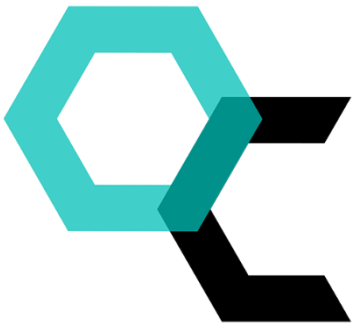
Palacký University in Olomouc
Faculty of Science
Department of Organic chemistry



Benzo[*d*]thiazole-2-sulfonamides: Their Synthesis and applications in the field of synthetic method development

Mgr. František Zálešák

Appendices to Ph.D. Thesis

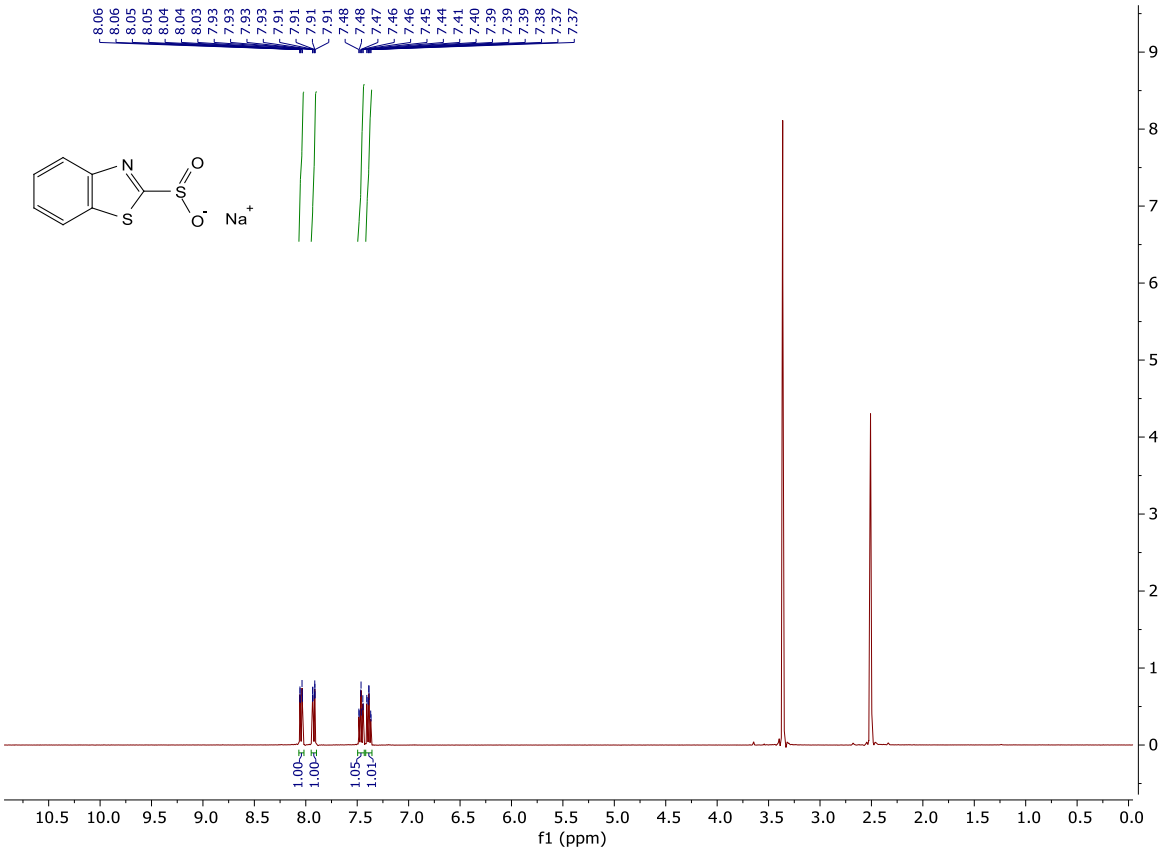
Supervisor: doc. RNDr. Jiří Pospíšil, Ph.D.

Academic Year: 2020/2021

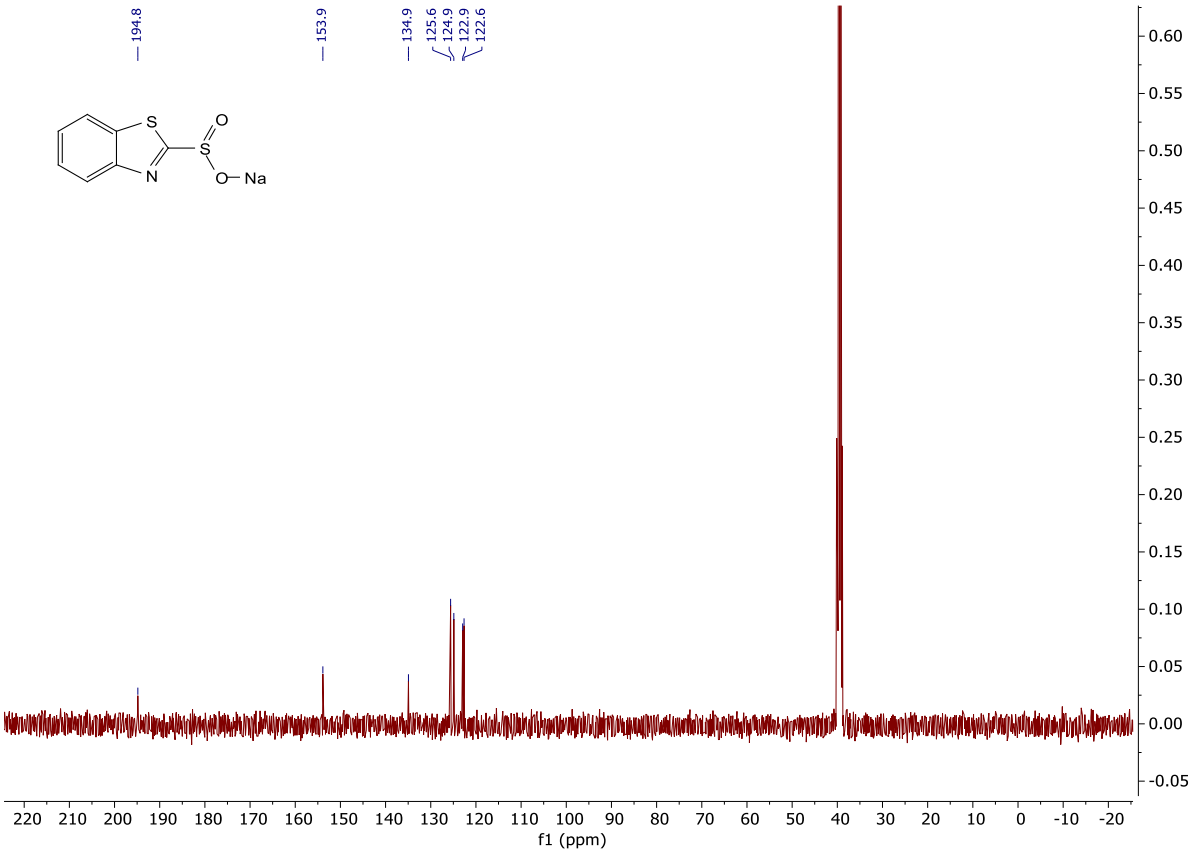
List of appendices

Appendix A - Copy of ^{1}H, ^{13}C and ^{19}F spectra

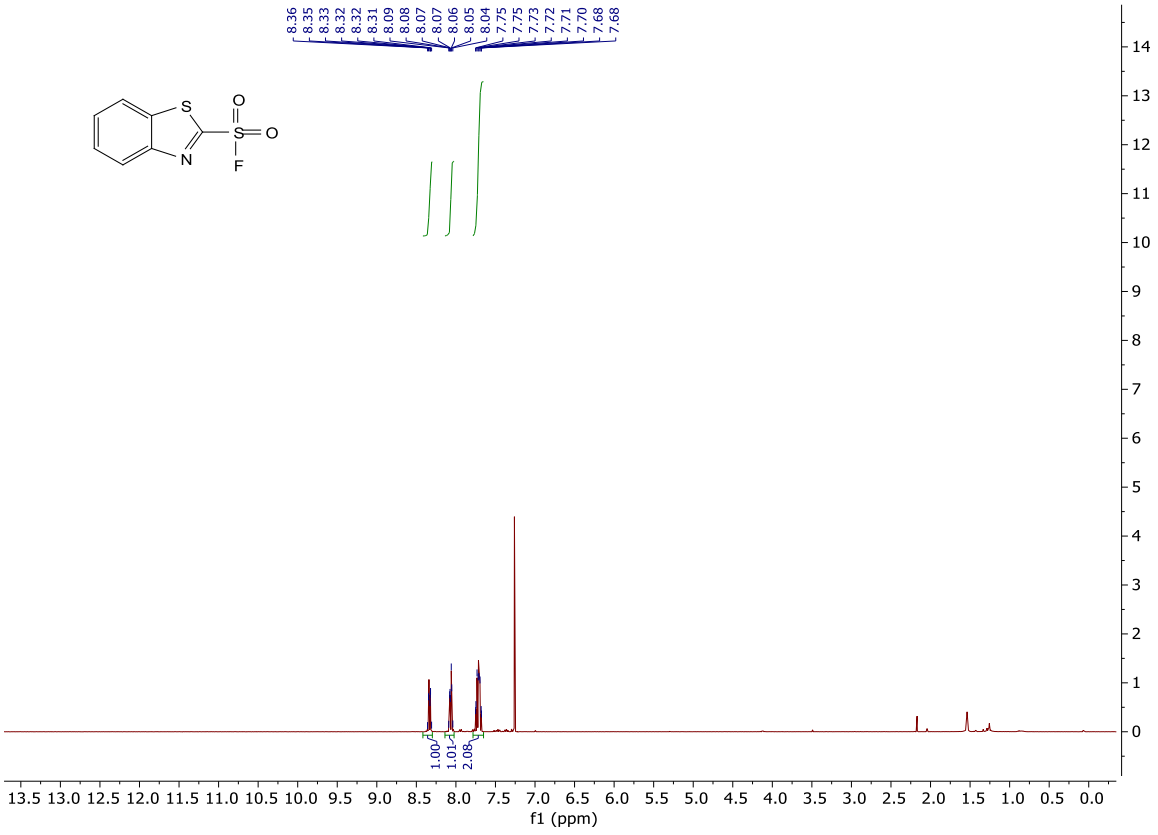
^{1}H NMR (400 MHz, DMSO) methyl benzo[d]thiazole-2-sulfinate (4-1)



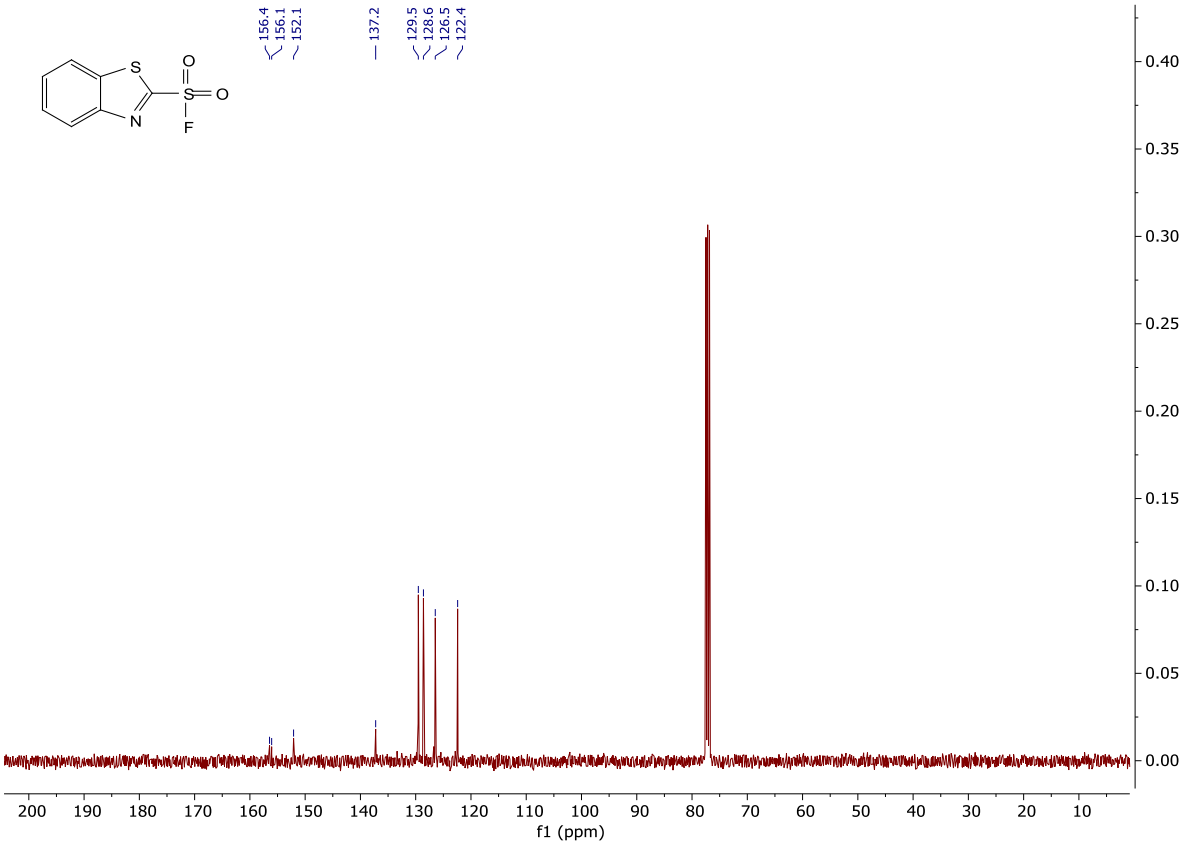
^{13}C {^{1}H} NMR (101 MHz, DMSO) of methyl benzo[d]thiazole-2-sulfinate (4-1)



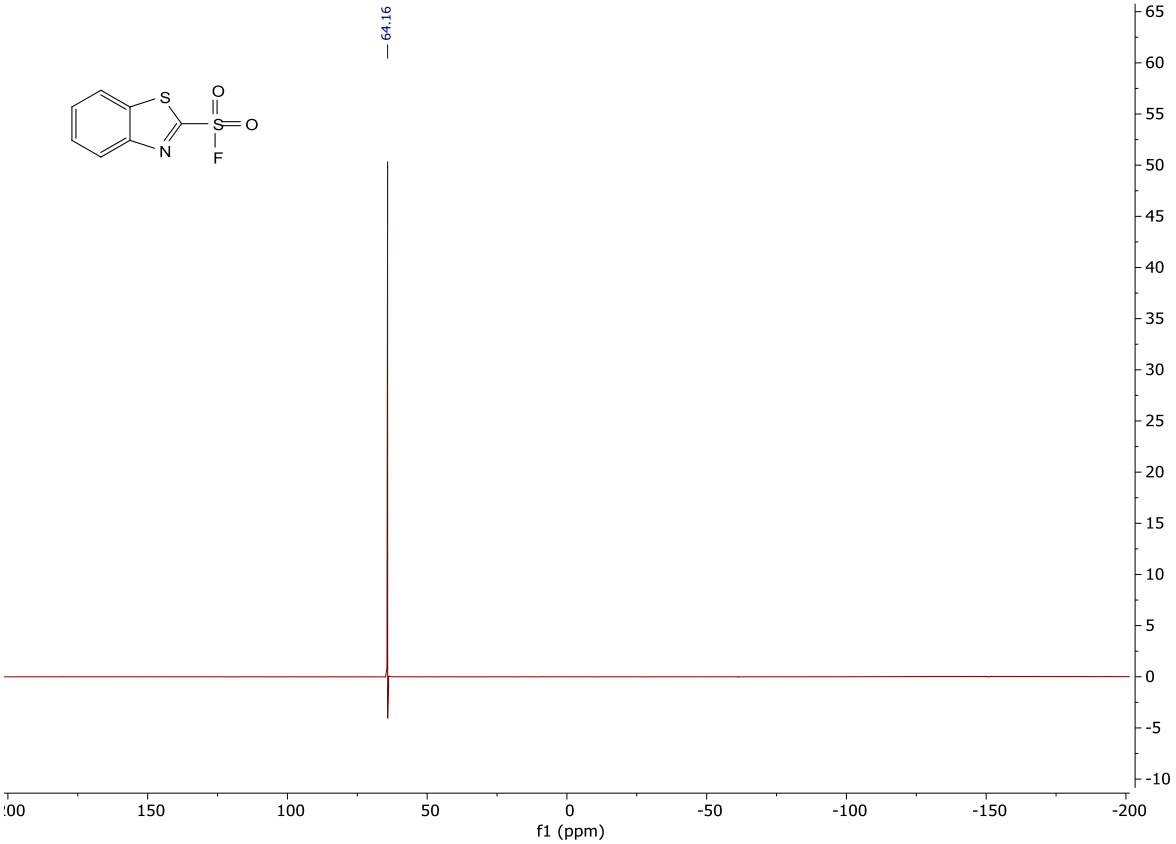
^{1}H NMR (400 MHz, $CDCl_3$) of benzo[d]thiazole-2-sulfonyl fluoride (4-2)



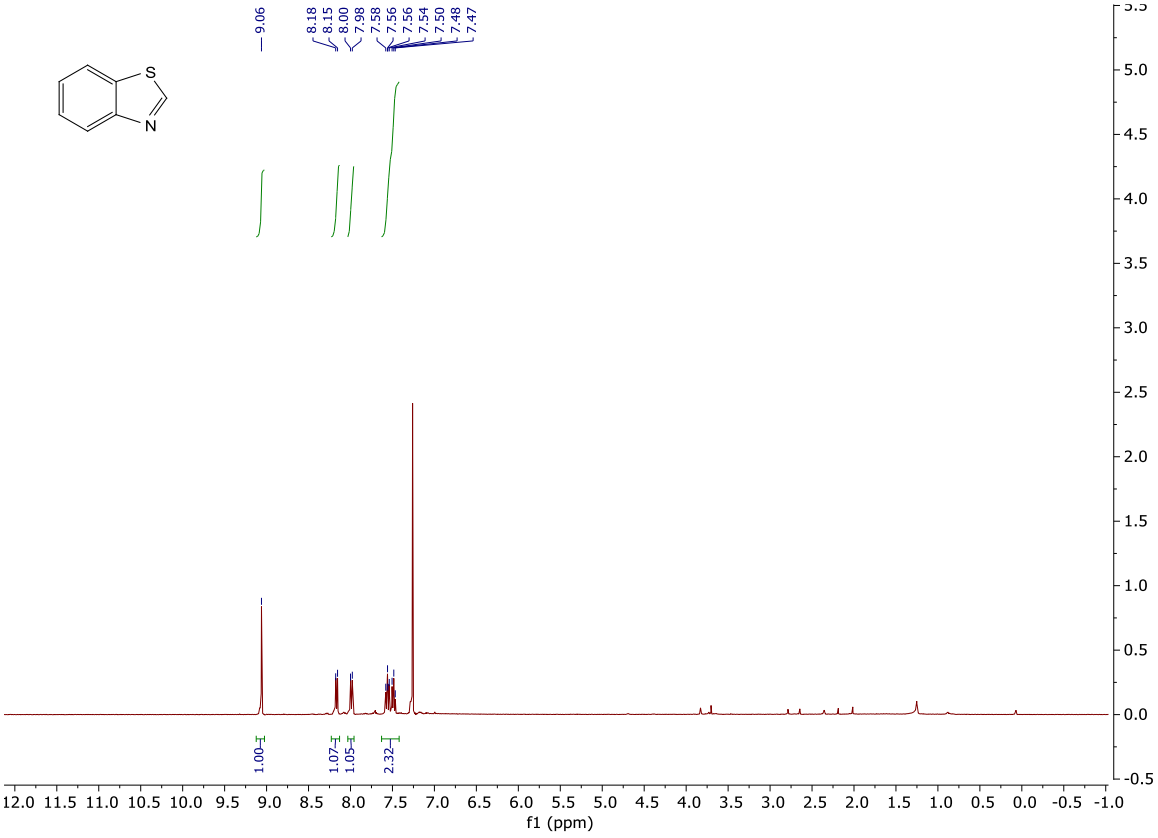
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of benzo[d]thiazole-2-sulfonyl fluoride (4-2)



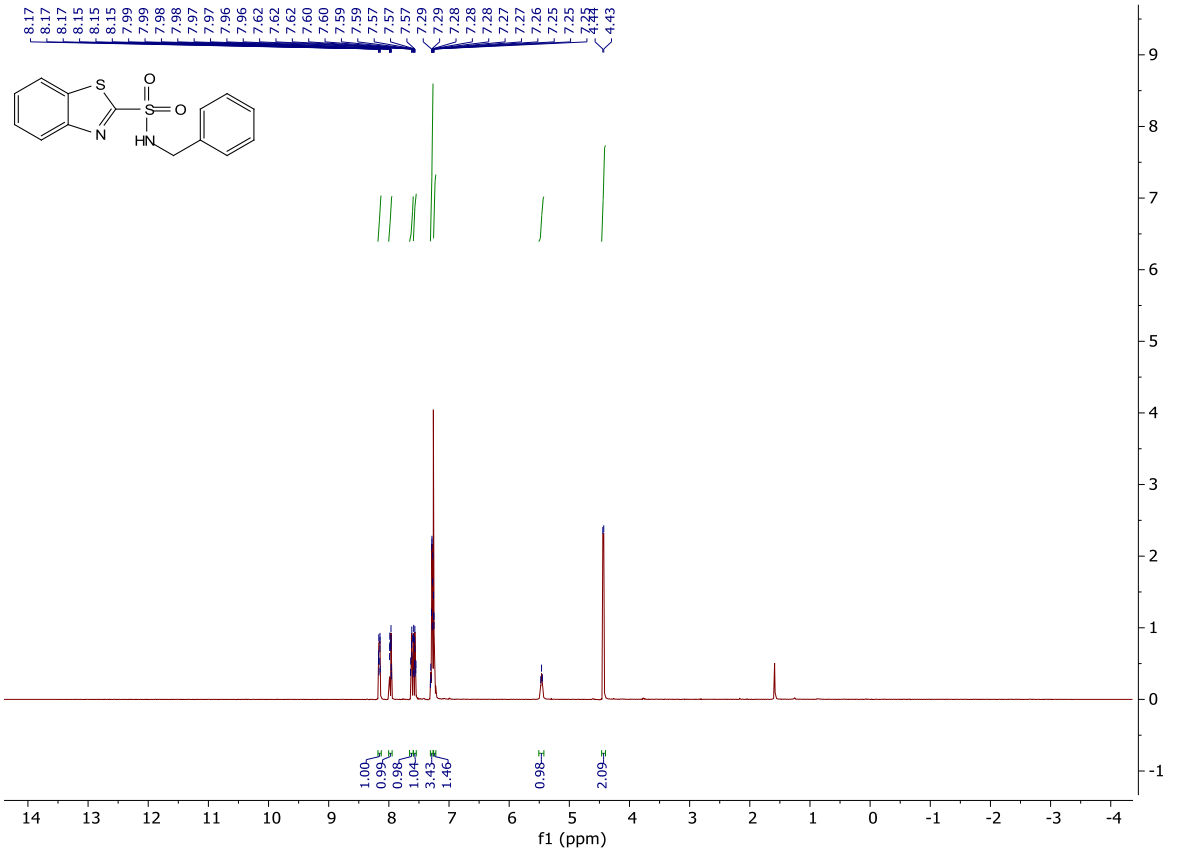
^{19}F NMR (376 MHz, $CDCl_3$) of benzo[d]thiazole-2-sulfonyl fluoride (4-2)



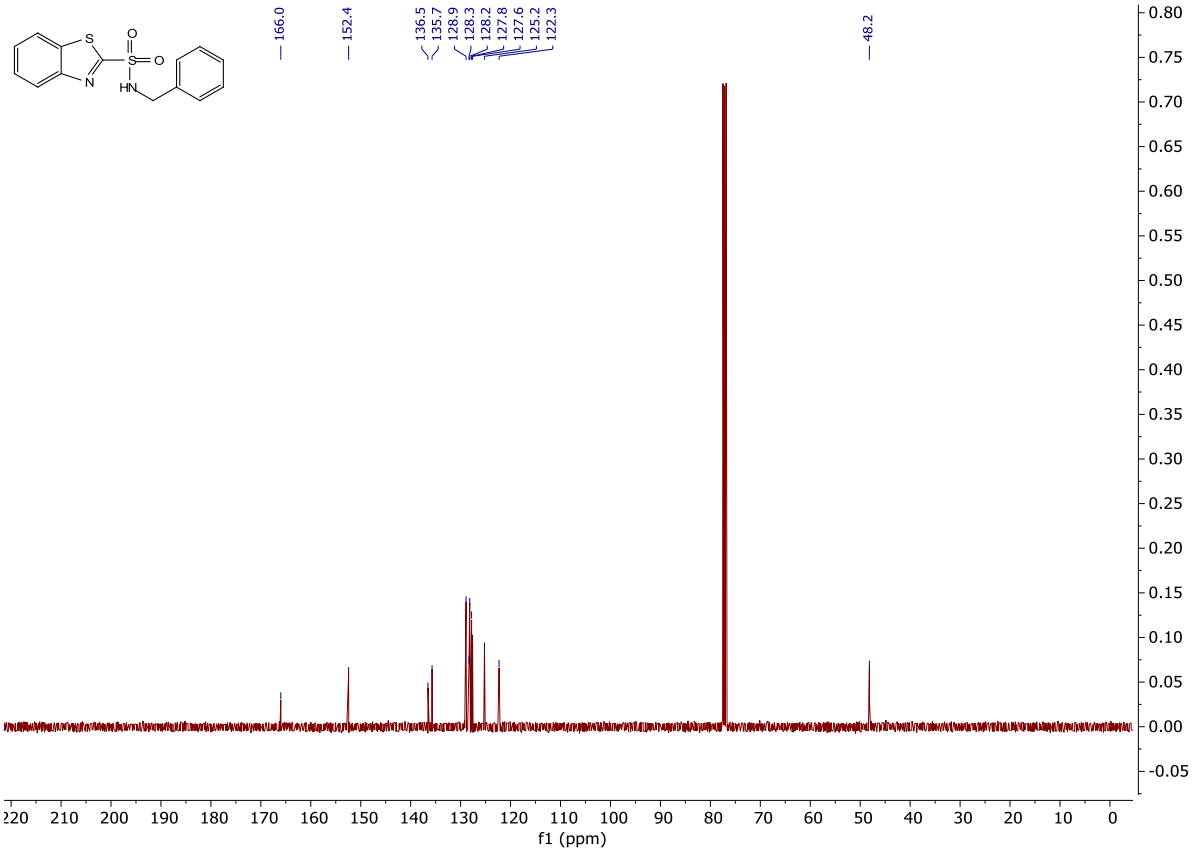
^{1}H NMR (400 MHz, $CDCl_3$) of benzo[d]thiazole (4-3)



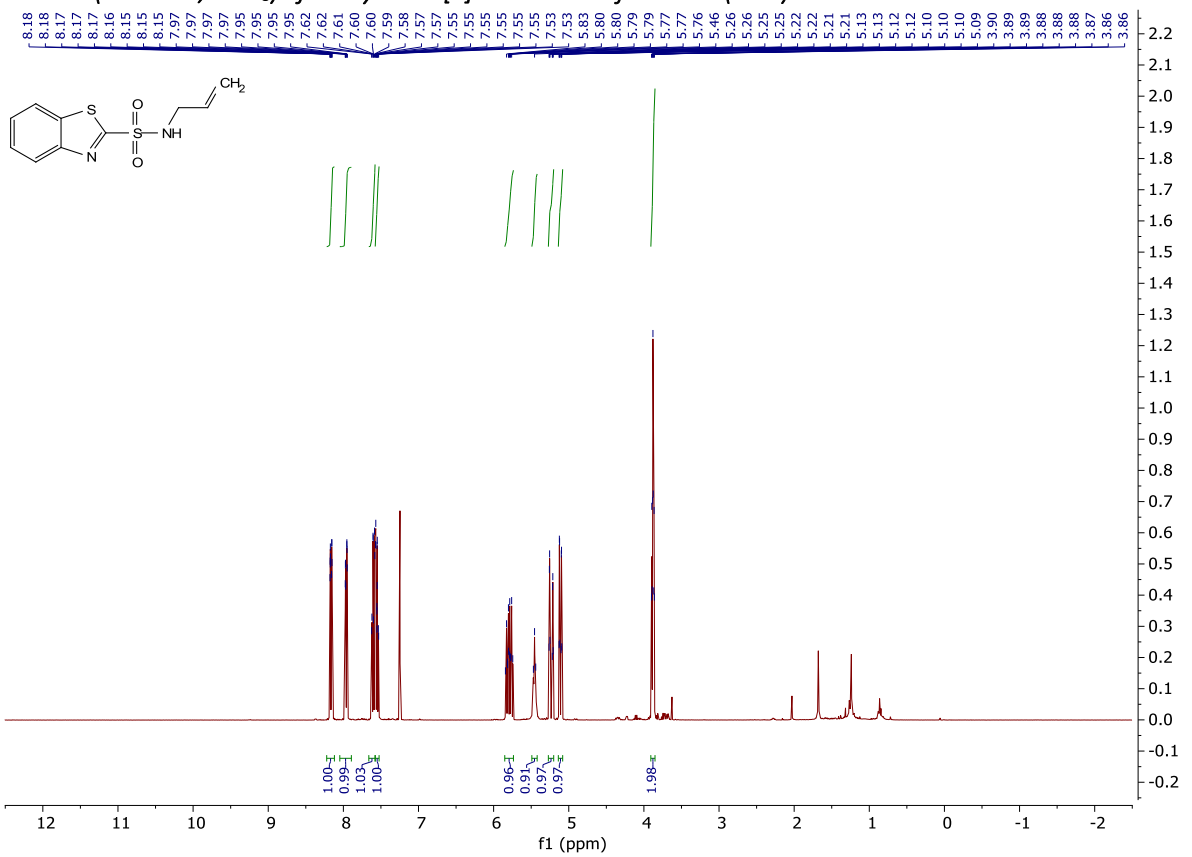
^{1}H NMR (400 MHz, $CDCl_3$) of N-benzylbenzo[d]thiazole-2-sulfonamide (4-6a)



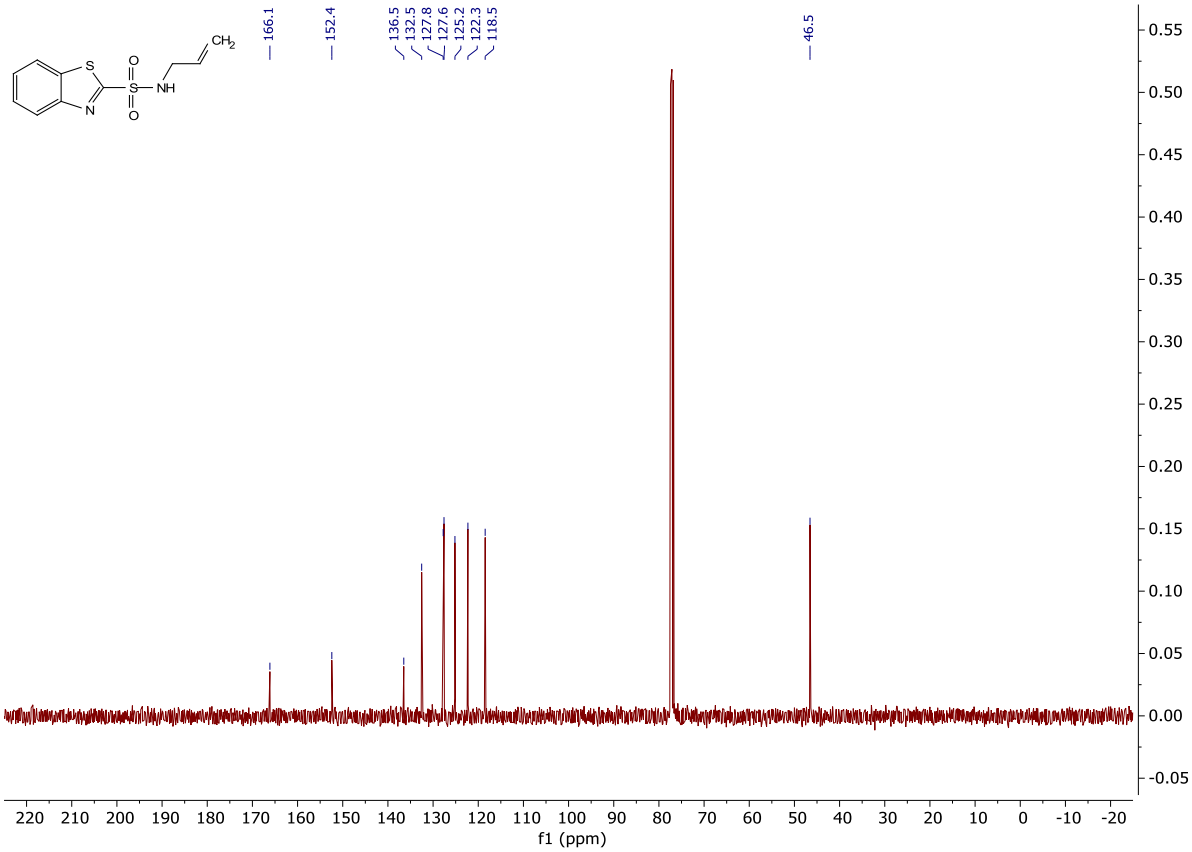
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-benzylbenzo[d]thiazole-2-sulfonamide (4-6a)



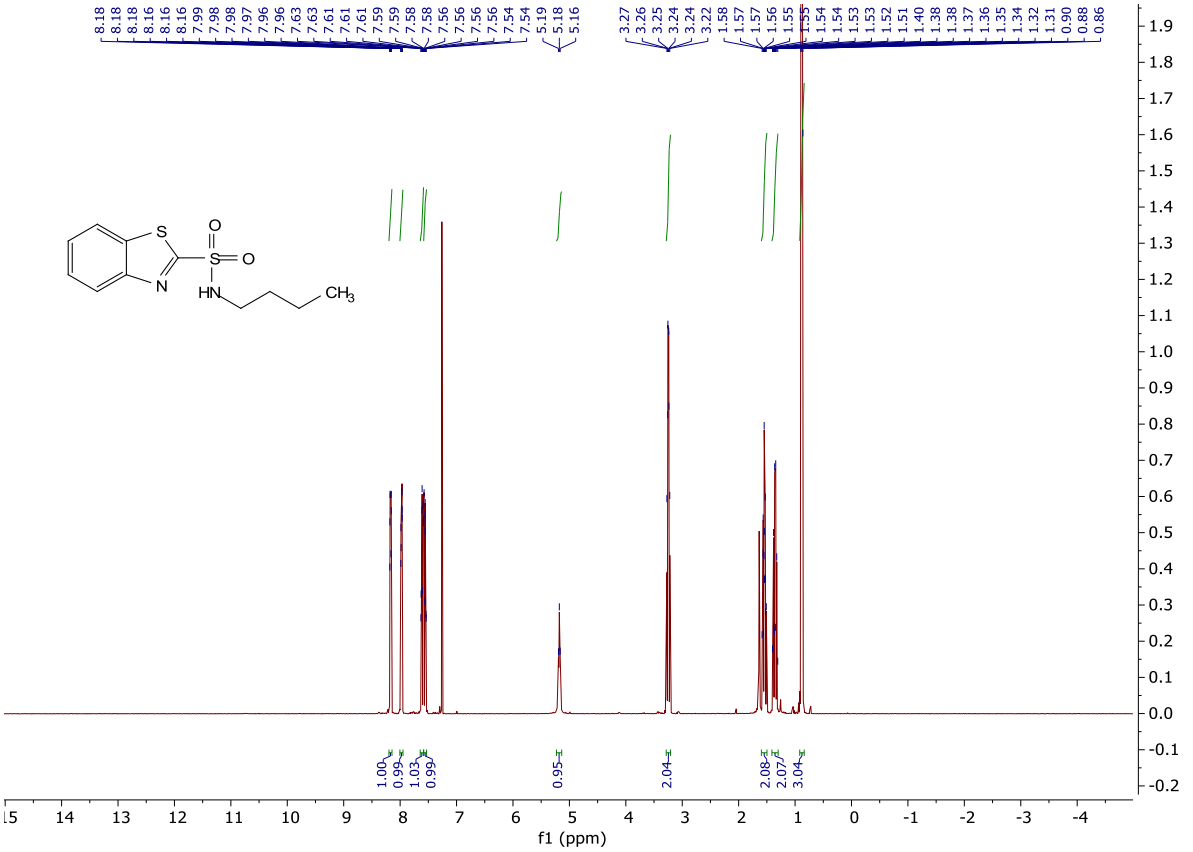
^{1}H NMR (400 MHz, $CDCl_3$) of N-allylbenzo[d]thiazole-2-sulfonamide (4-6b)



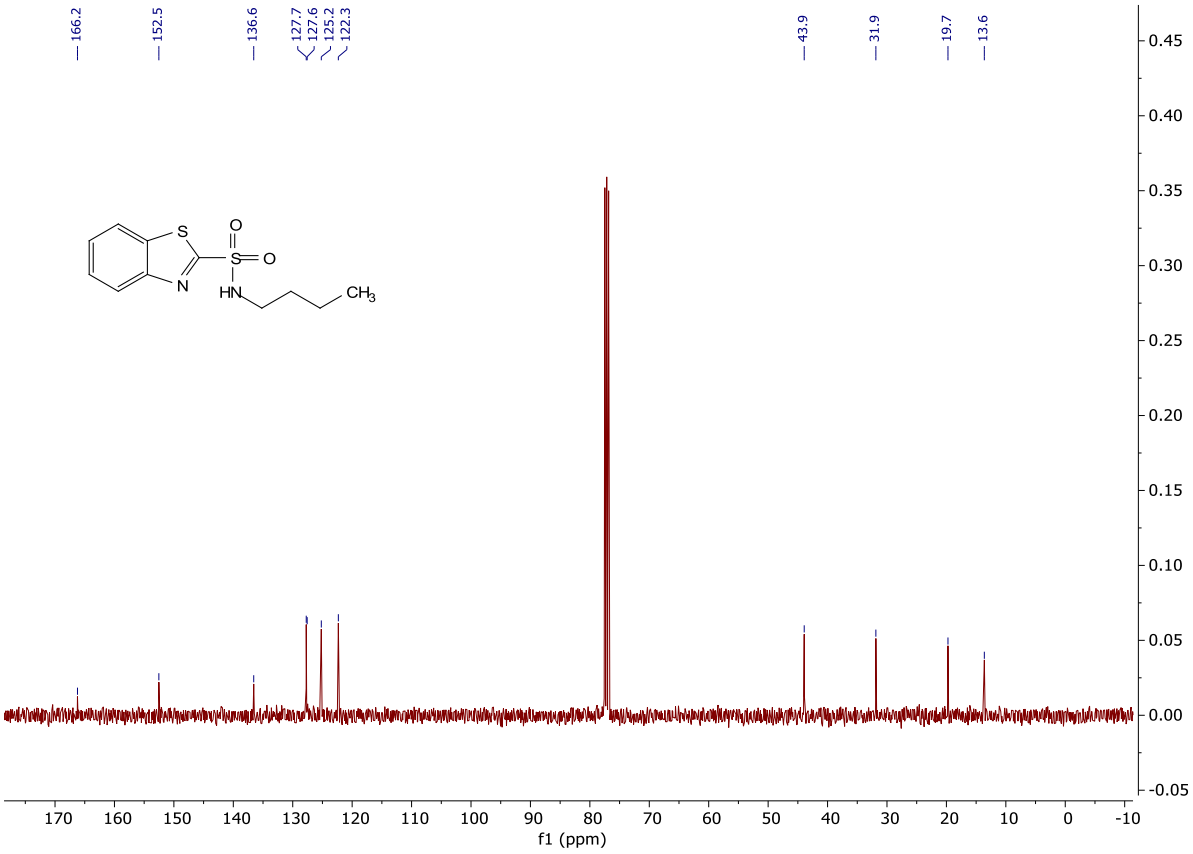
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-allylbenzo[d]thiazole-2-sulfonamide (4-6b)



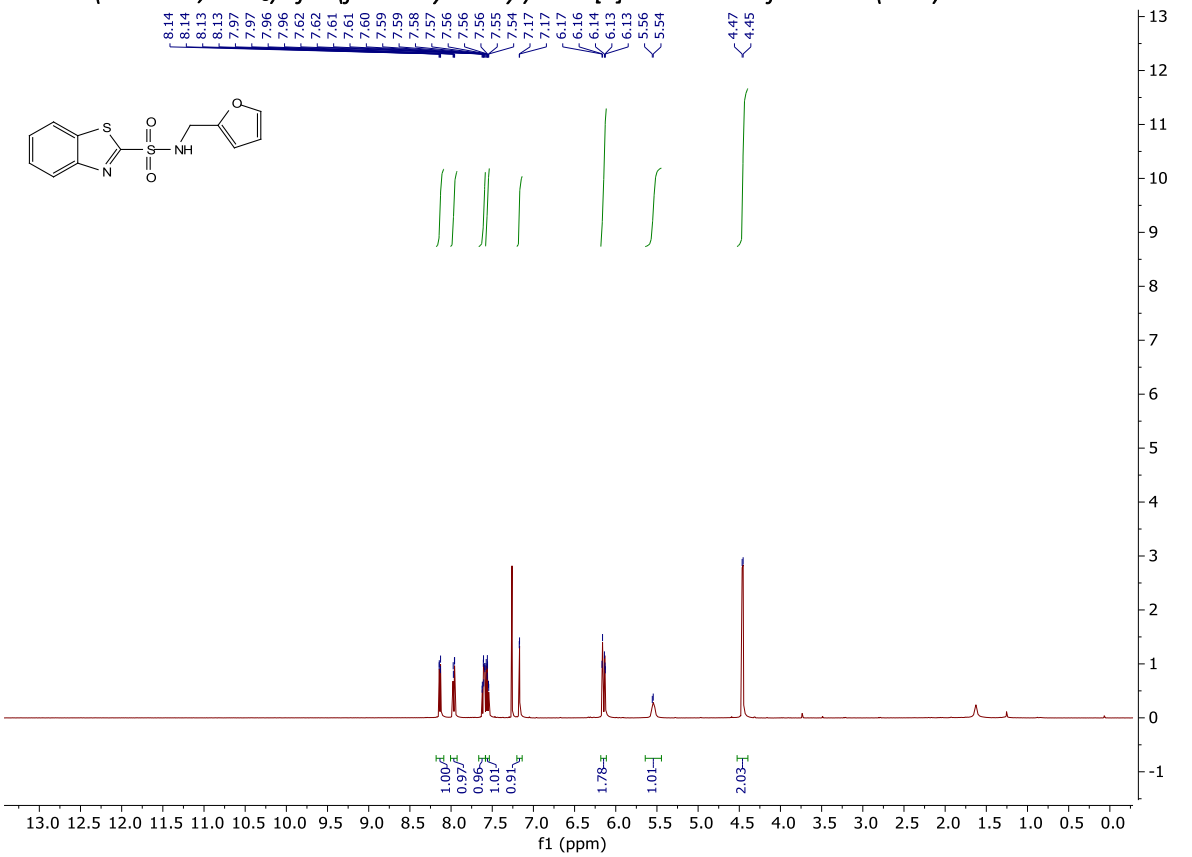
^{1}H NMR (400 MHz, $CDCl_3$) of N-butylbenzo[d]thiazole-2-sulfonamide (4-6c)



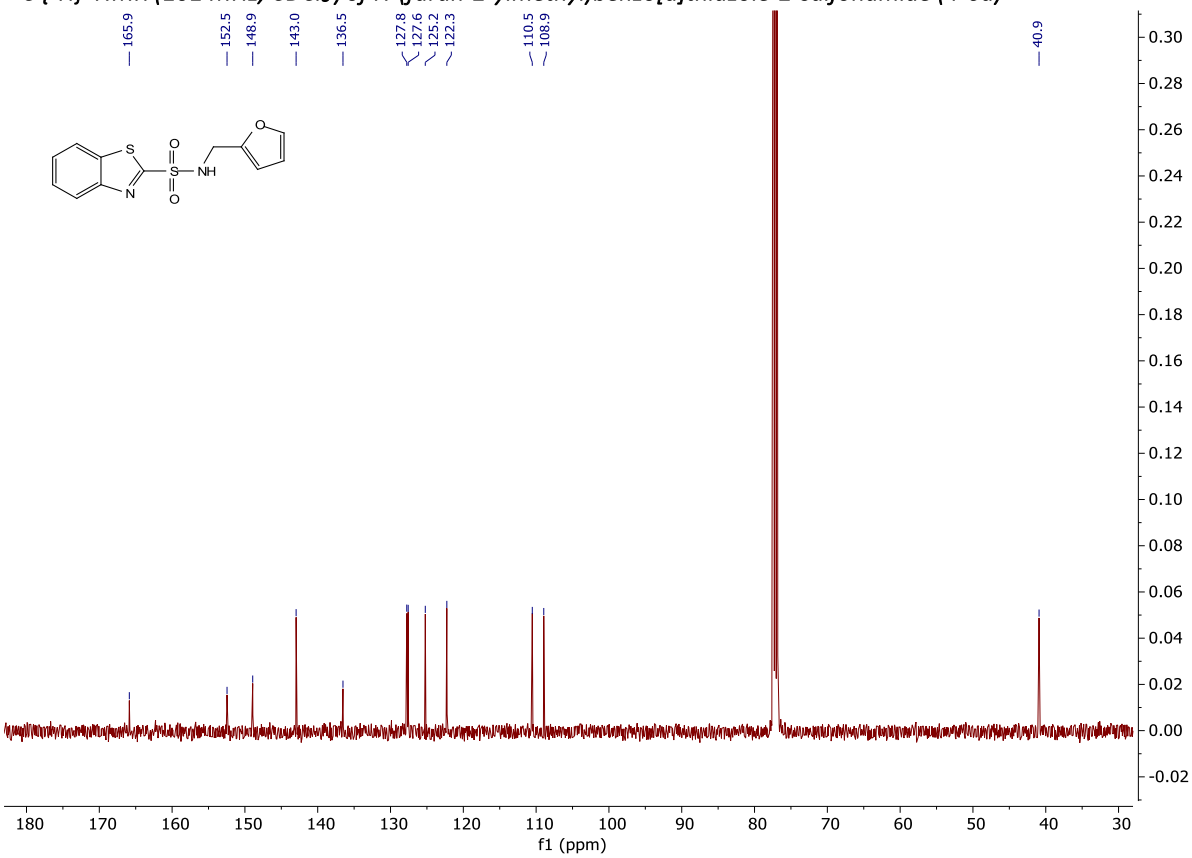
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-butylbenzo[d]thiazole-2-sulfonamide (4-6c)



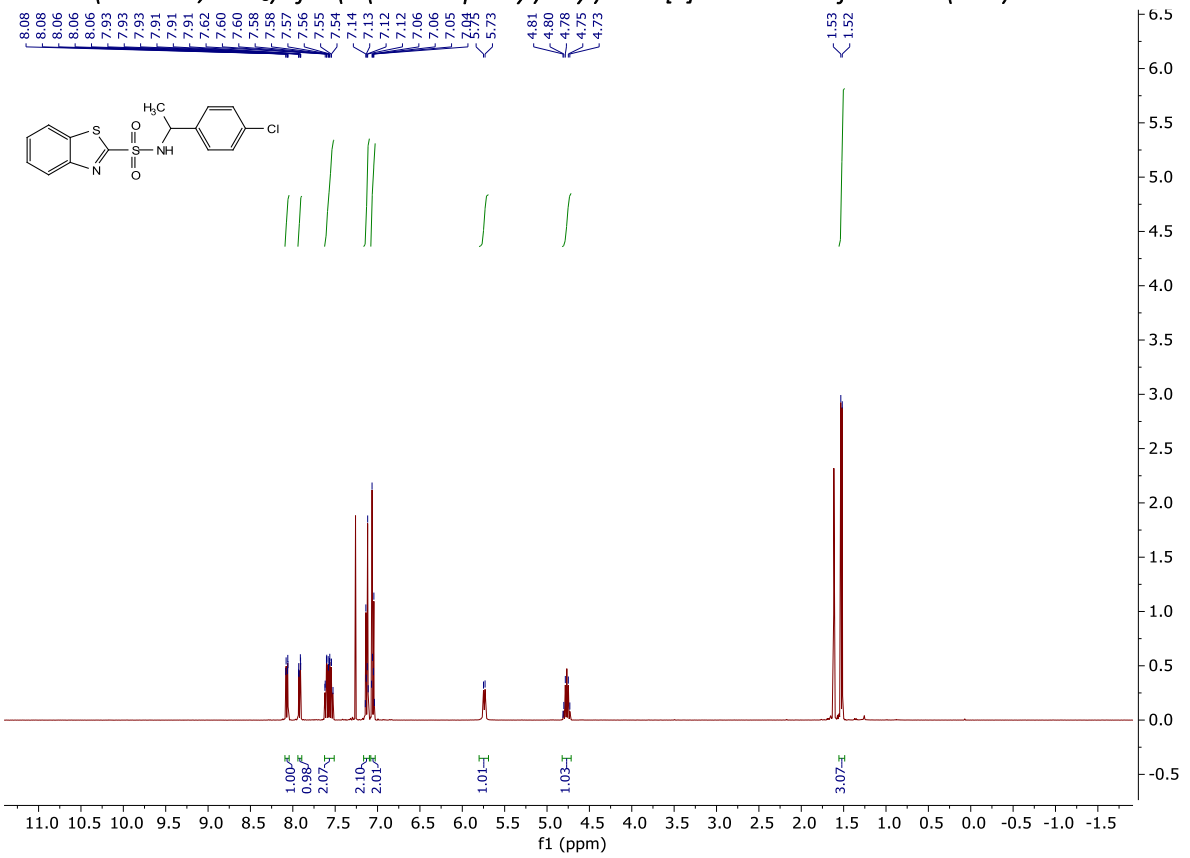
^{1}H NMR (400 MHz, $CDCl_3$) of N-(furan-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (4-6d)



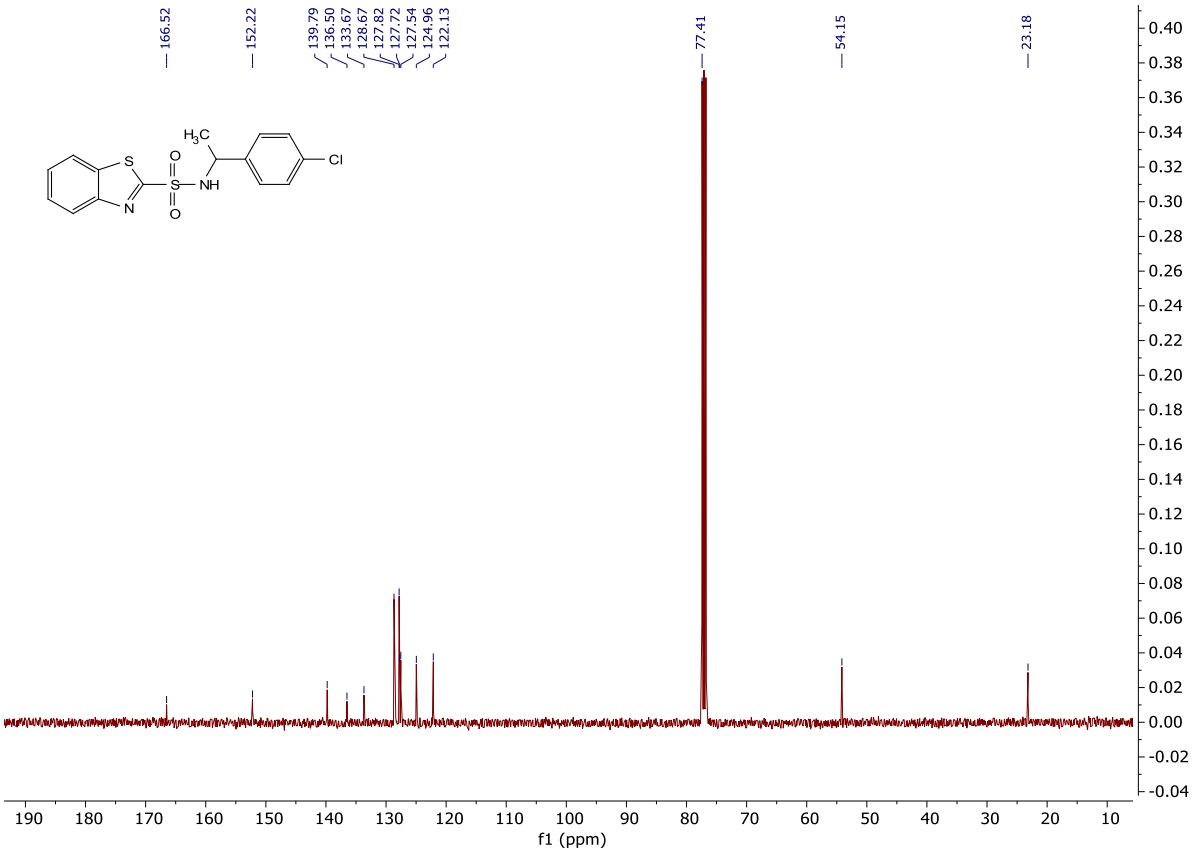
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-(furan-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (4-6d)



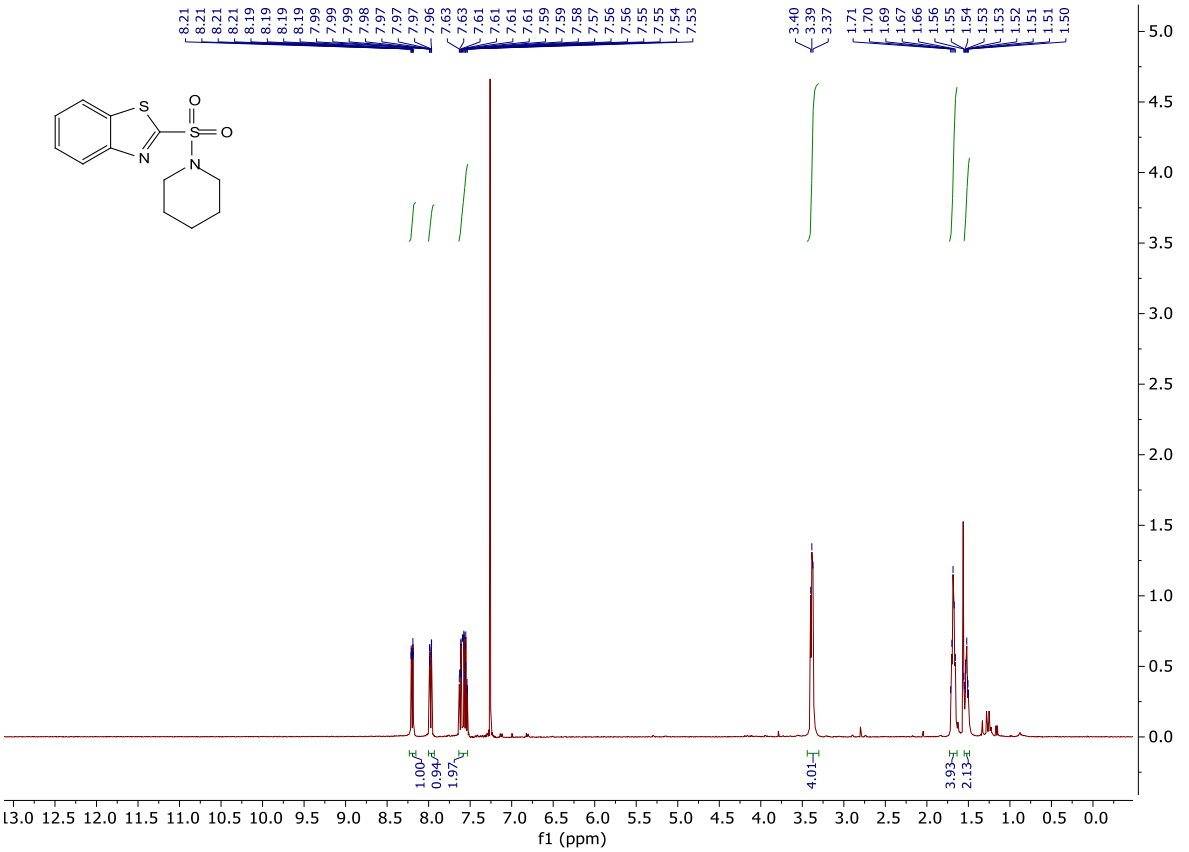
^{1}H NMR (400 MHz, $CDCl_3$) of N-(1-(4-chlorophenyl)ethyl)benzo[d]thiazole-2-sulfonamide (4-6e)



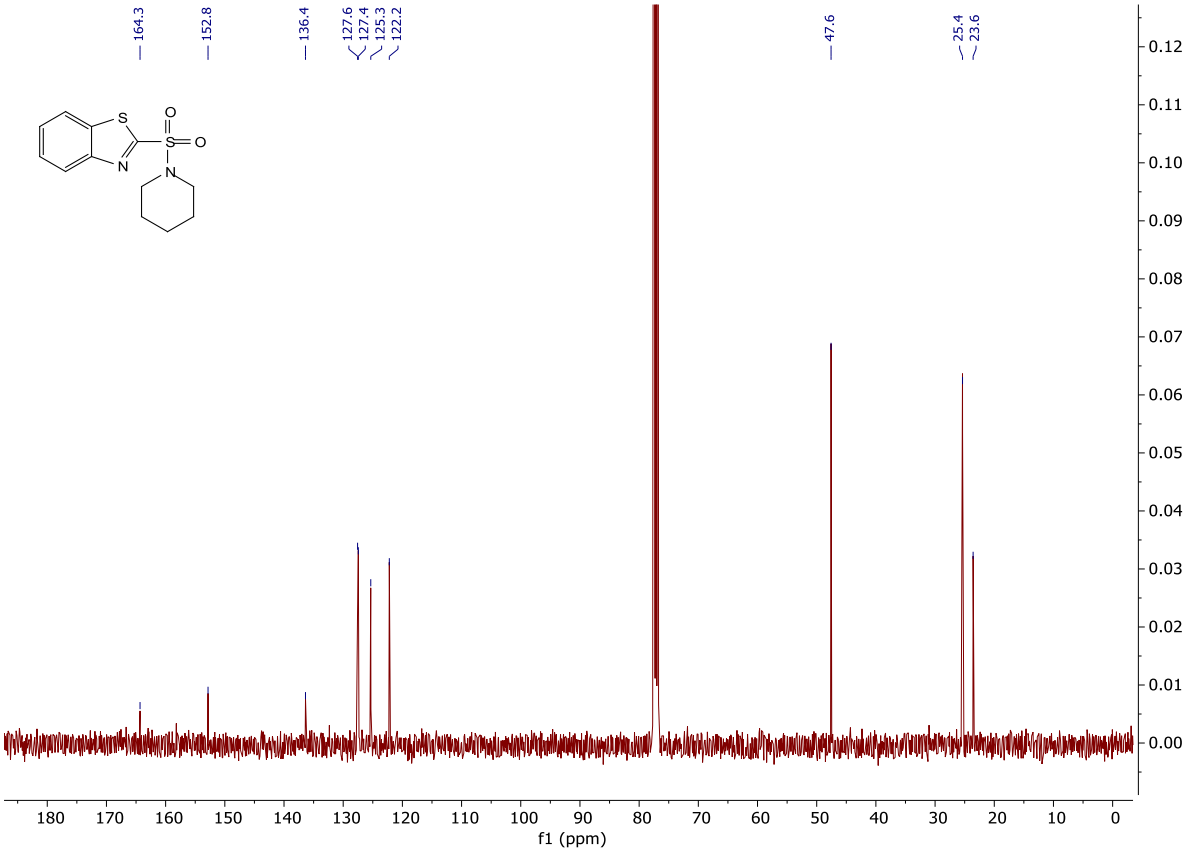
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-(1-(4-chlorophenyl)ethyl)benzo[d]thiazole-2-sulfonamide (4-6e)



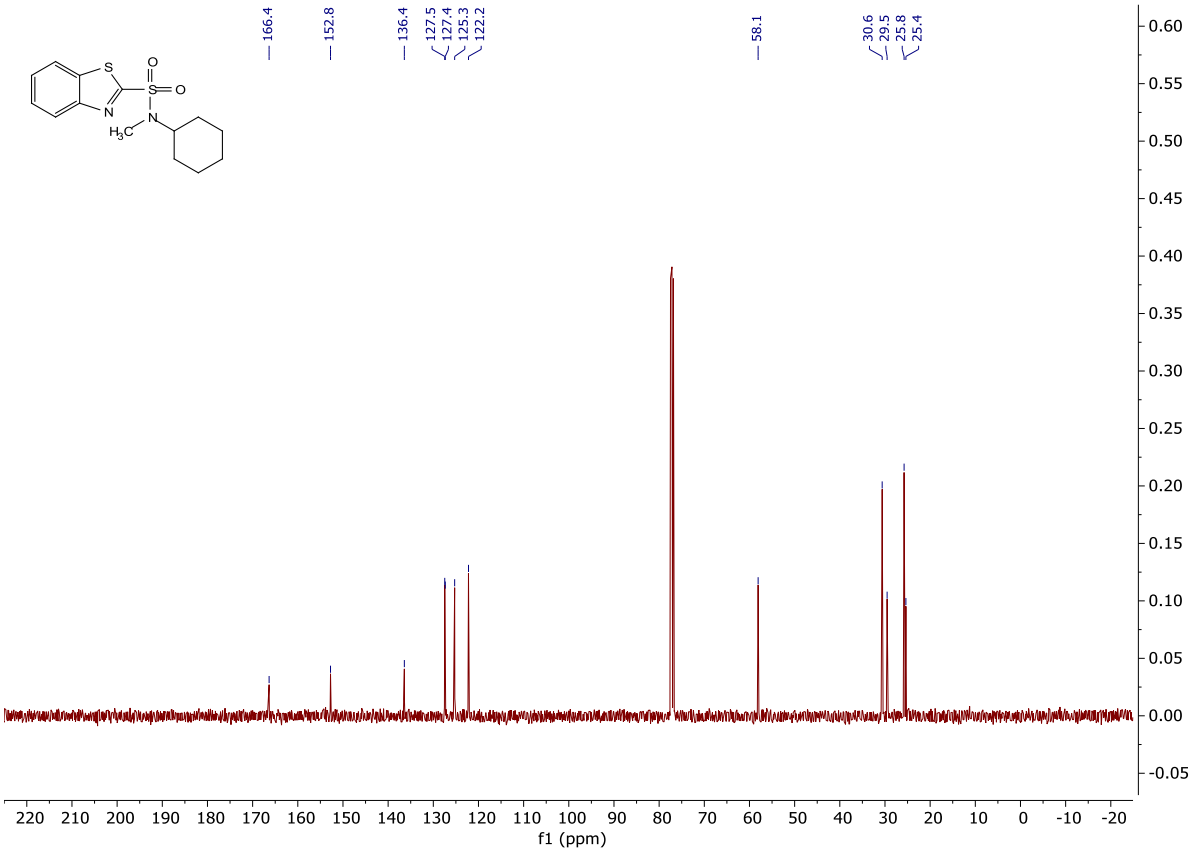
^{1}H NMR (400 MHz, $CDCl_3$) of 2-(piperidin-1-ylsulfonyl)benzo[d]thiazole (4-6f)



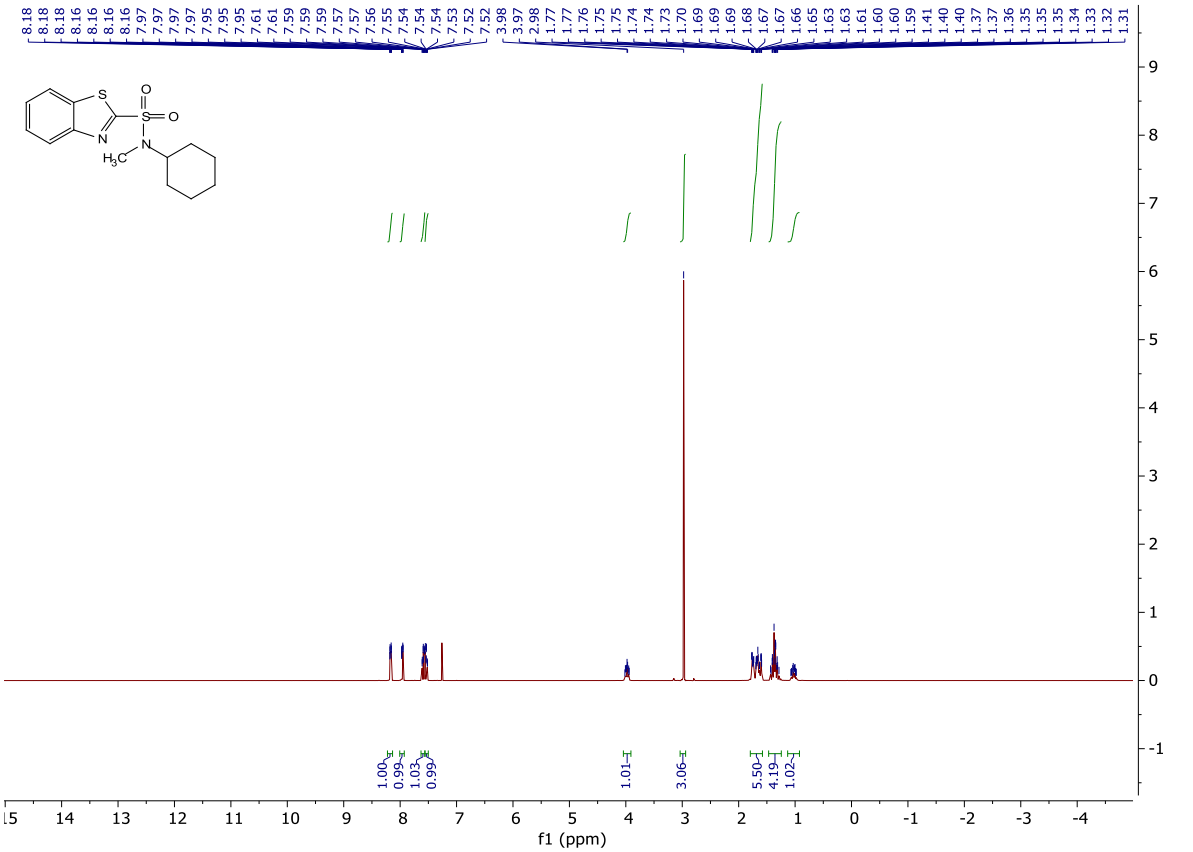
^{113}C {^{1}H} NMR (101 MHz, $CDCl_3$) of 2-(piperidin-1-ylsulfonyl)benzo[d]thiazole (4-6f)



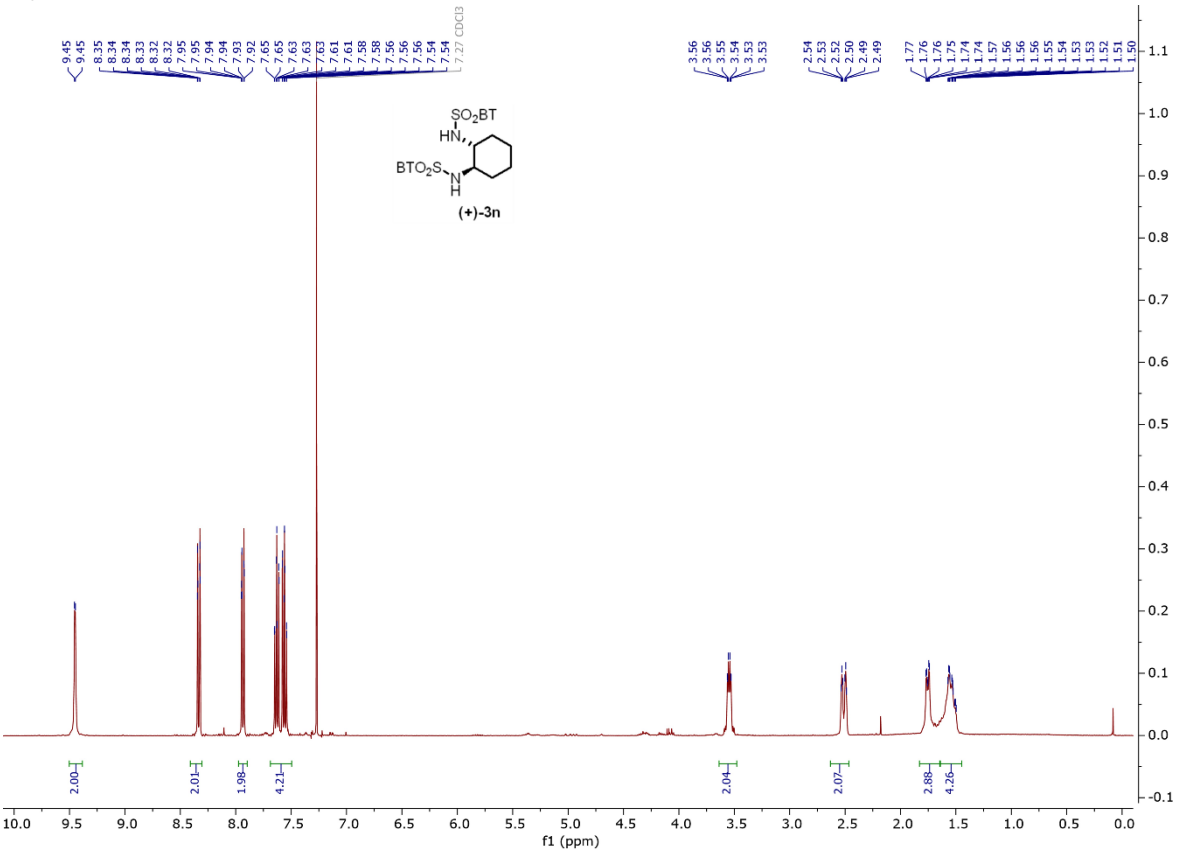
$^{13}C\ \{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of N-cyclohexyl-N-methylbenzo[d]thiazole-2-sulfonamide (4-6g)



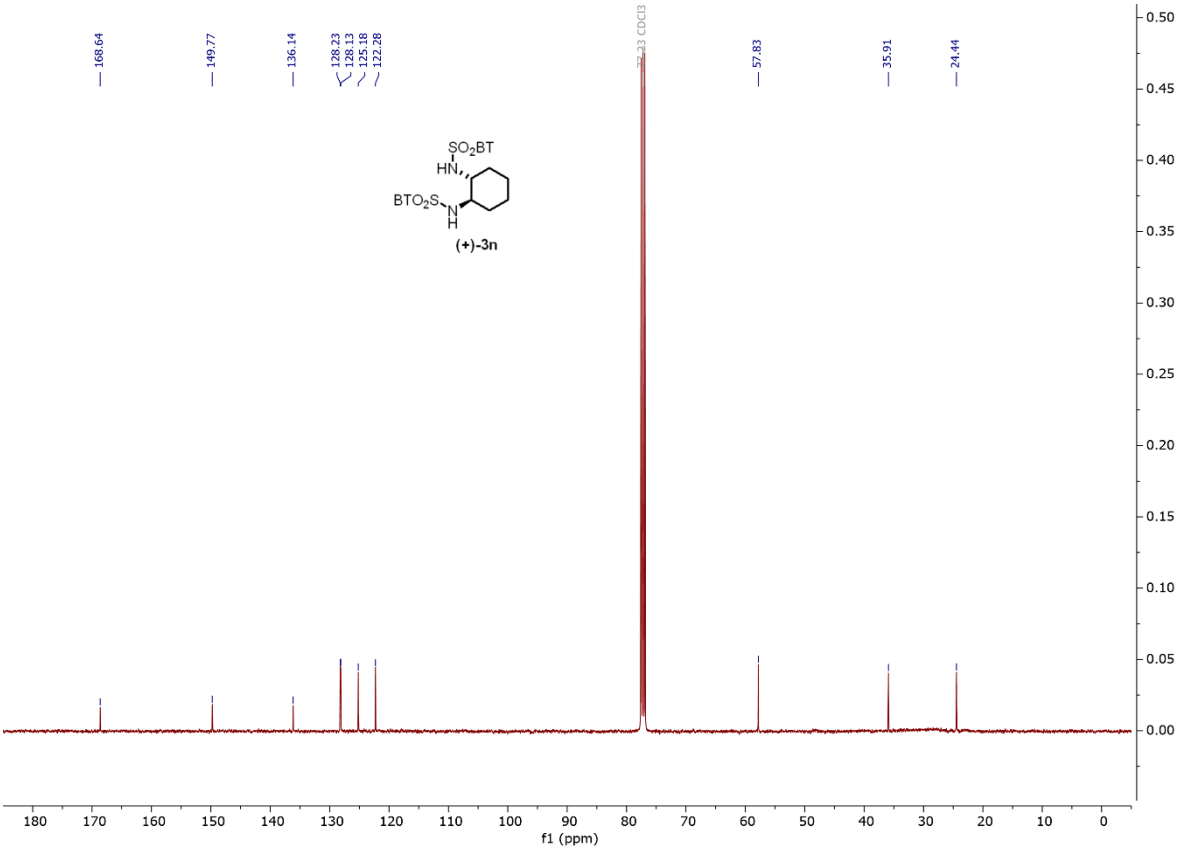
^{1}H NMR (400 MHz, $CDCl_3$) of N-cyclohexyl-N-methylbenzo[d]thiazole-2-sulfonamide (4-6g)



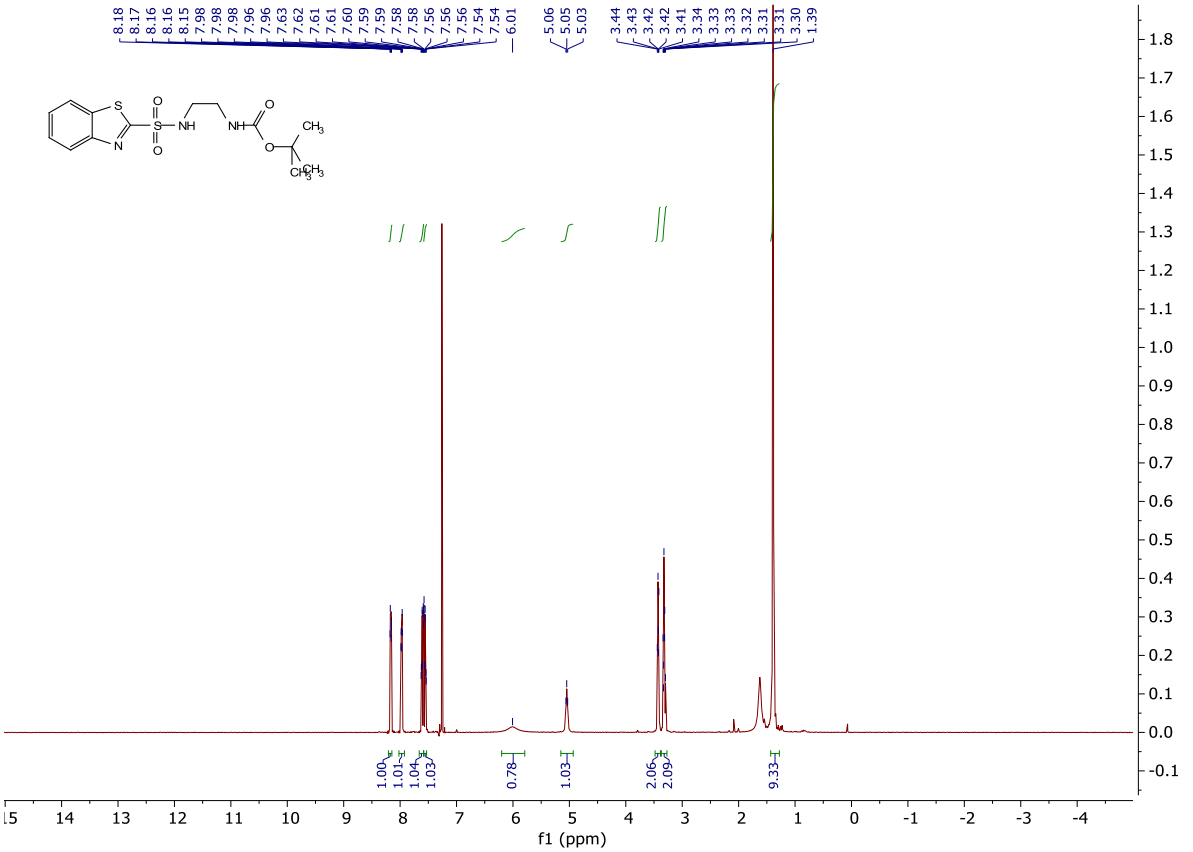
^{1}H NMR (400 MHz, $CDCl_3$) of (+)-N-((1R,2R)-2-(benzo[d]thiazole-2-sulfonamido)cyclohexyl)benzo[d]thiazole-2-sulfonamide (4-6h)



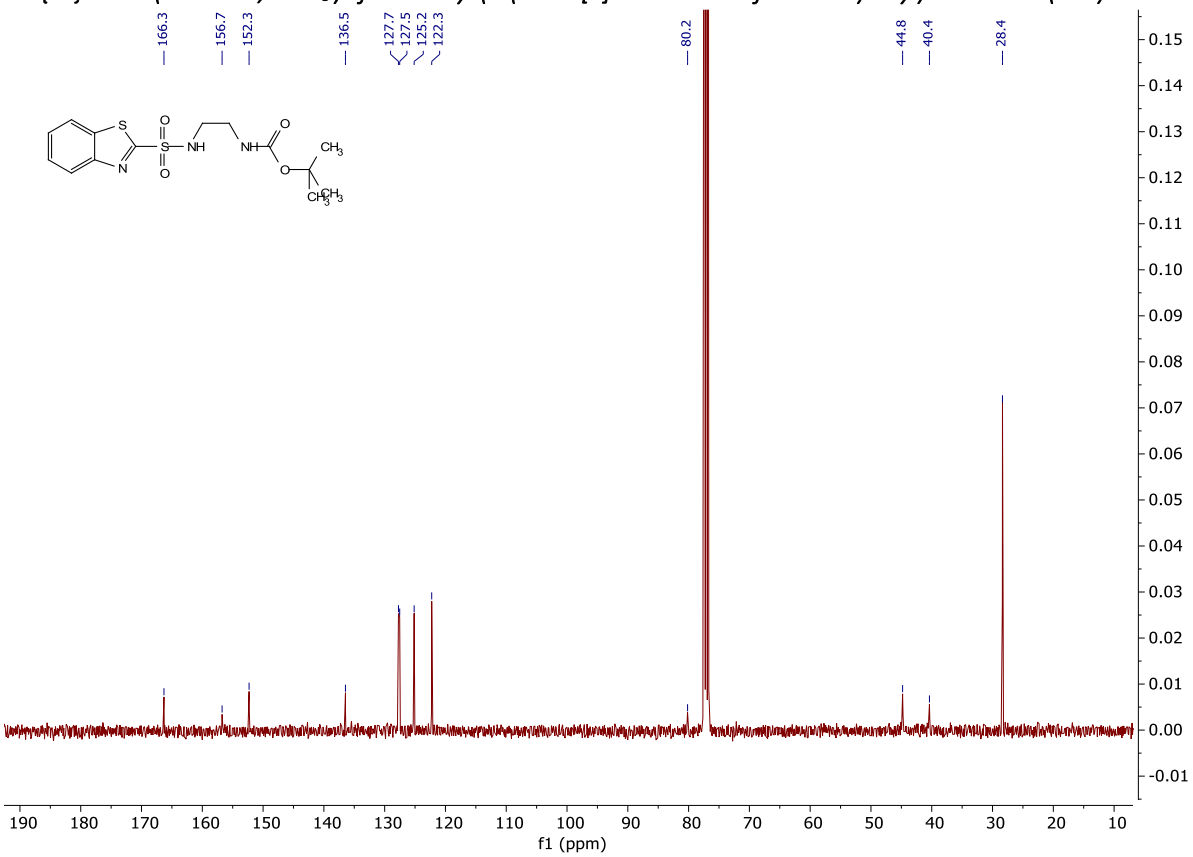
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of (+)-N-((1R,2R)-2-(benzo[d]thiazole-2-sulfonamido)cyclohexyl)benzo[d]thiazole-2-sulfonamide (4-6h)



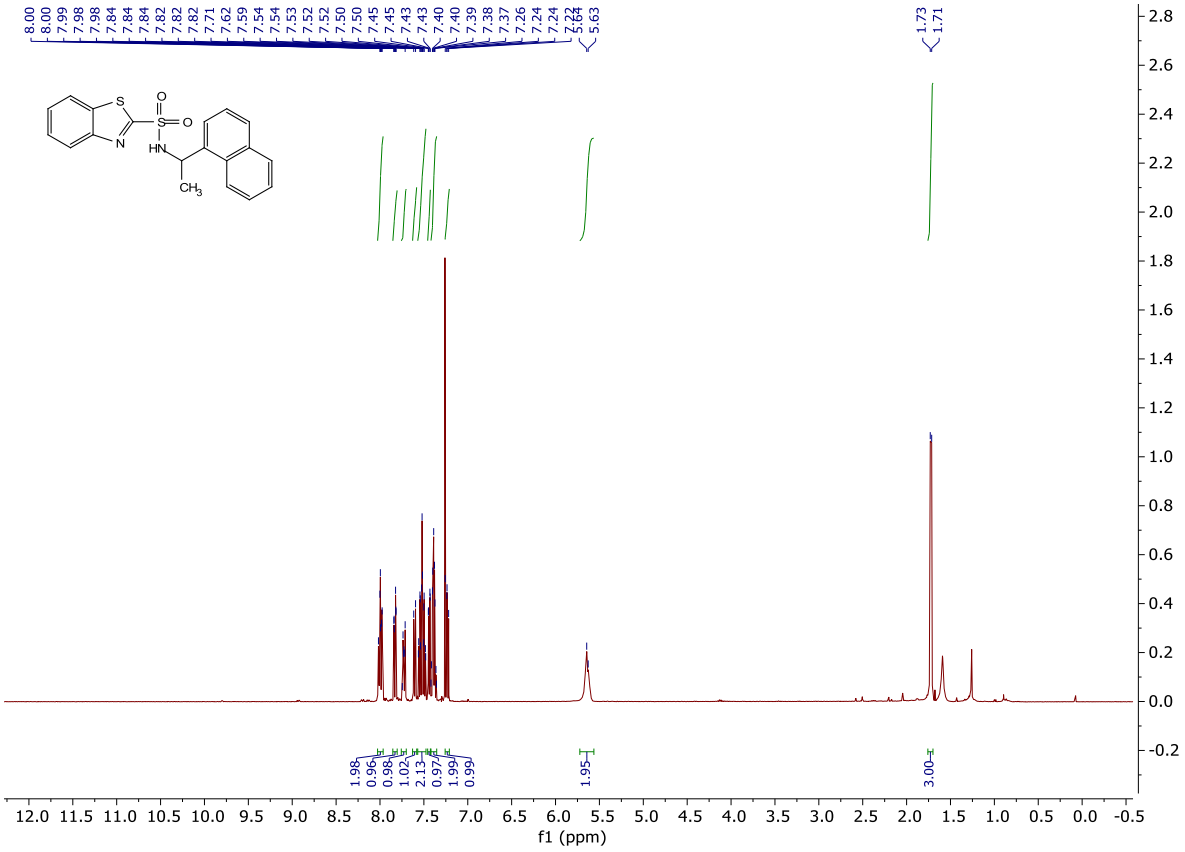
^{1}H NMR (400 MHz, $CDCl_3$) of tert-butyl (2-(benzo[d]thiazole-2-sulfonamido)ethyl)carbamate (4-6i)



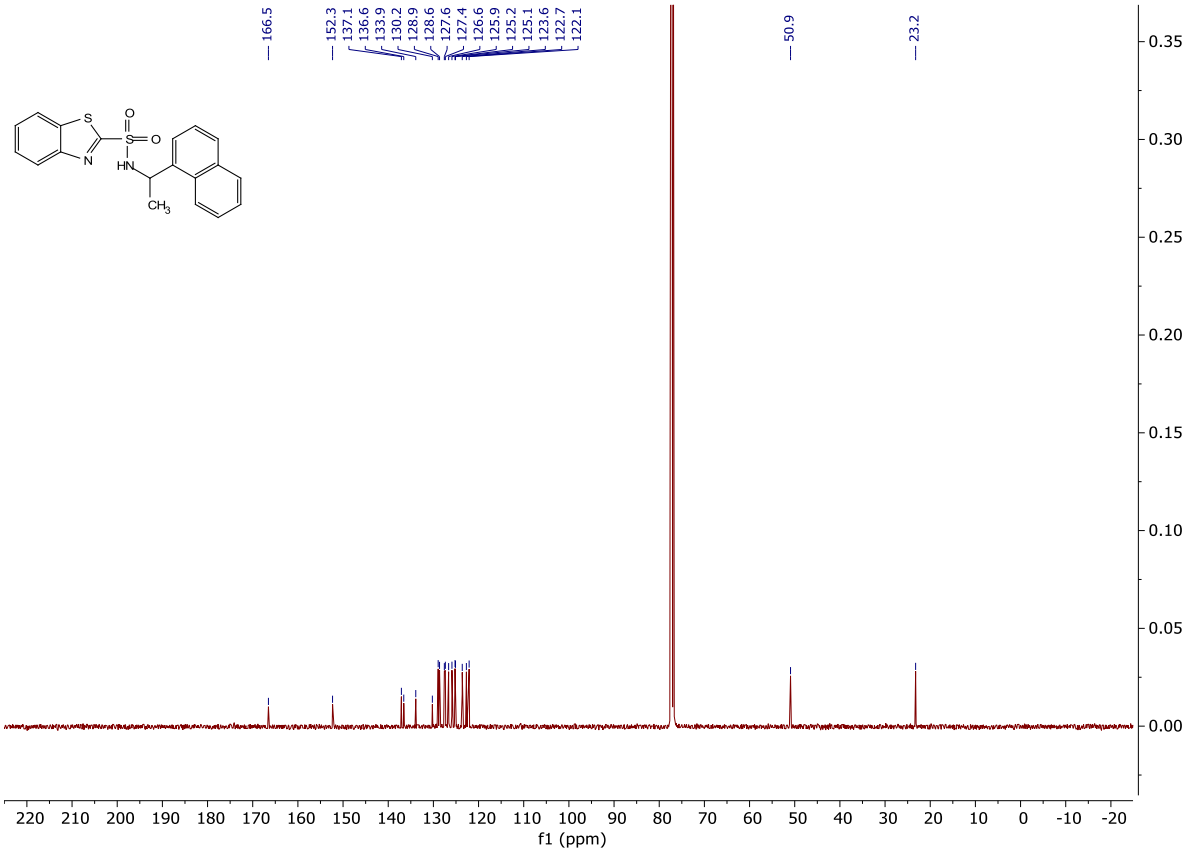
$^{13}C\ \{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of tert-butyl (2-(benzo[d]thiazole-2-sulfonamido)ethyl)carbamate (4-6i)



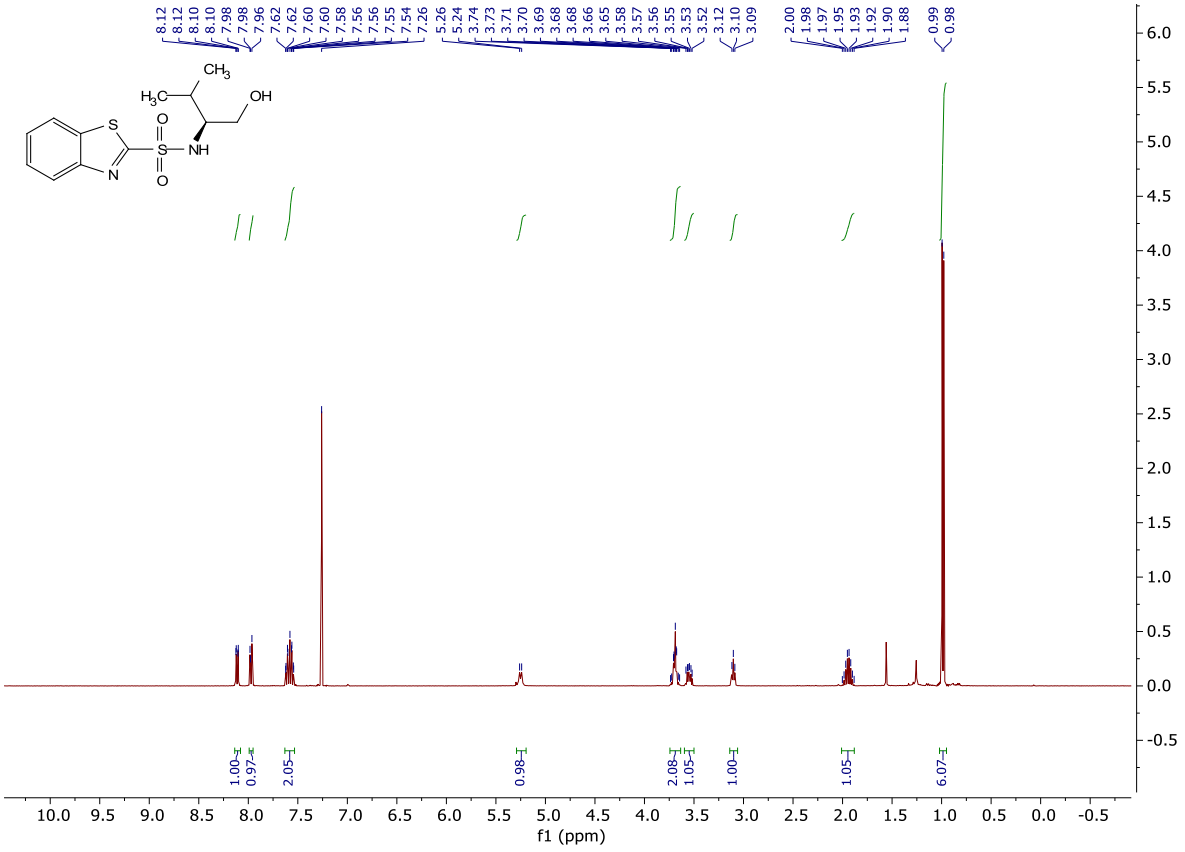
^{1}H NMR (400 MHz, $CDCl_3$) of N-(1-(naphthalen-1-yl)ethyl)benzo[d]thiazole-2-sulfonamide (4-6j)



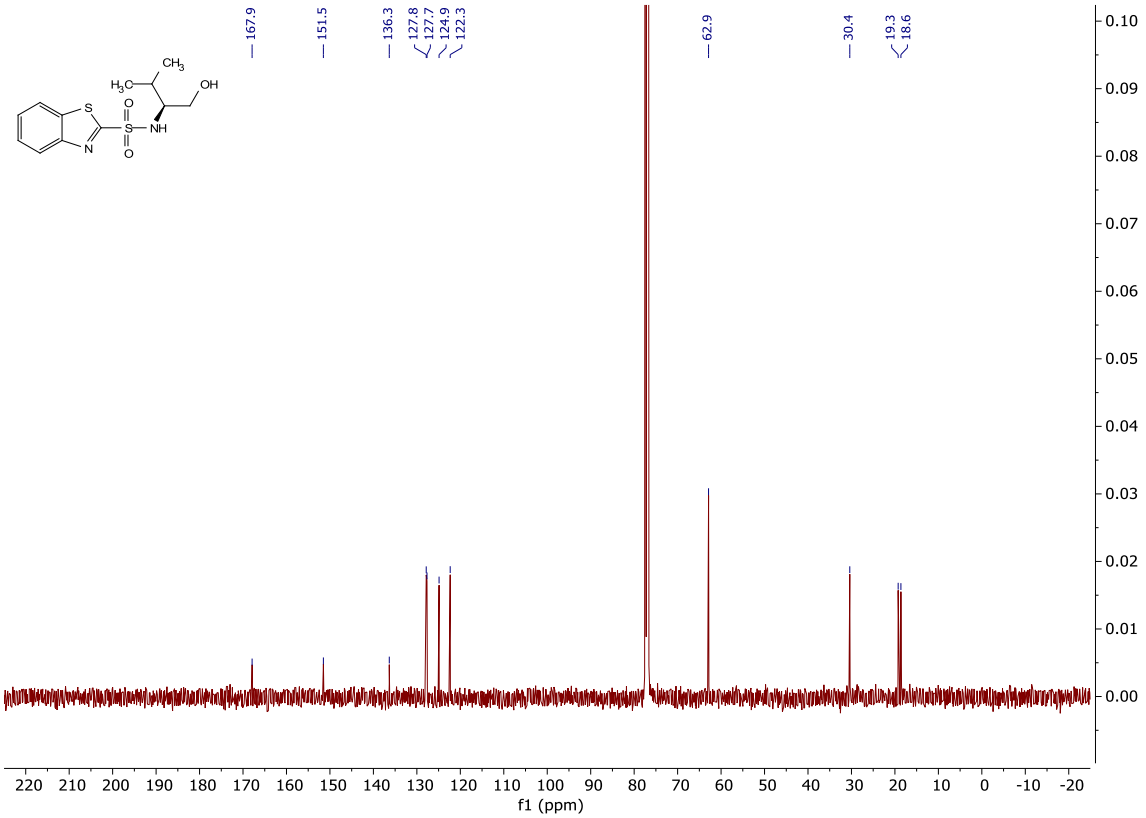
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-(1-(naphthalen-1-yl)ethyl)benzo[d]thiazole-2-sulfonamide (4-6j)



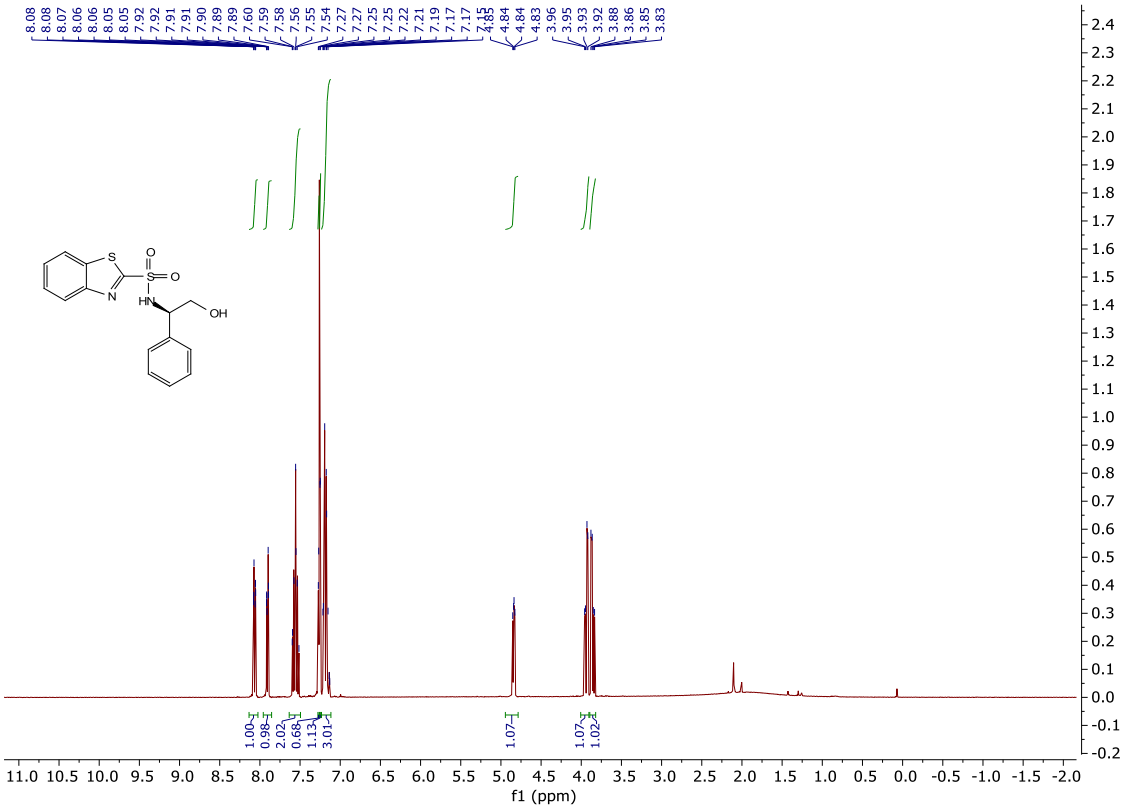
^{1}H NMR (400 MHz, CDCl$_3$) of (S)-N-(1-hydroxy-3-methylbutan-2-yl)benzo[d]thiazole-2-sulfonamide (4-6k)



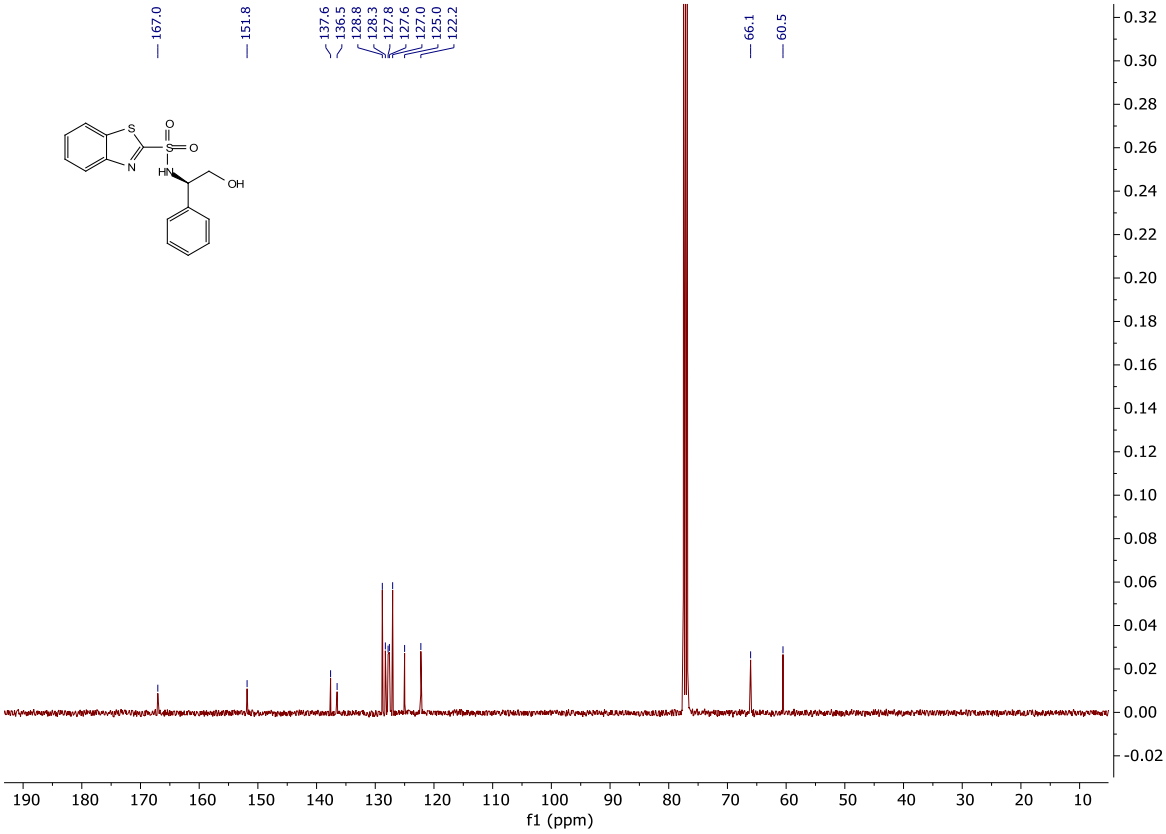
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) of (S)-N-(1-hydroxy-3-methylbutan-2-yl)benzo[d]thiazole-2-sulfonamide (4-6k)



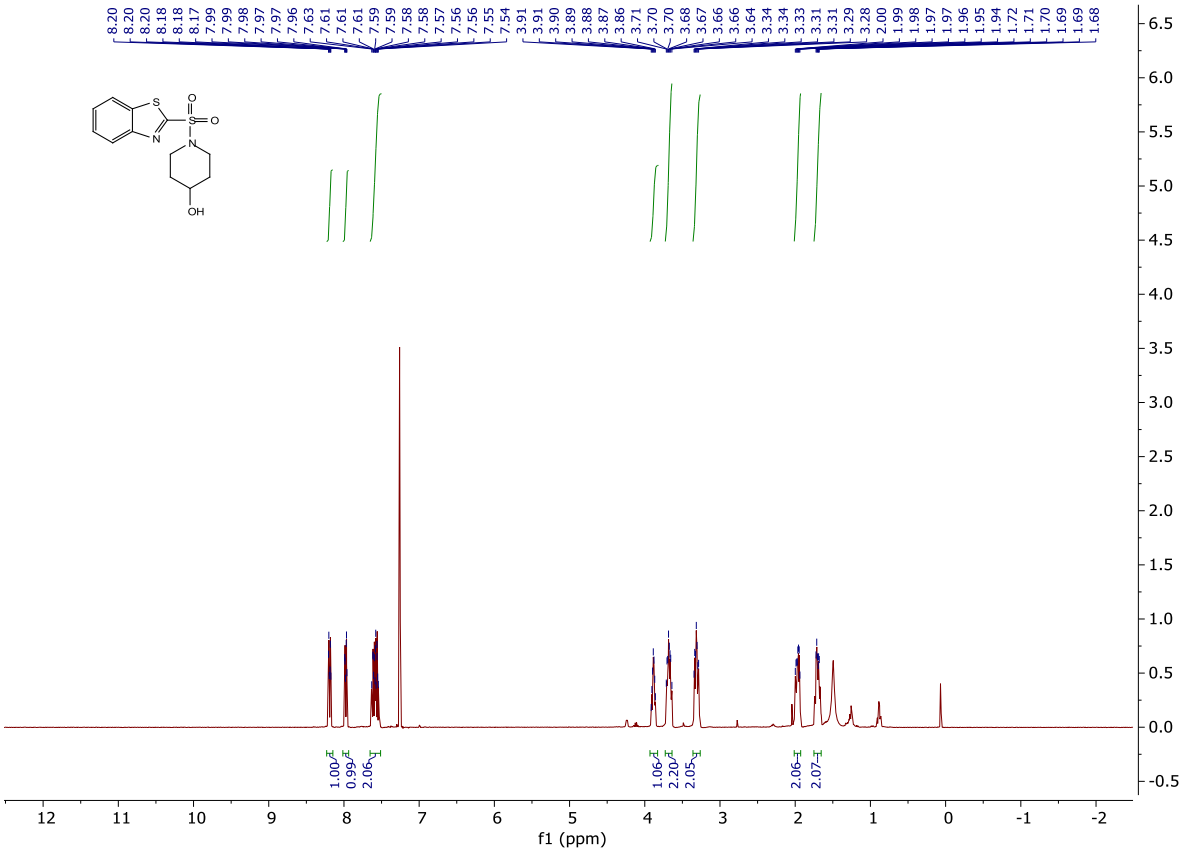
^{1}H NMR (400 MHz, $CDCl_3$) of N-(2-hydroxy-1-phenylethyl)benzo[d]thiazole-2-sulfonamide (4-6l)



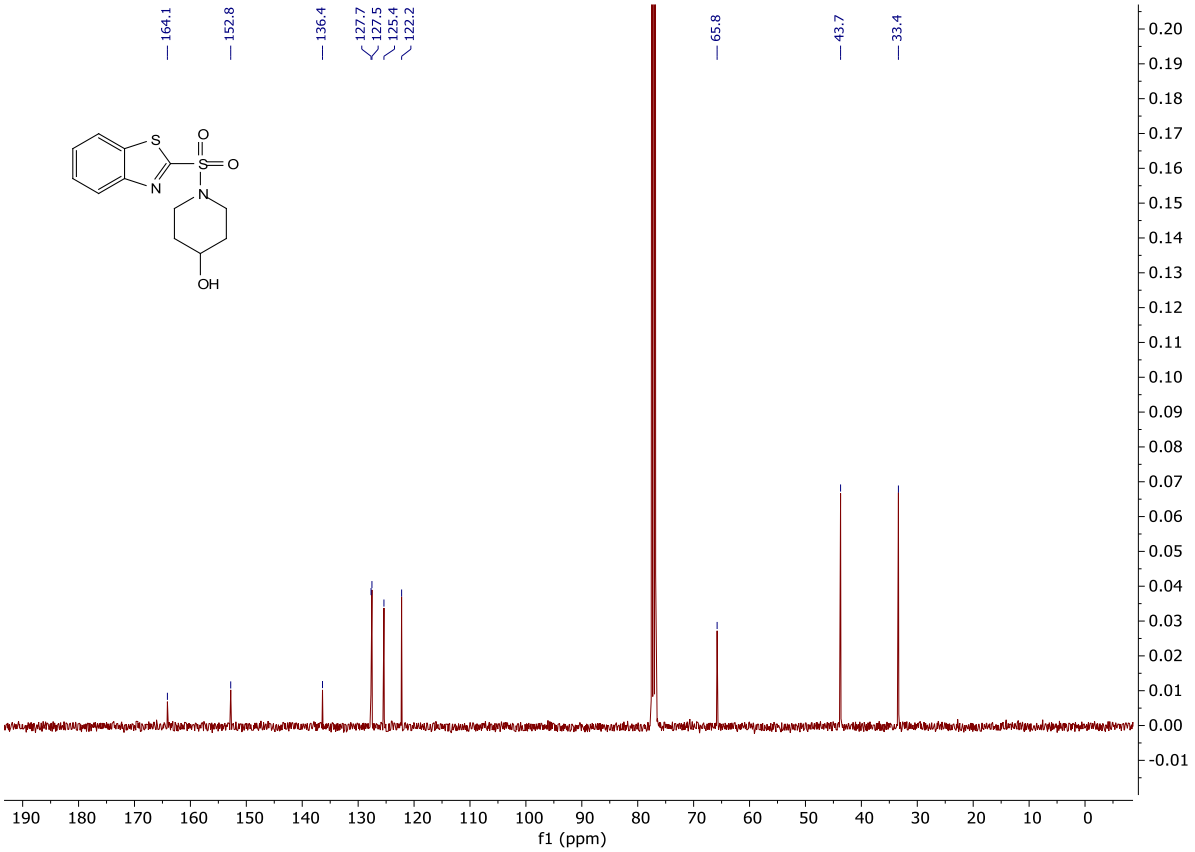
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-(2-hydroxy-1-phenylethyl)benzo[d]thiazole-2-sulfonamide (4-6l)



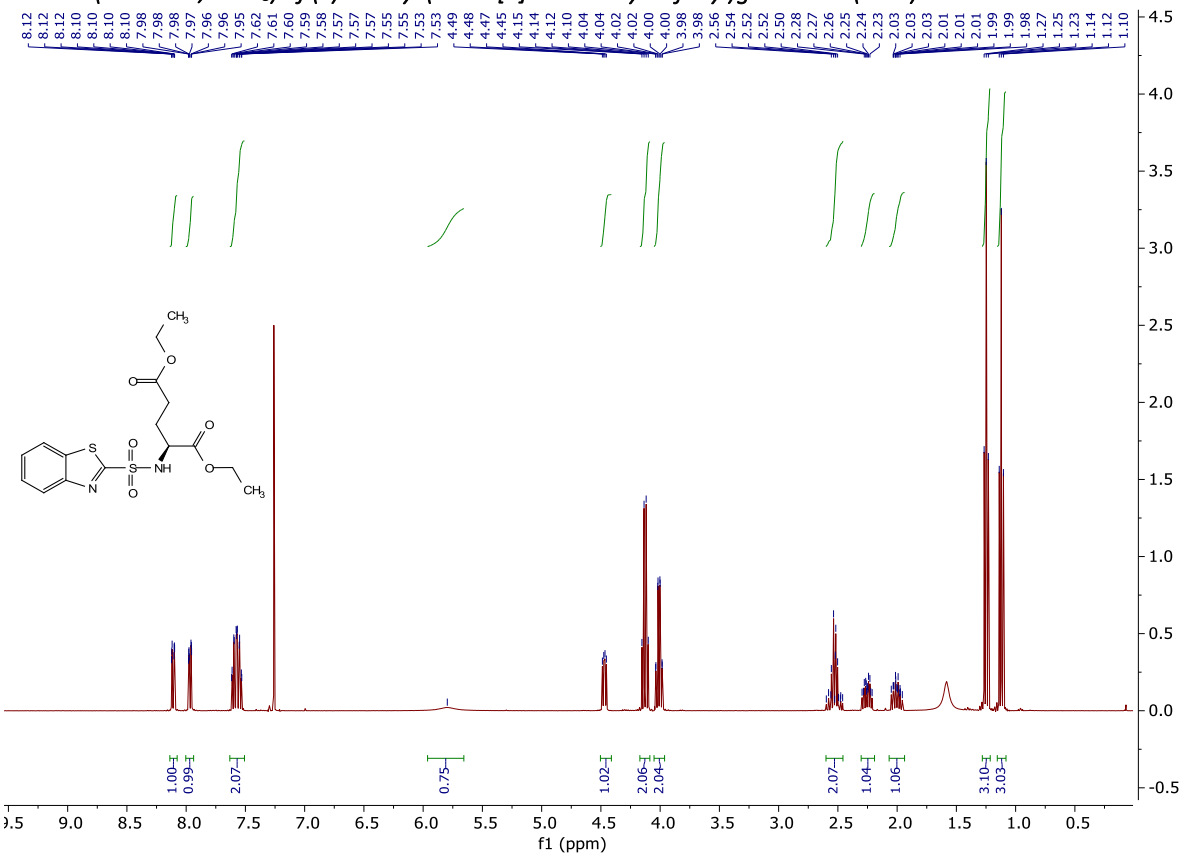
^{1}H NMR (400 MHz, $CDCl_3$) of 1-(benzo[d]thiazol-2-ylsulfonyl)piperidin-4-ol (4-6m)



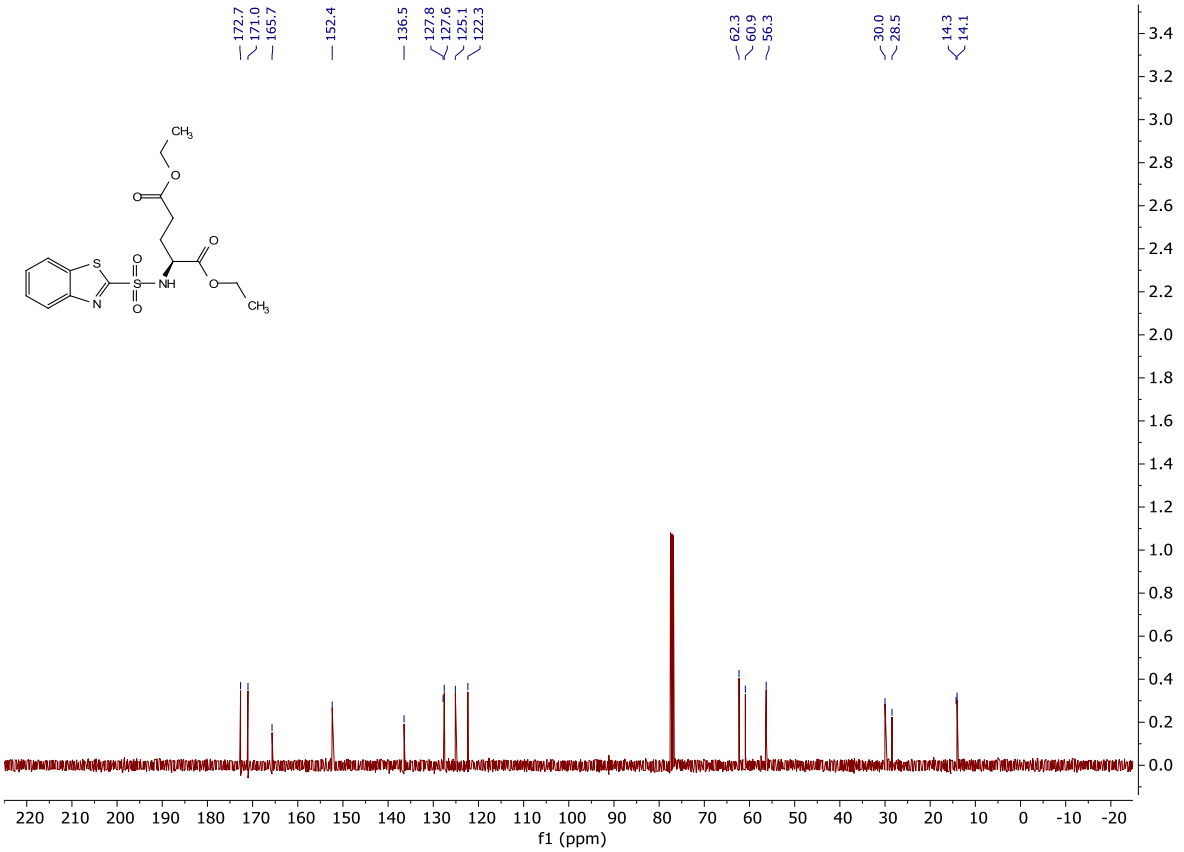
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of 1-(benzo[d]thiazol-2-ylsulfonyl)piperidin-4-ol (4-6m)



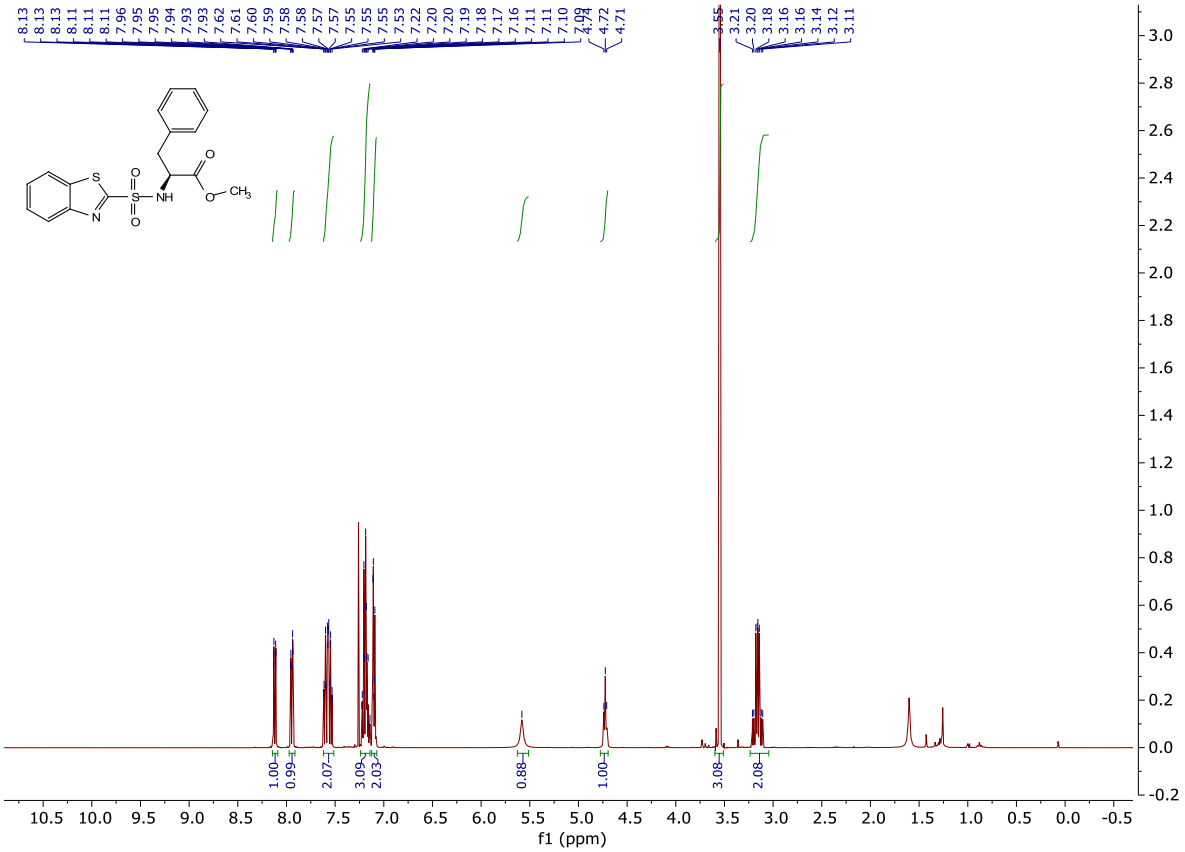
^{1}H NMR (400 MHz, $CDCl_3$) of (S)-diethyl (benzo[d]thiazol-2-ylsulfonyl)glutamate (4-6n)



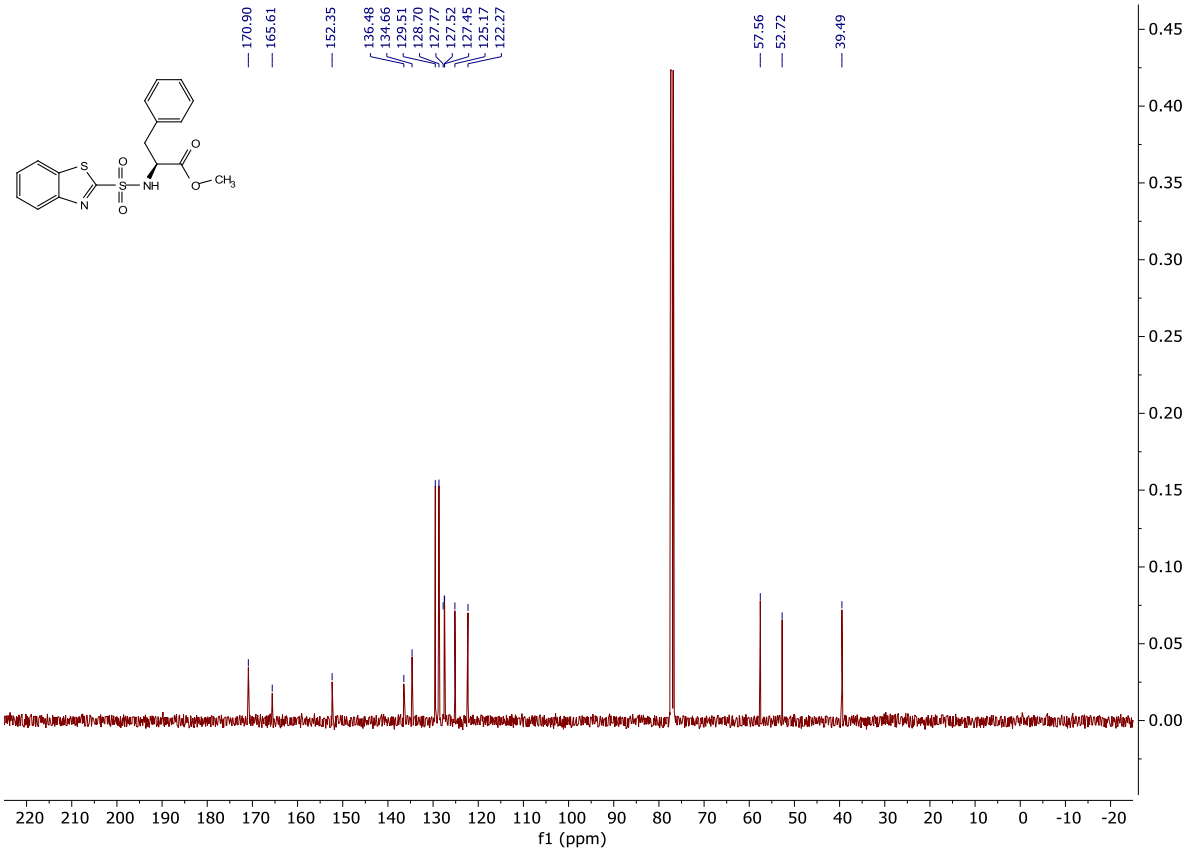
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of (S)-diethyl (benzo[d]thiazol-2-ylsulfonyl)glutamate (4-6n)



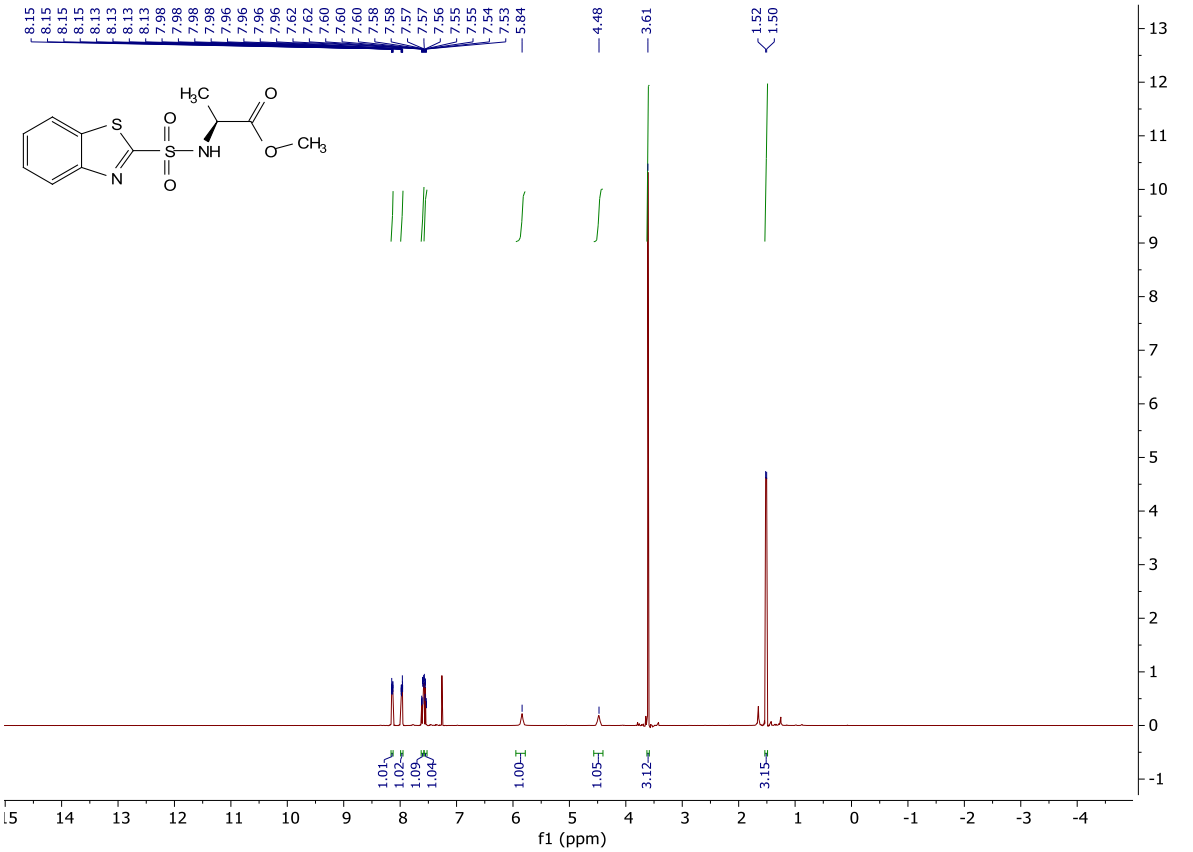
^{1}H NMR (400 MHz, $CDCl_3$) of methyl (benzo[d]thiazol-2-ylsulfonyl)-L-phenylalaninate (4-6o)



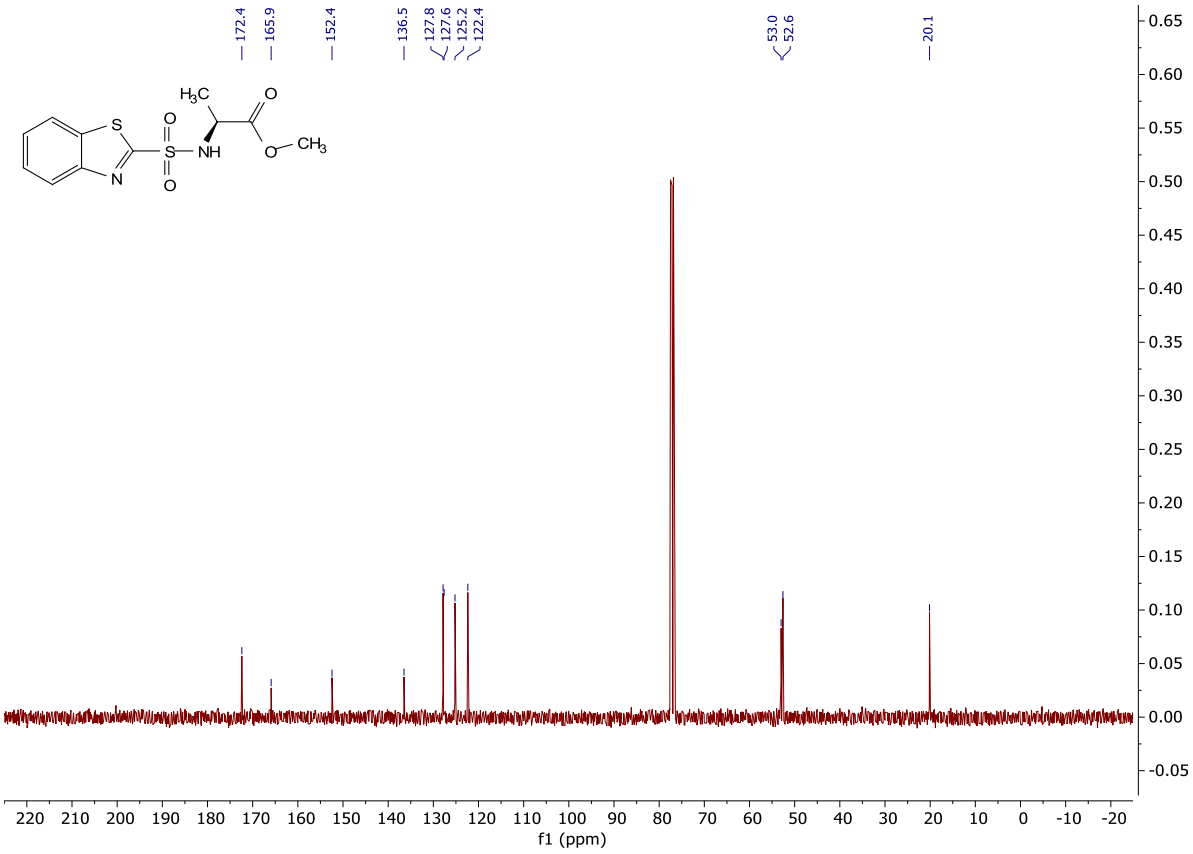
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of methyl (benzo[d]thiazol-2-ylsulfonyl)-L-phenylalaninate (4-6o)



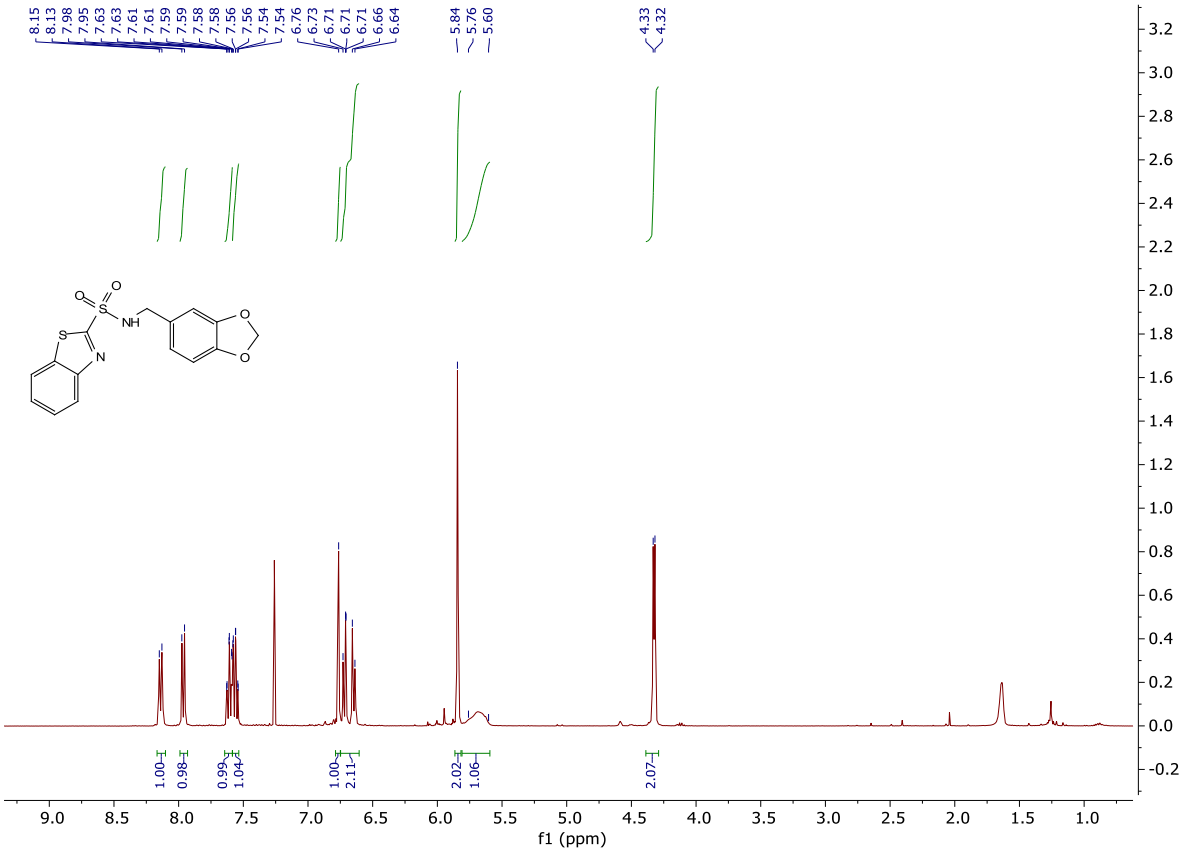
^{1}H NMR (400 MHz, $CDCl_3$) of methyl (benzo[d]thiazol-2-ylsulfonyl)alaninate (4-6p)



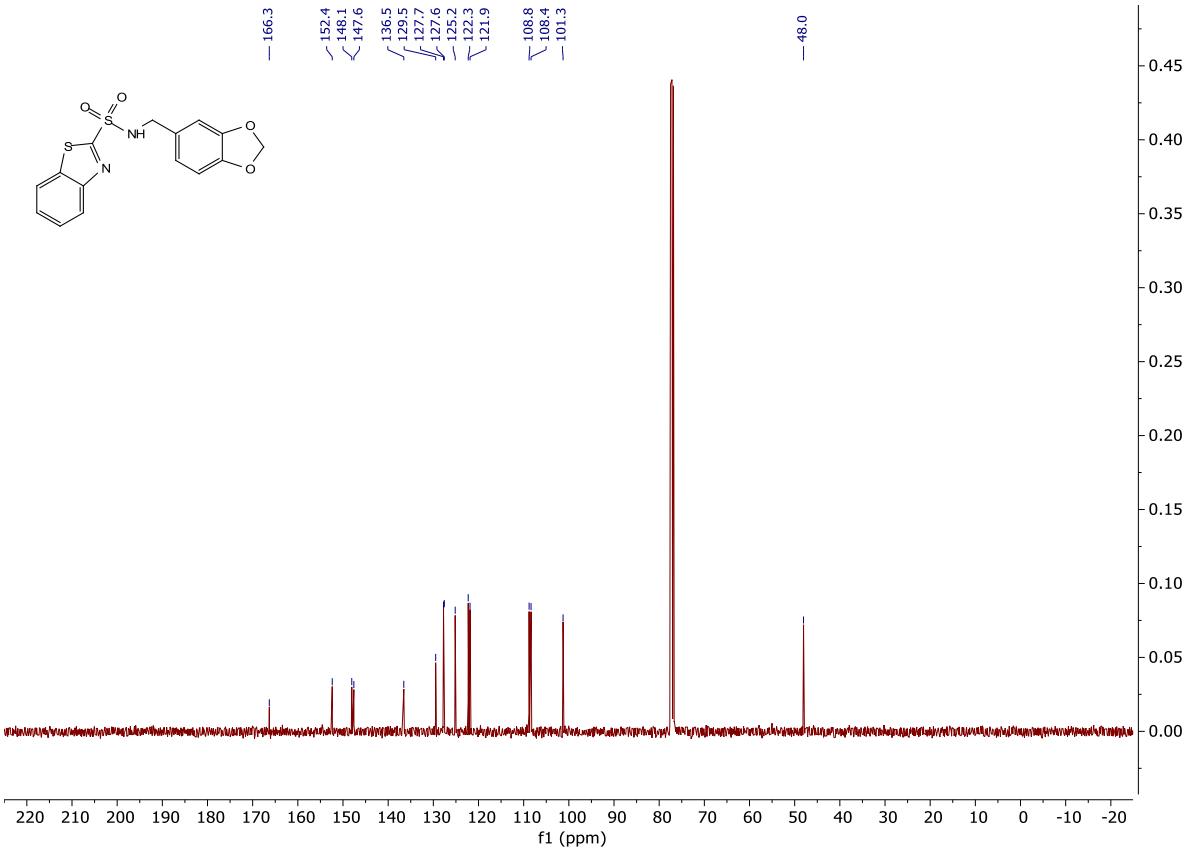
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of methyl (benzo[d]thiazol-2-ylsulfonyl)alaninate (4-6p)



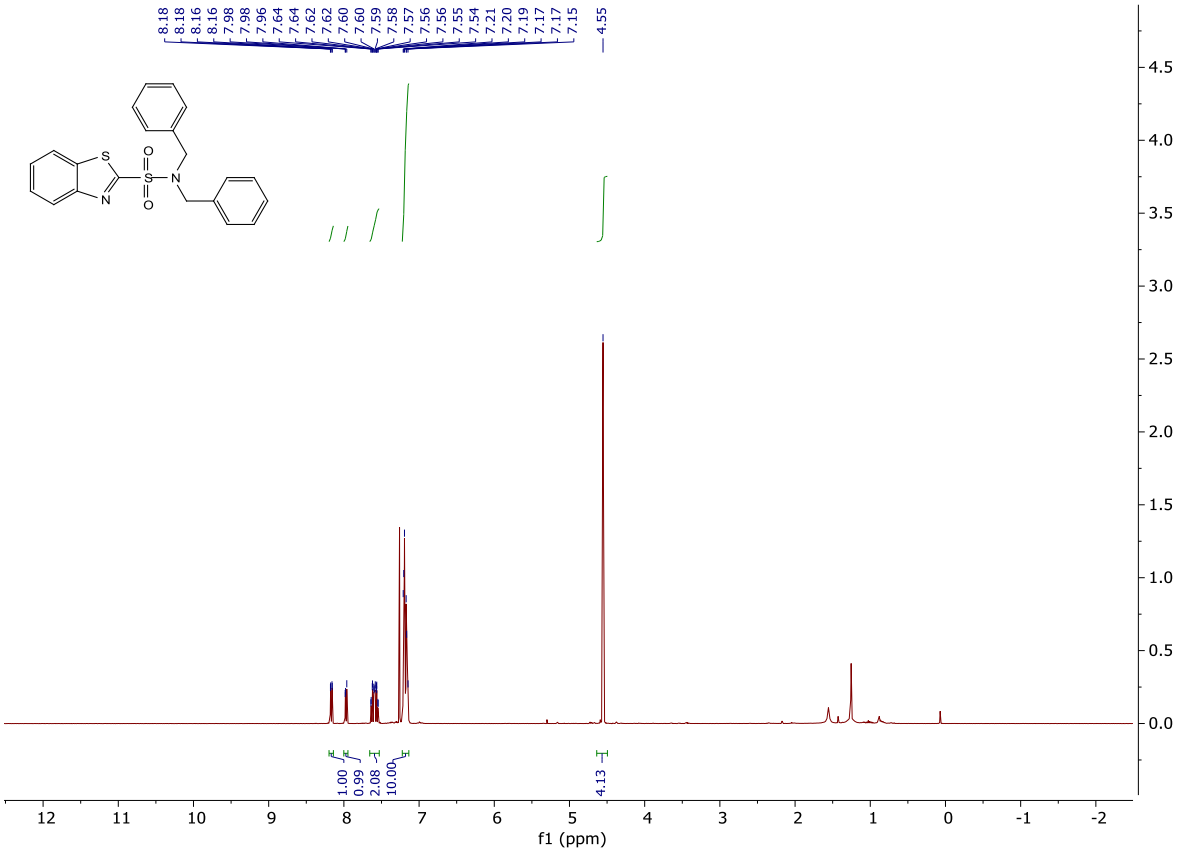
^{1}H NMR (400 MHz, CDCl$_3$) of N-(benzo[d][1,3]dioxol-5-ylmethyl)benzo[d]thiazole-2-sulfonamide (4-6r)



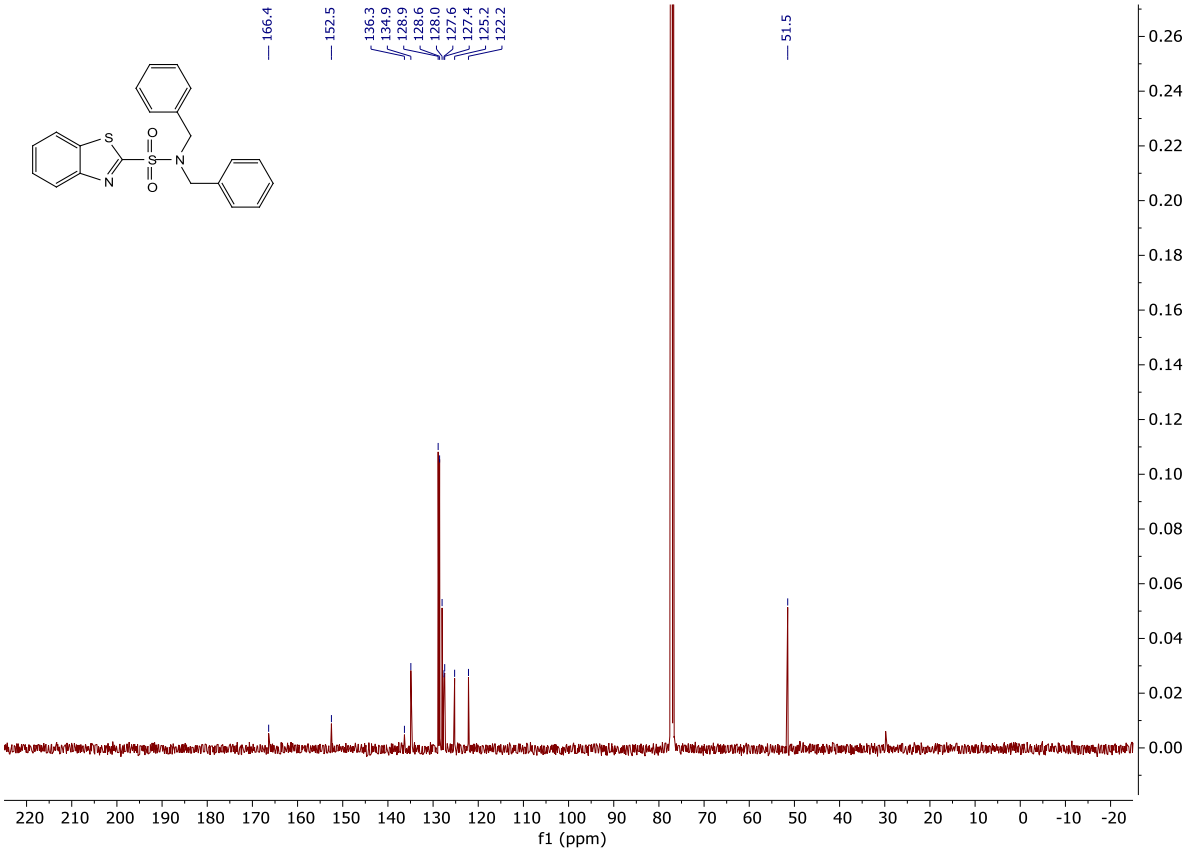
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) of N-(benzo[d][1,3]dioxol-5-ylmethyl)benzo[d]thiazole-2-sulfonamide (4-6r)



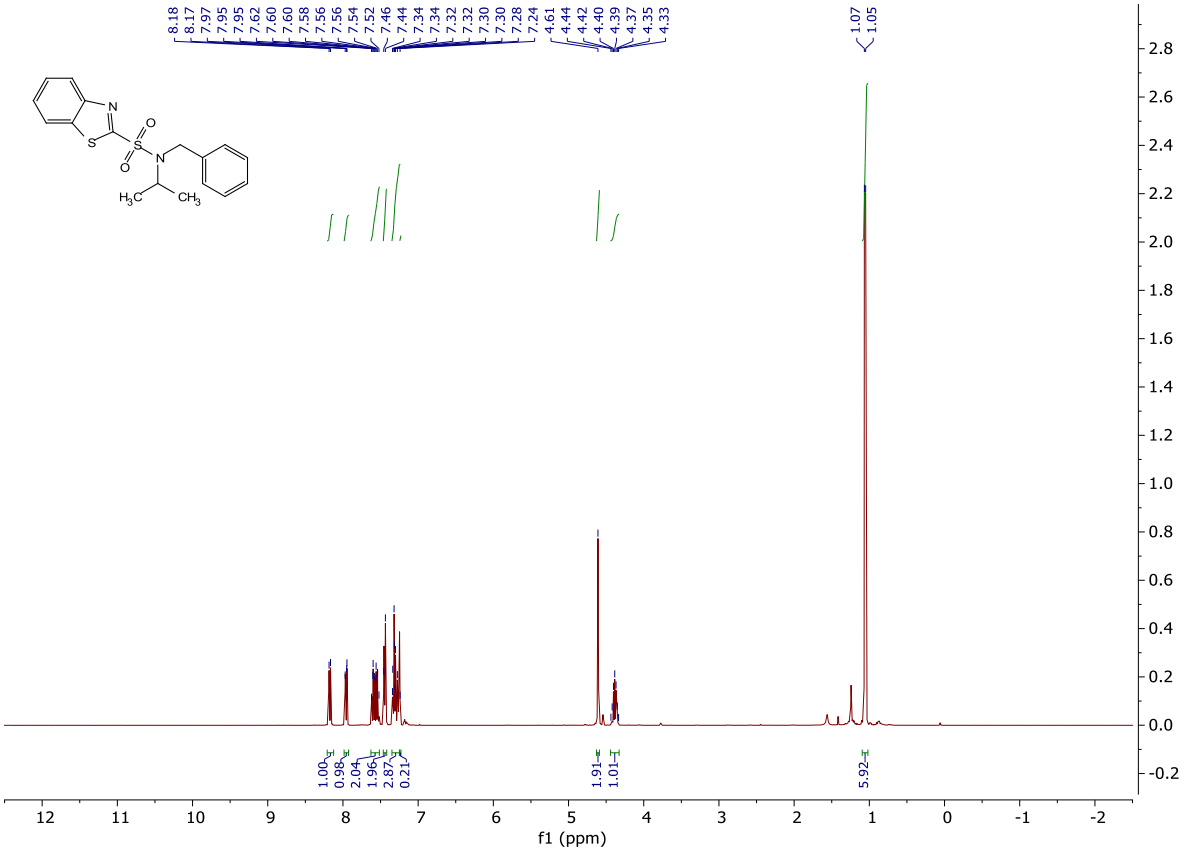
^{1}H NMR (400 MHz, $CDCl_3$) of N,N-dibenzylbenzo[d]thiazole-2-sulfonamide (4-6aa)



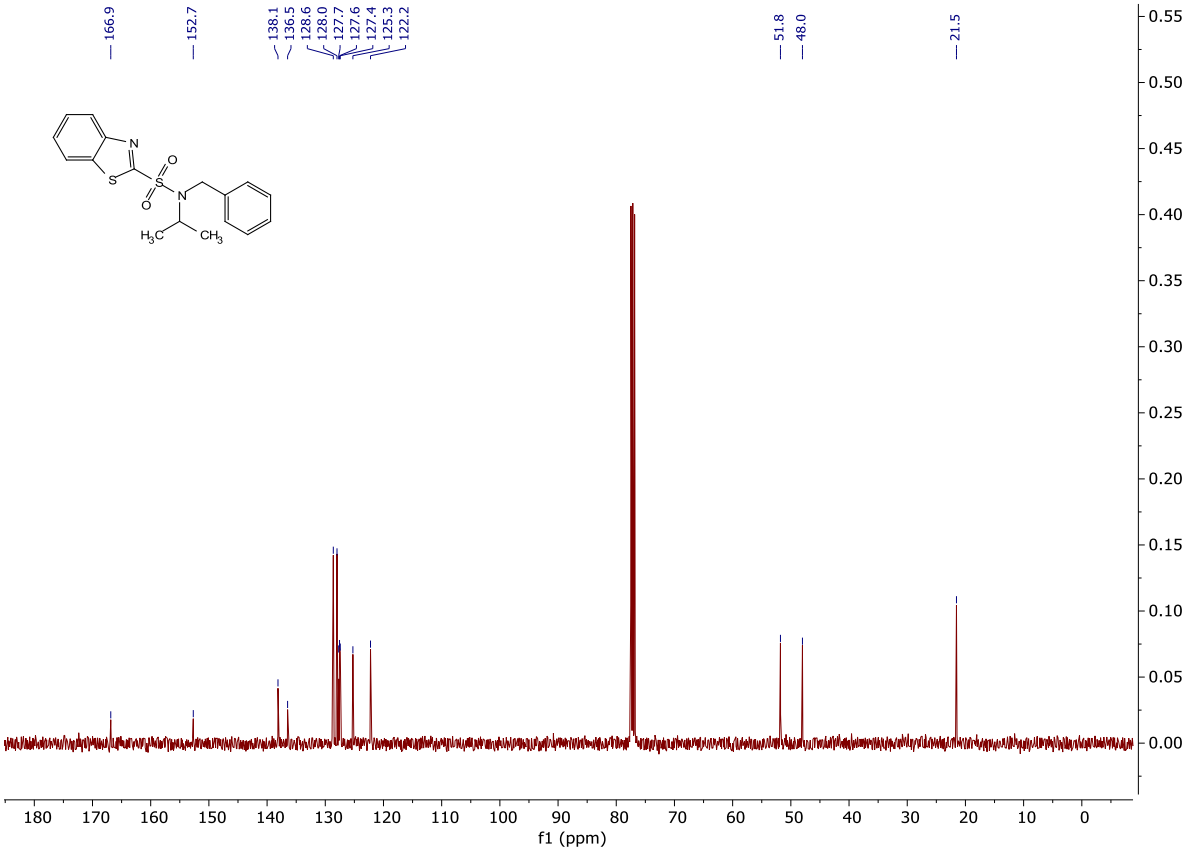
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N,N-dibenzylbenzo[d]thiazole-2-sulfonamide (4-6aa)



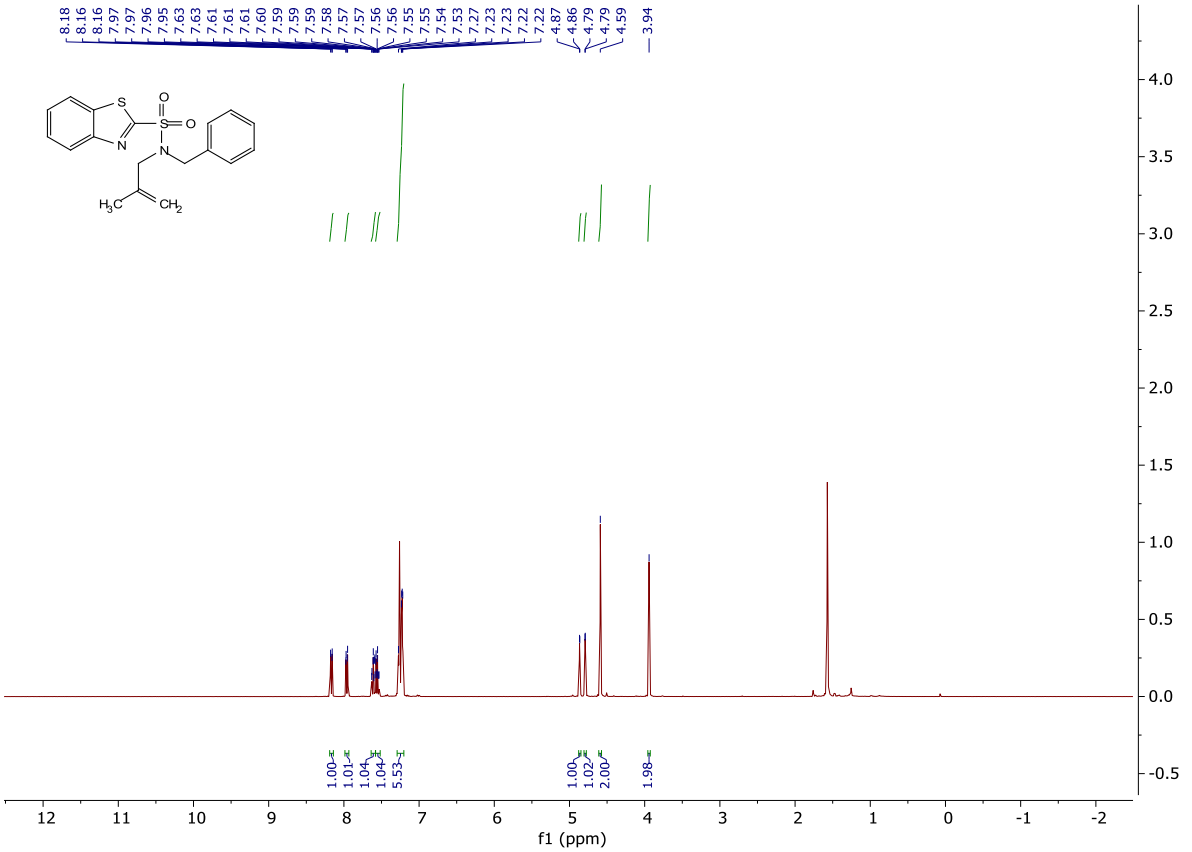
^{1}H NMR (400 MHz, $CDCl_3$) of N-benzyl-N-isopropylbenzo[d]thiazole-2-sulfonamide (4-6ab)



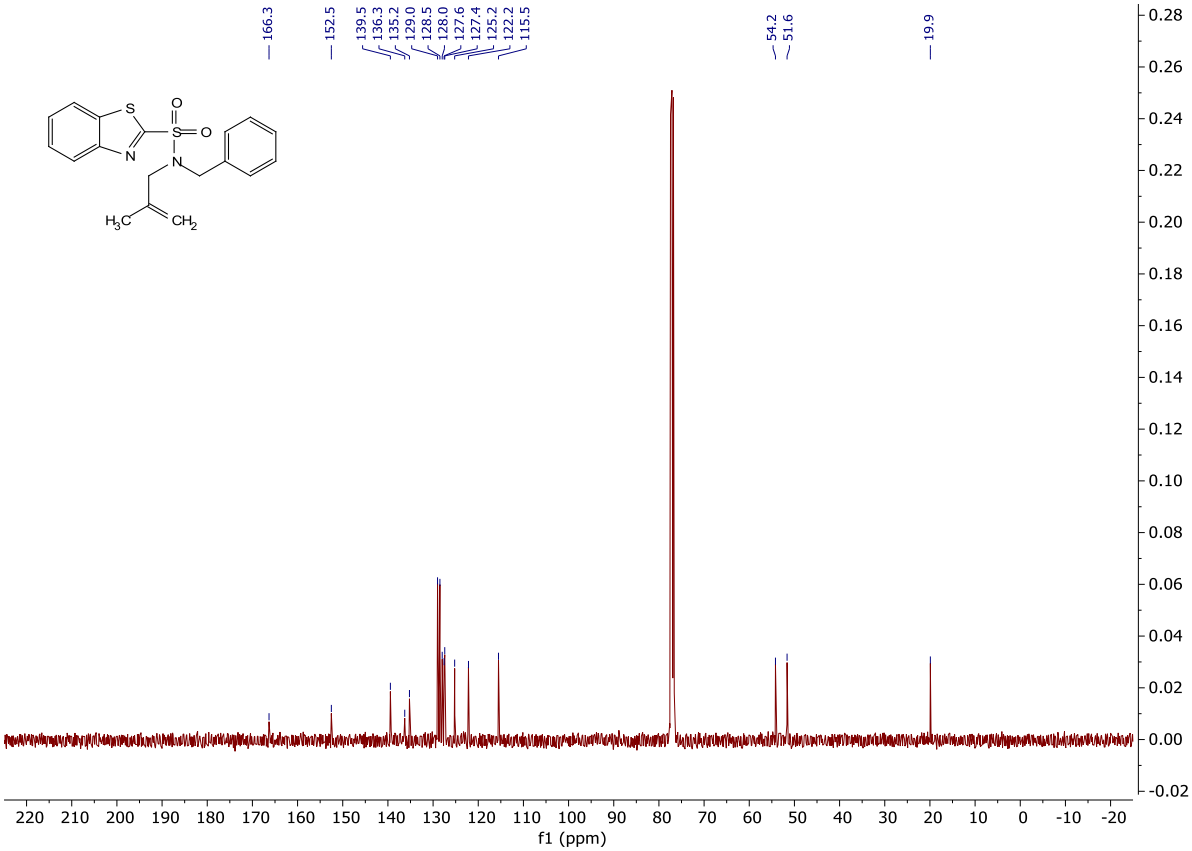
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-benzyl-N-isopropylbenzo[d]thiazole-2-sulfonamide (4-6ab)



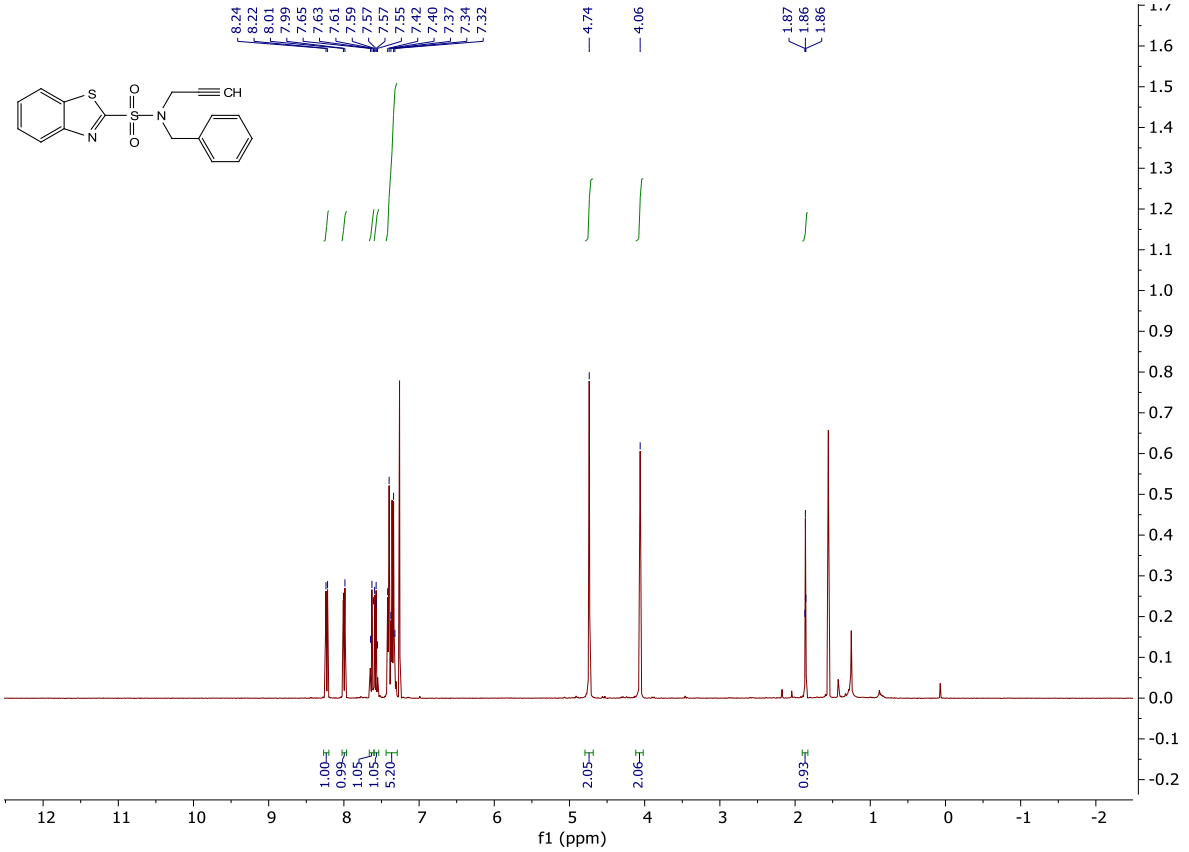
^{1}H NMR (400 MHz, $CDCl_3$) of N-benzyl-N-(2-methylallyl)benzo[d]thiazole-2-sulfonamide (4-6ac)



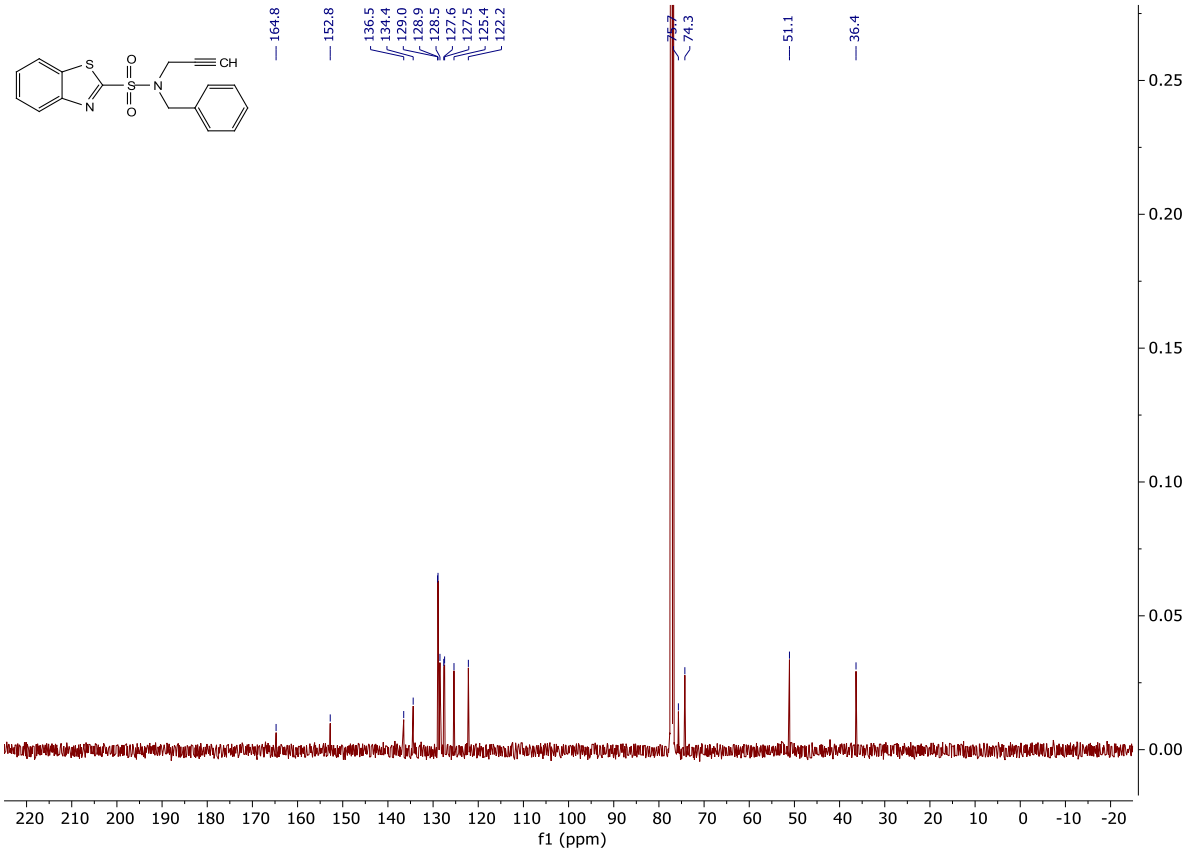
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-benzyl-N-(2-methylallyl)benzo[d]thiazole-2-sulfonamide (4-6ac)



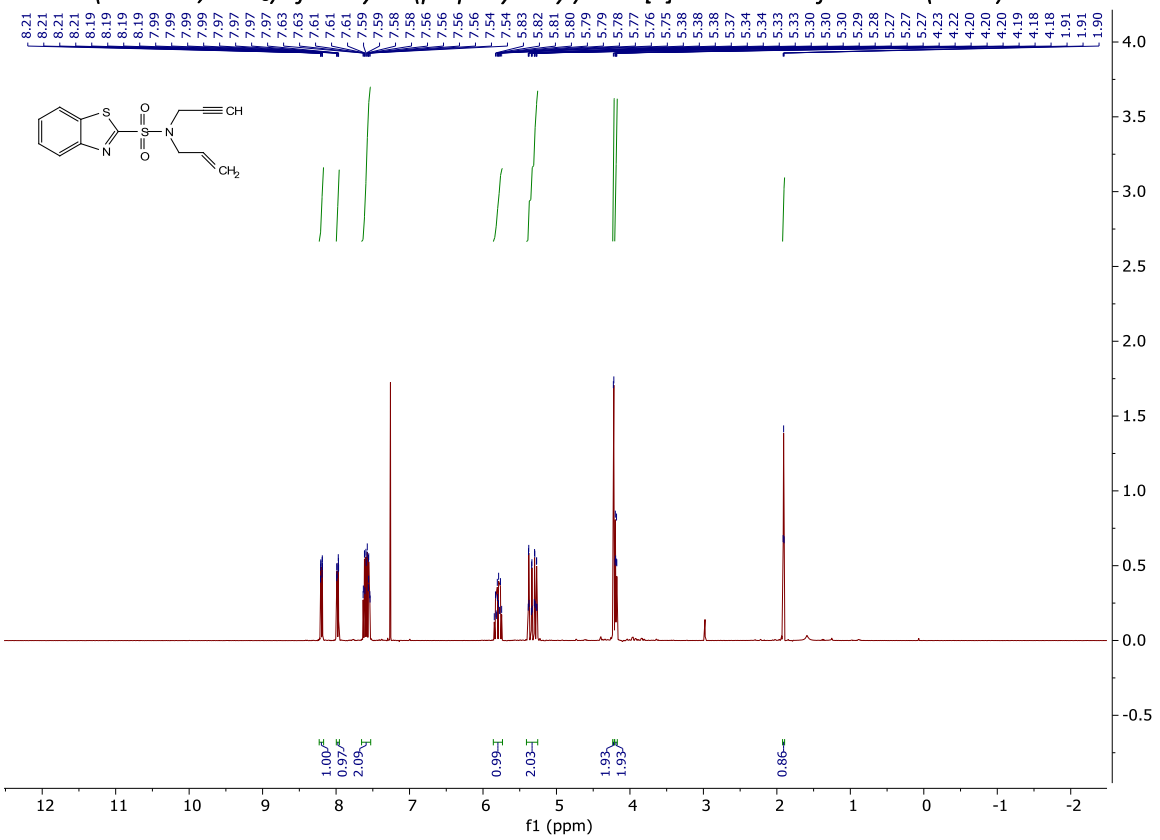
^{1}H NMR (400 MHz, CDCl3) of N-benzyl-N-(prop-2-yn-1-yl)benzo[d]thiazole-2-sulfonamide (4-6ad)



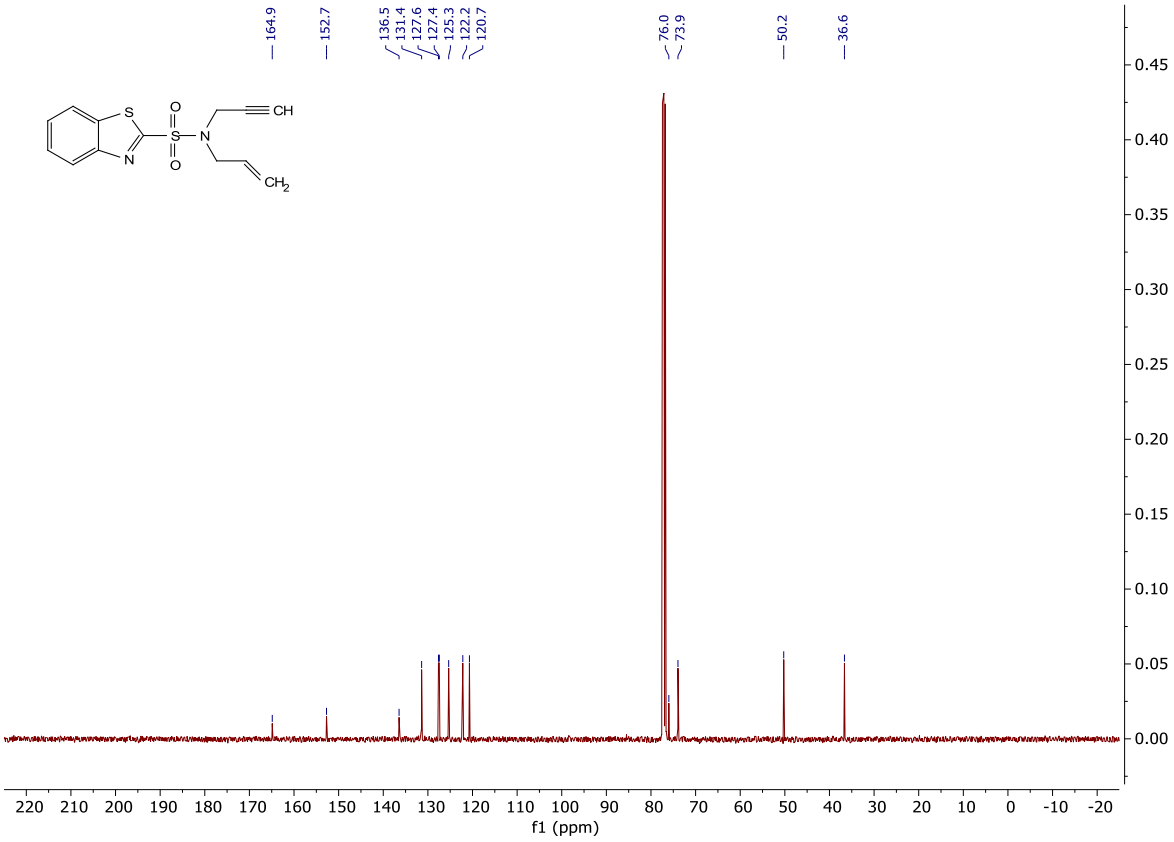
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) of N-benzyl-N-(prop-2-yn-1-yl)benzo[d]thiazole-2-sulfonamide (4-6ad)



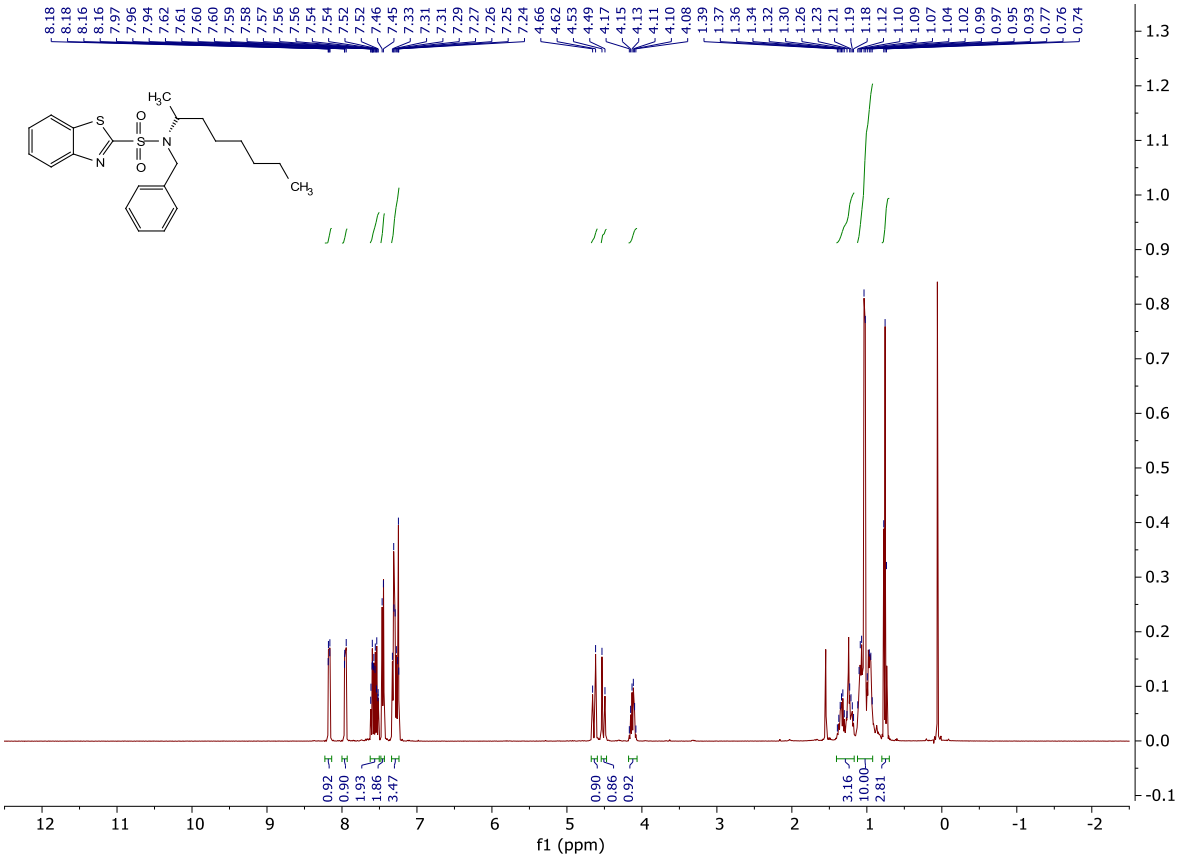
^{1}H NMR (400 MHz, $CDCl_3$) of N-allyl-N-(prop-2-yn-1-yl)benzo[d]thiazole-2-sulfonamide (4-6bd)



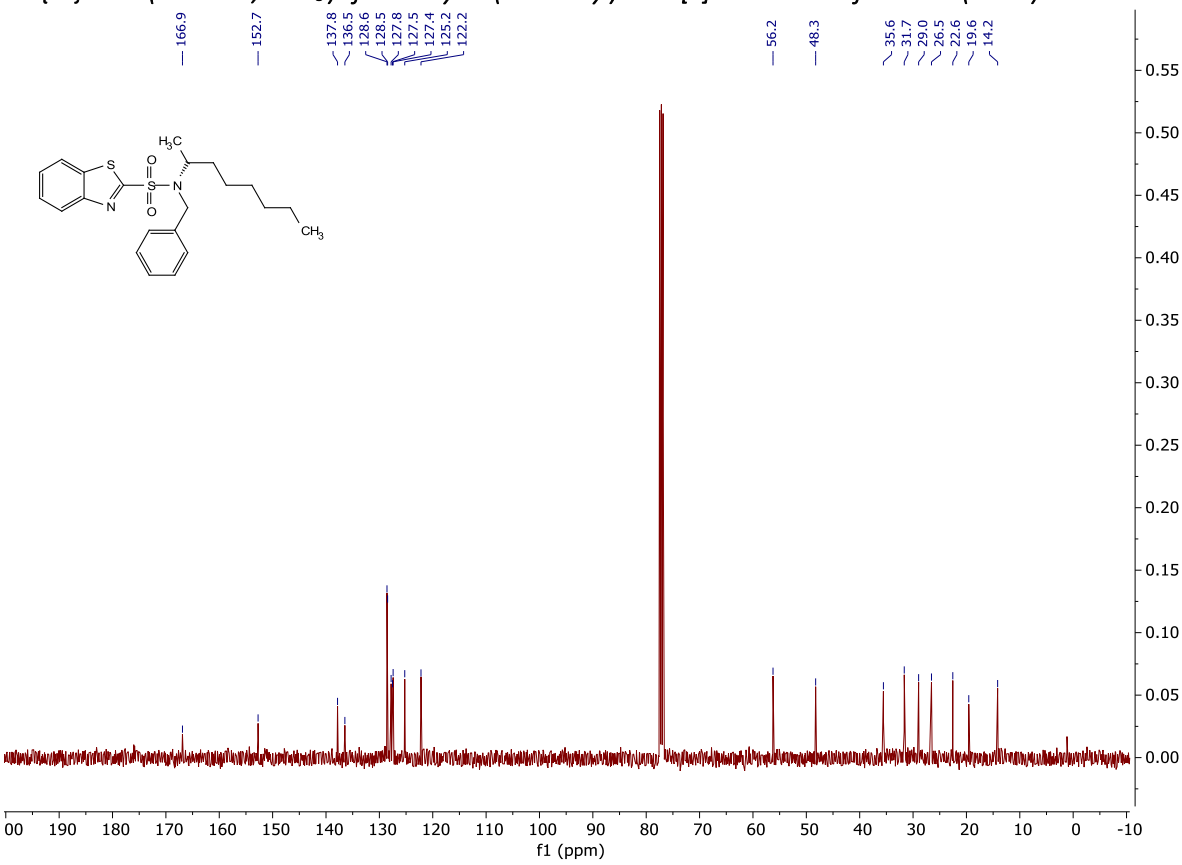
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-allyl-N-(prop-2-yn-1-yl)benzo[d]thiazole-2-sulfonamide (4-6bd)



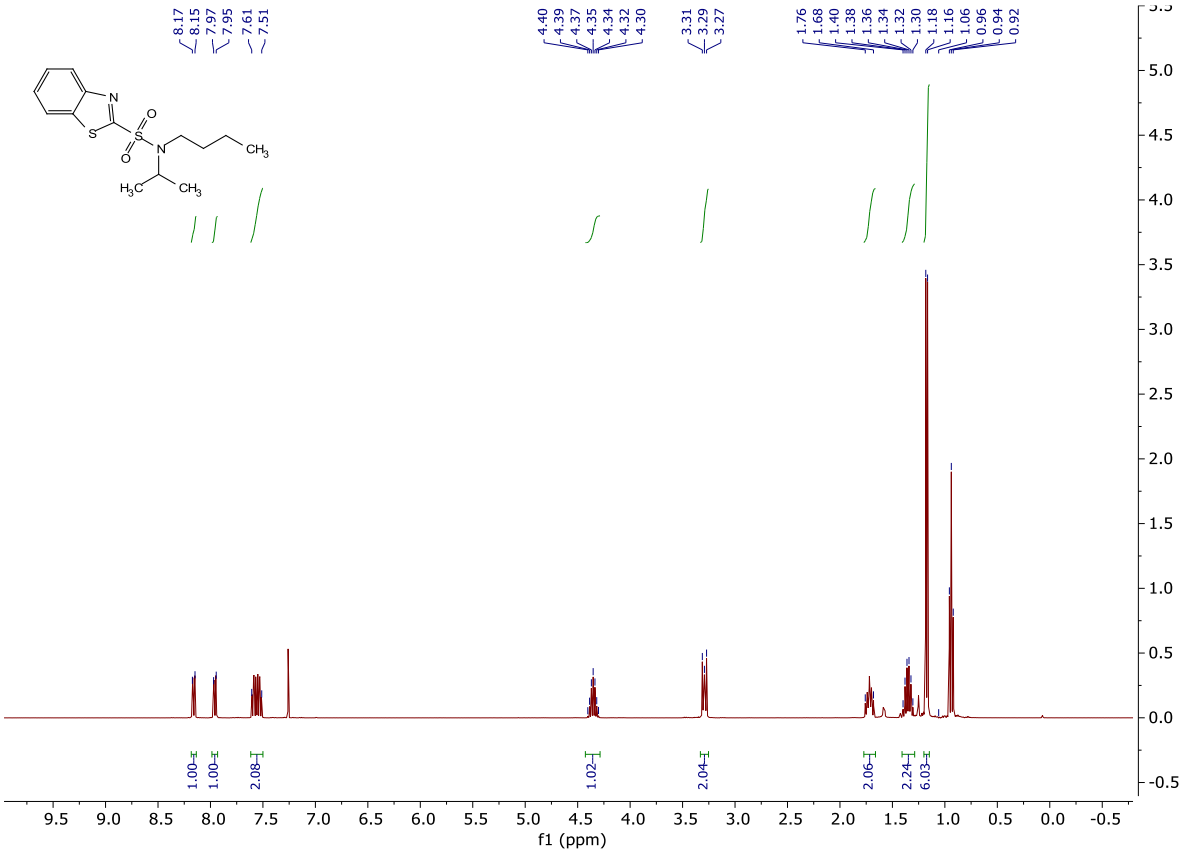
^{1}H NMR (400 MHz, $CDCl_3$) of N-benzyl-N-(octan-2-yl)benzo[d]thiazole-2-sulfonamide (4-6ae)



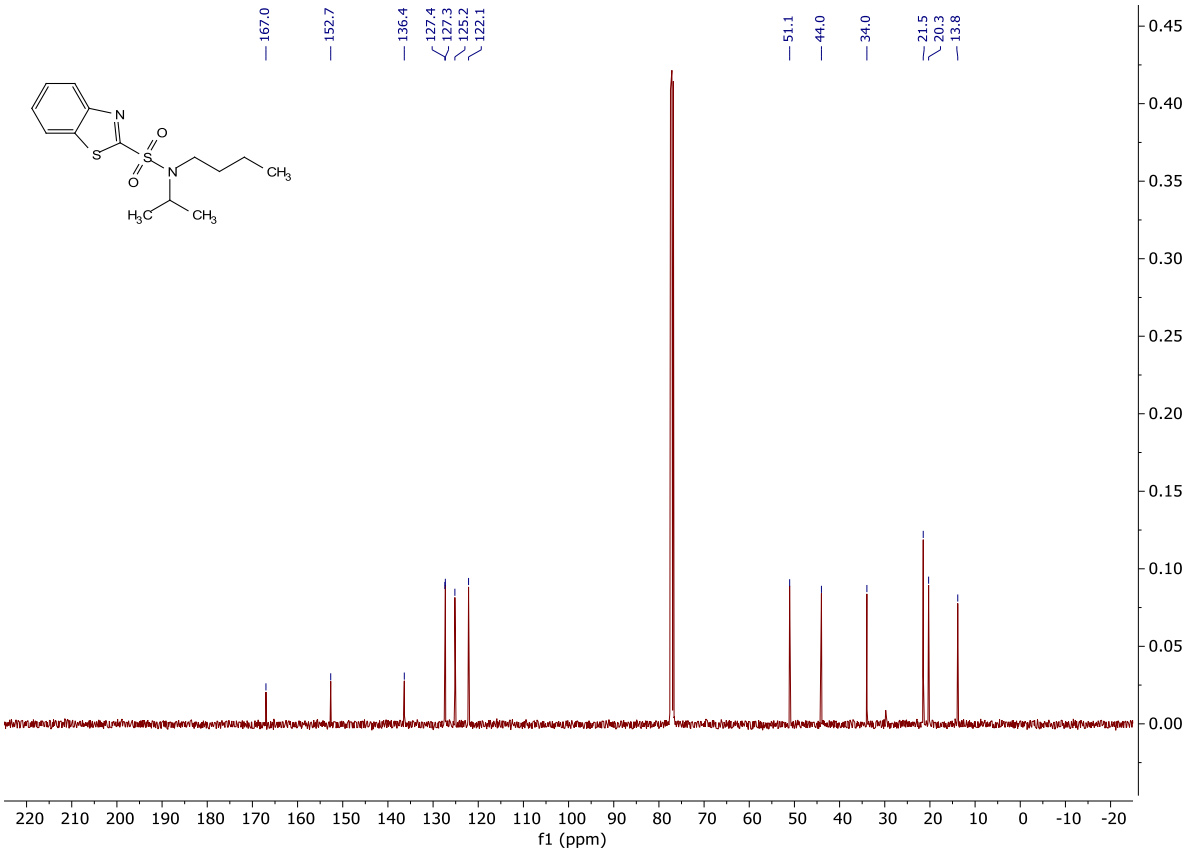
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-benzyl-N-(octan-2-yl)benzo[d]thiazole-2-sulfonamide (4-6ae)



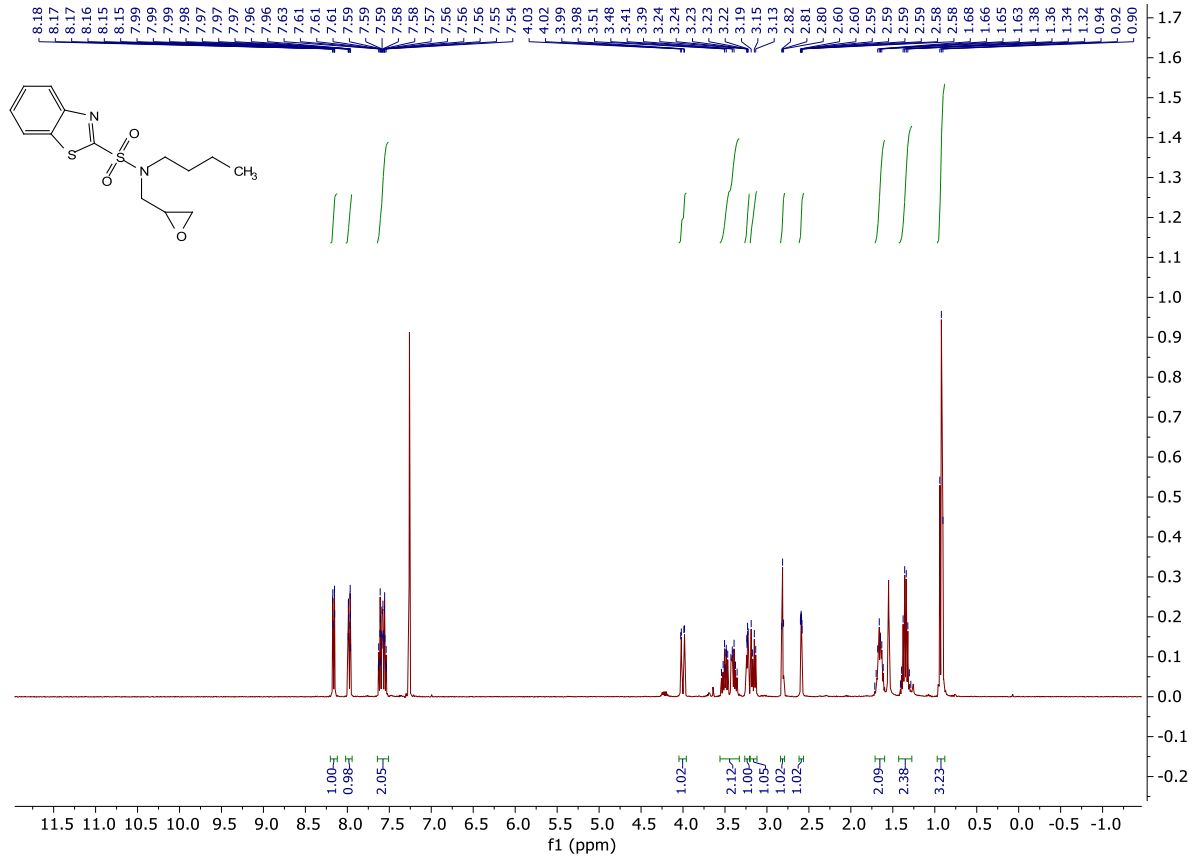
^{1}H NMR (400 MHz, $CDCl_3$) of N-butyl-N-isopropylbenzo[d]thiazole-2-sulfonamide (4-6ca)



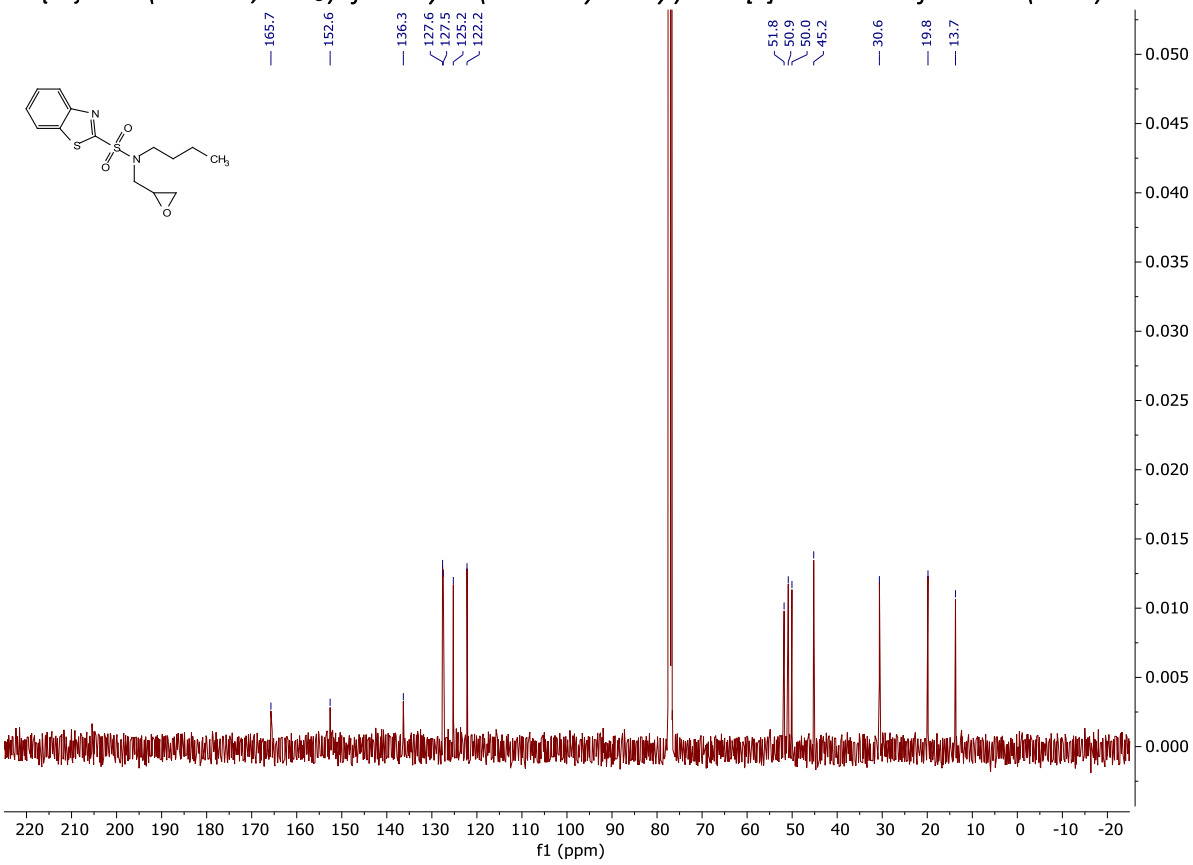
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-butyl-N-isopropylbenzo[d]thiazole-2-sulfonamide (4-6ca)



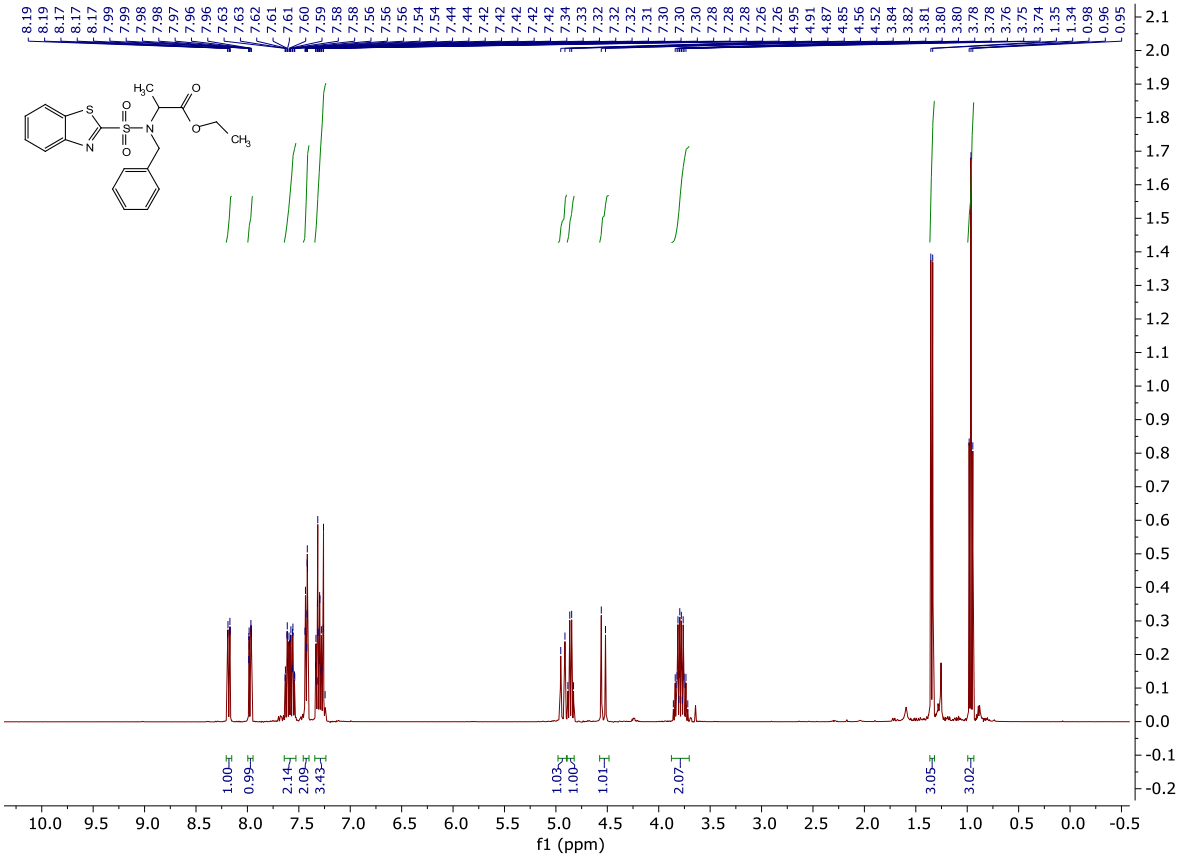
^{1}H NMR (400 MHz, $CDCl_3$) of N-butyl-N-(oxiran-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (4-6cb)



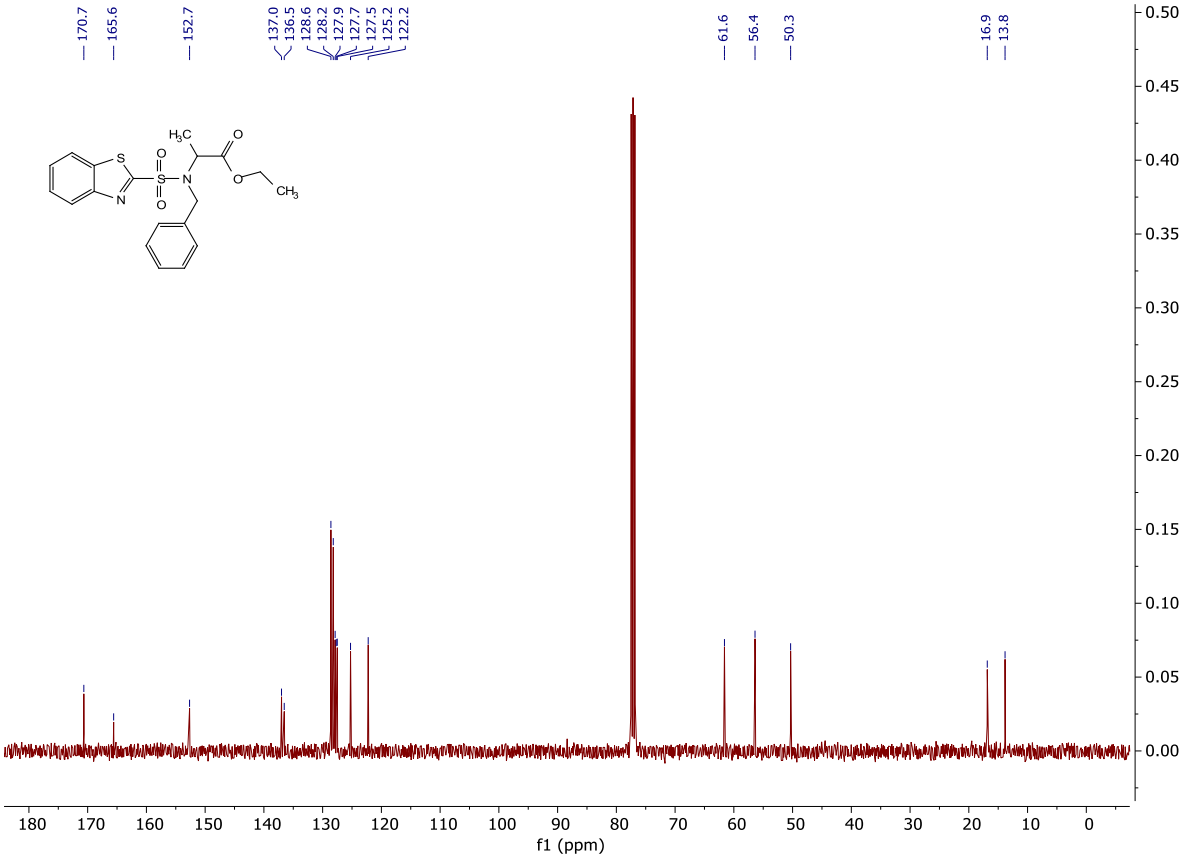
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-butyl-N-(oxiran-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (4-6cb)



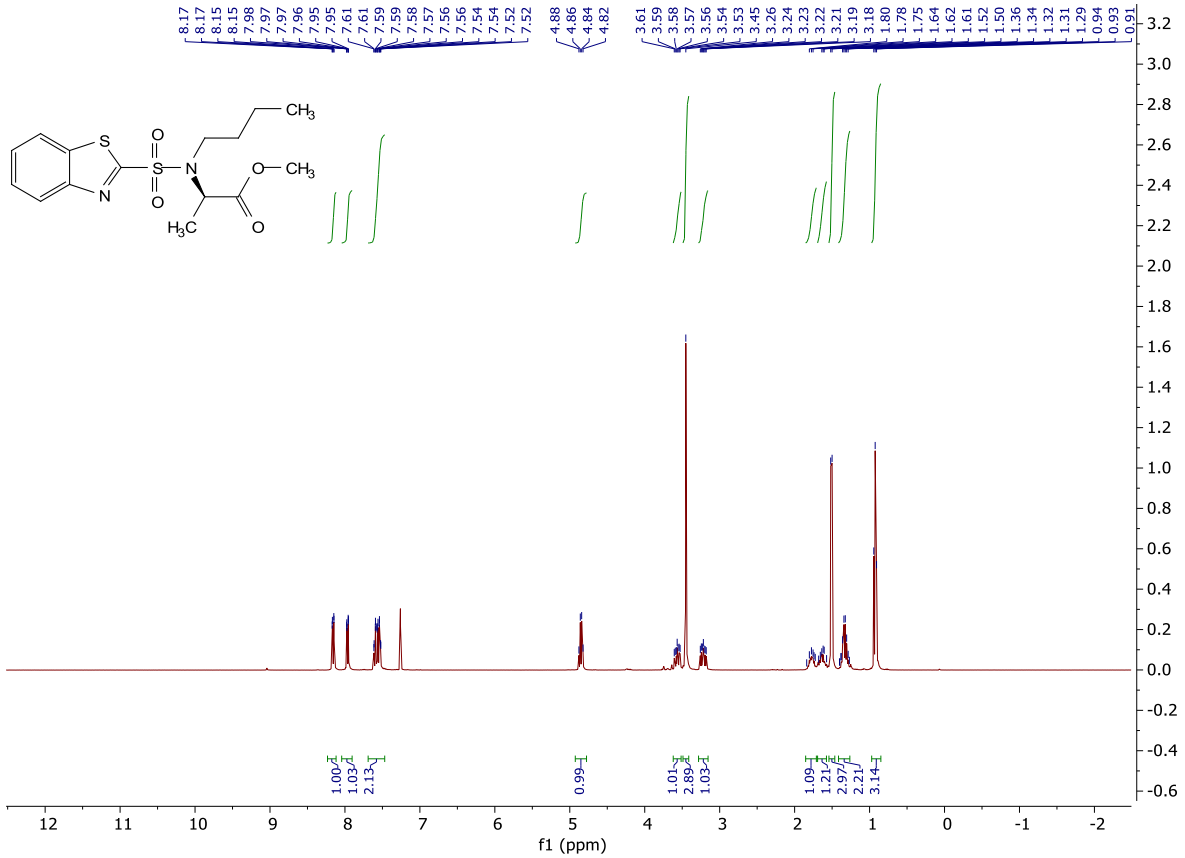
^{1}H NMR (400 MHz, $CDCl_3$) of ethyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzylalaninate (46af)



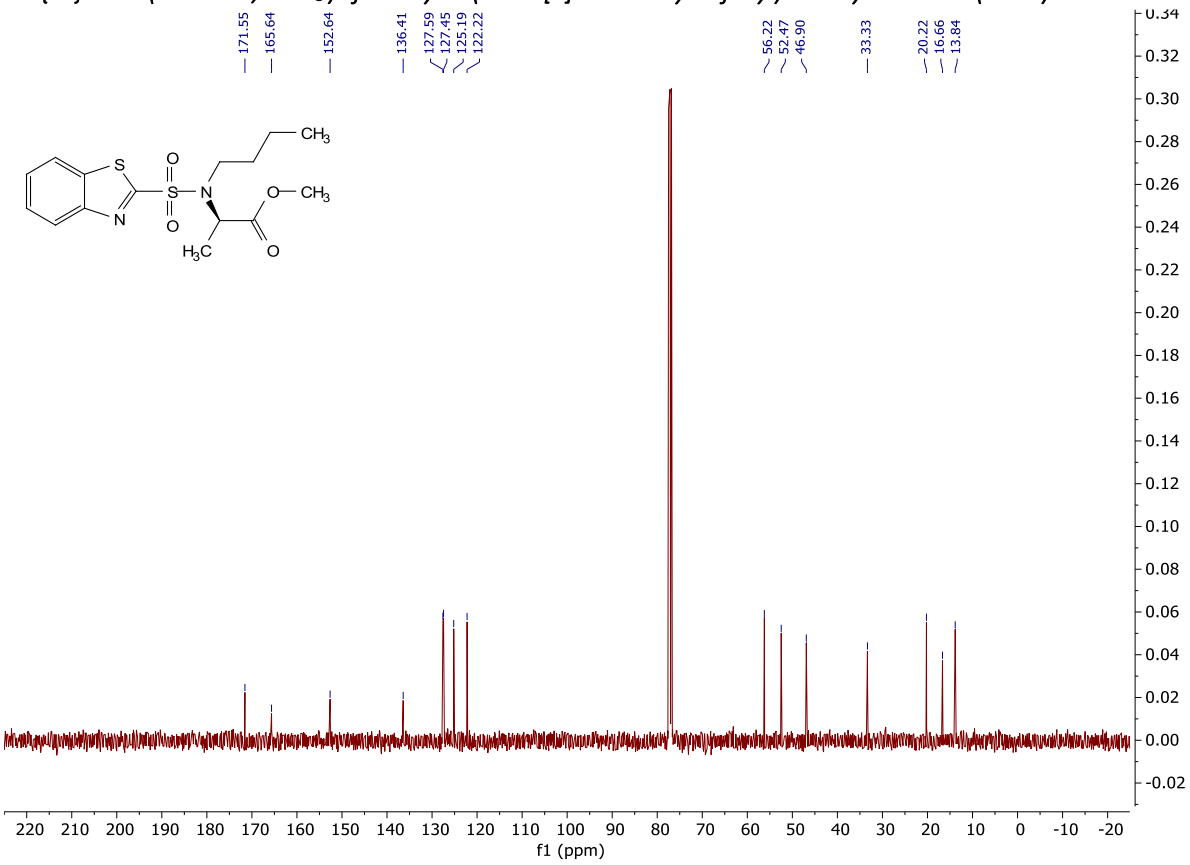
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of ethyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzylalaninate (4-6af)



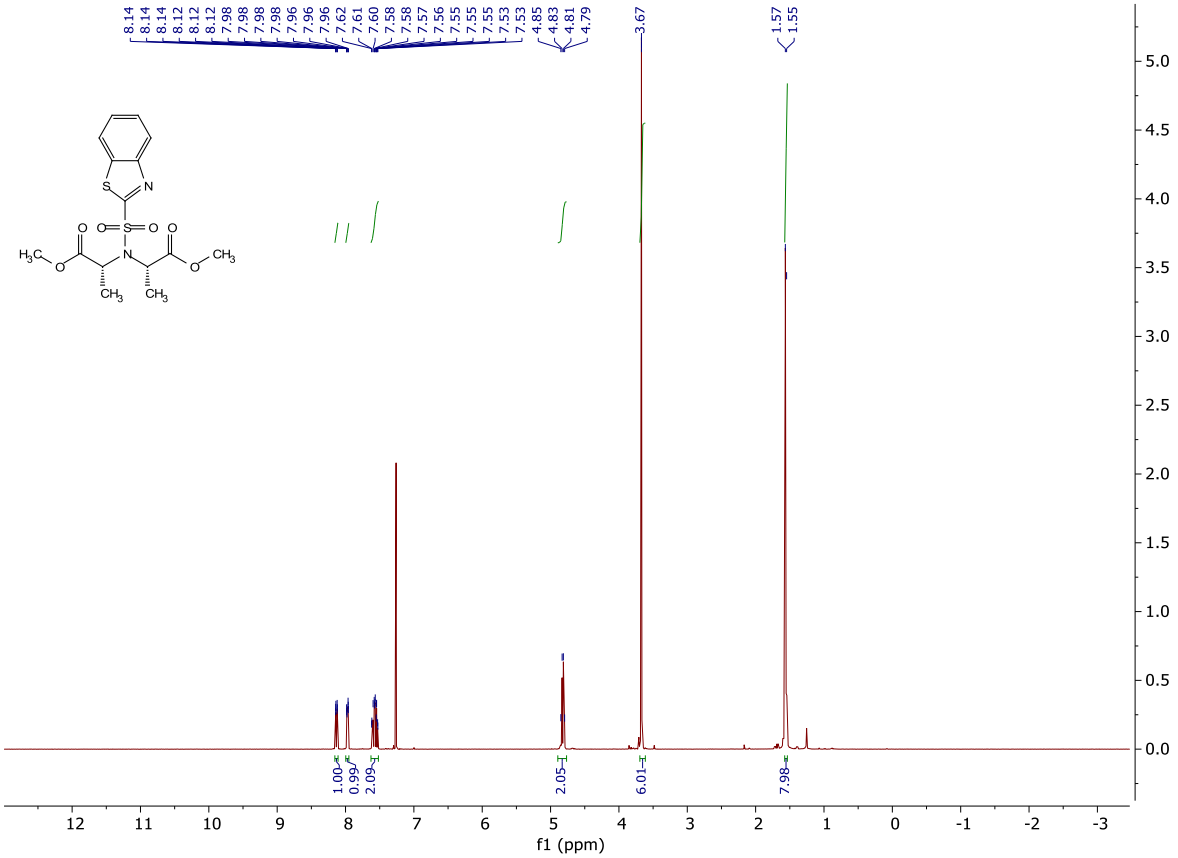
^{1}H NMR (400 MHz, $CDCl_3$) of methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-butylalaninate (4-6cc)



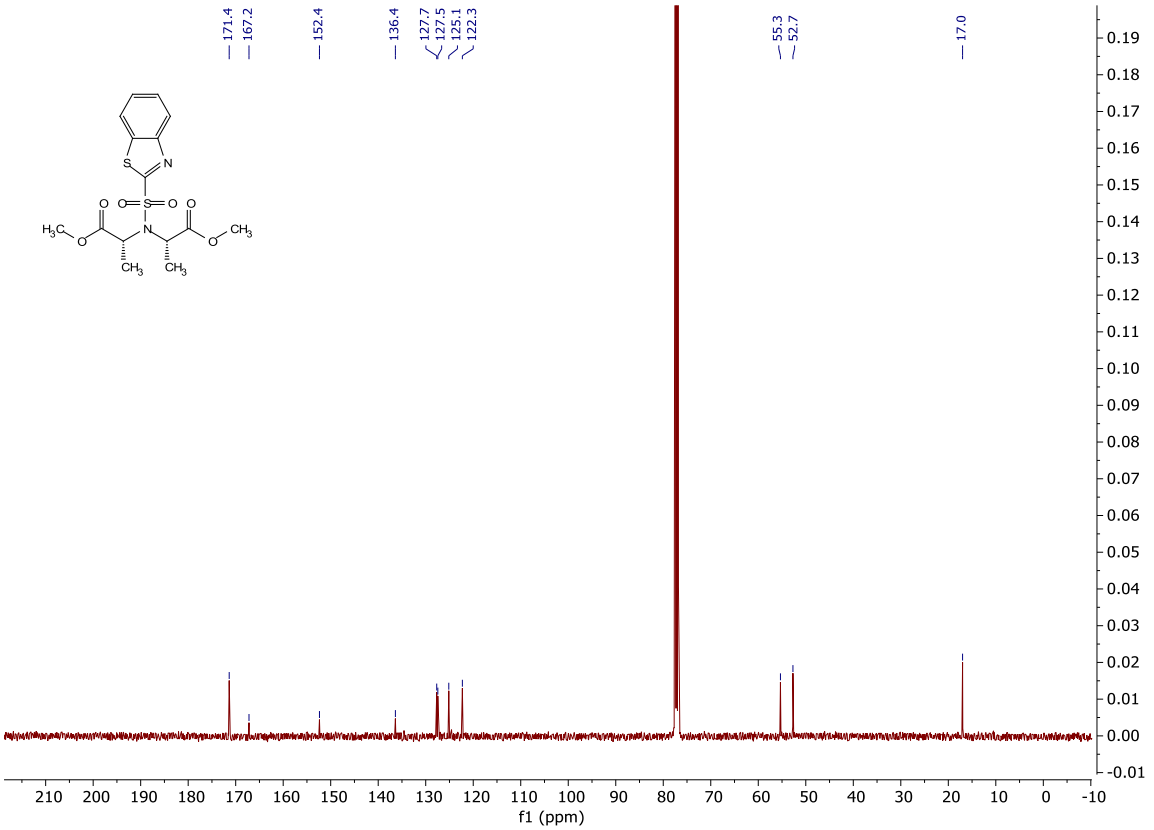
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-butylalaninate (4-6cc)



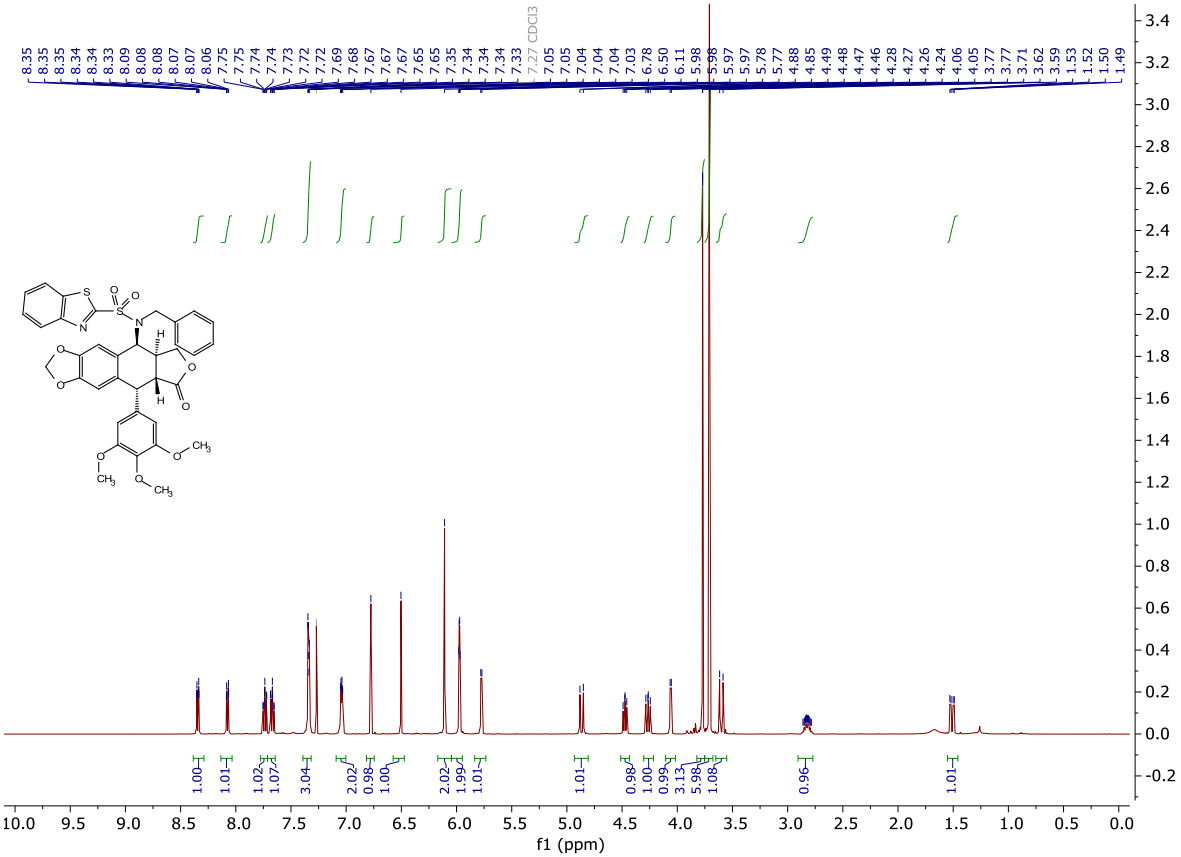
^{1}H NMR (400 MHz, $CDCl_3$) of methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-((R)-1-methoxy-1-oxopropan-2-yl)-L-alaninate (4-6da)



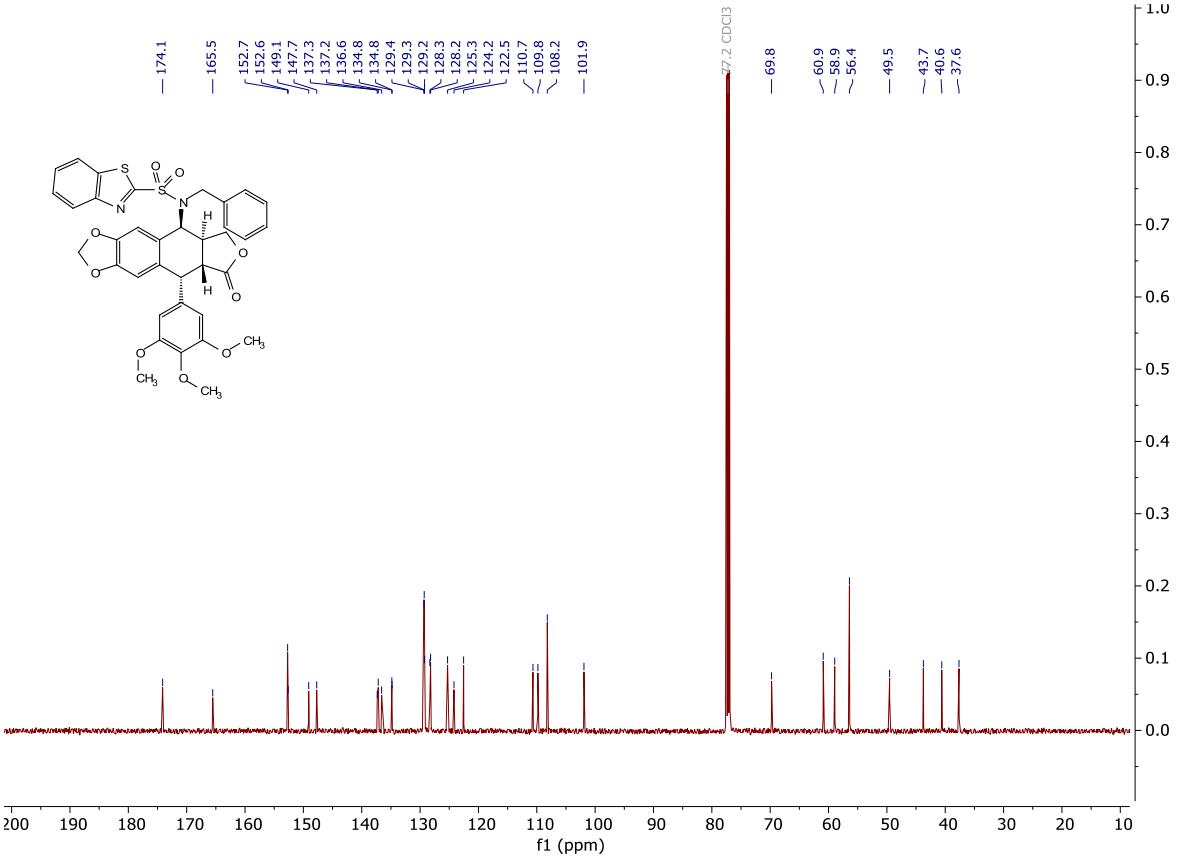
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-((R)-1-methoxy-1-oxopropan-2-yl)-L-alaninate (meso-4-6da)



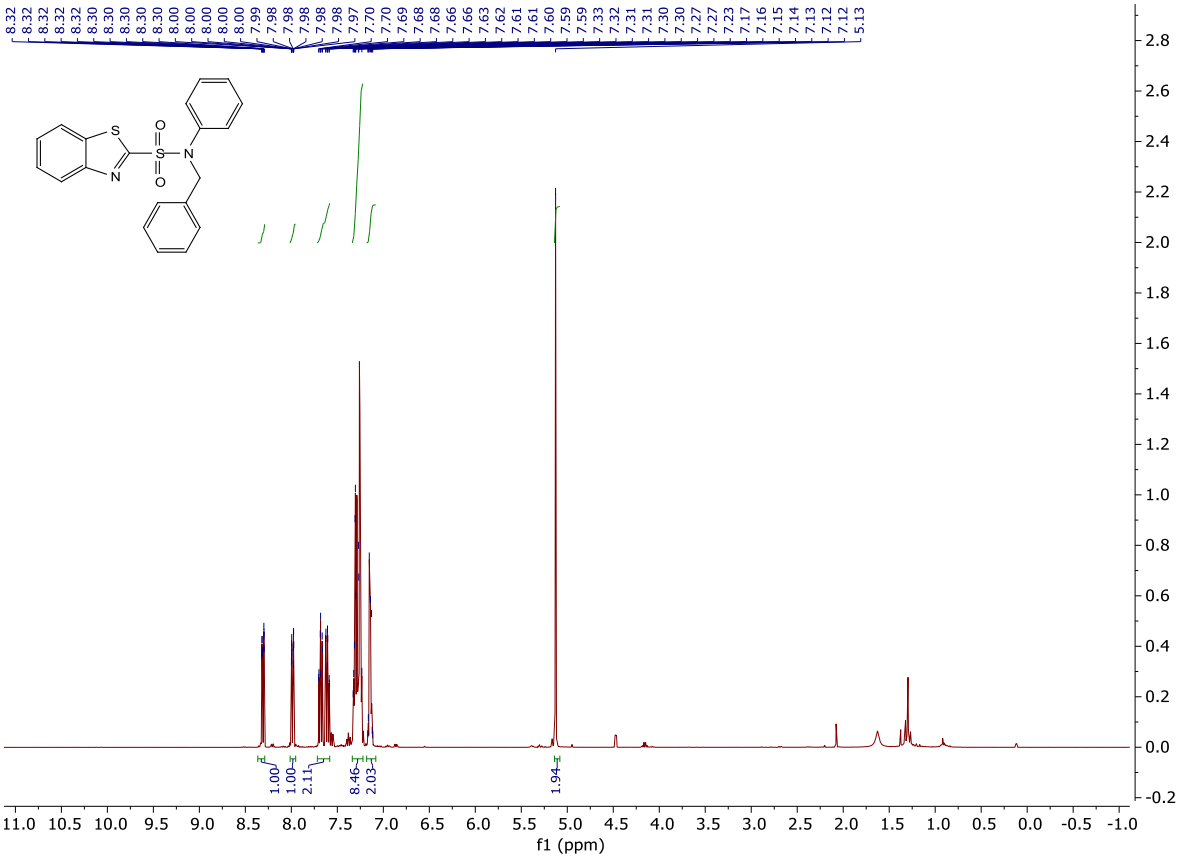
^{1}H NMR (400 MHz, $CDCl_3$) of (5R,5aR,8aS,9S)-9-(benzo[d]thiazol-2-yl(benzyl)amino)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one (4-6ag)



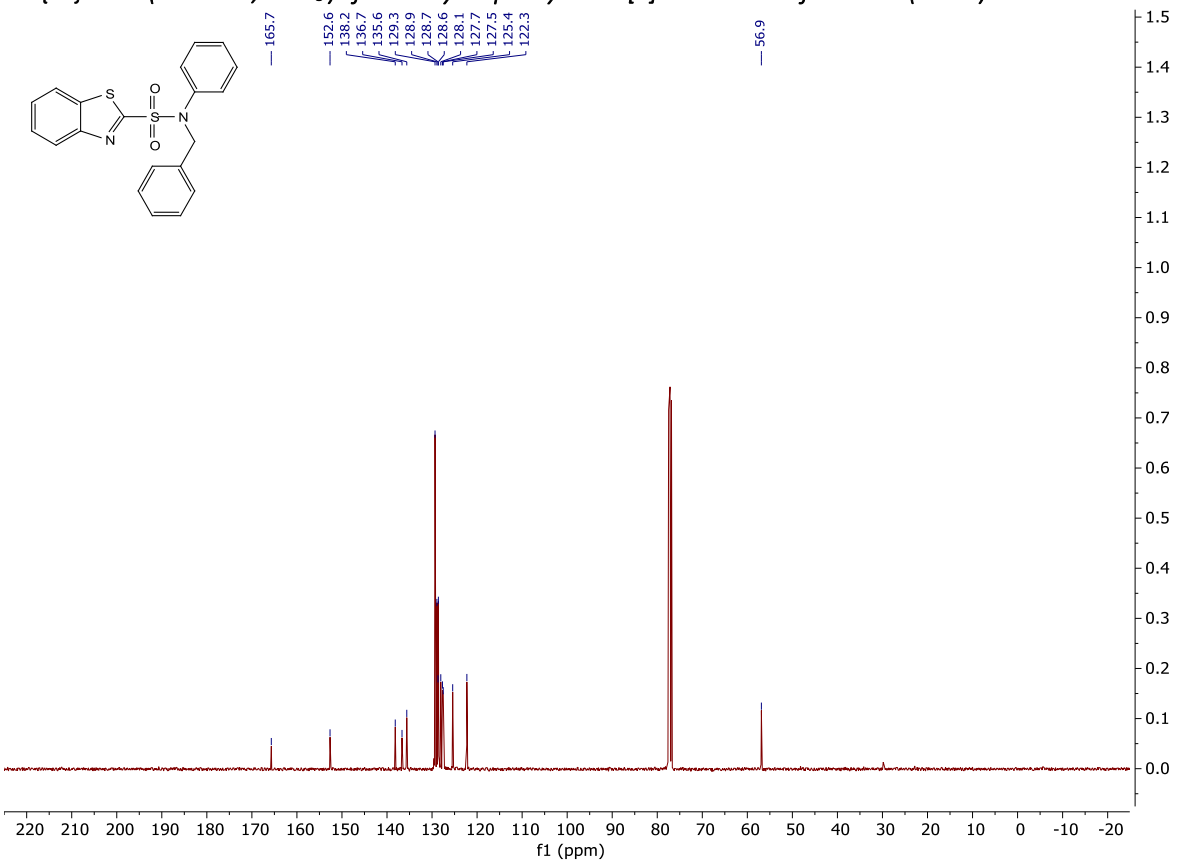
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of (5R,5aR,8aS,9S)-9-(benzo[d]thiazol-2-yl(benzyl)amino)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-on (4-6ag)



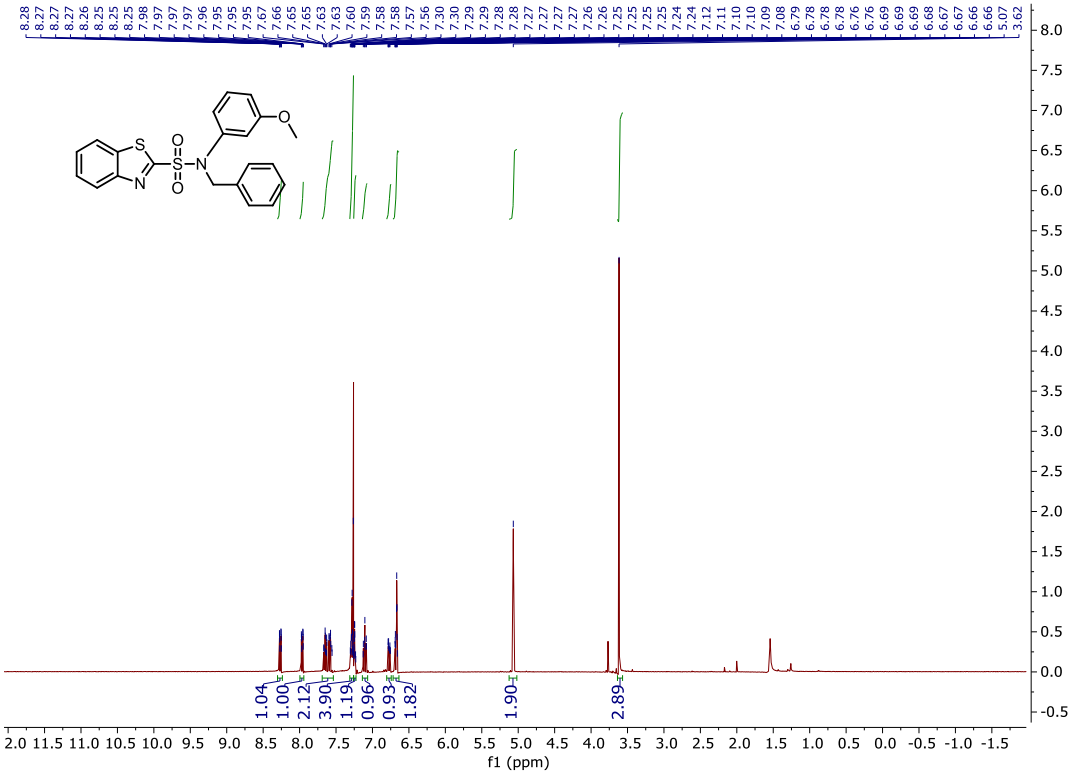
^{1}H NMR (400 MHz, $CDCl_3$) of N-benzyl-N-phenylbenzo[d]thiazole-2-sulfonamide (4-6ah)



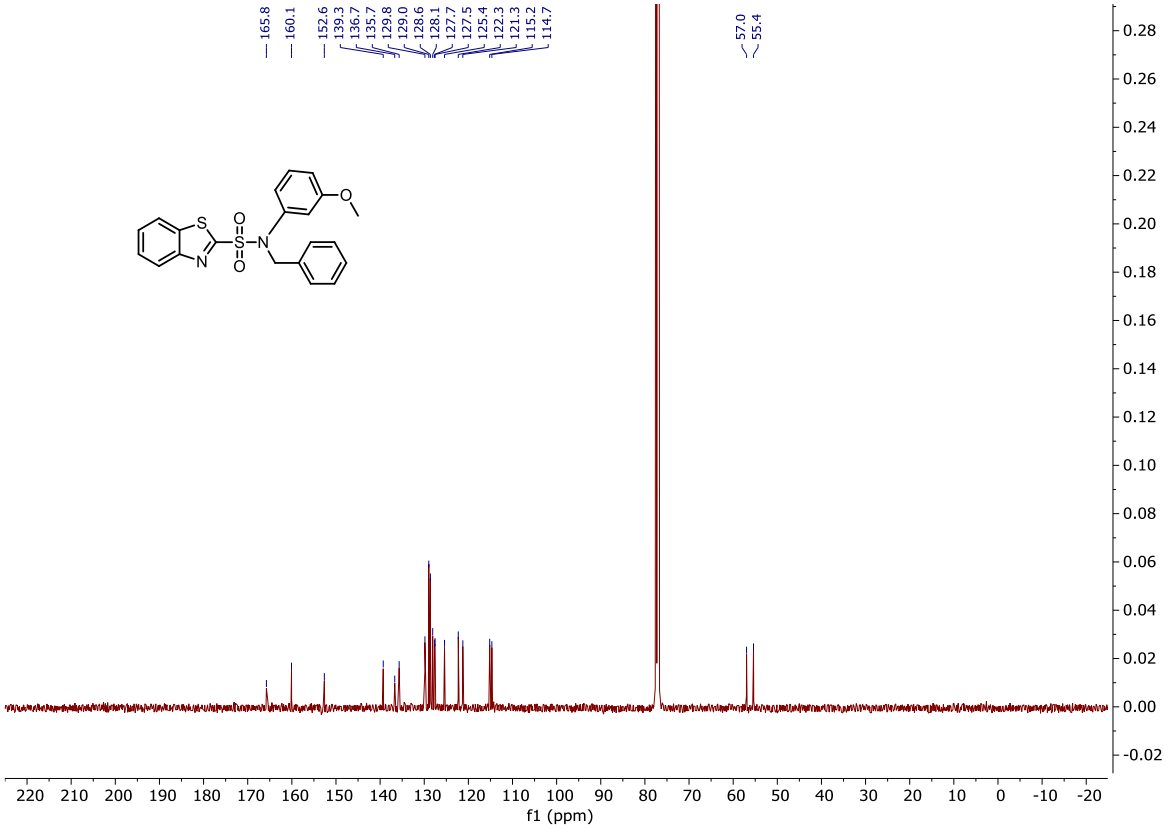
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-benzyl-N-phenylbenzo[d]thiazole-2-sulfonamide (4-6ah)



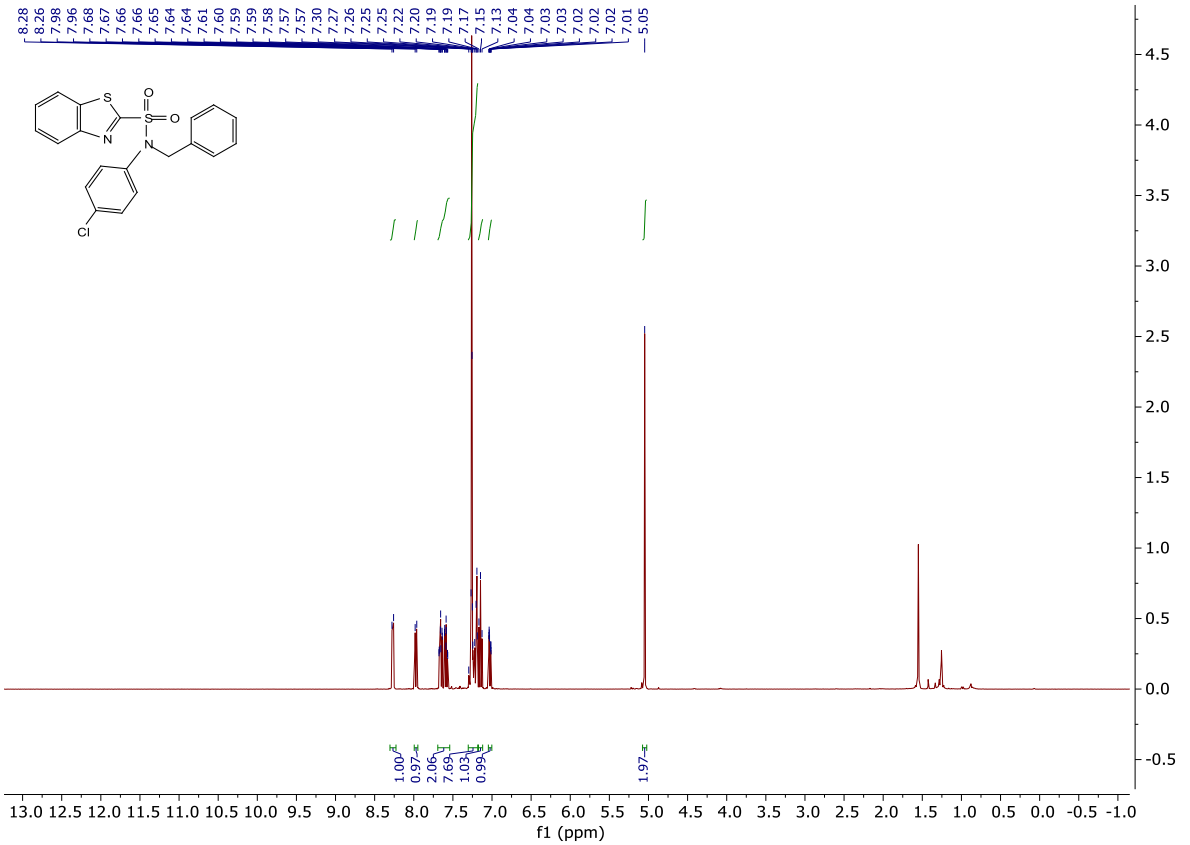
^{1}H NMR (400 MHz, $CDCl_3$) of N-benzyl-N-(3-methoxyphenyl)benzo[d]thiazole-2-sulfonamide (4-6ai)



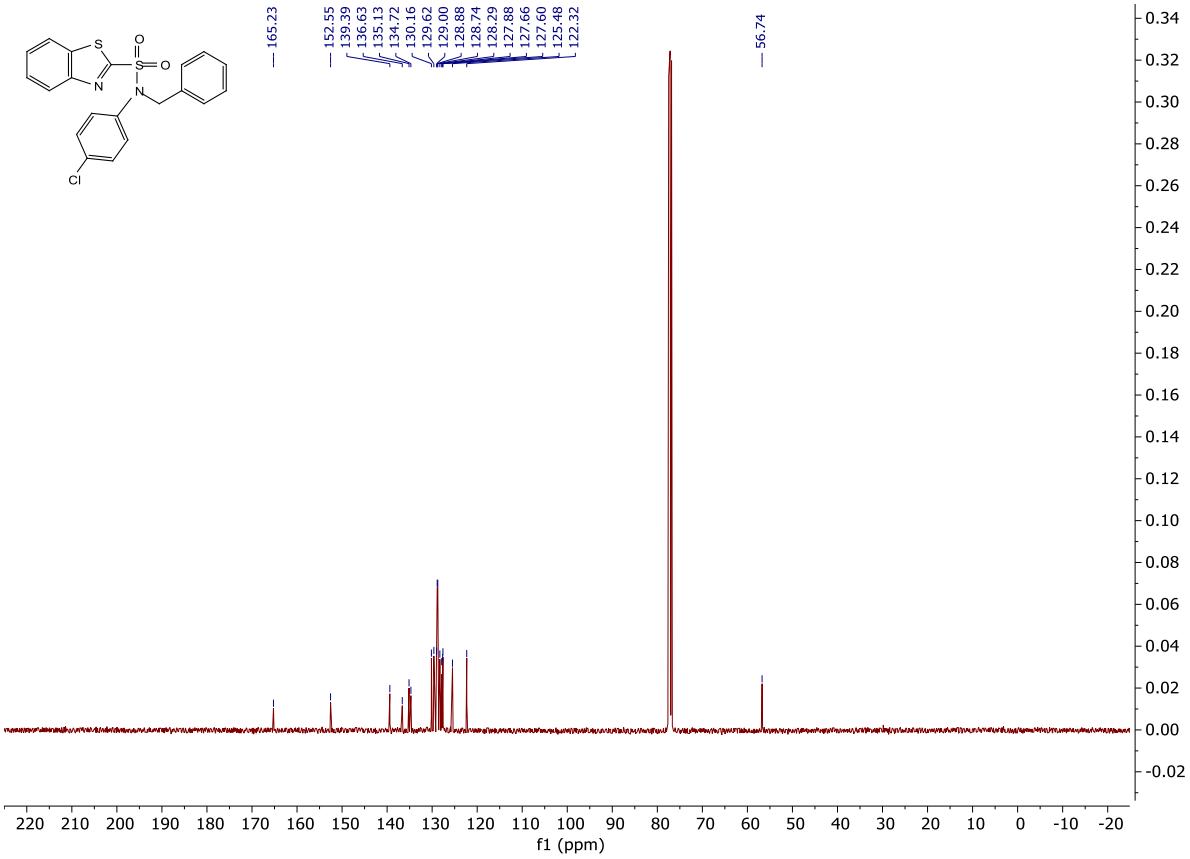
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-benzyl-N-(3-methoxyphenyl)benzo[d]thiazole-2-sulfonamide (4-6ai)



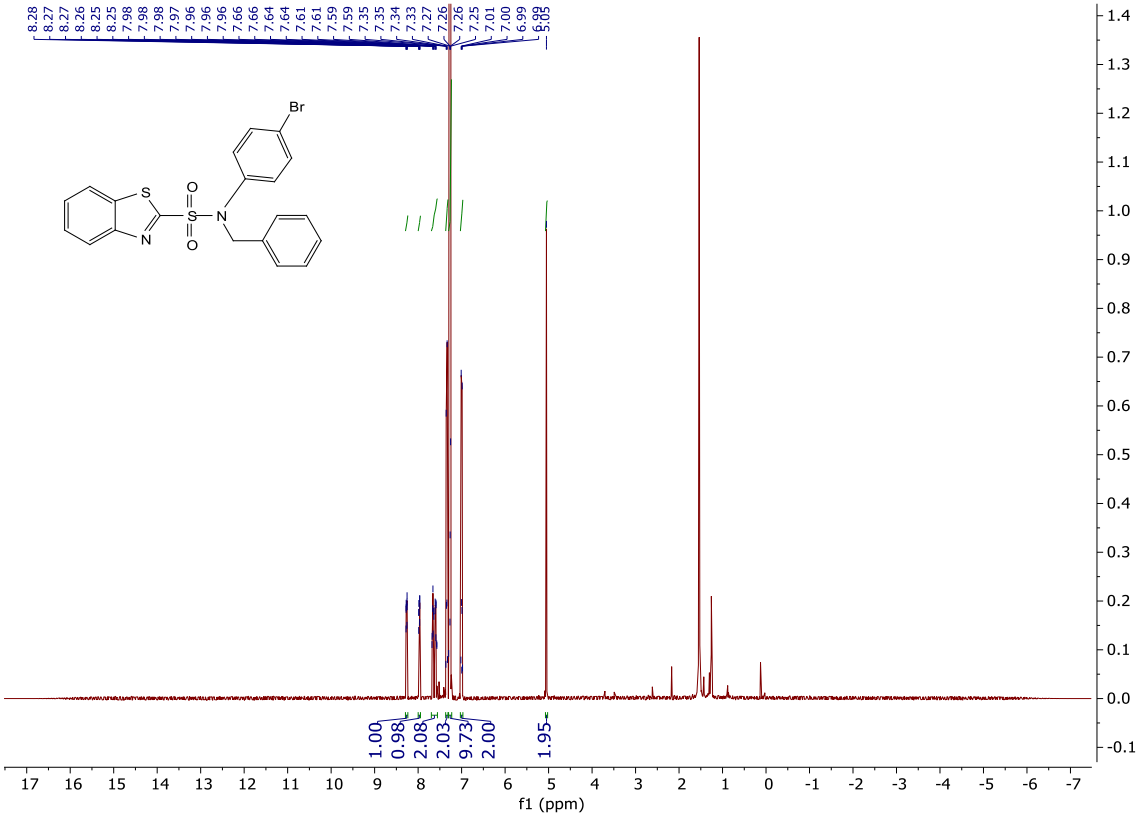
^{1}H NMR (400 MHz, CDCl$_3$) of N-benzyl-N-(4-chlorophenyl)benzo[d]thiazole-2-sulfonamide (4-6aj)



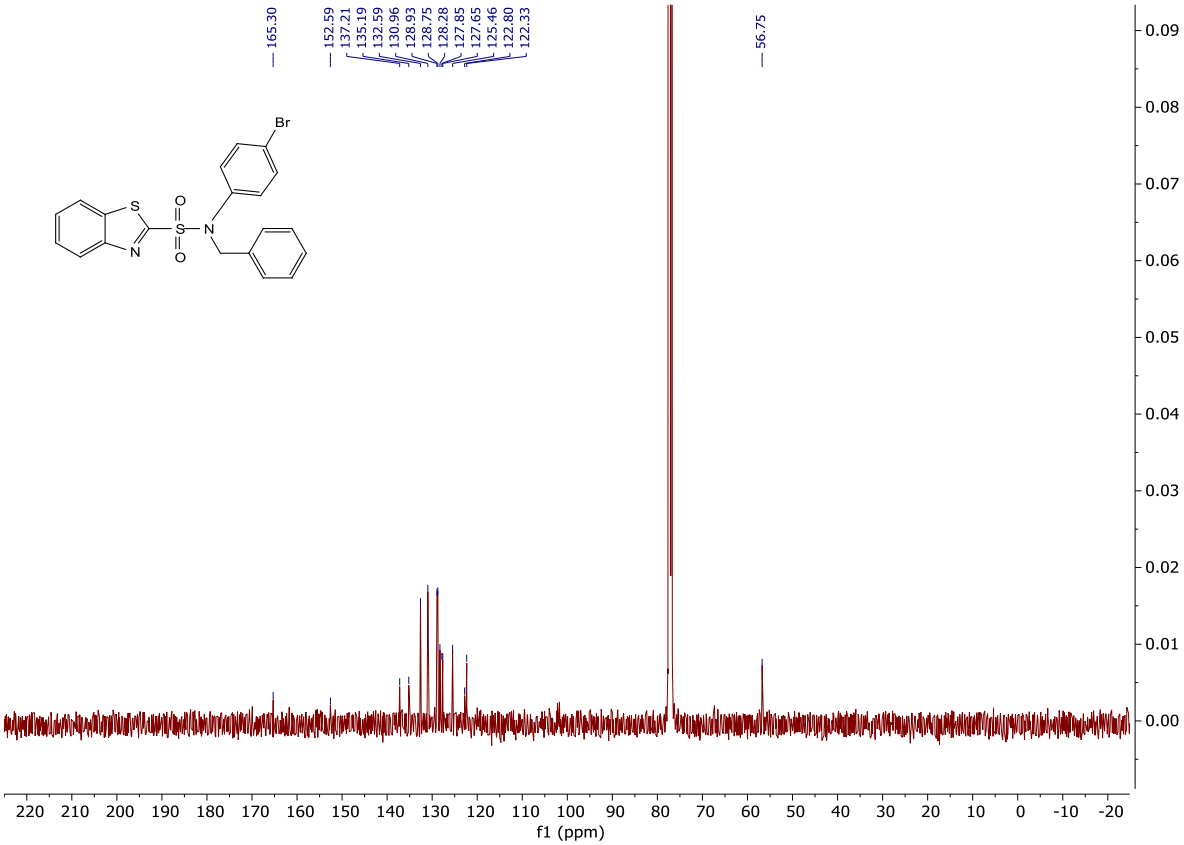
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$) of N-benzyl-N-(4-chlorophenyl)benzo[d]thiazole-2-sulfonamide (4-6aj)



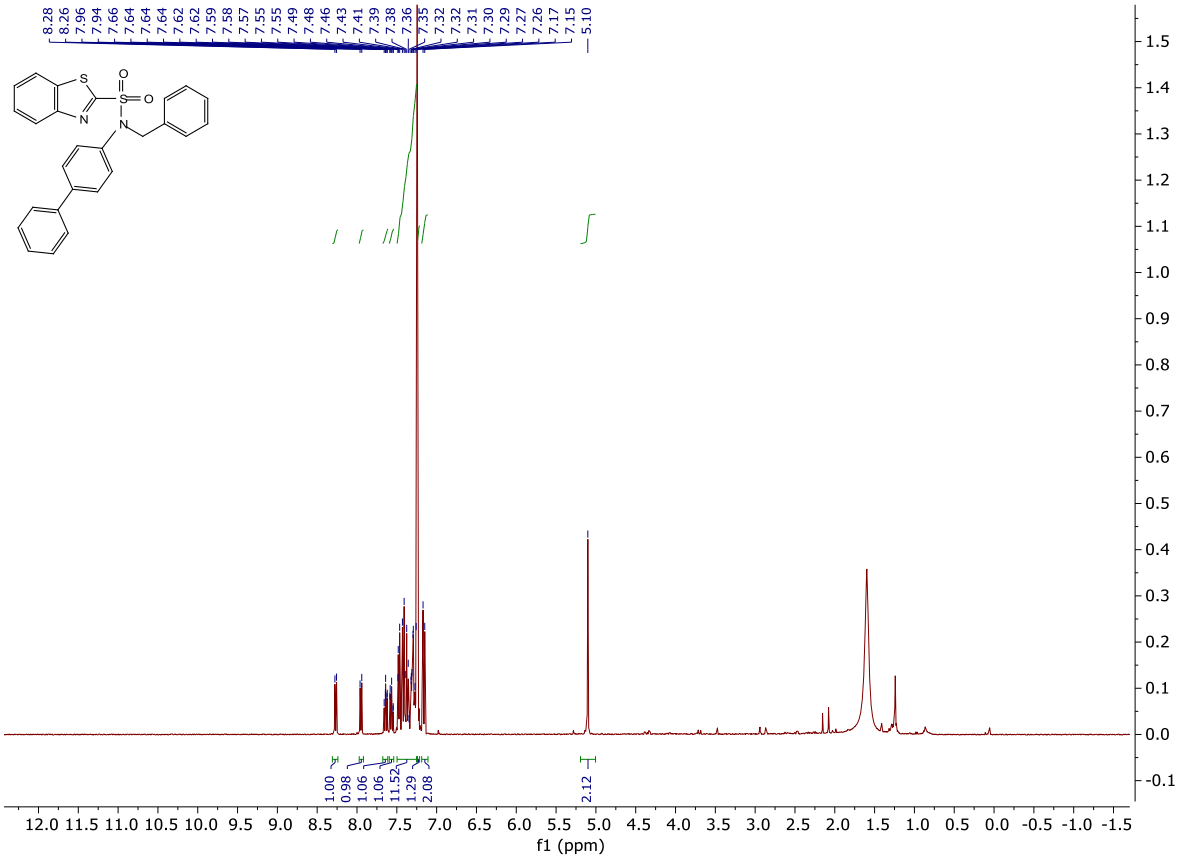
^{1}H NMR (400 MHz, CDCl$_3$) of N-benzyl-N-(4-bromophenyl)benzo[d]thiazole-2-sulfonamide (4-6ak)



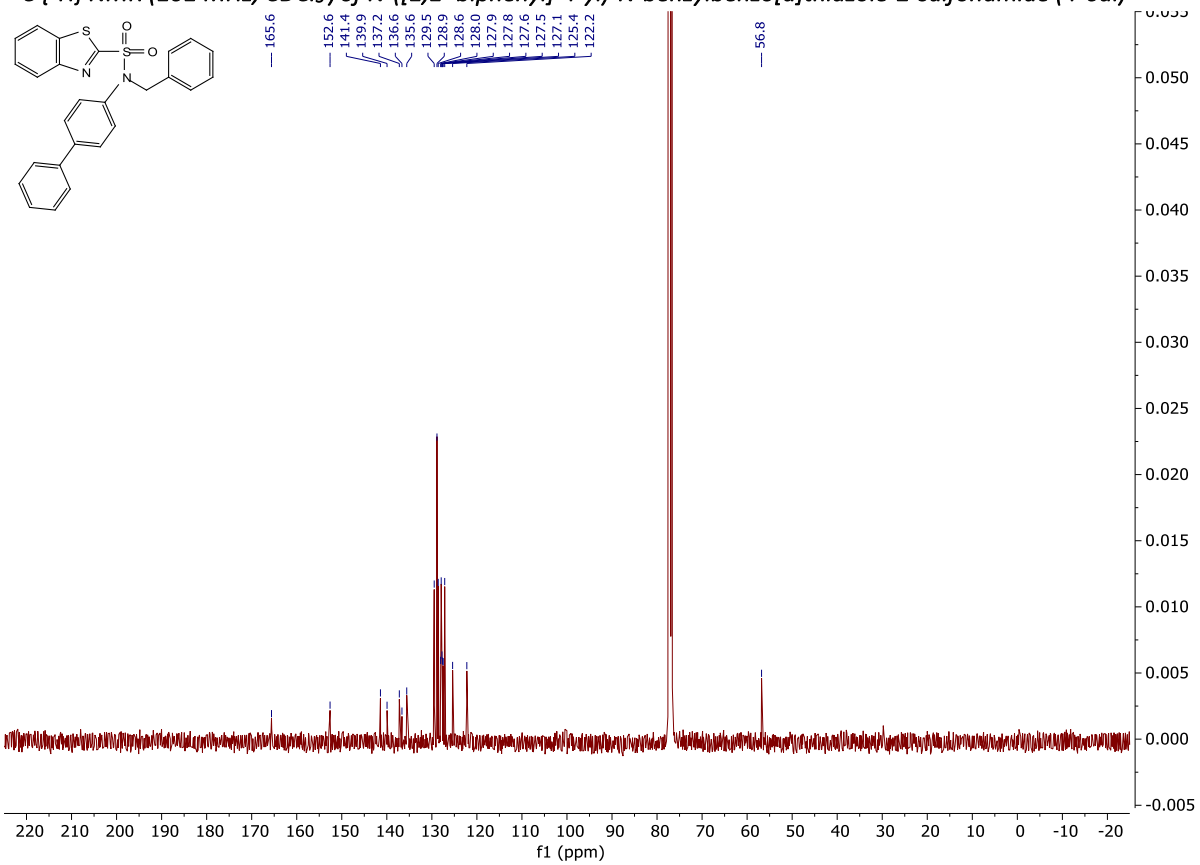
^{13}C {^{1}H} NMR (101 MHz, CDCl$_3$ of N-benzyl-N-(4-bromophenyl)benzo[d]thiazole-2-sulfonamide (4-6ak)



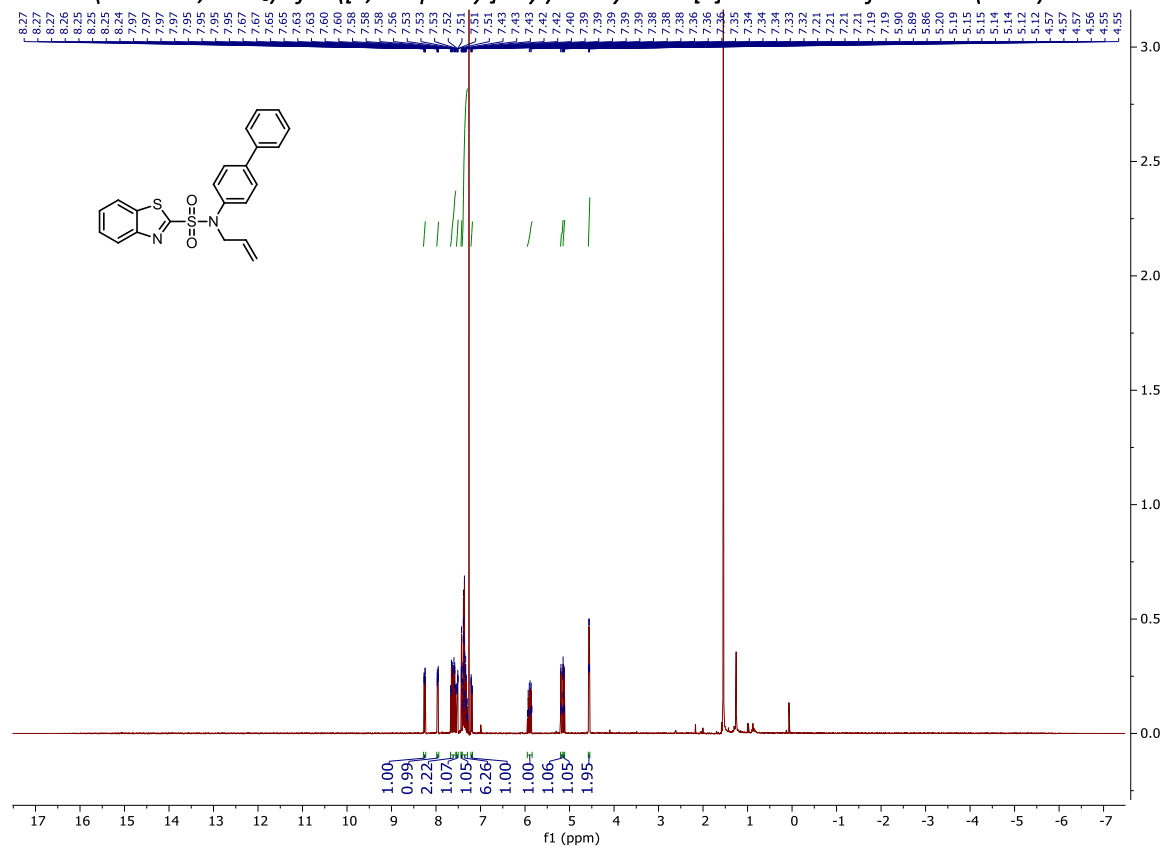
^{1}H NMR (400 MHz, $CDCl_3$) of N-([1,1'-biphenyl]-4-yl)-N-benzylbenzo[d]thiazole-2-sulfonamide (4-6al)



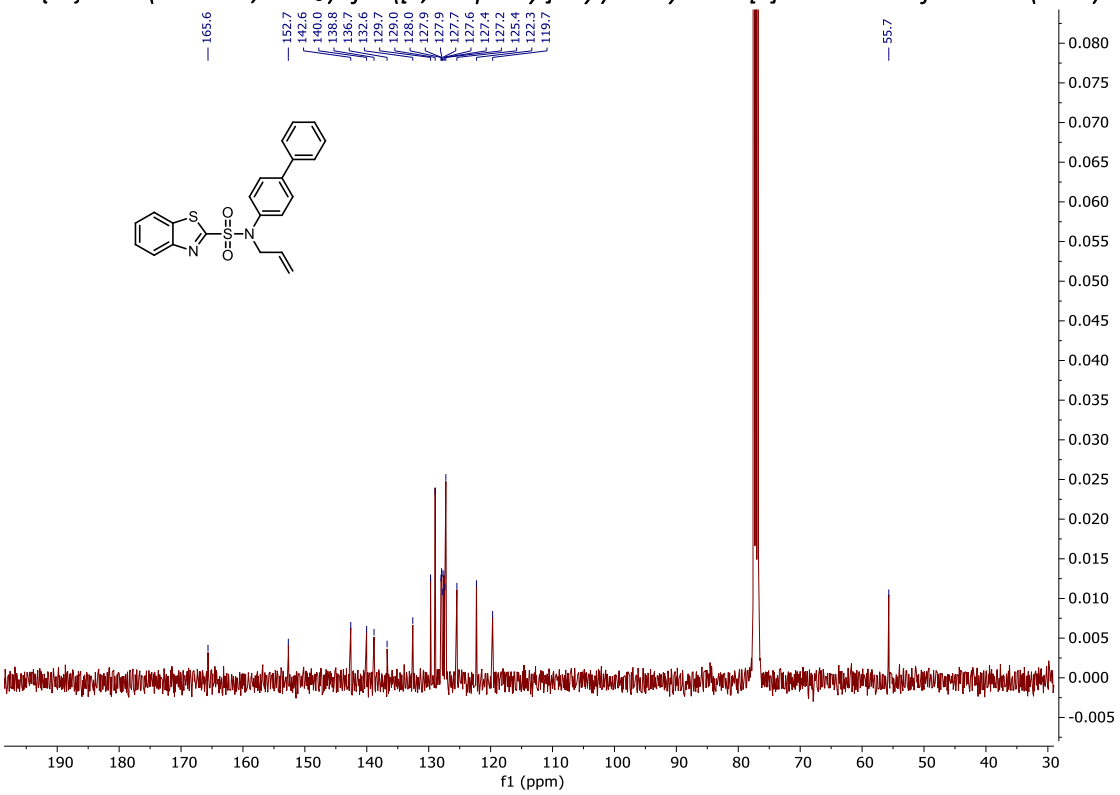
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-([1,1'-biphenyl]-4-yl)-N-benzylbenzo[d]thiazole-2-sulfonamide (4-6al)



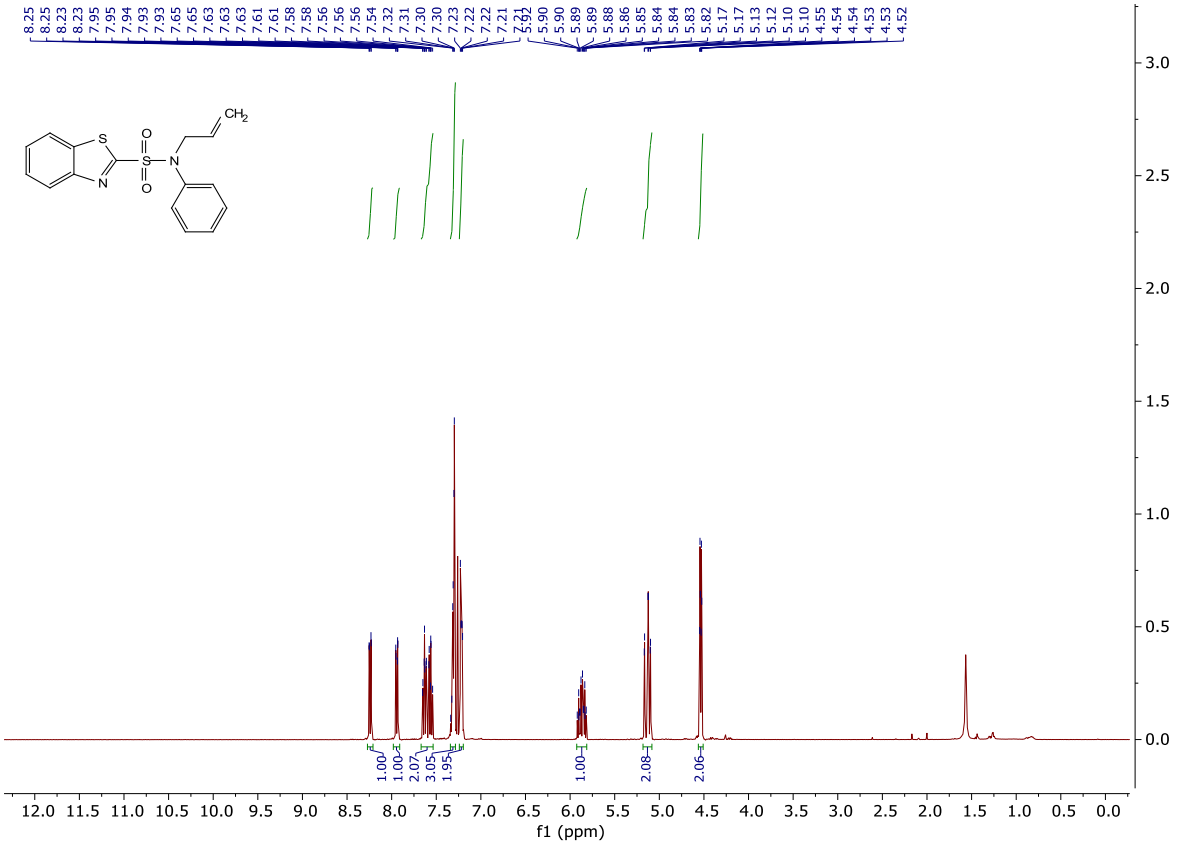
^{1}H NMR (400 MHz, $CDCl_3$) of N-([1,1'-biphenyl]-4-yl)-N-allylbenzo[d]thiazole-2-sulfonamide (4-6bl)



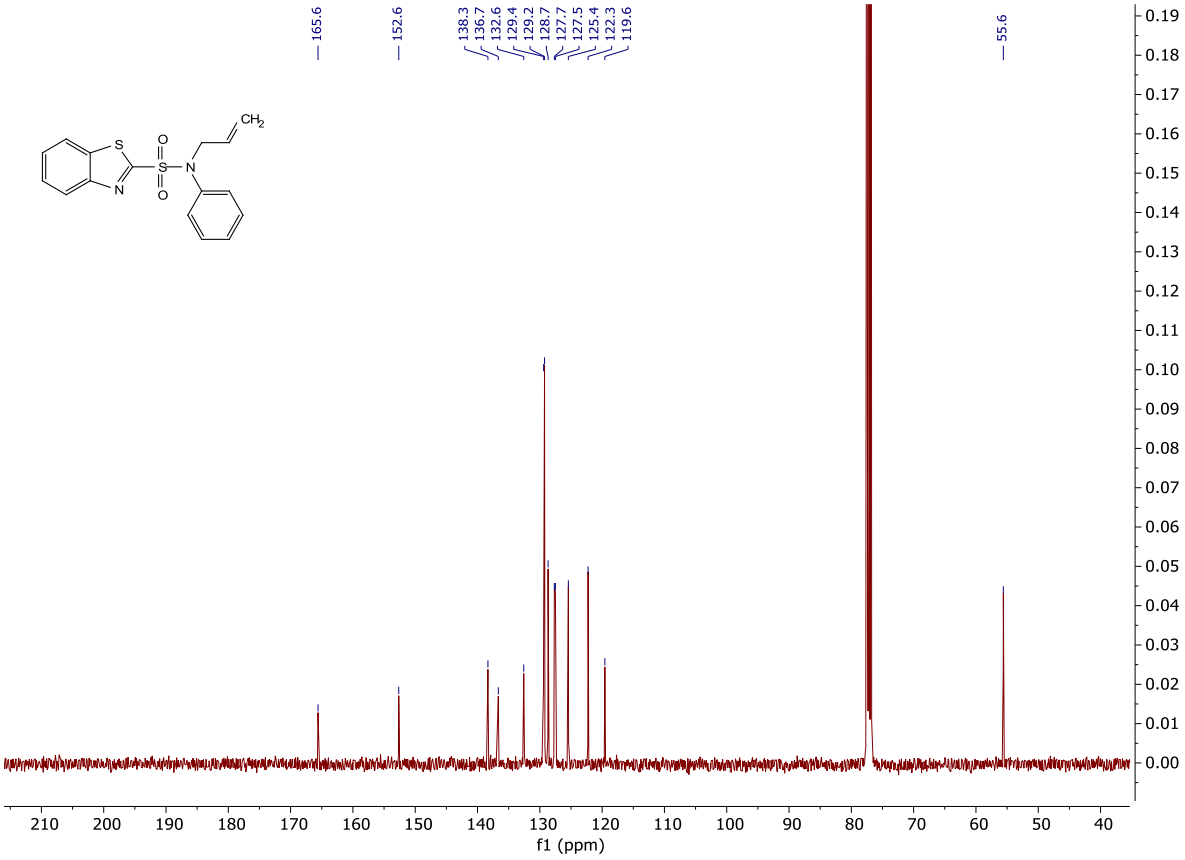
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-([1,1'-biphenyl]-4-yl)-N-allylbenzo[d]thiazole-2-sulfonamide (4-6bl)



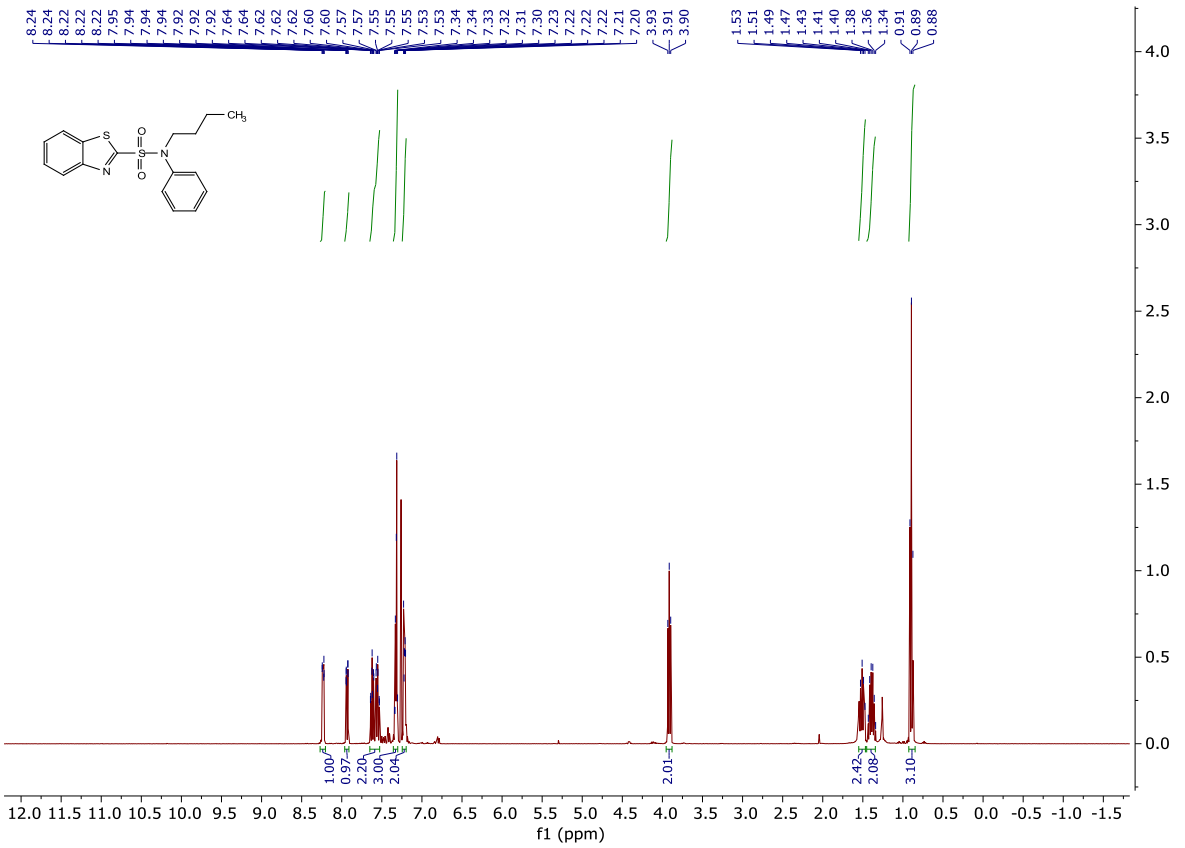
^{1}H NMR (400 MHz, $CDCl_3$) of N-allyl-N-phenylbenzo[d]thiazole-2-sulfonamide (4-6bh)



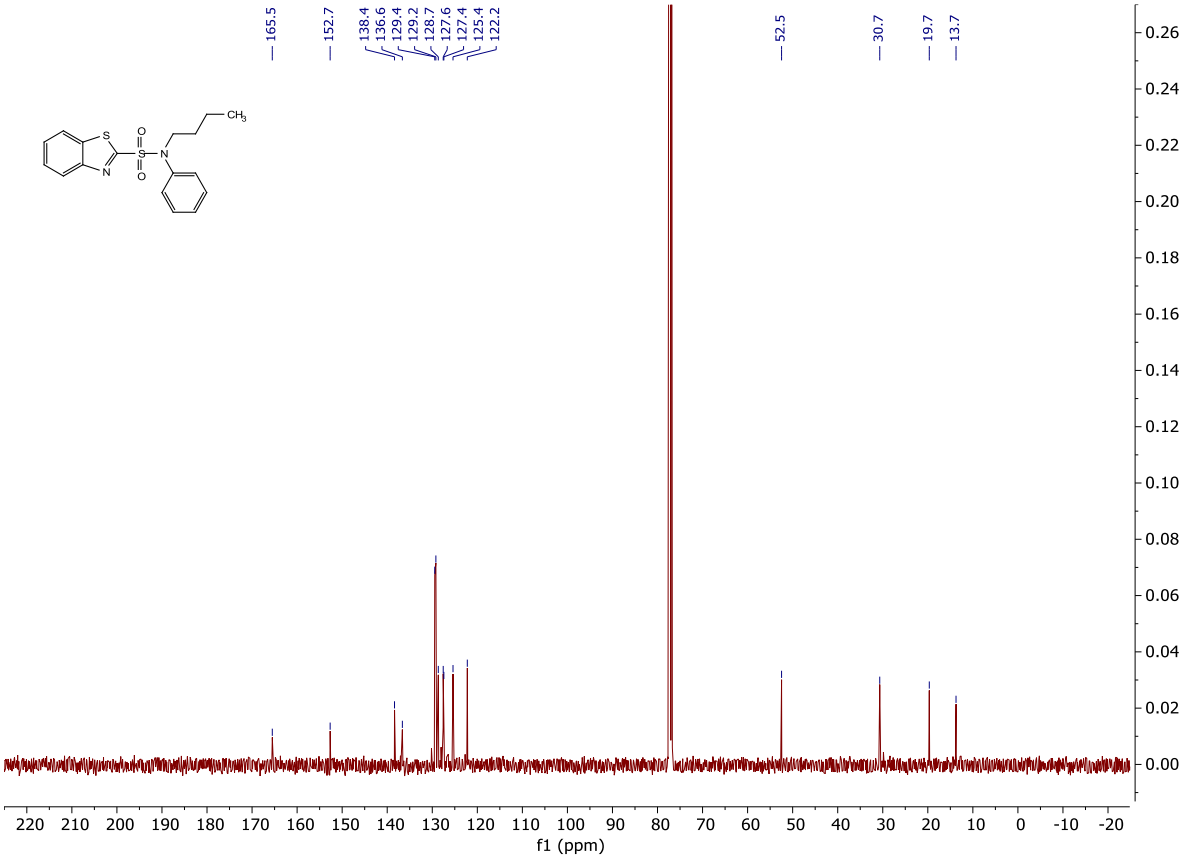
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-allyl-N-phenylbenzo[d]thiazole-2-sulfonamide (4-6bh)



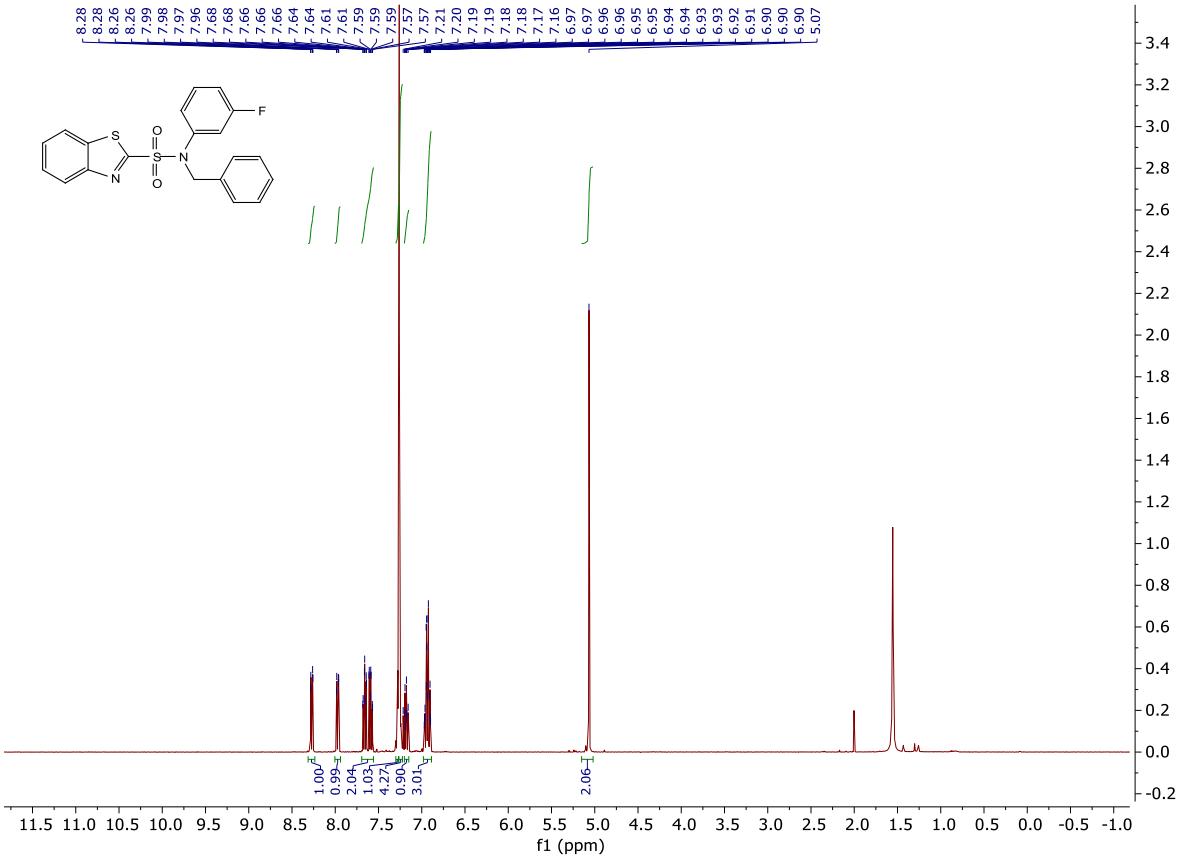
^{1}H NMR (400 MHz, $CDCl_3$) of N-butyl-N-phenylbenzo[d]thiazole-2-sulfonamide (4-6ch)



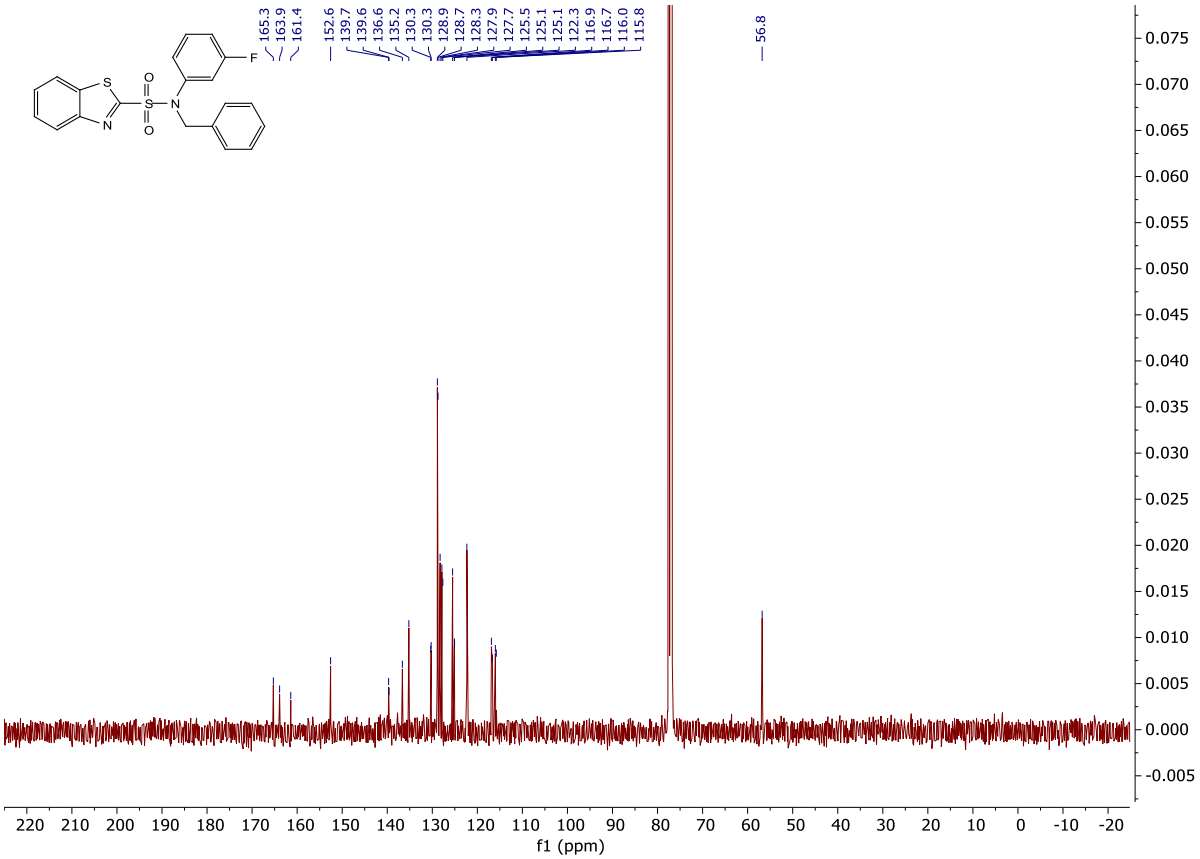
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-butyl-N-phenylbenzo[d]thiazole-2-sulfonamide (4-6ch)



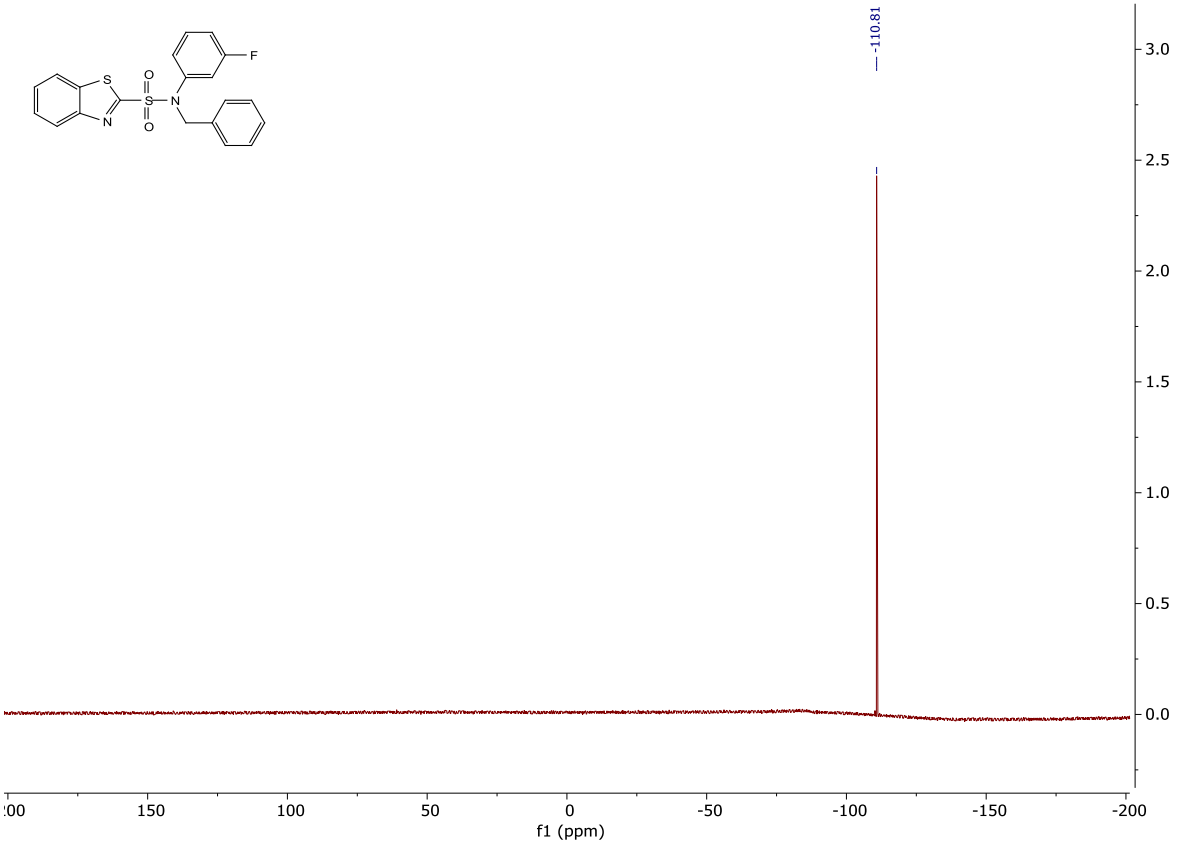
^{1}H NMR (400 MHz, $CDCl_3$) of N-benzyl-N-(3-fluorophenyl)benzo[d]thiazole-2-sulfonamide (4-6f



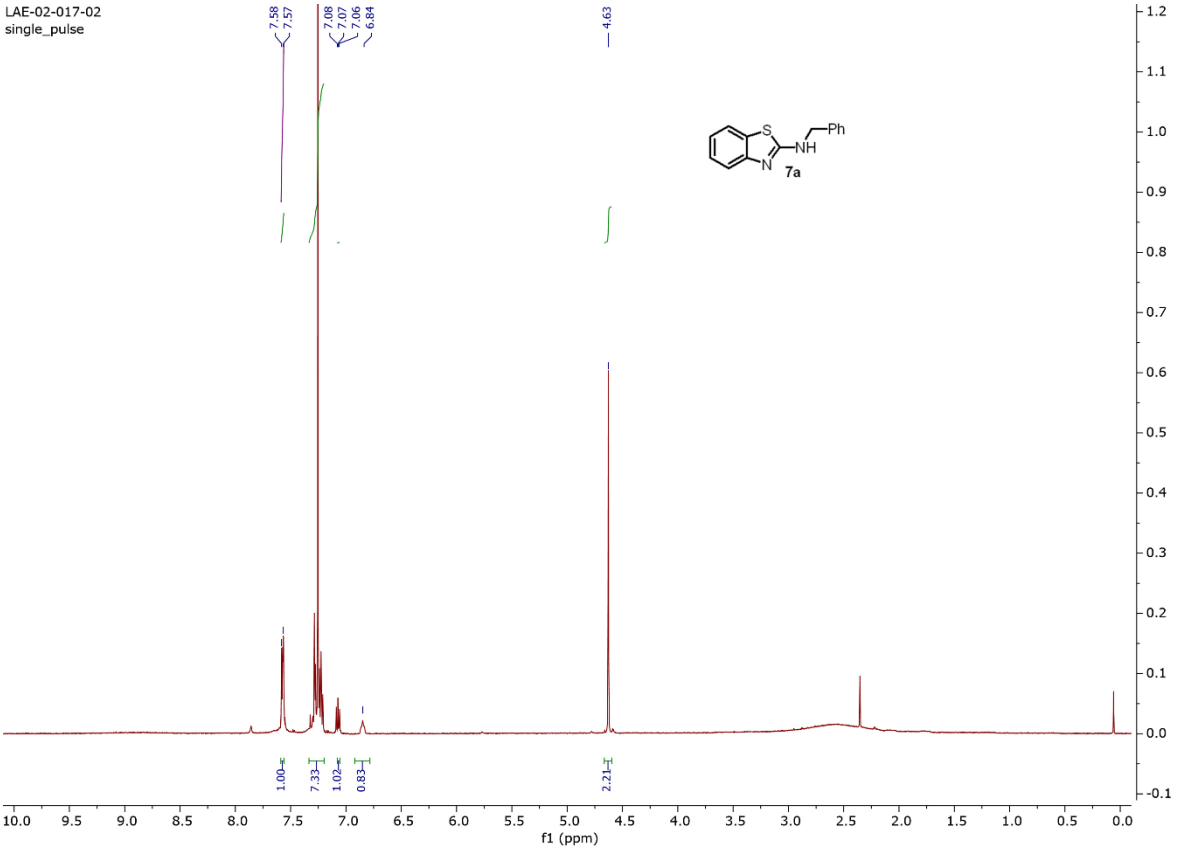
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of N-benzyl-N-(3-fluorophenyl)benzo[d]thiazole-2-sulfonamide (4-6fa)



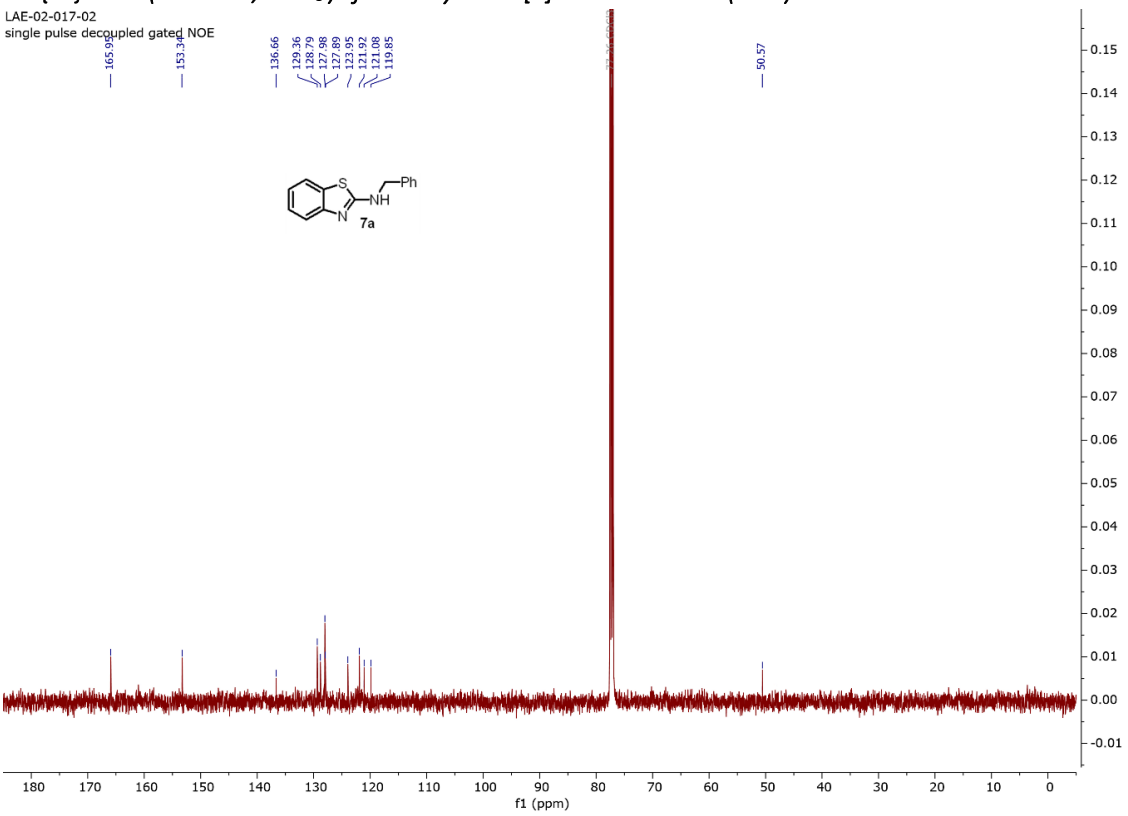
^{19}F NMR (376 MHz ,$CDCl_3$) N-benzyl-N-(3-fluorophenyl)benzo[d]thiazole-2-sulfonamide (4-6fa)



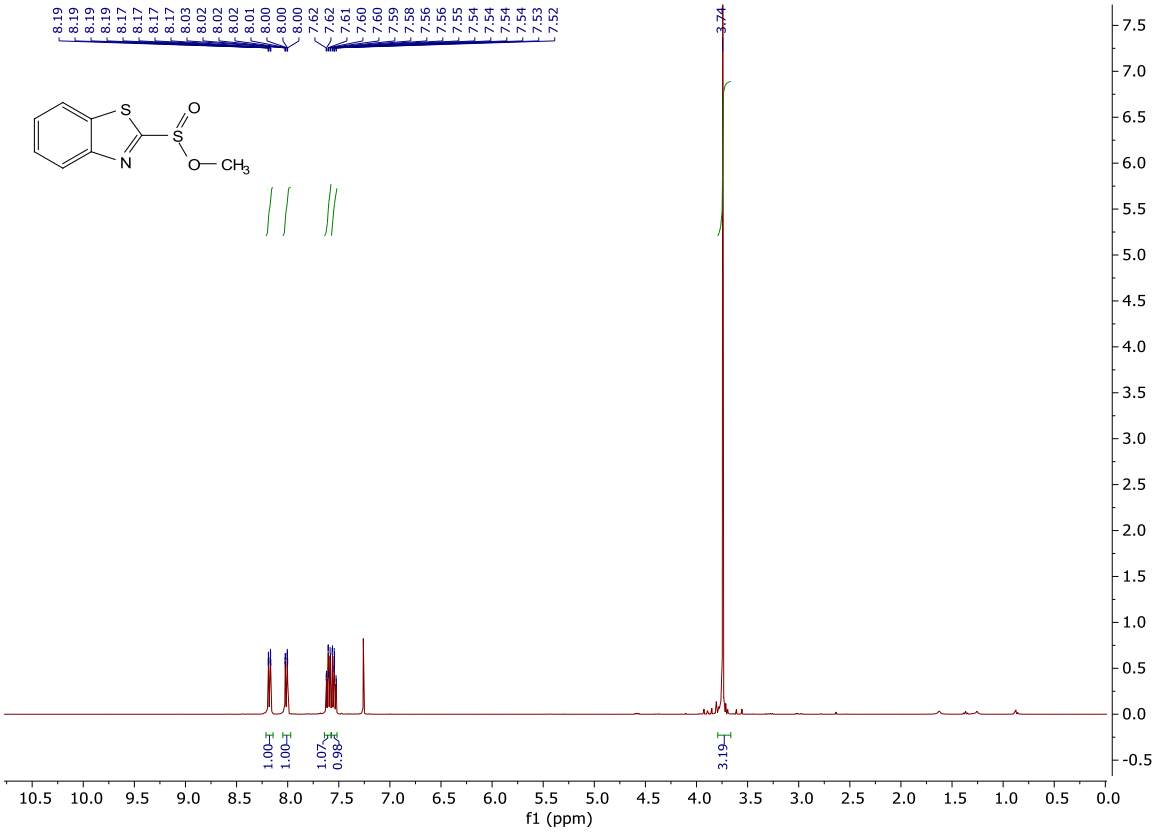
^{1}H NMR (500 MHz, $CDCl_3$) of N-benzylbenzo[d]thiazol-2-amine (4-62)



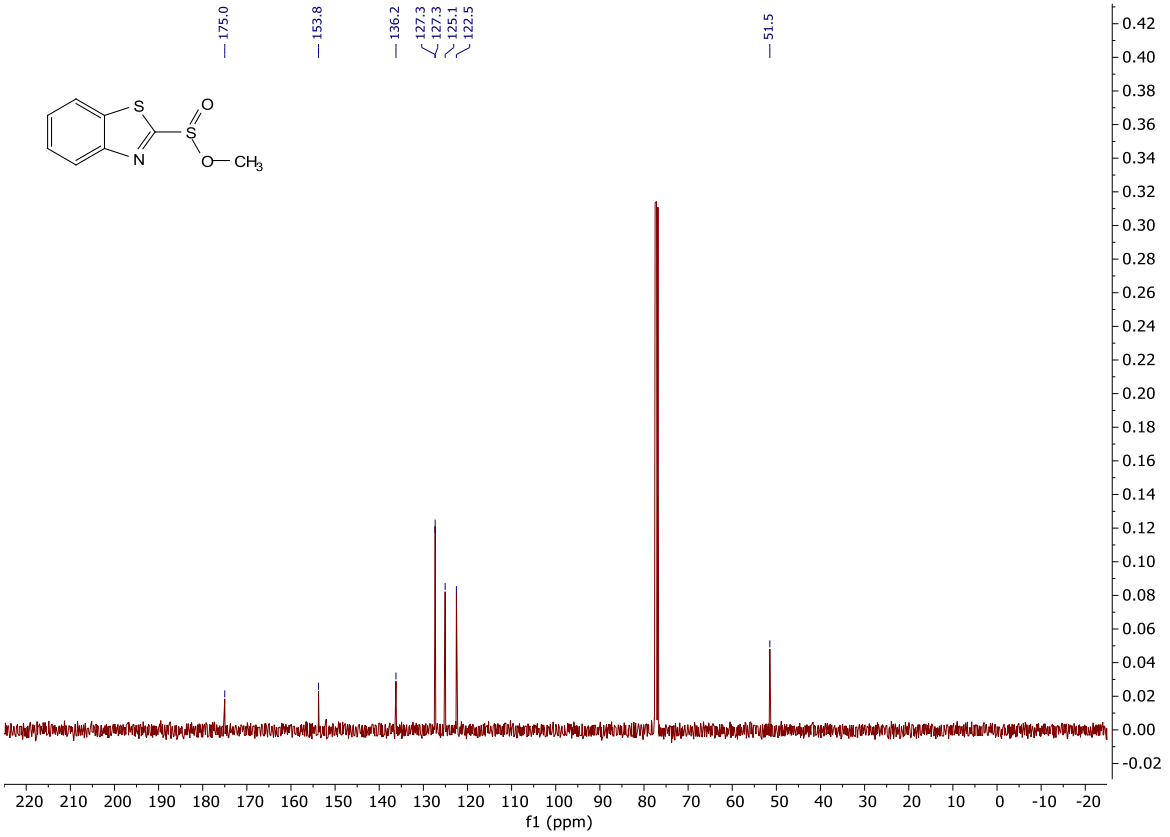
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) of N-benzylbenzo[d]thiazol-2-amine (4-62)



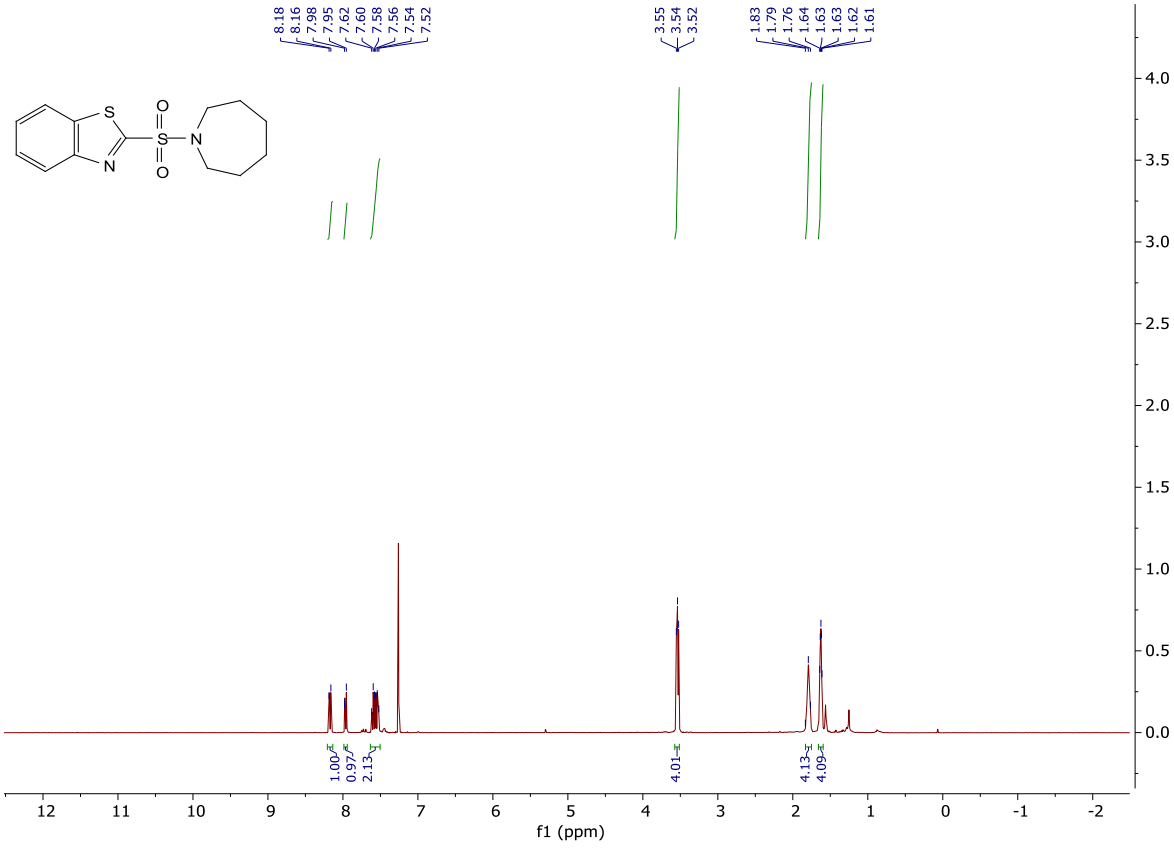
^{1}H NMR (400 MHz, $CDCl_3$) of methyl benzo[d]thiazole-2-sulfinate (4-16)



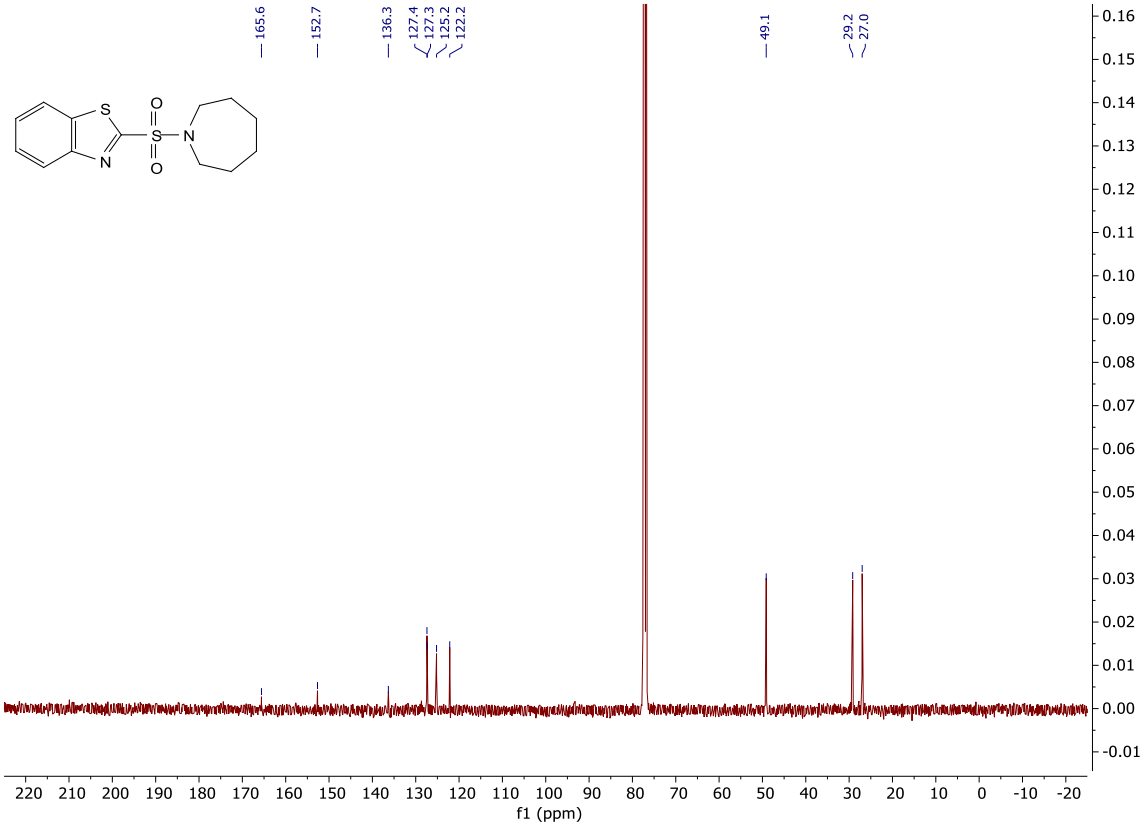
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of methyl benzo[d]thiazole-2-sulfinate (4-16)



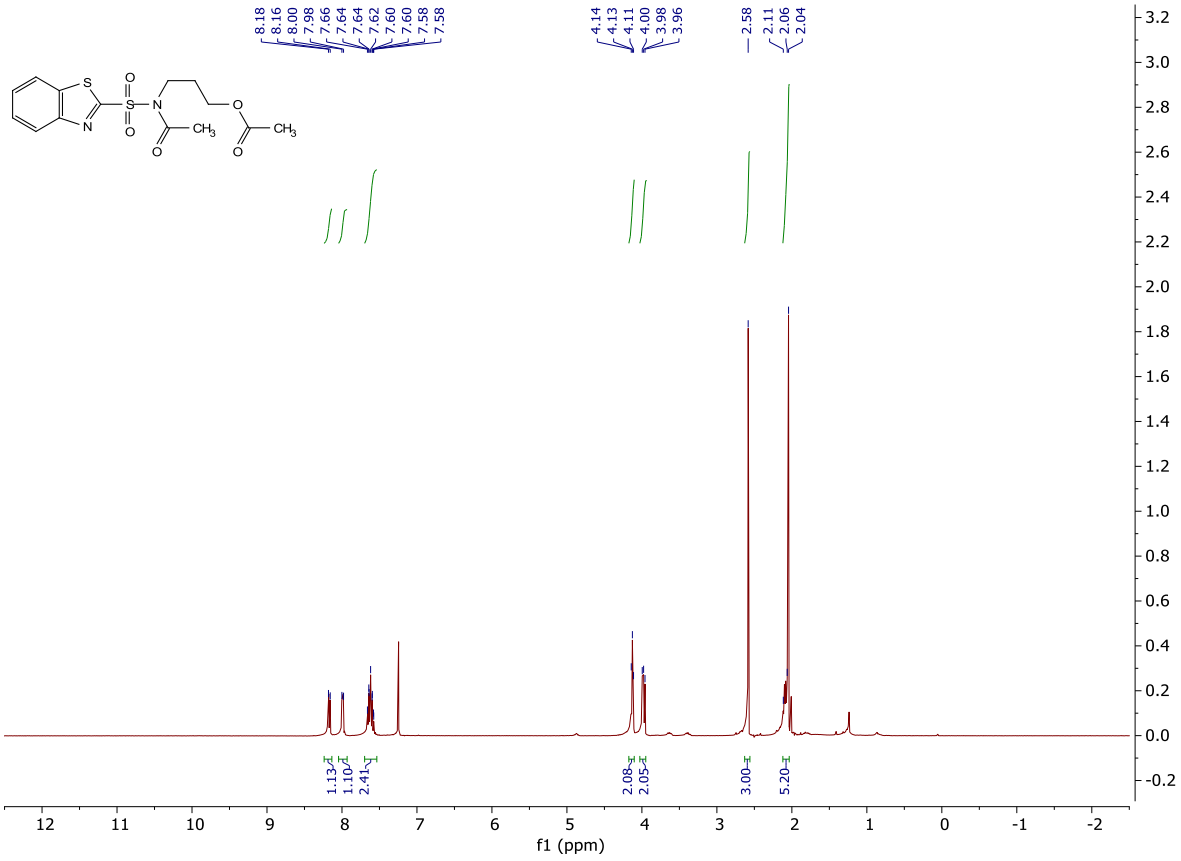
^{1}H NMR (400 MHz, $CDCl_3$) of 2-(azepan-1-ylsulfonyl)benzo[d]thiazole (4-51)



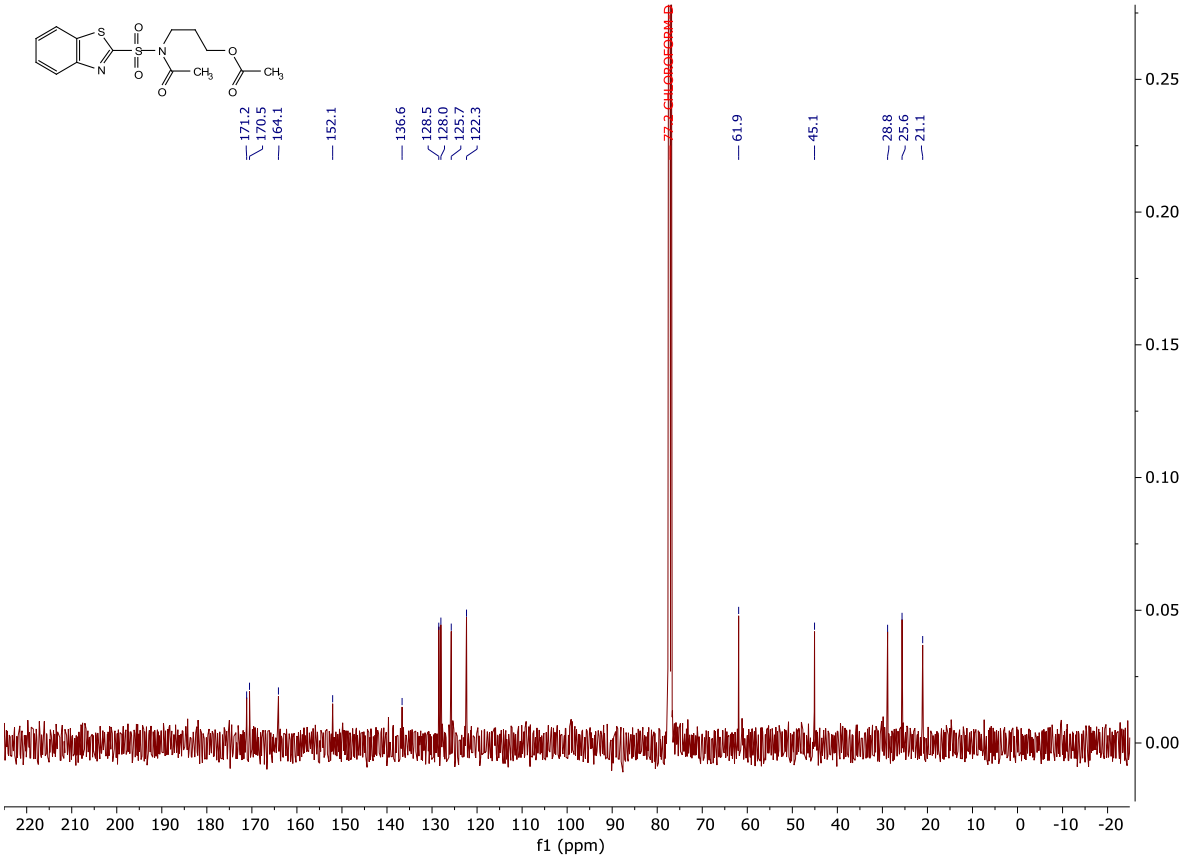
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of 2-(azepan-1-ylsulfonyl)benzo[d]thiazole (4-51)



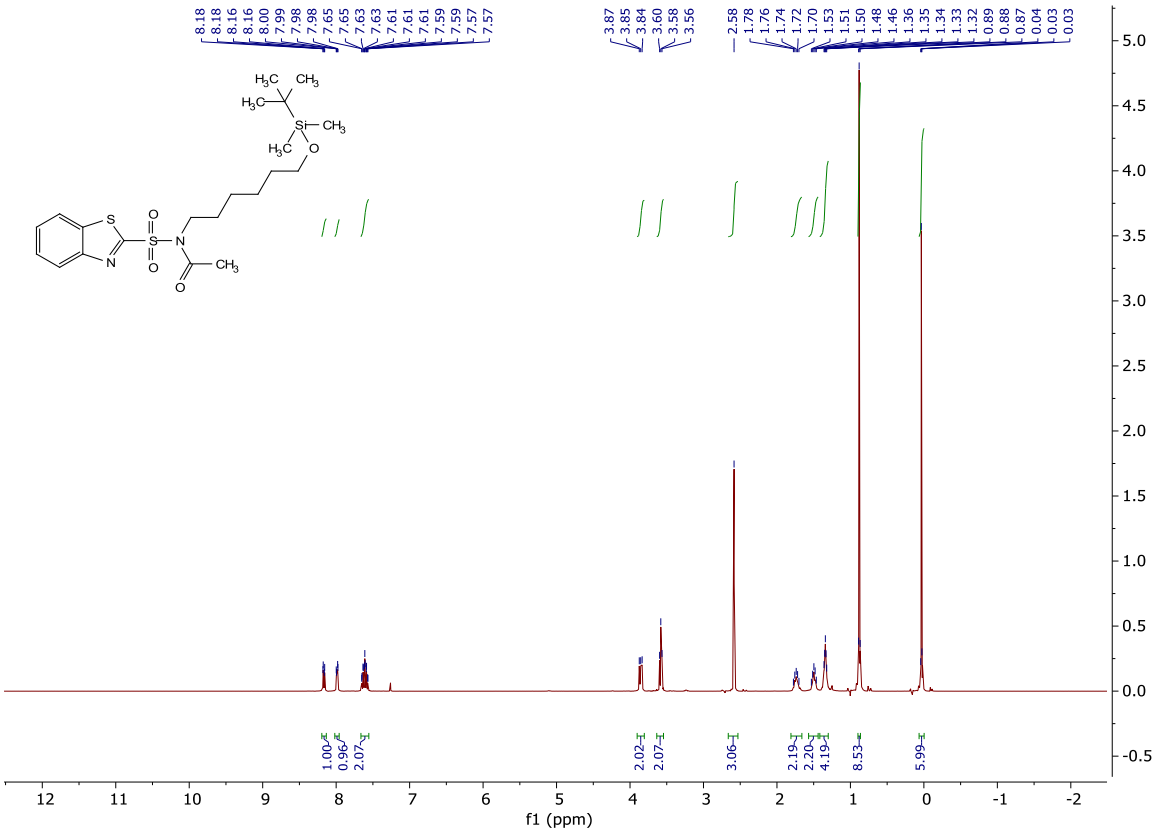
^{1}H NMR (400 MHz, $CDCl_3$) of 3-(N-(benzo[d]thiazol-2-ylsulfonyl)acetamido)propyl acetate (4-75)



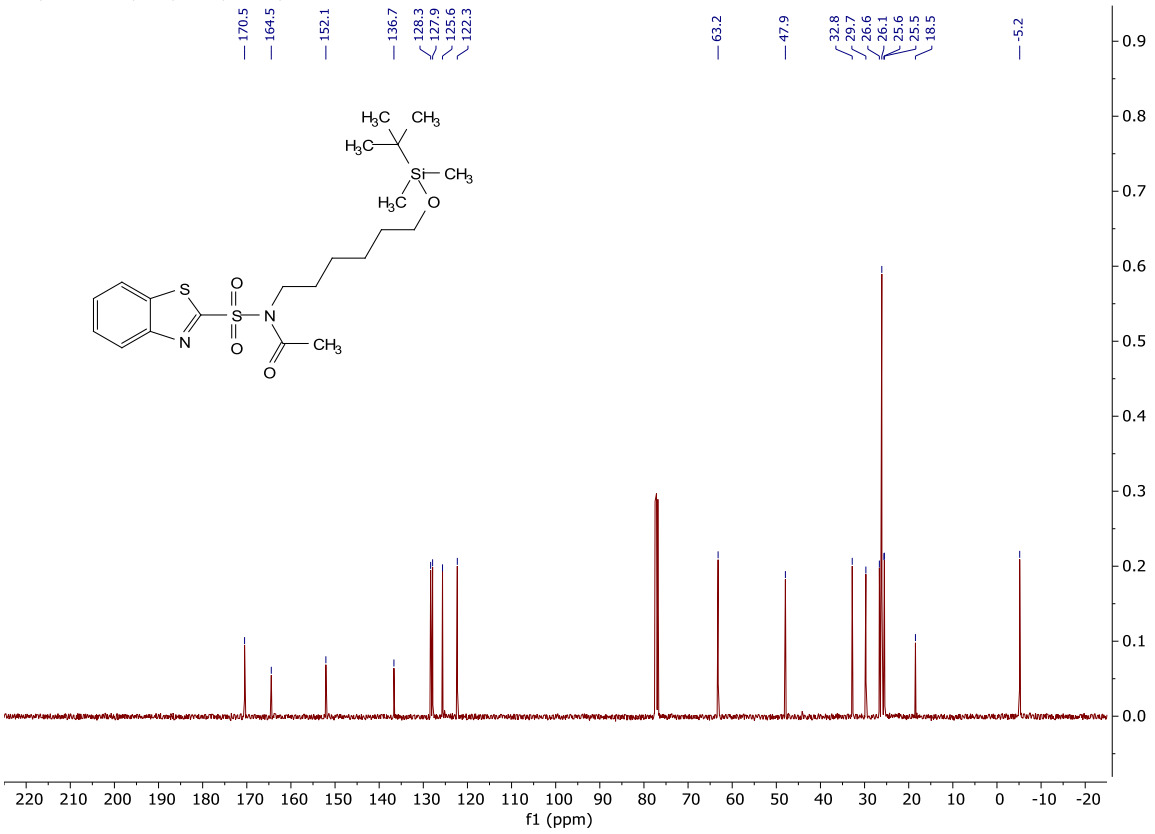
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of 3-(N-(benzo[d]thiazol-2-ylsulfonyl)acetamido)propyl acetate (4-75)



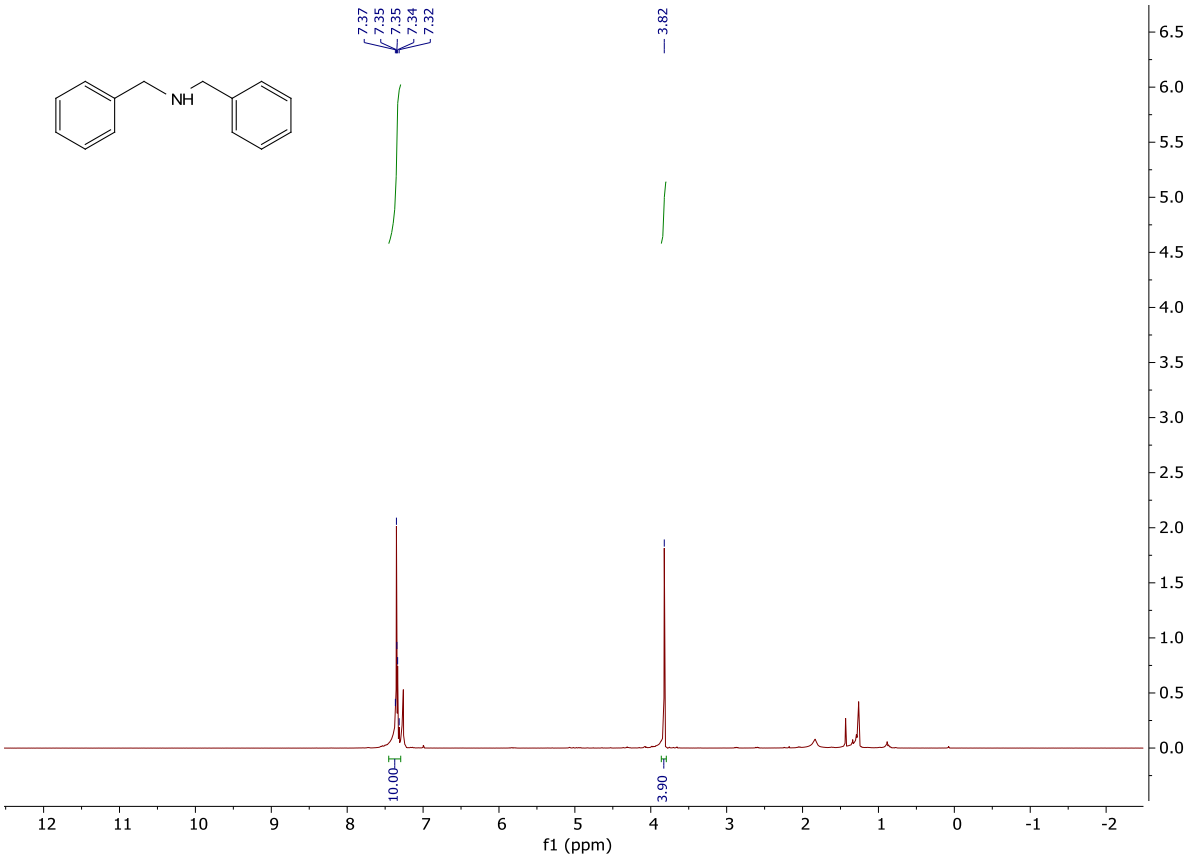
^{1}H NMR (400 MHz, $CDCl_3$) of N-(benzo[d]thiazol-2-ylsulfonyl)-N-(6-((tert-butyldimethylsilyl)oxy)hexyl)acetamide (4-77)



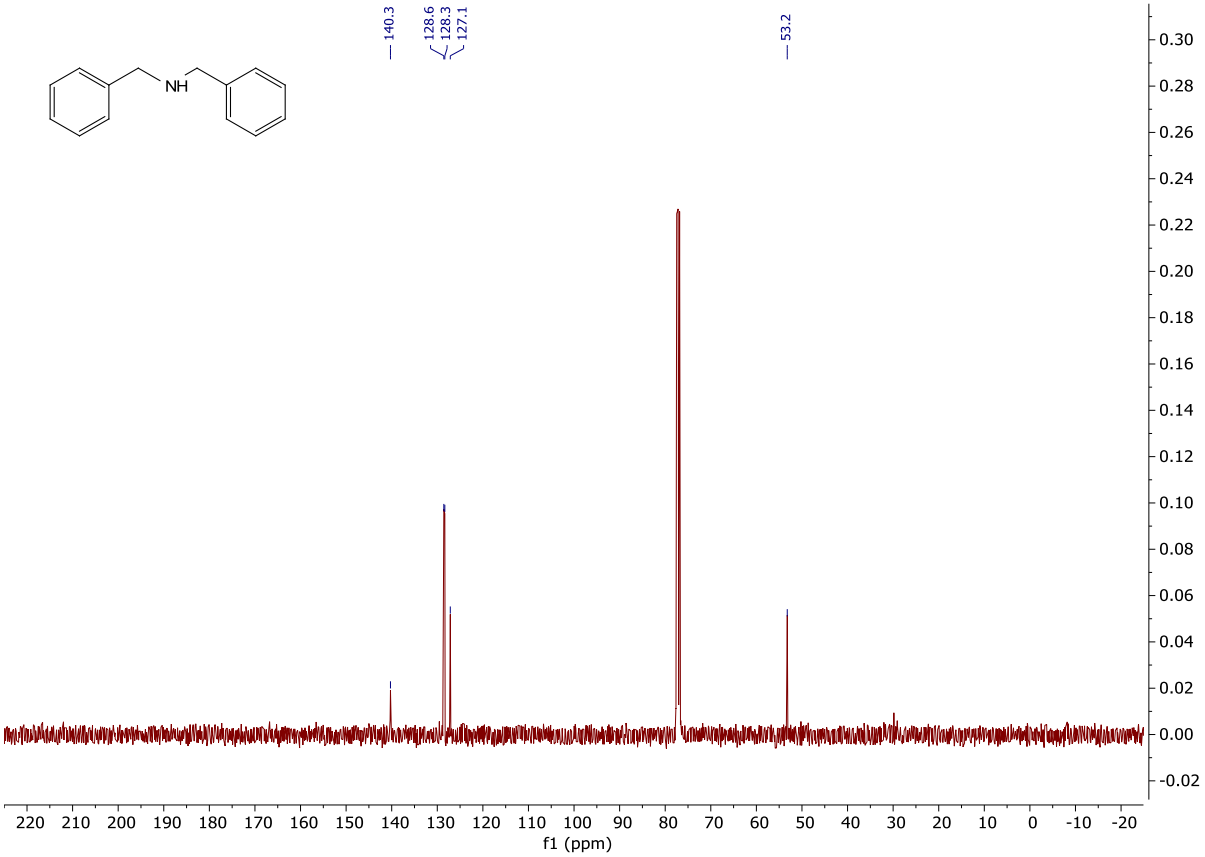
$^{13}C\ \{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of N-(benzo[d]thiazol-2-ylsulfonyl)-N-(6-((tert-butyldimethylsilyl)oxy)hexyl)acetamide (4-77)



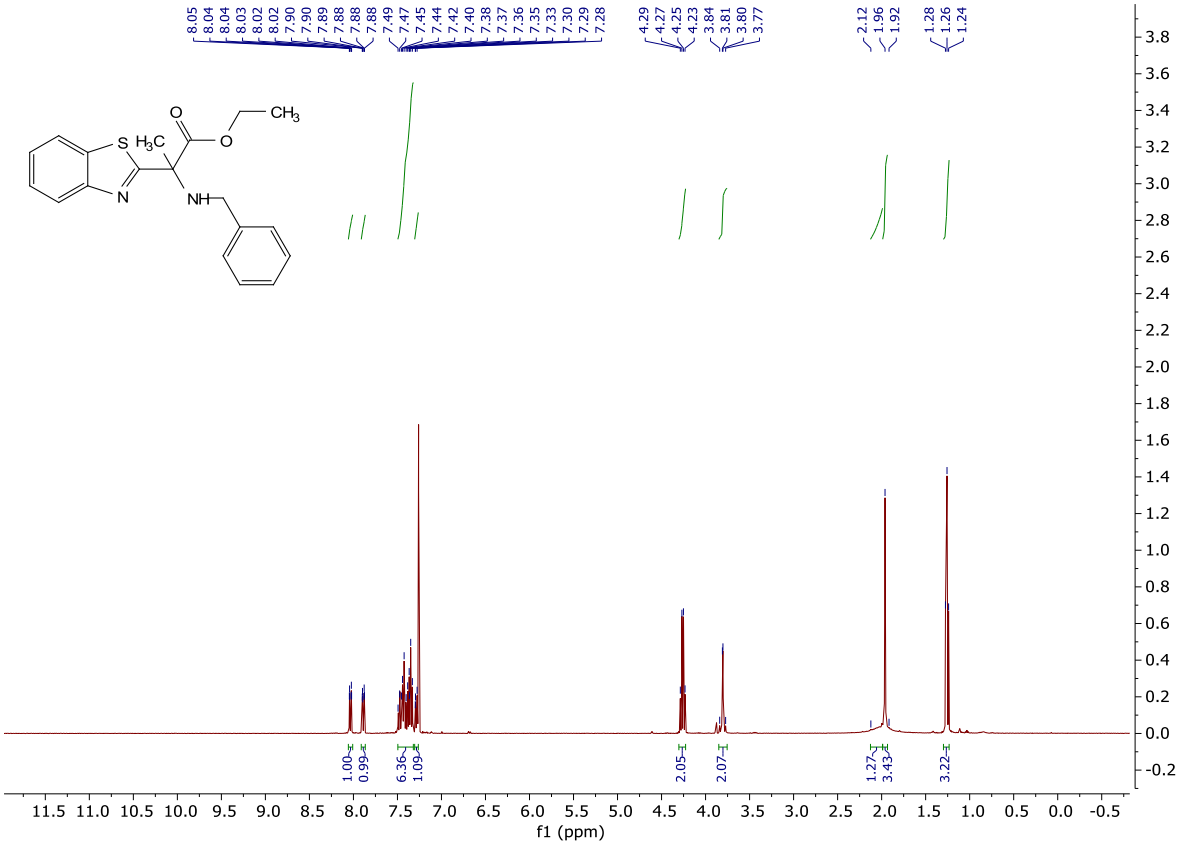
^{1}H NMR (400 MHz, $CDCl_3$) of dibenzylamine (4-78)



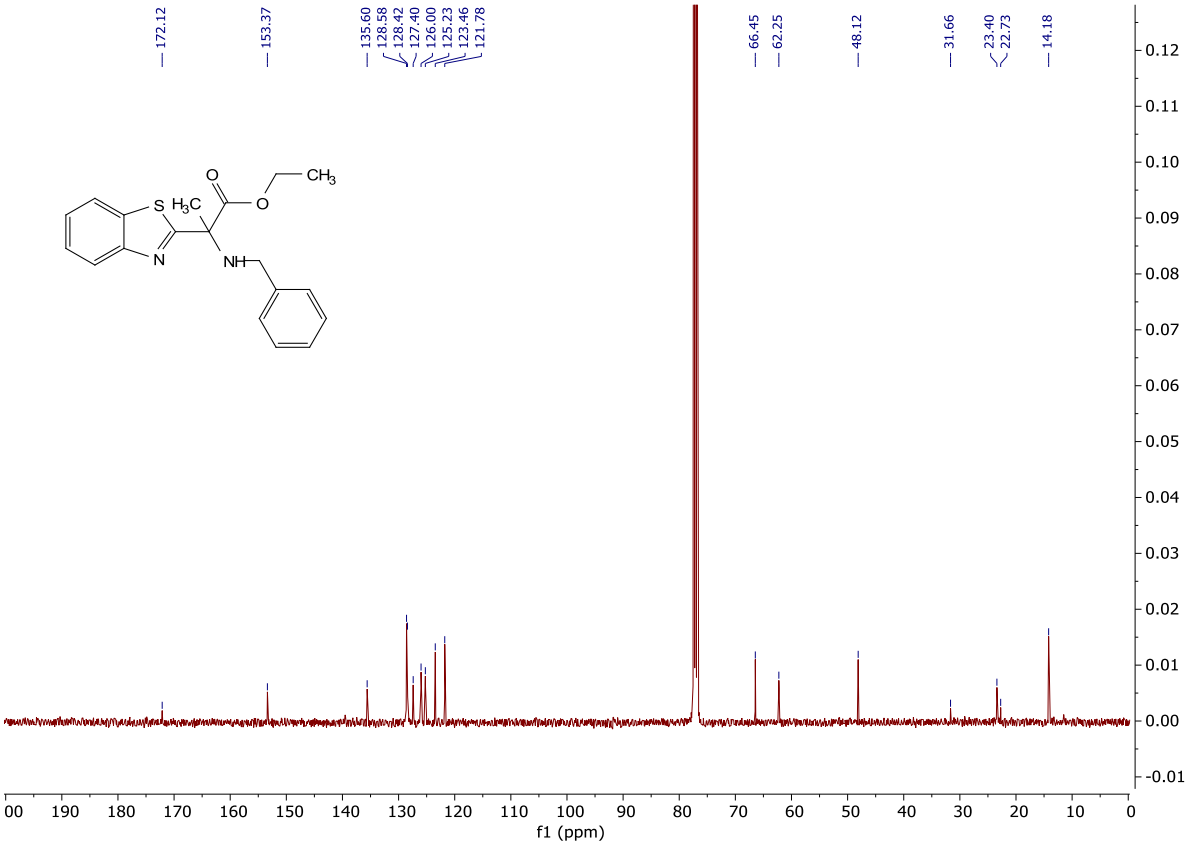
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of dibenzylamine (4-78)



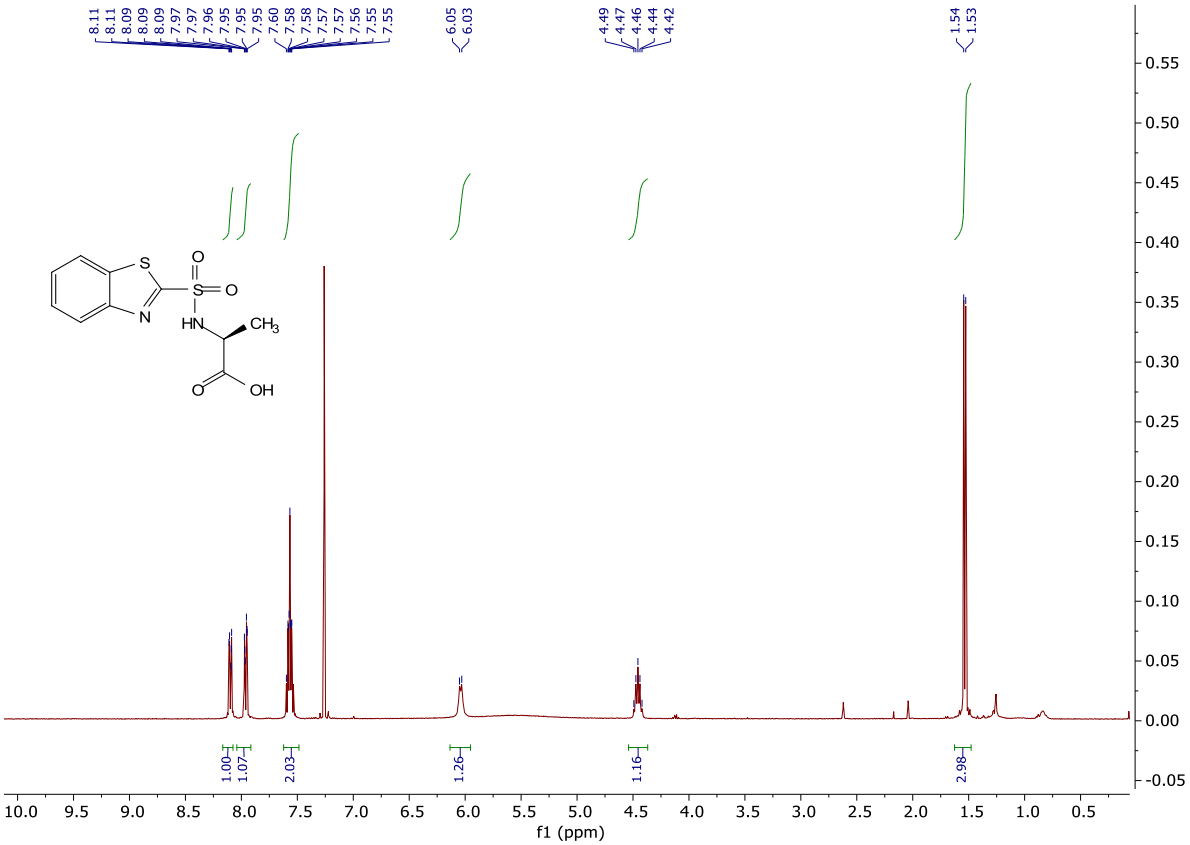
^{1}H NMR (400 MHz, $CDCl_3$) ethyl 2-(benzo[d]thiazol-2-yl)-2-(benzylamino)propanoate (4-73)



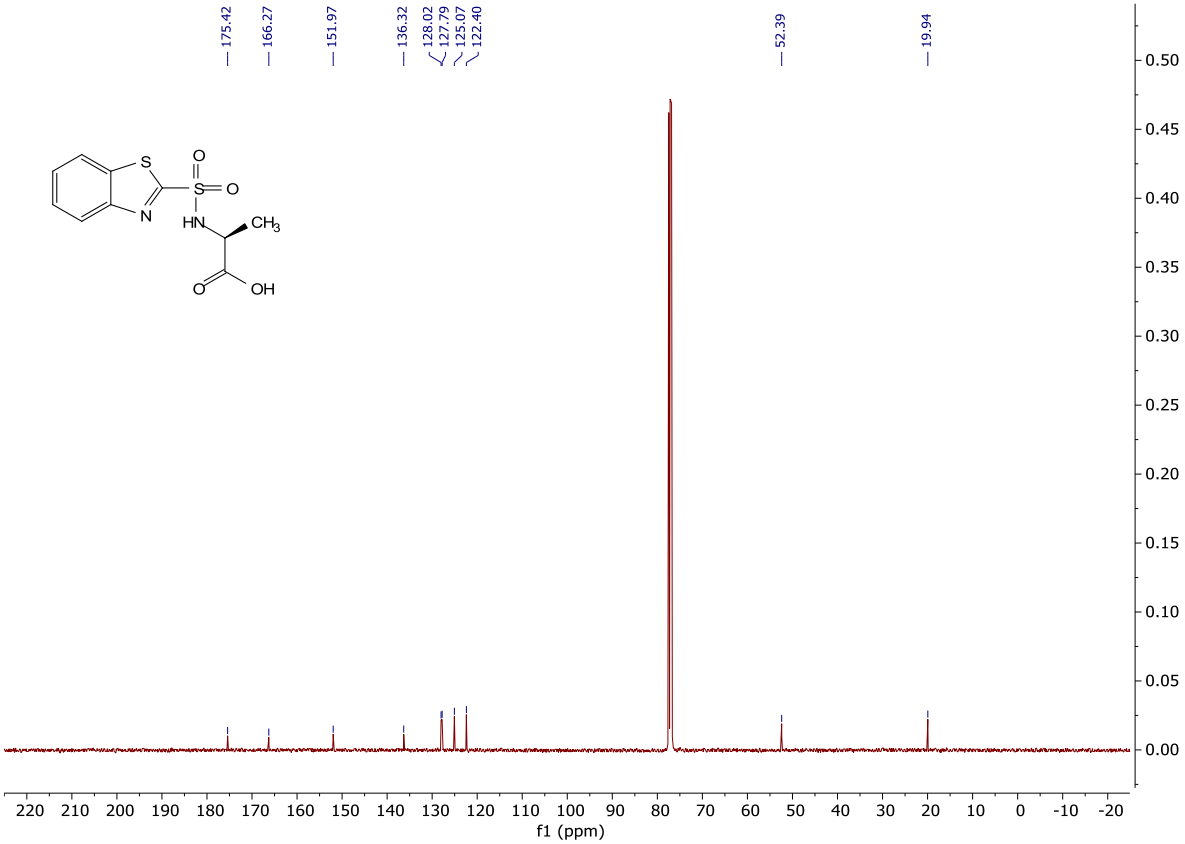
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of ethyl 2-(benzo[d]thiazol-2-yl)-2-(benzylamino)propanoate (4-73)



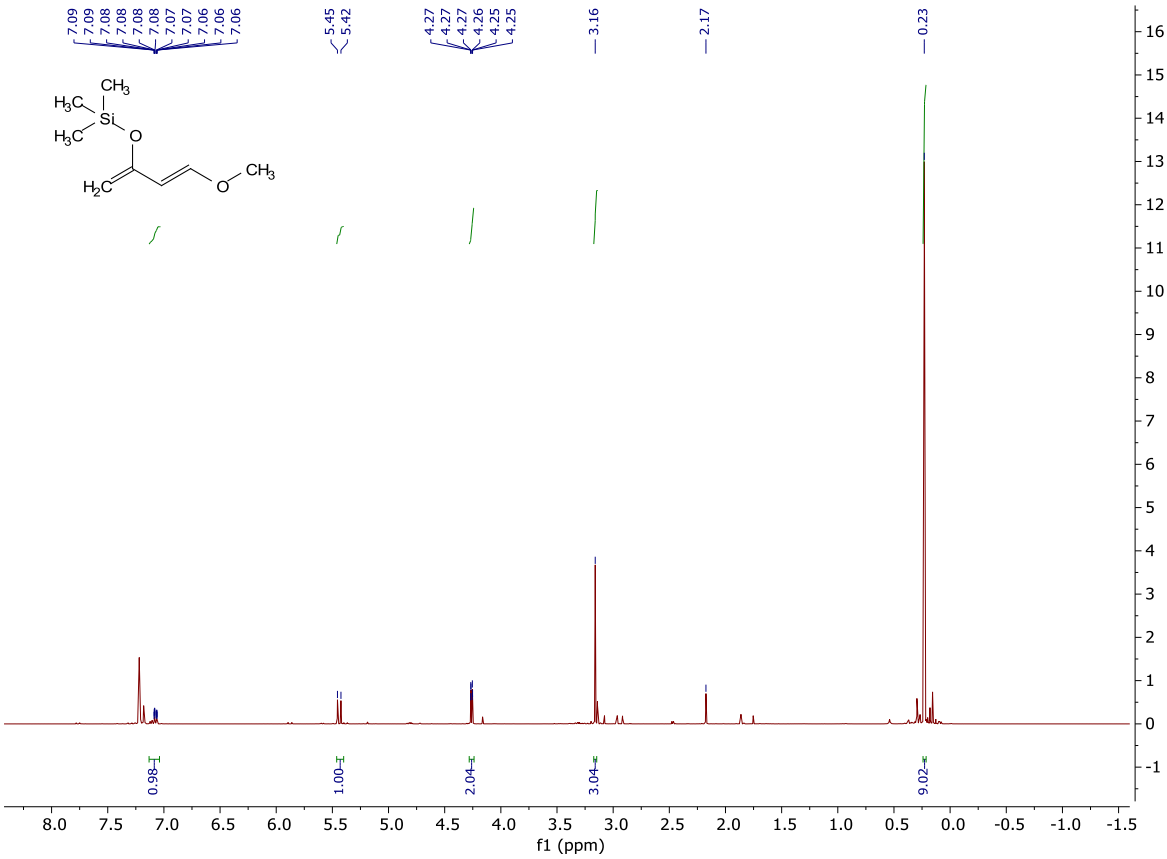
^{1}H NMR (400 MHz, $CDCl_3$) (benzo[d]thiazol-2-ylsulfonyl)-L-alanine (4-98):



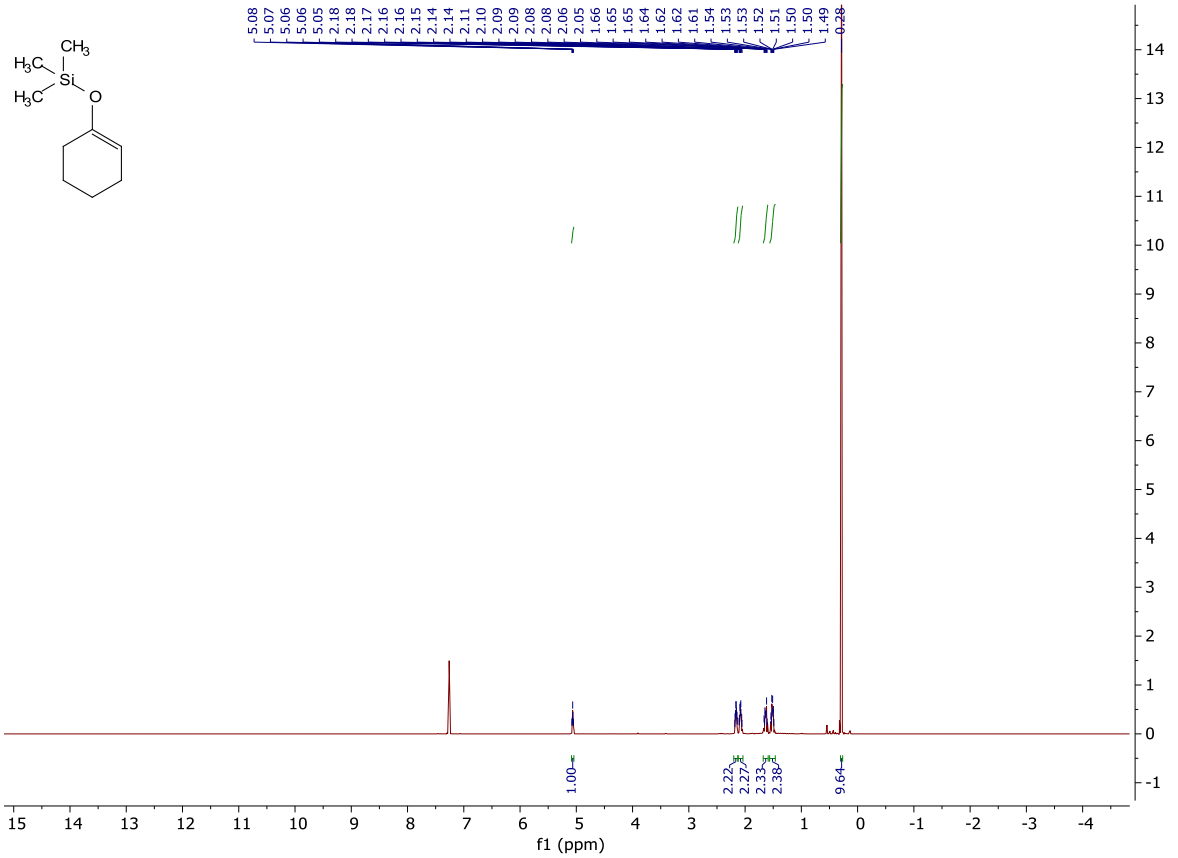
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) benzo[d]thiazol-2-ylsulfonyl)-L-alanine (4-98):



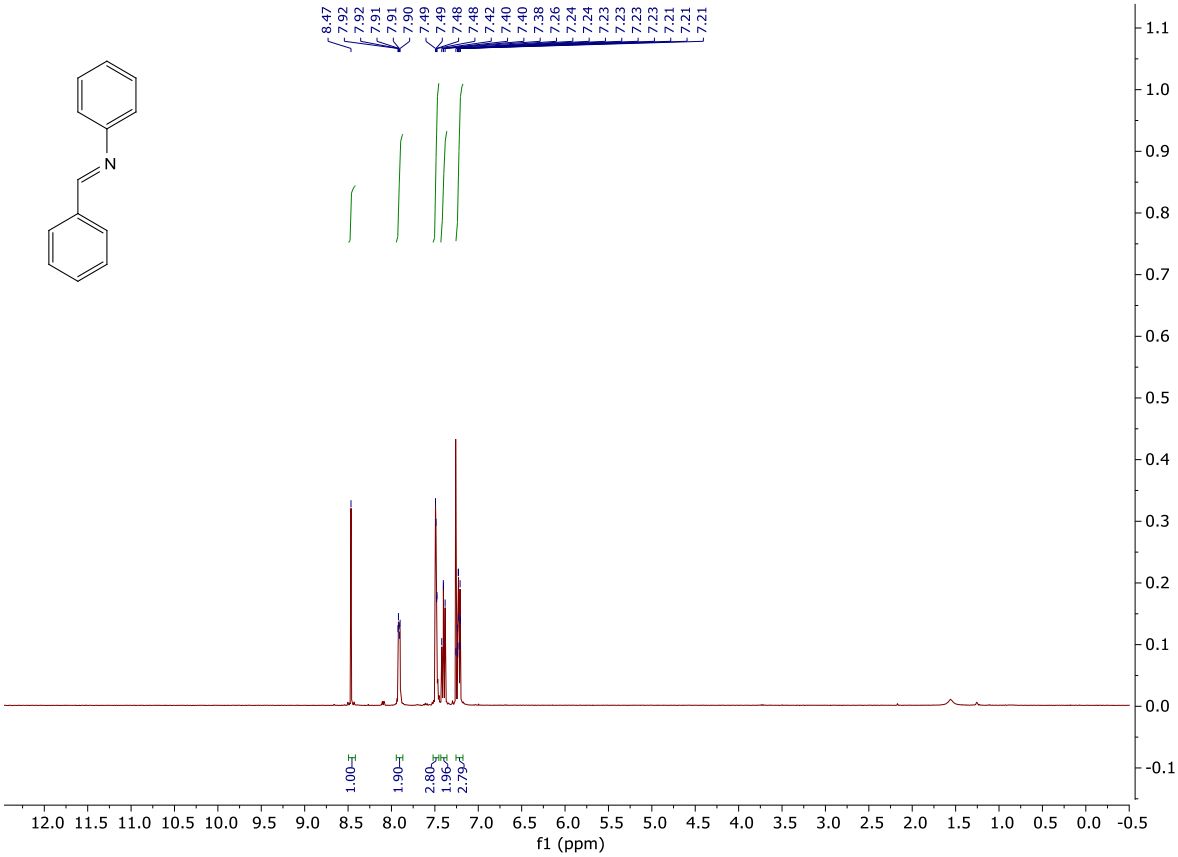
^{1}H NMR (400 MHz, $CDCl_3$) (E)-((4-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane (4-103)



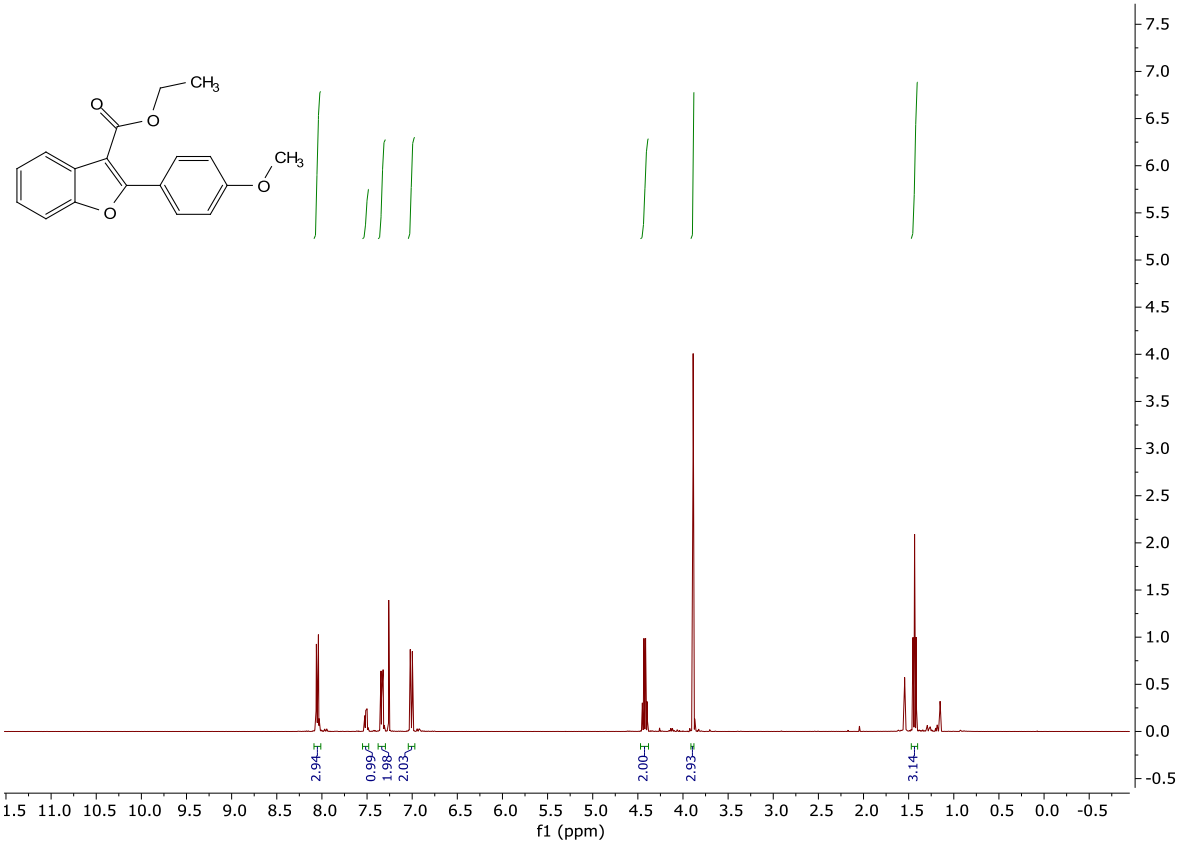
^{1}H NMR (400 MHz, $CDCl_3$) (cyclohex-1-en-1-yloxy)trimethylsilane (4-109)



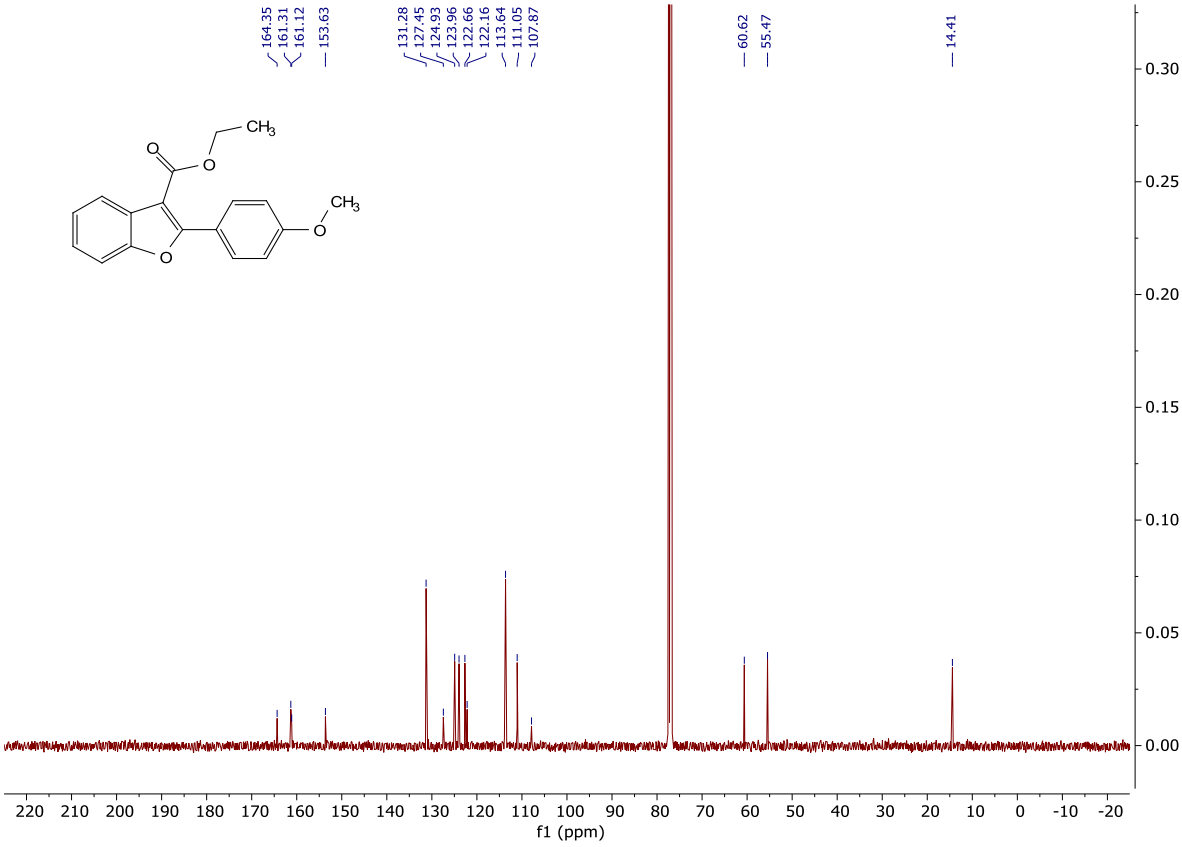
^{1}H NMR (400 MHz, $CDCl_3$) (E)-N,1-diphenylmethanimine (4-112)



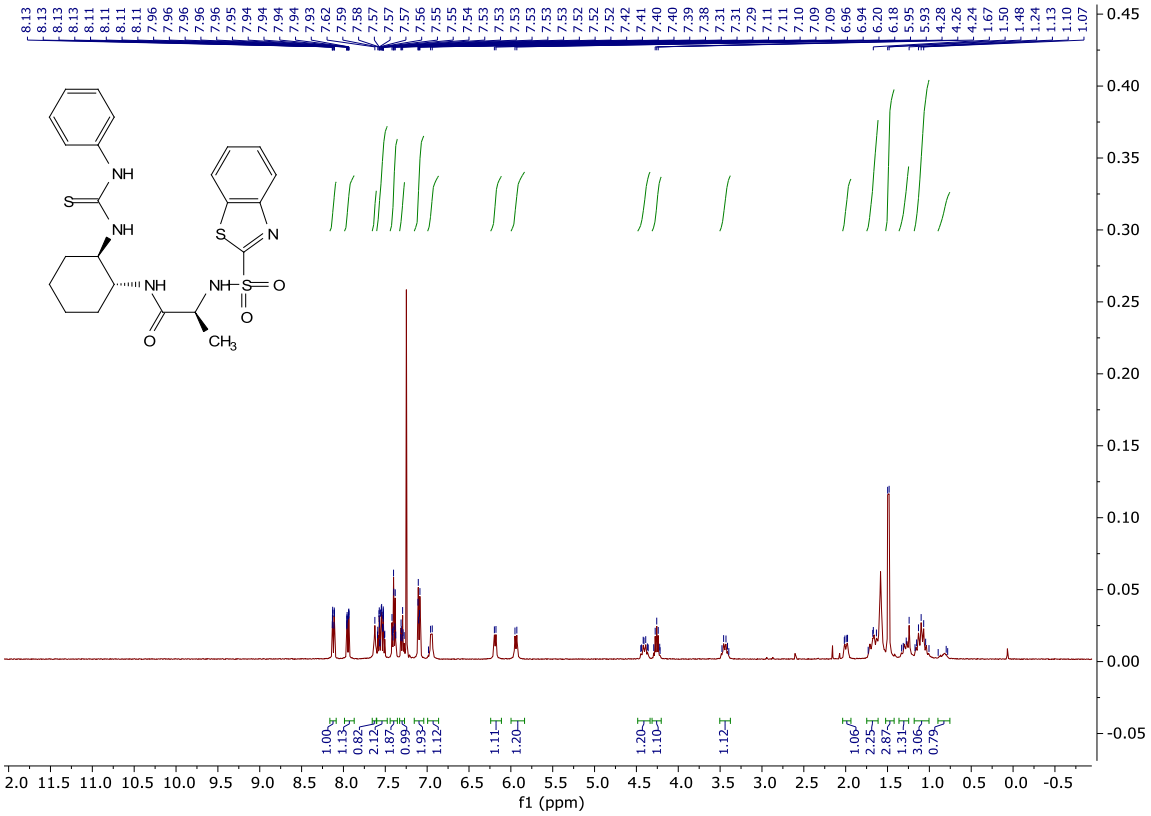
^{1}H NMR (400 MHz, $CDCl_3$) ethyl 2-(4-methoxyphenyl)benzofuran-3-carboxylate (4-145)



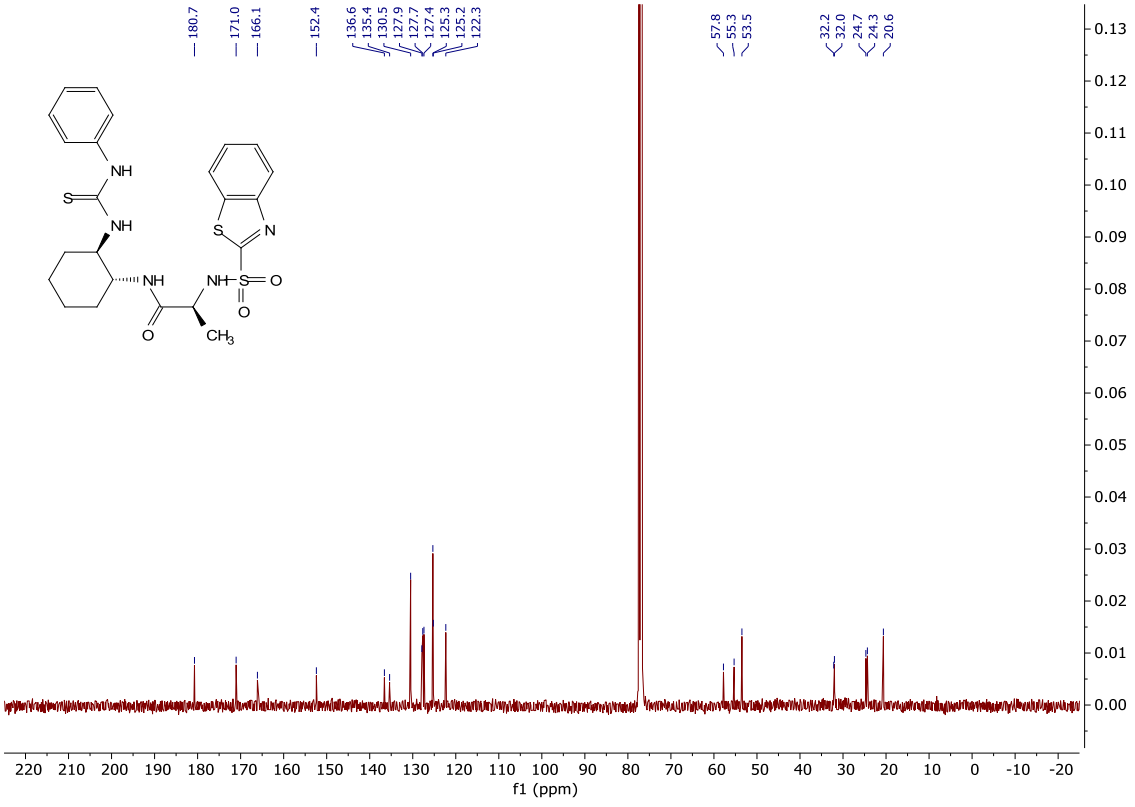
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) ethyl 2-(4-methoxyphenyl)benzofuran-3-carboxylate (4-145)



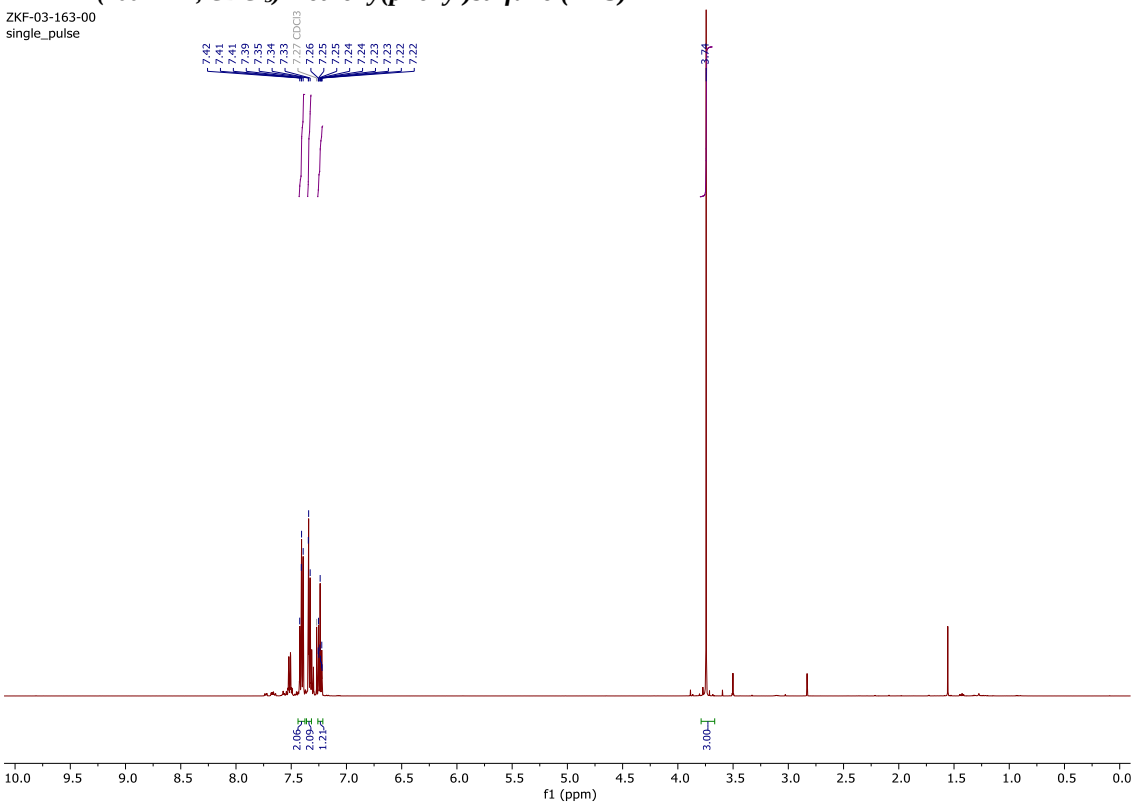
^{1}H NMR (400 MHz, $CDCl_3$) (S)-2-(benzo[d]thiazole-2-sulfonamido)-N-((1R,2R)-2-(3-phenylthioureido)cyclohexyl)propenamide (4-146):



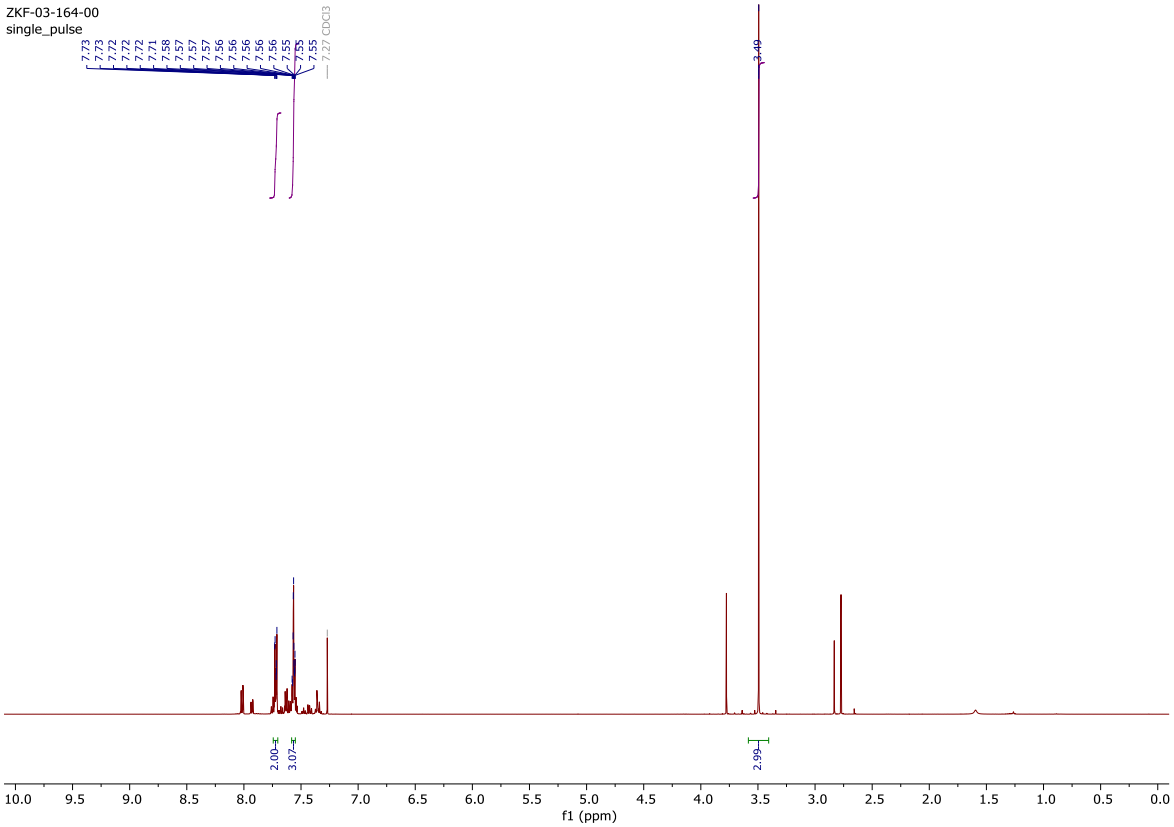
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) (S)-2-(benzo[d]thiazole-2-sulfonamido)-N-((1R,2R)-2-(3-phenylthioureido)cyclohexyl)propenamide (4-146):



^{1}H NMR (400 MHz, $CDCl_3$) methoxy(phenyl)sulfane (4-25)

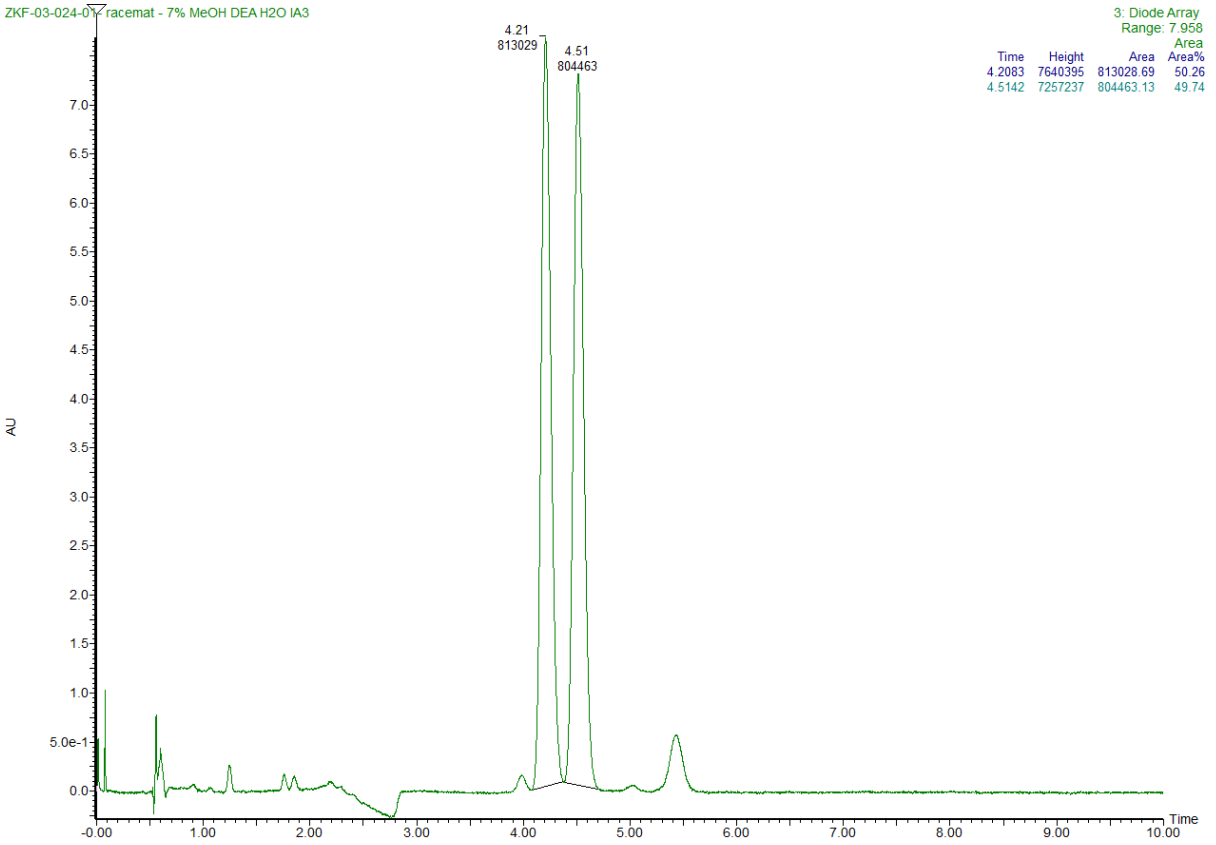


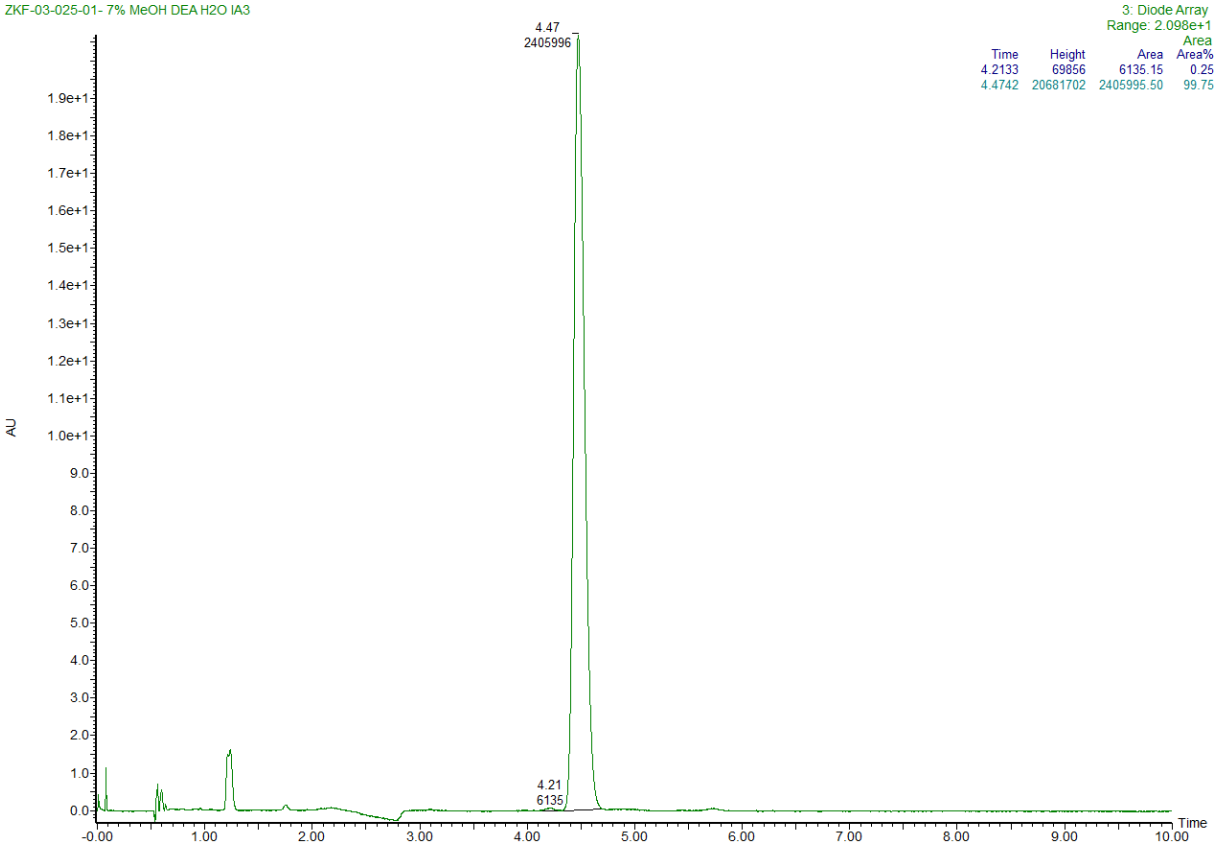
^{1}H NMR (400 MHz, $CDCl_3$) methyl benzenesulfinate (4-26)



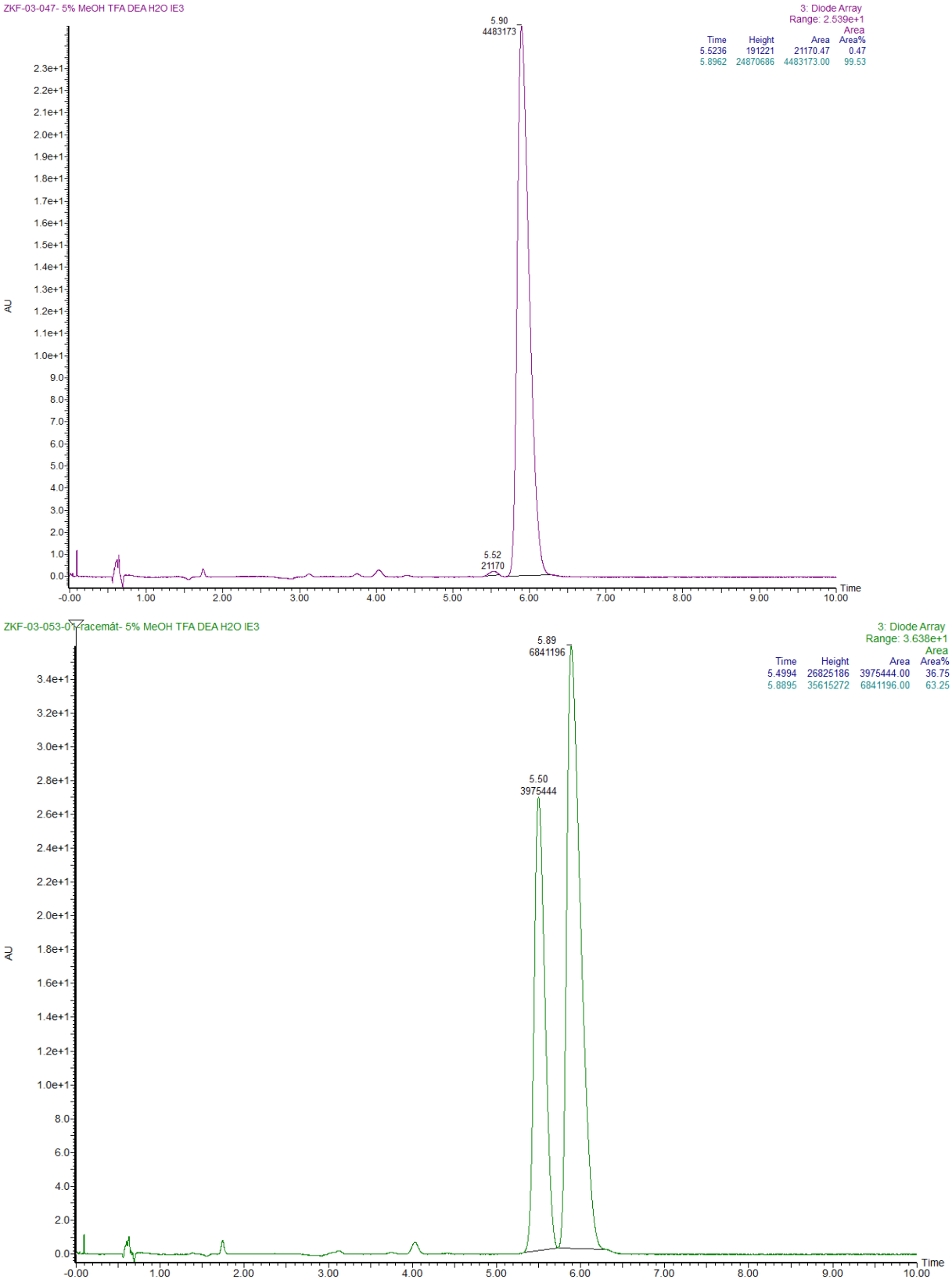
Appendix B - Copy of chromatograms from chiral separation

N-benzyl-N-(octan-2-yl) benzo[d]thiazole-2-sulfonamide (4-6ae)

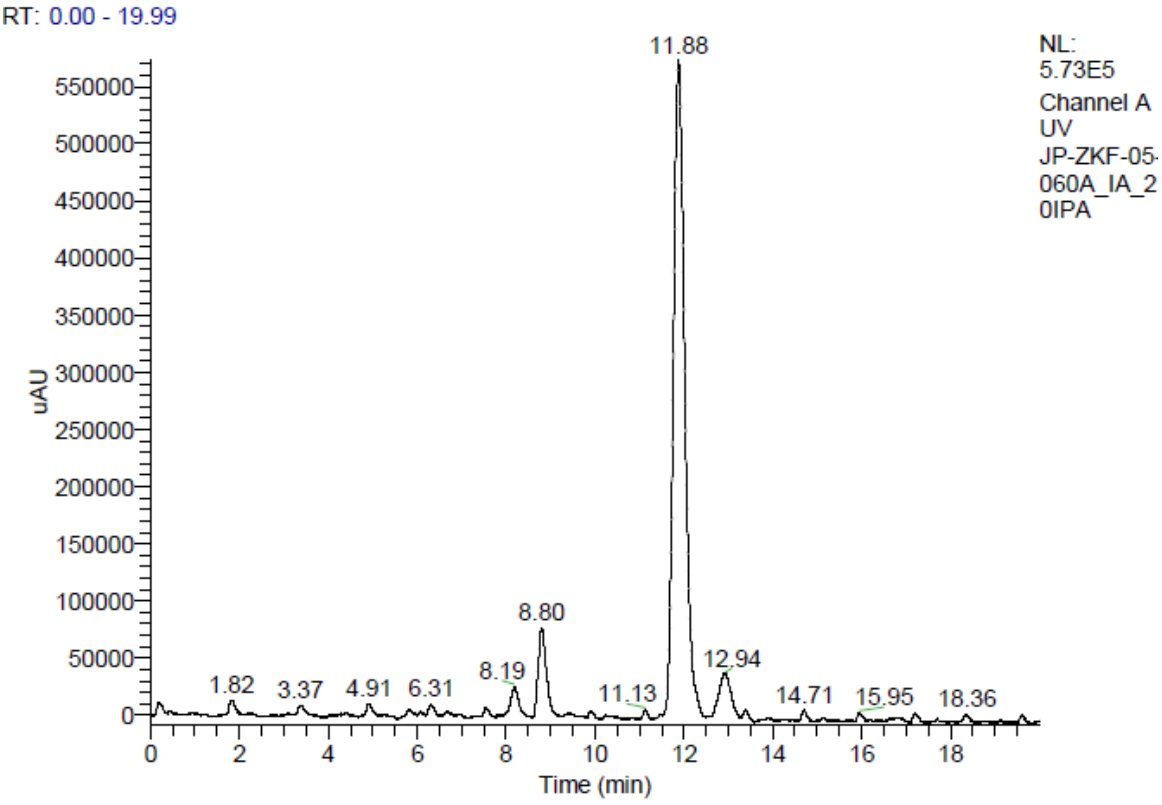


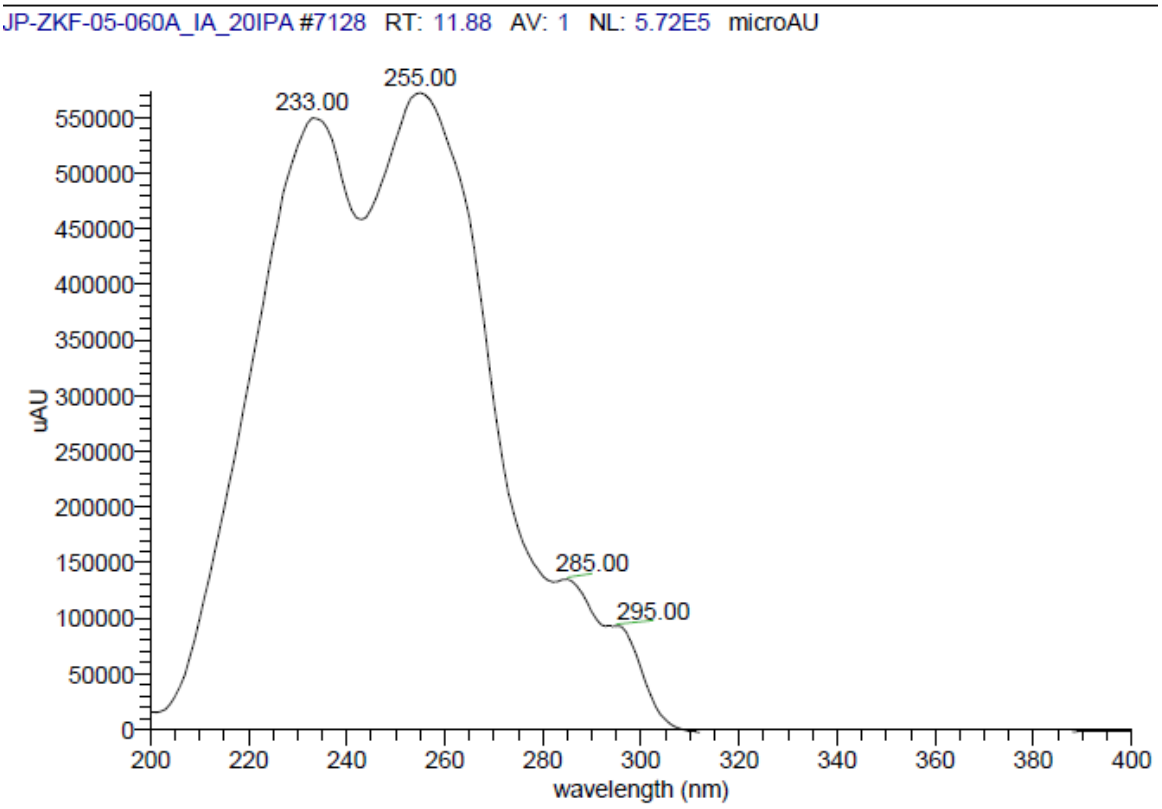


methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-butyl-L-alaninate (4-6cc)



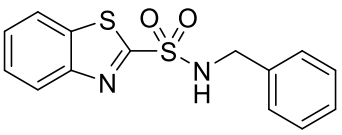
ethyl 2-(benzo[d]thiazol-2-yl)-2-(benzylamino)propanoate (4-73)

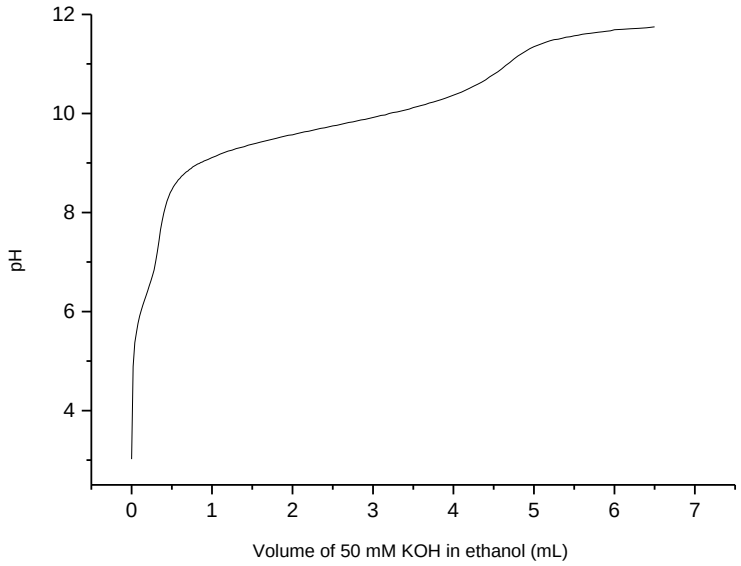




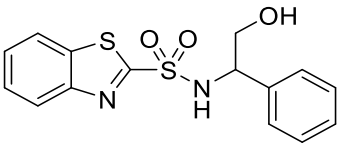
Appendix C - Titration curves for BT sulfonamides

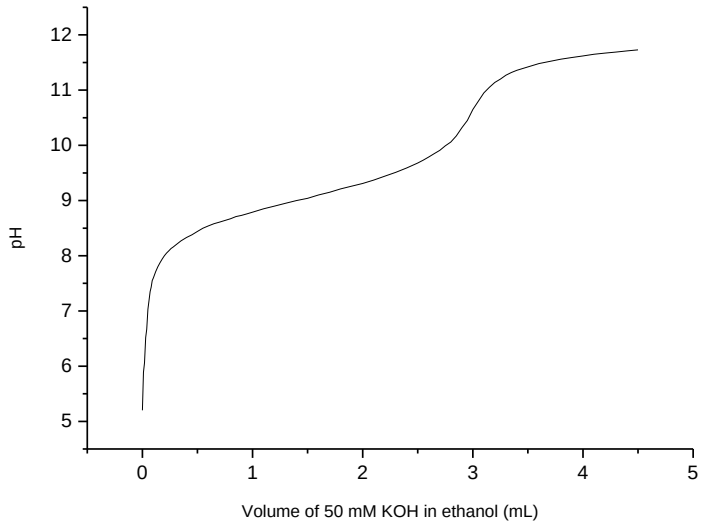
Titration curve of N-benzylbenzo[d]thiazole-2-sulfonamide (4-6a) pK_a = 9.67 (EtOH)



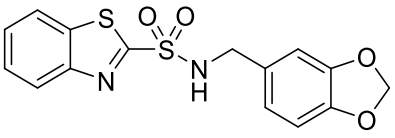


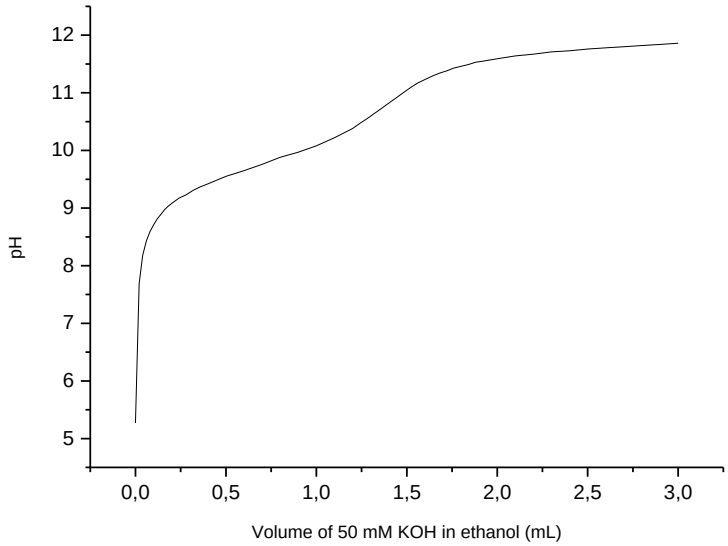
Titration curve of N-(2-hydroxy-1-phenylethyl)benzo[d]thiazole-2-sulonamide (4-6l) pK_a = 9.05 (EtOH)



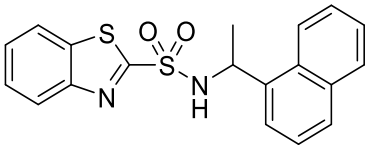


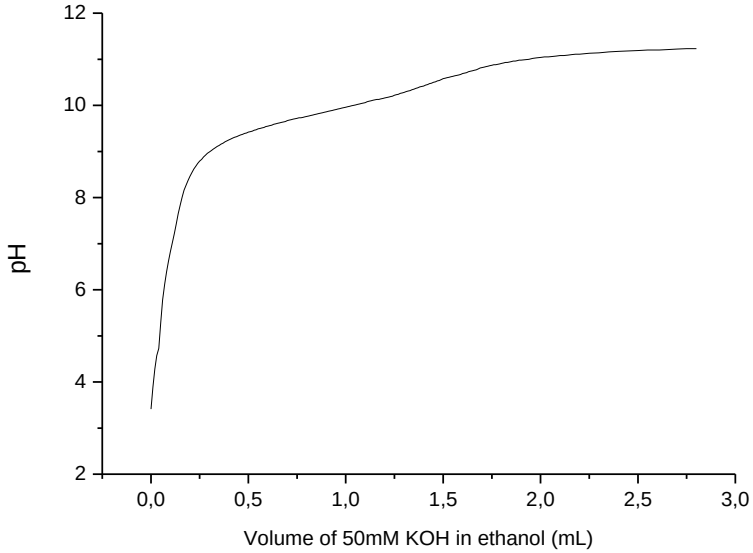
Titration curve N-(benzo[d][1,3]dioxol-5-ylmethyl)benzo[d]thiazole-2-sulfonamide (4-6r) pK_a = 9.77 (EtOH)



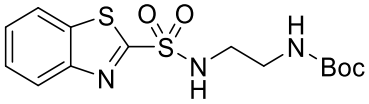


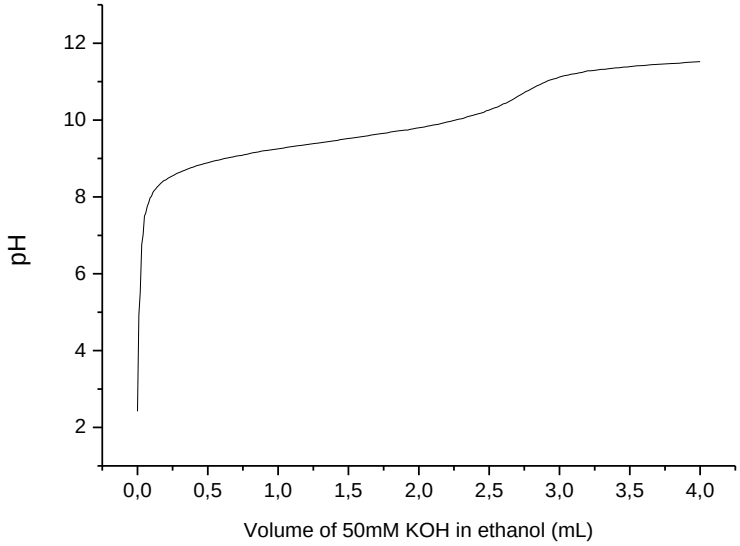
Titration curve of N-(1-(naphthalen-1-yl)ethyl)benzo[d]thiazole-2-sulfonamide (4-6j) pK_a = 9.71 (EtOH)



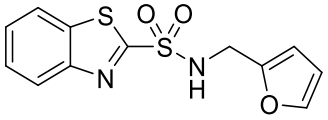


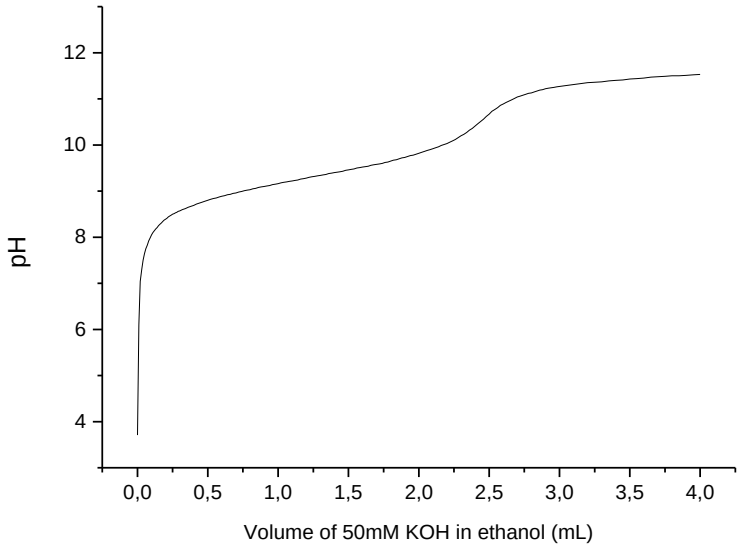
Titration curve of tert-butyl (2-(benzo[d]thiazole-2-sulfonamido) ethyl)carbamate (4-6i) pK_a = 9.44 (EtOH)



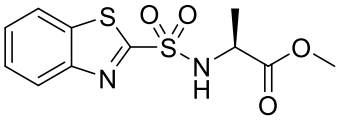


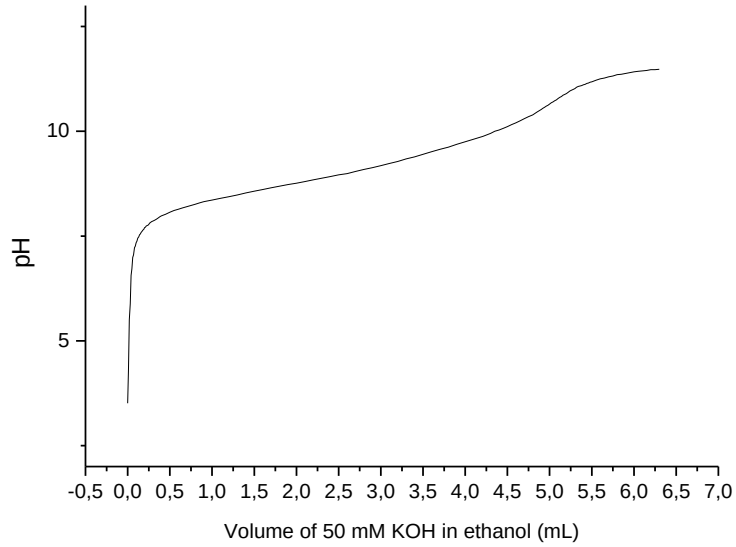
Titration curve of N-(furan-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (4-6d) pK_a = 9.31 (EtOH)



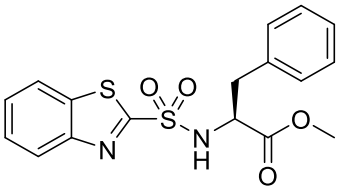


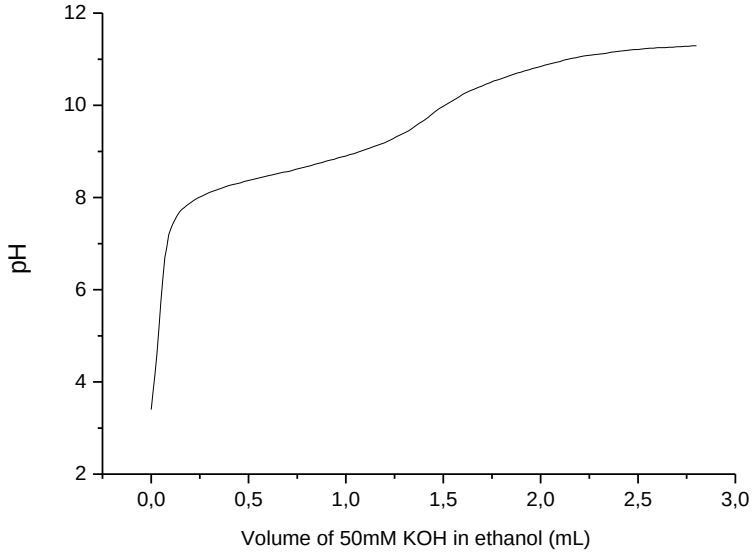
Titration curve of methyl (benzo[d]thiazol-2-ylsulfonyl)alaninate (4-6p) pK_a = 8.98 (EtOH)



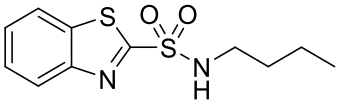


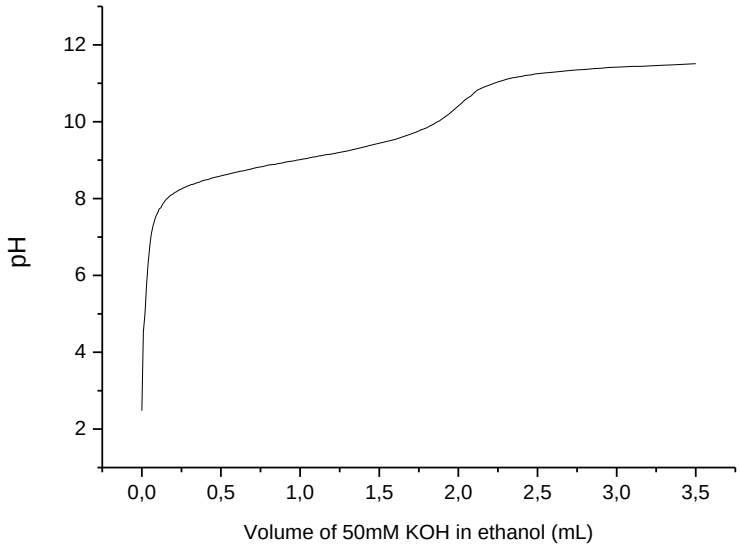
Titration curve of methyl (benzo[d]thiazol-2-ylsulfonyl)-L-phenylalaninate (4-6o) pK_a = 8.58 (EtOH)



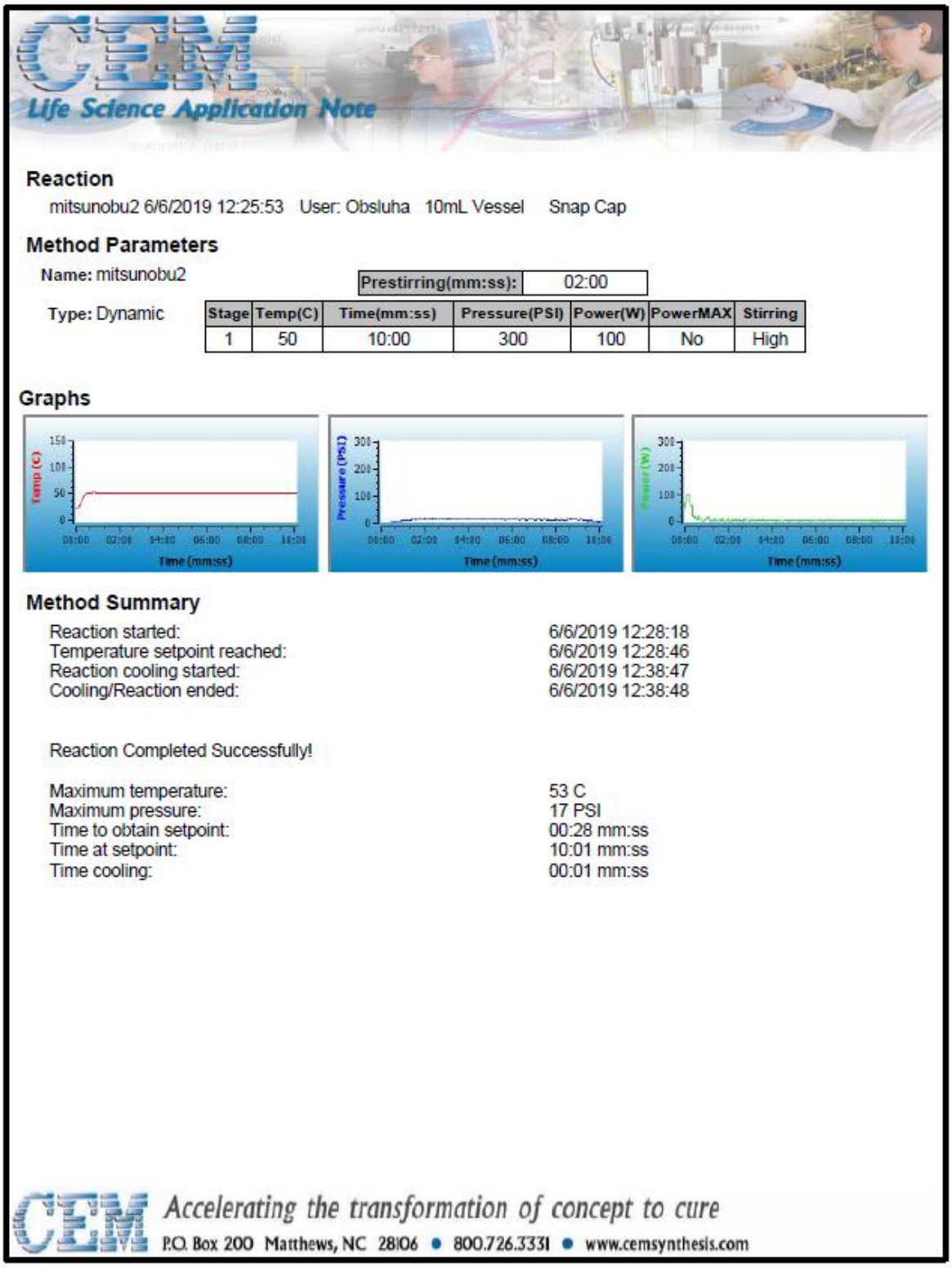


Titration curve of N-butylbenzo[d]thiazole-2-sulfonamide (4-6c) pK_a = 9.02 (EtOH)





Appendix D - Report from Microwave reactor for sulfonamide **4-6ac** synthesis under optimized reaction conditions



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Trisubstituted Highly Activated Benzo[*d*]thiazol-2-yl-sulfone-Containing Olefins as Building Blocks in Organic Synthesis

Ondřej Kováč, František Zálešák, David J.-Y. D. Bon, Lukas Roiser, Lubomír V. Baar, Mario Waser, and Jiří Pospíšil*

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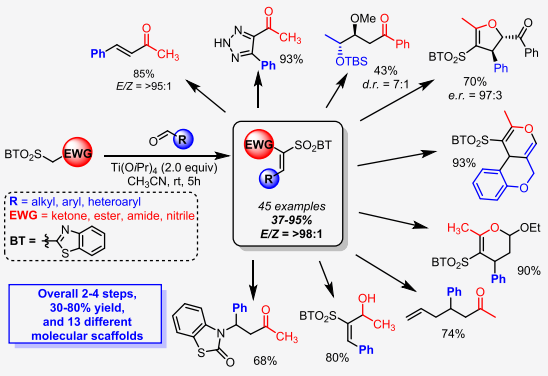
ABSTRACT: In this paper, we report the formation of highly electrophilic 1,1-deactivated olefins, their use as novel synthetic building blocks, and their transformation to structurally diverse molecular scaffolds. Synthesis of 1,1-deactivated olefins substituted with a BT-sulfonyl group and a carbonyl or nitrile, respectively, consists of unusual $Ti(OPr^i)_4$-mediated Knoevenagel-type condensation and proceed in good to excellent yields. Generated olefins can be further transformed in a highly stereoselective manner and in good yields to various polyfunctionalized heterocycles and acyclic molecular scaffolds. Overall, the obtained structures are accessed in two to four steps starting from the (mostly) commercially available aldehydes. In addition, the presence of the BT-sulfonyl group in prepared structures allows for further chemoselective functionalization/post-synthetic transformations to provide structurally diverse final compounds.



INTRODUCTION

Diversity-oriented synthesis is a synthetic strategy of choice when a chemical library of small organic molecules with a high degree of structural and functional variety have to be prepared.[1−4] In this strategy, rapid (3−5 steps) and efficient (high scaffold diversity) synthesis of structurally distinct molecules is achieved using specially designed readily available building blocks. Such building blocks are further transformed to structurally diverse frameworks.

For some time, our group has been interested in the development of such building blocks.[5,6] More recently, Michael-type acceptors, namely, aryl vinyl sulfones, have attracted our attention. Indeed, Michael-type additions to the vinylic group of aryl vinyl sulfones have attracted, over the past two decades, much attention of both the synthetic[7−11] and medicinal[12−14] community. At the same time, the use of heteroaryl vinyl sulfones as powerful electrophilic substrates was somewhat limited. Only roughly a dozen of seminal works (for selected examples see Scheme 1) focusing on the use of vinyl and/or 1,2-disubstituted olefin-bearing heteroaryl sulfones were reported.[15−22] Such olefins proved to be highly superior in their reactivity in comparison to aryl vinyl sulfones and even to 1,1-diphenylvinylsulfones.[16] We speculated that additional substitution with the electron-withdrawing (EWG) group on heteroaryl vinyl sulfone should broaden the synthetic utility of the vinyl sulfones (Figure 1). Newly generated Michael-type adducts should not only be more reactive toward external nucleophiles and radicals but should also react as substrates in cycloaddition reactions. In addition, the presence of the heteroaryl sulfonyl group in final adducts should allow further chemo selective transformations of obtained products.

In our group, we have a long-standing experience with benzo[*d*]thiazol-2-yl-sulfone chemistry, and thus we have designed the synthesis of sulfone **1** as a two-step protocol based on the Knoevenagel condensation[23] of aldehydes with readily available EWG α-substituted BT-sulfones **2**[24−26] (Figure 2). Herewith, we would like to present scope and limitations of such an approach and selected synthetic applications of prepared olefins **1**.

RESULTS AND DISCUSSIONS

Reaction Condition Optimization. Our approach to BT-sulfone **1** synthesis started with the condensation of BT-sulfone **2a** and benzaldehyde (for selected examples, see Table 1). Surprisingly, the reaction proved to be more challenging than expected, and all our efforts to obtain the desired product **3a** under the "classical" Knoevenagel reaction conditions failed (Table 1, entry 1).[27] In all cases, only the formation of olefin **4**, the product of Julia−Kocienski olefination,[28] was observed.[27] Interestingly when ethylenediamine diacetate (EDDA) was used to promote the condensation, product **3a** was isolated in

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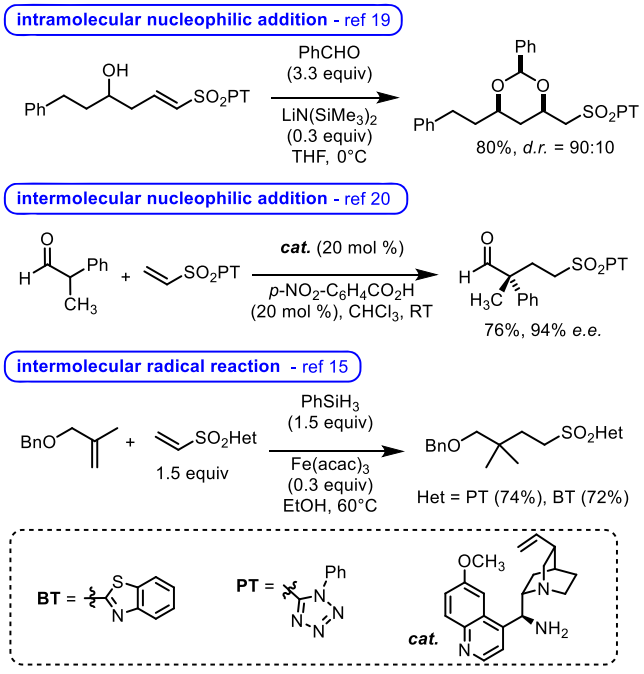
Scheme 1. Selected Examples of Previous Use of Heteroaryl Vinyl Sulfones as Substrates in Intramolecular, Intermolecular, and Radical Reactions



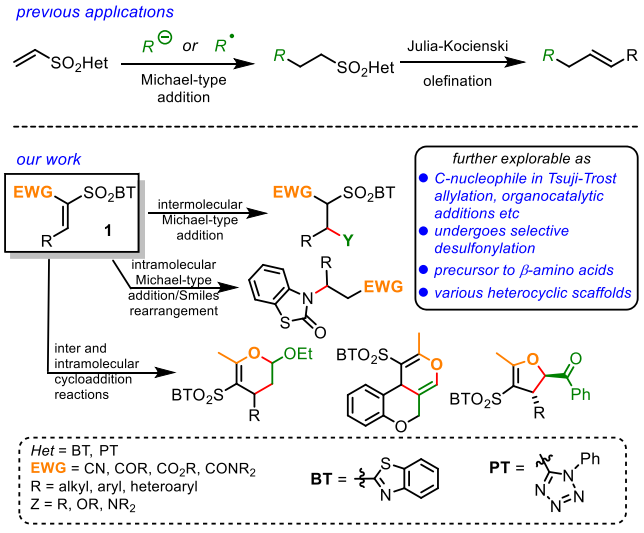


Figure 1. Comparison of previously exploited vinyl sulfones and our newly developed trisubstituted vinyl sulfones **1**.

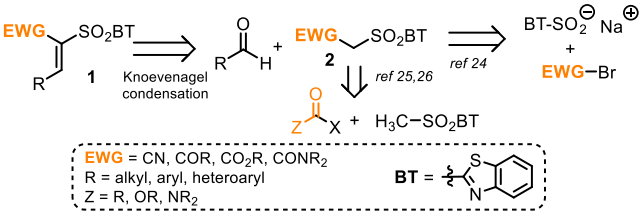
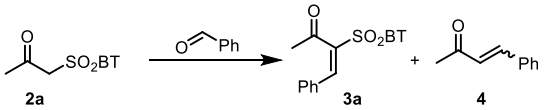


Figure 2. Retrosynthesis of trisubstituted vinyl sulfone **1**.

26% yield (Table 1, entry 2). However, further optimization and studies demonstrated that olefin **3a** is not stable under the reaction conditions and undergoes under prolonged reaction times to retro Knoevenagel reaction.[27] Observed olefin **3a**

Table 1. Knoevenagel Condensation of 1 with Benzaldehyde: Reaction Optimization



entry	conditions	3a/4 ratio[a]	yield[b] of **3a** (%)
1	various "standard" Knoevenagel reaction conditions[c]	<5:>95	n.d.
2	EDDA (10 mol %), DCE, reflux, 3 h	>95:<5	26%
3	$Ti(O\text{-}iPr)_4$ (2.0 equiv), toluene, r.t., 5 h	>95:<5	70%
4	$Ti(O\text{-}iPr)_4$ (1.0 equiv), CH_3CN, r.t., 5 h	>95:<5	35%
5	$Ti(O\text{-}iPr)_4$ (3.0 equiv), CH_3CN, r.t., 5 h	>95:<5	52%
6	$Ti(O\text{-}iPr)_4$ (2.0 equiv), CH_3CN, r.t., 5 h	>95:<5	71%
7	$Ti(O\text{-}iPr)_4$ (2.0 equiv), CH_3CN, reflux, 5 h	>95:<5	52%

[a]Based on the H NMR spectra of the crude reaction mixture. [b]Isolated yields. [c]For further details, see Supporting Information

instability under basic conditions prompted us to attempt the Knoevenagel condensation under Lewis acid catalysis (Table 1, entries 3−7). Gratifyingly, it was observed that the use of $Ti(OiPr)_4$ promotes the reaction yielding the desired BT-sulfone **3a** not only as the only product of the reaction but also as the single *E*-isomer (Table 1, entry 3). Further reaction optimization revealed that the condensation proceeds best when carried out in CH_3CN at r.t. in the presence of 2.0 equiv. of $Ti(OiPr)_4$ (Table 1, entry 6). The presence of two $Ti(OiPr)_4$ equivalents proved to be crucial for the reaction to drive it to completion. To shed some light on this intriguing observation, we carried out some additional experiments[27] that led us to propose the dual role of $Ti(OiPr)_4$ during the reaction: (a) it promotes enolate formation and (b) it works as a water molecule scavenger. The exclusive E-olefin formation can be also attributed to the presence of bulky Lewis acid during the condensation step.[27]

Scope and Limitations of Knoevenagel Condensation. Having determined the optimal reaction conditions, the reaction partners' scope and limitations were evaluated (Table 2). From the *E*/*Z* olefin stereochemistry viewpoint, the condensations proceed with virtually exclusive *E* selectivity. The only exception was observed in case of the olefin **3s** (prepared from sulfone **2a** and cinnamaldehyde) that was formed as a 7:1 *E*/*Z* mixture. From the substrate viewpoint, the influence of the aldehyde-coupling partner to reaction yield was first evaluated. It was observed that aryl and heteroaryl aldehydes substituted with alkoxy and halogen substituents including sterically crowded *ortho*-monosubstituted- or *o*,*o*′-disubstituted-ones are well-tolerated. In contrary, strong EWG substituents on the aryl ring (NO_2 and CF_3) led to the (partial in case of CF_3) product degradation under the reaction conditions or during the reaction work up. Indeed, it seems that the products of olefination **3f−h**, **3v**, **3ad**, **5h**, and **6f−h** are formed under the reaction conditions but immediately undergo reaction with *i*PrOH (or another nucleophile) present in the media.[29] Only in the case of nitrile bearing condensation product **6f**, no degradation occurred and the product was isolated in 93% yield.

α-Unbranched aldehydes represent the second limitation of the condensation reaction. In those cases, the products **7a** and **7b** and the products of the olefin migration were isolated instead of the expected condensation products **3q** and **3r**.[27]

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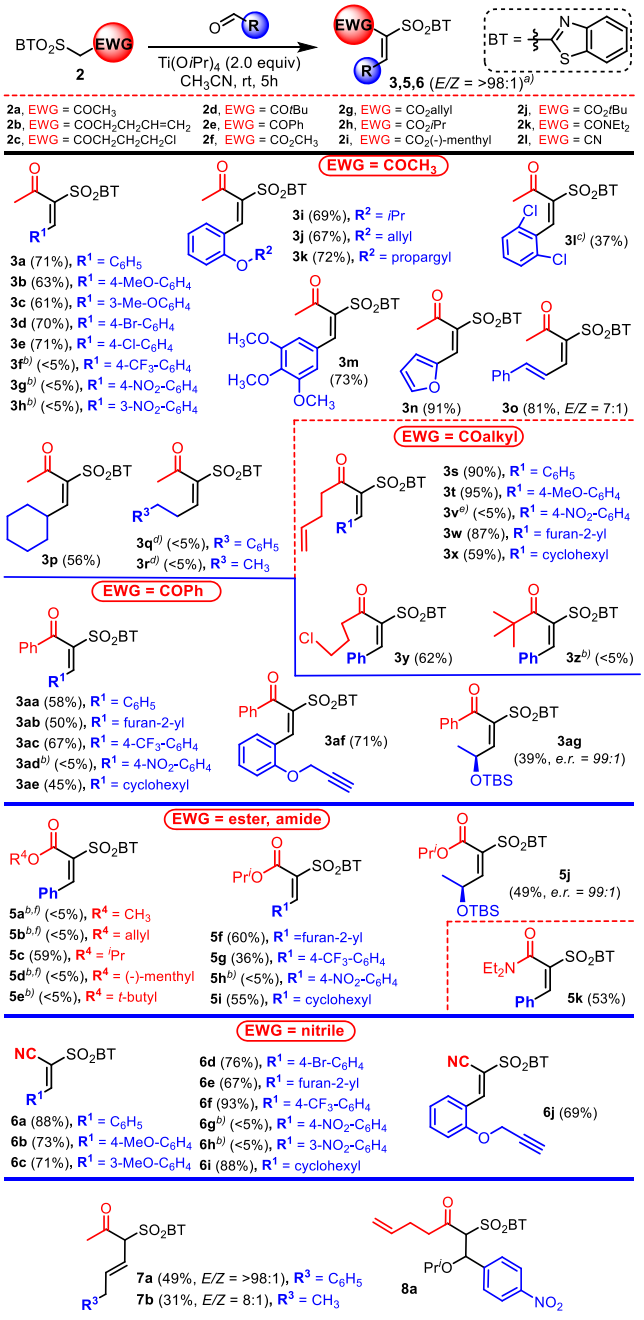
Table 2. Scope and Limitations of the Condensation Reaction



[a]Based on the ^{1}H NMR spectra of the crude reaction mixture. [b]No traces of the product observed. [c]Reaction carried out at 80 °C for 6 h. [d]Only olefin migration products **7a** and **7b** were isolated as the products of the reaction. [e]only the product of 1,4-addition of *i*-PrOH to **3v** (compound **8a**) were detected, suggesting that the trace amount of the desired product was formed. Similar observations were made when 4-cyanobenzaldehyde and 3-cyanobenzaldehyde were used as reaction substrates (not shown). [f]Only product **5c** was isolated in 58−61% yields.

Gratifyingly, when α-branched aldehydes were used, the desired products **3p**, **3x**, **3ae**, **3ag**, **5i**, **5j**, and **6i** were obtained in good to excellent yields. More importantly, when α-chiral aldehydes were used as the starting material, no stereo erosion was observed. When ketones were used as the condensation partners (not showed), no product of condensation was observed.

Next, the influence of the EWG group in **2** on the condensation was evaluated. It was observed that the condensation of alkyl ketone bearing sulfone **2d** is sensitive to the steric hindrance in carbonyl proximity (sulfone **2d** failed to yield adduct **3z**); methyl and α-unbranched functionalized BT-sulfoketones **2a**−**c** yielded the corresponding adducts **3a**−**y** in good to excellent yields; and arylketosulfone **2e** yielded the products **3aa**−**ag** in yields slightly lower to the corresponding alkyl sulfones **2a-c**. Ester, amide, and nitrile-bearing sulfones **2h**, **2k**, and **2l** reacted under the condensation conditions smoothly and yielded the corresponding adducts **5** and **6** in good to excellent yields and exclusive *E*-selectivity. In case of esters, however, only *i*-propyl-bearing ester adducts might be isolated after the reaction because the rapid *in situ* transesterification process of ester sulfones **2f**, **2g**, and **2i** to the sulfone **2h** occurs during the condensation.[27] In the case of *t*-butyl-bearing ester sulfone **2j**, no traces of transesterification was observed, however, no product of condensation either.

Applications of Activated Olefins in Organic Synthesis. Having desired activated olefins **3**, **5**, and **6** in hand, their reactivity in cycloadditions (Scheme 2), Michael-type (Lewis acid-mediated) nucleophilic additions (Schemes 3 and 4), hydride reductions, and radical reactions (Scheme 5) were evaluated. First, the hetero-Diels−Alder cycloaddition reaction of ketosulfones **3** with ethyl vinyl ether was investigated (Scheme 2, part A). It was observed that the reaction proceeds well and yields the desired dihydropyran **9** in excellent yields. Similarly, the intramolecular hetero-Diels−Alder reaction of ketosulfone function to alkynes can be performed albeit under harsher reaction conditions (μW, 150 °C, 200 W) (Scheme 2, part B). Ketosulfones **3** can also react with ammonium ylides to generate products of formal [4 + 1]-cycloaddition reaction in both racemic (Scheme 2, part C) and enantioselective manner (Scheme 2, part D). In both cases, the desired dihydrofurans **12** are formed in very good to excellent yields and, in the case of nonracemic ammonium ylides,[30] enantioselectivity. Lastly, activated olefins **3a**, **3p**, **3ac**, and **5c** were used as dipolarophiles in 1,3-cycloaddition reaction of sodium azide (Scheme 2, part E). In this case, products of [3 + 2]-cycloaddition **14** undergoes to spontaneous *in situ* $BTSO_2$-group elimination to provide solely corresponding triazoles **15** in good to excellent yields. In the case of compound **15e**, the reaction was chemoselective toward the activated olefin.

The reactivity of activated olefins toward nucleophiles under uncatalyzed (Scheme 3, part A) and Lewis acid-mediated (Scheme 3, part B, and Scheme 4) reaction conditions was also evaluated. It was observed that simple treatment of olefins **3a** and **3ag** with methanol at r.t. under prolonged reaction times results in the formation of 1,4-adducts **17** that can be further selectively desulfonylated[31] to yield β-methoxy ketones **16a** and **16b** (Scheme 3, part A). Interestingly, even under unoptimized reaction conditions, the addition of methanol to homochiral olefin **3ag** proceeds with high diastereoselectivity.[27] Similarly, olefins **3a** and **6a** were reacted with Et_3SiH and allylsilane in the presence of $TiCl_4$ (Scheme 3, part B). Rapid 1,4-addition followed by *in situ* desulfonylation[31] then yielded β-adducts **19a-c** in very good yields.

Another interesting reaction was observed when olefin **3a** was treated with $TiCl_4$ at r.t. without any additional additives (Scheme 4). In this case, an intramolecular smiles-like

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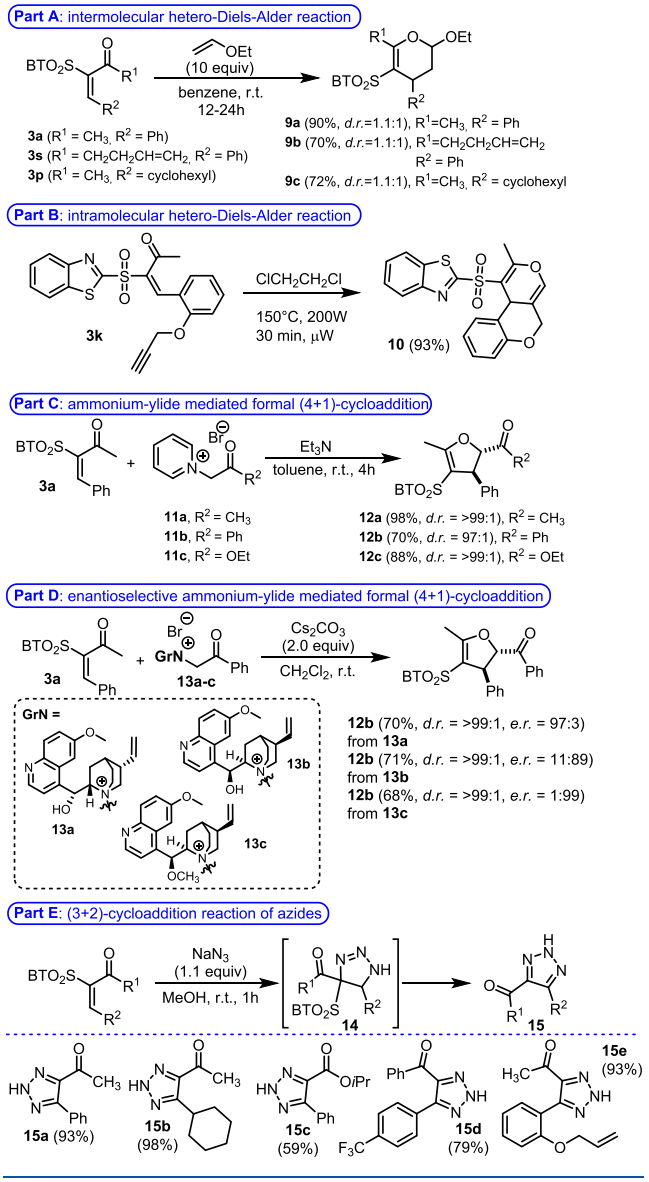
Scheme 2. Cycloaddition Reactions—Attempted Examples

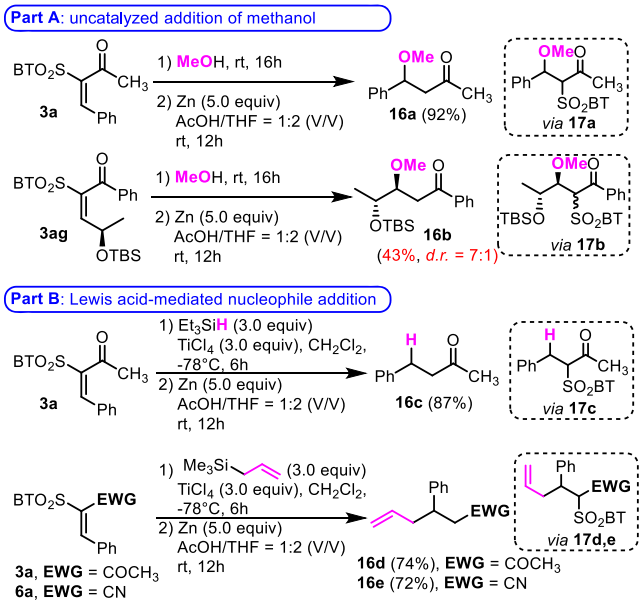


rearrangement followed with desulfonylation yielded *β*-functionalized ketone **18**.[32]

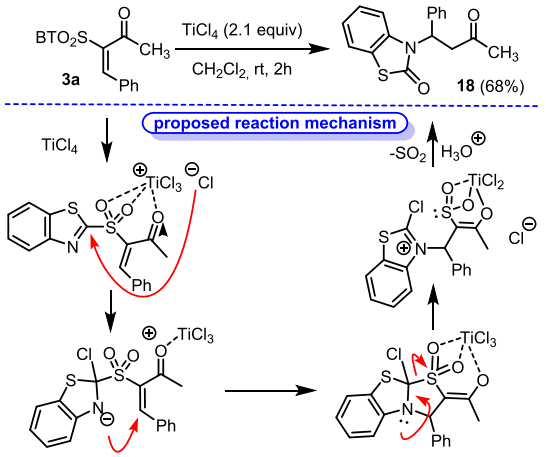
Because the Lewis acid-mediated Et_3SiH addition proceeded with exclusive 1,4-addition, selectivity of 1,2- versus 1,4-hydride reduction was investigated (Scheme 5).[27] It was observed that a vast majority of standard reducing agents, to mention just a few [nBu$_3$SnH[33] or DIBAL-H in tetrahydrofuran (THF)], favors 1,4-reduction products **17c,f** (Scheme 5, part A). In contrary, the selective 1,2-hydride reduction could be performed if DIBAL-H reduction was carried out in CH_2Cl_2 at −78 °C under high (0.01 M) dilution (Scheme 5, part B). Using such conditions, the desired allylic alcohols **19a,c** could be obtained in very good yields.[27] Interestingly, phenyl-substituted ketone **3aa** do not undergo to 1,2-reduction under such conditions and only 1,4-adduct **17f** is isolated.

Finally, we have decided to evaluate the radicophilic behavior of activated olefins **3**, **5**, and **6**. The original hypothesis was that these newly generated olefins will behave similarly as vinyl BT sulfone explored in the pioneering work of Baran et al. (Fe(acac)$_3$ promoted radical addition).[15] However, quick 1,4-addition of EtOH to **3** excluded such possibility.[34]

Scheme 3. Uncatalyzed and Lewis Acid-Mediated Reactions of Activated Olefins 3a, 3ag, and 6a



Scheme 4. $TiCl_4$-Mediated Rearrangement of 3a to Ketone 18



Thus, we have focused on classical Giese addition, in which an electron-deficient alkene (our olefins) is attacked by a nucleophilic alkyl radical.[35−38] Unfortunately, such conditions in general require a tin reagent. Because in our case nBu$_3$SnH spontaneously adds in a 1,4-manner to olefin **3a** even at low temperature, tris(trimethylsilyl)silane (TTMS) was used instead (Scheme 5, part C). Thus, olefins **3a**, **5c**, and **6a** were reacted with the ethyl radical generated in a TTMS/EtI/AIBN system. Surprisingly, only nitrile bearing olefin **6a** yielded the desired adduct **20**, while carbonyl bearing olefins **3a** and **5c** gave unsaturated carbonyl compounds **4** and **21**, respectively. Such an observation suggests that in the case of carbonyl-substituted olefins, the generated radical preferentially attacks the BT-sulfonyl group and, as suggested by the (*E*)-olefin **4** and **21** formation,[39] generates a vinylic radical as a reaction intermediate.

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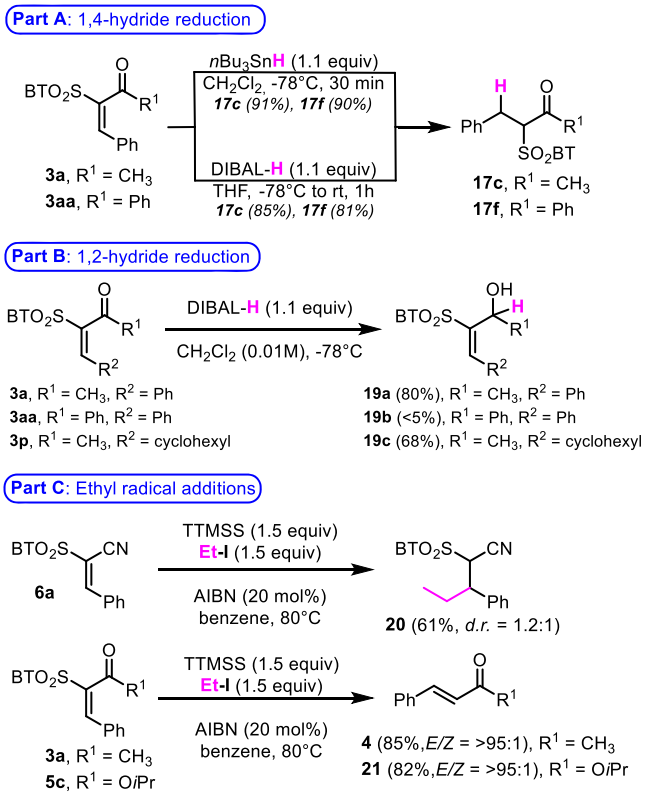
Scheme 5. Selective Hydride Reductions and Radical Addition



CONCLUSIONS

In conclusion, the synthesis of highly electrophilic olefins that can be in one or two steps transformed into valuable (enantio-enriched) heterocyclic and acyclic scaffolds has been developed. Prepared olefins can be used as hetero-dienes, dienophiles, and Michael-acceptors and can be reacted in various hetero-Diels–Alder, 1,3-dipolar, or formal [4 + 1]-cycloaddition reactions. Selective 1,2 and 1,4-hydride addition, respectively, are possible in the case of carbonyl-bearing olefins **3**. Such olefins also undergo Lewis acid-mediated 1,4-addition of allylsilanes or to unprecedented Smiles-like rearrangement products. Finally, classical Giese 1,4-radical addition of the nucleophilic ethyl radical was observed in case of nitrile-bearing olefin **6a** but not in case of the two carbonyl-group bearing analogues **3a** and **5c**. The last two transformations (smiles-like rearrangement and nucleophilic radical additions) are currently being further investigated in our group.

EXPERIMENTAL SECTION

General Information. All starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. Chiral aldehydes,[40] pyridium salts **11a–c**,[41] chiral ammonium salts **13a–c**,[30,42] BT-sulfones **2d**,[43] **2g**,[25,26] (−)-2-menthyl 2-bromoacetate,[44] and 2-(methylsulfonyl)benzo[*d*]thiazole[25,26] were prepared using reported procedures. Progress of reactions was monitored by thin-layer chromatography (TLC)—aluminum plates pre-coated with silica gel (silica gel 60 F254). Column chromatography was performed on silica gel 60 (40–63 μm) or neutralized silica gel (40–63 μm) using 5% solution of Et_3N in petroleum ether. Reactions run at elevated temperatures were carried out using an oil bath, and indicated temperatures refers to the oil bath temperature. Determination of melting points were done on a Büchi melting point apparatus and were uncorrected. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were measured on Jeol ECA400II (400 and 101 MHz) or Jeol 500 ECA (500 and 126 MHz) in $CDCl_3$ or dimethyl sulfoxide (DMSO). Chemical shifts are reported in ppm, and their calibration was performed (a) in case of ^1H NMR experiments on the residual peak of non-deuterated solvent δ ($CHCl_3$) = 7.26 ppm; δ (DMSO) = 2.50 ppm, (b) in case of ^{13}C NMR experiments on the middle peak of the ^{13}C signal in deuterated solvent δ ($CDCl_3$) = 77.2 ppm; δ (DMSO-d_6) = 39.5 ppm, and (c) in case of $^{19}F\{^1H\}$ NMR experiments on the external calibrant $CFCl_3$ [δ ($CFCl_3$) = 0 ppm]. Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of triplet (tt), and multiplet (m). High-resolution mass spectrometry (HRMS) data were obtained using a quadrupole/ion trap mass analyzer. High-performance liquid chromatography (HPLC) was performed using a Dionex Summit HPLC system with a CHIRAL ART Cellulose-SB (250 × 4.6 mm, 5 μm) or CHIRALPAK IE-3 chiral stationary phase with mobile phase 2-propanol/hexane, 2-propanol/CO_2, and MeOH/CO_2. HRMS analysis was performed using a LC chromatograph (Dionex UltiMate 3000, Thermo Fischer Scientific, MA, USA) + mass spectrometer Exactive Plus Orbitrap high-resolution (Thermo Fischer Scientific, MA, USA) with electrospray ionization; chromatographic separation: column Phenomenex Gemini (C18, 50 × 2 mm, 3 μm particle), isocratic elution, MP: 80% ACN and 20% buffer (0.01 M ammonium acetate) or 95% MeOH + 5% water + 0.1% HCOOH. Microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus. The reactor was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 30 mL glass vials sealed with an Silicone/PTFE Vial caps top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an infrared sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled to ambient temperature by gas jet cooling.

Synthesis of α-Electron-Withdrawing BT-Sulfones (2). *Method A.*[45] *Synthesis of a Sulfide Intermediate.* A mercaptobenzothiazole (10.0 g, 1.0 equiv) and α-halo compound (1.0 equiv) were dissolved in CH_2Cl_2 (0.2 M), and the mixture was cooled to 0 °C. Triethylamine (8.6 mL, 2.0 equiv) was added dropwise, and the resulting mixture was allowed to warm to r.t. and stirred for 4 h 2 M aq. HCl (20 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the resulting organic extracts were combined, washed with water (30 mL), brine (20 mL), and dried over $MgSO_4$, and solvents were evaporated under reduced pressure. The crude product was used in the next step without further purification.

Synthesis of targeted sulfone. Sulfide (1.1 g, 1.0 equiv) and periodic acid (2.8 g, 3.0 equiv) were dissolved in acetonitrile (0.2 M), and the mixture was cooled to 0 °C. CrO_3 (0.123 g, 0.3 equiv) was added portion wise, and the resulting mixture stirred for 30 min, before it was warmed to r.t. The reaction was stirred for another 4 h before it was cooled to 0 °C and quenched by adding sat. aq. Na_2SO_3. The mixture was filtered through Celite and washed (5 × 25 mL EtOAc). Layers were separated, and the organic phase was washed with sat. Na_2SO_3 (2 × 20 mL), water (2 × 20 mL), brine (2 × 20 mL), and dried over $MgSO_4$. Solvents were removed under the reduced pressure.

Method B.[25] A solution of 2-(methylsulfonyl)benzo[*d*]thiazole[25,26] (0.300 g, 1.41 mmol, 1.0 equiv) in dry THF (7.0 mL, 0.2 M) was cooled to −78 °C, and LiHMDS (1.0 M sol. in THF) (3.7 mL, 2.2 equiv) was added dropwise. The color of the reaction mixture turned from colorless or slightly yellow to orange/red. Immediately after, a solution of acyl halide (1.69 mmol, 1.2 equiv) in THF (3 mL) was added. The color of the reaction mixture faded within few minutes. The resulting mixture was stirred at −78 °C for 60 min, allowed to warm to r.t. within 1 h and stirred at r.t. for additional 60 min before sat. aq. NH_4Cl (15 mL) was added. The whole mixture was extracted with EtOAc (3 × 75 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure. The resulting crude

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product was used further without any purification, if not stated otherwise.

*1-(Benzo[d]thiazol-2-ylsulfonyl)propan-2-one (**2a**).* The crude product was prepared using method A and obtained with enough purity as a yellow solid (4.2 g, 89%). mp = 125−127 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.21 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.03−7.99 (m, 1H), 7.67−7.57 (m, 2H), 4.57 (s, 2H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 194.7, 164.9, 152.5, 137.0, 128.4, 127.9, 125.7, 122.5, 65.5, 31.6; MS (ESI) *m*/*z* (%) 256: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M - H]^-$ calcd for $C_{10}H_8NO_3S_2$, 253.9951; found, 253.9950.

*1-(Benzo[d]thiazol-2-ylsulfonyl)hex-5-en-2-one (**2b**).* The crude product was prepared using method B, purified using flash column chromatography (SiO_2; EtOAc:P.E. = 1:6), and isolated as a yellow oil (1.4 g, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.19 (m, 1H), 8.05−8.00 (m, 1H), 7.67−7.58 (m, 2H), 5.81−5.70 (m, 1H), 5.08−4.95 (m, 2H), 4.59 (s, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.41−2.29 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.4, 165.0, 152.5, 137.0, 136.0, 128.4, 127.9, 125.7, 122.5, 116.1, 64.7, 43.6, 27.1; MS (ESI) *m*/*z* (%) 294: $[M - H]^-$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{14}NO_3S_2$, 296.0410; found, 296.0407.

*1-(Benzo[d]thiazol-2-ylsulfonyl)-5-chloropentan-2-one (**2c**).* The crude product was prepared using method B, purified using flash column chromatography (SiO_2; diethylether:P.E. = 3:1), and isolated as an orange oil (0.485 g, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23−8.20 (m, 1H), 8.04−8.01 (m, 1H), 7.68−7.59 (m, 2H), 4.61 (s, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 2.96 (t, *J* = 6.8 Hz, 2H), 2.12−2.02 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.2, 164.9, 152.5, 137.0, 128.5, 128.0, 125.7, 122.6, 64.9, 43.8, 41.3, 26.0; MS (ESI) *m*/*z* (%) 282: $[M - Cl]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{13}ClNO_3S_2$, 318.0020; found, 318.0021.

*2-(Benzo[d]thiazol-2-ylsulfonyl)-1-phenylethan-1-one (**2e**).* The crude product was prepared using method A and obtained with enough purity as a light brown solid (3.9 g, 92%). mp = 118−120 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.21−8.18 (m, 1H), 8.02−7.99 (m, 1H), 7.95−7.90 (m, 2H), 7.66−7.57 (m, 3H), 7.50−7.44 (m, 2H), 5.20 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 187.3, 165.4, 152.6, 137.2, 135.6, 134.8, 129.1, 129.1, 128.3, 127.8, 125.7, 122.5, 61.3; MS (ESI) *m*/*z* (%) 318: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{12}NO_3S_2$, 318.0253; found, 318.0251.

*Methyl 2-(Benzo[d]thiazol-2-yl-sulfonyl)acetate (**2f**).* The crude product was prepared using method A and obtained as a yellow solid (2.8 g, 88%). mp = 68−70 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.21 (m, 1H), 8.04−8.01 (m, 1H), 7.68−7.59 (m, 2H), 4.58 (s, 2H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.0, 162.3, 152.6, 137.1, 128.4, 127.9, 125.7, 122.5, 58.7, 53.5; MS (ESI) *m*/*z* (%): 272 $[M + H]^+$ (27); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{10}NO_4S_2$, 272.0046; found, 272.0043.

*Isopropyl 2-(Benzo[d]thiazol-2-yl-sulfonyl)acetate (**2h**).* The crude product was prepared using method B and obtained as a light yellow solid (0.199 g, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.21 (m, 1H), 8.08−7.99 (m, 1H), 7.68−7.58 (m, 2H), 5.00 (hept, *J* = 6.4 Hz, 1H), 4.54 (s, 2H), 1.15 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.2, 161.2, 152.6, 137.1, 128.4, 127.9, 125.7, 122.5, 71.1, 59.1, 21.6; MS (ESI) *m*/*z* (%) 298: $[M - H]^-$ (100); HR-MS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{12}H_{13}NO_4S_2$, 299.0286; found, 299.0284.

*(2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(Benzo[d]thiazol-2-yl-sulfonyl)acetate (**2i**).* The crude product was prepared using method A from (−)-2-menthyl 2-bromoacetate[44] and obtained with enough purity as a green viscose syrup (2.24 g, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25−8.17 (m, 1H), 8.07−7.97 (m, 1H), 7.69−7.54 (m, 2H), 4.65 (td, *J* = 10.8, 4.4 Hz, 1H), 4.62 (d, *J* = 15.2 Hz, 1H), 4.52 (d, *J* = 15.2 Hz, 1H) 1.97−1.85 (m, 1H), 1.69−1.52 (m, 3H), 1.47−1.31 (m, 1H), 1.24−1.10 (m, 1H), 1.03−0.84 (m, 2H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.84−0.67 (m, 1H), 0.68 (d, *J* = 7.2 Hz, 3H), 0.61 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.3, 161.3, 152.6, 137.0, 128.3, 127.9, 125.6, 122.5, 58.9, 46.7, 40.4, 34.1, 31.4, 26.0, 23.1, 22.0, 20.6, 16.0; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{26}NO_4S_2$, 396.1298; found, 396.1300; α_D^{22} = −32.5 (c 0.2, $CHCl_3$).

*2-(Benzo[d]thiazol-2-yl-sulfonyl)-N,N-diethylacetamide (**2k**).* The crude product was prepared using method B, purified using flash column chromatography (SiO_2; EtOAc:P.E. = 3:1), and isolated as a yellow solid (0.366 g, 84%). mp = 125−126 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23−8.20 (m, 1H), 8.01−7.98 (m, 1H), 7.64−7.55 (m, 2H), 4.63 (s, 2H), 3.46 (q, *J* = 7.2 Hz, 2H), 3.35 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.5, 160.0, 152.6, 137.4, 128.1, 127.7, 125.7, 122.6, 58.0, 43.3, 41.1, 14.6, 12.9; MS (ESI) *m*/*z* (%) 313: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{16}N_2NaO_3S_2$, 335.0495; found, 335.0494.

*2-(Benzo[d]thiazol-2-yl-sulfonyl)acetonitrile (**2l**).* The crude product was prepared using the method A and obtained with enough purity as a brown solid (3.4 g, 95%). mp = 172−174 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.29−8.25 (m, 1H), 8.09−8.05 (m, 1H), 7.74−7.65 (m, 2H), 4.56 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 162.5, 152.4, 137.3, 129.1, 128.4, 126.0, 122.7, 109.2, 44.1; MS (ESI) *m*/*z* (%) 237: $[M - H]^-$ (25); HRMS (ESI) *m*/*z*: $[M - H]^-$ calcd for $C_9H_5N_2O_2S_2$, 236.9798; found, 236.9798.

Ti(O-*i*Pr)$_4$-Mediated Transesterification of 2f to 2h. To solution of sulfone **2f** (0.200 g, 0.73 mmol, 1.0 equiv) in CH_3CN (4.0 mL, 0.2 M), Ti(O-*i*Pr)$_4$ (0.435 mL, 1.46 mmol, 2.0 equiv) was added dropwise at r.t., and the resulting mixture was stirred for 2 h. CH_2Cl_2 (15 mL) and sat. aq. NH_4Cl (5 mL) were added, and the resulting mixture was filtered through Celite. The filtrate cake was washed with CH_2Cl_2 (5 × 20 mL), and the combined filtrates were washed with sat. aq. NH_4Cl (2 × 15 mL), brine (2 × 15 mL), and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the crude product was isolated as a light yellow solid (0.219 g, 95%)

General Procedure for Knoevenagel Condensation Reaction. To a sulfone (1.0 mmol, 1.0 equiv) in CH_3CN (5.0 mL, 0.2 M) at r.t. was added Ti(O-*i*Pr)$_4$ (0.925 mL, 3.0 equiv), and the resulting mixture was stirred for 30 min. An aldehyde (2.0 mmol, 2.0 equiv) was added dropwise, and the mixture was stirred for the indicated time. The reaction was quenched upon the addition of CH_2Cl_2 (15 mL) and sat. NH_4Cl (5 mL), and the resulting suspension was filtered through Celite. The filtrate cake was rinsed with CH_2Cl_2 (5 × 20 mL), and the combined filtrates were washed with sat. NH_4Cl (2 × 15 mL), brine (2 × 15 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-phenylbut-3-en-2-one (**3a**).* Reaction was carried out using the described procedure with 1.5 g (4.37 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3a** as a light yellow solid (1.43 g, 71%). mp = 104−107 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.18 (m, 1H), 8.14 (s, 1H), 8.01−7.98 (m, 1H), 7.59 (ddd, *J* = 7.2, 6.4, 1.6 Hz, 2H), 7.41 (s, 5H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 198.3, 166.0, 152.9, 145.1, 139.3, 137.6, 132.2, 131.3, 130.3, 129.4, 128.1, 127.6, 125.7, 122.40, 31.92; MS (ESI) *m*/*z* (%) 344: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{14}NO_3S_2$, 344.0410; found, 344.0413.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(4-methoxyphenyl)but-3-en-2-one (**3b**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3b** as a yellow solid (0.143 g, 63%). mp = 119−121 °C; ^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.20−8.18 (m, 1H), 8.07 (s, 1H), 8.00−7.98 (m, 1H), 7.62−7.55 (m, 2H), 7.39−7.36 (m, 2H), 6.94−6.91 (m, 2H), 3.85 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 198.7, 166.5, 163.0, 152.8, 145.1, 137.5, 136.2, 132.8, 128.0, 127.6, 125.7, 123.7, 122.4, 114.9, 55.7, 31.9; MS (ESI) *m*/*z* (%) 374: $[M + H]^+$ (50); HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{16}NO_4S_2$, 374.0515; found, 374.0519.

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*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(3-methoxyphenyl)but-3-en-2-one (**3c**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3c** as a yellow oil (0.138 g, 61%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.17 (m, 1H), 8.10 (s, 1H), 8.00−7.97 (m, 1H), 7.62−7.54 (m, 2H), 7.37−7.28 (m, 1H), 7.06−6.94 (m, 3H), 3.78 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 198.3, 165.9, 160.1, 152.8, 145.0, 139.5, 137.6, 132.5, 130.4, 128.1, 127.6, 125.7, 122.6, 122.4, 118.1, 115.0, 55.5, 32.0; MS (ESI) *m/z* (%) 374: $[M + H]^+$; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}NO_4S_2$, 374.0515; found, 374.0518.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(4-bromophenyl)but-3-en-2-one (**3d**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3d** as a yellow oil (0.231 g, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.22−8.19 (m, 1H), 8.05 (s, 1H), 8.03−8.00 (m, 1H), 7.65−7.59 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 198.0, 165.7, 152.9, 143.5, 140.1, 137.6, 132.8, 131.6, 130.2, 128.3, 127.8, 127.1, 125.8, 122.5, 32.0; MS (ESI) *m/z* (%) 422: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{13}BrNO_3S_2$, 421.9515; found, 421.9514.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(4-chlorophenyl)but-3-en-2-one (**3e**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3e** as a colorless oil (0.212 g, 71%). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.24−8.17 (m, 1H), 8.06 (s, 1H), 8.03−7.99 (m, 1H), 7.64−7.56 (m, 2H), 7.44−7.39 (m, 2H), 7.37−7.33 (m, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 198.0, 165.8, 152.9, 143.5, 140.0, 138.6, 137.6, 131.5, 129.8, 128.3, 127.8, 125.8, 122.4, 32.0; MS (ESI) *m/z* (%) 378: $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{12}ClNaNO_3S_2$, 399.0939; found, 399.0940.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(2-isopropoxyphenyl)but-3-en-2-one (**3i**).* Reaction was carried out using the described procedure with 0.233 g (0.92 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3i** as a yellow oil (0.274 g, 69%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.51 (s, 1H), 8.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.01 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.58 (tt, *J* = 7.2, 5.6 Hz, 2H), 7.43 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.02−6.85 (m, 2H), 4.63 (hept, *J* = 6.0 Hz, 1H), 2.30 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 197.8, 167.0, 157.0, 142.9, 138.2, 137.5, 133.8, 131.1, 127.9, 127.4, 125.5, 122.3, 121.5, 120.7, 114.0, 71.9, 53.6, 31.3, 21.9; MS (ESI) *m/z* (%) 402: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{19}NNaO_4S_2$, 424.0653; found, 424.0648.

*(E)-4-(2-(Allyloxy)phenyl)-3-(benzo[d]thiazol-2-yl-sulfonyl)but-3-en-2-one (**3j**).* Reaction was carried out using the described procedure with 0.255 g (1.0 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3j** as a yellow oil (0.267 g, 67%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.53 (s, 1H), 8.23−8.16 (m, 1H), 8.05−7.95 (m, 1H), 7.66−7.52 (m, 2H), 7.49−7.40 (m, 1H), 7.21 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.01−6.90 (m, 2H), 6.02 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.42 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.30 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.70−4.59 (m, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 197.8, 166.8, 157.4, 152.8, 142.2, 138.5, 137.5, 133.9, 132.2, 131.1, 128.0, 127.5, 125.6, 122.4, 121.1, 120.8, 118.3, 112.8, 69.4, 31.5; MS (ESI) *m/z* (%) 400: $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{17}NNaO_4S_2$, 422.0497; found, 422.0490.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(2-(prop-2-yn-1-yloxy)-phenyl)but-3-en-2-one (**3k**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided **3k** as a brown solid (0.224 g, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.45 (s, 1H), 8.19 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.00 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.63−7.53 (m, 2H), 7.51−7.45 (m, 1H), 7.24 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 2H), 2.54 (t, *J* = 2.4 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 197.8, 166.7, 156.2, 152.9, 141.7, 139.0, 137.6, 133.8, 131.4, 128.0, 127.6, 125.7, 122.4, 121.9, 121.3, 113.1, 56.2, 31.6; MS (ESI) *m/z* (%) 397: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{15}NNaO_4S_2$, 420.0340; found, 420.0335.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(2,6-dichlorophenyl)but-3-en-2-one (**3l**).* Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3l** as a yellow oil (0.06 g, 37%). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.31 (s, 1H), 8.21−8.18 (m, 1H), 8.04−8.01 (m, 1H), 7.65−7.58 (m, 2H), 7.41−7.38 (m, 2H), 7.35−7.30 (m, 1H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 193.6, 166.2, 152.7, 143.8, 137.5, 133.9, 131.6, 130.7, 128.6, 128.3, 127.7, 126.6, 125.8, 122.5, 30.2; MS (ESI) *m/z* (%) 412: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{11}Cl_2NNaO_3S_2$, 433.9455; found, 433.9449.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(3,4,5-trimethoxyphenyl)-but-3-en-2-one (**3m**).* Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3m** as a yellow oil (0.131 g, 73%). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.23−8.19 (m, 1H), 8.04 (s, 1H), 8.03−7.99 (m, 1H), 7.66−7.55 (m, 2H), 6.64 (s, 2H), 3.90 (s, 3H), 3.82 (s, 6H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 198.7, 166.0, 153.6, 152.9, 145.1, 141.6, 138.1, 137.6, 128.2, 127.7, 126.4, 125.8, 122.4, 107.7, 61.2, 56.3, 32.2; MS (ESI) *m/z* (%) 434: $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{20}NO_6S_2$, 423.0727; found, 423.0728.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(furan-2-yl)but-3-en-2-one (**3n**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3n** as a yellow oil (0.237 g, 91%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.17 (m, 1H), 7.99−7.96 (m, 1H), 7.74 (s, 1H), 7.62−7.58 (m, 3H), 7.04 (d, *J* = 3.6 Hz, 1H), 6.57 (dd, *J* = 3.6, 1.6 Hz, 1H), 2.61 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.8, 166.1, 152.9, 148.1, 147.6, 137.5, 134.3, 129.7, 128.1, 127.6, 125.7, 122.3, 122.0, 113.6, 32.3; MS (ESI) *m/z* (%) 334: $[M + H]^+$ (49); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{12}NO_4S_2$, 334.0202; found, 334.0203.

*(3E,5E)-3-(benzo[d]thiazol-2-ylsulfonyl)-6-phenylhexa-3,5-dien-2-one (**3o**).* Reaction was carried out using the described procedure with 0.740 g (2.9 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **3o** as a yellow solid (0.866 g, 81%, *E*/*Z* = 7:1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.14 (m, 1H), 8.02−7.97 (m, 2H), 7.69 (dd, *J* = 15.2, 11.6 Hz, 1H), 7.62−7.56 (m, 4H), 7.41 (m, 3H), 7.37 (d, *J* = 15.2 Hz, 1H), 2.65 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 194.1, 167.5, 152.7, 152.4, 152.3, 137.0, 135.7, 135.1, 131.4, 129.3, 128.9, 128.2, 127.7, 125.7, 123.0, 122.4, 31.9; MS (ESI) *m/z* (%) 370: $[M + 1]^+$ (60); HRMS (ESI) *m/z*: calcd for $C_{19}H_{16}NO_3S_2$ $[M + H]^+$, 370.0566; found, 370.0568.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-cyclohexylbut-3-en-2-one (**3p**).* Reaction was carried out using the described procedure with 1.0 g (3.9 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3p** as a colorless oil (0.764 g, 56%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.16 (m, 1H), 8.00−7.97 (m, 1H), 7.64−7.54 (m, 2H), 7.25 (d, *J* = 10.8 Hz, 1H), 2.57 (s, 3H), 1.76 (bs, 5H), 1.28 (bs, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 195.1, 166.5, 159.0, 152.6, 139.8, 137.1, 128.1, 127.7, 125.7, 122.4, 39.5, 32.2, 31.6, 25.5, 25.0; MS (ESI) *m/z* (%) 350: $[M + 1]^+$

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(100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{20}NO_3S_2$, 350.0879; found, 350.0877.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-phenylhepta-1,6-dien-3-one (**3s**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2b**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **3s** as a yellow oil (0.234 g, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.22−8.19 (m, 1H), 8.16 (s, 1H), 8.02−7.99 (m, 1H), 7.64−7.56 (m, 2H), 7.52−7.46 (m, 1H), 7.45−7.40 (m, 2H), 7.39−7.35 (m, 2H), 5.69 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.01−4.92 (m, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.39−2.32 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 200.1, 166.0, 153.0, 145.2, 139.2, 137.7, 136.1, 132.2, 131.4, 130.4, 129.4, 128.2, 127.7, 125.8, 122.4, 116.2, 43.5, 27.4; MS (ESI) *m/z* (%) 384: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{18}NO_3S_2$, 384.0723; found, 384.0720.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-(4-methoxyphenyl)hepta-1,6-dien-3-one (**3t**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2b**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **3t** as a yellow oil (0.266 g, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.21−8.17 (m, 1H), 8.07 (s, 1H), 8.01−7.97 (m, 1H), 7.62−7.54 (m, 2H), 7.35−7.31 (m, 2H), 6.93−6.89 (m, 2H), 5.73 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.04−4.94 (m, 2H), 3.85 (s, 3H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.42−2.35 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 200.5, 166.5, 163.0, 152.9, 145.2, 137.6, 136.3, 136.0, 132.9, 128.0, 127.6, 125.8, 123.8, 122.4, 116.1, 114.9, 55.7, 43.5, 27.5; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_4S_2$, 414.0828; found, 414.0827.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-(furan-2-yl)hepta-1,6-dien-3-one (**3w**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2b**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided **3w** as a yellow oil (0.220 g, 87%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.21−8.18 (m, 1H), 8.00−7.97 (m, 1H), 7.74 (s, 1H), 7.63−7.53 (m, 3H), 7.00−6.98 (m, 1H), 6.57 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.85 (ddt, *J* = 16.8, 10.0, 6.4 Hz, 1H), 5.06 (dq, *J* = 17.2, 1.6 Hz, 1H), 4.99 (ddt, *J* = 10.0, 1.6, 1.2 Hz, 1H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.50−2.43 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 198.6, 166.1, 152.9, 148.0, 147.7, 137.6, 136.8, 134.5, 129.7, 128.1, 127.7, 125.8, 122.4, 121.7, 115.7, 113.6, 43.9, 27.5; MS (ESI) *m/z* (%) 374: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}NO_4S_2$, 374.0515; found, 374.0513.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-cyclohexylhepta-1,6-dien-3-one (**3x**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2b**. Product **3x** was obtained with enough purity as a yellow oil (0.155 g, 59%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.16 (m, 1H), 8.01−7.97 (m, 1H), 7.64−7.55 (m, 2H), 7.21 (d, *J* = 10.8 Hz, 1H), 5.79 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1H), 5.07−4.94 (m, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.54−2.43 (m, 1H), 2.39 (dtd, *J* = 7.2, 6.0, 1.6 Hz, 2H), 1.82−1.68 (m, 5H), 1.33−1.22 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 197.4, 166.5, 158.1, 152.8, 139.9, 137.3, 136.5, 128.2, 127.7, 125.8, 122.4, 115.8, 43.7, 39.5, 31.7, 27.5, 25.6, 25.0; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{23}NNaO_3S_2$, 412.1012; found, 412.1013.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-6-chloro-1-phenylhex-1-en-3-one (**3y**).* Reaction was carried out using the described procedure with 0.100 g (0.68 mmol) of sulfone **2c**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3y** as a yellow oil (0.079 g, 62%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23−8.18 (m, 1H), 8.17 (s, 1H), 8.03−7.98 (m, 1H), 7.64−7.55 (m, 2H), 7.52−7.47 (m, 1H), 7.46−7.41 (m, 2H), 7.39−7.35 (m, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.13−2.03 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 199.9, 165.9, 152.9, 145.5, 139.0, 137.6, 132.3, 131.3, 130.2, 129.5, 128.2, 127.7, 125.8, 122.4, 43.7, 41.2, 26.4; MS (ESI) *m/z* (%) 406: $[M]^+$ (100), 407 [M +1]$^+$ (23); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{17}ClNO_3S_2$, 406.0333; found, 406.0333.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1,3-diphenylprop-2-en-1-one (**3aa**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2e**. Purification using flash chromatography (passive SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3aa** as a yellow solid (0.367 g, 58%). mp = 150−153 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.33 (s, 1H), 8.24−8.16 (m, 1H), 8.00−7.93 (m, 1H), 7.91−7.82 (m, 2H), 7.65−7.51 (m, 2H), 7.47 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.38−7.27 (m, 5H), 7.24−7.13 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 191.2, 166.0, 152.9, 145.9, 137.7, 136.7, 135.3, 134.7, 131.9, 131.2, 130.9, 129.9, 129.1, 128.9, 128.1, 127.6, 125.8, 122.4; MS (ESI) *m/z* (%) 406: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}NO_3S_2$, 406.0566; found, 406.0563.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**3ab**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **3ab** as a yellow solid (0.120 g, 50%). mp = 168−170 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.19 (m, 1H), 8.00 (s, 1H), 7.96−7.93 (m, 1H), 7.92−7.89 (m, 2H), 7.61−7.54 (m, 2H), 7.53−7.49 (m, 1H), 7.39−7.33 (m, 2H), 7.24 (dq, *J* = 1.6, 0.8 Hz, 2H), 6.85 (d, *J* = 3.2 Hz, 1H), 6.41 (dd, *J* = 3.6, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 190.1, 166.2, 152.9, 147.9, 147.5, 137.7, 136.4, 134.3, 132.3, 130.9, 129.7, 128.8, 128.0, 127.5, 125.7, 122.3, 121.4, 113.2; MS (ESI) *m/z* (%) 396: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{14}NO_4S_2$, 396.0359; found, 396.0359.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**3ac**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **3ac** as a white solid (0.200 g, 67%). mp = 57−59 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.34 (s, 1H), 8.23−8.20 (m, 1H), 8.00−7.97 (m, 1H), 7.88−7.85 (m, 1H), 7.65−7.56 (m, 2H), 7.54−7.44 (m, 5H), 7.36−7.31 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 190.6, 165.3, 153.0, 143.5, 139.5, 137.8, 135.1, 135.0, 134.5, 133.1 (q, *J* = 32.9 Hz), 130.8, 129.9, 129.1, 128.3, 128.2, 126.7 (d, *J* = 272.1 Hz), 126.0 (q, *J* = 3.7 Hz), 125.8, 122.4; ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*): δ −63.17(s, 3F); MS (ESI) *m/z* (%) 474: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{15}F_3NO_3S_2$, 474.0440; found, 474.0438.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-cyclohexyl-1-phenylprop-2-en-1-one (**3ae**).* Reaction was carried out using the described procedure with 0.050 g (0.16 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3ae** as a colorless oil (0.029 g, 45%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.15 (m, 1H), 7.97−7.93 (m, 1H), 7.91−7.87 (m, 2H), 7.63−7.58 (m, 2H), 7.57−7.53 (m, 1H), 7.43 (td, *J* = 8.4, 7.6, 0.8 Hz, 2H), 7.37 (d, *J* = 10.8 Hz, 1H), 2.12−1.99 (m, 1H), 1.75−1.57 (m, 4H), 1.39−1.14 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 190.0, 166.2, 155.5, 152.8, 137.7, 137.6, 136.5, 134.7, 129.9, 128.9, 128.0, 127.5, 125.7, 122.3, 39.8, 31.3, 25.3, 24.8; MS (ESI) *m/z* (%) 413: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{22}NO_3S_2$, 412.1036; found, 412.1038.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-phenyl-3-(2-(prop-2-yn-1-yl-oxy)phenyl)prop-2-en-1-one (**3af**).* Reaction was carried out using the described procedure with 0.100 g (0.31 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided **3af** as a light brown solid (0.103 g, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.72 (s, 1H), 8.22−8.17 (m, 1H), 7.97 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.87−7.82 (m, 2H), 7.57 (pd, *J* = 7.2, 1.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.27 (td, *J* = 8.4, 3.2 Hz, 3H), 7.12 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 4.72 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H).; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 191.1, 166.6, 156.3, 152.9, 142.0, 137.7,

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136.2, 135.6, 134.3, 133.4, 131.4, 129.7, 128.7, 127.9, 127.5, 125.7, 122.3, 121.5, 121.1, 112.7, 77.7, 76.5, 56.0; MS (ESI) *m/z* (%) 460 $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{17}NNaO_4S_2$, 482.0497; found, 482.0490.

*(S,E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-4-((tert-butyldimethylsilyl)oxy)-1-phenylpent-2-en-1-one (**3ag**).* Reaction was carried out using the described procedure with 0.100 g (0.31 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **3ag** as a colorless oil (0.059 g, 39%, e.r.= >99:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.22−8.19 (m, 1H), 7.97−7.94 (m, 1H), 7.90−7.85 (m, 2H), 7.64−7.57 (m, 2H), 7.57−7.54 (m, 1H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.44−7.39 (m, 2H), 4.49 (p, *J* = 6.4 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.70 (s, 9H), −0.15 (s, 3H), −0.19 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 189.3, 165.6, 153.0, 137.8, 137.6, 136.6, 134.5, 130.2, 128.8, 128.1, 127.6, 125.8, 122.4, 67.0, 25.8, 23.3, 18.2, −4.8, −5.1; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{30}NO_4S_2Si$, 488.1380; found, 88.1383; α_D^{27} = +31.4 (c 0.7,$CHCl_3$); HPLC (CHIRALPAK IE-3, eluent: CO_2: MeOH = 95:5, 2.2 mL/min, 38 °C, retention time: *t* = 13.22 min).

*Isopropyl (E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-phenylacrylate (**5c**).* Reaction was carried out using the described procedure with 2.4 g (8.86 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **5c** as a yellow solid (2.0 g, 59%). mp = 76−78 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.22 (s, 1H), 8.21−8.18 (m, 1H), 8.03−7.99 (m, 1H), 7.64−7.55 (m, 4H), 7.51−7.39 (m, 3H), 5.15 (hept, *J* = 6.0 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.6, 161.8, 152.8, 148.2, 137.4, 132.3, 132.2, 131.4, 130.8, 129.0, 128.1, 127.6, 125.7, 122.3, 71.2, 21.4; MS (ESI) *m/z* (%) 328: $[M - OiPr]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{18}NO_4S_2$, 388.0672; found, 388.0672.

*Isopropyl (E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(furan-2-yl)-acrylate (**5f**).* Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **5f** as a yellow oil (0.164 g, 60%). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.18−8.14 (m, 1H), 8.06 (s, 1H), 8.01−7.97 (m, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.61−7.52 (m, 2H), 7.43 (d, *J* = 3.6 Hz, 1H), 6.61 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.15 (hept, *J* = 6.4 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.3, 161.1, 152.7, 148.4, 148.0, 137.3, 134.6, 127.9, 127.6, 126.3, 125.6, 123.6, 122.3, 114.0, 70.8, 21.6; MS (ESI) *m/z* (%) 318: $[M]^+$ (100), 378 $[M + 1]^+$(21); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_5S_2$, 378.0464; found, 378.0461.

*Isopropyl (E)-2-(Benzo[d]thiazol-2-ylsulfonyl)-3-(4-(trifluoromethyl)phenyl)acrylate (**5g**).* Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **5g** as a white solid (0.120 g, 36%). mp = 135−137 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.27 (s, 1H), 8.22−8.19 (m, 1H), 8.05−8.01 (m, 1H), 7.68 (s, 4H), 7.65−7.57 (m, 2H), 5.12 (hept, *J* = 6.4 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.0, 161.1, 152.7, 146.4, 137.4, 135.0, 134.8, 133.2 (q, *J* = 33.0 Hz), 130.6, 128.2, 127.7, 125.8 (q, *J* = 3.7 Hz), 125.7, 123.6 (q, *J* = 273.2 Hz), 122.3, 71.5, 21.3; $^{19}F\{^1H\}$ NMR (376 MHz, Chloroform-*d*): δ −63.04 (s, 3F); MS (ESI) *m/z* (%) 414: $[M]^+$ (100), 456 $[M+1]^+$(32); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{17}F_3NO_4S_2$, 456.0546; found, 456.0548.

*Isopropyl (E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-cyclohexylacrylate (**5i**).* Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **5i** as a yellow oil (0.160 g, 55%). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.12 (m, 1H), 8.03−7.94 (m, 1H), 7.63 (d, *J* = 10.4 Hz, 1H), 7.60−7.53 (m, 2H), 5.05 (hept, *J* = 6.0, 1H), 3.17−3.04 (m, 1H), 1.90−1.68 (m, 5H), 1.37−1.24 (m, 5H), 1.13 (d, *J* = 6.0 Hz, 6H; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*)): δ 167.7, 164.5, 160.8, 152.9, 137.4, 132.3, 128.2, 127.8, 125.8, 122.6, 70.8, 39.9, 31.9, 26.0, 25.5, 21.9; MS (ESI) *m/z* (%) 352: $[M]^+$ (100), 394 $[M+1]^+$ (53); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{24}NO_4S_2$, 394.1141; found, 394.1141.

*Isopropyl (S,E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-4-((tert-butyldimethylsilyl)oxy)pent-2-enoate (**5j**).* Reaction was carried out using the described procedure with 0.100 g (0.37 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **5j** as a yellow oil (0.084 g, 49%, e.r. = >99:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.15−8.12 (m, 1H), 8.02−7.99 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.63−7.54 (m, 2H), 5.22 (dq, *J* = 7.6, 6.4 Hz, 1H), 5.04 (hept, *J* = 6.4 Hz, 1H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.08 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.9, 162.9, 160.0, 152.6, 137.1, 131.2, 128.0, 127.6, 125.5, 122.3, 70.8, 66.6, 25.9, 23.0, 21.6, 21.5, 18.3, −4.5, −4.7; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{32}NO_5S_2Si$, 470.1486; found, 470.1489; α_D^{27}= + 41.2 (c 1.0, $CHCl_3$); HPLC (CHIRALPAK IE-3, eluent: CO_2: *i*-PrOH = 95:5, 2.2 mL/min, 38 °C, retention time: *t* = 5.14 min).

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-N,N-diethyl-3-phenylacrylamide (**5k**).* Reaction was carried out using the described procedure with 0.070 g (0.22 mmol) of sulfone **2k**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **5k** as a white solid (0.048 g, 53%). mp= 158−161 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.22−8.19 (m, 1H), 8.01 (s, 1H), 7.98−7.95 (m, 1H), 7.60−7.51 (m, 4H), 7.48−7.41 (m, 1H), 7.41−7.33 (m, 2H), 3.62 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.38 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.27 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.3, 162.1, 152.9, 143.0, 138.0, 134.5, 132.0, 131.7, 130.3, 129.2, 128.0, 127.5, 125.9, 122.4, 43.5, 39.7, 13.7, 12.0; MS (ESI) *m/z* (%) 401: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{20}N_2NaO_3S_2$, 423.0808; found, 423.0809.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-phenylacrylonitrile (**6a**).* Reaction was carried out using the described procedure with 2.0 g (8.4 mmol) of sulfone **2l**. Crude product **6a** was isolated with enough purity as a light yellow solid (2.4 g, 88%). mp = 158−160 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.45 (s, 1H), 8.26−8.23 (m, 1H), 8.06−8.03 (m,1H), 8.03−7.99 (m, 2H), 7.69−7.60 (m, 3H), 7.58−7.52 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 164.0, 156.0, 153.3, 138.0, 135.5, 132.2, 130.5, 130.1, 129.0, 128.5, 126.4, 122.8, 112.8, 112.2; MS (ESI) *m/z* (%) 327: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{11}N_2O_2S_2$, 327.0256; found, 327.0254.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(4-methoxyphenyl)-acrylonitrile (**6b**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **6b** as a yellow oil (0.109 g, 73%). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.34 (s, 1H), 8.24−8.21 (m, 1H), 8.04−7.99 (m, 3H), 7.66−7.58 (m, 2H), 7.03−7.00 (m, 2H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 165.5, 164.4, 155.0, 152.9, 137.6, 134.7, 128.5, 128.0, 125.9, 123.0, 122.5, 115.3, 113.2, 107.7, 56.0; MS (ESI) *m/z* (%) 374: $[M + H_2O]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_3S_2$, 357.0362; found, 357.0359.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(3-methoxyphenyl)-acrylonitrile (**6c**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; acetone/petroleum ether = 1:3) and concentration of the relevant fractions provided **6c** as a yellow solid (0.106 g, 71%). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.40 (s, 1H), 8.28−8.19 (m, 1H), 8.08−7.99 (m, 1H), 7.70−7.57 (m, 2H), 7.61−7.50 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.18 (ddd, *J* = 8.4, 2.4, 1.2 Hz, 1H), 3.85 (s, 3H).; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 55.7, 112.0, 112.5, 114.9, 122.1, 122.5, 125.1, 126.0, 128.1, 128.7, 130.7, 131.2, 137.7, 152.9, 155.8, 160.3, 163.7; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_3S_2$, 357.0362; found, 357.0360.

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*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(4-bromophenyl)-acrylonitrile (**6d**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; acetone/petroleum ether = 1:3) and concentration of the relevant fractions provided **6d** as a light-yellow syrup (0.129 g, 76%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.38 (s, 1H), 8.27−8.22 (m, 1H), 8.06−8.03 (m, 1H), 7.89−7.85 (m, 2H), 7.71−7.67 (m, 2H), 7.67−7.61 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ(ppm): 163.5, 154.1, 153.0, 137.7, 133.3, 132.8, 130.5, 128.9, 128.8, 128.2, 126.1, 122.5, 112.6, 112.3; MS (ESI) *m/z* (%) 406: $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{10}BrN_2O_2S_2$, 404.9362; found, 404.9360.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(furan-2-yl)acrylonitrile (**6e**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **6e** as a yellow oil (0.089 g, 67%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25−8.22 (m, 1H), 8.18 (s, 1H), 8.05−8.02 (m, 1H), 7.83 (dt, *J* = 1.6, 0.4 Hz, 1H), 7.67−7.59 (m,2H), 7.43 (d, *J* = 3.6 Hz, 1H), 6.72 (dd, *J* = 3.6, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.0, 152.9, 150.3, 147.3, 139.5, 137.6, 128.6, 128.0, 125.9, 125.3, 122.5, 114.7, 112.2, 107.2; MS (ESI) *m/z* (%) 334: $[M + H_2O]^+$ (100), 317 $[M + 1]^+$ (34); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_9N_2O_3S_2$, 317.0049; found, 317.0047.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(4-(trifluoromethyl)-phenyl)acrylonitrile (**6f**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Crude product **6f** was isolated with enough purity as a colorless oil (0.157 g, 93%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.48 (s, 1H), 8.26−8.22 (m, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 8.07−8.04 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.70−7.62 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 163.0, 153.5, 152.9, 137.7, 135.7 (q, *J* = 33.4 Hz), 133.0, 131.7, 128.9, 128.2, 126.7 (q, *J* = 3.7 Hz), 126.5, 126.0, 123.4 (d, *J* = 272.7 Hz), 114.9, 111.9; ^{19}F{^{1}H} NMR (376 MHz, Chloroform-d): δ −63.34 (s, 3F); MS (ESI) *m/z* (%) 177: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{10}F_3N_2O_2S_2$, 395.0130; found, 395.0128.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-cyclohexylacrylonitrile (**6i**).* Reaction was carried out using the described procedure with 0.050 g (0.21 mmol) of sulfone **2l**. Crude product **6i** was isolated with enough purity as a yellow solid (0.060 g, 88%). mp= 112−114 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.26−8.23 (m, 1H), 8.05−8.02 (m, 1H), 7.76 (d, *J* = 10.4 Hz, 1H), 7.69−7.60 (m, 2H), 2.77−2.67 (m, 1H), 1.89−1.70 (m, 5H), 1.41−1.22 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 169.0, 163.5, 152.9, 137.6, 128.7, 128.1, 126.1, 122.5, 116.5, 110.6, 42.0, 31.1, 25.3, 24.8; MS (ESI) *m/z* (%) 333: $[M + 1]^+$ (100); HR-MS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_2S_2$, 333.0726; found, 333.0725.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(2-(prop-2-yn-1-yl-oxy)-phenyl)acrylonitrile (**6j**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **6j** as a brown solid (0.110 g, 69%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.96 (s, 1H), 8.35−8.20 (m, 2H), 8.05−8.00 (m, 1H), 7.63 (ddd, *J* = 9.2, 5.6, 2.0 Hz, 3H), 7.19−7.07 (m, 2H), 4.88 (d, *J* = 2.4 Hz, 2H), 2.58 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.0, 157.9, 152.9, 149.9, 137.6, 136.9, 129.7, 128.6, 128.0, 126.0, 122.5, 122.2, 119.8, 113.3, 112.9, 111.1, 77.3, 56.6; MS (ESI) *m/z* (%) 381: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{12}N_2NaO_3S_2$, 403.0187; found, 403.0181.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-6-phenylhex-4-en-2-one (**7a**).* Reaction was carried out using the described procedure with 0.050 g (0.2 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **7a** as a white solid (0.036 g, 49%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.16 (m, 1H), 8.01−7.95 (m, 1H), 7.69−7.56 (m, 2H), 7.13−7.06 (m, 3H), 6.94−−6.86 (m, 2H), 5.92−5.77 (m, 2H), 5.22 (d, *J* = 9.2 Hz, 1H), 3.35 (d, *J* = 6.0 Hz, 2H), 2.51 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.6, 164.2, 152.6, 142.5, 138.1, 137.1, 128.6, 128.4, 128.3, 127.8, 126.5, 125.7, 122.5, 117.5, 78.0, 39.1, 31.2; MS (ESI) *m/z* (%) 372: $[M + 1]^+$ (37); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{18}NO_3S_2$, 372.0723; found, 372.0725.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)hept-4-en-2-one (**7b**).* Reaction was carried out using the described procedure with 0.050 g (0.2 mmol) of sulfone **2a**. The crude product proved to be unstable on SiO_2. The yield of the crude material was 0.019 g, 31% (keto/enol = 1.7:1). Peaks attributed to the enol form is marked with *; ^{1}H NMR (400 MHz, Chloroform-*d*): δ(ppm): 0.84 (t, *J* = 7.6 Hz, 3H*), 1.00 (t, *J* = 7.6 Hz, 3H), 2.04 (qd, *J* = 7.6, 6.8, 5.2 Hz, 2H), 2.48 (dd, *J* = 7.6, 3.6 Hz, 1H*), 2.50 (s, 3H*), 2.52 (dd, *J* = 7.6, 0.4 Hz, 1H*), 2.57 (s, 3H), 5.16 (d, *J* = 9.2 Hz, 1H), 5.65−5.85 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H*), 7.55−7.69 (m, 2H & 2H*), 7.98−8.04 (m, 1H & 1H*), 8.17−8.20 (m, 1H), 8.24 (ddd, *J* = 8.4, 1.6, 0.8 Hz, 1H*); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{15}NNaO_3S_2$, 332.0391; found, 332.0393.

General Procedure for Dihydropyran 9 Synthesis. A vinyl-sulfone **3** (0.100 g, 0.29 mmol) was dissolved in benzene (1.5 mL, 0.2 M) and vinyl-ether (0.278 mL, 2.9 mmol) was added in one portion. The mixture was stirred for 24 h. Volatilities were evaporated under reduced pressure to yield the crude product.

*2-(((4S)-2-ethoxy-6-methyl-4-phenyl-3,4-dihydro-2H-pyran-5-yl)sulfonyl)benzo[d]thiazole (**9a**).* Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **9a** as a yellow oil (0.129 g, 90%, d.r. = 1 : 1.1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.15−8.08 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.60−7.54 (m, 2H), 7.53−7.44 (m, 2H), 7.08 (bs, 5H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 2H), 5.11 (dd, *J* = 6.8, 2.4 Hz, 1H), 4.95 (t, *J* = 6.0 Hz, 1H), 4.31 (t, *J* = 4.4 Hz, 1H), 4.19 (t, *J* = 7.6 Hz, 1H), 3.99−3.88 (m, 2H), 3.62−3.52 (m, 2H), 2.68 (bs, 3H), 2.64 (bs, 3H), 2.35 (ddd, *J* = 14.0, 7.6, 2.4 Hz, 1H), 2.12−2.04 (m, 3H), 1.19 (t, *J* = 6.0 Hz, 3H), 1.16 (t, *J* = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 170.2, 169.6, 168.1, 167.8, 152.7, 152.5, 142.7, 141.6, 137.2, 136.9, 128.9, 128.6, 128.1, 127.8, 127.4, 127.2, 127.2, 127.0, 126.8, 126.4, 125.3, 125.2, 122.1, 121.9, 113.9, 110.6, 100.2, 98.7, 65.6, 65.2, 39.1, 38.5, 37.7, 35.9, 21.2, 20.7, 15.2, 15.1; MS (ESI) *m/z* (%) 416: $[M + H]^+$ (62); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{22}NO_4S_2$, 416.0985; found, 416.0987.

*2-(((4S)-6-(but-3-en-1-yl)-2-ethoxy-4-phenyl-3,4-dihydro-2H-pyran-5-yl)sulfonyl)benzo[d]thiazole (**9b**).* Reaction was carried out using the described procedure with 0.100 g (0.26 mmol) of vinyl-sulfone **3s**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **9b** as a yellow oil (0.109 g, 70%, d.r. = 1 : 1.1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.11 (t, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.60−7.53 (m, 2H), 7.53−7.45 (m, 2H), 7.09 (bs, 5H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 2H), 5.97 (dddt, *J* = 20.8, 16.8, 10.4, 6.8 Hz, 2H), 5.19−5.07 (m, 3H), 5.06−4.98 (m, 2H), 4.96−4.89 (m, 1H), 4.33 (t, *J* = 4.8 Hz, 1H), 4.22 (t, *J* = 8.0 Hz, 1H), 3.94 (dqd, *J* = 9.6, 7.2, 2.4 Hz, 2H), 3.56 (ddq, *J* = 18.8, 9.6, 7.2 Hz, 2H), 3.33−3.15 (m, 3H), 3.09−3.01 (m, 1H), 2.60−2.48 (m, 4H), 2.35 (ddd, *J* = 14.0, 7.6, 2.4 Hz, 1H), 2.11−2.02 (m, 3H), 1.18 (dt, *J* = 14.0, 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 170.4, 170.1, 170.0, 169.7, 152.6, 152.5, 142.7, 141.6, 137.6, 137.4, 137.3, 137.0, 128.9, 128.5, 128.1, 127.8, 127.5, 127.3, 127.0, 126.8, 126.4, 125.2, 125.1, 122.1, 121.9, 115.6, 115.5, 114.4, 111.1, 100.1, 98.6, 65.5, 65.2, 39.3, 38.6, 37.8, 35.8, 33.3, 32.7, 32.1, 32.1, 29.8, 15.2, 15.1; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}NO_4S_2$, 456.1298; found, 456.1300.

*2-((4-Cyclohexyl-2-ethoxy-6-methyl-3,4-dihydro-2H-pyran-5-yl)-sulfonyl)benzo[d]thiazole (**9c**).* Reaction was carried out using the described procedure with 0.070 g (0.2 mmol) of vinyl-sulfone **3p**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided **9c** as a colorless oil (0.069 g, 72%, d.r. = 1.1:1). ^{1}H NMR (400 MHz,

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Chloroform-*d*): δ 8.13 (dddd, *J* = 8.0, 2.4, 1.6, 0.8 Hz, 2H), 7.96 (dddd, *J* = 8.0, 6.0, 1.6, 0.8 Hz, 2H), 7.61−7.49 (m, 4H), 5.16 (dd, *J* = 9.6, 3.6 Hz, 1H), 4.91 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.95 (ddq, *J* = 14.0, 9.6, 7.2 Hz, 2H), 3.61 (dq, *J* = 9.6, 7.2 Hz, 2H), 2.05−2.97 (m,1H), 2.95−2.88 (m,1H), 2.45 (d, *J* = 1.2 Hz, 3H), 2.39 (d, *J* = 0.8 Hz, 3H), 2.18 (dt, *J* = 14.0, 3.6 Hz, 1H), 2.10−1.88 (m, 2H), 1.88−1.75 (m, 3H), 1.73−1.57 (m, 9H), 1.55−1.46 (m, 1H), 1.41−1.31 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.20−0.81 (m, 8H), 0.77−0.59 (m, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 170.0, 169.8, 168.5, 166.8, 152.7, 152.6, 136.5, 136.5, 127.6, 127.6, 127.4, 125.3, 122.2, 114.9, 112.5, 101.5, 99.7, 65.5, 65.3, 41.1, 39.6, 38.5, 37.5, 31.8, 31.6, 30.2, 30.1, 29.4, 27.1, 27.0, 26.9, 26.8, 26.6, 26.5, 26.0, 21.3, 20.9, 15.2.; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{28}NO_4S_2$, 422.1454; found, 422.1456.

General Procedure for Intramolecular Het. Diels−Alder Reaction. A vinyl-sulfone (0.017 g, 0.04 mmol, 1.0 equiv) was dissolved in DCE (4.0 mL, 0.01 M), and the reaction mixture was stirred under microwave conditions (200 W, 150 °C, 5 min ramp, 30 min hold). The solvent was evaporated under reduced pressure to yield the crude product.

*2-((2-Methyl-5H,10bH-pyrano[3,4-c]chromen-1-yl)sulfonyl)-benzo[d]thiazole (**10**).* Reaction was carried out using the described procedure with 0.017 g (0.04 mmol) of vinyl-sulfone **3k**. Desired product **10** was isolated as a yellow oil (0.016 g, 93%) in sufficient purity. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.28−8.18 (m, 1H), 8.06−7.97 (m, 1H), 7.61 (dtd, *J* = 20.0, 7.6, 1.2 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.20−7.10 (m, 1H), 6.98 (td, *J* = 7.6, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.44−6.32 (m, 1H), 4.88−4.81 (m, 1H), 4.69 (s, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 2.45 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ(ppm): 19.5, 33.7, 67.8, 110.9, 113.7, 117.3, 121.3, 122.4, 125.7, 126.3, 127.7, 128.0, 128.2, 129.6, 134.4, 136.8, 152.8, 153.8, 165.2, 168.4; MS (ESI) *m/z* (%) 398: $[M + H]^+$ (30); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{15}NNaO_4S_2$, 420.0340; found, 420.0336.

General Procedure for Dihydrofurane 12 Synthesis. *Racemic protocol.* A vinyl-sulfone **3a** (0.050 g, 0.15 mmol, 1.0 equiv) and pyridinium salt **11a−c** (0.217 mmol, 1.5 equiv) were dissolved in toluene (1.5 mL, 0.1 M). After 5 min, Et_3N (0.030 mL, 1.5 equiv) was added, and the mixture was stirred for an additional 4 h at r.t. H_2O (10 mL), followed by the addition of EtOAc (10 mL), and the resulting layers were separated. The aqueous phase was extracted with EtOAc (4 × 10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

Asymmetric Protocol. A vinyl-sulfone **3a** (0.030 g, 0.086 mmol, 2.0 equiv) and chiral ammonium salt **13a−c** (0.043 mmol, 1.0 equiv) were dissolved in dry CH_2Cl_2 (1.0 mL, 0.043 M). After 5 min, Cs_2CO_3 (0.028 mg, 2.0 equiv.) was added in one portion, and the mixture was stirred for an additional 20 h. H_2O (10 mL) and EtOAc (10 mL) were added, and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*1-((2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-yl)ethan-1-one (**12a**).* Reaction was carried out using the described racemic procedure with 0.050 g (0.15 mmol) of vinyl-sulfone **3a**. Product **12a** was isolated in good crude purity as a yellow oil (0.062 g, 98%, d.r. = 99:1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.08−8.05 (m, 1H), 7.80−7.77 (m, 1H), 7.58−7.54 (m, 1H), 7.51−7.47 (m, 1H), 7.04−7.01 (m, 2H), 6.97−6.91 (m, 3H), 4.83 (d, *J* = 5.2 Hz, 1H), 4.58 (dd, *J* = 5.2, 1.2 Hz, 1H), 2.63 (d, *J* = 1.2 Hz, 3H), 2.26 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 203.7, 171.2, 168.9, 152.6, 139.5, 137.3, 128.7, 127.9, 127.7, 127.5, 127.2, 125.4, 122.0, 112.1, 93.2, 52.0, 26.1, 14.5; MS (ESI) *m/z* (%) 400: $[M + 1]^+$ (62); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{18}NO_4S_2$, 400.0672; found, 400.0669.

*((2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-yl) (phenyl)methanone (**12b**).* Reaction was carried out using the described asymmetric or racemic procedure with 0.050 g (0.2 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided **12b** as a colorless oil (0.068 g, 98%, d.r. = 97:1). Product **12b** was also prepared in an enantioenriched form purified using flash column chromatography (SiO_2; CH_2Cl_2:heptane = 6:1) and isolated as a light red oil in the following manner: starting from salt **13a**: 0.013 g, 70%, e.r. = 97:3, d.r. = 99:1; starting from salt **13c**: 0.012 g, 68%, e.r. = 1:99, d.r. = 99:1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.06−8.03 (m, 1H), 7.79−7.74 (m, 3H), 7.63−7.53 (m, 2H), 7.50−7.41 (m, 3H), 7.07−7.04 (m, 2H), 7.01−6.95 (m, 3H), 5.77 (d, *J* = 4.8 Hz, 1H), 4.64 (dd, *J* = 4.8, 1.2 Hz, 1H), 2.66 (d, *J* = 1.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 191.9, 172.0, 169.0, 152.6, 139.2, 137.3, 134.4, 133.0, 129.1, 129.0, 128.8, 128.2, 127.9, 127.4, 127.1, 125.4, 122.0, 111.9, 90.3, 52.2, 14.4; MS (ESI) *m/z* (%) 462: $[M + 1]^+$ (54); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}NO_4S_2$, 462.0828; found, 462.0827; α_D^{25} = +161.4 (c 0.5, $CHCl_3$)−first enantiomer (ret. time−29.35 min); α_D^{25} = −148.2 (c 0.5, $CHCl_3$)−second enantiomer (ret. time−32.7 min); HPLC (CHIRAL ART Cellulose-SB, eluent: *n*-hexane: *i*-PrOH = 4:1, 0.5 mL/min, 10 °C, retention times: *t* = 29.3 and *t* = 32.7 min).

*Ethyl (2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylate (**12c**).* Reaction was carried out using the described racemic procedure with 0.050 g (0.2 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided **12c** as a colorless oil (0.054 g, 88%, d.r. = 99:1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.08−8.05 (m, 1H), 7.80−7.77 (m, 1H), 7.58−7.53 (m, 1H), 7.51−7.46 (m, 1H), 7.04−7.01 (m, 2H), 6.97−6.91 (m, 3H), 4.90 (d, *J* = 4.8 Hz, 1H), 4.62 (dd, *J* = 4.8, 1.2 Hz, 1H), 4.30−4.20 (m, 2H), 2.62 (d, *J* = 1.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 171.8, 168.9, 168.7, 152.6, 139.4, 137.3, 128.6, 127.8, 127.8, 127.5, 127.2, 125.4, 122.0, 111.9, 86.7, 62.3, 53.3, 14.4, 14.2; MS (ESI) *m/z* (%) 430: $[M + 1]^+$ (48); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_5S_2$, 430.0777; found, 430.0777.

General Procedure for Triazole 15 Synthesis. To a vinyl-sulfone (0.291 mmol, 1.0 equiv) in MeOH (1.5 mL, 0.2 M) at r.t. was added sodium azide (0.021 g, 0.32 mmol, 1.1 equiv) in one portion, and the mixture was stirred for 20 h. H_2O (10 mL) and EtOAc (10 mL) were added, and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*1-(5-Phenyl-2H-1,2,3-triazol-4-yl)ethan-1-one (**15a**).* Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **15a** as a pale yellow solid (0.032 g, 93%). mp = 108−110 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.82−7.77 (m, 2H), 7.51−7.34 (m, 3H), 2.73 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 193.6, 141.9, 130.2, 129.2, 128.7, 127.5, 28.8; MS (ESI) *m/z* (%) 186: $[M - H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{10}O$, 188.0818; found, 188.0819.

*1-(5-Cyclohexyl-2H-1,2,3-triazol-4-yl)ethan-1-one (**15b**).* Reaction was carried out using the described procedure with 0.050 g (0.14 mmol) of vinyl-sulfone **3p**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **15b** as a white solid (0.027 g, 98%). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 3.42 (tt, *J* = 11.5, 3.5 Hz, 1H), 2.71 (s, 3H), 2.04−1.95 (m, 2H), 1.84 (dq, *J* = 13.5, 3.5 Hz, 2H), 1.78 (dqd, *J* = 12.5, 3.0, 1.5 Hz, 1H), 1.57−1.39 (m, 4H), 1.29 (qt, *J* = 13.0, 4.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*): δ 25.9, 26.3, 28.3, 31.9, 34.2, 141.9, 149.7, 194.4; MS (ESI) *m/z* (%) 192: $[M - H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{16}N_3O$, 194.1288; found, 194.1289.

*Isopropyl 5-Phenyl-2H-1,2,3-triazole-4-carboxylate (**15c**).* Reaction was carried out using the described procedure with 0.100 g (0.26 mmol) of vinyl-sulfone **5c**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **15c** as a yellow oil (0.034 g, 59%). ^{1}H

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NMR (400 MHz, Chloroform-*d*): δ 7.81−7.75 (m, 2H), 7.42−7.38 (m, 3H), 5.23 (h, *J* = 6.4 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 160.8, 134.4, 129.7, 129.4, 128.3, 114.0, 69.8, 21.8; MS (ESI) *m/z* (%) 230: $[M - H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}N_3O_2$, 232.1081; found, 232.1082.

*phenyl(5-(4-(trifluoromethyl)phenyl)-2H-1,2,3-triazol-4-yl)-methanone (**15d**).* Reaction was carried out using the described procedure with 0.100 g (0.21 mmol) of vinyl-sulfone **3ac**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **15d** as a yellow oil (0.051 g, 79%). ^1H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, *J* = 6.4 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 187.7, 156.0, 141.6, 136.9, 133.5, 130.1, 129.3, 128.4, 128.1, 125.4, 125.3 (q, *J* = 3.6 Hz), 122.7; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ −61.15 (s, 3F); MS (ESI) *m/z* (%) 316: $[M - H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{11}F_3N_3O$, 318.0849; found, 318.0850.

*1-(5-(2-(Allyloxy)phenyl)-2H-1,2,3-triazol-4-yl)ethan-1-one (**15e**).* Reaction was carried out using the described procedure with 0.050 g (0.125 mmol) of vinyl-sulfone **3j**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **15e** as a colorless oil (0.028 g, 93%). ^1H NMR (400 MHz, Chloroform-*d*): δ 13.00 (bs, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.6, 1.6 Hz, 1H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 7.04−6.95 (m, 1H), 6.01 (ddt, *J* = 17.2, 10.8, 5.6 Hz, 1H), 5.42−5.27 (m, 2H), 4.62 (dt, *J* = 5.4, 1.4 Hz, 2H), 2.76 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 29.0, 29.8, 69.9, 112.6, 115.0, 119.1, 121.5, 132.0, 132.1, 132.3, 142.5, 155.6, 193.6; MS (ESI) *m/z* (%) 200: $[M - allyl]^-$ (100), 242 $[M\text{-}H]^-$ (45); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{14}N_3O_2$ 244.1081; found, 244.1079.

General Procedure for Michael Type Addition and Desulfonation. A vinyl-sulfone (0.69 mmol, 1.0 equiv) was dissolved in MeOH (4.0 mL, 0.2 M), and the solution was stirred for 16 h. After consumption of the starting material, the solvent was evaporated under reduced pressure to yield the crude product, which was used in the next step without further purification. The resulting methoxy sulfone adduct was dissolved in THF (7.0 mL, 0.1 M), and AcOH (4.0 mL, 0.2 M). Zn (0.226 g, 5.0 equiv) was added in one portion, and the resulting mixture was stirred overnight. The reaction was quenched upon addition of EtOAc (20 mL), and the resulting suspension was filtered through Celite, and filtrate cake was washed with EtOAc (5 × 20 mL). The combined filtrates were washed with sat. $NaHCO_3$ (2 × 20 mL), brine (2 × 20 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*4-Methoxy-4-phenylbutan-2-one (**16a**).* Reaction was carried out using the described procedure with 0.238 g (0.69 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:9) and concentration of the relevant fractions provided **16a** as a colorless liquid (0.051 g, 92% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*): δ 7.36−7.26 (m, 5H), 4.62 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.18 (s, 3H), 2.95 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.57 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 206.4, 140.9, 128.5, 127.9, 126.4, 79.5, 56.6, 51.9, 31.0; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_2$, 201.0886; found, 201.0887.

*(3S,4S)-4-((tert-Butyldimethylsilyl)oxy)-3-methoxy-1-phenylpentan-1-one (**16b**).* Reaction was carried out using the described procedure with 0.336 g (0.69 mmol) of vinyl-sulfone **3ag**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:20) and concentration of the relevant fractions provided **16b** as a colorless liquid (0.102 g, 43% over 2 steps, d.r. = 7:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.01−7.95 (m, 2H), 7.60−7.53 (m, 1H), 7.49−7.43 (m, 2H), 4.08 (qd, *J* = 6.4, 4.4 Hz, 1H), 3.88 (ddd, *J* = 8.0, 4.4, 3.6 Hz, 1H), 3.37 (s, 3H), 3.19−3.06 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.07 (d, *J* = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 199.4, 137.6, 133.1, 128.7, 128.4, 80.8, 68.1, 58.6, 38.5, 26.0, 18.2, 17.9, −4.5, −4.7; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{30}NaO_3Si$, 345.1862; found, 345.1855; α_D^{22} = −7.1 (c 0.65, $CHCl_3$).

General Procedure for Michael Type Allylation or Reduction and Desulfonation. A vinyl-sulfone (0.290 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3.0 mL, 0.1 M), and the solution was cooled down to −78 °C (acetone/dry ice). After 30 min, **Nu** (0.290 mmol, 3.0 equiv) was added, and the mixture was stirred for another 30 min, followed by the addition of $TiCl_4$ (0.870 mL, 3.0 equiv, 1.0 M solution in CH_2Cl_2). The mixture was stirred for 6 h. $NaHCO_3$ (10 mL) was added, and the suspension warmed to r.t. The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure. The crude product was used in the next step without further purification. Crude sulfone was dissolved in THF (3.0 mL, 0.1 M) and AcOH (1.5 mL, 0.2 M), and Zn (0.019 g, 5.0 equiv) was added in one portion. The resulting heterogenic mixture was stirred overnight before it was quenched with the addition of EtOAc (20 mL). The resulting slurry was filtered through Celite, and the filtrate cake was washed with EtOAc (5 × 15 mL). The filtrates were washed with sat. $NaHCO_3$ (2 × 15 mL), brine (2 × 15 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to yield the crude product.

*4-Phenylbutan-2-one (**16c**).* Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:10) and concentration of the relevant fractions provided **16c** as a colorless liquid (0.037 g, 87% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*): δ 7.28−7.26 (m, 2H), 7.22−7.16 (m, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.76−2.72 (m, 2H), (t, *J* = 7.6 Hz, 2H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 207.8, 140.9, 128.4, 128.2, 126.0, 45.1, 30.1, 29.6; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{13}O$, 149.0961; found, 149.0961.

*4-Phenylhept-6-en-2-one (**16d**).* Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:8) and concentration of the relevant fractions provided **16d** as a colorless oil (0.040 g, 74% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*): δ 7.32−7.26 (m, 2H), 7.22−7.16 (m, 3H), 5.72−5.58 (m, 1H), 5.03−4.94 (m, 2H), 3.26 (p, *J* = 7.2 Hz, 1H), 2.82−2.68 (m, 2H), 2.39−2.33 (m, 2H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 207.8, 144.2, 136.3, 128.6, 127.6, 126.6, 116.9, 49.7, 41.0, 40.9, 30.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{17}O$, 189.1274; found, 189.1274.

*3-Phenylhex-5-enenitrile (**16e**).* Reaction was carried out using the described procedure with 0.050 g (0.153 mmol) of vinyl-sulfone **6a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided **16e** as a colorless oil (0.019 g, 72% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*): δ 7.39−7.32 (m, 2H), 7.30−7.27 (m, 1H), 7.25−7.21 (m, 2H), 5.66 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.12 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.07 (ddt, *J* = 10.0, 2.0, 1.2 Hz, 1H), 3.04 (p, *J* = 7.2 Hz, 1H), 2.70−2.57 (m, 2H), 2.55 (tt, *J* = 7.2, 1.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 141.4, 134.7, 128.9, 127.6, 127.3, 118.5, 118.2, 41.8, 39.2, 24.0; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{12}H_{13}N$, 171.1048; found, 171.1049.

General Procedure for Lewis Acid-Mediated Rearrangement. A vinyl-sulfone (0.050 g, 0.145 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.5 mL, 0.1 M) at r.t., and $TiCl_4$ (0.580 mL, 4.0 equiv, 1.0 M solution in CH_2Cl_2) was added. The mixture was stirred for 1 h at r.t. prior to addition of CH_2Cl_2 (10 mL) and sat. NH_4Cl (5 mL). The resulting suspension was filtered through Celite, and the filter cake was washed with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to yield the crude product.

*3-(3-Oxo-1-phenylbutyl)benzo[d]thiazol-2(3H)-one (**18**).* Reaction was carried out using the described procedure with 0.050 g (0.145 mmol) of vinyl-sulfone **3a**. Purification using flash chromatog-

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raphy (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided **18** as a pale-yellow oil (0.043 g, 68%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.41−7.35 (m, 3H), 7.35−7.27 (m, 1H), 7.16−7.10 (m, 2H), 6.01 (dd, J = 8.0, 6.0 Hz, 1H), 3.96 (dd, J = 18.0, 8.0 Hz, 1H), 3.44 (dd, J = 18.0, 6.0 Hz, 1H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 205.4, 138.2, 137.2, 129.1, 128.3, 127.0, 126.4, 122.9, 122.7, 111.9, 54.5, 45.8, 30.3.; MS (ESI) m/z (%) 297: $[M + 1]^+$ (100); HRMS (ESI) m/z: $[M]^+$ calcd for $C_{17}H_{15}NO_2S$, 297.0823; found, 297.0825.

General Procedure for 1,4 Reduction of Vinyl-Sulfones. *Procedure A.* A vinyl-sulfone (0.582 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (6.0 mL, 0.1 M), and the solution was cooled down to −78 °C (acetone/dry ice). After 15 min, nBu$_3$SnH (0.138 mL, 1.1 equiv) was added, and the mixture was stirred for additional 30 min. After consumption of the starting material, CH_2Cl_2 (10 mL) was added, and the reaction mixture was washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the volatiles were removed under reduced pressure. The crude material was dissolved in CH_3CN (25 mL) and washed with hexane (2 × 20 mL) to remove any remaining organotin compounds. The resulting acetonitrile solution was concentrated under reduced pressure to provide the crude product.

Procedure B. A vinyl-sulfone (0.582 mmol, 1.0 equiv) was dissolved in THF (0.1 M), and the solution was cooled down to −78 °C (acetone/dry ice). After 15 min, DIBAL (0.640 mL, 1.1 equiv, 1 M solution in hexane) was added dropwise, and the mixture was stirred at −78 °C for 10 min and at r.t. for another 1 h (consumption of the SM monitored by TLC). After consumption of the starting material, the reaction mixture was cooled down to −78 °C, and saturated aq. solution of Rochelle salt (5 mL) was added. The resulting mixture was allowed to warm to r.t. and stirred until the solution became clear (cca 6 h). The whole mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and solvents were removed under reduced pressure to provide the crude product.

*3-(Benzo[d]thiazol-2-ylsulfonyl)-4-phenylbutan-2-one (**17c**).* Reaction was carried out using the described procedure with 0.200 g (0.583 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **17c** as a yellow solid: Procedure A (0.181 g, 91%); Procedure B (0.170 g, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.32−8.23 (m, 1H), 8.09−7.95 (m, 1H), 7.76−7.55 (m, 2H), 7.25−7.16 (m, 3H), 7.14−7.08 (m, 2H), 4.91 (dd, J = 9.2, 5.6 Hz, 1H), 3.55−3.36 (m, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 32.8, 32.9, 75.6, 122.5, 125.9, 127.5, 128.0, 128.5, 129.0, 129.1, 135.4, 137.3, 152.7, 164.1, 198.2; MS (ESI) m/z (%) 346: $[M + 1]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3S_2$, 346.0566; found, 346.0563.

*2-(Benzo[d]thiazol-2-ylsulfonyl)-1,3-diphenylpropan-1-one (**17f**).* Reaction was carried out using the described procedure with 0.100 g (0.246 mmol) of vinyl-sulfone **3aa**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **17f** as a colorless oil: Procedure A: (0.090 g, 90%); Procedure B: (0.081 g, 81%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23−8.18 (m, 1H), 8.01−7.92 (m, 1H), 7.79−7.69 (m, 2H), 7.68−7.53 (m, 2H), 7.49−7.38 (m, 1H), 7.35−7.24 (m, 2H), 7.20−7.04 (m, 5H), 5.82 (dd, J = 10.8, 3.6 Hz, 1H), 3.82−3.62 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 33.7, 70.6, 122.4, 125.8, 127.3, 127.8, 128.4, 128.7, 128.9, 129.2, 134.1, 135.6, 137.0, 137.4, 152.6, 164.3, 191.0; MS (ESI) m/z (%) 408: $[M + 1]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{18}NO_3S_2$, 408.0723; found, 408.0725.

General Procedure for 1,2 Reduction of Vinyl Sulfones. A vinyl-sulfone (0.290 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL, 0.01 M), and the resulting solution was cooled to −78 °C (acetone/dry ice). After 15 min, DIBAL-H (0.320 mL, 1.1 equiv, 1 M solution in hexane) was added dropwise, and the mixture was stirred at −78 °C for an additional 4 h. After consumption of the starting material (checked via TLC), a saturated aqueous solution of Rochelle salt (5 mL) was added, and the reaction mixture was allowed to warm to r.t. The resulting mixture was stirred until the solution became clear (cca 6 h). The whole mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-phenylbut-3-en-2-ol (**19a**).* Reaction was carried out using the described procedure with 0.100 g (0.291 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **19a** as a pale-yellow oil (0.080 g, 80%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.14 (m, 1H), 8.07 (s, 1H), 8.02−7.97 (m, 1H), 7.67−7.52 (m, 4H), 7.45 (dd, J = 5.2, 2.0 Hz, 3H), 5.23 (q, J = 6.8 Hz, 1H), 1.63 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 22.2, 64.8, 122.5, 125.4, 127.7, 128.1, 129.0, 130.6, 130.6, 132.7, 136.7, 142.1, 145.3, 152.3, 169.2; MS (ESI) m/z (%) 346: $[M + 1]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3S_2$, 346.0566; found, 346.0565.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-cyclohexylbut-3-en-2-ol (**19c**).* Reaction was carried out using the described procedure with 0.050 g (0.143 mmol) of vinyl-sulfone **3p**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **19c** as a colorless oil (0.034 g, 68%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18−8.12 (m, 1H), 8.02−7.93 (m, 1H), 7.65−7.51 (m, 2H), 6.98 (d, J = 10.8 Hz, 1H), 5.04 (dt, J = 13.2, 6.8 Hz, 1H), 2.94 (d, J = 6.0 Hz, 1H), 2.76 (tdt, J = 10.8, 6.8, 3.6 Hz, 1H), 1.84−1.64 (m, 5H), 1.54 (d, J = 6.8 Hz, 3H), 1.34−1.17 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 23.6, 25.2, 25.2, 25.7, 31.8, 31.9, 38.3, 65.1, 122.4, 125.4, 127.6, 128.0, 136.7, 140.7, 152.3, 154.2, 169.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{22}NO_3S_2$, 352.1036; found, 352.1034.

General Procedure for Radical Addition. To a vinyl-sulfone (0.050 g, 0.153 mmol, 1.0 equiv) in benzene (1.5 mL, 0.1 M) was added ethyl iodide (0.019 mL, 1.5 equiv), (Me$_3$Si)$_3$SiH (0.071 μL, 1.5 equiv), and AIBN (0.005 g, 0.2 equiv), and the reaction mixture was heated (oil bath) to reflux. After consumption of starting vinyl-sulfone (8 h), the volatilities were evaporated under reduced pressure to yield the crude product.

*2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-phenylpentanenitrile (**20**).* Reaction was carried out using the described procedure with 0.050 g (0.153 mmol) of vinyl-sulfone **6a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **20** as a colorless oil (0.033 g, 61%, d.r. = 1.2:1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25−8.18 (m,2H), 8.01 (ddd, J = 9.6, 7.6, 2.0 Hz, 2H), 7.72−7.57 (m, 4H), 7.45−7.35 (m, 2H), 7.39−7.23 (m, 8H), 4.96 (d, J = 5.6 Hz, 1H), 4.88 (d, J = 3.6 Hz, 1H), 3.75−3.62 (m, 2H), 2.36 (dqd, J = 13.6, 7.2, 3.6 Hz, 1H), 2.21−1.95 (m, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 163.4, 163.2, 152.4, 138.2, 137.5, 136.7, 129.3, 129.3, 128.9, 128.8, 128.7, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 125.9, 125.8, 122.5, 122.5, 112.3, 112.1, 62.1, 61.2, 44.6, 44.1, 27.8, 25.1, 11.8, 11.7; MS (ESI) m/z (%) 357: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{16}N_2NaO_2S_2$, 379.0551; found, 379.0546.

*(E)-4-Phenylbut-3-en-2-one (**4**).* Reaction was carried out using the described procedure with 0.100 g (0.291 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **4** as a yellowish solid (0.036 g, 85%, >E/Z= 95:1). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.56−7.54 (m, 2H), 7.52 (d, J = 16.5 Hz, 1H), 7.42−7.38 (m, 3H), 6.72 (d, J = 16.5 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) 198.5, 143.5, 134.6, 130.7, 129.1, 128.4, 127.3, 27.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}O$, 147.0804; found, 147.0806.

*(E)-Isopropyl Cinnamate (**21**).* Reaction was carried out using the described procedure with 0.100 g (0.258 mmol) of vinyl-sulfone **5c**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **21** as a viscose oil (0.046 g, 82%, >E/Z= 95 : 1). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.67 (d, J = 16.0 Hz, 1H), 7.52 (dd, J = 7.0, 3.0 Hz, 2H), 7.41−7.35 (m, 3H), 6.42 (d, J = 16.0 Hz, 1H), 5.14 (hept, J = 6.0 Hz, 1H), 1.32 (d, J = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz,

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Chloroform-*d*): δ 166.7, 144.4, 134.6, 130.3, 129.0, 128.1, 118.9, 67.9, 22.1; MS (ESI) *m/z* (%) 191: $[M + 1]^+$ (10), 149 (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{15}O_2$, 191.1067; found, 191.1068.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00571.

Relevant optimization tables, discussion of the relevant stereochemical outcomes of reactions, discussion of the stereochemistry of obtained compounds, and a copy of ^1H and $^{13}C\{^1H\}$ NMR spectra (PDF)

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Author Contributions

O.K., F.Z., and D.J.-Y.D.B. performed most of the experiments and analyzed the experimental data. L.V.B. and O.K. carried out the Smiles-like rearrangement. L.R., O.K., and M.W. performed and optimized [4 + 1]-cycloaddition reaction. O.K. and D.J.-Y.D.B. partially designed the experimental plans. J.P. initiated the project, led the project team, designed experiments, analyzed results, and wrote the paper with input from all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Review

Lignans and Neolignans: Plant secondary metabolites as a reservoir of biologically active substances

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Terminaloside P

ABSTRACT

Lignans and neolignans are plant secondary metabolites derived from the oxidative coupling of phenylpropanoids. Biological activity of these phenolic compounds ranges from antioxidant, antitumor (terminaloside P, IC_{50} = 10 nM), anti-inflammatory, anti-neurodegenerative (schibitubin B, IC_{50} = 3.2 nM) and antiviral (patentiflorin A, IC_{50} = 14–23 nM) to antimicrobial. In addition, it was observed that several members of this group, namely enterolactone and its biochemical precursors also known as phytoestrogens, possess important protective properties. Most of these lignans and neolignans are presented in reasonable amounts in one's diet and thus the protection they provide against the colon and breast cancer, to name a few, is even more important to note. Similarly, neuroprotective properties were observed (schisanwilsonin G, IC_{50} = 3.2 nM) These structural motives also serve as an important starting point in the development of anticancer drugs. Presumably the most famous members of this family, etoposide and teniposide, synthetic derivatives of podophyllotoxin, are used in the clinical treatment of lymphocytic leukemia, certain brain tumors, and lung tumors already for nearly 20 years. This review describes 413 lignans and neolignans which have been isolated between 2016 and mid-2018 being reported in more than 300 peer-reviewed articles. It covers their source, structure elucidation, and bioactivity. Within the review, the structure-based overview of compounds as well as the bioactivity-based overview of compounds are described.

1. Introduction

Since the beginning of the 21st century one can notice a dramatic increase in the interest of pharmaceutical companies and medicinal chemists in the field of natural products. [1,2] Indeed the substantial progress of bioactivity driven high-throughput screening of biological plant extracts [3,4] in combination with the development of new more selective and mild extraction techniques [5] led to the identification of many novel natural products with interesting biological properties. Biological activity-driven structure determination of identified natural products then virtually opened the box revealing many novel structural scaffolds [6–8]. Scaffolds that are potential starting points (lead compounds) [9] in the search for new more active and/or more selective inhibitors/activators/etc. of various biological processes.

The aim of this review is to bring to a reader a short but comprehensive account of the recent achievements in the field of phenylpropanoid dimer-based natural products, lignans and neolignanes. These two groups of natural products represent a vast and diverse groups of plant secondary metabolites that are widely distributed in the kingdom of higher plants. In general, phenylpropanoid dimers possess a plethora of interesting biological properties making them an important source of novel drug candidates and/or leading structural scaffolds exploitable in the field of medicinal chemistry. As mentioned previously, novel milder extraction techniques hand-in-hand with more sensitive detection and identification of isolated compounds has increased considerably the amount of newly identified natural products. As a consequence, more than a thousand of new lignans and neolignans were isolated and identified since the beginning of millennium. Such an extensive increase in the newly isolated and identified structures of course triggered an interest in the scientific community and since then several excellent reviewing articles were published. However, most of these focused either on the structure [10,11]

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(identification or synthesis), or on the source of the compounds [12] (plant species and the part of the plant where the compounds were detected). Unfortunately, the biological activity of these compounds was noted only as secondary information not directly illustrating the associated structures and scaffolds if the biological activity was searched as the primary information. Additionally, the last review covering the selected topic includes the literature till the end of 2015, leaving additional 413 newly isolated and identified lignans and neolignans aside [10–12].

Thus in this review a comprehensive overview of newly isolated lignans and neolignans covering years 2016 till mid 2018 is presented. Natural products can be searched in terms of both, the structure and biological activity. Additionally, biological activity of already known bioactive lignans and neolignans isolated along with the new ones within the given period of time is also covered. Finally, we have also included known pathways of action of lignans and neolignans relevant to medicinal chemistry and clinical use of such compounds. To facilitate the above-mentioned search of structures and biological activity, the review is divided into two parts. In the first, newly isolated and identified natural products are gathered in the table along with brief additional information (source of the compound, brief biological activity data and the literature reference). The table is cross-linked with the second part focusing on the natural products in context of their biological activity. And the biological activity-data section is cross-linked back with the first section. We believe that such an arrangement will help to both, structure-based and biological activity-based search, respectively, within the newly identified phenylpropanoid-based dimers.

1.1. Biosynthesis

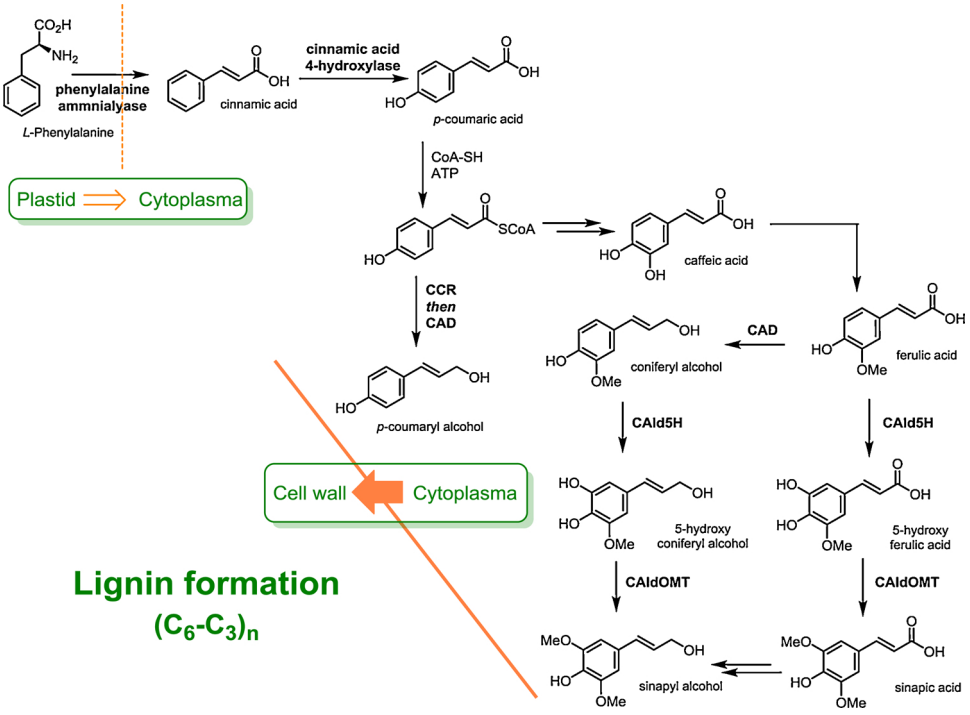
Lignans and neolignans are plant secondary metabolites originating from the shikimic acid biosynthetic pathway. Since the main goal of this review is not to detail the biosynthesis of titled classes of compounds, only a brief description of their origin will be highlighted. If interested, the detailed description of the up-to-date knowledge of the biosynthetic pathways may be found in these literature references. [13–16] Both classes of compounds are the dimers of the two phenylpropanoid subunits that originates from the metabolism of *L*-phenylalanine [15,17] (Scheme 1). Its deamination by phenylalanine ammonia-lyse to cinnamic acid and further hydroxylation via P450 enzymes leads to *p*-coumaric acid and/or its polyhydroxylated analogues such as caffeic acid. These subsequently can undergo *O*-methyltransferase-mediated methylation of introduced phenolic functionalities to yield the cinnamic acid derivatives – the basic phenylpropanoid monomeric subunits. This class of cinnamic acid derived carboxylic acids that comprises compounds such as ferulic acid or sinapic acid to name a few can be further reduced via the corresponding coenzyme A ester to an intermediate aldehyde (class of compounds that includes e.g. coniferyl aldehyde), which can be further reduced in the presence of NADPH to the corresponding alcohol (e.g. coniferyl alcohol).

These three groups of compounds, *p*-coumaric acid derivatives and the corresponding aldehydes and alcohols generated from those, further acts as starting monomers in the biosynthesis of lignans and neolignans (Scheme 2). [10,13–17] The dimerization of monomers (principally homodimerization) proceeds via a radical mechanism and is mediated by laccases and peroxidases, respectively. Interestingly, such a simple transformation, oxidase enzyme-mediated radical coupling, followed with post dimerization transformations (successive methylations and/or hydroxylation) literally opens the doors to the world of a large family of phenolic secondary metabolites derived from phenylpropanoid subunits – lignans and neolignans (see section 1.3). Indeed, it is expected that this class of compounds contains between 20 to 30 000 of members where only about 6 000 of which are known up to date. [10,12]

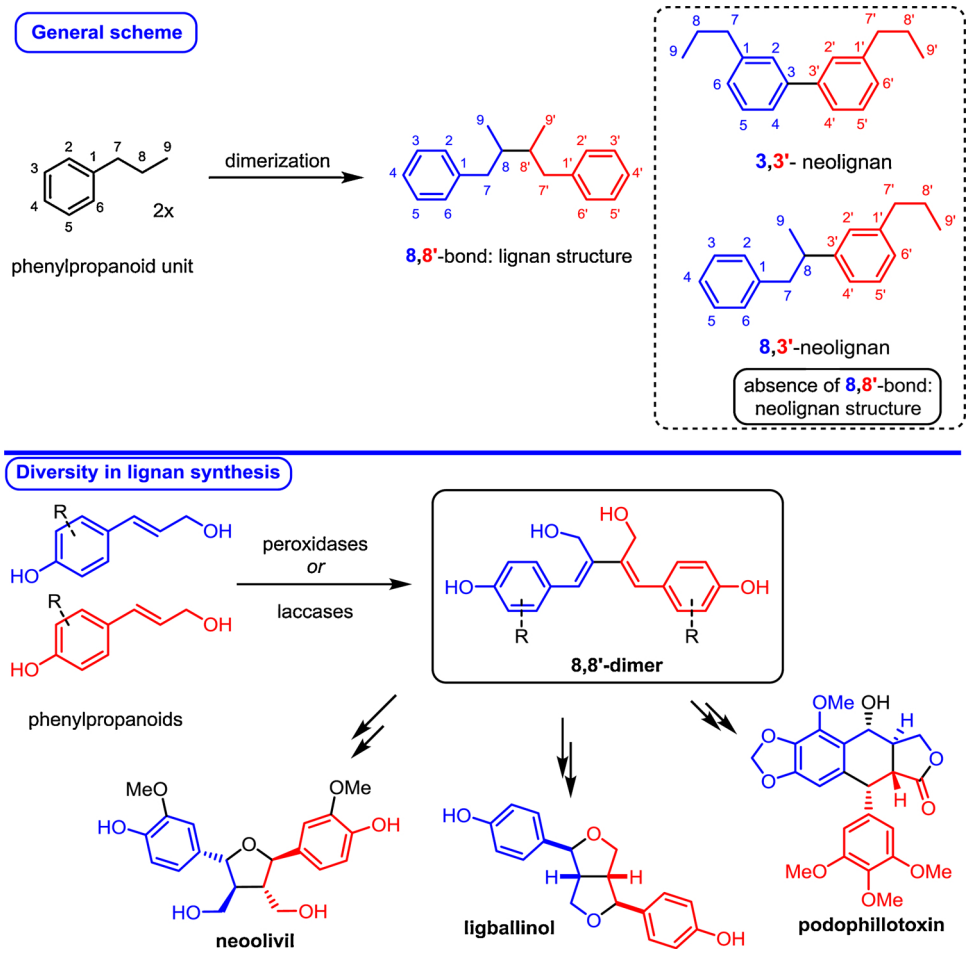
It should be also noted that many of lignans and neolignans serve as a building blocks in the biosynthesis of lignins. [18]

1.2. Biological properties of lignans and neolignans – known mode of action

In the form of plant extracts and remedies lignans and neolignans have been used since the onset of humanity. With advances in structure



Scheme 1. Biosynthesis of phenylpropanoid monomers from *L*-phenylalanine – general simplified overview. [13–17] (CCR = cinnamoyl CoA reductase; CAD = cinnamyl alcohol dehydrogenase; coniferaldehyde-5-hydroxylase = CAld5H; 5-hydroxyconiferylaldehyde *O*-methyltransferase = CAldOMT).



Scheme 2. Phenylpropanoid dimerization – lignan and neolignan synthesis: the diversity-driven biosynthesis of natural polyphenols. [12,19,20].

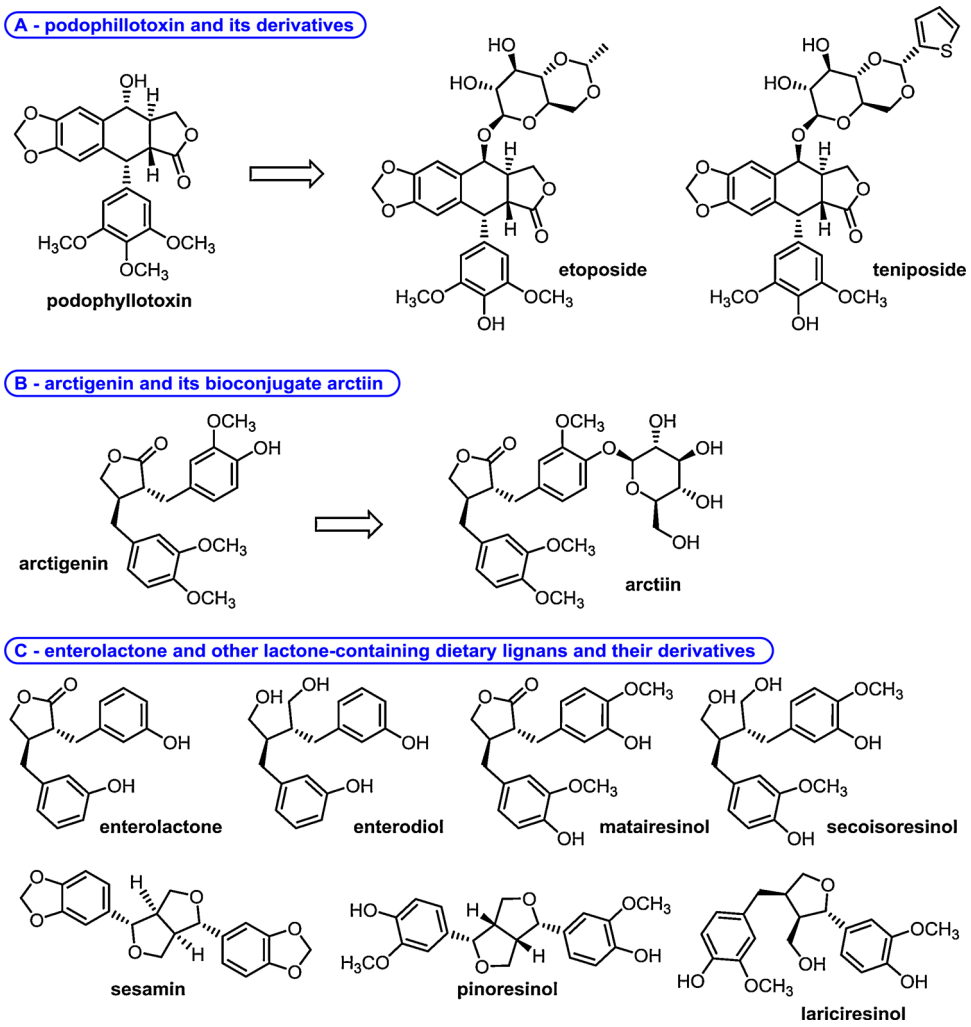
and biological activity determination, these classes of compounds are attributed with a range of biological activities including anticancer, insecticidal, estrogenic, antiviral, antihypersensitive and antioxidant properties. However, the real mode of action of such molecules is known only for a few members of this group.

Presumably the most well-known member of the lignan family is podophyllotoxin (Scheme 3). This non-alkaloid toxin is a major component of extracts from the roots and rhizomes of *Podophyllum peltatum* [21] and is used in the form of a medical cream to treat genital warts and molluscum. However, podophyllotoxin is also known for its severe secondary effects [22,23] that in the case of the cream are generally limited to the tissue surrounding its application (burning, itches, small sores, and skin peeling). Long term application can cause CNS depression and if ingested enteritis [24]. Despite these facts, antiviral action of podophyllotoxin has attracted a substantial interest of the scientific community and its role of action was systematically studied. It was found that on a molecular level podophyllotoxin prevents cell division through binding to tubulin and thus destabilizing microtubules [25,26]. Such results obviously further increased the scientific interest in this molecule, and initiated the search of podophyllotoxin derivatives with lower cytotoxicity. Shortly after which it was found out that conjugates of the C4 epimer of podophyllotoxin with D-glucose derivatives were the best match in terms of biological activity and low cytotoxicity, and two podophyllotoxin derivatives, etoposide and teniposide, were approved for clinical use by the FDA under the names ETOPOPHOS® and TENIPOSIDE® (Scheme 3). Etoposide is used as a form of chemotherapy for cancers such as Kaposi's sarcoma, Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, nonlymphocytic leukemia, and glioblastoma multiforme, and quite often is administrated in combination with other anticancer drugs.[2] Similarly teniposide is used to treat a number of cancer types but in general is administered to juvenile patients. Again in this case, it is often administered in combination with various antineoplastic drugs.[3]

From the structure view point, both podophyllotoxin derivatives approved for the clinical use differ in one stereogenic center (C4 carbon) and the incorporation of a D-glucose derivative. As was later on demonstrated, this induced structural change influenced the mechanism of action of both compounds. Etoposide and teniposide interact with the enzyme Topoisomerase II to prevent re-ligation of DNA strands. In the case of etoposide, a ternary complex with DNA and enzyme is formed, [27] while teniposide stabilizes the Topoisomerase II-DNA intermediate in a DNA-protein cross-linking process. [28] Both of these compounds were found to intercalate to DNA or bind strongly with DNA.

Another member of the lignan family with interesting anticancer properties is (–)-actigenin (Scheme 3). This lignan is a main component of the extracts of *Arctium lappa* and is used in Japanese Kampo medicine for its antioxidant, anti-inflammatory, antiproliferative, and antiviral activity. [29,30] From the mode of action view point, arctigenin can block the activation of Akt (protein Kinase B) that is induced by glucose starvation in pancreatic cancer PANC-1 cells. [31,32] Interestingly, a glucose conjugate of (–)-arctigenin, arctiin, has similar and in some points even better properties than (–)-arctigenin. It was shown that this glucose containing conjugate is a potent antiviral compound against

[2] https://www.drugs.com/mtm/etopophos.html07.01.2019
[3] https://www.drugs.com/monograph/teniposide.html07.01.2019



Scheme 3. Lignans and their derivatives with known modes of action used in clinical treatment or as preventive dietary additives.

influenza A virus and possesses also anti-inflammatory effects by decreasing the production of nitric oxide and pro-inflammatory cytokines. [30,33] More interestingly, if arctiin is ingested, it in the presence of human intestinal bacteria is metabolized into various bioactive metabolites including arctigenin or enterolactone [30,34].

The transformation of lignans by human intestinal bacteria is a significant process. It has been shown than many lactone-containing dietary plant lignans such as secoisolariciresinol, matairesinol, lariciresinol, pinoresinol, and sesamin, widely present in cereals, vegetables, fruits, and berries, are metabolized in the digestive tracts of humans to enterolactone [35–37] (the richest known dietary sources of enterolactone are flaxseed and sesame seeds [38–40]). Enterolactone is readily absorbed by human serum and its level can be readily determined with standard analytical methods. Furthermore, clinical studies showed that the levels of enterolactone in cancer-free patients are significantly higher than those measured for patients suffering with breast cancer. This observation along with other evidences strongly suggest that stable enterolactone levels can be associated with a reduced risk of hormone-dependent cancers, osteoporosis, and various coronary events. [41,42] Similarly, a strong inverse correlation between enterolactone-serum level and isoprostane-serum level suggests a protective effect of enterolactone against oxidative stress and damage. [43]

In addition, a group of compounds that comprises enterolactone, its diol (enterodiol) and their bioconjugates with glucose are known as mammalian phytoestrogens. [44,45] These compounds are capable of significant inhibition of human colon tumor cells and the E-2 induced proliferation of MCF-7 breast cancer cells [46]. In this case it is suggested that the protective effect of lignans is caused by their ability to compete with ligands of the type II estrogen receptors, to induce sex hormone binding globulin abilities, to inhibit placental aromatase, and to act as antioxidants [47–49].

1.3. Lignans and neolignans: definition and elemental skeletal types

Lignans and neolignans are dimeric structures formed by a β,β'-linkage between two phenylpropanoid units (Scheme 2). Such two phenylpropanoid units might differ in the degree of oxidation of their side-chains (C7-C9) and the substitution of the aromatic ring (C1-C6). For nomenclature purposes, phenylpropanoid monomers are numbered C1-C6 (aromatic ring) and C7-C9 (propyl chain) where C1 and C7 atoms are connected via a chemical bond. In the second phenylpropanoid monomer the numbering is the same but the numbers are primed.

Compounds that contains two phenylpropanoid monomers linked by a bond between carbons C8 and C8' are referred as "lignans". If such bond is missing and is replaced by any other type of connection including the oxygen etheric linking, the compounds are referred to as "neolignans". Sesquilignans and sesquineolignans are compounds that contains three phenylpropanoid subunits linked together by a carbon-carbon or carbon-oxygen bonds. "Norlignans" are referred to as all natural compounds that co-occur with lignans or neolignans and possess C15, C16 or C17 core structure. It is generally believed that such

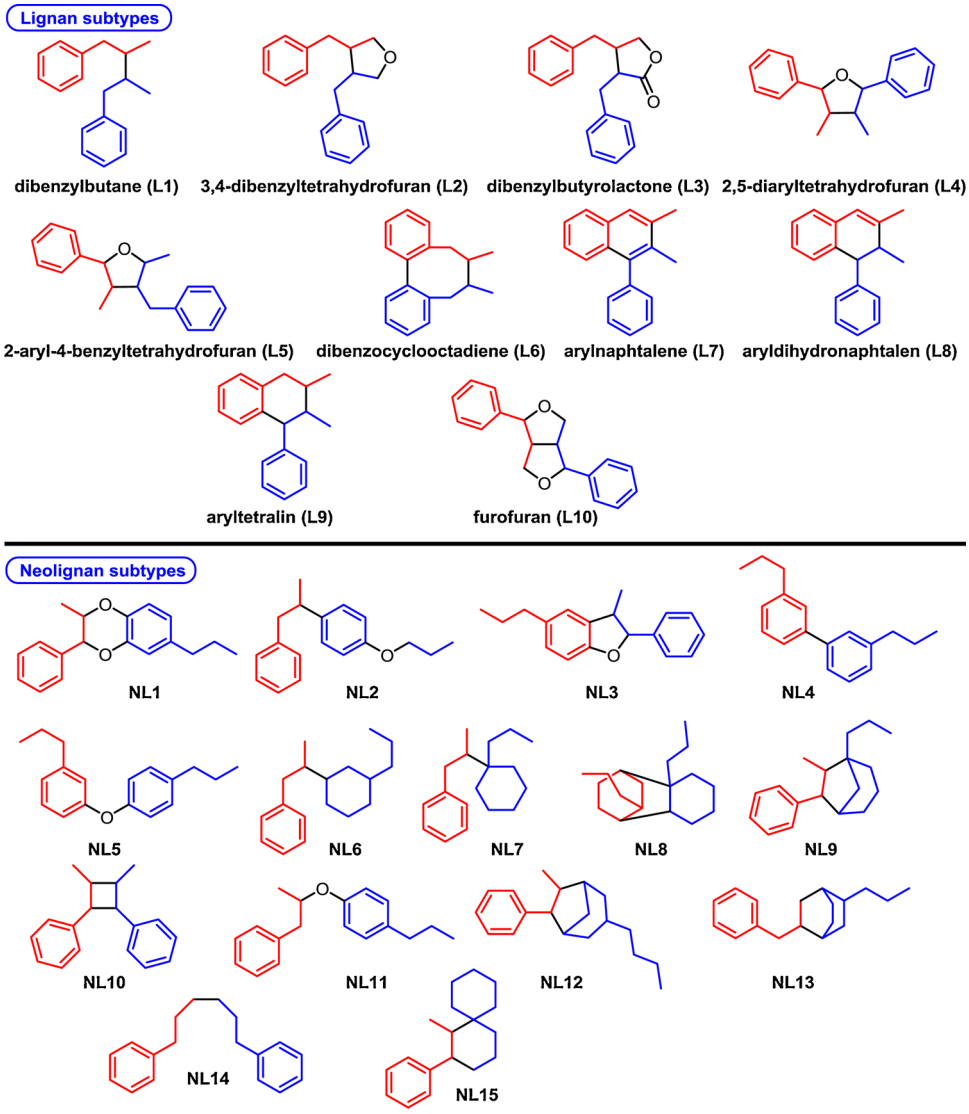


Fig. 1. Lignan [13,14] and neolignan [11,15] structural subtypes.

structures are derived from phenylpropanoid dimers by the loss of one or two carbons, probably through decarboxylation.

As was mentioned previously, phenylpropanoid dimers are classified as lignans or neolignans based on the presence or absence of the 8,8'-bond between phenylpropanoid monomers. Such classification is however very broad since they do not reflect any post/dimerization structural changes of the substrates. As a consequence lignans and neolignans were further divided into several structural subtypes that are depicted in Fig. 1 [11,13–15]. These subtypes simplifies further orientation within the lignan and neolignan structural motifs and will be extensively used further in this review to identify described structures.

2. Lignans and neolignans: structures, source and reported bioactivity

All-important information about newly isolated lignans, neolignans, sesquilignans and sesquineolignans are presented in form of a table where the structure of given natural product is showed along with the source and relevant biological activity. The Table can be found in Supplemental Material part of this review. The Table is subdivided into focused thematic sections, where lignans and neolignans of one subtype are presented (for subtypes see Fig. 1). The Entry number of the table refers to the lignan or neolignan subtype followed with the number of the entry. Thus Entry L1-1 corresponds to the first entry of lignan belonging to subtype L1. In the case of sesquilignans and sesquineolignans the compound number is SQL and SQNL, respectively. Neolignans that do not fit to any criteria are listed in the subsection Miscellaneous (NLM). Detailed discussion of the biological data can be found in the following Section 3 of this review, where the details about the searched compound can be found by looking for their Entry number (Figs. 2–15).

The following acronyms are used within this section: Ang – angeloyl, Api – apiose, Ara – arabinose, Glc = β-D-Glc, Rha = α-L-Rha, Suc – sucrose, Xyl – xylose.

3. Lignans and neolignans: biological activity

In this section the biological activities are organized and the compounds mentioned (in bold) have the activity values in IC_{50} or cell viability improved % in brackets. Other values and overall biological effects will also be discussed. The structures for newly isolated compounds can be found by looking for their Entry number (i.e NL1-1 in the supporting information) or literature reference. It should be noted that this section covers also all new bioactivity data about previously isolated lignans and neolignans that were reported within the cover period of time (Tables 1–7).

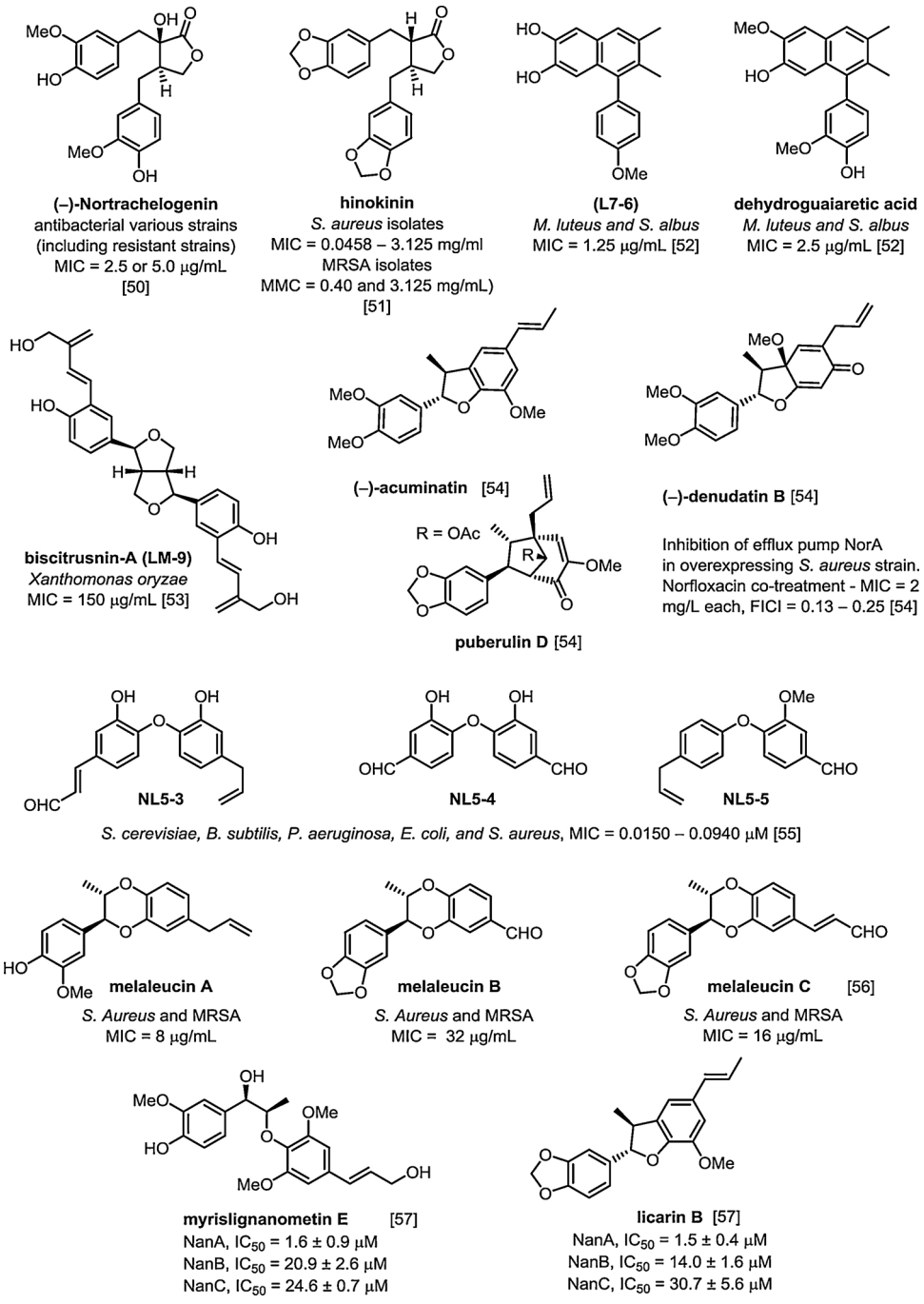


Fig. 2. Active antibacterial lignans and neolignans.

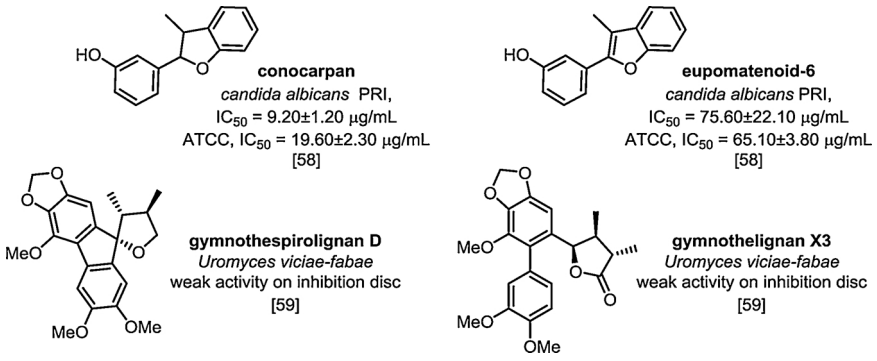


Fig. 3. Active antifungal lignans and neolignans.

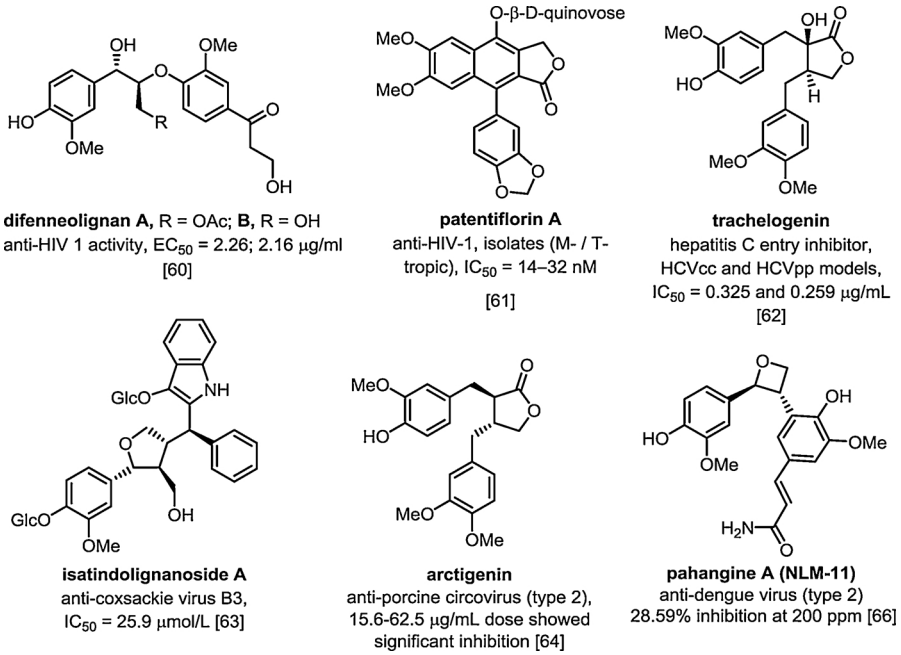


Fig. 4. Active antiviral lignans and neolignans.

3.1. Antibiotic and antimicrobial

Throughout history the eternal war between prokaryotes and eukaryotes has played out on an almost equal footing with persistent diseases and episodic plagues wreaking havoc on the human population. Until recently with the advent of antibiotics and antimicrobials, deaths from such events were common place. However resistant strains are becoming ever-more prevalent and so the search for new active compounds is on-going. One such source is lignans and neolignans, some of which have shown potent activity and even activity against resistant microbes.

3.1.1. Bacterial

(–)-Nortrachelogenin, a dibenzyl lignan presented potent and diverse antibacterial activity for a range of bacterial strains including antibiotic-resistant ones (MIC = 2.5 or 5.0 μg/mL). In a mechanistic study using *E. Coli* 0157 the compound was found to act through damage to the bacterial membrane. [50] Hinokinin displayed antibacterial effects against different isolates of *S. aureus* (MIC = 0.0458–3.125 mg/ml) and MRSA (from blood isolate and post-operative secretion, MMC = 0.40 and 3.125 mg/mL, respectively). [51] Significant antibiotic activity was seen in two aryl naphthalene lignans, dehydroguaiaretic acid (*M. luteus* and *S. albus* = 2.5 μg/mL) and a novel lignan (L7-6) (*E. coli* and *S. albus* = 1.25 μg/mL). [52] The novel prenylated furofuran biscitrusnin-A (LM-9) showed antibiotic activity against *Xanthomonas oryzae* (MIC = 150 μg/ml). [53] Three neolignans, (–)-acuminatin, (–)-denudatin B and puberulin D from *Piper betle* showed inhibition of the multi-drug antibiotic efflux pump NorA. Upon co-treatment with the antibiotic norfloxacin on a strain of *S. aureus* that overexpresses the efflux pump, the compounds synergistically gave MIC values of 2 mg/L each and fractional inhibition concentration indices (FICI) of 0.13, 0.25 and 0.25 respectively. [54] Four new and two known biphenyl neolignans (NL5-3, NL5-4 and NL5-5) from *Streblus asper* showed good activity against strains of *S. cerevisiae*, *B. subtilis*, *P. aeruginosa*, *E. coli*, and *S. aureus*, with MIC values ranging from 0.0150 to 0.0940 μM. [55] Three neolignans, melaleucins A–C (NL1-1, NL1-2 and NL1-3) were active *in vitro* against *S. Aureus* and *MRSA*, with the compounds showing no difference in activity between the methicillin-resistant and non-resistant strains (melaleucins A, B & C, MIC = 8, 32, 16 μg/mL respectively). [56] Six neolignans (myrislignan, myrislignanometin E, maceneolignan H, licarin A, licarin B, 5′-methoxylicarin B), and one furan lignan (verrucosin) from *myristica fragrans* were found to possess activity against *Streptococcus pneumoniae*, a major causal agent of meningitis and pneumonia. The compounds were found to act through inhibition of sialidase, and thus impeding bacterial adherence and colonization. The three sialidase isoforms (nanA–C) were evaluated and in general the compounds showed the highest activity for nanA (IC_{50} = 1.5 ± 0.4–294.5 ± 28.2 μM), then nanB

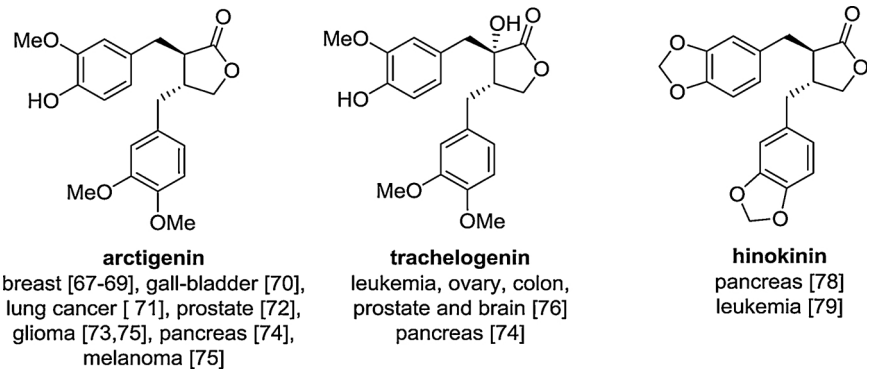


Fig. 5. Selected examples of active anticancer dibenzyl lignans.

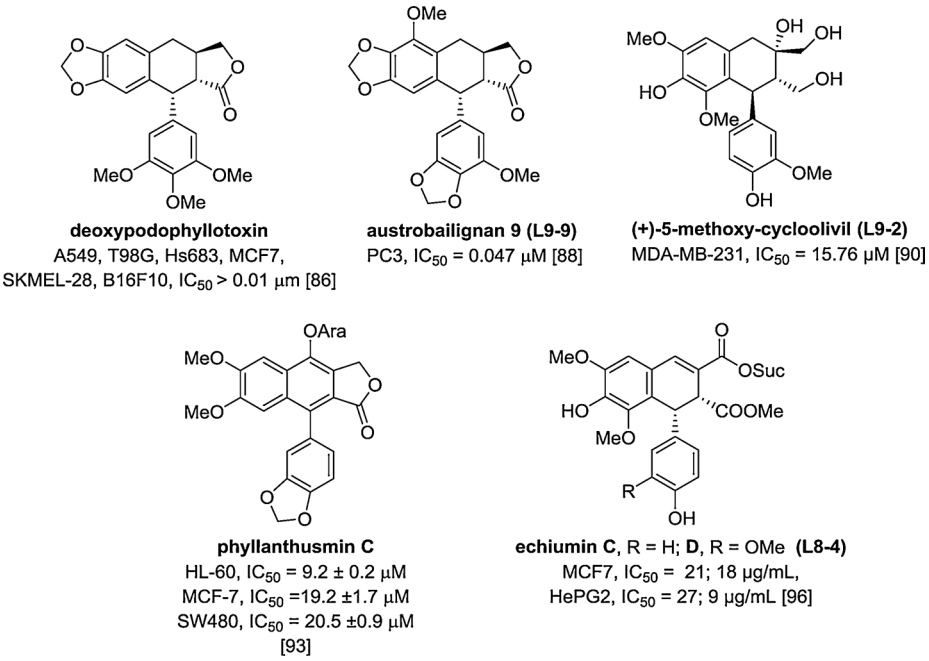


Fig. 6. Selected examples of active anticancer aryltetralins, arylnaphthalenes, and aryldihydronaphthalene lignans.

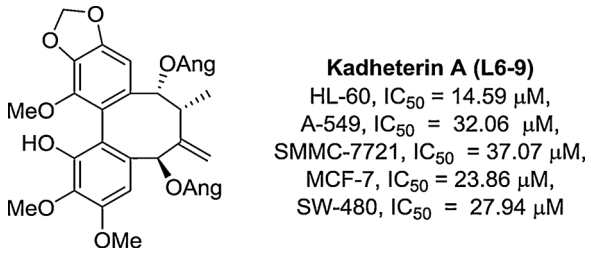


Fig. 7. Kadheterin A, an active anticancer biphenylcyclooctadiene lignan.

(IC_{50} = 14.0 ± 1.6–331.2 ± 22.3 μM) and lastly nanC (IC_{50} = 24.6 ± 0.7–317.3 ± 7.4 μM). Myrislignanometin E and licarin B showed the most promise being the most active neolignans. [57]

3.1.2. Fungal

Three benzofuran lignans (including eupomatenoid-6 and conocarpan) from *piper rivinoides* displayed antifungal activity against *candida albicans* strains (PRI, IC_{50} = 111.1 ± 38.80, 75.60 ± 22.10, 9.20 ± 1.20 μg/mL, ATCC 10231 = 113.40 ± 4.80, 65.10 ± 3.80, 19.60 ± 2.30 μg/mL), however they were also found to be cytotoxic to mammalian cells. [58] Rare biphenyl tetrafuranone and biphenyl spiro lignans from *Gymnotheca involucrate* were found to possess weak antifungal activity against *Uromyces viciae-fabae* (gymnothespirolignans D, gymnothelignan X4) and very weak activity against *Zymoseptoria tritici* (gymnothespirolignans E, gymnothelignan X5) (entries NL4–6 to NL4-9). [59]

3.1.3. Viral

Several lignans have been found to possess anti-viral activity. For instance, two 8-O-4′ neolignans, difenneolignan A and B (NL2-5) isolated from *Illicium difengpi* showed promising anti-HIV-1 activities in an inhibition assay of cytopathic effects with good therapeutic windows (EC_{50} = 2.26 and 2.16 mg/mL with therapeutic indexes of 95.5 and 114.4 respectively). [60] Patentiflorin A, an aryl naphthalene lignan is another potent anti-HIV compound showing activity against four different HIV-1 isolates (either M- or T- tropic), in human PBMCs (IC_{50} = 14–32 nM), being more active than the current drug azidothymidine (77–95 nM). [61] The dibenzyl lignan trachelogenin was found to be a novel inhibitor of hepatitis C, blocking the viruses entry into hepatocytes by preventing its interaction with host CD81 protein (In HCV cc and HCV pp models, IC_{50} = 0.325 and 0.259 mg/ml, respectively). [62] The unique indole lignan isatindolignanoside A (LM-5) showed activity against Coxsackie virus B3 (IC_{50} = 25.9 μmol/L, selectivity index > 3.9) [63]. Arctigenin was active against porcine

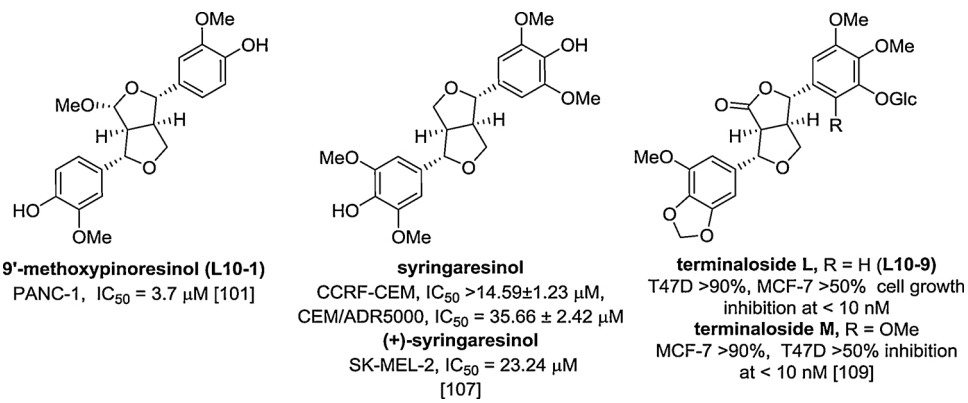


Fig. 8. Selected examples of active anticancer furofuran lignans.

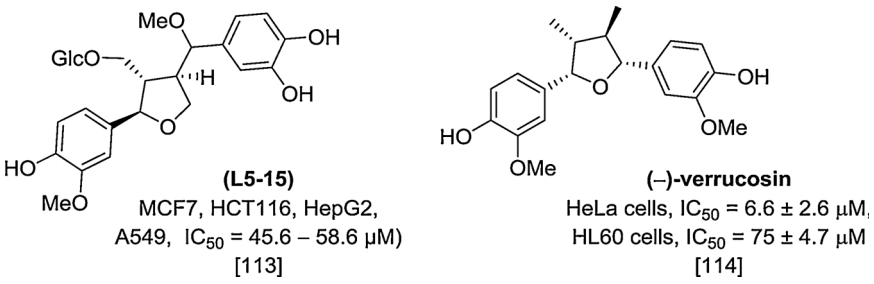


Fig. 9. Active anticancer furan lignans.

circovirus type 2 where dosages of 15.6–62.5 μg/mL significantly inhibited its proliferation in PK-15 cells. [64] Jiang et al carried out transcriptome profiling of influenza A infected lung epithelial cells (A549) which were treated with lariciresinol-4-β-D-glucopyranoside. The study revealed that the compound acted on the immune system, signal transduction, cell cycle and metabolism. [65] Pahangine A (NLM-11), a novel oxetane neolignan showed antiviral activity against Dengue virus (type 2) inhibiting a crucial protease, NS2B/NS3 (28.59% inhibition at 200 ppm). [66]

3.2. Anti-cancer

Many lignans and neolignans have shown significant activity against a wide range of cancers *in vitro* and/or *in vivo*. In this section the compounds, their base structure-type and their activity are discussed. When applicable their IC_{50} values, relevant activities and mode of action are mentioned along with their isolation source. If they are novel this is noted, and newly discovered activities or modes of action of previously known compounds are also discussed.

Arctigenin, a dibenzylbutyrolactone lignan is a powerful anti-cancer compound expressing activity on a wide range of cancers. One study showed arctigenin to be effective in treating triple-negative breast cancers (TNBC), an aggressive form of breast cancer with poor prognosis. The authors found it decreased proliferation and induced apoptosis and is thought to work through inhibiting the transcription factor STAT3. [67] Breast cancer cells lines MDA-MB-231, MDA-MB-468, MDA-MB-453, and MDA-MB-435S showed IC_{50} values ranging from 0.285 to 3.756 μM with the TNBC cell lines (MDA-MB-231 and MDA-MB-468 = 0.79 ± 0.06, 0.29 ± 0.04 μM) being most sensitive, while the breast cancer cell lines MCF-7 & 10A and SK-BR3 were less effected (40.81 ± 3.43, 24.10 ± 4.07, 20.67 ± 2.71 μM, respectively). A separate study showed arctigenin to reduce the expression of active β-catenin and cyclin D1, and to induce apoptosis in MCF-7 (estrogen receptor (ER) positive) but not MDA-MB-231 cell lines (ER-negative). Indicating arctigenin activity is ER-dependent. [68] Conversely, another study demonstrated arctigenin's anti-metastic effects on breast cancer cell lines by inhibiting MMP-9 and uPA via the Akt, NF-κB and MAPK signaling pathways and found this was independent from its estrogenic properties. [69] In gall-bladder cancer cells arctigenin was found to induce senescence through modulating of the epidermal growth factor receptor pathway. [70] In lung cancer cells (NSCLC) arctigenin suppressed TGF-β-induced changes of metastatic morphology, cell invasion and migration. [71] At low doses (< 2 μM) arctigenin showed anti-proliferation properties *in vitro* towards androgen-sensitive human prostate cancer cells (LNCaP and LAPC-4 = 30–50% inhibition) and pre-malignant cells (WPE1-NA22 = 75% inhibition), whereas *in vivo* (mouse xenografts of LAPC-4 cells) showed inhibition up to 70%. [72] In human glioma cell lines (U87MG and T98 G) arctigenin at ≤40 μM, substantially decreased growth, induced G0/G1 cell cycle arrest and initiated apoptosis. [73] (+)-Arctigenin was active against human pancreatic cancer cells (PANC-1) and showed preferential toxicity (PC_{50} = 32.9 μM) in nutrient deprived media thus showing promise as an anti-austerity agent. [74] The enantiomer, (–)-arctigenin isolated from *Centaurea diluta* showed activity against the glioma (Hs683 = 28 μM) and melanoma (B16-F1033 = 33 μM) cancer lines. [75]

(–)-Trachelogenin, another dibenzylbutyrolactone lignan displayed significant anti-tumor effects on a range of cancer cell lines: leukemia (HL.60, IC_{50} = 32.4 μM), ovary (OVCAR-8, IC_{50} = 3.5 μM), colon (HCT-116, HCT-8 IC_{50} = 1.9, 5.2 μM respectively), prostate (PC-3, IC_{50} = 15.0 μM) and brain (SF-295, IC_{50} = 0.8 μM) with no toxicity to non-tumor cell lines. It was found to be cytotoxic against all tumor cells and persistently induce autophagic cell death, causing cytoplasmic vacuolization, and autophagosome formation through the mediation of Beclin-1 and increased activation of L3. [76] In a separate study trachelogenin showed preferential toxicity in nutrient deprived media against human pancreatic cancer cells (PANC-1, PC_{50} = 13.3 μM) showing promise as an anti-austerity agent. [74] Similarly, dibenzylbutyrolactone (+)-hinokinin showed moderate anti-austerity activity on pancreatic cancer cell lines PANC-1, MIA PaCa2, CAPAN-1, PSN-1, and KLM-1 with the PC_{50} values 64.1, 21.3, 50.1, 60.1, 92.5 respectively. [77] The enantiomer, (−)-hinokinin was found to induce G2/M arrest and cause apoptosis in MCF-7 cancer cells (37.9% survival at 8 μM, 10 day dosage). When co-administered with doxorubicin the effects synergized and were also effective against SKBR-3 cancer cells as well. [78] Analysis of the isolates from cinnamon *(Cinnamomum parthenoxylon)* revealed hinokinin and its lower oxidation state congeners, cubenin and dehydroxycubenin were active against leukemia cell lines. The level of oxidation was found to influence the activity with hinokinin being most active followed by cubenin then dehydroxycubenin

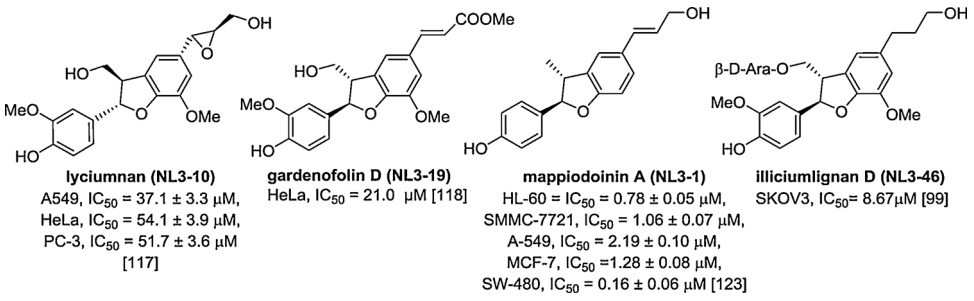


Fig. 10. Selected examples of active anticancer benzofuran lignans.

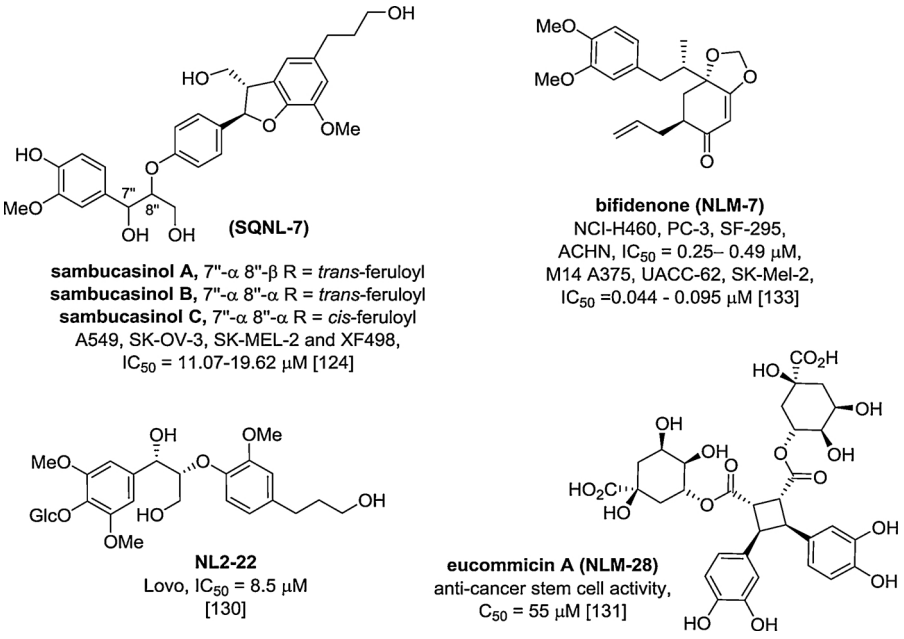


Fig. 11. Selected examples of active anticancer sesquineolignans, nor- and miscellaneous lignans/neolignans.

(HL-60, IC_{50} = 10.4 ± 0.3, 15.7 ± 1.1, 40.2 ± 2.4 μM; U937 = IC_{50} = 31.3 ± 0.5, 38.2 ± 0.7, 51.1 ± 0.9 μM respectively). [79] Another study examined the safety profile of (–)-cubenin and it was found to only be toxic at concentrations of 280 μM (HT29 cell line). [80] Cytotoxic assays (using A549, HepG2, U251, Bcap-37, and MCF-7 cell lines) on the compounds isolated from *Bupleurum chinense* revealed 6 active dibenzylbutyrolactone lignans, a furofuran lignan and a new 8-O-4′ neolignan. Notably the neolignan (saikolignanoside A) (NL2-9) and dibenzylbutyrolactone (guamarolin) showed activity against A549 (IC_{50} = 20.1 μM for both) and HepG2 (IC_{50} = 32.0 μM for both), while two more active dibenzylbutyrolactone lignans (including (+)-nortrachelogenin) showed activity against all tested cell lines with IC_{50} values ranging from 17.05 to 51.6 μM and were more active than the control 5-Fluorouracil. [81] Enterolactone treatment (10–100 μM) on lung cancer cells was found to suppresses their migration and invasion by altering FAK-Src signaling, [82] and in a separate study, to induce cell cycle arrest by downregulating cyclins and related kinases [83]. In high concentrations (100 μM), enterolactone was also found to decrease the viability of MCF7 cells through inhibiting the expression and activity of telomerases. [84] A study on the dibenzyl lactone diferuloyl secoisolariciresinol revealed it to elicit its antiproliferative effects on colon cancer cells by inducing lysosomal-dependent degradation of FoxM1 protein leading to the suppression of β-catenin nuclear translocation. [85]

Aryl tetralin and dibenzyl lignans from *Linum*, *Callitris* and *Juniperus* species were tested against a range of human and mouse cancer cell lines (A549, U373, T98 G, Hs683, MCF7, SKMEL-28, B16F10). Deoxypodophyllotoxin, podophyllotoxin, 6-methoxypodophyllotoxin were found to be very active (< 0.01 – 0.03 μM) and yatein moderately active (21.5–39.6 μM). [86] In another study aryl tetralin butyrolactones burseranin and picropolygamain (L9-13) were selectively active against HeLa cervical cancer cell line (21.72 ± 1.03, 9.31 ± 1.01 μM), and not cytotoxic against human non-cancer cell line ARPE-19. [87] 7 aryl tetralin lignans (including 2 new, austrobailignans 8 & 9 (L9-8 & L9-9)), a dibenzyl, and a furan lignan from *Austrobaileya scandens* showed promising activity against human prostate cancer PC3 cells with IC_{50} values ranging from 0.016 to 5.1 μM. [88] Deoxypodophyllotoxin *in vivo* activity on human breast cancer was evaluated using mice xenografted with MDA-MB-231 tumor cells. Tumor volumes were down to 9.63% the size of control mice when intravenous dosages of 20 mg/kg were given, being more effective than current treatments etoposide and docetaxel. [89] In a separate study (+)-5-methoxyl-cycloolivil (L9-2) displayed moderate *in vitro* cytotoxicity against MDA-MB-231 cells (IC_{50} = 15.76 μM). [90] Three new podophyllotoxin derivatives (L8-6) were isolated from *Bursera fagaroides* and evaluated against several cell lines: human nasopharyngeal (KB), colon (HF-6), breast (MCF-7) and prostate (PC-3). They showed activity for all where they were least active for MCF-7 cells (IC_{50} > 7.2–9.27 μM) and most potent for PC-3 cells (IC_{50} = 2.42×10^{-5} – 0.061 μM). [91] *In vivo* studies of developing zebrafish embryos revealed their antimitotic molecular activity is by disturbing tubulin. [91] In a second paper from the authors, five podophyllotoxin derivatives were evaluated for proliferative activity against lung (A549) and ovarian (A2780) human carcinoma cell lines, three were very active on both cancer cell lines

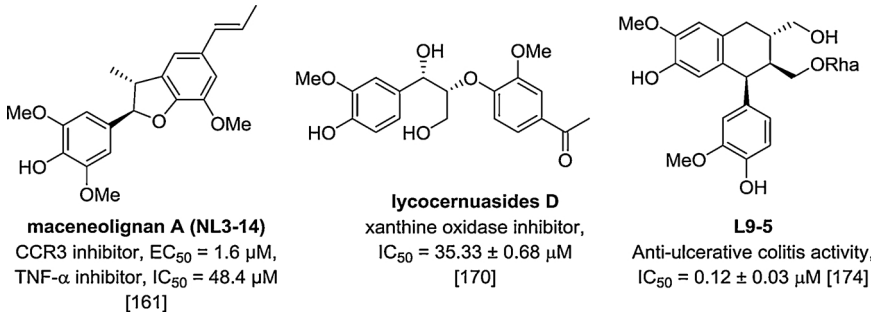


Fig. 12. Selected examples of active anti-allergenic lignans/neolignans.

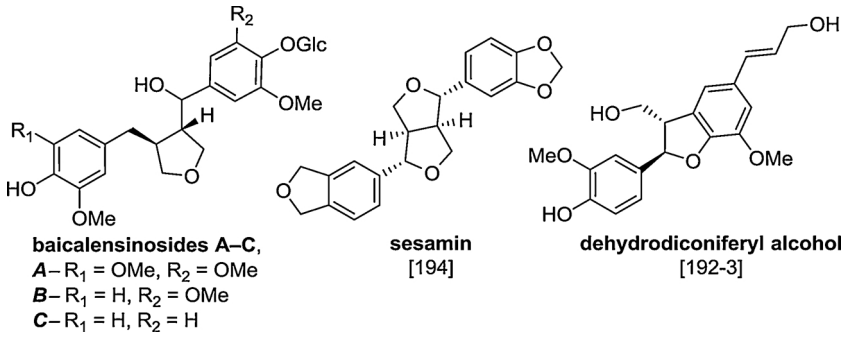


Fig. 13. Selected examples of active anti-allergenic lignans/neolignans.

(15–84 nM) and the remaining two comparatively less active [92]. Phyllanthusmin C, an aryl naphthalene lignan glycoside from *Phyllanthus poilanei* displayed *in vitro* activity against human cancer cell lines HL-60, MCF-7 and SW480 with IC_{50} values of 9.2 ± 0.2, 19.2 ± 1.7 and 20.5 ± 0.9, respectively. [93] In another study hypophyllanthin showed anticancer properties against human lung (A549, IC_{50} = 228 μM), hepatic (SMMC-7721, IC_{50} = 181 μM) and gastric cancer cell lines (MGC-803, IC_{50} = 184 μM) while phyllanthin was active against hepatic cancer cells (SMMC-7721 IC_{50} = 276 μM). [94] Aryl dihydronaphalene lignans from *Vitex negundo* were evaluated against three human cancers cell lines and the following IC_{50} activities were found: vitexnegheteroin F (L8-3) (HepG2 = 55.48 μM) [95], vitedoin A (L7-9) (HepG2 = 45.11, HCT116 = 10.18 μM) [95] and another aryl dihydronaphthalene lignan (L8-3) (HepG2 = 8.24, HCT116 = 57.52, A2780 = 77.85 μM) [95]. Structurally related esters echiumin C and D (L8-4) showed cytotoxic activity against MCF7 (IC_{50} = 21, 18 μg/ml, respectively) and HepG2 cells (IC_{50} = 26, 9 μg/ml, respectively). [96] Marginatoxin, an aryltetralin lignan isolated from *Bupleurum marginatum* displayed cyctotoxic activity against human hepatoma BEL-7402 (IC_{50} of 15.20 mg/ml). The study showed it to act both *in vitro* and *in vivo* through activation of Fas/FasL-mediated apoptotic pathway. [97] Pycnanthulignene A & B were investigated for activity against normal and multi-factorial drug-resistant cancer cells. They showed favorable selective cytotoxicity for resistant leukemia cell lines (CEM/ADR5000 (multidrug-resistant), IC_{50} = 7.52 ± 0.33, 17.04 μM respectively) compared to (CCRF-CEM (normal), IC_{50} = 5.84 ± 0.28, > 118.34 μM respectively). [98] Cytotoxic assays on the compounds isolated from *Illicium wardii* revealed an aryl tetralin active against ovarian cancer cell line SKOV3 (IC_{50} = 11.47 μM). [99]

Kadheterin A (L6-9), a biphenylcyclooctadiene lignan showed moderate activity against several cell lines (IC_{50}: HL-60 = 14.59 μM, A-549 = 32.06 μM, SMMC-7721 = 37.07 μM, MCF7 = 23.86 μM, SW-480 = 27.94 μM). [100] 9 biphenylcyclooctadienes and a dibenzyl lignan were isolated from *Schisandra chinensis* and found to be active against human ovarian cancer (A2780, IC_{50} = 16.88 ± 0.40–47.14 ± 3.21 μM) and endometrial cancer cells (Ishikawa, IC_{50} = 23.44 ± 4.98–137.38 ± 14.98 μM). [101]

Four furofuran lignans isolated from *Calotropis gigantean* showed cyctotoxicity against PANC-1 with IC_{50} values ranging from 3.7 to 63.4 μM with the newly isolated compound 9′-methoxypinoresinol (L10-1) showing the highest activity. [102] Medioresinol showed good cytotoxic effects against the cell lines HepG2, BxPC3, HL-60 and U87 with IC_{50} values ranging from 4.26 to 8.33 μM. [103] Sesamin, a previously known anticancer compound was found to elicit its effects by inducing endoplasmic reticulum stress-mediated apoptosis through the IREIα/JNK pathway, and by activating autophagy/autophagic death in HeLa cells. [104] Syringaresinol was investigated for activity against normal and multi-factorial drug-resistant cancer cells and although active for both, it was more active for the non-resistant strain (CCRF-CEM, IC_{50} > 14.59 ± 1.23 μM vs CEM/ADR5000 = 35.66 ± 2.42 μM). [98] (+)-Pinoresinol (12.5–100 μM) was found to induce apoptosis in hematoma cell line HepG2 through acting both on the mitochondrial and the Fas death receptor pathways, while also disrupting the cytoskeleton inhibiting invasion. [105] In another study (+)-8-hydroxy pinoresinol was cytotoxic against Hela cancer cells (IC_{50} = 41.0 μM). [106] 5 furofuran lignans, a furan and a new sequi-lignan (euonymolin A) were isolated from *Euonymus alatus* and were active against human skin melanoma cell line SK-MEL-2: (+)-syringaresinol (23.24 μM) [107], euonymolin A (SQL-4) (31.47 μM) [107], (+)-pinoresinol (37.96 μM) [107], (+)-medioresinol (42.80 μM) [107], (+)-lariciresinol 4′-*O*-β-D-glucopyranoside (42.85 μM) [107], (+)-de-*O*-methylepimagnolin A (43.89 μM) [107] and (–)-de-*O*-methylmagnolin (48.14 μM). [107] 13 furofuran lignans (terminalosides A–K, 2-epiterminaloside D, and 6-epiterminaloside K) were isolated from *Terminalia citrina* and their estrogenic/antiestrogenic activity evaluated against estrogen-responsive human breast cancer cell lines MCF-7 and T47D. Terminalosides B & G inhibited both cell lines, and a 90% decrease of estradiol-enhanced proliferation at concentrations < 10 μM was observed. Terminaloside E (L10-15) displayed activity against T47D while terminalosides C (L10-14), F (L10-16), I (L10-19)and 6-epiterminaloside K (L10-22) showed anti-estrogenic activity for MCF-7 cells. [108] The authors then isolated five furofuranone lignans (terminalosides L–P, (L10-9 to 11)) from the same plant and carried out the same evaluation. All compounds showed > 50% inhibition on both cell lines, and at the low

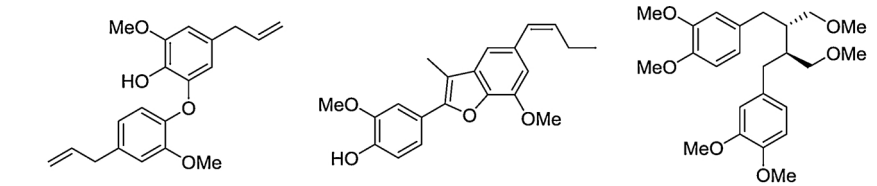


Fig. 14. Examples of antiparasitic lignans/neolignans.

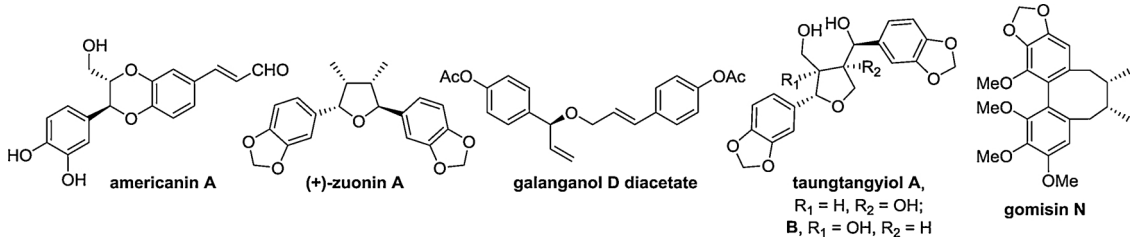


Fig. 15. Examples of melanogenesis inhibitors.

concentration of 10 nM, terminaloside P (L10-11) and inhibited proliferation up to 90% in T47D, and terminaloside M (L10-9) for MCF-7 cell lines. [109] In a separate study epimethoxypiperitol showed moderate inhibitory activity against MCF-7 (IC_{50} = 10.0 μM) and hypopharyngeal cancer (FaDu, IC_{50} = 20 μM). [110] Another furofuran, 2-methoxy-9β-hydroxydiasesamin from *Clinacanthus nutans* showed modest activity against human tumor cell lines Hela, MCF-7 and A549 (IC_{50} = 68.55, 60.00, 59.17 μM respectively). [111] Justicidin A (1 μM) was found to possess chemopreventive and chemotherapeutic roles in cancer cell lines (HT-29 and Hep3B) via suppression of NF-κB. [112]

A new furan glycoside lignan (L5-15) from *Calotropis procera* was evaluated against the cancer cell lines MCF-7, HCT-116, HepG-2 and A-549 and found to have moderate activity (IC_{50} = 45.6–58.6 μM). [113] Yamauchi and coworkers showed (−)-verrucosin was active against HeLa cells (6.6 ± 2.6 μM) and less so for HL60 cells (75 ± 4.7 μM). They also revealed the structure activity relationship between enantiomers and diasteriomers of many dietary furan lignans and synthetic analogues for these cell lines. [114]

The two benzofuran neoligans egonol and homoegonol were tested against tumor cell lines (B16F10, MCF-7, HeLa, HepG2, and MO59 J). Egonol IC_{50} values ranged 11.2 ± 0.4–180.9 ± 1.9 μM with the strongest activity against HepG2, while homoegonol ranged 40.6 ± 7.6–106.6 ± 16.2 μM with the strongest activity against MCF-7. [115] Another benzofuran neolignan, boehmenan isolated from *Clematis armandii* was active against human epidermoid carcinoma cells (A431, IC_{50} = 1.6 μM) and was found to inhibit cell growth via blocking the p70S6/S6 kinase pathway. [116] Lyciumnan (NL3-10), a new epoxide containing benzofuran neolignan displayed moderate cytotoxic activities against cell lines A549 (IC_{50} = 37.1 ± 3.3) HeLa (IC_{50} = 54.1 ± 3.9) and PC-3 (IC_{50} = 51.7 ± 3.6). [117] Two benzofuran neolignans isolated from *Tirpitzia ovoidea* exhibited cytotoxic activity against several cancer cell lines. Previously isolated hawthornnin G was active against HepG-2, BxPC-3 and HL-60 U87 (IC_{50} = 10.47–20.52 μM), while new tirpitzin A (NL3-36) was active against the BxPC-3 (IC_{50} = 19.51 μM) and HL-60 cell line (IC_{50} = 41.3 μM). [103] 8 new benzofuran neolignans, gardenofolins A – H (NL3-18 to 21) were isolated from *Gardenia ternifolia* and found to induce apoptosis in human cervical cancers (HeLa, IC_{50} = 21.0–105.0 μM), where gardenofolin D & E (NL3-19 and 20) were most active (IC_{50} = 21.0 and 32.5 μM respectively). [118] Two dihydrobenzofuran neolignans isolated from *Schisandra chinesis* were cytotoxic against Hela cancer cells *in vitro* with IC_{50} values of 30.6 μM (isomassonianoside B) and 86.3 μM, respectively. [106] The benzofuran neolignans balanophonin, dehydroconiferyl alcohol and *5´*-methoxy-balanophonin and their enantiomers were isolated from *Picrasma quassioides* and evaluated against human hepatocellular carcinoma HepG2 and Hep3B cells. Balanophonin was the most active and its enantiomers showed similar activity (HepG2, IC_{50} = 36.5–38.7 μM; Hep3B, IC_{50} = 22.4–31.5 μM), likewise for less active 5´-methoxy-balanophonin and its enantiomers (HepG2, IC_{50} = 80.5–104.1 μM; Hep3B, IC_{50} = 60.7–76.8 μM). Dehydroconiferyl alcohol and its enantiomers showed similar ranges for Hep3B (52.6–65.5 μM) however considerably different activities for HepG2 (35.6–104.4 μM). [119] In a separate study, two active benzofuran lignans from *Juglans mandshurica* displayed *in vitro* cancer cytotoxic activity. Juglansol A (NL3-37) was active against A549 (IC_{50} = 56.77 μM) and balanophonin against A549, HepG2, Hep3B, BCAP-37 and MCF-7 (IC_{50} = 23.42 ± 1.26, 40.68 ± 1.77, 14.02 ± 0.98, 66.07 ± 2.17, 25.41 ± 1.42, respectively). [120] While in another study balanophonin was found to have modest cytotoxic activity against A375, SK-Mel-28 and HeLa cancer cell lines (IC_{50} = 142.0–150 μM) and structurally related cedrusin against A375 (IC_{50} = 130.0 ± 4.2 μM). [121] The benzofuran lignan pharbilignan C isolated from *Pharbitis nil* showed cytotoxic activity against breast cancer cell lines (MDA-MB 231, IC_{50} = 7.0 ± 2.0 μM) and was found to act through a mitochondria-mediated intrinsic pathway. [122] Twelve dihydrobenzofuran neolignans including new mappiodoinins A–C isolated from *Mappianthus iodoies* showed significant cytotoxic effects (IC_{50} = 0.16–18.62 μM) against various human cancer cell lines (HL-60, SMMC-7721, A-549, MCF-7 and SW-480). [123] A new dihydrobenzofunan lignans, illiciumlignan D(NL3-46) isolated from *Illicium wardii* showed activity against ovarian cancer cell line SKOV3 (IC_{50} = 8.67). [99]

Benzofuran sesqui-lignans sambucasinols A–C (SQNL-7) showed consistent cytotoxic activity against cancer cell lines A549, SK-OV-3, SK-MEL-2 and XF498 with IC_{50} values ranging from 11.07 to 19.62 μM. [124] Cervical (HeLa) cytotoxic assays of the compounds isolated from *Ilex pubescens* revealed two active furofuran sesquineolignans (SQL-9) (IC_{50} = 50.60 ± 6.47, and 51.17 ± 8.12 μM) [125] and two coniferyl aldehyde ethers (23.88 ± 4.52, 29.14 ± 3.01 μM) [125]. Three active biphenyl neolignans illiciumlignan A, B & E (SQNL-4 to 6) isolated from *Illicium wardii* were revealed in cytotoxic assays on human cancer cell lines (A549, SKOV3, HepG2 and HCT116) with IC_{50} values ranging from 2.7 to 14.9 μM). [99]

Honokiol (100 μM) was found to elicit its antineoplastic effects on melanoma cells (SKMEL-2 and UACC-62) by substantially decreasing cell viability (reduction of 98, and 90% respectively) and proliferation (reduction of 93, and 87% respectively), causing cell cycle arrest, and also increasing apoptosis and the modulation of apoptic and cell cycle regulatory protein. [126] Two new biphenyl ether neolignans and previously described dehydrodieugenol B were isolated from *Nectrandra leucantha* and showed cytotoxic modest activities against six cancer cell lines (B16F10, SKBR-3, HCT, U87-MG, A2058, T75, IC_{50} = 78.8 ± 2.8–210.9 ± 3.1 μM). [127]

Two new benzofuran neolignans, three neolignans (including evofolin B), and a furofuran lignan (larreatricin) isolated from *Daphniphyllum macropodum* displayed cytotoxicity against two NSCLC human lung cancer cell lines (A549, H460 IC_{50} = 12–63 μg/mL). One of the benzofuran lignans (NL3-32) was the most active compound (A549, H460 IC_{50} = 12.69 ± 2.74, 25.72 ± 3.69 μg/mL respectively) and displayed higher activity than the control cisplatin with less toxicity to non-cancer bronchial epithelial (BEAS-2B) cells. [128] Three neolignans from *Myristica fragrans* showed activity against human colon cancer cells HT-29 cells, the 8-*O*-4′ neolignan expressed IC_{50} value of 3.07 μM while the two benzofurans were much more active with 0.024 and 0.003 μM (licarin C). [129] Several lignan glycosides (L5-21) were isolated from *Smilax trinervula* and two new neolignans (NL2-22, NL3-28) were found to be active against human colon (Lovo) cells (IC_{50} = 8.5 and 10.4 μM). [130]

Table 1
BV2 cell assay (IC_{50} values in μM in order, values above 100 μM are excluded).

Name	IC_{50} (μM)	Reference
erythro-(*7S,8R*)-guaiacylglycerol-β-coniferyl aldehyde ether	0.929	[136]
threo-(*7R,8R*)-guaiacylglycerol-β-coniferyl aldehyde ether	1.05	[136]
verniciasin A (NLM-12)	1.46 ± 0.91	[124]
epieudesmin	4.96	[138]
(+)-isolariciresinol	5.8 ± 0.5	[139]
(+)-pinoresinol	6.75	[107]
sambucasinol A (SQNL-7)	6.82	[124]
sambucasinol B (SQNL-7)	7.04	[124]
balanophonin	7.07	[136]
(+)-(*7S,8R,8′R*)-lariciresinol	7.21	[138]
(+)-syringaresinol	7.93	[107]
(–)-nortrachelogenin	8.7 ± 0.8	[139]
erythro-Syringylglycerol-8-O-4'-coniferyl alcohol ether	9.14	[136]
(–)-5-methoxybalanophonin	10.0	[136]
(–)-secoisolariciresinol	10.2 ± 0.9	[139]
euonymolin A (SQL-4)	10.93	[107]
7′R,8′S)-3,3',5,5'-tetramethoxy-9'-hydroxy-6,7-cyclolignan-7-ene-9-al	11.23	[140]
(–)-matairesinol	11.5	[141]
buddlenol D	13.04	[140]
sambucasinol C	14.70	[124]
buddlenol A	15.28	[136]
litsecol B	15.8	[142]
threo-3,3′-dimethoxy-4,8′-oxyneoligna-9,4′,7′,9′-tetraol-7(8)-ene	16.8 ± 1.0	[139]
vitexnegheteroin E	17.27 ± 6.10	[95]
verniciasin B (NLM-12)	17.35 ± 0.87	[137]
(+)-(*7′S,8R,8′R*)-5,5′-dimethoxylariciresinol	17.5	[143]
(+)-de-*O*-methylepimagnolin A	17.58	[107]
cinncassin E	17.6	[143]
(+)-*threo*-(7S,8S)-guaiacylglycerol-β-coniferyl aldehyde ether	17.7	[143]
threo-guaiacylglycerol-β-O-4-coniferyl	17.7 ± 1.4	[139]
longifloroside B	18.5 ± 1.2	[139]
(+)-*erythro*-(*7S,8R*)-guaiacylglycerol-β-coniferyl aldehyde ether	18.7	[143]
(–)-arctigenin	19.0	[141]
vitecannaside B	19.01 ± 2.49	[95]
buddlenol E	19.33	[136]
(+)-medioresinol	19.36	[107]
(*7S,8R*)-lawsonicin	20.5	[143]
(7'R,8'S)-3,3',5,5',9-pentamethoxy-9'-hydroxy-6,7-cyclolignan-7-ene (L5-27)	20.61	[140]
(–)-de-O-methylmagnolin	21.78	[107]
threo-Guaiacylglycerol-8-O-4'-sinapyl alcohol ether	23.53	[136]
(+)-lariciresinol 4'-O-β-D-glucopyranoside	23.53	[107]
cinncassin D	24.2	[143]
(–)-justiciresinol	24.7 ± 0.7	[136]
pinoresinol	25.1	[136]
8R,8′R)-bishydrosyringenin	25.3 ± 3.1	[144]
pinoresinol	25.4 ± 2.1	[39]
lariciresinol	25.9 ± 0.8	[139]
sesamin	26.26	[136]
(−)-*erythro*-(*7S,8R*)-syringylglycerol-8-O-4′-(sinapoyl alcohol) ether	27.0	[143]
syringaresinol	27.53	[136]
syringaresinol	27.9 ± 0.8	[139]
(–)-pinoresinol	31.1	[136]
5′-methoxylariciresinol	31.2	[143]
threo-guaiacylglycerol-8-O-4'-coniferyl alcohol ether	32.56	[136]
(+)-piperitol	32.65	[136]
(+)-7'-methoxylariciresinol	32.99	[136]
(–)-pinoresinol	34.25	[124]
firmianol A (L10-7)	35.39	[136]
medioresinol	36.0 ± 2.0	[139]
(−)-*erythro*-(*7R,8S*)-guaiacylglycerol-β-O-4′-sinapoyl ether	37.0	[143]
(+)-(*7′R,8R,8′R*)-5,5′-dimethoxylariciresinol	39.4	[143]
7R,8S-dihydrodehydrodiconiferyl alcohol	39.97	[124]
known furan-type lignan (L4-5)	≈40	[145]
9-O-formylaviculin	≈40	[145]
isolariciresinol 9′-O-β-D-glucopyranoside	≈40	[145]
lyoniresinol-9′-O-β-D-glucopyranoside (L9-12)	≈40	[145]
(+)-*erythro*-(*7R,8S*)-guaiacylglycerol-8-vanillin ether (NL2-30)	42.0	[143]
(–)-medioresinol	45.59	[124]
threo-guaiacylglycerol 8'-vanillin ether	47.59	[136]
(−)-(*7R,8S,7′R,8′S*)-syringaresinol	50.9	[143]
(+)-(*7'R,8S,8'R*)-4,4'-dihydroxy-3,3',5,5'-tetramethoxy-7',9-epoxy-lignan-9'-ol-7-one	57.79	[140]
a new tetrahydrofuran-type lignan from *Phaeanthus vietnamensis*	65.2 ± 2.6	[144]
9R-hydroxy-d-sesamin	69.1 ± 5.8	[146]
lariciresinol	72.58	[124]

(*continued on next page*)

Table 1 (*continued*)

Name	IC_{50} (μM)	Reference
(+)-isolariciresinol	73.4	[143]
one known tetrahydrofuran-type lignans from *Phaeanthus vietnamensis* (L2-3)	73.9 ± 4.5	[144]
(–)-7(S)-hydroxymatairesinol	78.9	[141]
alashinol F(L1-2)	86.9	[147]
Four known lignans isolated from *Datura metel* L	43-54% inhibition at 80 μM	[148]

Table 2
RAW 264.7 (IC_{50} values in μM in order, values above 100 μM are excluded).

Name	IC_{50} (μM)	Ref
(–)-3,4,3′,4′-tetrahydrocx-9,7′β-epoxylignano-7β,9′-lactone	4.60	[149]
lucidenal	4.8 ± 0.5	[150]
(±)-morfolia A	5.49, 5.99	[149]
(–)-3,3-bisdemethylpinoresinol	5.91	[107]
(+)-pinoresinol	6.57	[107]
(–)-pinoresinol (L2-3)	7.62	[144]
(+)-syringaresinol	7.93	[107]
obovatolignan B (NL5-1)	8.22 ± 2.01	[151]
(–)-dehydrodiconiferyl alcohol	8.5 ± 0.8	[152]
(+)-dehydrodiconiferyl alcohol	9.3 ± 1.4	[152]
(+)-dihydrodehydroconiferyl alcohol	9.8 ± 2.0	[152]
ternifoliuslignan D (L7-4)	9.98 ± 0.21	[153]
(+)-simulanol	11.7 ± 1.2	[152]
(–)-simulanol	12.8 ± 2.0	[152]
(+)-de-O-methylepimagnolin A	17.58	[107]
ternifoliuslignan C	18.64 ± 0.15	[153]
(+)-medioresinol	19.36	[107]
threo-buddlenol B	21.3 ± 3.3	[152]
(–)-de-O-methylmagnolin	21.78	[107]
(+)-laricresinol 4'-O-β-D-glucopyranoside	23.53	[107]
ternifoliuslignan B (L7-3)	23.90 ± 0.42	[153]
(+)-syringaresinol (NL3-36)	27.4 ± 4.1	[103]
ternifoliuslignan A (L8-5)	25.01 ± 0.29	[153]
9,9′-bisacetylneo-olivil	27.2 ± 4.3	[150]
(*2R,3S*)-dihydro-2-(3,5-dimethoxy-4-hydroxyphenyl)-7-methoxy-5-acetyl-benzofuran	32.3 ± 2.9	[154]
tamariscinoside E (NL3-48)	32.4 ± 3.0	[154]
A neolignan isolated from *Isodon ternifolius*	35.43 ± 0.64	[153]
dimeric coniferylacetate	36.0 ± 4.7	[150]
A furofuran lignan from *Zanthoxylum planispinum*	36.8 ± 2.8	[155]
(+)-syringaresinol	37.45 ± 0.43	[153]
moellenoside B	40.9 ± 3.7	[154]
alashinol D	43.3	[147]
(+)-isolariciresinol	46.0	[147]
sanshodiol	49.8	[147]
medioresinol	50.9 ± 3.6	[103]
tirpitzin A (NL3-36	44.7 ± 4.1% inhibition at 50 μM	[103]
(*7R,8S*)-9-acetyl-dehydrodiconiferyl alcohol	47.7% inhibition at 50 μM	[156]
schisphenlignan I	51.9 ± 4.7	[150]
tamariscinoside D (NL3-48)	55.8 ± 4.5	[154]
alashinol A	60.9	[147]
(+)-epi-syringaresinol	71.8 ± 7.2	[103]
a furofuran lignan from *Zanthoxylum planispinum*	81.2 ± 6.6	[155]
tirpitzin A (NL3-36)	44.7 ± 4.1 % at 50 μM	[103]

Eucommicin A (NLM-28), a β-truxinic lignan showed anti-cancer stem cell activity (IC_{50} = 55 μM) and inhibited tumor sphere formation. [131] *Ent*-sauchinone, an unusual hexacyclic lignan was shown to be a promising anti-metastasis agent through suppression of the STAT3 signaling pathway and possessed moderate antiproliferative effects against hepatoma cell lines (SMMC-7721, IC_{50} = 103.8 ± 2.77; HCCLM3, IC_{50} = 109.2 ± 3.86 μM). [132] Bifidenone (NLM-7), a novel neolignan was found to have potent anti-proliferative activity against a wide range of cell lines. For the cells lines NCI-H460, PC-3, SF-295 and ACHN the IC_{50} values ranged 0.25– 0.49 μM, while more

Table 3
IL-1-β treated hepatocytes (IC_{50}, μM).

IC_{50} (μM)	IC_{50} (μM)	Reference
(+)-*trans*-Dihydrodehydroguaiaretic acid	21.1	[158]
furoguaiaoxidin	24.7	[158]
meso-dihydroguaiaretic acid	29.0	[158]
furoguaiacin	36.1	[158]
dehydroguguaiaretic acid	37.6	[158]
nectarin B	43.4	[158]
(7S,8S)-3-methoxy-3′,7-epoxy-8,4′-oxyneolignan-4,9,9′-triol	79.0 ± 1.4% at 50 μM	[159]
icariresinol	32.9 ± 4.1% inhibition at 50 μM	[159]
(-)-olivil-4′-*O*- glucopyranoside	33.6 ± 4.0 inhibition at 50 μM	[159]

Table 4
TNF-α RAW264.7 macrophages (IC_{50}, μM).

Name	IC_{50} (μM)	Reference
Neolignans from hawtron seeds (NL2-3)	76.1, 47.9	[160]
(-)-olivil-4′-*O*- glucopyranoside	18 ± 2.8% inhibition at 50 μM	[159]
7S,8S)-3-methoxy-3′,7-epoxy-8,4′-oxyneolignan-4,9,9′-triol	40.9 ± 0.5 at 50 μM	[159]

Table 5
TNF-α RBL-2H3 cells (IC_{50}, μM).

Name	IC_{50} (μM)	Reference
Malabaricone C	39.5	[161]
maceneolignans A	48.4	[161]
verrucosin	51.2	[161]

potent activity was seen for the melanoma cell lines (M14 A375, UACC-62 and SK-Mel-2, IC_{50} = 0.044 – 0.095 μM). Upon screening the compound was found to elicit its effects by activation of caspase 3/7 and to bind directly to tubulin, acting as a tubulin polymerization inhibitor. [133]

3.3. Anti-inflammation

Inflammation is an essential defense mechanism in the body. If the body recognizes damage of cells as well as invaders, such as viruses and bacteria, it is a way of signaling to the immune system to heal and resolve the problem. However when the inflammation process lasts for a long period of time, or occurs in an area where it is not necessary, the chronic inflammation could lead to several health problems such as heart diseases, stroke or rheumatoid arthritis to name a few. [134]

3.3.1. Lipopolysaccharide (LPS)-induced NO production inhibition cell assay

Nitric oxide (NO) is a short-lived radical which is synthesized by nitric oxide synthase (NOS). NO mediates a broad scale of biological actions including anti-inflammatory effect under normal physiological

Table 6
Inhibition activity towards 5-LOX (IC_{50} in μM).

Name	IC_{50} (μM)	Reference
(+)-pinoresinol 4-O-[6”-O-vanillyl]-β-D-glucopyranoside	20.2 ± 0.35	[162]
(+)-pinoresinol 4-O-[6”-O-protocatechuoyl]-β-D-glucopyranoside	7.6 ± 0.55	[162]
pinoresinol-4'-O-[6”-O-(*E*)-feruloyl]-β-D-glucopyranoside	15.1 ± 1.2	[162]
(+)-pinoresinol 4-O-β-D-glucopyranoside	34.1 ± 0.80	[162]
eucommin A	31.5 ± 0.46	[162]

conditions. However if NO is over-produced, it is considered as a pro-inflammatory mediator which plays a key role in the pathogenesis of a variety inflammatory diseases. [135] Thus compounds that show inhibition of lipopolysaccharide (LPS)-induced NO production in BV-2 or RAW264.7 cell assays are considered to have anti-inflammatory properties.

3.3.2. IL-1-β (interleukin-1 β) and TNF-α (tumor necrosis factor α) inhibitors

Interleukin-1 β and TNF-α are pro-inflammatory cytokines regulating and initiating inflammatory response via stimulation of NOS. Anti-inflammation properties of isolated compounds were examined by using inhibiting assays of these two cytokines.

Alashinol A decreased the TNF-α and IL-6 level in a concentration-dependent manner at 40–160 μM and displayed a neuroprotective effect against the glutamate-induced injury in PC12 cell line. [157]

3.3.3. Lipooxygenase inhibitors

Lipooxygenases are enzymes that catalyze the oxygenation of polyunsaturated fatty acids to their hydroperoxyl derivatives that can be further transformed into leukotrienes which play important roles in many inflammatory conditions. Inhibition activity towards 5-LOX and 15-LOX was demonstrated in the following compounds (IC_{50} in μM):

3.3.4. Miscellaneous inflammatory inhibitors

The houpulins (NL4-2 to 4) isolated from *Magnolia officinalis* were examined for anti-inflammatory activity and significantly inhibited superoxide anion generation: houpulin F (IC_{50} = 8.16 ± 3.45 μM), houpulin G (IC_{50} = 4.21 ± 1.37 μM), houpulin H (IC_{50} = 15.11 ± 2.07 μM), houpulin I (IC_{50} = 4.17 ± 0.33 μM), houpulin J (IC_{50} = 3.54 ± 1.26 μM). [123]

Six new lignans (asarinin B (L10-3), neoasarinin A–C (NL2-36 and 37), neoasarinoside A & B (NL2-38 and 39)) from *Asarum heterotropoides* possessed anti-inflammatory properties against platelet-activating factor (PAF)-induced β–glucuronidase release in a PMNs cell assay (10^{-5} mol/L) exhibiting inhibition rates from 25.6% to 69.9%. [163] Secoisolariciresinol diglucoside a major lignan from flax seeds, reduces the inflammatory state of leukocytes via directly inhibited blood-brain barrier interactions with inflammatory cells. [164] In another study the furan lignan (+)-episesaminon showed anti-inflammatory activity in a concentration-dependent manner Inhibiting LPS-stimulated increase of NF-κB luciferase activity. [165] Schisandrin B elicitied it's anti-inflammatory effects in LPS-stimulated BV2 microglia through inhibition of TNF-α, IL-1ß, IL-6, PGE_2 production, and activation of PPAR-γ [166]. A similar effect was seen for (7R,8S)-dehydrodiconiferyl alcohol treatment of LPS-stimulated BV2 microglia where decreased release of TNF-α, IL-1ß and IL-6 was seen among other effects through the inhibition of MAPK signalling. [167]

3.4. Anti-allergic

Several ligans and neolignans were isolated from nutmeg (*Myristica fragrans*) were found to be potent inhibitors of CC chemokine receptor 3 (CCR3), a component that plays a major role in allergic diseases. Four newly isolated neolignans (maceneolignans A (NL3-14), D (NL3-17), G and H), and six known neolignans (including (+)-licarin A, nectandrin B, verrucosin, and myristicin) inhibited CCR3-mediated chemotaxis displaying EC50′s of ˜1 μM. [168] In a subsequent publication the authors found several neolignans (including maceneolignan A, D & H (NL3-14 and 17), (+) licarin A, nectandrin B, verrucosin, and malabaricone C) to be potent degranulation inhibitors (IC_{50} = 20.7–63.7 μM). Maceneolignans A, verrucosin, and malabaricone C also inhibited TNF-α production (IC_{50} = 39.5–51.2 μM), which plays a role in the late phase of type I allergic reactions. [161]

Several lignans from *Magnoliae Flos* displayed inhibitory effects against interleukin-2, a cytokine responsible for allergic diseases. Known isolated furafuran lignans ((+)-kobusin (L5-1) and (+)-aschantin) and known furan lignans ((+)-veraguensin, (±)-galgravin, nectandrin A, and futokadsurin C) showed significant activity in Jurkat T-cells. [169]

Seven neolignans from *Palhinhaea cernua* showed inhibition of xanthine oxidase, an ezyme associated with joint pain such as gout. The activities ranged from 30.36 to 88.44 μM with the new neolignans lycocernuasides B–D (NL2-28 and NL3-53) being most active (IC50 = 30.36, 42.65 and 35.33 μM, respectively). [170]

A benzofuran lignan glycoside was isolated from the twigs of *Litsea cubeba* and it demonstrated moderate inhibitory activities against HDAC1 (IC_{50} = 3.6 μM), an enzyme which may contribute to inflammatory diseases. [171]

Pretreatment of secoisolariciresinol diglucoside was found to significantly alleviate symptoms of colitis-induced mice and therefore may be a promising supplement for inflammatory bowel disease. [172] Similarly magnolol, a biphenyl neolignan was found to have anti-colitis activity, and was shown to act through the restoration of tryptophan metabolites that inhibit inflammation. [173] Several aryl tetralin lignan gylcosides (L9-5 and 6) isolated from the aerial parts of *Lespedeza cuneate* were tested for their anti-ulcerative colitis activity (dual luciferase report gene assay targeting xbp1) and were found to be active (EC_{50} = 0.09 – 0.25 μM). [174]

Table 7
Inhibition activity towards 15-LOX (IC_{50} in μM).

Name	IC_{50} (μM)	Reference
(+)-pinoresinol 4-O-[6”-O-vanillyl]-β-D-glucopyranoside	5.2 ± 0.13	[162]
(+)-pinoresinol 4-O-[6”-O-protocatechuoyl]-β-D-glucopyranoside	2.7 ± 0.02	[162]
pinoresinol-4'-O-[6”-O-(*E*)-feruloyl]-β-D-glucopyranoside	4.6 ± 0.08	[162]
(+)-pinoresinol 4-O-β-D-glucopyranoside	16.9 ± 0.28	[162]
eucommin A	12.4 ± 0.31	[162]

3.5. Anti-neurodegenerative activity

Neurodegenerative diseases are a serious problem especially in the developed world where increased dietary, lifestyle standards and medical technology has extended the natural life span to ages where they become more prevalent. Providing care for inflicted individuals is a costly endeavor, not to mention the hardship it creates for sufferers and their loved ones. Therefore developing anti-neurodegenerative drugs is an important area of research, several papers have isolated and described the activity of lignans and neolignans with such properties.

3.5.1. Alzheimer's disease

Alzheimer's disease primary affliction is memory impairment and is most prevalent in the elderly. It is a complex disease and our current understanding is that it is a result to the loss of cholinergic neurons. Several possible causes have been described, these include: accumulation of amyloid beta peptide (Aβ) and aggregates of hyperphosphorylated tau protein within the brain (generation of senile plaques and neurofibrillary tangles); metal ion toxicity; and oxidative stress. [175,176]

Arctigenin was administered to Alzheimer's disease (AD) induced mice (injections with $A\beta_{1-42}$) and found to attenuate memory and learning deficits. The suspected mode of action is by reduction of tau hyperphosphorylation *via* the phosphatidyl-inositol-3- kinase/protein kinase B–Dependent glycogen synthase kinase-3β signalling (PI3k/Akt/GSK-3β) pathway. [176] Another dibenzylbutyrolactone cubebin showed neuroprotective effects. When pre-administer it prevented scopolamine-induced learning and memory impairment while also lessening scopolamine-induced rise in brain AChE activity and oxidative stress. [177]

Treatment of the biphenyl neolignan honokiol on transgenic *C. elegans* expressing full length $A\beta_{42}$ (*in vivo* AD-model system) was found to have protective effects. It protected against $A\beta_{42}$-induced toxicity, exhibited modest inhibition of cholinesterases (acetylcholinesterase, $IC_{50} = 87.0 \pm 2.6\,\mu M$ and butyrylcholineesterase, $IC_{50} = 107.3 \pm 0.1\,\mu M$), scavenged DPPH radicals, and chelated Iron (II). [175] Justicidin A, an aryl naphthalene lignan possesses neuroprotective effects *via* inhibition of tau hyperphosphorylation and induction of autophagy in neuroblastoma SH-SY5Y cells treated with $A\beta_{25\text{-}35}$, thus showing promise in the treatment of AD and tau-related diseases. [178]

Aryl tetralin lignans (including newly isolated (7′R, 8′R, 8S)-isolariciresinol (L9-19)) from *Crataegus pinnatifida* showed inhibition properties against $A\beta_{1\text{-}42}$ aggregation with inhibition rates of 30–70% at 20 μM. [179] Similarly, benzofuran neolignans robussin A and B (each isolated as enantiomer pairs) were found to show good inhibition of $A\beta_{1\text{-}42}$ aggregation at 20 μM, where (–)-robussin A (NL3-4) and (+)-robussin B (NL3-5) were most active with 81.6% and 83.4% respectively. [180] Likewise the chiral resolved enantiomers of benzofurans (+/–)-ideausin A–D (NL3-6 to 9) isolated from red raspberries (*Rubus ideaus* L.) showed anti-$A\beta_{1\text{-}42}$ aggregation activities at 20 μM with inhibition values ranging 32.58–60.18%. [181] The same group also isolated enantiomeric 8-O-4′-type neolignans (including 3 new compounds (NL2-10 and NL2-12)), with the three most active compounds possessing significant activities of 73.4–76.8%. [182]

Several lignans were isolated from *Schisandra bicolor* Var. and tested for their neuroprotective effects on $A\beta_{25-35}$-induced SH-SY5Y cell injury. Of the active compounds, new lignans (schibitubin B (L1-4), F (L1-7), H (L4-1) and I) and previously isolated (galgravin, (−)-nectandrin-A, (−)-futokadsurin A, (+)-9′-hydroxygalbelgin, austrobailignan-6, oleiferin-F, (+)-dihydro-guaiaretic acid and (−)-isootobaphenol) displayed statistically significantly increased cell viability values in $A\beta_{25-35}$-induced SH-SY5Y cell injury models at 3.2 nM compared with the negative control group. [183] The same group also isolated seven active dibenzocyclooctadiene lignans (schirubrisin B, schisantherin A, schisanwilsonins G, tigloylgomisin P, schisphenin E, gomisin J, and (+)-gomisin K_3) from *Schisandra sphenanthera* displaying statistically significantly increased cell viability values in $A\beta_{25-35}$-induced SH-SY5Y cell injury models at 3.2 nM compared with the negative control group. [184] Two new dibenzocyclooctadiene lignans (L6-14, NL5-10) from *Schisandra chinensis* exhibited protective activity in neurotoxicity $A\beta_{1\text{-}42}$ induced PC12 cells, increasing cell viability at 25 μM to 84.1 ± 5.4% and 82.1 ± 4.3% vs the model (52.0 ± 3.2%). [185]

Four lignans (including new tatarinoid D (L5-6), and previously isolated nectandrin A) from *Acorus tatarinowii* were found to alleviate cognitive deterioration of $A\beta_{42}$ transgenic flies *Drosophila melanogaster* [186]. The novel tetralignan tartarinan T and known dibenzyl lignan tartarinan S also isolated from *Acorus tatarinowii* displayed potential protective effects against β-amyloid toxicity in a CL4176 transgenic *C. elegans* model. Tatarinan S significantly delayed Aβ-induced paralysis (PT_{50}) by 62.3% at 100 μM, and 30.8% at 10 μM, while tatarinan T (LM-1) delayed 38.8% at 100 μM respective to the control. [187]

The furan lignan talaumidin exhibits neurotrophic properties, and was found to promote stautosporine-induced neurite overgrowth in retinal ganglion cells (RGC-5) through the PI3K/Akt pathway. [188] This work suggests that talaumidin treatment could be beneficial for retinal degenerative disorders, glaucoma and neurodegenerative disorders like Alzheimer's disease. The authors later went on to synthesize analogues and establish a structure activity relationship. [189]

3.5.2. Parkinson's disease

Parkinson's disease (PD) is another common disease that again commonly afflicts the elderly and mainly affects the motor system resulting in pronounced shaky movements. Its pathology is primarily linked to the loss of dopaminergic neurons. Sesamin when administered at 10–20 mg/ kg for one week was found to have neuroprotective properties on intrastriatal 6−OHDA-lesioned rats (Parkinson's disease model) *via* reducing apoptosis, astrogliosis and oxidative stress. Suggesting it may be a beneficial neuroprotective therapy in the early stages of PD. [190]

3.6. Anti-osteoporotic activity

Osteoporosis as the name suggests is a condition where bones become porous and weakened, leading to increased risk of fractures and breakages. The following paragraph describes several active lignans and neolignans and their anti-osteoporotic activity.

Baicalenosides A–C, furan-type lignans isolated from *Scutellaria baicalensis* showed anti-osteoporotic activity in an *in vitro* osteoprotegerin (OPG) transcriptional activity assay. A target which has previously shown to have a pivotal role in the modulation of bone remodeling. Compared to the control group at 10 μmol/L the lignans increased the relative activating ratio of OPG transcription to 1.83, 0.84 and 0.98 times respectively. [290] Dehydrodiconiferyl alcohol inhibits osteoclast differentiation and promotes bone morphogenetic protein-2 (BMV-2)–induced osteoblastongenesis by acting as an agonist of estrogen receptors. This estrogenic effect may serve as a treatment for post-menopausal and ovariectomy-induced bone loss. [192,193] Sesamin showed promising effects on chondrogenic differentiation of human amniotic fluid-derived mesenchymal stem cells. Based on this finding sesamin can be considered a chondrogenic inducing factor and aid in cartilage regeneration. [194]

3.7. Antiradical activity

Oxygen is a highly reactive molecule that causes damage to living organism by a production of reactive oxygen species. These species also behave as signaling molecules and the equilibrium between their damage and useful effects depends on their production and scavenging. The optimum level of ROS is held by enzymatic and nonenzymatic antioxidant systems including compounds with phenolic moiety such as those contained in lignans and neolignans. [195] The antioxidant abilities are tested using several different assays.

3.7.1. ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) radical scavenging assay

(IC_{50}, μg/mL): (+)-pinoresinol-β-D-glucoside (3.6) [196], rubuslin D (NL3-50) (7.47) [197], (+)-pinoresinol (7.5) [196], rubuslin A (SQNL-10) (7.86) [197], olivil monoacetate (8.42) [197], cycloolivil (8.50) [197], furan-type lignan (8.6) [196], secoisolariciresinol (9.41) [197], olivil (9.78) [197], syringaresinol (9.78) [197], dihydrodehydrodiconiferyl alcohol (9.87) [197], rubuslin B (SQNL-11) (10.04) [197], 5-methoxydihydrodehydroconiferyl alcohol (10.21) [197], rubuslin E (NL2-44) (10.32) [197], lirioresinol-A (10.56) [197], (+)-medioresinol (10.7) [196], rubuslin C (SQNL-11) (11.39) [197], (*7R,8S,7″S,*8″*R*)-dihydrobuddlenol B (11.81) [197], (+)-syringaresinol (13.2) [196], (+)-syringaresinol-β-D-glucoside (18.0) [196], icariside E4 (18.48) [197], (+)-isolariciresinol (19.0) [196], (+)-medioresinol monoglucoside (23.7) [196].

(IC_{50}, μM): A glucosidic neolignan from *Patrinina villosa* (0.2 ± 0.03) [198], patrianian A (L3-2) (0.3 ± 0.04) [198], (+)-isolariciresinol (0.3 ± 0.06) [198], *erythro*-(*7S, 8R*)-guaiacyl-glycerol-β-O-4′-dihydroconiferyl ether (0.4 ± 0.05) [198], patrianian B (L3-3) (0.6 ± 0.08) [198], aryl dihydronaphthalene-type lignan (1.71 ± 0.22) [95], vitexdoin A (1.43 ± 0.03) [95], vitedoin A (1.63 ± 0.08) [95], vitexnegheteroin E (L8-3) (3.32 ± 0.12) [95], vitexnegheteroin F (L8-3) (3.39 ± 0.19) [95], miltiolignanolides C (LM-3) (3.73) [199], (+)-isolariciresinol-9′-glucoside (4.28 ± 0.08) [200]. Bai and co isolated six tetrahydrofuran-type lignans (5.2 ± 0.71 to 12.1 ± 1.02) [198], vitexnegheteroin G (L7-9) (7.89 ± 0.47) [95], massonianoside A (7.96 ± 0.08) [200], saikolignanoside A (8.34) [81], (−)-(7′S,8S,8′R)-4,4′-dihydroxy-3,3′,5,5′-tetramethoxy-7′,9-epoxylignan-9′-ol-7-one (8.6) [196], aviculin (8.71 ± 0.05) [200], (−)-isolariciresinol-9′-glucoside (9.11 ± 0.07) [200], miltiolignanolides D (LM-3) (9.20) [199], a glucosidic neolignan from *Patrinina villosa* (9.9 ± 1.02) [198], miltiolignanolides B (LM-3) (10.33) [199], 2-(3′′-methoxy-4′′-hydroxybenzyl)-3-(3′-methoxy-4′-hydroxybenzyl)-γ-butyrolactone (10.62) [81], two new neolignans isolated from hawtron seeds by Pent et all (NL2-3) (10.8 ± 0.2, 12.9 ± 1.0) [160], (+)-pinoresinol (13.43) [81], (+)-nortrachelogenin (15.13) [81], A neolignan from *Bupleurum chinense* (15.24) [81], (–)-secoisolariciresinol-4-glucoside (16.66 ± 0.02) [200], miltiolignanolide A (LM-3) (16.76) [199], cupressoside A (16.86 ± 0.46) [200], cedrusin (18.62 ± 0.04) [200], fordianole B (NL2-26) (20.20 ± 0.01) [201], (–)-pinoresinol 4-glucoside (22.50 ± 0.24) [200], pluviatolide (23.20) [81], salicifoline (25.62) [81], acutissimalignan B (32.70) [81], guamarolin (32.70) [81], fordianole A (NL2-26) (32.94 ± 0.05) [201], dihydrodehydrodiconiferyl alcohol 9′-glucoside (37.48 ± 0.94) [200], (±)-ideausin A (NL3-6) (41.97 ± 1.77, 56.19 ± 1.35) [181], (±)-ideausin C (NL3-8) (49.68 ± 0.88, 47.10 ± 1.91) [181], (±)-ideausin D (NL3-9) (45.03 ± 2.04,68.75 ± 2.17) [181], icariside E4 (57.70 ± 0.81) [200], (±)-ideausin B (NL3-7) (114.83 ± 3.04, 88.87 ± 1.33) [181]

3.7.2. DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity

(IC_{50}, μg/mL): Berchemol (1.06 ± 0.01) [202], one known lignan from *Syringa pinnatifolia* (1.08 ± 0.02) [202], 7-*O*-7-epoxylignan (1.37 ± 0.04 mg/ml) [202], one new lignan from *Syringa pinnatifolia* (L5-8) (1.76 ± 0.08) [202], rubuslin D (NL3-50) (15.86) [197], acortatarinowin L (16.437 ± 0.22) [203], syringaresinol (21.33) [197], rubuslin A (SQNL-10) (21.63) [197], lirioresinol-A (26.50) [197], cycloolivil (29.62) [197], olivil monoacetate (30.55) [197], (+)-medioresinol (37.5) [196], olivil (39.02) [197], furan-type lignan (40.4) [196], (*7R,8S,7″S,*8″*R*)-dihydrobuddlenol B (44.33) [197], (+)-syringaresinol (49.7) [196], rubuslin B (SQNL-11) (54.01) [197], rubuslin C (SQNL-11) (60.25) [197], 5-methoxydihydrodehydroconiferyl alcohol (65.22) [197], secoisolariciresinol (78.44) [197], icariside E4 (83.97) [197], (+)-syringaresinol-β-D-glucoside (104.2) [196], (+)-isolariciresinol (109.9) [196]

(IC_{50}, μM): Known glucosidic neolignans from *Patrinina villosa* (5.3 ± 1.35) [198], (+)-isolariciresinol 5.6 ± 0.16 μM [198], chilianthin A (6.54) [204], patrianian B (L3-3) (9.0 ± 1.91) [198], (+)-isoprincepin (9.2) [205], pinoresinol 4-O-[6″-O-protocatechuoyl]-β-D-glucopyranoside (L10-6) (10.6 ± 0.41) [162], chilianthin B (11.33) [204], princepin (11.7) [205], pinoresinol-4′-O-[6″-O-(E)-feruloyl]-β-D-glucopyranoside (13.1 ± 0.27) [162], 3,3′-bisdemethylpinoresinol (16.0) [205], 9′-O-methylisoamericanol A (18.3) [205], (+)-pinoresinol 4-O-[6″-O-vanillyl]-β-D-glucopyranoside (18.4 ± 0.74) [162], americanol A (18.9) [205], isoamericanol A (19.7) [205], isoamericanol A (24.6) [205], patrianians A (L3-2) (27.5 ± 3.72) [198], 9′-O-methy + lamericanol A (29.6) [205], erythro-(7S, 8R)-guaiacyl-glycerol-β-O-4′-dihydroconiferyl ether (40.1 ± 1.15) [198], cedrusin (42.7 ± 2.5) [121], chilianthin C (43.02) [204], (+)-isolariciresinol-9′-glucoside (47.23 ± 4.09) [200], fordianole B (NL2-26) (48.36 ± 0.87) [201], fordianole A (NL2-26) (51.13 ± 0.90) [201], (−)-isolariciresinol-9′-glucoside (51.48 ± 2.83) [200], officinalioside (L5-26) (52.6 ± 1.70) [206], eucommin A (57.2 ± 1.08) [162], balanophin (59.2 ± 2.9) [121], fordianoles C (NL2-27) (59.63 ± 0.98) [201], (+)-pinoresinol 4-O-β-D-glucopyranoside (62.3 ± 1.16) [162], lawsonicin (74.3 ± 3.8) [121], Ideausin D (NL3-9) (83.55 ± 2.71 μM, 89.33 ± 1.69) [181], pluviatolide (IC_{50} = 88.52 μM) [81], miltiolignanolide D (LM-3) (94.71) [199] aviculin (97.25 ± 2.19) [200], ideausin B (92.07 ± 2.61, 70.92 ± 2.54) [181]. Bai and co isolated six tetrahydrofuran-type lignan which displayed (6.6 ± 0.46 to 98.3 ± 0.73) [198]

DPPH (Scavenging value at 100 μM): (±)-pinoresinol (59.1 ± 1.3), (*7S,8R*)-9-O-β-D-glucopyranosyl-dihydrodehydrodiconiferyl alcohol (37.8 ± 0.6), (*7S,8R*)-9′-O-β-D-glucopyranosyl-dihydrodehydrodiconiferyl alcohol (34.2 ± 1.4) [207]

3.7.3. FRAP (Ferric reducing ability of plasma) assay

The FRAP assay is based on the reduction of ferric to ferrous ions which results in the formation of a blue complex in acidic media. The absorbance is then measured, and in this case, higher values correlate to better antioxidant properties. [208]

(+)-isolariciresinol-9′-glucoside (IC_{50} = 6.36 ± 0.34 mmol/g) and (−)-isolariciresinol-9′-glucoside (IC_{50} = 6.16 ± 0.17 mmol/g) [200] showed weak antioxidant activity compared to a positive control which was L-ascorbic acid (IC_{50} = 14.98 mmol/g) [200].

FRAP assay (at 0.75 mg/mL, the following compounds displayed strong antioxidant activity compared to positive control Trolox = 86.9 mg/mL): (+)-isolariciresinol (95.1) [258], (+)-pinoresinol-β-D-glucoside (72.1) [258], (+)-syringaresinol (98.5) [258], (+)-pinoresinol (95.0) [238], (+)-medioresinol (86.7)) [238], (+)-syringaresinol-β-D-glucoside (73.5) [258], (-)-(7′S,8S,8′R)-4,4′-dihydroxy-3,3′,5,5′-tetramethoxy-7′,9-epoxylignan-9′-ol-7-one (72.8) [258], (+)-medioresinol monoglucoside (48.8) [196].

Xu et all isolated following compounds from *Rubus ideaus* (Rhizomes) and evaluated antioxidant activity using FRAP assay (at 50 μg/mL) (Trolox 175.69 μg/mL): syringaresinol (173.47 μg/mL), lirioresinol-A (154.76 μg/mL) [197], rubuslin A (SQNL-10) (150.58), rubuslin D (NL3-50) (147.16), icariside E4 (145.28 μg/mL), rubuslin B (SQNL-11) (142.03), olivil monoacetate (121.36 μg/mL), secoisolariciresinol (120.42 μg/mL), cycloolivil (92.06 μg/mL), (7R,8S,7″S,8″R)-dihydrobuddlenol B (67.79 μg/mL) [117,137], rubuslin E (NL2-44) (64.63 μg/mL) [137], 5-methoxydihydrodehydroconiferyl alcohol (56.60 μg/mL), olivil (30.63 μg/mL) [197].

FRAP assay (at 12.5 μg/mL): Erythro-(7S, 8R)-guaiacyl-glycerol-β-O-4′-dihydroconiferyl ether (46.88 ± 5.8μg/mL). [198]

3.7.4. Miscellaneous anti-oxidant assay

Illisimonan A (NL1-9) showed *in vitro* antioxidant activity inhibiting microsome lipid peroxidation induced by a Fe^{2+} - cysteine system with IC_{50} = 59 ± 0.50 μM. [209] Gomisin D showed radical scavenger activity (determined using the HPLC-online Trolox Equivalent Antioxidant Capacity (TEAC) assay = 0.49 ± 0.03 (mmol trolox/g dw)).

[210] Similarly, several neolignans from hazelnuts Nocciola di Giffoni shells showed antioxidant activities in the TEAC assay with values ranging 0.51 to 0.82 mM [211]. Two dihydrobenzofurane neolignans isolated from sugarcane molasses were tested for their ability to protect DNA from free radical damage of hydroxyl and peroxyl radicals. The DNA damage protective concentrations for (*7R,8S*)-dehydrodiconiferyl alcohol-4-O-β-D-glucoside was 14.42 μmol/L for hydroxyl radicals and 48.07 μmol/L for peroxyl radicals while (*7S,8R*)-simulanol-9′-O-β-D-glucoside displayed values of 9.08 and 13.62 μmol /L, respectively. [212]

3.8. Anti-parasitic and anti-insecticide

3.8.1. Antiparasitic

Malaria, leishmaniasis and other parasitic infections are a common neglected diseases prevalent in third world countries and until recently have seen little attention from pharma due to the lack of financial gain. Interestingly lignans and neolignans with anti-parasitic properties are commonly present in plant kingdom. Not surprisingly, such natural products are common and important part of local remedies in third world countries. As such they might become a ready-made solution to these diseases. [9,10,12,213]

Four diphenyl ether neolignan derivatives isolated from leaves of *Nectandra leucantha*, including dehydrodieugenol displayed *in vitro* antitrypanosomal activity via plasma membrane and mitochondrial damages. Three of which displayed amastigote (IC_{50} = 15.2–86.5 μM) and trypomastigote (IC_{50} = 38.6–59.7 μM) activity and may serve as progenitors for development of drugs against Chargas disease. [214] Five neolignans including four biphenyl neolignans and one diphenyl ether derivative from *magnolia grandiflora* showed moderate to weak antiplasmodial activity against the Dd2 strain of *P. falciparum* with IC_{50} values ranging 2.8 ± 0.06 to 86.1 ± 0.6 μM. [215] A furofuran lignan from *piper jericoense* was active against amastigote (IC_{50} = 55.88 ± 2.5 μg/mL) and trypomastigote (IC_{50} = 97.62 ± 3.1 μg/mL) forms of *trypanosoma cruzi* [216]. *Cis*-eupomatenoid-7 (NL3-30), a benzofuran neolignan exhibited low activity against promastigotes forms of *leishmania amazonensis* (IC_{50} = 46 μM) however it was also toxic to macrophages at 50 μM and above. [217] Benzofuran lignans from *piper rivinoides* displayed very low activity against *Leishmania amazonensis* and *Leishmania chagasi* with IC_{50} values from 10.8 to 126.1 mM, and again being toxic to mammalian cells. [58] Arctiin, a dibenzyl lignan reduced the hepatic granuloma volume by 20% at 50 mg/kg when administered intraperitoneal to infected mice. [218] Two dibenzyl and four aryl tetralin lignans were isolated from *Larrea tridentata* and found to have anti-parasitic activities against *E. histolytica* (IC_{50} = 94–236 μM), *G. lamblia* (IC_{50} = 36–188 μM) and *N. fowleri* (IC_{50} = 37 – 155 μM). The two dibenzyl lignans, nordihydroguairetic acid and nor-3′-demethoxyisoguaiacin were potent against *G. lamblia* and *N. fowleri* (36, 38 μM and 37, 38 μM respectively) showing better activity for the later than the current drug miltefosine (54.5 μM) [219]. (+)-Phyllanthin, a dibenzyl lignan displayed potent antiplasmodial activity against 3D7 and W2 (chloroquinine-resistant) strains of *P. falciparum* (26.23 ± 3.47, 5.65 ± 1.48 μM, respectively) however it was also cytotoxic against human HUVEC cells (5.89 ± 0.77 μM) providing a selectivity index of 0.22 and 1.04 respectively). [220]

3.8.2. Antiinsecticide

Three rare spiro-tetrahydrofuran lignans from *Gymnotheca involucrate* were found to possess weak to moderate insecticidal activity. Gymnothespirolignan D showed weak activity to Aphid (*Heliothis virescens*) and gymnothespirolignan F to *D. balteata* while gymnothespirolignan C showed moderate activity to *D. balteata.* [59] Anti-feedant effects against male fruit flies were observed with the sesquilignans daphnauranins A and B (LM-6) with activities of 46.2 ± 7.1 and 44.7 ± 5.4% at 1 mM, respectively. [221] The lignan glycoside galiveroside A (SQL-8) showed modest insecticidal activity against 3 age cotton bollworm with a mortality of 16.3% at 5 mg/mL, this activity was increased to 36.6% with co-administration of recombinant scorpion toxin (rLqh α-IT-1). [222]

3.9. Melanogenesis inhibitors

Several lignans were found to be potent inhibitors of melanogenesis and therefore may have application in the cosmetic industry for skin whitening agents. Americanin A, a benzodioxan neolignan when administered up to 20 μM to melanocytes, was found to act via downregulation of microphthalmia-associated transcription factor (MITF) and tyrosinase (TYR) expression. [223] Gomisin N, a biphenylcyclooctadiene lignan when administered 1–10 μM to melanocytes, acted through the regulation of PI3K/Akt and MAPK/ERK signaling, in addition to downregulation of other pathways. [224] (+)-Zuonin A, a furan lignan showed notable inhibition of melanogenis (at 1–20 μM), analysis showed it to decrease levels of tyronisase and tyroninase related proteins (TRP-1 & 2) and is believed to act downsteam of the CREB phosphorylation pathway. [225] Galanganol D diacetate (NL2-1), a 7-O-9′ neolignan showed potent melanogenesis inhibition (IC_{50} = 2.5 μM) where treatment inhibited TYR, TRP-1 & 2 mRNA expression which may be the mechanism of action. [226]] In a separate study a rare neolignan from *Potentilla recta* was found to have *in vitro* inhibition of tyrosinase (IC_{50} = 44.62 ± 3.99 μg/mL), an enzyme involved in the development of Parkinson disease. [191] Furan and furofuran lignans isolated from the wood of *premna integrifolia* expressed potent anti-melanogenesis activity with the furofuran lignans presenting IC_{50} values < 10 μM (below minimum treated dose), while the newly isolated tetrahydrofuran lignans, taungtangyiols A and B (L5-5) values were higher (50.7 and 40.9 μM, respectively). [227]

3.10. Obesity, diabetes and cardiovascular diseases

Obesity is a serious world problem, especially in first-world countries where high calorie diets are common-place. High-sugar diets are also contributing to the increase in type II diabetes and collectively this can develop into serious cardiovascular diseases. Several lignans and neolignans have shown promise in the alleviation and treatment of these conditions.

Secoisolariciresinol diglucoside (SDG) is one such lignan. Mice fed on a high-fat diet and treated with dietary SGD (0.05% w/w supplementation) showed insulin resistance and alleviated hyperlipidaemia, hyperglycaemia and hepatic steatosis. It is believed that this improved lipid and glucose metabolism may be due to enhanced insulin signaling and activation of AMP-activated protein kinase in the liver. [228] Another study showed SDG to have an antioxidant protective role against oxidative stress for rats with metabolic syndrome (MS). In this study MS was induced with oral 30% fructose solution and SGD administered at dosages of 20 mg/kg body weight. [229] Gomisin N, a biphenylcyclooctadiene lignan at concentrations 10–100 μM was found to inhibit adipogenesis and prevent high-fat diet-induced obsesity through inhibition of the differentiation 3T3-L1 preadipocytes as well as acting on other pathways. [230] Similarily, arctigenin (up to 50 μM dosage) suppressed adipogenesis and fat accumulation in differentiated 3T3-L1 cells by reducing adipogenic transcription factor expression. [68] Gomsin N was also found to have antidiabetic effects via activation of AMPK and promoting of glucose uptake in C2C12 myotubes at dosages up to 100 μM. While in animal studies high-fat diet mice treated with 20 mg/kg body weight of gomsin N displayed higher tolerance to hyperglycemia and glucose tolerance. [231] Similarly, the dineolignans manassantin A and B acted by activation of AMPK as well as being potent and specific inhibitors of mitochondrial complex I and bioenergetic activity. The more active and abundant manassantin B was studied and showed activity in both *in vitro* (various cell lines - up to 100 nM) and *in vivo* (mice - 1.5 mg / kg). Therapeutic doses could potentially increase insulin sensitivity, promote catabolism of glucose and

fatty acids and avert obesity. [232] The benzofuran neolignan licarin B when administered at 5–15 μM dosages presented improved insulin sensitivity in 3T3-L1 adipocytes through PPARγ and activation of GLUT4 in the IRS-1/PI3K/AKT pathway. [233] Syringaresinol-4-O-β-D-glucoside (SSG), a furofuran lignan also shows promise as a treatment for metabolic diseases through the modulation of glucose and lipid metabolism. Activity was seen in the cell lines HepG2 cells and C2C12 myotubes following SSG treatment (up to 10 μmol/L). [234] Three new (NL2-20) and two known neolignans were isolated from *Juglans mandshurica* and their lypolytic activities were measured by levels of glycerol release from adipocytes (C3H10T1/2). However they were found to have only mild activity (0.97–1.48 mg/mL, control = 4.94 ± 0.90 mg/mL). [235] The dibenzyl lignan phyllanthin was found to be protective against diet-induced metabolic disorders in mice. Supplementation (2–4 mg/kg body weight) of high-fat diet mice decreased adipogenic and increased lypolytic gene expression, reduced serum and liver tryglycerides, and counteracted inflammation and insulin resistance. [236] Schisandrin B, a dibenzocyclooctadiene lignan when administered long-term low-doses (50–200 mg/kg, 4–6 days) was found to have beneficial activities against nonalcoholic fatty liver disease (NAFLD) in obese mice, while unexpectedly, a single high-dose (0.2–1.6 g/kg) was found to have negative effects. [237] Similarily, nectandrin B could be promising in the treatment of NAFLD through its activation of Nrf2 / ARE pathways leading to the stimulation of antioxidant enzymes (HepG2 cells at 10 μg/mL). [238] Two neolignans (including one new) and three benzofuran lignans (two new (NL2-24 and NL2-25) and known dehydrodiconiferyl alcohol) isolated from *Eleutherococcus senticosus* exhibited selective inhibitory activity on protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values ranging from 19.2 ± 1.2 to 32.7 ± 1.2 μM. [239] PTP1B is a negative regulator of insulin signaling and therefore is associated with type 2 diabetes mellitus and obesity [239]. The novel dibenzylbutyrolactone isocubebinic ether (LM-8) from *Knema patentinervia* showed activity in the uptake of glucose by 3T3-L1 adipocytes when administered in concentrations up to 50 μg/mL and therefore could have an anti-diabetic role. [240]

3.10.1. DGAT (diacylglycerol acyltransferase)

A study by Farese et al showed the relationship between diacylglycerol acyltransferase (DGAT), an enzyme involved in the synthesis of triglycerides, and metabolic syndrome diseases like obesity and type II diabetes. There are two enzyme isoforms, DGAT1 and 2, which vary by location. The study showed knockout DGTAT1 mice that were fed a high fat diet were resistant to weight gain, had higher energy expenditure and increased sensitivity to insulin and leptin. [241] Thus DGAT inhibition is an indicative assay for the determination of active compounds against these diseases.

Four sesqui-lignans from *Acanthopanax senticosus* were found to have selective diacylglycerol acyltransferase (DGAT1/2) inhibitory activity. Three of which were selective for DGAT1 (SQL-6 and SQL-7) (IC_{50} = 61.1–79.1 μM) and one, acanthopanax A (SQL-5), selective for DGAT2 (IC_{50} = 93.2 μM). [242] The same group later isolated a furofuran, a furan, and four nor-aryl lignans from the same plant exhibiting selective DGAT1 inhibition (IC_{50} = 57.5 ± 1.3–141.5 ± 1.2 μM). [243] Five neolignans and two furan lignans (including 4,5′-dimethoxy-lariciresinol) were isolated from *Eleutherococcus senticosus* and found to have selective *in vitro* DGAT1/2 activities. The neolignans (NL2-29) presented DGAT1 inhibition (IC_{50} = 66.5 ± 1.3–111.1 ± 1.4 μM), while the furan lignans (L5-17) showed less active DGAT2 inhibition (IC_{50} = 133.9 ± 1.4–137.9 ± 1.1 μM). [244]

3.10.2. α-Glucosidase

The enzyme α-glucosidase plays a role in the glycemic control in animals by digesting carbohydrates such as starch and disaccharides to release glucose molecules. Excess release can lead to hyperglycemia leading to diseases such as type II diabetes. α-Glucosidase inhibitory assays are therefore indicative of possible anti-diabetic compounds. Lignans and neolignans with α-glucosidase inhibitory values are listed below: (ordered by activity, values over 100 μM were excluded for conciseness).

Cupressoside A (25.39 ± 3.97 μM) [200], (+)-pinoresinol (26.7 and 37.9 μM) [245], [246], Rebaneolignan A (NL3-34) (31.6 μM) [246], (+)-medioresinol (33.8 μM) [245], formosanol (35.3 μM) [247], tsugacetal (38.8 μM) [247], (+)-syringaresinol (28.5 and 40.8 μM) [246], [245], echinoutilin (42.1 ± 1.3 μM) [248], 7′R*-methoxy-7-*epi*-lariciresinol (L5-19) (42.9 μM) [247], lanceolatanin C (52.2 μM) [247], Rebaneolignan A (NL3-34) (55.0 μM) [246], neolignan from *Echinochloa utilis* (58.9 ± 3.7 μM) [248], (−)-balanophonin (68.1 μM) [245], (+)-lyoniresinol (76.5 μM) [245], oxomataresinol (79.1 μM) [247], (–)-simulanol (99.4 ± 8.4 μM) [248]

The neolignan selamoellenin A (NL3-24) exhibited potent protective effects (up to 10^{-5} μM) against high-glucose induced injury on human umbilical vein endothelial cells (HUVECs), indicating it may serve a role treating vascular endothelial dysfunction, the main pathophysiological process of diabetic vascular complications. [249] In another study arctigenin treatment (3–100 μM) showed decreased inflammation and improved vascular tone in human saphenous vein studies. [250] Magnobovatol, a neolignan from *Magnolia obovata* inhibits vascular smooth muscle cells (VSMCs) migration by reducing MMP-2 expression *via* platelet-derived growth factor (PDGF) and the ERK1/2 and Akt pathway. VSMCs migration is thought to play a key role in the pathogenesis of vascular diseases like atherosclerosis and post-angioplasty restenosis. [251]

rel-(7R, 8R, 7′R, 8′R)-manglisin E a furan lignan and three dibenzycyclooctadiene lignans ((–)-schisandrin C, schinlignan D and (+)-schisandrol B) isolated from *Schisandra chinensis* were found to be potent PCSK9 (proprotein convertase subtilisin-kexin type) mRNA expression inhibitors in HepG2 cell bioassays (IC_{50} = 3.15, 3.85, 0.36, and 1.10 μM, respectively). Decreased PCSK9 leads to the reduction of LDL-C levels and therefore has implications in the treatment of cardiovascular diseases, in particular those with familial hypercholesterolemia. [252] Leoligin, a furan-type lignan was shown to inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase leading to reduced cholesterol in ApoE−/− mice. [253] In a separate study using THP-1 macrophages leoligin was found to promote cholesterol efflux, [254] taken together these studies suggest it may have potential in treating atherosclerosis.

3.11. Protective

As was mentioned previously, lignans and neolignans are widely distributed secondary plant metabolites in higher plants. [19,20,255] As a consequence, food plants are literally filled with such compounds. Thus, it is interesting to study their influence on living organisms, because even though daily uptake in lignans and neolignans is small, it is continuous. Therefore the long term effect of these compounds on the organism might, as was showed for example in the case of flaxseed lignans on colon cancer, be beneficial [256].

3.11.1. Hepatoprotective

In a study where mice were induced with acute hepatitis arctigenin (administered at 10–20 μg/g body weight) was found exhibit hepatoprotective properties by reducing congestion and necroinflammation through immunosuppression while improving hepatic function. [257] The biphenylcyclooctadiene lignans micrantherin A, gomisin M2 and schizandrin from *Schisandra chinensis* showed moderate hepatoprotective effects in human liver carcinoma (HepG2) cells against paracetamol (APAP)-induced damage with increased survival rates of 43–44% at 10 μM (APAP alone = 38.7%). [258] 28 biphenylcyclooctadiene lignans (including newly isolated longipedlignans A – J) (L6-3 to L6-7) were isolated from *Kadsura longipedunculata* and several displayed heptaoprotective activities in the APAP assay, the most active

compounds were longipedlignan F (L6-5) and schiarisanrin B (survival rates of 52.2% and 50.2% at 10 μM, respectively vs APAP alone = 38.4%). [259] A new 8-O-4′ type neolignan (NL2-15) and 5 benzofuran neolignans (including 2 new – NL3-22 and NL3-23) from *Litsea cubeba* showed relative protection rates ranging 30.5–46.0% at 10 μM in the APAP assay (APAP alone = 0%). [171] While a new 8-O-4′ neolignan (NL2-23) from *Imperata cylindrical* showed 51.7% increased survival at 10 μM (APAP alone = 29.2%). [260] The biphenylcyclooctadiene lignans angeloylgomisin R and schisantherin A from *Schisandra pubescens* showed increased survival of QSG7701 cells against *D*-galactosamine (D-GalN)-induced cell injury (at 10 μM, 50.4 and 48.9%, respectively vs D-GalN alone = 37.5%). [261] In another study schisantherin A pretreatment (mice, 200 mg/kg body weight / 5 days) was found to protect against liver ischemia-reperfusion injury by attenuation of the mitogen-activated protein kinase (MAPK) pathway, and thus may have potential as a prophylactic for liver transplantation. [262] Myrislignan, a 8-O-4′ neolignan from nutmeg (*Myristica fragrans*) displayed potent protective activity (when administered to mice at 200 mg/ kg body weight) against thioacetamide-induced liver injury and was found to act *via* the modulation of PPARα. [263] Nectandrin B a furan lignan also from nutmeg ilicited heptatoprotective effects preventing oxidative damage through the activation of Nrf2 leading to the stimulation of antioxidant enzymes. Pretreatment of nectandrin B (29 μM) was found to protect HepG2 cells from *t*-butylhydroxyperoxide-induced apoptosis (49% cell viability *vs* 39% without treatment). [238] Furofuran 3,3′-bisdemethylpinoresinol and two furofuran sesquilignans 7*S*,8*S*-isoprincepin, 7*S*,8*S*-princepin from *Opuntia ficus-indica* showed protective effects (EC_{50} = 13.7–22 μM) on rat hepatocytes with alcohol-induced oxidative stress. They were found to act by decreasing levels of intracellular reactive oxygen species and conserving activity of anti-oxidative defense enzymes. [264]

3.11.2. Neuroprotective

Two novel 1,2-dioxetane containing neolignans (cinncassin I & J (NL4-5)), a novel furan lignan (cinnacassin H (L5-9)), and three known dibenzylbutyrolactone lignans (cinncassin A, A_3 & A_5) isolated from *Cinnamomum cassia* were found to have neuroprotective effects against tunicamycin-induced cytotoxicity in SH-SY5Y cells (EC_{50} = 21–75 μM). [265] In a neuroprotection assay using rat primary cortical neurons challenged with *N*-methyl-*D*-aspartate (NMDA), two 8-O-4′ neolignans (including 1 new (NL2-31)), and a new benzofuran lignan (callislignan B (NL3-43)) from *Adelostemma gracillimum* showed significant neuroprotective effect (up to 50% decreased neuronal death at 30 μM). [266] Neolignans obovatolignan A (NLM-14) and B (NL5-1) from *Magnolia obovate* showed protective effects against glutamate-induced oxidative stress in immortalized mouse hippocampal cells (HT22, EC_{50} = 18.1 ± 1.23 and 7.10 ± 0.78 μM, respectively). [151] Novel seqsui-neolignans pictalignans A – C (NLM-16 to NLM-18) also showed neuroprotective effects in HT-22 cells induced by L-glutamate with increased cell viabilities at 15 μM of ˜70%, 40% and 40% respectively compared to the negative control value of ˜30%. [267] Similiarily alashinol A showed substantial neuroprotective activity in the glutamate-induced injury in PC12 cell line. [157]

Several dibenzylcyclooctadiene lignans from *Shisandra sphenanthera* showed statistically significant neuroprotective activities at the low concentration of 3.2 nM against H_2O_2 and $CoCl_2$-induced SH-SY5Y cell injury models. In the $CoCl_2$ model lignans schisanwilsonin G, schisantherins D & E, tigloylgomisin P and epigomisin O were statistically significant, while in the H_2O_2 model, schisphenlignan L (L6-8), schisantherins A & E, schisanwilsonins B, D & G, gomisin G, tigloylgomisin P, and schisphenin E were significantly active. [184] In another study isolates from *Schisandra bicolor* var.*tuberculata* revealed the lignans, new (schibitubins C, H & I) and known ((−)-futokadsurin A, (+)-9′-hydroxygalbelgin, austrobailignan-6, oleiferin-F, (+)-dihydroguaiaretic acid and (−)-isootobaphenol) having statistically significant protective activity at 3.2 nM against $CoCl_2$-induced SHSY5Y cell death. While lignans new (schibitubins G (L1-8) & H (L4-1)) and known ((−)-nectandrin-A, oleiferin-F and (+)-dihydroguaiaretic acid) were active against H_2O_2-induced cell death. [183] Similarly, three neolignans (including rubuslin E (NL2-44)) from *Rubus idaeus* showed statistically significant *in vitro* neuroprotective effects on H_2O_2-induced SHSY5Y cell death at 25, 50, and 100 μM. [197] A separate study also on *Rubus idaeus* isolated three neuroprotective 8-O-4′ neolignans (NL2-10 and NL2-12) showing increased cell viability (69.1–80.6%) in comparison to the negative control (53.5%) in the H_2O_2-induced SH-SY5Y cell death model at 100 μM. [182] Chirally resolved (–)-Ideausin C (NL3-8) and (+)-Ideausin D (NL3-9) again from *Rubus ideaus* showed protective effects on H_2O_2-induced SH-SY5Y cell death at 100 μM (66.16% and 64.88% respectively vs 43.14% for the H_2O_2 control). [181]

Arctigenin was found to cross the blood brain barrier and have protective effects against kainate-induced excitotoxicity in neurons through inhibition of kainate-sensitive ionotropic glutamate receptors (significant kainate binding reduction was seen at 1 mM). Thus arctigenin or analogues of may have find use in the treatment of neural diseases including schizophrenia, autism and bipolar disorders. [268] In a separate study arctigenin showed protective effects in *in vivo* rat models with ischemic stroke and was found to act *via* SIRT1-dependent inhibition of NLRP3 inflammasome. [269]

The sesqui-lignans sambucasinol A–C (SQNL-7) from *Sambucus williamsii* were found to have stimulatory effects on nerve growth factor (NGF) secretion in C6 cells, indicating neuroprotective properties (Increased NGF secretion = 183.95 ± 2.63%, 153.99 ± 5.15%, 155.96 ± 5.15%, respectively). [124]

3.11.3. Cardioprotective

Novel tetracyclic neolignans miltiolignanolides A & B (LM-3) from *Salvia miltiorrhiza* exhibited potent *in vitro* cardioprotective activity increasing the cell viability of H9c2 cells from H_2O_2-induced cell death at 100 μM to 80% vs 20% for the negative control. [199] Alashinol C (L5-25) and conicaoside significantly increased the cell viability against oxygen glucose deprivation/re-oxygenation injury in H9c2 cardiomyocytes (80.7 ± 5.6%, 79.8 ± 0.7% respectively, vs 67.0 ± 4.2% of the model group). [157]

3.11.4. Renoprotective

Pretereatment of the biphenylcyclooctadiene lignan schisantherin A demonstrated protective properties towards renal tubular epithelial cells with hypoxia/reoxygenation (H/R) injury (at 20 μM, increased cell viability to ˜80% vs H/R control ˜35%). The mode of action is believed to be through the activation of PI3K/Akt signaling pathway. [270] In rat models of obstructive nephropathy arctigenin (1–3 mg / kg/ day) was found to suppress renal interstitial fibrosis decreasing inflammation, oxidative stress and tubular epithelial-mesenchymal transition. This suggesting its possible use in renal fibrosis treatment. [271]

3.11.5. Miscellaneous protective

Neolignans isolated from *Isodon japonicas* were found to be chemo preventive agents against benzo[a]pyrene-induced oxidative stress and DNA damage on the human fibroblasts fibrosarcoma cell line (HT1080). Novel benozofuran neolignan isodonoside IV (NL3-25) and two known 8-O-4 'neolignans showed modest recovery rates of 23.2%, 37.0%, 14.1%, respectively at 10 μM. [272]

A novel sesquiterpene neolignan (NL5-8) and known neolignans obovatol, honokiol and magnolol were isolated from *Manglietia hookeri* and found to have protective effects against UV-induced DNA damage in mice lymphocyte cells. In Olive Tail Moment (OTM) Comet assays at 6×10^{-6} μM they expressed activities of 7.34 ± 2.09, 50.94 ± 5.03, 16.45 ± 3.01 and 12.89 ± 1.94 μM, respectively. [273]

3.12. Miscellaneous biological activity

The biphenylcyclooctadiene lignans gomisin C & G from *Schisandra chinensis* commonly used in Chinese traditional medicine was found to inhibit human CYP3A4 and CYP3A5 and thus potentially may cause harmful drug-herb interactions. [274] Similarly the furan grandisin was found to inhibit human CYP450 (1A2, 2C9, 3A4/5, 2D6 and 2E1). [275]

A study showed rats fed on a mixture of sesamin/*epi*-sesamin showed increased hepatic fatty acid oxidation, this effect was improved when fed oils high in γ-linolenic acid. [276]

Secoisolariciresinol showed promise as a suppressive agent for morphological abnormalities caused by dioxins and related compounds in zebrafish embryos. [277]

A furofuran lignan from *Piper amalago* was found to have anxiolytic activity. Its activity was determined in an *in vitro* $GABA_A$ competitive binding assay where it displaced [^{3}H]-Flunitrazepam down to 1.17 ± 0.18% (> 95% decrease) receptor binding. [278] The biphenylcyclooctadiene lignan schisandrin B also displayed sedative and hypnotic effects and it is believed to be due to act through up-regulation of the expression of the $GABA_A$ receptor while also modulating the levels of GABA and GLu in blood and brain. [279] The biphenyl lignans (novel tzumin A (NL4-10) & B (NL4-11) and known magnolol and erythro-7′-methoxyl strebluslignanol) and neolignan TRAL-1 from *Sassafras tzumu* showed potent acetylcholine esterase inhibition with values of ranging from 1.81 ± 0.66 to 6.56 ± 1.58 μM. [280] While, in another study the dibenzylbutyrolactone lignan dolichanthin A (L2-4) from *Wikstroemia dolichantha* displayed weak anti-acetylcholine esterase activity of 15.8% at 100 μM. [281]

In a study where mice were subjected to traumatic brain injury sesamin was found to alleviate blood-brain barrier disruption and is believed to act on endothelial cells through anti-oxidative and anti-apoptotic effects. [282]

One study found syringaresinol to induce mitochondrial biogenesis in skeletal muscle cells. It was revealed to do this through binding and activating peroxisome proliferator-activated receptors (PPAR) with K_D and EC_{50} values of 27.62 ± 15.76 lM and 18.11 ± 4.77 μM, respectively. [283]

The furofuran lignan medioresinol was found to have potent *in vitro* anticomplementary activity (CH_{50} = 0.07 mM). [284]

The simple dibenzyl lignan nordihydroguaiaretic acid currently in clinical trials as an anti-cancer agent was found also to have adverse effects on spermatogenesis where 13.7% of sperm were found to have shortened tails or rounded heads. [285]

Three dihydrobenzofuran neolignans from *Selaginella moellendorfii* exhibited inhibition activity of rabbit platelet aggregation induced by ADP (IC_{50} = 80.84, 35.76, 42.47 μM) or collagen (IC_{50} = 146.70, 31.17, 24.57 μM) and therefore may find a use in prevention of blood clots. [286] In another study piperbonin A (NL2-18) isolated from *Piper bonii* displayed weak activity against rabbit platelet aggregation induced by thrombin. [287]

The biphenyl neolignan 4-*O*-methylhonokiol previously shown to have hair growth promoting effects was investigated and the mode of action was revealed to be through inhibition of transforming growth factor-β (TGF-β) induced cell cycle arrest via inhibition of canonical and noncanonical pathways in keratinocytes. [288]

Two coniferyl alcohols (*erythro* and *threo*- diasteriomers) isolated from soybeans were found to have pro-angiogenic properties, significantly enhancing *in vitro* endothelial cell proliferation and tube formation on an artificial extracellular matrix. [289]

4. Concluding remarks

In this review we have extensively covered the last three years of lignan and neolignan research covering ˜300 papers. We have categorized 413 novel compounds and summarized their biological activity by chemical structure (in the form of a compound table), and also separately discussed the biological activity of these novel compounds along with new-found activity of previously described compounds. We believe this review serves to aid, chemists and biologist alike, seeking to find a relationship between activity and structure, or from the isolation sources of these bioactive compounds.

We expect that the future research in the field of the medicinal chemistry will be highly influenced by some of the recently isolated and identified lignans and neolignans highlighted in this review. For us, the most promising are lactone-ring containing lignans possessing interesting antiprotozoal activity against malaria and leishmania parasites. These compounds possess great potential for further development since they are rather small (low molecular weight) but sufficiently complex to be further successfully modified. Further modification of these lignans with natural and artificial carbohydrates (derived from glucose and ribose) might increase/modify its bioavailability as well as alter their mode of action. As examples of such a situation can be seen for well-known podophyllotoxin/etoposide or the arctigenin/arctiin couples.

The second main domain for further research and possible future application in the field of lignans and neolignans is connected with the natural source of these compounds – plants. Most of the lignans and neolignans are present in substantial amounts in fruits, vegetables, and cereals. It was already shown that compounds like enterolactone possess interesting protective properties against colon and breast cancer. However, there are many more lignans and neolignans present in food whose properties, biological activity, and biotransformation within human body is still unknown. Additionally, in light of recent changes of climate (drought, soil salinity,…) the metabolomic profile of plants and thus nutrients might undergo to substantial changes. Thus novel and potentially interesting secondary metabolites might be formed. Overall, we believe that further study, identification, isolation and evaluation of the biological activity of lignans and neolignans is worth of pursuing and might bring us various novel drug-like structures and compounds with interesting protective properties.

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Notes

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Appendix A. Supplementary data

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One and Two-Carbon Homologation of Primary and Secondary Alcohols to Corresponding Carboxylic Esters Using β-Carbonyl BT Sulfones as a Common Intermediate

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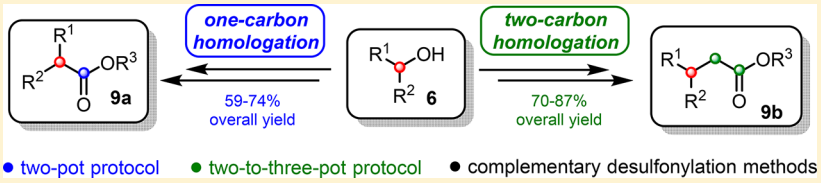
Supporting Information



ABSTRACT: Herein we report the efficient one- and two-carbon homologation of 1° and 2° alcohols to their corresponding homologated esters via the Mitsunobu reaction using β-carbonyl benzothiazole (BT) sulfone intermediates. The one-carbon homologation approach uses standard Mitsunobu C−S bond formation, oxidation and subsequent alkylation, while the two-carbon homologation uses a less common C−C bond forming Mitsunobu reaction. In this latter case, the use of β-BT sulfone bearing esters lowers the pK_a sufficiently enough for the substrate to be used as a carbon-based nucleophile and deliver the homologated β-BT sulfone ester, and this superfluous sulfone group can then be cleaved. In this paper we describe several methods for the effective desulfonylation of BT sulfones and have developed methodology for one-pot alkylation-desulfonylation sequences. As such, overall, a one-carbon homologation sequence can be achieved in a two-pot (four step) procedure and the two-carbon homologation in a two-pot (three step) procedure (three-pot; four step when C-acid synthesis is included). This methodology has been applied to a wide variety of functionality (esters, silyl ethers, benzyls, heteroaryls, ketones, olefins and alkynes) and are all tolerated well providing good to very good overall yields. The power of our method was demonstrated in site-selective ingenol C20 allylic alcohol two-carbon homologation.

INTRODUCTION

Elongation of the existing molecular framework by one or two functionalized carbon atoms is one of the most commonly encountered operations in organic synthesis. Such transformation is in general achieved in two to four (or more) synthetic transformations with regard of the oxidation state of the starting substrate and the desired product. Most commonly, carbonyl compounds are employed as starting materials within such transformations.[1] Among these, Arndt−Eistert homologation,[2] Wittig reaction,[3] or Julia olefination methods[4] are most commonly employed to successfully achieve such transformations.

However, when it comes to primary and secondary alcohols, in comparison only few options are available when the above-mentioned extensions are attempted.[5,6] The standard protocols used to extend an alcohol by one or two carbons requires in principle 3 distinct synthetic operations: (1) activation of the alcohol (transformation to a good-leaving group: GLG); (2) displacement of activated alcohol by C-nucleophile (e.g., cyanide for one carbon extension[7] or carbonyl enolate for two carbon extension[8]); and (3) transformation of the introduced functional group into the desired functionality (e.g., hydrolysis of nitrile to carboxylic acid; hydrolysis and monodecarboxylation of dimethylmalonate, etc.).

One can immediately recognize that in situ direct activation of alcohols would be beneficial for the overall transformation. In this context the Mitsunobu reaction is the first transformation that comes to mind.[9] Indeed, mild reaction conditions, wide substrate scope and high stereospecificity make the Mitsunobu reaction the reaction of the choice when it comes to the transformation of the C−O bond in primary and secondary alcohols to C−O, C−S, and C−N bond. Unfortunately when it comes to a C−C bond formation, the method is rather limited. The reason is that the Mitsunobu reaction requires rather acidic nucleophiles to proceed[10] (upper pK_a limit is ≤15;[11] but in general pK_a of 11 to 12 is required to achieve satisfactory results[12]). From the literature it is known

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that although bis(phenylsulfonyl)methane **1** (pK_a = 12.2)[13] is a suitable C-nucleophile for the Mitsunobu reaction,[14] sulfoesters **2** (pK_a ~ 13 to 13.5) or diesters 3 (pK_a ~ 16)[15] are rather poor ones. At this stage we speculated that the electrophilic properties of benzothiazole in BT-sulfonyl ester **4**[16,17] might diminish the pK_a value of β-alkoxycarbonyl BT-sulfones **4** to the suitable level allowing their use in the Mitsunobu reaction (Figure 1).

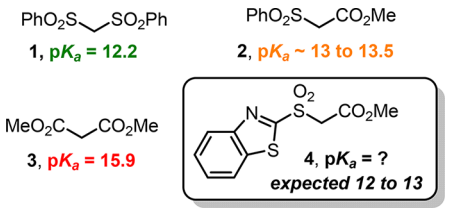
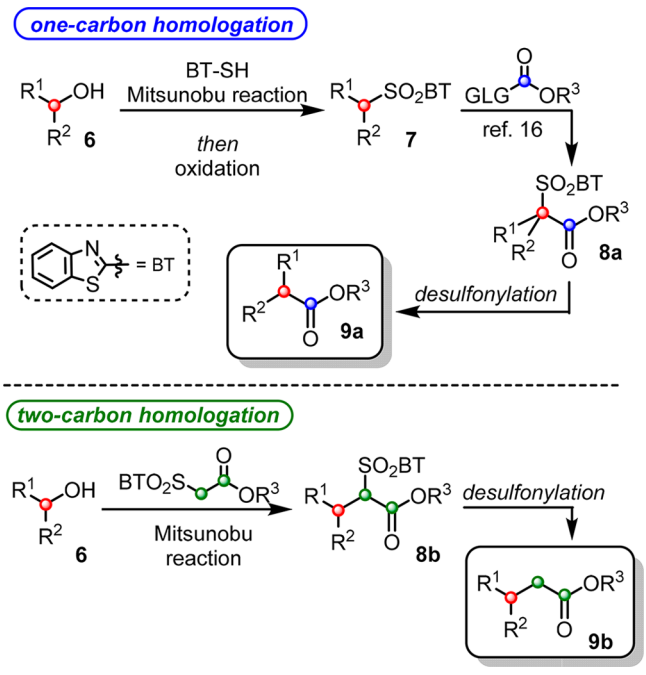


Figure 1. pK_a values of relevant C-acids used in the Mitsunobu reaction[13,15]

RESULTS AND DISCUSSION

Sometime ago we developed a short and efficient approach to β-carbonyl BT-sulfones,[18] and recently we have decided to extend their use as one and two carbon homologation-functionalization reagents (Scheme 1). In our design, common

Scheme 1. Planned One- and Two-Carbon Homologation Reaction Sequences



intermediate **8** of both homologation approaches plays a key role in our strategy, since we were expecting to develop the selective desulfonylation reaction of **8** to **9** under nucleophilic, radical or reductive-elimination conditions (Figure 2). Such approach should ensure wide functional group tolerance of the overall homologation transformations.

Since the first two steps of the one-carbon homologation approach have been already described,[18] our initial study was aimed to validate our homologation approaches focused on the Mitsunobu reaction required for the two-carbon homologation.

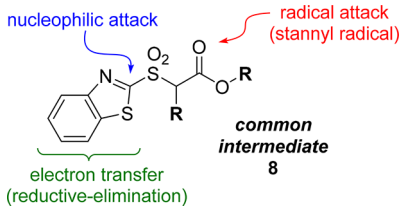


Figure 2. Three main approaches chosen to desulfonylate intermediate **8**.

Thus, the reaction of *tert*-butyl BT-sulfonyl acetate with primary alcohols was evaluated (Table 1, entry 1).[19] It was found that the use of ADDP (1.5 equiv) and PPh_3 (1.5 equiv) delivered the desired adduct in 87% yield (conditions A). Interestingly, when these conditions were applied to secondary or allylic alcohols (Table 1, entries 6 to 10), the desired product was obtained in very low yields. In these cases further reaction optimization revealed that the Mitsunobu reaction had to be carried out in the presence of DEAD instead of the ADDP-activating reagent (conditions B).[19]

Having secured the first step of the two carbon homologation process, we turned our attention to the desulfonylation step. First we decided to explore the reactivity of the nucleophilic attack to the C=N carbon atom in the BT group. Various nucleophilic reagents and conditions were screened[20] to accomplish the desired transformation and the combination of EtS^-Na^+/TFA were identified as the reagents of choice (Table 1, Method A).[21] In this one-pot two-step process the thiolate anion acts as the nucleophile that cleaves the BT-group. The resulting sodium sulfinate then, upon protonation with TFA, releases SO_2 and yields the desired ester **9** (Scheme 2).

Next we turned our attention to stannyl radical-mediated desulfonylation reaction. This approach is based on the work of Wnuk and Robbins[22] that previously reported selective and high yielding desulfonylation reaction of π-deficient heterocyclic sulfones. The desired transformation proceeded smoothly under "classical" nBu_3SnH (1.25 equiv)/AIBN (0.2 equiv)/benzene/80 °C conditions (Table 1, Method B) as well as catalytic Bu_3SnCl (0.10 equiv)/AIBN/PMHS/KF/H_2O/toluene/110 °C conditions[23] (Table 1, Method C) in very good to excellent yields.

Finally, the desulfonylation of the intermediate **8** was attempted using metal-mediated reductive conditions. Since many metals are known to promote desulfonylation of β-carbonyl phenyl sulfones,[24] we expected that the identification of the suitable conditions would be rather easy. Surprisingly this was not the case, and only SmI_2/MeOH and Zn_{dust}/AcOH systems were able to yield the desired desulfonylated products in good to excellent yields (Table 1, Methods D and E).[18] The disadvantage of the SmI_2/MeOH reduction conditions (Method D) is the use of large excess of SmI_2 (min 6.0 equiv) caused by the follow up reduction of the eliminated BT group to *N*-methyl-2-thioaniline **13** (Scheme 3). On the other hand, the transformation proceeds at low temperature and is rather fast. In the case of Zn_{dust}/AcOH, the reaction proceeds at RT in a mixture of THF/AcOH (5:1, V/V), and does not require anoxic or anhydrous conditions, making it more suitable for practical large-scale synthesis.

Having found suitable desulfonylation conditions our attention turned to a one-carbon homologation sequence. Since the synthesis of β-carbonyl BT-sulfones **8** has already

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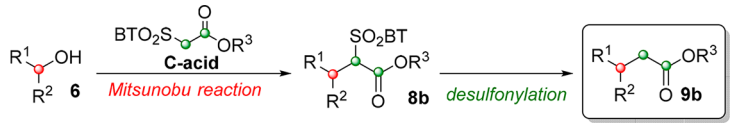
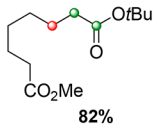
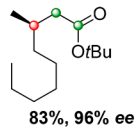
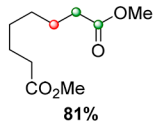
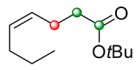
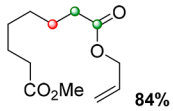
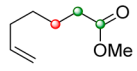
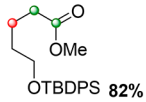
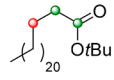
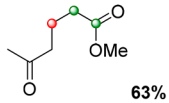
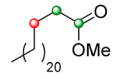
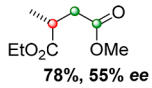
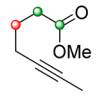
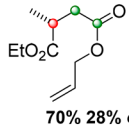
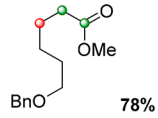
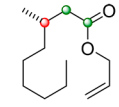
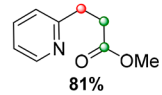
Table 1. Two-Carbon Homologation Two-Pot Process: Mitsunobu Reaction Followed by Desulfonylation



Entry	Mitsunobu reaction[a,b]	Desulfonylation method[b,c]	Product Overall yield[b,d]	Entry	Mitsunobu reaction[a,b]	Desulfonylation method[b,c]	Product Overall yield[b,d]
1	Cond. A (87%) Cond. B (53%)	**A** (44%) **B** (88%) **C** (81%) **D** (94%) **E** (78%)	 **82%**	9	Cond. A (18%) Cond. B (88%)	**A** (77%, 90% *ee*) **B** (94%, 95% *ee*) **C** (91%, 96% *ee*) **D** (81%, 96% *ee*) **E** (85%, 96% *ee*)	 **83%, 96% *ee***
2	Cond. A (89%) Cond. B (46%)	**A** (49%) **B** (87%) **C** (91%) **D** (85%) **E** (76%)	 **81%**	10	Cond. A (26%) Cond. B (86%)	**A** (35%) **B** (82%) **C** (83%) **D** (76%) **E** (74%)	 **71%**
3	Cond. A (91%) Cond. B (42%)	**A** (58%) **B** (87%) **C** (85%) **D** (92%) **E** (82%)	 **84%**	11	Cond. A (89%) Cond. B (46%)	**A** (83%) **B** (92%) **C** (90%) **D** (89%) **E** (89%)	 **82%**
4	Cond. A (88%) Cond. B (49%)	**A** (76%) **B** (93%) **C** (90%) **D** (86%) **E** (89%)	 **82%**	12	Cond. A (91%) Cond. B (62%)	**A** (45%) **B** (89%) **C** (93%) **D** (95%) **E** (69%)	 **87%**
5	Cond. A (78%) Cond. B (32%)	**A** (54%) **B** (81%) **C** (80%) **D** (71%) **E** (72%)	 **63%**	13	Cond. A (88%) Cond. B (56%)	**A** (34%) **B** (82%) **C** (84%) **D** (77%) **E** (71%)	 **72%**
6	Cond. A (11%) Cond. B (87%)	**A** (65%, 24% *ee*) **B** (90%, 55% *ee*) **C** (88%, 56% *ee*) **D** (90%, 55% *ee*) **E** (78%, 56% *ee*)	 **78%, 55% *ee***	14	Cond. A (91%) Cond. B (62%)	**A** (72%) **B** (88%) **C** (89%) **D** (93%) **E** (78%)	 **85%**
7	Cond. A (12%) Cond. B (79%)	**A** (42%, 12% *ee*) **B** (88%, 28% *ee*) **C** (81%, 27% *ee*) **D** (76%, 29% *ee*) **E** (73%, 28% *ee*)	 **70% 28% *ee***	15	Cond. A (78%) Cond. B (31%)	**A** (63%) **B** (89%) **C** (81%) **D** (82%) **E** (67%)	 **78%**
8	Cond. A (15%) Cond. B (83%)	**A** (73%, 71% *ee*) **B** (90%, 75% *ee*) **C** (89%, 75% *ee*) **D** (72%, 75% *ee*) **E** (76%, 75% *ee*)	 **75%, 75% *ee***	16	Cond. A (12%) Cond. B (92%)	**A** (72%) **B** (81%) **C** (84%) **D** (83%) **E** (71%)	 **81%**

[a]Conditions A: alcohol **6** (1.0 equiv), **C-acid** (1.2 equiv), ADDP (1.5 equiv), PPh_3 (1.5 equiv), toluene, 0 °C to RT, 12 h; Conditions B: alcohol **6** (1.0 equiv), **C-acid** (1.2 equiv), DEAD (1.5 equiv), PPh_3 (1.5 equiv), toluene, 0 °C to RT, 6 h. [b]Refers to pure isolated compounds. [c]Method A: EtS^-Na^+ (2.0 equiv, CH_2Cl_2, 0 °C, 1 h, *then* TFA (20 equiv), 2 h; Method B: nBu_3SnH (1.25 equiv), AIBN (0.2 equiv), benzene, 80 °C, 1 h; Method C: nBu_3SnCl (0.10 equiv), AIBN (0.03 equiv), PMHS (0.1 mL/mmol KF), KF (2.0 equiv), toluene/H_2O = 4/1 (V/V), 110 °C, 3 h. Method D: SmI_2 (6.5 equiv), MeOH (50 equiv), THF, −78 °C, 30 min; Method E: Zn_{dust} (5.0 equiv), THF/AcOH = 5:1 (V/V), 0 °C to RT, 8 h. [d]Yield over two steps related to the highest yielding Mitsunobu step and desulfonylation method.

been reported,[25] we have focused on the desulfonylation conditions (Table 2). At this stage we wished to develop a two-pot (four steps) protocol suitable for the direct transformation of alcohol **6** to ester **9a** (Table 2). The first "one-pot" transformation of alcohol **6** to BT-sulfone **7** via Mitsunobu reaction/oxidation sequence is well documented in the literature and commonly used in the context of total syntheses.[26] On the other hand the second part, one-pot two step procedure combining already known base-promoted coupling of sulfone **7** with carbonylating agent[18] with desulfonylation had to be developed. As a desulfonylating agent we decided to employ the Zn/AcOH system. Gratifyingly, the coupling adduct intermediate, upon the AcOH quench and subsequent Zn_{dust} addition, smoothly desulfonylated to yield the desired ester in good to very good overall yields (Table 2). Overall, the one-carbon homologation

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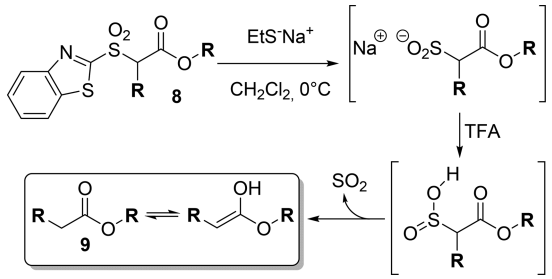
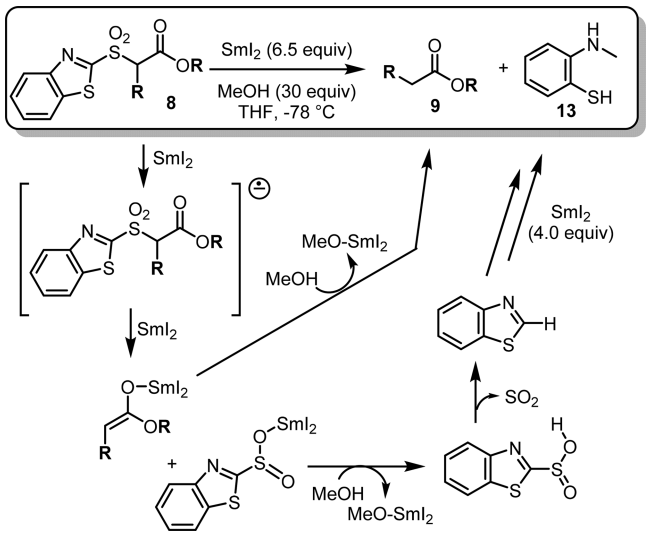
Scheme 2. EtS$^-$Na$^+$/TFA Promoted Desulfonylation Reaction[a]



[a]EtS$^-$Na$^+$, sodium ethanthiolate; TFA, trifluoracetic acid.

Scheme 3. SmI_2/MeOH Promoted Reductive Desulfonylation: Proposed Reaction Mechanism



reaction sequence can be easily achieved in a two-pot operationally simple protocol and yields the desired homologated products in good to excellent overall yields.

Finally the two important aspects of the two homologation sequences should be discussed, functional group tolerance and stereoselectivity. First, it was observed that radical-based (Methods B and C) and metal-mediated (Methods D and E) reductive desulfonylation conditions yields, in general, the desired esters in higher overall yields when compared to EtS$^-$Na$^+$/TFA (Method A) system (Table 1, Table 2). From the functional group point-of-view, esters (Table 1, entries 1, 2, 3, 6 and 7), TBDPS ether (Table 1, entry 4; Table 2, entry 5), benzyl ether (Table 1, entry 15), ketone (Table 1, entry 5), olefins (Table 1, entries 10 and 11; Table 2, entries 6 and 7), (hetero)aryls (Table 1, entry 16; Table 2, entries 1 and 2), and alkynes (Table 1, entry 14; Table 2, entry 8) are tolerated. From the stereoselectivity viewpoint, it was observed that the Mitsunobu reactions do not proceed with full inversion of the secondary alcohol and partial erosion of the inverted stereogenic center is observed (Table 1, entries 8 and 9). If ethyl lactate was used as the starting secondary alcohol, stereodegradation was even more significant (Table 1, entries 6 and 7). It seems that the degree of the stereo integrity strongly depends on the steric requirements of the C-acid. Additional epimerization of the alcohol-originated stereogenic center was also observed during the EtS$^-$Na$^+$/TFA promoted desulfonylation reaction (Table 1, entries 6 to 9).[27]

Finally, we were interested in evaluating the robustness and site-selectivity of our method. To evaluate the robustness, 2.52 g of *tert*-butyl tetracosonoate was prepared in 3 steps and 67% overall yield from the corresponding alcohol (Scheme 4).

To address the second challenge, two-carbon homologation of natural product ingenol (**14**) was attempted (Scheme 5). Recently, we have disclosed that C20 hydroxy group in **14** can be selectively (only one out of four hydroxy groups) transformed into its acetate.[36] Thus, we were interested if our C-acids could also be used in this reaction as nucleophiles. Gratifyingly, using our method the C20 hydroxy group was selectively in two steps and 45% overall yield transformed into the corresponding ingenol derivative **16**.

CONCLUSIONS

In conclusion, we have developed a new synthetic strategy allowing one and two-carbon homologation of primary and secondary alcohols in good to very good overall yields. The strong point of the overall processes is the desulfonylation reaction that could be carried out using several chemically different reaction conditions. In both cases, ester (one-carbon homologation) or alkyl acetate (two-carbon homologation) groups could be successfully introduced. Thus, developed methods are an alternative to already existing one- and two-carbon homologation/functionalization methods, and we believe that due to their versatile character they will soon find use in total synthesis of complex natural products.

EXPERIMENTAL SECTION

General Information. All reactions were performed in round-bottom flasks fitted with rubber septa using the standard laboratory techniques. Reactions sensitive to air and/or moisture were performed under a positive pressure of argon. Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with silica gel (silica gel 60 F254). TLC plates were visualized by exposure to ultraviolet light and then were stained by submersion in basic potassium permanganate solution or in ethanolic phosphomolybdic acid solution followed by brief heating. Flash-column chromatography was carried out on silica gel (60 Å, 230−400 mesh) using Petroleum ether/EtOAc solvent mixtures (for appropriate ratios see experimental part). All reagents were obtained from commercial suppliers and were used without further purification. Diethyl azodicarboxylate (DEAD, 97%) was purchased from Alpha Aesar. Dry solvents were obtained using standard drying protocols: THF was distilled under argon from sodium benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2; and CH_3CN from P_2O_5. Sulfones **7** and **8a** (Table 2), and **C-acids** used in two-carbon homologation protocol (Table 1) were prepared using the previously published protocols.[18] ^1H and ^{13}C spectra were recorded at 500, 400, or 300 MHz (for ^1H NMR), and 125, 100, or 75 MHz (for ^{13}C NMR), respectively, at 25 °C in $CDCl_3$. Chemical shifts (δ ppm) ^1H NMR are reported in a standard fashion with relative to the remaining $CHCl_3$ present in $CDCl_3$ (δH = 7.27 ppm). ^{13}C NMR chemical shifts (δ ppm) are reported relative to $CHCl_3$ (δC = 77.23 ppm, central line of triplet). Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quintet (quint), quintet of doublet (quintd), and multiplet (m), and coupling constants (J) are reported in Hz. Analysis and assignments were made by comparison with literature spectroscopic data or using 2D-COSY, HSQC, HMBC, 2D-NOESY and NOEdiff experiments. HRMS data were obtained using quadrupole/ion trap mass analyzer. Melting points (mp) were tested on a capillary melting point apparatus. The *ee* of products was determined by chiral GC using Chiraldex γ-TA capillary column, and Chiraldex β-PM column, respectively. The major enantiomer was determined with help of optical rotation measurement.

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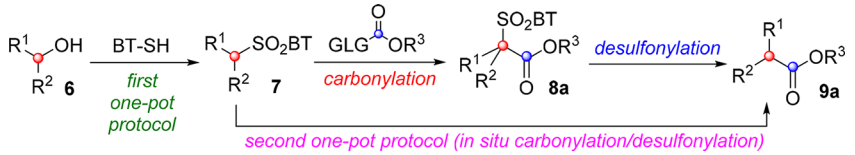
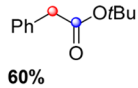
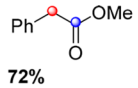
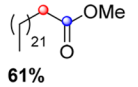
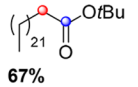
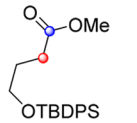
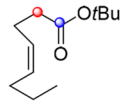
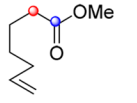
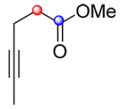
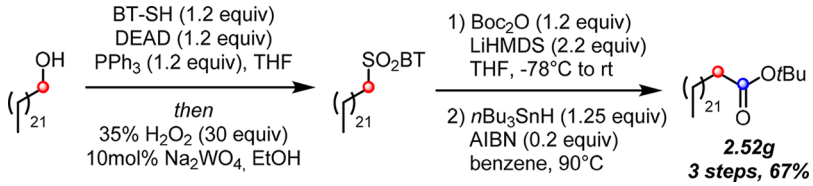
Table 2. One-Carbon Homologation via a Two-Pot Process: Mitsunobu Reaction Followed by Desulfonylation



Entry	1st one-pot protocol[a,b] / 2nd one-pot protocol[b,d]	Carbonylation step[b,c] (GLG group)	Desulfonylation method[b,d]	Product Overall yield[b,e]
1	96% / 62%	91% (OBoc)	**A** (65%) **B** (85%) **C** (75%) **D** (94%) **E** (67%)	 **60%**
2	96% / 75%	93% (CN)	**A** (45%) **B** (81%) **C** (80%) **D** (86%) **E** (67%)	 **72%**
3	89% / 69%	93% (CN)	**A** (34%) **B** (82%) **C** (84%) **D** (77%) **E** (71%)	 **61%**
4	89% / 75%	90% (OBoc)	**A** (45%) **B** (89%) **C** (93%) **D** (95%) **E** (69%)	 **67%**
5	90% / 82%	93% (CN)	**A** (76%) **B** (93%) **C** (90%) **D** (86%) **E** (89%)	 **74%**
6	78% / 75%	87% (OBoc)	**A** (35%) **B** (82%) **C** (83%) **D** (76%) **E** (74%)	 **59%**
7	89% / 75%	94% (CN)	**A** (83%) **B** (92%) **C** (90%) **D** (89%) **E** (89%)	 **67%**
8	86% / 71%	94% (CN)	**A** (72%) **B** (88%) **C** (89%) **D** (93%) **E** (78%)	 **61%**

[a]Conditions: alcohol **6** (1.0 equiv), **BT-SH** (1.2 equiv), DEAD (1.2 equiv), PPh_3 (1.2 equiv), THF, 0 °C to RT, 12 h *then* $Na_2WO_4{\cdot}2H_2O$ (0.1 equiv), 30% aq. H_2O_2 (30 equiv), EtOH, 0 °C to RT, 12 h. [b]Refers to pure isolated compounds. [c]Conditions: sulfone (1.0 equiv), carbonyl reagent (1.05 equiv), LiHMDS (2.2 equiv), THF, −78 °C, 30 min. [d]Method A: EtS^-Na^+ (2.0 equiv, CH_2Cl_2, 0 °C, 1 h, *then* TFA (20 equiv), 2 h; Method B: $n$$Bu_3SnH$ (1.25 equiv), AIBN (0.2 equiv), benzene, 80 °C, 1 h; Method C: $n$$Bu_3SnCl$ (0.10 equiv), AIBN (0.03 equiv), PMHS (0.1 mL/mmol KF), KF (2.0 equiv), toluene/H_2O = 4/1 (V/V), 110 °C, 3 h. Method D: SmI_2 (6.5 equiv), MeOH (30 equiv), THF, −78 °C, 30 min; Method E: Zn_{dust} (5.0 equiv), THF/AcOH = 5:1 (V/V), 0 °C to RT, 8 h. [e]Yields obtained over two one-pot protocols.

Scheme 4. Multigram Scale Synthesis of *tert*-Butyl Tetracosonoate



One-Carbon Homologation Protocol. General Procedure for Alcohol 6 to Sulfone 7 Transformation. A solution of benzo[*d*]-thiazol (BT-SH) (1.2 mmol, 1.2 equiv), PPh_3 (1.2 mmol, 1.2 equiv) and alcohol **6** (1.0 mmol, 1.0 equiv) in THF (10 mL, 0.1 M) was cooled to 0 °C and DEAD (1.2 mmol, 1.2 equiv) was added. The resulting solution was allowed to warm to rt and stirred for 5−8 h. The resulting solution was diluted with EtOH (25 mL), cooled to 0 °C and $Na_2WO_4{\cdot}2H_2O$ (0.1 mmol, 0.1 equiv) in one portion. After 5 min at 0 °C, an aqueous 35% solution of H_2O_2 (30.0 mmol, 30 equiv) was added dropwise with a use of pipet Pasteur. The resulting yellowish solution was allowed to warm to rt and stirred at rt for 10 h. Water (50 mL) was added and the whole mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on SiO_2 using the appropriate eluting system.

*2-(Benzylsulfonyl)benzo[d]thiazole (**7**, Table 2, Entries 1 and 2).*[19] The residue was purified by flash column chromatography (petroleum ether:EtOAc = 10:1 → 2:1) yielding the desired sulfone (0.278 g, 96%). mp = 112−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 1H, H-2), 7.23−7.38 (m, 5H), 7.56−7.75 (m, 2H), 7.96 (d, J = 8.0 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.2, 122.5, 125.7, 126.5, 127.9, 128.2, 129.1, 129.4, 131.3, 137.3, 152.8, 165.4; MS (CI), m/z (%) 290 (43) $[M]^+$. Anal. Calcd for $C_{14}H_{11}NO_2S_2$: C, 58.11; H, 3.83; N, 4.84. Found: C, 58.14; H, 3.80; N 4.86.

*2-(Tricosanylsulfonyl)benzo[d]thiazole (**7**, Table 2, Entries 3 and 4).*[19] Purification by flash chromatography (petroleum ether:EtOAc = 50:1 → 10:1) yielding the desired sulfone (0.459 g, 89%). mp = 35−36 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 6.8 Hz, 3H, H-3), 1.05−1.79 (m, 40H), 1.88 (dt, J = 12.1, 7.6 Hz, 2H, H-2), 3.51 (dd, J = 9.1, 7.0 Hz, 2H, H-1), 7.62 (quintd, J = 7.2, 1.4 Hz, 2H), 8.03 (dd, J =

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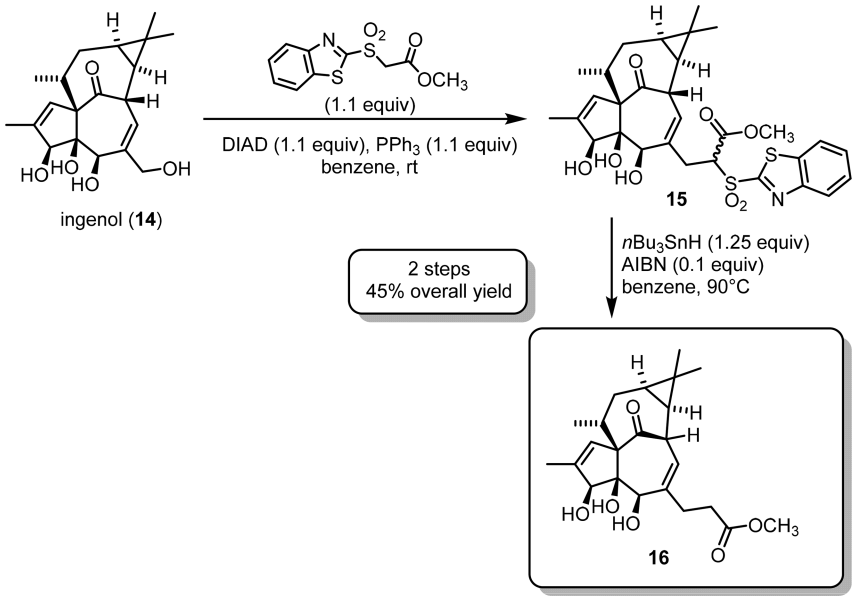
Scheme 5. Selective C20 Hydroxy Group Two-Carbon Homologation of Ingenol (14)



7.2, 1.7 Hz, 1H), 8.23 (dd, J = 7.3, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (C-6), 22.9, 26.4, 27.1, 29.2, 29.3, 29.6, 29.8, 29.9, 31.5, 54.8 (C-1), 122.4, 125.6, 127.8, 128.2, 136.9, 152.9, 166.1 (C-4); MS (APCI), m/z (%) 522 (100) $[M]^+$. Anal. Calcd for $C_{30}H_{51}NO_2S_2$: C, 69.05; H, 9.85; N, 2.68. Found: C, 69.07; H, 9.84; N, 2.69.

*2-(Hex-5-en-1-ylsulfonyl)benzo[d]thiazole (**7**, Table 2, Entry 7).*[19] Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1) yielded the desired sulfone (0.250 g, 89%). mp = 42−43 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.36 (m, 2H), 1.67 (dt, J = 14.6, 6.7 Hz, 2H), 2.34 (dt, J = 12.1, 7.6 Hz, 2H, H-5), 3.48 (dd, J = 9.3, 7.0 Hz, 2H, H-2), 4.92−5.08 (m, 2H, H-7), 5.65 (ddt, J = 16.1, 11.2, 6.4 Hz, 1H, H-6), 7.63 (quintd, J = 7.2, 1.3 Hz, 2H), 8.01 (dd, J = 7.2, 1.7 Hz, 1H), 8.22 (dd, J = 7.3, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 28.7, 31.5, 55.6, 115.8, 122.54, 125.63, 127.83, 128.18, 133.8, 136.95, 152.93, 166.1; MS (APCI), m/z (%) 282 (100) $[M]^+$. Anal. Calcd for $C_{13}H_{15}NO_2S_2$: C, 55.49; H, 5.37; N, 4.98. Found: C, 55.51; H, 5.38; N, 4.97.

*2-(Hex-3-yn-1-ylsulfonyl)benzo[d]thiazole (**7**, Table 2, Entry 8).*[19] Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1) yielded the desired sulfone (0.216 g, 86%). mp = 40−41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (t, J = 2.3 Hz, 3H, H-6), 2.03−2.23 (m, 2H, H-2), 2.38−2.52 (m, 2H, H-3), 3.25 (t, J = 8.2 Hz, 2H, H-2), 7.64 (quintd, J = 7.2, 1.5 Hz, 2H), 8.03 (dd, J = 7.2, 2.1 Hz, 1H), 8.26 (dd, J = 7.4, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 21.2, 25.8, 60.6, 75.9, 78.2, 122.5, 125.9, 128.0, 128.5, 137.4, 152.8, 164.2 (C-1); MS (APCI), m/z (%) 280 (100) $[M]^+$. Anal. Calcd for $C_{13}H_{13}NO_2S_2$: C, 55.89; H, 4.69; N, 5.01. Found: C, 55.90; H, 4.69; N, 5.00.

General Procedure for Sulfone 7 to Ester 9a Transformation. To a solution of sulfone 7 (1.0 mmol, 1.0 equiv) in THF (10 mL, 0.1 M) cooled to −78 °C was added LiHMDS (2.2 mL, 2.2 mmol, 2.2 equiv; 1.0 M sol. in THF). After 30 s acylating reagent (1.1 mmol, 1.1 equiv) in THF (1.1 mL, 1.0 M to acylating reagent) was added. The resulting mixture was stirred at −78 °C for an additional 30 min before it was allowed to warm to 0 °C (exchange of cooling baths). After 10 min at 0 °C, AcOH (5 mL, 0.2 M to BT-sulfone) was added and the resulting mixture was allowed to stir at RT for an additional hour. Zinc dust (0.327 g, 5.0 mmol, 5.0 equiv) was added and the resulting mixture was stirred at RT for 8 h. The mixture was diluted with EtOAc (50 mL), filtered through a pad of Celite and the filter cake was washed with an additional EtOAc (3× 25 mL). The combined organic filtrates were washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and evaporated under reduced pressure to provide the crude product.

General Procedure for Two Step Sulfone 7 to ester 9a Transformation. *Reaction of the BT-Sulfone 7 with Carbonylating Reagent.* A solution of BT-sulfone 7 (1.0 mmol, 1.0 equiv) in THF (5 mL, 0.20 M) was cooled to −78 °C and LiHMDS (1.0 M sol. in THF) (2.2 mL, 2.2 mmol, 2.2 equiv) was added dropwise. Immediately after the addition, a solution of alkoxy carbonylating agent (Boc_2O or methyl cyanoformate (Mander's reagent) or allyl cyanoformate) (1.1 mmol, 1.1 equiv) in THF (0.5 mL) was added. The resulting mixture was stirred at −78 °C for 30 min, allowed to warm to 0 °C within 1 h and stirred at 0 °C for a further 30 min before sat. aq. sol. of NH_4Cl (15 mL) was added. The whole mixture was extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with brine (50 mL), dried over $NaSO_4$, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 with appropriate solvent system to yield desired β-carbonyl sulfone **8a**.

General Protocols for Desulfonylation Reaction. *Method A.*[21] A solution of BT-sulfone ester **8** (0.5 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL, 0.1 M) was cooled to 0 °C and EtS^-Na^+ (0.084 g, 1.0 mmol, 2.0 equiv) was added. The resulting mixture was stirred at 0 °C for 1 h and trifluoroacetic acid (0.766 mL, 10.0 mmol, 20 equiv) was added. Stirring was continued for the next 2 h prior to toluene (10 mL) addition. The resulting mixture was evaporated under reduced pressure to provide the crude product.

Method B.[22] To a solution of BT-sulfone ester **8** (0.1 mmol, 1.0 equiv) in benzene (0.5 mL, 0.2 M) was added nBu$_3$SnH (0.336 mL, 0.125 mmol, 1.25 equiv) and the resulting mixture was stirred at rt for 5 min. AIBN (0.003 g, 0.02 mmol, 0.2 equiv) was added and the mixture was placed on a preheated oil bath (90 °C). The mixture was kept at 90 °C (external) for 60 min before it was allowed to cool to RT (heating bath removed). CH_3CN (10 mL) was added and the reaction mixture was extracted with n-pentane (3× 15 mL). The acetonitrile layer was dried over $MgSO_4$, filtered and evaporated to dryness to provide the crude product.

Method C.[23] Argon was bubbled (5 min) through a solution of BT-sulfone ester **8** (0.25 mmol, 1.0 equiv), Bu_3SnCl (0.007 mL, 0.025 mmol, 0.1 equiv), and AIBN (0.002 g, 0.008 mmol, 0.03 equiv) in toluene (2 mL) for 15 min. The solution was heated at reflux and PMHS (0.05 mL) and KF (0.03 g, 0.5 mmol, 2.0 equiv; in H_2O (0.5 mL)) were sequentially added in three portions (t = 0 min, 1 h and 2 h). After 3 h, the reaction mixture was cooled to RT and volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (10 mL) and sat. aq. $NaHCO_3$ (10 mL). Resulting layers were separated and the aqueous layer was extracted with EtOAc (2 × 10

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mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, and evaporated to dryness to provide the crude product.

Method D. A solution of SmI_2 (6.25 mL, 0.625 mmol, 6.25 equiv; 0.1 M solution in THF) was placed under inert atmosphere and MeOH (0.202 mL, 5.0 mmol, 50 equiv) was added. The resulting mixture was cooled to −78 °C (dry ice/acetone) and BT-sulfone ester **8** (0.1 mmol, 1.0 equiv) in dry THF (1 mL) was added. If the typical deep blue color of SmI_2 faded upon the sulfone solution addition, additional SmI_2 was added until the deep blue color persisted. The resulting mixture was stirred at −78 °C for an additional 15 min before the sat. aq. NH_4Cl (10 mL) was added. The resulting phases were separated and the water layer was extracted with EtOAc (3× 15 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (10 mL), brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to provide the crude product.

Method E. To a solution of BT-sulfone ester **8** (0.5 mmol, 1.0 equiv) in THF (5 mL, 1.0 M) was added zinc dust (0.163 g, 2.5 mmol, 5.0 equiv), the mixture was cooled to 0 °C and AcOH (1.0 mL) was added. The reaction was allowed to warm and stirred at RT for 8 h. The mixture was diluted with EtOAc (25 mL), filtered through a pad of Celite and the filter cake was washed with EtOAc (3× 20 mL). The combined filtrates were washed with brine (10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to provide the crude product.

*tert-Butyl 2-phenylacetate (**9**, Table 2, Entry 1).*[28] The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1 → 20:1) and yielded the targeted compound as colorless oil (R_f = 0.94, petroleum ether:EtOAc = 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.56 (s, 2H), 7.11−7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 42.8, 80.9, 122.0, 123.7, 125.7, 126.3, 126.9, 128.6, 129.3, 134.8, 154.0, 171.0; MS (CI$^+$), *m*/*z* (%) 193 (38) [M + H]$^+$; HRMS (ESI) calcd for $C_{12}H_{16}NaO_2$ [M + Na]$^+$: 215.1043, found 215.1044.

*Methyl 2-phenylacetate (**9**, Table 2, Entry 2).*[29] The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1 → 20:1) and yielded the targeted compound as colorless oil (R_f = 0.88, petroleum ether:EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 2H), 3.69 (s, 3H), 7.14−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.2, 52.1, 127.1, 128.6, 129.3, 134.0, 172.1; HRMS (ESI) calcd for $C_9H_{10}NaO_2$ [M + Na]$^+$: 173.0568, found 173.0573. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.01; H, 6.70.

*tert-Butyl tetracosanoate (**9**, Table 2, Entry 4; Table 1, Entry 12).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1) and yielded the targeted compound as white solid (R_f = 0.91, petroleum ether:EtOAc = 20:1). mp = 67−69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.7 Hz, 3H), 1.26 (s, 40H), 1.45 (s, 9H), 1.51−1.67 (m, 2H), 2.20 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 25.4, 28.3, 29.3, 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 32.2, 35.9, 80.1, 173.5; IR (film) ν^{-1} 3008 (w), 2982 (w), 2925 (m), 2853 (m), 1724 (m), 1467 (m), 1369 (m), 1155 (s), 908 (s), 729 (s); MS (APCI$^+$), *m*/*z* (%) 426 (12) [M + H]$^+$. Anal. Calcd for $C_{28}H_{56}O_2$: C, 79.28; H, 13.38. Found: C, 78.86; H, 13.38.

*Methyl tetracosanoate (**9**, Table 2, Entry 3; Table 1, Entry 13).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1) and yielded the targeted compound as white solid (R_f = 0.91, petroleum ether:EtOAc = 4:1). mp = 58−59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.26 (s, 40H), 1.62 (q, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 25.2, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 32.2, 34.3, 51.6, 174.5; IR (film) ν^{-1} 2921 (s), 2946 (s), 1749 (m), 1477 (m), 1467 (w), 1169 (m), 904 (s); MS (APCI$^+$), *m*/*z* (%) = 383 (100) [M]$^+$. Anal. Calcd for $C_{25}H_{50}O_2$: C, 78.47; H, 13.17. Found: C, 78.53; H, 13.24.

*1-(tert-Butyl) 8-methyl octanedioate (**9**, Table 1, Entry 1).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1) and yielded the targeted compound as colorless viscous oil (R_f = 0.71, petroleum ether:EtOAc = 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (dq, *J* = 7.3, 3.4 Hz, 4H), 1.44 (s, 9H), 1.51−1.70 (m, 4H), 2.20 (t, *J* = 7.4 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.1, 28.3, 28.9, 29.0, 34.2, 35.7, 51.7, 80.2, 173.4, 174.4; IR (film) ν^{-1} 2977 (w), 2948 (w), 2932 (m), 1733 (s), 1458 (m), 1434 (w), 1369 (m), 848 (w); MS (APCI$^+$), *m*/*z* (%) = 245 (27) [M + H]$^+$. Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 64.22; H, 9.95.

*Dimethyl octanedioate (**9**, Table 1, Entry 2).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1 → 4:1) and yielded the targeted compound as colorless viscous oil (R_f = 0.73, petroleum ether:EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (quint, *J* = 3.7 Hz, 4H), 1.62 (t, *J* = 7.3 Hz, 4H), 2.30 (td, *J* = 7.3, 2.2 Hz, 4H), 3.66 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 28.9, 34.1, 51.7, 174.3; IR (film) ν^{-1} 2948 (w), 2929 (w), 1739 (s), 1436 (m); MS (APCI$^+$), *m*/*z* (%) 203 (55) [M + H]$^+$. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.67; H, 9.21.

*1-Allyl 8-methyl octanedioate (**9**, Table 1, Entry 3).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1) and yielded the targeted compound as colorless oil (R_f = 0.68, petroleum ether:EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (quint, *J* = 3.6 Hz, 4H), 1.53−1.76 (m, 4H), 2.31 (q, *J* = 7.8 Hz, 4H), 3.65 (d, *J* = 2.2 Hz, 3H), 4.53−4.62 (m, 2H), 5.22 (dt, *J* = 10.4, 1.5 Hz, 1H), 5.30 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.80−6.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 28.9, 34.2, 34.3, 51.6, 65.1, 118.3, 132.5, 173.5, 174.3; IR (film) ν^{-1} 2949 (w), 2926 (w), 1732 (s), 1435 (m); MS (APCI$^+$), *m*/*z* (%) 229 (100) [M + H]$^+$. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.96; H, 9.04.

*Methyl 5-((tert-butyldiphenylsilyl)oxy)pentanoate (**9**, Table 1, Entry 4; Table 2, Entry 5).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1) and yielded the targeted compound as a slightly yellow oil (R_f = 0.83, petroleum ether:EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.53−1.70 (m, 2H), 1.70−1.83 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 3.68 (s, 3H), 7.32−7.48 (m, 7H), 7.60−7.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 21.6, 27.1, 32.1, 34.0, 51.7, 63.6, 127.8, 129.8, 134.1, 135.8, 174.3; IR (film) ν^{-1} 2949 (w), 2950 (w), 2940 (w), 2895 (w), 1739 (s), 1429 (m), 1111 (s); MS (APCI$^+$), *m*/*z* (%) = 371 (48) [M + H]$^+$. Anal. Calcd for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.49; H, 8.25.

*Methyl 5-oxohexanoate (**9**, Table 1, Entry 5).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1 → 4:1 → 2:1) and yielded the targeted compound as a colorless oil (R_f = 0.65, petroleum ether:EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (quint, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 30.1, 33.2, 42.6, 51.8, 173.8, 208.2; IR (film) ν^{-1} 2961 (w), 2952 (w), 1729 (s), 1712 (s), 1438 (m), 1253 (m); MS (APCI$^+$), *m*/*z* (%) 145 (73) [M + H]$^+$. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.57; H, 8.19.

*1-Ethyl 4-methyl (R)-2-methylsuccinate (**9**, Table 1, Entry 6).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1 → 4:1) and yielded the targeted compound as a colorless oil (R_f = 0.70, petroleum ether:EtOAc = 4:1). α_D^{23} = +3.02 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 7.1 Hz, 3H), 2.38 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.72 (dd, *J* = 16.4, 8.2 Hz, 1H), 2.89 (dq, *J* = 13.9, 7.1 Hz, 1H), 3.66 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 17.1, 36.0, 37.5, 51.8, 60.8, 172.4, 175.3; IR (film) ν^{-1} 2963 (w), 2949 (w), 1730 (s), 1716 (s), 1434 (m), 1251 (m); MS (CI$^+$), *m*/*z* (%) 175 (41) [M + H]$^+$; HRMS (EI$^+$), *m*/*z* calcd. for $C_8H_{14}O_4$ [M]$^+$: 174.0892, found 174.0886; *ee* = 56%. The *ee* of the product was determined by chiral GC using γ-TA column (80 °C, $\tau_{(S)\text{-minor}}$ = 30.6 min, $\tau_{(R)\text{-major}}$ = 34.3 min). The major enantiomer was determined to be (*R*) with help of optical rotation measurement (the sign of the measured value was compared with known values).[30]

*4-Allyl 1-ethyl (R)-2-methylsuccinate (**9**, Table 1, Entry 7).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 10:1) and yielded the targeted compound as a colorless oil (R_f = 0.55, petroleum ether:EtOAc = 10:1). α_D^{23} = +0.62 (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ

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1.21 (d, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 2.42 (dd, J = 16.4, 6.0 Hz, 1H), 2.76 (dd, J = 16.4, 8.2 Hz, 1H), 2.89 (dt, J = 14.0, 7.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.57 (dt, J = 5.7, 1.3 Hz, 2H), 5.21 (dq, J = 10.5, 1.2 Hz, 1H), 5.30 (dq, J = 17.1, 1.5 Hz, 1H), 5.89 (ddt, J = 17.3, 10.4, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 17.2, 36.0, 37.7, 60.8, 65.4, 118.4, 132.2, 171.7, 175.3; IR (film) ν^{-1} 2990 (w), 2979 (w), 2921 (w), 2875 (w), 1729 (s), 1381 (m); MS (CI^+), m/z (%) 201 (100) $[M + H]^+$; HRMS(EI^+), m/z calcd for $C_{10}H_{17}O_4$ $[M + H]^+$: 201.1127, found 201.1125; *ee* = 28%. The *ee* of the product was determined by chiral GC using γ-TA column (110 °C (25 min) → 10 °C/min until 170 °C → 170 °C (15 min), $\tau_{(S)\text{-minor}}$ = 32.50 min, $\tau_{(R)\text{-major}}$ = 32.81 min). The major enantiomer was determined to be (R) with help of optical rotation measurement (the sign of the measured value was compared with known values).[31]

*Allyl (S)-3-methylnonanoate (**9**, Table 1, Entry 8).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1 → 20:1) and yielded the targeted compound as a colorless oil (R_f = 0.75, petroleum ether:EtOAc = 10:1). α_D^{23} = −0.14 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.2 Hz, 7H), 0.93 (d, J = 6.6 Hz, 3H), 1.13−1.38 (m, 10H), 1.96 (quint, J = 6.5 Hz, 1H), 2.13 (dd, J = 14.7, 8.2 Hz, 1H), 2.33 (dd, J = 14.6, 6.1 Hz, 1H), 4.57 (dd, J = 5.7, 1.5 Hz, 2H), 5.22 (dt, J = 10.4, 1.2 Hz, 1H), 5.31 (dt, J = 17.2, 1.4 Hz, 1H), 5.91 (dddd, J = 17.4, 11.5, 5.7, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.9, 22.8, 27.1, 29.6, 30.6, 32.0, 36.9, 42.0, 65.0, 118.2, 132.6, 173.1; IR (film) ν^{-1} 2959 (w), 2927 (w), 2855 (w), 1739 (s), 1381 (w); MS (CI^+), m/z (%) = 213 (100) $[M + H]^+$; HRMS (ESI^+), m/z calcd. for $C_{13}H_{24}O_2Na$ $[M + Na]^+$: 235.1669, found 235.1669. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39; Found: C, 73.55; H 11.41; *ee* = 75%. The *ee* of the product was determined by chiral GC using CHIRALDEX β-PM column (100 °C (25 min) → 10 °C/min until 160 °C → 160 °C (4 min), $\tau_{(R)\text{-minor}}$ = 27.80 min, $\tau_{(S)\text{-major}}$ = 29.05 min). The major enantiomer was determined to be (S) with help of optical rotation measurement (the sign of the measured value was compared with known values).[32]

*tert-Butyl (R)-3-methylnonanoate (**9**, Table 1, Entry 9).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1) and yielded the targeted compound as a colorless oil (R_f = 0.81, petroleum ether:EtOAc = 50:1). α_D^{23} = +1.07 (*c* 1.1, *hexane*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 7.6 Hz, 2H), 1.17−1.40 (m, 6H), 1.44 (s, 9H), 1.46−1.64 (m, 4H), 1.89 (q, J = 5.2 Hz, 1H), 2.00 (dd, J = 14.2, 8.0 Hz, 1H), 2.20 (dd, J = 14.1, 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.9, 22.9, 26.8, 28.3, 30.7, 32.2, 36.9, 43.4, 80.1, 173.0; IR (film) ν^{-1} = 2956 (w), 2930 (w), 2853 (w), 1702 (s), 1465 (w); MS (CI^+), m/z (%) 229 (100) $[M + H]^+$; HRMS(CI^+), m/z calcd. for $C_{14}H_{29}O_2H$ $[M + H]^+$: 229.2162, found 229.2161; *ee* = 95%. The *ee* of the product was determined by chiral GC using CHIRALDEX β-PM column (100 °C (25 min) → 10 °C/min until 160 °C → 160 °C (4 min), $\tau_{(R)\text{-major}}$ = 27.49 min, $\tau_{(S)\text{-minor}}$ = 28.38 min). The major enantiomer was determined to be (R) with help of optical rotation measurement (the sign of the measured value was compared with known values).[32]

*tert-Butyl (Z)-oct-4-enoate (**9**, Table 1, Entry 10; Table 2, Entry 6).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1) and yielded the targeted compound as a colorless oil (R_f = 0.98, petroleum ether:EtOAc = 4:1). (E/Z) = 2:>95. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.38 (dt, J = 14.9, 7.5 Hz, 2H), 1.45 (s, 9H), 2.03 (dd, J = 13.9, 6.7 Hz, 2H), 2.20−2.39 (m, 4H), 5.37 (quintd, J = 10.8, 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.0, 23.2, 28.3, 29.5, 35.8, 80.3, 128.0, 131.2, 172.0; IR (film) ν^{-1} 2959 (w), 2934 (w), 2921 (w), 1733 (s), 1460 (w); MS ($APCI^+$), m/z (%) 199 (24) $[M + H]^+$; HRMS (EI^+), m/z calcd. for $C_{12}H_{22}O_2H$ $[M + H]^+$: 199.1693, found 199.1695. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.73; H, 11.10.

*Methyl hept-6-enoate (**9**, Table 1, Entry 11; Table 2, Entry 7).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 20:1) and yielded the targeted compound as a colorless oil (R_f = 0.88, petroleum ether:EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (quint, J = 7.5, 7.1 Hz, 2H), 1.58−1.72 (m, 2H), 2.07 (q, J = 7.2 Hz, 2H), 2.31 (t, J = 7.5 Hz, 2H), 3.66 (s, 3H), 4.95 (dq, J = 10.1, 1.2 Hz, 1H), 5.01 (q, J = 17.4, 2.0 Hz, 1H), 5.79 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 28.5, 33.5, 34.1, 51.7, 114.9, 138.6, 174.3; HRMS (ESI^+), m/z calcd. for $C_8H_{14}O_2Na$ $[M + Na]^+$: 165.0886, found 165.0892.

*tert-Butyl tetracosanoate (**9**, Table 1, Entry 12; Table 2, Entry 4).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1) and yielded the targeted compound as a colorless solid (R_f = 0.92, petroleum ether:EtOAc = 4:1). mp = 62−63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 6.6 Hz, 3H), 1.28 (s, 40H), 1.48 (s, 9H), 1.63 (quint, J = 7.1 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.8, 25.2, 28.0, 29.3, 29.5, 29.6, 29.7, 29.83, 29.89, 29.93, 32.2, 34.3, 80.1, 174.8; MS (CI), m/z (%) 426 (72) $[M + H]^+$; HRMS (ESI^+), m/z calcd. for $C_{28}H_{56}O_2Na$ $[M + Na]^+$: 447.41725, found 447.41733.

*Methyl tetracosanoate (**9**, Table 1, Entry 13; Table 2, Entry 3).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1) and yielded the targeted compound as a colorless solid (R_f = 0.88, petroleum ether:EtOAc = 4:1). mp = 53−54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3H), 1.26 (s, 40H), 1.62 (quint, J = 7.1 Hz, 2H), 2.31 (t, J = 7.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 25.2, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 32.2, 34.3, 51.6, 174.5; MS (APCI), m/z (%) 383 (23) $[M + H]^+$; HRMS (ESI^+), m/z calcd. for $C_{25}H_{50}O_2Na$ $[M + Na]^+$: 405.3703, found 405.3705.

*Methyl hept-5-ynoate (**9**, Table 1, Entry 14; Table 2, Entry 8).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1) and yielded the targeted compound as a colorless oil (R_f = 0.82, petroleum ether:EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (t, J = 2.5 Hz, 3H), 1.83 (quint, J = 7.1 Hz, 2H), 2.20 (ddq, J = 7.1, 5.1, 2.5 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.6, 22.6, 26.1, 34.4, 51.7, 76.6, 78.1, 174.0; MS (APCI), m/z (%) 141 (15) $[M + H]^+$; HRMS (EI^+), m/z calcd. for $C_8H_{12}O_2H$ $[M + H]^+$: 141.0910, found 141.0919.

*Methyl 6-(benzyloxy)hexanoate (**9**, Table 1, Entry 15).*[33] The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 4:1 → 2:1 → 1:1) and yielded the targeted compound as colorless oil (R_f = 0.16, petroleum ether:EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.52 (m, 2H), 1.62−1.70 (m, 4H), 2.34 (t, J = 7.5 Hz, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.69 (s, 3H), 4.52 (s, 2H), 7.33−7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 25.6, 29.5, 33.7, 51.5, 70.5, 73.0, 127.8, 128.0, 128.3, 138.1, 174.2; HRMS (ESI) calcd. for $C_{14}H_{20}NaO_3$ $[M + Na]^+$: 259.1305, found 259.1301. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.50.

*Methyl 3-(pyridin-2-yl)propanoate (**9**, Table 1, Entry 16).*[34] The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1 → 4:1→ 2:1) and yielded the targeted compound as colorless oil (R_f = 0.26, petroleum ether:EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (t, J = 7.5 Hz, 2H), 3.12 (t, J = 7.5 Hz, 2H), 3.66 (s, 3H), 7.07−7.14 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.58 (td, J = 7.7, 1.8 Hz, 1H), 8.52 (d, J = 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 33.2, 51.6,121.4,122.9, 136.4,149.3,160.0, 173.5; HRMS (ESI) calcd. for $C_9H_{11}NNaO_2$ $[M + Na]^+$: 188.0682, found 188.0686. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; N, 8.48; H, 6.71. Found: C, 65.45; N, 8.52; H, 6.70.

General Protocol for Mitsunobu Reaction Reactions. *Conditions A.* A solution of BT-sulfone (**C-acid**) (1.2 mmol, 1.2 equiv), PPh_3 (0.393 g, 1.5 mmol, 1.5 equiv) and alcohol **6** (1.0 mmol, 1.0 equiv) in toluene (10 mL, 0.1 M) was cooled to 0 °C and ADDP (1,1′-(azodicarbonyl)dipiperidine) (0.378 g, 1.5 mmol, 1.5 equiv) was added. The resulting solution was allowed to warm to rt and stirred at this temperature for additional 12 h. Silica gel (2 g per 1 mmol of alcohol **6**) was added and the whole mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 with appropriate solvent system.

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Conditions B. A solution of BT-sulfone (**C-acid**) (1.2 mmol, 1.2 equiv), PPh_3 (0.393 g, 1.5 mmol, 1.5 equiv) and alcohol **6** (1.0 mmol, 1.0 equiv) in toluene (10 mL, 0.1 M) was cooled to 0 °C and DEAD (Diethyl azodicarboxylate) (0.238 mL, 1.5 mmol, 1.5 equiv) was added. The resulting solution was allowed to warm to rt and stirred at this temperature for additional 6 h. Silica gel (2 g per 1 mmol of alcohol **6**) was added and the whole mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 with appropriate solvent system.

Products 8b Prepared via Mitsunobu Reaction. *1-(tert-Butyl) 8-methyl 2-(benzo[d]thiazol-2-ylsulfonyl)octanedioate (**8b**, Table 1, Entry 1).* Starting from methyl 5-hydroxypentanoate. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); R_f = 0.34 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.45−1.59 (m, 4H), 1.58−1.75 (m, 2H), 2.05−2.29 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 3.67 (s, 3H), 4.36 (dd, J = 8.9, 6.2 Hz, 1H), 7.61−7.66 (m, 2H), 8.03 (dd, J = 7.9, 0.3 Hz, 1H), 8.25 (dd, J = 7.8, 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 25.8, 26.6, 27.6, 28.5, 33.8, 51.5, 70.3, 84.0, 122.3, 125.6, 127.7, 128.2, 137.0, 152.6, 163.6, 164.7, 173.9; MS (CI^+), m/z (%) 442 (11) $[M + H]^+$; HRMS (ESI) calcd. for $C_{20}H_{27}NNaO_6S_2$ $[M + Na]^+$: 464.1172, found 464.1170.

*Dimethyl 2-(benzo[d]thiazol-2-ylsulfonyl)octanedioate (**8b**, Table 1, Entry 2).* Starting from methyl 5-hydroxypentanoate. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1); R_f = 0.71 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.51 (m, 4H), 1.62 (quint, J = 7.3 Hz, 2H), 2.14−2.35 (m, 4H), 3.65 (s, 3H), 3.73 (s, 3H), 4.44 (dd, J = 8.6, 6.2 Hz, 1H), 7.55−7.72 (m, 2H), 8.02 (ddd, J = 7.4, 1.4, 0.7 Hz, 1H), 8.19−8.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 26.2, 26.8, 28.6, 33.9, 51.7, 53.5, 69.8, 122.5, 125.9, 127.9, 128.5, 137.3, 152.8, 164.4, 165.5, 174.0; MS (CI^+), m/z (%) 401 $[M + H]^+$; HRMS (ESI) calcd. for $C_{17}H_{21}NNaO_6S_2$ $[M + Na]^+$: 422.0702, found 422.0702.

*1-Allyl 8-methyl 2-(benzo[d]thiazol-2-ylsulfonyl)octanedioate (**8b**, Table 1, Entry 3).* Starting from methyl 5-hydroxypentanoate. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1); R_f = 0.22 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03−1.57 (m, 4H), 1.54−1.81 (m, 2H), 2.15−2.37 (m, 4H), 3.65 (s, 3H), 4.46 (dd, J = 8.6, 6.2 Hz, 1H), 4.58 (ddd, J = 6.0, 2.7, 1.2 Hz, 2H), 5.12 (dd, J = 10.4, 1.2 Hz, 1H), 5.19 (dt, J = 17.2, 1.4 Hz, 1H), 5.70 (ddt, J = 17.2, 10.4, 5.9 Hz, 1H), 7.52−7.79 (m, 2H), 7.92−8.09 (m, 1H), 8.17−8.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 26.1, 26.7, 28.6, 33.9, 51.7, 67.2, 69.8, 119.7, 119.8, 122.4, 125.8, 127.9, 128.4, 130.7, 137.3, 152.8, 164.4, 164.7, 174.0; MS (CI^+), m/z (%) 427 $[M + H]^+$; HRMS (ESI) calcd. for $C_{19}H_{23}NO_6S_2H$ $[M + H]^+$: 426.1040, found 426.1042.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)-5-((tert-butyldiphenylsilyl)oxy)pentanoate (**8b**, Table 1, Entry 4).* Starting from 4-hydroxybutan-2-one. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); Keto/enol = ∼6:1; Peaks belonging to enol form are marked with *; R_f = 0.46 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 9H, H-9), 1.58−1.77 (m, 2H), 2.33−2.48 (m, 2H), 3.68 (t, J = 5.9 Hz, 2H), 3.73 (s, 3H), 4.62 (dd, J = 9.6, 5.4 Hz, 1H), 5.30 (s, 1H*), 7.30−7.47 (m, 6H), 7.57−7.69 (m, 6H), 7.85−7.94 (m, 2H*), 8.02 (dd, J = 6.7, 2.1 Hz, 1H), 8.24 (dd, J = 7.2, 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 23.6, 26.9, 29.7, 53.5 (C-4), 63.0, 69.7, 122.5, 126.0, 127.9, 128.4, 129.9, 133.6, 135.7, 137.4, 152.9, 164.5, 165.5; MS (APCI), m/z (%) 568 (100) $[M^+]$. Anal. Calcd for $C_{29}H_{33}NO_5S_2Si$: C, 61.35; H, 5.86; N, 2.47. Found: C, 61.34; H, 5.89; N, 2.48.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)-5-oxohexanoate (**8b**, Table 1, Entry 5).*[18b] Starting from 4-hydroxybutan-2-one. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1 → 1:1); R_f = 0.36 (petroleum ether:EtOAc = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.37−2.89 (m, 4H), 3.70 (s, 3H), 4.60 (dd, J = 8.3, 5.8 Hz, 1H), 7.51−7.73 (m, 2H), 8.02 (d, J = 7.9 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 30.0, 39.8, 53.5, 68.4, 122.5, 125.8, 127.9, 128.5, 137.3, 152.7, 164.3, 165.3, 206.4; IR (film) ν^{-1} 2957 (w), 2938 (w), 2929 (w), 2855 (w), 1747 (s), 1471 (m), 1429 (m), 1340 (s), 1317 (m), 1151 (s), 1111 (s), 910 (s), 764 (s), 704 (s), 600 (w); MS (CI^+), m/z (%) 342 $[M + H]^+$; HRMS (ESI) calcd. for $C_{14}H_{15}NNaO_5S_2$ $[M + Na]^+$: 364.0284, found 364.0284.

*4-Ethyl 1-methyl (3S)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-methylsuccinate (**8b**, Table 1, Entry 6).* Starting from ethyl (*R*)-2-hydroxypropanoate. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); As a mixure of stereoisomers; R_f = 0.73 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17−1.35 (m, 3H), 1.41 (d, J = 6.9 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.61 (d, J = 7.2 Hz, 3H), 2.87 (d, J = 5.0 Hz, 1H), 3.53−3.63 (m, 1H), 3.63 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 4.06−4.33 (m, 2H), 4.59 (s, 1H), 4.90 (d, J = 8.6 Hz, 1H), 5.25 (d, J = 6.7 Hz, 1H), 7.53−7.72 (m, 2H), 8.02 (dt, J = 6.6, 1.5 Hz, 1H), 8.16−8.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.3, 15.8, 20.6, 37.6, 38.9, 53.4, 53.5, 58.7, 61.8, 61.9, 66.9, 70.0, 71.5, 122.5, 122.6, 125.7, 125.8, 127.9, 127.9, 128.5, 137.3, 152.6, 162.3, 164.1, 165.1, 172.2, 172.7, 175.9; MS (CI^+), m/z (%) 372 $[M + H]^+$; HRMS (ESI) calcd. for $C_{15}H_{17}NNaO_6S_2$ $[M + Na]^+$: 394.0389, found 394.0390.

*1-Allyl 4-ethyl (3S)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-methylsuccinate (**8b**, Table 1, Entry 7).* Starting from ethyl (*R*)-2-hydroxypropanoate. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1); as a mixure of stereoisomers; R_f = 0.54 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13−1.30 (m, 3H), 1.51 (dd, J = 7.2, 1.2 Hz, 3H), 1.63 (dd, J = 7.2, 1.2 Hz, 3H), 1.69 (d, J = 7.3 Hz, 3H), 3.54−3.68 (m, 1H), 3.94−4.26 (m, 3H), 4.40−4.52 (m, 1H), 4.56 (dt, J = 5.9, 1.3 Hz, 2H), 4.93 (dd, J = 8.6, 1.2 Hz, 1H), 5.01−5.22 (m, 2H), 5.28 (d, J = 6.6 Hz, 1H), 5.48−5.82 (m, 1H), 7.47−7.75 (m, 2H), 7.94−8.09 (m, 1H), 8.16−8.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 14.1, 14.2, 14.2, 15.9, 17.0, 37.6, 38.8, 42.0, 61.4, 61.8, 61.9, 67.1, 67.3, 69.8, 71.0, 71.4, 119.5, 119.7, 122.4, 125.8, 125.8, 127.7, 127.9, 127.9, 128.4, 128.5, 130.5, 132.5, 137.2, 137.3, 152.6, 163.3, 164.3, 164.8, 165.3, 172.1, 172.7; MS (CI^+), m/z (%) 399 $[M + H]^+$; HRMS (ESI) calcd. for $C_{17}H_{19}NNaO_6S_2$ $[M + Na]^+$: 420.0546, found 420.0545.

*Allyl (3S)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-methylnonanoate (**8b**, Table 1, Entry 8).* Starting from ethyl (*R*)-octan-2-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); As a mixure of stereoisomers; R_f = 0.45 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72−0.96 (m, 3H), 1.08−1.46 (m, 13H), 1.55−1.75 (m, 1H), 2.54−2.78 (m, 1H), 2.89−3.17 (m, 1H), 4.41−4.69 (m, 2H), 4.90 (q, J = 6.3 Hz, 1H), 5.04−5.29 (m, 2H), 5.60−5.90 (m, 1H), 7.56−7.71 (m, 2H), 8.02 (dt, J = 7.3, 2.4 Hz, 1H), 8.23 (ddd, J = 8.5, 7.4, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 16.8, 18.0, 19.8, 22.7, 25.3, 26.6, 29.2, 29.3, 30.4, 30.7, 31.8, 32.6, 33.1, 33.8, 35.2, 35.7, 66.8, 66.9, 69.2, 72.8, 74.4, 74.9, 119.7, 119.8, 122.5, 125.7, 125.9, 127.8, 127.9, 128.3, 128.4, 130.9, 131.6, 137.2, 152.7, 164.0, 164.5, 165.9; MS (CI^+), m/z (%) 411 $[M + H]^+$; HRMS (ESI) calcd. for $C_{20}H_{27}NNaO_4S_2$ $[M + Na]^+$: 432.1274, found 432.1273.

*tert-Butyl (3R)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-methylnonanoate (**8b**, Table 1, Entry 9).* Starting from ethyl (*S*)-octan-2-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); As a mixure of stereoisomers; R_f = 0.87 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (dt, J = 13.5, 6.9 Hz, 3H), 1.16−1.37 (m, 20H), 1.37−1.56 (m, 1H), 1.56−1.77 (m, 1H), 2.59 (dt, J = 12.7, 6.4 Hz, 1H), 4.41 (d, J = 7.3 Hz, 1H), 4.51 (d, J = 4.9 Hz, 1H), 7.62 (quintd, J = 7.2, 1.5 Hz, 2H), 7.98−8.05 (m, 1H), 8.17−8.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 16.8, 18.0, 22.7, 26.4, 27.8, 27.9, 31.7, 31.9, 32.5, 33.1, 33.6, 35.2, 73.3, 75.6, 84.0, 122.5, 125.6, 127.8, 128.2, 137.1, 152.7, 163.6, 164.1, 166.4; MS (CI^+), m/z (%) 427 $[M + H]^+$; HRMS (ESI) calcd. for $C_{21}H_{31}NNaO_4S_2$ $[M + Na]^+$: 448.1587, found 448.1586.

*tert-Butyl (Z)-2-(benzo[d]thiazol-2-ylsulfonyl)oct-4-enoate (**8b**, Table 1, Entry 10).* (*Z*)-Hex-2-en-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1); As a mixure of stereoisomers; R_f = 0.73 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3H), 1.34 (s, 9H), 1.32−1.45 (m, 2H), 2.05 (tdd, J = 9.2, 6.4, 1.9 Hz, 2H), 2.87−3.19 (m, 2H), 4.38 (dd, J = 10.5, 4.5 Hz, 1H), 5.24−5.39 (m, 1H), 5.50−5.64 (m, 1H), 7.54−7.85 (m, 2H), 7.98−8.11 (m, 1H), 8.18−8.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.7, 24.5, 27.8, 29.5, 70.2, 84.1,

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122.3, 122.5, 125.8, 127.9, 128.4, 134.9, 137.2, 152.9, 160.5, 164.9; MS (CI^+), m/z (%) 397 $[M + H]^+$; HRMS (ESI) calcd. for $C_{19}H_{25}NNaO_4S_2$ $[M + Na]^+$: 418.1117, found 418.1112.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)hept-6-enoate (**8b**, Table 1, Entry 11).*[18b] Starting from pent-4-en-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); Keto/enol forms = ∼11:1; R_f = 0.51 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45−1.58 (m, 2H), 2.11 (dt, J = 14.2, 4.7 Hz, 2H), 2.20−2.32 (m, 2H), 3.73 (s, 3H), 4.47 (td, J = 7.9, 5.4 Hz, 1H), 4.95 (dd, J = 10.5, 1.3 Hz, 1H), 5.05 (dt, J = 3.0, 1.5 Hz, 1H), 5.73 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 7.64 (quintd, J = 7.2, 1.5 Hz, 2H), 8.03 (dd, J = 7.2, 2.1 Hz, 1H), 8.25 (dd, J = 7.4, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 26.3, 33.1, 53.5, 69.8, 115.9, 122.5, 125.9, 127.9, 128.5, 137.2, 137.3, 152.8, 164.4, 165.5; IR (film) ν^{-1} = 2940 (w), 2932 (w), 2923 (w), 2911 (w), 2903 (w), 1739 (s), 1641 (w), 1554 (w), 1471 (m), 1338 (s), 1149 (s), 1024 (m), 854 (m), 764 (s), 731 (s), 619 (m); MS (APCI), m/z (%) 340 (100) $[M^+]$. Anal. Calcd for $C_{15}H_{17}NO_4S_2$: C, 53.08; H, 5.05; N, 4.13. Found: C, 52.95; H, 5.17; N 4.16.

*tert-Butyl 2-(benzo[d]thiazol-2-ylsulfonyl)tetracosanoate (**8b**, Table 1, Entry 12).*[18b] Starting from docosan-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 50:1 → 20:1). mp = 101−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.05−1.46 (m, 40H), 1.51 (s, 9H), 2.14−2.34 (m, 2H), 4.42 (dd, J = 8.8, 6.1 Hz, 1H), 7.59−7.72 (m, 2H), 8.02 (dd, J = 7.1, 1.9 Hz, 1H), 8.25 (dd, J = 7.2, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 26.4, 27.1, 28.9, 29.2, 29.3, 29.6, 29.6, 29.8, 29.8, 29.9, 29.9, 32.1, 70.0, 81.0, 122.5, 125.9, 127.9, 128.4, 137.4, 152.8, 164.5, 165.6.; IR (film) ν^{-1} = 3062 (w), 2997 (s), 2929 (s), 1802 (w), 1748 (s), 1471 (m), 1331 (s), 1142 (s), 1122 (s); MS (APCI), m/z (%) 622 (100) $[M^+]$. Anal. Calcd for $C_{35}H_{59}NO_4S_2$: C, 67.59; H, 9.56; N, 2.25. Found: C, 67.62; H, 9.52; N, 2.29.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)tetracosanoate (**8b**, Table 1, Entry 13).*[18b] Starting from docosan-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 20:1 → 10:1). Keto/enol forms = ∼8:1. Peaks belonging to enol form are marked with *. mp = 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3H), 1.05−1.71 (m, 40H), 2.14−2.34 (m, 2H), 3.64 (t, J = 6.7 Hz, 2H*), 3.74 (s, 3H, H-4), 4.44 (dd, J = 8.8, 6.0 Hz, 1H, H-2), 5.30 (s, 1H*), 7.58−7.71 (m, 2H), 8.03 (dd, J = 7.1, 1.9 Hz, 1H), 8.26 (dd, J = 7.2, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 26.4, 27.1, 29.2, 29.3, 29.6, 29.8, 29.9, 32.1, 53.5, 70.0, 122.5, 125.9, 127.9, 128.4, 137.4, 152.8, 164.5, 165.6; IR (film) ν^{-1} = 3061 (w), 2996 (s), 2929 (s), 1801 (w), 1744 (s), 1472 (m), 1331 (s), 1143 (s), 1122 (s), 761 (s), 727 (s); MS (APCI), m/z (%) 580 (100) $[M^+]$. Anal. Calcd for $C_{32}H_{53}NO_4S_2$: C, 66.28; H, 9.21; N, 2.42. Found: C, 66.49; H, 9.17; N, 2.57.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)hept-5-ynoate (**8b**, Table 1, Entry 14).*[18b] Starting from pent-3-yn-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1 → 2:1 → 1:1). Keto/enol forms = ∼8:1. Peaks belonging to enol form are marked with *. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (t, J = 2.3 Hz, 3H), 2.13−2.33 (m, 1H), 2.34−2.49 (m, 3H), 2.67−2.87 (m, 2H*), 3.74 (s, 3H), 4.70 (dd, J = 7.8, 6.1 Hz, 1H), 5.31 (s, 1H*), 5.39−5.55 (m, 1H), 7.49−7.37 (m, 1H*), 7.63 (quint, J = 7.2 Hz, 1H), 7.65 (quint, J = 7.2 Hz, 1H), 7.94−7.80 (m, 2H*), 8.03 (dd, J = 7.2, 2.1 Hz, 1H), 8.26 (dd, J = 7.4, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 3.6, 14.4, 16.7, 21.2, 25.8, 53.6, 60.6, 68.9, 75.8, 78.6, 122.5, 125.9, 128.0, 128.5, 137.4, 152.8, 164.2, 165.2; IR (film) ν^{-1} = 2954 (w), 2917 (w), 1739 (s), 1471 (m), 1436 (m), 1336 (s), 1149 (s), 1024 (m), 854 (m), 764 (s), 731 (s), 694 (m), 640 (m); MS (APCI), m/z (%) 338 (100) [M+]. Anal. Calcd for $C_{15}H_{15}NO_4S_2$: C, 53.40; H, 4.48; N, 4.15. Found: C, 53.71; H, 4.63; N, 4.25.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)-6-(benzyloxy)hexanoate (**8b**, Table 1, Entry 15).* Starting from 4-(benzyloxy)butan-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1 → 2:1); R_f = 0.34 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38−1.52 (m, 1H), 1.53−1.77 (m, 3H), 2.21 (dtd, J = 11.3, 6.5, 5.6 Hz, 1H), 2.29−2.41 (m, 1H), 3.32−3.48 (m, 2H), 3.73 (s, 3H), 4.36 (d, J = 11.9 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.49 (t, J = 5.9 Hz, 1H), 7.23−7.32 (m, 5H), 7.37−7.45 (m, 2H), 7.91 (dd, J = 7.5, 1.6 Hz, 1H), 7.95 (dd, J = 7.1, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 24.7, 29.5, 52.9, 68.9, 70.5, 73.0, 122.5, 124.4, 127.7, 127.9, 127.9, 128.0, 128.4, 135.2, 138.2, 153.1, 164.5, 165.5; MS (CI^+), m/z (%) 435 $[M + H]^+$; HRMS (ESI) calcd. for $C_{21}H_{23}NNaO_5S_2$ $[M + Na]^+$: 456.0910, found 456.0908. Anal. Calcd for $C_{21}H_{23}NO_5S_2$: C, 58.18; H, 5.35. Found: C, 58.21; H, 5.33.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)-3-(pyridin-2-yl)-propanoate (**8b**, Table 1, Entry 16).* Starting from pyridin-2-ylmethanol. Purification by flash chromatography (petroleum ether:-EtOAc = 10:1 → 4:1); R_f = 0.46 (petroleum ether:EtOAc = 4:1); mp = 143−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (d, J = 7.6 Hz, 2H), 3.73 (s, 2H), 4.44 (t, J = 7.6 Hz, 1H), 7.09−7.15 (m, 2H), 7.40−7.48 (m, 2H), 7.86 (td, J = 7.6, 1.5 Hz, 1H), 7.92−7.98 (m, 2H), 8.54 (dd, J = 3.8, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.8, 52.7, 69.0, 122.1, 122.7, 124.2, 127.7, 128.8, 136.5, 137.0, 149.5, 153.1, 155.2, 166.0, 172.7; MS (ESI^+), m/z (%) 363 $[M + H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}N_2NaO_4S_2$ $[M + Na]^+$: 385.0287, found 385.0291. Anal. Calcd for $C_{16}H_{14}N_2O_4S_2$: C, 53.03; H, 3.89. Found: C, 53.05; H, 3.88.

Side Products of the SmI_2-Mediated Reductive Elimination. *Benzo[d]thiazole.* Purification by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1 → 4:1) and yielded the targeted compound as colorless oil (R_f = 0.56, petroleum ether:EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.59−7.50 (m, 1H), 7.50−7.42 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 122.1, 123.7, 125.8, 126.4, 133.7, 153.0, 154.2.

*2-(Methylamino)benzenethiol (**13**).*[35] Purification by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1 → 4:1) and yielded the targeted compound as colorless oil (R_f = 0.42, petroleum ether:EtOAc = 4:1). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (s, 3H), 4.90 (t, J = 1.3 1H), 6.49−6.63 (m, 2H), 7.12−7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 122.1, 123.9, 125.8, 126.4, 154.1; MS (ESI^+), m/z (%) 140 $[M + H]^+$; HRMS (ESI) calcd. for C_7H_9NNaS $[M + Na]^+$: 162.03479, found 162.03480. Anal. Calcd for C_7H_9NS: C, 60.39; H, 6.52; N, 10.06. Found: C, 60.43; H, 6.57; N, 9.97.

Multigram Scale Synthesis of *tert*-Butyl Tetracosanoate (Scheme 4). *Sulfone (**7**, Table 2, Entry 4).* A solution of benzo[*d*]thiazol (BT-SH) (1.77 g, 10.6 mmol, 1.2 equiv), PPh_3 (2.77 g, 10.6 mmol, 1.2 equiv) and docosan-1-ol (3.0 g, 8.8 mmol, 1.0 equiv) in THF (88 mL, 0.1 M) was cooled to 0 °C and DEAD (1.67 mL, 10.6 mmol, 1.2 equiv) was added. The resulting solution was allowed to warm to rt and stirred for 12 h. The resulting solution was diluted with EtOH (250 mL), cooled to 0 °C and $Na_2WO_4.2H_2O$ (413 mg, 1.1 mmol, 0.1 equiv) was added in one portion. After 15 min at 0 °C, an aqueous 35% solution of H_2O_2 (25.6 mL, 264 mmol, 30 equiv) was added dropwise with the use of a dropping funnel over a period of 45 min. The resulting yellowish solution was allowed to warm to rt and stirred at rt for 18 h. Deionized water (500 mL) was added and the mixture was extracted with EtOAc (6× 250 mL). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (petroleum ether:EtOAc = 50:1 → 10:1) yielding the desired sulfone (4.22 g, 91%).

*β-Carbonyl Sulfone (**8a**, Table 2, Entry 4).* A solution of BT-sulfone 7 (4.22 g, 8.1 mmol, 1.0 equiv) and Boc_2O (2.12 g, 9.7 mmol, 1.2 equiv) in THF (41 mL, 0.20 M) was cooled to −78 °C and precooled (−20 °C) LiHMDS (1.0 M sol. in THF) (17.8 mL, 17.8 mmol, 2.2 equiv) was added within 2 min. The resulting mixture was stirred at −78 °C for 30 min, allowed to warm to 0 °C within 3 h and stirred at 0 °C for a further 60 min before sat. aq. sol. of NH_4Cl (150 mL) was added. The mixture was extracted with EtOAc (3× 250 mL) and the combined organic layers were washed with brine (250 mL), dried over $NaSO_4$, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (petroleum ether:EtOAc = 50:1 → 20:1) yielding the desired product (3.98 g, 79%).

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*tert-Butyl Tetracosanoate (**9**, Table 2, Entry 4).* To a solution of BT-sulfone ester (3.98 g, 6.4 mmol, 1.0 equiv) in benzene (35 mL, 0.2 M) was added nBu$_3$SnH (2.16 mL, 8.0 mmol, 1.25 equiv) and the resulting mixture was stirred at rt for 5 min. AIBN (0.21 g, 1.28 mmol, 0.2 equiv) was added and the mixture was placed on a preheated oil bath (90 °C). The mixture was kept at 90 °C (external) for 60 min before it was allowed to cool to rt (heating bath removed). CH_3CN (250 mL) was added and the reaction mixture was extracted with n-pentane (3× 100 mL). The acetonitrile layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1) and yielded the targeted compound as colorless viscous oil (2.52 g, 93%).

Two-Carbon Homologation of Ingenol (16, Scheme 5). *Ingenol Derivative **15**.* A solution of ingenol **14** (0.032 g, 0.09 mmol, 1.0 equiv), methyl ester C-acid (0.028 g, 0.1 mmol, 1.1 equiv) and PPh_3 (0.027 g, 0.1 mmol, 1.1 equiv) in dry benzene (1.0 mL, 0.1 M) was cooled to 0 °C and the resulting mixture was stirred for 5 min prior to DIAD (19.8 μL, 0.1 mmol, 1.1 equiv) addition. The resulting mixture was stirred at 0 °C for an additional 30 min and then at rt for 12 h. The resulting mixture was evaporated under reduced pressure to dryness and the residue was purified by column chromatography on silica gel ($CHCl_3$/EtOAc = 4:1 → 2:1 → 1:1 → 0:100) to give 0.028g (51%) of desired adduct **15** (two diastereoisomers in ∼1:1 ratio). R_f = 0.11 ($CHCl_3$/EtOAc = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71 (td, J = 8.6, 6.3 Hz, 1H), 0.96 (d, J = 7.0 Hz, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.27 (dt, J = 9.9, 7.2 Hz, 1H), 1.76 (ddd, J = 15.7, 6.3, 5.2 Hz, 1H), 1.85 (d, J = 1.4 Hz, 3H), 2.27 (ddd, J = 15.6, 8.9, 3.1 Hz, 1H), 2.30−2.38 (m, 1H), 3.35−3.48 (m, 2H), 3.68 (s, 1H), 3.78 (s, 3H), 4.08 (dd, J = 11.3, 3.6 Hz, 1H), 4.43 (s, 1H), 4.63−4.79 (m, 1H), 5.94 (d, J = 1.5 Hz, 1H), 6.10 (dd, J = 4.7, 1.3 Hz, 1H), 7.56−7.71 (m, 2H), 8.01 (dd, J = 7.1, 1.7 Hz, 1H), 8.27 (dd, J = 7.0, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 15.6, 17.1, 17.4, 21.2, 22.9, 23.0, 23.1, 23.2, 23.8, 23.9, 30.6, 30.9, 33.1, 33.2, 39.2, 39.8, 44.1, 44.2, 53.0, 53.4, 68.8, 70.9, 72.5, 72.6, 73.7, 79.8, 79.9, 84.3, 84.4, 122.4, 125.8, 125.9, 127.7, 128.5, 132.3, 136.0, 136.3, 137.3, 137.4, 139.5, 139.6, 152.7, 164.1, 164.2, 165.3, 165.5, 207.1, 207.2; HRMS (ESI) m/z calcd. for $C_{30}H_{35}NNaO_8S_2$ $[M + Na]^+$ 624.1696, found 624.1697.

*Product of Ingenol Homologation (**16**).* To a solution of BT-sulfone ester **15** (0.027 g, 0.045 mmol, 1.0 equiv) in benzene (0.5 mL) was added nBu$_3$SnH (0.056 mL, 0.056 mmol, 1.25 equiv) and the resulting mixture was stirred at rt for 5 min. AIBN (0.002 g, 0.009 mmol, 0.2 equiv) was added and the mixture was placed on a preheated oil bath (90 °C). The mixture was kept at 90 °C (external) for 60 min before it was allowed to cool to rt (heating bath removed). CH_3CN (10 mL) was added and the reaction mixture was extracted with n-pentane (3× 10 mL). The acetonitrile layer was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel ($CHCl_3$/EtOAc = 4:1 → 2:1 → 1:1 → 0:100) and yielded the targeted compound **16** (0.016 g, 89%). R_f = 0.15 ($CHCl_3$/EtOAc = 1:1); α_D^{23} = +39 (c 1.01, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (td, J = 8.5, 6.3 Hz, 1H), 0.93 (dd, J = 11.5, 8.5 Hz, 1H), 0.96 (d, J = 7.0 Hz, 3H), 1.05 (s, 3H), 1.11 (s, 3H), 1.20 (t, J = 7.0 Hz, 1H), 1.39−1.71 (broad s, 3H), 1.71−1.79 (m, 2H), 1.85 (d, J = 1.2 Hz, 3H), 2.09−2.21 (m, 2H), 2.27−2.39 (m, 2H), 2.62−2.75 (m, 2H), 3.72 (s, 3H), 3.81 (s, 1H), 4.11 (ddd, J = 10.4, 6.4, 2.1 Hz, 1H), 4.40 (s, 1H), 5.94 (quint, J = 1.5 Hz, 1H), 6.04 (d, J = 5.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 15.5, 15.6, 17.6, 21.2, 23.0, 23.4, 23.9, 28.6, 31.0, 31.1, 32.4, 39.4, 44.1, 51.8, 72.7, 74.9, 79.9, 84.3, 127.3, 128.9, 139.3, 140.7, 171.4, 208.4; HRMS (ESI) m/z calcd. for $C_{23}H_{32}NaO_6$ $[M + Na]^+$ 427.2091, found 427.2090.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00112.

Additional optimization data for Mitsunobu reaction (Table S1 and S2) and desulfonylation reactions (Table S3 and Table S4), Scheme S1 and accompanying text, copies of ^{1}H, and ^{13}C NMR spectra, and relevant chromatograms (PDF)

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Author Contributions

D.J.-Y.D.B., O.K., V.F. and F.Z. performed most of the experiments. D.J.-Y.D.B. and J.P. led the team for synthesis and analyzed chemistry and structure-related results. D.J.-Y.D.B. partially designed the experimental plans. J.P. initiated the project, led the project team, designed experiments, analyzed results and wrote the paper with input from all authors.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated with deep respect to Professor Miroslav Strnad on the occasion of his 60th birthday.

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ORIGINAL PAPER

General approach to neolignan-core of the boehmenan natural product family

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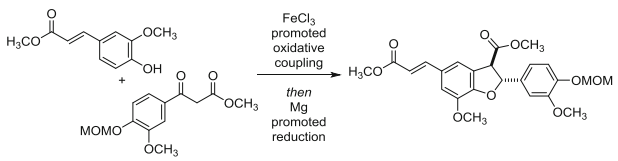
Abstract A novel approach to the neolignan-core skeletons of boehmenan natural products and to dehydrodiconiferyl alcohol glucosides based on the Fe(III)-promoted oxidative coupling has been achieved. Obtained common intermediates were further selectively modified to yield the basic molecular core possessing three orthogonally protected alkoxy functionalities available for further selective modifications.

Graphical abstract



Keywords Biomimetic synthesis · Natural products · Enzymes · Oxidative coupling

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Introduction

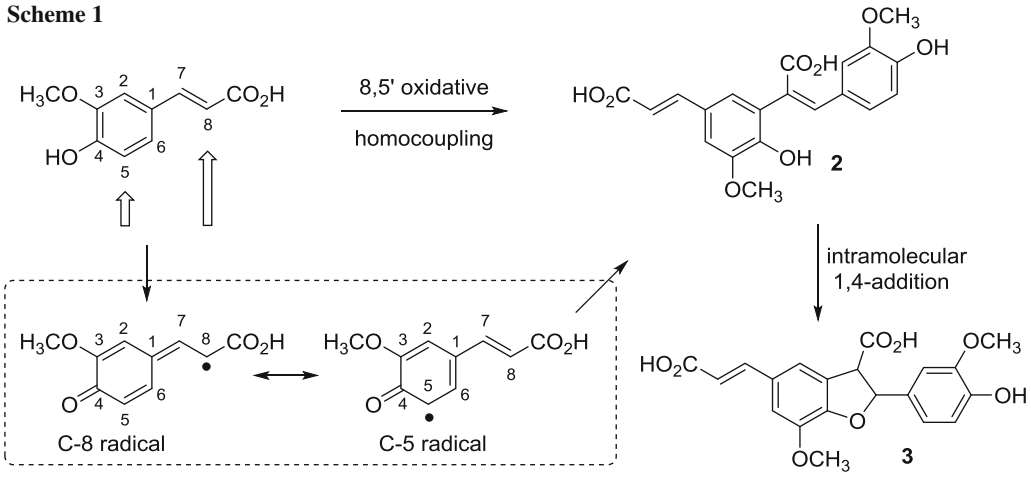
Neolignans belong to the phenylpropanoid-derived family of plant secondary metabolites that are obtained via the Shikimate biosynthetic pathway [1]. Phenylpropanoids, the direct secondary metabolites obtained from the Shikimate pathway, are further modified within plant cells to furnish structurally diverse biologically active natural products. In nature, basic phenylpropanoids are further dimerized or polymerized with the help of peroxidases, laccases, and enzyme-promoted phenol oxidative coupling [2, 3], furnishing various classes of natural products [4] (lignins, lignans, neolignans, etc.).

Our interest is to understand the oxidation processes [2, 3] related to the phenolic plant secondary metabolites on a molecular level and relate their effects on human health. Thus, we are focused on the investigation of plant produced phenolic compounds and their oxidative coupling products [5]. Unfortunately, the plant metabolome contains virtually thousands of various phenylpropanoid-related compounds. As a consequence, identification of compounds of interest is challenging. To face such problems, we have focused our synthetic efforts on the development of synthetic strategies that allows us to yield the majority of phenylpropanoid-based phytochemicals in a short end efficient manner.

The first step in this quest was establishing a short and efficient way to phenylpropanoid monomers and structurally related coumarins [6]. Next, we focused our attention to phenylpropanoid C-8, C-5 homocoupling products—8-5′-neolignans **2**—and their functional group derivatives containing the 2,3-dihydrobenzofuran motive **3** (Scheme 1).

In the literature, the synthesis of benzofurans is widely covered [7, 8] and many different approaches to

Scheme 1

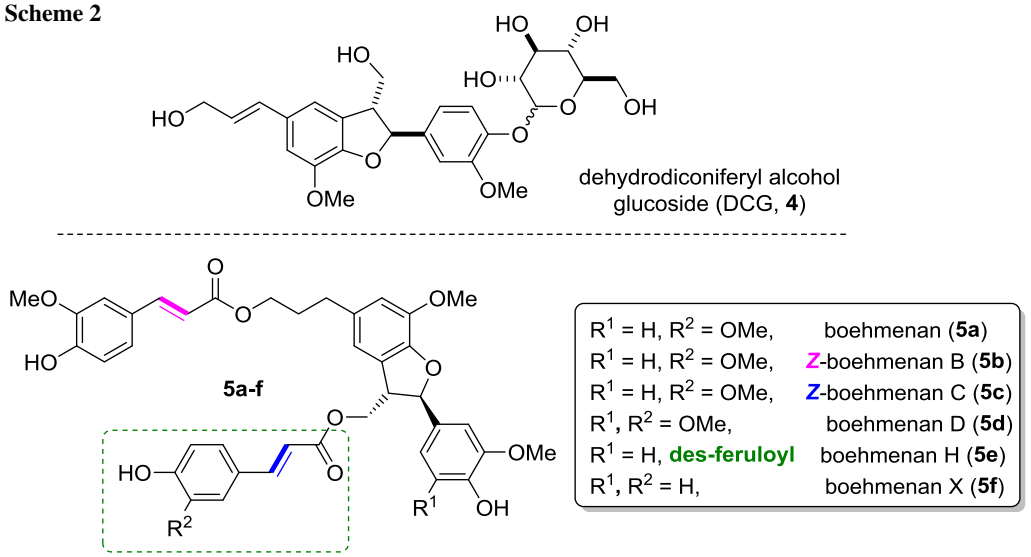


benzofuran-core structures have been developed. Most of these approaches are based either on the use of enzymes (peroxidases, laccases) [9], biomimicking radical homocouplings [10], or on the use of transition metal-mediated coupling reactions [11]. In our case, we wished to adopt a short, efficient and easy to scale-up approach to benzofuran skeletons included in boehmenan family natural products **4** and dehydrodiconiferyl glucose (DCG) derivatives **5** (Scheme 2). Our interest in these two targets arose from their biological activity. Some time ago, it was suggested that DCG **5** derivatives may act as cytokinins (phytohormones) within the plant signaling pathways [12]. On the other hand, boehmenans **5** were identified from extraction-driven biological tests of various plant extracts used in traditional Chinese medicine [13]. Based on the preliminary studies, boehmenan-type structures **5** regulate the Wnt/β-catenin signaling pathway important to treat, e.g. ,non-small cell lung cancer [14]. From a synthesis view point, DCG structure **4** [15] and boehmenan **5a** [16] have been already published. However, in our case, we wished to develop a short and efficient approach that would allow us to prepare not only targeted compounds but also their structural analogues.

Results and discussion

We planned to approach the synthesis of dihydrobenzofuran-core skeleton of **4** and **5** in a modular fashion where both aromatic rings of the core scaffold could be possibly

Scheme 2



modified prior to the dihydrofuran-ring assembly. Such approach, thus, excluded all homodimerization methods commonly based on the transition metal-promoted oxidative coupling reactions (e.g., starting from methyl ferulate and catalyzed by Fe^{III} [17] or Ag^{I} [18] salts). On the other hand, oxidative coupling reactions allow rapid, short and very convenient assembly of the targeted benzofuran molecular core of the neolignan natural products. Thus, we decided to base our approach on iron(III)-catalyzed oxidative coupling of β-ketoester **7** and phenol **6** [19, 20] followed by Mg-promoted *trans* reduction of the formed benzofurane adduct **8** [21] (Scheme 3).

The synthesis of targeted neolignans **4** and **5** core structure started with the preparation of the coupling partners methyl ferulate **6a** and β-ketoester **7a** (Scheme 4). In the case of ester **6a**, our recently developed microwave-assisted synthetic protocol was applied and the desired compound was prepared in 98% yield and > 95:1 *E/Z* selectivity starting from vanillin **10** [6]. β-Ketoester **7a** was prepared from vanillin (**10**) in three steps consisting of phenolic group MOM protection, followed by Fe-promoted Reformatsky-type condensation [22], and finished with PCC oxidation of β-hydroxy group. The desired product **7a** was prepared in 18% overall yield.

The Reformatsky reaction—transformation of aldehyde **11** to hydroxyester **12** in this sequence— is worth of mentioning. Surprisingly, we found that the Fe^{III} modification of the Reformatsky protocol gave in our hands superior yields over the "classical" Zn-promoted protocols (Table 1). Although, even in this case, the desired product **12** was formed in rather low yield of 25%. We speculate that the presence of electron-rich aromatic aldehyde might be a reason for the observed low yields.

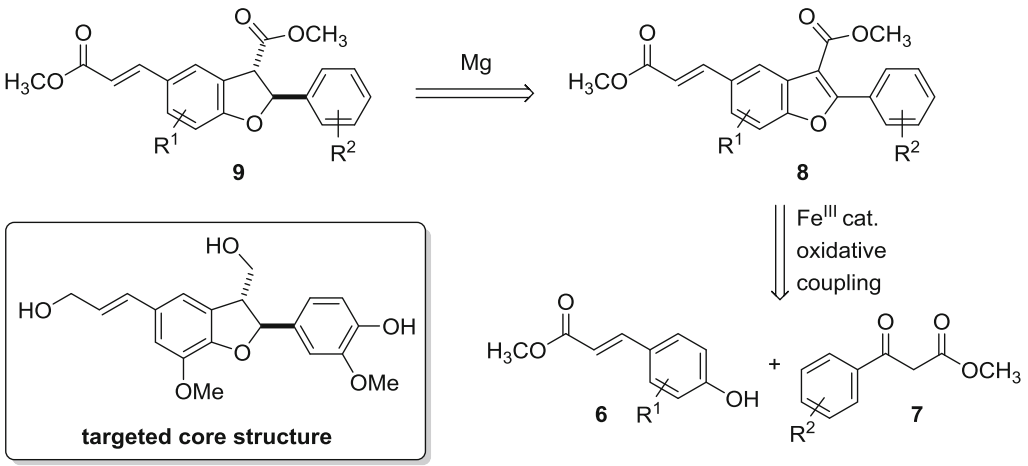
Having an access to the desired starting materials, the Fe^{III}-promoted oxidative coupling could then be attempted (Table 2). Upon screening of various reported oxidative coupling conditions [19, 20], we were delighted to observe the formation of the desired benzofuran **8a** albeit in moderate yield (Table 2, entry 3). Subsequent *trans* selective reduction [21] of the furan core **8a** to the dihydrofuran skeleton yielded the desired neolignan **9a** in 59% yield (Scheme 5).

Alternatively, we decided to prepare the same product **9a** via a homodimerization process. Thus, methyl fumarate **6a** was reacted under various literature protocols to yield the desired product **13** (Table 3). Both enzymatic as well as transition metal-catalyzed homocoupling conditions were attempted, and the desired product **13** was obtained in the best case in 28% yield and 91:9 *trans*/*cis* selectivity (Table 3, entry 2). The corresponding MOM-protected neolignan derivative **9a** was then prepared in 89% yield using the standard protecting group protocol (Scheme 6).

Finally having acquired the substantial amount of neolignan core **9a**, we could start the second aim of our project—selective modification of the ester groups. First, global DIBAL-H reduction of both methyl esters in **9a** to the corresponding alcohols was attempted. The reduction proceeded well and no product of undesired unsaturated olefin reduction was observed. Desired diol **14** was then per acetylated and the MOM-protected phenolic group was removed to yield DCG **4** core neolignan structure **16** in 3 steps (from intermediate **9a**) in 59% yield.

Next, selective monoreduction of the dihydrofuran ring-attached methyl ester group was attempted (Table 4). In our synthetic plans, it was important to distinguish both ester groups (respectively, generated primary alcohols) to

Scheme 3



Scheme 4

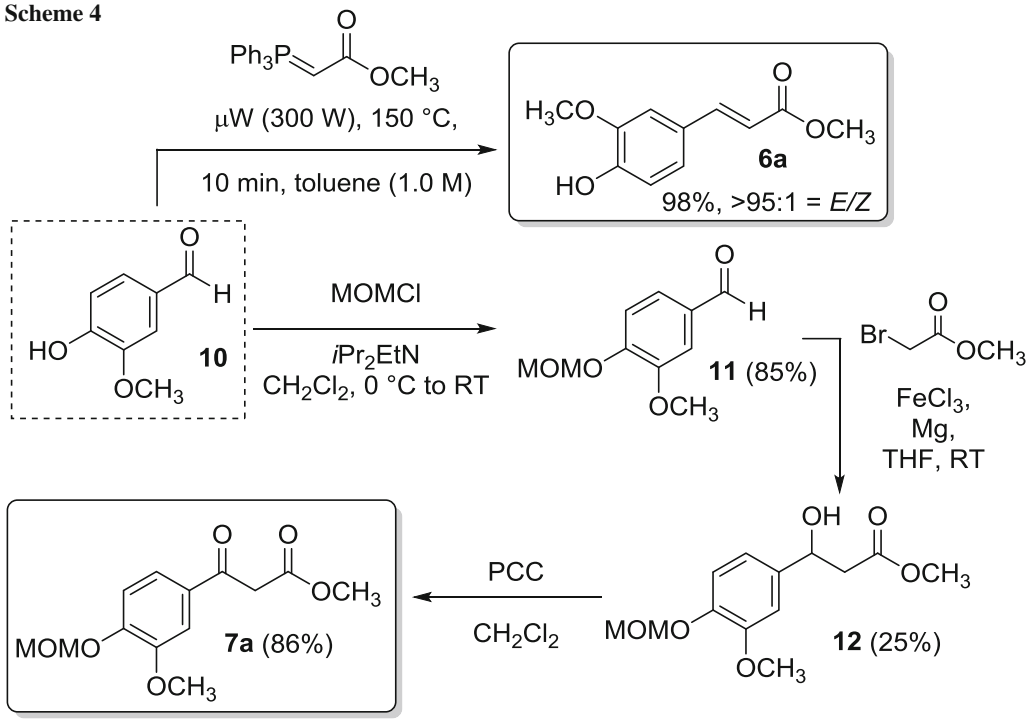
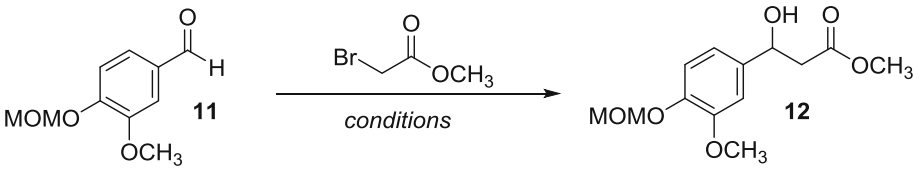


Table 1 Reformatsky reaction between aldehyde **11** and methyl α-bromo acetate—reaction conditions optimization



Entry	Conditions	**11**[a]/%	**12**[a]/%
1	Zn (10 equiv), $BrCH_2CO_2Me$ (5 equiv), toluene, 90 °C	65	4
2	Zn (10 equiv), $BrCH_2CO_2Me$ (5 equiv), THF, 60 °C	81	6
3[b]	Zn (10 equiv), $BrCH_2CO_2Me$ (5 equiv), THF, 60 °C	43	2
4	$FeCl_3$ (3 equiv), Mg (10 equiv), $BrCH_2CO_2Me$ (2 equiv), THF, 60 °C	73	5
5	$FeCl_3$ (3 equiv), Mg (10 equiv), $BrCH_2CO_2Me$ (2 equiv), THF, RT	29	25

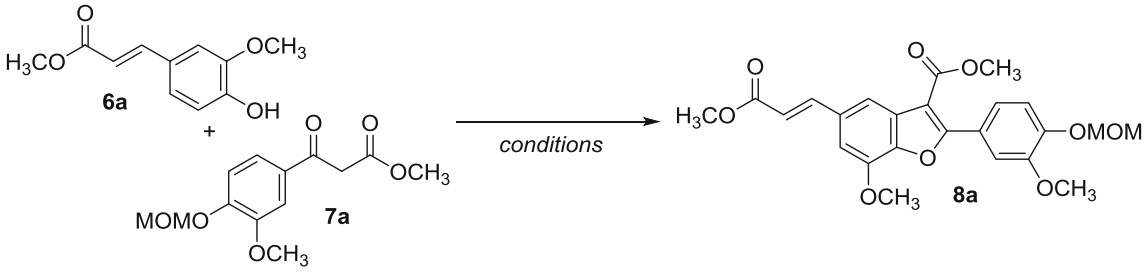
[a]Refers to pure isolated compounds

[b]$BrCH_2CO_2Me$ was slowly added as a THF solution

be able to later on selectively introduce various ester functionalities or other substituents to prepare all possible members of the boehmenan family (Scheme 1). First, the reduction of MOM-protected diester **9b** was attempted. Unfortunately, the desired alcohol product **18** was not obtained under any evaluated reaction conditions (Table 4, entries 1–8). In all cases, nonselective reduction of both ester functionalities and/or complex mixture of partially reduced products were/was obtained. It was speculated that the reason for this reaction mixture behaving this way is due to the stabilization of the mono-reduced DHF-ring placed ester functionality.

It was speculated that the presence of the MOM-protecting group might stabilize the monoreduced intermediate 20 (Scheme 7). To disrupt generated intermediate **20,** the reaction mixture must be warmed up and the competitive reduction of α,β-unsaturated ester group in the side chain occurs. To test our hypothesis, the phenol functionality in neolignan **13** was protected in the form of TBS ether and the reduction of the resulting TBS –

Table 2 Screening of oxidative radical coupling reaction conditions



Entry	Conditions	Yield[a]/%
1	$FeCl_3$ (10 mol%), 2,2′-dipyridine (5 mol%), DTBP (2.5 equiv), DCE, 70 °C	23
2	$FeCl_3$ (10 mol%), 2,2′-dipyridine (10 mol%), DTBP (2.5 equiv), DCE, 70 °C	11
3	$FeCl_3$ (10 mol%), NHPI (5 mol%), DTBP (2.5 equiv), DCE, 70 °C	36
4	$FeCl_3$ (10 mol%), NHPI (10 mol%), DTBP (2.5 equiv), DCE, 70 °C	12
5	$FeCl_3$ (10 mol%), DTBP (2.5 equiv), DCE, 70 °C	5
6	$FeCl_3$ (10 mol%), atmospheric air, DCE, 70 °C	14

DTBP diterbutylperoxide, *NHPI N*-hydroxyphthalimide

[a]Refer to pure isolated compound

Scheme 5

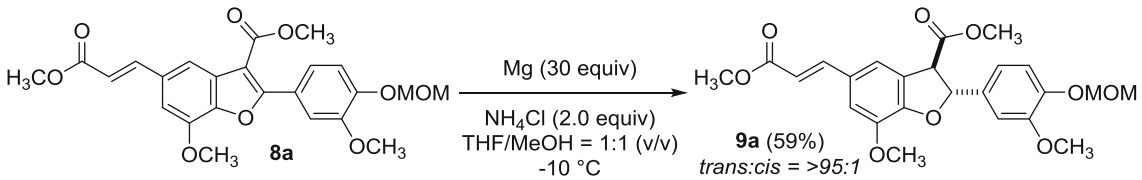
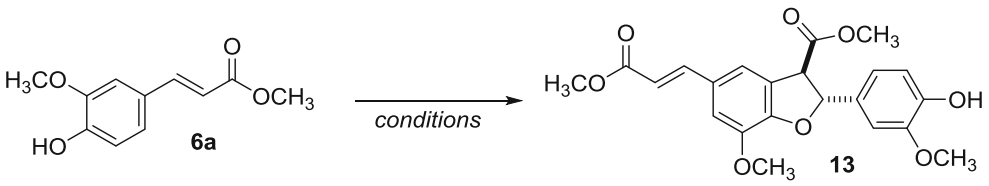


Table 3 Benzofuran **9a** synthesis: oxidative homocoupling reaction



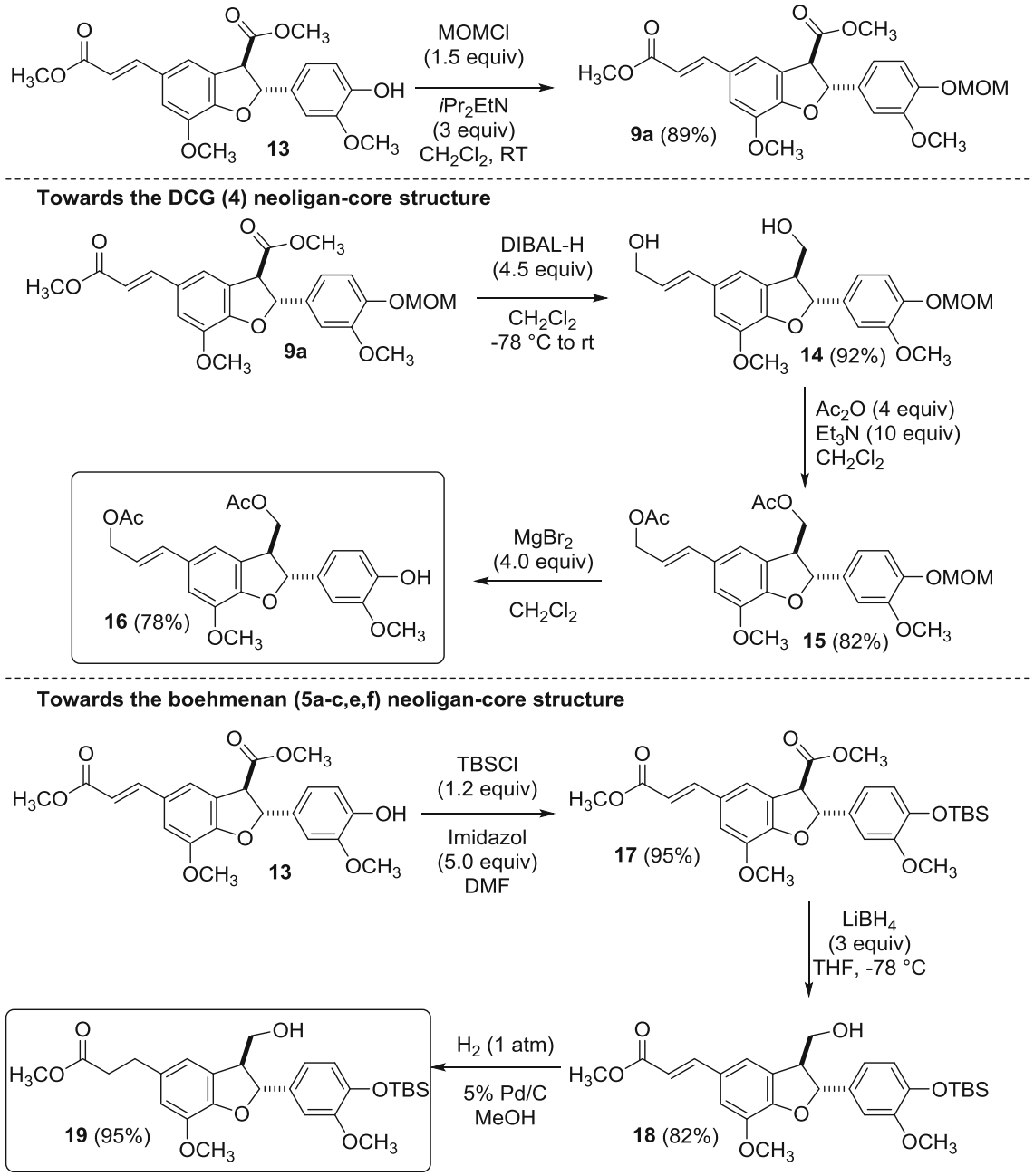
Entry	Conditions	Yield[a]/%	*trans/cis*[b]
1	$K_3[Fe(CN)_6]$ (2.1 equiv), $CH_2Cl_2/CHCl_3$ = 1:9 (V/V), RT	22	82:18
2	Ag_2O (2.1 equiv), acetone/benzene = 3:1, RT	28	91:9
3	Ag_2O (2.1 equiv), CH_2Cl_2, RT	7	89:11
4	Ag_2O (2.1 equiv), CH_2Cl_2/H_2O = 1:1 (v/v), RT	13	92:8
5	HRP[c], 1 M aq. H_2O_2 (10 equiv), phosphate buffer pH = 7.3	7	81:19
6	HRP[c], 1 M aq. H_2O_2 (10 equiv), phosphate buffer pH = 4.5	11	71:29
7	HRP[c], 1 M aq. H_2O_2 (10 equiv), phosphate buffer pH = 7.3 (dark)	10	89:11

[a]Refer to pure isolated compound

[b]Based on the ^1H NMR analysis

[c]25KU HRP used (1 mg per 1 mmol of **6a**)

Scheme 6



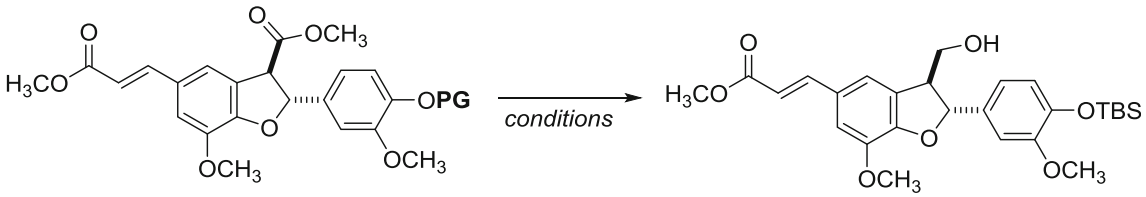
neolignan **17** was attempted. Gratifyingly, the desired alcohol **18b** was prepared selectively with use of $LiBH_4$ in 82% (Table 4, entry 12). No product of the second ester reduction was observed during the reaction.

Finally, selective hydrogenation of α,β-unsaturated olefin function in **18b** yielded the key intermediate **19**. The switch in the protecting group, thus, allowed us to achieve the synthesis of the boehmenan-core skeleton **19** that possesses three key oxygenated functional groups with orthogonal protecting groups—free hydroxy, TBS-protected phenol (to be removed with TBAF/AcOH system), and methyl ester group (transformed to the corresponding alcohol with TMSOK hydrolysis followed by a BH_3-reduction system).

Conclusion

We have developed a novel approach to the core skeleton of boehmenan (**5**) and DCG (**4**) natural products. Our approach allows the preparation of such neolignan-type skeletons via an oxidative coupling reaction. However, in

Table 4 Selective reduction of diester **9a** or **17** to alcohol **18**



9a, PG = MOM
17, PG = TBS

18a, PG = MOM
18b, PG = TBS

Entry	PG	Conditions	Yield[a]/%
1	MOM	DIBAL-H (2.1 equiv), CH_2Cl_2, − 78 °C	No reaction
2	MOM	DIBAL-H (2.1 equiv), CH_2Cl_2, − 50 °C	n.d.[b]
3	MOM	DIBAL-H (2.1 equiv), toluene, − 35 °C	No reaction
4	MOM	DIBAL-H (2.1 equiv), toluene, 0 °C	n.d.
5	MOM	DIBAL-H (2.1 equiv), THF, − 78 °C	No reaction
6	MOM	DIBAL-H (2.1 equiv), THF, − 20 °C	n.d.[b]
7	MOM	$LiBH_4$ (2.1 equiv), THF, − 78 °C	No reaction
8	MOM	$LiBH_4$ (2.1 equiv), THF, − 40 °C	n.d.[b]
9[c]	TBS	DIBAL-H (2.1 equiv), THF, − 78 °C	23%
10	TBS	DIBAL-H (2.1 equiv), THF, − 40 °C	n.d.[b]
11[d]	TBS	$LiBH_4$ (2.1 equiv), THF, − 78 °C	57%
12	TBS	$LiBH_4$ (3.0 equiv), THF, − 78 °C	82%

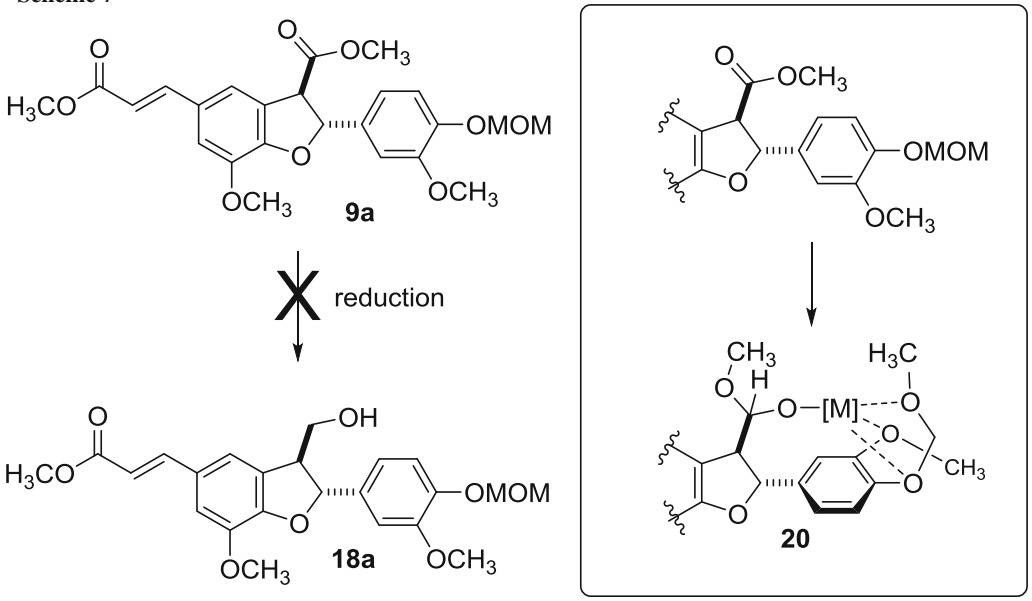
[a]Refer to pure isolated compound

[b]Complex mixture

[c]Reaction mixture also contained unreacted diester **17** (54%)

[d]Incomplete conversion of **17**

Scheme 7



comparison with the literature, our approach is versatile allowing the synthesis of products possessing a variety of substitution patterns on the presented aromatic rings. For the time being our approach suffers from the low yielding coupling step. We believe that systematic evaluation of the aromatic substitution influence of the phenolic coupling partner on the reactivity of the system will allow us to carry out the coupling reaction with better yields. On the other hand, our approach allows the preparation of the desired dihydrobenzofuran skeleton with superior *trans/cis* selectivity than that of any of the tested literature homocoupling reaction conditions could provide.

At this time, we are developing a new set of conditions that will hopefully allow the desired oxidative coupling reaction to occur in greater yields. The Mg-promoted selective *trans* reduction followed by the resulting stereoisomer separation should allow us to prepare targeted natural products as single enantiomers and to establish the absolute stereochemistry of the isolated boehmenan natural products.

Experimental

All reactions were performed in round-bottom flasks fitted with rubber septa using the standard laboratory techniques. Reactions sensitive to air and/or moisture were performed under a positive pressure of argon. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with silica gel (silica gel 60 F254, Merck). TLC plates were visualized by exposure to ultraviolet light and then were stained by submersion in basic potassium permanganate solution or in ethanolic phosphomolybdic acid solution followed by brief heating. Flash-column chromatography was carried out on silica gel (60 Å, 230–400 mesh, Sigma-Aldrich) using Petroleum ether/EtOAc solvent mixtures.

All reagents and enzymes were obtained from commercial suppliers (Sigma-Aldrich or Acros Organics) and were used without further purification. Dry solvents were obtained using standard drying protocols: THF was distilled under argon from sodium benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2.

Nuclear magnetic resonance spectra were recorded using Bruker Avance II 300, JEOL 400ECS or JEOL 500ECA instruments at 25 °C. 1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts (δ/ppm) ^1H NMR are reported in a standard fashion relative to the remaining $CHCl_3$ present in $CDCl_3$ ($\delta_H = 7.27$ ppm). ^{13}C NMR chemical shifts (δ/ppm) are reported relative to $CHCl_3$ ($\delta_C = 77.23$ ppm, central line of triplet). Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), and multiplet (m), and coupling constants (J) are reported in Hz. HRMS data were obtained using quadrupole/ion trap mass analyzer. Analysis and assignments were made by comparison with literature spectroscopic data or using 2D-COSY, HSQC, HMBC, 2D-NOESY, and NOEdiff experiments.

All microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus. The reactor was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 30 cm^3 glass vials sealed with a Silicone/PTFE Vial caps top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled to ambient temperature by gas jet cooling.

*Methyl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate (***6a**)
A suspension of 0.76 g of vanillin **10** (5.00 mmol) and 1.84 g of stabilized Wittig ylide (5.5 mmol) in 5.0 cm^3 of toluene was placed in a microwave vial (35 cm^3) equipped with a magnetic stirring bar. The vial was sealed with a Silicone/PTFE Vial cap and placed in a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 10 min (fixed time) at 150 °C. The reaction mixture was allowed to cool down, transferred to a round-bottom flask and the toluene was removed under vacuum. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1) yielded 1.02 g of resulting ester **6a** (98%) in > 95:1 *E/Z* ratio. M.p.: 64–65 °C (Ref. [6], 63–65 °C); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 16.0$ Hz, 1H), 7.03 (ddd, $J = 16.2$, 7.9, 1.9 Hz, 2H), 6.90 (d, $J = 8.2$ Hz, 1H), 6.27 (d, $J = 15.9$ Hz, 1H), 6.15–5.98 (m, 1H), 3.89 (s, 3H), 3.78 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 167.92$, 148.10, 146.89, 145.11, 126.98, 123.13, 115.15, 114.87, 109.48, 56.00, 51.74 ppm; MS (ESI): $m/z = 209$ ($[M+H]^+$); HRMS (ESI): m/z calculated (for $C_{11}H_{13}O_4^+$) 209.0814, found 209.0815.

*3-Methoxy-4-(methoxymethoxy)benzaldehyde (***11**)
A solution of 10.0 g of vanillin (**10**, 65.7 mmol) in 66 cm^3 CH_2Cl_2 was cooled to 0 °C and 18.3 cm^3 of iPr$_2$EtN (105 mmol) was added. After 5 min, 40.7 cm^3 of MOM-Cl in toluene (85.4 mmol, 2.1 M solution in toluene) was added dropwise and the resulting mixture was stirred at RT for 24 h. Saturated aq. NH_4Cl (50 cm^3) was added and the resulting layers were separated. Aqueous layer was extracted with CH_2Cl_2 (3 × 50 cm^3) and combined organic layers were washed with 50 cm^3 brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1) yielded 12.5 g of **11** (85%). M.p.: 40–41 °C (Ref. [23], 39–40 °C); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.53$ (s, 3H), 3.95 (s, 3H), 5.33 (s,

2H), 7.15–7.19 (m, 1H), 7.28 (dd, $J = 7.7$, 1.0 Hz, 1H), 7.44 (d, $J = 1.1$ Hz, 1H), 9.87 (s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 56.2$, 56.7, 95.2, 109.7, 114.8, 126.6, 131.2, 150.2, 152.2, 191.2 ppm; MS (ESI): $m/z = 197$ ($[M+H]^+$); HRMS (ESI): m/z calculated (for $C_{10}H_{13}O_4^+$) 197.0808, found 197.0808.

Methyl 3-hydroxy-3-[3-methoxy-4-(methoxymethoxy)-phenyl]propanoate (**12**, $C_{13}H_{18}O_6$)

A mixture of 1.0 g **11** (5.1 mmol), 0.96 cm^3 of methyl bromoacetate (10.2 mmol), and 2.48 g of $FeCl_3$ (15.3 mmol) in 51 cm^3 of dry THF was stirred at RT and 372 mg of Mg (124 mmol, fine powder) was added at once. The resulting mixture was stirred at RT for 24 h before it was diluted with 35 cm^3 H_2O and 65 cm^3 EtOAc. The resulting suspension was stirred for additional 15 min before it was filtered through Celite®. The whole mixture was diluted with 20 cm^3 2% HCl and the layers were separated. The aqueous layer was extracted with EtOAc (3×25 cm^3). Combined organic layers were washed with 25 cm^3 water and 25 cm^3 brine, dried over Na_2SO_4, evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1–> 1:1) yielding 0.345 g of resulting hydroxy ester **12** (25%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.71$ (dd, $J = 16.4$, 3.6 Hz, 1H), 2.78 (dd, $J = 16.3$, 9.3 Hz, 1H), 3.52 (s, 3H), 3.74 (s, 3H), 3.90 (s, 3H), 5.10 (dd, $J = 9.2$, 3.6 Hz, 1H), 5.22 (s, 2H), 5.64 (broad s, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.98 (d, $J = 2.0$ Hz, 1H), 7.12 (d, $J = 8.3$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 43.4$, 52.2, 56.1, 56.4, 70.3, 95.7, 109.4, 116.5, 137.1, 146.2, 150.1, 173.1 ppm; MS (ESI): $m/z = 271$ ($[M+H]^+$); HRMS (ESI): m/z calculated (for $C_{13}H_{19}O_6^+$) 271.1176, found 271.1179.

Methyl 3-[3-methoxy-4-(methoxymethoxy)phenyl]-3-oxo-propanoate (**7a**, $C_{13}H_{16}O_6$)

A solution of 0.11 g of **12** (0.4 mmol) in 4 cm^3 of dry CH_2Cl_2 was stirred at RT and 0.176 g of PCC (pyridinium chlorochromate, 0.8 mmol) was added. The resulting mixture was stirred at RT for 12 h before 0.3 g of Celite® was added in one portion. The whole mixture was stirred at RT for additional 10 min. The whole mixture was filtered through a plug of 2 g of Celite®. Filter cake was washed with CH_2Cl_2 (3×25 cm^3) and combined filtrates were dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1–> 1:1) and yielded 0.092 g of ketoester **7a** (86%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.53$ (s, 3H), 3.76 (s, 3H), 3.95 (s, 3H), 3.98 (s, 2H), 5.33 (s, 2H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.51 (dd, $J = 8.3$, 2.1 Hz, 1H), 7.57 (d, $J = 2.1$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 45.4$, 52.2, 56.0, 56.4, 95.9, 112.2, 116.6, 135.4, 142.8, 150.4, 151.7, 170.8, 193.8 ppm; MS (ESI): $m/z = 269$ ($[M+H]^+$); HRMS (ESI): m/z calculated (for $C_{13}H_{17}O_6^+$) 269.1020, found 269.1021.

Methyl (E)-7-methoxy-5-(3-methoxy-3-oxoprop-1-en-1-yl)-2-[3-methoxy-4-(methoxymethoxy)phenyl]benzofuran-3-carboxylate (**8a**, $C_{24}H_{24}O_9$)

A solution of 0.366 g di-*tert*-butyl peroxide (2.5 mmol) in 1.0 cm^3 of 1,2-dichloroethane was added drop-wise into a stirred solution of 0.268 g of **7a** (1.0 mmol), 0.229 g of phenol **6a** (1.1 mmol), 0.09 g *N*-hydroxyphthalimide (0.05 mmol), and 0.16 g $FeCl_3$ (0.1 mmol) in 2 cm^3 of 1,2-dichloroethane under an argon atmosphere at room temperature. The reaction mixture was heated at 70 °C (external) for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1–> 1:1) and yielded 0.164 g of benzofuran **8a** (36%). M.p.: 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.50$ (s, 3H), 3.94 (s, 3 H), 3.96 (s, 3 H), 4.02 (s, 3 H), 4.04 (s, 3H), 5.06 (s, 2 H), 6.41 (d, $J = 15.9$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 7.23 (d, $J = 2.1$ Hz, 1H), 7.44 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.56 (d, $J = 1.7$ Hz, 1H), 7.76 (d, $J = 15.8$ Hz, 1H), 7.80 (s, 1 H) ppm; ^{13}C NMR (100.1 MHz, $CDCl_3$): $\delta = 51.2$, 52.4, 54.2, 56.4, 58.9, 92.7, 110.0, 111.5, 111.6, 114.5, 115.6, 116.2, 121.2, 122.9, 128.1, 131.2, 143.3, 146.4, 146.6, 148.9, 149.9, 160.4, 167.5, 167.9 ppm; MS (ESI): $m/z = 457$ ($[M+H]^+$); HRMS (ESI): m/z calculated (for $C_{24}H_{25}O_9^+$) 457.1493, found 457.1490.

Methyl (2R,3R)-7-methoxy-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-2-[3-methoxy-4-(methoxymethoxy)phenyl]-2,3-dihydrobenzofuran-3-carboxylate (**9a**, $C_{24}H_{26}O_9$)

Magnesium powder (0.08 g, 3.3 mmol) followed by 0.012 g of NH_4Cl (0.22 mmol) were added to a solution of 0.05 g of **8a** (0.11 mmol) in 4 cm^3 of THF/MeOH [1:1 (v/v)] mixture cooled to − 10 °C. The resulting mixture was vigorously stirred and then slowly allowed warm to RT over 4 h. The reaction was cooled to − 40 °C before being quenched by the addition of 20 cm^3 of saturated aqueous NH_4Cl. The mixture was allowed to warm to RT before being partitioned between 20 cm^3 of H_2O and 20 cm^3 of CH_2Cl_2. Resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 cm^3). The combined organic phases were dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1–> 1:1) and yielded 0.060 g of dihydrobenzofuran **9a** (59%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.50$ (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 4.35 (d, $J = 8.1$ Hz, 1H), 5.22 (s, 2H), 6.14 (d, $J = 8.1$ Hz, 1H), 6.33 (d, $J = 15.9$ Hz, 1H), 6.92 (dd, $J = 12.0$, 2.5 Hz, 1H), 6.95

(s, 2H), 7.03 (d, $J = 1.6$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.19 (d, $J = 1.3$ Hz, 1H), 7.65 (d, $J = 16.0$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 51.9$, 53.1, 55.6, 56.2, 56.3, 56.4, 87.4, 95.6, 109.8, 112.3, 115.8, 116.5, 118.1, 118.9, 125.8, 128.8, 133.8, 144.9, 146.9, 150.1, 150.1, 167.8, 170.9 ppm; MS (ESI): *m/z* = 459 ($[M+H]^+$); HRMS (FAB): *m/z* calculated (for $C_{24}H_{26}NaO_9^+$) 481.1469, found 481.1470.

(E)-3-[(2R,3S)-3-(Hydroxymethyl)-7-methoxy-2-[3-methoxy-4-(methoxymethoxy)phenyl]-2,3-dihydrobenzofuran-5-yl]prop-2-en-1-ol (**14**, $C_{22}H_{26}O_7$)

A solution of 0.436 g **9a** (0.95 mmol) in 10 cm^3 of CH_2Cl_2 was cooled to − 78 °C and 4.8 cm^3 of DIBAL-H (4.73 mmol, as 1 M solution in CH_2Cl_2) was added dropwise. The resulting solution was stirred at − 78 °C for 30 min and additional 2 h at RT. The resulting mixture was re-cooled to − 78 °C and 10 cm^3 of sat. aq. sol. of Rochel's salt was added. The whole mixture was allowed to stir at RT for 12 h. The resulting layers were separated and the aqueous layer was extracted with DCM (3 × 20 cm^3). Combined organic layers were washed with 20 cm^3 of brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 2:1–> 1:1) and yielded 0.400 g of diol **14** (92%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.07$ (d, $J = 8.3$ Hz, 1H), 6.94 (d, $J = 1.8$ Hz, 1H), 6.89 (dd, $J = 8.3$, 2.1 Hz, 1H), 6.84 (d, $J = 3.1$ Hz, 2H), 6.50 (d, $J = 15.9$ Hz, 1H), 6.19 (dt, $J = 15.6$, 5.8 Hz, 1H), 5.57 (d, $J = 6.7$ Hz, 1H), 5.18 (s, 2H), 4.24 (d, $J = 6.1$ Hz, 2H), 3.90 (dd, $J = 11.0$, 6.4 Hz, 1H), 3.87 (s, 3H), 3.84 (dd, $J = 10.7$, 5.8 Hz, 1H), 3.82 (s, 3H), 3.57 (dd, $J = 11.9$, 6.1 Hz, 1H), 3.47 (s, 3H), 2.79 (s, $J = 31.1$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 150.00$, 148.31, 146.43, 144.46, 135.50, 131.29, 131.02, 128.35, 126.53, 118.71, 116.39, 115.05, 110.56, 109.83, 95.54, 88.05, 77.23, 63.76, 60.60, 56.30, 56.11, 56.05, 53.66 ppm; MS (ESI): *m/z* = 403 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{22}H_{27}O_7^+$) 403.1751, found 403.1748.

(E)-3-[(2R,3S)-3-(Acetoxymethyl)-7-methoxy-2-[3-methoxy-4-(methoxymethoxy)phenyl]-2,3-dihydrobenzofuran-5-yl]allyl acetate (**15**, $C_{26}H_{30}O_9$)

A solution of 0.241 g of **14** (0.6 mmol) in 6 cm^3 of CH_2Cl_2 was cooled to 0 °C and 0.886 cm^3 of Et_3N (6.35 mmol) was added. The resulting mixture was stirred for 5 min and 0.213 cm^3 of acetyl chloride (3 mmol) was added. The resulting mixture was allowed to warm to RT and stirred for additional 36 h. Saturated aq. $NaHCO_3$ (20 cm^3) was added and resulting layers were separated. Aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3) and the combined organic layers were washed with 10 cm^3 of brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1– > 2:1) and yielded 0.239 g of diacetal **15** (82%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.05$ (s, 3H), 2.11 (s, 3H), 3.51 (s, 3H), 3.78 (td, $J = 7.2$, 5.3 Hz, 1H), 3.86 (s, 3H), 3.92 (s, 3H), 4.31 (dd, $J = 11.1$, 7.5 Hz, 1H), 4.44 (dd, $J = 11.2$, 5.4 Hz, 1H), 4.72 (dd, $J = 6.7$, 1.2 Hz, 2H), 5.22 (s, 2H), 5.51 (d, $J = 7.1$ Hz, 1H), 6.16 (dt, $J = 15.9$, 6.6 Hz, 1H), 6.61 (d, $J = 16.0$ Hz, 1H), 6.89 (s, 2H), 6.92 (dd, $J = 11.1$, 2.1 Hz, 2H), 7.12 (d, $J = 8.2$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 20.9$, 21.1, 50.4, 56.0, 56.1, 56.3, 65.3, 65.4, 88.5, 95.5, 109.6, 110.6, 115.4, 116.3, 118.8, 121.2, 127.7, 130.6, 134.5, 134.7, 144.5, 146.7, 148.3, 150.0, 170.9, 171.0 ppm; MS (ESI): *m/z* = 488 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{26}H_{31}O_9^+$) 487.1962, found 487.1966.

(E)-3-[(2R,3S)-3-(Acetoxymethyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl]allyl acetate (**16**, $C_{24}H_{26}O_8$)

A solution of 0.331 g of **15** (0.68 mmol) in 10 cm^3 of Et_2O was cooled to 0 °C and 0.525 g of $MgBr_2{\cdot}Et_2O$ (2.0 mmol) was added. The resulting mixture was allowed to warm to RT and stirred for 3 h. Water (15 cm^3) was added and the whole mixture was extracted with CH_2Cl_2 (3 × 20 cm^3). Combined organic layers were washed with 10 cm^3 brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 2:1–> 1:1) and yielded 0.235 g of phenol **16** (78%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.06$ (s, 3H), 2.11 (s, 3H), 3.19–3.33 (m, 1H), 3.74 (s, 3H), 3.93 (s, 3H), 4.70 (s, 2H), 4.72 (dd, $J = 6.6$, 1.3 Hz, 2H), 5.64 (broad s, 1H), 6.16 (s, 1H), 6.19 (td, $J = 15.8$, 6.5 Hz, 1H), 6.58 (d, $J = 15.7$ Hz, 1H), 6.81 (d, $J = 8.2$ Hz, 1H), 6.85 (dd, $J = 7.9$, 2.0 Hz, 1H), 6.90 (d, $J = 8.2$ Hz, 1H), 6.99 (dd, $J = 7.2$, 1.7 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 20.8$, 21.1, 55.8, 56.2, 64.1, 65.3, 77.4, 93.2, 110.3, 111.2, 114.3, 116.6, 119.0, 120.0, 122.4, 123.3, 126.3, 129.2, 132.0, 134.1, 144.6, 150.1, 170.8, 171.2 ppm; MS (ESI): *m/z* = 443 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{24}H_{27}O_8^+$) 443.1700, found 443.1702.

Methyl (2R,3R)-2-[4-[(tert-butyldimethylsilyl)oxy]-3-methoxyphenyl]-7-methoxy-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate
(**17**, $C_{28}H_{36}O_8Si$)

A solution of 0.414 g of **13** (1.0 mmol) and 0.340 g of imidazole (5.0 mmol) in 10 cm^3 of dry DMF was cooled to 0 °C and 0.181 g of TBSCl was added in one portion. The resulting mixture was stirred at RT for 12 h before it was diluted with 25 cm^3 of sat. aq. $NaHCO_3$. The whole mixture was extracted with EtOAc (3 × 25 cm^3) and the organic layers were combined, washed with 10 cm^3 brine,

dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 20:1–> 10:1) and yielded 0.501 g of TBS-protected phenol **17** (95%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.13 (s, 6H), 0.96 (s, 9H), 3.81 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 4.35 (d, J = 8.1 Hz, 1H), 6.14 (d, J = 8.1 Hz, 1H), 6.33 (d, J = 15.9 Hz, 1H), 6.92 (dd, J = 12.0, 2.5 Hz, 1H), 6.95 (s, 2H), 7.03 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 1.3 Hz, 1H), 7.65 (d, J = 16.0 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = − 4.5, 19.1, 25.8, 53.1, 55.6, 56.2, 56.3, 56.4, 87.4, 109.8, 112.3, 115.8, 116.5, 118.1, 118.9, 125.8, 128.8, 133.8, 144.9, 146.9, 150.1, 150.1, 167.8, 170.9 ppm; MS (ESI): *m/z* = 530 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{28}H_{37}O_8Si^+$) 529.2252, found 529.2250.

Methyl (E)-3-[(2R,3S)-2-[4-[(tert-butyldimethylsilyl)oxy]-3-methoxyphenyl]-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl]acrylate (**18**, $C_{27}H_{36}O_7Si$)

A solution of 0.264 g of **17** (0.5 mmol) in 10 cm^3 of THF was cooled to − 78 °C and 1.5 cm^3 of $LiBH_4$ (3.0 mmol, 1.0 M solution in THF) was added dropwise. Resulting mixture was stirred at − 78 °C for additional 30 min. The cooling bath was removed and the whole mixture was stirred at RT for additional 2 h. Saturated aqueous NH_4Cl (20 cm^3) was added and resulting layers were separated. Aqueous layer was extracted with EtOAc (3 × 25 cm^3) and combined organic layers were washed with 15 cm^3 brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 2:1–> 1:1) and yielded 0.202 g of monoester **18** (82%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, benzene-d_6): δ = 0.11 (s, 6H), 1.01 (s, 9H), 3.18 (s, 3H), 3.26 (p, J = 6.1 Hz, 1H), 3.29 (s, 3H), 3.34 (dd, J = 10.2, 6.5 Hz, 1H), 3.38 (dd, J = 10.7, 5.5 Hz, 1H), 3.49 (s, 3H), 5.55 (d, J = 6.5 Hz, 1H), 6.43 (d, J = 15.9 Hz, 1H), 6.69 (d, J = 1.4 Hz, 1H), 6.71 (d, J = 1.5 Hz, 1H), 6.82 (6.69 (d, J = 1.4 Hz, 1H), 6.86 (d, J = 1.1 Hz, 1H), 7.86 (d, J = 15.9 Hz, 1H) ppm; ^{13}C NMR (126 MHz, benzene-d_6): δ = − 4.7, 18.4, 25.7, 50.9, 53.5, 54.8, 55.4, 64.0, 88.2, 110.0, 112.6, 115.2, 117.5, 118.5, 120.9, 128.0, 128.4, 129.2, 135.1, 145.0, 145.1, 145.2, 151.3, 167.2 ppm; MS (ESI): *m/z* = 502 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{27}H_{37}O_7Si^+$) 501.2303, found 501.2304.

Methyl 3-[(2R,3S)-2-[4-[(tert-butyldimethylsilyl)oxy]-3-methoxyphenyl]-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl]propanoate (**19**, $C_{27}H_{38}O_7Si$)

A solution of 0.05 g of olefin **18** (0.1 mmol) in 5 cm^3 of MeOH stirred at RT and 4 mg of 5 mol% Pd/C was added. Resulting mixture was placed under the atmosphere of H_2 (1.3 atm) and stirred at RT for 2 h. The resulting mixture was then filtered through a pad of Celite® and the filter cake was washed with EtOAc (3 × 20 cm^3). Combined organic layers were evaporated under reduced pressure and the residue was purified by column chromatography (SiO_2; CH_2Cl_2:MeOH = 100:1–> 70:1) yielding 0.047 g of desired reduced product **19** (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.13 (s, 6H), 0.98 (s, 9H), 2.58 (dd, J = 8.4, 7.1 Hz, 1H), 2.64 (dd, J = 8.4, 7.1 Hz, 1H), 2.85 (t, J = 7.8 Hz, 1H), 2.88–2.99 (m, 1H), 3.46 (p, J = 7.2 Hz, 1H), 3.69 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 3.98 (dd, J = 11.1, 5.8 Hz, 1H), 4.04 (dd, J = 12.6, 5.9 Hz, 1H), 5.54 (d, J = 7.4 Hz, 1H), 6.66–6.70 (m, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.85 (dd, J = 8.2, 2.1 Hz, 1H), 6.91 (d, J = 2.1 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = − 4.5, − 4.4, 18.7, 25.6, 25.9, 31.1, 36.4, 51.9, 53.9, 55.6, 55.7, 64.1, 88.1, 110.4, 112.5, 116.1, 119.0, 121.0, 132.0, 134.2, 134.7, 142.4, 144.4, 147.1, 151.3, 173.7 ppm; MS (ESI): *m/z* = 504 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{27}H_{39}O_7Si^+$) 503.2460, found 503.2459.

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Unified approach to benzo[*d*]thiazol-2-yl-sulfonamides

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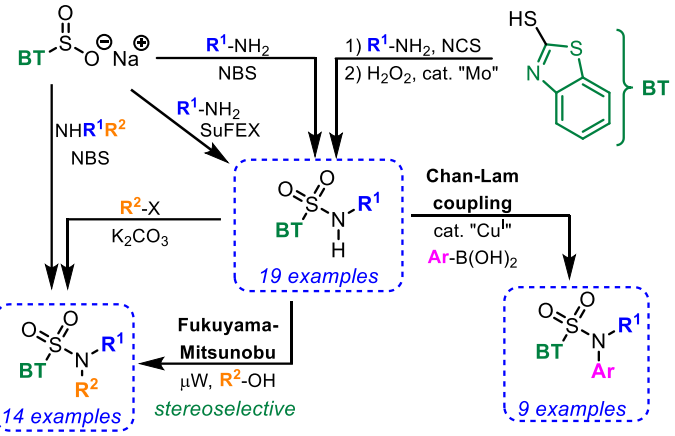


ABSTRACT: In this paper, we report a unified approach to *N*-substituted and *N,N*-disubstituted benzothiazole (BT) sulfonamides. Our approach to BT-sulfonamides starts from simple commercially available building blocks (benzo[d]thiazole-2-thiol and primary and secondary amines) that are connected via (a) S-oxidation/S-N coupling approach, (b) S-N coupling/S-oxidation sequence, or via (c) S-oxidation/S-F bond formation/SuFEx approach. Labile N-H bond in *N*-monoalkylated BT-sulfonamides (p*K*a ($BTSO_2N(\mathbf{H})Bn$) = 3.34±0.05) further allowed us to develop simple weak base-promoted *N*-alkylation method and stereoselective microwave promoted Fukuyama-Mitsunobu reaction. *N*-alkyl-*N*-aryl BT-sulfonamides were accessed with the help of Chan-Lam coupling reaction. Developed methods were further used in stereo and chemoselective transformations of podophyllotoxin and several amino alcohols.

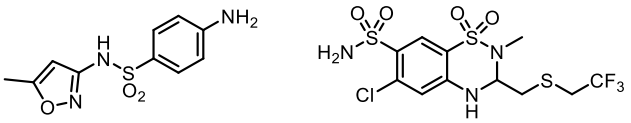
Introduction

Sulfonamide-containing natural products[1–4] occupy a privileged place in the group of biologically active compounds. The biological activity of such compounds varies from antibacterial,[5] antiviral,[6] antiretroviral,[7] and diuretical,[8] to anticonvulsant[9] (Figure 1). Such a broad spectrum of biological activities triggered the interest of the synthetic community and led to the development of several interesting ways for sulfonamide moiety synthesis (Scheme 1). The most commonly used approach is based on the reaction of amines and sulfonyl chlorides,[10–12] that are in their turn obtained via chlorosulfonylation of (hetero)aryl compounds,[13,14] via sulfochorination of hydrocarbons,[15] or via thiol oxidation[16]/chlorination[17] sequence (Scheme 1A). The main drawbacks of these methods are (a)

low thermal stability of (heteroaryl) sulfonyl chlorides, and (b) rather limited functional group tolerance.

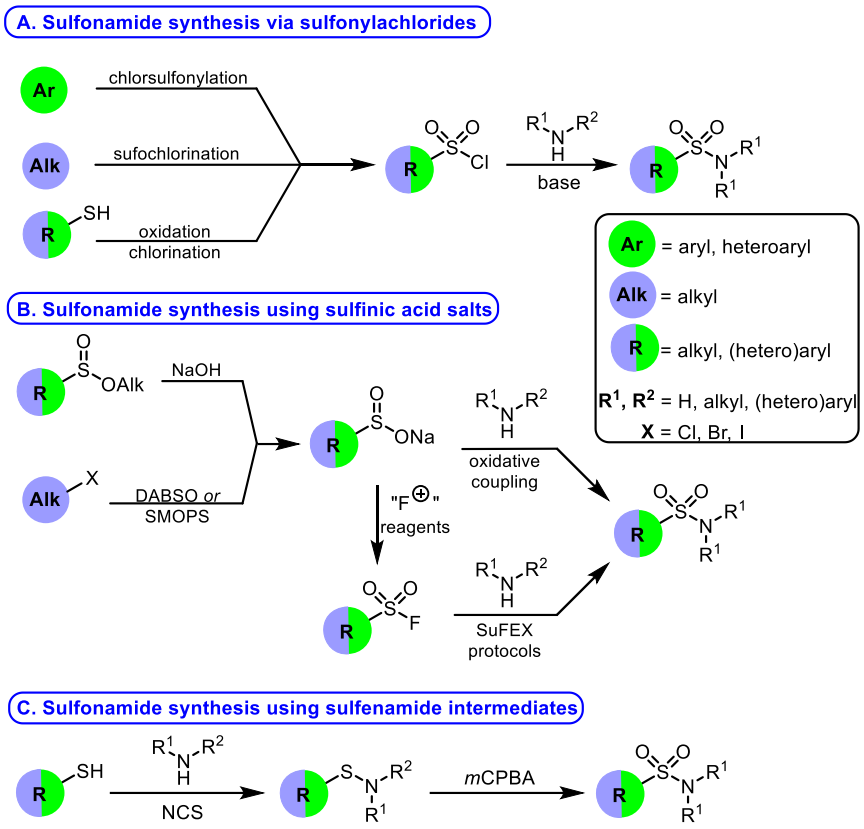
These limitations led scientists to develop an alternative synthetic route based on the use of sulfinic salts (Scheme 1B). In this approach, sulfinic salts are smoothly prepared via sulfinic ester hydrolysis,[18] or by sulfonylation (using DABSO reagent)[19,20] or trans-sulfonylation (using SMOPS reagent)[21] of alkyl halides. Generated sulfinic salts are usually thermally and moisture insensitive solids that can be readily transformed to the desired sulfonamides using various oxidative protocols. In such cases, sulfinic salts are reacted with *in situ* generated electrophilic brominating or iodinating species (*in situ* generation of the corresponding sulfonyl halides) in the presence of an excess of amine.[22–26] Alternatively, sulfinic salts can be also oxidized in the presence of amines to sulfonamides with help of electrochemistry.[27] Finally, sulfinic salts can be readily converted to sulfonamides using SuFEx chemistry approach.[28,29] The last approach, that is only scarcely used, is based on the transformation of thiols to sulfenamides, that are further oxidized to sulfonamides (Scheme 1C).[30–32] The main drawback of this approach is the oxidation step that yields the desired sulfonamides in low yields.

All three described methods are working well in the case of alkyl or aryl sulfonamide synthesis. However, in the case of heteroaryl sulfonamides (Scheme 2), generated reaction intermediates are either unstable,[33] prepared under harsh reaction conditions (use of Cl_2(g)),[34,35] obtained in low reaction yields, or unsuitable for *N,N*-arylalkyl sulfonamide synthesis.[26,34–36] In our contribution, we wish to report a unified approach to *N*-monoalkyl, *N,N*-dialkyl-, and *N,N*-alkylaryl benzothiazole sulfonamides. Several approaches to target *N*-substituted, and *N,N*-disubstituted benzothiazole sulfonamides are (mechanistically) investigated and scope and limitations are established.

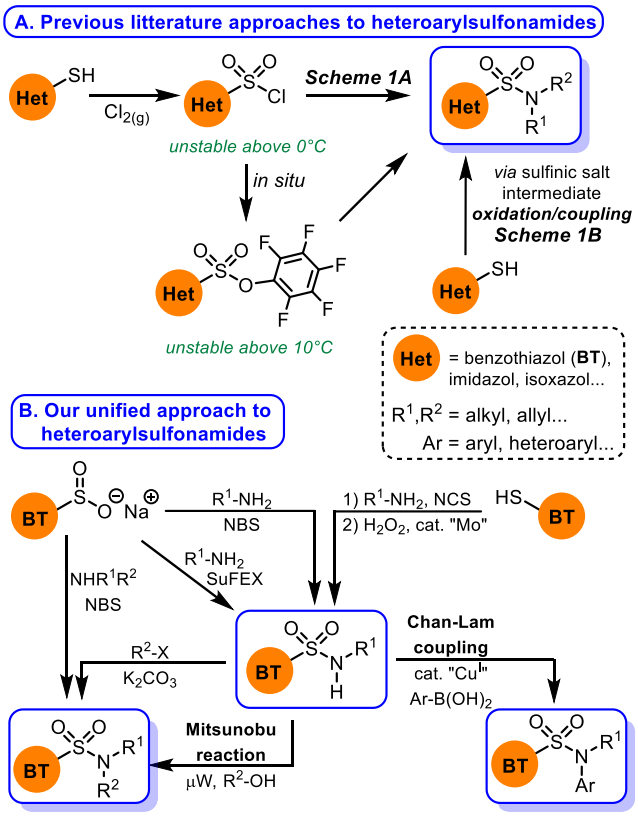


Sulfamethoxazole (antibiotic) **Polythiazide** (diuretic)

Figure 1. Two examples of sulfonamides containing antibiotic (sulfametoxazole) and diuretic[8] (polythiazide) drugs.



Scheme 1. Current methods of sulfonamide synthesis – general overview.



Scheme 2. (**A**) Previous approaches to various heteroarylsulfones,[34–36] and (**B**) our unified approach to such structures.

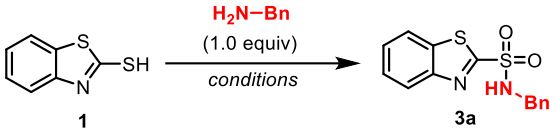
Results and discussions

Approaches based on S-oxidation and S-N bond formation sequences

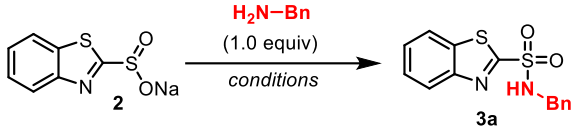
At the onset of our project was the desire to extend our research interest from benzothiazoylsulfones[37–39] ($BTSO_2R$) to the corresponding amides ($BTSO_2NR_2$). To do so, a short, practical, and convenient way of BT-sulfonamides was searched. Unfortunately, most of the common synthetic paths to such heteroaryl sulfonamides proved to be either unpractical (e.g., use of Cl_2(g)),[33,35] or failed in our hands (for selected examples see Table 1, entries 1 to 3).[34,36] Thus, readily available BT-sulfinic acid salt **2** was used as a starting material for the sulfonamide synthesis. In this regard, the conditions of Yan and co-workers[22] proved to be suitable and generated the desired sulfonamide **2a** in 77% yield (Table 1, entry 7). The protocol, however, lacks the atom economy. Fortunately, the reaction mechanism evaluation identified bromine cations as the key reagent of transformation[40] and a simplified version of the protocol based on the use of Br_2 (suitable for small-scale reactions) and NBS (safer bromine cation source), respectively, (Table 1, entries 8 and 9) was developed.[41] Under such conditions, the reaction was fast and yields the desired sulfonamide **3a** in excellent isolated yields (86% and 91%, respectively) even in 10 mmol scale (Table 1, entry 10).

Eventhough we had a short and efficient way to **3a** starting from sulfinic salt **2**, an alternative way starting from sulfide **1** was searched. As demonstrated in Tables 1A and 1B, all previously tested methods employ the same sequence, S^{-II}/S^{IV}-oxidation followed by the S-N bond formation. Interestingly, the S-N[32] bond formation followed by S^{-II}/S^{IV}-oxidation approach is scarcely used in the literature when heterocyclic sulfonamides are targeted.[42,43] The main drawback of such approach is the low-yielding oxidation step. After the careful reaction optimization, the combination of Brownbridge's[32] sulfenamide formation and Mo-promoted[37-39] H_2O_2-based oxidation sequence was found as the most suitable (Table 1, entry 5). The reaction was again readily scalable up to the 10 mmol scale (Table 1, entry 6).

Table 1. Selected examples of *N-benzylbenzo[d]thiazole-2-sulfonamide* **3a** synthesis optimization.



Entry	Conditions	Yield [%][a)]
1[35]	1) **1** (5.0 equiv), HCl, NaClO, 0°C, CH_2Cl_2, 1h 2) **BnNH₂**, CH_2Cl_2, -10°C, 4h	15%
2[33]	1) **1** (5.0 equiv), HCl, NaClO, 0°C, CH_2Cl_2, 1h, then -30°C, C_6F_5OH (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 5h 2) **BnNH₂**, CH_2Cl_2, -30°C to 0°C, 1h	48%
3[36]	**1** (1.0 equiv), $ZrCl_4$ (1 equiv), H_2O_2 (4 equiv), pyr, rt, 1h	n.d.
4[44]	1) **1** (1.0 equiv), NCS (1.2 equiv), -40°C, CH_2Cl_2, 1h *then* **BnNH₂** (2.0 equiv), -40°C to rt, 24h 2) $KMnO_4/CuSO_4$, CH_3CN, rt	<5%
5	**1** (1.0 equiv), **BnNH₂** (3.0 equiv), NCS (1.0 equiv), rt, CH_2Cl_2, 30 min *then* H_2O_2 (10 equiv), $(NH_4)_6MoO_4 \bullet 4H_2O$ (0.2 equiv), EtOH, 0°C to rt, 5h	92%
6[b)]	**1** (1.0 equiv), **BnNH₂** (3.0 equiv), NCS (1.0 equiv), rt, CH_2Cl_2, 30 min *then* H_2O_2 (10 equiv), $(NH_4)_6MoO_4 \bullet 4H_2O$ (0.2 equiv), EtOH, 0°C to rt, 5h	94%



7[22]	**2** (1.0 equiv), DIPEA (1.5 equiv), TBAB (1.5 equiv), *m*CPBA (3 equiv), THF:EtOH (30:1), rt, 4h	77 %
8	**2** (1.0 equiv), DIPEA (1.5 equiv), Br_2 (2 equiv) THF:EtOH (1:1), rt, 5 min	86%
9	**2** (1.0 equiv), NBS (1.5 equiv) THF:EtOH (4:1), rt, 5 min	91%
10[b)]	**2** (1.0 equiv), NBS (1.25 equiv) THF:EtOH (4:1), rt, 10 min	90%

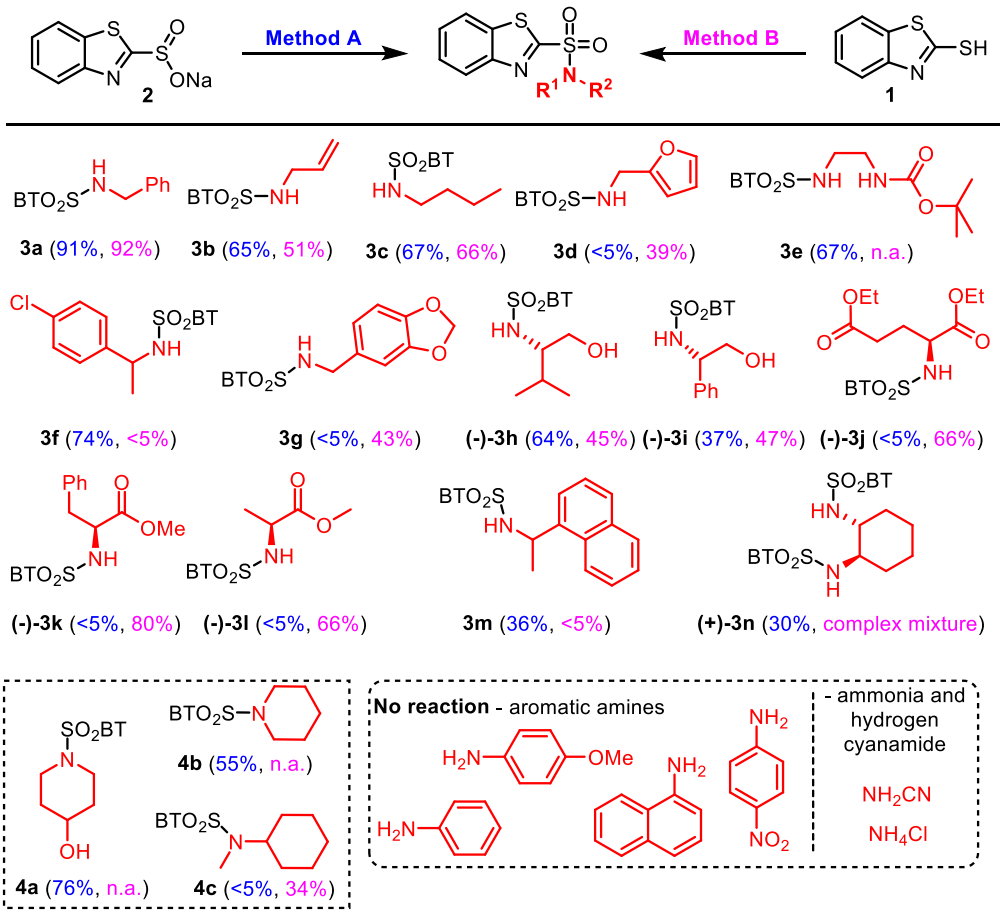
[a)] Refers to isolated yield. [b)] Performed on a 10 mmol scale of **2**. DIPEA – diisopropylethylamine; TBAB – tetrabutylammonium bromide; *m*CPBA – *m*-chloroperbenzoic acid, NBS – *N*-bromosuccinimide, NCS – *N*-chlorosuccinimide.

Having found suitable and robust reaction conditions for sulfonamide **3a** synthesis, the scope and limitations of both methods were established (Table 2). In general, both methods yielded the desired *N*-substituted sulfonamides **3** in good to very good yields if unfunctionalized primary α-unbranched

amines were used as the starting material (**3a-c**). The methods became supplementary if heteroaryl substituted amine (**3d**), aryl substituted amines (**3f, 3g, 3m**), and ester or carbamoyl group bearing amines were used ((–)-**3j-l**). Both methods tolerate the free hydroxy groups ((–)-**3h,i**). If a diamino-substituted substrate was used, both amino groups were transformed to the corresponding sulfonamides albeit in low reaction yield ((+)-**3n**). When homochiral amines with α-stereogenic centers were used as a starting material ((–)-**3h-l**, (+)-**3n**), no breach in stereo integrity was observed.

The reactivity of secondary amines proved to be problematic, and the corresponding sulfonamides **4** were obtained in reasonable yields only in the case of piperidine derivatives **4a** and **b**. The only exception was sulfonamide **4c** that was prepared in 34% yield.[40] Aromatic amines and simple amine sources such as NH_4Cl (to generate ammonia *in situ*) and NH_2CN failed to generate the desired products. In both cases, we speculate that the stability or inability to generate the key intermediates, sulfonyl bromide (Method A) and sulfenyl chloride (Method B), respectively, is responsible for the observed nonreactivity.[40]

Table 2. Scope and limitations of sulfonamide **3** and **4** synthesis.[a)]



[a)] The reactions were performed with 2 mmol of substrate **2** (Method A) and 1 mmol of substrate **1** (Method B); Yields refer to pure isolated compounds; *Conditions.* **Method A**: Substrate **2** (1 equiv), RNH_2 (1.2 equiv), NBS (2 equiv), THF/EtOH, rt, 10 mins. **Method B**: Substrate **1** (1 equiv), NCS (1 equiv), RNH_2 (3 equiv), CH_2Cl_2, rt, 30 min, *then* $(NH_4)_6MoO_4•4H_2O$ (0.3 equiv), H_2O_2 (20 equiv), EtOH, 0°C to rt, 5h. NBS – *N*-bromosuccinimide, NCS – *N*-chlorosuccinimide.

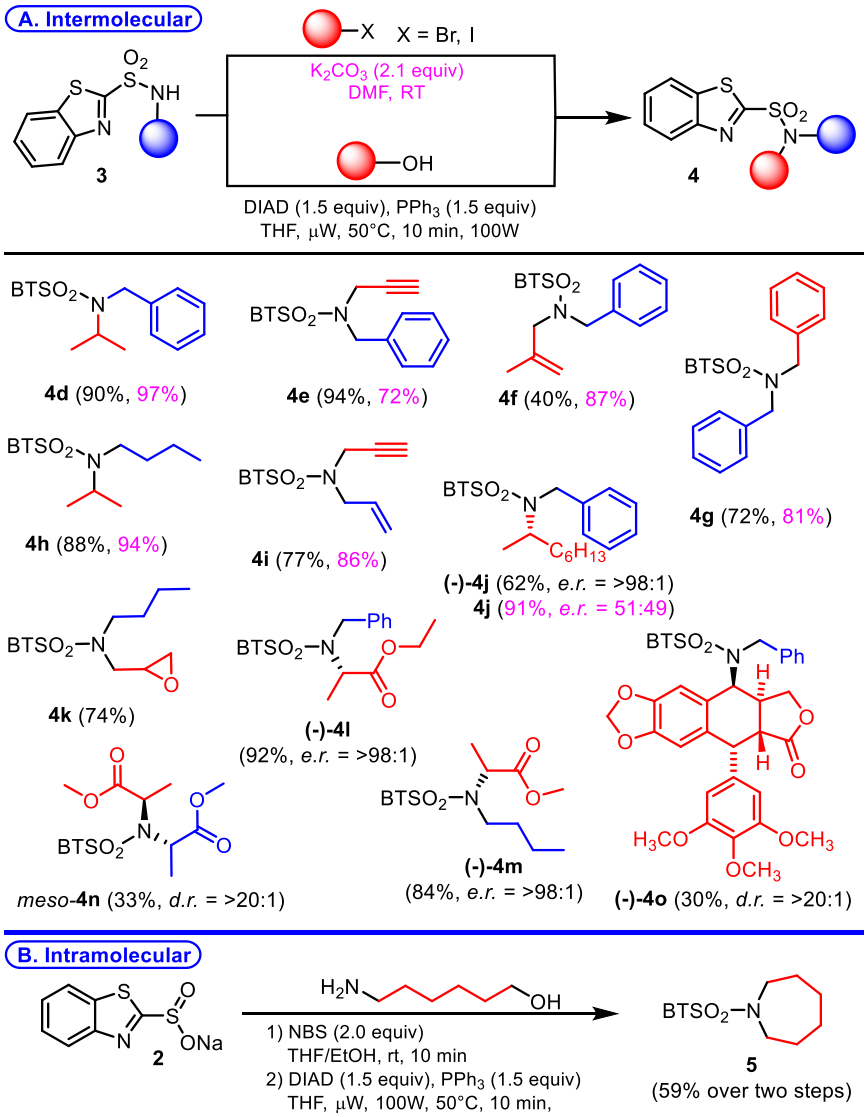
***N*-alkylation of *N*-monosubstituted sulfonamides**

Having an easy access to *N*-monosubstituted sulfonamides, *N*-alkylation of the prepared sulfonamides **3** seemed to use as the best synthetic path to *N,N*-disubstituted sulfonamides. To evaluate the feasibility of this approach, the *p*Ka value of **3a** was determined.[45] Low pKa value of sulfonamide N-H hydrogen (pKa(**3a**) = 3.34±5) suggested that two different approaches to *N,N*-disubstituted sulfonamide **4** be considered (Table 3). The first approach relied on the reaction with alkyl halides in the presence of K_2CO_3, and the second explored sulfonamides **3** as *N*-nucleophiles in the microwave irradiation-promoted[40,46] Fukuyama-Mitsunobu alkylation reaction.[47] Scope and limitations of those transformations are highlighted in Table 3.

It was observed that both primary and secondary alkyl halides react with *N*-monosubstituted **3a-c** smoothly and yielded the desired *N,N*-disubstituted sulfonamides **4d-i** in good to excellent yields (Table 3A). In addition microwave-promoted Fukuyama-Mitsunobu alkylation (FMA) reaction of sulfonamides **3a-c** with primary, allylic and even secondary alcohols resulted in the formation of *N,N*-disubstituted sulfonamides **4d-o** in good to excellent yields (Table 3A). In all evaluated examples, microwave conditions tolerated a wide range of functional groups (alkenes and alkynes (**4e,f,i**), epoxide (**4k**), esters ((−)-**4l-n**), or lactone ((−)-**4o**)), and the transformation proceeded with complete stereoinversion of hydroxy group bearing carbon center ((−)-**4l,m,o**). If several stereogenic centers were present, no influence of the substrate on the FMA selectivity was observed. Using such an approach, a meso sulfonamide *meso*-**4n** was prepared starting from N-monosubstituted sulfonamide (−)-**3l** and methyl lactate, and C4-hydroxy group in podophyllotoxin was transformed to BT-sulfonamide (−)-**4o**. No competitive elimination was observed.

FMA substitution can also be successfully applied in an intramolecular fashion (Table 3B). Combination of the primary BT-sulfonamide coupling with FMA step yields in two-pot inter/intra-molecular approach to cyclic *N,N*-disubstituted sulfonamide **5** in 59% overall yield.

Table 3. Synthesis of *N,N*-Disubstituted sulfonamides **4** and **5**.[a)]



[a)] Reactions were performed with 1 mmol of **3**; Yields refer to pure isolated compounds. DIAD – diethyl azodicarboxylate, NBS – *N*-bromosuccinimide, μW – microwave irradiation.

Buchwald-Hartwig amination

Having secured the synthesis of *N,N*-dialkylsubstituted sulfonamides **4** and **5**, our attention turned to *N,N*-alkylarylsulfonamides **6**. Based on the literature analogy with phenylsulfonamides, we expected that either Buchwald-Hartwig amination[48,49] or Chan-Lam coupling[50–51] would smoothly accomplish such transformation. Unfortunately, in our hands, Buchwald-Hartwig amination failed to generate any traces of the desired arylated sulfonamide **6a** (Scheme 3A).[41] In most cases only the product of compound **3a** formal SO_2 extrusion, compound **7a**, was isolated (Scheme 3B, eq. 1). In analogy with Ni^0-promoted SO_2 extrusion observed in the case of sulfonamides[52], the same mechanism of compound **7a** formation was expected. Much to our surprise, no product **7a** was formed if Pd^0-mediated SO_2 extrusion was attempted (Scheme 3B, eq. 2, and 3). Thus, the role of phenyl iodide under the reaction conditions was questioned (Scheme 3B, eq. 4). It was observed that if 0.2 equiv of phenyl iodide is used, SO_2-free compound **7a** is obtained in 11% yield. This observation suggested

that Pd^{II} that is generated via oxidative addition of Pd^0 to phenyl iodide is the real reaction promoter. To validate this hypothesis, the reaction was carried out in the presence of a catalytic amount of $(PPh_3)_2PdCl_2$ (Scheme 3B, eq. 5). Expected product **7** was obtained in 6% isolated yield. When the transformation was attempted in the presence of base (Scheme 3B, eq. 6), compound **7a** was isolated in 76% yield. The last two observations led us to propose a tentative reaction mechanism shown in Scheme 3B below. It is expected that Pd^{II} interacts with **3a** to yield intermediate **A**. The interaction with strong Lewis acid increases the acidity of the sulfonamide-placed hydrogen atom that might be readily removed with an external base to yield intermediate **B**. Newly generated 5-membered ring in **B** further undergo to intramolecular rearrangement via intermediate **C** to anion **D**. The loss of SO_2 followed by the resulting amide anion reprotonation leads to the Pd^{II} release and the formation of final product **7a**.

Chan-Lam coupling

Having failed to generate the desired C-N bond in sulfonamides with Pd-mediated coupling, our attention turned to copper-promoted Chan-Lam coupling (Scheme 4).[50,51] Being aware that the use of heteroarylsulfonamides as substrates in Chan-Lam coupling might be problematic,[53] intensive reaction conditions screening was carried out.[40] Based on obtained data, we concluded that the reaction has to be carried out starting from copper(I) pre-catalyst with nonnucleophilic counter ion, under the atmosphere of oxygen (1 atm), in the presence of bidentate diamine ligand, and that DCE is an optimal solvent. Using such reaction conditions, the scopes and limitations of the transformation were established (Scheme 4A). Consequently, a tentative reaction mechanism of sulfonamide-based Chan-Lam coupling that is based on our experimental results and previously published Chan-Lam coupling mechanistical studies[51,53,54] was proposed (Scheme 4B). The key observations are listed below:

Copper – no reaction was observed when copper(II) precatalysts were used to promote the reaction.[51]

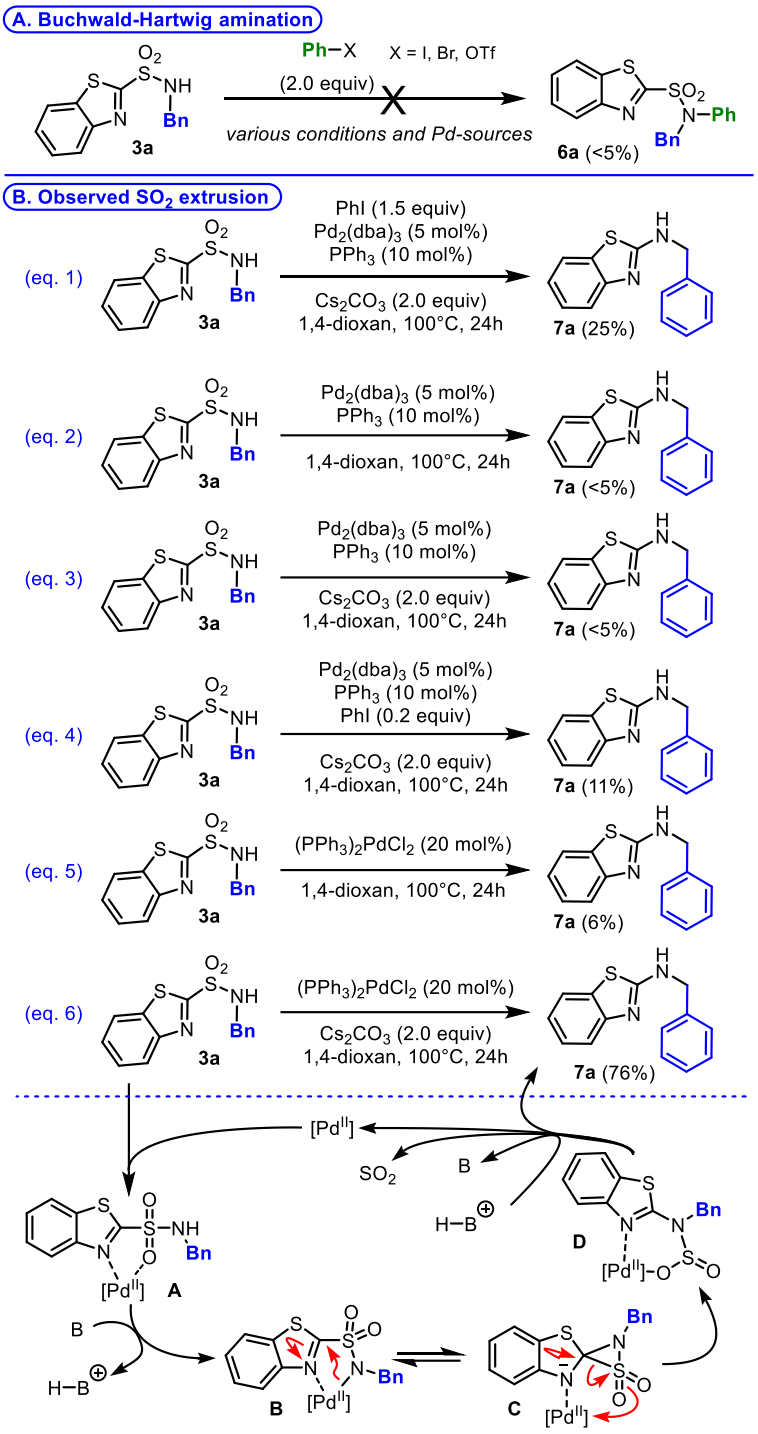
Anion – the nature of copper(I) anion proved to be essential for the reaction yields. In agreement with previously published observations, it was observed that if strongly binding anions such as Cl^-, Br^-, I^-, CN^-, or AcO^- were present in the copper(I) precatalyst, weakly nucleophilic BT-sulfonamides **3** were slow to replace them. Consequently, low BT-sulfonamide **3** conversion was observed.

Ligand – the use of tetramethylendiamine (TMEDA) as a ligand proved to be crucial to promote the coupling reaction. Based on the literature,[51] the presence of TMEDA is increasing the electron density on copper(I) intermediate and facilitates its oxidation to copper(II). In addition, the bidentate character of TMEDA[55] seems to be also beneficial in regard to transmetalation of intermediate **F** to **G**, and possibly also during the selective C-N disproportionation reaction[55] (**G** to **H**) that generates product **6** and regenerates the copper(I) complex. The amount of the TMEDA ligand proved in our case also a dramatic impact on the reaction yield. It was observed that 4 equivalents of TMEDA were the optimal loading. If lower TMEDA loading was used, the conversion of sulfonamide **3** dropped rapidly. Higher loading of TMEDA increased the formation of biphenyl side products.

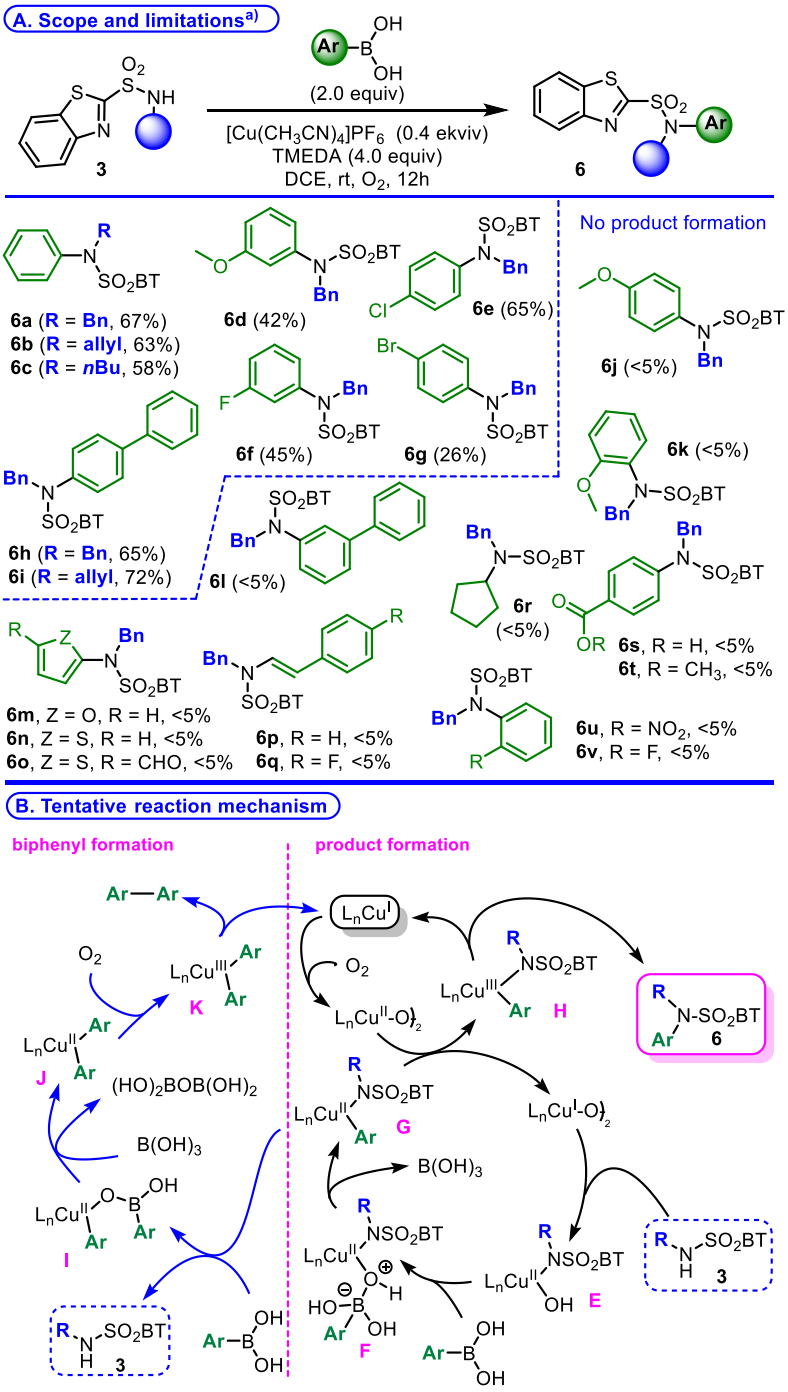
Based on these findings, we speculate that the biphenyl formation can be traced to the intermediate **G** (Scheme 4B). The presence of the excess of TMEDA (bidentate ligand) around copper(II) intermediate **G** is presumably increasing the lability of the sulfonamide ligand. Aryl boronic acid

presented in excess in the reaction mixture can further occupy the free coordination place on copper (and protonate sulfonamide anion) and yield intermediate **I**. Intermediate **I** can further undergo to intramolecular migration to yield complex **J**, so that upon oxidation (Cu^{II} to Cu^{III}; intermediate **K**) and reductive elimination yields the observed biphenyl and regenerated copper(I) complex.[56] It should be noted that the products of homocoupling reaction of boronic acids were commonly present in the reaction mixture during all our experiments since boronic acid was used in large excess[56]

Unfortunately, even under the optimized reaction conditions, the scope of the Chan-Lam coupling proved to be limited (Scheme 4A). Evaluated sulfonamides **3a-c** reacted under such conditions only with phenyl boronic acid (yielding sulfonamides **6a-c**), 4-biphenyl (**6h,i**), 3-methoxyphenyl (**6d**), and 3-fluoro and 4-halogensubstituted phenyl boronic acids (**6i-k**). When heteroaryl substituted (expected products **6m-o**), 4-carboxylic acid or ester-substituted phenyl (**6s,t**), 4-methoxyphenyl (**6j**), styryl (**6p,q**), all tested 2-substituted phenyl (**6k,u,v**), or cyclopentyl boronic acid (**6r**) were reacted, no conversion of sulfonamide **3a** was observed. The only detected products in the reaction mixture were the homocoupling products generated from the boronic acid employed.[40]



Scheme 3. Buchwald-Hartwig amination of sulfonamide **3a**. (A) Attempted amination reactions. (B) Evaluation of the side product formation.



[a)] Reactions were performed with 1 mmol of **3**; Yields refer to pure isolated compounds. TMEDA – tetramethylethylendiamine; DCE – dichloroethane; Bn – benzyl.

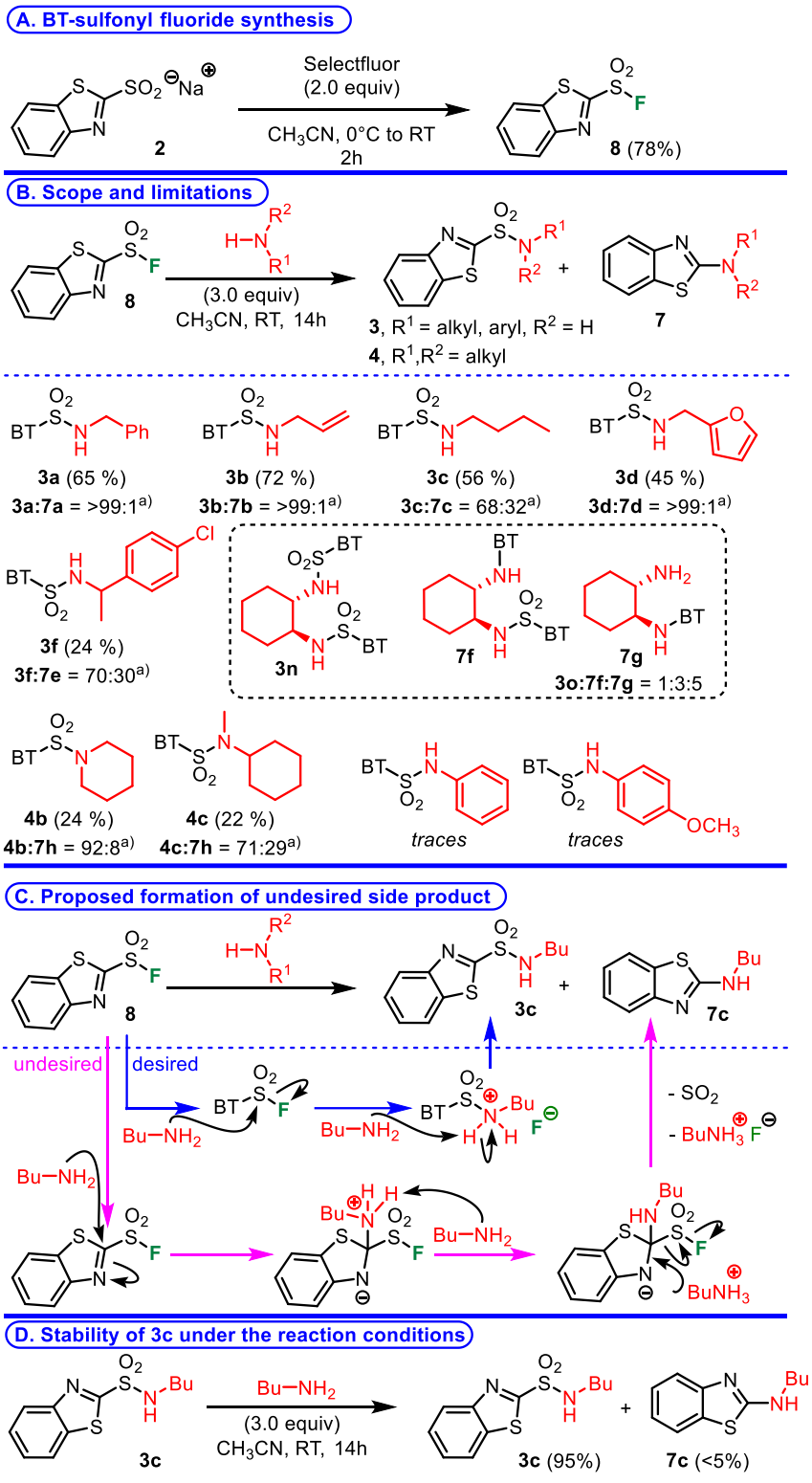
Scheme 4. Chan-Lam coupling of sulfonamides **3**. (A) Scope and Limitations. (B) Proposed reaction mechanism of copper catalyzed Chan-Lam coupling of sulfonamides **3**. [a)] Reactions were performed on 1 mmol of **3**; Yields refer to pure isolated compounds. TMEDA – tetramethylethylendiamine; DCE – dichloroethane; Bn – benzyl.

Benzothiazoyl sulfonyl fluoride

Facing the problems in *N,N*-alkylaryl BT-sulfonamide synthesis related to either high reactivity of phenylamines towards NBS (Table 2, Method A), low phenylamine nucleophilicity (Table 2, Method

B), or low nucleophilicity of *N*-alkylsulfonamides **3** in Chan-Lam coupling (Scheme 4), our attention turned to benzothiazoyl sulfonyl fluoride **8** (Scheme 5).[57] We expected that $BTSO_2F$ (**8**) could be a shelf-stable but still very reactive $BTSO_2Cl$ equivalent. Sulfonyl fluoride **8** was readily prepared by the reaction of sulfinic salt **2** with Selectfluor® in 73% yield (Scheme 5A). Thus, its reactivity towards a wide range of alkyl and aryl amines could be readily evaluated (Scheme 5B).

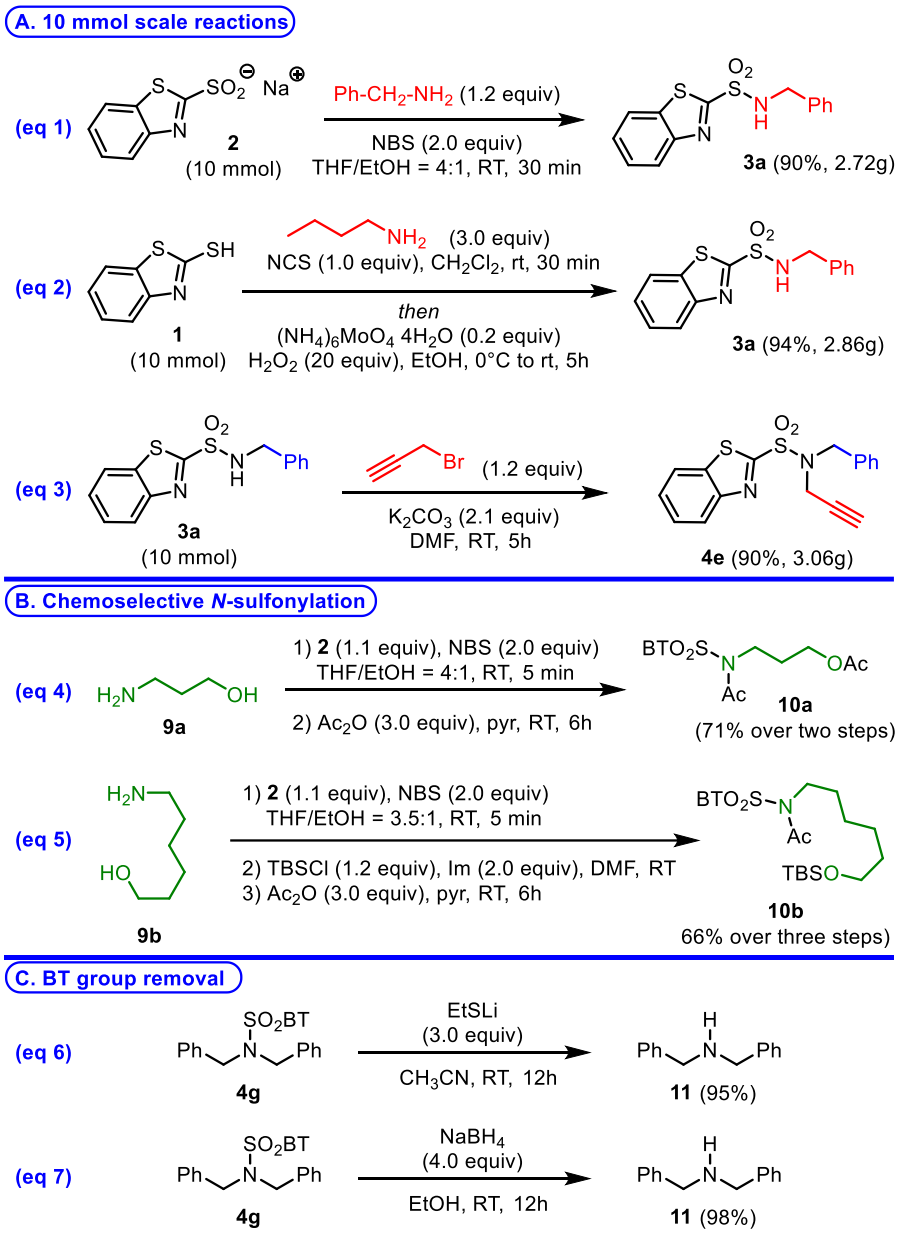
It was observed that primary and α-unbranched alkyl amines react smoothly and yield the desired sulfonamides **3a-c,n** in moderate to good yields. Unfortunately, a competitive attack of butyl amine (sulfonamide **3c** synthesis) to C-electrophilic center in benzothiazole ring of **8** that yielded the undesired side product **7c** was observed even in the case of such sterically undemanding amine (Scheme 5B). Observed phenomenon were even more pronounced when α-branched primary amines (compounds **3q** and **3n**) and secondary amines (**4b,c**) were reacted with **8**. When cyclohexane-1,2-diamine was used as a reaction partner, a mixture of bis-sulfonamide **3n**, monosulfonamide BT-amine **7f**, and mono BT-amine **7g** was formed in 1:3:5 ratio (based on ^{1}H NMR analysis). In the case of tested anilines, only traces of desired products were detected. Nonreactivity of anilines towards sulfonyl fluoride **8** was again attributed to their weak nucleophilicity since no traces of possible side product **7** were detected. Control experiments showed that the side product **7c** is not generated from sulfonamide **3c** (Scheme 5C).



Scheme 5. SuFEx approach to BT-sulfonamides **3** and **4**. (A) BT-sulfonyl fluoride synthesis. (B) SuFEx approach-based scope and limitations. (C) Formation of the desired sulfonamide **3c** and side product **7c** – proposed mechanism. (D) Evaluation of the BT-sulfonamide **3c** stability under the reaction conditions.

Applications

Having assessed short and robust methods for BT-sulfonamide synthesis, we wished to demonstrate their synthetic utility. First, three representative sulfonamide syntheses were carried out on a 10 mmol scale without any significant erosion in the reaction yields (Scheme 6A). Next, one-pot synthesis of orthogonally protected amino alcohols **9a** and **b** was carried out with excellent *N* and *O*-chemoselectivity. Targeted products **10a** and **b** were isolated in very good overall yields (Scheme 6B). Finally, BT-sulfonyl group removal was achieved using either thiolate anion or $NaBH_4$ (Scheme 6C).[38]



Scheme 6. Demonstration of the synthetic utility of BT-sulfonamides. (A) three key sulfonamide preparations carried out on a 10 mmol scale, (B) nitrogen atom selective chemoprotection, (C) BT-sulfonyl group removal.

Conclusions

In short, we have developed a unified approach to *N*-monosubstituted and *N,N*-disubstituted BT-sulfonamides that relies on several independent synthetic pathways. First, targeted BT-sulfonamides are prepared from simple and commercially available starting compounds, benzothiazole, and primary and secondary amines, using three approaches that differ in their elemental steps. The first approach is based on sulfur oxidation/S-N bond formation sequence, the second on the S-N bond formation/sulfur oxidation process, and the third one is based on sulfur oxidation/S-F formation/SuFEx coupling process. These approaches allowed us to access *N*-monoalkyl BT-sulfonamides that were further used as a starting building block for additional *N,N*-disubstituted BT-sulfonamide synthesis. The alkylation processes were achieved under mild reaction conditions using weak base-promoted alkylation with alkyl halides, stereospecific microwave-assisted Fukuyama-Mitsunobu alkylation using alcohols, and aryl substituents were installed with the help of Chan-Lam coupling reaction. The key coupling reaction sequences proved to be readily scalable (10 mmol scale), chemoselective (*N*-sulfonylation in the presence of, e.g., free hydroxy group), and it was shown that BT-groups can be readily removed using either $NaBH_4$ or thiolate anions.

EXPERIMENTAL PART

General information. All reactions were performed in round-bottom flasks fitted with rubber septa using standard laboratory techniques. Reactions sensitive to air and/or moisture were performed under a positive pressure of argon. Reactions run at elevated temperatures were carried out in the oil bath and the indicated temperature refer to the oil bath temperature. All starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. Progress of the reactions was monitored by thin-layer chromatography (TLC) - aluminum plates precoated with silica gel (silica gel 60 F254). Column chromatography was performed on silica gel 60 (40-63 µm). Determination of melting points were done on a Büchi melting point apparatus and were uncorrected. ^{1}H NMR, ^{19}F {^{1}H} NMR, and ^{13}C {^{1}H} NMR spectra were measured on Jeol ECA400II (400 MHz, 376 MHz, and 100 MHz, respectively) or Jeol 500 ECA (500 and 126 MHz) in $CDCl_3$ or DMSO. Chemical shifts are reported in ppm and their calibration was performed (a) in the case of ^{1}H NMR experiments on the residual peak of non-deuterated solvent δ ($CHCl_3$) = 7.26 ppm; δ (DMSO) = 2.50 ppm, and (b) in case of ^{13}C NMR experiments on the middle peak of the ^{13}C signal in deuterated solvent δ ($CDCl_3$) = 77.2 ppm; δ (DMSO-d_6) = 39.5 ppm. Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of triplet (tt) and multiplet (m). HRMS analyses were performed on Thermo Exactive Plus high-resolution mass spectrometer with electrospray ionization (ESI) and Orbitrap analyzer operating at positive or negative full scan mode in the range of 60-800 m/z or on Agilent 6230 high resolution mass spectrometer with electrospray ionization (ESI) and time-of-flight analyzer operating at positive or negative full scan mode in the range of 100-1700 m/z. SFC chiral analyses were performed using an Acquity UPC2 system (Waters) consisting of a binary solvent manager, sample manager, column manager, column heater, convergence manager, PDA detector 2998, QDa mass detector and chiral analytical column Chiralpak IA3 (4.6 mm × 100 mm, 3 µm particle size) and Chiralpak IE3 (4.6 mm × 100 mm, 3 µm particle size) . The chromatographic runs were performed at a flow rate of 2.2 mL/min, column temperature of 38 °C, and ABPR 2000 psi. Microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus. The reactor was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 10 mL glass vials sealed

with a silicone/PTFE Vial cap top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled to ambient temperature by gas jet cooling. Purification using semiprep HPLC was carried out on Agilent 1200 series using the C18 reverse-phase column (YMC Pack ODS-A, 20x100 mm, 5 mm particles). Gradient was formed from 10 mM aqueous ammonium acetate (buffer) and CH_3CN with a flow rate of 15 mL/min. Potentiometric titration for the determination of dissociation constant was carried out using a benchtop meter pH 50+ DHS (Instruments XS, Italy) equipped with ATC glass electrode. Before each measurement, a pH meter was calibrated with pH 4.01 and 7.00 buffer solutions. The titration was performed using Titronic® basic piston burette (Schott Instruments, Germany). A 0.01 M basic solution was prepared by dissolving of an appropriate amount of 50% (w/v) aqueous sodium hydroxide solution purchased from Sigma-Aldrich in deionized water (Merck Millipore, USA). The titrant was added in 0.02 mL increments. Dissociation constants were calculated from titration curves.

Sodium benzo[d]thiazole-2-sulfinate (2) synthesis[18]

Disulfide (2.0 g, 6.0 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (25 mL) and MeOH (25 mL). NBS (5.36 g, 30 mmol, 5 equiv) was added portionwise within 5 min and the reaction progress was followed by TLC. After disulfide consumption, the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and the whole mixture was extracted with CH_2Cl_2 (3 x 30 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc/petroleum ether = 1:3) and the concentration of relevant fractions yielded the desired product as yellowish amorphous solid (0.83 g, 65%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.54 (ddd, J = 8.0, 7.2, 1.3 Hz, 1H), 7.60 (ddd, J = 8.3, 7.2, 1.4 Hz, 1H), 8.01 (ddd, J = 7.9, 1.4, 0.7 Hz, 1H), 8.18 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H), 3.74 (s, 3H); ^{13}C {^{1}H} NMR (101 MHz, Chloroform-*d*): δ 175.0, 153.8, 136.2, 127.3, 127.3, 125.1, 122.5, 51.5; MS (ESI) *m/z* (%) 214: $[M+H]^+$ (78); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_8H_8NO_2S_2$, 213.9991; found 213.9994.

Methyl sulfinate (1.3 g, 6 mmol, 1 equiv) was dissolved in THF (3 mL), and H_2O (3 mL) was added. Sodium hydroxide (0.243 g, 6 mmol, 1 equiv; powder) was added to the suspension at RT. The whole mixture became clear within 1 min and the conversion of starting methyl ester was monitored by TLC. After the reaction completion, the organic solvents were evaporated under reduced pressure and the remaining water was removed with the help of freeze-dry technique to yield compound **2** as a white powder (1.02 g, 93 %). (ATTENTION: all water content must be carefully removed to avoid lousy reactivity of **2** in subsequent reactions). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (ddd, J = 8.1, 7.3, 1.3 Hz, 2H), 7.46 (ddd, J = 8.2, 7.3, 1.3 Hz, 2H), 7.92 (ddd, J = 8.1, 1.1, 0.6 Hz, 2H), 8.05 (ddd, J = 7.9, 1.2, 0.6 Hz, 2H); ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ 194.8, 153.9, 134.9, 125.6, 124.9, 122.9, 122.6.

Preparation of benzo[d]thiazole-2-sulfonyl fluoride (8)

Sulfinic salt **2** (0.5 g, 2.26 mmol, 1 equiv) was suspended in CH_2Cl_2 (23 mL) and the resulting suspension was cooled to 0°C (ice/water). After 5 min at 0°C, a Selecfluor® (1.60 g, 4.52 mmol, 2 equiv) was added in ten portions. After 5 min at 0°C, the mixture was allowed to warm to RT (cooling bath removed), and the resulting mixture was stirred for an additional 30 min at RT. Water (25 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL). Combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield a white crystalline product (0.383 g, 78 %). mp = 94-96°C (litt.[57b] mp = 95-96°C); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.36 – 8.31 (m, 1H), 8.09 – 8.04 (m, 1H), 7.75 – 7.68 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 156.3 (d, *J* = 38.2 Hz), 152.1, 137.2, 129.5, 128.6, 126.5, 122.4; ^{19}F{^{1}H} NMR (376 MHz, Chloroform-d): δ 64.2; MS (ESI) *m/z* (%) 218: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_7H_5FNO_2S_2$, 217.9746; found, 217.9755.

Sulfonamide 3, 4 and 10 preparation

Method A (Table 2, method A): Sulfinic salt **2** (0.5 g, 2.22 mmol, 1 equiv) and amine (2.71 mmol, 1.2 equiv) were added to the solvent mixture of THF/EtOH = 4:1 (V/V) (25 mL) at RT. The resulting mixture was stirred at RT for 5 min and NBS (0.800 g, 4.52 mmol, 2 equiv) was added portion wise over a period of 5 min. The reaction mixture turned color to orange upon the NBS addition. After an additional 10 min at RT, the reaction mixture was partitioned between CH_2Cl_2 (25 mL) and water (25 mL). Resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated under reduced pressure to provide the crude product.

Method B (Table 2, method B): Benzo[d]thiazole-2-thiol (0.167 g, 1 mmol, 1.0 equiv) and amine (3 mmol, 3.0 equiv) were dissolved in CH_2Cl_2 (5 ml) at RT, and NCS (0.133 g, 1mmol, 1.0 equiv) was added portion wise over the period of 5 min. The resulting mixture was stirred at RT for 30 minutes, before the solvent was removed under reduced pressure. The residue was suspended in EtOH (5 mL) and $(NH_4)_6Mo_7O_{24}.4H_2O$ (0.37 g, 0.3 equiv) was added at once. The resulting mixture was cooled to 0°C (ice/water bath) and a solution of H_2O_2 in water (2 mL, 20 equiv; 30% in water) was added dropwise (AVOID metallic needle). After 30 min at 0°C, the cooling bath was removed, and the reaction mixture was allowed to warm to RT. The progress was monitored by TLC. Resulting mixture was repartitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL). Resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield the crude product.

Method C (Scheme 5B): Sulfonyl fluoride **8** (0.050 g, 0.23 mmol, 1 equiv) was dissolved in CH_3CN (2.3 mL) and amine (0.69 mmol, 3 equiv) was added at RT. The reaction mixture was stirred overnight at RT. Aq. sat. NH_4Cl (10 mL) was added, and the resulting layers were separated. Aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield the crude product.

*N-benzylbenzo[d]thiazole-2-sulfonamide (**3a**)*. The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:4) and obtained as a white solid. **Method A**: starting from 0.050 g (0.22 mmol) of **2**, yielded 0.061 g (91%); starting from 2.13 g (10.0 mmol) of **2**, yielded 2.72 g (90%); **Method B**: starting from 0.167 g (1.0 mmol) of **1**, yielded 0.279 g (92% over two steps); starting from 1.67 g (10.0 mmol) of **1**, yielded 2.86 g (94% over two steps); **Method C**: starting from 0.050 g (0.23 mmol) of **8**, yielded 0.032 g (65 %). mp = 108 – 112 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.17 – 8.14 (m, 1H), 7.99 – 7.96 (m, 1H), 7.62 (ddd, *J* = 8.1, 7.2, 1.5 Hz, 1H), 7.57 (ddd, *J* = 7.8, 7.2, 1.4 Hz, 1H), 5.46 (t, J = 5.4 Hz, 1H), 4.44 (d, J = 6.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.0, 152.4, 136.5, 135.7, 128.9, 128.3, 128.2, 127.8, 127.6, 125.2, 122.3, 48.2; MS (ESI) *m/z* (%) 305: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{13}N_2O_2S_2$, 305.0413; found, 305.0412.

*N-allylbenzo[d]thiazole-2-sulfonamide (**3b**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1) and obtained as a slightly yellow solid. **Method A**: starting from 0.044 g (0.20 mmol) of **2**, yielded 0.033 g (65%); **Method B**: starting from 0.167 g (1.0 mmol) of **1**, yielded 0.129 g (51% over two steps); **Method C**: starting from 0.050 g (0.23 mmol) of **8**, yielded 0.0292 g (72%). mp = 106 – 110 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.16 (ddd, J = 8.2, 1.3, 0.7 Hz, 1H), 7.96 (ddd, *J* = 7.8, 1.5, 0.7 Hz, 1H), 7.60 (ddd, *J* = 8.0, 7.2, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.1, 7.3, 1.5, 1H), 5.79 (ddt, J = 17.1, 10.2, 5.9 Hz, 1H), 5.46 (t, J = 6.2 Hz, 1H), 5.24 (dq, J = 17.1, 1.5 Hz, 1H), 5.11 (dq, J = 10.2, 1.3 Hz, 1H), 3.88 (tt, J = 6.0, 1.5 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.1, 152.4, 136.5, 132.5, 127.8, 127.6, 125.2, 122.3, 118.5, 46.5; MS (ESI) m/z (%) 255: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{11}N_2O_2S_2$, 255.0256; found, 255.0257.

*N-butyl benzo[d]thiazole-2-sulfonamide (***3c***).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as colorless oil. **Method A**: starting from 0.044 g (0.20 mmol) of **2**, yielded 0.036 g (67%); **Method B**: starting from 0.167 g (1.0 mmol) of **1**, yielded 0.178 g (66% over two steps); **Method C**: starting from 0.050 g (0.23 mmol) of **8**, yielded 0.035 g (56%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18 – 8.16 (m, 1H), 7.99 – 7.96 (m, 1H), 7.56 (ddd, J = 8.1, 7.2, 1.4 Hz, 1H), 7.61 (ddd, J = 8.2, 7.2, 1.4 Hz, 1H), 5.18 (t, *J* = 6.0 Hz, 1H), 3.25 (td, *J* = 7.1, 6.1 Hz, 2H), 1.58 – 1.51 (m, 2H), 1.40 – 1.30 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.2, 152.5, 136.6, 127.7, 127.6, 125.2, 122.3,

43.9, 31.9, 19.7, 13.6; MS (ESI) m/z (%) 271: $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calcd. for $C_{11}H_{15}N_2O_2S_2$, 271.0569; found, 271.0569.

*N-(furan-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (**3d**)*. The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1) and obtained as colorless oil. **Method B**: starting from 0.167 g (1.0 mmol) of **1**, yielded 0.114 g (39% over two steps); **Method C**: starting from 0.050 g (0.23 mmol) of **8**, yielded 0.031 g (45%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.14 – 8.13 (m, 1H), 7.97 – 7.96 (m, 1H), 7.56 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.61 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.17 (m, 1H), 6.16 (dd, *J* = 3.1, 0.7 Hz, 1H), 6.13 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.56 – 5.54 (m, 1H), 4.46 (d, *J* = 6.0 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 165.9, 152.5, 148.9, 143.0, 136.5, 127.8, 127.6, 125.2, 122.3, 110.5, 108.9, 40.9; MS (ESI) *m/z* (%) 295: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd. for $C_{12}H_{10}KN_2O_3S_2$, 332.9764; found, 332.9767.

*tert-butyl (2-(benzo[d]thiazole-2-sulfonamido)ethyl)carbamate (**3e**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 2:3) and obtained as a white solid. **Method A**: starting from 0.221 g (1.0 mmol) of **2**, yielded 0.172 g (67%). mp = 142 – 146 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.17 (ddd, *J* = 8.3, 1.5, 0.7 Hz, 1H), 7.97 (ddd, *J* = 7.6, 1.3, 0.6 Hz, 1H), 7.61 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 7.56 (ddd, *J* = 7.9, 7.2, 1.5 Hz, 1H), 6.01 (bs, 1H), 5.05 (t, *J* = 5.2 Hz, 1H), 3.44 – 3.41 (m, 2H), 3.44 – 3.30 (m, 2H), 1.39 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.3, 156.7, 152.3, 136.5, 127.7, 127.5, 125.2, 122.3, 80.2, 44.8, 40.4, 28.4; MS (ESI) *m/z* (%) 356: $[M+H]^+$ (100); HRMS (ESI) *m/z* $[M+K]^+$ calcd. for $C_{14}H_{19}N_3O_4S_2K$, 396.0449; found, 396.0452.

*N-(1-(4-chlorophenyl)ethyl)benzo[d]thiazole-2-sulfonamide (**3f**)*. The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:10) and obtained as a colorless oil. **Method A**: starting from 0.044 g (1.0 mmol) of **2**, yielded 0.052 g (74%); **Method C**: starting from 0.050 g (0.23 mmol) of **8**, yielded 0.0196 g (24%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.07 (ddd, *J* = 8.2, 1.3, 0.6 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.3, 0.6 Hz, 1H), 7.60 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 2H), 7.12 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.05 (dt, *J* = 8.9, 2.4 Hz, 2H), 5.74 (d, *J* = 7.4 Hz, 1H), 4.77 (p, J = 7.0 Hz, 1H), 1.53 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.5, 152.2, 139.8, 136.5, 133.7, 128.7, 127.8, 127.7, 127.5, 125.0, 122.1, 54.2, 23.2; MS (ESI) *m/z* (%) 351: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{14}ClN_2O_2S_2$, 353.0180; found, 353.0178.

*N-(benzo[d][1,3]dioxol-5-ylmethyl)benzo[d]thiazole-2-sulfonamide (**3g**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 3:4) and obtained as a white solid. **Method B**: starting from 0.167 g (1.0 mmol) of **1**, yielded 0.150 g (43% over two steps). mp = 140 – 141 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.14 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.61 (dt, *J* = 7.2, 1.1 Hz), 7.56 (dt, *J* = 8.1, 1.4 Hz, 1H), 7.59 - 7.54 (m, 1H), 6.76 (s, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 5.84 (s, 2H), 5.76 – 5.60 (bs, 1H), 4.32 (d, *J* = 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.3, 152.4, 148.1, 147.6, 136.5, 129.5, 127.7, 127.6, 125.2, 122.3, 121.9, 108.8, 108.4, 101.3, 48.0; MS (ESI) *m/z* (%) 349: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{13}N_2O_4S_2$, 349.0311; found, 349.0307.

*(–)-(S)-N-(1-hydroxy-3-methylbutan-2-yl)benzo[d]thiazole-2-sulfonamide ((–)-**3h**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1) and obtained as colorless oil. **Method A**: starting from 0.044 g (0.20 mmol) of **2**, yielded 0.038 g (64%); **Method B**: starting from 0.167 g (1.0 mmol) of **1**, yielded 0.135 g (45% over two steps). $[\alpha]_D^{21} = -335°$ (c 0.2, MeOH); ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.11 (ddd, *J* = 7.4, 1.6, 0.5 Hz, 1H), 7.98 – 7.96 (m, 1H), 7.62 – 7.54 (m, 2H), 5.25 (d, *J* = 8.3 Hz, 1H), 3.74 – 3.65 (m, 2H), 3.58 – 3.52 (m, 1H), 3.10 (t, *J* = 5.9 Hz, 1H), 1.94 (oct, *J* = 6.8 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 167.9, 151.5, 136.3, 127.8, 127.7, 124.9, 122.3, 62.9, 30.4, 19.3, 18.6; MS (ESI) *m/z* (%) 301: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{17}N_2O_3S_2$, 301.0675; found, 301.0677.

*(–)-N-(2-hydroxy-1-phenylethyl)benzo[d]thiazole-2-sulfonamide ((–)-**3i**)*. The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 4:5) and obtained as a white solid. **Method A**: starting from 0.044 g (0.20 mmol) of **2**, yielded 0.024 g (37%); **Method B**: starting from 0.167 g (1.0 mmol) of **1**, yielded 0.160 g (47% over two steps). mp = 118–120 °C); $[\alpha]_D^{23} = -144°$ (c 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.07 (ddd, *J* = 7.9, 1.5, 0.5 Hz, 1H), 7.90 (ddd, *J* = 7.5, 1.5, 0.6 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.27 – 7.25 (m, 2H), 7.22 – 7.13 (m, 3H), 4.84 (dd, *J* = 6.3, 4.3 Hz, 1H), 3.94 (dd, *J* = 11.7, 4.3 Hz, 1H), 3.86 (dd, *J* = 11.7, 6.4 Hz,

1H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): *δ* 167.0, 151.8, 137.6, 136.5, 128.8, 128.3, 127.8, 127.6, 127.0, 125.0, 122.2, 66.1, 60.5; MS (ESI) *m/z* (%) 335: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{15}N_2O_3S_2$, 335.0519; found, 335.0516.

*(S)-diethyl (benzo[d]thiazol-2-ylsulfonyl)glutamate ((–)-**3j**).* **Method B** (method was slightly modified since hydrochloride salt was used): L-glutamate hydrochloride (0.215 g, 0.9 mmol) was suspended in CH_2Cl_2 (3 mL) at RT, and Et_3N (0.125 mL, 0.9 mmol, 9 equiv) followed with **1** (0.050 g, 0.3 mmol, 3 equiv) were added. After 5 min at RT, *N*-chlorosuccinimide (0.040 g, 0.3 mmol, 3.0 equiv) was added, and the resulting mixture was stirred at RT for 2 hours. CH_2Cl_2 (20 mL) and H_2O (20 mL) were added, and the resulting layers were separated. Aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was suspended in EtOH (2 mL) and $(NH_4)_6M_7O_4$ x $4H_2O$ (0.123 g, 0.1 mmol, 0.1 equiv) was added. The resulting slurry was cooled to 0 °C (ice/water) and H_2O_2 in water (0.610 mL, 20 equiv; 30% in water) was added dropwise. The resulting mixture was stirred at 0 °C for 5 min before the cooling bath was removed. After 12h at RT, the whole mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The purification of the crude product using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) yielded 0.114 g (66 % over two steps) of **3j** as viscose syrup. $[\alpha]_D^{20} = -112°$ (*c* 0.44, CH_2Cl_2); ^1H NMR (400 MHz, Chloroform-*d*): *δ* 8.11 (ddd, *J* = 8.2, 1.6, 0.6 Hz, 1H), 7.97 (ddd, *J* = 7.7, 1.6, 0.7 Hz, 1H), 7.62 – 7.53 (m, 2H), 5.80 (bs, 1H), 4.47 (dd, *J* = 8.8, 4.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.04 - 3.98 (m, 2H), 2.60 – 2.46 (m, 2H), 2.25 (dtd, *J* = 14.2, 7.5, 4.7 Hz, 1H), 2.00 (dddd, *J* = 14.3, 8.8, 7.8, 6.4 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): *δ* 172.7, 171.0, 165.7, 152.4, 136.5, 127.8, 127.6, 125.1, 122.3, 62.3, 60.9, 56.3, 30.0, 28.5, 14.3, 14.1; MS (ESI) *m/z* (%) 401: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd. for $C_{16}H_{20}KN_2O_6S_2$, 439.0394; found, 439.0396.

*(–)-Methyl (benzo[d]thiazol-2-ylsulfonyl)-L-phenylalaninate ((–)-**3k**).* **Method B** (method was slightly modified since hydrochloride salt was used): Methyl L-phenylalaninate hydrochloride (0.193 g, 0.9 mmol) was suspended in CH_2Cl_2 (3 mL) at RT, and Et_3N (0.125 mL, 0.9 mmol, 9 equiv) followed with **1** (0.050 g, 0.3 mmol, 3 equiv) were added. After 5 min at RT, *N*-chlorosuccinimide (0.040 g, 0.3 mmol, 3.0 equiv) was added, and the resulting mixture was stirred at RT for 2 hours. CH_2Cl_2 (20 mL) and H_2O (20 mL) were added, and the resulting layers were separated. Aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was suspended in EtOH (2 mL) and $(NH_4)_6M_7O_4$ x $4H_2O$ (0.123 g, 0.1 mmol, 0.1 equiv) was added. The resulting slurry was cooled to 0 °C (ice/water) and H_2O_2 in water (0.610 mL, 20 equiv; 30% in water) was added dropwise. The resulting mixture was stirred at 0 °C for 5 min before the cooling bath was removed. After 12h at RT, the whole mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The purification of the crude product using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) yielded 0.27 g (80 % over two steps) of **3k** as viscose syrup. $[\alpha]_D^{23} = -129°$ (*c* 0.51, CH_2Cl_2); ^1H NMR (400 MHz, Chloroform-*d*): *δ* 8.12 (ddd, *J* = 7.9, 1.7, 0.6 Hz, 1H), 7.95 (ddd, *J* = 7.7, 1.5, 0.6 Hz, 1H), 7.60 (ddd, *J* = 8.2, 7.2, 1.5 Hz, 1H), 7.55 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 7.26 – 7.14 (m, 3H), 7.11 – 7.09 (m, 2H), 5.58 (bs, 1H), 4.72 (t, *J* = 5.8 Hz, 1H), 3.55 (s, 3H), 3.19 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.13 (dd, *J* = 13.9, 5.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): *δ* 170.9, 165.6, 152.4, 136.5, 134.7, 129.5, 128.7, 127.8, 127.5, 127.4, 125.2, 122.3, 57.6, 52.7, 39.5; MS (ESI) *m/z* (%) 377: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{17}N_2O_4S_2$, 377.0624; found, 377.0627.

*(–)-Methyl (benzo[d]thiazol-2-ylsulfonyl)alaninate ((–)-**3l**).* **Method B** (method was slightly modified since hydrochloride salt was used): Methyl alaninate hydrochloride (0.125 g, 0.9 mmol) was suspended in CH_2Cl_2 (3 mL) at RT, and Et_3N (0.125 mL, 0.9 mmol, 9 equiv) followed with **1** (0.050 g, 0.3 mmol, 3 equiv) were added. After 5 min at RT, *N*-chlorosuccinimide (0.040 g, 0.3 mmol, 3.0 equiv) was added, and the resulting mixture was stirred at RT for 2 hours. CH_2Cl_2 (20 mL) and H_2O (20 mL) were added, and the resulting layers were separated.

Aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was suspended in EtOH (2 mL) and $(NH_4)_6M_7O_4$ x $4H_2O$ (0.123 g, 0.1 mmol, 0.1 equiv) was added. The resulting slurry was cooled to 0 °C (ice/water) and H_2O_2 in water (0.610 mL, 20 equiv; 30% in water) was added dropwise. The resulting mixture was stirred at 0 °C for 5 min before the cooling bath was removed. After 12h at RT, the whole mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The purification of the crude product using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) yielded 0.059 g (66 % over two steps) of **3l** as viscose syrup. $[\alpha]_D^{20} = -18.2°$ (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.14 (ddd, *J* = 8.3, 1.3, 0.6 Hz, 1H), 7.97 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.58 – 7.65 (m, 1H), 7.50 – 7.60 (m, 1H), 5.84 (bs, 1H), 4.48 (bs, 1H), 3.61 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): *δ* 172.4, 165.9, 152.4, 136.5, 127.8, 127.6, 125.2, 122.4, 53.0, 52.6, 20.1; MS (ESI) *m/z* (%) 301: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calc. for $C_{11}H_{12}KN_2O_4S_2$, 338.9870; found, 338.9873.

*N-(1-(naphthalen-1-yl)ethyl)benzo[d]thiazole-2-sulfonamide (**3m**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil. **Method A**: starting from 0.050 g (0.226 mmol) of **2**, yielded 0.029 g (36%). ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.02 – 7.98 (m, 2H), 7.84 -7.82 (m, 1H), 7.75 - 7.71 (m, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.44 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.24 (dd, *J* = 8.2, 7.3 Hz, 1H), 5.65 – 5.63 (m, 1H), 1.72 (d, *J* = 6.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): *δ* 166.5, 152.3, 137.1, 136.6, 133.9, 130.2, 128.9, 128.6, 127.6, 127.4, 126.6, 125.9, 125.2, 125.1, 123.6, 122.7, 122.1, 50.9, 23.2; MS (ESI) *m/z* (%) 370: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{17}N_2O_4S_2$, 369.0726; found, 369.0734.

*(+)-N-((1R,2R)-2-(benzo[d]thiazole-2-sulfonamido)cyclohexyl)benzo[d]thiazole-2-sulfonamide ((+)-**3n**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:5->1:3) and obtained as a viscose syrup. **Method A**: starting from 0.100 g (0.452 mmol, 2.2 equiv) of **2**, and (1R,2R)-cyclohexane-1,2-diamine (0.0235 g, 0.205 mmol, 1.0 equiv); yielded 0.031 g (30%). $[\alpha]_D^{21} = -5.63°$ (*c* 0.16, CH_2Cl_2); ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 9.43 (d, *J* = 3.2 Hz, 2H), 8.31 (dt, *J* = 8.3, 1.0 Hz, 2H), 7.95 – 7.89 (m, 2H), 7.61 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 2H), 7.54 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 2H), 3.58 – 3.49 (m, 2H), 2.49 (dt, *J* = 14.0, 2.7 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.64 – 1.45 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): *δ* 168.6, 149.8, 136.1, 128.2, 128.13, 125.2, 122.3, 57.8, 35.9, 24.4; MS (ESI) *m/z* (%) 510: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd. for $C_{20}H_{21}N_4O_4S_4$, 509.0440; found, 509.0442.

*1-(benzo[d]thiazol-2-ylsulfonyl)piperidin-4-ol (**4a**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1 -> 4:3 -> 8:3) and obtained as a colorless oil. **Method A**: starting from 0.044 g (0.20 mmol) of **2**, yielded 0.045 g (76%). ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.20 - 8.17 (m, 1H), 7.99 – 7.96 (m, 1H), 7.63 – 7.54 (m, 2 H), 3.91 – 3.86 (m, 1H), 3.71 – 3.64 (m, 2H), 3.34 – 3.28 (m, 2H), 2.00 – 1.94 (m, 2H), 1.72 – 1.68 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): *δ* 164.1, 152.8, 136.4, 127.7, 127.5, 125.4, 122.2, 65.8, 43.7, 33.4; MS (ESI) *m/z* (%) 290: $[M+H]^+$ (100); HRMS (ESI) *m/z*, $[M+H]^+$ calcd. for $C_{12}H_{15}N_2O_3S_2$, 299.0519; found, 299.0521.

*2-(piperidin-1-ylsulfonyl)benzo[d]thiazole (**4b**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/$CHCl_3$ = 1:1 -> 0:1) and obtained as a white solid. **Method A**: starting from 0.044 g (0.20 mmol) of **2**, yielded 0.031 g (55%). **Method C**: starting from 0.050 g (0.23 mmol) of **8**, yielded 0.0156 g (24%). mp = 109 – 113 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.20 (ddd, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.98 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H), 7.61 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1H), 7.56 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 3.40 – 3.37 (m, 4H), 1.71 – 1.66 (m, 4H), 1.56 – 1.50 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): *δ* 164.6, 152.8, 136.4, 127.6, 127.4, 125.3, 122.2, 47.6, 25.4, 23.6; MS (ESI) *m/z* (%) 283: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{15}N_2O_2S_2$, 283.0569; found, 283.0570.

*N-cyclohexyl-N-methylbenzo[d]thiazole-2-sulfonamide (**4c**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a white solid. **Method B**: starting from 0.167 g (1.0 mmol) of **1**, yielded 0.107 g (34%); **Method C**: starting from 0.050 g (0.23 mmol) of **8**, yielded 0.011 g (22%). mp

= 80 – 82 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18 – 8.16 (m, 1H), 7.97 – 7.95 (m, 1H), 7.59 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.56 – 7.52 (m, 1H), 3.98 (tt, *J* = 11.6, 3.8 Hz, 1H), 2.98 (s, 3H), 1.77 – 1.59 (m, 5H), 1.43 – 1.29 (m, 4H), 1.07 – 0.98 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.4, 152.8, 136.4, 127.5, 127.4, 125.3, 122.2, 58.1, 30.6, 29.5, 25.8, 25.4; MS (ESI) *m/z* (%) 311: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$calcd. for $C_{14}H_{19}N_2O_2S_2$, 311.0882; found, 311.0886.

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*3-(N-(benzo[d]thiazol-2-ylsulfonyl)acetamido)propyl acetate (**10a**)* **(Scheme 5B, equation 4)**. Prepared using the **Method A** from **2** (0.100 g, 0.45 mmol). The crude product obtained using the **Method A** was dissolved in pyridine (2 mL) and Ac_2O (0.128 mL, 1.35 mmol, 3.0 equiv) was added at RT. The resulting mixture was stirred for 12h at RT before sat. aq. NH_4Cl (5 mL) was added. The resulting mixture was extracted with EtOAc (3 x 15 mL) and the resulting organic layers were combined and washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; EtOAc:hexane = 1:2) to yield 0.113 g (71 % over two steps) of **10a** and obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18 – 8.16 (m, 1H), 8.00 – 7.98 (m, 1H), 7.66 – 7.58 (m, 2H), 4.13 (t, *J* = 6.1 Hz, 2H), 4.00 – 3.96 (m, 2H), 2.58 (s, 3H), 2.11 – 2.08 (m, 2H), 2.04 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 171.2, 170.5, 164.1, 152.1, 136.6, 128.5, 128.0, 125.7, 122.3, 61.9, 45.1, 28.8, 25.6, 21.1; MS (ESI) *m/z* (%) 357: $[M+H]^+$ (100); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{14}H_{17}N_2O_5S_2$, 357.0573; found, 357.0576.

*N-(benzo[d]thiazol-2-ylsulfonyl)-N-(6-((tert-butyldimethylsilyl)oxy)hexyl)acetamide (**10b**)* **(Scheme 5B, equation 5)**. Prepared using the **Method A** from **2** (0.100 g, 0.45 mmol). The crude product obtained using the **Method A** was dissolved in DMF (9 mL) at RT, and imidazole (0.183 g, 2.7 mmol, 6 equiv) was added. After 5 min at RT, TBSCl (0.202 g, 1.35 mmol, 3.0 equiv) was added and the resulting mixture was stirred at RT for 12h. The solvent was removed from the reaction mixture by freeze-drying technique. The crude product was suspended in pyridine (4 mL) and Ac_2O (0.127 ml, 1.35 mmol, 3.0 equiv) was added at RT. The resulting mixture was stirred for an additional 12h before sat. aq. NH_4Cl (10 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 x 15 mL), and the resulting organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; EtOAc:hexane = 1:3) to yield 0.279 g (66 % over 3 steps) of **10b** and obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.17 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.99 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.65 – 7.57 (m, 2H), 3.87 – 3.84 (m, 2H), 3.58 (t, *J* = 6.5 Hz, 1H), 2.58 (s, 3H), 1.78 – 1.70 (m, 2H), 1.53 – 1.46 (m, 2H), 1.36 – 1.32 (m, 4H), 0.89 – 0.88 (m, 9H), 0.04 – 0.03 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 170.5, 164.5, 152.1, 136.7, 128.3, 127.9, 125.6, 122.3, 63.2, 47.9, 32.8, 29.7, 26.6, 26.1, 25.6, 25.5, 18.5, -5.2; MS (ESI) *m/z* (%) 472: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{35}N_2O_4S_2Si$, 471.1802; found, 417.1805.

N-alkylation of *N*-monosubstituted sulfonamides (Table 3)

General procedure for Fukuyama-Mitsunobu alkylation (FM alkylation). A sulfonamide **3** (0.18 mmol, 1.0 equiv) was dissolved in dry THF (4.5 mL) at RT in the 10 mL microwave vial, and alcohol (0.36 mmol, 2 equiv), PPh_3 (0.070 g, 0.27 mmol, 1.5 equiv) and DIAD (0.052 mL, 0.27 mmol, 1.5 equiv) were successfully added. The microwave vial was placed in the microwave reactor and heated for 10 min at 50 °C (100 W power). The resulting reaction mixture was placed to a 25 mL flask and the solvents were removed under reduced pressure to yield the crude product.

General procedure for base-promoted alkylation using alkyl halides (base-promoted alkylation). A sulfonamide (0.098 mmol, 1.0 equiv) was added to DMF (2 mL) at RT. The whole mixture was cooled to 0 °C and alkyl halide (0.196 mmol, 2.0 equiv) followed by the addition of K_2CO_3 (0.196 mmol, 2.0 equiv) were added. The resulting mixture was stirred at 0 °C for 5 min. The cooling bath was removed and the whole mixture was stirred at for 12h at rt (for primary alkyl halides) or at 50 °C (for secondary alkyl halides; external temperature, oil bath). Sat. aq. NH_4Cl (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 15 mL). Combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give the crude product.

*N-benzyl-N-isopropylbenzo[d]thiazole-2-sulfonamide (**4d**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil. **FM alkylation**: starting from 0.030 g (0.09 mmol) of **3a**, yielded 0.030 g (90%); **Base-promoted alkylation**: starting from 0.030 g (0.09 mmol) of **3a**, carried out at 50 °C, yielded 0.032 g (97%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18 - 8.17 (m, 1H), 7.97 -7.95 (m, 1H), 7.62 - 7.58 (m, 1H), 7.56 - 7. 52 (m, 1H), 7.46 – 7.44 (m, 2H), 7.34 – 7.24 (m, 3H), 4.61 (s, 2H), 4.39 (hept, *J* = 6.8 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.9, 152.7, 138.1, 136.5, 128.6, 128.0, 127.7, 127.6, 127.4, 125.3, 122.2, 51.8, 48.0, 21.5; MS (ESI) *m/z* (%) 347: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{19}N_2O_2S_2$, 347.0882; found, 347.0884.

*N-benzyl-N-(prop-2-yn-1-yl)benzo[d]thiazole-2-sulfonamide (**4e**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:4) and obtained as a colorless oil. **FM alkylation**: starting from 0.030 g (0.09 mmol) of **3a**, yielded 0.031 g (94%); **Base-promoted alkylation**: starting from 0.030 g (0.09 mmol) of **3a**, carried out at RT, yielded 0.024 g (72%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23 (ddd, *J* = 8.2, 1.3, 0.6 Hz, 2H), 8.00 (ddd, *J* = 7.9, 1.4, 0.6 Hz, 2H), 7.67 – 7.60 (m, 1H), 7.60 – 7.54 (m, 1H), 7.42 – 7.32 (m, 5H), 4.74 (s, 2H), 4.06 (s, 2H), 1.87 – 1.86 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.8, 152.8, 136.5, 134.4, 129.0, 128.9, 128.5, 127.6, 127.5, 125.4, 122.2, 75.7, 74.3, 51.1, 36.4; MS (ESI) *m/z* (%) 343: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{16}N_2O_2S_2$, 343.0569; found, 343.0571.

*N-benzyl-N-(2-methylallyl)benzo[d]thiazole-2-sulfonamide (**4f**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:6->1:3) and obtained as a colorless oil. **FM alkylation**: starting from 0.055 g (0.18 mmol) of **3a**, yielded 0.026 g (40%); **Base-promoted alkylation**: starting from 0.055 g (0.18 mmol) of **3a**, carried out at RT, yielded 0.056 g (87%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.17 (ddd, *J* = 8.5, 1.3, 0.7 Hz, 2H), 7.96 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.58 - 7.53 (m, 1H), 7.27 – 7.22 (m, 5H), 4.87 – 4.86 (m, 1H), 4.79 – 4.78 (m, 1H), 4.59 (s, 2H), 3.94 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.3, 152.5, 139.5, 136.3, 135.2, 129.0, 128.5, 128.0, 127.6, 127.4, 125.2, 122.2, 115.5, 54.2, 51.6, 19.9; MS (ESI) *m/z* (%) 359: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for for $C_{21}H_{19}N_2O_2S_2$, 359.0882; found, 359.0880.

*N,N-dibenzylbenzo[d]thiazole-2-sulfonamide (**4g**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil. **FM alkylation**: starting from 0.070 g (0.23 mmol) of **3a**, yielded 0.065 g (72%); **Base-promoted alkylation**: starting from 0.030 g (0.09 mmol) of **3a**, carried out at RT, yielded 0.031 g (81%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.17 (ddd, J = 8.3, 1.2, 0.5 Hz, 1H), 7.97 (ddd, J = 7.9, 1.3, 0.5 Hz, 1H), 7.62 (ddd, J = 8.2, 7.3, 1.4 Hz, 1H), 7.57 (ddd, J = 7.9, 7.2, 1.3 Hz, 1H), 7.21 – 7.15 (m, 10H), 4.55 (s, 4H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 166.4, 152.5, 136.3, 134.9, 128.9, 128.6, 128.0, 127.6, 127.4, 125.2, 122.2, 51.5; MS (ESI) *m/z* (%) 395: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{19}N_2O_2S_2$, 395.0882; found, 395.0885.

*N-butyl-N-isopropylbenzo[d]thiazole-2-sulfonamide (**4h**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 2:5) and obtained as a colorless oil. **FM alkylation**: starting from 0.045 g (0.17 mmol) of **3c**, yielded 0.049 g (88%); **Base-promoted alkylation**: starting from 0.024 g (0.09 mmol) of **3c**, carried out at 50 °C, yielded 0.028 g (94%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.16 (ddd, J = 8.4, 1.3, 0.6 Hz, 1H), 7.96 (ddd, J = 7.8, 1.4, 0.6 Hz, 1H), 7.61 - 7.55 (m, 1H), 7.53 (ddd, J = 8.0, 7.3, 1.4 Hz, 3H), 4.35 (hept, 1H), 3.31 - 3.27 (m, 2H), 1.76 - 1.68 (m, 2H), 1.35 (sext, 2H), 1.17 (d, 6H), 0.94 (t, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.00, 152.7, 136.4, 127.4, 127.3, 125.2, 122.1, 51.1, 44.0, 34.0, 21.5, 20.3, 13.8; MS (ESI) *m/z* (%) 313: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{21}N_2O_2S_2$, 313.1039; found, 313.1041.

*N-allyl-N-(prop-2-yn-1-yl)benzo[d]thiazole-2-sulfonamide (**4i**)*. The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil. **FM alkylation**: starting from 0.025 g (0.098 mmol) of **3b**, yielded 0.022 g (77%); **Base-promoted alkylation**: starting from 0.023 g (0.09 mmol) of **3b**, carried out at RT, yielded 0.024 g (86%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H), 7.98 (ddd, J = 7.9, 1.5, 0.7 Hz, 1H), 7.61 (ddd, J = 8.2, 7.2, 1.4 Hz, 1H), 7.56 (ddd, J = 7.9, 7.2, 1.4 Hz, 1H), 5.78 (ddt, J = 17.1, 10.0, 6.5 Hz, 1H), 5.36 (dq, J = 17.1, 1.4 Hz, 1H), 5.28 (dq, J = 10.1, 1.2 Hz, 1H), 4.22 (d, J = 2.5 Hz, 2H), 4.18 (d, J = 6.5, 2H), 1.90 (t, J = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.9, 152.7, 136.5, 131.4, 127.6, 127.4, 125.3, 122.2, 120.7, 76.0, 73.9, 50.2, 36.6; MS (ESI) *m/z* (%) 293: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{13}N_2O_2S_2$, 293.0413; found, 293.0416.

*(S)-N-benzyl-N-(octan-2-yl)benzo[d]thiazole-2-sulfonamide ((–)-**4j**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:8) and obtained as a colorless oil. **FM alkylation**: starting from 0.060 g (0.18 mmol) of **3a** and (*R*)-octan-2-ol (0.057 mL, 0.36 mmol, *e.r.* = >99:1), yielded 0.051 g (62%), *e.r.* = >98:2; **Base-promoted alkylation**: starting from 0.060 g (0.18 mmol) of **3a** and (±)-2-bromooctan (0.063 mL, 036 mmol), carried out at 50 °C, yielded 0.068 g (91%), *e.r.* = 51:49. $[\alpha]_D^{22}$ = −183° (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.18 – 8.16 (m, 1H), 7.96 (ddd, J = 7.9, 1.3, 0.6 Hz, 1H), 7.60 (ddd, *J* = 8.2, 7.3, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.46 – 7.45 (m, 2H), 7.33 – 7.24 (m, 3H), 4.64 (d, J = 15.9 Hz, 1H), 4.51 (d, J = 15.9 Hz, 1H), 4.12 (hept, *J* = 6.8 Hz, 1H), 1.39 – 1.30 (m, 1H), 1.26 – 1.18 (m, 1H), 1.12 – 1.05 (m, 4H), 1.03 (d, J = 6.8 Hz, 3H), 1.02 – 0.93 (m, 4H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 166.9, 152.7, 137.8, 136.5, 128.6, 128.5, 127.8, 127.5, 127.4, 125.2, 122.2, 56.2, 48.3, 35.6, 31.7, 29.0, 26.5, 22.6, 19.6, 14.2; MS (ESI) *m/z* (%) 417: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{21}N_2O_4S_2$, 417.1665; found, 417.1667; HPLC (Chiralpak IA3, CO_2/MeOH = 93/7, flow rate = 2.2 mL/min, I = 272 nm) tR = 4.21 min (minor), 4.51 min (major).

*N-butyl-N-(oxiran-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (**4k**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:35) and obtained as a colorless oil. **FM alkylation**: starting from 0.048 g (0.18 mmol) of **3c**, yielded 0.043 g (74%). ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.16 (ddd, *J* = 8.5, 1.3, 0.6 Hz, 1H), 7.98 (ddd, J = 8.0, 1.5, 0.8 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.58 – 7.53 (m, 1H), 4.00 (dd, *J* = 15.1, 3.0 Hz, 1H), 3.56 – 3.45 (m, 1H), 3.34 – 3.36 (m, 1H), 3.24 – 3.22 (m, 1H), 3.16 (dd, J = 15.0, 6.6 Hz, 1H), 2.81 (t, *J* = 4.3 Hz, 1H), 2.59 (ddd, *J* = 4.6, 2.5, 1.0 Hz, 1H), 1.71 – 1.61 (m, 2H), 1.41 – 1.29 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 165.7, 152.6, 136.3, 127.6, 127.5, 125.2, 122.2, 51.8, 50.9, 50.0, 45.2, 30.6, 19.8, 13.7; MS (ESI) *m/z* (%) 327: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{19}N_2O_3S_2$, 327.0832; found, 327.0838.

*Ethyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzylalaninate ((–)-**4l**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:4) and obtained as a slightly yellow oil. **FM alkylation**: starting from 0.054 g (0.17 mmol) of **3a**, yielded 0.066 g (92%). $[\alpha]_D^{23}$ = − 440° (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.19 – 8.17 (m, 1H), 7.99 – 7.96 (m, 1H), 7.61 (ddd, J = 8.3, 7.2, 1.4 Hz, 1H), 7.56 (ddd, J = 8.5, 7.2, 1.4 Hz, 1H), 7.44 – 7.42 (m, 2H), 7.34 – 7.24 (m, 3H), 4.93 (d, *J* = 16.4 Hz, 1H), 4.86 (q, *J* = 7.3 Hz, 1H), 4.54 (d, *J* = 16.4 Hz, 1H), 3.70 – 3.88 (m, 2H), 1.34 (d, *J* = 7.4 Hz, 1H), 0.96 (t, *J* = 7.1 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 170.7, 165.6, 152.7, 137.0, 136.5, 128.6, 128.2, 127.9, 127.7, 127.5, 125.2, 122.2, 61.6, 56.4, 50.3, 16.9, 13.8; MS (ESI) *m/z* (%) 405: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{21}N_2O_4S_2$, 405.0937; found, 405.0938.

*methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-butyl-L-alaninate ((–)-**4m**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless solid. **FM alkylation**: starting from 0.048 g (0.17 mmol) of **3c** and methyl (*R*)-2-hydroxypropanoate (0.032 mL, 0.34 mmol, *e.r.* = >99:1), yielded 0.053 g (84%, *e.r.* = >98:1). mp = 53 – 55 °C; $[\alpha]_D^{23}$ = −101° (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.17 - 8.15 (m, 1H), 7.98 -7.95 (m, 1H), 7.61 - 7.57 (m, 1H), 7.56 - 7.52 (m, 1H), 4.85 (q, *J* = 7.3 Hz, 2H), 3.57 (ddd, *J* = 15.6, 10.9, 5.2 Hz, 1H), 3.45 (s, 3H), 3.22 (ddd, J = 15.2, 10.9, 5.5 Hz, 1H), 1.84 – 1.73 (m, 1H), 1.68 – 1.58 (m, 1H), 1.51 (d, *J* = 7.3 Hz, 3H), 1.40 – 1.27 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 171.6, 165.6, 152.6, 136.4, 127.6, 127.4, 125.2, 122.2, 56.2, 52.5, 46.9, 33.3, 20.2, 16.7, 13.8; MS (ESI) *m/z* (%) 358: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{21}N_2O_4S_2$, 357.0937; found, 357.0936; HPLC (Chiralpak IE3, CO_2/MeOH = 95/5, flow rate = 2.2 mL/min, I = 272 nm) tR = 5.50 min (minor), 5.89 min (major).

*methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-((R)-1-methoxy-1-oxopropan-2-yl)-L-alaninate (meso-**4n**).* The crude product was purified using flash column chromatography (SiO_2; acetone/petroleum ether = 1:2) and obtained as a colorless oil. **FM alkylation**: starting from 0.023 g (0.08 mmol) of **3m** and methyl (*R*)-2-hydroxypropanoate (0.016 mL, 0.16 mmol, *e.r.* = >99:1), yielded 0.010 g (33%, *d.r.* = >20:1). $[\alpha]_D^{23}$ = 0° (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.13 (ddd, *J* = 8.2, 1.4, 0.6 Hz, 1H), 7.97 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.57 - 7.53 (m, 1H), 4.82 (q, *J* = 7.3 Hz, 1H), 3.67 (s, 6H), 1.56 (d, *J* = 7.3 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 171.4, 167.2, 152.4, 136.4, 127.7, 127.5, 125.1, 122.3, 55.3, 52.7, 17.0; MS (ESI) *m/z* (%) 387: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{19}N_2O_4S_2$, 387.0679; found, 387.0684.

*(5R,5aR,8aS,9S)-9-(benzo[d]thiazol-2-yl(benzyl)amino)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one ((–)-**4o**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:8) and obtained as a colorless solid. **FM alkylation**: starting from 0.096 g (0.32 mmol) of **3a**, yielded 0.067 g (30%, *d.r.* = >20:1) as a white solid. mp = 139-141 °C; $[\alpha]_D^{21}$ = −64.6° (*c* 3.51, CH_2Cl_2); ^{1}H NMR (500 MHz, Chloroform-*d*): *δ* 8.35 – 8.33 (m, 1H), 8.09 – 8.06 (m, 1H), 7.75 – 7.65 (m, 2H), 7.35 – 7.33 (m, 3H), 7.05 – 7.03 (m, 2H), 6.78 (s, 1H), 6.50 (s, 1H), 6.11 (s, 2H), 5.98 – 5.97 (m, 2H) , 5.78 (d, *J* = 5.1 Hz, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.47 (dd, *J* = 9.2, 7.5 Hz, 1H), 4.26 (dd, *J* = 11.0, 9.2 Hz, 1H), 4.06 (d, *J* = 5.5 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.60 (d, *J* = 15.4 Hz, 1H),), 2.82 (dddd, *J* = 14.7, 10.9, 7.6, 5.0 Hz, 1H), 1.51 (dd, *J* = 14.7, 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): *δ* 174.1, 165.5, 152.7, 152.6, 149.1, 147.7, 137.3, 137.2, 136.6, 134.8, 134.8, 129.4, 129.3, 129.2, 128.3, 128.2, 125.3, 124.2, 122.5, 110.7, 109.8, 108.2, 101.9, 69.8, 60.9, 58.9, 56.4, 49.5, 43.7, 40.6, 37.6; MS (ESI) *m/z* (%) 701: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{36}H_{33}N_2O_9S_2$, 701.1622; found, 701.1625.

Intramolecular cyclization of aminoalcohol based on N-BT-sulfonylation/intramolecular Fukuyama-Mitsunobu alkylation (Table 3B): *2-(azepan-1-ylsulfonyl)benzo[d]thiazole (**5**).* Sulfinic salt **2** (0.200 g, 0.9 mmol, 1.0 equiv) was added to a mixture of THF (8 mL) and H_2O (2 mL) at RT and the resulting mixture was stirred for 5 min. 6-aminohexan-1-ol (0.107 g, 1 mmol, 1.1 equiv) followed by NBS (0.318 g, 1.8 mmol, 2.0 equiv) were added. After 10 min at RT, the whole mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the resulting layers were separated. Aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was placed into a microwave reaction vessel and dissolved in THF (8 mL). DIAD (0.264 ml, 1.35 mmol, 1.5 equiv) and PPh_3 (0.262 g, 1.35 mmol, 1.5 mmol) were added and the reaction mixture was heated in a microwave reactor for 10 min at 50 °C (100 W). Reaction mixture was transferred to a flask and the solvents were removed under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO_2; EtOAc/hexane = 3:8) to yield the desired cyclized sulfonamide **5** (0.139 g, 59 % over two steps) in the form of colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.17 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 2H), 7.97 (ddd, *J* = 7.8, 1.3, 0.6 Hz, 2H), 7.62 – 7.58 (m, 1H), 7.56 - 7.52 (m, 1H), 3.55 – 3.52 (m, 4H), 1.83 – 1.76 (m, 4H), 1.64 – 1.61 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 165.6, 152.7, 136.3, 127.4, 127.3, 125.2, 122.2, 49.1, 29.2, 27.0; MS (ESI) *m/z* (%) 297: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{17}N_2O_2S_2$, 297.0726; found, 297.0728.

N-benzylbenzo[d]thiazol-2-amine (7a) synthesis (Scheme 3B, equation 6): A solution of sulfonamide **3a** (0.127 g, 0.42 mmol, 1.0 equiv) and Cs_2CO_3 (0.274 g, 0.84 mmol, 2.0 equiv) were added to 1,4-dioxane (5 mL) and the resulting mixture was degassed using freeze-pump-thaw technique (three times). $(PPh_3)_2PdCl_2$ (0.059 g, 0.084 mmol, 0.2 equiv) was added and the resulting mixture was heated at 100 °C (external temperature, oil bath) for 24h. The resulting mixture was cooled to RT, diluted with CH_2Cl_2 (25 mL), and filtered through a pad of Celite®. Filter cake was washed with additional CH_2Cl_2 (3 x 25 mL) and the combined filtrates were evaporated under reduced pressure. Residue was purified by flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:5->1:2->1:1) to yield the desired product **7a** (0.077 g, 76%) as a colorless oil. mp = 163-165 °C (164-168 °C lit[58]); ^{1}H NMR (500 MHz, Chloroform-*d*): *δ* 7.58 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.20 (m, 7H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.84 (broad s, 1H), 4.64 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): *δ* 165.9, 153.3, 136.6, 129.3, 128.8, 128.0, 127.9, 123.9, 121. 9, 121.1, 119.8, 50.5; MS (ESI) *m/z* (%) 241: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{13}N_2S$, 241.0794; found, 241.0796.

General procedure for Chan-Lam coupling

Sulfonamide **3** (0.1 mmol, 1 equiv) was dissolved in dry DCE (2.0 mL, 0.05 M), and boronic acid (0.2 mmol, 2 equiv), TMEDA (0.06 mL, 0.4 mmol, 4 equiv) and $[Cu(CH_3CN)_4]PF_6$ (0.015 g, 0.04 mmol, 0.4 equiv) were added. The resulting mixture was placed under an atmosphere of O_2 (1 atm) and stirred for 4h at RT. The whole mixture was filtered over a pad of Celite®, and the filter cake was washed with CH_2Cl_2 (3 x 25 mL). Resulting filtrates were combined and the solvents were removed under reduced pressure.

*N-benzyl-N-phenylbenzo[d]thiazole-2-sulfonamide (**6a**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and phenylboronic acid (0.022 g, 0.18 mmol). The crude product was purified using flash column

chromatography (SiO_2; EtOAc/hexane = 1:3) to yield 0.025 g (67%) of **6a** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.31 (ddd, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.99 (ddd, *J* = 8.1, 1.3, 0.7 Hz, 1H), 7.68 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.61 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.33 – 7.23 (m, 8H), 7.17 – 7.12 (m, 2H), 5.13 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 165.7, 152.6, 138.2, 136.7, 135.6, 129.3, 128.9, 128.7, 128.6, 128.1, 127.7, 127.5, 125.4, 122.3, 56.9; MS (ESI) *m/z* (%) 381: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{17}N_2O_2S_2$, 381.0726; found, 381.0728

*N-allyl-N-phenylbenzo[d]thiazole-2-sulfonamide (**6b**).* Prepared starting from sulfonamide **3b** (0.024 g, 0.09 mmol) and phenylboronic acid (0.022 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) to yield 0.020 g (63%) of **6b** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.25 – 8.23 (m, 1H), 7.95 – 7.93 (m, 1H), 7.63 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.23 – 7.21 (m, 2H), 5.87 (ddt, *J* = 16.6, 10.2, 6.4 Hz, 1H), 5.15 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.11 (dd, *J* = 9.7, 1.4 Hz, 1H), 4.54 (dt, *J* = 6.5, 1.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 165.6, 152.6, 138.3, 136.7, 132.6, 129.4, 129.2, 128.7, 127.7, 127.5, 125.4, 122.3, 119.6, 55.6; MS (ESI) *m/z* (%) 331: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{15}N_2O_2S_2$, 331.0569; found, 331.0573.

*N-butyl-N-phenylbenzo[d]thiazole-2-sulfonamide (**6c**).* Prepared starting from sulfonamide **3c** (0.062 g, 0.22 mmol) and phenylboronic acid (0.054 g, 0.44 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:4) to yield 0.044 g (58%) of **6c** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.24 – 8.22 (m, 1H), 7.95 – 7.92 (m, 1H), 7.62 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.55 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.23 – 7.20 (m, 2H), 3.92 (t, *J* = 7.1 Hz, 2H), 1.53 – 1.47 (m, 2H), 1.43 – 1.34 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 165.5, 152.7, 138.4, 136.6, 129.4, 129.2, 128.7, 127.6, 127.4, 125.4, 122.2, 52.5, 30.7, 19.7, 13.7; MS (ESI) *m/z* (%) 347: $[M+H]^+$ (100); HRMS (ESI) *m/z*: calcd. for $C_{17}H_{19}N_2O_2S_2$, 347.0882; found, 347.0885.

*N-benzyl-N-(3-methoxyphenyl)benzo[d]thiazole-2-sulfonamide (**6d**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 3-methoxyphenylboronic acid (0.027 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:5->1:3) and the collected fractions containing the product were concentrated under reduced pressure. The resulting crude product was purified by semiprep HPLC (MeCN/buffer, gradient 9:1 to 3:2 over 6 min) to yield 0.0155 g (42%) of **6d** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.28-8.25 (m, 1H), 7.98-7.95 (m, 1H), 7.67-7.63 (m, 1H), 7.60 - 7.55 (m, 1H), 7.30 – 7.23 (m, 5H), 7.11 (ddd, *J* = 8.3, 7.9, 0.8 Hz, 1H), 6.77 (ddd, *J* = 8.4, 2.3, 1.1 Hz, 1H), 6.69 – 6.66 (m, 2H), 5.07 (s, 2H), 3.62 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 165.8, 160.1, 152.6, 139.3, 136.7, 135.7, 129.8, 128.9, 128.6, 128.1, 127.7, 127.5, 125.4, 122.3, 121.3, 115.2, 114.7, 56.9, 55.4; MS (ESI) *m/z* (%) 411: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{19}N_2O_3S_2$, 411.0832; found, 411.0833.

*N-benzyl-N-(4-chlorophenyl)benzo[d]thiazole-2-sulfonamide (**6e**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 4-chlorophenylboronic acid (0.028 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:6) to yield 0.026 g (65%) of **6e** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.27 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.66 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H), 7.30 – 7.19 (m, 7H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.03 (ddd, *J* = 7.9, 2.0, 1.2 Hz, 1H), 5.05 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 165.2, 152.6, 139.4, 136.6, 135.1, 134.7, 130.2, 129.6, 129.0, 128.9, 128.7, 128.3, 127.9, 127.7, 127.6, 125.5, 122.3, 56.7; MS (ESI) *m/z* (%) 415: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{16}ClN_2O_2S_2$, 415.0336; found, 415.0341.

*N-benzyl-N-(3-fluorophenyl)benzo[d]thiazole-2-sulfonamide (**6f**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 3-fluorophenylboronic acid (0.025 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) to yield 0.017 g (45%) of **6f** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): *δ* 8.27 (dd, *J* = 9.2, 0.9 Hz, 1H), 7.97 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.28 – 7.23 (m, 5H), 7.19 (td, *J* = 8.2, 6.3 Hz, 1H), 6.97 - 6.90 (m, 3H), 5.07 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): *δ* 165.3, 162.66 (d, *J* = 248.6 Hz), 152.6, 139.6 (d, *J* = 9.7 Hz), 136.6, 135.2, 130.3 (d, *J* = 9.0 Hz), 128.9, 128.7, 128.3, 127.9, 127.7, 125.5, 125.0 (d, *J* = 3.3 Hz), 122.3, 116.7 (d, *J* = 22.8 Hz), 115.9 (d, J = 20.8 Hz), 56.8; ^{19}F{^{1}H} NMR (376 MHz,

Chloroform-*d*): δ -110.8; MS (ESI) *m/z* (%) 399: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{35}N_2O_4S_2Si$, 399.0632; found, 399.0635.

*N-benzyl-N-(4-bromophenyl)benzo[d]thiazole-2-sulfonamide (**6g**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 4-bromophenylboronic acid (0.036 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexan = 1:3) and the collected fractions containing the product were concentrated under reduced pressure. The resulting crude product was purified by semiprep HPLC (MeCN/buffer, gradient 9:1 to 3:2 over 6 min) to yield 0.0107 g (26%) of **6g** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.26 (ddd, *J* = 8.3, 1.2, 0.7 Hz, 1H), 7.97 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.66 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.36 – 7.33 (m, 2H), 7.27 – 7.25 (m, 9H), 7.02 – 6.98 (m, 2H), 5.05 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.3, 152.6, 137.2, 135.2, 132.6, 130.9, 128.9, 128.8, 128.3, 127.9, 127.7, 125.5, 122.8, 122.3, 56.8; MS (ESI) *m/z* (%) 459: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{16}BrN_2O_2S_2$, 458. 9831; found 458.9833.

*N-([1,1'-biphenyl]-4-yl)-N-benzylbenzo[d]thiazole-2-sulfonamide (**6h**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 1,1'-biphenyl]-4-ylboronic acid (0.036 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) to yield 0.026 g (65%) of **6h** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.27 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.66 – 7.62 (m, 1H), 7.59 - 7.55 (m, 1H), 7.49 - 7.35 (m, 6H), 7.32 - 7.24 (m, 6H), 7.17 – 7.15 (m, 2H), 5.12 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.6, 152.6, 141.4, 139.9, 137.2, 136.6, 135.6, 129.5, 128.9, 128.6, 128.0, 127.9, 127.8, 127.6, 127.5, 127.1, 125.4, 122.2, 56.8; MS (ESI) *m/z* (%) 457: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{26}H_{21}N_2O_2S_2$, 457.1039; found 457.1040.

*N-([1,1'-biphenyl]-4-yl)-N-allylbenzo[d]thiazole-2-sulfonamide (**6i**).* Prepared starting from sulfonamide **3b** (0.030 g, 0.09 mmol) and 1,1'-biphenyl]-4-ylboronic acid (0.036 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and the collected fractions containing the product were concentrated under reduced pressure. The resulting crude product was purified by semiprep HPLC (MeCN/buffer, gradient 9:1 to 3:2 over 6 min) to yield 0.026 g (72%) of **6i** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.26 (ddd, *J* = 8.3, 1.3, 0.7 Hz, 1H), 7.96 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.65 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.1, 7.2, 1.3 Hz, 1H), 7.52 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.43 (td, *J* = 2.0, 0.4 Hz, 2H), 7.41 – 7.30 (m, 6H), 7.20 (ddd, *J* = 7.9, 2.1, 1.1 Hz, 1H), 5.90 (ddt, *J* = 16.5, 10.2, 6.4 Hz, 1H), 5.17 (ddd, *J* = 16.9, 2.6, 1.3 Hz, 1H), 5.13 (ddd, *J* = 10.1, 2.3, 1.1 Hz, 1H), 4.56 (dt, *J* = 6.4, 1.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.6, 152.7, 142.6, 140.0, 138.8, 136.7, 132.6, 129.7, 129.0, 128.0, 127.9, 127.9, 127.7, 127.6, 127.4, 127.2, 125.4, 122.3, 119.7, 55.7; MS (ESI) *m/z* (%) 407: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{19}N_2O_2S_2$, 407.0882; found, 407.0886.

Benzo[d]thiazol-2-ylsulfonyl group cleavage (Scheme 6C)

Ethanthiolysis (Scheme 6C, equation 6): *N,N*-Dibenzylsulfonamide **4g** (0.050 g, 0.12 mmol) was dissolved in CH_3CN (1.2 mL) at RT, and EtSLi (0.024 g, 0.36 mmol, 3.0 equiv) was added. The resulting mixture was stirred at RT for 12h. Solvents were removed under reduced pressure and the resulting crude product was purified with flash column chromatography (SiO_2; EtOAc/hexane = 1:1) to yield compound **11** (0.022g, 95%) as a yellowish oil. **$NaBH_4$ reduction (Scheme 6C, equation 7):** *N,N*-Dibenzylsulfonamide **4g** (0.129 g, 0.33 mmol) was dissolved in EtOH (2 mL) at RT, and $NaBH_4$ (0.049 g, 1.3 mmol, 4.0 equiv) was added. The resulting mixture was stirred at RT for 12h. The whole mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the layers were separated. Aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL), and the organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; EtOAc/hexane = 1:1) to give the desired compound **11** (0.063 g, 98%) as yellowish oil. **Dibenzylamine (11)**: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.37 - 7.32 (10 H), 3.82 (4 H); 13C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 140.3, 128.6, 128.3, 127.1, 53.2; MS (ESI) *m/z* (%) 198: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{16}N$, 198.1277; found 198.1277.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Relevant optimization tables, discussion related to the proposed reaction mechanisms, and a copy of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra. (PDF)

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Author Contributions

F.Z. performed most of the experiments and analyzed the experimental data. O.K. carried out the experiments and analyzed the experimental data. F.Z., E.L. and O.K. performed and optimized Chan-Lam coupling. F.Z., O.K. and N.S. performed and optimized SuFEX experiments. F.Z. partially designed the experimental plans. J.P. initiated the project, led the project team, designed the experiments, and analyzed results. F.Z. and J.P. co-wrote the paper with input from all authors. All authors have given approval to the final version of the manuscript.

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Notes

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