The Development of α,β Unsaturated Sultam Probes for use in Chemical Biology

By Andie Jo Cassity

Submitted to the graduate degree program in the Department of Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Chair: Paul R. Hanson

Michael Rubin

Helena C. Malinakova

David R. Benson

Michael S. Wolfe

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The dissertation committee for Andie Jo Cassity certifies that this is the approved version of the following dissertation:

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Chair: Paul R. Hanson

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Abstract

The field of chemical biology has become a powerful driving force among the continuing effort to elucidate medicinally relevant biological hot spots. These so called hot spots consist of reactive nucleophiles and electrophiles found along bio-pathways. Many nucleophilic amino acid residues, such as cysteine and serine, are known to react with α–β unsaturated electrophiles like Michael acceptors. In recent years systematic assays to uncover hot spot reactivity, including Activity Based Protein Profiling (ABPP), have risen to the forefront of chemical biology. However, these assays are dependent upon chemical probe molecules designed to interact with a given type of biological entity. Therefore, a persistent need exists for novel chemical probes with easily modifiable chemical, stereochemical, and electronic properties. Ideally these chemical properties are synthetically built into the probe in a rapid and combinatorial manner to yield a unique and easily modified probe molecule.

This dissertation presents the design and synthesis of sultam chemical probes with a focus on α–β unsaturated systems. Chapter 1 contains a short review on α–β unsaturated Michael acceptors and biological reactivity, as well as the pharmaceutical history of enolic α–β unsaturated tetramic acids when combined with sultam molecules. Chapter 2 outlines the synthesis of six membered-triazole-fused sultams containing α–β unsaturated Michael acceptors. These chemical probes were generated via intermolecular click chemistry and ring closer by a novel *C*-vinylation reaction to form the sultam itself. Chapter 3 highlights the α-functionalization of tetramic acid inspired sultam probes or 'sultamic acids,' to generate endo-enol and exo-enamine-α–β unsaturated sultam probes. These probes will be given to collaborators for use in chemical biology assays.

Acknowledgements

I think my biggest thank-you has to go to my family, my mom, dad, brother, and grandparents. I would not have made it through without the emotional and financial support my parents always extended to me without a second thought. My brother for always giving me someone to talk to and look forward to seeing. A big thank-you goes to my grandparents for their constant prayers, as well as allowing me to live with them at the very beginning of my education. I even feel I should thank my dogs for their unconditional love no matter how frustrated or tired I felt.

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I also want to thank my friends in the rest of the chemistry department; the office staff for always being so encouraging, as well as Sarah Neuenswander and Justin Douglas for their technical NMR support and constant friendship. I'm also grateful to the professors who taught me in class, as well as Marina Rubina, and Roderick Black for being great TA managers. Finally I want to thank my committee for taking the time to wade through this document, and for being very available and amenable.

Table of Contents

List of Abbreviations

Abbreviation	Definition
° C	Celsius
1 H	Proton Nuclear magnetic resonance spectroscopy
13 C NMR	Carbon 13 Nuclear magnetic resonance spectroscopy
3-AT	3-acyltetramic acids
3-Ets	3-enaminetetramic acids
A-549	adenocarcinomic human alveolar basal epithelial cells
α–β	alpha-beta
α-CPA	α-cyclopiazonic acid
ABPP	activity based protein profiling
AcCl	Acetyl chloride
AcOH	acetic acid
ADC	4-amino-4-deoxychorismate
ALDH3A1	aldehyde dehydrogenase 3A1
AMM	Amycolamicin
aq	aqueous
Ar	aromatic
ArH	aromatic proton
AsnRS	asparaginyl-tRNA synthetase
Bn	Benzyl
BSA	Bovine Serum Albumin
C_{AR}	Carbon (aromatic)
CatC	Cathepsin C
CDC_{l3}	deuterated chloroform
CF_3	trifluoromethyl
cm	centimeter
CRM1	Chromosome Region Maintenance 1
CS_2	carbon disulfide
CuAAC	Copper-catalyzed Azide-to-Alkyne Cycloaddition
Cys (C)	cysteine
d	doublet
DAAs	Direct-Acting Antivirals
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N, N′-Dicyclohexylcarbodiimide
DCM	methylene chloride (dichloromethane)
dd	doublet of doublets
DENV	Dengue virus
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide

DNA	Deoxyribonucleic acid
DSPs	dual-specificity protein phosphatases
dt	doublet of triplets
DUBS	Deubiquitinating enzymes
E	entgegen (opposite)
EBOV NP	Ebola virus Nucleocapside
EC_{50}	Half maximal effective concentration
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EGFR	epidermal growth factor receptor
eq	equivalent
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	ethanol
FDA	Food and Drug Administration
FTIR	Fourier-transform infrared spectroscopy
g	grams
GSH	glutathione
GSK	GlaxoSmithKline
GSTO1	glutathione *S*-transferase pi
h	hour
H	proton
HCV	hepatitis C virus
HDAC	histone deacetylase
HIV	human immunodeficiency virus
HMDS	Bis(trimethylsilyl)amine
HRMS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	half maximal inhibitory concentration
IM	intramolecular click
^{i}Pr	isopropyl
IR	Infrared spectroscopy
IsoTOP-ABPP	isotopic tandem orthogonal proteolysis-activity based protein profiling
J	coupling constant
KEAP-1	Kelch Like ECH Associated Protein 1
KO*t*-Bu	Potassium tert-butoxide
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
M	Molar
m	meta
m	multiplet
Me	methyl
MeCN	Acetonitrile

MeI	iodomethane
MEK	mitogen-activated protein kinase kinase
MeOH	methanol
mg	milligrams
MHz	Megahertz
min	minutes
mM	millimolar
μM	micromolar
mol %	mole percent
MsCl	Methanesulfonyl Chloride
μW	microwave
N-Ac-Cys-OMe	*N*-Acetyl-*L*-cysteine methyl ester
na	not applicable
$NaBH_3CN$	Sodium cyanoborohydride
Nfκβ	Nuclear factor kappa-light-chain-enhancer of activated B cells
nM	nanomolar
NMR	Nuclear Magnetic Resonance
o	ortho
OMe	methoxy
Ox	oxidation
p	para
PAI-1	plasminogen activator inhibitor-1
Ph	phenyl
PKS-NRPS	polyketide synthase non-ribosomal peptide synthetase
ppm	parts per million
PSA	polar surface area
RCEM	ring closing enyne metathesis
RCM	ring closing metathesis
RdRp	RNA-dependent RNA polymerase
R_f	retention factor
RNA	Ribonucleic acid
rt	room temperature
s	singlet
SAHA	Suberanilohydroxamic acid
SAR	structure activity relationship
SERCA	sarcoplasmic or endoplasmic reticulum calcium dependent ATPase
t	triplet
t-BuOH	tert-Butyl alcohol
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
^{t}Bu	tert Butyl
TFA	Trifluoroacetic acid
TGF-β	Transforming Growth Factor Beta

THF	Tetrahydrofuran
topo IV	topoisomerase IV
UPPS	undecaprenyl pyrophosphate synthase
vide infra	see below
XPO1	Exportin 1
Z	zusammen (together)

Chapter 1:
The use of Electrophilic α,β Unsaturated Systems in Chemical Biology and Drug Discovery

Section 1.1 *The use of α,β Unsaturated Systems in Biological Discovery Assays.*

The development of synthetic methods capable of rapidly generating diverse and novel chemical probes for use in biological discovery assays remains a staple of scientific endeavor. Electrophilic probe compounds with Michael acceptors have become of particular interest, due to the pervasive presence of nucleophilic amino acid residues such as cysteine and serine, in enzymatic active sites and protein function. There are many examples of α,β-unsaturated Michael accepting systems in natural products, as well as small molecule fragment-like warheads used in activity-based protein profiling assays (ABPP, vide infra).[1] While lactams are not uncommon in natural products,[2] the α,β-unsaturated lactam remains relatively underrepresented in ABPP.[3] Furthermore, non-natural lactam analogs, sultams, are also underrepresented in protein profiling experiments.[4]

The disclosed dissertation work is designed to address the lack of sultams for use in chemical biology,[5] methods like ABPP, with a particular focus on combinatorial methods for the generation of acyl, enamine, and α,β-unsaturated Michael-accepting sultams. Sultams,[6] or cyclic sulfonamides, are non-hydrolyzable lactam surrogates[7] possessing unique chemical properties. These attributes include a reduced pka compared to carbon analogs,[8] as well as the inherent soft nucleophilicity of sulfur. Furthermore, the SO_2N moiety has sp^3 geometry,[9] as compared the sp^2 geometry of a lactam. This additional three-dimensional geometry and augmented physiochemical properties have engendered sultams as a privileged scaffold in medicinal chemistry.[10]

The Hanson group has a long-standing interest in the development of new chemistry to *S*-heterocycles (sulfur-containing heterocycles), with a more focused interest

in the generation of molecular libraries of sultams for biological testing.[11] **Figure 1.1.1** illustrates a brief history of α,β–unsaturated Michael-accepting sultams generated by the Hanson group. Many of these compounds have been found to possess various biological activities, ranging from thioredoxin activity, TGF-β/Nrf2 inhibition, and Scp-1 phosphatase inhibition.[11]

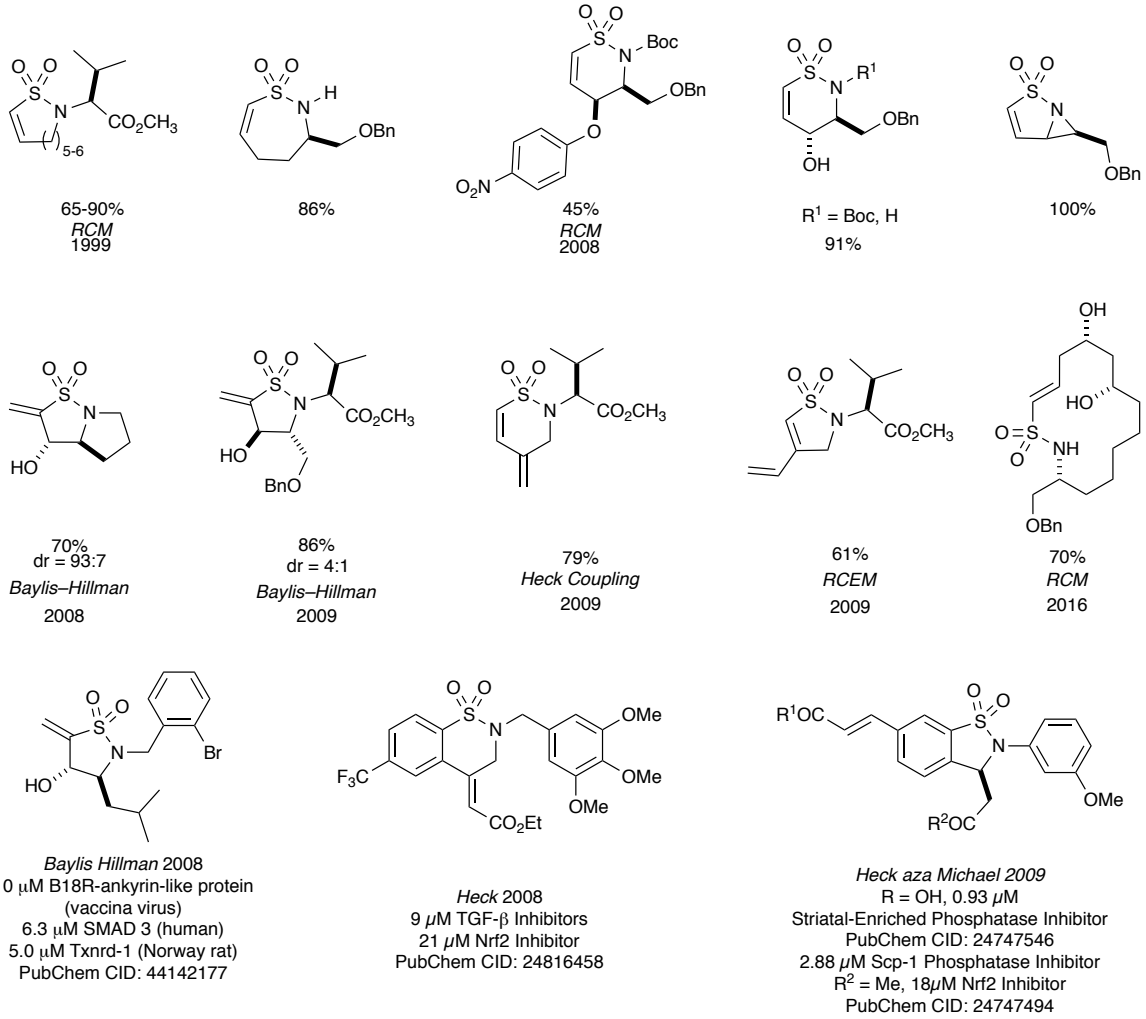


Figure 1.1.1. Hanson group published and un-published sultam Michael acceptors

Inspired by this rich history, the presented dissertation work focuses on the use of tuneable coupling partners such as triazoles, benzyl groups, isocyanates and amines in an effort to modulate sultam reactivity. This chemistry was utilized to generate tunable acyl,

enamine, and α,β-unsaturated sultam systems for use as probes in chemical biology screens.[12]

Cysteine (Cys) modification is a ubiquitous control mechanism in biology[13] and can be found at every level of cellular activity from, protein structure,[14] cellular signaling,[15] transcriptional regulation,[16] protein degradation,[17] and cell death.[18] Many cysteine dependent biological pathways are implicated in major world health burdens such as cancer,[19] inflammation,[20] and infection.[21] Critical cell signaling pathways known to be modulated by cysteine include: TGFβ□(cell differentiation),[22] Nfκβ (inflammation),[23] KEAP1[24] ubiquitination/deubiquitination (protein degradation),[25] as well as kinase and phosphatase pathways (cell signaling).[26] The inherent soft nucleophilicity,[27] and varying pka[28] of the cysteine residue afford multiple possibilities for post-translational states[29] including oxidation,[30] nitrosylation,[31] alkylation/acylation,[32] ubiquitination,[25] disulfide formation,[33] phosphorylation,[26] and metal chelation.[34] Furthermore the cysteine-containing biomolecule glutathione (GSH)[35] is critical for cellular redox control.

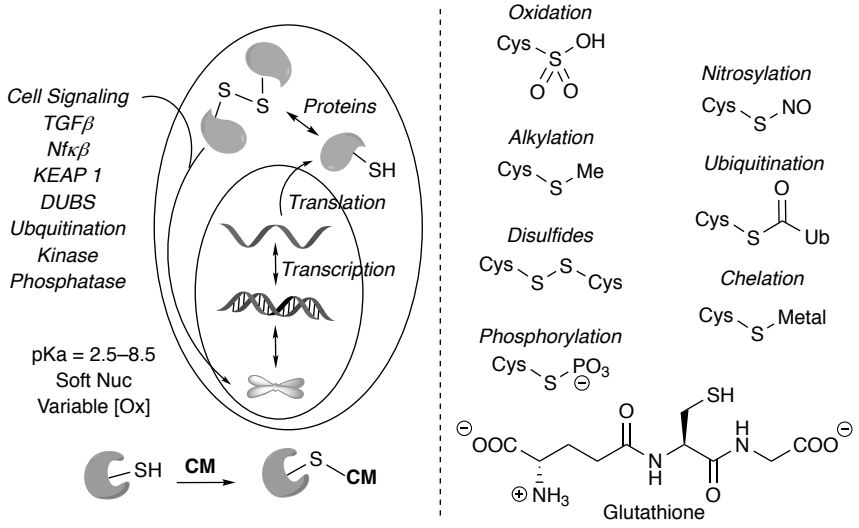


Figure 1.1.2. Diverse role of cysteine in biological pathways.[36]

The rich biological chemistry of cysteine has made the residue an attractive target for drug development,[37] as well as the object of intense fundamental scientific research. These general research efforts include chemical proteomic screens,[38] such as activity-based protein profiling (ABPP)[39], which are designed to uncover reactive amino acid residues in proteins. ABPP efforts typically focus on nucleophilic moieties like cysteine and serine, as these residues are frequently found in enzyme active sites.[13,15] The laboratories of Cravatt[40] and Weerapana[41] have championed ABPP chemical reactivity screening, and along with other researchers[42] have made significant strides towards generating a body of data designed to elucidate the reactivity,[43] selectivity,[44] and biological function[13-26] of numerous enzymatic and protein residues.

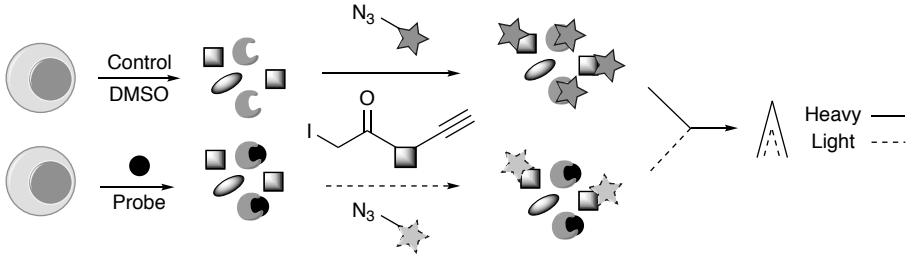


Figure 1.1.3 IsoTOP-ABPP for whole proteome screening.

An ABPP screen used by Cravatt and co-workers is termed isotopic tandem orthogonal proteolysis activity-based protein profiling (IsoTOP-ABPP)[45] and is illustrated in **Figure 1.1.3**. The assay consists of two parts and begins with a cell or cell lysate undergoing treatment with DMSO, followed by a broad-spectrum cysteine reactive probe, such as an iodoacetamide functionality linked to an alkyne. An azide-to-alkyne click reaction then attaches a heavy isotope labeled biotin tag. The second part of the assay involves another cell or cell lysate undergoing doping with a chemical probe. The probe forms a complex with any protein cysteine residues capable of reacting with molecules. The probe-protein complex is then inert to the broad-spectrum cysteine

reactive probe, while unreacted thiols still complex. This mixture is then subjected to an azide-to-alkyne click reaction that attaches a light or normal isotope labeled biotin tag. The heavy and light mixes are then combined, enriched using streptavidin and analyzed by mass spectrometry. The heavy isotope tag forms a baseline thiol reactivity signal pattern, which is altered by any proteins attached to the chemical probe linked to the light tag. Thus IsoTOP-ABPP is a rapid proteome-wide tool for thiol reactivity discovery and is capable of identifying hundreds of "hot-spot" residues.[45]

While the sheer power of ABPP has boosted drug lead discovery efforts, and underpinned reactivity screening, the utility of these assays is dependent upon the design and use of novel chemical probes. A variety of chemical warheads have been found to react with various nucleophilic residues in ABPP assays.[46] **Figure 1.1.4** emphasizes serine specific probe warheads while **Figure 1.1.5** showcases cysteine probes. Lysine, tyrosine and threonine covalent probes are also known,[46] but are omitted in the interest of space and scope. As seen in **Figure 1.1.5**, Michael acceptors occupy privileged space within cysteine reactivity profiling, and have begun to emerge in drug discovery as promising therapeutic candidates (*vide infra*).

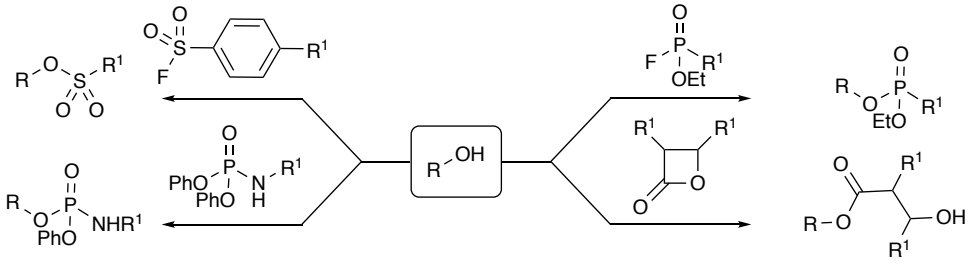


Figure 1.1.4. Serine-reactive probes used in ABPP.

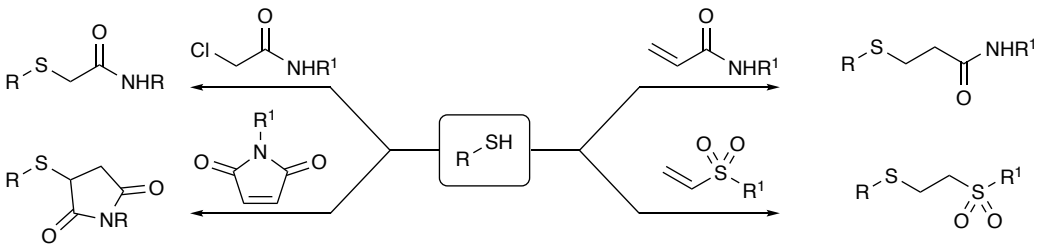


Figure 1.1.5. Cysteine-reactive probes used in ABPP.

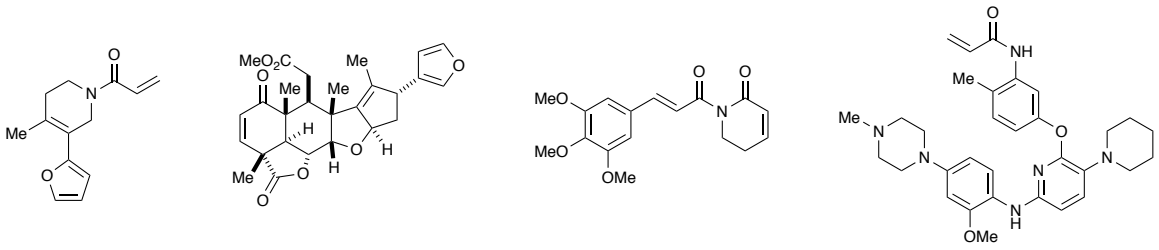


Figure 1.1.6 Michael acceptors discovered and analyzed via ABPP.

In addition to the use of fragment warheads for proteome reactivity analysis, natural and synthetic thiol-Michael acceptors have been uncovered and studied by activity-based protein profiling (**Figure 1.1.6**). The furan containing covalent modifier EN40 was found to react with the catalytic Cys244 of aldehyde dehydrogenase 3A1 (ALDH3A1) which has been implicated in lung cancer.[47] Nimbolide is terpenoid natural product derived from the Neem tree and is known to impair cancer pathogenicity. Nomura and co-workers used an ABPP assay to uncover the targets and potential mechanism for Nimbolide inhibition. This effort revealed the Nimbolide targets an E3 ubiquitin ligase RNF114 via Cys8, thereby preventing the degradation of tumor suppressor CDKN1A (p21) in breast cancer cells.[48]

Piperlongumine targets glutathione *S*-transferase *pi* (GSTO1) by the catalytic site Cys32. Piperlongumine exhibited an IC_{50} = 2.88 μM against NCI-H1975 cells, and was found to have synergistic action with the PI3K inhibitor pictilisib, which dropped the IC_{50}

to 0.015 μM.[49] A Piperlongumine analog without the endo Michael acceptor was shown to be significantly less active.

Zhang and co-workers disclosed Compound 22, a novel Cathepsin C (CatC) inhibitor, which is thought to bind via catalytic Cys234.[50] CatC is a lysosomal cysteine protease responsible for regulating neutrophil serine proteases, which are implicated in chronic inflammatory diseases such as rheumatoid arthritis.[51] The Michael acceptor and clinical candidate GSK-2793660 is one of only two compounds to ever enter trials for CatC inhibition (**Figure 1.1.7**).[50]

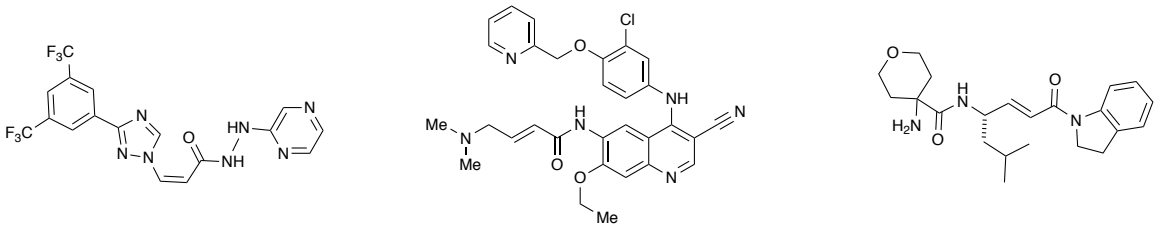


Figure 1.1.7. Michael accepting covalent drugs and drug candidates.

Michael accepting drugs and clinical candidates include Selinexor, a selective inhibitor of nuclear transport, which has been studied in over 40 clinical trials culminating in a FDA orphan drug fast track designation for penta-refractory multiple myeloma.[52] Selinexor operates by binding to Cys528[53] in Exportin 1 (XPO1), also known as chromosome region maintenance 1 (CRM1), a protein responsible for nucleus-to-cytoplasm transportation frequently up-regulated in many cancers.[54] The Michael acceptor Neratinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor and is an approved treatment for $HER2^+$ breast cancer.[55] Neratinib acts in the ATP binding pocket of EGFR and HER2 via inhibition of Cys773 and Cys805 respectively.[56]

Despite success of Michael acceptors as ABPP probes and covalent drug[57] compounds, a systematic reactivity analysis of electrophilic motifs, like Michael acceptors, is an emerging field.[1b,58] In 2014 Pfizer characterized GSH reactivity with simple electrophilic warheads including Michael acceptors. **Figure 1.1.8** simplifies the general reactivity and half-life of electrophiles such as acrylamides, cyanamides, sulfones, and sulfonamides, with glutathione at a pH of 7.4.[59] This seemingly simple assay reinvigorated the notion of tunable covalent warheads for therapeutic use.

Eli Lilly, another pharmaceutical giant, reported a systematic reactivity profiling *N*-acryloyl azetidines with GSH at near physiological conditions,[60] while Pfizer continued reactivity-profiling efforts with a 2016 manuscript detailing the intrinsic reactivity of electrophilic moieties with *N*-acetyl-*L*-lysine. The general reactivity trend with the amine nucleophile was found to mirror that of **Figure 1.1.8**.[61]

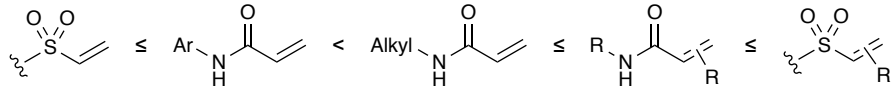


Figure 1.1.8. Summary of Pfizer systematic electrophilic warhead reactivity with GSH

Along with ABPP and reactivity profiling, non-systematic thiol screening have been performed on Michael acceptors with medicinally relevant cysteine residues and non-biological thiols.[62] Roush and co-workers[63] disclosed a vinyl sulfone as an inhibitor of cysteine protease cruzain, found in *T. cruzi,* the primary cause of Chagas' disease. The Rosenthal[64] group reported the synthesis of dipeptide vinyl sultams, which were found to have mild activity against the cysteine protease falcipain-2 found in *P. falciparum* (malaria).[65]

Poulsen and co-workers synthesized a Rakicidin-like macrocycle, and subsequently screened for thiol reactivity with bovine serum albumin (BSA) and

thioglycolate.[66] No protein-macrocycle adduct was found even though BSA contains 35 cysteine residues. Only one of these 35 cysteine residues is free, therefore denaturation and reduction was carried out before incubation with the macrocycle. A δ-thiol adduct was found to be the sole product after 72 hours. The Love group disclosed and measured rates of thiol addition into vinyl sulfones mimics of the known *T. cruzi* inhibitor K777.[67] In 2016, Bogyo and co-workers reported a dipeptide vinyl sulfone capable of arresting the development, and causing the eventual death of *P. falciparum* via cysteine protease inhibition.[68]

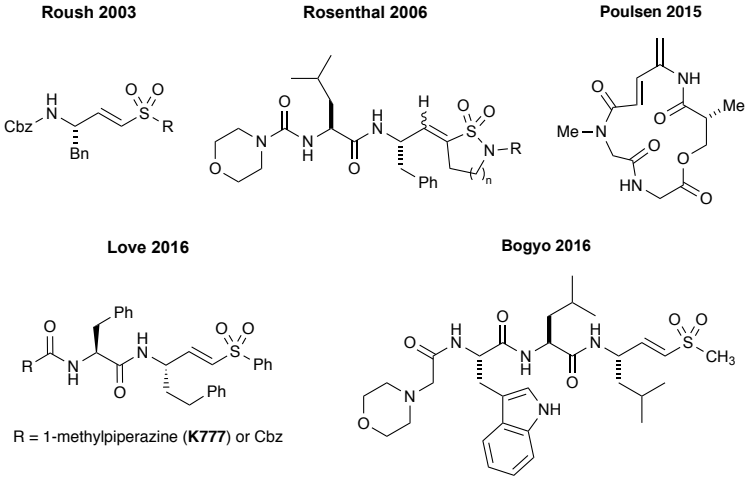


Figure 1.1.9 Non-systematic thiol screening

The unique biological activity of cysteine has given rise to the burgeoning field of chemical biology, with ABPP and reactivity screening at the forefront. While these studies have tremendous potential and advantages, the more traditional field of natural product screening is also rich with electrophilic Michael acceptors known to modify cysteine residues (**Figure 1.1.10**).[1b] The α,β-unsaturated Michael accepting lactone leptomycin B[69] attacks the Cys528 residue in XPO1 preventing nuclear export in a manner analogues to Selinexor. The α,β-unsaturated lactone Fostriecin[70] possesses

activity against mouse leukemia cells and has been shown to bind Cys269 of protein phosphatase 2A, and thereby disrupt cellular mitotic entry.[71]

Hypothemycin [72] inhibits mitogen-activated protein kinase kinase (MEK) by binding to a conserved cysteine found in 46 protein kinases.[73] Hypothemycin is also a known inhibitor of oncogenic *ras*-transformation.[74] 5Z-7-Oxozeaenol[75] has been shown to inhibit several protein kinases, including ERK2 and TAK1, via a free cysteine gatekeeper residue.[76] Furthermore 5Z-7-Oxozeaenol was found to bind to the hinge region residue Cys218 of MAP2K7, a kinase implicated in arthritis,[77] hepatoma,[78] and cardiac hypertrophy.[79] The antibiotic abyssomicin C,[80] binds to a cysteine near the active site of 4-amino-4-deoxychorismate (ADC) synthase, which is part of the biosynthesis of *p*-aminobenzoic acid. This critical bacterial pathway is not found in humans which makes it an attractive antibiotic route.[81] Recently, studies have been directed at elucidating the reactivity and mechanism of action of the anticancer macrocycle rakicidin.[82] This macrocycle was shown to undergo an unprecedented reversible thiol addition into dehydroalanine via acyl-imine tautomerism. The emergence of ABPP, and the renewed interest in covalent modifiers as feasible drug candidates, has led to biological reexamination of electrophilic molecules such as Michael acceptors. Recent toxicology work has been geared towards evaluating, quantifying and predicting the potential toxic effect of these compounds.[83]

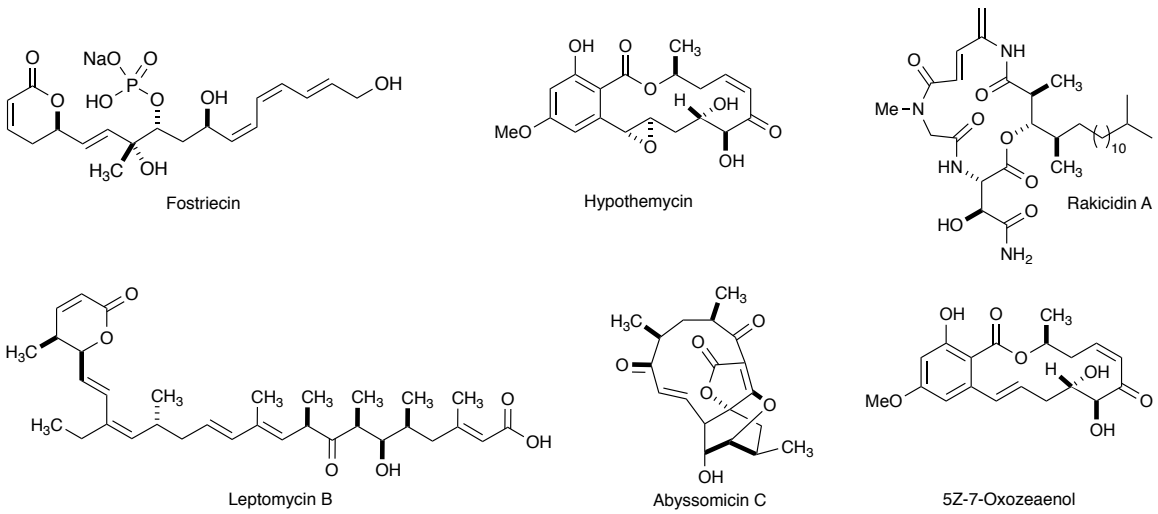


Figure 1.1.10 Natural biologically active Michael-acceptors.

One scaffold in need of re-examination is the α-methylene-γ-lactone Michael acceptor. This well-known motif is found in 2–3% of all known natural products[84] including sesquiterpene lactones. **Figure 1.1.11** shows Parthenolide, and Helenalin, both of which modulate Nfkβ,[85] as well as Deoxyelephantopin, a sesquiterpene lactone known to induce apoptosis in cancer cells.[86] While lactone–derived natural products are relatively ubiquitous in nature; the lactam counterparts are far less prevalent. Indeed, α-methylene-δ-lactams are very rare.[87] The recently isolated humantenine-type alkaloid Gelegamine B possesses a novel exo-methylene, however any biological activity remains unknown.[88] Equally rare in nature are α-methylene-γ-lactams, such as tetramic acid derivative Pukeleimid E,[89] a compound isolated from *Lyngbya majuscula*.[87] While Pukeleimide E itself has not been evaluated for biological activity, similar five membered exo-methylene core scaffolds,[90] such as 3-(3,5-di-tert-butyl-4-hydroxybenzylidene)pyrrolidin-2-ones have been shown to possess anti-inflammatory activity.[91]

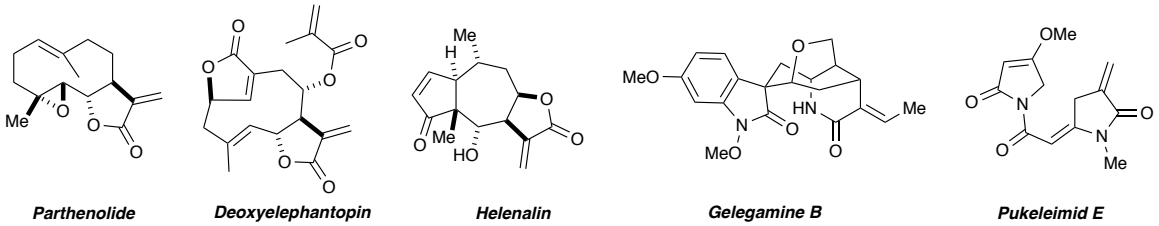


Figure 1.1.11. Exo methylene natural products

The utility of Michael acceptors in ABPP as well as the prevalence of α,β-unsaturated moieties in natural products has been reviewed above. Sultams bearing an exo-methylene Michael acceptor remain relativity-underexplored scaffolds in synthetic chemistry,[92] and ABPP assays. Sultams are non-natural analogs of lactams and hold novel intrinsic properties such as sp^3 geometry and attenuated pka. These novel scaffolds are promising probes for chemical biology due to these inherent properties, and have been found to have biological activity (**Figure 1.1.1**). Despite this, the current literature has few examples of any small, medium or macrocyclic α,β-unsaturated sultams in chemical biology assays. Therefore, the goal of Chapter 2 is to generate novel six membered exo-methylene α,β-unsaturated sultams for use as probes in chemical biology assays.

Section 1.2 *Combination of Tetramic Acids and Sultams*

The combination of enolic α,β-unsaturated systems with sultams has a remarkable place in antiviral research. The hepatitis C virus (HCV) was discovered in 1988 and rapidly became a major world health concern. The disease accounts for roughly 300,000 deaths per year, and effects an estimated 3% (180 million people) of the world's population.[93] HCV is predominantly transmitted by exposure to infected blood, and up to 90% of those infected will not develop symptoms upon acute infection, and therefore not realize their medical condition.[93]

A member of the *Flaviviridae* family, with relatives including dengue, West Nile, and yellow fever, HCV replicates at a rapid rate with approximately 10^{12} virions produced daily.[94] This rapid proliferation has a high error rate of 10^{-2}–10^{-3} nucleotide substitutions per site per year,[95] and is caused by the absence of proofreading ability in the HCV NS5B RNA-dependent RNA polymerase (RdRp).[96] Thus HCV has seven known genotypes with a staggering estimation of 30% divergence among the amino acids of each genotype.[97] The lack of fail-safes in HCV and other viral genetic replication machinery not only gives rise to genome variability, but also is an evolutionary driving force for drug resistance. In fact the death rate of HCV was once estimated to exceed the combined total from 60 other infection diseases including HIV.[98]

In recent years these intense drug development efforts have produced medication regiments capable of curing over 90 % of individuals afflicted with HCV (**Figure 1.2.1**).[94] Drug combinations are needed to help prevent the development of viral resistance, for example the drug trade-named Harvoni is the combination of

Ledipasvir/Sofosbuvir, while Epclusa makes use of Sofosbuvir/Velpatavir and is capable of treating six of the seven HCV genotypes.[94]

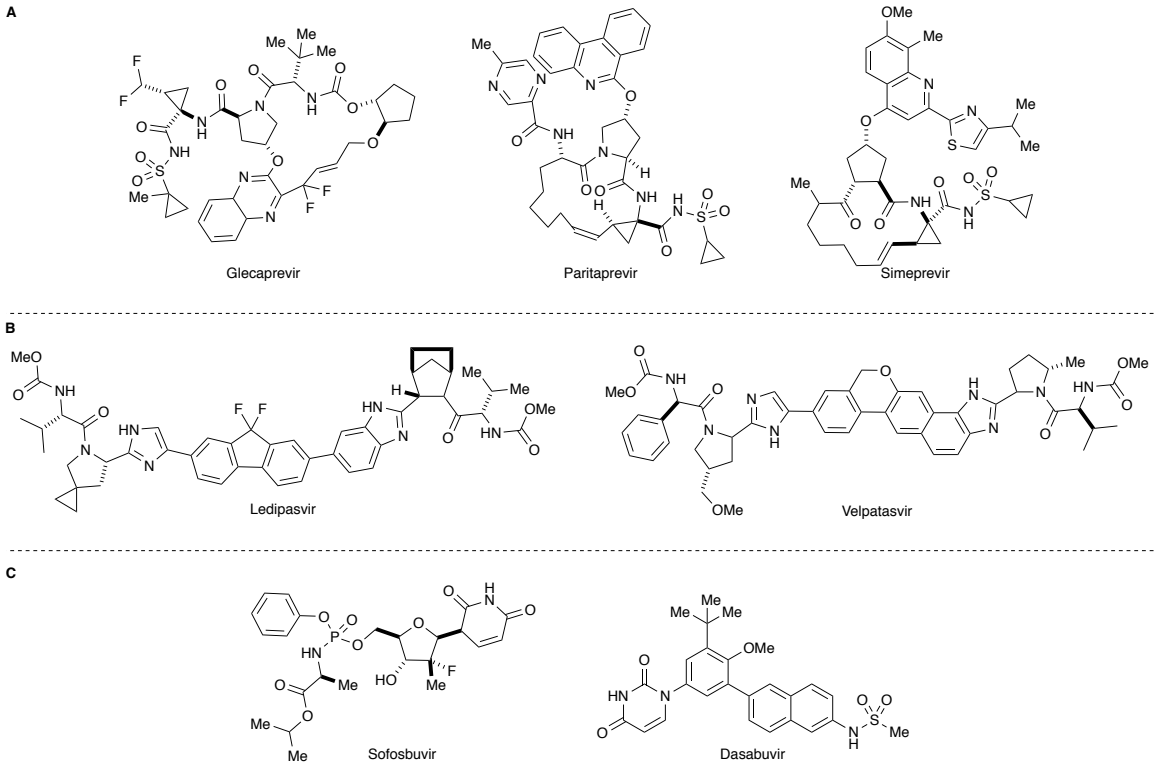


Figure 1.2.1 HCV drugs[93]: **A**: macrocyclic NS3/4A protease inhibitors. **B**: NS5A serine protease inhibitors. **C**: NS5B polymerase inhibitors.

Modern HCV drugs include direct-acting antivirals (DAAs), molecules that are intended to directly inhibit viral proteins involved in the HCV life cycle.[99] There are three well-known inhibition sites for HCV drugs within the DAAs paradigm. The NS3/4A protease is responsible for polyprotein cleavage, while NS5B polymerase inhibitors are capable of negating HCV RNA replication. Finally the NS5A inhibitors are a class of molecules able to inhibit viral replication and assembly processes, although the exact mechanism remains ambiguous.[100,93,94] Of these targets, inhibition of the NS5B HCV polymerase is very promising, as this mechanism directly interferes with the reproduction of viral RNA, and there are no known mammalian RdRp.[101] The NS5B RdRp has a right

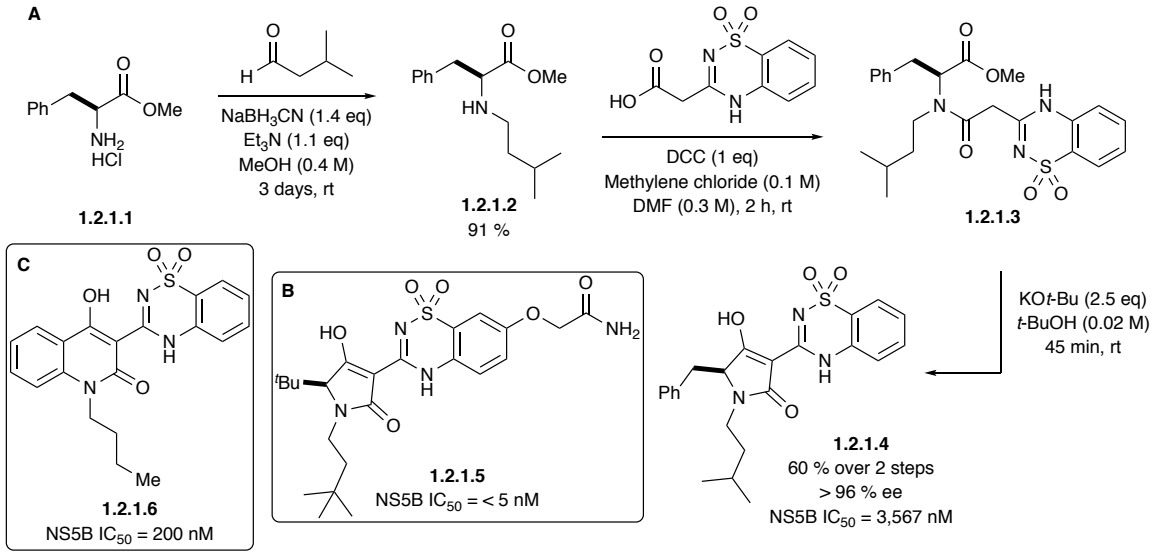
handed topology with a three-dimensional structure containing domains commonly denoted the finger, palm and thumb regions. The interactions of the finger and thumb domain maintain the enzyme's active conformation, and control RNA synthesis.[102]

Despite the undeniable advancement of HCV treatment the overall nature of the virus unfortunately lends itself to mutation and subsequent drug-resistance. As such the continuing development of molecules within privileged medicinal chemistry structural classes is needed for the continuing examination of HCV and other diseases. One such scaffold is the sulfonamide. In the realm of HCV research the sulfonamide is represented in a number of drugs,[93] HCV inhibitory lead compounds, and biological hits.

With such a heavy sulfonamide presence in HCV research it is not surprising that a cyclic variant, benzothiadiazine analogs, are also well represented. These benzothiadiazine molecules are a fusion of two well-known cores: thiadiazine and 4-hydroxyquinolin-2(1*H*)-one.[96] A 2002 high-throughput screen of the GlaxoSmithKline (GSK) proprietary compound collection with a NS5B derived assay discovered the HCV inhibitory activity of benzothiadiazine compounds and inspired over a decade of HCV research (**Scheme 1.2.1**).[103]

Three years after this initial screening hit researchers at GlaxoSmithKline followed up with a two-pot asymmetric synthesis of benzothiadiazine-substituted tetramic acids. **Scheme 1.2.1** illustrates the use of reductive amination, followed by amide bond formation and Dieckmann cyclization, to provide a unique fusion of sultam derivatives and tetramic acids. A small structure activity study found that increased steric bulk around the stereocenter, in addition to a meta amide moiety lead to a compound capable of reaching an IC_{50} against NS5B below 5 nM (**Scheme 1.2.1)**.[101]

Scheme 1.2.1 A) Synthesis of tetramic derivatives. B) Tetramic lead compound. C) 2002 GSK HTS lead compound.



The tetramic acid core was found to be a suitable mimic for the quinolone moiety, allowing GSK researchers to continue their efforts with a solid-phase synthesis of benzothiadiazine-substituted tetramic acids. This combinatorial project generated two libraries of 96 products each for SAR studies. In short, the *S* configuration was preferred, while initial R1 studies gave an order of ^{t}Bu > ^{i}Pr > Me > H. **Figure 1.2.2** illustrates the prototypical scaffold used by GSK for these tests as well as the more potent NS5B inhibitors.[104]

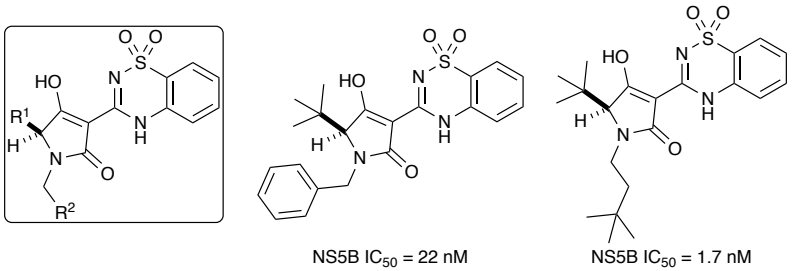
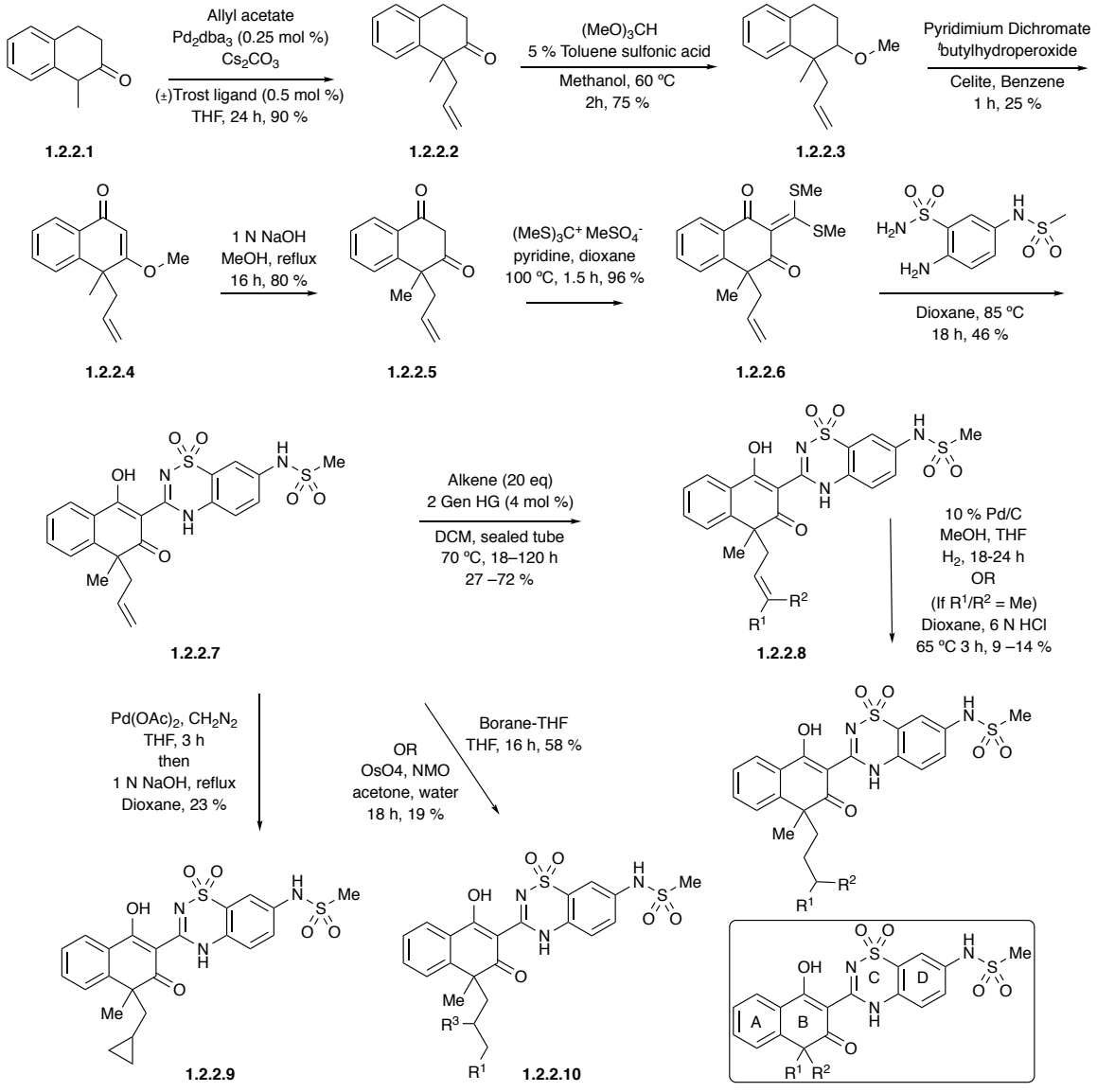


Figure 1.2.2. GSK solid-phase SAR products.

Abbott Laboratories continued the benzothiadiazine HVC work with a series of publications from 2007 to 2009. The inhibitory target remained the NS5B RNA polymerase, however Abbott opted to focus on a series of 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalenes bearing the generic ABCD ring structure, as shown in **Scheme 1.2.2**.

Scheme 1.2.2. Synthesis of Abbott ABCD benzothiadiazine ring core and products.



This publication focused on a 7- or 8-step synthesis to derivatives of the generic ABCD core. Hydroboration, dihydroxylation, and cross metathesis products were generated on the B ring and tested for inhibitory potency against genotype 1 HCV NS5B polymerase. Of particular note to the herein disclosed dissertation work is the use of the geminal methyl thioether as a functional handle, as this is part of the disclosed sultam synthesis seen in Chapter 3. The most potent analogs from this very linear route are shown in **Figure 1.2.3** with the top hit affording an IC_{50} of 4 nM against NS5B.[105]

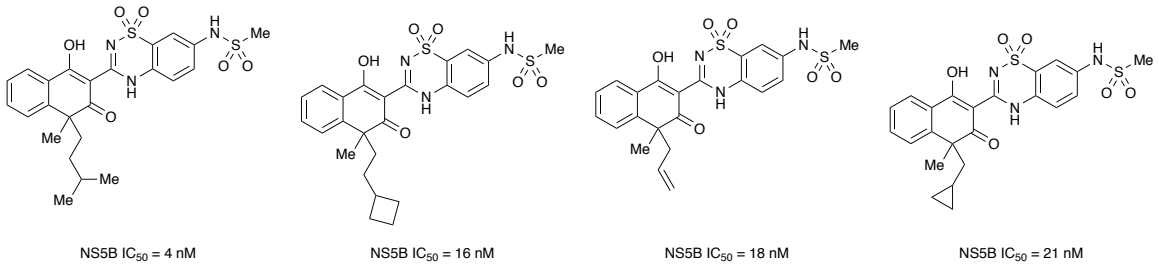
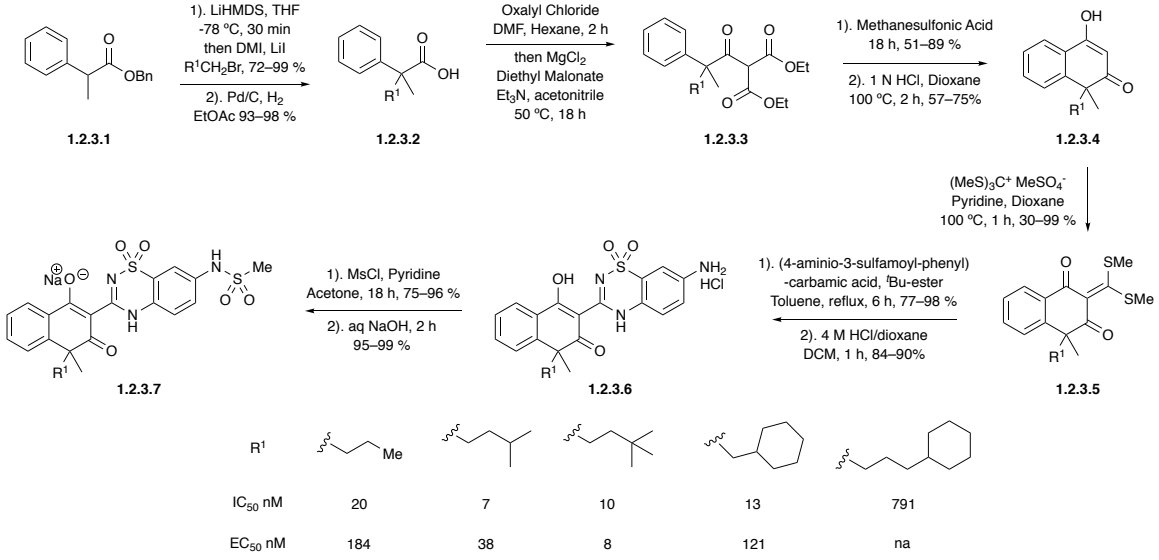


Figure 1.2.3 Most active compounds from Abbott 2007 benzothiadiazine synthesis.

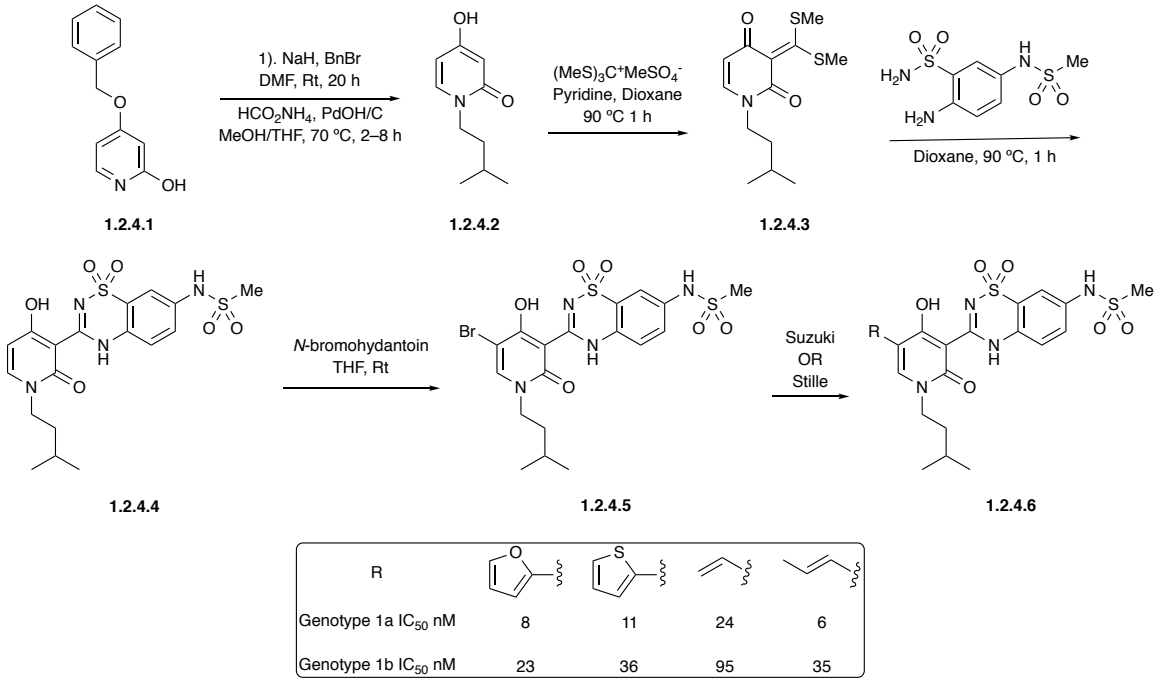
Abbott Laboratories continued to explore these benzo-sultam/naphthalenone fused cores in a series of SAR papers. A 2008 manuscript detailed a series of gem-dialkyl naphthalenones with variations of the "B" ring,[106] as previous work had illustrated the best thiadiazine substitution to be a meta-methyl sulfonamide.[107] Aside from a shorter overall synthesis, with the key step still relying on diaza addition elimination of methyl sulfide, this publication confirmed the high bioactivity of the core scaffold, particularly the 10 nM hit containing a *neo*-hexyl α-substituent (**Scheme 1.2.3**). Although the *neo*-hexyl analog did not have the lowest IC_{50} value, it was superior in the cell-based assay with an EC_{50} of 8 nM.[106] This was due in part to the metabolic oxidation of the neopenyl substrate to a tertiary alcohol.

Scheme 1.2.3. SAR of 1,1-dialkyl-2(1*H*)-naphthalenones



Abbott continued SAR studies with Des-A ring trials in combination with the use of *N*-1alkyl-4hydroxyquinolon-3-yl benzothiadiazines, a class of inhibitors known to bind to the palm domain of the HCV NS5B polymerase.[108] By early 2008 these pharmaceutical researchers had a variety of enzymatic inhibition data to work with, and it was known from models and X-ray data that the A-ring of the core scaffold fit into a small hydrophobic area of the binding site.[109] This publication concluded that small aromatic rings and alkenyl groups in the 5-position of the "B" ring stand in for a removed "A" ring. The inhibitory retention was caused by "B" ring substitutions moving into the space previously taken up by the "A" ring.

Scheme 1.2.4. Des-A-ring *N*-1-alkyl-4-hydroxyquinolon-3-yl benzothiadiazine synthesis and SAR.



The construction of these *N*-1alkyl-4hydroxyquinolon-3-yl benzothiadiazines was dependent upon the formation and substitution of a dithioketene acetal intermediate, as well as Suzuki or Stille coupling reactions (**Scheme 1.2.4**). Products performed well in enzymatic assays giving low nanomolar IC_{50} values, as well as in cellular culture replicon assays with the 2-Furyl derivative affording an EC_{50} of 2.5 nM against NS5B in genotype 1b of HCV. [110]

Abbott released *in vivo* rat pharmacokinetics in two 2008 and 2009 publications. **Figure 1.2.4** details the *in vivo* findings of Compound **26** and Compound **30**. Compound **26** was found to have a half-life of 4.3 hours, and a liver concentration of up to 21 ug/g after six hours. High liver concentration is vital to HCV treatment as the disease chiefly attacks this organ. Abbott found an excellent liver to plasma ratio of 48:1 for Compound **26**, and an overall estimated bioavailability of 94 %.[111]

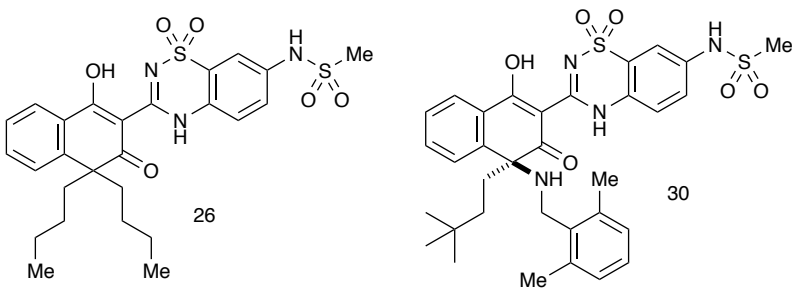


Figure 1.2.4 Abbott rat pharmacokinetics compounds

Benzylamine analog Compound **30** also demonstrated good oral bioavailability of 55.9 %, a liver concentration of 3.25 uM at 12 hours, with a liver to plasma ration of greater than 10. This data lead Abbott to describe Compound **30** as an attractive potential HCV therapeutic with the option for convenient dosing regiments.[112]

In addition to Abbott and GSK, other pharmaceutical companies[113] attempted to develop drugs targeting the HCV NS5B polymerase. Anadys Pharmaceuticals disclosed an evaluation 4-(1',1'-dioxo-1',4'-dihydro-1'λ^6-benzo[1',2',4'] thiadiazin-3'-yl)-5-hydroxy-2*H*-pyridazin-3-ones. **Figure 1.2.5** shows the most promising Anadys inhibitor **A**, which was found to possess an IC_{50} of less than 10 nM against genotype 1b, and an antiviral potency (EC_{50}) of 5 nM against 1b. Despite the promising initial *in vitro* and *in vivo* activity, orally administration to cynomolgus monkeys found a very low bioavailability. Anadys postulated this was caused by the low gut permeability associated with the highly polar nature of this molecule (PSA) = 203 Å.[114] Thus, to reduce this polarity of the lead compound, 5,6-Dihydro-1H-pyridin-2-one **B** was generated (**Figure 1.2.5**).

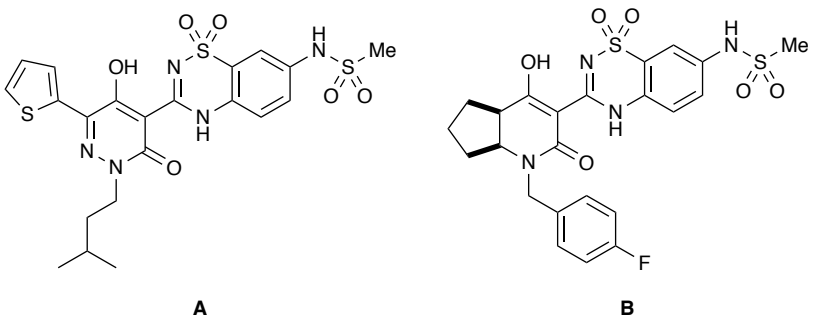
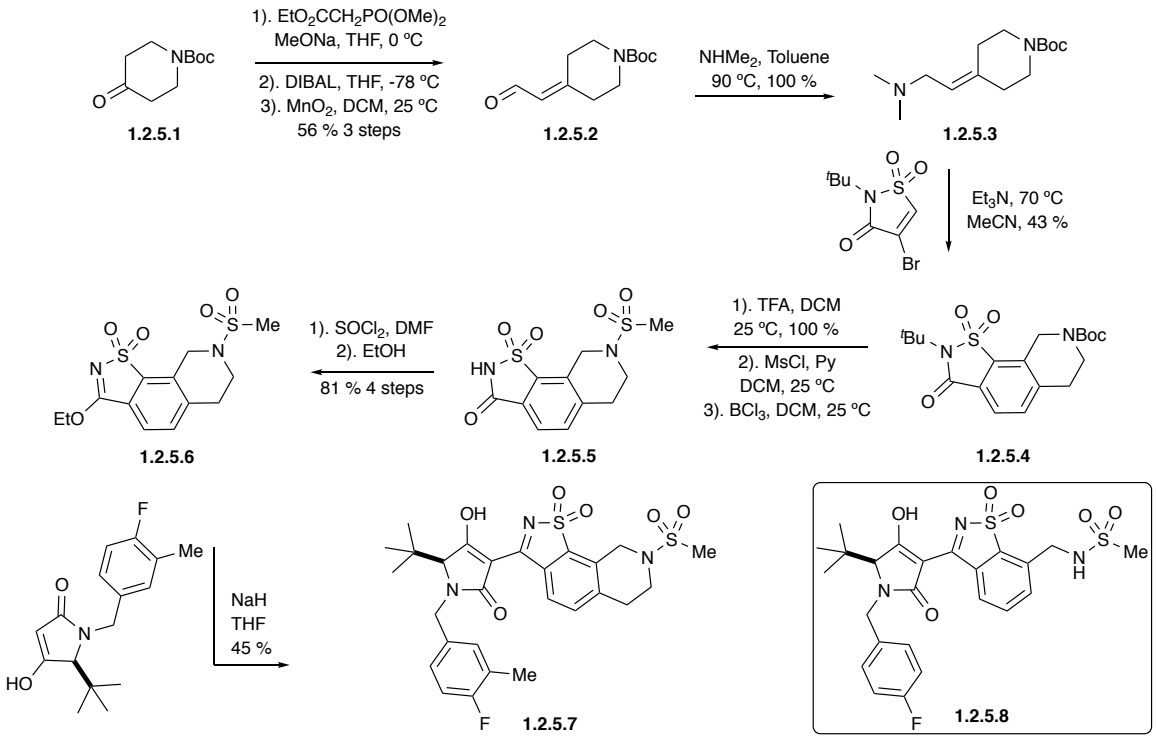


Figure 1.2.5. Anadys bioactive pyridazine-3-ones and pyridine-2-ones

Anadys compound **B** had a much lower PSA of approximately 162 Å, as well as an improved bioavailability of 24 % in monkeys. The IC_{50} for genotype 1b was less than 10 nM and the EC_{50} was 16 nM.[115] This work again demonstrates the power of combining sultams with a tetramic acid core, as well as the use of benzyl amine functionality[116] when designing biological leads or probe compounds.

Roche, in conjunction with Array BioPharma, reported slightly less dramatic biological activity held by five membered tetramic acid/sultam compound. Compound **1.2.5.8** showed good inhibitory activity against HCV NS5B with an enzymatic IC_{50} of 0.003 μM, and a replicon EC_{50} of 0.1 μM. Crystallography suggested the sulfonamide oxygen was interacting with Asn291 and Ser288 via a water molecule; however, no interaction with Asp318 was seen as is common in the analogous benzothiazine series. Thus, a slightly bulkier more ridged sulfonamide analog was generated to improve this interaction, as well as cell permeation, and potency (**Scheme 1.2.5**). While these fused-piperidine analogs did show a NS5B inhibition in the replicon assay with an EC_{50} of 0.005 μM, there was significant binding to human serum, which lead Roche to conclude these promising bioactive molecules were not good drug candidates.[117]

Scheme 1.2.5. Roche synthesis of benzo[d]isothiazole-1,1-dioxides



Despite intense pharmaceutical development by multiple companies, no tetramic acid/sultam compound passed clinical trials and became a drug. However these efforts highlight the potential for such a combination to be used in chemical biology studies designed to uncover novel biological reactivity. The combination of tetramic acids and sultams shown above gives compelling reason to generate fully fused 'sultamic acids' wherein the sultam moiety is included in the tetramic core scaffold. Chapter 3 focuses on the design and synthesis of novel enamine and enolic α,β-unsaturated sultamic acids for use as probe molecules in chemical biology assays.

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Chapter 2:
Synthesis of Triazole-Fused α-Methylene δ-Sultams via Pd-catalyzed Heck-type Intramolecular *C*-vinylation of an Appendant Triazole

Section 2.1 *Small Molecules for Chemical Biology*

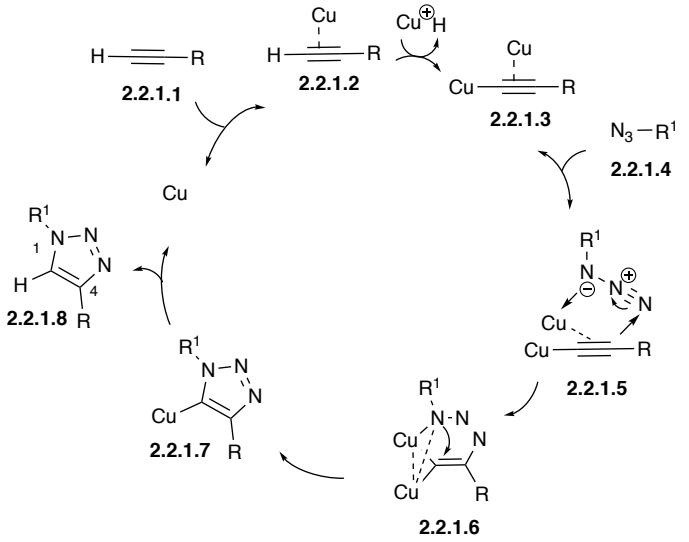
The development of small molecules containing chemically, sterically and stereochemically modifiable electrophilic warheads is paramount for the advancement of chemical biology. These electrophilic motifs are capable of modulating nucleophilic biological interactions, and are well-known probe molecules in chemical biology assays.[1] Previously, electrophilic molecules such as α,β-unsaturated Michael acceptors were excluded from screening decks due to fear of promiscuous, and off-target activity.[2] However in recent years advancements in the field of chemical biology, particularly the advent of activity-based-protein-profiling (ABPP),[3] has demonstrated the possibility for selectivity and thus utility for electrophilic chemical probes, including α,β-unsaturated Michael acceptors.[1]

Despite the advancements in ABPP and the re-emergence of electrophilic and covalent molecules for chemical biology assays, a majority of probe molecules remain small fragment-like warheads lacking modifiable attenuation parameters. An electrophilic sultam was designed in an effort to achieve a chemically, sterically and stereochemically modifiable Michael accepting probe for use in chemical biology. This sultam was generated via the well-known click reaction,[4] which afforded an advanced synthetic intermediate with interchangeable and modifiable azide-derived substituents. The intermediate was then subjected to a novel Pd-catalyzed Heck-Type intramolecular *C*-vinylation of an appendant triazole, generating a novel triazole-fused α-methylene δ-sultam chemotype, *vide infra*.

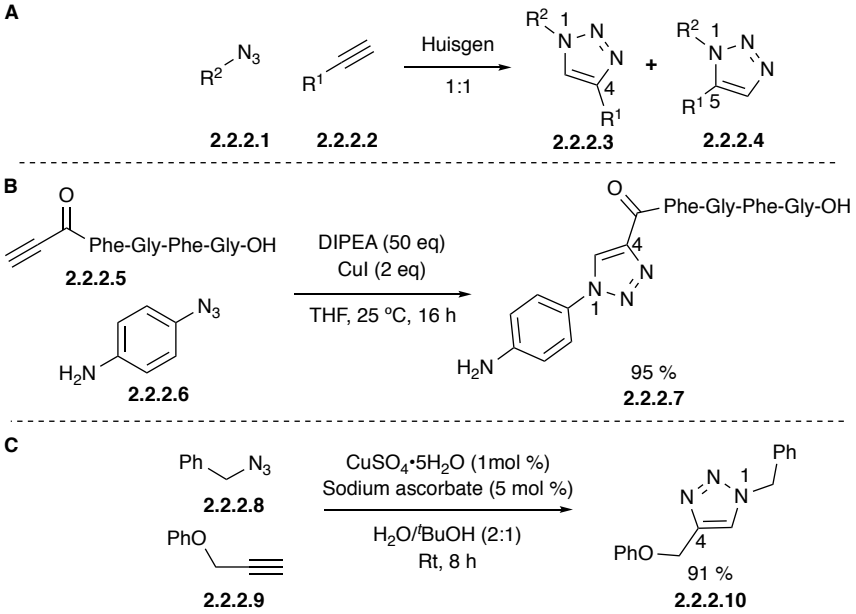
2.2. *The use of Click Chemistry in the Synthesis of Small Molecules.*

The highly selective and bio-orthogonal[5] Copper-catalyzed Cycloaddition-of-Azide-to-Alkyne "click" reaction[6] was disclosed almost simultaneously in 2002 by co-authors Fokin and Sharpless[7], along with Meldal[8]. This copper-catalyzed azide-to-alkyne cycloaddition (CuAAC) selectively forms 1,4-disubstituted 1,2,3-triazoles. The novelty of this copper catalyzed reaction lies with the virtual non-existence of side products, or regioisomers, and established a new outlook on the well-known, but non-regioselective Huisgen 1,3-dipolar cycloaddition (**Schemes 2.2.1, and 2.2.2**).[9] The triazole formed via CuAAC is itself found in a variety of biologically relevant[10] molecules possessing anti-HIV[11], anti-cancer[12], anti-bacterial,[13] antifungal[14] and antiepileptic[15] activities. Furthermore, the triazole has been found to be a rigid non-hydrolyzable mimic for an amide or peptide bond in regards to both atom placement, and electronic properties making it a useful bioisostere.[16] While it is possible to form 1,5-disubstituted triazoles regioselectively utilizing ruthenium catalysis,[17] the scope of this chapter is limited to the discussion of thermal or copper-catalyzed formation of di-substituted 1,2,3-triazoles, as this is the derivative represented in the disclosed thesis work. Furthermore, the extensive contributions of CuAAC in the fields of macrocyclic scaffolds,[18] cyclic peptides,[19] and polymers[20] for material science or medicinal chemistry[21] are not discussed.

Scheme 2.2.1 The Cu (I) catalyzed azide to alkyne click reaction[22]



Scheme 2.2.2. A). Huisgen 1,3-dipolar cycloaddition. B). Meldal's solid support CuAAC. C). The Fokin and Sharpless CuAAC reaction



The development of CuAAC or 'click' chemistry transformed the burgeoning field of chemical biology,[23] by revolutionizing the utility of probe molecules used in screening.[24] The orthogonality between an azide and alkyne along with the robust nature of the click reaction allows for use in biological settings. Therefore *in vivo* and *in vitro*

uses for CuAAC are well established in the fields of protein tagging[25], chemical biology/ activity-based protein profiling[26], and biocompatible conjugation reactions.[27] The utility of CuAAC in biological studies is extensive,[28] and has become instrumental in the development of new therapeutics.[29] With this in mind, the disclosed thesis work focuses on the utilization of the CuAAC click reaction for the generation of small molecule electrophilic probes for use in chemical biology assays. There is a significant need for the development of novel electrophilic chemical probes, as identifying medicinally relevant nucleophiles in cells is critical to the continued advancement of therapeutic development.

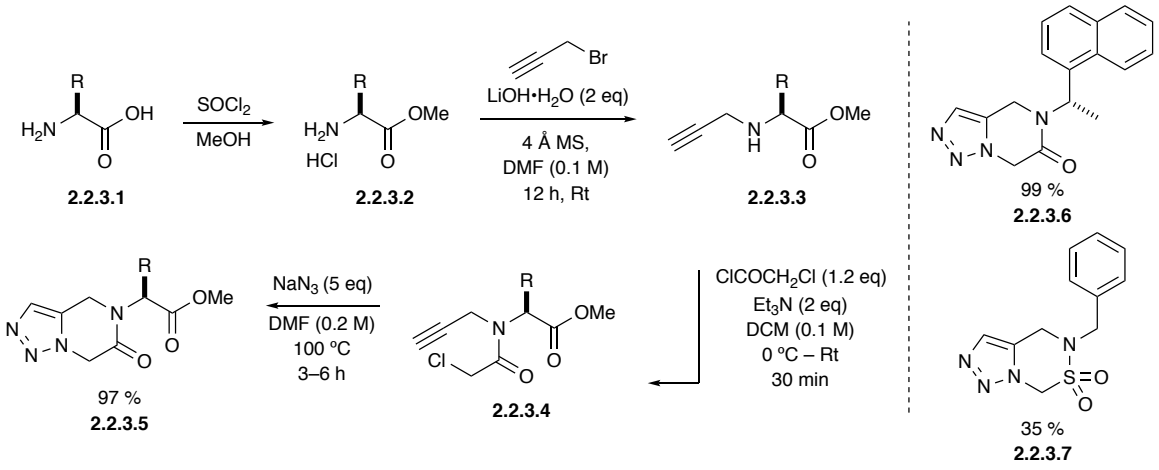
The synthetic work in this chapter involves the intramolecular functionalization of triazoles generated via intermolecular click.[30] This work utilizes intermolecular CuAAC to generate a triazole with an unsubstituted *C*5 position. Subsequent Pd-mediated intramolecular cyclization between the *C*5 and a vinylic *C*-sp^2 (*C*-vinylation) affords an α–β unsaturated electrophilic sultam. Despite the use of intermolecular CuAAC, the disclosed sultams are formed via an intramolecular triazole fusion process, which can be envisioned as an alternative for an IM click reaction strategy. Therefore, an overview of small molecules generated via intramolecular click and/or intramolecular triazole fusion reactions is given below. This overview of chemical literature reveals a relative underutilization of intramolecular click chemistry in small molecule cyclization (when compared to intermolecular click approaches), as well as the still emerging field of intramolecular triazole functionalization and cyclization.

The intramolecular click (IM) reaction is a powerful transformation that is underutilized when compared with its intermolecular counterpart. A 2009 Scifinder search by Dutta found that 95% of ‘hits’ regarding the phrase “azide-alkyne

cycloaddition" referred to the intermolecular reaction.[31a] A similar search on June 21, 2019 using the above phrase found 11,651 Scifinder references, standing in stark contrast to the search phrase "intramolecular azide-alkyne cycloaddition" which uncovered only 184 references. Despite this remarkable literature disparity, a variety of IM click themed synthetic routes do exist for the formation of small molecules.[32]

In 2008, Chandrasekaran and co-workers reported an enantiopure route to 1,2,3-triazole-fused 4,5,6,7-tetrahydropyrazin-6-ones (**Scheme 2.2.3**) via an intramolecular click cyclization. This method began with the esterification of amino acids, followed by alkylation, acylation and thermal azide to alkyne ring closer to form a 1,5 disubstituted triazole. An analogous procedure utilized the propargylation of primary amines, followed by acylation and IM click to generate *N*-benzyl derivatives. Notably, a sultam scaffold was generated by this protocol albeit in modest yield.[33]

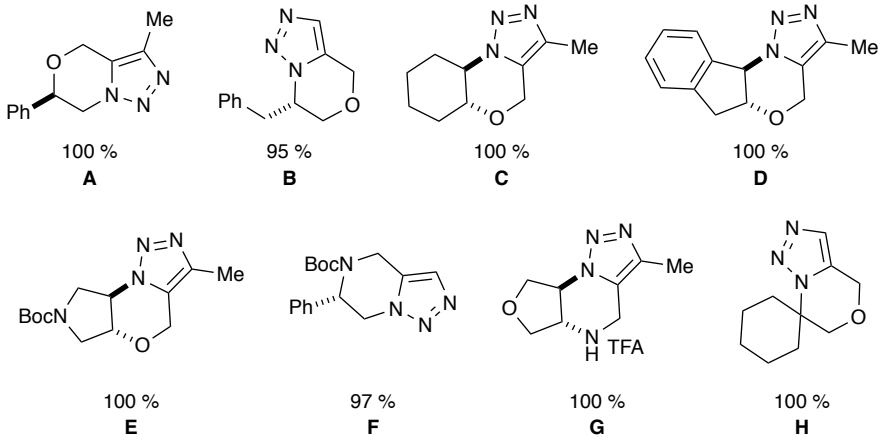
Scheme 2.2.3. Chandrasekaran's amino acid derived IM click cyclization to fused 1,2,3-triazoles.



The Dutta group published a systematic investigation of the IM click reaction in 2009.[31] **Figure 2.2.1**. shows an assortment of small heterocycles achieved by thermal click cyclization. A large pool of easily assessable starting materials such as olefins,

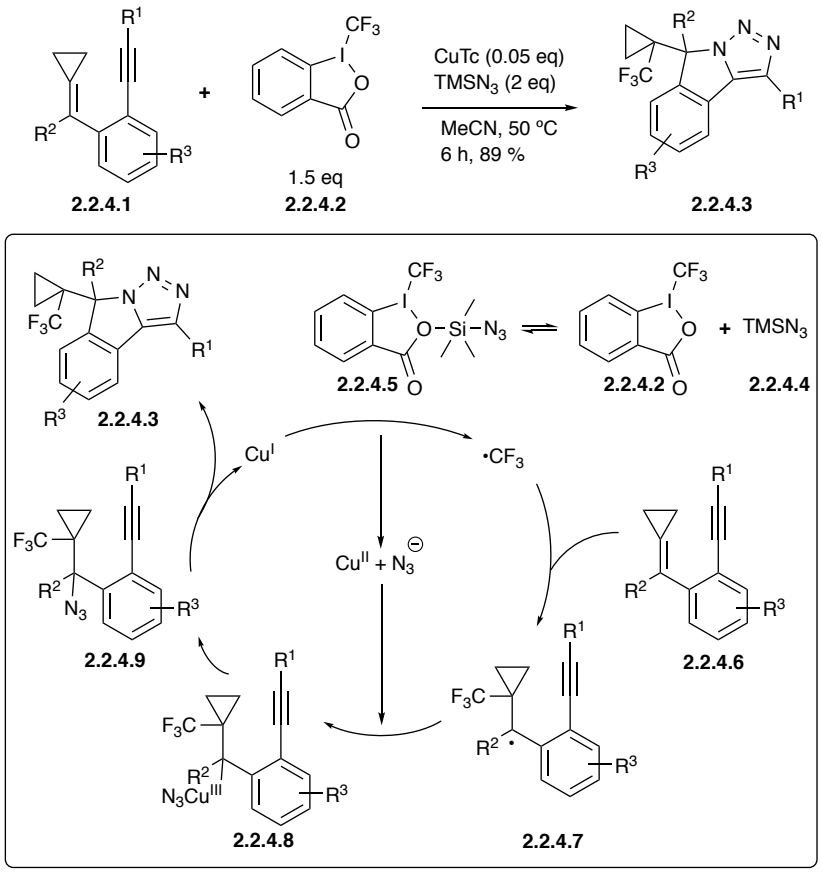
epoxides, amino acids and ketones underpinned these synthetic efforts. Furthermore, stereoselective product formation was possible, as well as routes requiring only four or five transformations to generate these drug-like molecules.

Figure 2.2.1 IM click products generated by Dutta and co-workers.



Shi and co-workers published a novel synthesis of triazole-fused, trifluoromethyl substituted isoindolines in a 2016 communication.[34] This work consisted of the use of hypervalent reagents acting in consort to achieve a trifluoromethylazidation/diazidation cascade. Intramolecular CuAAC was the final step in constructing the scaffold core. The proposed mechanism (**Scheme 2.2.4**) began with the *in situ* formation of a CF_3 radical that was trapped by the alkylidenecyclopropane, without the generation of ring-opening side products. This benzyl radical is then proposed to combine with the azide coordinated Cu(II) complex, followed by a reductive elimination to form the diazidation product. Finally, IM CuAAC takes place to generate the fused product.

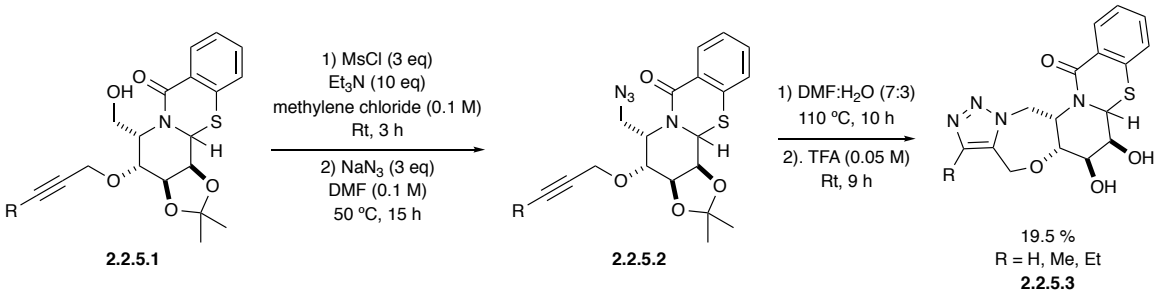
Scheme 2.2.4. Shi group's radical cascade IM CuAAc cyclization to isoindolines.



Alkyne substrate scope included a proton, TMS, *n*butyl, cyclopropyl groups as well as both electron donating and withdrawing phenyl substituents. The vinyl R^2 group also contained phenyl derivatives such as 4-Me, 4-OMe, 4-Cl, and 4-CF_3. The R^3 aryl group consisted of chlorine and a methoxy group. This remarkable reaction showcases the power of IM click when used in conjunction with radical cascade chemistry.

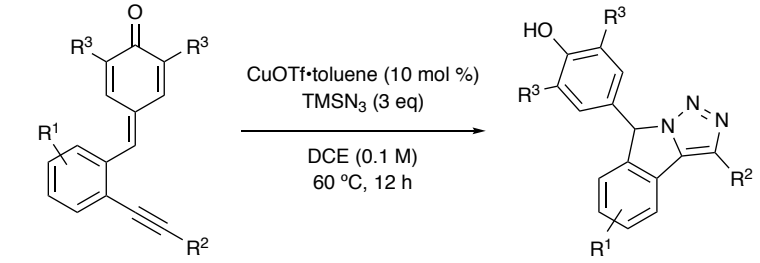
In 2018, the Chen group published a thermal intramolecular click reaction for the generation of pentacyclic iminosugars.[35] These scaffolds were found to be inhibitors of HIV reverse transcriptase with activity ranging from IC_{50} values between 0.69–14.38 μM.

Scheme 2.2.5. Chen group's synthesis of iminosugars.



The Anand group reported an intramolecular azide-to-alkyne cycloaddition catalyzed by CuOTf•toluene in 2018.[36] This tandem method utilized a 1,6-conjugate addition of $TMSN_3$ to *o*-alkynylated *p*-quinone methides followed by an intramolecular CuAAC cyclization to generate 1,2,3-triazole-fused isoindoline products. **Scheme 2.2.6**. illustrates the transformation wherein the azide performs a Michael addition into the quinone methide, which subsequently undergoes intramolecular click to form the isoindoline system. Mechanistic NMR and IR studies confirmed the addition-click mechanistic sequence.

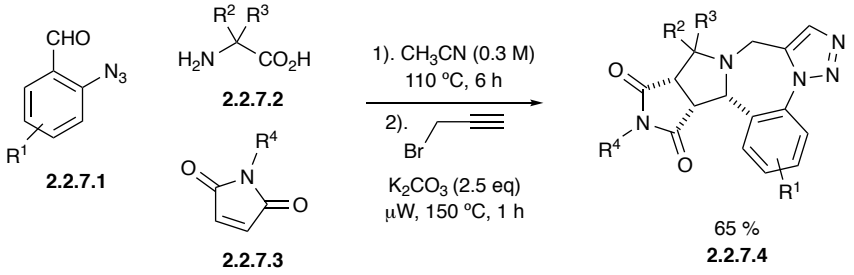
Scheme 2.2.6. The Anand 1,2,3-triazole fused isoindoline addition-click reaction.



Most recently (2019), Zhang and co-workers disclosed a microwave-induced thermal intramolecular click reaction.[37] This multicomponent one-pot synthesis of triazolobenzodiazepine-containing polycyclic compounds was accomplished via an

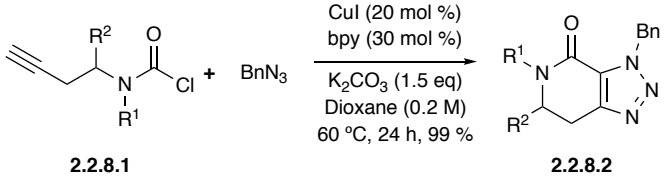
amine condensation, followed by decarboxylative non-stabilized azomethine ylide formation and subsequent [3 + 2] maleimide cycloaddition (**Scheme 2.2.7**). To this was added propargyl bromide, which underwent *N*-propargylation, and finally thermal intramolecular click cyclization to form products in up to 65 % and a diastereomeric ratio (dr) of up to 7:1. While the Zhang and co-workers IM click reaction was copper free,[38] the use of microwaves as a facilitating synthetic tool is highly relevant to the disclosed thesis work.

Scheme 2.2.7. Zhang's copper-free one-pot synthesis of triazolobenzodiazepine compounds



A recent 2019 publication by Larin and Lautens highlighted the need for methods capable of installing a substituent and the triazole 5-position.[39] To accomplish diversity at the 5-position while subsequently performing a ring closing acylation reaction, the Lautens group made use of a method denoted "interrupted click".[40] An interrupted click reaction involves trapping a nascent Cu(I)-triazole with an electrophile, effectively installing a species other than hydrogen at the 5-position.

Scheme 2.2.8. Larin and Lautens interrupted click-acylation domino reaction



Scheme 2.2.8 shows the Larin and Lautens interrupted click-acylation domino reaction. Here the use of alkyne functionalized carbamoyl chlorides were subjected to a copper mediated click reaction. The copper triazolide formed by this intermolecular click was then trapped via acylation generating product **2.2.8.2** in yields up to 99 %. Benzylic and alkyl azides were well tolerated by the reaction, as were *N*-aryl groups. Benzene, 2-MePh, 4-CF_3Ph, 4-OMePh, 3-BrPh, and 4-BrPh were all compatible with the R2 position shown in **Scheme 2.2.8**. This work constitutes the first copper-catalyzed interrupted click formation of 5-acyl triazoles. The use of interrupted click to install a bromine or iodine at the *C*-5 triazole position could become of great facilitating value to a *C*-vinylation or *C*-arylation synthetic pathway (vide infra).

2.3. *C-arylation and C-vinylation of Triazoles*

The functionalization of any unsubstituted *C*4 or *C*5 triazole carbons remains a developing field. The majority of the above examples showcase pathways designed with pre-determined triazole differentiation or leave the *C*4/*C*5 carbons unfunctionalized. There are fewer methods for the subsequent intramolecular C-H functionalization of triazole carbons, and the literature that exists contains a lack of substrate scope and functionality. Indeed, many synthetic methods are limited to mostly carbon backbone and aromatic structures. Therefore, a need exists for methods capable of intramolecular triazole substitution; most notably alkene-to-triazole fusion, (*C*-vinylation), of the *C*5 on 1,4-disubstituted 1,2,3-triazoles. Ideally such methods would also demonstrate a tolerance for non-carbon scaffold backbones and a wide substrate scope.

Previous work in our group demonstrated the synthesis of 7- and 8-membered tricyclic biaryl sultams using an intramolecular Pd-catalyzed C-arylation reaction of an appendant triazole (**Figure 2.3.1**).[41] This synthetic method was part of our larger efforts in the development of new chemistry to S-heterocycles (See Chapter 1 Figure 1.1.1). We envisioned that this chemistry could be adapted for intramolecular C-vinylation in the generation of triazole-fused sultams. As will be disclosed, refinement of this design affords a novel triazole-fused α-methylene δ-sultam Michael-accepting chemotype, a well-known medicinal chemistry warhead,[42] capable of interaction with nucleophilic moieties in biomolecules[43] (**Figure 2.3.1**).

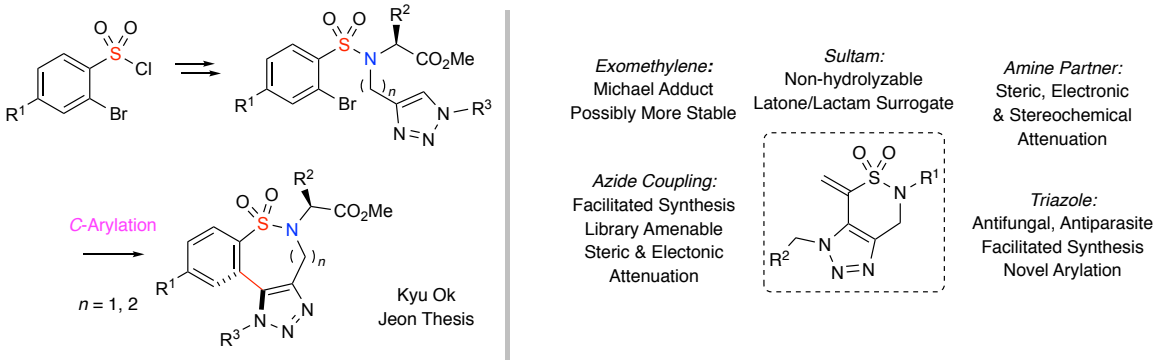


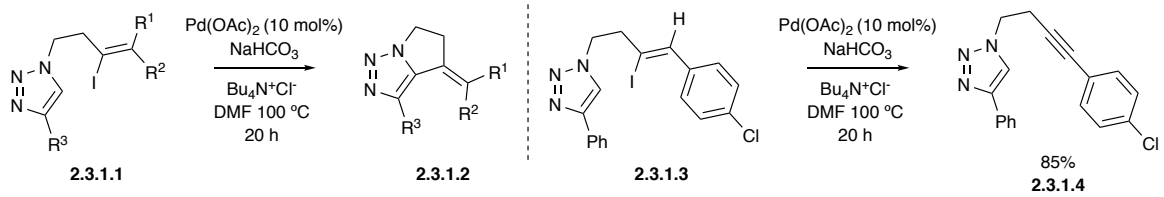
Figure 2.3.1 α-Methylene δ-sultam chemotype core disclosed in dissertation.

Thus, we herein present a method to generate an α-methylene δ-sultam Michael-accepting chemotype utilizing an intermolecular click and subsequent *C*-vinylation of the C5 position of an appendant triazole. To our knowledge, this sultam is the first of its kind to undergo such a fusion reaction, however there are several examples of *C*-arylation to form small molecules, as well as small number of *C*-vinylation methods. Below is the development of the intramolecular triazole fusion field, as well as seminal intermolecular examples. Ullmann-type copper mediated triazole-fusion reactions[44] are well represented in this field, however in the interest of space, all but the methods capable of generating scaffolds most relevant to the dissertation work are omitted.

Huang and co-workers disclosed an early example of an intramolecular vinyl-to-triazole *C*-vinylation method in 2006. This arylation generated pyrrolotriazoles, a novel class of bioactive heterocycles,[45] and was prefaced by the Cu (I) catalyzed synthesis of 4-alkylidene-5,6-dihydro- 4*H*-pyrrolo[1,2-*c*][1,2,3]triazoles **2.3.1.1**. A Pd-mediated intramolecular Heck-type reaction afforded arylation products in good yield as shown by a selection seen in **Scheme 2.3.1**. Linear by-product **2.3.1.4** was found when click substituents with a terminal *anti*-vinylic proton were utilized. Product **2.3.1.4** shows that

the elimination of hydroiodic acid and formation of an alkyne was favored over than the *C*-vinylation ring closing products **2.3.1.2**.[46]

Scheme 2.3.1. Huang's intramolecular vinyl-to-triazole *C*-vinylation method.



2.3.1.1 **2.3.1.2** **2.3.1.3** **2.3.1.4**

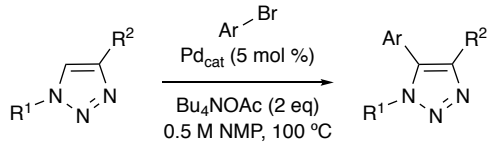
Entry	$R^1/R^2/R^3$	Time h	% Yield
1	Ph/Ph/$MeOCH_2$	19	52
2	Me/Ph/C_5H_{11}	20	71
3	*p*-ClC_6H_4/*p*-ClC_6H_4/Bu	21	82
4	Ph/Ph/C_5H_{11}	20	85

One year after Huang's formative triazole *C*-vinylation method, the Gevorgyan lab detailed a direct Pd-catalyzed 1,2,3-triazole arylation in another seminal manuscript.[47] To the best of Gevorgyan's knowledge, only one example of a *C*-arylation on 1,2,4-triazoles, [48] and no methods for arylation of 1,2,3-triazoles previously existed. Furthermore, the only *C*-vinylation method highlighted in this publication was Huang's 2006 Synlett.[46] The Gevorgyan group's method, as shown in **Scheme 2.3.2**, consisted of an intermolecular *C*-arylation between 1,4-disubstituted 1,2,3-triazoles and aryl bromides. Various palladium catalysts were used to generate the product in yields of up to 99 %, and good functional group tolerance.

Remarkably, 4,5-unsubsituted 1,2,3-triazoles demonstrated high regioselectivity forming *C*5 arylated products in yields of up to 83 %. The authors studied this

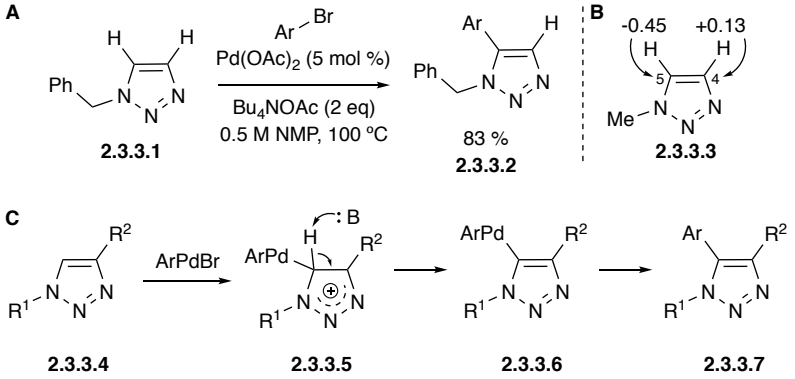
phenomenon with DFT calculations and found negative charge building upon the *C*5 carbon (**Scheme 2.3.3**). This caused Gevorgyan to postulate a more electrophilic mechanism for the *C*5 arylation, as seen in **Scheme 2.3.3**.[47] A review on the subject of electrophilic, and transition metal-catalyzed heteroaromatic functionalization was published by the same group in 2007.[49]

Scheme 2.3.2. Gevorgyan 2007 seminal *C*-arylation.



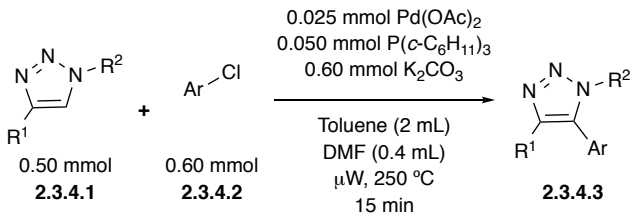
Entry	R^1/R^2	ArBr	% Yield
1	*n*-C_7H_{15}/Ph	1-bromo-4-methoxybenzene	97
2	*n*-C_7H_{15}/Ph	2-Br-naphthalene	99
3	*p*-MePh/CO_2Et	ethyl 4-bromobenzoate	84
4	Bn/CH_3CHOH	1-bromo-3-methylbenzene	61
5	Bn/Ph	3-bromopyridine	77

Scheme 2.3.3. A. Gevorgyan regioselective C5 arylation. B. Electrostatic charges. C. Proposed electrophilic arylation mechanism.



Oshima and co-workers divulged a microwave-assisted bimolecular arylation of 1,4-disubstituted 1,2,3-triazoles with aryl chlorides in a 2007 publication. **Scheme 2.3.4** shows a complex reaction mixture containing triazole, aryl chloride, palladium acetate, P(*c*-C_6H_{11})$_3$, and potassium carbonate dissolved in toluene and DMF. This reaction was then microwaved at 250 ºC for 15 minutes to afford product 2.3.4.3 in quantitative yields. While the scope of *N*-substituents (R^2) of **2.3.4.1** was limited to benzyls, and 4-toluene; the reaction was compatible with benzyl, *n*-C_6H_{13}, 4-pyridyl, and phenyl groups on the 4-triazole position (R^1). Compatible aryl chlorides included, chlorobenzene, 1-chloro-2-methylbenzene, ethyl 4-chlorobenzoate, 1-chloro-4-methoxybenzene, and 4-chlorobenzyl acetate. The use of *p*-chlorobenzyl alcohol afforded only benzaldehyde as an oxidation by-product.[50]

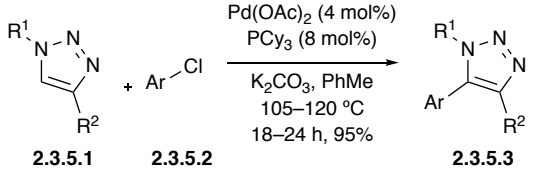
Scheme 2.3.4 Oshima 2007 intermolecular microwave *C*-arylation of triazoles



The Ackermann lab disclosed in 2008 a widely applicable Pd-catalyzed direct arylation of 1,2,3-triazoles with aryl chlorides. This paper highlighted the use of aryl chlorides in direct arylation reactions. As of 2008, the majority of direct arylations had been carried out on aryl iodides, bromides, and triflates via palladium or rhodium catalysis. While the Ackermann group highlighted Oshima and co-workers direct arylation of 1,2,3-triazoles with aryl chlorides; they did not fail to point out the limitations of Oshima's method such as the required use of a microwave, and reaction temperatures of 250 ºC.

Thus, Ackermann and co-workers sought to improve the applicability of 1,2,3-triazoles direct arylations with aryl chlorides. **Scheme 2.3.5** is a subset of the Ackermann method, which consists of simple $Pd(OAc)_2$ catalysis in combination with a PCy_3 ligand and the mild base K_2CO_3 with conventional heating at 120 ºC. Alkyl groups, phenyl, benzyl, substituted benzyls, PMB, and Ph groups were tolerated as *N*-substituents, while phenyl derivatives such as methyl, esters, ketones, and heteroaromatics were found to be adequate coupling partners.[51]

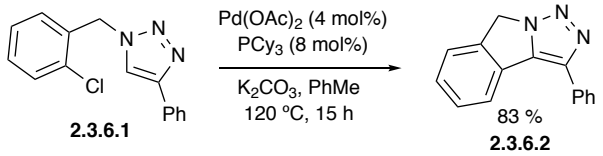
Scheme 2.3.5 Ackermann's 2008 palladium direct triazole arylation.



Entry	R^1	R^2	Ar	% Yield
1	Bn	Ph	2-$MeOC_6H_4$	95
2	Bn	Ph	2-pyridine	82
3	Octane	Ph	4-MeC_6H_4	70
4	Bn	Pentane	4-MeC_6H_4	66

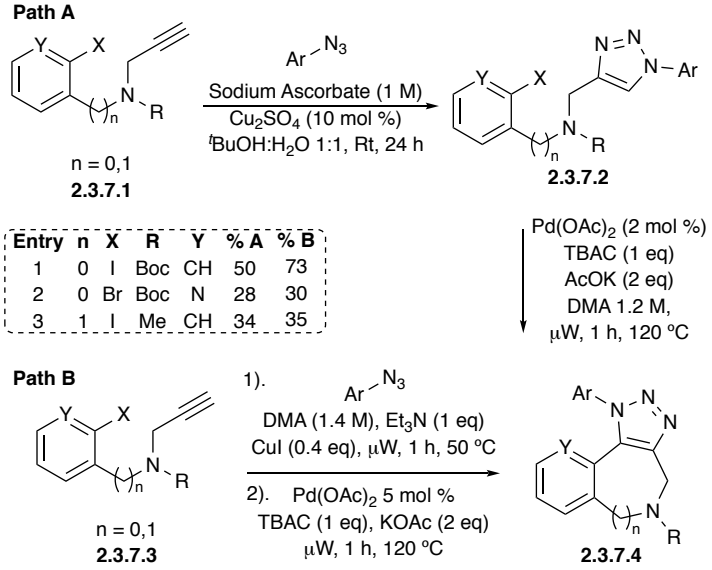
In addition to the above intermolecular triazole coupling, Ackermann also demonstrated an early example of intramolecular C-sp^2 to C-sp^2-triazole coupling in the same manuscript. **Scheme 2.3.6** details the co-opting of the bimolecular conditions to this intramolecular reaction generating a fused three-membered ring.[51]

Scheme 2.3.6 Ackermann's 2008 intramolecular triazole coupling.



The Beccalli group published a 2008 manuscript detailing the intramolecular cyclization of an aromatic C-sp^2 carbon to a triazole (**Scheme 2.3.7**). This synthesis of fused polyheterocyclic ring systems began as a step-wise procedure (Path A) utilizing aqueous copper click chemistry and Pd-catalyzed *C*-arylation via microwave irradiation.

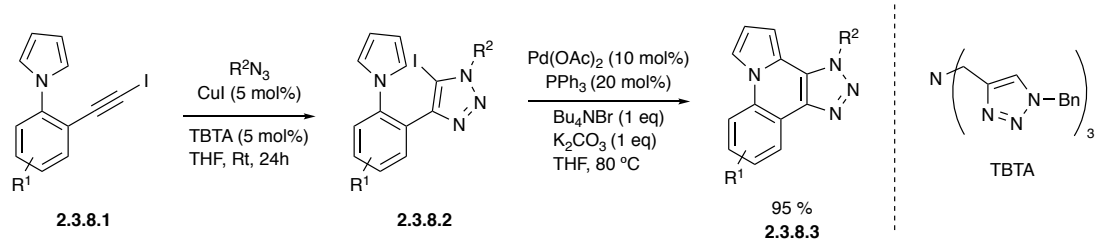
Scheme 2.3.7 Beccalii one-pot sequential *C*-arylation



Upon development of the step-wise protocol, a one-pot sequential method (Path B) was uncovered by changing the click solvent, base, and catalysts to DMA, Et_3N and CuI respectively.[52] This was a step forward in the realm of 'green' chemistry, however the reaction suffered from relatively low overall yields. Furthermore, as this work ran concurrently with other early triazole arylation examples, the only similar work Beccalli and co-workers disclosed knowledge of was the Gevorgyan 2007 Organic Letters publication.

Lautens and co-workers carried the one-pot arylation mentality forward by publishing a 2010 synthesis of fused 1,2,3-triazoles heterocycles.[53] This method (**Scheme 2.3.8**) made use of 5-iodo-1,2,3-triazoles in an arylation reaction.

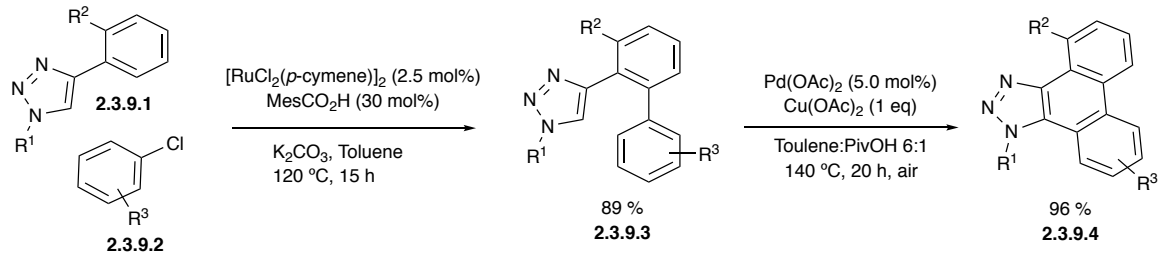
Scheme 2.3.8 Lautens *C*-arylation via 5-iodo-1,2,3- triazoles.



This one-pot reaction consisted of the addition of azide, CuI and TBTA to an iodo alkyne in order to form 5-iodo-1,2,3-triazole products. The palladium mediated intramolecular *C*5 arylation reaction could then be immediately carried out to afford fused heterocycles in up to 95 %. A variety of R^1 substitutions were tolerated on the alkyne benzene ring (**Scheme 2.3.8**) including 4-chloro, *para*-methylbenzoate, 2,4-difloro, and 3-nitro groups. Azide coupling partners (**Scheme 2.3.8** R^2) consisted of benzyl, PMP, hexyl, TMS and PMP groups.

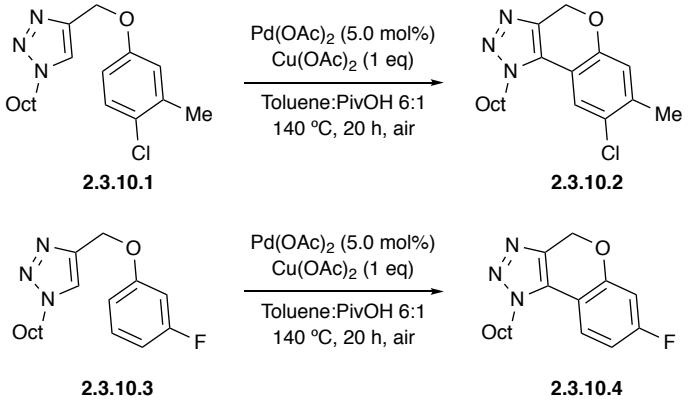
The Ackermann group returned in 2010 to publish an unprecedented intramolecular dehydrogenative arylation of 1,2,3-triazoles for the generation of annulated phenanthrenes.[54] **Scheme 2.3.9** details this intramolecular *C*5 arylation, that does not utilize pre-functionalized aromatic systems (C–H functionalization). It is important to note that no coupling occurred in the absence of palladium, and the highest yields were achieved with $Cu(OAc)_2$ as a stoichiometric terminal oxidant, even in the presence of air. A variety of functional groups were amenable with this coupling, including enolizable ketones or esters. Furthermore, in addition to the phenanthrene derivatives, 1,4-dihydrochromeno[3,4-*d*][1,2,3]triazole derived scaffolds were also generated by this method in yields up to 93%. Two of these scaffolds were utilized in intramolecular competition experiments designed to probe the coupling mechanism **Scheme 2.3.10**. Here the less sterically hindered position on the arene, as well as the less acidic C–H bond, where principally arylated.

Scheme 2.3.9 Ackermann's dehydrogenative arylation of 1,2,3-triazoles.



Entry	$R^1/R^2/R^3$	% Yield
1	Oct/CO_2Et/*p*-CO_2Et	96
2	Hex/Me/*p*-F	89
3	Oct/C_6H_4p-COPh/ C_6H_4p-COPh	78
4	Hex/OMe/*p*-Me	71

Scheme 2.3.10 1,4-dihydrochromeno[3,4-*d*][1,2,3]triazole competition experiments

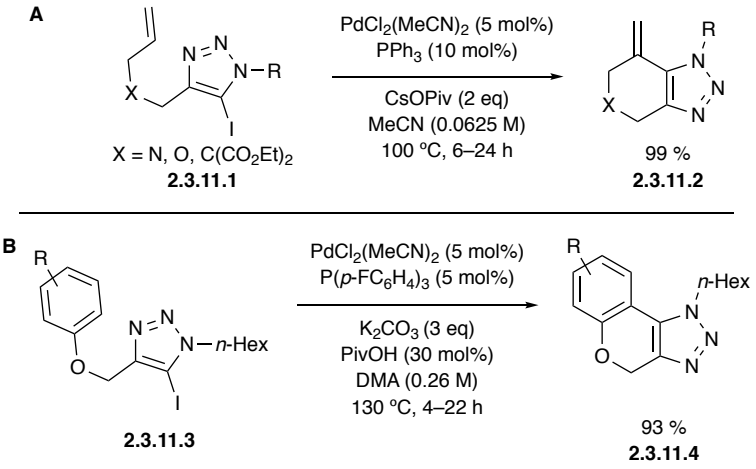


The Lautens group continued their own efforts in the generation and cyclization of 5-iodotriazoles with a 2012 communication detailing both triazole *C*-vinylation and *C*-arylation reactions.[55] The Pd-catalyzed triazole *C*5 to vinyl C-sp^2 intramolecular cyclization is yet another seminal example of such a reaction, which was accomplished in yields of up to 99 %. **Scheme 2.3.11** shows that ether, amino and carbon linkers were

tolerated by the reaction, while nitrogen substitutions included hexane, *p*-OMeBn, *p*-NO_2Bn, and 3-thiophene.

The intramolecular *C*-arylation of 5-iodotriazoles is also shown in **Scheme 2.3.11**. and made use of phenol-derived linkers with the *N*-substitution limited to hexane. Phenolic R groups included *p*-OMe, *p*-^{t}Bu, *m*-CF_3 and *o*-Cl, with product generated in up to 93 %. This publication by the Lautens group was novel, not only for the intramolecular *C*-vinylation, but also for the use of the 5-iodotriazoles, as this pathway allowed for a three-step synthesis of biologically intriguing molecules.

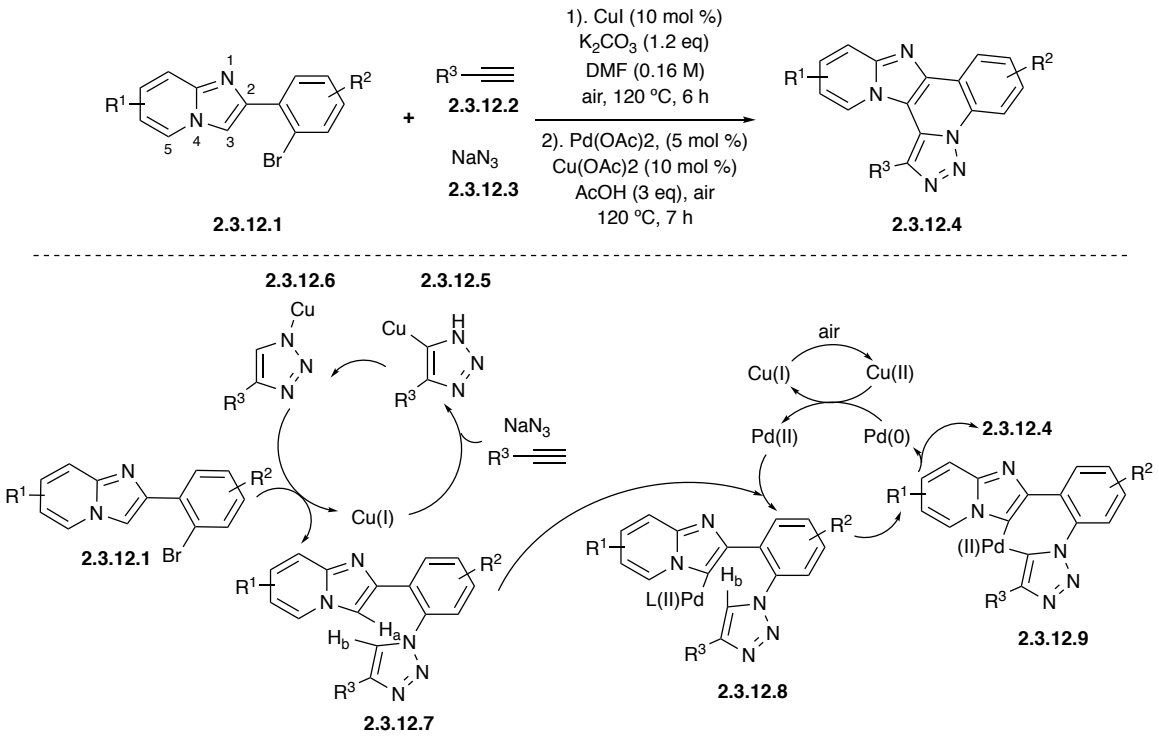
Scheme 2.3.11. Lautens intramolecular *C*-vinylation and arylation reactions.



In 2016, the Fan group published a bimetallic relay catalytic cycle for the generation of 1,2,3-triazole-fused quinolone imidazo[1,2-a]pyridines. [56] This intramolecular cross-dehydrogenative coupling was similar in principle to the 2010 Ackermann publication, and made use of air as a terminal oxidant. **Scheme 2.3.12** shows the one-pot reaction mechanism proposed by Fan. This method used copper iodide catalysis to form a 1,2,3 triazole, which then enters into the *C*-arylation pathway. Palladation and subsequent reductive elimination generated products in yields of up to 75 %. The substrate scope was limited to fully aromatic systems, with 2-(2-

bromophenyl)imidazole[1,2-a]pyridine substitutions R^1 limited to protons, or 6-Me/ CF_3/Cl, as well as 7-OMe. Similar groups were utilized for R^2 with F, Cl, and OMe on the 5-position of the benzene ring.

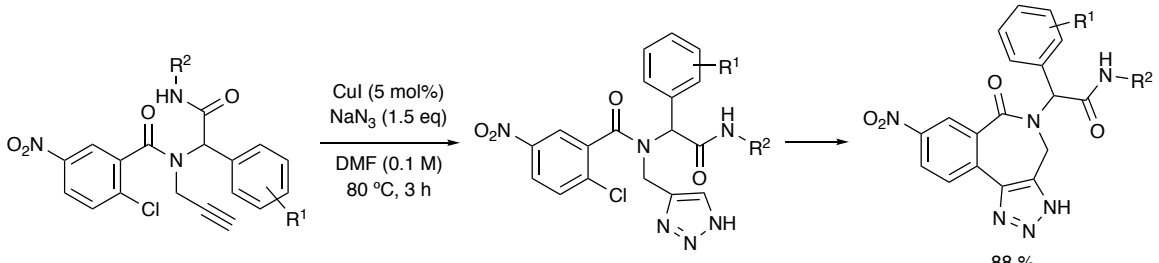
Scheme 2.3.12 Fan's bimetallic intramolecular cross-dehydrogenative *C*-arylation.



The 2016 Ullmann-type *C*-arylation to fused benzazepines by Homami and Rezaei bears loose resemblance to the disclosed thesis intramolecular triazole *C*-vinylation and α-methylene δ-sultam formation.[57] Homami and Rezaei generated a triazole-fused 7- membered lactam, a surrogate of the herein divulged α-methylene δ-sultams. As seen in **Scheme 2.3.13**, Ugi product **2.3.13.1** undergoes a CuI-catalyzed click and subsequent *C*-arylation to form 1,2,3-triazole fused benzazepine derivatives of biological interest. Various aryl R^1 group substitutions including 2-NO_2, 4-Cl, and 4-OMe were tolerated, while the *N*-alkyl group R^2 was limited to only cyclohexyl and 1,1,3,3-tetramethylbutyl. Although only eight products were generated, the method itself

is quite rapid, and amenable to further library development, with the caveat of no stereocontrol disclosed.

Scheme 2.3.13 Homami and Rezaei's Ullmann-type *C*-arylation to fused benzazepines



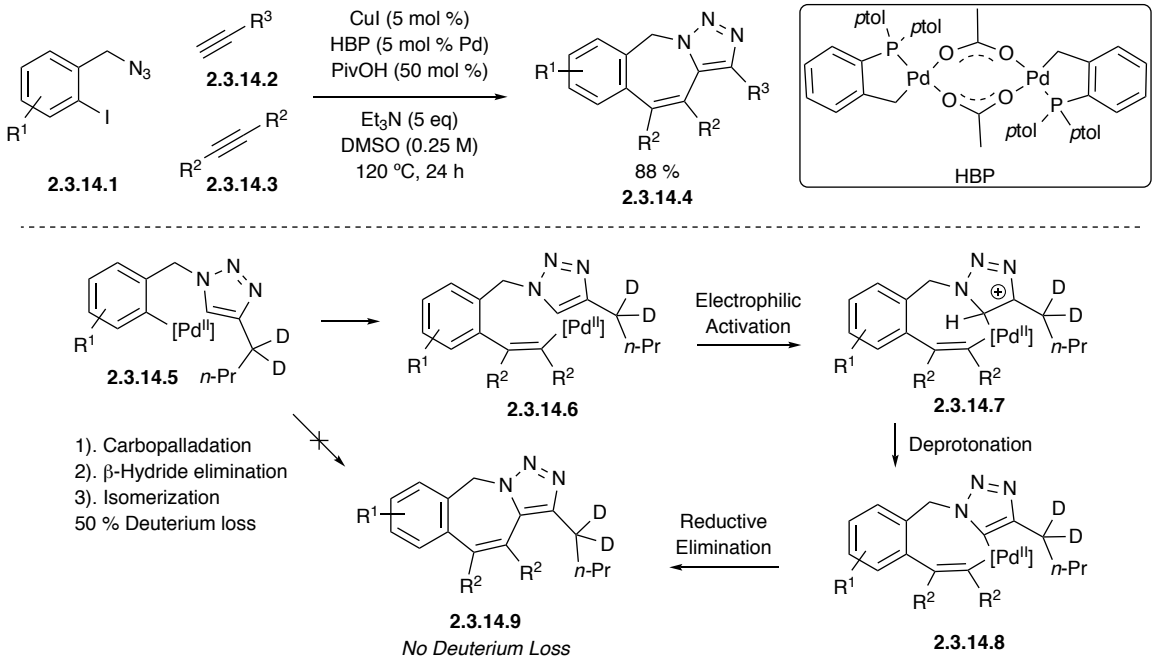
2.3.13.1 **2.3.13.2** **2.3.13.3**

The Lautens group published a multicomponent and multicatalytic *C*-vinylation reaction in a 2016 ACS Catalysis article.[58] This outstanding work featured a three component coupling reaction. Derivatives of 1-(azidomethyl)-2-iodobenzene, were combined with both internal and terminal alkynes, and concurrent Cu and Pd catalysis, to generate benzo and triazole fused seven membered heterocycles. As seen in **Scheme 2.3.14**, copper iodide, in combination with the Herrmann-Beller palladacycle (HBP), pivalic acid, and triethylamine were dissolved in DMSO and heated for 24 hours at 120 °C.

The Lautens group then sought to determine if an electrophilic cyclization pathway was operative as previous literature suggested, or if a carbopalladation, β-hydride pathway was active. The deuterium-based mechanistic analysis was used to probe the possible pathways. Should the carbopalladation route occur, subsequent β-hydride elimination would form an exocyclic methylene via loss of a deuterium, and isomerization with re-aromatization of the triazole would then form the expected product. However, these tests showed no loss of deuterium illustrating that an electrophilic activation and reductive elimination mechanism was probable. The substrate scope for

the internal alkyne was limited to aromatic rings, while methyl and heteroatoms were tolerated on the azide-coupling partner. The terminal alkyne was shown to have excellent scope, with alkyl, aromatic, heteroaromatic, as well as cholesterol, proline, and glucose derivatives proved compatible with this method. This method can be classified as a *C*-vinylation because the operative alkene is exo to the aromatic system, however there is conjugation with the benzene ring, highlighting how the dissertation work discussed below is unique among *C*-vinylations.

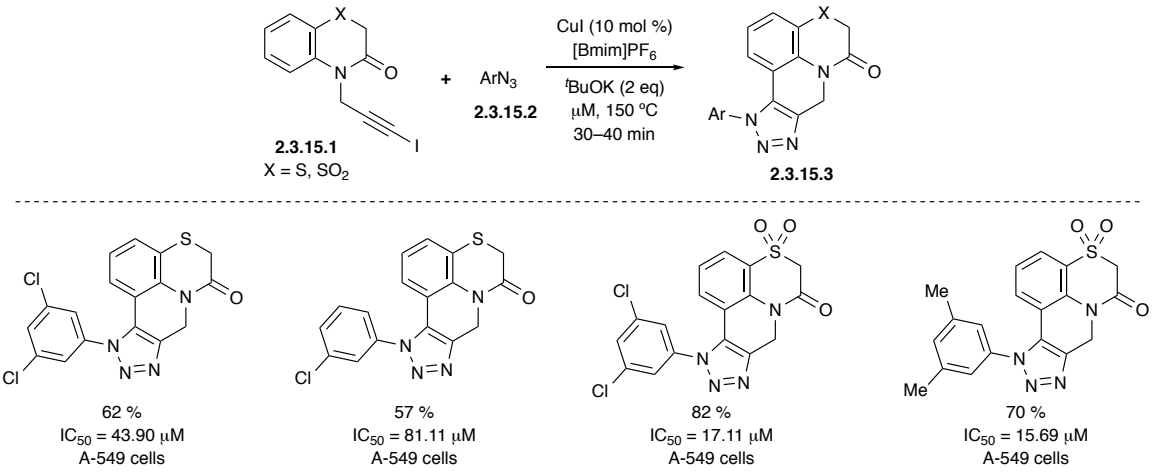
Scheme 2.3.14 Lautens 2016 *C*-vinylation to 7 membered heterocycles.



More recently in 2018, Nagavelli and co-workers disclosed a microwave assisted one pot synthesis of fused benzothiazino[1,2,3]triazole[4,5-*c*]quinolinone derivatives.[59] This Ullmann-type coupling made use of iodoalkynes, which as described above, has become an established method of deriving *C*5-substitution on 1,4-substituted 1,2,3-triazoles. These alkynes were subjected to microwave activation with CuI, ^{t}BuOK, in recyclable [Bmim]PF_6 solvent, in order to generate the product in yields of up to 88 %. A

two-part copper catalyzed mechanism was proposed consisting of triazole formation, followed by *C*-arylation via oxidative addition into the iodo-*C*5 triazole bond, re-aromatization via deprotonation, and finally reductive elimination to form the compounds shown in **Scheme 2.3.15**. Notably, these compounds were tested for anticancer activity against A-549 cells (adenocarcinomic human alveolar basal epithelial cells) and modest activity was found. Finally, this arylation detailed a more robust tolerance for the backbone scaffold, namely the incorporation of a quinolinone, as well as sulfur, into the products.

Scheme 2.3.15 Nagavelli's *C*-arylation to form bioactive quinolinone derivatives.



2.4 *Synthesis of Michael-Accepting α-Methylene δ-Sultams Scaffolds (4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide derivatives)*

The above summary of intramolecular click and *C*-arylation/vinylation highlighted many chemical scaffolds, some of which held biological activity. However, as previously stated there exists a shortage of synthetic triazole vinylation methods designed for non-aromatic or non-carbon backboned motifs. These differentiation methods augment CuAAC reactions by achieving chemical diversity, and can be thought of as an alternative ring closing process to intramolecular click reactions. The dissertation work now disclosed was designed to address the gap in *C*-vinylation methods as well as generate a novel electrophilic chemical probe capable of aza/thiol Michael additions reactions. Michael additions are frequently used in chemical biology assays designed to illuminate biological processes (See Chapter 1 Figure 1.1.9, 1.1.10, and 1.1.11).[60]

A Michael-accepting triazole-fused sultam probe was designed for use in chemical biology screening. While Pd-catalyzed Heck-type reactions have been previously utilized by Metz[61] and co-workers, to generate the α-methylene γ-sultams shown in **Figure 2.4.1**, to the best of the author's knowledge,[62,63] the method disclosed herein is the first *C*-vinylation of an appendant triazole to generate a triazole-fused α-methylene δ-sultam chemotype. In this regard, a scalable synthetic method for the generation of Michael-accepting 1,2,3-triazole-fused α-methylene δ-sultams is disclosed.

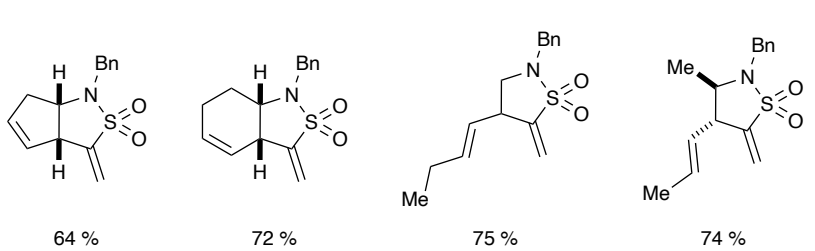
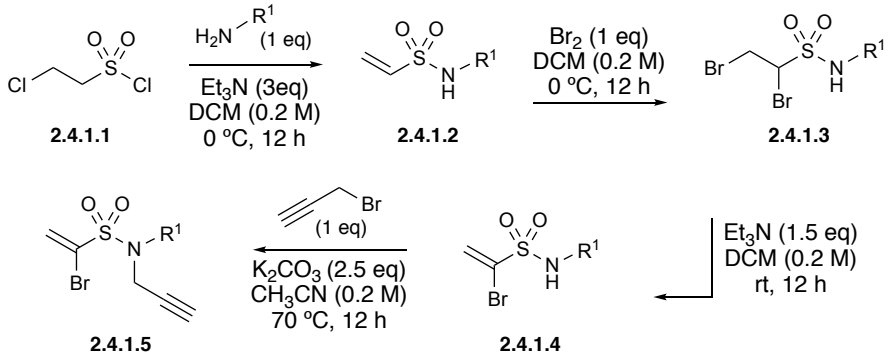


Figure 2.4.1. Metz and co-workers Heck sultam products.

The synthesis of the 1,2,3-triazole-fused α-methylene δ-sultam scaffolds began with the formation of the requisite sulfonamide.[64] An amine was dissolved in dichloromethane at 0 °C in the presence of Et_3N as a base, followed by the slow addition of 2-chloroethanesulfonyl chloride. The *N*-substituted vinyl sulfonamide **2.4.1.2** was formed in high yield after five hours (**Scheme 2.4.1**). Next, the olefin of sulfonamide **2.4.1.2** was then subjected to a bromination reaction in order to generate dibromo-compound **2.4.1.3**. This intermediate was quenched with sodium thiosulfate, before undergoing extraction with brine and methylene chloride (DCM). The organic layer was condensed via rotary evaporation before the dibromo intermediate was immediately re-dissolved in DCM and subjected to dehydrohalogenation by Et_3N. Thus α-bromo vinyl sulfonamide **2.4.1.4** was obtained in good yield after column chromatography. An *N*-alkylation was then carried out with propargyl bromide and K_2CO_3 in refluxing CH_3CN in order to form the terminal alkyne click precursor sulfonamide **2.4.1.5**. The yields of sulfonamide intermediates **2.4.1.2**, **2.4.1.4** and **2.4.1.5** are summarized in **Scheme 2.4.1**.

Scheme 2.4.1. Synthesis, substitutions and yields for sulfonamides.



Sulfonamide R^1	**2.4.1.2**	**2.4.1.4**	**2.4.1.5**
Cyclohexane (Cy)	**2.4.1.2.1** (96 %)	**2.4.1.4.1** (75 %)	**2.4.1.5.1** (90 %)
$(CH_2)_3OCH_3$	**2.4.1.2.2** (92 %)	**2.4.1.4.2** (71 %)	**2.4.1.5.2** (18 %)

Benzyl (Bn)	**2.4.1.2.3** (76 %)	**2.4.1.4.3** (79 %)	**2.4.1.5.3** (94 %)
Tert-butyl (^{t}Bu)	**2.4.1.2.4** (77 %)	**2.4.1.4.4** (78 %)	**2.4.1.5.4** (95 %)
L-Val•OMe	**2.4.1.2.5** (52 %)	**2.4.1.4.5** (73 %)	**2.4.1.5.5** (57 %)
L-Leu•OMe	**2.4.1.2.6** (91 %)	**2.4.1.4.6** (74 %)	**2.4.1.5.6** (89 %)
L-Ile•OMe	**2.4.1.2.7** (76 %)	**2.4.1.4.7** (74 %)	**2.4.1.5.7** (85 %)
L-Phe•OMe	**2.4.1.2.8** (92 %)	**2.4.1.4.8** (62 %)	**2.4.1.5.8** (55 %)

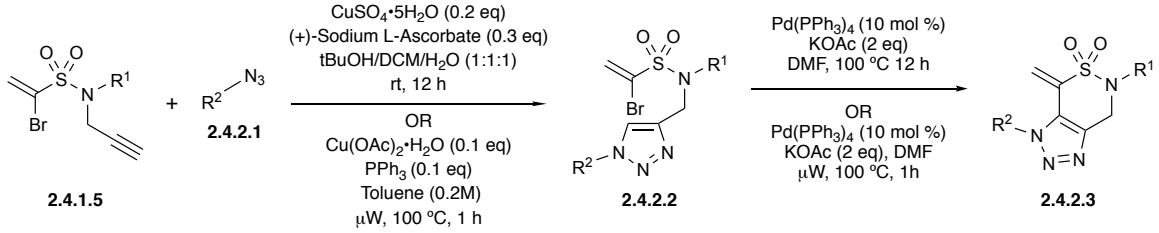
Sulfonamide derivatives **2.4.1.5** were filtered, condensed and purified via normal phase silica chromatography before being subjected to a CuAAC reaction. As discussed above, it is well documented that Cu(I)-catalyst[65] and Ru(II)-catalyst[66] regioselectively generate 1,4- or 1,5-disubstituted triazoles, respectively. The method called for CuAAC[67] reaction in order to synthesize 1,4-disubstiuted 1,2,3-triazoles. This was accomplished by dissolving alkyne sulfonamide **2.4.1.5** in a mix of *t*-BuOH/CH_2Cl_2/H_2O (1:1:1, 0.2 M) at room temperature before $CuSO_4$•$5H_2O$ (0.2 eq) and (+)-sodium *L*-ascorbate (0.3 eq) were added. The reaction was stirred at room temperature overnight to obtain the triazole substituted sulfonamide intermediates **2.4.2.2.1-2.4.2.2.33** in moderate to high yields (57–96 %) after column chromatography.

The preparation of compounds **2.4.2.2.1-2.4.2.2.33** set the stage for the titled intramolecular *C*-vinylation cyclization. The novel Csp^2-Csp^2 bond formation occurred between the α-bromo-substituted vinylic carbon, and the unsubstituted *C*5 carbon of the triazole. The method for this Heck-type reaction consisted of mixing sulfonamide with 10 mol% $Pd(PPh_3)_4$, 2 equivalents of KOAc, in 0.5M of anhydrous DMF, and heating overnight at 110 ºC. These conditions successfully formed bicyclic 1,2,3-triazole-fused Michael accepting sultams **2.4.2.3.1–2.4.2.3.33** in isolated yields of 49–88%. Overall the *C*-vinylation reaction showed compatibility with a wide range of substituted triazoles

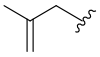
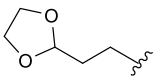
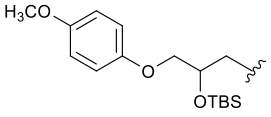
including electron donating, withdrawing, and protected triazole coupling partners. Assortments of simple alkyl amines were also well tolerated.

After successful synthesis of achiral products with this six-step protocol, the method was applied to amines bearing a stereogenic center. Sulfonylation of optically pure amino esters occurred with no changes to the overall synthetic method required. **Scheme 2.4.2** shows the click (**2.4.2.2.1-2.4.2.2.33**) and *C*-vinylation (**2.4.2.3.1–2.4.2.3.33**) yields for these chiral bicyclic sultams comparable with the achiral derivatives.

Scheme 2.4.2 Yields for sulfonamides and *4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide*.



Entry	R^1	R^2	**2.4.2.2**	**2.4.2.3**
1	Cy	*p*-CH_3Bn	**2.4.2.2.1** (78%)[a]	**2.4.2.3.1** (59%)[c]
2	Cy	*p*-CF_3-Bn	**2.4.2.2.2** (65%)[a]	**2.4.2.3.2** (80%)[c]
3	Cy	*p*-F-Bn	**2.4.2.2.3** (88%)[b]	**2.4.2.3.3** (79%)[c]
4	Cy	Bn	**2.4.2.2.4** (91%)[b]	**2.4.2.3.4** (49%)[c]
5	Cy	*o*-F-Bn	**2.4.2.2.5** (76%)[a]	**2.4.2.3.5** (55%)[c]
6	Cy	*p*-OCH_3-Bn	**2.4.2.2.6** (84%)[b]	**2.4.2.3.6** (65%)[c]
7	$(CH_2)_3OCH_3$	*p*-CH_3-Bn	**2.4.2.2.7** (78%)[a]	**2.4.2.3.7** (na)[c,d]

8	$(CH_2)_3OCH_3$	*o*-F-Bn	**2.4.2.2.8** (84%)[a]	**2.4.2.3.8** (na)[c,d]
9	$(CH_2)_3OCH_3$	*p*-CF_3-Bn	**2.4.2.2.9** (89%)[a]	**2.4.2.3.9** (66%)[d]
10	Bn	*p*-CF_3-Bn	**2.4.2.2.10** (35%)[a]	**2.4.2.3.10** (12%)[d]
11	Bn	*o*-F-Bn	**2.4.2.2.11** (14%)[a]	**2.4.2.3.11** (na)[c,d]
12	^{t}Bu	Bn	**2.4.2.2.12** (74%)[b]	**2.4.2.3.12** (88%)[d]
13	^{t}Bu	*p*-CF_3-Bn	**2.4.2.2.13** (87%)[b]	**2.4.2.3.13** (72%)[d]
14	^{t}Bu	*p*-CH_3-Bn	**2.4.2.2.14** (66%)[a]	**2.4.2.3.14** (73%)[c]
15	^{t}Bu	*o*-F-Bn	**2.4.2.2.15** (57%)[a]	**2.4.2.3.15** (75%)[c]
16	^{t}Bu	*p*-OCH_3-Bn	**2.4.2.2.16** (78%)[b]	**2.4.2.3.16** (84 %)[d]
17	^{t}Bu		**2.4.2.2.17** (65%)[a]	**2.4.2.3.17** (79%)[c]
18	^{t}Bu	$(CH_2)_2OCH_3$	**2.4.2.2.18** (78%)[a]	**2.4.2.3.18** (81%)[c]
19	^{t}Bu	$(CH_2)_2OCOCH_3$	**2.4.2.2.19** (96%)[a]	**2.4.2.3.19** (84%)[c]
20	^{t}Bu		**2.4.2.2.20** (81%)[a]	**2.4.2.3.20** (85%)[c]
21	^{t}Bu	$CyCH_2$	**2.4.2.2.21** (78%)[a]	**2.4.2.3.21** (88%)[c]
22	^{t}Bu		**2.4.2.2.22** (88%)[a]	**2.4.2.3.22** (86%)[c]
23	*L*-Val•OMe	*p*-CF_3-Bn	**2.4.2.2.23** (70%)[a]	**2.4.2.3.23** (60%)[d]
24	*L*-Val•OMe	*o*-F-Bn	**2.4.2.2.24** (74%)[a]	**2.4.2.3.24** (89%)[e]
25	*L*-Val•OMe	*p*-OCH_3-Bn	**2.4.2.2.25** (83%)[b]	**2.4.2.3.25** (73%)[d]
26	*L*-Leu•OMe	*p*-CF_3-Bn	**2.4.2.2.26** (63%)[b]	**2.4.2.3.26** (64%)[d]
27	*L*-Leu•OMe	*o*-F-Bn	**2.4.2.2.27** (80 %)[a]	**2.4.2.3.27** (na)[e]
28	*L*-Leu•OMe	*p*-F-Bn	**2.4.2.2.28** (74%)[a]	**2.4.2.3.28** (78%)[d]

29	*L*-Leu•OMe	*p*-OCH_3-Bn	**2.4.2.2.29** (78%)[a]	**2.4.2.3.29** (71%)[d]
30	*L*-Ile•OMe	*p*-CF_3-Bn	**2.4.2.2.30** (79%)[b]	**2.6.3.30** (72 %)[d]
31	*L*-Ile•OMe	*p*-F-Bn	**2.4.2.2.31** (78 %)[a]	**2.6.3.31** (61 %)[d]
32	*L*-Ile•OMe	*p*-OCH_3-Bn	**2.4.2.2.32** (83%)[a]	**2.6.3.32** (87 %)[d]
33	*L*-Phe•OMe	*m*-F-Bn	**2.4.2.2.33** (49%)[a]	**2.6.3.33** (71 %)[d]

[a]**Condition D.1 for click:** $CuSO_4 \cdot 5H_2O$, (+)-Sodium *L*-ascorbate, *t*-BuOH/CH_2Cl_2/H_2O (1:1:1), room temperature, 12 h. [b]**Condition D.2 for click**: $Cu(OAc)_2 \cdot H_2O$, PPh_3, toluene, microwave, 100 °C, 1 h. [c]**Condition E.1 for C-vinylation**: $Pd(PPh_3)_4$, KOAc, DMF, 100 °C, 12 h. [d] **Condition E.2 for C-vinylation**: $Pd(PPh_3)_4$, KOAc, DMF, microwave, 100 °C, 1 h

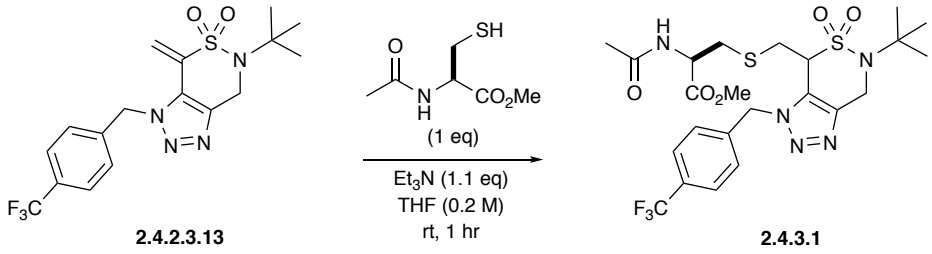
While the overnight copper-click and refluxing *C*-vinylation conditions worked satisfactorily, more rapid microwave-assisted methods were developed for both CuAAc and *C*-vinylation reactions. Microwave click methodology [68] consisted of alkyne sulfonamide **2.4.1.5**, dissolved in 0.2 M anhydrous toluene, followed by the addition of 1 equivalent of azide, 10 mol% of copper (II) acetate, and 10 mol% of triphenylphosphine. The reaction was then microwaved at 100 ºC for an hour, affording product 4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide with comparable yields and greatly reduced reaction times. The applicability of the intramolecular triazole *C*-vinylation was further increased by the substrate **2.4.2.2** compatibility with a microwave-mediated *C*-vinylation. [69] This reaction consisted of dissolving α-bromo-triazole sulfonamide **2.4.2.2** in 0.05 M DMF followed by the addition of KOAc, and $Pd(PPh_3)_4$ in a microwave reaction vial that was next irradiated at 100 ºC for an hour. Comparable

yields were found between the microwave and conventional heating *C*-vinylation methods.

Despite large substrate scope, some SMs proved incompatible with either *C*-vinylation methods, for reason not apparently clear at this time. These products consisted of *L*-leucine or ether derived amines combined with azide coupling partners generated from *p*-Me and *o*-F benzyl bromides. Despite repeated attempts, these intermediates never formed the required sultam via the *C*-vinylation reaction.

Next, the electrophilic nature of these sultams was probed by examining a representative compound for thiol reactivity. Sultam **2.4.2.3.13** was dissolved in THF with an equivalent of *N*-Ac-Cys-OMe and 1.1 equivalents of Et_3N. The reaction was stirred for an hour before purification on normal phase silica to afford thiol adduct **2.4.3.1** (**Scheme 2.4.3**). However, when the reaction was monitored by proton NMR, the disappearance of exo-cyclic vinyl peaks can be observed within five minutes, suggesting this thiol Michael addition is quite rapid.

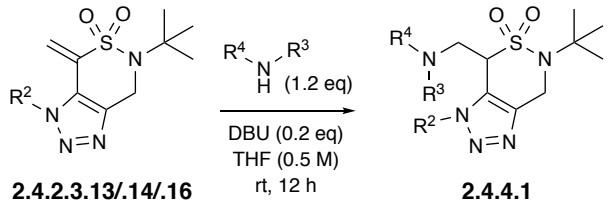
Scheme 2.4.3. Synthesis of Sultam-thiol adduct via thiol-Michael addition.



After showing these sultams are capable of rapid thiol addition, we sought to attenuate the electrophilic reactivity. In order to accomplish this, we performed an aza-Michael addition into a small subsection of the original library (**Scheme 2.4.4**). This 'masking' of the *exo*-cyclic Michael acceptor stands to fundamentally alter the reactivity of our sultam probe in chemical biology assays. There are examples of masked or latent

Michael acceptors in the literature where such chemical modifications have transformed the reactivity of natural products and pro-drugs.[70]

Scheme 2.4.4 Aza-Michael reaction on 4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide derivatives.

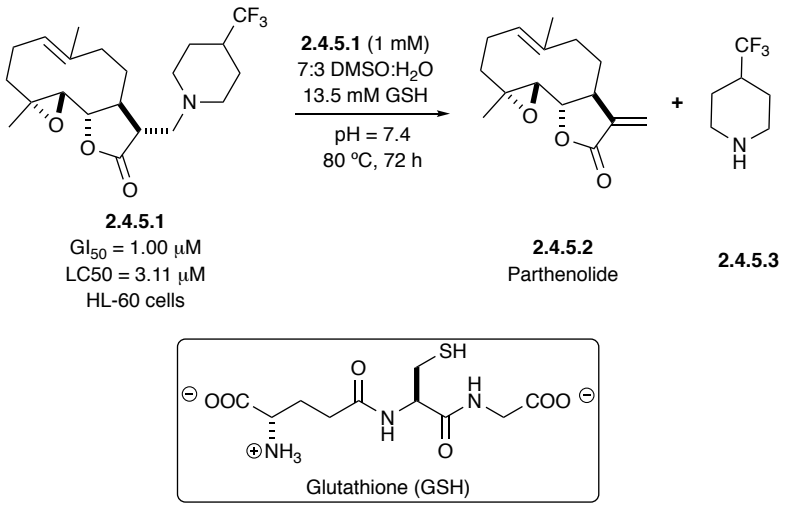


2.4.2.3.13/.14/.16 **2.4.4.1**

Amine (R^3/R^4)	R^2		
	p-CF_3-Bn	Bn	*p*-OMe-Bn
Morpholine	**2.4.4.1.1** (96 %)	**2.4.4.1.5** (96 %)	**2.4.4.1.9** (90 %)
Piperidine	**2.4.4.1.2** (72 %)	**2.4.4.1.6** (93 %)	**2.4.4.1.10** (84 %)
$BnNH_2$	**2.4.4.1.3** (95 %)	**2.4.4.1.7** (80 %)	**2.4.4.1.11** (95 %)
^{i}Pr-NH_2	**2.4.4.1.4** (99 %)	**2.4.4.1.8** (49 %)	**2.4.4.1.12** (60 %)

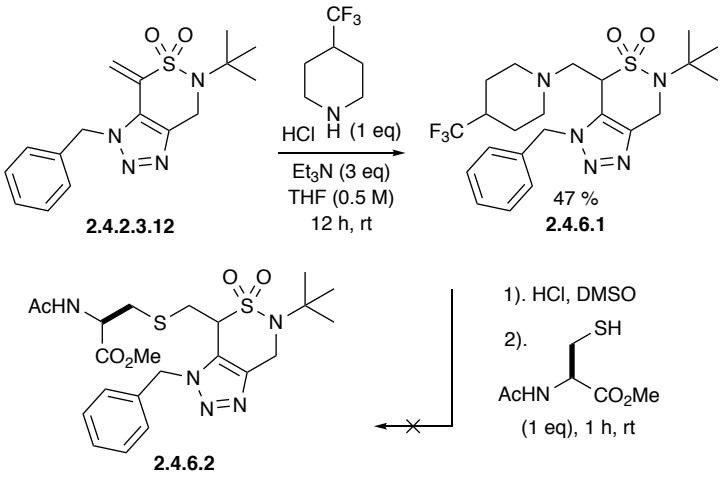
In 2011, Colby and co-workers, illustrated how under near physiological conditions, an amino-masked parthenolide underwent a retro aza-Michael reaction in the presence of glutathione (GSH) to unveil the original α,β-unsaturated methylene-γ-lactone motif.[71] This retro-aza Michael reaction was more rapid in the presence of GSH than in its absence, leading Colby and co-workers to imply that an amino-masked Michael acceptor could be activated in the presence of a biological thiol (**Scheme 2.4.5**). This strategy has been explored in numerous medicinal chemistry manuscripts in an attempt to attenuate chemical reactivity and medicinal properties.[72]

Scheme 2.4.5 Colby and co-workers retro aza-Michael of parthenolide.



In order to examine the possibility of the amino-masked α,β-unsaturated sultam undergoing a retro aza-Michael in the presence of a thiol, product **2.4.6.1** was dissolved in DMSO, before the addition of an equivalent 1 M HCl and *N*-Ac-Cys•OMe (**Scheme 2.21**). Despite overnight stirring and gentle heating, no product was observed after normal phase chromatography. This preliminary result suggests the amino masked sultam probes may be less activated for retro-aza-Michael than their carbon analogs, presumable due to the uniquely different properties of a sultam,[73] when compared to a *C*-sp^2 lactam or lactone structure. It is possible that differences sultam pKa, electronic properties and the inherent sp^3 geometry of the SO_2N warhead reinforce each other in such a way that makes retro-aza Michael unfavorable. Efforts to further explore these masked systems are in progress and will be reported in due course.

Scheme 2.4.6. Attempted un-masking of aza-Michael acceptor and subsequent thiol Michael addition.



The above dissertation work involved the development of a scalable six-step synthesis consisting of copper catalyzed azide to alkyne click chemistry and a novel palladium mediated intramolecular α-bromo vinyl-to-triazole cyclization. The method is amenable to both conventional and microwave irradiation, with achiral and chiral products generated in good yields. The potential for rapid thiol reactivity was illustrated and tempered by masking the Michael acceptor with amines. Acid-mediated unmasking was preliminarily examined however, no product was found, alluding to the possibility that these amino adducts are more stable than their carbon analogs.

In conclusion, a scalable six-step synthesis utilizing copper catalyzed azide-to-alkyne click chemistry and Pd-mediated intramolecular vinyl-to-triazole cyclization was utilized to generate novel α-methylene, δ-sultams, namely 4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxides. The intermolecular click reaction, followed by a *C*-vinylation of a triazole to a *C*-sp^2 vinyl carbon, can be thought of as an alternative to IM click cyclization, and affords the possibility of further chemical

diversification. This method is amenable to both conventional and microwave irradiation and provided a range of products in good yields. These attenuated α,β unsaturated sultams were ultimately designed to be utilized as chemical probes for ABPP and chemical biology assays, in hope of uncovering biological reactivity in medicinally relevant systems.

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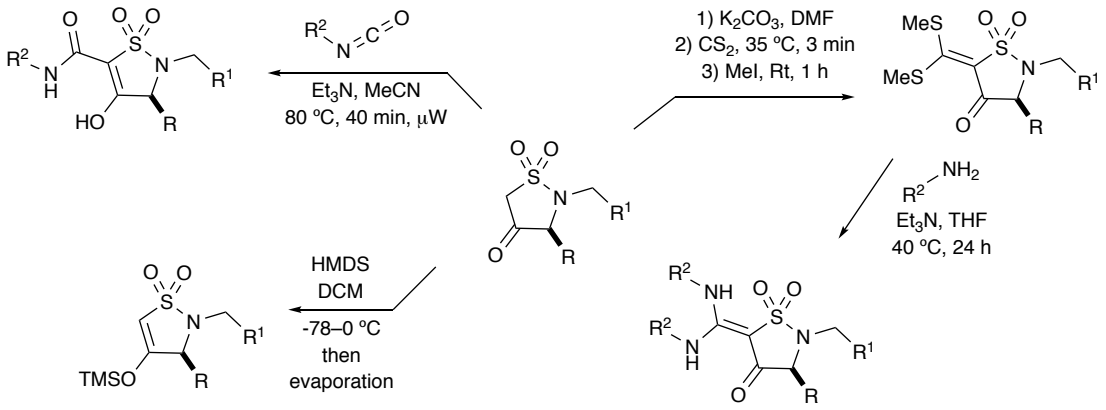
Chapter 3:
Synthesis of Analogs of the Core Scaffold: Isothiazolidin-4-one 1,1-dioxide

Section 3.1 *Tetramic Acid Natural Products and Synthesis*

Tetramic acids are a well-known class of natural products and a privileged scaffold in medicinal chemistry. Many tetramic acids hold promising antibacterial and antifungal activity, motivating the development of rapid and scalable syntheses of these natural products, as well as non-natural synthetic analogs for screening in drug and chemical biology assays. Despite a number of synthetic efforts and a vast array of biological data pertaining to tetramic acids; the sultam analogs of tetramic acids, β-keto sultams, (analogs of isothiazolidin-4-one 1,1-dioxide), are far less prevalent in the literature, thus warranting the current body of work. Furthermore, use of β-keto sultams in chemical biology for the discovery and elucidation of novel biological reactivity is void in the literature.

This chapter focuses on the development and α-functionalization of β-keto sultams (analogs of isothiazolidin-4-one 1,1-dioxide) for eventual use in chemical biology assays. The development of these analogs of isothiazolidin-4-one 1,1-dioxide β-keto sultams will aid in addressing the ever-present need for novel and functionalizable biomimetic chemical probes for elucidating novel bio-reactivity. The use of α-functionalization enables further probe diversification, and is frequently found in natural tetramic acids themselves. **Figure 3.1.1** illustrates the disclosed synthetic efforts towards α-functionalization of β-keto sultams.

Figure 3.1.1. Reported dissertation work towards α-functionalization of β-keto sultams



Exo-enol tetramic acids are well represented in nature, and can be isolated from a wide variety of terrestrial and marine bacteria, fungi and sponges.[1] Naturally occurring tetramic acids arise from a mixed polyketide synthase and non-ribosomal peptide synthetase (PKS-NRPS) pathways. The keto tautomer is usually the predominate form. Many tetramic cores are substituted with an acyl group at the 3 position, with an amino acid derivative usually occupying the 5 position.[1] **Figure 3.1.2** shows the possible interconverting tautomers commonly seen in tetramic acids, a property which gives rise to a natural affinity to metals such as Fe^{3+}, Zn^{2+}, and Cu^{2+}.[1]

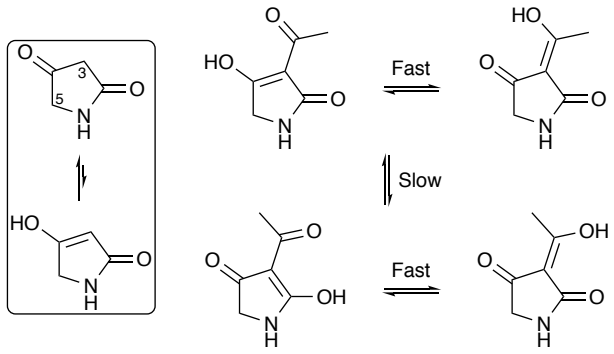


Figure 3.1.2. Tetramic core and tautomers.

One of the most well-known exo-enol tetramic acids is *L*-tenuazonic acid isolated from the phytopathogenic fungi *Alternaria alternate* the culprate behind brown leaf spot

on *Eupatorium adenophorum*.[2] *L*-tenuazonic itself is a photosynthesis inhibitor known to block the electron flow from QA to QB in photosystem II acceptor sites, and thereby cause cell necrosis via chloroplast-mediated reactive oxygen species.[3] Melophlin B is known to display cytotoxic activity against HL60, HeLa and TF-1 cells, and is capable of reverting *ras*-transformed NIH3T3 cells to their "normal" state at concentrations of 5 μg mL^{-1}, in addition to arresting the same cell line at the G1 phase at 1 μg mL^{-1}.[4]

The 3-decalinoyltetramic acid family member Equisetin was isolated from Fusarium equisetin and displays biological activity ranging from antibiotic activity, HIV inhibition, cytotoxicity and mammalian DNA binding.[5] Related compound paecilosetin was isolated from the fungus *Paecilomyces farinosus* and displays cytotoxic activity against leukemia P388 cells with an IC_{50} of 3.2 μg mL^{-1}, in addition to antibacterial and antifungal activity.[6] This class of tetramic acids also includes Sch213766 a potent chemokine receptor CCR-5 inhibitor with an IC_{50} of 8.6 μM.[7b]

Sugars are a reasonably common substituent among tetramic acids.[1] Amycolamicin (AMM) was discovered in the broth of a soil *actinomycete Amycolatopsis* sp MK575-fF5, and contains the unusual sugars amycolose and amykitanose. AMM is a specific inhibitor of bacterial type II topoisomerase, inhibiting *E. coli* DNA gyrase with an IC_{50} of 24.4 ng mL^{-1}. Furthermore, AMM did not inhibit human type II topoisomerase and is thought to possess a binding mode different to that of coumarin and quinolone antibiotics.[8]

Tirandamycin B contains both an exo-enol tetramic core and a bicyclic ketal structure. It was isolated from *S. flaveolus* and has a modest IC_{50} of 30 μM against *Brugia malayi* asparaginyl-tRNA synthetase (AsnRS). *Brugia malayi* worms cause River

Blindness Disease, and Tirandamycin B was found to kill adult worms *in vitro* with an IC_{50} of 1 μM. The *in vitro* activity, as well as the 10-fold selectivity for nematode over human AsnRS, suggests Tirandamycin B could be a promising anti-filarial lead.[9]

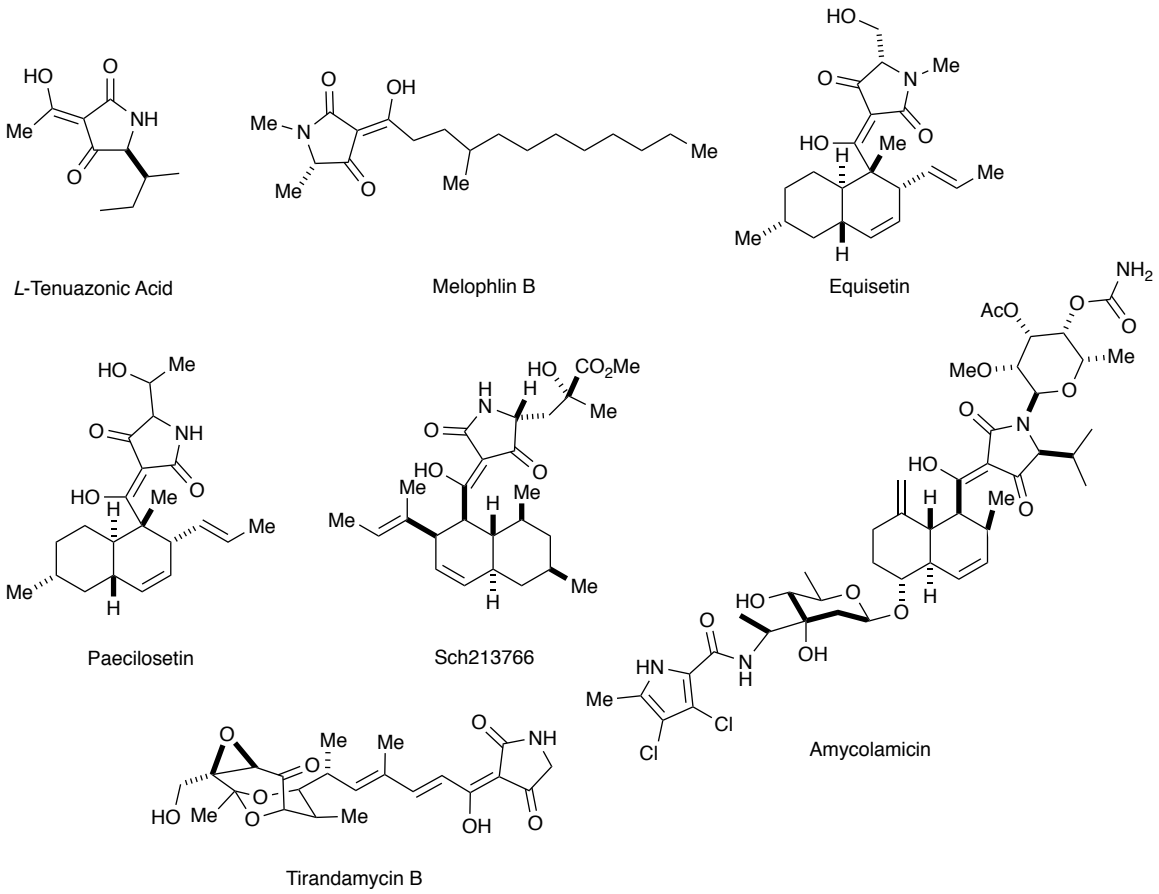


Figure 3.1.3. Natural products with exo-enol tetramic acid core.

The large scaffold diversity found in exo-enol tetramic acid natural products have given rise to many synthetic efforts,[10] particularly in recent years as more biological activity has been found.[1,11] A summary of several standard methods to 3-acyltetramic acids (3ATs) as put forth by the Schobert group,[10b] can be seen in **Figure 3.1.4**.

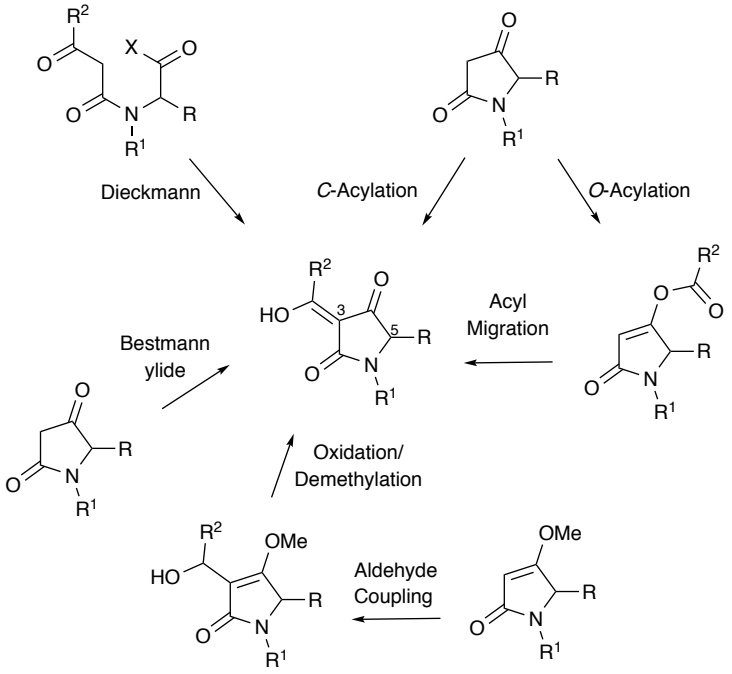


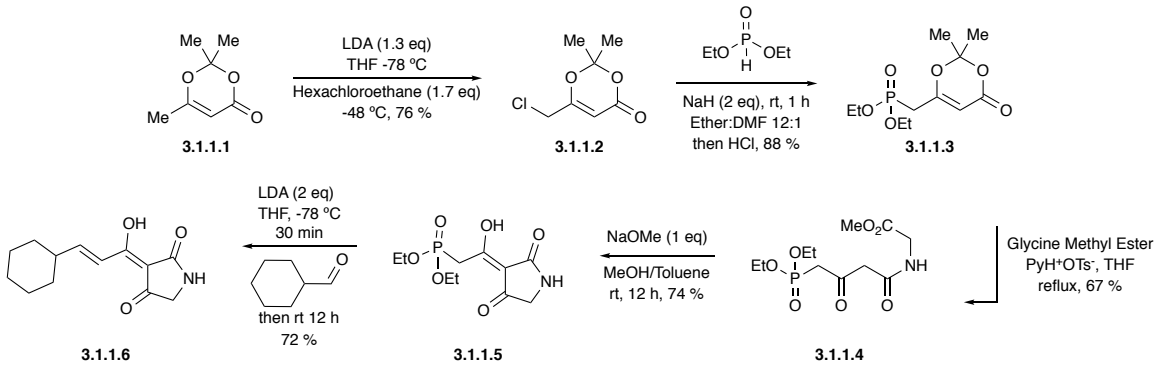
Figure 3.1.4. Common synthetic routes to 3-acyltetramic acids

The Dieckmann cyclization is a well-known method for intramolecular cyclization, and prominent in tetramic acid synthesis. Boeckman and co-workers utilized an intramolecular Lacey-Dieckmann cyclization [12] followed by Horner-Wadsworth-Emmons reaction in order to generate non-natural tetramic acids. [13] **Scheme 3.1.1** illustrates the use of a protected phosphonate as a starting point for 3At synthesis. This phosphonate underwent mild acid catalyzed amidation, followed by Lacey-Dieckmann cyclization to derive the acyl tetramic acid core. The core was then subjected to LDA mediated Horner-Wadsworth-Emmons reaction to generate a cyclohexane substituted non-natural 3Ats.

These conditions improved the synthetic toolbox for tetramic acid natural product synthesis, and can be thought of as the precursor to the Bestmann ylide tetramic acid chemistry. The Boeckamn group also utilized a *tert*-butoxide intramolecular Dieckmann

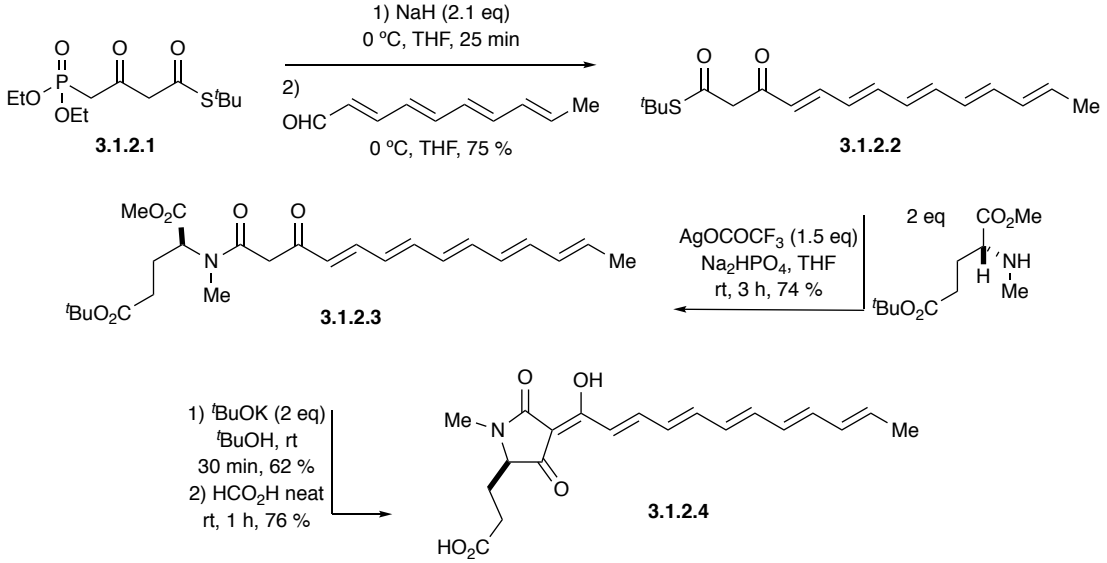
cyclization for the formation of the 3Ats core in the enantioselective synthesis of (+)-Ikarugamycin.[14]

Scheme 3.1.1 Use of Lacey-Dieckmann by Boeckman, followed by HWE.



The Ley group also developed Dieckmann routes to 3Ats.[15] One of their most notable efforts in this area can be seen in the synthesis of Fuligorubin A. **Scheme 3.1.2** illustrates the use of *t*butyl-4-diethylphosphono-3-oxobutanethioate and deca-2,4,6,8-tetraenal coupling in conjunction with a glutamic acid derivative to arrive at Fuligorubin A.

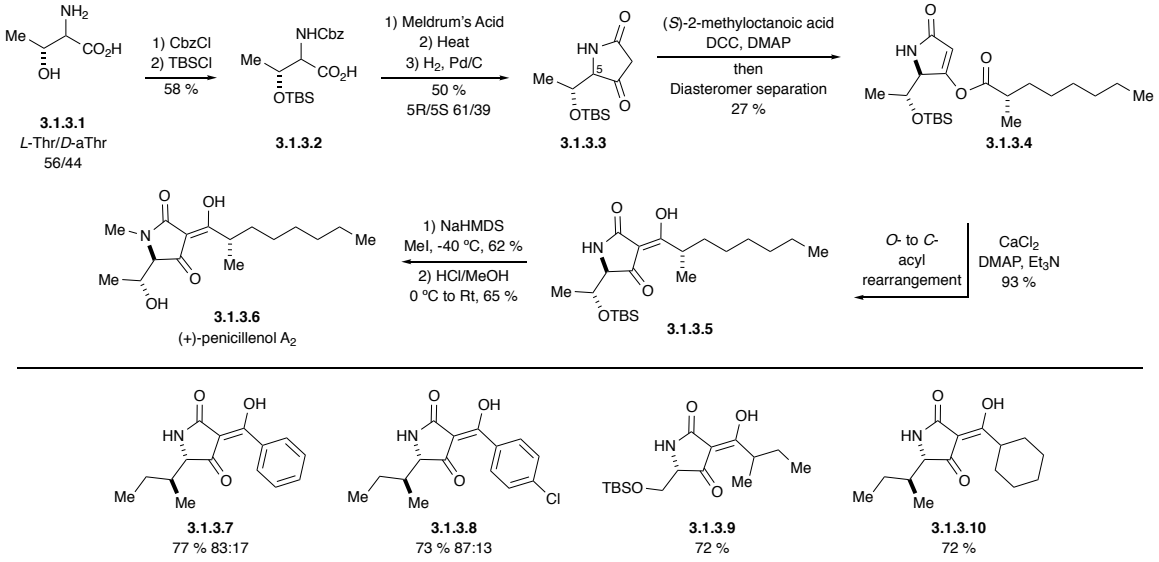
Scheme 3.1.2. Ley group tert-butoxide intramolecular Dieckmann on β-ketoamides.



Stoichiometric silver(I) trifluoroacetate was necessary for β-ketoamides formation, while *tert*-butoxide formed the 3 acyl tetramic acid core. Deprotection of the ^{t}Bu group with formic acid then unveiled the natural product.[16]

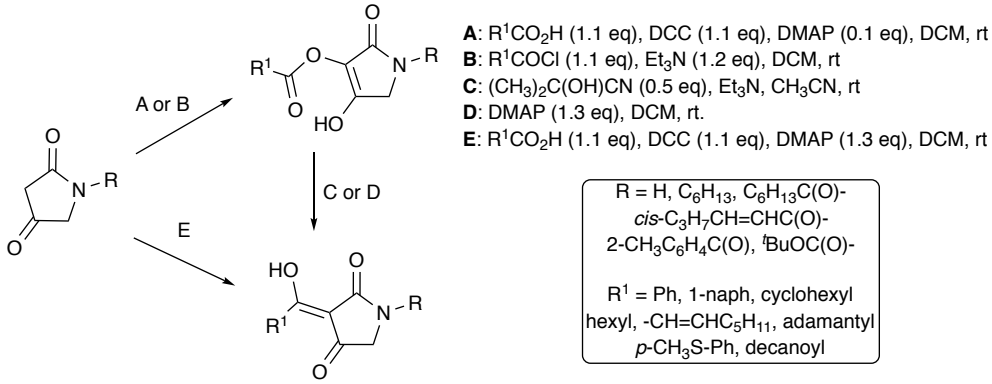
Yoda and co-workers used *O*-acylation followed by an *O*- to *C*-acyl rearrangement to generate penicillenol A_1[17] and penicillenol A_2.[18] These two natural products are cytotoxic to HL-60 cell with an IC_{50} of 0.76 μM and 16.26 μM respectively, and were discovered in endophytic fungus *Penicillium* sp. GQ-7.[19] The Yoda group synthesis began with protecting group installation, followed by Meldrum's acid-derived tetramic acid core cyclization then Pd-mediated deprotection. An *O*- to *C*-acyl rearrangement with DCC and DMAP with $CaCl_2$ to suppress racemization was used to form the core and 3Ats side-chain. Finally, *N*-methylation and TBS deprotection afforded (+)-penicillenol A_2. Furthermore, Yoda and co-workers also utilized this powerful method, to generate a library of small 3Ats from isoleucine, TBS-protected threonine and serine, phenylalanine, and alanine. Carboxylic acid *O*-coupling partners included alkanes, cycloalkanes, benzyl and halogen-substituted benzyl groups (**Scheme 3.1.3.**).[18] This method has also generated the tyrosine-derived antibacterial 3AT Epicoccarine A.[20]

Scheme 3.1.3. Yoda's *O*- to *C*-acyl rearrangement to natural and un-natural 3Ats



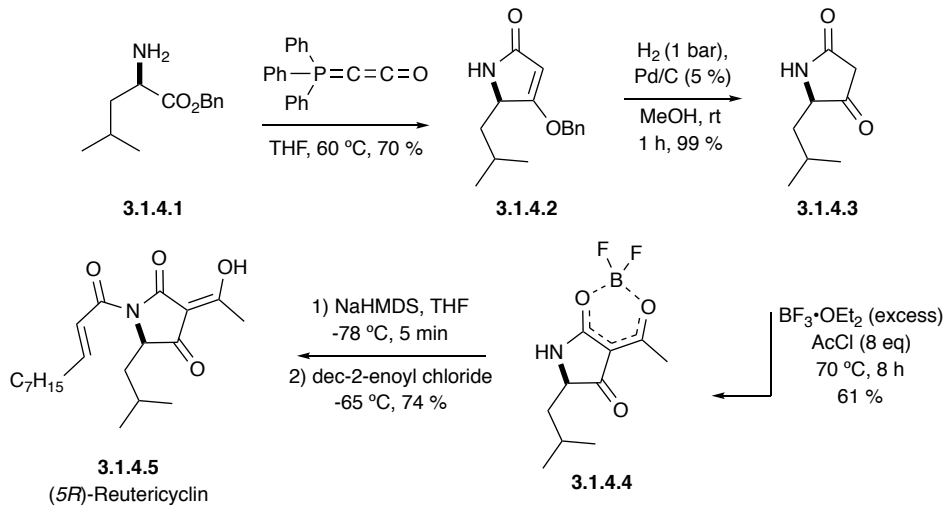
Moloney and co-workers have also performed significant work on the formation of synthetic 3Ats (**Figure 3.1.5**).[21] Traditional coupling conditions for carboxylic acids with DCC and catalytic DMAP were shown to afford the *O*-Acyl products in yields up to 77 %. The use of acid chlorides and triethylamine also produced product in up to 95 % with fewer by-products. A Fries-type acyl migration was then shown to proceed with the addition of acetone cyanohydrin and triethylamine, or in the presence of excess DMAP. This led to the development of a procedure utilizing excess DMAP which was capable of directly generating 3-Ats in yields of up to 77 %.

Figure 3.1.5. Moloney group routes to synthetic 3-Ats



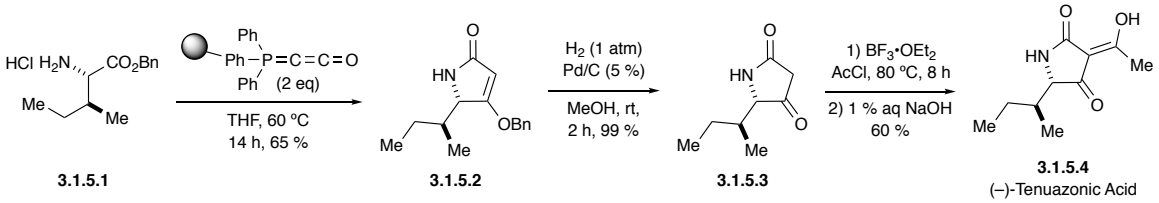
The Schobert group has made use of the use of Bestmann ylide method for a powerful and robust tetramic acid synthesis.[22] The importance of this method to the field of 3-Ats natural product generation is best demonstrated by three total syntheses completed by Schobert and coworkers. [23] The 1,3-bis-acylated tetramic acid, Reutericyclin, was isolated from *Lactobacillus reuteri*[24] and is active against the ulcer-causing bacteria *Helicobacter pylori* plausibly due to its proton-ionophoric nature.[25] **Scheme 3.1.4** illustrates the formation of a leucine-derived tetramic acid via Bestmann ylide addition and subsequent elimination of triphenylphosphine oxide. Deprotection, and BF_3•OEt_2 mediated acylation affords the 3-acyl tetramic acid, which is then *N*-acylated to generate (*5R*)-Reutericyclin in good yield.[22]

Scheme 3.1.4. Synthesis of (*5R*)-Reutericyclin utilizing the Bestmann ylide.



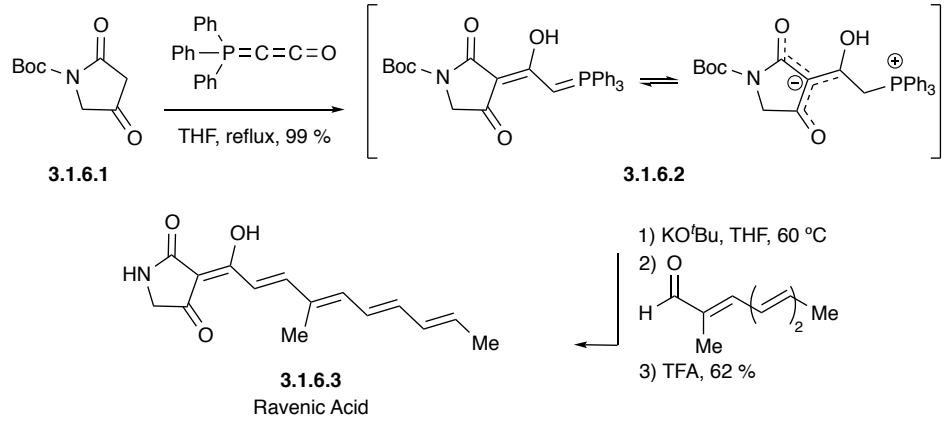
An immobilized Bestmann ylide also proved efficient in tetramic acid formation, and was used to generate the isoleucine-derived tenuazonic acid.[26] This three-step method proved analogous to the synthesis of (*5R*)-Reutericyclin, with debenzylation, and boron-induced acylation as the final reaction (**Scheme 3.1.5**).

Scheme 3.1.5. Three step synthesis of Tenuazonic Acid



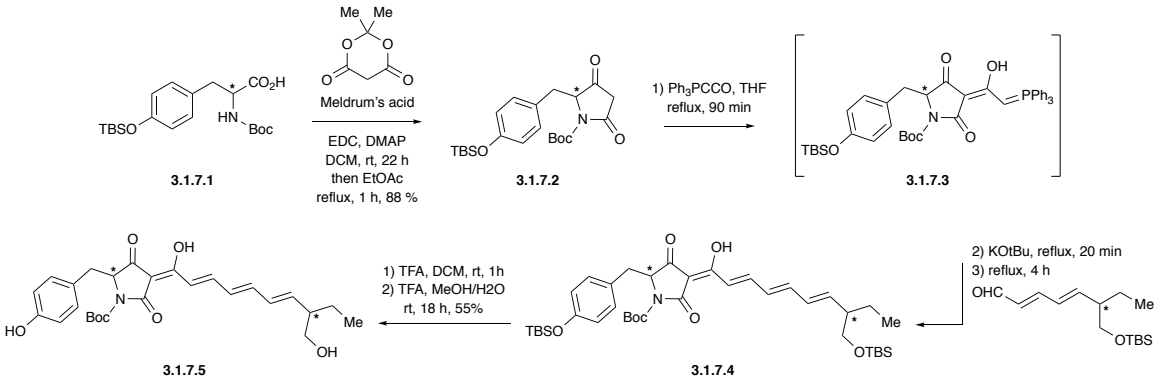
The above natural product synthesis utilizes the Bestmann ylide to generate the tetramic core, however the true power of this reagent in 3-Ats synthesis lies in its ability to act as a Wittig intermediate. **Scheme 3.1.6** shows a glycine-derived tetramic core undergoing an addition into the ylide to form a stable 3-(triphenylphosphoranylidene)acetyl intermediate. These intermediates can exit as a mix of ylide and betaine forms, and must be deprotonated with potassium *tert*-butoxide before undergoing *E*-selective Wittig reaction. Thus, the highly unsaturated tetramic acid Ravenic acid was generated, by Wittig addition elimination into (2*E*,4*E*,6*E*)-2-methylocta-2,4,6-trienal.[27]

Scheme 3.1.6. Synthesis of Ravenic acid using a Wittig method.



A mix of the Meldrum's acid tetramic core formation and Wittig side-chain differentiation was used to generate the four diastereomers of Torrubiellone D (**Scheme 3.1.7**)[28] The most laborious section of this route was the construction of the aldehyde coupling partner, itself a ten-step protocol.

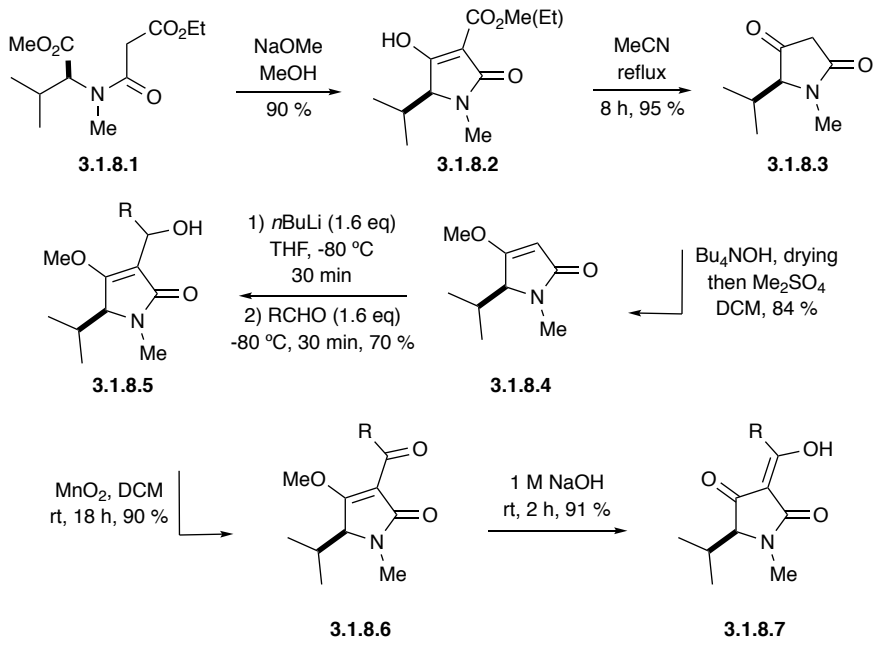
Scheme 3.1.7. Synthesis of Torrubiellone D diastereomers



The diastereomers of Torrubiellone D were found to have weak antibiotic activity against gram-positive *Staphylococcus aureus* and *Enterococcus faecium*. Wild-type *E. coli* was also not susceptible due to insufficient penetration through the outer LPS layer. However, when the four diastereomers of Torrubiellone D were tested against *E. coli* lacking a TolC efflux pump, or had a truncated LPS layer, an IC_{50} of 35 μM was seen for the (5R)-isomers; showing Torrubiellone D is bioactive but requires modifications to enter a cell.

The final well-known synthetic route to 3-Ats is one of the oldest, and consists of aldehyde coupling followed by oxidation and demethylation. **Scheme 3.1.8** shows a 3-acyl tetramic acid synthetic pathway as developed by Jones and co-workers.[29] Here, Dieckmann cyclization affords a mixture of ethyl and methyl esters, which is then subjected to hydrolysis and decarboxylation in refluxing acetonitrile, in order to afford the tetramic core. This valine-derived core was dried with tetrabutylammonium salt and methylated with Me_2SO_4. The α–position was then deprotonated with *n*BuLi and mixed with an aldehyde (benzaldehyde, heptanal, *E*-2-butenal or *E,E*-2,4-hexadienal) to afford the alcohol product. This alcohol was immediately oxidized and subjected to NaOH-mediated demethylation generating 3-At products.

Scheme 3.1.8. Synthesis of 3 Ats via aldehyde addition and oxidation/demethylation.

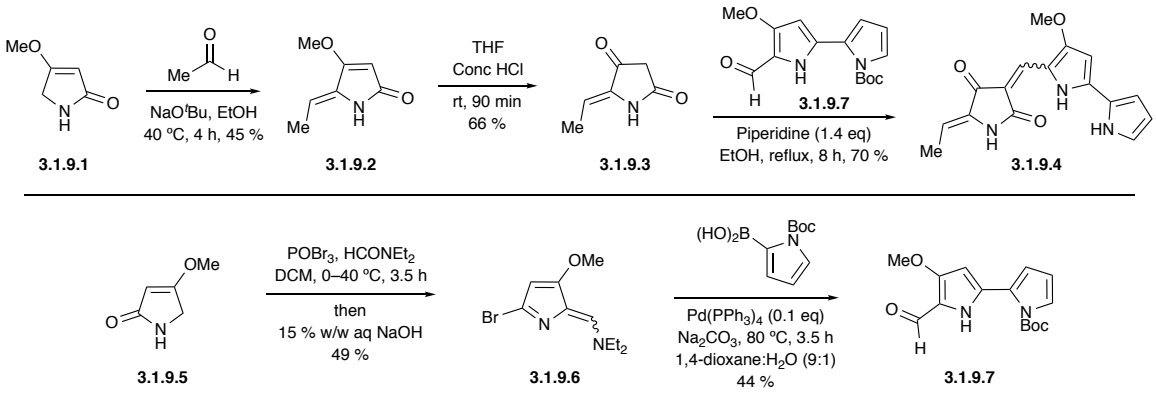


The first total synthesis of novel exo-methylene containing tetramic acid Hybrubin A was also accomplished via a piperidine-mediated Aldol condensation seen in **Scheme 3.1.9**.[30] Treatment of the methyl enol tetramic core with acetaldehyde and sodium *tert*-butoxide selectively installed a *Z*-olefin. This scaffold was subjected to demethylation with HCl in order to generate the reactive α-CH bond needed for the Aldol condensation. This synthesis afforded Hybrubin A, in 20 % overall yield, by a shortest linear three step sequence containing only 20.5 total hours of chemistry.

This robust method allowed for biological testing of Hybrubin A. Remarkably, a 10 μM sample of this tetramic acid was not cytotoxic after 48 hours of incubation in HCT-116 cells. Furthermore, Hybrubin A was active against only 4 of 68 available targets in a radioligand binding assay. These hits were adenosine receptors A_1, A_{2a}, and A_3, the last of which had a binding of 54 nM. Furthermore, a wild-type and mutant kinase screen also showed Hybrubin A was selective, as it reduced the enzymatic activity of

only 7 out of a possible 369 kinases. Moreover, nanomolar potency was found against FLT3, an acute myeloid leukemia target,[31] with an IC_{50} = 505 nM. This led Lindsley and co-workers to postulate that Hybrubin A could be an attractive lead compound.

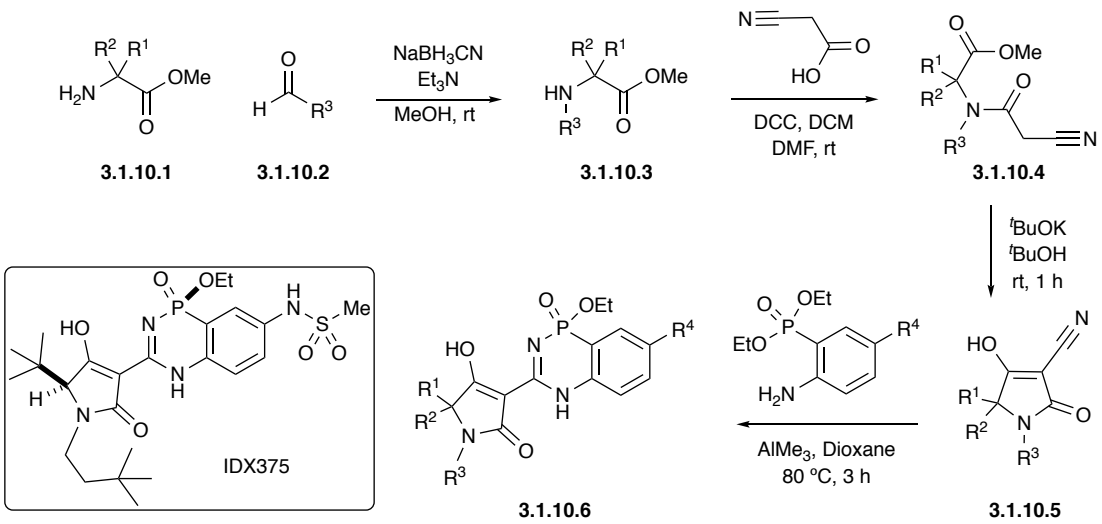
Scheme 3.1.9. Synthesis of Hybrubin A



In more recent years there has been a renewed interest in tetramic acids and sultams as antiviral compounds. Although effective HCV treatment exists, viral mutation and drug resistance remains a threat. Furthermore, HCV related viruses such as Dengue and Zika, constitute a substantial world health burden.[32] To this end, two 2017 publications by Idenix pharmaceuticals detailed the use of bioisosterism between sulfonamides and phosphonamides resulting in the generation of NS5B inhibitors (**Scheme 3.1.10**). The generation of racemic inhibitors provided low μM inhibition against HCV genotypes 1a and 1b. The top racemic hit possessed an EC_{50} of 0.009 μM in a Luciferase HCV replicon assays as well as an IC_{50} of 0.059 and 0.012 μM against genotypes 1a and 1b respectively. Idenix then separated this compound into the four possible diastereomers. This led to the now discontinued clinical candidate IDX375 that possessed an (*S*, S_p) configuration. While this candidate was discontinued in favor of pan-genotype inhibitors, once again the use of tetramic acid derivatives in conjunction with

sulfonamides and now benzophosphadiazine proved valuable in the study of critical biopathways.[33]

Scheme 3.1.10. Idenix 2017 Bioisosterism synthesis and NS5B inhibitor IDX375.



Another Idenix publication was released along with the synthesis and bioactivity of IDX375, and disclosed the generation of molecules for the companies HCV polymerase inhibitor program. While no biological data was provided this short communication highlighted the generation of 1,5,2-diazaphosphinines by combining amidine with 1-alkynylphosphonates or dithioketene phosphonates. **Figure 3.1.6** shows examples of these compounds, which possess not only a tetramic acid, but also a potentially electrophilic α–β unsaturated moiety.[34]

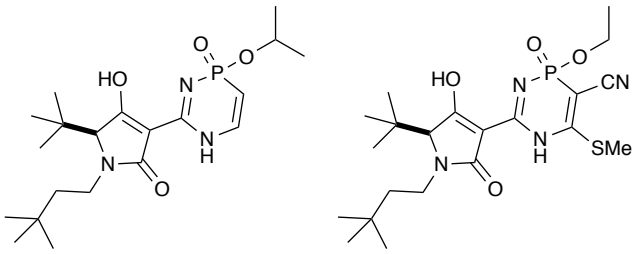
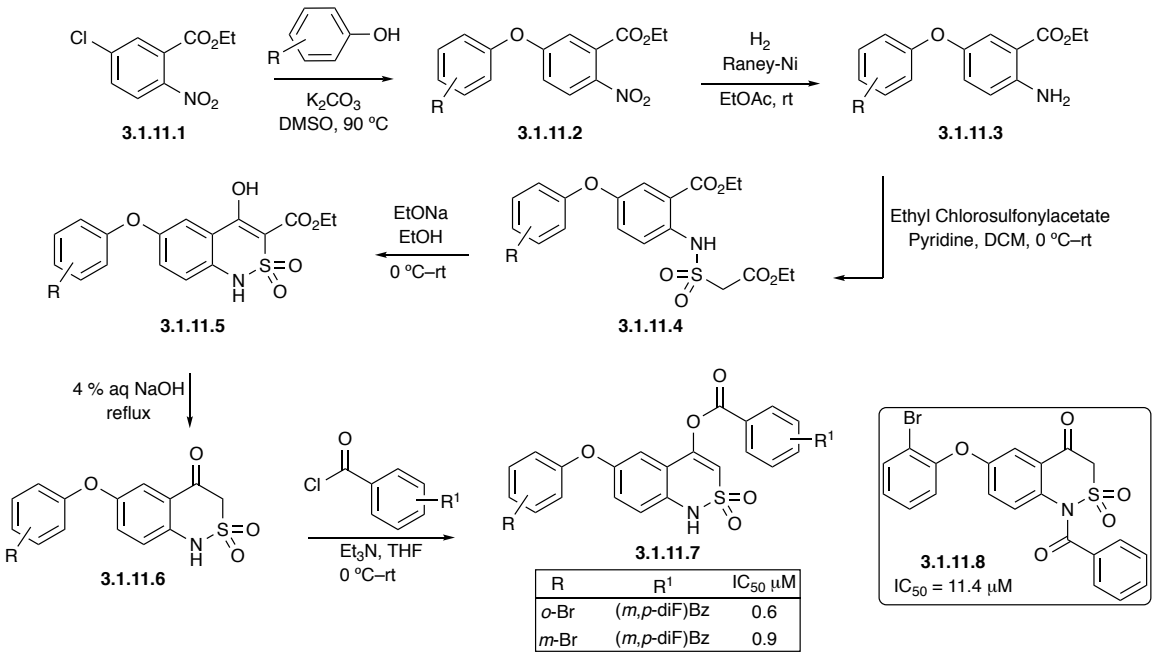


Figure 3.1.6. Idenix additions to in-house HCV polymerase inhibition program.

The massive potential tetramic acids and sultams hold for antiviral research was again shown in 2018, when Italian and French scientists published work on a Dengue virus (DENV) inhibitor.[32] A close relative of HCV, the Dengue virus is the most common mosquito transferred virus and affects around 390 million people a year. There are four distinct types of Dengue all of which are dependent on the NS5 RNA-dependent RNA polymerase.

Scheme 3.1.11 shows the synthesis of these 2,3-dihydro-4H-1,2-benzothiazin-4one 1,1-dioxide derived compounds, as well as a keto-tautomer,[35] also found to have intriguing activity against DENV3 NS5 RdRp. The two best enolic inhibitors possessed an IC_{50} of 0.6 and 0.9 μM inhibition against DENV3 NS5 RdRp, while the keto tautomer displayed an activity of 11.4 μM. Interestingly, when the sultam core was replaced with a comparatively less enolizable 2,3-dihydroquinoline scaffold, the inhibitory activity rose to above 50 μM indicating the importance of the sultam core. *In silico* modeling suggested that one of the sulfonamide oxygens of the core was in a direct interaction with Ser710.

Scheme 3.1.11. Synthesis and activity of 2,3-dihydro-4H-1,2-benzothiazin-4one 1,1-dioxide core scaffolds and keto tautomer.



R	R^1	IC_{50} μM
o-Br	(*m*,*p*-diF)Bz	0.6
m-Br	(*m*,*p*-diF)Bz	0.9

While these sultams were shown to be bona-fide inhibitors via negative tests for assay interference and aggregation, the *in vivo* activity has yet to bear fruit. Attempts to inhibit DENV2 and DENV3 within Vero E6 cells showed no anti-viral activity, possibly due to membrane sequestration, thus further development and exploration is needed.[32]

Section 3.2 *Enamine Tetramic Acids*

Although there is a plethora of literature highlighting the use of both intra- and exo-cyclic enolic α–β unsaturated tetramic acids in natural products, synthesis and biology, very little exploration has been done on the enamine counterparts. Indeed, a July 2, 2019 Scifinder search on the phrase "enamine tetramic acid" returned only four references.[36] Furthermore, enamine tetramic acid natural products are rare.[37] **Figure 3.2.1** shows known enamine tetramic acids. Fischerellin A, a natural product derived from the cyanobacteria *Fisherella muscicola,* has been shown to be a potent photosystem II inhibitor, with a 60 % photosynthesis inhibition and a total of 44 % grow inhibition against the common duckweed *Lemna minor*. Fungicidal activity for Fischerellin A includes the total growth inhibition against *Uromyces appendiculatus* (bean brown rust), and *Erysiphe graminis* (barley powdery mildew).[38]

Cladosin C, another rare enamine tetramic acid, was isolated in 2014 from the deep-sea fungus *Cladosporium sphaerospermum* 2005-01-E3, and shows an IC_{50} of 276 μM against the influenza A H1N1 virus.[39] Finally a derivative of Cyclopiazonic acid, α-cyclopiazonic acid-imine (α-CPA-imine), is a third example of the incredibly rare enamine tetramic acid.[40] Although nature is not yet known to generate much in the way of enamine tetramic acid natural products, new research is beginning to uncover exciting possibilities for these scaffolds in the realm of synthetic biology (*vide infra*).[41]

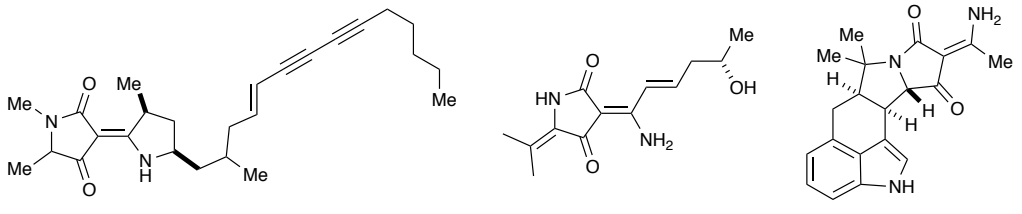
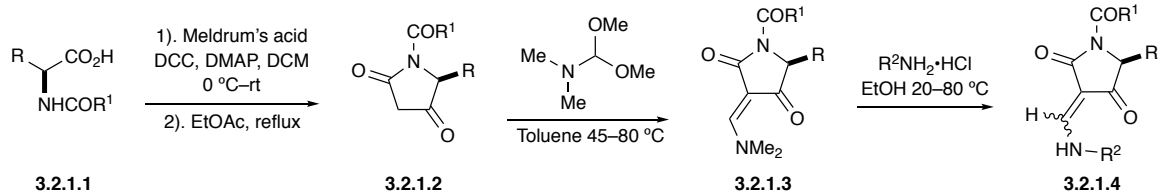


Figure 3.2.1. Rare natural enamine tetramic acids.

A 2004 review on ex-chiral pool enaminones highlighted the synthesis of Meldrum's acid-derived enamine tetramic acids (**Scheme 3.2.1**). NMR analysis of final enamine product **3.2.1.4** showed a mix of major (*Z*)-isomers and the minor (*E*)-isomer, despite the immediate precursor dimethylamine **3.2.1.3** existing and the single (*E*)-isomer.[42]

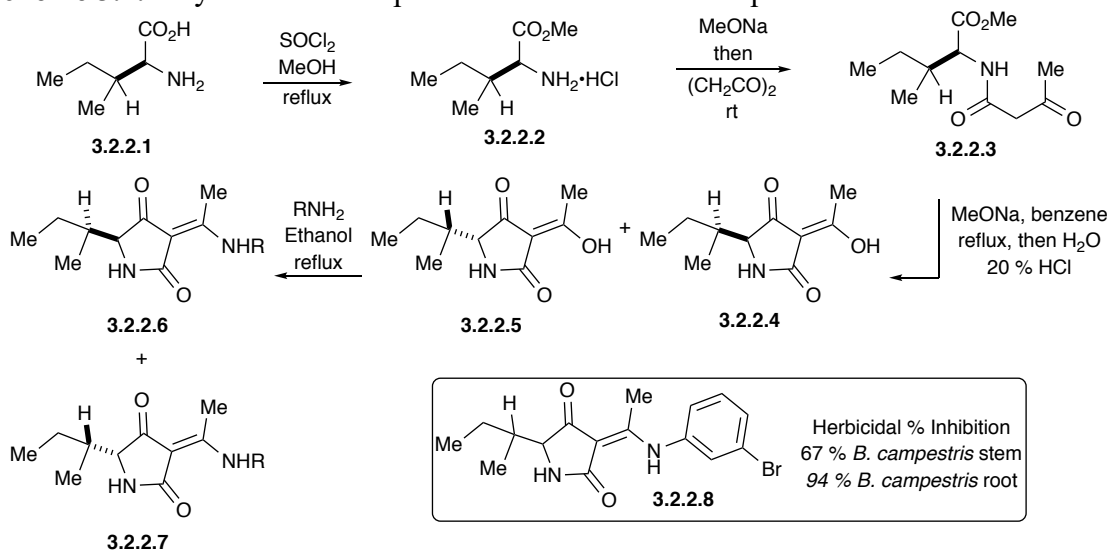
Scheme 3.2.1 Synthesis of enamine tetramic acids via chiral pool



Compound	R	R^1	R^2	% yield
1	Bn	*O*-^{t}Bu	CH_2CO_2Me	88
2	Bn	*O-Bn*	CH_2CO_2Me	75
3	H	CH_2NHCO_2Bn	CH_2CO_2Me	35
4	Bn	*O*-^{t}Bu	Ph	87
5	Bn	*O-Bn*	Ph	83
6	H	CH_2NHCO_2Bn	Ph	92

A 2010 publication by Yang and co-workers highlighted the synthesis of 5-*sec*-butyl-3-(1substituted amino)ethylidene-1*H*-pyrrolidine-2,4-diones, along with the related anti-fungal and herbicidal activities. A twenty-five membered library was constructed via esterification, *N*-aceto-acetylation and a cyclization, which resulted in epimerization. Subsequent ethanolic reflux in the presence of an amine resulted in the formation of inseparable mixture of enamine products (**Scheme 3.2.2**).

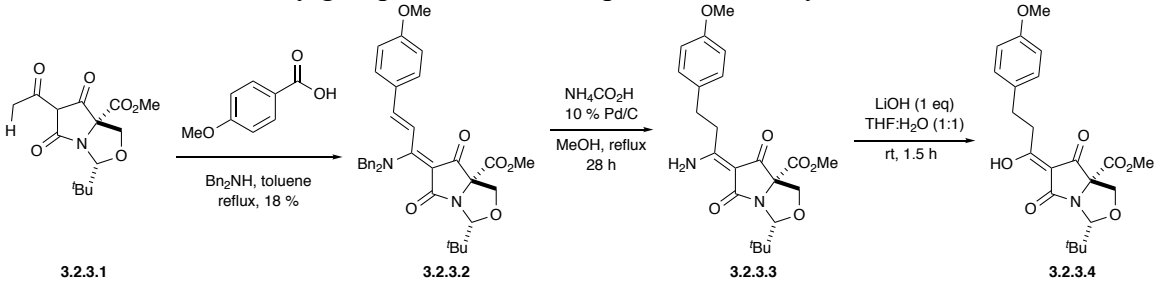
Scheme 3.2.2. Synthesis of inseparable mono-enamine compounds



These enamine tetramic products possessed a herbicidal activity of up to 94 % growth inhibition against *Brassica campestris* as well as moderate activity against *Echinochloa crusgalli* or barnyard grass. Compound **3.2.2.8** also exhibited a growth inhibition of 70 % against the fungus *B. cinerea*.[43] This same team of researchers followed up in a 2016 publication with additional 3-ETs showing growth rate inhibitions ranging from 45–82 % for the fungi *F. graminearaum*, *B. cinerea*, *R. solani*.[44]

Moloney and co-workers disclosed the synthesis of 3-acyltetramates via an enamine intermediate.[45] As seen in **Scheme 3.2.3**, acetic acid substituted tetramic core **3.2.3.1** was treated with 4-methoxybenzoic acid, in the presence of dibenzylamine, to afford dibenzyl enamine **3.2.3.2** in low yield. This enamine was constructed as starting material for a two-step hydrogenolysis and hydrolysis protocol used to generate the enone tetramic acid **3.2.3.4**, a derivative of the difficult to build[46] β-tricarbonyl systems.

Scheme 3.2.3. Moloney group side chain manipulation to 3-acyltetramates



A concurrent study in the Moloney lab was performed on the SAR and antibiotic activity of 3-enaminetetramic acids. These analogs show the same type of tautomeric nature as their 3-acyltetramic acid counterparts. **Figure 3.2.2** illustrates the imine and enamine possibilities for these scaffolds.[47] The predominate tautomers of 3-enaminetetramic acids are the enamine forms B and D.

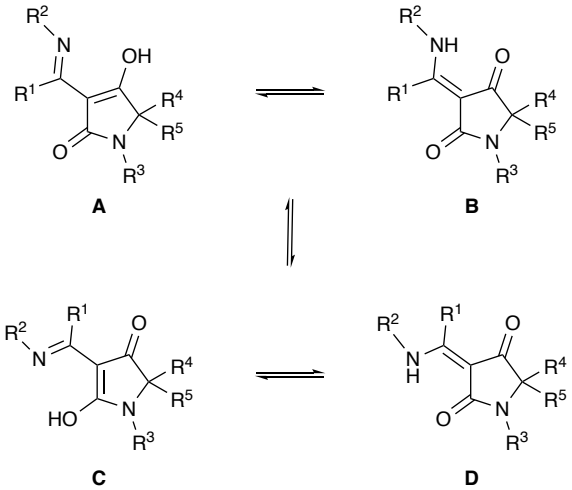
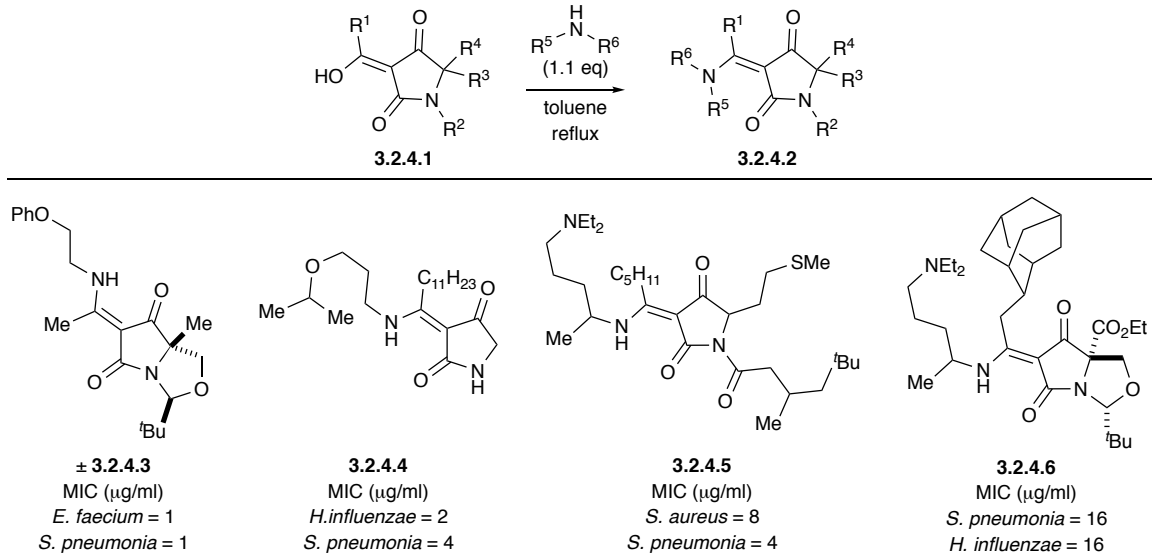


Figure 3.2.2 Tautomerism of 3-enaminetetramic acids, with B & D predominant.

The Moloney group synthesis was straightforward and is shown in **Scheme 3.2.4**. This simple direct nucleophilic attack was used to construct a library of 58 products, which were tested for antibiotic activity; the best results are shown in **Scheme 3.2.4**. While some biological activity was found against organisms such a *H. influenzae*, and *S. pneumonia*, the majority of analogs lacked potent activity. This was correlated with the

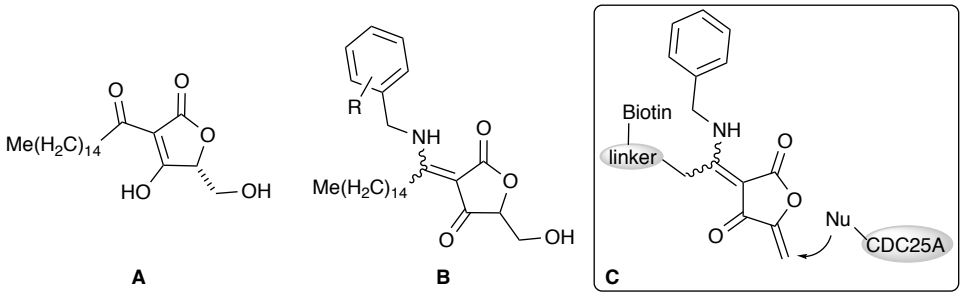
rather lipophilic nature of tetramic enamines, which is contrary to the typically polar attributes found in most known antibacterial compounds.[47]

Scheme 3.2.4 Moloney anti-bacterial activity of 3-enaminetetramic acids



A 2015 manuscript by Hirai and Sodeoka focused on uncovering inhibitors for dual-specificity protein phosphatases (DSPs).[48] DSPs are capable of dephosphorylating both phosphotyrosine and phosphoserine/threonine on the same proteins.[49] The authors began with a 3-acyltetronic acid, as this structure resembled that of the transition state in the dephosphorylation reaction of DSPs. However, the library derived from this scaffold yielded no selective inhibitors. This, in combination with the weak *in cellulo* activity inherent to acidic and poorly permeable nature of 3-acyltetronic acid, prompted the authors to alter the library in favor of a neutral enamine scaffold. This alteration improved cell permeability, and selectivity but altered the mode of action as well. The 3-acyltetronic acid derivates were found to be a competitive inhibitor of the DSP VHR, while the enamine analogs were shown to bind to a neighboring pocket of the DSP CDC25A. This pocket contains the residues C384, R385 and Y386 near the bottom.

Enamine **C** of **Table 3.2.1** was found to bind covalently to one of these residues, with the cysteine put forward as the most promising nucleophile. These enamine scaffolds were the first inhibitors shown to bind to the pocket and not active site of CDC25A. This change in the mechanism of inhibition accounts for the alterations in activity seen in **Table 3.2.1**. The enamines also possessed inhibitory activity against HL60 cells, the best of which was enamine **B** (R = *o*-OH) at 2.4 μM, while 3-acyltetronic acid **A** was over 100 μM.



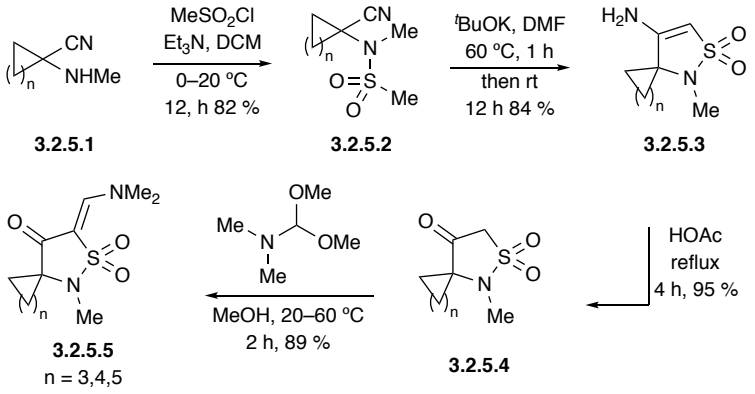
DSP Inhibitor	Tetronic acid **A**	Enamine **B** R = H	Enamine **B** R = *m*-Me	Enamine **B** R = *o*-OH
VHR	4.9 μM	11.4 μM	1.6 μM	24.9 μM
CDC25A	6.2 μM	16.6 μM	>100 μM	13.5 μM
CDC25B	5.3 μM	8.4 μM	>100 μM	4.3 μM
MKP-3	4.3 μM	>100 μM	>100 μM	>100 μM

Table 3.2.1. Hirai and Sodeoka enamine DSP library

Ukrainian and French researchers disclosed a synthesis of sultam enamine tetramic cores in 2017.[50] These spirocycloalkane 1λ^6-isothiazolidine-1,1,4-triones were constructed via mesylation, alkylation and *tert*-butoxide mediated cyclization. As seen in **Scheme 3.2.5** this work, while limited in substrate scope made use of enamine tetramic

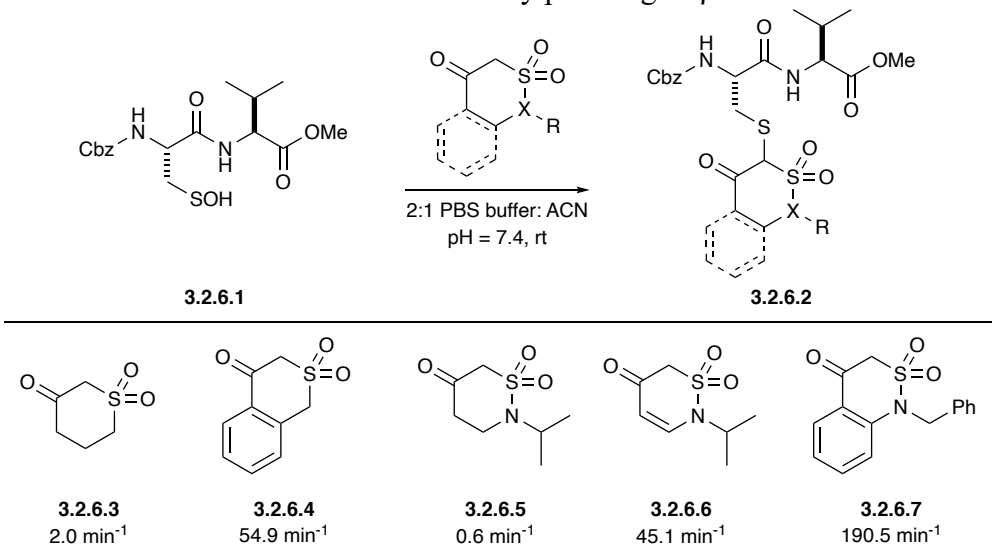
acids not only as a synthetic intermediate in route to the core, but as an end product themselves.[51]

Scheme 3.2.5. Synthesis of spirocycloalkane 1λ^6-isothiazolidine-1,1,4-triones



In 2016, Carroll and co-workers reported a mass spectrometry-based assay designed to screen a library of cyclic *C*-nucleophilies, including dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide derivatives, for reactivity with a dipeptide sulfenic acid.[52] **Scheme 3.2.6** highlights these sulfur-functionalized carbon nucleophiles undergoing a dehydration-like reaction with sulfenic acid compound **3.2.6.1** under near physiological conditions. This work highlights the use of β-keto sultams in reactivity profiling. These sultams were found to have enhanced reactivity when compared to dimedone analogs. The Carroll group postulated this reactivity was do to the destabilization of the carbanion via reduced resonance into the sulfur, and the non-planer ring characteristics of sultams.

Scheme 3.2.6. Carroll and co-workers reactivity profiling of β-keto sultams.



Just as chemical synthesis begins to explore enamine tetramic acids, so has the field of synthetic biology. Zhang, Li, and co-workers disclosed a series of noteworthy aniline substituted tetramic acids in 2018.[41] Cladosins H-K (**Figure 3.2.3**) were isolated from a culture of *Cladosporium sphaerospermum* L3P3, a fungus found in the Mariana Trench at a depth of 6562 meters underwater. Remarkably, these tetramic acids were found after an epigenetic modification designed to inhibit histone deacetylase (HDAC) was utilized. Standard laboratory conditions are known to suppress some secondary metabolite biosynthetic gene clusters, causing non-standard and novel methods such as HDAC inhibition to be used in an attempt to discover new "natural products."[53]

The HDAC modifiers themselves can be degraded and metabolized by the organism to generate a new scaffold, via the process of biotransformation.[54] Thus, incubation experiments with exogenous aniline and *N*-phenyloctanamide lead Zhang, Li, and co-works to postulate that the metabolism of HDAC inhibitor Suberanilohydroxamic acid (SAHA) provided an aniline moiety capable of reacting with polyketides in a

nucleophilic non-enzymatic process to form enamine tetramic acids.[41] Cladosin I was found to be cytotoxic against HL-60 cells with an IC_{50} of 2.8 μM.

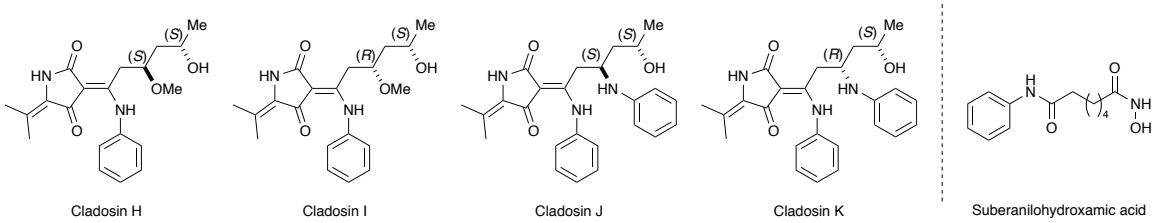


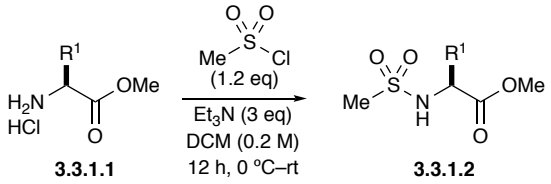
Figure 3.2.3. Cladosins H–K along with aniline donor and HDAC inhibitor SAHA

Section 3.3 *Synthesis of isothiazolidin-4-one 1,1-dioxides and 5-(diaminomethylene)isothiazolidin-4-one 1,1-dioxide Derivatives*

The above review showcased natural products containing tetramic acids, along with the common methods for tetramic acid synthesis. Furthermore, the unique chemical niche for sultams and tetramic acids was discussed in a brief synopsis of HCV drug development. The use of novel non-natural sultam-derived tetramic acids (β-keto sultams) as chemical biology probes has to the best of the author's knowledge yet to be established. Therefore, the disclosed dissertation work details the use of Dieckmann cyclization followed by α-functionalization in order to generate α,β-unsaturated β-keto sultams, including enamine derivatives, for use as chemical probe molecules.

The dissertation work began with the synthesis of sulfonamides **3.3.1.2.1**–**3.3.1.2.3** as seen in **Scheme 3.3.1**. An amino methyl ester was dissolved in dry methylene chloride and brought to 0 °C before the drop-wise addition of methanesulfonyl chloride. This sulfonylation reaction was allowed to warm to room temperature and stirred overnight, before being subjected to an aqueous work-up followed by normal-phase silica column chromatography purification. The amino esters of *L*-leucine, *L*-isoleucine and *L*-alanine were chosen due to the presence of these amino acids in natural products such as Reutericyclin, Tenuazonic Acid and Fischerellin A.

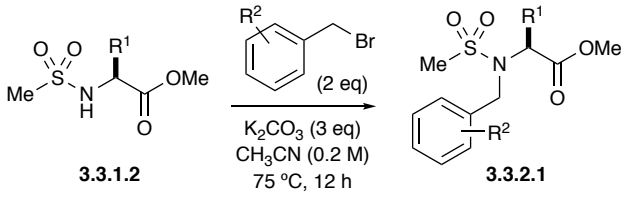
Scheme 3.3.1 Yields of Mesylated amino esters



Entry	Amino ester R^1	Yield
1	*L*-Leucine	**3.3.1.2.1** 89 %
2	*L*-Isoleucine	**3.3.1.2.2** 98 %
3	*L*-Alanine	**3.3.1.2.3** 19 %

The formation of mesyl-amino esters **3.3.1.2.1–3.3.1.2.3** afforded both the Dieckmann cyclization nucleophile (SO_2Me) as well as the methoxy leaving group. However, the Dieckmann was delayed in order to increase diversity, and avoid potential cross-reactivity with the relatively acidic NH. A simple *N*–benzylation reaction was utilized to accomplish both goals. This *N*–benzylation involved dissolving mesyl-amino esters **3.3.1.2.1–3.3.1.2.3** in acetonitrile, followed by the addition of potassium carbonate, and drop-wise addition of the desired benzyl bromide. The resulting mixture was refluxed at 75 °C overnight. The carbonate was then filtered off and the resulting residue was condensed and purified via normal phase silica column chromatography. **Scheme 3.3.2** highlights the diversification and yields of the pre-cyclization intermediates **3.3.2.1.1–3.3.2.1.10**

Scheme 3.3.2 Synthesis of *N*-benzylated intermediates.

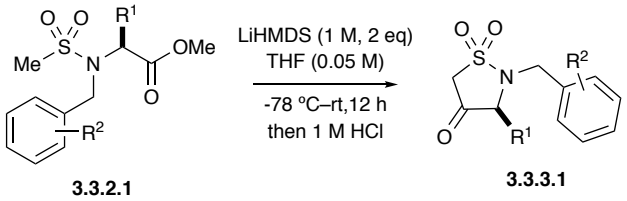


Entry	R1	R2	Yield
1	*L*-Leu	*p*-CF_3	**3.3.2.1.1** 81 %
2	*L*-Leu	*p*-F	**3.3.2.1.2** 76 %
3	*L*-Leu	*o*-Cl	**3.3.2.1.3** 86 %
4	*L*-Leu	H	**3.3.2.1.4** 87 %
5	*L*-Leu	*p*-Me	**3.3.2.1.5** 72 %
6	*L*-Ile	*p*-F	**3.3.2.1.6** 78 %
7	*L*-Ile	*o*-Cl	**3.3.2.1.7** 90 %
8	*L*-Ile	H	**3.3.2.1.8** 63 %
9	*L*-Ile	*p*-Me	**3.3.2.1.9** 87 %
10	*L*- Ala	*p*-F	**3.3.2.1.10** 81 %

Next, the Dieckmann cyclization was achieved with the use of slow addition of a LiHMDS-THF into a solution of intermediates **3.3.2.1.1–3.3.2.1.10** at -78 °C. The reaction was allowed to warm overnight to room temperature before being cooled to 0 °C and 1 M HCl was added until the pH = 3. The solvent was then removed by rotary evaporation, and the aqueous layer was extracted with methylene chloride and washed brine. The organic layers were combined, dried with (Na2SO4) and the solvent was

removed under reduced pressure to afford β-keto sultams **3.3.3.1.1–3.3.3.1.9** in yields up to 95 %. Interestingly, the *L*-alanine derivative **3.3.2.1.10** failed to cyclize.

Scheme 3.3.3 Synthesis of isothiazolidin-4-one 1,1-dioxides derivatives



3.3.2.1 3.3.3.1

Entry	R^1	R^2	Yield
1	*L*-Leu	*p*-CF_3	**3.3.3.1.1** 41 %
2	*L*-Leu	*p*-F	**3.3.3.1.2** 82 %
3	*L*-Leu	*o*-Cl	**3.3.3.1.3** 95 %
4	*L*-Leu	H	**3.3.3.1.4** 74 %
5	*L*-Leu	4-Me	**3.3.3.1.5** 28 %
6	*L*-Ile	4-F	**3.3.3.1.6** 25 %
7	*L*-Ile	*o*-Cl	**3.3.3.1.7** 72 %
8	*L*-Ile	H	**3.3.3.1.8** 81 %
9	*L*-Ile	4-Me	**3.3.3.1.9** 77 %
10	*L*- Ala	*p*-F	na

After the formation of isothiazolidin-4-one 1,1-dioxides derivatives **3.3.3.1.1–3.3.3.1.9** experimentation towards generating enamine α,β-unsaturated β-keto sultams began. Three initial synthetic routes were designed. The first pathway involved the installation of an α-ketone via direct acylation, followed by amine addition and tautomerization. The second route consisted of coupling chemistry followed by amine

addition,[47] while the third pathway made used of an aldol addition, followed by oxidation,[55] amine addition and tautomerization (**Figure 3.3.1**).

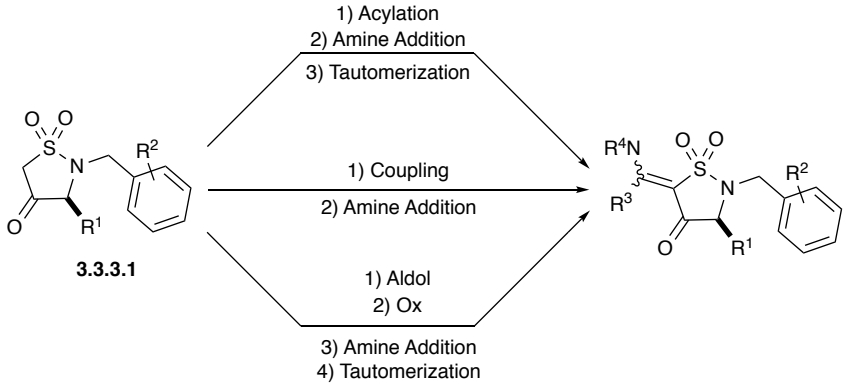


Figure 3.3.1 Initial proposed routes to enamine sultam products.

First, simple α-functionalization was attempted with simple acyl chlorides.[56] **Figure 3.3.2** shows four representative trials. Unfortunately, BF_3•OEt_2 returned only starting material, while Et_3N and acryloyl chloride afforded only a mass spectra trace of the desired product. Switching electrophiles or attempting to trap the alcohol adduct generated by 4-methoxybenzoyl chloride with TBSCl showed only degradation.

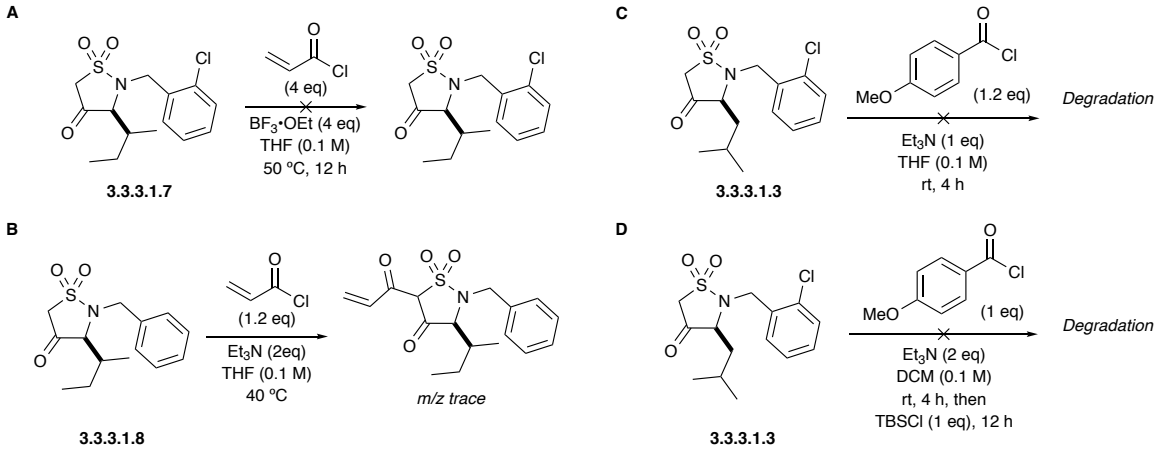
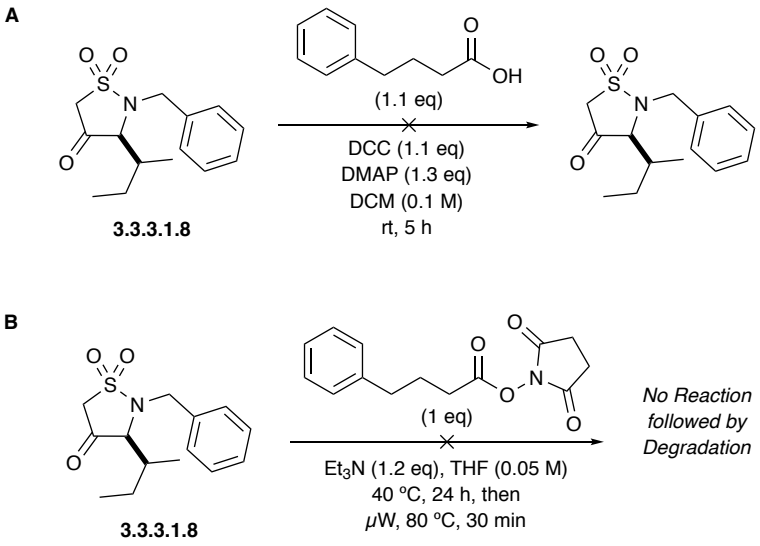


Figure 3.3.2 Attempts at α-functionalization with acyl chlorides

Since α-functionalization by substitution with acyl chlorides failed, coupling chemistry reminiscent of the Yoda[17,18,20] and Moloney[11,21,45-47] chemistry was attempted.

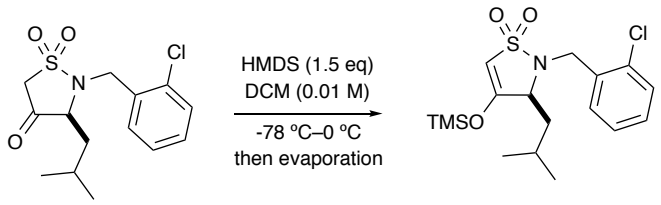
However, DCC- or EDC-mediated coupling failed, as did combining β-keto sultam **3.3.3.1.8** with a preformed coupling intermediate. Forcing conditions such as microwave heating showed only starting material degradation. Indeed, after multiple reactions only starting material or unidentifiable degradation material was isolated. Thus, coupling chemistry was also abandoned.

Figure 3.3.3. Coupling attempts for α-functionalization



With the failures of simple acyl installation, and traditional tetramic acid coupling chemistry, synthetic efforts turned towards the well-known Mukaiyama aldol reaction.[57] This reaction was chosen in an attempt to avoid degradation by stepwise silyl enol ether formation, and to prevent retro-aldol by trapping the resulting product as a Lewis acid adducts. A reliable method for the formation of an *endo*-cyclic enol sultam intermediate was therefore required. A little utilized method for generating TMS-enol ethers from a 1,3-cyclohexanedione core, disclosed by Chu and Huckin,[58] was found to generate product in quantitative yields.

Scheme 3.3.4 Generation of TMS protected enolic β-keto sultams



3.3.3.1.3

3.3.4.1
Quantitative

Scheme 3.3.4 shows the formation of silyl enol ether **3.3.4.1**. β-keto sultam **3.3.3.1.3** was dissolved in methylene chloride and brought to -78°C before drop-wise addition of HMDS. The reaction was allowed to warm to 0°C before solvent and volatile HMDS by-product removal via rotary evaporation. The mechanism proposed by Chu and co-workers involved α-deprotonation, and enol protection by HMDS itself. This method proved extremely reliable and generated product cleanly in quantitative yield. However, the scaffold itself was highly labile, and was prone to desilylation if not immediately utilized. Thus **Figure 3.3.4** shows a representative proton NMR of silyl enol ether **3.3.4.1** as evidence for the existence of this class of protected β-keto sultams.

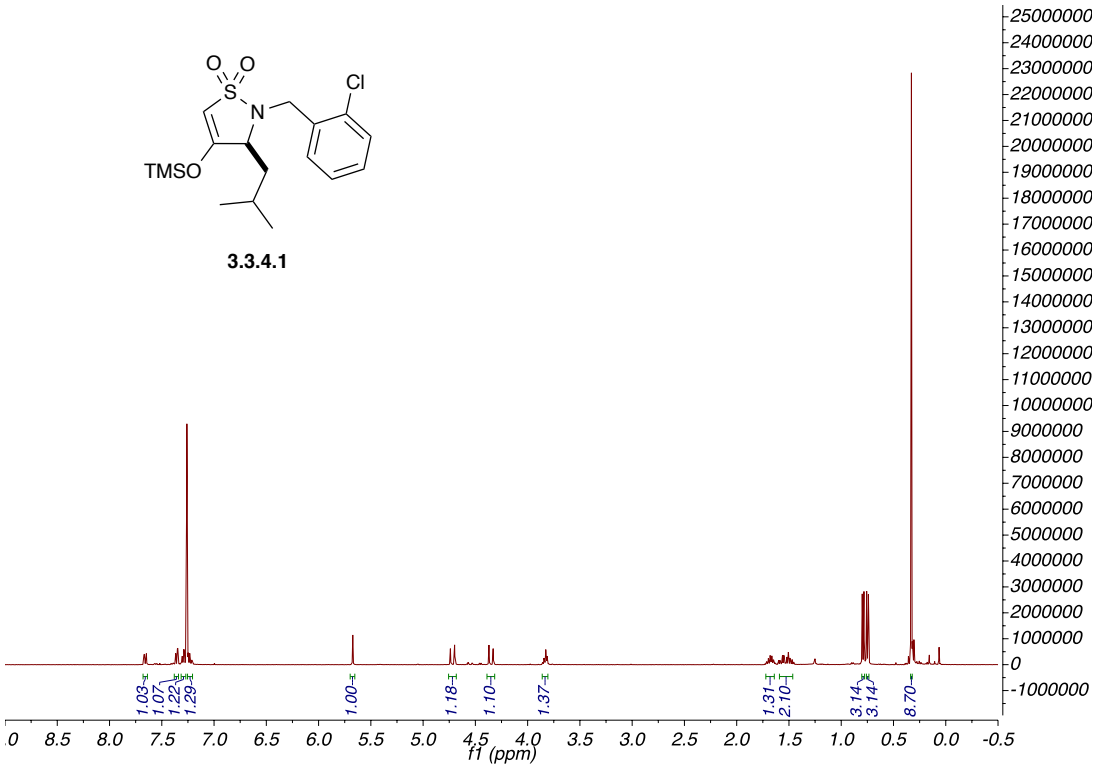


Figure 3.3.4. Proton NMR spectra of **3.3.4.1**

When read left to right, **Figure 3.3.4** shows the four aromatic protons of the *o*-Cl ring, followed by the silyl enol-ether proton at approximately 5.7 ppm. The benzylic hydrogens can be seen as two doublets between 4.0 and 5.0 ppm, while the NCH-Leucine peak follows at 3.8 ppm. The *L*-Leucine fragment falls between 0.5 and 2.0 ppm, and the TMS protons were found at 0.4 ppm. The spectrum in **Figure 3.3.4** was taken in deuterated chloroform, and is the crude product after solvent evaporation.

With a reliable silyl enol ether synthesis in hand, attempts towards the Mukaiyama aldol began. **Figure 3.3.5** details examples of titanium tetrachloride, and BF_3•OEt_2 trials, however protodesilylation was uniformly seen across all attempts.

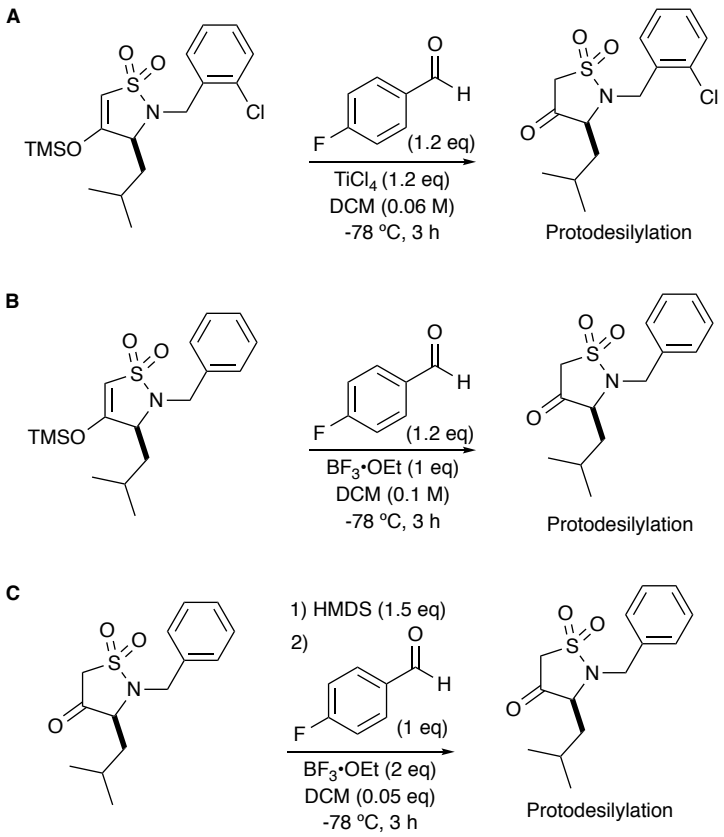
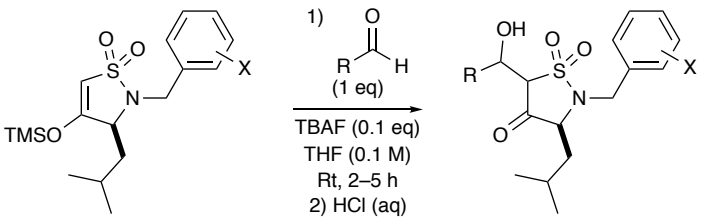


Figure 3.3.5 Lewis-Acid Mediated Mukaiyama aldol

Lewis acid-mediated reactions were abandoned in favor of a novel TBAF-catalyzed Mukaiyama Aldol reaction.[59] A promising first attempt showed traces of product, however subsequent trials revealed only starting material degradation or the all-too-familiar protodesilylation product (**Table 3.3.1**). Acidic conditions were completely abandoned, and after cursory attempts with basic Mukaiyama aldol conditions showed only degradation (**Figure 3.3.6**), the use of aldol chemistry was abandoned altogether.



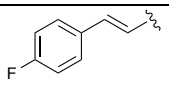
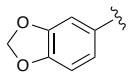
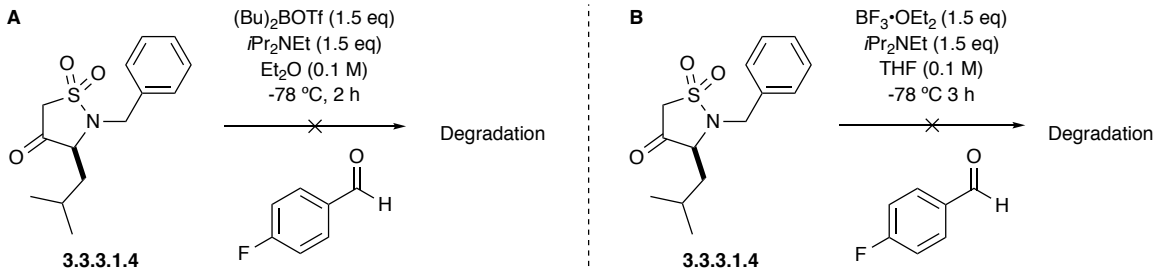
Entry	X	R	Yield
1	*o*-Cl		Trace
2	*o*-Cl		Degradation
3	*o*-Cl		Degradation
4	*o*-Cl	4-Pyridine	Protodesilylation
5	*p*-F	*p*-Anisaldehyde	Protodesilylation
6	*o*-Cl	Benzaldehyde	Protodesilylation

Table. 3.3.1 TBAF mediated Mukaiyama aldol attempts.

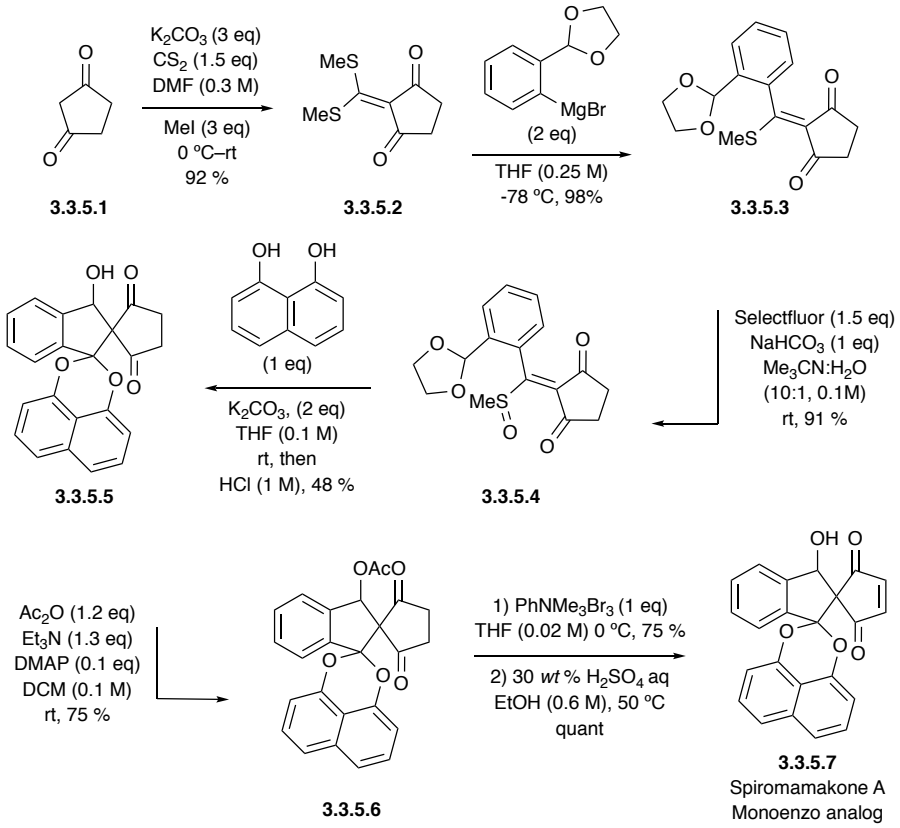


Scheme 3.3.6 Base-mediated Mukaiyama aldol reaction

The seemingly unfavored nature of aldol adducts momentarily hampered synthetic efforts towards α,β-unsaturated β-keto sultams. However, 1,3-cyclohexanedione-derived methods had in fact successfully generated an *endo*-cyclic α,β-unsaturated β-keto sultams, albeit one that was not further utilized. Dione literature was then searched for a method to directly install a double bond to the α-position in order to generate α,β-unsaturation directly without the need for subsequent acyl transfer or

tautomerization. Such a direct double bond installation was found in a 2016 manuscript published by Doi and co-workers.[60] **Scheme 3.3.5** highlights the use of ketene dithioacetals chemistry in the beginning steps of the synthesis of a monobenzo analog of Spiromamakone A. Here, cyclopentane-1,3-dione was dissolved in DMF before the addition of K_2CO_3 and carbon disulfide (CS_2). The resulting thiolate was quenched with methyl iodide to afford ketene dithioacetal intermediate **3.3.5.2**. This intermediate was subjected to an addition-elimination reaction with an Ar-MgBr, followed by oxidation and oxa-Michael addition in route to monobenzo Spiromamakone A.

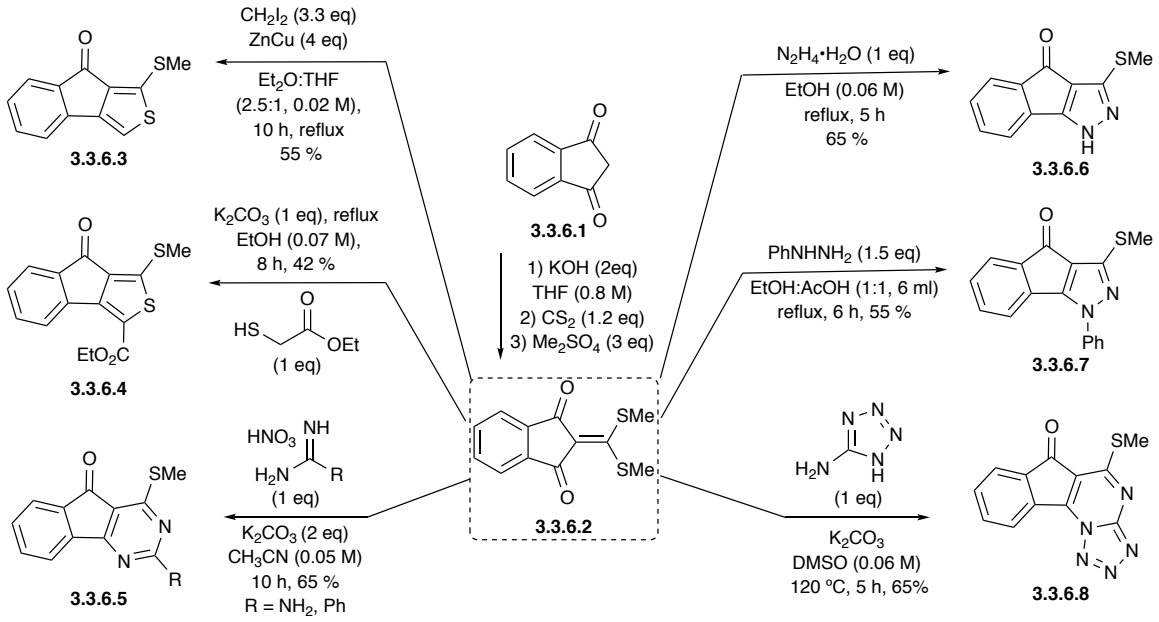
Scheme 3.3.5 ketene dithioacetal synthesis of a monobenzo Spiromamakone A



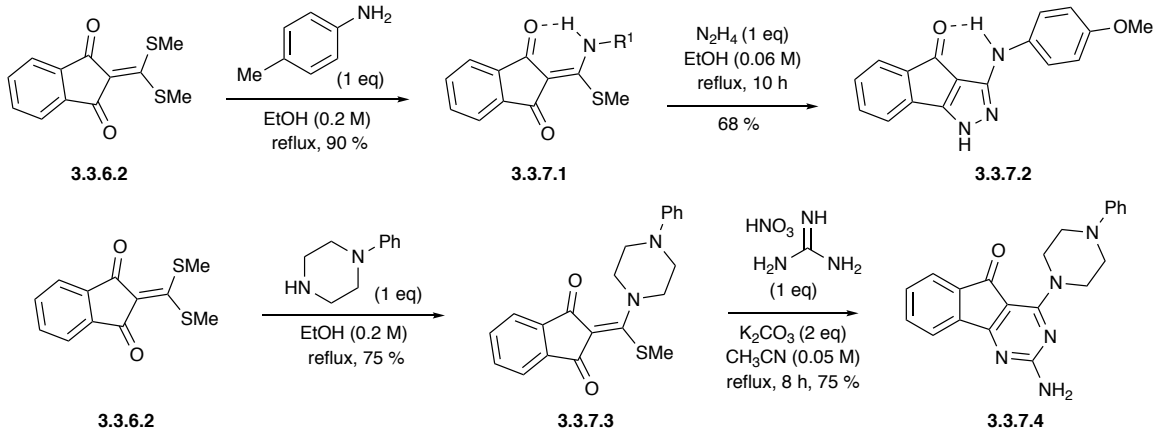
Further investigation into the utility of ketene dithioacetals[61] uncovered the generation of multiple heterocyclic compounds by Singh and co-workers.[62] Scheme 3.3.6

and **Scheme 3.3.7** illustrates the use of various reagents, including primary amines, to generate substituted α,β-unsaturated products.

Scheme 3.3.6 Singh synthesis of heterocyclic amines by ketene dithioacetal chemistry.



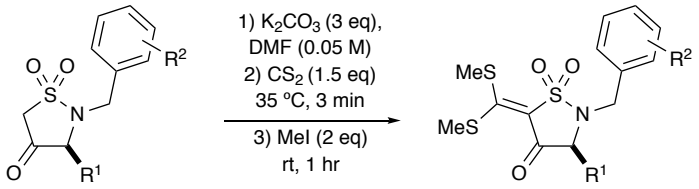
Scheme 3.3.7 Singh addition of simple amines into ketene dithioacetals.



The use of ketene dithioacetal pi-bond installation and subsequent amine differentiation fit well within the goal α,β-unsaturated β-keto sultam synthesis and diversification. Therefore, ketene dithioacetal chemistry was carried out by dissolving a β-keto sultam in DMF, followed by the addition of K_2CO_3, and heated to 35 °C. Carbon

disulfide was added drop-wise and the reaction stirred for 3 minutes at 35 °C. Methyl iodide was added to the mixture, which was allowed to stir for one hour at room temperature.[63] Minimal reaction optimization was needed, and products **3.3.8.1.1–3.3.8.1.4** were generated in yields 85% (**Scheme 3.3.8**).

Scheme 3.3.8. Synthesis of ketene dithioacetal intermediates.



Entry	R^1	R^2	Yield
1	*L*-Leu	H	**3.3.8.1.1** 77 %
2	*L*-Leu	*o*-Cl	**3.3.8.1.2** 85 %
3	*L*-Ile	4-Me	**3.3.8.1.3** 26 %
4	*L*-Ile	4-F	**3.3.8.1.4** 23 %

Ketene dithioacetal formation proved a reliable and robust reaction until utilized with a more sterically encumbered amino acid derivative such as *L*-Isoleucine. The yields dropped considerably with such derivatives possibly due to the added sterics impeding the enol formation.[64] **Figure 3.3.7** shows the proton NMR for β-keto sultam **3.3.8.1.1** after ketene dithioacetal formation. When read left to right the aromatic proton signals can be seen between 7.5 and 7.0 ppm. The benzylic protons are seen at 4.3 ppm, with the NCH-Leucine proton immediately after at 3.5 ppm. The dithioacetal SMe groups appear as two broad semi-merged singlets between 3.0 and 2.0 ppm. Finally, the *L*-Leucine fragment can be seen below 2.0 ppm. While compounds **3.3.8.1.1–3.3.8.1.4** were purified

by normal-phase silica column chromatogram, these scaffolds proved rather sensitive and were typically used immediately after purification.

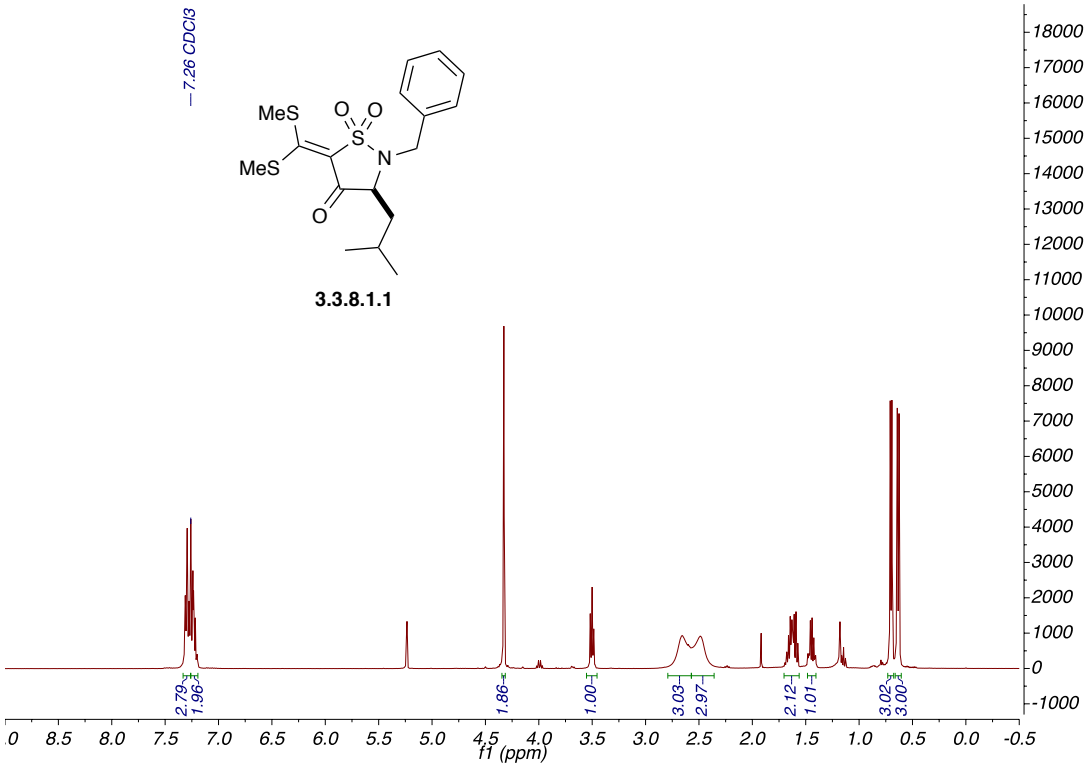
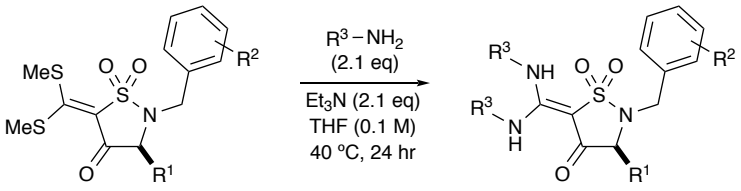


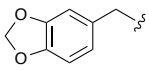
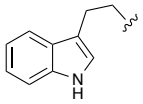
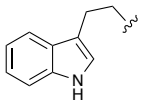
Figure 3.3.7. Representative spectra for ketene dithioacetal intermediates.

With a reliable synthetic method for the installation of a diversifiable exocyclic α,β-unsaturated system in hand, experimentation next turned to functionalizing the Michael acceptor. Double aza-Michael addition was chosen for this purpose. The aza-Michael addition was accomplished by dissolving ketene dithioacetal **3.3.8.1.1–3.3.8.1.4** in dry THF, followed by the addition of the desired amine, and triethylamine. Full consumption of starting material required the reaction to be heated to 40 °C for 24 hours. **Scheme 3.3.9** highlights the synthesis and products formed by this double aza-Michael addition.

Scheme 3.3.9. Synthesis of 5-(diaminomethylene)isothiazolidin-4-one 1,1-dioxide sultam derivatives.



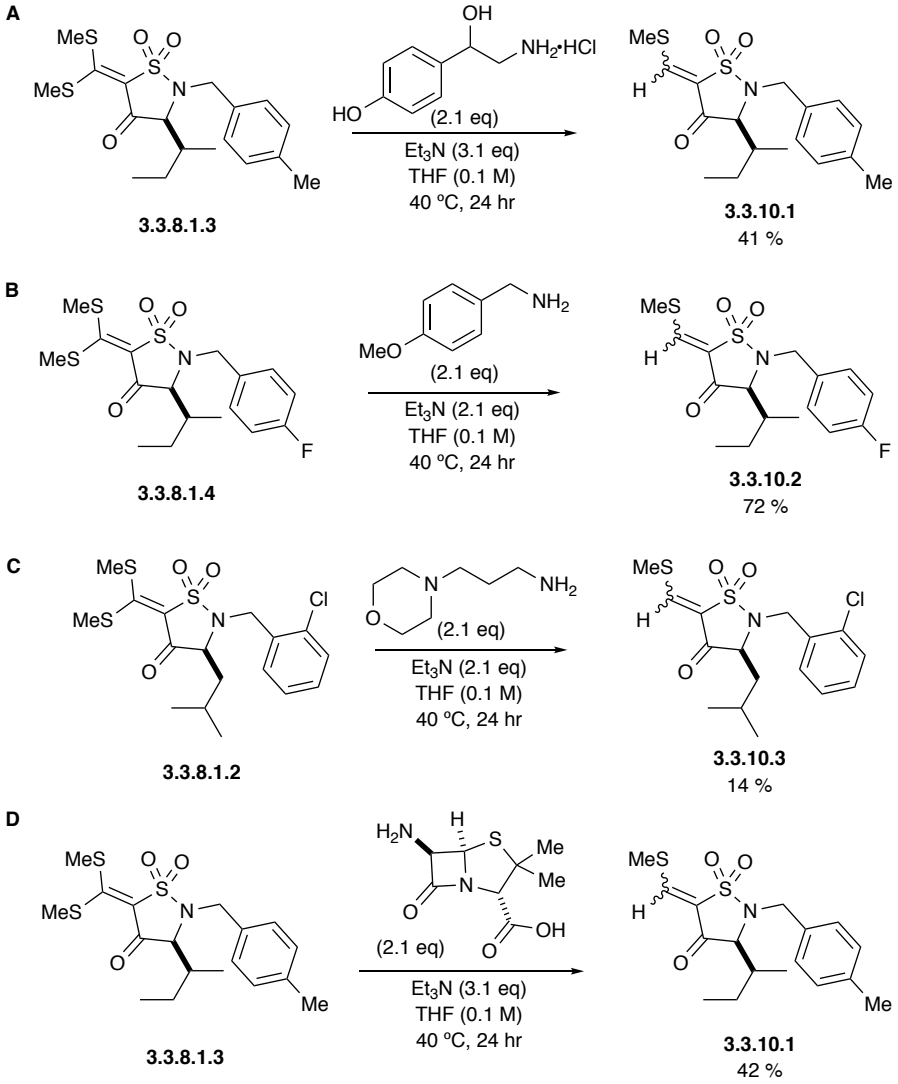
3.3.8.1 **3.3.9.1**

Entry	R^1	R^2	R^3	Yield
1	*L*-Leu	*o*-Cl	Bn	**3.3.9.1.1** 23 %
2	*L*-Leu	*o*-Cl	Propargyl	**3.3.9.1.2** 54 %
3	*L*-Leu	H	4-Me-Bn	**3.3.9.1.3** 83 %
4	*L*-Leu	H	2-OMe-Bn	**3.3.9.1.4** 42 %
5	*L*-Ile	*o*-Cl		**3.3.9.1.5** 24 %
6	*L*-Leu	H	Propargyl	**3.3.9.1.6** 50 %
7	*L*-Ile	4-Me		**3.3.9.1.7** 57 %
8	*L*-Ile	*o*-Cl		**3.3.9.1.8** 64 %
9	*L*-Ile	*o*-Cl	2-OMeBn	**3.3.9.1.9** 31 %
10	*L*-Leu	H	4-OMeBn	**3.3.9.1.10** 52 %
11	*L*-Ile	*o*-Cl	4-MeBn	**3.3.9.1.11** 44 %
12	*L*-Ile	*o*-Cl	4-OMeBn	**3.3.9.1.12** 44 %
13	*L*-Ile	4-Me	4-OMeBn	**3.3.9.1.13** 20 %

Benzyl amine derivatives proved to be competent addition partners, as did propargyl amine, and the biologically interesting piperonylamine and the monoamine

alkaloid tryptamine. Interestingly, several reactions produced mono thiol ether side products as seen in **Scheme 3.3.10**. At, first condensation into the ketone and subsequent benzylic hydrogen abstraction was considered as a possible mechanism. However, when the non-benzylic amine 3-morpholinopropan-1-amine was utilized the side-product was again uncovered. Effort influenced by Lee and co-workers hybrid ampicillin-tetramic acid chemistry[65] afforded only side-product as shown by the combination of **3.3.8.1.3** and 6-aminopenicillanic acid.

Scheme 3.3.10. Discovery of mono-methyl thiol ethers



Unfortunately, the exact mechanism for the formation of these mono-thiol ether side-products remains ambiguous. Furthermore, despite extensively long efforts, no X-ray quality crystals of any side-products could be obtained. Therefore, *E*/*Z* geometry on the pi bond also cannot be confirmed at this time. In summary, isothiazolidin-4-one 1,1-dioxides were generated via intramolecular Dieckmann cyclization and functionalization of the α-position with carbon disulfide and amines to generate β-keto sultams 5-(diaminomethylene)isothiazolidin-4-one 1,1-dioxide compounds **3.3.9.1.1–3.3.9.1.13**. The long medicinal history of sultams and tetramic acids, the unique activity held by the fusion of these scaffolds and the relative scarcity of enamine derivatives was the driving force behind this thesis work. These novel chemical probes will be handed to collaborators for use in chemical biology assays and results shall be reported in due course.

Section 3.4 *Synthesis of 4-hydroxy-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide Derivatives*

While the exo-enol tetramic acid is a common natural product, the endo-enol scaffold is just as prevalent.[1] **Figure 3.4.1** shows natural products and drug candidates containing an endo α,β-unsaturated tetramic acid.

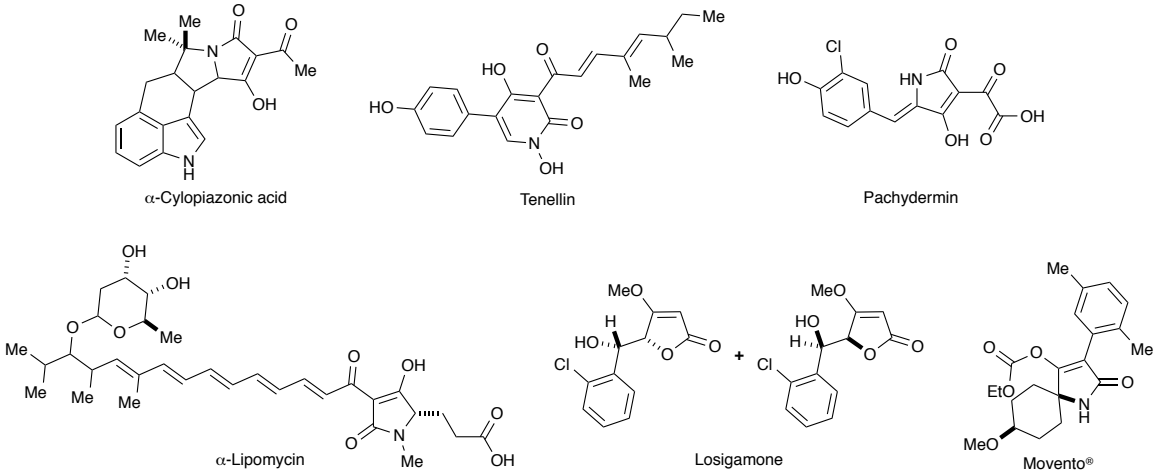


Figure 3.4.1. Natural products and drug candidates containing an endo-enol scaffold.

One of the more common endo-enol natural products is the prenylated indole alkaloid α-cyclopiazonic acid (α-CPA).[66] This scaffold is produced by numerous *penicillium* species, in addition to fungi relevant to the meat and cheese industry. α-CPA is a specific inhibitor of sarcoplasmic or endoplasmic reticulum calcium-dependent ATPase (SERCA). As the SERCA enzyme is directly involved in muscular calcium level control, α-CPA disrupts the muscle contraction-relaxation cycle.[67]

The pathogenic insect fungus *Beauveria bassiana* is known to generate the tetramic acid tenellin. Aside from inhibit equine erythrocyte membrane ATPase activity,[68] tenellin has been shown to decrease iron-induced oxidative stress by acting as a siderophore during iron-overload conditions.[69] The novel oxalylated tetramic acid

pachydermin was isolated from the New Zealand basidiomycete *Chamonixia pachydermis.*[70] This *m*-chloro natural product is known to degrade to a α-unsubstituted endo-enol analog via cyclization of the keto-tautomer, followed by decarbonylation and decarboxylation to release carbon monoxide and carbon dioxide.[71]

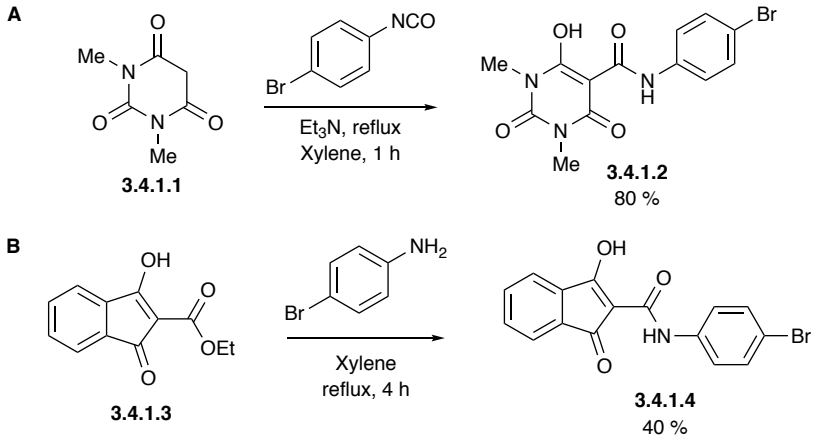
The lipophilic tetramic acid α-Lopomycin was isolated from *Streptomyces aureofaciens,* and possesses a modest MIC = 0.78 μg ml^{-1} against *B. subtilis*.[72] Furthermore, a *in silico* flexible docking-based molecular dynamics simulation of 190,084 natural product compounds against the Ebola virus Nucleocapside (EBOV NP) identified two compounds, one of which was α-Lopomycin, as promising lead compounds in the development of Ebola treatment.[73] The experimental anticonvulsant phase III clinical candidate Losigamone is a methyl-substituted, and *o*-chloro racemic mixture of two *threo* isomers. Losigamone reduces the frequency of spontaneous and stimulus-induced epileptiform discharges in hippocampal slices by pre-synaptically effecting sodium channels.[10c, 74] The spirotetramat pesticide Movento was developed by Bayer and is active against piercing-sucking insects.[75]

The above natural products and drug candidates have elicited numerous synthetic efforts to generate α-functionalized scaffolds. Many recent efforts have on generating small molecule heterocycles for drug lead compound development. Tetramic acid endo-enol α-functionalization to generate amides has historically been a focal point for pharmaceutical and university researchers intent on drug development.

A team from Pharmacia & Upjohn Inc disclosed the synthesis of amide functionalized tetramic acids with anti-parasitic activity. **Scheme 3.4.1** shows the

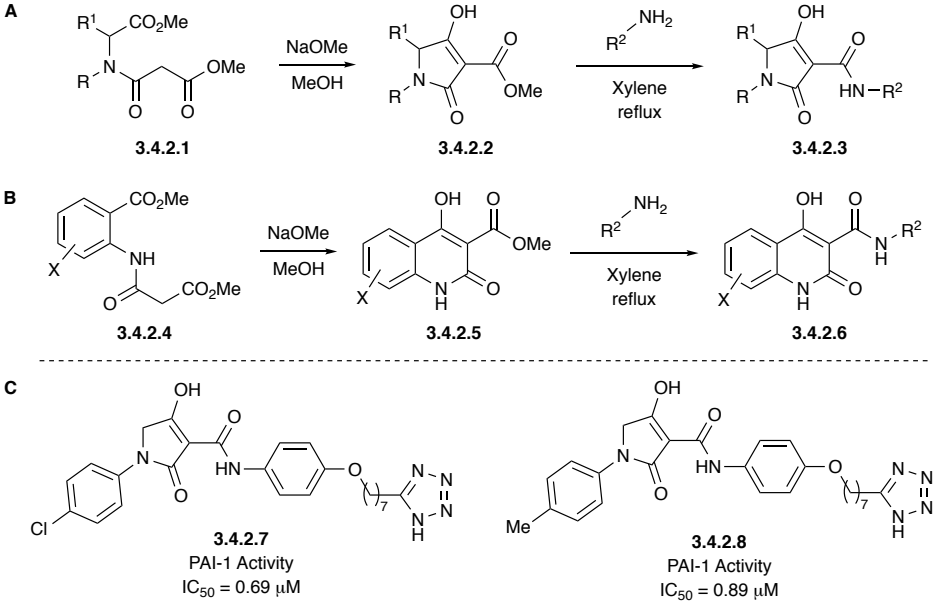
α-functionalization with 4-bromophenylisocyanate in the presence of triethylamine and refluxing xylene to form compound **3.4.1.2** in 80 % yield. Alternatively, ester **3.4.1.3** underwent aminolysis with 4-bromoaniline to generate a similar benzofused product. These compounds were found to be active against the parasitic barber's pole worm *Haemonchus contortus*.[76]

Scheme 3.4.1 Pharmacia & Upjohn Inc anti-parasitic compounds



Scientists from Xenova Limited disclosed a similar amide synthesis in a 2002 publication concerning plasminogen activator inhibitor-1 (PAI-1) inhibitor development.[77] PAI-1 is a serine protease implicated in thromboembolic disease[78] and cancer.[79] A Dieckmann cyclization route was utilized to generate esters **3.4.2.2** and **3.4.2.5**, which were then subjected to aminolysis. Tetrazole-containing compounds **3.4.2.7** and **3.4.2.8** were found to possess good inhibitory activity against PAI-1. The substrate scope included substituted phenyls on the amine, as well as phenyl and protons at the R^1 position. The R^2 group was held to an aniline-4-ether-octanoic side chain, which terminated in a free carboxylic acid, ester, or tetrazole functionality.[77]

Scheme 3.4.2. Xenova Limited amide functionalization



In 2008, researchers from Novartis detailed a study on the design of undecaprenyl pyrophosphate synthase (UPPS) inhibitors. The UPPS is critical for bacterial survival, as it catalyzes cis double bond formation during the condensation isopentenyl pyrophosphate with farnesyl pyrophosphate to generate C_{55} undecaprenyl pyrophosphate, a required lipid.[80] Similar to the above examples, a Lacey-Dieckmann cyclization with NaOMe in methanol was utilized to form an enolic methyl ester tetramic acid. This methyl ester intermediate was then mixed with an amine in THF or EtOH and subjected to microwave heating at 120 °C for up to eight minutes, to generate amides via aminolysis[81] (**Figure 3.4.2**).

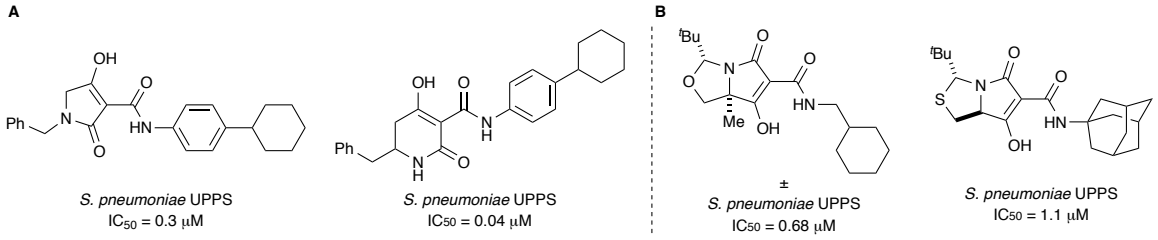
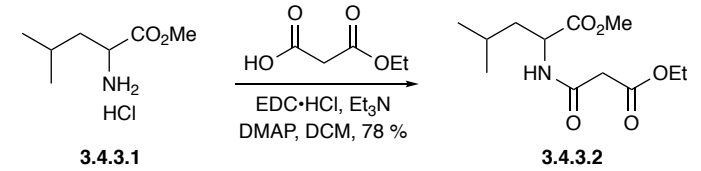


Figure 3.4.2. A). Novartis antibacterial compounds. B) Moloney UPPS inhibitors

Moloney and co-workers also disclosed UPPS inhibitors (**Figure 3.4.2**). These scaffolds were formed by butyl chloroformate and DMAP-mediated endo-enol α-esterification followed by aminolysis in refluxing toluene.[82] The authors noted the potential of these compounds as topical antibiotics, while acknowledging the need for further optimization towards oral and injectable drugs.

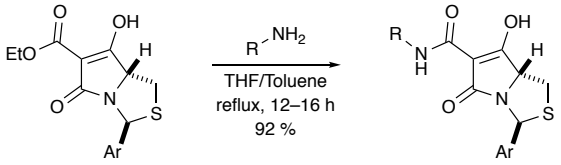
In 2014 Wang and co-workers reported a microwave-assisted amide formation on leucine-derived tetramic acids.[83] As seen in **Scheme 3.4.3**, these products were generated via aminolysis in 15 minutes with yields up to 72%. These products showed good antifungal activity against *Pythium dissimile.* Most recently in 2019, Moloney and co-workers disclosed a cysteine-derived, bicyclic tetramic amide synthesis (**Scheme 3.4.4**).[84] These α-amide substituted products were found to be active against gram-positive bacteria via inhibition of bacterial topoisomerase IV (topo IV) or DNA gyrase, both of which are critical for DNA replication.[85]

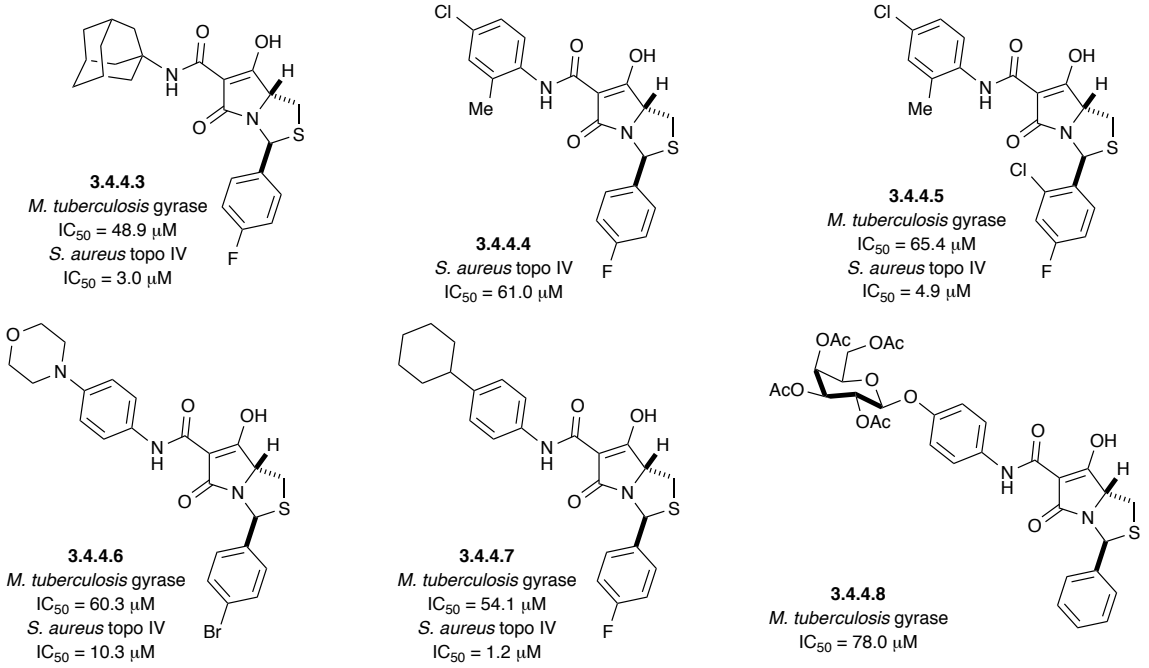
Scheme 3.4.3. Wang and co-workers microwave assisted synthesis.



R	% Yield	R	% Yield
Me	66	*p*-ClC_6H_4	59
n-C_3H_7	43	$C_6H_5CH_2$	68
t-C_4H_9	72	*p*-$FC_6H_4CH_2$	65

Scheme 3.4.4 Moloney aminolysis to bioactive bicyclic tetramic acid amides.

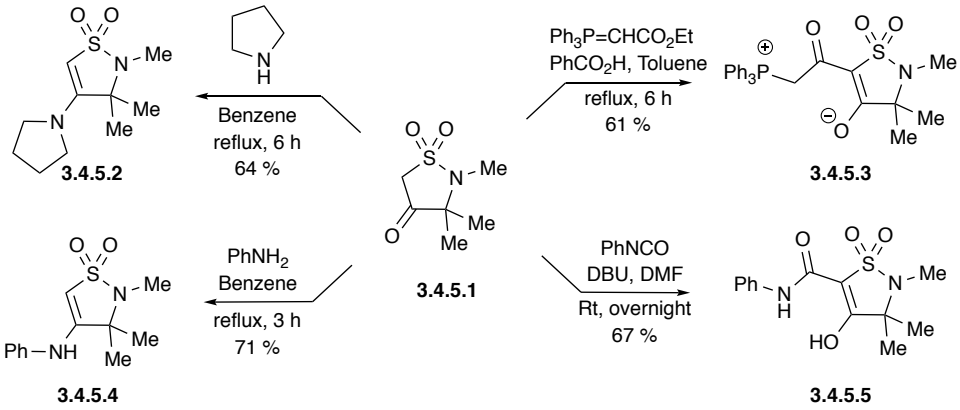




Dobrydnev and co-workers disclosed a rare sultam tetramic acid synthesis in early 2019. [86] Here, the reactivity of the sultam scaffold was tested with a variety of

nucleophiles and electrophiles, the most relevant of which are shown in **Scheme 3.4.5**. Primary and secondary amines were found to react with the ketone to afford *endo*-enamine scaffolds **3.4.5.2** and **3.4.5.4**. A Wittig reagent was found to react with the α-position to generate product **3.4.5.3**, while phenyl isocyanate was shown to produce amide product **3.4.5.5**.

Scheme 3.4.5. Dobrydnev sultam α-position differentiation.

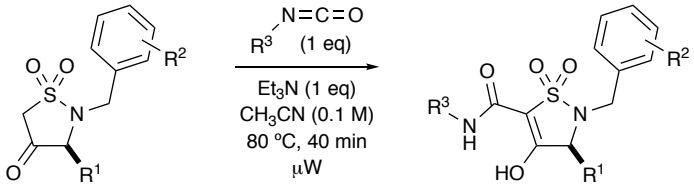


The above examples detail promising biological activity but are relatively limited to aminolysis with only a handful of direct amide α-functionalization examples. While the Dobrydnev sultam α-amide formation is conceptually similar to the disclosed thesis work, the reaction scope was limited to only phenyl isocyanate or phenyl isothiocyanate. Furthermore, the Dobrydnev 2019 α-amide formation was published after work towards the disclosed α–amide functionalization was well underway.

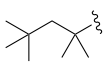
Scheme 3.4.6 highlights the dissertation work for direct α-amide formation of endo-enol β-keto sultams, via the use of various isocyanates for direct α-functionalization. A sultam was placed in a pressure vial and dissolved in dry acetonitrile before triethylamine and isocyanate were added. The reaction was then microwaved at 80 °C for 40 minutes before the solvent was removed via rotary vacuum. The crude residue

was then purified by normal-phase silica column chromatography to afford α-amide β-keto sultams in yields of up to 93%.

Scheme 3.4.6. Synthesis of 4-hydroxy-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



3.3.3.1 **3.4.6.1**

Entry	R^1	R^2	R^3	Yield
1	*L*-Leu	H	4-Me-C_6H_6	**3.4.6.1.1** 65 %
2	*L*-Leu	*o*-Cl	4-Me-C_6H_6	**3.4.6.1.2** 67 %
3	*L*-Leu	*o*-Cl	4-OMeBn	**3.4.6.1.3** 28 %
4	*L*-Leu	*o*-Cl	Ph	**3.4.6.1.4** 93 %
5	*L*-Ile	4-Me	4-Me$C_6H_4SO_2$	**3.4.6.1.5** 40 %
6	*L*-Leu	H	4-F-Ph	**3.4.6.1.6** 72 %
7	*L*-Leu	H	Ph	**3.4.6.1.7** 88 %
8	*L*-Leu	*o*-Cl	4-F-Ph	**3.4.6.1.8** 91 %
9	*L*-Leu	*o*-Cl	4-Me$C_6H_4SO_2$	**3.4.6.1.9** 60 %
10	*L*-Leu	H	4-Me$C_6H_4SO_2$	**3.4.6.1.10** 57 %
11	*L*-Leu	*o*-Cl	Cyclohexyl	na
12	*L*-Ile	4-Me	4-F-Ph	na
13	*L*-Leu	H		na
14	*L*-Leu	H		na

The amino ester *L*-leucine was well tolerated by the reaction while *L*-isoleucine suffered from decreased yields or failed to react. An isocyanate containing a 4-methoxy-benzyl group delivered product in only 28% yield. Indeed, aromatic isocyanates proved necessary for product formation, as alkyl variants 2-isocyanato-2,4,4-trimethylpentane, Cyclohexyl isocyanate and 1-adamantyl isocyanate failed to react. *N*-substituents included benzyl rings, as well as *o*-Cl, and 4-Me benzyl substitutions.

In conclusion, this dissertation chapter has detailed the use of a rapid and scalable synthesis capable of producing novel tetramic acid derivatives termed β-keto sultams. These sultams were α-functionalized by amine and amides in order to generate novel chemical probes in good yields. Thanks to the rarity of α-substituted β-keto sultams, these scaffolds are understudied within chemical biology and medicinal chemistry. The scarcity, as well as the wealth of bioactivity found in carbon analogs was the driving force behind thesis synthetic effort. These compounds will be used in chemical biology assays by collaborators in an effort to elucidate novel biological activity.

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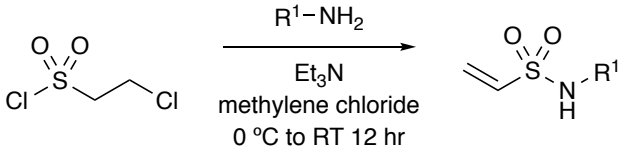
Chapter 4:
Supporting Information

General Experimental:

All reactions were carried out in oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. THF and CH_2Cl_2 were purified by passage through a purification system (Pure Process Technology). Anhydrous Et_3N was obtained from an Aldrich and used without further purification. Anhydrous CH_3CN, and anhydrous toluene were obtained from Aldrich and used without further purification. $Pd(PPh_3)_4$ was kept in a glove box under argon. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 μm) and thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. 1H and 13C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-500 or Bruker DRX-400 spectrometer operating at 500 MHz, 400 MHz, 300 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). Observed rotations at 589 nm were measured using POL-301 Polarimeter by LAXCO. The IR spectrum was recorded using a Nicolet iS 5 FTIR by ThermoFisher. Microwave irradiation was carried out using a *Biotage*® Initiator.

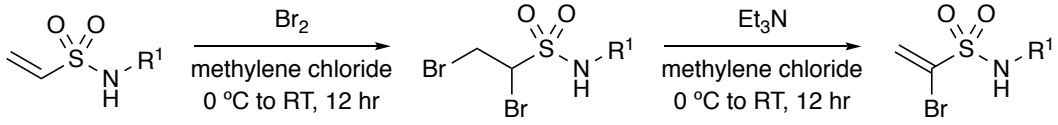
General Procedures

General Procedure A for the synthesis of *N*-ethenesulfonamides **2.4.1.2.1**–**2.4.1.2.8**:



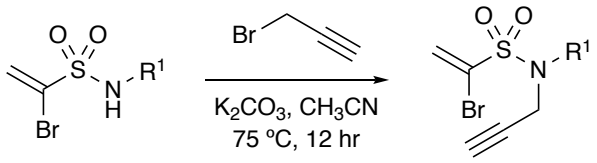
An amine, or amino ester hydrochloride (1 equivalent) was dissolved in anhydrous CH_2Cl_2 (0.2 M) and equipped with a septa and argon. The solution was cooled to 0 ºC, and subjected to dropwise addition of Et_3N (3 equivalents), and drop-wise addition of 2-chloroethanesulfonyl chloride (1.2 equivalents). Upon completion of the reaction, as monitored by normal phase TLC, the reaction was diluted with CH_2Cl_2, washed with H_2O, brine, and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude oil was subjected to normal phase silica flash chromatography utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc), to afford compounds **2.4.1.2.1**–**2.4.1.2.8** in yields ranging from 52–96 %.

General Procedure B for the synthesis of 1-bromo ethenesulfonamides **2.4.1.4.1–2.4.1.4.8**:



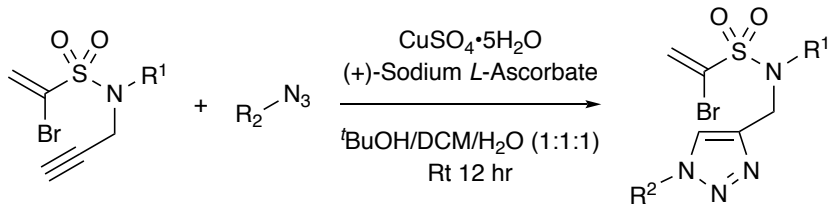
To a flame-dried round-bottomed flask, was added a sulfonamide **2.4.1.2.1**–**2.4.1.2.8** (1 equivalent). The flask was equipped with a septa, and argon before anhydrous CH_2Cl_2 (0.2 M) was added. The reaction was cooled to 0 ºC, and a needle was used to effect drop-wise Br_2 (3 equivalents) addition. The reaction was allowed to warm to room temperature, and stirred overnight. The reaction mixture, containing crude dibrominated sulfonamides **2.4.1.3.1–2.4.1.3.8**, was cooled to 0 ºC and quenched with sat'd $Na_2S_2O_3$, extracted with CH_2Cl_2, and washed with H_2O, brine. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude products **2.4.1.3.1–2.4.1.3.8** were immediately placed in an oven dried flask, dissolved in anhydrous CH_2Cl_2 (0.2 M), and cooled to 0 ºC before Et_3N (1.5 equivalents) was added. The reaction was stirred at room temperature overnight, and monitored by TLC. Upon completion, the reaction mixture was diluted with CH_2Cl_2, washed with H_2O, brine, and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude oil was subjected to normal phase silica flash chromatography utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc), to afford compounds **2.4.1.4.1–2.4.1.4.8** in yields ranging from 62–79 %.

General Procedure C for the synthesis of *N*-propargyl sulfonamides **2.4.1.5.1–2.4.1.5.8**:



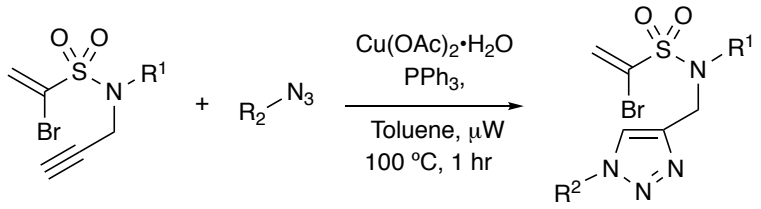
To a flame-dried round-bottomed flask was added α-bromo sulfonamides **2.4.1.3.1–2.4.1.3.8** (1 equivalent). Anhydrous acetonitrile (0.2 M), K_2CO_3 (2.5 equivalents) and propargyl bromide (1.5 equivalents) were added to the flask, which was then placed on an oil bath and fitted to a reflux apparatus and argon. The reaction was heated at 75 ºC under the condenser overnight. Upon completion as shown by TLC, the reaction was filtered and the solvent concentrated under reduced pressure. The resulting crude oil was then purified on a normal phase silica flash column, utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc), to afford sulfonamide products **2.4.1.5.1–2.4.1.5.8** in yields of 18–95 %.

General Procedure D.1 for the aqueous synthesis of 1H-1,2,3-triazol-4-yl "click" sulfonamides **2.4.2.2.1**–**2.4.2.2.33:**



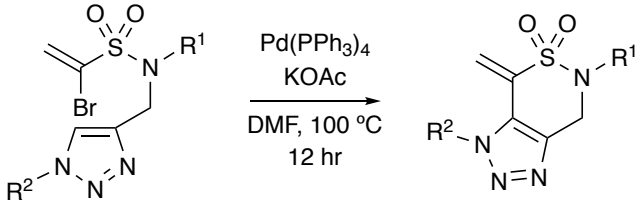
To a flask was added *N*-propargyl sulfonamides **2.4.1.5.1–2.4.1.5.8** (1 equivalent). A 1:1:1 solution of CH_2Cl_2:^{t}BuOH:H_2O (0.2 M for total solution) was then added to the flask. The flask was then equipped with a septa and argon, before drop-wise addition of an azide (1.5 equivalents), followed by drop-wise addition of aqueous solutions of $CuSO_4$•$5H_2O$ (0.2 equivalents, 25% total H_2O volume required), and (+)-Na-*L*-$C_6H_7O_6$ (0.3 equivalents, 25% the total H_2O volume required). The reaction was then stirred at room temperature overnight. Upon reaction completion as seen by TLC, the reaction extracted with brine and CH_2Cl_2. The organic layer was separated and dried (Na_2SO_4), then filtered, and concentrated under reduced pressure. The resulting crude oil was purified by normal phase silica flash column chromatography utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc), to afford 1H-1,2,3-triazol-4-yl "click" sulfonamides **2.4.2.2.1**–**2.4.2.2.33** in yields of up to 14–96 %.

General Procedure D.2 for the microwave synthesis of 1H-1,2,3-triazol-4-yl "click" sulfonamides **2.4.2.2.1**–**2.4.2.2.33**:



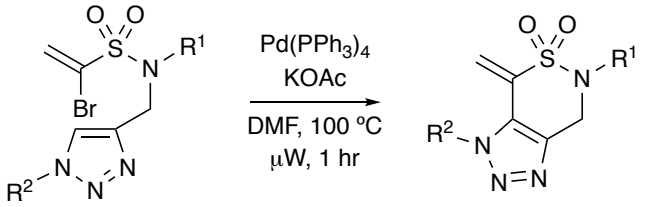
To an oven-dried microwave vial was added *N*-propargyl sulfonamides **2.4.1.5.1–2.4.1.5.8** (1 equivalent). Anhydrous toluene (0.2 M) was added followed by drop-wise addition of an azide (1.1 equivalent). PPh_3 (0.09 equivalents) and $Cu(OAc)_2•H_2O$ (0.08 equivalents) were then added to the vial. The reaction vial was crimped shut before undergoing microwave irradiation for one hour at 100 ºC. Upon reaction completion as shown by TLC, the reaction was extracted with EtOAc and saturated brine. The organic layer was separated and dried with Na_2SO_4, then filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by normal phase silica flash chromatography utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc) to afford 1H-1,2,3-triazol-4-yl "click" sulfonamides **2.4.2.2.1**–**2.4.2.2.33** in yields of 63–91 %.

General Procedure E.1 for the overnight synthesis of triazole-fused sultams **2.4.2.3.1**–**2.4.2.3.33:**



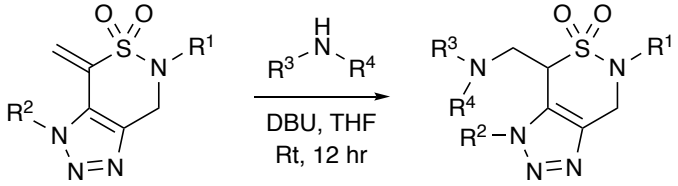
To a flame-dried round bottom flask was added sulfonamides **2.4.2.2.1**–**2.4.2.2.33** (1 equivalent). Anhydrous DMF (0.05 M) was then added to the flask followed by KOAc (2 equivalents), and $Pd(PPh_3)_4$ (0.1 equivalent). The flask was then fitted with a reflux condenser, argon, and an oil bath before undergoing overnight heating at 100 ºC. Upon completion as seen by TLC, the reaction was extracted with EtOAc and brine. The organic layer was separated and dried with Na_2SO_4, then filtered and concentrated under reduced pressure. The resulting crude oil was purified by normal phase silica flash chromatography, utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc), to afford sultams **2.4.2.3.1**–**2.4.2.3.33** in yields of 49–89 %.

General Procedure E.2 for the microwave synthesis of triazole-fused sultams **2.4.2.3.1**–**2.4.2.3.33**:



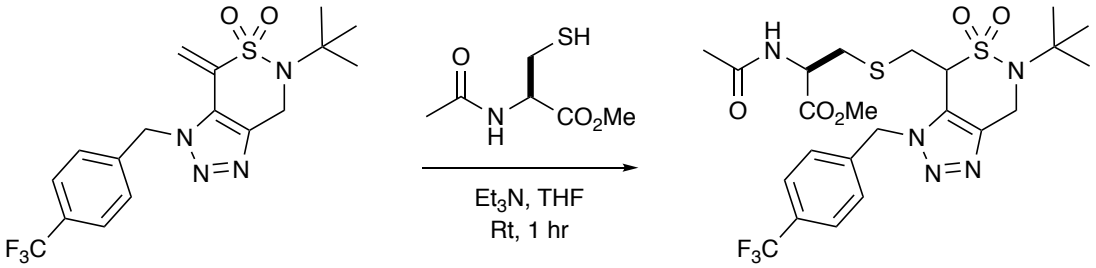
To an oven-dried microwave vial was added sulfonamides **2.4.2.2.1**–**2.4.2.2.33** (1 equivalent). Anhydrous DMF (0.05 M) was added to the vial followed by KOAc (2 equivalents), and $Pd(PPh_3)_4$ (0.1 equivalent). The reaction vial was crimped shut before undergoing microwave irradiation at 100 ºC for one hour. Upon reaction completion as monitored by TLC, the reaction was extracted with EtOAc and brine. The organic layer was separated and dried with Na_2SO_4, then filtered and concentrated under reduced pressure. The resulting crude oil was purified by normal phase silica flash chromatography, utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc) to afford sultams **2.4.2.3.1**–**2.4.2.3.33** in yields of 12–88 %.

General procedure F for the synthesis of aza-Michael sultams **2.4.4.1.1–2.4.4.1.13**:



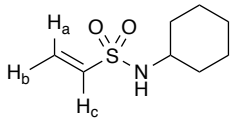
To an oven-dried round bottom flask was added sultams **2.4.2.3.12**/**.13**/**.16** (1 equivalent). Anhydrous THF (0.5 M) was added to the flask, and the reaction equipped with a septa and argon. The flask then underwent drop-wise addition of DBU (0.2 equivalents), followed by drop-wise addition of an amine (1.2 equivalents). The reaction stirred at room temperature for 12 hours, or until completion as indicated by normal phase silica TLC. The reaction was then extracted with brine and EtAOc. The organic layer was separated and dried with Na_2SO_4, then filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by normal phase silica chromatography, utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc) to afford aza-Michael products **2.4.4.1.1–2.4.4.1.13** in yields of 49–99 %.

General Procedure G for the synthesis of *N*-Ac-Cysteine Methyl Ester thiol adduct **2.4.3.1**:



To an oven-dried flask was added sultam **2.4.2.3.13** (1 equivalent) and equipped with a septa and argon. Anhydrous THF (0.2 M) was added to the flask, followed by *N*-Ac-Cysteine Methyl Ester (1 equivalent), and Et_3N (1.1 equivalent). The reaction stirred at room temperature for an hour, and monitored by TLC. The crude oil was then purified on a normal phase silica flash column, utilizing a gradient of 10:1–8:1–5:1–3:1–1:1 (hexanes:EtOAc) to afford thiol adduct **2.4.3.1** was isolated in 75 %.

***N*-cyclohexylethenesulfonamide**



According to the reaction protocol described in general procedure **A**, compound **2.4.1.2.1** (96%, 4.8 g) was isolated as brownish oil.

R_f = 0.29 (EtOAc:Hexane = 1:2);

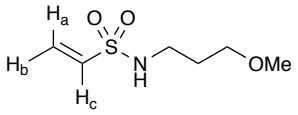
FTIR (neat): 2934, 1326, 1067 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (ddd, *J* = 16.5, 9.9, 0.9 Hz, 1H, CH_aH_b=C<u>H</u>$_c$-), 6.22 (dd, *J* = 16.5, 3.4 Hz, 1H, C<u>H</u>$_a$$H_b$=$CH_c$-), 5.87 (dd, *J* = 9.9, 2.3 Hz, 1H, CH_a<u>H</u>$_b$=CH_c-), 4.68 (s, 1H, N<u>H</u>), 3.13 (dddd, *J* = 13.8, 10.2, 7.4, 4.1 Hz, 1H, -CH_2CH_2C<u>H</u>$CH_2CH_2CH_2$-), 1.91 (d, *J* = 9.6 Hz, 2H, -CH_aH_b-C<u>H</u>$_a$$H_b$-CH-C<u>H</u>$_a$$H_b$-$CH_aH_b$-$CH_aH_b$-), 1.69 (d, *J* = 9.7 Hz, 2H, -CH_aH_b-CH_a<u>H</u>$_b$-CH-CH_a<u>H</u>$_b$-CH_aH_b-CH_aH_b-), 1.54 (d, *J* = 12.5 Hz, 1H, -C<u>H</u>$_a$$H_b$-$CH_aH_b$-CH-$CH_aH_b$-$CH_aH_b$-$CH_aH_b$-), 1.28 (dq, *J* = 21.5, 11.3, 10.0 Hz, 4H, -CH_a<u>H</u>$_b$-CH_aH_b-CH-CH_aH_b-C<u>H</u>$_a$<u>H</u>$_b$-C<u>H</u>$_a$$H_b$-), 1.16 (dd, *J* = 19.7, 7.9 Hz, 1H, -CH_aH_b-CH_aH_b-CH-CH_aH_b-CH_aH_b-CH_a<u>H</u>$_b$-);

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3 (CH), 125.6 (CH_2), 52.7 (CH), 34.2 (CH_2), 25.2 (CH_2, CH_2), 24.8 (CH_2, CH_2);

HRMS calculated for $C_8H_{15}NO_2S$ 190.0896 $(M+H)^+$; found 190.0905 (TOF MS ES^+).

***N*-(3-methoxypropyl)ethenesulfonamide**



According to the reaction protocol described in general procedure **A**, compound **2.4.1.2.2** (92%, 1.10 g) was isolated as brownish oil.

R_f = 0.28 (EtOAc:Hexane = 1:1);

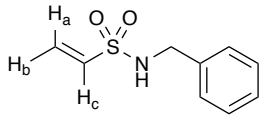
FTIR (neat): 3300, 3057, 2931, 2877, 1387, 1187, 1028, 972, 925 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 16.6, 9.9 Hz, 1H,CH_aH_b=C$\underline{H}_c$), 6.22 (dt, *J* = 16.6, 1.3 Hz, 1H, C$\underline{H}_aH_b$=CH_c), 5.93 (d, *J* = 9.9 Hz, 1H, $CH_a\underline{H}_b$=CH_c), 4.99 (s, 1H N$\underline{H}$), 3.51–3.46 (m, 2H, C$\underline{H}_2CH_2CH_2OMe$), 3.33–3.30 (m, 3H, OC$\underline{H}_3$), 3.13 (qd, *J* = 6.2, 1.6 Hz, 2H, $CH_2CH_2C\underline{H}_2OMe$), 1.81 (p, *J* = 6.0 Hz, 2H, $CH_2C\underline{H}_2CH_2OMe$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.03 (CH_2=$\underline{C}$HS), 126.54 ($\underline{C}H_2$=CHS), 71.52 ($\underline{C}H_2OCH_3$), 58.98 (OCH_3), 41.92 (CH_2), 29.35(CH_2);

HRMS calculated for $C_6H_{13}NO_3S$ 202.0508 $(M+Na)^+$; found 202.0525 (TOF MS ES^+).

***N*-benzylethenesulfonamide**



According to the reaction protocol described in general procedure **A**, compound **2.4.1.2.3** (76%, 92 mg) was isolated as brownish oil.

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

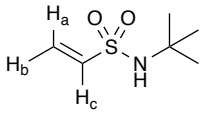
FTIR (neat): 3279, 3087, 3030, 2930, 2850, 1674, 1604, 1585, 1495, 1454, 1323, 1063, 1002, 915, 737, 700 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dt, *J* = 11.1, 6.7 Hz, 5H Ph), 6.49 (dd, *J* = 16.5, 9.8 Hz, 1H CH_aH_b=C$\underline{H}_c$), 6.26 (d, *J* = 16.5 Hz, 1H C$\underline{H}_aH_b$=CH_c), 5.92 (d, *J* = 9.9 Hz, 1H, $CH_a\underline{H}_b$=CH_c), 4.62 (s, 1H, N$\underline{H}$), 4.22 (d, *J* = 6.1 Hz, 2H, C$\underline{H}_2$);

^{13}C NMR (126 MHz, $CDCl_3$) 136.6 (C_{Ar}), 136.1 (CH_2=$\underline{C}$HS), 128.9 (2 C_{Ar}), 128.2 (C_{Ar}), 128.0 (2 C_{Ar}), 126.9 ($\underline{C}H_2$=CHS), 47.1 (Bn)

HRMS calculated for $C_9H_{11}NO_2S$ 198.0583 $(M+H)^+$; found 198.0597 (TOF MS ES^+).

***N*-(tert-butyl)ethenesulfonamide**



According to the reaction protocol described in general procedure **A**, compound **2.4.1.2.4** (77%, 5.16 g) was isolated as brownish oil.

R_f = 0.50 (EtOAc:Hexane = 1:1);

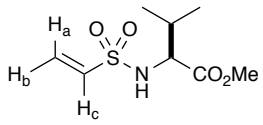
FTIR (neat): 3285, 2976, 2876, 1477, 1428, 1393, 1321, 1041, 997 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (dd, *J* = 16.5, 9.9 Hz, 1H, CH_aH_b=C<u>H</u>$_c$), 6.23 (d, *J* = 16.5 Hz, 1H, C<u>H</u>$_a$H$_b$=CH$_c$), 5.83 (d, *J* = 9.9 Hz, 1H, CH$_a$<u>H</u>$_b$=CH$_c$), 4.21 (s, 1H, N<u>H</u>), 1.35 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7 (CH_2=<u>C</u>HS), 124.5 (<u>C</u>H_2=CHS), 54.7 (C), 30.4 (3Me);

HRMS calculated for $C_6H_{13}NO_2S$ 164.0740 $(M+H)^+$; found 164.0749 (TOF MS ES^+).

Methyl (vinylsulfonyl)-*L*-valinate



According to the reaction protocol described in general procedure **A**, compound **2.4.1.2.5** (52%, 69 mg) was isolated as brownish oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -55.3 (*c* = 0.023, CH_2Cl_2);

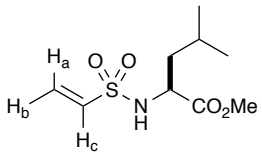
FTIR (neat): 3282, 3108, 3060, 2967, 2877, 1742, 1435, 1388, 1336, 1264, 1157, 1052, 993, 921 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 16.5, 9.9 Hz, 1H, CH_aH_b=C<u>H</u>$_c$), 6.17 (d, *J* = 16.5 Hz, 1H, C<u>H</u>$_a$H$_b$=CH$_c$), 5.86 (d, *J* = 9.9 Hz, 1H CH$_a$<u>H</u>$_b$=CH$_c$), 5.24 (s, 1H, N<u>H</u>), 3.70 (s, 3H, OC<u>H</u>$_3$), 2.09 (dtd, *J* = 13.6, 6.8, 4.9 Hz, 1H, CH_3C<u>H</u>CH_3), 0.96 (d, *J* = 6.8 Hz, 3H, C<u>H</u>$_3$), 0.84 (d, *J* = 6.9 Hz, 3H, C<u>H</u>$_3$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3 (<u>C</u>O$_2$Me), 136.0 (CH_2=<u>C</u>HS), 126.7 (<u>C</u>H$_2$=CHS), 61.0 (NH<u>C</u>CO$_2$Me), 52.4 (OMe), 31.4 (CH_3<u>C</u>HCH_3), 19.0 (CH_3), 17.3 (CH_3);

HRMS calculated for $C_8H_{15}NO_4S$ 222.0795 $(M+H)^+$; found 222.0802 (TOF MS ES^+).

Methyl (vinylsulfonyl)-*L*-leucinate



According to the reaction protocol described in general procedure **A**, compound **2.4.1.2.6** (91%, 3.5 g) was isolated as brownish oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -50.2 (*c* = 0.0045, CH_2Cl_2);

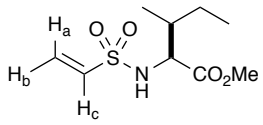
FTIR (neat): 2967, 1740, 1435, 1388, 1335, 1252, 1138, 1052 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 16.5, 9.9 Hz, 1H, CH_aH_b=C<u>H</u>$_c$), 6.23 (dd, *J* = 16.6, 1.0 Hz, 1H, C<u>H</u>$_a$$H_b$=$CH_c$), 5.90 (d, *J* = 9.9 Hz, 1H, CH_a<u>H</u>$_b$=CH_c), 4.92 (t, *J* = 10.6 Hz, 1H, NH), 3.79–3.76 (m, 1H, NHC<u>H</u>CO_2Me), 3.75 (s, 3H, Me), 2.19–2.09 (m, 1H, CH), 1.02 (d, *J* = 6.8 Hz, 3H, CH_3), 0.88 (d, *J* = 6.9 Hz, 3H, CH_3);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5 (<u>C</u>O_2Me), 136.1 (CH_2=<u>C</u>HS), 127.0 (<u>C</u>H_2=CHS), 61.0 (NH<u>C</u>HCO_2Me), 52.6 (OMe), 31.6 (CH_2), 19.2 (2-CH_3), 17.3 (CH);

HRMS calculated for $C_9H_{17}NO_4S$ 253.1217 $(M+NH_4)^+$; found 253.1231 (TOF MS ES^+).

Methyl (vinylsulfonyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **A**, compound **2.4.1.2.7** (76%, 1.96 g) was isolated as brownish oil.

R_f = 0.25 (EtOAc:Hexane = 1:2);

$[\alpha]_D^{20}$ = -42.57 (*c* = 0.007, CH_2Cl_2);

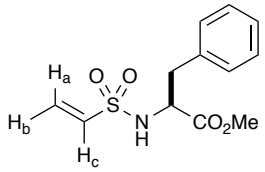
FTIR (neat): 3108, 2966, 2879, 1740, 1455, 1385, 1337, 1275, 1157, 1087, 882 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 16.5, 9.9 Hz, 1H, CH_aH_b=C<u>H</u>$_c$), 6.22 (d, *J* = 16.5 Hz, 1H, C<u>H</u>$_a$H$_b$=CH$_c$), 5.90 (d, *J* = 9.9 Hz, 1H, CH$_a$<u>H</u>$_b$=CH$_c$), 4.97 (d, *J* = 9.8 Hz, 1H, NH), 3.81 (dd, *J* = 9.8, 4.9 Hz, 1H, NHC<u>H</u>CO_2Me), 3.74 (s, 3H, OMe), 1.87 (dddd, *J* = 13.5, 8.9, 5.7, 2.4 Hz, 1H, CHC<u>H</u>$_2$CH$_3$), 1.39 (ddq, *J* = 14.8, 7.4, 4.5, 3.7 Hz, 1H, CHC<u>H</u>$_2$CH$_3$), 1.22–1.12 (m, 1H, CH_3C<u>H</u>CH_2), 0.97 (d, *J* = 6.8 Hz, 3H, Me), 0.90 (t, *J* = 7.4 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5 (<u>C</u>O_2Me), 136.1 (CH_2=<u>C</u>HS), 127.0 (<u>C</u>H_2=CHS), 60.4 (NH<u>C</u>HCO_2Me), 52.5 (OMe), 38.4 (CH), 24.7 (CH_2), 15.6 (Me), 11.5 (Me);

HRMS calculated for $C_9H_{17}NO_4S$ 253.1217 $(M+NH_4)^+$; found 253.1231 (TOF MS ES^+).

Methyl (vinylsulfonyl)-*L*-phenylalaninate



According to the reaction protocol described in general procedure **A**, compound **2.4.1.2.8** (92 %, 3.04 g) was isolated as brownish oil.

R_f = 0.60 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -20.0 (*c* = 0.0115, CH_2Cl_2);

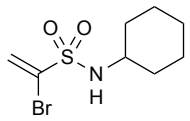
FTIR (neat): 3062, 3030, 2954, 1743, 1604, 1455, 1436, 1385, 1275, 1151, 1109, 1030, 904, 748, 702 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.24 (m, 3H, *m*-C<u>H</u>-*p*-C<u>H</u>-*m*-C<u>H</u>), 7.17–7.14 (m, 2H, 2-*o*-C<u>H</u>), 6.26 (dd, *J* = 16.5, 9.8 Hz, 1H, CH_aH_b=C<u>H</u>$_c$), 6.13 (d, *J* = 16.5 Hz, 1H, C<u>H</u>$_a$$H_b$=$CH_c$), 5.78 (d, *J* = 9.7 Hz, 1H, CH_a<u>H</u>$_b$=CH_c), 4.97 (s, 1H, NH), 4.23 (dt, *J* = 8.5, 6.3 Hz, 1H, NHC<u>H</u>CO_2Me), 3.73 (s, 3H, OMe), 3.15–3.03 (m, 2H, CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7 (<u>C</u>O_2Me), 136.0 (CH_2=<u>C</u>HS), 135.2 (C_{Ar}), 129.6 (2 C_{Ar}), 128.8 (2 C_{Ar}), 127.5 (CH_2<u>C</u>HS), 126.6 (C_{Ar}), 56.8 (NH<u>C</u>HCO_2Me), 52.7 (OMe), 39.5 (CH_2);

HRMS calculated for $C_{12}H_{15}NO_4S$ 270.0795 $(M+H)^+$; found 270.0804 (TOF MS ES^+).

1-Bromo-*N*-cyclohexylethenesulfonamide



According to the reaction protocol described in general procedure **B**, compound **2.4.1.4.1** (75%, 150.2 mg) was isolated as brownish oil.

R_f = 0.73 (EtOAc:Hexane = 1:2);

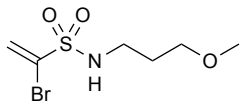
FTIR (neat): 3280, 2955, 1601, 1433, 1423, 1326, 1165, 1103, 925, 910, 755, 599, 552 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 6.18 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 4.52 (s, 1H, NH), 3.21 (dddd, *J* = 7.8, 5.7, 3.9, 3.9 Hz, 1H, CH), 2.10–1.89 (m, 2H, Cy), 1.84–1.66 (m, 2H, Cy), 1.63–1.51 (m, 1H, Cy), 1.40–1.25 (m, 4H, Cy), 1.24–1.12 (m, 1H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 128.5 (CH_2=$\underline{C}$HBrS), 127.8 ($\underline{C}H_2$=CHBrS), 53.4 (Cy), 33.8 (2 Cy), 25.1 (2) (Cy), 24.6 (Cy);

HRMS calculated for $C_8H_{14}BrNO_2S$ 269.1792 $(M+H)^+$; found 269.1796 (TOF MS ES^+).

1-Bromo-*N*-(3-methoxypropyl)ethenesulfonamide



According to the reaction protocol described in general procedure **B**, compound **2.4.1.4.2** (71%, 120.6 mg) was isolated as brownish oil.

R_f = 0.46 (EtOAC:Hexane = 1:1);

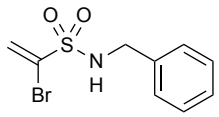
FTIR (neat): 3236, 3112, 2971, 2879, 1619, 1453, 1349, 1193 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 6.21 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 5.51 (s, 1H, NH), 3.63–3.46 (m, 2H, CH_2), 3.35 (s, 3H, OMe), 3.25–3.02 (m, 2H, CH_2), 1.92–1.77 (m, 2H, CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 128.3 (CH_2=$\underline{C}$HBrS), 127.1 ($\underline{C}H_2$=CHBrS), 71.7 ($\underline{C}H_2$OMe), 58.9 (OMe), 42.8 (CH_2), 28.6 (CH_2);

HRMS calculated for $C_6H_{12}BrNO_3S$ 257.9794 $(M+H)^+$; found 257.9804 (TOF MS ES^+).

***N*-Benzyl-1-bromoethenesulfonamide**



According to the reaction protocol described in general procedure **B**, compound **2.4.1.4.3** (79%, 132.5 mg) was isolated as brownish oil.

R_f = 0.69 (EtOAc:Hexane 1:1);

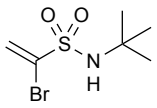
FTIR (neat): 3106, 2999, 2910, 1612, 1457, 1341, 1201 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H, Ph), 6.88 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.23 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 5.04–4.63 (m, 1H, NH), 4.24 (d, *J* = 6.0 Hz, 2H CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6 (C_{Ar}), 128.8 (2C_{Ar}), 128.7 (C_{Ar}), 128.3 ($\underline{C}H_2$=CH), 128.1 (2C_{Ar}), 127.1 (CH_2=$\underline{C}$H), 47.7 (CH_2);

HRMS calculated for $C_9H_{10}BrNO_2S$ 275.9688 $(M+H)^+$; found 275.9692 (TOF MS ES^+).

1-Bromo-*N*-(*tert*-butyl)ethenesulfonamide



According to the reaction protocol described in general procedure **B**, compound **2.4.1.4.4** (78%, 118.5 mg) was isolated as white solid.

R_f = 0.51 (EtOAc:Hexane = 1:2);

M. P. = 96–97 ºC;

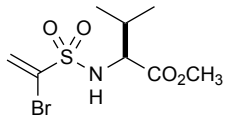
FTIR (neat): 3102, 2991, 2901, 1612, 1453, 1349, 1193 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 6.13 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 1.37 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.2 (C$\underline{H}_2$=CBrS), 126.9 (CH_2=C$\underline{B}$rS), 55.4 (C$\underline{\ }^t$Bu), 29.7 (^{t}Bu,);

HRMS calculated for $C_6H_{12}BrNO_2S$ 259.0110 $(M+H)^+$; found 259.0106 (TOF MS ES^+).

Methyl ((1-bromovinyl)sulfonyl)-*L*-valinate



According to the reaction protocol described in general procedure **B**, compound **2.4.1.4.5** (73%, 2.89 g) was isolated as brownish oil.

R_f = 0.44 (EtOAC:Hexane = 1:2);

$[\alpha]_D^{20}$ = -2.62 (*c* = 0.008, CH_2Cl_2);

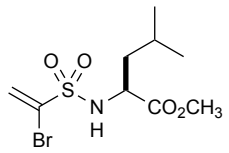
FTIR (neat): 2987, 1737, 1435, 1344, 1275, 1260, 1149, 1047, 888 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H, C<u>H</u>$_2$=CBrS), 6.17 (s, 1H, C<u>H</u>$_2$=CBrS), 5.23 (d, *J* = 9.1 Hz, 1H, N<u>H</u>), 3.87 (dd, *J* = 9.4, 4.9 Hz, 1H N<u>H</u>CO_2Me), 3.78 (s, 3H, OMe), 2.14 (dq, *J* = 13.5, 6.8 Hz, 1H, CH_3C<u>H</u>CH_3), 1.02 (d, *J* = 6.8 Hz, 3H, Me), 0.93 (d, *J* = 6.9 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (<u>C</u>O_2Me), 128.3 (<u>C</u>H_2CBrS), 127.4 (CH_2<u>C</u>BrS), 61.8 (NH<u>C</u>HCO_2Me), 52.5 (OMe), 31.8 (Me<u>C</u>HMe), 18.8 (Me), 17.3(Me);

HRMS calculated for $C_8H_{14}BrNO_4S$ 321.9719 $(M+Na)^+$; found 321.9734 (TOF MS ES^+).

Methyl ((1-bromovinyl)sulfonyl)-*L*-leucinate



According to the reaction protocol described in general procedure **B**, compound **2.4.1.4.6** (74%, 3.54 g) was isolated as syrup.

R_f = 0.82 (EtOAc:Hexane = 1/1);

$[\alpha]_D^{20}$= -13.2 (*c* = 0.0016, CH_2Cl_2);

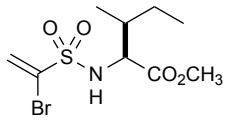
FTIR (neat): 3112, 2966, 1739, 1602, 1435, 1343, 1273, 1169, 1095, 1056, 885 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H, C<u>H</u>$_2$=CBrS), 6.17 (s, 1H, C<u>H</u>$_2$=CBrS), 5.14 (d, *J* = 9.2 Hz, 1H, NH), 4.04 (td, *J* = 8.7, 6.3 Hz, 1H, N<u>H</u>CO_2Me), 3.77 (s, 3H, OMe), 1.84 (dp, *J* = 13.4, 6.7 Hz, 1H, MeC<u>H</u>Me), 1.65–1.53 (m, 2H, C<u>H</u>$_2$), 0.95 (t, *J* = 6.3 Hz, 6H, 2Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2 (<u>C</u>O_2Me), 128.2 (CH_2=<u>C</u>BrS), 127.4 (<u>C</u>H_2=CBrS), 55.1 (NH<u>C</u>HCO_2Me), 52.5 (OMe), 42.5 (CH_2), 24.3 (Me<u>C</u>HMe), 22.6 (Me), 21.6 (Me);

HRMS calculated for $C_9H_{16}BrNO_4S$ 314.0056 $(M+H)^+$; found 314.0049 (TOF MS ES^+).

Methyl ((1-bromovinyl)sulfonyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **B**, compound **2.4.1.4.7** (74%, 3.54 g) was isolated as brownish oil.

R_f = 0.82 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = 9.37 (*c* = 0.0858, CH_2Cl_2);

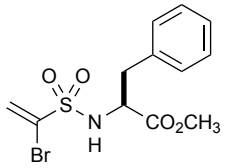
FTIR (neat): 3112, 2966, 1739, 1602, 1435, 1343, 1273, 1169, 1095, 1056, 885 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, 1H C$\underline{H}_2$=CBrS), 6.19 (d, 1H, C$\underline{H}_2$=CBrS), 5.24 (d, *J* = 9.2 Hz, 1H, NH), 3.92 (dd, *J* = 9.3, 5.1 Hz, 1H, NHC$\underline{H}$CO$_2$Me), 3.77 (s, 3H, OMe), 1.87 (dddt, *J* = 11.4, 6.8, 4.6, 2.3 Hz, 1H, MeC$\underline{H}$CH$_2$Me), 1.46 (dtd, *J* = 14.9, 7.4, 4.5 Hz, 1H, CHC$\underline{H}_2$Me), 1.34 – 1.13 (m, 1H, CHC$\underline{H}_2$Me), 0.97 (d, *J* = 6.8 Hz, 3H, Me), 0.92 (t, *J* = 7.4 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (C$\underline{O}_2$Me), 128.3(CH$_2$=C$\underline{C}$BrS), 127.4 (C$\underline{H}_2$=CBrS), 61.0 (NH$\underline{C}$HCO$_2$Me), 52.4 (OMe), 38.6 (Me$\underline{C}$HCH$_2$), 24.6 (CH$_2$), 15.3 (Me), 11.3 (Me);

HRMS calculated for $C_9H_{16}BrNO_4S$ 314.0056 $(M+H)^+$; found 314.0049 (TOF MS ES^+).

Methyl ((1-bromovinyl)sulfonyl)-*L*-phenylalaninate



According to the reaction protocol described in general procedure **B**, compound **2.4.1.4.8** (62%, 2.6 g) was isolated as brownish oil.

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

$[\alpha]_D^{20}$ = -5.5 (*c* = 0.004, CH_2Cl_2);

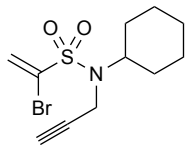
FTIR (neat): 2955, 2910, 1734, 1458, 1364, 1182, 1094, 1038, 922, 781 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.26 (m, 3H, 2*m*/1*p*-CH), 7.21–7.13 (m, 2H, 2*o*-CH), 6.78 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.12 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 5.20 (d, *J* = 8.5 Hz, 1H, NH), 4.33 (dt, *J* = 8.5, 5.7 Hz, 1H, NHC$\underline{H}CO_2Me$), 3.74 (d, *J* = 1.5 Hz, 3H, OMe), 3.14 (d, *J* = 5.7 Hz, 2H, CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 ($\underline{C}O_2Me$), 134.5 (C_{Ar}), 129.5 (2 C_{Ar}), 128.7 (2 C_{Ar}), 128.6 (C_{Ar}), 128.2 (CH_2=$\underline{C}$BrS), 127.4 ($\underline{C}H_2$=CBrS), 57.3 (NH$\underline{C}HCO_2Me$), 52.6 (OMe), 39.5 (CH_2);

HRMS calculated for $C_{12}H_{14}BrNO_4S$ 369.9719 $(M+Na)^+$; found 369.9750 (TOF MS ES^+).

1-Bromo-*N*-cyclohexyl-*N*-(prop-2-yn-1-yl)ethene-1-sulfonamide



According to the reaction protocol described in general procedure **C**, compound **2.4.1.5.1** (90%, 3.02g) was isolated as a brown syrup.

R_f = 0.64 (EtOAc:Hexane = 1:2);

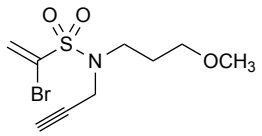
FTIR (neat): 3283, 2935, 2857, 1602, 1338, 1050, 884 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 6.14 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 4.09 (d, *J* = 2.5 Hz, 2H, NC$\underline{H}_2$CCH), 3.69 (tt, *J* = 12.1, 3.7 Hz, 1H, CH), 2.26 (t, *J* = 2.5 Hz, 1H, $NCH_2C\underline{C}H$), 2.01 – 1.92 (m, 2H, Cy), 1.88 – 1.78 (m, 2H, Cy), 1.63 (td, *J* = 12.3, 3.5 Hz, 2H, Cy), 1.58 (dd, *J* = 12.4, 3.6 Hz, 1H, Cy), 1.32 (qt, *J* = 13.2, 3.5 Hz, 2H, Cy), 1.09 (qt, *J* = 13.1, 3.7 Hz, 1H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 128.0 (CH_2=$\underline{C}$HBrS), 127.8 ($\underline{C}H_2$=CHBrS), 79.5 ($CH_2\underline{C}CH$), 72.3 ($CH_2C\underline{C}H$), 59.2 (N$\underline{C}$HCy), 33.2 ($\underline{C}H_2CCH$), 31.6 (2 Cy), 25.9 (2 Cy), 25.1 (Cy);

HRMS calculated for $C_{11}H_{16}BrNO_2S$ 306.0158 $(M+H)^+$; found 306.0164 (TOF MS ES^+).

1-Bromo-*N*-(3-methoxypropyl)-*N*-(prop-2-yn-1-yl)ethene-1-sulfonamide



According to the reaction protocol described in general procedure **C**, compound **2.4.1.5.2** (18%, 22 mg) was isolated as a brown syrup.

R_f = 0.57 (EtOAc:Hexane = 1:1);

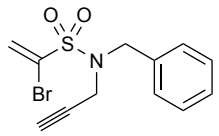
FTIR (neat): 3279, 3111, 3057, 2927, 2876, 1622, 1331, 1163, 1068, 882, 631 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 2.7 Hz, 1H, C$\underline{H}_2$=CBrS), 6.19 (d, *J* = 2.7 Hz, 1H, C$\underline{H}_2$=CBrS), 4.14 (d, *J* = 1.9 Hz, 2H, NC$\underline{H}_2$CC), 3.53 (t, *J* = 7.1 Hz, 2H, NC$\underline{H}_2$), 3.44 (t, *J* = 6.0 Hz, 2H, C$\underline{H}_2$OMe), 3.33 (s, 3H, OMe), 2.33 (s, 1H, CCH), 1.90 (p, *J* = 6.4 Hz, 2H, $CH_2C\underline{H}_2CH_2$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 128.6 (CH_2=$\underline{C}$BrS), 126.9 ($\underline{C}H_2$=CBrS), 76.6 ($CH_2\underline{C}$CH), 74.0 ($CH_2C\underline{C}$H), 69.5 (CH_2OMe), 58.8 (OMe), 45.6 (CH_2), 37.4 (N$\underline{C}H_2$CCH), 28.4 (CH_2);

HRMS calculated for $C_9H_{14}BrNO_3S$ 317.9770 $(M+Na)^+$; found 317.9759 (TOF MS ES^+).

***N*-Benzyl-1-bromo-*N*-(prop-2-yn-1-yl)ethene-1-sulfonamide**



According to the reaction protocol described in general procedure **C**, compound **2.4.1.5.3** (94%, 63 mg) was isolated as a brown syrup.

R_f = 0.48 (EtOAc:Hexane = 1:3);

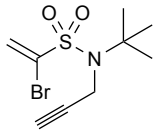
FTIR (neat): 3285, 3062, 2932, 2871, 2123, 1601, 1497, 1454, 1358, 1061, 905, 736, 700 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H, Ph), 6.91 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.24 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 4.64 (s, 2H, NC$\underline{H}_2$CC), 3.94 (d, *J* = 2.4 Hz, 2H, CH_2), 2.37 (t, *J* = 2.4 Hz, 1H, CCH);

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.8 (C_{Ar}), 128.9 (2 C_{Ar}), 128.8 (2 C_{Ar}), 128.6 (C_{Ar}), 128.4 ($\underline{C}H_2$=CBrS), 127.2 (CH_2=$\underline{C}$BrS), 75.9 ($\underline{C}$CH), 74.5 (C$\underline{C}$H), 51.4 ($\underline{C}H_2$Ph), 36.0 (N$\underline{C}H_2$CH);

HRMS calculated for $C_{12}H_{12}BrNO_2S$ 313.9845 $(M+H)^+$; found 313.9854 (TOF MS ES^+).

1-Bromo-*N*-(*tert*-butyl)-*N*-(prop-2-yn-1-yl)ethene-1-sulfonamide



According to the reaction protocol described in general procedure **C**, compound **2.4.1.5.4** (95%, 2.87 g) was isolated as a brown syrup.

R_f = 0.43 (EtOAc:Hexane = 1:1);

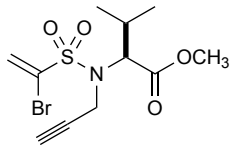
FTIR (neat): 2957, 2884, 2400, 1773, 1724, 1182, 1069, 1036, 991, 959, 922 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 2.7 Hz, 1H, C$\underline{H}_2$=CBrS), 6.10 (d, *J* = 2.8 Hz, 1H, C$\underline{H}_2$=CBrS), 4.24 (s, 2H, NC$\underline{H}_2$CCH), 2.33 (s, 1H, NCH$_2$CC$\underline{H}$), 1.54 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.0 (CH$_2$=$\underline{C}$BrS), 126.9 ($\underline{C}$H$_2$=CBrS), 81.0 (NCH$_2$$\underline{C}$CH), 72.5 (NCH$_2$$\underline{C}$CH), 61.0 ($\underline{C}$^{t}Bu) , 37.1 (N$\underline{C}H_2$CCH), 29.7 (^{t}Bu);

HRMS calculated for $C_9H_{14}BrNO_2S$ 280.0001 $(M+H)^+$; found 280.0013 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-*L*-valinate



According to the reaction protocol described in general procedure **C**, compound **2.4.1.5.5** (57%, 11.9g) was isolated as an orange oil.

R_f = 0.63 (EtOAc:Hexane = 1:2);

$[\alpha]_D^{20}$ = -22.8 (*c* = 0.007, CH_2Cl_2);

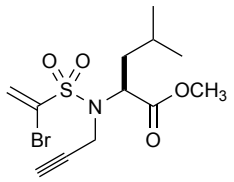
FTIR (neat): 1205, 1255, 1300, 1346, 1435, 1469, 1600, 1739, 2848, 2875, 2966, 3022, 3111, 3284 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.20 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 4.52 (dd, *J* = 18.8, 2.5 Hz, 1H, NC$\underline{H}_2$CCH), 4.29 (dd, *J* = 18.8, 2.5 Hz, 1H, NC$\underline{H}_2$CCH), 4.03 (d, *J* = 10.4 Hz, 1H CCH), 3.73 (s, 3H, OMe), 2.20 (m, 2H, NC$\underline{H}$C$\underline{H}$), 1.16 (d, *J* = 6.6 Hz, 3H, Me), 0.97 (d, *J* = 6.6 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 ($\underline{C}O_2$Me), 129.3 ($\underline{C}H_2$=CBrS), 126.5 (CH_2=$\underline{C}$BrS), 78.9 ($\underline{C}$CH), 72.4 (C$\underline{C}$H),), 65.6 (N$\underline{C}$HCO_2Me), 51.7 (OMe), 35.1 ($\underline{C}H_2$CCH), 28.9 (Me$\underline{C}$HMe), 19.9 (Me), 19.1 (Me);

HRMS calculated for $C_{11}H_{16}BrNO_4S$ 338.0056 $(M+H)^+$; found 338.0054 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-*L*-leucinate



According to the reaction protocol described in general procedure **C**, compound **2.4.1.5.6** (89%, 3.1g) was isolated as a white solid.

R_f = 0.71 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -0.6 (*c* = 0.0016, CH_2Cl_2);

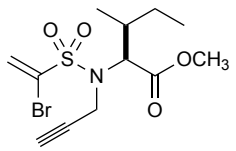
FTIR (neat): 2958, 2870, 1741, 1642, 1469, 1273, 1156, 1055, 873 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.18 (d, *J* = 2.9 Hz, 1H, C$\underline{H}_2$=CBrS), 4.54 (dd, *J* = 9.7, 5.1 Hz, 1H, NC$\underline{H}_2$CCH), 4.36–4.26 (m, 2H, C$\underline{H}_2$CCH), 3.73 (s, 3H, OMe), 2.29 (t, *J* = 2.4 Hz, 1H, CCH), 1.91 (tdd, *J* = 13.1, 8.3, 4.5 Hz, 2H, C$\underline{H}_2$MeCHMe), 1.71 (td, *J* = 8.7, 3.7 Hz, 1H, CH_2MeC$\underline{H}$Me), 0.99 (d, *J* = 6.4 Hz, 3H, Me), 0.97 (d, *J* = 6.5 Hz, 3H, Me)

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7 ($\underline{C}O_2$Me), 128.8 ($\underline{C}H_2$=CBrS), 127.0 (CH_2=$\underline{C}$BrS), 79.0 ($\underline{C}$CH), 72.6 (C$\underline{C}$H), 58.5 (N$\underline{C}$HCO_2Me), 52.3 (OMe), 39.2 (CH_2), 35.4 (CH_2), 24.5 (CH), 22.7 (Me), 21.5(Me)

HRMS calculated for $C_{12}H_{18}BrNO_4S$ 352.0213 $(M+H)^+$; found 352.0240 (TOF MS ES^+)

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **C**, compound **2.4.1.5.7** (85%, 3.4g) was isolated as a clear oil.

R_f = 0.68 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -41.5; (*c* = 0.004, CH_2Cl_2);

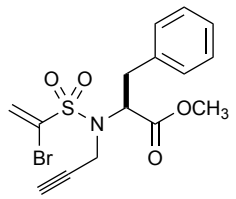
FTIR (neat): 3284, 2967, 2936, 2878, 1738, 1602, 1462, 1435, 1258, 1150, 1048, 880 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.20 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 4.55 (dd, *J* = 18.9, 2.5 Hz, 1H, NC$\underline{H}_2$CCH), 4.30 (dd, *J* = 18.9, 2.5 Hz, 1H, NC$\underline{H}_2$CCH), 4.09 (d, *J* = 10.4 Hz, 1H, CCH), 3.72 (s, 3H, OMe), 2.30 (t, *J* = 2.5 Hz, 1H, NC$\underline{H}CO_2$Me), 2.13-1.84 (m, 2H, MeC$\underline{H}_2$CHMe), 1.27-1.11 (m, 1H, MeCH$_2$C$\underline{H}$Me), 1.02-0.82 (m, 6H, 2Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 ($\underline{C}O_2$Me), 129.5 ($\underline{C}H_2$=CBrS), 126.5 (CH_2=$\underline{C}$BrS), 79.3 ($\underline{C}$CH), 72.2 (C$\underline{C}$H), 64.5 (NC$\underline{H}CO_2$Me), 51.8 (OMe), 35.2 (NCH_2), 35.0 (MeC$\underline{H}CH_2$), 25.7 ($\underline{C}H_2$Me), 15.3 (Me), 10.7 (Me);

HRMS calculated for $C_{12}H_{18}BrNO_4S$ 352.0213 $(M+H)^+$; found 352.0239 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-*L*-phenylalaninate



According to the reaction protocol described in general procedure **C**, compound **2.4.1.5.8** (55%, 2.6 g) was isolated as a clear oil.

R_f = 0.65 (EtOAc:Hexane = 1:2);

$[\alpha]_D^{20}$ = -27.81 (*c* = 0.0055, CH_2Cl_2);

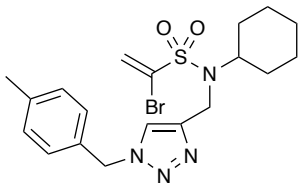
FTIR (neat): 3283, 2970, 2359, 2341, 1742, 1344, 1286, 1226, 1163, 1149, 700 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5H, Ph), 6.81 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.13 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 4.73 (ddd, *J* = 8.8, 6.7, 2.4 Hz, 1H NC$\underline{H}CO_2$Me), 4.45–4.29 (m, 2H, CH_2Ph), 3.71 (s, 1H, CCH) 3.65 (s, 3H, OMe), 3.41 (dd, *J* = 13.8, 8.8 Hz, 1H, NC$\underline{H}_2$CCH), 3.28 (dd, *J* = 13.8, 6.4 Hz, 1H, NC$\underline{H}_2$CCH);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3 ($\underline{C}O_2$Me), 136.0 (C_{Ar}), 129.2 (2 C_{Ar}), 128.7 (C_{Ar}), 128.6 (2 C_{Ar}), 128.6 ($\underline{C}H_2$=CBrS), 127.1 (CH_2=$\underline{C}$BrS), 78.2 ($\underline{C}$CH), 73.4 (C$\underline{C}$H), 61.4 (N$\underline{C}$HCO$_2$Me), 52.1 (OMe), 36.7 (C$\underline{H}_2$CCH), 35.6 (CH$\underline{C}H_2$Ph);

HRMS calculated for $C_{15}H_{16}BrNO_4S$ 403.0322 $(M+NH_4)^+$; found 403.0345 (TOF MS ES^+).

1-Bromo-*N*-cyclohexyl-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.1** (78%, 0.97 g) was isolated as brownish oil.

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

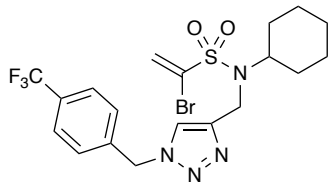
FTIR (neat): 2934, 2857, 1642, 1601, 1547, 1516, 1451, 1338, 1051, 886, 815 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H, C<u>H</u>NNN), 7.18–7.11 (m, 4H Ar), 6.76 (d, *J* = 2.8 Hz, 1H, C<u>H</u>CBr), 6.09 (d, *J* = 2.8 Hz, 1H, C<u>H</u>CBr), 5.46 (s, 2H, NC<u>H</u>$_2$Ar), 4.59 (s, 2H, NC<u>H</u>$_2$NNN), 3.56 (tt, *J* = 12.1, 3.7 Hz, 1H, NC<u>H</u>CH$_2$), 2.34 (s, 3H, Me), 1.80–1.66 (m, 4H, Cy), 1.61–1.44 (m, 4H, Cy), 1.30–1.18 (m, 2H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5 (C_{Ar}), 138.6 (C_{Ar}), 131.6 ($SO_2NCH_2\underline{C}C$), 129.7 (2 C_{Ar}), 128.0 ($\underline{C}H_2$=CBrS), 127.9 (CH_2=$\underline{C}$BrS), 127.8 (2 C_{Ar}), 123.7 ($SO_2NCH_2C\underline{C}$), 59.1 (Ar$\underline{C}H_2$), 54.0 (N$\underline{C}$H), 40.1 (N$\underline{C}H_2$), 31.6 (2Cy), 26.0 (2Cy), 24.9 (Cy), 21.1 (Me);

HRMS calculated for $C_{19}H_{25}BrN_4O_2S$ 453.0954 $(M+H)^+$; found 453.0967 (TOF MS ES^+).

1-Bromo-*N*-cyclohexyl-*N*-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.2** (65%, 0.906 g) was isolated as brownish oil.

R_f = 0.26 (EtOAc:Hexane = 1:2);

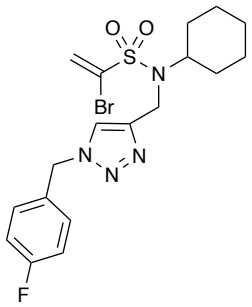
FTIR (neat): 3145, 3112, 3057, 2937, 2859, 1621, 1601, 1452, 1324, 1052, 886, 817 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H, C<u>H</u>NNN), 7.54 (d, *J* = 8.1 Hz, 2H, *m*-<u>C</u>H), 7.29 (d, *J* = 8.1 Hz, 2H, *o*-<u>C</u>H), 6.71 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 6.05 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 5.54 (s, 2H, Ar<u>C</u>H_2), 4.55 (s, 2H, NCH_2), 3.51 (tt, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.72–1.61 (m, 4H, Cy), 1.54–1.38 (m, 4H, Cy), 1.24–1.12 (m, 2H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8 (SO_2NCH_2<u>C</u>C), 138.7 (C_{AR}), 130.5 (C_{Ar}, q, $^2J_{C–CF3}$ = 32.81 Hz), 127.9 (<u>C</u>H_2=CBrS), 127.8 (2 C_{Ar}), 127.5 (CH_2=<u>C</u>BrS), 125.71 (q, $^3J_{C–CF3}$ = 3.79 Hz, 2 C_{Ar}), 123.9 (SO_2NCH_2<u>C</u><u>C</u>), 123.5 (q, $^1J_{C–CF3}$ = 272.10 Hz, CF_3), 58.9 (NCH), 53.1 (Ar<u>C</u>H_2), 39.8 (NCH_2), 31.5 (2 Cy), 25.7 (Cy), 24.7 (2 Cy);

HRMS calculated for $C_{19}H_{22}BrF_3N_4O_2S$ 507.0672 $(M+H)^+$; found 507.0675 (TOF MS ES^+).

1-Bromo-*N*-cyclohexyl-*N*-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.3** (88%, 0.36 g) was isolated as a white solid.

R_f = 0.29 (EtOAc:Hexane = 1:2);

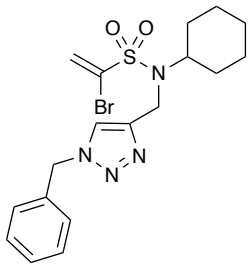
FTIR (neat): 3005, 2989, 1605, 1337, 1275, 1260, 1224, 1154, 1128, 1092, 750 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H, C<u>H</u>NNN), 7.17 (dd, *J* = 12.7, 4.8 Hz, 2H, ArH), 6.98 (t, *J* = 8.4 Hz, 2H, ArH), 6.71 (d, *J* = 2.4 Hz, 1H, C<u>H</u>CBr), 6.04 (d, *J* = 2.4 Hz, 1H, C<u>H</u>CBr), 5.40 (s, 2H, Ar<u>C</u>H_2), 4.53 (s, 2H, NCH_2), 3.49 (t, *J* = 12.0 Hz, 1H, NCH), 1.66 (dd, *J* = 22.5, 13.0 Hz, 4H, Cy), 1.59 – 1.32 (m, 3H, Cy), 1.17 (q, *J* = 13.0 Hz, 2H, Cy), 1.01 (t, *J* = 12.9 Hz, 1H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 (d, *J* = 247.5 Hz, C_{Ar}), 147.0 (SO_2NCH_2<u>C</u>C), 130.6 (d, *J* = 3.3 Hz, SO_2NCH_2C<u>C</u>), 129.9 (d, *J* = 8.5 Hz, 2 C_{Ar}), 128.2 (<u>C</u>H_2=CBrS), 127.8 (CH_2=<u>C</u>BrS), 123.8 (C_{Ar}), 116.2 (d, *J* = 21.8 Hz, 2 C_{Ar}), 59.2 (Ar<u>C</u>H_2), 53.5 (NCH), 40.2 (NCH_2), 31.7 (2 Cy), 26.1 (Cy), 25.0 (2 Cy);

HRMS calculated for $C_{18}H_{22}BrFN_4O_2S$ 457.0709 $(M+H)^+$; found 457.0720 (TOF MS ES^+).

***N*-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-1-bromo-*N*-cyclohexylethene-1-sulfonamide**



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.4** (91%, 0.44 g) was isolated as brown oil.

R_f = 0.33 (EtOAc:Hexane = 1:2);

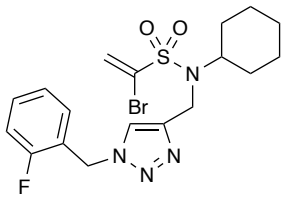
FTIR (neat): 3120, 2934, 2857, 1601, 1454, 1338, 1167, 1153, 1090, 1031, 916, 816, 718 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H, C<u>H</u>NNN), 7.39 (d, *J* = 5.9 Hz, 3H, ArH), 7.29 (d, *J* = 6.0 Hz, 2H, ArH), 6.79 (d, *J* = 2.3 Hz, 1H, C<u>H</u>CBr), 6.12 (d, *J* = 2.3 Hz, 1H, C<u>H</u>CBr), 5.54 (s, 2H, Ar<u>C</u>H_2), 4.63 (s, 2H, NCH_2), 3.60 (t, *J* = 11.9 Hz, 1H, NCH), 1.88–1.70 (m, 4H, Cy), 1.68–1.44 (m, 3H, Cy), 1.28 (q, *J* = 13.0 Hz, 2H, Cy), 1.12 (t, *J* = 12.8 Hz, 1H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6 (SO_2NCH_2<u>C</u>C), 134.6 (C_{Ar}), 129.0 (2 C_{Ar}), 128.7 (<u>C</u>H_2=CBrS), 128.0 (CH_2=<u>C</u>BrS), 127.8 (SO_2NCH_2<u>C</u>C), 127.8 (2 C_{Ar}), 123.8 (C_{Ar}), 59.1 (Ar<u>C</u>H_2), 54.2 (NCH), 40.1 (NCH_2), 31.6 (Cy), 26.0 (2 Cy), 24.9 (2 Cy);

HRMS calculated for $C_{18}H_{23}BrN_4O_2S$ 439.0798 $(M+H)^+$; found 439.0807 (TOF MS ES^+).

1-bromo-*N*-cyclohexyl-*N*-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.5** (76%, 0.955 g) was isolated as colorless oil.

R_f = 0.63 (EtOAc:Hexane = 1:1);

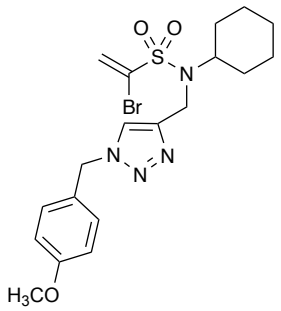
FTIR (neat): 3147, 3110, 3053, 2935, 2857, 1618, 1600, 1589, 1493, 1455, 1051, 886, 759 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H, CHNNN), 7.14 (td, *J* = 7.5, 1.8 Hz, 1H, ArH), 7.08–7.05 (m, 1H, ArH), 7.31–7.24 (m, 1H, ArH), 7.05–7.01 (m, 1H, ArH), 6.69 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 6.02 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 5.51 (s, 2H, $ArCH_2$), 4.54 (s, 2H, NCH_2), 3.52 (tt, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.74–1.62 (m, 4H, Cy), 1.55–1.39 (m, 4H, Cy), 1.24–1.10 (m, 2H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3 (d, J = 248.1 Hz, C_{AR}), 146.2 ($SO_2NCH_2\underline{C}C$), 130.6 (d, $^3J_{C-F}$ = 8.19 Hz, C_{Ar}), 130.0 (d, $^5J_{C-F}$ = 3.08 Hz, C_{Ar}), 127.8 ($\underline{C}H_2$=CBrS), 127.6 (CH_2=$\underline{C}$BrS), 124.5 (d, $^4J_{C-F}$ = 3.70 Hz, C_{Ar}), 123.73 ($SO_2NCH_2C\underline{C}$), 121.7 (d, $^2J_{C-F}$ = 14.61 Hz, C_{Ar}), 115.5 (d, $^6J_{C-F}$ = 20.95 Hz, C_{Ar}), 58.9 (NCH), 47.5 (d, $_{benzylCH2}J_{C-F}$ = 4.46 Hz), 39.8 (NCH_2), 31.4 (2, Cy), 25.8 (Cy), 24.7 (2, Cy);

HRMS calculated for $C_{18}H_{22}BrFN_4O_2S$ 457.0704 $(M+H)^+$; found 457.0712 (TOF MS ES^+).

1-Bromo-*N*-cyclohexyl-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.6** (84%, 0.395 g) was isolated as colorless oil.

R_f = 0.24 (EtOAc:Hexane = 1:2);

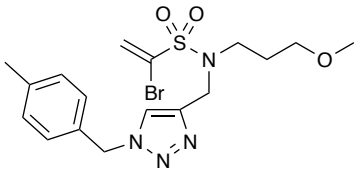
FTIR (neat): 3145, 3110, 3055, 2936, 2858, 1613, 1547, 1586, 1340, 1304, 1222, 1154, 1129, 1092, 999, 916, 886, 850, 736, 702 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H, C<u>H</u>NNN), 7.20 (d, *J* = 8.6 Hz, 2H, ArH), 6.88 (d, *J* = 8.6 Hz, 2H, ArH), 6.76 (d, *J* = 2.8 Hz, 1H, C<u>H</u>CBr), 6.09 (d, *J* = 2.8 Hz, 1H, C<u>H</u>CBr), 5.43 (s, 2H, Bn), 4.58 (s, 2H, NCH_2), 3.80 (s, 3H, OCH_3), 3.60–3.50 (m, 1H, NCH), 1.73 (dd, *J* = 27.2, 13.1 Hz, 4H, Cy), 1.55–1.44 (m, 3H, Cy), 1.25 (ddd, *J* = 16.3, 8.5, 3.3 Hz, 2H, Cy), 1.15–1.02 (m, 1H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8 (<u>C</u>OCH_3), 146.5 (SO_2NCH_2<u>C</u>C), 129.4 (2 C_{Ar}), 128.0 (SO_2NCH_2C<u>C</u>), 127.8 (<u>C</u>H_2=CBrS), 126.6 (CH_2=<u>C</u>BrS), 123.5 (C_{Ar}), 114.4 (2 C_{Ar}), 59.1 (Bn), 55.3 (NCH), 53.7 (O<u>C</u>H_3), 40.1 (NCH_2), 31.6 (Cy), 26.0 (Cy), 24.9 (Cy);

HRMS calculated for $C_{19}H_{25}BrN_4O_3S$ 469.0904 $(M+H)^+$; found 469.0919 (TOF MS ES^+).

1-Bromo-*N*-(3-methoxypropyl)-*N*-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.7** (78%, 1.81 g) was isolated as brown oil.

R_f = 0.25 (EtOAc:Hexane = 1:1);

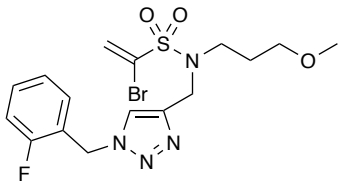
FTIR (neat): 2955, 2883, 1724, 1182, 1070, 1036, 991, 922 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H, CHNNN), 7.17 (d, *J* = 3.1 Hz, 4H, ArH), 6.78 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 6.09 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 5.47 (s, 2H, Bn), 4.56 (s, 2H, NCH_2), 3.40 (t, *J* = 7.4Hz, 2H, C<u>H</u>$_2$OMe), 3.31 (t, *J* = 6.1 Hz, 2H, NC<u>H</u>$_2$), 3.26 (s, 3H, OMe), 2.35 (s, 3H, Me), 1.90–1.78 (m, 2H, CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1 (<u>C</u>$_{Ar}$), 138.8 (CH<u>C</u>CH_2), 131.3 (SO_2NCH_2<u>C</u>C), 129.8 (2 C_{Ar}), 128.2 (<u>C</u>H_2=CBrS), 128.1 (2 C_{Ar}), 127.2 (CH_2=<u>C</u>BrS), 123.1 (SO_2NCH_2C<u>C</u>), 69.3 (<u>C</u>H_2OMe), 58.5 (OMe), 54.1 (Ar<u>C</u>H_2), 46.5 (NCH_2), 44.0 (N<u>C</u>H_2CH_2), 28.2 (CH_2), 21.1 (Me);

HRMS calculated for $C_{17}H_{23}BrN_4O_3S$ 443.0747 $(M+H)^+$; found 443.0753 (TOF MS ES^+).

1-bromo-*N*-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-(3-methoxypropyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.8** (84%, 1.97 g) was isolated as brownish oil.

R_f = 0.28 (EtOAc:Hexane = 1:1);

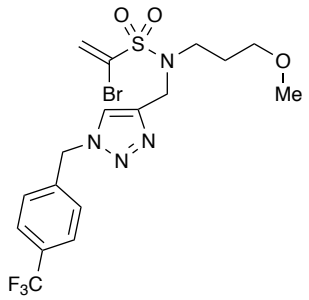
FTIR (neat): 2931, 2876, 1641, 1618, 1452, 1339, 1158, 1115, 1051, 881, 754 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H, CHNNN), 7.35 (td, *J* = 8.0, 5.8 Hz, 1H, ArH), 7.08–7.02 (m, 2H, ArH), 6.94 (dt, *J* = 9.1, 2.1 Hz, 1H, ArH), 6.80 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 6.13 (d, *J* = 2.8 Hz, 1H, C<u>H</u>CBr), 5.52 (s, 2H, Bn), 4.59 (s, 2H, NCH_2), 3.43–3.39 (m, 2H, $C\underline{H}_2OMe$), 3.32 (t, *J* = 6.0 Hz, 2H, NCH_2CH_2), 3.26 (s, 3H, OMe), 1.87–1.80 (m, 2H, CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0 (d, $^1J_{C–F}$ = 247.47 Hz, C_{Ar}), 144.6 ($SO_2NCH_2\underline{C}C$), 136.8 (d, $^3J_{C–F}$ = 6.93 Hz, C_{Ar}), 130.8 (d, $^5J_{C–F}$ = 7.71 Hz, C_{Ar}), 128.4 ($\underline{C}H_2$=CBrS), 127.1 (CH_2=$\underline{C}$BrS), 123.5 (d, $^4J_{C–F}$ = 3.03 Hz, C_{Ar}), 123.4 ($SO_2NCH_2C\underline{C}$), 115.9 (d, $^2J_{C–F}$ = 20.95 Hz, C_{Ar}), 114.9 (d, $^6J_{C–F}$ = 22.21 Hz, C_{Ar}), 69.3 ($\underline{C}H_2OMe$), 58.5 (OMe), 53.6 ($N\underline{C}H_2$), 46.6 ($N\underline{C}H_2CH_2$), 44.2 (Bn), 28.3 (CH_2);

HRMS calculated for $C_{16}H_{20}BrFN_4O_3S$ 447.0496 $(M+H)^+$; found 447.0508 (TOF MS ES^+).

1-bromo-*N*-(3-methoxypropyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.9** (89%, 2.32 g) was isolated as brownish oil.

R_f = 0.23 (EtOAc:Hexane = 1:1);

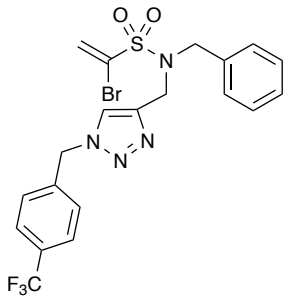
FTIR (neat): 3223, 2999, 2961, 2905, 1612, 1458, 1353, 1201 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H, C<u>H</u>NNN), 7.57 (d, *J* = 8.2 Hz, 2H, *m*-ArH), 7.37–7.29 (m, 2H, *o*-ArH), 6.73 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 6.08 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 5.56 (s, 2H, Ar<u>C</u>H_2), 4.54 (s, 2H, NCH_2), 3.39–3.34 (m, 2H, NC<u>H</u>$_2CH_2CH_2O$), 3.26 (t, *J* = 6.0 Hz, 2H, NCH_2CH_2C<u>H</u>$_2O$), 3.19 (s, 3H, OC<u>H</u>$_3$), 1.81–1.74 (m, 2H, NCH_2C<u>H</u>$_2CH_2O$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4 (SO_2NCH_2<u>C</u>C), 138.5 (SO_2NCH_2<u>C</u>C), 130.6 (q, $^2J_{C–CF3}$ = 32.65 Hz, C_{Ar}), 128.3 (<u>C</u>H_2=CBrS), 128.0 (2 C_{Ar}), 126.8 (CH_2=<u>C</u>BrS), 125.8 (q, $^3J_{C–CF3}$ = 3.81 Hz 2 C_{Ar}), 123.6 (q, $^1J_{C–CF3}$ = 270.36 Hz, CF_3), 123.4, (C_{Ar}), 69.1 (NCH_2CH_2<u>C</u>H_2OCH_3), 58.3 ($NCH_2CH_2CH_2O$<u>C</u>H_3), 53.2 (Ar<u>C</u>H_2), 46.4 (NCH), 43.9 (N<u>C</u>$H_2CH_2CH_2OCH_3$), 28.1 (NCH_2<u>C</u>$H_2CH_2OCH_3$);

HRMS calculated for $C_{17}H_{20}BrF_3N_4O_3S$ 497.0464 $(M+H)^+$; found 497.0460 (TOF MS ES^+).

***N*-Benzyl-1-bromo-*N*-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide**



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.10** (35%, 0.773 mg) was isolated as brownish oil.

R_f = 0.50 (EtOAc:Hexane = 1:1);

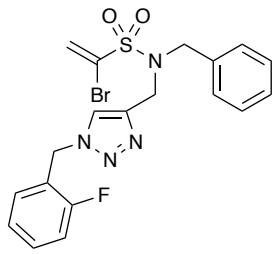
FTIR (neat): 3110, 3064, 3031, 2932, 1646, 1621, 1495, 1325, 1067, 901, 822 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 2H, ArH), 7.39 – 7.28 (m, 6H, ArH), 7.27 – 7.23 (m, 2H, ArH), 6.79 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 6.09 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 5.50 (s, 2H, $ArCH_2$), 4.50 (s, 4H, NCH_2:N_3CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6 ($SO_2NCH_2\underline{C}C$), 138.3 ($SO_2NCH_2C\underline{C}$), 135.1 (C_{Ar}), 130.9 (q, *J* = 32.7 Hz, C_{Ar}), 128.8 ($\underline{C}H_2$=CBrS), 128.4 (2 C_{Ar}), 128.2 (2 C_{Ar}), 128.1 (2 C_{Ar}), 127.9 (CH_2=$\underline{C}$BrS), 127.4 (2 C_{Ar}), 125.9 (q, $J_{C–CF3}$ = 3.7 Hz, C_{Ar}), 123.6 (q, $^1J_{C–CF3}$ = 272.3 Hz, CF_3), 123.3 (C_{Ar}), 53.3 (Bn), 52.4 (NCH), 42.8 (Bn);

HRMS calculated for $C_{20}H_{18}BrF_3N_4O_2S$ 515.0359 $(M+H)^+$; found 515.0363 (TOF MS ES^+).

***N*-benzyl-1-bromo-*N*-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide**



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.11** (14 %, 0.321 mg) was isolated as brownish oil.

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

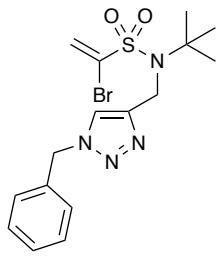
FTIR (neat): 2955, 2885, 1458, 1345, 1036, 854, 734 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.34 (m, 4H, ArH), 7.32–7.27 (m, 3H, ArH), 7.23 (dd, *J* = 7.5, 1.9 Hz, 1H, ArH), 7.19–7.11 (m, 2H, ArH), 6.78 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 6.04 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 5.51 (d, *J* = 1.1 Hz, 2H, ArC<u>H</u>$_2$), 4.52 (s, 2H, NCH_2), 4.47 (s, 2H, N_3CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5 (C_{Ar}), 143.1 (SO_2NCH_2<u>C</u>C), 135.2 (SO_2NCH_2C<u>C</u>), 131.0 (d, *J* = 8.3 Hz, C_{Ar}), 130.6 (d, *J* = 3.2 Hz, C_{Ar}), 130.6 (<u>C</u>H_2=CBrS), 128.9 (2 C_{Ar}), 128.7 (d, *J* = 11.7 Hz, C_{Ar}), 128.5 (2 C_{Ar}), 128.0 (d, J = 8.3 Hz, C_{Ar}), 127.8 (CH_2=<u>C</u>BrS), 124.8 (d, *J* = 3.7 Hz, C_{Ar}), 123.4 (C_{Ar}), 115.8 (d, *J* = 21.1 Hz, C_{Ar}), 52.3 (Ar<u>C</u>H_2), 47.6 (NCH_2), 42.4 (NCH_2);

HRMS calculated for $C_{19}H_{18}BrFN_4O_2S$ 465.0391 $(M+H)^+$; found 465.0396 (TOF MS ES^+).

***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1-bromo-*N*-(*tert*-butyl)ethenesulfonamide**



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.12** (74%, 877 mg) was isolated as brownish oil.

R_f = 0.22 (EtOAc:Hexane = 1:2);

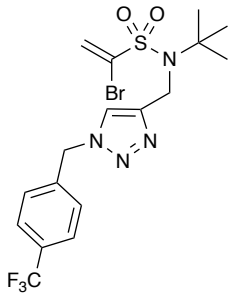
FTIR (neat): 3138, 3034, 3011, 2983, 2926, 1601, 1497, 1457, 1367, 1053, 876, 754, 699 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H, C<u>H</u>NNN), 7.38–7.33 (m, 3H, ArH), 7.26–7.17 (m, 2H, ArH), 6.79 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 6.10 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 5.53 (s, 2H, $ArCH_2$), 4.78 (s, 2H, NCH_2), 1.42 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.81 (SO_2NCH_2<u>C</u>C), 131.23 (SO_2NCH_2C<u>C</u>), 129.09 (2 C_{Ar}), 128.70 (<u>C</u>H_2=CBrS), 127.88 (2 C_{Ar}), 126.98 (CH_2=<u>C</u>BrS), 60.83 (Bn), 54.24 (<u>C</u> ^{t}Bu), 43.76 (NCH_2), 29.96 (C <u>^{t}Bu</u>);

HRMS calculated for $C_{16}H_{21}BrN_4O_2S$ 413.0641 $(M+H)^+$; found 413.0649 (TOF MS ES^+).

1-bromo-*N*-(*tert*-butyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.13** (87%, 1.085 g) was isolated as brownish oil.

R_f = 0.60 (EtOAc:Hexane = 1:1);

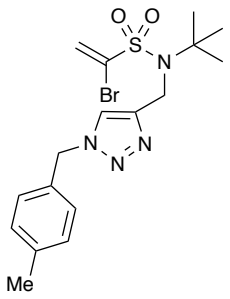
FTIR (neat): 2981, 1644, 1512, 1438, 1370, 1067, 876, 819 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H, C<u>H</u>NNN), 7.67–7.56 (m, 2H, ArH), 7.35 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 2H, ArH), 6.80 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 6.12 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 5.59 (s, 2H, ArC<u>H</u>$_2$), 4.79 (d, *J* = 0.6 Hz, 2H, NCH_2), 1.42 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7 (SO_2NCH_2<u>C</u>C), 138.8 (SO_2NCH_2C<u>C</u>), 131.2 (<u>C</u>H_2=CBrS), 130.9 (m, C_{Ar}) 128.1 (2 C_{Ar}), 127.2 (CH_2=<u>C</u>BrS), 126.2 (q, *J* = 11.6 Hz, C_{Ar}), 124.5 (2 C_{Ar}), 123.9 (d, *J* = 272.4, CF_3), 60.9 (Bn), 53.6 (C^{t}Bu), 43.8 (NCH_2), 30.0 (^{t}Bu).

HRMS calculated for $C_{17}H_{20}BrF_3N_4O_2S$ 481.0515 $(M+H)^+$; found 481.0527 (TOF MS ES^+).

1-Bromo-*N*-(*tert*-butyl)-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.14** (66%, 1.465 g) was isolated as brownish oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

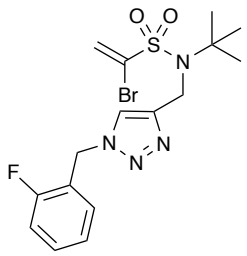
FTIR (neat): 3111, 3053, 2979, 2944, 2925, 1644, 1616, 1516, 1440, 1370, 1072, 930, 843 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H, CHNNN), 7.18–7.12 (m, 4H, ArH), 6.79 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 6.10 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 5.47 (s, 2H, ArC<u>H</u>$_2$), 4.77 (s, 2H, NC<u>H</u>$_2$), 2.35 (s, 3H, ArMe), 1.41 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.0 (SO_2NCH_2<u>C</u>C), 138.6 (SO_2NCH_2C<u>C</u>), 131.6 (C_{Ar}), 131.1 (<u>C</u>H$_2$=CBrS), 129.7 (2 C_{Ar}), 127.9 (2, C_{Ar}), 126.9 (CH_2=<u>C</u>BrS), 124.1 (C_{Ar}), 60.8 (Bn), 54.0 (C^{t}Bu), 43.7 (NCH_2), 29.9 (3 ^{t}Bu), 21.1 (ArMe);

HRMS calculated for $C_{17}H_{23}BrN_4O_2S$ 427.0798 $(M+H)^+$; found 427.0811 (TOF MS ES^+).

1-bromo-*N*-(*tert*-butyl)-*N*-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.15** (57%, 0.572 g) was isolated as brownish oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

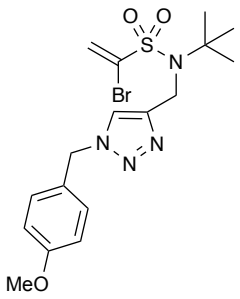
FTIR (neat): 3060, 2980, 2944, 1644, 1618, 1593, 1452, 1401, 1370, 1040m 931, 875, 737 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H, CHNNN), 7.34 (ddd, *J* = 8.3, 7.6, 5.8 Hz, 1H, ArH), 7.12–6.98 (m, 2H, ArH), 6.92 (dt, *J* = 9.4, 2.1 Hz, 1H, ArH), 6.80 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 6.11 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBr), 5.52 (s, 2H, $ArCH_2$), 4.79 (d, *J* = 0.6 Hz, 2H, NCH_2), 1.42 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1 (d, *J* = 247.2 Hz, C_{Ar}), 147.4 ($SO_2NCH_2\underline{C}C$), 137.1 (d, $^3J_{C-F}$ = 7.36 Hz, C_{Ar}), 131.1 ($\underline{C}H_2$=CBrS), 130.7 (d, $^5J_{C-F}$ = 8.19 Hz, C_{Ar}), 127.0 ($SO_2NCH_2C\underline{C}$), 124.3 (CH_2=$\underline{C}$BrS), 123.30 (d, $^4J_{C-F}$ = 3.07 Hz, C_{Ar}), 115.7 (d, $^2J_{C-F}$ = 22.12 Hz, C_{Ar}), 114.7 (d, $^6J_{C-F}$ = 22.35 Hz, C_{Ar}), 60.8 (Bn), 53.5 ($\underline{C}^t$Bu), 43.7 (NCH_2), 29.9 (^{t}Bu);

HRMS calculated for $C_{16}H_{20}BrFN_4O_2S$ 437.0629 $(M+Li)^+$; found 437.0649 (TOF MS ES^+).

1-Bromo-*N*-(tert-butyl)-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.16** (78%, 0.97 g) was isolated as brownish oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

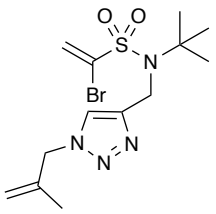
FTIR (neat): 3144, 3107, 2978, 2938, 1613, 1514, 1334, 1250, 1151, 1031, 813 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H, CHNNN), 7.20 (d, *J* = 8.3 Hz, 2H, ArH), 6.87 (d, *J* = 8.2 Hz, 2H, ArH), 6.78 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 6.09 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBr), 5.44 (s, 2H, $ArCH_2$), 4.75 (s, 2H, NCH_2), 3.80 (d, *J* = 1.0 Hz, 3H, OMe), 1.40 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (C_{Ar}), 146.4 ($SO_2NCH_2\underline{C}C$), 130.6 ($C\underline{H}_2$=CBrS), 128.9 (2 C_{Ar}), 126.5 (C_{Ar}), 126.5 (CH_2=<u>C</u>BrS), 123.5 ($SO_2NCH_2C\underline{C}$), 113.8 (2 C_{Ar}), 60.2 (CH_2), 54.8 (OMe), 53.1 (C^tBu), 43.2 (CH_2), 29.4 (^{t}Bu);

HRMS calculated for $C_{17}H_{23}BrN_4O_3S$ 443.0747 $(M+H)^+$; found 443.0745 (TOF MS ES^+).

1-bromo-*N*-(*tert*-butyl)-*N*-((1-(2-methylallyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.17** (65%, 0.65 g) was isolated as brownish oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

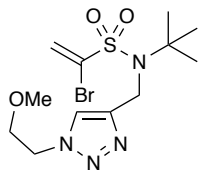
FTIR (neat): 2978, 1658, 1603, 1459, 1442, 1402, 1335, 1036 876 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H, CHNNN), 6.82 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBrS), 6.13 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBrS), 5.04–5.01 (m, 1H, C<u>H</u>$_2$=CMe), 4.89 (s, 3H, C<u>H</u>$_2$=CMe:CH_2), 4.80 (s, 2H, CH_2), 1.68 (s, 3H, Me), 1.42 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1 (SO_2NCH_2<u>C</u>C), 139.1 (CH_2=<u>C</u>Me), 131.2 (SO_2NCH_2C<u>C</u>), 126.9 (<u>C</u>H_2=CBrS), 124.1 (CH_2=<u>C</u>BrS), 115.4 (<u>C</u>H_2=CMe), 60.8 (CH_2), 56.3 C^{t}Bu), 43.9 (CH_2), 29.9 (^{t}Bu), 19.6 (Me);

HRMS calculated for $C_{13}H_{21}BrN_4O_2S$ 375.0490 $(M-H)^+$; found 375.0507 (TOF MS ES^+).

1-bromo-*N*-(*tert*-butyl)-*N*-((1-(2-methoxyethyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.18** (78 %, 0.54 g) was isolated as brown oil.

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

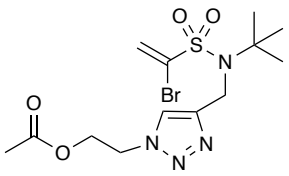
FTIR (neat): 3114, 2980, 2934, 2834, 1645, 1474, 1440, 1370, 1345, 1157, 1077, 1043, 878 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 2.9 Hz, 1H, C<u>H</u>CBrS), 6.12 (d, *J* = 2.8 Hz, 1H, C<u>H</u>CBrS), 4.78 (s, 2H, NCH_2), 4.58 (s, 2H, CH_2), 3.79 (s, 2H, CH_2), 3.33 (s, 3H, OMe), 1.44 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.4 (SO_2NCH_2<u>C</u>C), 127.0 (SO_2NCH_2C<u>C</u>), 70.6 (CH_2), 68.1 (CH_2), 60.9 (C^{t}Bu), 59.1 (OMe), 30.0 (^{t}Bu);

HRMS calculated for $C_{12}H_{21}BrN_4O_3S$ 381.0591 $(M+H)^+$; found 381.0571 (TOF MS ES^+).

2-(4-((1-bromo-*N*-(*tert*-butyl)vinylsulfonamido)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl acetate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.19** (96%, 0.91 g) was isolated as brownish oil.

R_f = 0.33 (EtOAc:Hexane = 1:1);

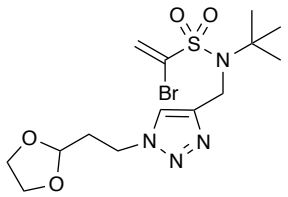
FTIR (neat): 2989, 2902, 2912, 1605, 1459, 1359, 1175 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H, CHNNN), 6.82 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBrS), 6.13 (d, *J* = 3.0 Hz, 1H, C<u>H</u>CBrS), 4.80 (d, *J* = 0.6 Hz, 2H, NCH_2), 4.62 (dd, *J* = 5.9, 4.6 Hz, 2H, CH_2), 4.46 (dd, *J* = 5.9, 4.6 Hz, 2H, CH_2), 2.06 (s, 3H, CO_2Me), 1.42 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4 (CO), 141.1 ($SO_2NCH_2\underline{C}C$), 136.9 ($\underline{C}H_2$=CBrS), 127.1 ($SO_2NCH_2C\underline{C}$), 114.0 (CH_2=$\underline{C}$BrS), 61.9 (CH_2), 60.9 (CH_2), 48.1, (C^{t}Bu) 43.5 (NCH_2), 29.9 (^{t}Bu), 20.6 ($CO_2\underline{Me}$);

HRMS calculated for $C_{13}H_{21}BrN_4O_4S$ 409.0540 $(M+H)^+$; found 409.0555 (TOF MS ES^+).

***N*-((1-(2-(1,3-dioxolan-2-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1-bromo-*N*-(*tert*-butyl)ethenesulfonamide**



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.20** (81%, 0.89 g) was isolated as brownish oil.

R_f = 0.28 (EtOAc:Hexane = 1:1);

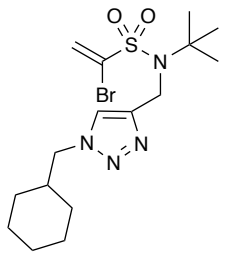
FTIR (neat): 2978, 2890, 1643, 1474, 1402, 1437, 1402, 1370, 1157, 1101, 1043, 904, cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H, CHNNN), 6.82 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 6.13 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 4.92 (t, *J* = 4.2 Hz, 1H, OCHO), 4.79 (s, 2H, CH_2), 4.50 (t, *J* = 7.2 Hz, 2H, CH_2), 4.03–3.94 (m, 2H, CH_2), 3.91–3.82 (m, 2H, CH_2), 2.30 (ddd, *J* = 7.2, 7.2, 4.2 Hz, 2H, CH_2), 1.42 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.7 (SO_2NCH_2<u>C</u>C), 131.2 (SO_2NCH_2C<u>C</u>), 126.9 (<u>C</u>H_2=CBrS), 124.5 (CH_2=<u>C</u>BrS), 101.5 (O<u>C</u>HO), 65.1 (2 CH_2), 60.8 (C^{t}Bu), 45.3 (CH_2), 43.9 (CH_2), 34.0 (CH_2), 29.9 (^{t}Bu);

HRMS calculated for $C_{14}H_{23}BrN_4O_4S$ 423.0696 $(M+H)^+$; found 423.0710 (TOF MS ES^+).

1-bromo-*N*-(*tert*-butyl)-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.21** (78%, 0.26 g) was isolated as brownish oil.

R_f = 0.68 (EtOAc:Hexane = 1:1);

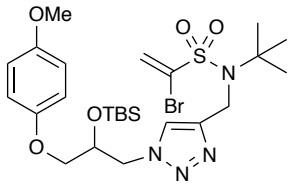
FTIR (neat): 3137, 3002, 2991, 2905, 1612, 1453, 1347, 1197 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H, CHNNN), 6.82 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 6.13 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 4.80 (s, 2H, CH_2), 4.17 (d, *J* = 7.2 Hz, 2H, CH_2), 1.89 (ttt, *J* = 11.0, 7.2, 3.5 Hz, 1H, $NCH_2C\underline{H}$), 1.81–1.64 (m, 4H, CH_2), 1.42 (s, 9H, ^{t}Bu), 1.32–1.11 (m, 4H, CH_2), 1.07–0.93 (m, 2H, CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5 ($SO_2NCH_2\underline{C}C$), 131.2 ($SO_2NCH_2C\underline{C}$), 126.8 ($\underline{C}H_2$=CBrS), 124.5 (CH_2=$\underline{C}$BrS), 60.8 ($\underline{C}^t$Bu), 56.6 (CH_2), 43.9 (CH_2), 38.7 (CH), 30.4 ($2CH_2$), 29.9 (^{t}Bu), 26.1 (CH_2), 25.5 ($2CH_2$);

HRMS calculated for $C_{16}H_{27}BrN_4O_2S$ 419.1111 $(M+H)^+$; found 419.1100 (TOF MS ES^+).

1-bromo-*N*-(*tert*-butyl)-*N*-((1-(2-((*tert*-butyldimethylsilyl)oxy)-3-(4-methoxyphenoxy)propyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.22** (88%, 0.67 g) was isolated as brownish oil.

R_f = 0.63 (EtOAc:Hexane = 1:1);

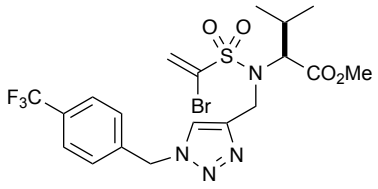
FTIR (neat): 3050, 2954, 2930, 2896, 2857, 1745, 1646, 1612, 1592, 1509, 1442, 1400, 1389, 1370, 1232, 1163, 1043, 882, 826 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H, CHNNN), 6.83 (s, 4H, ArH), 6.81 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 6.12 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 4.85–4.73 (m, 2H, CH_2), 4.61 (dd, *J* = 13.8, 3.6 Hz, 1H, CH_2), 4.50 (dd, *J* = 13.8, 6.5 Hz, 1H, CH_2), 4.44 (qd, *J* = 5.8, 3.6 Hz, 1H, C<u>H</u>OTBS), 3.82–3.80 (m, 2H, CH_2), 3.77 (s, 3H, OMe), 1.42 (s, 9H, ^{t}Bu), 0.87 (s, 9H, ^{t}Bu), 0.04 (s, 3H, Me), -0.06 (s, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1 (C_{Ar}), 152.4 (C_{Ar}), 146.5 ($SO_2NCH_2C\underline{C}$), 131.2 ($SO_2NCH_2\underline{C}C$), 126.9 ($\underline{C}H_2$=CBrS), 125.8 (CH_2=$\underline{C}$BrS), 115.5 (2 C_{Ar}), 114.7 (2 C_{Ar}), 69.9 (OCH_2), 60.7 (CH_2), 55.7 (OMe), 53.9 ($\underline{C}^t$Bu), 43.8 (CH_2), 29.9 (3 $\underline{C}H_3$ ^{t}Bu), 25.7 (Si^{t}Bu), 17.9 (3 $\underline{C}H_3$ Si^{t}Bu), -4.8 (SiMe), -5.1 (SiMe);

HRMS calculated for $C_{25}H_{41}BrN_4O_5SiS$ 617.1823 $(M+H)^+$; found 617.1836 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-valinate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.23** (70 %, 162 mg) was isolated as brownish oil.

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

$[\alpha]_D^{20}$ = -8.52 (*c* = 0.118, CH_2Cl_2);

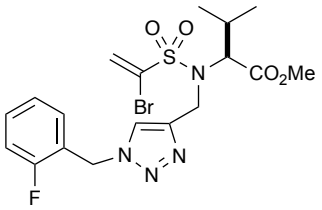
FTIR (neat): 3146, 3111, 2967, 2876, 1740, 1437, 1325, 1165, 1126, 1018, 773, 704 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 3.1 Hz, 1H), 6.14 (d, *J* = 3.0 Hz, 1H), 5.58 (d, *J* = 3.1 Hz, 2H), 5.16 (d, *J* = 16.6 Hz, 1H), 4.79 (d, *J* = 16.6 Hz, 1H), 3.89 (d, *J* = 10.7 Hz, 1H), 3.72 (s, 3H), 2.39 (dp, *J* = 10.6, 6.5 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.67 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) 170.7 (CO), 145.9 ($SO_2NCH_2\underline{C}C$), 138.8, (C_{Ar}) 131.1 (q, *J* = 32.8 Hz, C_{Ar}), 129.5 ($C\underline{H}_2$=CBrH), 128.1 (2 C_{Ar}), 126.4 ($SO_2NCH_2C\underline{C}$) 126.2 (q, *J* = 3.8 Hz, 2 C_{Ar}), 124.8 ($CH_2=\underline{C}BrS$), 123.8 (d, *J* = 272.6 Hz, CF_3) 66.5, ($NC\underline{H}CO_2Me$) 53.6 (CH_2), 51.7 (OMe), 41.9 (CH_2), 28.6 ($C\underline{H}MeMe$), 19.6 (Me), 19.1 (Me);

HRMS calculated for $C_{19}H_{22}BrF_3N_4O_4S$ 537.0419 $(M-H)^+$; found 537.0430 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-valinate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.24** (74%, 0.391 g) was isolated as clear oil.

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

$[\alpha]_D^{20}$ = -2.6 (*c* = 0.015, CH_2Cl_2);

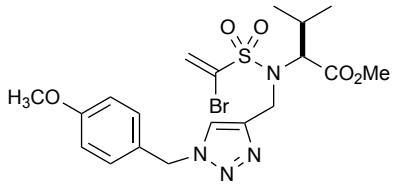
FTIR (neat): 3148, 3113, 2968, 2876, 1739, 1604, 1545, 1512, 1436, 1391, 1268, 1146, 1051, 888, 737 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H, CHNNN), 7.26 (s, 3H, ArH), 7.05 (t, *J* = 8.6 Hz, 2H, ArH), 6.77 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 6.12 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 5.48 (d, *J* = 1.2 Hz, 2H, Bn), 5.13 (d, *J* = 16.6 Hz, 1H, CH_2), 4.77 (d, *J* = 16.6 Hz, 1H, CH_2), 3.89 (d, *J* = 10.6 Hz, 1H, NC<u>H</u>CO_2Me), 3.72 (s, 3H, OMe), 2.37 (dq, *J* = 10.7, 6.5 Hz, 1H, C<u>H</u>MeMe), 0.88 (d, *J* = 6.6 Hz, 3H, Me), 0.65 (d, *J* = 6.4 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (CO), 163.8 (d, *J* = 248.0 Hz, C_{AR}), 145.6 (SO_2NCH_2<u>C</u>C), 130.6 (d, *J* = 2.7 Hz, C_{Ar}), 129.8 (d, *J* = 8.6 Hz, C_{Ar}), 129.4 (<u>C</u>H_2=CBrS), 126.4 (SO_2NCH_2C<u>C</u>), 124.5 (CH_2=<u>C</u>BrS), 116.1 (d, *J* = 21.7 Hz, C_{AR}), 66.5 (NC<u>H</u>CO_2Me), 53.5 (CH_2), 51.7 (OMe), 41.9 (CH_2), 28.6 (<u>C</u>HMeMe), 19.6 (Me), 19.2 (Me) (*Note: 2 Carbon resonances are missing in this ^{13}C spectra);

HRMS calculated for $C_{18}H_{22}BrFN_4O_4S$ 511.0421 $(M+Na)^+$; found 511.0420 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-valinate



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.25** (83%, 0.379 g) was isolated as clear oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -13.5 (*c* = 0.004, CH_2Cl_2);

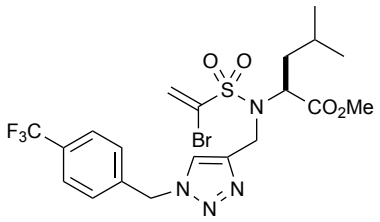
FTIR (neat): 2966, 2875, 1739, 1643, 1516, 1436, 1390, 1206, 1149, 1071, 890, 843 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H, CHNNN), 7.22 - 7.09 (m, 4H, ArH), 6.74 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 6.08 (d, *J* = 3.1 Hz, 1H, C<u>H</u>=CBrS), 5.46 (d, *J* = 1.4 Hz, 2H, CH_2), 5.11 (d, *J* = 16.5 Hz, 1H, CH_2), 4.76 (d, *J* = 16.5 Hz, 1H, CH_2), 3.89 (d, *J* = 10.6 Hz, 1H, NC<u>H</u>CO_2Me), 3.71 (s, 3H, OMe), 2.39 (dtd, *J* = 13.2, 6.6, 4.1 Hz, 1H, C<u>H</u>MeMe), 2.34 (s, 3H, OMe), 0.88 (d, *J* = 6.6 Hz, 3H, Me), 0.67 (d, *J* = 6.5 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (CO), 145.8 (SO_2NCH_2<u>C</u>C), 139.2 (C_{Ar}), 132.2 (C_{Ar}), 129.8 (2 C_{Ar}), 129.3 (<u>C</u>H_2=CBrS), 128.5 (2 C_{Ar}), 127.0 (SO_2NCH_2C<u>C</u>), 124.9 (CH_2=<u>C</u>BrS), 67.0, 61.0, 54.5, 52.2 (CH_2), 42.3 (CH_2), 21.2 (<u>C</u>HMeMe), 19.6 (Me), 19.2 (Me);

HRMS calculated for $C_{19}H_{25}BrN_4O_5S$ 501.0801 $(M+H)^+$; found 501.0782 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-leucinate



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.26** (63%, 0.328 g) was isolated as clear oil.

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

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -22.8 (*c* = 0.007, CH_2Cl_2);

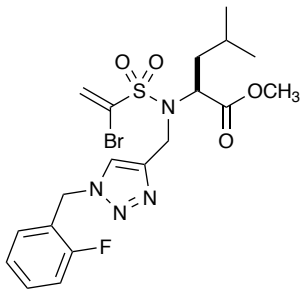
FTIR (neat): 2958, 2871, 1743, 1621, 1601, 1436, 1422, 1325, 1271, 1167, 1067, 993, 908, 824 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H, CHNNN), 7.63 (d, *J* = 8.1 Hz, 2H, ArH), 7.38 (d, *J* = 8.0 Hz, 2H, ArH), 6.79 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 6.16 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 5.57 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 4.46 (dd, *J* = 10.7, 4.3 Hz, 1H, NC<u>H</u>CO_2Me), 3.70 (s, 3H, OMe), 1.92 (ddd, *J* = 14.5, 10.8, 3.8 Hz, 1H, C<u>H</u>MeMe), 1.64 - 1.48 (m, 1H, C<u>H</u>$_2$CHMeMe), 1.24 -1.12 (m, 1H, C<u>H</u>$_2$CHMeMe), 0.85 (d, *J* = 6.5 Hz, 3H, Me), 0.60 (d, *J* = 6.7 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 171.4 (CO), 146.0 (SO_2NCH_2<u>C</u>C), 138.7 (C_{Ar}), 131.1 (q, *J* = 32.7 Hz, C_{Ar}), 128.8 (<u>C</u>H_2=CBrS), 128.3 (2 C_{Ar}), 126.6 (SO_2NCH_2C<u>C</u>), 126.2 (q, *J* = 3.6 Hz, 2 C_{Ar}) 124.6 (CH_2=<u>C</u>BrS), 59.1 (N<u>C</u>HCO_2Me), 123.3 (d, *J* = 271 Hz, CF_3), 53.6 (CH_2), 52.3 (OMe), 42.3 (CH_2), 38.9 (<u>C</u>H_2CHMeMe), 24.4 (Me<u>C</u>HMe), 22.6 (Me), 21.1 (Me).

HRMS calculated for $C_{20}H_{24}BrF_3N_4O_4S$ 575.0546 $(M+Na)^+$; found 575.0553 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-leucinate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.27** (80%, 0.379 g) was isolated as clear oil.

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

$[\alpha]_D^{20}$ = -9.66 (*c* = 0.012, CH_2Cl_2);

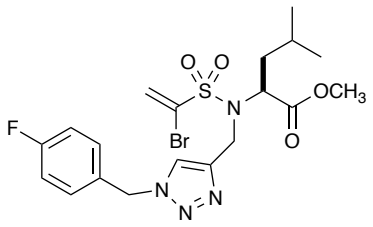
FTIR (neat): 3148, 3112, 3055, 2957, 2870, 1743, 1647, 1603, 1546, 1511, 1436, 1269, 1151, 1046, 993, 908, 737 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H, CHNNN), 7.25 (m, 2H, ArH), 7.09 - 7.01 (m, 2H, ArH), 6.78 (d, *J* = 2.9 Hz, 1H, ArH), 6.14 (d, *J* = 3.0 Hz, 1H, ArH), 5.47 (d, *J* = 1.8 Hz, 2H), 4.79 (s, 2H), 4.45 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.69 (s, 3H, OMe), 1.91 (ddd, *J* = 14.4, 10.7, 3.8 Hz, 1H, C<u>H</u>$_2$CHMeMe), 1.62 - 1.52 (m, 1H, C<u>H</u>$_2$CHMeMe), 1.18 (ddt, *J* = 13.5, 6.7, 3.7 Hz, 1H, C<u>H</u>MeMe), 0.84 (d, *J* = 6.5 Hz, 3H, Me), 0.59 (d, *J* = 6.7 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 171.4 (CO), 162.9 (d, *J* = 248.9 Hz, C_{Ar}), 145.8 ($SO_2NCH_2\underline{C}C$), 130.7 (d, *J* = 3.0 Hz, C_{Ar}) 130.0 (d, *J* = 8.1 Hz, C_{Ar}) 128.7 ($\underline{C}H_2$=CBrS), 126.7 ($SO_2NCH_2C\underline{C}$), 124.3 (CH_2=$\underline{C}$BrS), 116.2 (d, *J* = 21.8 Hz, C_{Ar}), 59.1 (N<u>C</u>HCO$_2$Me), 53.6 (CH_2), 52.3 (OMe), 42.3 (CH_2), 38.8 (<u>C</u>H$_2$CHMeMe), 24.3 (Me<u>C</u>HMe), 22.5 (Me), 21.13 (Me) (*Note: 2 Carbon resonances are missing in this ^{13}C spectra).

HRMS calculated for $C_{19}H_{24}BrFN_4O_4S$ 525.0578 $(M+Na)^+$; found 525.0580 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-leucinate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.28** (74%, 0.246 g) was isolated as brown oil.

R_f = 0.43 (EtOAc:Hexane = 1:1);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -6.6 (*c* = 0.015, CH_2Cl_2);

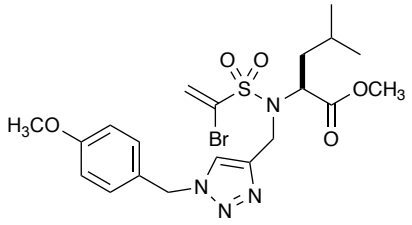
FTIR (neat): 2957, 1741, 1604, 1511, 1436, 1343, 1275, 1152, 1090, 1047, 764, 750 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H, CHNNN), 7.27 (dt, *J* = 8.7, 2.4 Hz, 2H, ArH), 7.09–7.02 (m, 2H, ArH), 6.78 (d, *J* = 2.9 Hz, 1H, C<u>H</u>=CBrS), 6.14 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 5.47 (d, *J* = 1.8 Hz, 2H, CH_2), 4.79 (s, 2H, CH_2), 4.45 (dd, *J* = 10.8, 4.3 Hz, 1H, NC<u>H</u>CO_2Me), 3.69 (s, 3H, OMe), 1.91 (ddd, *J* = 14.4, 10.7, 3.8 Hz, 1H, C<u>H</u>$_2$CHMeMe), 1.57 (ddd, *J* = 14.3, 9.9, 4.3 Hz, 1H, C<u>H</u>$_2$CHMeMe), 1.18 (ddq, *J* = 13.0, 6.5, 3.3, 2.8 Hz, 1H, C<u>H</u>MeMe), 0.84 (d, *J* = 6.5 Hz, 3H, Me), 0.59 (d, *J* = 6.7 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (CO), 162.8 (d, $^1J_{C–F}$ = 248.2 Hz, C_{Ar}), 145.6 (SO_2NCH_2<u>C</u>C), 130.5 (d, $^4J_{C–F}$ = 3.4 Hz, C_{Ar}), 129.8 (d, $^3J_{C–F}$ = 8.6 Hz, 2 C_{Ar}), 128.6 (<u>C</u>H_2=CBrS), 126.5 (SO_2NCH_2C<u>C</u>), 124.1 (CH_2=<u>C</u>BrS), 116.0 (d, $^2J_{C–F}$ = 21.8 Hz, 2 C_{Ar}), 59.0 (N<u>C</u>HCO_2Me), 53.4 (CH_2), 52.1 (OMe), 42.1 (CH_2), 38.7 (<u>C</u>H_2CHMeMe), 24.2 (Me<u>C</u>HMe), 22.4 (Me), 20.9 (Me);

HRMS calculated for $C_{19}H_{24}BrFN_4O_4S$ 525.0578 $(M+Na)^+$; found 525.0562 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-leucinate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.29** (78%, 0.411 g) was isolated as clear oil.

R_f = 0.42 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -21.1 (*c* = 0.05, CH_2Cl_2);

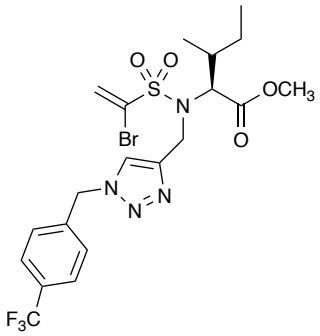
FTIR (neat): 1206, 1223, 1250, 1304, 1344, 1439, 1462, 1514, 1586, 1599, 1613, 1744, 2330, 2342, 2359, 2837, 2870, 2957, 3001 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H, CHNNN), 7.24 - 7.19 (m, 2H, ArH), 6.91 - 6.85 (m, 2H, ArH), 6.76 (d, *J* = 2.9 Hz, 1H, C<u>H</u>=CBrS), 6.12 (d, *J* = 3.0 Hz, 1H, C<u>H</u>=CBrS), 5.49 - 5.36 (m, 2H, CH_2), 4.78 (s, 2H, CH_2), 4.45 (dd, *J* = 10.7, 4.3 Hz, 1H, NC<u>H</u>CO_2Me), 3.80 (s, 3H, OMe), 3.68 (s, 3H, OMe), 1.91 (ddd, *J* = 14.5, 10.8, 3.8 Hz, 1H, C<u>H</u>$_2$CHMeMe), 1.56 (ddd, *J* = 14.3, 9.8, 4.3 Hz, 1H, C<u>H</u>$_2$CHMeMe), 1.20 (ttt, *J* = 13.3, 6.6, 3.6 Hz, 1H, CH_2C<u>H</u>MeMe), 0.83 (d, *J* = 6.5 Hz, 3H, Me), 0.59 (d, *J* = 6.7 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4 (CO), 160.0 (C_{AR}), 145.4 (SO_2NCH_2<u>C</u>C), 129.6 (2 C_{Ar}), 128.7 (<u>C</u>H_2=CBrS), 126.7 (C_{Ar}), 126.6 (SO_2NCH_2C<u>C</u>) 124.0 (CH_2=<u>C</u>BrS), 114.5 (2 C_{Ar}), 59.1 (N<u>C</u>HCO_2Me), 55.4 (OMe), 53.9 (CH_2), 52.1 (OMe), 42.3 (CH_2), 38.8 (<u>C</u>H_2CHMeMe), 24.3 (Me<u>C</u>HMe), 22.5 (Me), 21.1 (Me);

HRMS calculated for $C_{20}H_{27}BrN_4O_5S$ 537.0778 $(M+Na)^+$; found 537.0779 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **D.2**, compound **2.4.2.2.30** (79 %, 0.384 g) was isolated as clear oil.

R_f = 0.54 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -12.0 (*c* = 0.0036, CH_2Cl_2);

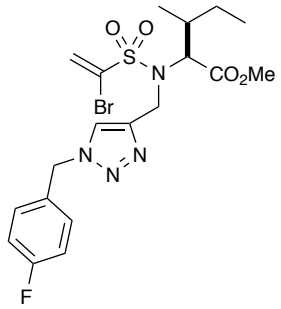
FTIR (neat): 3112, 2967, 2879, 1739, 1647, 1612, 1455, 1269, 1169, 1067, 882, 824 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 7.77 (s, 1H, CHNNN), 7.62 (d, *J* = 8.1 Hz, 2H, ArH), 7.37 (d, *J* = 8.1 Hz, 2H, ArH), 6.80 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.16 (d, *J* = 3.1 Hz, 1H, C$\underline{H}_2$=CBrS), 5.57 (s, 2H, CH_2), 5.21 (d, *J* = 16.8 Hz, 1H, CH_2), 4.78 (d, *J* = 16.8 Hz, 1H, CH_2), 3.97 (d, *J* = 10.6 Hz, 1H, NC$\underline{H}CO_2$Me), 3.72 (s, 3H, OMe), 2.12 (dtd, *J* = 13.2, 6.7, 2.7 Hz, 1H, C$\underline{H}$Me), 1.22 (dtt, *J* = 18.6, 7.6, 3.6 Hz, 1H, C$\underline{H}_2$Me), 0.94 (m, *J* = 6.6 Hz, 1H, C$\underline{H}_2$Me), 0.82 (d, *J* = 6.7 Hz, 3H, Me), 0.53 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (CO), 146.1 ($SO_2NCH_2\underline{C}C$), 138.7 (C_{Ar}), 131.1 (q, *J* = 32.8 Hz, C_{Ar}), 129.6 (2 C_{Ar}), 128.2 ($\underline{C}H_2$=CBrS), 126.2 ($SO_2NCH_2C\underline{C}$), 126.2 (q, *J* = 3.8 Hz 2 C_{Ar}), 124.6 (CH_2=$\underline{C}$BrS), 123.8 (d, *J* = 271.2 Hz, CF_3) 65.0 (N$\underline{C}HCO_2$Me), 53.6 (CH_2), 51.7 (OMe), 42.0 (CH_2), 34.2 ($\underline{C}$HMe), 25.6 ($\underline{C}H_2$Me), 15.1 (Me), 10.5 (Me);

HRMS calculated for $C_{20}H_{24}BrF_3N_4O_4S$ 575.0546 $(M+Na)^+$; found 575.0550 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.31** (78 %, 0.369 g) was isolated as white solid.

R_f = 0.57 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{25}$ = -12.07 (*c* = 0.0825, CH_2Cl_2);

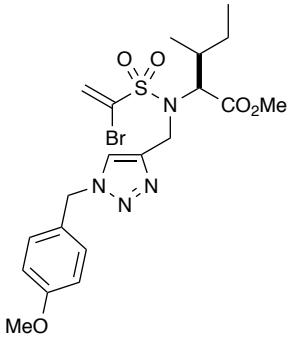
FTIR (neat): 3147, 3112, 2967, 2878, 1738, 1604, 1436, 1344, 1269, 1146, 1093, 1051, 881, 735 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H, CHNNN), 7.28–7.23 (m, 2H, ArH), 7.06–7.00 (m, 2H, ArH), 6.77 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.13 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 5.46 (s, 2H, CH_2), 5.17 (d, *J* = 16.7 Hz, 1H, CH_2), 4.76 (d, *J* = 16.7 Hz, 1H, CH_2), 3.96 (d, *J* = 10.7 Hz, 1H, NC$\underline{H}CO_2Me$), 3.71 (s, 3H, OMe), 2.10 (dtq, *J* = 13.4, 6.7, 4.0, 3.3 Hz, 1H, C$\underline{H}$Me), 1.20 (dqd, *J* = 15.1, 7.8, 2.8 Hz, 1H, C$\underline{H}_2$Me), 0.81 (d, *J* = 6.7 Hz, 3H, Me), 0.79–0.75 (m, 1H, C$\underline{H}_2$Me), 0.51 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (CO), 162.9 (d, *J* = 248.4 Hz, C_{Ar}), 145.8 ($SO_2NCH_2\underline{C}C$), 130.7 (d, *J* = 2.8 Hz, C_{Ar}), 129.9 (d, *J* = 8.1 Hz, 2 C_{Ar}), 129.5 ($\underline{C}H_2$=CBrS), 126.2 ($SO_2NCH_2C\underline{C}$), 124.3 (CH_2=$\underline{C}$BrS), 116.1 (d, *J* = 21.7 Hz, 2 C_{Ar}), 65.0 (N$\underline{C}HCO_2Me$), 53.5 (CH_2), 51.6 (OMe), 41.9 (CH_2), 34.2 ($\underline{C}$HMe), 25.5 ($\underline{C}H_2$Me), 15.1 (Me), 10.1 (Me);

HRMS calculated for $C_{19}H_{24}BrFN_4O_4S$ 525.0578 $(M+Na)^+$; found 525.0580 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.32** (83%, 0.379 g) was isolated as clear oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{25}$ = -13.5 (*c* = 0.054, CH_2Cl_2);

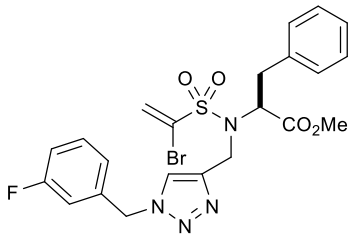
FTIR (neat): 2965, 1738, 1645, 1436, 1343, 1199, 1169, 1091, 1051, 880, 819 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H, CHNNN), 7.16 (s, 4H, ArH), 6.77 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.12 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 5.45 (s, 2H, CH_2), 5.17 (d, *J* = 16.7 Hz, 1H, CH_2), 4.77 (d, *J* = 16.7 Hz, 1H, CH_2), 3.97 (d, *J* = 10.6 Hz, 1H, NC$\underline{H}CO_2$Me), 3.72 (s, 3H, OMe), 2.34 (s, 3H, OMe), 2.13 (dpt, *J* = 16.1, 6.7, 3.1 Hz, 1H, C$\underline{H}$-Ile), 1.28–1.19 (m, 1H, C$\underline{H}_2$Me), 0.82 (d, *J* = 6.7 Hz, 3H, Me), 0.80–0.75 (m, 1H, C$\underline{H}_2$Me), 0.55 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (CO), 145.6 ($SO_2NCH_2\underline{C}C$), 138.8 (C_{Ar}), 131.8 (C_{Ar}), 129.8 (2 C_{Ar}), 129.5 ($\underline{C}H_2$=CBrS), 128.1 (2 C_{Ar}), 126.4 ($SO_2NCH_2C\underline{C}$), 124.3 (CH_2=$\underline{C}$BrS), 65.1 (N$\underline{C}HCO_2$Me), 54.1 (CH_2), 51.7 (OMe), 42.0 (CH_2), 34.2 (OMe), 25.6 ($\underline{C}H_2$Me), 21.3 ($\underline{C}$HMe), 15.2 (Me), 10.2 (Me);

HRMS calculated for $C_{20}H_{27}BrN_4O_5S$ 515.0958 $(M+H)^+$; found 515.0975 (TOF MS ES^+).

Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-phenylalaninate



According to the reaction protocol described in general procedure **D.1**, compound **2.4.2.2.33** (49%, 1.79 g) was isolated as brown oil.

R_f = 0.18 (EtOAc:Hexane = 1:2);

$[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -14.72 (*c* = 0.174, CH_2Cl_2);

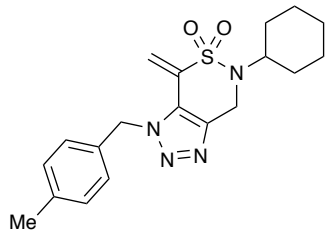
FTIR (neat): 2955, 2882, 1772, 1724, 1420, 1170, 1069, 1036, 991, 922, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H, CHNNN), 7.41–7.30 (m, 1H, ArH), 7.22–7.01 (m, 8H, ArH), 6.69 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 6.04 (d, *J* = 3.0 Hz, 1H, C$\underline{H}_2$=CBrS), 5.58–5.38 (m, 2H, CH_2), 4.91–4.77 (m, 2H, CH_2), 4.76 (dd, *J* = 8.1, 6.9 Hz, 1H, NC$\underline{H}CO_2Me$), 3.61 (s, 3H, OMe), 3.36 (dd, *J* = 14.6, 7.1 Hz, 1H, CH_2-Phe), 3.10 (dd, *J* = 14.6, 8.4 Hz, 1H, C$\underline{H}_2Ar_{Phe}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9 (CO), 160.1 (d, *J* = 249.6 Hz, C_{Ar}), 144.0 ($SO_2NCH_2\underline{C}C$), 135.8 (C_{Ar}), 130.6 (d, *J* = 8.2 Hz, C_{Ar}), 130.2 (d, J = 3.6 Hz, C_{Ar}), 128.5 (2 C_{Ar}), 128.5 ($\underline{C}H_2$=CBrS), 128.0 (2 C_{Ar}), 126.4 (C_{Ar}), 126.3 ($SO_2NCH_2C\underline{C}$), 124.4 (d, *J* = 3.6 Hz, C_{Ar}), 124.1 (CH_2=$\underline{C}$BrS), 121.6 (d, *J* = 14.5 Hz, C_{Ar}) 115.5 (d, *J* = 21.3 Hz, C_{AR}), 61.0 ($N\underline{C}HCO_2Me$), 51.8 (CH_2), 47.2 (CH_2), 41.9 (OMe), 36.0 ($\underline{C}H_2$-Ar_{Phe});

HRMS calculated for $C_{22}H_{22}BrFN_4O_4S$ 537.0602 $(M+H)^+$; found 537.0609 (TOF MS ES^+).

6-Cyclohexyl-3-(4-methylbenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.1** (48 mg, 59%) was isolated as colorless syrup.

R_f = 0.51 (EtOAc:Hexane = 1:2);

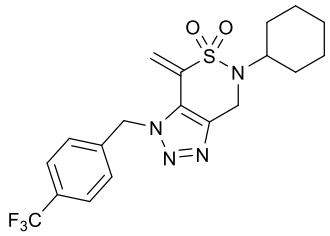
FTIR (neat): 2932, 2857, 1645, 1516, 1451, 1344, 1271, 1211, 1171, 1114, 1086, 1071, 1042, 999, 850, 808 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.8 Hz, 2H, ArH), 6.90 (d, *J* = 7.8 Hz, 2H, ArH), 6.10 (s, 1H, $C\underline{H}_2{=}CSO_2$), 5.65 (s, 2H, $Ar\underline{C}H_2$), 5.60 (s, 1H, $C\underline{H}_2{=}CSO_2$), 4.66 (s, 2H, NCH_2), 3.77 (dt, *J* = 11.3, 5.2 Hz, 1H, NCH), 2.32 (s, 3H, $ArCH_3$), 1.73 (d, *J* = 10.2 Hz, 2H, Cy), 1.63 (d, *J* = 9.1 Hz, 2H, Cy), 1.34–1.19 (m, 6H, Cy);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 ($CH_2{=}\underline{C}SO_2$), 138.6 ($SO_2NCH_2\underline{C}C$), 135.7 (C_{Ar}), 130.8 (C_{Ar}), 130.1 (2 C_{Ar}), 127.0 ($SO_2NCH_2C\underline{C}$), 126.0 (2 C_{Ar}), 115.5 ($\underline{C}H_2{=}CSO_2$), 58.5 ($ArCH_2$), 53.1 (NCH), 40.8 (NCH_2), 30.4 (2 Cy), 25.6 ($Ar\underline{C}H_3$), 25.1 (2 Cy), 21.2 (Cy);

HRMS calculated for $C_{19}H_{24}N_4O_2S$ 373.1693 $(M+H)^+$; found 373.1738 (TOF MS ES^+).

6-Cyclohexyl-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.2** (71 mg, 80%) was isolated as colorless syrup.

R_f = 0.45 (EtOAc:Hexane = 1:2);

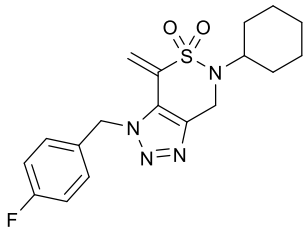
FTIR (neat): 2935, 2858, 1622, 1452, 1327, 1067, 890 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 (d, *J* = 7.9 Hz, 2H, ArH), 6.14 (s, 1H, $C\underline{H}_2$=CSO_2), 5.75 (s, 2H, Ar$\underline{C}H_2$), 5.54 (s, 1H, $C\underline{H}_2$=CSO_2), 4.68 (s, 2H, NCH_2), 3.83–3.75 (m, 1H, NCH), 1.74 (d, *J* = 11.7 Hz, 2H, Cy), 1.61 (d, *J* = 14.7 Hz, 3H, Cy), 1.29 (dd, *J* = 21.2, 12.2 Hz, 5H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.6 (CH_2=$\underline{C}SO_2$), 137.6 ($SO_2NCH_2\underline{C}C$), 135.7 (C_{Ar}), 131.0 (q, $^2J_{C–CF3}$ = 32.8 Hz, C_{Ar}), 127.2 (d, *J* = 52.3 Hz, 2 C_{Ar}), 126.4 ($SO_2NCH_2C\underline{C}$), 126.3 (q, $^3J_{C–CF3}$ = 3.8 Hz, 2 C_{Ar}), 123.5 (q, $^1J_{C–CF3}$ = 272.4 Hz CF_3), 115.0 ($\underline{C}H_2$=CSO_2), 58.4 ($ArCH_2$), 52.5 (NCH), 40.6 (NCH_2), 30.3 (2 Cy), 29.6 (Cy), 25.5 (2 Cy);

HRMS calculated for $C_{19}H_{21}F_3N_4O_2S$ 427.1410 $(M+H)^+$; found 427.1467 (TOF MS ES^+).

6-Cyclohexyl-3-(4-fluorobenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.3** (30 mg, 79%) was isolated as colorless syrup.

R_f = 0.34 (EtOAc:Hexane = 1:2);

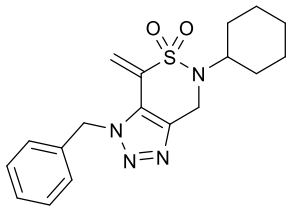
FTIR (neat): 2928, 2855, 1511, 1343, 809, 764, 750 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–6.94 (m, 4H, ArH), 6.14 (s, 1H, C$\underline{H}_2$=CSO_2), 5.66 (s, 2H, Ar$\underline{C}H_2$), 5.60 (s, 1H, C$\underline{H}_2$=CSO_2), 4.66 (s, 2H, NCH_2), 3.93–3.67 (m, 1H, NCH), 1.73 (d, *J* = 8.7 Hz, 2H, Cy), 1.60 (d, *J* = 13.6 Hz, 2H, Cy), 1.28 (h, *J* = 13.1 Hz, 4H, Cy), 1.10 – 0.96 (m, 1H, Cy), 0.91 (d, *J* = 6.7 Hz, 1H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (d, $^1J_{C-F}$ = 248.4 Hz, C_{Ar}), 141.5 (CH_2=$\underline{C}SO_2$), 135.7 ($SO_2NCH_2\underline{C}C$), 129.5 (2 C_{Ar}), 128.0 (d, $^3J_{C-F}$ = 8.4 Hz, C_{Ar}), 126.8 ($SO_2NCH_2C\underline{C}$), 116.4 (d, $^2J_{C-F}$ = 21.9 Hz, 2 C_{Ar}), 115.1 ($\underline{C}H_2$=CSO_2), 58.3 ($ArCH_2$), 52.4 (NCH), 40.6 (NCH_2), 30.3 (2 Cy), 25.5 (2 Cy), 25.0 (Cy);

HRMS calculated for $C_{18}H_{21}FN_4O_2S$ 377.1442 $(M+H)^+$; found 377.1580 (TOF MS ES^+).

3-Benzyl-6-cyclohexyl-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.4** (41 mg, 49%) was isolated as colorless syrup.

R_f = 0.42 (EtOAc:Hexane = 1:2);

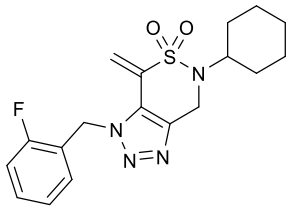
FTIR (neat): 3061, 2933, 2857, 1644, 1606, 1497, 1482, 1041, 890, 735 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 3H, ArH), 7.01 (d, *J* = 7.0 Hz, 2H, ArH), 6.10 (s, 1H, $C\underline{H}_2$=CSO_2), 5.70 (s, 2H, Ar$\underline{C}H_2$), 5.59 (s, 1H, $C\underline{H}_2$=CSO_2), 4.67 (s, 2H, NCH_2), 3.77 (dt, *J* = 11.3, 5.5 Hz, 1H, NCH), 1.73 (d, *J* = 10.7 Hz, 2H, Cy), 1.61 (t, *J* = 12.6 Hz, 3H, Cy), 1.28 (h, *J* = 16.2, 14.3 Hz, 5H, Cy);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (CH_2=$\underline{C}SO_2$), 135.7 ($SO_2NCH_2\underline{C}C$), 133.9 ($SO_2NCH_2C\underline{C}$), 129.4 (2 C_{Ar}), 128.7 (C_{Ar}), 127.0 (C_{Ar}), 126.1 (2 C_{Ar}), 115.4 ($\underline{C}H_2$=CSO_2), 58.5 ($ArCH_2$), 53.2 (NCH), 40.8 (NCH_2), 30.4 (2 Cy), 25.6 (2 Cy), 25.1 (Cy);

HRMS calculated for $C_{18}H_{22}N_4O_2S$ 359.1536 $(M+H)^+$; found 359.1555 (TOF MS ES^+).

6-Cyclohexyl-3-(2-fluorobenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.5** (46 mg, 55%) was isolated as colorless syrup.

$\mathbf{R_f}$ = 0.36 (EtOAc:Hexane = 1:2);

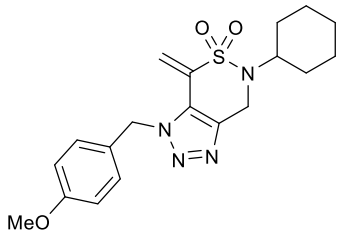
FTIR (neat): 2934, 2858, 1701, 1619, 1593, 1490, 1453, 1172, 1156, 1072, 926, 809, 737 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (q, *J* = 7.2 Hz, 1H, ArH), 7.03 (t, *J* = 8.2 Hz, 1H, ArH), 6.83 (d, *J* = 7.6 Hz, 1H, ArH), 6.68 (d, *J* = 9.1 Hz, 1H, ArH), 6.13 (s, 1H, C$\underline{H}_2$=CSO_2), 5.69 (s, 2H, Ar$\underline{C}H_2$), 5.56 (s, 1H, C$\underline{H}_2$=CSO_2), 4.67 (s, 2H, NCH_2), 3.78 (t, *J* = 9.3 Hz, 1H, NCH), 1.74 (d, *J* = 10.6 Hz, 2H, Cy), 1.61 (t, *J* = 12.5 Hz, 3H, Cy), 1.28 (dq, *J* = 23.4, 12.9 Hz, 5H, Cy);

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (d, $^1J_{C-F}$ = 248.8 Hz, C_{Ar}), 141.7 (CH_2=$\underline{C}SO_2$), 136.4 (d, $^5J_{C-F}$ = 7.3 Hz, C_{Ar}), 135.8 ($SO_2NCH_2\underline{C}C$), 131.2 (d, $^3J_{C-F}$ = 8.4 Hz, C_{Ar}), 127.1 ($SO_2NCH_2C\underline{C}$), 121.7 (d, $^4J_{C-F}$ = 3.1 Hz, C_{Ar}), 115.9 (d, $^2J_{C-F}$ = 21.0 Hz, C_{Ar}), 115.3 ($\underline{C}H_2$=CSO_2), 113.3 (d, $^5J_{C-F}$ = 22.9 Hz, C_{Ar}), 58.5 ($ArCH_2$), 52.5 (NCH), 40.8 (NCH_2), 30.5 (2 Cy), 25.6 (2 Cy), 25.1 (Cy);

HRMS calculated for $C_{18}H_{21}FN_4O_2S$ 377.1442 $(M+H)^+$; found 377.1460.

6-Cyclohexyl-3-(4-methoxybenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.6** (63 mg, 65%) was isolated as colorless syrup.

R_f = 0.38 (EtOAc:Hexane = 1:2);

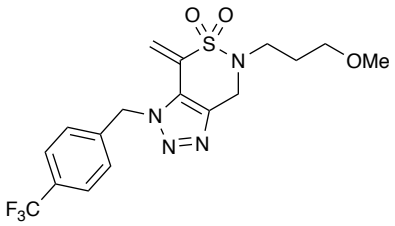
FTIR (neat): 2934, 2857, 1613, 1514, 1452, 1380, 1250, 1211, 1171, 1155, 1071, 1040, 926, 809, 735 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.3 Hz, 2H, ArH), 6.85 (d, *J* = 8.3 Hz, 2H, ArH), 6.11 (s, 1H, $C\underline{H}_2$=CSO_2), 5.64 (s, 1H, $C\underline{H}_2$=CSO_2), 5.62 (s, 2H, $ArCH_2$), 4.65 (s, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 1.72 (d, *J* = 9.5 Hz, 2H, Cy), 1.58 (d, *J* = 14.2 Hz, 3H, Cy), 1.35 – 1.15 (m, 5H, Cy);

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (C_{Ar}), 141.4 (CH_2=$\underline{C}SO_2$), 135.7 ($SO_2NCH_2\underline{C}C$), 127.6 (2 C_{Ar}), 126.8 ($SO_2NCH_2C\underline{C}$), 125.7 (C_{Ar}), 115.5 ($\underline{C}H_2$=CSO_2), 114.7 (2 C_{Ar}), 58.4 ($ArCH_2$), 55.3 (OCH_3), 52.8 (NCH), 40.7 (NCH_2), 30.4 (2 Cy), 25.6 (2 Cy), 25.1 (Cy);

HRMS calculated for $C_{19}H_{24}N_4O_3S$ 389.1647 $(M+H)^+$; found 389.1690.

6-(3-methoxypropyl)-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.9** (66%, 106 mg) was isolated as yellow oil.

R_f = 0.17 (EtOAc:Hexane = 1:1);

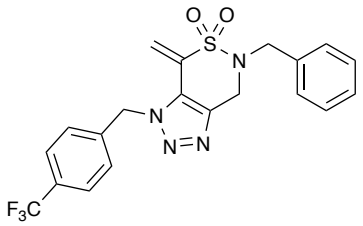
FTIR (neat): 3055, 2928, 2877, 1622, 1531, 1514, 1481, 1421, 1327, 1169, 1127, 1068, 896, 819 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H, ArH), 7.20 (d, *J* = 8.1 Hz, 2H, ArH), 6.16 (d, *J* = 2.1 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.75 (s, 2H, $ArCH_2$), 5.70 (d, *J* = 2.1 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.66 (s, 2H, NCH_2), 3.42 (t, *J* = 5.9 Hz, 2H, $NCH_2CH_2C\underline{H}_2O$), 3.29 (s, 3H, OCH_3), 3.09 (t, *J* = 6.9 Hz, 2H, $NC\underline{H}_2CH_2CH_2O$), 1.82 (ddd, *J* = 11.7, 6.0, 5.5 Hz, 2H, $NCH_2C\underline{H}_2CH_2O$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.2 (CH_2=$\underline{C}SO_2$), 137.7 ($SO_2NCH_2\underline{C}C$), 133.3 ($SO_2NCH_2C\underline{C}$), 131.2 (q, $^2J_{C–CF3}$ = 32.65 Hz, C_{Ar}), 126.8 (2 C_{Ar}), 126.5 (q, $^3J_{C–CF3}$ = 3.5 Hz, 2 C_{Ar}), 126.2 (q, $^4J_{C–CF3}$ = 3.41 Hz, C_{Ar}), 124.2 (q, $^1J_{C–CF3}$ = 272.2 Hz, CF_3), 118.2 ($\underline{C}H_2$=CSO_2), 69.1 ($NCH_2CH_2\underline{C}H_2OCH_3$), 58.7 ($NCH_2CH_2CH_2O\underline{C}H_3$), 52.7 ($Ar\underline{C}H_2$), 47.4 (NCH), 47.0 ($N\underline{C}H_2CH_2CH_2OCH_3$), 28.8 ($NCH_2\underline{C}H_2CH_2OCH_3$).

HRMS calculated for $C_{17}H_{19}F_3N_4O_3S$ 417.1203 $(M+H)^+$; found 417.1206.

6-benzyl-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.10** (12%, 11 mg) was isolated as yellow oil.

R_f = 0.42 (EtOAc:Hexane = 1:1);

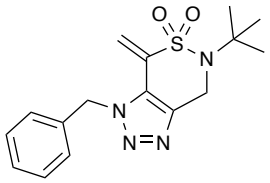
FTIR (neat): 2927, 1621, 1326, 1066, 899, 821, 789, 701 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H, ArH), 7.34 (d, *J* = 4.6 Hz, 3H, ArH), 7.32 (d, *J* = 8.0 Hz, 2H, ArH), 7.28 (d, *J* = 6.3 Hz, 1H, ArH), 7.24 (d, *J* = 7.2 Hz, 1H, ArH), 6.81 (d, *J* = 2.9 Hz, 1H, $C\underline{H}_2$=CSO_2), 6.11 (d, *J* = 2.9 Hz, 1H, $C\underline{H}_2$=CSO_2), 5.50 (s, 2H, CF_3-$ArCH_2$), 4.51 (s, 2H, NCH_2Ar), 4.50 (s, 2H, NCH_2triazole).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0 (CH_2=$\underline{C}SO_2$), 138.5 ($SO_2NCH_2\underline{C}C$), 135.4 ($SO_2NCH_2C\underline{C}$), 129.1 (2 C_{Ar}), 128.7 (2 C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (2 C_{Ar}), 127.7 (2 C_{Ar}), 126.3 (q, $J_{C–CF3}$ = 3.86 Hz, 2 C_{Ar}), 123.8 (d, *J* = 273.0 Hz, CF_3), 123.5 ($\underline{C}H_2$=CSO_2), 53.6 (N_3CH_2Ar), 52.7 (NCH_2Ar), 43.2 (NCH_2triazole), 29.8.

HRMS calculated for $C_{20}H_{17}F_3N_4O_2S$ 435.1097 $(M+H)^+$; found 435.1081.

***3*-Benzyl-6-(tert-butyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide**



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.12** (88%, 135.5 mg) was isolated as brownish oil.

R_f = 0.18 (EtOAc:Hexane = 1:2);

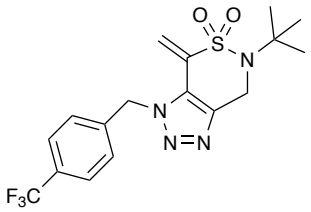
FTIR (neat): 3112, 3062, 3032, 2979, 1739, 1644, 1605, 1588, 1497, 1074, 877, 735 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.31 (m, 3H, ArH), 7.09–7.02 (m, 2H, ArH), 6.14 (d, *J* = 2.1 Hz, 1H, $C\underline{H}_2$=CSO_2), 5.72 (d, *J* = 1.2 Hz, 2H, $ArCH_2$), 5.63–5.60 (m, 1H, $C\underline{H}_2$=CSO_2), 4.83 (d, *J* = 1.6 Hz, 2H, NCH_2), 1.38 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8 (CH_2=$\underline{C}SO_2$), 136.5 ($SO_2NCH_2\underline{C}C$), 133.8 (C_{Ar}), 129.4 (2 C_{Ar}), 128.7 (C_{Ar}), 126.9 ($SO_2NCH_2C\underline{C}$), 126.0 (2 C_{Ar}), 115.3 ($\underline{C}H_2$=CSO_2), 61.0 ($ArCH_2$), 53.5 (NC), 43.8 (NCH_2), 29.7 (^{t}Bu);

HRMS calculated for $C_{16}H_{20}N_4O_2S$ 333.1380 $(M+H)^+$; found 333.1387 (TOF MS ES^+).

6-(*tert*-Butyl)-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.13** (72%, 0.346 g) was isolated as brownish oil.

R_f = 0.41 (EtOAc:Hexane =1:1);

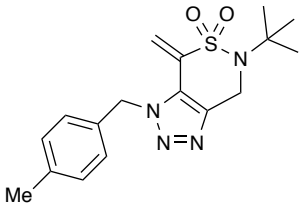
FTIR (neat): 2980, 1643, 1622, 1508, 1472, 1439, 1370, 1326, 1067, 876, 840 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H, ArH), 7.23–7.16 (m, 2H, ArH), 6.17 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.77 (s, 2H, $ArCH_2$), 5.56 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.84 (s, 2H, NCH_2), 1.39 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1 (CH_2=$\underline{C}SO_2$), 137.7 ($SO_2NCH_2\underline{C}C$), 136.5 ($SO_2NCH_2C\underline{C}$), 131.2 (q, $^2J_{C–CF3}$ = 32.9 Hz, C_{Ar}), 128.0 (C_{Ar}), 127.0 (2 C_{Ar}), 126.5 (q, $^3J_{C–CF3}$ = 3.9 Hz, 2 C_{Ar}), 123.7 (q, ^1J = 270.76 Hz, CF_3), 115.0 ($\underline{C}H_2$=CSO_2), 61.2, 52.6, 43.7, 29.7 (^{t}Bu);

HRMS calculated for $C_{17}H_{19}F_3N_4O_2S$ 401.1254 $(M+H)^+$; found 401.1256 (TOF MS ES^+).

6-(*tert*-butyl)-3-(4-methylbenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.14** (73%, 0.303 g) was isolated as brownish oil.

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

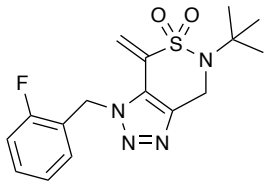
FTIR (neat): 2979, 2944, 2924, 1697, 1644, 1616, 1581, 1516, 1473, 1369, 1040, 876, 843 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2H, ArH), 6.93 (d, *J* = 8.0 Hz, 2H, ArH), 6.12 (d, *J* = 2.1 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.66 (s, 2H, $ArCH_2$), 5.63 (d, *J* = 2.1 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.81 (s, 2H, NCH_2), 2.33 (s, 3H, $ArCH_3$), 1.36 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7 (CH_2=$\underline{C}SO_2$), 138.4 ($SO_2NCH_2\underline{C}C$), 136.4 ($SO_2NCH_2C\underline{C}$), 130.6 (C_{Ar}), 129.9 (2 C_{Ar}), 126.8 (2 C_{Ar}), 125.9 (C_{Ar}), 115.3 ($\underline{C}H_2$=CSO_2), 60.9 (NCH_2), 52.9 ($Ar\underline{C}H_2$), 43.7 (NC), 29.6 (^{t}Bu), 21.0 CH_3;

HRMS calculated for $C_{17}H_{22}N_4O_2S$ 347.1536 $(M+H)^+$; found 347.1552 (TOF MS ES^+).

6-(*tert*-Butyl)-3-(2-fluorobenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.15** (75%, 0.316 g) was isolated as brownish oil.

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

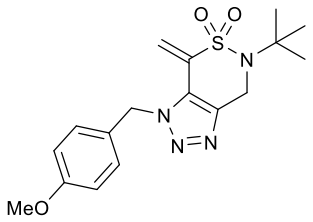
FTIR (neat): 3137, 3101, 2971, 2911, 1610, 1459, 1352, 1206 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.0, 5.7 Hz, 1H, ArH), 7.05 (ddd, *J* = 8.5, 2.6, 0.9 Hz, 1H, ArH), 6.85 (ddd, *J* = 7.7, 1.8, 0.9 Hz, 1H ArH), 6.74 (ddd, *J* = 9.4, 2.6, 1.5 Hz, 1H ArH), 6.16 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.71 (s, 2H, $ArCH_2$), 5.59 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.83 (s, 2H, NCH_2), 1.38 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (d, $^1J_{C-F}$ = 248.56 Hz, C_{Ar}), 141.9 (CH_2=$\underline{C}SO_2$), 136.5 ($SO_2NCH_2\underline{C}C$), 136.2 (d, $^3J_{C-F}$ = 7.2 Hz, C_{Ar}), 131.1 (d, $^5J_{C-F}$ = 8.2 Hz, C_{Ar}), 127.0 ($SO_2NCH_2C\underline{C}$), 121.6 (d, $^4J_{C-F}$ = 3.10 Hz, C_{Ar}), 115.8 (d, $^2J_{C-F}$ = 20.25 Hz, C_{Ar}), 115.1 ($\underline{C}H_2$=CSO_2), 113.2 (d, $^6J_{C-F}$ = 22.8 Hz, C_{Ar}), 61.1, 52.5 (d, $^{CH2\text{-}Benzyl}J_{C-F}$ = 2.04 Hz, $Ar\underline{C}H_2$), 43.7, 29.9 (^{t}Bu);

HRMS calculated for $C_{16}H_{19}FN_4O_2S$ 351.1286 $(M+H)^+$; found 351.1298 (TOF MS ES^+).

6-(*tert*-Butyl)-3-(4-methoxybenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.16** (84%, 200 mg) was isolated as brownish oil.

R_f = 0.40 (EtOAc:Hexane = 1:1);

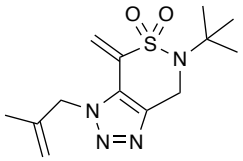
FTIR (neat): 3004, 2980, 2918, 2848, 1612, 1585, 1514, 1457, 1344, 1259, 1155, 1097, 875 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.6 Hz, 2H, ArH), 6.86 (d, *J* = 8.7 Hz, 2H, ArH), 6.14 (d, *J* = 2.1 Hz, 1H, $C\underline{H}_2$=CSO_2), 5.66 (d, *J* = 2.1 Hz, 1H, $C\underline{H}_2$=CSO_2), 5.63 (s, 2H, $ArCH_2$), 4.80 (s, 2H, NCH_2), 3.78 (s, 3H, OCH_3), 1.36 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (C_{Ar}), 141.7 ($CH_2\underline{C}SO_2$), 136.4 ($SO_2NCH_2\underline{C}C$), 127.4 (2 C_{Ar}), 126.6 (C_{Ar}), 125.5 ($SO_2NCH_2C\underline{C}$), 115.3 ($\underline{C}H_2$=CSO_2), 114.6 (2 C_{Ar}), 60.9, 55.2, 52.7, 43.7, 29.6 (^{t}Bu);

HRMS calculated for $C_{17}H_{22}N_4O_3S$ 362.1413 $(M+)^+$; found 362.1429 (TOF MS ES^+).

6-(*tert*-Butyl)-3-(2-methylallyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.17** (79%, 0.281 g) was isolated as brownish oil.

$\mathbf{R_f}$ = 0.71 (EtOAc:Hexane =1:1);

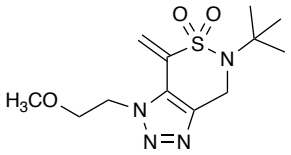
FTIR (neat): 3083, 2979, 2941, 1706, 1659, 1607, 1448, 1379, 1071, 873 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (d, *J* = 1.0 Hz, 1H, $C\underline{H_2}{=}CSO_2$), 6.11 (d, *J* = 1.0 Hz, 1H, $C\underline{H_2}{=}CSO_2$), 5.05 – 5.03 (m, 1H, $C\underline{H_a}H_bC$), 4.95 (s, 2H, N_3CH_2), 4.91 (dt, *J* = 2.3, 1.2 Hz, 1H, $CH_a\underline{H_b}C$), 4.76 (s, 2H, NCH_2), 1.70 (t, *J* = 1.2 Hz, 3H, C^{t}Bu), 1.37 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9 ($CH_2{=}\underline{C}SO_2$), 139.5 ($SO_2NCH_2\underline{C}C$), 139.1 ($N_3CH_2\underline{C}CH_2$), 139.0 ($SO_2NCH_2C\underline{C}$), 115.4 ($\underline{C}H_2{=}CSO_2$), 113.5 ($N_3CH_2C\underline{C}H_2$), 61.4, 60.5, 43.6, 29.8 (^{t}Bu), 19.7 $C\underline{C}H_3$;

HRMS calculated for $C_{13}H_{20}N_4O_2S$ 297.1380 $(M+H)^+$; found 297.1380 (TOF MS ES^+).

6-(*tert*-butyl)-3-(2-methoxyethyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.18** (81%, 0.292 g) was isolated as brownish oil.

R_f = 0.34 (EtOAc:Hexane =1:1);

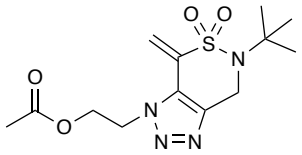
FTIR (neat): 3111, 3100, 2912, 1601, 1473, 1356, 1205 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (q, *J* = 1.9 Hz, 2H, $C\underline{H}_2$=CSO_2), 4.76 (s, 2H, NCH_2), 4.60 (t, *J* = 5.3 Hz, 2H, $OC\underline{H}_2CH_2N$), 3.87 (t, *J* = 5.3 Hz, 2H, $OCH_2C\underline{H}_2N$), 3.29 (s, 3H, OCH_3), 1.39 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7 (CH_2=$\underline{C}SO_2$), 136.7 ($SO_2NCH_2\underline{C}C$), 127.6 ($SO_2NCH_2C\underline{C}$), 115.7 ($\underline{C}H_2$=CSO_2), 71.0 ($CH_3O\underline{C}H_2CH_2N_3$), 60.9, 59.1, 49.6, 43.6, 29.6 (^{t}Bu);

HRMS calculated for $C_{12}H_{20}N_4O_3S$ 301.1329 $(M+H)^+$; found 301.1339 (TOF MS ES^+).

2-(6-(*tert*-butyl)-4-methylene-5,5-dioxido-6,7-dihydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazin-3(4*H*)-yl)ethyl acetate



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.19** (84%, 0.331 g) was isolated as brownish oil.

R_f = 0.26 (EtOAc:Hexane =1:1);

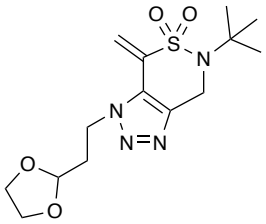
FTIR (neat): 2977, 2923, 1743, 1643, 1439, 1344, 1229, 1148, 1043, 877 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.3 Hz, 1H, C<u>H</u>$_2$=CSO$_2$), 6.09 (d, *J* = 2.3 Hz, 1H, C<u>H</u>$_2$=CSO$_2$), 4.79 (s, 2H, CO$_2$C<u>H</u>$_2$CH$_2$N$_3$), 4.73 (t, *J* = 5.7 Hz, 2H, CO$_2$CH$_2$C<u>H</u>$_2$N$_3$), 4.53 (t, *J* = 5.7 Hz, 2H, NCH$_2$), 2.03 (s, 3H, CH$_3$CO$_2$), 1.41 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4 (CO$_2$), 141.3 (CH$_2$=<u>C</u>SO$_2$), 137.1 (SO$_2$NCH$_2$<u>C</u>C), 127.1 (SO$_2$NCH$_2$C<u>C</u>), 114.4 (<u>C</u>H$_2$=CSO$_2$), 61.9, 61.1, 48.1, 43.6, 29.7 (^{t}Bu), 20.5 (C<u>H</u>$_3$CO$_2$);

HRMS calculated for $C_{13}H_{20}N_4O_4S$ 329.1278 $(M+H)^+$; found 329.1296 (TOF MS ES^+).

3-(2-(1,3-dioxolan-2-yl)ethyl)-6-(*tert*-butyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.20** (85%, 0.349 g) was isolated as brownish oil.

R_f = 0.28 (EtOAc:Hexane =1:1);

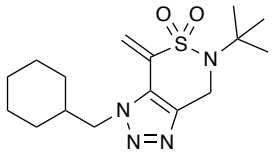
FTIR (neat): 2938, 3110, 2989, 2915, 1612, 1453, 1359, 1216 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.4 Hz, 1H, C$\underline{H}_2$=CSO_2), 6.11 (d, *J* = 2.4 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.99 (t, *J* = 3.8 Hz, 1H, C$\underline{H}O_2CH_2CH_2N_3$), 4.79 (s, 2H, NCH_2), 4.65–4.59 (m, 2H, $CHO_2CH_2C\underline{H}_2N_3$), 4.04–4.00 (m, 2H, $OC\underline{H}_2CH_2O$), 3.92–3.88 (m, 2H, $OCH_2C\underline{H}_2O$), 2.37–2.29 (m, 2H, $CHO_2C\underline{H}_2CH_2N_3$), 1.40 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4 (CH_2=$\underline{C}SO_2$), 137.1 ($SO_2NCH_2\underline{C}C$), 126.3 ($SO_2NCH_2C\underline{C}$), 114.5 ($\underline{C}H_2$=CSO_2), 101.1 ($O\underline{C}HO$), 65.2 (2 OCH_2CH_2O), 61.0, 44.6, 43.7, 32.9, 29.7 (^{t}Bu);

HRMS calculated for $C_{14}H_{22}N_4O_4S$ 343.1435 $(M+H)^+$; found 343.1449 (TOF MS ES^+).

6-(*tert*-butyl)-3-(cyclohexylmethyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.21** (88%, 0.157 g) was isolated as brownish oil.

R_f = 0.68 (EtOAc:Hexane =1:1);

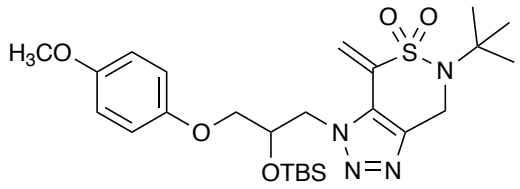
FTIR (neat): 2978, 2927, 2853, 1643, 1531, 1474, 1450, 1369, 1153, 1061, 876 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.87 (d, *J* = 2.1 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.77 (s, 2H, NCH_2), 4.28 (d, *J* = 7.3 Hz, 2H, CH_2Cy), 1.92–1.80 (m, 1H, Cy), 1.77 – 1.70 (m, 2H, Cy), 1.70–1.58 (m, 3H, Cy), 1.39 (s, 9H, ^{t}Bu), 1.28–1.14 (m, 3H, Cy), 1.13–1.01 (m, 2H, Cy);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.2 (CH_2=$\underline{C}SO_2$), 137.4 ($SO_2NCH_2\underline{C}C$), 126.3 ($SO_2NCH_2C\underline{C}$), 113.8 ($\underline{C}H_2$=CSO_2), 60.9, 55.9, 43.6, 37.8 (Cy), 30.4 (2 Cy), 29.7 (^{t}Bu), 25.9 (Cy), 25.3 (2 Cy);

HRMS calculated for $C_{16}H_{26}N_4O_2S$ 339.1849 $(M+H)^+$; found 339.1863 (TOF MS ES^+).

6-(*tert*-butyl)-3-(2-((*tert*-butyldimethylsilyl)oxy)-3-(4-methoxyphenoxy)propyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.22** (86%, 0.156 mg) was isolated as brownish oil.

R_f = 0.65 (EtOAc:Hexane =1:1);

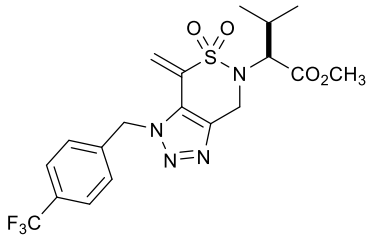
FTIR (neat): 2953, 2929, 2896, 1643, 1508, 1441, 1400,1388, 1232, 1162, 1107, 1043, 881, 826 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 4H, (ArH), 6.33 (dd, *J* = 12.3, 1.9 Hz, 2H, C$\underline{H}_2$=CSO_2), 4.93–4.68 (m, 3H, (OC$\underline{H}_2$C$\underline{H}$(OTBS)CH_2N_3), 4.65–4.47 (m, 2H, NC$\underline{H}_2$), 4.08–3.87 (m, 2H, (OCH_2CH(OTBS)C$\underline{H}_2N_3$)), 3.79 (s, 3H, OC$\underline{H}_3$), 1.43 (s, 9H, ^{t}Bu), 0.80 (s, 9H, $OSiCH_3CH_3C(C\underline{H}_3)_3$), -0.03 (s, 3H, $OSiCH_3C\underline{H}_3C(CH_3)_3$), -0.27 (s, 3H, $OSiC\underline{H}_3CH_3C(CH_3)_3$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4 (C_{Ar}), 152.1 (C_{Ar}), 140.9 (CH_2=$\underline{C}SO_2$), 136.9 ($SO_2NCH_2\underline{C}C$), 127.5 ($SO_2NCH_2C\underline{C}$), 115.4 (2 C_{Ar}), 115.0 ($\underline{C}H_2CSO_2$), 114.8 (2 C_{Ar}), 70.3 ($O\underline{C}H_2$CH(OTBS)), 70.2 ($OCH_2\underline{C}$H(OTBS), 61.1 (OCH_3), 55.7, 53.0, 43.5, 30.0 (^{t}Bu), 25.6 (3 $OSiCH_3CH_3C(\underline{C}H_3)_3$), 17.8, ($OSiCH_3CH_3\underline{C}(CH_3)_3$), -5.14, ($OSiCH_3\underline{C}H_3C(CH_3)_3$), -5.4, ($OSi\underline{C}H_3CH_3(CH_3)_3$);

HRMS calculated for $C_{25}H_{40}N_4O_5SiS$ 537.2561 $(M+H)^+$; found 537.2575 (TOF MS ES^+).

Methyl (*S*)-3-methyl-2-(4-methylene-5,5-dioxido-3-(4-(trifluoromethyl)benzyl)-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)butanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.23** (60%, 15 mg) was isolated as yellow oil.

R_f = 0.28 (EtOAc:Hexane =1:1);

$[\alpha]_D^{20}$ = 0.545 (*c* = 0.0055, CH_2Cl_2);

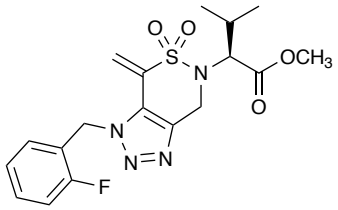
FTIR (neat): 2968, 1740, 1622, 1436, 1422, 1327, 1274, 1169, 1067, 934, 819 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H, ArH), 7.20 (d, *J* = 8.1 Hz, 2H, ArH), 6.11 (d, *J* = 2.3 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.89 (d, *J* = 16.6 Hz, 1H, N_3CH_2), 5.62 (d, *J* = 16.6 Hz, 1H, N_3CH_2), 5.52 (d, *J* = 2.3 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.84 (s, 2H, NCH_2), 4.10 (d, *J* = 10.2 Hz, 1H, NCH), 3.40 (s, 3H, OCH_3), 2.37–2.10 (m, 1H, $CH_3C\underline{H}CH_3$), 1.03 (d, *J* = 6.7 Hz, 3H, $\underline{Me}$CHMe), 0.96 (d, *J* = 6.6 Hz, 3H, MeCH$\underline{Me}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8 (CO), 141.0 (CH_2=$\underline{C}SO_2$), 137.7 (C_{Ar}), 134.5 ($SO_2NCH_2\underline{C}C$), 128.3 ($SO_2NCH_2C\underline{C}$), 131.1 (q, $^2J_{C–CF3}$ =32.9 Hz, C_{Ar}), 126.5 (2 C_{Ar}), 126.3 (q, $^3J_{C–CF3}$ = 3.7 Hz, 2 C_{Ar}), 123.5 (q, $^1J_{C–CF3}$ = 272.3 Hz, CF_3), 115.3 ($\underline{C}H_2$=CSO_2), 65.3 (NCH), 52.3 (Ar$\underline{C}H_2$), 51.5 (OCH_3), 42.2 (NCH_2), 28.3 (Me$\underline{C}$HMe), 19.2 (MeCH$\underline{Me}$), 19.1 ($\underline{Me}$CHMe);

HRMS calculated for $C_{19}H_{21}F_3N_4O_4S$ 459.1308 (M+H); found 459.1344 (TOF MS ES^+).

Methyl (*S*)-2-(3-(2-fluorobenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazin-6(3*H*)-yl)-3-methylbutanoate



According to the reaction protocol described in general procedure **E.1**, compound **2.4.2.3.24** (89%, 0.079g) was isolated as yellow oil.

R_f = 0.48 (EtOAc:Hexane =1:1);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -26.0 (*c* = 0.0005, CH_2Cl_2);

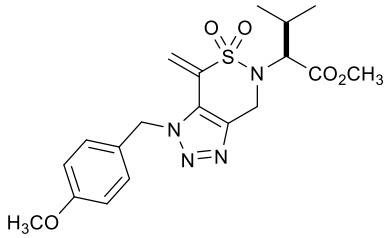
FTIR (neat): 1207, 1227, 1273, 1348, 1437, 1512, 1738, 2342, 2359, 2967 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 2H, ArH), 7.06 (d, *J* = 1.6 Hz, 2H, ArH), 6.11 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.80 (d, *J* = 16.0 Hz, 1H, CH_2), 5.59 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.52 (d, *J* = 16.1 Hz, 1H, CH_2), 4.82 (s, 2H, CH_2), 4.08 (d, *J* = 10.2 Hz, 1H, NC$\underline{H}CO_2Me$), 3.37 (s, 3H, OMe), 2.18 (ddt, *J* = 13.3, 10.3, 6.6 Hz, 1H, C$\underline{H}$MeMe), 1.02 (d, *J* = 6.7 Hz, 3H, Me), 0.95 (d, *J* = 6.6 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8 (CO), 162.8 (d, *J* = 248.3 Hz, C_{Ar}), 141.0 (CH_2=$\underline{C}SO_2$), 134.7 ($SO_2NCH_2\underline{C}C$), 130.4 (d, *J* = 8.3 Hz, C_{Ar}), 129.7 (d, *J* = 3.6 Hz, C_{Ar}), 128.2 (d, *J* = 8.2 Hz, C_{Ar}), 126.4 ($SO_2NCH_2C\underline{C}$), 116.5 (d, J = 21.8 Hz, C_{Ar}), 115.6 ($\underline{C}H_2$=CSO_2), 65.4 (N$\underline{C}HCO_2Me$), 52.4 (CH_2), 51.6 (OMe), 42.3 (CH_2), 28.4 (Me$\underline{C}$HMe), 19.3 (Me), 19.2 (Me) (*Note: identification of a quat Carbon not made);

HRMS calculated for $C_{18}H_{21}FN_4O_4S$ 409.1340 $(M+H)^+$; found 409.1344 (TOF MS ES^+).

Methyl (*S*)-2-(3-(4-methoxybenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-3-methylbutanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.25** (73%, 0.081 g) was isolated as clear oil.

$\mathbf{R_f}$ = 0.61 (EtOAc:Hexane =1:1);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -2.97 (*c* = 0.0235, CH_2Cl_2);

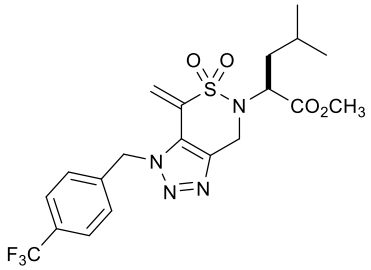
FTIR (neat): 2964, 2927, 2874, 1739, 1642, 1516, 1436, 1347, 1273, 1167, 1041, 889 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.9 Hz, 2H, ArH), 6.98 (d, *J* = 7.8 Hz, 2H, ArH), 6.11 (d, *J* = 2.3 Hz, 1H C$\underline{H}_2$=CSO_2), 5.83 (d, *J* = 16.0 Hz, 1H, $N_3C\underline{H}_2$), 5.64 (d, *J* = 2.1 Hz, 1H C$\underline{H}_2$=CSO_2), 5.51 (d, *J* = 16.2 Hz, 1H, N_3CH_2), 4.84 (s, 2H, NCH_2), 4.09 (dd, *J* = 10.4, 1.2 Hz, 1H, NCH), 3.38 (d, *J* = 1.5 Hz, 3H, OMe), 2.36 (s, 3H, CO_2Me), 2.20 (dp, *J* = 10.2, 6.6 Hz, 1H, MeC$\underline{H}$Me), 1.05 (d, *J* = 6.6 Hz, 3H, $\underline{Me}CHCH_3$), 0.97 (d, *J* = 6.6 Hz, 3H, MeCH$\underline{Me}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7 (COO), 140.7 (CH_2=$\underline{C}SO_2$), 138.6 (C_{Ar}), 134.5 ($SO_2NCH_2\underline{C}C$), 130.1 (2 C_{Ar}), 130.0 (C_{Ar}), 126.3 ($SO_2NCH_2C\underline{C}$), 126.1 (2 C_{Ar}), 115.8 ($\underline{C}H_2$=CSO_2), 65.4 (NCH), 52.8 (Ar$\underline{C}H_2$), 51.5 (OCH_3), 42.2 (NCH_2), 28.3 (Me$\underline{C}$HMe), 21.1, 19.2 (MeCH$\underline{Me}$), 19.1 ($\underline{Me}$CHMe);

HRMS calculated for $C_{19}H_{24}N_4O_5S$ 421.1540 $(M+H)^+$; found 421.1525 (TOF MS ES^+).

Methyl (*S*)-4-methyl-2-(4-methylene-5,5-dioxido-3-(4-(trifluoromethyl)benzyl)-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)pentanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.26** (64%, 0.053 g) was isolated as yellow oil.

R_f = 0.50 (EtOAc:Hexane =1:1);

$[\alpha]_D^{20}$ = -4.218 (*c* = 0.0275, CH_2Cl_2);

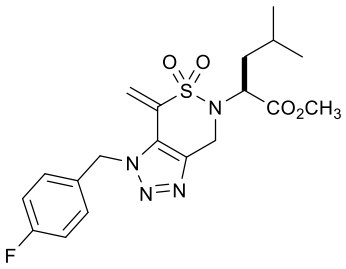
FTIR (neat): 2959, 2872, 1743, 1644, 1514, 1327, 1251, 1171, 1051, 883, 820 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H, ArH), 7.13 (d, *J* = 8.0 Hz, 2H, ArH), 6.01 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.81 (d, *J* = 16.7 Hz, 1H, N_3CH_2), 5.60 (d, *J* = 16.7 Hz, 1H, N_3CH_2), 5.43 (d, *J* = 2.3 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.71 (d, *J* = 16.9 Hz, 1H, NC$\underline{H}CO_2$Me), 4.68 – 4.58 (m, 2H, NCH_2), 3.46 (s, 3H, OMe), 1.69 – 1.62 (m, 2H, C$\underline{H}_2$CHMeMe), 1.62 – 1.53 (m, 1H, MeC$\underline{H}$Me), 0.90 (t, *J* = 6.5 Hz, 6H, 2Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (COO), 141.2 (CH_2=$\underline{C}SO_2$), 137.9 (C_{Ar}), 135.0 ($SO_2NCH_2\underline{C}C$), 131.1 (q, $^2J_{C-CF3}$ =32.7 Hz, C_{Ar}), 126.9 ($SO_2NCH_2C\underline{C}$), 126.6 (2 C_{Ar}), 126.4 (q, $^3J_{C-CF3}$ = 3.7 Hz, 2 C_{Ar}), 123.5 (q, $^1J_{C-CF3}$ = 272.8 Hz, CF_3), 114.6 ($\underline{C}H_2$=CSO_2), 58.4 (NCH), 52.5 (Ar$\underline{C}H_2$), 52.2 (OMe), 41.9 (NCH_2), 38.0 ($\underline{C}H_2$CHMeMe), 24.8 (Me$\underline{C}$HMe), 23.1, ($\underline{Me}$CHMe), 21.0, (MeCH$\underline{Me}$);

HRMS calculated for $C_{20}H_{23}F_3N_4O_4S$ 473.1465 $(M+H)^+$; found 473.1469 (TOF MS ES^+).

Methyl (*S*)-2-(3-(4-fluorobenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-4-methylpentanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.28** (78%, 0.074 g) was isolated as clear oil.

R_f = 0.57 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -4.549 (*c* = 0.0255, CH_2Cl_2);

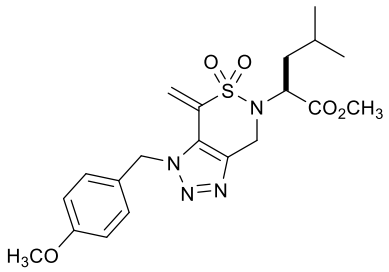
FTIR (neat): 2958, 2872, 1742, 1644, 1512, 1438, 1388, 1270, 1159, 1050, 883, 823, cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.05 (m, 4H, ArH), 6.11 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.80 (dd, *J* = 16.2, 1.2 Hz, 1H, $N_3C\underline{H}_2$), 5.64 – 5.57 (m, 2H, N_3CH_2, C$\underline{H}_2$=CSO_2), 4.78 (d, *J* = 16.7 Hz, 1H, NC$\underline{H}CO_2Me$), 4.74 (d, *J* = 11.0 Hz, 2H, NCH_2), 3.53 (s, 3H, OMe), 1.81 – 1.54 (m, 4H, C$\underline{H}_2$CHMeMe, MeC$\underline{H}$Me), 0.98 (t, J = 6.2 Hz, 6H, 2Me).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9 (CO), 162.8 ($^1J_{C-F}$ = 246.5 Hz, C_{Ar}), 141.0 (CH_2=$\underline{C}SO_2$), 135.0 ($SO_2NCH_2\underline{C}C$), 129.7 ($^4J_{C-F}$ = 3.64 Hz, C_{Ar}), 128.1 ($^3J_{C-F}$ = 8.05 Hz, 2, C_{Ar}), 126.5 ($SO_2NCH_2C\underline{C}$), 116.4 ($^2J_{C-F}$ = 21.56 Hz, 2, C_{Ar}), 114.7 ($\underline{C}H_2$=CSO_2), 58.2 (NCH), 52.3 (Ar$\underline{C}H_2$), 52.1 (OCH_3), 42.8 (NCH_2), 38.0 ($CH\underline{C}H_2CHNCOOCH_3$), 24.7 ($CH_3\underline{C}HCH_3$), 23.0, ($\underline{C}H_3CHCH_3$), 21.0, ($CH_3CH\underline{C}H_3$);

HRMS calculated for $C_{19}H_{23}FN_4O_4S$ 423.1497 $(M+H)^+$; found 423.1491 (TOF MS ES^+).

Methyl (*S*)-2-(3-(4-methoxybenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-4-methylpentanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.29** (71%, 0.068 g) was isolated as clear oil.

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

$[\alpha]_D^{20}$ = -42.7 (*c* = 0.004, CH_2Cl_2);

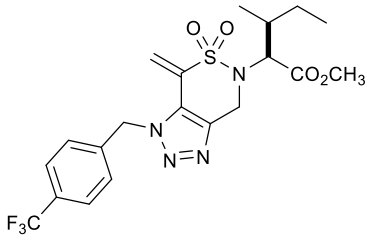
FTIR (neat): 2957, 2871, 1742, 1612, 1586, 1514, 1439, 1250, 1156, 1032, 818 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 - 6.96 (m, 2H, ArH), 6.92 - 6.82 (m, 2H, ArH), 6.08 (d, *J* = 2.1 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.73 (dt, *J* = 16.0, 0.8 Hz, 1H, $N_3C\underline{H}_2$), 5.62 (d, *J* = 2.1 Hz, 1H C$\underline{H}_2$=CSO_2), 5.54 (d, *J* = 16.0 Hz, 1H, N_3CH_2), 4.77 - 4.63 (m, 3H, NC$\underline{H}_2$, NC$\underline{H}CO_2$Me), 3.79 (s, 3H, ArOMe), 3.47 (s, 3H, CO_2Me), 1.72 - 1.58 (m, 3H, C$\underline{H}_2$CHMeMe, C$\underline{H}$MeMe), 0.94 (t, *J* = 6.4 Hz, 6H, 2Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9 (CO), 159.8 (C_{Ar}), 140.8 (CH_2=$\underline{C}SO_2$), 135.0 ($SO_2NCH_2\underline{C}C$), 127.7 (2 C_{Ar}), 126.6 ($SO_2NCH_2C\underline{C}$), 125.9 (C_{Ar}), 115.0 ($\underline{C}H_2$=CSO_2), 114.7 (2 C_{Ar}), 58.2 (N$\underline{C}HCO_2$Me), 55.4 (ArO$\underline{Me}$), 52.7 (Bn), 52.1 (OMe), 41.9 (N$\underline{C}H_2$), 38.0 ($\underline{C}H_2$CHMeMe), 24.8 (Me$\underline{C}$HMe), 23.1 (Me), 21.1 ($\underline{Me}$);

HRMS calculated for $C_{20}H_{26}N_4O_5S$ 435.1697 $(M+H)^+$; found 435.1704 (TOF MS ES^+).

Methyl (2*S*,3*S*)-3-methyl-2-(4-methylene-5,5-dioxido-3-(4-(trifluoromethyl)benzyl)-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)pentanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.30** (72 %, 0.67 g) was isolated as clear oil.

R_f = 0.60 (EtOAc:Hexane =1:1);

$[\alpha]_D^{20}$ = -6.41 (*c* = 0.0265, CH_2Cl_2);

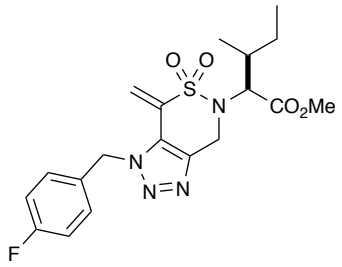
FTIR (neat): 1209, 1242, 1265, 1322, 1392, 1421, 1435, 1469, 1625, 1745, 2878, 2963 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H, ArH), 7.13 (d, *J* = 8.1 Hz, 2H, ArH), 6.03 (d, *J* = 2.3 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.82 (d, *J* = 16.6 Hz, 1H, $N_3C\underline{H}_2$), 5.55 (d, *J* = 16.6 Hz, 1H, N_3CH_2), 5.46 (d, *J* = 2.3 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.93 – 4.65 (m, 2H, NCH_2), 4.13 (d, *J* = 10.4 Hz, 1H, NC$\underline{H}CO_2Me$), 3.32 (s, 3H, $CO_2C\underline{H}_3$), 2.00 – 1.88 (m, 1H, MeC$\underline{H}$Me), 1.55 (dqd, *J* = 15.1, 7.6, 3.3 Hz, 1H, C$\underline{H}_2$Me), 1.23 – 1.10 (m, 1H, C$\underline{H}_2$Me), 0.93 – 0.78 (m, 6H, 2Me).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0 (CO), 141.1 (CH_2=$\underline{C}SO_2$), 137.9 (C_{Ar}), 134.5 ($SO_2NCH_2\underline{C}C$), 131.1 (q, $^2J_{C–CF3}$ =31.9 Hz, C_{Ar}), 126.6 (2 C_{Ar}), 126.5, 126.4 (q, $^3J_{C–CF3}$ = 3.7 Hz, 2 C_{Ar}), 123.6 (q, $^1J_{C–CF3}$ = 270.8 Hz, CF_3), 115.5 ($\underline{C}H_2$=CSO_2), 63.9 (NCH), 52.4 (Ar$\underline{C}H_2$), 51.6 (OMe), 42.3 (NCH_2), 34.1, ($\underline{C}$HMe), 25.2, ($\underline{C}H_2$Me), 15.4, (Me), 10.2, (Me);

HRMS calculated for $C_{20}H_{23}F_3N_4O_4S$ 473.1465 $(M+H)^+$; found 473.1469 (TOF MS ES^+).

Methyl (2*S*,3*S*)-2-(3-(4-fluorobenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazin-6(3*H*)-yl)-3-methylpentanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.31** (61 %, 0.049 g) was isolated as clear oil.

R_f = 0.65 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -6.47 (*c* = 0.0105, CH_2Cl_2);

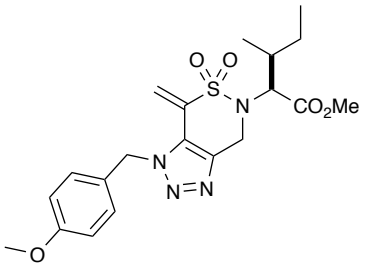
FTIR (neat): 2962, 2928, 1740, 1643, 1512, 1436, 1152, 1043, cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 - 7.10 (m, 2H, ArH), 6.96 (d, *J* = 8.2 Hz, 2H, ArH), 6.08 (d, *J* = 2.1 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.80 (d, *J* = 16.2 Hz, 1H, $N_3C\underline{H}_2$), 5.61 (d, *J* = 2.2 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.48 (d, *J* = 16.2 Hz, 1H, N_3CH_2), 4.88 - 4.75 (m, 2H, CH_2), 4.17 (d, *J* = 10.5 Hz, 1H, NC$\underline{H}CO_2Me$), 3.34 (s, 3H, CO_2Me), 2.07 - 1.91 (m, 1H, C$\underline{H}$Me), 1.31 - 1.15 (m, 2H, C$\underline{H}_2$Me), 0.97 - 0.84 (m, 6H, 2Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8 (CO), 140.8 (CH_2=$\underline{C}SO_2$), 138.7 (C_{Ar}), 134.5 ($SO_2NCH_2\underline{C}C$), 131.0 (C_{Ar}), 130.1 (2 C_{Ar}), 126.3 ($SO_2NCH_2C\underline{C}$) 126.2 (2 C_{Ar}), 115.9 ($\underline{C}H_2$=CSO_2), 63.8 (N$\underline{C}HCO_2Me$), 52.9 (CH_2), 51.6 (CO_2Me), 42.3 (CH_2), 33.9 ($\underline{C}HMe$), 25.1 ($\underline{C}H_2Me$), 15.4 (Me), 10.2 (Me);

HRMS calculated for $C_{19}H_{23}FN_4O_4S$ 440.1762 $(M+NH_4)^+$; found 440.1772 (TOF MS ES^+).

Methyl (2*S*,3*S*)-2-(3-(4-methoxybenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazin-6(3*H*)-yl)-3-methylpentanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.32** 87 %, 0.078 g) was isolated as clear oil.

R_f = 0.60 (EtOAc:Hexane = 1:1);

$[\alpha]_D^{20}$ = -5.75 (*c* = 0.029, CH_2Cl_2);

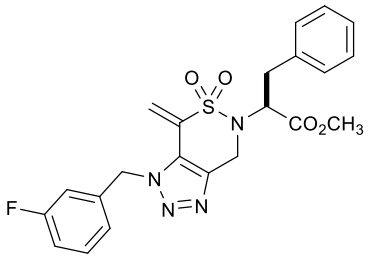
FTIR (neat): 2966, 2929, 2878, 1739, 1644, 1516, 1454, 1317, 1233, 1199, 1071, 889 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H, ArH), 7.24–7.14 (m, 2H, ArH), 6.10 (d, *J* = 2.3 Hz, 1H, C$\underline{H}_2$=CSO_2), 5.95 - 5.81 (m, 1H, $N_3C\underline{H}_2$), 5.62 (d, *J* = 16.6 Hz, 1H, N_3CH_2), 5.52 (d, *J* = 2.3 Hz, 1H, C$\underline{H}_2$=CSO_2), 4.93 - 4.77 (m, 2H, NC$\underline{H}_2$), 4.19 (d, *J* = 10.4 Hz, 1H, NC$\underline{H}$), 3.39 (s, 3H, O$\underline{Me}$), 2.33 (s, 3H, OMe) 2.08 - 1.92 (m, 1H, C$\underline{H}$Me), 1.62 (dqd, *J* = 15.1, 7.5, 3.3 Hz, 1H, C$\underline{H}_2$Me), 1.29 - 1.13 (m, 1H, C$\underline{H}_2$Me), 0.92 (dd, *J* = 8.0, 7.1 Hz, 6H, 2Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8 (CO), 140.8 (CH_2=$\underline{C}SO_2$), 138.7 ($SO_2NCH_2\underline{C}C$), 134.5 (C_{Ar}), 131.0 (C_{Ar}), 130.1 (2 C_{Ar}), 126.3 ($SO_2NCH_2C\underline{C}$), 126.2 (2C_{Ar}), 115.9 ($\underline{C}H_2$=CSO_2), 63.8 (N$\underline{C}$HCO_2Me), 52.9 ($BnCH_2$), 51.5 ($CO_2\underline{Me}$), 42.2 (CH_2), 33.9 ($\underline{C}$H-Ile), 25.1 ($\underline{C}H_2$Me), 21.2 (OMe), 15.3 (Me), 10.2 (Me);

HRMS calculated for $C_{20}H_{26}N_4O_5S$ 435.1697 $(M+H)^+$; found 435.1709 (TOF MS ES^+).

Methyl (*S*)-2-(3-(3-fluorobenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-3-phenylpropanoate



According to the reaction protocol described in general procedure **E.2**, compound **2.4.2.3.33** (71 %, 0.0181 g) was isolated as clear oil.

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

$[\alpha]_D^{20}$ = -16.5 (*c* = 0.00133, CH_2Cl_2);

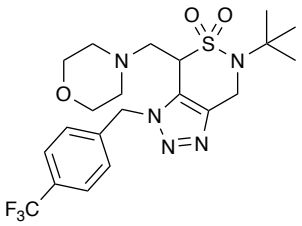
FTIR (neat): 2953, 1730, 1456, 1359, 1260, 1178, 1035, 764, 750, 702 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (ddd, *J* = 8.0, 4.2, 2.7 Hz, 1H, ArH), 7.19 – 7.11 (m, 2H, ArH), 7.07 (dd, *J* = 5.0, 2.0 Hz, 3H, ArH), 7.00 (dd, *J* = 6.6, 2.8 Hz, 2H, ArH), 6.94 (td, *J* = 7.7, 1.6 Hz, 1H, ArH), 5.81 (d, *J* = 2.5 Hz, 1H, $C\underline{H}_b{=}CSO_2$), 5.70 – 5.52 (m, 2H, $N_3C\underline{H}_2Ar$), 5.38 (d, *J* = 2.5 Hz, 1H, $C\underline{H}_2{=}CSO_2$), 4.98 (dd, *J* = 10.3, 5.6 Hz, 1H, $NC\underline{H}CO_2Me$), 4.86 – 4.71 (m, 2H, $NC\underline{H}_2$), 3.64 (s, 3H, OMe), 3.30 (dd, *J* = 14.5, 5.7 Hz, 1H, CH_2-Ar_{Phe}), 2.90 (dd, *J* = 14.5, 10.3 Hz, 1H, CH_2-Ar_{Phe})

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0 (CO), 159.4 (d, $^1J_{C-F}$ = 246.7 Hz, C_{Ar}), 135.3 ($CH_2{=}\underline{C}SO_2$), 134.2 ($SO_2NCH_2\underline{C}C$), 130.6 (d, $^{3'}J_{C-F}$ = 8.2 Hz, C_{Ar}), 129.1 (2 C_{Ar}), 129.0 (C_{Ar}), 128.5 (d, $^4J_{C-F}$ 2.9 Hz, C_{Ar}), 128.4 (2 C_{Ar}), 128.1 (C_{Ar}), 127.0 ($SO_2NCH_2C\underline{C}$), 125.0 (d, $^3J_{C-F}$ 3.6 Hz, C_{Ar}), 120.7 (d, $^2J_{C-F}$ 14.1 Hz, C_{Ar}), 115.7 (d, $^{2'}J_{C-F}$ = 21.0 Hz, C_{Ar}), 114.2 (d, J = 2.6 Hz, ($\underline{C}H_2{=}CSO_2$), 60.9 (NCH), 52.4 (OCH_3), 46.3 ($N_3\underline{C}H_2Ph$), 42.0 (NCH_2), 35.8 ($Ph\underline{C}H_2$);

HRMS calculated for $C_{22}H_{21}FN_4O_4S$ 479.1160 $(M+Na)^+$; found 479.1169 (TOF MS ES^+).

6-(*tert*-butyl)-4-(morpholinomethyl)-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.1** (96%, 29 mg) was isolated as colorless oil.

R_f = 0.28 (EtOAc:Hexane = 1:1);

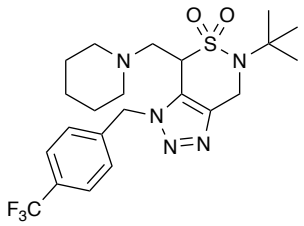
FTIR (neat): 2957, 2360, 1724, 1621, 1421, 1326, 1167, 1129, 1067, 827 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H, ArH), 7.12 (d, *J* = 8.0 Hz, 2H, ArH), 6.00 (d, *J* = 16.1 Hz, 1H, CH_2), 5.84 (d, *J* = 16.0 Hz, 1H, CH_2), 4.70 (d, *J* = 14.6 Hz, 1H, CH_2), 4.45 (d, *J* = 14.6 Hz, 1H, CH_2), 3.92 (dd, *J* = 9.2, 2.3 Hz, 1H, $NCH_2C\underline{H}S$), 3.66 (t, *J* = 4.5 Hz, 4H, $2CH_2$), 3.22 (dd, *J* = 13.2, 2.6 Hz, 1H, $NC\underline{H}_2CHS$), 2.73 (dd, *J* = 13.0, 9.5 Hz, 1H, $NC\underline{H}_2CHS$), 2.60 (dt, *J* = 9.4, 4.5 Hz, 2H, CH_2), 2.38 (m 2H, CH_2), 1.51 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2 (C_{Ar}), 138.8 ($SO_2NCH_2\underline{C}C$), 130.9 (d, *J* = 33.4 Hz, C_{Ar}), 130.4 ($SO_2NCH_2C\underline{C}$), 126.7 (2 C_{Ar}), 126.3 (q, *J* = 10.8 Hz, 2 C_{Ar}), 124. 9 (CF_3) 66.9 (2 $O\underline{C}H_2CH_2N$), 61.1, 56.2, 54.4, 51.9, 43.4, 30.0 (^{t}Bu);

HRMS calculated for $C_{21}H_{28}F_3N_5O_3S$ 488.1938 $(M+H)^+$; found 488.1956 (TOF MS ES^+).

6-(*tert*-butyl)-4-(piperidin-1-ylmethyl)-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.2** (72%, 8.7 mg) was isolated as colorless oil.

R_f = 0.60 (EtOAc:Hexane = 1:1);

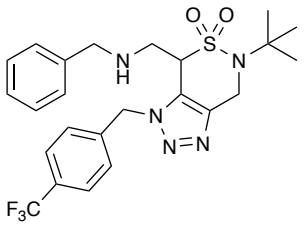
FTIR (neat): 2952, 1723, 1421, 1327, 1164, 1127, 1067, 1036, 991 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H, ArH), 7.15 (d, *J* = 8.0 Hz, 2H, ArH), 6.12 (d, *J* = 15.9 Hz, 1H, CH_2), 5.82 (d, *J* = 16.0 Hz, 1H, CH_2), 4.69 (d, *J* = 14.6 Hz, 1H, CH_2), 4.43 (d, *J* = 14.6 Hz, 1H, CH_2), 3.92 (d, *J* = 9.4 Hz, 1H, $NCH_2C\underline{H}S$), 3.16 (dd, *J* = 13.0, 2.5 Hz, 1H, $NC\underline{H}_2CHS$), 2.71 (dd, *J* = 12.8, 10.4 Hz, 1H, $NC\underline{H}_2CHS$), 2.51 (m, 2H, CH_2), 2.28 (dt, *J* = 10.4, 4.6 Hz, 2H CH_2), 1.59 (m, 4H 2 CH_2), 1.50 (s, 9H, ^{t}Bu), 1.25 (s, 2H, CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1 (d, = 1.0 Hz, C_{Ar}), 139.0 ($SO_2NCH_2\underline{C}C$), 130.7 (q, J = 32.8 Hz, C_{Ar}), 130.6 ($SO_2NCH_2C\underline{C}$), 126.8 (2 C_{Ar}), 126.2 (q, *J* = 3.6, 2 C_{Ar}), 123.92 (d, *J* = 272.3 Hz, CF_3) 61.4, 60.9, 56.5, 55.5, 51.9, 43.4, 30.0 (^{t}Bu), 26.1, 23.9;

HRMS calculated for $C_{22}H_{30}F_3N_5O_2S$ 486.2145 $(M+H)^+$; found 486.2170 (TOF MS ES^+).

4-((benzylamino)methyl)-6-(*tert*-butyl)-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.3** (95%, 30 mg) was isolated as colorless oil.

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

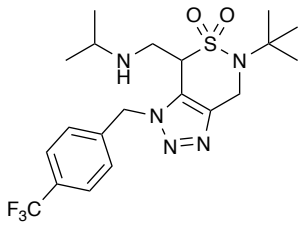
FTIR (neat): 2953, 1723, 1421, 1326, 1168, 1127, 1067, 1035 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2H, ArH), 7.32 (dt, *J* = 13.9, 6.0 Hz, 3H, ArH), 7.22 (d, *J* = 7.3 Hz, 2H, ArH), 7.06 (d, *J* = 7.9 Hz, 2H, ArH), 5.58 (m, 2H, CH_2), 4.64 (d, *J* = 14.9 Hz, 1H, CH_2), 4.45 (d, *J* = 14.9 Hz, 1H CH_2), 4.00 (m, 1H, $CH_2C\underline{H}S$), 3.77 (d, *J* = 13.4 Hz, 1H, CH_2), 3.64 (d, *J* = 13.3 Hz, 1H, CH_2), 3.19 (dd, *J* = 13.5, 7.0 Hz, 1H, $C\underline{H}_2CHS$), 2.84 (dd, *J* = 13.6, 4.1 Hz, 1H, $C\underline{H}_2CHS$), 1.45 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0 (C_{Ar}), 139.1 ($SO_2NCH_2\underline{C}C$), 138.2 (C_{Ar}), 131.0 (d, *J* = 32.8 Hz, C_{Ar}) 128.8 (2 C_{Ar}), 128.7 (d, *J* = 13.9 Hz, C_{Ar}), 128.4 (2 C_{Ar}), 128.3 ($SO_2NCH_2C\underline{C}$), 127.6 (C_{Ar}), 127.4 (C_{Ar}), 126.2 (q, *J* = 3.7 Hz, 2 C_{Ar}), 123.8 (d, *J* = 273.0 Hz, CF_3), 61.1, 58.8, 53.7, 51.8, 48.9, 43.1, 30.0 (^{t}Bu);

HRMS calculated for $C_{24}H_{28}F_3N_5O_2S$ 506.1838 $(M-H)^+$; found 506.1814 (TOF MS ES^+).

6-(*tert*-butyl)-4-((isopropylamino)methyl)-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.4** (99%, 29 mg) was isolated as colorless oil.

R_f = 0.28 (EtOAc:Hexane = 1:1);

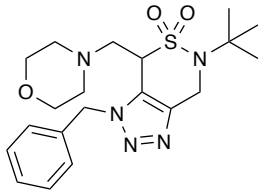
FTIR (neat): 2967, 2929, 2870, 1621, 1468, 1370, 1326, 1067, 817 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H, C_{AR}), 7.24 (d, 2H, C_{AR}), 5.87 (d, *J* = 16.0 Hz, 1H, CH_2), 5.67 (d, *J* = 16.0 Hz, 1H, CH_2), 4.68 (d, *J* = 14.8 Hz, 1H, CH_2), 4.44 (d, *J* = 14.7 Hz, 1H, CH_2), 3.98 (t, *J* = 5.8 Hz, 1H, $CH_2C\underline{H}S$), 3.27 (dd, *J* = 13.2, 6.6 Hz, 1H, $C\underline{H}_2CHS$), 2.83 (dd, *J* = 13.2, 5.4 Hz, 1H, $C\underline{H}_2CHS$), 2.66 (dq, *J* = 11.9, 5.9 Hz, 1H, $MeC\underline{H}Me$), 1.50 (s, 9H, ^{t}Bu), 1.00 (d, *J* = 6.2 Hz, 3H, Me), 0.95 (d, *J* = 6.2 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8 ($SO_2NCH_2\underline{C}C$), 138.5 (d, *J* = 1.1 Hz, C_{Ar}), 131.0 (d, *J* = 32.8 Hz, C_{Ar}), 128.6 ($SO_2NCH_2C\underline{C}$), 127.3 (2 C_{Ar}), 126.3 (q, J = 3.7 Hz, 2 C_{Ar}), 123.8 (d, *J* = 273.0 Hz, CF_3) 61.1, 59.0, 51.9, 49.1, 48.4, 43.2, 30.0 (^{t}Bu), 22.9 (Me), 22.8 (Me);

HRMS calculated for $C_{20}H_{28}F_3N_5O_2S$ 458.1838 $(M-H)^+$; found 458.1819 (TOF MS ES^+).

3-benzyl-6-(*tert*-butyl)-4-(morpholinomethyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.5** (96%, 24 mg) was isolated as colorless oil.

R_f = 0.13 (EtOAc:Hexane = 1:2);

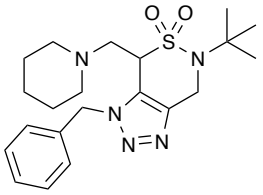
FTIR (neat): 2964, 2359, 1497, 1455, 1325, 1196, 1130, 1116, 1071, 1033, 1005, 731, 708 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (q, *J* = 7.6, 6.9 Hz, 3H, ArH), 7.00 (d, *J* = 7.0 Hz, 2H, ArH), 5.94 (m, 2H, CH_2), 4.69 (d, *J* = 14.7 Hz, 1H, CH_2), 4.44 (d, *J* = 14.6 Hz, 1H, CH_2), 3.92 (dd, *J* = 9.1, 3.2 Hz, 1H, $CH_2C\underline{H}S$), 3.68 (t, *J* = 4.5 Hz, 4H, CH_2), 3.18 (dd, *J* = 13.2, 3.2 Hz, 1H, $C\underline{H}_2CHS$), 2.73 (dd, *J* = 13.1, 9.3 Hz, 1H, $C\underline{H}_2CHS$), 2.58 (dt, *J* = 9.7, 4.5 Hz, 2H, CH_2), 2.33 (dt, *J* = 10.5, 4.6 Hz, 2H, CH_2), 1.49 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1 ($SO_2NCH_2\underline{C}C$), 134.7 (C_{Ar}), 130.1 (C_{Ar}), 129.3 (2 C_{Ar}), 128.6 ($SO_2NCH_2C\underline{C}$), 126.4 (2 C_{Ar}), 66.9 (2 OCH_2), 61.0, 60.9, 56.3, 54.3, 52.6, 30.0 (^{t}Bu);

HRMS calculated for $C_{20}H_{29}N_5O_3S$ 420.2064 $(M+H)^+$; found 420.2061 (TOF MS ES^+).

3-benzyl-6-(*tert*-butyl)-4-(piperidin-1-ylmethyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.6** (93%, 25 mg) was isolated as colorless oil.

R_f = 0.70 (EtOAc:Hexane = 2:1);

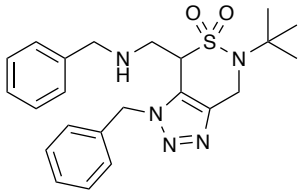
FTIR (neat): 3032, 2934, 2853, 2799, 2762, 2359, 1590, 14.55, 1327, 1077, 772, 734 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (q, *J* = 9.5, 8.0 Hz, 3H, ArH), 7.04 (d, *J* = 7.4 Hz, 2H, ArH), 6.02 (d, *J* = 15.6 Hz, 1H, CH_2), 5.79 (d, *J* = 15.6 Hz, 1H, CH_2), 4.68 (d, *J* = 14.5 Hz, 1H, CH_2), 4.42 (d, *J* = 14.6 Hz, 1H, CH_2), 3.93 (dd, *J* = 10.0, 2.7 Hz, 1H, $CH_2C\underline{H}S$), 3.14 (dd, *J* = 12.9, 3.0 Hz, 1H, $C\underline{H}_2CHS$), 2.71 (dd, *J* = 12.9, 10.2 Hz, 1H, $C\underline{H}_2CHS$), 2.60 (m, 2H, CH_2), 2.28 (dt, *J* = 10.8, 5.2 Hz, 2H, CH_2), 1.57 (dd, *J* = 12.3, 6.9 Hz, 6H, $3CH_2$), 1.49 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8 ($SO_2NCH_2\underline{C}C$), 135.0 (C_{Ar}), 130.4 (C_{Ar}), 129.2 (2 C_{Ar}), 128.4 ($SO_2NCH_2C\underline{C}$), 126.5 (2 C_{Ar}), 61.5, 60.8, 56.6, 55.5, 52.5, 43.4, 30.0 (^{t}Bu), 26.2, 24.0;

HRMS calculated for $C_{21}H_{31}N_5O_2S$ 418.2271 $(M+H)^+$; found 418.2220 (TOF MS ES^+).

3-benzyl-4-((benzylamino)methyl)-6-(*tert*-butyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.7** (80%, 21 mg) was isolated as colorless oil.

R_f = 0.31 (EtOAc:Hexane = 1:1);

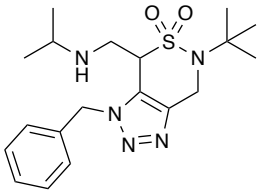
FTIR (neat): 2954, 2360, 1714, 1414, 1181, 1036, cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.1 Hz, 3H, ArH), 7.23 (d, *J* = 6.8 Hz, 1H, ArH), 7.21 (m, 3H, ArH), 6.98 (m, 2H, ArH), 5.47 (d, *J* = 15.7 Hz, 1H, CH_2), 5.34 (d, *J* = 15.7 Hz, 1H, CH_2), 4.58 (d, *J* = 15.0 Hz, 1H, CH_2), 4.38 (d, *J* = 14.9 Hz, 1H, CH_2), 3.92 (dd, *J* = 7.0, 3.0 Hz, 1H, $CH_2C\underline{H}S$), 3.71 (d, *J* = 13.3 Hz, 1H, CH_2), 3.54 (d, *J* = 13.3 Hz, 1H, CH_2), 3.07 (dd, *J* = 13.6, 7.5 Hz, 1H, $C\underline{H}_2CHS$), 2.73 (dd, *J* = 13.6, 3.4 Hz, 1H, $C\underline{H}_2CHS$), 1.36 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.9 ($SO_2NCH_2\underline{C}C$), 139.2 (C_{Ar}), 134.1 (C_{Ar}), 129.3 (2 C_{Ar}), 128.8 (C_{Ar}), 128.7 (2 C_{Ar}), 128.4 (2 C_{Ar}), 128.0 ($SO_2NCH_2C\underline{C}$), 127.5 (C_{Ar}), 127.1 (2 C_{Ar}), 60.9, 58.9, 53.6, 52.6, 48.7, 43.1, 29.9 (^{t}Bu);

HRMS calculated for $C_{23}H_{29}N_5O_2S$ 440.2115 $(M+H)^+$; found 440.2133 (TOF MS ES^+).

3-benzyl-6-(*tert*-butyl)-4-((isopropylamino)methyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.8** (49%, 30 mg) was isolated as colorless oil.

R_f = 0.28 (EtOAc:Hexane = 1:1);

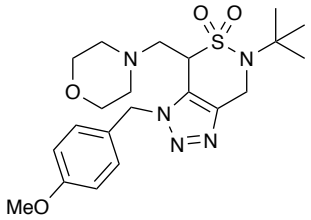
FTIR (neat): 2952, 1722, 1443, 1326, 1034, 990, 920 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.3 Hz, 3H, ArH), 7.17 (d, *J* = 6.9 Hz, 2H, ArH), 5.75 (d, *J* = 15.6 Hz, 1H, CH_2), 5.65 (d, *J* = 15.6 Hz, 1H, CH_2), 4.66 (d, *J* = 14.8 Hz, 1H, CH_2), 4.43 (d, *J* = 14.8 Hz, 1H, CH_2), 4.12 (d, *J* = 5.8 Hz, 1H, $CH_2C\underline{H}S$), 3.20 (dd, *J* = 13.3, 7.5 Hz, 1H, $C\underline{H}_2CHS$), 2.85 (dd, *J* = 13.5, 4.0 Hz, 1H, $C\underline{H}_2CHS$), 2.72 (dt, *J* = 12.2, 6.2 Hz, 1H, $MeC\underline{H}Me$), 1.49 (s, 9H, ^{t}Bu), 1.01 (dd, *J* = 13.1, 6.2 Hz, 6H, 2Me);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7 ($SO_2NCH_2\underline{C}C$), 134.4 (C_{Ar}), 129.3 9 (2 $C_{\underline{Ar}}$), 128.7 ($SO_2NCH_2C\underline{C}$), 128.0 (C_{Ar}), 127.1 (2 C_{Ar}), 61.0, 58.6, 52.6, 49.2, 47.9, 43.2, 30.0 (^{t}Bu), 22.5 (2 $MeCH\underline{Me}$);

HRMS calculated for $C_{19}H_{29}N_5O_2S$ 392.2115 $(M+H)^+$; found 392.2131 (TOF MS ES^+).

6-(tert-butyl)-3-(4-methoxybenzyl)-4-(morpholinomethyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.9** (90%, 38 mg) was isolated as colorless oil.

R_f = 0.28 (EtOAc:Hexane = 1:1);

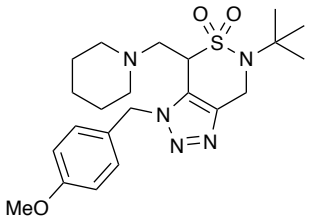
FTIR (neat): 2961, 2853, 1612, 1514, 1458, 1326, 1179, 1033, 815 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) 6.96 (d, *J* = 8.2 Hz, 2H, ArH), 6.85 (d, *J* = 8.4 Hz, 2H, ArH), 5.83–5.71 (m, 2H, CH_2), 4.67 (d, *J* = 14.6 Hz, 1H, CH_2), 4.41 (d, *J* = 14.6 Hz, 1H, CH_2), 3.96–3.90 (m, 1H, $CH_2C\underline{H}S$), 3.78 (s, 3H, OMe), 3.70 (t, *J* = 4.3 Hz, 4H, $2CH_2$), 3.18 (dd, *J* = 13.2, 2.9 Hz, 1H, $C\underline{H}_2CHS$), 2.74 (dd, *J* = 13.1, 9.2 Hz, 1H, $C\underline{H}_2CHS$), 2.60 (dt, *J* = 9.0, 4.0 Hz, 2H, CH_2), 2.36 (dt, *J* = 10.0, 4.4 Hz, 2H, CH_2), 1.49 (s, 9H, ^{t}Bu).

^{13}C NMR (126 MHz, $CDCl_3$) 159.7 (C_{Ar}), 139.0 ($SO_2NCH_2\underline{C}C$), 129.8 (C_{Ar}), 127.9 (2 C_{Ar}), 126.5 ($SO_2NCH_2C\underline{C}$), 114.6 (2 C_{Ar}), 66.9 (2 OCH_2), 61.0, 60.9, 56.3, 55.4, 54.3, 52.2, 43.4, 29.9 (^{t}Bu);

HRMS calculated for $C_{21}H_{31}N_5O_4S$ 450.2170 $(M+H)^+$; found 450.2173 (TOF MS ES^+).

6-(*tert*-butyl)-3-(4-methoxybenzyl)-4-(piperidin-1-ylmethyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.10** (84%, 41 mg) was isolated as colorless oil.

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

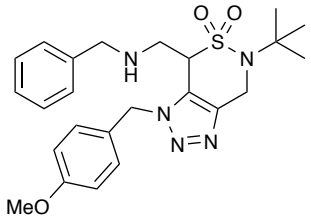
FTIR (neat): 3054, 2934, 2853, 2799, 1613, 1514, 1455, 1326, 1133, 1032, 817 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (t, *J* = 7.2 Hz, 2H, ArH), 6.86 (t, *J* = 9.1 Hz, 2H, ArH), 5.91 (d, *J* = 15.3 Hz, 1H, CH_2), 5.72 (d, *J* = 15.2 Hz, 1H, CH_2), 5.65 (d, *J* = 8.3 Hz, 1H), 4.66 (d, *J* = 14.5 Hz, 1H, CH_2), 4.39 (d, *J* = 14.5 Hz, 1H, CH_2), 3.97–3.91 (m, 1H, $CH_2C\underline{H}S$), 3.79 (s, 1H), 3.78 (s, 3H, OMe), 3.14 (dd, *J* = 13.1, 2.6 Hz, 1H, $C\underline{H}_2CHS$), 2.70 (dd, *J* = 12.9, 10.1 Hz, 1H, $C\underline{H}_2CHS$), 2.61–2.52 (m, 2H, CH_2), 2.35–2.26 (m, 2H, CH_2), 1.60 (s, 4H, $2CH_2$), 1.48 (s, 9H, ^{t}Bu);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (C_{Ar}), 138.8 ($SO_2NCH_2\underline{C}C$), 130.1 (C_{Ar}), 128.1 (2 C_{Ar}), 127.6 ($SO_2NCH_2C\underline{C}$), 114.5 (2 C_{Ar}), 61.5, 60.7, 56.6, 55.5, 55.4, 52.2, 43.4, 29.9 (^{t}Bu), 26.2 (2), 24.0;

HRMS calculated for $C_{22}H_{33}N_5O_3S$ 448.2377 $(M+H)^+$; found 448.2369 (TOF MS ES^+).

4-((benzylamino)methyl)-6-(*tert*-butyl)-3-(4-methoxybenzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.11** (95%, 23 mg) was isolated as colorless oil.

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

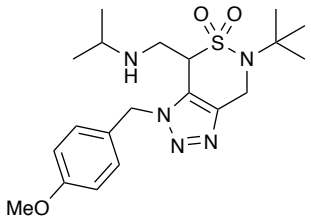
FTIR (neat): 2953, 1722, 1613, 1515, 1442, 1182, 1032, 851 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 3H, ArH), 7.26 – 7.23 (m, 2H, ArH), 6.97 – 6.92 (m, 2H, ArH), 6.85 – 6.80 (m, 2H, ArH), 5.45 (d, *J* = 15.4 Hz, 1H, CH_2), 5.31 (d, *J* = 15.4 Hz, 1H, CH_2), 4.62 (d, *J* = 14.9 Hz, 1H, CH_2), 4.42 (dd, *J* = 14.9, 1.1 Hz, 1H, CH_2), 3.95 (dd, *J* = 7.5, 3.3 Hz, 1H, $CH_2C\underline{H}S$), 3.78 (s, 3H, OMe), 3.76 (d, *J* = 4.5 Hz, 1H, CH_2), 3.62 (d, *J* = 13.4 Hz, 1H, CH_2), 3.13 (dd, *J* = 13.6, 7.6 Hz, 1H, $C\underline{H}_2CHS$), 2.78 (dd, *J* = 13.6, 3.6 Hz, 1H, $C\underline{H}_2CHS$), 1.42 (s, 9H, ^{t}Bu).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 (C_{Ar}), 139.9 ($SO_2NCH_2\underline{C}C$), 139.2 (C_{Ar}), 132.2 (C_{Ar}) 128.7 (2 C_{Ar}), 128.7 (2 C_{Ar}), 128.4 (2 C_{Ar}), 127.8 ($SO_2NCH_2C\underline{C}$), 127.5 (C_{Ar}), 114.6 (2 C_{Ar}), 60.9, 58.9, 55.4, 53.6, 52.3, 48.9, 43.1, 29.9 (^{t}Bu);

HRMS calculated for $C_{24}H_{31}N_5O_3S$ 470.2220 $(M+H)^+$; found 470.2242 (TOF MS ES^+).

6-(*tert*-butyl)-4-((isopropylamino)methyl)-3-(4-methoxybenzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.4.1.12** (60%, 16 mg) was isolated as colorless oil.

R_f = 0.14 (EtOAc:Hexane = 1:1);

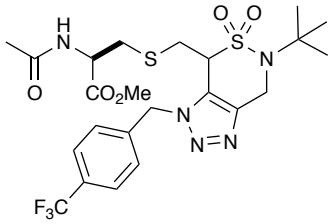
FTIR (neat): 2964, 1612, 1585, 1514, 1464, 1370, 1324, 1249, 1032, 815, cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.66 - 5.51 (m, 2H), 4.64 (d, *J* = 14.8 Hz, 1H), 4.41 (dd, *J* = 14.7, 1.2 Hz, 1H), 3.99 (dd, *J* = 6.8, 4.6 Hz, 1H), 3.78 (s, 3H), 3.21 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.82 (dd, *J* = 13.3, 4.5 Hz, 1H), 2.68 (hept, *J* = 6.3 Hz, 1H), 2.01 (s, 1H), 1.48 (s, 9H), 1.02 (d, *J* = 6.2 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 (C_{Ar}), 139.6 ($SO_2NCH_2\underline{C}C$), 128.6 (2 C_{Ar}), 128.1 (C_{Ar}), 126.2 ($SO_2NCH_2C\underline{C}$), 114.6 (2 C_{Ar}), 60.9, 59.0, 55.4, 52.3, 49.0, 48.2, 43.2, 30.0 (^{t}Bu), 22.9 (MeCH<u>Me</u>), 22.8 (MeCH<u>Me</u>);

HRMS calculated for $C_{20}H_{31}N_5O_3S$ 444.2040 $(M+Na)^+$; found 444.2068 (TOF MS ES^+).

Methyl *N*-acetyl-*S*-((6-(*tert*-butyl)-5,5-dioxido-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazin-4-yl)methyl)-*L*-cysteinate



According to the reaction protocol described in general procedure **G**, compound **2.4.3.1** (75%, 15 mg) was isolated as colorless oil.

R_f = 0.01 (EtOAc:Hexane = 1:1);

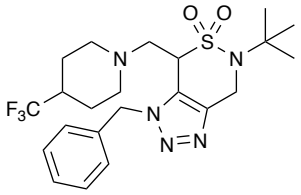
FTIR (neat): 3368, 3289, 3056, 2982, 2956, 1744, 1666, 1589, 1536, 1437, 1403, 1372, 1067, 817 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 2H, ArH), 7.22 (t, *J* = 7.4 Hz, 2H, ArH), 6.27 (dd, *J* = 29.7, 7.1 Hz, 1H, NHC<u>H</u>CO_2Me), 5.83 (d, *J* = 2.3 Hz, 2H, CH_2), 4.77 (ddt, *J* = 10.5, 7.3, 5.3 Hz, 1H, CH_2C<u>H</u>S), 4.69 (dd, *J* = 14.6, 2.6 Hz, 1H, C<u>H</u>$_2$), 4.40 (d, *J* = 14.6 Hz, 1H, CH_2), 3.99–3.93 (m, 1H, C<u>H</u>$_2$CHS), 3.76 (d, *J* = 5.9 Hz, 3H, OMe), 3.42–3.34 (m, 1H, C<u>H</u>$_2$CHS), 3.03 (td, *J* = 13.4, 12.8, 5.0 Hz, 1H, C<u>H</u>$_2$S), 2.97–2.90 (m, 1H, C<u>H</u>$_2$S), 2.02 (d, *J* = 1.3 Hz, 3H, COMe), 1.51 (d, *J* = 2.8 Hz, 9H, ^{t}Bu).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9 (d, *J* = 3.5 Hz, CO), 170.0 (CO), 139.7 (SO_2NCH_2<u>C</u>C), 138.2 (t, *J* = 8.2, 6.7 Hz, C_{Ar}), 131.0 (q, *J* = 32.1 Hz, C_{Ar}) 128.9 (dd, *J* = 13.1, 1.7 Hz, SO_2NCH_2C<u>C</u>), 127.4 (d, *J* = 5.7 Hz, 2 C_{Ar}), 126.3 (dp, *J* = 28.9, 3.4 Hz, 2 C_{Ar}), 124.9 (d, *J* = 271.7 Hz, CF_3) 61.3, 58.2 (d, J = 17.3 Hz,), 53.1 (d, *J* = 7.2 Hz,), 52.2 (dd, *J* = 9.1 Hz,), 51.9, 43.4 (d, *J* = 5.6 Hz,), 35.6 (d, *J* = 9.2 Hz,), 34.9 (d, J = 50.9 Hz,), 29.9 (dd, *J* = 5.9, 3.6 Hz, ^{t}Bu), 23.2 (t, *J* = 2.9, 1.7 Hz,)

HRMS calculated for $C_{23}H_{30}F_3N_5O_5S_2$ 600.1533 $(M+Na)^+$; found 600.1541 (TOF MS ES^+).

3-benzyl-6-(tert-butyl)-4-((4-(trifluoromethyl)piperidin-1-yl)methyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide



According to the reaction protocol described in general procedure **F**, compound **2.4.6.1** (47%, 55 mg) was isolated as colorless oil.

R_f = 0.66 (EtOAc:Hexane = 1:1);

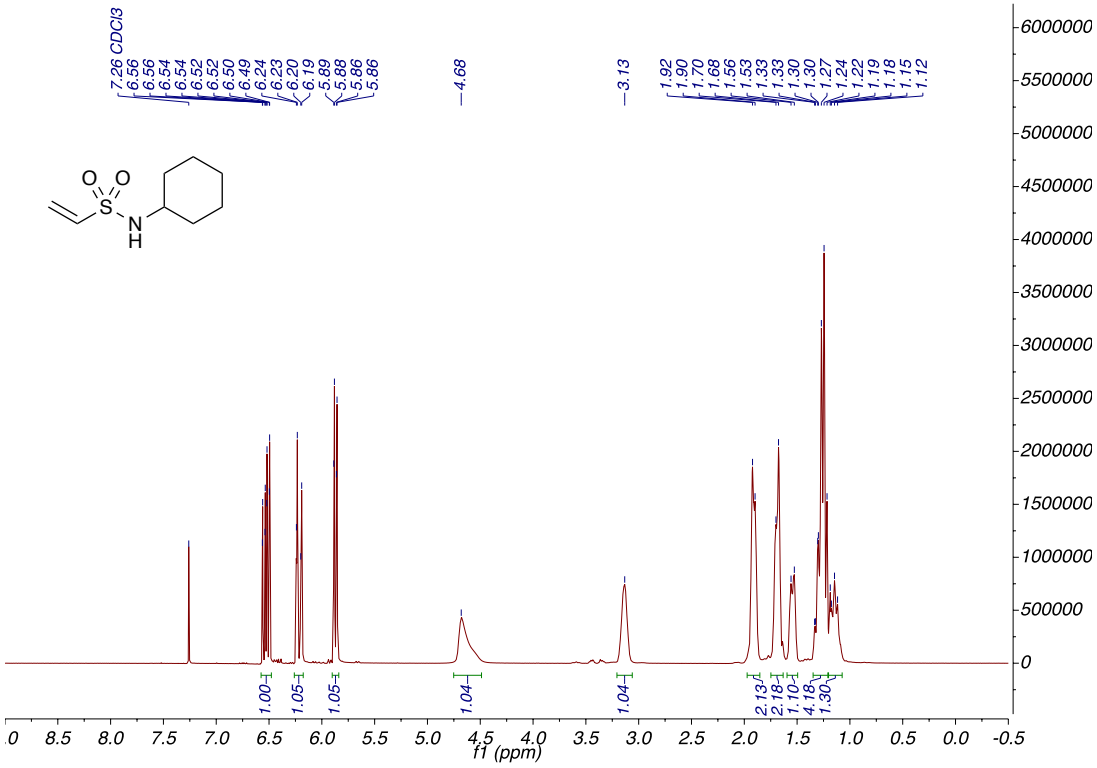
FTIR (neat): 3033, 2932, 2850, 2813, 1677, 1605, 1455, 1370, 1084, 730, 670 cm^{-1}

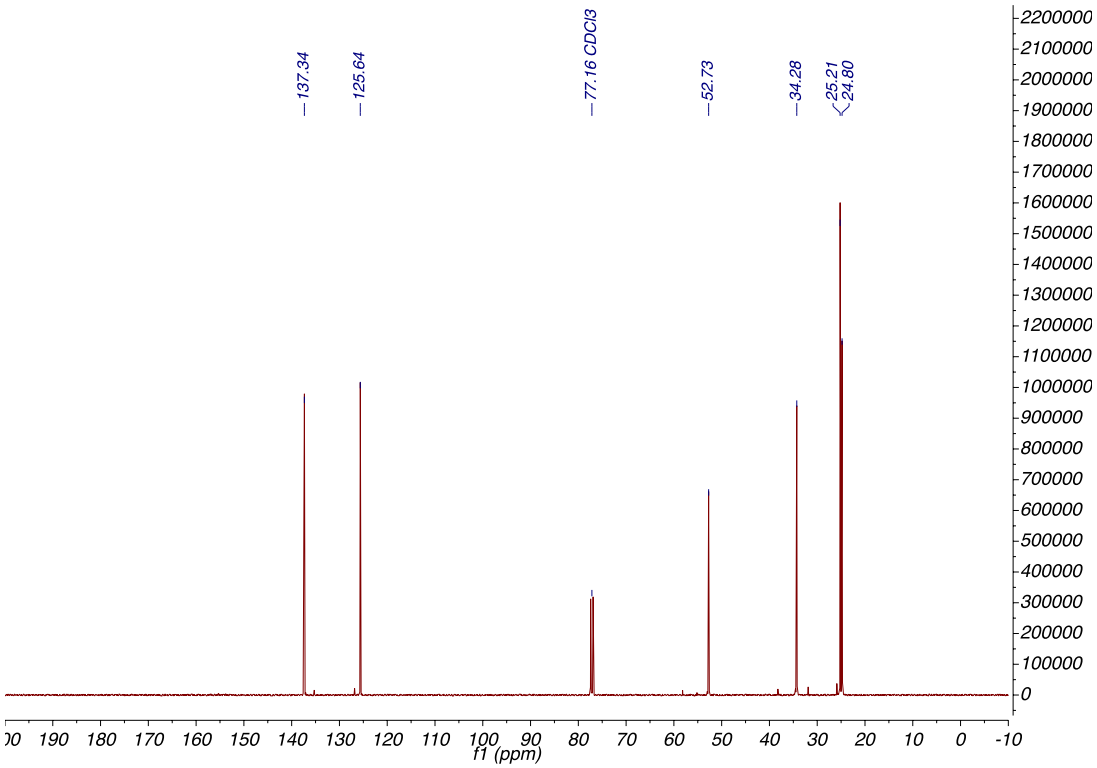
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (tt, *J* = 8.8, 4.6 Hz, 3H, ArH), 6.99 (d, *J* = 6.5 Hz, 2H, ArH), 5.85–5.74 (m, 2H, CH_2), 4.68 (d, *J* = 14.6 Hz, 1H, CH_2), 4.42 (dd, *J* = 14.6, 1.1 Hz, 1H, CH_2), 3.92 (dd, *J* = 9.4, 2.4 Hz, 1H, $CH_2C\underline{H}S$), 3.15 (dd, *J* = 13.2, 3.2 Hz, 1H, $C\underline{H}_2CHS$), 3.06 (d, *J* = 11.8 Hz, 1H, CH_2), 2.74 (dd, *J* = 13.2, 9.4 Hz, 1H, $C\underline{H}_2CHS$), 2.63 (d, *J* = 11.4 Hz, 1H, CH_2), 2.15 (td, *J* = 11.9, 2.5 Hz, 1H, CH_2), 2.10–1.97 (m, 2H, CH_2), 1.95–1.89 (m, 1H, CH_2), 1.78 (dt, *J* = 12.9, 2.6 Hz, 1H, CH_2), 1.58 (qd, *J* = 12.5, 3.8 Hz, 1H, CH_2), 1.48 (s, 9H, ^{t}Bu), 1.42 (dd, *J* = 13.2, 3.5 Hz, 1H, CH_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0 ($SO_2NCH_2\underline{C}C$), 134.7 (C_{Ar}), 130.1 (C_{Ar}), 129.2 (2 C_{Ar}), 128.5 ($SO_2NCH_2C\underline{C}$), 127.30 (d, *J* = 278.3 Hz, CF_3), 126.3 (2 C_{Ar}), 60.9, 60.5, 56.7, 54.2, 52.4 (d, *J* = 23.0 Hz,), 43.4, 40.0 (q, *J* = 27.4 Hz, $\underline{C}CF_3$) 29.9 (^{t}Bu) 24.75 (dd, *J* = 19.8, 2.6 Hz,) (*Note: Have not identified symmetric equivalent carbons in piperidine and aromatic group);

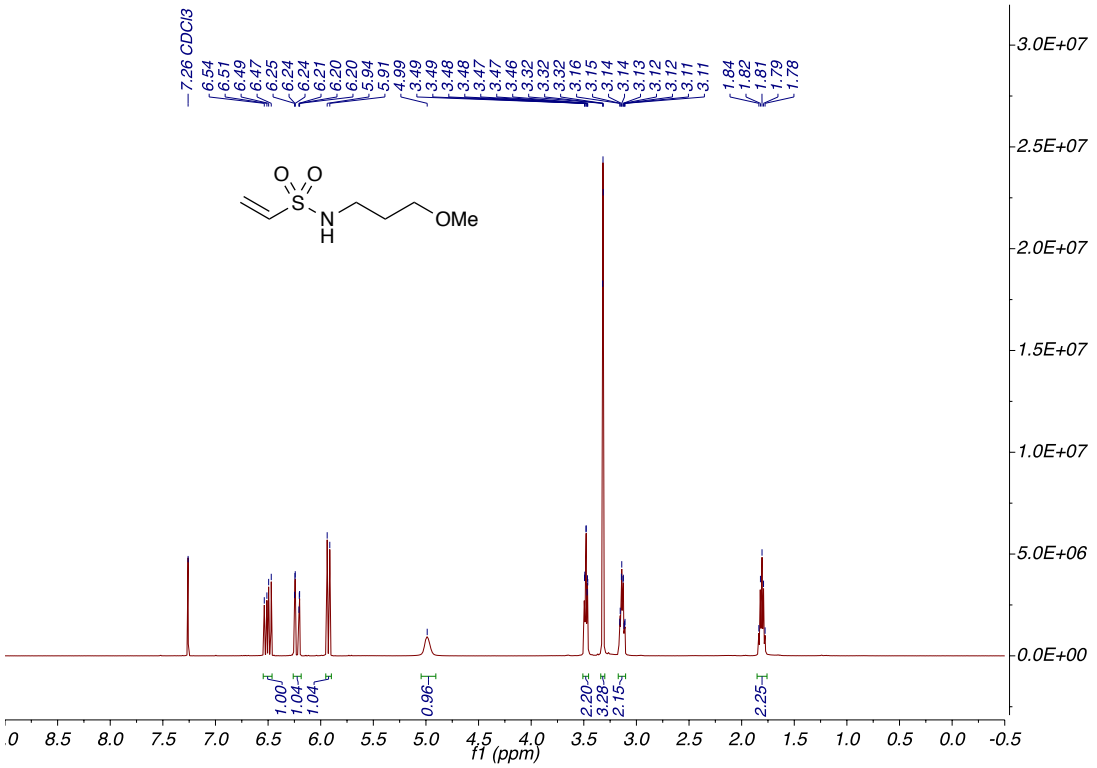
HRMS calculated for $C_{22}H_{30}F_3N_5O_2S$ 486.2145 $(M+H)^+$; found 486.2140 (TOF MS ES^+).

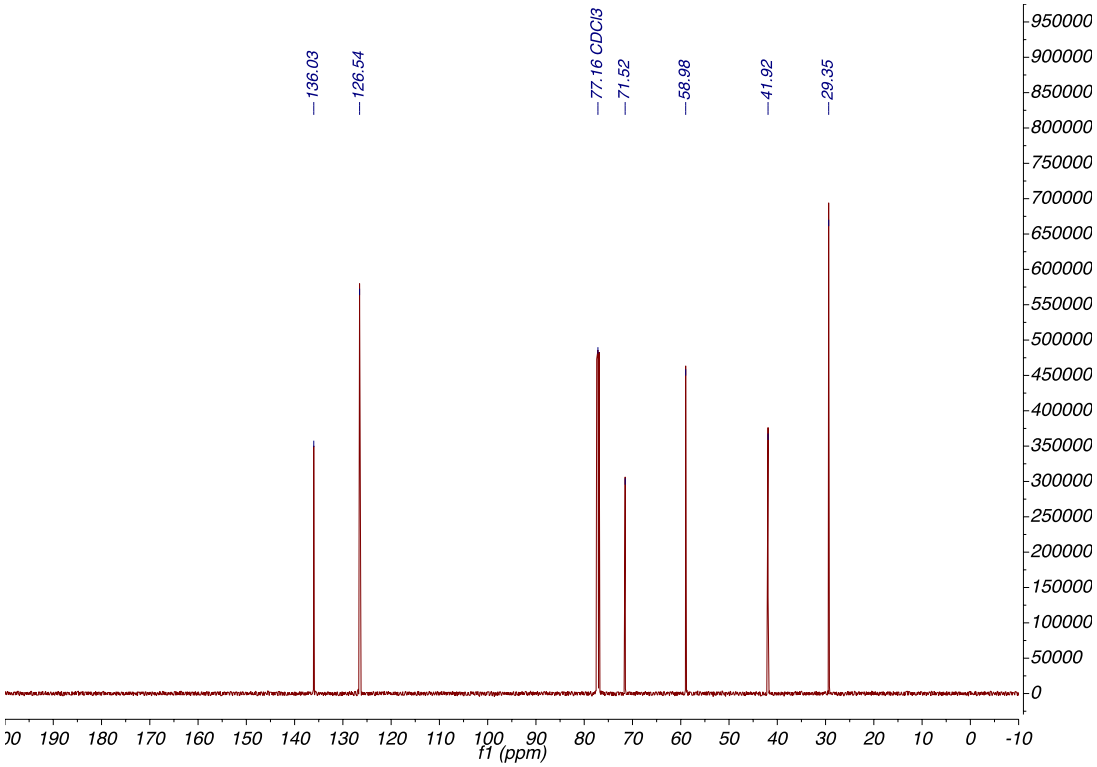
_N_-cyclohexylethenesulfonamide (2.4.1.2.1)



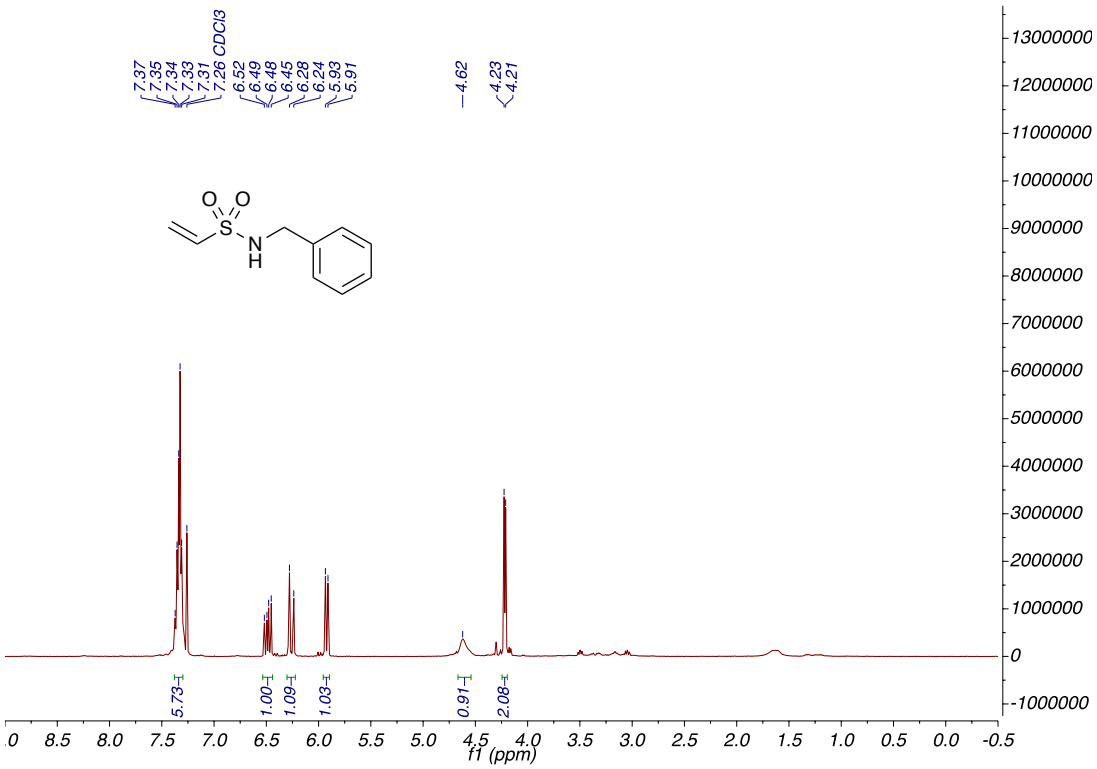


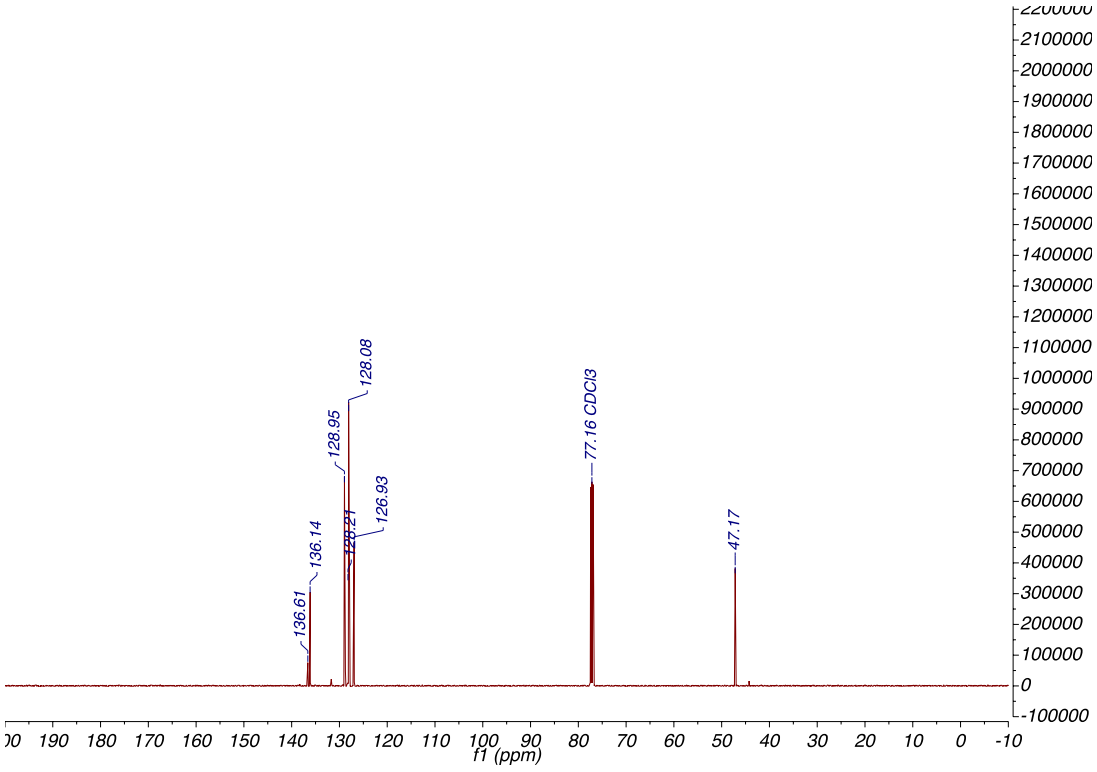
***N*-(3-methoxypropyl)ethenesulfonamide (2.4.1.2.2)**



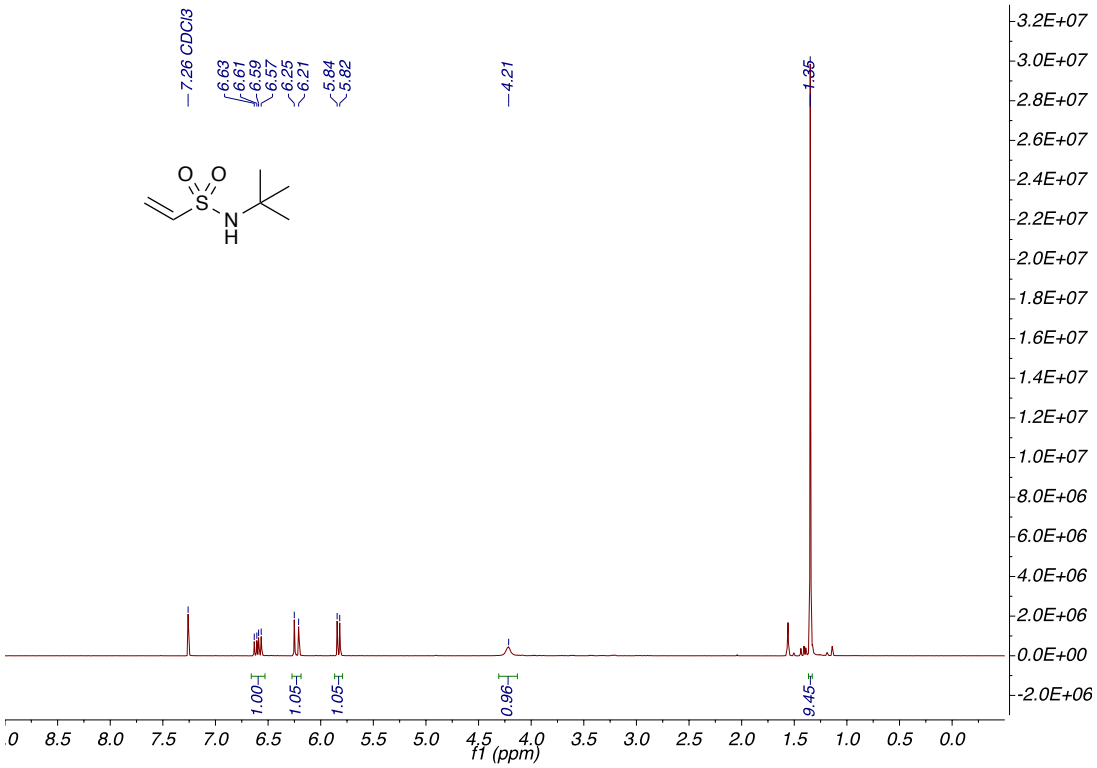


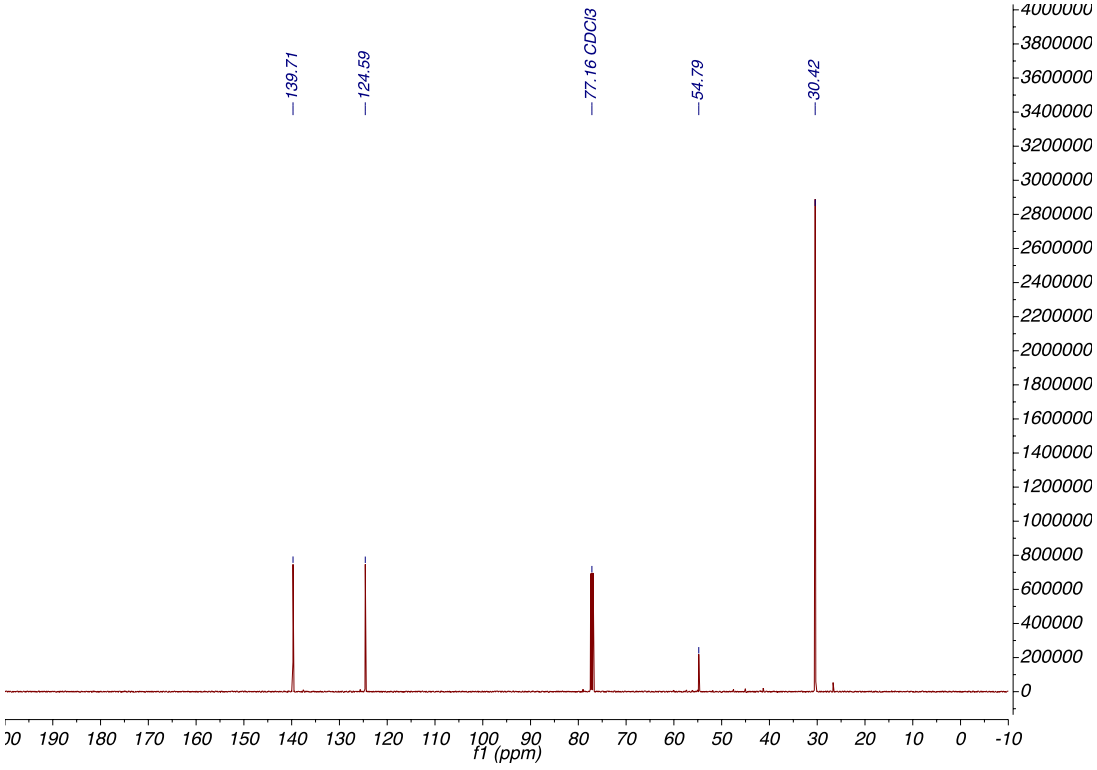
***N*-benzylethenesulfonamide (2.4.1.2.3)**



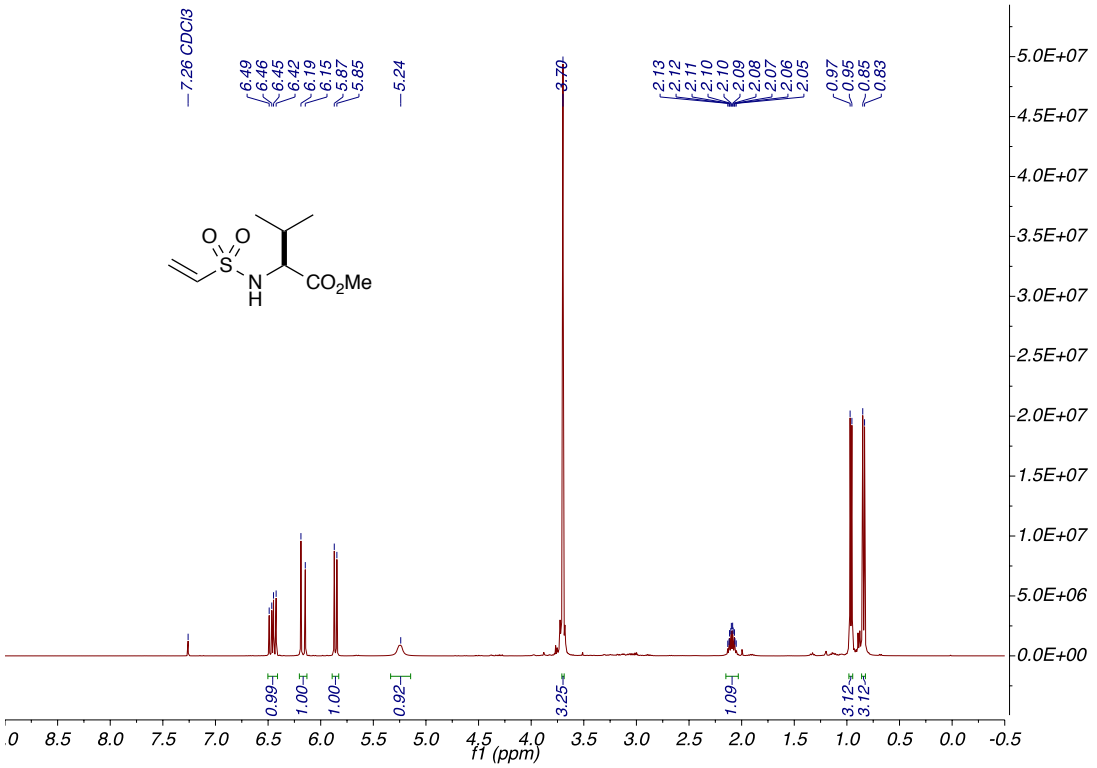


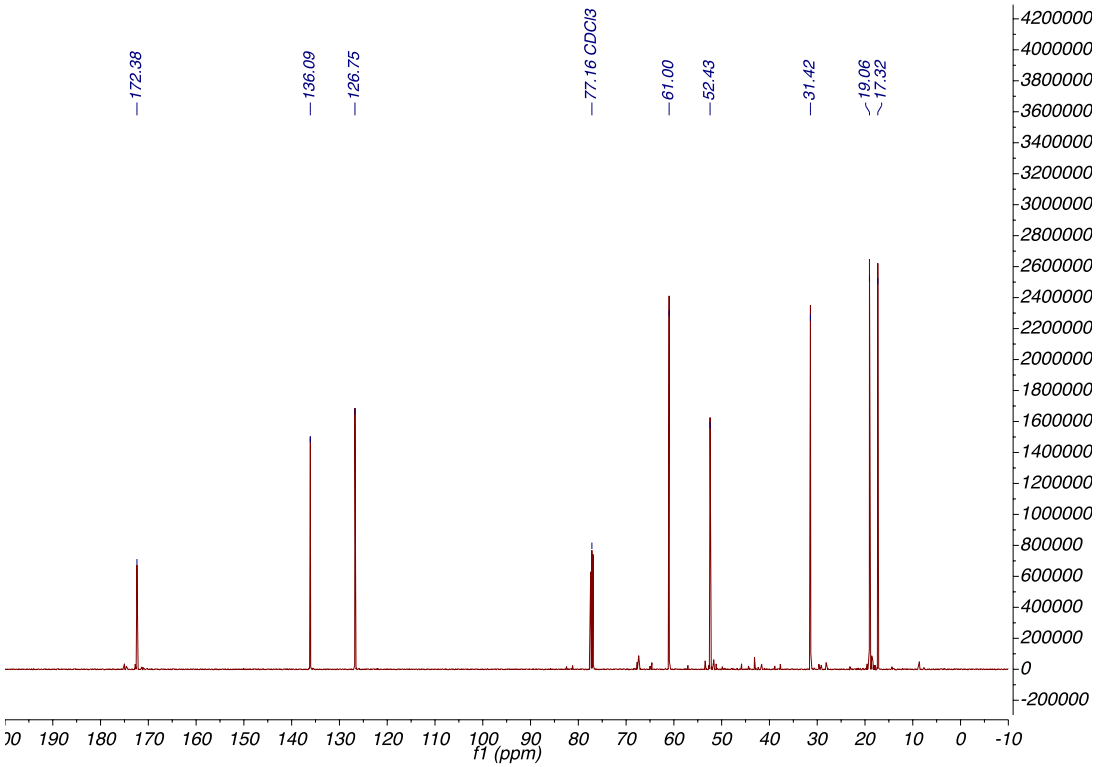
***N*-(tert-butyl)ethenesulfonamide (2.4.1.2.4)**



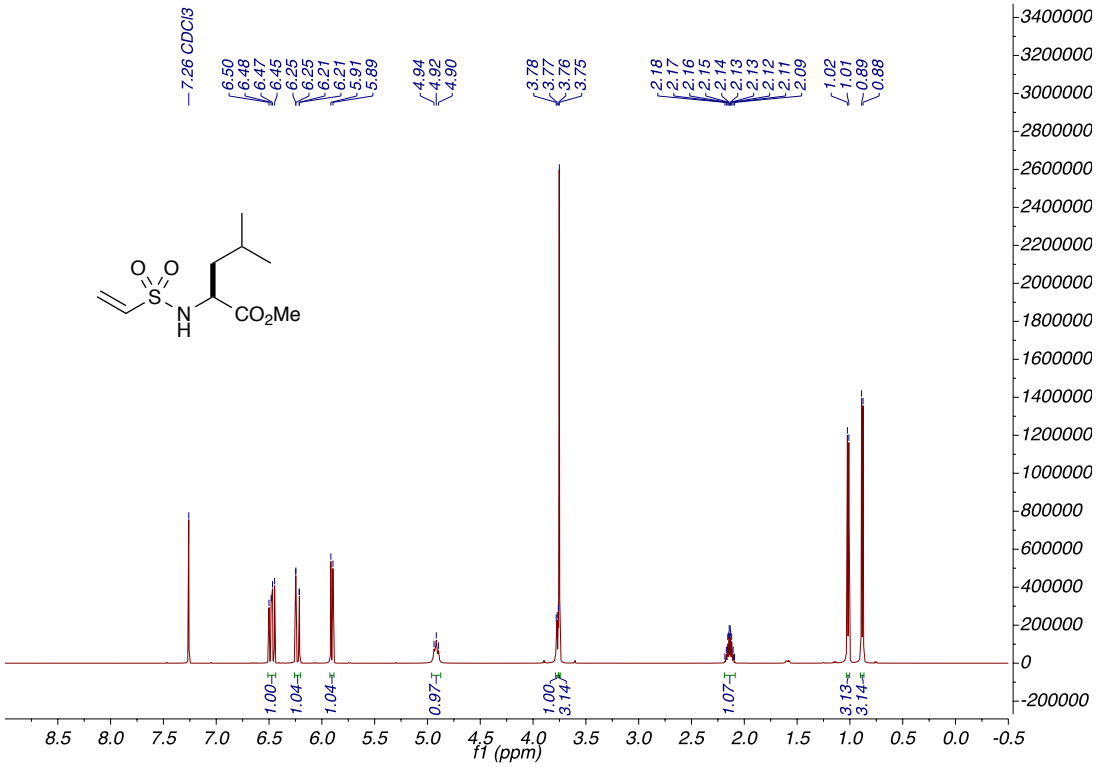


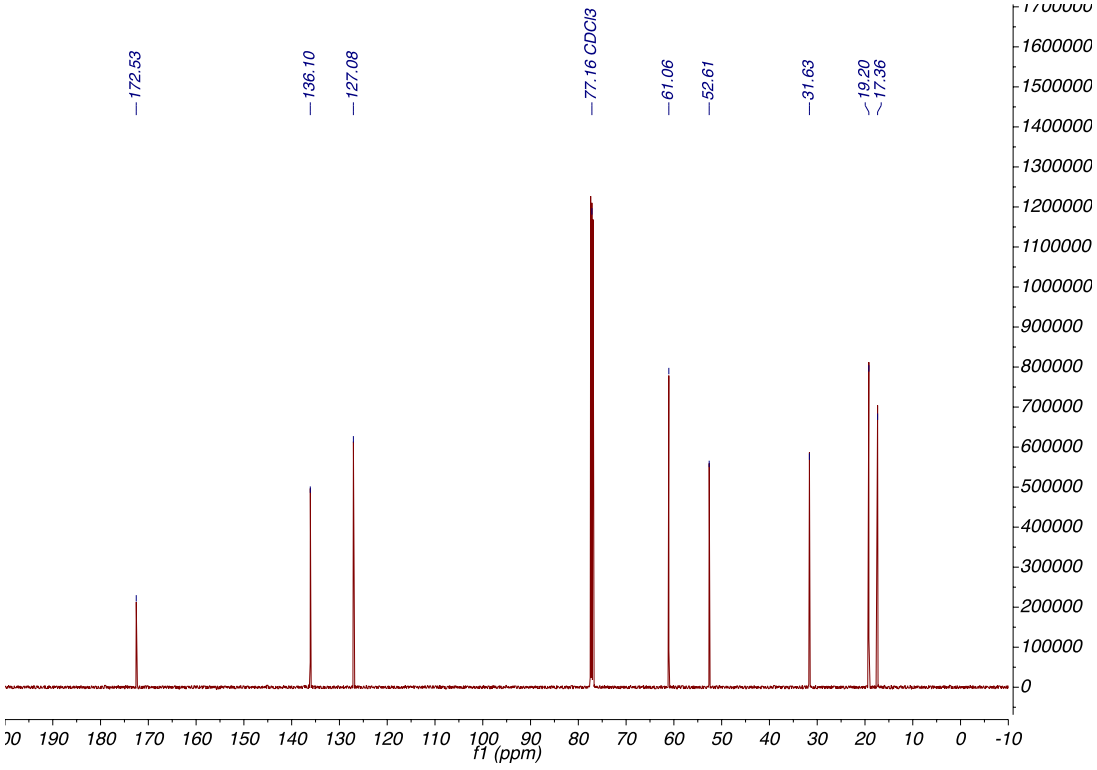
Methyl (vinylsulfonyl)-*L*-valinate (2.4.1.2.5)



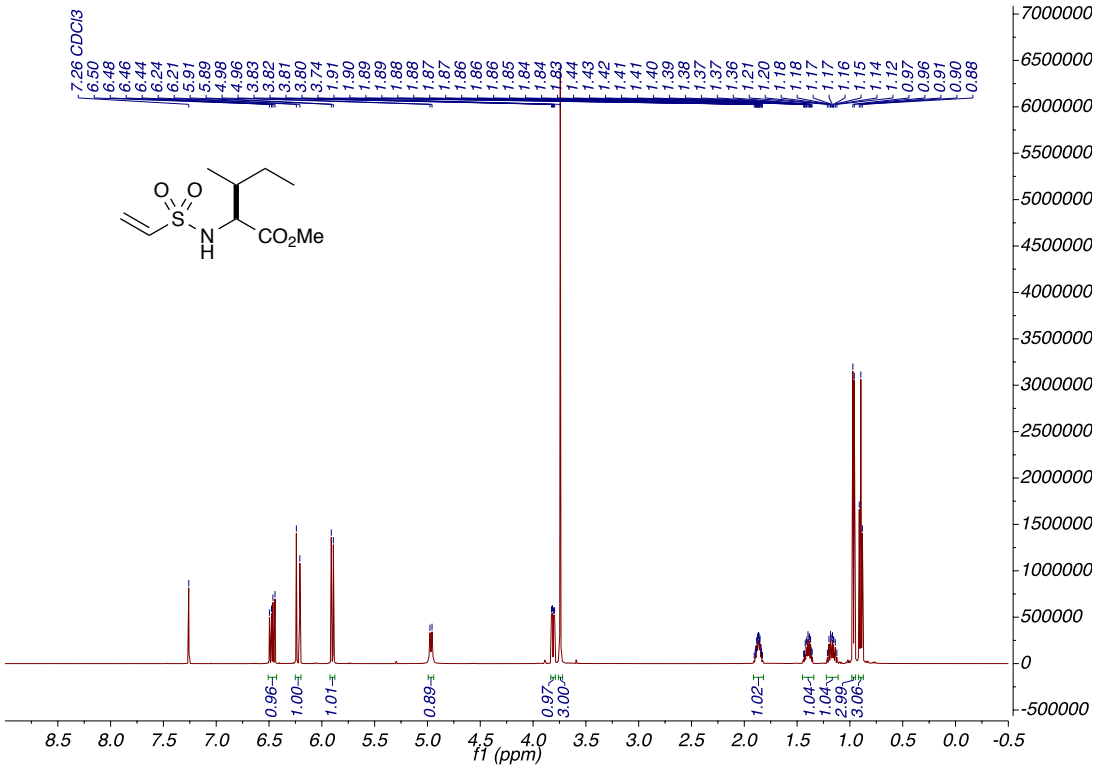


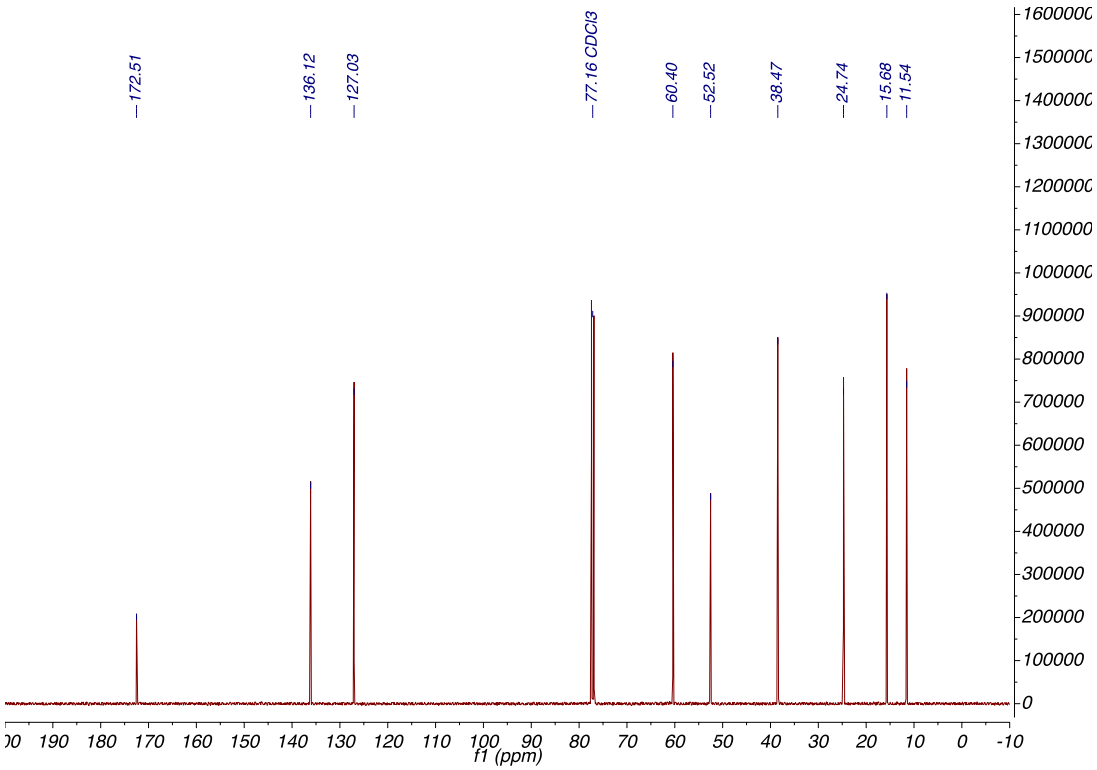
Methyl (vinylsulfonyl)-*L*-leucinate (2.4.1.2.6)



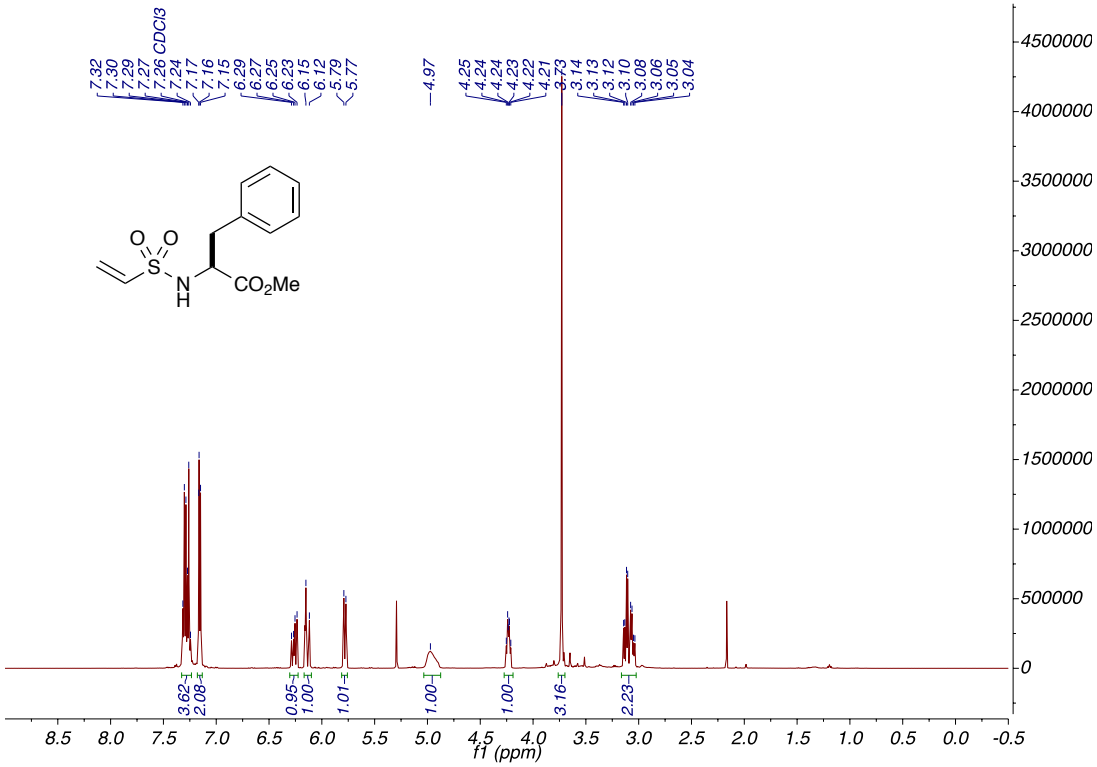


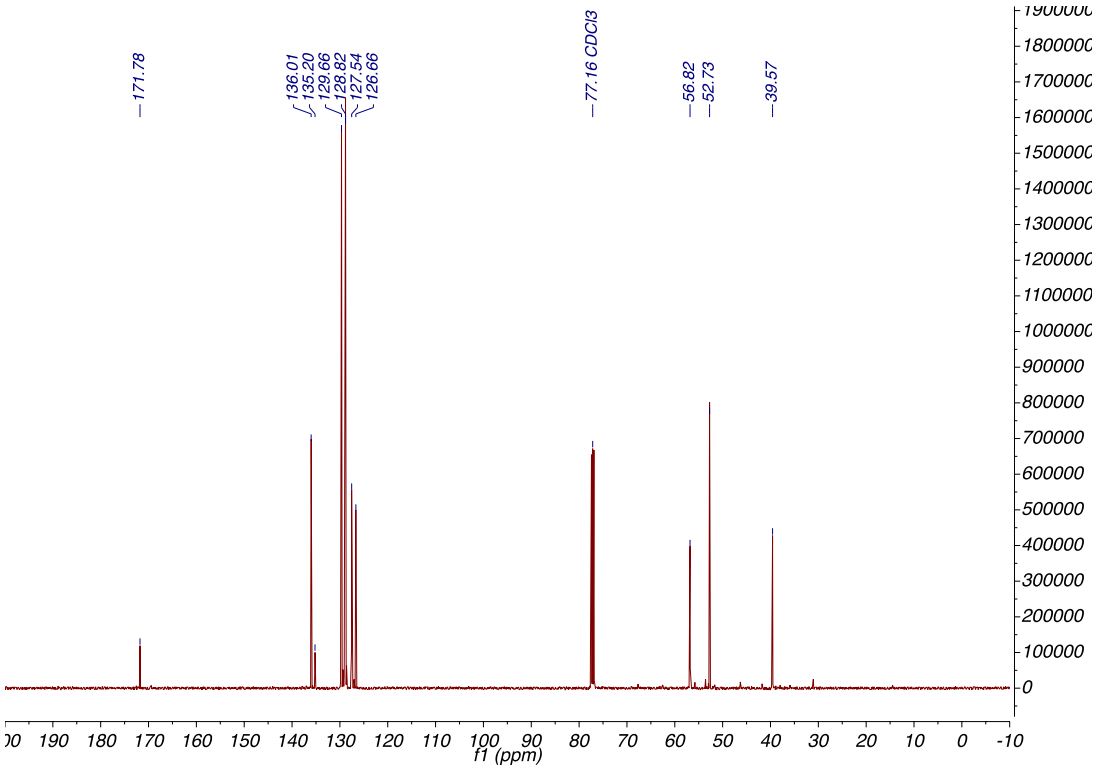
Methyl (vinylsulfonyl)-*L*-isoleucinate (2.4.1.2.7)



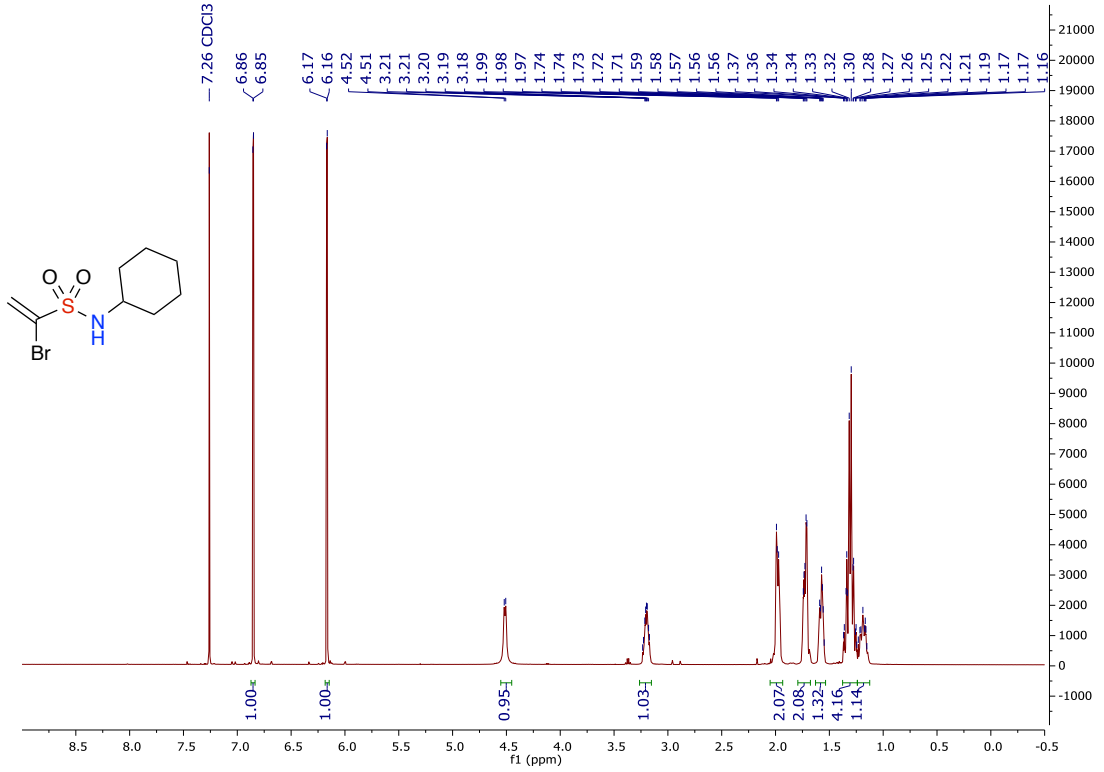


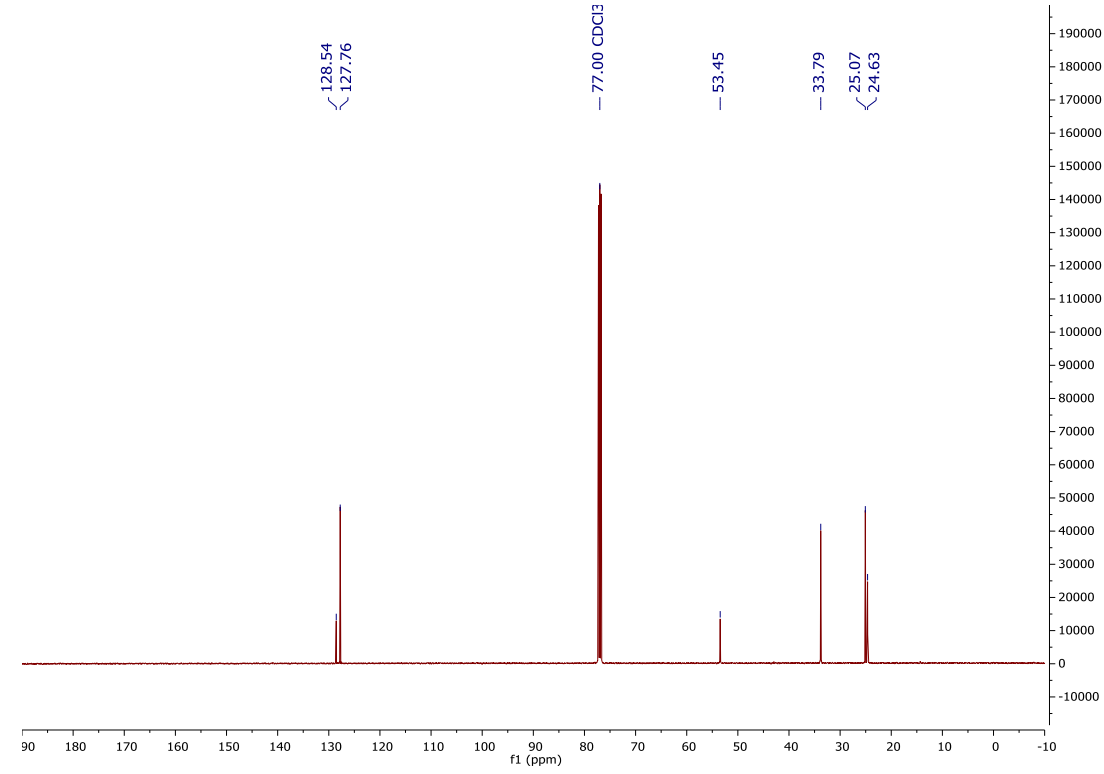
Methyl (vinylsulfonyl)-*L*-phenylalaninate (2.4.1.2.8)



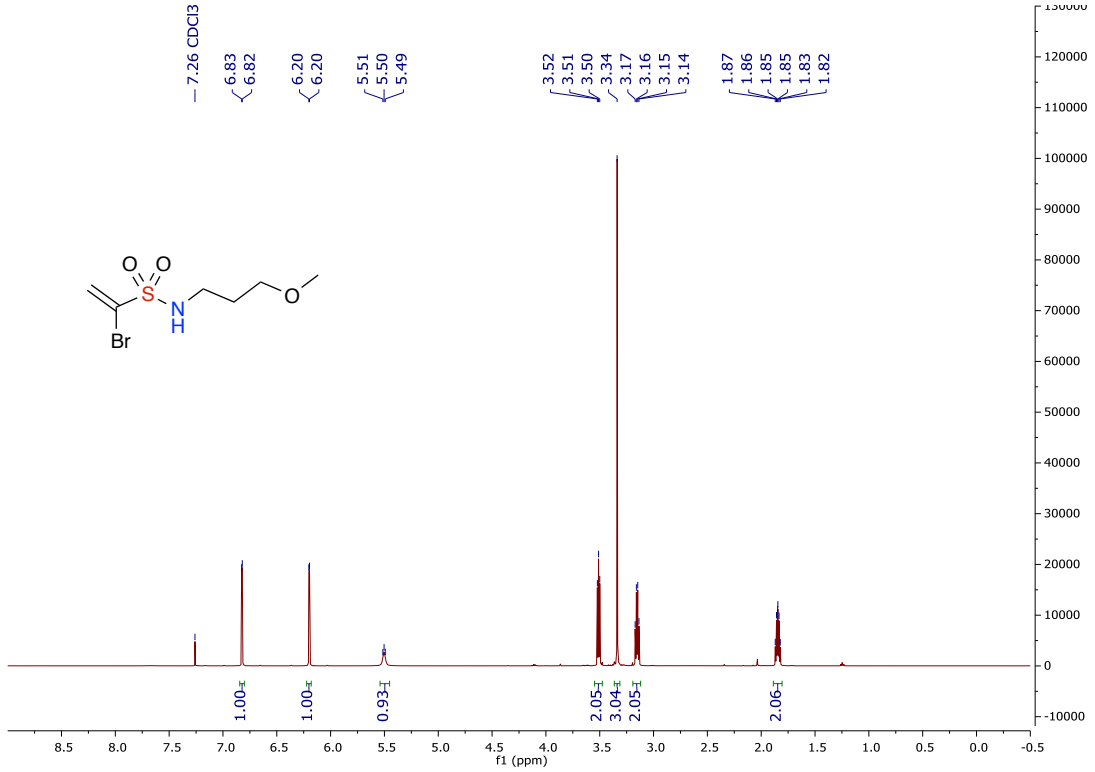


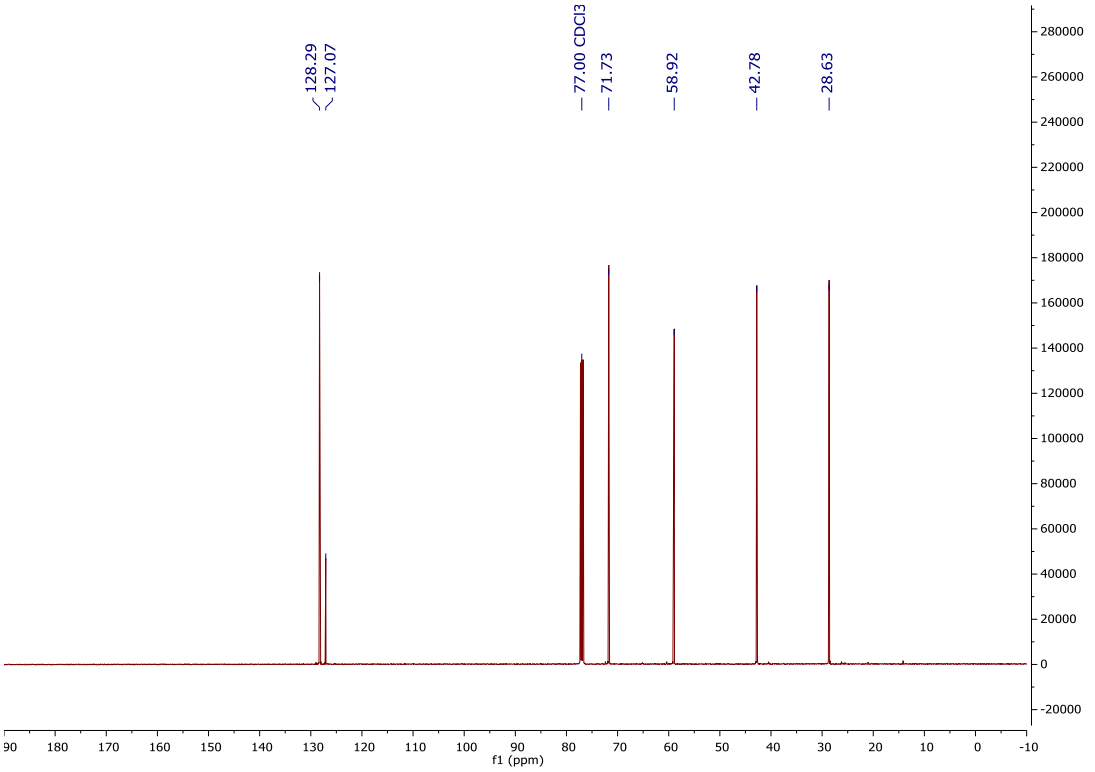
1-bromo-*N*-cyclohexylethenesulfonamide (2.4.1.4.1)



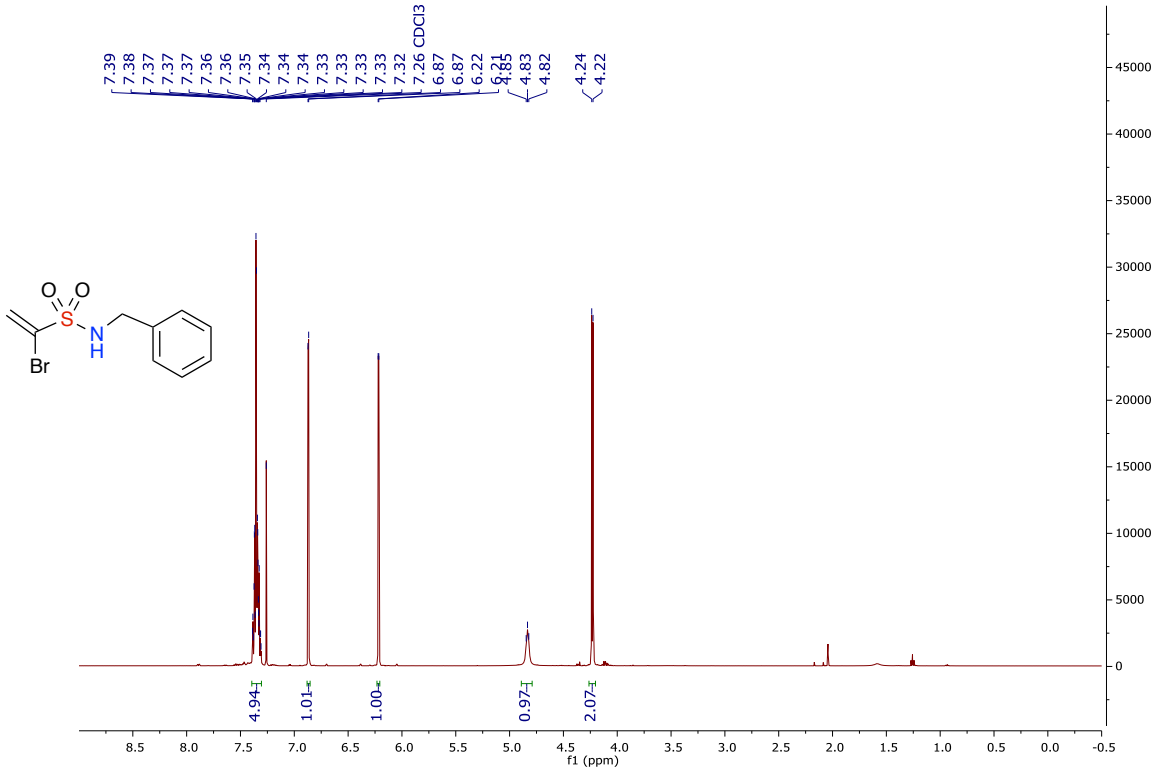


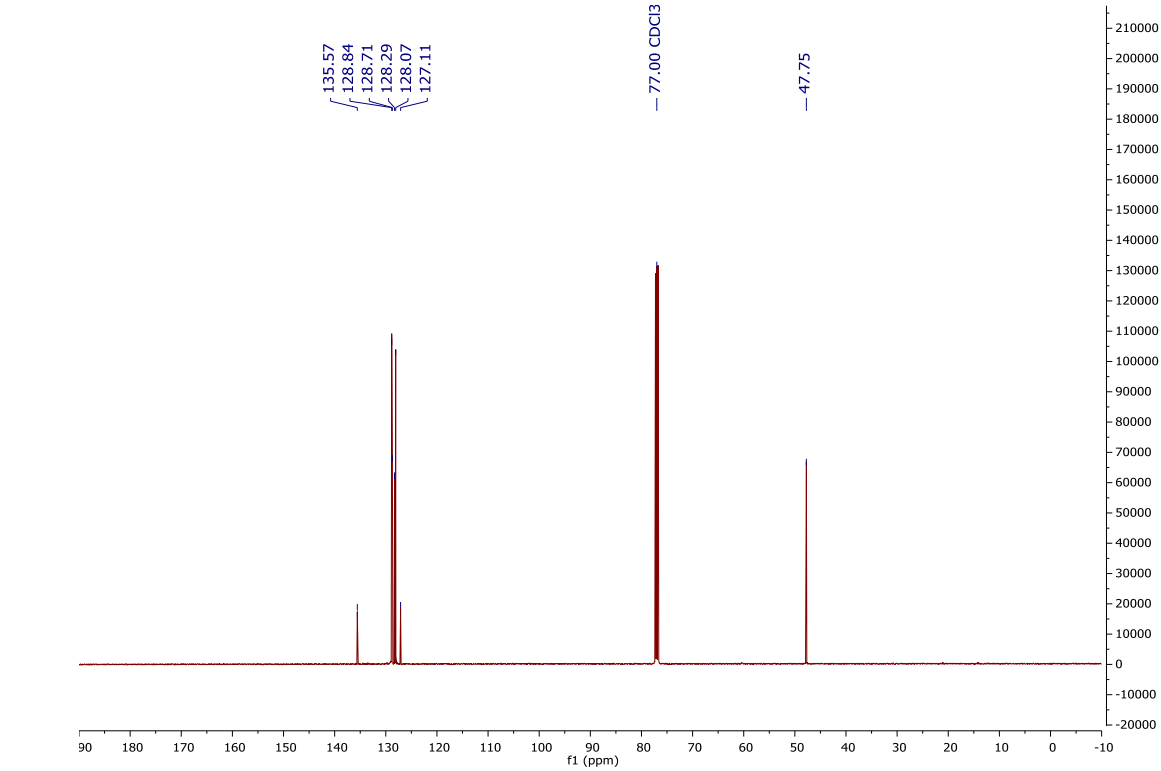
1-bromo-*N*-(3-methoxypropyl)ethenesulfonamide (2.4.1.4.2)



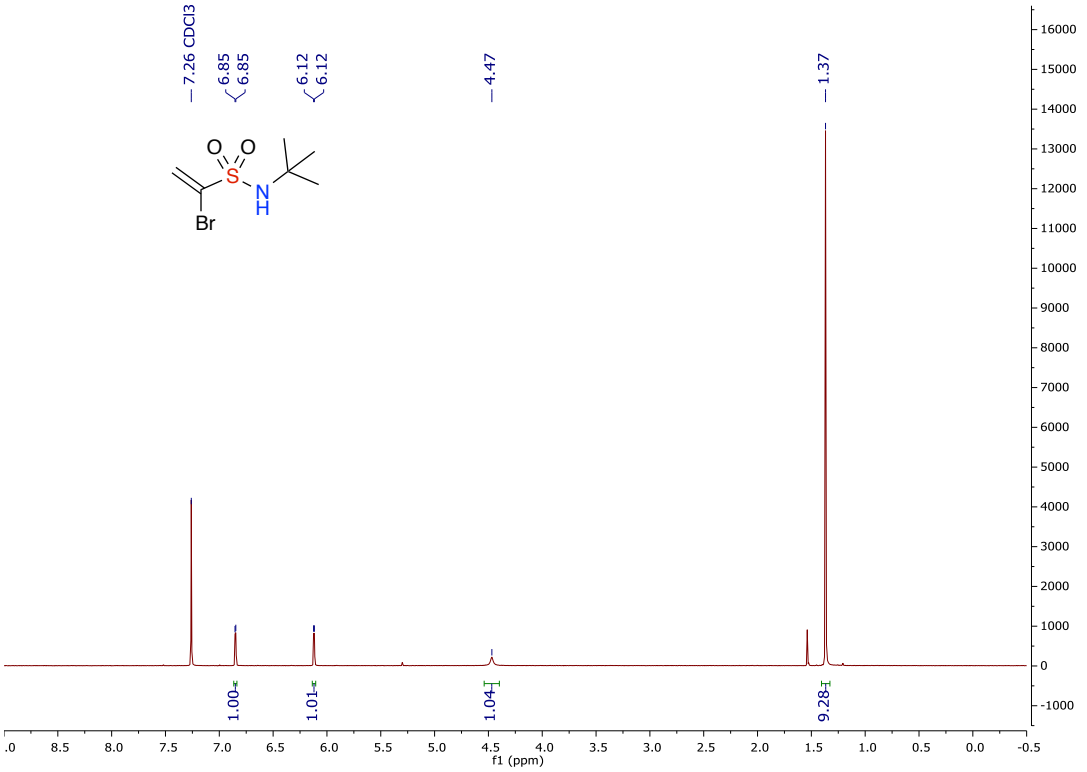


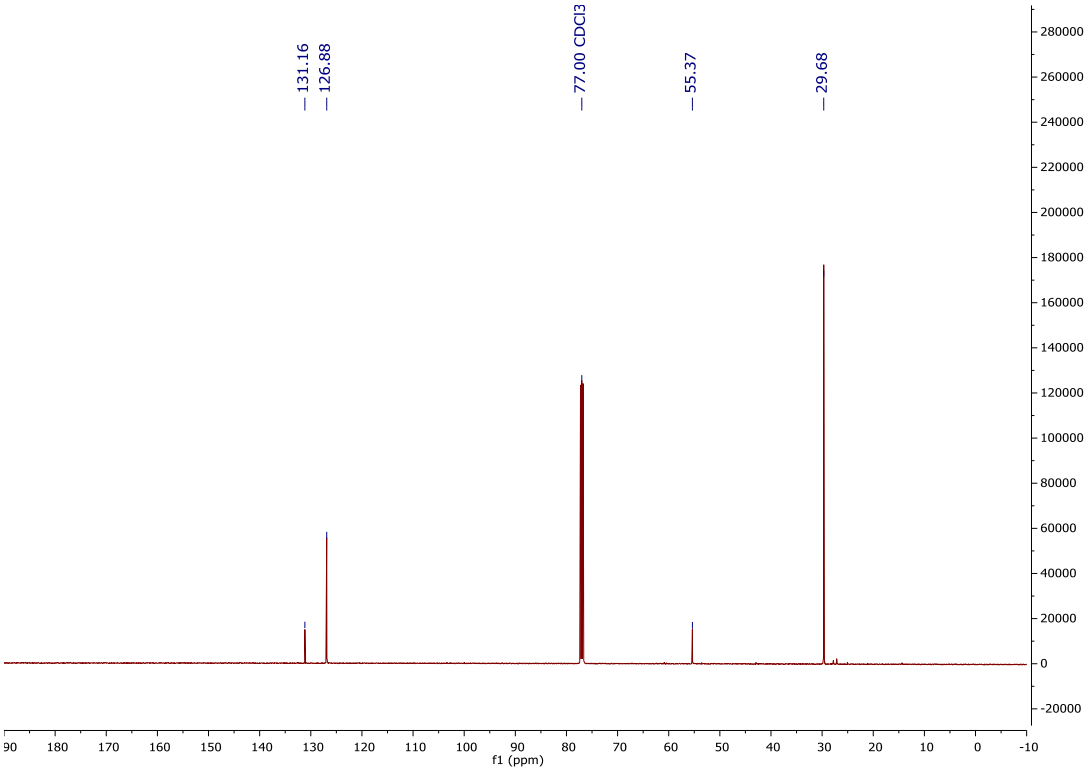
_N_-benzyl-1-bromoethenesulfonamide (2.4.1.4.3)



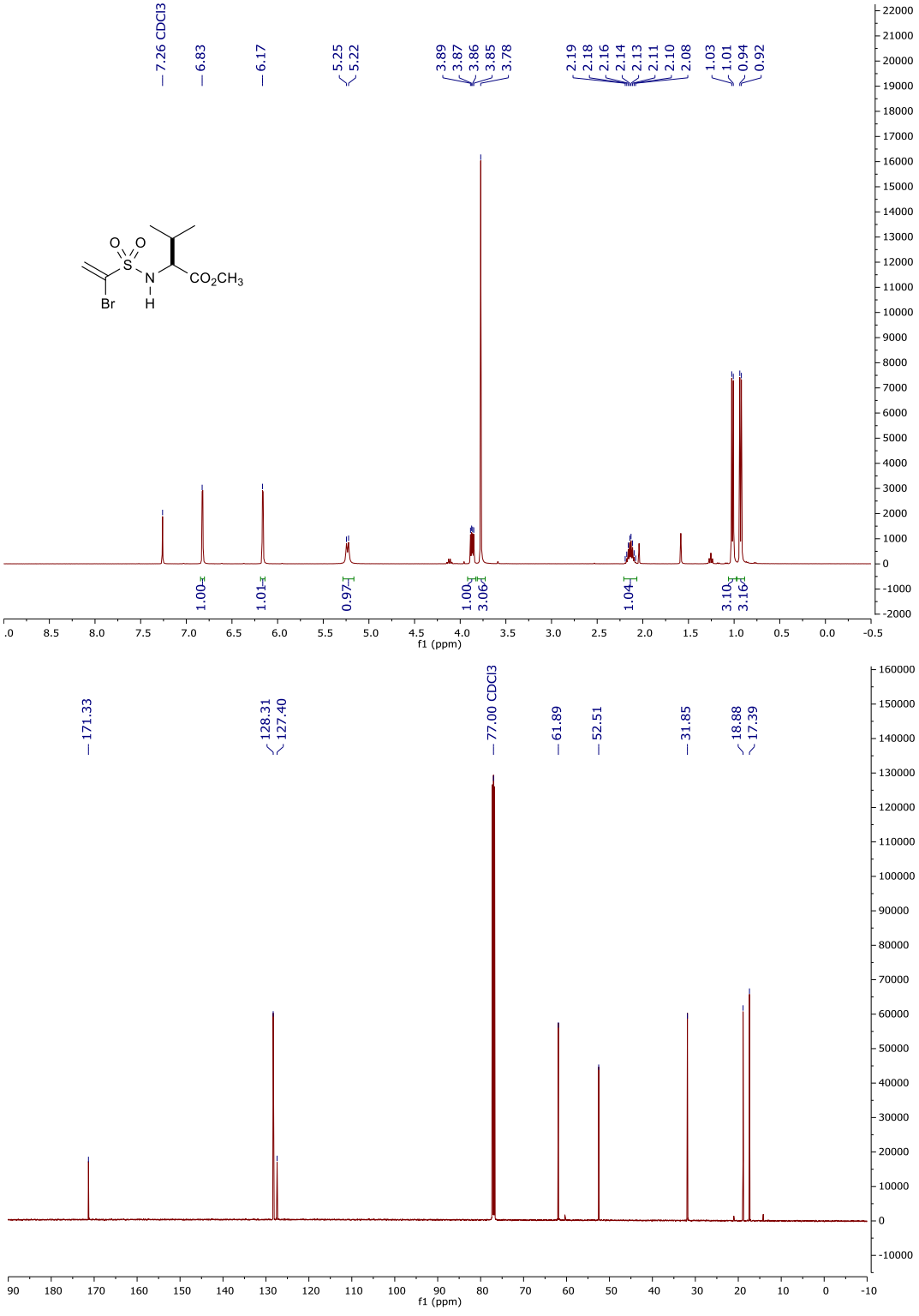


1-Bromo-*N*-(*tert*-butyl)ethenesulfonamide (2.4.1.4.4)

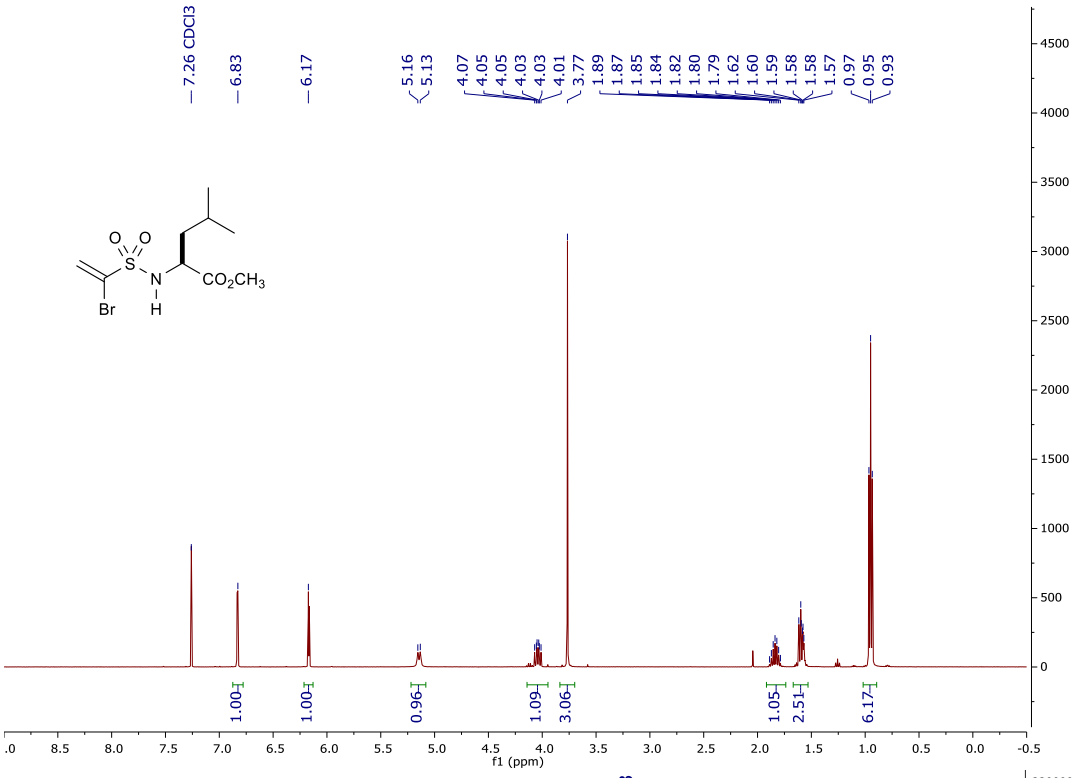


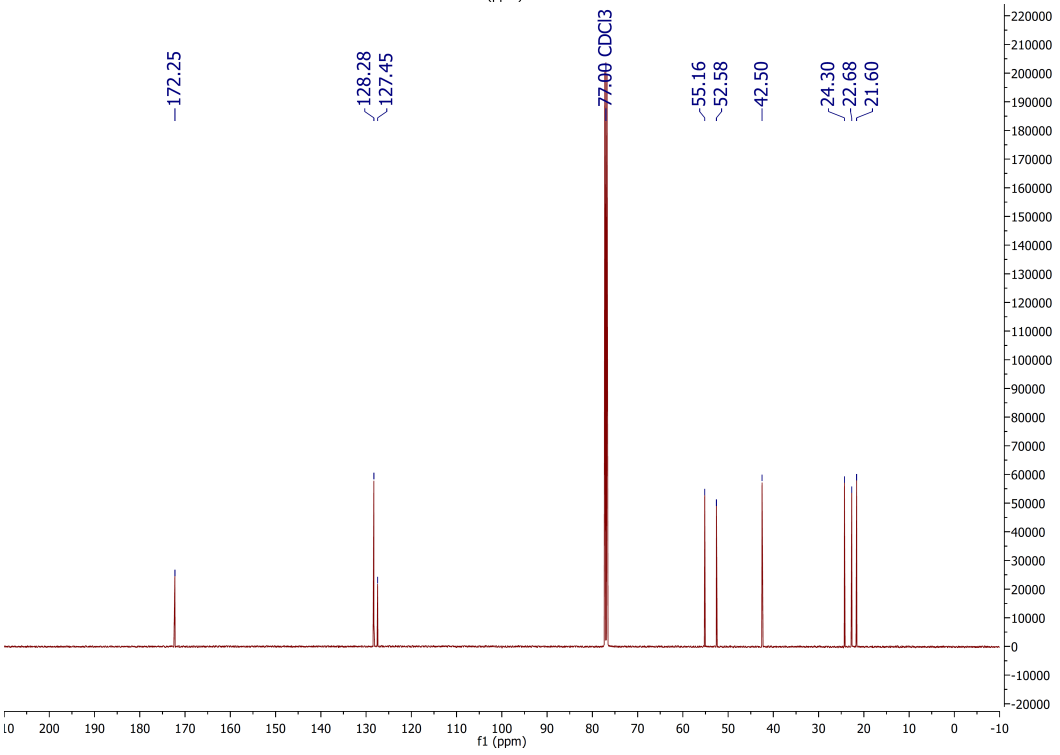


Methyl ((1-bromovinyl)sulfonyl)-*L*-valinate (2.4.1.4.5)

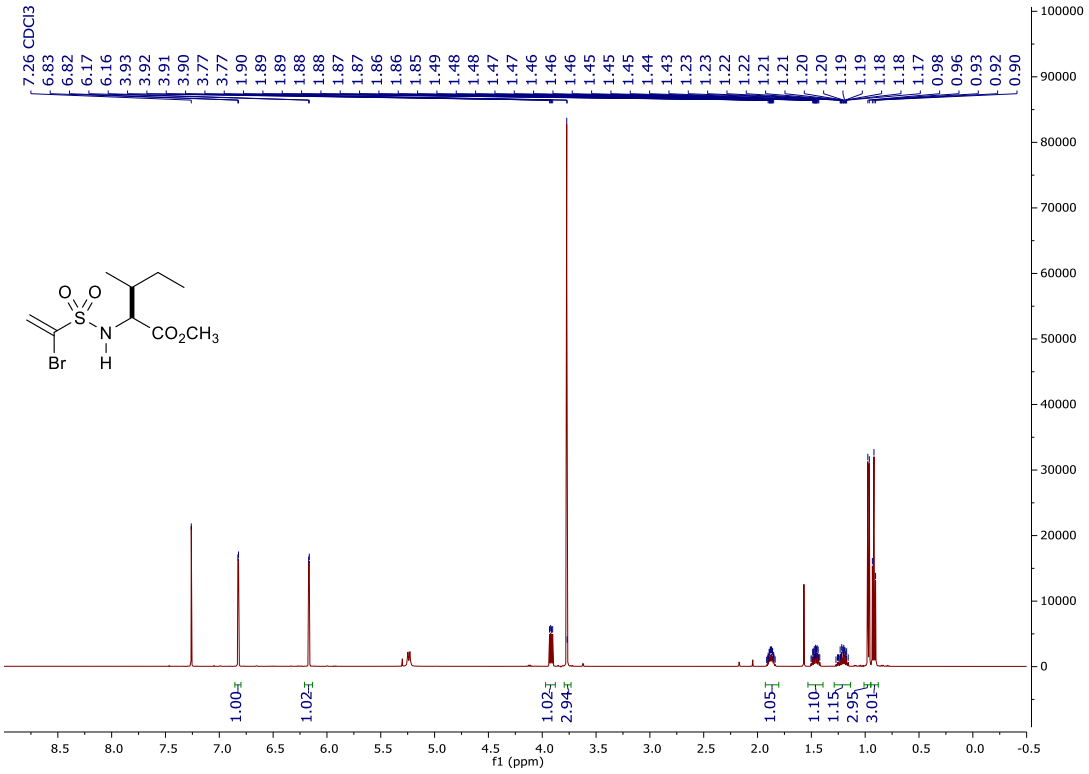


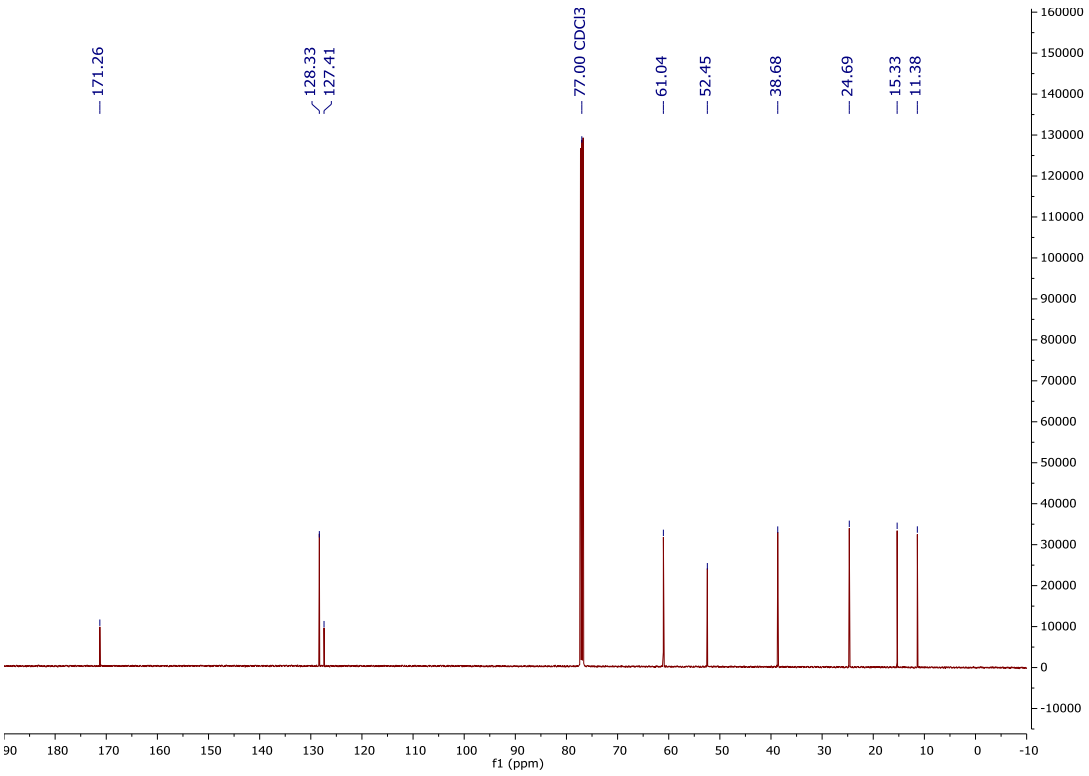
Methyl ((1-bromovinyl)sulfonyl)-*L*-leucinate (2.4.1.4.6)



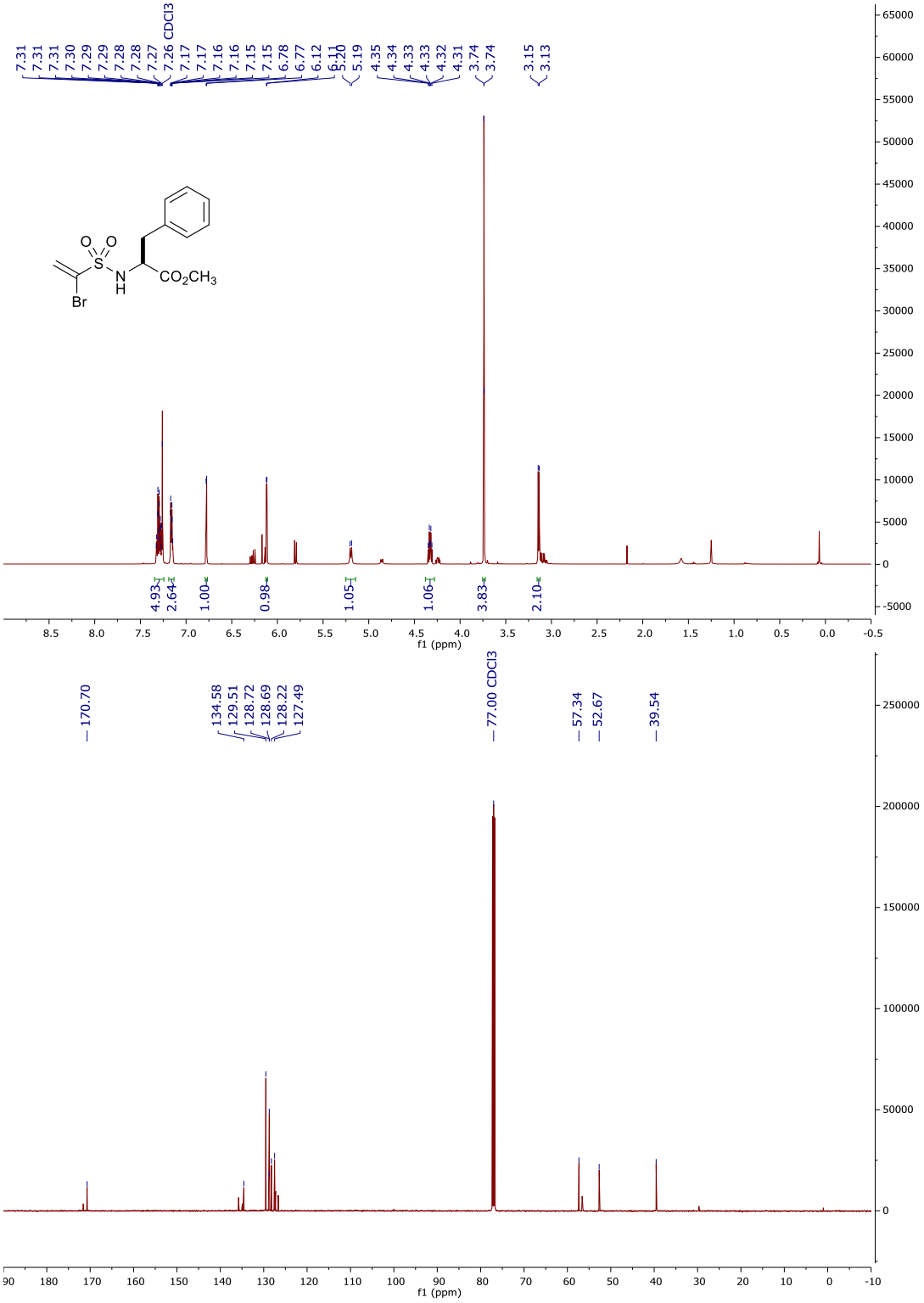


Methyl ((1-bromovinyl)sulfonyl)-*L*-isoleucinate (2.4.1.4.7)

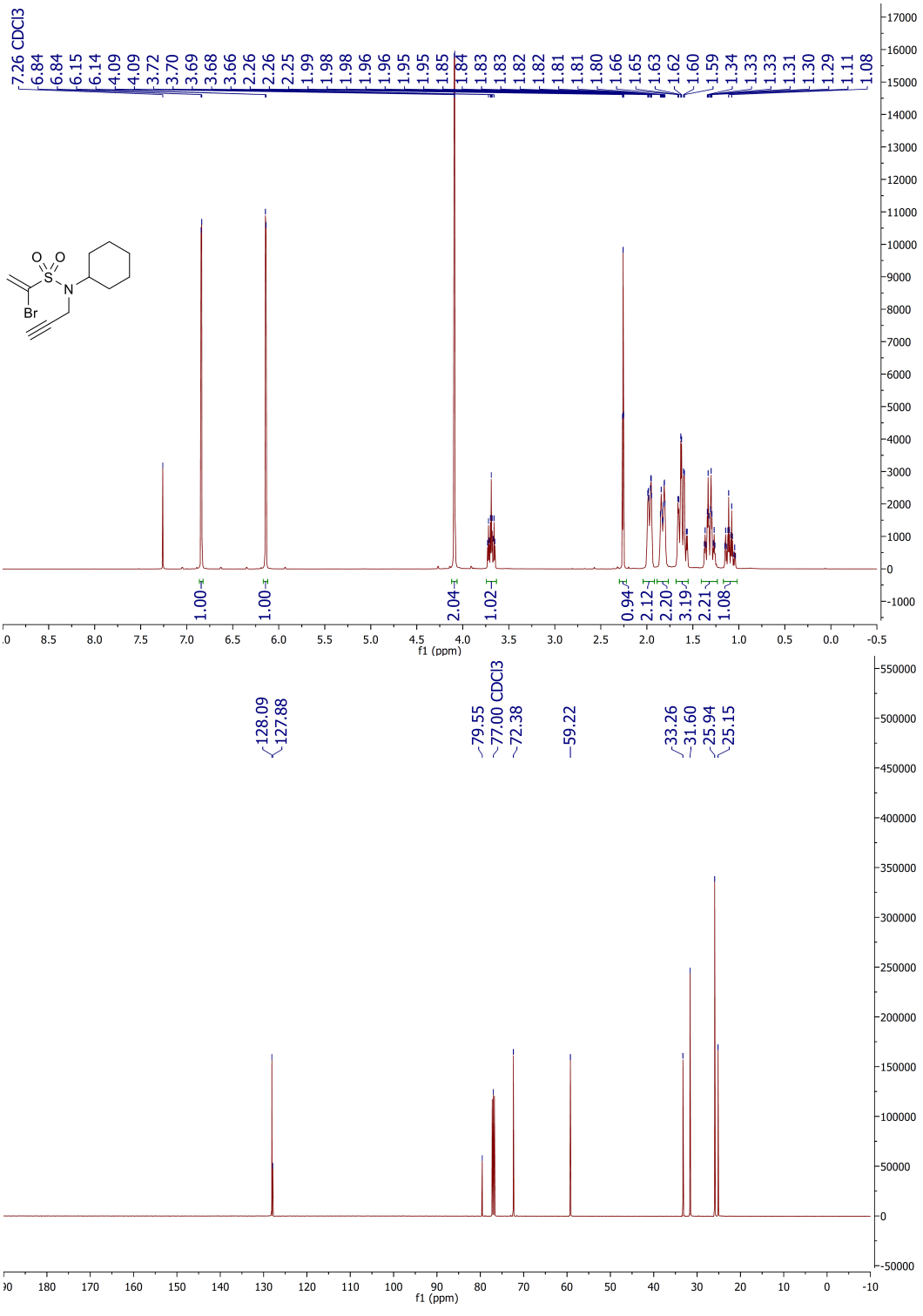




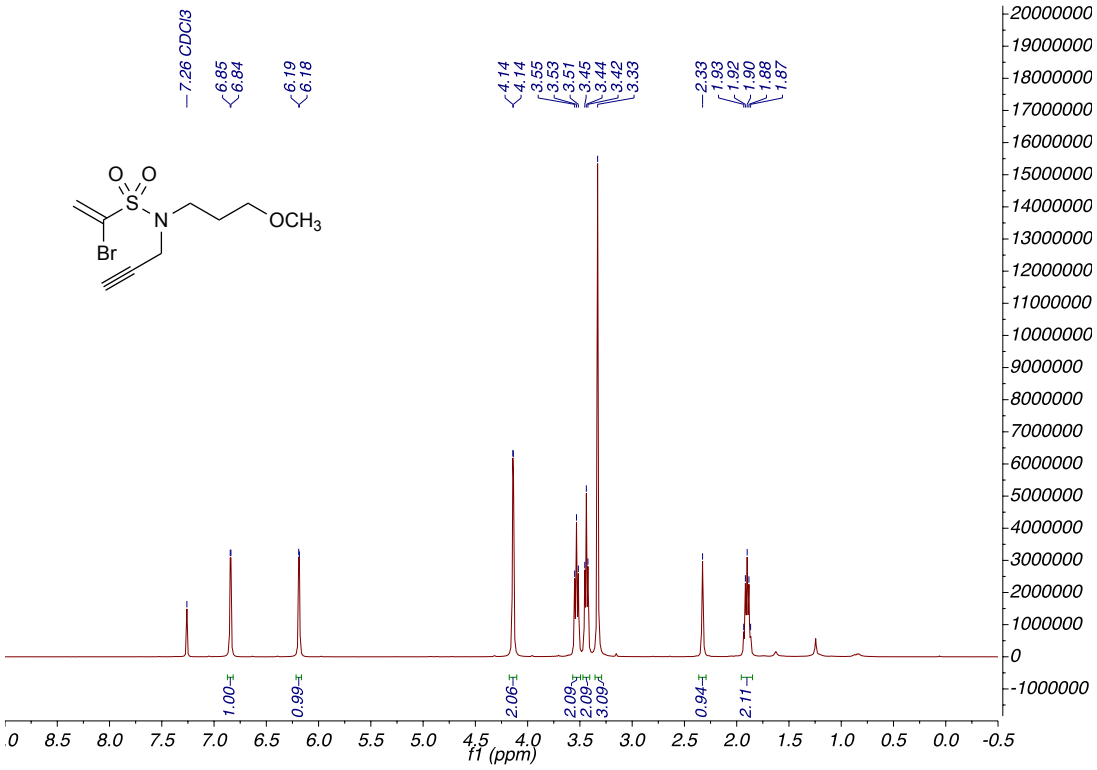
Methyl ((1-bromovinyl)sulfonyl)-*L*-phenylalaninate (2.4.1.4.8)

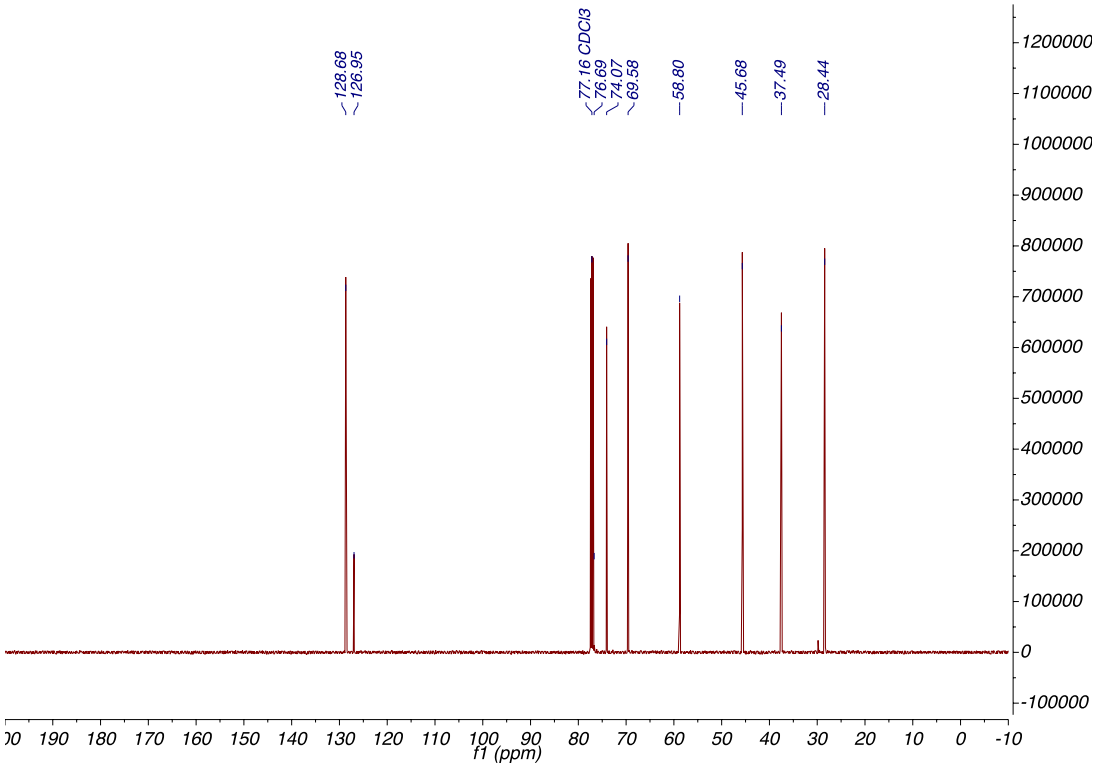


1-Bromo-*N*-cyclohexyl-*N*-(prop-2-yn-1-yl)ethene-1-sulfonamide (2.4.1.5.1)

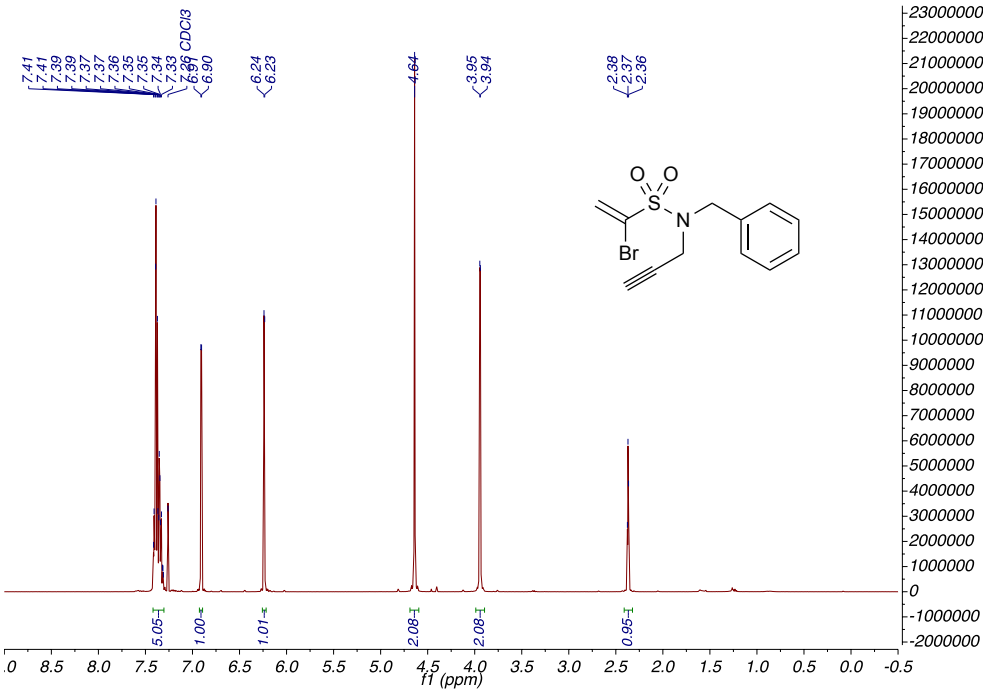


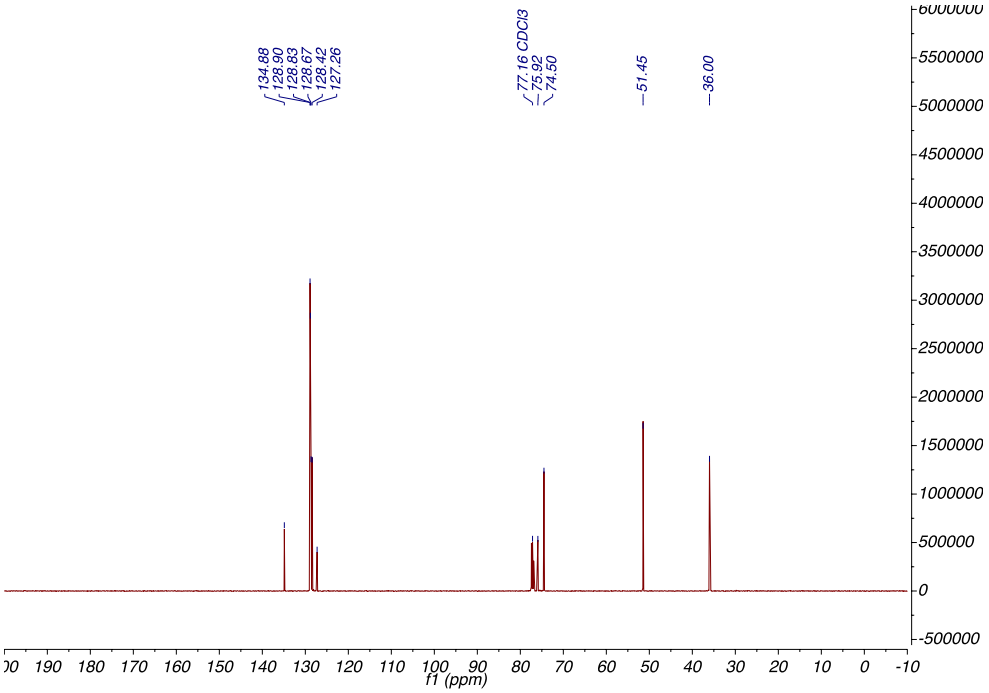
1-Bromo-*N*-(3-methoxypropyl)-*N*-(prop-2-yn-1-yl)ethene-1-sulfonamide (2.4.1.5.2)



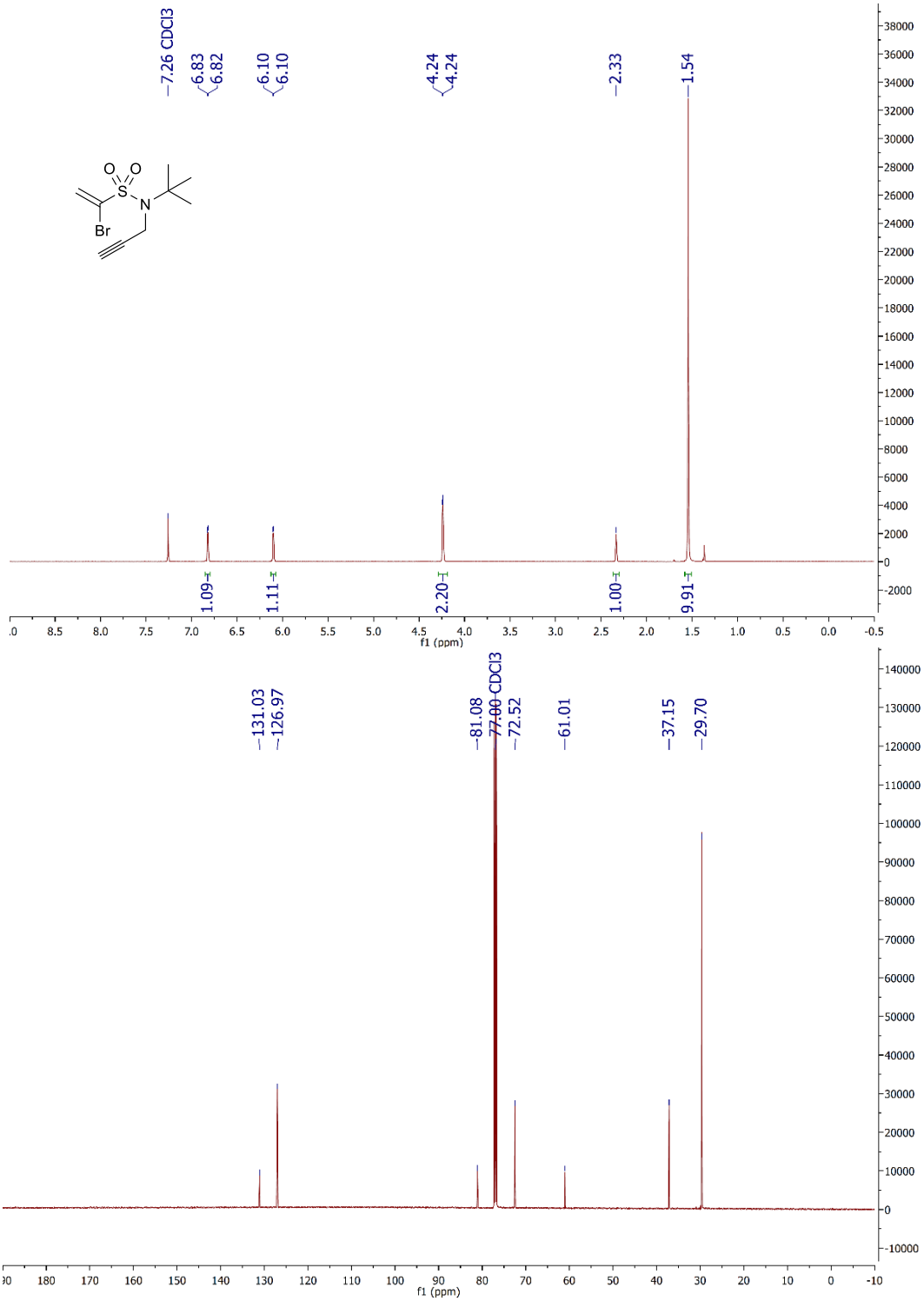


***N*-Benzyl-1-bromo-N-(prop-2-yn-1-yl)ethene-1-sulfonamide (2.4.1.5.3)**

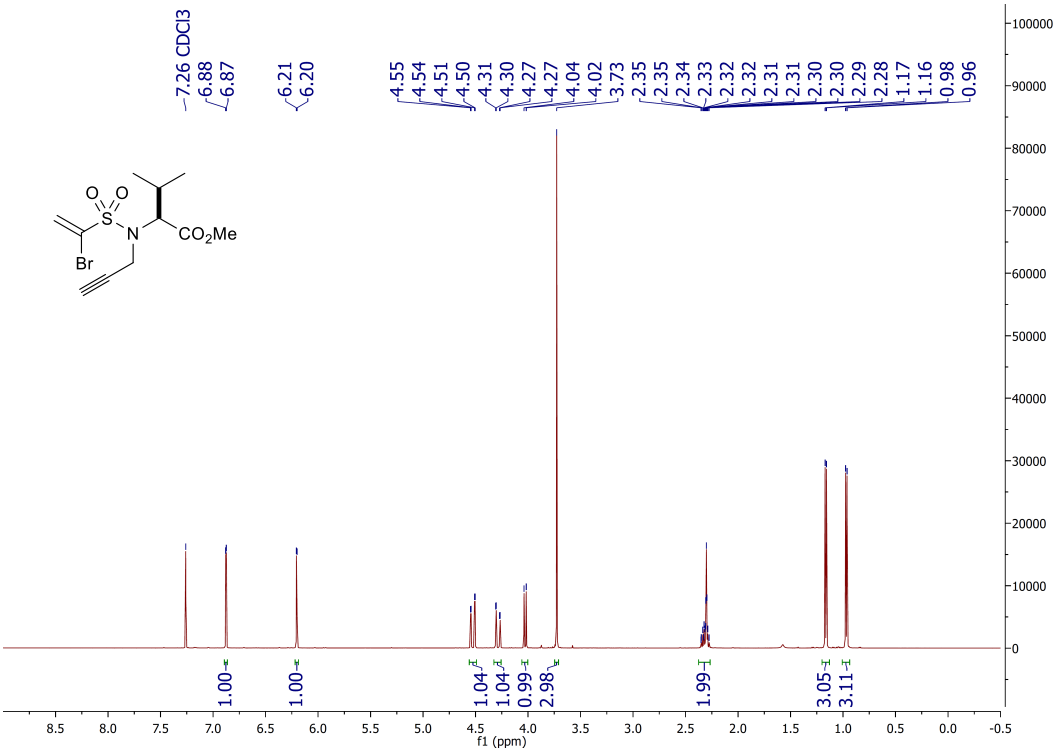


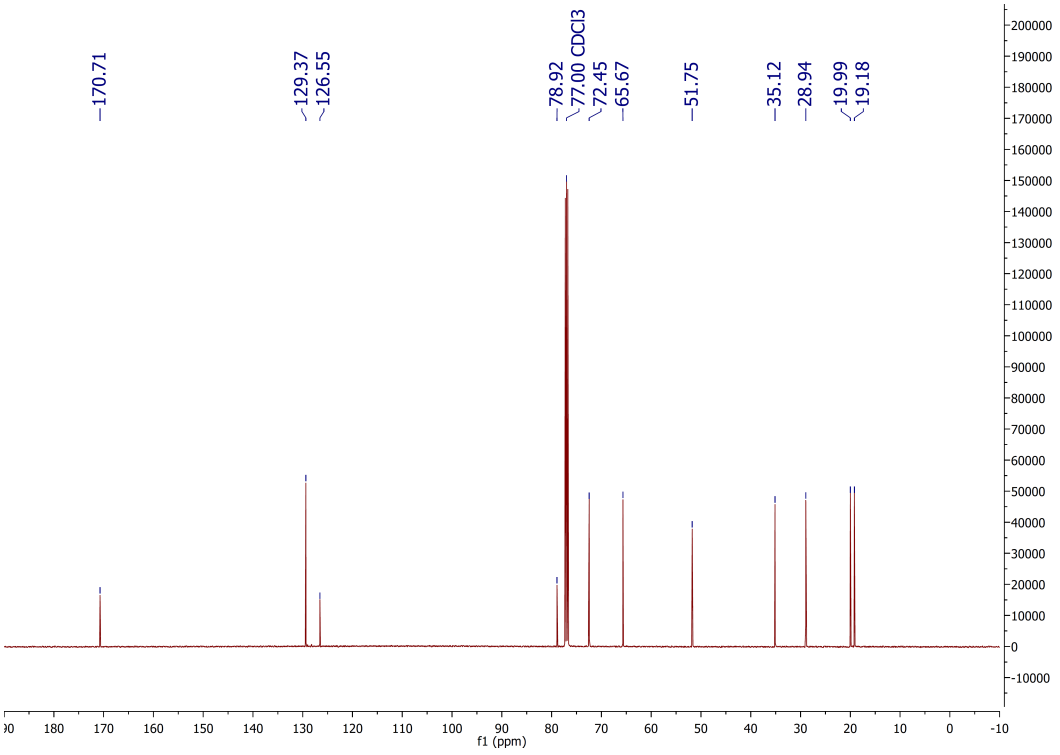


1-Bromo-*N*-(*tert*-butyl)-*N*-(prop-2-yn-1-yl)ethene-1-sulfonamide (2.4.1.5.4)

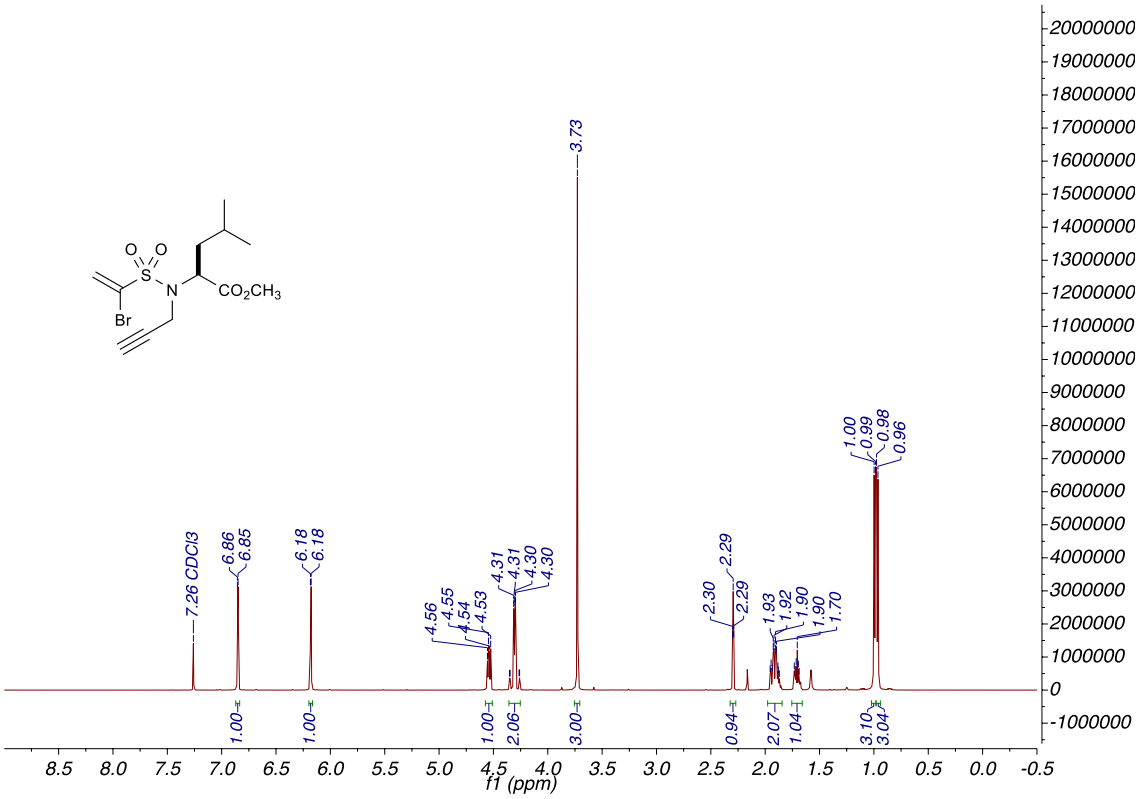


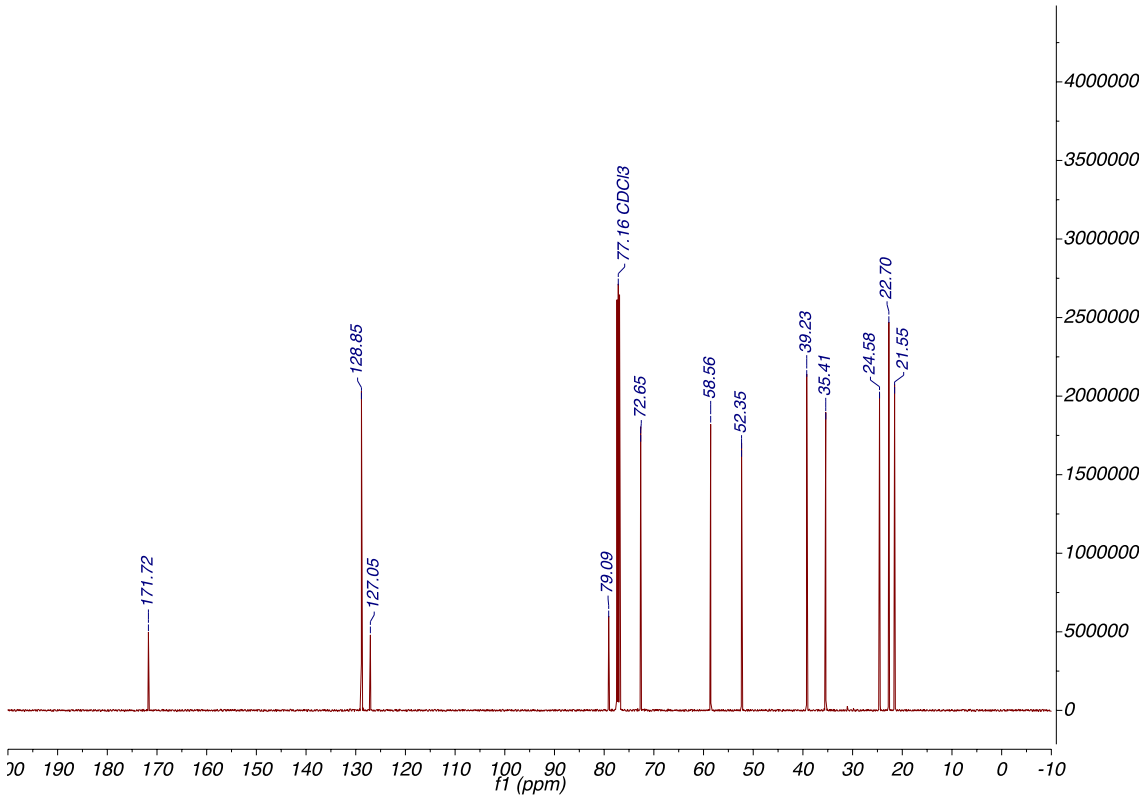
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-*L*-valinate (2.4.1.5.5)



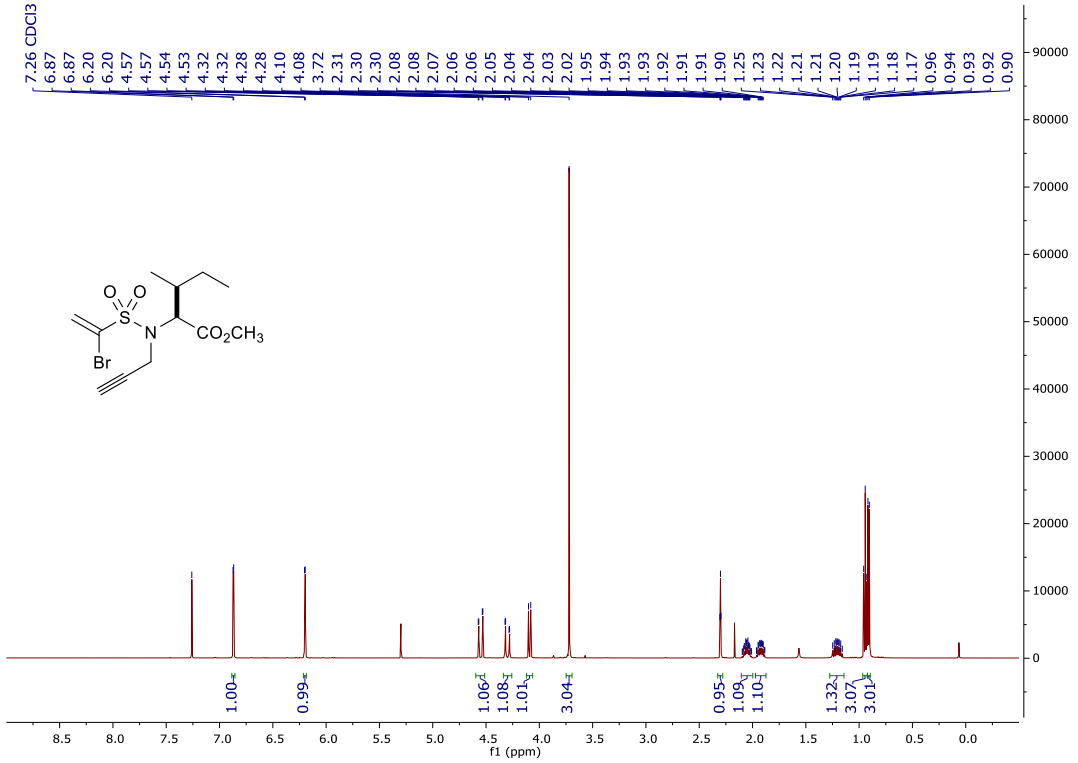


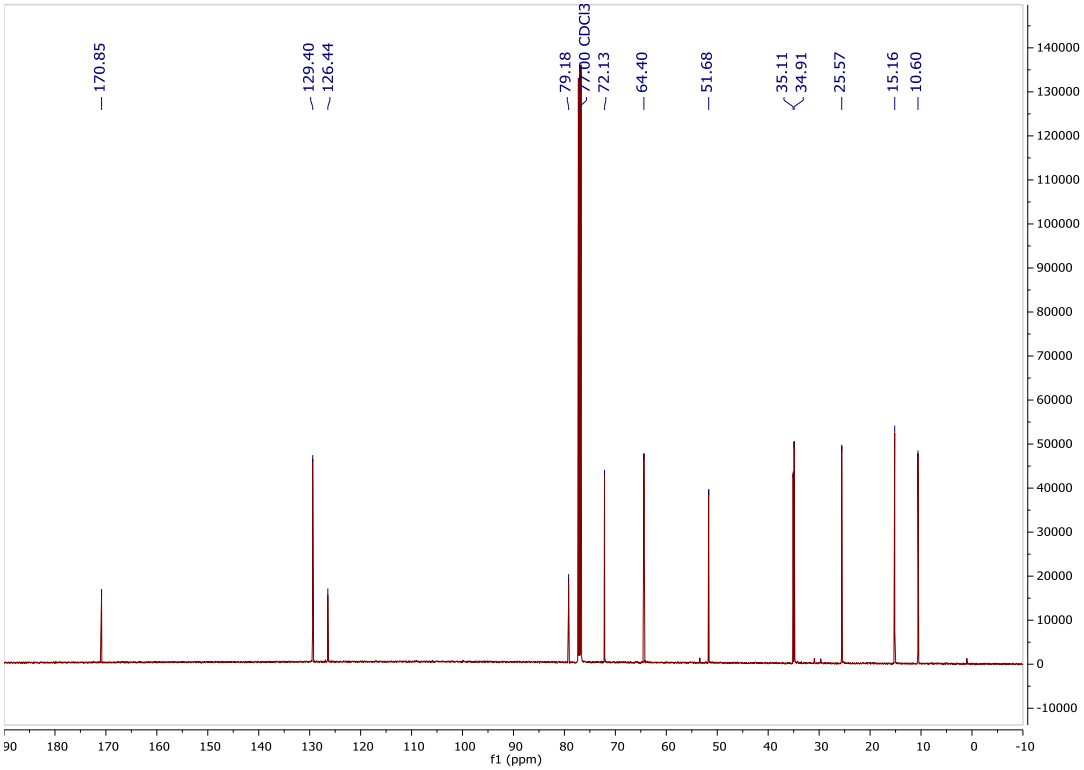
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-*L*-leucinate (2.4.1.5.6)



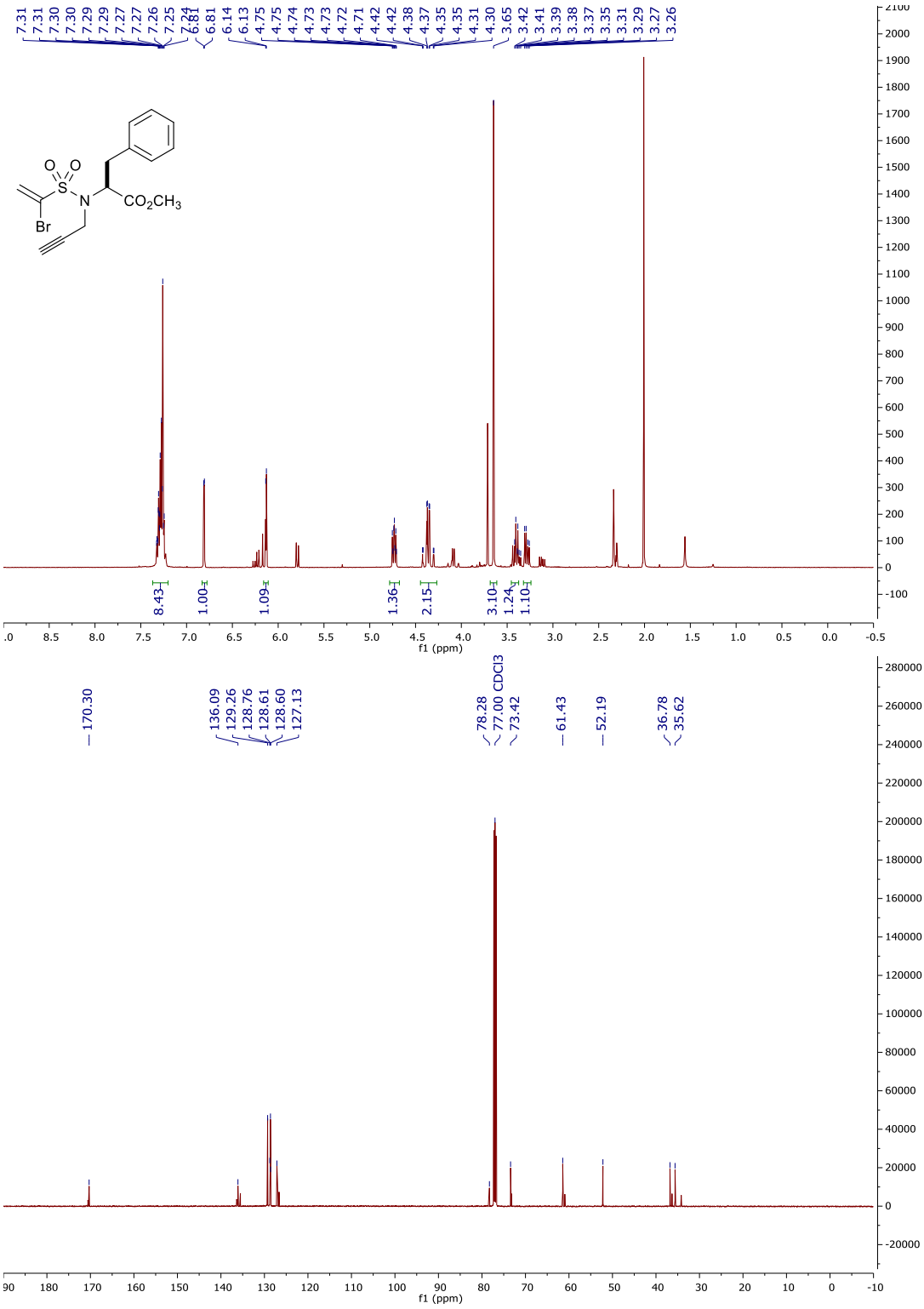


Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-*L*-isoleucinate (2.4.1.5.7)

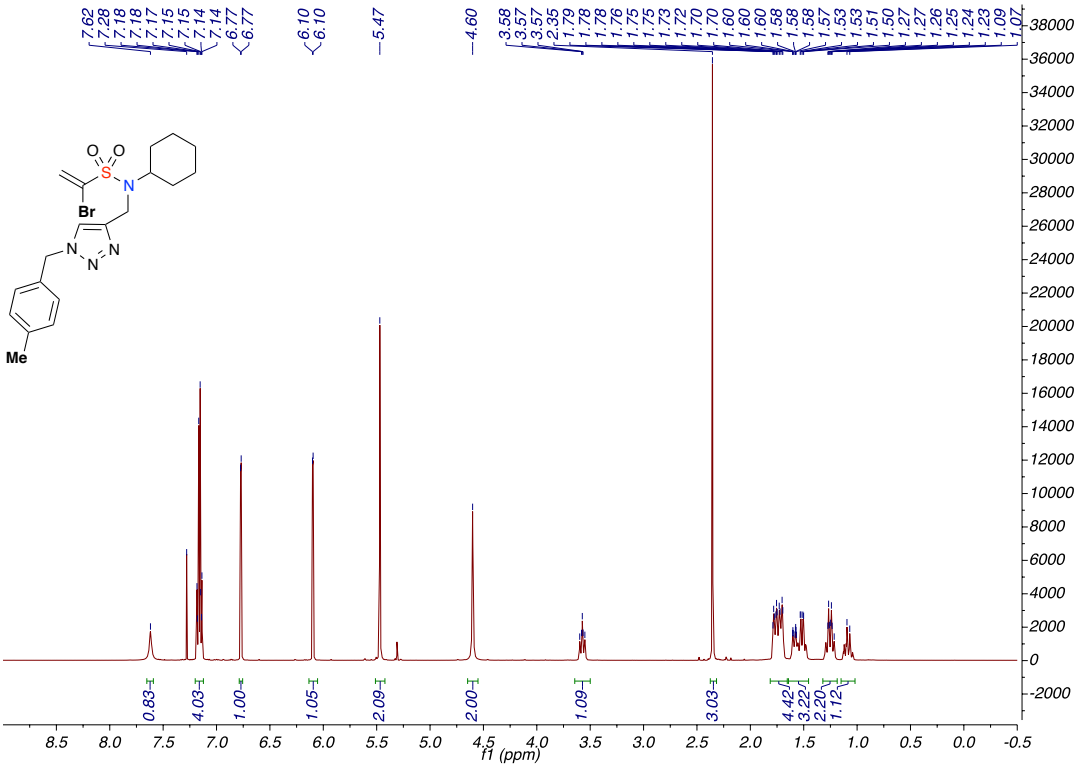


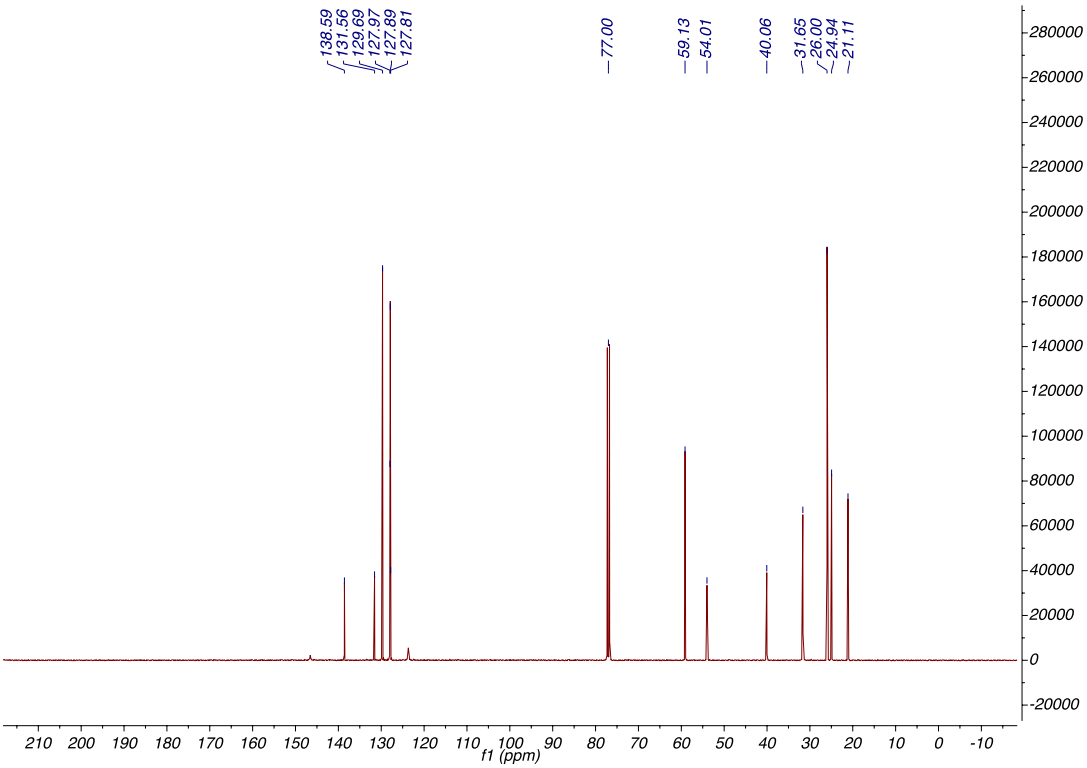


Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-*L*-phenylalaninate (2.4.1.5.8)

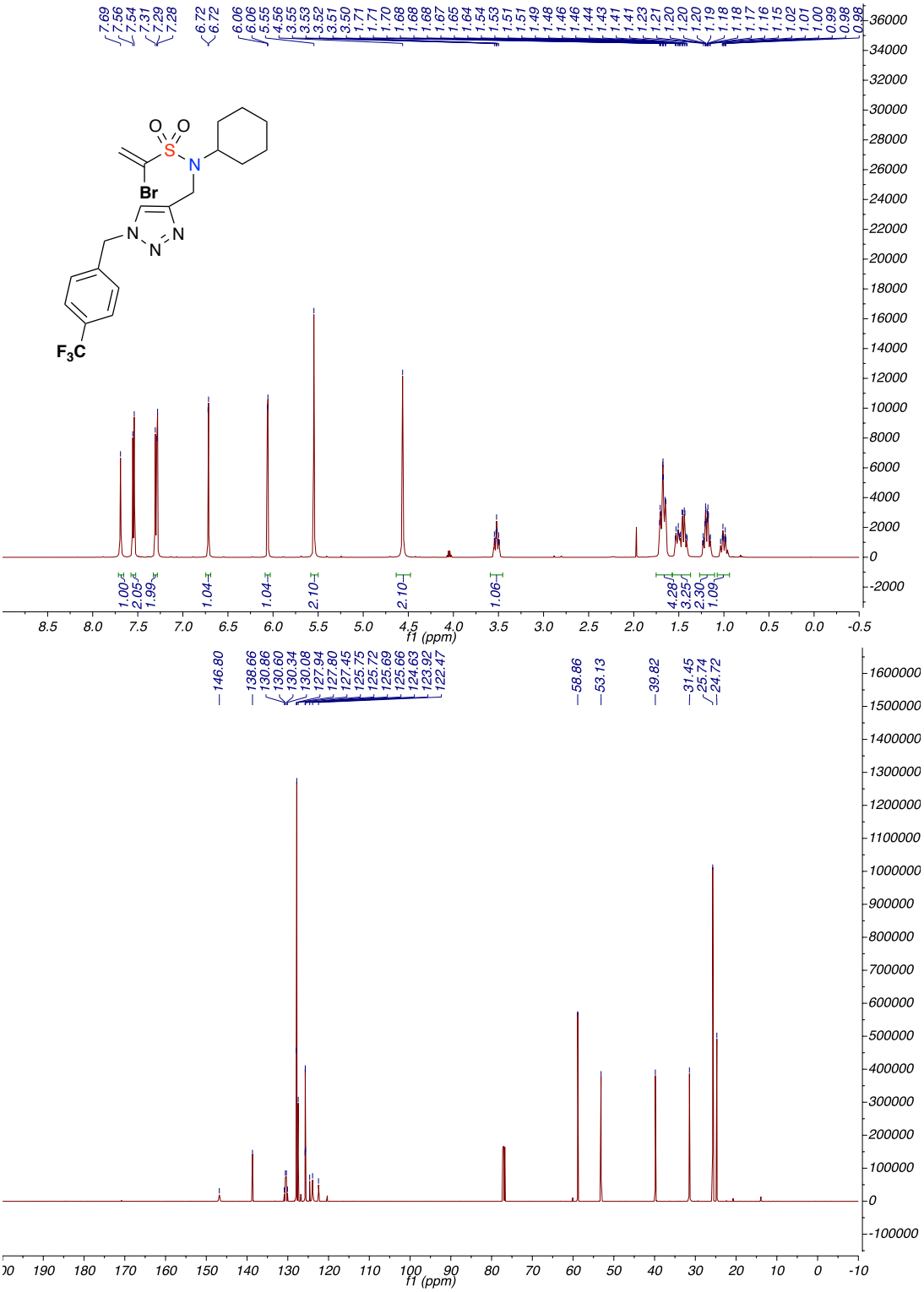


1-Bromo-*N*-cyclohexyl-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.1)

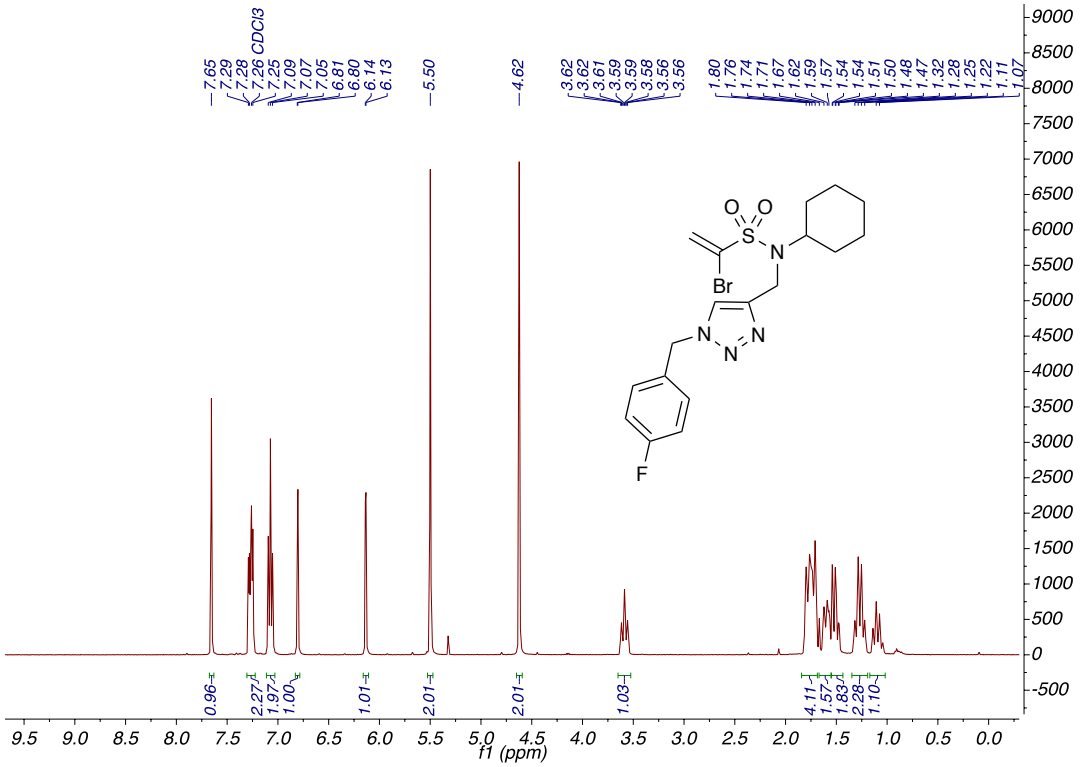


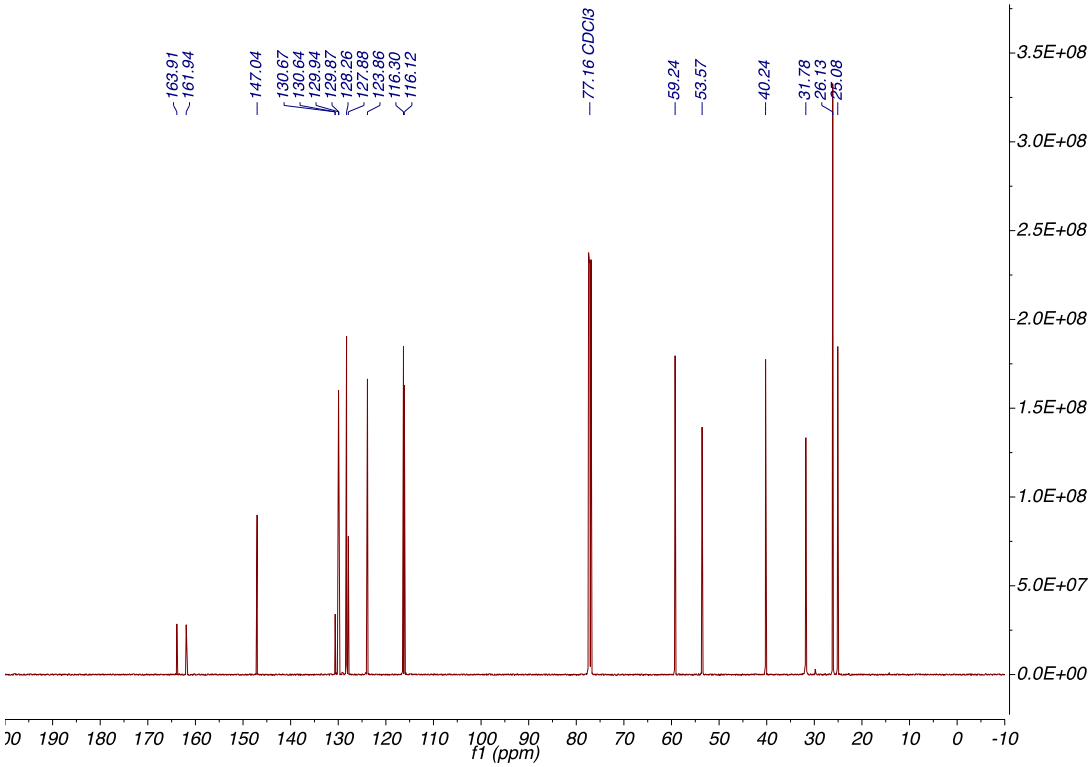


1-Bromo-*N*-cyclohexyl-*N*-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethane-sulfonamide (2.4.2.2.2)

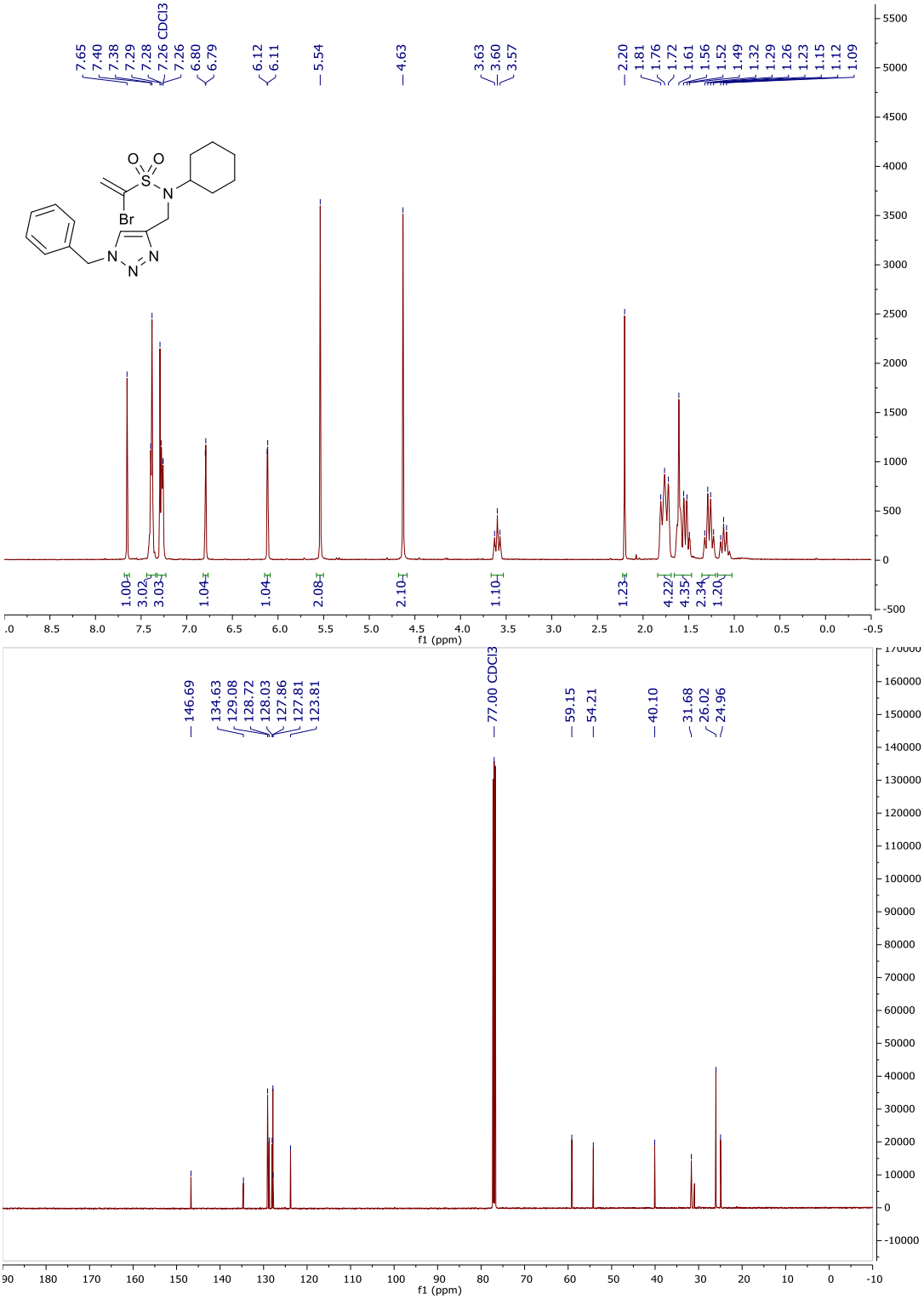


1-Bromo-*N*-cyclohexyl-*N*-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide (2.4.2.2.3)

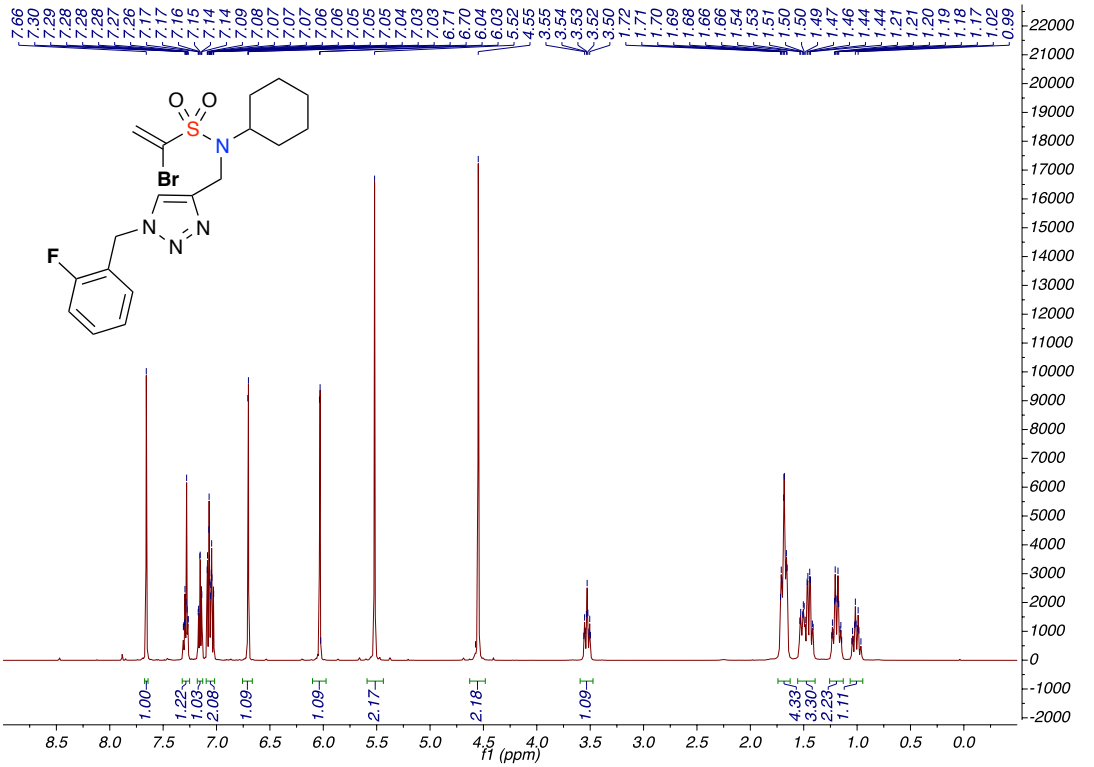


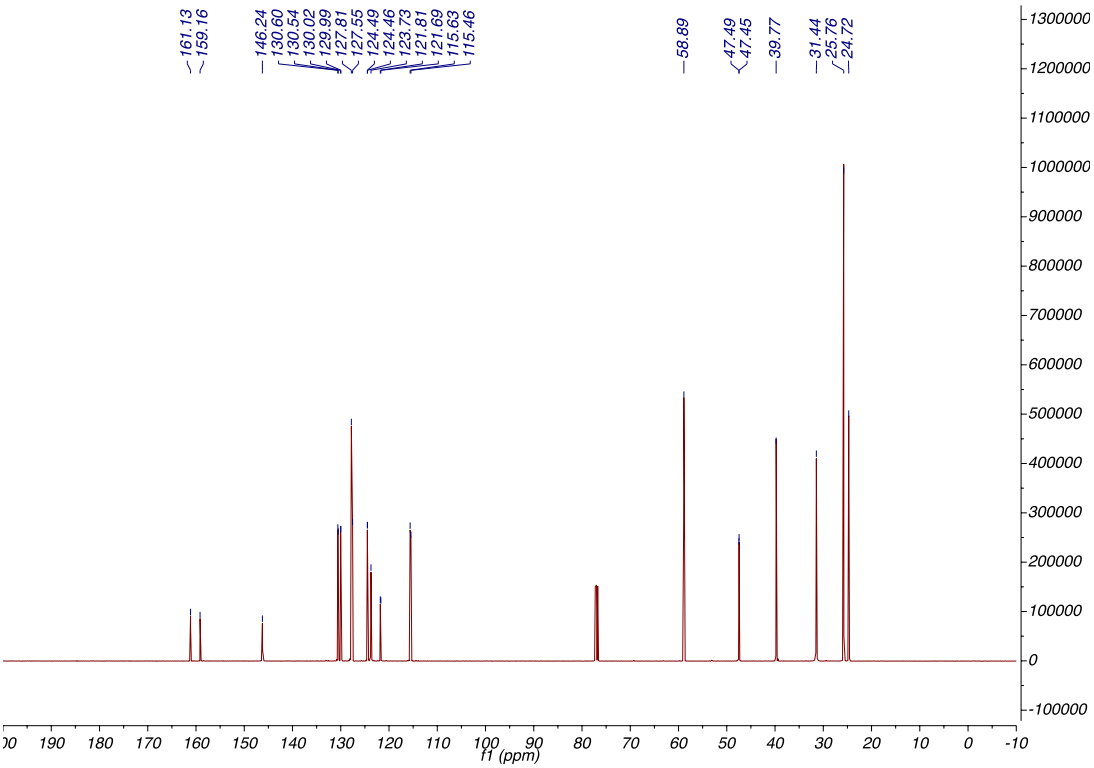


_N_-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-1-bromo-_N_-cyclohexylethene-1-sulfonamide (2.4.2.2.4)

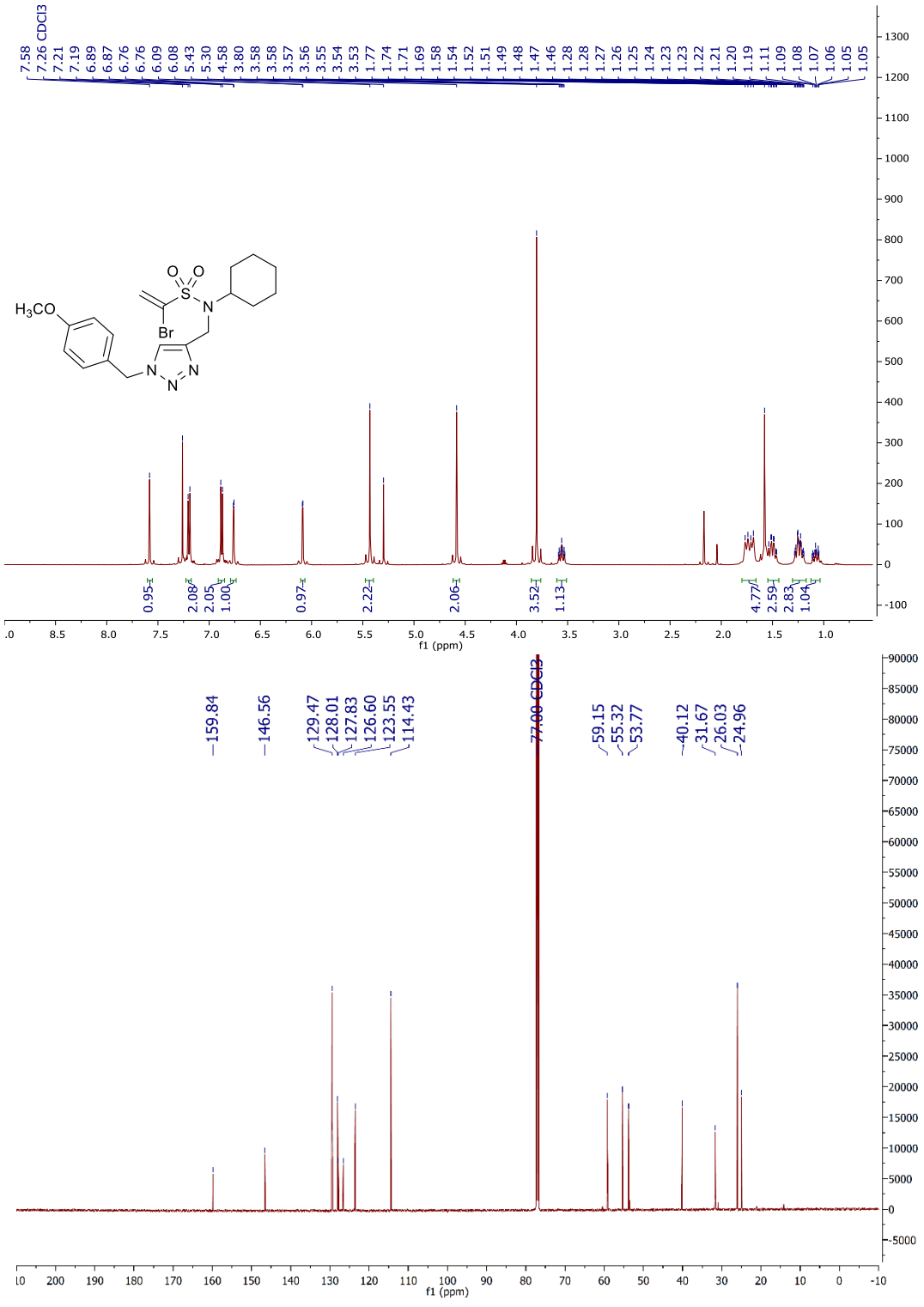


1-Bromo-*N*-cyclohexyl-*N*-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.5)

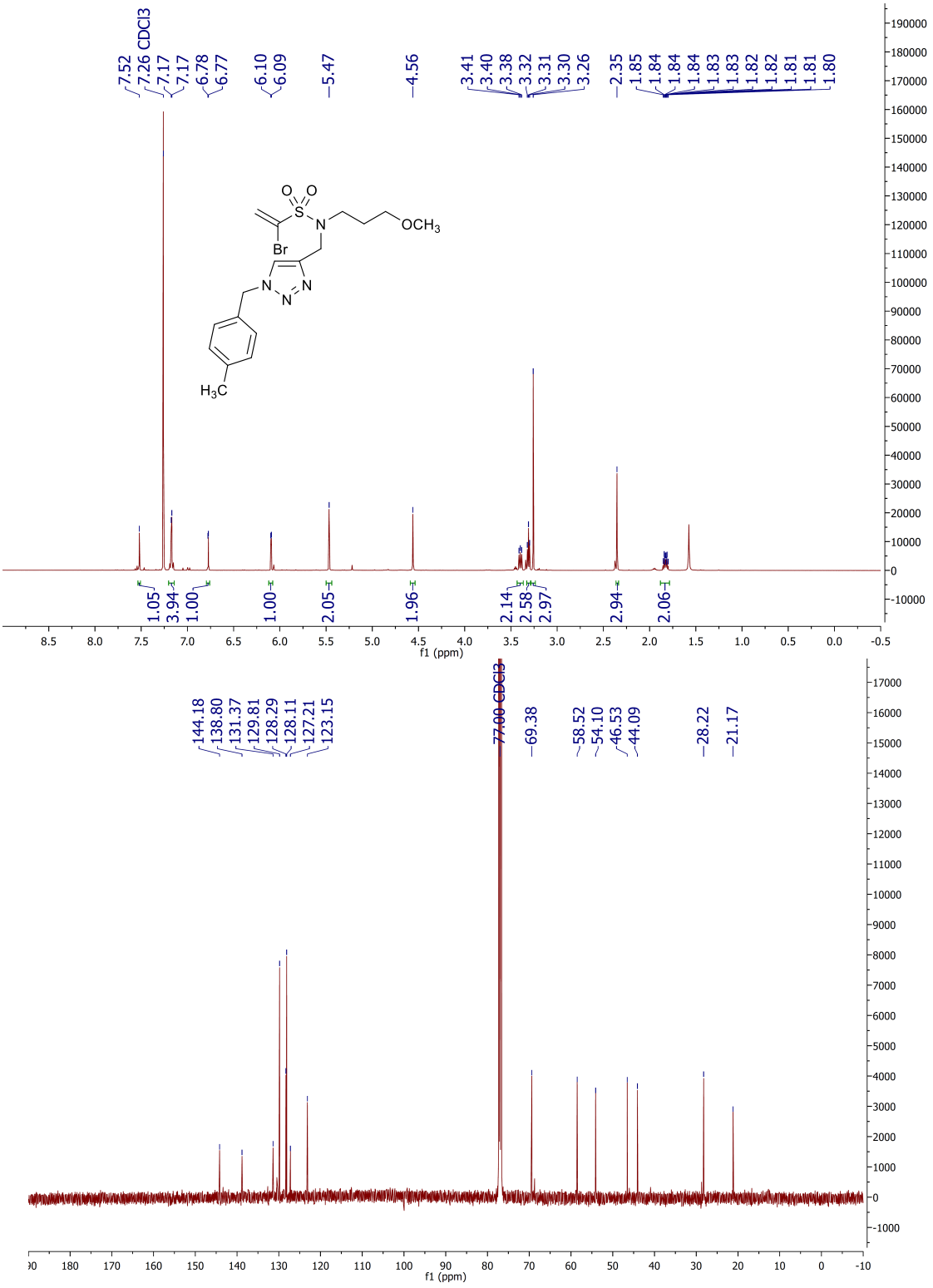




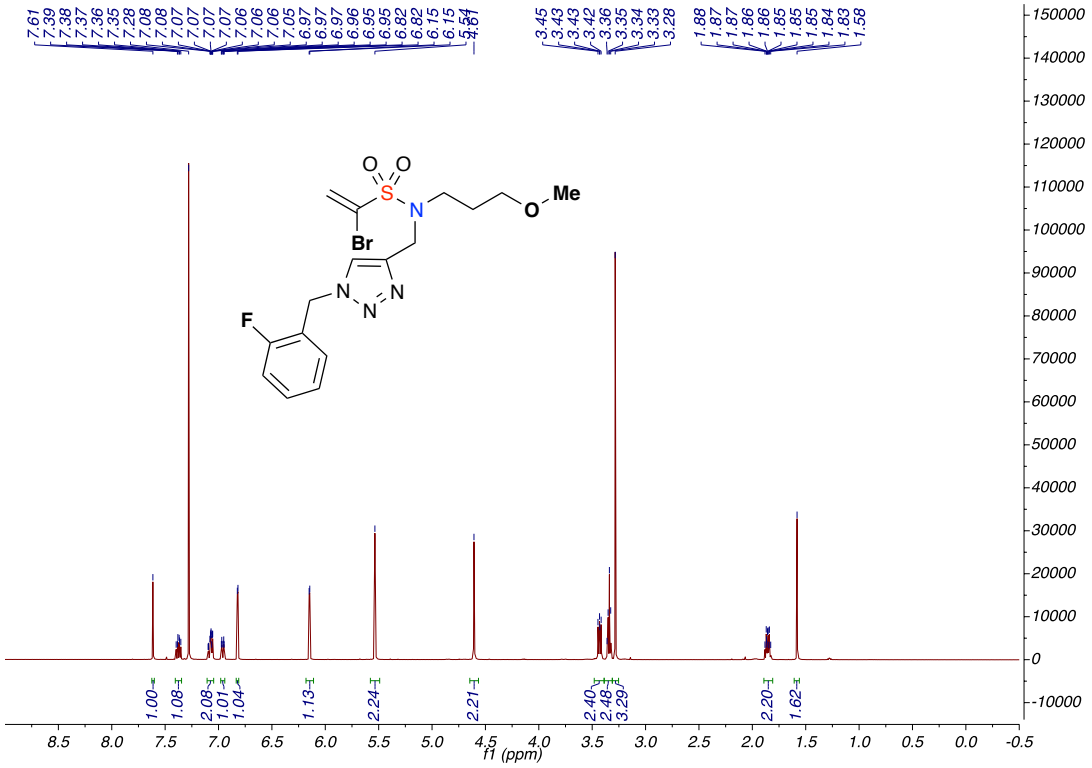
1-Bromo-*N*-cyclohexyl-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide (2.4.2.2.6)

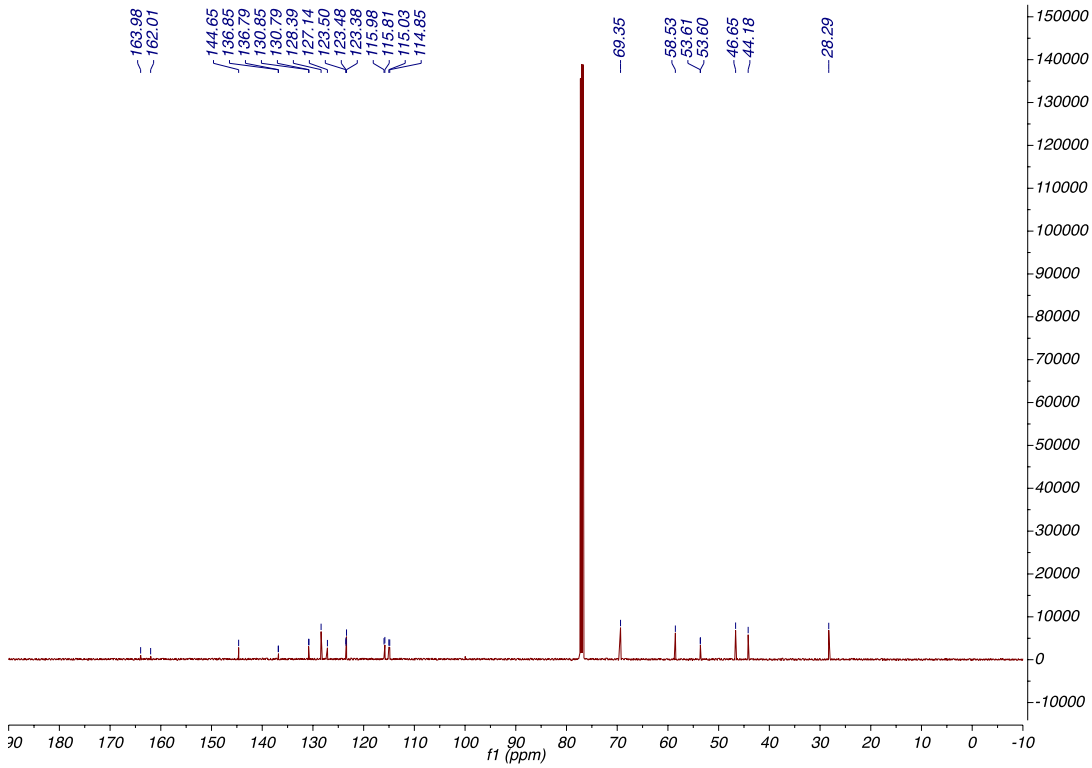


1-Bromo-*N*-(3-methoxypropyl)-*N*-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide (2.4.2.2.7)

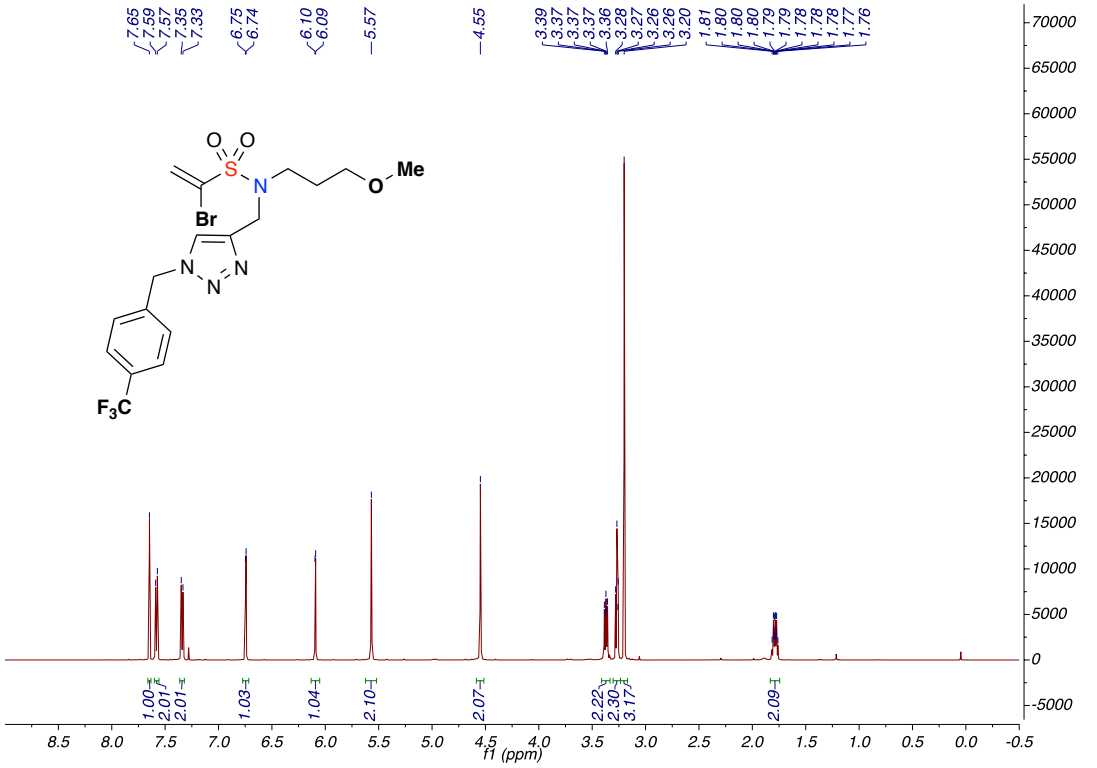


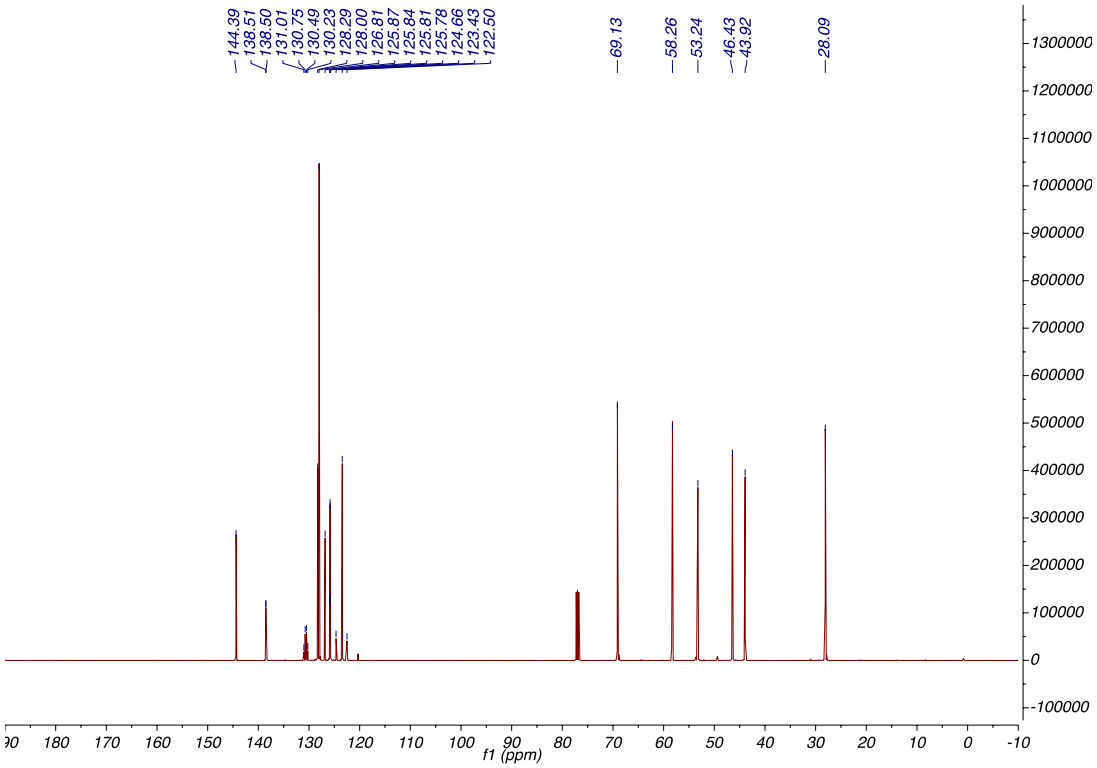
1-bromo-*N*-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-(3-methoxypropyl)ethenesulfonamide (2.4.2.2.8)



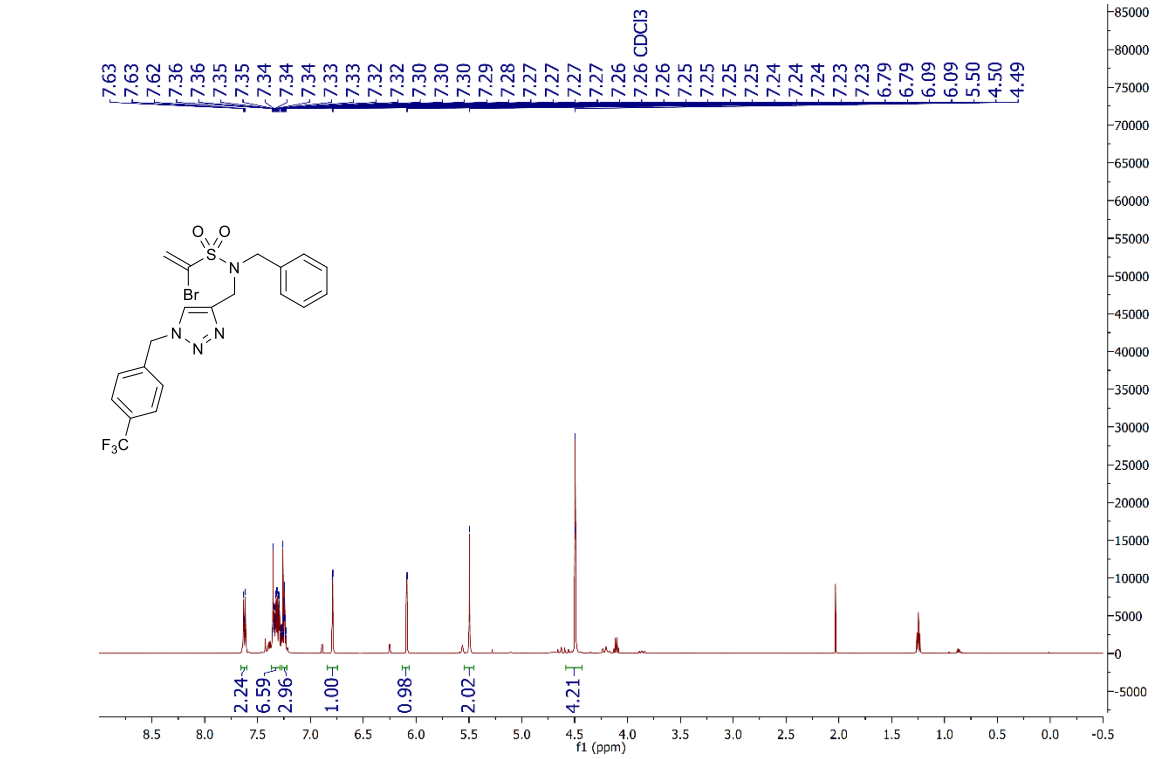


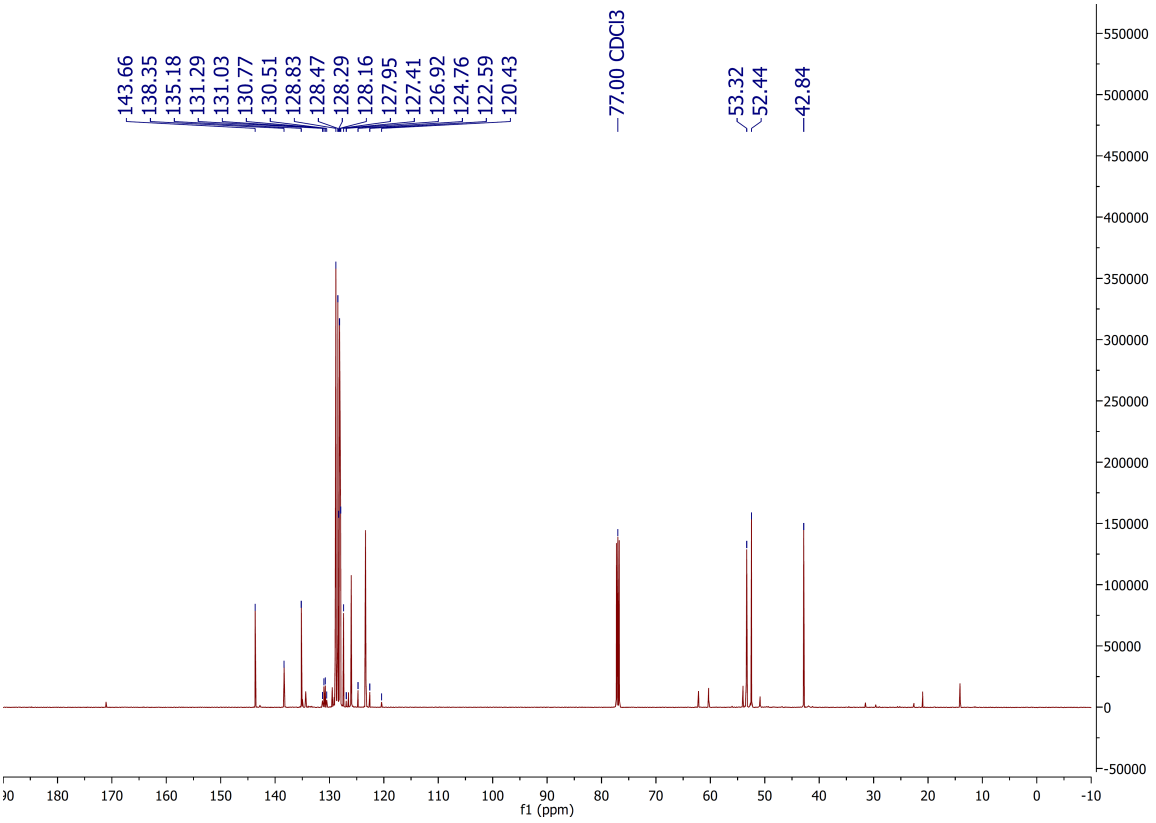
1-bromo-*N*-(3-Methoxypropyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.9)



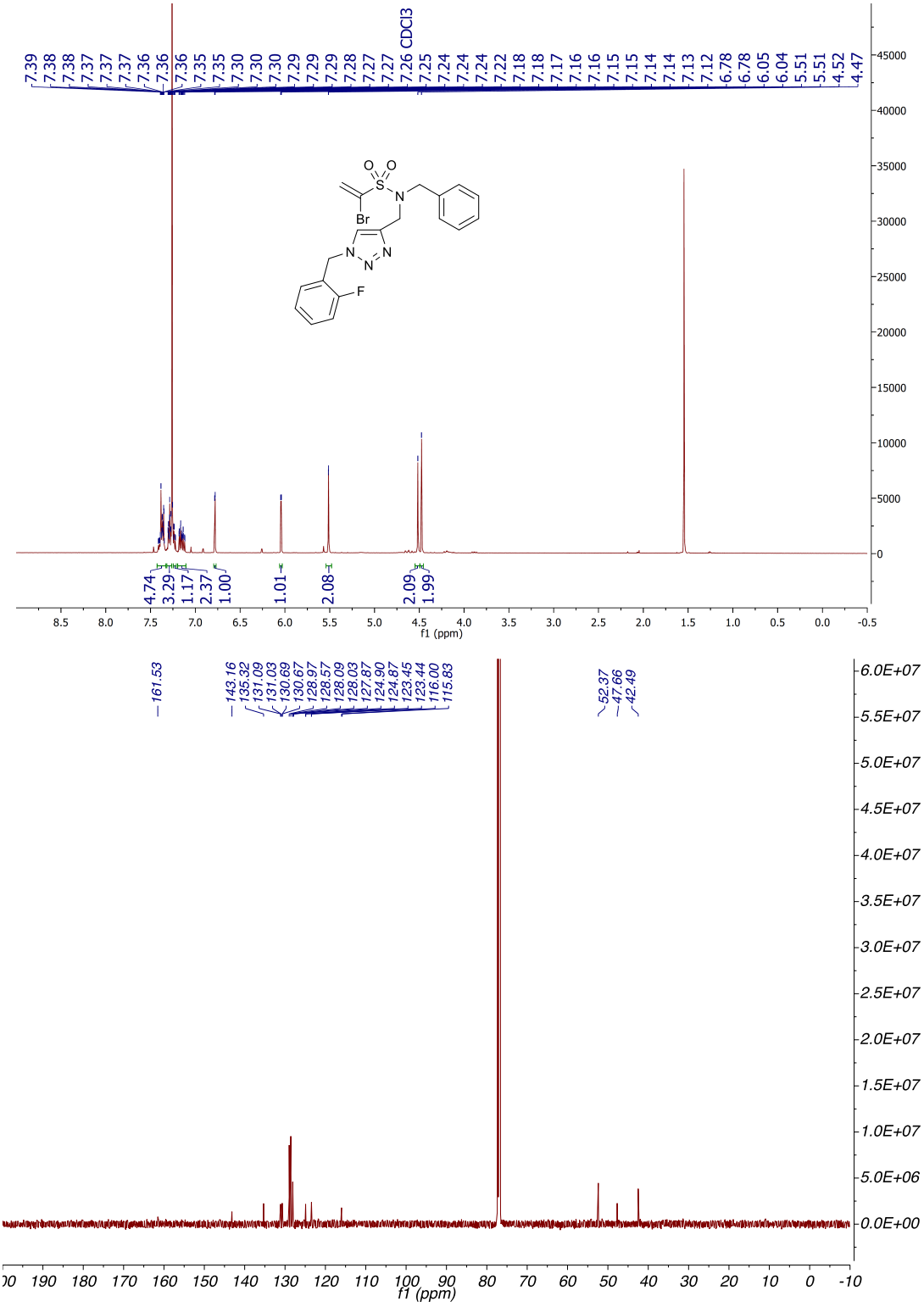


_N_-Benzyl-1-bromo-N-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide (2.4.2.2.10)

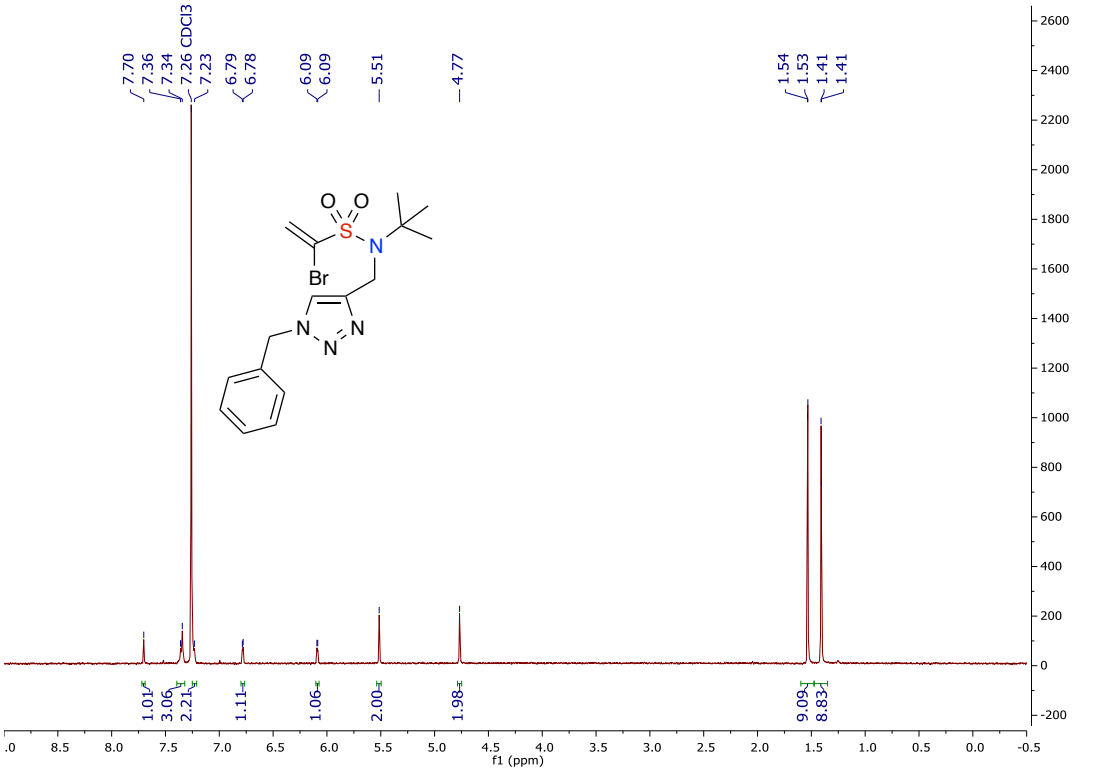


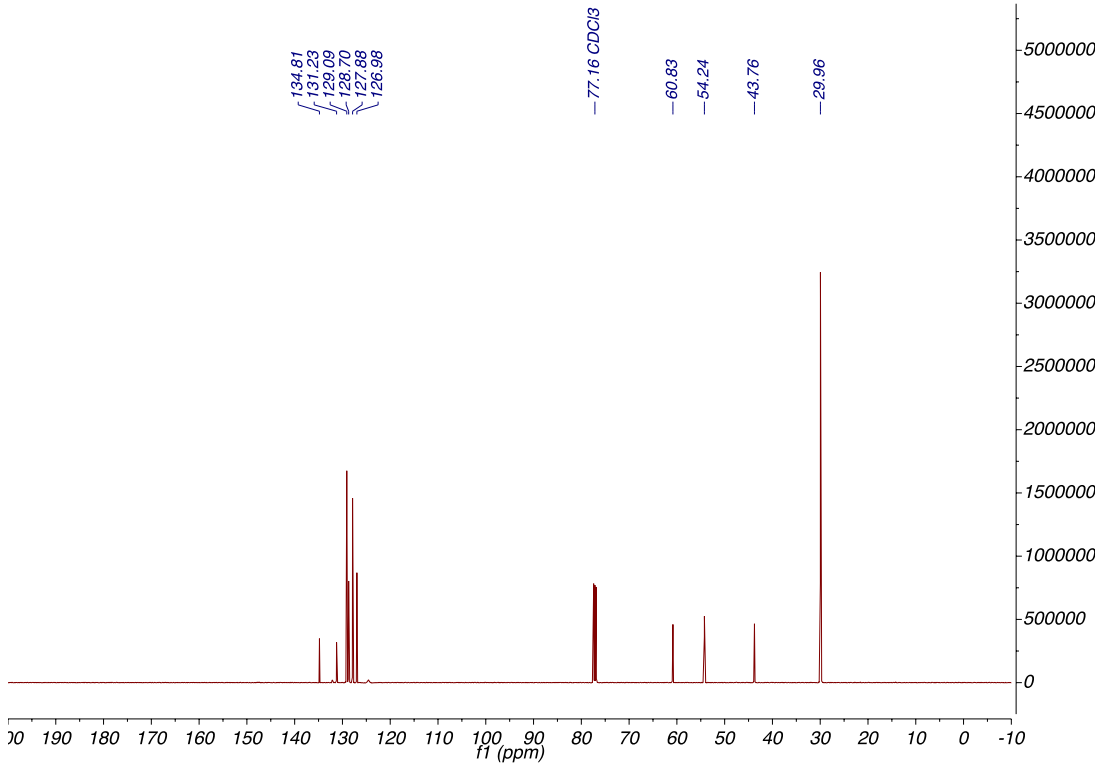


***N*-benzyl-1-bromo-*N*-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide (2.4.2.2.11)**

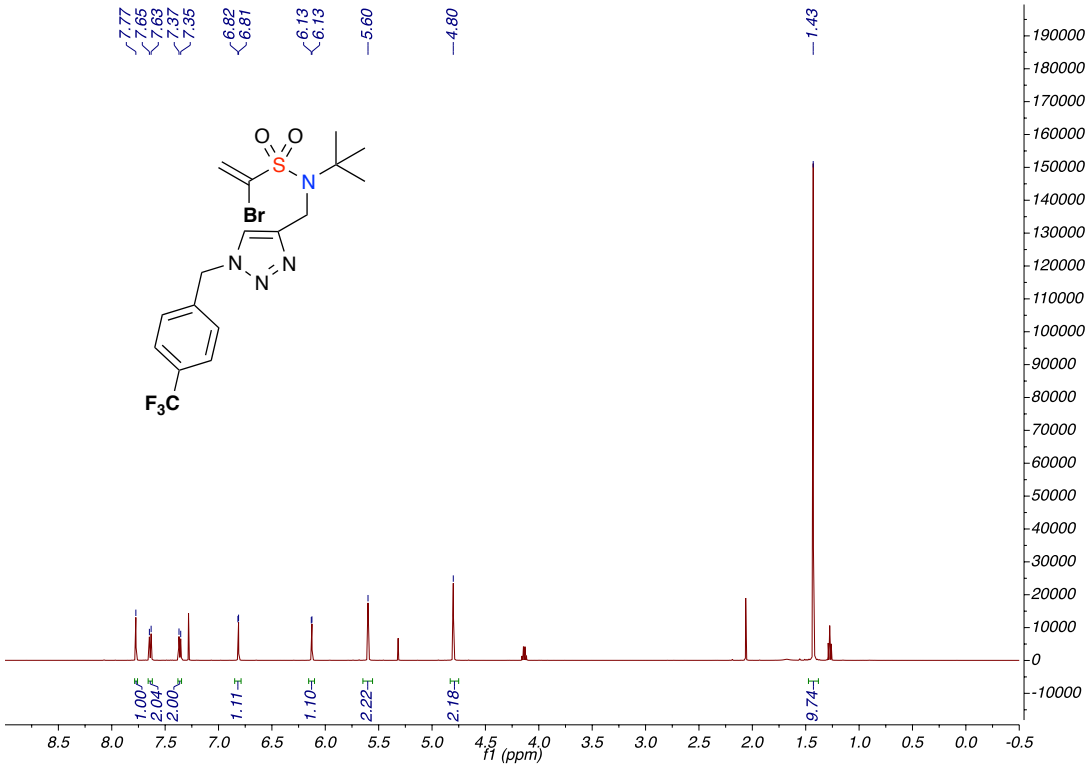


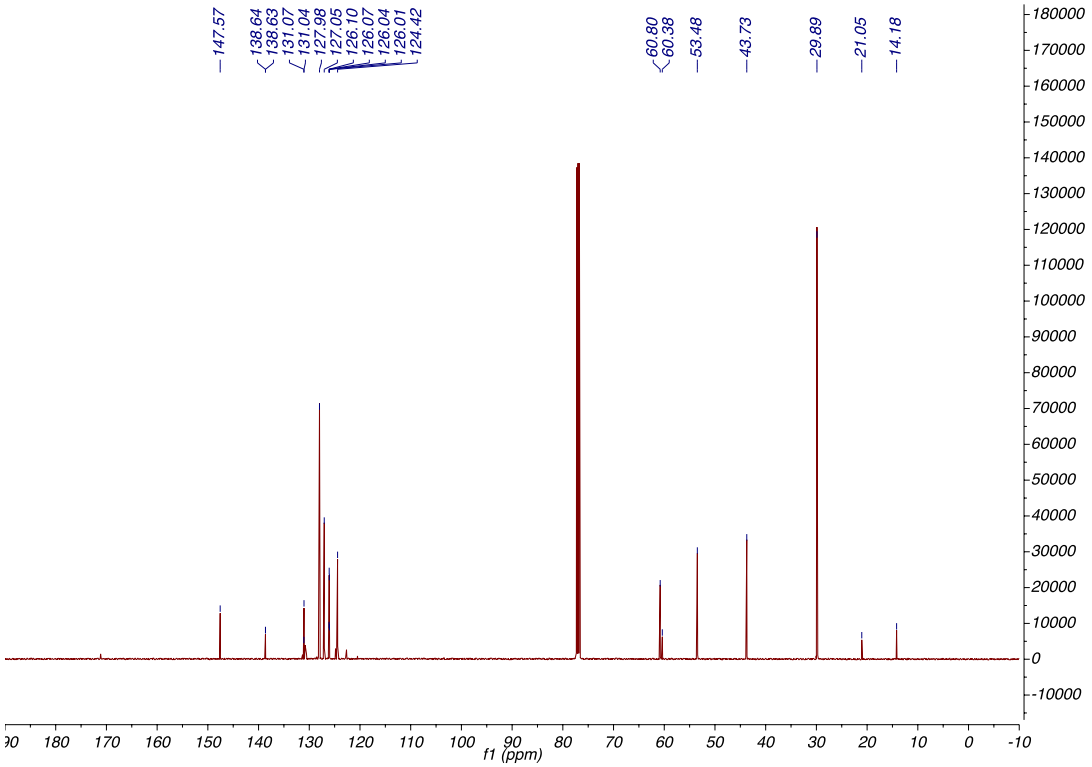
_N_-((1-benzyl-1_H_-1,2,3-triazol-4-yl)methyl)-1-bromo-_N_-(_tert_-butyl)ethenesulfonamide (2.4.2.2.12)



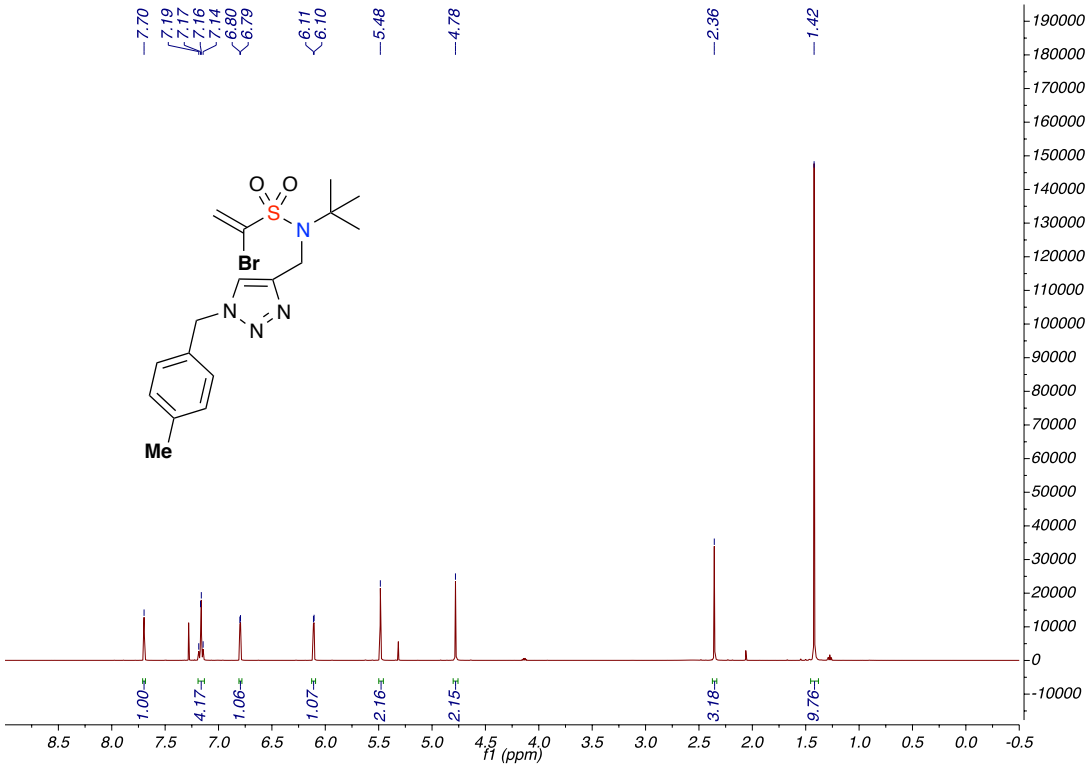


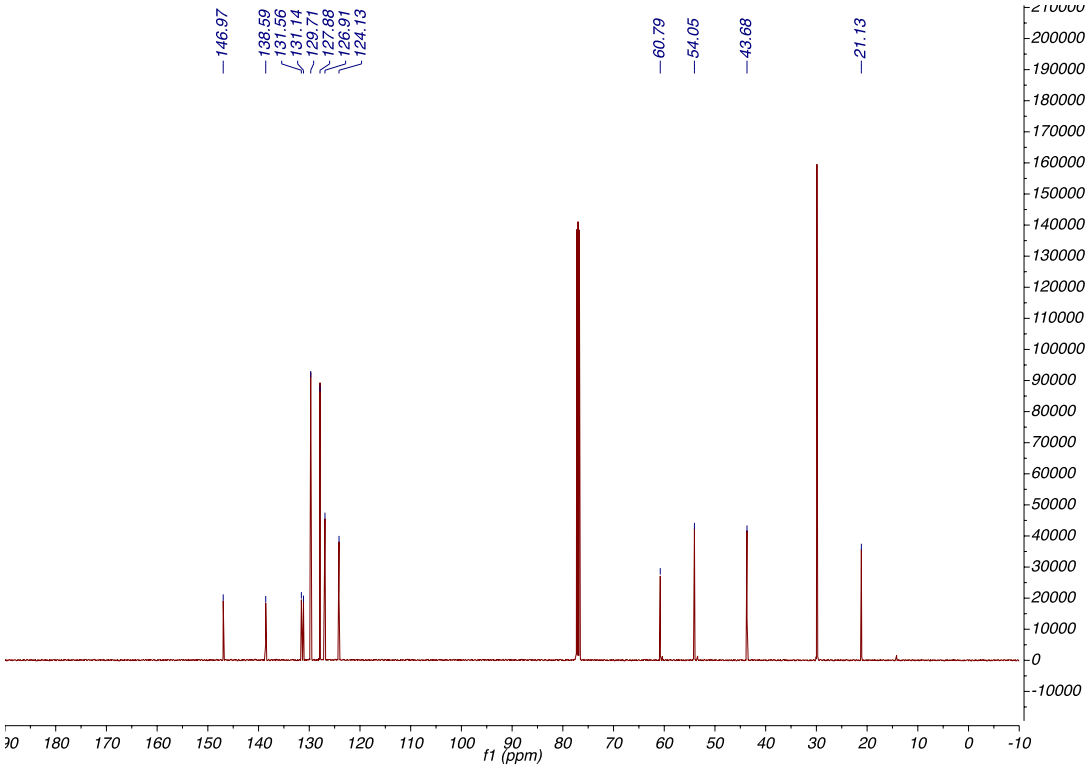
1-bromo-*N*-(*tert*-butyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.13)



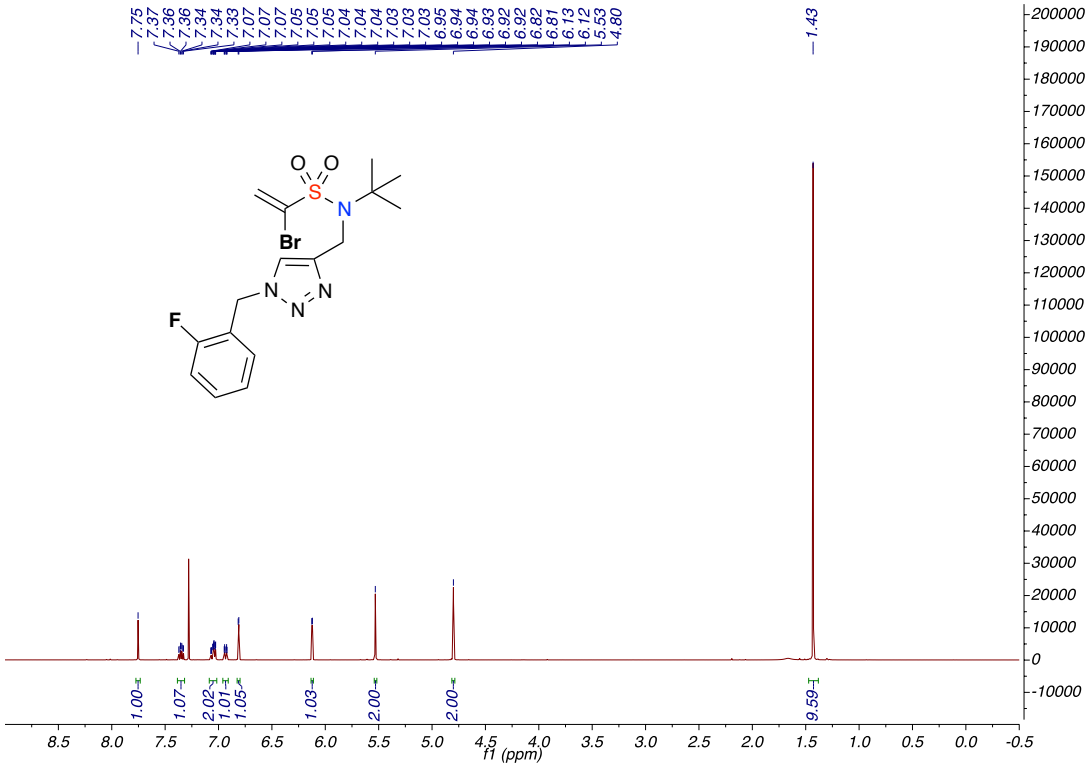


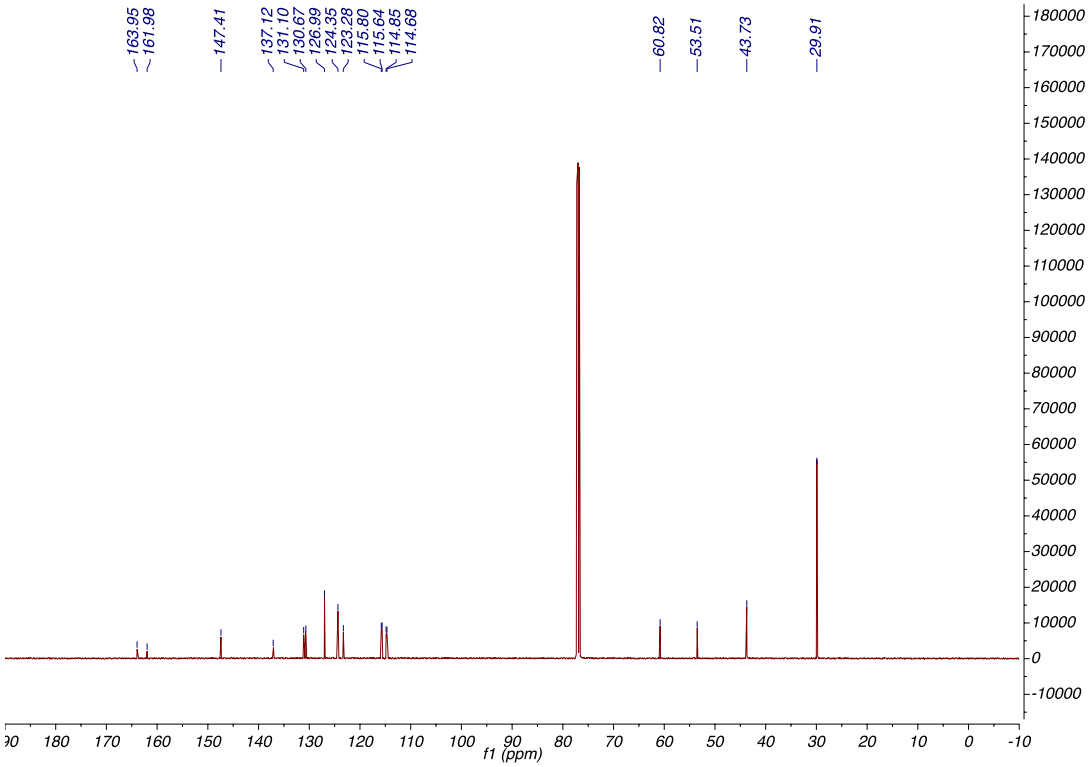
1-bromo-*N*-(*tert*-butyl)-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.14)



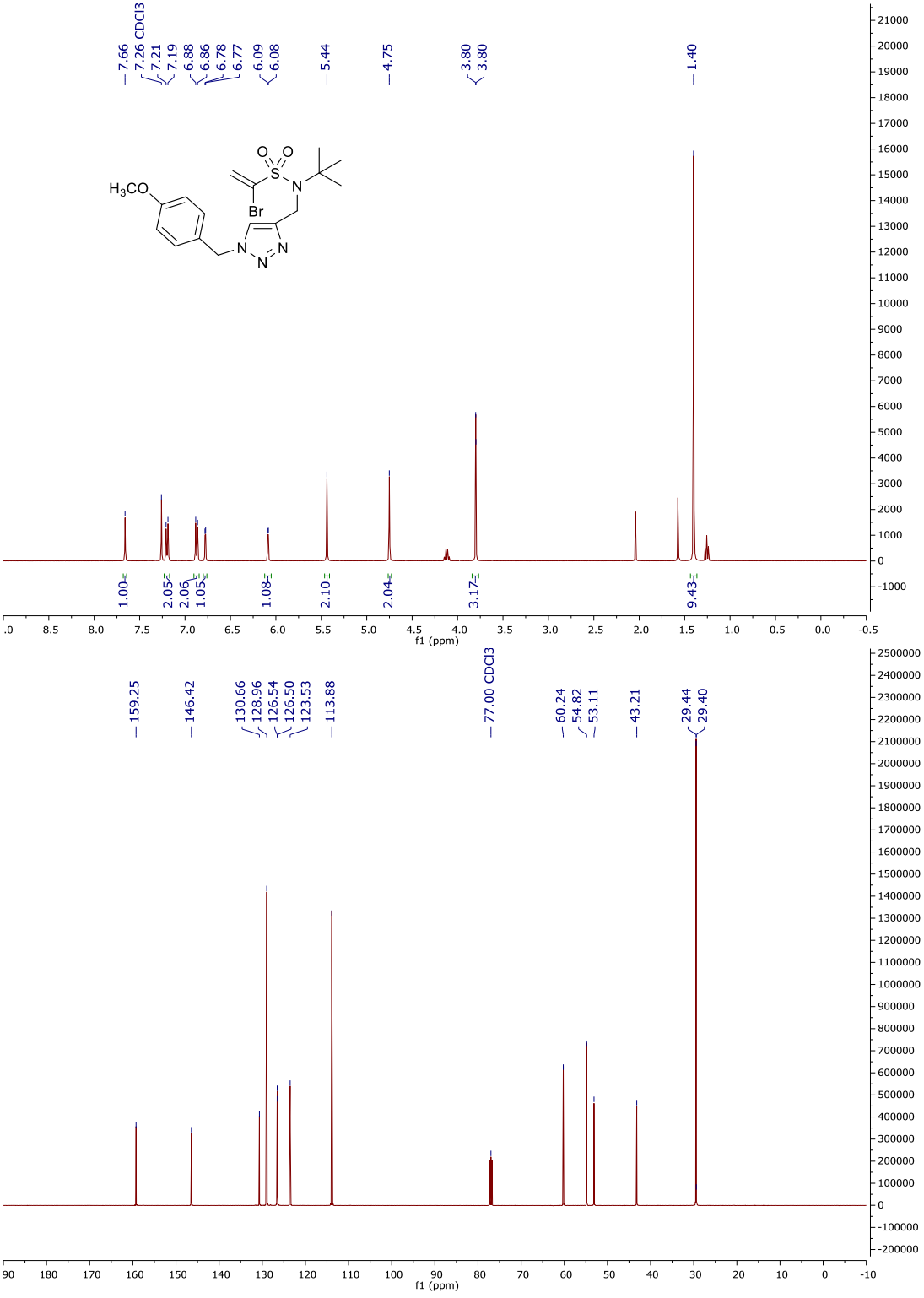


1-bromo-*N*-(*tert*-butyl)-*N*-((1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.15)

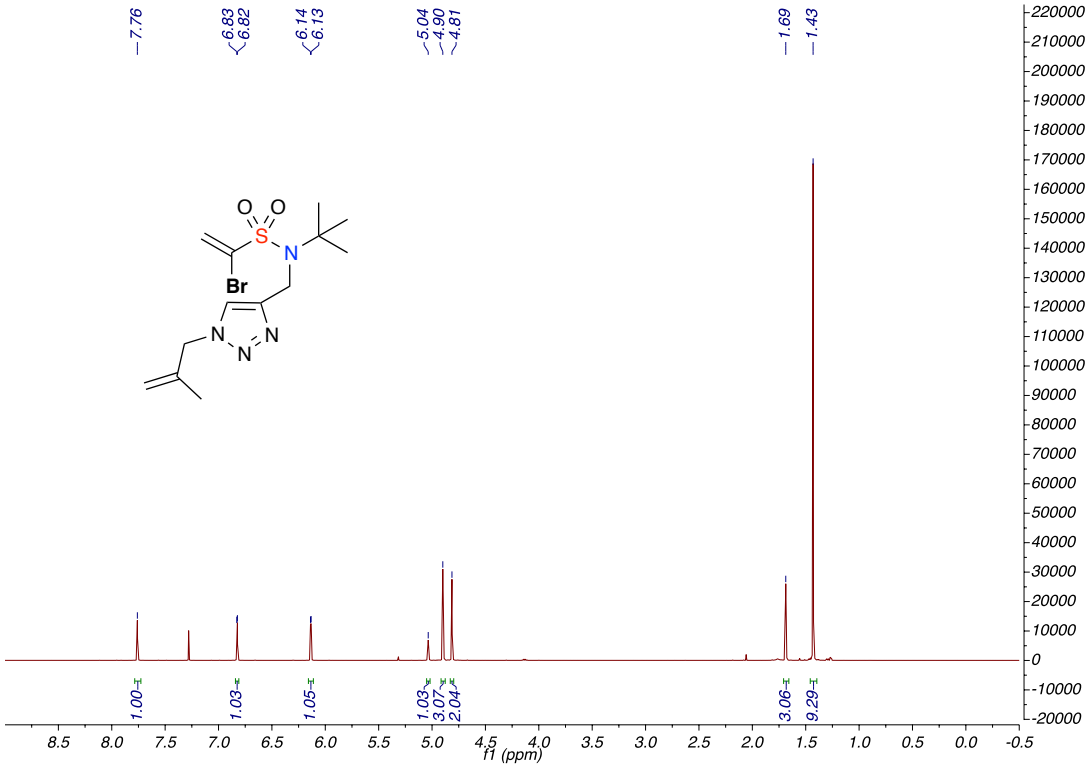


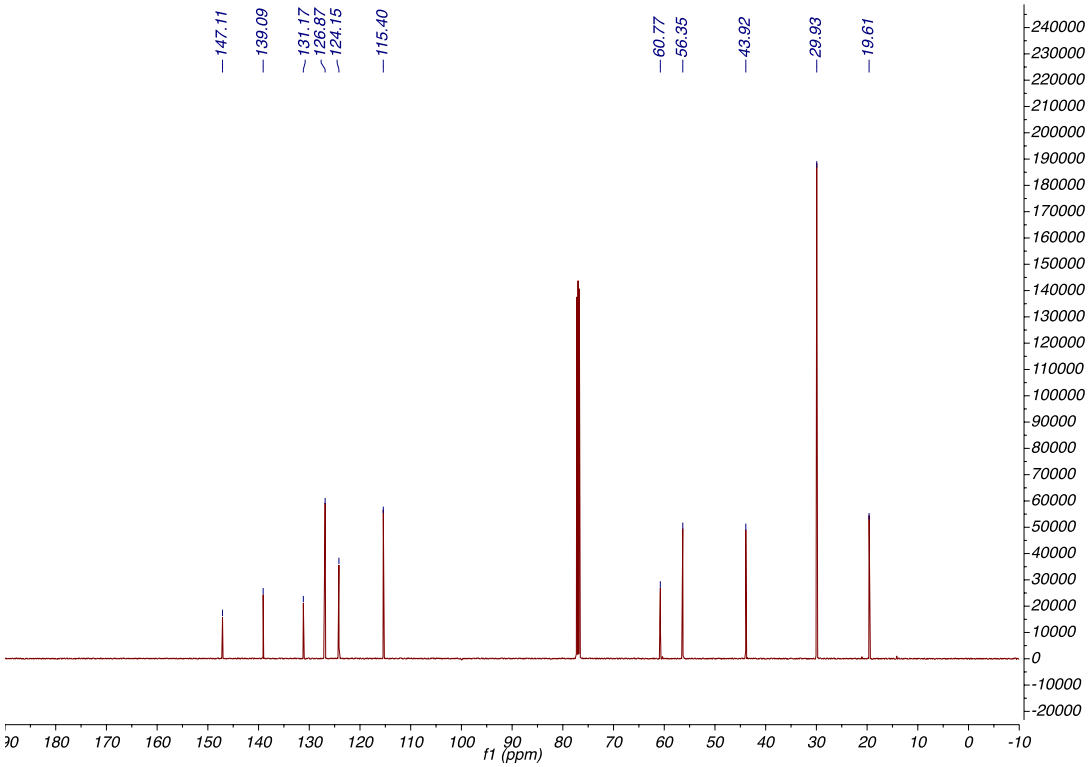


1-Bromo-*N*-(tert-butyl)-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide (2.4.2.2.16)

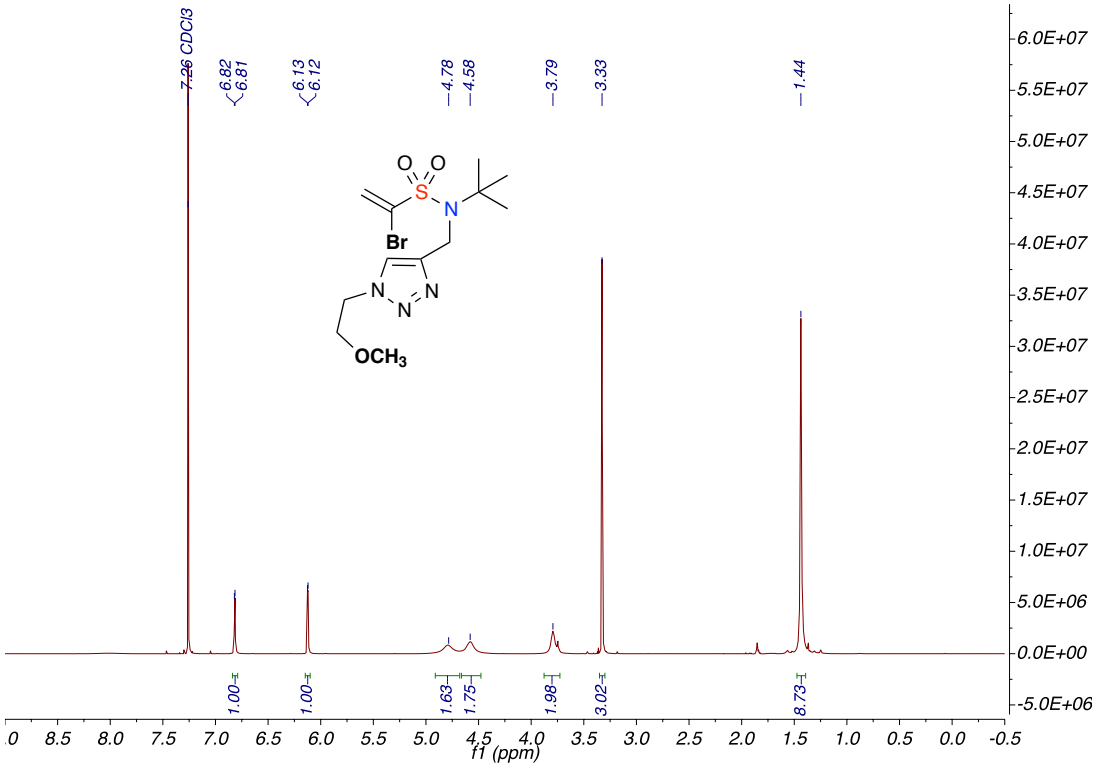


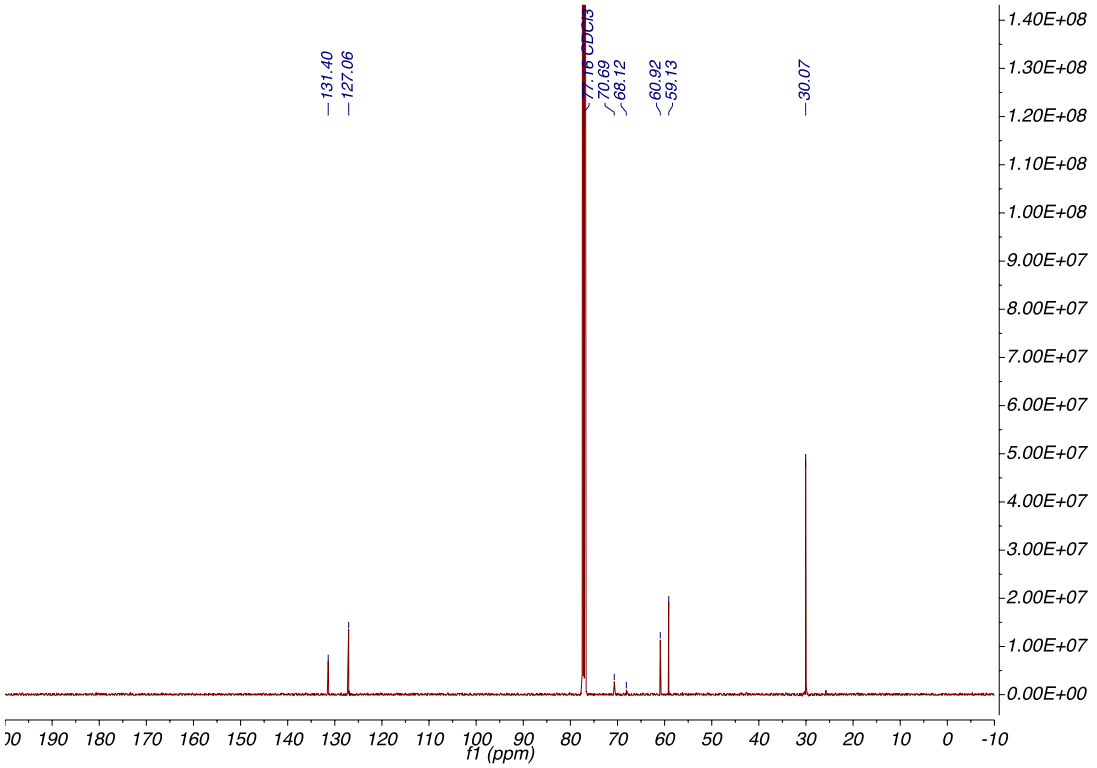
1-Bromo-*N*-(*tert*-butyl)-*N*-((1-(2-methylallyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.17)



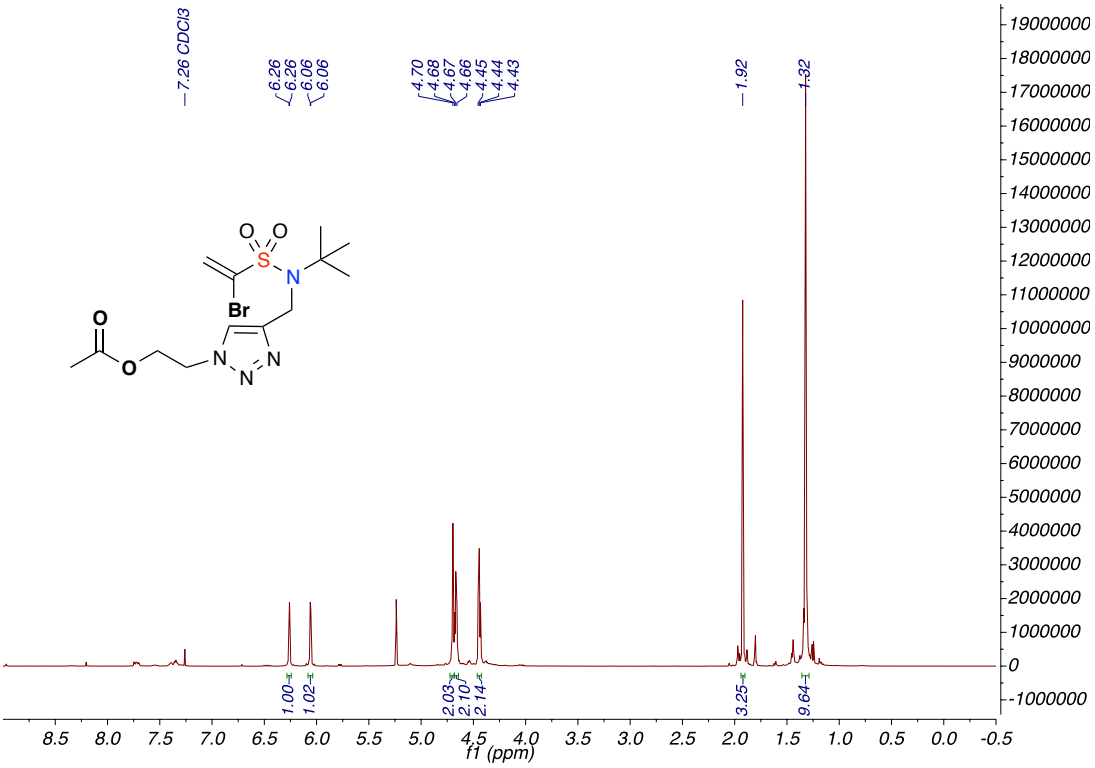


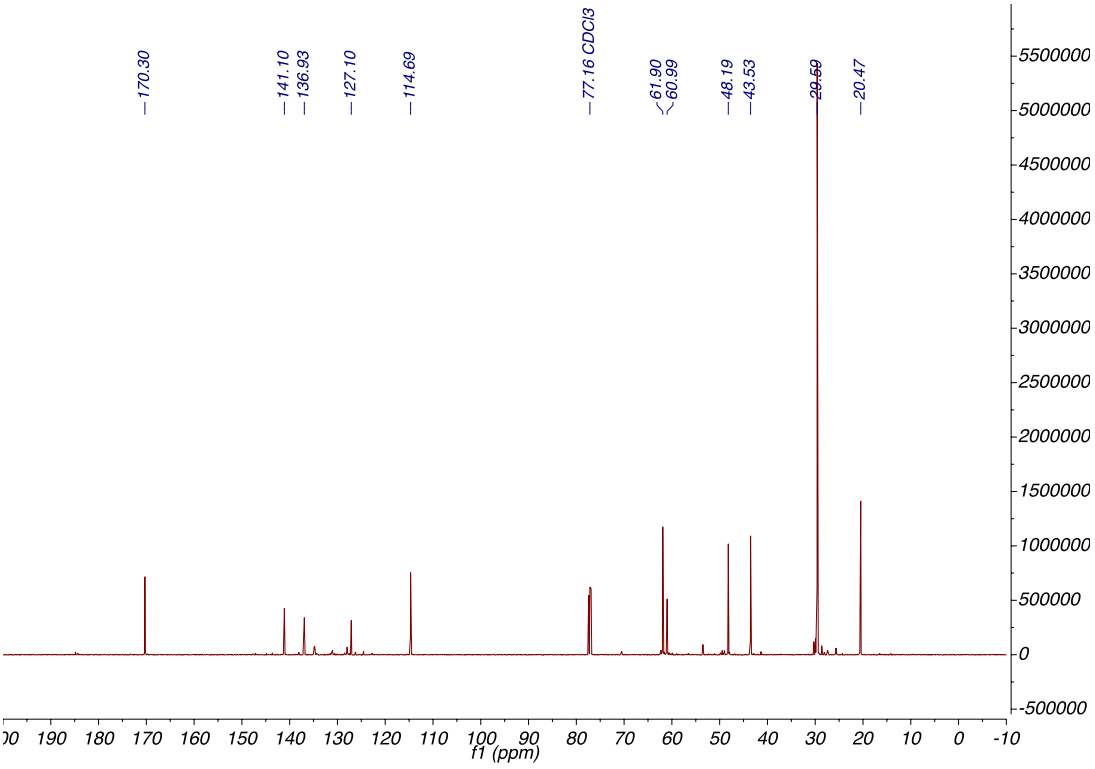
1-bromo-*N*-(*tert*-butyl)-*N*-((1-(2-methoxyethyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethene-1-sulfonamide (2.4.2.2.18)



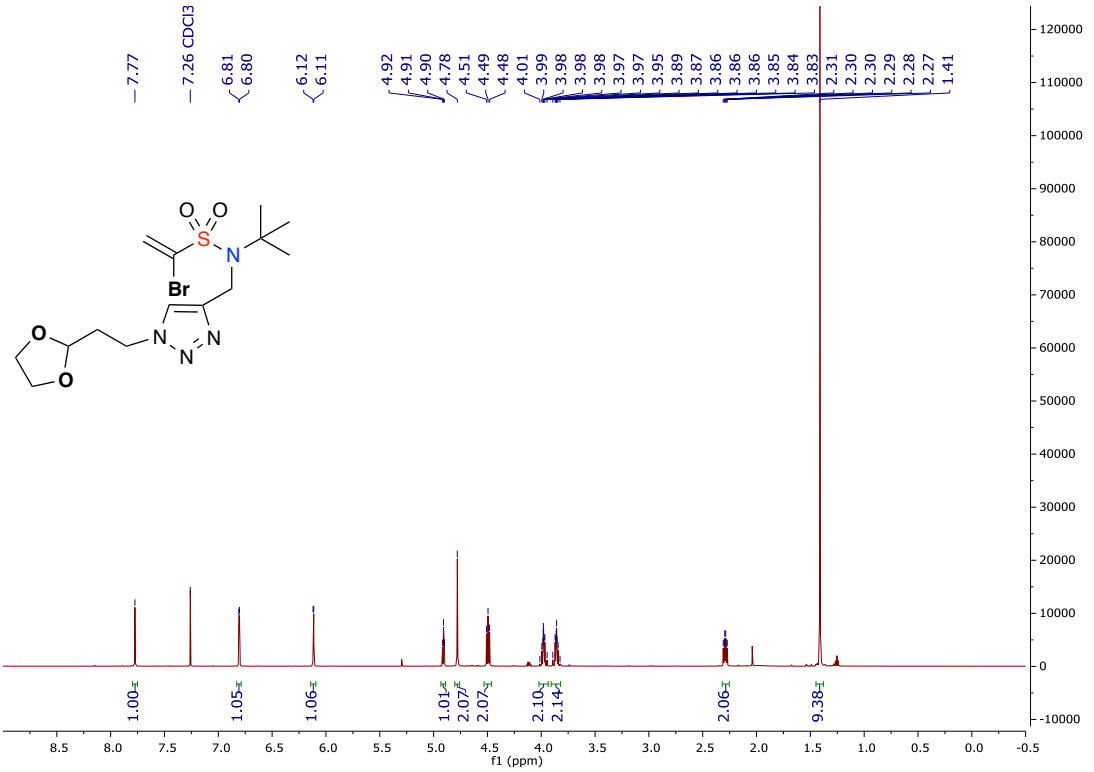


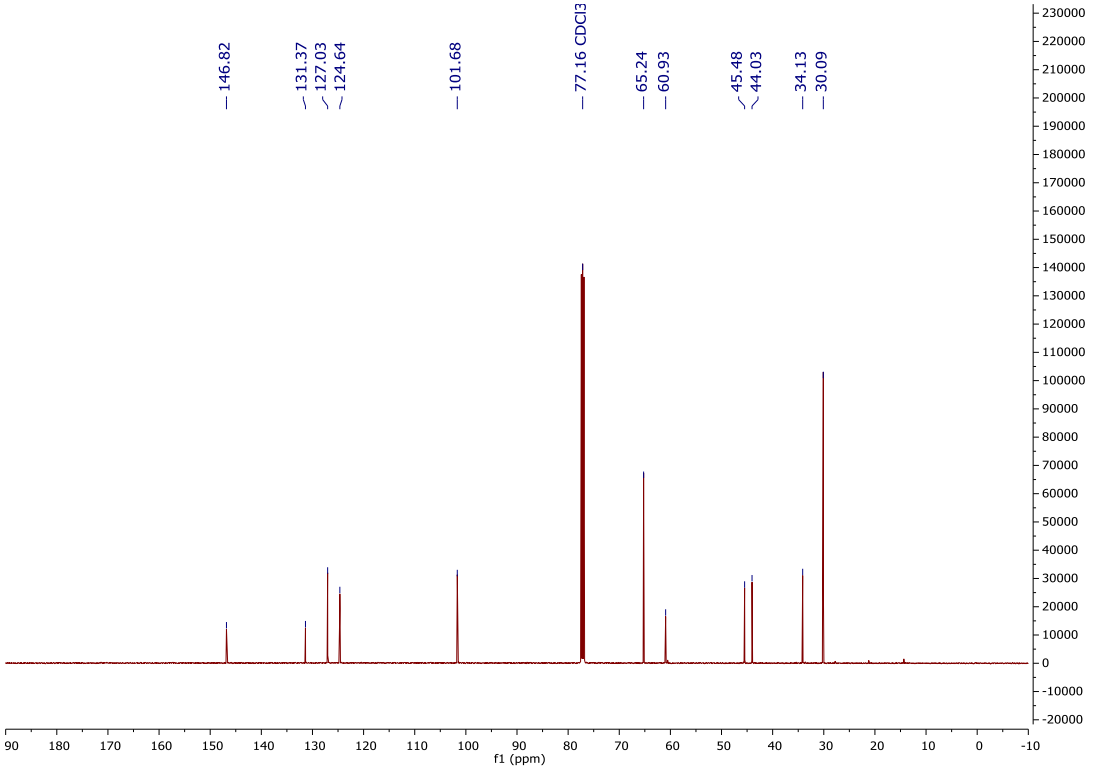
2-(4-((1-bromo-*N*-(*tert*-butyl)vinylsulfonamido)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl acetate (2.4.2.2.19)



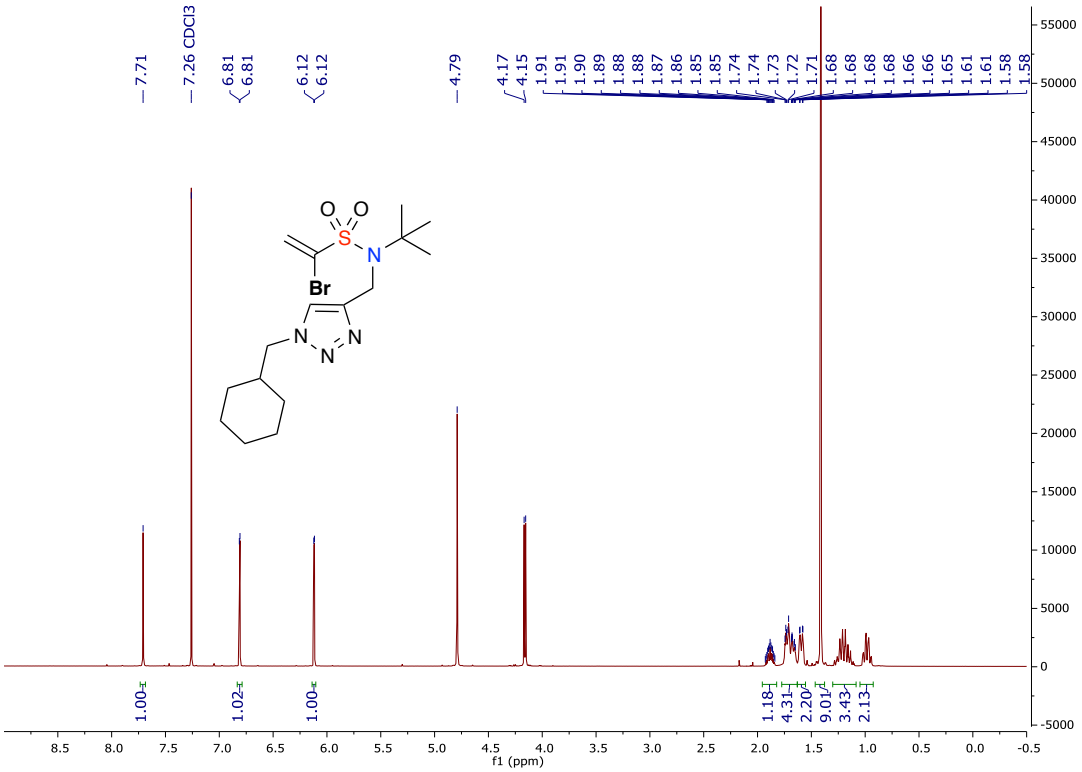


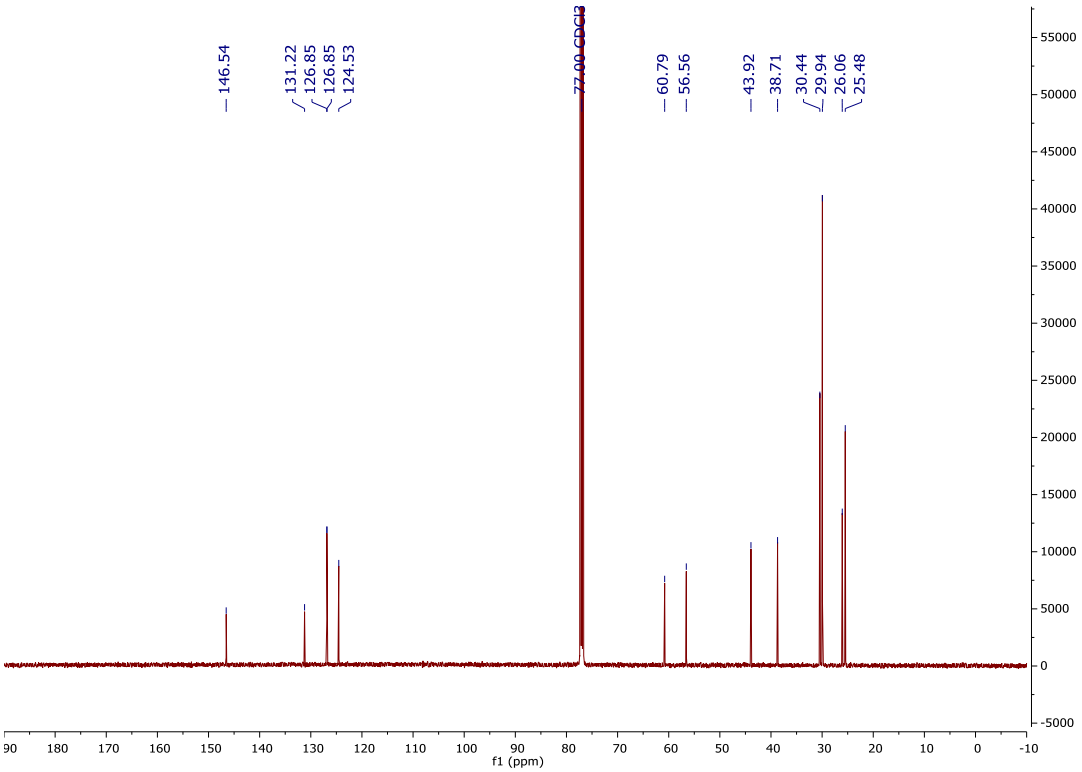
_N_-((1-(2-(1,3-dioxolan-2-yl)ethyl)-1_H_-1,2,3-triazol-4-yl)methyl)-1-bromo-_N_-(_tert_-butyl)ethenesulfonamide (2.4.2.2.20)



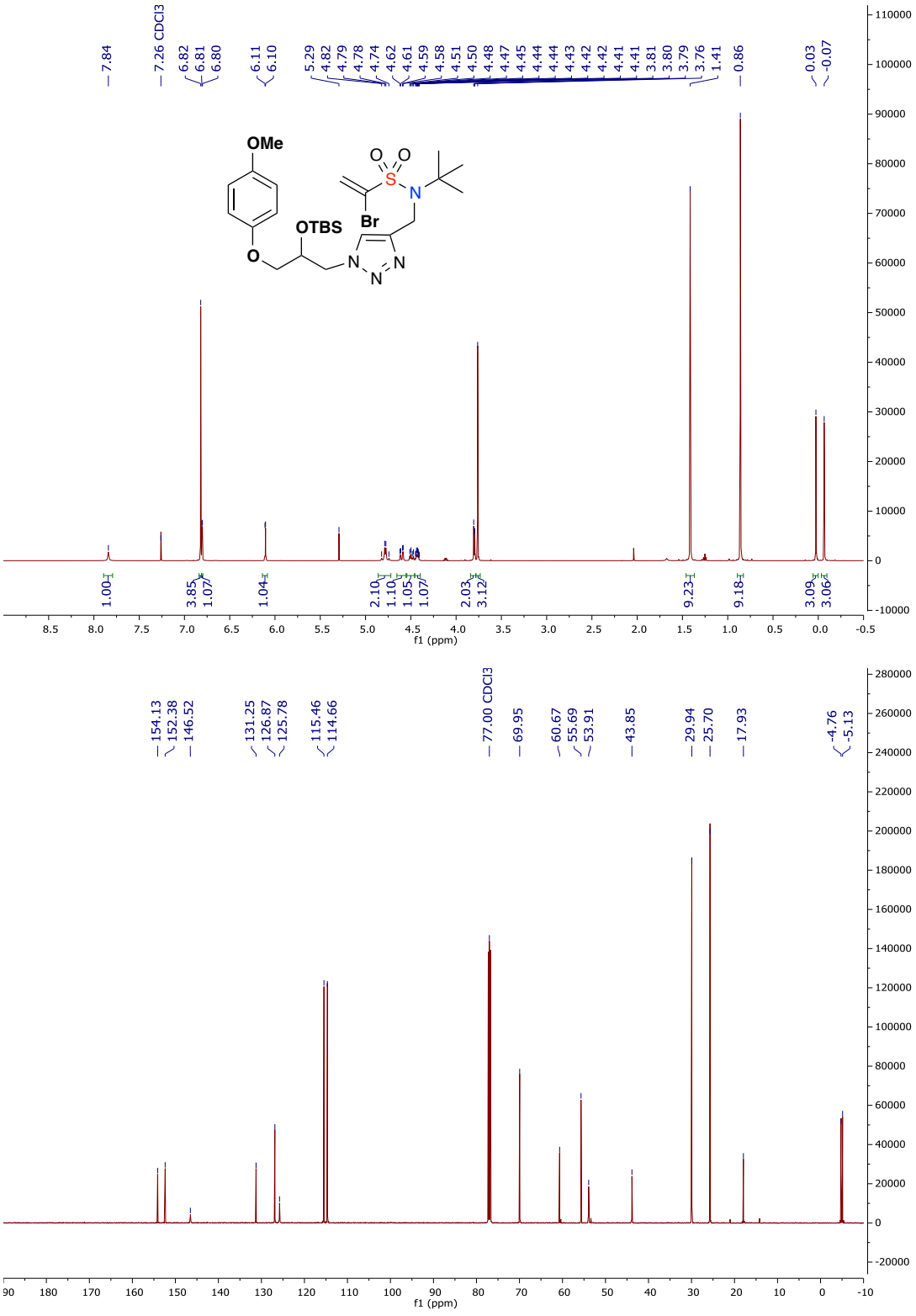


1-Bromo-*N*-(*tert*-butyl)-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.21)

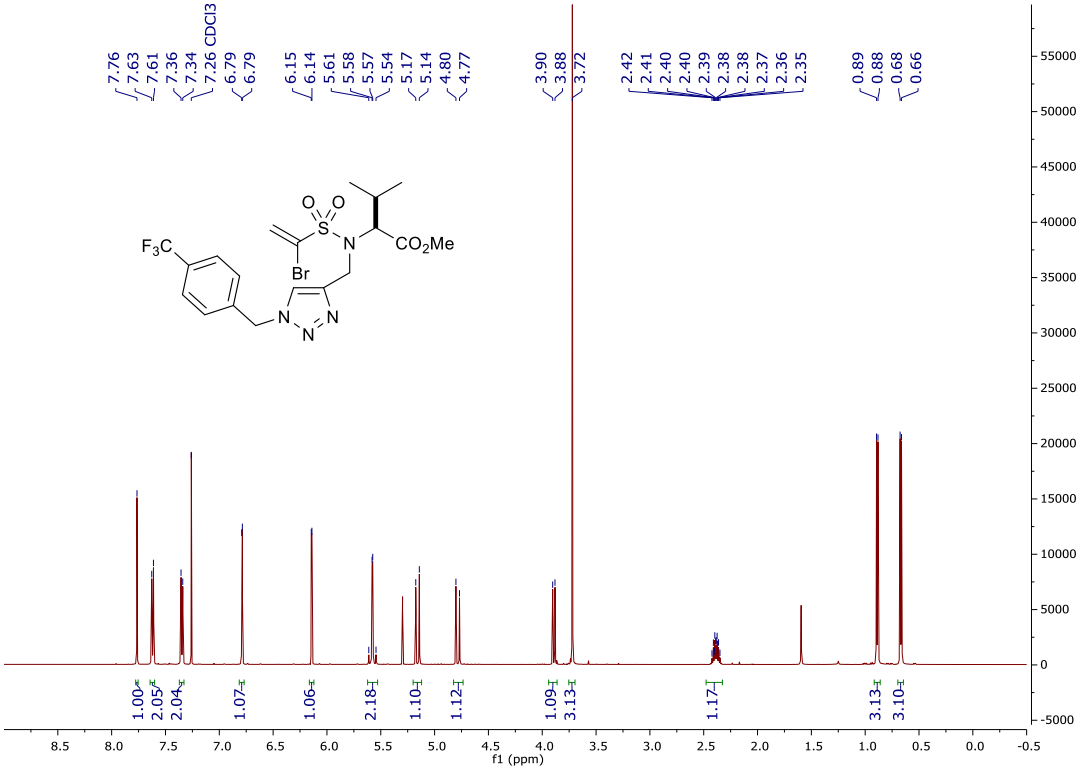


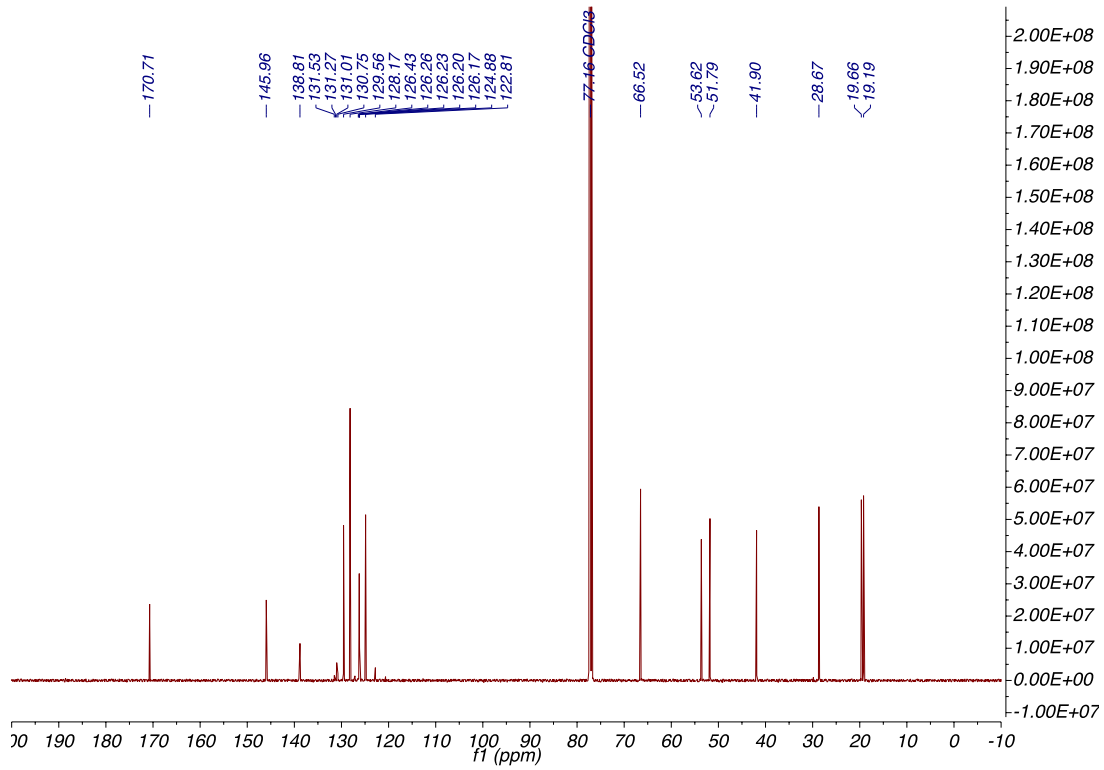


1-Bromo-*N*-(*tert*-butyl)-*N*-((1-(2-((*tert*-butyldimethylsilyl)oxy)-3-(4-methoxyphenoxy)propyl)-1*H*-1,2,3-triazol-4-yl)methyl)ethenesulfonamide (2.4.2.2.22)

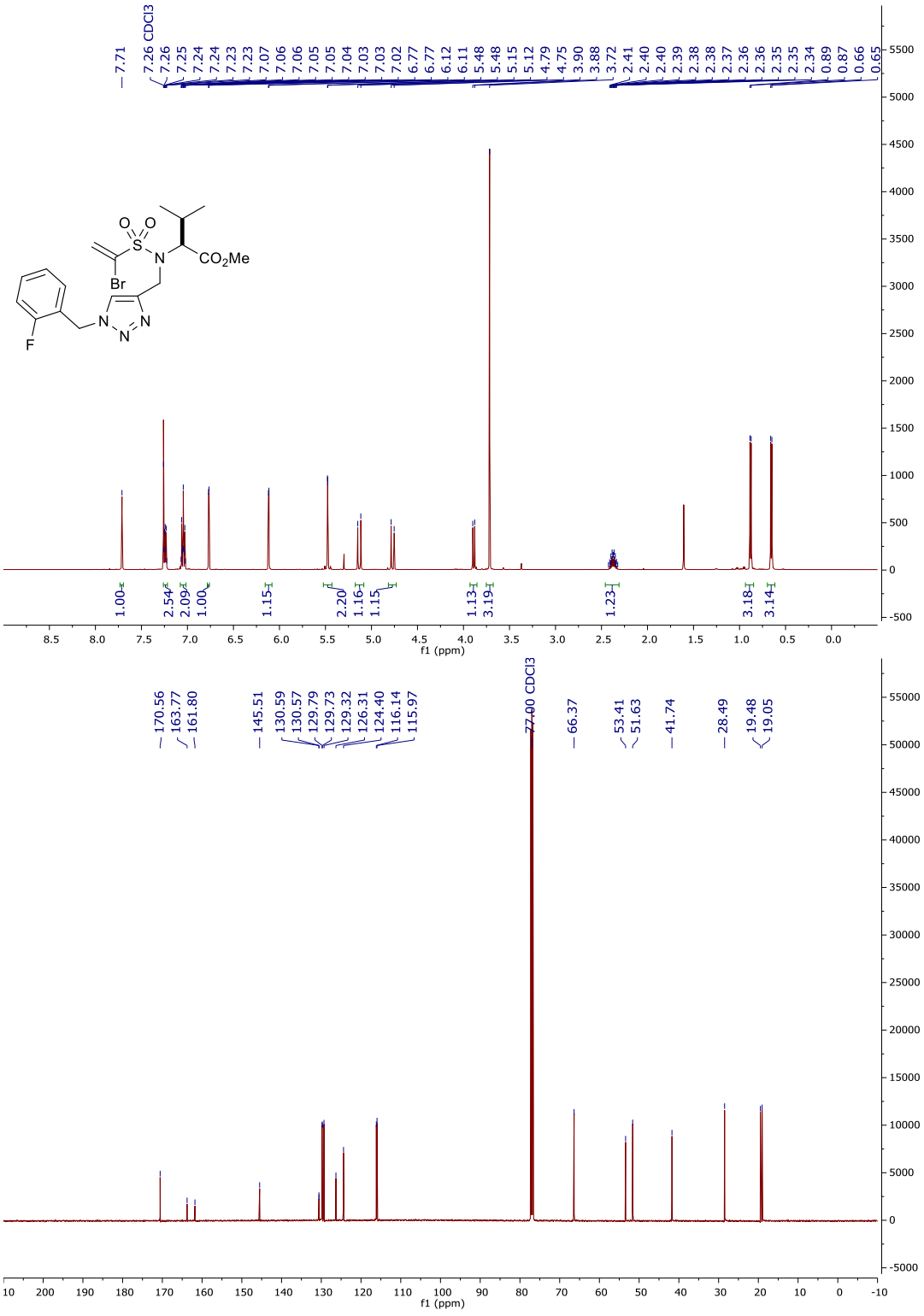


Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-valinate (2.4.2.2.23)

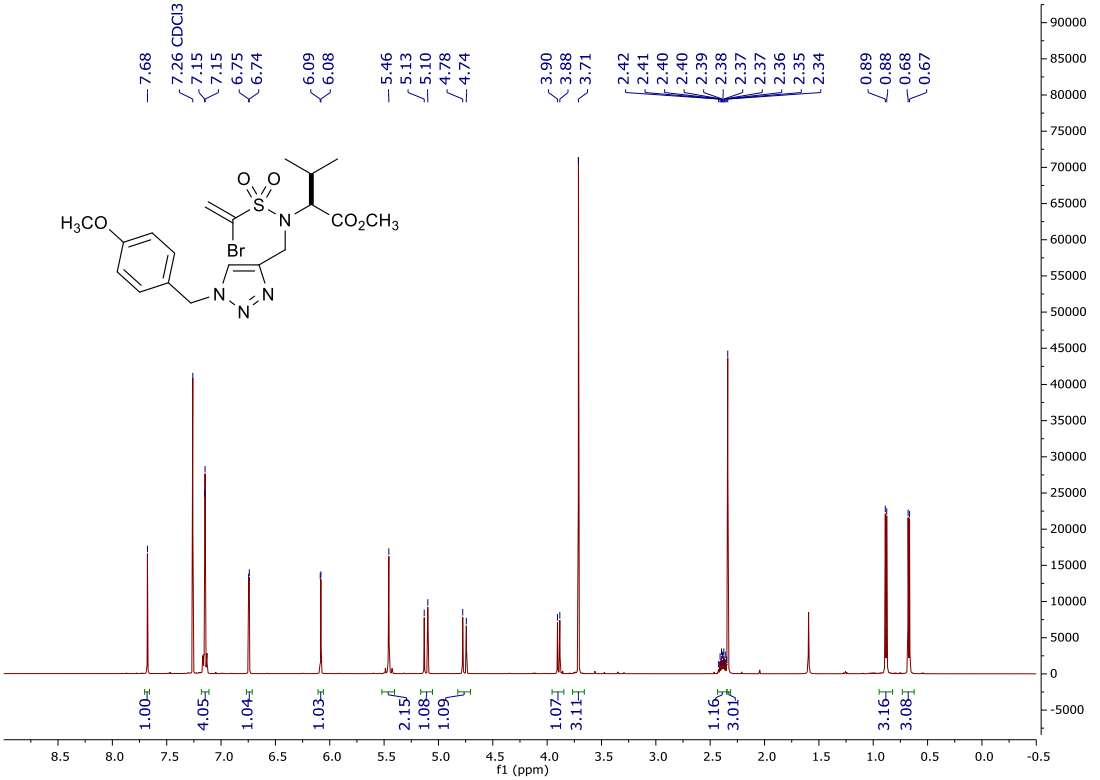


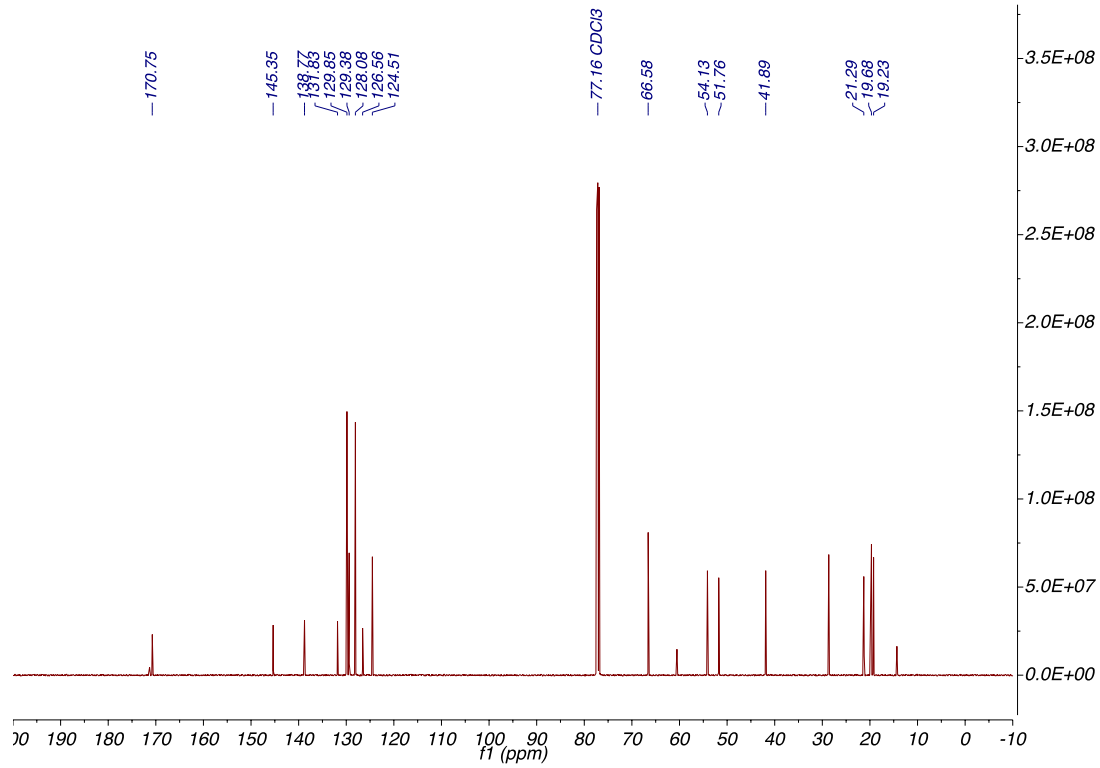


Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-valinate (2.4.2.2.24)

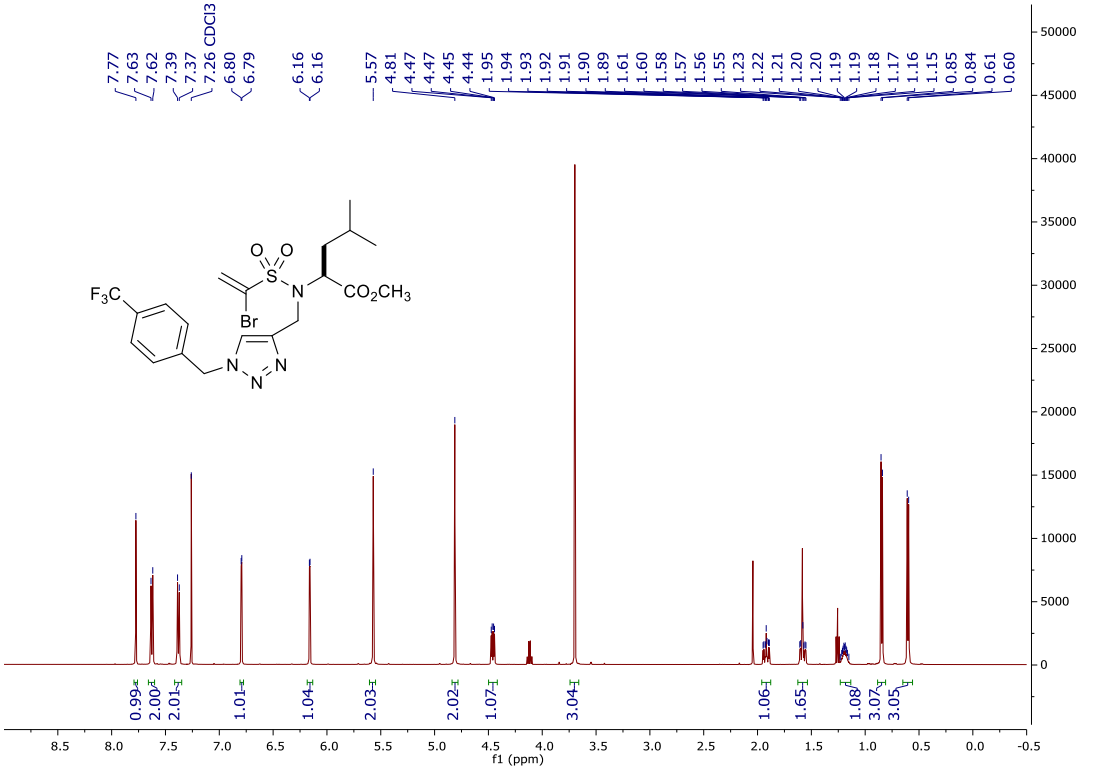


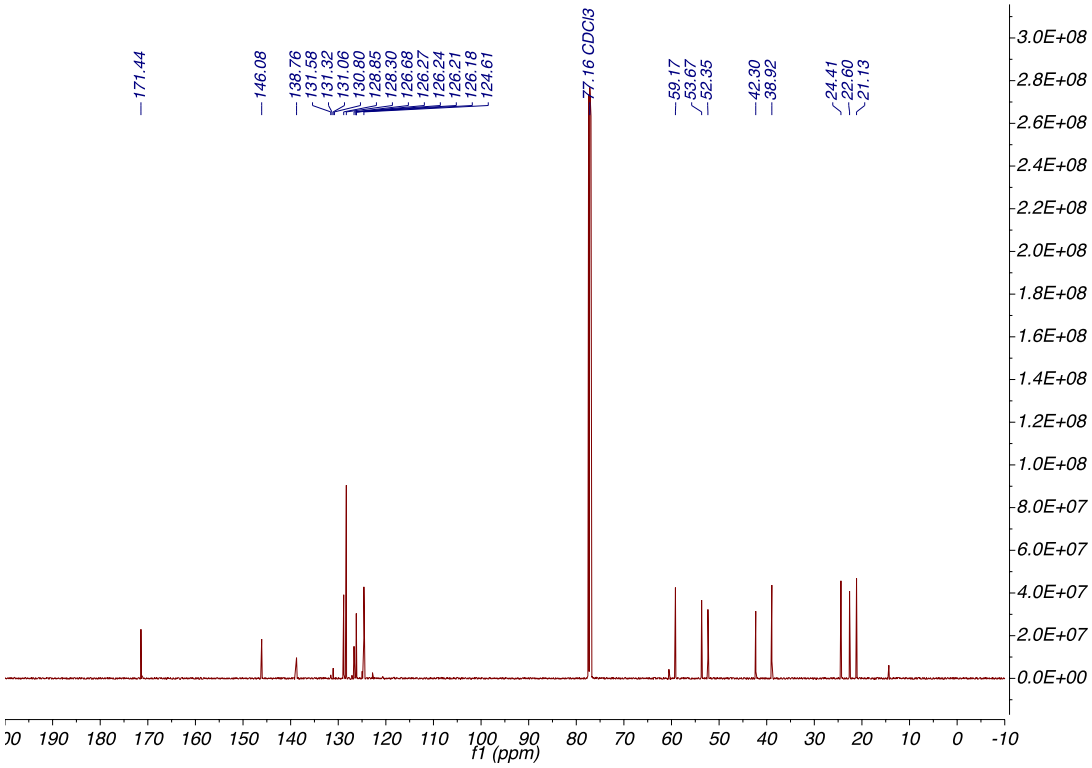
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-valinate (2.4.2.2.25)



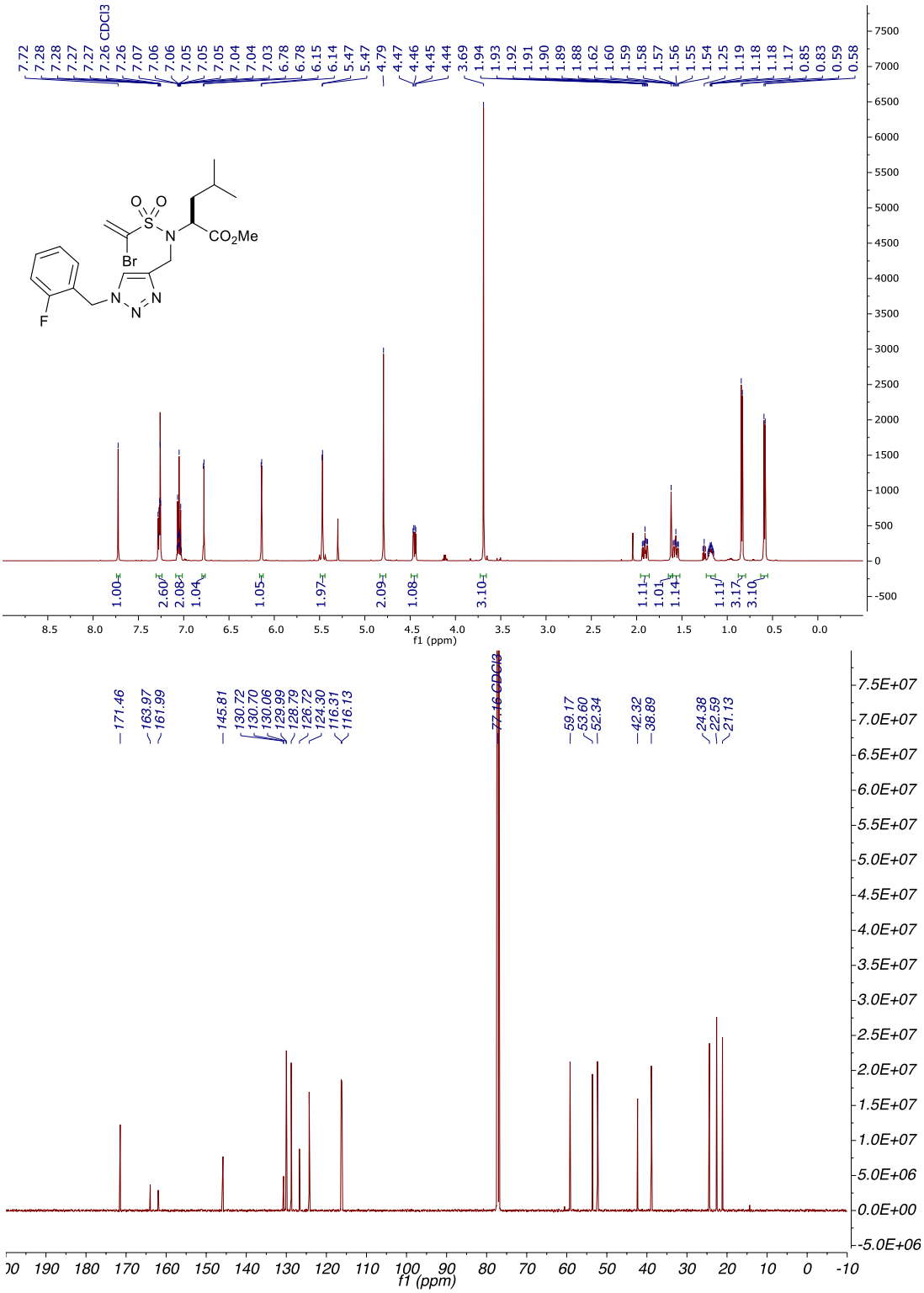


Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-leucinate (2.4.2.2.26)

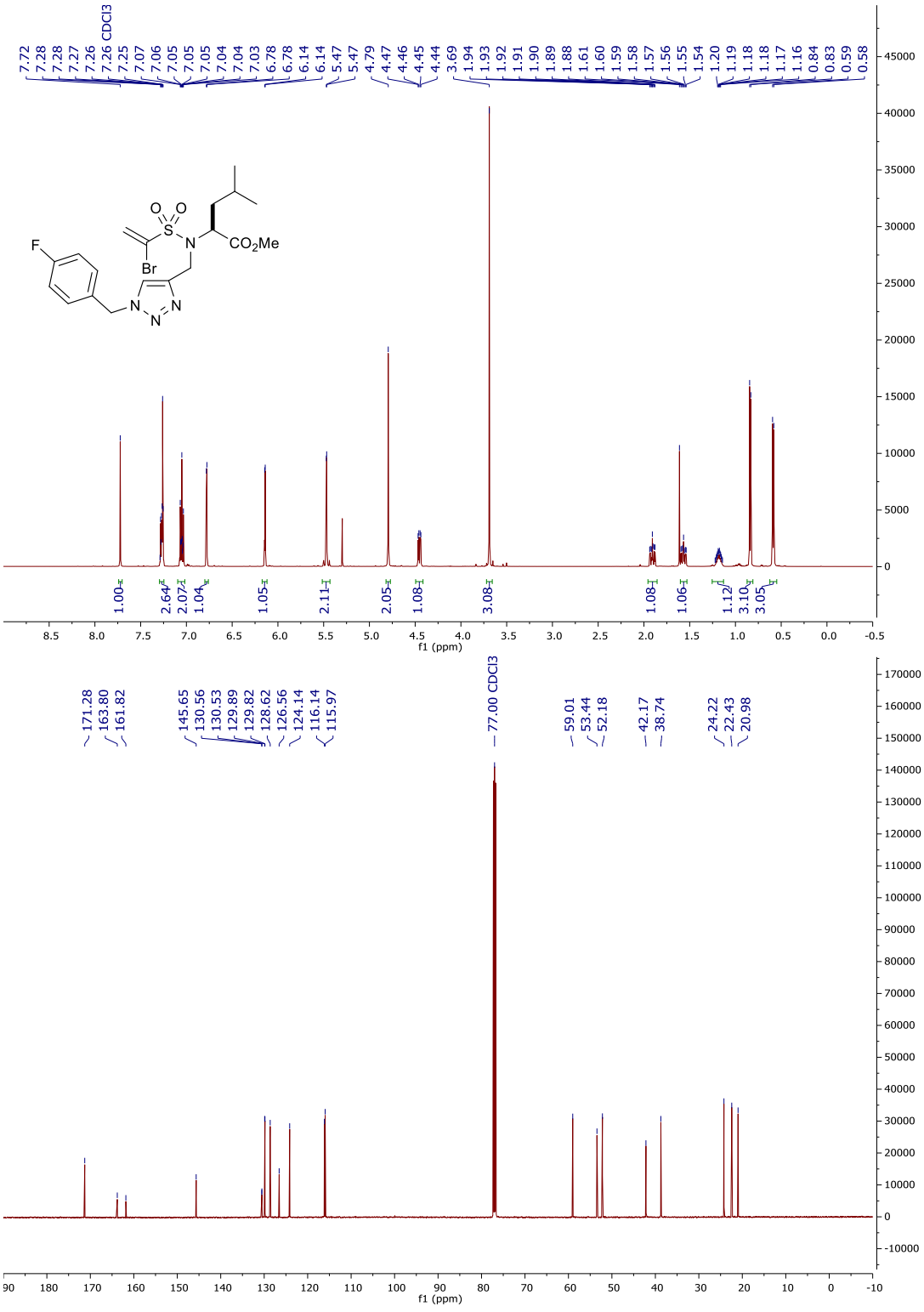




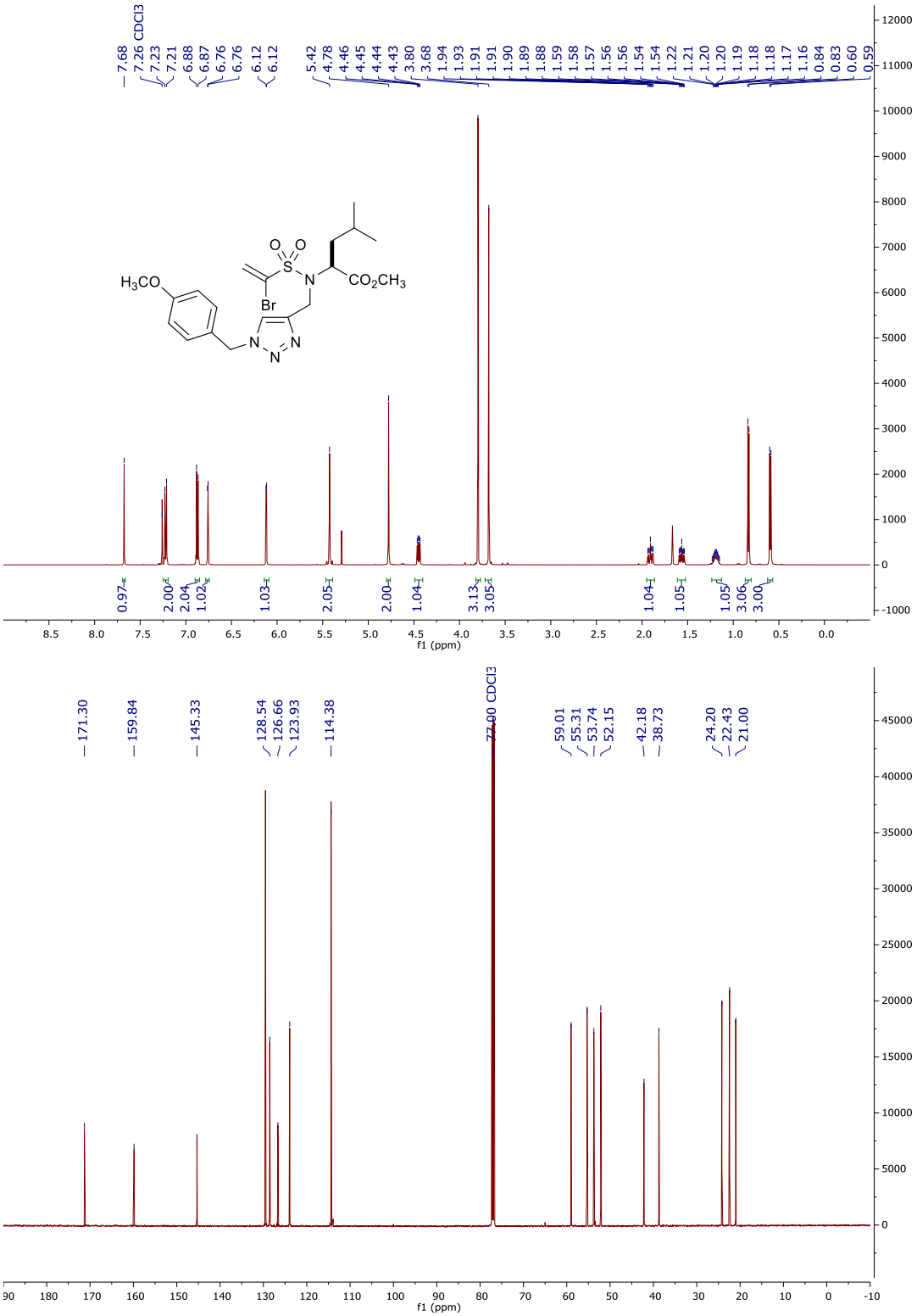
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-leucinate (2.4.2.2.27)



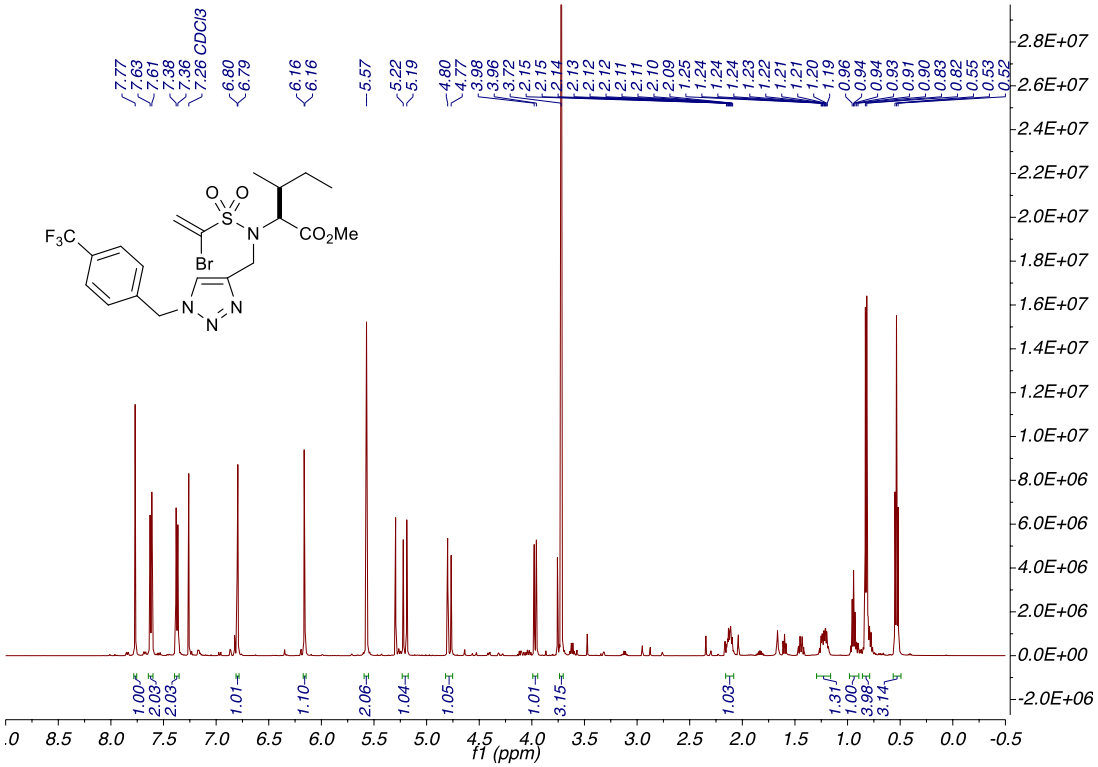
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-leucinate (2.4.2.2.28)

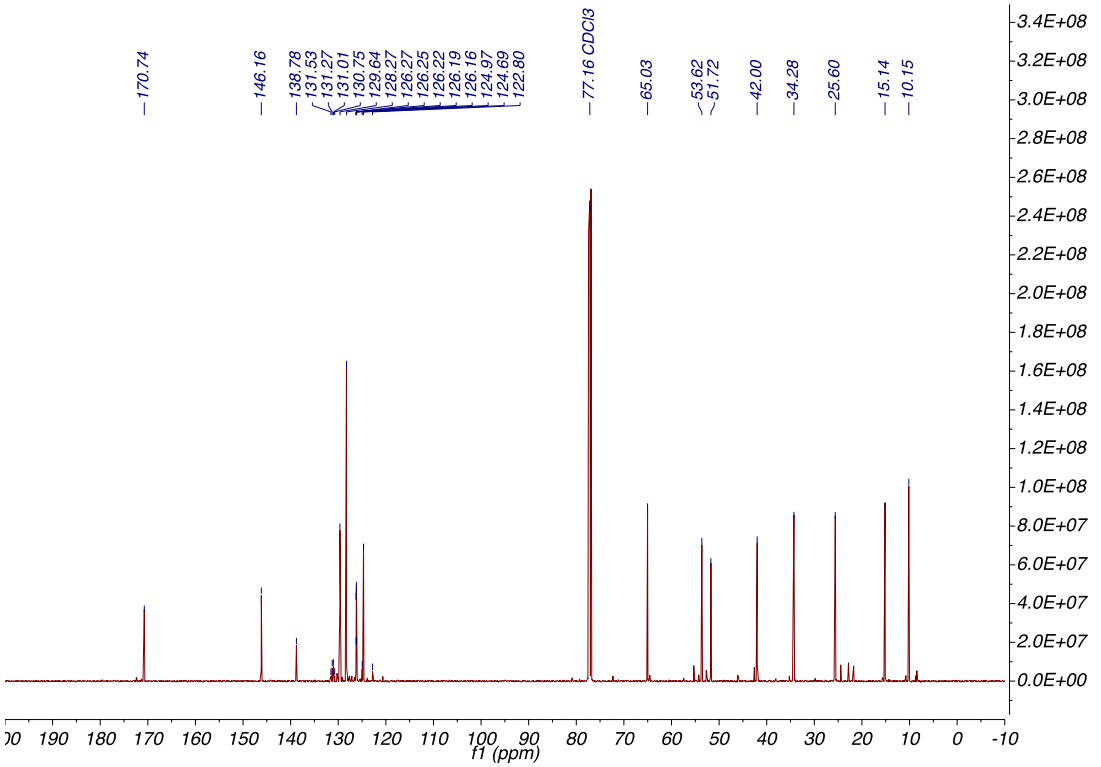


Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-leucinate (2.4.2.2.29)

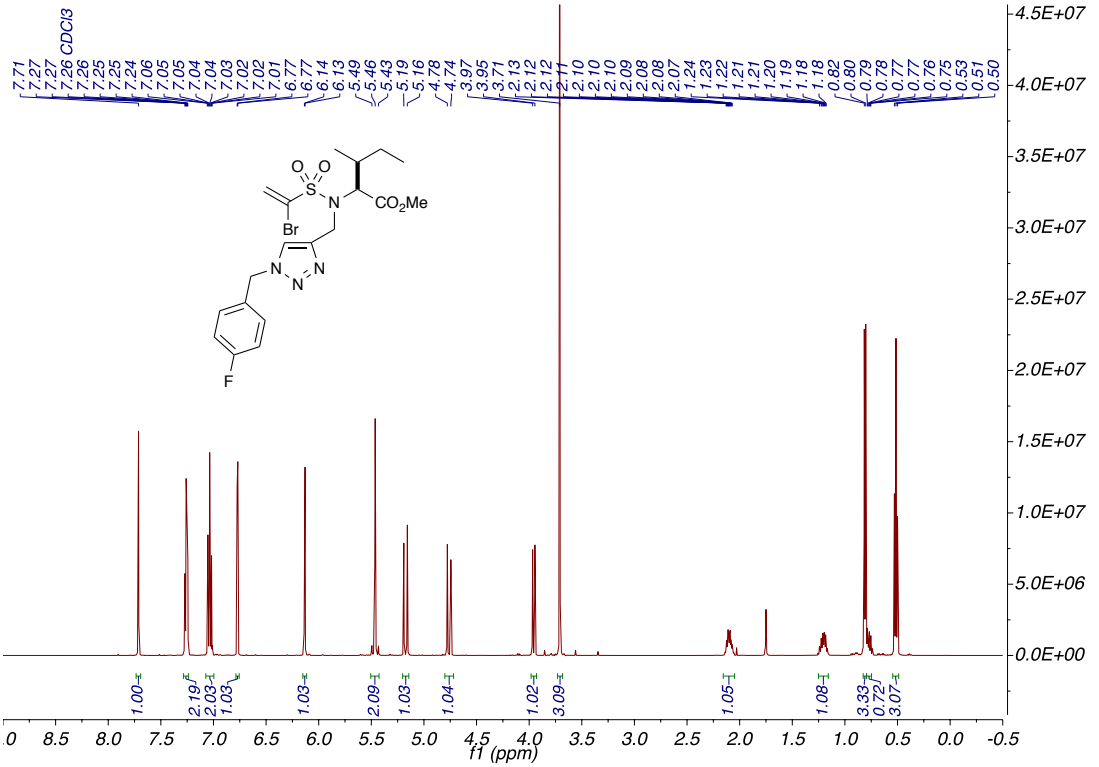


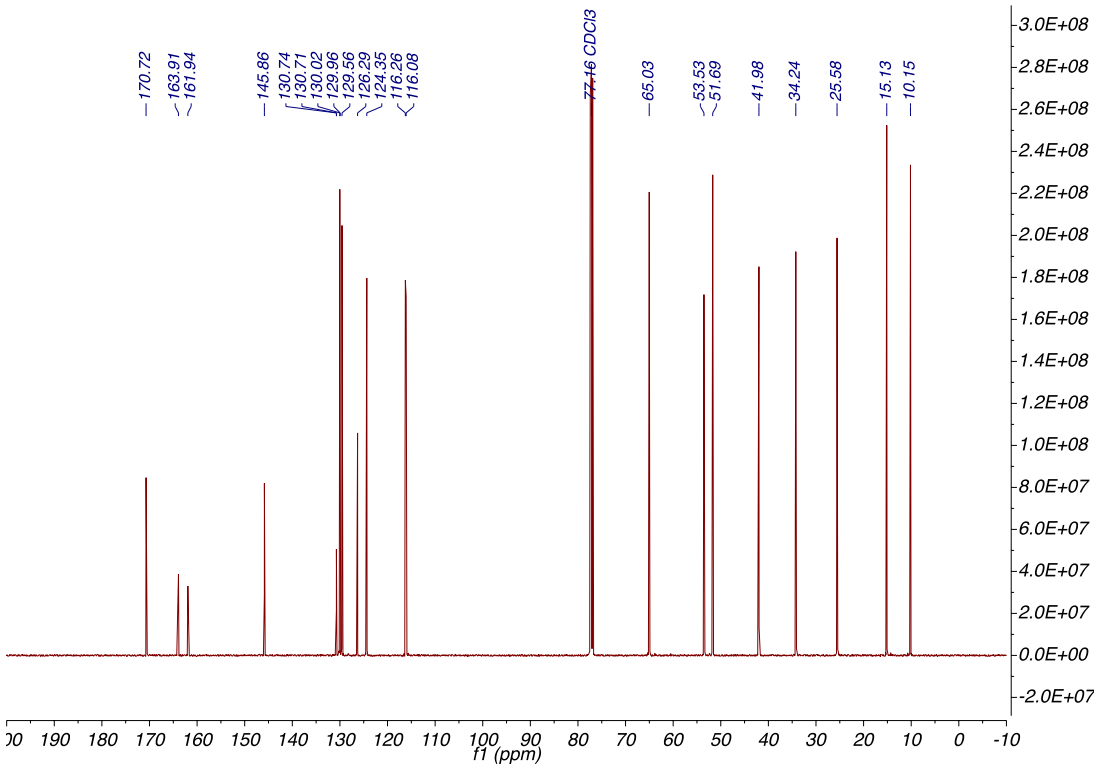
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-isoleucinate (2.4.2.2.30)



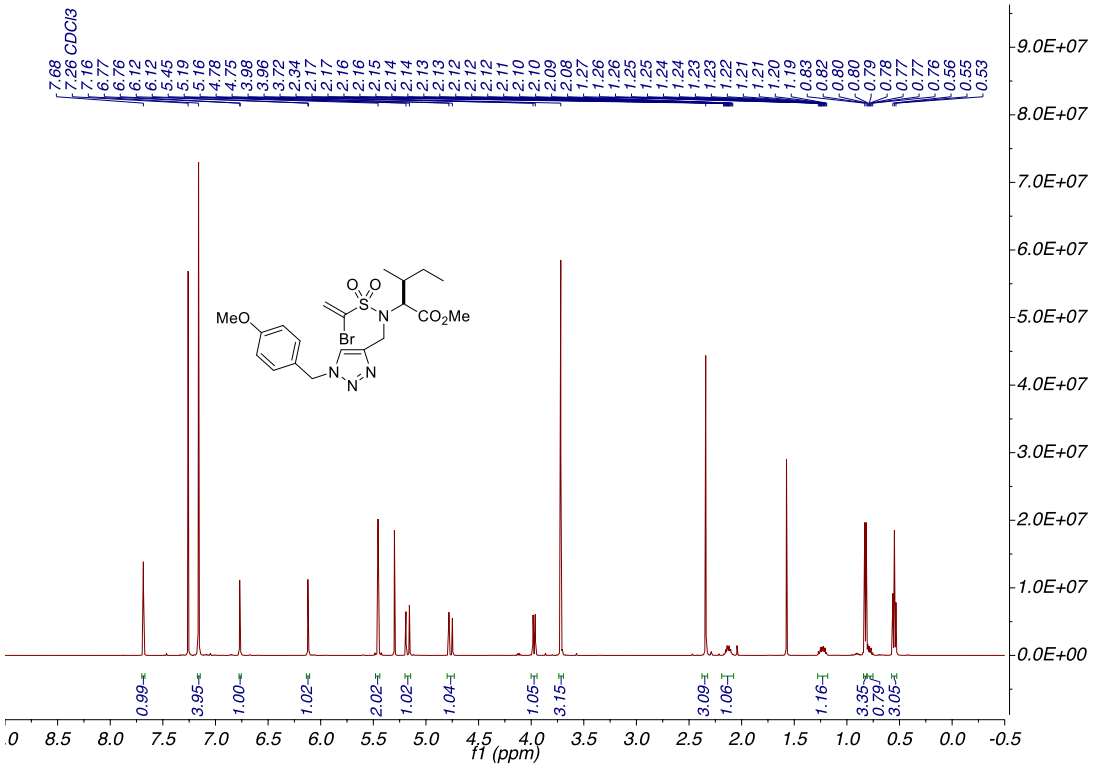


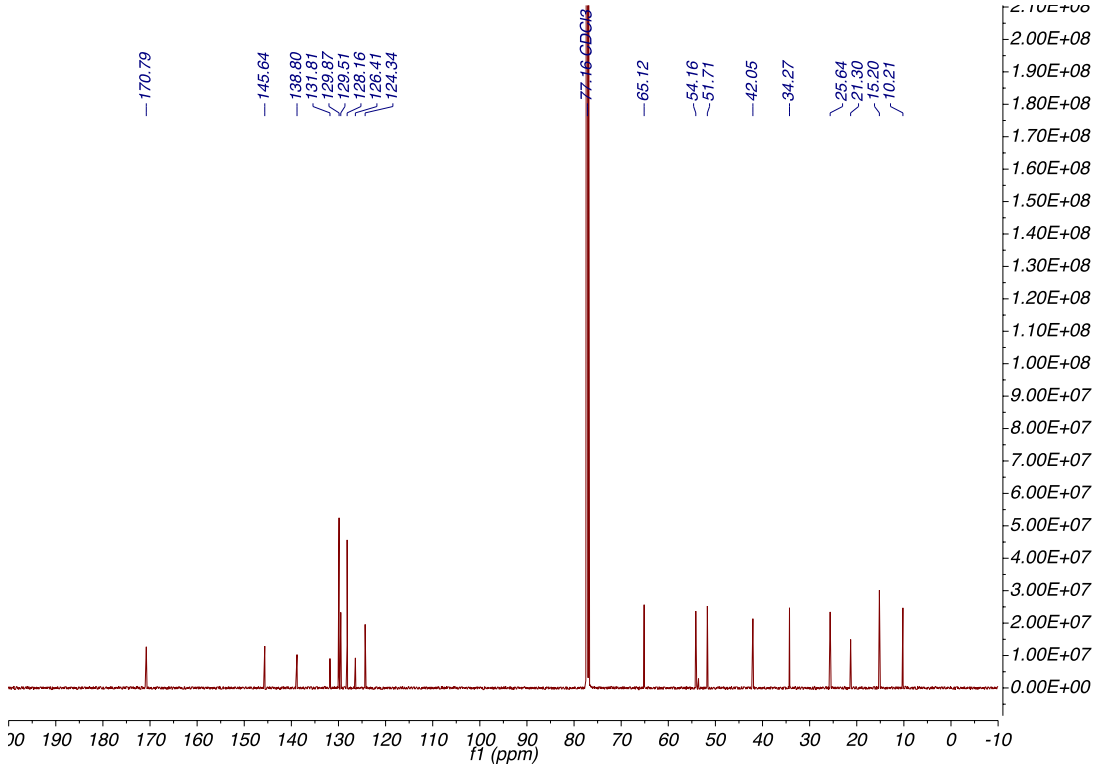
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-isoleucinate (2.4.2.2.31)



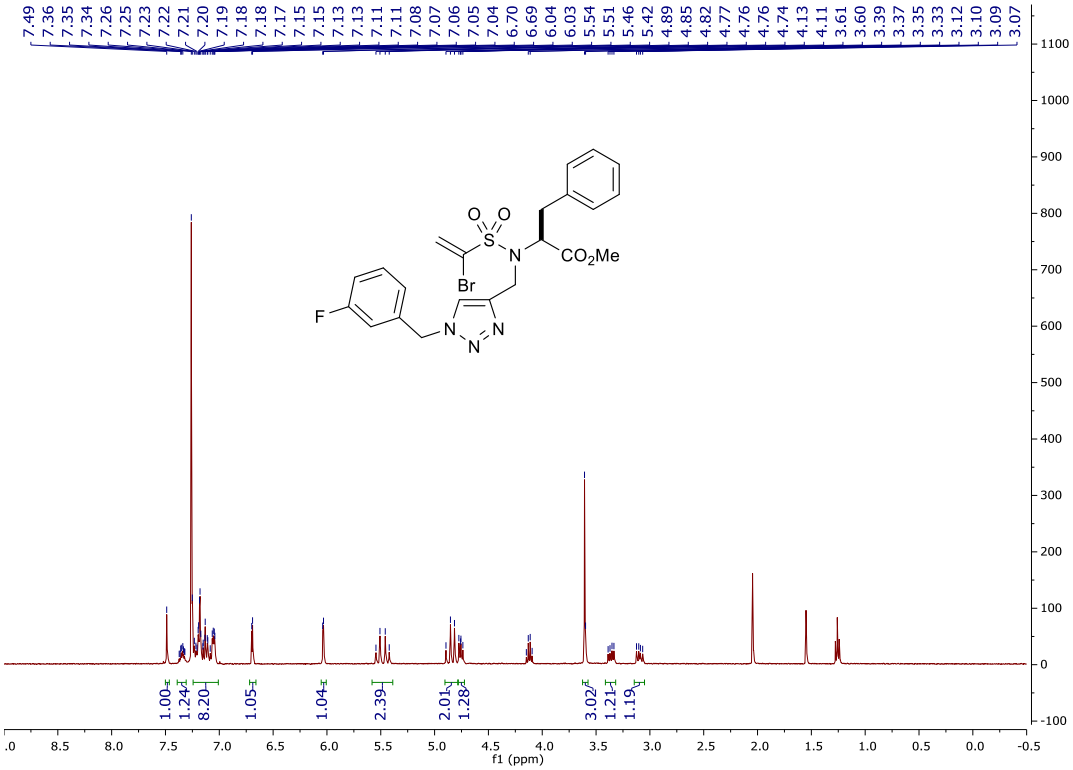


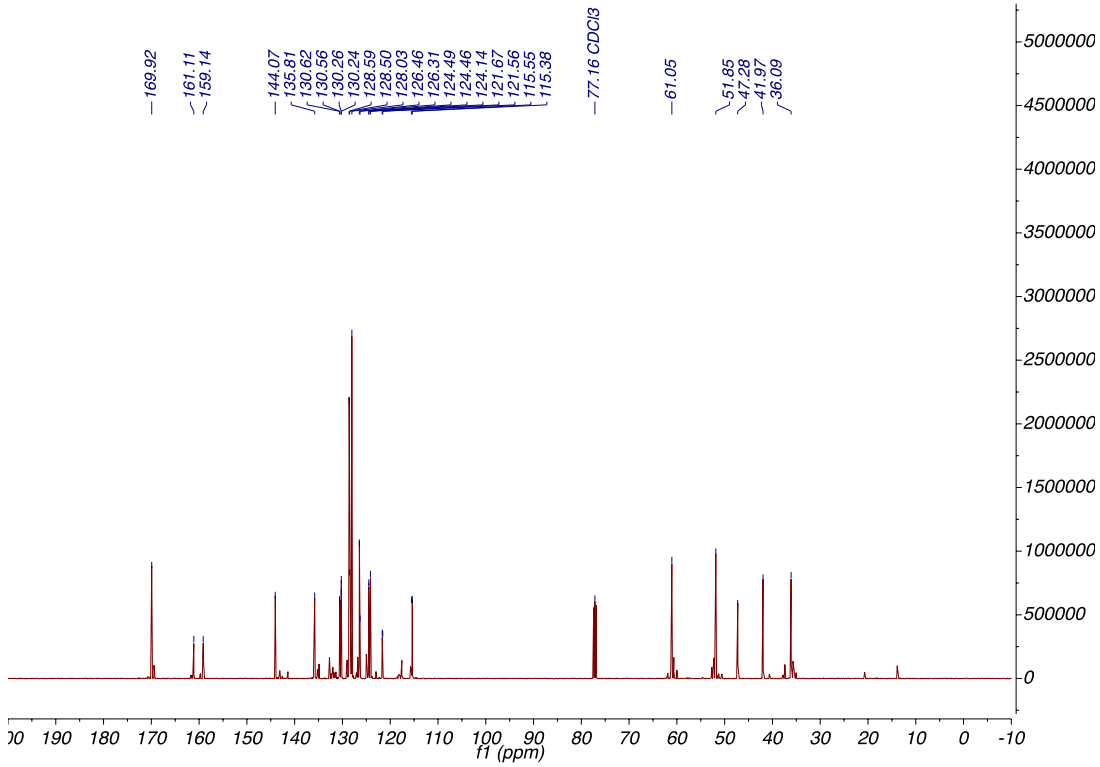
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-isoleucinate (2.4.2.2.32)



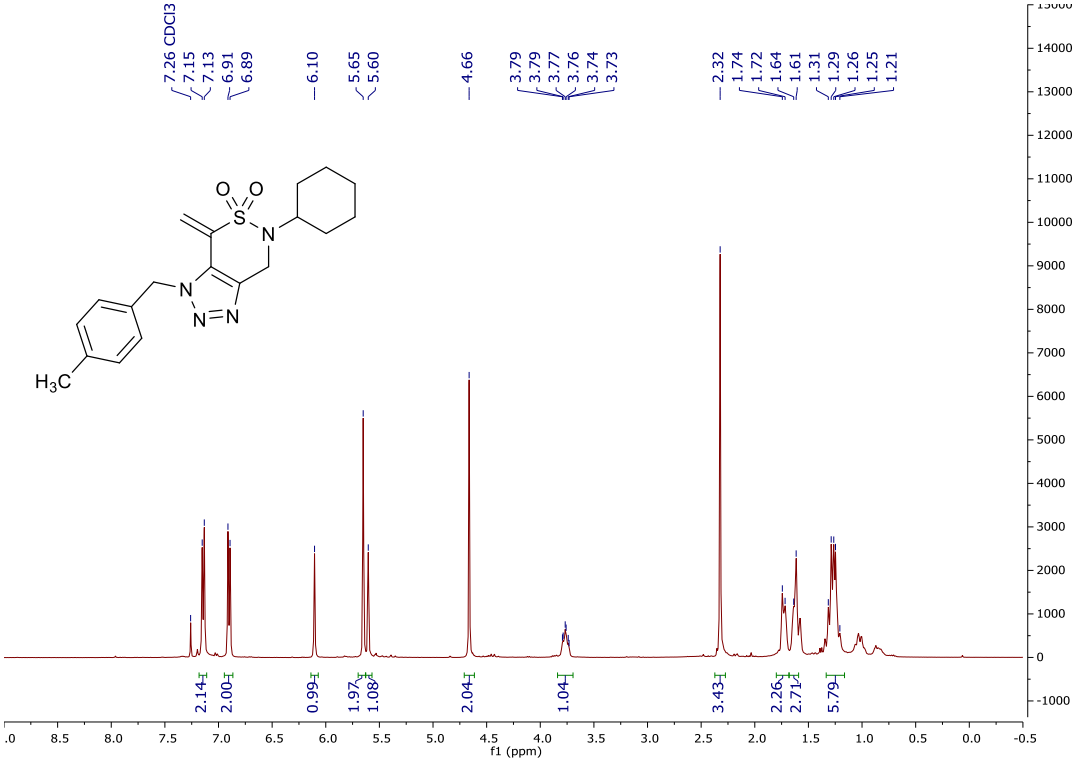


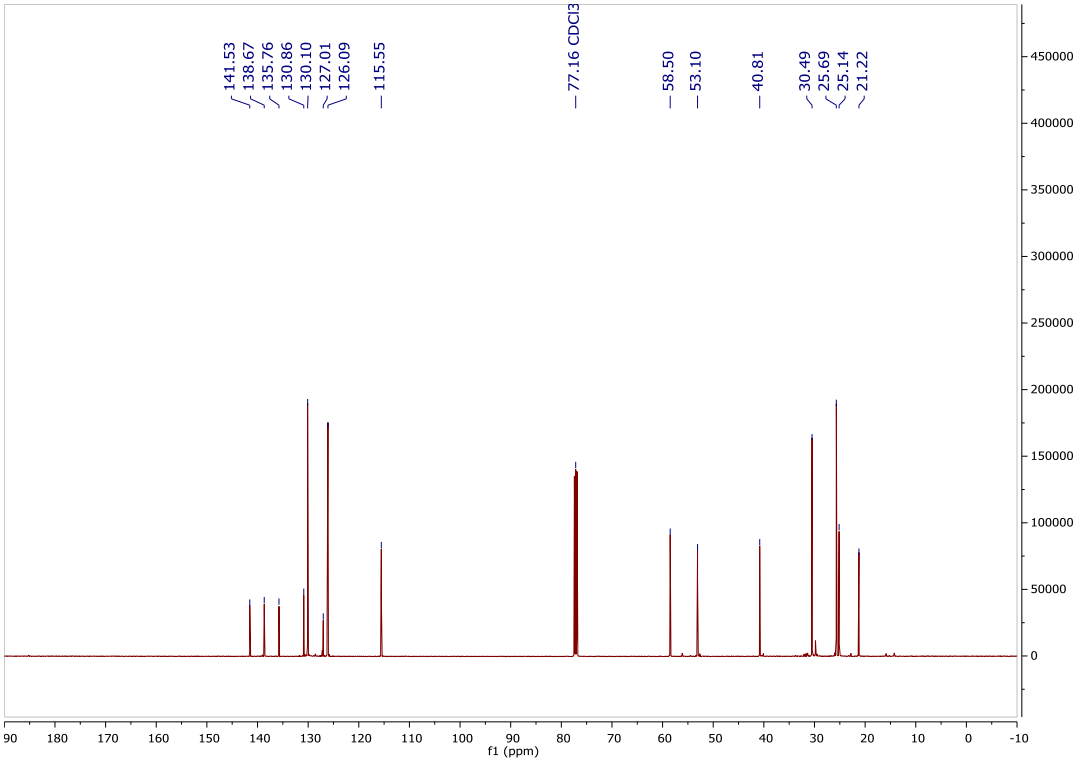
Methyl *N*-((1-bromovinyl)sulfonyl)-*N*-((1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-*L*-phenylalaninate (2.4.2.2.33)



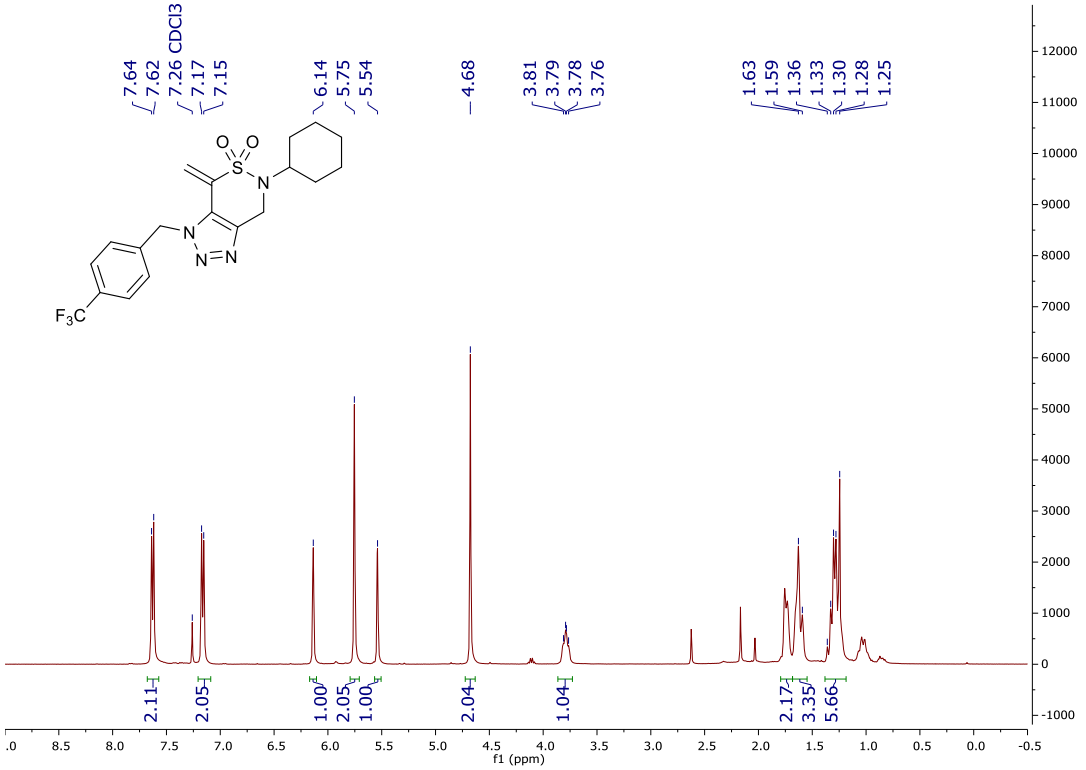


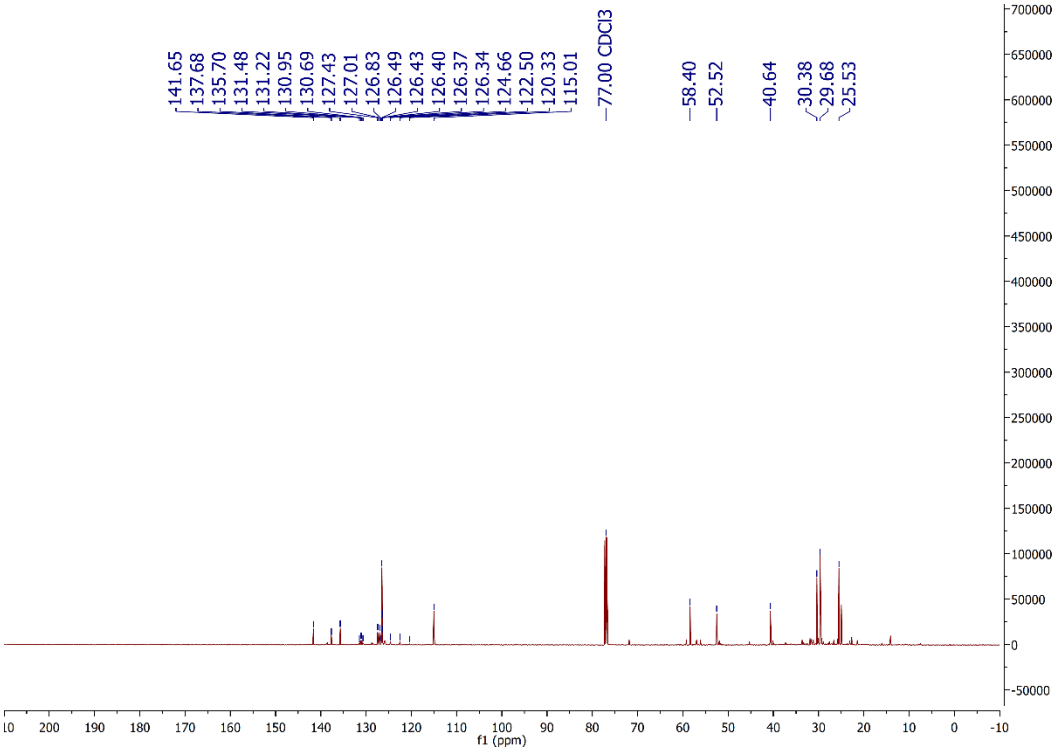
6-Cyclohexyl-3-(4-methylbenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.1)



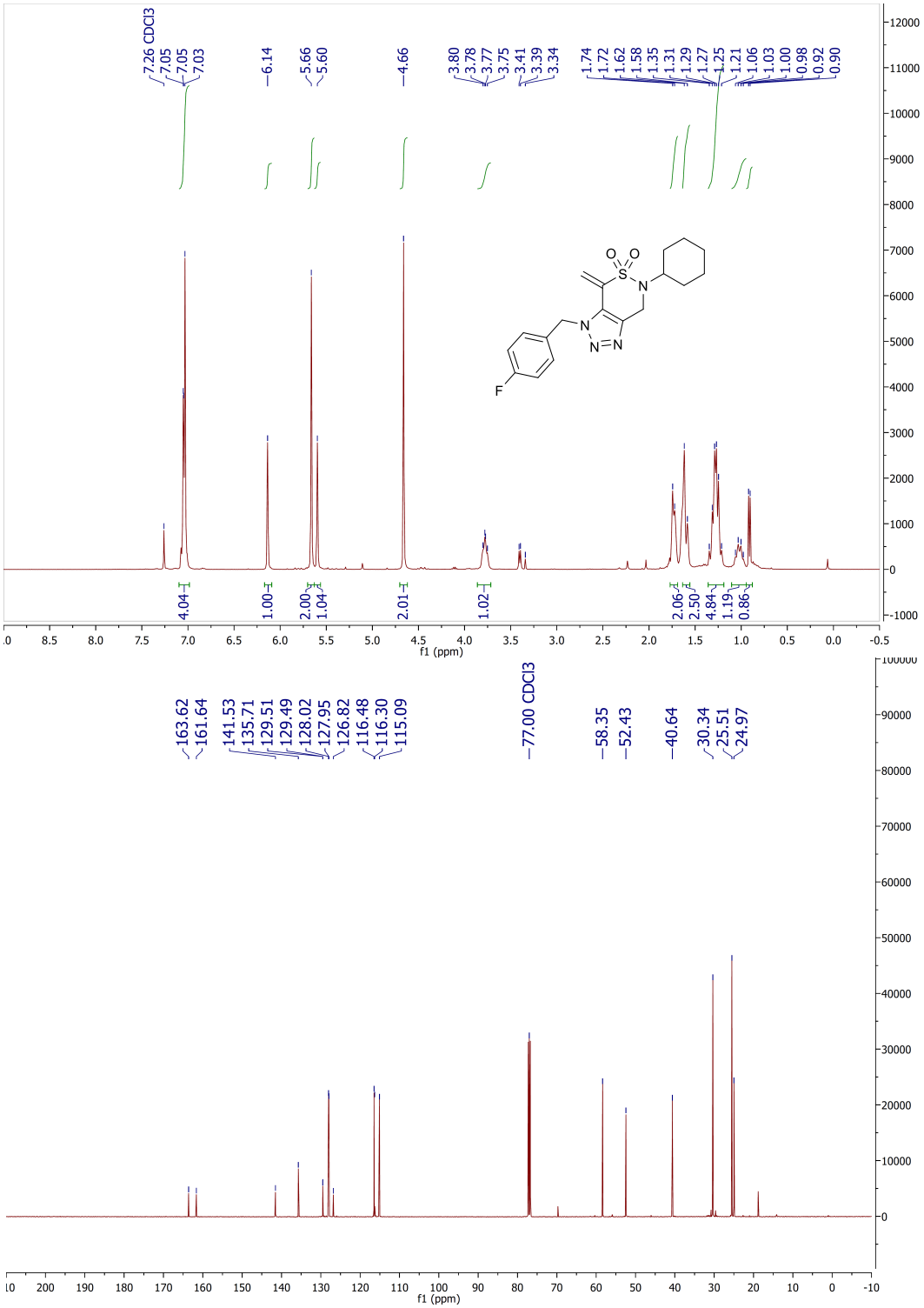


6-cyclohexyl-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.2)

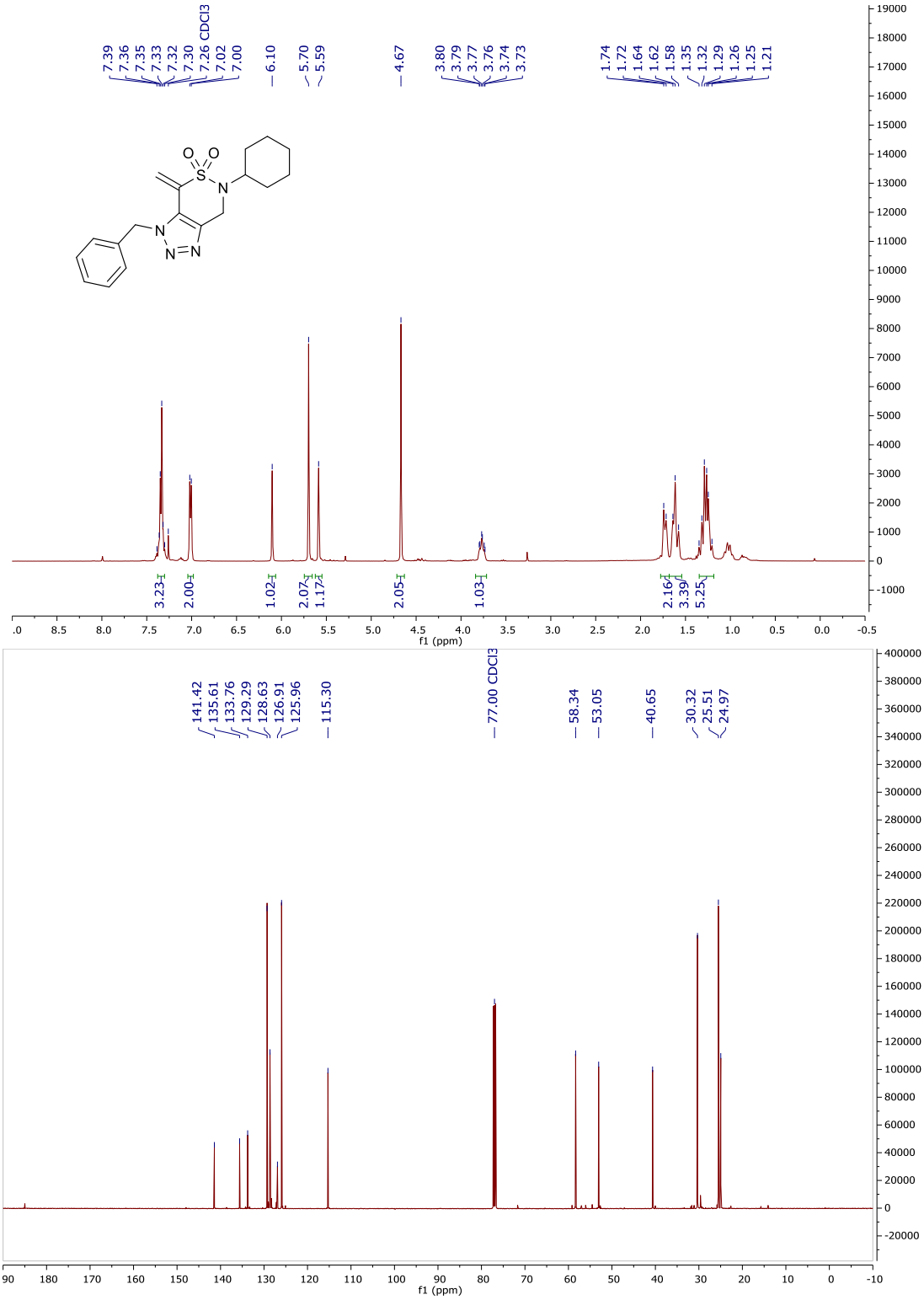




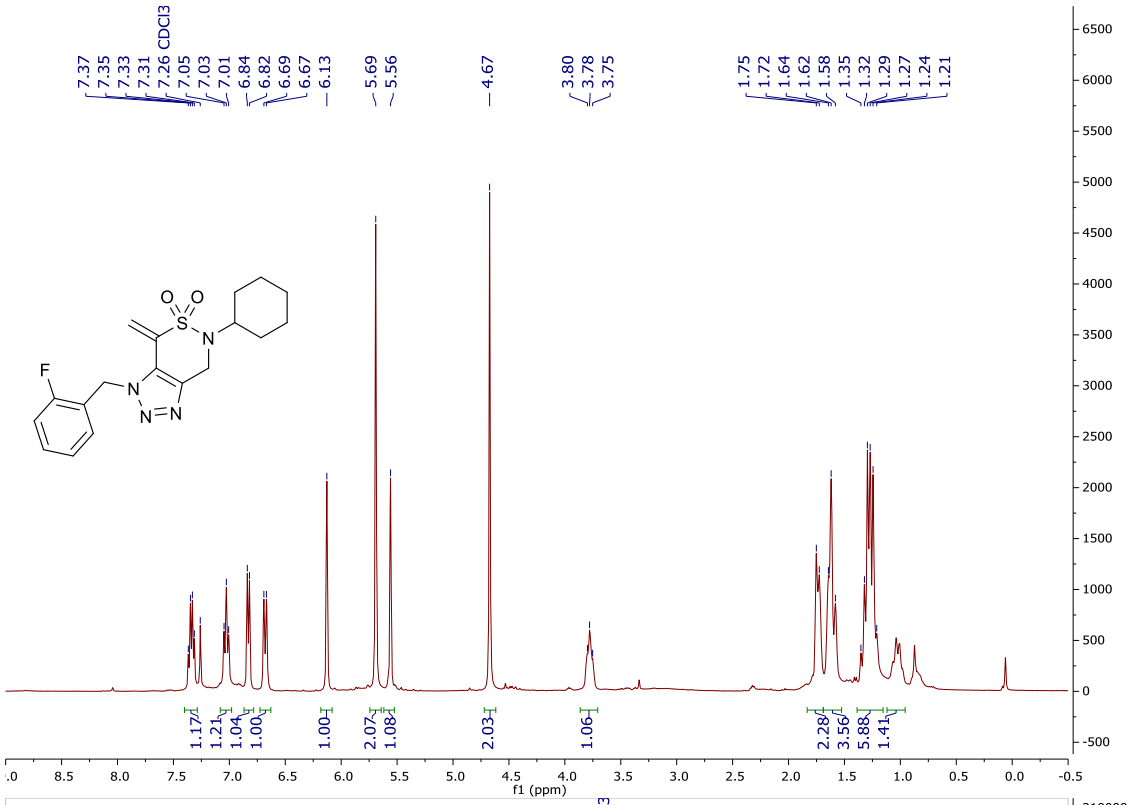
6-cyclohexyl-3-(4-fluorobenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.3)

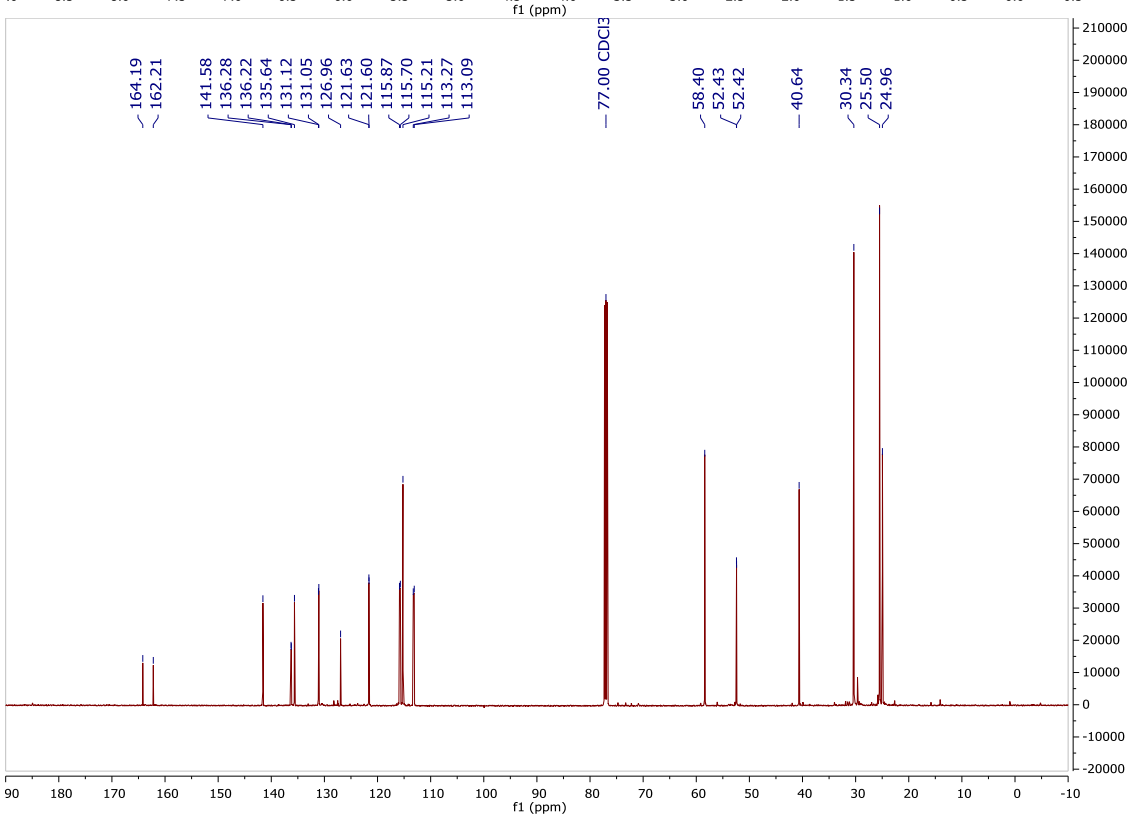


3-Benzyl-6-cyclohexyl-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.4)

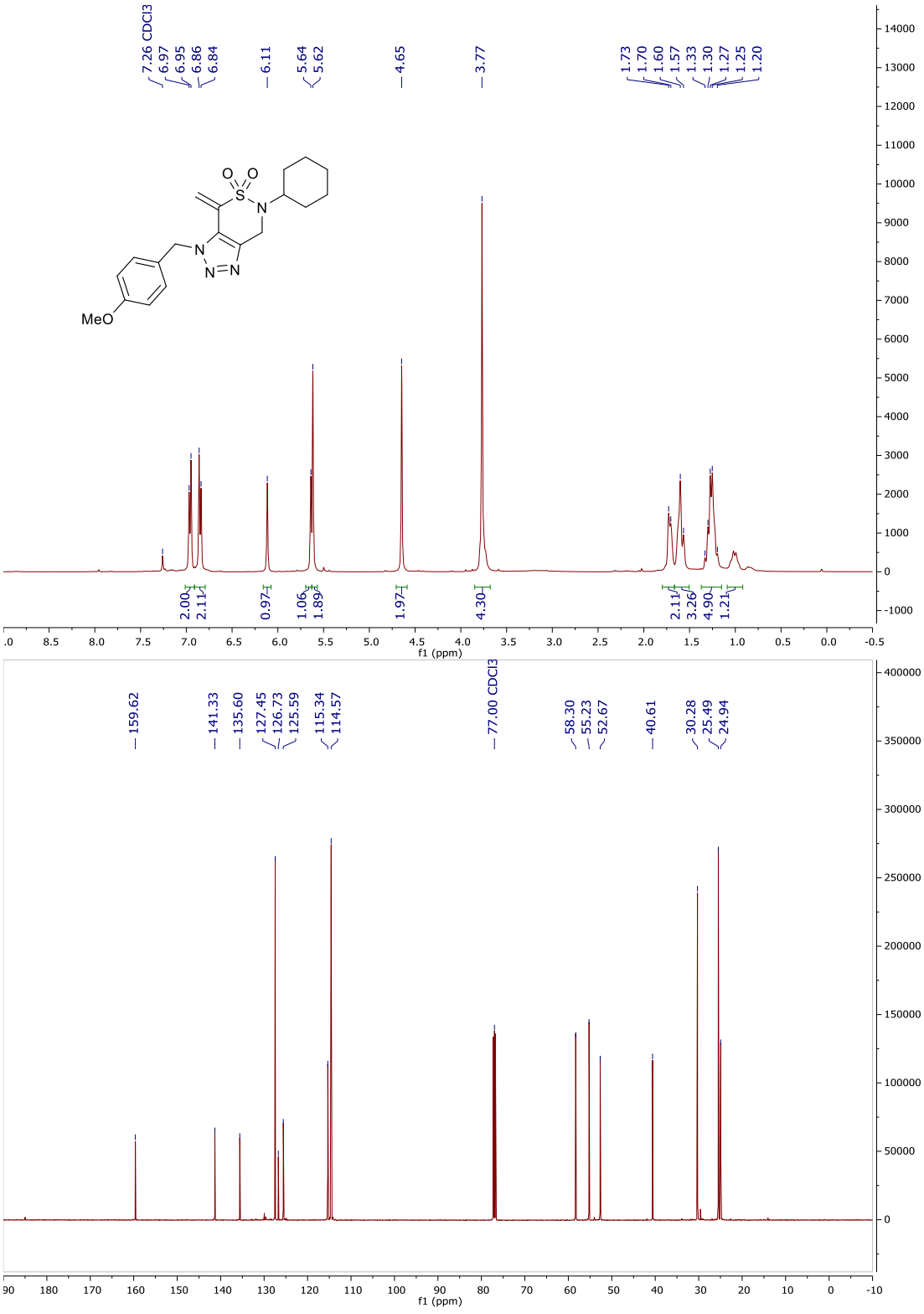


6-Cyclohexyl-3-(2-fluorobenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.5)

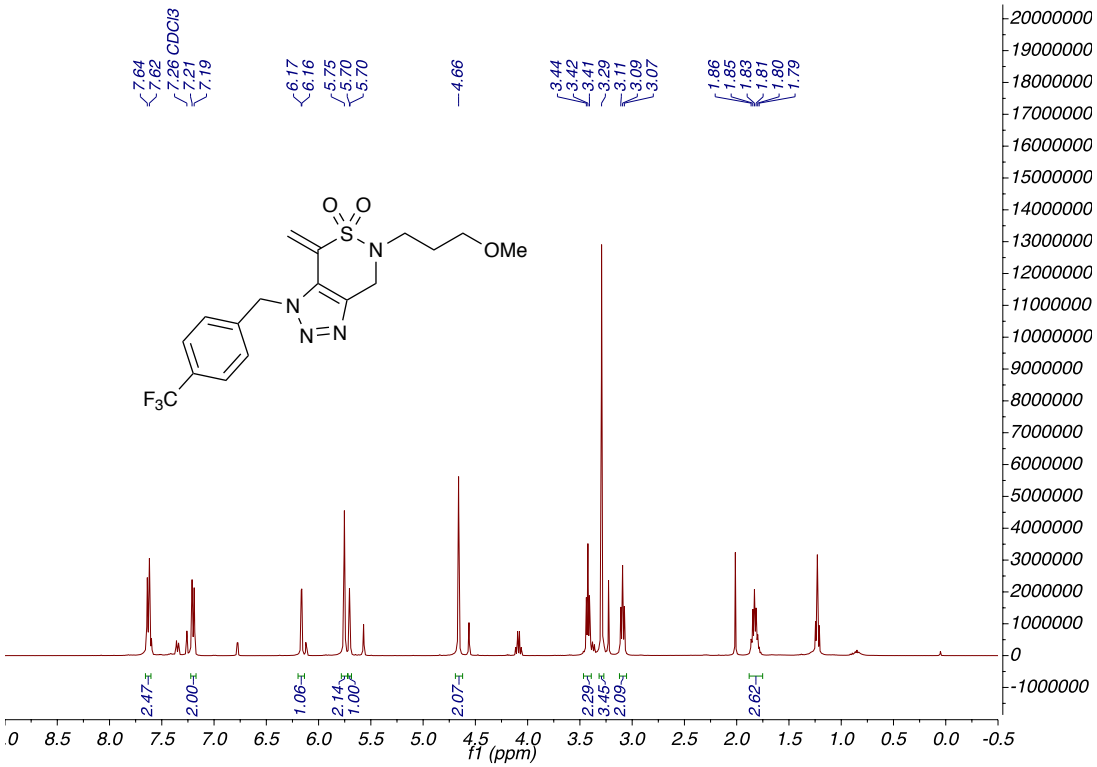


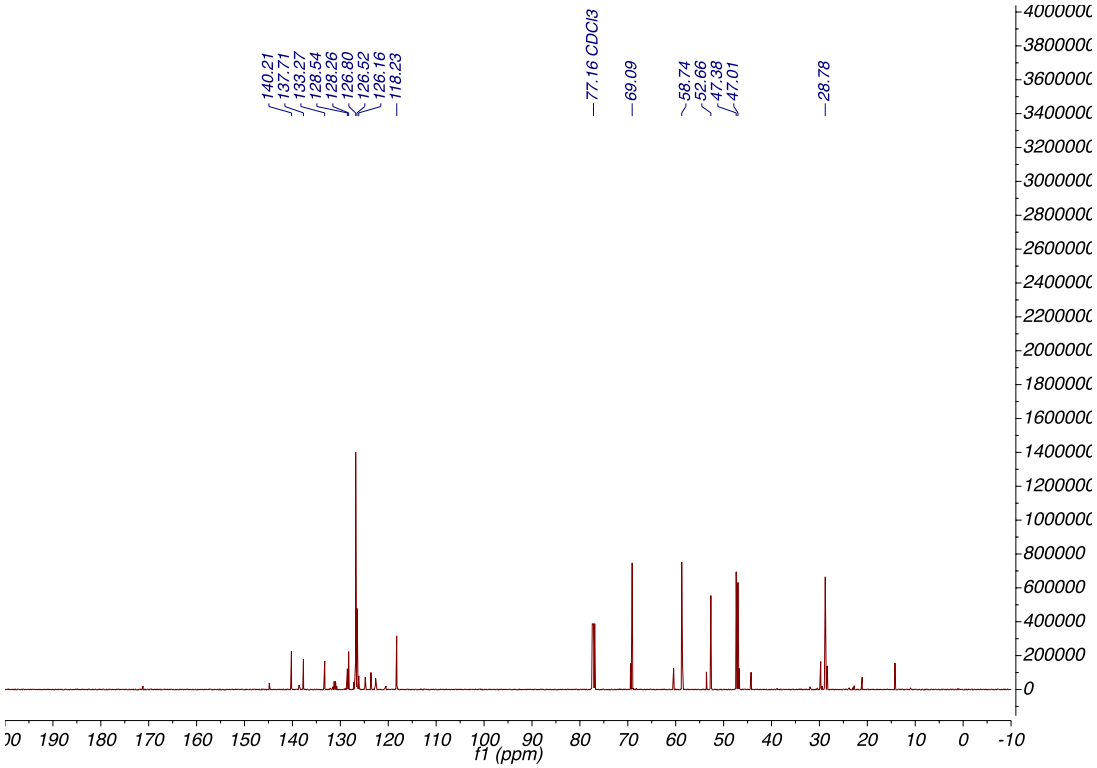


6-Cyclohexyl-3-(4-methoxybenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.6)

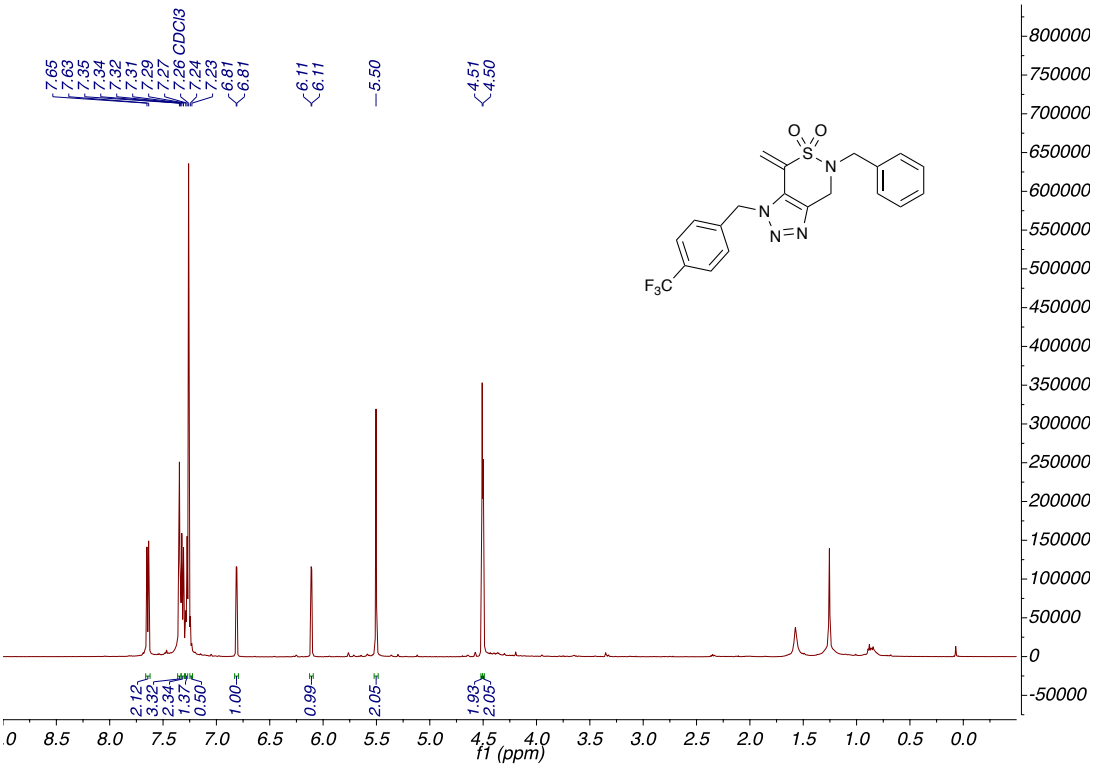


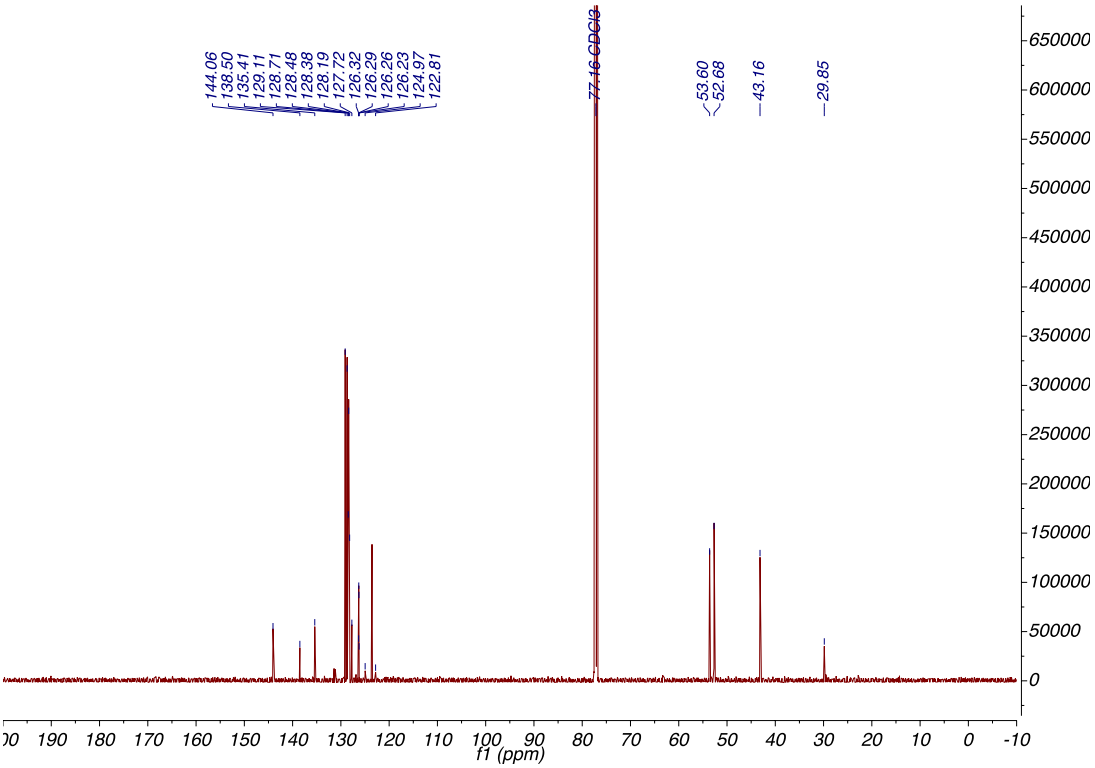
6-(3-methoxypropyl)-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.9)



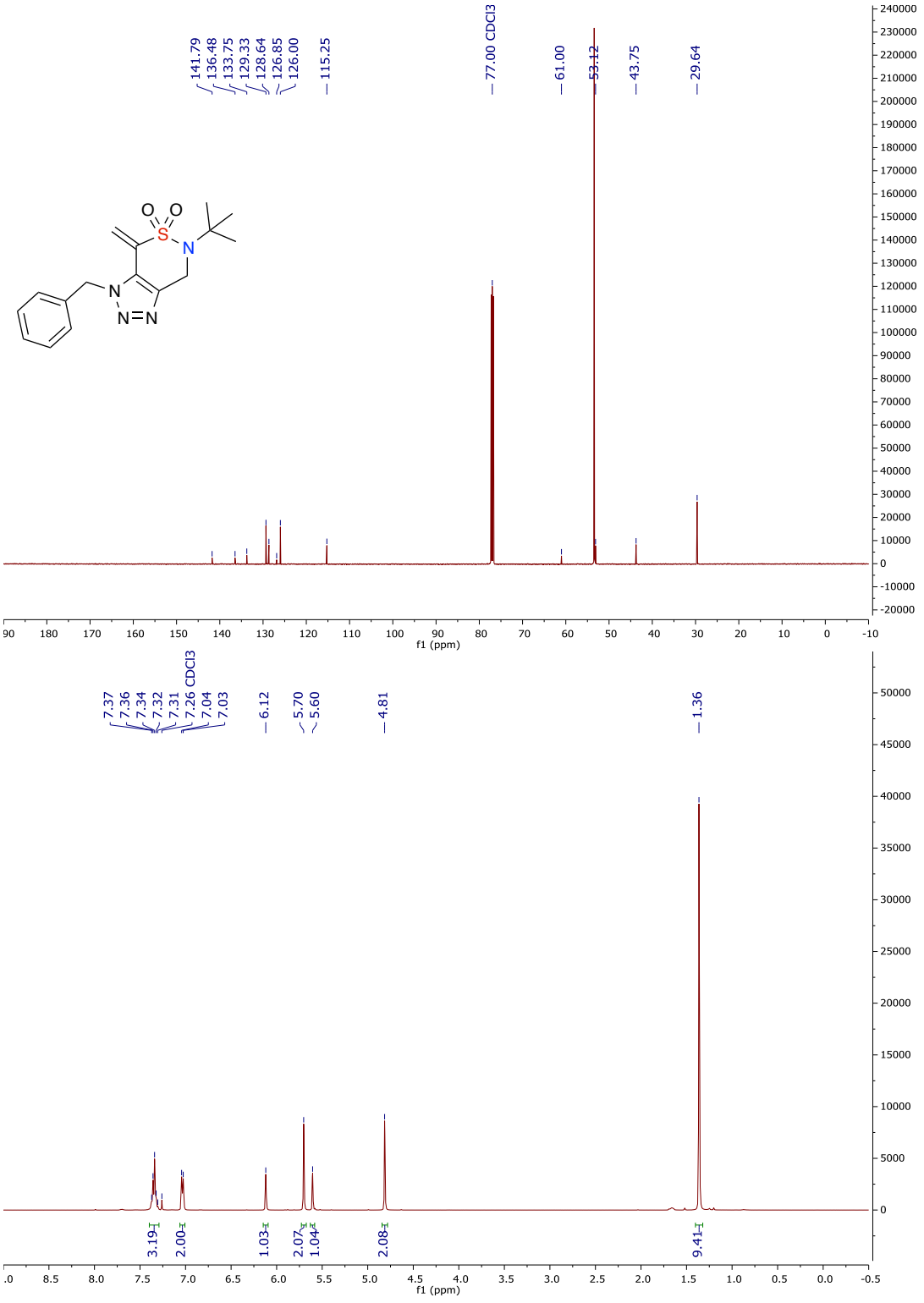


6-benzyl-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.10)

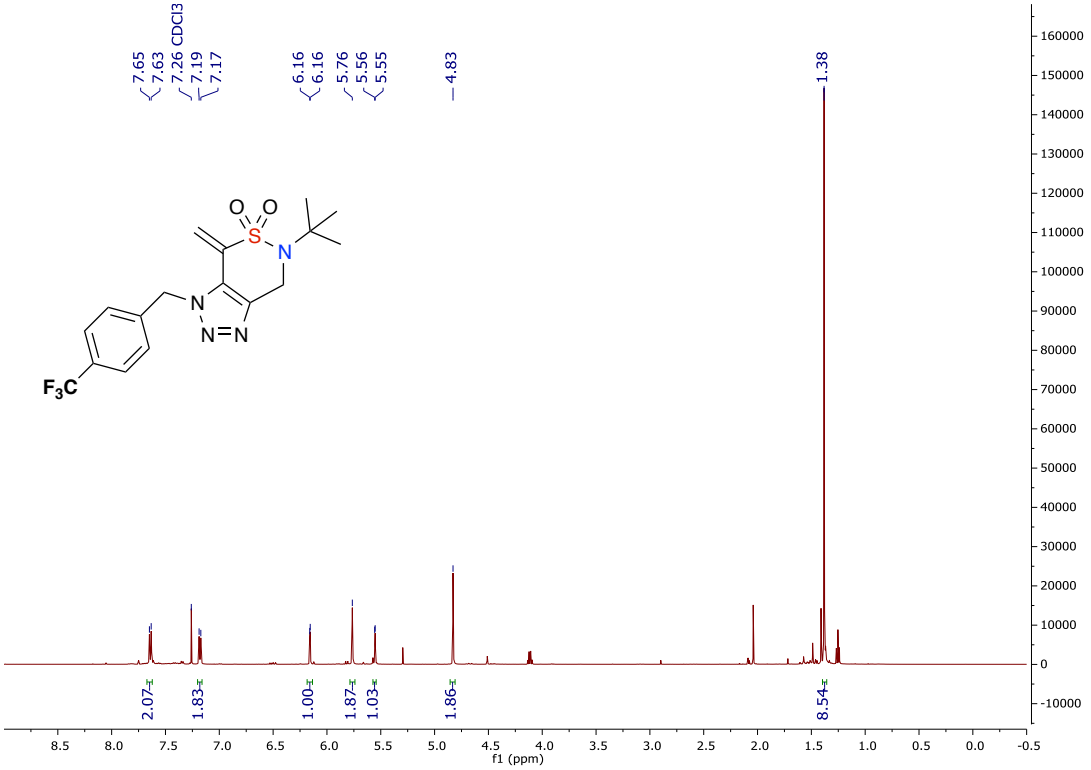


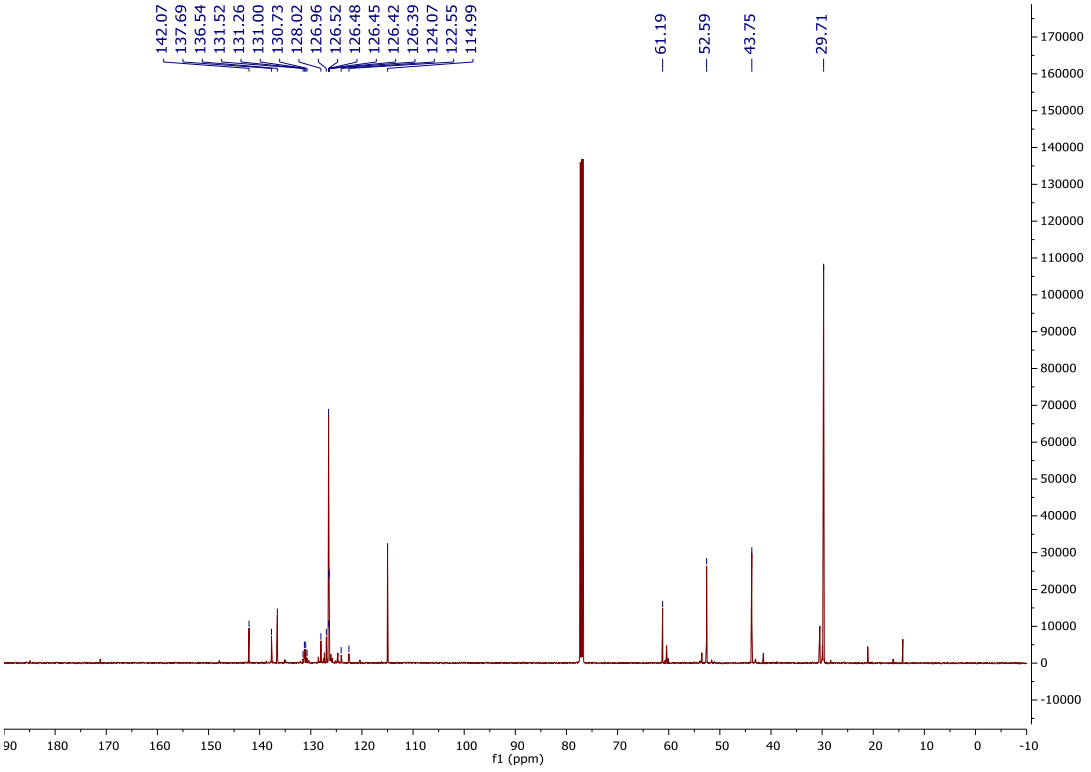


***3*-benzyl-6-(tert-butyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.12)**

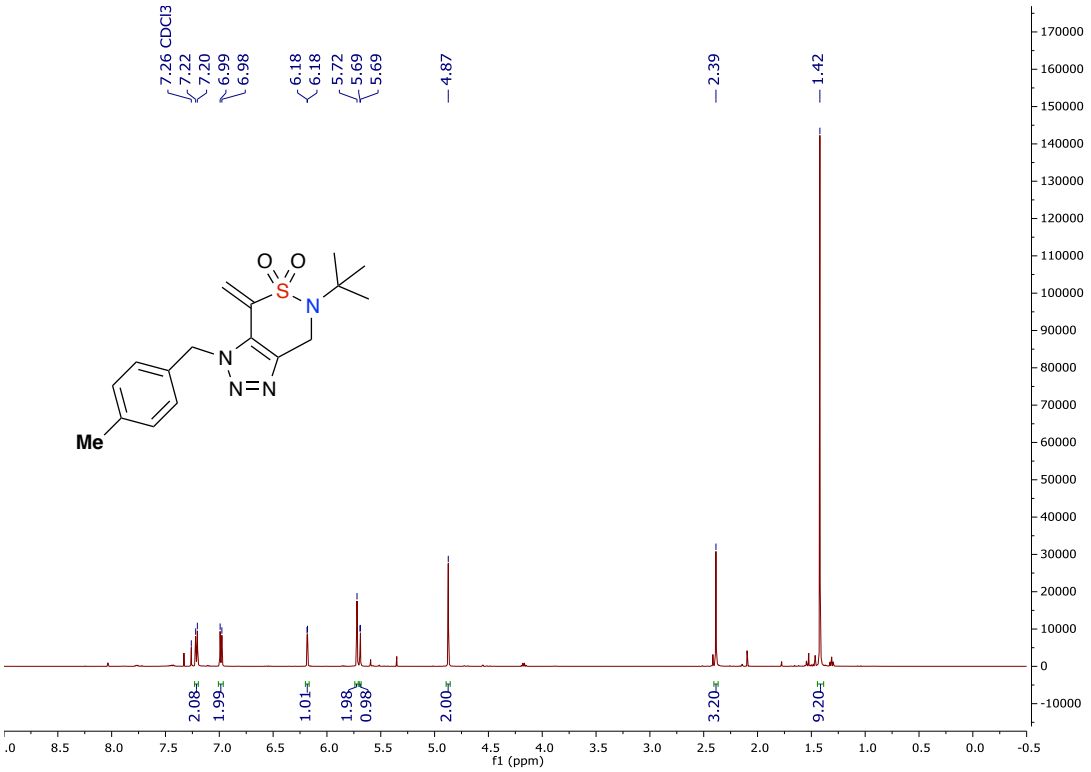


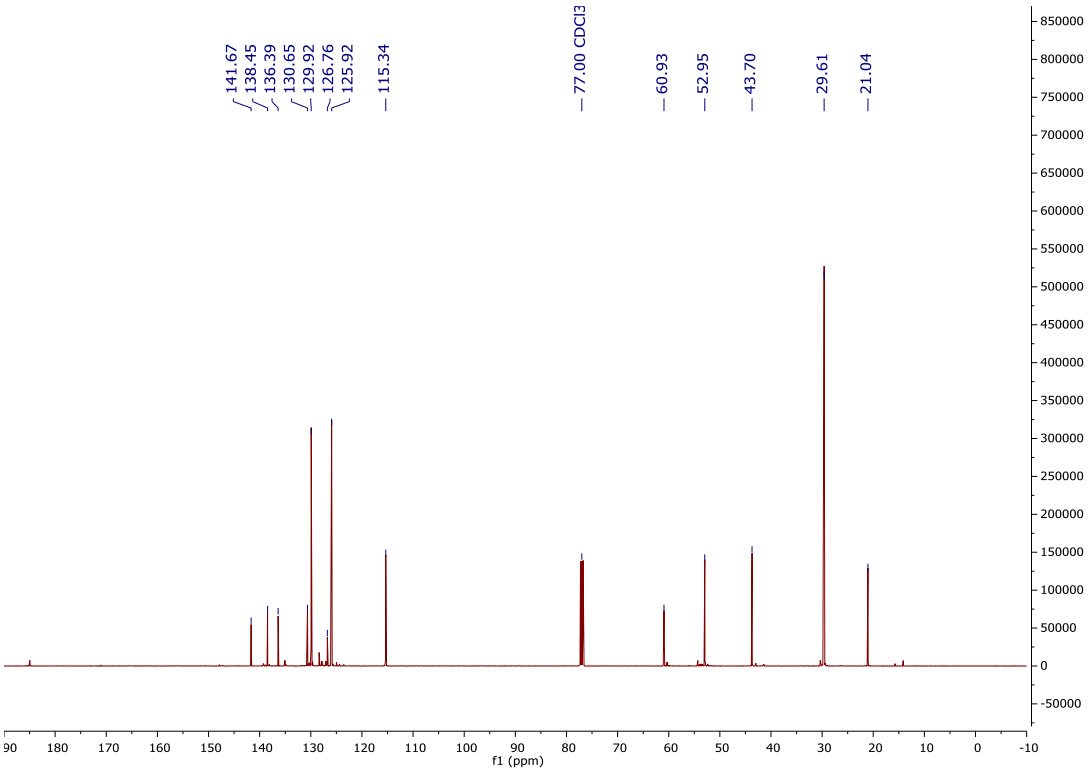
6-(*tert*-butyl)-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.2.3.13)



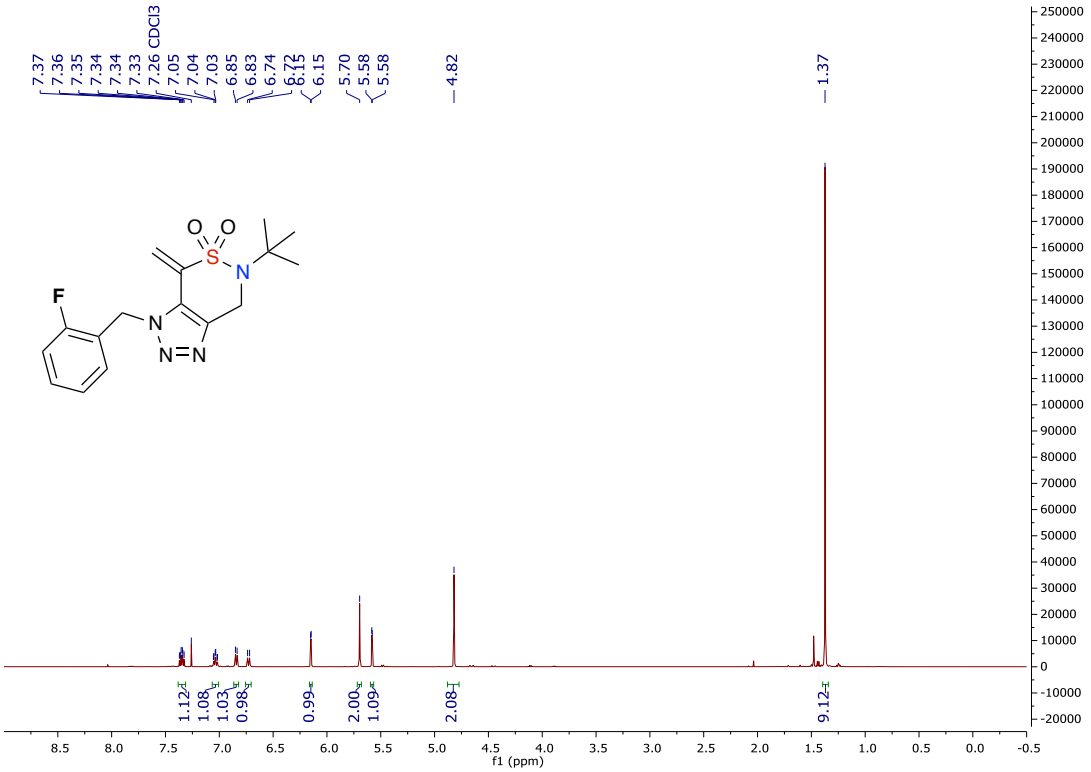


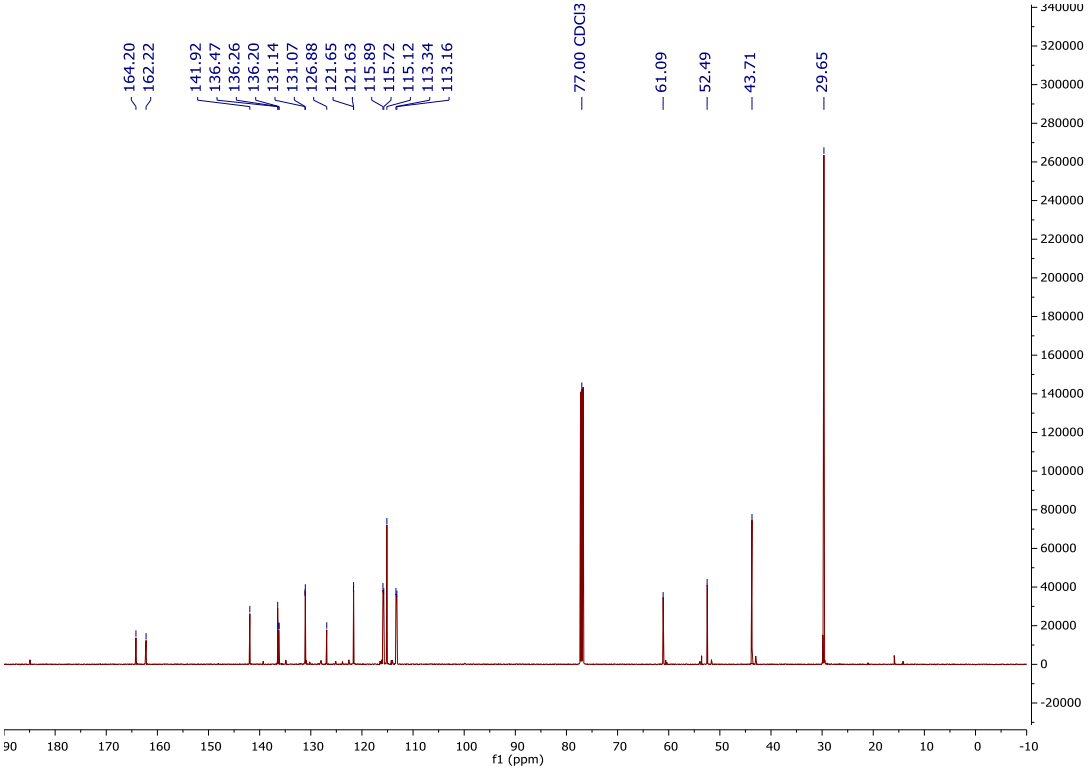
6-(*tert*-Butyl)-4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.2.3.14)



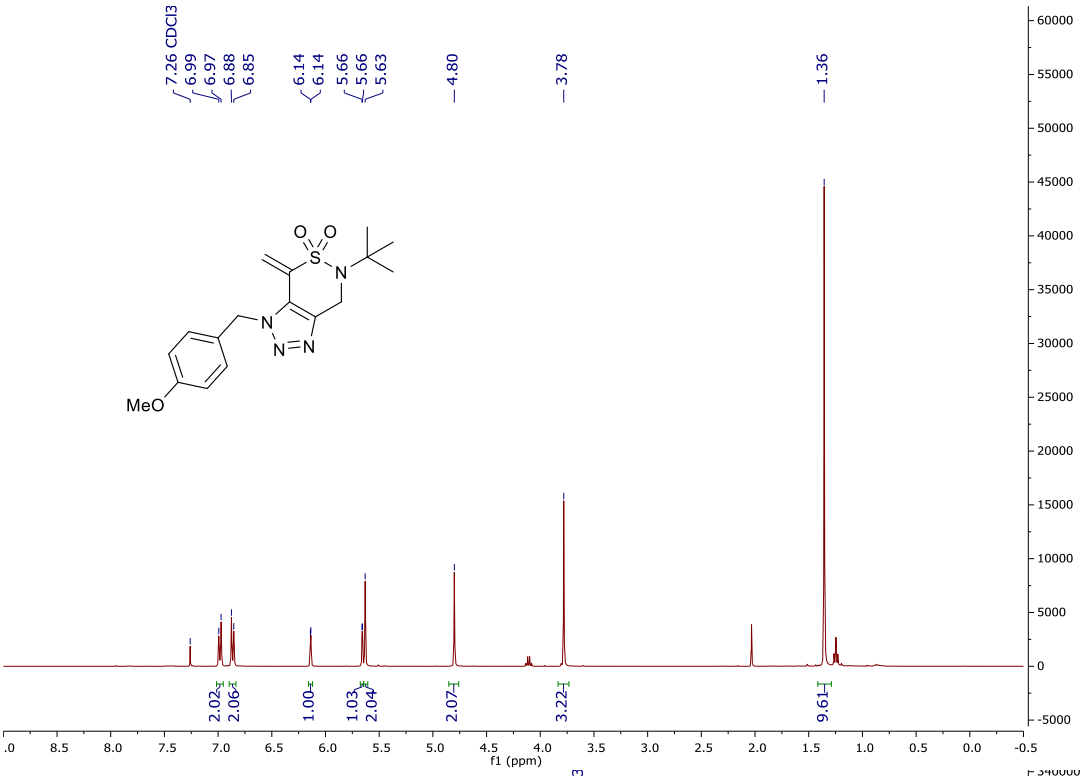


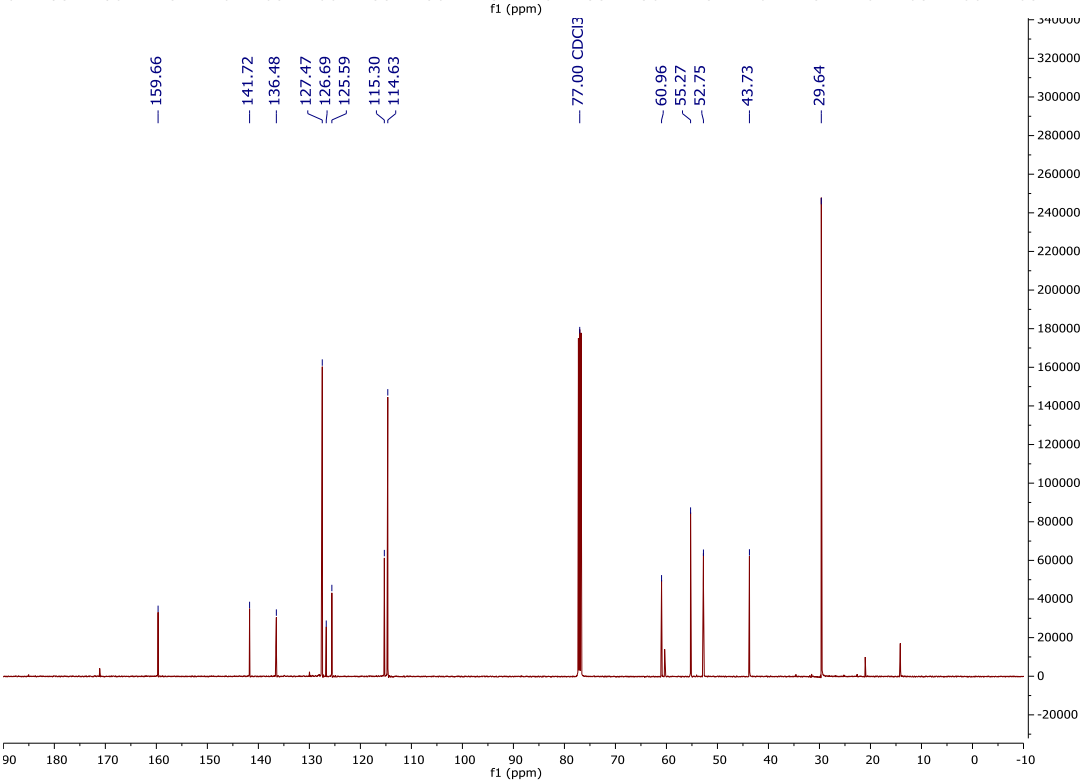
6-(*tert*-Butyl)-3-(2-fluorobenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.2.3.15)



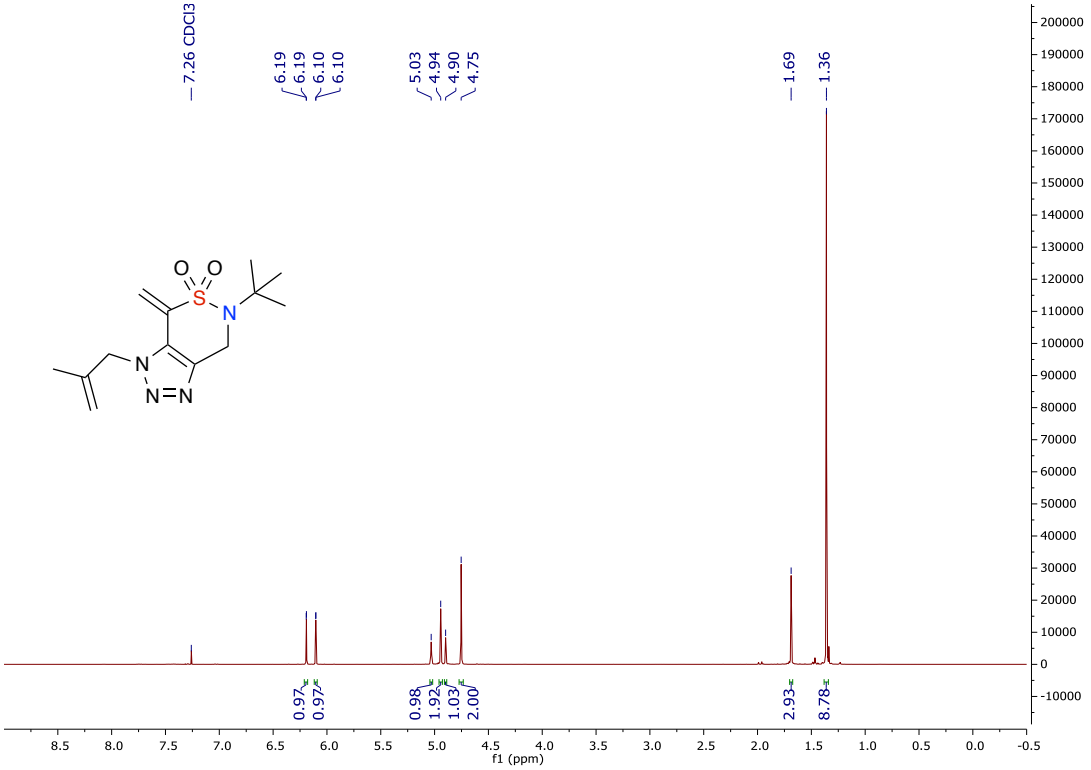


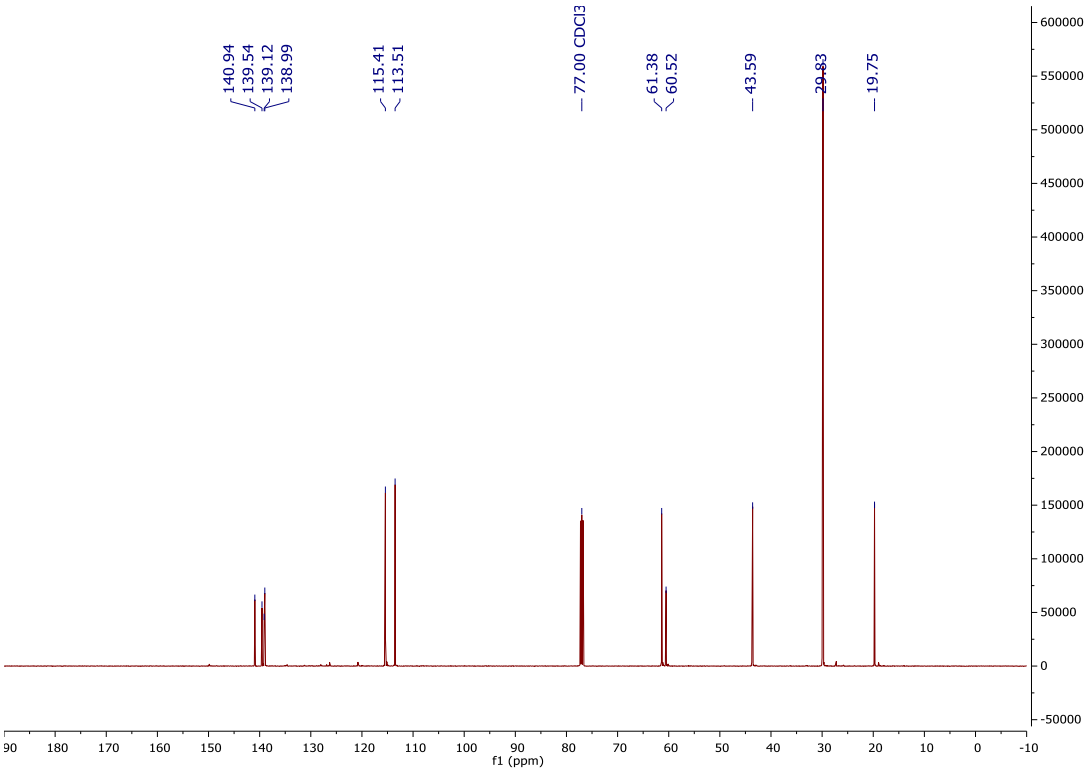
6-(*tert*-butyl)-3-(4-methoxybenzyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.2.3.16)



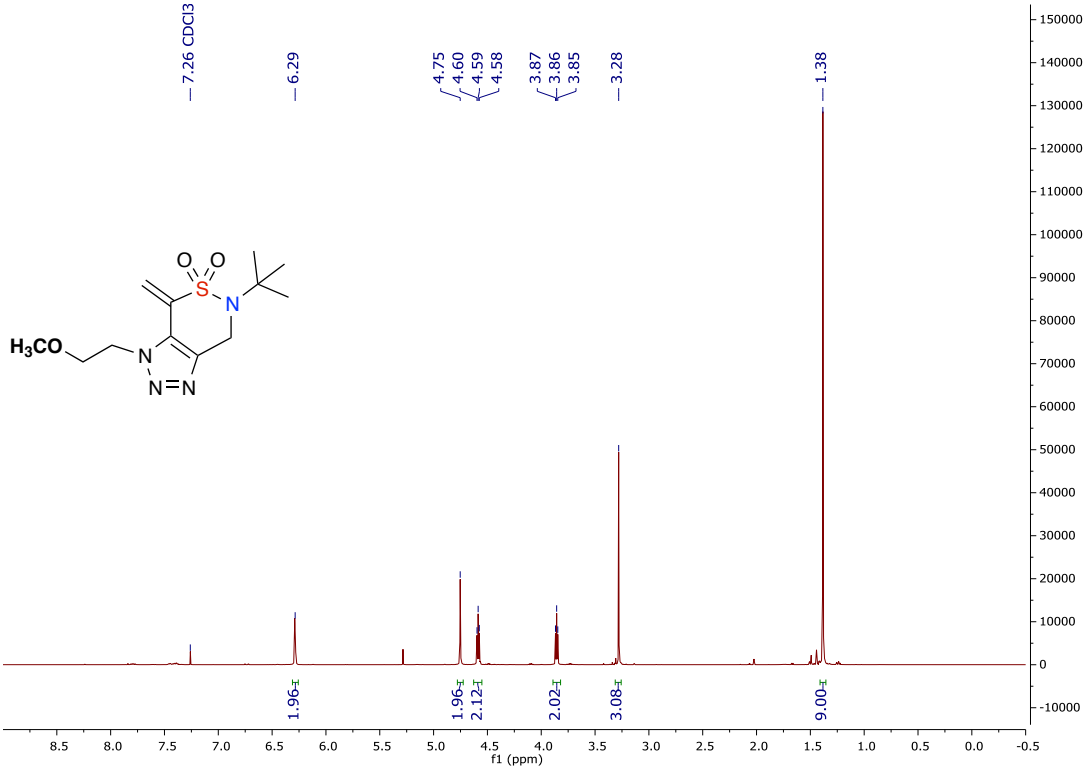


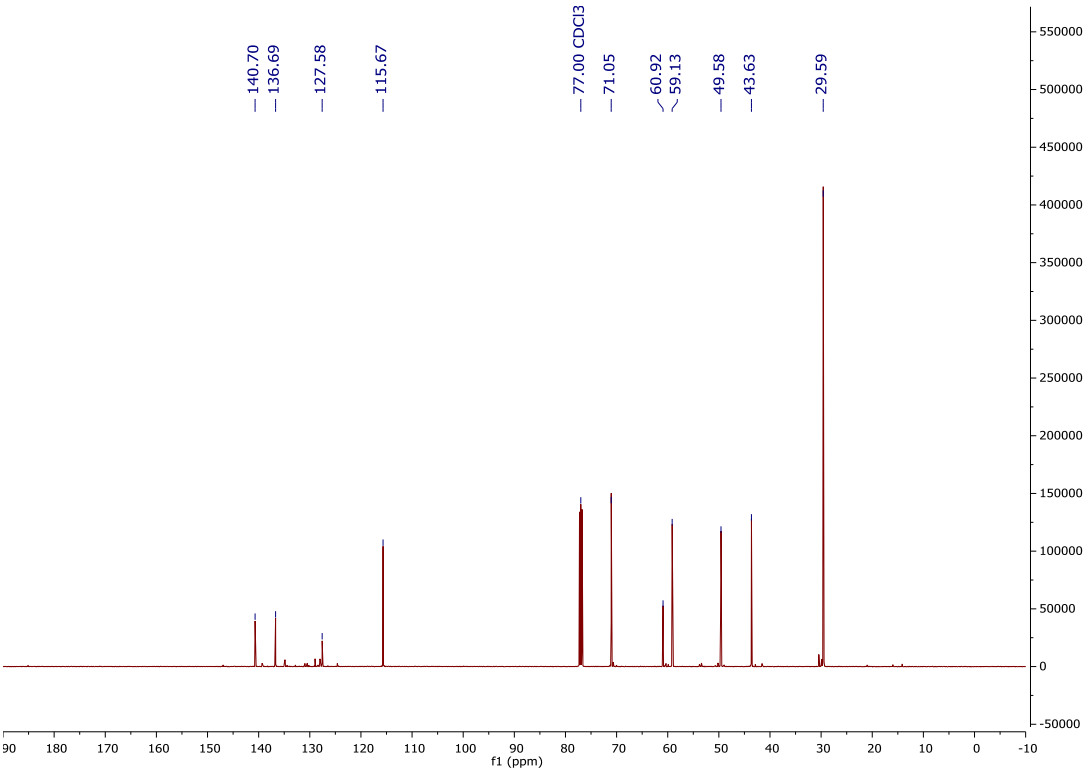
6-(*tert*-butyl)-3-(2-methylallyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.2.3.17)



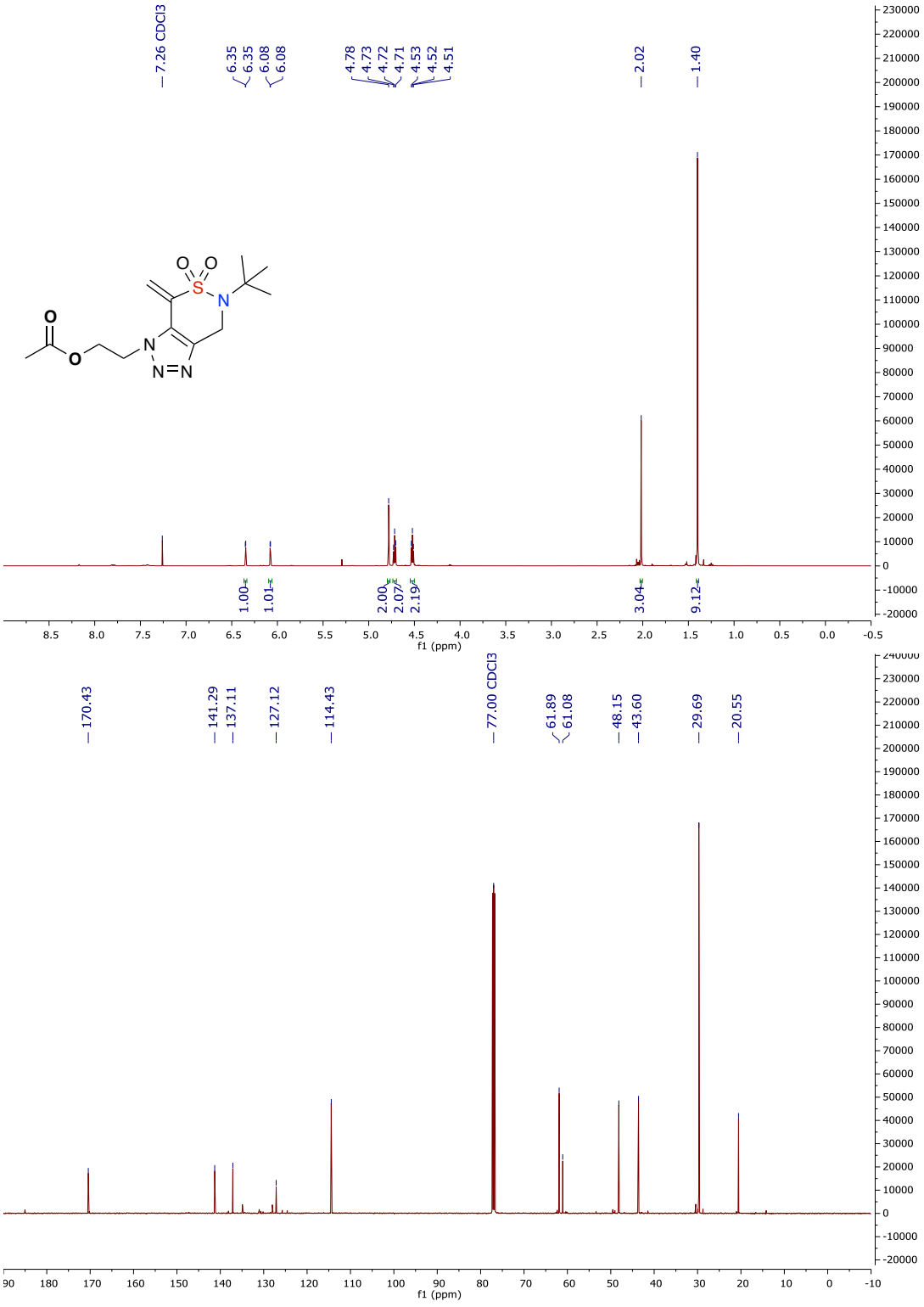


6-(*tert*-butyl)-3-(2-methoxyethyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.2.3.18)

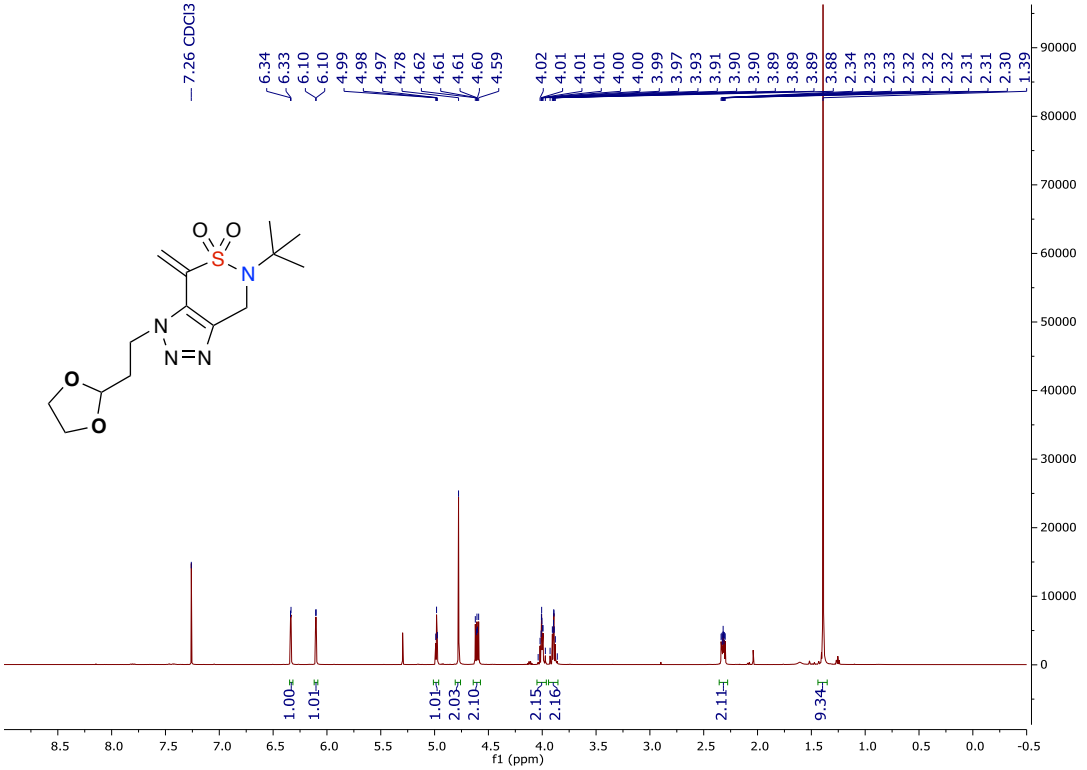


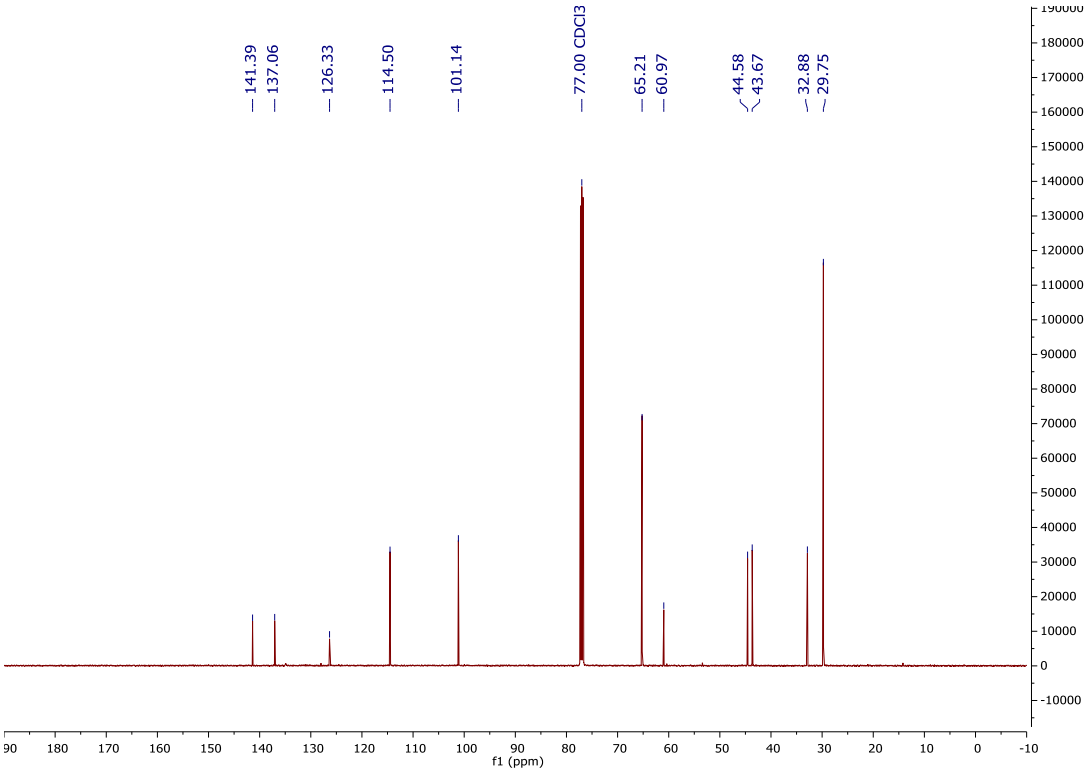


2-(6-(*tert*-butyl)-4-methylene-5,5-dioxido-6,7-dihydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazin-3(4*H*)-yl)ethyl acetate (2.4.2.3.19)

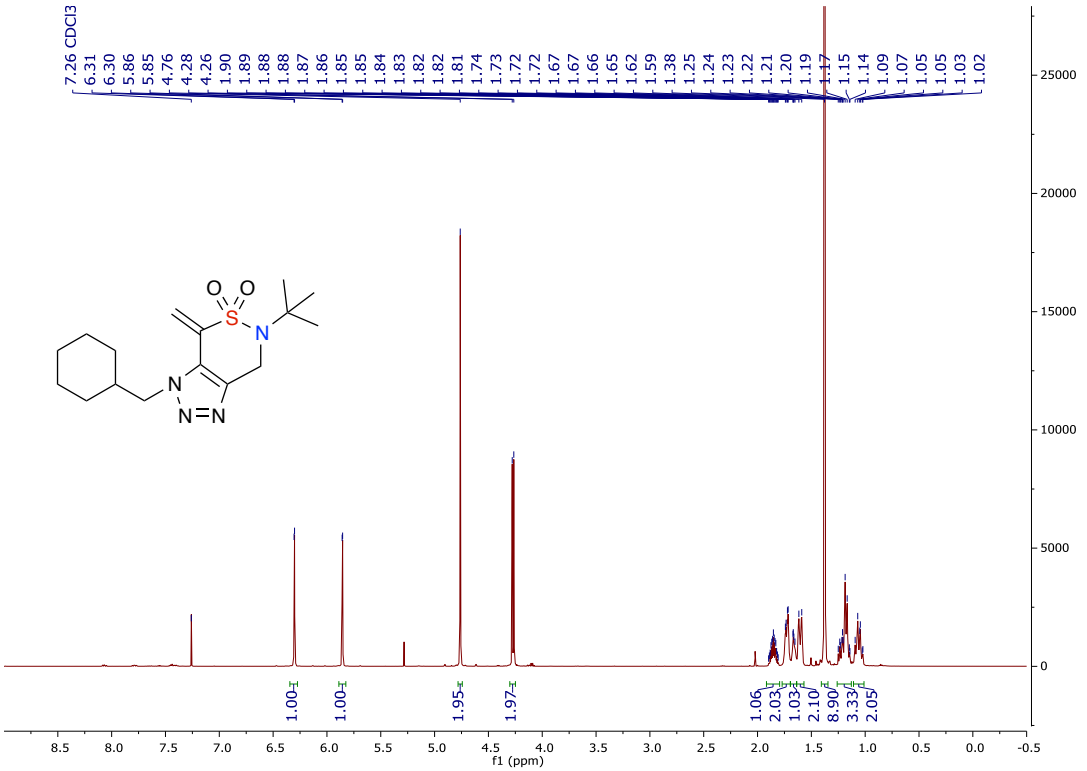


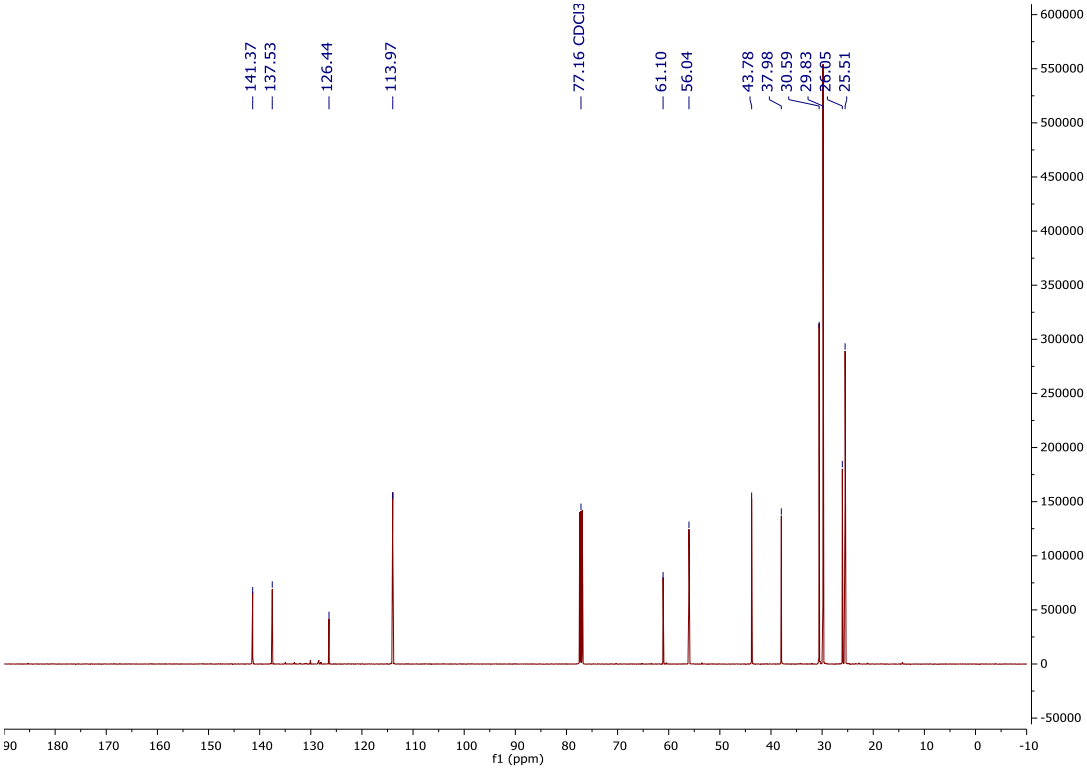
3-(2-(1,3-dioxolan-2-yl)ethyl)-6-(*tert*-butyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.2.3.20)



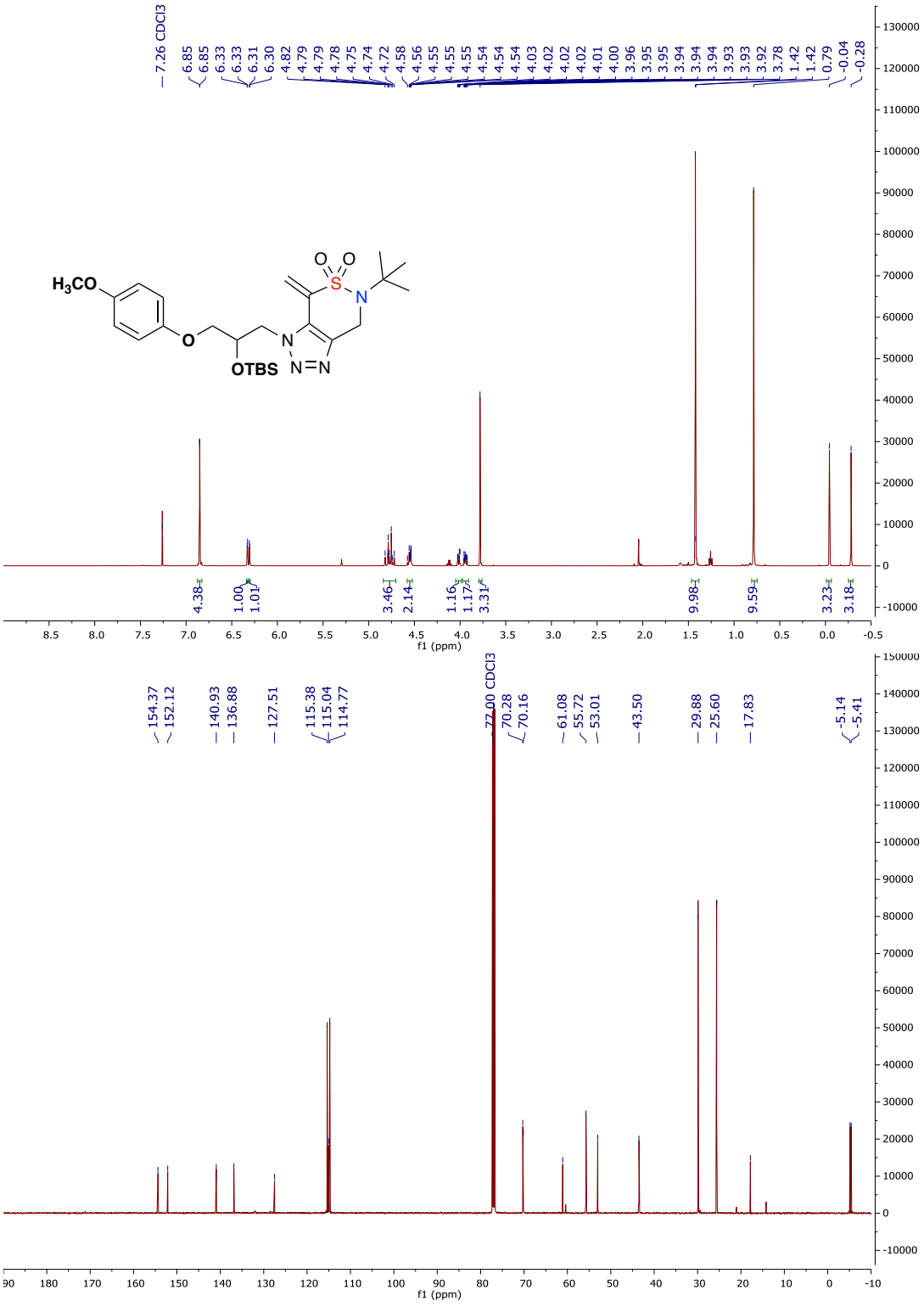


6-(*tert*-butyl)-3-(cyclohexylmethyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.2.3.21)

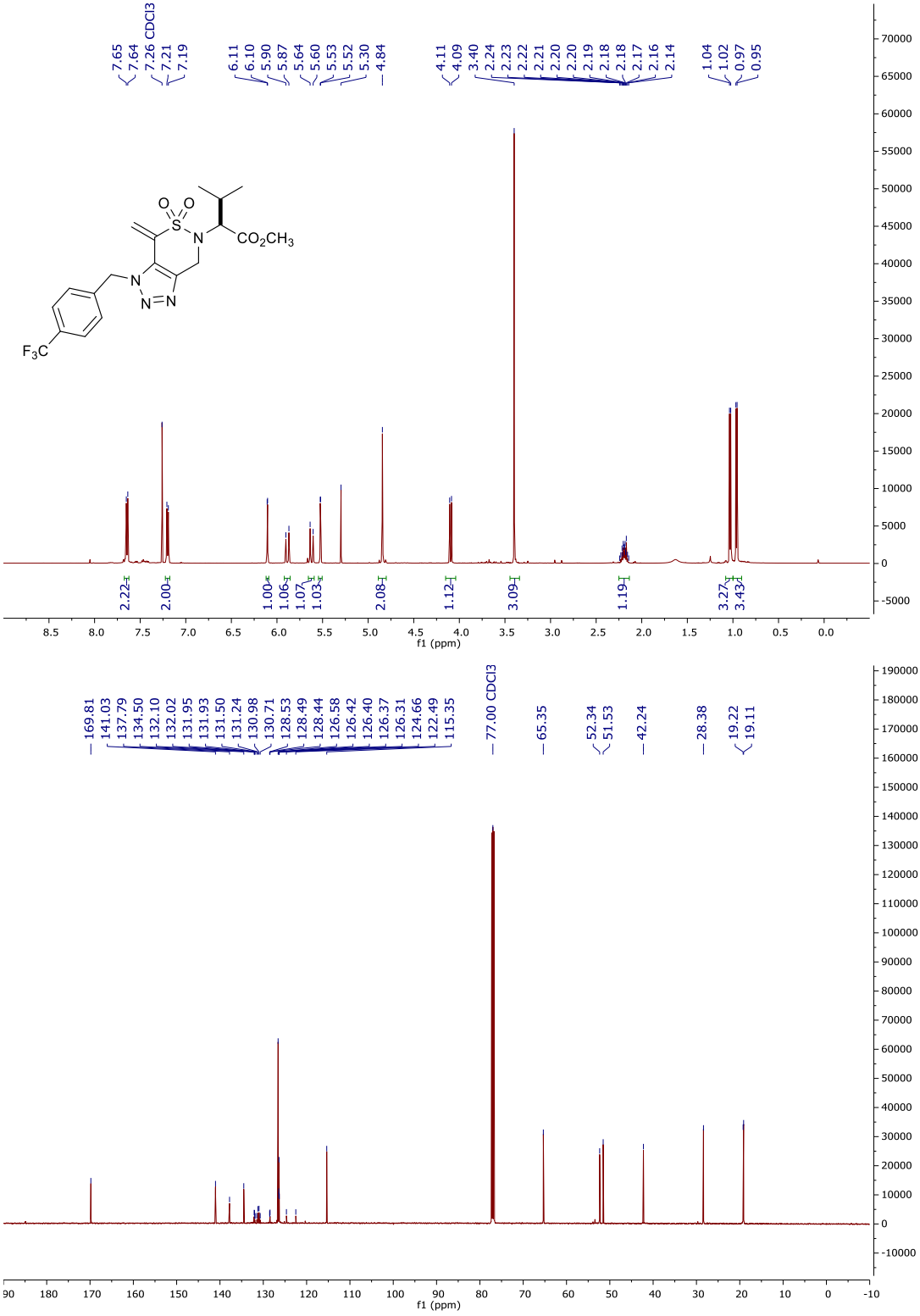




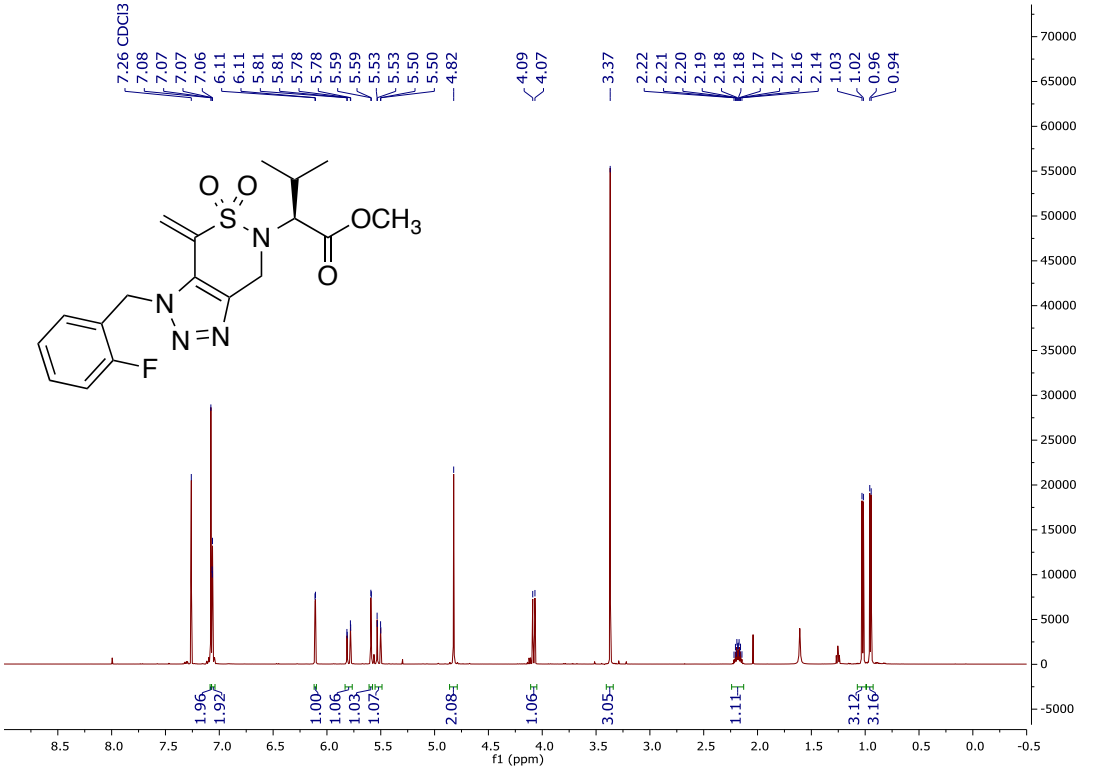
6-(*tert*-butyl)-3-(2-((*tert*-butyldimethylsilyl)oxy)-3-(4-methoxyphenoxy)propyl)-4-methylene-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.2.3.22)

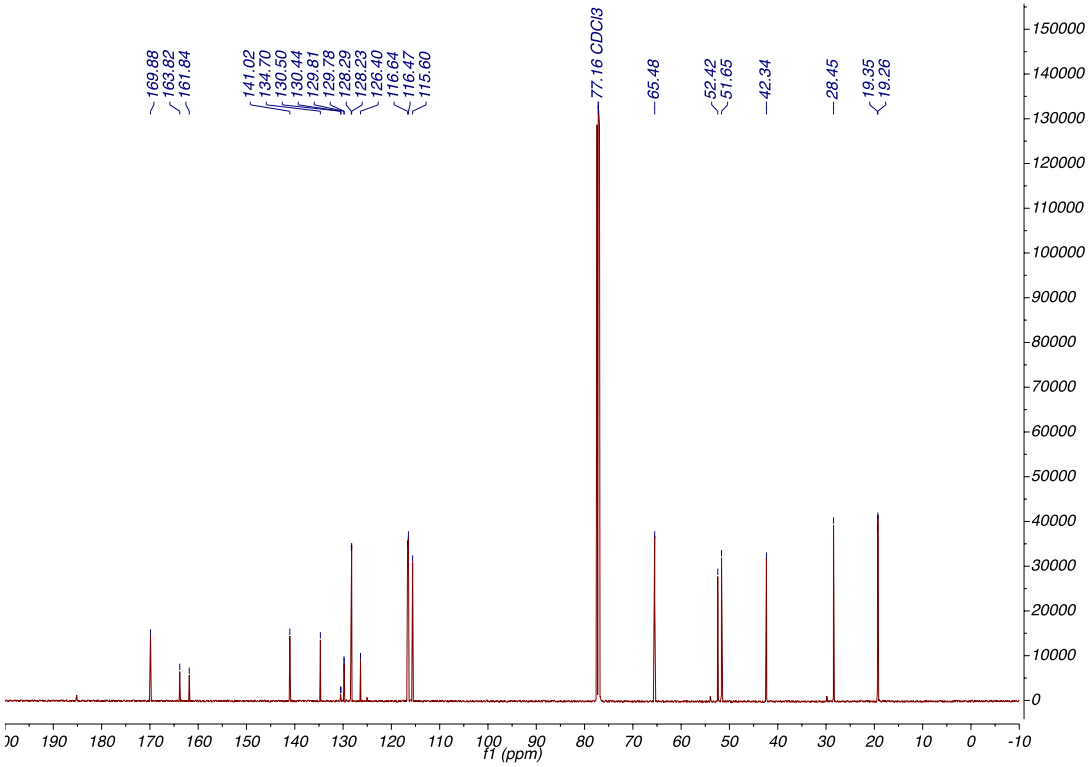


Methyl (*S*)-3-methyl-2-(4-methylene-5,5-dioxido-3-(4-(trifluoromethyl)benzyl)-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)butanoate (2.4.2.3.23)

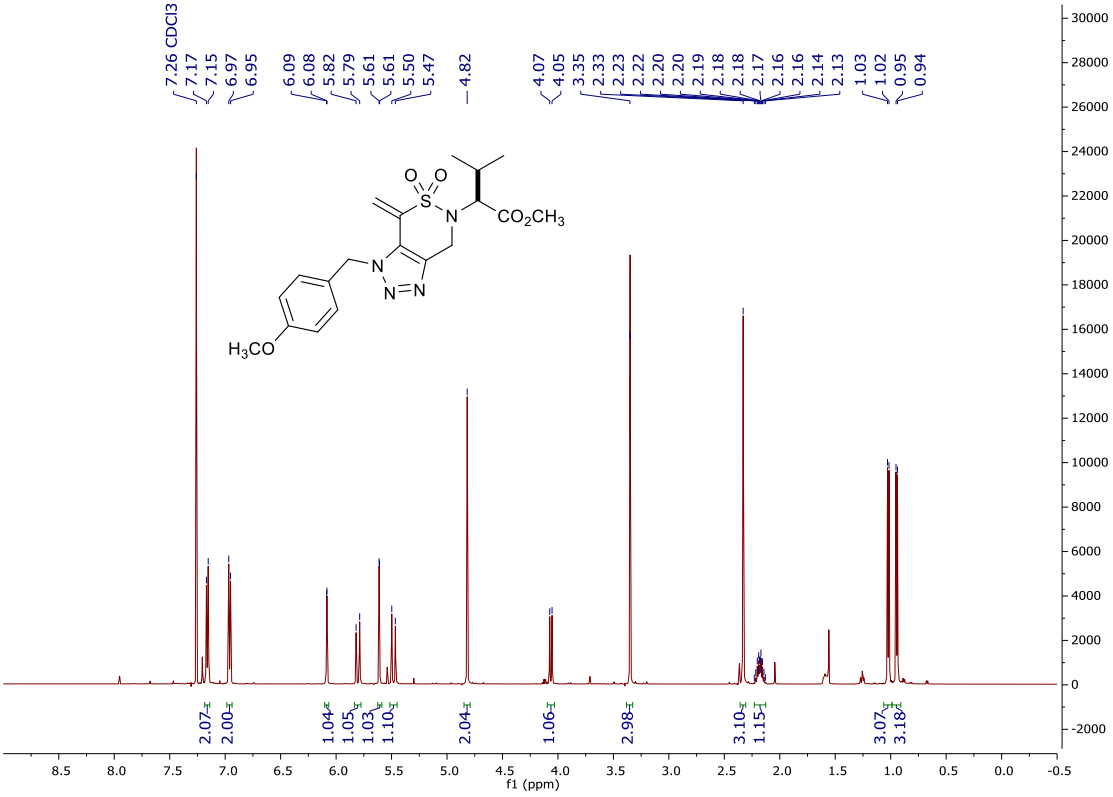


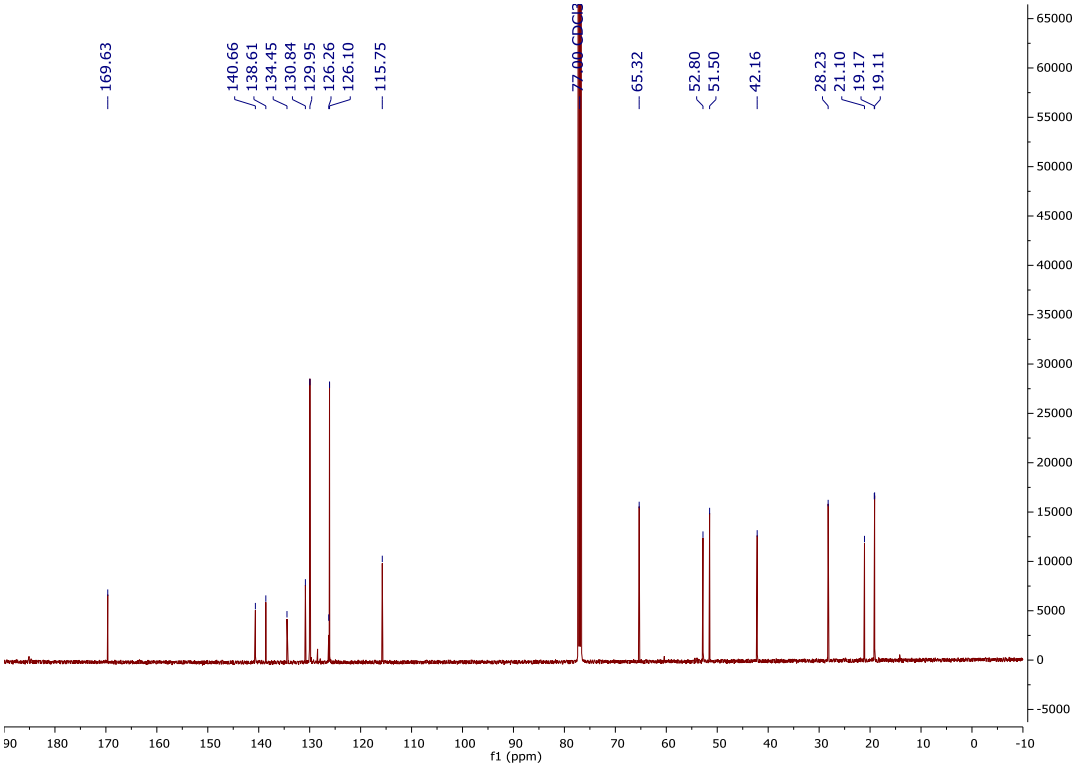
Methyl(*S*)-2-(3-(2-fluorobenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazin-6(3*H*)-yl)-3-methylbutanoate (2.4.2.3.24)



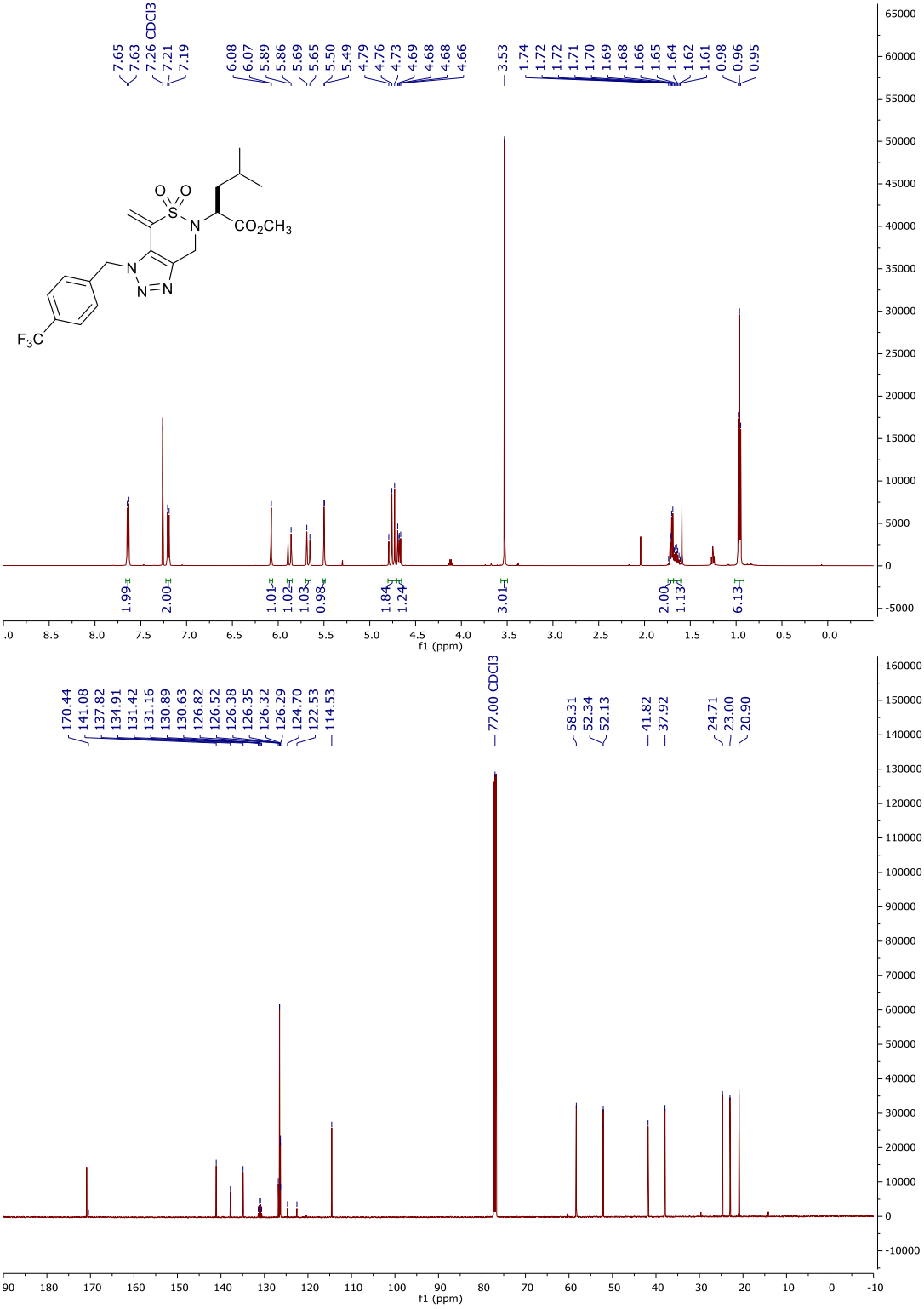


Methyl (*S*)-2-(3-(4-methoxybenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-3-methylbutanoate (2.4.2.3.25)

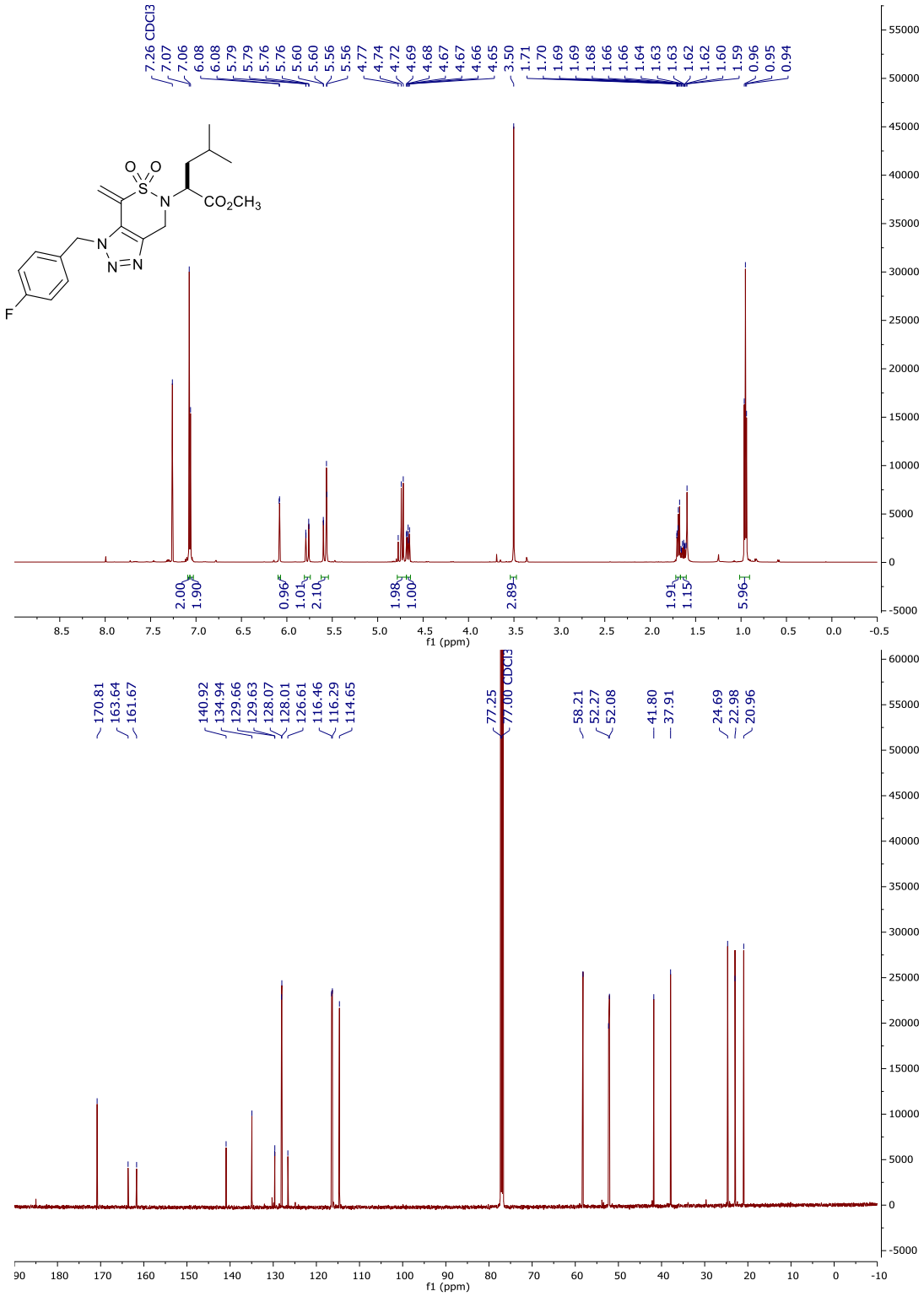




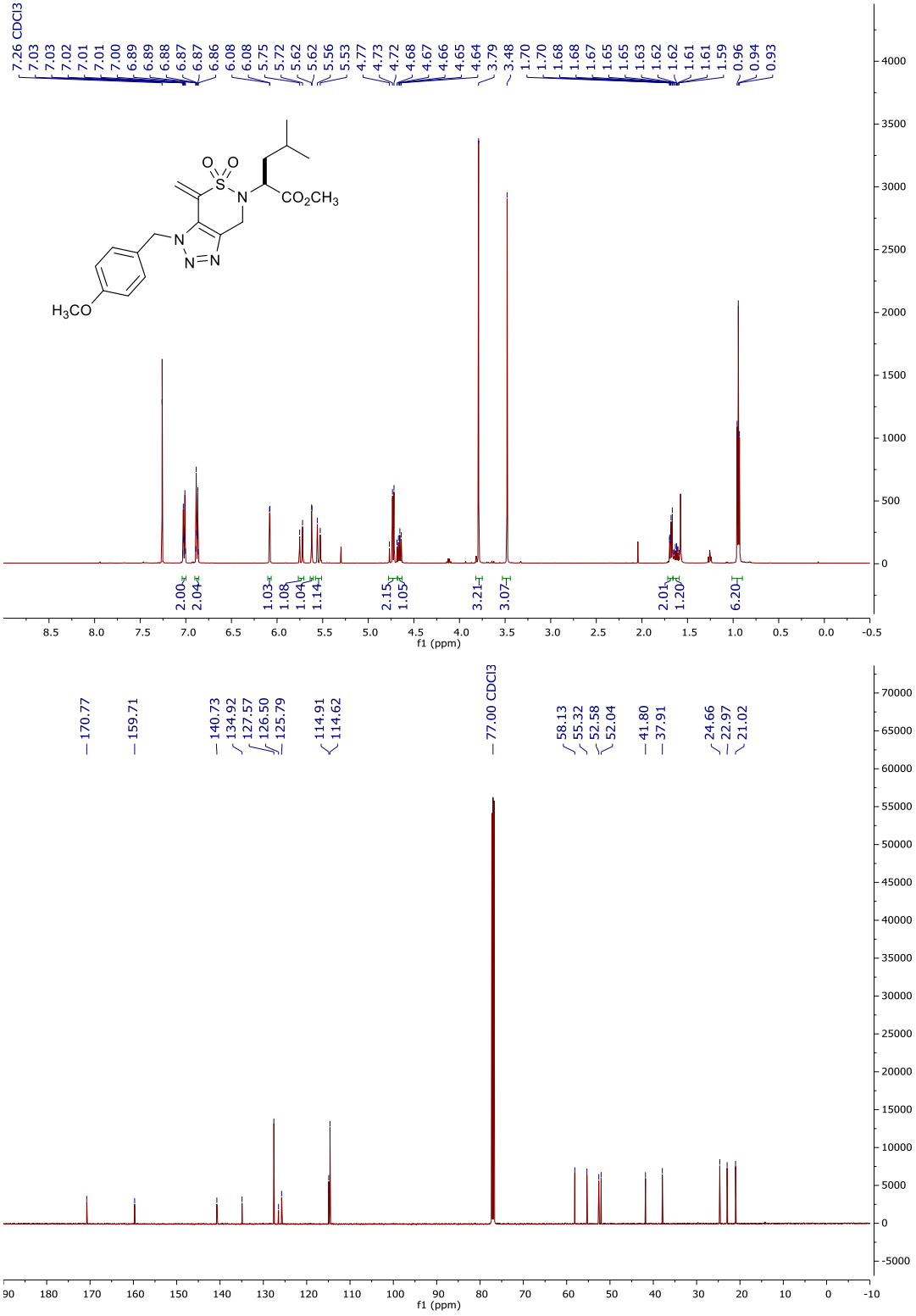
Methyl (*S*)-4-methyl-2-(4-methylene-5,5-dioxido-3-(4-(trifluoromethyl)benzyl)-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)pentanoate (2.4.2.3.26)



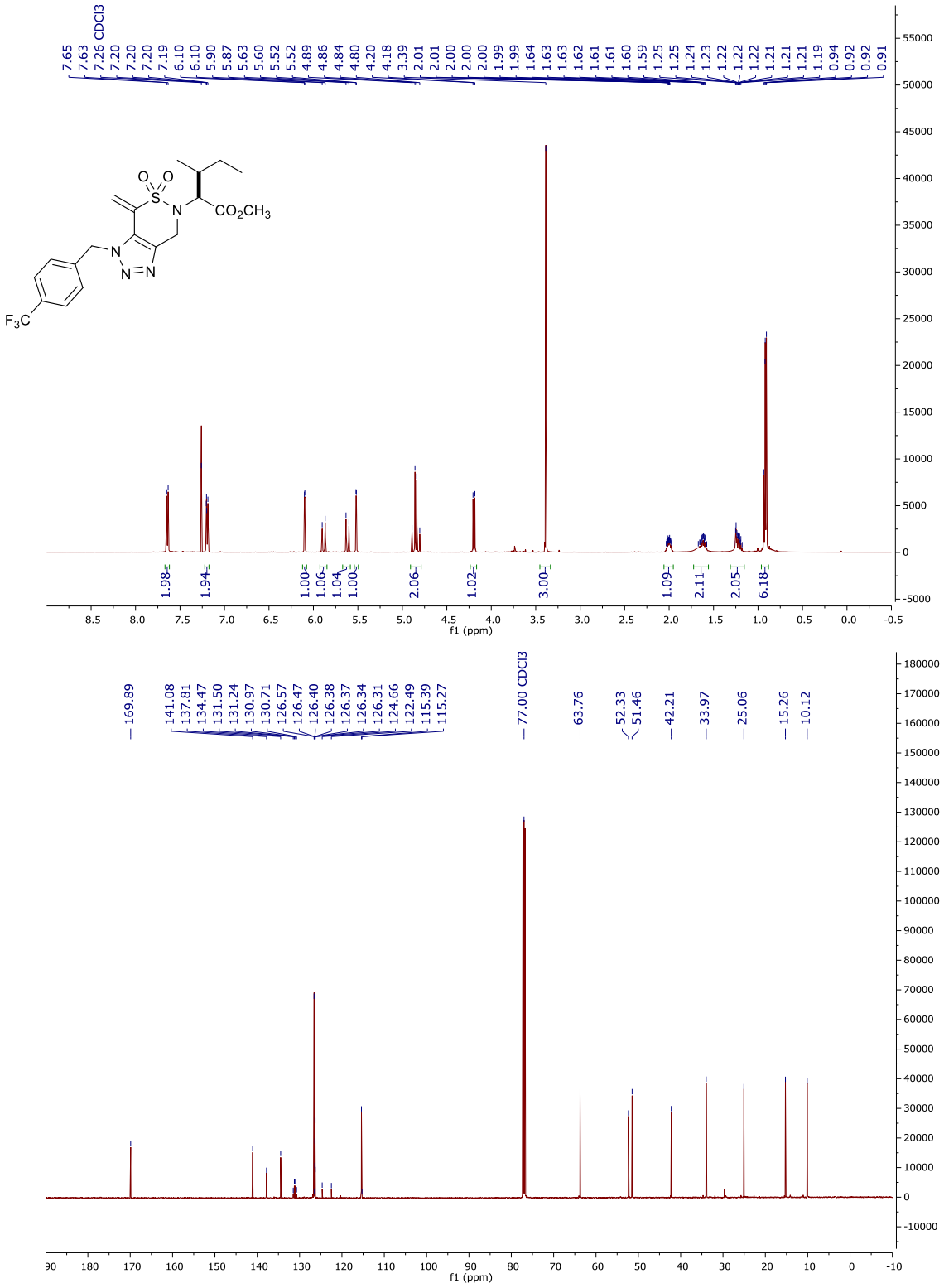
Methyl (*S*)-2-(3-(4-fluorobenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-4-methylpentanoate (2.4.2.3.28)



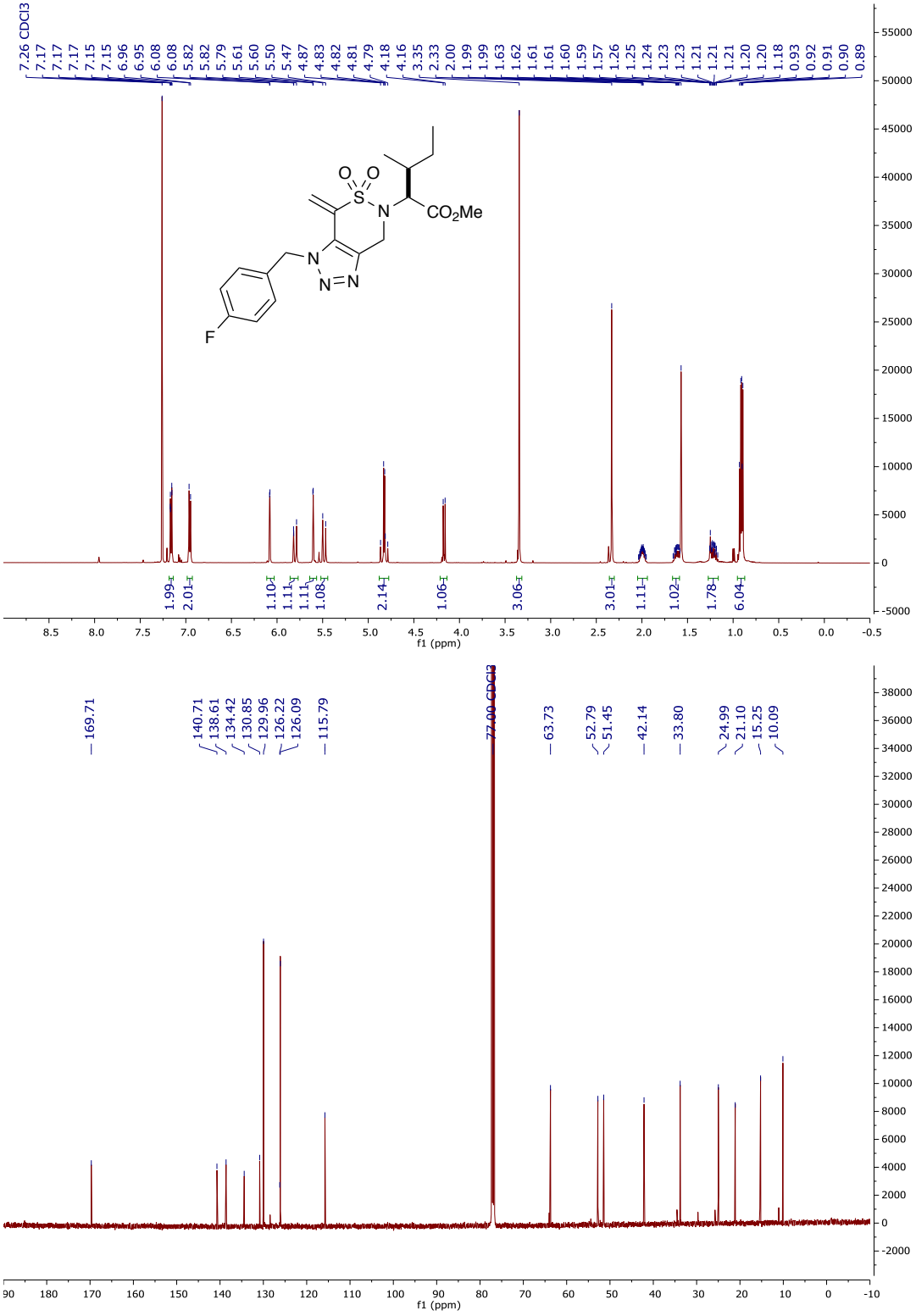
Methyl (*S*)-2-(3-(4-methoxybenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-4-methylpentanoate (2.4.2.3.29)



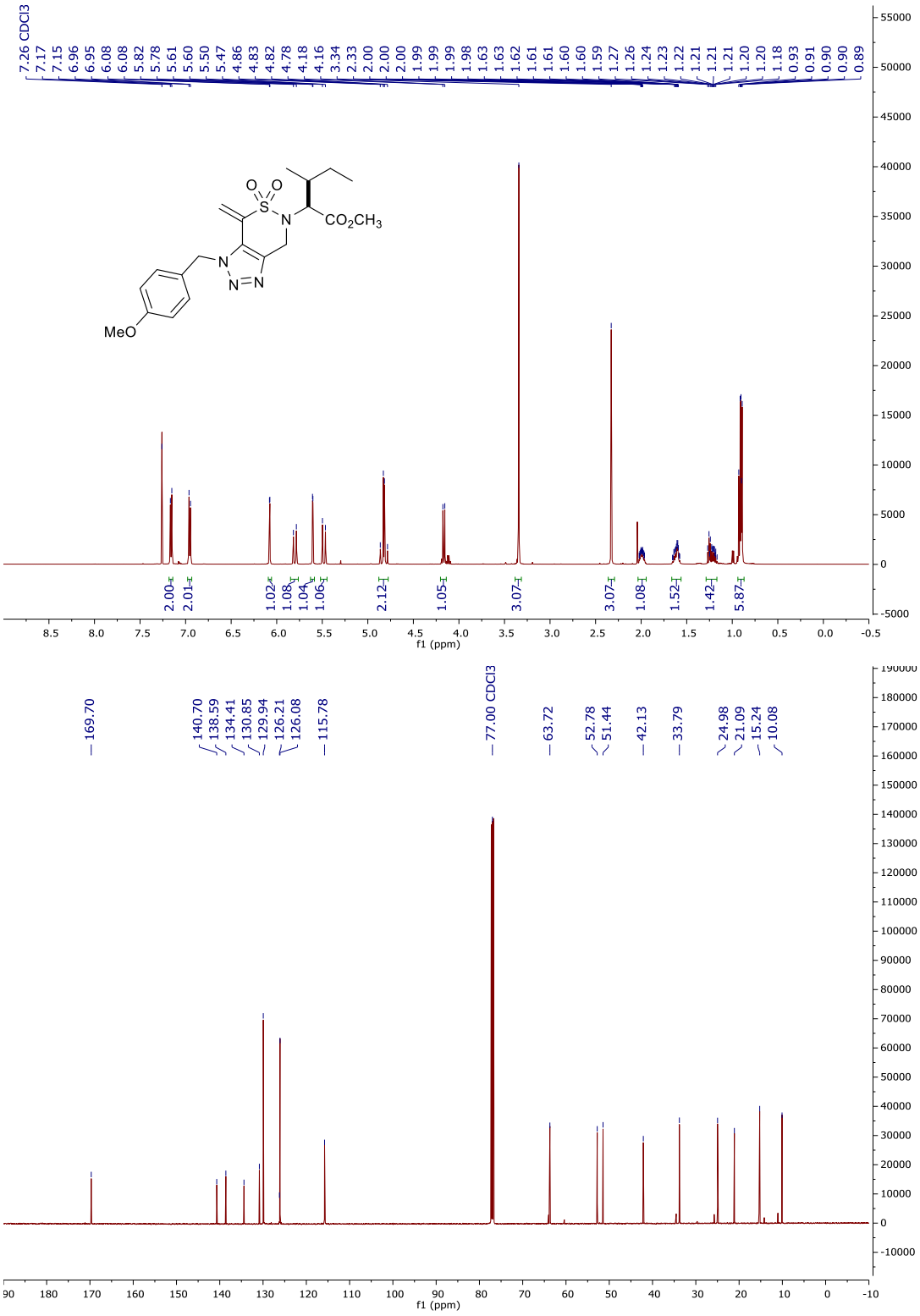
Methyl (2*S*,3*S*)-3-methyl-2-(4-methylene-5,5-dioxido-3-(4-(trifluoromethyl)benzyl)-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)pentanoate (2.6.3.30)



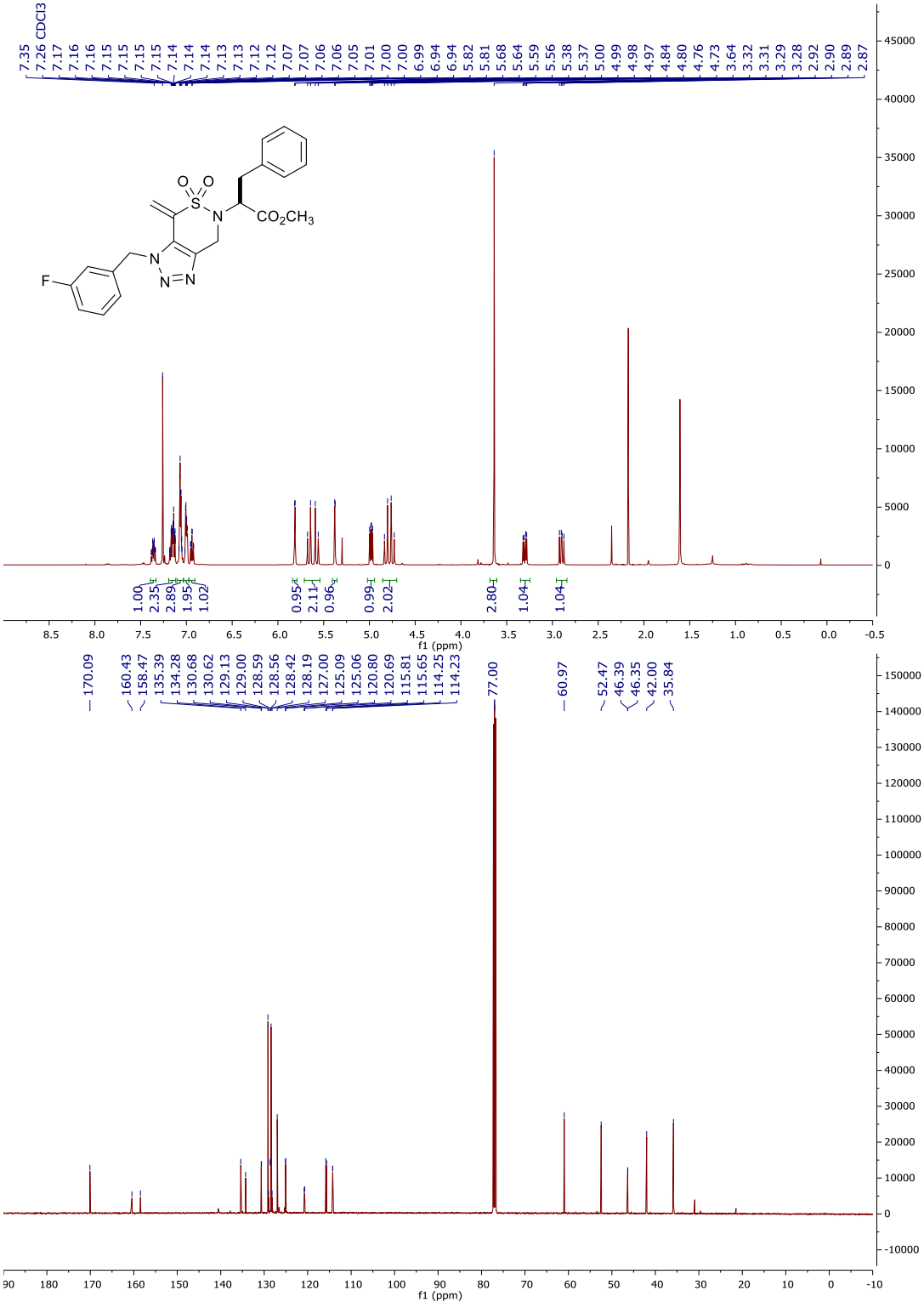
Methyl (2*S*,3*S*)-2-(3-(2-fluorobenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-3-methylpentanoate (2.4.2.3.31)



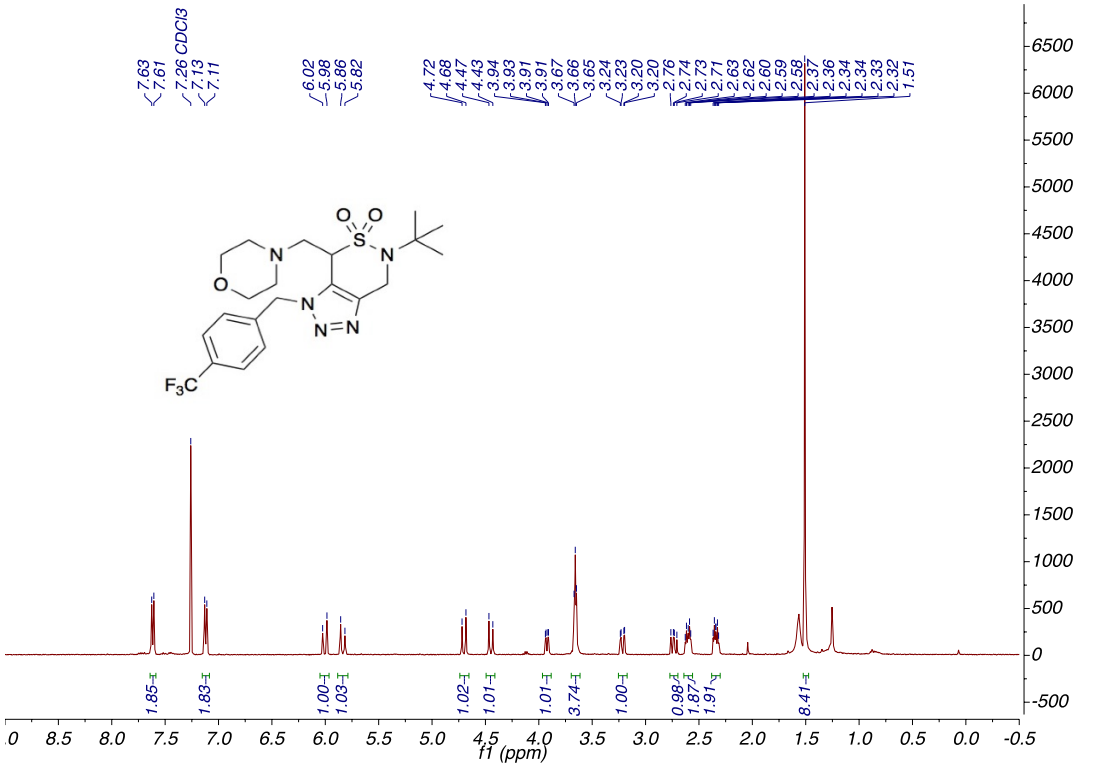
Methyl (2*S*,3*S*)-2-(3-(4-methoxybenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-3-methylpentanoate (2.4.2.3.32)

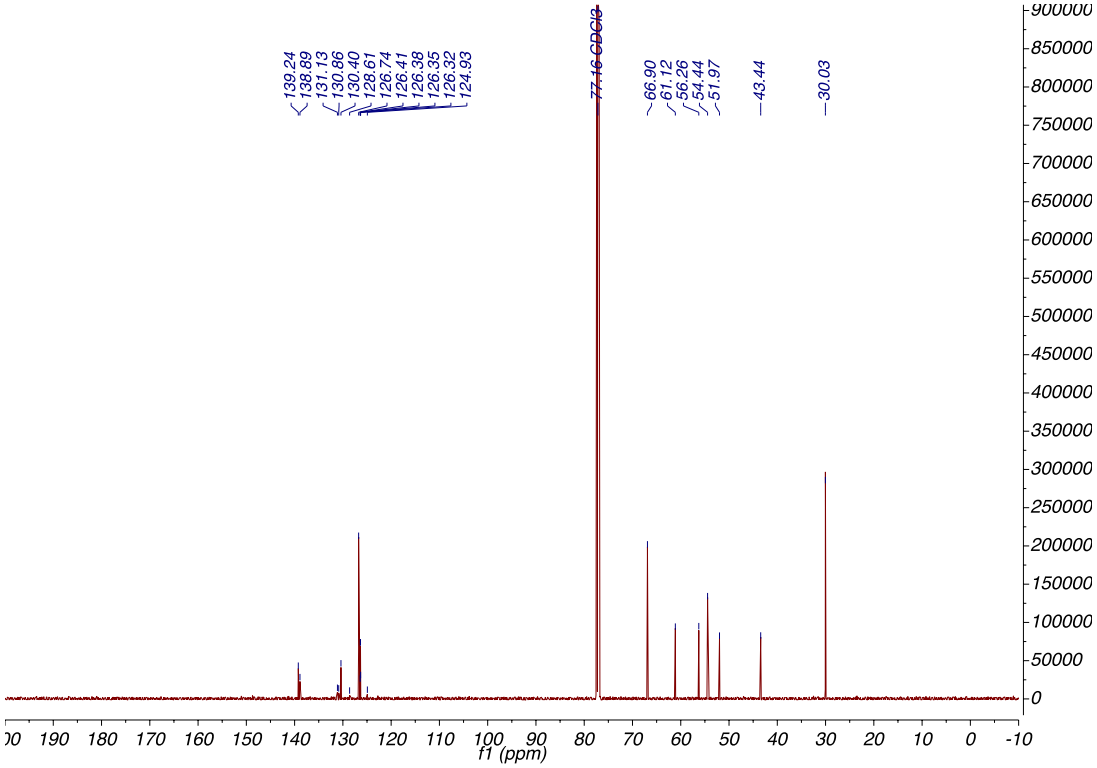


Methyl (*S*)-2-(3-(3-fluorobenzyl)-4-methylene-5,5-dioxido-4,7-dihydro-[1,2,3]triazolo[4,5-d][1,2]thiazin-6(3H)-yl)-3-phenylpropanoate (2.4.2.3.33)

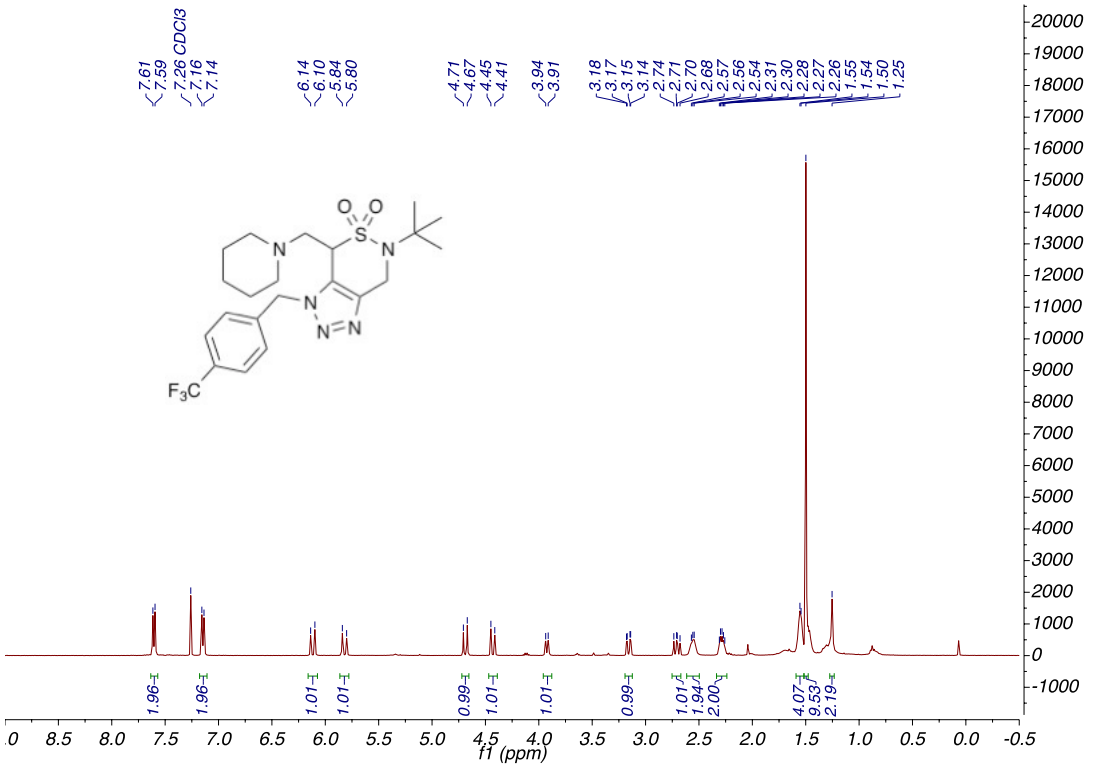


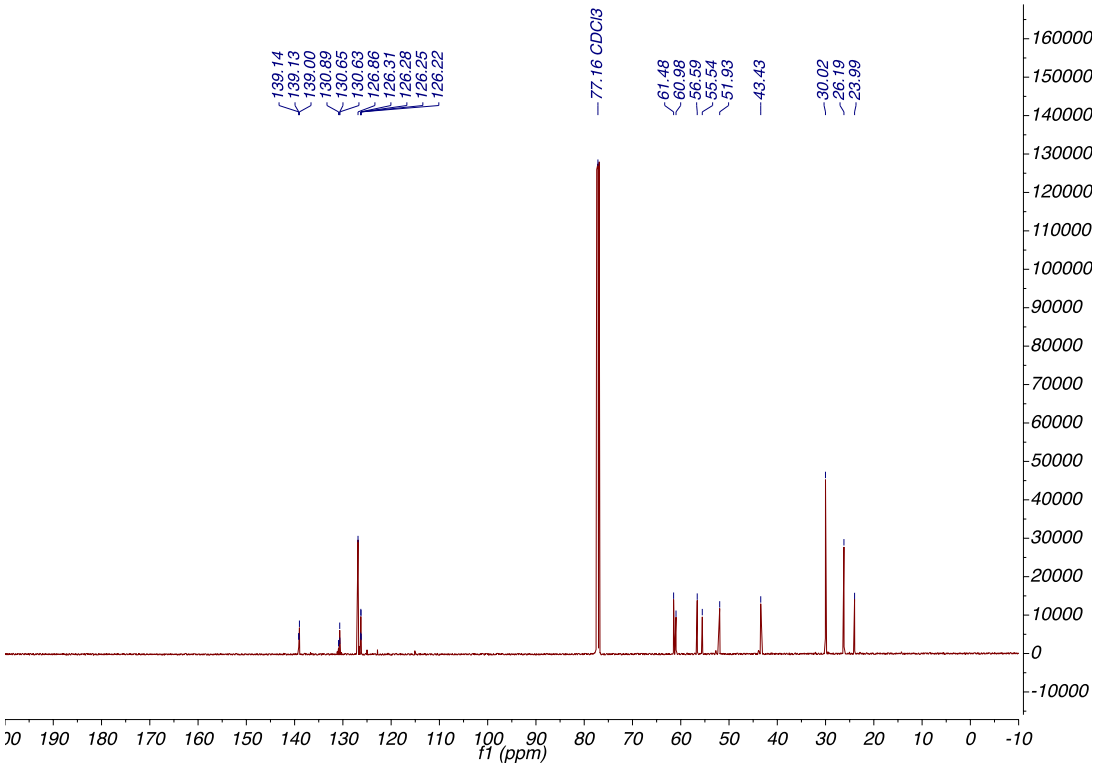
6-(*tert*-butyl)-4-(morpholinomethyl)-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.1)



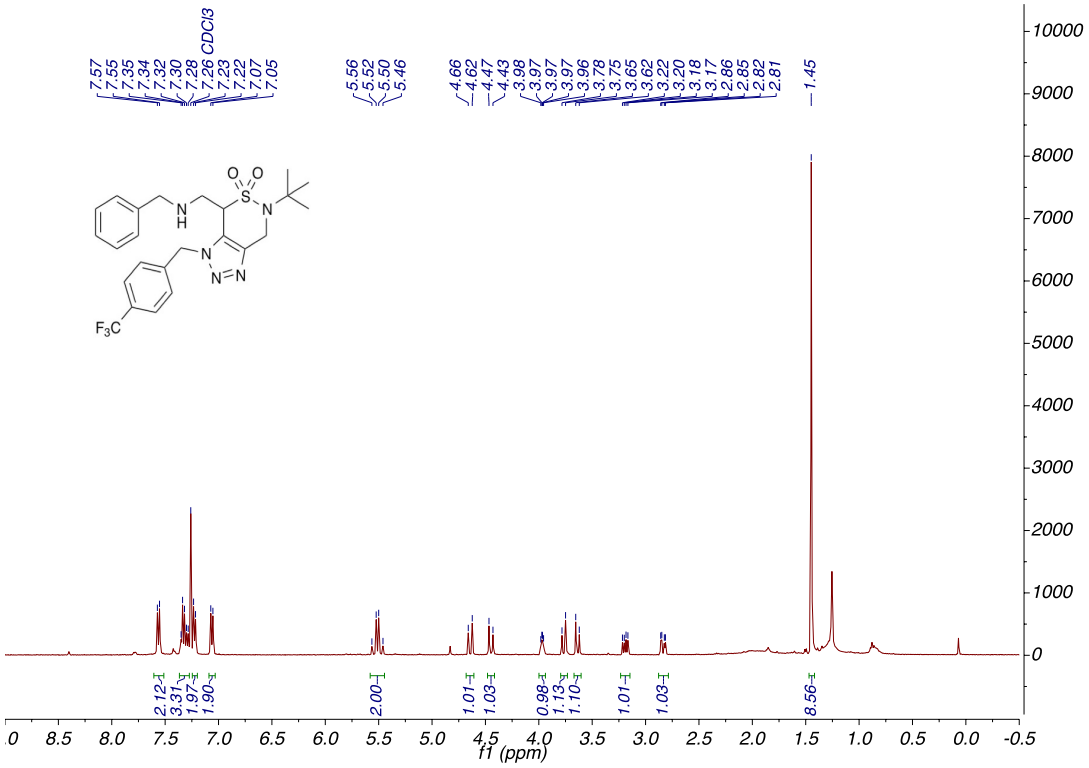


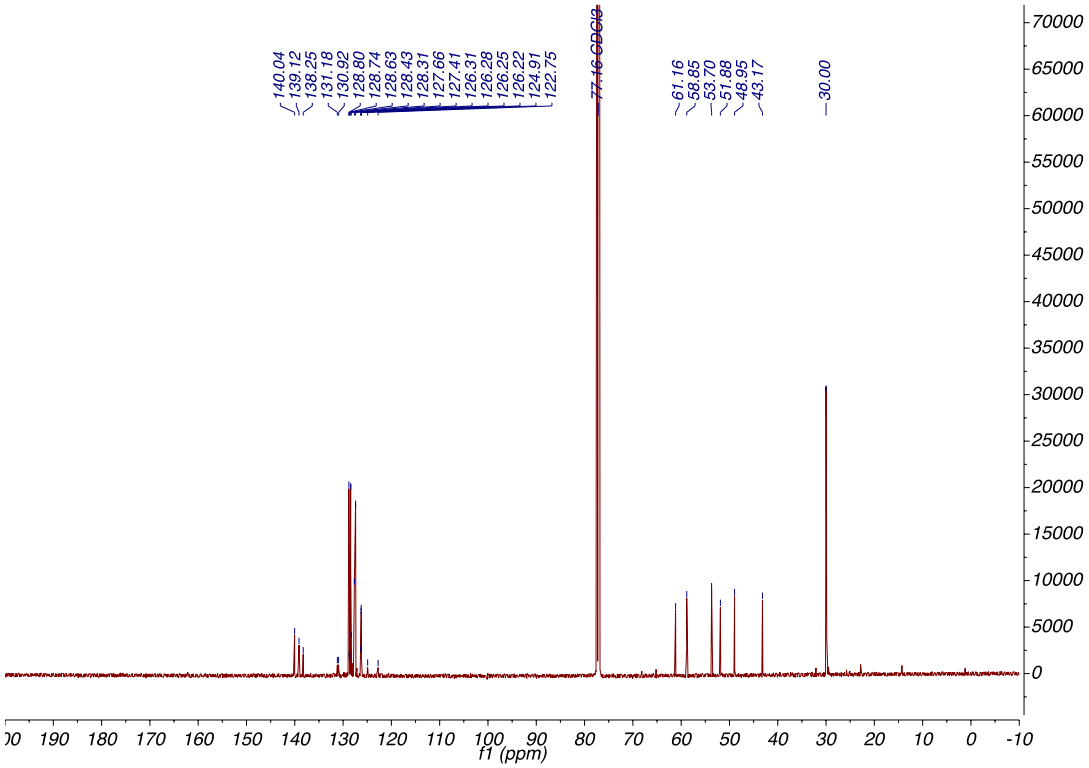
6-(*tert*-butyl)-4-(piperidin-1-ylmethyl)-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.2)



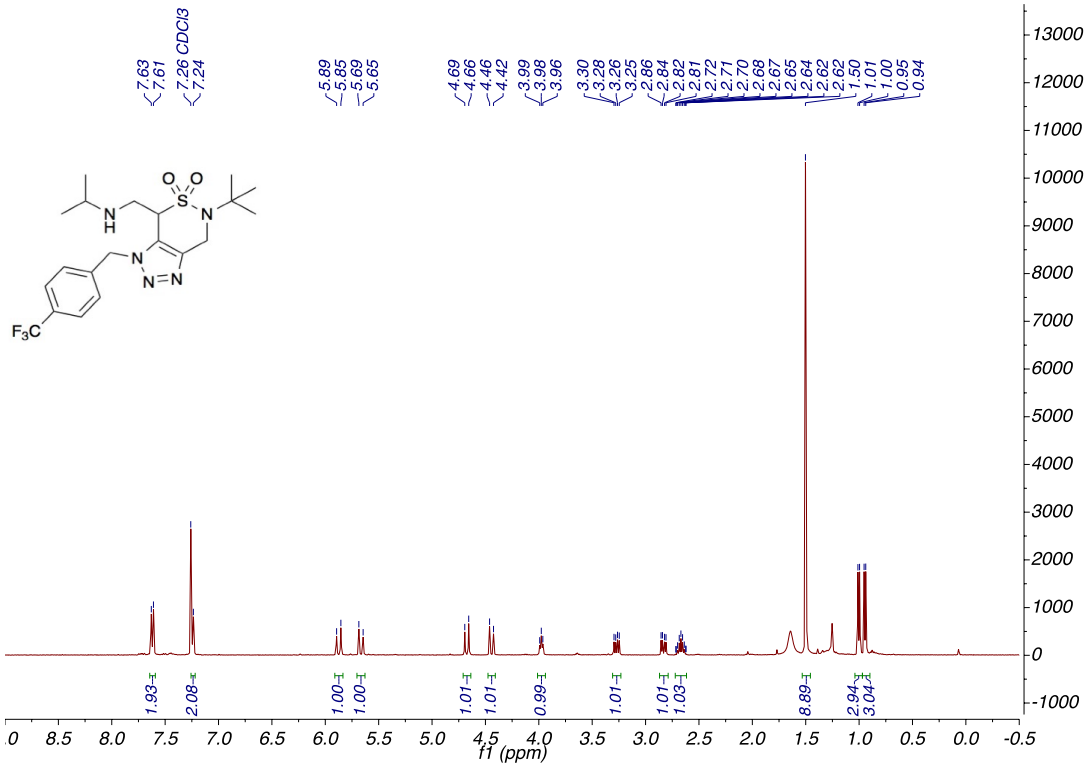


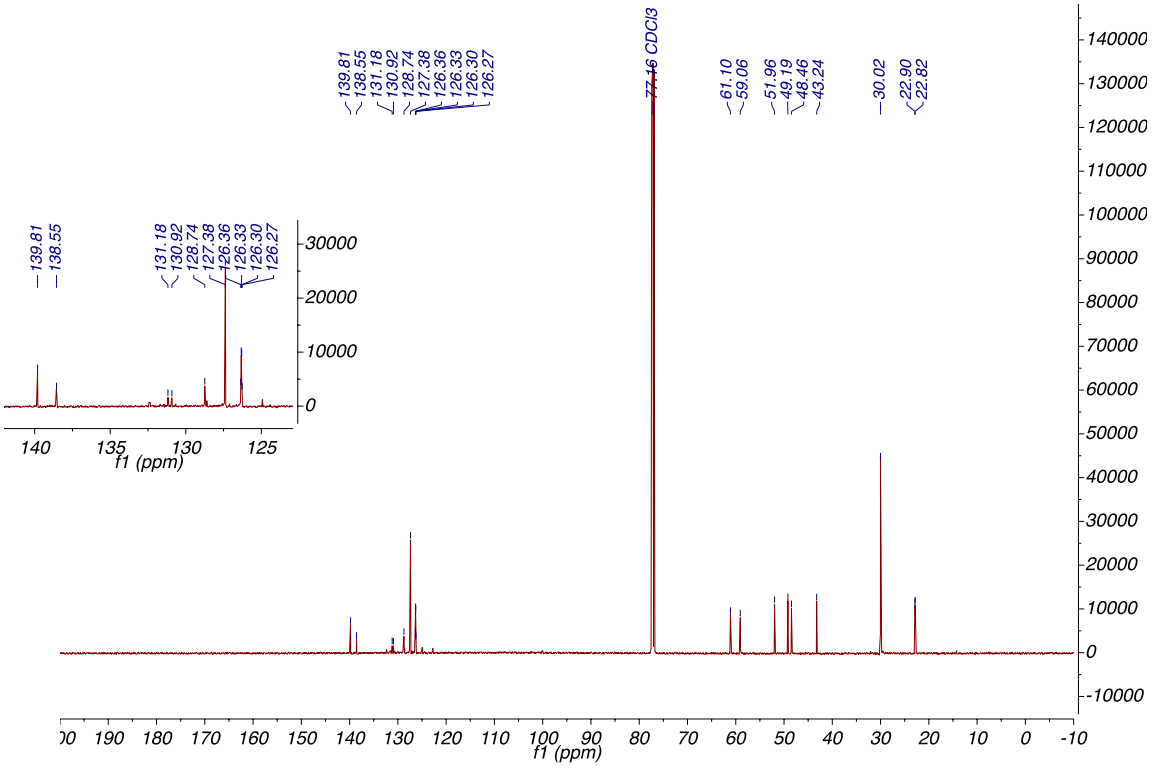
4-((benzylamino)methyl)-6-(*tert*-butyl)-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.3)



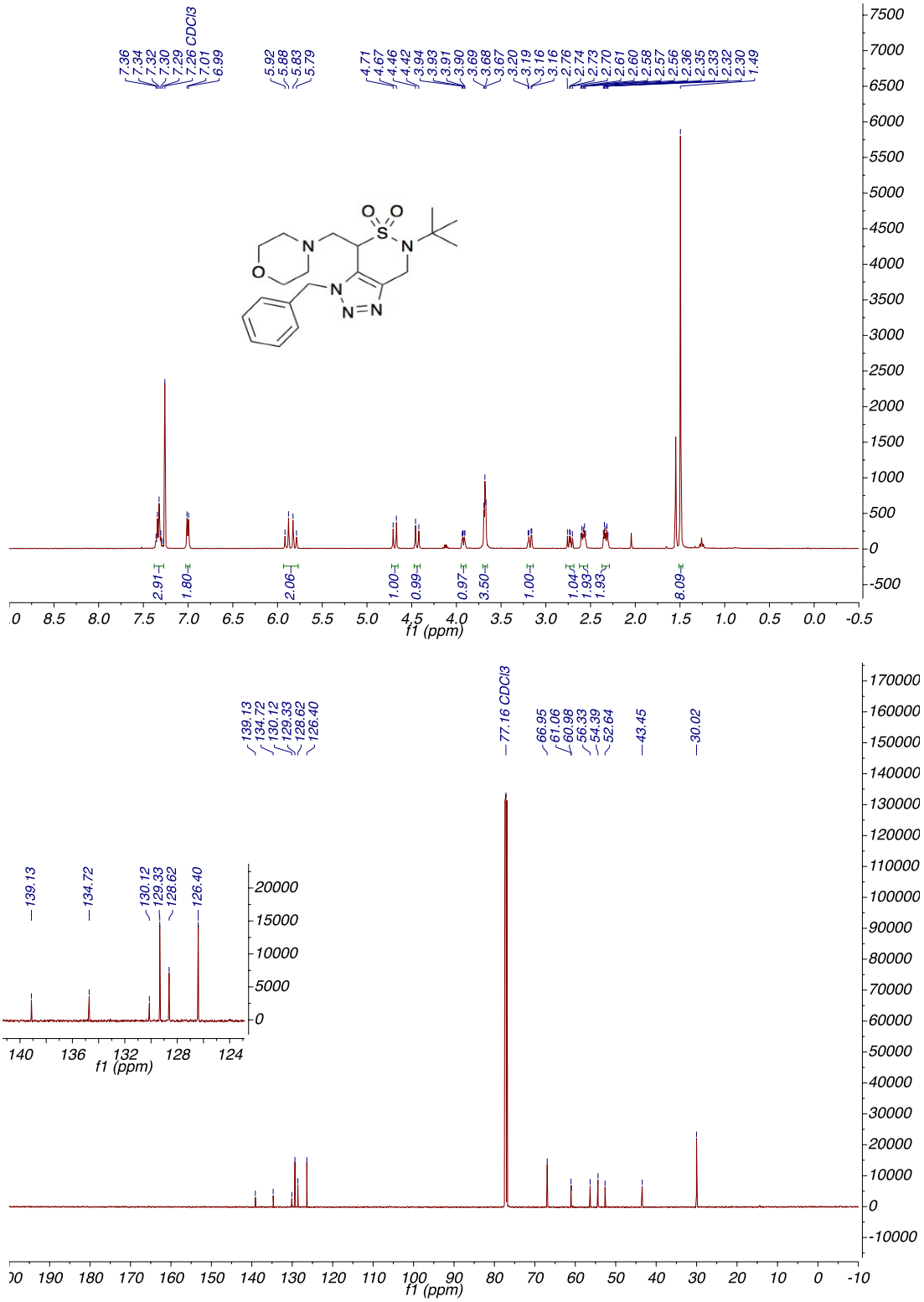


6-(*tert*-butyl)-4-((isopropylamino)methyl)-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.4)

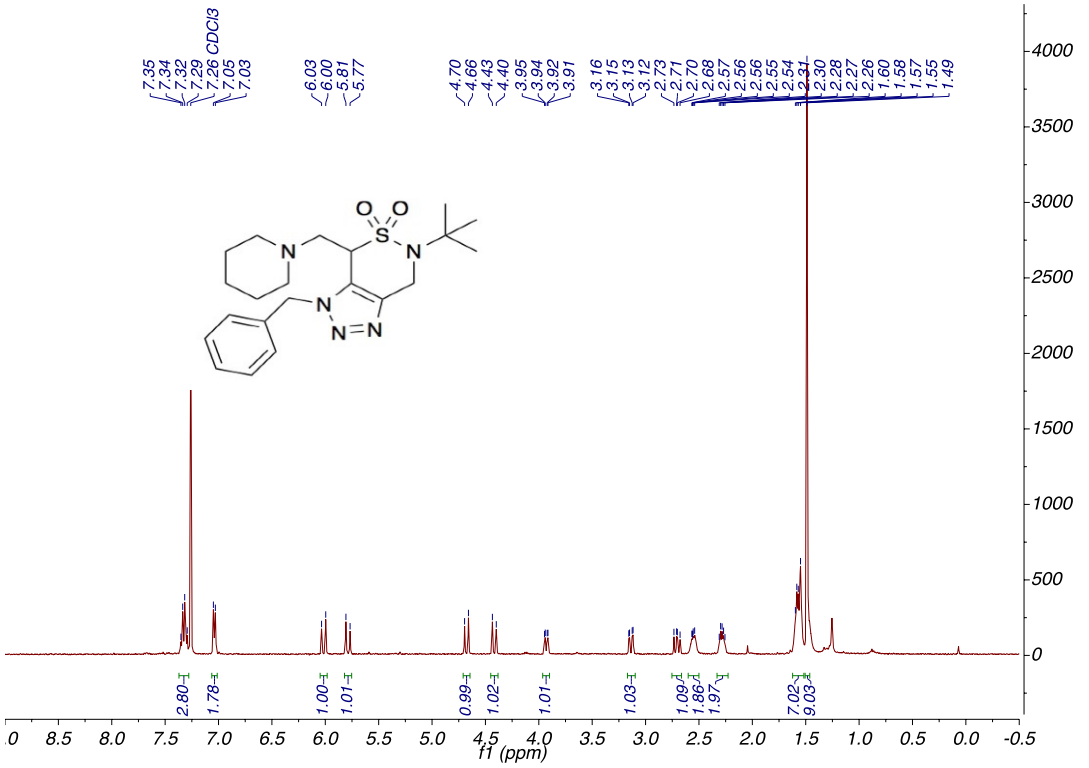


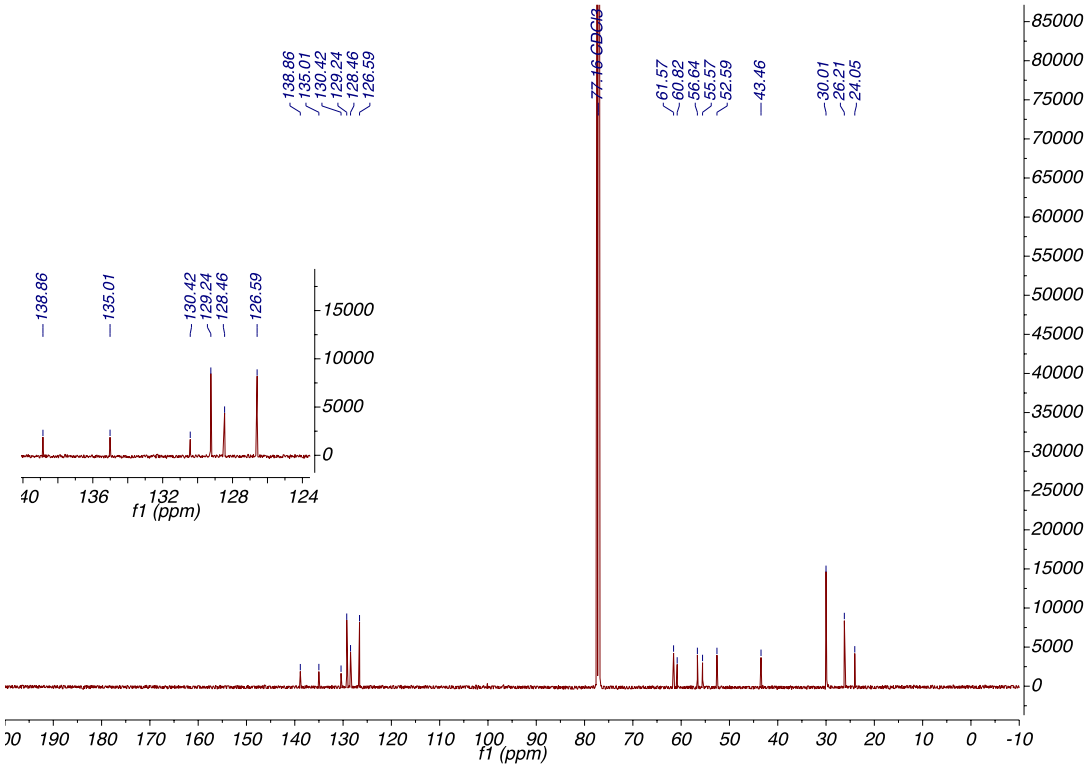


3-benzyl-6-(*tert*-butyl)-4-(morpholinomethyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.5)

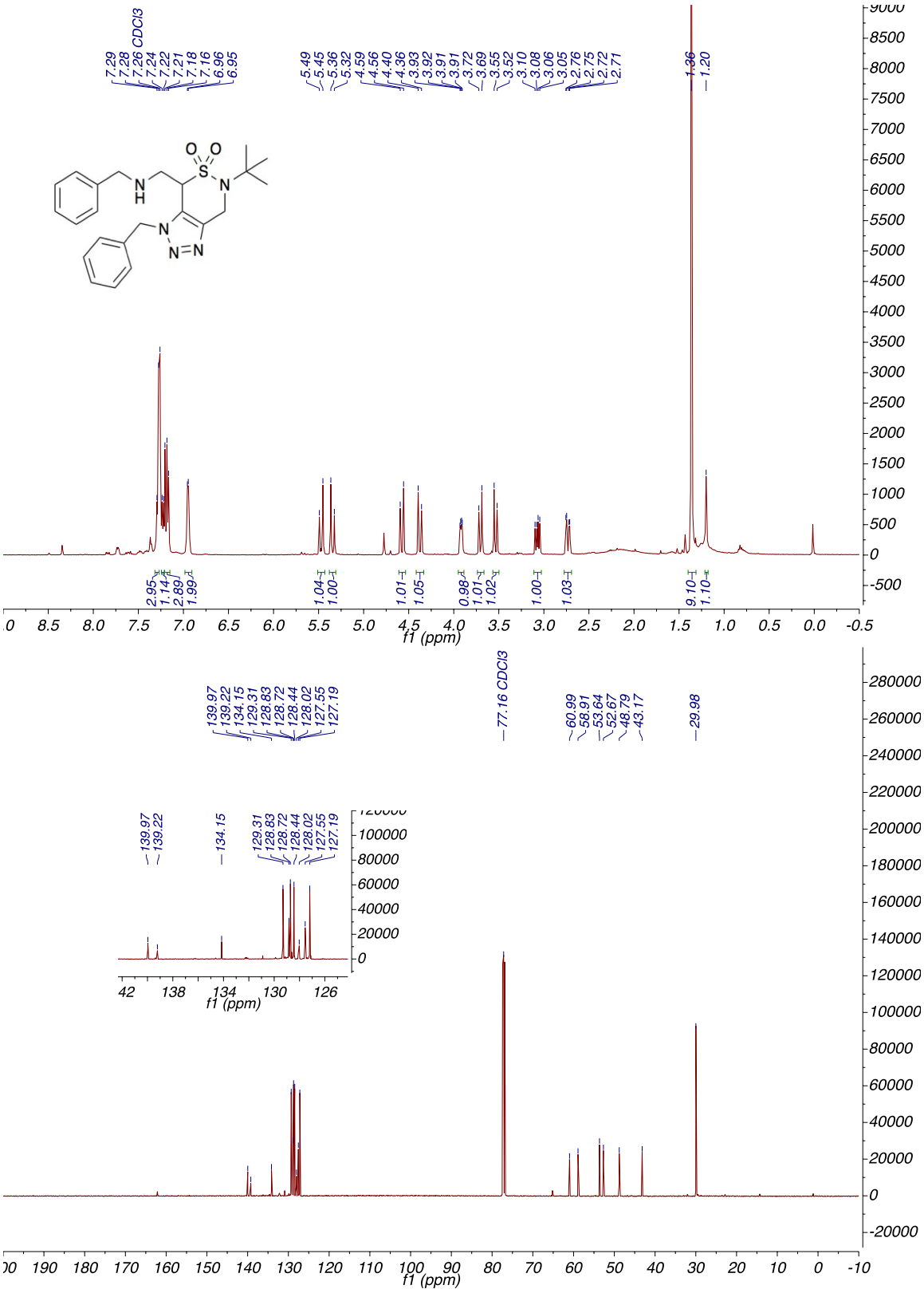


3-benzyl-6-(*tert*-butyl)-4-(piperidin-1-ylmethyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.6)

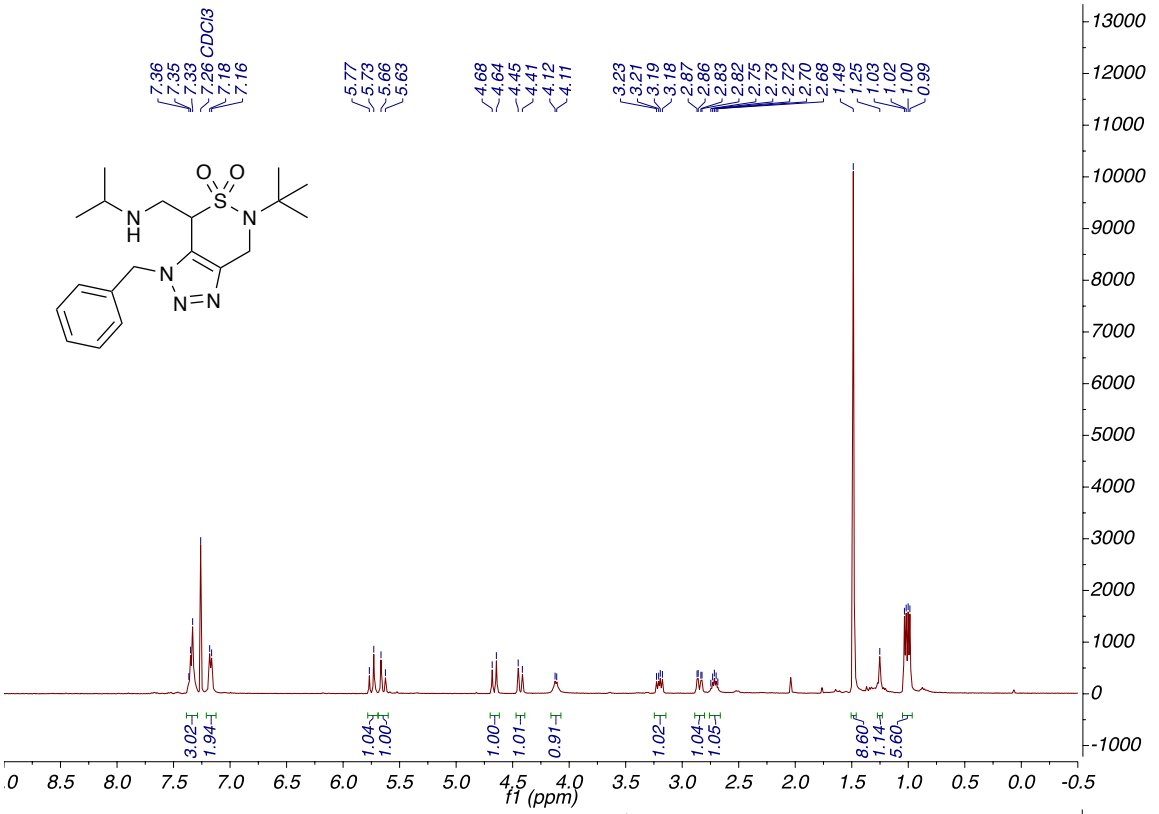


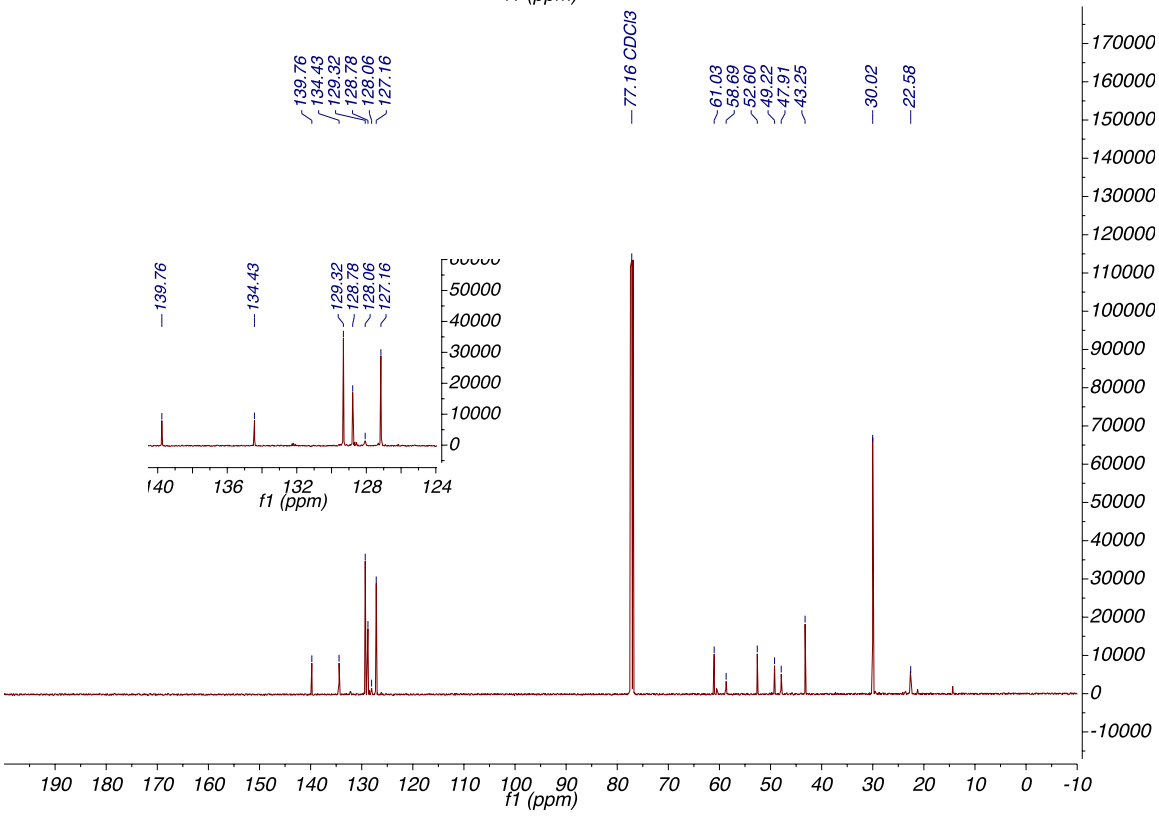


3-benzyl-4-((benzylamino)methyl)-6-(*tert*-butyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.7)

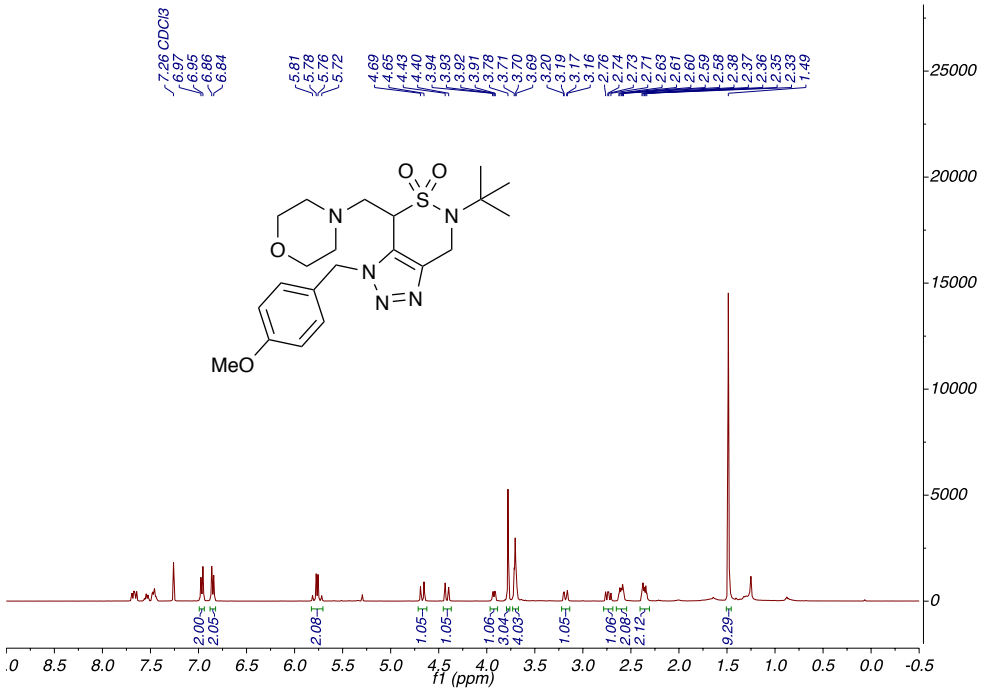


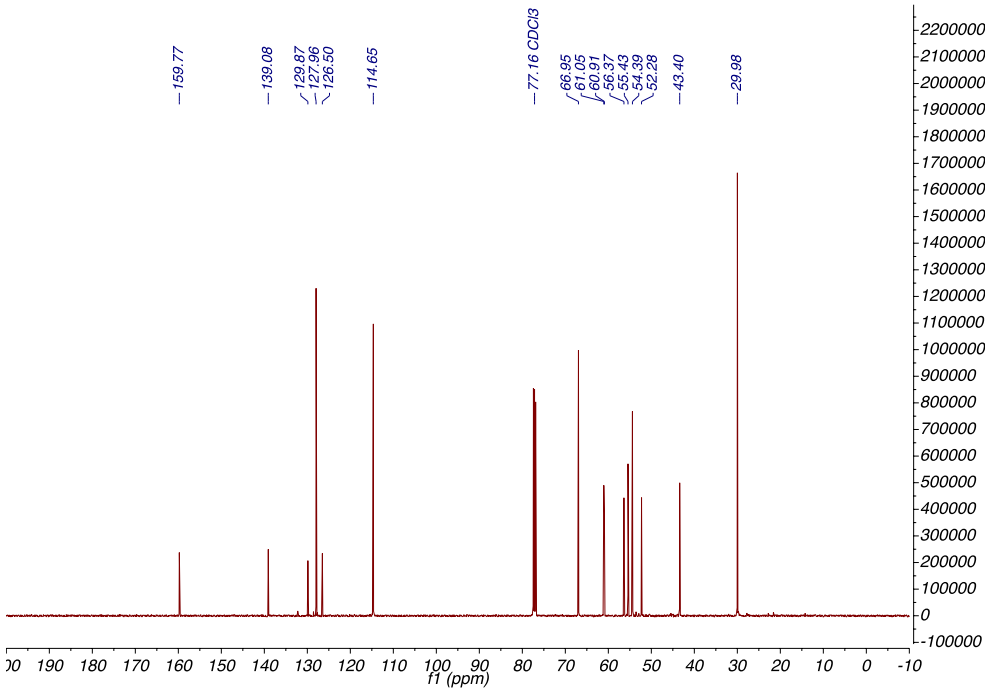
3-benzyl-6-(*tert*-butyl)-4-((isopropylamino)methyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.8)



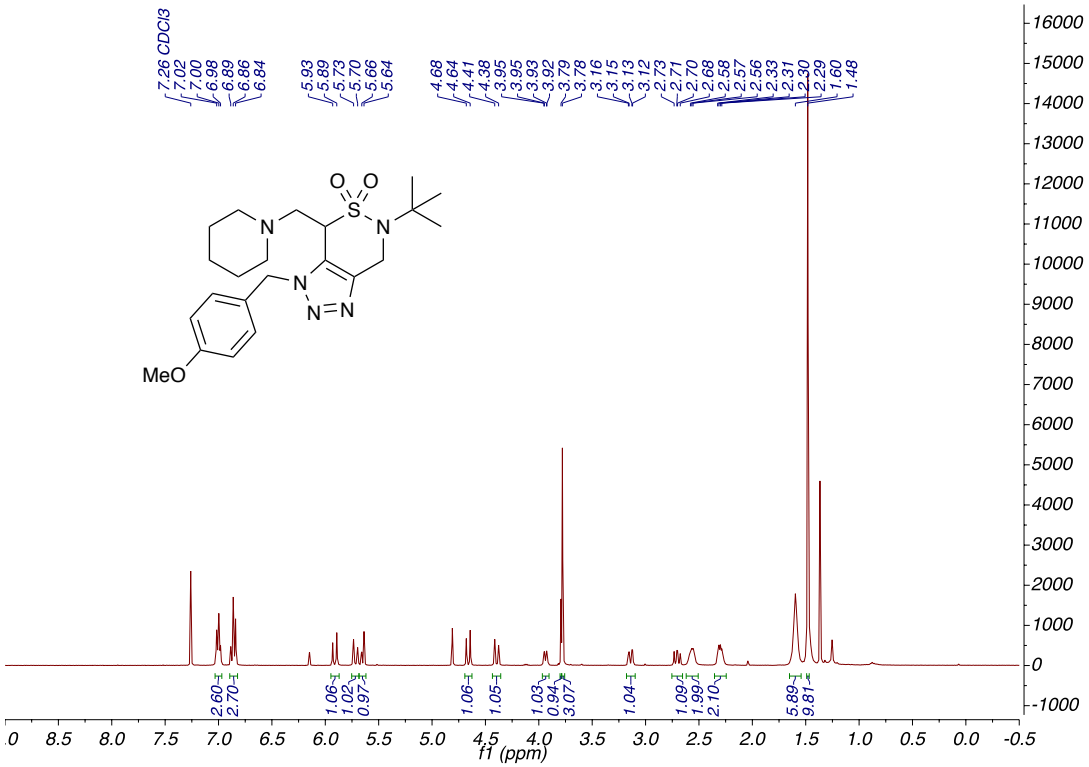


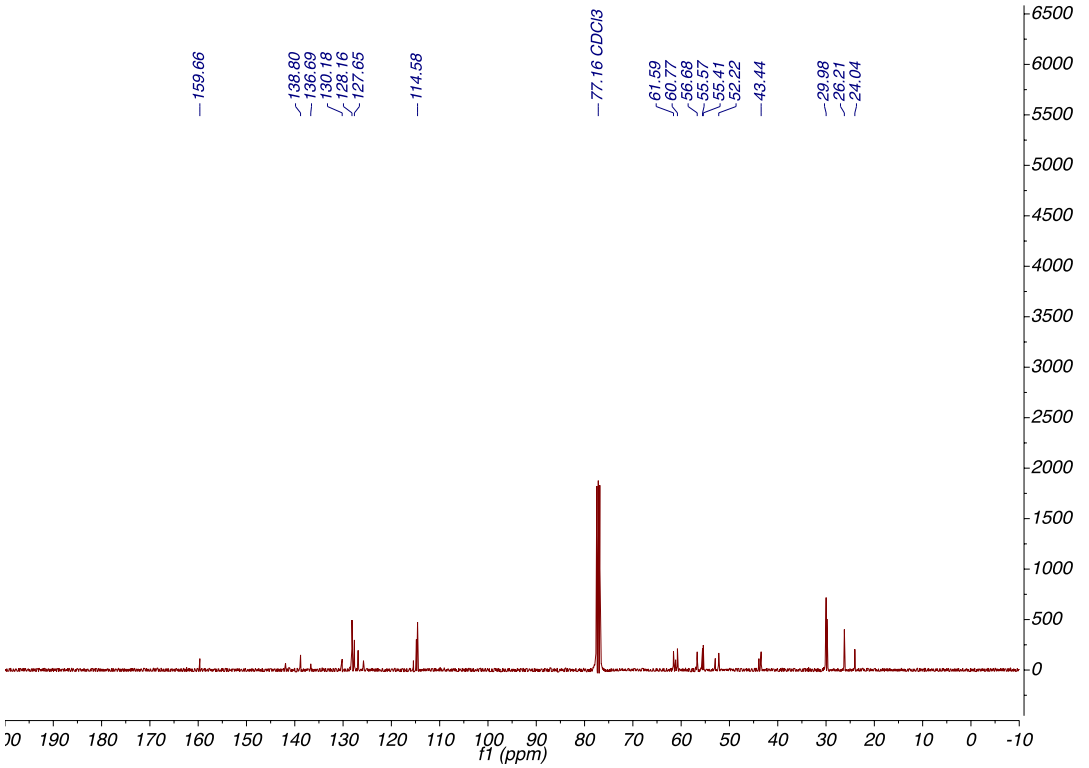
6-(tert-butyl)-3-(4-methoxybenzyl)-4-(morpholinomethyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.4.1.9)



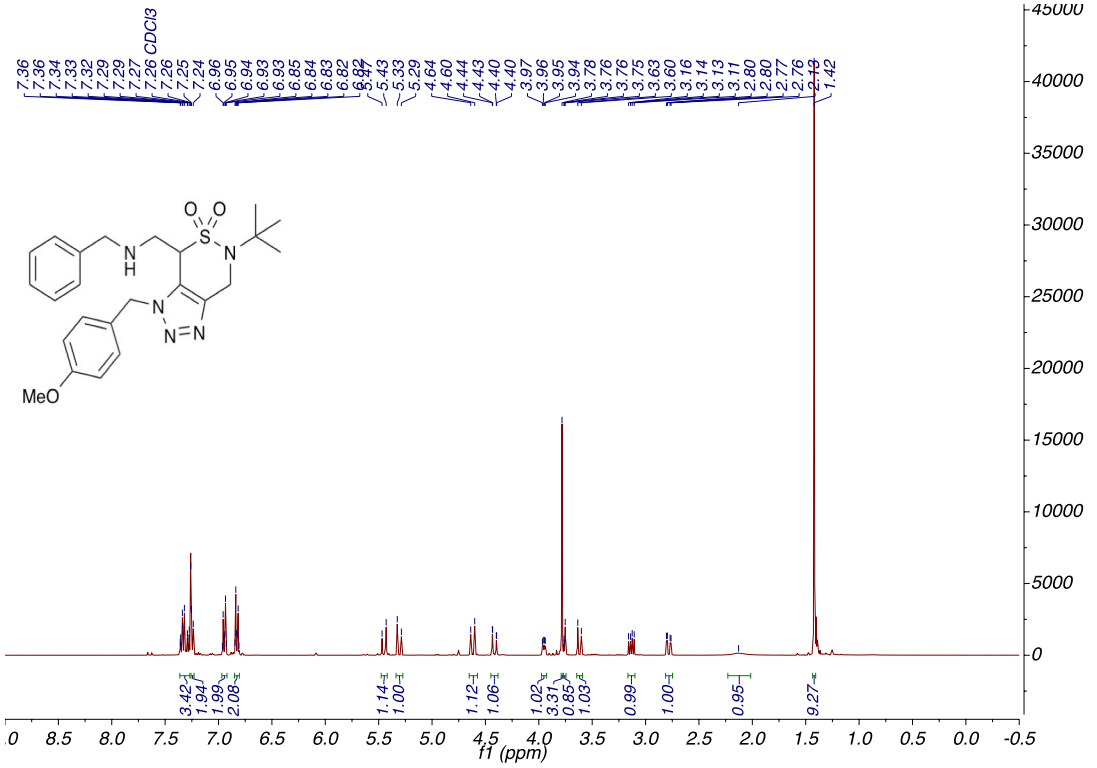


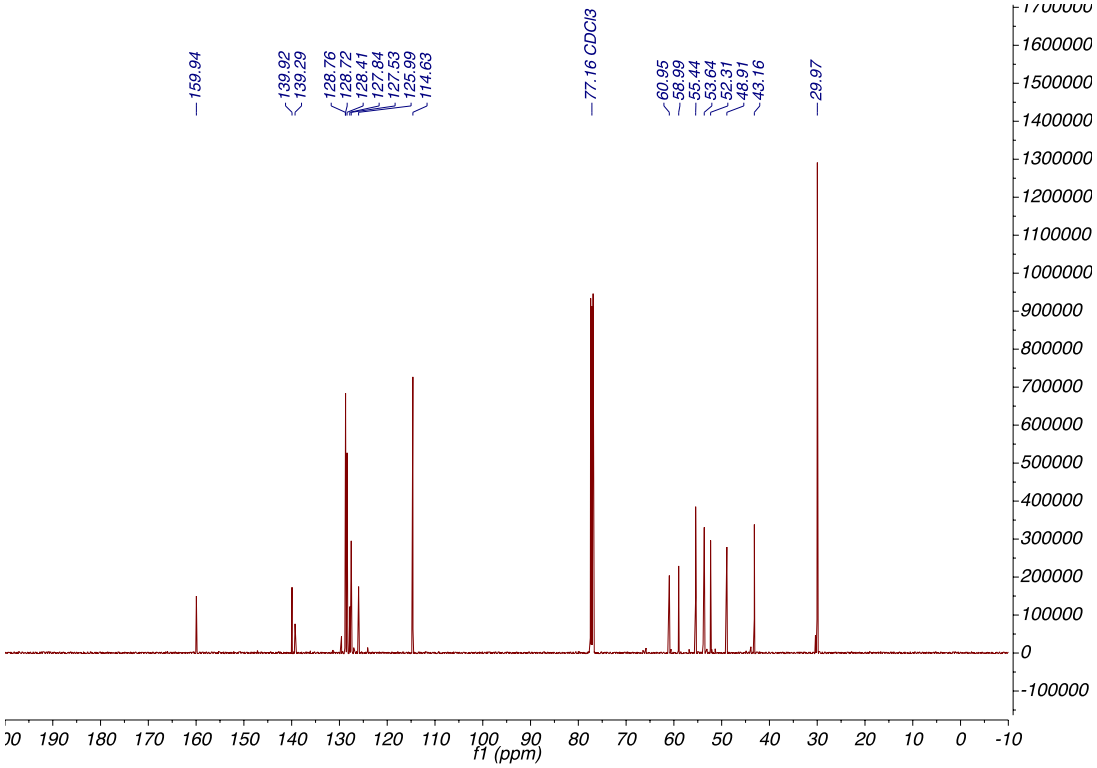
6-(*tert*-butyl)-3-(4-methoxybenzyl)-4-(piperidin-1-ylmethyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.10)



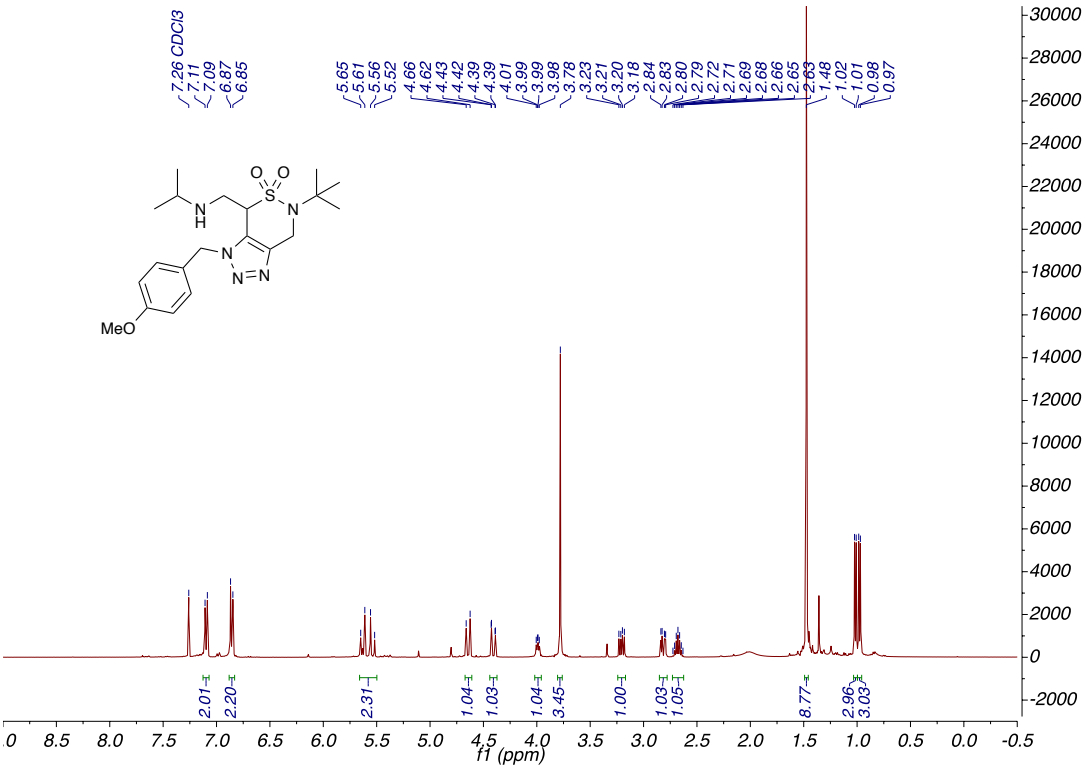


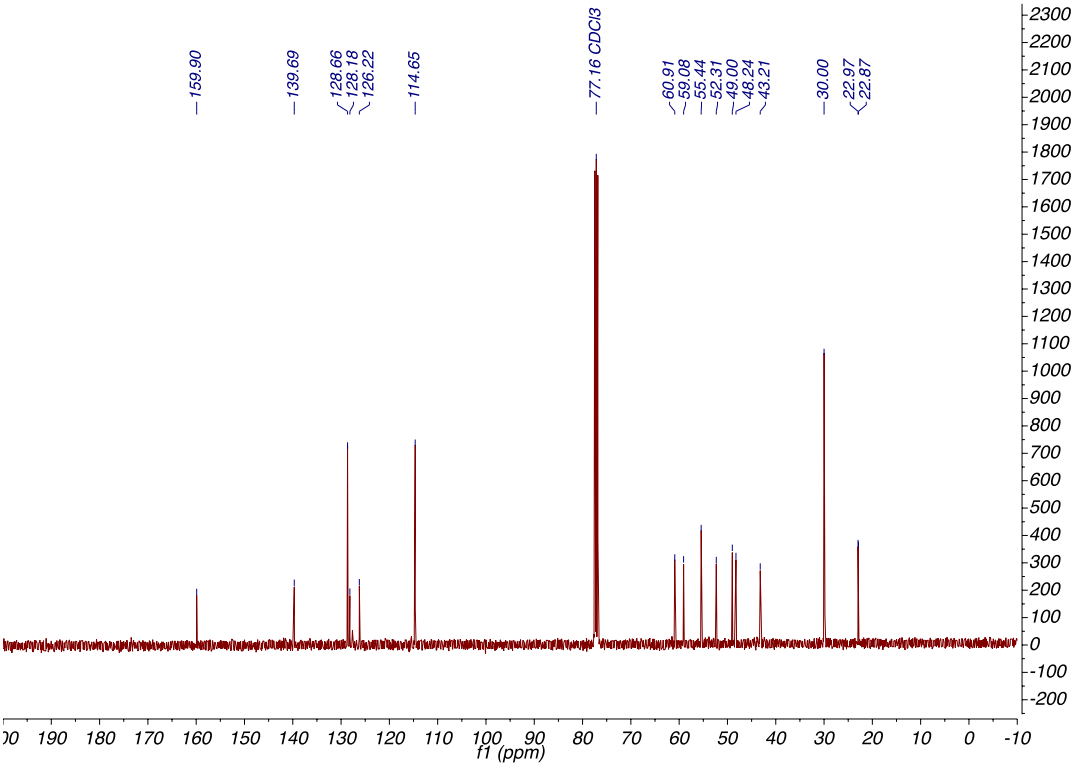
4-((benzylamino)methyl)-6-(*tert*-butyl)-3-(4-methoxybenzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.11)



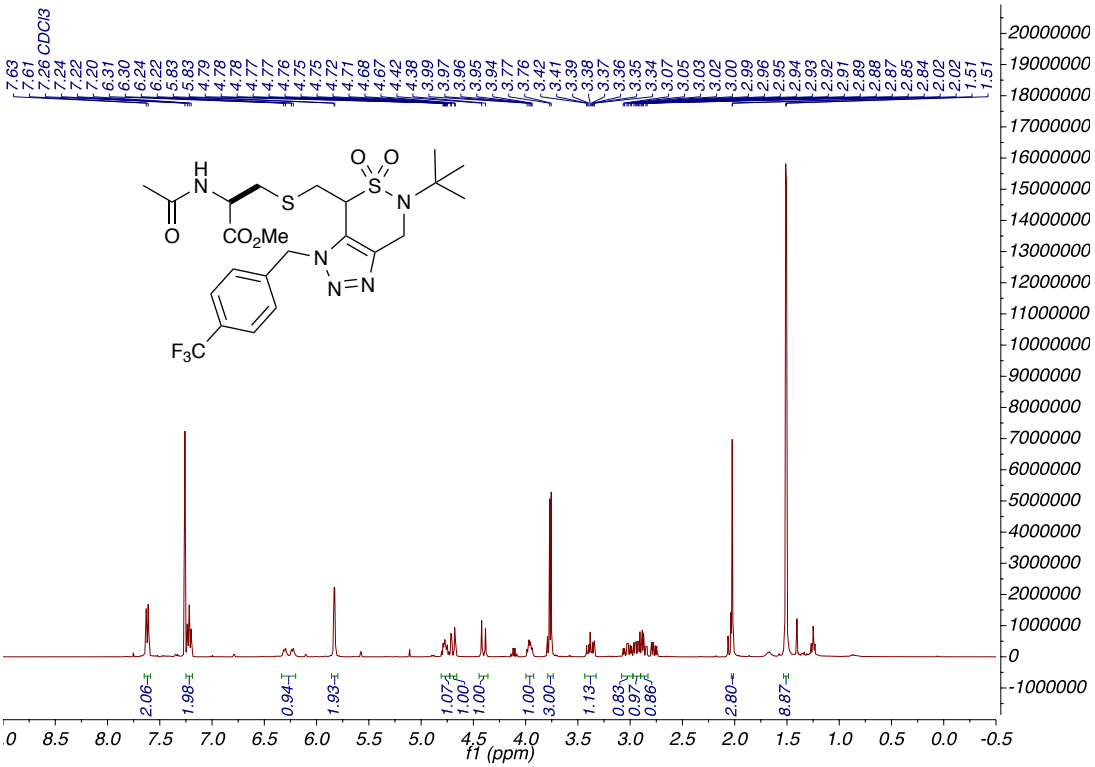


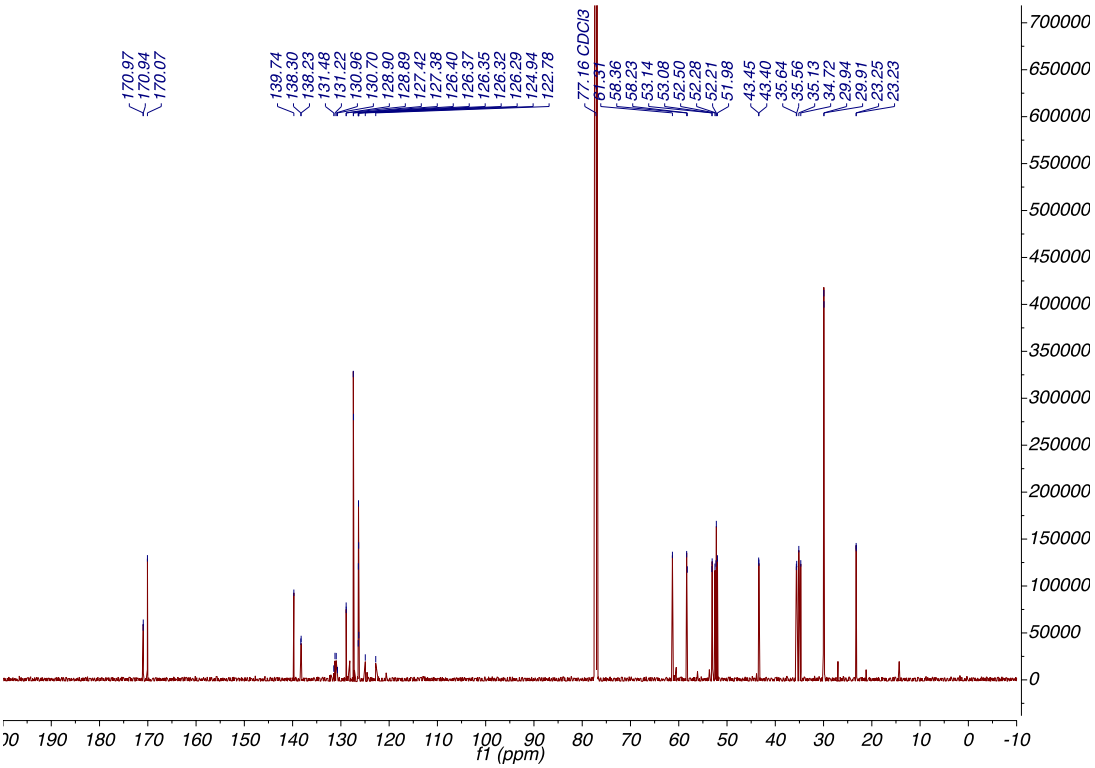
6-(*tert*-butyl)-4-((isopropylamino)methyl)-3-(4-methoxybenzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazine 5,5-dioxide (2.4.4.1.12)



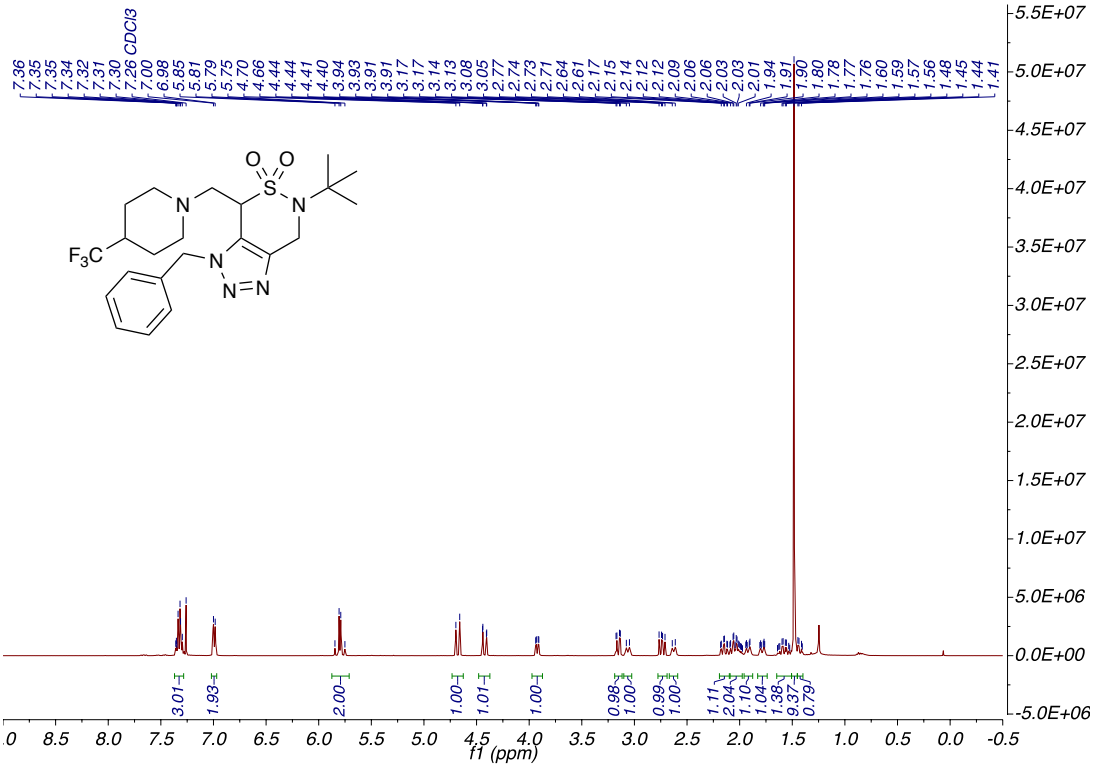


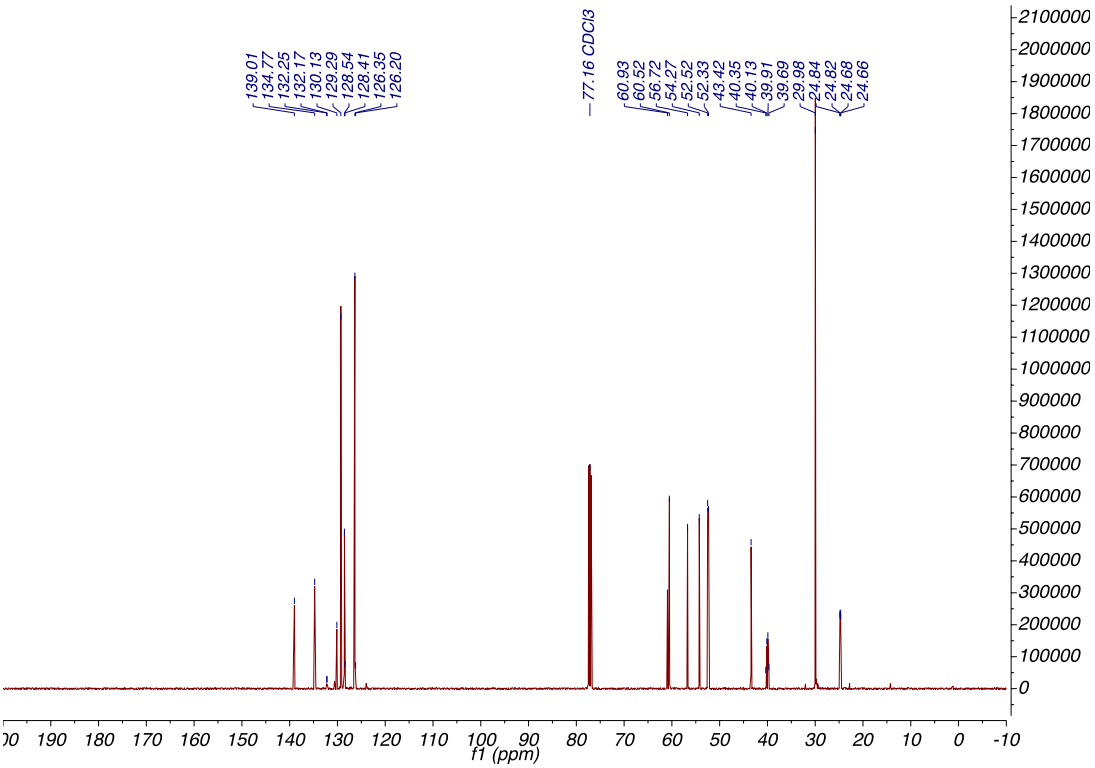
Methyl *N*-acetyl-*S*-((6-(*tert*-butyl)-5,5-dioxido-3-(4-(trifluoromethyl)benzyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*d*][1,2]thiazin-4-yl)methyl)-*L*-cysteinate (2.4.3.1)





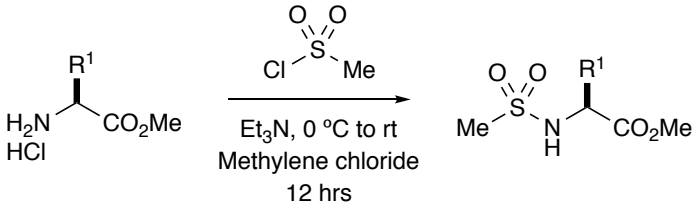
3-benzyl-6-(tert-butyl)-4-((4-(trifluoromethyl)piperidin-1-yl)methyl)-3,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d][1,2]thiazine 5,5-dioxide (2.4.6.1)





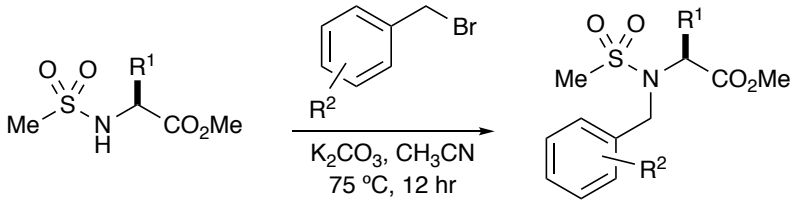
General Procedures

General Procedure **A** for Mestyl-sulfonamide compounds **3.3.1.2.1–3.3.1.2.3**:



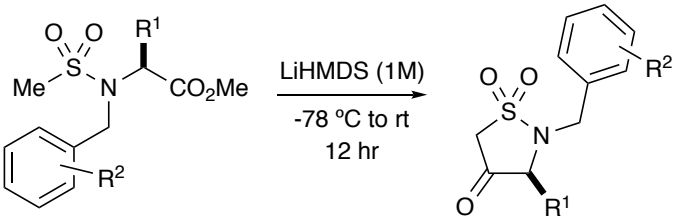
The HCl salts of Amino esters (1 equivalent) were dissolved in methylene chloride (0.2 M) and triethylamine (3 equivalents) was added. The reaction was brought to 0 ºC in an ice bath before Methanesulfonyl chloride (1.2 equivalents) was added. The reaction was stirred 0 ºC to room temperature overnight. Upon completion by normal phase thin-layer-chromatography, the reaction was extracted with saturated brine and methylene chloride, dried with sodium sulfate, filtered and condensed. The product was purified with normal phase silica flash chromatography to afford mestylated amino esters **3.3.1.2.1–3.3.1.2.3** in yields up to 98 %.

General Procedure **B** for *N*-benzylated sulfonamide compounds **3.3.2.1.1–3.3.2.1.10**:



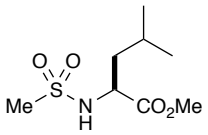
Mestyl-sulfonamides **3.3.1.2.1–3.3.1.2.3** (1 equivalent) were dissolved in anhydrous acetonitrile (0.2 M) before K_2CO_3 (3 equivalents) was added. Next, a benzyl bromide (2 equivalents) was added to the flask and the reaction was heated at 75 ºC overnight using a condenser. Upon reaction completion by normal phase thin layer chromatography, the K_2CO_3 was filtered off, the reaction condensed and the product purified by normal phase flash chromatography to afford *N*-benzylated sulfonamide **3.3.2.1.1–3.3.2.1.10** in yields up to 90 %.

General Procedure **C** for Dieckmann cyclization to sultams **3.3.3.1.1–3.3.3.1.9**:



N-benzylated sulfonamide **3.3.2.1.1–3.3.2.1.10** (1 equivalent) were dissolved in anhydrous tetrahydrofuran under argon before the solution was brought to -78 ºC via a dry ice and acetone bath. Next, LiHMDS (1M in THF, 2 equivalents) was with added drop-wise to the flask, and the reaction was stirred from -78 ºC to room temperature overnight. The reaction was quenched with 1 M HCl until the solution was pH = 3 by pH paper. Rotary evaporation was used to remove the solvent, before the product was re-dissolved in ethyl acetate and extracted with saturated brine. The organic layer was dried with sodium sulfate, filtered, and condensed. The residue was then purified by normal phase flash chromatography to afford sultams **3.3.3.1.1–3.3.3.1.9** in yields of up to 95 %.

Methyl (methylsulfonyl)-*L*-leucinate



According to the reaction protocol described in general procedure **A**, compound **3.3.1.2.1** (89 %, 2.18 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -8.05 (*c* = 0.018, CH_2Cl_2);

$\mathbf{R_f}$ = 0.54 (EtOAc:Hexane = 1:1);

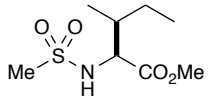
FTIR (neat): 3281, 2958, 2872, 1743, 1435, 1369, 1327, 1273, 1143, 1096 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 4.81 (s, 1H, NH), 4.13 (td, *J* = 9.1, 5.1 Hz, 1H, C<u>H</u>CO_2Me), 3.78 (s, 3H, OMe), 2.94 (s, 3H, SO_2<u>Me</u>), 1.89–1.78 (m, 1H, MeC<u>H</u>Me), 1.62 (ddd, *J* = 13.7, 8.6, 5.0 Hz, 1H, CH_2), 1.58–1.50 (m, 1H, CH_2), 0.96 (t, *J* = 6.9 Hz, 6H, 2Me);

^{13}C NMR (126 MHz, $CDCl_3$) 173.6 (CO), 54.6 (NH<u>C</u>HCO_2Me), 52.8 (CO_2<u>Me</u>), 42.3 (SO_2Me), 41.4 (CH_2), 24.5 (Me<u>C</u>HMe), 22.9 (Me), 21.4 (Me);

HRMS calculated for $C_8H_{17}NO_4S$ 246.0776 $(M+Na)^+$; found 246.0779 (TOF MS ES^+).

Methyl (methylsulfonyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **A**, compound **3.3.1.2.2** (98 %, 3.02 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -2.54 (*c* = 0.011, CH_2Cl_2);

$\mathbf{R_f}$ = 0.40 (EtOAc:Hexane = 1:1);

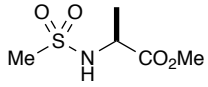
FTIR (neat): 3426, 2966, 2936, 1736, 1454, 1382, 1327, 1252, 1157, 1057, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 4.92 (d, *J* = 29.5 Hz, 1H, NH), 4.03–3.97 (m, 1H, NHCHCO$_2$Me), 3.79 (d, *J* = 3.1 Hz, 3H, OMe), 2.93 (s, 3H, SO_2Me), 1.91 (dtq, *J* = 10.4, 7.6, 5.3 Hz, 1H, CHMe), 1.39 (dtt, *J* = 14.7, 7.4, 3.7 Hz, 1H, CH_2Me), 1.22–1.09 (m, 1H, CH_2Me), 0.99 (dd, *J* = 6.8, 2.6 Hz, 3H, Me), 0.91 (td, *J* = 7.2, 2.2 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 172.6 (CO), 60.7 (NHCHCO$_2$Me), 52.6 (CO_2Me), 41.1 (SO_2Me), 38.3 (CHMe), 24.6 (CH_2Me), 15.7 (Me), 11.5 (Me);

HRMS calculated for $C_8H_{17}NO_4S$ 246.0776 $(M+Na)^+$; found 246.0782 (TOF MS ES^+).

Methyl (methylsulfonyl)-*L*-alaninate



According to the reaction protocol described in general procedure **A**, compound **3.3.1.2.3** (19 %, 0.25 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -24.00 (*c* = 0.0035, CH_2Cl_2);

$\mathbf{R_f}$ = 0.17 (EtOAc:Hexane = 1:1);

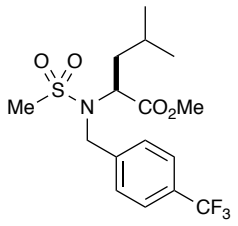
FTIR (neat): 3421, 2959, 1736, 1440, 1312, 1260, 1160, 1053 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 4.98 (s, 1H, NH), 4.21 (p, *J* = 7.2 Hz, 1H, NHC<u>H</u>CO_2Me), 3.79 (s, 3H, OMe), 2.98 (s, 3H, SO_2Me), 1.48 (d, *J* = 7.2 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 173.28 (CO), 53.01 (NH<u>C</u>HCO_2Me), 51.81 (OMe), 41.76 (SO_2Me), 20.0 (Me).

HRMS calculated for $C_5H_{11}NO_4S$ 199.0753 $(M+NH_4)^+$; found 199.0743 (TOF MS ES^+).

Methyl *N*-(methylsulfonyl)-*N*-(4-(trifluoromethyl)benzyl)-*L*-leucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.1** (81 %, 0.373 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -42.0 (*c* = 0.041, CH_2Cl_2);

R_f = 0.60 (EtOAc:Hexane = 1:1);

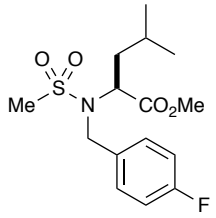
FTIR (neat): 3011, 2959, 2871, 1743, 1619, 1470, 1438, 1387, 1269, 1147, 1054, 818 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.56 (d, *J* = 5.8 Hz, 4H, ArH), 4.70 (d, *J* = 16.6 Hz, 1H, Bn), 4.61 (dd, *J* = 9.7, 4.3 Hz, 1H, NHC<u>H</u>CO_2Me), 4.28 (d, *J* = 16.6 Hz, 1H, Bn), 3.72 (s, 3H, OMe), 2.92 (s, 3H, SO_2Me), 1.51 (ddd, *J* = 13.1, 6.0, 3.2 Hz, 1H, MeC<u>H</u>Me), 1.45–1.34 (m, 2H, C<u>H</u>$_2$CHMeMe), 0.83 (d, *J* = 6.1 Hz, 3H, Me), 0.45 (d, *J* = 6.2 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 172.3 (CO), 141.9 (ArC), 130.30 (q, *J* = 32.4 Hz, *p*-CCF_3), 128.7 (2 *o*-ArC), 125.4 (q, *J* = 3.8 Hz, 2 *m*-ArC), 124.6 (m, CF_3) 59.3 (N<u>C</u>HCO_2Me), 52.5 (CO_2<u>Me</u>), 49.1 (Bn), 39.4 (SO_2Me), 39.1 (<u>C</u>H_2CHMeMe), 24.3 (<u>C</u>HMeMe), 22.3 (Me), 21.1 (Me);

HRMS calculated for $C_{16}H_{22}F_3NO_4S$ 404.1119 $(M+Na)^+$; found 404.1103 (TOF MS ES^+).

Methyl *N*-(4-fluorobenzyl)-*N*-(methylsulfonyl)-*L*-leucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.2** (76 %, 0.563 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -31.44 (*c* = 0.058, CH_2Cl_2);

R_f = 0.54 (EtOAc:Hexane = 1:1);

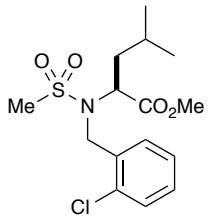
FTIR (neat): 3009, 2958, 2870, 1731, 1605, 1510, 1336, 1221, 1140, 1050, 833 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.44–7.36 (m, 2H, ArH), 7.02–6.93 (m, 2H, ArH), 4.64–4.54 (m, 2H, Bn), 4.19 (d, *J* = 16.1 Hz, 1H, NC<u>H</u>CO_2Me), 3.73–3.69 (m, 3H, OMe), 2.89 (d, *J* = 1.9 Hz, 3H, SO_2Me), 1.56–1.37 (m, 3H, C<u>H</u>MeMe:C<u>H</u>$_2$CHMeMe), 0.82 (d, *J* = 5.4 Hz, 3H, Me), 0.50 (d, *J* = 5.5 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 172.1 (CO), 163.3, 161.3 (Ar<u>C</u>F), 133.2 (ArC, d, *J* = 2.77 Hz), 130.3 (2 ArC d, *J* = 8.3 Hz) 115.2 (2 ArC d, J = 22.4 Hz), 59.0 (N<u>C</u>HCO_2Me), 52.3 (CO_2Me), 48.8 (Bn), 39.5 (SO_2Me), 38.9 (<u>C</u>H_2CHMeMe), 24.1 (Me<u>C</u>HMe), 22.4 (Me), 21.0 (Me);

HRMS calculated for $C_{15}H_{22}FNO_4S$ 354.1151 $(M+Na)^+$; found 354.1157 (TOF MS ES^+).

Methyl *N*-(2-chlorobenzyl)-*N*-(methylsulfonyl)-*L*-leucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.3** (86 %, 0.331 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -63.14 (*c* = 0.0035, CH_2Cl_2);

R_f = 0.68 (EtOAc:Hexane = 1:1);

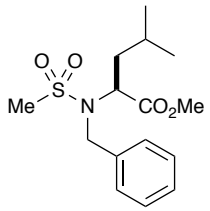
FTIR (neat): 2957, 2928, 1744, 1643, 1442, 1327, 1269, 1152, 1065, 759 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.77 (dd, *J* = 7.7, 1.4 Hz, 1H, ArH), 7.30 (ddd, *J* = 10.7, 7.7, 1.4 Hz, 2H, ArH), 7.21 (td, *J* = 7.6, 1.7 Hz, 1H, ArH), 4.63 (d, *J* = 10.8 Hz, 2H, Bn), 4.61–4.58 (m, 1H, NC<u>H</u>CO_2Me), 3.77 (s, 3H, OMe), 3.01 (s, 3H, SO_2Me), 1.61–1.47 (m, 2H, C<u>H</u>$_2$CHMeMe), 1.40 (ddd, *J* = 13.0, 9.9, 3.0 Hz, 1H, MeC<u>H</u>Me), 0.86 (d, *J* = 6.2 Hz, 3H, Me), 0.52 (d, *J* = 6.4 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 172.3 (CO), 135.1 (ArC), 132.6 (ArC), 130.7 (ArC), 129.3 (ArC), 128.9 (ArC), 127.1 (ArC), 59.4 (N<u>C</u>HCO_2Me), 52.5 (CO_2Me), 46.5 (Bn), 39.2 (SO_2Me), 38.9 (<u>C</u>H_2CHMeMe), 24.5 (Me<u>C</u>HMe), 22.5 (Me), 21.3 (Me);

HRMS calculated for $C_{15}H_{22}ClNO_4S$ 370.0856 $(M+Na)^+$; found 370.0858 (TOF MS ES^+).

Methyl *N*-benzyl-*N*-(methylsulfonyl)-*L*-leucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.4** (87 %, 0.661 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -4.57 (*c* = 0.007, CH_2Cl_2);

R_f = 0.65 (EtOAc:Hexane = 1:1);

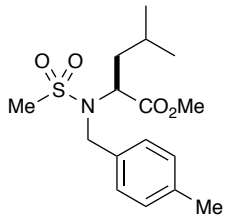
FTIR (neat): 3064, 3030, 2957, 2869, 1739, 1604, 1496, 1455, 1333, 1268, 1146, 1082, 1048, 750, 699 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.44 (d, *J* = 7.3 Hz, 2H, ArH), 7.31 (q, *J* = 6.4 Hz, 3H, ArH), 4.65 (d, *J* = 16.0 Hz, 1H, Bn), 4.61 (d, *J* = 5.7 Hz, 1H, NC<u>H</u>CO_2Me), 4.26 (d, *J* = 15.9 Hz, 1H, Bn), 3.73 (s, 3H, OMe), 2.92 (s, 3H, SO_2<u>Me</u>), 1.56–1.46 (m, 3H, C<u>H</u>MeMe:C<u>H</u>$_2$CHMeMe), 0.85 (d, *J* = 6.0 Hz, 3H, Me), 0.53 (d, *J* = 6.2 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 172.4 (CO), 137.3 (ArC), 128.7 (2 ArC), 128.6 (2 ArC), 127.9 (ArC), 59.1 (N<u>C</u>HCO_2Me), 52.4 (CO_2<u>Me</u>), 49.7 (Bn), 39.9 (SO_2Me), 39.0 (<u>C</u>H_2CHMeMe), 24.3 (Me<u>C</u>HMe), 22.5 (Me), 21.2 (Me);

HRMS calculated for $C_{15}H_{23}NO_4S$ 336.1246 $(M+Na)^+$; found 336.1251 (TOF MS ES^+).

Methyl *N*-(4-methylbenzyl)-*N*-(methylsulfonyl)-*L*-leucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.5** (72 %, 1.17 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -25.75 (*c* = 0.02, CH_2Cl_2);

$\mathbf{R_f}$ = 0.67 (EtOAc:Hexane = 1:1);

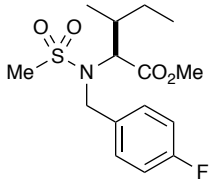
FTIR (neat): 2957, 2870, 1739, 1515, 1440, 1333, 1249, 1146, 1038, 809 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.30 (d, *J* = 8.0 Hz, 2H, ArH), 7.12 (d, *J* = 7.8 Hz, 2H, ArH), 4.59 (dd, *J* = 15.1, 8.0 Hz, 2H, Bn:NC<u>H</u>CO_2Me), 4.22 (d, *J* = 15.8 Hz, 1H, Bn), 3.72 (s, 3H, OMe), 2.90 (s, 3H, SO_2Me), 2.32 (s, 3H, ArMe), 1.53 (qq, *J* = 13.2, 6.7, 6.0 Hz, 3H, C<u>H</u>$_2$CHMeMe:C<u>H</u>MeMe), 0.85 (d, *J* = 6.2 Hz, 3H, Me), 0.57 (d, *J* = 6.3 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 172.4 (CO), 137.6 (ArC), 134.1 (ArC), 129.2 (2 ArC), 128.8 (2 ArC), 59.0 (N<u>C</u>HCO_2Me), 52.4 (CO_2<u>Me</u>), 49.4 (Bn), 40.0 (SO_2Me), 39.0 (<u>C</u>H_2CHMeMe), 24.3 (Me<u>C</u>HMe), 22.6 (Me), 21.3 (Me), 21.2 (Me);

HRMS calculated for $C_{16}H_{25}NO_4S$ 350.1402 $(M+Na)^+$; found 350.1385 (TOF MS ES^+).

Methyl *N*-(4-fluorobenzyl)-*N*-(methylsulfonyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.6** (78 %, 0.836 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -37.61 (*c* = 0.013, CH_2Cl_2);

R_f = 0.57 (EtOAc:Hexane = 1:1);

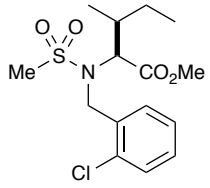
FTIR (neat): 3074, 2967, 2935, 2877, 1738, 1605, 1510, 1438, 1257, 1144, 1040, 822 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.46–7.41 (m, 2H, ArH), 7.05–6.98 (m, 2H, ArH), 4.55 (d, *J* = 15.5 Hz, 1H, Bn), 4.41 (d, *J* = 15.5 Hz, 1H, Bn), 4.19 (d, *J* = 10.8 Hz, 1H, NC<u>H</u>CO_2Me), 3.77 (s, 3H, OMe), 2.76 (s, 3H, SO_2Me), 1.70 (dddq, *J* = 13.0, 9.3, 6.5, 3.3, 2.7 Hz, 1H, C<u>H</u>Me), 1.47 (dqd, *J* = 15.2, 7.6, 2.6 Hz, 1H, C<u>H</u>$_2$Me), 0.91 (dtd, *J* = 13.7, 7.2, 2.6 Hz, 1H, C<u>H</u>$_2$Me), 0.81 (d, *J* = 6.5 Hz, 3H, Me), 0.57 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) 171.5 (CO), 163.7 (ArC), 132.85 (d, *J* = 3.4 Hz, ArC), 131.0 (d, *J* = 8.18 Hz, 2 ArC), 115.4 (d, *J* = 21.51 Hz, 2 ArC), 65.3 (N<u>C</u>HCO_2Me), 52.0 (CO_2<u>Me</u>), 48.0 (Bn), 39.9 (SO_2Me), 34.3 (<u>C</u>HMe), 25.3 (<u>C</u>H_2Me), 15.8 (Me), 10.7 (Me);

HRMS calculated for $C_{15}H_{22}FNO_4S$ 309.1549 $(M+)^+$; found 309.1542 (TOF MS ES^+).

Methyl *N*-(2-chlorobenzyl)-*N*-(methylsulfonyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.7** (90 %, 2.20 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -21.67 (*c* = 0.0245, CH_2Cl_2);

R_f = 0.71 (EtOAc:Hexane = 1:3);

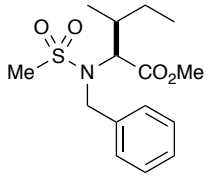
FTIR (neat): 3070, 2967, 2934, 2876, 1738, 1643, 1471, 1444, 1377, 1339, 1146, 1057, 753 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.73 (d, *J* = 7.7 Hz, 1H, ArH), 7.32 (d, *J* = 7.9 Hz, 1H, ArH), 7.28 (d, *J* = 7.0 Hz, 1H, ArH), 7.22–7.18 (m, 1H, ArH), 5.00 (d, *J* = 17.2 Hz, 1H, Bn), 4.54 (d, *J* = 17.2 Hz, 1H, Bn), 4.25 (d, *J* = 9.6 Hz, 1H, NC<u>H</u>CO_2Me), 3.75 (d, *J* = 0.8 Hz, 3H, OMe), 2.92–2.91 (m, 3H, SO_2Me), 1.66 (tqd, *J* = 9.6, 6.6, 2.8 Hz, 1H, C<u>H</u>Me), 1.55 (dqd, *J* = 15.2, 7.6, 2.8 Hz, 1H, C<u>H</u>$_2$Me), 1.01–0.87 (m, 1H, C<u>H</u>$_2$Me), 0.83 (d, *J* = 6.6 Hz, 3H, Me), 0.55 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 171.6 (CO), 135.1 (ArC), 132.7 (ArC), 130.5 (ArC), 129.4 (ArC), 128.7 (ArC), 127.0 (ArC), 65.3 (N<u>C</u>HCO_2Me), 52.0 (CO_2<u>Me</u>), 46.1 (Bn), 38.7 (SO_2Me), 34.9 (<u>C</u>HMe), 26.2 (<u>C</u>H_2Me), 15.9 (Me), 10.8 (Me);

HRMS calculated for $C_{15}H_{22}ClNO_4S$ 370.0856 $(M+Na)^+$; found 370.0875 (TOF MS ES^+).

Methyl *N*-benzyl-*N*-(methylsulfonyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.8** (63 %, 1.32 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -34.87 (*c* = 0.0425, CH_2Cl_2);

R_f = 0.61 (EtOAc:Hexane = 1:1);

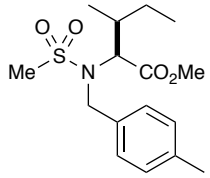
FTIR (neat): 3031, 2967, 2935, 2876, 1739, 1496, 1456, 1437, 1340, 1267, 1151, 1038, 751, 702 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.46–7.42 (m, 2H, ArH), 7.35–7.27 (m, 3H, ArH), 4.58 (d, *J* = 15.4 Hz, 1H, Bn), 4.43 (d, *J* = 15.4 Hz, 1H, Bn), 4.21 (d, *J* = 10.8 Hz, 1H, NC<u>H</u>CO_2Me), 3.76 (s, 3H, OMe), 2.75 (s, 3H, SO_2Me), 1.74 (dddq, *J* = 13.1, 9.4, 6.6, 3.3, 2.7 Hz, 1H, C<u>H</u>Me), 1.57–1.46 (m, 1H, C<u>H</u>$_2$Me), 0.92 (ddq, *J* = 14.4, 10.0, 7.3 Hz, 1H, C<u>H</u>$_2$Me), 0.82 (d, *J* = 6.5 Hz, 3H, Me), 0.57 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 171.5 (CO), 136.9 (ArC), 129.3 (2 ArC), 128.5 (2 ArC), 127.9 (ArC), 65.4 (N<u>C</u>HCO_2Me), 52.0 (OMe), 48.7 (Bn), 40.0 (SO_2Me), 34.2 (<u>C</u>HMe), 25.4 (<u>C</u>H$_2$Me), 15.9 (Me), 10.7 (Me);

HRMS calculated for $C_{15}H_{23}NO_4S$ 312.1270 $(M-H)^+$; found 312.1255 (TOF MS ES^+).

Methyl *N*-(4-methylbenzyl)-*N*-(methylsulfonyl)-*L*-isoleucinate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.9** (87 %, 0.530 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -37.27 (*c* = 0.011, CH_2Cl_2);

$\mathbf{R_f}$ = 0.62 (EtOAc:Hexane = 1:1);

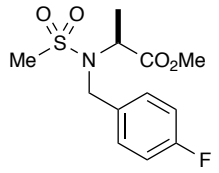
FTIR (neat): 3009, 2967, 2933, 1739, 1515, 1437, 1380, 1143, 1041, 833 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.30 (d, *J* = 8.0 Hz, 2H, ArH), 7.12 (d, *J* = 7.9 Hz, 2H, ArH), 4.51 (d, *J* = 15.3 Hz, 1H, Bn), 4.38 (d, *J* = 15.3 Hz, 1H, Bn), 4.20 (d, *J* = 10.8 Hz, 1H, NC<u>H</u>CO_2Me), 3.76 (s, 3H, OMe), 2.72 (s, 3H, SO_2Me), 2.33 (s, 3H, ArMe), 1.78 (dddq, *J* = 13.0, 9.4, 6.5, 3.3, 2.7 Hz, 1H, C<u>H</u>Me), 1.53 (dqd, *J* = 15.1, 7.3, 2.4 Hz, 1H, C<u>H</u>$_2$Me), 0.93 (ddt, *J* = 14.5, 10.0, 7.2 Hz, 1H, C<u>H</u>$_2$Me), 0.83 (d, *J* = 6.5 Hz, 3H, Me), 0.62 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 171.5 (CO), 137.7 (ArC), 133.7 (ArC), 129.3 (2 ArC), 129.2 (2 ArC), 65.3 (N<u>C</u>HCO_2Me), 52.0 (OMe), 48.4 (Bn), 40.3 (SO_2Me), 34.1 (<u>C</u>HMe), 25.3 (<u>C</u>H$_2$Me), 21.2 (ArMe), 15.9 (Me), 10.7 (Me);

HRMS calculated for $C_{16}H_{25}NO_4S$ 350.1402 $(M+Na)^+$; found 350.1391 (TOF MS ES^+).

Methyl *N*-(4-fluorobenzyl)-*N*-(methylsulfonyl)-*L*-alaninate



According to the reaction protocol described in general procedure **B**, compound **3.3.2.1.10** (81 %, 0.328 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -19.69 (*c* = 0.0695, CH_2Cl_2);

$\mathbf{R_f}$ = 0.24 (EtOAc:Hexane = 1:3);

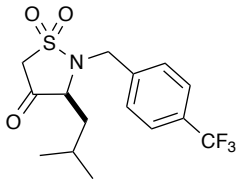
FTIR (neat): 3071, 3001, 2953, 1747, 1605, 1510, 1455, 1381, 1144, 1040, 847 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.41–7.36 (m, 2H, ArH), 7.05–6.99 (m, 2H, ArH), 4.67 (q, *J* = 7.4 Hz, 1H, NC<u>H</u>CO_2Me), 4.59 (d, *J* = 16.0 Hz, 1H, Bn), 4.28 (d, *J* = 16.2 Hz, 1H, Bn), 3.72 (s, 3H, OMe), 2.94 (s, 3H, SO_2Me), 1.32 (d, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 172.2 (CO), 163.4 (ArC), 133.4 (d, *J* = 2.8 Hz, ArC) 129.7 (d, *J* = 7.9 Hz, 2 ArC), 115.5 (d, *J* = 21.3 Hz, 2 ArC), 56.2 (N<u>C</u>HCO_2Me), 52.6 (OMe), 48.8 (Bn), 40.0 (SO_2Me), 17.5 (Me);

HRMS calculated for $C_{12}H_{16}FNO_4S$ 288.0706 $(M-H)^+$; found 288.0704 (TOF MS ES^+).

(*S*)-3-isobutyl-2-(4-(trifluoromethyl)benzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.1** (41 %, 0.741 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 2.78 (*c* = 0.033, CH_2Cl_2);

R_f = 0.65 (EtOAc:Hexane = 1:1);

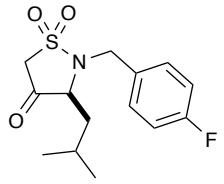
FTIR (neat): 2960, 1770, 1620, 1461, 1421, 1326, 1166, 1067, 860 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 7.65 (d, *J* = 8.1 Hz, 2H, ArH), 7.53 (d, *J* = 8.0 Hz, 2H, ArH), 4.58 (d, *J* = 15.5 Hz, 1H, Bn), 4.45 (d, *J* = 15.5 Hz, 1H, Bn), 3.84 (d, *J* = 17.9 Hz, 2H, $COC\underline{H}_2SO_2$), 3.76–3.72 (m, 1H, $NC\underline{H}CO_2Me$), 1.76–1.70 (m, 1H, $MeC\underline{H}Me$), 1.67–1.65 (m, 1H, CH_2), 1.65–1.63 (m, 1H, CH_2), 0.79 (d, *J* = 6.6 Hz, 3H, Me), 0.77 (d, *J* = 6.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 198.7 (CO), 138.9 (ArC), 130.9 (q, *J* = 32.7 Hz *p*-ArC), 129.1 (2 *o*-ArC), 126.1 (q, *J* = 3.7 Hz, 2 *m*-ArC), 123.9 (d, *J* = 272.3 Hz, CF_3), 67.4 ($N\underline{C}HCO_2Me$), 55.2 ($CO\underline{C}H_2SO_2$), 47.1 (Bn), 39.2 ($\underline{C}H_2CHMeMe$), 24.7 ($Me\underline{C}HMe$), 22.6 (Me), 22.2 (Me);

HRMS calculated for $C_{15}H_{18}F_3NO_3S$ 367.1303 $(M+NH_4)^+$; found 367.1296 (TOF MS ES^+).

(*S*)-2-(4-fluorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.2** (82 %, 0.354 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 26.17 (*c* = 0.040, CH_2Cl_2);

R_f = 0.71 (EtOAc:Hexane = 1:1);

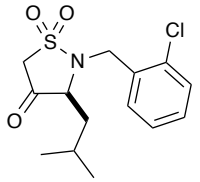
FTIR (neat): 3073, 2959, 2872, 1763, 1604, 1511, 1467, 1321, 1037, 839 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.37 (ddd, *J* = 8.2, 5.2, 2.5 Hz, 2H, ArH), 7.10–7.04 (m, 2H, ArH), 4.56 (d, *J* = 15.1 Hz, 1H, Bn), 4.32 (d, *J* = 15.1 Hz, 1H, Bn), 3.84 (dd, *J* = 17.0, 1.2 Hz, 1H, $COC\underline{H}_2SO_2$), 3.75 (d, *J* = 17.0 Hz, 1H, $COC\underline{H}_2SO_2$), 3.73 (td, *J* = 6.7, 1.2 Hz, 1H, $NC\underline{H}CO_2Me$), 1.73 (dq, *J* = 12.6, 6.4 Hz, 1H, C<u>H</u>MeMe), 1.67–1.62 (m, 2H, $C\underline{H}_2CHMeMe$), 0.81 (d, *J* = 6.5 Hz, 3H, Me), 0.78 (d, *J* = 6.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 199.2 (CO), 163.8 (ArC), 130.8 (d, *J* = 8.1 Hz, 2 ArC), 130.3 (d, J = 3.4 Hz, ArC), 116.0 (d, *J* = 21.6 Hz, 2 ArC), 67.0 ($N\underline{C}HCO_2Me$), 55.3 ($CO\underline{C}H_2SO_2$), 47.1 (Bn), 39.3 ($\underline{C}H_2CHMeMe$), 24.6 (Me<u>C</u>HMe), 22.6 (Me), 22.2 (Me);

HRMS calculated for $C_{14}H_{18}FNO_3S$ 322.0889 $(M+Na)^+$; found 322.0878 (TOF MS ES^+).

(*S*)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.3** (95%, 0.589 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -47.68 (*c* = 0.0095, CH_2Cl_2);

R_f = 0.37 (EtOAc:Hexane = 1:3);

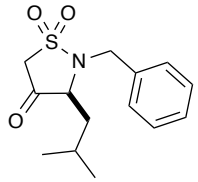
FTIR (neat): 2959, 2871, 1718, 1471, 1336, 1038, 848 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.56 (dd, *J* = 7.2, 2.1 Hz, 1H, ArH), 7.42–7.38 (m, 1H, ArH), 7.34–7.28 (m, 2H, ArH), 4.71 (d, *J* = 15.4 Hz, 1H, Bn), 4.55 (d, *J* = 15.4 Hz, 1H, Bn), 3.85 (d, *J* = 0.9 Hz, 1H, $COCH_2SO_2$), 3.84 (s, 1H, $COCH_2SO_2$), 3.83–3.79 (m, 1H, $NCHCO_2Me$), 1.67 (qd, *J* = 7.7, 5.1 Hz, 3H, CHMeMe:$CH_2CHMeMe$), 0.77 (d, *J* = 6.3 Hz, 3H, Me), 0.75 (d, *J* = 6.3 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 199.2 (CO), 133.9 (ArC), 132.7 (ArC), 131.0 (ArC), 130.0 (ArC), 129.9 (ArC), 127.5 (ArC), 68.1 ($NCHCO_2Me$), 55.1 ($COCH_2SO_2$), 45.2 (Bn), 39.6 ($CH_2CHMeMe$), 24.6 (MeCHMe), 22.7 (Me), 22.0 (Me);

HRMS calculated for $C_{14}H_{18}ClNO_3S$ 315.0696 $(M+)^+$; found 315.0691 (TOF MS ES^+).

(*S*)-2-benzyl-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.4** (74 %, 0.448 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -55.86 (*c* = 0.045, CH_2Cl_2);

R_f = 0.57 (EtOAc:Hexane = 1:3 x2);

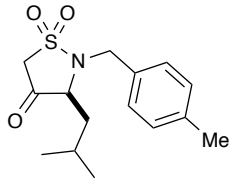
FTIR (neat): 3065, 3006, 2958, 2870, 1760, 1496, 1456, 1319, 1053, 749, 699 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.40–7.32 (m, 5H, ArH), 4.63 (d, *J* = 14.9 Hz, 1H, Bn), 4.32 (d, *J* = 14.9 Hz, 1H, Bn), 3.82 (dd, *J* = 17.0, 1.1 Hz, 1H, $COC\underline{H}_2SO_2$), 3.77 (d, *J* = 3.0 Hz, 1H, $COC\underline{H}_2SO_2$), 3.76–3.72 (m, 1H, $NC\underline{H}CO_2Me$), 1.74 (tt, *J* = 13.2, 6.6 Hz, 1H, $C\underline{H}MeMe$), 1.65 (td, *J* = 6.6, 4.1 Hz, 2H, $C\underline{H}_2CHMeMe$), 0.80 (d, *J* = 6.5 Hz, 3H, Me), 0.77 (d, *J* = 6.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 199.5 (CO), 134.4 (ArC), 129.1 (2 ArC), 128.6 (2 ArC), 66.9 ($NCHCO_2Me$), 55.3 ($COCH_2SO_2$), 47.9 (Bn), 39.4 ($CH_2CHMeMe$), 24.6 ($CHMeMe$), 22.6 (Me), 22.2 (Me);

HRMS calculated for $C_{14}H_{19}NO_3S$ 304.0983 $(M+Na)^+$; found 304.1000 (TOF MS ES^+).

(*S*)-3-isobutyl-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.5** (28 %, 0.303 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -12.75 (*c* = 0.004, CH_2Cl_2);

R_f = 0.51 (EtOAc:Hexane = 1:3);

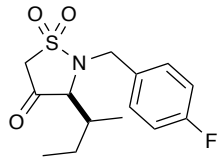
FTIR (neat): 3007, 2959, 2931, 1735, 1642, 1515, 1467, 1331, 1054, 808 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 7.17 (d, *J* = 7.9 Hz, 2H, ArH), 4.64 (d, *J* = 14.9 Hz, 1H, Bn), 4.23 (d, *J* = 14.9 Hz, 1H, Bn), 3.80 (dd, *J* = 16.9, 1.1 Hz, 1H, $COCH_2SO_2$), 3.77–3.74 (m, 1H, $NCHCO_2Me$), 3.71 (d, *J* = 16.9 Hz, 1H, $COCH_2SO_2$), 2.35 (s, 3H, ArMe), 1.82–1.72 (m, 1H, MeCHMe), 1.72–1.59 (m, 2H, $CH_2CHMeMe$), 0.82 (d, *J* = 6.5 Hz, 3H, Me), 0.79 (d, *J* = 6.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 199.8 (CO), 138.6 (ArC), 131.2 (ArC), 129.7 (2 ArC), 129.1 (2 ArC), 66.7 ($NCHCO_2Me$), 55.5 ($COCH_2SO_2$), 47.8 (Bn), 39.5 ($CH_2CHMeMe$), 24.7 (MeCHMe), 22.6 (ArMe), 22.3 (Me), 21.2 (Me);

HRMS calculated for $C_{15}H_{21}NO_3S$ 318.1140 $(M+Na)^+$; found 318.1130 (TOF MS ES^+).

(*S*)-3-((*S*)-sec-butyl)-2-(4-fluorobenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.6** (25 %, 0.193 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -35.55 (*c* = 0.0045, CH_2Cl_2);

R_f = 0.66 (EtOAc:Hexane = 1:1);

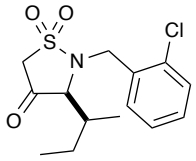
FTIR (neat): 2964, 2879, 1771, 1604, 1510, 1460, 1036, 841 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.42–7.37 (m, 2H, ArH), 7.10–7.03 (m, 2H, ArH), 4.56 (d, *J* = 15.7 Hz, 1H, Bn), 4.33 (d, *J* = 15.7 Hz, 1H, Bn), 3.77 (s, 2H, $COC\underline{H}_2SO_2$), 3.67 (d, *J* = 3.9 Hz, 1H, $NC\underline{H}CO_2Me$), 1.83–1.73 (m, 1H, C<u>H</u>Me), 1.56–1.45 (m, 1H, $C\underline{H}_2Me$), 1.39 (dp, *J* = 15.1, 7.5 Hz, 1H, $C\underline{H}_2$-Ile), 0.90 (d, *J* = 6.9 Hz, 3H, Me), 0.80 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) 197.8 (CO), 162.7 (d, *J* = 247.6 Hz, ArC), 130.8 (d, *J* = 8.1 Hz, 2 ArC), 130.2 (d, *J* = 2.9 Hz, ArC) 116.0 (d, *J* = 21.5 Hz, 2 ArC), 71.8 ($N\underline{C}HCO_2Me$), 56.6 ($CO\underline{C}H_2SO_2$), 45.8 (Bn), 36.3 (<u>C</u>HMe), 25.8 ($\underline{C}H_2Me$), 14.1 (Me), 12.0 (Me);

HRMS calculated for $C_{14}H_{18}FNO_3S$ 322.0889 $(M+Na)^+$; found 322.0889 (TOF MS ES^+).

(*S*)-3-((*S*)-*sec*-butyl)-2-(2-chlorobenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.7** (72 %, 0.593 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 47.5 (*c* = 0.004, CH_2Cl_2);

R_f = 0.65 (EtOAc:Hexane = 1:1);

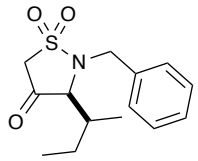
FTIR (neat): 2966, 2934, 1758, 1444, 1324, 1036, 755 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.65 (dd, *J* = 7.3, 2.0 Hz, 1H, ArH), 7.39 (dd, *J* = 7.7, 1.6 Hz, 1H, ArH), 7.34–7.27 (m, 2H, ArH), 4.73 (d, *J* = 16.0 Hz, 1H, Bn), 4.53 (d, *J* = 16.0 Hz, 1H, Bn), 3.81 (s, 2H, $COC\underline{H}_2SO_2$), 3.77 (d, *J* = 3.8 Hz, 1H, $NC\underline{H}CO_2Me$), 1.75 (dddd, *J* = 13.3, 11.1, 6.6, 4.3 Hz, 1H, C<u>H</u>Me), 1.53 (dtd, *J* = 14.8, 7.4, 6.2 Hz, 1H, $C\underline{H}_2Me$), 1.42–1.30 (m, 1H, $C\underline{H}_2Me$), 0.88 (d, *J* = 6.9 Hz, 3H, Me), 0.82 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 197.9 (CO), 133.6 (ArC), 132.8 (ArC), 131.0 (ArC), 129.9 (ArC), 129.7 (ArC), 127.5 (ArC), 73.6 ($N\underline{C}HCO_2Me$), 56.5 ($CO\underline{C}H_2SO_2$), 44.3 (Bn), 36.7 (<u>C</u>HMe), 25.9 ($\underline{C}H_2Me$), 14.1 (Me), 11.9 (Me);

HRMS calculated for $C_{14}H_{18}ClNO_3S$ 338.0594 $(M+Na)^+$; found 338.0601 (TOF MS ES^+).

(*S*)-2-benzyl-3-((*S*)-*sec*-butyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.8** (81 %, 0.92 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -4.68 (*c* = 0.054, CH_2Cl_2);

$\mathbf{R_f}$ = 0.71 (EtOAc:Hexane = 1:1);

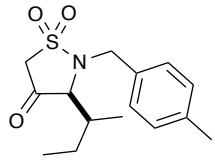
FTIR (neat): 3064, 2965, 2877, 1754, 1604, 1588, 1496, 1456, 1320, 1086, 1045, 738, 700 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.43–7.30 (m, 5H, ArH), 4.62 (d, *J* = 15.6 Hz, 1H, Bn), 4.33 (d, *J* = 15.6 Hz, 1H, Bn), 3.77 (s, 2H, $COC\underline{H_2}SO_2$), 3.68 (d, *J* = 4.0 Hz, 1H, $NC\underline{H}CO_2Me$), 1.79 (dtq, *J* = 10.8, 6.8, 4.0, 3.4 Hz, 1H, C<u>H</u>Me), 1.50 (tt, *J* = 13.9, 7.4 Hz, 1H, $C\underline{H_2}Me$), 1.37 (dp, *J* = 15.2, 7.5 Hz, 1H, $C\underline{H_2}Me$), 0.90 (d, *J* = 6.9 Hz, 3H, Me), 0.78 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 198.1 (CO), 134.3 (ArC), 129.0 (2 ArC), 129.0 (2 ArC), 128.5 (ArC), 71.8 ($NC\underline{H}CO_2Me$), 56.7 ($CO\underline{C}H_2SO_2$), 46.6 (Bn), 36.3 (<u>C</u>HMe), 25.8 ($\underline{C}H_2Me$), 14.1 (Me), 11.9 (Me);

HRMS calculated for $C_{14}H_{19}NO_3S$ 282.1164 $(M+H)^+$; found 282.1161 (TOF MS ES^+).

(*S*)-3-((*S*)-sec-butyl)-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **C**, compound **3.3.3.1.9** (77 %, 0.566 g)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -34.22 (*c* = 0.0045, CH_2Cl_2);

$\mathbf{R_f}$ = 0.67 (EtOAc:Hexane = 1:1);

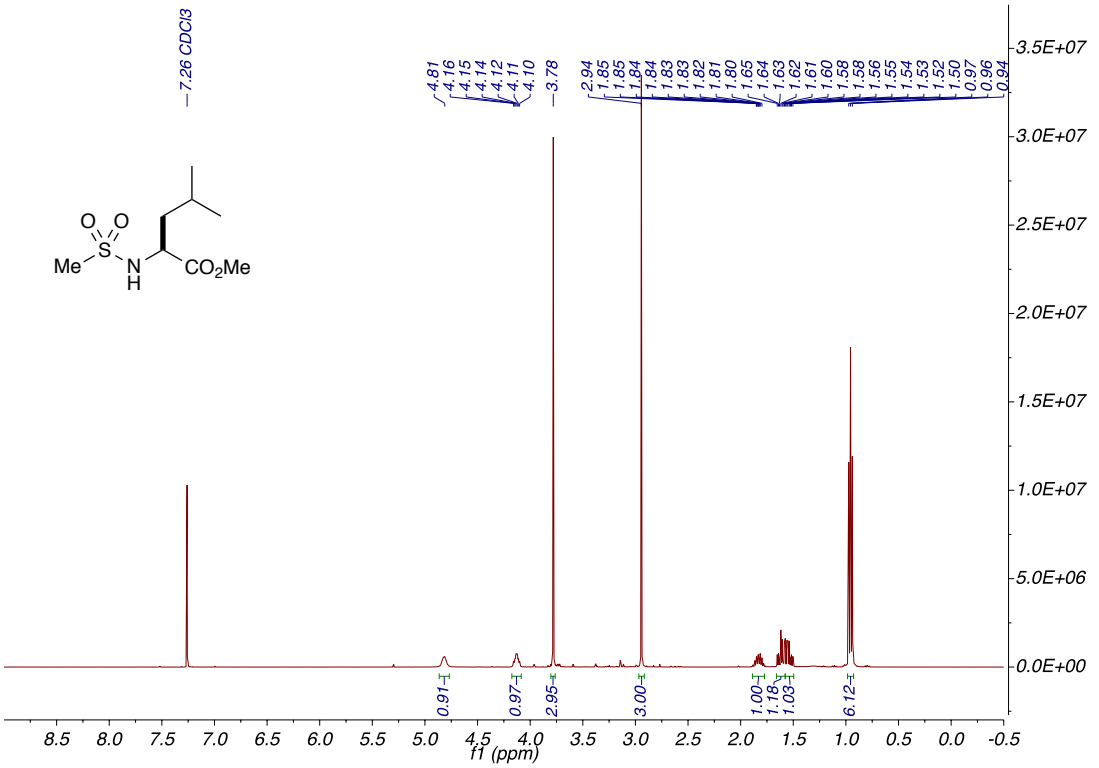
FTIR (neat): 2965, 2930, 1758, 1515, 1459, 1313, 1045, 818 cm^{-1};

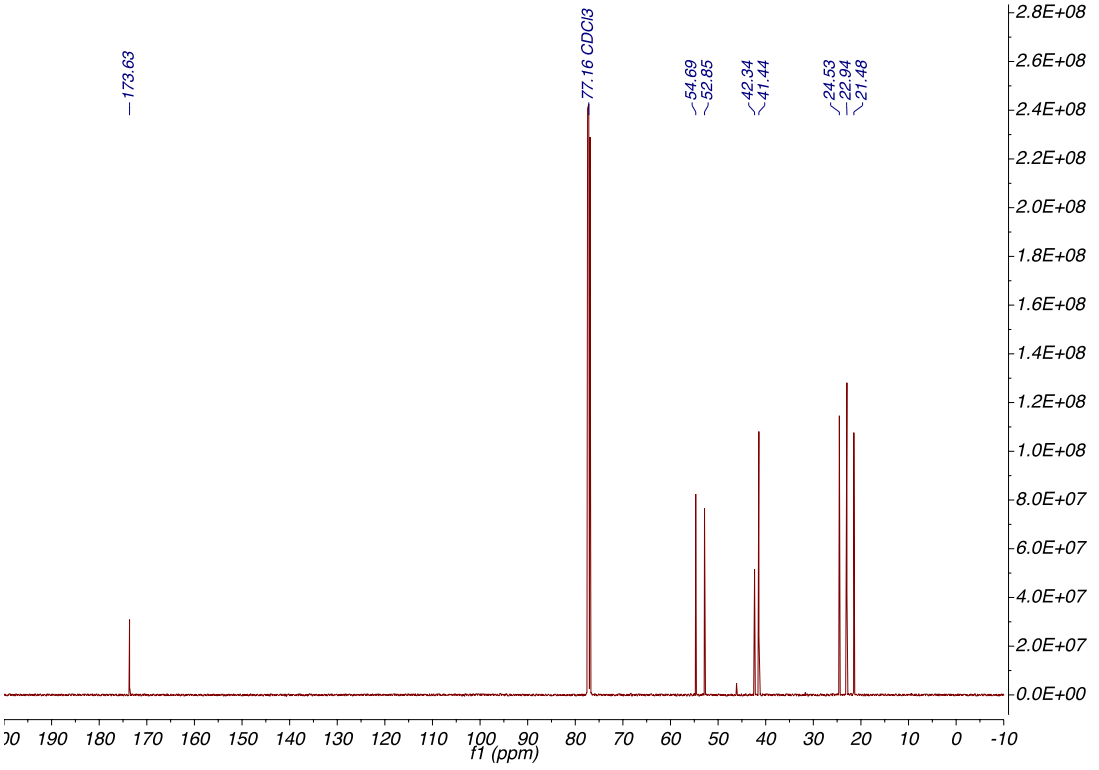
^{1}H NMR (400 MHz, $CDCl_3$) 7.29 (d, *J* = 8.0 Hz, 2H, ArH), 7.17 (d, *J* = 7.9 Hz, 2H, ArH), 4.63 (d, *J* = 15.5 Hz, 1H, Bn), 4.25 (d, *J* = 15.5 Hz, 1H, Bn), 3.75–3.74 (m, 2H, $COC\underline{H_2}SO_2$), 3.67 (d, *J* = 3.9 Hz, 1H, $NC\underline{H}CO_2Me$), 2.35 (s, 3H, ArMe), 1.82 (dtq, *J* = 13.6, 6.8, 4.2, 3.4 Hz, 1H, C<u>H</u>Me), 1.57–1.45 (m, 1H, $C\underline{H_2}Me$), 1.39 (td, *J* = 14.5, 13.9, 7.7 Hz, 1H, $C\underline{H_2}Me$), 0.91 (d, *J* = 6.9 Hz, 3H, Me), 0.80 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 198.3 (CO), 138.3 (ArC), 131.1 (ArC), 129.7 (2 ArC), 129.1 (2 ArC), 71.7 ($NC\underline{C}HCO_2Me$), 56.7 ($CO\underline{C}H_2SO_2$), 46.4 (Bn), 36.3 (<u>C</u>HMe), 25.8 ($\underline{C}H_2Me$), 21.3 (ArMe), 14.1 (Me), 11.9 (Me);

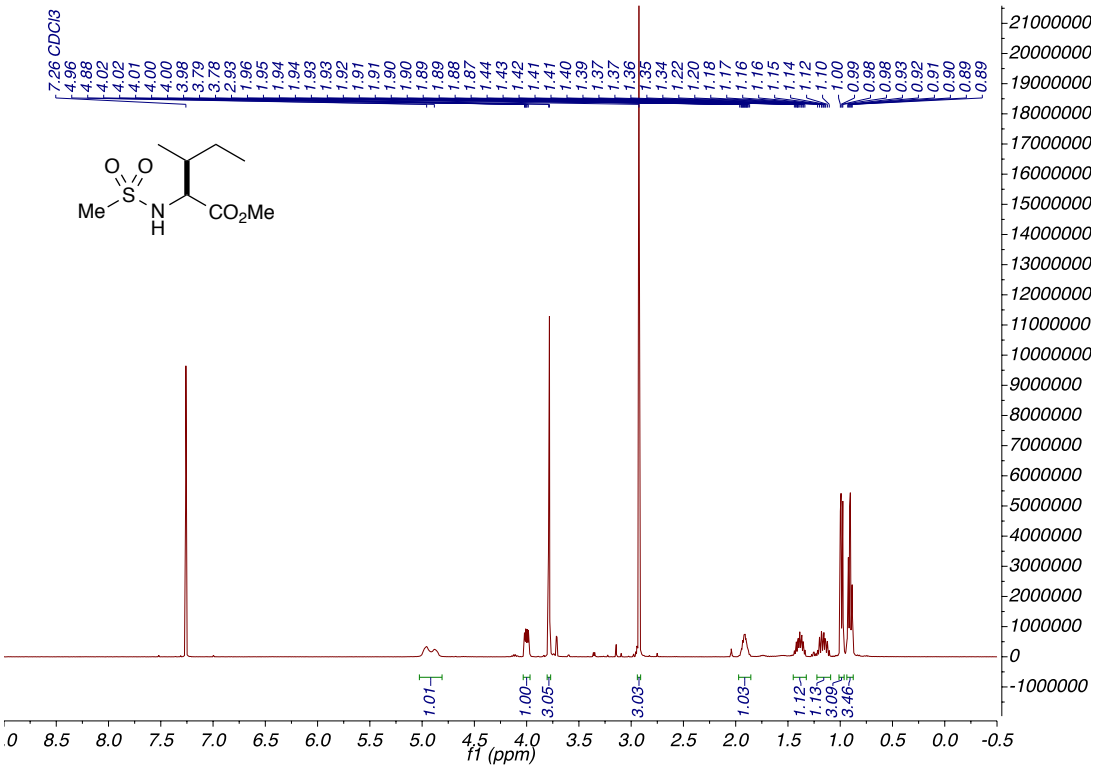
HRMS calculated for $C_{15}H_{21}NO_3S$ 318.1140 $(M+Na)^+$; found 318.1151 (TOF MS ES^+).

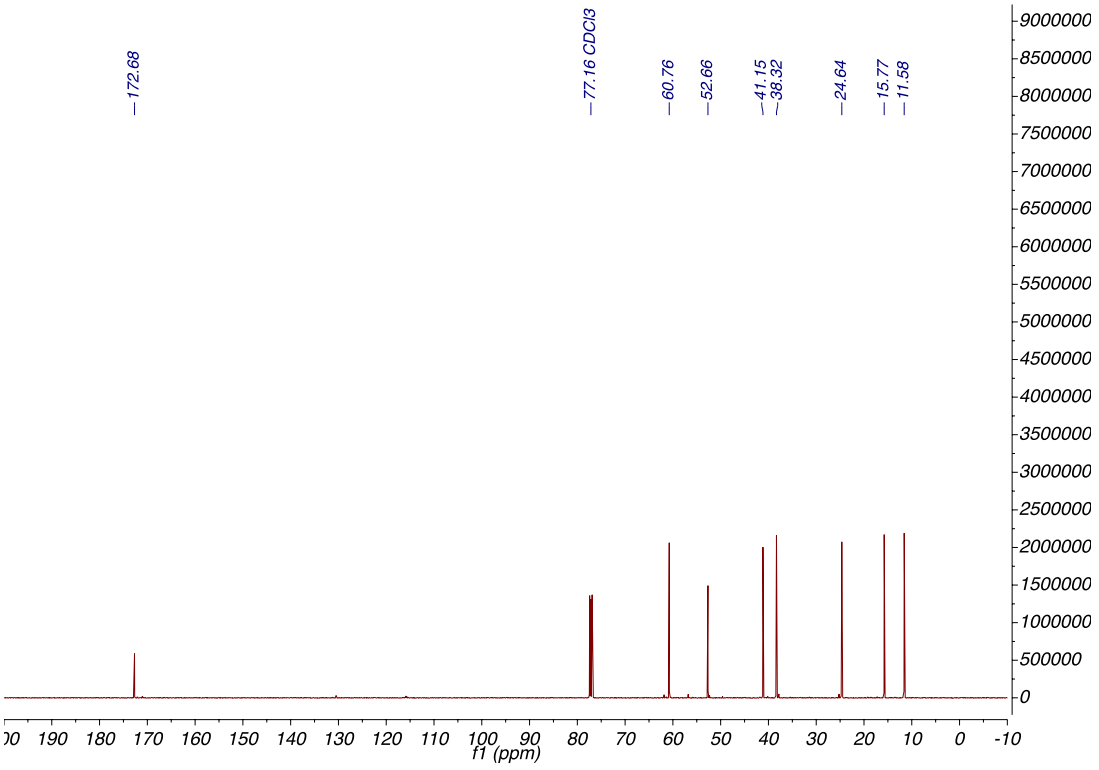
Methyl (methylsulfonyl)-*L*-leucinate 3.3.1.2.1



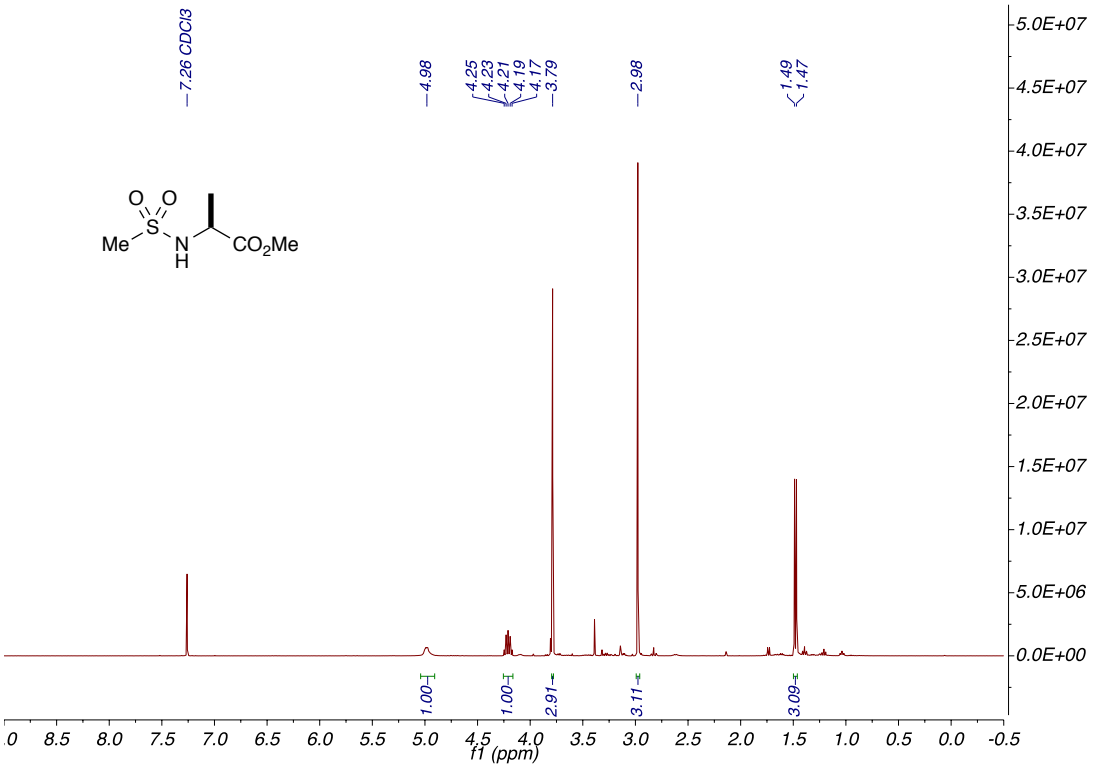


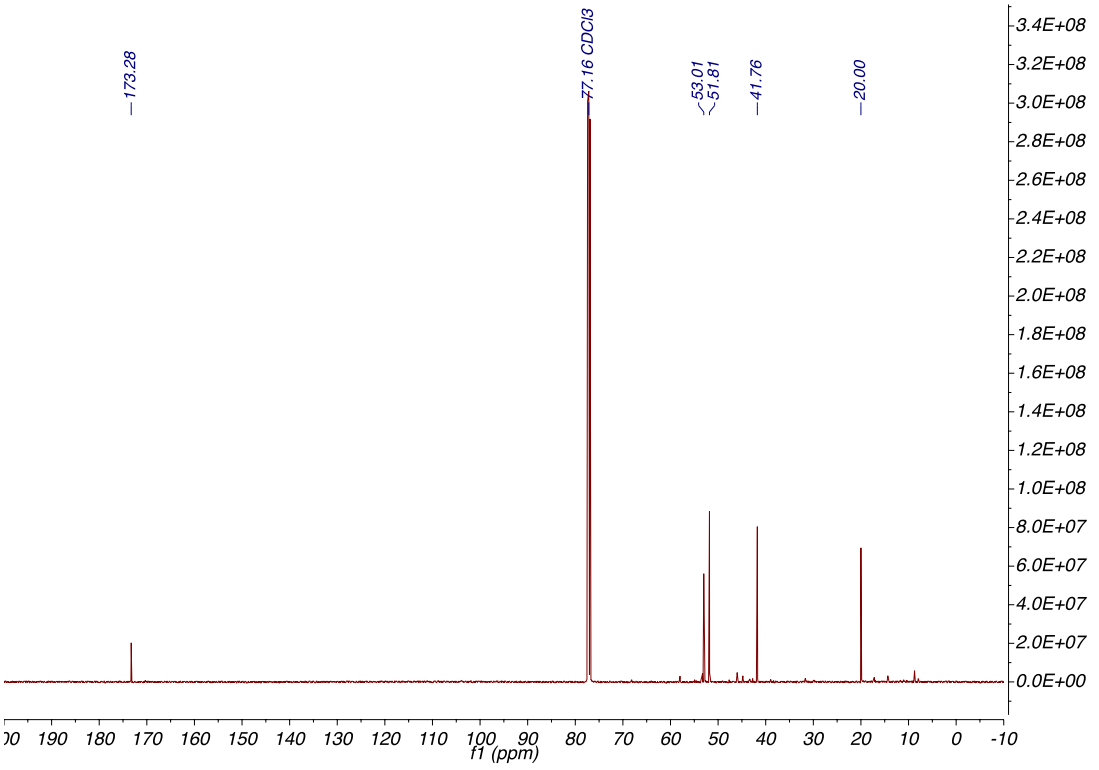
Methyl (methylsulfonyl)-*L*-isoleucinate 3.3.1.2.2



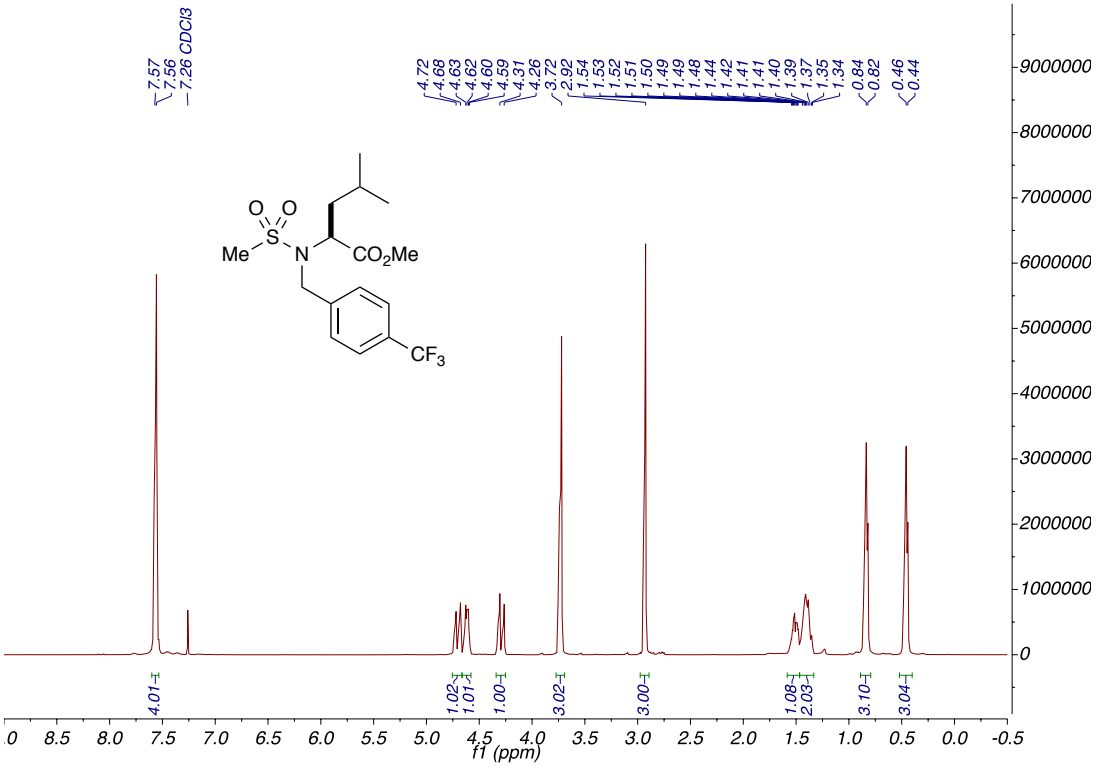


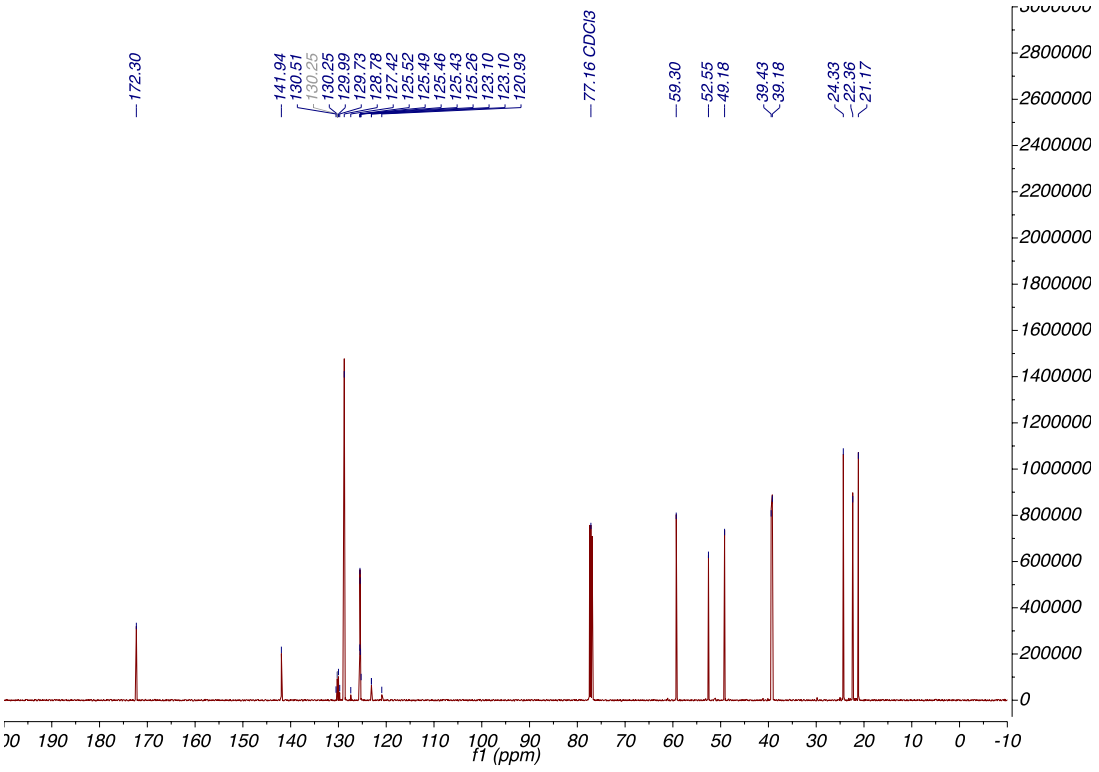
Methyl (methylsulfonyl)-*L*-alaninate 3.3.1.2.3



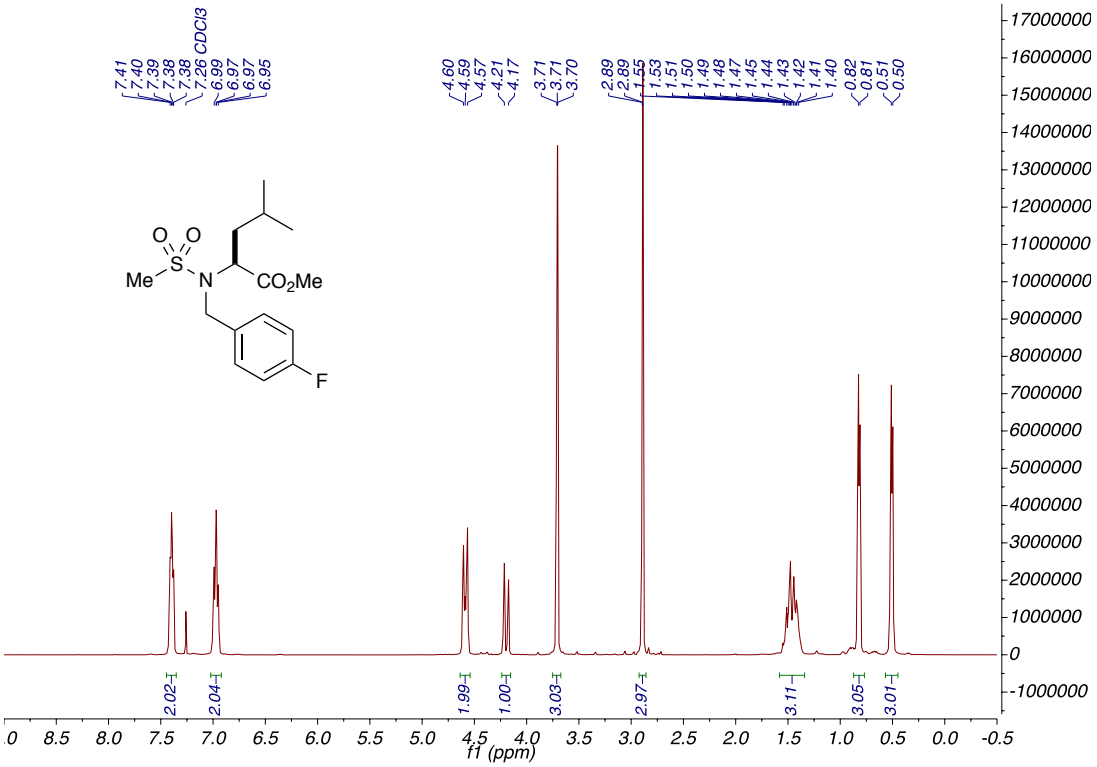


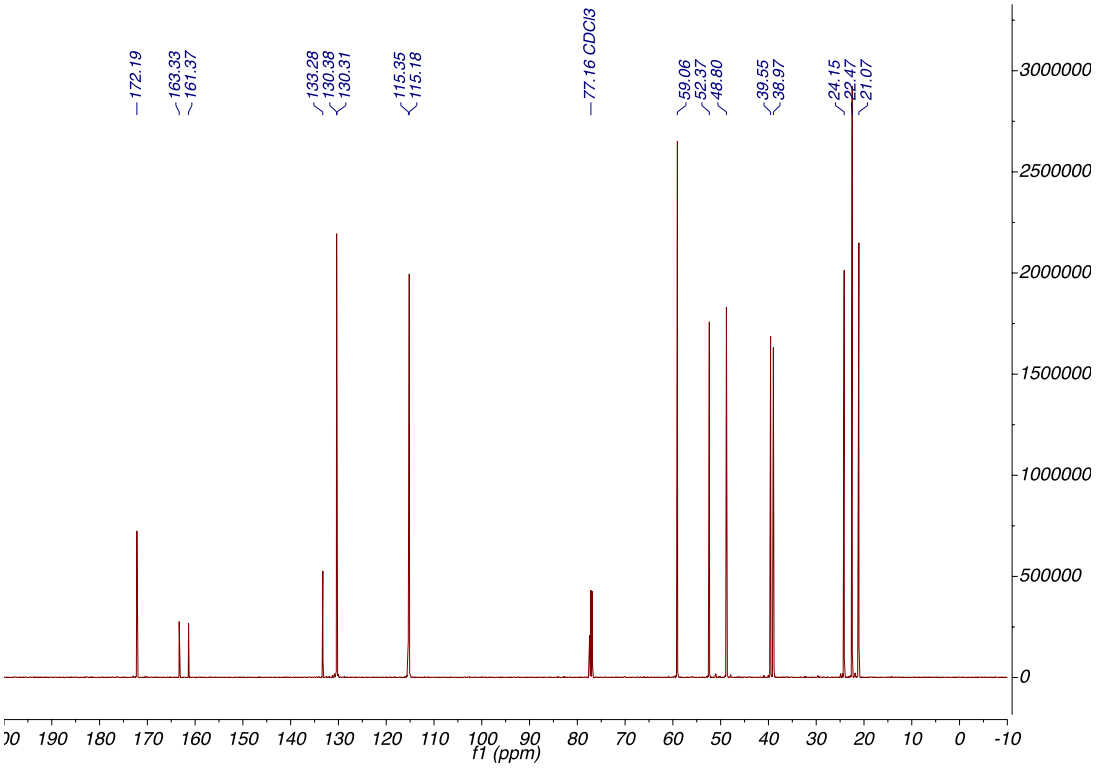
Methyl *N*-(methylsulfonyl)-*N*-(4-(trifluoromethyl)benzyl)-*L*-leucinate 3.3.2.1.1



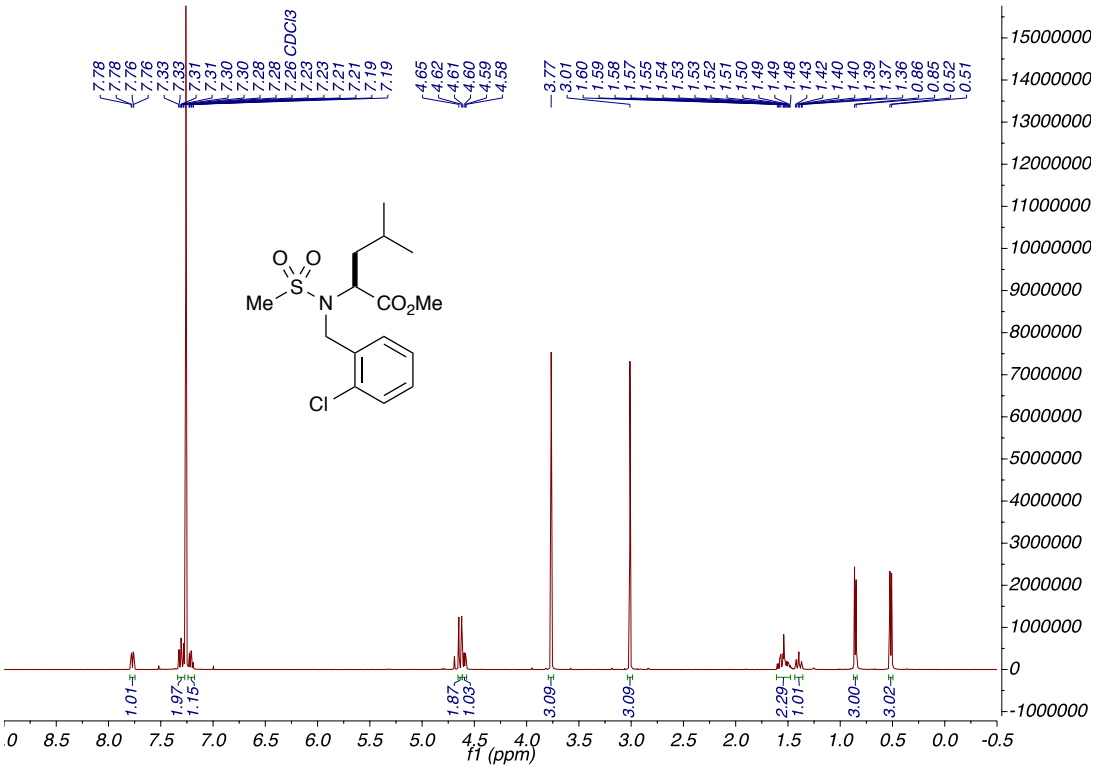


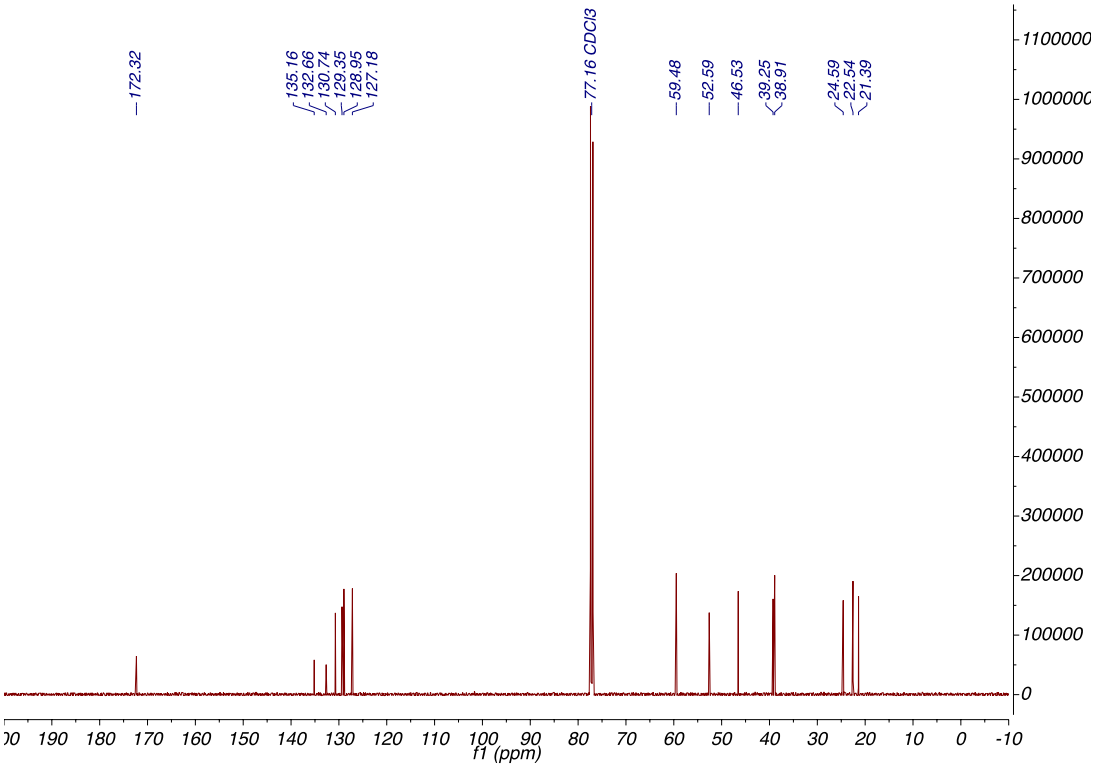
Methyl *N*-(4-fluorobenzyl)-*N*-(methylsulfonyl)-*L*-leucinate 3.3.2.1.2



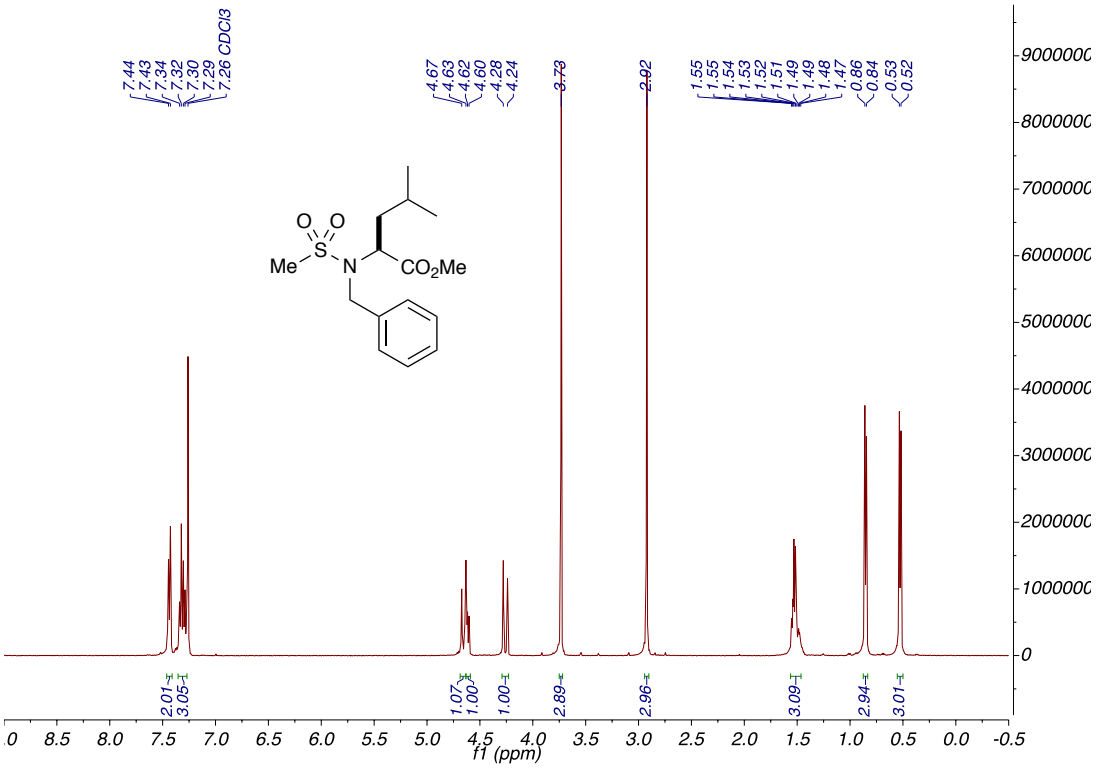


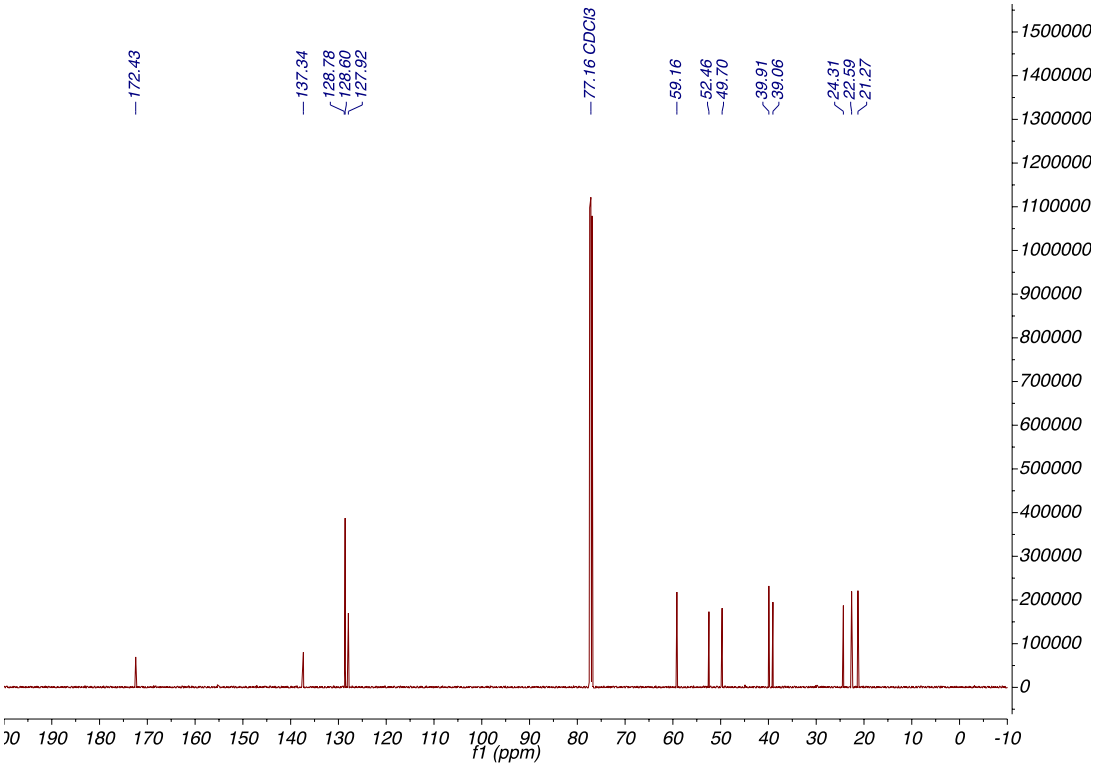
Methyl *N*-(2-chlorobenzyl)-*N*-(methylsulfonyl)-*L*-leucinate 3.3.2.1.3



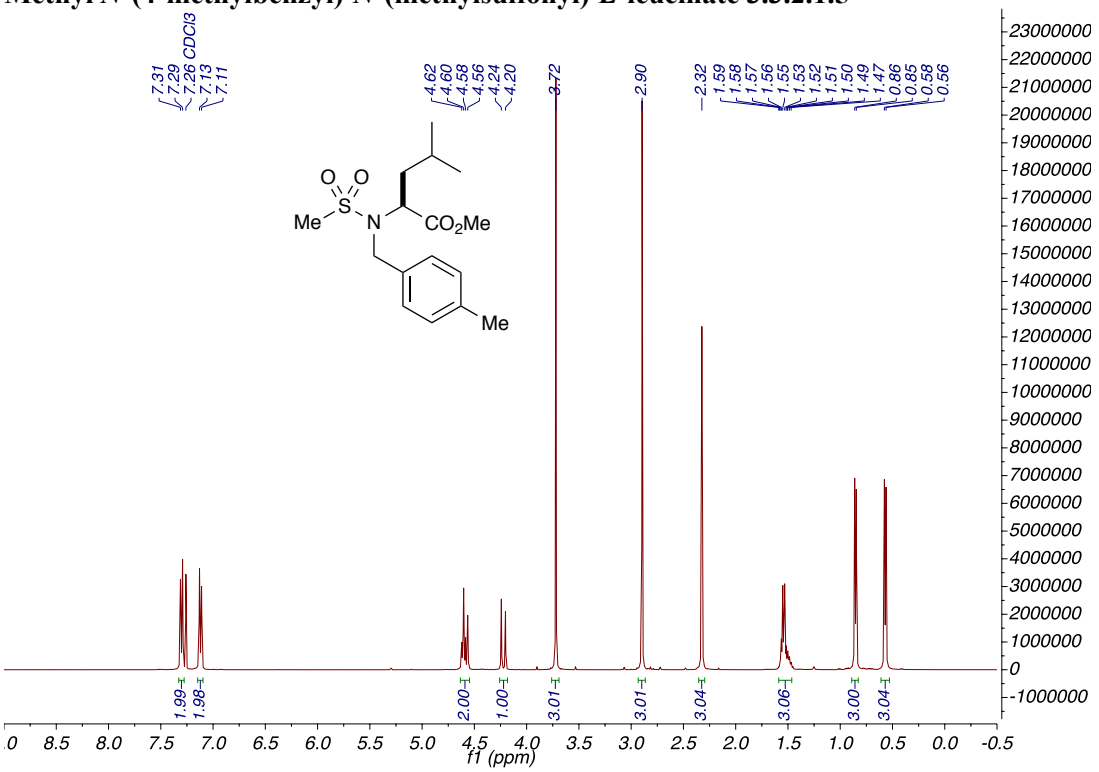


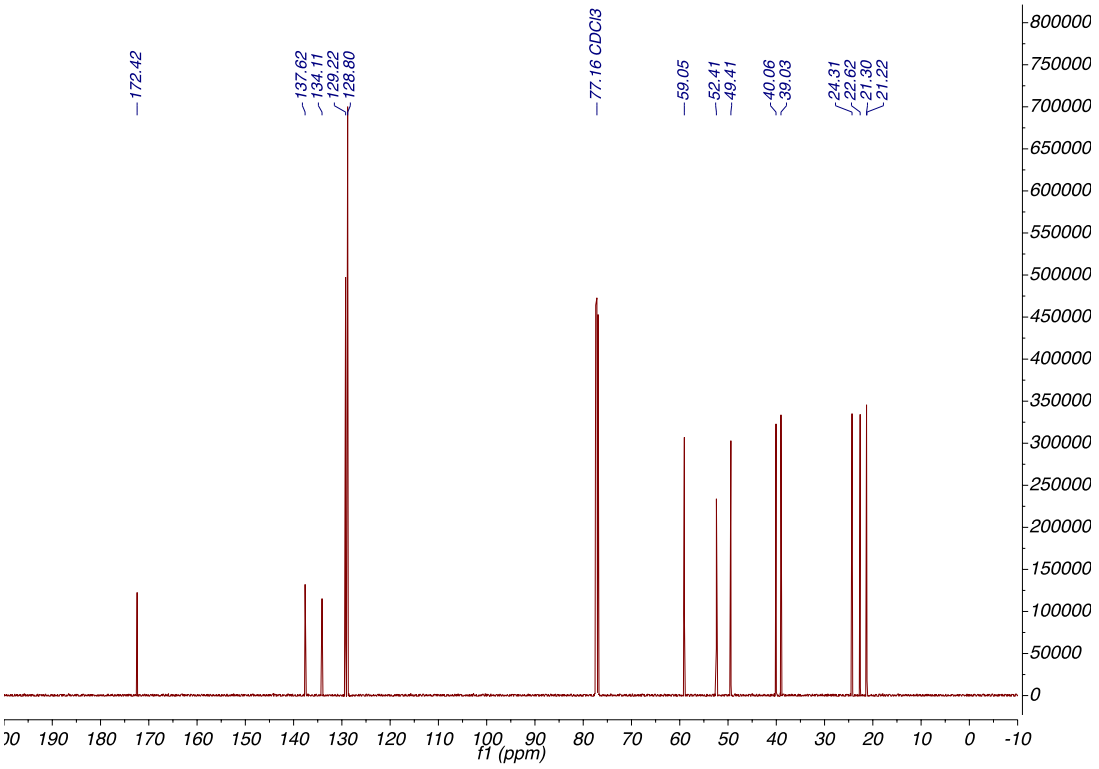
Methyl *N*-benzyl-*N*-(methylsulfonyl)-*L*-leucinate 3.3.2.1.4



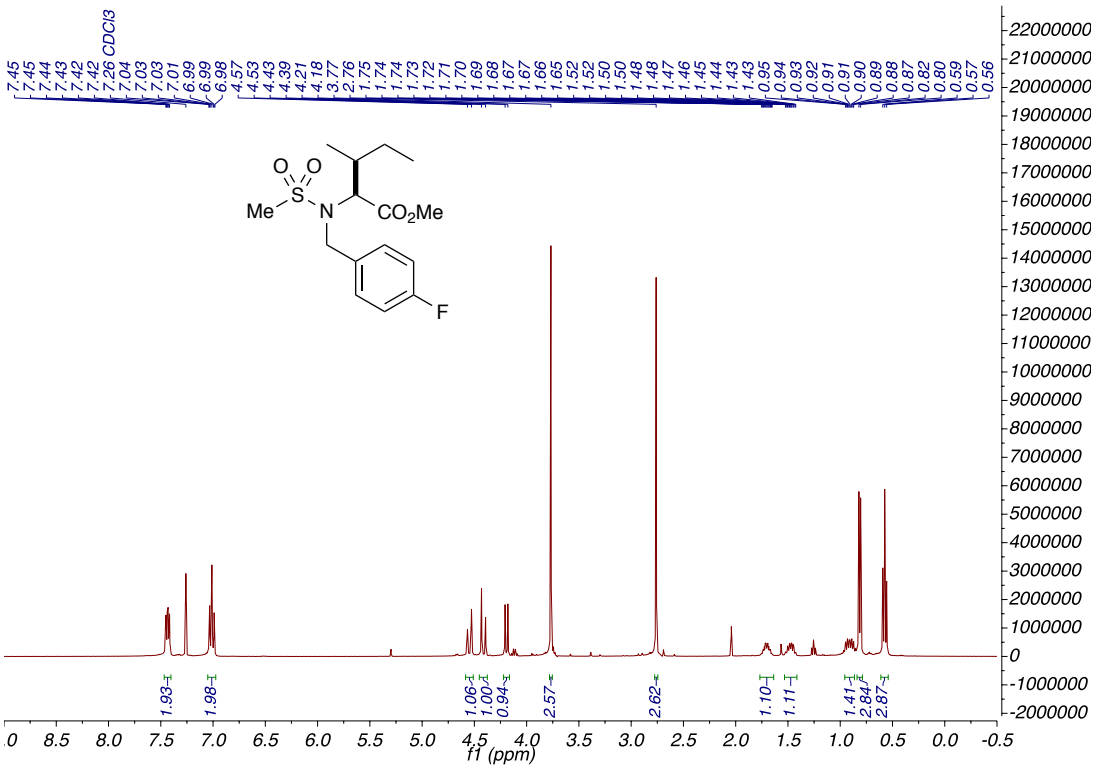


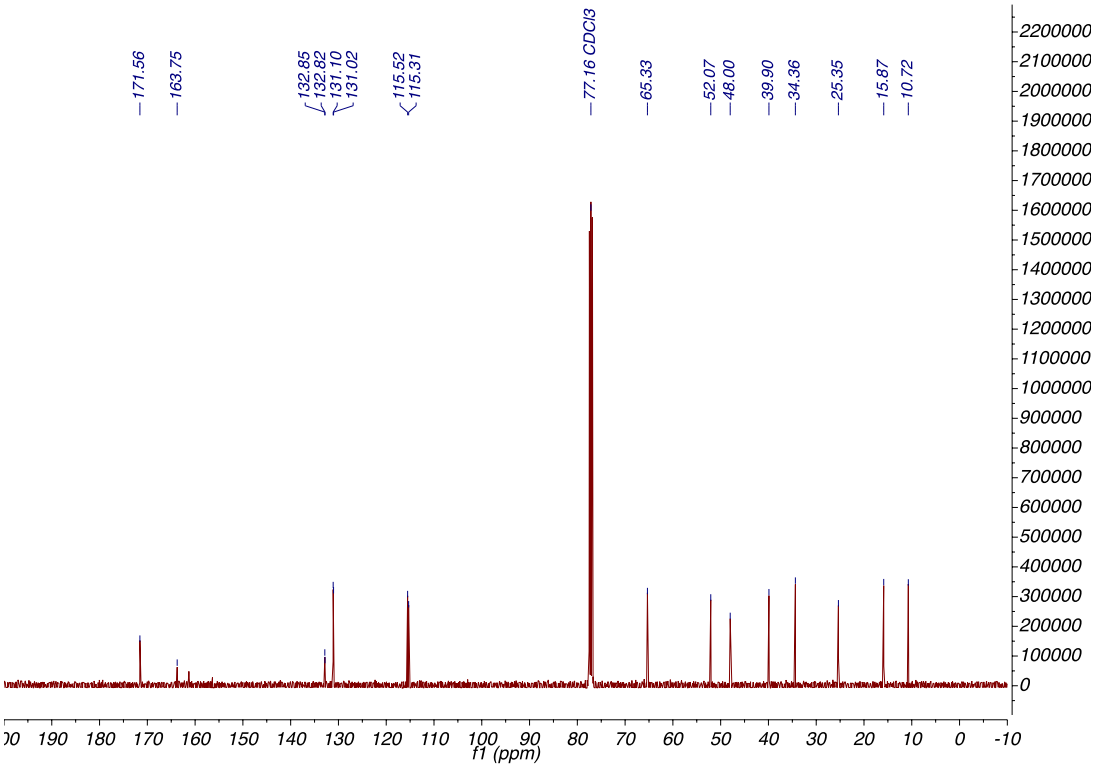
Methyl *N*-(4-methylbenzyl)-*N*-(methylsulfonyl)-*L*-leucinate 3.3.2.1.5



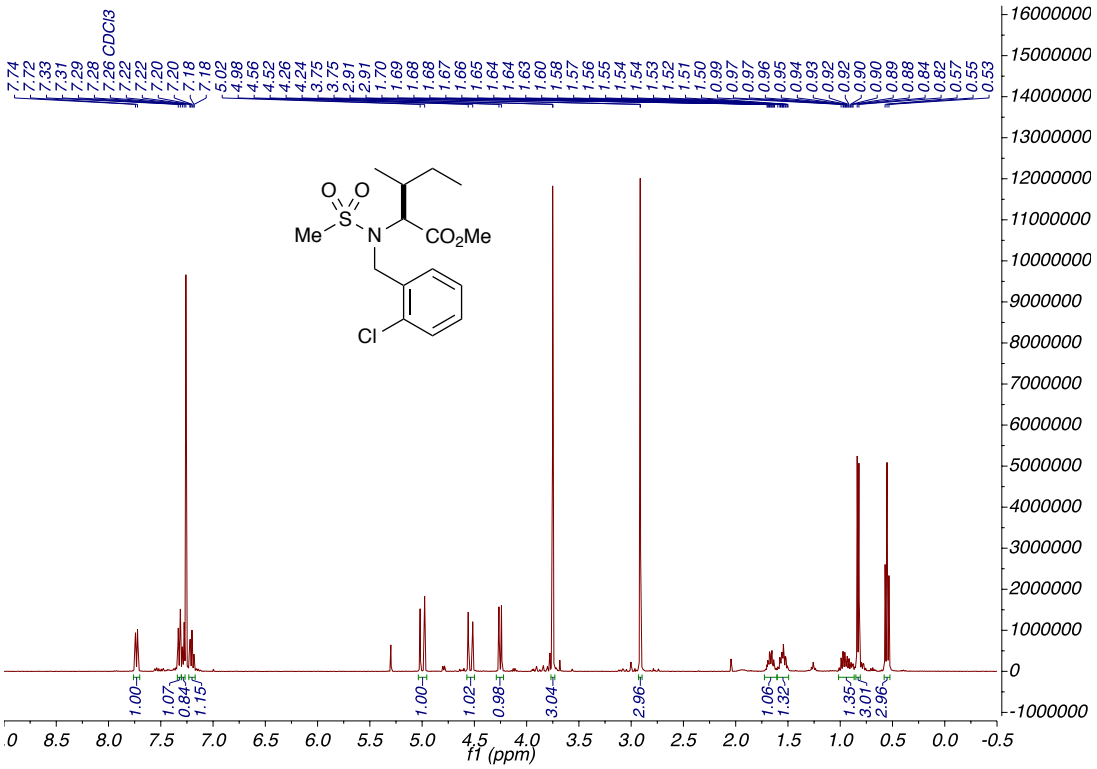


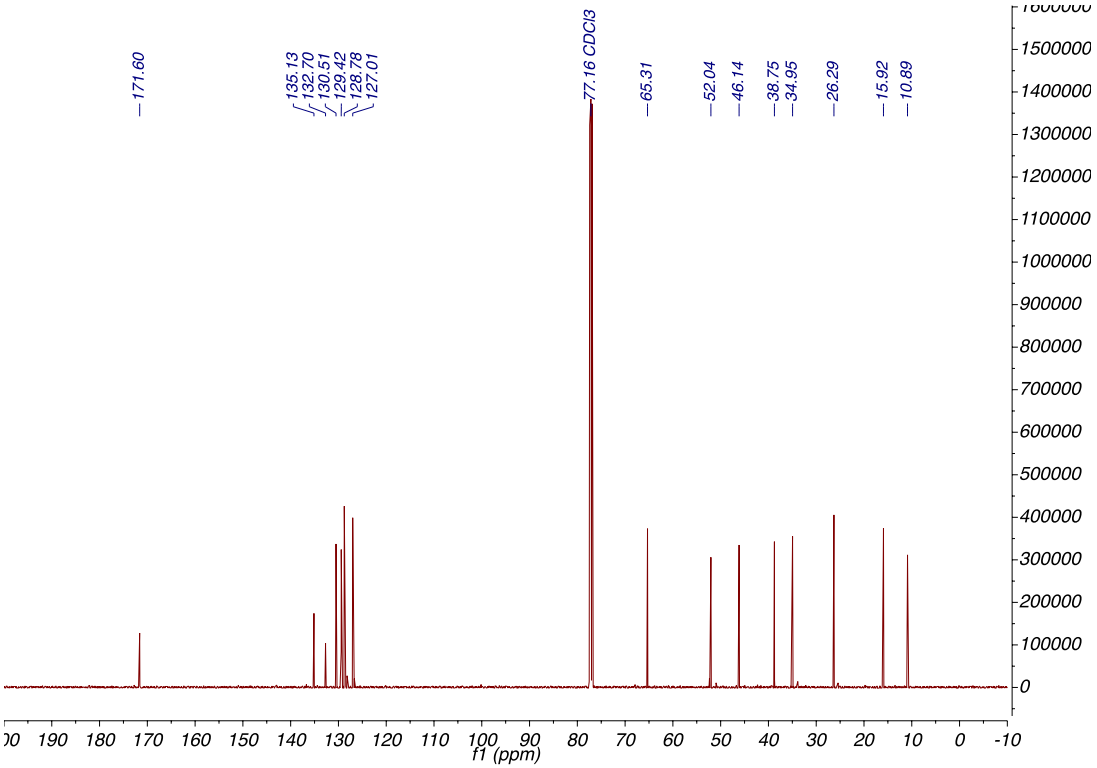
Methyl *N*-(4-fluorobenzyl)-*N*-(methylsulfonyl)-*L*-isoleucinate 3.3.2.1.6



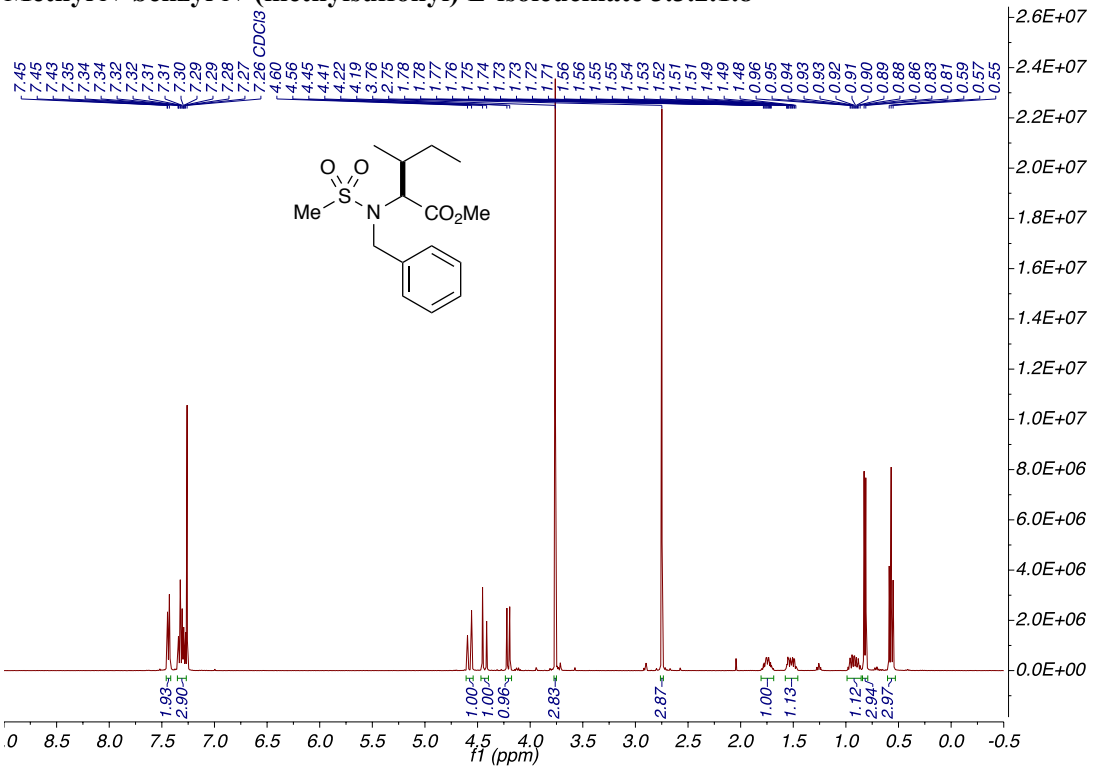


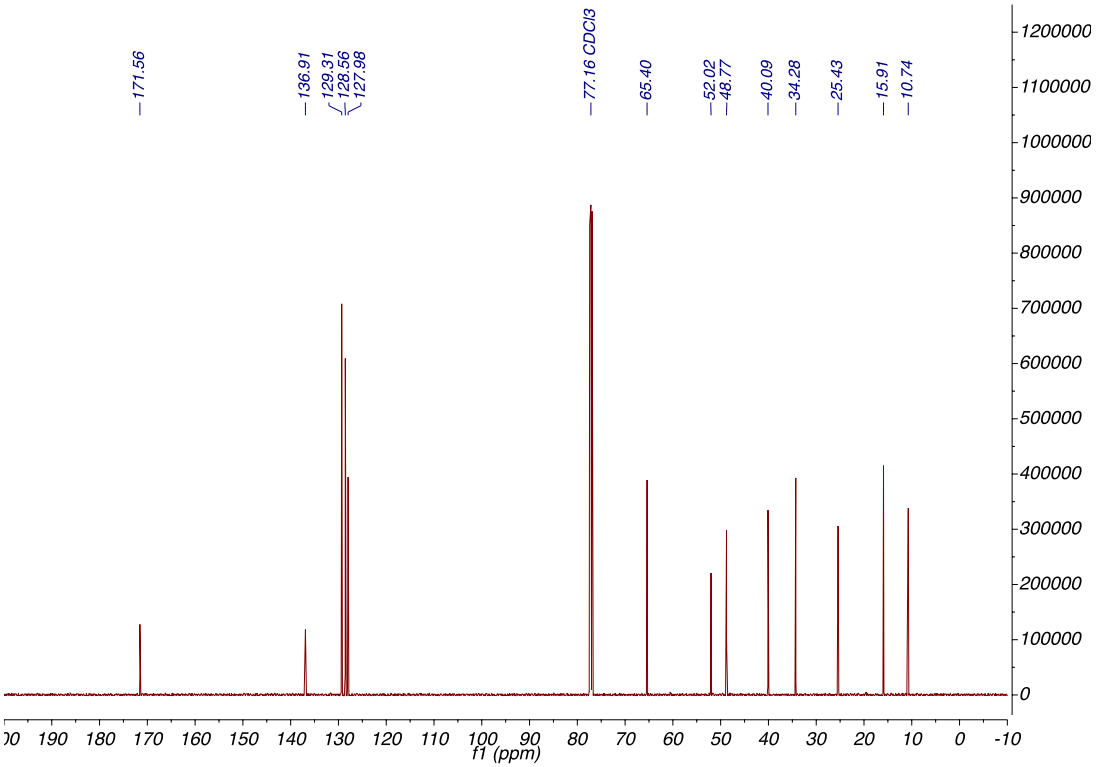
Methyl *N*-(2-chlorobenzyl)-*N*-(methylsulfonyl)-*L*-isoleucinate 3.3.2.1.7



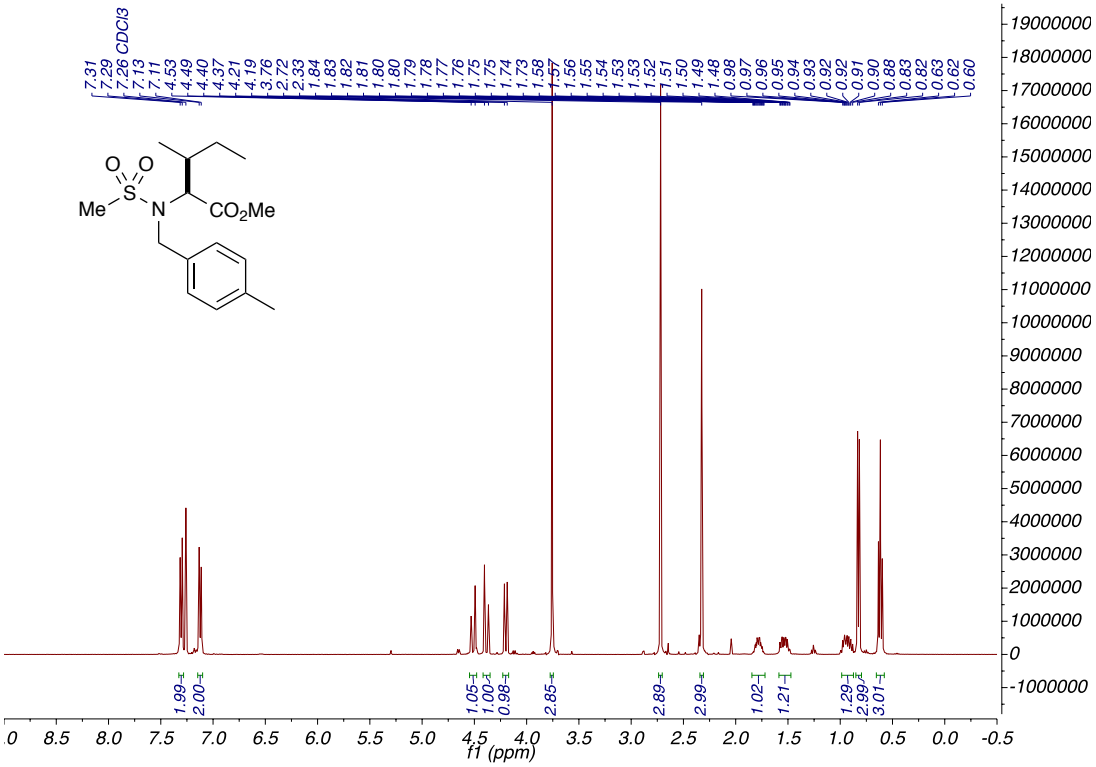


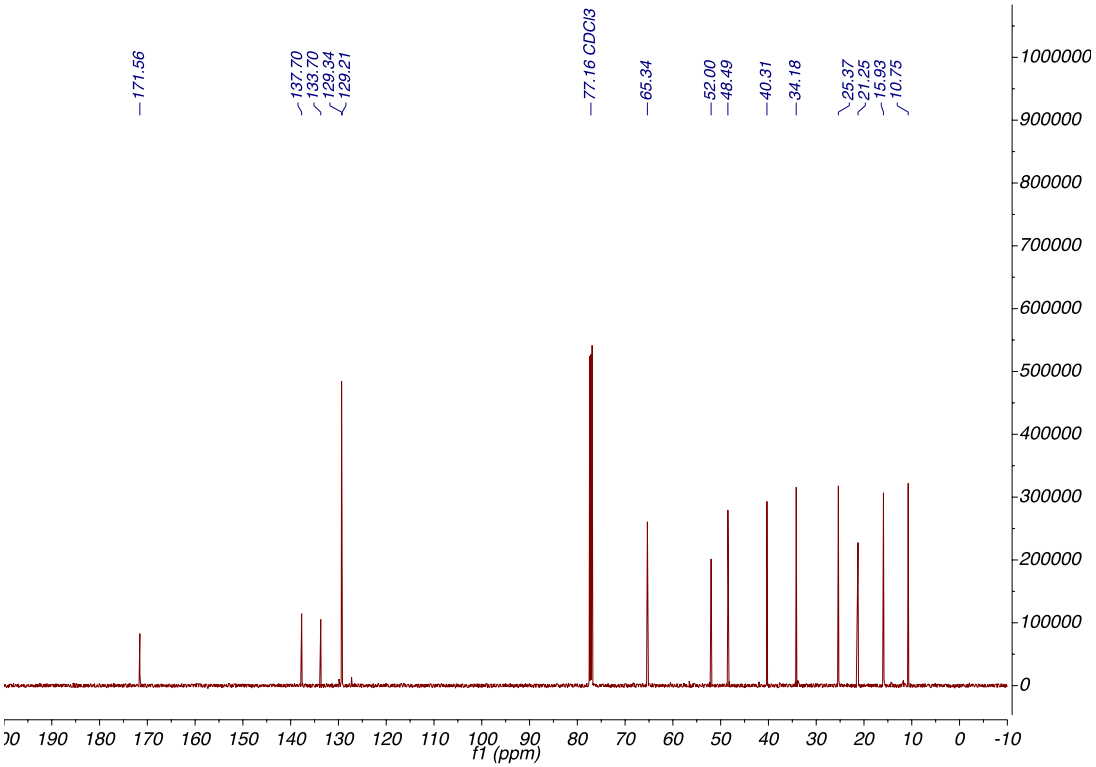
Methyl *N*-benzyl-*N*-(methylsulfonyl)-*L*-isoleucinate 3.3.2.1.8



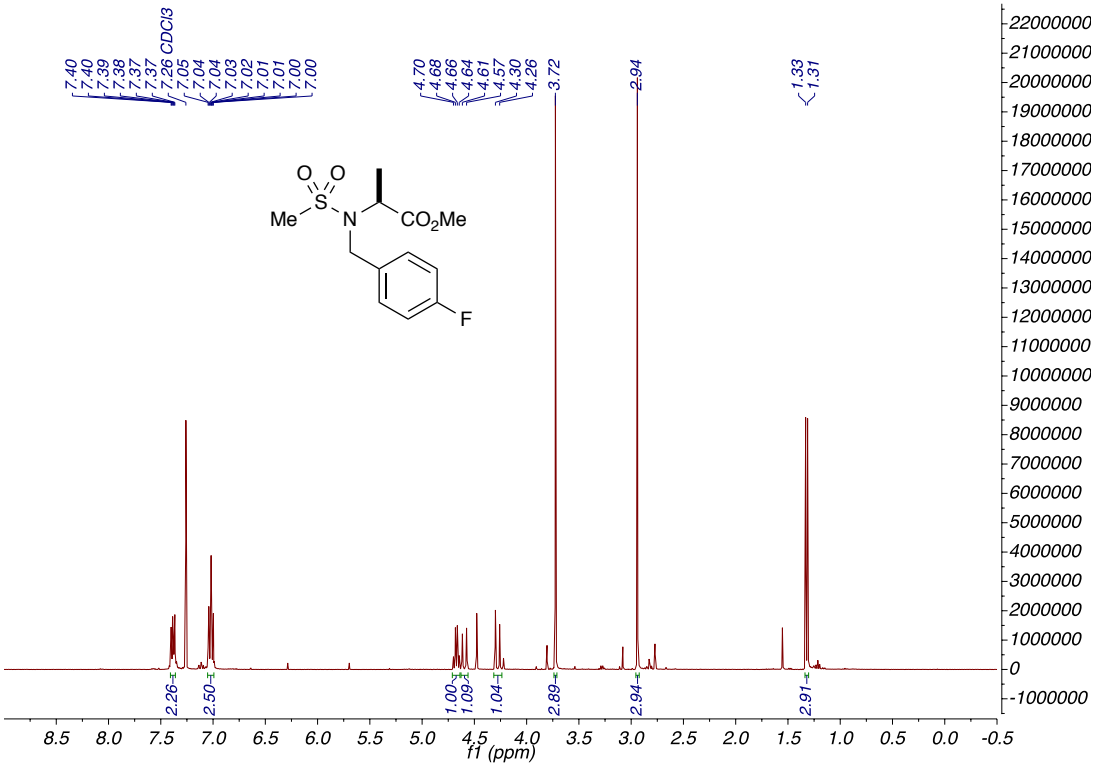


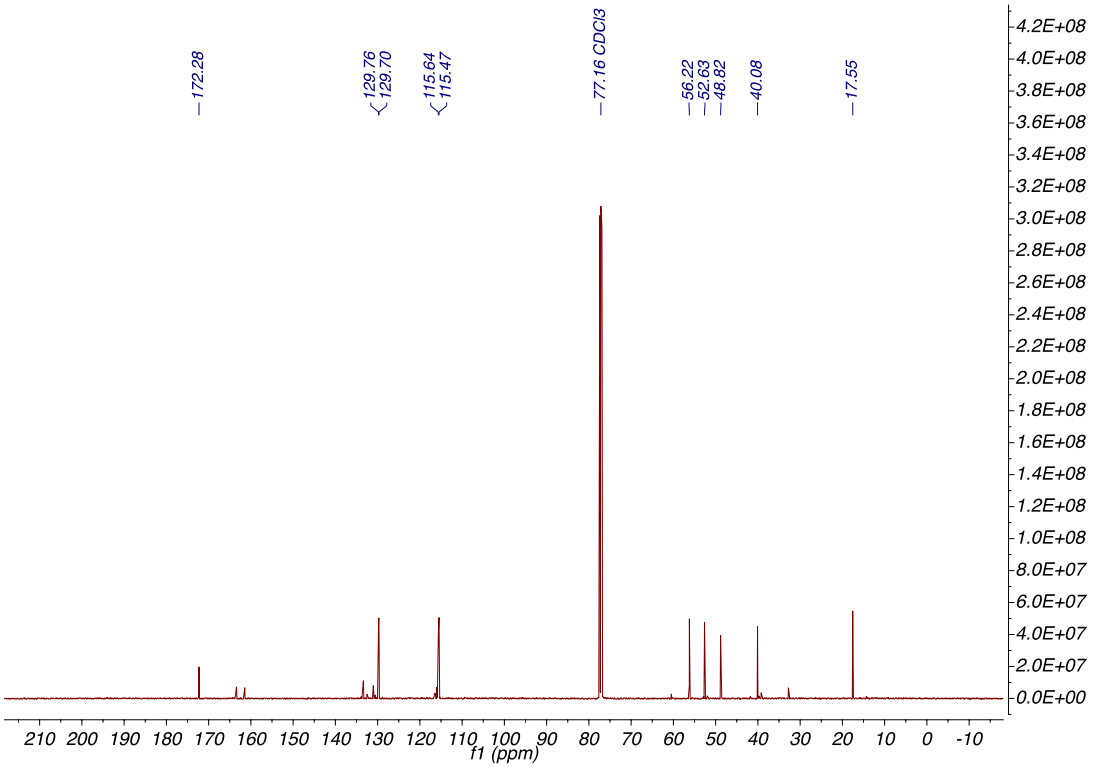
Methyl *N*-(4-methylbenzyl)-*N*-(methylsulfonyl)-*L*-isoleucinate 3.3.2.1.9



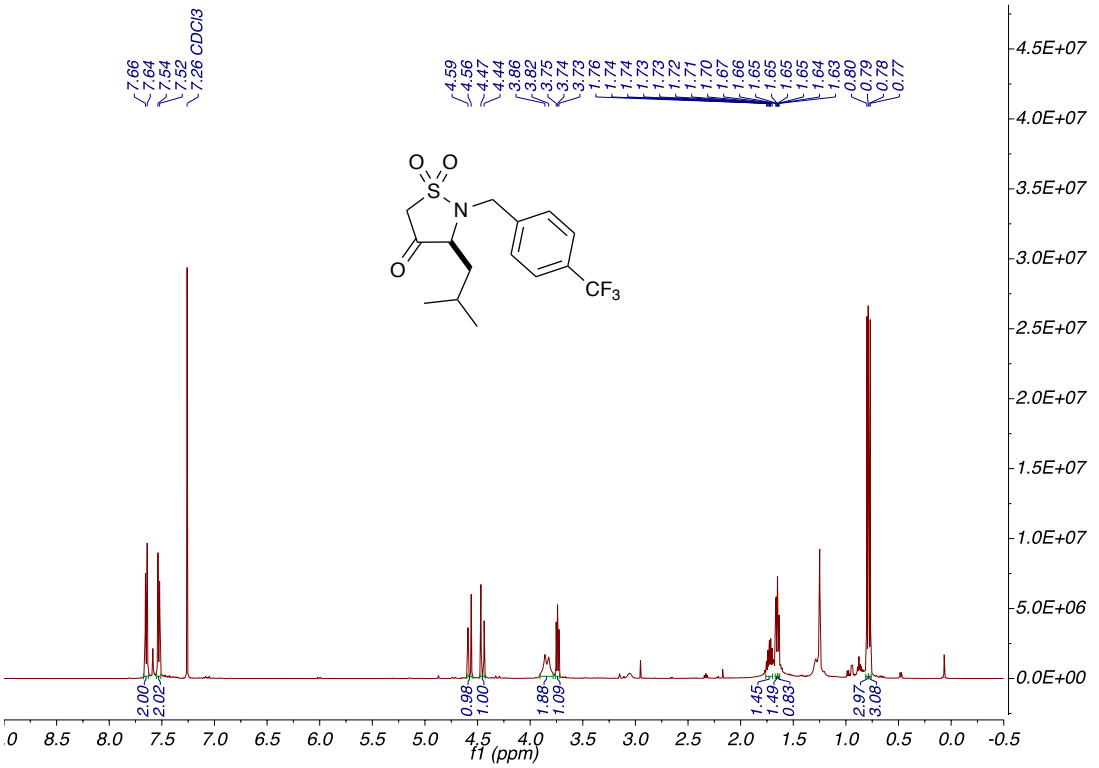


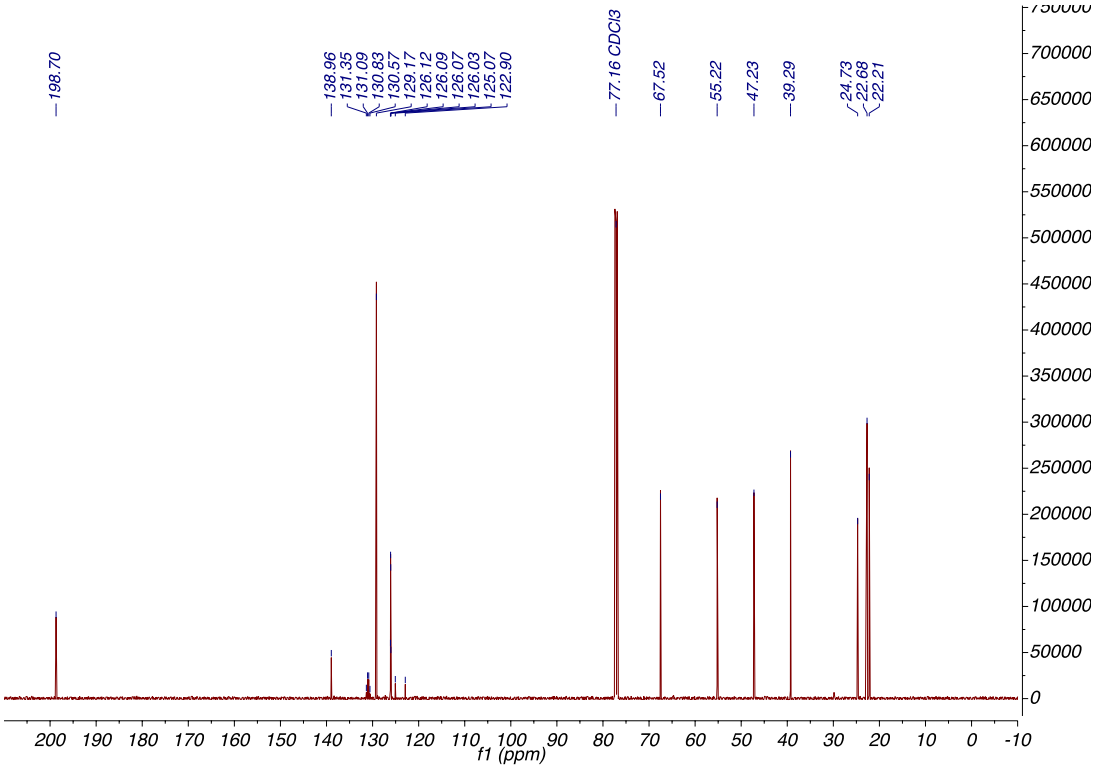
Methyl *N*-(4-fluorobenzyl)-*N*-(methylsulfonyl)-*L*-alaninate 3.3.2.1.10



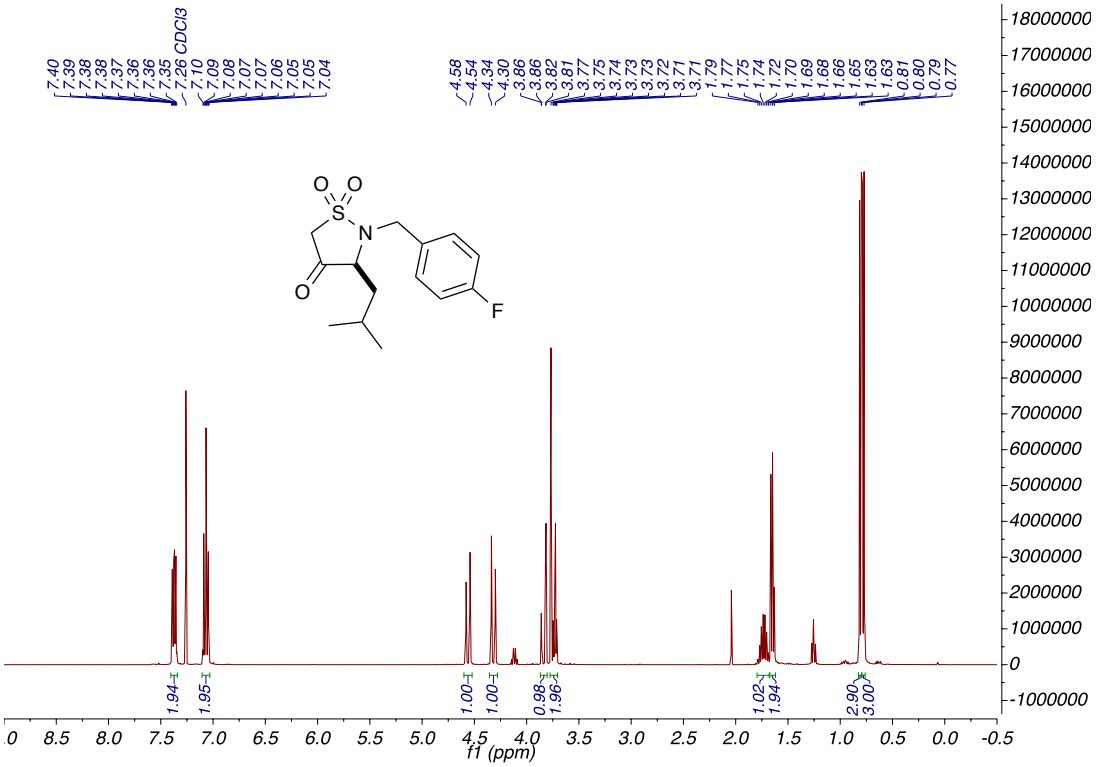


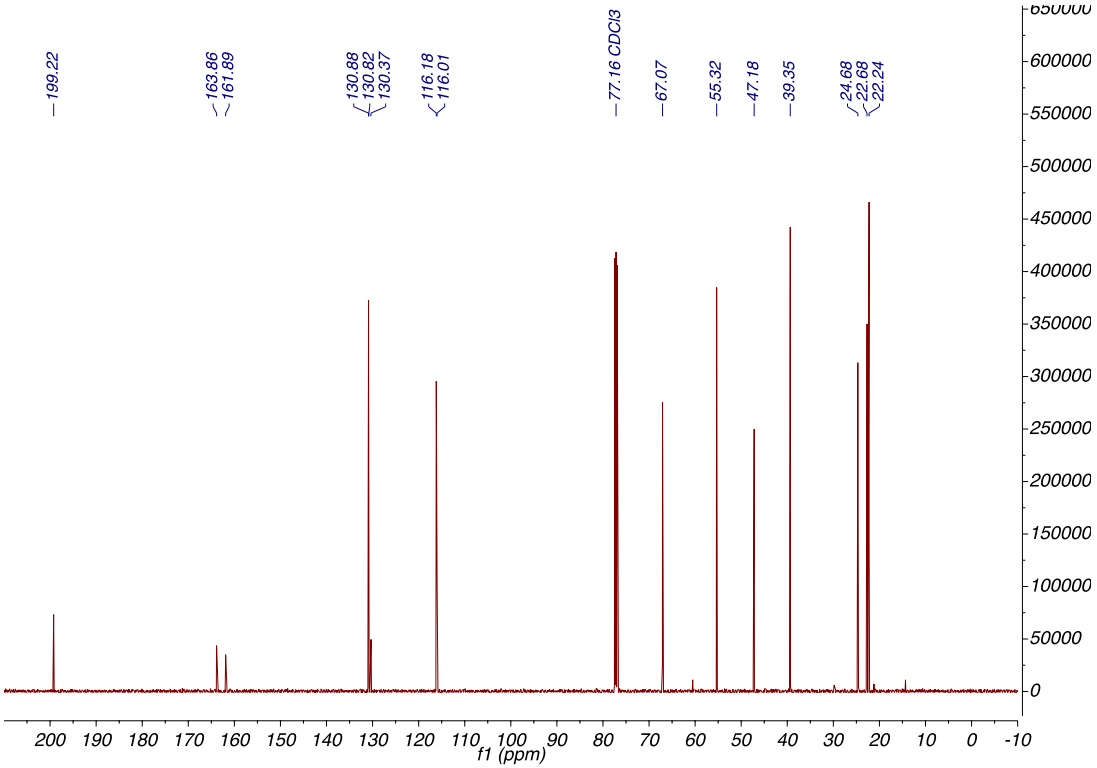
(*S*)-3-isobutyl-2-(4-(trifluoromethyl)benzyl)isothiazolidin-4-one 1,1-dioxide 3.3.3.1.1



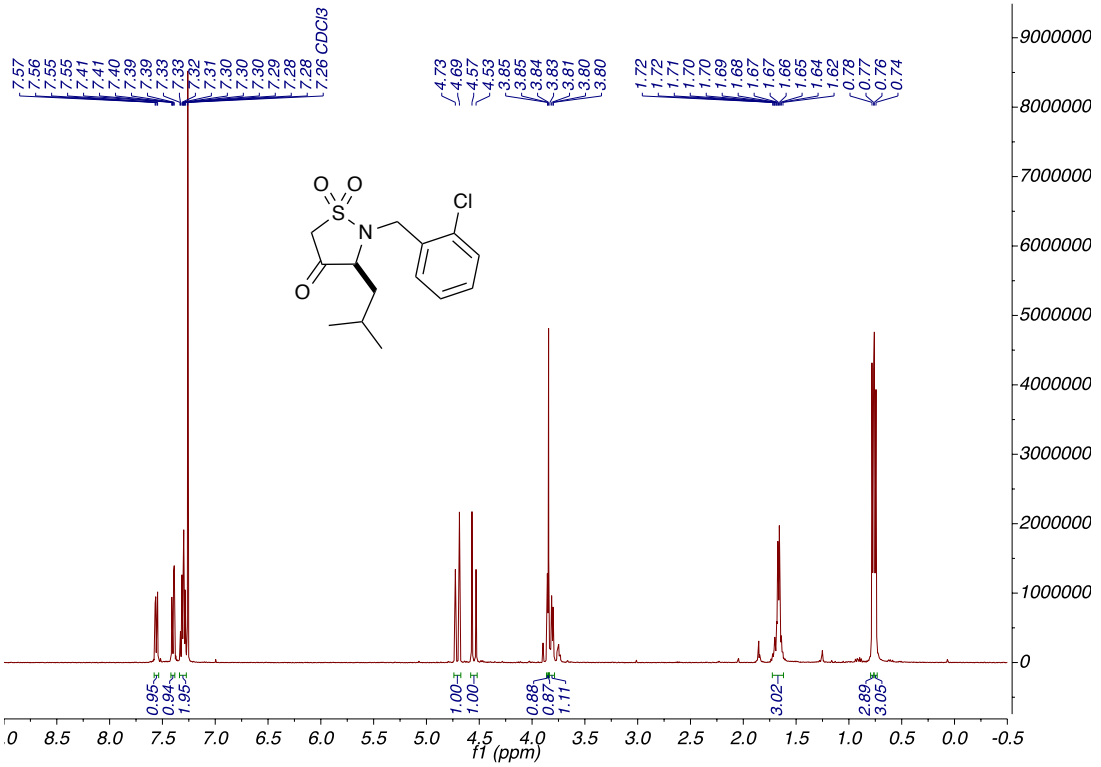


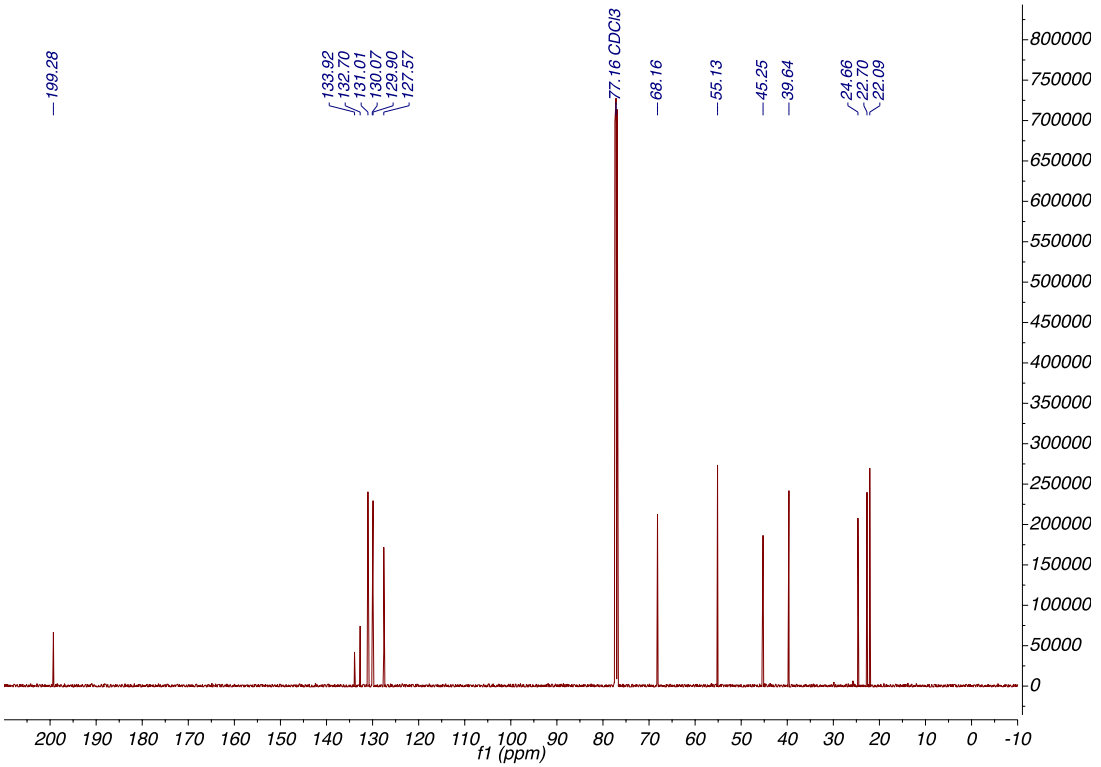
(*S*)-2-(4-fluorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.3.1.2



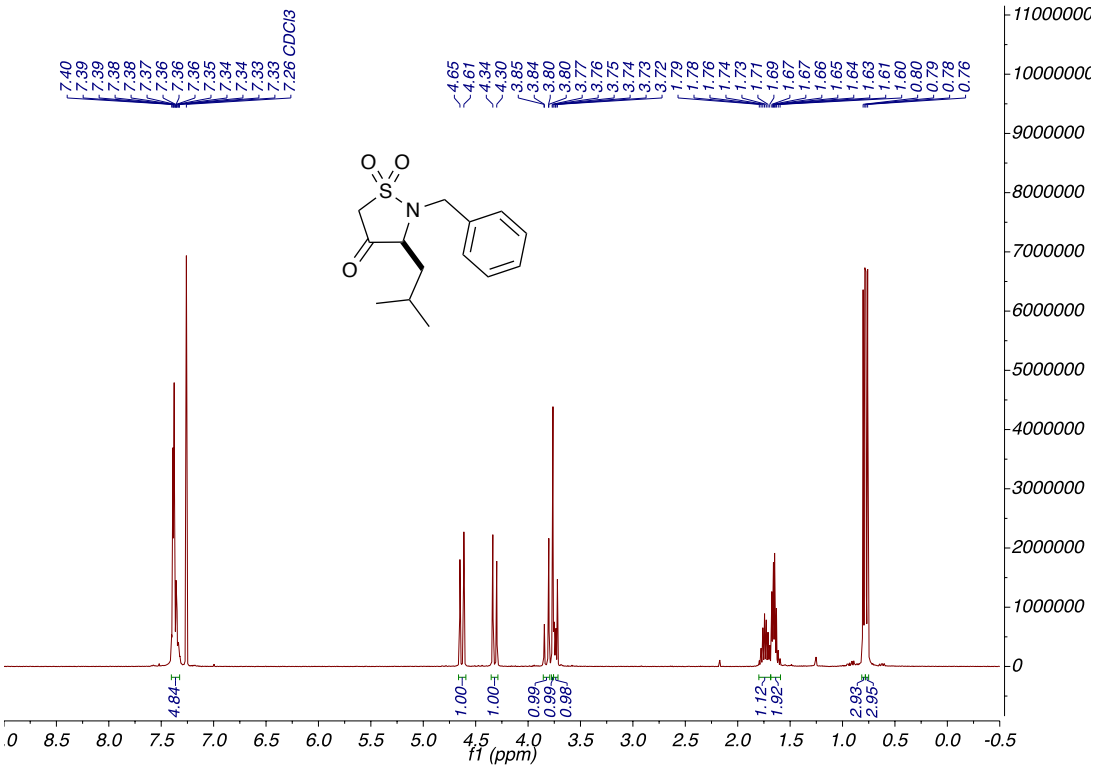


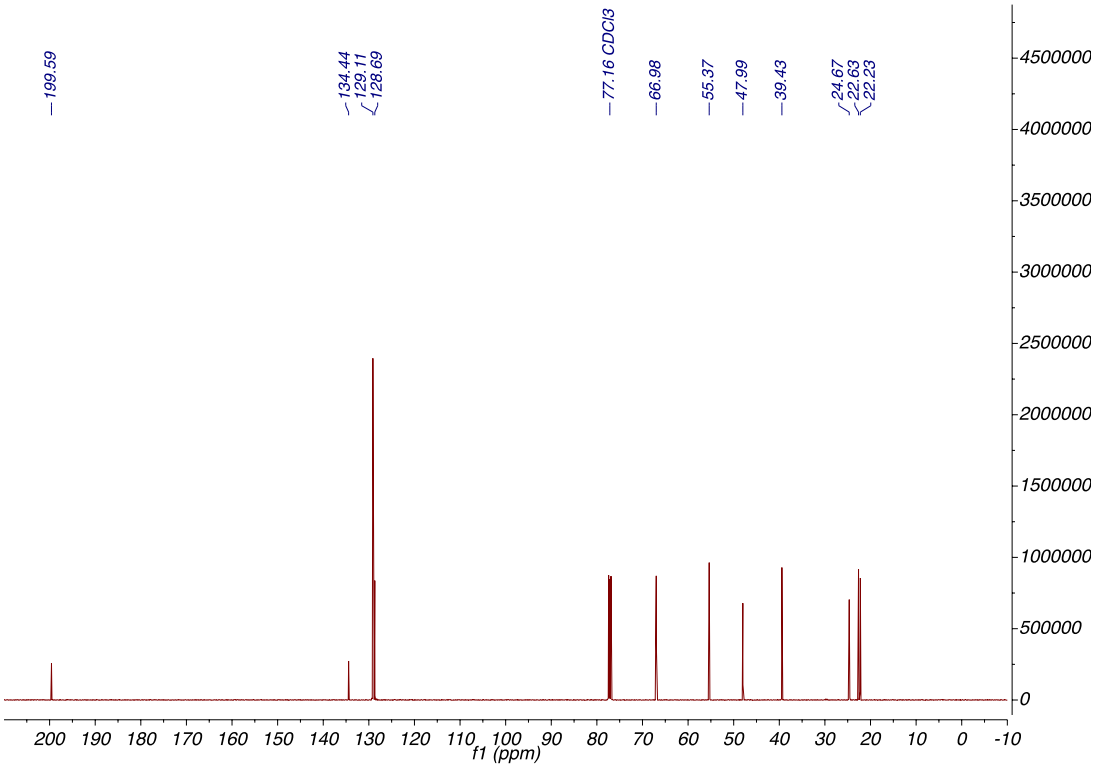
(*S*)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.3.1.3



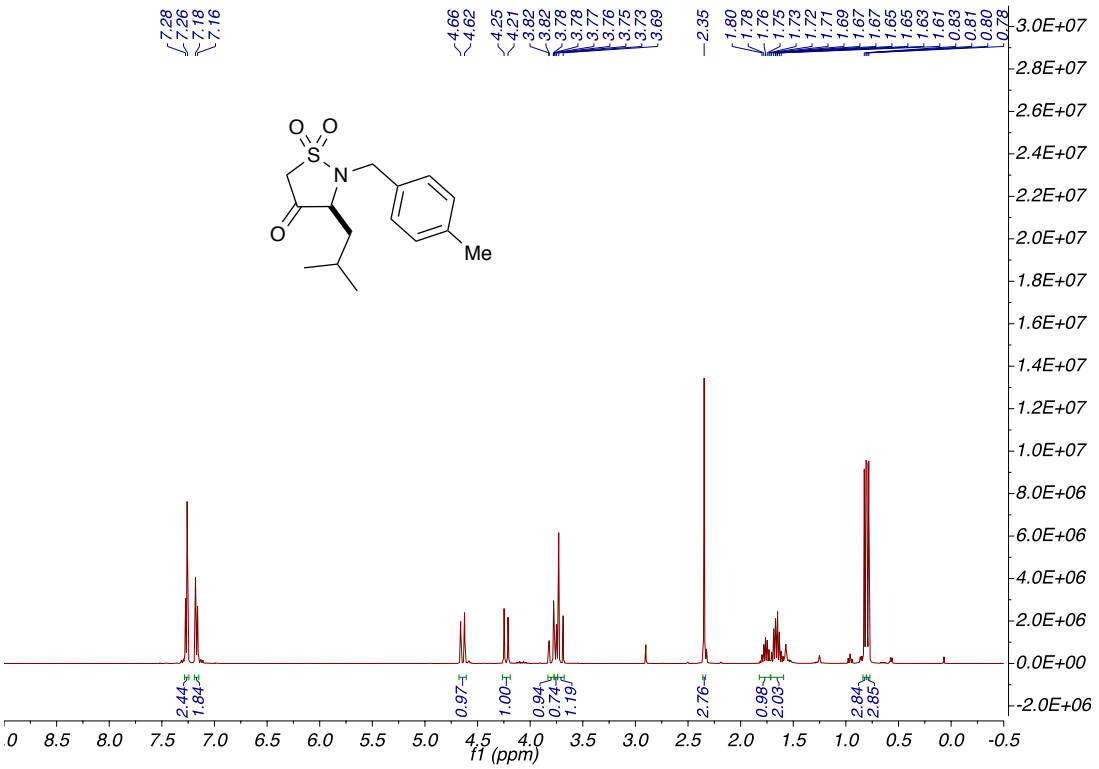


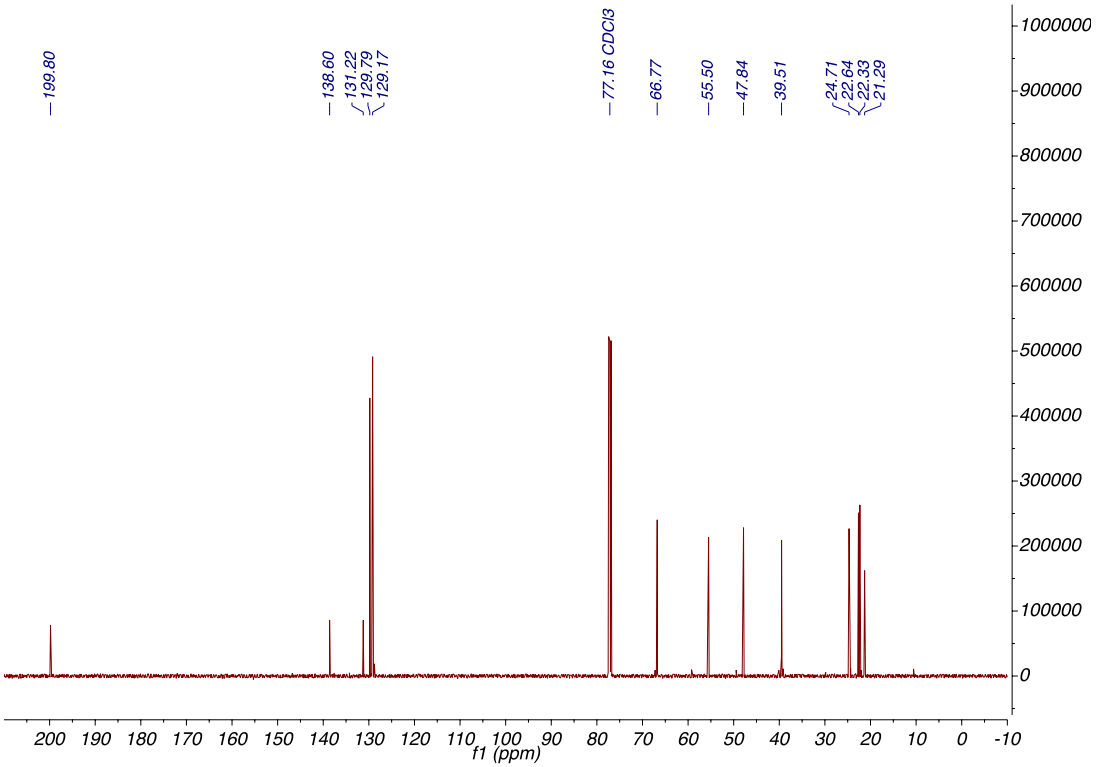
(*S*)-2-benzyl-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.3.1.4



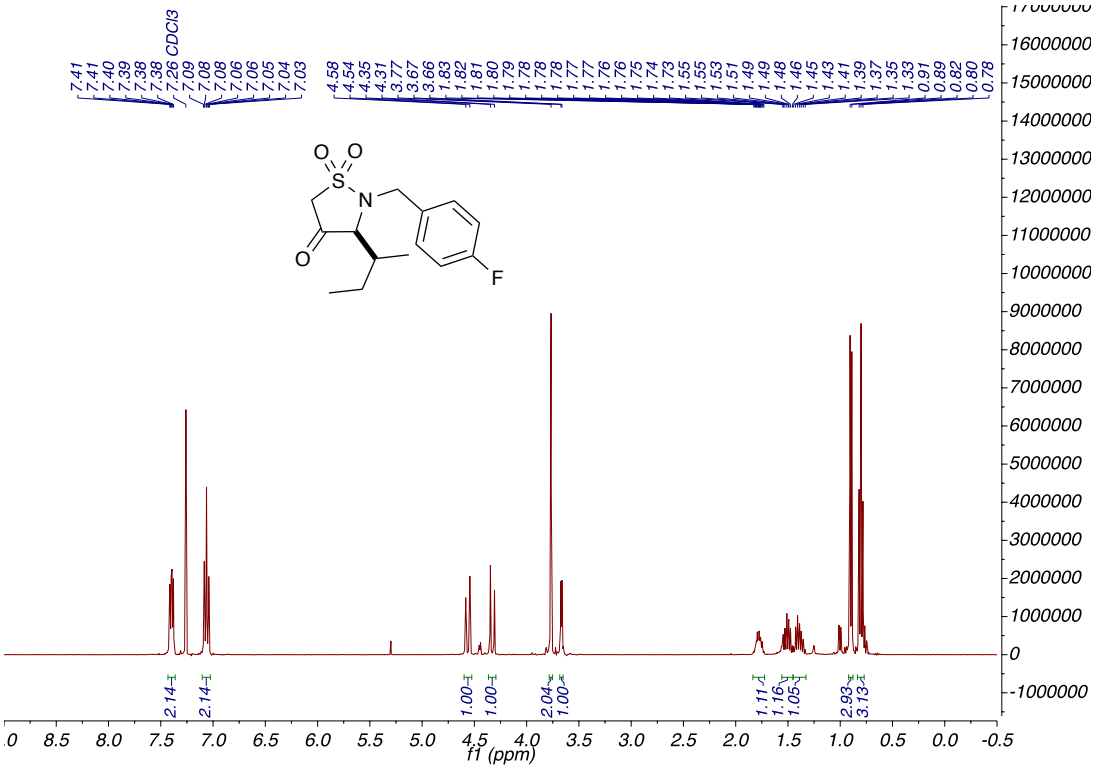


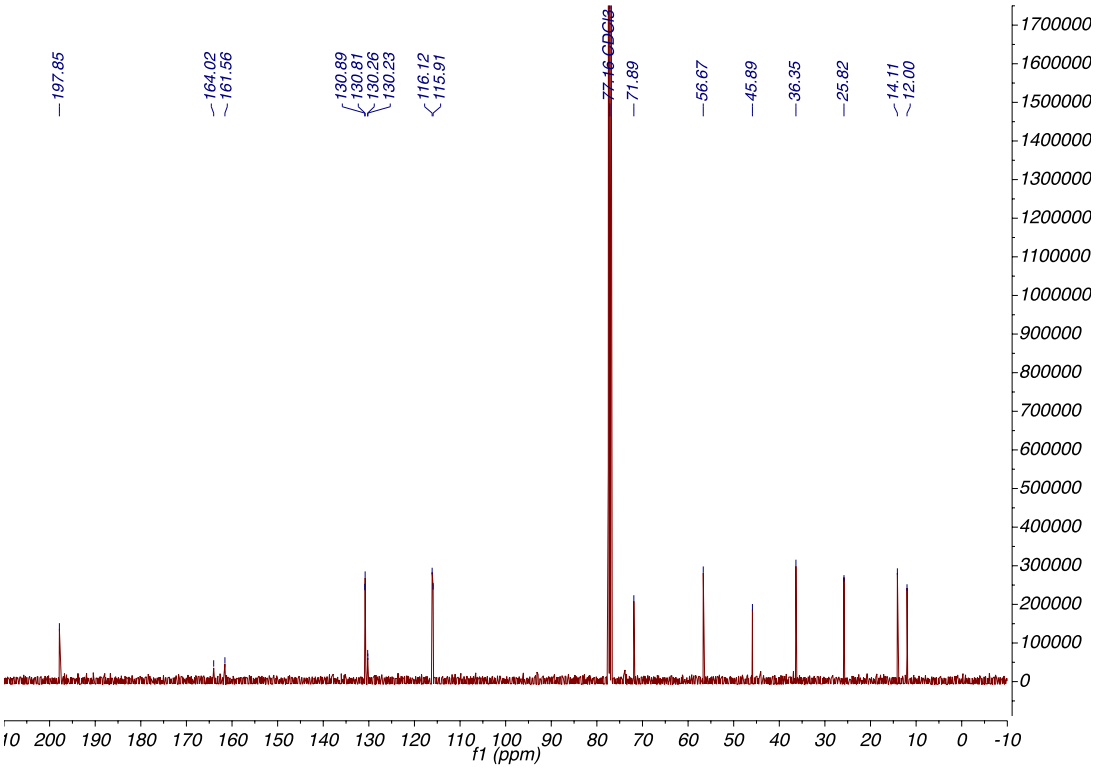
(*S*)-3-isobutyl-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide 3.3.3.1.5



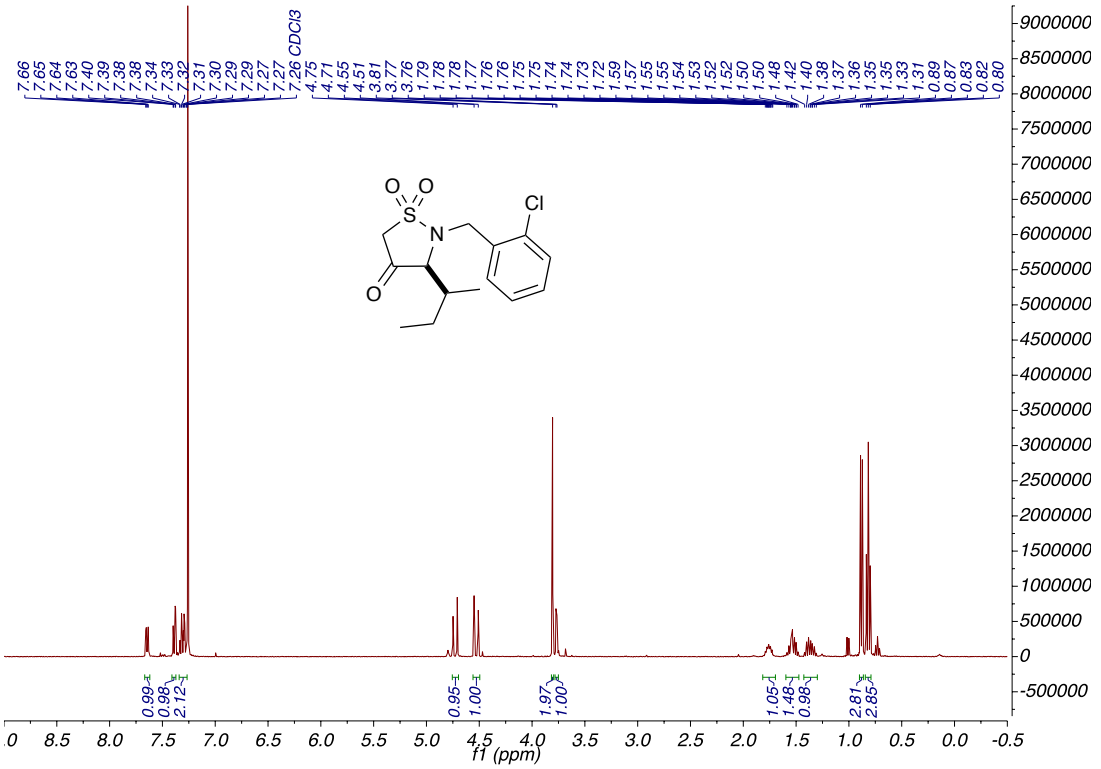


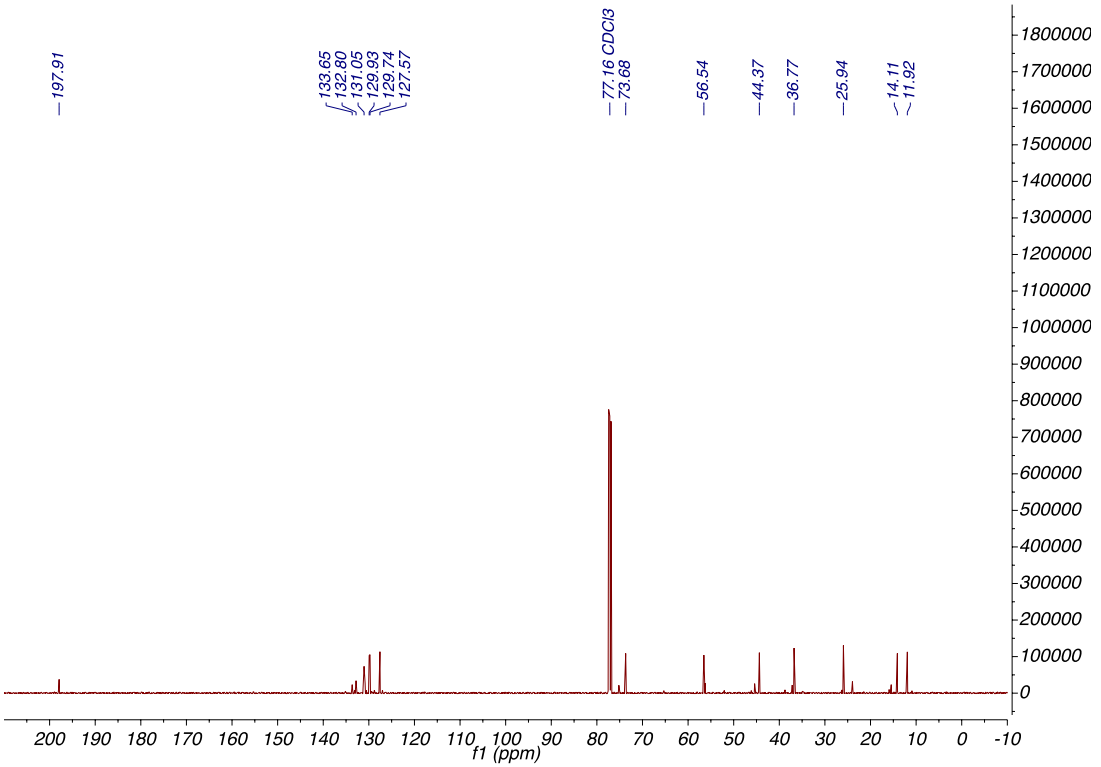
(*S*)-3-((*S*)-sec-butyl)-2-(4-fluorobenzyl)isothiazolidin-4-one 1,1-dioxide 3.3.3.1.6



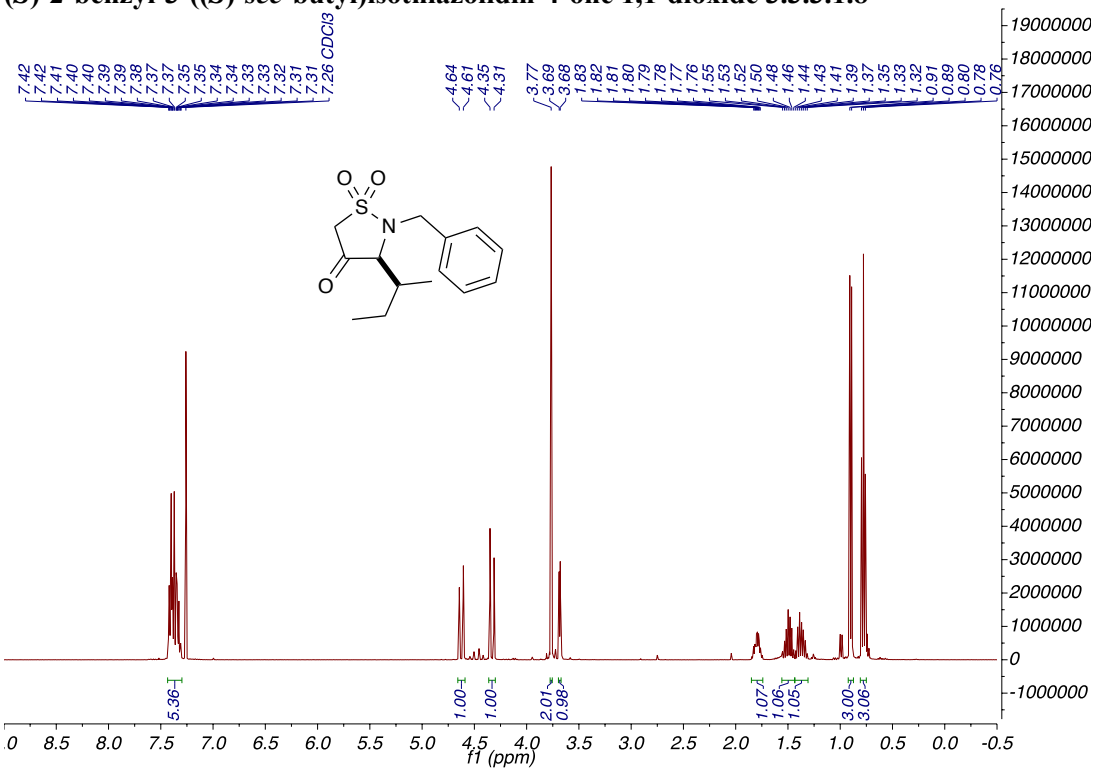


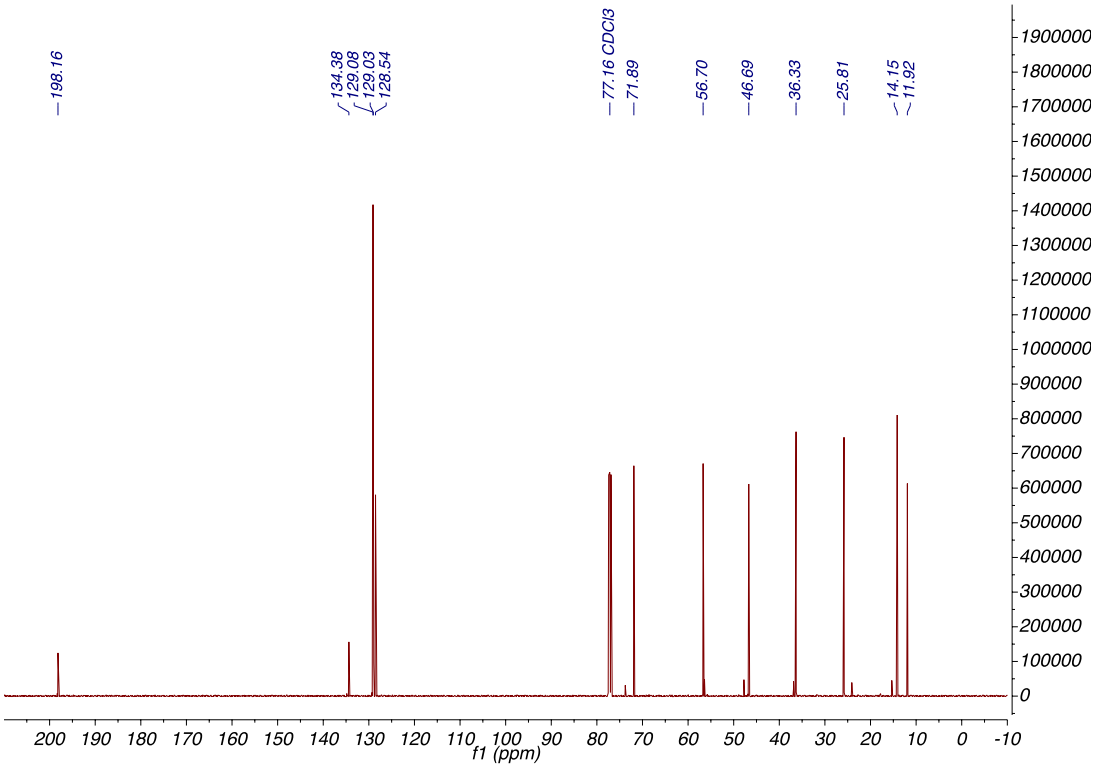
(*S*)-3-((*S*)-*sec*-butyl)-2-(2-chlorobenzyl)isothiazolidin-4-one 1,1-dioxide 3.3.3.1.7



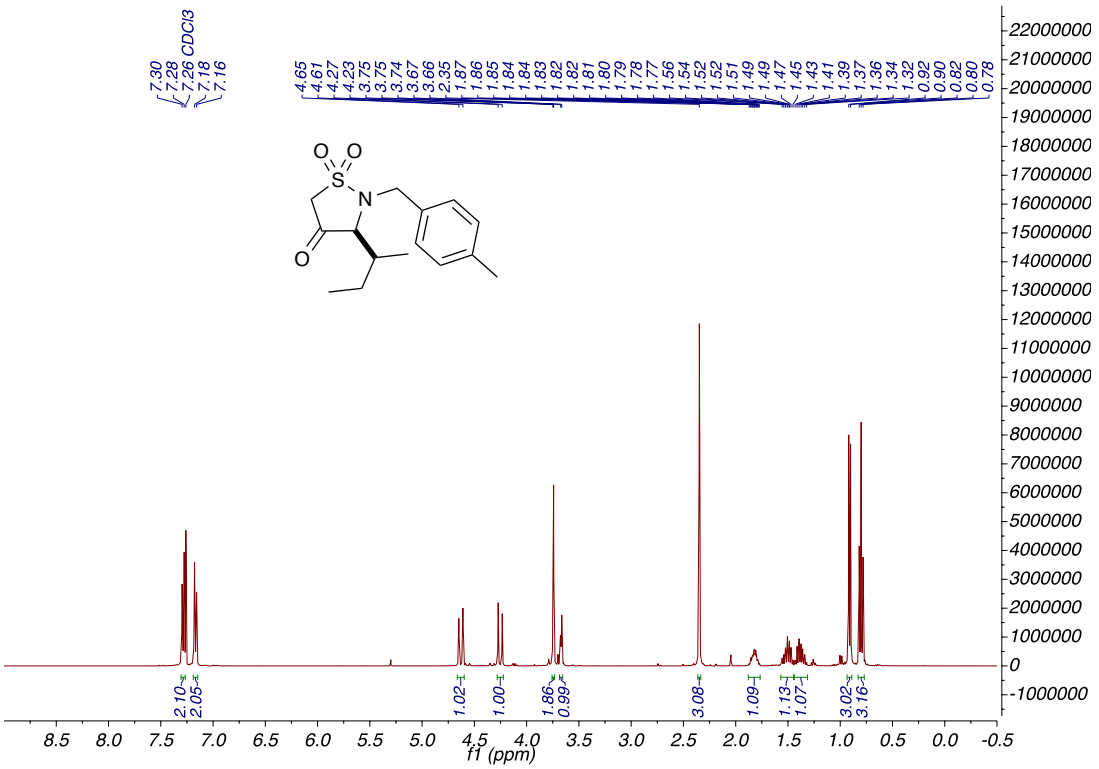


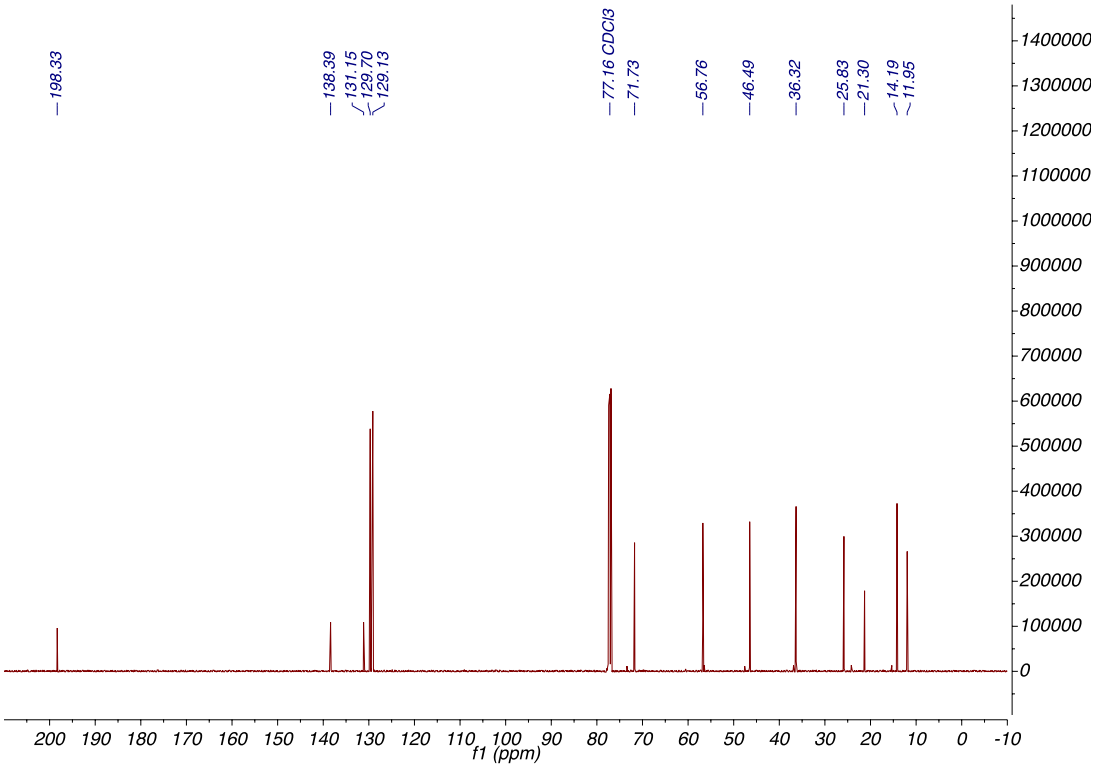
(*S*)-2-benzyl-3-((*S*)-*sec*-butyl)isothiazolidin-4-one 1,1-dioxide 3.3.3.1.8





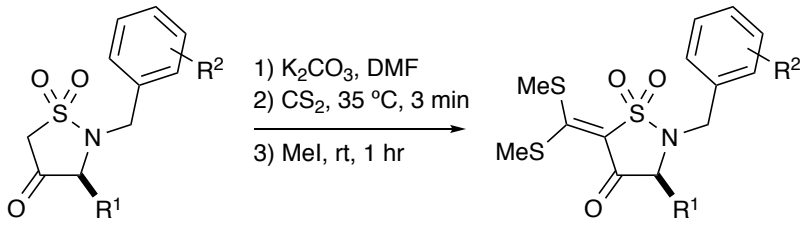
(*S*)-3-((*S*)-sec-butyl)-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide 3.3.3.1.9





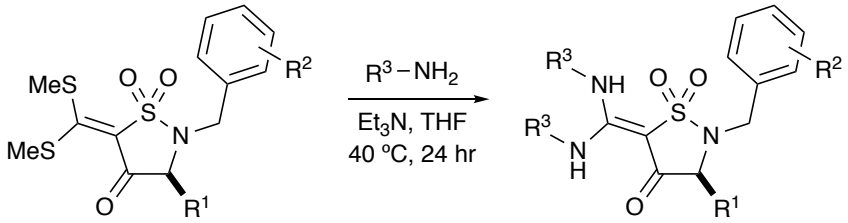
General Procedure

General Procedure **A** to Bis-thiol ethers **3.3.8.1.1–3.3.8.1.4**:



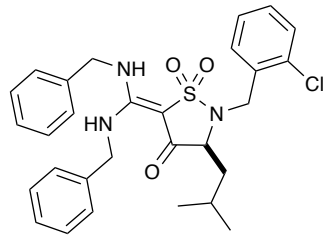
A sultam (1 equivalent) was dissolved in dimethylformamide (0.05 M) before K_2CO_3 (3 equivalents) was added. The reaction was warmed to 35 °C in an oil bath before carbon disulfide (1.5 equivalents) was added drop-wise to the flask. The reaction was stirred at 35 °C for 3 min before methyl iodide (2 equivalents) was added. The flask was removed from the oil bath and stirred at room temperature for an additional hour. The mixture was extracted with ethyl acetate, and brine. The organic layer was then dried with sodium sulfate before being filtered and condensed by rotary evaporation. A normal phase silica flash column was then utilized to purify the product in yields of up to 85 %.

General Procedure **B** for the synthesis of Bis enamines **3.3.9.1.1–3.3.9.1.13**:



Bis thiol ether sultams **3.3.8.1.1–3.3.8.1.4** (1 equivalent) was dissolved in tetrahydrofuran (0.1 M) before Et_3N (2.1 equivalents) and amine (2.1 equivalents) were added to the flask. The reaction was stirred at 40 ºC for 24 hours. Then mixture was then transferred to a normal phase silica flash column for purification in order to yield product in up to 83 %.

(*S*)-5-(bis(benzylamino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.1** (23%, 15 mg) was isolated as clear oil.

$\mathbf{R_f}$ = 0.31 (EtOAc:Hexane = 1:3 x 3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -0.38 (*c* = 0.0105, CH_2Cl_2);

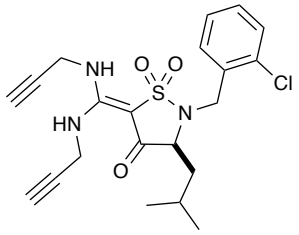
FTIR (neat): 3335, 3063, 3031, 2955, 2926, 2868, 1616, 1548, 1496, 1443, 1247, 1177, 1049, 732, 697 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.65 (dd, *J* = 7.5, 1.7 Hz, 1H, ArH), 7.39–7.27 (m, 8H, ArH), 7.24 (td, *J* = 4.7, 4.3, 2.8 Hz, 5H, ArH), 4.76 (d, *J* = 15.8 Hz, 1H, NCH_2-*o*-ClBn), 4.58 (d, *J* = 5.8 Hz, 4H, 2-NCH_2Bn), 4.30 (d, *J* = 15.8 Hz, 1H, NCH_2-*o*-ClBn), 3.72 (t, *J* = 5.8 Hz, 1H, NCHCH_2CHMeMe), 1.78 (dq, *J* = 13.1, 6.6 Hz, 1H, MeCHMe), 1.69 (dt, *J* = 12.8, 6.3 Hz, 1H, CH_2), 1.64–1.57 (m, 1H, CH_2), 0.81 (d, *J* = 6.4 Hz, 3H, Me), 0.73 (d, *J* = 6.5 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) 186.9 (CO), 158.6 (C$(NH)_2$), 136.0 (2 ArC), 133.9 (ArC), 133.7 (ArC), 130.9 (ArC), 129.6 (ArC), 129.3 (4 ArC), 129.1 (ArC), 128.5 (2 ArC), 127.1 (ArC), 127.0 (4 ArC), 91.8 (COCC$(NH)_2$), 66.5 (NCHCH_2CHMeMe), 48.5 (Bn), 46.6 (Bn), 40.4 (Bn), 24.6 (CH_2CHMeMe), 22.8 (Me), 22.8 (Me);

HRMS calculated for $C_{29}H_{32}ClN_3O_3S$ 560.1751 $(M+Na)^+$; found 560.1780 (TOF MS ES^+).

(*S*)-5-(bis(prop-2-yn-1-ylamino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.2** (54%, 12 mg)

was isolated as clear oil.

R_f = 0.14 (EtOAc:Hexane = 1:3 x 3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -3.0 (*c* = 0.006, CH_2Cl_2);

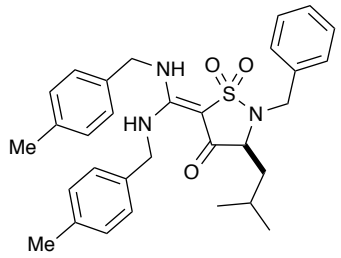
FTIR (neat): 3299, 3060, 2957, 2928, 2869, 2124, 1617, 1470, 1443, 1403, 1344, 1263, 1134, 1049, 754 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.61 (dd, *J* = 7.3, 1.5 Hz, 1H, ArH), 7.36 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.28 (dd, *J* = 7.4, 1.4 Hz, 1H, ArH), 7.26–7.20 (m, 1H, ArH), 4.72 (d, *J* = 15.7 Hz, 1H, Bn), 4.33 (dd, *J* = 6.1, 2.3 Hz, 4H, 2CH_2NH), 4.28 (d, *J* = 15.7 Hz, 1H, Bn), 3.67 (t, *J* = 6.0 Hz, 1H, NCHCH$_2$CHMeMe), 2.49 (t, *J* = 2.4 Hz, 2H, 2CCH), 1.74 (dq, *J* = 13.1, 6.5 Hz, 1H, MeCHMe), 1.65 (dt, *J* = 12.9, 6.3 Hz, 1H, CH_2CHMeMe), 1.56 (dt, *J* = 14.0, 6.4 Hz, 1H, CH_2CHMeMe), 0.78 (d, *J* = 6.5 Hz, 3H, Me), 0.71 (d, *J* = 6.5 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) 187.4 (CO), 158.6 (C(NH)$_2$), 133.7 (ArC), 133.7 (ArC), 130.9 (ArC), 129.7 (ArC), 129.2 (ArC), 127.1 (ArC), 91.9 (COCC(NH)$_2$), 77.7 (2 CCH), 74.9 (2 CCH), 66.3 (NCHCH$_2$CHMeMe), 46.5 (BnC), 40.4 (CH$_2$CHMeMe), 34.3 (2 NHCH$_2$CCH), 24.6 (MeCHMe), 22.7 (2Me);

HRMS calculated for $C_{21}H_{24}ClN_3O_3S$ 434.1305 $(M+H)^+$; found 434.1288 (TOF MS ES^+).

(*S*)-2-benzyl-5-(bis((4-methylbenzyl)amino)methylene)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.3** (83%, 25 mg) was isolated as clear oil.

$\mathbf{R_f}$ = 0.25 (EtOAc:Hexane = 1:3 x 3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -8.28 (*c* = 0.007, CH_2Cl_2);

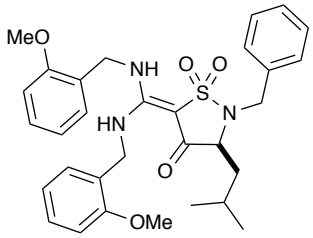
FTIR (neat); 3338, 3053, 3028, 2955, 2923, 2867, 1617, 1550, 1516, 1495, 1454, 1262, 1131, 1065, 801, 736, 699 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.43 (d, *J* = 6.9 Hz, 2H, ArH), 7.37–7.28 (m, 3H, ArH), 7.14 (q, *J* = 8.1 Hz, 8H, ArH), 4.53 (d, *J* = 5.6 Hz, 4H, 2C$\underline{H_2}$NH), 4.45 (d, *J* = 14.8 Hz, 1H, Bn), 4.28 (d, *J* = 14.8 Hz, 1H, Bn), 3.62 (t, *J* = 5.8 Hz, 1H, NC$\underline{H}$CH_2CHMeMe), 2.34 (s, 6H, 2Me), 1.80 (dp, *J* = 13.1, 6.6 Hz, 1H, MeC$\underline{H}$Me), 1.72–1.64 (m, 1H, C$\underline{H_2}$CHMeMe), 1.54 (dt, *J* = 14.0, 6.3 Hz, 1H, C$\underline{H_2}$CHMeMe), 0.79 (d, *J* = 6.5 Hz, 3H, Me), 0.72 (d, *J* = 6.6 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) 186.9 (CO), 158.5 ($\underline{C}(NH)_2$), 138.3 (ArC), 135.8 (ArC), 133.0 (ArC), 129.9 (4 ArC), 129.1 (2 ArC), 128.6 (2 ArC), 127.9 (ArC), 127.0 (4 ArC), 91.7 (CO$\underline{C}$C(NH)$_2$), 65.2 (N$\underline{C}$HCH_2CHMeMe), 49.0 (2 BnC), 48.4 (BnC), 40.1 ($\underline{C}H_2$CHMeMe), 24.6 (Me$\underline{C}$HMe), 22.8 ($\underline{Me}$), 22.8 ($\underline{Me}$), 21.2 (2 $\underline{Me}$Ar);

HRMS calculated for $C_{31}H_{37}N_3O_3S$ 532.2634 $(M+H)^+$; found 532.2631 (TOF MS ES^+).

(*S*)-2-benzyl-5-(bis((2-methoxybenzyl)amino)methylene)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.4** (42%, 8 mg) was isolated as clear oil.

R_f = 0.17 (EtOAc:Hexane = 1:3 x 3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -11.0 (*c* = 0.004, CH_2Cl_2);

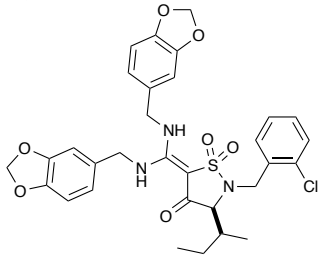
FTIR (neat): 3342, 3063, 3030, 3006, 2955, 2926, 2867, 1615, 1555, 1494, 1464, 1438, 1351, 1247, 1170, 1063, 755, 700 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.45–7.40 (m, 2H, ArH), 7.35–7.27 (m, 5H, ArH), 7.21 (dd, *J* = 7.4, 1.4 Hz, 2H, ArH), 6.94 (td, *J* = 7.5, 0.9 Hz, 2H, ArH), 6.87 (d, *J* = 8.1 Hz, 2H, ArH), 4.58 (d, *J* = 5.6 Hz, 4H, 2NHC$\underline{H_2}$Ar), 4.46 (d, *J* = 14.8 Hz, 1H, Bn), 4.26 (d, *J* = 14.8 Hz, 1H, Bn), 3.76 (s, 6H, 2O$\underline{Me}$), 3.58 (t, *J* = 5.8 Hz, 1H, NC$\underline{H}CH_2CHMeMe$), 1.77 (dp, *J* = 13.2, 6.6 Hz, 1H, MeC$\underline{H}$Me), 1.70–1.61 (m, 1H, C$\underline{H_2}$CHMeMe), 1.51 (dt, *J* = 14.0, 6.3 Hz, 1H, C$\underline{H_2}$CHMeMe), 0.77 (d, *J* = 6.5 Hz, 3H, Me), 0.69 (d, *J* = 6.6 Hz, 3H, Me);

^{13}C NMR (101 MHz, $CDCl_3$) 186.5 (CO), 158.5 ($\underline{C}(NH)_2$), 157.1 (2 ArC), 136.1 (ArC), 129.8 (2 ArC), 129.1 (2 ArC), 129.1 (2 ArC), 128.6 (2 ArC), 127.8 (ArC), 124.5 (2 ArC), 121.0 (2 ArC), 110.6 (2 ArC), 91.6 (CO$\underline{C}C(NH)_2$), 65.1 (N$\underline{C}HCH_2CHMeMe$), 55.3 (2 OMe), 49.2 (2 Bn), 40.2 ($\underline{C}H_2CHMeMe$), 24.6 (Me$\underline{C}$HMe) , 22.9 (Me), 22.8 (Me);

HRMS calculated for $C_{31}H_{37}N_3O_5S$ 564.2532 $(M+H)^+$; found 564.2556 (TOF MS ES^+).

(*S*)-5-(bis((benzo[*d*][1,3]dioxol-5-ylmethyl)amino)methylene)-3-((*S*)-*sec*-butyl)-2-(2-chlorobenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.5** (24%, 8 mg) was isolated as clear oil.

R_f = 0.43 (EtOAc:Hexane = 1:1);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -0.2 (*c* = 0.005, CH_2Cl_2);

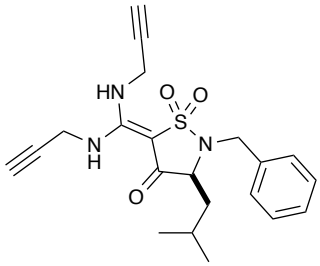
FTIR (neat): 3349, 3063, 2961, 2920, 2875, 1614, 1548, 1503, 1490, 1445, 1374, 1323, 1251, 1128, 1038, 808, 755 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.73 (ddd, *J* = 12.4, 7.7, 1.4 Hz, 1H, ArH), 7.37–7.27 (m, 2H, ArH), 7.24–7.18 (m, 1H, ArH), 6.77 (d, *J* = 8.5 Hz, 2H, ArH), 6.69 (d, *J* = 6.2 Hz, 4H, ArH), 5.97 (s, 4H, 2OC$\underline{H_2}$O), 4.85 (dd, *J* = 28.0, 16.6 Hz, 1H, NC$\underline{H_2}$Ar), 4.48 (d, *J* = 5.3 Hz, 4H, 2NHC$\underline{H_2}$Ar), 4.32 (dd, *J* = 16.6, 14.1 Hz, 1H, NC$\underline{H_2}$Ar), 3.74 (dd, *J* = 17.9, 2.7 Hz, 1H, NC$\underline{H}$CHMe), 1.91–1.73 (m, 1H, C$\underline{H}$Me), 1.65–1.52 (m, 1H, C$\underline{H_2}$Me), 1.52–1.39 (m, 1H, C$\underline{H_2}$Me), 0.92 (d, *J* = 6.9 Hz, 3H, Me), 0.83 (q, *J* = 7.5 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 185.32 (CO), 158.22 ($\underline{C}(NH)_2$), 148.58 (2 C_{AR}), 147.95 (d, J = 1.76 Hz, 2 C_{Ar}) 133.8 (d, J= 122.8 Hz, C_{Ar}), 133.8 (d, J = 199.8 Hz, C_{Ar}), 129.76 (d, *J* = 203.2 Hz, C_{Ar}), 129.60 (d, *J* = 13.8 Hz, C_{Ar}), 129.54 (d, *J* = 14.0 Hz, C_{Ar}), 129.45 (d, *J* = 170.9 Hz, C_{Ar}), 127.22 (2 C_{Ar}), 120.71 (2 C_{Ar}), 108.87 (2 C_{Ar}), 107.68 (2 C_{Ar}), 101.53 (2 OCH_2O), 92.91 (CO$\underline{C}$C(NH)$_2$), 72.12 (N$\underline{C}$HCHMe), 48.53 (Bn), 46.41 (2 Bn), 37.60 ($\underline{C}$HMe), 25.62 (CH_2Me), 14.5 (Me), 12.3 (Me)

HRMS calculated for $C_{31}H_{32}ClN_3O_7S$ 648.1547 $(M+Na)^+$; found 648.1544 (TOF MS ES^+).

(*S*)-2-benzyl-5-(bis(prop-2-yn-1-ylamino)methylene)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.6** (50%, 9 mg) was isolated as clear oil.

$\mathbf{R_f}$ = 0.13 (EtOAc:Hexane = 1:3 x3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = 15.1 (*c* = 0.0045, acetone);

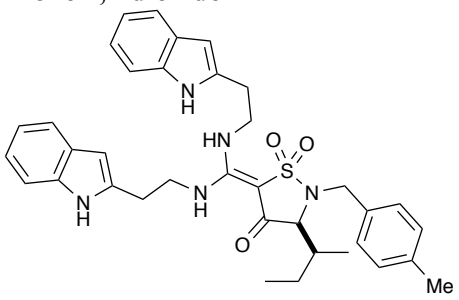
FTIR (neat) 3438, 3028, 2969, 2955, 2868, 2122, 1738, 1628, 1495, 1454, 1066.81, 698 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.41 (d, *J* = 7.0 Hz, 2H, ArH), 7.36–7.31 (m, 2H, ArH), 7.29 (d, *J* = 7.0 Hz, 1H, ArH), 4.41 (d, *J* = 14.8 Hz, 1H, Bn), 4.33 (dd, *J* = 6.1, 2.3 Hz, 4H, 2NC$\underline{H}_2$CCH), 4.28 (d, *J* = 14.8 Hz, 1H, Bn), 3.60 (t, *J* = 5.9 Hz, 1H, NC$\underline{H}$CH$_2$CHMeMe), 2.49 (t, *J* = 2.4 Hz, 2H, 2CC$\underline{H}$), 1.77 (dp, *J* = 13.2, 6.6 Hz, 1H, MeC$\underline{H}$Me), 1.69–1.60 (m, 1H, C$\underline{H}_2$CHMeMe), 1.52 (dt, *J* = 14.0, 6.4 Hz, 1H, C$\underline{H}_2$CHMeMe), 0.77 (d, *J* = 6.5 Hz, 3H, Me), 0.71 (d, *J* = 6.6 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 187.7 (CO), 158.7 ($\underline{C}$(NH)$_2$), 135.5 (ArC), 129.1 (2 ArC), 128.7 (2 ArC), 128.1 (ArC), 92.0 (CO$\underline{C}$C(NH)$_2$), 77.7 (2 $\underline{C}$CH), 74.8 (2 C$\underline{C}$H), 65.1 (N$\underline{C}$HCH$_2$CHMeMe), 48.9 (Bn), 40.1 ($\underline{C}$H$_2$CHMeMe), 34.3 (2 NH$\underline{C}$H$_2$CCH), 24.6 (Me$\underline{C}$HMe), 22.8 (Me), 22.8 (Me);

HRMS calculated for $C_{21}H_{25}N_3O_3S$ 400.1695 $(M+H)^+$; found 400.1704 (TOF MS ES^+).

(*S*)-5-(bis((2-(1*H*-indol-2-yl)ethyl)amino)methylene)-3-((*S*)-*sec*-butyl)-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.7** (57%, 15 mg) was isolated as clear oil.

R_f = 0.08 (EtOAc:Hexane = 1:3 x3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -41.3 (*c* = 0.003, CH_2Cl_2);

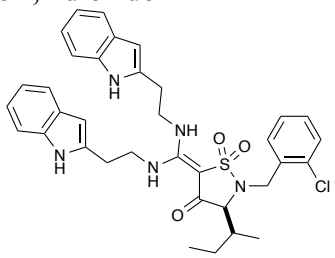
FTIR (neat): 3346, 3053, 3012, 2962, 2923, 2874, 1609, 1552, 1515, 1457, 1420, 1355, 1233, 1174, 1125, 1094, 810, 740 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 8.13 (s, 2H, 2 ArNH), 7.48 (d, *J* = 7.8 Hz, 2H, ArH), 7.32 (dd, *J* = 12.7, 8.0 Hz, 4H, ArH), 7.20 (t, *J* = 7.5 Hz, 2H, ArH), 7.12 (dd, *J* = 17.5, 7.9 Hz, 4H, ArH), 7.06 (s, 2H, ArH), 4.46 (d, *J* = 15.4 Hz, 1H, Bn), 4.34 (d, *J* = 15.3 Hz, 1H, Bn), 3.63–3.58 (m, 1H, NCHCHMe), 3.56 (s, 3H, CH_2), 2.99 (d, *J* = 5.9 Hz, 4H, 2CH_2), 2.33 (s, 3H, *p*-Me), 1.89–1.73 (m, 2H, CHMe), 1.54 (tt, *J* = 13.9, 7.2 Hz, 1H, CH_2Me), 1.44 (tt, *J* = 15.5, 8.0 Hz, 1H, CH_2Me), 0.93 (d, *J* = 6.8 Hz, 3H, Me), 0.83 (q, *J* = 7.8 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 184.6 (CO), 158.2 (C$(NH)_2$), 137.5 (ArC), 136.5 (2 ArC), 132.9 (2 ArC), 129.3 (2 ArC), 128.7 (2 ArC), 128.5 (2 ArC), 126.8 (2 ArC), 123.5 (ArC), 122.4 (2 ArC), 119.7 (2 ArC), 118.3 (2 ArC), 111.6 (2 ArC), 92.7 (COCC$(NH)_2$), 69.6 (NCHCHMe), 47.4 (Bn), 45.1 (2 CH_2), 37.2 (CHMe), 25.9 (2 CH_2), 25.4 (CH_2Me), 21.2 (ArMe), 14.7 (Me), 12.3 (Me);

HRMS calculated for $C_{36}H_{41}N_5O_3S$ 624.3008 $(M+H)^+$; found 624.3038 (TOF MS ES^+).

(*S*)-5-(bis((2-(1*H*-indol-2-yl)ethyl)amino)methylene)-3-((*S*)-*sec*-butyl)-2-(2-chlorobenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.8** (64%, 22 mg) was isolated as clear oil.

$\mathbf{R_f}$ = 0.31 (EtOAc:Hexane = 1:1);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -0.27, (*c* = 0.011, CH_2Cl_2);

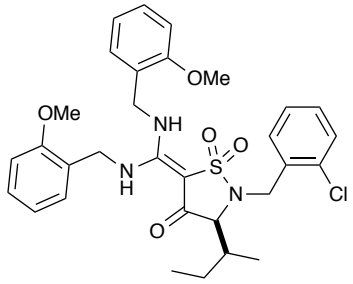
FTIR (neat): 3349, 3056, 2962, 2925, 2874, 1609, 1552, 1457, 1443, 1354, 1263, 1048, 865, 811, 741 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 8.08 (s, 2H, 2 ArN<u>H</u>), 7.75–7.68 (m, 1H, ArH), 7.49 (d, *J* = 7.8 Hz, 2H, ArH), 7.35 (d, *J* = 8.0 Hz, 3H, ArH), 7.31–7.27 (m, 1H, ArH), 7.24–7.18 (m, 3H, ArH), 7.14–7.08 (m, 4H, ArH), 4.85 (dd, *J* = 26.9, 16.9 Hz, 1H, Bn), 4.32 (dd, *J* = 16.8, 13.6 Hz, 1H, Bn), 3.69 (dd, *J* = 19.7, 2.7 Hz, 1H, NC<u>H</u>CHMe), 3.59 (s, 4H, C<u>H</u>$_2$), 3.01 (t, *J* = 6.4 Hz, 4H, C<u>H</u>$_2$), 1.90–1.70 (m, 1H, C<u>H</u>Me), 1.55 (ddd, *J* = 20.4, 10.1, 6.5 Hz, 1H, C<u>H</u>$_2$Me), 1.50–1.38 (m, 1H, C<u>H</u>$_2$Me), 0.89 (d, *J* = 6.9 Hz, 3H, Me), 0.86–0.78 (m, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 184.4 (CO), 158.3 (<u>C</u>(NH)$_2$), 136.5 (2 ArC), 134.6 (d, J = 37.4 Hz, ArC), 133.1 (d, J = 40.2 ArC), , 130.4 (ArC), 129.9 (ArC), 129.5 (2 ArC), 128.8 (2 ArC), 128.6 (ArC), 127.2 (ArC), 126.8 (2 ArC), 122.4 (2 ArC), 119.7 (2 ArC), 118.3 (2 ArC), 111.6 (2 ArC), 92.7 (CO<u>C</u>C(NH)$_2$), 72.0 (N<u>C</u>HCHMe), 47.5 (2 <u>C</u>H$_2$), 46.3 (Bn), 45.2 (2 <u>C</u>H$_2$), 37.5 (<u>C</u>HMe), 25.7 (d, J = 59.9 Hz, <u>C</u>H$_2$Me), 14.6 (Me), 12.3 (Me).

HRMS calculated for $C_{35}H_{38}ClN_5O_3S$ 644.2462 $(M+H)^+$; found 644.2454 (TOF MS ES^+).

(*S*)-5-(bis((2-methoxybenzyl)amino)methylene)-3-((*S*)-*sec*-butyl)-2-(2-chlorobenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.9** (31%, 9 mg) was isolated as clear oil.

R_f = 0.33 (EtOAc:Hexane = 1:3 x3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 1.3 (*c* = 0.0045, CH_2Cl_2);

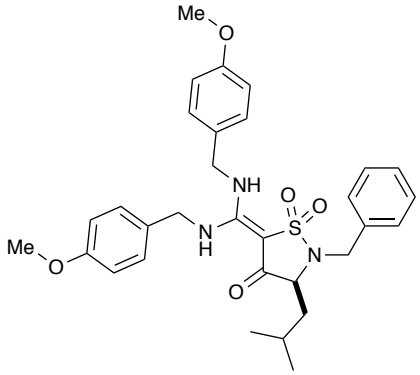
FTIR (neat): 3345, 3065, 2961, 2928, 2874, 2838, 1614, 1554, 1494, 1463, 1439, 1378, 1320, 1248, 1178, 1048, 754 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.80–7.71 (m, 1H, ArH), 7.33–7.27 (m, 4H, ArH), 7.21 (d, *J* = 7.5 Hz, 3H,ArH), 6.94 (t, *J* = 7.5 Hz, 2H, ArH), 6.87 (d, *J* = 8.2 Hz, 2H, ArH), 4.87 (dd, *J* = 27.5, 16.8 Hz, 1H, Bn-*o*-Cl), 4.58 (d, *J* = 4.9 Hz, 4H, 2Bn), 4.31 (dd, *J* = 16.8, 12.7 Hz, 1H, Bn-*o*-Cl), 3.76 (s, 6H, 2OMe), 3.68 (d, *J* = 2.8 Hz, 1H, NC<u>H</u>CHMe), 1.63–1.53 (m, 2H, C<u>H</u>$_2$Me), 1.50–1.39 (m, 1H, C<u>H</u>Me), 0.91 (d, *J* = 6.9 Hz, 3H, Me), 0.82 (t, *J* = 7.3 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) 184.4 (CO), 158.3 (<u>C</u>(NH)$_2$), 134.9 (ArC), 134.6 (ArC), 133.2 (ArC), 130.5 (ArC), 129.8 (2 ArC), 129.4 (ArC), 129.1 (ArC), 128.7 (ArC), 128.5 (2 ArC), 127.1 (ArC), 124.5 (2 ArC), 121.0 (2 ArC), 110.6 (2 ArC), 72.1 (N<u>C</u>HCHMe), 55.4 (2 OMe), 46.5 (<u>Bn</u>-*o*-Cl), 37.6 (CHMe), 25.5 (<u>C</u>H$_2$Me), 14.6 (Me), 12.3 (Me);

HRMS calculated for $C_{31}H_{36}ClN_3O_5S$ 598.2142 $(M+H)^+$; found 598.2151 (TOF MS ES^+).

(*S*)-2-benzyl-5-(bis((4-methoxybenzyl)amino)methylene)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.10** (52%, 10 mg) was isolated as clear oil.

R_f = 0.11 (EtOAc:Hexane = 1:3 x3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -3.86 (*c* = 0.0075, CH_2Cl_2);

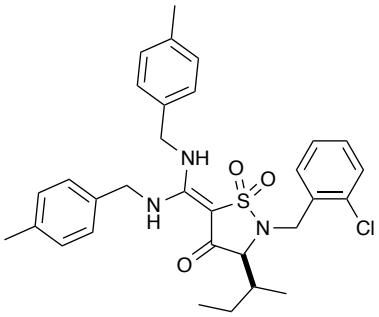
FTIR (neat): 3346, 3063, 3032, 2999, 2955, 2931, 2868, 1613, 1549, 1514, 1496, 1455, 1440, 1250, 1177, 1064, 825, 759, 700 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.45–7.41 (m, 2H, ArH), 7.37–7.29 (m, 3H, ArH), 7.17 (d, *J* = 8.7 Hz, 4H, ArH), 6.91–6.86 (m, 4H, ArH), 4.52 (d, *J* = 5.5 Hz, 4H, 2Bn), 4.45 (d, *J* = 14.8 Hz, 1H, Bn), 4.28 (d, *J* = 14.8 Hz, 1H, Bn), 3.81 (s, 6H, 2OMe), 3.62 (t, *J* = 5.8 Hz, 1H, NC<u>H</u>CH_2CHMeMe), 1.79 (dt, *J* = 13.3, 6.5 Hz, 1H, MeC<u>H</u>Me), 1.72–1.63 (m, 1H, C<u>H$_2$</u>CHMeMe), 1.58–1.49 (d, *J* = 6.6 Hz, 1H, C<u>H$_2$</u>CHMeMe), 0.79 (d, *J* = 6.5 Hz, 3H, Me), 0.71 (d, *J* = 6.6 Hz, 3H, Me);

^{13}C NMR (126 MHz, $CDCl_3$) 186.9 (CO), 159.7 (<u>C</u>$(NH)_2$), 158.4 (2 ArC), 135.8 (ArC), 129.1 (2 ArC), 128.7 (2 ArC), 128.5 (4 ArC), 128.0 (2 ArC), 114.7 (4 ArC), 91.8 (CO<u>C</u>C$(NH)_2$), 65.2 (N<u>C</u>HCH_2CHMeMe), 55.4 (2 OMe), 49.0 (2 Bn), 48.2 (Bn), 40.1 (C<u>H$_2$</u>CHMeMe), 24.6 Me<u>C</u>HMe), 22.8 (2 Me).

HRMS calculated for $C_{31}H_{37}N_3O_5S$ 586.2352 $(M+Na)^+$; found 586.2375 (TOF MS ES^+).

(*S*)-5-(bis((4-methylbenzyl)amino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.11** (44 %, 12 mg) was isolated as clear oil.

$\mathbf{R_f}$ = 0.24 (EtOAc:Hexane = 1:3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = 0.83 (*c* = 0.006, CH_2Cl_2);

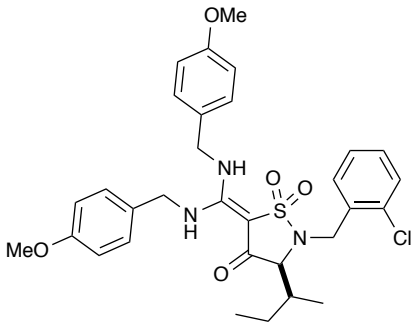
FTIR (neat): 3342, 3056, 3024, 2962, 2925, 2874, 1615, 1551, 1516, 1443, 1379, 1263, 1048, 802, 753 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.78–7.68 (m, 1H, ArH), 7.36–7.32 (m, 1H, ArH), 7.31–7.27 (m, 1H, ArH), 7.22 (dd, *J* = 7.5, 1.8 Hz, 1H, ArH), 7.18–7.10 (m, 8H, ArH), 4.86 (dd, *J* = 28.2, 16.7 Hz, 1H, Bn), 4.53 (t, *J* = 4.6 Hz, 4H, 2Bn), 4.38–4.27 (m, 1H, Bn), 3.77 (d, *J* = 5.2 Hz, 1H, NC<u>H</u>CHMe), 2.34 (s, 6H, 2Me), 1.63–1.54 (m, 1H, C<u>H</u>Me), 1.52–1.39 (m, 2H, CH_2), 0.93 (d, *J* = 6.9 Hz, 3H, Me), 0.88–0.83 (m, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 185.08 (CO), 158.40 (<u>C</u>$(NH)_2$), 138.34 (2 C_{Ar}), 134.36 (2 C_{Ar}), 133.06 (C_{Ar}), 130.57 (C_{Ar}), 130.01 (4 C_{Ar}), 129.53 (C_{Ar}), 128.92 (C_{Ar}), 127.38 (C_{Ar}), 127.21 (C_{Ar}), 127.04 (4 C_{Ar}), 92.87 (CO<u>C</u>C$(NH)_2$), 72.17 (N<u>C</u>HCHMe), 48.48 (Bn), 46.41 (2 Bn), 37.59 (<u>C</u>HMe), 25.61 (<u>C</u>H_2Me), 21.27 (2 ArMe), 14.58 (Me), 12.36 (Me).

HRMS calculated for $C_{31}H_{36}ClN_3O_3S$ 551.2373 $(M+)^+$; found 551.2391 (TOF MS ES^+).

(*S*)-5-(bis((4-methoxybenzyl)amino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.12** (44 %, 13 mg) was isolated as clear oil.

R_f = 0.10 (EtOAc:Hexane = 1:3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 5.14 (*c* = 0.0105, CH_2Cl_2);

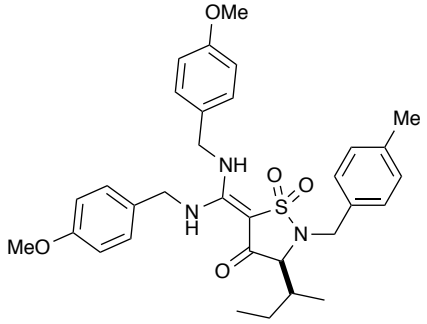
FTIR (neat): 3350, 3063, 2961, 2928, 2874, 2837, 1711, 1612, 1549, 1514, 1462, 1443, 1378, 1250, 1203, 1035, 824, 755 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.74 (ddd, *J* = 13.1, 7.7, 1.3 Hz, 1H, ArH), 7.40–7.28 (m, 2H, ArH), 7.22 (dt, *J* = 5.8, 1.7 Hz, 1H, ArH), 7.16 (dd, *J* = 8.6, 2.0 Hz, 4H, ArH), 6.88 (d, *J* = 8.6 Hz, 4H, ArH), 4.86 (dd, *J* = 28.3, 16.7 Hz, 1H, Bn), 4.53 (t, *J* = 4.5 Hz, 4H, 2Bn), 4.32 (dd, *J* = 16.5, 14.3 Hz, 1H, Bn), 3.80 (s, 6H, 2OMe), 3.74 (dd, *J* = 19.0, 2.7 Hz, 1H, NC<u>H</u>CHMe), 1.62–1.53 (m, 2H, CH_2), 1.52–1.45 (m, 1H, C<u>H</u>Me), 0.92 (d, *J* = 6.9 Hz, 3H, Me), 0.86–0.81 (m, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 185.1 (CO), 159.7 (<u>C</u>$(NH)_2$), 158.2 (d, J = 10.3 Hz, 2 C_{Ar}), 134.5 (d, J = 38.2 Hz, C_{Ar}), 133.1 (d, J = 40.3 Hz, C_{Ar}), 130.55 (2 C_{Ar}), 129.54 (C_{Ar}), 128.93 (C_{Ar}), 128.56 (4 C_{Ar}), 127.96 (C_{Ar}), 127.21 (C_{Ar}), 114.75 (4 C_{Ar}), 92.87 (CO<u>C</u>C$(NH)_2$), 72.17 (N<u>C</u>HCHMe), 55.47 (2 OMe), 48.32 (Bn), 46.45 (2 Bn), 37.60 (<u>C</u>HMe), 25.59 (<u>C</u>H_2Me), 14.59 (Me), 12.36 (Me).

HRMS calculated for $C_{31}H_{36}ClN_3O_5S$ 598.2142 $(M+H)^+$; found 598.2156 (TOF MS ES^+).

(*S*)-5-(bis((4-methoxybenzyl)amino)methylene)-3-((*S*)-*sec*-butyl)-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.9.1.13** (20 %, 3 mg) was isolated as clear oil.

R_f = 0.17 (EtOAc:Hexane = 1:3 x3);

$[\alpha]_D^{20}$ = -0.92 (*c* = 0.0065, CH_2Cl_2);

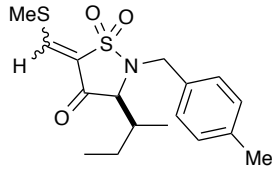
FTIR (neat): 3434, 3092, 3023, 2963, 2926, 2875, 1627, 1515, 1458, 1378, 1284, 1204, 1180, 1117, 1021, 839 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.32 (d, *J* = 7.7 Hz, 2H, ArH), 7.15 (t, *J* = 8.1 Hz, 6H, ArH), 6.88 (d, *J* = 8.5 Hz, 4H, ArH), 4.51 (d, *J* = 5.1 Hz, 4H, 2Bn), 4.44 (d, *J* = 15.7 Hz, 1H, Bn-*p*-Me), 4.34 (d, *J* = 15.3 Hz, 1H, Bn-*p*-Me), 3.80 (s, 6H, 2OMe), 3.63 (d, *J* = 2.5 Hz, 1H, NCHCHMe), 2.33 (s, 3H, ArMe), 1.61–1.50 (m, 2H, CH_2), 1.45 (dt, *J* = 15.2, 7.7 Hz, 1H, CHMe), 0.96 (d, *J* = 6.9 Hz, 3H, Me), 0.83 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 185.3 (CO), 159.7 ($C(NH)_2$), 158.3 (2 ArC), 137.5 (ArC), 132.9 (ArC), 129.3 (2 ArC), 128.8 (2 ArC), 128.5 (4 ArC), 128.0 (2 ArC), 114.7 (4 ArC), 92.9 ($COCC(NH)_2$), 69.8 (NCHCHMe), 55.4 (2 OMe), 53.5 (Bn-*p*-Me), 47.5 (2 Bn), 37.2 (CHMe), 25.5 (CH_2Me), 21.2 (ArMe), 14.7 (Me), 12.3 (Me).

HRMS calculated for $C_{32}H_{39}N_3O_5S$ 600.258 $(M+Na)^+$; found 600.2435 (TOF MS ES^+).

(*S*)-3-((*S*)-*sec*-butyl)-2-(4-methylbenzyl)-5-((methylthio)methylene)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.10.1** (42 %, 9 mg) was isolated as clear oil.

R_f = 0.13 (MeOH:DCM= 1:10);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 24.6 (*c* = 0.0045, acetone);

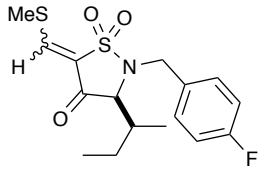
FTIR (neat): 3437, 3027, 3016, 2969, 1738, 1636, 1616, 1517, 1454, 1365, 1216, 1112, 1091, 835 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 7.29 (d, *J* = 7.9 Hz, 2H, ArH), 7.14 (d, *J* = 7.8 Hz, 2H, ArH), 5.71 (s, 1H, MeSC<u>H</u>C), 4.46 (d, *J* = 15.4 Hz, 1H, Bn), 4.27 (d, *J* = 15.4 Hz, 1H, Bn), 3.81 (d, *J* = 2.4 Hz, 1H, NC<u>H</u>CHMe), 3.73 (s, 3H, SMe), 2.33 (s, 3H, ArMe), 1.71 (qd, *J* = 7.7, 6.9, 2.1 Hz, 1H, C<u>H</u>Me), 1.35 (pd, *J* = 7.4, 2.5 Hz, 2H, CH_2), 0.89 (d, *J* = 6.9 Hz, 3H, Me), 0.79 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 167.2 (CO), 137.7 (ArC), 132.5 (ArC), 129.4 (2 ArC), 128.8 (2 ArC), 128.5 (COC<u>C</u>(SMe), 97.4 (CO<u>C</u>C(SMe), 65.4 (N<u>C</u>HCHMe), 58.5 (SMe), 46.9 (Bn), 36.8 <u>C</u>HMe), 25.4 (CH_2), 21.2 (Ar<u>Me</u>), 14.0 (Me), 12.4 (Me).

HRMS calculated for $C_{17}H_{23}NO_3S_2$ 352.1041 $(M-H)^+$; found 352.1048 (TOF MS ES^+).

(*S*)-3-((*S*)-*sec*-butyl)-2-(4-fluorobenzyl)-5-((methylthio)methylene)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.10.2** (72 %, 13 mg) was isolated as clear oil.

R_f = 0.54 (EtOAc:Hexane = 1:3 x3);

$[\alpha]_D^{20}$ = 6.4 (*c* = 0.005, acetone);

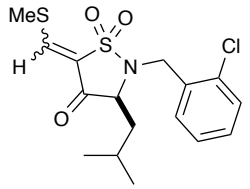
FTIR (neat): 2963, 2935, 1628, 1510, 1459, 1390, 1014, 968, 825, 731 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 7.40 (dd, *J* = 8.0, 5.8 Hz, 2H, ArH), 7.03 (t, *J* = 8.6 Hz, 2H, ArH), 5.72 (s, 1H, MeSC<u>H</u>C), 4.45–4.31 (m, 2H, Bn), 3.80 (d, *J* = 2.2 Hz, 1H, NC<u>H</u>CHMe), 3.74 (s, 3H, SMe), 1.74–1.66 (m, 1H, C<u>H</u>Me), 1.41–1.32 (m, 2H, C<u>H_2</u>Me), 0.90 (d, *J* = 6.9 Hz, 3H, Me), 0.81 (t, *J* = 7.4 Hz, 3H, Me).

^{13}C NMR (126 MHz, $CDCl_3$) 167.0 (CO), 163.5 (<u>C</u>(SMe)), 131.6 (d, *J*= 2.9 Hz, ArC), 130.5 (d, *J*= 8.3Hz, 2 ArC), 130.2 (d, *J*= 8.1 Hz, ArC), 115.7 (d, *J*= 21.3 Hz, 2 ArC), 97.4 (CO<u>C</u>C(SMe), 65.8 (N<u>C</u>HCHMe), 58.6 (SMe), 46.8 (Bn), 36.9 (<u>C</u>HMe), 25.4 (<u>C</u>H_2Me), 14.1 (Me), 12.4 (Me).

HRMS calculated for $C_{16}H_{20}FNO_3S_2$ 380.0766 $(M+Na)^+$; found 380.0782 (TOF MS ES^+).

(*S*)-2-(2-chlorobenzyl)-3-isobutyl-5-(methylthio)methylene)isothiazolidin-4-one 1,1-dioxide



According to the reaction protocol described in general procedure **B**, compound **3.3.10.3** (14 %, 5 mg) was isolated as clear oil.

R_f = 0.30 (EtOAc:Hexane = 1:3);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 1.12 (*c* = 0.008, CH_2Cl_2);

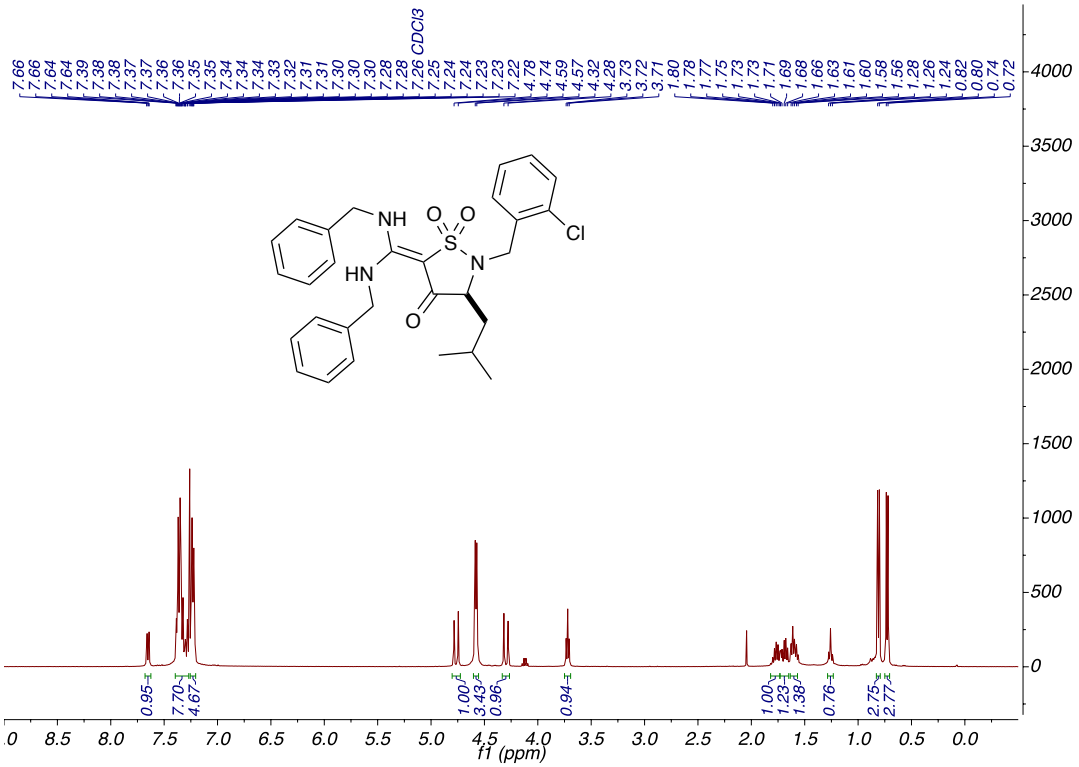
FTIR (neat): 3423, 3094, 2956, 2926, 2869, 1630, 1573, 1444, 1389, 1285, 1118, 1050, 1038, 756, 735, 714, 684 cm^{-1};

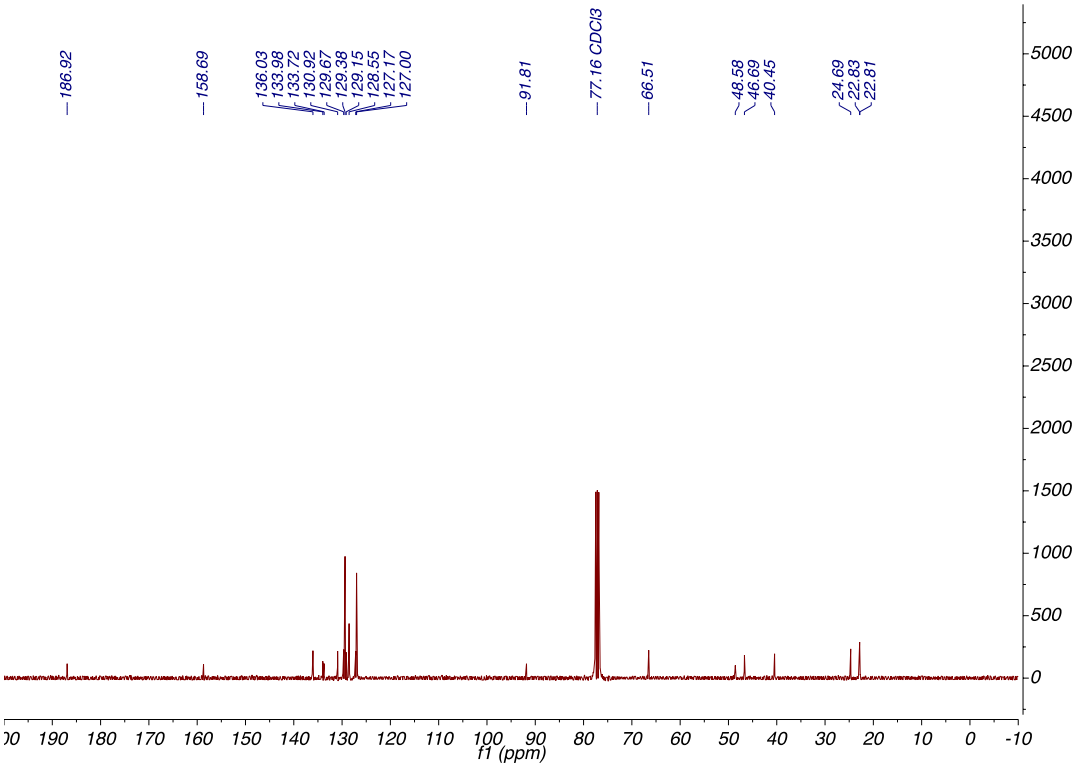
^{1}H NMR (400 MHz, $CDCl_3$) 7.66–7.63 (m, 1H, ArH), 7.36 (dd, *J* = 7.7, 1.2 Hz, 1H, ArH), 7.31–7.27 (m, 1H, ArH), 7.23 (td, *J* = 7.7, 1.8 Hz, 1H, ArH), 5.73 (s, 1H, MeSC<u>H</u>C), 4.72 (d, *J* = 16.1 Hz, 1H, Bn), 4.34 (d, *J* = 16.1 Hz, 1H, Bn), 3.93 (t, *J* = 5.1 Hz, 1H, NC<u>H</u>CH_2CHMeMe), 3.78 (s, 3H, SMe), 1.69 (tt, *J* = 13.1, 6.5 Hz, 1H, MeC<u>H</u>Me), 1.61–1.48 (m, 2H, C<u>H_2</u>CHMeMe), 0.76 (d, *J* = 6.5 Hz, 3H, Me), 0.73 (d, *J* = 6.6 Hz, 3H, Me).

^{13}C NMR (101 MHz, $CDCl_3$) 168.3 (CO), 133.7 (ArC), 133.5 (ArC), 130.8 (ArC), 129.6 (ArC), 129.2 (ArC), 127.3 (ArC), 96.4 (CO<u>C</u>CSMe), 62.2 (N<u>C</u>HCH_2CHMeMe), 58.6 (SMe), 45.5 (CH_2), 40.0 (CH_2), 24.0 (Me<u>C</u>HMe), 23.2 (Me), 22.7 (Me).

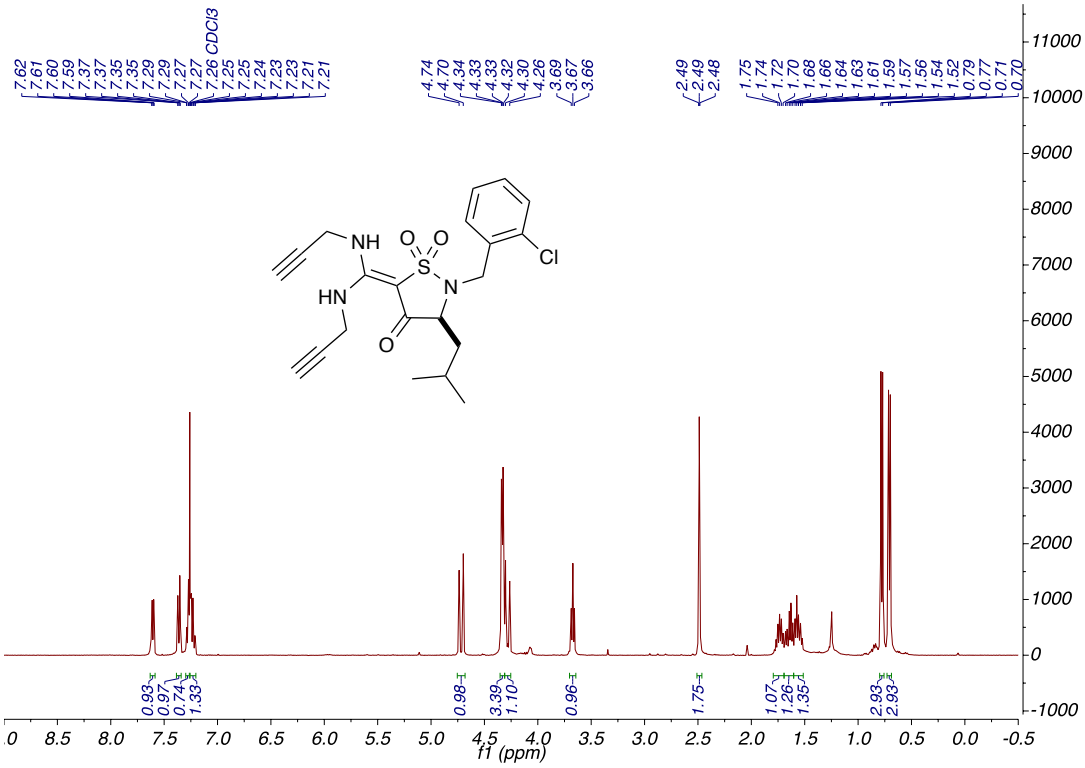
HRMS calculated for $C_{16}H_{20}ClNO_3S_2$ 372.0495 $(M-H)^+$; found 372.0510 (TOF MS ES^+).

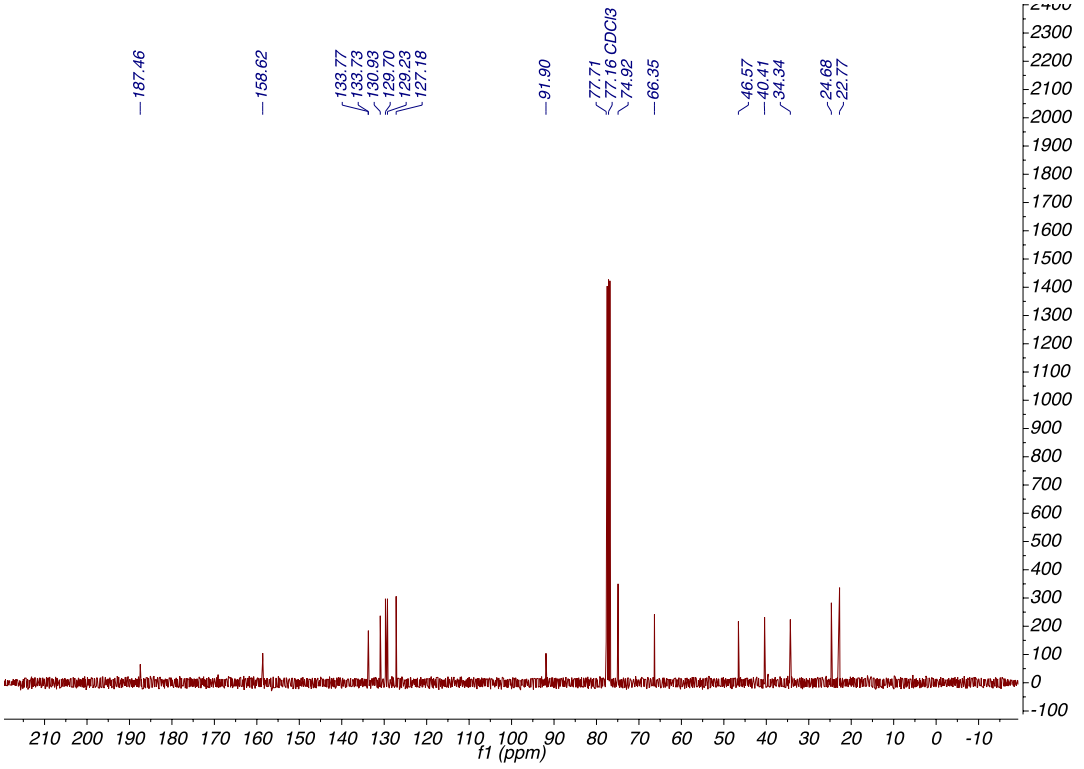
(*S*)-5-(bis(benzylamino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.1



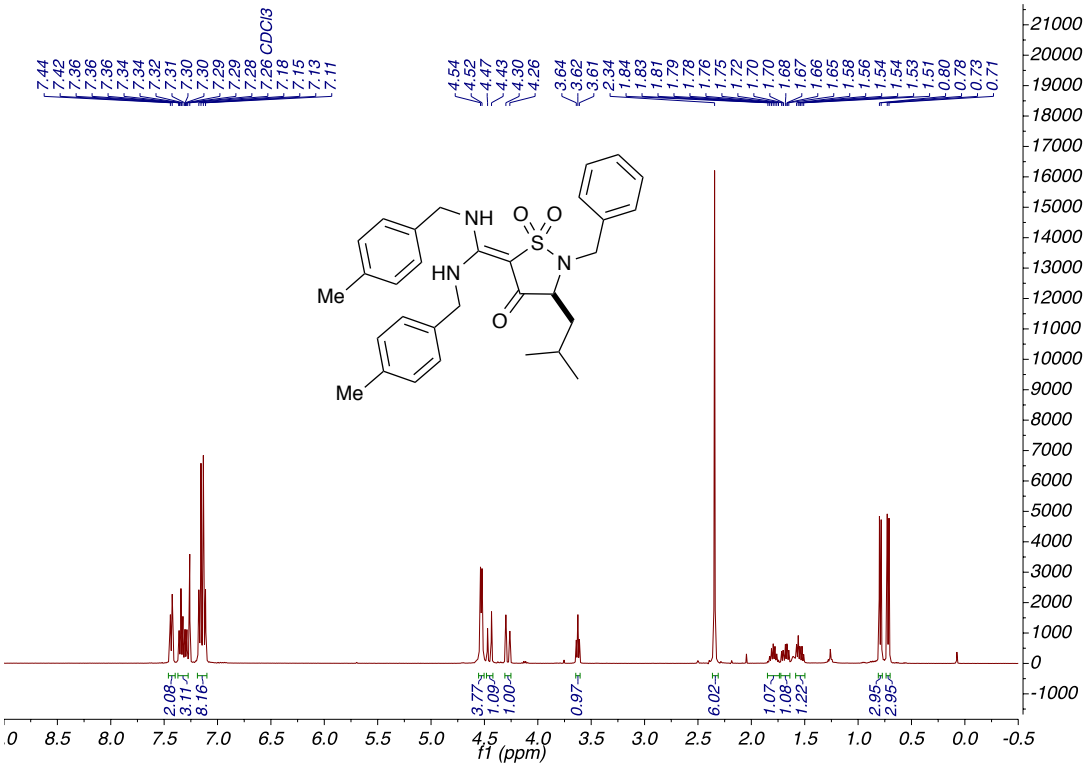


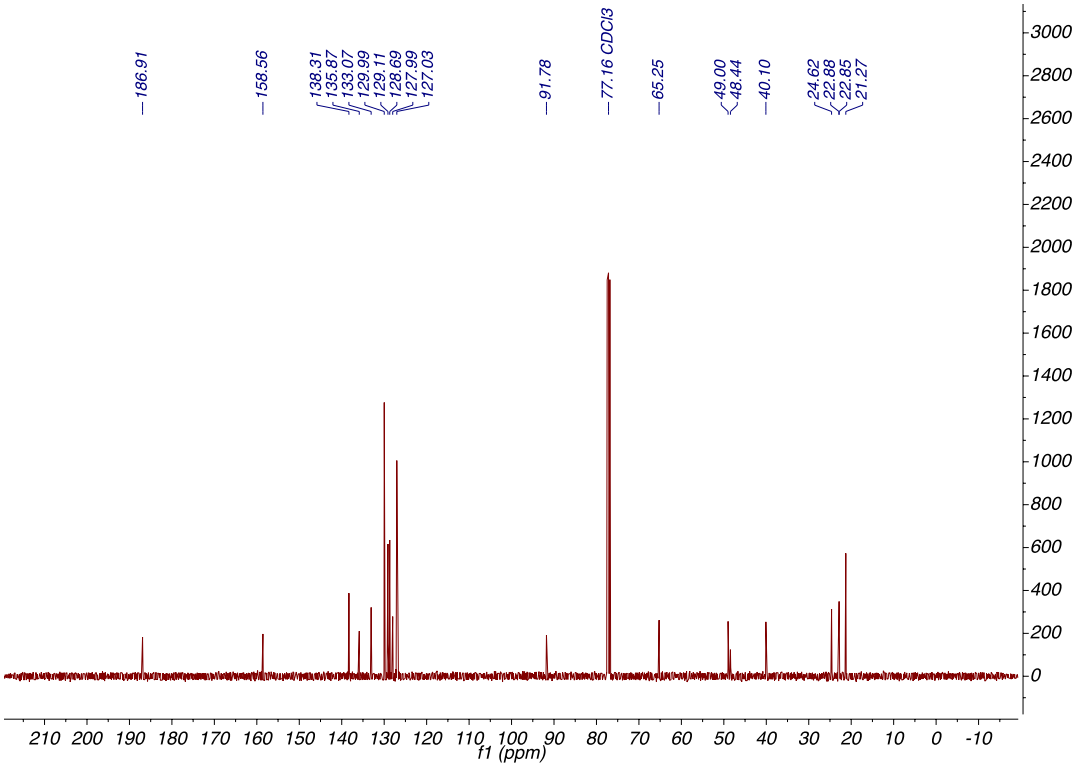
(*S*)-5-(bis(prop-2-yn-1-ylamino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.2



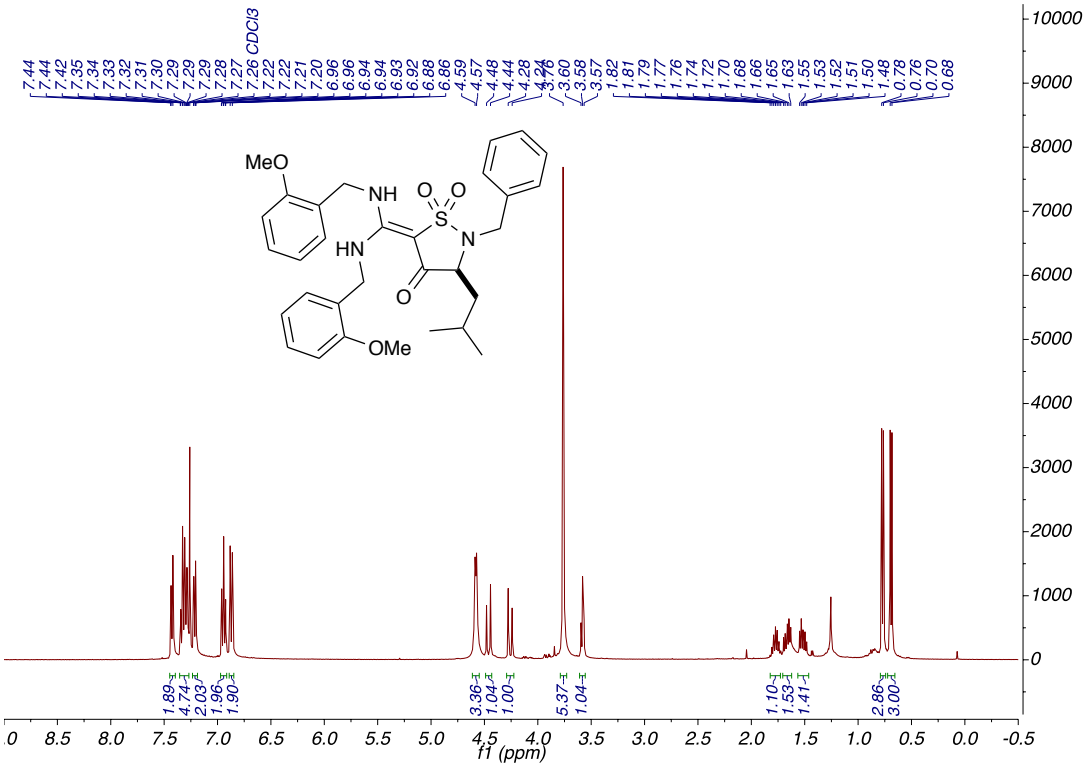


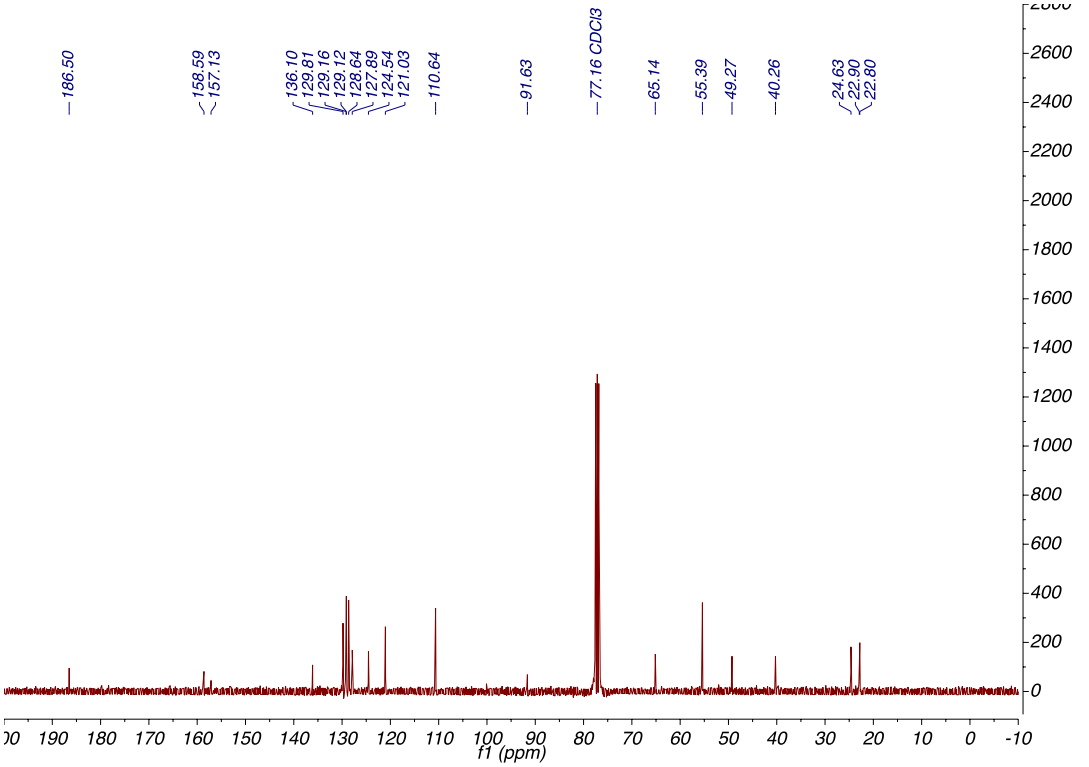
(*S*)-2-benzyl-5-(bis((4-methylbenzyl)amino)methylene)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.3



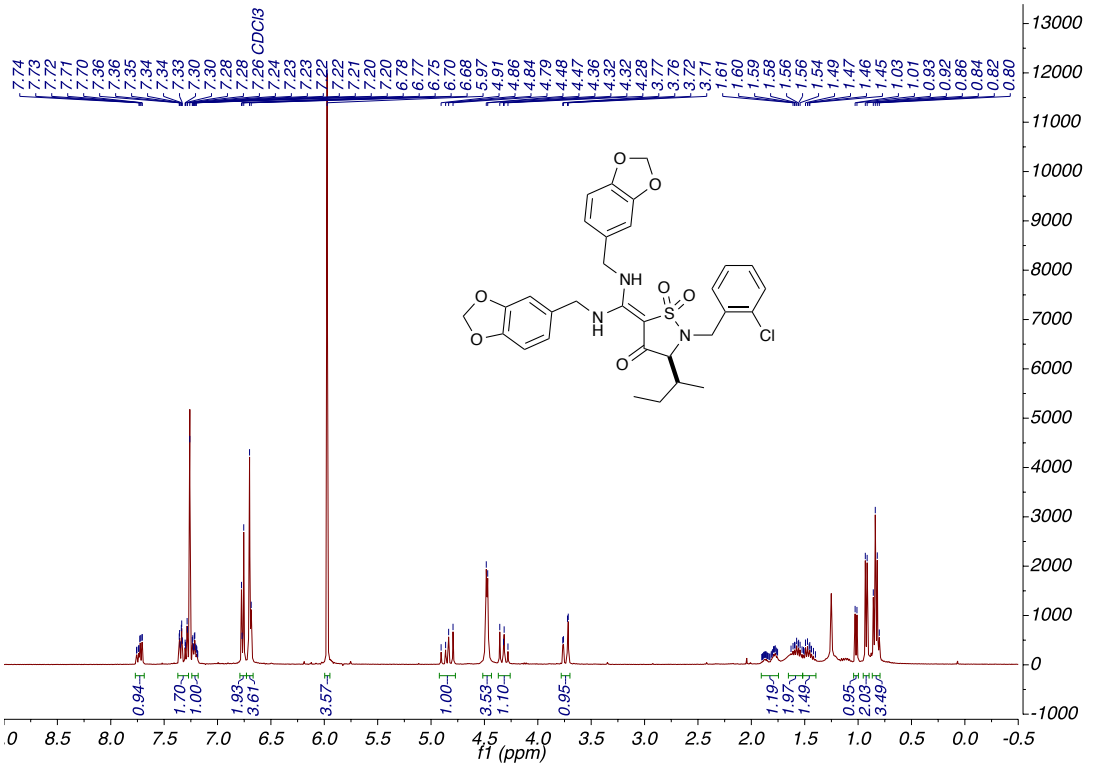


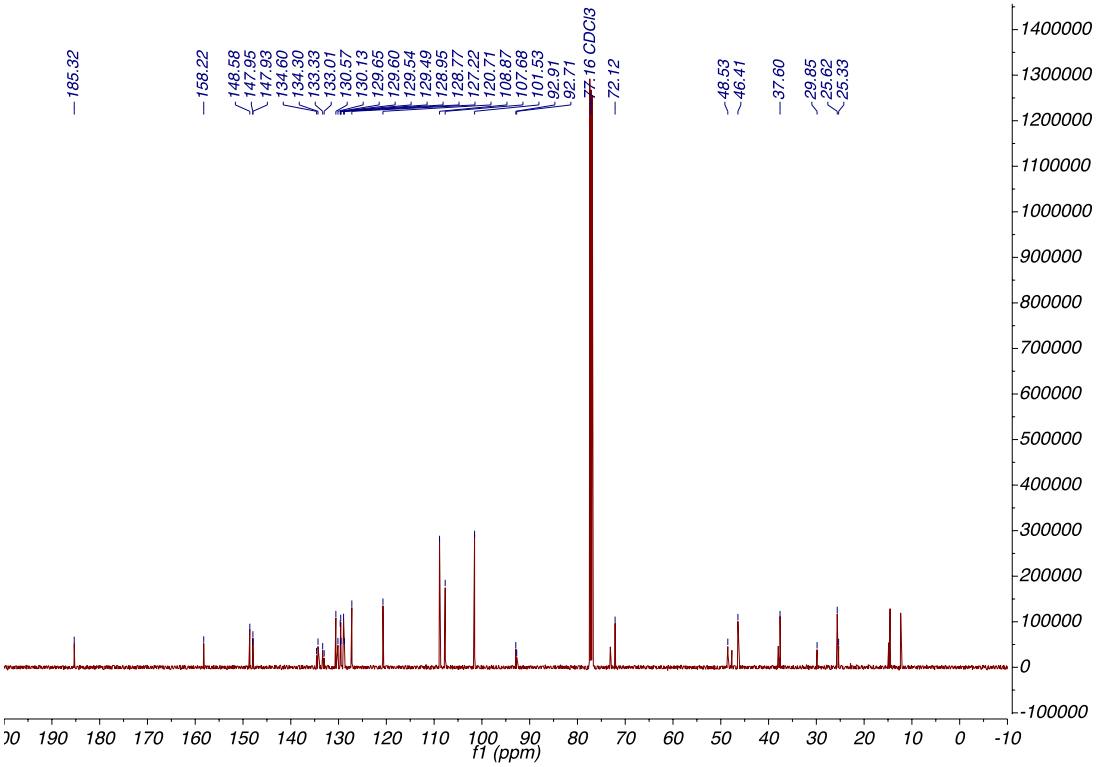
(*S*)-2-benzyl-5-(bis((2-methoxybenzyl)amino)methylene)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.4



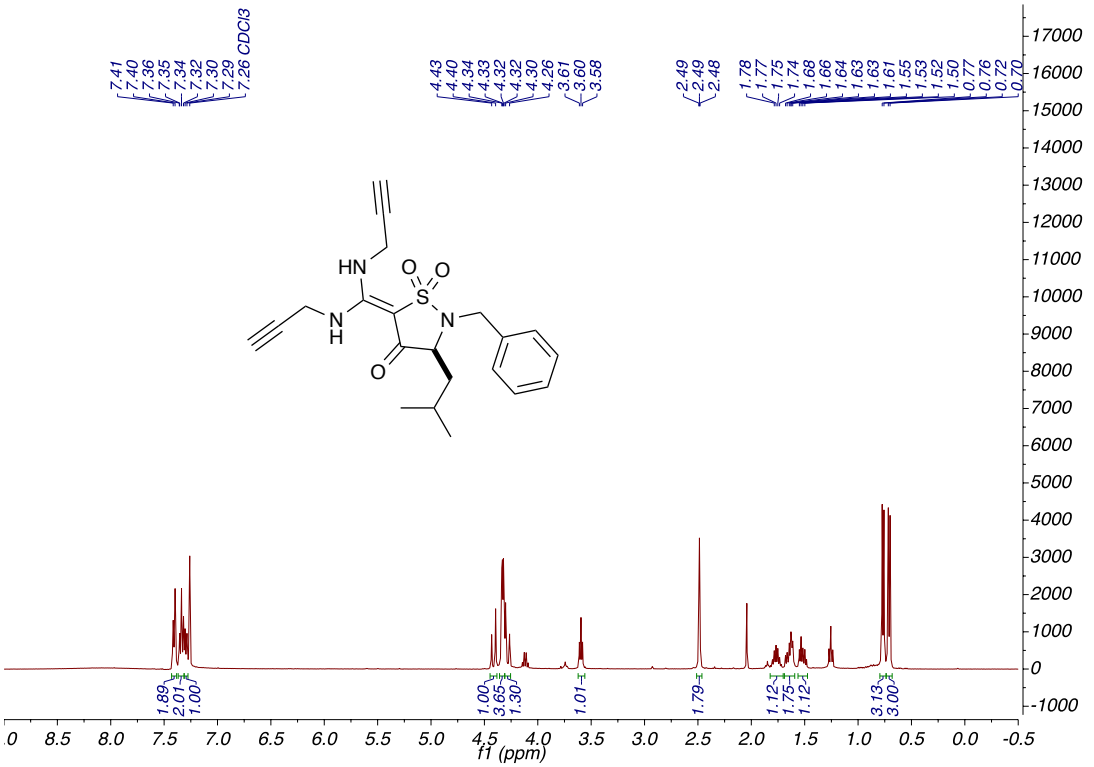


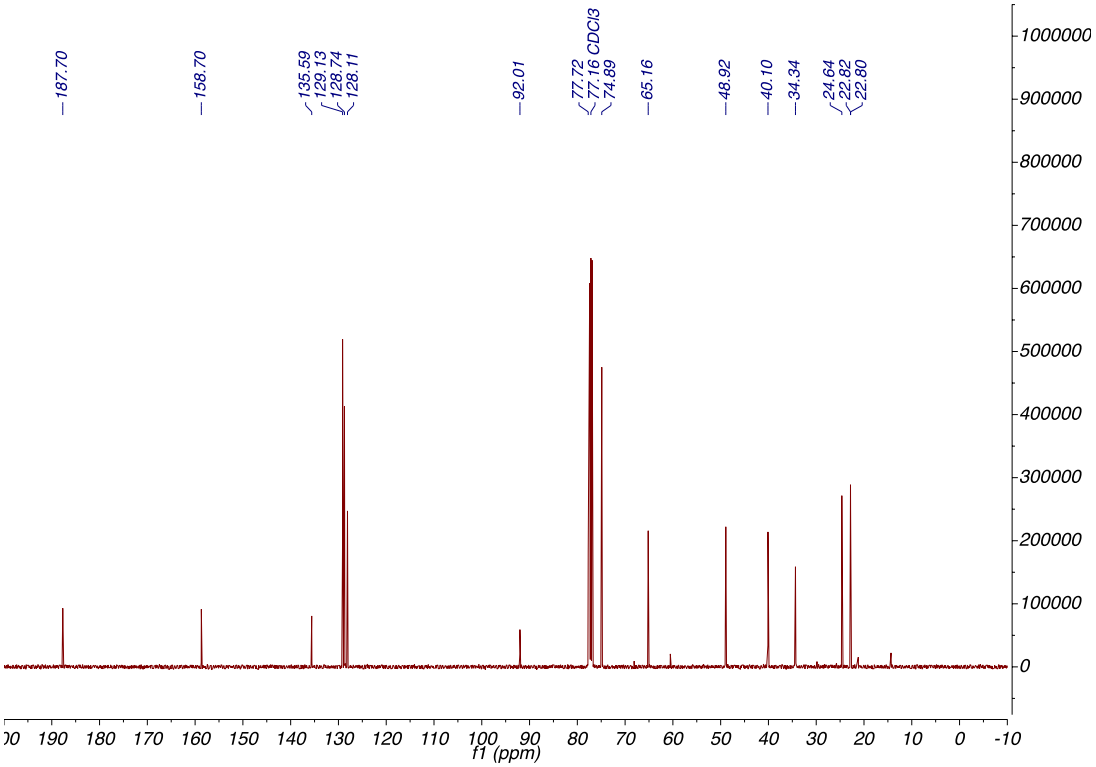
(*S*)-5-(bis((benzo[*d*][1,3]dioxol-5-ylmethyl)amino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.5



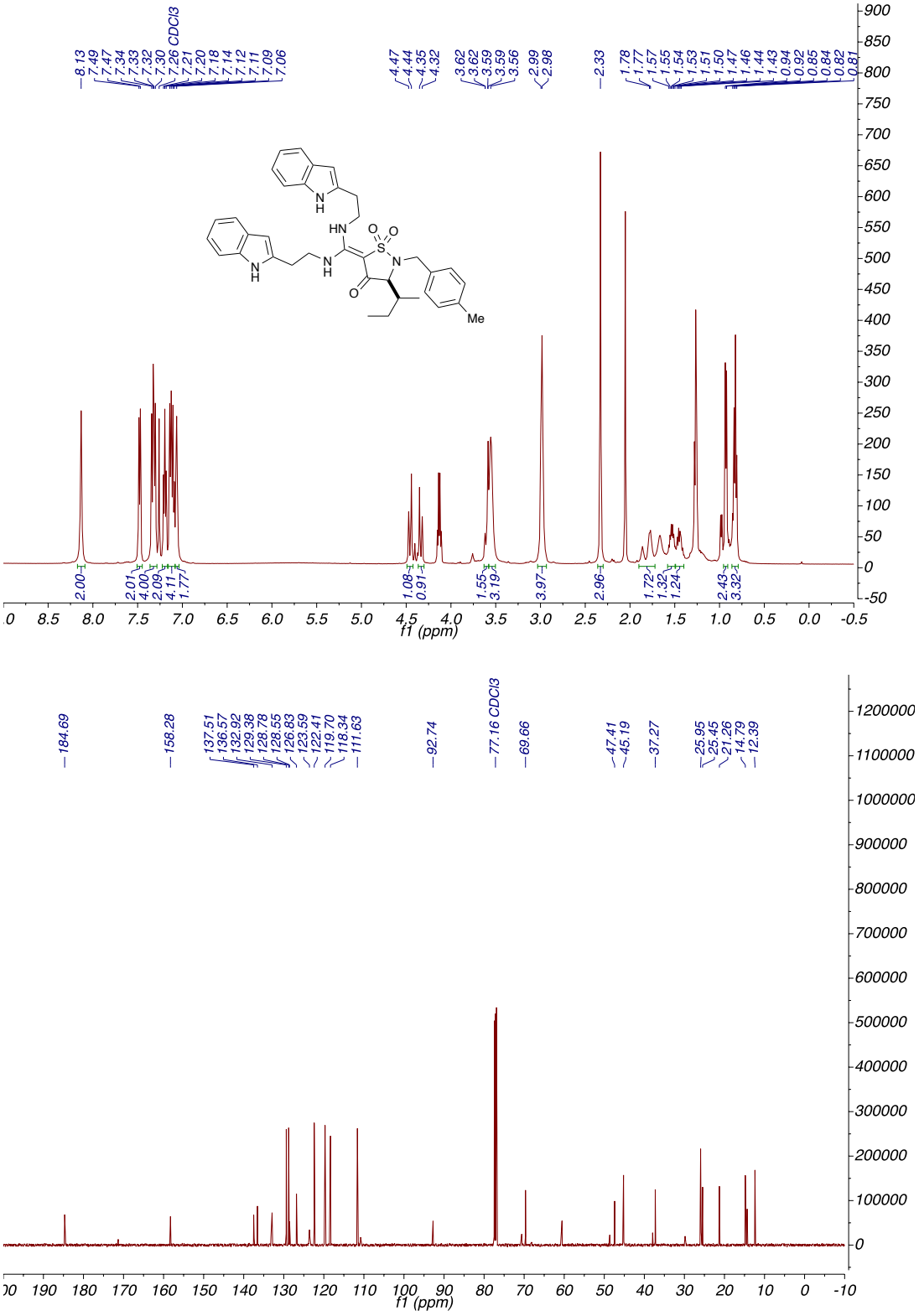


(*S*)-2-benzyl-5-(bis(prop-2-yn-1-ylamino)methylene)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.6

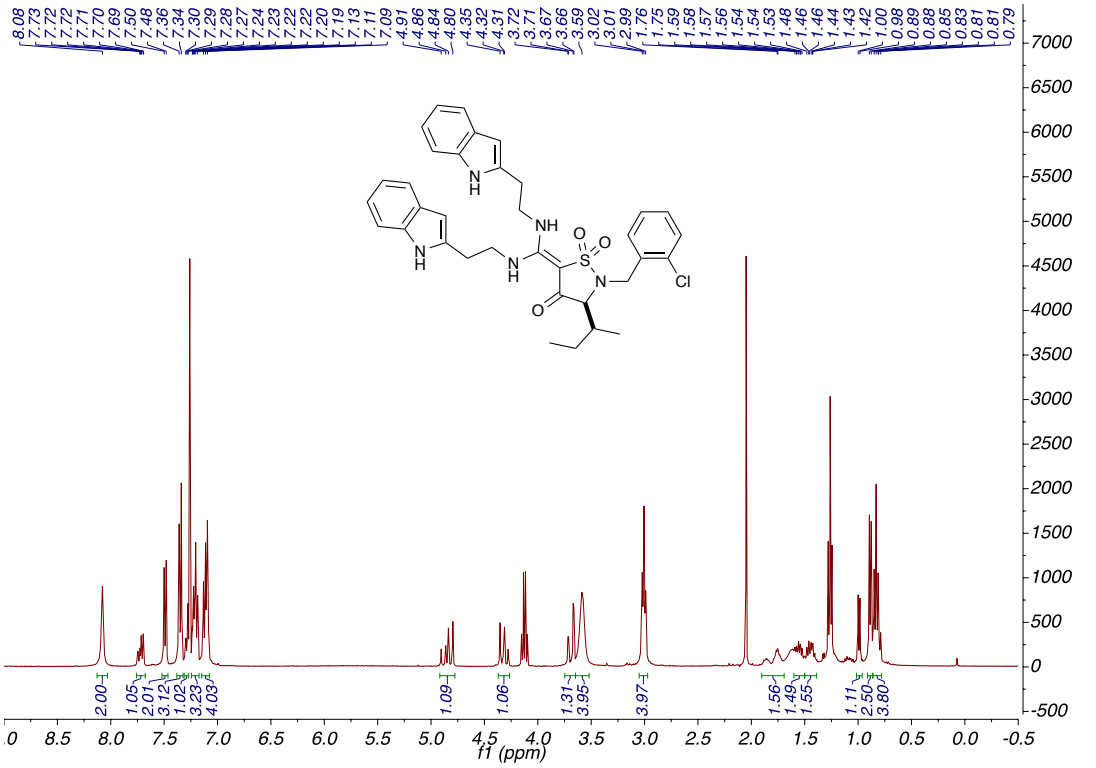


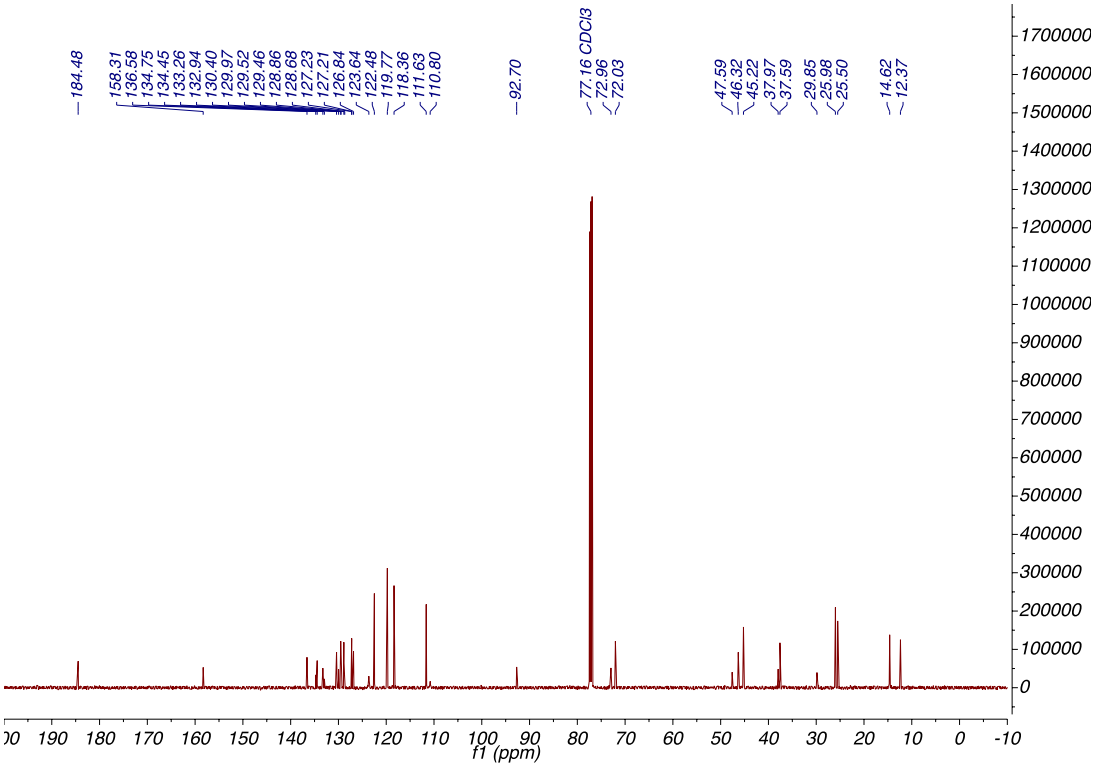


(*S*)-5-(bis((2-(1*H*-indol-2-yl)ethyl)amino)methylene)-3-((*S*)-*sec*-butyl)-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide 3.3.9.1.7

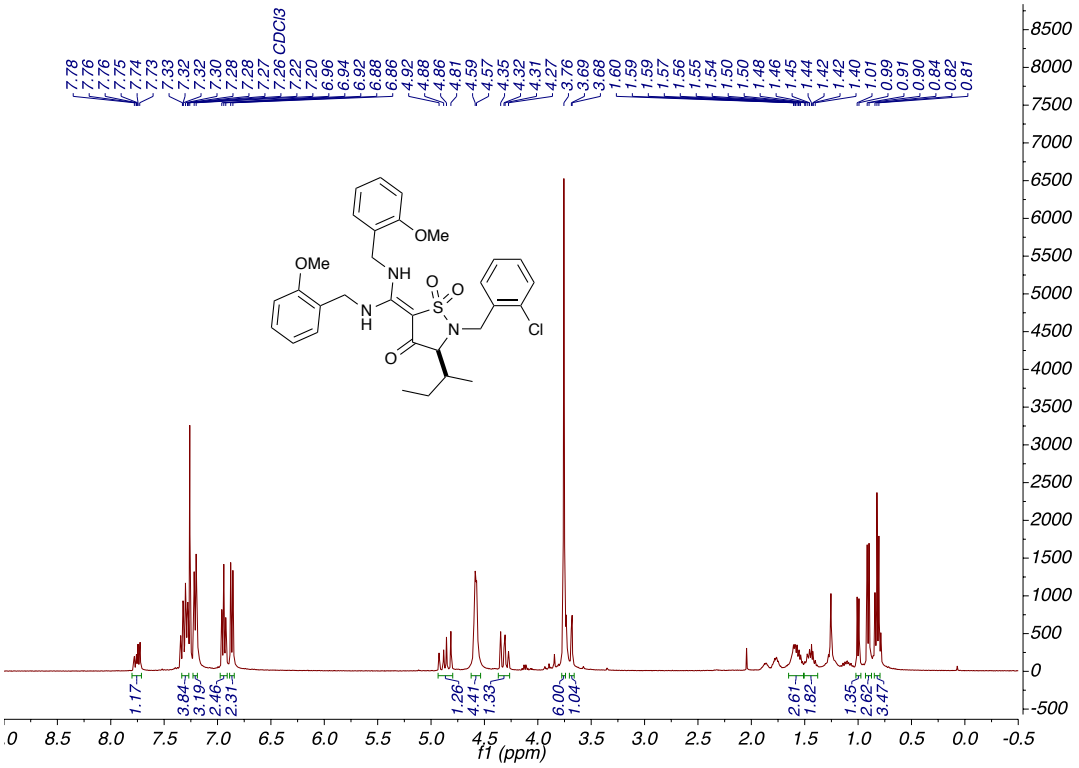


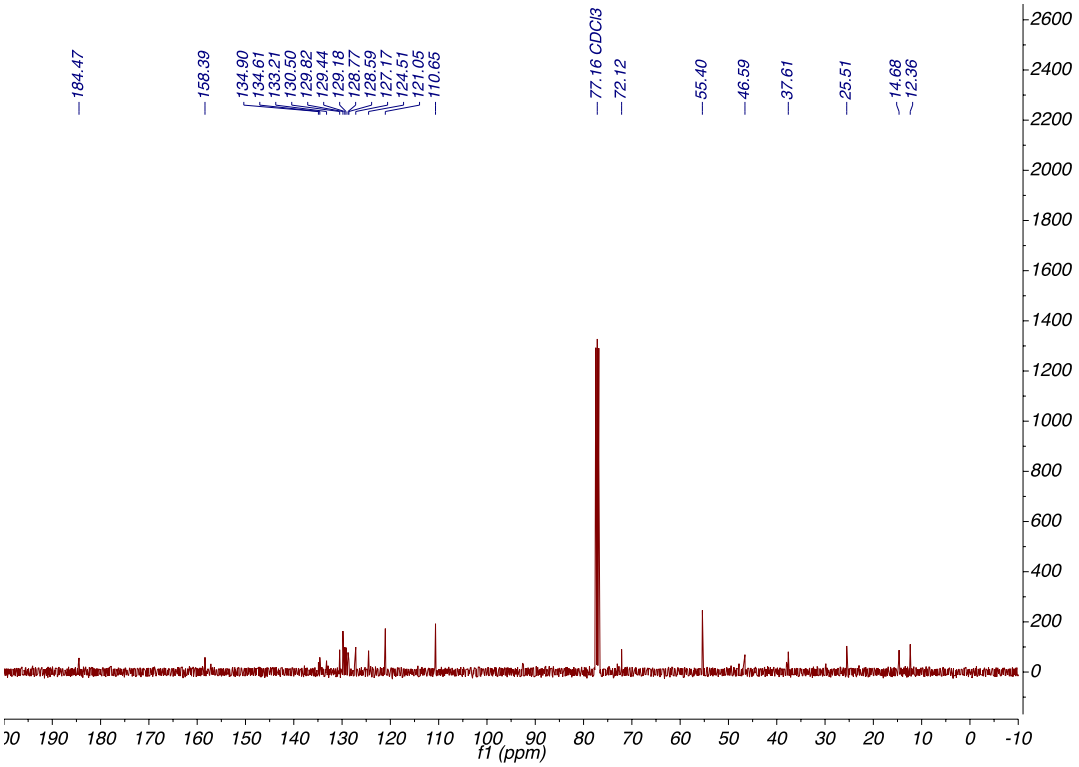
(*S*)-5-(bis((2-(1*H*-indol-2-yl)ethyl)amino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.8



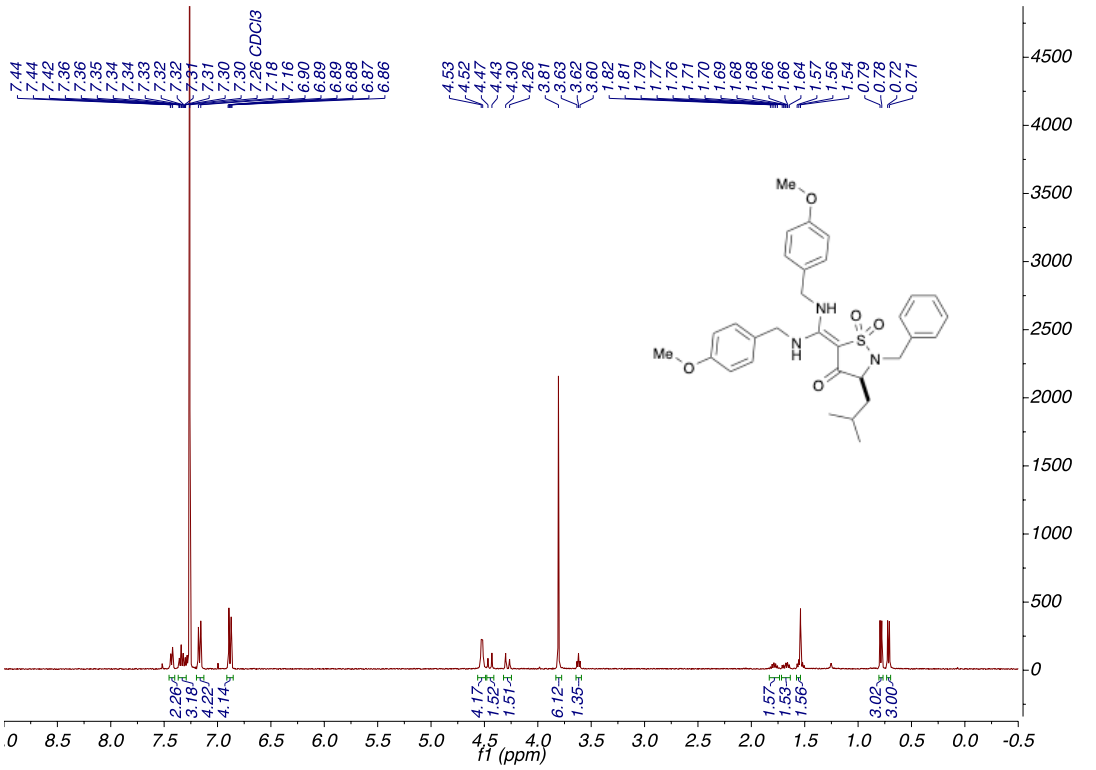


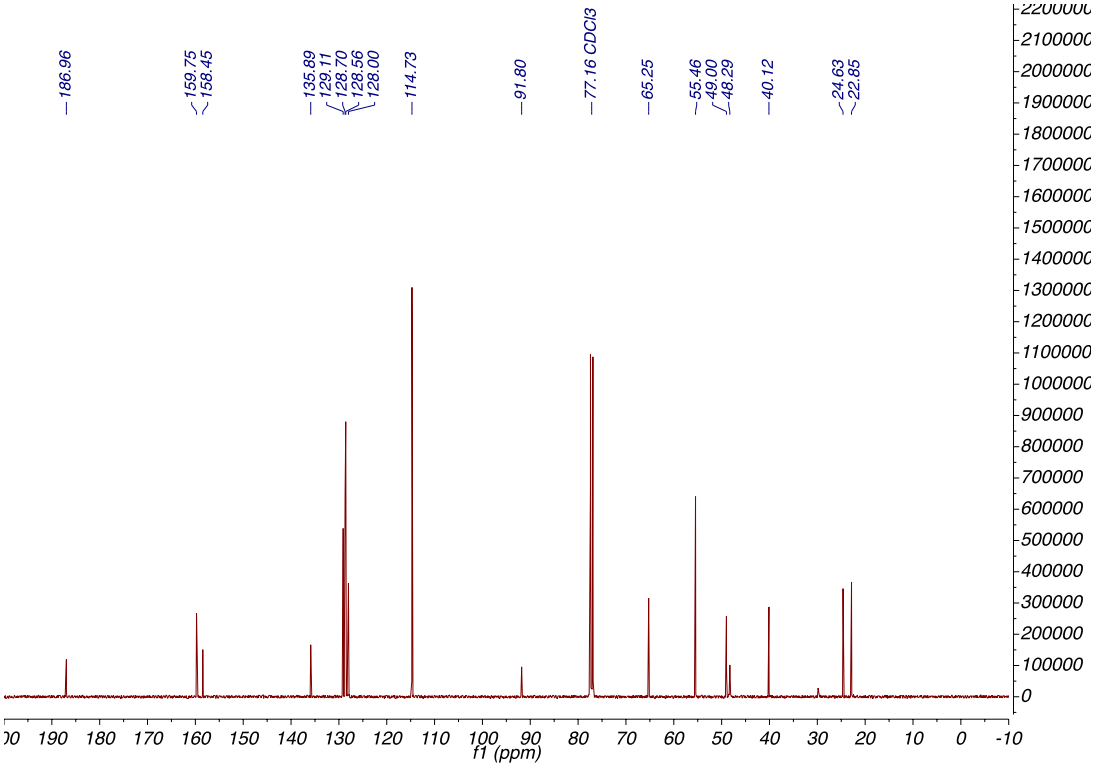
(*S*)-5-(bis((2-methoxybenzyl)amino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.9



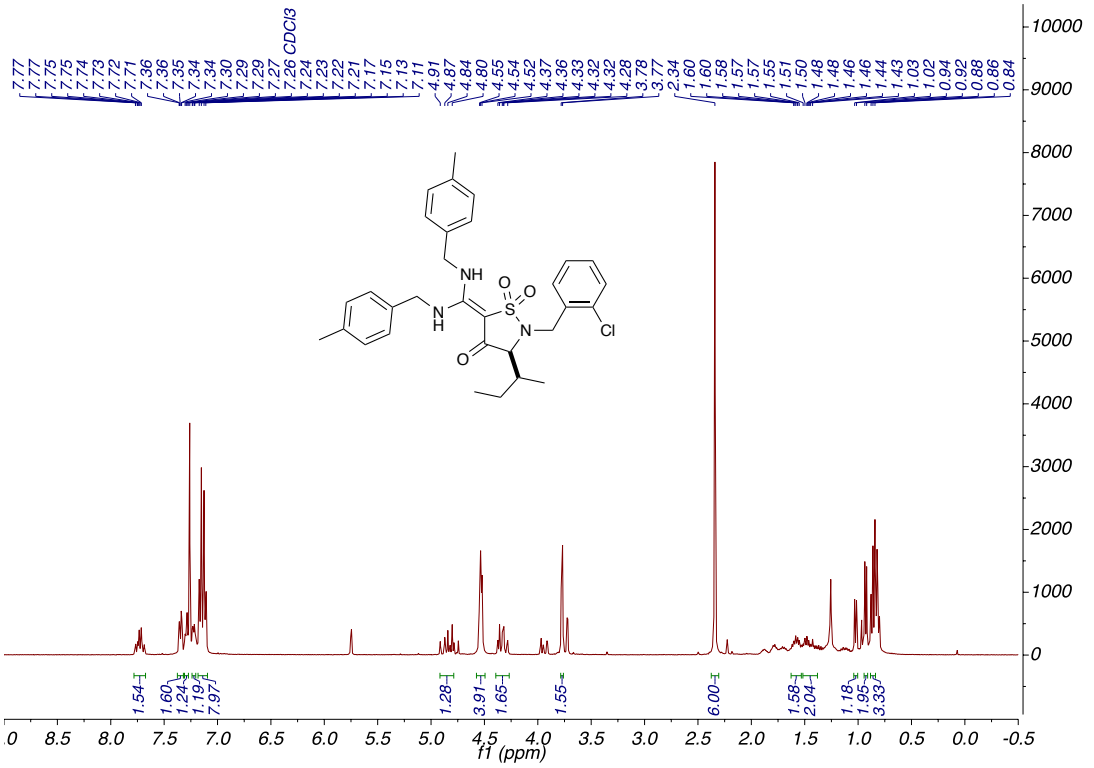


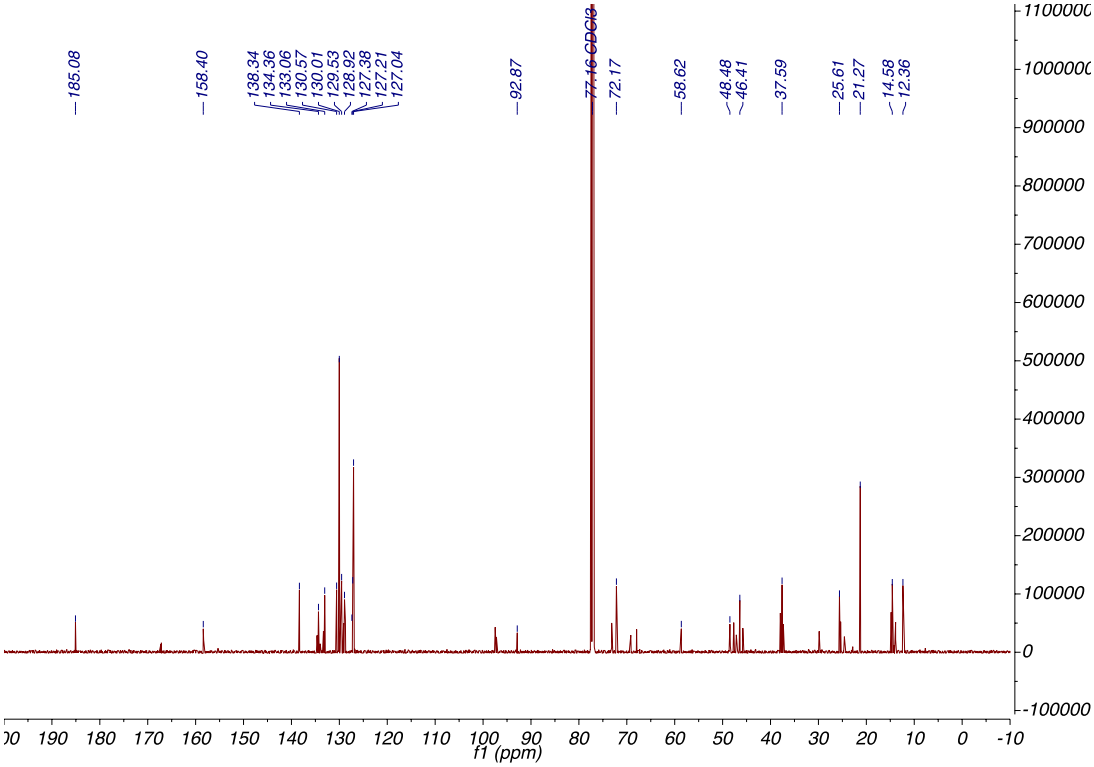
(*S*)-2-benzyl-5-(bis((4-methoxybenzyl)amino)methylene)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.10



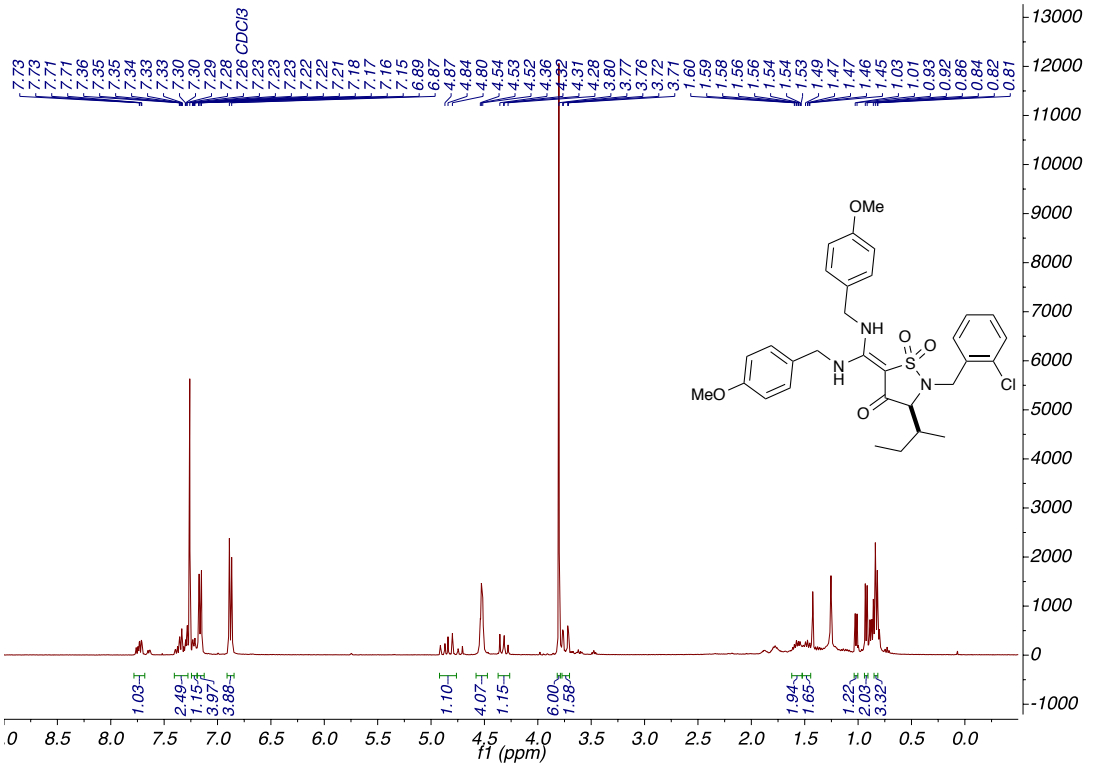


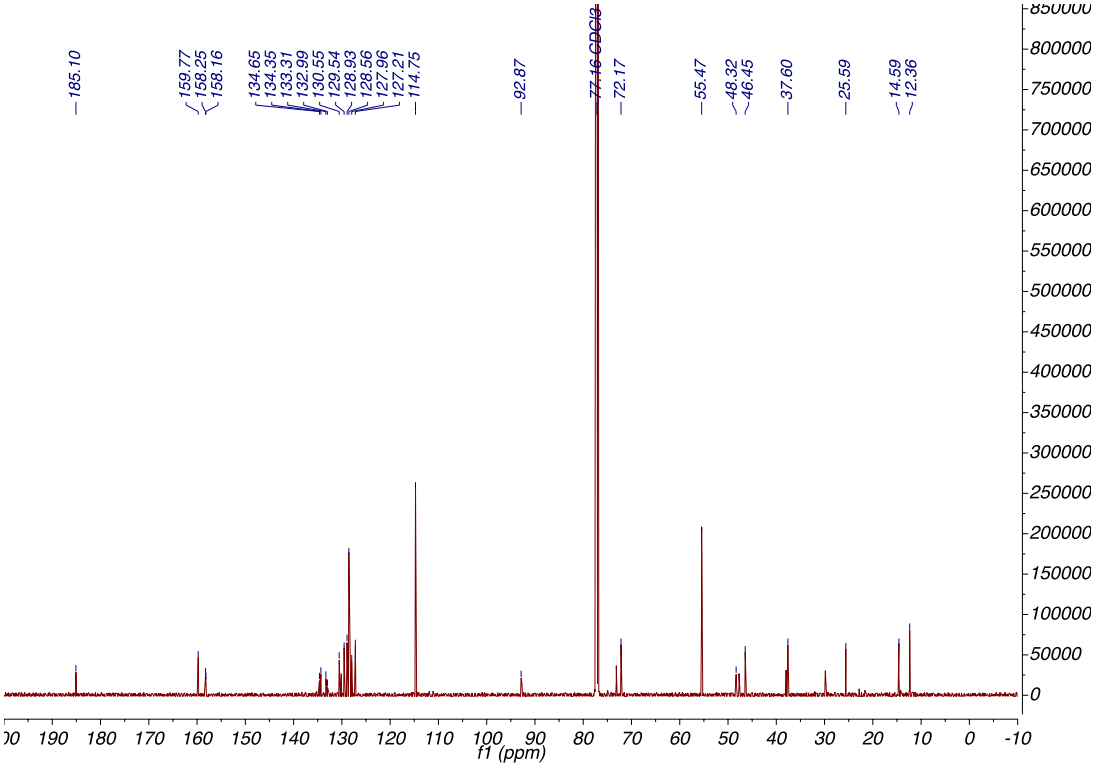
(*S*)-5-(bis((4-methylbenzyl)amino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.11



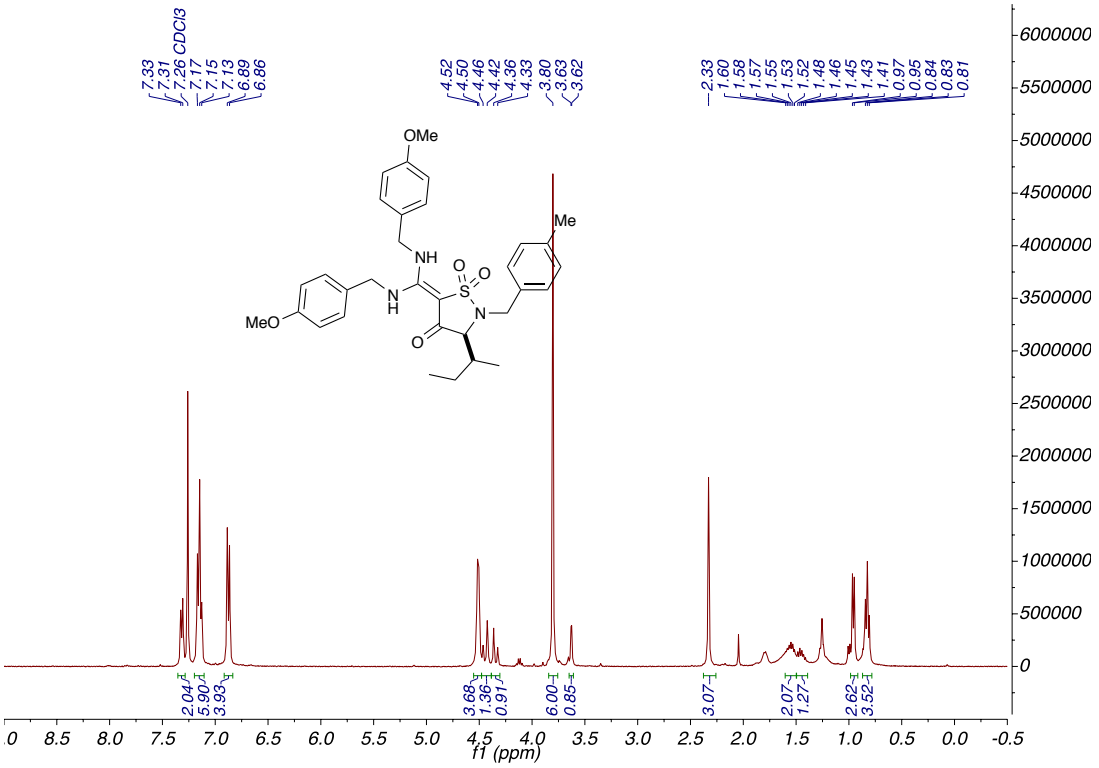


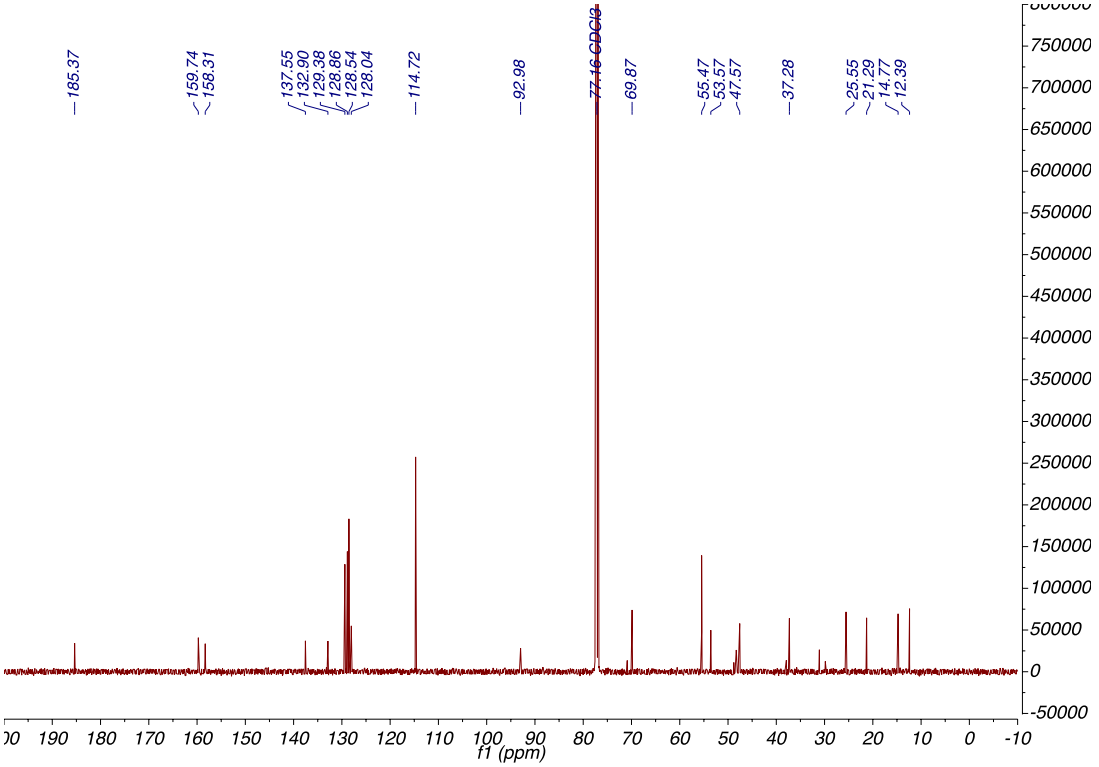
(*S*)-5-(bis((4-methoxybenzyl)amino)methylene)-2-(2-chlorobenzyl)-3-isobutylisothiazolidin-4-one 1,1-dioxide 3.3.9.1.12



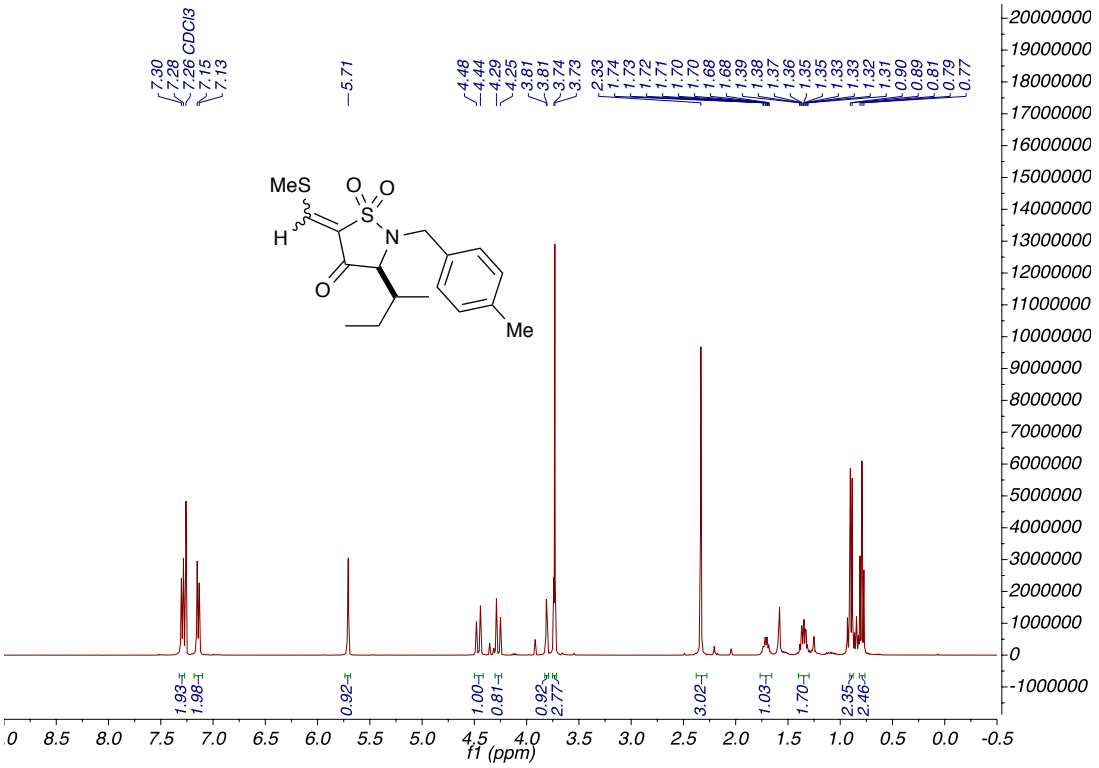


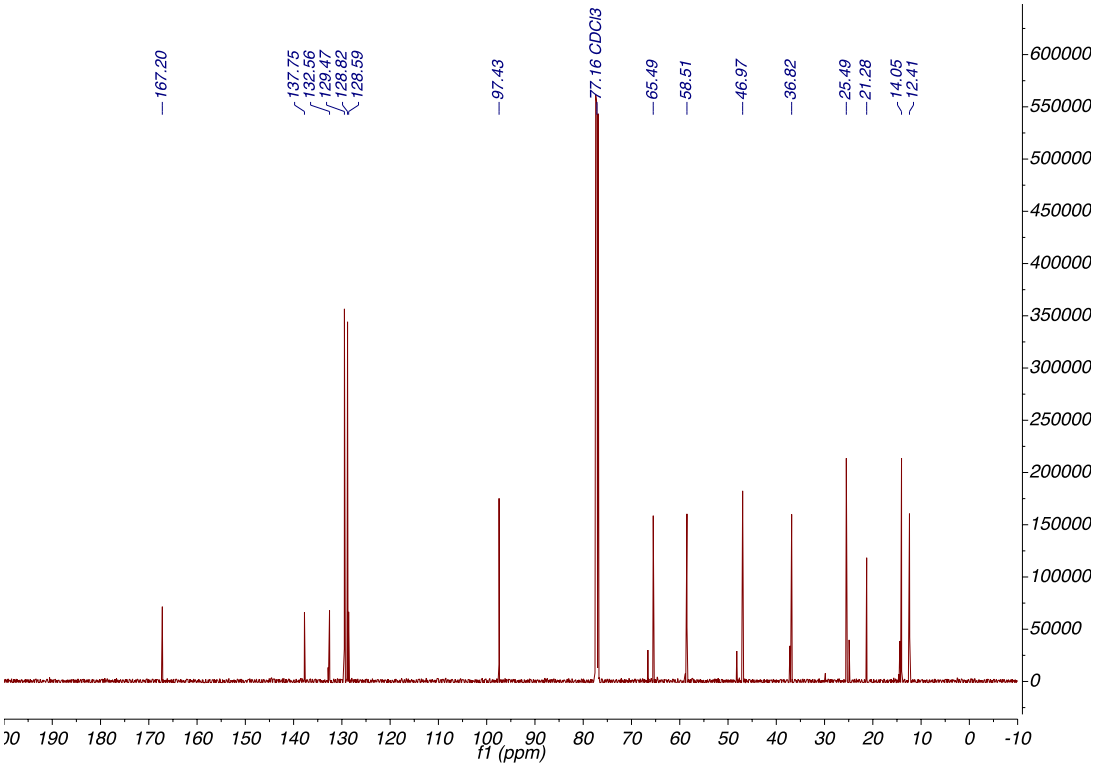
(*S*)-5-(bis((4-methoxybenzyl)amino)methylene)-3-((*S*)-*sec*-butyl)-2-(4-methylbenzyl)isothiazolidin-4-one 1,1-dioxide 3.3.9.1.13



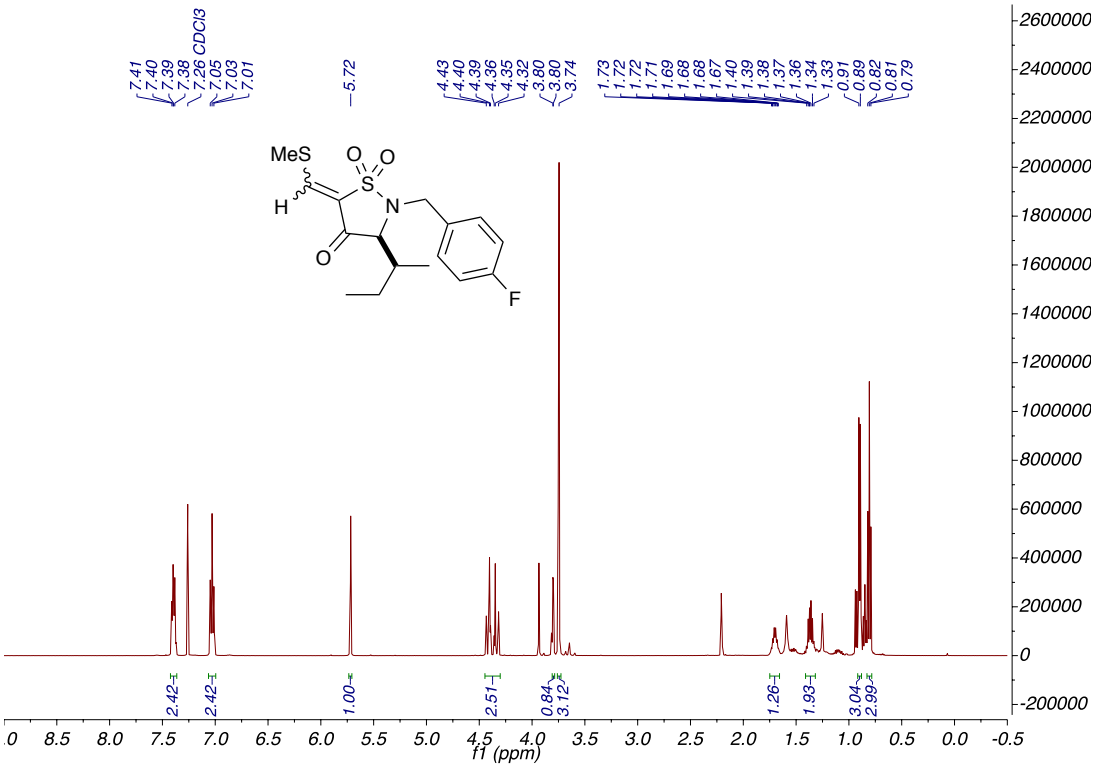


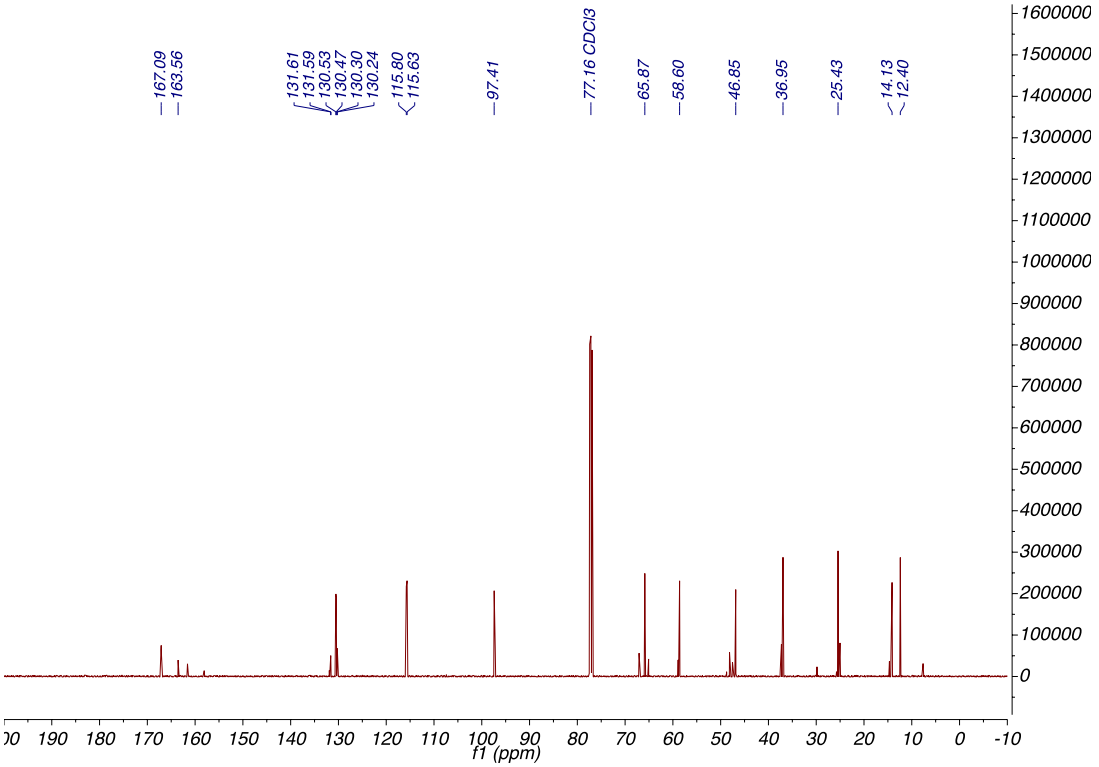
(*S*)-3-((*S*)-*sec*-butyl)-2-(4-methylbenzyl)-5-((methylthio)methylene)isothiazolidin-4-one 1,1-dioxide 3.3.10.1



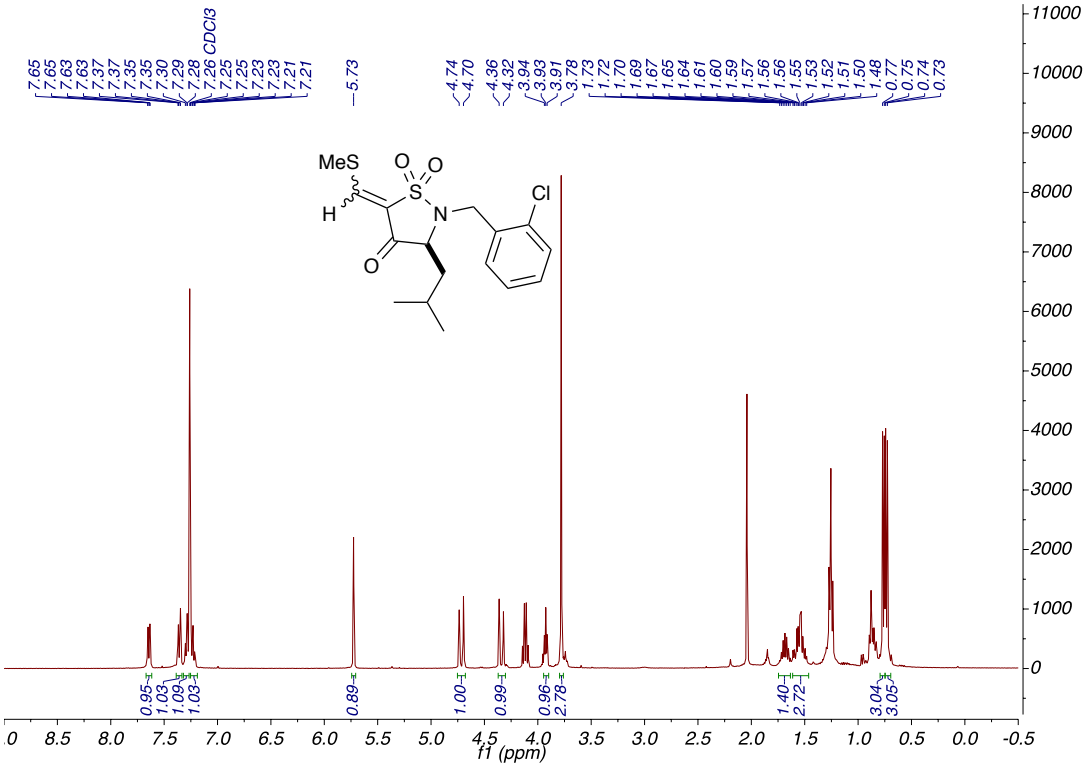


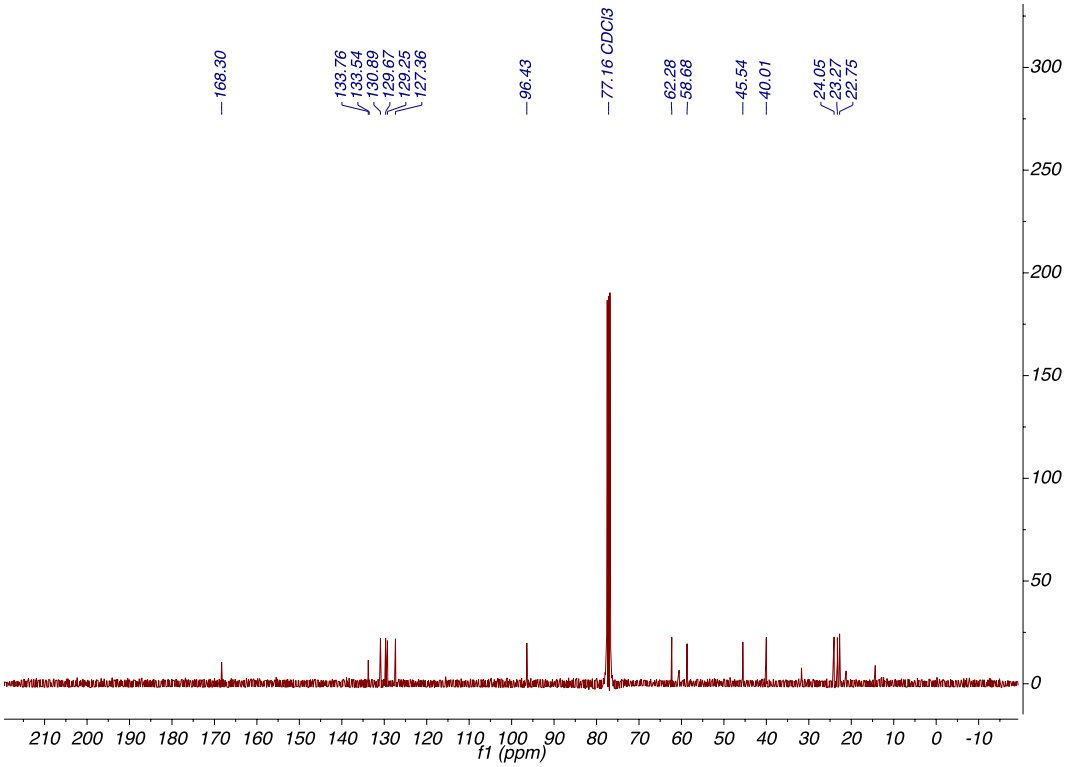
(*S*)-3-((*S*)-*sec*-butyl)-2-(4-fluorobenzyl)-5-((methylthio)methylene)isothiazolidin-4-one 1,1-dioxide 3.3.10.2





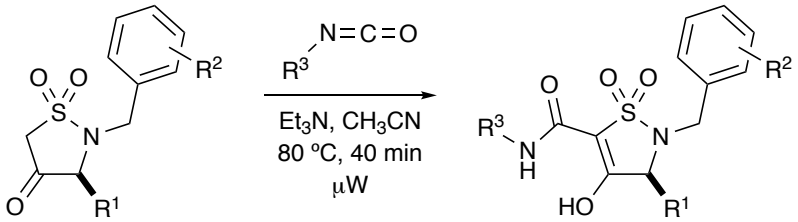
(*S*)-2-(2-chlorobenzyl)-3-isobutyl-5-((methylthio)methylene)isothiazolidin-4-one 1,1-dioxide 3.3.10.3





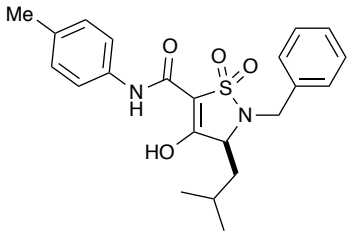
General Procedure

General Procedure **A** for the generation of α-amide enolic sultams **3.4.6.1.1–3.4.6.1.10**:



A sultam (1 equivalent) was added to a microwave vial, and dissolved in acetonitrile (0.1 M). Triethylamine (1 equivalent) was then added, followed by isocyanate (1 equivalent). The vial lid was seal using a crimp head, and the reaction was microwaved at 80 ºC for 40 min. The solvent was then removed using a rotary evaporator, and a normal phase silica flash column was used to purify the product affording sultams **3.4.6.1.1–3.4.6.1.10** in yields up to 93 %.

(*S*)-2-benzyl-4-hydroxy-3-isobutyl-*N*-(*p*-tolyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.1** (65%, 21 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -15.42 (*c* = 0.0105, CH_2Cl_2);

R_f = 0.57 (EtOAc:Hexane = 1:1);

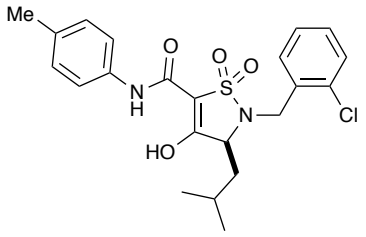
FTIR (neat): 3367, 3268, 3031, 2955, 2925, 2868, 1638, 1582, 1537, 1496, 1454, 1386, 1238, 1140, 1051, 819, 766, 698 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) 10.74 (s, 1H, NH), 7.37 (d, *J* = 7.4 Hz, 4H, ArH), 7.29 (t, *J* = 7.2 Hz, 2H, ArH), 7.22 (t, *J* = 7.1 Hz, 1H, ArH), 7.01 (d, *J* = 7.8 Hz, 2H, ArH), 4.31 (d, *J* = 15.4 Hz, 1H, Bn), 4.01 (d, *J* = 15.4 Hz, 1H, Bn), 2.46 (s, 1H, NC<u>H</u>CH_2CHMeMe), 2.19 (s, 3H, ArMe), 1.66 (dp, *J* = 12.5, 6.2 Hz, 1H, MeC<u>H</u>Me), 1.41 (dt, *J* = 12.0, 5.6 Hz, 1H, C<u>H_2</u>CHMeMe), 1.30 (dt, *J* = 12.8, 5.7 Hz, 1H, C<u>H_2</u>CHMeMe), 0.66 (d, *J* = 6.4 Hz, 3H, Me), 0.61 (d, *J* = 6.5 Hz, 3H, Me);

^{13}C NMR (126 MHz, DMSO-d_6) 180.8 (COH), 161.0 (CO), 137.9 (ArC), 137.7 (ArC), 130.0 (ArC), 129.1 (2 ArC), 128.5 (2 ArC), 128.1 (2 ArC), 127.0 (ArC), 118.2 (2 ArC), 96.8 (COH<u>C</u>CO), 63.8 (N<u>C</u>HCH_2CHMeMe), 48.0 (Bn), 40.4 (<u>C</u>H_2CHMeMe), 23.8 (Me<u>C</u>HMe), 22.9 (Me), 22.8 (Me), 20.3 (ArMe);

HRMS calculated for $C_{22}H_{26}N_2O_4S$ 437.1511 $(M+Na)^+$; found 437.1510 (TOF MS ES^+).

(*S*)-2-(2-chlorobenzyl)-4-hydroxy-3-isobutyl-*N*-(*p*-tolyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.2** (67 %, 35mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -8.03 (*c* = 0.029, CH_2Cl_2);

R_f = 0.16 (EtOAc:Hexane = 1:1);

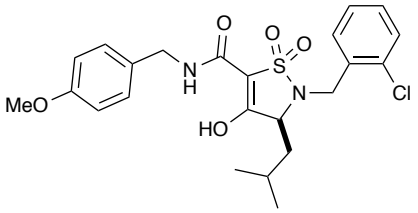
FTIR (neat): 3436, 3026, 2969, 2954, 2868, 1738, 1636, 1585, 1539, 1515, 1425, 1365, 1229, 1140, 1048, 816, 754 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) 10.73 (s, 1H, NH), 7.64 (d, *J* = 7.5 Hz, 1H, ArH), 7.38 (t, *J* = 8.1 Hz, 3H, ArH), 7.31 (t, *J* = 7.4 Hz, 1H, ArH), 7.26 (t, *J* = 7.4 Hz, 1H, ArH), 7.01 (d, *J* = 8.1 Hz, 2H, ArH), 4.57 (d, *J* = 16.2 Hz, 1H, Bn), 3.99 (d, *J* = 16.3 Hz, 1H, Bn), 2.46 (s, 1H, NC<u>H</u>CH_2CHMeMe), 2.19 (s, 3H, ArMe), 1.62 (dp, *J* = 13.2, 6.6 Hz, 1H, MeC<u>H</u>Me), 1.42 (dt, *J* = 12.9, 6.2 Hz, 1H, C<u>H$_2$</u>CHMeMe), 1.33 (dt, *J* = 13.5, 6.2 Hz, 1H, C<u>H$_2$</u>CHMeMe), 0.68 (d, *J* = 6.6 Hz, 3H, Me), 0.61 (d, *J* = 6.6 Hz, 3H, Me).

^{13}C NMR (126 MHz, DMSO-d_6) 180.7 (COH), 161.0 (CO), 137.6 (ArC), 135.6 (ArC), 132.2 (ArC), 130.6 (ArC), 130.2 (ArC), 129.1 (2 ArC), 129.0 (ArC), 128.8 (ArC), 127.0 (ArC), 118.3 (2 ArC), 96.7 (COHCCO), 65.1 (NCHCH$_2$CHMeMe), 46.7 (Bn), 40.4 (CH$_2$CHMeMe), 23.9 (MeCHMe), 22.9 (Me), 22.7 (Me), 20.3 (ArMe);

HRMS calculated for $C_{22}H_{25}ClN_2O_4S$ 471.1121 $(M+Na)^+$; found 471.1144 (TOF MS ES^+).

(*S*)-2-(2-chlorobenzyl)-4-hydroxy-3-isobutyl-*N*-(4-methoxybenzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.3** (28%, 15 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 10.0 (*c* = 0.0015, CH_2Cl_2);

R_f = 0.28 (EtOAc:Hexane = 1:0);

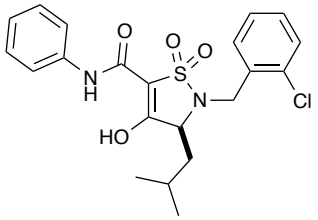
FTIR (neat): 3407, 2975, 2956, 2932, 2869, 1700, 1612, 1545, 1513, 1466, 1248, 1174, 1034, 817, 754 cm^{-1};

^{1}H NMR (600 MHz, CD_3CN-*d*$_3$) 7.60 (s, 1H, ArH), 7.40–7.36 (m, 1H, ArH), 7.27–7.24 (m, 2H, ArH), 7.16 (dd, *J* = 21.2, 6.8 Hz, 2H, ArH), 6.79 (dd, *J* = 13.0, 8.6 Hz, 2H, ArH), 4.67 (d, *J* = 15.9 Hz, 1H, Bn-*o*-Cl), 4.33 (s, 2H, Bn-*p*-OMe), 4.04 (d, *J* = 15.7 Hz, 1H, Bn-*o*-Cl), 3.70 (s, 3H, OMe), 3.56 (s, 1H, NC<u>H</u>CH_2CHMeMe), 1.61 (dq, *J* = 12.5, 6.3 Hz, 1H, MeC<u>H</u>Me), 1.53 (s, 1H, C<u>H$_2$</u>CHMeMe), 1.42 (s, 1H, C<u>H$_2$</u>CHMeMe), 0.68 (d, *J* = 6.0 Hz, 3H, Me), 0.59 (d, *J* = 6.1 Hz, 3H, Me).

^{13}C NMR (151 MHz, CD_3CN-*d*$_3$) 159.8 (CO), 135.8 (ArC), 134.1 (ArC), 132.1 (ArC), 131.9 (ArC), 130.3 (2 ArC), 130.1 (ArC), 130.0 (ArC), 129.7 (ArC), 128.0 (ArC), 114.8 (2 ArC), 67.3 (N<u>C</u>HCH_2CHMeMe), 55.8 (OMe), 44.1 (Bn), 42.6 (Bn), 41.3 (<u>C</u>H_2CHMeMe), 25.1 (Me<u>C</u>HMe), 23.5 (Me), 23.0 (Me);

HRMS calculated for $C_{23}H_{27}ClN_2O_5S$ 501.1227 $(M+Na)^+$; found 501.1230 (TOF MS ES^+).

(*S*)-2-(2-chlorobenzyl)-4-hydroxy-3-isobutyl-*N*-phenyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.4** (93%, 55 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -1.77 (*c* = 0.027, CH_2Cl_2);

$\mathbf{R_f}$ = 0.13 (EtOAc:Hexane = 1:1);

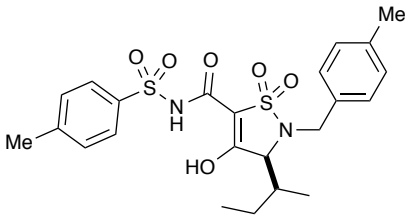
FTIR (neat): 3386, 3059, 2955, 2929, 2868, 1641, 1584, 1543, 1445, 1238, 1140, 1050, 765, 755, 693 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) 10.83 (s, 1H, NH), 7.64 (d, *J* = 7.6 Hz, 1H, ArH), 7.48 (d, *J* = 8.1 Hz, 2H, ArH), 7.40 (d, *J* = 7.8 Hz, 1H, ArH), 7.31 (t, *J* = 7.4 Hz, 1H, ArH), 7.26 (t, *J* = 7.5 Hz, 1H, ArH), 7.20 (t, *J* = 7.8 Hz, 2H, ArH), 6.88 (t, *J* = 7.3 Hz, 1H, ArH), 4.57 (d, *J* = 16.2 Hz, 1H, Bn), 3.98 (d, *J* = 16.3 Hz, 1H, Bn), 3.42 (t, *J* = 5.6 Hz, 1H, NC<u>H</u>CH_2CHMeMe), 1.62 (dp, *J* = 13.3, 6.6 Hz, 1H, MeC<u>H</u>Me), 1.41 (dt, *J* = 12.6, 6.2 Hz, 1H, C<u>H_2</u>CHMeMe), 1.33 (dt, *J* = 13.5, 6.1 Hz, 1H, C<u>H_2</u>CHMeMe), 0.68 (d, *J* = 6.6 Hz, 3H, Me), 0.61 (d, *J* = 6.6 Hz, 3H, Me).

^{13}C NMR (126 MHz, DMSO-d_6) 180.9 (COH), 161.0 (CO), 140.2 (ArC), 135.6 (ArC), 132.2 (ArC), 130.6 (ArC), 129.0 (ArC), 128.7 (ArC), 128.7 (2 ArC), 127.0 (ArC), 121.4 (ArC), 118.2 (2 ArC), 96.8 (COHCCO), 65.0 (NCHCH_2MeMe), 46.7 (Bn), 40.4 (C<u>H_2</u>CHMeMe), 23.9 (MeCHMe), 22.9 (Me), 22.7 (Me);

HRMS calculated for $C_{21}H_{23}ClN_2O_4S$ 457.0965 $(M+Na)^+$; found 457.0961 (TOF MS ES^+).

(*S*)-3-((*S*)-*sec*-butyl)-4-hydroxy-2-(4-methylbenzyl)-*N*-tosyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.5** (40 %, 28 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -29.42 (*c* = 0.014, CH_2Cl_2);

R_f = 0.08 (EtOAc:Hexane = 1:0);

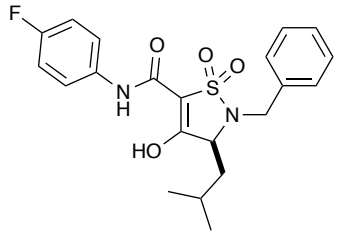
FTIR (neat): 3443, 3029, 2963, 2925, 2874, 1708, 1651, 1593, 1515, 1447, 1163, 1088, 848, 816 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) 12.17 (s, 1H, NH), 7.83 (d, *J* = 7.7 Hz, 2H, ArH), 7.40 (d, *J* = 7.7 Hz, 2H, ArH), 7.25 (d, *J* = 7.2 Hz, 2H, ArH), 7.11 (d, *J* = 7.3 Hz, 2H, ArH), 4.26 (d, *J* = 16.0 Hz, 1H, Bn), 4.11 (d, *J* = 15.8 Hz, 1H, Bn), 2.39 (s, 3H, ArMe), 2.36 (d, *J* = 7.8 Hz, 1H, NC<u>H</u>Me), 2.27 (s, 3H, ArMe), 1.63–1.56 (m, 1H, MeC<u>H</u>Me), 1.42 (dq, *J* = 13.7, 6.6 Hz, 1H, C<u>H$_2$</u>Me), 1.30 (dq, *J* = 13.4, 7.1, 6.7 Hz, 1H, C<u>H$_2$</u>-Ile), 0.75 (d, *J* = 7.2 Hz, 3H, Me), 0.71 (d, *J* = 7.1 Hz, 3H, Me);

^{13}C NMR (126 MHz, DMSO-d_6) 182.2 (COH), 157.9 (CO), 143.5 (ArC), 137.7 (ArC), 136.0 (ArC), 134.6 (ArC), 129.3 (2 ArC), 128.7 (2 ArC), 128.1 (2 ArC), 127.4 (2 ArC), 97.5 (COH<u>C</u>CO), 68.6 (N<u>C</u>HMe), 47.0 (Bn), 36.6 (CH-Ile), 24.7 (C<u>H$_2$</u>Me), 21.0 (ArMe), 20.6 (ArMe), 14.4 (Me), 12.1 (Me);

HRMS calculated for $C_{23}H_{28}N_2O_6S_2$ 515.1287 $(M+Na)^+$; found 515.1276 (TOF MS ES^+).

(*S*)-2-benzyl-*N*-(4-fluorophenyl)-4-hydroxy-3-isobutyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.6** (72%, 21 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -14.95 (*c* = 0.0105, CH_2Cl_2);

$\mathbf{R_f}$ = 0.62 (EtOAc:Hexane = 1:0);

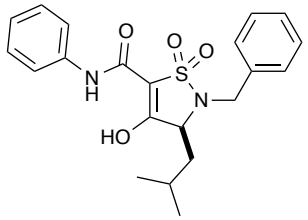
FTIR (neat): 3432, 3269, 3064, 2956, 2928, 2868, 1640, 1582, 1546, 1509, 1454, 1210, 1140, 1052, 835, 766, 698 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) 10.89 (s, 1H, NH), 7.53 (dd, *J* = 9.0, 5.0 Hz, 2H, ArH), 7.41 (d, *J* = 7.4 Hz, 2H, ArH), 7.33 (t, *J* = 7.5 Hz, 2H, ArH), 7.25 (t, *J* = 7.3 Hz, 1H, ArH), 7.07 (t, *J* = 8.9 Hz, 2H, ArH), 4.35 (d, *J* = 15.4 Hz, 1H, Bn), 4.05 (d, *J* = 15.4 Hz, 1H, Bn), 3.32 (d, *J* = 5.5 Hz, 1H, NC<u>H</u>CH_2CHMeMe), 1.69 (dp, *J* = 13.3, 6.6 Hz, 1H, MeC<u>H</u>Me), 1.44 (dt, *J* = 12.4, 6.0 Hz, 1H, C<u>H</u>$_2$CHMeMe), 1.33 (dt, *J* = 13.5, 6.1 Hz, 1H, C<u>H</u>$_2$CHMeMe), 0.70 (d, *J* = 6.6 Hz, 3H, Me), 0.64 (d, *J* = 6.7 Hz, 3H, Me).

^{13}C NMR (126 MHz, DMSO-d_6) 181.0 (COH), 161.0 (CO), 156.96 (d, *J* = 237.6 Hz, ArC), 137.9 (ArC), 136.6 (d, *J* = 1.8 Hz, ArC), 128.5 (2 ArC), 128.1 (2 ArC), 127.0 (ArC), 119.7 (d, J = 7.5 Hz, 2 ArC), 115.2 (d, *J* = 21.9 Hz, 2 ArC), 96.7 (COH<u>C</u>CO), 63.7 (N<u>C</u>HCH_2CHMeMe), 48.0 (Bn), 23.8 (Me<u>C</u>HMe), 22.8 (Me), 22.8 (Me);

HRMS calculated for $C_{21}H_{23}FN_2O_4S$ 441.1260 $(M+Na)^+$; found 441.1280 (TOF MS ES^+).

(*S*)-2-benzyl-4-hydroxy-3-isobutyl-*N*-phenyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.7** (88%, 37 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -13.05 (*c* = 0.018, CH_2Cl_2);

$\mathbf{R_f}$ = 0.11 (EtOAc:Hexane = 1:1);

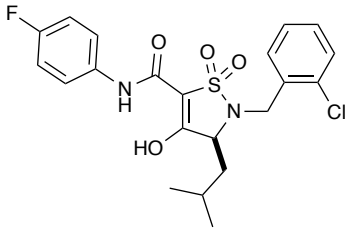
FTIR (neat): 3430, 3259, 3110, 3060, 3031, 2955, 2927, 2868, 1643, 1583, 1543, 1497, 1445, 1387, 1237, 1139, 1052, 766, 697 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) 10.87 (s, 1H, NH), 7.52 (d, *J* = 7.8 Hz, 2H, ArH), 7.41 (d, *J* = 7.4 Hz, 2H, ArH), 7.33 (t, *J* = 7.5 Hz, 2H, ArH), 7.25 (q, *J* = 7.9 Hz, 3H, ArH), 6.92 (t, *J* = 7.3 Hz, 1H, ArH), 4.36 (d, *J* = 15.4 Hz, 1H, Bn), 4.06 (d, *J* = 15.4 Hz, 1H, Bn), 3.33 (t, *J* = 5.4 Hz, 1H, NC<u>H</u>CH_2CHMeMe), 1.70 (dp, *J* = 13.2, 6.6 Hz, 1H, MeC<u>H</u>Me), 1.45 (dt, *J* = 12.4, 6.0 Hz, 1H, C<u>H_2</u>CHMeMe), 1.34 (dt, *J* = 13.4, 6.1 Hz, 1H, C<u>H_2</u>CHMeMe), 0.71 (d, *J* = 6.6 Hz, 3H, Me), 0.65 (d, *J* = 6.7 Hz, 3H, Me).

^{13}C NMR (126 MHz, DMSO-d_6) 180.9 (COH), 161.1 (CO), 140.2 (ArC), 137.9 (ArC), 128.7 (2 ArC), 128.5 (2 ArC), 128.1 (2 ArC), 127.0 (ArC), 121.3 (ArC), 118.2 (2 ArC), 96.8 (COH<u>C</u>CO), 63.8 (N<u>C</u>HCH_2CHMeMe), 48.0 (Bn), 23.8 (Me<u>C</u>HMe), 22.8 (Me), 22.8 (Me);

HRMS calculated for $C_{21}H_{24}N_2O_4S$ 423.1355 $(M+Na)^+$; found 423.1354 (TOF MS ES^+).

(*S*)-2-(2-chlorobenzyl)-*N*-(4-fluorophenyl)-4-hydroxy-3-isobutyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.8** (91%, 65 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -13.62 (*c* = 0.032, CH_2Cl_2);

R_f = 0.60 (EtOAc:Hexane = 1:0);

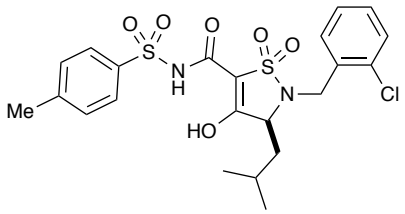
FTIR (neat): 3431, 3270, 3135, 3065, 2956, 2929, 2868, 1643, 1584, 1545, 1509, 1470, 1240, 1210, 1141, 1052, 835, 764 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) 10.84 (s, 1H, NH), 7.65 (d, *J* = 7.5 Hz, 1H, ArH), 7.52 (dd, *J* = 8.7, 5.0 Hz, 2H, ArH), 7.39 (d, *J* = 7.8 Hz, 1H, ArH), 7.31 (t, *J* = 7.4 Hz, 1H, ArH), 7.26 (t, *J* = 7.4 Hz, 1H, ArH), 7.04 (t, *J* = 8.8 Hz, 2H, ArH), 4.58 (d, *J* = 16.2 Hz, 1H, Bn), 4.00 (d, *J* = 16.2 Hz, 1H, Bn), 3.44 (t, *J* = 5.4 Hz, 1H, NC<u>H</u>CH_2CHMeMe), 1.63 (dp, *J* = 13.2, 6.5 Hz, 1H, MeC<u>H</u>Me), 1.42 (dt, *J* = 12.9, 6.2 Hz, 1H, C<u>H$_2$</u>CHMeMe), 1.34 (dt, *J* = 13.5, 6.2 Hz, 1H, C<u>H$_2$</u>CHMeMe), 0.68 (d, *J* = 6.6 Hz, 3H, Me), 0.62 (d, *J* = 6.6 Hz, 3H, Me).

^{13}C NMR (126 MHz, DMSO-d_6) 181.0 (COH), 161.1 (CO), 157.1 (d, *J* = 236.9 Hz, ArC), 136.5 (d, J = 1.5 Hz, ArC), 135.5 (ArC), 132.3 (ArC), 130.7 (ArC), 129.1 (ArC), 128.8 (ArC), 127.1 (2 ArC), 119.8 (d, *J* = 7.2 Hz, ArC), 115.2 (d, *J* = 22.6 Hz, 2 ArC), 96.6 (COH<u>C</u>CO), 65.1 (N<u>C</u>HCH_2CHMeMe), 46.7 (Bn), 40.4 (C<u>H$_2$</u>CHMeMe), 23.9 (Me<u>C</u>HMe), 22.9 (Me), 22.7 (Me);

HRMS calculated for $C_{21}H_{22}ClFN_2O_4S$ 475.0871 $(M+Na)^+$; found 475.0886 (TOF MS ES^+).

(*S*)-2-(2-chlorobenzyl)-4-hydroxy-3-isobutyl-*N*-tosyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.9** (60%, 49 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -4.66 (*c* = 0.018, CH_2Cl_2);

R_f = 0.28 (EtOAc:Hexane = 1:0 x 2);

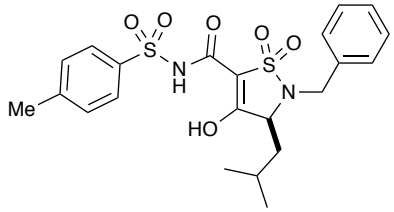
FTIR (neat): 3431, 3065, 2955, 2927, 2868, 1667, 1589, 1443, 1259, 1140, 1087, 822, 763 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) 11.96 (s, 1H, NH), 7.37 (t, *J* = 9.0 Hz, 4H, ArH), 7.26 (dq, *J* = 22.3, 7.0 Hz, 4H, ArH), 4.51 (d, *J* = 16.1 Hz, 1H, Bn), 3.95 (d, *J* = 16.1 Hz, 1H, Bn), 3.49 (t, *J* = 5.6 Hz, 1H, NC<u>H</u>CH_2CHMeMe), 2.35 (s, 3H, ArMe), 1.55 (tt, *J* = 13.0, 6.1 Hz, 1H, MeC<u>H</u>Me), 1.37 (dt, *J* = 12.8, 6.2 Hz, 1H, C<u>H$_2$</u>CHMeMe), 1.27 (dt, *J* = 13.4, 6.0 Hz, 1H, C<u>H$_2$</u>CHMeMe), 0.64 (d, *J* = 6.6 Hz, 3H, Me), 0.58 (d, *J* = 6.7 Hz, 3H, Me).

^{13}C NMR (126 MHz, DMSO-d_6) 183.5 (COH), 158.0 (CO), 143.6 (ArC), 137.6 (ArC), 135.1 (ArC), 132.3 (ArC), 130.6 (ArC), 129.3 (2 ArC), 129.1 (ArC), 128.9 (ArC), 127.4 (2 ArC), 127.1 (ArC), 96.2 (COH<u>C</u>CO), 65.2 (N<u>C</u>HCH_2CHMeMe), 46.7 (Bn), 40.4 (<u>C</u>H_2CHMeMe), 23.8 (Me<u>C</u>HMe), 22.7 (Me), 22.6 (Me), 21.0 (ArMe);

HRMS calculated for $C_{22}H_{25}ClN_2O_6S_2$ 535.0740 $(M+Na)^+$; found 535.0732 (TOF MS ES^+).

(*S*)-2-benzyl-4-hydroxy-3-isobutyl-*N*-tosyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide



According to the reaction protocol described in general procedure **A**, compound **3.4.6.1.10** (57%, 31 mg) was isolated as clear oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -13.48 (*c* = 0.0155, CH_2Cl_2);

R_f = 0.18 (EtOAc:Hexane = 1:0);

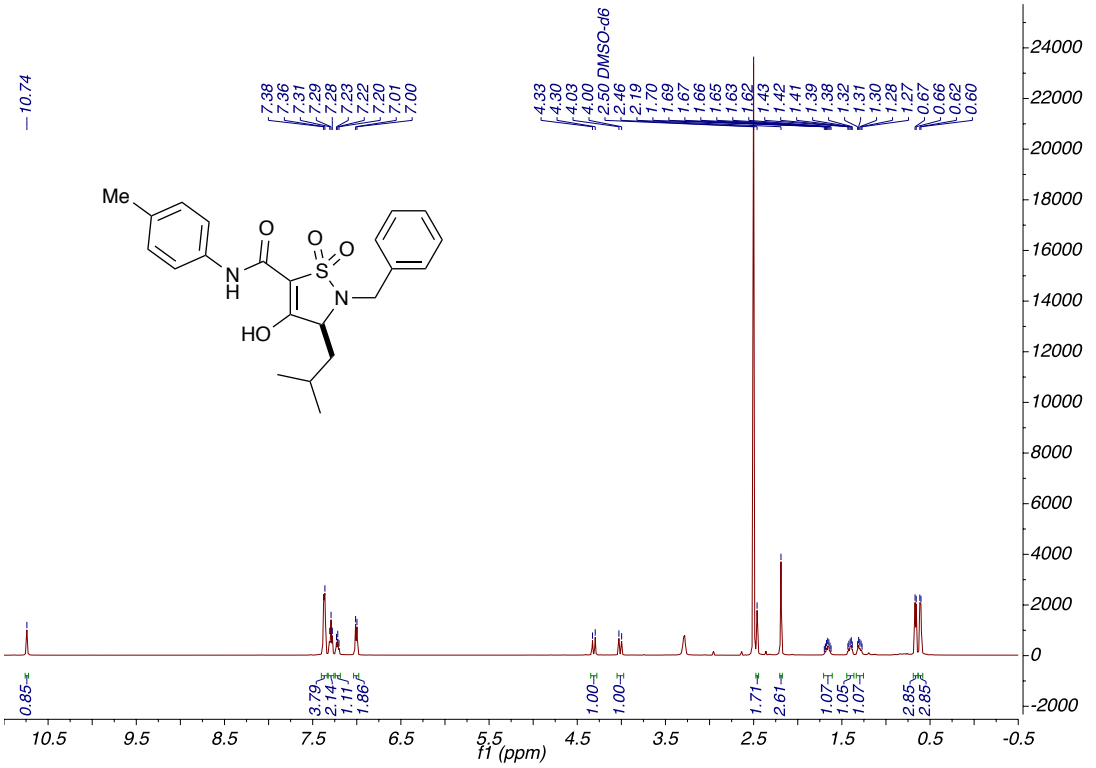
FTIR (neat): 3422, 3064, 3031, 2955, 2925, 2868, 1666, 1631, 1588, 1451, 1386, 1322, 1256, 1162, 1085, 1051, 822, 764, 697 cm^{-1};

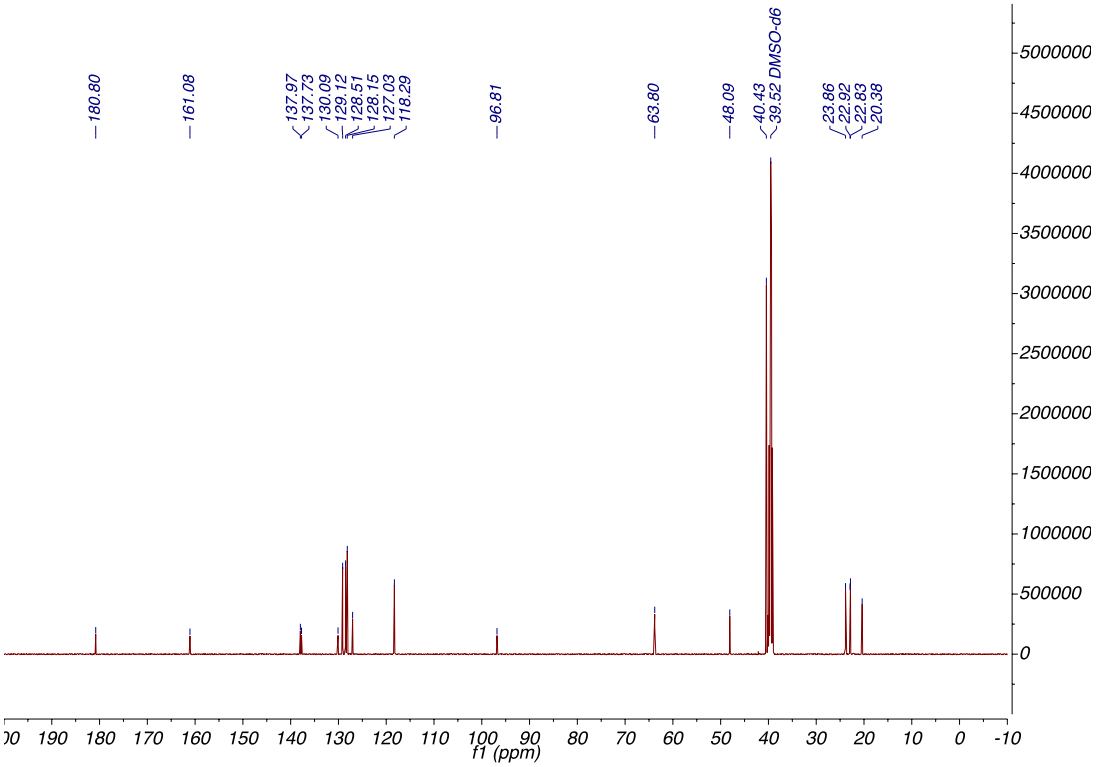
^{1}H NMR (500 MHz, DMSO-d_6) 11.98 (s, 1H, NH), 7.34 (dd, *J* = 16.5, 7.0 Hz, 4H, ArH), 7.29–7.19 (m, 5H, ArH), 4.26 (d, *J* = 15.2 Hz, 1H, Bn), 3.99 (d, *J* = 15.1 Hz, 1H, Bn), 3.19 (s, 1H, NC<u>H</u>CH_2CHMeMe), 2.35 (s, 3H, ArMe), 1.63–1.55 (m, 1H, MeC<u>H</u>Me), 1.41–1.34 (m, 1H, C<u>H$_2$</u>CHMeMe), 1.29–1.23 (m, 1H, C<u>H$_2$</u>CHMeMe), 0.64–0.61 (m, 3H, Me), 0.60–0.57 (m, 3H, Me).

^{13}C NMR (126 MHz, DMSO-d_6) 183.5 (COH), 158.0 (CO), 143.5 (ArC), 137.6 (ArC), 137.4 (ArC), 129.3 (2 ArC), 128.4 (2 ArC), 128.2 (2 ArC), 127.4 (2 ArC), 127.1 (ArC), 96.2 (COH<u>C</u>CO), 63.9 (N<u>C</u>HCH_2CHMeMe), 47.8 (Bn), 40.4 (<u>C</u>H_2CHMeMe), 23.7 (Me<u>C</u>HMe), 22.8 (Me), 22.7 (Me), 21.0 (ArMe);

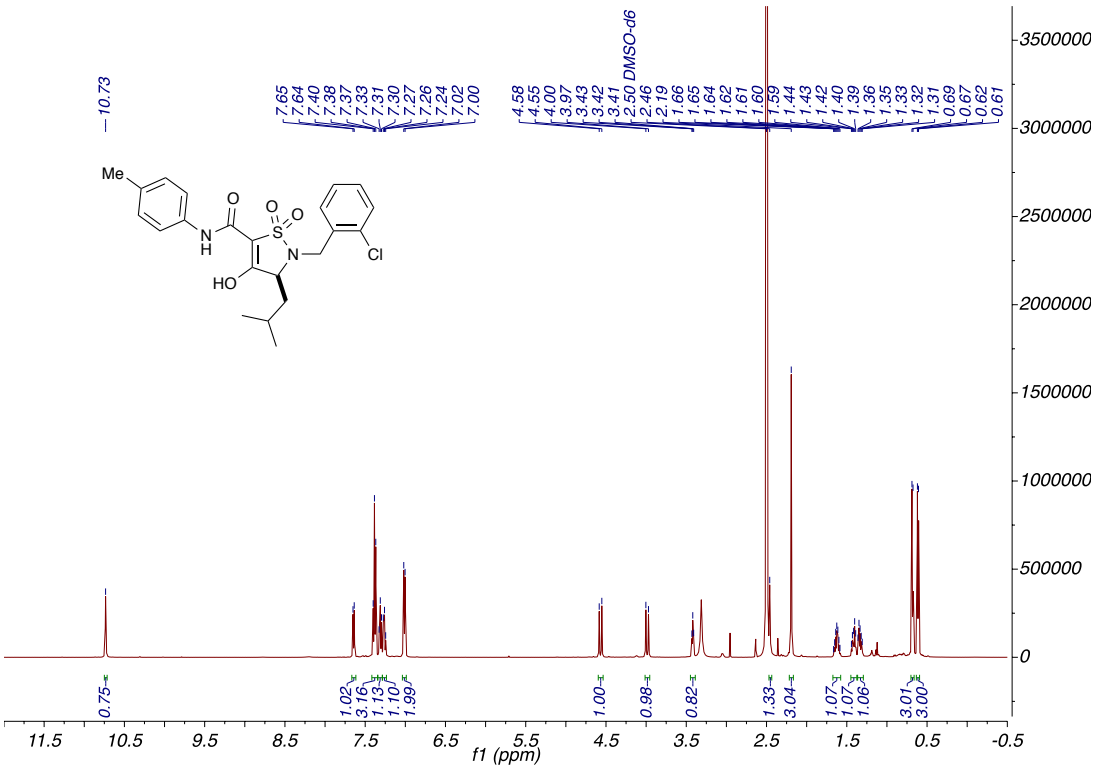
HRMS calculated for $C_{22}H_{26}N_2O_6S_2$ 501.1130 $(M+Na)^+$; found 501.1132 (TOF MS ES^+).

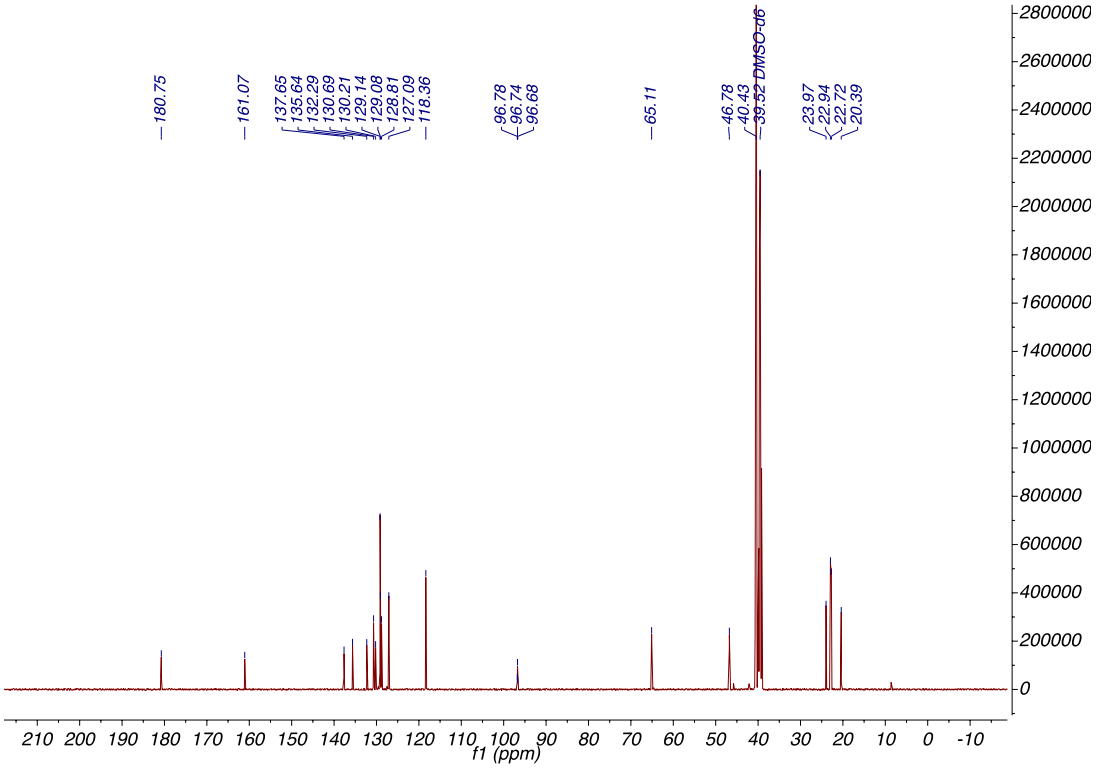
(*S*)-2-benzyl-4-hydroxy-3-isobutyl-*N*-(*p*-tolyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.1



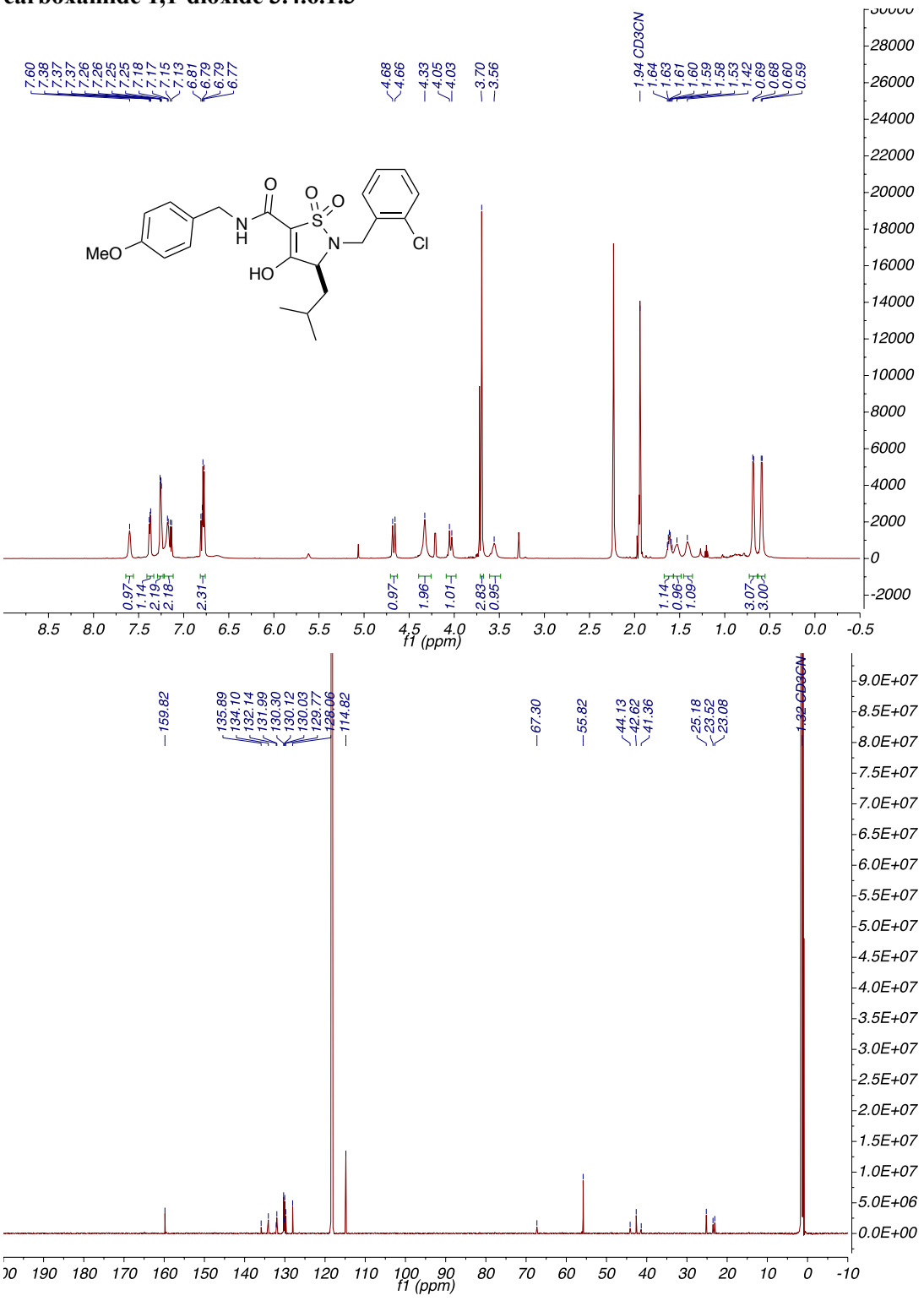


(*S*)-2-(2-chlorobenzyl)-4-hydroxy-3-isobutyl-*N*-(*p*-tolyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.2

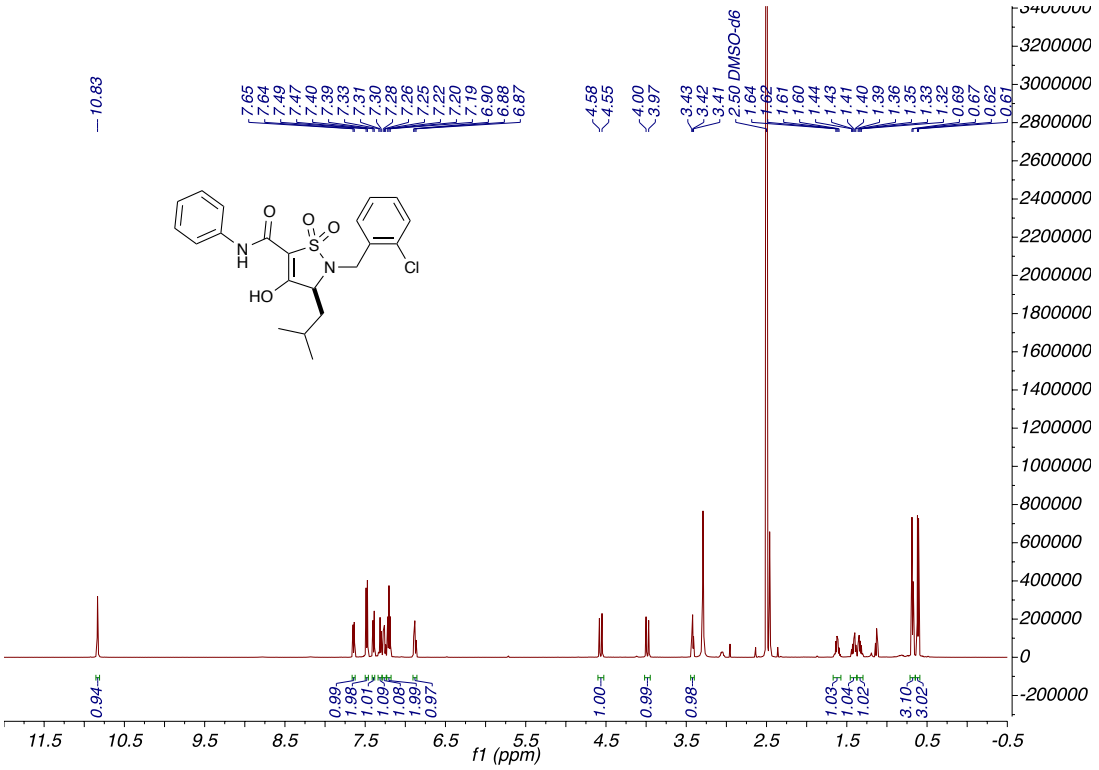


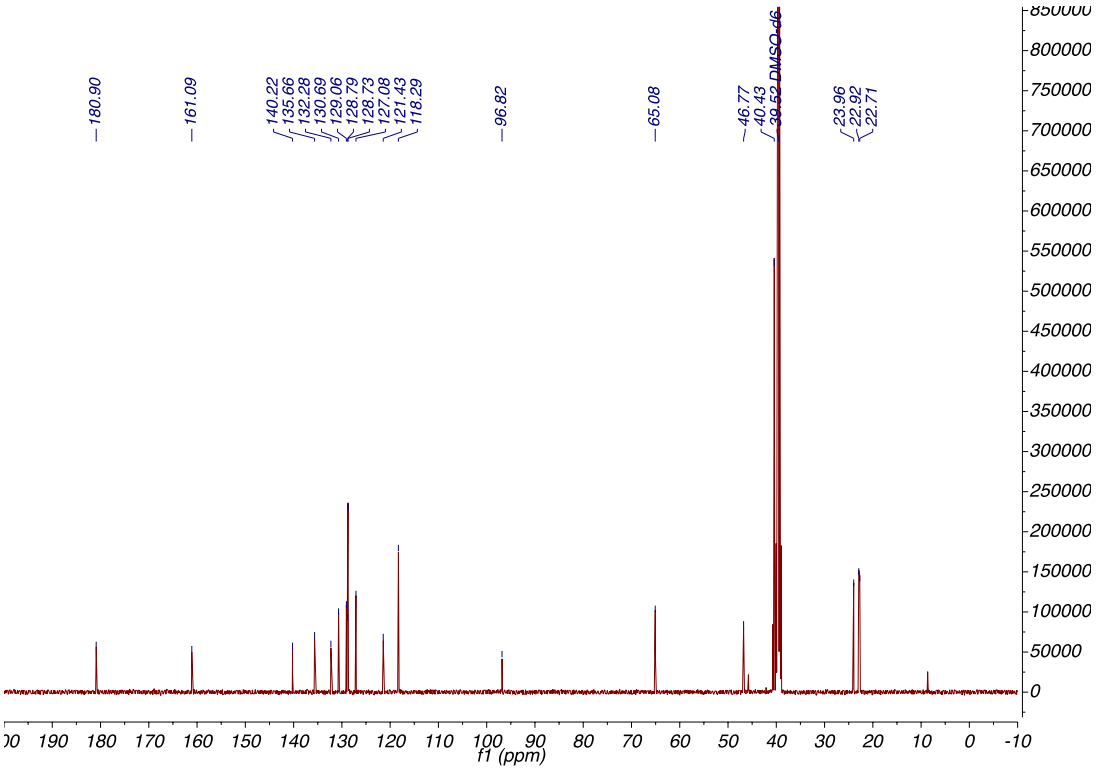


(*S*)-2-(2-chlorobenzyl)-4-hydroxy-3-isobutyl-*N*-(4-methoxybenzyl)-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.3

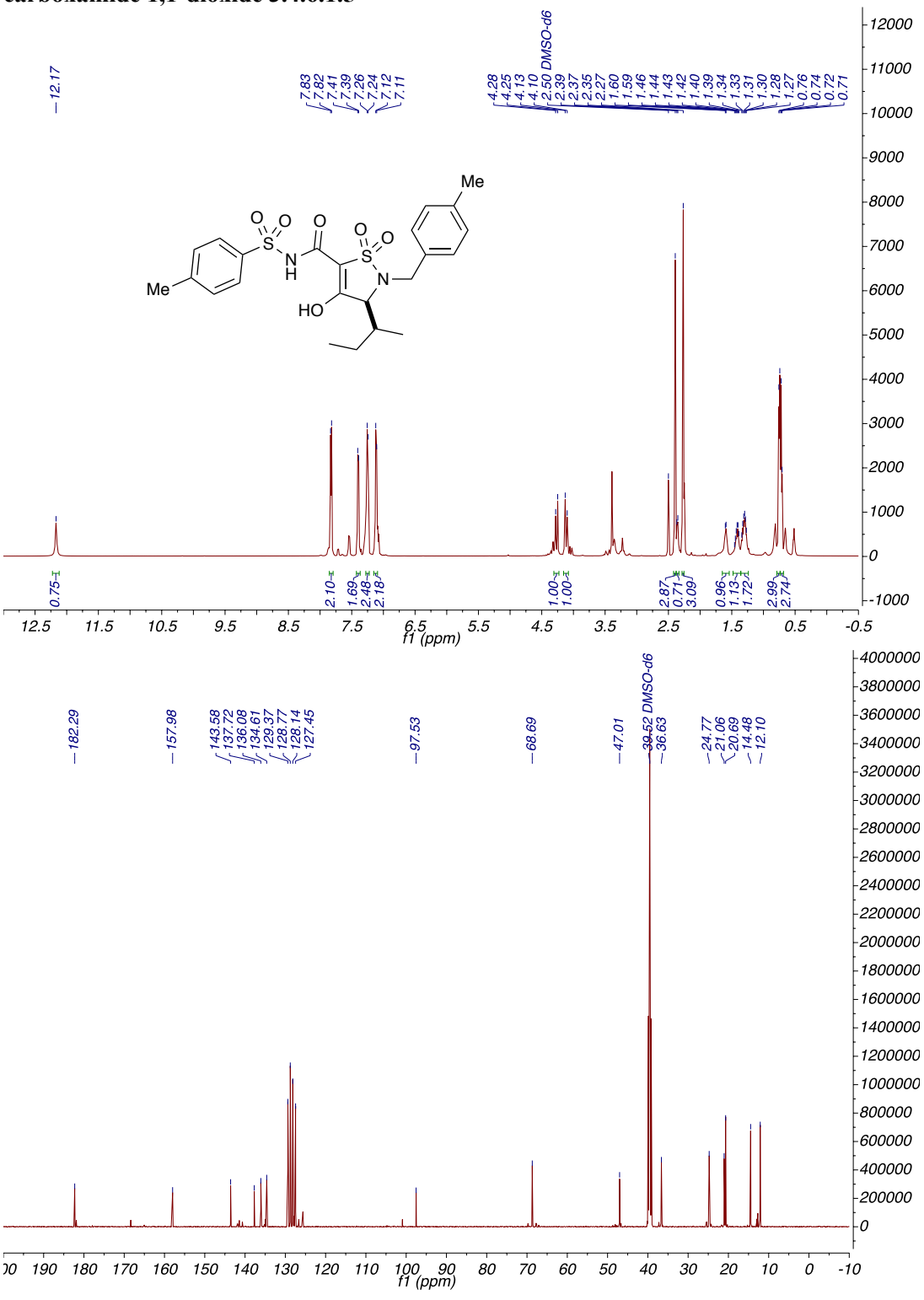


(*S*)-2-(2-chlorobenzyl)-4-hydroxy-3-isobutyl-*N*-phenyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.4

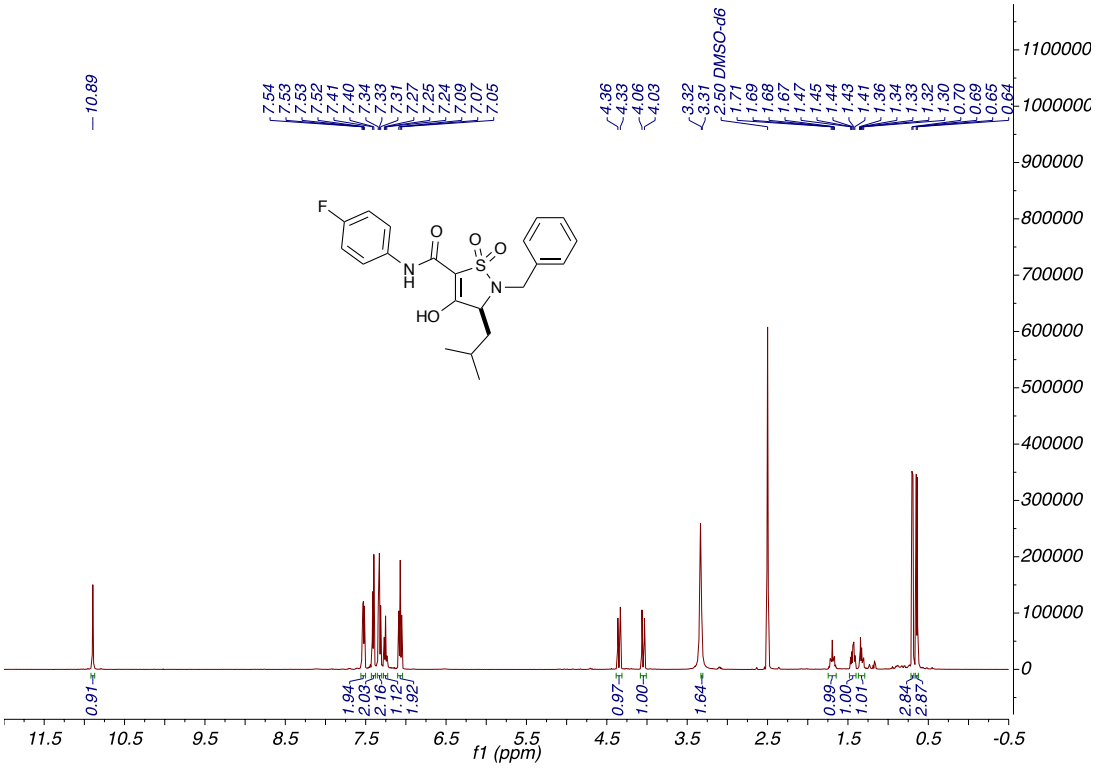


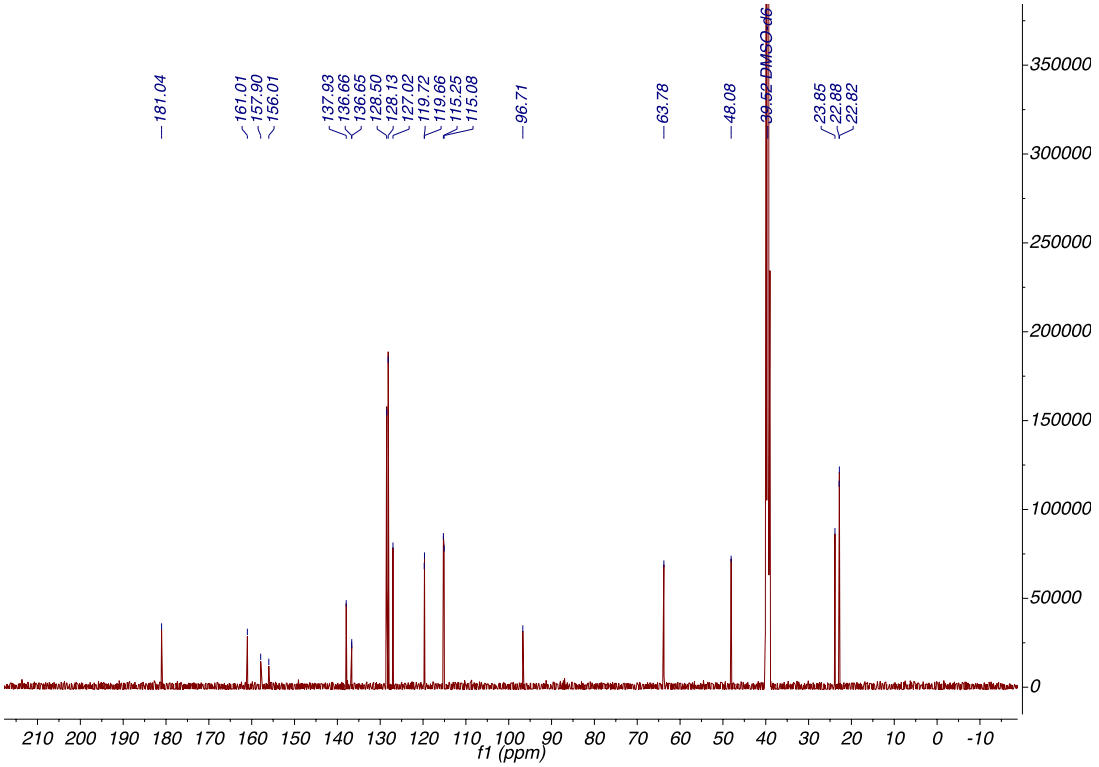


(*S*)-3-((*S*)-*sec*-butyl)-4-hydroxy-2-(4-methylbenzyl)-*N*-tosyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.5

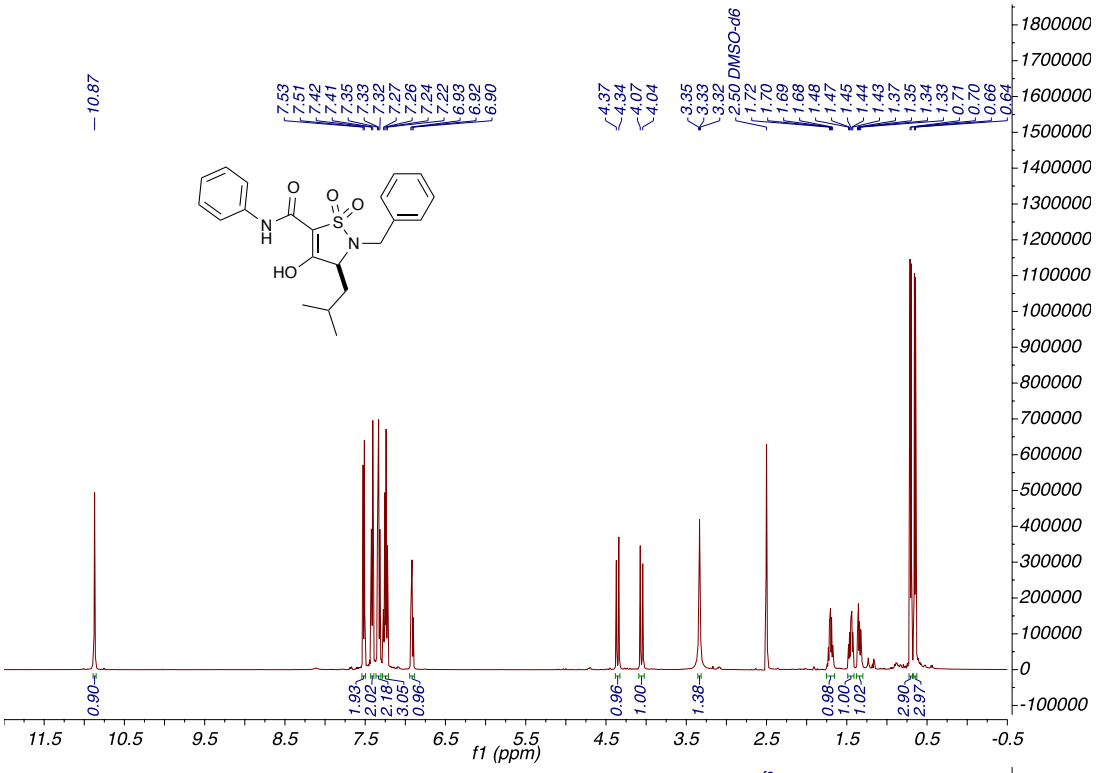


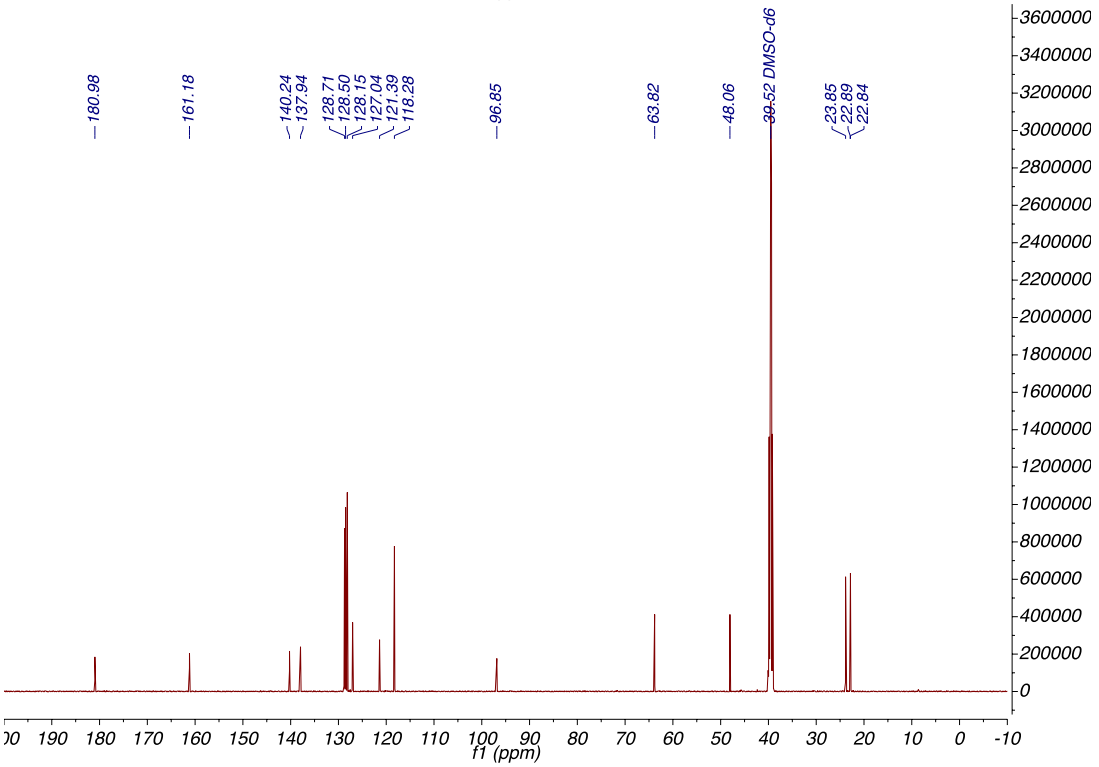
(*S*)-2-benzyl-*N*-(4-fluorophenyl)-4-hydroxy-3-isobutyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.6



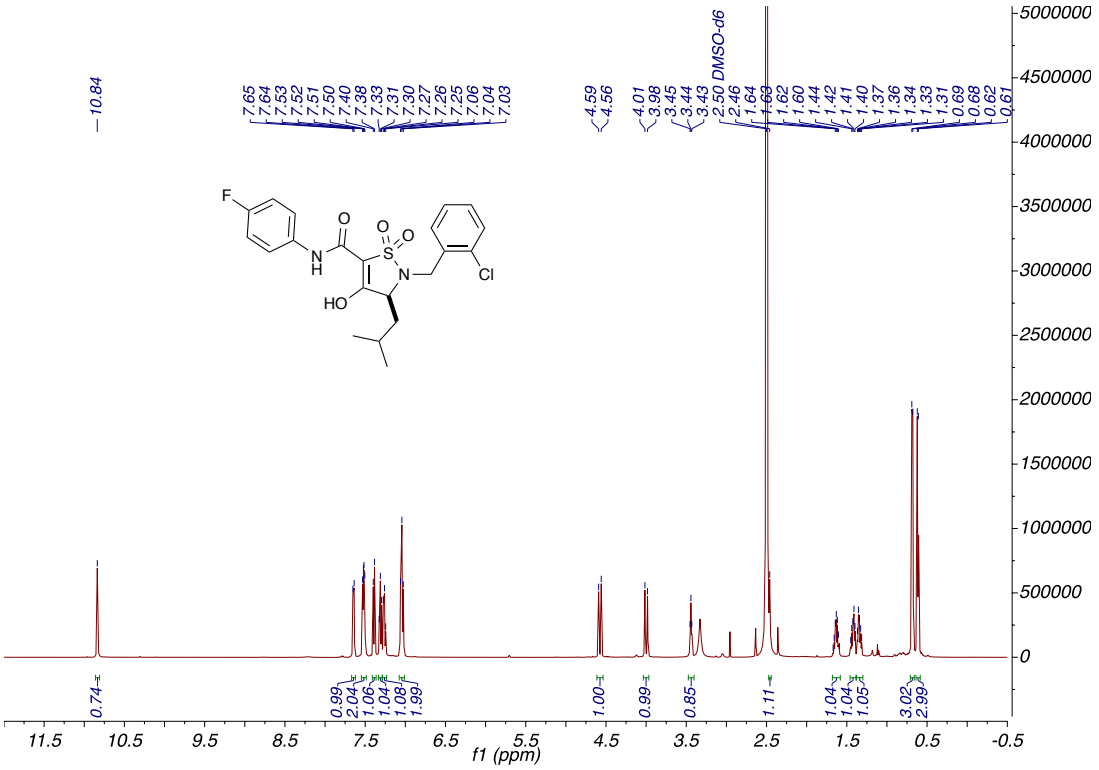


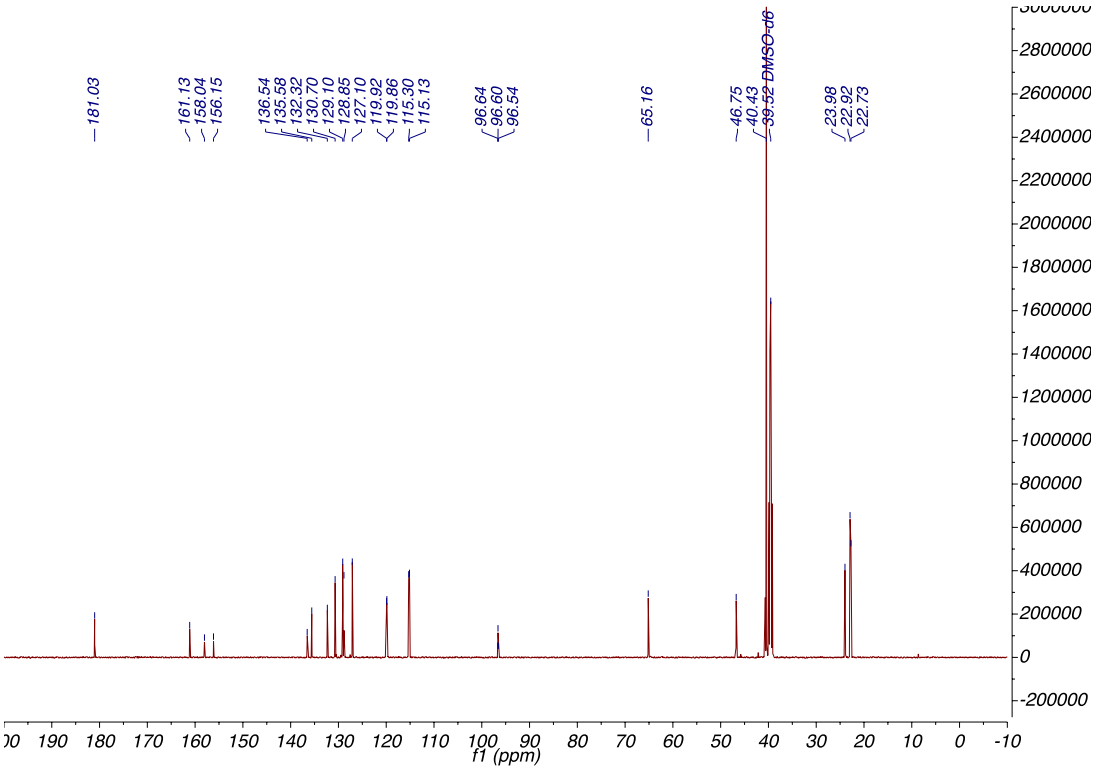
(*S*)-2-benzyl-4-hydroxy-3-isobutyl-*N*-phenyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.7



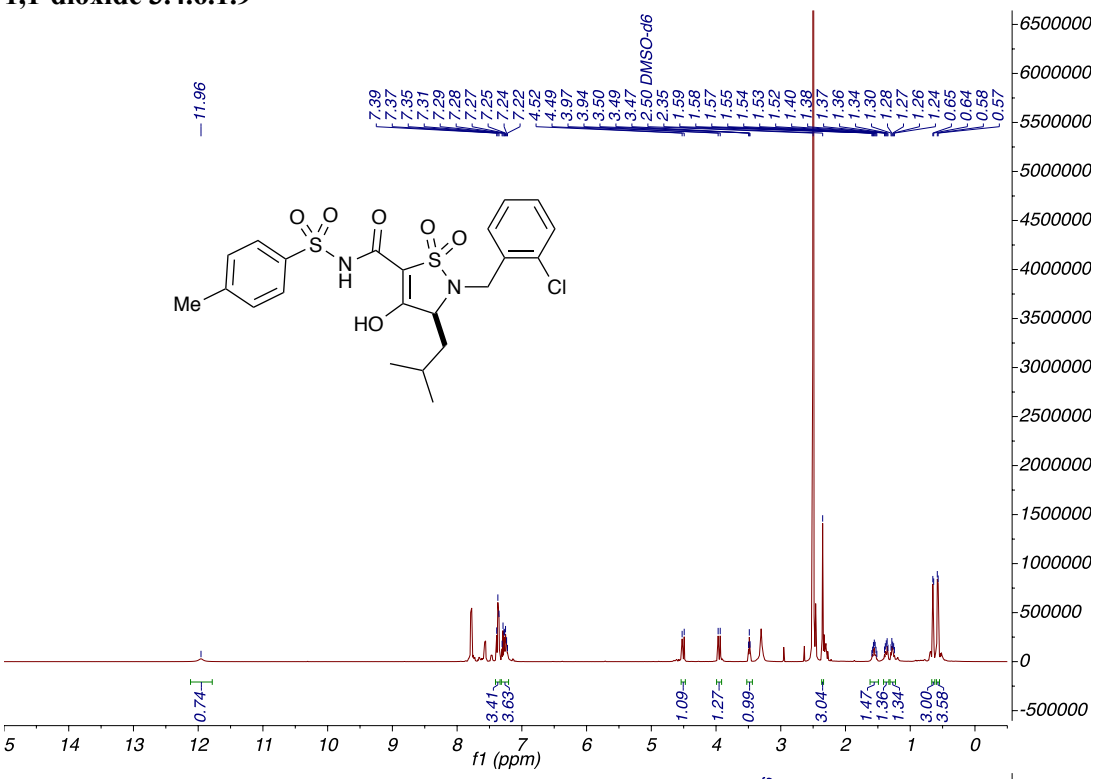


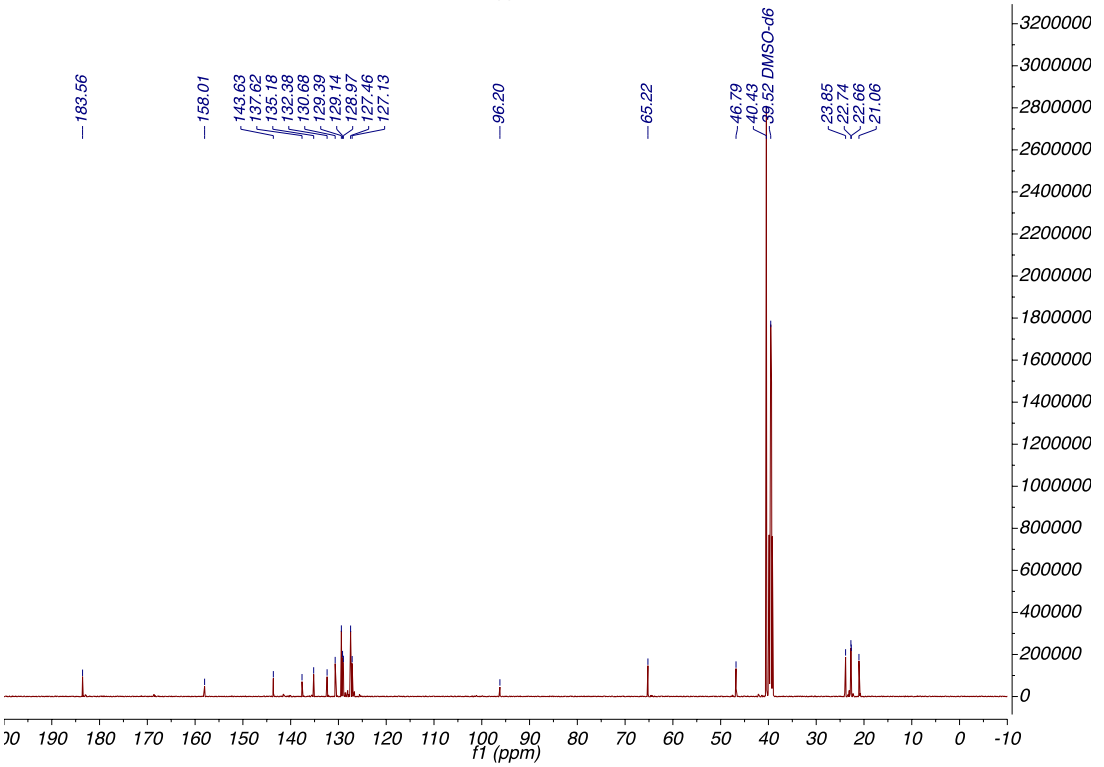
(*S*)-2-(2-chlorobenzyl)-*N*-(4-fluorophenyl)-4-hydroxy-3-isobutyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.8





(*S*)-2-(2-chlorobenzyl)-4-hydroxy-3-isobutyl-*N*-tosyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.9





(*S*)-2-benzyl-4-hydroxy-3-isobutyl-*N*-tosyl-2,3-dihydroisothiazole-5-carboxamide 1,1-dioxide 3.4.6.1.10