f 0.15 (10% EtOAc/petroleum ether); **mp** 65-66 °C (lit.[176] **mp** 65 °C); ν_{max} (thin film, cm^{-1}) 3570, 3300, 3055, 1614; δ_H (CDCl$_3$, 300 MHz) 9.12 (1 H, br s, O*H*), 8.39 (1 H, s, C*H*N), 7.72-7.84 (1 H, m, Ar*H*), 7.37 (1 H, t, J = 7.4 Hz, Ar*H*), 7.16-7.25 (1 H, m, Ar*H*), 7.08 (1 H, d, J = 7.5 Hz, Ar*H*); δ_C (CDCl$_3$, 75 MHz) 160.8 (s, J_{CF} = 252.6 Hz), 144.4 (d, J_{CF} = 3.2 Hz), 131.6 (d, J_{CF} = 8.8 Hz), 127.3 (d), 124.5 (d, J_{CF} = 3.5 Hz), 119.8 (s, J_{CF} = 10.6 Hz), 116.1 (d, J_{CF} = 21.1 Hz); **LRMS** (EI) 139 (M$^{+\bullet}$, 25), 121 (100), 111 (30), 94 (72); **HRMS** (EI) calcd for C$_7$H$_6$FNO (M$^{+\bullet}$) 139.0428, observed 139.0430

4-Nitrobenzoxime (117j)
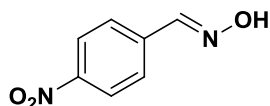
According to general procedure 1 to give the title compound as a yellow solid (7.6 g, 46 mmol, 91%).

R_f 0.26 (20% EtOAc/petroleum ether); **mp** 129-131 °C; ν_{max} (thin film, cm^{-1}) 3556,

3300, 3053, 2987, 1601, 1558, 1361; δ_H (CDCl$_3$, 300 MHz) 8.24 (2 H, d, J = 6.9 Hz, ArH), 8.20 (1 H, s, CHN), 7.90 (1 H, br s, OH), 7.75 (2 H, d, J = 6.9 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 149.4 (s), 148.0 (s), 140.9 (d), 128.4 (d), 124.8 (d); **LRMS** (EI) 166 (M$^{+\bullet}$, 35), 136 (100), 65 (35); **HRMS** (EI) calcd for C$_7$H$_6$N$_2$O$_3$ (M$^{+\bullet}$) 166.0372, observed 166.0376
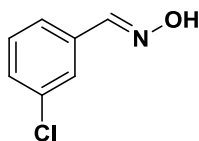
2-Naphthaloxime (17l)[177]
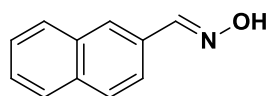
According to general procedure 1 to give the title compound as a white solid (7.9 g, 46 mmol, 92%).

R$_f$ 0.30 (20% EtOAc/petroleum ether); **mp** 152-154 °C (lit.[178] **mp** 154 °C); ν_{max} (thin film, cm^{-1}) 3265, 3053, 2929, 2854; δ_H (CDCl$_3$, 300 MHz) 8.30 (1 H, s, CHN), 7.89 (1 H, s, ArH), 7.62-7.80 (4 H, m, ArH), 7.52-7.59 (2 H, m, ArH); δ_C (CDCl$_3$, 75 MHz) 166.1 (s), 157.2 (d), 151.0 (s), 134.8 (s), 129.8 (d), 129.4 (d), 129.2 (d), 128.9 (d), 127.9 (d), 127.7 (d), 123.9 (d); **LRMS** (EI) 171 (M$^{+\bullet}$, 100), 153 (47), 144 (54), 128 (49), 127 (50), 115 (32); **HRMS** (EI) calcd for C$_{11}$H$_9$NO (M$^{+\bullet}$) 171.0678, observed 171.0680

2-Iodobenzoxime (117m)[174]
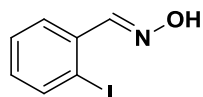
According to general procedure 1 to give the title compound as a cream solid (1.0 g, 4.2 mmol, 97%).

R$_f$ 0.23 (20% EtOAc/petroleum ether); **mp** 105-107 °C (lit.[176] **mp** 107 °C); ν_{max} (thin film, cm^{-1}) 3170, 2057, 2995; δ_H (CDCl$_3$, 300 MHz) 8.42 (1 H, s, CHN), 7.86 (1 H, dd, J = 8.0, 1.6 Hz, ArH), 7.75 (1 H, dd, J = 8.0, 1.3 Hz, ArH), 7.35 (1 H, t, J = 7.8 Hz, ArH), 7.07 (1H, td, J = 8.3, 1.6 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 154.0 (s), 139.8 (d), 134.3 (s), 131.4 (d), 128.4 (d), 127.4 (d), 98.8 (d); **LRMS** (EI) 247 (M$^{+\bullet}$, 95), 120 (100), 103 (90); **HRMS** (EI) calcd for C$_7$H$_6$INO (M$^{+\bullet}$) 246.9488, observed 246.9492

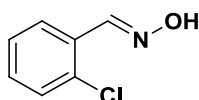## 2-Furoxime (117n)[179]
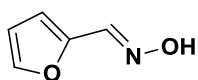
According to general procedure 1 to give the title compound as a white solid and as a 48:1 diastereo-mixture (2.6 g, 23 mmol, 46%).

R_f 0.17 (10% EtOAc/petroleum ether); **mp** 92-94 °C (lit.[180] **mp** 92 °C); ν_{max} (thin film, cm^{-1}) 3230, 2960, 2929, 2869; δ_H (CDCl$_3$, 300 MHz) 10.34 (1 H, s, O*H*), 7.44-7.61 (2 H, m, C*H*N & Furyl*H*), 7.30 (1 H, t, J = 3.1 Hz, Furyl*H*), 6.65 (1 H, m, Furyl*H*); δ_C (CDCl$_3$, 75 MHz) 145.1 (s), 143.5 (d), 137.0 (d), 118.2 (d), 112.3 (d); **LRMS** (CI) 112 (MH$^+$, 68), 94 (100); **HRMS** (CI) calcd for C$_5$H$_5$NO$_2$ (MH$^+$) 112.0398 observed 112.0397

Cyclohexanal oxime (117o)[181]
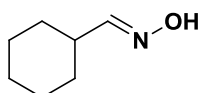
According to general procedure 1 to give the title compound as a white solid and as a 8:1 diastereo-mixture (4.4 g, 35 mmol, 70%).

R_f 0.54 (20% EtOAc/petroleum ether); **mp** 88-91 °C (lit.[181] **mp** 90 °C); ν_{max} (thin film, cm^{-1}) 3258, 3111, 1653; δ_H (CDCl$_3$, 300 MHz) 9.25 (1 H, br s, O*H*), 7.29 (1 H, d, J = 6.2 Hz, C*H*N), 2.18-2.25 (1 H, m, C*H*), 1.23-1.77 (10 H, m, C*H*$_2$); δ_C (CDCl$_3$, 75 MHz) 155.9 (d), 38.5 (d), 30.2 (t), 29.4 (t), 25.4 (t); **LRMS** (EI) 128 (MH$^{+\bullet}$, 26), 127(M$^+$, 100); **HRMS** (EI) calcd for C$_7$H$_{13}$NO (M$^{+\bullet}$) 127.0991, observed 127.0993

Pentoxime (117p)[182]

According to general procedure 1 to give the title compounds as a white solid and as a 1:1 diastereo-mixture (2.3 g, 23 mmol, 46%).

R_f 0.14 and 0.10 (10% EtOAc/petroleum ether); **mp** 49-52 °C (lit.[182] **mp** 51 °C); ν_{max} (thin film, cm^{-1}) 3249, 3055, 2960, 2864; δ_H (CDCl$_3$, 300 MHz) 10.12 (1 H, br s, O*H*), 9.81 (1 H, br s, O*H*), 7.34 (1 H, t, J = 6.2 Hz, C*H*N), 6.62 (1 H, t, J = 5.4 Hz, C*H*N), 2.30 (2 H, q, J = 5.4 Hz, NCC*H*$_2$), 2.14 (2 H, q, J = 6.2 Hz, NCC*H*$_2$), 1.31-1.40 (8 H, m, NCCC*H*$_2$C*H*$_2$), 0.85 (3 H, t, J = 7.2 Hz, C*H*$_3$), 0.84 (3 H, t, J = 7.2 Hz, C*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 152.6 (d), 152.1 (d), 29.0 (t), 28.6 (t), 28.1 (t), 24.6 (t), 22.6 (t), 22.4 (t), 13.6 (q) 13.5 (q); **LRMS** (EI) 102 (MH$^{+\bullet}$, 100), 97 (33), 84 (66), 69

(65); **HRMS** (EI) calcd for $C_5H_{11}NO$ (MH$^{+\bullet}$) 102.0918, observed 102.0918

4.2.2 Preparation of α-chloroaldoximes

General procedure 2

Oxime **117** (30 mmol) was dissolved in dry DMF (0.5 mL/mmol). A premixed solution of NCS (30 mmol) in dry DMF (15 mL) was added to the mixture at such a rate that the internal temperature did not rise above 40 °C. After the addition of NCS solution the reaction was stirred at RT for 1 h. The reaction mixture was added Et$_2$O (100 mL) and washed with water. The organic layer was dried with MgSO$_4$, filtered and solvent was removed i*n vacuo*. All products were collected as a single diastereoisomer as judged by NMR unless otherwise stated.[167]

α-Chloro-4-methoxybenzoxime (116a)[183]
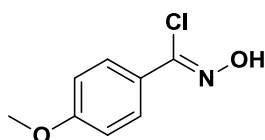
According to general procedure 2, **117a** gave the title compound as a yellow solid (5.2 g, 28 mmol, 94%).

R$_f$ 0.45 (10% Et$_2$O/petroleum ether); **mp** 82-84 °C (lit.[184] **mp** 86 °C); **ν$_{max}$** (thin film, cm^{-1}) 3541, 3330, 3053, 2985, 1606, 1510; **δ$_H$** (CDCl$_3$, 300 MHz) 8.71 (1 H, br s, O*H*), 7.78 (2 H, d, *J* = 8.9 Hz, Ar*H*), 6.91 (2 H, d, *J* = 8.9 Hz, Ar*H*), 3.84 (3 H, s, C*H$_3$*); **δ$_C$** (CDCl$_3$, 75 MHz) 161.6 (s), 140.1 (s), 128.7 (d), 124.9 (s) 113.9 (d), 55.5 (q); **LRMS** (CI$^+$) 188 (M$^+$, ^{37}Cl, 1), 186 (M$^+$, ^{35}Cl, 3), 152 (26), 150 (75), 134 (100); **HRMS** (CI$^+$) calcd for $C_8H_8ClNO_2$ (M$^+$) 186.0321, observed 186.0324

α-Chlorobenzoxime (116b)[182]

According to general procedure 2, **117b** gave the title compound as a white solid (4.5 g, 29 mmol, 98%).

R$_f$ 0.26 (10% Et$_2$O/petroleum ether); **mp** 46-49 °C (lit.[185] **mp** 45 °C); **ν$_{max}$** (thin film, cm^{-1}) 3533, 3330, 3055, 1610; **δ$_H$** (CDCl$_3$, 300 MHz) 8.99 (1 H, br s, O*H*), 7.82-7.85 (3 H, m, Ar*H*), 7.38-7.42 (2 H, m, Ar*H*); **δ$_C$** (CDCl$_3$, 75 MHz) 132.2 (d), 132.1 (s),

130.8 (d), 124.3 (d), 116.8 (d); **LRMS** (EI) 157 (M$^{+\bullet}$, ^{37}Cl, 6), 155 (M$^{+\bullet}$, ^{35}Cl, 19), 119 (72), 105 (100); **HRMS** (EI) calcd for C$_7$H$_6$ClNO (M$^{+\bullet}$) 155.0083, observed 155.0085

α-Chloro-4-chlorobenzoxime (116c)[186]
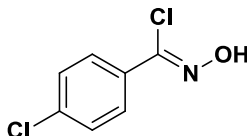
According to general procedure 2, **117c** gave the title compound as a white solid and as a 8:1 diastereo-mixture (5.5 g, 29 mmol, 96%).

R$_f$ 0.32 (10% Et$_2$O/petroleum ether); **mp** 87-89 °C (lit.[173] **mp** 85 °C); **ν$_{max}$** (thin film, cm^{-1}) 3533, 3319, 3053, 1595, 1490; **δ$_H$** (CDCl$_3$, 300 MHz) 8.48 (1 H, br s, OH), 7.77 (2 H, d, J = 8.8 Hz, ArH), 7.38 (2 H, d, J = 8.8 Hz, ArH); **δ$_C$** (CDCl$_3$, 75 MHz) 139.3 (s), 137.0 (s), 130.8 (s), 128.8 (d), 128.4 (d); **LRMS** (CI$^+$) 194 (M$^+$, ^{37}Cl^{37}Cl, 0.5), 192 (M$^+$, ^{37}Cl^{35}Cl, 2.5), 190 (M$^+$, ^{35}Cl^{35}Cl, 4), 154 (50), 156 (100), 138 (39); **HRMS** (CI$^+$) calcd for C$_7$H$_5$Cl$_2$NO (M$^+$) 189.9826, observed 189.9828

α-Chloro-3-chlorobenzoxime (116d)[187]
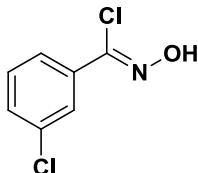
According to general procedure 2, **117d** gave the title compound as a white solid and as a 6:1 diastereo-mixture (5.6 g, 29 mmol, 98%).

R$_f$ 0.32 (10% Et$_2$O/petroleum ether); **mp** 69-70 °C (lit.[173] **mp** 69 °C); **ν$_{max}$** (thin film, cm^{-1}) 3533, 3332, 3053, 2985, 1598; **δ$_H$** (CDCl$_3$, 300 MHz) 8.65 (1 H, br s, OH), 7.83 (1 H, s, ArH), 7.73 (1 H, d, J = 7.5 Hz, ArH), 7.42 (1 H, d, J = 7.3 Hz, ArH), 7.34 (1 H, t, J = 7.2 Hz, ArH); **δ$_C$** (CDCl$_3$, 75 MHz) 138.7 (s), 134.6 s), 134.1 (s), 130.7 (d), 129.7 (d), 127.2 (d), 125.3 (d); **LRMS** (CI$^+$) 194 (M$^+$, ^{37}Cl^{37}Cl, 3), 192 (M$^+$, ^{37}Cl^{35}Cl, 14), 190 (M$^+$, ^{35}Cl^{35}Cl, 23), 155 (92), 154 (37), 139 (40), 137 (42), 125 (30), 123 (31), 111 (42); **HRMS** (CI$^+$) calcd for C$_7$H$_5$Cl$_2$NO (M$^+$) 189.9826, observed 189.9820

α-Chloro-2-chlorobenzoxime (116e)[187]
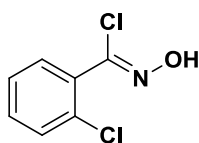
According to general procedure 2, **117e** gave the title compound as a yellow solid (5.5 g, 29 mmol, 96%).

R_f 0.25 (10% Et$_2$O/petroleum ether); **mp** 50-52 °C (lit.[188] **mp** 54 °C); ν_{max} (thin film, cm^{-1}) 3329, 3053, 2985, 1593; δ_H (CDCl$_3$, 300 MHz) 9.36 (1 H, br s, OH), 7.31-7.49 (4 H, m, ArH); δ_C (CDCl$_3$, 75 MHz) 137.2 (s), 133.7 (s), 133.1 (s), 131.5 (d), 131.1 (d), 130.3 (d), 126.9 (d); **LRMS** (CI$^+$) 194 (M$^+$, ^{37}Cl^{37}Cl, 5), 192 (M$^+$, ^{37}Cl^{35}Cl, 26), 190 (M$^+$, ^{35}Cl^{35}Cl, 42), 156 (100), 154 (92), 153 (62), 126 (52); **HRMS** (CI$^+$) calcd for C$_7$H$_5$Cl$_2$NO (M$^+$) 189.9826, observed 189.9820

α-Chloro-4-bromobenzoxime (116f)[189]
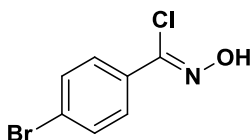
According to general procedure 2, **117f** gave the title compound as a white solid and as a 6:1 diastereo-mixture (6.5 g, 28 mmol, 93%).

R_f 0.29 (10% Et$_2$O/petroleum ether); **mp** 89-93 °C (lit.[190] **mp** 89 °C); ν_{max} (thin film, cm^{-1}) 3533, 3335, 3053, 1596; δ_H (CDCl$_3$, 300 MHz) 8.73 (1 H, br s, OH), 7.69 (2 H, d, J = 8.6 Hz, ArH), 7.53 (2 H, d, J = 8.6 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 139.6 (s), 131.8 (s), 131.2 (s), 132.1 (d), 128.6 (d); **LRMS** (CI$^+$) 236 (M$^+$, ^{81}Br^{37}Cl, 16), 234 (M$^+$, $^{81/79}$Br$^{37/35}$Cl, 22), 232 (M$^+$, ^{79}Br^{35}Cl, 5), 156 (100), 154 (92), 153 (62), 126 (52); **HRMS** (EI) calcd for C$_7$H$_5$BrClNO (M$^{+\bullet}$) 232.9237, observed 232.9234

α-Chloro-3-bromobenzoxime (116g)
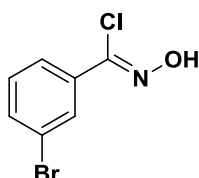
According to general procedure 2, **117g** gave the title compound as a white solid and as a 7:1 diastereo-mixture (6.9 g, 29 mmol, 98%).

R_f 0.38 (10% Et$_2$O/petroleum ether); **mp** 71-72 °C; ν_{max} (thin film, cm^{-1}) 3533, 3319,

3053, 2985, 1597; δ_H (CDCl$_3$, 300 MHz) 8.53 (1 H, br s, OH), 7.99 (1 H, s, ArH), 7.77 (1 H, dd, J = 7.9, 0.9 Hz, ArH), 7.57 (1 H, dd, J = 7.9, 1.0 Hz, ArH), 7.28 (1 H, t, J = 7.9 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 138.7 (s), 134.3 (s), 133.7 (d), 130.1 (d), 130.0 (d), 125.8 (d), 122.6 (s); **LRMS** (EI) 236 (M$^{+\bullet}$, ^{81}Br^{37}Cl, 36), 234 (M$^{+\bullet}$, $^{81/79}$Br$^{37/35}$Cl, 51), 232 (M$^{+\bullet}$, ^{79}Br^{35}Cl, 12), 102 (26), 90 (100); **HRMS** (EI) calcd for C$_7$H$_5$BrClNO (M$^{+\bullet}$) 232.9237, observed 232.9241

α-Chloro-2-bromobenzoxime (116h)
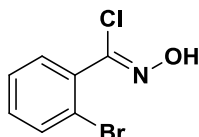
According to general procedure 2, **117h** gave the title compound as a yellow solid (6.5 g, 28 mmol, 92%).

R$_f$ 0.34 (10% Et$_2$O/petroleum ether); **mp** 66-68 °C; ν_{max} (thin film, cm^{-1}) 3286, 3058, 2977, 1589; δ_H (CDCl$_3$, 300 MHz) 9.82 (1 H, br s, OH), 7.60 (1 H, dd, J = 7.7, 1.4 Hz, ArH), 7.43 (1 H, d, J = 7.6 Hz, ArH), 7.33 (1 H, td, J = 7.6, 1.1 Hz, ArH), 7.25 (1 H, td, J= 7.5, 1.5 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 138.3 (s), 134.5 (s), 133.5 (d), 131.7 (d), 131.3 (d), 127.6 (d), 122.2 (s); **LRMS** (EI) 236 (M$^{+\bullet}$, ^{81}Br^{37}Cl, 3), 234 (M$^{+\bullet}$, $^{81/79}$Br$^{37/35}$Cl, 3), 232 (M$^{+\bullet}$, ^{79}Br^{35}Cl, 1), 199 (100), 197 (93), 102 (26), 90 (91), 88 (49); **HRMS** (EI) calcd for C$_7$H$_5$BrClNO (M$^{+\bullet}$) 232.9237, observed 232.9237
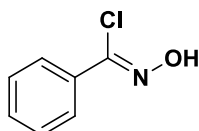
α-Chloro-2-fluorobenzoxime (116i)
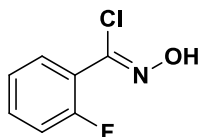
According to general procedure 2, **117i** gave the title compound as a white solid (5.1 g, 29 mmol, 98%).

R$_f$ 0.32 (10% Et$_2$O/petroleum ether); **mp** 98-100 °C; ν_{max} (thin film, cm^{-1}) 3531, 3330, 3055, 2987, 1616; δ_H (CDCl$_3$, 300 MHz) 9.22 (1 H, br s, OH), 7.69 (1 H, td, J = 7.6, 1.8 Hz, ArH), 7.44 (1 H, dddd, J = 7.6, 7.4, 5.0 (F), 1.8 Hz, ArH), 7.23 (1 H, td, J = 7.6, 1.2 Hz, ArH), 7.16 (1 H, ddd, J = 11.0 (F), 7.6, 1.2 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 159.9 (s, J_{CF} = 255.6 Hz), 135.4 (s, J_{CF} = 5.6 Hz), 132.2 (d, J_{CF} = 8.5 Hz), 130.8 (s), 124.3 (d, J_{CF} = 3.8 Hz), 120.9 (d, J_{CF} = 10.3 Hz), 116.6 (d, J_{CF} = 22.1 Hz); **LRMS** (FAB$^+$) 174 (M$^+$, 37), 154 (100); **HRMS** (FAB$^+$) calcd for C$_7$H$_5$FClNO (M$^+$) 174.0122, observed 174.0118

**α-Chloro-4-nitrobenzoxime (116j)**
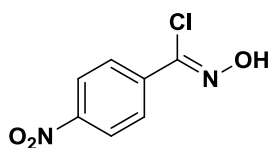
According to general procedure 2, **117j** gave the title compound as a yellow solid (5.1 g, 25 mmol, 87%).

R_f 0.02 (10% Et_2O/petroleum ether); **mp** 126-129 °C; ν_{max} (thin film, cm^{-1}) 3386, 2987, 1593, 1360; δ_{Hv}(CDCl$_3$, 300 MHz) 8.27 (2 H, d, J = 7.2 Hz, ArH), 8.05 (2 H, d, J = 7.2 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 138.7 (s), 132.2 (s), 131.8 (s) 128.0 (d), 123.6 (d); **LRMS** (EI) 202 (M$^{+\bullet}$, ^{37}Cl, 25), 200 (M$^{+\bullet}$, ^{35}Cl, 83), 166 (85), 164 (100); **HRMS** (EI) calcd for C$_7$H$_5$N$_2$O$_3$(M$^{+\bullet}$) 199.9983, observed 199.9977

α-Chloronaphthyloxime (116l)[186]
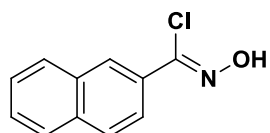
According to general procedure 2, **117l** gave the title compound as a white solid (4.3 g, 21 mmol, 99%).

R_f 0.25 (10% Et_2O/petroleum ether); **mp** 113-115 °C (lit.[191] **mp** 127 °C); ν_{max} (thin film, cm^{-1}) 3480, 3332, 3053, 2987, 1603; δ_H (CDCl$_3$, 300 MHz) 8.93 (1 H, br s, OH), 8.34 (1 H, s, ArH), 7.94 (2 H, d, J = 8.6 Hz, ArH), 7.83 (2 H, d, J = 3.6 Hz, ArH), 7.55 (2 H, t, J = 8.6 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 151.1 (s), 140.7 (s), 134.3 (s), 132.7 (s), 128.9 (d), 128.3 (d), 128.2 (d), 127.9 (d), 127.7 (d), 126.8 (d), 123.3 (d); **LRMS** (EI) 207 (M$^{+\bullet}$, ^{37}Cl, 4), 205 (M$^{+\bullet}$, ^{35}Cl, 12), 169 (73), 153 (66), 140 (100), 114 (33); **HRMS** (EI) calcd for C$_{11}$H$_8$ClNO (M$^{+\bullet}$) 205.0288, observed 205.2792

α-Chloro-2-iodobenzoxime (116m)
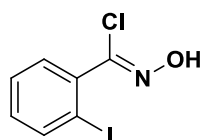
According to general procedure 2, **117m** gave the title compound as a yellow oil (0.60 g, 2.13 mmol, 99%).

R_f 0.32 (10% Et_2O/petroleum ether); ν_{max} (thin film, cm^{-1}) 3271, 3052, 2861; δ_H (CDCl$_3$, 300 MHz) 9.68 (1 H, br s, OH), 7.88 (1 H, d, J = 7.7 Hz, ArH), 7.34-7.43 (2

H, m, ArH), 7.08-7.19 (1 H, m, ArH); δ_C (CDCl$_3$, 75 MHz) 139.9 (d), 139.5 (s), 138.5 (s), 131.5 (d), 130.6 (d), 128.3 (d), 96.3 (s); **LRMS** (EI) 283 (M$^{+\bullet}$, ^{37}Cl, 5), 281 (M$^{+\bullet}$, ^{35}Cl, 22), 245 (100), 229 (21), 203 (28), 102 (53); **HRMS** (EI) calcd for C$_7$H$_5$ClNO (M$^{+\bullet}$) 280.9098, observed 280.9088

α-Chloro-cyclohexyloxime (116o)
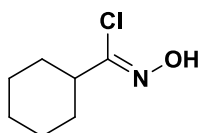
According to general procedure 2, **117o** gave the title compound as a yellow oil and as a 7:1 diastereo-mixture (1.9 g, 12 mmol, 94%).

R$_f$ 0.38 (10% Et$_2$O/petroleum ether); ν_{max} (thin film, cm^{-1}) 3331, 3053, 2937; δ_H (CDCl$_3$, 300 MHz) 9.48 (1 H, br s, OH), 2.38-2.46 (1 H, m, CH), 1.65-1.90 (5 H, m, CH_2), 1.06-1.41 (5 H, m, CH_2); δ_C (CDCl$_3$, 75 MHz) 146.6 (s), 45.3 (d), 30.2 (t), 30.6 (t), 25.7 (t), 25.6 (t), 25.3 (t); **LRMS** (CI$^+$) 250 (2M-2Cl, 100), 162 (M+H, 7), 151 (13), 144 (21), 126 (16)

α-Chloropentoxime (116p)
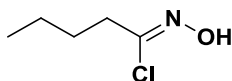
According to general procedure 2, **117p** gave the title compound as a yellow oil and as a 4:1 diastereo-mixture (0.91 g, 6.7 mmol, 89%).

R$_f$ 0.35 (10% Et$_2$O/petroleum ether); ν_{max} (thin film, cm^{-1}) 3332, 2962, 2935; δ_H (CDCl$_3$, 300 MHz) 9.06 (1 H, br s, OH), 2.50 (2 H, t, J = 7.2 Hz, ClCCH_2), 1.62 (2 H, quin, J = 7.2 Hz, ClCCCH_2), 1.32 (2 H, hex, J = 7.3 Hz, ClCCCCH_2), 0.90 (3 H, t, J = 7.2 Hz, CH_3); δ_C (CDCl$_3$, 75 MHz) 142.9 (s), 36.3 (t), 28.2 (t), 21.6 (t), 13.6 (q); **LRMS** (EI) 137 (M$^{+\bullet}$, ^{37}Cl, 6), 135 (M$^{+\bullet}$, ^{35}Cl, 21), 114 (22), 101 (100), 84 (91); **HRMS** (EI) calcd for C$_5$H$_{10}$ClNO (M$^{+\bullet}$) 135.0396, observed 135.0393

4.2.3 Preparation of nitrones

N-(^{t}Butyl)-C-phenylnitrone (113)
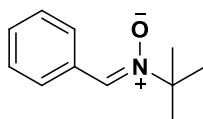
N-^{t}BuNHOH **112** (0.63 g, 5.0 mmol), benzaldehyde (0.53 g, 5.0 mmol) and NaHCO$_3$ (1.3 g, 15 mmol, 3 eq.) were mixed in dichloromethane (20 mL) and refluxed overnight. NaHCO$_3$ was filtered off by gravity and solvent was removed i*n vacuo*. The remaining solid was recrystallized from EtOAc and petroleum ether to give the title compound as a cream solid and as a single diastereoisomer as judged by NMR (0.39 g, 2.2 mmol, 44%).

ν$_{max}$ (thin film, cm^{-1}) 3049, 2978, 2937, 1577; **mp** 127-129 °C; **δ$_H$** (CDCl$_3$, 300 MHz) 8.28 (2 H, d, J = 9.7 Hz, Ar*H*), 7.56 (1 H, s, C*H*), 7.38-7.44 (3 H, m, Ar*H*), 1.61 (9 H, s, C(C*H$_3$*)$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 131.2 (s), 130.1 (d), 129.6 (d), 128.8 (d), 128.4 (d), 34.2 (s), 28.3 (q); **LRMS** (CI$^+$) 178 (M+H, 100), 162 (4), 136 (1), 122 (75); **HRMS** (CI$^+$) calcd for C$_{11}$H$_{16}$NO (M+H) 178.1226, observed 178.1230

4.2.4   Preparation of isoxazolidines-4-PFP sulfonates

2-(^{t}Butyl)-3-phenylisoxazole-4-pentafluorophenyl sulfonate ester (114)
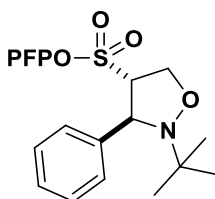
To a solution of pentafluorophenyl ethanesulfonate **110** (0.27 g, 1.0 mmol) in dry toluene (10 mL) was added N-(tert-butyl)-C-phenylnitrone **113** (0.35 g, 2.0 mmol, 2 eq.) and was refluxed overnight. The crude product was purified by flash chromatography (10% Et$_2$O/petroleum ether) to give title compound as a white solid and as a single diastereoisomer as judged by NMR (0.23 g, 0.50 mmol, 50%).

R$_f$ 0.55(10% Et$_2$O/petroleum ether); **mp** 101-104 °C; **ν$_{max}$** (thin film, cm^{-1}) 3057, 2977, 2935, 2871, 1517, 1367, 1140; **δ$_H$** (CDCl$_3$, 300 MHz) 7.54 (2 H, dd, J = 7.9, 1.2 Hz, Ar*H*), 7.29-7.32 (3 H, m, Ar*H*), 4.65 (1 H, d, J = 5.2 Hz, NC*H*), 4.57 (1 H, dd, J = 10.6, 1.8 Hz, SCHCH*H*), 4.40 (1H, dd, J = 10.6, 6.9 Hz, SCHC*H*H), 4.10-4.15 (1H, m, SC*H*), 1.06 (9 H, s, C(C*H$_3$*)$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 136.5 (s), 128.9 (d), 128.3 (d), 127.4 (d), 73.1 (d), 65.6 (t), 64.3 (d), 60.7 (s), 26.2 (q); **LRMS** (EI) 451 (M$^{+•}$, 18), 436 (20), 395 (100); **HRMS** (EI) calcd for C$_{19}$H$_{18}$F$_5$NO$_4$ (M$^{+•}$) 451.0871, observed 451.0866

4.2.5 Preparation of isoxazole-5- pentafluorophenyl sulfonate esters

General procedure 3

α-Chloroaldoxime **116** (7.2 mmol), α-bromo-pentafluorophenyl ethenesulfonate **115** (6 mmol) and NEt$_3$ (30 mmol) were mixed in toluene (6.9 mL/mmol) and stirred at RT for 1 h. The solvent was removed *in vacuo* and crude product was purified by flash chromatography (2-10% Et$_2$O/petroleum ether). Product was recrystallized from EtOAc/hexane and all products were collected as a single regioisomer as judged by NMR.

3-(4-Methoxyphenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118a)
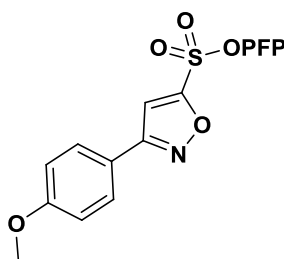
According to general procedure 3, **116a** gave the title compound as white crystals (0.09 g, 0.21 mmol, 92%).

R$_f$ 0.32 (10% Et$_2$O/petroleum ether); **mp** 133-135 °C; **ν$_{max}$** (thin film, cm^{-1}) 3055, 2987, 1612, 1309, 1130; **δ$_H$** (CDCl$_3$, 300 MHz) 7.76 (2 H, d, *J* = 8.9 Hz, Ar*H*), 7.32 (1 H, s, Isox*H*), 7.01 (2 H, d, *J* = 8.9 Hz, Ar*H*), 3.87 (3 H, s, OC*H$_3$*); **δ$_C$** (CDCl$_3$, 75 MHz) 162.6 (s), 162.1 (s), 160.3 (s), 118.8 (s), 128.5 (d), 114.7 (d), 109.4 (d), 55.5 (q); **δ$_F$** (CDCl$_3$, 282 MHz) -150.9 (Ar*F*), -153.6 (Ar*F*), -160.3 (Ar*F*); **LRMS** (EI) 421 (M$^{+\bullet}$, 81), 174 (51), 146 (100), 92 (39); **HRMS** (EI) calcd for C$_{16}$H$_8$F$_5$NO$_5$S (M$^{+\bullet}$) 420.9988, observed 420.9989; ***Anal*. calcd** C, 45.61, H, 1.91, N, 3.32, found: C, 45.49, H, 1.83, N, 3.12.

3-Phenyl isoxazole-5-pentafluorophenyl sulfonate ester (118b)
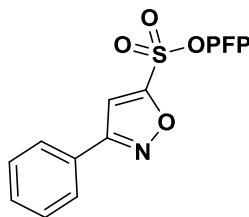
According to general procedure 3, **116b** gave the title compound as white crystals (1.9 g, 4.9 mmol, 86%).

$\mathbf{R_f}$ 0.26 (10% Et$_2$O/petroleum ether); **mp** 105-107 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3055, 1593, 1346, 1130; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.82 (1 H, s, Isox*H*), 7.38-7.53 (5 H, m, Ar*H*); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 163.1 (s), 160.7 (s), 129.0 (s), 131.0 (d), 128.9 (d), 126.6 (d), 109.6 (d); $\mathbf{\delta_F}$ (CDCl$_3$, 282 MHz) -151.0 (Ar*F*), -153.6 (Ar*F*), -160.2 (Ar*F*); **LRMS** (EI) 391 (M$^{+\bullet}$, 40), 238 (31), 178 (100); **HRMS** (EI) calcd for C$_{15}$H$_6$F$_5$NO$_4$S (M$^{+\bullet}$) 390.9932, observed 390.9934

3-(4-Chlorophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118c)
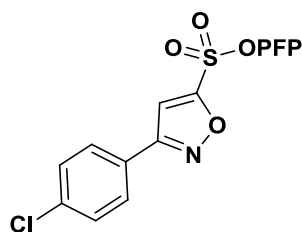
According to general procedure 3, **116c** gave the title compound as white crystals (2.2 g, 5.1 mmol, 88%).

$\mathbf{R_f}$ 0.32 (10% Et$_2$O/petroleum ether); **mp** 106-107 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3055, 1519, 1327, 1149; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.78 (2 H, d, J = 8.5 Hz, Ar*H*), 7.51 (2 H, d, J = 8.5 Hz, Ar*H*), 7.37 (1 H, s, Isox*H*); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 162.1 (s), 161.4 (s), 137.8 (s), 129.7 (d), 128.3 (d), 124.9 (s), 109.3 (d); $\mathbf{\delta_F}$ (CDCl$_3$, 282 MHz) -150.9 (Ar*F*), -153.4 (Ar*F*), -160.0 (Ar*F*); **LRMS** (EI) 427 (M$^{+\bullet}$, ^{37}Cl, 30), 425 (M$^{+\bullet}$, ^{35}Cl, 89), 242 (67), 150 (100), 111 (53); **HRMS** (EI) calcd for C$_{15}$H$_5$ClF$_5$NO$_4$S (M$^{+\bullet}$) 424.9493, observed 424.9483

3-(3-Chlorophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118d)
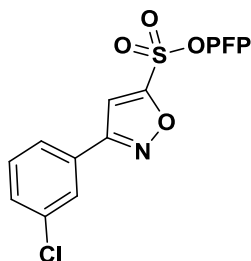
According to general procedure 3, **116d** gave the title compound as white crystals (1.3 g, 3.9 mmol, 75%).

$\mathbf{R_f}$ 0.3 (10% Et$_2$O/petroleum ether); **mp** 93-95 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3055, 1525, 1324, 1136; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.85 (1 H, s, Ar*H*), 7.72 (1 H, dd, J = 7.3, 1.5 Hz, Ar*H*), 7.45-7.54 (2 H, m, Ar*H*), 7.36 (1 H, s, Isox*H*); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 135.5 (s),

131.5 (s), 130.7 (d), 130.5 (s), 128.1 (d) 127.1 (d), 125.1 (d), 124.3 (s), 109.4 (d); δ_F (CDCl$_3$, 282 MHz) -150.9 (ArF), -153.4 (ArF), -160.0 (ArF); **LRMS** (EI) 427 (M$^{+\bullet}$, ^{37}Cl, 33), 425 (M$^{+\bullet}$, ^{35}Cl, 100), 242 (16); **HRMS** (EI) calcd for C$_{15}$H$_5$ClF$_5$NO$_4$S (M$^{+\bullet}$) 424.9542, observed 424.9543

3-(2-Chlorophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118e)
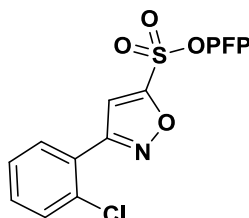
According to general procedure 3, **116e** gave the title compound as white crystals (2.1 g, 5.0 mmol, 87%).

R$_f$ 0.3 (10% Et$_2$O/petroleum ether); **mp** 89-90 °C; ν_{max} (thin film, cm^{-1}) 3055, 2985, 1596, 1317, 1132; δ_H (CDCl$_3$, 300 MHz) 7.79 (1 H, dd, J = 7.3, 1.8 Hz, ArH), 7.56 (1 H, s, Isox$H$), 7.40-7.54 (3 H, m, ArH); δ_C (CDCl$_3$, 75 MHz) 162.8 (s), 161.7 (s), 159.7 (s), 132.9 (s), 132.3 (d), 131.0 (d), 130.7 (d), 127.6 (d), 112.7 (d); δ_F (CDCl$_3$, 282 MHz) -151.0 (ArF), -153.5 (ArF), -160.1 (ArF); **LRMS** (EI) 427 (M$^{+\bullet}$, ^{37}Cl, 18), 425 (M$^{+\bullet}$, ^{35}Cl, 45), 242 (35), 178 (100), 155 (40), 150 (79); **HRMS** (EI) calcd for C$_{15}$H$_5$ClF$_5$NO$_4$S (M$^{+\bullet}$) 424.9542, observed 424.9546

3-(4-Bromophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118f)
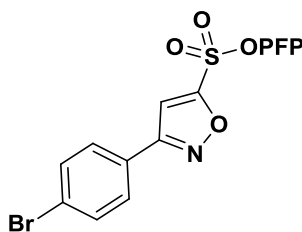
According to general procedure 3, **116f** gave the title compound as white crystals (2.5 g, 5.2 mmol, 87%).

R$_f$ 0.29 (10% Et$_2$O/petroleum ether); **mp** 110-113 °C; ν_{max} (thin film, cm^{-1}) 3055, 1596, 1519, 1340, 1139; δ_H (CDCl$_3$, 300 MHz) 7.72 (2 H, d, J = 8.6 Hz, ArH), 7.67 (2 H, d, J = 8.6 Hz, ArH), 7.37 (1 H, s, Isox$H$); δ_C (CDCl$_3$, 75 MHz) 162.2 (s), 161.0 (s), 132.7 (d), 128.4 (d), 126.1 (s), 125.4 (s), 109.3 (d); δ_F (CDCl$_3$, 282 MHz) -151.0 (ArF), -153.4 (ArF), -160.1 (ArF); **LRMS** (EI) 471 (M$^{+\bullet}$, ^{81}Br, 100), 469 (M$^{+\bullet}$, ^{79}Br, 96), 336 (22), 288 (30), 186 (26), 224 (32), 196 (86), 194 (96), 157 (42); **HRMS** (EI)

calcd for $C_{15}H_5BrF_5NO_4S$ ($M^{+\bullet}$) 468.8987, observed 468.8990

3-(3-Bromophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118g)
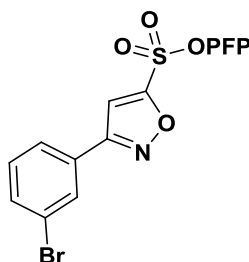
According to general procedure 3, **116g** gave the title compound as cream coloured crystals (1.6 g, 3.5 mmol, 69%).

R_f 0.18 (10% Et$_2$O/petroleum ether); **mp** 106-107 °C; ν_{max} (thin film, cm^{-1}) 3055, 2987, 1525, 1367, 1134; δ_H (CDCl$_3$, 300 MHz) 8.00 (1 H, s, Ar*H*), 7.78 (1 H, d, J = 7.7 Hz, Ar*H*), 7.68 (1 H, d, J = 7.7 Hz, Ar*H*), 7.41 (1 H, t, J = 7.7 Hz, Ar*H*), 7.38 (1 H, s, Isox*H*); δ_C (CDCl$_3$, 75 MHz) 162.2 (s), 162 0 (s), 153. (s), 130.8 (s), 134.4 (d), 130.9 (d), 130.0 (d), 125.6 (d), 109.3 (d); δ_F (CDCl$_3$, 282 MHz) -151.0 (Ar*F*), -153.4 (Ar*F*), -160.1 (Ar*F*); **LRMS** (EI) 471 (M$^{+\bullet}$, ^{81}Br, 70), 469 (M$^{+\bullet}$, ^{79}Br, 67), 288 (62), 286 (61), 224 (63), 222 (64), 196 (42), 194 (44), 157 (62), 155 (100), 102 (35), 76 (55), 75 (53); **HRMS** (EI) calcd for $C_{15}H_5BrF_5NO_4S$ (M$^{+\bullet}$) 468.9037, observed 468.9025

3-(2-Bromophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118h)
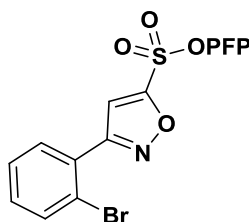
According to general procedure 3, **116h** gave the title compound as white crystals (2.1 g, 4.5 mmol, 86%).

R_f 0.25 (10% Et$_2$O/petroleum ether); **mp** 100-102 °C; ν_{max} (thin film, cm^{-1}) 3055, 2985, 1519, 1199; δ_H (CDCl$_3$, 300 MHz) 7.68-7.75 (2 H, m, Ar*H*), 7.53 (1 H, s, Isox*H*), 7.40-7.48 (2 H, m, Ar*H*); δ_C (CDCl$_3$, 75 MHz) 163.1 (s), 159.6 (s), 133.9 (d), 132.3 (d), 131.4 (d), 128.1 (d), 127.8 (s), 122.2 (s), 112.9 (d); δ_F (CDCl$_3$, 282 MHz) -150.9 (Ar*F*), -153.4 (Ar*F*), -160.1 (Ar*F*) ; **LRMS** (EI) 471 (M$^{+\bullet}$, ^{81}Br, 9), 469 (M$^{+\bullet}$, ^{79}Br, 8), 288 (7), 286 (7), 222 (15), 220 (17), 196 (24), 194 (27), 155 (25), 115 (100),

88 (75); **HRMS** (EI) calcd for $C_{15}H_5BrF_5NO_4S$ ($M^{+\bullet}$) 468.8987, observed 468.8982

3-(2-Fluorophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118i)
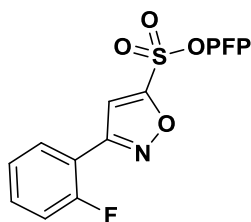
According to general procedure 3, **116i** gave the title compound as white crystals (1.6 g, 4.0 mmol, 68%).

Rf 0.30 (10% Et$_2$O/petroleum ether); **mp** 76-77 °C; **v$_{max}$** (thin film, cm^{-1}) 3055, 2987, 1519, 1360, 1197; **δ$_H$** (CDCl$_3$, 300 MHz) 8.05 (1 H, td, J = 7.6, 1.7 Hz, ArH), 7.54 (1 H, s, Isox$H$), 7.51-7.58 (1 H, m, ArH), 7.23-7.34 (2 H, m, ArH); **δ$_C$** (CDCl$_3$, 75 MHz) 161.4 (s), 159.6 (s, J_{CF} = 259.1 Hz), 159.4 (s), 133.4 (s, J_{CF} = 8.6 Hz), 129.0 (d), 125.1 (d, J_{CF} = 3.8 Hz), 116.7 (d, J_{CF} = 22.1 Hz), 114.8 (s, J_{CF} = 11.5 Hz), 112.0 (d, J_{CF} = 11.5 Hz); **δ$_F$** (CDCl$_3$, 282 MHz) -114.4 (ArF), -150.9 (ArF), -153.6 (ArF), -160.3 (ArF); **LRMS** (EI) 409 ($M^{+\bullet}$, 100), 226 (45), 162 (35), 134 (45), 107 (19); **HRMS** (EI) calcd for $C_{15}H_5F_6NO_4S$ ($M^{+\bullet}$) 408.9788, observed 408.9781

3-(4-Nitrophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118j)
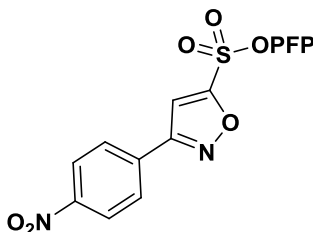
According to general procedure 3, **116j** gave the title compound as a cream solid (1.1 g, 3.6 mmol, 50%).

Rf 0.2 (20% Et$_2$O/petroleum ether); **mp** 126-128 °C; **v$_{max}$** (thin film, cm^{-1}) 3131, 1567, 1516, 1341, 1198; **δ$_H$** (CDCl$_3$, 300 MHz) 8.40 (2 H, d, J = 8.7 Hz, ArH), 8.06 (2 H, d, J = 8.7 Hz, ArH), 7.48 (1 H, s, Isox$H$); **δ$_C$** (CDCl$_3$, 75 MHz) 162.1 (s), 161.3 (s), 132.1 (s), 129.8 (s), 128.1 (d), 124.6 (d), 109.4 (d); **δ$_F$** (CDCl$_3$, 282 MHz) -151.0 (ArF), -153.1 (ArF), -159.7 (ArF); **LRMS** (EI) 436 ($M^{+\bullet}$, 57), 253 (79), 189 (36), 143 (100); **HRMS** (EI) calcd for $C_{15}H_5F_5N_2O_3S$ ($M^{+\bullet}$) 435.9783, observed 435.9798

**3-naphthyl-isoxazole-5-pentafluorophenyl sulfonate ester (118k)**
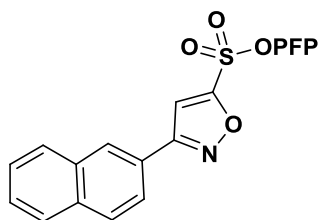
According to general procedure 3, **116k** gave the title compound as white crystals (2.1 g, 4.8 mmol, 80%).

R_f 0.25 (10% Et$_2$O/petroleum ether); **mp** 120-121 °C; ν_{max} (thin film, cm^{-1}) 3055, 2987, 1517, 1351, 1136; δ_H (CDCl$_3$, 300 MHz) 8.28 (1 H, s, ArH), 7.89-8.01 (4 H, m, ArH), 7.57-7.63 (2 H, m, ArH), 7.53 (1 H, s, Isox$H$); δ_C (CDCl$_3$, 75 MHz) 163.1 (s), 160.2 (s), 140.0 (d), 134.6 (s), 130.0 (s), 129.4 (d), 128.6 (d), 127.9 (d), 127.4 (d), 127.2 (d), 123.8 (s), 123.3 (d), 109.7 (d); δ_F (CDCl$_3$, 282 MHz) -150.9 (ArF), -153.6 (ArF), -160.2 (ArF); **LRMS** (EI) 441 (M$^{+\bullet}$, 17), 184 (100), 74 (45), 70 (44); **HRMS** (EI) calcd for C$_{19}$H$_8$F$_5$NO$_4$S (M$^{+\bullet}$) 441.0088, observed 441.0084

3-(2-Iodophenyl) isoxazole-5-pentafluorophenyl sulfonate ester (118l)
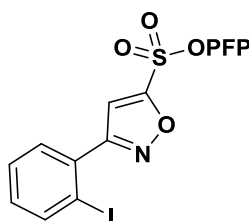
According to general procedure 3, **116l** gave the title compound as a cream solid (0.7 g, 1.4 mmol, 50%).

R_f 0.25 (10% Et$_2$O/petroleum ether); **mp** 109-110 °C; ν_{max} (thin film, cm^{-1}) 3177, 1515, 1321, 1156; δ_H (CDCl$_3$, 300 MHz) 8.01 (1 H, d, J = 7.5 Hz, ArH), 7.56 (1 H, dd, J = 7.7, 1.8 Hz, ArH), 7.50 (1 H, t, J = 7.6 Hz, ArH), 7.45 (1H, s, Isox$H$), 7.23 (1H, td, J = 7.7, 1.7 Hz, ArH); δ_C (CDCl$_3$, 75 MHz) 165.3 (s), 160.2 (s), 132.2 (s), 131.9 (s), 131.1 (d), 128.7 (d), 125.2 (d), 112.8 (d), 96.1 (d); δ_F (CDCl$_3$, 282 MHz) -150.9 (ArF), -153.6 (ArF), -160.2 (ArF); **LRMS** (EI) 517 (M$^{+\bullet}$, 68), 275 (95), 242 (100), 203 (37), 155 (27), 155 (64); **HRMS** (EI) calcd for C$_{15}$H$_5$IF$_5$NO$_4$S (M$^{+\bullet}$) 516.8850, observed 516.8856

4.2.6 Preparation of isoxazole-5-sulfonic-acid-4-methylbenzene- sulfonamide

General procedure 4

To a stirred solution of the isoxazole-5-pentafluorophenyl sulfonate esters **118** (0.5 mmol) in dry THF (12 mL/mmol) was added 4-methylbenzylamine (1.5 mmol) followed by NEt$_3$ (0.75 mmol). The reaction was refluxed for 0.5-1 h and the mixture was diluted with dichloromethane (20 mL), washed with 2M HCl (20 mL), saturated NaHCO$_3$ (20 mL) and water (20 mL). The organic layer was dried over MgSO$_4$, filtered, and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (20% Et$_2$O/petroleum ether) and all products were collected as a single regioisomer as judged by NMR.

3-(4-Methoxyphenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119a)
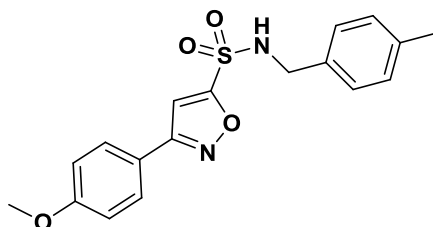
According to general procedure 4, **118a** gave the title compound as a white solid (78 mg, 0.22 mmol, 71%).

R$_f$ 0.09 (20% Et$_2$O/petroleum ether); **mp** 135-137 °C; **ν$_{max}$** (thin film, cm^{-1}) 3369, 3055, 2985, 1612, 1346, 1170; **δ$_H$** (CDCl$_3$, 300 MHz) 7.70 (2 H, d, $J = 8.7$ Hz, ArH), 7.16 (2 H, d, $J = 8.1$ Hz, ArH), 7.10 (2 H, d, $J = 8.1$ Hz, ArH), 7.00 (2H, d, $J = 8.6$ Hz, ArH), 6.93 (1 H, s, Isox$H$), 5.19 (1 H, t, $J = 5.9$ Hz, NH), 4.33 (2 H, d, $J = 5.9$ Hz, NCH_2), 3.87 (3 H, s, OCH_3), 2.25 (3 H, s, CH_3); **δ$_C$** (CDCl$_3$, 75 MHz) 165.5 (s), 162.4 (s), 162.3 (s), 138.2 (s), 132.2 (s), 119.9 (s), 129.5 (d), 128.4 (d), 128.0 (d), 114.6 (d), 105.7 (d), 55.4 (q), 47.4 (t), 21.0 (q); **LRMS** (FAB$^+$) 359 (M+H, 15), 307 (27), 154 (100); **HRMS** (FAB$^+$) calcd for C$_{18}$H$_{19}$N$_2$O$_4$S (M+H) 359.1065, observed 359.1057; ***Anal*. calcd**: C, 60.32, H, 5.06, N, 7.82, found: C, 59.99, H, 5.20, N, 8.38.

3-Phenyl isoxazole-5-sulfonic acid-4-methylbenzylamide (119b)
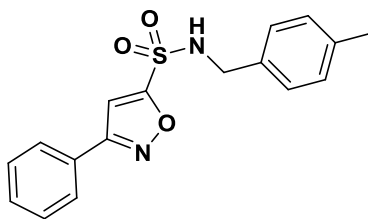
According to general procedure 4, **118b** gave the title compound as a white solid (0.18 g, 0.55 mmol, 95%).

R_f 0.06 (20% Et$_2$O/petroleum ether); **mp** 119-120 °C; ν_{max} (thin film, cm^{-1}) 3363, 3055, 2985, 1595, 1342, 1168; δ_H (CDCl$_3$, 300 MHz) 7.74-7.77 (2 H, m, Ar*H*), 7.47-7.50 (3 H, m, Ar*H*), 7.15 (2 H, d, *J* = 8.1 Hz, Ar*H*), 7.08 (2 H, d, *J* = 8.1 Hz, Ar*H*), 6.96 (1 H, s, Isox*H*), 5.33 (1 H, t, *J* = 5.8 Hz, N*H*), 4.34 (2 H, d, *J* = 5.8Hz, NC*H*$_2$), 2.23 (3 H, s, C*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 162.4 (s), 161.9 (s), 147.5 (s), 138.3 (s), 132.2 (s), 130.9 (d), 129.5 (d), 129.2 (d), 128.0 (d), 126.9 (d), 105.9 (d), 47.4 (t), 21.2 (q); **LRMS** (FAB$^+$) 329 (M+H, 100), 237 (8); **HRMS** (FAB$^+$) calcd for C$_{17}$H$_{16}$N$_2$O$_3$S (M+H) 329.0959, observed 329.0951

3-(4-Chlorophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119c)
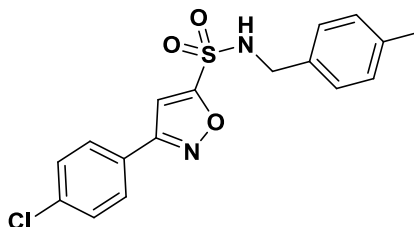
According to general procedure 4, **118c** gave the title compound as a white solid (0.16 g, 0.44 mmol, 83%).

R_f 0.10 (20% Et$_2$O/petroleum ether); **mp** 153-155 °C; ν_{max} (thin film, cm^{-1}) 3375, 3053, 2985, 1170; δ_H (CDCl$_3$, 300 MHz) 7.70 (2 H, d, *J* = 8.6 Hz, Ar*H*), 7.47 (2 H, d, *J* = 8.6 Hz, Ar*H*), 7.15 (2 H, d, *J* = 8.1 Hz, Ar*H*), 7.09 (2 H, d, *J* = 8.1 Hz, Ar*H*), 6.93 (1 H, s, Isox*H*), 5.27 (1 H, t, *J* = 5.9 Hz, N*H*), 4.34 (2 H, d, *J* = 5.9 Hz, NC*H*$_2$, 2.24 (3 H, s, C*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 166.8 (s), 161.5 (s), 138.2 (s), 137.1 (s), 132.1 (s), 129.5 (d), 129.5 (d), 128.2 (d), 128.0 (d), 125.8 (s), 105.3 (d), 47.5 (t), 21.0 (q); **LRMS** (FAB$^+$) 365 (M$^+$, ^{37}Cl, 6), 363 (M$^+$, ^{35}Cl, 18), 289 (10), 220 (6), 154 (100); **HRMS** (FAB$^+$) calcd for C$_{17}$H$_{15}$ClN$_2$O$_3$S (M$^+$) 363.0570, observed 363.0579

3-(3-Chlorophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119d)
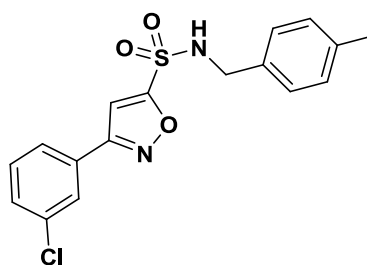
According to general procedure 4, **118d** gave the title compound as a white solid (0.11 g, 0.31 mmol, 72%).

R_f 0.08 (20% Et$_2$O/petroleum ether); **mp** 101-104 °C; ν_{max} (thin film, cm^{-1}) 3363, 3055, 2985, 1575, 1172; δ_H (CDCl$_3$, 300 MHz) 7.74 (1 H, s, ArH), 7.62 (1 H, d, J = 6.7 Hz, ArH), 7.46 (1 H, t, J = 6.7 Hz, ArH), 7.41 (1 H, d, J = 6.9 Hz, ArH), 7.14 (2 H, d, J = 7.0 Hz, ArH), 7.08 (2 H, d, J = 7.0 Hz, ArH), 6.91 (1 H, s, Isox$H$), 5.43 (1 H, br s, NH), 4.34 (2 H, s, NCH_2), 2.22 (3 H, s, CH_3); δ_C (CDCl$_3$, 75 MHz) 166.9 (s), 161.4 (s), 138.5 (s), 135.2 (s), 132.1 (s), 130.9 (d), 130.5 (d), 129.5 (d), 129.0 (s), 128.1 (d), 127.0 (d), 125.0 (d), 105.8 (d), 47.4 (t), 21.0 (q); **LRMS** (FAB$^+$) 365 (M$^+$, ^{37}Cl, 13), 363 (M$^+$, ^{35}Cl, 40), 289 (12), 154 (100); **HRMS** (FAB$^+$) calcd for C$_{17}$H$_{15}$ClN$_2$O$_3$S (M$^+$) 363.0570, observed 363.0576

3-(2-Chlorophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119e)
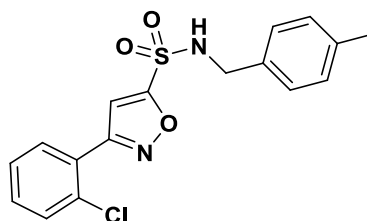
According to general procedure 4, **118e** gave the title compound as a pale yellow solid (0.15 g, 4.2 mmol, 82%).

R_f 0.06 (20% Et$_2$O/petroleum ether); **mp** 84-86 °C; ν_{max} (thin film, cm^{-1}) 3300, 3055, 1353, 1170; δ_H (CDCl$_3$, 300 MHz) 7.68 (1 H, dd, J = 7.3, 1.9 Hz, ArH), 7.52 (1 H, dd, J = 7.3, 1.9 Hz, ArH), 7.44 (1 H, td, J = 7.3, 2.1 Hz, ArH), 7.37 (1 H, td, J = 7.4, 2.0 Hz, ArH), 7.15 (2 H, d, J = 8.1 Hz, ArH), 7.15 (1 H, s, Isox$H$), 7.08 (2 H, d, J = 8.1 Hz, ArH), 5.65 (1 H, t, J = 5.9 Hz, NH), 4.35 (2 H, d, J = 6.0 Hz, NCH_2), 2.25 (3 H, s, CH_3); δ_C (CDCl$_3$, 75 MHz) 165.9 (s), 161.1 (s), 138.0 (s), 132.9 (s), 132.3 (s), 131.7 (d), 131.0 (d), 130.6 (d), 129.5 (d), 128.0 (d), 127.3 (d), 126.6 (s), 108.8 (d), 47.4 (t), 21.0 (q); **LRMS** (FAB$^+$) 365 (M$^+$, ^{37}Cl, 30), 363 (M$^+$, ^{35}Cl, 86), 307 (34),

289 (18), 165 (100); **HRMS** (FAB$^+$) calcd for C$_{17}$H$_{15}$ClN$_2$O$_3$S (M$^+$) 363.0570, observed 363.0573

3-(4-Bromophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119f)
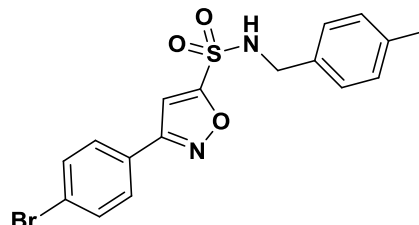
According to general procedure 4, **118f** gave the title compound as a white solid (0.2 g, 0.3 mmol, 73%).

R$_f$ 0.06 (20% Et$_2$O/petroleum ether); **mp** 156-158 °C; **ν$_{max}$** (thin film, cm^{-1}) 3373, 3053, 2985, 1170; **δ$_H$** (CDCl$_3$, 300 MHz) 7.63 (4 H, s, ArH), 7.15 (2 H, d, J = 8.1 Hz, ArH), 7.09 (2 H, d, J = 8.1 Hz, ArH), 6.93 (1 H, s, Isox$H$), 5.25 (1 H, t, J = 5.9 Hz, NH), 4.34 (2 H, d, J = 5.9 Hz, NCH_2), 2.24 (3 H, s, CH_3) ; **δ$_C$** (CDCl$_3$, 75 MHz) 166.1 (s), 161.3 (s), 138.2 (s), 132.5 (d), 132.2 (s), 129.5 (d), 128.3 (d), 128.0 (d), 125.0 (s), 114.7 (s), 105.7 (d), 47.5 (t), 21.0 (q); **LRMS** (FAB$^+$) 409 (M$^+$, ^{81}Br, 26), 407 (M$^+$, ^{79}Br, 26), 307 (17), 286 (33), 154 (100); **HRMS** (FAB$^+$) calcd for C$_{17}$H$_{15}$BrN$_2$O$_3$S (M$^+$) 407.0065, observed 407.0048

3-(3-Bromophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119g)
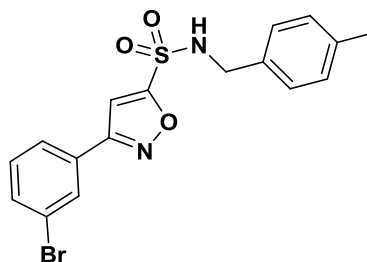
According to general procedure 4, **118g** gave the title compound as a white solid (0.18 g, 0.46 mmol, 84%).

R$_f$ 0.06 (20% Et$_2$O/petroleum ether); **mp** 101-103 °C; **ν$_{max}$** (thin film, cm^{-1}) 3367, 3055, 2985, 1326, 1172; **δ$_H$** (CDCl$_3$, 300 MHz) 7.89 (1 H, s, ArH), 7.61-7.68 (2 H, m, ArH), 7.36 (1 H, t, J = 7.8 Hz, ArH), 7.14 (2 H, d, J = 7.8 Hz, ArH), 7.08 (2 H, d, J = 7.8 Hz, ArH), 6.90 (1 H, s, Isox$H$), 5.47 (1 H, br s, NH), 4.34 (2 H, s, NCH_2), 2.22 (3 H, s, CH_3); **δ$_C$** (CDCl$_3$, 75 MHz) 166.9 (s), 161.3 (s), 138.2 (s), 133.8 (d), 132.1 (s), 130.7 (d), 129.9 (d), 129.5 (d), 129.3 (s), 128.1 (d), 125.5 (d), 123.2 (s), 105.7 (d),

47.4 (t), 21.0 (q); **LRMS** (FAB$^+$) 409 (M$^+$, ^{81}Br, 44), 407 (M$^+$, ^{79}Br, 46), 307 (15), 154 (100); **HRMS** (FAB$^+$) calcd for $C_{17}H_{15}BrN_2O_3S$ (M$^+$) 407.0065, observed 407.0060

### 3-(2-Bromophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119h)
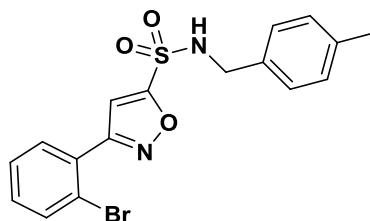
According to general procedure 4, **118h** gave the title compound as a waxy white solid (0.18 g, 0.46 mmol, 90%).

R$_f$ 0.10 (20% Et$_2$O/petroleum ether); **mp** 102-104 °C; **v$_{max}$** (thin film, cm^{-1}) 3365, 2052, 2985, 1170; **δ$_H$** (CDCl$_3$, 300 MHz) 7.70 (1 H, dd, J = 7.6, 1.8 Hz, ArH), 7.61 (1 H, dd, J = 7.6, 1.8 Hz, ArH), 7.44 (1H, td, J= 7.5, 1.8 Hz, ArH), 7.36 (1H, td, J= 7.6, 2.1 Hz, ArH), 7.15 (1 H, s, Isox$H$), 7.15 (2 H, d, J = 8.2 Hz, ArH), 7.10 (2 H, d, J = 8.2 Hz, ArH), 5.47 (1 H, t, J = 5.8 Hz, NH), 4.36 (2 H, d, J = 5.8 Hz, NCH_2), 2.29 (3 H, s, CH_3); **δ$_C$** (CDCl$_3$, 75 MHz) 165.7 (s), 162.5 (s), 138.1 (s), 133.8 (d), 132.3 (s), 131.8 (d), 131.4 (d), 129.5 (d), 128.7 (s), 122.2 (s), 127.9 (d), 127.8 (d), 108.9 (d), 47.4 (t), 21.1 (q); **LRMS** (FAB$^+$) 409 (M$^+$, ^{81}Br, 91), 407 (M$^+$, ^{79}Br, 100), 219 (30), 154 (36); **HRMS** (FAB$^+$) calcd for $C_{17}H_{15}BrN_2O_3S$ (M$^+$) 407.0065, observed 407.0061

3-(2-Fluorophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119i)
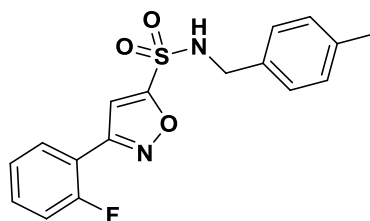
According to general procedure 4, **118i** gave the title compound as a white solid (0.13 g, 0.38 mmol, 84%).

R$_f$ 0.08 (20% Et$_2$O/petroleum ether); **mp** 111-113 °C; **v$_{max}$** (thin film, cm^{-1}) 3365, 3055, 2985, 1170; **δ$_H$** (CDCl$_3$, 300 MHz) 7.96 (1 H, td, J = 5.8, 1.7 Hz, ArH), 7.50-7.61 (1 H, m, ArH), 7.18-7.30 (2 H, m, ArH), 7.15 (2 H, d, J = 8.9 Hz, ArH), 7.12 (1 H, s, Isox$H$), 7.09 (2 H, d, J = 8.9 Hz, ArH), 5.30 (1 H, t, J = 5.9 Hz, NH), 4.34 (2 H,

d, J = 5.9 Hz, NCH_2), 2.24 (3 H, s, CH_3); δ_C (CDCl$_3$, 75 MHz) 166.4 (s), 160.1 (s, J_{CF} = 252.6 Hz), 157.9 (s), 138.2 (s), 132.7 (s, J_{CF} = 8.5 Hz), 132.2 (s), 129.5 (d), 129.0 (d), 128.0 (d), 125.3 (d), 124.8 (d, J_{CF} = 3.8 Hz), 116.6 (d, J_{CF} = 21.4 Hz), 108.2 (d, J_{CF} = 9.7 Hz), 47.4 (t), 21.0 (q); **LRMS** (FAB$^+$) 347 (M$^+$, 100), 251 (20), 154 (58) ; **HRMS** (FAB$^+$) calcd for C$_{17}$H$_{15}$FN$_2$O$_3$S (M$^+$) 347.0865, observed 347.0869

3-(4-Nitrophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119j)

According to general procedure 4, **118j** gave the title compound as a white solid (0.13 g, 0.36 mmol, 72%).

R$_f$ 0.10 (40% Et$_2$O/petroleum ether); **mp** 183-184 °C; ν_{max} (thin film, cm^{-1}) 3274, 3055, 1328, 1164; δ_H (CDCl$_3$, 300 MHz) 8.37 (2 H, d, J = 8.9 Hz, ArH), 7.96 (2 H, d, J = 8.9 Hz, ArH), 7.16 (2 H, d, J = 8.1 Hz, ArH), 7.10 (2 H, d, J = 8.1 Hz, ArH), 7.01 (1 H, s, Isox$H$), 5.24 (1 H, br s, NH), 4.37 (2 H, s, NCH_2), 2.24 (3 H, s, CH_3); δ_C (CDCl$_3$, 75 MHz) 167.8 (s), 160.8 (s), 149.3 (s), 138.4 (s), 133.4 (s), 132.0 (s), 129.6 (d), 128.1 (d), 127.9 (d), 124.5 (d), 105.8 (d), 47.6 (t), 21.1 (q); **LRMS** (FAB$^+$) 374 (M+H, 6), 307 (24), 289 (14), 154 (100); **HRMS** (FAB$^+$) calcd for C$_{17}$H$_{16}$N$_3$O$_5$S (M+H) 374.0810, observed 374.0806

3-Naphthyl isoxazole-5-sulfonic acid-4-methylbenzylamide (119k)
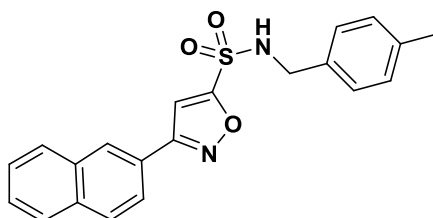
According to general procedure 4, **118k** gave the title compound as a white solid (0.14 g, 0.36 mmol, 83%).

R$_f$ 0.06 (20% Et$_2$O/petroleum ether); **mp** 131-133 °C; ν_{max} (thin film, cm^{-1}) 3365, 3307, 3055, 2985, 1341, 1170; δ_H (CDCl$_3$, 300 MHz) 8.20 (1 H, s, ArH), 7.88-7.97 (4 H, m, ArH), 7.54-7.61 (2 H, m, ArH), 7.17 (2 H, d, J = 8.2 Hz, ArH), 7.12 (1 H, s,

Isox$H$), 7.10 (2 H, d, J = 8.2 Hz, ArH), 5.28 (1 H, t, J = 5.8 Hz, NH), 4.37 (2 H, d, J = 5.8 Hz, NCH_2), 2.22 (3 H, s, CH_3); δ_C (CDCl$_3$, 75 MHz) 166.6 (s), 162.5 (s), 138.3 (s), 134.3 (s), 133.0 (s), 132.2 (s), 129.5 (d), 129.1 (d), 128.6 (d), 128.0 (d), 127.9 (d), 127.6 (d), 127.1 (d), 127.0 (d), 124.7 (s), 123.5 (d), 106.0 (d), 47.5 (t), 21.0 (q); **LRMS** (FAB$^+$) 379 (M+H, 100), 307 (11), 194 (18), 154 (83); **HRMS** (FAB$^+$) calcd for C$_{21}$H$_{19}$N$_2$O$_3$S (M+H) 379.1116, observed 379.1107

**3-(2-Iodophenyl) isoxazole-5-sulfonic acid-4-methylbenzylamide (119l)**
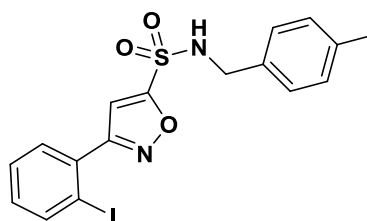
According to general procedure 4, **118l** gave the title compound as a yellow solid (0.20g, 0.45 mmol, 71%).

R_f 0.2 (20% Et$_2$O/petroleum ether); **mp** 115-117 °C; ν_{max} (thin film, cm^{-1}) 3297, 1354, 1165; δ_H (CDCl$_3$, 300 MHz) 8.02 (1 H, dd, J = 7.5, 1.1 Hz, ArH), 7.52 (1 H, td, J = 7.6, 1.1 Hz, ArH), 7.43 (1 H, dd, J = 7.5, 1.3 Hz, ArH), 7.24 (1 H, td, J = 7.8, 1.1 Hz, ArH), 7.14 (2 H, d, J = 8.3 Hz, ArH), 7.09 (2 H, d, J = 8.3 Hz, ArH), 7.01 (1 H, s, Isox$H$), 6.82 (1 H, t, J = 5.9 Hz, NH), 4.28 (2 H, d, J = 5.9 Hz, NCH_2), 2.24 (3 H, s, CH_3); δ_C (CDCl$_3$, 75 MHz) 167.2 (s), 165.9 (s), 141.3 (d), 138.6 (s), 134.4 (s), 134.0 (s), 132.9 (d), 131.9 (d), 130.2 (d), 129.7 (d), 129.0 (d), 109.7 (d), 97.0 (s), 47.7 (t), 21.3 (q); **LRMS** (EI) 454 (M$^{+\bullet}$, 22), 336 (20), 270 (44), 242 (55), 229 (86), 118 (86), 104 (100); **HRMS** (EI) calcd for C$_{17}$H$_{16}$N$_2$O$_3$S (M$^{+\bullet}$) 453.9846, observed 453.9864.

4.2.7 Preparation of 5-sulfonic-acid-allylsulfonamide

General Procedure 5

To a stirred solution of the isoxazole-5-pentafluorophenyl sulfonate ester **118** (0.5 mmol) in dry THF (12 mL/mmol) was added allylamine (1.5 mmol) followed by NEt$_3$ (0.75 mmol). The reaction was refluxed for 1.5-2 h and the mixture was diluted with dichloromethane (20 mL), washed with 2M HCl (20 mL), saturated NaHCO$_3$ (20 mL) and water (20 mL). The organic layer was dried over MgSO$_4$ and filtered, and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (10% EtOAc/petroleum ether) and all products were collected as a

single regioisomer as judged by NMR.

### 3-(4-Methoxyphenyl) isoxazole-5-sulfonic-acid-allylamide (120a)
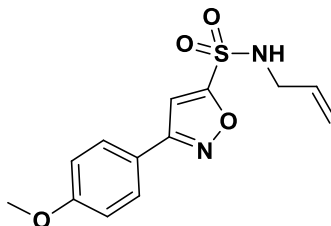
According to general procedure 5, **118a** gave the title compound as a cream solid (92 mg, 0.31 mmol, 66%).

R_f 0.1 (20% EtOAc/petroleum ether); **mp** 106-108 °C; ν_{max} (thin film, cm^{-1}) 3277, 1606, 1589, 1344, 1162; δ_H (CDCl$_3$, 300 MHz) 7.73 (2 H, d, J = 8.9 Hz, ArH), 7.06 (1 H, s, Isox$H$), 6.99 (2 H, d, J = 8.9 Hz, ArH), 5.80-5.88 (1 H, m, CH$_2$CH), 5.26 (1 H, dd, J = 17.1, 0.8 Hz, CHCHHtrans), 5.19 (1 H, dd, J= 10.2, 0.8 Hz, CHCHHcis), 3.86 (3 H, s, OCH_3), 3.80-3.87 (2 H, m, NCH_2); δ_C (CDCl$_3$, 75 MHz) 166.7 (s), 161.7 (s), 132.1 (d), 128.4 (d), 119.4 (s), 118.2 (t), 114.6 (d), 105.6 (d), 68.2 (s), 55.4 (q), 46.0 (t); **LRMS** (EI) 294 (M$^{+\bullet}$, 46), 174 (85), 146 (100); **HRMS** (EI) calcd for C$_{13}$H$_{14}$N$_2$O$_4$S (M$^{+\bullet}$) 294.0668, observed 294.0673; ***Anal*. calcd**: C, 53.05, H, 4.79, N, 9.52, found: C, 53.18, H, 5.04, N, 9.96.

3-Phenylisoxazole-5-sulfonic-acid-allylamide (120b)
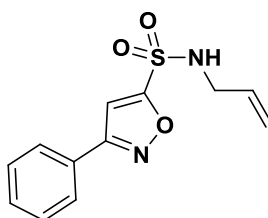
According to general procedure 5, **118b** gave the title compound as a cream solid (85 mg, 0.32 mmol, 64%).

R_f 0.1 (20% EtOAc/petroleum ether); **mp** 74-76 °C; ν_{max} (thin film, cm^{-1}) 3256, 1352, 1169; δ_H (CDCl$_3$, 300 MHz) 7.81-7.90 (2 H, m, ArH), 7.50-7.65 (3 H, m, ArH), 7.12 (1 H, s, Isox$H$), 5.80-5.89 (1 H, m, CH$_2$CH), 5.27 (1 H, dd, J = 17.1, 1.0 Hz, CHCHHtrans), 5.19 (1H, dd, J = 10.2, 1.0 Hz, CHCHHcis), 5.10 (1 H, t, J = 5.9 Hz, NH), 3.86 (2 H, app.t, J = 5.9 Hz, NCH_2); δ_C (CDCl$_3$, 75 MHz) 166.5 (s), 162.6 (s), 132.1 (d), 131.0 (s), 129.2 (d), 127.3 (d), 126.9 (d), 118.6 (t), 105.6 (d), 46.0 (t); **LRMS** (EI) 264 (M$^{+\bullet}$, 12), 144 (100), 116 (74), 103 (25), 89 (37), 77 (96); **HRMS** (EI) calcd for C$_{12}$H$_{12}$N$_2$O$_3$S (M$^{+\bullet}$) 264.0563, observed 264.0570

3-(4-Chlorophenyl) isoxazole-5-sulfonic-acid-allylamide (120c)
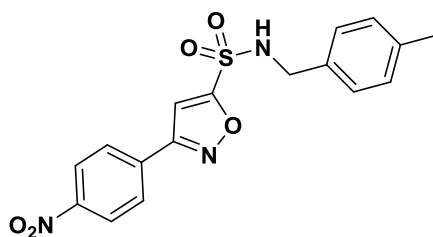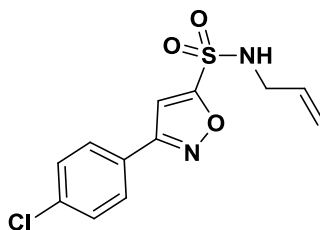

According to general procedure 5, **118c** gave the title compound as a white solid (90 mg, 0.30 mmol, 60%).

R_f 0.13 (20% EtOAc/petroleum ether); **mp** 123-125 °C; ν_{max} (thin film, cm^{-1}) 3273, 1601, 1329, 1159; δ_H (CDCl$_3$, 300 MHz) 7.75 (2 H, d, J = 8.6 Hz, ArH), 7.47 (2 H, d, J = 8.6 Hz, ArH), 7.10 (1 H, s, Isox$H$), 5.74-5.87 (1 H, m, CH$_2$CH), 5.27 (1 H, dd, J = 17.1, 0.9 Hz, CHCHHtrans), 5.19 (1 H, dd, J = 10.2, 0.9 Hz, CHCHHcis), 5.12 (1 H, t, J = 6.0 Hz, NH), 3.85 (2 H, app.tt, J = 5.9, 1.4 Hz, NHCH_2); δ_C (CDCl$_3$, 75 MHz) 166.9 (s), 161.7 (s), 137.2 (s), 132.0 (d), 129.5 (d), 128.2 (d), 125.8 (s), 118.7 (t), 105.6 (d), 46.0 (t); **LRMS** (EI) 300 (M$^{+\bullet}$, ^{37}Cl, 9), 298 (M$^{+\bullet}$, ^{35}Cl, 24), 178 (100), 152 (40), 150 (98), 123 (34), 111 (60), 75 (56); **HRMS** (EI) calcd for C$_{12}$H$_{11}$ClN$_2$O$_3$S (M$^{+\bullet}$) 298.0173, observed 298.0169

### 3-(3-Chlorophenyl) isoxazole-5-sulfonic-acid-allylamide (120d)
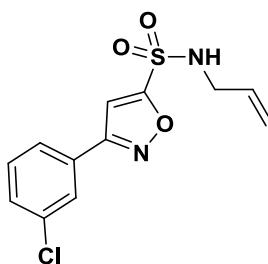
According to general procedure 5, **118d** gave the title compound as a white solid (78 mg, 0.27 mmol, 53%).

R_f 0.16 (20% EtOAc/petroleum ether); **mp** 76-79 °C; ν_{max} (thin film, cm^{-1}) 3271, 1347, 1169; δ_H (CDCl$_3$, 300 MHz) 7.82 (1 H, s, ArH), 7.68 (1 H, dt, J = 7.2, 1.6 Hz, ArH), 7.42-7.51 (2 H, m, ArH), 7.10 (1 H, s, Isox$H$), 5.73-5.87 (1 H, m, CH$_2$CH), 5.27 (1 H, dd, J = 17.1, 1.1 Hz, CHCHHtrans), 5.20 (1 H, dd, J = 10.2, 1.1 Hz, CHCHHcis), 5.09 (1 H, t, J = 5.9 Hz, NH), 3.85 (2 H, app.tt, J = 5.9, 1.3 Hz, NCH_2); δ_C (CDCl$_3$, 75 MHz) 167.0 (s), 161.5 (s), 135.3 (s), 132.0 (d), 131.0 (d), 130.5 (d), 129.0 (s), 127.0 (d), 125.0 (d), 118.7 (t), 105.7 (d), 46.0 (t); **LRMS** (EI) 300 (M$^{+\bullet}$,

^{37}Cl, 5), 298 (M$^{+\bullet}$, ^{35}Cl, 13), 207 (15), 178 (100), 150 (52), 111 (60); **HRMS** (EI) calcd for $C_{12}H_{11}ClN_2O_3S$ (M$^{+\bullet}$) 298.0173, observed 298.0163

3-(2-Chlorophenyl) isoxazole-5-sulfonic-acid-allylamide (120e)
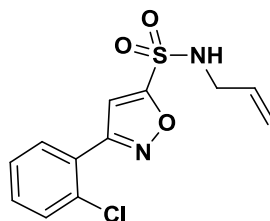
According to general procedure 5, **118e** gave the title compound as a yellow oil (96 mg, 0.32 mmol, 64%).

R$_f$ 0.11 (20% EtOAc/petroleum ether); ν_{max} (thin film, cm^{-1}) 3292, 1351, 1166; δ_H (CDCl$_3$, 300 MHz) 7.71 (1 H, dd, J = 7.5, 0.8 Hz, ArH), 7.48-7.54 (1 H, m, ArH), 7.41 (1 H, dd, J = 7.5, 0.8 Hz, ArH), 7.36 (1 H, td, J = 7.5, 0.8 Hz, ArH), 7.27 (1 H, s, Isox$H$), 5.71-5.85 (1 H, m, CH$_2$CH), 5.57 (1 H, t, J = 5.9 Hz, NH), 5.24 (1 H, dd, J = 17.1, 1.1 Hz, CHCHHtrans), 5.15 (1H, dd, J = 10.2, 1.1 Hz, CHCHHcis), 3.85 (2 H, t, J = 5.9 Hz, NCH_2); δ_C (CDCl$_3$, 75 MHz) 165.9 (s), 161.2 (s), 132.9 (s), 132.1 (d), 131.8 (d), 131.0 (d), 130.6 (d), 127.4 (d), 126.6 (s), 118.5 (t), 108.8 (d), 46.0 (t); **LRMS** (EI) 300 (M$^{+\bullet}$, ^{37}Cl, 2), 298 (M$^{+\bullet}$, ^{35}Cl, 5), 207 (21), 178 (100), 150 (94), 123 (53), 111 (43), 97 (40), 75 (68); **HRMS** (EI) calcd for $C_{12}H_{11}ClN_2O_3S$ (M$^{+\bullet}$) 298.0173, observed 298.0160

### 3-(4-Bromophenyl) isoxazole-5-sulfonic-acid-allylamide (120f)

According to general procedure 5, **118f** gave the title compound as a white solid (0.11 g, 0.33 mmol, 67%).

R$_f$ 0.13 (20% EtOAc/petroleum ether); **mp** 134-135 °C; ν_{max} (thin film, cm^{-1}) 3272, 1595, 1329, 1159; δ_H (CDCl$_3$, 300 MHz) 7.68 (2 H, d, J = 8.8 Hz, ArH), 7.63 (2 H, d, J = 8.8 Hz, ArH), 7.09 (1 H, s, Isox$H$), 5.73-5.87 (1 H, m, CH$_2$CH), 5.26 (1 H, dd, J

= 17.1, 0.8 Hz, CHC*H*Htrans), 5.19 (1 H, dd, *J* = 10.2, 0.8 Hz, CHCH*H*cis), 5.00 (1 H, t, *J* = 5.9 Hz, N*H*), 3.85 (2 H, app.tt, *J* = 5.9, 1.3 Hz, NC*H*$_2$); δ_C (CDCl$_3$, 75 MHz) 168.1 (s), 162.5 (s), 137.4 (s), 132.5 (d), 132.0 (d), 128.4 (d), 125.0 (s), 118.7 (t), 105.6 (d), 46.1 (t); **LRMS** (EI) 344 (M$^{+\bullet}$, ^{81}Br, 39), 342 (M$^{+\bullet}$, ^{79}Br, 36), 224 (100), 222 (100), 196 (74), 194 (75), 157 (35), 155 (57), 102 (35); **HRMS** (EI) calcd for C$_{12}$H$_{11}$BrN$_2$O$_3$S (M$^{+\bullet}$) 341.9668, observed 341.9664

3-(3-Bromophenyl) isoxazole-5-sulfonic-acid-allylamide (120g)

According to general procedure 5, **118g** gave the title compound as a white solid (0.11 g, 0.33 mmol, 67%).

R$_f$ 0.14 (20% EtOAc/petroleum ether); **mp** 90-92 °C; **ν$_{max}$** (thin film, cm^{-1}) 3287, 1350, 1169; δ_H (CDCl$_3$, 300 MHz) 7.97 (1 H, t, *J* = 1.3 Hz, Ar*H*), 7.73 (1 H, app. dt, *J* = 7.7, 1.6 Hz, Ar*H*), 7.63 (1 H, app. dt, *J* = 7.6, 1.6 Hz, Ar*H*), 7.37 (1 H, t, *J* = 7.7 Hz, Ar*H*), 7.10 (1 H, s, Isox*H*), 5.79-5.86 (1 H, m, CH$_2$C*H*), 5.26 (1 H, dd, *J* = 16.8, 0.8 Hz, CHC*H*Htrans), 5.19 (1 H, dd, *J* = 10.2, 0.8 Hz, CHCH*H*cis), 5.12 (1 H, t, *J* = 6.2 Hz, N*H*), 3.85 (2 H, t, *J* = 6.2 Hz, NC*H*$_2$); δ_C (CDCl$_3$, 75 MHz) 167.0 (s), 161.4 (s), 133.9 (d), 132.0 (d), 130.7 (d), 129.9 (d), 129.3 (s), 125.5 (d), 123.3 (s), 118.7 (t), 105.6 (d), 46.0 (t); **LRMS** (EI) 344 (M$^{+\bullet}$, ^{81}Br, 30), 342 (M$^{+\bullet}$, ^{79}Br, 28), 253 (22), 251 (29), 224 (100), 222 (100), 196 (56), 194 (56), 157 (77), 155 (80); **HRMS** (EI) calcd for C$_{12}$H$_{11}$BrN$_2$O$_3$S (M$^{+\bullet}$) 341.9668, observed 341.9669

3-(2-Bromophenyl) isoxazole-5-sulfonic-acid-allylamide (120h)
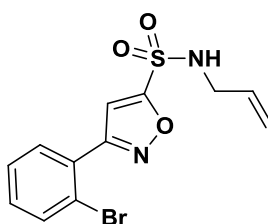
According to general procedure 5, **118h** gave the title compound as a yellow oil (0.13 g, 0.37 mmol, 68%).

R$_f$ 0.19 (20% EtOAc/petroleum ether); **ν$_{max}$** (thin film, cm^{-1}) 3287, 1351, 1165; **δ$_H$** (CDCl$_3$, 300 MHz) 7.68 (1 H, dd, J = 7.7, 1.6 Hz, ArH), 7.62 (1 H, dd, J = 7.7, 1.8 Hz, ArH), 7.41 (1 H, td, J = 7.7, 1.7 Hz, ArH), 7.34 (1 H, td, J = 7.7, 1.8 Hz, ArH), 7.24 (1 H, s, Isox$H$), 5.71-5.85 (1 H, m, CH$_2$CH), 5.58 (1 H, t, J = 5.9 Hz, NH), 5.24 (1 H, dd, J = 16.8, 0.8 Hz, CHCHHtrans), 5.15 (1 H, dd, J = 10.2, 0.8 Hz, CHCHHcis), 3.85 (2 H, t, J = 5.9 Hz, NCH_2); **δ$_C$** (CDCl$_3$, 75 MHz) 165.7 (s), 162.6 (s), 133.8 (d), 132.1 (d), 131.9 (d), 131.4 (d), 128.6 (s), 127.9 (d), 122.6 (s), 118.5 (t), 108.9 (d), 46.0 (t); **LRMS** (EI) 344 (M$^{+\bullet}$, ^{81}Br, 4), 342 (M$^{+\bullet}$, ^{79}Br, 4), 224 (100), 222 (100), 197 (85), 194 (83), 115 (52); **HRMS** (EI) calcd for C$_{12}$H$_{11}$BrN$_2$O$_3$S (M$^{+\bullet}$) 341.9668, observed 341.9664

3-(2-Fluorophenyl) isoxazole-5-sulfonic-acid-allylamide (120i)
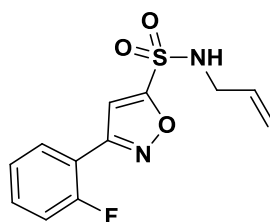
According to general procedure 5, **118i** gave the title compound as a white solid (0.11 g, 0.38 mmol, 77%).

R$_f$ 0.14 (20% EtOAc/petroleum ether); **mp** 80-83 °C; **ν$_{max}$** (thin film, cm^{-1}) 3263, 1353, 1168; **δ$_H$** (CDCl$_3$, 300 MHz) 7.98 (1 H, td, J = 7.5, 1.6 Hz, ArH), 7.49-7.61 (1 H, m, ArH), 7.21-7.31 (2 H, m, ArH), 7.18 (1 H, d, J = 7.5 Hz, Isox$H$), 5.73-5.87 (1 H, m, CH$_2$CH), 5.27 (1 H, dd, J = 16.8, 0.8 Hz, CHCHHtrans), 5.19 (1 H, dd, J = 10.4, 0.8 Hz, CHCHHcis), 5.04 (1 H, t, J = 5.8 Hz, NH), 3.86 (2 H, app.tt, J = 5.8, 1.3 Hz, NCH_2); **δ$_C$** (CDCl$_3$, 75 MHz) 166.5 (s), 160.6 (s, J_{CF} = 253.9 Hz), 158.1 (s), 132.8 (d, J_{CF} = 7.7 Hz), 132.1 (d), 129.1 (d, J_{CF} = 2.7 Hz), 124.9 (d, J_{CF} = 3.8 Hz), 118.7 (t), 116.7 (d, J_{CF} = 21.6 Hz), 115.6 (s, J_{CF} = 12.1 Hz), 108.2 (d, J_{CF} = 9.6 Hz), 45.9 (t); **LRMS** (CI$^+$) 283 (M+H, 100), 219 (31), 164 (67), 162 (73), 122 (70); **HRMS** (CI$^+$) calcd for C$_{12}$H$_{12}$FN$_2$O$_3$S (M+H) 283.0552, observed 283.0557

### 3-(4-Nitrophenyl) isoxazole-5-sulfonic-acid-allylamide (120j)
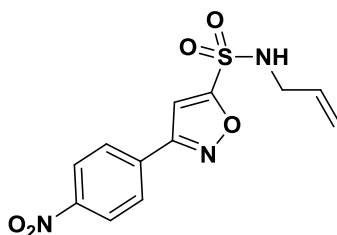
According to general procedure 5, **118j** gave the title compound as a cream solid (0.11 g, 0.34 mmol, 69%).

R_f 0.10 (20% EtOAc/petroleum ether); **mp** 131-133 °C; ν_{max} (thin film, cm^{-1}) 3247, 1613, 1536, 1343, 1160; δ_H (CDCl$_3$, 300 MHz) 8.36 (2 H, d, J = 7.5 Hz, ArH), 8.00 (2 H, d, J = 7.5 Hz, ArH), 7.19 (1 H, s, Isox$H$), 5.72-5.88 (1 H, m, CH$_2$CH), 5.27 (1 H, d, J = 14.0 Hz, CHCHHtrans), 5.20 (1 H, d, J = 9.9 Hz, CHCHHcis), 3.88 (2 H, d, J = 5.3 Hz, NCH_2); δ_C (CDCl$_3$, 75 MHz) 167.8 (s), 160.8 (s), 149.1 (s), 133.3 (s), 131.9 (d), 127.9 (d), 124.5 (d), 118.7 (t), 105.7 (d), 46.0 (t); **LRMS** (CI$^+$) 310 (M+H, 100), 248 (27), 216 (26), 189 (48); **HRMS** (CI$^+$) calcd for C$_{12}$H$_{12}$N$_3$O$_5$S (M+H) 310.0497, observed 310.0501

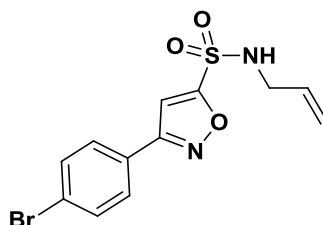### 3-Naphthyl-isoxazole-5-sulfonic-acid-allylamide (120k)
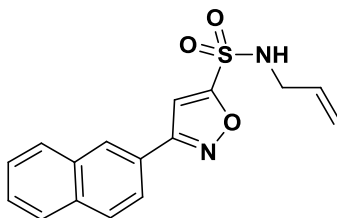
According to general procedure 5, **118k** gave the title compound as a white solid (0.11 g, 0.33 mmol, 69%).

R_f 0.20 (20% EtOAc/petroleum ether); **mp** 112-114 °C; ν_{max} (thin film, cm^{-1}) 3280, 1347, 1166; δ_H (CDCl$_3$, 300 MHz) 8.25 (1 H, s, ArH), 7.91-8.02 (4 H, m, ArH), 7.56-7.62 (2 H, m, ArH), 7.25 (1 H, s, Isox$H$), 7.75-7.89 (1 H, m, CH$_2$CH), 5.29 (1 H, d, J = 16.8 Hz, CHCHHtrans), 5.20 (1 H, d, J = 10.4 Hz, CHCHHcis), 5.10 (1 H, t, J = 5.7 Hz, NH), 3.88 (2 H, t, J = 5.7 Hz, NCH_2); δ_C (CDCl$_3$, 75 MHz) 167.3 (s), 162.6 (s), 134.3 (s), 133.0 (s), 132.1 (d), 129.2 (d), 128.6 (d), 127.9 (d), 127.6 (d), 127.2 (d), 127.0 (d), 124.7 (s), 123.5 (d), 118.6 (t), 105.9 (d), 46.1 (t); **LRMS** (EI) 314 (M$^+$·, 73), 194 (94), 166 (45), 127 (100); **HRMS** (EI) calcd for C$_{16}$H$_{14}$N$_2$O$_3$S (M$^+$·) 314.0719, observed 314.0720

4.2.8 Preparation of isoxazole-5-sulfonic-acid-*tert*-butylsulfonamide

General Procedure 6

To a stirred solution of the isoxazole pentafluorophenyl sulfonate esters **118** (0.5 mmol) in dry THF (12 mL/mmol) was added TBAC (1 mmol) followed by NEt$_3$ (0.75 mmol) and *tert*-butylamine (1.5 mmol). The reaction was refluxed for 1-3 h and the mxture was diluted with dichloromethane (20 mL), washed with 2M HCl (20 mL), saturated NaHCO$_3$ (20 mL) and water (20 mL). The organic layer was dried over MgSO$_4$, filtered under gravity, and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (20% EtOAc/petroleum ether) and all products were collected as a single regioisomer as judged by NMR.

3-(4-Methoxyphenyl)-isoxazole-5-sulfonic-acid-*tert*-butylamide (121a)
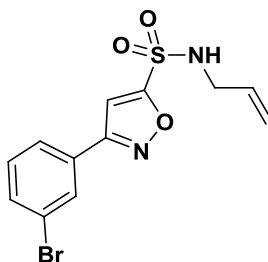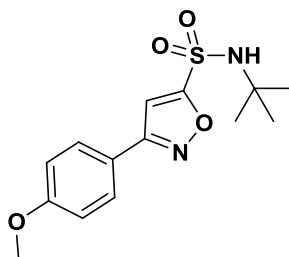

According to general procedure 6, **118a** gave the title compound as a cream solid (89 mg, 0.29 mmol, 63%).

R$_f$ 0.18 (20% EtOAc/petroleum ether); **mp** 143-146 °C; ν_{max} (thin film, cm^{-1}) 3281, 1346, 1154; δ_H (CDCl$_3$, 300 MHz) 7.73 (2 H, d, J = 8.8 Hz, ArH), 7.04 (1 H, s, Isox$H$), 6.97 (2 H, d, J = 8.8 Hz, ArH), 5.28 (1 H, br s, NH), 3.85 (3 H, s, OCH_3), 1.34 (9 H, s, C(CH_3)$_3$); δ_C (CDCl$_3$, 75 MHz) 168.4 (s), 162.2 (s), 161.6 (s), 128.4 (d), 119.9 (s), 114.5 (d), 104.8 (d), 56.1 (s), 55.4 (q), 29.8 (q); **LRMS** (EI) 310 (M$^{+\bullet}$, 47), 174 (100), 146 (60), 92 (14); **HRMS** (EI) calcd for C$_{14}$H$_{18}$N$_2$O$_4$S (M$^{+\bullet}$) 310.0981, observed 310.0985; **_Anal_. calcd**: C, 54.18, H, 5.85, N, 9.03, found: C, 54.16, H, 5.84, N, 9.02.

3-Phenyl-isoxazole-5-sulfonic-acid-*tert*-butylamide (121b)
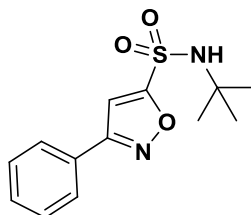
According to general procedure 6, **118b** gave the title compound as a white solid (69 mg, 0.25 mmol, 49%).

R$_f$ 0.19 (20% EtOAc/petroleum ether); **mp** 121-124 °C; **ν$_{max}$** (thin film, cm^{-1}) 3282, 3158, 1345, 1156; **δ$_H$** (CDCl$_3$, 300 MHz) 7.82-7.93 (2 H, m, Ar*H*), 7.48-7.58 (3 H, m, Ar*H*), 7.11 (1 H, s, Isox*H*), 5.21 (1 H, br s, N*H*), 1.35 (9 H, s, C(C*H$_3$*)$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 168.7 (s), 162.6 (s), 130.8 (d), 129.1 (d), 127.5 (s), 126.9 (d), 105.0 (d), 56.2 (s), 29.9 (q); **LRMS** (EI) 280 (M$^{+\bullet}$, 6), 265 (58), 144 (100), 116 (15); **HRMS** (EI) calcd for C$_{13}$H$_{16}$N$_2$O$_3$S (M$^{+\bullet}$) 280.0876, observed 280.0868

3-(4-Chlorophenyl)-isoxazole-5-sulfonic-acid-*tert*-butylamide (121c)
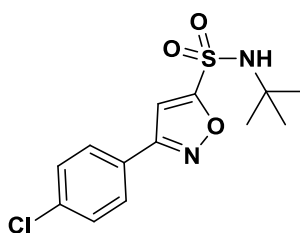
According to general procedure 6, **118c** gave the title compound as a white solid (74 mg, 0.24 mmol, 47%).

R$_f$ 0.26 (20% EtOAc/petroleum ether); **mp** 153-156 °C; **ν$_{max}$** (thin film, cm^{-1}) 3295, 3153, 1602, 1346, 1160; **δ$_H$** (CDCl$_3$, 300 MHz) 7.75 (2 H, d, *J* = 8.8 Hz, Ar*H*), 7.46 (2 H, d, *J* = 8.8 Hz, Ar*H*), 7.08 (1 H, s, Isox*H*), 5.17 (1 H, br s, N*H*), 1.35 (9 H, s, C(C*H$_3$*)$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 169.0 (s), 161.7 (s), 137.0 (s), 129.4 (d), 128.2 (d), 126.0 (s), 104.8 (d), 56.3 (s), 30.0 (q); **LRMS** (EI) 316 (M$^{+\bullet}$, ^{37}Cl, 2), 314 (M$^{+\bullet}$, ^{35}Cl, 5), 301 (6), 299 (18), 180 (12), 178 (35); **HRMS** (EI) calcd for C$_{13}$H$_{15}$ClN$_2$O$_3$S (M$^{+\bullet}$) 314.0486, observed 310.0480

3-(3-Chlorophenyl)-isoxazole-5-sulfonic-acid-*tert*-butylamide (121d)
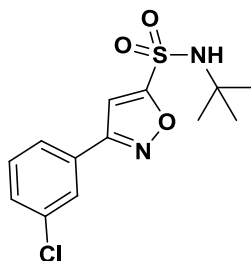
According to general procedure 6, **118d** gave the title compound as a white solid (69 mg, 0.22 mmol, 44%).

R$_f$ 0.29 (20% EtOAc/petroleum ether); **mp** 122-125 °C; **ν$_{max}$** (thin film, cm^{-1}) 3303,

3158, 1345, 1159; δ_H (CDCl$_3$, 300 MHz) 7.81 (1 H, t, J = 1.6 Hz, ArH), 7.69-7.77 (1 H, m, ArH), 7.38-7.49 (2 H, m, ArH), 7.10 (1 H, s, Isox$H$), 5.34 (1 H, br s, NH), 1.35 (9 H, s, C(CH_3)$_3$); δ_C (CDCl$_3$, 75 MHz) 169.1 (s), 161.6 (s), 135.2 (s), 130.9 (d), 130.5 (d), 129.2 (s), 127.0 (d), 125.1 (d), 104.8 (d), 56.3 (s), 29.9 (q); **LRMS** (EI) 316 (M$^{+\bullet}$, ^{37}Cl, 2), 314 (M$^{+\bullet}$, ^{35}Cl, 5), 301 (9), 299 (18), 281 (100), 265 (47), 180 (17), 178 (34); **HRMS** (EI) calcd for C$_{13}$H$_{15}$ClN$_2$O$_3$S (M$^{+\bullet}$) 314.0486, observed 310.0484

3-(2-Chlorophenyl)-isoxazole-5-sulfonic-acid-*tert*-butylamide (121e)
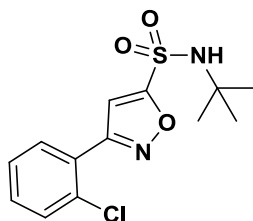
According to general procedure 6, **118e** gave the title compound as a cream solid (82 mg, 0.26 mmol, 52%).

R$_f$ 0.27 (20% EtOAc/petroleum ether); **mp** 91-95 °C; ν_{max} (thin film, cm^{-1}) 3279, 1345, 1155; δ_H (CDCl$_3$, 300 MHz) 7.74 (1 H, dd, J = 7.5, 1.6 Hz, ArH), 7.51 (1 H, dd, J = 7.5, 1.6 Hz, ArH), 7.35-7.48 (2 H, m, ArH), 7.25 (1 H, s, Isox$H$), 5.16 (1 H, br s, NH), 1.36 (9 H, s, C(CH_3)$_3$); δ_C (CDCl$_3$, 75 MHz) 167.9 (s), 161.2 (s), 132.9 (s), 132.1 (d), 131.5 (s), 130.9 (d), 130.3 (d), 127.1 (d), 108.2 (d), 56.2 (s), 29.9 (q); **LRMS** (EI) 316 (M$^{+\bullet}$, ^{37}Cl, 1), 314 (M$^{+\bullet}$, ^{35}Cl, 3), 301 (19), 299 (51), 180 (30), 178 (100); **HRMS** (EI) calcd for C$_{13}$H$_{15}$ClN$_2$O$_3$S (M$^{+\bullet}$) 314.0486, observed 310.0480

3-(4-Bromophenyl)-isoxazole-5-sulfonic-acid-*tert*-butylamide (121f)
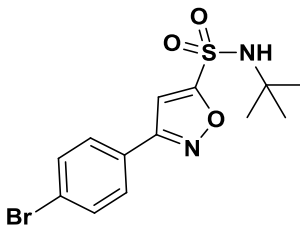
According to general procedure 6, **118f** gave the title compound as a cream solid (70 mg, 0.19 mmol, 41%).

R$_f$ 0.28 (20% EtOAc/petroleum ether); **mp** 160-163 °C; ν_{max} (thin film, cm^{-1}) 3324, 3161, 1596, 1343, 1157; δ_H (CDCl$_3$, 300 MHz) 7.68 (2 H, d, J = 8.8 Hz, ArH), 7.61 (2 H, d, J = 8.8 Hz, ArH), 7.07 (1 H, s, Isox$H$), 5.13 (1 H, br s, NH), 1.35 (9 H, s,

C(CH_3)$_3$); δ_C (CDCl$_3$, 75 MHz) 169.0 (s), 161.7 (s), 132.4 (d), 128.0 (d), 126.4 (s), 125.3 (s), 104.7 (d), 56.2 (s), 30.0 (q); **LRMS** (EI) 360 (M$^{+\bullet}$, ^{81}Br, 22), 358 (M$^{+\bullet}$, ^{79}Br, 21), 345 (100), 343 (93), 224 (85), 222 (90), 196 (29), 194 (24); **HRMS** (EI) calcd for C$_{13}$H$_{15}$BrN$_2$O$_3$S (M$^{+\bullet}$) 357.9861, observed 357.9857

3-(3-Brorophenyl)-isoxazole-4-sulfonic-acid-*tert*-butylamide (121g)
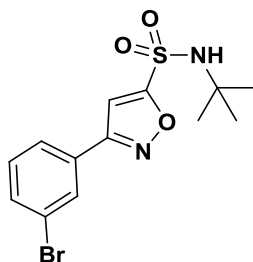
According to general procedure 6, **118g** gave the title compound as a cream solid (71 mg, 0.20 mmol, 41%).

R$_f$ 0.27 (20% EtOAc/petroleum ether); **mp** 130-133 °C; ν_{max} (thin film, cm^{-1}) 3293, 3148, 1598, 1500, 1339, 1157; δ_H (CDCl$_3$, 300 MHz) 7.97 (1 H, t, J = 1.9 Hz, ArH), 7.73 (1 H, app.dt, J = 7.7, 1.9 Hz, ArH), 7.61-7.68 (1 H, m, ArH), 7.36 (1 H, t, J = 7.7 Hz, ArH), 7.09 (1 H, s, Isox$H$), 5.20 (1 H, br s, NH), 1.35 (9 H, s, C(CH_3)$_3$); δ_C (CDCl$_3$, 75 MHz) 169.1 (s), 161.4 (s), 133.8 (d), 130.7 (d), 129.9 (d), 129.4 (s), 125.5 (d), 123.2 (d), 104.8 (d), 56.2 (s), 30.0 (q); **LRMS** (EI) 360 (M$^{+\bullet}$, ^{81}Br, 10), 358 (M$^{+\bullet}$, ^{79}Br, 10), 345 (94), 343 (100), 224 (69), 222 (67), 196 (13), 194 (12), 157 (17), 155 (19); **HRMS** (EI) calcd for C$_{13}$H$_{15}$BrN$_2$O$_3$S (M$^{+\bullet}$) 357.9861, observed 357.9863

3-(2-Bromophenyl)-isoxazole-5-sulfonic-acid-*tert*-butylamide (121h)
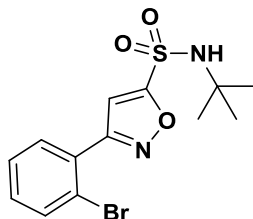
According to general procedure 6, **118h** gave the title compound as a white solid (89 mg, 0.25 mmol, 52%).

R$_f$ 0.28 (20% EtOAc/petroleum ether); **mp** 111-113 °C; ν_{max} (thin film, cm^{-1}) 3284, 1595, 1347, 1158; δ_H (CDCl$_3$, 300 MHz) 7.69 (1 H, dd, J = 7.7, 1.3 Hz, ArH), 7.64 (1 H, dd, J = 7.7, 1.3 Hz, ArH), 7.43 (1 H, td, J = 7.7, 1.4 Hz, ArH), 7.38 (1 H, td, J =

7.7, 1.3 Hz, ArH), 7.22 (1 H, s, Isox$H$), 5.26 (1 H, br s, NH), 1.35 (9 H, s, C(CH_3)$_3$); δ_C (CDCl$_3$, 75 MHz) 167.7 (s), 162.6 (s), 133.7 (d), 132.7 (s), 131.8 (d), 131.3 (d), 128.9 (s), 127.8 (d), 108.3 (d), 56.2 (s), 29.9 (q); **LRMS** (EI) 360 (M$^{+\bullet}$, ^{81}Br, 6), 358 (M$^{+\bullet}$, ^{79}Br, 6), 345 (82), 343 (82), 224 (98), 222 (100), 196 (48), 194 (51); **HRMS** (EI) calcd for C$_{13}$H$_{15}$BrN$_2$O$_3$S (M$^{+\bullet}$) 357.9861, observed 357.9855

3-(2-Fluorophenyl)-isoxazole-5-sulfonic-acid-*tert*-butylamide (121i)
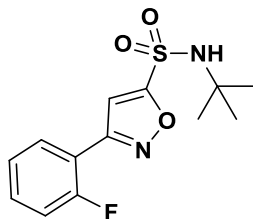
According to general procedure 6, **118i** gave give the title compound as a cream solid (85 mg, 0.28 mmol, 60%).

R_f 0.21 (20% EtOAc/petroleum ether); **mp** 115-117 °C; ν_{max} (thin film, cm^{-1}) 3275, 1591, 1505, 1345, 1153; δ_H (CDCl$_3$, 300 MHz) 7.99 (1 H, td, J = 7.5, 1.6 Hz, ArH), 7.44-7.53 (1 H, m, ArH), 7.28 (1 H, dd, J = 7.5, 1.4 Hz, ArH), 7.23 (1 H, s, Isox$H$), 7.17-7.23 (1 H, m, ArH), 5.10 (1 H, br s, NH), 1.35 (9 H, s, C(CH_3)$_3$); δ_C (CDCl$_3$, 75 MHz) 168.6 (s), 159.9 (s, J_{CF} = 252.6 Hz), 158.0 (s), 132.6 (d, J_{CF} = 8.5 Hz), 129.0 (d, J_{CF} = 2.6 Hz), 124.8 (d, J_{CF} = 3.2 Hz), 116.6 (d, J_{CF} = 21.7 Hz), 115.7 (s, J_{CF} = 11.7 Hz), 107.4 (d, J_{CF} = 9.7 Hz), 56.2 (s), 30.0 (q); **LRMS** (EI) 298 (M$^{+\bullet}$, 3), 283 (96), 162 (100), 134 (22); **HRMS** (EI) calcd for C$_{13}$H$_{15}$FN$_2$O$_3$S (M$^{+\bullet}$) 298.0782, observed 298.0776

3-(4-Nitrophenyl)-isoxazole-5-sulfonic-acid-*tert*-butylamide (121j)
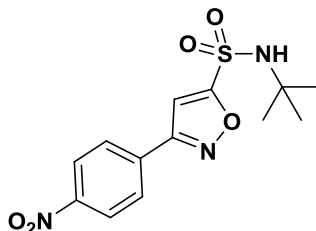
According to general procedure 6, **118j** gave the title compound as a cream solid (60 mg, 0.18 mmol, 37%).

R_f 0.2 (20% EtOAc/petroleum ether); **mp** 167-168 °C; ν_{max} (thin film, cm^{-1}) 3203, 3148, 1343, 1157; δ_H (CDCl$_3$, 300 MHz) 8.26 (2 H, d, J = 8.8 Hz, ArH), 8.01 (2 H, d, J = 8.8 Hz, ArH), 7.17 (1 H, s, Isox$H$), 5.09 (1 H, br s, NH), 1.37 (9 H, s, C(CH_3)$_3$);

δ_C (CDCl$_3$, 75 MHz) 169.8 (s), 160.9 (s), 149.2 (s), 133.5 (s), 127.9 (d), 124.4 (d), 104.9 (d), 56.4 (s), 30.0 (q); **LRMS** (EI) 326 (M$^{+\bullet}$, 7), 310 (80), 189 (100), 143 (96), 115 (40); **HRMS** (EI) calcd for C$_{13}$H$_{15}$N$_3$O$_5$S (M$^{+\bullet}$) 326.0810, observed 326.0813

**3-Naphthyl-isoxazole-5-sulfonic-acid-*tert*-butylamide (121k)**
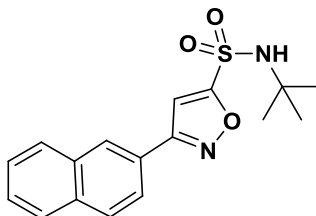
According to general procedure 6, **118k** gave the title compound as a cream solid (70 mg, 0.21 mmol, 42%).

R$_f$ 0.3 (20% EtOAc/petroleum ether); **mp** 143-148 °C; **ν$_{max}$** (thin film, cm^{-1}) 3285, 1604, 1514, 1334, 1154; δ_H (CDCl$_3$, 300 MHz) 8.25 (1 H, s, Ar*H*),, 7.86-7.96 (4 H, m, Ar*H*), 7.25-7.34 (2 H, m, Ar*H*), 7.25 (1 H, s, Isox*H*), 5.20 (1 H, br s, N*H*), 1.38 (9 H, s, C(C*H*$_3$)$_3$); δ_C (CDCl$_3$, 75 MHz) 168.8 (s), 162.7 (s), 134.3 (s), 133.1 (s), 129.1 (d), 128.6 (d), 127.9 (d), 127.5 (d), 127.1 (d), 126.9 (d), 124.9 (s), 123.5 (d), 105.1 (d), 56.2 (s), 30.0 (q); **LRMS** (EI) 330 (M$^{+\bullet}$, 45), 194 (100), 166 (27), 127 (65); **HRMS** (EI) calcd for C$_{17}$H$_{18}$N$_2$O$_3$S (M$^{+\bullet}$) 330.1032, observed 330.1026

4.2.9 Preparation of isoxazole-5-sulfonic-acid-isopropylsulfonamide

General Procedure 7

To a stirred solution of the isoxazole pentafluorophenyl sulfonate esters **118** (0.5 mmol) in dry THF (12 mL/mmol) was added TBAC (1 mmol) followed by NEt$_3$ (0.75 mmol) and isopropylamine (1.5 mmol). The reaction was refluxed for 1-3 h and the mixture was diluted with dichloromethane (20 mL), washed with 2M HCl (20 mL), saturated NaHCO$_3$ (20 mL) and water (20 mL). The organic layer was dried over MgSO$_4$, filtered under gravity, and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (20% EtOAc/petroleum ether) and all products were collected as a single regioisomer as judged by NMR.

### 3-(4-Methoxyphenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122a)
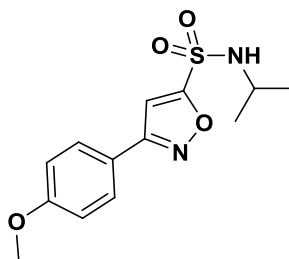
According to general procedure 7, **118a** gave the title compound as a cream solid (0.13 g, 0.44 mmol, 89%).

R_f 0.15 (20% EtOAc/petroleum ether); **mp** 98-101 °C; ν_{max} (thin film, cm^{-1}) 3155, 1610, 1520, 1346, 1176; δ_H (CDCl$_3$, 300 MHz) 7.73 (2 H, d, J = 8.8 Hz, Ar*H*), 7.07 (1 H, s, Isox*H*), 6.97 (2 H, d, J = 8.8 Hz, Ar*H*), 5.13 (1 H, d, J = 7.5 Hz, N*H*), 3.85 (3 H, s, OC*H*$_3$), 3.73-3.80 (1 H, m, C*H*), 1.21 (6 H, d, J = 6.7 Hz, C*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 166.9 (s), 162.2 (s), 161.7 (s), 128.5 (s), 119.8 (d), 114.6 (d), 105.3 (d), 55.4 (q), 47.3 (d), 23.7 (q); **LRMS** (EI) 296 (M$^{+\bullet}$, 50), 174 (100), 146 (79), 84 (22); **HRMS** (EI) calcd for C$_{13}$H$_{16}$N$_2$O$_4$S (M$^{+\bullet}$) 296.0825, observed 296.0823; ***Anal. calcd***: C, 52.69, H, 5.44, N, 9.45, found: C, 52.46, H, 5.35, N, 9.82.

3-Phenyl-isoxazole-5-sulfonic-acid-isopropylamide (122b)
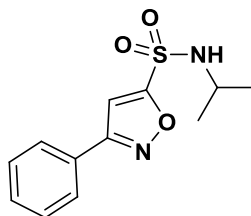
According to general procedure 7, **118b** gave the title compound as white crystals (0.11 g, 0.39 mmol, 79%).

R_f 0.24 (20% EtOAc/petroleum ether); **mp** 117-120 °C; ν_{max} (thin film, cm^{-1}) 3272, 1605, 1351, 1171; δ_H (CDCl$_3$, 300 MHz) 7.79-7.84 (2 H, m, Ar*H*), 7.46-7.51 (3 H, m, Ar*H*), 7.14 (1 H, s, Isox*H*), 5.19 (1 H, d, J = 7.3 Hz, N*H*), 3.75 (1 H, oct, J = 7.3 Hz, C*H*), 1.21 (6 H, d, J = 7.3 Hz, C*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 167.3 (s), 162.6 (s), 130.9 (d), 129.2 (d), 127.4 (s), 126.9 (d), 105.5 (d), 47.3 (d), 23.7 (q); **LRMS** (EI) 266 (M$^{+\bullet}$, 28), 251 (100), 144 (75); **HRMS** (EI) calcd for C$_{12}$H$_{14}$N$_2$O$_3$S (M$^{+\bullet}$) 266.0719, observed 266.0712

**3-(4-Chlorophenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122c)**
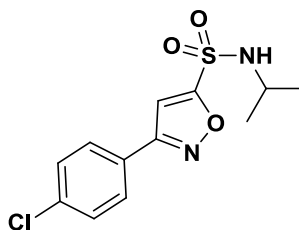
According to general procedure 7, **118c** gave the title compound as a white solid (0.11 g, 0.37 mmol, 74%).

$\mathbf{R_f}$ 0.28 (20% EtOAc/petroleum ether); **mp** 121-124 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3150, 1601, 1507, 1353, 1179; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.74 (2 H, d, J = 8.8 Hz, ArH), 7.45 (2 H, d, J = 8.8 Hz, ArH), 7.10 (1 H, s, Isox$H$), 5.07 (1 H, d, J = 7.2 Hz, NH), 3.75 (1H, oct, J = 7.2 Hz, CH), 1.22 (6 H, d, J = 7.2 Hz, CH_3); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 167.6 (s), 161.7 (s), 137.1 (s), 129.5 (d), 128.2 (d), 125.9 (s), 105.3 (d), 47.3 (d), 23.7 (q); **LRMS** (EI) 302 (M$^{+\bullet}$, ^{37}Cl, 34), 300 (M$^{+\bullet}$, ^{35}Cl, 100), 287 (18), 285 (53); **HRMS** (EI) calcd for C$_{12}$H$_{13}$ClN$_2$O$_3$S (M$^{+\bullet}$) 300.0330, observed 300.0332

3-(3-Chlorophenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122d)
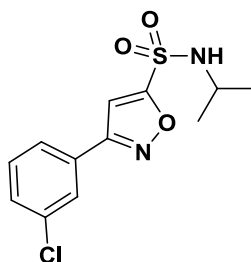
According to general procedure 7, **118d** gave the title compound as a cream solid (0.11 g, 0.36 mmol, 72%).

$\mathbf{R_f}$ 0.22 (20% EtOAc/petroleum ether); **mp** 108-110 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3226, 1356, 1175; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.82 (1 H, s, ArH), 7.69 (1 H, d, J = 8.2 Hz, ArH), 7.48 (1 H, dt, J = 8.3 Hz, ArH), 7.43 (1 H, t, J = 8.3 Hz, ArH), 7.09 (1 H, s, Isox$H$), 4.83 (1 H, d, J = 7.2 Hz, NH), 3.75 (1H, oct, J = 7.2 Hz, CH), 1.23 (6 H, d, J = 7.2 Hz, CH_3); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 168.1 (s), 161.0 (s), 136.6 (s), 130.9 (d), 130.5 (d), 129.8 (s), 127.0 (d), 125.0 (d), 105.3 (d), 47.3 (d), 23.8 (q); **LRMS** (EI) 302 (M$^{+\bullet}$, ^{37}Cl, 5), 300 (M$^{+\bullet}$, ^{35}Cl, 15), 287 (30), 285 (92), 180 (28), 178 (100); **HRMS** (EI) calcd for C$_{12}$H$_{13}$ClN$_2$O$_3$S (M$^{+\bullet}$) 300.0330, observed 300.0320

3-(2-Chlorophenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122e)
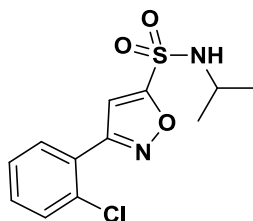
According to general procedure 7, **118e** gave the title compound as a cream solid (0.12 g, 0.38 mmol, 75%).

R_f 0.20 (20% EtOAc/petroleum ether); **mp** 88-89 °C; ν_{max} (thin film, cm^{-1}) 3266, 1339, 1122; δ_H (CDCl$_3$, 300 MHz) 7.73 (1 H, dd, J = 7.5, 1.5 Hz, ArH), 7.51 (1 H, dd, J = 7.5, 1.3 Hz, ArH), 7.43 (1 H, td, J = 7.5, 1.5 Hz, ArH), 7.37 (1 H, td, J = 7.5, 1.5 Hz, ArH), 7.27 (1 H, s, Isox$H$), 5.13 (1 H, d, J = 7.2 Hz, NH), 3.77 (1 H, oct, J = 7.2 Hz, CH), 1.22 (6 H, d, J = 7.2 Hz, CH_3); δ_C (CDCl$_3$, 75 MHz) 166.6 (s), 161.2 (s), 132.9 (s), 131.7 (d), 131.1 (d), 130.6 (d), 127.3 (d), 126.7 (s), 108.5 (d), 47.3 (d), 23.7 (q); **LRMS** (EI) 302 (M$^{+\bullet}$, ^{37}Cl, 5), 300 (M$^{+\bullet}$, ^{35}Cl, 14), 287 (30), 285 (92); **HRMS** (EI) calcd for C$_{12}$H$_{13}$ClN$_2$O$_3$S (M$^{+\bullet}$) 300.0330, observed 300.0320

**3-(4-Bromophenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122f)**
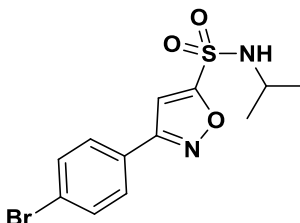
According to general procedure 7, **118f** gave the title compound as a cream solid (0.13 g, 0.38 mmol, 75%).

R_f 0.26 (20% EtOAc/petroleum ether); **mp** 132-135 °C; ν_{max} (thin film, cm^{-1}) 3283, 1598, 1502, 1354, 1116; δ_H (CDCl$_3$, 300 MHz) 7.67 (2 H, d, J = 8.6 Hz, ArH), 7.60 (2 H, d, J = 8.6 Hz, ArH), 7.09 (1 H, s, Isox$H$), 5.29 (1 H, d, J = 7.2 Hz, NH), 3.73 (1 H, oct, J = 7.2 Hz, CH), 1.23 (6 H, d, J = 7.2 Hz, CH_3); δ_C (CDCl$_3$, 75 MHz) 167.7 (s), 161.7 (s), 132.4 (d), 128.4 (d), 126.3 (s), 125.4 (s), 105.2 (d), 47.3 (d), 23.7 (q); **LRMS** (EI) 346 (M$^{+\bullet}$, ^{81}Br, 7), 344 (M$^{+\bullet}$, ^{79}Br, 7), 331 (40), 329 (39), 224 (100), 222 (98), 196 (49), 194 (50), 157 (49), 155 (52); **HRMS** (EI) calcd for C$_{12}$H$_{13}$BrN$_2$O$_3$S (M$^{+\bullet}$) 343.9825, observed 343.9816

3-(3-Bromophenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122g)
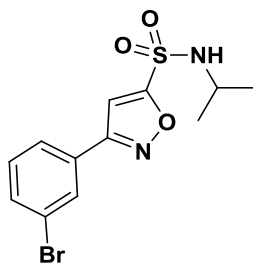
According to general procedure 7, **118g** gave the title compound as a cream solid (0.12 g, 0.36 mmol, 72%).

R_f 0.22 (20% EtOAc/petroleum ether); **mp** 110-114 °C; ν_{max} (thin film, cm^{-1}) 3224, 1357, 1125; δ_H (CDCl$_3$, 300 MHz) 7.96 (1 H, t, J = 1.8 Hz, ArH), 7.73-7.82 (1 H, m, ArH), 7.61-7.69 (1 H, m ArH), 7.35 (1 H, t, J = 7.7 Hz, ArH), 7.12 (1 H, s, Isox$H$), 5.30 (1 H, d, J = 7.2 Hz, NH), 3.74 (1 H, oct, J = 7.2 Hz, CH), 1.21 (6 H, d, J = 7.2 Hz, CH_3); δ_C (CDCl$_3$, 75 MHz) 167.7 (s), 161.4 (s), 133.9 (d), 130.7 (d), 129.9 (d), 129.3 (s), 125.5 (d), 123.2 (s), 105.3 (d), 47.3 (d), 23.7 (q); **LRMS** (EI) 346 (M$^{+\bullet}$, ^{81}Br, 21), 344 (M$^{+\bullet}$, ^{79}Br, 21), 331 (100), 329 (95), 224 (86), 222 (86); **HRMS** (EI) calcd for C$_{12}$H$_{13}$BrN$_2$O$_3$S (M$^{+\bullet}$) 343.9825, observed 343.9832

3-(2-Bromophenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122h)
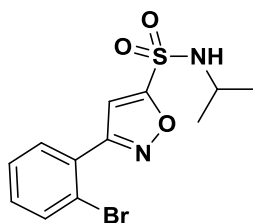
According to general procedure 7, **118h** gave the title compound as a cream solid (0.13 g, 0.38 mmol, 75%).

R_f 0.2 (20% EtOAc/petroleum ether); **mp** 70-71 °C; ν_{max} (thin film, cm^{-1}) 3301, 1353, 1123; δ_H (CDCl$_3$, 300 MHz) 7.68 (1 H, dd, J = 7.5, 1.6 Hz, ArH), 7.63 (1 H, dd, J = 7.5, 1.5 Hz, ArH), 7.41 (1 H, td, J = 7.5, 1.5 Hz, ArH), 7.34 (1 H, td, J = 7.5, 1.5 Hz, ArH), 7.24 (1 H, s, Isox$H$), 5.30 (1 H, d, J = 7.2 Hz, NH), 3.76 (1 H, oct, J = 7.2 Hz, CH), 1.21 (6 H, d, J = 7.2 Hz, CH_3); δ_C (CDCl$_3$, 75 MHz) 166.4 (s), 162.6 (s), 133.7 (d), 131.8 (d), 131.4 (d), 128.8 (s), 127.9 (d), 122.2 (s), 108.6 (d), 47.3 (d), 23.6 (q); **LRMS** (EI) 346 (M$^{+\bullet}$, ^{81}Br, 9), 344 (M$^{+\bullet}$, ^{79}Br, 10), 331 (47), 329 (46), 224 (98), 222 (100), 196 (67), 194 (68); **HRMS** (EI) calcd for C$_{12}$H$_{13}$BrN$_2$O$_3$S (M$^{+\bullet}$) 343.9825, observed 343.9814

### 3-(2-Fluorophenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122i)
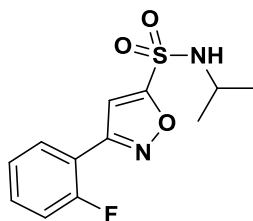
According to general procedure 7, **118i** gave the title compound as a cream solid (0.13 g, 0.45 mmol, 90%).

R_f 0.24 (20% EtOAc/petroleum ether); **mp** 86-89 °C; ν_{max} (thin film, cm^{-1}) 3293, 1343, 1119; δ_H (CDCl$_3$, 300 MHz) 7.99 (1 H, td, J = 7.5, 1.8 Hz, ArH), 7.45-7.54 (1 H, m, ArH), 7.24 (1 H, s, Isox$H$), 7.17-7.31 (2 H, m, ArH), 4.79 (1 H, d, J = 7.2 Hz, NH), 3.76 (1 H, oct, J = 7.2 Hz, , CH), 1.23 (6 H, d, J = 7.2 Hz, CH_3); δ_C (CDCl$_3$, 75 MHz) 167.22 (s), 160.4 (s, J_{CF} = 253.5 Hz), 158.1 (s), 132.7 (d, J_{CF} = 8.3 Hz), 129.0 (d, J_{CF} = 1.9 Hz), 124.9 (d, J_{CF} = 3.9 Hz), 116.6 (d, J_{CF} = 22.6 Hz), 115.6 (s, J_{CF} = 11.3 Hz), 107.9 (d, J_{CF} = 9.9 Hz), 47.4 (d), 23.8 (q); **LRMS** (EI) 284 (M$^{+\bullet}$, 7), 269 (87), 162 (100), 134 (44); **HRMS** (EI) calcd for C$_{12}$H$_{13}$FN$_2$O$_3$S (M$^{+\bullet}$) 284.0625, observe 284.0629

3-(4-Nitrophenyl)-isoxazole-5-sulfonic-acid-isopropylamide (122j)
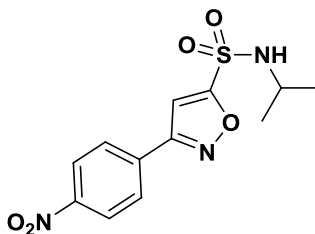
According to general procedure 7, **118j** gave the title compound as a cream solid (0.13 g, 0.41 mmol, 81%).

R_f 0.16 (20% EtOAc/petroleum ether); **mp** 150-152 °C; ν_{max} (thin film, cm^{-1}) 3337, 1606, 1560, 1353, 1114; δ_H (CDCl$_3$, 300 MHz) 8.36 (2 H, d, J = 8.8 Hz, ArH), 8.01 (2 H, d, J = 8.8 Hz, ArH), 7.18 (1 H, s, Isox$H$), 4.85 (1 H, d, J = 7.2 Hz, NH), 3.78 (1 H, oct, J = 7.2 Hz, CH), 1.24 (6 H, d, J = 7.2 Hz, CH_3); δ_C (CDCl$_3$, 75 MHz) 169.7 (s), 160.9 (s), 149.4 (s), 144.6 (s), 127.9 (d), 124.4 (d), 105.3 (d), 47.4 (d), 23.8 (q); **LRMS** (CI$^+$) 312 (M+H, 100), 147 (19); 312.0654; **HRMS** (CI$^+$) calcd for C$_{12}$H$_{14}$N$_3$O$_5$S (M+H) 312.0654, observed 312.0654

3-Naphthyl-isoxazole-5-sulfonic-acid-isopropylamide (122k)
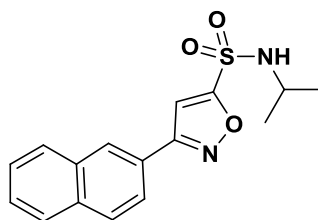
According to general procedure 7, **118k** gave the title compound as a white solid (0.13 g, 0.41 mmol, 82%).

R_f 0.2 (20% EtOAc/petroleum ether); **mp** 163-165 °C; v_{max} (thin film, cm^{-1}) 3288, 1349, 1126; δ_H (CDCl$_3$, 300 MHz) 8.25 (1 H, s, Ar*H*), 7.85-7.95 (4 H, m, Ar*H*), 7.52-7.60 (2 H, m, Ar*H*), 7.27 (1 H, s, Isox*H*), 5.04 (1 H, d, *J* = 7.2 Hz, N*H*), 3.79 (1 H, oct, *J* = 7.2 Hz, C*H*), 1.24 (6 H, d, *J* = 7.2 Hz, C*H$_3$*); δ_C (CDCl$_3$, 75 MHz) 167.3 (s), 162.9 (s), 134.3 (s), 133.0 (s), 129.1 (d), 128.6 (d), 127.9 (d), 127.6 (d), 127.1 (d), 127.0 (d), 124.7 (s), 123.5 (d), 105.6 (d), 47.3 (d), 23.8 (q); **LRMS** (EI) 316 (M$^{+\bullet}$, 70), 194 (100), 127 (49), 84 (54); **HRMS** (EI) calcd for C$_{16}$H$_{16}$N$_2$O$_3$S (M$^{+\bullet}$) 316.0876, observed 316.0880

4.2.10 Preparation of isoxazole-5-sulfonic-acid-*N*-methylbenzene sulfonamide

General Procedure 8

To a stirred solution of the isoxazole pentafluorophenyl sulfonate esters **118** (0.5 mmol) in dry THF (12 mL/mmol) was added TBAC (1 mmol) followed by NEt$_3$ (0.75 mmol) and *N*-methylbenzylamine (1.5 mmol). The reaction was refluxed for 16-24 h and the mixture was diluted with dichloromethane (20 mL), washed with 2M HCl (20 mL), saturated NaHCO$_3$ (20 mL) and water (20 mL). The organic layer was dried over MgSO$_4$, filtered under gravity, and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (10% EtOAc/petroleum ether) and all products were collected as a single regioisomer as judged by NMR.

3-(4-Methoxyphenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123a)
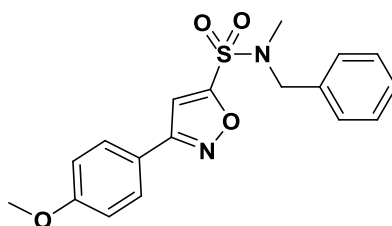
According to general procedure 8, **118a** gave the title compound as a cream solid

(0.15 g, 0.42 mmol, 84%).

$\mathbf{R_f}$ 0.19 (20% EtOAc/petroleum ether); **mp** 98-100 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3132, 1610, 1589, 1495, 1350, 1163; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.75 (2 H, d, J = 8.5 Hz, Ar*H*), 7.29-7.41 (5 H, m, Ar*H*), 7.04 (1 H, s, Isox*H*), 7.00 (2 H, d, J = 8.5 Hz, Ar*H*), 4.41 (2 H, s, NC*H₂*), 3.87 (3 H, s, OC*H₃*), 2.85 (3 H, s, NC*H₃*); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 165.6 (s), 162.1 (s), 161.7 (s), 134.7 (s), 128.8 (d), 128.4 (d), 128.4 (d), 128.3 (d), 119.8 (s), 114.6 (d), 105.9 (d), 55.4 (q), 54.2 (t), 34.5 (q); **LRMS** (EI) 358 (M$^{+\bullet}$, 45), 239 (100), 174 (65), 146 (70), 118 (37); **HRMS** (EI) calcd for C$_{18}$H$_{18}$N$_2$O$_4$S (M$^{+\bullet}$) 358.0982, observed 358.0976; ***Anal*. calcd**: C, 60.32, H, 5.06, N, 7.82, found: C, 60.36, H, 5.01, N, 8.00.

## 3-Phenyl-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123b)

According to general procedure 8, **118b** gave the title compound as a cream solid (0.11 g, 0.34 mmol, 69%).

$\mathbf{R_f}$ 0.31 (20% EtOAc/petroleum ether); **mp** 86-89 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3153, 1350, 1153; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.83 (1 H, d, J = 2.4 Hz, Ar*H*), 7.81 (1 H, d, J = 2.4 Hz, Ar*H*), 7.51-7.54 (3 H, m, Ar*H*), 7.49-7.51 (1 H, m, Ar*H*), 7.31-7.39 (4 H, m, Ar*H*), 7.11 (1 H, s, Isox*H*), 4.43 (2 H, s, NC*H₂*), 2.86 (3 H, s, NC*H₃*); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 165.9 (s), 162.5 (s), 134.7 (s), 130.9 (d), 130.6 (s), 129.2 (d), 129.0 (d), 128.9 (d), 128.8 (d), 128.4 (d), 106.1 (d), 54.3 (t), 34.5 (q); **LRMS** (EI) 328 (M$^{+\bullet}$, 15), 263 (26), 178 (100), 119 (78); **HRMS** (EI) calcd for C$_{17}$H$_{16}$N$_2$O$_3$S (M$^{+\bullet}$) 328.0876, observed 328.0870

3-(4-Chlorophenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123c)
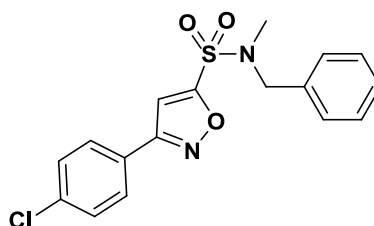
According to general procedure 8, **118c** gave the title compound as a cream solid

(0.11 g, 0.29 mmol, 62%).

$\mathbf{R_f}$ 0.34 (20% EtOAc/petroleum ether); **mp** 124-1127 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3150, 1600, 1504, 1361, 1161; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.76 (2 H, dd, J = 8.5, 1.8 Hz, ArH), 7.48 (2 H, dd, J = 8.5, 1.8 Hz, ArH), 7.31-7.40 (5 H, m, ArCH), 7.07 (1 H, s, Isox$H$), 4.42 (2 H, s, NCH_2), 2.86 (3 H, s, NCH_3); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 166.3 (s), 161.6 (s), 137.2 (s), 134.6 (s), 129.9 (d), 128.8 (d), 128.4 (d), 128.3 (d), 128.2 (d), 125.9 (s), 105.8 (d), 54.8 (t), 34.5 (q); **LRMS** (EI) 364 (M$^{+\bullet}$, ^{37}Cl, 3), 362 (M$^{+\bullet}$, ^{35}Cl, 8), 196 (5), 194 (19), 120 (38), 118 (100); **HRMS** (EI) calcd for C$_{17}$H$_{15}$ClN$_2$O$_3$S (M$^{+\bullet}$) 362.0486, observed 362.0491

3-(3-Chlorophenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123d)

According to general procedure 8, **118d** gave the title compound as a cream solid (0.11 g, 0.31 mmol, 66%).

$\mathbf{R_f}$ 0.42 (20% EtOAc/petroleum ether); **mp** 93-95 °C; $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3160, 1601, 1495, 1353, 1162; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.81 (1 H, t, J = 1.8 Hz, ArH), 7.69 (1 H, dt, J = 7.2, 1.8 Hz, ArH), 7.49 (1 H, dt, J = 7.2, 1.8 Hz, ArH), 7.44 (1 H, d, J = 7.2 Hz, ArH), 7.20-7.39 (5 H, m, ArH), 7.08 (1 H, s, Isox$H$), 4.42 (2 H, s, NCH_2), 2.86 (3 H, s, NCH_3) ; $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 166.3 (s), 161.4 (s), 135.3 (s), 134.6 (s), 131.0 (d), 130.5 (d), 129.3 (d), 128.9 (s), 128.4 (d), 128.3 (d), 127.0 (d), 125.1 (d), 105.9 (d), 54.2 (t), 34.6 (q); **LRMS** (EI) 364 (M$^{+\bullet}$, ^{37}Cl, 3), 362 (M$^{+\bullet}$, ^{35}Cl, 8), 180 (6), 178 (15), 120 (42), 118 (100); **HRMS** (EI) calcd for C$_{17}$H$_{15}$ClN$_2$O$_3$S (M$^{+\bullet}$) 362.0486, observed 362.0482

3-(2-Chlorophenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123e)
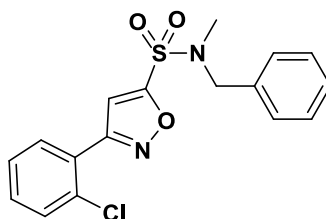
According to general procedure 8, **118e** gave the title compound as a yellow solid (0.14 g, 0.37 mmol, 79%).

R_f 0.34 (20% EtOAc/petroleum ether); **mp** 70-73 °C; ν_{max} (thin film, cm^{-1}) 3146, 1598, 1494, 1355, 1162; δ_H (CDCl$_3$, 300 MHz) 7.76 (1 H, dd, $J = 7.5$, 1.8 Hz, ArH), 7.52 (1 H, dd, $J = 7.5$, 1.7 Hz, ArH), 7.46 (1 H, dd, $J = 7.5$, 1.8 Hz, ArH), 7.42 (1 H, t, $J = 7.5$ Hz, ArH), 7.32-7.38 (5 H, m, ArH), 7.28 (1 H, s, Isox$H$), 4.44 (2 H, s, NCH_2), 2.87 (3 H, s, NCH_3); δ_C (CDCl$_3$, 75 MHz) 165.2 (s), 161.2 (s), 134.5 (s), 132.9 (s), 131.8 (d), 131.5 (d), 130.6 (d), 130.4 (d), 130.3 (d), 128.8 (d), 128.3 (d), 122.0 (s), 109.1 (d), 54.2 (t), 34.5 (q); **LRMS** (EI) 364 (M$^{+\bullet}$, ^{37}Cl, 2), 362 (M$^{+\bullet}$, ^{35}Cl, 5), 120 (20), 118 (69); **HRMS** (EI) calcd for C$_{17}$H$_{15}$ClN$_2$O$_3$S (M$^{+\bullet}$) 362.0486, observed 362.0478

3-(4-Bromophenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123f)
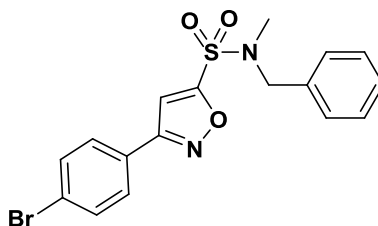
According to general procedure 8, **118f** gave the title compound as a cream solid (0.12 g, 0.30 mmol, 62%).

R_f 0.36 (20% EtOAc/petroleum ether); **mp** 126-128 °C; ν_{max} (thin film, cm^{-1}) 2157, 1595, 1495, 1361, 1161; δ_H (CDCl$_3$, 300 MHz) 7.69 (2 H, d, $J = 8.6$ Hz, ArH), 7.63 (2 H, d, $J = 8.6$ Hz, ArH), 7.29-7.38 (5 H, m, ArH), 7.07 (1 H, s, Isox$H$), 4.42 (2 H, s, NCH_2), 2.88 (3 H, s, NCH_3); δ_C (CDCl$_3$, 75 MHz) 166.3 (s), 161.6 (s), 134.6 (s), 132.5 (d), 128.8 (d), 128.4 (d), 128.4 (d), 128.3 (d), 126.3 (s), 125.4 (s), 105.8 (d), 54.2 (t), 34.5 (q); **LRMS** (EI) 408 (M$^{+\bullet}$, ^{81}Br, 6), 406 (M$^{+\bullet}$, ^{79}Br, 6), 336 (14), 246 (71), 118 (100); **HRMS** (EI) calcd for C$_{17}$H$_{15}$BrN$_2$O$_3$S (M$^{+\bullet}$) 405.9981, observed 405.9991

3-(3-Bromophenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123g)
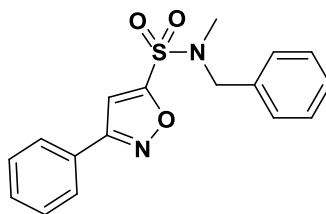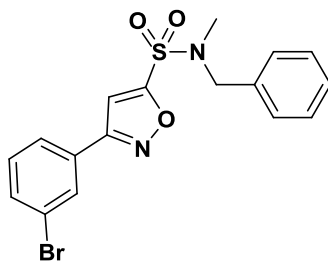

According to general procedure 8, **118g** gave the title compound as a cream solid (0.12 g, 0.29 mmol, 60%).

R_f 0.3 (20% EtOAc/petroleum ether); **mp** 111-112 °C; ν_{max} (thin film, cm^{-1}) 3164, 1599, 1494, 1364, 1166; δ_H (CDCl$_3$, 300 MHz) 7.97 (1 H, t, J = 1.8 Hz, Ar*H*), 7.74 (1 H, dt, J = 7.7, 1.8 Hz, Ar*H*), 7.63 (1 H, d, J = 7.7 Hz, Ar*H*), 7.31-7.41 (6 H, m, Ar*H*), 7.07 (1 H, s, Isox*H*), 4.42 (2 H, s, NC*H*$_2$), 2.86 (3 H, s, NC*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 166.3 (s), 161.3 (s), 134.6 (s), 133.9 (d), 130.8 (d), 129.9 (d), 129.3 (s), 128.8 (d), 128.4 (d), 128.3 (d), 125.5 (d), 123.3 (s), 105.9 (d), 54.3 (t), 34.6 (q); **LRMS** (EI) 408 (M$^{+\bullet}$, ^{81}Br, 9), 406 (M$^{+\bullet}$, ^{79}Br, 8), 336 (10), 246 (40), 120 (100); **HRMS** (EI) calcd for C$_{17}$H$_{15}$BrN$_2$O$_3$S (M$^{+\bullet}$) 405.9981, observed 406.0021

3-(2-Bromophenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123h)
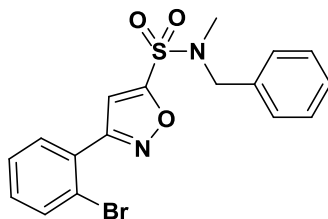
According to general procedure 8, **118h** gave the title compound as a cream solid (0.17 g, 0.41 mmol, 86%).

R_f 0.24 (20% EtOAc/petroleum ether); **mp** 70-71 °C; ν_{max} (thin film, cm^{-1}) 3147, 1595, 1495, 1367, 1165; δ_H (CDCl$_3$, 300 MHz) 7.71 (1 H, dd, J = 7.5, 1.0 Hz, Ar*H*), 7.66 (1 H, dd, J = 7.5, 1.0 Hz, Ar*H*), 7.44 (1 H, td, J = 7.5, 1.0 Hz, Ar*H*), 7.30-7.40 (6 H, m, Ar*H*), 7.26 (1 H, s, Isox*H*), 4.44 (2 H, s, NC*H*$_2$), 2.87 (3 H, s, NC*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 165.0 (s), 162.5 (s), 134.6 (s), 133.6 (d), 132.2 (d), 131.4 (d), 128.9 (d), 128.7 (s), 128.4 (d), 128.3 (d), 127.7 (d), 122.2 (s), 109.2 (d), 54.2 (t), 34.5 (q); **LRMS** (EI) 408 (M$^{+\bullet}$, ^{81}Br, 8), 406 (M$^{+\bullet}$, ^{79}Br, 8), 336 (10), 246 (16), 120 (100); **HRMS** (EI) calcd for C$_{17}$H$_{15}$BrN$_2$O$_3$S (M$^{+\bullet}$) 405.9981, observed 405.9989

3-(2-Fluorophenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123i)
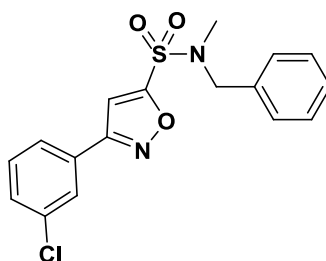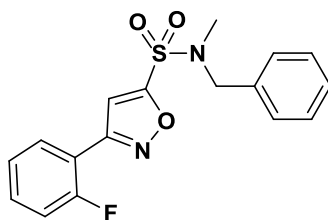

According to general procedure 8, **118i** gave the title compound as a cream solid (0.13 g, 0.36 mmol, 73%).

R_f 0.44 (20% EtOAc/petroleum ether); **mp** 99-102 °C; ν_{max} (thin film, cm^{-1}) 3134, 1599, 1493, 1364, 1166; δ_H (CDCl$_3$, 300 MHz) 7.99 (1 H, td, J = 7.7, 1.1 Hz, Ar*H*), 7.45-7.55 (1 H, m, Ar*H*), 7.33-7.37 (5 H, m, Ar*H*), 7.29 (1 H, dd, J = 7.7, 1.0 Hz, Ar*H*), 7.24 (1 H, s, Isox*H*), 7.20 (1 H, t, J = 7.7 Hz, Ar*H*), 4.43 (2 H, s, NC*H$_2$*), 2.86 (3 H, s, NC*H$_3$*); δ_C (CDCl$_3$, 75 MHz) 165.7 (s, J_{CF} = 1.7 Hz), 160.3 (s, J_{CF} = 252.3 Hz), 158.0 (s, J_{CF} = 1.5 Hz), 134.6 (s), 132.8 (d, J_{CF} = 8.8 Hz), 129.0 (d, J_{CF} = 2.3 Hz), 128.8 (d), 128.4 (d), 128.3 (d), 124.9 (d, J_{CF} = 3.5 Hz), 116.6 (d, J_{CF} = 21.7 Hz), 115.6 (s, J_{CF} = 11.7 Hz), 108.4 (d, J_{CF} = 9.9 Hz), 54.2 (t), 34.3 (q); **LRMS** (EI) 346 (M$^{+\bullet}$, 14), 281 (23), 162 (29), 134 (43), 120 (100); **HRMS** (EI) calcd for C$_{17}$H$_{15}$FN$_2$O$_3$S (M$^{+\bullet}$) 346.0782, observed 346.0780

3-(4-Nitrophenyl)-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123j)
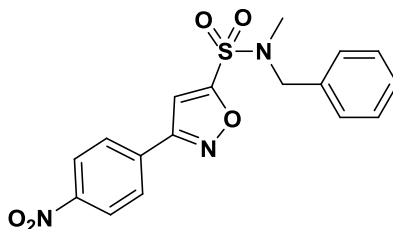
According to general procedure 8, **118j** gave the title compound as a cream solid (42 mg, 0.11 mmol, 23%).

R_f 0.19 (20% EtOAc/petroleum ether); **mp** 163-167 °C; ν_{max} (thin film, cm^{-1}) 3184, 1609, 1560, 1495, 1361, 1164; δ_H (CDCl$_3$, 300 MHz) 8.37 (2 H, d, J = 9.1 Hz, Ar*H*), 8.01 (2 H, d, J = 9.1 Hz, Ar*H*), 7.31-7.38 (5 H, m, Ar*H*), 7.15 (1 H, s, Isox*H*), 4.44 (2 H, s, NC*H$_2$*), 2.88 (3 H, s, NC*H$_3$*); δ_C (CDCl$_3$, 75 MHz) 167.2 (s), 160.7 (s), 149.2 (s), 134.4 (s), 133.3 (d), 128.9 (d), 128.4 (d), 128.4 (d), 127.9 (d), 124.5 (s), 105.9 (d), 54.3 (t), 34.6 (q); **LRMS** (EI) 373 (M$^{+\bullet}$, 100), 343 (24), 189 (91), 143 (39); **HRMS** (EI) calcd for C$_{17}$H$_{15}$N$_3$O$_5$S (M$^{+\bullet}$) 373.0727, observed 373.0733

3-Naphthyl-isoxazole-5-sulfonic-acid-*N*-methylbenzylamide (123k)
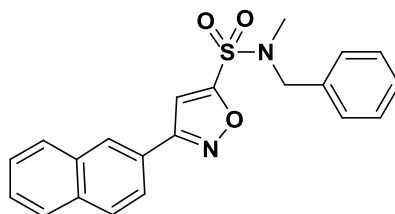
According to general procedure 8, **118k** gave the title compound as a cream solid (0.14 g, 0.36 mmol, 73%).

R_f 0.36 (20% EtOAc/petroleum ether); **mp** 105-108 °C; ν_{max} (thin film, cm^{-1}) 3156, 1605, 1515, 1362, 1165; δ_H (CDCl$_3$, 300 MHz) 8.25 (1 H, s, Ar*H*), 7.87-7.97 (4 H, m, Ar*H*), 7.55-7.60 (2 H, m, Ar*H*), 7.32-7.39 (5 H, m, Ar*H*), 7.25 (1 H, s, Isox*H*), 4.46 (2 H, s, NC*H*$_2$), 2.89 (3 H, s, NC*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 165.9 (s), 162.6 (s), 134.7 (s), 134.4 (s), 133.1 (s), 129.2 (d), 128.9 (d), 128.6 (d), 128.4 (d), 128.3 (d), 127.9 (d), 127.7 (d), 127.2 (d), 127.1 (d), 124.7 (s), 123.5 (d), 106.2 (d), 54.3 (t), 34.6 (q); **LRMS** (EI) 378 (M$^{+\bullet}$, 100), 259 (57), 194 (36), 119 (100); **HRMS** (EI) calcd for C$_{21}$H$_{18}$N$_2$O$_3$S (M$^{+\bullet}$) 378.1032, observed 378.1043

4.2.11 Preparation of isoxazole-5-sulfonic-acid-*N*-phenyl sulfonamide

General Procedure 9

To a stirred solution of the isoxazole pentafluorophenyl sulfonate ester **118** (0.5 mmol) in dry THF (12 mL/mmol) was added TBAC (1 mmol) followed by NEt$_3$ (0.75 mmol) and *N*-methylbenzylamine (1.5 mmol). The reaction was refluxed for 20 h and the mixture was diluted with dichloromethane (20 mL), washed with 2M HCl (20 mL), saturated NaHCO$_3$ (20 mL) and water (20 mL). The organic layer was dried over MgSO$_4$, filtered under gravity, and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (10% EtOAc/petroleum ether) and all products were collected as a single regioisomer as judged by NMR.

3-(4-Methoxyphenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124a)

According to general procedure 9, **118a** gave the title compound as a cream solid (0.15 g, 0.46 mmol, 93%).

R_f 0.13 (10% EtOAc/petroleum ether); **mp** 116-117 °C; ν_{max} (thin film, cm^{-1}) 3167, 2968, 1608, 1512, 1351, 1162; δ_H (CDCl$_3$, 300 MHz) 7.65 (2 H, d, J = 8.8 Hz, ArH), 7.32 (2 H, t, J = 7.8 Hz, ArH), 7.20-7.24 (3 H, m, ArH), 7.12 (1 H, s, NH), 6.97 (1 H, s, Isox$H$), 6.95 (2 H, d, J = 8.8 Hz, ArH) 3.84 (3H, s, OCH_3); δ_C (CDCl$_3$, 75 MHz) 164.9 (s), 162.2 (s), 161.8 (s), 134.5 (s), 129.7 (d), 128.5 (d), 127.0 (s), 123.2 (d), 119.6 (d), 114.6 (d), 106.5 (d), 55.5 (q); **LRMS** (EI) 330 (M$^{+\bullet}$, 14), 174 (63), 146 (100); **HRMS** (EI) calcd for C$_{16}$H$_{14}$N$_2$O$_4$S (M$^{+\bullet}$) 330.0668, observed 330.0653;

### 3-Phenyl-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124b)[192]
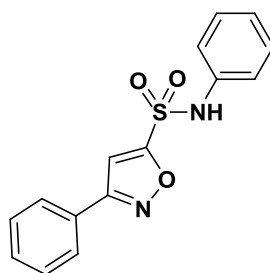
According to general procedure 9, **118b** gave the title compound as a cream solid (0.10 g, 0.34 mmol, 68%).

R_f 0.13 (10% EtOAc/petroleum ether); **mp** 114-116 °C (lit.[192] **mp** 120 °C); ν_{max} (thin film, cm^{-1}) 3290, 3067, 1599, 1498, 1353, 1159; δ_H (CDCl$_3$, 300 MHz) 7.74 (2 H, dd, J = 8.2, 1.4 Hz, ArH), 7.46-7.53 (3 H, m, ArH), 7.32 (2 H, dd, J = 7.2, 1.6 Hz, ArH), 7.20-7.25 (3 H, m, ArH), 7.04 (1 H, s, Isox$H$); δ_C (CDCl$_3$, 75 MHz) 165.3 (s), 162.7 (s), 134.4 (s), 131.1 (d), 129.7 (d), 129.2 (d), 127.2 (s), 127.0 (d), 127.0 (d), 123.2 (d), 107.1 (d); **LRMS** (EI) 300 (M$^{+\bullet}$, 13), 236 (54), 144 (87), 116 (100), 105 (63); **HRMS** (EI) calcd for C$_{15}$H$_{12}$N$_2$O$_3$S (M$^{+\bullet}$) 300.0563, observed 300.0574

3-(4-Chlorophenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124c)
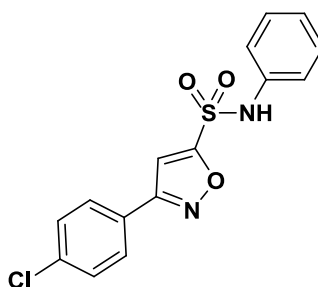
According to general procedure 9, **118c** gave the title compound as a cream solid

(0.11 g, 0.34 mmol, 68%).

R$_f$ 0.10 (20% EtOAc/petroleum ether); **mp** 153-155 °C; **ν$_{max}$** (thin film, cm^{-1}) 3238, 3152, 1601, 1492, 1351, 1169; **δ$_H$** (CDCl$_3$, 300 MHz) 7.66 (2 H, d, J = 8.5 Hz, Ar*H*), 7.43 (2 H, d, J = 8.5 Hz, Ar*H*), 7.32 (2 H, t, J = 7.2 Hz, Ar*H*), 7.20-7.25 (3 H, m, Ar*H*), 7.10 (1 H, s, N*H*), 7.01 (1 H, s, Isox*H*); **δ$_C$** (CDCl$_3$, 75 MHz) 165.7 (s), 161.6 (s), 137.2 (s), 134.0 (s), 129.7 (d), 129.5 (d), 128.2 (d), 127.1 (d), 125.6 (s), 123.1 (d), 106.8 (d); **LRMS** (EI) 336 (M$^{+\bullet}$, ^{37}Cl, 9), 334 (M$^{+\bullet}$, ^{35}Cl, 26), 272 (24), 270 (63), 152 (35), 150 (100); **HRMS** (EI) calcd for C$_{15}$H$_{11}$ClN$_2$O$_3$S (M$^{+\bullet}$) 334.0173, observed 334.0176

3-(3-Chlorophenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124d)

According to general procedure 9, **118d** gave the title compound as a cream solid (0.10 g, 0.31 mmol, 62%).

R$_f$ 0.11 (10% EtOAc/petroleum ether); **mp** 138-139 °C; **ν$_{max}$** (thin film, cm^{-1}) 3255, 3076, 1597, 1493, 1348, 1171; **δ$_H$** (CDCl$_3$, 300 MHz) 7.74 (1 H, t, J = 1.9 Hz, Ar*H*), 7.62 (1 H, dt, J = 7.7, 1.6 Hz, Ar*H*), 7.45 (1 H, t, J = 7.6 Hz, Ar*H*), 7.39 (1 H, t, J = 7.7 Hz, Ar*H*), 7.33 (2 H, t, J = 8.2 Hz, Ar*H*), 7.21-7.25 (3 H, m, Ar*H*), 7.08 (1 H, s, N*H*), 7.02 (1 H, s, Isox*H*); **δ$_C$** (CDCl$_3$, 75 MHz) 165.7 (s), 161.6 (s), 135.3 (s), 134.3 (s), 131.1 (d), 130.5 (d), 129.8 (d), 128.9 (s), 127.2 (d), 127.1 (d), 125.1 (d), 123.1 (d), 107.0 (d); **LRMS** (EI) 336 (M$^{+\bullet}$, ^{37}Cl, 19), 334 (M$^{+\bullet}$, ^{35}Cl, 59), 272 (17), 270 (23), 180 (24), 178 (71); **HRMS** (EI) calcd for C$_{15}$H$_{11}$ClN$_2$O$_3$S (M$^{+\bullet}$) 334.0173, observed 334.0183

3-(2-Chlorophenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124e)
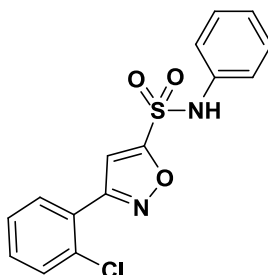
According to general procedure 9, **118e** gave the title compound as a cream solid (73 mg, 0.22 mmol, 43%).

R_f 0.10 (10% EtOAc/petroleum ether); **mp** 94-96 °C; ν_{max} (thin film, cm^{-1}) 3149, 1596, 1494, 1362, 1168; δ_H (CDCl$_3$, 300 MHz) 7.68 (1 H, d, J = 7.5 Hz, Ar*H*), 7.45 (1 H, t, J = 7.5 Hz, Ar*H*), 7.35-7.42 (2 H, m, Ar*H*), 7.32 (2 H, t, J = 7.5 Hz , Ar*H*), 7.20-7.25 (3 H, m, Ar*H*), 7.18 (1 H, s, Isox*H*); δ_C (CDCl$_3$, 75 MHz) 164.4 (s), 161.3 (s), 134.5 (s), 132.9 (s), 131.8 (d), 130.9 (d), 130.5 (d), 129.6 (d), 127.3 (d), 126.9 (d), 126.4 (s), 123.1 (d), 110.2 (d); **LRMS** (EI) 336 (M$^{+\bullet}$, ^{37}Cl, 6), 334 (M$^{+\bullet}$, ^{35}Cl, 21), 272 (17), 270 (54), 180 (28), 178 (76), 152 (34), 150 (100); **HRMS** (EI) calcd for C$_{15}$H$_{11}$ClN$_2$O$_3$S (M$^{+\bullet}$) 334.0173, observed 334.0183

3-(4-Bromophenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124f)
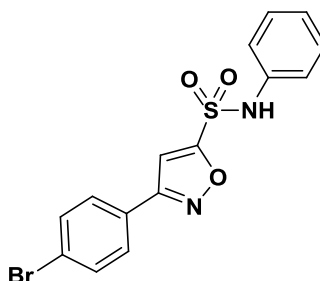
According to general procedure 9, **118f** gave the title compound as a cream solid (0.15 g, 0.40 mmol, 80%).
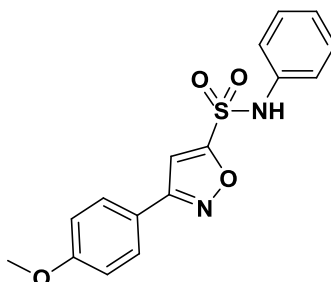
R_f 0.15 (10% EtOAc/petroleum ether); **mp** 156-158 °C; ν_{max} (thin film, cm^{-1}) 3241, 3151, 1597, 1492, 1350, 1175; δ_H (CDCl$_3$, 300 MHz) 7.60 (4 H, br s, Ar*H*), 7.32 (2 H, t, J = 7.3 Hz, Ar*H*), 7.21-7.25 (3 H, m, Ar*H*), 7.09 (1 H, s, N*H*), 7.00 (1 H, s, Isox*H*); δ_C (CDCl$_3$, 75 MHz) 166.0 (s), 161.6 (s), 135.7 (s), 132.2 (d), 129.3 (d), 128.9 (d), 126.0 (s), 125.4 (d), 124.6 (s), 121.2 (d), 106.9 (d); **LRMS** (EI) 380 (M$^{+\bullet}$, ^{81}Br, 17), 378 (M$^{+\bullet}$, ^{79}Br, 17), 316 (46), 314 (53), 224 (100), 222 (93), 196 (93), 194 (96); **HRMS** (EI) calcd for C$_{15}$H$_{11}$BrN$_2$O$_3$S (M$^{+\bullet}$) 377.9668, observed 377.9672

3-(3-Bromophenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124g)
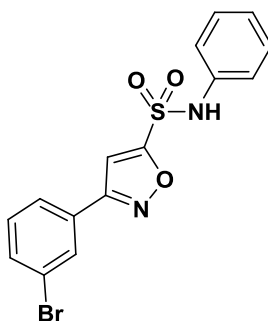
According to general procedure 9, **118g** gave the title compound as a cream solid (79 mg, 0.21 mmol, 42%).

R_f 0.13 (10% EtOAc/petroleum ether); **mp** 137-140 °C; ν_{max} (thin film, cm^{-1}) 3256, 3074, 1596, 1493, 1349, 1169; δ_H (CDCl$_3$, 300 MHz) 7.89 (1 H, s, Ar*H*), 7.66 (1 H, d, *J* = 7.2 Hz, Ar*H*), 7.60 (1 H, d, *J* = 7.2 Hz, Ar*H*), 7.33-7.41 (3 H, m, Ar*H*), 7.20-7.25 (3 H, m, Ar*H*), 7.02 (1 H, s, Isox*H*); δ_C (CDCl$_3$, 75 MHz) 165.7 (s), 161.4 (s), 134.3 (s), 134.0 (d), 130.7 (d), 129.9 (d), 129.8 (d), 129.1 (s), 127.2 (d), 125.5 (d), 123.3 (s), 123.2 (d), 107.0 (d); **LRMS** (EI) 380 (M$^{+\bullet}$, ^{81}Br, 15), 378, (M$^{+\bullet}$, ^{79}Br, 15), 316 (49), 314 (51), 224 (65), 222 (67), 196 (43), 194 (41), 157 (45), 155 (47), 105 (100); **HRMS** (EI) calcd for C$_{15}$H$_{11}$BrN$_2$O$_3$S (M$^{+\bullet}$) 377.9668, observed 377.9668

### 3-(2-Bromophenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124h)
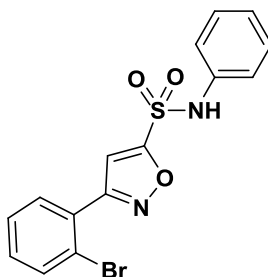
According to general procedure 9, **118h** gave the title compound as a cream solid (88 mg, 0.23 mmol, 47%).

R_f 0.12 (10% EtOAc/petroleum ether); **mp** 81-83 °C; ν_{max} (thin film, cm^{-1}) 3149, 1593, 1493, 1362, 1169; δ_H (CDCl$_3$, 300 MHz) 7.66 (1 H, dd, *J* = 8.0, 1.3 Hz, Ar*H*), 7.59 (1 H, dd, *J* = 8.0, 1.3 Hz, Ar*H*), 7.39 (1 H, td, *J* = 8.0, 1.4 Hz, Ar*H*), 7.30-7.35 (3 H, m, Ar*H*), 7.21-7.25 (3 H, m, Ar*H*), 7.13 (1 H, s, Isox*H*); δ_C (CDCl$_3$, 75 MHz) 164.1 (s), 162.6 (s), 134.1 (s), 133.7 (d), 131.9 (d), 131.3 (d), 129.6 (d), 128.5 (s), 127.8 (d), 127.9 (d), 123.2 (d), 122.2 (s), 110.4 (d); **LRMS** (EI) 380 (M$^{+\bullet}$, ^{81}Br, 13), 378 (M$^{+\bullet}$, ^{79}Br, 13), 316 (64), 314 (63), 224 (55), 222 (58), 196 (99), 194 (100);

HRMS (EI) calcd for $C_{15}H_{11}BrN_2O_3S$ ($M^{+\bullet}$) 377.9668, observed 377.9668

3-(2-Fluorophenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124i)
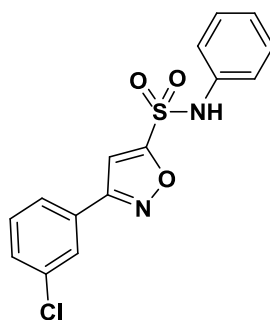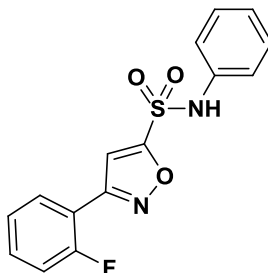

According to general procedure 9, **118i** gave the title compound as a cream solid (27 mg, 0.08 mmol, 17%).

R_f 0.15 (10% EtOAc/petroleum ether); **mp** 120-122 °C; ν_{max} (thin film, cm^{-1}) 3218, 2923, 1598, 1462, 1414, 1360, 1154; δ_H (CDCl$_3$, 300 MHz) 7.93 (1 H, t, J = 7.6 Hz, Ar*H*), 7.46 (1 H, t, J = 7.5 Hz, Ar*H*), 7.28-7.35 (3 H, m, Ar*H*), 7.18-7.27 (4 H, m, Ar*H* & Isox*H*), 7.17 (1 H, t, J= 8.3 Hz, Ar*H*); δ_C (CDCl$_3$, 75 MHz) 165.2 (s), 160.2 (s, J_{CF} = 252.4 Hz), 158.1 (s), 134.0 (s), 132.8 (d, J_{CF} = 8.6 Hz), 129.7 (d), 129.0 (d, J_{CF} = 2.9 Hz), 126.9 (d), 124.9 (d, J_{CF} = 3.8 Hz), 122.9 (d), 116.6 (d, J_{CF} = 21.1 Hz), 115.4 (s, J_{CF} = 11.5 Hz), 109.4 (d, J_{CF} = 9.6 Hz); **LRMS** (EI) 318 ($M^{+\bullet}$, 100), 254 (15); **HRMS** (EI) calcd for $C_{15}H_{11}FN_2O_3S$ ($M^{+\bullet}$) 318.0469, observed 318.0472

3-(4-Nitrophenyl)-isoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124j)
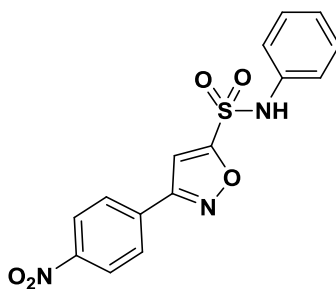
According to general procedure 9, **118j** gave the title compound as a cream solid (76 mg, 0.22 mmol, 44%).

R_f 0.09 (10% EtOAc/petroleum ether); **mp** 168-171 °C; ν_{max} (thin film, cm^{-1}) 3283, 3103, 1611, 1562, 1491, 1355, 1338, 1174; δ_H (CDCl$_3$, 300 MHz) 8.33 (2 H, d, J = 8.8 Hz, Ar*H*), 7.94 (2 H, d, J = 8.8 Hz, Ar*H*), 7.34 (2 H, t, J = 7.8 Hz, Ar*H*), 7.20-7.25 (3 H, m, Ar*H*), 7.09 (1 H, m, Isox*H*), 6.97 (1 H, s, N*H*); δ_C (CDCl$_3$, 75 MHz) 166.5 (s), 160.9 (s), 149.3 (s), 134.1 (s), 133.1 (s), 129.8 (d), 127.9 (d), 127.3 (d), 124.0 (d), 123.28 (d), 107.0 (d); **LRMS** (EI) 345 ($M^{+\bullet}$, 100), 281 (62), 189 (71), 163

(22); **HRMS** (EI) calcd for $C_{15}H_{11}N_3O_5S$ (M$^{+\bullet}$) 345.0414, observed 345.0414

**3-Naphthylisoxazole-5-sulfonic-acid-*N*-phenylsulfonamide (124k)**
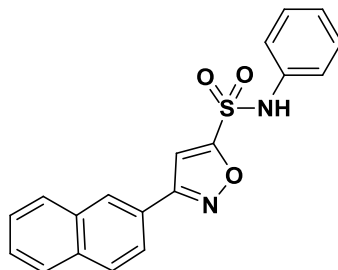
According to general procedure 9, **118k** gave the title compound as a pink solid (80 mg, 0.23 mmol, 46%).

R$_f$ 0.08 (10% EtOAc/petroleum ether); **mp** 139-141 °C; **ν$_{max}$** (thin film, cm^{-1}) 3220, 3051, 1595, 1494, 1352, 1170; **δ$_H$** (CDCl$_3$, 300 MHz) 8.17 (1 H, s, Ar*H*), 7.89 (1 H, t, *J* = 8.2 Hz, Ar*H*), 7.84-7.87 (3 H, m, Ar*H*), 7.54-7.61 (2 H, m, Ar*H*), 7.33 (2 H, t, *J* = 7.2 Hz, Ar*H*), 7.20-7.25 (3 H, m, Ar*H*), 7.19 (1 H, s, Isox*H*); **δ$_C$** (CDCl$_3$, 75 MHz) 165.4 (s), 162.7 (s), 134.5 (s), 134.4 (s), 133.0 (s), 129.7 (s), 129.2 (d), 128.6 (d), 127.9 (d), 127.7 (d), 127.3 (d), 127.1 (d), 127.0 (d), 124.5 (d), 123.5 (d), 123.2 (d), 107.3 (d); **LRMS** (EI) 350 (M$^{+\bullet}$, 30), 286 (23), 194 (100), 166 (61), 127 (65); **HRMS** (EI) calcd for $C_{19}H_{14}N_2O_3S$ (M$^{+\bullet}$) 350.0719, observed 350.0707

4.3   Experimental procedure for Chapter 2.4

Ethenesulfonic acid-4-methylbenzylamide (141)[113]
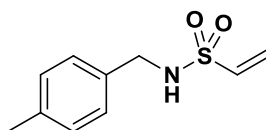
A premixed suspension of 4-methylbenzylamine (15 mL, 55 mmol, 1.1 eq.) and NEt$_3$ (14.6 mL, 105 mmol, 2.1 eq.) in dichloromethane (19 mL) was added dropwise to a stirring solution of 2-chloroethane sulfonylchloride **111** (8.2 g, 50 mmol) in dichloromethane (75 mL) at -10 °C. The reaction mixture was stirred for further 30 min after the addition and warmed slowly to RT. The reaction mixture was diluted with dichloromethane and washed with 2M HCl and water. The organic layer was dried with MgSO$_4$, filtered and solvent removed *in vacuo*. Crude residue was purified by flash chromatography (starting 3:1 petroleum ether/Et$_2$O) to give the title

compound as a white solid (7.8 g, 37 mmol, 74%).

R_f 0.21 (1:1 petroleum ether/Et$_2$O); mp 83-86 °C (lit.[113] mp 87 °C); ν_{max} (thin film, cm^{-1}) 3222, 3043, 1611, 1515, 1317, 1146; δ_H (CDCl$_3$, 500 MHz) 7.19 (2 H, d, J = 8.2 Hz, ArH), 7.14 (2 H, d, J = 8.2 Hz, ArH), 6.46 (1 H, dd, J = 16.5, 9.9 Hz, CH$_2$CH), 6.23 (1 H, d, J = 16.5 Hz, CHCHHtrans), 5.88 (1 H, d, J = 9.9 Hz, CHCHHcis), 4.71 (1 H, t, J = 4.9 Hz, NH), 4.15 (2 H, d, J = 4.9 Hz, NCH_2), 2.33 (3 H, s, CH_3); δ_C (CDCl$_3$, 125 MHz) 137.9 (s), 136.1 (d), 133.5 (s), 129.5 (d), 128.0 (d), 126.7 (t), 46.9 (t), 21.2 (q); LRMS (EI) 211 (M$^{+\bullet}$, 6), 120 (100), 105 (23); HRMS (EI) calcd for C$_{10}$H$_{13}$NO$_2$S (M$^{+\bullet}$) 211.0661, observed 211.0666

4.3.1   Preparation of *N*-methyl nitrone

General Procedure 10

To *N*-methylhydroxylamine.HCl (24 mmol) in dry dichloromethane (1 mL/mmol) was added aldehyde (20 mmol) and NaHCO$_3$ (60 mmol). The mixture was refluxed for 2 h and the resulting suspension was filtered. Solid residue was washed with dichloromethane and the combined organic layer was dried with MgSO$_4$, filtered and solvent was removed *in vacuo*. All products were collected as a single diastereoisomer as judged by NMR

C-(5-Bromofuryl)-N-methyl nitrone (140a)[113]
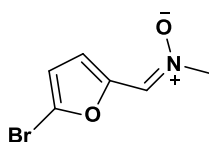
According to general procedure 10 to give the title compound as a white solid (2.7 g, 13 mmol, 67%).

R_f 0.56 (9:1 CH$_2$Cl$_2$/MeOH); mp 143-144 °C (lit.[113] mp 143 °C); ν_{max} (thin film, cm^{-1}) 3177, 2942, 1601, 1549, 1483, 1385, 686; δ_H (CDCl$_3$, 500 MHz) 7.68 (1 H, d, J = 3.7 Hz, furyl$H$), 7.47 (1 H, s, NCH), 6.46 (1 H, d, J = 3.7 Hz, furyl$H$), 3.80 (3 H, s, NCH_3); δ_C (CDCl$_3$, 125 MHz) 148.7 (s), 125.3 (d), 124.4 (s), 117.5 (d), 114.3 (d), 52.9 (q); LRMS (EI) 205 (M$^{+\bullet}$, ^{81}Br, 98), 203 (M$^{+\bullet}$, ^{79}Br, 100); HRMS (EI) calcd for C$_6$H$_7$BrNO$_2$ (M$^{+\bullet}$) 202.9576, observed 202.9567

C-(5-Chlorofuryl)-*N*-methyl nitrone (140b)
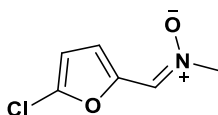
According to general procedure 10 to give the title compound as a yellow oil (1.9 g, 12 mmol, 64%).

R_f 0.52 (9:1 CH$_2$Cl$_2$/MeOH); ν_{max} (thin film, cm^{-1}) 3167, 3079, 2941, 1598, 1493, 1393, 783; δ_H (CDCl$_3$, 500 MHz) 7.67 (1 H, d, *J* = 3.6 Hz, furyl*H*), 7.43 (1 H, s, NC*H*), 6.28 (1 H, d, *J* = 3.6 Hz, furyl*H*), 3.77 (3 H, s, NC*H$_3$*); δ_C (CDCl$_3$, 75 MHz) 148.5 (s), 125.2 (d), 124.5(s), 117.2 (d), 109.1 (d), 25.8 (q); **LRMS** (EI) 161 (M$^{+\bullet}$, ^{37}Cl, 35), 159 (M$^{+\bullet}$, ^{35}Cl, 100), 129 (41); **HRMS** (EI) calcd for C$_6$H$_7$ClNO$_2$ (M$^{+\bullet}$) 159.0081, observed 159.0086

N-Methyl-*C*-phenyl nitrone (140c)[113]
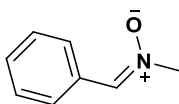
According to general procedure 10 to give the title compound as a white solid (1.8 g, 13 mmol, 66%).

R_f 0.5 (9:1 CH$_2$Cl$_2$/MeOH); **mp** 87-89 °C (lit.[113] **mp** 90 °C); ν_{max} (thin film, cm^{-1}) 3058, 2932, 1693, 1594, 1399, 1163, 942, 754; δ_H (CDCl$_3$, 300 MHz) 8.14-8.22 (2 H, m, Ar*H*), 7.36-7.43 (3 H, m, Ar*H*), 7.33 (1 H, s, NC*H*), 3.81 (3 H, s, NC*H$_3$*); δ_C (CDCl$_3$, 75 MHz) 135.2 (d), 130.5 (d), 130.4 (s), 128.4 (d), 128.4 (d), 54.4 (q); **LRMS** (EI) 135 (M$^{+\bullet}$, 93), 134 (M-H, 92), 118 (21); **HRMS** (EI) calcd for C$_8$H$_9$NO (M$^{+\bullet}$) 135.0678, observed 135.0673

C-(4-Chlorophenyl)-*N*-methyl nitrone (140d)[113]
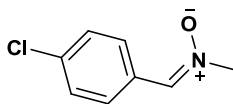
According to general procedure 10 to give the title compound as a white solid (2.7 g, 16 mmol, 78%).

R_f 0.5 (9:1 CH$_2$Cl$_2$/MeOH); **mp** 130-133 °C (lit.[113] **mp** 135 °C); ν_{max} (thin film, cm^{-1}) 3084, 3036, 2944, 1590, 1556, 1482, 704; δ_H (CDCl$_3$, 300 MHz) 8.13 (2 H, d, *J* = 8.5 Hz, Ar*H*), 7.34 (2 H, d, *J* = 8.5 Hz, Ar*H*), 7.32 (1 H, s, NC*H*), 3.83 (3 H, s,

NCH_3); δ_C (CDCl$_3$, 75 MHz) 171.8 (s), 135.8 (s), 134.0 (d), 129.5 (d), 128.9 (d), 54.4 (q); **LRMS** (EI) 171 (M$^{+\bullet}$, ^{37}Cl, 34), 169 (M$^{+\bullet}$, ^{35}Cl, 97), 141 (22); **HRMS** (EI) calcd for C$_8$H$_8$ClNO (M$^{+\bullet}$) 169.0289, observed 169.0287

N-Methyl-*C*-(2-nitrophenyl) nitrone (140e)

According to general procedure 10 to give the title compound as a yellow solid (2.9 g, 16 mmol, 81%).

R$_f$ 0.52 (9:1 CH$_2$Cl$_2$/MeOH); **mp** 122-123 °C; **ν_{max}** (thin film, cm^{-1}) 3101, 3051, 1605, 1508, 1420, 1345; δ_H (CDCl$_3$, 500 MHz) 9.13 (1 H, dd, *J* = 7.8, 1.4 Hz, Ar*H*), 8.01 (1 H, dd, *J* = 7.8, 1.4 Hz, Ar*H*), 8.01 (1 H, s, NC*H*), 7.68 (1 H, td, *J* = 7.6, 1.4 Hz, Ar*H*), 7.51 (1 H, td, *J* = 7.8, 1.4 Hz, Ar*H*), 3.93 (3 H, s, NC*H$_3$*); δ_C (CDCl$_3$, 125 MHz) 147.2 (s), 133.5 (d), 130.2 (d), 129.4 (d), 129.1 (d), 124.9 (d), 124.4 (s), 55.6 (q); **LRMS** (EI) 180 (M$^{+\bullet}$, 3), 135 (100); **HRMS** (EI) calcd for C$_8$H$_9$N$_2$O$_3$ (M$^{+\bullet}$) 180.0529, observed 180.0525

C-(4-Fluorophenyl)-*N*-methyl nitrone (140f)
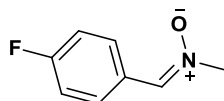
According to general procedure 10 to give the title compound as a white solid (2.9 g, 19 mmol, 96%).

R$_f$ 0.48 (9:1 CH$_2$Cl$_2$/MeOH); **mp** 113-115 °C; **ν_{max}** (thin film, cm^{-1}) 3079, 3010, 2946, 1595, 1578, 1499, 1167, 858; δ_H (CDCl$_3$, 500 MHz) 8.23 (2 H, dd, *J* = 8.8, 2.0 Hz, Ar*H*), 7.33 (1 H, s, NC*H*), 7.07 (2 H, d, *J* = 8.8 Hz, Ar*H*), 3.83 (3 H, s, NC*H$_3$*); δ_C (CDCl$_3$, 125 MHz) 163.3 (s, *J*$_{CF}$ = 252.4 Hz), 134.1 (d), 130.6 (d, *J*$_{CF}$ = 8.6 Hz), 127.0 (s, *J*$_{CF}$ = 2.9 Hz), 115.7 (d, *J*$_{CF}$ = 21.1 Hz), 54.3 (q); **LRMS** (EI) 153 (M$^{+\bullet}$, 82), 152 (M-H, 100), 107 (15); **HRMS** (EI) calcd for C$_8$H$_8$FNO (M$^{+\bullet}$) 153.0584, observed 153.0578

C-(2-Fluorophenyl)-*N*-methyl nitrone (140g)[113]
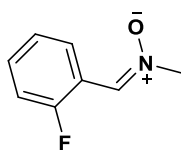
According to general procedure 10 to give the title compound as a white solid (2.8 g, 18 mmol, 92%).

R$_f$ 0.52 (9:1 CH$_2$Cl$_2$/MeOH); **mp** 58-60 °C (lit.[113] **mp** 59 °C); **ν$_{max}$** (thin film, cm^{-1}) 3111, 3053, 3001, 2942, 1650, 1609, 1586, 1476, 802; **δ$_H$** (CDCl$_3$, 300 MHz) 9.20-9.27 (1 H, m, Ar*H*), 7.64 (1 H, s, NC*H*), 7.35-7.42 (1 H, m, Ar*H*), 7.19 (1 H, t, *J* = 7.5 Hz, Ar*H*), 7.05-7.09 (1 H, m, Ar*H*), 3.89 (3 H, s, NC*H*$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 160.1 (s, *J$_{CF}$* = 252.9 Hz), 131.7 (d, *J$_{CF}$* = 8.8 Hz), 128.6 (d), 127.4 (d, *J$_{CF}$* = 7.9 Hz), 124.4 (d, *J$_{CF}$* = 3.5 Hz), 118.9 (s, *J$_{CF}$* = 9.1 Hz), 114.6 (d, *J$_{CF}$* = 21.1 Hz), 54.9 (q); **LRMS** (EI) 153 (M$^{+•}$, 88), 152 (M-H, 19), 136 (32), 125 (68), 107 (100); **HRMS** (EI) calcd for C$_8$H$_8$FNO (M$^{+•}$) 153.0584, observed 153.0579

C-(4-Iodophenyl)-*N*-methyl nitrone (140h)
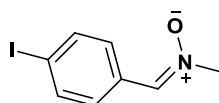
According to general procedure 10 to give the title compound as a white solid (1.9 g, 7.2 mmol, 92%).

R$_f$ 0.52 (9:1 CH$_2$Cl$_2$/MeOH); **mp** 162-164 °C; **ν$_{max}$** (thin film, cm^{-1}) 3075, 1927, 1621, 1589, 1477, 1389, 1165, 827; **δ$_H$** (CDCl$_3$, 300 MHz) 7.93 (2 H, dd, *J* = 8.5, 1.6 Hz, Ar*H*), 7.73 (2 H, dd, *J* = 8.5, 1.4 Hz, Ar*H*), 7.31 (1 H, s, NC*H*), 3.84 (3 H, s, NC*H*$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 137.7 (d), 134.3 (s), 129.8 (d), 129.6 (d), 96.4 (s), 54.6 (q); **LRMS** (EI) 261 (M$^{+•}$, 100), 260 (M-H, 12); **HRMS** (EI) calcd for C$_8$H$_8$INO (M$^{+•}$) 260.9645, observed 260.9633

C-(2-Iodophenyl)-*N*-methyl nitrone (140i)[113]
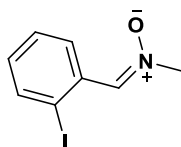
According to general procedure 10 to give the title compound as a white solid (2.0 g, 7.7 mmol, 98%).

R_f 0.58 (9:1 CH_2Cl_2/MeOH); **mp** 146-147 °C (lit.[113] **mp** 124 °C); ν_{max} (thin film, cm^{-1}) 3085, 3020, 1572, 1459, 1163, 674; δ_H (CDCl$_3$, 300 MHz) 9.19 (1 H, dd, J = 8.0, 1.6 Hz, ArH), 7.90 (1 H, dd, J = 8.0, 1.5 Hz, ArH), 7.70 (1 H, s, NCH), 7.42 (1 H, t, J = 8.0 Hz, ArH), 7.06 (1 H, td, J = 8.0, 1.6 Hz, ArH), 3.92 (3 H, s, NCH_3); δ_C (CDCl$_3$, 75 MHz) 139.7 (d), 132.3 (s), 131.8 (d), 131.5 (d), 129.1 (d), 128.4 (d), 96.4 (s), 55.2 (q); **LRMS** (EI) 261 (M$^{+\bullet}$, 3), 107 (7), 91 (100); **HRMS** (EI) calcd for C_8H_8INO (M$^{+\bullet}$) 260.9645, observed 260.9644
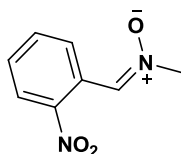
N-Methyl-C-(4-nitrophenyl) nitrone (140j)[113]
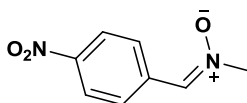
According to general procedure 10 to give the title compound as a yellow solid (2.3 g, 13 mmol, 67%).

R_f 0.58 (9:1 CH_2Cl_2/MeOH); **mp** 216-218 °C (lit.[113] **mp** 219 °C); ν_{max} (thin film, cm^{-1}) 3112, 3082, 3022, 2953, 1708, 1597, 1508, 1333, 1164; δ_H (CDCl$_3$, 300 MHz) 8.37 (2 H, d, J = 8.9 Hz, ArH), 8.25 (2 H, d, J = 8.9 Hz, ArH), 7.52 (1 H, s, NCH), 3.95 (3 H, s, NCH_3); δ_C (CDCl$_3$, 75 MHz) 147.9 (s), 136.0 (s), 133.2 (d), 128.7 (d), 123.9 (d), 55.2 (q); **LRMS** (EI) 180 (M$^{+\bullet}$, 100), 179 (M-H, 56), 133 (54); **HRMS** (EI) calcd for $C_8H_9N_2O_3$ (M$^{+\bullet}$) 180.0529, observed 180.0533

4.3.2   Preparation of isoxazolidine pentafluorophenyl sulfonate ester

(3S*, 4S*)-3-Furyl-2-methylisoxazolidine-4-pentafluorophenyl sulfonate ester (135)[122]
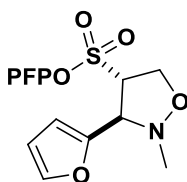
To a stirred solution of pentafluorophenyl ethenesulfonate **110** (0.41 g, 1.5 mmol) in toluene (5 mL) was added C-furyl-N-methyl nitrone (0.27 g, 2.2 mmol, 1.5 eq.) and refluxed for 3 h. Solvent was removed *in vacuo* and the residue was purified by flash chromatography (2:1 petroleum ether/Et$_2$O) to give the title compound as a clear oil and as a single diastereoisomer as judged by NMR (0.40 g, 1.0 mmol, 67%).

R_f 0.37 (2:1 petroleum ether/Et$_2$O); ν_{max} (thin film, cm^{-1}) 2881, 1736, 1515, 1381, 1187, 990; δ_H (CDCl$_3$, 500 MHz) 7.46 (1 H, br s, furyl$H$), 6.48 (1 H, d, J = 3.2 Hz,

furyl*H*), 6.38 (1 H, d, *J* = 3.2 Hz, furyl*H*), 4.69 (1 H, td, *J* = 8.8, 3.3 Hz, SC*H*), 4.59 (1 H, dd, *J* = 10.3, 3.3 Hz, SCHC*H*H), 4.48 (1 H, dd, *J* = 10.3, 8.8 Hz, SCHCH*H*), 4.17 (1 H, br s, NC*H*), 2.76 (3 H, s, NC*H*$_3$); δ_C (CDCl$_3$, 125 MHz) 146.7 (s), 144.0 (d), 111.1 (d), 110.9 (d), 69.8 (d), 67.6 (d), 66.8 (t), 43.0 (q); **LRMS** (EI) 399 (M$^{+\bullet}$, 14), 125 (20), 107 (43), 94 (100); **HRMS** (EI) calcd for C$_{14}$H$_{10}$F$_5$NO$_5$S (M$^{+\bullet}$) 399.0194, observed 399.0206

(3S*, 4S*)-3-(5-Bromofuryl)-2-methylisoxazolidine-4-pentafluorophenyl sulfonate ester (136)[113]
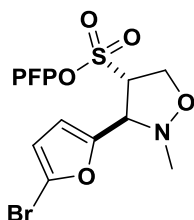
To a stirred solution of pentafluorophenyl ethenesulfonate **110** (0.41 g, 1.5 mmol) in toluene (5 mL) was added *C*-(5-bromofuryl)-*N*-methyl nitrone **140a** (0.45 g, 2.2 mmol, 1.5 eq.) and refluxed for 3 h. Solvent was removed *in vacuo* and the residue was purified by flash chromatography (2:1 petroleum ether/Et$_2$O) to give the title compound as a clear oil and as a single diastereoisomer as judged by NMR (0.52 g, 1.1 mmol, 73%).

R$_f$ 0.48 (2:1 petroleum ether/Et$_2$O); ν_{max} (thin film, cm^{-1}) 3059, 2919, 1728, 1598, 1577, 1515, 1388, 1186; δ_H (CDCl$_3$, 500 MHz) 6.47 (1 H, d, *J* = 3.3 Hz, furyl*H*), 6.31 (1 H, d, *J* = 3.3 Hz, furyl*H*), 4.65 (1 H, td, *J* = 8.5, 3.1 Hz, SC*H*), 4.57 (1 H, dd, *J* = 10.2, 3.1 Hz, SCHC*H*H), 4.49 (1 H, dd, *J* = 10.2, 8.4 Hz, SCHCH*H*), 4.11 (1 H, br s, NC*H*), 2.78 (3 H, s, NC*H*$_3$); δ_C (CDCl$_3$, 125 MHz) 148.7 (s), 123.9 (s), 113.9 (d), 112.7 (d), 69.7 (d), 67.5 (d), 66.8 (t), 42.9 (q); **LRMS** (EI) 479 (M$^{+\bullet}$, ^{81}Br, 96), 478 (M$^{+\bullet}$, ^{79}Br, 95), 433 (^{81}Br, 37), 431 (^{79}Br, 34), 205 (^{81}Br, 77), 203 (^{79}Br, 74), 184 (100), 120 (64); **HRMS** (EI) calcd for C$_{14}$H$_9$BrF$_5$NO$_5$S (M$^{+\bullet}$) 476.9299, observed 476.9303

4.3.3 Preparation of isoxazolidine-4-methylbenzyl sulfonamide

General procedure 11

To a stirred solution of 4-methylbenzyl ethenesulfonamide **141** (1 mmol) in toluene (5 mL/mmol) was added nitrone **140** (3 mmol) and the mixture was then heated in

microwave at 140 °C for 30 min. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether/Et$_2$O) and all products were collected as a single diastereoisomer as judged by NMR.

(3S*, 4S*)-2-Methyl-3-phenylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (142a)[113, 122]
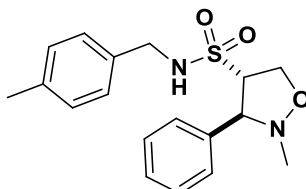
According to general procedure 11, **140c** gave the title compound as a yellow oil (0.10 g, 0.30 mmol, 34%).

R$_f$ 0.29 (1:2 petroleum ether/Et$_2$O); **v$_{max}$** (thin film, cm^{-1}) 3284, 2922, 2874, 1736, 1516, 1455, 1327, 1147; **δ$_H$** (CDCl$_3$, 500 MHz) 7.41-7.45 (2 H, m, ArH), 7.37-7.40 (3 H, m, ArH), 7.05 (2 H, d, J = 7.9 Hz, ArH), 6.94 (2 H, d, J = 7.9 Hz, ArH), 5.09 (1 H, t, J = 5.6 Hz, NH), 4.33 (1 H, dd, J = 9.7, 3.6 Hz, SCHCHH), 4.22 (1 H, app dt, J = 9.7, 8.3 Hz, SCHCHH), 4.07 (1 H, dd, J = 13.8, 5.6 Hz, NCHHAr), 3.92 (1 H, td, J = 8.0, 3.6 Hz, SCH), 3.85 (1 H, d, J = 13.8 Hz, NCHHAr), 3.83 (1 H, d, J = 8.0 Hz, NCH), 2.57 (3 H, s, NCH_3), 2.31 (3 H, s, CH_3); **δ$_C$** (CDCl$_3$, 125 MHz) 137.9 (s), 136.9 (s), 133.6 (s), 129.6 (d), 129.0 (d), 128.8 (d), 128.5 (d), 128.2 (d) , 74.5 (d), 73.3 (d), 66.9 (t), 47.0 (t), 42.8 (q), 21.2 (q); **LRMS** (EI) 346 (M$^{+•}$, 12), 160 (100), 134 (21), 117 (46); **HRMS** (EI) calcd for C$_{18}$H$_{22}$N$_2$O$_3$S (M$^{+•}$) 346.1345, observed 346.1353

(3S*, 4S*)-3-(4-Fluorophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (142b)
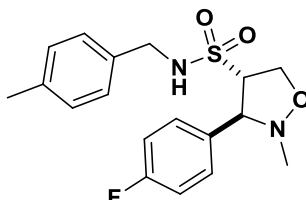
According to general procedure 11, **140f** gave the title compound as a cream solid (94 mg, 0.26 mmol, 26%).

R$_f$ 0.29 (1:2 petroleum ether/Et$_2$O); **mp** 129-132 °C; **v$_{max}$** (thin film, cm^{-1}) 3284,

2923, 2874, 1606, 1510, 1324, 1146, 841; δ_H (CDCl$_3$, 500 MHz) 7.37 (2 H, d, J = 8.5 Hz, ArH), 7.07 (2 H, d, J = 8.0 Hz, ArH), 7.03 (2 H, d, J = 8.5 Hz, ArH), 6.97 (2 H, d, J = 8.0 Hz, ArH), 4.93 (1 H, t, J = 5.3 Hz, NH), 4.31 (1 H, dd, J = 9.7, 3.3 Hz, SCHCHH), 4.19 (1 H, dd, J = 9.7, 7.8 Hz, SCHCHH), 4.11 (1 H, dd, J = 13.7, 5.3 Hz, NCHHAr), 3.96 (1H, dd, J = 13.7, 5.3 Hz, NCHHAr), 3.79-3.84 (2 H, m, SCH & NCH), 2.57 (3 H, s, NCH_3), 2.31 (3 H, s, CH_3); δ_C (CDCl$_3$, 125 MHz) 162.9 (s, J_{CF} = 248.6 Hz), 138.0 (s), 133.3 (s), 132.8 (s, J_{CF} = 2.9 Hz), 130.0 (d, J_{CF} = 8.6 Hz), 129.6 (d), 128.0 (d), 116.0 (d, J_{CF} = 22.1 Hz), 73.6 (d), 72.2 (d), 66.9 (t), 46.3 (t), 42.7 (q), 21.2 (q); **LRMS** (EI) 364 (M$^{+\bullet}$, 8), 178 (100), 135 (30); **HRMS** (EI) calcd for C$_{18}$H$_{21}$FN$_2$O$_3$S (M$^{+\bullet}$) 364.1251, observed 364.1246

(3S*, 4S*)-3-(4-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (142c)[113]

According to general procedure 11, **140d** gave the title compound as a yellow oil (0.11 g, 0.30 mmol, 31%).

R$_f$ 0.29 (1:2 petroleum ether/Et$_2$O); ν_{max} (thin film, cm^{-1}) 3285, 2922, 2874, 1736, 1599, 1492, 1323, 1145, 736; δ_H (CDCl$_3$, 500 MHz) 7.31-7.34 (4 H, m, ArH), 7.07 (2 H, d, J = 8.0 Hz, ArH), 6.96 (2 H, d, J = 8.0 Hz, ArH), 5.00 (1 H, t, J = 5.5 Hz, NH), 4.30 (1 H, dd, J = 9.7, 3.3 Hz, SCHCHH), 4.18 (1 H, dd, J = 9.7, 7.9 Hz, SCHCHH), 4.11 (1 H, dd, J = 13.8, 5.6 Hz, NCHHAr), 3.97 (1H, dd, J = 13.8, 5.5 Hz, NCHHAr), 3.77-3.82 (2 H, m, SCH & NCH), 2.57 (3 H, s, NCH_3), 2.32 (3 H, s, CH_3); δ_C (CDCl$_3$, 125 MHz) 137.9 (s), 135.6 (s), 134.6 (s), 133.2 (s), 129.6 (d), 129.2 (d), 128.9 (d), 128.0 (d), 73.6 (d), 72.2 (d), 67.0 (t), 47.5 (t), 42.8 (q), 21.2 (q); **LRMS** (EI) 382 (M$^{+\bullet}$, ^{37}Cl, 2), 380 (M$^{+\bullet}$, ^{35}Cl, 5), 196 (^{37}Cl, 38), 194 (^{35}Cl, 100), 178 (25), 151 (42), 120 (51); **HRMS** (EI) calcd for C$_{18}$H$_{21}$ClN$_2$O$_3$S (M$^{+\bullet}$) 380.0956, observed 380.0963

(3S*, 4S*)-3-(4-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (142d)[113]
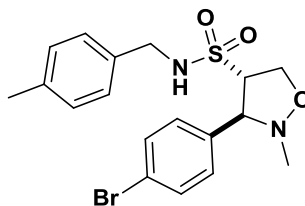
According to general procedure 11 to give the title compound as a cream solid (0.13 g, 0.31 mmol, 30%).

R_f 0.31 (1:2 petroleum ether/Et$_2$O); **mp** 112-113 °C (lit.[113] **mp** 98 °C); ν_{max} (thin film, cm^{-1}) 3284, 2920, 2873, 1736, 1592, 1488, 1324, 1146, 686; δ_H (CDCl$_3$, 500 MHz) 7.47 (2 H, d, J = 8.2 Hz, ArH), 7.26 (2 H, d, J = 8.2 Hz, ArH), 7.07 (2 H, d, J = 7.7 Hz, ArH), 6.96 (2 H, d, J = 7.7 Hz, ArH), 5.04 (1 H, t, J = 5.5 Hz, NH), 4.30 (1 H, dd, J = 9.7, 3.3 Hz, SCHCHH), 4.15-4.19 (1 H, dd, J = 9.7, 8.5 Hz, SCHCHH), 4.11 (1 H, dd, J = 13.8, 5.5 Hz, NCHHAr), 3.97 (1 H, dd, J = 13.8, 5.5 Hz, NCHHAr), 3.76-3.80 (2 H, m, SCH & NCH), 2.56 (3 H, NCH_3), 2.32 (3 H, s, CH_3); δ_C (CDCl$_3$, 125 MHz) 138.0 (s), 136.2 (s), 133.2 (s), 132.2 (d), 129.9 (d), 129.4 (d), 128.2 (d), 122.8 (s), 73.6 (d), 72.1 (d), 67.0 (t), 47.1 (t), 42.8 (q), 21.2 (q); **LRMS** (EI) 426 (M$^{+\bullet}$, ^{81}Br, 7), 424 (M$^{+\bullet}$, ^{79}Br, 6), 240 (^{81}Br, 100), 238 (^{79}Br, 95), 214 (^{81}Br, 14), 212 (^{79}Br, 16), 116 (43); **HRMS** (EI) calcd for C$_{18}$H$_{21}$BrN$_2$O$_3$S (M$^{+\bullet}$) 424.0450, observed 424.0447

(3S*, 4S*)-3-(4-Iodophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (142e)
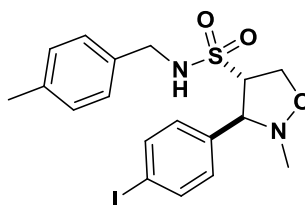
According to general procedure 11, **140h** gave the title compound as a cream solid (0.17 g, 0.36 mmol, 35%).

R_f 0.27 (1:2 petroleum ether/Et$_2$O); **mp** 132-134 °C; ν_{max} (thin film, cm^{-1}) 3283, 2956, 2899, 1737, 1515, 1327, 1148; δ_H (CDCl$_3$, 500 MHz) 7.68 (2 H, d, J = 8.3 Hz, ArH), 7.13 (2 H, d, J = 8.3 Hz, ArH), 7.07 (2 H, d, J = 7.9 Hz, ArH), 6.95 (2 H, d, J = 7.9 Hz, ArH), 4.97 (1 H, t, J = 5.6 Hz, NH), 4.30 (1 H, d, J = 9.7 Hz, SCHCHH),

4.17 (1 H, dd, J = 9.7, 3.3 Hz, SCHCHH), 4.10 (1 H, dd, J = 13.8, 5.6 Hz, NCHHAr), 3.96 (1 H, dd, J = 13.8, 5.6 Hz, NCHHAr), 3.74-3.81 (2 H, m, SCH & NCH), 2.56 (3 H, s, NCH_3), 2.32 (3 H, s, CH_3); δ_C (CDCl$_3$, 125 MHz) 138.1 (d), 136.8 (s), 132.9 (s), 129.9 (d), 129.6 (d), 128.9 (s), 128.2 (d), 94.6 (s), 73.7 (d), 73.5 (d), 67.0 (t), 47.5 (t), 42.8 (q), 21.3 (q); **LRMS** (EI) 472 (M$^{+\bullet}$, 5), 286 (100), 260 (12), 120 (30); **HRMS** (EI) calcd for C$_{18}$H$_{21}$IN$_2$O$_3$S (M$^{+\bullet}$) 472.0312, observed 472.0309

(3S*, 4S*)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-4sulfonic acid 4-methylbenzylamide (142f)[113, 122]
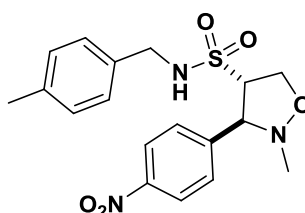
According to general procedure 11, **140j** gave the title compound as a yellow solid (0.11 g, 0.28 mmol, 32%).

R$_f$ 0.16 (1:2 petroleum ether/Et$_2$O); **mp** 151-154 °C(lit.[113] **mp** 149 °C); ν_{max} (thin film, cm^{-1}) 3276, 2956, 1737, 1525, 1348, 1150; δ_H (CDCl$_3$, 500 MHz) 8.15 (2 H, d, J = 8.8 Hz, ArH), 7.57 (2 H, d, J = 8.8 Hz, ArH), 7.05 (2 H, d, J = 8.3 Hz, ArH), 7.02 (2 H, d, J = 8.3 Hz, ArH), 5.23 (1 H, t, J = 5.6 Hz, NH), 4.36 (1 H, dd, J = 9.9, 3.7 Hz, SCHCHH), 4.14-4.19 (1 H, m, SCHCHH), 4.12 (1 H, d, J = 5.6 Hz, NCHHAr), 4.09 (1 H, d, J = 5.6 Hz, NCHHAr), 3.97 (1 H, d, J = 6.6 Hz, NCH), 3.73 (1 H, dt, J = 6.6, 3.7 Hz, SCH), 2.61 (3 H, s, NCH_3), 2.29 (3 H, s, CH_3); δ_C (CDCl$_3$, 125 MHz) 148.0 (s), 145.0 (s), 138.2 (s), 135.9 (s), 129.6 (d), 129.1 (d), 128.2 (d), 124.1 (d), 74.1 (d), 72.9 (d), 67.2 (t), 47.5 (t), 43.0 (q), 21.3 (q); **LRMS** (EI) 391 (M$^{+\bullet}$, 14), 205 (78), 120 (100); **HRMS** (EI) calcd for C$_{18}$H$_{21}$N$_3$O$_5$S (M$^{+\bullet}$) 391.1196, observed 391.1199

(3S*, 4S*)-3-(2-Fluorophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (142g)[113, 122]
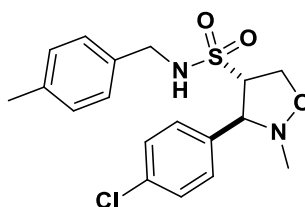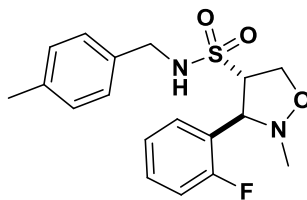

According to general procedure 11, **140g** gave the title compound as a yellow oil (0.14 g, 0.38 mmol, 35%).

R_f 0.29 (1:2 petroleum ether/Et$_2$O); ν_{max} (thin film, cm^{-1}) 3286, 2924, 2877, 1737, 1617, 1588, 1327, 1146, 844; δ_H (CDCl$_3$, 500 MHz) 7.41 (1 H, t, J = 7.1 Hz, Ar*H*), 7.33-7.38 (1 H, m, Ar*H*), 7.18-7.23 (1 H, m, Ar*H*), 7.07 (1H, t, J = 7.1 Hz, Ar*H*), 7.04 (2 H, d, J = 7.9 Hz, Ar*H*), 6.95 (2 H, d, J = 7.9 Hz, Ar*H*), 4.85 (1 H, t, J = 5.3 Hz, N*H*), 4.38 (1 H, dd, J = 9.7, 3.5 Hz, SCHC*H*H), 4.27 (1 H, dd, J = 9.7, 8.3 Hz, SCHCH*H*), 4.14 (1 H, dd, J = 13.7, 5.3 Hz, NCH*H*Ar), 4.11 (1 H, app d, J = 3.5 Hz, SC*H*), 4.02 (1 H, d, J = 3.7 Hz, NC*H*), 3.94 (1 H, dd, J = 13.7, 5.2 Hz, NC*H*HAr), 2.60 (3 H, s, NC*H*$_3$), 2.30 (3 H, s, C*H*$_3$); δ_C (CDCl$_3$, 125 MHz) 161.1 (s, J_{CF} = 248.6 Hz), 137.9 (s), 113.9 (s), 130.5 (d, J_{CF} = 8.6 Hz), 129.9 (d, J_{CF} = 3.8 Hz), 129.5 (d), 128.0 (d), 125.0 (d, J_{CF} = 3.8 Hz), 123.7 (s, J_{CF} = 10.6 Hz), 116.2 (d, J_{CF} = 22.1 Hz), 72.2 (d), 68.1 (d), 67.1 (t), 47.5 (t), 42.9 (q), 21.2 (q); **LRMS** (CI$^+$) 365 (M+H, 100), 178 (24), 120 (4); **HRMS** (CI$^+$) calcd for C$_{18}$H$_{22}$FN$_2$O$_3$S (M+H) 365.1335, observed 365.1345

(3S*, 4S*)-3-(2-Chlorophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (138)[113]
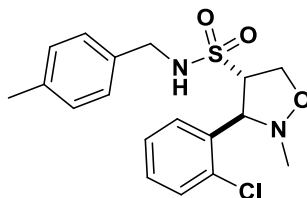
According to general procedure 11 to give the title compound as a yellow oil (87 mg, 0.23 mmol, 23%).

R_f 0.25 (1:2 petroleum ether/Et$_2$O); ν_{max} (thin film, cm^{-1}) 3283, 2922, 1737, 1438, 1328, 1148, 704; δ_H (CDCl$_3$, 500 MHz) 7.49 (1 H, d, J = 7.3 Hz, Ar*H*), 7.40 (1 H, app dd, J = 7.4, 1.9 Hz, Ar*H*), 7.33-7.36 (2 H, m, Ar*H*), 7.05 (2 H, J = 7.9 Hz, Ar*H*), 7.02 (2 H, d, J = 7.9 Hz, Ar*H*), 4.54 (1 H, t, J = 5.8 Hz, N*H*), 4.48 (1 H, d, J = 8.2 Hz,

NC*H*), 4.45 (1 H, dd, J = 9.8, 3.8 Hz, SCHC*H*H), 4.35 (1 H, dd, J = 9.8, 8.5 Hz, SCHCH*H*), 4.13 (1 H, dd, J = 13.5, 5.7 Hz, NC*H*HAr), 3.97 (1 H, app.td, *J*= 8.3, 3.8 Hz, SC*H*), 3.80 (1 H, dd, J = 13.5, 5.8 Hz, NCH*H*Ar), 2.63 (3 H, s, NC*H*$_3$), 2.30 (3 H, s, C*H*$_3$); **δ$_C$** (CDCl$_3$, 125 MHz) 138.0 (s), 134.5 (s), 134.3 (s), 133.0 (s), 130.1 (d), 129.9 (d), 129.5 (d), 128.0 (d), 127.9 (d), 127.3 (d), 73.0 (d), 70.2 (d), 67.2 (t), 47.3 (t), 42.9 (q), 21.2 (q); **LRMS** (CI$^+$) 383 (M+H, ^{37}Cl, 34), 381 (M+H, ^{35}Cl, 100), 197 (^{37}Cl, 17), 195 (^{35}Cl, 50), 120 (14); **HRMS** (CI$^+$) calcd for C$_{18}$H$_{22}$ClN$_2$O$_3$S (M+H) 381.1039, observed 381.1045

(3S*, 4S*)-3-(2-Bromophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (139)[113]
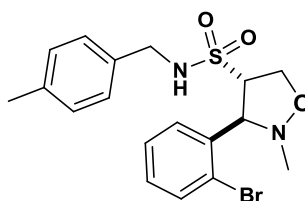
According to general procedure 11 to give the title compound as a yellow oil (96 mg, 0.23 mmol, 23%).

R$_f$ 0.25 (1:2 petroleum ether/Et$_2$O); **ν$_{max}$** (thin film, cm^{-1}) 3251, 2978, 1737, 1328, 1148, 698; **δ$_H$** (CDCl$_3$, 500 MHz) 7.59 (1 H, dd, J = 7.6, 1.1 Hz, Ar*H*), 7.48 (1 H, d, J = 7.6 Hz, Ar*H*), 7.38 (1 H, t, J = 7.7 Hz, Ar*H*), 7.24 (1 H, t, J = 7.6 Hz, Ar*H*), 7.01 (2 H, d, J = 7.7 Hz, Ar*H*), 6.88 (2 H, d, J = 7.7 Hz, Ar*H*), 4.60 (1 H, t, J = 5.7 Hz, N*H*), 4.50 (1 H, d, J = 6.9 Hz, NC*H*), 4.46 (1 H, dd, J = 9.8, 3.6 Hz, SCHC*H*H), 4.36 (1 H, dd, J = 9.8, 8.5 Hz, SCHCH*H*), 4.13 (1 H, dd, J = 13.6, 5.7 Hz, NC*H*HAr), 3.95 (1 H app.td, J = 8.5, 3.6 Hz, SC*H*), 3.77 (1 H, dd, J = 13.6, 5.7 Hz, NCH*H*Ar), 2.64 (3 H, s, NC*H*$_3$), 2.30 (3 H, s, C*H*$_3$); **δ$_C$** (CDCl$_3$, 125 MHz) 137.9 (s), 133.4 (d), 132.9 (s), 130.2 (d), 130.1 (d), 129.5 (d), 128.5 (s), 128.0 (d), 127.4 (d), 124.8 (s), 73.1 (d), 71.7 (d), 67.2 (t), 47.3 (t), 46.8 (q), 21.2 (q); **LRMS** (EI) 426 (M$^{+•}$, ^{81}Br, 4), 424 (M$^{+•}$, ^{79}Br, 4), 240 (39), 197 (10), 120 (17), 105 (17); **HRMS** (EI) calcd for C$_{18}$H$_{21}$BrN$_2$O$_3$S (M$^{+•}$) 424.0450, observed 424.0446

## (3S*, 4S*)-3-(2-Iodophenyl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (142h)[113]
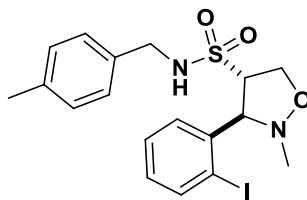
According to general procedure 11, **140i** gave the title compound as a yellow oil (0.17 g, 0.42 mmol, 42%).

R_f 0.27 (1:2 petroleum ether/Et$_2$O); ν_{max} (thin film, cm^{-1}) 3310, 2922, 2874, 1736, 1515, 1432, 1326, 1147; δ_H (CDCl$_3$, 500 MHz) 7.87 (1 H, d, J = 7.9 Hz, ArH), 7.40 (2 H, d, J = 7.7 Hz, ArH), 7.06-7.10 (1 H, m, ArH), 7.01 (2 H, J = 7.9 Hz, ArH), 6.89 (2 H, d, J = 7.9 Hz, ArH), 4.70 (1 H, t, J = 5.8 Hz, NH), 4.44 (1 H, d, J = 9.8 Hz, SCHCHH), 4.38 (1 H, d, J = 7.1 Hz, NCH), 4.34 (1 H, dd, J = 9.8, 8.3 Hz, SCHCHH), 4.13 (1 H, dd, J = 13.5 , 5.9 Hz, NCHHAr), 3.91-4.04 (1 H, m, SCH), 3.78 (1 H, dd, J = 13.5, 5.8 Hz, NCHHAr), 2.64 (3 H, s, NCH_3), 2.30 (3 H, s, CH_3); δ_C (CDCl$_3$, 125 MHz) 140.1 (d), 139.1 (s), 137.9 (s), 133.0 (s), 130.5 (d), 129.8 (d), 129.5 (d), 129.3 (d), 128.0 (d), 101.2 (s), 76.9 (d), 73.4 (d), 67.2 (t), 47.3 (t), 42.6 (q), 21.2 (q); **LRMS** (CI$^+$) 473 (M+H, 100), 287 (52), 120 (20); **HRMS** (CI$^+$) calcd for C$_{18}$H$_{22}$IN$_2$O$_3$S (M+H) 473.0395, observed 473.0403

(3S*, 4S*)-2-Methyl-3-(2-Nitrophenyl)-isoxazolidine-4-sulfonic acid 4-methylbenzylamide (142i)
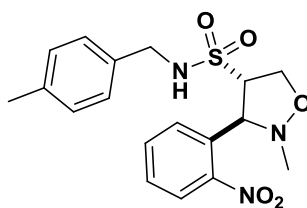
According to general procedure 11, **140e** gave the title compound as a yellow oil (61 mg, 0.15 mmol, 16%).

R_f 0.21 (1:2 petroleum ether /Et$_2$O); ν_{max} (thin film, cm^{-1}) 3302, 2923, 2877, 1609, 1579, 1327, 1147; δ_H (CDCl$_3$, 500 MHz) 7.72 (1 H, d, J = 8.3 Hz, ArH), 7.64 (1 H, d, J = 8.2 Hz, ArH), 7.59 (1 H, t, J = 8.2 Hz, ArH), 7.48 (1 H, t, J = 8.2 Hz, ArH), 6.99-7.02 (4 H, m, ArH), 5.03 (1 H, t, J = 5.8 Hz, NH), 4.47 (1 H, d, J = 6.6 Hz, NCH), 4.34 (1 H, dd, J = 9.8, 3.8 Hz, SCHCHH), 4.26 (1 H, dd, J = 9.8, 8.4 Hz, SCHCHH),

4.16 (1 H, dd, J = 13.9, 5.8 Hz, NCHHAr), 4.08 (1 H, dd, J = 13.9, 5.8 Hz, NCHHAr), 3.97-4.05 (1 H, m, SCH), 2.63 (3 H, s, NCH_3), 2.29 (3 H, s, CH_3); δ_C (CDCl$_3$, 125 MHz) 150.4 (s), 137.9 (s), 133.4 (s), 133.1 (d), 131.4 (s), 130.7 (d), 129.5 (d), 129.4 (d), 128.0 (d), 124.4 (d), 74.0 (d), 68.5 (d), 67.3 (t), 47.4 (t), 43.3 (q), 21.2 (q); **LRMS** (CI$^+$) 392 (M+H, 100), 374 (50), 206 (38), 120 (30), 105 (52); **HRMS** (CI$^+$) calcd for $C_{18}H_{22}N_3O_5S$ (M+H) 392.1280, observed 392.1286

4.3.4   Preparation of biotinylated compounds

2-(*tert*-Butyldimethylsilanyloxy)ethanol (144)[193]
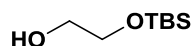
To a stirred suspension of ethylene glycol (23.8 mL, 384 mmol, 5 eq.), NEt$_3$ (58.7 mL, 422 mmol, 5.5 eq.) and DMAP (0.94 g, 7.68 mmol, 0.1 eq.) in dichloromethane (390 mL) at 0 °C was added a pre-mixed solution of *tert*-butyldimethylsilyl chloride (11.6 g, 76.8 mmol) in dichloromethane (30 mL) dropwise over 10 min. Stirring was continued overnight at RT. The reaction mixture was washed with 10% HCl, saturated NaHCO$_3$ and brine. The organic layer was dried with MgSO$_4$, filtered and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (starting 6:1 petroleum ether/EtOAc) to give the title compound as a clear oil (8.14 g, 46.2 mmol, 60%).

R_f 0.36 (2:1 petroleum ether/EtOAc); ν_{max} (thin film, cm^{-1}) 3271, 3081, 2929, 2858, 1607, 1519, 1310, 1149, 1041, 824; δ_H (CDCl$_3$, 300 MHz) 3.66 (2 H, t, J = 4.0 Hz, OCH_2), 3..63 (2 H, t, J = 4.0 Hz, CH_2), 2.03 (1 H, br s, OH), 0.84 (9 H, s, C(CH_3)$_3$), 0.07 (6 H, s, CH_3); δ_C (CDCl$_3$, 75 MHz) 64.1 (t), 63.7 (t), 25.9 (q), 25.6 (q), 18.3 (s); **LRMS** (CI$^+$) 177 (M+H, 6), 161 (5), 110 (100); **HRMS** (CI$^+$) calcd for $C_8H_{21}O_2Si$ (M+H) 177.1310, observed 177.1312

(*tert*-Butyldimethylsilanyloxy)acetaldehyde (145)[194]
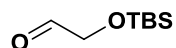
To a stirred solution of oxalyl chloride (12.6 g, 106 mmol, 2 eq.) in dichloromethane (200 mL) at -78 °C was added slowly DMSO (18.8 mL, 265 mmol, 5 eq.) followed by dropwise addition of 2-(*tert*-butyldimethylsilanyloxy)ethanol **144** (9.5 g, 53 mmol) in dichloromethane (40 mL) then 20 min stirring at -78 °C. NEt$_3$ (37.6 mL, 270 mmol, 5.1 eq.) was added dropwise to the reaction and allowed to warm slowly

to RT. Solvent was removed *in vacuo* and the residue remaining was triturated with 4:1 hexane/EtOAc (400mL) before filtering through a small silica pad. The filtrate was concentrated *in vacuo* and crude residue was purified by flash chromatography (starting 12:1 petroleum ether/EtOAc) to give the title compound as a clear oil (5.0 g, 29 mmol, 53%).

$\mathbf{R_f}$ 0.36 (12:1 petroleum ether /EtOAc); $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3272, 3082, 2929, 2858, 1607, 1519, 1310; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 9.73 (1 H, t, J = 1.1 Hz, CHO), 4.21 (2 H, d, J = 1.0 Hz, CH_2), 0.86 (9 H, s, C(CH_3)$_3$), 0.10 (6 H, s, CH_3); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 202.3 (d), 69.6 (t), 25.8 (q), 25.7 (q), 18.3 (s); **LRMS** (CI$^+$) 175 (M+H, 5), 159 (5), 147 (5), 117 (100); **HRMS** (CI$^+$) calcd for C$_8$H$_{19}$O$_2$Si (M+H) 175.1154, observed 175.1151

(*tert*-Butyldimethylsilanyloxy)acetaldehyde oxime (146)[195]
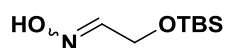
(*tert*-Butyl-dimethylsilanyloxy)acetaldehyde **145** (5.1 g, 29 mmol) was dissolved in EtOH (98 mL) and treated with hydroxylamine.HCl (6.1 g, 87 mmol, 3 eq.) followed by NEt$_3$ (13.3 mL, 95.7 mmol, 3.3 eq.). The suspension was stirred at RT for 4 h, then diluted with water (100 mL) followed by extraction with EtOAc (3 x 100 mL). The organic layer was dried with MgSO$_4$, filtered and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (starting 12:1 petroleum ether/EtOAc) to give 1:1 diastereo-mixture of the title compound as a clear oil (3.9 g, 21 mmol, 72%).

$\mathbf{R_f}$ 0.21 (12:1 petroleum ether/EtOAc); $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3271, 3081, 2887, 2858, 1607, 1519, 1310 1149; $\mathbf{\delta_H}$ (CDCl$_3$, 500 MHz) 9.43 (1 H, s, OH), 9.11 (1 H, s, OH), 7.39 (1 H, t, J = 5.5 Hz, CH), 6.77 (1 H, t, J = 5.5 Hz, CH), 4.46 (2 H, d, J = 5.5 Hz, CH_2), 4.19 (2 H, d, J = 5.5 Hz, CH_2), 0.84 (9 H, s, C(CH_3)$_3$), 0.83 (9 H, s, C(CH_3)$_3$), 0.02 (6 H, s, CH_3), 0.02 (6 H, s, CH_3); $\mathbf{\delta_C}$ (CDCl$_3$, 125 MHz) 153.8 (d), 151.2 (d), 60.6 (t), 57.9 (t), 26.1 (q), 21.2 (q), 18.5 (q), 14.3 (s), 4.4 (q), 3.7 (q); **LRMS** (EI) 189 (M$^{+\bullet}$, 2), 174 (8), 144 (12), 132 (100), 123 (20), 105 (74); **HRMS** (EI) calcd for C$_8$H$_{19}$NO$_2$Si (M$^{+\bullet}$) 189.1179, observed 189.1177

N-[2-(*tert*-Butyldimethylsilanyloxy)ethyl] hydroxylamine (147)[195]
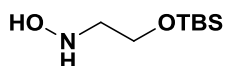
To a stirred solution of (*tert*-butyldimethylsilanyloxy)acetaldehyde oxime **146** (4.0 g, 21 mmol) in MeOH (150 mL) was treated with NaBH$_3$CN (2.6 g, 42 mmol, 2 eq.) and followed by dropwise addition of conc. HCl and maintained the solution at pH 4 for 45 min. Solvent was removed *in vacuo*, the white residue suspended in water (150 mL) was basified to pH >9 with 6N KOH. The aqueous layer was saturated with NaCl and extracted with chloroform (4 x 70 mL). The organic layer was dried with MgSO$_4$, filtered and filtrate concentrated *in vacuo* to give the title compound as a yellow oil (3.48 g, 18.2 mmol, 87%).

R$_f$ 0.14 (5:1 petroleum ether/EtOAc); **ν$_{max}$** (thin film, cm^{-1}) 3356, 3280, 2953, 2929, 2857, 1706; **δ$_H$** (CDCl$_3$, 300 MHz) 3.77 (2 H, t, *J* = 5.1 Hz, NC*H*$_2$), 3.02 (2 H, t, *J* = 5.1 Hz, C*H*$_2$), 0.89 (9 H, s, C(C*H*$_3$)$_3$), 0.06 (6 H, s, C*H*$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 59.2 (t), 55.6 (t), 25.6 (q), 21.1 (q), 18.3 (s); **LRMS** (ES$^+$) 192 (M+H, 100) ; **HRMS** (ES$^+$) calcd for C$_8$H$_{22}$NO$_2$Si (M+H) 192.1420, observed 192.1417

C-(2-Fluorophenyl)-*N*-[2-(*tert*-Butyldimethylsilanyloxy)ethyl] nitrone (148a)
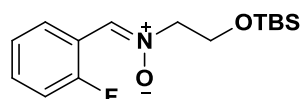
To *N*-[2-(*tert*-butyl-dimethyl-silanyloxy)ethyl] hydroxylamine **147** (1.70 g, 8.91 mmol, 1.1 eq.) in dry dichloromethane (25 mL) was added 2-fluorobenzaldehyde (1.0 g, 8.1 mmol) and NaHCO$_3$ (2.04 g, 24.3 mmol, 3 eq.). The mixture was refluxed at 45 °C for 6 h then resulting suspension was filtered and remaining residue washed thoroughly with dichloromethane (4 x 40 mL). The solvent was removed *in vacuo* to give the title compound as a yellow oil and as a single diastereoisomer as judged by NMR (2.35 g, 7.91 mmol, 97%).

R$_f$ 0.2 (5:1 petroleum ether /EtOAc); **ν$_{max}$** (thin film, cm^{-1}) 3360, 3136, 2954, 2929, 2856, 1710; **δ$_H$** (CDCl$_3$, 300 MHz) 9.36 (1 H, t, *J* = 7.5 Hz, Ar*H*), 7.70 (1 H, s, C*H*N), 7.35-7.41 (1 H, m, Ar*H*), 7.23 (1 H, t, *J* = 7.3 Hz, Ar*H*), 7.06 (1 H, d, *J* = 7.3 Hz, Ar*H*), 4.10-4.23 (2 H, m, NC*H*$_2$), 4.03-4.08 (2 H, m, OC*H*$_2$CH$_2$), 0.82 (9 H, s, C(C*H*$_3$)$_3$), 0.05 (6 H, s, C*H*$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 131.6 (d), 131.5 (d), 128.8 (d), 124.3 (d), 119.0 (s), 114.7 (d), 114.4 (s), 62.2 (t), 59.6 (t), 25.9 (q), 25.7 (q), 18.2 (s); **LRMS** (FAB$^+$) 298 (M+H, 100), 282 (22), 240 (85), 224 (15); **HRMS** (FAB$^+$) calcd for C$_{15}$H$_{25}$FNO$_2$Si (M+H) 298.1638, observed 298.1630

C-(2-Bromophenyl)-N-[2-(tert-Butyldimethylsilanyloxy)ethyl] nitrone (148b)
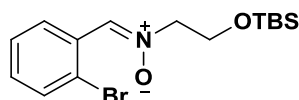
To N-[2-(tert-butyldimethylsilanyloxy)ethyl] hydroxylamine **147** (1.70 g, 8.91 mmol, 1.1 eq.) in dry dichloromethane (25 mL) was added 2-bromobenzaldehyde (1.5 g, 8.1 mmol) and NaHCO$_3$ (2.04 g, 24.3 mmol, 3 eq.). The mixture was refluxed at 45 °C for 6 h then resulting suspension was filtered and remaining residue washed thoroughly with dichloromethane (4 x 40 mL). The solvent was removed *in vacuo* and crude residue was purified by flash chromatography (starting 7:1 petroleum ether/EtOAc) to give the title compound as a yellow oil and as a single diastereoisomer as judged by NMR (1.9 g, 5.3 mmol, 65%).

R$_f$ 0.1 (5:1 petroleum ether/EtOAc); **ν$_{max}$** (thin film, cm^{-1}) 3326, 2952, 2928, 2855, 1462, 1157, 1111, 935, 776; **δ$_H$** (CDCl$_3$, 300 MHz) 9.34 (1 H, dd, J = 8.0, 1.6 Hz, ArH), 7.88 (1 H, s, CHN), 7.61 (1 H, dd, J = 8.0, 1.4 Hz, ArH), 7.36 (1 H, t, J = 8.3 Hz, ArH), 7.21 (1 H, dd, J = 8.2, 1.6 Hz, ArH), 4.11-4.20 (2 H, m, NCH_2), 4.04-4.10 (2 H, m, OCH_2CH$_2$), 0.84 (9 H, s, C(CH_3)$_3$), 0.02 (6 H, s, CH_3); **δ$_C$** (CDCl$_3$, 75 MHz) 135.3 (s), 134.0 (d), 132.8 (d), 131.2 (d), 129.5 (d), 127.9 (d), 123.2 (s), 70.7 (t), 59.6 (t), 25.9 (q), 25.8 (q), 18.2 (s); **LRMS** (EI) 358 (M$^{+•}$, ^{81}Br, 18), 356 (M$^{+•}$, ^{79}Br, 18), 302 (^{81}Br, 100), 300 (^{79}Br, 98), 286 (^{81}Br, 19), 284 (^{79}Br, 18), 204 (22); **HRMS** (EI) calcd for C$_{15}$H$_{25}$BrNO$_2$Si (M$^{+•}$) 357.0754, observed 357.0764

(3S*, 4S*)-2-[2-(tert-Butyldimethylsilanyloxy)ethyl]-3-(2-fluorophenyl)-isoxazolidine-4-sulfonic acid pentafluorophenyl ester (149a)
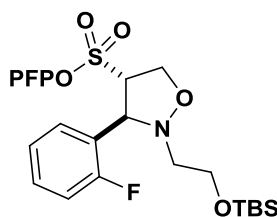
To pentafluorophenyl ethenesulfonate **110** (1.8 g, 6.6 mmol) in dry toluene (40 mL) was added C-(2-fluorophenyl)-N-[2-(tert-butyldimethylsilanyloxy)ethyl] nitrone **148a** (2.3 g, 7.9 mmol, 1.2 eq.) and the mixture was heated to reflux for 6 h. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 20:1 petroleum ether/Et$_2$O) to give the title compound as a yellow oil and as a single diastereoisomer as judged by NMR (1.3 g, 2.2 mmol,

33%).

R$_f$ 0.85 (2:1 petroleum ether/Et$_2$O); **ν$_{max}$** (thin film, cm^{-1}) 2955, 2930, 1517, 1390, 1185, 993; **δ$_H$** (CDCl$_3$, 300 MHz) 7.48-7.60 (1 H, m, Ar*H*), 7.31-7.39 (1 H, m, Ar*H*), 7.17 (1 H, td, *J* = 7.5, 1.1 Hz, Ar*H*), 7.11 (1 H, d, *J* = 7.5 Hz, Ar*H*), 4.62 (1 H, d, *J* = 6.9 Hz, NC*H*), 4.44-4.56 (3 H, m, SC*H* & SCHC*H$_2$*), 3.79 (2 H, t, *J* = 5.1 Hz, NC*H$_2$*), 2.91 (2 H, t, *J* = 5.0 Hz, OC*H$_2$*CH$_2$), 0.84 (9 H, s, C(C*H$_3$*)$_3$), 0.01 (6 H, s, C*H$_3$*); **δ$_C$** (CDCl$_3$, 75 MHz) 130.9 (s, *J$_{CF}$* = 247.6 Hz), 130.8 (s, *J$_{CF}$* = 10.6 Hz), 130.0 (d), 124.7 (d), 116.4 (d, *J$_{CF}$* = 3.8 Hz), 116.1 (d, *J$_{CF}$* = 22.1 Hz), 72.1 (d), 66.9 (t), 66.4 (d), 60.7 (t), 57.9 (t), 25.9 (q), 25.8 (q), 18.3 (s); **LRMS** (EI) 571 (M$^{+•}$, 72), 456 (32), 323 (100), 167 (43), 124 (30); **HRMS** (EI) calcd for C$_{23}$H$_{27}$F$_6$NO$_5$SSi (M$^{+•}$) 571.1283, observed 571.1280

(3S*, 4S*)-3-(2-Bromophenyl)-2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-isoxazolidine-4-sulfonic acid pentafluorophenyl ester (149b)
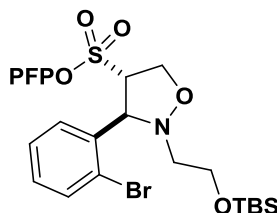
To pentafluorophenyl ethenesulfonate **110** (1.2 g, 4.4 mmol) in dry toluene (28 mL) was added *C*-(2-bromophenyl)-*N*-[2-(*tert*-butyldimethylsilanyloxy)ethyl] nitrone **148b** (1.9 g, 5.3 mmol, 1.2 eq.) and the mixture was heated to reflux for 3 h. The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (starting 14:1 petroleum ether/Et$_2$O) to give the title compound as a yellow oil and as a single diastereoisomer as judged by NMR (1.1 g, 1.67 mmol, 38%).

R$_f$ 0.6 (2:1 petroleum ether/Et$_2$O); **ν$_{max}$** (thin film, cm^{-1}) 2954, 2929, 1516, 1394, 1185, 775; **δ$_H$** (CDCl$_3$, 300 MHz) 7.58 (1 H, dd, *J* = 8.0, 1.8 Hz, Ar*H*), 7.54 (1 H, dd, *J* = 8.0, 1.8 Hz, Ar*H*), 7.35 (1 H, t, *J* = 8.0 Hz, Ar*H*), 7.20 (1 H, td, *J* = 8.0, 1.6 Hz, Ar*H*), 4.86 (1 H, d, *J* = 6.9 Hz, NC*H*), 4.63 (1 H, dd, *J* = 10.4, 2.9 Hz, SCHC*H*H), 4.51-4.61 (1 H, m, SCHCH*H*), 4.36 (1 H, td, *J* = 7.1, 2.9 Hz, SC*H*), 3.76 (2 H, dd, *J* = 6.9, 5.4 Hz, NC*H$_2$*), 2.97-3.11 (1 H, m, OC*H*HCH$_2$), 2.84-2.93 (1 H, m, OCH*H*CH$_2$), 0.84 (9 H, s, C(C*H$_3$*)$_3$), 0.01 (6 H, s, C*H$_3$*); **δ$_C$** (CDCl$_3$, 75 MHz) 134.6 (s), 133.5 (d), 130.4 (d), 130.2 (d), 128.1 (d), 124.8 (s), 72.9 (d), 70.5 (d), 67.2 (t),

60.7 (t), 57.8 (t), 25.9 (q), 25.8 (q), 18.3 (s); **LRMS** (EI) 633 (M$^{+\bullet}$, ^{81}Br, 11), 631 (M$^{+\bullet}$, ^{79}Br, 13), 515 (^{81}Br, 25), 513 (^{79}Br, 24), 385 (^{81}Br, 14), 383 (^{79}Br, 14), 318 (100), 182 (76); **HRMS** (EI) calcd for $C_{23}H_{27}BrF_5NO_5SSi$ (M$^{+\bullet}$) 631.0483, observed 631.0487

(3S*, 4S*)-2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-3-(2-fluorophenyl)-isoxazolidine-4-sulfonic acid 4-methylbenzylamide and (3S*, 4R*)-2-[2-(*tert*-Butyl dimethylsilanyloxy)ethyl]-3-(2-fluorophenyl)-isoxazolidine-4-sulfonic acid 4- methylbenzylamide (150a &151a)

To a stirred solution of (3S*, 4S*)-2-[2-(*tert*-butyldimethylsilanyloxy) ethyl]-3-(2-fluorophenyl)-isoxazolidine-4-sulfonic acid pentafluorophenyl ester **149a** (1.3 g, 2.3 mmol), in dry THF (35 mL) was added 4-methylbenzylamine (0.8 mL, 6.9 mmol, 3 eq.) followed by DBU (0.5 mL, 3.45 mmol, 1.5 eq.). The mixture was refluxed for 2 h and reaction was concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 15:1 petroleum ether/EtOAc) to give 4$_{(anti)}$:1$_{(syn)}$ mixture of the title compound as a yellow oil (0.31 g, 0.61 mmol, 27%). A small amount of each diastereoisomer was able to be separated for analysis; however the yields quoted were referred as the overall yield.

R$_{f (syn)}$ 0.18 (2:1 petroleum ether/Et$_2$O); **ν$_{max}$** (thin film, cm^{-1}) 3286, 2928, 2856, 1588, 1516, 1491, 1331, 1148, 833; **δ$_H$** (CDCl$_3$, 300 MHz) 7.68 (1 H, td, J = 7.5, 1.6 Hz, Ar*H*), 7.21-7.28 (2 H, m, Ar*H*), 7.11 (4 H, br s, Ar*H*), 6.99 (1 H, J = 7.5 Hz, Ar*H*), 4.34-4.20 (2 H, m, SCHC*H*$_2$), 4.24-4.30 (2 H, m, OC*H*$_2$CH$_2$), 4.01 (1 H, dd, J = 13.9, 5.2 Hz, NC*H*HAr), 3.82-3.90 (2 H, m, NC*H* & NCH*H*Ar), 3.54 (1 H, t, J = 5.2 Hz, N*H*), 3.43-3.50 (1 H, m, SC*H*), 2.91-3.01 (1 H, m, OCH$_2$C*H*H), 2.62-2.72 (1 H, m, OCH$_2$CH*H*), 2.32 (3 H, s, ArC*H*$_3$), 0.86 (9 H, s, C(C*H*$_3$)$_3$), 0.05 (6 H, s, C*H*$_3$); **δ$_C$** (CDCl$_3$, 75 MHz) 161.2 (s, J_{CF} = 253.2 Hz), 137.8 (s), 133.4 (d, J_{CF} = 3.1 Hz), 130.5 (d, J_{CF} = 3.6 Hz), 129.9 (s), 129.4 (d), 127.9 (d), 124.2 (s, J_{CF} = 9.1 Hz), 114.7 (d, J_{CF} = 21.3 Hz), 66.8 (d), 64.6 (d), 60.7 (t), 60.4 (t), 58.6 (t), 46.9 (t), 41.3 (q), 22.6 (q), 21.1 (q), 14.3 (s); **LRMS** (ES$^-$) 507 (M-H, 100), 393 (4); **HRMS** (ES$^-$) calcd for

$C_{25}H_{36}FN_2O_4SSi$ (M-H) 507.2149, observed 507.2154

$R_{f\ (anti)}$ 0.11 (2:1 petroleum ether/Et$_2$O); ν_{max} (thin film, cm^{-1}) 3285, 2928, 2857, 1589, 1517, 1494, 1327, 1147, 833; δ_H (CDCl$_3$, 500 MHz) 7.44 (1 H, t, J = 6.9 Hz, Ar*H*), 7.33 (1 H, d, J = 6.9 Hz, Ar*H*), 7.17 (1 H, t, J = 7.1 Hz, Ar*H*), 7.07 (1 H, br s, Ar*H*), 7.04 (2 H, d, J = 8.0 Hz, Ar*H*), 6.96 (2 H, d, J = 8.0 Hz, Ar*H*), 4.89 (1 H, t, J = 5.8 Hz, N*H*), 4.37 (1 H, dd, J = 9.7, 3.3 Hz, SCHCH*H*), 4.30 (1 H, d, J = 7.4 Hz, NC*H*), 4.23 (1 H, dd, J = 9.7, 8.5 Hz, SCHC*H*H), 4.12 (1 H, dd, J = 13.8, 5.8 Hz, NCH*H*Ar), 3.92-3.98 (2 H, m, OC*H*$_2$CH$_2$)3.70-3.79 (2 H, m, SC*H* & NC*H*HAr), 2.78-2.89 (2 H, m, OCH$_2$C*H*$_2$), 2.31 (3 H, s, ArC*H*$_3$), 0.84 (9 H, s, C(C*H*$_3$)$_3$), 0.01 (6 H, s, C*H*$_3$); δ_C (CDCl$_3$, 125 MHz) 161.2 (s, J_{CF} = 247.6 Hz), 137.8 (d), 133.4 (s), 130.3 (d, J_{CF} = 8.6 Hz), 130.1 (d, J_{CF} = 2.9 Hz), 129.5 (d), 128.3 (s), 128.0 (d), 124.9 (d, J_{CF} = 3.8 Hz), 124.1 (s, J_{CF} = 11.5 Hz), 116.0 (d, J_{CF} = 22.1 Hz), 72.1 (d), 67.0 (t), 66.1 (t), 58.6 (t), 56.1 (q), 46.9 (t), 26.1 (q), 21.1 (q), 15.4 (s); **LRMS** (ES$^-$) 507 (M-H, 100), 477 (10), 393 (3); **HRMS** (ES$^-$) calcd for $C_{25}H_{36}FN_2O_4SSi$ (M-H) 507.2149, observed 507.2157

(3S*,   4S*)-3-(2-Bromophenyl)-2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-isoxazolidine-4-sulfonic   acid   4-methylbenzylamide   and   (3S*, 4R*)-3-(2-Bromophenyl)-2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-isoxazolidine-4-sulfonic acid 4-methylbenzylamide (150b & 151b)

To   a   stirred   solution   of   (3S*,   4S*)-3-(2-bromophenyl)-2-[2-   (*tert*-butyldimethylsilanyloxy)ethyl]-isoxazolidine-4-sulfonic acid pentafluorophenyl ester **149b** (1.28 g, 2.02 mmol), in dry THF (30 mL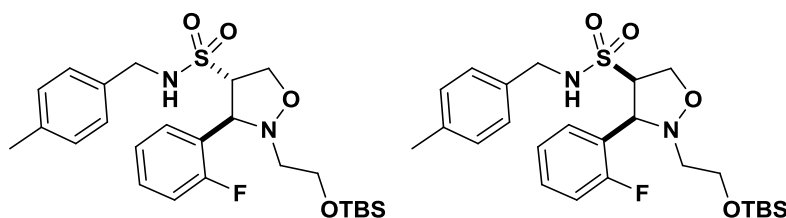) was added 4-methylbenzylamine (0.77 ml, 6.07 mmol, 3 eq.) followed by DBU (0.45 mL, 3.04 mmol, 1.5 eq.). The mixture was refluxed for 2 h and reaction was concentrated *in vacuo*. The crude residue was purified by flash chromatography (starting 15:1 petroleum ether/EtOAc) to give 4$_{(anti)}$:1$_{(syn)}$ mixture of the title compound as a yellow oil (0.72 g, 1.2 mmol, 63 %). A small amount of each diastereoisomer was able to be separated for analysis; however the yields quoted were referred as the overall yield.

R$_{f (syn)}$ 0.19 (2:1 petroleum ether/Et$_2$O); **ν$_{max}$** (thin film, cm^{-1}) 3282, 2928, 2856, 1516, 1372, 1149, 833; **δ$_H$** (CDCl$_3$, 300 MHz) 7.74 (1 H, d, J = 7.9 Hz, ArH), 7.51 (1 H, d, J = 7.7 Hz, ArH), 7.36 (1 H, t, J = 7.7 Hz, ArH), 7.15 (1 H, t, J = 7.4 Hz, ArH), 7.11 (4 H, br s, ArH), 4.35-4.41 (3 H, m, NCH&SCHCH_2), 4.25-4.29 (1 H, m, SCH), 4.10 (1 H, dd, J = 13.9, 5.8 Hz, NCHHAr), 4.02 (1 H, dd, J = 13.9, 5.6 Hz, NCHHAr), 3.82-3.94 (2 H, m, OCH_2CH$_2$), 3.64 (1 H, t, J = 5.9 Hz, NH), 2.90-3.01 (1 H, m, OCH$_2$CHH), 2.60-2.69 (1 H, m, OCH$_2$CHH), 2.32 (3 H, s, ArCH_3), 0.90 (9 H, s, C(CH_3)$_3$), 0.07 (6 H, s, CH_3); **δ$_C$** (CDCl$_3$, 75 MHz) 137.7 (s), 133.7 (s), 132.9 (s), 132.2 (d), 131.5 (d), 129.9 (d), 129.4 (d), 127.8 (d), 127.5 (d), 125.3 (s), 71.3 (d), 66.9 (t), 66.1 (d), 60.8 (t), 58.5 (t), 47.0 (t), 25.9 (q), 23.8 (q), 20.8 (q), 18.3 (s); **LRMS** (ES$^-$) 569 (M-H, ^{81}Br, 100), 567 (M-H, ^{79}Br, 96) 443 (9); **HRMS** (ES$^-$) calcd for C$_{25}$H$_{36}$BrN$_2$O$_4$SSi (M-H) 567.1348, observed 567.1353

R$_{f (anti)}$ 0.12 (2:1 petroleum ether/Et$_2$O); **ν$_{max}$** (thin film, cm^{-1}) 3298, 2928, 2856, 1517, 1326, 1147, 832; **δ$_H$** (CDCl$_3$, 500 MHz) 7.56 (1 H, dd, J = 8.0, 1.0 Hz, ArH), 7.48 (1 H, dd, J = 8.0, 1.1 Hz, ArH), 7.35 (1 H, td, J = 7.9, 1.1 Hz, ArH), 7.22 (1 H, td, J = 8.0, 1.0 Hz, ArH), 7.01 (2 H, d, J = 7.8 Hz, ArH), 6.90 (2 H, d, J = 7.8 Hz, ArH), 4.85 (1 H, t, J = 5.8 Hz, NH), 4.60 (1 H, d, J = 7.4 Hz, NCH), 4.41 (1 H, dd, J = 9.7, 3.6 Hz, SCHCHH), 4.29 (1 H, dd, J = 9.7, 8.3 Hz, SCHCHH), 4.11 (1 H, dd, J = 13.7, 5.8 Hz, NCHHAr), 3.88-4.01 (1 H, m, SCH), 3.79 (1 H, dd, J = 13.7, 5.8 Hz, NCHHAr), 3.73 (2 H, dd, J = 7.1, 4.9 Hz, OCH_2CH$_2$), 2.90-2.96 (1 H, m, OCH$_2$CH_2), 2.74-2.80 (1 H, m, OCH$_2$CH_2), 2.30 (3 H, s, ArCH_3), 0.83 (9 H, s, C(CH_3)$_3$), 0.00 (6 H, s, CH_3); **δ$_C$** (CDCl$_3$, 125 MHz) 137.7 (s), 136.2 (s), 133.2 (d), 133.1 (d), 130.4 (d), 130.1 (d), 129.4 (d), 128.3 (s), 127.9 (d), 124.8 (s), 72.8 (d), 70.8 (d), 67.1 (t), 60.9 (t), 57.9 (t), 47.1 (t), 41.0 (q), 25.9 (q), 21.1 (q), 20.9 (s); **LRMS** (ES$^-$) 569 (M-H, ^{81}Br, 100), 567 (M-H, ^{79}Br, 94), 539 (^{81}Br, 9), 537 (^{79}Br, 8), 183 (34); **HRMS** (ES$^-$) calcd for C$_{25}$H$_{36}$BrN$_2$O$_4$SSi (M-H) 567.1348, observed 567.1339

(3S*, 4S*)-3-(2-Fluorophenyl)-2-(2-hydroxyethyl)-isoxazolidine-4-sulfonic acid 4- methylbenzylamide (152a)
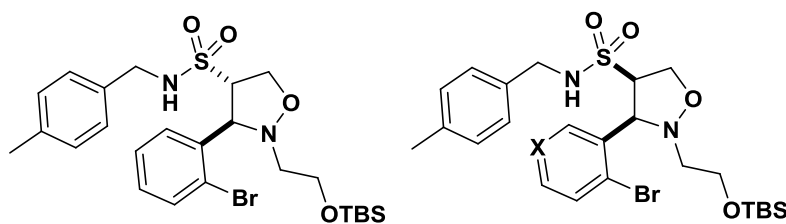

To a stirred solution of (3S*, 4S*)-2-[2-(*tert*-butyldimethylsilanyloxy)- ethyl]-3-(2-fluorophenyl)-isoxazolidine-4-sulfonic acid-4-methylbenzylamide **150a** (0.24 g, 0.48 mmol) in dry THF (7.2 mL) at 0 °C was added TBAF (1 M in THF, 0.72 mL, 0.72 mmol, 1.5 eq.). After 2 h at 0 °C the reaction was concentrated *in vacuo* and the residue was purified by flash chromatography (starting 1:2 petroleum ether/EtOAc) to give the title compound as a clear gel (0.12 g, 0.30 mmol, 63%).

R_f 0.25 (9:1 CHCl$_3$/MeOH); ν_{max} (thin film, cm^{-1}) 3503, 3281, 2926, 1515, 1326, 1146, 1043; δ_H (CDCl$_3$, 300 MHz) 7.32-7.43 (2 H, m, Ar*H*), 7.18 (1 H, td, *J* = 7.5, 1.1 Hz, Ar*H*), 7.06-7.12 (1 H, m, Ar*H*), 7.04 (2 H, d, *J* = 7.7 Hz, Ar*H*), 6.94 (2 H, d, *J* = 7.7 Hz, Ar*H*), 4.95 (1 H, br s, O*H*), 4.40 (1 H, dd, *J* = 9.9, 3.7 Hz, SCHC*H*H), 4.33 (1 H, d, *J* = 6.4 Hz, NC*H*), 4.27 (1 H, d, *J* = 9.9 Hz, SCHCH*H*), 4.13 (1 H, d, *J* = 13.9 Hz, NC*H*HAr), 3.90-4.02 (2 H, m, SC*H* & NCH*H*Ar), 3.71-3.79 (1 H, m, OC*H*HCH$_2$), 3.57-3.65 (1 H, m, OCH*H*CH$_2$), 2.88-2.96 (1 H, m, OCH$_2$C*H*H), 2.76-2.84 (1 H, m, OCH$_2$CH*H*), 2.30 (3 H, s, ArC*H*$_3$); δ_C (CDCl$_3$, 75 MHz) 161.1 (s, J_{CF} = 248.5 Hz), 137.8 (s), 133.1 (s), 130.5 (d, J_{CF} = 8.5 Hz), 129.8 (d, J_{CF} = 3.5 Hz), 129.4 (d), 127.9 (d), 125.0 (d, J_{CF} = 3.5 Hz), 123.6 (s, J_{CF} = 11.7 Hz), 116.1 (d, J_{CF} = 22.0 Hz), 71.6 (d), 67.2 (t), 66.2 (d), 60.4 (t), 57.4 (t), 47.1 (t), 21.1 (q); **LRMS** (ES$^-$) 393 (M-H, 100), 363 (40), 184 (51); **HRMS** (ES$^-$) calcd for C$_{19}$H$_{22}$FN$_2$O$_4$S (M-H) 393.1284, observed 393.1291

(3S*, 4S*)-3-(2-Bromophenyl)-2-(2-hydroxyethyl)-isoxazolidine-4-sulfonic acid 4-methylbenzylamide (152b)[113]

To a stirred solution of (3S*, 4S*)-3-(2-bromophenyl)-2-[2-(*tert*-

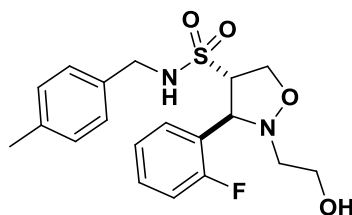butyldimethylsilanyloxy)- ethyl]-isoxazolidine-4-sulfonic acid-4-methylbenzylamide **150b** (0.57 g, 1.0 mmol) in dry THF (16 mL) at 0 °C was added TBAF (1 M in THF, 1.5 mL, 1.5 mmol, 1.5 eq.). After 2 h at 0 °C the reaction was concentrated *in vacuo* and the residue was purified by flash chromatography (starting 6:1 petroleum ether/EtOAc) to give the title compound as a clear gel (0.36 g, 0.79 mmol, 79%).

R$_f$ 0.30 (9:1 CHCl$_3$/MeOH); **ν$_{max}$** (thin film, cm^{-1}) 3497, 3141, 2928, 1874, 1514, 1320, 1147; **δ$_H$** (CDCl$_3$, 300 MHz) 7.59 (1 H, dd, J = 8.0, 0.8 Hz, ArH), 7.46 (1 H, dd, J = 8.0, 1.0 Hz, ArH), 7.38 (1 H, t, J = 8.3 Hz, ArH), 7.21-7.28 (1 H, m, ArH), 7.01 (2 H, d, J = 7.7 Hz, ArH), 6.88 (2 H, d, J = 7.7 Hz, ArH), 7.62-7.72 (2 H, m, NCH & NCHHAr), 4.48 (1 H, dd, J = 9.9, 3.5 Hz, SCHCHH), 4.37 (1 H, t, J = 9.9 Hz, SCHCHH), 4.13 (1 H, dd, J = 13.4, 6.2 Hz, NCHHAr), 3.93 (1 H, td, J = 8.0, 3.5 Hz, OCHHCH$_2$), 3.74-3.79 (1 H, m, SCH), 3.58-3.65 (1 H, m, OCHHCH$_2$), 2.97-3.05 (1 H, m, OCH$_2$CHH), 2.76-2.90 (1 H, m, OCH$_2$CHH), 2.30 (3 H, s, ArCH_3); **δ$_C$** (CDCl$_3$, 75 MHz) 171.2 (s), 137.3 (s), 135.8 (s), 133.4 (d), 133.1 (d), 130.2 (d), 129.4 (d), 128.4 (d), 127.9 (d), 124.6 (s), 72.4 (d), 70.7 (d), 67.4 (t) 60.4 (t), 57.2 (t), 47.0 (t), 21.1 (q); **LRMS** (ES$^-$) 455 (M-H, ^{81}Br, 100), 453 (M-H, ^{79}Br, 98), 425 (^{81}Br, 41), 423 (^{79}Br, 40), 184 (62); **HRMS** (ES$^-$) calcd for C$_{19}$H$_{22}$BrN$_2$O$_4$S (M-H) 453.0484, observed 453.0490

(3S*, 4S*)-2-(2-Ethylamino)-3-(2-fluorophenyl)-isoxazolidine-4-sulfonic acid 4-methylbenzylamide (153a)

To a stirred solution of (3S*, 4S*)-3-(2-fluorophenyl)-2-(2-hydroxyethyl)-isoxazolidine- 4-sulfonic acid 4-methylbenzylamide **152a** (98 mg, 0.25 mmol), NEt$_3$ (48 µL, 0.35 mmol, 1.4 eq.) and dichloromethane (3.0 mL), was added methanesulfonyl chloride (21 µL, 0.28 mmol, 1.1 eq.) and reaction was stirred at 0 °C for 30 min. The reaction was diluted with dichloromethane and washed with 1% HCl. The organic layer was dried over MgSO$_4$, filtered and solvent was removed *in vacuo*. The crude compound (0.15 g, 0.31 mmol) was added DMF (3 mL) and NaN$_3$ (48 mg, 0.74 mmol 2.4 eq.) and refluxed at 90 °C for 2 h. Solvent was removed *in*

vacuo and the residue was diluted with water and extracted with EtOAc. The organic layer dried over MgSO$_4$, filtered and solvent was removed *in vacuo* to yield crude azide. Azide was hydrogenated at 1 atm over 10% Pd/C (20 mg) in MeOH for 1 h. The solid residue was filtered under gravity and rinsed thoroughly with MeOH; filtrate was concentrated *in vacuo* to give the title compound as a clear gel (43 mg, 0.11 mmol, 44%).

R$_f$ 0.13 (9:1 CHCl$_3$/MeOH); **v$_{max}$** (thin film, cm^{-1}) 3386, 3273, 2924, 1616, 1493, 1311, 1143, 760; **δ$_H$** (CDCl$_3$, 500 MHz) 7.40-7.49 (1 H, m, Ar*H*), 7.32 (1 H, d, *J* = 7.4 Hz, Ar*H*), 7.16 (1 H, t, *J* = 7.4 Hz, Ar*H*), 7.04-7.12 (1 H, m, Ar*H*), 7.01 (2 H, d, *J* = 7.8 Hz, Ar*H*), 6.96 (2 H, d, *J* = 7.8 Hz, Ar*H*), 4.35 (1 H, dd, *J* = 9.7, 3.3 Hz, SCHC*H*H), 4.31 (1 H, d, *J* = 6.9 Hz, NC*H*), 4.22 (1 H, app. t, *J* = 9.6 Hz, SCHCH*H*), 4.10 (1 H, d, *J* = 14.1 Hz, NC*H*HAr), 3.94 (1 H, d, *J* = 14.1 Hz, NCH*H*Ar), 3.88-3.92 (1 H, m, SC*H*), 2.83-2.94 (2 H, m, NH$_2$C*H*$_2$CH$_2$), 2.65-2.77 (2 H, m, NH$_2$CH$_2$C*H*$_2$), 2.28 (3 H, s, ArC*H*$_3$); **δ$_C$** (CDCl$_3$, 125 MHz) 161.0 (s, *J*$_{CF}$ = 248.6 Hz), 137.7 (s), 133.5 (s), 130.5 (d, *J*$_{CF}$ = 8.6 Hz), 130.0 (d, *J*$_{CF}$ = 3.2 Hz), 129.4 (d), 128.0 (d), 125.0 (d, *J*$_{CF}$ = 2.9 Hz), 124.1 (s, *J*$_{CF}$ = 11.5 Hz), 116.1 (d, *J*$_{CF}$ = 22.1 Hz), 71.9 (d), 67.2 (t), 66.1 (d), 57.9 (t), 47.0 (t), 39.9 (t), 21.2 (q); **LRMS** (ES$^-$) 392 (M-H, 100), 362 (61), 184 (50); **HRMS** (ES$^-$) calcd for C$_{19}$H$_{23}$FN$_3$O$_3$S (M-H) 392.1444, observed 392.1450
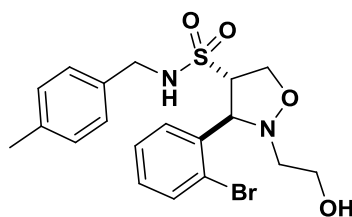
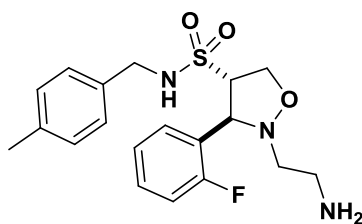**(3S*, 4S*)-3-(2-Bromophenyl)-2-(2-ethylamino)-isoxazolidine-4-sulfonic acid 4-methylbenzylamide (153b)**
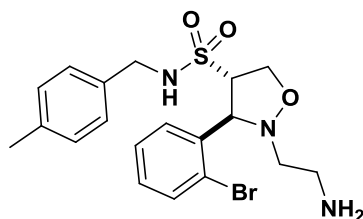
To a stirred solution of (3S*, 4S*)-3-(2-bromophenyl)-2-(2-hydroxyethyl)-isoxazolidine- 4-sulfonic acid 4-methylbenzylamide **152b** (0.15 g, 0.33 mmol), NEt$_3$ (69 µL, 0.50 mmol, 1.5 eq.) and dichloromethane (3.0 mL), was added methanesulfonyl chloride (28 µL, 0.36 mmol, 1.1 eq.) and reaction was stirred at 0 °C for 30 min. The reaction was diluted with dichloromethane and washed with 1% HCl. The organic layer was dried over MgSO$_4$, filtered and solvent was removed *in vacuo*. The crude compound (0.19 g, 0.35 mmol) was added DMF (3.0 mL) and NaN$_3$ (51 mg, 0.79 mmol 2.4 eq.) and refluxed at 90 °C for 2 h. Solvent was removed

in vacuo and residue was diluted with water and extracted with EtOAc. The organic layer dried over MgSO$_4$, filtered and solvent was removed in vacuo to yield crude azide. Azide was hydrogenated at 1 atm over 10% Pd/C (20 mg) in MeOH for 1 h. The solid residue was filtered under gravity and rinsed thoroughly with MeOH; filtrate was concentrated *in vacuo* to give title compound as a clear gel (0.12 g, 0.27 mmol, 82%).

R$_f$ 0.10 (9:1 CHCl$_3$/MeOH); **ν$_{max}$** (thin film, cm^{-1}) 3374, 3274, 2925, 1655, 1515, 1311, 1143, 699; **δ$_H$** (CDCl$_3$, 500 MHz) 7.58 (2 H, br s, N*H$_2$*), 7.39-7.42 (2 H, m, Ar*H*), 7.27-7.31 (2 H, m, Ar*H*), 7.02 (2 H, d, *J* = 7.8 Hz, Ar*H*), 6.94 (2 H, d, *J* = 7.8 Hz, Ar*H*), 6.75 (1 H, br s, N*H*), 4.50 (1 H, d, *J* = 8.0 Hz, SCHC*H*H), 4.23 (1 H, d, *J* = 5.6 Hz, NC*H*), 4.17 (1 H, app. t, *J* = 8.0 Hz, SCHCH*H*), 4.02 (1 H, dd, *J* = 14.4, 5.8 Hz, NC*H*HAr), 3.93 (1 H, dd, *J* = 14.1, 5.8 Hz, NCH*H*Ar), 3.69-3.73 (1 H, m, SC*H*), 3.58-3.62 (1 H, m, NH$_2$CH$_2$C*H*H), 3.23-3.28 (1 H, m, NH$_2$CH$_2$CH*H*), 3.09-3.19 (2 H, m, NH$_2$C*H$_2$*CH$_2$), 2.22 (3 H, s, ArC*H$_3$*); **δ$_C$** (CDCl$_3$, 125 MHz) 162.7 (s), 137.6 (s), 137.2 (s), 135.4 (s), 130.4 (d), 129.4 (d), 129.4 (d), 129.0 (d), 128.7 (d), 128.2 (d), 72.7 (d), 71.2 (d), 67.6 (t), 51.5 (t), 46.8 (t), 39.7 (t), 21.2 (q); **LRMS** (ES$^+$) 456 (M+H, ^{81}Br, 63), 454 (M+H, ^{79}Br, 60), 398 (98), 176 (100); **HRMS** (ES$^+$) calcd for C$_{19}$H$_{25}$BrN$_3$O$_3$S (M+H) 454.0800, observed 454.0809

N-(2-(3S*, 4S*)-3-(2-fluorophenyl)-4-(N-(methylbenzyl)sulfamoyl)isoxazolidin-2-yl)-5- (2-oxohexahydrothieno [3, 4-d]imidazole-4-yl) pentanamide (154a)

To a stirred solution of (3S*, 4S*)-2-(2-ethylamino)-3-(2-fluorophenyl)-isoxazolidine- 4-sulfonic acid 4-methylbenzylamide **153a** (20 mg, 0.05 mmol) in 10:1 mixture CH$_2$Cl$_2$/DMF (3.0 mL) was added *D*-biotin (14 mg, 0.05 mmol), HOBt (7.5 mg, 0.50 mmol, 10 eq.) and *N*-methylmorpholine (5.6 mg, 0.05 mmol). The reaction was cooled to -10 °C before the addition of EDC.HCl (11 mg, 0.05 mmol) and was stirred at 0 °C for 1 h. The reaction mixture was allowed to warm slowly to RT and left overnight stirring. The solvent was removed *in vacuo* and the crude

residue was purified by flash chromatography (starting 5% MeOH/CH$_2$Cl$_2$) to give 1:1 diastereo-mixture of the title compound as a clear gel (9.4 mg, 0.01 mmol, 30%). **R$_f$** 0.24 (9:1 CH$_2$Cl$_2$/MeOH); **ν_{max}** (thin film, cm^{-1}) 3405, 3312, 3283, 1699, 1609, 1530, 1332, 1134, 788; **δ_H** (CDCl$_3$, 600 MHz) 7.27-7.40 (4 H, m, Ar*H*), 7.04-7.20 (4 H, m, Ar*H*), 7.02 (2 H, d, *J* = 7.2 Hz, Ar*H*), 6.99 (2 H, d, *J* = 7.2 Hz, Ar*H*), 6.95 (2 H, d, *J* = 8.0 Hz, Ar*H*), 6.89 (2 H, d, *J* = 8.0 Hz, Ar*H*), 6.42 (1 H, br s, N*H*), 6.20 (2 H, br s, N*H*), 6.16 (1 H, br s, N*H*), 5.69 (1 H, br s, N*H*), 5.46 (2 H, br s, N*H*), 5.20 (1 H, br s, N*H*), 4.49 (1 H, d, *J* = 12.1 Hz, NC*H*HAr), 4.44 (1 H, dd, *J* = 9.9, 2.8 Hz, SCHC*H*H), 4.40 (1 H, d, *J* = 10.3 Hz, SCHC*H*H), 4.25-4.35 (3 H, m, SC*H* & biotinyl-C*H*), 4.18-4.23 (2 H, m, SCHCH*H*), 4.09-4.15 (1 H, m, SC*H*), 4.10-4.14 (2 H, m, NC*H*$_2$Ar), 3.90-4.04 (3 H, m, NCH$_2$C*H*$_2$ & NCH*H*Ar), 3.85-3.87 (1 H, br s, NC*H*), 3.79-3.83 (2 H, m, NC*H*$_2$CH$_2$), 3.65-3.70 (1 H, m, NC*H*), 3.26-3.53 (4 H, m, NC*H*$_2$), 3.15-3.20 (3 H, m, biotinyl-C*H*), 2.91 (1 H, td, *J* = 12.6, 5.0 Hz, biotinyl-C*H*), 2.78-2.86 (2 H, m, biotinyl-C*H*$_2$), 2.71 (2 H, d, *J* = 13.5 Hz, biotinyl-C*H*$_2$), 2.33 (3 H, s, ArC*H*$_3$), 2.29 (3 H, s, ArC*H*$_3$), 2.00-2.24 (4 H, m, biotinyl-C*H*$_2$), 1.56-1.80 (8 H, m, biotinyl-C*H*$_2$), 1.39-1.50 (4 H, m, biotinyl-C*H*$_2$); **δ_C** (CDCl$_3$, 150 MHz) 173.1 (s), 164.0 (s), 161.5 (s, *J*$_{CF}$ = 256.3 Hz), 147.9 (s), (147.7 (s), 137.6 (d, *J*$_{CF}$ = 17.5 Hz), 133.7 (s), 130.5 (d, *J*$_{CF}$ = 3.2 Hz), 129.3 (d), 127.9 (d), 127.9 (d), 124.8 (d, *J*$_{CF}$ = 13.6 Hz), 123.6 (s, *J*$_{CF}$ = 9.2 Hz), 123.6 (s, *J*$_{CF}$ = 9.3 Hz), 116.3 (d, *J*$_{CF}$ = 22.1 Hz), 116.1 (d, *J*$_{CF}$ = 22.2 Hz), 71.4 (d), 71.3 (d), 67.5 (t), 62.0 (d), 62.0 (d), 60.1 (d), 55.7 (d), 55.0 (d), 47.0 (t), 46.9 (t), 40.8 (t), 40.6 (t), 38.3 (t), 38.0 (t), 36.1 (t), 29.7 (t), 28.1 (t), 27.6 (t), 27.4 (t), 25.6 (t), 21.2 (q); **LRMS** (ES$^-$) 618 (M-H, 100), 325 (5); **HRMS** (ES$^-$) calcd for C$_{29}$H$_{37}$FN$_5$O$_5$S$_2$ (M-H) 618.2220, observed 618.2215

***N*-(2-(3S*, 4S*)-3-(2-bromophenyl)-4-(*N*-(methylbenzyl)sulfamoyl)isoxazolidin-2-yl)-5- (2-oxohexahydrothieno [3, 4-d]imidazole-4-yl) pentanamide (154b)**
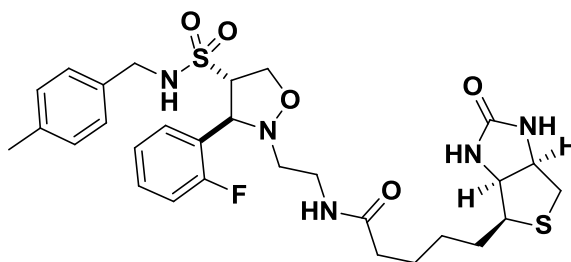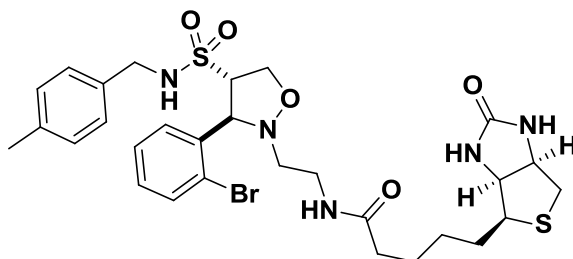

To a stirred solution of (3S*, 4S*)-2-(2-ethylamino)-3-(2-bromophenyl)-isoxazolidine- 4-sulfonic acid 4-methylbenzylamide **153b** (13 mg, 0.03 mmol) in

DMF (2.0 mL) was added *D*-biotin (8.4 mg, 0.03 mmol) and DMAP (3.6 mg, 0.30 mmol, 10 eq.). The reaction was cooled to -10 °C before the addition of EDC.HCl (5.9 mg, 0.03 mmol) and stirred at RT overnight. The reaction mixture was diluted with water and extracted with chloroform. The organic layer was dried over MgSO$_4$, filtered and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (starting 5% MeOH/CH$_2$Cl$_2$) to give 1:1 diastereo-mixture of the title compound as a clear gel (17.6 mg, 0.025 mmol, 92%).

R$_f$ 0.26 (9:1 CH$_2$Cl$_2$/MeOH); **ν$_{max}$** (thin film, cm^{-1}) 3408, 3302, 3277, 1692, 1601, 1536, 1323, 1133, 689; **δ$_H$** (CDCl$_3$, 600 MHz) 7.34-7.43 (8 H, m, Ar*H*), 7.02 (2 H, d, *J* = 8.0 Hz, Ar*H*), 6.98 (2 H, d, *J* = 8.0 Hz, Ar*H*), 6.85 (2 H, d, *J* = 7.8 Hz, Ar*H*), 6.82 (2 H, d, *J* = 7.7 Hz, Ar*H*), 6.70-6.74 (2 H, br s, N*H*), 6.62 (1 H, br s, N*H*), 6.51 (2 H, br s, N*H*), 6.31 (1 H, br s, N*H*), 6.27 (1 H, br s, N*H*), 4.39-4.47 (4 H, m, NC*H*HAr & SCHC*H*H), 4.30-4.36 (1 H, m, SC*H*), 4.28 (1 H, t, *J* = 6.4 Hz, N*H*), 4.17-4.25 (1 H, m, SC*H*), 4.15 (1 H, d, *J* = 13.6 Hz, NCH*H*Ar), 4.03-4.12 (3 H, m, SCHCH*H* & biotinyl-C*H*), 3.92 (1 H, dd, *J* = 13.9, 5.1 Hz, NCH*H*Ar), 3.76-3.90 (2 H, m, NC*H*), 3.49-3.65 (6 H, m, NC*H$_2$* & biotinyl-C*H*), 3.17-3.30 (4 H, m, NCH$_2$C*H$_2$*), 2.78-2.92 (6 H, m, biotinyl-C*H* & biotinyl-C*H$_2$*), 2.69 (1 H, d, *J* = 11.6 Hz, biotinyl-C*H*), 2.29 (3 H, s, ArC*H$_3$*), 2.24 (3 H, s, ArC*H$_3$*), 2.13-2.19 (4 H, m, biotinyl-C*H$_2$*), 1.55-1.75 (8 H, m, biotinyl-C*H$_2$*), 1.36-1.46 (4 H, m, biotinyl-C*H$_2$*); **δ$_C$** (CDCl$_3$, 150 MHz) 173.1 (s), 173.0 (s), 164.0 (s), 137.6 (s), 137.5 (s), 137.5 (s), 133.8 (s), 133.7 (s), 133.5 (s), 133.4 (d), 129.4 (d), 129.3 (d), 129.0 (d), 129.0 (d), 128.8 (d), 128.8 (d), 128.2 (d), 127.9 (d), 127.9 (d), 72.4 (d), 72.2 (d), 67.4 (t), 67.3 (t), 62.0 (d), 61.9 (d), 60.2 (d), 60.1 (d), 55.7 (d), 55.2 (d), 55.1 (d), 53.5 (t), 46.7 (t), 46.6 (t), 40.7 (t), 40.6 (t), 38.3 (t), 38.0 (t), 36.1 (t), 36.0 (t), 31.0 (t), 27.7 (t), 27.6 (t), 25.5 (t), 25.2 (t), 21.2 (q); **LRMS** (ES$^-$) 680 (M-H, ^{81}Br, 11), 678 (M-H, ^{79}Br, 10), 600 (100); **HRMS** (ES$^-$) calcd for C$_{29}$H$_{37}$BrN$_5$O$_5$S$_2$ (M-H) 678.1419, observed 678.1426

4.4 Miscellaneous compounds

N-(*p*-Methoxybenzyl)-*C*-phenylnitrone (155)[113]
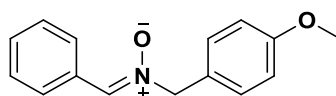
4-Methoxybenzyl hydroxylamine (2.1 g, 14 mmol), benzaldehyde (1.5 g, 14 mmol) and NaHCO$_3$ (3.5 g, 42 mmol, 3 eq.) were mixed in dichloromethane and refluxed

overnight. NaHCO$_3$ was filtered off under gravity and the solvent was removed *in vacuo*. The remaining solid was recrystallized in EtOAc and petroleum ether to give the title compound as a white solid and as a single diastereoisomer as judged by NMR (2.9 g, 12 mmol, 86%).

mp 97-99 °C (lit.[113] **mp** 97 °C); $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 3053, 1612, 1514; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 8.19-8.24 (2 H, m, Ar*H* and C*H*N), 7.33-7.41 (6 H, m, Ar*H*), 7.93 (2 H, d, *J* = 6.8 Hz, Ar*H*), 4.99 (2 H, s, C*H*$_2$), 3.81 (3 H, s, OC*H*$_3$); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 160.2 (s), 149.6 (s), 125.2 (s), 130.1 (d), 130.5 (d), 128.7 (d), 128.4 (d), 114.4 (d), 114.1 (d), 70.6 (t), 55.3 (q); **LRMS** (FAB$^+$) 241 (M$^+$, 36), 199 (51), 173 (100); **HRMS** (FAB$^+$) calcd for C$_{15}$H$_{15}$NO$_2$(M+Na) 264.1000, observed 264.1006

2-(*p*-Methoxybenzyl)-3-phenylisoxazole-4-pentafluorophenyl ethenesulfonate (156)[113]
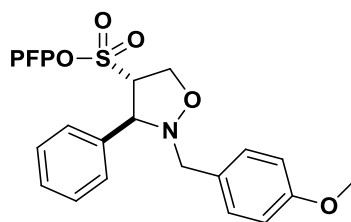
Pentafluorophenyl ethenesulfonate **110** (1.5 g, 5.5 mmol) and *N*-(*p*-methoxybenzyl)-*C*-phenylnitrone **155** (1.99 g, 8.25 mmol, 1.5 eq.) were mixed in toluene (10 mL) and refluxed overnight. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (20% EtOAc/petroleum ether) to give the title compound as a white solid and as a single diastereoisomer as judged by NMR (1.51 g, 2.93 mmol, 55%).

R$_f$ 0.69 (20% EtOAc/petroleum ether); **mp** 90-92 °C (lit.[113] **mp** 90 °C); $\mathbf{\nu_{max}}$ (thin film, cm^{-1}) 2950, 1505, 1367, 1162; $\mathbf{\delta_H}$ (CDCl$_3$, 300 MHz) 7.59 (2 H, dd, *J* = 7.7, 1.6 Hz, Ar*H*), 7.42 (3 H, d, *J* = 6.4 Hz, Ar*H*), 7.28 (2 H, d, *J* = 6.0 Hz, Ar*H*), 6.88 (2 H, d, *J* = 7.7 Hz, Ar*H*), 4.62-4.66 (1 H, m, SC*H*), 4.50-4.62 (1 H, m, NC*H*), 4.46 (2 H, m, SCHC*H*$_2$), 4.00 (1 H, d, *J* = 13.9 Hz, NC*H*HAr), 3.87 (1 H, d, *J* = 13.9 Hz, NCH*H*Ar), 3.80 (3 H, s, OC*H*$_3$); $\mathbf{\delta_C}$ (CDCl$_3$, 75 MHz) 159.1 (s), 136.2 (s), 130.2 (d), 129.1 (d), 128.6 (d), 128.4 (s), 128.3 (d), 113.7 (d), 73.6 (d), 71.5 (d), 66.9 (t), 58.8 (t), 55.2 (q); **LRMS** (FAB$^+$) 515 (M$^+$, 23), 333 (12), 154 (100); **HRMS** (FAB$^+$) calcd for C$_{23}$H$_{19}$F$_5$NO$_5$S (M+H) 516.0904, observed 516.0901

Preparation of α-bromoethene phenylsulfone (157)[124]
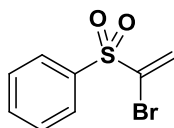
Bromine (1 mL) was dissolved in CCl_4 (15 mL), and was added dropwise to a premixed solution of phenyl ethenesulfone (2.5 g, 15 mmol) and AIBN (0.10 g), in CCl_4 (75 mL) under heating (70 °C). Additional AIBN was added after the addition of the bromine solution. The reaction was refluxed for 4 h followed by 24 h stirring at RT, and the solvent was removed *in vacuo*. The mixture was dissolved in benzene (75 mL) and a premixed solution of NEt_3 (1.5 g, 15 mmol) in benzene (15 mL) was added and the reaction was stirred at RT for 3 h. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (10% Et_2O/petroleum ether) to give the title compound as a white solid (2.9 g, 12 mmol, 80 %).

R_f 0.14 (10% Et_2O/petroleum ether); **mp** 46-48 °C (lit.[196] **mp** 44 °C); ν_{max} (thin film, cm^{-1}) 3058, 1601, 1448, 1326, 1180; δ_H ($CDCl_3$, 75 MHz) 7.91 (2 H, d, $J = 7.1$ Hz, Ar*H*), 7.94 (1 H, t, $J = 7.1$ Hz, Ar*H*), 7.52 (2 H, t, $J = 7.2$ Hz, Ar*H*), 7.06 (1 H, d, $J = 3.2$ Hz, C*H*H), 6.24 (1 H, d, $J = 3.2$ Hz, CH*H*); δ_C ($CDCl_3$, 75 MHz) 136.4 (s), 134.4 (d), 129.3 (d), 129.1 (d), 119.2 (s) 68.1 (t); **LRMS** (EI) 248 ($M^{+\bullet}$, ^{81}Br, 6), 246 ($M^{+\bullet}$, ^{79}Br, 6), 141 (18), 125 (52), 103 (100), 77 (54); **HRMS** (EI) calcd for $C_8H_7BrO_2S$ ($M^{+\bullet}$) 245.9344, observed 245.9341

Preparation of 3-phenyl isoxazole-5-phenylsulfone (158)[124]
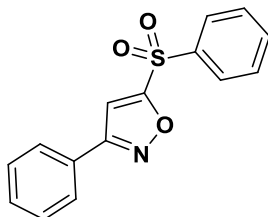
α-Chlorobenzoxime **116b** (62 mg, 0.40 mmol, 1 eq.), α-bromoethene phenylsulfone **157** (99 mg, 0.40 mmol, 1 eq.) and NEt_3 (0.06 mL, 0.44 mmol, 1.1 eq.) were mixed in dichloromethane (5 mL) and stirred at RT for 72 h. The solvent removed *in vacuo* and crude residue was purified by flash chromatography (10% Et_2O/petroleum ether) to give the title compound as a white solid and as a single regioisomer as judged by NMR (50 mg, 0.17 mmol, 44%).

R$_f$ 0.08 (10% Et$_2$O/petroleum ether); **mp** 128-131 °C (lit.[124] **mp** 127 °C); **ν$_{max}$** (thin film, cm^{-1}) 3055, 1596, 1166; **δ$_H$** (CDCl$_3$, 300 MHz) 8.11 (2 H, d, J = 8.0 Hz, ArH), 7.69-7.78 (3 H, m, ArH), 7.61 (2 H, t, J = 8.1 Hz, ArH), 7.45-7.48 (3 H, m, ArH), 7.25 (1 H, s, Isox$H$); **δ$_C$** (CDCl$_3$, 75 MHz) 167.7 (s), 162.71 (s), 138.0 (s), 131.6 (s), 135.0 (d), 131.0 (d), 129.7 (d), 129.2 (d), 128.6 (d), 127.3 (d), 106.6 (d); **LRMS** (EI) 285 (M$^{+•}$, 43), 144 (41), 116 (24), 77 (100); **HRMS** (EI) calcd for C$_{15}$H$_{11}$NO$_3$S (M$^{+•}$) 285.0454, observed 285.0447

α-Bromoethenesulfonic acid 4-methylbenzylamide (159)
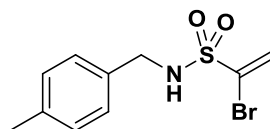
To a stirred solution of ethenesulfonic acid-4-methylbenzylamide **141** (1.1 g, 5.0 mmol) in chloroform (15 mL), was slowly added pre-mixed solution of bromine (2.6 mL, 50 mmol, 10 eq.) in chloroform (10 mL) and stirred at RT for 1 h. Solvent was removed *in vacuo* and the reaction mixture was then added toluene (10 mL) and NEt$_3$ (0.69 mL, 5.0 mmol, 1 eq.). The reaction was further stirred at RT for 3 h, and mixture was then washed with water. The organic layer was dried over MgSO$_4$ and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (starting 9:1 petroleum ether/Et$_2$O) to give the title compound as a cream solid (1.0 g, 3.4 mmol, 68%).

R$_f$ 0.10 (9:1 petroleum ether/Et$_2$O); **mp** 78-79 °C; **ν$_{max}$** (thin film, cm^{-1}) 3304, 3107, 1604, 1514, 1329, 1160, 940, 706; **δ$_H$** (CDCl$_3$, 500 MHz) 7.22 (2 H, d, J = 7.7 Hz, ArH), 7.16 (2 H, d, J = 7.7 Hz, ArH), 6.84 (1 H, d, J = 3.1 Hz, CHCHH), 6.20 (1 H, d, J = 3.1 Hz, CHCHH), 4.89 (1 H, br s, NH), 4.17 (2 H, d, J = 5.8 Hz, NCH_2), 2.34 (3 H, s, CH_3); **δ$_C$** (CDCl$_3$, 125 MHz) 138.4 (s), 132.7 (s), 129.6 (d), 128.7 (t), 128.2 (d), 127.0 (s), 47.6 (t), 21.2 (q); **LRMS** (EI) 291 (M$^{+•}$, ^{81}Br, 4), 289 (M$^{+•}$, ^{79}Br, 4), 184 (7), 119 (100), 105 (42); **HRMS** (EI) calcd for C$_{10}$H$_{12}$BrNO$_2$S (M$^{+•}$) 288.9766, observed 288.9750

(3S*, 4S*)-2-Methyl-3-(4-nitrophenyl)isoxazolidine-4-pentafluorophenyl sulfonate ester (160)[113]
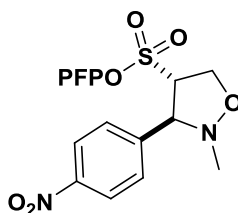
To a stirred solution of pentafluorophenyl ethenesulfonate **110** (1.4 g, 5.0 mmol) in toluene (20 mL) was added *N*-methyl-*C*-(4-nitrophenyl) nitrone **140j** (1.1 g, 6.0 mmol, 1.2 eq.) and refluxed for 3 h. Solvent was removed *in vacuo* and the residue was purified by flash chromatography (starting 10:1 petroleum ether/Et$_2$O) to give the title compound as a cream solid and as a single diastereoisomer as judged by NMR (1.3 g, 2.9 mmol, 58%).

R$_f$ 0.35 (2:1 petroleum ether/EtOAc); **mp** 125-127 °C (lit.[113] **mp** 128 °C); **v$_{max}$** (thin film, cm^{-1}) 3102, 2976, 1743, 1598, 1515, 1393, 1350, 992; **δ$_H$** (CDCl$_3$, 500 MHz) 8.25 (2 H, d, *J* = 8.8 Hz, Ar*H*), 7.70 (2 H, d, *J* = 8.8 Hz, Ar*H*), 4.62 (1 H, dd, *J* = 10.2, 3.1 Hz, SCHC*H*H), 4.49 (1 H, dd, *J* = 10.2, 8.2 Hz, SCHCH*H*), 4.27 (1 H, td, *J* = 8.2, 7.5 Hz, SC*H*), 4.20 (1 H, d, *J* = 7.5 Hz, NC*H*), 2.72 (3 H, s, NC*H$_3$*); **δ$_C$** (CDCl$_3$, 125 MHz) 148.5 (s), 143.2 (s), 129.1 (d), 124.4 (d), 73.8 (d), 73.0 (d), 66.9 (t), 42.9 (q); **LRMS** (EI) 454 (M$^{+•}$, 65), 207 (19), 155 (34), 116 (100); **HRMS** (EI) calcd for C$_{16}$H$_{11}$F$_5$N$_2$O$_6$S (M$^{+•}$) 454.0252, observed 454.0258

(3S*, 4S*)-3-(5-Bromofuryl)-2-methylisoxazolidine-4-sulfonic acid 4-methylbenzylamide (161)[113]
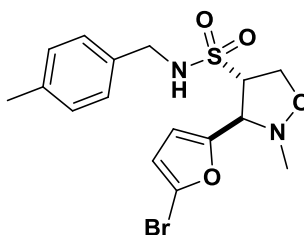
To a stirred solution of (3S*, 4S*)-3-(5-bromofuryl)-2-methylisoxazolidine- 4-pentafluorophenyl sulfonate ester **136** (0.47 g, 1.0 mmol) in dry THF (9 mL) was added 4-methylbenzylamine (0.36 mL, 3.0 mmol, 3 eq.) followed by DBU (0.17 mL, 1.5 mmol, 1.5 eq.). The mixture was refluxed for 1 h. Reaction mixture was diluted with dichloromethane and washed with 2M HCl, saturated NaHCO$_3$ and water. The organic layer was dried with MgSO$_4$, filtered and solvent was removed *in vacuo*. The

crude residue was purified by flash chromatography (starting 10:1 petroleum ether/Et$_2$O) to give title compound as a cream solid and as a single diastereoisomer as judged by NMR (0.23 g, 0.55 mmol, 56%).

R$_f$ 0.31 (1:2 petroleum ether/Et$_2$O); **mp** 122-125 °C (lit.[113] brown oil); **ν$_{max}$** (thin film, cm^{-1}) 3280, 3141, 2853, 1736, 1504, 1320, 1141, 794; **δ$_H$** (CDCl$_3$, 500 MHz) 7.12 (2 H, d, J = 8.0 Hz, ArH), 7.08 (2 H, d, J = 8.0 Hz, ArH), 6.36 (1 H, d, J = 3.3 Hz, furyl$H$), 6.29 (1 H, d, J = 3.3 Hz, furyl$H$), 5.01 (1 H, br s, NH), 4.30 (1 H, dd, J = 9.1, 6.8 Hz, SCHCHH), 4.19 (1 H, dd, J = 9.1, 3.1 Hz, SCHCHH), 4.16 (1 H, d, J = 13.7 Hz, NCHHAr), 4.11 (1 H, app td, J = 6.9, 3.1 Hz, SCH), 4.07 (1 H, d, J = 13.7 Hz, NCHHAr), 3.87 (1 H, br s, NCH), 2.65 (3 H, s, NCH_3), 2.33 (3 H, s, CH_3); **δ$_C$** (CDCl$_3$, 125 MHz) 150.7 (s), 138.1 (s), 133.3 (s), 129.6 (d), 128.1 (d), 123.0 (s), 113.0 (d), 112.6 (d), 69.4 (d), 67.6 (d), 66.9 (t), 47.2 (t), 43.1 (q), 21.2 (q); **LRMS** (EI) 416 (M$^{+•}$, ^{81}Br, 2), 414 (M$^{+•}$, ^{79}Br, 2), 230 (^{81}Br, 100), 228 (^{79}Br, 98), 205 (^{81}Br, 17), 203 (^{79}Br, 15), 187 (^{81}Br, 34), 185 (^{79}Br, 30), 120 (79), 105 (45); **HRMS** (EI) calcd for C$_{16}$H$_{19}$BrN$_2$O$_4$S (M$^{+•}$) 414.0243, observed 414.0250

(3S*, 4S*)-2-Methyl-3-(4-Nitrophenyl)-isoxazolidine-4-sulfonic acid allylamide (162)[113]
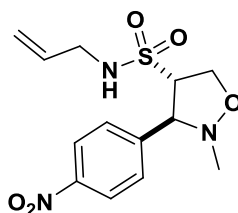
To a stirred solution of (3S*, 4S*)-2-methyl-3-(4-nitrophenyl)-isoxazolidine- 4-pentafluorophenyl sulfonate ester **160** (0.45 g, 1.0 mmol) in dry THF (10 mL), was added allylamine (0.17 g, 3.0 mmol, 3 eq.) followed by DBU (0.22 g, 1.5 mmol, 1.5 eq.) The mixture was refluxed for 1 h. The reaction was diluted with dichloromethane and washed with 2M HCl, saturated NaHCO$_3$ and water. The organic layer was dried with MgSO$_4$, filtered and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (starting 10:1 petroleum ether/EtOAc) to give the title compound as a cream solid and as a single diastereoisomer as judged by NMR (0.10 g, 0.31 mmol, 31%).

R$_f$ 0.21 (1:2 petroleum ether/EtOAc); **mp** 153-155 °C (lit.[113] **mp** 160 °C); **ν$_{max}$** (thin film, cm^{-1}) 3264, 3117, 2984, 2888, 1650, 1608, 1519, 1339, 1149; **δ$_H$** (CDCl$_3$, 300

MHz) 8.23 (2 H, d, J = 8.8 Hz, ArH), 7.68 (2 H, d, J = 8.8 Hz, ArH), 5.68-5.75 (1 H, m, NHCH$_2$CH), 5.26 (1 H, app.d, J = 9.7 Hz, NCH$_2$CHCHH)5.14 (1 H, dd, J = 9.7, 1.3 Hz, NCH$_2$CHCHH), 4.61 (1 H, t, J = 5.9 Hz, NH), 4.36 (1 H, dd, J = 9.7, 7.0 Hz, SCHCHH), 4.29 (1 H, br d, J = 9.7 Hz, SCHCHH), 4.01 (1 H, d, J = 6.9 Hz, NCH), 3.93-3.97 (1 H, m, SCH), 3.60-3.74 (2 H, m, NCH_2), 2.68 (3 H, s, NCH_3); δ_C (CDCl$_3$, 75 MHz) 148.0 (s), 144.9 (s), 133.0 (d), 128.9 (d), 124.0 (d), 118.3 (t), 74.1 (d), 72.9 (d), 67.1 (t), 46.0 (t), 43.0 (q); **LRMS** (EI) 327 (M$^{+\bullet}$, 4), 211 (6), 205 (19), 120 (100), 105 (15); **HRMS** (EI) calcd for C$_{14}$H$_{19}$N$_3$O$_4$S (M$^{+\bullet}$) 327.0883, observed 327.0888

5 **Appendices**

5.1 **Crystal Structure of 3-(4-chlorophenyl) isoxazole-5-PFP sulfonate (118c)**
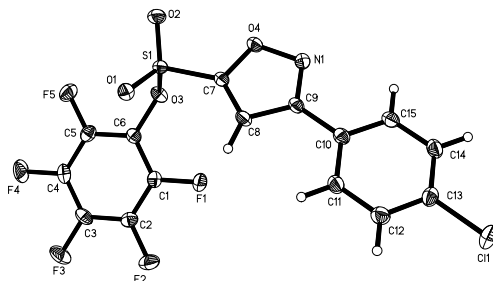
Identification code	str0635
Chemical formula	$C_{15}H_5ClF_5NO_4S$
Formula weight	425.71
Temperature	150(2) K
Radiation, wavelength	MoKα, 0.71073 Å
Crystal system, space group	orthorhombic, Pbca
Unit cell parameters	a = 11.2886(14) Å α = 90°
	b = 12.1223(15) Å β = 90°
	c = 22.253(3) Å γ = 90°
Cell volume	3045.2(6) Å^3
Z	8
Calculated density	1.857 g/cm^3
Absorption coefficient μ	0.471 mm^{-1}
F(000)	1696
Crystal colour and size	colourless, 0.36 × 0.16 × 0.05 mm^3
Data collection method	Bruker SMART APEX CCD diffractometer
ω rotation with narrow frames	
θ range for data collection	2.63 to 28.35°
Index ranges	h −15 to 14, k −16 to 15, l −29 to 29
Completeness to θ = 26.00°	99.8 %
Reflections collected	24452
Independent reflections	3713 (R_{int} = 0.0540)
Reflections with $F^2 > 2\sigma$	2979

Absorption correction semi-empirical from equivalents

Min. and max. transmission	0.8488 and 0.9768
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0694, 7.3487
Data / restraints / parameters	3713 / 0 / 244
Final R indices [F^2>2σ]	R1 = 0.0499, wR2 = 0.1158
R indices (all data)	R1 = 0.0676, wR2 = 0.1283
Goodness-of-fit on F^2	0.873
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.680 and −0.442 e Å^{-3}

5.2 Crystal Structure of 3-(4-nitrophenyl) isoxazole-5-PFP sulfonate (118j)
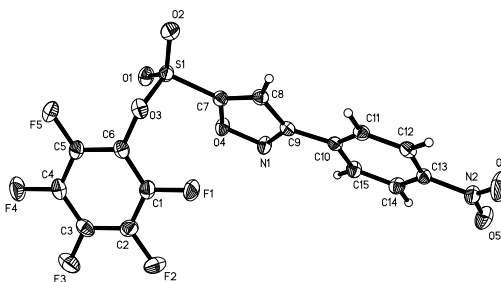
Identification code	str0639
Chemical formula	$C_{15}H_5F_5N_2O_6S$
Formula weight	436.27
Temperature	150(2) K
Radiation, wavelength	MoKα, 0.71073 Å
Crystal system, space group	orthorhombic, Pbca
Unit cell parameters	a = 11.1025(10) Å α = 90°
	b = 12.8648(11) Å β = 90°
	c = 21.7271(19) Å γ = 90°
Cell volume	3103.3(5) Å^3
Z	8
Calculated density	1.868 g/cm^3
Absorption coefficient μ	0.309 mm^{-1}
F(000)	1744

Crystal colour and size	colourless, $0.35 \times 0.32 \times 0.16$ mm^3
Data collection method	Bruker SMART APEX CCD diffractometer

ω rotation with narrow frames

θ range for data collection	3.06 to 28.31°
Index ranges	h -14 to 14, k -17 to 17, l -28 to 28
Completeness to $\theta = 26.00°$	99.8 %
Reflections collected	25038
Independent reflections	3791 ($R_{int} = 0.0367$)
Reflections with $F^2 > 2\sigma$	3136

Absorption correction semi-empirical from equivalents

Min. and max. transmission	0.8995 and 0.9522
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0615, 1.1805
Data / restraints / parameters	3791 / 0 / 262
Final R indices [$F^2 > 2\sigma$]	R1 = 0.0371, wR2 = 0.0982
R indices (all data)	R1 = 0.0474, wR2 = 0.1039
Goodness-of-fit on F^2	0.988
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.341 and -0.380 e Å^{-3}

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