Methods for Sultam Library Synthesis:

One-pot, Sequential Protocols

By

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Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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July 21, 2014
Date Defended

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Abstract

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The focus of this dissertation is to utilize vinyl sulfonamides in a series of reaction protocols towards the synthesis of sultam molecules by exploiting several salient features inherent to sulfonamides, including (i) electrophilicity of the β-carbon for Michael addition, (ii) low p*K*a suitable for alkylation, (iii) exploitation of the double bond for Heck, Diels-Alder and metathesis reactions. Overall, vinyl sulfonamides undergo several selective transformations to allow access to diverse sultams, which can be further utilized in library synthesis. Chapter one outlines the biological activity of sulfonamides and sultams and ends with a mini-review on the use of vinyl sulfonamides for sultam synthesis. Chapter two begins with a brief review of the bioactivity of acyl sulfonamides and acyl sultams, and then details a one-pot, sequential protocol employing complementary ambiphile (an entity having a nucleophilic and an electrophilic center) pairing (CAP) of vinyl sulfonamides with a variety of unprotected amino acids *via* aza-Michael addition followed by intramolecular EDC coupling (amidation). Utilizing this methodology diverse, sp^3-rich mono- and bicyclic acyl sultams were synthesized in a highly scalable manner. In addition, stereochemically-rich building blocks were constructed and a method was developed to provide quick access to all possible isomers. This method was also further extended to include one-pot, sequential 3-, 4-, and 5-multicomponent

protocols. Chapter 3 describes a stereo-controlled diversification of (8*R*,9a*S*)-8-hydroxy-2-(prop-2-yn-1-yl)hexahydro-pyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide **3.1.1**, utilizing a one-pot, click–OACC esterification protocol and a one-pot, sequential Mitsunobu alkylation pathway. The core (8*R*,9a*S*)-8-hydroxy-2-(prop-2-yn-1-yl)hexahydropyrrolo[2,1-*d*][1,2,5]thia-diazepin-1(2*H*)-one 3,3-dioxide, was synthesized rapidly on a multi-gram scale by a one-pot, sequential sulfonylation, Michael and EDC/amide coupling protocol. A compound library comprised of 135/158-members was generated utilizing these protocols. Chapter 3 also describes an efficient one-pot, sequential or 4-component protocol to access a library of stereochemically-rich acyl sultams containing varied elements of skeletal and peripheral diversity. The 3-component protocol consisted of sulfonylation of amines with 2-chloroethane sulfonyl chloride, aza-Michael with amino acids and amide coupling, and was extended to a similar 4-component procedure involving the aforementioned reactions followed by the fourth reaction, including: (i) a [3+2] Huisgen cycloaddition when propargyl amine was utilized in the sulfonylation step and (ii) carbamoylation when *L*-trans-hydroxyproline was employed in the aza-Michael reaction.

The construction of two libraries of triazole-containing isothiazolidine 1,1-dioxides utilizing click/OACC esterification protocol is also reported in chapter 3. A core dihydroisothiazole 1,1-dioxide scaffold was prepared rapidly on multi-gram scale via ring-closing metathesis (RCM), followed by propargylation. In this method, an aza-Michael reaction employing three amino alcohols was used to generate three

daughter scaffolds. This was followed by a one-pot, click/esterification protocol utilizing an oligomeric coupling reagent (OACC) to generate a 41-member library of triazole-containing isothiazole 1,1-dioxides.

Chapter 4 describes the utilization of facilitated, chromatography-free intermolecular Monomer-on-Monomer Mitsunobu protocols on hydroxy-pyrrolo thiadiazepin-dioxide scaffolds. The MoM Mitsunobu reaction was employed by norbornenyl-tagged benzyl ethyl azodicarboxylate (Nb-BEAD) and Nb-tagged triphenylphosphine (Nb-TPP) whereby purification/sequestration of excess and spent reagents was rapidly achieved using ring-opening metathesis (ROM) polymerization. Facile purification was carried-out utilizing surface-initiated polymerization by three sequestration methods: (i) from free metathesis catalyst (G-II) (ii) Nb-tagged silica (Nb-Si) (iii) Nb-tagged Cobalt-graphite (Nb-Co/C) magnetic nanoparticles. Another purification protocol is reported which utilizes a ROMP derived process for the diversification of tricyclic sultams (epoxybenzo[d]isothiazole 1,1-dioxides). This chromatography-free method permits easy isolation of reductive-Heck products and retrieval of excess starting material utilizing a sequestration protocol involving metathesis catalysts and a catalyst-armed Si-surface.

To my Mother Sakina Sardar Khan for the continual prayers and her support for my success

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Abbreviations

CH_3CN	Acetonitrile
Aq	aqueous
ALR2	aldose reductase
BEAD	benzylethyl azodicarboxylate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
t-BuOH	*t*-Butanol
$CHCl_3$	Chloroform
CuI	copper iodide
CAR	conditioned avoidance response
CAP	complementary ambiphilic pairing
cat.	catalytic
CM	cross metathesis
CP	Complementary Ambiphilic Pairing
CMLD	Chemical Methodologies and Library Development
COX	Cyclooxygenase
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCM (CH_2Cl_2)	dichloromethane
Et_2O	diethyl ether
DMF	dimethylformamide
DOS	diversity oriented synthesis
DMSO	dimethylsulfoxide
DIAD	diisopropyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
FG	Functional Group
EDC (EDCI)	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate

G-I	Grubbs-I
G-II	Grubbs-II
h	hours
HTS	high throughput screening
HIV	human immunodeficiency virus
HOBt	1-hydroxybenzotriazole
IC_{50}	inhibitory concentration at 50%
IMDA	Intermolecular Diels-Alder
i-Pr	isopropyl
IR	infrared radiation
LiOH	Lithium hydroxide
LCMS	Liquid chromatography–mass spectrometry
LG	leaving group
M	molarity
MACOS	Microwave-Assisted, Continuous Flow Organic Synthesis
Methanol	MeOH
MoM	Monomer on monomer
MLPCN	Molecular Libraries Probe Production Centers Network
NSAIDs	Non-steroidal anti-inflammatory drugs
NMR	nuclear magnetic resonance
NIH	National Institute of Health
NiT	naphtha [1,2-d]isothiazole
Nb	norbornenyl
Nuc	nucleophile
OACC	oligomeric alkyl carbodiimide
OSC	oligomeric sulfonyl chloride
PRAR	peroxisome proliferator-activated receptor
Ph	phenyl
PMB	*para*-methoxybenzyl

PoP	polymer on polymer
ppm	parts per million
PTP	protein-tyrosine phosphatase
PTSA	*p*-toluenesulfonic Acid
RCM	ring closing metathesis
ROMP	ring closing metathesis polymerization
ROM	ring opening metathesis
RCM	ring-closing metathesis
rt	room temperature
SAR	structure activity relationship
SPE	solid phase extraction
NaO^{t}Bu	Sodium *tert*-Butoxide
TBAF	Tetrabutyl ammonium flouride
TBS	*tert*-butyldimethylsilyl
TLC	thin layer chromatography
t-Bu	*tert*-butyl
Et_3N	triethylamine
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TLC	thin layer chromatography
TPP	triphenylphosphine

Chapter 1

Introduction

Vinyl Sulfonamides:

Versatile Linchpins for the

Synthesis of Diverse Sultams

Preface

This dissertation is focused on the development of new methods for the facile construction of cyclic sulfonamide-based (sultam) scaffolds, with an emphasis on the use of vinyl sulfonamides as the central building block for the assembly of sultam-based libraries for biological screening (Figure 1). Chapter one begins with a brief introduction of the biological profiles of sulfonamides and their cyclic analogs, and is followed by a mini-review of the utilization of vinyl sulfonamides in the field for the synthesis of sultam-based scaffolds. Chapter two starts with a survey of the biological properties of acyl sulfonamides and acyl sultams, before providing a detailed account of a new strategy to synthesize amino acid-derived 7- and 8-membered acyl sultams, in particular pyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxides. Chapter three encompasses utilization of ring opening metathesis (ROM) polymerization technologies for facilitated synthesis, as well as one-pot sequential protocols, towards the diversification of hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide libraries. Finally, chapter four reports on the development of sequestration protocols aimed at integrating synthesis/diversification and purification, of hydroxyhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide sultam scaffolds.

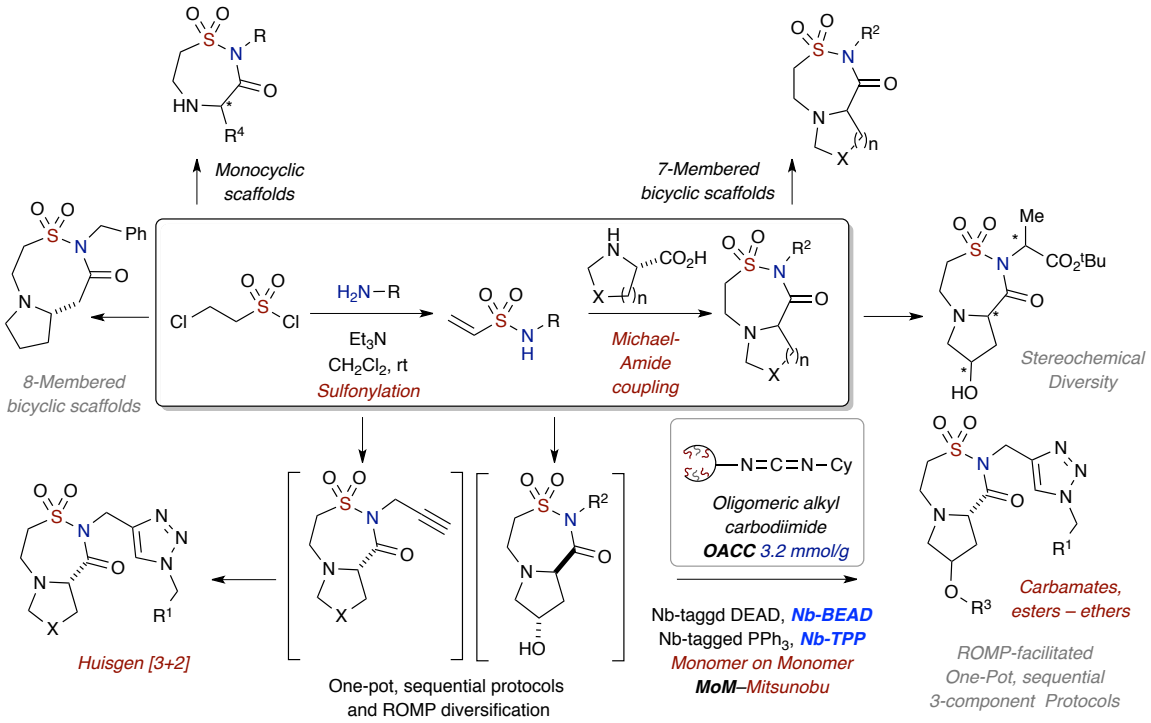


Figure 1.1 *One-pot sequential, protocols towards sultam libraries.*

1.1 Introduction

1.2 Sulfonamides: An Important Class of Medicinal Agents

New advances in genomics and proteomics have paved the pathway for the discovery of an estimated 20,000–25,000 genes, which are believed to encode up to one million proteins.[1] Despite this vast wealth of information, small-molecule therapeutic agents currently target only a small fraction of these proteins (approximately 500).[2] In order to address this void in chemical space, there has been enormous growth in high throughput screening (HTS), emphasizing the demand for diverse small molecule libraries to discover biologically active compounds. It has been estimated that there are approximately 10^{60} small molecule structures of molecular weight (MW) less than 500; however, only 10^{8} chemical entities meeting this requirement have either been synthesized or isolated from natural sources.[3] Since it is impractical to survey this vast chemical space,[4] the chosen space to explore must be ideally biologically relevant, as well as sparsely populated in order to be most productive in assisting efforts in both drug design and basic biology. Interest in this regard, has led efforts at exploring sulfonamides and their corresponding cyclic analogs (sultams), as this subset of chemical space has gained increasing acclamation due to their inherent chemical and biological properties, making them promising candidates in library development and drug discovery.[2]

Sulfonamides have vast potential as pharmaceutical and agricultural agents owing to their distinct and extensive biological profiles. A survey of chemical properties involving p*K*a measurements reveals that p*K*a's of sulfonamides span a rough range from that of a carboxylate (p*K*a ~5) to the higher, less acidic, carboxamides (p*K*a ~ 15). This property has

prompted their use as amide surrogates and carboxylic acid replacement groups.[5] Hofmann performed a systematic study of the conformation of the sulfonamide bond at different levels of ab initio MO theory.[6] Their studies revealed distinct differences between the sulfonamide and the amide/peptide bond. Some important differences include (i) different values of the torsion angle ω (<$C^{\alpha}SNC^{\alpha}$) that are about 100 and 60º in the two basic conformers of the sulfonamide bond, but about 180 and 0º for the amide peptide bond. The rotation barriers around the S-N bond were distinctly lower than the amide peptide bond making the sulfonamide bond more flexible. Also the nature of the sulfonamide nitrogen was pyramidal compared to the amide nitrogen, which had a planar geometry.

As sulfonamides possess both hydrogen bond donor and acceptor sites, they are armed to potentially coordinate to amino acid residues located within enzymes.[7] Sulfonamides bearing acidic N–H moieties are usually more bioavailable and have increased water solubility relative to other polar groups such as amides.[7] In addition, these non-hydrolyzable amide surrogates possess other unique physical properties, such as crystallinity, tunable p*K*a's ($R^1SO_2NHR^2$), and hydrolytic stability. Taken collectively, these interesting properties have promoted the incorporation of the sulfonamide group into a growing number of compounds, many of which have demonstrated interesting biological activity, *vide infra*.

The biological properties of sulfonamides encompass a wide array of activities. In this regard, sulfonamides have been utilized in the development of novel peptidomimetics[8] matrix metalloproteinase inhibitors,[9] thrombin inhibitors,[10] fibrinogen receptor antagonists,[11] endothelin-A receptor antagonists,[12] and glycoprotein IIB/IIIA inhibitors,[13] as well as squalene epoxidase inhibitors[14] and sultam herbicides.[15]

The aforementioned non-hydrolyzability of the sulfonamide moiety imparts an increase in metabolic stability towards protease-catalyzed degradation of peptidosulfonamides.[16] Thus, they have found widespread use as transition state analogues for amide bond hydrolysis and have found applications as novel non-peptidal HIV protease inhibitors.[17] In addition, studies on histamine H_3 receptor antagonists have demonstrated superior *in vitro* profiles of sulfonamides when compared to their corresponding amide analogs.[18]

Sulfonamides have also been found to be promising carbonic anhydrase and matrix metalloproteinase inhibitors, two members of a family of zinc-containing enzymes whose function is related to arthritis and cancer.[19] Further studies have revealed that inhibition towards these enzymes is attributed to their ability to mimic the tetrahedral transition state when binding to catalytic zinc ions located at the active site of the enzymes.[20]

Sulfonamides also display other wide-ranging activities, including antibacterial, diuretic, hypoglycemic, anti-thyroid, and most recently, anti-tumor activity.[21] Some biologically active sulfonamides on the market include the antibacterial agent sulfathiazole,[2a] the carbonic anhydrase inhibitor acetazolamide[2] which has been clinically used for more than 45 years, the anticancer agent E7070 (Figure 1.2), which is currently in advanced clinical trials,[22] the HIV protease inhibitor amprenavir,[23] and most recently Viagra (Sildenafil),[24] one of the most marketable drugs used for male erectile dysfunction.

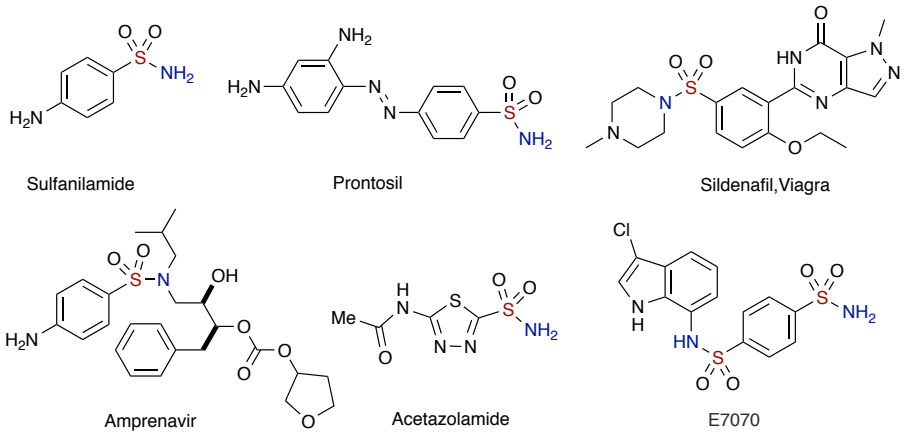


Figure 1.2 *Representative bioactive sulfonamides.*

While naturally occurring sulfonamides are relatively scarce, there are a few examples, namely altemicidin[25] and psammaplin C.[26] Altemicidin was isolated from the actinomycete strain *Streptomyces sioyaensis*, which has shown tumor cell growth inhibition, and Psammaplin C, was isolated from the marine sponge *Psammaplysilla purpurea* (Figure 1.3). Due to their scarcity as well as their attractive biological features, sulfonamides are lucrative targets for organic synthesis and biological testing.

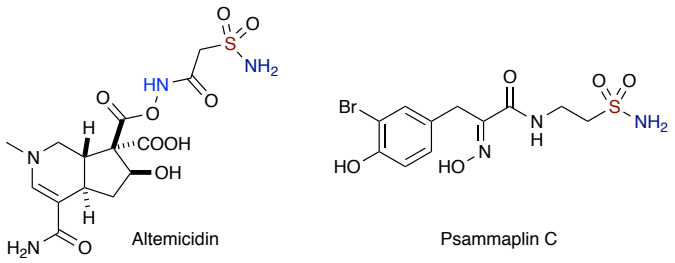


Figure 1.3 *Naturally occurring sulfonamides.*

1.3 Sultams: Cyclic Sulfonamides

1.3.1 Biological Properties of Sultams

Sultams, the cyclic analogs of sulfonamides, are cyclic amide surrogates that represent an important medicinal chemo-type due to their wide chemical and biological profiles.[27] Although not found in nature,[28] they possess potent biological activity, including several with medicinal value, and have thus found extensive use in drug development. Their innate properties have enabled their widespread use as reagents,[29] chiral auxiliaries in asymmetric synthesis,[30,31,32] artificial sweeteners (saccharin) in food industry,[33] and ionic liquids serving as novel reaction media.[34] In addition, they have also found use in a number of medicinal and agricultural agents.[35] As non-hydrolyzable cyclic amide surrogates, sultams are also an ideal functional group in the synthesis of cyclic peptidomimetics.[36]

Sultams have also been shown to exhibit broad inhibitory properties against a variety of enzymes including: HIV integrase,[37] lipoxygenase,[38] TNF a-converting enzyme,[39] Calpain I[40] and MMP-2[41] (Figure 1.4). Sultams also possess an array of biological activity, such as anticancer,[42] antimicrobial,[43] antimalarial,[44] antileukemic,[45] and AMPA receptor modulatory properties with potential for treating disorders of the brain.[46] In addition, this impressive biological profile is supplemented by a number of chemical properties including facile coupling pathways for their formation, stability to hydrolysis, polarity and their crystalline nature. Taken collectively, these attributes have allowed sultams to emerge as privileged structures in drug discovery.

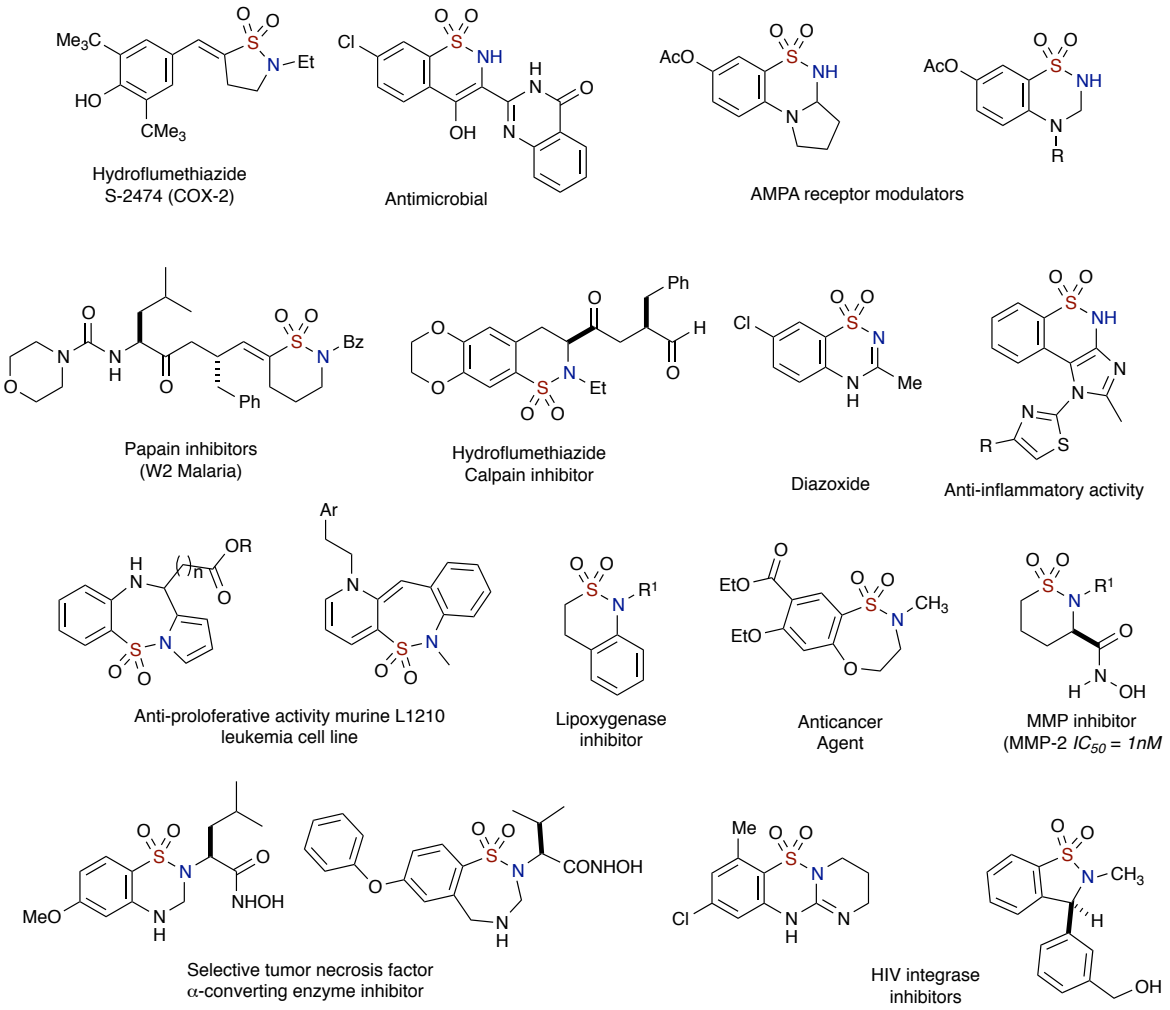


Figure 1.4 *Representative bioactive cyclic sulfonamides (sultams).*

Sultams have also gained prominence as attractive drug targets due to their extensive chemical and biological profiles.[2a] Sultams have been utilized as drugs (Figure 1.5), such as the anti-epileptic agent sulthiame,[47] the anti-inflammatory agents ampiroxicam[48] S-2474[49] and acetazolamide [50] (carbonic anhydrase) used to treat glaucoma and seizures. Brinzolamide[51] [trade name: Azopt®] is also as a carbonic anhydrase inhibitor, as well as a treatment for glaucoma. Chlorothiazide[52] [trade name: Diuril] as a thiazide diuretic, and

Benzthiazide [53] [trade name: Exna] is used for the treatment of blood pressure. Bendroflumethiazide[54] [trade name: Naturetin] is used to treat hypertension, as well as heart failure. Naturetin also treats hypertension and heart failure, while Methyclothiazide[55] [trade name: Aquatensen, Enduron] is used to treat high blood pressure and fluid retention. Hydrochlorothiazide[56] [trade name: HydroDiuril, Esidrix] is utilized for the treatment of hypertension. Trichlormethiazide [trade name: Achetin] has similar properties to hydrochlorothiazide, Polythiazide[57] [trade name: Aquatensen, Renese] treats hypertension, congestive heart failure, edema, diabetes insipidus, renal tubular acidosis and prevents kidney stones to name a few uses. Cyclothiazide[58] [trade name: Anhydron] is a positive allosteric modulator of the AMPA receptor, as well as a GABAA receptor negative allosteric modulator. Cyclothiazide[59] is used as an adjunctive therapy in edema and is also used for the treatment of hypertension. Hydroflumethiazide[60] [trade name: Saluron, Diucardin] is a drug for acute or chronic vascular hypertension. Diazoxide [61] [trade name: Proglycem] is potassium channel activator and inhibits the secretion of insulin from the pancreas.

A second family of sultam drugs is a class of medications called non-steroidal anti-inflammatory drugs (NSAIDs), including piroxicam[62] [trade name: Feldene], meloxicam[63] [trade name: Mobic], Iornoxicam [trade name: Xefo] and Tenoxicam [trade name: Mobiflex]. These drugs impart both analgesic and antipyretic properties by a non-selective inhibition of cyclooxygenase (COX). Meloxicam, introduced by Boehringer-Ingelheim, selectively inhibits COX-2 over COX-1 and is usually used for pain relief. Lornoxicam and tenoxicam are utilized for the treatment of various types of pain resulting from inflammation of joints

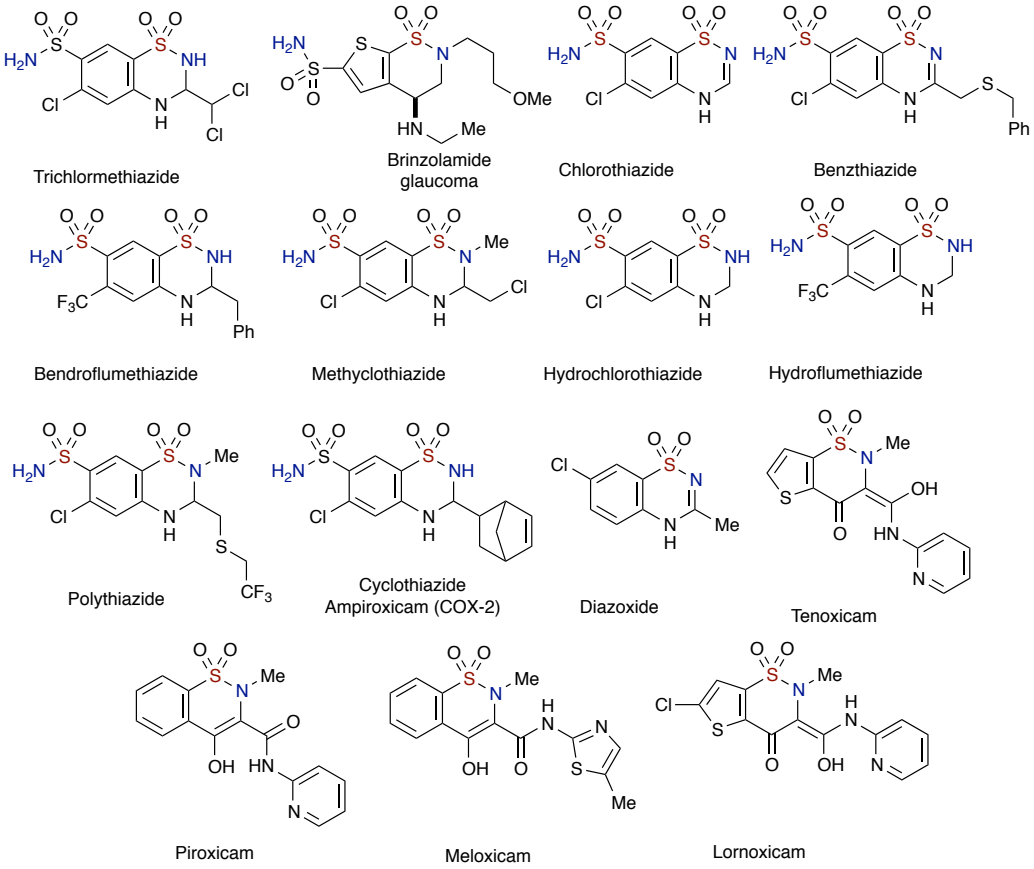


Figure 1.5 *Sultam drugs*

such as osteoarthritis, surgery, sciatica and other inflammations.

1.4 Reactivity of Sulfonamides

The biological activity of sultams has warranted them as attractive targets in drug discovery and inspired chemical methods for their synthesis. In 2011, Majumdar and co-workers,[64] reported an extensive review of recent methods developed to access condensed (fused) sultams, including ring-closing metathesis (RCM), Diels-Alder,[65] and [3+2]-cycloaddition reactions. Our group has recently reported a number of methodologies for generation of various sultams.[66] The aim of this introductory chapter will be to discuss

recent methods utilizing the versatile vinyl sulfonamide moiety.

Methodologies employed for the synthesis of lactams can also be applied to sultams. However, sulfonamides differ in their physical and chemical attributes, when compared to their amide counterparts. The presence of two electronegative oxygen atoms within the SO_2 moiety imparts greater inductive effect within sulfonamide than amide, and thus typically imparts a lower p*K*a, which enables alkylation under mild conditions (Figure 1.6).

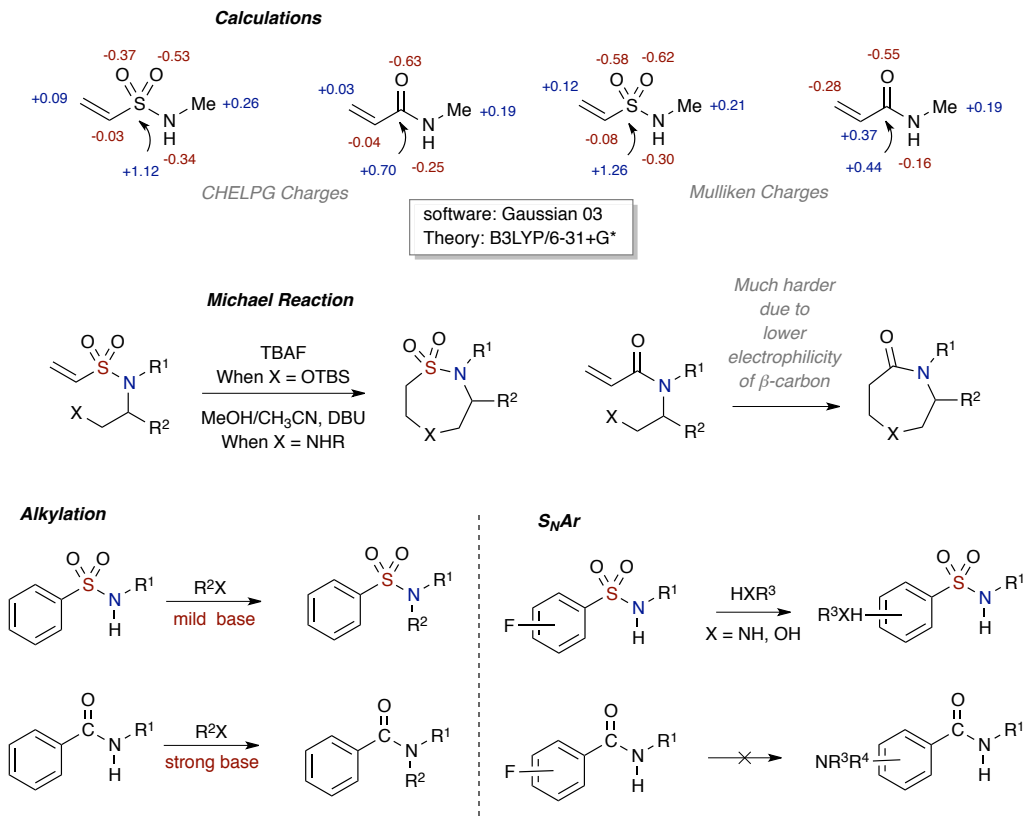


Figure 1.6 *Sulfonamides vs amides.*

In addition to p*K*a properties, the electrophilic character of the β-carbon of vinyl sulfonamides is more enhanced compared to the β-carbon of vinyl amides, and thus

engenders vinyl sulfonamides as potentially better Michael acceptors compared to the amide counterparts.[66a,b,g-i]

This fact is substantiated by *in silico* calculations, which demonstrate a more electron deficient sulfur atom within the SO_2 moiety than the carbonyl carbon atom of the lactam functional group (Figure 1.6).[67] This property was exploited in a number of intramolecular oxa/aza-Michael reactions on vinyl sulfonamides furnishing 7- and 8-membered sultams, the latter in a unique "contra Baldwin Rules", 8-*endo*-trig pathway.[68] This cyclization is also aided by additional differences of atomic radius between sulfur and carbon (sulfur 100 pm, carbon 70 pm). The properties outlined above for vinyl sulfonamides were also utilized in S_NAr reactions of α-fluoro-benzenesulfonamides as compared to their amide analogs (Figure 1.6).[69] Benzene sulfonamides also undergo alkylation under mild conditions while the corresponding amides require much harsher conditions (usually a strong base).

Taken collectively, the properties of sulfonamides such as low p*K*a and the ability to have highly electrophilic carbon centers (α- and β-) next to the sulfonamide functionality can be exploited in a number of reactions. The next section will discuss methods developed utilizing the highly electrophilic double bond of vinyl sulfonamides in Michael additions, Heck reactions, Diels-Alder reactions and metathesis reactions towards the synthesis of complex sultams.

1.5 Use of Vinyl Sulfonamide Synthons in the Construction of Sultams

Ethylenesulfonic acids were first synthesized in 1887, however, it was more than a decade later for higher derivatives such as sulfonamides to be prepared by Autenreith and

Rudolph in 1901.[70] While 2-aminoalkanesulfonic acids, ethylenesulfonic acid esters and propenesulfonic acids were synthesized in 1949.[71] The reactivity of β-chloroethanesulphonyl chloride was explored by Leymann[72] as early as 1885 who suggested the reaction of this compound with 3 equivalents of aniline in dry ether resulted in the synthesis of β-phenylaminoethanesulphonanilide and a small amount of phenylanhydrotaurine. In 1901, Autenreith and Rudolph [73] identified Leymann's phenylanhydrotaurine as ethylene sulphonanilide and stated that it is due to the interaction of β-chloroethanesulphonyl chloride with aniline in cold benzene. Leymann had presumed the presence of β-chloroethanesulphonanilide in the oily residue isolated from their reaction. Goldberg[74] attempted to isolate the β-chloroethanesulphonanilide by the reaction of β-chloroethanesulphonyl chloride (1 equiv.) with aniline (2 equiv.) in acetone without the presence alkali yielding only ethylenesulphonilide together with a small amount of phenylaminoethanesulphonanilide. Goldberg postulated three reactions were involved in this process which included (i) formation of the sulfonamide (ii) dehydrohalogenation and (iii) addition of amine to the double bond of the ethylenesulfonamide produced in the reaction. They also found out that alkyl amines reacted faster than aryl amines. This was further substantiated by the fact that it was possible to isolate the ethylenesulfonarylamide in substantial yield when employing aryl amines, while the faster reacting alkyl amines only provided alkylaminoethanesulfonalkylamides. Their route was more direct for the synthesis of ethylenesulfonarylamides by reaction of arylamines with β-chloroethanesulphonyl chloride compared with the routes described by others, including Kohler (1897,)[75] Autenreith and Rudolph (1901), Autenreith and Koburger (1903),[76] and Cohen and

Clutterbuck (1922)[77] that involves the utilization of ethane-α,β-disulfonyl chloride (Figure 1.7).

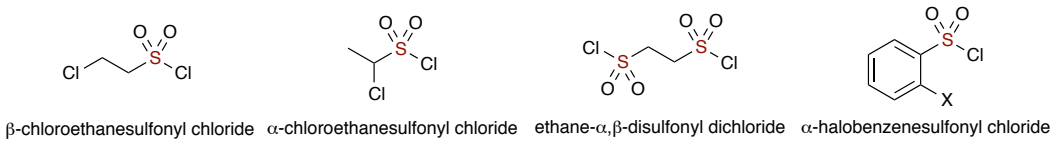
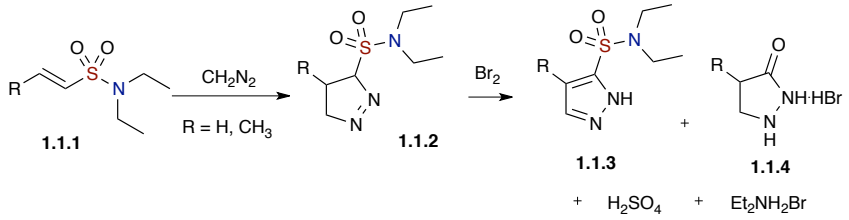


Figure 1.7 *Various sulfonyl chlorides.*

Goldberg and co-workers also suggested that the low reactivity of α-chloroethanesulphonyl chloride,[78] compared to β-chloroethanesulphonyl chloride, was due to the lability of the β-halogen in β-chloroethanesulphonyl chloride. In 1951 Snyder[79] and co-workers, as well as Rondestvedt and Wygant[80] (1952) further tried to carry out the first examples of Diels-Alder reactions with vinyl sulfonamides. However, thermal conditions failed to produce products in contrast to the successful Diels-Alder reactions of vinyl sulfonyl chlorides, vinyl sulfonic acids and vinyl methyl sulfone.

In 1955, when Rondestvedt and Chang[81] were able to carry out Michael additions of diazomethane and phenyl azide into various derivatives of ethylenesulfonic acid, including *N*,*N*-diethylethylenesulfonamide (Scheme 1.1). The addition of diazomethane generated pyrazoles, which underwent isomerization by reaction with bromine forming the sulfonamide **1.1.3**, and also yielding compound **1.1.4** as an HBr salt.

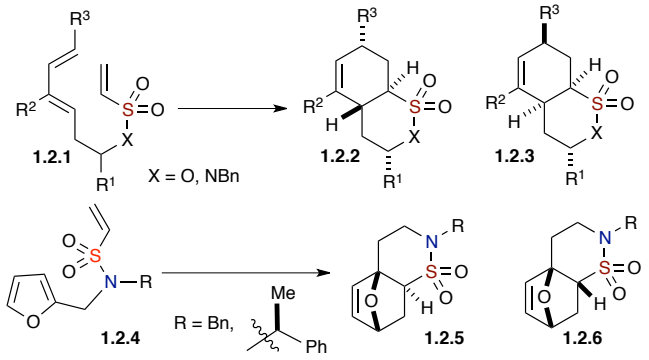
Scheme 1.1 *Addition of diazomethane and phenyl azide to derivatives of ethylenesulfonamide.*



1.5.1 Diels-Alder and metathesis strategies

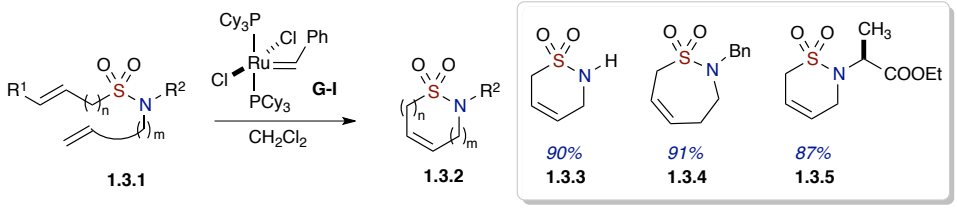
In 1996, Metz and co-workers used Lewis acid-catalyzed Diels-Alder conditions to carry out the first synthesis of sultams using vinyl sulfonamides, whereby they reported a highly diastereoselective intramolecular Diels-Alder of vinyl sulfonamides bearing furans or 1,3-diene moieties to access δ– and γ-sultams (Scheme 1.2).[65] They also synthesized enantiomerically pure δ- and γ-sultams utilizing Lewis acid-catalyzed intramolecular [4+2] cycloaddition of *N*-1-phenylethyl and furan-substituted vinyl sulfonamides by thermal activation and under high pressure. The method was further optimized for reductive debenzylation of the sultams.

Scheme 1.2 *Accessing δ– and γ–sultams via intramolecular Diels-Alder.*



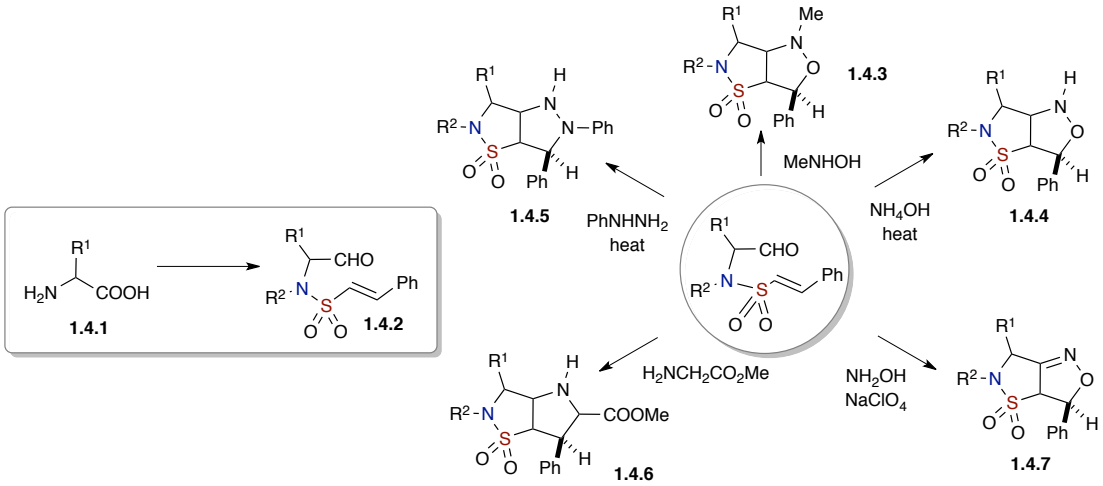
In 1999, Hanson and co-workers[82] reported the first examples of ring closing metathesis (RCM) reactions on allyl- and vinyl sulfonamide templates utilizing the Grubbs ruthenium alkylidene **G-I**[83] (Scheme 1.3). The rate of RCM was noted to be sensitive to simple olefin substitution whereby RCM of the phenyl-substituted vinyl sulfonamides (R^1 = Ph) gave superior yields, presumably due to regeneration of the Ru-benzylidene. These RCM reactions yielded novel amino acid-derived cyclic allyl- and vinyl sultams.

Scheme 1.3 *Ring closing metathesis (RCM) reactions on allyl- and vinyl sulfonamides.*



In 2001, Chiacchio and co-workers[84] synthesized a number of homo-chiral dipoles bearing a sulfonamide group from *L*-aminoacids (Scheme 1.4). These dipoles were further utilized for the synthesis of enantiomerically pure, annulated sultams with different functional handles.

Scheme 1.4 *Homochiral annulated sultams via intramolecular [3+2] cycloaddition.*

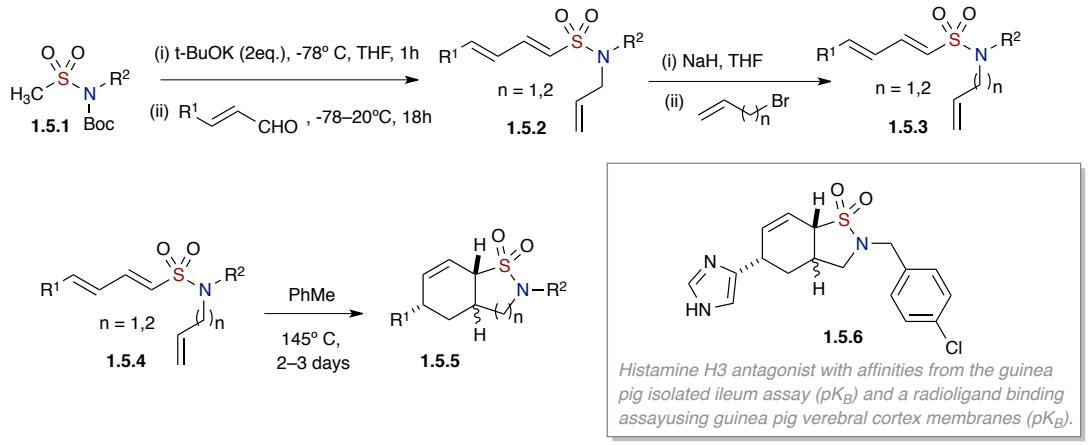


They investigated the intramolecular cycloaddition of different dipoles such that the sulfonamide group was in α-position with respect to the reactive aldehydic center. Utilizing the aforementioned methodology, synthesis of isoxazole-, pyrazole-, pyrrolo-fused

iosthiazole-1,1-dioxides was accomplished using different dipolarophiles as shown in Scheme 1.4.

In 2001, Tozer and coworkers [85] synthesized substituted 2,3,3a-hexahydrobenzo[*d*]isothiazole 1,1-dioxides and 3,4,4a,5,6,8a-hexahydro-*2H*-benzo[*e*][1,2]thiazine 1,1-dioxides by a thermal Diels-Alder reaction of triene derivatives of buta-1,3-diene-1-sulfonic acid amides (Scheme 1.5). A histamine H_3 receptor antagonist 2-(4-chlorobenzyl)-5-(1*H*—imidazol-4-yl)-2,3,3a,4,5,7a-hexahydrobenzo[*d*]isothiazole 1,1dioxide **1.5.6** was synthesized utilizing the aforementioned methodology.

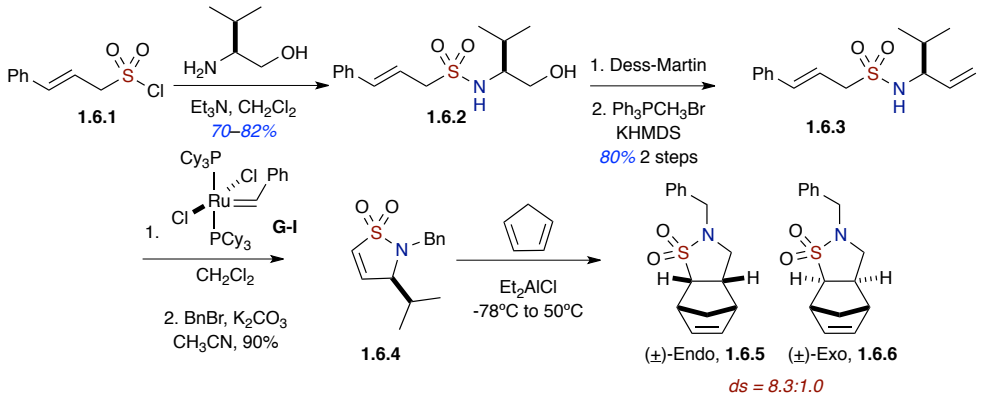
Scheme 1.5 *Hexahydrobenzo[d]isothiazoles and Hexahydro-2H-benzo[e]thiazine 1,1-dioxides via Diels-Alder reaction..*



In 2002, Hanson and co-workers reported an RCM/Diels-Alder strategy, followed by ring opening metathesis (ROM) polymerization for the synthesis of oligomeric sulfonamides[86] (Scheme 1.6). In this method, RCM was utilized for the synthesis of amino acid-derived α,β-unsaturated γ-sultams bearing either *exo*-cyclic or γ-endo-cyclic stereogenic centers. This was followed by Diels-Alder reactions using Metz conditions[65] to furnish the *endo*-norbornenyl sulfonamides as the major diastereoisomers. Use of ring opening

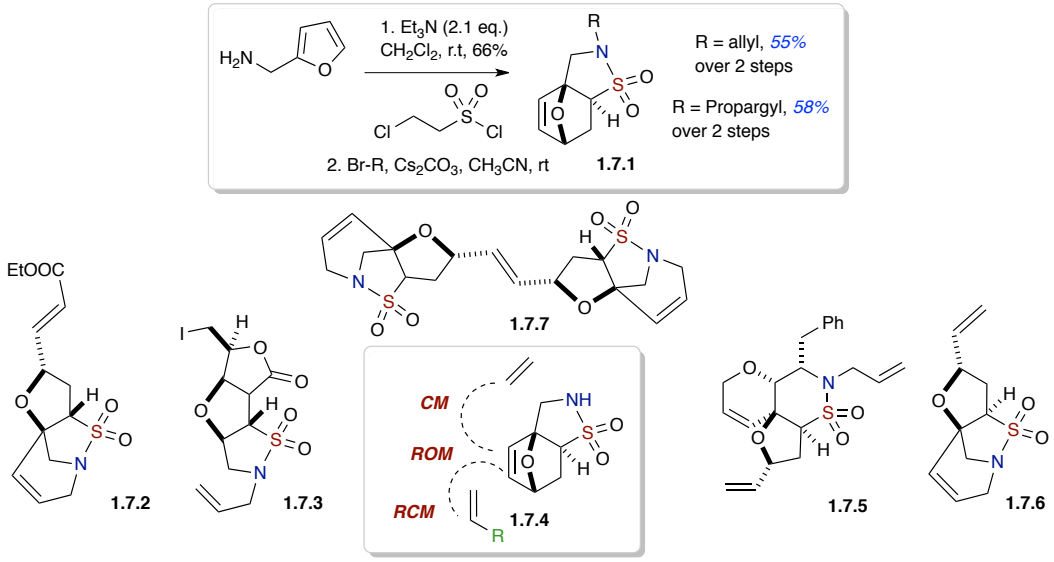
metathesis polymerization (ROMP or ROM polymerization) afforded the oligomeric sulfonamides of various length that were shown to be soluble in CH_2Cl_2.

Scheme 1.6 *RCM towards α,β-unsaturated γ-sultams.*



In 2009, Hanson and coworkers [87] reported a ring opening metathesis/ring-closing metathesis/cross metathesis (ROM–RCM–CM) cascade strategy furnishing a diverse collection of bi- and tricyclic sultams (Scheme 1.7). This strategy allowed for the synthesis

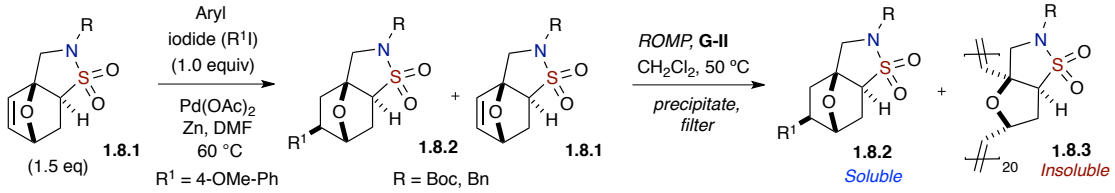
Scheme 1.7 *Ring opening metathesis–ring closing metathesis–cross metathesis (ROM–RCM–CM) protocol towards tricyclic sultams.*



of functionalized sultam scaffolds via intramolecular Diels-Alder (IMDA) reactions in good yields and selectivity, which underwent metathesis cascades producing a variety of tricyclic sultams. The ROM–RCM–CM protocol furnished sultams in good to excellent yields. The skeletal and appendage-based diversity was controlled by elements incorporated into the sultam precursors or *via* the CM partner.

In 2011, Hanson and coworkers reported a purification protocol involving the sequestration of excess IMDA-derived scaffold by employing ROM polymerization (ROMP) furnishing the oxa-norbornene scaffolds **1.8.1** (6-epoxybenzo[*d*]isothiazole-2-carboxylate 1,1-dioxides) (Scheme 1.8).[88] The method utilized excess scaffold and the diversification protocol included a reductive Heck reaction. Upon completion of the reaction the separation of the starting material (excess scaffold) and the product was very tedious using standard column chromatography. However, sequestration of the excess material was possible via a

Scheme 1.8 *Oxa-norbornene sequestrations by ROM polymerization (ROMP).*



ROM-based polymerization approach with either metathesis catalyst or catalyst-armed silica particles. The oligomeric starting material was then further diversified using simple reactions into new sultam moieties. This project will be discussed in detail in Chapter 4.

1.5.2 Click, Click, Cyclize

The need for the synthesis of small molecules for high throughput screening presents challenging opportunities in the field of organic synthesis. Although there have been

significant advances in this aspect, library planning is still the limiting factor in these strategies.[89] In this regard, diversity-oriented synthesis (DOS)[89,90] has surfaced as a means to address this issue by devising strategies for the facile synthesis of multiple scaffolds[89-91] possessing skeletal diversity.[90-92] Forward-synthetic analysis[89,90] and functional group (FG) pairing[93] are important tools utilized in DOS. Forward-synthetic analysis defines strategies, which generate multiple scaffolds in the fewest possible steps, while FG pairing involves selective pairing of functional groups on a central functionalized linchpin, affording a variety of scaffolds with minimum steps. These concepts form the basis of "Build/Couple/Pair (BCP)" paradigm established by Schreiber and co-workers.[93b] This approach involves a "build phase" to construct chiral building blocks. These building blocks possess orthogonal sets of functionalities which can be exploited for subsequent "Coupling and FG pairing" providing access to different scaffolds.

In 2008–2009, Hanson and co-workers devised a functional group (FG) pairing cyclization approach termed, "Click, Click Cyclize" that is essentially a sub-set of the BCP paradigm. The approach is premised on FG pairing between a central FG and an array of functional groups affording skeletally diverse sultams. This method was designed to gain access to skeletally diverse five-, six-, seven-, eight-, and nine-membered diverse sultams. Central to this protocol was the design and construction of building blocks termed as sulfonamide-linchpins that can be assembled via use of two consecutive "Click" reactions inherent to sulfonamide formation.[94] In the formation of the sulfonamide linchpins, the first "Click" reaction is a sulfonylation of an amine with a sulfonyl chloride under mild conditions to generate a 2º sulfonamide, having a free SO_2NH group of suitable p*K*a to allow a second

"Click" alkylation reaction to occur furnishing a 3º sulfonamide (Figure 1.8). Once assembled, the 3º sulfonamide linchpin can undergo FG pairing[95] with the respective functional handles leading to subsequent cyclization and facile assembly of skeletally and peripherally diverse sultam heterocycles.

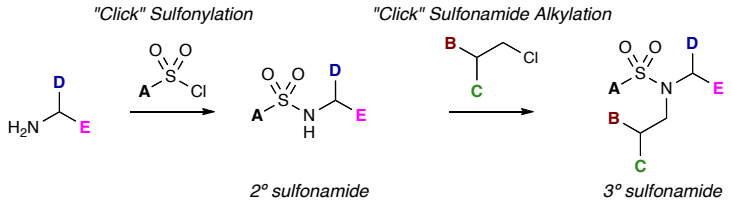


Figure 1.8 *Sulfonamide linchpins*

Within the realm of Click, Click Cyclize we are continually exploring a number of reaction pathways involving FG-pairing between a central **A** sulfonamide-FG and different incorporated FG's within the sulfonamide linchpin (i.e **B**, **C** and **D**) (Figure 1.9). Among the most commonly employed linchpins studied in our laboratory include those possessing a vinyl sulfonamide moiety (the focus of this chapter) as well as α-halo benzene sulfonamides.

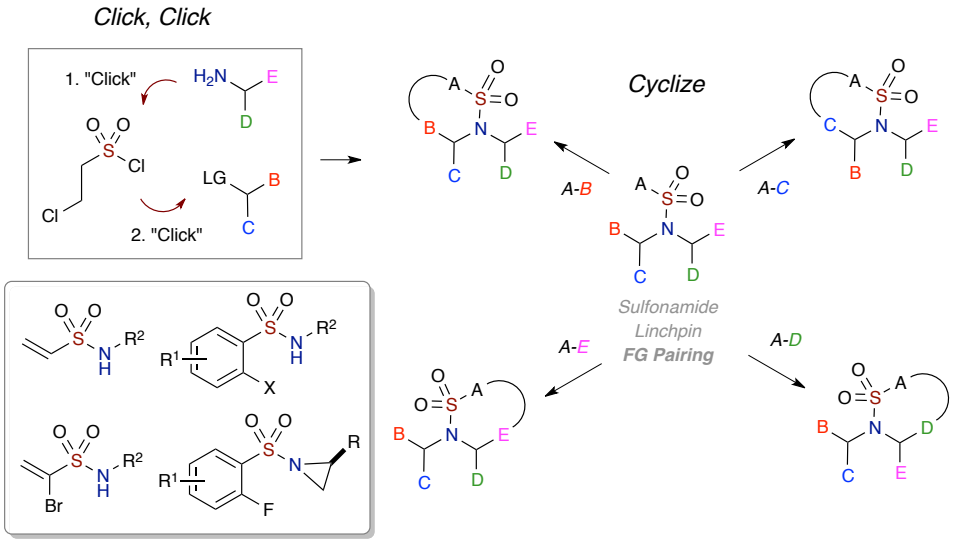


Figure 1.9 *Click Click Cyclize.*

More recent efforts have now been expanded to aziridinyl α-fluorobenzene sulfonamides, α-Br-vinyl sulfonamides, and methyl aminoester/anthranilic ester sulfonamides (ongoing work in the group). A rationally designed sulfonamide linchpin can produce a reaction manifold yielding at least four different scaffolds displaying skeletal diversity and peripheral ligand disparity (ie. pairing between **A** and **B**, **A–C**, **A–D** and **A–E**). Overall, a number of strategies have been developed in our group utilizing Click, Click Cyclize and exploiting the FG-pairing strategies. A brief overview utilizing vinyl and α-halobenzene sulfonamides is highlighted in Figure 1.10.[66]

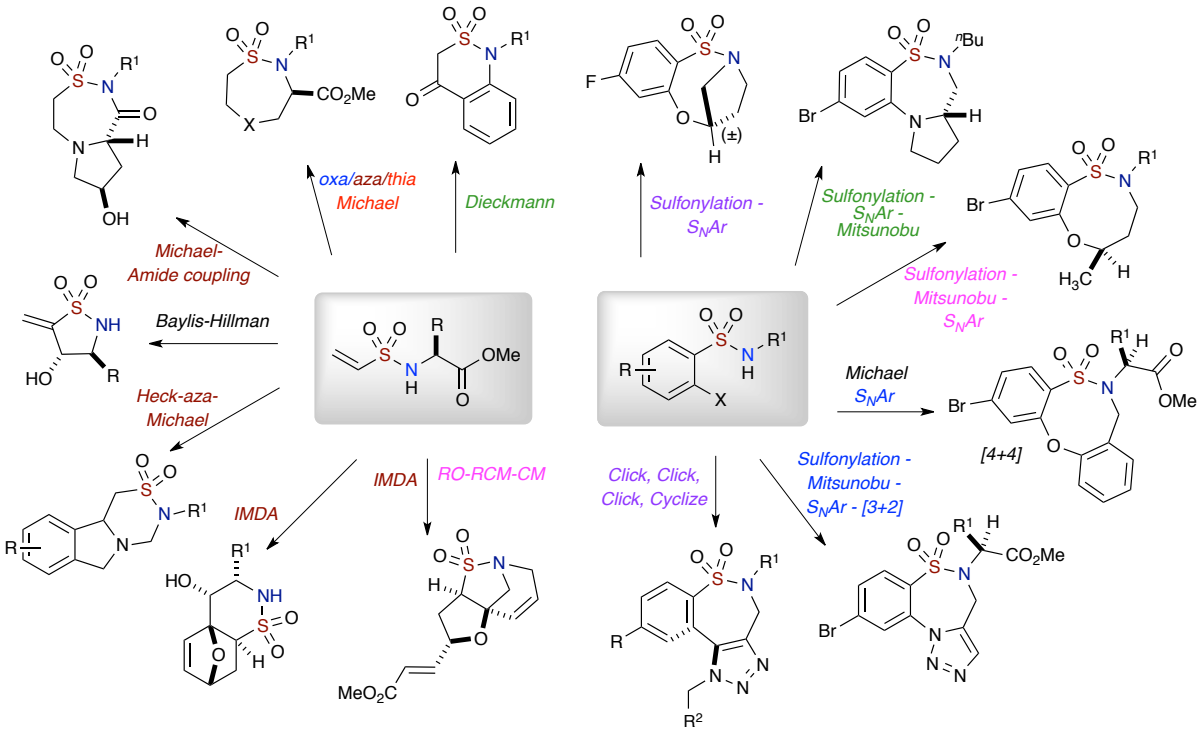


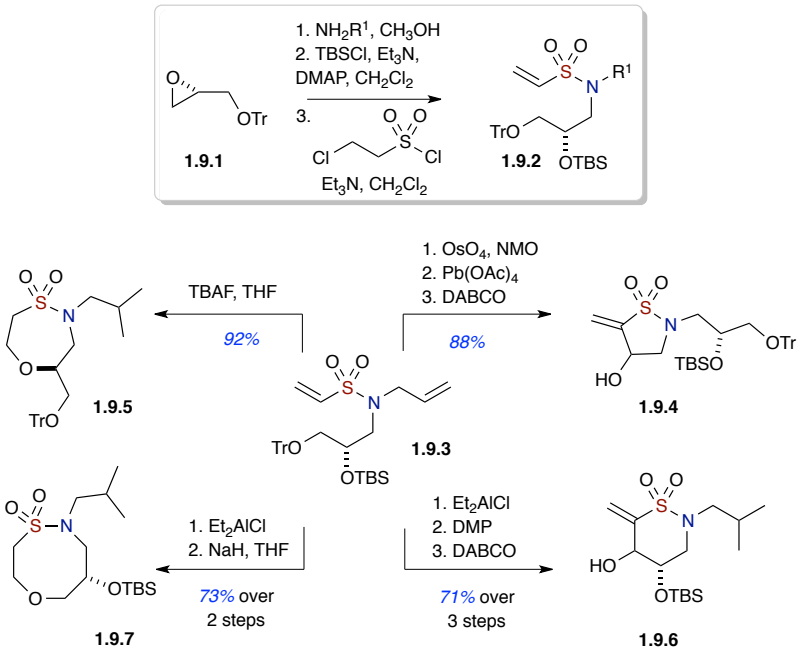
Figure 1.10 *Representative methods developed utilizing click–click–cyclize.*

1.5.3 Oxa-Michael and Baylis-Hillman

In 2008, Hanson and co-workers reported the synthesis of sultam scaffolds via both intramolecular oxa-Michael and diastereoselective Baylis−Hillman reactions.[68] Employing

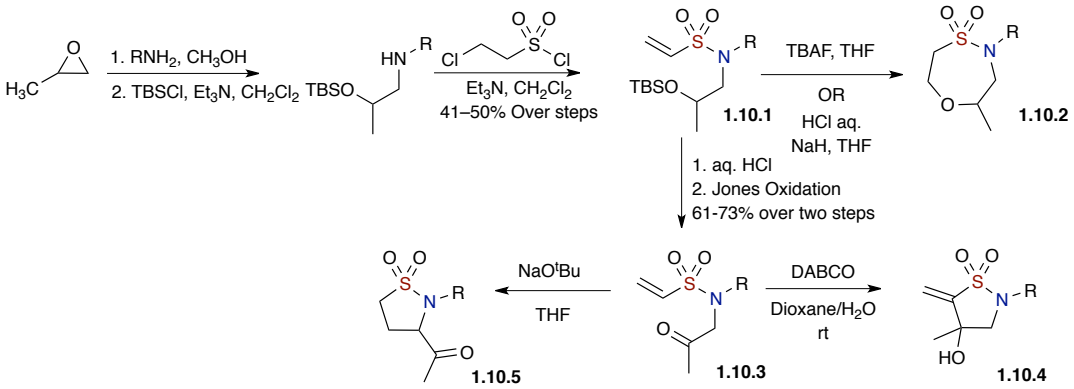
the oxa-Michael and Baylis−Hillman reactions on vinyl sulfonamides (prepared by suitably protected amino alcohols) a divergent synthetic approach was devised for the synthesis of new sultams (Scheme 1.9). In this method, which was later termed Click, Click, Cyclize, both 7- and 8-membered ring sultam scaffolds were synthesized using oxa-Michael pathways, whereas the Baylis-Hillman pathway provided five- and six-membered ring sultams. Good to excellent diastereoselectivity was obtained in Baylis-Hillman protocol. A notable feature was that the oxa-Michael reaction to synthesize the 8-membered ring sultams provides empirical evidence validating 8-*endo-trig* cyclization pathways.

Scheme 1.9 *Oxa-Michael and Baylis-Hillman routes.*



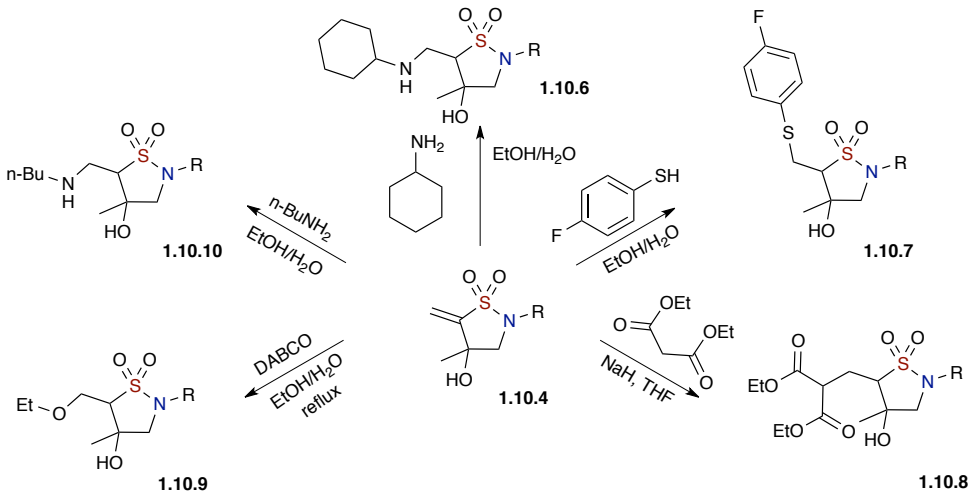
In 2013, Zhou and coworkers continued this work further in their synthesis five- and seven-membered sultam derivatives through intra-Michael additions and they improved the conditions of the vinyl sulfonamide Baylis-Hillman reaction.[96] In this work, they explored

Scheme 1.10a *Oxa-Michael and Baylis-Hillman.*



two different pathways in which they opened up an epoxide with an amine, followed by TBS-protection and subsequent sulfonylation with 2-chloroethane sulfonylchloride to furnish the Michael accepting linchpin **1.10.1** (Scheme 1.10a). The reaction of linchpin **1.10.1** with TBAF afforded scaffold **1.10.2** *via* an oxa-Michael reaction (Scheme 1.10b).

Scheme 1.10b *Different Michael addition protocols.*



TBS-Deprotection was also affected utilizing aqueous HCl, followed by intramolecular Michael reaction, which took place *via* reaction with NaH to generate the same scaffold. Alternatively, deprotection with aqueous HCl, followed by Jones oxidation,

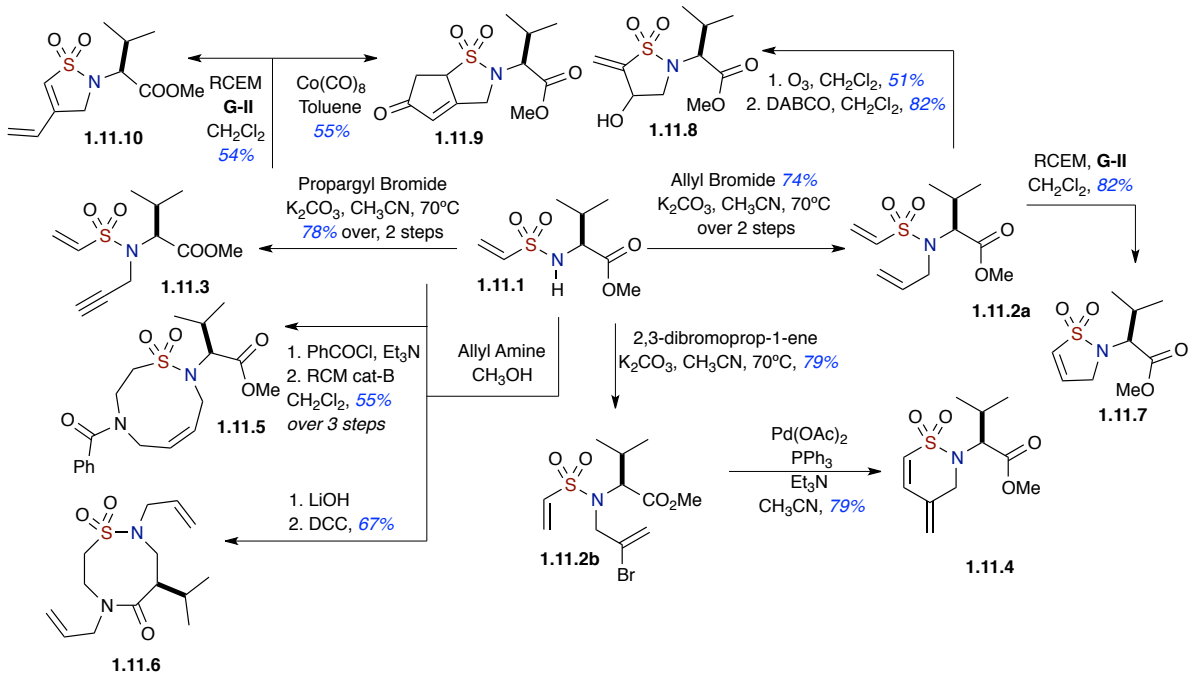
furnished ketone **1.10.3**. Reaction of **1.10.3** with NaO^tBu provided the five-membered scaffolds **1.10.5** through an intra-Michael reaction with the carbon next to the carbonyl group bearing an acidic hydrogen undergoing 5-*endo*-trig intramolecular cyclizations, which are traditionally disfavored according to Baldwin's rules. The same ketone **1.10.3** also underwent Baylis-Hillman reaction with DABCO and dioxane/H_2O, which proved to be a good solvent for an otherwise sluggish ketone-type Baylis–Hillman reaction. After the synthesis of the scaffold **1.10.4**, four intermolecular Michael reactions with carbon-, nitrogen-, oxygen-, and sulfur-based nucleophiles were carried out.

1.5.4 Click, Click, Cyclize and Functional Group Pairing

In 2009, Hanson and co-workers reported a diversity-oriented synthesis (DOS) strategy termed "Click, Click, Cyclize" (Scheme 1.11).[97] The central tertiary vinyl sulfonamide linchpins were exposed to a number of FG pairing pathways, which encompassed intramolecular Heck, aza-Michael, ring-closing enyne metathesis, Pauson-Khand, and chemoselective oxidation/Baylis-Hillman reactions. A sulfonylation/allylation sequence yielded tertiary vinyl sulfonamide **1.11.2**. However, when the allylation was done with 2,3-dibromoprop-1-ene it furnished **1.11.2b**, followed by a regioselective 6-*endo*-trig intramolecular Heck cyclization to afford the δ-sultam **1.11.4**. Allylation of sulfonamide linchpin **1.11.1** with allyl bromide provided **1.11.2a**, which upon RCM yielded the five-membered Michael accepting sultam scaffold **1.11.7**. Alternatively, ozonolysis of the allylated linchpin **1.11.2a** followed by the Baylis-Hillman reaction, afforded scaffold **1.11.8**. Michael reaction with allyl amine on the allylated linchpin followed by reaction with PhCOCl and then RCM produced the 10-membered scaffold **1.11.5**. In addition, hydrolysis

with LiOH, and DCC coupling, after the Michael reaction with allyl amine generated the amide-containing scaffold **1.11.6**.

Scheme 1.11 *Click–click–cyclize and functional group pairing.*



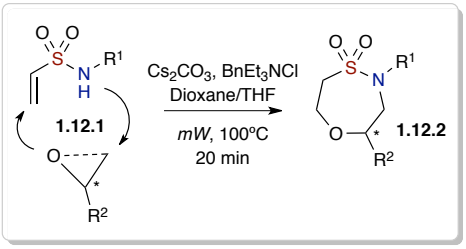
Alkylation with propargyl bromide generated linchpin **1.7.3** which underwent an intramolecular enyne metathesis yielding sultam **1.11.10**. Pauson-Khand reaction on propargylated linchpin **1.11.3** afforded scaffold **1.11.9**. Collectively, the ease of substrate assembly and the breadth of chemistry carried out, highlighted the early potential of the Click, Click, Cyclize paradigm.

Different Hetero-Michael Strategies (Oxa-, Aza- and Thia-Michael)

1.5.5. Oxa-Michael

In 2010, a formal [4+3] epoxide cascade protocol utilizing vinyl sulfonamides and a variety of epoxides was developed for the generation of oxathiazepine-1,1′-dioxides[98] (Scheme 1.12). This protocol combines an epoxide ring opening with an S_NAr on α-fluorobenzene sulfaamides as well as oxa-Michael cyclization pathway on vinylsulfonamides. Using this method, oxathiazepine-1,1′-dioxides were synthesized in good yields as shown in Scheme 12.

Scheme 1.12 *Formal [4+3] epoxide cascade protocol.*



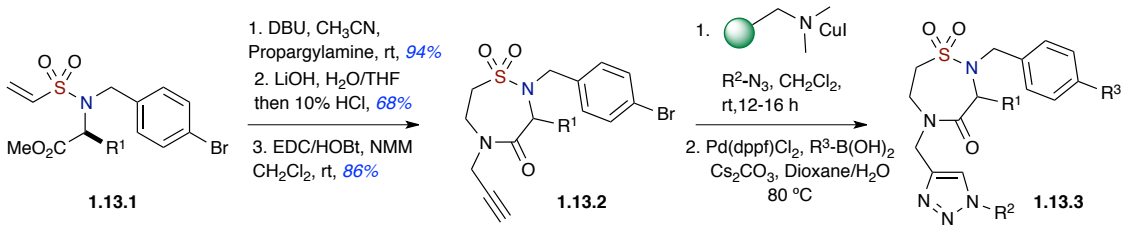
entry	R^1	R^2	Yield, %
1	allyl	CH_2OBn	65
2	allyl	(*S*)-CH_2OBn	63
3	$(CH_2)_3CH_3$	CH_2OBn	58
4	Bn	4-Me-$PhOCH_2$	62
5	allyl	4-Me-$PhOCH_2$	57
6	cyclopentyl	4-Me-$PhOCH_2$	55
7	propargyl	CH_2OPh	53
8	(*R*)-$CH(CH_3)Ph$	(*R*)-$CH_2CO_2(CH_2)_2CH_3$	60

1.5.6 Aza-Michael

In 2011, the aza-Michael pathway was exploited in the synthesis of a 225-member (3x5x15) library of thiadiazepan-1,1-dioxide-4-ones (Scheme 1.13).[99] A Chemspeed Accelerator (SLT-100) automated parallel synthesis platform was utilized for the synthesis of the aforementioned library. The success rate of the library was 184/225 sultams. The linchpin **1.13.1** was synthesized by sulfonylation of different amino methyl esters followed by alkylation with 2-bromobenzyl bromides. Michael addition with propargyl amine and subsequent LiOH hydrolysis followed by EDC coupling afforded the scaffold **1.13.2**. Three

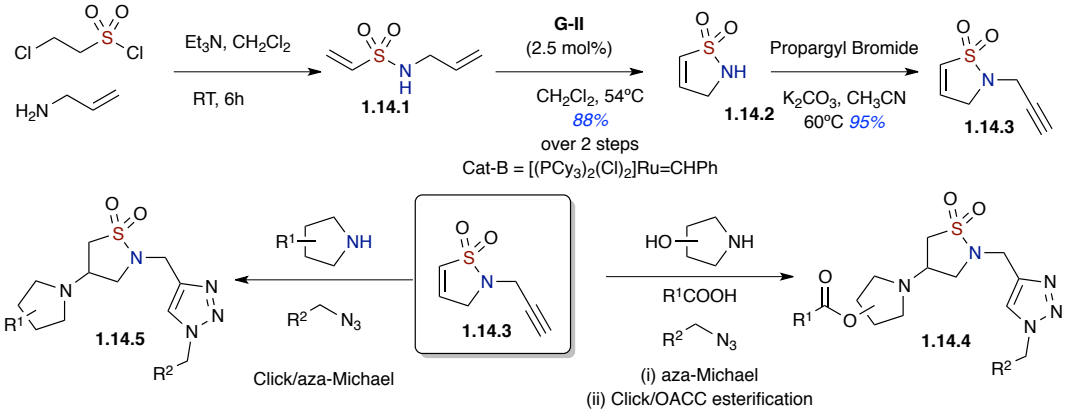
sultam core scaffolds were synthesized based upon the protocol described above. The peripheral diversity was performed in the form of a sequential, two-step [3+2] Huisgen and cycloaddition/Pd-catalyzed Suzuki-Miyaura coupling sequence to afford the aforementioned library.

Scheme 1.13 *Automated synthesis of of thiadiazepan-1,1-dioxide-4-ones.*



In 2011, Hanson and co-workers[100] also reported the construction of two libraries of triazol-isothiazolidine 1,1-dioxides employing a one-pot Click/aza-Michael as well as a Click/OACC esterification protocol (Scheme 1.14). The core dihydroisothiazole 1,1-dioxide scaffold was synthesized on multi-gram scale utilizing RCM. The scaffold was diversified via a one-pot multi-component Click/aza-Michael utilizing a variety of amines and azides to

Scheme 1.14 *Synthesis of triazol-isothiazolidine 1,1-dioxides employing a one-pot click/aza-Michael as well as a click/OACC esterification protocol.*

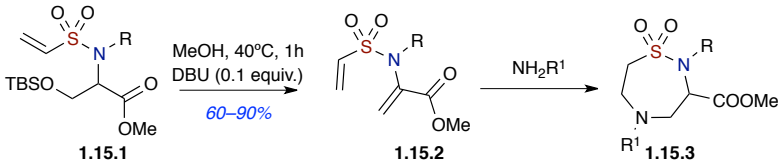


furnish a 180-member triazol-isothiazolidine 1,1-dioxide library. In order to exploit the click-esterification protocol, three different scaffolds were synthesized by an aza-Michael of three different amino alcohols. The aforementioned scaffolds were diversified by a one-pot, multi-component click/esterification protocol employing a ROMP-derived coupling reagent (OACC) affording a 41-member library of triazol-isothiazole 1,1-dioxides. This methodology will be further elaborated in Chapter 3.

1.5.7 Double-aza-Michael (DaM strategy)

In 2011, the electrophilic nature of the vinyl sulfonamides in aza-Michael reactions was further exploited to generate 1,2,5-thiadiazepane 1,1-dioxides using a strategy, termed double aza-Michael (DaM) (Scheme 1.15).[101] In this approach, linchpin **1.15.1** was prepared by sulfonylation of 2-chloroethane sulfonyl chloride with TBS-protected serine methyl ester.

Scheme 1.15 *Double-aza-Michael (DaM strategy).*



entry	R	R^1	Yield, %
1	4-MeO-Benzyl	*n*-C_8H_{17}	65
2	Benzyl	*n*-Bu	74
3	Benzyl	4-$FC_4H_4CH_2$	69
4	4-Cl-Benzyl	4-$MeOC_4H_4CH_2$	82
5	4-Cl-Benzyl	$PhCH_2CH_2$	77
6	4-F-Benzyl	*i*-Bu	65
7	4-CF_3-Benzyl	Bn	79
8	4-Me-Benzyl	*c*-C_5H_9	60
	Benzyl	*n*-Bu	71

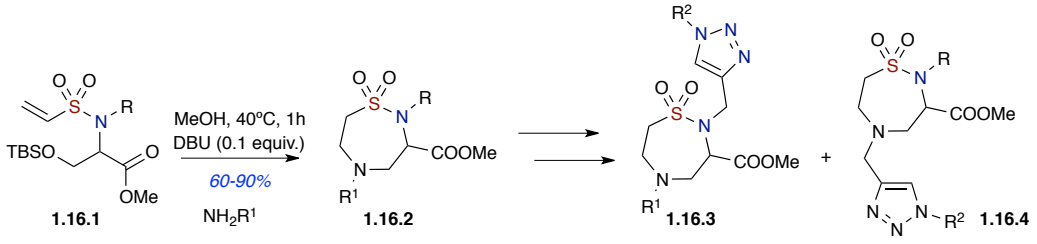
Upon treatment with an appropriate base, elimination of the OTBS group afforded vinyl sulfonamide **1.15.2** containing two Michael acceptors. The subsequent double aza-Michael

reaction took place with primary amines to generate functionalized 1,2,5-thiadiazepane 1,1-dioxides. The reaction was further optimized to include the elimination and the double aza-Michael in a one-pot sequence.

In 2012, this method was optimized further on a continuous flow chemistry platform in collaboration with the Organ group at York University, resulting in scale out of the inter-/intramolecular double aza-Michael addition using microwave-assisted, continuous flow organic synthesis platform (MACOS).[102] The protocol was optimized for utilization in scale-out on a MACOS platform. This protocol was utilized for the synthesis of a 50-member library of functionalized 1,2,5 thiadiazepane 1,1-dioxides on a 100–300 mg scale with overall yields between 50–80% and over 90% purity utilizing a multicapillary flow reactor.

In 2012, a facile one-pot, sequential strategy utilizing *in situ* Huisgen cycloaddition following the double-aza-Michael was also developed, making this method amenable to library synthesis (Scheme 1.16). Thus, a 96-member library of triazolated 1,2,5-thiadiazepane 1,1-dioxides was completed on a Chemspeed Accelerator (SLT-100) automated parallel synthesis platform, resulting in the successful preparation of 94 out of 96

Scheme 1.16 *One-pot sequential double-aza-Michael (DaM strategy) and Huisgen cycloaddition.*

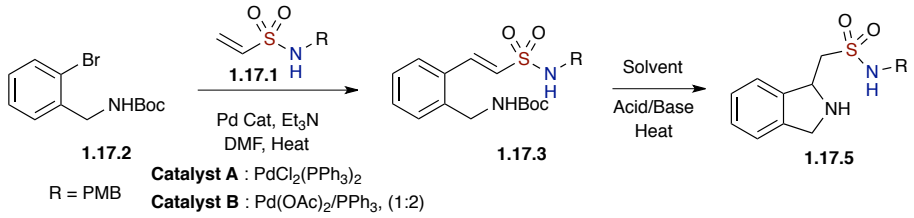


possible products.[103] The key step was a one-pot, sequential elimination, double-aza-Michael reaction, and [3+2] Huisgen cycloaddition pathway that were automated and utilized in the production of two sets of triazolated sultam products.

1.5.8 Heck-Aza-Michael

In 2012, Hanson and co-workers developed the synthesis of unique isoindoline- and tetrahydroisoquinoline (THIQ)-containing tricyclic sultams, utilizing a Heck-aza-Michael (HaM) strategy (Scheme 1.17a).[104] The isoindoline and the THIQ rings were installed through a Heck reaction on a vinylsulfonamide, followed by one-pot deprotection and intramolecular aza-Michael reaction. Subsequent cyclizations were carried out with either paraformaldehyde condensation or 1,1′-carbonyldiimidazole coupling yielding a number of tricyclic sultams. This strategy was utilized for the synthesis of 160-member library, along with their isoindolines/THIQ and secondary sulfonamides precursors.

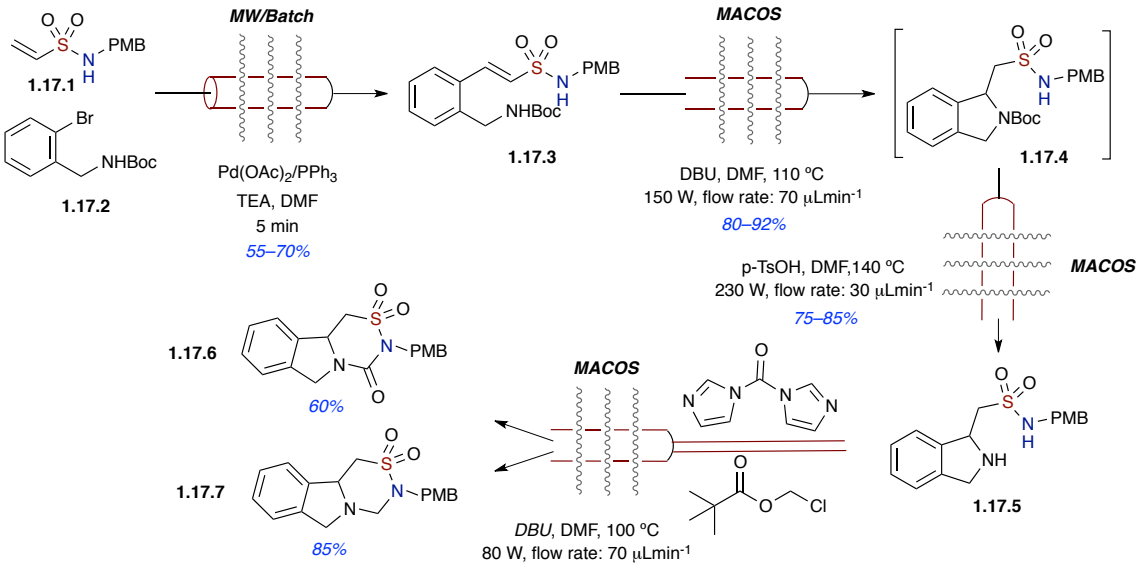
Scheme 1.17a *Heck-aza-Michael (HaM).*



In 2012, Hanson and co-workers further extended this work to a MACOS protocol (Scheme 1.17b).[105] The sequence utilized a Heck reaction on vinyl sulfonamides with batch microwave heating and then a subsequent one-pot, sequential intramolecular aza-Michael/Boc-deprotection protocol. Cyclization with either chloromethyl pivalate or 1,1'-carbonyldiimidazole furnished tricyclic sultams. This three-step protocol yielded a 38-

member library of isoindoline-annulated sultams in a few hours with excellent overall yields (54–87%) from simple starting materials.

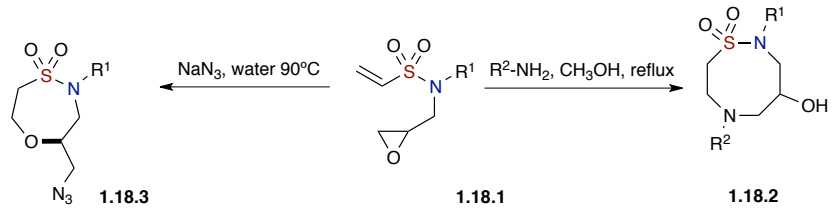
Scheme 1.17b Utilization of MACOS in the *Heck-aza-Michael (HaM)* pathway.



1.5.9 Oxa-Michael and Aza-Michael

In 2012, Zhou and coworkers reported a method in which two tandem processes to synthesize seven and eight membered sultams from the same starting material were developed (Scheme 1.18).[106] The first protocol involved the synthesis of a seven membered scaffold utilizing an intermolecular epoxide ring opening by sodium azide and then subsequent intramolecular 7-*endo*-trig oxa-Michael addition. The second protocol utilizes an aza-Michael reaction of a primary amine followed by an 8-endo-tet intramolecular epoxide ring opening to furnish the eight membered scaffolds. The conditions for the synthesis of the seven membered scaffold involved heating at 90ºC and lower yields while the synthesis of the eight membered scaffold occurred at room temperature with higher yields.

Scheme 1.18 *Selective synthesis of seven- and eight-membered ring sultams via two tandem reaction protocols.*



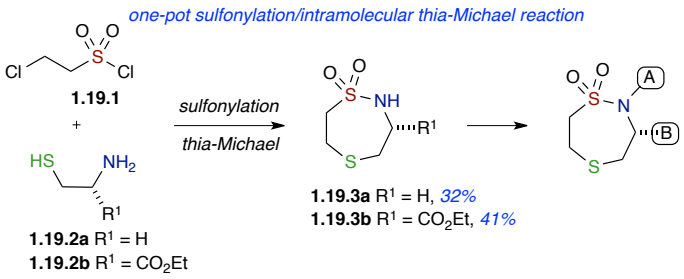
entry	R^1	Yield, %
1	$-CH(CH_3)_2$	67
2	$-CH_2CH(CH_3)_2$	61
3	$-(CH_3)_2CH_3$	63
4	$-CH(CH_2)_5$	56
5	$-C(CH_3)_3$	62
6	$-CH_2Ph$	65
7	$-CH_2CH_2CH_3$	60
8	$-CH_2CH_2Ph$	56

entry	R^1	R^2	Yield, %
1	$-CH(CH_3)_2$	$-CH(CH_3)_2$	87
2	$-CH_2CH(CH_3)_2$	$-CH_2Ph$	78
3	$-(CH_3)_2CH_3$	$-CH(CH_3)_2$	85
4	$-CH(CH_2)_5$	$-CH(CH_3)_2$	79
5	$-C(CH_3)_3$	$-(CH_2)_2CH_3$	88
6	$-C(CH_3)_3$	$-CH_2Ph$	80
7	$-C(CH_3)_3$	$-(CH_2)_2CH_3$	79
8	$-C(CH_3)_3$	$-(CH_2)_3CH_3$	79

1.5.10 Thia-Michael

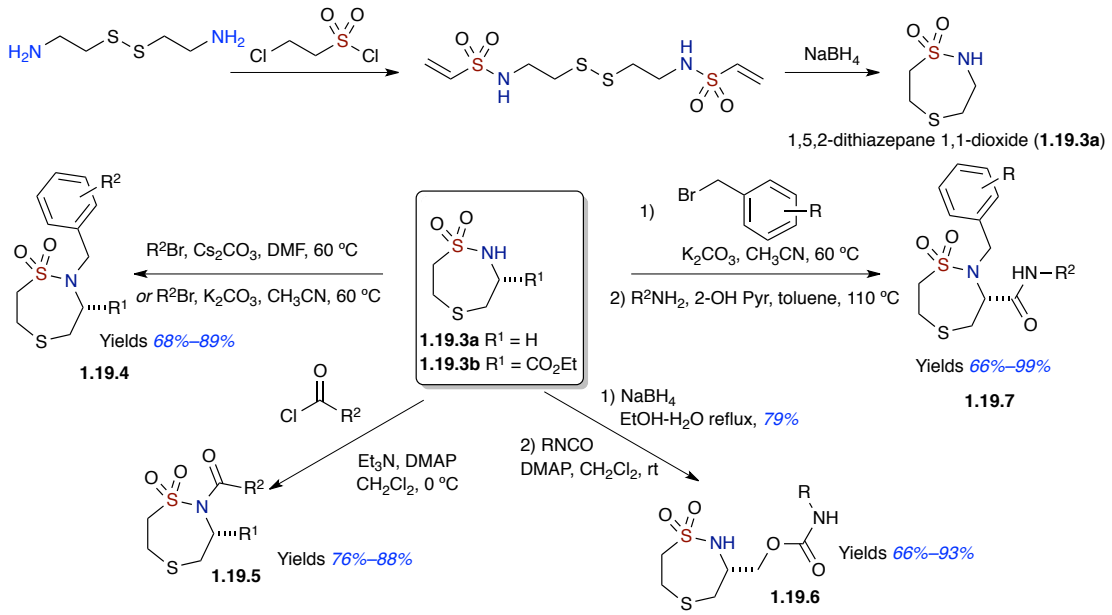
In 2012, Hanson and co-workers continued to further explore the Michael reaction with other nucleophiles and reported a thia-Michael protocol on the vinyl sulfonamide in a one-pot sulfonylation/intramolecular thia-Michael reactions for the synthesis of 1,5,2-dithiazepine 1,1-dioxide (Scheme 1.19a).[107] Sulfonylation was carried out by utilizing cysteine ethyl ester/cysteamine and 2-chloroethanesulfonyl chloride, and subsequent *in situ* intramolecular thia-Michael addition yielded the 1,5,2-dithiazepine-1,1-dioxide scaffolds.

Scheme 1.19a *One-pot sulfonylation and intramolecular thia-Michael.*



Notably, the only report of synthesis of 1,5,2-dithiazepane 1,1-dioxide (**1.19.3a**) utilized 2,2'-dithiobis(ethylamine) dihydrochloride[108] in a two-step sequence involving sulfonylation and utilization of sodium borohydride to cleave the S–S bond resulting in the thia-Michael to afford desired product (Scheme 1.19b). During optimization studies a survey of base, additive, solvent and temperature showed that 3.5 equivalent of Et_3N, 0.1 equivalent of DMAP, 40 ºC in CH_2Cl_2 provided the best results. The reaction was carried out under mild conditions and the products were easily recrystallized and isolated as colorless needles albeit in moderate yields. The moderate yields were attributed to polymerization *via* intermolecular pathways,[109] decomposition of cysteine ethyl ester was also noticed due to the detection of hydrogen sulfide smell. The reaction was carried out up to 40-gram scale

Scheme 1.19b *Thia-Michael and further diversifications*

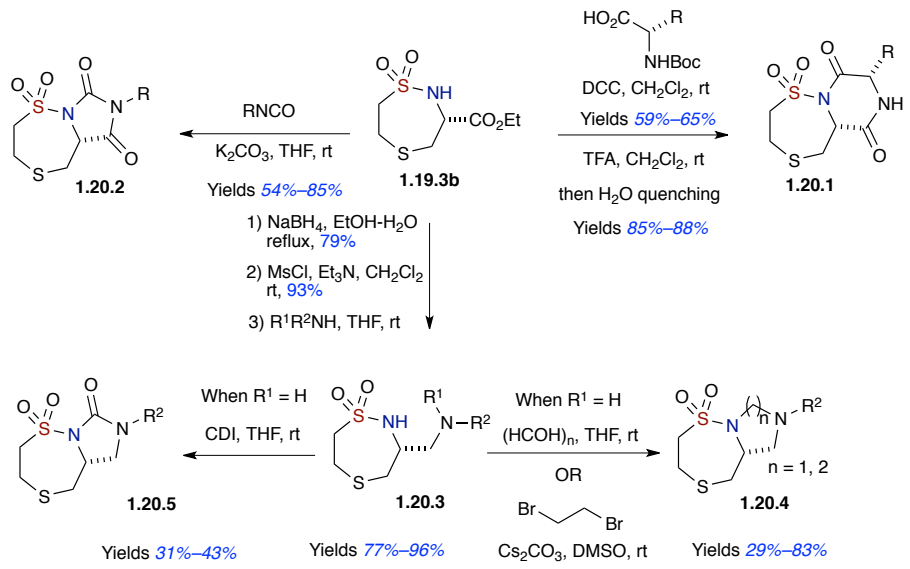


(cysteine ethyl ester) and roughly 20 grams of the desired product was obtained after recrystallization ($CHCl_3$) in a single reaction step. After the synthesis of sultams **1.19.3b**

various diversification pathways were explored as outlined in Scheme 18. Benzylation of **1.19.3b** using substituted benzyl bromides gave products **1.19.4** in good yield. Reaction with acyl chloride, in the presence of Et_3N and DMAP resulted in acyl-products **1.19.5**. Reduction of the ester group with $NaBH_4$ followed by reaction with isocyanates furnished carbamates **1.19.6**. Amides **1.19.7** were synthesized via a two-step sequence of benzylation and amidation of the ester.

The aforementioned method was extended to include a library of bicyclic sultams incorporating 1,5,2-dithiazepine 1,1-dioxides.[110] As already mentioned, the desired product **1.19.3** was obtained in a single reaction step on 20-gram scale after recrystallization ($CHCl_3$). With the large quantity of scaffold in hand, the free sulfonamide N-H and the nearby ester group were utilized for functional group manipulations and additional cyclization as shown is Scheme 1.20.

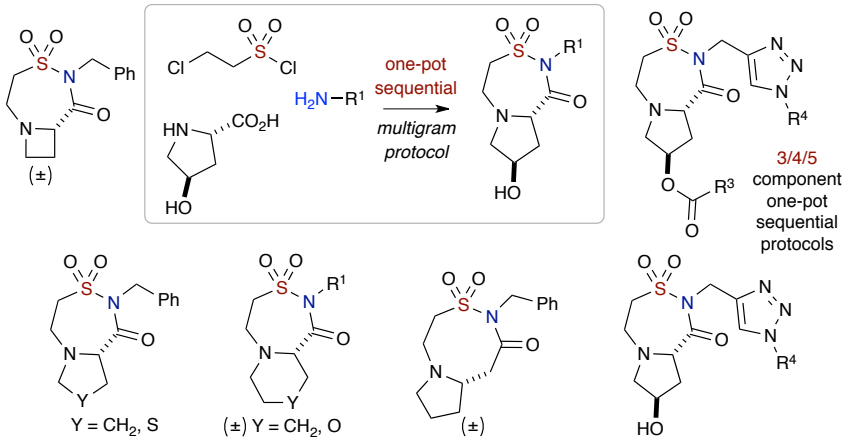
Scheme 1.20 *Thia-Michael and secondary cyclizations.*



Amidation utilizing Boc-protected amino acids and subsequent treatment with TFA followed by quenching with water affected the *in situ* cyclization affording the secondary cyclization to form fused sultams **1.20.1** (Scheme 1.20). A number of *N*-substituted (*R*)-dihydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine-6,8(3*H*,7*H*)-dione 1,1-dioxides **1.20.2** were synthesized by treatment of **1.19.3b** with isocyanates utilizing basic condition (K_2CO_3) in THF. Reduction of **1.20.3b** followed by mesylation and then treatment with primary and secondary amines furnished the diamines **1.20.3**. The primary amines provided additional cyclization oppurtunities. Reaction of **1.20.3b** with 1,1'-carbonyldiimidazole (CDI), 1,2-dibromoethane afforded the sultams **1.20.5**, reaction with paraformaldehyde and 1,2-dibromoethane furnished bicyclic products **1.20.4**.

In 2014, Hanson and coworkers [111] developed a one-pot, sequential protocol encompassing complementary ambiphile pairing (CAP) strategy involving the union of a vinyl sulfonamide with a variety of unprotected amino acids via aza-Michael addition and subsequent intramolecular amidation (Scheme 1.21). Diverse, sp^3-rich and stereochemically

Scheme 1.21 *Assembly of stereochemically rich acyl sultams.*



rich mono- and bicyclic acyl sultams were assembled in a highly scalable manner. Modular pairing of stereochemically rich building blocks could be utilized to gain quick access to all possible isomers just by the change of the starting material stereochemistry. This method was further extrapolated to one-pot, sequential 3-, 4-, and 5-multicomponent protocols. The aforementioned method will be discussed thoroughly in Chapter 2.

1.6 Conclusion

In conclusion, the electrophilicity of the vinyl sulfonamide has been explored in a number of reactions including RCM, Diels-Alder, Baylis-Hillman Michael, as well as the Heck reaction, to develop methodologies for synthesis of a number of novel sultam scaffolds. Ring closing metathesis was employed to synthesize 5–, 6–, 7–membered sultams bearing the vinyl functionality in the ring, which was further employed in the Michael reaction. Vinyl sulfonamides underwent Diels Alder reaction with side chains containing furans forming tricyclic 6-epoxybenzo[*d*]isothiazole 1,1-dioxide. Vinyl sulfonamides were also utilized in the Baylis-Hillman reaction to construct five membered 4-hydroxy-5-methyleneisothiazolidine 1,1-dioxides and six membered 5-hydroxy-6-methylene-1,2-thiazinane 1,1-dioxides. The vinyl sulfonamides were also exploited in a number of Michael reactions utilizing different nitrogen, oxygen as well as sulfur nucleophiles towards a number of sultams. Heck reaction was also exploited on vinyl sulfonamide giving rise to the Heck-aza-Michael (HaM) strategy. These sultam moieties are void in the literature and have been synthesized for the exploration of chemical and biological space.

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Chapter 2

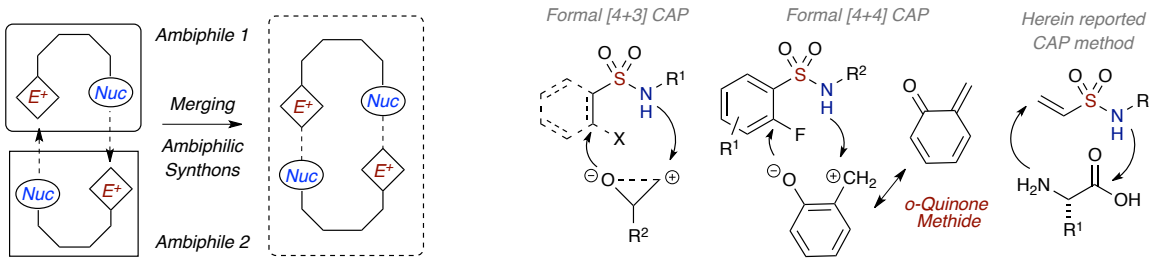
Rapid, Scalable Assembly of Stereochemically Rich, Mono- and Bicyclic Acyl Sultams

2.1 Introduction

2.1.1 Complementary Ambiphilic Pairing Strategy (CAP-strategy)

The rapid synthesis of novel small molecule collections for high throughput screening (HTS), with a minimum number of steps and minimal use of protecting groups is an important goal in modern drug discovery.[1] Ambiphilic reagents,[2] also referred to as amphoteric molecules[3] and amphiphilic molecules,[4] have been utilized in organic synthesis in order to achieve step and atom economy,[5] by taking advantage of the nucleophilicity and electrophilicity[2,6,7,8,9] of orthogonal functional groups, thus increasing synthetic efficiency. Recently, our group reported methods using ambiphilic vinyl sulfonamides or 2-fluorobenzenesulfonamides with other ambiphilic reagents, namely epoxides[10] and *ortho*-quinone methides[11] for formal [4+3] and [4+4] complementary ambiphilic pairing (CAP) reactions in the synthesis of sultams (Scheme 2.1). This chapter details our efforts toward the synthesis of non-benzofused sp^3-rich[12] mono- and bicyclic acyl sultams displaying skeletal and stereochemical diversity.

Scheme 2.1. *CAP strategies utilizing epoxides, ortho-quinone methides, and amino acids.*



Amino acids are ideal starting materials due to their resident stereocenters, enriched functional group variance and extensive commercial availability. In addition, they incorporate ambiphilic FGs that could undergo aza-Michael addition (amino group) and a

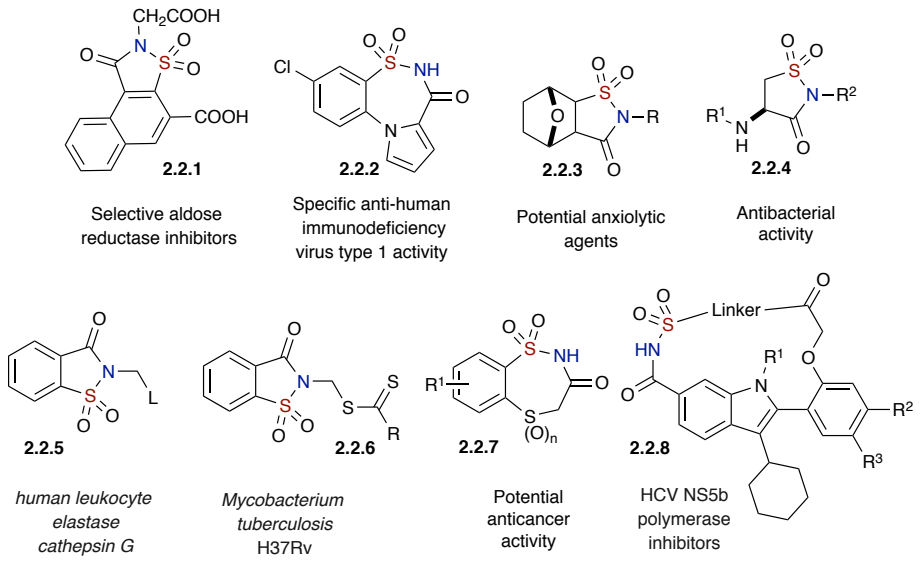
coupling reaction (carboxylic acid). To the best of our knowledge, the literature contains only a few reports since the early studies of the Michael addition of unprotected amino acids to acrylonitrile.[13] Specifically, addition to acrylonitrile has been utilized to provide precursors for the synthesis of polyamines via reduction of cyano groups[14] and pyrrolidone[15] or pyrazoles[16] through Dieckmann condensations. Other Michael acceptors for the addition of amino acids that have been reported include: esters,[17] acrylaldehyde,[18] vinyl sulfones,[19] and vinyl phosphoryl compounds.[20] In spite of the versatile Michael reactions of unprotected amino acids, their addition to vinyl sulfonamides was absent from the literature before our work in this area.

2.1.2 Bioactive acyl sultams/sulfonamides

Acyl sultams, which are a subset of sultams, that encompass unique physical and chemical properties rendering them attractive targets for probing biological systems. They exhibit a variety of biological activities, including antibacterial, anticancer, and anti-inflammatory properties, as well as unique biological profiles in different cell assays.[21] A few important acyl sulfonamides and sultams with their relevant biological activity are discussed below.

In 2005, La Motta[21a] and coworkers synthesized acetic acid derivatives of naphtho [1,2-*d*]isothiazole (NiT) which proved to be aldose reductase (ALR2) inhibitors (Scheme 2.2). Compound **2.2.1** exhibited modest inhibitory activity (IC_{50}) 10 μM), but when the acetic acid functionality was replaced with a non-polar group, inactive or poorly active compounds were obtained. This indicated that the 2-acetic acid group is most plausibly the pharmacophore, while the 4-carboxylic moiety has only an ancillary role.

Scheme 2.2. *Some bioactive acyl sultams.*



In 1998, Di Santo[21b] and co-workers synthesized novel inhibitors of human immunodeficiency virus type 1 (HIV-1) 1,2,5-benzothiadiazepine and pyrrolo[2,2-*d*]benzothiadiazepine derivatives **2.2.2** possessing specific anti-human immunodeficiency virus type 1 (anti-HIV-1) activity (Scheme 2.2). Bi- and tricyclic thiadiazine ring homologues of 7-chloro-2-ethyl-2H-1,2,4-benzothiadiazin-3-(4H)-one 1,1-dioxide were synthesized which possessed anti-HIV-1 activity.

In 1989, Abou-Gharbia and co-workers[21c] tested a variety of tetrahydro- and hexahydro-1,2-benzisothiazol-3-one 1,1-dioxides and thiadiazinones **2.2.3** in a series of *in vitro* and *in vivo* tests to determine their pharmacological profile. These compounds were orally active in blocking the conditioned avoidance response (CAR) but did not antagonize stereotypical apomorphine-induced behavior (Scheme 2.2). Several compounds demonstrated moderate to high affinity for the 5-HT_{1A} receptor-binding site. These compounds were also found to have potential anxiolytic activity.

In 1989, Chen and co-workers[21e] reported a variety of 4-amido-isothiazolidinone

oxide derivatives **2.2.4**. They designed these compounds as bacterial serine protease inhibitors. However, some of these compounds portrayed weak antibacterial activity as well.

In 1993, Groutas and co-workers[21f] synthesized a number of saccharin derivatives **2.2.5** and evaluated their inhibitory activity towards human leukocyte elastase and cathepsin G. A number of these compounds proved to be efficient and time-dependent inhibitors of elastase (Scheme 2.2).

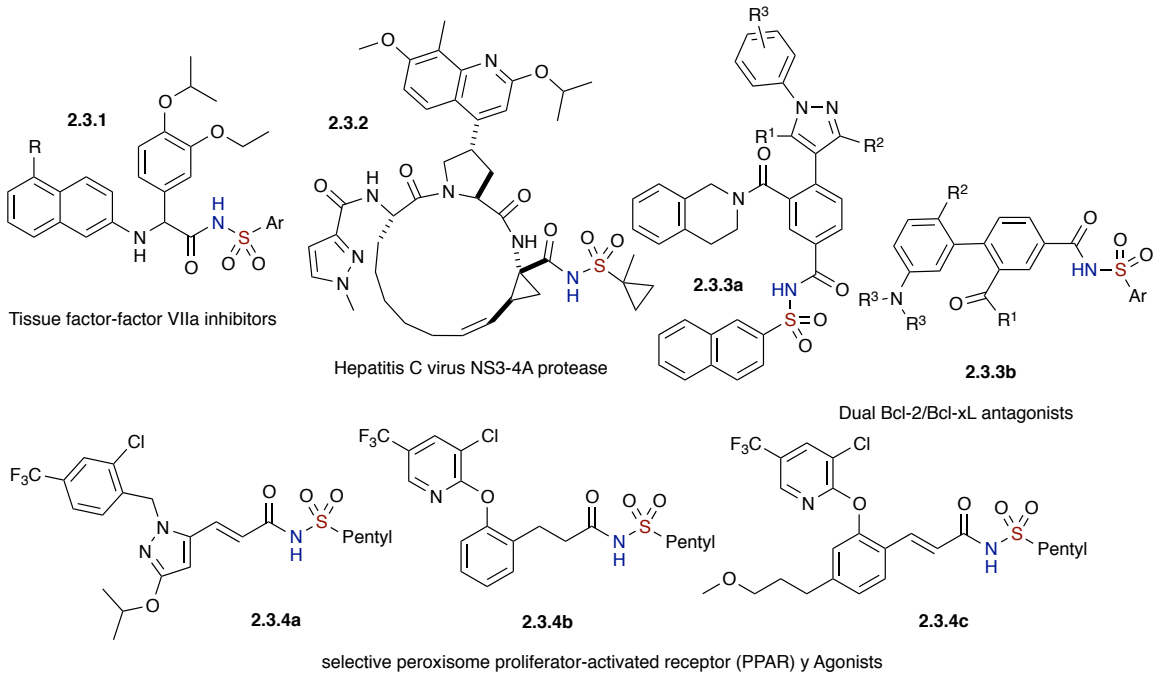
In 2006, Güzel and co-workers[21g] demonstrated that reacting 2-chloromethylsaccharin with substituted potassium dithiocarbamates and substituted potassium dithiocarbonates yielded (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl *N*,*N*-disubstituted dithiocarbamates and (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl *O*-alkyldithiocarbonates, respectively **2.2.6** (Scheme 2.2). Evaluation of these compounds showed they possessed *in vitro* anti-mycobacterial activity against Mycobacterium tuberculosis H37Rv. Some of these compounds showed cytotoxicity, especially against leukemia cell lines CCRF-CEM, HL-60(TB), RPMI-8226, SR and against the non-small cell lung cancer NCI-H522 cell line. Cytotoxicity against the leukemia cell line HL-60(TB) and favorable cytotoxicity against the ovarian cancer cell line OVCAR-3 was also portrayed by some compounds.

In 2001, Pomarnacka and co-workers[21i] reported the syntheses of 3,4-dihydro-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxides **2.2.7** and their corresponding 1,1,5,5-tetraoxides (Scheme 2.2). They were evaluated at the US National Cancer Institute (Bethesda) revealing the *in vitro* antitumor activity of 7-chloro-3,4-dihydro-8-methyl-4-phenyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide.

In 2012, McGow and co-workers[22] synthesized conformationally constrained 1,6- and 2,6-macrocyclic HCV NS5b **2.2.8** as polymerase inhibitors (Scheme 2.2). The nitrogen or phenyl ring in the C2 position of the central indole core was tethered to an acylsulfamide acid bioisostere. These macrocycles were designed and tested for their anti-HCV potency. This transformational route afforded non-zwitterionic finger loop-directed inhibitors with improved cell potency and pharmacokinetic profile.

In 2013, Glunz and co-workers[23] successfully replaced the more basic P1 benzamidine of an acylsulfonamide factor VIIa inhibitor with aminoisoquinoline and isoquinoline groups that improved the bioavailability in this chemotype (Scheme 2.3a). In 2014, Llinàs[24] and co-workers discovered inhibitors of hepatitis C virus NS3-4A protease with an improved barrier to resistance and had a favorable liver distribution. They reported that the macrocyclic acylsulfonamide **2.3.2** was an HCV protease inhibitor that displayed potency against relevant clinically resistant variants (Scheme 2.3a).

Scheme 2.3a. *Some bioactive acyl sulfonamides.*



In 2012, Schroeder and co-workers[25] synthesized 5-butyl-1,4-diphenyl pyrazole and 2-amino-5-chloro pyrimidine acylsulfonamides **2.3.3a** and **2.3.3b** as potent dual antagonists of Bcl-2 and Bcl-xL (Scheme 2.3a). In 2012, Rikimaru and co-workers[26] synthesized non-TZD, non-carboxylic acid peroxisome proliferator-activated receptor (PPARy) agonists by replacing the benzylpyrazole core of the previously reported agonists. They introduced a pentylsulfonamide group into arylpropionic acids derived from previously synthesized PPARy ligands and identified 2-pyridyloxybenzene-acylsulfonamide **2.3.4a** as their lead compound.

In 2012, Chen[27] began with an indole-based C3 pyridone lead HCV polymerase inhibitor **2.3.5a**, and performed structure activity relationship (SAR) studies at various positions of the indole core. Acylsulfonamides were incorporated as acid isosteres to improve pharmacokinetic (PK) properties at the C2 position (Scheme 2.3b). Further optimization resulted in the identification of compound **2.3.5b** as having excellent potency in both NS5B enzyme (IC_{50} = 8 nM) and cell-based replicon (EC50 = 0.02 μM) assays. Zhu[28] designed and synthesized a series of pyridine acyl sulfonamide derivatives as potential cyclooxygenase-2 (COX-2) inhibitors. Compound **2.3.6** displayed the most potent COX-2 inhibitory activity with an IC_{50} of 0.8 μM. Antitumor and anti-inflammatory assays showed that compound **2.3.6** possessed high anti-proliferative activity against B16-F10, HepG2 and MCF-7 cancer cell lines as well as COX-2-derived prostaglandin E_2 (PGE_2) inhibitory activity of murine macrophage RAW 264.7 cell line with IC_{50} values of 2.8, 1.2, 1.8 and 0.15 μM, respectively. Docking studies were performed to determine the probable binding model at the COX-2 active site.

In 2009, Singh and co-workers[29] developed a series of potent and selective EP_3

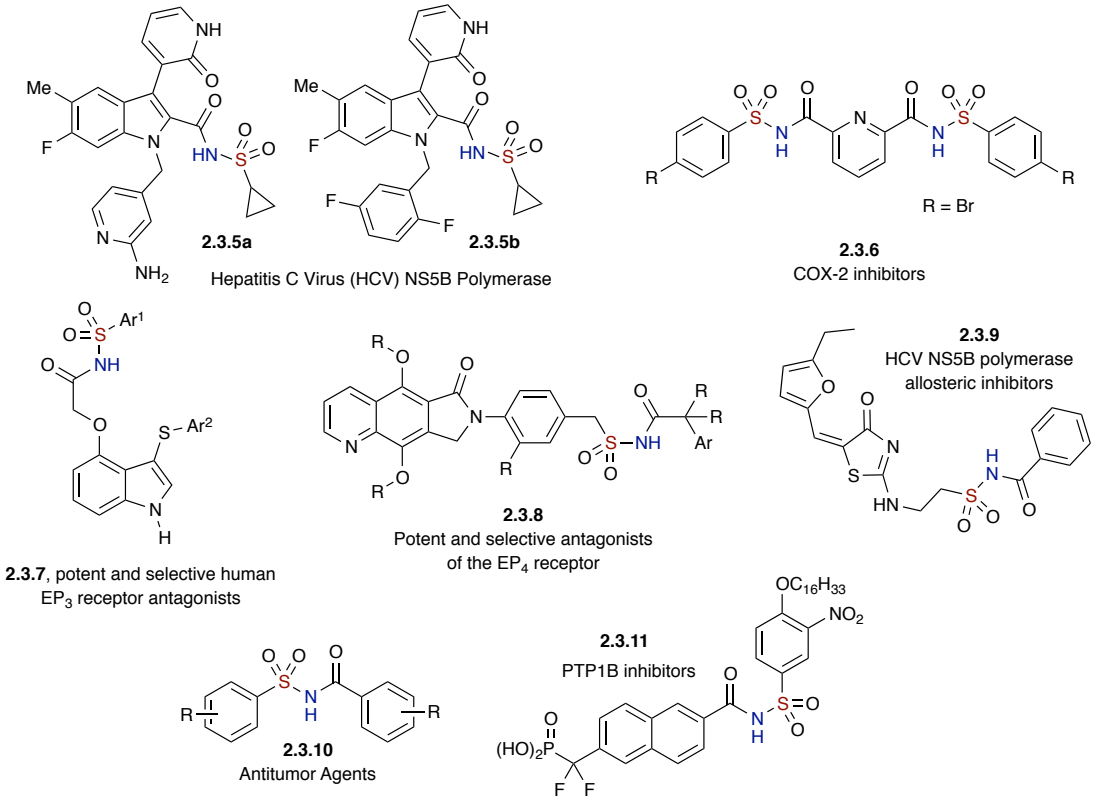
receptor antagonists. Utilizing a pharmacophore model developed for the EP_3 receptor, they synthesized a series of 3,4-disubstituted indoles **2.3.7**, which proved to be high affinity ligands for the EP_3 receptor (Scheme 2.3b). In 2008, Burch and co-workers[30] discovered a new series of EP_4 antagonists based on a quinoline acylsulfonamide scaffold **2.3.8** for the treatment of chronic inflammation. The binding potency of these compounds was at sub-nanomolar level, and they exhibited intrinsic binding potency towards the EP_4 receptor. These molecules also portrayed excellent selectivity towards other prostanoid receptors.

In 2007, Yan and co-workers [31] designed a novel series of thiazolone-acylsulfonamides **2.3.9** as HCV NS5B polymerase allosteric inhibitors (Scheme 2.3b). The potential of these moieties to explore an additional pocket in the allosteric site was steered by structure based drug designs (SBDD) utilizing the docking results. These molecules contain thiazolone and an acylsulfonamide linker that was connected with a substituted aromatic ring. These compounds portrayed low μM activity.

In 2004, Lobb[32] reported two closely related diaryl acylsulfonamides **2.3.10** as potent antitumor agents against a broad spectrum of human tumor xenografts (colon, lung, breast, ovary, and prostate) in nude mice (Scheme 2.3b). Their activity against colorectal cancer xenografts was most interesting. Although the molecular target of the compounds is still unclear, it was found that the vascular endothelial growth factor-dependent human umbilical vein endothelial cells assay in combination with a soft agar disk diffusion assay, allowed for optimization of potency in the series. The authors also reported pharmacokinetic properties and *in vivo* activity in an HCT116 xenograft model for the mentioned compounds.

Burke [33] reported a family of new analogues that utilize acylsulfonamido functionality **2.3.11** to both mimic water of hydration and to provide an additional new site for elaboration not found in the parent carboxyl-containing analogue (Scheme 2.3b). This work was built on a previous report, which stated that 6-(phosphonodifluoromethyl)-2-naphthoic acid binds to the protein-tyrosine phosphatase PTP1B with its 2-carboxyl group, interacting through a bridging water molecule. Aryl acylsulfonamides studied in this paper are a structure-based extension of inhibitor design in the development of PTP1B inhibitors.

Scheme 2.3b. *Some bioactive acyl sulfonamides.*



Taken collectively, as highlighted in this section, the synthesis and biological activity of acyl sulfonamides/benzofused sultams are well documented in the literature.[21] However, to the best of our knowledge the synthesis of non-benzofused, 7-membered

acyl sultams were absent from the literature before we started this work. The next section of chapter two details our efforts in this regard.

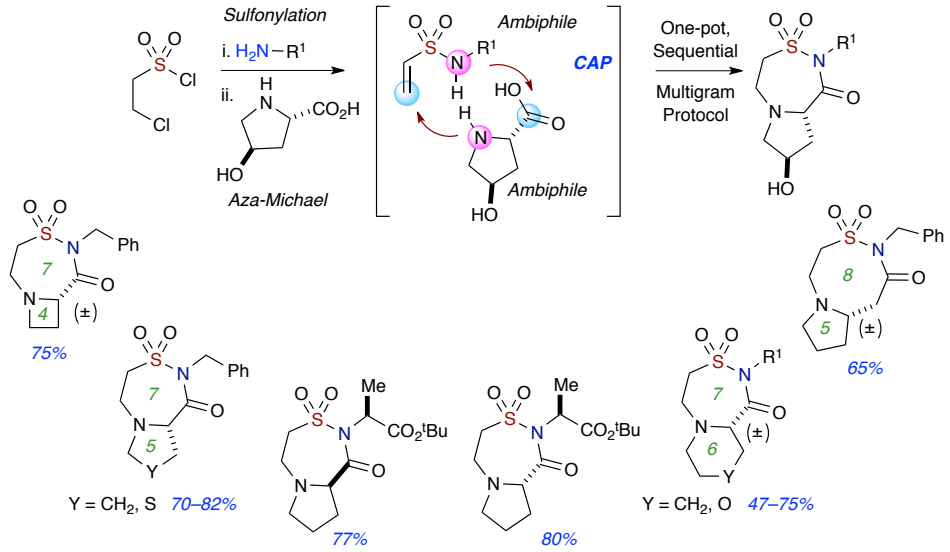
2.2 Results and Discussions

In light of the rich biological profile highlighted in the preceding section, we focused efforts toward the generation of an unexplored class of acylsultams, namely non-benzofused sp^3-rich [34] mono- and bicyclic acyl sultams displaying skeletal and stereochemical diversity. In this approach, we utilized a strategy, termed complementary ambiphilic pairing (CAP), *vide infra*, whereby vinyl sulfonamides and unprotected amino acids were employed in a one-pot, sequential aza-Michael addition/intramolecular amidation reaction (formally a [4+3] heterocyclization) (Figure 2.1).

The development of multicomponent, one-pot reaction strategies that allow for facile assembly of heterocyclic scaffolds, with minimum purification is particularly desirable in modern organic synthesis.[35] These one-pot strategies are amenable to diversity-oriented synthesis (DOS), which has emerged as a powerful strategy for systematically probing biological space aimed at uncovering novel leads.[36] Among several approaches, the build-couple-pair,[37] and functional group pairing[37b] strategies (Chapter 1) have featured prominently in advancing DOS. We recently reported the concepts of complementary ambiphilic pairing (CAP)[38] and reaction pairing[39] as DOS strategies for the facile generation of diverse sultam scaffolds. In this regard, the complementary union of ambiphilic[40] synthons, in a formal [m+n] fashion ([4+3] and [4+4]), allows access to diverse cyclic heterocycles in a step-economical approach.[41] It was envisioned that the combination of ambiphilic vinyl sulfonamides and amino acids

could be used in a CAP reaction to generate sp^3-rich[34] monocyclic and bicyclic 7-membered acyl sultams in a library amenable approach (Figure 2.1).

Figure 2.1. *Complementary ambiphilic pairing (CAP): vinyl sulfonamides and unprotected amino acids*



The CAP method employed utilizes the ambiphilic nature of both vinyl sulfonamides and amino acids, whereby sulfonamides due to their ambiphilic nature, can readily undergo hetero-Michael additions as well as facile amidation. Moreover, amino acids are ideal starting materials as they allow for encoding stereochemical, skeletal and peripheral diversity. Previous investigations have shown that vinyl sulfonamides are ambiphilic synthons that readily undergo *N*-alkylations,[42] and participate in [4+3] epoxide-opening/Michael protocols.[38a] However, while amino acids have been shown to undergo aza-Michael to acrylonitrile,[43] acrylate esters,[44] acrylaldehydes,[45] sulfones,[46] and vinylphosphoryl compounds[47], the aza-Michael addition of unprotected amino acids to vinyl sulfonamides was void in the literature before we started this body of work.

2.2.1 Optimization of conditions

Our investigation started with the Michael addition of *trans*-3-hydroxy-(*L*)-proline to *N*-propargylic vinyl sulfonamide in the presence of 0.2 equivalents of DBU. Different solvents (MeOH and CH_3CN) were probed for this reaction. It was noticed that overnight stirring with these solvents at 60 ºC did not furnish the product (Table 2.1, entry 2). However, changing the base to Et_3N generated the product in moderate yield. Due to the partial solubility of amino acids in MeOH a 1:1 mixture of MeOH/H_2O was employed as the solvent, along with Et_3N as the base, cleanly furnishing the desired Michael adduct with complete consumption of the starting material. The reaction mixture was further concentrated to dryness followed by the addition of DMF along with EDC, HOBt and Et_3N with overnight stirring to afford the desired bicyclic acyl sultam **2.4.2e** in 64% yield.

2.2.2 Scope and scale-up of reaction

Investigation of the substrate scope and the scalability disclosed that the reaction worked well with a variety of alkyl- and benzyl amine-derived vinyl sulfonamides affording the desired products in good to excellent yields on multi-gram scales (Scheme 2.4). This one-pot protocol was shown to be scalable to produce 28 grams of **2.4.2e** (64% isolated yield). Also significant, is the ability to utilize a hydroxy-functionalized amino acid without the need for any protection in the Michael addition step (Table 2.1).

Scheme 2.4. *Scope and scale-up of bicyclic acyl sultam **2.4.2e**.*

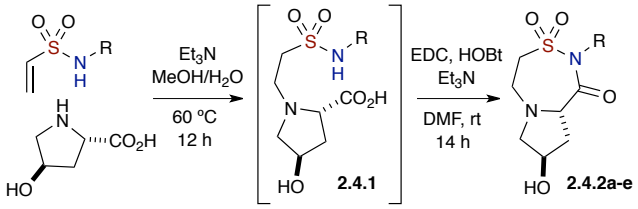


Table 2.1.

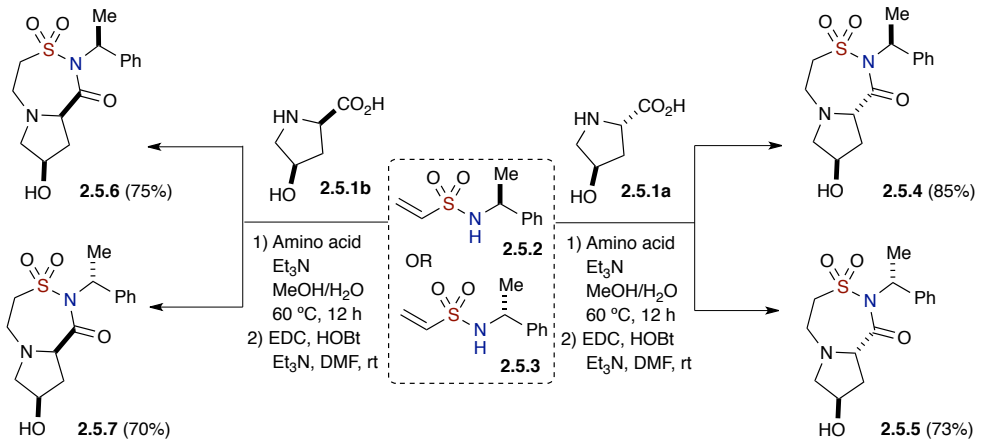
entry	R	scale	2.4.2	yield %[a]
1	Bn	0.2 g	NR	0[b]
2	propargyl	0.2 g	NR	0[b]
3	*n*-butyl	2 g	**2.4.2a**	67[c]
4	4-OMe-Bn	1 g	**2.4.2b**	72[c]
5	allyl	12 g	**2.4.2c**	86[c]
6	Bn	12 g	**2.4.2d**	76[c]
7	propargyl	28 g	**2.4.2e**	64[c]

[a]Final isolated yield after flash chromatography. [b]Conditions: DBU (0.2 equiv) in MeOH or DBU (0.2 equiv) in MeCN. [c]**Aza-Michael**: *trans-L*-Hydroxyproline (1.0 equiv), Et_3N (3.0 equiv), MeOH/H_2O (0.5 M, 1:1), 60 ºC, 12 h. **Amidation**: EDC (2.0 equiv), HOBt (0.2 equiv), Et_3N (2.0 equiv), DMF (0.05 M), rt, 14 h.

2.2.3 Stereochemical diversity

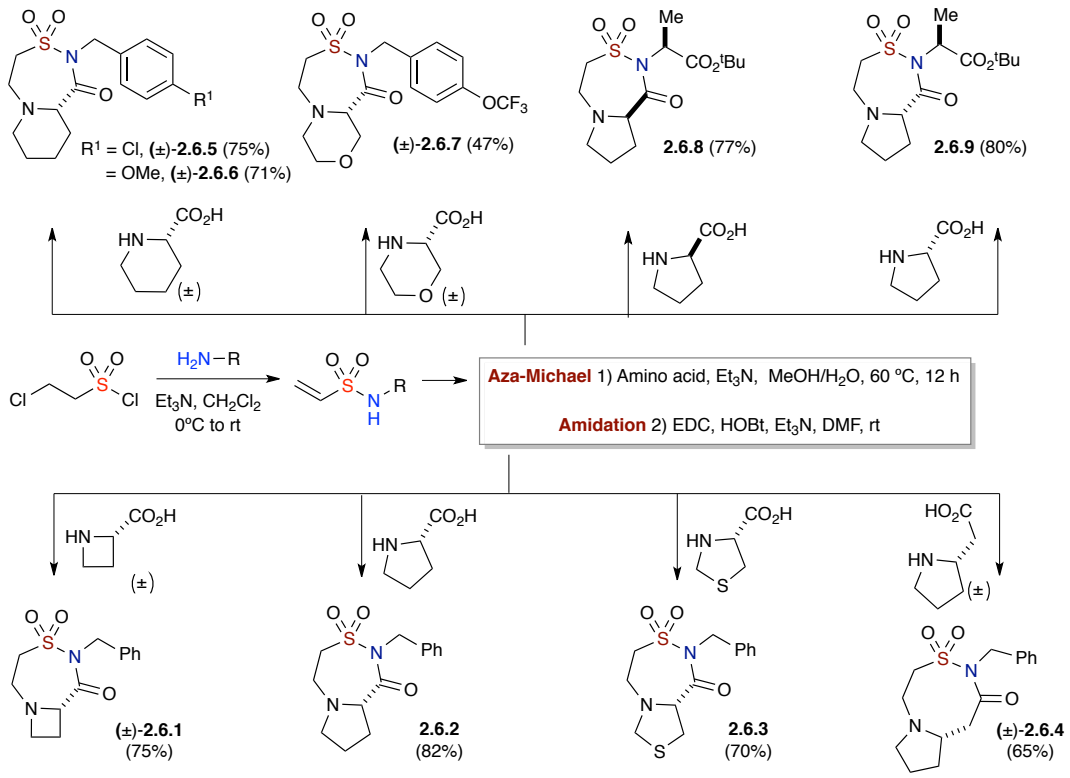
Investigations were next focused on a modular approach using chiral amino ester-derived vinyl sulfonamides. Utilizing the enantiomers of α-methylbenzylamine-derived vinyl sulfonamides, **2.5.2** and **2.5.3**, together with both *L-trans-* and *D-cis-* hydroxyproline in the aforementioned CAP method, gratifyingly furnished a collection of four diastereoisomers (**2.5.4, 2.5.5, 2.5.6** and **2.5.7**) in good yields without any signs of racemization (Scheme 2.5).

Scheme 2.5. *Generation of stereochemical diversity.*



Further extension to bicyclic acyl sultams was realized utilizing a variety of cyclic amino acids (Scheme 2.6). In this method, the generation of stereochemically-rich libraries could be achieved by a simple change in the amino acid/amino ester pair.

Scheme 2.6. *One-pot, sequential [4+3] CAP strategy to generate bicyclic sultams with an array of cyclic amino acids.*



Hence, (*L*)-alanine *tert*-butyl ester-derived vinyl sulfonamide was subjected to the established one-pot, CAP protocol employing *D*- and *L*-proline affording the acyl sultams **2.6.8** and **2.6.9** without decomposition of the ester (Scheme 2.6). Some interesting examples include azetidine 2-carboxylic acid, (*R*)-thiazolidine-4-carboxylic acid, 2-(pyrrolidin-2-yl)acetic acid and morpholine 3-carboxylic acid to provide the 4,7-fused, 5,7-fused, 5,8-fused, and 6,7-fused bicyclic systems, respectively.

The methodology was further extended to acyclic amino acids with a variety of *N*-substituted vinyl sulfonamides utilizing the same protocol (Table 2.2). Amino acids bearing alkyl side chains (leucine, isoleucine, valine and alanine) gave good yields in a highly scalable manner. The reaction conditions also tolerated amino acids with

Scheme 2.7. *Substrate scope – acyclic amino acids*.

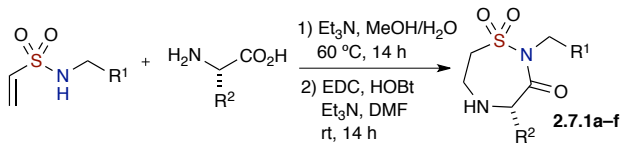


Table 2.2. *Monocyclic scaffolds.*

entry	R^1	R^2	**2.7.1**	yield %[a]
1	Ph	^{i}Bu	**2.7.1a**	63
2	4-F-Ph	*sec*-Bu	**2.7.1b**	65
3	4-F-Ph	^{i}Pr	**2.7.1c**	67
4	4-Cl-Ph	Me	**2.7.1d**	65
5	$(CH_2)_6CH_3$	CH_2SH	**2.7.1e**	33
6	Ph	(4-OH)-Bn	**2.7.1f**	41

[a] Final isolated yield after flash chromatography.

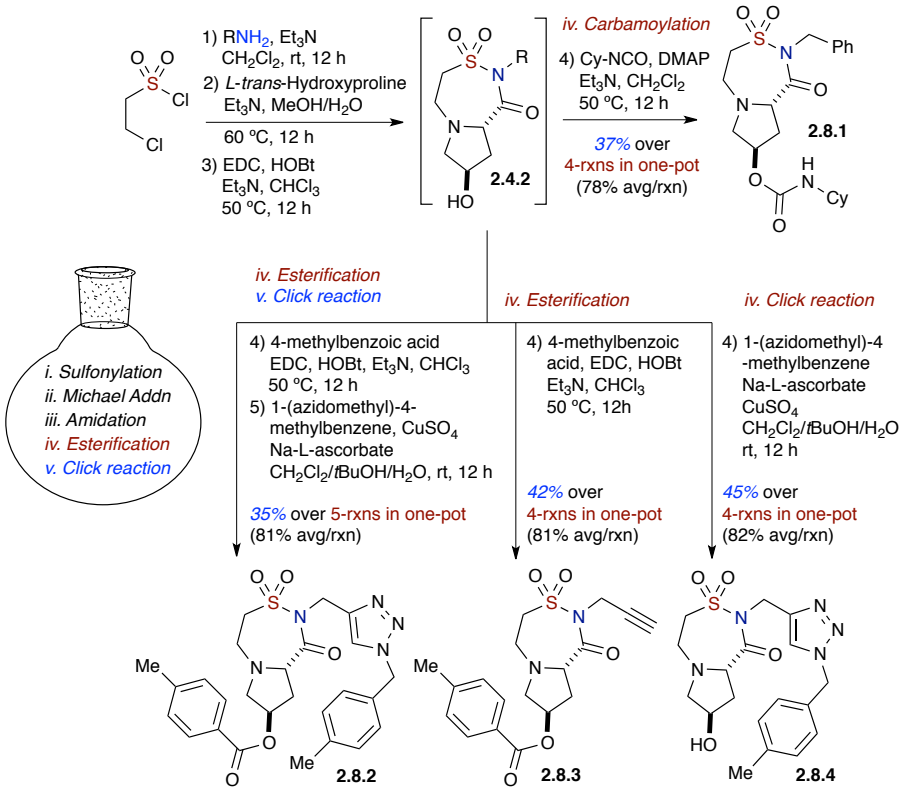
unprotected nucleophilic side chains (unprotected, trifunctional amino acids) such as tyrosine and cysteine, which reacted well, albeit in lower yields.

2.2.4 One-pot, sequential [4+3] CAP 3/4/5-component reaction

Synthesis of functionally diverse small molecule collections for high throughput screening is an important aspect of modern drug discovery. In this respect, the development of multicomponent, one-pot reaction strategies is particularly important for the facile assembly of heterocyclic scaffolds, with minimum purification is highly desirable.[48] Moreover, methods that aspire to the step, atom, and redox economy, as well as the virtues of protecting-group-free synthesis are among the most efficient.[5] Recently, Hayashi and coworkers[49] have brought to light the significance of multi-reaction, one-pot protocols. Building on these results the CAP method was next extended to a one-pot, sequential protocol by increasing the number of reactions that could be carried out before chromatographic intervention, and thus increasing synthetic efficiency.[35a-d] In this regard, a one-pot, sequential 3-component protocol was devised and started with the sulfonylation of 2-chloroethane sulfonyl chloride with benzyl amine utilizing Et_3N (2.0 equiv). Upon completion of reaction, the mixture was concentrated to dryness and the crude sulfonamide was subjected to the established one-pot, aza-Michael addition–intramolecular amidation with a variety of cyclic amino acids, to furnish the desired products in 39–85% final isolated yields. This one-pot, sequential 3-component protocol was also found to work with acyclic amino acids (DMF was the preferred solvent for cyclic amino acids, while $CHCl_3$ at 50 ºC was used for acyclic amino acids) to furnish the corresponding acyl sultams in moderate to good overall yields.

Building upon these results, a one-pot process that would also incorporate diversification was devised (Scheme 2.8). In this regard, highly functionalized sultam scaffolds were constructed utilizing one-pot, sequential, 4 and 5-component reaction sequences. Initially, the method was further extended to a one-pot, sequential, 4-component reaction protocol using different pathways (Scheme 2.8). Four reactions were set up employing the one-pot sulfonylation–aza-Michael−intramolecular amidation sequence with benzyl and propargyl amines and trans -3-hydroxy-(*L*)-proline. Upon completion of the four parallel reactions, solvent was evaporated, followed by the addition of CH_2Cl_2. To the first crude reaction a fourth component, cyclohexyl isocyanate, was added followed by DMAP and heating at 50ºC to furnish the desired carbamate **2.8.1** in 37% yield after chromatography (78% avg yield/rxn). To the second reaction, CH_2Cl_2/*t*-BuOH/H_2O were added in a 1:1:1 ratio, followed by the addition of copper sulfate, sodium *L*-ascorbate and 4-methylbenzyl azide, to generate the corresponding triazoylated thiadiazepin-1(2H)-one-3,3-dioxide **2.8.2** in 45% yield after chromatography (82% avg yield/rxn). The third crude reaction was carried on to an esterification reaction with 4-methyl benzoic acid utilizing EDC, HOBt, Et_3N to afford the corresponding esterified product **2.8.3** in 42% yield after chromatography (81% avg yield/rxn). The fourth reaction mixture, esterification with 4-methyl benzoic acid (fourth component) was performed in the same manner as above, followed by the subsequent click reaction with 4-methylbenzyl azide (fifth component) furnishing the desired triazolyl esterified [1,2,5]thiadiazepin-1(2*H*)-one-3,3-dioxide **2.8.2** in 35% yield (81% avg yield/rxn).

Scheme 2.8. *One-pot, sequential 4/5-component reaction to stereochemically-rich sultams.*



2.3 Conclusion

In conclusion, a highly scalable, one-pot CAP reaction employing vinyl sulfonamides and amino acids for the preparation of skeletally, stereochemically and peripherally diverse sp^3-rich acyl sultam scaffolds has been developed. The methodology was also extended to various one-pot, sequential 3-, 4- and 5-component reaction protocols. The developed method is easily adaptable for the preparation of stereochemically rich acyl sultam libraries. The synthesized libraries utilizing this method will be discussed in Chapter 3.

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developments in asymmetric multicomponent reactions. *Chem. Soc. Rev.* **2012**, *41*, 3969–4009. (e) Brauch, S.; van Berkel, S. S.; Westermann, B. Higher-order multicomponent reactions: beyond four reactants. *Chem. Soc. Rev.* **2013**, *42*, 4948–4962. (f) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev.* **2006**, *106*, 17–89. (g) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. Multicomponent Reaction Design in the Quest for Molecular Complexity and Diversity. *Angew. Chem., Int. Ed*. **2011**, *60*, 6234–6246.

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Chapter 3:

One-pot, Sequential Methods and ROMP-Facilitated Protocols for use in the Synthesis of Sultams Libraries

The development of protocols for the rapid synthesis of novel/privileged heterocyclic small molecule collections for high throughput screening (HTS) with minimized steps and protecting group manipulations is an important aspect in modern drug discovery.[1] The necessity for the synthesis of these small molecules, which can act as new pharmaceutical leads and small molecular probes, is an important objective of NIH (National Institute of Health). In order to pursue this goal, the development and emergence of new methods, protocols and technologies to access diverse collections of small molecules in a rapid fashion is very important.[2]

Section: 3.1 Stereo-controlled Diversification of sp^3-Rich Bicyclic Acyl Sultams via One-pot Click-Esterification and One-pot Sequential Click-Mitsunobu Protocols

Building on the importance of sultams as drug-like molecules, a library of thiadiazepan-1,1-dioxide-4-ones [3] was synthesized and sent to different biological collaborators for testing. These compounds demonstrated promising activity in a number of assays. The results prompted us to synthesize analogs of these compounds. Initially, a simple change in the location of the carbonyl within the side chain was targeted, (derived from the corresponding amino acid) affording novel acyl sultams as shown in Figure 3.1. Acyl sultams, which are a subset of sultams, possess unique physical and chemical properties rendering them attractive targets for probing biological systems. During the last decade a variety of bioactive acyl sulfonamides/sultams pharmacophores have been reported that embody an array of bioactivities, including antibacterial, anticancer and anti-inflammatory properties as highlighted in Figure 3.2.[4]

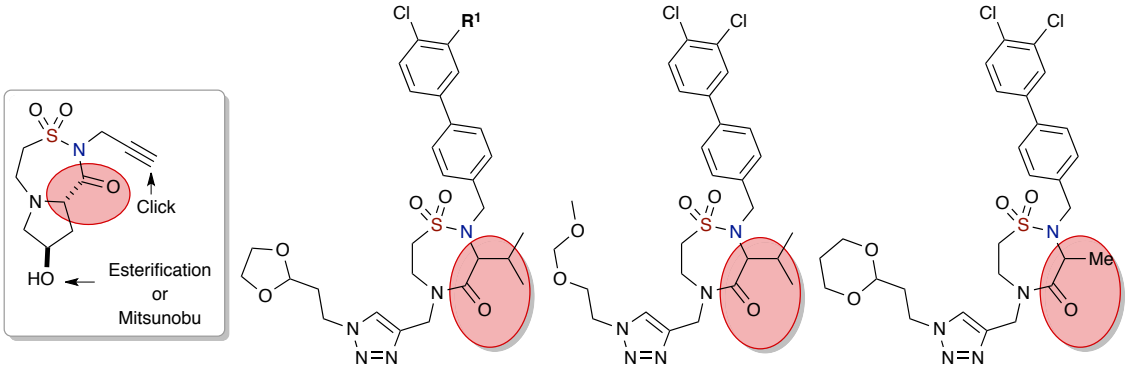


Figure 3.1. *Thiadiazepin-1(2H)-one 3,3-dioxide vs thiadiazepan-1,1-dioxide-4-ones.*

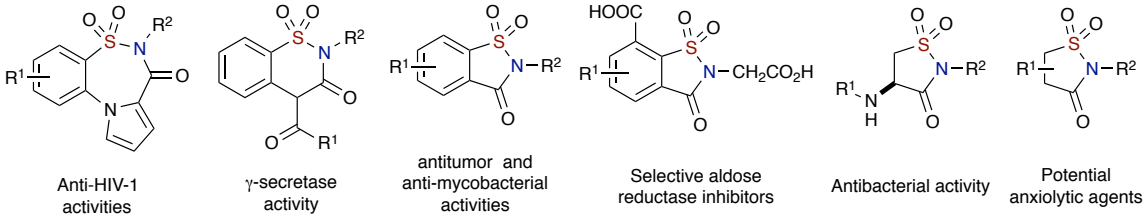
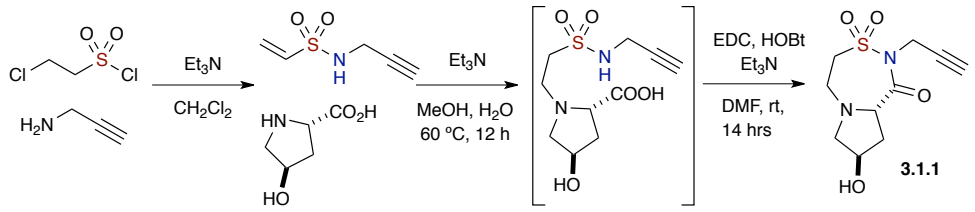


Figure 3.2 *Bioactive acyl sultams.*

Acyl sultam scaffold **3.1.1** was synthesized according to the procedure reported previously in our group and detailed in Chapter 2 (Scheme 3.1).[5] The protocol for the synthesis of the scaffold comprised of sulfonylation with propargyl amine, Michael addition with *L-trans*-hydroxyproline and amide coupling to afford the scaffold (8,9a*S*)-8-hydroxy-2-(prop-2-yn-1-yl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide **3.1.1** on a 28 gram scale with 64% yield over three steps in a one-pot sequence (average yield of 87% per step). In addition, the core scaffold contains a propargyl handle, which can undergo Huisgen [3+2] cycloaddition and also bears an alcohol moiety, which can be esterified utilizing classical coupling conditions as well as the Mitsunobu[6] alkylation reaction. Overall, this approach imparts the element of stereochemical diversity, since both *cis*- and *trans*-diastereoisomers can be generated in a facile manner.

Scheme 3.1 *Synthesis of the core scaffold* ***3.1.1***.



For diversification, a simple strategy employing esterification and Huisgen [3+2] cycloaddition on the propargyl moiety was utilized (Figure 3.3). Alternatively, Mitsunobu alkylation of the carbinol, followed by Huisgen [3+2] cycloaddition, would provide the diastereoisomer (*L-cis*-hydroxyproline-derived compound). The protocol was fine-tuned to carry out these processes in a one-pot (esterification-click) and one-pot sequential manner (Mitsunobu-click). A 135/158-member compound library was generated utilizing these protocols.

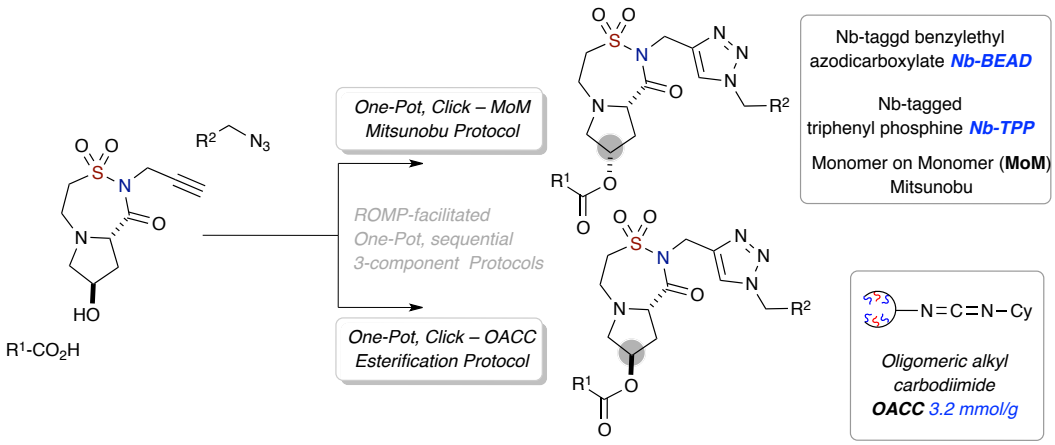


Figure 3.3 *Stereochemical diversification via Mitsunobu and esterification.*

3.1.1 Results and Discussion

For the one-pot click esterification protocol, an oligomeric alkyl carbodiimide (OACC) [7] was employed as the coupling reagent and the click reaction was carried out in the

same pot utilizing a protocol previously developed in the Hanson laboratory.[8] Minimal optimization was required for the employment of this methodology. The first condition investigated utilized 1 equivalent of scaffold, 1.1 equivalents of azide, 1.1 equivalents of carboxylic acid, 10 mol% equivalents of CuI as well as 10 mol% equivalents of DBU and DMAP along with 1.1 equivalents of OACC yielding 54% of the product. Increasing the mol% of CuI to 30 resulted in a slight decrease in the yield, and heating at 50ºC also resulted in a 45% yield. Increasing the mol % of CuI to 30 mol% and DBU as well as DMAP to 50 mol% again resulted in a similar yield. However, a marked increase in yield was noticed with

Scheme 3.2 *One-pot, click esterification protocol.*

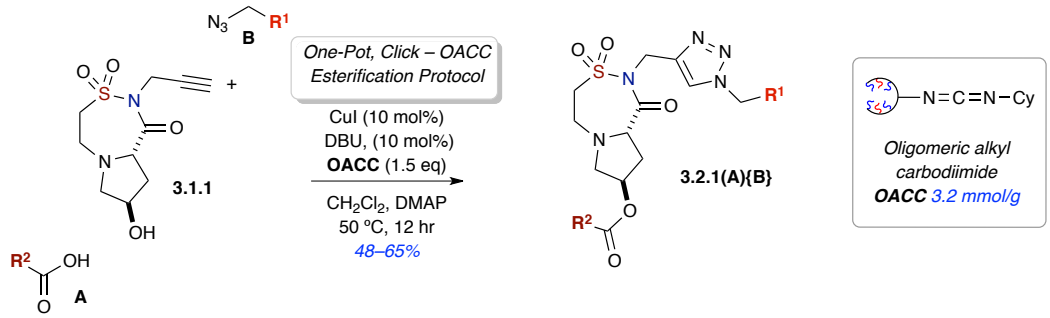


Table 3.1 *Optimization of conditions for the one-pot, click esterification protocol.*

entry[a]	azide (1) (equiv.)	RCO_2H {1} (equiv.)	CuI (mol %)	DBU (mol%)	DMAP (mol%)	OACC (equiv.)	Temp.	Isolated yield (%)
1	1.1	1.1	10	10	10	1.1	rt	54%
2	1.1	1.1	30	10	10	1.1	rt	45%
3	1.1	1.1	30	10	10	1.1	50ºC	47%
4	1.1	1.1	30	50	50	1.1	rt	46%
5	1.1	1.1	**30**	**10**	**10**	1.5	50ºC	**64%**

[a]Reactions carried out utilizing **3.1.1** (50 mg, 0.2 mmol, 1 equiv.) in 0.5 M CH_2Cl_2 for 12 hrs

30 mol% CuI, 10 mol% DBU and DMAP, 1.1 equiv. azide and carboxylic acid and most notably, increasing the equivalents of OACC to 1.5 at 50ºC afforded the desired product in 64% yield in a one-pot protocol over two steps (84% yield per reaction). This protocol was considered adequate for the synthesis of a library.

Stereochemical diversification was further exploited by utilizing the Mitsunobu reaction to furnish the *cis*-diastereoisomer from the same starting material. Steps were taken for the development of a one-pot, sequential click Mitsunobu protocol to access the derivatized *cis*-diastereomer as shown in Scheme 3.4. This streamlined route would avoid utilizing expensive *L-cis*-hydroxyproline, as well as proceeding through the whole process of making a new starting material, emphasizing the importance of the Mitsunobu reaction, which affords the *cis*-diastereoisomer of the esterified product in a single step. In addition, developing a one-pot, sequential protocol for both the Mitsunobu and click reactions was deemed challenging, as any remaining unspent triphenyl phosphine (utilized in the Mitsunobu) and azide (utilized in the click) would react with each other to form an iminophosphorane, which on hydrolysis would yield the corresponding amine (Staudinger reaction).[9] The Mitsunobu reaction, being more sensitive, was performed first followed by addition of the excess azide, CuI and DMAP to effect the Huisgen [3+2]. Even though the Mitsunobu reaction is widely used for stereospecific inversion of an alcoholic stereocenter, the purification procedure is tedious due to the formation of a number of side products. Thus, utilizing monomeric norbornenyl (Nb) tagged-BEAD and monomeric Nb tagged-PPh_3 for the Mitsunobu[10] reaction facilitated the purification of these reagents as well as of the by-

products, the monomeric norbornenyl (Nb) tagged-reduced-BEAD and monomeric Nb-tagged-PPh_3=O by application of ROMP sequestration using Nb-tagged silica as the last step.

In order to develop this protocol, a variety of conditions were investigated. The initial conditions employed included adding 1 equivalent of the scaffold, 1.2 equivalents of carboxylic acid, 1.2 equivalents of NB-BEAD, 1.2 equivalents of Nb tagged-PPh_3, in CH_2Cl_2 at rt and stirring for 10 minutes, followed by the addition of 2 equivalents of azide and subsequent addition of 20 mol % of CuI as well as 20 mol % of DBU followed by subsequent sequestration with the Grubbs second generation catalyst (**G-II** catalyst)[11] which afforded no product. Changing the equivalents of the acid component from 1.2 to 2.0 still afforded no product. Heating in THF at 45ºC afforded no product as well. However, when the reaction was carried out in THF at room temperature the required product was isolated in 26% yield after column chromatography. Increasing the equivalents of the azide to 3.0, and performing the reaction in THF at room temperature, as well as increasing the time for the Mitsunobu reaction from 10 minutes to 12 hours, provided a boost in the yield to 47%.

Further optimization revealed that addition of 1.0 equivalent of the scaffold, 1.2 equivalents of carboxylic acid, 1.5 equivalents of NB-BEAD, 1.5 equivalents of PPh_3, in THF at room temperature and running the reaction for 12 hours afforded the Mitsunobu intermediate with complete consumption of the starting material by TLC. After the completion of the Mitsunobu reaction, 3.0 equivalents of azide were added, followed by the addition of 20 mol% CuI and 20 mol% DBU (Table 3.2, entry 6). The reaction was run for another 12 h, and sequestered by the addition of the **G-II** catalyst[11] followed by the addition of Nb-tagged silica to scavenge the by-products and excess starting material. The

polymerization reaction was left to stir at 45ºC overnight, and was followed by cooling of the reaction to room temperature and subsequent addition of ethyl vinyl ether (EVE) to quench

Scheme 3.3. *One-pot, sequential click Mitsunobu protocol.*

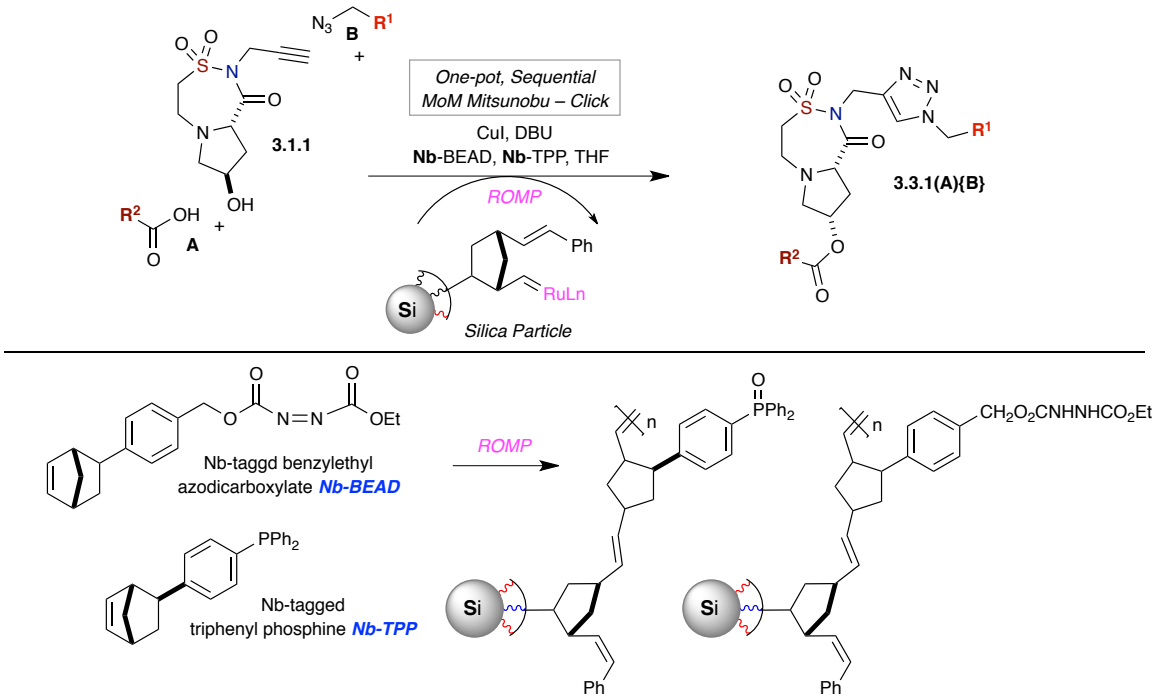


Table 3.2 *Optimization of one-pot, sequential click Mitsunobu protocol.*

entry[a]	azide {1} (equiv.)	RCO_2H (1) (equiv.)	CuI (mol %)	DBU (mol%)	Grubbs-II (mol%)	Nb-BEAD (equiv.)	Nb-PPh_3 (equiv.)	Solvent	Temp.	Isolated yield (%)
1	2	1.2	20	20	20	1.2	1.2	CH_2Cl_2	rt	No Pdt.
2	2	2	20	20	20	1.2	1.2	CH_2Cl_2	rt	No Pdt.
3	2	1.2	20	20	20	2	2	THF	45ºC	No Pdt.
4	2	1.2	20	20	20	1.2	1.2	THF	rt	26%
5	3	1.2	20	20	20	1.2	1.2	THF	rt	47%
6	3	1.2	20	20	20	1.5	1.5	THF	rt	63%

[a]Reactions carried out utilizing **3.1** (10 mg, 0.04 mmol, 1 equiv.) for 12 hrs

the reaction. The reaction was run for an additional 30 minutes, followed by addition of EtOAc, and filtration through an SiO_2 SPE. After purification through a column, the final product was obtained in 63% yield. These reaction conditions were considered satisfactory to carry on to a library platform. After optimizing the conditions, a prototype library was synthesized utilizing the click-esterification protocol employing 4-fluorobenzoic acid and azides {1}, {2}, {3}, {9} and {10} as shown in Table 3.3.

Table 3.3. *Prototype library demonstrating utilization of carboxylic acid **1** with azides azides {1}, {2}, {3}, {9} and {10} Scaffold (Carboxylic acid, {Azide}).*

entry[a]	Compound	Isolated yield (%)	entry[a]	Compound	Isolated yield (%)
1	**3.2.1(1) {1}**	92	4	**3.2.1 (1) {4}**	68
2	**3.2.1 (1) {2}**	77	5	**3.2.1 (1) {9}**	64
3	**3.2.1 (1) {3}**	74	6	**3.2.1 (1) {10}**	54

All samples were submitted to purification by reverse-phase automated mass-directed LCMS. The LCMS traces showed these compounds could be easily purified, and the yields were good to excellent.

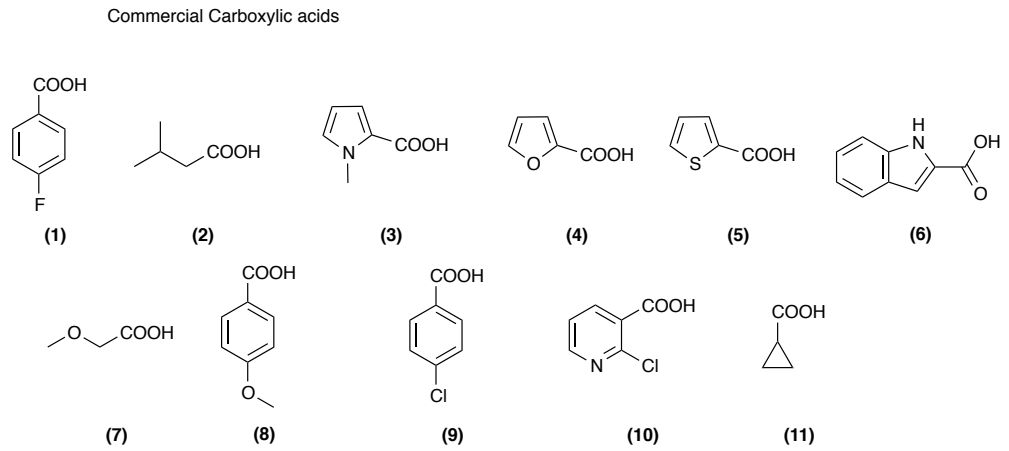


Figure 3.4a. *Carboxylic acids (**1–11**) building blocks for the click esterification library.*

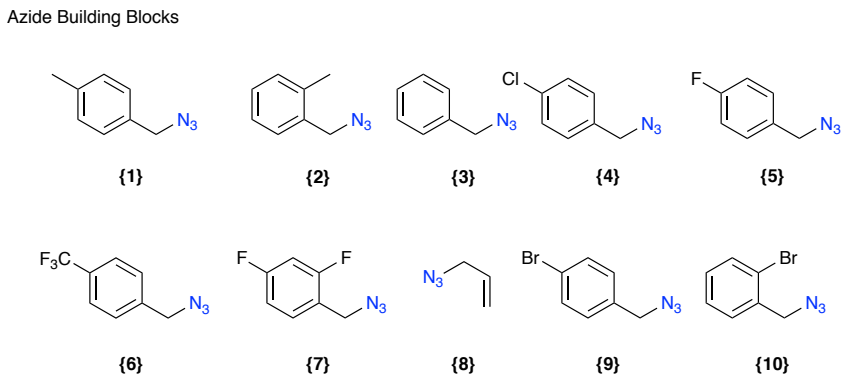


Figure 3.4b. *Azides {1–10} building blocks for the click esterification library*

After successful synthesis of the prototype library, a 110-member library utilizing the one pot click-esterification methodology was synthesized. The carboxylic acids and the azides utilized for this library are shown in Figure 3.4. A 48-member library utilizing click-Mitsunobu was also synthesized utilizing carboxylic acids and azides as shown in Figure 3.5.

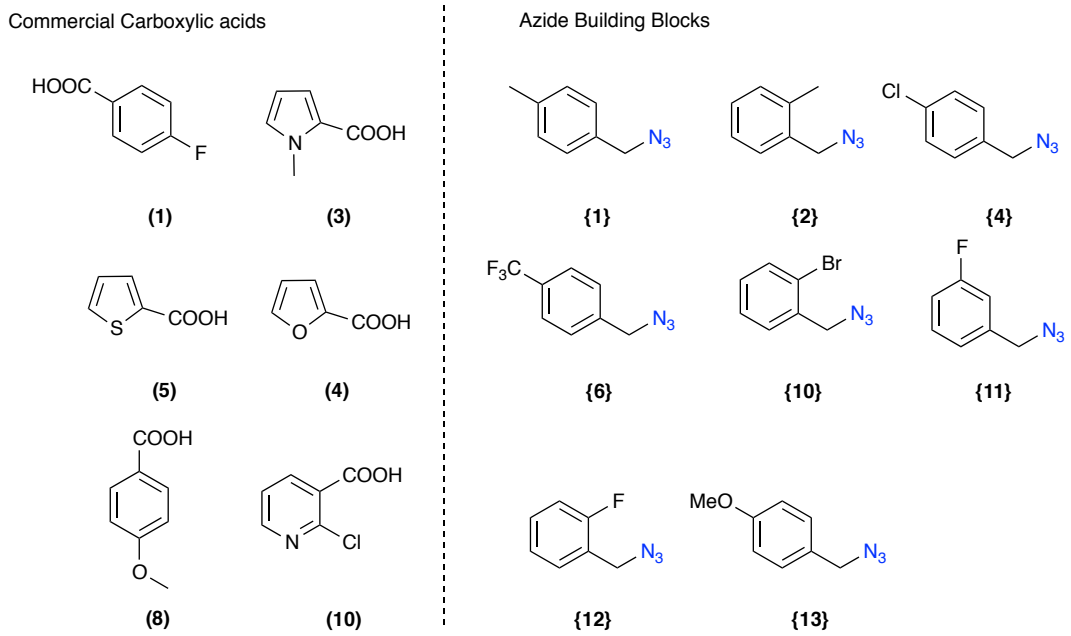


Figure 3.5. *Carboxylic acids (1), (3), (4), (5), (8), (10) and azides {1}, {2}, {4}, {5}, {6}, {10}, {11},{12}, {13} building blocks for the click Mitsunobu library.*

Efficacious synthesis of 98/110 compounds from one-pot click-esterification protocol and 37/48 compounds from the click Mitsunobu protocol was carried out possessing >90% purity by automated mass-directed LCMS. A total of 135 acyl sultams were successfully generated (85% success rate) with purities >90%. Building blocks for the click Mitsunobu library are shown in Figure 3.5. All samples were submitted to purification by reverse-phase automated mass-directed LCMS.

Overall, the core scaffold was synthesized on a multigram scale by utilizing a one-pot sulfonylation, Michael and amidation protocol. Two libraries of triazole-containing hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide were synthesized. The libraries were synthesized by one-pot protocols utilizing either a one-pot click-esterification or a one-pot click-Mitsunobu protocol. The success rate of these protocols was 85%. The minimal optimization indicated the applicability and generalizability of these protocols to other complicated systems. The employment of esterification and Mitsunobu showcased the importance of stereochemical diversity attainable in a single step from the same starting material. These acyl sultams are a diverse set of molecules that have not been reported and which are currently being submitted for evaluation of their biological activity in high-throughput screening efforts.

Section: 3.2 Modular One-pot, Sequential Protocols Towards Diverse Acyl Sultam Libraries

Part 2 of chapter 3 describes an efficient one-pot, sequential 4-component protocol to access a library of stereochemically-rich acyl sultams containing varied elements of skeletal and peripheral diversity. A sequence involving a 4-component procedure that includes sulfonylation, Michael and EDC coupling, followed by a fourth reaction: (i) a [3+2] Huisgen cycloaddition when propargyl amine was utilized in the sulfonylation step and (ii) carbamoylation when L-hydroxyproline was employed in the aza-Michael reaction to form scaffolds with skeletal and peripheral diversity (Figure 3.6).

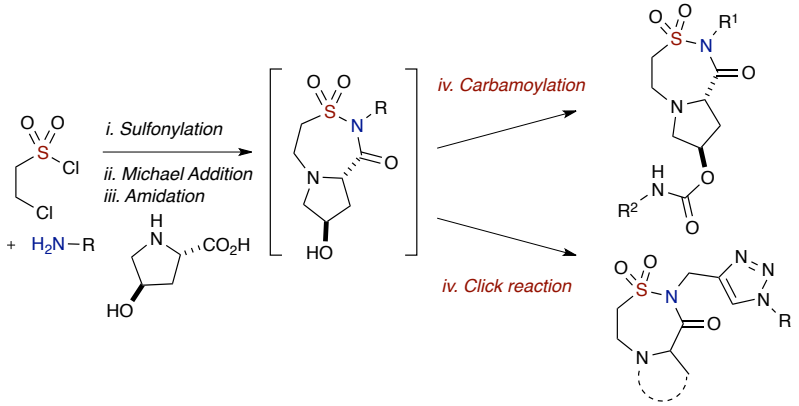


Figure 3.6. *One-pot, four component protocol.*

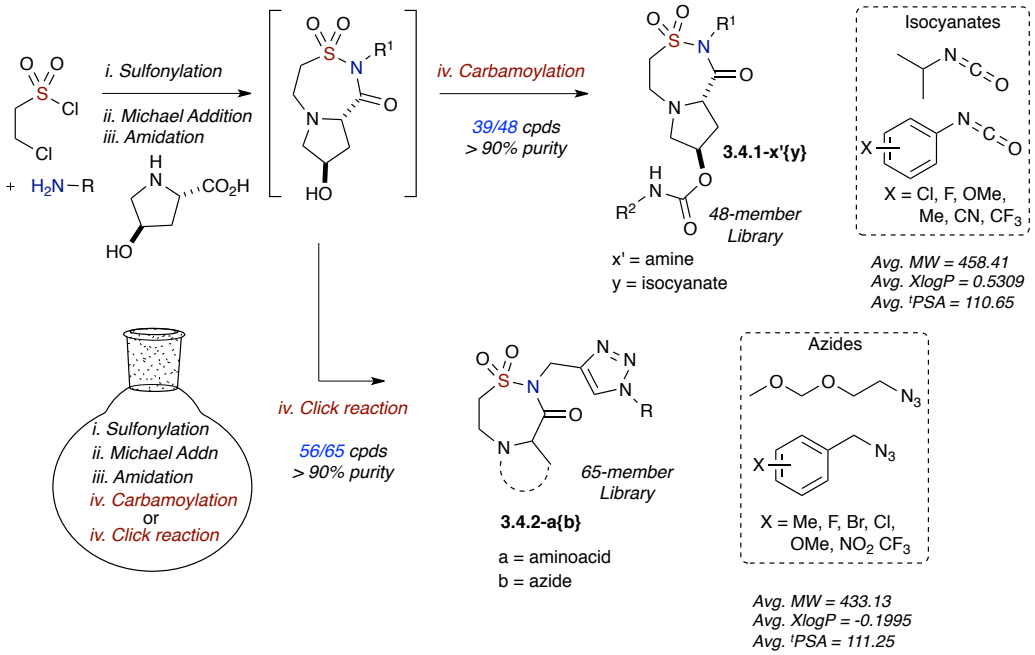
One-pot, sequential multicomponent protocols are versatile strategies to rapidly generate structurally distinct and complex moieties in an efficient manner. These methods have important ramifications in economical, environmental and synthetic aspects and as a result, these procedures have gained prominence in modern organic synthesis.[12] One-pot, sequential strategies can be utilized to effect multiple transformations in the same flask thus, avoiding several purification steps and minimizing hazardous chemical waste making this

process green and eco-friendly. In contrast, these one-pot/one-pot sequential transformations have several obstacles that need to be circumvented. Some of these hurdles include compatibility of the multiple reactions; side products from earlier reactions may interfere with the one-pot protocols and minimal usage of solvents and reagents. Nevertheless, these one-pot protocols are highly desirable for the utility of time, energy and purification as well as less accumulation of waste.

Application of these one-pot, sequential protocols to diversity-oriented synthesis (DOS) has emerged as a facilitating platform for the synthesis of new heterocyclic small molecules for high throughput screening (HTS).[13] Within the realms of DOS, accessing diversity elements including skeletal, stereo-chemical, functional and appendage on small multiple scaffold libraries are highly desired for probing chemical space. Incorporating these essential elements into library synthesis generally affords considerable 'molecular shape space' coverage, which correlates to broad biological space.[14]

Keeping these parameters in mind a second one-pot, sequential 4-component protocol was developed involving sulfonylation of amine with 2-chloroethane sulfonyl chloride, followed by the Michael reaction with an amino acid and subsequent amide cyclization to access desired acyl sultam scaffolds followed by either a carbamoylation or Huisgen [3 + 2] affording the desired diversified products. Two pathways were envisioned – (i) sulfonylation with propargylamine afforded a propargylic handle for a click reaction as the fourth step providing the triazolated product and (ii) aza-Michael reaction with hydroxyproline afforded a hydroxyl functional handle for carbamoylation with isocyanates.

Scheme 3.4. *One-pot, sequential 4-component pathways to diverse sultams.*



3.2.1 Results and Discussion

Library Synthesis. The one-pot, sequential 4-component protocol commenced with the sulfonylation of an amine utilizing 2-chloroethane sulfonyl chloride in the presence of Et_3N and CH_2Cl_2 followed by removal of the solvent *in vacuo* and then subsequent Michael addition with the corresponding amino acid using Et_3N as the reaction promoter/proton scavenger and MeOH:H_2O 1:1 as the solvent. The reaction went to completion only after stirring for 12 h at 60 ºC and the resulting concentrated crude mixture proceeded to the amidation step with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt), Et_3N and DMF as solvent.

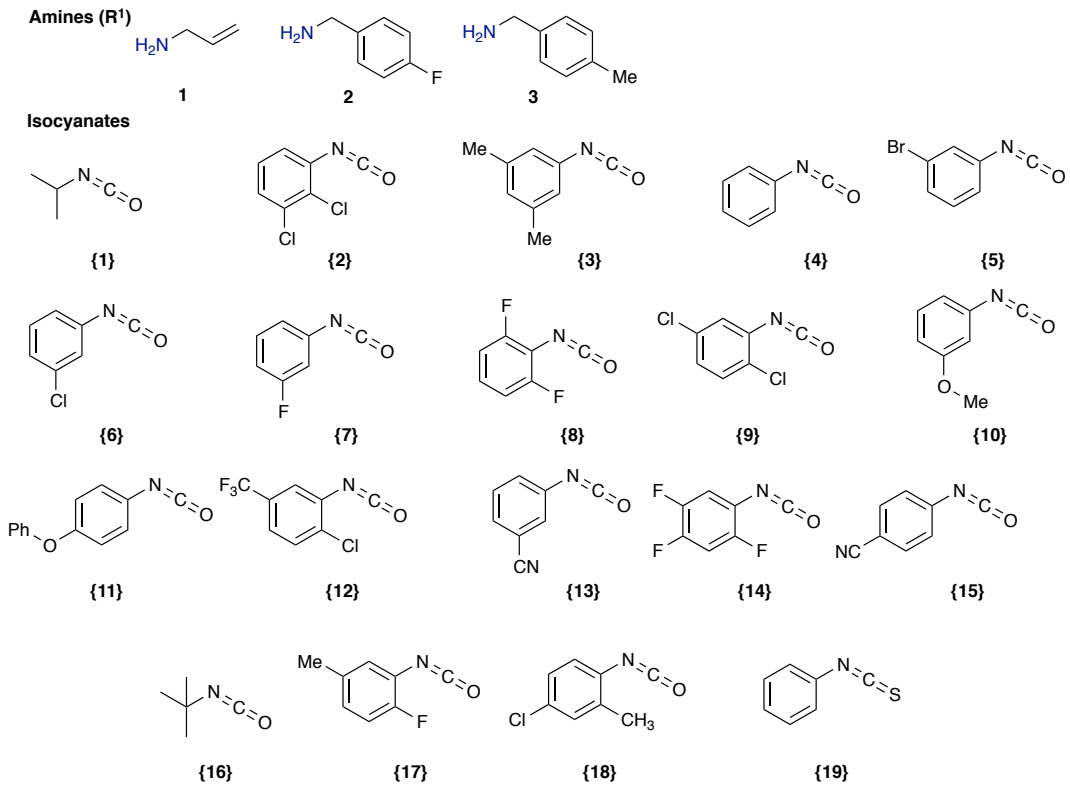


Figure 3.7. *One-pot, sequential 4-component utilizing isocyanates to carbamates.*

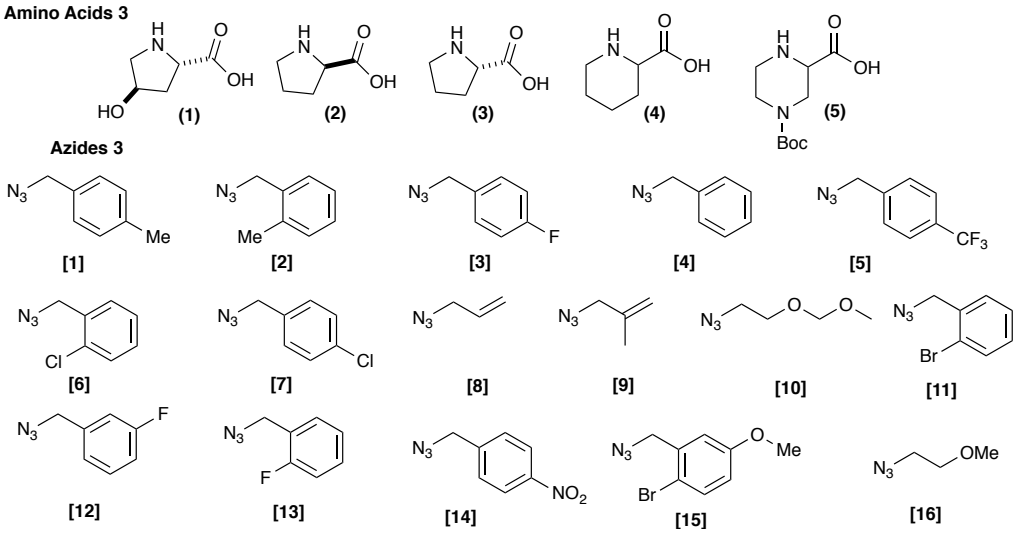


Figure 3.8. *One-pot, sequential 4-component utilizing azides for the click reaction.*

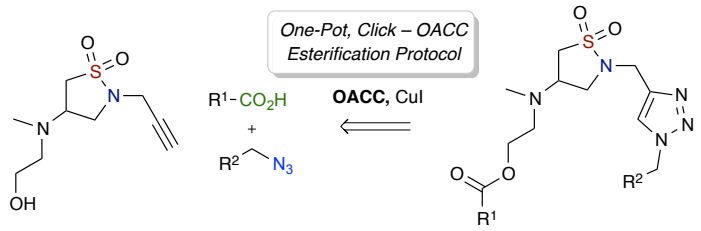
This was followed by distributing the DMF (containing the product) into small vials of equal volume followed by the evaporation of the solvent and then addition of CH_2Cl_2 as the new solvent, followed by the addition of a stock solution of DMAP and the isocyanate. The reaction was run at 50ºC for 12 hours followed by washing with water and extraction of the water layer with EtOAc. The starting materials for this protocol are shown in Scheme 3. Similarly for the click reaction, DMF was distributed into small vials followed by evaporation as before followed by the addition of CH_2Cl_2/t-BuOH/H_2O in a 1:1:1 ratio. This was followed by the addition of the azide, $CuSO_4$ and sodium-*L*-Ascorbate. The reaction was then run for 12 hours washed with water and extracted with EtOAc. The amines and isocyanates utilized for the carbamate library are shown in Scheme 3 while the amino acids and azides employed for the click library are shown in Scheme 4. The diversity reagents were selected based on the physico-chemical property filters that were applied during the in silico analysis (see Supp Info).

Over all, the automated production of a library of 66/85-member triazolated 1,2,5-thiadiazepane 1,1-dioxides and 39/48-member carbamate library was successfully completed. The products have been submitted for evaluation of their biological activity in high-throughput screening assays at the NIH MLPCN and the results will be reported in due course.

Section: 3.3 Triazole-containing Isothiazolidine 1,1-dioxide Library Synthesis: One-Pot, Multi-Component Protocols for Small Molecular Probe Discovery

Part 3 describes the synthesis of two libraries of triazole-containing isothiazolidine 1,1-dioxides employing either a one-pot click-OACC esterification protocol. The core dihydroisothiazole 1,1-dioxide scaffold was synthesized rapidly on multi-gram scale via RCM. Next, three daughter scaffolds were generated by the aza-Michael of three amino alcohols. The scaffolds were diversified by a one-pot, multi-component click-esterification protocol utilizing a ROMP-derived coupling reagent (OACC) to generate a 41-member library of triazole-containing isothiazole 1,1-dioxides (Figure 3.9).

Figure 3.9. *One-pot, click esterification.*



A new chemotype, the β-amino sultams and their corresponding sulfonate analogues have shown interesting biological properties. Such reports include the inhibition of HIV-1 replication and antibacterial activity (Figure 3.10).[15]

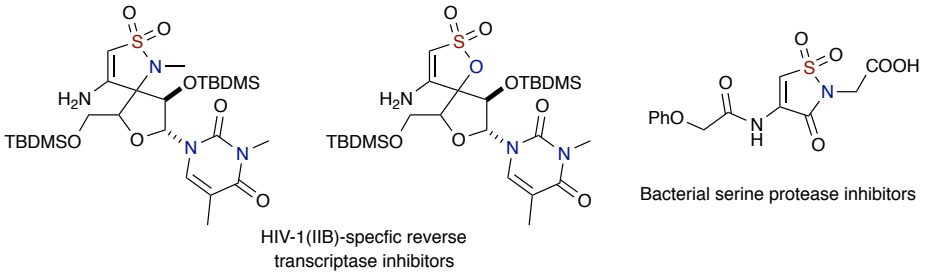


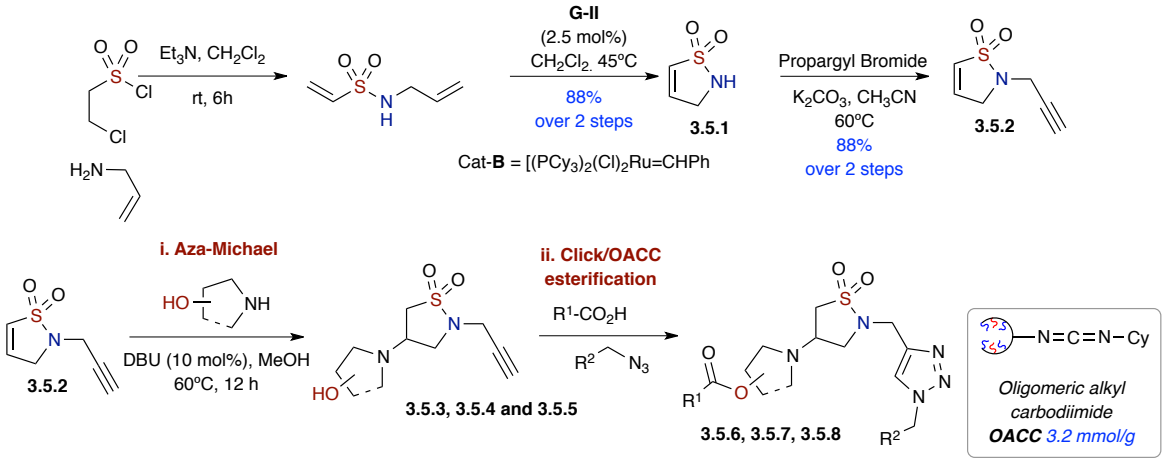
Figure 3.10. *Biologically active β-amino sultams and sulfonates.*

Ring closing metathesis (RCM)[16] can be utilized for the synthesis of 5-, 6- and 7-membered sultams from the corresponding vinyl and allyl sulfonamides. When the RCM is carried out with vinyl sulfonamides, the corresponding sultam retains the α,β-unsaturated functionality incorporated within the ring, and can be further diversified utilizing hetero-Michael reactions. Hetero-Michael reactions have been broadly utilized to access a variety of heterocycles.[17] The Michael reaction is also an efficient cyclization protocol to access a variety of sultam motifs leading to the proposed triazole-containing isothiazolidine 1,1-dioxide library.[18]

3.3 Results and Discussion

The corresponding core scaffold 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **3.5.1** was rapidly generated on multi-gram scale *via* a 3-step sulfonylation, RCM, propargylation protocol (Scheme 3.5). Notably, the addition of metathesis catalyst [(IMesH$_2$)(PCy$_3$)(Cl)$_2$Ru=CHPh] (**G-II**),[11] in 5 equal portions every 30 minutes was key to maintaining the observed high conversation of the RCM cyclization.

Scheme 3.5. *Gram-scale syntheses of core 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **3.7** via RCM.*



Diversification was achieved by utilizing two orthogonal reaction pathways, the Huisgen [3+2] and the esterification reaction. The esterification was carried out by the utilization of an immobilized, soluble ROMP-derived coupling reagent OACC.[19] This high load reagent afforded efficient coupling of a variety of acids with **3.9**, **3.10** or **3.11**, followed by facile removal via a simple precipitation/filtration protocol.

Three daughter isothiazole 1,1-dioxide scaffolds **3.5.3**, **3.5.4** and **3.5.5** were synthesized by utilization of aza-Michael of the corresponding amino alcohols with dihydroisothiazole 1,1-dioxide **3.5.2** in an efficient multi-gram synthesis. After the synthesis of these core isothiazole 1,1-dioxide (**3.5.3**, **3.5.4** and **3.5.5**) scaffolds prepared, a 90-member library was designed (Figure 3.11).

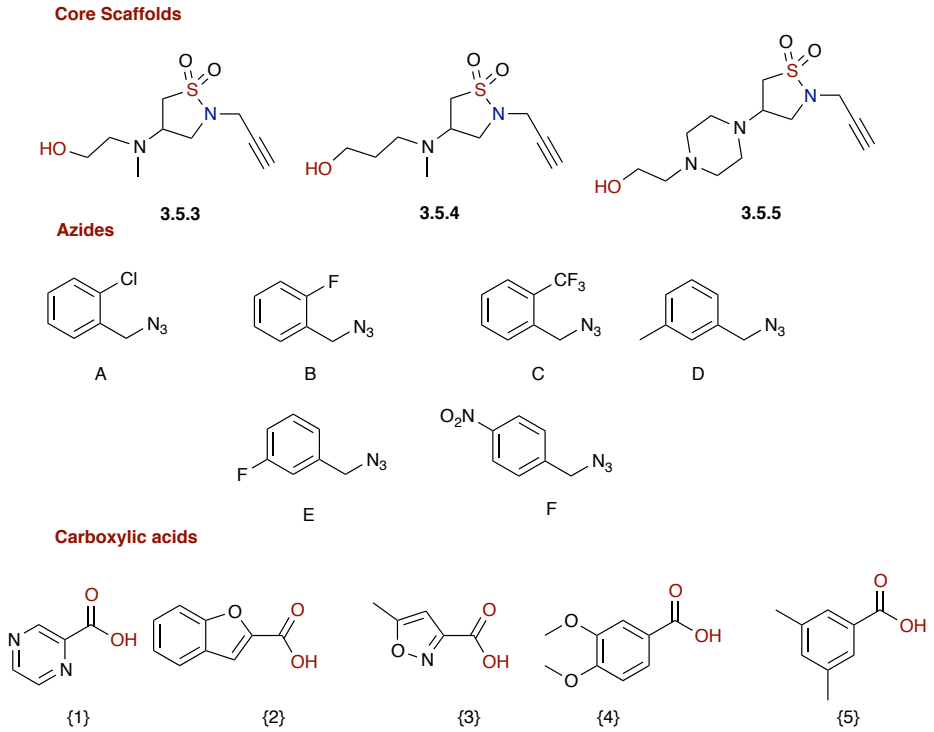
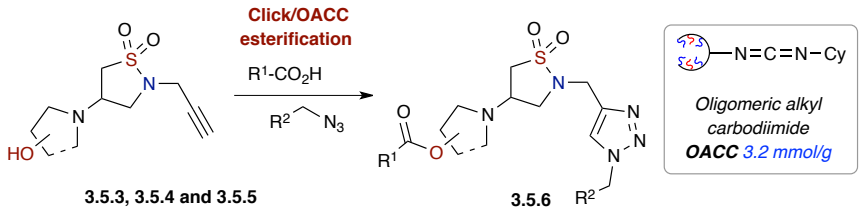


Figure 3.11. *Core Scaffolds* **3.5.3**, **3.5.4** and **3.5.5**, *azide building blocks* ***A–F*** *and acid building blocks {1–5}.*

A one-pot click/OACC esterification protocol for the synthesis of the library was achieved utilizing 1.2 equivalents of acid {1–5}, azide (2 equiv.), OACC (1.5 equiv.), CuI (30 mol%), DBU (10 mol%) and anhydrous CH_2Cl_2 (Table 3.4). Reactions were carried out at 50 ºC for 12 h, whereby upon completion the crude reactions were diluted, filtered and concentrated. Utilizing these conditions, an initial validation set of isothiazolidine-1,1-dioxides was investigated to evaluate the reaction conditions (Table 3.4).

Table 3.4. *One-Pot, click/OACC esterification.*



entry	scaffold	azide	acid	yield (%)
1	**3.5.3**	D	1	48
2	**3.5.3**	A	2	52
3	**3.5.3**	A	3	47
4	**3.5.3**	A	3	60
5	**3.5.4**	A	2	40
6	**3.5.4**	A	3	42
7	**3.5.4**	A	3	43

[a] Reaction conditions: Isothiazole 1,1-dioxide (40 mg, 1 equiv.), acid (1.2 equiv.), azide (2 equiv.), OACC (1.5 equiv.), CuI (30 mol%), DBU (10 mol%), dry CH_2Cl_2 (0.2M), 50 ºC, 12 h. [b] Isolated yields after standard column chromatography (EtOAc, R_f = 0.3–0.6).

Upon completion, the validation set was diluted in EtOAc to precipitate the spent oligomer, followed by filtration through silica SPE and concentration. All samples were purified by column chromatography, characterized and then submitted to purification by

reverse-phase automated mass-directed LCMS. Despite their stability when isolated after standard chromatography, it was observed that esters generated with acids {**1**} and {**3**} underwent complete hydrolysis during automated mass-directed LCMS. Analysis indicated that after successful purification, hydrolysis occurred during the final step of removal of the solvent utilized (CH_3CN, H_2O, DMSO and NH_4OH). Due to this observation, another library was redesigned removing acids {1} and {3} to propose a 54-member library.

Under these conditions, 41 out of 54 compounds were successfully isolated >90% purity after purification by automated mass-directed LCMS. Crude reaction analysis indicated that all 54 reactions worked, however it is proposed that the failed reactions and low yields observed were due to hydrolysis of the desired product in the final stages of purification.

In conclusion, a library of triazole-containing isothiazolidine 1,1-dioxides was prepared utilizing a click-esterification protocol for utilization in HTS screening collections. A 41-member library of triazole-containing isothiazole 1,1-dioxide library was prepared *via* a one-pot, click/OACC esterification utilizing a soluble oligomeric coupling reagent OACC. This screening set of sultams represent a diverse motif not currently reported and have been submitted for evaluation of their biological activity in high-throughput screening.

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Chapter 4:

ROMP-Facilitated Sequestration Protocols Towards the Synthesis of Sultams

Section 4.1 Facilitated Intermolecular Monomer-on-Monomer (MoM) Mitsunobu Reaction on Hydroxy-pyrrolo Thiadiazepin-dioxide Scaffolds

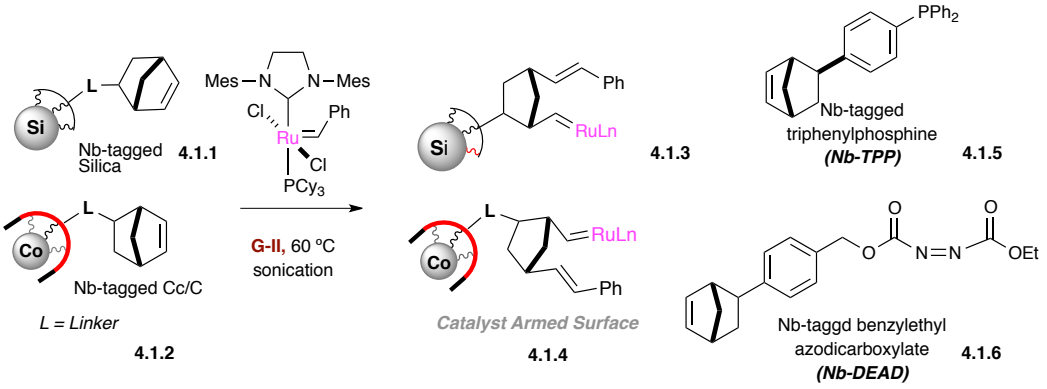
The Mitsunobu Reaction, discovered by Prof. Oyo Mitsunobu[1] in 1967, is a stereospecific redox reaction of an alcohol and a carboxylic acid in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) to furnish the corresponding ester with inversion of stereochemistry. The Mitsunobu reaction has a number of variants[2] that have a privileged role in organic synthesis and medicinal chemistry due to its ability to access small molecules for drug discovery.[3] It also provides stereospecificity, compatibility with a wide range of functional groups, wide substrate scope and mild reaction conditions. Utilizing the Mitsunobu reaction, primary or secondary alcohols can be substituted by nucleophiles employing a redox combination of a trialkyl or triarylphosphine and a dialkyl azodicarboxylate (usually DEAD or DIAD) yielding the C-C, C-S, C-N, and C-O bond formation, as well as inverting the stereochemistry of the alcoholic moiety without the need for pre-activation of the alcohol. The Mitsunobu reaction is also promoted under relatively mild conditions by a combination of a tertiary phosphine and an azodicarboxylate, usually triphenylphosphine (PPh_3) and diethyl or diisopropyl ester (DEAD or DIAD), respectively.

Despite these attributes, one major drawback of this reaction is the tedious and time-consuming purification protocols usually required for the isolation of the pure product from the unreacted reagents (DEAD, PPh_3) and by-products (reduced DEAD and $O{=}PPh_3$). Due to these implications the Mitsunobu is not ideal for parallel synthesis and high-throughput chemistry, and thus has inspired several variants aimed at circumventing purification issues.[4]

We have reported separation-friendly strategies utilizing ring opening metathesis

polymerization (ROMP) reagents in order to facilitate the isolation of the products in the Mitsunobu reactions. These protocols included ROMP-derived oligomeric triphenylphosphine and oligomeric azodicarboxylate on a polymer-on-polymer (PoP) Mitsunobu reaction[5] under purification-free processes and a monomer-on-monomer (MoM) [6] Mitsunobu reaction, employing monomeric norbornenyl-tagged triphenylphosphine and benzyl/ethyl azodicarboxylate reagents followed by subsequent sequestration. The sequestration in the second case was carried out using ring-opening metathesis polymerization (ROMP) initiated by any one of these three methods utilizing Grubbs catalyst[7] [$(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, **G-II**]: (i) free Grubbs catalyst in solution, (ii) silica-armed surface or (iii) surface-immobilized catalyst-armed with Co/C magnetic nanoparticles (Nps) (Scheme 4.1).

Scheme 4.1: *Surface-immobilized catalyst-armed silica and Co/C magnetic nanoparticle.*



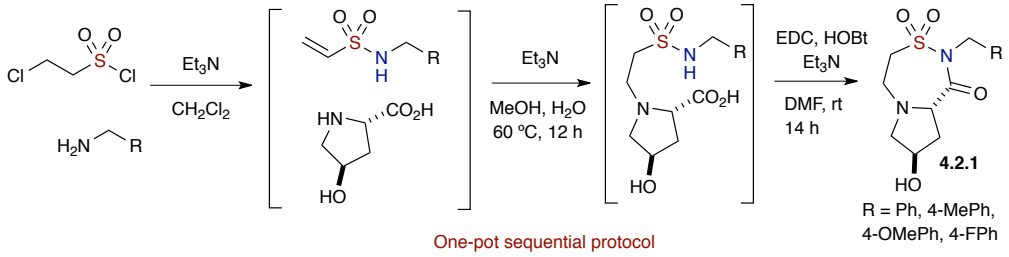
4.2 Results and Discussion

In 2011, Hanson and co-workers reported the first use of MoM Mitsunobu[6a] as well as its use for the synthesis of benzofused thiadiazepine-dioxides[6b] *via* an intramolecular 7-membered MoM Mitsunobu cyclization reaction. Facile purification was accomplished utilizing ROMP sequestration initiated by free metathesis catalyst or

catalyst-armed particle surfaces. Building on these efforts, we have developed an intermolecular MoM Mitsunobu esterification and etherification on hydroxy-pyrrolo thiadiazepin-dioxide scaffolds to generate heterocyclic molecules.

The hydroxy-pyrrolo thiadiazepin-dioxide scaffolds were rapidly synthesized *via* sulfonylation on the 2-chloroethane sulfonyl chloride followed by a Michael addition of *L-trans*-hydroxyproline to vinyl sulfonamide affording the desired Michael adduct (Scheme 4.2).[8] The cyclization was effected by the addition of EDCI, HOBT and Et_3N in DMF as a solvent to generate the hydroxypyrrolo-thiadiazepin 1,1-dioxide scaffolds in good yields.

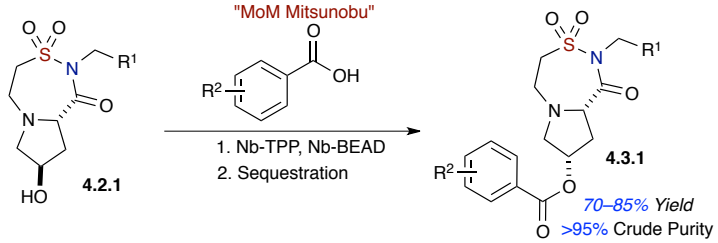
Scheme 4.2. *Synthesis of hydroxy-pyrrolo thiadiazepin-dioxide scaffolds.*



After synthesizing the bicyclic acyl sultams (hydroxy-pyrrolo thiadiazepin-dioxide) in a one-pot sequential protocol, we carried out MoM-Mitsunobu esterification with different aromatic acids utilizing Nb-TPP and Nb-BEAD in THF to afford the esterified and etherified products with an inversion of stereochemistry (Scheme 4.3). The reaction mixture was purified by ROM polymerization utilizing addition of free metathesis catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh, **G-II**].[7] The protocol included the removal of THF from reaction mixture followed by ROM polymerization, which was carried out in degassed CH_2Cl_2 with the **G-II** catalyst. This was followed by precipitation of the spent reagents and by-products to generate the desired esterified/etherified

thiadiazepin-dioxide scaffolds in good yields and excellent crude purity. The typical multi-spot crude reaction mixture was purified, giving a single TLC spot for the product, utilizing the polymerization sequestration protocol. Precipitation of the excess reagents and by-products was carried out by slow addition of diethyl ether (Et_2O). Even though removal of the polymerized and spent reagents from the crude reaction mixture was successful, the method was still not ideal for a high-throughput platform. Thus, alternative sequestration methods were investigated, utilizing a catalyst-armed surface generated either from Nb-tagged silica or an Nb-tagged Co/C magnetic particle to yield the esterified/etherified hydroxypyrrolo-thiadiazepin-dioxide scaffolds without the need for SiO_2 purification.

Scheme 4.3. *Intermolecular MoM Mitsunobu esterification on hydroxypyrrolo-thiadiazepin-dioxide scaffolds.*



In the Nb-tagged SiO_2 method, sequestration of excess reagents and by-products was carried out after ROM polymerization, using Nb-tagged SiO_2. This method yielded products in >95% crude purity by simple filtration through Celite® SPE and collecting the solution, followed by evaporating the solvent. Alternatively, Nb-tagged Co/C magnetic particles were applied for the sequestration of excess reagents/spent reagents on the surface of the magnetic Co/C beads. Using this procedure, compounds could be obtained in good yields and >95% crude purity by collecting the nanobeads with an external magnet, decanting the solution and evaporating the solvent. The important thing to note

about this protocol is the ease with which it is carried out by simple introduction of an external magnet on the wall of the tube, being an operational advantage to conventional filtration techniques (Figure 4.1).

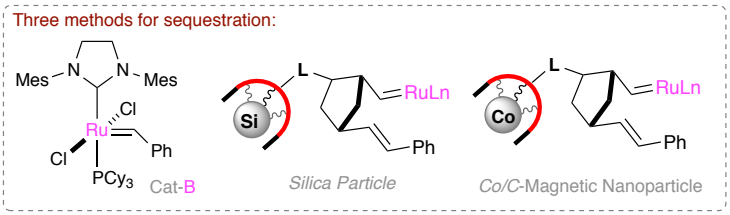


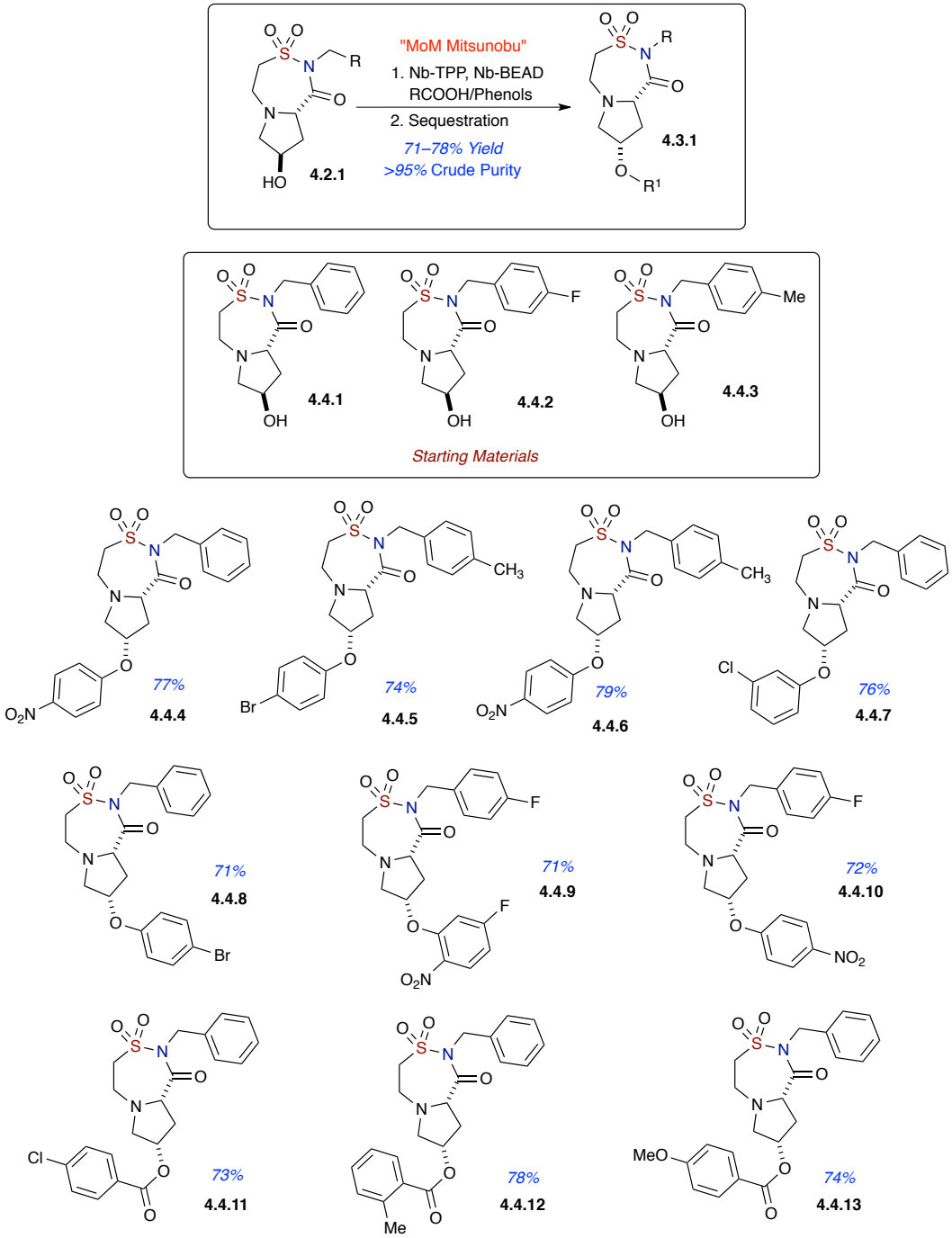
Figure 4.1: (a) *Sequestration utilizing Co/C magnetic nanoparticles* (a) *Nb-tagged Co/C nanoparticles* (c) *Nb-tagged silica particles*.

Building upon these results, the diversification of the scaffolds utilizing the MoM Mitsunobu were expanded to the etherification reactions on hydroxypyrrolo-thiadiazepin-dioxide scaffolds using the intermolecular MoM Mitsunobu reaction employing aromatic phenols to generate etherified and esterified sultams with inversion of stereochemistry **4.4.4–4.4.13** (Scheme 4.4).

4.3 Conclusion

In conclusion, MoM intermolecular Mitsunobu protocol was utilized for the esterification/etherification of hydroxypyrrolo-thiadiazepin-dioxide scaffolds synthesizing new heterocyclic sulfonamide molecules. Facile purification of crude reaction mixtures was carried out by utilization of ROM polymerization, which resulted in sequestration of excess reagents/spent reagents. Three methods of sequestration were utilized for the purification protocols that included; free metathesis catalyst **G-II**,[7] catalyst-armed surfaces generated from Nb-tagged Si-particles and catalyst-armed surfaces generated from Nb-tagged Co/C magnetic nanoparticles.

Scheme 4.4. *Intermolecular MoM Mitsunobu etherification on hydroxy-pyrrolo thiadiazepin-dioxide scaffolds.*



Section 4.4. Synthesis of epoxybenzo[d]isothiazole 1,1-dioxides via a reductive-Heck, metathesis-sequestration protocol

Development of new methodologies and technologies is required for the growing need of new pharmaceutical leads in high throughput screening.[9] Accessing novel heterocyclic scaffolds with a minimum number of steps is one key strategy being developed in modern drug discovery.

In order to facilitate protocols for the synthesis of compounds in an abridged manner, the integration of synthesis and purification has led to seminal advances in both combinatorial and parallel synthetic chemistry.[10] This approach is possible utilizing resin-bound substrates bearing excess reagents or employing solution phase substrates with excess immobilized reagents.[11] These protocols have been employed extensively in organic synthesis. Although less commonly encountered, there is a third scenario, which utilizes the excess precious starting material that can be recovered by ring opening metathesis polymerization. The promising approach would reclaim the starting material for further conversion to the desired product.

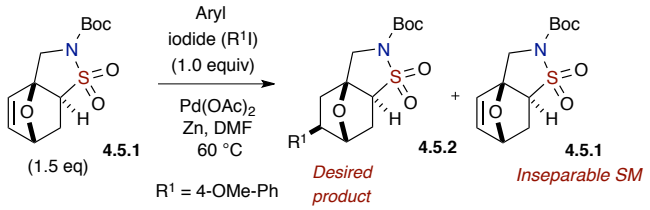
The following represents a new chromatography-free method for the synthesis of complex sultams[12,13] which affords easy isolation of reductive-Heck products and reclamation of excess starting material *via* sequestration by metathesis catalysts and catalyst-armed surfaces.

4.5 Results and Discussion

The Hanson group reported synthesis of a number of sultams derived by intramolecular Diels-Alder (IMDA) reactions to afford the oxa-norbornene scaffold **4.5.1** utilizing metathesis cascade protocols.[14] The core scaffold was synthesized on a gram-scale utilizing a method reported by Metz and coworkers.[15] This scaffold could undergo

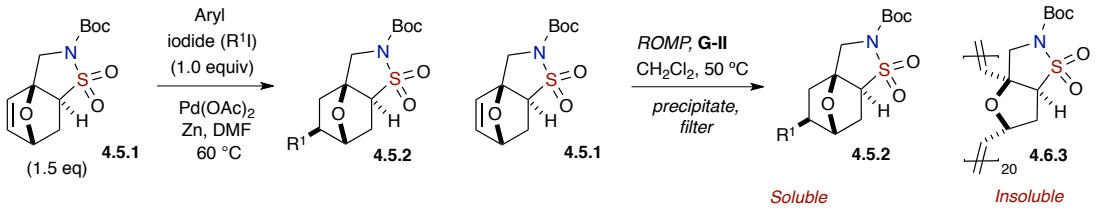
a ring-opening, ring-closing, cross-metathesis (ROM-RCM-CM) with a variety of CM partners in one-pot protocols. The diversification pathways were further expanded by investigating reductive Heck reactions with the scaffold **4.5.1**. It was noted that employing $Pd(OAc)_2$, Zn and excess scaffold **4.5.1** (1.5 equiv.) with the aryl coupling partner (1 equiv.) did push the reaction to completion.[16] Even though an excess of the scaffold **4.5.1** was utilized, only 60% of the product was obtained albeit with excellent regio- and diastereoselectivity (>19:1). The drawback was the difficulty of purification of the crude reaction mixture via standard chromatography because the R_f values of the desired product **4.5.2a** and the starting material **4.5.1** (Scheme 4.5) were nearly identical.

Scheme 4.5. *Reductive Heck diversification of **4.5.1** utilizing excess reagent.*



As previously noted, yields could be improved if an excess of scaffold **4.5.1** (1.5 equiv.) was employed. However, the usual purification protocols limited the application of this method for high-throughput generation of sultam derivatives **4.5.2**.[17] It was envisioned that the remaining starting material **4.5.1**, possessing an oxa-norbornene motif ("armed scaffold"), could be removed via exposure to metathesis catalyst and phase trafficking through ROM polymerization (ROMP) to afford the oligomeric scaffold **4.6.3**.[18,19] A simple precipitation of the oligomeric reagent would result in facile isolation of the desired product and the starting material oligomer could be recovered, an atom economical approach (Scheme 4.6).

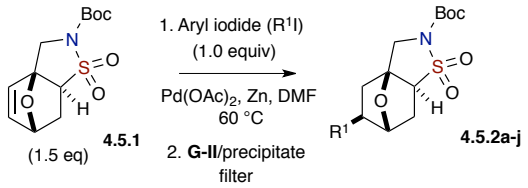
Scheme 4.6. *Reductive Heck diversification of **4.5.1** utilizing its excess.*



To test this protocol, we began with the reductive Heck reaction of the sultam **4.5.1** (1.5 equiv.) with 4-MeO-PhI (1 equiv.) in the presence of $Pd(OAc)_2$ and Zn in DMF at 60 ºC. When the reaction was complete, the mixture was filtered through Celite to remove Zn, concentrated, and subjected to ROM polymerization using the **G-II** catalyst.[7] Precipitation of the oligomeric starting material with ethyl acetate, followed by a filtration yield the reductive Heck sultam **4.5.2a** in 82% yield and >95% pure (Table 1, entry 1). Based on the success of the reductive-Heck, metathesis-sequestration protocol, nine aryl iodides were converted to reductive Heck products with yields ranging from 65 to 89% (Table 1, entry 2–10).

Although this protocol was successful, the required precipitation of each reaction was not suitable for application of this method as a high throughput platform. This was addressed by the employing a catalyst-armed surface generated from Nb-tagged silica particles.[20,21] This protocol was superior because purification only required filtration rather than added solvent (EtOAc) to precipitate the spent oligomer. Sultam **4.7.1** was subjected to standard reductive-Heck conditions and upon completion of the reaction

Table 4.1. *Reductive Heck, followed by ROMP sequestration.*

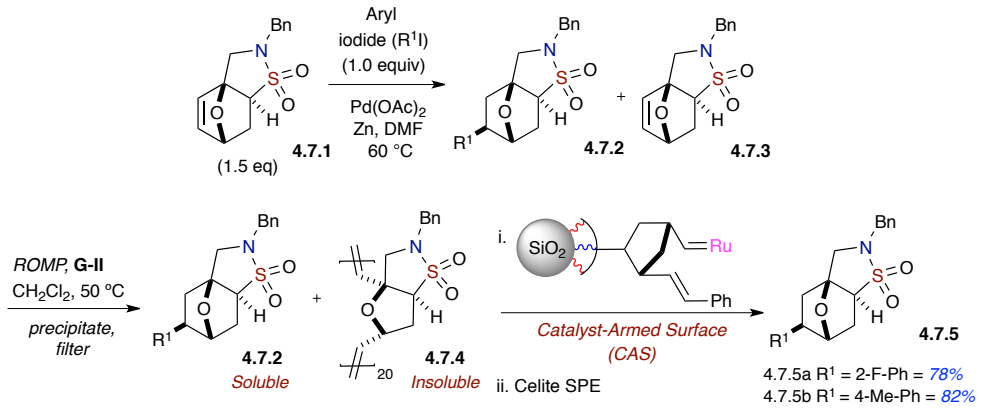


Entry	R^1	Yield %	Purity %[a]	Pdt.
1	*p*-CH_3O-Ph	82	>95	**4.5.2a**
2	*p*-F-Ph	77	>95	**4.5.2b**
3	*p*-CO_2CH_3-Ph	86	>95	**4.5.2c**
4	*p*-OH-Ph	89	>95	**4.5.2d**
5	*m*-F-Ph	82	>95	**4.5.2e**
6	3,5 di-CH_3-Ph	76	>95	**4.5.2f**
7	*p*-CH_3-Ph	75[b]	>95	**4.5.2g**
8	2-thiophene-Ph	81[b]	>95	**4.5.2h**
9	*p*-CF_3O-Ph	73 [c]	>95	**4.5.2i**
10	*p*-CN-Ph	65[c]	>95	**4.5.2j**

[a] Purity determined by ^{1}H NMR, [b] dr = 3:1 determined by ^{1}H NMR. [c] dr = 4:1 determined by ^{1}H NMR.

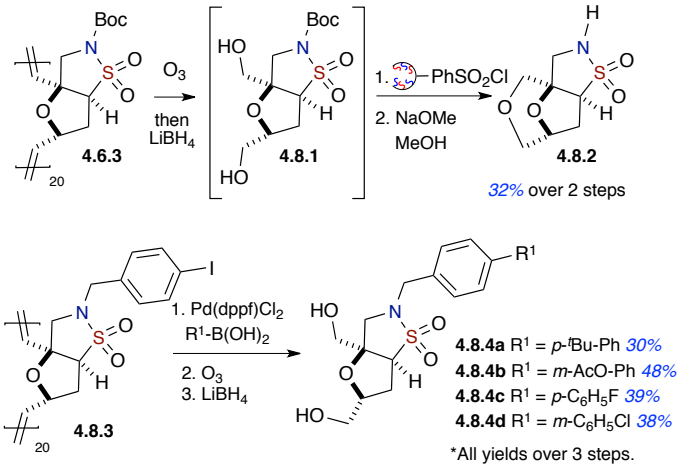
the crude mixture was cannulated into a reaction vessel containing "pre-armed" Nb-tagged Si-particles. This was monitered by heating for 30 minutes – 1 hr (TLC monitoring) and subsequent filtration of the crude reaction mixture through a Celite® SPE to furnish the desired product **4.7.5a-b** in good to excellent crude yields and greater than 95% purity (Scheme 4.7).

Scheme 4.7. *Sequestration of excess SM **4.7.1** via catalyst-armed Si-particles.*



After the reductive-Heck-metathesis sequestration protocol, the reclaimed oligomerized scaffold **4.6.3** was exposed to reductive ozonolysis[22] furnishing diol intermediate **4.8.1**, which on reaction with ROMP-derived oligomeric sulfonyl chloride (OSC)[23] yielded polyether **4.8.2** without a need for further purification (Scheme 4.8).

Scheme 4.8. *Diversification-release of corresponding derived-sultams from reclaimed oligomer **4.6.3**.*



The oligomer **4.6.3** was converted into **4.8.3** without further purification by deprotection and benzylation with benzyl iodide. The diversification and subsequent release of the oligomer was accomplished by a Barrett's vanishing support[24] protocol

using a 3-step Suzuki,[25] reductive ozonolysis that furnished the corresponding diols **4.8.4a–d** in good overall yield and purities. Filtration through SiO_2 SPE afforded pure products, whereas, in some cases, a simple filtration through a SiO_2 SPE provided X-ray quality crystals.

This methodology has several advantages, which include: atom economy, oligomeric starting materials (i.e. reclaimed scaffolds) were diversified to afford new compounds, additional linker (in contrast to traditional SPOC) were not needed, and parallel processing could be carried out with minimal waste stream.

4.6 Conclusion

ROM polymerization has been employed for the development of an atom-economical and purification friendly protocol for the diversification of sultam scaffolds *via* a reductive-Heck reaction. Isolation of reductive-Heck products and reclamation of excess oligomeric sultam scaffolds *via* precipitation were accomplished in a convenient manner utilizing chromatography-free methods. The recovered oligomeric scaffold was diversified into an array of new, skeletally diverse sultam scaffolds *via* a vanishing support protocol using solution phase processing. Furthermore this method can be exploited for different types of norbornene systems for high-throughput platforms.

4.7 References

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Chapter 5:

Supporting Information

Experimental for Chapters 2-4

5.1: Experimental for Chapter 2

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_2Cl_2 was purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Organometallics 1996, 15, 1518-1520). Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 from Mallinckrodt Chemicals (V120-25, Silica gel, 60 A, 40–63 **μ**m). Thin layer chromatography was performed on silica gel 60F254 plates (EMD-5715-7, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. 1H, 13C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz as well as a Bruker DRX-500 spectrometer operating at 500 MHz, 126 MHz respectively. The reference for $CDCl_3$ was set up at 7.28 ppm and acetone at 2.05 ppm. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained in one of two manners: (i) on a VG Instrument ZAB double-focusing mass spectrometer and (ii) on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). Gas chromatography (GC) was performed using an Agilent Technologies 6890N. GC/mass spectrometry was performed using a Quattro micro GC (Micromass UK Limited).

Rapid, Scalable Assembly of Stereochemically Rich, Mono- and Bicyclic Acyl Sultams

General Procedure A: preparation of vinyl sulfonamide. To a round bottom flask containing a solution of amine (1.0 equiv.) in dry CH_2Cl_2 (0.5 M), was added Et_3N (2.0 equiv.). The reaction mixture was cooled to 0 ºC, stirred for 20 min, after which 2-chloroethane sulfonyl chloride (1.0 equiv.) was added to the reaction mixture in a drop-wise fashion. The reaction was warmed to rt and stirred overnight. The reaction was quenched with 10% aq. HCl, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford the desired vinyl sulfonamide.

General Procedure B: one-pot, sequential (Michael and amide coupling). To a round-bottomed flask attached with a condenser/pressure tube containing a solution of sulfonamide (172 mmol, 1.0 equiv.) in MeOH (0.5 M) and water (0.5 M), was added Et_3N (516 mmol, 3.0 equiv.) followed by amino acid (172 mmol, 1.0 equiv.). The reaction mixture was stirred at 60 ºC for 12 h, after which the solvents were evaporated to dryness. To the crude mixture, DMF (0.05 M) was added, followed by EDC (344 mmol, 2.0 equiv.), HOBt (34.4 mmol, 0.2 equiv.) and Et_3N (344 mmol, 2.0 equiv.). The reaction was stirred at rt for 12 h followed by evaporation of DMF upon completion of reaction. Water was added to the crude mixture, which was extracted with EtOAc (2x). The organic layer was separated and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (100% EtOAc).

General Procedure C: one-pot, sequential 3-component (sulfonylation, Michael and amide coupling). To a round bottom flask/pressure tube containing a solution of amine (3.8 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.5 M), was added Et_3N (7.6 mmol, 2.0 equiv.). The reaction mixture was cooled to 0 ºC, stirred for 20 min followed by the drop-wise addition of 2-chloroethane sulfonyl chloride (3.8 mmol, 1.0 equiv.). The reaction was warmed to rt and left to stir overnight. CH_2Cl_2 was removed *in vacuo* upon completion of the reaction. MeOH (0.5 M),

water (0.5 M), Et_3N (11.4 mmol, 3.0 equiv.) and amino acid (3.8 mmol, 1.0 equiv.) were added to the reaction mixture, which was stirred at 60 ºC for 12 h, after which the solvents were evaporated to dryness. DMF (0.05 M) (for cyclic amino acids), EDC (7.6 mmol, 2.0 equiv.), HOBt (0.76 mmol, 0.2 equiv.) and Et_3N (7.6 mmol, 2.0 equiv.) were added to the crude mixture. The reaction was stirred at rt for 12 h, followed by evaporation of DMF. Water was added to the crude mixture, which was extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (100% EtOAc). For acyclic amino acids, $CHCl_3$ was utilized as the solvent, followed by addition of EDC (7.6 mmol, 2.0 equiv.), HOBt (0.76 mmol, 0.2 equiv.) and Et_3N (7.6 mmol, 2.0 equiv.). The reaction was stirred at 50 ºC for 12 h after which time; water (equal volume of $CHCl_3$ used) was added to the crude mixture and extraction of aqueous layer with EtOAc (2x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (100% EtOAc).

General Procedure D: one-pot, sequential 4-component (sulfonylation, Michael addition, amide coupling and carbamate formation. To a pressure tube containing a solution of amine (0.38 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.5 M), was added Et_3N (0.76 mmol, 2.0 equiv.). The reaction mixture was cooled to 0 ºC, stirred for 20 min, after which 2-chloroethane sulfonyl chloride (0.38 mmol, 1.0 equiv.) was added drop-wise. The reaction mixture was warmed to rt and left to stir overnight. CH_2Cl_2 was removed *in vacuo* upon the completion of reaction, followed by addition of MeOH (0.5 M), water (0.5 M), Et_3N (1.14 mmol, 3.0 equiv.) and amino acid (0.38 mmol, 1.0 equiv.). The reaction was stirred at 60 ºC for 12 h. Upon the removal of solvents, $CHCl_3$ (0.05 M) was added to the crude mixture followed by EDC (0.46 mmol, 1.2 equiv.), HOBt (0.076 mmol, 0.2 equiv.) and Et_3N (0.76 mmol, 2.0 equiv.) for the amide coupling reaction. The reaction was stirred at 50 ºC for 12 h, followed by evaporation of solvent. Carbamoylation commenced with addition of CH_2Cl_2 (0.5 M), isocyanate (0.76 mmol, 2 equiv.), DMAP (0.19 mmol, 0.5 equiv.) and Et_3N (0.76 mmol, 2 equiv.). The reaction was stirred overnight at 50 ºC after which time, water was added to the crude mixture, followed by extraction with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x). The

combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (1:1 EtOAc:Hexane).

General Procedure E: one-pot, sequential 4-component (sulfonylation, Michael addition, amide coupling and click reaction). To a pressure tube containing a solution of amine (0.38 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.5 M), was added Et_3N (0.79 mmol, 2.0 equiv.). The reaction mixture was cooled to 0 ºC, stirred for 20 min, after which 2-chloroethane sulfonyl chloride (0.38 mmol, 1.0 equiv.) was added drop-wise. The reaction was warmed to rt and left to stir overnight. After completion of the reaction, CH_2Cl_2 was removed under reduced pressure. MeOH (0.5 M), water (0.5 M), Et_3N (1.14 mmol, 3.0 equiv.) and amino acid (0.38 mmol, 1.0 equiv.) were next added to the mixture for the Michael reaction. The mixture was stirred at 60 ºC in a sealed tube for 12 h, after which the solvents were again evaporated to dryness. $CHCl_3$ (0.05 M) was added to the crude mixture followed by EDC (0.46 mmol, 1.2 equiv.), HOBt (0.076 mmol, 0.2 equiv.) and Et_3N (0.76 mmol, 2.0 equiv.) for the amide formation reaction. The reaction was stirred at 50 ºC for 12 h, followed by evaporation of solvent. Next, step-wise addition of CH_2Cl_2, alkyl azide and *t*-butanol was performed, followed by sequential addition of aqueous solutions of $CuSO_4$ (0.19 mmol, 0.5 equiv.) and L-Na-Ascorbate (0.23 mmol, 0.6 equiv.). The reaction was stirred overnight at rt, after which time, water was added to the crude mixture, followed by extraction with EtOAc. The organic layer was separated, and the aqueous layer extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (100% EtOAc).

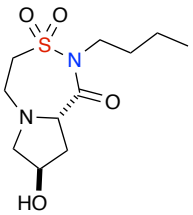
General Procedure F: one-pot, sequential 4-component (sulfonlation, Michael, amide coupling and esterification). A solution of amine (0.38 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.5 M), along with Et_3N (0.76 mmol, 2.0 equiv.) was added to a pressure tube. The reaction mixture was cooled to 0 ºC, stirred for 20 min, after which 2-chloroethane sulfonyl chloride (0.38 mmol, 1.0 equiv.) was added to the reaction mixture in a drop-wise manner. The reaction was warmed to rt and left to stir overnight. CH_2Cl_2 was removed *in vacuo* upon the completion of reaction, followed by addition of MeOH (0.5 M), water (0.5 M), Et_3N (1.14 mmol, 3.0 equiv.) and amino acid (0.38 mmol, 1 equiv.) for the Michael reaction. The reaction mixture was stirred at 60

ºC in a sealed tube for 12 h, after which solvents were evaporated to dryness. $CHCl_3$ (0.05 M) was added to the crude mixture followed by EDC (0.46 mmol, 1.2 equiv.), HOBt (0.076 mmol, 0.2 equiv.) and Et_3N (0.76 mmol, 2.0 equiv.) for the amide coupling reaction. The reaction was stirred for 12 h at 50 ºC. After completion of the reaction, additional EDC (0.46 mmol, 1.2 equiv.), HOBt (0.57 mmol, 1.5 equiv.), Et_3N (0.76 mmol, 2.0 equiv.) and carboxylic acid were added to the mixture for the esterification step. The reaction was again stirred overnight at 50 ºC. Upon completion of the reaction, water was added to the crude mixture, which was extracted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (1:1 EtOAc:Hexane).

General Procedure G: one-pot, sequential 5-component (sulfonylation, Michael addition, amide coupling, esterification and click reaction). To a pressure tube containing a solution of amine (0.38 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.5 M), was added Et_3N (0.76 mmol, 2.0 equiv.). The reaction mixture was cooled to 0 ºC, stirred for 20 min, after which 2-chloroethane sulfonyl chloride (0.38 mmol, 1.0 equiv.) was added in a drop-wise manner. The reaction was warmed to rt and left to stir overnight. After completion of the reaction, CH_2Cl_2 was removed *in vacuo,* followed by addition of MeOH (0.5 M), water (0.5 M), Et_3N (1.14 mmol, 3.0 equiv.) and amino acid for the Michael reaction. The reaction mixture was stirred at 60 ºC for 12 h in the sealed tube. The solvents were evaporated to dryness. Amide coupling reaction commenced with addition of $CHCl_3$ (0.05 M), followed by EDC (0.46 mmol, 1.2 equiv.), HOBt (0.076 mmol, 0.2 equiv.) and Et_3N (0.76 mmol, 2.0 equiv.). The reaction was stirred at 50 ºC for 12 h. Upon completion of the reaction, EDC (0.76 mmol, 1.2 equiv.), HOBt (0.57 mmol, 1.5 equiv.) and Et_3N (0.76 mmol, 2.0 equiv.) were added to the crude mixture, followed by the carboxylic acid for the esterification step. The reaction was heated at 50 ºC for 12 h and solvent was removed under reduced pressure. Next, step-wise addition of CH_2Cl_2, alkyl azide and *t*-BuOH was performed, followed by sequential addition of aqueous solutions of $CuSO_4$ (0.19 mmol, 0.5 equiv.) and L-Na-ascorbate (0.23 mmol, 0.6 equiv.). The reaction was stirred overnight at rt, after which time, water was added to the crude mixture, followed by extraction with EtOAc. The organic layer was separated, and the aqueous

layer extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (2:1 EtOAc:Hexane).

(8*R*,9a*S*)-8-hydroxy-2-butylhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.4.2a)



According to the reaction protocol described in general procedure **B**, compound **2.4.2a** (67%, 2.04 g) was isolated after chromatography as a light orange solid.

M. P. 112–113 ºC;

R_f = 0.56 (100% EtOAc);

FTIR (neat) 3637, 3102, 2991, 2901, 1712, 1453, 1349, 1193 cm^{-1};

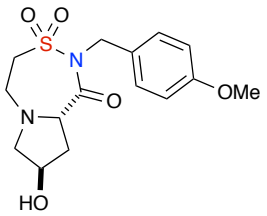
$[\alpha]_D^{20}$ = +23.2° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.44–4.36 [m, 2H, $NCH_2C\underline{H}(OH)CH_2C\underline{H}(C{=}O)$], 3.90–3.74 [m, 2H, $(C{=}O)NC\underline{H}_2CH_2CH_2CH_3$], 3.50–3.35 [m, 4H, $O_2SC\underline{H}_2C\underline{H}_aH_bNC\underline{H}_aH_bCH(OH)$], 3.27 (dt, *J* = 12.2, 3.2 Hz, 1H, $O_2SCH_2CH_a\underline{H}_bN$), 2.75 [dddd, *J* = 12.8, 5.9, 5.9 1.0 Hz, 1H, $NCH_2CH(OH)C\underline{H}_aH_bCH(C{=}O)$], 2.67 [ddd, *J* = 9.9, 5.2, 1.2 Hz, 1H, $NCH_a\underline{H}_bCH(OH)CH_2CH(C{=}O)$], 1.96 [dddd, *J* = 13.2, 8.9, 5.6, 1.2 Hz, 1H, $NCH_2CH(OH)CH_a\underline{H}_bCH(C{=}O)$], 1.68–1.56 (m, 3H, OH, n-butyl), 1.41–1.30 (m, 2H, n-butyl), 0.94 (td, *J* = 7.4, 1.8 Hz, 3H, n-butyl);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.0, 62.9, 61.5, 58.7, 55.9, 50.4, 46.8, 32.4, 31.5, 19.6, 13.5;

HRMS calculated for $C_{11}H_{20}N_2O_4SH$ $(M+H)^+$ 277.1222; found 277.1222 (TOF MS ES^+).

(8*R*,9a*S*)-8-hydroxy-2-(4-methoxybenzyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.4.2b)



According to the reaction protocol described in general procedure **B**, compound **2.4.2b** (72%, 1.02 g) was isolated after chromatography as a dark orange solid.

M. P. 125–127 ºC;

R_f = 0.38 (100% EtOAc);

FTIR (thin film) 3365, 3299, 3155, 2956, 1708, 1444, 1355, 1155, 1213, 835 cm^{-1};

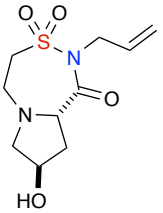
$[\alpha]_D^{20}$ = +26.6° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.37–7.33 (m, 2H), 6.87–6.83 (m, 2H), 5.09 (d, *J* = 15.0 Hz, 1H, NC$\underline{H}_a$$H_b$Ph), 4.85 (d, *J* = 14.9 Hz, 1H, NC$H_a$$\underline{H}_b$Ph), 4.42 [dd, *J* = 8.8, 5.8 Hz, 1H, $NCH_2CH(OH)CH_2C\underline{H}(C{=}O)$], 4.39 [dddd, *J* = 5.4, 5.4, 5.3, 5.3 Hz, 1H, $NCH_2C\underline{H}(OH)CH_2CH(C{=}O)$], 3.80 (s, 3H, Ar-OC$\underline{H}_3$), 3.45–3.33 (m, 3H, $O_2SC\underline{H}_2C\underline{H}_aH_bN$), 3.23–3.10 [m, 2H, $O_2SCH_2CH_a\underline{H}_bNC\underline{H}_aH_bCH(OH)$], 2.75 [dddd, *J* = 12.5, 5.8, 5.8, 1.0 Hz, 1H, $NCH_2CH(OH)C\underline{H}_aH_bCH(C{=}O)$], 2.64 [ddd, *J* = 9.8, 5.3, 1.1 Hz, 1H, $O_2SCH_2CH_aH_bNCH_a\underline{H}_bCH(OH)$], 1.95 [dddd, *J* = 14.4, 8.7, 5.7, 1.1 Hz, 1H, $NCH_2CH(OH)CH_a\underline{H}_bCH(C{=}O)$], 1.89 (s, 1H, OH);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.5, 159.1, 130.1 (2), 128.7, 113.8 (2), 77.3, 70.17, 64.1, 56.5, 55.3, 52.4, 48.1, 36.6;

HRMS calculated for $C_{15}H_{20}N_2O_5SNa$ $(M+Na)^+$ 363.0991; found 363.1004 (TOF MS ES^+).

(8*R*,9a*S*)-2-allyl-8-hydroxyhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.4.2c)



According to the reaction protocol described in general procedure **B**, compound **2.4.2c** (86%, 12.1 g) was isolated after chromatography as a light brown solid.

According to the reaction protocol described in general procedure **C**, compound **2.4.2c** (39%, 0.15 g) was isolated after chromatography as a white solid.

M. P. 113–116 ºC;

R_f = 0.42 (100% EtOAc);

$[\alpha]_D^{20}$ = +25.8° (*c* = 0.36, MeOH);

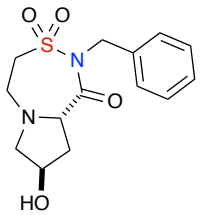
FTIR (thin film) 3373, 3331, 2928, 1705, 1647, 1447, 1344, 1150, 1082, 989, 915 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.88 (dddd, *J* = 17.2, 10.3, 6.2, 5.3 Hz, 1H, $CH_2C\underline{H}{=}CH_2$), 5.35 (dddd, *J* = 17.1, 1.4, 1.4, 1.4 Hz, 1H, $CH_2CH{=}CH_{cis}\underline{H}_{trans}$), 5.24 (dddd, *J* = 10.3, 1.2, 1.2, 1.2 Hz, 1H, $CH_2CH{=}C\underline{H}_{cis}H_{trans}$), 4.51–4.36 [m, 4H, $NCH_2C\underline{H}(OH)CH_2C\underline{H}(C{=}O)NC\underline{H}_2$], 3.52–3.33 [m, 4H, $O_2SC\underline{H}_2C\underline{H}_aH_bNC\underline{H}_aH_bCH(OH)$], 3.29 (dt, *J* = 12.7, 3.5 Hz, 1H, $O_2SCH_2CH_a\underline{H}_bN$), 2.76 [dddd, *J* = 12.8, 5.8, 5.8, 1.0 Hz, 1H, $NCH_2CH(OH)C\underline{H}_aH_bCH(C{=}O)$], 2.68 [ddd, *J* = 9.9, 5.3, 1.2 Hz, 1H, $NCH_a\underline{H}_bCH(OH)CH_2CH(C{=}O)$], 1.96 [dddd, *J* = 14.2, 8.8, 5.7, 1.2 Hz, 1H, $NCH_2CH(OH)CH_a\underline{H}_bCH(C{=}O)$], 1.57 (s, 1H, OH);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.3, 132.2, 118.5, 70.4, 64.3, 64.3, 56.7, 52.7, 47.8, 36.7;

HRMS calculated for $C_{10}H_{16}N_2O_4SH$ $(M + H)^+$ 261.0909; found 261.0894 (TOF MS ES^+).

(8*R*,9a*S*)-2-benzyl-8-hydroxyhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.4.2d)



According to the reaction protocol described in general procedure **B**, compound **2.4.2d** (76%, 5.05 g) was isolated after chromatography as a light brown solid.

According to the reaction protocol described in general procedure **C**, compound **2.4.2d** (69%, 0.51 g) was isolated after chromatography as a light brown solid.

M. P. 109–110 ºC;

R_f = 0.52 (100% EtOAc);

FTIR (neat) 3639, 3109, 2953, 2901, 1701, 1454, 1360, 1142, 1102, 712 cm^{-1};

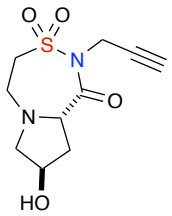
$[\alpha]_D^{20}$ = +25.2° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.42–7.37 (m, 2H), 7.36–7.32 (m, 2H), 7.31–7.28 (m, 1H), 5.13 (d, *J* = 15.1 Hz, 1H, $NC\underline{H}_aH_bPh$), 4.90 (d, *J* = 15.1 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.46 [dd, *J* = 10.6, 6.0 Hz, 1H, $NCH_2CH(OH)CH_2C\underline{H}(C{=}O)$], 4.42 [dddd, *J* = 5.2, 5.2, 5.2, 5.2 Hz, 1H, $NCH_2C\underline{H}(OH)CH_2CH(C{=}O)$], 3.49–3.42 (m, 1H, $O_2SC\underline{H}_aH_bCH_2N$), 3.41–3.35 (m, 2H, $O_2SCH_a\underline{H}_bC\underline{H}_aH_bN$), 3.26–3.17 (m, 2H, $O_2SCH_2CH_a\underline{H}_bNC\underline{H}_aH_b$), 2.76 [dddd, *J* = 13.5, 5.9, 5.9, 1.0 Hz, 1H $NCH_2CH(OH)C\underline{H}_aH_bCH(C{=}O)$], 2.65 [ddd, *J* = 9.9, 5.2, 1.2 Hz, 1H, $O_2SCH_2CH_2NCH_a\underline{H}_b$)], 2.07 (bs, 1H, OH), 1.95 [dddd, *J* = 13.3, 8.5, 5.6, 1.0 Hz, 1H, $NCH_2CH(OH)CH_a\underline{H}_bCH(C{=}O)$];

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.6, 136.3, 128.6, 128.1(2), 127.7(2), 63.9, 61.6, 58.9, 55.4, 50.3, 49.0, 32.3;

HRMS calculated for $C_{14}H_{18}N_2O_4SH$ $(M+H)^+$ 311.1066; found 311.1061 (TOF MS ES^+).

(8*R*,9a*S*)-8-hydroxy-2-(prop-2-yn-1-yl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.4.2e)



According to the reaction protocol described in general procedure **B**, compound **2.4.2e** (64%, 28.1 g) was isolated after chromatography as a light brown solid.

M. P. 94–95 ºC;

R_f = 0.38 (100% EtOAc);

FTIR (thin film) 3566, 3172, 2979, 2077, 1681, 1357, 1155, 1070 cm^{-1};

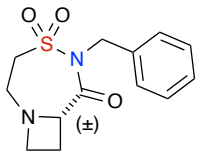
$[\alpha]_D^{20}$ = +22.7° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.73 (dd, *J* = 17.5, 2.4 Hz, 1H, $NC\underline{H}_aH_bCCH$), 4.51 (dd, *J* = 17.5, 2.4 Hz, 1H, $NCH_a\underline{H}_bCCH$), 4.47–4.40 [m, 2H, $NCH_2C\underline{H}(OH)CH_2C\underline{H}(C{=}O)$], 3.55–3.44 (m, 3H, $O_2SC\underline{H}_2C\underline{H}_aH_bN$), 3.42 [ddd, *J* = 9.9, 4.7, 1.0 Hz, 1H, $NC\underline{H}_aH_bCH(OH)CH_2$], 3.30 (dd, *J* = 9.1, 3.4 Hz, 1H, $O_2SCH_2CH_a\underline{H}_bN$), 2.76 [dddd, *J* = 13.0, 6.0, 5.9, 1.0 Hz, 1H, $NCH_2CH(OH)C\underline{H}_aH_b$], 2.69 [ddd, *J* = 9.9, 5.2, 1.1 Hz, 1H, $NCH_a\underline{H}_bCH(OH)CH_2$], 2.30 (dd, *J* = 2.4, 2.3 Hz, 1H, $NCH_2CC\underline{H}$), 1.98 [dddd, *J* = 13.3, 8.6, 5.6, 1.1 Hz, 1H, $NCH_2CH(OH)CH_a\underline{H}_b$], 1.61 (s, 1H, OH);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.2, 77.8, 71.9, 70.2, 64.1, 63.7, 56.6, 52.3, 36.5, 34.4;

HRMS calculated for $C_{10}H_{14}N_2O_4SNa$ $(M+Na)^+$ 281.0572; found 281.0580 (TOF MS ES^+).

5-benzyl-4-thia-1,5-diazabicyclo[5.2.0]nonan-6-one 4,4-dioxide (2.6.1)



According to the reaction protocol described in general procedure **B**, compound **2.6.1** (75%, 0.21 g) was isolated after chromatography as a yellow solid.

According to the reaction protocol described in general procedure **C**, compound **2.6.1** (85%, 0.102 g) was isolated after chromatography as a white solid.

M. P. 82–84 ºC;

R_f = 0.53 (1:1 Hexane:EtOAc);

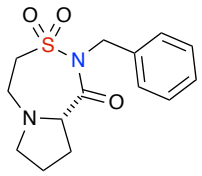
FTIR (thin film) 2974, 2839, 1712, 1693, 1496, 1371, 1149, 1037, 727 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.44–7.39 (m, 2H), 7.38–7.33 (m, 2H), 7.32–7.27 (m, 1H), 5.17 (d, *J* = 15.2 Hz, 1H, $NC\underline{H}_aH_bPh$), 4.87 (d, *J* = 15.3 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.56 (dd, *J* = 8.2, 8.2 Hz, 1H, $C{=}OC\underline{H}CH_2$), 3.38–3.29 (m, 2H, $O_2SC\underline{H}_aH_bCH_2NC\underline{H}_aH_bCH_2$), 3.22–3.09 (m, 3H, $O_2SCH_a\underline{H}_bC\underline{H}_aH_bNCH_a\underline{H}_bCH_2$), 3.05–3.00 (m, 1H, $O_2SCH_2CH_a\underline{H}_bNCH_2$), 2.61 [dddd, *J* = 10.4, 10.4, 8.5, 8.5 Hz, 1H, $NCH_2C\underline{H}_aH_bCH(C{=}O)$], 2.13 [dddd, *J* = 10.4, 7.6, 7.6, 2.0 Hz, 1H, $NCH_2CH_a\underline{H}_bCH(C{=}O)$];

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.9, 136.5, 128.5 (2), 128.1 (2), 127.6, 65.8, 55.4, 51.4, 50.5, 48.0, 20.5;

HRMS calculated for $C_{13}H_{16}N_2O_3SH$ $(M+H)^+$ 281.0960, found 281.0968 (TOF MS ES^+).

(*S*)-2-benzylhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.6.2)



According to the reaction protocol described in general procedure **B**, compound **2.6.2** (82%, 0.097 g) was isolated after chromatography as a white solid.

According to the reaction protocol described in general procedure **C**, compound **2.6.2** (85%, 0.098 g) was isolated after chromatography as a white solid.

M. P. 89–91 ºC;

R_f = 0.52 (1:1 Hexane:EtOAc);

FTIR (thin film) 2927, 1701, 1454, 1365, 1218, 1151, 732 cm^{-1};

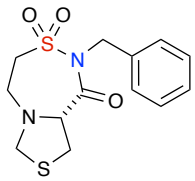
$[\alpha]_D^{20}$ = +29.2° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.43–7.39 (m, 2H), 7.36–7.31 (m, 2H), 7.30–7.26 (m, 1H), 5.14 (d, *J* = 15.2 Hz, 1H, $NC\underline{H}_aH_bPh$), 4.93 (d, *J* = 15.1 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.16 (dd, *J* = 9.8, 2.5 Hz, 1H, $C{=}OC\underline{H}CH_2$), 3.39–3.34 (m, 1H, $O_2SC\underline{H}_aH_bCH_2$), 3.28–3.19 (m, 3H, $O_2SCH_a\underline{H}_bC\underline{H}_2N$), 3.17–3.12 [m, 1H, $NC\underline{H}_aH_bCH_2CH_2CH(C{=}O)$], 2.70–2.63 [m, 1H, $NCH_a\underline{H}_bCH_2CH_2CH(C{=}O)$], 2.63–2.54 [m, 1H, $NCH_2CH_2CH_a\underline{H}_bCH(C{=}O)$], 1.95–1.85 [m, 1H, $NCH_2CH_2C\underline{H}_aH_bCH(C{=}O)$], 1.82–1.74 [m, 2H $NCH_2C\underline{H}_2CH_2CH(C{=}O)$];

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.9, 136.5, 128.5 (2), 128.3 (2), 127.6, 64.3, 57.8, 56.2, 50.7, 48.6, 27.2, 24.7;

HRMS calculated for $C_{14}H_{18}N_2O_3SH$ $(M+H)^+$ 295.1116, found 295.1116 (TOF MS ES^+).

(*R*)-2-benzylhexahydro-1*H*-thiazolo[4,3-*d*][1,2,5]thiadiazepin-1-one 3,3-dioxide (2.6.3)



According to the reaction protocol described in general procedure **B**, compound **2.6.3** (70%, 0.098 g) was isolated after chromatography as a brown solid.

According to the reaction protocol described in general procedure **C**, compound **2.6.3** (76%, 0.21 g) was isolated after chromatography as a brown solid.

M. P. 98–99 ºC;

R_f = 0.51 (1:1 Hexane:EtOAc);

FTIR (thin film) 2927, 1701, 1496, 1456, 1373, 1151, 1022, 730 cm^{-1};

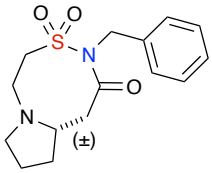
$[\alpha]_D^{20}$ = -21.7° (c = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.43–7.39 (m, 2H), 7.37–7.32 (m, 2H), 7.32–7.27 (m, 1H), 5.17 (d, J = 15.1 Hz, 1H, NC$\underline{H}_a$H$_b$Ph), 4.92 (d, J = 15.1 Hz, 1H, NCH$_a$$\underline{H}_b$Ph), 4.44 (dd, J = 7.3, 5.4 Hz, 1H, C=OC$\underline{H}$CH$_2$), 4.21 (d, J = 9.1 Hz, 1H, NC$\underline{H}_a$H$_b$S), 3.89 (d, J = 9.1 Hz, 1H, NCH$_a$$\underline{H}_b$S), 3.69 (dd, J = 12.1, 5.4 Hz, 1H, NCH$_2$SC$\underline{H}_a$H$_b$CH), 3.61–3.54 (m, 1H, O$_2$SC$\underline{H}_a$H$_b$CH$_2$N), 3.43–3.38 (m, 1H, O$_2$SCH$_2$C$\underline{H}_a$H$_b$N), 3.34–3.23 (m, 2H, O$_2$SCH$_a$$\underline{H}_bCH_a$$\underline{H}_b$N), 3.16 (dd, J = 12.1, 7.3 Hz, 1H, NCH$_2$SCH$_a$$\underline{H}_b$CH);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 167.0, 136.4, 128.6 (2), 128.4 (2), 127.8, 67.3, 60.9, 55.8, 51.7, 48.7, 34.1;

HRMS calculated for $C_{13}H_{16}N_2O_3S_2H$ $(M+H)^+$ 313.0681, found 313.0685 (TOF MS ES^+).

3-benzylhexahydro-1*H*-pyrrolo[2,1-*e*][1,2,6]thiadiazocin-2(3*H*)-one 4,4-dioxide (2.6.4)



According to the reaction protocol described in general procedure **B**, compound **2.6.4** (65%, 0.096 g) was isolated after chromatography as a light yellow solid.

M. P. 87–90 ºC;

R_f = 0.70 (1:1 Hexane:EtOAc);

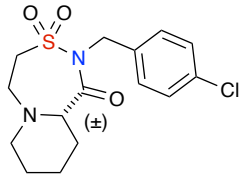
FTIR (thin film) 3286, 2931, 1703, 1645, 1494, 1454, 1398, 1284, 1137, 730 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.48–7.43 (m, 2H), 7.34–7.25 (m, 3H), 5.51 (d, *J* = 14.9 Hz, 1H, NC$\underline{H}_a$$H_b$Ph), 4.75 (d, *J* = 14.8 Hz, 1H, NC$H_a$$\underline{H}_b$Ph), 4.08 (dd, *J* = 12.4, 8.6 Hz, 1H, O_2SC$\underline{H}_a$$H_b$$CH_2$N), 3.30–3.20 (m, 1H, O_2SC$H_a$$\underline{H}_b$$CH_2$N), 3.07–2.93 (m, 4H, O_2SCH_2C$\underline{H}_2$NC$\underline{H}$, NC$\underline{H}_a$$H_b$$CH_2$), 2.81–2.68 [m, 1H, NCHC$\underline{H}_a$$H_b$(C=O)], 2.54 [d, *J* = 13.0 Hz, 1H, NCHC$H_a$$\underline{H}_b$(C=O)], 2.47 (dd, *J* = 16.8, 8.2 Hz, 1H, NC$H_a$$\underline{H}_b$$CH_2$), 2.10–1.91 [m, 2H, N$CH_2C\underline{H}_a$$H_bC\underline{H}_a$$H_b$CH(C=O)], 1.85–1.71 [m, 2H, NCH_2C$H_a$$\underline{H}_bCH_a$$\underline{H}_b$CH(C=O)];

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.7, 136.4, 129.2 (2), 128.2 (2), 127.7, 64.2, 56.8, 56.2, 48.5, 47.7, 37.5, 29.8, 22.6;

HRMS calculated for $C_{15}H_{20}N_2O_3SH$ $(M+H)^+$ 309.1273, found 309.1282 (TOF MS ES^+).

2-(4-chlorobenzyl)octahydro-1*H*-pyrido[2,1-*d*][1,2,5]thiadiazepin-1-one 3,3-dioxide (2.6.5)



According to the reaction protocol described in general procedure **B**, compound **2.6.5** (75%, 0.105 g) was isolated after chromatography as a brown solid.

According to the reaction protocol described in general procedure **C**, compound **2.6.5** (82%, 0.11 g) was isolated after chromatography as a brown solid.

M. P. 88–91 ºC;

R_f = 0.45 (1:1 Hexane:EtOAc);

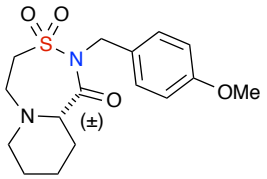
FTIR (thin film) 2975, 2923, 2833, 1704, 1444, 1355, 1153, 825 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.43–7.38 (m, 2H), 7.32–7.28 (m, 2H), 5.06 (d, *J* = 15.0 Hz, 1H, $NC\underline{H}_aH_bPh$), 4.88 (d, *J* = 15.0 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.28 (dd, *J* = 3.8, 3.4 Hz, 1H, $C{=}OC\underline{H}CH_2$), 3.79 (m, 1H, $O_2SC\underline{H}_aH_bCH_2N$), 3.40–3.32 (m, 1H, $O_2SCH_2C\underline{H}_aH_bN$), 3.28–3.19 (m, 2H, $O_2SCH_a\underline{H}_bCH_a\underline{H}_bN$), 2.52–2.42 (m, 2H, $NC\underline{H}_2CH_2$), 2.10–2.03 (m, 1H, $NCH_2CH_2CH_2C\underline{H}_aH_bCH$), 1.80–1.67 (m, 1H, $NCH_2CH_2C\underline{H}_aH_bCH_2CH$), 1.63 (m, 1H, $NCH_2C\underline{H}_aH_bCH_2CH_2CH$), 1.60–1.49 (m, 3H, $NCH_2CH_a\underline{H}_bCH_a\underline{H}_bCH_a\underline{H}_bCH$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 173.0, 135.7, 133.7, 130.2 (2), 128.7 (2), 60.7, 53.0, 52.1, 47.7, 47.6, 27.4, 25.8, 19.9;

HRMS calculated for $C_{15}H_{19}ClN_2O_3SH$ $(M+H)^+$ 343.0883, found 343.0883 (TOF MS ES^+).

2-(4-methoxybenzyl)octahydro-1*H*-pyrido[2,1-*d*][1,2,5]thiadiazepin-1-one 3,3-dioxide (2.6.6)



According to the reaction protocol described in general procedure **B**, compound **2.6.6** (71%, 0.105 g) was isolated after chromatography as a dark yellow solid.

M. P. 91–93 ºC;

R_f = 0.37 (1:1 Hexane:EtOAc);

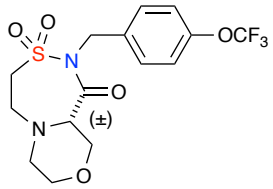
FTIR (thin film) 2979, 2927, 1704, 1444, 1357, 1155, 842 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.44–7.40 (m, 2H), 6.87–6.84 (m, 2H), 5.13 (d, *J* = 14.7 Hz, 1H, $NC\underline{H}_aH_bPh$), 4.85 (d, *J* = 14.7 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.28 (dd, *J* = 4.7, 2.7 Hz, 1H, $C{=}OC\underline{H}CH_2$), 3.81 (s, 3H, $Ar\text{-}OC\underline{H}_3$), 3.79–3.71 (m, 1H, $O_2SC\underline{H}_aH_bCH_2N$), 3.35–3.28 (m, 1H, $O_2SCH_2C\underline{H}_aH_bN$), 3.25–3.17 (m, 2H, $O_2SCH_a\underline{H}_bCH_a\underline{H}_bN$), 2.45–2.39 (m, 2H, $NC\underline{H}_2CH_2$), 2.13–2.05 (m, 1H, $NCH_2CH_2CH_2C\underline{H}_aH_bCH$), 1.81–1.70 (m, 1H, $NCH_2CH_2C\underline{H}_aH_bCH_2CH$), 1.62 (m, 1H, $NCH_2C\underline{H}_aH_bCH_2CH_2CH$), 1.65–1.47 (m, 3H, $NCH_2CH_a\underline{H}_bCH_a\underline{H}_bCH_a\underline{H}_bCH$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 173.0, 159.2, 130.5 (2), 129.4, 113.6 (2), 60.6, 55.2, 53.0, 52.1, 47.6, 27.4, 29.7, 25.8, 19.8;

HRMS calculated for $C_{16}H_{22}N_2O_4SH$ $(M+H)^+$ 339.1379, found 339.1388 (TOF MS ES^+).

2-(4-(trifluoromethoxy)benzyl)hexahydro-[1,4]oxazino[3,4-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.6.7)



According to the reaction protocol described in general procedure **B**, compound **2.6.7** (47%, 0.18 g) was isolated after chromatography as a yellow solid.

M. P. 102–107 ºC;

R_f = 0.53 (100% EtOAc);

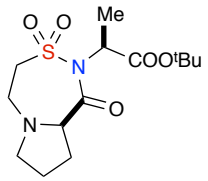
FTIR (thin film) 3121, 2962, 2916, 1682, 1508, 1435, 1346, 1219, 1151, 1043, 851 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.55 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 5.12 (d, *J* = 14.9 Hz, 1H, $NC\underline{H}_aH_bPh$), 4.95 (d, *J* = 14.9 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.34 (d, *J* = 10.9 Hz, 1H, $NCH_2CH_2OC\underline{H}_aH_bCH$), 4.11 [m, 1H, $OCH_2C\underline{H}(C{=}O)$], 3.94–3.84 (m, 1H, $O_2SC\underline{H}_aH_bCH_2N$), 3.76 (ddd, *J* = 10.9, 3.3, 1.6 Hz, 1H, $NCH_2C\underline{H}_aH_bOCH_2CH$), 3.69–3.60 (m, 2H, $NCH_2CH_aH_bOCH_a\underline{H}_bCH$), 3.47–3.39 (m, 1H, $O_2SCH_2C\underline{H}_aH_bN$), 3.31 (dd, *J* = 14.3, 14.2 Hz, 2H, $O_2SCH_a\underline{H}_bCH_a\underline{H}_bN$), 2.77 (dd, *J* = 11.2, 11.1 Hz, 1H, $NC\underline{H}_aH_bCH_2O$), 2.38 (d, *J* = 11.9 Hz, 1H, $NCH_a\underline{H}_bCH_2O$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.2, 148.9, 135.6, 130.6 (2), 121.0 (2), 120.4 (d, $J_{C–F}$ = 257.4 Hz), 67.5, 66.9, 61.3, 52.7, 51.7, 47.8, 47.2;

HRMS calculated for $C_{15}H_{17}F_3N_2O_5SH$ $(M + H)^+$ 395.0898; found 395.0913 (TOF MS ES^+).

(*S*)-*tert*-butyl 2-((*S*)-3,3-dioxido-1-oxohexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-2(1*H*)-yl)propanoate (2.6.8)



According to the reaction protocol described in general procedure **B**, compound **2.6.8** (77%, 0.49 g) was isolated after chromatography as a light brown solid.

M. P. 84–86 ºC;

R_f = 0.55 (1:1 Hexane:EtOAc);

FTIR (thin film) 2943, 2829, 1731, 1703, 1697, 1444, 1357, 1182 cm^{-1};

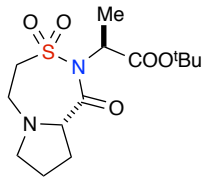
$[\alpha]_D^{20}$ = -29.2° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.90 [q, *J* = 6.9 Hz, 1H, NC$\underline{H}$(CH_3)$CO_2{}^t$Bu], 4.14 (dd, *J* = 9.8, 2.5 Hz, 1H, C=OC$\underline{H}$$CH_2$), 3.70 (ddd, *J* = 14.0, 10.2, 6.0 Hz, 1H, $O_2SC\underline{H}_aH_bCH_2$), 3.40 (dt, *J* = 14.0, 2.8 Hz, 1H, $O_2SCH_a\underline{H}_bCH_2$), 3.35–3.22 (m, 2H, $O_2SCH_2C\underline{H}_2N$), 3.16–3.11 (m, 1H, $NC\underline{H}_aH_bCH_2CH_2CH$), 2.66–2.56 (m, 2H, $NCH_a\underline{H}_bCH_2CH_a\underline{H}_bCH$), 1.93–1.83 (m, 1H, $NCH_2CH_2C\underline{H}_aH_bCH$), 1.83–1.70 (m, 2H, $NCH_2C\underline{H}_2CH_2CH$), 1.57 [d, *J* = 6.9 Hz, 3H, NCH(C$\underline{H}_3$)$CO_2{}^t$Bu], 1.45 [s, 9H, $CO_2C(C\underline{H}_3)_3$];

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.6, 168.6, 82.0, 63.6, 57.7, 56.1, 55.4, 50.5, 27.8, 27.2, 24.8, 16.3 (3);

HRMS calculated for $C_{14}H_{24}N_2O_5SNa$ $(M+Na)^+$ 355.1304, found 355.1309 (TOF MS ES^+).

(*S*)-*tert*-butyl 2-((*R*)-3,3-dioxido-1-oxohexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-2(1*H*)-yl)propanoate (2.6.9)



According to the reaction protocol described in general procedure **B**, compound **2.6.9** (80%, 0.51 g) was isolated after chromatography as a dark brown solid.

M. P. 84–85 ºC;

R_f = 0.51 (1:1 Hexane:EtOAc);

FTIR (thin film) 2943, 2871, 1737, 1703, 1697, 1444, 1384, 1325, 1126 cm^{-1};

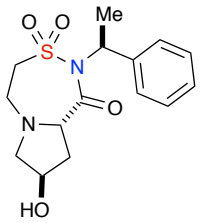
$[\alpha]_D^{20}$ = +15.7° (c = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.91 [q, J = 6.9 Hz, 1H, NC$\underline{H}$(CH_3)$CO_2{}^t$Bu], 4.46–4.37 (m, 2H, C=OC$\underline{H}$$CH_2$, $O_2SC\underline{H}_aH_bCH_2N$), 3.69 (ddd, J = 13.4, 12.1, 4.3 Hz, 1H, $O_2SCH_a\underline{H}_bCH_2N$), 3.51–3.36 (m, 3H, $O_2SCH_2C\underline{H}_2N\underline{H}_aH_b$), 3.33–3.26 (m, 1H, $O_2SCH_2CH_2NH_a\underline{H}_b$), 2.74 (ddd, J = 12.9, 5.8, 5.8 Hz, 1H, $NCH_2CH_2CH_a\underline{H}_bCH$), 2.67 (dd, J = 9.6, 5.6 Hz, 1H, $NCH_2CH_2C\underline{H}_aH_bCH$), 1.94 (ddd, J = 13.2, 8.5, 5.6 Hz, 1H, $NCH_2C\underline{H}_aH_bCH_2CH$), 1.64–1.60 (m, 1H, $NCH_2CH_a\underline{H}_bCH_2CH$), 1.58 [d, J = 7.0 Hz, 3H, NCH(C$\underline{H}_3$)$CO_2{}^t$Bu], 1.46 [s, 9H, $CO_2C(C\underline{H}_3)_3$];

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.3, 169.3, 82.1, 64.3, 57.8, 56.6, 55.0, 50.8, 27.9, 27.3, 24.5, 16.7 (3);

HRMS calculated for $C_{14}H_{24}N_2O_5SNa$ $(M+Na)^+$ 355.1304, found 355.1304 (TOF MS ES^+).

(8*R*,9a*S*)-8-hydroxy-2-((*S*)-1-phenylethyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.5.7)



According to the reaction protocol described in general procedure **B**, compound **2.5.7** (85%, 0.50 g) was isolated after chromatography as a dark yellow solid.

M. P. 104–106 ºC;

R_f = 0.52 (100% EtOAc);

FTIR (thin film) 3523, 3392, 2835, 1701, 1496, 1375, 1276, 1147, 734 cm^{-1};

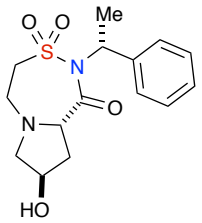
$[\alpha]_D^{20}$ = +23.7° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.44–7.39 (m, 2H), 7.37–7.32 (m, 2H), 7.28–7.24 (m, 1H), 5.89 (q, *J* = 7.1 Hz, 1H, NC<u>H</u>CH_3Ph), 4.41 (dd, *J* = 8.7, 6.0 Hz, 1H, C=OC<u>H</u>CH_2), 4.29 [dddd, *J* = 5.4, 5.4, 5.3, 5.3 Hz, 1H, CH_2C<u>H</u>(OH)CH_2], 3.54–3.41 (m, 3H, O_2SC<u>H_2</u>C<u>H_a</u>H_bN), 3.35 [dd, *J* = 9.9, 4.6 Hz, 1H, NC<u>H_a</u>H_bCH(OH)CH_2CH(C=O)], 3.31–3.25 (m, 1H, O_2SCH_2CH_a<u>H_b</u>N), 2.68–2.60 [m, 2H, NCH_a<u>H_b</u>CH(OH)C<u>H_a</u>H_bCH(C=O)], 1.97–1.92 [m, 1H, (OH)CHCH_a<u>H_b</u>CH(C=O)], 1.91 (d, *J* = 7.1 Hz, 3H, NCHC<u>H_3</u>Ph), 1.61 (bs, 1H, OH);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.0, 138.8, 126.7 (2), 125.6, 125.1 (2), 68.6, 63.7, 62.6, 55.5, 55.0, 50.9, 35.2, 16.5;

HRMS calculated for $C_{15}H_{20}N_2O_4SNa$ $(M+Na)^+$ 347.1041, found 347.1042 (TOF MS ES^+).

(8*R*,9a*S*)-8-hydroxy-2-((*R*)-1-phenylethyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.5.8)



According to the reaction protocol described in general procedure **B**, compound **2.5.8** (73%, 0.48 g) was isolated after chromatography as a brown solid.

M. P. 106–109 ºC;

R_f = 0.47 (100% EtOAc);

FTIR (thin film) 3651, 3276, 2979, 1713, 1435, 1383, 1221, 1151, 742 cm^{-1};

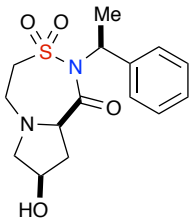
$[\alpha]_D^{20}$ = +21.6° (c = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.35–7.31 (m, 2H), 7.30–7.24 (m, 2H), 7.21–7.16 (m, 1H), 5.88 (q, J = 7.1 Hz, 1H, NC$\underline{H}$CH$_3$Ph), 4.36–4.28 [m, 2H, CH$_2$C$\underline{H}$(OH)CH$_2$C$\underline{H}$CH$_2$(C=O)], 3.35–3.27 (m, 2H, O$_2$SC$\underline{H_2}$CH$_2$N), 3.19 (dt, J = 13.5, 3.4 Hz, 1H, O$_2$SCH$_2$C$\underline{H}_a$H$_b$N), 3.13 (dt, J = 13.2, 3.4 Hz, 1H, O$_2$SCH$_2$CH$_a$$\underline{H}_b$N), 3.03 [ddd, J = 13.8, 12.4, 4.0 Hz, 1H, NCH$_a$$\underline{H}_b$CH(OH)CH$_2$CH(C=O)], 2.62 [ddd, J = 12.9, 7.0, 6.0 Hz, 1H, NC$\underline{H}_a$H$_b$CH(OH)CH$_2$CH(C=O)], 2.57 [ddd, J = 9.8, 5.2, 0.8 Hz, 1H, NCH$_2$CH(OH)CH$_a$$\underline{H}_b$CH(C=O)], 1.84 [dddd, J = 14.2, 8.6, 5.5, 1.1 Hz, 1H, NCH$_2$CH(OH)C$\underline{H}_a$H$_b$CH(C=O)], 1.77 (d, J = 7.1 Hz, 3H, NCHC$\underline{H}_3$Ph), 1.60 (bs, 1H, OH);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.6, 139.8, 128.2 (2), 127.2, 127.1 (2), 70.2, 65.0, 64.2, 57.0, 56.0, 52.4, 36.8, 17.4;

HRMS calculated for $C_{15}H_{20}N_2O_4SH$ $(M+H)^+$ 325.1222, found 325.1221 (TOF MS ES^+).

(8*R*,9a*R*)-8-hydroxy-2-((*S*)-1-phenylethyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.5.9)



According to the reaction protocol described in general procedure **B**, compound **2.5.9** (75%, 0.51 g) was isolated after chromatography as a dark yellow solid.

M. P. 106–107 ºC;

R_f = 0.58 (100% EtOAc);

FTIR (thin film) 3539, 3280, 2975, 1755, 1631 1452, 1321, 1276, 1151, 734 cm^{-1};

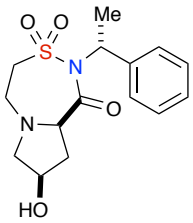
$[\alpha]_D^{20}$ = -19.7° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.42–7.35 (m, 4H), 7.34–7.29 (m, 1H), 5.22–5.10 (m, 1H, NC<u>H</u>CH_3Ph), 4.82 (bs, 1H, OH), 4.63 [dddd, *J* = 6.9, 6.9, 6.8, 6.8 Hz, 1H, CH_2C<u>H</u>(OH)CH_2], 3.47–3.45 (m, 1H, C=OC<u>H</u>CH_2), 3.07 [dd, *J* = 12.4, 1.4 Hz, 1H, NC<u>H</u>$_a$H$_b$CH(OH)CH_2], 3.01–2.82 (m, 3H, O_2SC<u>H$_2$</u>C<u>H</u>$_a$H$_b$N), 2.70 (ddd, *J* = 12.3, 7.3, 5.4 Hz, 1H, O_2SCH_2CH$_a$<u>H</u>$_b$N), 2.16 [d, *J* = 11.3 Hz, 1H, NCH$_a$<u>H</u>$_b$CH(OH)CH_2], 2.05 [ddd, *J* = 12.4, 4.6, 1.6 Hz, 1H, NCH_2CH(OH)CH$_a$<u>H</u>$_b$], 1.78 [dd, *J* = 10.7, 1.8 Hz, 1H, NCH_2CH(OH)C<u>H</u>$_a$H$_b$], 1.55 (d, *J* = 7.3 Hz, 3H, NCHC<u>H</u>$_3$Ph);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.4, 142.7, 129.0 (2), 128.0, 126.3 (2), 79.5, 62.5, 55.6, 53.9, 52.4, 48.7, 39.1, 24.2;

HRMS calculated for $C_{15}H_{20}N_2O_4SNa$ $(M+Na)^+$ 347.1041, found 347.1037 (TOF MS ES^+).

(8*R*,9a*R*)-8-hydroxy-2-((*R*)-1-phenylethyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.5.7)



According to the reaction protocol described in general procedure **B**, compound **2.5.7** (70%, 0.49 g) was isolated after chromatography as a dark yellow solid.

M. P. 108–110 ºC;

R_f = 0.53 (100% EtOAc);

FTIR (thin film) 3523, 3110, 2941, 2835, 1701, 1448, 1375, 1209, 1151, 734 cm^{-1};

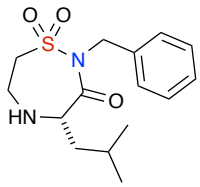
$[\alpha]_D^{20}$ = -15.7° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.39–7.35 (m, 4H), 7.33–7.26 (m, 1H), 5.61 (d, *J* = 7.34, 1H, NC<u>H</u>CH_3Ph), 4.81 (bs, 1H, OH), 4.61 [dddd, *J* = 7.0, 7.0, 6.9, 6.9 Hz, 1H, CH_2C<u>H</u>(OH)CH_2], 3.46–3.43 (m, 1H, C=OC<u>H</u>CH_2), 3.11 [dd, *J* = 10.7, 1.4 Hz, 1H, NC<u>H</u>$_a$H$_b$CH(OH)CH_2], 3.01–2.91 (m, 2H, O_2SC<u>H$_2$</u>CH_2N), 2.81–2.74 (m, 1H, O_2SCH_2C<u>H</u>$_a$H$_b$N), 2.64–2.56 (m, 1H, O_2SCH_2CH$_a$<u>H</u>$_b$N), 2.02–1.97 [m, 1H, NCH$_a$<u>H</u>$_b$CH(OH)CH_2], 1.89–1.85 [m, 1H, NCH_2CH(OH)CH$_a$<u>H</u>$_b$], 1.76 [dd, *J* = 10.8, 1.8 Hz, 1H, NCH_2CH(OH)C<u>H</u>$_a$H$_b$], 1.53 (d, *J* = 6.9 Hz, 3H, NCHC<u>H</u>$_3$Ph);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.7, 143.0, 129.1 (2), 127.8, 126.4 (2), 79.5, 62.4, 55.3, 53.8, 52.1, 48.3, 39.1, 24.1;

HRMS calculated for $C_{15}H_{20}N_2O_4SNa$ $(M+Na)^+$ 347.1041, found 347.1044 (TOF MS ES^+).

(*S*)-2-benzyl-4-isobutyl-1,2,5-thiadiazepan-3-one 1,1-dioxide (2.7.1a)



According to the reaction protocol described in general procedure **B**, compound **2.7.1a** (63%, 5.05 g) was isolated after chromatography as a light yellow solid.

According to the reaction protocol described in general procedure **C**, compound **2.7.1a** (61%, 0.49 g) was isolated after chromatography as a light yellow solid.

M. P. 74–76 ºC;

R_f = 0.56 (100% EtOAc);

FTIR (thin film) 3357, 3087, 2952, 1697, 1585, 1467, 1365, 1209, 1147 cm^{-1};

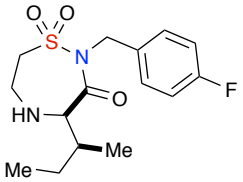
$[\alpha]_D^{20}$ = +25.0° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.43–7.39 (m, 2H), 7.36–7.31 (m, 2H), 7.31–7.25 (m, 1H), 5.18 (d, *J* = 15.0 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.89 (d, *J* = 14.9 Hz, 1H, $NC\underline{H}_aH_bPh$), 4.18 (dd, *J* = 8.6, 4.7 Hz, 1H, $HNC\underline{H}CH_2$), 3.55–3.45 (m, 1H, $O_2SC\underline{H}_aH_bCH_2$), 3.36 (ddd, *J* = 14.7, 4.1, 2.8 Hz, 1H, $O_2SCH_a\underline{H}_bCH_2$), 3.28 (dt, *J* = 14.3, 2.7 Hz, 1H, $CH_2CH_a\underline{H}_bNH$), 2.94 (ddd, *J* = 14.2, 12.1, 4.1 Hz, 1H, $CH_2C\underline{H}_aH_bNH$), 1.78–1.69 (m, 2H, $CHC\underline{H}_2CH$), 1.41 (p, *J* = 9.2 Hz, 1H, $CH_3C\underline{H}CH_3$), 0.95 (d, *J* = 6.1 Hz, 3H, $C\underline{H}_3CHCH_3$), 0.93 (d, *J* = 6.0 Hz, 3H, $CH_3CHC\underline{H}_3$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 173.2, 147.2, 136.5, 128.4 (2), 127.6 (2), 58.3, 56.8, 48.2, 45.3, 40.7, 24.5, 23.0, 22.1;

HRMS calculated for $C_{15}H_{22}N_2O_3SNa$ $(M+Na)^+$ 333.1429; found 333.1429 (TOF MS ES^+).

(4*S*)-4-(*sec*-butyl)-2-(4-fluorobenzyl)-1,2,5-thiadiazepan-3-one 1,1-dioxide (2.7.1b)



According to the reaction protocol described in general procedure **B**, compound **2.7.1b** (65%, 0.21 g) was isolated after chromatography as a light yellow solid.

According to the reaction protocol described in general procedure **C**, compound **7.1b** (65%, 0.21 g) was isolated after chromatography as a light yellow solid.

M. P. 79–81 ºC;

R_f = 0.45 (100% EtOAc);

FTIR (thin film) 3363, 2960, 2929, 2873, 1697, 1467, 1365, 1147, 812 cm^{-1};

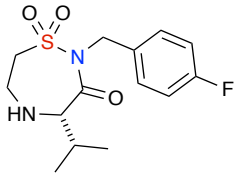
$[\alpha]_D^{20}$ = +32.2° (c = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.45–7.39 (m, 2H), 7.06–6.99 (m, 2H), 5.12 (d, J = 14.9 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.87 (d, J = 14.9 Hz, 1H, $NC\underline{H}_aH_bPh$), 3.93 [d, J = 6.8 Hz, 1H, $HNC\underline{H}(C{=}O)$], 3.52–3.42 (m, 2H, $O_2SC\underline{H}_2CH_2NH$), 3.29 (dt, J = 14.2, 2.7 Hz, 1H, $O_2SCH_2C\underline{H}_aH_bNH$), 2.89 (ddd, J = 14.2, 10.7, 5.7 Hz, 1H, $O_2SCH_2CH_a\underline{H}_bNH$), 1.92 (ddqd, J = 9.4, 7.4, 6.6, 3.1 Hz, 1H, $CH_3CH_2C\underline{H}CH_3$), 1.66 (dqd, J = 13.4, 7.6, 3.2 Hz, 1H, $CH_3C\underline{H}_aH_bCHCH_3$), 1.16 (ddq, J = 13.0, 9.1, 7.3 Hz, 1H, $CH_3CH_a\underline{H}_bCHCH_3$), 0.98 (d, J = 6.6 Hz, 3H, $CH_3CH_2CHC\underline{H}_3$), 0.93 (t, J = 7.4 Hz, 3H, $C\underline{H}_3CH_2CHCH_3$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 172.7, 162.3 ($^1J_{C-F}$ = 246.5 Hz), 132.6 ($^4J_{C-F}$ = 3.25 Hz), 130.7 ($^3J_{C-F}$ = 8.12 Hz, 2), 115.5 ($^2J_{C-F}$ = 21.42 Hz, 2), 64.6, 56.9, 47.5, 45.5, 35.9, 24.5, 16.4, 11.3;

HRMS calculated for $C_{15}H_{21}FN_2O_3SNa$ $(M+Na)^+$ 351.1155; found 351.1154 (TOF MS ES^+).

(*S*)-2-(4-fluorobenzyl)-4-isopropyl-1,2,5-thiadiazepan-3-one 1,1-dioxide (2.7.1c)



According to the reaction protocol described in general procedure **B**, compound **2.7.1c** (67%, 0.21 g) was isolated after chromatography as a light brown solid.

M. P. 85–87 ºC;

R_f = 0.39 (100% EtOAc);

FTIR (thin film) 3357, 2954, 2929, 1697, 1693, 1540, 1457, 1365, 1209, 1141, 842 cm^{-1};

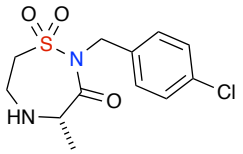
$[\alpha]_D^{20}$ = +31.4° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.45–7.40 (m, 2H), 7.05–7.00 (m, 2H), 5.13 (d, *J* = 14.9 Hz, 1H, NC$\underline{H}_a$H$_b$Ph), 4.88 (d, *J* = 15.0 Hz, 1H, NCH$_a$$\underline{H}_b$Ph), 3.85 [d, *J* = 6.5 Hz, 1H, HNC$\underline{H}$(C=O)], 3.50–3.46 (m, 2H, $O_2SC\underline{H}_2CH_2NH$), 3.31 (ddd, *J* = 14.2, 2.6, 2.6 Hz, 1H, $O_2SCH_2C\underline{H}_aH_bNH$), 2.90 (ddd, *J* = 14.3, 9.0, 7.4 Hz, 1H, $O_2SCH_2CH_a\underline{H}_bNH$), 2.23–2.13 (dqq, *J* = 6.5, 6.5, 6.5 Hz, 1H, $CH_3C\underline{H}CH_3$), 1.00 (d, *J* = 6.7 Hz, 6H, $C\underline{H}_3CHC\underline{H}_3$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 172.8, 163.3 ($^1J_{C–F}$ = 242.5 Hz), 132.5 ($^4J_{C–F}$ = 3.28 Hz), 130.5 ($^3J_{C–F}$ = 8.11 Hz, 2), 115.5 (^2J = 21.42 Hz, 2), 65.6, 57.0, 47.5, 45.6, 29.3, 20.3, 17.7;

HRMS (ESI) m/z calculated for $C_{14}H_{19}FN_2O_3SNa$ $(M+Na)^+$ 337.0998, found 337.0998 (TOF MS ES^+).

(*S*)-2-(4-chlorobenzyl)-4-methyl-1,2,5-thiadiazepan-3-one 1,1-dioxide (2.7.1d)



According to the reaction protocol described in general procedure **B**, compound **2.7.1d** (65%, 0.102 g) was isolated after chromatography as a light yellow solid.

M. P. 98–100 ºC;

R_f = 0.53 (100% EtOAc);

FTIR (thin film) 3357, 2954, 2867, 1697, 1496, 1456, 1336, 1209, 1147, 862 cm^{-1};

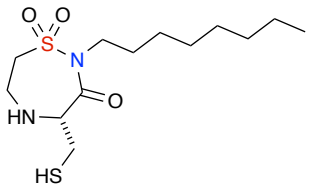
$[\alpha]_D^{20}$ = +22.2° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.38–7.32 (m, 2H), 7.31–7.24 (m, 2H), 5.09 (d, *J* = 15.0 Hz, 1H, NC$\underline{H}_a$$H_b$Ph), 4.84 (d, *J* = 15.0 Hz, 1H, NC$H_a$$\underline{H}_b$Ph), 4.21 [q, *J* = 6.8, Hz, 1H, HNC$\underline{H}$(C=O)], 3.55 (ddd, *J* = 15.2, 12.0, 3.2 Hz, 1H, O_2SC$\underline{H}_a$$H_b$$CH_2$NH), 3.40–3.27 (m, 2H, O_2SC$H_a$$\underline{H}_bC\underline{H}_a$$H_b$N), 3.04–2.93 (m, 1H, O_2SCH_2C$H_a$$\underline{H}_b$N), 1.30 (d, *J* = 6.7 Hz, 3H, NHCHC$\underline{H}_3$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 175.9, 136.1, 134.0, 129.4 (2), 128.9 (2), 56.3, 52.2, 46.5, 42.4, 19.0;

HRMS (ESI) m/z calculated for $C_{12}H_{15}ClN_2O_3SH$ $(M+H)^+$ 303.0570, found 303.0566 (TOF MS ES^+).

(*R*)-4-(mercaptomethyl)-2-octyl-1,2,5-thiadiazepan-3-one 1,1-dioxide (2.7.1e)



According to the reaction protocol described in general procedure **B**, compound **2.7.1e** (33%, 0.051 g) was isolated after chromatography as a light yellow solid.

M. P. 124–126 ºC;

R_f = 0.41 (100% EtOAc);

FTIR (thin film) 2954, 2931, 1693, 1456, 1355, 1209, 1151 cm^{-1};

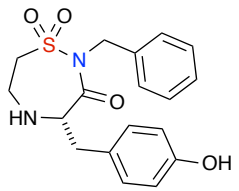
$[\alpha]_D^{20}$ = +20.2° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.18–4.05 [m, 1H, HNC<u>H</u>(C=O)], 3.87–3.72 (m, 2H, $O_2SC\underline{H}_2CH_2N$), 3.46–3.34 (m, 2H, $NC\underline{H}_2CH_2$), 3.32–3.20 (m, 2H, $O_2SCH_2C\underline{H}_2N$), 3.16–3.10 (m, 1H, $NHCHC\underline{H}_aH_bSH$), 2.68–2.61 (m, 1H, $NHCHCH_a\underline{H}_bSH$), 2.62–2.55 (m, 1H, among n-octyl), 1.93–1.83 (m, 1H, among n-octyl), 1.81–1.71 (m, 2H, among n-octyl), 1.69–1.58 (m, 2H, among n-octyl), 1.36–1.25 (m, 6H, among n-octyl) 0.92 (t, *J* = 6.8 Hz, 3H, among n-octyl);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.5, 64.3, 58.1, 55.7, 51.0, 46.4, 31.3, 29.4, 27.0, 26.1, 24.7, 22.8, 14.0;

HRMS calculated for $C_{13}H_{26}N_2O_3S_2Na$ $(M+Na)^+$ 345.1283, found 345.1284 (TOF MS ES^+).

(*S*)-2-benzyl-4-(4-hydroxybenzyl)-1,2,5-thiadiazepan-3-one 1,1-dioxide (2.7.1f)



According to the reaction protocol described in general procedure **B**, compound **2.7.1f** (41%, 0.11 g) was isolated after chromatography as a white solid.

M. P. 106–109 ºC;

R_f = 0.31 (100% EtOAc);

FTIR (thin film) 3601, 3200, 2946, 2933, 2870, 1693, 1612, 1454, 1305, 1149, 831, 703 cm^{-1};

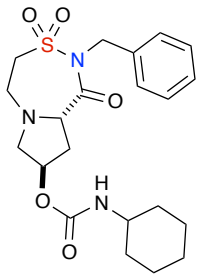
$[\alpha]_D^{20}$ = -28.2° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, Acetone) δ ppm 8.16 (s, 1H, Ar-OH), 7.39–7.34 (m, 2H), 7.34–7.29 (m, 2H), 7.28–7.23 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.01 (d, *J* = 15.5 Hz, 1H, NC$\underline{H}_a$$H_b$Ph), 4.92 (d, *J* = 15.3 Hz, 1H, NC$H_a$$\underline{H}_b$Ph), 4.33 [dd, *J* = 8.6, 5.6 Hz, 1H, HNC$\underline{H}$(C=O)], 3.51–3.38 (m, 2H, O_2SC$\underline{H}_2$$CH_2$NH), 3.32–3.22 (m, 2H, O_2SCH_2C$\underline{H}_2$NH), 3.12 (dd, *J* = 14.3, 5.6 Hz, 1H, HNCHC$\underline{H}_a$$H_b$PhOH), 2.64 (dd, *J* = 14.3, 8.6 Hz, 1H, HNCH$CH_a$$\underline{H}_b$PhOH);

^{13}C NMR (126 MHz, Acetone) δ ppm 173.9, 156.9, 138.6, 131.3 (2), 130.2, 129.2 (2), 128.8 (2), 128.2, 116.0 (2), 63.0, 57.1, 49.1, 46.6, 38.0;

HRMS calculated for $C_{18}H_{20}N_2O_4SH$ $(M+H)^+$ 361.1222, found 361.1200 (TOF MS ES^+).

(8*R*,9a*S*)-2-benzyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl cyclohexylcarbamate (2.8.1)



According to the reaction protocol described in general procedure **D**, compound **2.8.1** (37%, 0.102 g) was isolated after chromatography as a white solid.

M. P. 125–126 ºC;

R_f = 0.32 (1:1 Hexane:EtOAc);

FTIR (thin film) 3328, 2927, 1693, 1625, 1573, 1446, 1347, 1244, 1153, 1026, 742 cm^{-1};

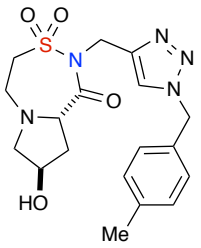
$[\alpha]_D^{20}$ = +17.5° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 (d, *J* = 7.2 Hz, 2H), 7.34 (dd, *J* = 8.1, 6.8 Hz, 2H), 7.30–7.26 (m, 1H), 5.16 (d, *J* = 15.1 Hz, 1H, $NC\underline{H}_aH_bPh$), 5.11–5.05 (m, 1H, $NCH_2C\underline{H}CH_2CH$), 4.91 (d, *J* = 15.1 Hz, 1H, $NCH_a\underline{H}_bPh$), 4.66 (bs, 1H, NH), 4.38 [t, *J* = 7.8 Hz, 1H, $NCH_2CHCH_2C\underline{H}(C{=}O)$], 3.55 (dd, *J* = 11.4, 4.4 Hz, 1H, $NC\underline{H}_aH_bCHCH_2$), 3.51–3.31 (m, 3H, $O_2SC\underline{H}_aH_bC\underline{H}_aH_bNCH_2CHOCONHC\underline{H}$), 3.28–3.15 (m, 2H, $O_2SCH_a\underline{H}_bCH_a\underline{H}_bN$), 2.78–2.68 (m, 2H, $NCH_a\underline{H}_bCHC\underline{H}_aH_bCH$), 2.14–2.06 (m, 1H, $NCH_2CHCH_a\underline{H}_bCH$), 1.98–1.89 (m, 2H, among Cy), 1.76–1.67 (m, 2H, among Cy), 1.65–1.57 (m, 1H, among Cy), 1.42–1.29 (m, 2H, among Cy), 1.23–1.02 (m, 3H, among Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.0, 154.8, 136.5, 128.6 (2), 128.3 (2), 127.7, 73.2, 64.4, 62.5, 56.5, 52.9, 49.9, 48.5, 34.4, 33.4 (2), 25.4 (2), 24.8;

HRMS calculated for $C_{21}H_{29}N_3O_5SH$ $(M+H)^+$ 436.1906, found 436.1910 (TOF MS ES^+).

(8*R*,9a*S*)-8-hydroxy-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (2.8.4)



According to the reaction protocol described in general procedure **E**, compound **2.8.4** (45%, 0.097 g) was isolated after chromatography as a white solid.

M. P. 125–126 ºC;

R_f = 0.27 (100% EtOAc);

FTIR (neat) 3685, 3380, 3353, 2972, 1708, 1444, 1355, 1218, 1151, 881 cm^{-1};

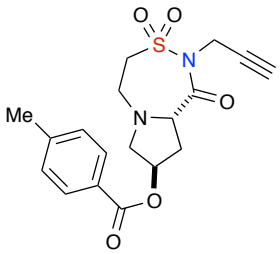
$[\alpha]_D^{20}$ = +17.5° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.45 (s, 1H, c-N=NN<u>H</u>C=C), 7.21–7.13 (m, 4H), 5.49 (d, *J* = 14.8 Hz, 1H, NCH_2-triazole-C<u>H</u>$_a$H$_b$-Ar), 5.44 (d, *J* = 14.7 Hz, 1H, NCH_2-triazole-CH$_a$<u>H</u>$_b$-Ar), 5.12 (d, *J* = 15.6 Hz, 1H, NC<u>H</u>$_a$H$_b$-triazole-CH_2-Ar), 5.06 (d, *J* = 15.5 Hz, 1H, NCH$_a$<u>H</u>$_b$-triazole-CH_2-Ar), 4.50–4.42 [m, 1H, $NCH_2CH(OH)CH_2C$<u>H</u>(C=O)], 4.34 [dddd, *J* = 5.2, 5.2, 5.1, 4.7 Hz, 1H, NCH_2C<u>H</u>$(OH)CH_2$], 3.77–3.67 (m, 1H, O_2SC<u>H</u>$_a$H$_b$$CH_2$N), 3.52–3.23 [m, 5H, O_2SCH_a<u>H</u>$_b$C<u>H</u>$_2$NC<u>H</u>$_a$H$_b$CH(O<u>H</u>)CH_2], 2.78–2.62 [m, 2H, NCH$_a$<u>H</u>$_b$CH(OH)C<u>H</u>$_a$H$_b$], 2.36 (s, 3H, Ar-CH_3), 1.99–1.92 [m, 1H, $NCH_2CH(OH)CH_a$<u>H</u>$_b$];

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.0, 143.6, 138.6, 131.5, 129.8 (2), 128.0 (2), 122.6, 70.0, 64.0, 63.6, 55.7, 53.7, 52.0, 40.1, 36.4, 21.1;

HRMS calculated for $C_{18}H_{23}N_5O_4SH$ $(M+H)^+$ 406.1549, found 406.1558 (TOF MS ES^+).

(8*R*,9a*S*)-3,3-dioxido-1-oxo-2-(prop-2-yn-1-yl)octahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-methylbenzoate (2.8.3)



According to the reaction protocol described in general procedure **F**, compound **2.8.3** (42%, 0.096 g) was isolated after chromatography as a white solid.

M. P. 117–119 ºC;

R_f = 0.62 (1:1 Hexane:EtOAc);

FTIR (thin film) 3365, 2975, 2929, 2254, 1735, 1708, 1444, 1355, 1220, 1153, 887 cm^{-1};

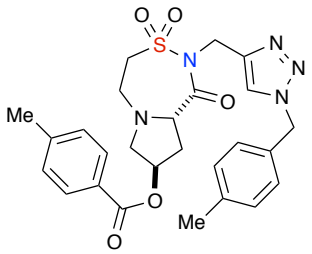
$[\alpha]_D^{20}$ = +18.4° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.93 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 5.42 [dd, *J* = 4.1, 4.0 Hz, 1H, $NCH_2C\underline{H}(OCOAr)CH_2CH$], 4.76 (dd, *J* = 17.5, 2.5 Hz, 1H, $NC\underline{H}_aH_bCCH$), 4.53 (dd, *J* = 17.6, 2.5 Hz, 1H, $NCH_a\underline{H}_bCCH$), 4.49 [t, *J* = 8.0 Hz, 1H, $NCH_2CHCH_2C\underline{H}(C{=}O)$], 3.72 (dd, *J* = 11.3, 4.5 Hz, 1H, $O_2SC\underline{H}_aH_bCH_2N$), 3.60–3.44 (m, 3H, $O_2SCH_a\underline{H}_bC\underline{H}_aH_bNC\underline{H}_aH_b$), 3.37–3.29 (m, 1H, $O_2SCH_2CH_a\underline{H}_bN$), 2.95–2.87 (m, 2H, $NCH_a\underline{H}_bCHC\underline{H}_aH_bCH$), 2.44 (s, 3H, Ar-$C\underline{H}_3$), 2.32 (t, *J* = 2.5 Hz, 1H, $NCH_2CC\underline{H}$), 2.31–2.28 (m, 1H, $NCH_2CHCH_a\underline{H}_bCH$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.0, 165.6, 144.1, 129.6 (2), 129.2 (2), 127.0, 77.8, 73.4, 72.1, 64.2, 62.3, 56.6, 52.9, 34.4, 34.1, 21.7;

HRMS calculated for $C_{18}H_{20}N_2O_5SH$ $(M+H)^+$ 377.1171, found 377.1171 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-methylbenzoate (2.8.2)



According to the reaction protocol described in general procedure **G**, compound **2.8.2** (35%, 0.091 g) was isolated after chromatography as a yellow solid.

M. P. 127–129 ºC;

R_f = 0.65 (100% EtOAc);

FTIR (thin film) 3392, 2931, 2854, 1701, 1693, 1496, 1352, 1220, 1151, 1058, 891 cm^{-1};

$[\alpha]_D^{20}$ = +18.8° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.92 (d, *J* = 8.2 Hz, 2H), 7.45 (s, 1H, c-N=NN$\underline{H}$C=C), 7.31–7.24 (m, 2H), 7.22–7.14 (m, 4H), 5.51 (d, *J* = 14.6 Hz, 1H, NCH_2-triazole-C$\underline{H}_a$$H_b$-Ar), 5.44 (d, *J* = 14.6 Hz, 1H, NCH_2-triazole-$CH_a$$\underline{H}_b$-Ar), 5.34 [dddd, *J* = 4.5, 4.4, 4.4 and 4.3 Hz, 1H, $NCH_2C\underline{H}$(OCOAr)CH_2], 5.13 (d, *J* = 15.3 Hz, 1H, NC$\underline{H}_a$$H_b$-triazole-$CH_2$-Ar), 5.11 (d, *J* = 15.3 Hz, 1H, $NCH_a$$\underline{H}_b$-triazole-$CH_2$-Ar), 4.49 [t, *J* = 7.8 Hz, 1H, $NCH_2CHCH_2C\underline{H}$(C=O)], 3.81–3.71 (m, 1H, $O_2SC\underline{H}_a$$H_b$$CH_2N$), 3.60 (dd, *J* = 11.2, 4.5 Hz, 1H, NC$\underline{H}_a$$H_b$$CHCH_2$), 3.52–3.37 (m, 2H, $O_2SCH_a$$\underline{H}_bC\underline{H}_a$$H_b$N), 3.26 (dt, *J* = 12.8, 3.7 Hz, 1H, $O_2SCH_2CH_a$$\underline{H}_b$N), 2.88–2.78 (m, 2H, $NCH_a$$\underline{H}_bCHC\underline{H}_a$$H_b$), 2.43 (s, 3H, Ar-C$\underline{H}_3$), 2.37 (s, 3H, Ar-C$\underline{H}_3$), 2.24 (dddd, *J* = 13.9, 8.2, 4.2, 1.5 Hz, 1H, $NCH_2CHCH_a$$\underline{H}_b$);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.4, 166.0, 144.1, 143.4, 139.0, 131.5, 129.8 (2), 129.6 (2), 129.2 (2), 128.1 (2), 127.0, 122.7, 73.3, 64.2, 62.1, 55.9, 54.0, 52.8, 40.3, 34.0, 21.8, 21.2;

HRMS calculated for $C_{26}H_{29}N_5O_5SH$ $(M+H)^+$ 524.1968, found 524.1968 (TOF MS ES^+).

5.2 Experimental for Chapter 3.1

One-pot Click-Esterification and One-pot Click-Mitsnobu Protocols to a sp^3-Rich Library of Bicyclic Acyl Sultams

General procedures: All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_2Cl_2 was purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Organometallics 1996, 15, 1518-1520). Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. 1H and ^{13}C NMR spectra were recorded on a Bruker Avance operating at 500 MHz and 126 MHz respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained in one of two manners: (i) on a VG Instrument ZAB double-focusing mass spectrometer and (ii) on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). All library syntheses were carried out in 1 dram. Automated preparative reverse-phase HPLC purification was performed using an Waters Mass-Directed Fractionation system (Prep Pump 2525, Make-up pump 515, Sample Manager 2767, UV-DAD detection 2996, Micromass ZD quadrapole spectrometer) and a Waters X-Bridge C18 column (19 x 150mm, 5um, w/ 19 x 10mm guard column). Samples were diluted in DMSO and purified utilized an elution of water (modified to pH 9.8 through addition of NH_4OH) and CH_3CN, with a gradient increasing to 20% in CH_3CN over 4 minutes at a flow rate of 20ml/min,. The preparative gradient, triggering thresholds, and UV wavelength were selected based on the HPLC analysis of each crude sample. Analytical analysis of each sample after purification employed an Waters Acquity system with UV and mass detection (Waters LCT Premier). The analytical method utilized a Waters Aquity BEH C18 column (2.1 x 50mm, 1.7um) eluting with a linear gradient of 5% water (modified to pH 9.8 through addition of NH_4OH) to 100% CH_3CN at 0.6 mL/min flow rate were purity was determined using UV peak area at 214 nm.

Note: All reactions involving the use and heating of azides were carried out behind a safety shield taking extra precaution due to the explosive nature of these materials.

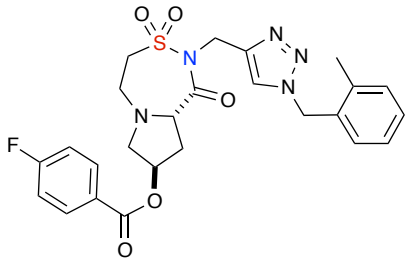
General procedure A for the synthesis of core via sulfonylation, aza-Michael and amide coupling. To a round-bottom flask containing CH_2Cl_2 (344 mL, 0.5 M), propargyl amine (9.46 g, 172 mmol, 1 equiv.) and Et_3N (44.5 mL, 344 mmol, 2 equiv.) at 0ºC was added 2-chloro-sulfonyl chloride (18 mL, 172 mmol, 1 equiv.) drop-wise. The reaction was stirred overnight at room temperature. After the completion of the reaction, the solvent was evaporated to dryness. Methanol (172 mL, 1 M) and water (172 mL, 1 M) were added to the crude mixture followed by the addition of Et_3N (67 mL, 516 mmol, 3 equiv.), then *L*-trans Hydroxyproline (23.84 g, 186 mmol, 1.05 equiv.) was added to the reaction mixture. The reaction was stirred at 60ºC for 12 h. After the disappearance of the starting material the solvents were again evaporated to dryness. Next Dimethyl formamide (DMF) (860 mL, 0.2 M) was added followed by EDC (53.4 g, 344 mmol, 2 equiv.), HOBt (4.6 g, 34.4 mmol, 0.2 equiv.) and Et_3N (44.5 mL, 344 mmol, 2 equiv.). The reaction was stirred for 12 h at rt. After the completion of the reaction DMF was evaporated followed by addition of EtOAc and work up with water.

General procedure B for the synthesis of library I via a one-pot click/Esterification protocol. To a 1-dram vial containing (8*R*,9a*S*)-8-hydroxy-2-(prop-2-yn-1-yl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide **3.1.1** (50 mg, 0.29 mmol, 1 equiv.) was added OACC (64 mg, 0.25 mmol, 1 equiv.) DBU (6 μL, 10 mol%), CH_2Cl_2 (1.2 mL, 0.5 M), DMAP (2.2 mg, 10 mol%), azide (0.3 mmol, 1.2 equiv.), Carboxylic acid (0.3 mmol, 1.2 equiv.) and CuI (11 mg, 30 mol%). The reaction was heated at 60 ºC on a reaction block for for 12 hrs, after which time the reactions were cooled. The OACC polymer was precipitated with EtOAc and filtered through an SiO_2 SPE into apre-weighed bar-coded vial, washed with eluent (2 mL, EtOAc) and concentrated under reduced pressure. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

General procedure C for the synthesis of library I via a one-pot click/Mitsunobu protocol. To a 1-dram vial containing (8*R*,9a*S*)-8-hydroxy-2-(prop-2-yn-1-yl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide **3.1.1** (10 mg, 0.004 mmol, 1 equiv.), was added carboxylic acid (0.0048 mmol, 1.2 equiv.)

followed by the dropwise addition of a stock solution Nb-PPh_3 (0.008 mmol, 2 equiv.) and Nb-BEAD (0.008 mmol, 2 equiv.) in THF. The reaction was run for 12 h. After the completion of the reaction was added CuI (0.152 mg, 0.0008 mmol, 0.2 equiv.) and DBU (2 μL, 0.0008 mmol, 0.2 equiv.). The reaction mixture was stirred for 12 h. After such time Grubbs-II catalyst (0.0008 mmol, 0.2 equiv.) was added and the reaction was run at 45ºC for 12 h. The reaction was cooled to rt, quenched by the addition of ethyl vinyl ether (EVE) and stirred for 30 minutes followed by addition of EtOAc and passing through a silica SPE. The SPE was washed 1x with EtOAc. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

(8*R*,9a*S*)-2-((1-(2-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-fluorobenzoate 3.2.1(1){2} **(NA-6-156B)**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(1){2}** (77%, 118.5 mg) was isolated as brownish oil.

FTIR (neat) 1712, 1602, 1433, 1311, 1174, 856, 769, 688, 513 cm^{-1};

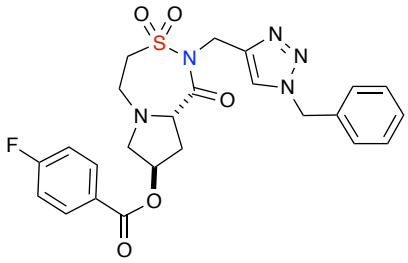
$[\alpha]_D^{20}$ = +21.2° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 8.00 (m, 2H), 7.35 (s, 1H), 7.32 – 7.27 (m, 1H), 7.25 – 7.20 (m, 2H), 7.16 – 7.10 (m, 3H), 5.55 (d, J = 14.8 Hz, 1H), 5.50 (d, J = 14.8 Hz, 1H), 5.32 (dddd, J = 4.7, 4.7, 4.5, 4.5 Hz, 1H), 5.12 (d, J = 15.6 Hz, 1H), 5.07 (d, J = 15.6 Hz, 1H), 4.47 (t, J = 7.7 Hz, 1H), 3.83–3.74 (m, 1H), 3.59 (dd, J = 11.1, 4.5 Hz 1H), 3.49 – 3.37 (m, 2H), 3.25 (ddd, J = 13.7, 4.3, 3.4 Hz, 1H), 2.92 – 2.78 (m, 2H), 2.26 (s, 3H), 2.22 (dddd, J = 13.9, 8.2, 4.4, 1.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.3, 165.6 ($^1J_{C–F}$ = 254.45 Hz), 164.9, 143.2, 136.9, 132.4, 132.1 ($^3J_{C–F}$ = 9.41 Hz, 2), 131.0, 129.3, 129.1, 126.6, 125.9 ($^4J_{C–F}$ = 3.28 Hz), 122.6, 115.7 (^2J = 21.90 Hz, 2), 73.5, 64.0, 62.0, 55.8, 52.6, 52.4, 40.2, 33.9, 18.9;

HRMS calculated for $C_{25}H_{26}FN_5O_5SH$ $(M+H)^+$ 528.1717; found 528.1702 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-fluorobenzoate 3.2.1(1){3} **(NA-6-156C)**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(1){3}** (74%, 109.7 mg) was isolated as dark orange oil.

FTIR (thin film) 2352, 2320, 1714, 1695, 1602, 1427, 1353, 1153, 1053, 555 cm^{-1};

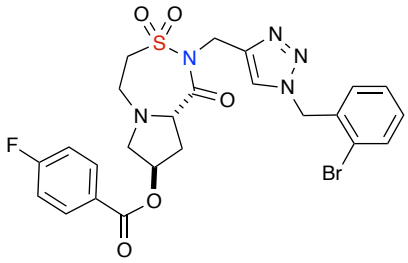
$[\alpha]_D^{20}$ = +22.6 ° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 –8.01 (m, 2H), 7.47 (s, 1H), 7.42 – 7.34 (m, 3H), 7.28 – 7.25 (m, 2H), 7.17 – 7.10 (m, 2H), 5.55 (d, *J* = 14.9 Hz, 1H), 5.48 (d, *J* = 14.9 Hz, 1H), 5.33 (dddd, *J* = 4.7, 4.7, 4.5, 4.5 Hz, 1H), 5.14 (d, *J* = 15.5, Hz, 1H), 5.08 (d, *J* = 15.6 Hz, 1H), 4.48 (t, *J* = 7.8 Hz, 1H), 3.83–3.74 (m, 1H), 3.60 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.50 – 3.39 (m, 2H), 3.26 (ddd, *J* = 14.1, 4.3, 3.4 Hz, 1H), 2.89 – 2.79 (m, 2H), 2.23 (dddd, *J* = 13.8, 8.2, 4.2, 1.4 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.2, 165.92 ($^1J_{C–F}$ = 254.60 Hz), 164.9, 143.4, 134.5, 132.1 ($^3J_{C–F}$ = 9.45 Hz, 2), 129.1 (2), 128.8, 128.0 (2), 125.9 ($^4J_{C–F}$ = 3.04 Hz), 122.8, 115.7 (^2J = 22.07 Hz, 2), 73.5, 64.0, 62.0, 55.8, 54.2, 52.7, 40.3, 33.9;

HRMS calculated for $C_{24}H_{24}FN_5O_5SH$ $(M+H)^+$ 514.1560; found 514.1574 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(2-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-fluorobenzoate 3.2.1(1){10} **(NA-6-156-I)**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(1){10}** (54%, 92.6 mg) was isolated as dark brown oil.

FTIR (thin film) 1712, 1602, 1506, 1409, 1355, 1271, 1153, 1118, 854, 769, 553 cm^{-1};

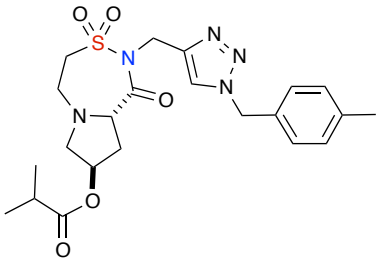
$[\alpha]_D^{20}$ = +25.5° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.07 – 8.01 (m, 2H), 7.53 – 7.49 (m, 2H), 7.47 (s, 1H), 7.17–7.10 (m, 4H), 5.50 (d, J = 15.0 Hz, 1H), 5.44 (d, J = 15.0 Hz, 1H), 5.33 (dddd, J = 4.7, 4.7, 4.5, 4.5 Hz, 1H), 5.14 (d, J = 15.6 Hz, 1H), 5.07 (d, J = 15.5 Hz, 1H), 4.47 (t, J = 7.7 Hz, 1H), 3.81–3.72 (m, 1H), 3.60 (dd, J = 11.1, 4.6 Hz, 1H), 3.50 – 3.40 (m, 2H), 3.27 (ddd, J = 13.6, 4.2, 3.4 Hz, 1H), 2.89 – 2.80 (m, 2H), 2.23 (dddd, J = 13.9, 8.2, 4.3, 1.4 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.4, 165.91, ($^1J_{C–F}$ = 254.50 Hz), 164.9, 143.7, 133.5, 132.3, 132.2, 132.1 ($^3J_{C–F}$ = 9.30 Hz, 2), 129.6, 125.95, 125.9 ($^4J_{C–F}$ = 3.10 Hz), 122.9, 122.8, 115.8 (^2J = 22.47 Hz, 2), 73.5, 64.1, 61.9, 55.8, 53.5, 52.6, 40.3, 33.9;

HRMS calculated for $C_{24}H_{23}BrFN_5O_5SH$ $(M+H)^+$ 592.0666; found 592.0646 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl isobutyrate 3.2.1(2){1} **(NA-6-165-IA)**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(2){1}** (61%, 83.5 mg) was isolated as dark orange oil.

FTIR (thin film) 2974, 1731, 1703, 1434, 1353, 1151, 1053, 781, 555 cm^{-1};

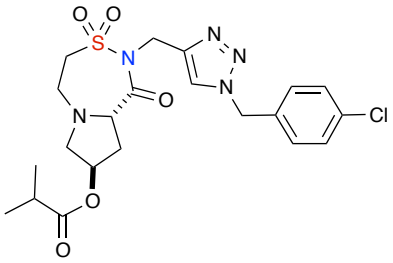
$[\alpha]_D^{20}$ = +26.4° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.19 – 7.13 (m, 4H), 5.49 (d, *J* = 14.8 Hz, 1H), 5.42 (d, *J* = 14.8 Hz, 1H), 5.13–5.02 (m, 3H), 4.36 (t, *J* = 7.8 Hz, 1H), 3.78 – 3.68 (m, 1H), 3.47 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.44 – 3.35 (m, 2H), 3.23–3.16 (m, 1H), 2.77 – 2.63 (m, 2H), 2.59–2.46 (m, 1H), 2.35 (s, 3H), 2.06 (dddd, *J* = 13.7, 8.1, 4.1, 1.5 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 6H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 176.4, 170.4, 143.4, 138.6, 131.4, 129.7 (2), 128.0 (2), 122.6, 76.7, 72.6, 64.0, 61.9, 55.8, 53.9, 52.6, 40.2, 33.9, 21.1, 18.9, 18.9;

HRMS calculated for $C_{22}H_{29}N_5O_5SH$ $(M+H)^+$ 476.1968; found 476.2006 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl isobutyrate 3.2.1(2){4} **NA-6-165-I-D**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(2){4}** (39%, 56.5 mg) was isolated as dark brown oil.

FTIR (thin film) 2974, 1731, 1704, 1492, 1434, 1353, 1151, 904 cm^{-1};

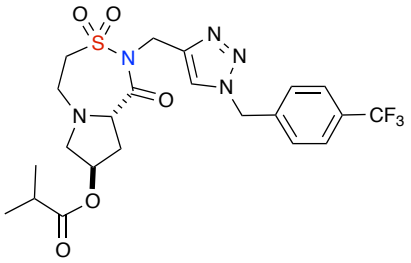
$[\alpha]_D^{20}$ = +29.9° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.46 (s, 1H), 7.37 – 7.33 (m, 2H), 7.22 – 7.17 (m, 2H), 5.51 (d, *J* = 15.0 Hz, 1H), 5.44 (d, *J* = 15.0 Hz, 1H), 5.13 (d, *J* = 15.6 Hz, 1H), 5.10 – 5.02 (m, 2H), 4.37 (t, *J* = 7.8 Hz, 1H), 3.77–3.67 (m, 1H), 3.48 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.45 – 3.37 (m, 2H), 3.22 (ddd, *J* = 13.1, 3.6, 3.5 Hz, 1H), 2.77 – 2.64 (m, 2H), 2.59 – 2.48 (m, 1H), 2.07 (dddd, *J* = 13.7, 8.1, 4.0, 1.5 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 170.5, 143.7, 134.8, 133.0, 129.3 (2), 129.3 (2), 122.8, 72.5, 64.0, 61.9, 55.9, 53.4, 52.6, 40.2, 33.9, 33.8, 18.9, 18.9;

HRMS calculated for $C_{21}H_{26}ClN_5O_5SH$ $(M+H)^+$ 496.1421; found 496.1421 (TOF MS ES^+).

(8*R*,9a*S*)-3,3-dioxido-1-oxo-2-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl) octahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl isobutyrate 3.2.1(2){6} **NA-6-165-I-F**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(2){6}** (53%, 81.2 mg) was isolated as dark yellow solid.

M.P. 124 – 129ºC

FTIR (thin film) 2975, 1731, 1704, 1463, 1355, 1325, 1153, 1124, 825 cm^{-1};

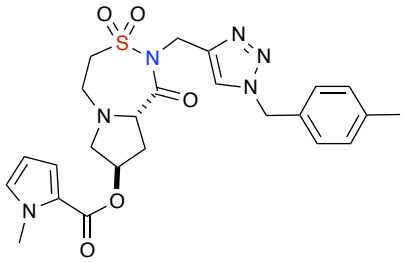
$[\alpha]_D^{20}$ = +26.8° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.64 (d, J = 7.8 Hz, 2H), 7.51 (s, 1H), 7.36 (d, J = 8.1 Hz, 2H), 5.61 (d, J = 15.2 Hz, 1H), 5.54 (d, J = 15.3 Hz, 1H), 5.15 (d, J = 15.6 Hz, 1H), 5.11 – 5.03 (m, 2H), 4.38 (t, J = 7.8 Hz, 1H), 3.77–3.69 (m, 1H), 3.49 (dd, J = 11.1, 4.5 Hz, 1H), 3.46–3.38 (m, 2H), 3.23 (ddd, J = 13.1, 3.6, 3.6 Hz, 1H), 2.72 (ddd, J = 13.5, 7.5, 6 Hz, 1H), 2.67 (ddd, J = 11.1, 3.9, 1.4 Hz, 1H), 2.54 (hept, J = 7.0 Hz, 1H), 2.08 (dddd, J = 13.8, 8.2, 4.3, 1.4 Hz, 1H), 1.17 (d, J = 7.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 176.5, 170.5, 143.9, 138.5, 131.1 (q, $^2J_{C–F}$ = 36.37 Hz), 128.2 (2), 126.1 (q, $^3J_{C–F}$ = J = 3.81 Hz (2)), 124.0 (q, $^1J_{C–F}$ = 273.37 Hz), 123.0, 72.5, 64.1, 61.4, 55.9, 53.5, 52.6, 40.3, 33.9, 33.8, 18.9, 18.9;

HRMS calculated for $C_{22}H_{26}F_3N_5O_5SH$ $(M+H)^+$ 530.1685; found 530.1682 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 1-methyl-1*H*-pyrrole-2-carboxylate 3.2.1(3){1} **NA-6-165-2A**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(3){1}** (28%, 42.1 mg) was isolated as dark brown solid.

M.P. 128 – 134ºC

FTIR (thin film) 1699, 1681, 1411,1353, 1153, 1114, 821 cm^{-1};

$[\alpha]_D^{20}$ =+27.7° (*c* = 2.0, CH_2Cl_2);

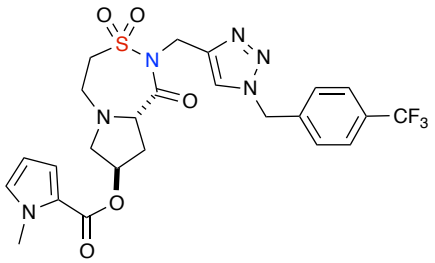
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.20 – 7.13 (m, 4H), 6.94 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.82 (dd, *J* = 2.2, 2.2 Hz, 1H), 6.13 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.50 (d, *J* = 14.8 Hz, 1H), 5.43 (d, *J* = 14.8 Hz, 1H), 5.25 (ddd, *J* = 8.7, 5.4, 4.0 Hz, 1H), 5.12 (d, *J* = 15.5 Hz, 1H), 5.06 (d, *J* = 15.5 Hz, 1H), 4.46 (t, *J* = 7.8 Hz, 1H), 3.93 (s, 3H), 3.75 (*J* = ddd, 14.1, 12.1, 4.2 Hz, 1H), 3.55 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.50 – 3.43 (m, 1H), 3.40 (ddd, *J* = 14.1, 2.5, 2.5 1H), 3.24 (ddd, *J* = 13.2, 3.7, 3.5 Hz, 1H), 2.83 – 2.74 (m, 2H), 2.35 (s, 3H), 2.19 (dddd, *J* = 13.6, 7.9, 3.9, 1.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.3, 160.4, 143.4, 138.7, 131.5, 130.0, 129.7 (2), 128.0 (2), 122.7, 121.9, 118.2, 108.0, 72.2, 64.2, 62.2, 55.8, 53.9, 52.8, 40.3, 36.8, 34.1, 21.2;

HRMS calculated for $C_{24}H_{28}N_6O_5SH$ $(M+H)^+$ 513.1920; found 513.1926 (TOF MS ES^+).

(8*R*,9a*S*)-3,3-dioxido-1-oxo-2-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)octahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 1-methyl-1*H*-pyrrole-2-carboxylate 3.2.1(3){6}

NA-6-165-2F



According to the reaction protocol described in general procedure **B**, compound **3.2.1(3){6}** (26%, 43.3 mg) was isolated as dark orange oil.

M.P. 137 – 144ºC

FTIR (thin film) 2360, 1710, 1510, 1473, 1353, 1294, 1153, 1122, 827 cm^{-1};

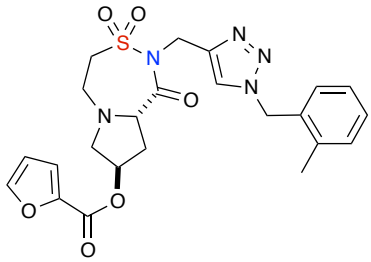
$[\alpha]_D^{20}$ =+29.7° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.65 (d, J = 8.0 Hz, 2H), 7.52 (s, 1H), 7.36 (d, J = 8.1 Hz, 2H), 6.94 (dd, J = 4.0, 1.8 Hz, 1H), 6.82 (dd, J = 2.2, 2.2 Hz, 1H), 6.13 (dd, J = 4.0, 2.5 Hz, 1H), 5.61 (d, J = 15.3 Hz, 1H), 5.55 (d, J = 15.3 Hz, 1H), 5.26 (ddd, J = 8.9, 4.4, 4.4 Hz 1H), 5.17 (d, J = 15.6 Hz, 1H), 5.07 (d, J = 15.6 Hz, 1H), 4.46 (t, J = 7.8 Hz, 1H), 3.93 (s, 3H), 3.80 – 3.70 (m, 1H), 3.56 (dd, J = 11.1, 4.5 Hz, 1H), 3.52 – 3.39 (m, 2H), 3.30–3.23 (m, 1H), 2.84 – 2.75 (m, 2H), 2.20 (dddd, J = 13.9, 8.2, 4.3, 1.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.4, 160.4, 144.0, 138.5, 131.1, 130.1 (q, $^2J_{C–F}$ = 36.37 Hz), 130.0, 128.1 (2), 126.2 (q, $^3J_{C–F}$ = 3.63 Hz (2)), 123.3 ($^1J_{C–F}$ = 273.88 Hz), 121.9, 118.3, 108.0, 72.1, 64.2, 62.1, 55.8, 53.4, 52.8, 40.3, 36.8, 34.0;

HRMS calculated for $C_{24}H_{25}F_3N_6O_5SH$ $(M+H)^+$ 567.1637; found 567.1629 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(2-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl furan-2-carboxylate 3.2.1(4){2} **NA-6-165-3B**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(4){2}** (54%, 78.6 mg) was isolated as a dark brownoil.

FTIR (thin film) 2351, 1714, 1722, 1695, 1446, 1353, 1294, 1151, 1053, 1012, 775 cm^{-1};

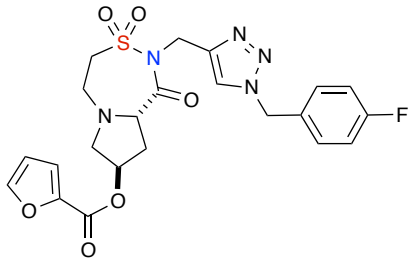
$[\alpha]_D^{20}$ = +33.1° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.35 (s, 1H), 7.32 – 7.27 (m, 1H), 7.25 – 7.20 (m, 2H), 7.20 (dd, *J* = 3.5, 0.8 Hz, 1H), 7.16 – 7.13 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.53 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.55 (d, *J* = 14.9 Hz, 1H), 5.50 (d, *J* = 14.8 Hz, 1H), 5.30 (ddd, *J* = 9.3, 4.9, 4.8 Hz, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 4.47 (t, *J* = 7.7 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.57 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.50 – 3.38 (m, 2H), 3.28–3.21 (m, 1H), 2.86 – 2.78 (m, 2H), 2.26 (s, 3H), 2.22 (dddd, *J* = 13.9, 8.3, 4.4, 1.4 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.2, 157.9, 146.7, 144.2, 143.1, 136.9, 132.4, 131.0, 129.4, 129.2, 126.6, 122.6, 118.5, 112.0, 73.2, 64.0, 62.0, 55.7, 52.5, 41.0, 40.2, 33.7, 18.9;

HRMS calculated for $C_{23}H_{25}N_5O_6SH$ $(M+H)^+$ 500.1604; found 500.1612 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl furan-2-carboxylate 3.2.1(4){5} **NA-6-165-3E**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(4){5}** (60%, 87.8 mg) was isolated as dark orange solid.

FTIR (thin film) 2358, 1704, 1525, 1492, 1417, 1353, 1259, 1222, 1095, 1014 852 cm^{-1};

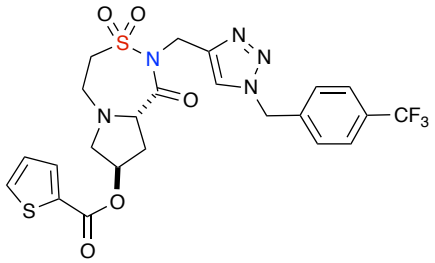
$[\alpha]_D^{20}$ = +27.4° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (dd, J = 1.7, 0.9 Hz, 1H), 7.46 (s, 1H), 7.28 – 7.23 (m, 2H), 7.20 (dd, J = 3.5, 0.9 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.53 (dd, J = 3.5, 1.7 Hz, 1H), 5.52 (d, J = 14.9 Hz, 1H), 5.45 (d, J = 14.9 Hz, 1H), 5.32 (ddd, J = 9.3, 4.5, 4.5 Hz, 1H), 5.13 (d, J = 15.6 Hz, 1H), 5.07 (d, J = 15.6 Hz, 1H), 4.46 (t, J = 7.7 Hz, 1H), 3.81–3.72 (m, 1H), 3.57 (dd, J = 11.1, 4.6 Hz, 1H), 3.50 – 3.39 (m, 2H), 3.26 (ddd, J = 14.4, 4.5, 3.3 Hz, 1H), 2.87 – 2.79 (m, 2H), 2.22 (dddd, J = 13.9, 8.2, 4.3, 1.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.2, 165.9 ($^1J_{C–F}$ = 254.60 Hz), 164.9, 143.4, 134.5, 132.1 ($^3J_{C–F}$ = 9.45 Hz, 2), 129.1, 128.8, 128.0, 125.9 ($^4J_{C–F}$ = 3.04 Hz), 122.8, 115.7 (^2J = 22.07 Hz, 2), 73.5, 64.0, 62.0, 55.8, 54.2, 52.7, 40.3, 33.9;

HRMS calculated for $C_{22}H_{22}FN_5O_6SH$ $(M+H)^+$ 504.1353; found 504.1354 (TOF MS ES^+).

(8*R*,9a*S*)-3,3-dioxido-1-oxo-2-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)octahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl thiophene-2-carboxylate 3.2.1(5){6} **NA-6-165-4F**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(5){6}** (39%, 65.0 mg) was isolated as a dark brown solid.

M.P. 145 – 149ºC

FTIR (thin film) 2351, 1697, 1556, 1446, 1355, 1325, 1263, 1153, 1122, 1018, 823 cm^{-1};

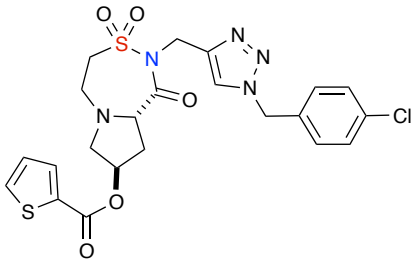
$[\alpha]_D^{20}$ =+29.7° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.81 (dd, J = 3.8, 1.3 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.59 (dd, J = 4.9, 1.3 Hz, 1H), 7.52 (s, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.13 (dd, J = 5.0, 3.7 Hz, 1H), 5.62 (d, J = 15.3 Hz, 1H), 5.55 (d, J = 15.3 Hz, 1H), 5.32 (ddd, J = 8.8, 5.5, 4.2 Hz, 1H), 5.16 (d, J = 15.6 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 4.46 (t, J = 7.8 Hz, 1H), 3.75 (ddd, J = 16.0, 12.2, 4.5 Hz, 1H), 3.57 (dd, J = 11.2, 4.4 Hz, 1H), 3.52 – 3.40 (m, 2H), 3.27 (ddd, J = 13.0, 3.9, 3.2 Hz, 1H), 2.87 – 2.77 (m, 2H), 2.24 (dddd, J = 13.8, 8.1, 4.1, 1.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.5, 161.4, 143.9, 138.4, 133.8, 133.2, 133.0, 131.1 (q, $^2J_{C–F}$ = 32.26 Hz), 128.1 (2), 128.0, 126.1 (q, $^3J_{C–F}$ = 3.63 Hz (2)), 123.1 (q, $^1J_{C–F}$ = 273.07 Hz), 123.0, 73.6, 64.1, 61.9, 55.9, 53.4, 52.8, 40.3, 33.9;

HRMS calculated for $C_{23}H_{22}F_3N_5O_5S_2H$ $(M+H)^+$ 570.1093; found 570.1103 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl thiophene-2-carboxylate 3.2.1(5){4} **NA-6-165-4D**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(5){4}** (52%, 81.5 mg) was isolated as dark orange oil.

FTIR (thin film) 1718, 1701, 1510, 1473, 1388, 1353, 1294,1180, 1153, 827 cm^{-1};

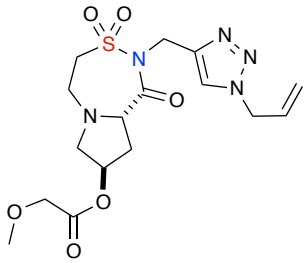
$[\alpha]_D^{20}$ =+31.7° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.81 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.59 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.48 (s, 1H), 7.37 – 7.33 (m, 2H), 7.22 – 7.18 (m, 2H), 7.13 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.52 (d, *J* = 15.0 Hz, 1H), 5.45 (d, *J* = 15.1 Hz, 1H), 5.32 (ddd, *J* = 8.8, 5.4, 3.9 Hz, 1H), 5.14 (d, *J* = 15.7 Hz, 1H), 5.07 (d, *J* = 15.4 Hz, 1H), 4.48 (t, *J* = 7.8 Hz, 1H), 3.76 (ddd, *J* = 14.2, 12.1, 4.2 Hz, 1H), 3.58 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.53 – 3.40 (m, 2H), 3.27 (ddd, *J* = 13.1, 3.6, 3.6 Hz, 1H), 2.89 – 2.77 (m, 2H), 2.24 (dddd, *J* = 13.7, 8.0, 4.0, 1.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.3, 161.4, 143.71, 134.8, 133.8, 133.2, 133.0, 132.9, 129.4 (2), 129.3 (2), 128.0, 122.8, 73.6, 64.2, 61.9, 55.9, 53.4, 52.8, 40.3, 34.0;

HRMS calculated for $C_{22}H_{22}ClN_5O_5S_2H$ $(M+H)^+$ 536.0829; found 536.0826 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-allyl-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 2-methoxyacetate 3.2.1(7){8} **NA-6-165-6H**



According to the reaction protocol described in general procedure **B**, compound **3.2.1(7){8}** (40%, 48.1 mg) was isolated as dark brown oil.

FTIR (thin film) 2931, 2833, 1751, 1704, 1431, 1353, 1191, 1153, 1128, 1051 cm^{-1};

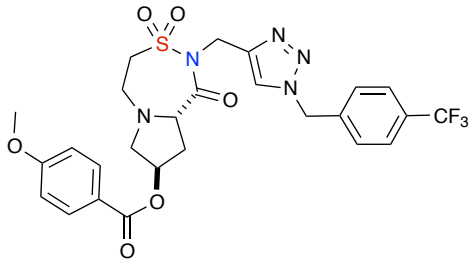
$[\alpha]_D^{20}$ = +35.6° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.53 (s, 1H), 6.01 (dddd, *J* = 16.5, 10.2, 6.2, 6.2 Hz, 1H), 5.36 (ddd, *J* = 10.2, 2.6, 1.1 Hz, 1H), 5.28 (ddd, *J* = 17.1, 2.4, 1.5 Hz, 1H), 5.19 (ddd, *J* = 9.6, 4.5, 4.5 Hz, 1H), 5.14 (d, *J* = 15.5 Hz, 1H), 5.08 (d, *J* = 15.6 Hz, 1H), 5.01 – 4.91 (m, 2H), 4.46 – 4.33 (m, 1H), 4.04 – 4.02 (m, 1H), 3.81 – 3.71 (m, 1H), 3.51 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.46 – 3.44 (m, 2H), 3.45 (s, 3H), 3.23 (ddd, *J* = 13.3, 4.0, 3.8 Hz, 1H), 2.83 – 2.75 (m, 1H), 2.73 – 2.67 (m, 1H), 2.40 – 2.23 (m, 1H), 2.10 (dddd, *J* = 14.0, 8.4, 4.6, 1.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.3, 169.7, 143.3, 131.0, 122.7, 120.2, 73.1, 69.7, 63.7, 61.5, 59.5, 55.8, 52.7, 52.3, 40.3, 33.7;

HRMS calculated for $C_{16}H_{23}N_5O_6SH$ $(M+H)^+$ 414.1447; found 414.1477 (TOF MS ES^+).

(8*R*,9a*S*)-3,3-dioxido-1-oxo-2-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)octahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-methoxybenzoate 3.2.1(8){6} **NA-6-165-7F**



According to the reaction protocol described in general procedure **C**, compound **3.2.1(8){6}** (35%, 60.7 mg) was isolated as dark brown solid.

M.P. 138 – 142ºC

FTIR (thin film) 2956, 2939, 1708, 1605, 1512, 1421, 1355, 1325, 1255, 1168, 1153, 1122 cm^{-1};

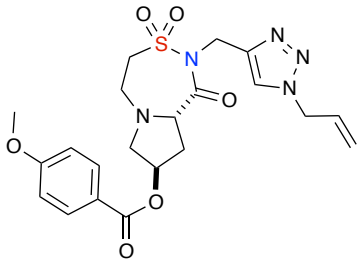
$[\alpha]_D^{20}$ =+29.3° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.99 – 7.95 (m, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.52 (s, 1H), 7.36 (d, J = 8.1 Hz, 2H), 6.96 – 6.91 (m, 2H), 5.62 (d, J = 15.3 Hz, 1H), 5.55 (d, J = 15.3 Hz, 1H), 5.32 (ddd, J = 9.0, 4.8, 4.8 Hz, 1H), 5.16 (d, J = 15.6 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 4.46 (t, J = 7.8 Hz, 1H), 3.88 (s, 3H), 3.79 – 3.71 (m, 1H), 3.58 (dd, J = 11.1, 4.5 Hz, 1H), 3.51 – 3.40 (m, 2H), 3.26 (ddd, J = 14.2, 4.4, 3.2 Hz, 1H), 2.86 – 2.78 (m, 2H), 2.23 (dddd, J = 13.7, 8.1, 4.2, 1.4 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.6, 165.6, 163.6, 143.9, 138.5, 131.6 (2), 131.1 (q, $^2J_{C–F}$ = 32.98 Hz), 130.9, 128.1 (2), 126.1 (q, $^3J_{C–F}$ = 3.65 Hz (2)), 123.7 ($^1J_{C–F}$ = 273.07 Hz), 123.0, 122.1, 113.7 (2), 73.0, 64.2, 62.1, 56.0, 55.8, 53.4, 52.8, 34.0;

HRMS calculated for $C_{26}H_{26}F_3N_5O_6SH$ $(M+H)^+$ 594.1634; found 594.1618 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-allyl-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-methoxybenzoate 3.2.1(8){8} **NA-6-165-7H**



According to the reaction protocol described in general procedure **C**, compound **3.2.1(8){8}** (25%, 33.6 mg) was isolated as dark brown oil.

FTIR (thin film) 1701, 1604, 1512, 1421, 1355, 1257, 1168, 1153, 825 cm^{-1};

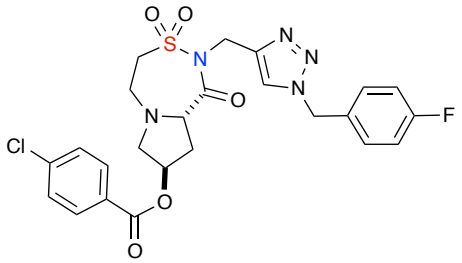
$[\alpha]_D^{20}$ = +36.8° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.99 – 7.95 (m, 2H), 7.55 (s, 1H), 6.95 – 6.91 (m, 2H), 6.02 (dddd, *J* = 17.1, 10.2, 6.1, 6.1 Hz, 1H), 5.36 (ddd, *J* = 10.2, 2.2, 1.2 Hz, 1H), 5.34 – 5.31 (m, 1H), 5.29 (ddd, *J* = 17.0, 2.4, 1.5 Hz, 1H), 5.17 (d, *J* = 15.6 Hz, 1H), 5.10 (d, *J* = 15.5 Hz, 1H), 5.02 – 4.92 (m, 2H), 4.48 (t, *J* = 7.8 Hz, 1H), 3.87 (s, 3H), 3.80 – 3.72 (m, 1H), 3.60 (dd, *J* = 11.2, 4.5 Hz, 1H), 3.51 – 3.40 (m, 2H), 3.26 (ddd, *J* = 14.1, 4.5, 4.0 Hz, 1H), 2.87 – 2.79 (m, 2H), 2.24 (dddd, *J* = 13.8, 8.1, 4.1, 1.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.5, 165.6, 163.6, 143.4, 131.6 (2), 131.1, 122.8, 122.1, 120.2, 113.7 (2), 73.1, 64.2, 62.1, 56.0, 55.5, 52.8, 52.7, 40.3, 34.0;

HRMS calculated for $C_{21}H_{25}N_5O_6SH$ $(M+H)^+$ 476.1604; found 476.1591 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-chlorobenzoate 3.2.1(9){5} **NA-6-165-8E**



According to the reaction protocol described in general procedure **C**, compound **3.2.1(9){5}** (45%, 72.4 mg) was isolated as golden oil.

FTIR (thin film) 1718, 1701, 1512, 1431, 1355, 1271, 1153, 1120, 1014, 827 cm^{-1};

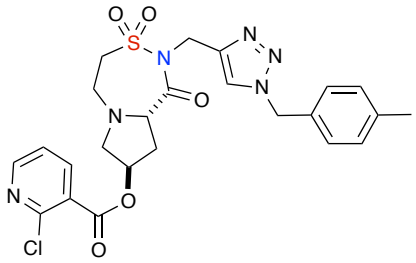
$[\alpha]_D^{20}$ = +35.7° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.97 – 7.93 (m, 2H), 7.47 (s, 1H), 7.45 – 7.42 (m, 2H), 7.27 – 7.22 (m, 2H), 7.11 – 7.04 (m, 2H), 5.52 (d, J = 15.0 Hz, 1H), 5.45 (d, J = 14.8 Hz, 1H), 5.33 (ddd, J = 9.3, 5.5, 4.8 Hz, 1H), 5.14 (d, J = 15.6 Hz, 1H), 5.07 (d, J = 15.6 Hz, 1H), 4.47 (t, J = 7.7 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.60 (dd, J = 11.1, 4.6 Hz, 1H), 3.50 – 3.39 (m, 2H), 3.27 (ddd, J = 13.6, 4.2, 3.4 Hz, 1H), 2.90 – 2.80 (m, 2H), 2.23 (dddd, J = 13.9, 8.1, 4.3, 1.4 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.3, 165.0, 163.6 ($^1J_{C–F}$ = 249.11 Hz), 143.7, 139.8, 131.0 (2), 130.4 ($^4J_{C–F}$ = 2.76 Hz), 130.0 ($^3J_{C–F}$ = 8.48 Hz, 2), 129.0 (2), 128.1, 122.7, 116.2 (^2J = 22.38 Hz, 2), 73.5, 64.1, 61.9, 55.8, 53.4, 52.6, 40.3, 33.9;

HRMS calculated for $C_{24}H_{23}ClFN_5O_5SH$ $(M+H)^+$ 548.1171; found 548.1190 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 2-chloronicotinate 3.2.1(10){1} **NA-6-165-9A**



According to the reaction protocol described in general procedure **C**, compound **3.2.1(10){1}** (37%, 58.1 mg) was isolated as yellow oil.

FTIR (thin film) 1733, 1706, 1579, 1434, 1402, 1355, 1294, 1218, 1151, 1053, 825 cm^{-1};

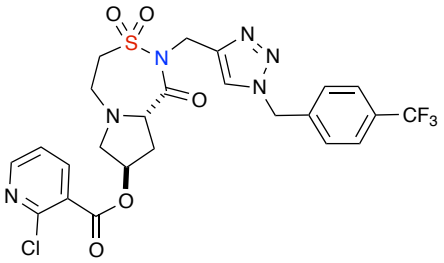
$[\alpha]_D^{20}$ = +33.4° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.55 (dd, J = 4.8, 2.0 Hz, 1H), 8.14 (dd, J = 7.8, 2.0 Hz, 1H), 7.43 (s, 1H), 7.36 (dd, J = 7.7, 4.8 Hz, 1H), 7.20 – 7.12 (m, 4H), 5.50 (d, J = 14.8 Hz, 1H), 5.43 (d, J = 14.8 Hz, 1H), 5.37 (ddd, J = 8.8, 5.4, 3.9 Hz, 1H), 5.11 (d, J = 15.6 Hz, 1H), 5.06 (d, J = 15.6 Hz, 1H), 4.49 (t, J = 7.8 Hz, 1H), (dddd, J = 14.2, 12.1, 3.9 Hz, 1H), 3.62 (dd, J = 11.4, 4.6 Hz, 1H), 3.50 (ddd, J = 13.1, 12.1, 2.2 Hz, 1H), 3.42 (ddd, J = 14.2, 3.5, 2.1 Hz, 1H), 3.25 (ddd, J = 13.3, 3.7, 3.7 Hz, 1H), 2.91 – 2.83 (m, 2H), 2.35 (s, 3H), 2.25 (dddd, J = 13.7, 7.9, 3.9, 1.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.2, 164.0, 152.1, 149.8, 143.3, 140.3, 138.7, 131.4, 129.7, 128.1 (2), 126.6 (2), 122.6, 122.2, 74.7, 63.9, 61.6, 55.8, 53.9, 52.40 41.1, 34.0, 21.1;

HRMS calculated for $C_{24}H_{25}ClN_6O_5SH$ $(M+H)^+$ 545.1374; found 545.1378 (TOF MS ES^+).

(8*R*,9a*S*)-3,3-dioxido-1-oxo-2-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)octahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 2-chloronicotinate 3.2.1(10){6} **NA-6-165-9F**



According to the reaction protocol described in general procedure **C**, compound **3.2.1(10){6}** (24%, 41.0 mg) was isolated as dark brown oil.

FTIR (thin film) 1735, 1701, 1421, 1404, 1355, 1325, 1151, 1066, 825 cm^{-1};

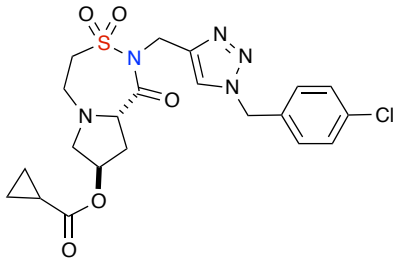
$[\alpha]_D^{20}$ = +28.6° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.55 (dd, J = 4.8, 2.0 Hz, 1H), 8.14 (dd, J = 7.7, 2.0 Hz, 1H), 7.64 (d, J = 7.9 Hz, 2H), 7.51 (s, 1H), 7.38 – 7.34 (m, 3H), 5.62 (d, J = 15.3 Hz, 1H), 5.55 (d, J = 15.3 Hz, 1H), 5.38 (ddd, J = 14.2, 5.4, 4.4 Hz, 1H), 5.15 (d, J = 15.6 Hz, 1H), 5.07 (d, J = 15.5 Hz, 1H), 4.49 (t, J = 7.8 Hz, 1H), 3.77 (ddd, J = 14.1, 12.1, 3.9 Hz, 1H), 3.62 (dd, J = 11.3, 4.6 Hz, 1H), 3.51 (ddd, J = 14.0, 12.2, 2.1 Hz, 1H), 3.44 (ddd, J = 14.2, 3.4, 2.0 Hz, 1H), 3.27 (ddd, J = 13.2, 3.7, 3.6 Hz, 1H), 2.92 – 2.83 (m, 2H), 2.26 (dddd, J = 13.8, 8.1, 4.2, 1.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.3, 164.0, 152.2, 149.9, 140.3, 138.4, 131.1 (q, $^2J_{C-F}$ = 32.74 Hz), 130.89, 128.1 (2), 126.6, 126.1(q, $^3J_{C-F}$ = 4.05 Hz, 2), 123.5 ($^1J_{C-F}$ = 272.04 Hz), 122.9, 122.2, 74.7, 64.0, 61.6, 55.9, 53.4, 52.4, 41.0, 34.0;

HRMS calculated for $C_{24}H_{22}ClF_3N_6O_5SH$ $(M+H)^+$ 599.1091; found 599.1075 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl cyclopropanecarboxylate 3.2.1(11){9} **NA-6-165-10D**



According to the reaction protocol described in general procedure **C**, compound **3.2.1(11){9}** (32%, 42.4 mg) was isolated as dark orange oil.

FTIR (thin film) 2358, 2341, 1718, 1703, 1492, 1353, 1172, 1153, 1053, 821 cm^{-1};

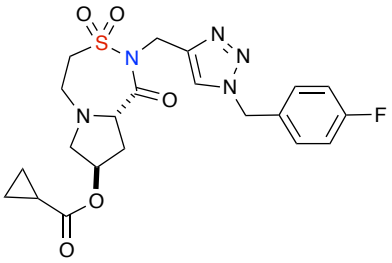
$[\alpha]_D^{20}$ = +29.7° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.45 (s, 1H), 7.36 – 7.33 (m, 2H), 7.21 – 7.17 (m, 2H), 5.51 (d, *J* = 15.0 Hz, 1H), 5.44 (d, *J* = 15.0 Hz, 1H), 5.17 – 5.02 (m, 3H), 4.37 (t, *J* = 7.7 Hz, 1H), 3.71 (ddd, *J* = 14.0, 12.1, 4.1 Hz, 1H), 3.49 – 3.38 (m, 3H), 3.22 (ddd, *J* = 13.7, 4.4, 3.3 Hz, 1H), 2.75 – 2.65 (m, 2H), 2.08 (dddd, *J* = 13.8, 8.1, 4.2, 1.4 Hz, 1H), 1.59 (tt, *J* = 7.9, 4.6 Hz, 1H), 1.03 – 0.96 (m, 2H), 0.92 – 0.86 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 174.3, 170.5, 134.8, 133.0, 129.4 (2), 129.3 (2), 122.8, 72.7, 64.0, 61.8, 55.9, 53.4, 52.5, 41.0, 40.2, 33.8, 13.0, 8.7 (2);

HRMS calculated for $C_{21}H_{24}ClN_5O_5SH$ $(M+H)^+$ 494.1265; found 494.1292 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl cyclopropanecarboxylate 3.2.1(11){5} **NA-6-165-10E**



According to the reaction protocol described in general procedure **C**, compound **3.2.1(11){5}** (27%, 36.5) was isolated as dark orange oil.

FTIR (thin film) 1720, 1512, 1421, 1384, 1353, 1222, 1172, 1153, 1053, 825 cm^{-1};

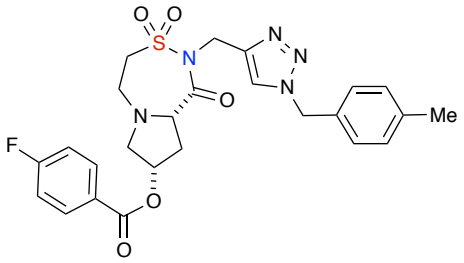
$[\alpha]_D^{20}$ = +32.4° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.45 (s, 1H), 7.26 – 7.22 (m, 2H), 7.09 – 7.03 (m, 2H), 5.51 (d, J = 15.0 Hz, 1H), 5.44 (d, J = 14.9 Hz, 1H), 5.15 – 5.01 (m, 3H), 4.37 (t, J = 7.7 Hz, 1H), 3.72 (ddd, J = 14.1, 12.1, 4.1 Hz, 1H), 3.48 – 3.38 (m, 3H), 3.22 (ddd, J = 13.7, 4.2, 3.3 Hz, 1H), 2.77 – 2.66 (m, 2H), 2.08 (dddd, J = 13.8, 8.1, 4.3, 1.4 Hz, 1H), 1.59 (tt, J = 7.9, 4.6 Hz, 1H), 1.02 – 0.97 (m, 2H), 0.92 – 0.86 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 174.3, 170.5, 162.8 ($^1J_{C–F}$ = 250.55 Hz), 143.6, 130.3 ($^4J_{C–F}$ = 3.42 Hz), 129.9 ($^3J_{C–F}$ = 8.41 Hz, 2), 122.7, 116.1 (^2J = 21.76 Hz, 2), 72.7, 63.9, 61.8, 55.9, 53.4, 52.5, 41.0, 33.8, 12.9, 8.7 (2);

HRMS calculated for $C_{21}H_{24}FN_5O_5SH$ $(M+H)^+$ 478.1560; found 478.1559 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-fluorobenzoate 3.3.1(1){1} **(NA-7-42-IA)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(1){1}** (48%, 10.2 mg) was isolated as brownish solid.

M.P. 148 – 153ºC

FTIR (neat) 2974, 1718, 1699, 1490, 1353, 1153, 1051 cm^{-1};

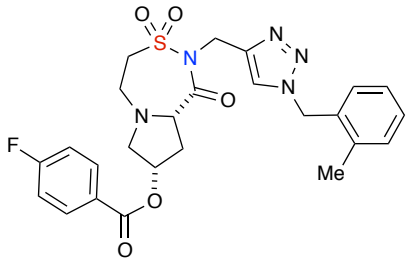
$[\alpha]_D^{20}$ =+17.6° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H), 7.41 (s, 1H), 7.16 – 7.12 (m, 2H), 7.11 – 7.03 (m, 4H), 5.39 – 5.36 (m, 1H), 5.33 (d, J = 14.7 Hz, 1H), 5.28 (d, J = 14.7 Hz, 1H), 5.17 (d, J = 15.7 Hz, 1H), 5.10 (d, J = 15.7 Hz, 1H), 4.33 (dd, J = 10.4, 2.8 Hz, 1H), 3.57 (ddd, J = 14.2, 11.9, 4.4 Hz, 1H), 3.39 (dt, J = 14.2, 2.8 Hz, 1H), 3.32 – 3.23 (m, 2H), 3.22 – 3.16 (m, 1H), 3.04 – 2.98 (m, 1H), 2.93 (dd, J = 10.5, 3.6 Hz, 1H), 2.39 – 2.34 (m, 1H), 2.34 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.3, 165.8 ($^1J_{C–F}$ = 253.53 Hz), 165.2, 143.8, 138.6, 132.4 ($^3J_{C–F}$ = 10.09 Hz, 2), 131.5, 129.7 (2), 127.9 (2), 126.4 ($^4J_{C–F}$ = 2.95 Hz), 122.3, 115.5 (^2J = 21.95 Hz, 2), 73.3, 63.6, 61.9, 55.4, 53.8, 50.3, 40.5, 32.9, 21.1;

HRMS calculated for $C_{25}H_{26}FN_5O_5SH$ $(M+H)^+$ 528.1717; found 528.1694 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-fluorobenzoate 3.3.1(1){2} **(NA-7-42-IB)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(1){2}** (70.5%, 14.9 mg) was isolated as brownish oil.

FTIR (neat) 2918, 2848, 1693, 1641, 1483, 1352, 1178, 1053 cm^{-1};

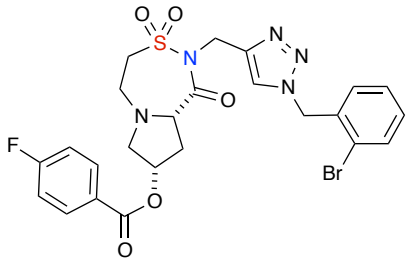
$[\alpha]_D^{20}$ =+13.2° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.04 – 7.98 (m, 2H), 7.34 (s, 1H), 7.31 – 7.24 (m, 2H), 7.22 – 7.11 (m, 2H), 7.10 – 7.05 (m, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 5.41 (d, *J* = 15.7 Hz, 1H), 5.32 (d, *J* = 15.7 Hz, 1H), 5.18 (d, *J* = 15.8 Hz, 1H), 5.10 (d, *J* = 15.8 Hz, 1H), 4.32 (dd, *J* = 10.4, 2.8 Hz, 1H), 4.26 – 4.14 (m, 1H), 3.56 (ddd, *J* = 14.2, 11.9, 4.4 Hz, 1H), 3.38 (dt, *J* = 14.2, 2.7 Hz, 1H), 3.31 (dd, *J* = 10.9, 2.3 Hz, 1H), 3.26 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.22 – 3.16 (m, 1H), 3.04 – 2.98 (m, 1H), 2.93 (dd, *J* = 10.4, 3.6 Hz, 1H), 2.42 – 2.28 (m, 1H), 2.21 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.8, 165.8 ($^1J_{C–F}$ = 253.93 Hz), 165.2, 143.8, 137.4, 137.2, 136.7, 132.5, 132.4 ($^3J_{C–F}$ = 9.03 Hz, 2), 129.0 ($^4J_{C–F}$ = 2.72 Hz), 126.6, 125.8, 122.3, 115.5 (^2J = 21.78 Hz, 2), 73.3, 63.7, 61.9, 55.4, 52.2, 50.3, 40.5, 32.9, 18.9;

HRMS calculated for $C_{25}H_{26}FN_5O_5SH$ $(M+H)^+$ 528.1717; found 528.1694 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(2-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-fluorobenzoate 3.3.1(1){10} **(NA-7-42-IF)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(1){10}** (51%, 12.0 mg) was isolated as brownish solid.

M.P. 147 – 152ºC

FTIR (neat) 2974, 1718, 1490, 1436, 1386, 1353, 1213, 1153, 1051, 896, 784 cm^{-1};

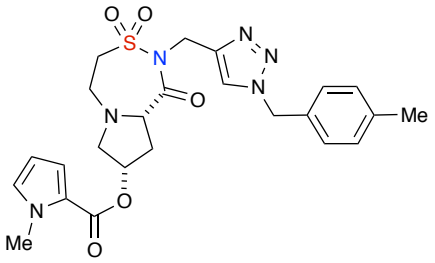
$[\alpha]_D^{20}$ = +9.8° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.03 – 7.97 (m, 2H), 7.58 (dd, J = 7.9, 1.4 Hz, 1H), 7.56 (s, 1H), 7.25 (dd, J = 7.5, 1.4 Hz, 1H), 7.21 (td, J = 7.7, 1.8 Hz, 1H), 7.09 – 7.04 (m, 2H), 6.99 (dd, J = 7.6, 1.8 Hz, 1H), 5.51 (d, J = 15.3 Hz, 1H), 5.44 (d, J = 15.3 Hz, 1H), 5.38 (ddt, J = 5.4, 3.8, 0.9 Hz, 1H), 5.21 (d, J = 15.7 Hz, 1H), 5.14 (d, J = 15.6 Hz, 1H), 4.35 (dd, J = 10.4, 2.8 Hz, 1H), 3.61 (ddd, J = 14.2, 11.4, 4.6 Hz, 1H), 3.41 (dt, J = 14.3, 2.8 Hz, 1H), 3.36 – 3.28 (m, 2H), 3.28 – 3.21 (m, 1H), 3.05 – 3.00 (m, 1H), 2.95 (dd, J = 10.5, 3.6 Hz, 1H), 2.37 (ddd, J = 14.8, 10.4, 5.4 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.3, 165.8 ($^1J_{C–F}$ = 253.98 Hz), 165.7, 143.7, 134.0, 133.1, 132.4 ($^3J_{C–F}$ = 9.58 Hz, 2), 129.0 ($^4J_{C–F}$ = 2.72 Hz), 130.3, 130.0, 128.2, 123.2, 122.9, 115.5 (^2J = 21.88 Hz, 2), 73.3, 63.7, 62.0, 55.5, 53.7, 50.4, 40.5, 32.9;

HRMS calculated for $C_{24}H_{23}BrN_5O_5SH$ $(M+H)^+$ 592.0666; found 592.0667 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 1-methyl-1*H*-pyrrole-2-carboxylate 3.3.1(3){1} **(NA-7-42-IIIA)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(3){1}** (34%, 6.9 mg) was isolated as brownish oil.

FTIR (neat) 2956, 1710, 1679, 1433, 1353, 1224, 1153, 1051, 856, 769 cm^{-1};

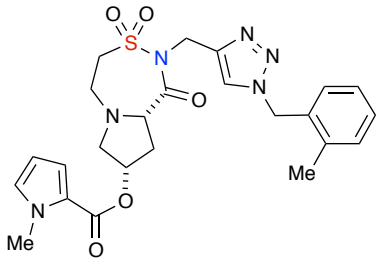
$[\alpha]_D^{20}$ =+12.2° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.14 (d, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.89 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.77 (t, *J* = 2.2 Hz, 1H), 6.09 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.37 – 5.10 (m, 6H), 4.28 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.85 (s, 3H), 3.49 (ddd, *J* = 14.2, 12.0, 4.3 Hz, 1H), 3.36 (dt, *J* = 14.2, 2.7 Hz, 1H), 3.27 – 3.19 (m, 2H), 3.14 (ddd, *J* = 13.3, 4.4, 3.2 Hz, 1H), 3.01 – 2.95 (m, 1H), 2.88 (dd, *J* = 10.4, 3.7 Hz, 1H), 2.34 (s, 3H), 2.33 – 2.28 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 160.8, 143.7, 138.49, 131.7, 129.6 (3), 127.9 (2), 122.8, 122.5, 118.5, 107.9, 72.2, 63.8, 62.2, 55.2, 54.0, 50.4, 41.0, 36.8, 32.9, 21.1;

HRMS calculated for $C_{24}H_{28}N_6O_5SH$ $(M+H)^+$ 513.1920; found 513.1901 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 1-methyl-1*H*-pyrrole-2-carboxylate 3.3.1(1){2} **(NA-7-42-IIIB)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(1){2}** (40%, 8.2 mg) was isolated as brownish oil.

FTIR (neat) 2839, 1710, 1683, 1456, 1419, 1379, 1259, 1168, 1043, 815, 757 cm^{-1};

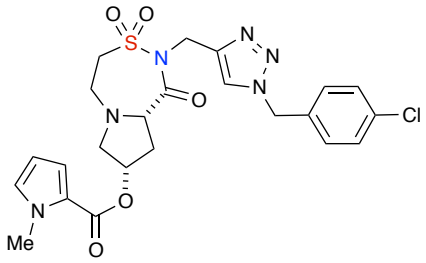
$[\alpha]_D^{20}$ = +13.6° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.25 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.20 – 7.14 (m, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.77 (t, *J* = 2.1 Hz, 1H), 6.07 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.41 (d, *J* = 14.9 Hz, 1H), 5.32 – 5.25 (m, 2H), 5.14 (d, *J* = 1.37 Hz, 2H), 4.27 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.85 (s, 3H), 3.49 (ddd, *J* = 14.2, 11.9, 4.3 Hz, 1H), 3.36 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.29 – 3.19 (m, 2H), 3.14 (ddd, *J* = 13.4, 4.4, 3.2 Hz, 1H), 2.97 (dddd, *J* = 14.7, 3.1, 2.1, 1.0 Hz, 1H), 2.88 (dd, *J* = 10.4, 3.8 Hz, 1H), 2.33 (ddd, *J* = 14.7, 10.5, 5.7 Hz, 1H), 2.22 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 160.7, 143.6, 136.6, 132.7, 130.8 (2), 129.6, 128.9, 126.5, 122.6, 122.4, 118.5, 107.9, 72.1, 63.8, 62.3, 55.2, 52.1, 50.4, 41.0, 36.8, 32.9, 18.9;

HRMS calculated for $C_{24}H_{28}N_6O_5SH$ $(M+H)^+$ 513.1920; found 513.1902 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 1-methyl-1*H*-pyrrole-2-carboxylate 3.3.1(3){4} **(NA-7-42-IIIC)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(3){4}** (40%, 8.5 mg) was isolated as brownish oil.

FTIR (neat) 2966, 1710, 1604, 1514, 1438, 1353, 1257, 1153, 1066, 823 cm^{-1};

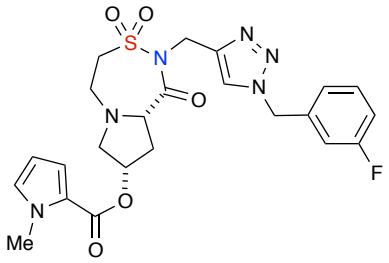
$[\alpha]_D^{20}$ = +7.2° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.33 – 7.28 (m, 2H), 7.09 – 7.05 (m, 2H), 6.89 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.78 (t, *J* = 2.2 Hz, 1H), 6.08 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.37 – 5.24 (m, 3H), 5.18 – 5.09 (m, 2H), 4.27 (dd, *J* = 10.4, 2.9 Hz, 1H), 3.86 (s, 3H), 3.49 (ddd, *J* = 14.2, 11.8, 4.4 Hz, 1H), 3.39 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.31 – 3.21 (m, 2H), 3.17 (ddd, *J* = 13.4, 4.5, 3.2 Hz, 1H), 3.04 – 2.94 (m, 1H), 2.89 (dd, *J* = 10.5, 3.7 Hz, 1H), 2.37 – 2.29 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 160.7, 144.0, 134.6, 133.2, 129.6, 129.2 (2), 129.1 (2), 122.9, 122.5, 118.5, 107.9, 72.2, 63.8, 62.2, 55.3, 53.1, 50.4, 41.0, 36.8, 32.9;

HRMS calculated for $C_{23}H_{25}ClN_6O_5SH$ $(M+H)^+$ 533.1374; found 533.1372 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(3-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 1-methyl-1*H*-pyrrole-2-carboxylate 3.3.1(3){12} **(NA-7-42-IIID)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(3){12}** (35%, 7.3 mg) was isolated as brownish oil.

FTIR (neat) 2956, 1710, 1679, 1224, 1051, 769, 734 cm^{-1};

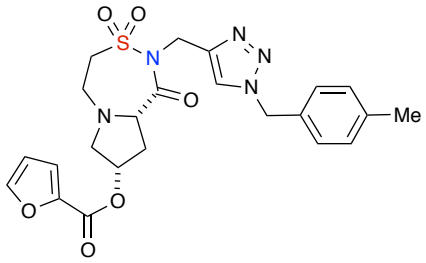
$[\alpha]_D^{20}$ = +11.5° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.37 – 7.30 (m, 1H), 7.15 – 7.06 (m, 3H), 6.87 (dd, J = 4.0, 1.8 Hz, 1H), 6.76 (t, J = 2.1 Hz, 1H), 6.08 (dd, J = 4.0, 2.5 Hz, 1H), 5.45 (dd, J = 15.0, 1.1 Hz, 1H), 5.35 (dd, J = 15.1, 1.1 Hz, 1H), 5.30 – 5.27 (m, 1H), 5.15 (s, 2H), 4.29 (dd, J = 10.4, 2.9 Hz, 1H), 3.84 (s, 3H), 3.57 (ddd, J = 14.2, 11.7, 4.6 Hz, 1H), 3.39 (dt, J = 14.3, 2.8 Hz, 1H), 3.34 – 3.22 (m, 2H), 3.20 (ddd, J = 13.3, 4.7, 3.2 Hz, 1H), 3.02 – 2.96 (m, 1H), 2.90 (dd, J = 10.5, 3.7 Hz, 1H), 2.34 (ddd, J = 14.7, 10.4, 5.6 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 161.3 ($^1J_{C–F}$ = 248.99 Hz), 160.7, 143.8, 130.7 ($^3J_{C–F}$ = 8.25 Hz), 130.2 ($^5J_{C–F}$ = 3.25 Hz), 129.6, 124.7 ($^4J_{C–F}$ = 3.31 Hz), 123.0, 122.4, 122.0 ($^2J_{C–F}$ = 14.56 Hz), 118.5, 115.7 ($^6J_{C–F}$ = 21.12 Hz), 107.8, 72.1, 63.8, 62.3, 55.3, 50.4, 47.5, 40.6, 36.8, 32.9;

HRMS calculated for $C_{23}H_{25}FN_6O_5SH$ $(M+H)^+$ 517.1669; found 517.1664 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl furan-2-carboxylate 3.3.1(4){1} **(NA-7-42-IVA)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(4){1}** (59%, 11.7 mg) was isolated as brownish oil.

FTIR (neat) 1964, 1712, 1604, 1514, 1463, 1353, 1325, 1280, 1153, 823 cm^{-1};

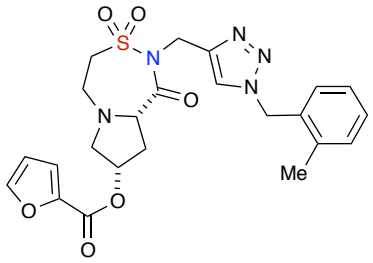
$[\alpha]_D^{20}$ = +15.2° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 1.7, 0.9 Hz, 1H), 7.46 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.12 (dd, J = 3.4, 0.88 Hz, 1H), 7.08 – 7.04 (m, 2H), 6.48 (dd, J = 3.5, 1.7 Hz, 1H), 5.41 (d, J = 14.7 Hz, 1H), 5.36 (ddt, J = 5.7, 3.9, 0.9 Hz, 1H), 5.31 – 5.27 (m, 1H), 5.15 (d, J = 15.7 Hz, 1H), 5.11 (d, J = 15.6 Hz, 1H), 4.28 (dd, J = 10.3, 3.0 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.36 (dt, J = 14.2, 2.8 Hz, 1H), 3.27 – 3.20 (m, 2H), 3.15 (ddd, J = 13.4, 4.4, 3.2 Hz, 1H), 3.01 – 2.94 (m, 1H), 2.90 (dd, J = 10.6, 3.8 Hz, 1H), 2.38 – 2.34 (m, 1H), 2.34 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 158.2, 146.4, 144.5, 143.9, 138.6, 131.6, 129.7 (2), 127.9 (2), 122.7, 118.5, 111.9, 73.2, 63.7, 61.8, 55.2, 53.8, 50.3, 41.0, 33.0, 21.1;

HRMS calculated for $C_{23}H_{25}N_5O_6SH$ $(M+H)^+$ 500.1604; found 500.1570 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(2-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl furan-2-carboxylate 3.3.1(4){2} **(NA-7-42-IVB)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(4){2}** (43%, 8.6 mg) was isolated as brownish oil.

FTIR (neat) 2968, 1712, 1604, 1514, 1421, 1353, 1257, 1224, 1153, 771 cm^{-1};

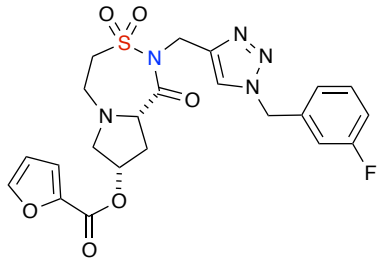
$[\alpha]_D^{20}$ =+10.2° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, J = 1.8, 0.9 Hz, 1H), 7.39 (s, 1H), 7.30 – 7.24 (m, 1H), 7.20 – 7.16 (m, 2H), 7.11 (dd, J = 3.5, 0.9 Hz, 1H), 6.99 (dd, J = 7.1, 1.8 Hz, 1H), 6.48 (dd, J = 3.5, 1.7 Hz, 1H), 5.47 (d, J = 14.9 Hz, 1H), 5.37 (t, J = 5.3 Hz, 1H), 5.32 (d, J = 18.5 Hz, 1H), 5.16 (d, J = 15.7 Hz, 1H), 5.11 (d, J = 15.6 Hz, 1H), 4.28 (dd, J = 10.3, 3.1 Hz, 1H), 3.45 (ddd, J = 14.2, 11.8, 4.4 Hz, 1H), 3.36 (dt, J = 14.3, 2.8 Hz, 1H), 3.29 – 3.21 (m, 2H), 3.16 (ddd, J = 13.4, 4.4, 3.1 Hz, 1H), 3.00 – 2.94 (m, 1H), 2.90 (dd, J = 10.7, 3.8 Hz, 1H), 2.39 – 2.31 (m, 1H), 2.22 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 158.3, 146.5, 144.6, 143.8, 136.7, 132.6, 130.9, 129.2, 129.1, 126.6, 122.6, 111.9, 111.8, 73.2, 63.8, 61.9, 55.3, 52.3, 50.4, 41.0, 33.1, 18.9;

HRMS calculated for $C_{23}H_{25}N_5O_6SH$ $(M+H)^+$ 500.1604; found 500.1580 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(3-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl furan-2-carboxylate 3.3.1(4){11} **(NA-7-42-IVD)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(4){11}** (43%, 8.7 mg) was isolated as brownish oil.

FTIR (neat) 2962, 1712, 1591, 1492 1433, 1353, 1118, 1053, 759, 702 cm^{-1};

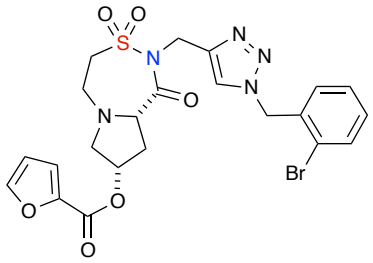
$[\alpha]_D^{20}$ = +15.8° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.55 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.34 (dddd, *J* = 8.1, 7.2, 5.4, 1.9 Hz, 1H), 7.20 – 7.06 (m, 4H), 6.48 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.50 (d, *J* = 15.0 Hz, 1H), 5.45 (d, *J* = 15.0 Hz, 1H), 5.38 (ddt, *J* = 5.8, 3.9, 1.0 Hz, 1H), 5.16 (d, *J* = 15.7 Hz, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 4.30 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.52 (ddd, *J* = 14.2, 11.5, 4.7 Hz, 1H), 3.39 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.33 – 3.19 (m, 3H), 3.02 – 2.96 (m, 1H), 2.92 (dd, *J* = 10.6, 3.8 Hz, 1H), 2.36 (ddd, *J* = 14.8, 10.4, 5.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 159.7 ($^1J_{C–F}$ = 246.77 Hz), 158.3, 146.4, 144.5, 143.9, 130.8 ($^3J_{C–F}$ = 7.99 Hz), 130.3 ($^5J_{C–F}$ = 3.42 Hz), 124.8 ($^4J_{C–F}$ = 3.79 Hz), 122.4, 122.0 ($^2J_{C–F}$ = 14.73 Hz), 118.4, 115.8 ($^6J_{C–F}$ = 21.80 Hz), 111.8, 72.2, 63.8, 62.3, 55.3, 50.4, 47.6, 41.0, 33.0;

HRMS calculated for $C_{22}H_{22}N_5O_6SH$ $(M+H)^+$ 504.1353; found 504.1340 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(2-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl furan-2-carboxylate 3.3.1(4){10} **(NA-7-42-IVF)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(4){10}** (43%, 8.7 mg) was isolated as brownish oil.

FTIR (neat) 2974, 1712, 1618, 1433, 1353, 1276, 1224, 1153, 1118, 761 cm^{-1};

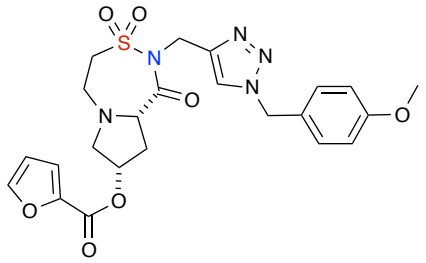
$[\alpha]_D^{20}$ =+19.2° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.54 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.29 – 7.19 (m, 3H), 7.10 (dd, *J* = 3.5, 0.9 Hz, 1H), 6.99 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.47 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.57 (d, *J* = 15.3 Hz, 1H), 5.49 (d, *J* = 15.3 Hz, 1H), 5.37 (ddt, *J* = 5.7, 3.9, 1.0 Hz, 1H), 5.19 (d, *J* = 15.8 Hz, 1H), 5.16 (d, *J* = 15.5 Hz, 1H), 4.30 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.53 (ddd, *J* = 14.2, 11.5, 4.7 Hz, 1H), 3.40 (dt, *J* = 14.3, 2.8 Hz, 1H), 3.31 – 3.19 (m, 3H), 3.02 – 2.96 (m, 1H), 2.92 (dd, *J* = 10.7, 3.8 Hz, 1H), 2.36 (ddd, *J* = 14.9, 10.4, 5.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 158.24 146.5, 144.52, 143.8, 134.1, 133.1, 130.3, 123.0, 128.2, 123.2, 118.4, 111.9, 111.8, 73.2, 63.7, 61.9, 55.3, 53.7, 50.4, 41.0, 33.0;

HRMS calculated for $C_{22}H_{22}BrN_5O_6SH$ $(M+H)^+$ 564.0552; found 564.0555 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl furan-2-carboxylate 3.3.1(4){13} **(NA-7-42-IVH)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(4){13}** (33%, 6.9 mg) was isolated as brownish oil.

FTIR (neat) 2929, 2852, 1714, 1446, 1353, 1224, 1153, 1118, 823, 769, 686 cm^{-1};

$[\alpha]_D^{20}$ = +9.8° (*c* = 2.0, CH_2Cl_2);

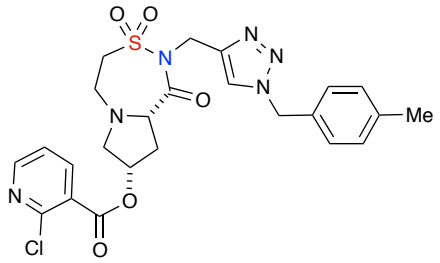
M.P. 153 – 157ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.44 (s, 1H), 7.14 – 7.11 (m, 2H), 7.11 – 7.09 (m, 1H), 6.88 – 6.84 (m, 2H), 6.49 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.42 – 5.35 (m, 2H), 5.33 – 5.25 (m, 1H), 5.15 (d, *J* = 15.6 Hz, 1H), 5.11 (d, *J* = 15.5 Hz, 1H), 4.28 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.80 (s, 3H), 3.44 (ddd, *J* = 14.2, 11.7, 4.4 Hz, 1H), 3.37 (dt, *J* = 14.2, 2.9 Hz, 1H), 3.28 – 3.21 (m, 2H), 3.16 (ddd, *J* = 13.4, 4.5, 3.2 Hz, 1H), 3.01 – 2.95 (m, 1H), 2.90 (dd, *J* = 10.6, 3.7 Hz, 1H), 2.35 (ddd, *J* = 14.9, 10.4, 5.6 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 159.8, 158.2, 146.5, 144.6, 143.9, 129.4 (2), 126.6, 122.5, 118.5, 114.4, 111.9 (2), 73.2, 63.7, 61.9, 55.3, 55.2, 53.6, 50.37, 41.0, 33.0;

HRMS calculated for $C_{23}H_{25}N_5O_7SH$ $(M+H)^+$ 516.1553; found 516.1547 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 2-chloronicotinate 3.3.1(10){1} **(NA-7-42-IXA)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(10){1}** (60%, 13.0 mg) was isolated as brownish oil.

FTIR (neat) 2950, 1745, 1708, 1514, 1433, 1353, 1249, 1153, 837, 732 cm^{-1};

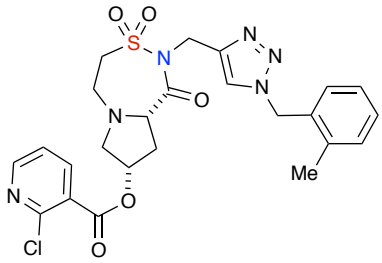
$[\alpha]_D^{20}$ =+12.4° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.22 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.42 (s, 1H), 7.29 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.18 – 7.10 (m, 4H), 5.45 – 5.40 (m, 2H), 5.38 (d, *J* = 15.7 Hz, 1H), 5.18 (d, *J* = 15.7 Hz, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 4.33 (dd, *J* = 10.5, 2.6 Hz, 1H), 3.57 (ddd, *J* = 14.2, 11.6, 4.6 Hz, 1H), 3.40 (dt, *J* = 14.3, 2.7 Hz, 1H), 3.35 – 3.20 (m, 3H), 3.05 (dt, *J* = 15.2, 2.0 Hz, 1H), 2.95 (dd, *J* = 10.5, 3.5 Hz, 1H), 2.38 (ddd, *J* = 15.6, 10.3, 5.4 Hz, 1H), 2.35 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 163.9, 151.8, 150.0, 143.6, 141.2, 138.7, 131.4, 129.7 (2), 128.0 (2), 126.6, 122.5, 122.4, 74.3, 63.4, 61.5, 55.5, 53.9, 50.2, 41.0, 32.1, 21.1;

HRMS calculated for $C_{24}H_{25}ClN_6O_5SH$ $(M+H)^+$ 545.1374; found 545.1364 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(2-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 2-chloronicotinate 3.3.1(10){2} **(NA-7-42-IXB)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(10){2}** (48%, 10.4 mg) was isolated as brownish oil.

FTIR (neat) 2956, 1712, 1602, 1421, 1353, 1325, 1280, 1153, 1120, 769 cm^{-1};

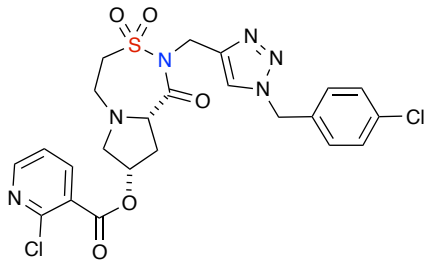
$[\alpha]_D^{20}$ =+13.7° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.22 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.34 (s, 1H), 7.31 – 7.25 (m, 2H), 7.22 – 7.17 (m, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 5.49 (d, *J* = 14.9 Hz, 1H), 5.45 – 5.41 (m, 2H), 5.18 (d, *J* = 15.6 Hz, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 4.33 (dd, *J* = 10.4, 2.7 Hz, 1H), 3.55 (ddd, *J* = 14.2, 11.6, 4.6 Hz, 1H), 3.39 (dt, *J* = 14.3, 2.7 Hz, 1H), 3.30 (ddd, *J* = 24.1, 11.1, 2.3 Hz, 2H), 3.27 – 3.20 (m, 1H), 3.06 (dt, *J* = 15.2, 2.4 Hz, 1H), 2.95 (dd, *J* = 10.5, 3.5 Hz, 1H), 2.37 (ddd, *J* = 15.4, 10.3, 5.4 Hz, 1H), 2.24 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 163.9, 151.8, 150.0, 143.5, 141.2, 136.7, 132.5, 131.0, 130.1, 129.2, 129.1, 126.6, 122.5, 122.4, 74.3, 63.4, 61.6, 55.5, 52.3, 50.2, 41.0, 32.9, 18.9;

HRMS calculated for $C_{24}H_{25}ClN_6O_5SH$ $(M+H)^+$ 545.1374; found 545.1367 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 2-chloronicotinate 3.3.1(10){4} **(NA-7-42-IXC)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(10){4}** (46%, 10.4 mg) was isolated as brownish oil.

FTIR (neat) 2966, 1710, 1604, 1512, 1442, 1353, 1280, 1257, 1222, 1153, 1056, 1027, 848, 815, 771 cm^{-1};

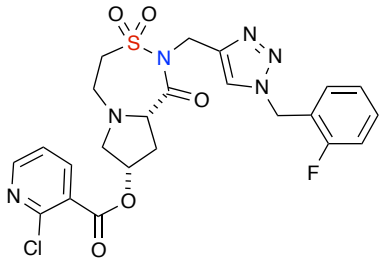
$[\alpha]_D^{20}$ =+16.2° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.23 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.44 (s, 1H), 7.35 – 7.29 (m, 3H), 7.19 – 7.15 (m, 2H), 5.47 – 5.41 (s, 3H), 5.15 (d, *J* = 15.6 Hz, 1H), 5.08 (d, *J* = 15.6 Hz, 1H), 4.32 (dd, *J* = 10.5, 2.7 Hz, 1H), 3.57 (ddd, *J* = 14.2, 11.1, 5.1 Hz, 1H), 3.42 (dt, *J* = 14.3, 2.7 Hz, 1H), 3.34 (dd, *J* = 10.7, 2.3 Hz, 1H), 3.31 – 3.22 (m, 2H), 3.06 (dt, *J* = 17.3, 2.2 Hz, 1H), 2.96 (dd, *J* = 10.6, 3.6 Hz, 1H), 2.39 (ddd, *J* = 15.4, 10.5, 5.4 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 164.0, 151.8, 150.0, 143.9, 141.1, 134.7, 133.0, 129.3 (2), 129.2 (2), 126.69, 122.7, 122.4, 74.3, 63.5, 61.6, 55.6, 53.3, 50.2, 41.0, 32.9;

HRMS calculated for $C_{23}H_{22}Cl_2N_6O_5SH$ $(M+H)^+$ 565.0828; found 565.0816 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 2-chloronicotinate 3.3.1(10){12} **(NA-7-42-IXE)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(10){12}** (47%, 10.4 mg) was isolated as brownish oil.

FTIR (neat) 2931, 2852, 1708, 1593, 1431, 1353, 1274, 1271, 1218, 1153, 1118, 781, 761 cm^{-1};

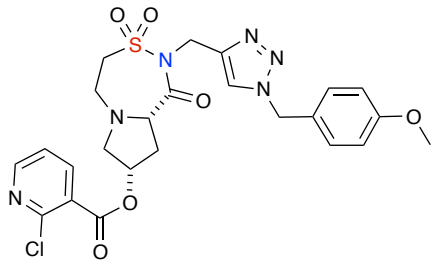
$[\alpha]_D^{20}$ =+15.4° (c = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (dd, J = 4.8, 2.0 Hz, 1H), 8.24 (dd, J = 7.7, 2.0 Hz, 1H), 7.46 (s, 1H), 7.36 – 7.30 (m, 2H), 7.09 – 6.98 (m, 2H), 6.88 (dt, J = 9.3, 2.1 Hz, 1H), 5.55 – 5.41 (m, 3H), 5.18 (d, J = 15.6 Hz, 1H), 5.10 (d, J = 15.6 Hz, 1H), 4.34 (dd, J = 10.5, 2.7 Hz, 1H), 3.55 (ddd, J = 14.2, 11.2, 5.0 Hz, 1H), 3.42 (dt, J = 14.3, 2.8 Hz, 1H), 3.37 – 3.32 (m, 1H), 3.31 – 3.22 (m, 2H), 3.10 – 3.03 (m, 1H), 2.96 (dd, J = 10.6, 3.6 Hz, 1H), 2.39 (ddd, J = 15.4, 10.5, 5.3 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 164.0, 162.9 ($^1J_{C–F}$ = 247.86 Hz), 151.8, 150.0, 143.9, 141.1, 136.9 ($^3J_{C–F}$ = 7.33 Hz), 130.7 ($^5J_{C–F}$ = 8.12 Hz), 126.7, 123.4 ($^4J_{C–F}$ = 3.14 Hz), 122.9, 122.4, 115.7 ($^6J_{C–F}$ = 21.01 Hz), 114.8 ($^2J_{C–F}$ = 22.07 Hz), 74.3, 63.5, 61.6, 55.6, 53.4, 50.2, 41.0, 32.9;

HRMS calculated for $C_{23}H_{22}ClFN_6O_5SH$ $(M+H)^+$ 549.1123; found 549.1107 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 2-chloronicotinate 3.3.1(10){13} **(NA-7-42-IXH)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(10){13}** (75%, 15.5 mg) was isolated as brownish oil.

FTIR (neat) 2968, 1703, 1531, 1413, 1353, 1245, 1224, 1155, 118, 1054, 823, 777 cm^{-1};

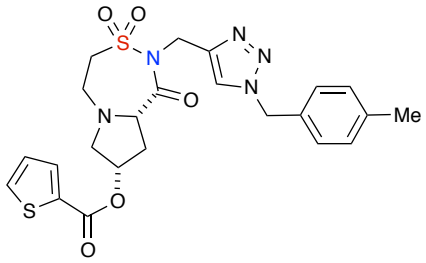
$[\alpha]_D^{20}$ =+19.5° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.22 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.40 (s, 1H), 7.29 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.20 – 7.15 (m, 2H), 6.90 – 6.85 (m, 2H), 5.42 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.40 (d, *J* = 14.7 Hz, 1H), 5.35 (d, *J* = 14.7 Hz, 1H), 5.17 (d, *J* = 15.7 Hz, 1H), 5.05 (dd, *J* = 15.6, 0.6 Hz, 1H), 4.32 (dd, *J* = 10.5, 2.6 Hz, 1H), 3.80 (s, 3H), 3.56 (ddd, *J* = 14.2, 11.5, 4.7 Hz, 1H), 3.40 (dt, *J* = 14.3, 2.7 Hz, 1H), 3.35 – 3.20 (m, 3H), 3.08 – 3.01 (m, 1H), 2.94 (dd, *J* = 10.6, 3.5 Hz, 1H), 2.38 (ddd, *J* = 15.4, 10.5, 5.3 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 164.0, 159.8, 151.8, 150.0, 143.5, 141.2, 129.6 (2), 126.6, 126.4, 122.4, 122.3, 114.4 (2), 74.3, 63.4, 61.5, 55.5, 55.3, 53.6, 50.2, 41.0, 32.9;

HRMS calculated for $C_{24}H_{25}ClN_6O_6SH$ $(M+H)^+$ 561.1323; found 561.1316 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl thiophene-2-carboxylate 3.3.1(5){1} **(NA-7-42-VA)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(5){1}** (52%, 10.8 mg) was isolated as brownish oil.

FTIR (neat) 2970, 1712, 1531, 1492, 1434, 1353, 1224, 1153, 1054, 823, 761 cm^{-1};

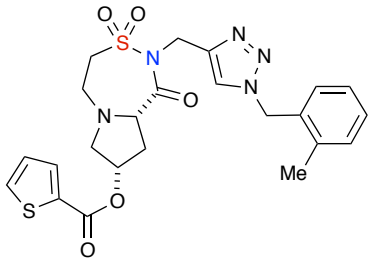
$[\alpha]_D^{20}$ =+16.3° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.54 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.45 (s, 1H), 7.15 – 7.11 (m, 2H), 7.08 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.05 – 7.01 (m, 2H), 5.37 – 5.32 (m, 2H), 5.24 (d, *J* = 14.7 Hz, 1H), 5.16 (d, *J* = 15.7 Hz, 1H), 5.12 (dd, *J* = 15.8, 0.65 Hz, 1H), 4.29 (dd, *J* = 10.4, 2.9 Hz, 1H), 3.44 (ddd, *J* = 14.2, 11.8, 4.3 Hz, 1H), 3.36 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.28 – 3.20 (m, 2H), 3.14 (ddd, *J* = 13.3, 4.3, 3.1 Hz, 1H), 3.03 – 2.97 (m, 1H), 2.90 (dd, *J* = 10.6, 3.7 Hz, 1H), 2.38 – 2.35 (m, 1H), 2.34 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 161.8, 143.8, 138.5, 133.9, 133.8, 132.6, 131.6, 129.6 (2), 127.9 (2), 127.8, 122.7, 73.5, 63.7, 61.9, 55.2, 53.8, 50.3, 41.0, 32.8, 21.1;

HRMS calculated for $C_{23}H_{25}N_5O_5S_2H$ $(M+H)^+$ 516.1375; found 516.1357 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(2-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl thiophene-2-carboxylate 3.3.1(5){2} **(NA-7-42-VB)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(5){2}** (40%, 8.3 mg) was isolated as brownish oil.

FTIR (neat) 2970, 1714, 1473, 1415, 1353, 1325, 1153, 1120, 1066, 1018, 784, 763, 700 cm^{-1};

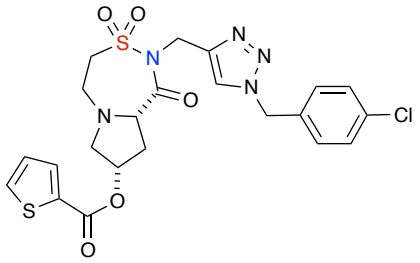
$[\alpha]_D^{20}$ =+15.5° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.53 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.39 (s, 1H), 7.27 – 7.24 (m, 1H), 7.20 – 7.15 (m, 2H), 7.07 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 5.42 (d, *J* = 14.9 Hz, 1H), 5.35 (ddt, *J* = 5.8, 3.8, 1.0 Hz, 1H), 5.29 (d, *J* = 14.8 Hz, 1H), 5.17 (d, *J* = 15.8 Hz, 1H), 5.14 (dd, *J* = 15.6, 0.65 Hz, 1H), 4.29 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.45 (ddd, *J* = 14.2, 11.8, 4.3 Hz, 1H), 3.36 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.31 – 3.21 (m, 2H), 3.15 (ddd, *J* = 13.4, 4.4, 3.1 Hz, 1H), 3.03 – 2.97 (m, 1H), 2.90 (dd, *J* = 10.6, 3.7 Hz, 1H), 2.35 (ddd, *J* = 14.8, 10.4, 5.6 Hz, 1H), 2.20 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 161.8, 143.8, 136.6, 133.9, 133.7, 132.6, 132.5, 130.9, 129.0, 128.0, 127.8, 126.6, 122.5, 73.4, 63.8, 61.9, 55.3, 52.2, 50.4, 41.0, 33.0, 18.9;

HRMS calculated for $C_{23}H_{25}N_5O_5S_2H$ $(M+H)^+$ 516.1375; found 516.1355 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl thiophene-2-carboxylate 3.3.1(5){4} **(NA-7-42-VC)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(5){4}** (47%, 10.1 mg) was isolated as brownish oil.

FTIR (neat) 2797, 1716, 1492, 1434, 1353, 1215, 1153, 1051, 846 cm^{-1};

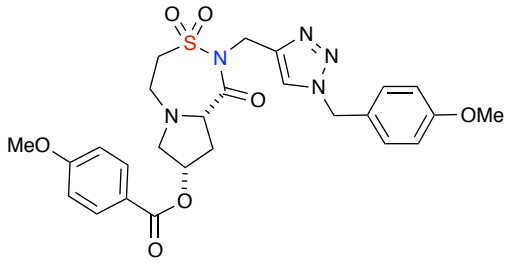
$[\alpha]_D^{20}$ =+16.3° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.54 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.47 (s, 1H), 7.33 – 7.28 (m, 2H), 7.11 – 7.06 (m, 3H), 5.38 – 5.30 (m, 2H), 5.28 (d, *J* = 15.1 Hz, 1H), 5.16 (dd, *J* = 15.7, 0.66 Hz, 1H), 5.12 (d, *J* = 15.7 Hz, 1H), 4.29 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.47 (ddd, *J* = 14.2, 11.7, 4.4 Hz, 1H), 3.39 (dt, *J* = 14.3, 2.8 Hz, 1H), 3.32 – 3.22 (m, 2H), 3.18 (ddd, *J* = 13.4, 4.4, 3.1 Hz, 1H), 3.03 – 2.98 (m, 1H), 2.92 (dd, *J* = 10.6, 3.7 Hz, 1H), 2.35 (ddd, *J* = 14.7, 10.4, 5.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 161.8, 144.2, 134.7, 133.9, 133.8, 133.1, 132.6, 129.2 (2), 129.1 (2), 127.8, 122.8, 73.5, 63.8, 61.9, 55.3, 53.2, 50.4, 41.0, 33.0;

HRMS calculated for $C_{22}H_{22}ClN_5O_5S_2H$ $(M+H)^+$ 536.0829; found 536.814 (TOF MS ES^+).

(8*S*,9a*S*)-2-((1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl 4-methoxybenzoate 3.3.1(8){13} **(NA-7-42-VIIH)**



According to the reaction protocol described in general procedure **C**, compound **3.3.1(8){13}** (40%, 8.8 mg) was isolated as brownish oil.

FTIR (neat) 2954, 1693, 1413, 1352, 1317, 1247, 1153, 1112, 1053, 1027 cm^{-1};

$[\alpha]_D^{20}$ =+17.2° (*c* = 2.0, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 2H), 7.30 (s, 1H), 6.97 – 6.94 (m, 2H), 6.84 – 6.80 (m, 2H), 6.77 – 6.72 (m, 2H), 5.26 (ddt, *J* = 5.7, 3.8, 0.9 Hz, 1H), 5.15 (d, *J* = 14.6 Hz, 1H), 5.09 – 4.99 (m, 3H), 4.22 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.38 – 3.24 (m, 2H), 3.22 – 3.12 (m, 2H), 3.05 (ddd, *J* = 13.2, 4.3, 3.1 Hz, 1H), 2.96 – 2.90 (m, 1H), 2.82 (dd, *J* = 10.5, 3.7 Hz, 1H), 2.26 (ddd, *J* = 14.8, 10.4, 5.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 165.9, 163.5, 159.8, 143.9, 131.9 (2), 129.4 (2), 126.6, 122.5, 122.4, 114.3 (2), 113.6 (2), 72.9, 63.8, 62.0, 55.5, 55.3, 55.2, 53.4, 50.3, 41.0, 32.8;

HRMS calculated for $C_{26}H_{29}N_5O_7SH$ $(M+H)^+$ 556.1866; found 556.1877 (TOF MS ES^+).

5.3 Experimental for Chapter 3.2

Exploring Chemical Diversity via a Modular Reaction Pairing Strategy

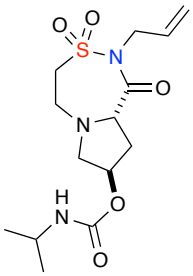
General Procedure A: one-pot, sequential 4-component (sulfonylation, Michael, amide coupling and Carbamoylation). To a pressure tube containing a solution of amine (1.0 mmol, 1.05 equiv.) in dry CH_2Cl_2 (0.5 M), was added Et_3N (1.91 mmol, 2.0 equiv.). The reaction mixture was stirred for 20 min and 2-chloroethane sulfonyl chloride (0.96 mmol, 1.0 equiv.) was added in a drop-wise fashion. The reaction was left to stir overnight and CH_2Cl_2 was removed *in vacuo* upon completion of the reaction. MeOH/water (0.5 M, 5:1), Et_3N (2.87 mmol, 3.0 equiv.) and amino acid (1.0 mmol, 1.05 equiv.) were added to the reaction mixture, which was stirred at 60 ºC for 12 h, after which solvents were evaporated to dryness. DMF (0.08 M) EDC (1.91 mmol, 2.0 equiv.), HOBt (0.48 mmol, 0.5 equiv.) and Et_3N (1.91 mmol, 2.0 equiv.) were added to the crude mixture. The reaction was stirred at rt for 12 h. Upon completion of the reaction it was divided into small vials of equal volume followed by evaporation of the DMF on a genevac and then addition of CH_2Cl_2. This was followed by the addition isocyanate (2.5 equiv.) and DMAP (0.5 equiv.). The reaction was again run for 12 hours. Water was added to the crude mixture, which was extracted with EtOAc (3x). Layers were separated and solvent was removed under reduced pressure to afford the crude product. The crude product was QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

General Procedure B: one-pot, sequential 4-component (sulfonylation, Michael, amide coupling and Click). To a pressure tube containing a solution of amine (1.0 mmol, 1.05 equiv.) in dry CH_2Cl_2 (0.5 M), was added Et_3N (1.91 mmol, 2.0 equiv.). The reaction mixture was stirred for 20 min and 2 chloroethane sulfonyl chloride (0.96 mmol, 1.0 equiv.) was added in a drop-wise fashion. The reaction was left to stir overnight and CH_2Cl_2 was removed *in vacuo* upon completion of the reaction. MeOH/water (0.5 M, 5:1), Et_3N (2.87 mmol, 3.0 equiv.) and amino acid (1.0 mmol, 1.05 equiv.) were added to the reaction mixture, which was stirred at 60 ºC for 12 h, after which solvents were evaporated to dryness. DMF (0.08 M) EDC (1.91 mmol, 2.0 equiv.), HOBt (0.48 mmol, 0.5 equiv.) and Et_3N (1.91 mmol, 2.0 equiv.) were added to the crude mixture. The reaction was stirred at rt for 12 h. Upon completion of the reaction it was divided into small vials of equal volume

followed by evaporation of the DMF on a genevac. Dissolution of the crude reactions in (0.5 M, CH_2Cl_2, ^{t}-BuOH, and water in a 1:1:1 ratio) was followed by the addition of $CuSO_4$, L-sodium Ascorbate and the azide. The reaction was run at r.t. for 12 hours. Water was added to the crude mixture, which was extracted with EtOAc (3x). Layers were separated and solvent was removed under reduced pressure to afford the crude product. The crude product was QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

(8*R*,9a*S*)-2-allyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl isopropylcarbamate

(NA-7-278-I-A) 3.4.1(1){1}



According to general procedure **C**, **3.4.1(1){1}** (58.2 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +49.1° (*c* = 0.239, CH_2Cl_2);

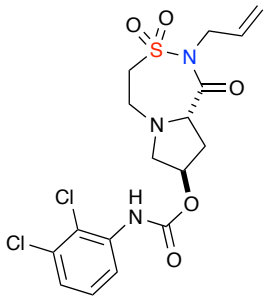
FTIR (thin film) 1703, 1693, 1596, 1537, 1485, 1427, 1353, 1274, 1224, 1151, 1078, 1022 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.86 (dddd, *J* = 17.1, 10.3, 6.2, 5.4 Hz, 1H), 5.33 (dddd, *J* = 17.1, 1.5, 1.4, 1.4 Hz, 1H), 5.22 (dddd, *J* = 10.2, 1.2, 1.2, 1.2 Hz, 1H), 5.08 (p, *J* = 3.7 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 1H), 4.49 – 4.39 (m, 2H), 4.34 (t, *J* = 7.9 Hz, 1H), 3.86 – 3.72 (m, 1H), 3.56 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.49 – 3.35 (m, 3H), 3.31 – 3.21 (m, 1H), 2.80 – 2.65 (m, 2H), 2.15 – 2.06 (m, 1H), 1.17 (d, *J* = 3.0 Hz, 3H), 1.16 (d, *J* = 3.0 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 154.7, 131.9, 118.4, 73.2, 64.5, 62.6, 56.6, 53.0, 47.6, 43.1, 34.33, 22.98 (2);

HRMS calculated for $C_{14}H_{23}N_3O_5SH$ $(M + H)^+$ 346.1437; found 346.1435 (TOF MS ES^+).

(8*R*,9a*S*)-2-allyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (2,3-dichlorophenyl)carbamate (NA-7-278-I-B) 3.4.1(1){2}



According to general procedure **C**, **3.4.1(1){2}** (130.0 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +37.2° (*c* = 0.239, CH_2Cl_2);

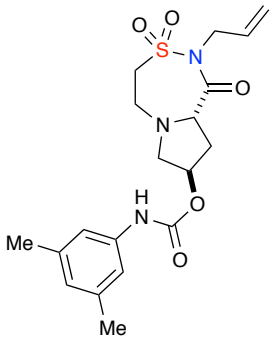
FTIR (thin film) 2960, 2923, 1728, 1701, 1487, 1434, 1353, 1313, 1226, 1151, 1089, 1047, 952, 848, 734 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.18 (m, 3H), 5.88 (dddd, *J* = 17.1, 10.2, 6.3, 5.3 Hz, 1H), 5.35 (dddd, *J* = 17.1, 1.5, 1.4, 1.4 Hz, 1H), 5.26 – 5.19 (m, 2H), 4.52 – 4.40 (m, 3H), 3.64 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.54 – 3.37 (m, 3H), 3.32 – 3.27 (m, 1H), 2.91 – 2.82 (m, 2H), 2.22 (dddd, *J* = 13.9, 8.2, 4.1, 1.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 152.2, 136.0, 132.9, 131.9, 127.8, 124.7, 120.8, 118.5, 117.8, 74.3, 64.2, 62.1, 56.5, 52.6, 47.7, 33.9;

HRMS calculated for $C_{17}H_{19}Cl_2N_3O_5SH$ $(M + H)^+$ 448.0501; found 448.0499 (TOF MS ES^+).

(8*R*,9a*S*)-2-allyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3,5-dimethylphenyl)carbamate (NA-7-278-I-C) 3.4.1(1){3}



According to general procedure **C**, **3.4.1(1){3}** (67.0 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +48.5° (*c* = 0.239, CH_2Cl_2);

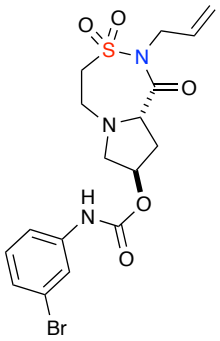
FTIR (thin film) 3249, 3215, 1728, 1703, 1614, 1541, 1510, 1353, 1307, 1218, 1174, 1151, 1045, 1024, 835 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.02 (s, 2H), 6.73 (s, 1H), 6.65 (s, 1H), 5.87 (dddd, *J* = 17.1, 10.3, 6.2, 5.3 Hz, 1H), 5.35 (dddd, *J* = 17.1, 1.4, 1.4, 1.4 Hz, 1H), 5.24 (dddd, *J* = 10.2, 1.1, 1.1, 1.1 Hz, 1H), 5.21 – 5.15 (m, 1H), 4.48 – 4.43 (m, 1H), 4.41 (t, *J* = 7.9 Hz, 1H), 3.62 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.52 – 3.44 (m, 1H), 3.44 – 3.36 (m, 2H), 3.28 (ddd, *J* = 12.0, 3.2, 3.2 Hz, 1H), 2.84 (ddd, *J* = 11.5, 3.3, 1.7 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.30 (s, 6H) 2.22 – 2.15 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 152.6, 138.8 (2), 137.3, 131.9, 125.4 (2), 118.5, 116.4, 64.5, 62.5, 56.6, 53.0, 47.6, 34.2, 30.9, 21.4 (2);

HRMS calculated for $C_{19}H_{25}N_3O_5SH$ $(M + H)^+$ 408.1593; found 408.1594 (TOF MS ES^+).

(8*R*,9a*S*)-2-allyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3-bromophenyl)carbamate (NA-7-278-I-E) 3.4.1(1){5}



According to general procedure **C**, **3.4.1(1){5}** (128.4 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +36.2° (*c* = 0.239, CH_2Cl_2);

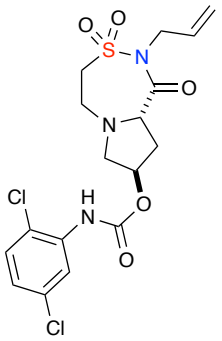
FTIR (thin film) 3218, 3049, 1778, 1591, 1481, 1383, 1319, 1174, 1130, 1033, 952, 827 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.36 (m, 3H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.86 (dddd, *J* = 17.1, 10.2, 6.2, 5.3 Hz, 1H), 5.33 (dddd, *J* = 17.1, 1.4, 1.4, 1.4 Hz, 1H), 5.22 (dddd, *J* = 10.3, 1.2, 1.2, 1.2 Hz, 1H), 5.20 – 5.16 (m, 1H), 4.49 – 4.37 (m, 3H), 3.61 (dd, *J* = 11.5, 4.3 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.45 – 3.34 (m, 2H), 3.27 (dt, *J* = 12.5, 3.4 Hz, 1H), 2.83 (ddd, *J* = 11.6, 3.2, 1.7 Hz, 1H), 2.80 – 2.73 (m, 1H), 2.20 – 2.13 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 152.6, 137.0, 131.9, 131.8, 129.3, 128.3, 120.3, 118.5, 115.9, 64.4, 62.4, 56.6, 53.0, 47.6, 34.2, 30.9;

HRMS calculated for $C_{17}H_{20}BrN_3O_5SH$ $(M + H)^+$ 458.0385; found 458.0392 (TOF MS ES^+).

(8*R*,9a*S*)-2-allyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (2,5-dichlorophenyl)carbamate (NA-7-278-I-I) 3.4.1(1-{9})



According to general procedure **C**, **3.4.1(1-{9})** (220.2 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +28.9° (*c* = 0.239, CH_2Cl_2);

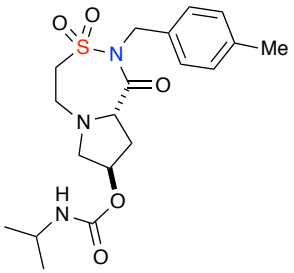
FTIR (thin film) 3240, 3174, 3053, 2960, 1728, 1703, 1596, 1539, 1515, 1427, 1353, 1224, 1151, 1047, 1024, 950, 877, 779, 734, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.15 (s, 1H), 7.01 (dd, *J* = 8.6, 2.4 Hz, 1H), 5.88 (dddd, *J* = 17.1, 10.2, 6.2, 5.4 Hz, 1H), 5.35 (dddd, *J* = 17.2, 1.4, 1.4, 1.4 Hz, 1H), 5.26 – 5.19 (m, 2H), 4.52 – 4.40 (m, 3H), 3.64 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.54 – 3.37 (m, 3H), 3.29 (dt, *J* = 16.0, 3.5 Hz, 1H), 2.90 – 2.82 (m, 2H), 2.22 (dddd, *J* = 13.9, 8.2, 4.1, 1.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 152.0, 135.2, 133.6, 131.9, 129.8, 123.9, 120.1, 119.7, 118.6, 74.5, 64.2, 62.1, 56.5, 52.7, 47.7, 33.9;

HRMS calculated for $C_{17}H_{19}Cl_2N_3O_5SH$ $(M + H)^+$ 448.0501; found 448.0477 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-methylbenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl isopropylcarbamate (NA-7-278-II-A) 3.4.1(3-{1})



According to general procedure **C**, **3.4.1(1-{1})** (22.8 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +45.1° (*c* = 0.239, CH_2Cl_2);

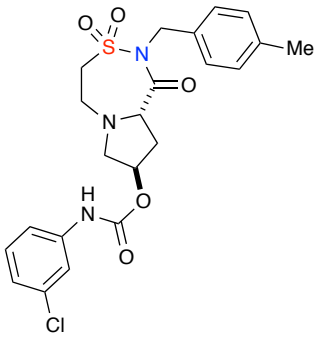
FTIR (thin film) 2972, 1712, 1695, 1515, 1353, 1242, 1151, 1091, 1022, 885, 829, 732, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.13 (d, *J* = 15.0 Hz, 1H), 5.11 – 5.05 (m, 1H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.52 (d, *J* = 7.8 Hz, 1H), 4.38 (t, *J* = 7.9 Hz, 1H), 3.81 (h, *J* = 6.8, 6.2 Hz, 1H), 3.58 – 3.48 (m, 1H), 3.46 – 3.31 (m, 2H), 3.24 – 3.13 (m, 2H), 2.80 – 2.68 (m, 2H), 2.33 (s, 3H), 2.15 – 2.04 (m, 1H), 1.18 (d, *J* = 3.6 Hz, 3H) 1.16 (d, *J* = 3.5 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 154.7, 137.4, 133.4, 129.2 (2), 128.4 (2), 73.3, 64.4, 62.5, 56.6, 52.9, 48.3, 43.1, 34.4, 23.0 (2), 21.1;

HRMS calculated for $C_{19}H_{27}N_3O_5SH$ $(M + H)^+$ 410.1750; found 410.1720 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-methylbenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3-chlorophenyl)carbamate (NA-7-278-II-F) 3.4.1(3-{6})



According to general procedure **C**, **3.4.1(3-{6})** (41.8 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +46.3° (*c* = 0.239, CH_2Cl_2);

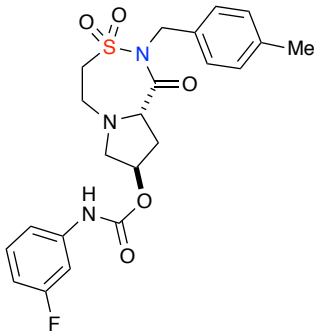
FTIR (thin film) 3380, 3176, 1703, 1693, 1596, 1515, 1485, 1427, 1353, 1307, 1224, 1151, 1078, 1022, 952, 896 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 (s, 1H), 7.31 – 7.27 (m, 2H), 7.24 – 7.19 (m, 2H), 7.14 (d, *J* = 7.0 Hz, 2H), 7.08 – 7.03 (m, 1H), 6.96 (s, 1H), 5.20 (ddd, *J* = 8.2, 4.4, 3.8 Hz, 1H), 5.14 (d, *J* = 15.0 Hz, 1H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.43 (t, *J* = 7.9 Hz, 1H), 3.61 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.50 – 3.41 (m, 1H), 3.40 – 3.32 (m, 1H), 3.26 – 3.15 (m, 2H), 2.85 – 2.78 (m, 2H), 2.33 (s, 3H), 2.21 – 2.13 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 152.4, 138.8, 137.5, 134.8, 133.3, 130.0, 129.2 (2), 128.4 (2), 123.6, 118.6, 116.5, 74.2, 64.3, 62.3, 56.5, 52.8, 48.3, 34.2, 21.1;

HRMS calculated for $C_{22}H_{24}ClN_3O_5SH$ $(M + H)^+$ 478.1203; found 478.1190 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-methylbenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3-fluorophenyl)carbamate (NA-7-278-II-G) 3.4.1(3-{7})



According to general procedure **C**, **3.4.1(3-{7})** (33.5 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +29.6° (*c* = 0.239, CH_2Cl_2);

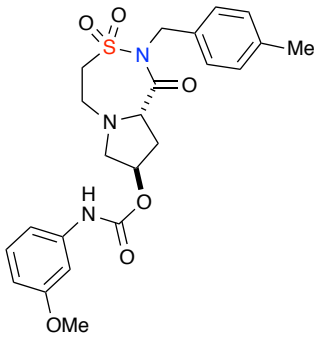
FTIR (thin film) 3281, 2959, 1778, 1512, 1445, 1383, 1325, 1143, 1086, 1059, 820 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.32 (m, 2H), 7.31 – 7.28 (m, 2H), 7.16 – 7.12 (m, 2H), 7.05 – 6.99 (m, 2H), 6.83 (s, 1H), 5.20 (ddd, *J* = 8.2, 4.5, 3.7 Hz, 1H), 5.14 (d, *J* = 15.0 Hz, 1H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.43 (t, *J* = 7.9 Hz, 1H), 3.60 (dd, *J* = 11.5, 4.3 Hz, 1H), 3.52 – 3.40 (m, 1H), 3.39 – 3.33 (m, 1H), 3.25 – 3.15 (m, 2H), 2.84 – 2.75 (m, 2H), 2.33 (s, 3H), 2.21 – 2.11 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 159.0 ($^1J_{C-F}$ = 247.23 Hz), 152.7, 137.5, 133.3 (2), 129.2 (2), 128.4 (2), 120.3, 115.7 (^2J = 22.61 Hz, (2)), 74.02, 64.3, 62.3, 56.5, 52.8, 48.3, 34.2, 30.9, 21.1;

HRMS calculated for $C_{22}H_{24}FN_3O_5SH$ $(M + H)^+$ 462.1499; found 462.1497 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-methylbenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3-methoxyphenyl)carbamate (NA-7-278-II-J) 3.4.1(3-{10})



According to general procedure **C**, **3.4.1(3-{10})** (28.0 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +39.1° (*c* = 0.239, CH_2Cl_2);

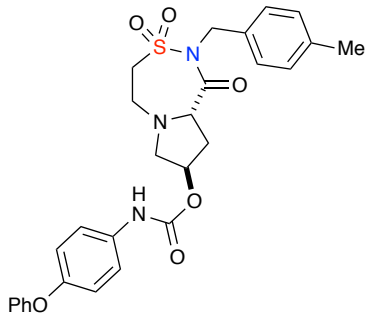
FTIR (thin film) 2997, 2968, 1699, 1604, 1593, 1539, 1510, 1409, 1379, 1352, 1305, 1220, 1182, 1151, 1089, 1014, 833 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.28 (m, 2H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.16 – 7.11 (m, 3H), 6.91 – 6.86 (m, 1H), 6.78 (s, 1H), 6.64 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 5.20 (ddd, *J* = 8.2, 4.5, 3.7 Hz, 1H), 5.14 (d, *J* = 15.0 Hz, 1H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.43 (t, *J* = 7.9 Hz, 1H), 3.81 (s, 3H), 3.61 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.51 – 3.40 (m, 1H), 3.39 – 3.32 (m, 1H), 3.25 – 3.14 (m, 2H), 2.86 – 2.75 (m, 2H), 2.33 (s, 3H), 2.21 – 2.13 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.76, 160.3, 152.5, 138.8, 137.5, 133.3, 129.8 (2), 129.2 (2), 128.4 (2), 109.4 (2), 74.0, 64.3, 62.3, 56.5, 55.3, 52.9, 48.3, 34.2, 21.1;

HRMS calculated for $C_{23}H_{27}N_3O_6SH$ $(M + H)^+$ 474.1699; found 474.1696 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-methylbenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (4-phenoxyphenyl)carbamate (NA-7-278-II-L) 3.4.1(3-{11})



According to general procedure **C**, **3.4.1(3-{11})** (42.5 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +42.2° (*c* = 0.239, CH_2Cl_2);

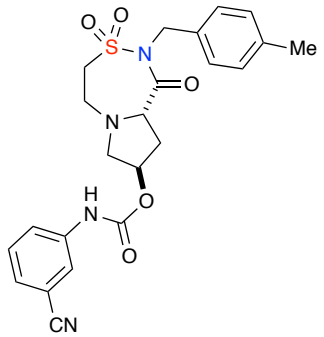
FTIR (thin film) 3053, 3039, 2956, 1710, 1589, 1546, 1504, 1488, 1431, 1413, 1353, 1307, 1222, 1151, 1047, 1024, 950, 871, 842, 779, 736, 692, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.26 (m, 5H), 7.19 – 7.02 (m, 4H), 7.01 – 6.93 (m, 4H), 5.19 (ddd, *J* = 8.2, 4.4, 3.6 Hz, 1H), 5.13 (d, *J* = 15.0 Hz, 1H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.43 (t, *J* = 7.9 Hz, 1H), 3.60 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.49 – 3.40 (m, 2H), 3.39 – 3.31 (m, 1H), 3.25 – 3.15 (m, 2H), 2.85 – 2.75 (m, 2H), 2.32 (s, 3H), 2.20 – 2.13 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 158.0, 156.2, 148.8, 137.4, 133.3, 129.9 (2), 129.64 (2), 129.1 (2), 128.4 (2), 124.0, 122.9, 119.8, 119.6, 118.8, 118.2, 73.9, 64.3, 62.4, 56.5, 52.9, 48.3, 34.2, 21.1;

HRMS calculated for $C_{28}H_{29}N_3O_6SH$ $(M + H)^+$ 536.1855; found 536.1835 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-methylbenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3-cyanophenyl)carbamate (NA-7-278-II-O) 3.4.1(3-{13})



According to general procedure **C**, **3.4.1(3-{13})** (27.0 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +26.9° (*c* = 0.239, CH_2Cl_2);

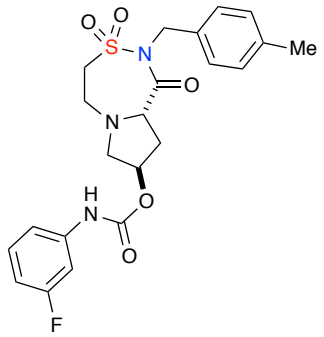
FTIR (thin film) 2950, 1770, 1731, 1699, 1591, 1558, 1506, 1434, 1352, 1226, 1149 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.36 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.31 – 7.27 (m, 3H), 7.16 – 7.12 (m, 2H), 5.22 (ddd, *J* = 8.2, 4.4, 3.8 Hz, 1H), 5.14 (d, *J* = 15.0 Hz, 1H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.44 (t, *J* = 7.9 Hz, 1H), 3.62 (dd, *J* = 11.5, 4.3 Hz, 1H), 3.51 – 3.41 (m, 1H), 3.40 – 3.34 (m, 1H), 3.26 – 3.16 (m, 2H), 2.86 – 2.79 (m, 2H), 2.33 (s, 3H), 2.21 – 2.14 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 152.6, 138.7, 137.5, 133.3, 129.9 (2), 129.2 (2), 128.4, 127.0, 122.6, 121.5, 118.5, 113.1, 74.4, 64.3, 62.2, 56.5, 52.8, 48.3, 34.2, 21.1;

HRMS calculated for $C_{23}H_{24}N_4O_5SH$ $(M + H)^+$ 469.1546; found 469.1533 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-methylbenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3-fluorophenyl)carbamate (NA-7-278-II-Q) 3.4.1(3-{7})



According to general procedure **C**, **3.4.1(3-{7})** (32.2 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +33.2° (*c* = 0.239, CH_2Cl_2);

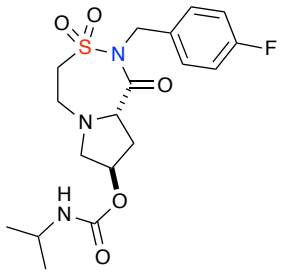
FTIR (thin film) 3064,3026, 2975, 1726, 1703, 1608, 1546, 1533, 1494, 1446, 1353, 1226, 1151, 1056, 1043, 1024, 972, 952, 883, 777, 734, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.31 (m, 1H), 7.31 – 7.21 (m, 3H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 6.77 (tdd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 5.21 (ddd, *J* = 8.2, 3.9, 3.9 Hz, 1H), 5.14 (d, *J* = 14.9 Hz, 1H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.43 (t, *J* = 7.9 Hz, 1H), 3.61 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.51 – 3.41 (m, 1H), 3.40 – 3.32 (m, 1H), 3.25 – 3.15 (m, 2H), 2.85 – 2.77 (m, 2H), 2.33 (s, 3H), 2.22 – 2.13 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 164.1 ($^1J_{C–F}$ = 245.53 Hz), 152.3, 139.2 ($^3J_{C–F}$ = 11.10 Hz), 137.5, 133.3, 130.1 ($^5J_{C–F}$ = 9.37 Hz), 129.2 (2), 128.4 (2), 113.8, 110.3, ($^2J_{C–F}$ = 21.45 Hz), 106.1 ($^6J_{C–F}$ = 25.97 Hz), 74.1, 64.3, 62.3, 56.5, 52.8, 48.3, 34.2, 21.1;

HRMS calculated for $C_{22}H_{24}FN_3O_5SH$ $(M + H)^+$ 462.1499; found 462.1472 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl isopropylcarbamate (NA-7-278-III-A) 3.4.1(2-{1})



According to general procedure **C**, **3.4.1(2-{1})** (77.8 mg, 24%) as yellow oil.

M.P. 95 – 99ºC

$[\alpha]_D^{20}$ = +45.3° (*c* = 0.239, CH_2Cl_2);

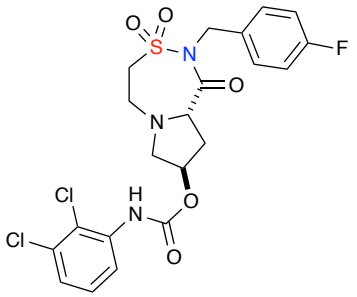
FTIR (thin film) 3388, 2972, 2931, 1701, 1510, 1353, 1244, 1222, 1151, 1093, 1076, 1058, 1024, 954, 902, 885, 840, 779, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.36 (m, 2H), 7.03 – 6.98 (m, 2H), 5.11 – 5.05 (m, 2H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.58 (d, *J* = 8.1 Hz, 1H), 4.35 (t, *J* = 7.9 Hz, 1H), 3.85 – 3.75 (m, 1H), 3.53 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.45 – 3.33 (m, 2H), 3.24 – 3.11 (m, 2H), 2.77 – 2.66 (m, 2H), 2.14 – 2.05 (m, 1H), 1.17 (d, *J* = 3.1 Hz, 3H), 1.15 (d, *J* = 3.1 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 162.2 ($^1J_{C–F}$ = 244.94 Hz), 154.7, 132.2 ($^4J_{C–F}$ = 3.22 Hz), 130.4 ($^3J_{C–F}$ = 8.17 Hz) (2), 115.4($^2J_{C–F}$ = 21.36 Hz) (2), 73.1, 64.4, 62.5, 56.6, 52.9, 47.7, 43.1, 34.3, 23.0 (2);

HRMS calculated for $C_{18}H_{24}FN_3O_5SH$ $(M + H)^+$ 414.1499; found 414.1476 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (2,3-dichlorophenyl)carbamate (NA-7-278-III-B) 3.4.1(2-{2})



According to general procedure **C**, **3.4.1(2-{12})** (112.1 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +26.3° (*c* = 0.239, CH_2Cl_2);

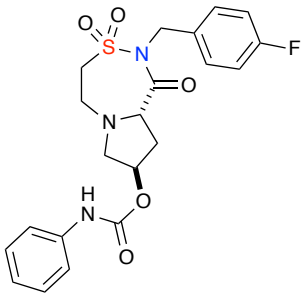
FTIR (thin film) 2989, 2956, 1741, 1693, 1591, 1413, 1348, 1215, 1157, 1026, 964, 952, 877, 854, 775 551 cm^1;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.28 – 7.17 (m, 3H), 7.04 – 6.98 (m, 2H), 5.21 (ddd, *J* = 8.5, 5.7, 4.2 Hz, 1H), 5.10 (d, *J* = 15.0 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.44 (t, *J* = 7.7 Hz, 1H), 3.60 (dd, *J* = 11.0, 4.5 Hz, 1H)), 3.51 – 3.36 (m, 2H), 3.28 – 3.13 (m, 2H), 2.90 – 2.80 (m, 2H), 2.25 – 2.18 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 162.1 ($^1J_{C–F}$ = 245.86 Hz), 152.1, 136.0, 132.8, 132.2 ($^4J_{C–F}$ = 3.22 Hz), 130.4 ($^3J_{C–F}$ = 8.27 Hz) (2), 127.8 (2), 124.7, 117.9, 115.4 ($^2J_{C–F}$ = 21.56 Hz) (2), 74.2, 64.1, 61.9, 56.5, 52.5, 47.8, 33.9;

HRMS calculated for $C_{21}H_{20}Cl_2FN_3O_5SH$ $(M + H)^+$ 516.0563; found 516.0554 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl phenylcarbamate (NA-7-278-III-D) 3.4.1(2-{4})



According to general procedure **C**, **3.4.1(2-{4})** (91.2 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +46.5° (*c* = 0.239, CH_2Cl_2);

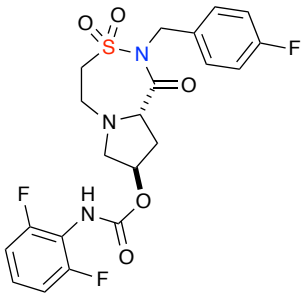
FTIR (thin film) 3245, 3039, 3014, 1724, 1704, 1602, 1544, 1510, 1444, 1353, 1315, 1224, 1151, 1047, 1027, 952, 889, 840, 759, 694, 607, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.37 (m, 4H), 7.33 – 7.28 (m, 2H), 7.07 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.04 – 6.98 (m, 3H), 5.20 (ddd, *J* = 8.1, 4.0, 3.5 Hz, 1H), 5.09 (d, *J* = 15.0 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.41 (t, *J* = 7.9 Hz, 1H), 3.60 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.50 – 3.43 (m, 1H), 3.41 – 3.35 (m, 1H), 3.26 – 3.12 (m, 2H), 2.85 – 2.74 (m, 2H), 2.21 – 2.13 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 162.2 ($^1J_{C–F}$ = 246.60 Hz), 152.6, 137.6, 132.2 ($^4J_{C–F}$ = 3.23 Hz), 130.4 ($^3J_{C–F}$ = 8.25 Hz) (2), 129.03 (3), 123.6, 118.5, 115.3 ($^2J_{C–F}$ = 21.56 Hz) (2), 73.81, 64.3, 62.3, 56.6, 52.9, 47.8, 34.2;

HRMS calculated for $C_{21}H_{22}FN_3O_5SH$ $(M + H)^+$ 448.1342; found 448.1315 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (2,6-difluorophenyl)carbamate (NA-7-278-III-H) 3.4.1(2-{8})



According to general procedure **C**, **3.4.1(2-{8})** (36.7 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +39.1° (*c* = 0.239, CH_2Cl_2);

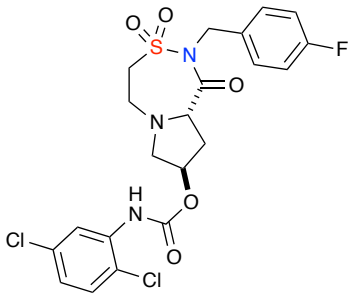
FTIR (thin film) 3184, 2952, 1721, 1716, 1699, 1510, 1471, 1353, 1296, 1242, 1222, 1151, 1008, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.21 (dddd, *J* = 8.5, 8.4, 6.1, 6.1 Hz, 1H), 7.04 – 6.94 (m, 4H), 6.29 (s, 1H), 5.23 – 5.19 (m, 1H), 5.09 (d, *J* = 15.0 Hz, 1H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.37 (t, *J* = 6.2 Hz, 1H), 3.59 (dd, *J* = 11.6, 4.2 Hz, 1H), 3.41 – 3.33 (m, 2H), 3.24 – 3.11 (m, 2H), 2.86 – 2.72 (m, 2H), 2.22 – 2.15 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 162.3 (d, $^1J_{C–F}$ = 244.40 Hz), 158.8 (dd, $^{2'}J_{C–F}$ = 250.69, 4.57 Hz) (2), 153.0, 132.2 (d, $^4J_{C–F}$ = 3.48 Hz), 130.4 (d, $^3J_{C–F}$ = 8.12 Hz) (2), 127.6 (t, $^{4'}J_{C–F}$ = 9.58 Hz), 115.4 (d, $^2J_{C–F}$ = 22.58 Hz) (2), 113.8 (t, $^{1'}J_{C–F}$ = 16.70 Hz), 111.87 (dd, $^{3'}J_{C–F}$ = 19.07, 4.51 Hz) (2), 74.9, 64.3, 62.2, 56.6, 52.8, 47.8, 34.3;

HRMS calculated for $C_{21}H_{20}F_3N_3O_5SH$ $(M + H)^+$ 484.1154; found 484.1150 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (2,5-dichlorophenyl)carbamate (NA-7-278-III-I) 3.4.1(2-{9})



According to general procedure **C**, **3.4.1(2-{9})** (134.5 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +25.3° (*c* = 0.239, CH_2Cl_2);

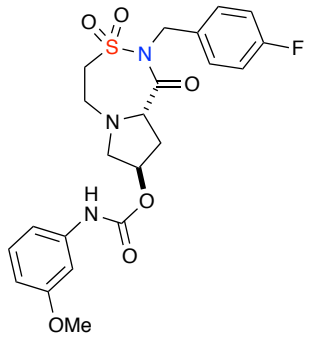
FTIR (thin film) 2954, 2923, 1701, 1602, 1529, 1348, 1224, 1151, 1043, 1024, 829, 636 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 7.44 – 7.38 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.15 (s, 1H), 7.07 – 6.99 (m, 3H), 5.25 – 5.19 (m, 1H), 5.11 (d, *J* = 15.0 Hz, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.44 (t, *J* = 7.7 Hz, 1H), 3.62 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.51 – 3.37 (m, 2H), 3.27 – 3.13 (m, 2H), 2.91 – 2.81 (m, 2H), 2.21 (dddd, *J* = 12.4, 8.1, 4.2, 2.1 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 163.3 ($^1J_{C–F}$ = 246.72 Hz), 152.0, 135.2, 133.6, 132.2 ($^4J_{C–F}$ = 3.36 Hz), 130.4 ($^3J_{C–F}$ = 8.28 Hz) (2), 129.8, 123.9, 120.1, 119.7, 115.4 ($^2J_{C–F}$ = 21.44 Hz) (2), 74.4, 64.1, 62.0, 56.5, 52.5, 47.8, 33.9;

HRMS calculated for $C_{21}H_{20}Cl_2FN_3O_5SH$ $(M + H)^+$ 516.0563; found 516.0543 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3-methoxyphenyl)carbamate (NA-7-278-III-J) 3.4.1(2-{10})



According to general procedure **C**, **3.4.1(2-{10})** (134.5 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +27.8° (*c* = 0.239, CH_2Cl_2);

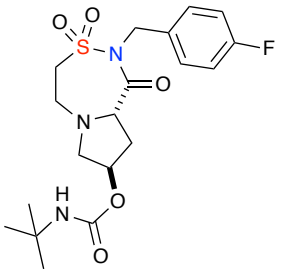
FTIR (thin film) 3390, 3240, 3056, 2999, 2916, 1701, 1596, 1541, 1510, 1483, 1427, 1353, 1224, 1151, 1045, 1026, 952, 877, 852, 781, 734, 696, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.13 (s, 1H), 7.05 (s, 1H), 7.03 – 6.96 (m, 2H), 6.89 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.62 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 5.19 (ddd, *J* = 7.6, 3.7, 3.7 Hz, 1H), 5.09 (d, *J* = 15.0 Hz, 1H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.41 (t, *J* = 7.9 Hz, 1H), 3.79 (s, 3H), 3.59 (dd, *J* = 11.5, 4.3 Hz, 1H), 3.50 – 3.34 (m, 2H), 3.25 – 3.11 (m, 2H), 2.85 – 2.74 (m, 2H), 2.21 – 2.12 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 163.2 ($^1J_{C–F}$ = 244.30 Hz), 160.2, 152.5, 138.8, 132.2 ($^4J_{C–F}$ = 3.28 Hz), 130.4 ($^3J_{C–F}$ = 8.02 Hz) (2), 129.7, 115.4 ($^2J_{C–F}$ = 21.43 Hz) (2), 110.7, 109.3, 104.2, 73.8, 64.3, 62.3, 56.6, 55.2, 52.9, 47.7, 34.2;

HRMS calculated for $C_{22}H_{24}FN_3O_6SH$ $(M + H)^+$ 478.1448; found 478.1444 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl *tert*-butylcarbamate (NA-7-278-III-W) 3.4.1(2-{16})



According to general procedure **C**, **3.4.1(2-{16})** (66.8 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +24.9° (*c* = 0.239, CH_2Cl_2);

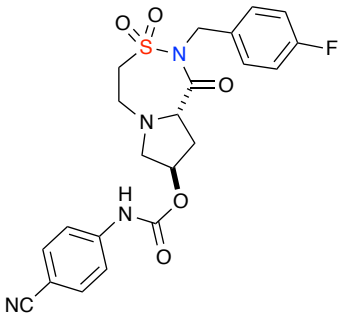
FTIR (thin film) 2995, 2974, 1720, 1701, 1512, 1433, 1353, 1224, 1153, 1045, 1024, 952, 838, 821, 783, 734, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.04 – 6.98 (m, 2H), 5.10 (d, *J* = 15.0 Hz, 1H), 5.05 (bs, 1H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.65 (s, 1H), 4.35 (t, *J* = 7.6 Hz, 1H), 3.53 (dd, *J* = 11.2, 3.9 Hz, 2H), 3.47 – 3.33 (m, 2H), 3.24 – 3.12 (m, 2H), 2.77 – 2.67 (m, 2H), 2.13 – 2.05 (m, 1H), 1.32 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 163.3 ($^1J_{C–F}$ = 246.99 Hz), 153.8, 132.2 ($^4J_{C–F}$ = 3.41 Hz), 130.4 ($^3J_{C–F}$ = 8.32 Hz) (2), 115.4 ($^2J_{C–F}$ = 21.44 Hz) (2), 72.7, 64.4, 62.5, 56.6, 52.9, 50.5, 47.7, 34.3, 28.8 (3);

HRMS calculated for $C_{19}H_{27}FN_3O_5SH$ $(M + H)^+$ 428.1655; found 428.1638 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (4-cyanophenyl)carbamate (NA-7-278-III-R) 3.4.1(2-{15})



According to general procedure **C**, **3.4.1(2-{15})** (104.6 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +34.5° (*c* = 0.239, CH_2Cl_2);

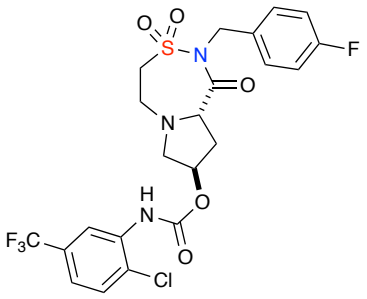
FTIR (thin film) 238, 2341, 1730, 1701, 1598, 1529, 1510, 1413, 1353, 1222, 1151, 1047, 1024, 840, 732, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.64 – 7.60 (m, 2H), 7.55 – 7.51 (m, 2H), 7.44 – 7.38 (m, 2H), 7.06 – 6.99 (m, 3H), 5.27 – 5.19 (m, 1H), 5.11 (d, *J* = 15.0 Hz, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.43 (t, *J* = 7.9 Hz, 1H), 3.62 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.52 – 3.36 (m, 2H), 3.28 – 3.14 (m, 2H), 2.87 – 2.80 (m, 2H), 2.23 – 2.15 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 162.3 ($^1J_{C–F}$ = 246.20 Hz), 151.9, 141.6, 133.4 (2), 132.1 ($^4J_{C–F}$ = 3.30 Hz), 130.5 ($^3J_{C–F}$ = 8.16 Hz) (2), 118.8, 118.3 (2), 115.4 ($^2J_{C–F}$ = 21.63 Hz) (2), 106.7, 74.5, 64.2, 62.1, 56.6, 52.7, 47.8, 34.1;

HRMS calculated for $C_{22}H_{21}FN_4O_5SH$ $(M + H)^+$ 473.1295; found 473.1271 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (2-chloro-5-(trifluoromethyl)phenyl)carbamate 3.4.1(NA-7-278-III-N) (2-{12})



According to general procedure **C**, **3.4.1(2-{12})** (80.6 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +37.8° (*c* = 0.239, CH_2Cl_2);

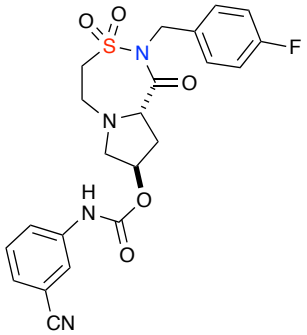
FTIR (thin film) 1730, 1701, 1604, 1591, 1529, 1210, 1433, 1355, 1332, 1220, 1170, 1153, 1128, 1083, 1045, 896, 885, 823, 734, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 7.49 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.30 – 7.26 (m, 2H), 7.05 – 6.99 (m, 2H), 5.25 – 5.20 (m, 1H), 5.11 (d, *J* = 15.0 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.44 (t, *J* = 7.7 Hz, 1H), 3.62 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.50 – 3.36 (m, 2H), 3.27 – 3.14 (m, 2H), 2.93 – 2.81 (m, 2H), 2.21 (dddd, *J* = 13.9, 8.2, 4.2, 1.4 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 163.3 ($^1J_{C–F}$ = 247.70 Hz), 152.1, 135.0, 132.1 ($^4J_{C–F}$ = 3.27 Hz), 130.5 ($^3J_{C–F}$ = 8.14 Hz) (2), 130.0 ($^{2'}J_{C–F}$ = 33.25 Hz), 129.6, 125.3, 123.4 ($^{1'}J_{C–F}$ = 273.10 Hz), 120.4 ($^{3'}J_{C–F}$ = 3.90 Hz), 116.7, 115.5 ($^2J_{C–F}$ = 21.55 Hz) (2), 74.5, 64.1, 61.9, 56.5, 52.5, 47.8, 33.9;

HRMS calculated for $C_{22}H_{20}ClF_4N_3O_5SH$ $(M + H)^+$ 550.0827; found 550.0805 (TOF MS ES^+).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-8-yl (3-cyanophenyl)carbamate (NA-7-278-III-O) 3.4.1(2-{13})



According to general procedure **C**, **3.4.1(2-{13})** (27.0 mg, 24%) as white solid.

$[\alpha]_D^{20}$ = +47.2° (*c* = 0.239, CH_2Cl_2);

M.P. 106 – 110ºC

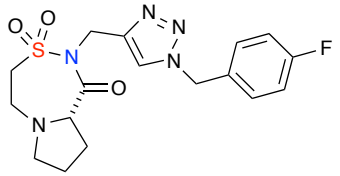
FTIR (thin film) 3564, 2968, 2893, 1731, 1699, 1645, 1606, 1593, 1510, 1434, 1353, 1292, 1222, 1087, 1078, 1024, 956, 883, 852, 790, 682 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.58 – 7.54 (m, 1H), 7.46 – 7.36 (m, 4H), 7.06 – 7.00 (m, 2H), 6.77 (s, 1H), 5.25 – 5.20 (m, 1H), 5.11 (d, *J* = 15.0 Hz, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.43 (t, *J* = 7.9 Hz, 1H), 3.62 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.52 – 3.36 (m, 2H), 3.28 – 3.14 (m, 2H), 2.87 – 2.80 (m, 2H), 2.23 – 2.15 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.62 162.3 ($^1J_{C–F}$ = 246.86 Hz), 152.2, 138.4, 132.1 ($^4J_{C–F}$ = 3.29 Hz), 130.5 ($^3J_{C–F}$ = 8.29 Hz) (2), 130.0, 127.2, 122.6, 121.5, 118.4, 115.4 ($^2J_{C–F}$ = 21.44 Hz) (2), 113.3, 74.4, 64.2, 62.1, 56.6, 52.7, 47.8, 34.1;

HRMS calculated for $C_{22}H_{21}FN_4O_5SH$ $(M + H)^+$ 473.1295; found 473.1270 (TOF MS ES^+).

(*S*)-2-((1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (KC-1-153-III) 3.4.2(3)-[3]



According to general procedure **B**, **3.4.2(3)-[3]** (68.3 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +9.1° (*c* = 0.239, CH_2Cl_2);

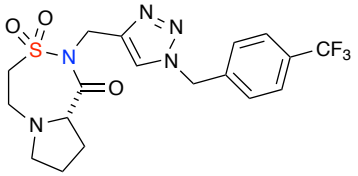
FTIR (thin film) 1704, 1512, 1352, 1222, 1153, 1053, 1020, 892, 844, 783 551 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (s, 1H), 7.26 – 7.21 (m, 2H), 7.08 – 7.02 (m, 2H), 5.49 (d, *J* = 14.9 Hz, 1H), 5.45 (d, *J* = 15.0 Hz, 1H), 5.13 (d, *J* = 15.6 Hz, 1H), 5.02 (d, *J* = 15.5 Hz, 1H), 4.10 (dd, *J* = 9.9, 2.5 Hz, 1H), 3.64 (ddd, *J* = 14.1, 8.9, 7.5 Hz, 1H), 3.40 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.24 (d, *J* = 2.8 Hz, 1H), 3.23 – 3.20 (m, 1H), 3.03 (t, *J* = 7.3 Hz, 1H), 2.60 – 2.51 (m, 2H), 1.91 – 1.80 (m, 1H), 1.76 – 1.68 (m, 1H), 1.68 – 1.56 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.4, 162.8 ($^1J_{C–F}$ = 247.60 Hz), 144.0, 130.4 ($^4J_{C–F}$ = 3.31 Hz), 129.8 ($^3J_{C–F}$ = 8.31 Hz, 2), 122.8, 116.1 (^2J = 21.67 Hz, 2), 64.0, 57.7, 55.7, 53.3, 50.6, 41.0, 27.0, 24.5;

HRMS calculated for $C_{17}H_{20}FN_5O_3SH$ $(M + H)^+$ 394.1349; found 394.1341 (TOF MS ES^+).

(*S*)-2-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (KC-1-153-V) 3.4.2(3)-[5]



According to general procedure **B**, **3.4.2(3)-[5]** (80.2 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +8.6° (*c* = 0.239, CH_2Cl_2);

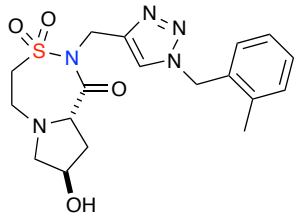
FTIR (thin film) 2972, 2947, 2829, 1704, 1444, 1382, 1353, 1325, 1121, 1178, 1153, 1116, 1066, 1051, 1020, 892, 833, 775, 732, 595, 551 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.50 (s, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 5.58 – 5.55 (m, 2H), 5.15 (d, *J* = 15.5 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.09 (dd, *J* = 9.9, 2.4 Hz, 1H), 3.63 (ddd, *J* = 14.2, 9.1, 7.3 Hz, 1H), 3.41 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.24 (d, *J* = 2.8 Hz, 1H), 3.24 – 3.21 (m, 1H), 3.05 – 3.00 (m, 1H), 2.60 – 2.51 (m, 2H), 1.91 – 1.80 (m, 1H), 1.76 – 1.68 (m, 1H), 1.67 –1.55 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 144.2, 138.6, 131.5 (q, $^2J_{C–F}$ = 32.89 Hz), 128.1 (2), 126.03 (q, $^3J_{C–F}$ = 3.79 Hz (2)), 123.6 ($^1J_{C–F}$ = 271.73 Hz), 123.1, 64.0, 57.7, 55.8, 53.4, 50.6, 41.0, 27.0, 24.5;

HRMS calculated for $C_{18}H_{20}F_3N_5O_3SH$ $(M + H)^+$ 444.1317; found 444.1327 (TOF MS ES^+).

(8*R*,9a*S*)-8-hydroxy-2-((1-(2-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-219-A) 3.4.2(1)-[2]



According to general procedure **B**, **3.4.2(1)-[2]** (91.1 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +15.9° (*c* = 0.239, CH_2Cl_2);

M.P. 201– 206ºC

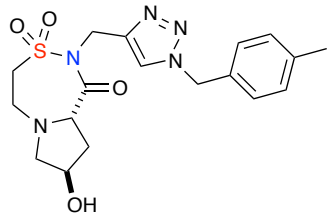
FTIR (thin film) 3334, 3315, 2927, 2835, 1701, 1629, 1431, 1377, 1352, 1326, 1218, 1172, 1151, 1101, 1053, 1020, 898, 879, 850, 777, 734, 555 cm^{-1};

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.88 (s, 1H), 7.37 (td, *J* = 8.0, 5.9 Hz, 1H), 7.16 – 6.98 (m, 3H), 5.58 (s, 1H), 5.04 (s, 2H), 4.31 (dd, *J* = 8.8, 5.7 Hz, 1H), 4.18 – 4.12 (m, 1H), 3.53 (ddd, *J* = 13.9, 3.3, 2.1 Hz, 1H), 3.45 – 3.33 (m, 2H), 3.28 – 3.18 (m, 3H), 2.61 – 2.53 (m, 2H), 2.14 (s, 3H), 1.86 (dddd, *J* = 12.9, 8.9, 6.1, 1.0 Hz, 1H);

^{13}C NMR (126 MHz, MeOD) δ 173.0, 145.6, 132.0, 125.6, 124.9, 116.5, 116.3, 116.0, 115.8, 70.6, 65.5, 65.1, 57.2, 54.3, 54.2, 53.6, 41.1, 37.0;

HRMS calculated for $C_{18}H_{23}N_5O_4SH$ $(M + H)^+$ 406.1549; found 406.1518 (TOF MS ES^+).

(8*R*,9a*S*)-8-hydroxy-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-219-B) 3.4.2(1)-[1]



According to general procedure **B**, **3.4.2(1)-[1]** (91.1 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +19.9° (*c* = 0.239, CH_2Cl_2);

M.P. 206 – 209ºC

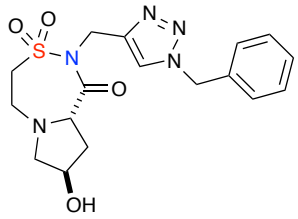
FTIR (thin film) 3355, 3338, 3280, 2945, 2627, 2835, 1701, 1431, 1352, 1217, 1151, 1053, 1020, 898, 879, 850, 825, 734, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 (s, 1H), 7.20 – 7.13 (m, 4H), 5.48 (d, *J* = 14.8 Hz, 1H), 5.43 (d, *J* = 14.8 Hz, 1H), 5.11 (d, *J* = 15.6 Hz, 1H), 5.05 (d, *J* = 15.5 Hz, 1H), 4.44 (s, 1H), 4.32 (dddd, *J* = 5.3, 5.3, 5.2, 5.2 Hz, 1H), 3.71 (s, 1H), 3.50 – 3.37 (m, 2H), 3.37 – 3.30 (m, 1H), 3.28 – 3.20 (m, 1H), 2.74 – 2.64 (m, 2H), 2.35 (s, 3H), 1.94 (dt, *J* = 13.8, 7.4 Hz, 1H);

^{13}C NMR (126 MHz, Acetone) δ 175.6, 148.2, 142.3, 137.6, 133.8 (2), 132.1 (2), 127.3, 73.6, 68.5, 68.3, 60.0, 57.4, 56.8, 44.9, 44.6, 24.6;

HRMS calculated for $C_{18}H_{23}N_5O_4SH$ $(M + H)^+$ 406.1549; found 406.1549 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-8-hydroxyhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-219-D) 3.4.2(1)-[4]



According to general procedure **B**, **3.4.2(1)-[4]** (24.8 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +13.8° (*c* = 0.239, CH_2Cl_2);

M.P. 204 – 207ºC

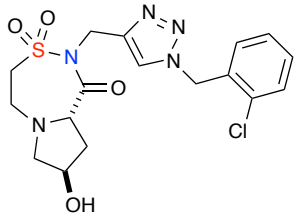
FTIR (thin film) 3143, 3074, 2945, 2837, 1704, 1631, 1433, 1352, 1220, 1151, 1053, 1020, 898, 879, 850, 734, 555 cm^{-1};

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.82 (s, 1H), 7.40 – 7.26 (m, 5H), 5.56 (s, 2H), 5.03 (s, 2H), 4.30 (dd, *J* = 8.8, 5.6 Hz, 1H), 4.14 (p, *J* = 5.7 Hz, 1H), 3.74 (dd, *J* = 12.2, 4.4 Hz, 1H), 3.69 – 3.58 (m, 1H), 3.56 – 3.41 (m, 1H), 3.40 – 3.31 (m, 1H), 3.27 – 3.17 (m, 2H), 2.61 – 2.52 (m, 2H), 1.85 (dddd, *J* = 13.0, 8.9, 6.2, 1.0 Hz, 1H).

^{13}C NMR (126 MHz, MeOD) δ 173.0, 145.5, 137.0, 130.12 (2), 129.6 (2), 129.7, 125.3, 71.1, 65.5, 65.0, 57.1, 55.1, 53.6, 41.15, 37.0;

HRMS calculated for $C_{17}H_{21}N_5O_4SH$ $(M + H)^+$ 392.1392; found 392.1412 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-8-hydroxyhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-219-FMe) 3.4.2(1)-[2]



According to general procedure **B**, **3.4.2(1)-[2]** (55.1 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +12.7° (*c* = 0.239, CH_2Cl_2);

M.P. 215 – 219ºC

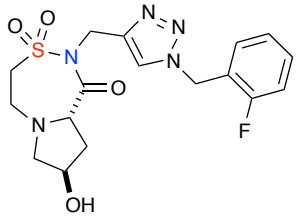
FTIR (thin film) 3321, 3296, 3282, 2945, 2927, 1704, 1639, 1434, 1352, 1292, 1222, 1151, 1053, 1020, 900, 879, 850, 734, 555 cm^{-1};

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.81 (s, 1H), 7.46 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.39 – 7.25 (m, 3H), 7.21 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.70 (s, 2H), 5.04 (s, 2H), 4.30 (dd, *J* = 8.9, 5.5 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.59 – 3.48 (m, 2H), 3.41 – 3.32 (m, 1H), 3.27 – 3.19 (m, 2H), 2.61 – 2.53 (m, 2H), 1.86 (dddd, *J* = 13.1, 9.0, 6.3, 0.9 Hz, 1H);

^{13}C NMR (126 MHz, MeOD) δ 173.0, 145.2, 134.9, 134.3, 131.8, 131.6, 131.1, 128.9, 125.7, 70.6, 65.4, 65.0, 57.1, 53.5, 52.7, 40.5, 37.0;

HRMS calculated for $C_{17}H_{20}ClN_5O_4SH$ $(M + H)^+$ 426.1003; found 426.0995 (TOF MS ES^+).

(8*R*,9a*S*)-2-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-8-hydroxyhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-259) 3.4.2(1)-[13]



According to general procedure **B**, **3.4.2(1)-[12]** (85 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +19.1° (*c* = 0.239, CH_2Cl_2);

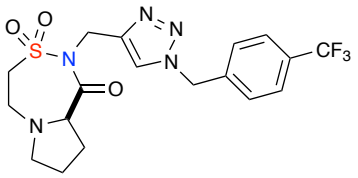
FTIR (thin film) 3281, 2959, 1778, 1512, 1445, 1383, 1325, 1143, 1086, 1059, 820 cm^{-1};

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.88 (s, 1H), 7.37 (ddd, *J* = 8.2, 8.1, 5.9 Hz, 1H), 7.11 – 6.98 (m, 3H), 5.58 (s, 2H), 5.04 (s, 2H), 4.31 (dd, *J* = 8.9, 5.7 Hz, 1H), 4.15 (p, *J* = 5.7 Hz, 1H), 3.53 (ddd, *J* = 13.9, 3.3, 2.1 Hz, 1H), 3.44 – 3.34 (m, 2H), 3.27 – 3.18 (m, 3H), 2.61 – 2.53 (m, 2H) (dddd, *J* = 13.0, 8.9, 6.1, 1.0 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 164.5 ($^1J_{C–F}$ = 245.52 Hz), 145.6, 139.7 ($^3J_{C–F}$ = 7.33 Hz), 132.0 ($^5J_{C–F}$ = 8.19 Hz), 125.6, 124.9 ($^4J_{C–F}$ = 2.93 Hz), 116.4 ($^6J_{C–F}$ = 21.21 Hz), 116.0 ($^2J_{C–F}$ = 22.60 Hz), 70.6, 65.5, 65.1, 57.2, 54.2, 53.6, 41.1, 37.0;

HRMS calculated for $C_{17}H_{20}ClN_5O_4SH$ $(M + H)^+$ 410.1298; found 410.1443 (TOF MS ES^+).

(*R*)-2-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-274-VA) 3.4.2(2)-[5]



According to general procedure **B**, **3.4.2(2)-[5]** (110.7 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +29.6° (*c* = 0.239, CH_2Cl_2);

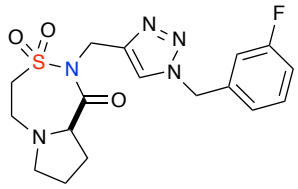
FTIR (thin film) 2970, 2945, 2827, 1704, 1444, 1382, 1352, 1211, 1180, 1153, 1051, 892, 775, 732, 551 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 7.7 Hz, 2H), 7.50 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.56 (d, *J* = 2.1 Hz, 2H), 5.15 (d, *J* = 15.6 Hz, 1H), 5.03 (d, *J* = 15.5 Hz, 1H), 4.09 (dd, *J* = 9.9, 2.4 Hz, 1H), 3.63 (ddd, *J* = 14.1, 9.2, 7.3 Hz, 1H), 3.41 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.24 (d, *J* = 2.8 Hz, 1H), 3.2 (t, *J* = 2.4 Hz, 1H), 3.03 – 3.00 (m, 1H), 2.59 – 2.51 (m, 2H), 1.91 – 1.80 (m, 1H), 1.76 – 1.69 (m, 1H), 1.67 – 1.55 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 144.2, 138.6, 131.5 (q, $^2J_{C–F}$ = 34.23 Hz), 128.1 (2), 126.1 (q, $^3J_{C–F}$ = 3.82 Hz (2)), 123.6 ($^1J_{C–F}$ = 271.73 Hz), 123.1, 64.0, 57.7, 55.8, 53.4, 50.6, 41.0, 27.0, 24.5;

HRMS calculated for $C_{18}H_{20}F_3N_5O_3SH$ $(M + H)^+$ 444.1317; found 444.1321 (TOF MS ES^+).

(*R*)-2-((1-(3-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-274-XIIIA) 3.4.2(2)-[12]



According to general procedure **B**, **3.4.2(2)-[11]** (68.8 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +25.3° (*c* = 0.239, CH_2Cl_2);

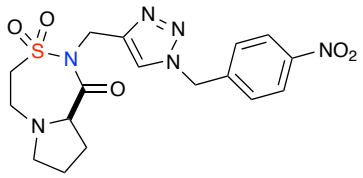
FTIR (thin film) 2972, 2948, 1704, 1589, 1494, 1352, 1232, 1215, 1151, 1051, 892, 846, 777, 732, 555 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 7.38 – 7.32 (m, 1H), 7.22 (td, *J* = 7.6, 1.8 Hz, 1H), 7.16 – 7.08 (m, 2H), 5.57 (s, 2H), 5.14 (d, *J* = 15.6 Hz, 1H), 5.07 (d, *J* = 15.5 Hz, 1H), 4.12 (dd, *J* = 9.9, 2.4 Hz, 1H), 3.65 (ddd *J* = 14.2, 8.2, 8.2 Hz, 1H), 3.40 (dt, *J* = 14.1, 2.7 Hz, 1H), 3.26 – 3.21 (m, 2H), 3.07 – 3.02 (m, 1H), 2.60 – 2.51 (m, 2H), 1.91 – 1.81 (m, 1H), 1.76 – 1.59 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 160.4 ($^1J_{C–F}$ = 248.15 Hz), 143.8, 130.8 ($^3J_{C–F}$ = 8.11 Hz), 130.4 ($^5J_{C–F}$ = 3.30 Hz), 124.8 ($^4J_{C–F}$ = 3.76 Hz), 123.0, 121.9 ($^2J_{C–F}$ = 8.11 Hz), 115.85 ($^6J_{C–F}$ = 21.10 Hz), 63.9, 57.6, 55.7, 50.6, 47.6 ($^{CH2}J_{C–F}$ = 4.58 Hz), 41.0, 27.0, 24.5;

HRMS calculated for $C_{17}H_{20}FN_5O_3SH$ $(M + H)^+$ 394.1349; found 394.1337 (TOF MS ES^+).

(*R*)-2-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-274-XVA) 3.4.2(2)-[14]



According to general procedure **B**, **3.4.2(2)-[15]** (122.4 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +24.8° (*c* = 0.239, CH_2Cl_2);

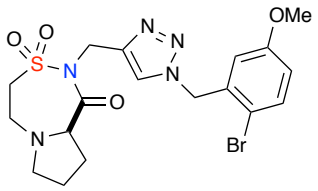
FTIR (thin film) 2974, 2945, 1701, 1637, 1523, 1477, 1427, 1350, 1217, 1178, 1153, 1114, 1051, 1018, 952, 891, 732, 599, 551 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.24 – 8.20 (m, 2H), 7.55 (s, 1H), 7.40 – 7.34 (m, 2H), 5.64 (d, *J* = 15.7 Hz, 1H), 5.59 (d, *J* = 15.8 Hz, 1H), 5.17 (d, *J* = 15.5 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 4.09 (dd, *J* = 9.9, 2.4 Hz, 1H), 3.65 (ddd, *J* = 14.1, 10.5, 5.9 Hz, 1H), 3.42 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.30 – 3.20 (m, 2H), 3.09 – 3.03 (m, 1H), 2.60 – 2.52 (m, 2H), 1.92 – 1.81 (m, 1H), 1.78 – 1.70 (m, 1H), 1.69 – 1.57 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 148.0, 144.5, 141.6, 128.4, 124.2 (2), 123.3 (2), 64.0, 57.7, 55.8, 53.0, 50.6, 41.0, 27.0, 24.6;

HRMS calculated for $C_{17}H_{20}N_6O_5SH$ $(M + H)^+$ 421.1294; found 421.1303 (TOF MS ES^+).

(*R*)-2-((1-(2-bromo-5-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-274-XVI A) 3.4.2(2)-[15]



According to general procedure **B**, **3.4.2(2)-[13]** (48.2 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +29.5° (*c* = 0.239, CH_2Cl_2);

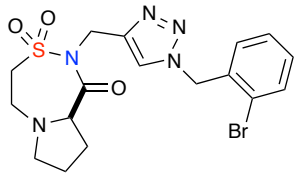
FTIR (thin film) 2968, 2943, 2835, 1703, 1595, 1573, 1477, 1429, 1382, 1352, 1292, 1244, 1178, 1153, 1114, 1153, 1114, 1051, 1020, 891, 732, 601, 549 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.57 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 6.77 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.62 (d, *J* = 3.0 Hz, 1H), 5.58 (s, 2H), 5.14 (d, *J* = 15.5 Hz, 1H), 5.07 (d, *J* = 15.6 Hz, 1H), 4.11 (dd, *J* = 9.9, 2.4 Hz, 1H), 3.73 (s, 3H), 3.67 – 3.56 (m, 1H), 3.39 (dt, *J* = 14.1, 2.8 Hz, 1H), 3.23 (d, *J* = 2.9 Hz, 1H), 3.23 – 3.20 (m, 1H), 3.07 – 3.01 (m, 1H), 2.60 – 2.50 (m, 2H), 1.90 – 1.79 (m, 1H), 1.75 – 1.67 (m, 1H), 1.67 – 1.57 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 159.4, 143.8, 134.9, 133.7, 123.2, 116.2, 115.6, 113.4, 63.9, 57.6, 55.8, 55.5, 53.8, 50.6, 41.0, 27.0, 24.5;

HRMS calculated for $C_{18}H_{22}BrN_5O_4SH$ $(M + H)^+$ 484.0654; found 484.0669 (TOF MS ES^+).

(*R*)-2-((1-(2-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-274-XII A) 3.4.2(2)-[11]



According to general procedure **B**, **3.4.2(2)-[10]** (50.0 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +25.2° (*c* = 0.239, CH_2Cl_2);

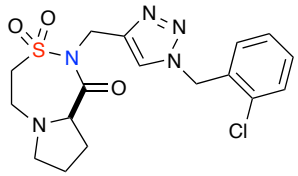
FTIR (thin film) 2968, 2945, 2825, 1750, 1703, 1494, 1352, 1303, 1290, 1211, 1180, 1153, 1114, 1095, 1051, 1027, 891, 732, 549 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.56 (s, 1H), 7.30 (td, *J* = 7.5, 1.3 Hz, 1H), 7.23 (td, *J* = 7.7, 1.8 Hz, 1H), 7.10 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.63 (s, 2H), 5.15 (d, *J* = 15.6 Hz, 1H), 5.08 (d, *J* = 15.6 Hz, 1H), 4.11 (dd, *J* = 9.8, 2.4 Hz, 1H), 3.69 – 3.59 (m, 1H), 3.39 (dt, *J* = 14.1, 2.7 Hz, 1H), 3.25 – 3.23 (m, 1H), 3.22 (d, *J* = 2.8 Hz, 1H), 3.06 – 3.01 (m, 1H), 2.61 – 2.51 (m, 2H), 1.91 – 1.80 (m, 1H), 1.76 – 1.69 (m, 1H), 1.69 – 1.50 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 143.7, 134.1, 133.1, 130.3, 130.2, 128.1, 123.4, 123.3, 63.9, 57.7, 55.8, 53.8, 50.6, 40.3, 27.0, 24.6;

HRMS calculated for $C_{17}H_{20}BrN_5O_3SH$ $(M + H)^+$ 454.0548; found 454.0555 (TOF MS ES^+).

(*R*)-2-((1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (NA-6-274-VI A) 3.4.2(2)-[6]



According to general procedure **B**, **3.4.2(2)-[6]** (62.8 mg, 24%) as yellow oil.

$[\alpha]_D^{20}$ = +21.3° (*c* = 0.239, CH_2Cl_2);

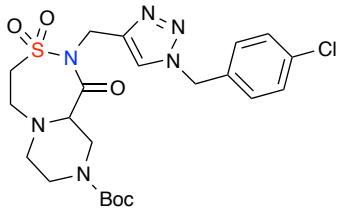
FTIR (thin film) 2975, 2921, 2860, 1685, 1425, 1365, 1348, 1288, 1163, 1149, 1120, 1018, 960, 885, 865, 821, 790, 777,736, 622, 590 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 (s, 1H), 7.42 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.31 (td, *J* = 7.7, 1.7 Hz, 1H), 7.25 (td, *J* = 7.6, 1.4 Hz, 1H), 7.13 (dd, *J* = 7.6, 1.8 Hz, 1H), 5.63 (s, 2H), 5.14 (d, *J* = 15.6 Hz, 1H), 5.06 (d, *J* = 15.5 Hz, 1H), 4.10 (dd, *J* = 9.9, 2.4 Hz, 1H), 3.67 – 3.57 (m, 1H), 3.38 (dt, *J* = 14.2, 2.8 Hz, 1H), 3.25 – 3.20 (m, 2H), 3.06 – 2.98 (m, 1H), 2.60 – 2.50 (m, 2H), 1.91 – 1.79 (m, 1H), 1.76 – 1.68 (m, 1H), 1.68 – 1.56 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 143.7, 133.4, 132.4, 130.1 (2), 129.8, 127.5, 123.2, 63.9, 57.6, 55.7, 51.4, 50.6, 40.3, 27.0, 24.5;

HRMS calculated for $C_{17}H_{20}ClN_5O_3SH$ $(M + H)^+$ 410.1054; found 410.1060 (TOF MS ES^+).

***tert*-butyl 2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1-oxohexahydro-1*H*-pyrazino[2,1-*d*][1,2,5]thiadiazepine-9(2*H*)-carboxylate 3,3-dioxide (NA-6-274-VI B) 3.4.2(5)-[7]**



According to general procedure **B**, **3.4.2(5)-[7]** (67.2 mg, 24%) as yellow oil.

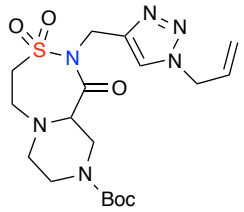
FTIR (thin film) 2975, 2925, 1689, 1425, 1365, 1348, 1288, 147, 1240, 1163, 1149, 1120, 1054, 1018, 962, 885, 864, 821, 756, 736, 545 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 (s, 1H), 7.47 – 7.43 (m, 2H), 7.36 – 7.30 (m, 2H), 5.66 (s, 2H), 5.16 (d, *J* = 15.6 Hz, 1H), 5.05 (d, *J* = 15.7 Hz, 1H), 4.36 (d, *J* = 12.3 Hz, 2H), 4.30 – 4.00 (m, 1H), 3.93 (t, *J* = 14.4 Hz, 1H), 3.85 – 3.69 (m, 1H), 3.35 (dt, *J* = 15.6, 3.1 Hz, 1H), 3.21 (dt, *J* = 14.3, 2.6 Hz, 1H), 3.06 – 2.92 (m, 2H), 2.89 – 2.78 (m, 1H), 2.47 – 2.30 (m, 1H), 1.50 (s, 9H);

^{13}C NMR δ (126 MHz, $CDCl_3$) δ 170.9, 154.9, 143.5, 132.2, 130.3 (2), 130.0, 127.6 (2), 123.0, 79.6, 60.3, 51.9, 51.5, 46.0, 45.1, 42.4, 39.7, 30.9, 28.5 (3);

HRMS calculated for $C_{22}H_{29}ClN_6O_5SH$ $(M + H)^+$ 525.1687; found 525.1686 (TOF MS ES^+).

***tert*-butyl 2-((1-allyl-1*H*-1,2,3-triazol-4-yl)methyl)-1-oxohexahydro-1*H*-pyrazino[2,1-*d*][1,2,5]thiadiazepine-9(2*H*)-carboxylate 3,3-dioxide (NA-6-274-VIII B) 3.4.2(5)-[8]**



According to general procedure **B**, **3.4.2(5)-[7]** (37.2 mg, 24%) as yellow oil.

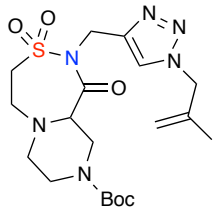
FTIR (thin film) 1691, 1504, 1425, 1365, 1348, 1288, 1240, 1163, 1149, 1120, 1054, 1018, 865, 732, 547 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (s, 1H), 6.10 – 5.90 (m, 1H), 5.40 – 5.25 (m, 1H), 5.18 – 5.04 (m, 2H), 4.97 (d, *J* = 6.1 Hz, 2H), 4.45 – 4.30 (m, 1H), 4.20 (s, 1H), 4.06 (ddd, *J* = 14.5, 12.7, 3.2 Hz, 1H), 3.90 (t, *J* = 13.9 Hz, 1H), 3.79 (d, *J* = 12.7 Hz, 1H), 3.34 (d, *J* = 16.0 Hz, 1H), 3.21 (dt, *J* = 14.4, 2.7 Hz, 1H), 2.97 (dd, *J* = 12.7, 3.6 Hz, 1H), 2.87 – 2.65 (m, 2H), 2.48 – 2.29 (m, 1H), 1.70 – 1.58 (m, 1H), 1.50 (s, 9H);

^{13}C NMR δ (126 MHz, $CDCl_3$) δ 171.3, 154.8, 143.5, 131.0, 123.0, 120.5, 79.6, 60.6, 53.0, 52.0, 45.8, 45.3, 42.3, 39.9, 31.0, 28.4 (3);

HRMS calculated for $C_{18}H_{28}N_6O_5SH$ $(M + H)^+$ 441.1920; found 441.1911 (TOF MS ES^+).

***tert*-butyl 2-((1-(2-methylallyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1-oxohexahydro-1*H*-pyrazino[2,1-*d*][1,2,5]thiadiazepine-9(2*H*)-carboxylate 3,3-dioxide (NA-6-274-IX B) 3.4.2(5)-[9]**



According to general procedure **B**, **3.4.2(5)-[8]** (57.1 mg, 24%) as yellow oil.

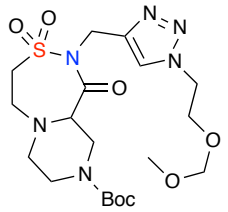
FTIR (thin film) 2975, 2927, 1693, 1683, 1454, 1427, 1365, 1348, 1288, 1247, 1240, 1163, 1149, 1056, 1018, 962, 918, 885, 865, 736, 624, 547 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 (s, 1H), 5.27 – 4.98 (m, 3H), 4.94 – 4.82 (m, 3H), 4.36 (d, *J* = 13.6 Hz, 1H), 4.21 (s, 1H), 4.11 – 4.03 (m, 1H), 3.90 (t, *J* = 13.8 Hz, 1H), 3.77 (d, *J* = 12.4 Hz, 1H), 3.34 (d, *J* = 15.3 Hz, 1H), 3.21 (dt, *J* = 14.4, 2.6 Hz, 1H), 3.02 – 2.90 (m, 1H), 2.86 – 2.76 (m, 1H), 2.46 – 2.31 (m, 1H), 2.28 – 2.19 (m, 1H), 1.68 (s, 3H), 1.47 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 154.8, 143.5, 139.1, 123.1, 115.6, 79.5, 60.4, 56.3, 51.9, 45.9, 45.2, 43.8, 42.3, 39.9, 28.4 (3), 19.7;

HRMS calculated for $C_{19}H_{30}N_6O_5SH$ $(M + H)^+$ 455.2077; found 455.2081 (TOF MS ES^+).

***tert*-butyl 2-((1-(2-(methoxymethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1-oxohexahydro-1*H*-pyrazino[2,1-*d*][1,2,5]thiadiazepine-9(2*H*)-carboxylate 3,3-dioxide (NA-6-274-X B) 3.4.2(5)-[10]**



According to general procedure **B**, **3.4.2(5)-[9]** (29.6 mg, 24%) as yellow oil.

FTIR (thin film) 2975, 2935, 2875, 2835, 1730, 1701, 1492, 1353, 1193, 1151, 1089, 1053, 1016, 904, 852, 823, 810, 781601, 555 cm^{-1};

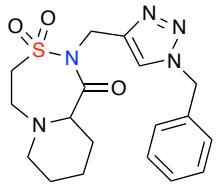
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 (s, 1H), 5.30 – 5.12 (m, 1H), 5.10 – 4.96 (m, 1H), 4.65 – 4.50 (m, 4H), 4.37 (d, *J* = 13.5 Hz, 1H), 4.21 (s, 1H), 4.07 (t, *J* = 13.6 Hz, 1H), 3.91 (tt, *J* = 11.3, 4.5 Hz, 2H), 3.80 (d, *J* = 12.7 Hz, 1H), 3.35 (d, *J* = 17.6 Hz, 1H), 3.28 (s, 3H), 3.20 (dt, *J* = 14.3, 2.6 Hz, 1H), 2.98 (dd, *J* = 12.8, 3.6 Hz, 1H), 2.86 – 2.77 (m, 2H), 2.33 (dd, *J* = 34.1, 11.7 Hz, 2H), 1.48 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 154.8, 143.2, 123.9, 96.4, 79.6, 65.7, 60.5, 55.4, 52.0, 51.8, 50.4, 45.9, 45.3, 42.3, 39.91, 28.4 (3);

HRMS calculated for $C_{19}H_{32}N_6O_7SH$ $(M + H)^+$ 489.2131; found 489.2142 (TOF MS ES^+).

2-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)octahydro-1*H*-pyrido[2,1-*d*][1,2,5]thiadiazepin-1-one 3,3-dioxide

(NA-6-274-IV E) 3.4.2(4)-[4]



According to general procedure **B**, **3.4.2(4)-[4]** (209.1 mg, 24%) as yellow oil.

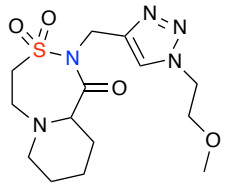
FTIR (thin film) 2945, 2869, 1691, 1496, 1456, 1433, 1369, 1344, 1288, 1147, 1051, 883, 862, 725, 543 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.48 (s, 1H), 7.39 – 7.33 (m, 3H), 7.26 – 7.21 (m, 2H), 5.54 (d, *J* = 14.9 Hz, 1H), 5.46 (d, *J* = 14.8 Hz, 1H), 5.15 (d, *J* = 15.5 Hz, 1H), 5.04 (d, *J* = 15.5 Hz, 1H), 4.30 – 4.27 (m, 1H), 3.97 – 3.88 (m, 1H), 3.87 – 3.79 (m, 1H), 3.28 (dt, *J* = 15.2, 3.0 Hz, 1H), 3.20 – 3.13 (m, 1H), 2.45 – 2.37 (m, 1H), 2.36 – 2.28 (m, 1H), 2.05 – 1.97 (m, 1H), 1.62 – 1.40 (m, 4H), 1.38 – 1.28 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 144.0, 134.5, 129.1 (2), 128.8, 127.9 (2), 122.7, 60.6, 54.1, 52.3, 52.2, 47.3, 39.8, 27.3, 25.8, 19.7;

HRMS calculated for $C_{18}H_{23}N_5O_3SH$ $(M + H)^+$ 390.1600; found 390.1604 (TOF MS ES^+).

2-((1-(2-methoxyethyl)-1*H*-1,2,3-triazol-4-yl)methyl)octahydro-1*H*-pyrido[2,1-*d*][1,2,5]thiadiazepin-1-one 3,3-dioxide (NA-6-274-XVII E) 3.4.2(4)-[16]



According to general procedure **B**, **3.4.2(4)-[9]** (131.3 mg, 24%) as yellow oil.

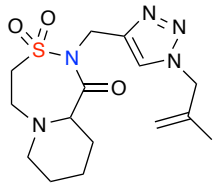
FTIR (thin film) 2943, 2871, 2852, 1689, 1496, 1456, 1433, 1369, 1344, 1207, 1147, 1118, 1051, 883, 862, 796, 732, 636, 582, 543 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.67 (s, 1H), 5.21 (d, *J* = 15.6 Hz, 1H), 5.05 (d, *J* = 15.6 1H), 4.51 (ddd, *J* = 5.4, 4.2, 2.4 Hz, 2H), 4.34 – 4.30 (m, 1H), 3.99 – 3.90 (m, 1H), 3.90 – 3.81 (m, 1H), 3.73 (td, *J* = 5.2, 1.9 Hz, 2H), 3.34 (s, 3H), 3.30 (dt, *J* = 15.2, 3.0 Hz, 1H), 3.21 – 3.13 (m, 1H), 2.49 – 2.40 (m, 2H), 2.10 – 2.01 (m, 1H), 1.70 – 1.47 (m, 4H), 1.47 – 1.39 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 143.5, 123.7, 70.7, 60.6, 59.0, 52.3, 52.2, 50.3, 50.2, 39.8, 27.4, 25.9, 19.7;

HRMS calculated for $C_{14}H_{23}N_5O_4SH$ $(M + H)^+$ 358.1549; found 358.1541 (TOF MS ES^+).

2-((1-(2-methylallyl)-1*H*-1,2,3-triazol-4-yl)methyl)octahydro-1*H*-pyrido[2,1-*d*][1,2,5]thiadiazepin-1-one 3,3-dioxide (NA-6-274-IX E) 3.4.2(4)-[9]



According to general procedure **B**, **3.4.2(4)-[8]** (184.8 mg, 24%) as yellow oil.

FTIR (thin film) 2923, 2871, 2852, 1693, 1434, 1369, 1344, 1209, 1147, 1053, 1004, 883, 862, 796, 746, 732, 638, 543 cm^{-1};

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 (s, 1H), 5.18 (d, *J* = 15.5 Hz, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 5.03 – 5.01 (m, 1H), 4.93 – 4.81 (m, 3H), 4.34 – 4.28 (m, 1H), 3.99 – 3.90 (m, 1H), 3.89 – 3.80 (m, 1H), 3.30 (dt, *J* = 15.3, 3.0 Hz, 1H), 3.22 – 3.13 (m, 1H), 2.49 – 2.36 (m, 2H), 2.10 – 1.97 (m, 1H), 1.66 (s, 3H), 1.65 – 1.44 (m, 4H), 1.44 – 1.36 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 143.9, 139.1, 122.8, 115.4, 60.6, 56.3, 52.3, 52.2, 47.4, 39.8, 27.4, 25.8, 19.7, 19.6;

HRMS calculated for $C_{15}H_{23}N_5O_3SH$ $(M + H)^+$ 354.1600; found 354.1594 (TOF MS ES^+).

5.4 Experimental for Chapter 3.3

Triazole-containing Isothiazolidine 1,1-dioxide Library Synthesis: One-Pot, Multi-Component protocols for small molecular probe discovery

2,3-Dihydroisothiazole 1,1-dioxide (3.5.1).

Into a r.b flask was added allyl amine (6.57 mL, 87.6 mmol, 1.1 equiv.), dry DCM (160 mL, 0.5 M), and Et_3N (36.6 mL, 262.2 mmol, 3 equiv.). The stirring solution was cooled to 0 ºC to which was added dropwise 2-chloroethanesulfonyl chloride (8.32 ml, 79.6 mmol, 1 equiv.). After addition, the reaction was warmed to rt and stirrd for an additional 4 hrs. Upon completion the reaction was quenched with 10% HCl aq. (60 ml), the organic layer extracted and washed with 10% HCl aq. (60 ml), H_2O (60 ml) and Brine (60 ml). The combined organic was dried over $MgSO_4$, filtered and concentrated.

To the crude material *N*-allylethenesulfonamide (11.5g, yellow oil) in a rb flask was added Ar degassed dry DCM (0.07M, 111 ml), and the reaction was heated at 45 ºC. Over the required 3 hr reaction period at 45 ºC, Cat **A** [(IMesH_2)(PCy_3)(Cl)$_2$Ru]CHPh] (2.5 mol%) was added in 5 equal portions every 30mins, essential for compelte converstion of the starting material to product. After such time the reaction was concentrated and purified by flash chromatography (7:3 EtOAc:hexane, R_f **1** = 0.3, R_f *N*-allylethenesulfonamide = 0.7) to yield the desired product as a brown oil (8.35g, 70 mmol, 88% over 2 steps).

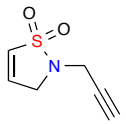
FTIR (neat): 3552, 3274, 1386, 1274, 1151, 1103 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (dt, *J* = 6.5, 2.3 Hz, 1H), 6.71 (dt, *J* = 6.5, 2.3 Hz, 1H), 5.23 (br s, 1H), 4.10 (dt, *J* = 4.4, 2.3 Hz, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 127.2, 47.8;

HRMS calculated for $C_3H_6NO_2S$ $(M+H)^+$ 120.0119; found 120.0121 (TOF MS ES+).

2-(Prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide (3.5.2).



Into a 500 ml rb flask under Ar, was added 2,3-dihydroisothiazole 1,1-dioxide **3.5.1** (4.05g, 33.9 mmol, 1 equiv), dry CH_3CN (170 mL, 0.2 M) and K_2CO_3 (9.36g, 67.8 mmol, 2 equiv). To the stirring slurry was added propargyl bromide ([80% in tol.], 7.58g, 50.9 mmol, 1.5 equiv), after which the reaction was heated at 60 ºC for 5 hrs [TLC monitoring (7:3 EtOAc:hexane, R_f **2** = 0.5, R_f **1** = 0.3]. After such time the reaction was cooled to rt, filtered through a SiO_2 SPE, washed with EtOAC (200 ml) and concentrated. The resulting crude liquid was diluted in toluene (200 ml), concentrated and dried under vacuum to yield the desired product **2** (5.06g, 32.2 mmol, 95%) as an yellow oil.

FTIR (neat): 3274, 1386, 1274, 1141, 1103 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (dt, *J* = 7.0, 2.4 Hz, 1H), 6.72 – 6.65 (m, 1H), 4.15 – 4.10 (m, 2H), 3.99 (d, *J* = 2.2 Hz, 2H), 2.35 (t, *J* = 2.5 Hz, 1H);

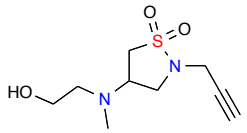
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 127.1, 74.1, 51.4, 33.8;

HRMS calculated for $C_6H_8NO_2S$ $(M+H)^+$ 158.0276; found 158.0279 (TOF MS ES+).

General procedure C for the synthesis of cores 3.5.3, **3.5.4** and **3.5.5** ***via*** **aza-Michael.**

Into a rb flask was added a solution of 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **2** (1 equiv.) in dry MeOH (1M). To the stirring solution was added DBU (10 mol %), the corresponding amino alcohol (1.5 equiv.) and the reaction mixture was heated at 60 ºC for 12 hrs. After such time the reaction was diluted in DCM:MeOH (9:1), filtered through a silica SPE and flushed with DCM:MeOH (9:1). The resulting isothiazolidine 1,1-dioxide (**16**, **17 or 18)** was concentrated and carried forward without the need for further purification.

4-((2-Hydroxyethyl)(methyl)amino)-2-(prop-2-yn-1-yl)isothiazolidine 1,1-dioxide (3.5.3).



According to general procedure **C, 3.5.3** (0.89g, 3.85 mmol, 61%) was isolated as a yellow oil.

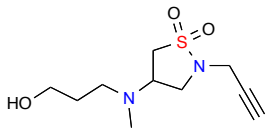
FTIR (neat): 3271, 2952, 1305, 1234 1145, 1033 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 – 3.81 (m, 1H), 3.87 (t, *J* = 2.4 Hz, 2H), 3.63 (t, *J* = 4.8 Hz, 2H), 3.52 (dd, *J* = 10.1, 7.9 Hz, 1H), 3.34 – 3.25 (m, 2H), 3.15 (dd, *J* = 13.0, 7.5 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.57 (dt, *J* = 12.9, 4.8 Hz, 1H), 2.36 (dd, *J* = 5.7, 3.2 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 74.2, 58.3, 57.0, 55.0, 49.1, 47.1, 37.8, 33.6;

HRMS calculated for $C_9H_{17}N_2O_3S$ $(M+H)^+$ 233.0960; found 233.0962 (TOF MS ES+).

4-((3-Hydroxypropyl)(methyl)amino)-2-(prop-2-yn-1-yl)isothiazolidine 1,1-dioxide (3.5.4).



According to general procedure **C, 3.5.4** (0.70g, 2.85 mmol, 59%) was isolated as a yellow oil.

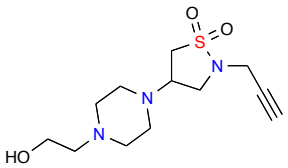
FTIR (neat): 3274, 2948, 2358, 1305, 1234 1145, 1054 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (dd, *J* = 5.7, 2.5 Hz, 2H), 3.85 – 3.80 (m, 1H), 3.76 (t, *J* = 5.5 Hz, 2H), 3.52 (dd, *J* = 10.1, 7.9 Hz, 1H), 3.31 – 3.25 (m, 2H), 3.14 (dd, *J* = 13.0, 7.7 Hz, 1H), 2.68 (ddd, *J* = 12.7, 7.3, 5.4 Hz, 1H), 2.63 – 2.57 (m, 1H), 2.36 (t, *J* = 2.5 Hz, 1H), 2.32 (s, 3H), 1.80 – 1.66 (m, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 74.2, 63.2, 56.9, 53.3, 49.0, 46.6, 38.1, 33.7, 28.3;

HRMS calculated for $C_{10}H_{19}N_2O_3S$ $(M+H)^+$ 247.1116; found 247.1117 (TOF MS ES+).

4-(4-(2-Hydroxyethyl)piperazin-1-yl)-2-(prop-2-yn-1-yl)isothiazolidine 1,1-dioxide (3.5.5).



According to general procedure **C, 3.5.5** (0.545g, 1.89 mmol, 60 %) was isolated as a yellow oil.

FTIR (neat): 3267, 2945, 2823, 1649, 1458, 1305, 1143, 1051 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (dd, *J* = 2.4, 1.2 Hz, 2H), 3.62 (dd, *J* = 9.5, 4.6 Hz, 3H), 3.51 (dd, *J* = 9.6, 7.5 Hz, 1H), 3.36 – 3.26 (m, 2H), 3.17 (dd, *J* = 12.8, 8.0 Hz, 1H), 2.64 – 2.51 (m, 11H), 2.35 (t, *J* = 2.5 Hz, 1H);

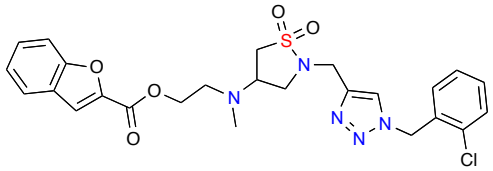
^{13}C NMR (126 MHz, $CDCl_3$) δ 74.1, 59.1, 57.7, 57.1, 52.5, 49.8, 49.0, 48.3, 33.8;

HRMS calculated for $C_{12}H_{22}N_3O_3S$ $(M+H)^+$ 288.1382; found 288.1379 (TOF MS ES+).

General procedure D for synthsis of Library C via one-pot Click/ OACC esterification protocol.

To a 1-dram vial containing sultam **3.5.3**, **3.5.4** or **3.5.5** (40 mg, 1 equiv.) was added CuI (30 mol%), DBU (10 mol%), dry DCM (0.2 M), acid (1.2 equiv.) and azide (2 equiv.). To the crude mixture was added a solution of OACC (1.5 eq.) in dry DCM (0.2M) and the resulting reaction mixture was heated at 50 ºC on a reaction block for for 12 hrs. After which time the reactions were cooled, diluted in EtOAc (2 ml) and the correspondiong suspention filtered through SiO_2 SPE into pre-weighed barcoded vials, washed with eluent (2 ml, EtOAc) and concentrated. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

2-((2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)(methyl)amino) ethyl benzofuran-2-carboxylate (3.5.6-A{2}).



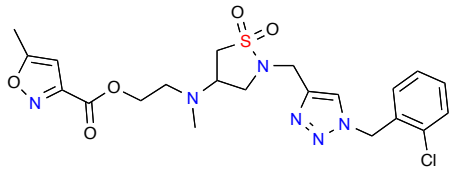
FTIR (neat): 2358, 1724, 1446, 1296, 1222, 1178, 1143 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.70 (m, 1H), 7.64 (s, 1H), 7.60 (dt, *J* = 6.0, 3.0 Hz, 1H), 7.50 (d, *J* = 0.9 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.41 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.25 – 7.21 (m, 1H), 7.18 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.63 (s, 2H), 4.44 – 4.38 (m, 1H), 4.37 (dd, *J* = 4.7, 2.5 Hz, 2H), 3.83 – 3.75 (m, 1H), 3.43 (dt, *J* = 12.7, 6.3 Hz, 1H), 3.35 (dd, *J* = 13.0, 8.6 Hz, 1H), 3.14 (ddd, *J* = 17.2, 11.5, 7.3 Hz, 2H), 2.85 (ddd, *J* = 13.9, 6.7, 4.9 Hz, 1H), 2.79 – 2.73 (m, 1H), 2.34 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 155.8, 145.0, 142.5, 133.6, 132.2, 130.4, 130.4, 130.0, 127.8, 127.6, 126.9, 123.9, 123.7, 123.0, 114.3, 112.4, 62.5, 56.8, 51.9, 51.2, 49.4, 47.6, 38.9, 38.8;

HRMS calculated for $C_{25}H_{27}ClN_5O_5SNa$ $(M+H)^+$ 544.1421; found 544.1405 (TOF MS ES+).

2-((2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)(methyl)amino) ethyl 5-methylisoxazole-3-carboxylate (3.5.6-A{3}).



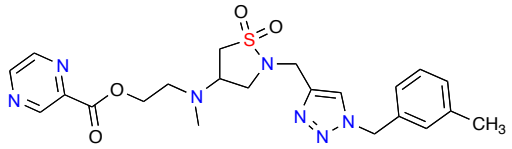
FTIR (neat): 2952, 1735, 1598, 1458, 1305, 1205, 1143, 1047 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.42 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.31 (td, *J* = 7.7, 1.8 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.20 – 7.18 (m, 1H), 6.38 (d, *J* = 0.9 Hz, 1H), 5.65 (s, 2H), 4.42 – 4.31 (m, 2H), 4.34 (d, *J* = 1.5 Hz, 2H), 3.74 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.40 (dd, *J* = 10.1, 7.8 Hz, 1H), 3.30 (dd, *J* = 13.0, 8.7 Hz, 1H), 3.09 (ddd, *J* = 15.0, 11.6, 7.2 Hz, 2H), 2.85 – 2.78 (m, 1H), 2.72 (dt, *J* = 14.0, 5.4 Hz, 1H), 2.50 (d, *J* = 0.8 Hz, 3H), 2.31 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) 171.6, 159.9, 156.0, 142.5, 133.5, 132.2, 130.4, 130.3, 130.0, 127.6, 127.6, 123.7, 102.3, 62.9, 56.8, 51.8, 51.6, 49.3, 47.5, 38.8, 38.7, 12.4;

HRMS calculated for $C_{21}H_{26}ClN_6O_5SNa$ $(M+Na)^+$ 509.1374; found 509.1379 (TOF MS ES+).

2-(Methyl(2-((1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)amino)ethyl pyrazine-2-carboxylate (3.5.6-D{1}).



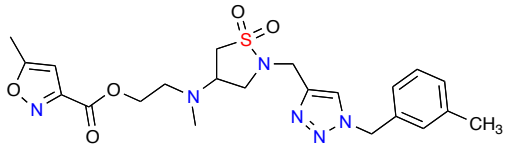
FTIR (neat): 1724, 1303, 1141, 1049, 1018, 775 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, *J* = 1.3 Hz, 1H), 8.78 (d, *J* = 2.4 Hz, 1H), 8.74 (dd, *J* = 2.4, 1.5 Hz, 1H), 7.53 (d, *J* = 4.0 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.09 – 7.03 (m, 2H), 5.51 – 5.43 (m, 2H), 4.50 – 4.41 (m, 2H), 4.32 (d, *J* = 15.6 Hz, 2H), 3.80 – 3.72 (m, 1H), 3.42 (dd, *J* = 9.5, 8.3 Hz, 1H), 3.35 (dd, *J* = 13.0, 8.6 Hz, 1H), 3.13 (ddd, *J* = 20.7, 12.6, 6.4 Hz, 2H), 2.91 – 2.84 (m, 1H), 2.79 (dt, *J* = 13.9, 5.5 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 147.9, 146.3, 144.6, 143.2, 142.6, 139.0, 134.3, 129.6, 129.0, 128.8, 125.1, 123.3, 63.1, 56.8, 54.3, 52.1, 49.4, 47.6, 38.8, 38.7, 21.3;

HRMS calculated for $C_{22}H_{27}N_7O_4S$ $(M+H)^+$ 508.1743; found 508.1750 (TOF MS ES+).

2-(Methyl(2-((1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)amino)ethyl 5-methylisoxazole-3-carboxylate (3.5.6-D{3}).



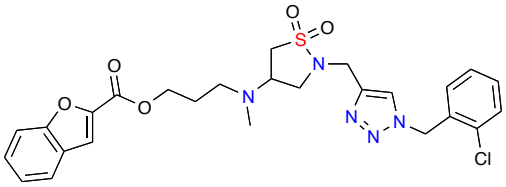
FTIR (neat): 1733, 1458, 1305, 1205, 1143, 1049, 100 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 5.3 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.09 – 7.04 (m, 2H), 6.39 (d, *J* = 0.9 Hz, 1H), 5.48 (s, 2H), 4.43 – 4.34 (m, 2H), 4.33 (d, *J* = 3.7 Hz, 2H), 3.77 – 3.68 (m, 1H), 3.40 (dd, *J* = 10.1, 7.8 Hz, 1H), 3.29 (dd, *J* = 13.0, 8.7 Hz, 1H), 3.09 (ddd, *J* = 16.8, 11.6, 7.3 Hz, 2H), 2.81 (ddd, *J* = 13.8, 6.5, 5.2 Hz, 1H), 2.73 (dt, *J* = 13.9, 5.5 Hz, 1H), 2.50 (d, *J* = 0.8 Hz, 3H), 2.34 (s, 3H), 2.30 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 159.9, 156.0, 142.5, 139.0, 134.3, 129.6, 129.0, 128.8, 125.2, 123.3, 102.3, 62.9, 56.8, 54.3, 51.8, 49.3, 47.5, 38.8, 38.7, 21.3, 12.4;

HRMS calculated for $C_{22}H_{29}N_6O_5S$ $(M+H)^+$ 489.1920; found 489.1921 (TOF MS ES+).

3-((2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)(methyl)amino) propyl benzofuran-2-carboxylate (3.5.7-A{2}).



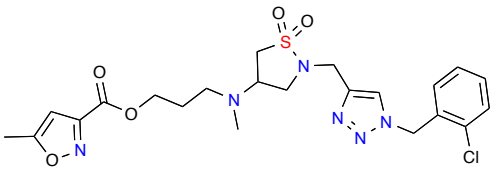
FTIR (neat): 1724, 1564, 1446, 1296, 1178, 1143, 1047 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ δ 7.73 – 7.69 (m, 1H), 7.63 – 7.58 (m, 2H), 7.54 (d, *J* = 0.9 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.34 – 7.29 (m, 2H), 7.29 – 7.24 (m, 3H), 7.19 (dd, *J* = 7.6, 1.7 Hz, 1H), 4.39 (dd, *J* = 10.2, 3.8 Hz, 2H), 4.34 (d, *J* = 8.6 Hz, 2H), 3.71 – 3.64 (m, 1H), 3.41 (dd, *J* = 9.9, 7.7 Hz, 1H), 3.28 (dd, *J* = 12.9, 8.5 Hz, 1H), 3.17 – 3.09 (m, 2H), 2.53 (t, *J* = 6.8 Hz, 2H), 2.22 (s, 3H), 1.91 (dq, *J* = 13.4, 6.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 155.7, 145.3, 142.5, 133.6, 132.2, 130.4, 130.4, 130.0, 127.7, 127.6, 126.9, 123.8, 123.7, 122.9, 114.1, 112.4, 62.9, 56.9, 51.6, 50.3, 49.1, 47.6, 38.8, 37.6, 26.5;

HRMS calculated for $C_{26}H_{29}ClN_5O_5S$ $(M+H)^+$ 558.1578; found 558.1582 (TOF MS ES+).

3-((2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)(methyl)amino) propyl 5-methylisoxazole-3-carboxylate (3.5.7-C{3}).



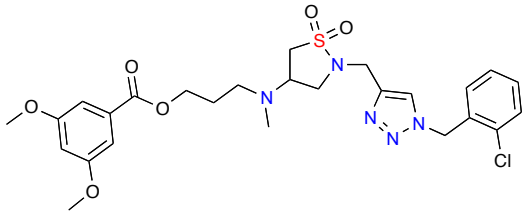
FTIR (neat): 2956, 2358, 1731, 1458, 1305, 1271, 1205, 1143, 1047 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.43 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.32 (td, *J* = 7.7, 1.8 Hz, 1H), 7.29 (d, *J* = 1.4 Hz, 1H), 7.19 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.40 (d, *J* = 0.8 Hz, 1H), 5.66 (s, 2H), 4.39 – 4.32 (m, 3H), 3.69 – 3.60 (m, 1H), 3.37 (dd, *J* = 9.9, 7.7 Hz, 1H), 3.24 (dd, *J* = 12.9, 8.5 Hz, 1H), 3.13 – 3.05 (m, 2H), 2.50 (m, 2H), 2.50 (d, *J* = 0.8 Hz, 3H), 2.19 (s, 3H), 1.91 – 1.85 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 160.2, 156.3, 142.6, 133.5, 132.2, 130.4, 130.0, 127.6, 123.7, 102.3, 63.5, 56.9, 51.6, 50.3, 49.2, 47.4, 38.8, 37.5, 26.2, 12.4;

HRMS calculated for $C_{22}H_{28}ClN_6O_5S$ $(M+H)^+$ 523.1530; found 523.1520 (TOF MS ES+).

3-((2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)(methyl)amino) propyl 3,5-dimethoxybenzoate (3.5.7-A{4}).



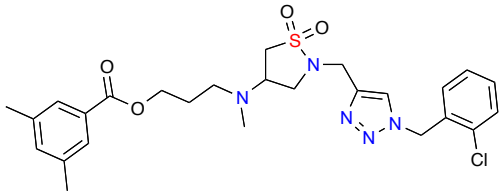
FTIR (neat): 1706, 1514, 1292, 1271, 1222, 1141 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 7.64 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.61 (s, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.31 (tt, *J* = 7.3, 1.9 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.18 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.90 (t, *J* = 6.9 Hz, 1H), 5.64 (s, 2H), 4.38 – 4.26 (m, 4H), 3.93 (t, *J* = 4.3 Hz, 5H), 3.69 – 3.61 (m, 1H), 3.39 (dd, *J* = 9.9, 7.7 Hz, 1H), 3.28 – 3.22 (m, 1H), 3.14 – 3.06 (m, 2H), 2.53 – 2.48 (m, 2H), 2.21 (s, 3H), 1.91 – 1.84 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 153.1, 148.7, 142.5, 133.6, 132.2, 130.4, 130.0, 127.6, 123.7, 123.4, 122.6, 111.9, 110.3, 62.4, 56.9, 56.0, 51.6, 50.5, 49.2, 47.6, 38.8, 37.7, 26.6;

HRMS calculated for $C_{26}H_{33}ClN_5O_6S$ $(M+H)^+$ 578.1840; found 578.1832 (TOF MS ES+).

3-((2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)(methyl)amino) propyl 3,5-dimethylbenzoate (3.5.7-A{5}).



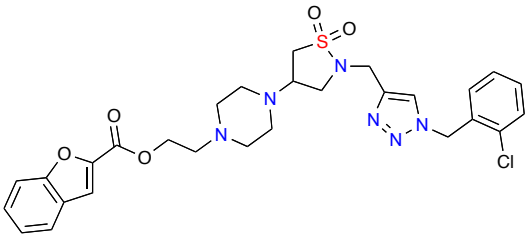
FTIR (neat): 1772, 1446, 1349, 1210, 1143, 1045 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.60 (s, 1H), 7.42 (dt, *J* = 7.9, 2.4 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.28 – 7.24 (m, 1H), 7.18 (dd, *J* = 7.4, 1.7 Hz, 2H), 5.64 (s, 2H), 4.38 – 4.26 (m, 4H), 3.69 – 3.62 (m, 1H), 3.41 – 3.36 (m, 1H), 3.27 – 3.21 (m, 1H), 3.14 – 3.06 (m, 2H), 2.50 (ddd, *J* = 7.9, 6.4, 2.5 Hz, 2H), 2.35 (s, 6H), 2.20 (s, 3H), 1.88 (tt, *J* = 13.5, 4.0 Hz, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 142.6, 138.1, 134.7, 133.5, 132.2, 130.4, 130.0, 127.6, 127.2, 123.7, 62.5, 56.9, 51.6, 50.6, 49.2, 47.5, 38.8, 37.6, 26.6, 21.2;

HRMS calculated for $C_{26}H_{33}ClN_5O_4S$ $(M+H)^+$ 546.1942; found 546.1943 (TOF MS ES+).

2-(4-(2-((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,1-dioxidoisothiazolidin-4-yl)piperazin-1-yl)ethyl benzofuran-2-carboxylate (3.3.8-A{2}).



FTIR (neat): 1726, 1296, 1178, 1145, 1047 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 7.69 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 1H), 7.60 – 7.56 (m, 2H), 7.46 (ddd, *J* = 10.6, 5.9, 2.3 Hz, 1H), 7.43 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.29 – 7.27 (m, 1H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.65 (s, 2H), 4.63 (s, 2H), 4.34 (s, 2H), 3.54 – 3.47 (m, 1H), 3.43 (dd, *J* = 9.7, 7.4 Hz, 1H), 3.33 – 3.26 (m, 1H), 3.14 (ddd, *J* = 20.7, 11.3, 7.5 Hz, 2H), 2.95 (br m, 2H), 2.90 – 2.72 (br m, 4H), 2.65 (s, 4H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 142.3, 133.6, 132.1, 130.5, 130.4, 130.0, 127.9, 127.6, 126.8, 123.9, 123.8, 122.9, 112.4, 57.0, 56.1, 52.8, 51.7, 49.2, 48.6, 38.9;

HRMS calculated for $C_{28}H_{32}ClN_6O_5S$ $(M+H)^+$ 599.1843; found 599.1837 (TOF MS ES+).

5.5 Experimental for Chapter 4.1

Facilitated Intermolecular Monomer-on-Monomer (MoM) Mitsunobu Reaction on Hydroxy-pyrrolo thiadiazepin-dioxide Scaffolds

General procedures and reagents: All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, canullas and septa. CH_2Cl_2 and toluene were purified by passage through a Solv-Tek[i] (www.solvtek.com) purification system employing activated Al_2O_3 and degassed with argon. Flash column chromatography was performed with SiO_2 (Sorbent Technologies 30930M-25, Silica Gel 60 Å, 40-63 μm). Thin layer chromatography was performed on silica gel 60F 254 plates. Visualization of TLC spots was effected using $KMnO_4$ stain. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-400 spectrometer operating at 400 MHz, and 100 MHz respectively as well as Bruker DRX-500 spectrometer operating at 500 MHz, and 125 MHz, respectively and calibrated to the solvent peak. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). The nanoparticles were analyzed by scanning electron microscopy (Hitachi S-2700 equipped with a quartz PCI digital capture) and FTIR Perkin Elmer Spectrum 100 FT-IR spectrometer. All other commercially available compounds were used as received. metathesis catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$; cat-**B**] was provided by Materia Inc. and used without further purification. Deuterated solvents were purchased from Cambridge Isotope laboratories.

General procedure A: Synthesis of Hydroxy-pyrrolo thiadiazepin-dioxide Scaffolds.

To a round bottom flask/pressure tube containing a solution of amine (1.0 equiv.) in dry CH_2Cl_2 (0.5 M), was added Et_3N (2.0 equiv.). The reaction mixture was cooled to 0 ºC, stirred for 20 min followed by the drop-wise addition of 2-chloroethane sulfonyl chloride (1.0 equiv.). The reaction was warmed to rt and left to stir overnight. After the completion of the reaction CH_2Cl_2 was removed by evaporation. MeOH (0.5 M), water (0.5 M), Et_3N (3.0 equiv.) and amino acid (1.0 equiv.) were added to the reaction mixture, which was stirred at 60 ºC for 12 h, after which the solvents were evaporated to dryness. This was followed by the addition of DMF (0.05 M) EDC (2.0 equiv.), HOBt (0.2 equiv.) and Et_3N (2.0 equiv.) to the crude mixture. The reaction was stirred at rt for 12 h, followed by evaporation of DMF. Water was added to the crude mixture, which was extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (100% EtOAc).

General procedure B: Intermolecular monomer-on-monomer (MoM) Mitsunobu reaction utilizing metathesis catalyst B [Method A].

To a round-bottom under argon atmosphere was added hydroxy-pyrrolo thiadiazepin-dioxide (1 equiv) in dry THF (0.1 M). The reaction was cooled to 0 ºC, stirred for 15 min, after which Nb-TPP (3 equiv) and Nb-BEAD (3 equiv) were added to the reaction mixture and stirred at room temperature for 2-12 hrs (TLC monitoring). The reaction was concentrated and resolvated in degassed CH_2Cl_2 (0.1 M), cat-**B** (0.05 equiv)[[$(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh] was added and reaction heated at 50 ºC for 30 mins to 1 hr (TLC monitoring). Upon completion, the reaction was cooled to room temperature, quenched with ethyl vinyl ether (4 equiv) and stirred for an additional 30 mins. After such time was added Na_2CO_3 (10 equiv) followed by dropwise addition of tetrakis(hydroxymethyl) phosphonium chloride (THPC) 80% in water (10 equiv) while stirring and was refluxed for 4 h. The reaction mixture was cooled to room temperature, extracted with dichloromethane (2 x 20 mL), washed with water and brine. The organic layer was dried over $MgSO_4$, filtered through a celite plug and concentrated in *vacuo*. The resulting solution was filtered through a plug of silica, eluting with 2:1-Hexane/EtOAc. The resulting eluent was then concentrated *in vacuo* to yield the desired products in good to excellent yields and purities.

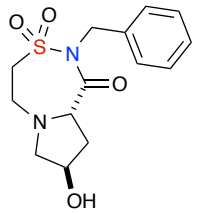
General procedure C: Intermolecular monomer-on-monomer (MoM) Mitsunobu reaction utilizing Nb-tagged Co/C magnetic nanoparticles [Method C].

To a round-bottom flask under argon atmosphere was added hydroxy-pyrrolo thiadiazepin-dioxide (1 equiv) solvated in dry THF (0.1 M). The reaction was cooled to 0 °C, stirried for 20 mins, after which was added Nb-TPP (3.0 equiv.) and Nb-BEAD (3.0 equiv.) and the reaction warmed to room temperature and stirred for 2–12 h (TLC monitoring). Upon completion of the reaction, the solvent was removed, the crude mixture was dissolved in degassed CH_2Cl_2 (0.1 M) and added to a pressure tube containing a mixture of Co/C-Nb (3 mol %) and Grubbs catalyst [3 mol %, $(IMesH_2)(PCy_3)$-$(Cl)_2Ru$=CHPh, cat-**II**] in dry degassed CH_2Cl_2 (0.05 M), that had been sonicated at 60 °C for 30 min. After additional sonication for 1–5 h at 60 ºC (TLC monitoring), a neodymium based magnet was attached to the side of the tube and the crude reaction mixture was decanted, filtered through a silica SPE and concentrated *in vacuo*, yielding the desired products in good purities.

General procedure D: Intermolecular monomer-on-monomer (MoM) Mitsunobu reaction utilizing catalyst-armed Nb-tagged silica particles [Method D].

Into a 1-dram vial was added hydroxy-pyrrolo thiadiazepin-dioxide (1 equiv), dry THF (0.1 mL) and Nb-TPP (2.04 10^{-4} mol, 1.6 equiv) under an argon atmosphere. After stirring for 5 mins, a solution of Nb-BEAD (2.04 10^{-4} mol, 1.6 equiv) in dry THF (0.156 mL) was added dropwise and the reaction was stirred at room temperature for 2–12 h (TLC monitoring). After evaporation of the solvent, Nb-tagged silica (6.12 10^{-4} mol, 3 mol %) was added followed by the addition of a solution of cat-**II** [3 mol %, $(IMesH_2)(PCy_3)$-$(Cl)_2Ru$=CHPh] in dry Ar degassed CH_2Cl_2 (2 mL). The reaction was heated at 50 ºC for 30 mins (TLC monitoring), after which the crude reaction was diluted with EtOAc, filtered through a silica SPE washing the SPE and residual Si-ROMP gel with EtOAc, concentrated, yielding the desired products in good purities.

(8*S*,9a*S*)-2-benzyl-8-hydroxyhexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.1)



Utilizing general procedure **A**, **4.5.1** compound (69%, 0.51 g) was isolated after chromatography as a light brown solid.

M. P. 109–110 ºC;

R_f = 0.52 (100% EtOAc);

FTIR (neat) 3639, 3109, 2953, 2901, 1701, 1454, 1360, 1142, 1102, 712 cm^{-1};

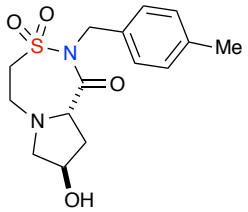
$[\alpha]_D^{20}$ = +25.2° (*c* = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.42–7.37 (m, 2H), 7.36–7.32 (m, 2H), 7.31–7.28 (m, 1H), 5.13 (d, *J* = 15.1 Hz, 1H), 4.90 (d, *J* = 15.1 Hz, 1H), 4.46 (dd, *J* = 10.6, 6.0 Hz, 1H), 4.42 (dddd, *J* = 5.2, 5.2, 5.2, 5.2 Hz, 1H), 3.49–3.42 (m, 1H), 3.41–3.35 (m, 2H), 3.26–3.17 (m, 2H), 2.76 (dddd, *J* = 13.5, 5.9, 5.9, 1.0 Hz, 1H), 2.65 (ddd, *J* = 9.9, 5.2, 1.2 Hz, 1H), 2.07 (bs, 1H, OH), 1.95 (dddd, *J* = 13.3, 8.5, 5.6, 1.0 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.6, 136.3, 128.6, 128.1(2), 127.7(2), 63.9, 61.6, 58.9, 55.4, 50.3, 49.0, 32.3;

HRMS calculated for $C_{14}H_{18}N_2O_4SH$ $(M+H)^+$ 311.1066; found 311.1061 (TOF MS ES^+).

(8*S*,9a*S*)-8-hydroxy-2-(4-methylbenzyl)hexahydropyrrolo[2,1-*d*][1,2,5] thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.3)



Utilizing general procedure **A**, **4.5.3** (34.7 mg, 0.107 mmol, 83%) was isolated as a white solid.

$[\alpha]_D^{20}$ = +22.2 ° (c = 0.25, $CHCl_3$);

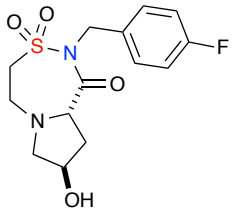
FTIR (neat, cm^{-1}): 2360, 1637, 1346, 1211, 1151.

1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 5.10 (d, *J* = 15.0 Hz, 1H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.42 (ddd, *J* = 15.8, 9.6, 5.7 Hz, 2H), 3.48 – 3.33 (m, 4H), 3.26 – 3.14 (m, 2H), 2.78 – 2.70 (m, 1H), 2.65 (dd, *J* = 9.8, 5.2 Hz, 1H), 2.33 (s, 3H), 1.95 (ddd, *J* = 13.9, 8.6, 5.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 137.4, 133.5, 129.2 (2), 128.4 (2), 77.2, 70.2, 64.1, 56.4, 52.4, 48.4, 36.6, 21.1.

HRMS calculated for $C_{15}H_{21}N_2O_4S$ $(M+H)^+$ 325.1222; found 325.1210 (TOF MS).

(8*S*,9a*S*)-2-(4-fluorobenzyl)-8-hydroxyhexahydropyrrolo[2,1-*d*] [1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.2)



Utilizing general procedure **A**, **4.5.2** (37 mg, 0.115 mmol, 86%) was isolated as a white solid.

Melting Point 109-110ºC

FTIR (neat) 3639, 3109, 3053, 2901, 1701, 1602, 1454, 1360, 1142 cm^{-1};

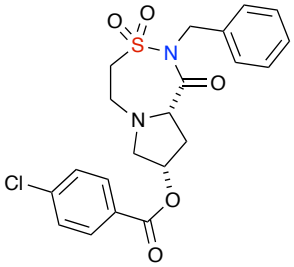
$[a]_D^{20}$ = +23.9° (c = 2.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2H), 7.04–6.99 (m, 2H), 5.07 (d, J = 15.1 Hz, 1H), 4.88 (d, J = 15.1 Hz, 1H), 4.43 (dd, J = 8.7, 6.1 Hz, 1H), 4.39 (t, J = 5.2 Hz, 1H), 3.49 – 3.35 (m, 3H), 3.30–3.16 (m, 3H), 2.72 (dddd, J = 13.0, 5.9, 5.9, 1.0 Hz, 1H), 2.66 (ddd, J = 9.9, 5.1, 1.1 Hz, 1H), 1.97 (dddd, J = 13.2, 8.6, 5.5, 1.2 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 162.3 ($^1J_{C–F}$ = 248.8 Hz), 132.4 ($^4J_{C–F}$ = 3.27 Hz), 130.4 ($^3J_{C–F}$ = 8.17 Hz, 2), 115.4 (^2J = 21.42 Hz 2), 70.1, 64.1, 64.2, 56.5, 52.5, 48.0, 36.6;

HRMS calculated for $C_{14}H_{17}FN_2O_4SH$ $(M+H)^+$ 329.0971; found 329.0971 (TOF MS ES^+).

(8*R*,9a*S*)-2-benzyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5] thiadiazepin-8-yl 4-chlorobenzoate (4.5.7)



Utilizing general procedure **B**, **4.5.7** (39 mg, 0.087 mmol, 73%) was isolated as a white solid.

$[\alpha]_D^{20}$ = +67.6 º (c = 0.25, $CHCl_3$).

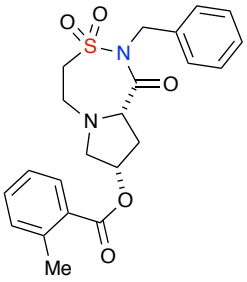
FTIR (neat, cm^{-1}): 2920, 2360, 2333, 1712, 1593, 1353, 1276, 1218, 1153, 1118.

^{1}H NMR (500 MHz, CDCl3) δ 7.88 – 7.84 (m, 2H), 7.30–7.28 (m, 3H), 7.20 – 7.12 (m, 4H), 5.34 – 5.31 (m, 1H), 5.18 (d, *J* = 15.3 Hz, 1H), 4.81 (d, *J* = 15.3 Hz, 1H), 4.29 (dd, *J* = 10.5, 2.6 Hz, 1H), 3.34 – 3.24 (m, 2H), 3.24 – 3.07 (m, 3H), 3.00 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.86 (dt, *J* = 14.8, 7.4 Hz, 1H), 2.34 – 2.25 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.8, 165.5, 139.5, 136.4, 131.2 (2), 128.7 (2), 128.6, 128.5 (2), 128.1 (2), 127.7, 73.6, 63.8, 61.9, 55.9, 50.38, 48.3, 32.9.

HRMS calculated for $C_{21}H_{21}ClN_2O_5SH$ $(M+H)^+$ 449.0938; found 449.0901 (TOF MS);

(8*R*,9a*S*)-2-benzyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5] thiadiazepin-8-yl 2-methylbenzoate (4.5.12)



Utilizing general procedure **B**, **4.5.12** (45 mg, 0.105 mmol, 78%) was isolated as a white solid.

$[\alpha]_D^{20}$ = +48.0 ° (c = 0.30, $CHCl_3$);

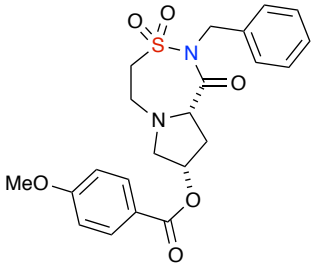
FTIR (neat, cm^{-1}): 2958, 2833, 1712, 1456, 1352, 1294, 1257, 1224, 1153, 1081;

^{1}H NMR (500 MHz, CDCl3) δ 7.83 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.32 – 7.25 (m, 2H), 7.16 – 7.08 (m, 5H), 5.32 (dd, *J* = 4.9, 4.2 Hz, 1H), 5.15 (d, *J* = 15.2 Hz, 1H), 4.79 (d, *J* = 15.2 Hz, 1H), 4.25 (dd, *J* = 10.5, 2.9 Hz, 1H), 3.32 – 3.23 (m, 2H), 3.21 – 3.06 (m, 3H), 3.02 (dt, *J* = 14.9, 2.2 Hz, 1H), 2.85 (dd, *J* = 10.5, 3.7 Hz, 1H), 2.51 (s, 3H), 2.35 – 2.26 (m, 1H).

^{13}C NMR (126 MHz, CDCl3) δ 170.7, 167.3, 140.4, 136.4, 132.1, 131.6, 131.0, 129.4, 128.5 (2), 128.3 (2), 127.7, 125.8, 73.0, 64.0, 62.3, 55.9, 50.5, 48.4, 33.1, 21.8.

HRMS calculated for $C_{22}H_{24}N_2O_5SH$ $(M+H)^+$ 429.1484; found 429.1443 (TOF MS);

(8*R*,9a*S*)-2-benzyl-3,3-dioxido-1-oxooctahydropyrrolo[2,1-*d*][1,2,5] thiadiazepin-8-yl 4-methoxybenzoate (4.5.13)



Utilizing general procedure **B**, **4.5.13** (42 mg, 0.094 mmol, 74%) was isolated as a white solid.

$[\alpha]_D^{20} = +44.2\ ^{\circ}$ (c = 0.43, $CHCl_3$);

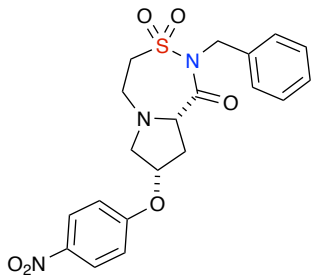
FTIR (neat, cm^{-1}): 2360, 2331, 1731, 1520, 1286, 1255, 1205, 1151, 769.

^{1}H NMR (400 MHz, CDCl3) δ 8.03 – 7.98 (m, 2H), 7.44 – 7.38 (m, 2H), 7.26–7.24 (m, 3H), 6.92 – 6.87 (m, 2H), 5.45 – 5.39 (m, 1H), 5.31 (d, *J* = 15.3 Hz, 1H), 4.92 (d, *J* = 15.3 Hz, 1H), 4.37 (dt, *J* = 11.7, 5.8 Hz, 1H), 3.87 (s, 3H), 3.46 – 3.32 (m, 2H), 3.32 – 3.16 (m, 3H), 3.10 (d, *J* = 14.8 Hz, 1H), 2.96 (dt, *J* = 12.0, 6.0 Hz, 1H), 2.40 (ddd, *J* = 15.7, 10.5, 5.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.8, 166.1, 163.4, 136.5, 131.8 (2), 128.5 (2), 128.2 (2), 127.6, 122.6, 113.6 (2), 73.0, 64.0, 62.2, 55.8, 55.4, 50.4, 48.3, 33.0.

HRMS calculated for $C_{22}H_{24}N_2O_6SH$ $(M+H)^+$ 445.1433; found 445.1392 (TOF MS);

(8*R*,9a*S*)-2-benzyl-8-(4-nitrophenoxy)hexahydropyrrolo[2,1-*d*][1,2,5] thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.4).



Utilizing general procedure **C**, **4.5.4** (39 mg, 0.090 mmol, 77%) was isolated as a brown thick liquid.

$[\alpha]_D^{20} = +80.16$ ° (c = 0.62, $CHCl_3$);

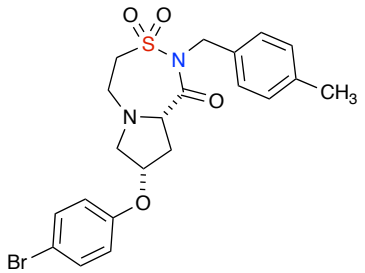
FTIR (neat, cm^{-1}): 2356, 2329, 1704, 1591, 1508, 1494, 1340, 1259, 1153, 1110;

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 – 8.09 (m, 2H), 7.33 – 7.28 (m, 2H), 7.26 – 7.17 (m, 3H), 6.85 – 6.80 (m, 2H), 5.06 (d, *J* = 15.2 Hz, 1H), 4.84 (d, *J* = 15.2 Hz, 1H), 4.82 (t, *J* = 4.3 Hz, 1H), 4.25 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.38 (dd, *J* = 10.4, 2.3 Hz, 1H), 3.34 – 3.29 (m, 1H), 3.28 – 3.17 (m, 3H), 3.01 (dt, *J* = 14.7, 2.5 Hz, 1H), 2.90 (dd, *J* = 10.4, 3.6 Hz, 1H), 2.34 – 2.25 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 162.3, 141.7, 136.4, 128.6 (2), 128.2 (2), 127.7, 126.0 (2), 115.4 (2), 76.0, 64.2, 62.0, 55.6, 50.5, 48.8, 32.7.

HRMS calculated for $C_{20}H_{21}N_3O_6SNH_4$ $(M+NH_4)^+$ 449.1495; found 449.0728 (TOF MS);

(8*R*,9a*S*)-8-(4-bromophenoxy)-2-(4-methylbenzyl)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.5)



Utilizing general procedure **C**, **4.5.5** (49 mg, 0.102 mmol, 74%) was isolated as a colorless thick liquid.

$[\alpha]_D^{20}$ = +29.5 º (c = 0.22, $CHCl_3$);

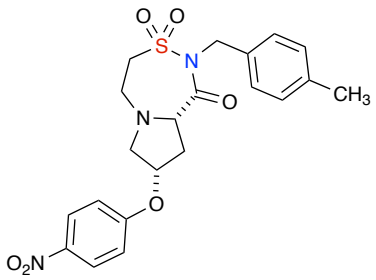
FTIR (neat, cm^{-1}): 2952, 1704, 1487, 1352, 1240, 1153, 1058, 849;

^{1}H NMR (400 MHz, CDCl3) δ 7.40 – 7.33 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.79 – 6.75 (m, 2H), 5.11 (d, *J* = 15.1 Hz, 1H), 4.89 (d, *J* = 15.1 Hz, 1H), 4.75 (t, *J* = 4.4 Hz, 1H), 4.27 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.43 (dd, *J* = 10.3, 2.2 Hz, 1H), 3.37–3.32 (m, 2H), 3.29–3.24 (m, 2H), 3.07 (dt, *J* = 14.6, 2.5 Hz, 1H), 2.90 (dd, *J* = 10.3, 3.8 Hz, 1H), 2.33 (s, 3H), 2.32 –2.26 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 156.3, 137.4, 133.5, 132.4 (2), 129.2 (2), 128.3 (2), 117.7 (2), 113.5, 75.6, 64.3, 62.4, 55.6, 50.7, 48.7, 32.9, 21.2.

HRMS calculated for $C_{21}H_{23}BrN_2O_4SH$ $(M+H)^+$ 479.0640; found 479.0651 (TOF MS);

(8*R*,9a*S*)-2-(4-methylbenzyl)-8-(4-nitrophenoxy)hexahydropyrrolo[2,1-*d*] [1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.6):



Utilizing general procedure **C**, **4.5.6** (43 mg, 0.096 mmol, 79%) was isolated as a brown thick liquid.

$[\alpha]_D^{20}$ = +87.7 º (c = 1.06, $CHCl_3$);

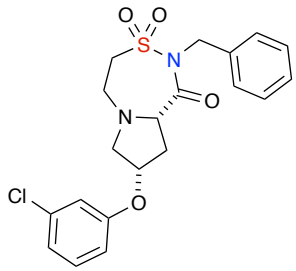
FTIR (neat, cm^{-1}): 2925, 2850, 1703, 1591, 1512, 1340, 1259, 1153, 1110;

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 – 8.08 (m, 2H), 7.22 – 7.15 (m, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.85 – 6.77 (m, 2H), 5.03 (d, *J* = 15.1 Hz, 1H), 4.84 – 4.80 (m, 1H), 4.78 (d, *J* = 15.1 Hz, 1H), 4.24 (dd, *J* = 10.4, 3.1 Hz, 1H), 3.37 (dd, *J* = 10.4, 2.2 Hz, 1H), 3.33 – 3.17 (m, 4H), 3.01 (dt, *J* = 14.7, 2.5 Hz, 1H), 2.90 (dd, *J* = 10.4, 3.6 Hz, 1H), 2.33 – 2.26 (m, 1H), 2.24 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 162.3, 141.7, 137.5, 133.4, 129.2 (2), 128.3 (2), 126.0 (2), 115.4 (2), 76.0, 64.2, 62.1, 55.6, 50.5, 48.6, 32.7, 21.2.

HRMS calculated for $C_{21}H_{23}N_3O_6SH$ $(M+H)^+$ 446.1386; found 446.1378 (TOF MS);

(8*R*,9a*S*)-2-benzyl-8-(3-chlorophenoxy)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.7):



Utilizing general procedure **D**, **4.5.7** (38 mg, 0.090 mmol, 71%) was isolated as a olorless thick liquid.

$[\alpha]_D^{20} = +52.8\ ^{o}$ (c = 0.21, $CHCl_3$);

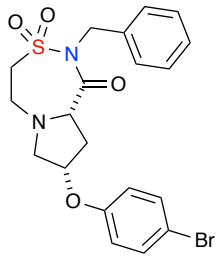
FTIR (neat, cm^{-1}): 2943, 1708, 1595, 1477, 1352, 1222, 1153, 1058, 1026;

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.30 – 7.25 (m, 1H), 7.20 (t, *J* = 8.2 Hz, 1H), 6.95 (ddd, *J* = 7.9, 1.7, 0.6 Hz, 1H), 6.87 (t, *J* = 2.1 Hz, 1H), 6.77 (ddd, *J* = 8.2, 2.3, 0.5 Hz, 1H), 5.18 – 5.13 (m, 1H), 4.96 – 4.91 (m, 1H), 4.80 – 4.76 (m, 1H), 4.29 (dt, J = 8.7, 4.3 Hz, 1H), 3.47 – 3.32 (m, 3H), 3.31 – 3.23 (m, 2H), 3.09 (dt, J = 14.7, 2.5 Hz, 1H), 2.92 (dd, J = 10.3, 3.8 Hz, 1H), 2.39 – 2.31 (m, 1H).

^{13}C NMR (126 MHz, CDCl3) δ 170.5, 157.9, 136.5, 134.9, 130.3, 128.6 (2), 128.3(2), 127.7, 121.3, 116.1, 114.3, 75.5, 64.4, 62.3, 55.6, 50.63, 48.9, 33.0;

HRMS calculated for $C_{20}H_{21}ClN_2O_4SH$ $(M+H)^+$ 421.0989; found 421.0952 (TOF MS);

(8*R*,9a*S*)-2-benzyl-8-(4-bromophenoxy)hexahydropyrrolo[2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.8):



Utilizing general procedure **D**, **4.5.8** (42 mg, 0.090 mmol, 71%) was isolated as a brown thick liquid.

$[\alpha]_D^{20} = +35.5\ ^{\circ}$ (c = 0.245, $CHCl_3$);

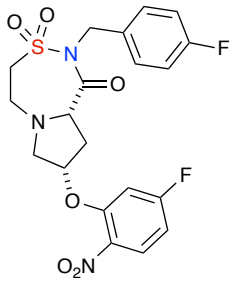
FTIR (neat, cm^{-1}): 2962, 1706, 1487, 1352, 1240, 1218, 1153, 1060;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.35 (m, 4H), 7.35 – 7.28 (m, 3H), 6.81 – 6.72 (m, 2H), 5.31 – 5.07 (m, 1H), 4.94 (d, *J* = 15.2 Hz, 1H), 4.81 – 4.71 (m, 1H), 4.29 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.44 (dd, *J* = 10.3, 2.3 Hz, 1H), 3.42 – 3.25 (m, 4H), 3.07 (dt, *J* = 14.7, 2.8 Hz, 1H), 2.92 (dd, *J* = 10.2, 3.8 Hz, 1H), 2.32 (ddd, *J* = 14.7, 10.5, 5.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 156.3, 136.5, 132.4 (2), 128.5 (2), 128.3 (2), 127.7, 117.7 (2), 113.5, 75.6, 64.4, 62.4, 55.6, 50.6, 48.9, 32.9.

HRMS calculated for $C_{20}H_{21}BrN_2O_4SH$ $(M+H)^+$ 465.0484; found 465.0489 (TOF MS);

(8*R*,9a*S*)-8-(5-fluoro-2-nitrophenoxy)-2-(4-fluorobenzyl)hexahydropyrrolo [2,1-*d*][1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.9)



Utilizing general procedure **D**, **4.5.9** (37 mg, 0.078 mmol, 71%) was isolated as a brown thick liquid.

$[\alpha]_D^{20} = +109.6\ ^{o}$ (c = 0.75, $CHCl_3$);

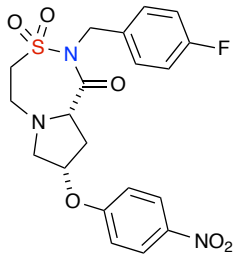
FTIR (neat, cm^{-1}): 2966, 1722, 1436, 1330, 1220, 1176, 1118, 1058.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 – 7.96 (m, 1H), 7.39 – 7.34 (m, 2H), 7.08 – 7.04 (m, 2H), 6.82 – 6.77 (m, 2H), 5.18 (d, *J* = 15.1 Hz, 1H), 4.90 – 4.86 (m, 1H), 4.78 (d, *J* = 14.9 Hz, 1H), 4.34 (dt, *J* = 12.5, 6.2 Hz, 1H), 4.22–4.13 (m, 1H), 3.50 – 3.37 (m, 1H), 3.36 – 3.25 (m, 3H), 3.09 (dt, *J* = 14.8, 2.5 Hz, 1H), 3.00 (dd, *J* = 10.4, 3.6 Hz, 1H), 2.44 – 2.34 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 165.3 ($^1J_{C–F}$ = 254.92 Hz), 163.3 ($^1J_{C–F'}$ = 243.42 Hz), 161.0 ($^4J_{C–F'}$ = 1.93 Hz), 152.9 ($^3J_{C–F'1}$ = 11.18 Hz), 132.1 ($^4J_{C–F}$ = 3.14 Hz), 130.3 ($^3J_{C–F}$ = 8.48 Hz, 2), 128.3 ($^3J_{C–F'2}$ = 11.53 Hz), 115.4 ($^2J_{C–F}$ = 21.35 Hz, 2), 107.9 ($^2J_{C–F'1}$ = 23.58 Hz), 103.4 ($^2J_{C–F'2}$ = 26.90 Hz), 77.8, 63.9, 61.8, 55.7, 50.2, 48.2, 32.2.

HRMS calculated for $C_{20}H_{19}F_2NO_6SH$ $(M+H)^+$ 468.1041; found 468.1050 (TOF MS).

(8*R*,9a*S*)-2-(4-fluorobenzyl)-8-(4-nitrophenoxy)hexahydropyrrolo[2,1-*d*] [1,2,5]thiadiazepin-1(2*H*)-one 3,3-dioxide (4.5.10)



Utilizing general procedure **D**, **4.5.10** (39 mg, 0.087 mmol, 72%) was isolated as a brown thick liquid.

$[\alpha]_D^{20} = +42.4\ ^{\circ}$ (c = 0.75, $CHCl_3$);

FTIR (neat, cm^{-1}): 2954, 2358, 2341, 1704, 1591, 1510, 1340, 1259, 1222, 1153, 1110;

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 – 8.19 (m, 2H), 7.43 – 7.34 (m, 2H), 7.05 – 6.97 (m, 2H), 6.94 – 6.89 (m, 2H), 5.07 (d, *J* = 15.1 Hz, 1H), 4.94 – 4.85 (m, 2H), 4.32 (dt, *J* = 12.5, 6.2 Hz, 1H), 3.50 – 3.37 (m, 2H), 3.36 – 3.25 (m, 3H), 3.09 (dt, *J* = 14.8, 2.5 Hz, 1H), 3.00 (dd, *J* = 10.4, 3.6 Hz, 1H), 2.39 (ddd, *J* = 15.1, 10.5, 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 162.3 ($^1J_{C-F}$ = 246.6 Hz), 162.2, 141.7, 132.2 ($^4J_{C-F}$ = 3.45 Hz), 130.3 ($^3J_{C-F}$ = 8.13 Hz, 2), 126.0 (2), 115.4 ($^2J_{C-F}$ = 21.16 Hz, 2), 115.3 (2), 76.0, 64.1, 62.1, 55.7, 50.5, 48.2, 32.7.

HRMS calculated for $C_{20}H_{20}FN_3O_6SH$ $(M+H)^+$ 450.1135; found 450.1124 (TOF MS);

5.6 Experimental for Chapter 4.2

Synthesis of epoxybenzo[d]isothiazole 1,1-dioxides via a reductive-Heck, metathesis-sequestration protocol

General procedure A for reductive Heck followed by in-situ ROMP

To a 25 mL round-bottom flask, sultam **4.5.1** (50 mg, 0.174 mmol, 1.5 equiv.), aryl iodide (28.3 mg, 0.12 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4 mg, 0.017 mmol, 15 mol%), PPh_3 (9 mg, 0.036 mmol, 30 mol%), 4-MeOPhOH (9.3 mg, 0.06 mmol, 0.5 equiv.), Zn (227 mg, 3.48 mmol, 10 equiv.) and HCO_2H (0.00856 mL, 0.12 mmol, 1.0 equiv.) were added under argon and followed by addition of dry DMF (6 mL). The resulting mixture was heated w/ stirring at 60 ºC for 14 hours until the iodide was consumed as indicated by TLC. The reaction mixture was allowed to cool to room temperature and DMF was evaporated, followed by the addition of 4:1 EtOAc/hexanes (30 mL). The mixture was extracted with brine (4 x 5 mL), the organic layer was separated, dried over $MgSO_4$ and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the crude product was treated with cat-**B** [$(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$] (2.43 mg, 2.9 umol mol) in deoxygenated CH_2Cl_2 (0.1 M) at 50 ºC overnight in a round-bottom flask under argon w/ water condenser. The reaction mixture was allowed to cool to RT and 0.1 mL of ethyl vinyl ether (EVE) was added and stirred for 30 min. The reaction mixture was concentrated *in vacuo* until slight viscosity is observed and the resulting viscous liquid is then precipitated drop-wise into Et_2O (40 mL). Simple filtration through a medium glass frit afforded the dry (reclaimed) oligomer **4.5.3**. The filtrate was concentrated *in vacuo* and filtered through a SiO_2 SPE with 50% EtOAc/hexanes to afford reductive Heck products **4.5.2a-j**.

General procedure B for reductive Heck followed by in-situ ROMP utilizing catalyst-armed surface

To a 25 mL round-bottom flask, sultam **4.5.1** (50 mg, 0.174 mmol, 1.5 equiv.), aryl iodide (28.3 mg, 0.12 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4 mg, 0.017 mmol, 15 mol%), PPh_3 (9 mg, 0.036 mmol, 30 mol%), 4-MeOPhOH (9.3 mg, 0.06 mmol, 0.5 equiv.), Zn (227 mg, 3.48 mmol, 10 equiv.) and HCO_2H (0.00856 mL, 0.12 mmol, 1.0 equiv.) were added under argon and followed by addition of dry DMF (6 mL). The resulting mixture was heated w/ stirring at 60 ºC for 14 hours until the iodide was consumed as indicated by TLC. The reaction mixture was allowed to cool to room temperature and DMF was evaporated, followed by the addition of 4:1 EtOAc/hexanes

(30 mL). This mixture was extracted 4 times with brine using 5 mL each. The organic layer was separated and dried over $MgSO_4$ and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the crude mixture was added to a second round-bottom flask containing Nb-Si (5 mol%), cat-**B** (3 mol%) [[$(IMesH_2)(PCy_3)(Cl)_2$ Ru=CHPh;] in dry degassed CH_2Cl_2 (0.1M), that had been stirring at 50 ºC for 30 min. After stirring for an additional 30 min to 1 hr (TLC monitoring), the crude reaction mixture was filtered through a celite SPE with 50% EtOAc/hexanes to afford reductive Heck products **4.5.2a**-**j**.

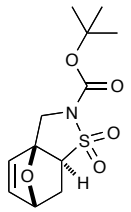
General procedure C for oligomeric-bound Suzuki-coupling (reclaimed scaffold)

In a 15–20 mL round bottom flask w/ condenser under argon was added reclaimed oligomeric-bound sultam **4.8.3** (100 mg, 0.25 mmol, 20-*mer*), Cs_2CO_3 (155 mg, 1 mmol), Pd(dppf)Cl_2 (37 mg, 50 μmol), boronic acid (155 mg, 1 mmol), and dry THF:DMF (5:1 v/v, 2.5 mL, 0.1 M). The reaction was stirred at 70 ºC for 14-16 hours and allowed to return to rt. The reaction was quenched via addition of aqueous NaOH (5 mL, 2.5 M) and stirred for 30-45 min. The reaction was washed w/ additional aqueous NaOH (3 x 5 ml, 2.5 M), dried ($MgSO_4$), and rinsed through a pad of Celite w/ multiple portions of CH_2Cl_2. The oligomeric-containing filtrate was concentrated *in vacuo* until slightly viscous and precipitated drop-wise into Et_2O (200 mL). The oligomeric precipitate was then filtered via glass frit, washed w/ excess anhydrous Et_2O, and dried *in vacuo* to yield the light grey, powdered oligomer in excellent yield.

General procedure D for reductive-ozonolysis of oligomer

The oligomeric-bound sultam (post coupling) was added to a 50 mL round bottom flask, dissolved in CH_2Cl_2, and cooled to -78 ºC. This solution was then subjected to ozonolysis via bubbling ozone gently through the solution in the open flask. After 1 hour the solution was allowed to warm to -30 ºC while being purged with an argon-filled balloon and 4 in. needle. Excess solid $LiBH_4$ was added to the flask at -30 ºC while stirring and the flask was sealed over argon. The cool bath was removed and the resulting solution was slowly warmed to RT and stirred overnight. The reaction was quenched with water over 1 hour, extracted w/

chloroform (3 x 5 mL), and concentrated *in vacuo* to yield the pure sultam diol. No further purification was carried out.



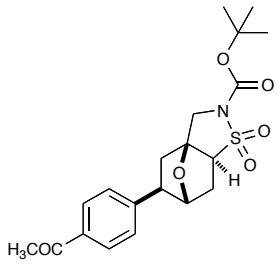
(±) tert-Butyl3,6,7,7a-tetrahydro-2H-3a,6-epoxybenzo[d] isothiazole-2-carboxylate 1,1-dioxide (4.5.1)

FTIR (neat) 1720, 1330, 1170, 1135, 983 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.55 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.27 (d, *J* = 6.0 Hz, 1H), 5.20 (dd, *J* = 4.7, 1.6 Hz, 1H), 4.20 (q, *J* = 12.3 Hz, 2H), 3.30 (dd, *J* = 7.6, 3.2 Hz, 1H), 2.66 (ddd, *J* = 12.5, 4.6, 3.2 Hz, 1H), 1.81 (dd, *J* = 12.5, 7.7 Hz, 1H), 1.48 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 149.7, 140.5, 132.7, 88.1, 84.4, 79.5, 62.2, 47.1, 30.1, 28.0;

HRMS calculated for $C_{12}H_{17}NO_5SNa$ $(M+Na)^+$ = 310.0725; found 310.0698 (TOF MS ES+).



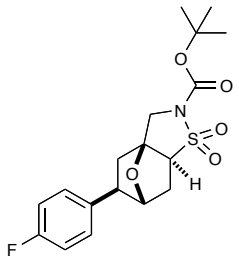
(±) tert-Butyl-5-(4-acetylphenyl)hexahydro-2H-3a,6-epoxybenzo[d]isothiazole-2-carboxylate 1,1-dioxide (4.5.2a)

FTIR (neat) 1720, 1679, 1332, 1309, 1135 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.93 (d, *J* = 8.2 Hz, 2H); 7.40 (d, *J* = 8.2 Hz, 2H), 4.76 (d, *J* = 5.4 Hz, 1H), 4.35 (d, *J* = 12.3 Hz, 1H), 3.98 (d, *J* = 12.3 Hz, 1H), 3.70 (dd, *J* = 8.5, 4.1 Hz, 1H), 3.17 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.78 (dt, *J* = 13.3, 4.7 Hz, 1H), 2.62 (s, 3H), 2.45 (dd, *J* = 12.6, 8.8 Hz, 1H), 2.31 (dd, *J* = 13.4, 8.3 Hz, 1H), 1.91 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.58 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 197.5, 149.6, 149.3, 135.9, 128.9, 127.2, 85.7, 84.5, 83.4, 65.2, 48.2, 46.6, 41.9, 35.3, 28.0, 26.6;

HRMS calculated for $C_{20}H_{25}NO_6SNa$ $(M+Na)^+$ = 430.1300; found 430.1296 (TOF MS ES+).



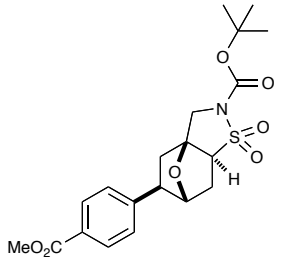
(±) tert-Butyl-5-(4-acetylphenyl)hexahydro-2H-3a,6-epoxybenzo[d]isothiazole-2-carboxylate 1,1-dioxide (4.5.2b)

FTIR (neat) 2983, 1720, 1330, 1309, 1157, 1132 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.16 (dd, *J* = 8.7, 5.2 Hz, 2H), 6.92 (dd, *J* = 8.5, 4.4 Hz, 2H), 4.62 (d, *J* = 5.0 Hz, 1H), 3.87 (d, *J* = 12.3 Hz, 1H), 3.58 (dd, *J* = 8.5, 4.1 Hz, 1H), 2.99 (dd, *J* = 8.8, 5.4 Hz, 1H), 2.65 (ddd, *J* = 13.2, 4.9, 4.6 Hz, 1H), 2.33 (dd, *J* = 12.8, 8.7 Hz, 1H), 2.18 (dd, *J* = 13.4, 8.4 Hz, 1H), 1.77 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.49 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 161.8 (d, $^{1}J_{CF}$ = 246 Hz), 160.8, 149.7, 139.9 (d, $^{4}J_{CF}$ = 3.8 Hz), 128.5 (d, $^{3}J_{CF}$ = 7.6 Hz), 115.6 (d, $^{2}J_{CF}$ = 20.2 Hz), 85.6, 84.5, 83.8, 47.5, 46.6, 42.2, 35.3, 28.0;

HRMS calculated for $C_{18}H_{22}FNO_5SNa$ $(M+Na)^+$ = 406.1100; found 406.0997 (TOF MS ES+).



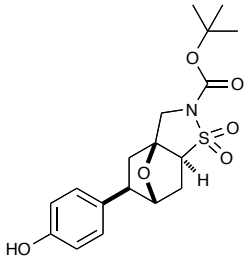
(±) tert-Butyl 5-(4-(methoxycarbonyl)phenyl)hexahydro-2H-3a,6-epoxybenzo[d]isothiazole-2-carboxylate 1,1-dioxide (4.5.2c)

FTIR (neat) 1720, 1332, 1280, 1166, 985 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.00 (d, *J* = 8.5 Hz, 2H), 7.34 – 7.40 (m, 2H), 4.76 (d, *J* = 5.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 3.94 – 4.01 (m, 1H), 3.93 (s, 3H), 3.70 (dd, *J* = 8.5, 4.1 Hz, 1H), 3.16 (dd, *J* = 8.8, 5.4 Hz, 1H), 2.77 (d, *J* = 13.2 Hz, 1H), 2.45 (dd, *J* = 12.9, 8.8 Hz, 1H), 2.30 (dd, *J* = 13.4, 8.4 Hz, 1H), 1.91 (dd, *J* = 12.9, 5.4 Hz, 1H), 1.58 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 166.7, 149.6, 149.1, 130.1, 128.9, 127.0, 85.7, 84.5, 83.4, 65.2, 52.1, 48.2, 46.6, 41.9, 35.3, 28.0;

HRMS calculated for $C_{20}H_{25}NO_7SNa$ $(M+Na)^+$ = 446.1249; found 446.1235 (TOF MS ES+).



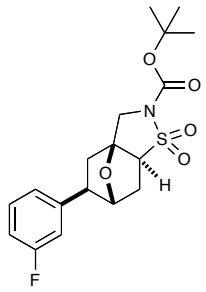
(±)-tert-Butyl-5-(4-hydroxyphenyl)hexahydro-2H-3a,6-epoxybenzo[d]isothiazole-2-carboxylate 1,1-dioxide (4.5.2d)

FTIR (neat) 2979, 1722, 1515, 1371, 1290, 1238 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.06 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.60 (s, 1H), 4.23 (d, *J* = 12.3 Hz, 1H), 3.86 (d, *J* = 12.3 Hz, 1H), 3.57 (dd, *J* = 8.4, 3.9 Hz, 1H), 2.94 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.63 (dt, *J* = 13.3, 4.7 Hz, 1H), 2.29 (dd, *J* = 12.6, 8.8 Hz, 1H), 2.16 (dd, *J* = 13.2, 8.5 Hz, 1H), 1.77 (dd, *J* = 12.9, 5.0 Hz, 1H), 1.48 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 154.4, 149.7, 136.5, 128.2, 115.5, 85.6, 84.5, 83.9, 65.4, 47.5, 46.7, 42.2, 35.3, 28.0;

HRMS calculated for $C_{18}H_{23}NO_6SNa$ $(M+Na)^+$ = 404.1144; found 404.1120 (TOF MS ES+).



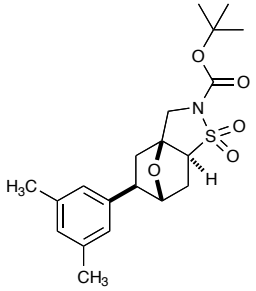
(±) tert-Butyl-5-(3-fluorophenyl) hexahydro-2H-3a,6-epoxybenzo[d]isothiazole-2-carboxylate 1,1-dioxide (4.5.2e)

FTIR (thin film) 2978, 1720, 1371, 1329,1310, 1242, 1138, 984, 735 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.29 – 7.25 (m, 3H), 7.02 (ddd, *J* = 10.1, 8.8, 4.7 Hz, 3H), 6.94 (td, *J* = 8.4, 2.2 Hz, 1H), 4.73 (d, *J* = 5.2 Hz, 1H), 4.32 (d, *J* = 12.1 Hz, 1H), 3.94 (t, *J* = 9.9 Hz, 1H), 3.66 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.08 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.77 – 2.69 (m, 1H), 2.41 (dd, *J* = 12.8, 8.8 Hz, 1H), 2.26 (dd, *J* = 13.4, 8.4 Hz, 2H), 1.88 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.56 (d, *J* = 7.3 Hz, 12H), 1.50 (s, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 163.2 (d, $^1J_{CF}$ = 247 Hz), 149.9, 146.7 (d, $^2J_{CF}$ = 7.2 Hz), 130.5 (d, $^2J_{CF}$ = 8.3 Hz), 122.9 (d, $^4J_{CF}$ = 2.7 Hz), 114.2 (d, $^3J_{CF}$ = 6.2 Hz), 114.1 (d, $^3J_{CF}$ = 5.4 Hz), 85.8, 84.7, 83.7, 48.1, 46.8, 42.2, 35.3, 28.2;

HRMS calculated for $C_{18}H_{22}FNO_5SNa$ $(M+Na)^+$ 406.1100; found 406.1101 (TOF MS ES+).



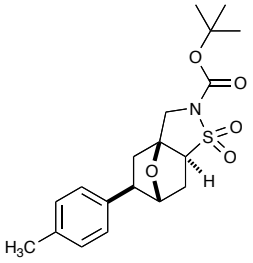
(±) tert-Butyl 5-(3,5-dimethylphenyl) hexahydro-2H-3a,6 epoxybenzo [d]iso thiazole-2-carboxylate 1,1-dioxide (4.5.2f)

FTIR (thin film) 2980, 1724, 1345, 1310, 1259, 1138, 845, 735 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.22 – 7.07 (m, 4H), 4.70 (d, *J* = 5.2 Hz, 1H), 4.31 (d, *J* = 12.1 Hz, 1H), 3.94 (d, *J* = 12.1 Hz, 1H), 3.66 (dd, *J* = 8.4, 4.1 Hz, 1H), 3.04 (dd, *J* = 8.7, 5.3 Hz, 1H), 2.78 – 2.63 (m, 1H), 2.38 (dd, *J* = 12.7, 8.8 Hz, 1H), 2.33 (s, 3H), 2.29 – 2.21 (m, 1H), 1.88 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.56 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 149.7, 144.0, 138.3, 128.5, 124.7, 85.6, 84.4, 83.7, 65.4, 48.1, 46.7, 41.9, 35.4, 28.0, 28.0, 21.3;

HRMS calculated for $C_{20}H_{27}NO_5SNa$ $(M+Na)^+$ = 416.1508; found 416.1510 (TOF MS ES+).



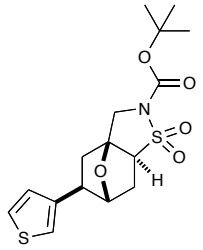
(±) *tert*-Butyl-5-(*p*-tolyl) hexahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole-2-carboxylate 1,1-dioxide (4.5.2g)

FTIR (thin film) 2982, 1722, 1333, 1167, 1136, 735 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.20 – 7.09 (m, 4H), 4.70 (d, *J* = 5.2 Hz, 1H), 4.31 (d, *J* = 12.1 Hz, 1H), 3.94 (d, *J* = 12.1 Hz, 1H), 3.65 (dt, *J* = 17.6, 8.8 Hz, 1H), 3.04 (dd, *J* = 8.7, 5.3 Hz, 1H), 2.77 – 2.66 (m, 1H), 2.38 (dd, *J* = 12.7, 8.8 Hz, 1H), 2.33 (s, 3H), 2.25 (dd, *J* = 13.3, 8.4 Hz, 1H), 1.88 (dd, *J* = 12.8, 5.2 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 149.8, 141.1, 136.6, 129.4, 126.8, 85.6, 84.4, 83.9, 65.4, 47.8, 46.7, 42.1, 35.4, 28.0, 21.0;

HRMS calculated for $C_{19}H_{25}NO_5SNa$ $(M+Na)^+$ = 402.1351; found 402.1357 (TOF MS ES+).



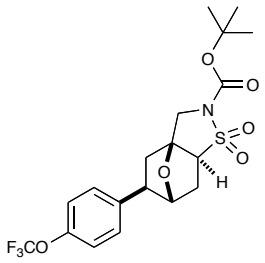
(±) tert-Butyl-5-(4-(thiophen-3-yl)phenyl) hexahydro-2H-3a,6-epoxybenzo[d]isothia-zole-2-carboxylate 1,1-dioxide (4.5.2h)

FTIR (thin film) 2980, 1722, 1333, 1136, 735 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.29 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.06 – 7.00 (m, 2H), 4.71 (d, *J* = 5.2 Hz, 1H), 4.28 (d, *J* = 12.1 Hz, 1H), 3.95 – 3.90 (m, 1H), 3.67 – 3.60 (m, 1H), 3.24 (dd, *J* = 8.6, 5.0 Hz, 1H), 2.75 – 2.69 (m, 1H), 2.38 – 2.32 (m, 1H), 2.23 (dt, *J* = 20.7, 10.4 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.56 (d, *J* = 4.8 Hz, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 144.6, 126.5, 126.4, 120.2, 85.7, 84.4, 83.3, 65.3, 46.7, 43.5, 41.3, 35.5, 34.9, 30.6, 29.3, 28.0, 27.9;

HRMS calculated for $C_{16}H_{21}NO_5S_2Na$ $(M+Na)^+$ = 394.0759; found 394.0750 (TOF MS ES+).

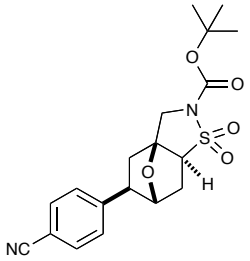


(±) tert-Butyl-5-(4-(trifluoromethoxy)phenyl) hexahydro-2H-3a,6-epoxybenzo[d]iso thiazole -2-carboxylate 1,1-dioxide (4.5.2i)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 – 7.29 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.72 (d, *J* = 5.2 Hz, 1H), 4.31 (d, *J* = 12.1 Hz, 1H), 3.95 (d, *J* = 12.2 Hz, 1H), 3.66 (dt, *J* = 8.5, 4.3 Hz, 1H), 3.10 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.42 (dd, *J* = 12.8, 8.8 Hz, 1H), 2.27 (dd, *J* = 13.4, 8.4 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.56 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 149.1 (d, $^{1}J_{CF}$ = 200 Hz), 143.1, 128.6, 121.5, 85.9, 84.8, 83.8, 65.5, 47.8, 42.4, 35.5, 28.3 cm^{-1};

HRMS calculated for $C_{19}H_{22}F_3NO_6SNa$ $(M+Na)^+$ = 472.1018; found 472.1023 (TOF MS ES+).



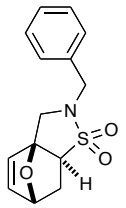
(±) tert-Butyl-5-(4-cyanophenyl) hexahydro-2H-3a,6-epoxybenzo[d]isothiazole-2-carboxylate 1,1-dioxide (4.5.2j)

FTIR (thin film) 2928, 2359, 1722, 1606, 1332, 1138, 835 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 4.73 (d, *J* = 5.2 Hz, 1H), 4.32 (d, *J* = 12.2 Hz, 1H), 3.96 (d, *J* = 12.2 Hz, 1H), 3.69 – 3.65 (m, 1H), 3.14 (dd, *J* = 8.6, 5.2 Hz, 1H), 2.79 – 2.73 (m, 1H), 2.45 (dd, *J* = 12.9, 8.8 Hz, 1H), 2.29 (dt, *J* = 13.5, 6.1 Hz, 1H), 1.87 (dd, *J* = 12.9, 5.1 Hz, 1H), 1.57 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 149.5, 132.9, 129.1, 128.1, 118.9, 111.3, 86.0, 84.9, 83.5, 65.4, 48.5, 46.7, 42.2, 35.5, 29.9, 28.3, 28.2;

HRMS; calculated for $C_{19}H_{22}N_2O_5SNa$ $(M+Na)^+$ = 413.1147; found 413.1147 (TOF MS ES+).

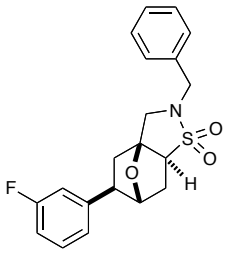


(±) Benzyl-6,7,7a-tetrahydro-2H-3a,6-epoxybenzo[d] isothiazole-2-carboxylate 1,1-dioxide (4.7.1)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.29 – 7.25 (m, 3H), 7.02 (ddd, *J* = 10.1, 8.8, 4.7 Hz, 3H), 6.94 (td, *J* = 8.4, 2.2 Hz, 1H), 4.73 (d, *J* = 5.2 Hz, 1H), 4.32 (d, *J* = 12.1 Hz, 1H), 3.94 (t, *J* = 9.9 Hz, 1H), 3.66 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.08 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.77 – 2.69 (m, 1H), 2.41 (dd, *J* = 12.8, 8.8 Hz, 1H), 2.26 (dd, *J* = 13.4, 8.4 Hz, 2H), 1.88 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.56 (d, *J* = 7.3 Hz, 12H), 1.50 (s, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 139.4, 134.1, 128.8, 128.6, 128.0, 90.4, 79.7, 77.4, 77.1, 76.8, 60.4, 48.8, 48.4, 29.1

HRMS calculated for $C_{14}H_{16}NO_3S$ $(M+H)^+$ = 278.0851; found 278.0846 (TOF MS ES+).

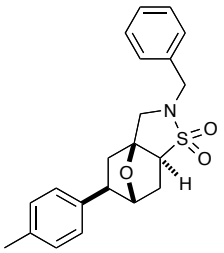


(3a*S*,5*R*,6*R*,7a*S*)-2-benzyl-5-(3-fluorophenyl)hexahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole 1,1-dioxide (4.7.5a)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.41 – 7.34 (m, 4H), 7.32 (d, *J* = 6.8 Hz, 1H), 7.22 (dd, *J* = 14.0, 8.0 Hz, 1H), 6.97 (dd, *J* = 15.5, 8.9 Hz, 2H), 6.89 (t, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 5.0 Hz, 1H), 4.32 (dd, *J* = 41.2, 14.5 Hz, 2H), 3.55 (d, *J* = 11.2 Hz, 1H), 3.50 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.39 (d, *J* = 11.2 Hz, 1H), 3.03 (dd, *J* = 8.6, 5.5 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.36 (dd, *J* = 12.6, 8.7 Hz, 1H), 2.23 (dd, *J* = 13.1, 8.6 Hz, 1H), 1.72 (dd, *J* = 12.6, 5.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 164.0, 162.0, 146.9, 135.2, 130.2, 130.1, 128.8, 128.6, 122.7, 113.8, 113.6 88.1, 83.7, 63.3, 48.6, 35.3, 29.7;

HRMS calculated for $C_{20}H_{20}FNO_5SNa$ $(M+Na)^+$ = 396.1046; found 396.1039 (TOF MS ES+).

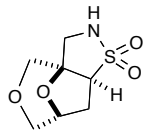


(3aS,5R,6R,7aS)-2-benzyl-5-(p-tolyl)hexahydro-2H-3a,6-epoxybenzo[d]isothiazole 1,1-dioxide (4.7.5b)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.36 – 7.27 (m, 4H), 7.28 – 7.22 (m, 1H), 7.07 – 6.99 (m, 4H), 4.58 (d, *J* = 5.0 Hz, 1H), 4.33 – 4.17 (m, 2H), 3.48 (d, *J* = 11.1 Hz, 1H), 3.44 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.32 (d, *J* = 11.1 Hz, 1H), 2.93 (dd, *J* = 8.6, 5.6 Hz, 1H), 2.52 (dt, *J* = 13.1, 4.9 Hz, 1H), 2.27 (dd, *J* = 12.5, 8.7 Hz, 1H), 2.23 (s, 3H), 2.21 – 2.13 (m, 1H), 1.66 (dd, *J* = 12.5, 5.6 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 141.5, 135.2, 129.4, 128.8, 128.6, 128.0, 126.9, 88.1, 84.1, 63.4, 48.7, 48.7, 47.8, 43.0, 35.4, 21.0;

HRMS calculated for $C_{21}H_{23}NO_3SNa$ $(M+Na)^+$ = 392.1296; found 392.1289 (TOF MS ES+).



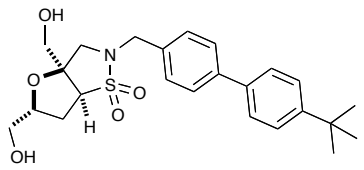
(±) Hexahydro-2H-3a,7-epoxyoxepino[3,4-d]isothiazole 1,1-dioxide (4.8.2)

FTIR (neat) 1771, 1615, 1460, 1371, 1312 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.63 (br s, 1H); 4.47 (d, *J* = 6.3 Hz, 1H), 3.80 (dd, *J* = 9.3, 4.6 Hz, 1H), 3.75 (d, *J* = 11.7 Hz, 1H), 3.66 (t, *J* = 11.0 Hz, 1H), 3.61 (t, *J* = 11.2 Hz, 1H), 3.51 (d, *J* = 11.7 Hz, 1H), 3.23 (dd, *J* = 13.7, 5.8 Hz, 1H), 3.09 (t, *J* = 11.3 Hz, 1H), 2.63 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.44 (dd, *J* = 13.4, 9.6 Hz, 1 H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 93.3, 78.4, 70.1, 69.9, 64.3, 44.8, 33.2;

HRMS calculated for $C_7H_{11}NO_4SNa$ $(M+Na)^+$ = 228.0306; found 228.0291 (TOF MS ES+).



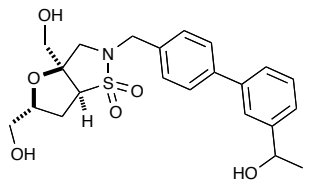
(±) 2-((4'-(tert-Butyl)-[1,1'-biphenyl]-4-yl)methyl)-3a,5-bis(hydroxymethyl) hexahydro- furo[2,3-d]isothiazole 1,1-dioxide (4.8.4a)

FTIR (neat) 3377, 2960, 2924, 2866, 1772, 1612, 1499, 1460, 1439, 1364, 1310, 1150, 1057, 951, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.65 – 7.43 (m, 6H), 7.36 (d, 7.4 Hz, 2H), 4.46 (s, 1H), 4.38 (d, *J* = 13.8 Hz, 1H), 4.07 (d, *J* = 13.7 Hz, 1H), 3.93 (d, *J* = 9.6 Hz, 1H), 3.83 (d, 6.9 Hz, 1Hz), 3.78 – 3.45 (m, 3H), 3.10 (d, *J* = 10.0 Hz, 1H), 2.92 (d, *J* = 10.2 Hz, 1H), 2.63 – 2.48 (m, 2H), 1.37 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) 150.6, 141.0, 137.5, 133.3, 128.9, 127.4, 126.7, 125.8, 87.7, 81.2, 66.2, 63.6, 62.4, 53.4, 47.0, 34.6, 30.4, 29.7;

HRMS calculated for $C_{24}H_{31}NO_5SNa$ $(M+Na)^+$ = 468.1821; found 468.1801 (TOF MS ES+).



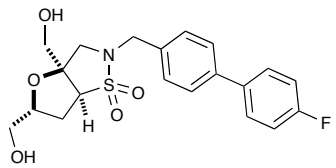
(±) 2-((3'-(1-Hydroxyethyl)-[1,1'-biphenyl]-4-yl)methyl)-3a,5-bis(hydroxymethyl) hexa- hydrofuro[2,3-d]isothiazole 1,1-dioxide (4.8.4b) – mixture of diastereomers

FTIR (neat) 3381, 2966, 2924, 2854, 1439, 1306, 1150, 1076, 797, 752, 706 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 – 7.53 (m, 3H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 6.8 Hz, 3H) 4.94 (q, *J* = 6.2 Hz, 1H), 4.40 – 4.25 (m, 1H), 4.32 (d, *J* = 14.0 Hz, 1H), 4.00 (d, *J* = 14.0 Hz, 1H), 3.95 (s, 1H), 3.85 (d, *J* = 12.0 Hz, 1H), 3.73 (d, *J* = 9.2 Hz, 1H), 3.65 (d, *J* = 11.7 Hz, 1H), 3.56 (d, *J* = 12.1 Hz, 1H), 3.51 (d, *J* = 12.1 Hz, 1 H), 3.36 (s, 1H), 3.01 (d, *J* = 10.7 Hz, 1H), 2.87 (d, *J* = 10.8 Hz, 1H), 2.68 (s, 1H), 2.5 (dd, *J* = 13.6, 5.5 Hz, 1H), 2.40 – 2.31 (m, 1H), 1.52 (d, *J* = 6.4 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.4, 141.0, 140.9, 140.6, 133.8, 130.7, 129.1, 129.0, 127.6, 126.2, 124.7, 87.6, 81.2, 70.4, 65.9, 63.4, 62.2, 61.3, 53.3, 46.9, 30.3, 25.3;

HRMS calculated for $C_{22}H_{28}NO_6S$ $(M+H)^+$ = 434.1639; found 434.1621 (TOF MS ES+).



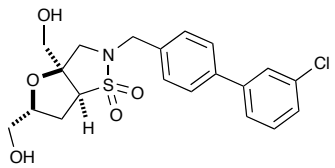
(±) 2-((4'-Fluoro-[1,1'-biphenyl]-4-yl)methyl)-3a,5-bis(hydroxymethyl)hexahydrofuro[2,3-d]isothiazole 1,1-dioxide (4.8.4c)

FTIR (neat) 3381, 2953, 2918, 2849, 1603, 1499, 1308, 1232, 1150, 1059, 947, 822, 756 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 – 7.48 (m, 4 H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 4.47 – 4.38 (m, 1H), 4.35 (d, *J* = 13.9 Hz, 1H), 4.15 (d, *J* = 13.9 Hz, 1H), 3.91 (d, *J* = 11.1 Hz, 1H), 3.79 (d, *J* = 8.5 Hz, 1H), 3.78 – 3.48 (m, 3H), 3.06 (d, *J* = 10.7 Hz, 1H), 2.91 (d, *J* = 10.7 Hz, 1H), 2.54 (dd, *J* = 13.1, 5.3 Hz, 1H), 2.50 – 2.38 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.6 (d, ^{1}J = 247 Hz), 140.1, 136.6 (d, ^{4}J = 3.4 Hz), 133.7, 129.0, 128.6 (d, ^{3}J = 8.1 Hz), 127.4, 115.7 (d, ^{2}J = 21.6 Hz);

HRMS calculated for $C_{20}H_{22}FNO_5SNa$ $(M+Na)^+$ = 430.1100; found 430.1104 (TOF MS ES+).



(±) 2-((3'-Chloro-[1,1'-biphenyl]-4-yl)methyl)-3a,5-bis(hydroxymethyl)hexahydrofuro[2,3-d]isothiazole 1,1-dioxide (4.8.4d)

FTIR (neat) 3354, 2924, 1664, 1595, 1440, 1396, 1308, 1150, 1037, 787 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 (dd, *J* = 8.92, 2.0 Hz, 3H), 7.46 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.42 – 7.32 (m, 4H), 4.49 – 4.42 (m, 1H), 4.38 (d, *J* = 14.0 Hz, 1H), 4.06 (d, *J* = 14.0 Hz, 1H), 3.95 (d, *J* = 11.9 Hz, 1H), 3.82 (d, *J* = 8.9 Hz, 1H), 3.73 (d, *J* = 11.7 Hz, 1H), 3.68 – 3.57 (m, 2H), 3.07 (d, *J* = 10.7 Hz, 1H), 2.93 (d, *J* = 10.7 Hz, 1H), 2.58 (dd, *J* = 13.0, 6.0 Hz, 1H), 2.47 (dt, *J* = 13.8, 9.6 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) 142.2, 139.7, 134.7, 134.3, 130.1, 129.1, 127.2, 125.18, 87.6, 81.2, 66.1, 63.5, 62.3, 53.3, 46.9, 30.4;

HRMS calculated for $C_{20}H_{22}ClNO_5SNa$ $(M+Na)^+$ = 446.0805; found 446.0812 (TOF MS ES+).
