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Leighann Lam Date

Acylative Redox Dehydration of Carboxylic Acids and Benzoisothiazolones in the Synthesis of Thioesters with Triethylphosphite as a Terminal Reductant

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Master of Science

Chemistry

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By

Leighann Lam

B.S., University of North Carolina at Chapel Hill, 2011

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An abstract of

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Abstract

Acylative Redox Dehydration of Carboxylic Acids and Benzoisothiazolones in the Synthesis of Thioesters with Triethylphosphite as a Terminal Reductant

By Leighann Lam

A series of structurally diverse thioesters was synthesized through a redox dehydration reaction with carboxylic acids using a benzoisothiazolone / $P(OEt)_3$ system. Unlike previous systems that utilized various triorganophosphines as the reductant, pure product was typically obtained in good yield after a basic wash and trituration with no need for chromatography. The thioester scope included products derived from amino acids, lipoic acid, and abscisic acid, as well as acids containing oxadiazole or azide functional groups. Acids that possessed steric hindrance around the carbonyl group were found to give lower yields, possibly due to the intermediate thiolate being unable to easily approach the cationic acyl phosphorous intermediate. Though 5-nitro benzoisothiazolones consistently provided good product yields, 2-pyridyl benzoisothiazolones were more troublesome as their thiolate intermediate preferentially tautomerizes into the unreactive thione form. Future work will delve into expanding the library of benzoisothiazolones and optimizing the reaction conditions towards a catalytic system for the formation of amides, peptides, ketones, and esters.

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Abbreviations

AcOH	acetic acid
APCI	atmospheric-pressure chemical ionization
Ar	argon
B*i*T	benzoisothiazolone
Calcd	calculated
Cbz	carboxybenzyl
$CDCl_3$	deuterated chloroform
CF_3CO_2D	deuterated trifluoroacetic acid
CH_2Cl_2	dichloromethane
d	doublet
dd	doublet of doublets
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dq	doublet of quartets
ESI	electrospray ionization
EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
h	hour(s)
HCl	hydrochloric acid
HRMS	high resolution mass spectroscopy
Hz	hertz
i-Pr	isopropyl
IR	infrared
J	coupling constant
lit.	literature
Lys	lysine
M	molarity
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
$MgSO_4$	magnesium sulfate
MHz	megahertz
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
µL	microliter(s)
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
NPS	*o*-nitrophenylsulfenyl

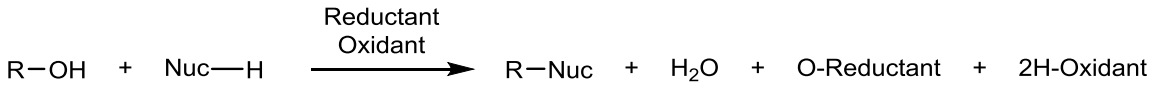
Nuc	nucleophile
Pc	phthalocyanine
$P(OEt)_3$	triethylphosphite
ppm	parts per million
Pro	proline
Py	pyridyl
q	quartet
RT	room temperature
s	singlet
sept	septet
sext	sextet
$SOCl_2$	thionyl chloride
δ	chemical shift
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
Tyr	tyrosine
Z	carboxybenzyl

Introduction

Dehydrative condensation reactions are an important and widely used process for the easy construction of new chemical bonds. Proceeding through the overall elimination of water, two molecules can be combined under generally mild conditions. Unsurprisingly, this reaction has found wide uses in synthetic chemistry and is continuously evolving. Recent developments include the nucleophilic substitution of alcohols through cyclopropenium ion activation,[1] the phosphonium-catalyzed conversion of aldoximes to nitriles,[2] and the cyclodehydrogenation of diols to ethers.[3]

In particular, redox dehydrative reactions have been invaluable in organic synthesis for their versatility in combining two molecules by removing the formal elements of H_2O under neutral conditions. This is carried out using a weak reducing agent to accept [O] and a gentle organic oxidizing agent to accept [2H].[4] Developed initially by Mukaiyama for the condensation of carboxylic acids with protic nucleophiles, an oxidant is paired with a reductant to produce an acylative product in an overall dehydrative transformation (Scheme 1).

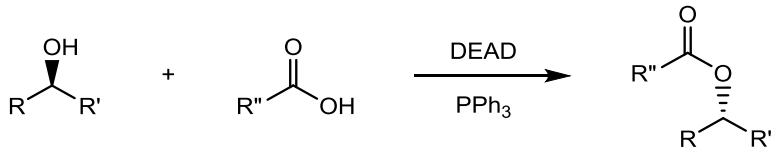
Scheme 1. General Mukaiyama redox condensation reaction



Mitsunobu, a student of Mukaiyama, would later develop an alkylative version between alcohols and relatively acidic pronucleophiles that used a diazodicarboxylate as the oxidant and a phosphine as the reductant (Scheme 2).[5] Not only does it allow for the alkylation of a wide range of nucleophiles including nitrogen, oxygen, and sulfur, it is

also tolerant of a variety of functional groups and enables the inversion of secondary alcohols.

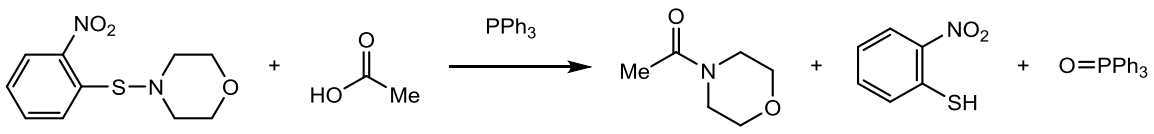
Scheme 2. General Mitsunobu reaction



One reason for the enduring appeal of Mukaiyama's acylative redox dehydration is its versatility and mildness in forming amides, peptides, and esters. Early exploratory versions of the chemistry used a diaryl-mercury reagent as an oxidant in conjunction with tributylphosphine as a reductant to form acid anhydrides from carboxylic acids. By-products consisted of mercury, phosphine oxide, and an aryl compound.[6] Other early oxidant variations included conjugated dicarbonyl compounds such as dibenozoylethylene[7] and *N*, *N*'-dibenzoyl-*p*-benzoquinone.[4] In the presence of carboxylic acids and phosphine, acid anhydrides could be obtained in high yields along with the reduced conjugated compound.

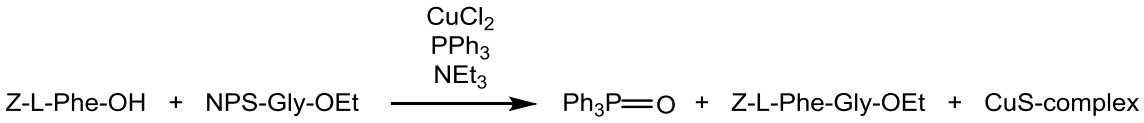
Sulfenamides have also been successfully used for oxidation in redox dehydration, particularly those based on the *o*-nitrophenylsulfenyl (NPS) residue (Scheme 3). Because NPS moieties can function as an α-amino protecting group in amino acids, this suggested that the method could be used to form peptides.[8]

Scheme 3. Redox dehydration with sulfenamide



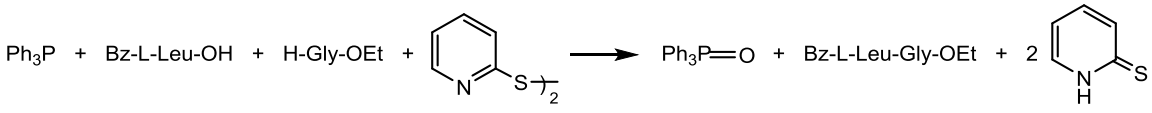
However, the process liberates a free thiol that tends to form disulfide with the starting oxidant, thereby requiring the inclusion of a thiol trap such as copper (II) salts. Upon addition of copper(II) chloride to a mixture of an N-protected, C-terminal CO_2H amino acid and an NPS-protected amino acid ester in the presence of phosphine and base, dipeptide was successfully obtained in up to 90% yield and the copper mercaptide precipitate could be easily removed through filtration (Scheme 4). Unfortunately, up to four equivalents of phosphine were required to make up for its coordination to the copper(II) thiolate.[8-9] Other successful thiol traps include sulfenic acid esters, vinyl ethers,[10] and mercury salts.[8]

Scheme 4. Redox dehydration with sulfenamide and a copper salt scavenger



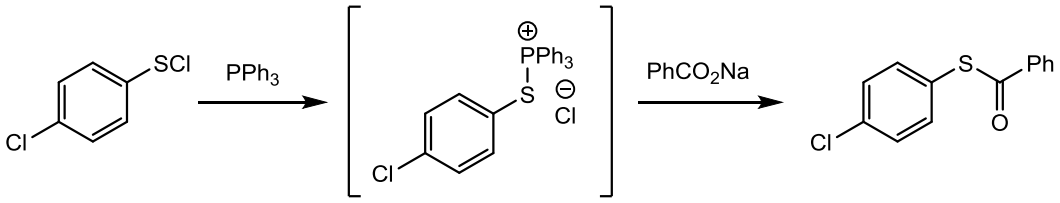
When the oxidant was dipyridyl-2,2'-disulfide ($(PyS)_2$), no extra thiol trap was needed because the resulting 2-pyridinethiol preferentially isomerizes into its more stable thione form[11] which is unreactive under the reaction conditions (Scheme 5). With amino acids, optical purity upwards of 96% could be obtained.[10] If the crude dipeptide was treated with another round of NPS-amino acid, phosphine, and $(PyS)_2$, the peptide chain could be further extended by one unit.[4] Replacing the free amino acid ester with an alcohol provided a handy procedure for synthesizing N-protected amino acid esters.[12]

Scheme 5. Redox dehydration with isomerizing disulfane



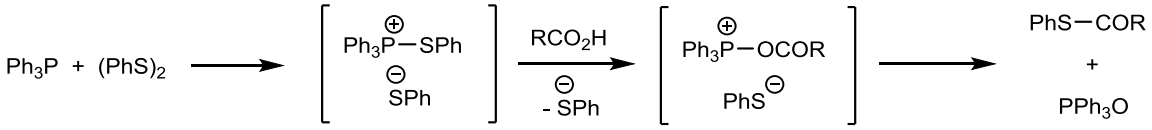
In an effort to find a convenient method for thioester synthesis, Mukaiyama also studied the use of sulfenyl chloride in redox dehydration. When used in combination with phosphine at room temperature, the reaction would proceed through a quaternary phosphonium salt intermediate that could then react with a free carboxylic acid to produce thioester in one step (Scheme 6).[13]

Scheme 6. Formation of thioester from sulfenyl chlorides



Disulfides proceed via a similar mechanism, but necessitate acetonitrile reflux temperatures to progress. Initially, a phosphonium salt forms and undergoes a nucleophilic attack by carboxylate that liberates thiolate. A return attack on the carbonyl by the ejected thiolate subsequently forms the thioester and the phosphine oxide by-product (Scheme 7).[14] In both of these cases involving a sulfur oxidant, stoichiometric amounts of both oxidant and reductant were required, which is decidedly one of the main disadvantages of redox dehydration. Some oxidants and their by-products such as the azodicarboxylate in the Mitsunobu reaction are unstable, toxic, or both, and the reductant by-products can often be difficult to remove.[15] Thus, although redox dehydration has great utility in organic synthesis, it finds limited use in commercial settings.

Scheme 7. Formation of thioester from disulfides

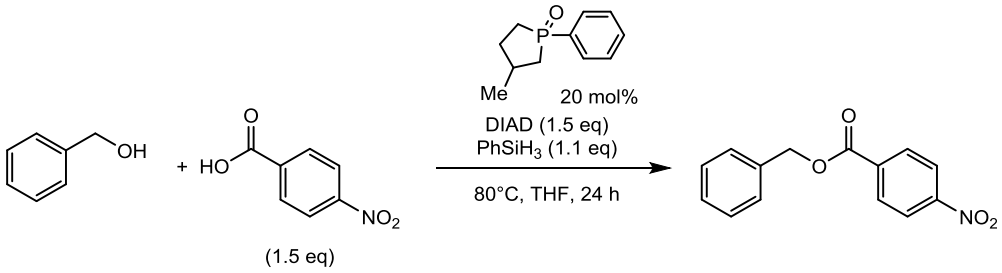


The Liebeskind group is interested in developing practical, catalytic variants of acylative and alkylative redox dehydration reactions that can function with economical and environmentally palatable terminal oxidants and reductants. As one aspect of the overall plan, the group is seeking inexpensive terminal reductants that can act as alternatives to the high molecular weight triorganophosphines used in Mukaiyama's redox dehydration chemistry. Because those oxide by-product can be troublesome and time-consuming to extract from the reaction mixture,[15] the ideal solution is to find a reductant whose oxidized by-product is more easily removed and to avoid using high molecular weight triorganophosphines altogether.

In 1973, hoping to reduce the racemization of peptides in polar solvents during redox condensation, Mukaiyama experimented with replacing triarylphosphines with less reactive triarylphosphites. Upon stirring N-benzoyl-L-leucine, ethyl glycinate, and triphenylphosphite overnight at 30°C, the corresponding peptide was obtained in 89% yield with 94% optical purity.[16] Although Mukaiyama used a high molecular weight triarylphosphite, low molecular weight phosphates derived from the oxidation of small trialkylphosphites are water-soluble and require only an aqueous wash for removal. Thus, Mukaiyama's experiment with triarylphosphites as terminal reductants was an encouraging sign that small trialkylphosphites could potentially solve the phosphine purification problem of redox dehydration.

The drawbacks of redox dehydration continue to be addressed in more recent years. Although redox condensation with a catalytic organic reductant has not been studied as extensively as its oxidant counterpart, progress has been made in recycling a triorganophosphine oxide *in situ* with an inexpensive terminal reductant. In this case, the challenge was finding the proper terminal reducing agent that would selectively reduce the phosphine oxide but leave functional groups such as carbonyls intact. In 2009, O'Brien and coworkers reported the use of the mild reducing agent, phenylsilane, in conjunction with catalytic amounts of 3-methyl-1-phenyl-2-phospholene-1-oxide in one of the first examples of a catalytic Wittig reaction.[17] Later, in a subsequent 2010 patent, O'Brien applied these same conditions to one example of a simple catalytic Mitsunobu reaction. Even with the presence of both a reducing agent and an oxidizing agent in the same reaction system, the resulting ester between benzyl alcohol and 4-nitrobenzoic acid in the presence of excess DIAD was achieved in 63% yield (Scheme 8).[18]

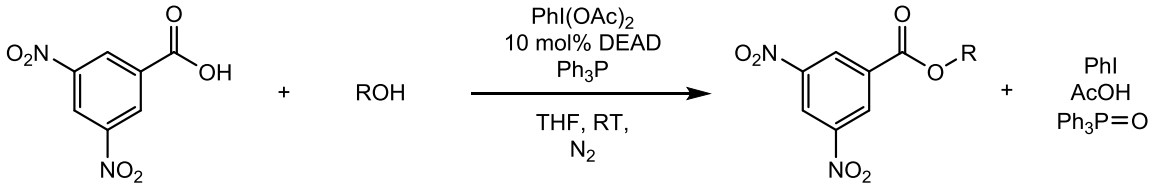
Scheme 8. Mitsunobu reaction with catalytic phosphine



That same year, Toy and coworkers addressed the other problem of using stoichiometric amounts of diazodicarboxylate. By employing diacetoxyiodobenzene as a stoichiometric oxidant to reoxidize the hydrazine back to its azo form, only catalytic amounts of DEAD were required to drive the redox dehydration reaction forward. The main oxidant by-products were then iodobenzene and acetic acid, both of which are easy

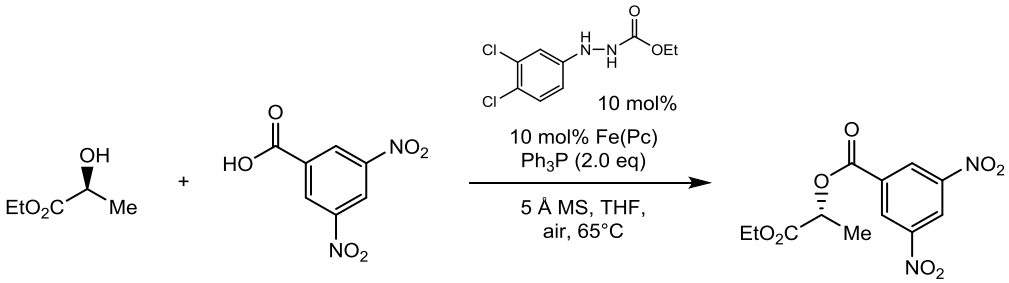
to remove (Scheme 9). However, this setup required the use of two equivalents of triphenylphosphine in order to obtain satisfactory yields.[19]

Scheme 9. Mitsunobu reaction with catalytic DEAD



A second catalytic Mitsunobu reaction was developed by Taniguchi et al. in 2013 which employed ethyl 2-(3,4-dichlorophenyl)hydrazinecarboxylate as an organocatalytic oxidant. Although the yields were not as high as those seen with Toy's conditions, this system was noteworthy in that the hydrazine was recycled via an *in situ* aerobic oxidation catalyzed by iron. In the presence of catalytic hydrazine, air, triphenylphosphine, and an iron phthalocyanine catalyst, esters could be generated from alcohols and carboxylic acids in up to 79% yield (Scheme 10).[20]

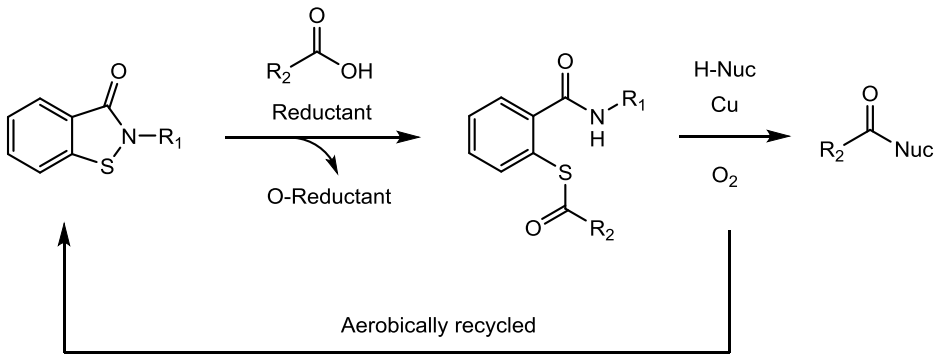
Scheme 10. Mitsunobu reaction with catalytic hydrazine using air as terminal oxidant



The Liebeskind laboratory has been interested in new redox dehydration systems that overcome the limitations of current catalytic redox dehydration reactions. Benzoisothiazolones (B*i*Ts) are cyclic heterocycles whose reduced forms, the mercaptobenzamides, can be aerobically recycled back to the oxidized form in the

presence of catalytic Cu and O_2.[21] This led us to believe that thioesters derived from the reduced B*i*T's could possibly be engaged in catalytic redox dehydrations where O_2 is the terminal oxidant (Scheme 11).

Scheme 11. Catalytic cycle with benzoisothiazolone

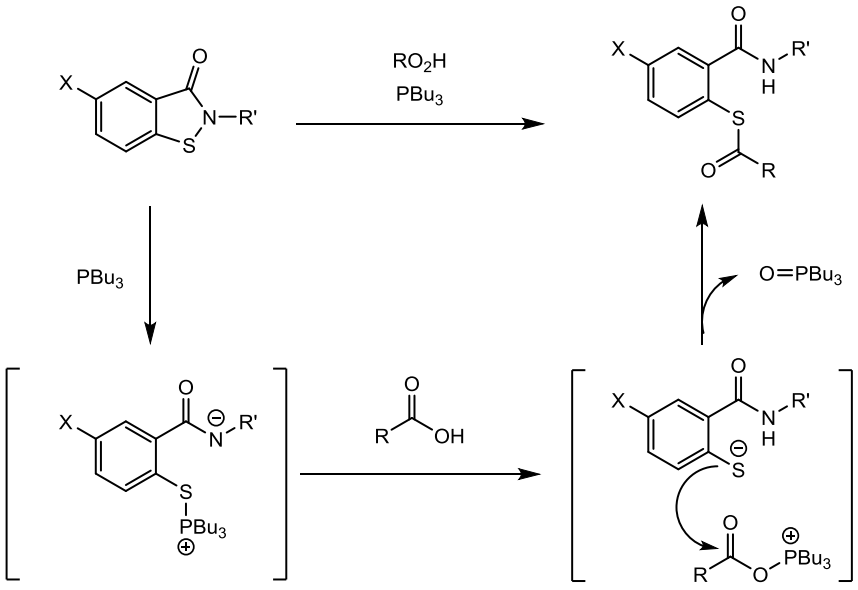


Aside from their prevalence in biochemical processes, thioesters are a valuable functional group in organic synthesis and are usually used as the stepping stones for creating more valuable C-N, C-C, and C-O bonds.[22] Hence, mild and general improvements in thioester synthesis are sought-after in chemical and biochemical research. Although Mukaiyama offered one such route for their formation from disulfides, his reaction was atom-inefficient in that half of the disulfide was eliminated as a thiol that could then participate in side reactions.[14] Mukaiyama's sulfenamide procedure does not suffer from this drawback;[13] however, using B*i*T's in place of acyclic sulfenamides as the organic oxidant in redox dehydrative routes to thioesters could potentially offer new catalytic redox dehydration reactions in which the B*i*T functions organocatalytically.

In 2008, Srogl reported a thioester synthesis via redox dehydration of carboxylic acids with B*i*T's using triorganophosphines as reductants.[23] Similar to Mukaiyama's

disulfide reaction, the mechanism first proceeds through a nucleophilic attack by phosphorous at the S-N bond to form a phosphonium zwitterion. After the carboxylate attacks the cationic phosphorus and displaces the thiolate, the thiolate then returns to attack the acyloxyphosphonium intermediate to produce thioester and triorganophosphine oxide (Scheme 12).

Scheme 12. Formation of thioesters from benzoisothiazolones



Building on the observations of Srogl, the Liebeskind group conceived of the use of B*i*T-derived thioesters in practical *catalytic* redox dehydration reactions. An essential variant of the Srogl system would be replacement of the triorganophosphine with an inexpensive, low-molecular weight terminal reductant that would generate an easily removable oxidized product. Thus, an exploration of triethylphosphite as a terminal reducing agent for the redox dehydrative coupling of B*i*T's and carboxylic acids to generate thioesters was undertaken. If this system can be shown to be efficient at the redox dehydration production of thioesters from benzoisothiazolones, then future studies

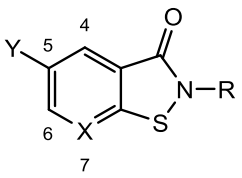
can be done to examine the potential of the system with catalytic B*i*T's as oxidants in the formation of synthetically useful products such as amides, peptides, ketones, and esters.

Results / Discussion

Benzoisothiazolone Synthesis

Our studies began with the synthesis of benzoisothiazolones using the procedure developed by Srogl.[23] N-Substituted 5-nitrobenzoisothiazolones were initially chosen for study because they represent the precedent developed by previous members of the Liebeskind group.[24] Three different substituents (*i*-Pr, *p*-C_6H_4OMe, phenyl) were considered on the amidic nitrogen atom of the B*i*T. The N-isopropyl B*i*T, **4a** (Figure 1) has consistently provided good yields of thioesters from carboxylic acids and triorganophosphines in the past[23] and so was used for a comparison against newly synthesized B*i*Ts in the triethylphosphite-focused reactions. Several N-aryl BiTs and 2-pyridyl-based B*i*T's were also chosen for study (**4b**-**4e**)**.**

Figure 1. Benzoisothiazolone library

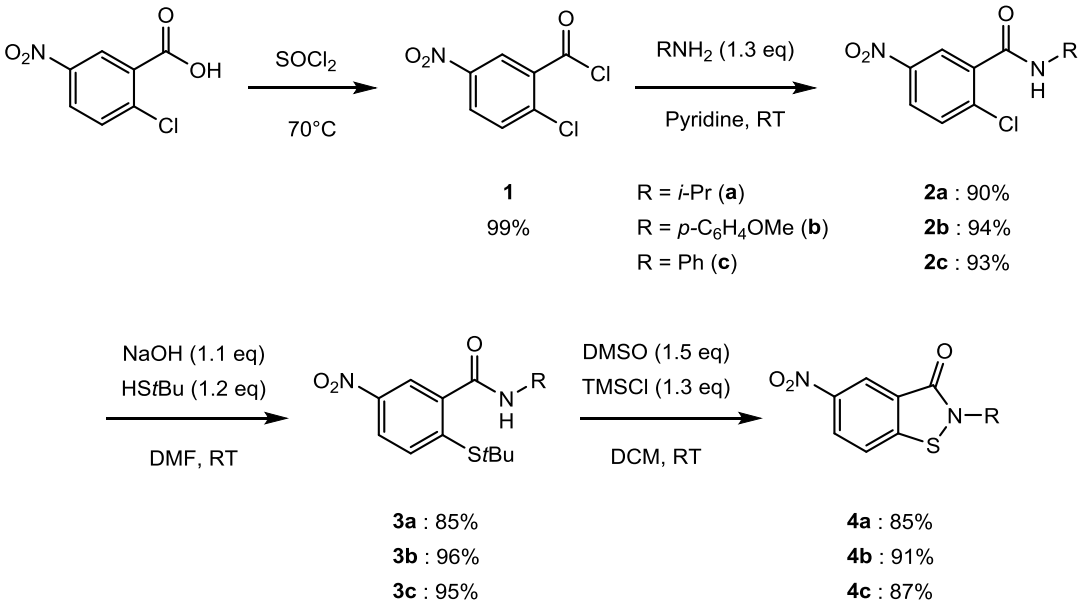


4a : X = CH, Y = NO_2, R = *i*-Pr
4b : X = CH, Y = NO_2, R = *p*-C_6H_4OMe
4c : X = CH, Y = NO_2, R = Ph
4d : X = N, Y = H, R = *p*-C_6H_4OMe
4e : X = N, Y = H, R = *p*-$C_6H_4NO_2$

As shown in Scheme 13, all 5-nitro B*i*T's were synthesized first by formation of the amide (**2a-2c**) from 2-chloro-5-nitrobenzoic acid followed by nucleophilic aromatic substitution with *t*-butylthiol. The thioether (**3a-3c**) was then oxidatively closed using

DMSO and TMSCl to provide the desired benzoisothiazolone.[24] B*i*T **4a** was crystallized from ethanol and obtained in 85% yield. B*i*T's **4b** and **4c** were more difficult to dissolve and were purified through recrystallization from DMF, providing tan and yellow crystals in 91% and 87% yields respectively.

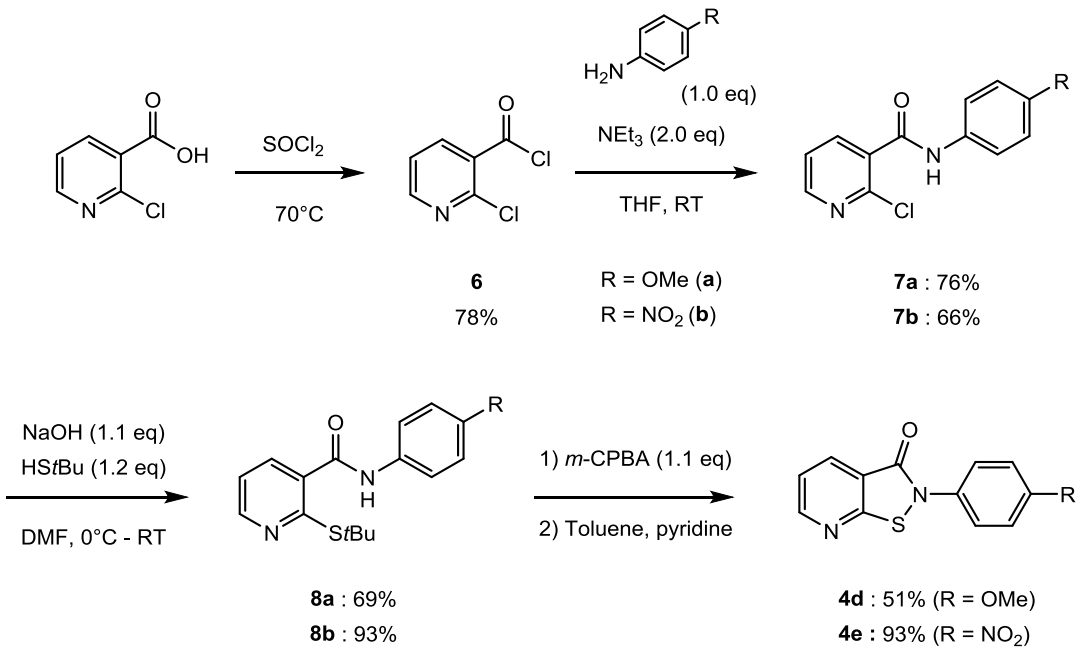
Scheme 13. Synthesis of N-substituted 5-nitrobenzoisthiazolones



Wishing to see how the electron deficiency of the aromatic ring would affect reactivity, two 2-pyridyl B*i*T's were also considered, one containing an electron-donating N-aryl group (**4d**) and another possessing an electron-withdrawing N-aryl group (**4e**). The procedure for B*i*T **4d** was developed by Dr. Pavan Gangireddy of the Liebeskind group. The synthesis of the pyridyl B*i*T's started with 2-chloronicotinic acid and involved a nearly identical process as that used to prepare the 5-nitro analog save for the oxidative ring closure step. In this case, after formation of the thioether, it was oxidized to a sulfoxide with *m*-CPBA whereupon heating in pyridine and toluene induced ring

closure and produced benzoisothiazolones **4d** and **4e** in moderate and high yields respectively (Scheme 14).[24]

Scheme 14. 2-Pyridyl benzoisothiazolone synthesis



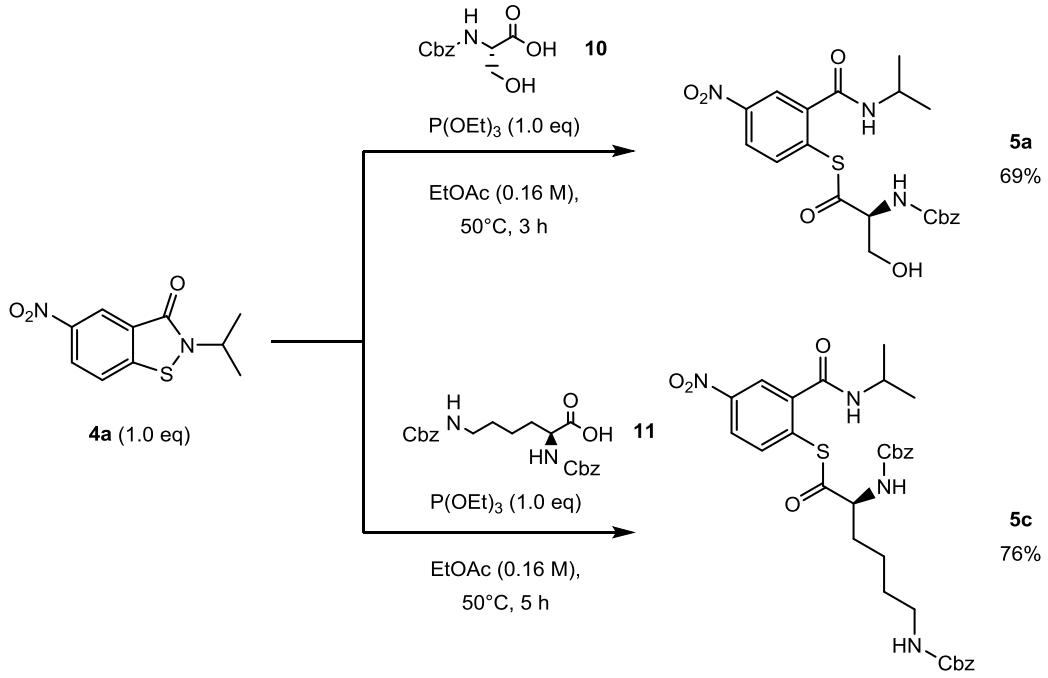
Thioester Synthesis

With a variety of B*i*T's in hand, the versatility of triethylphosphite as a terminal reductant in the redox dehydration of carboxylic acids with B*i*T's to form B*i*T-derived thioesters was explored. In order to show the range of thioesters possible with this system, carboxylic acids with either complex structures or several functional groups were chosen. Four amino acids were among the candidates, including two possessing free hydroxyl groups. Using BiT **4a**, the sole N-alkyl B*i*T in the library used in this study, the thioester derived from N-Cbz-L-serine (**10**) was obtained in 69% yield (**5a**) by the following procedure established by Mr. Matthew G. Lindale of the Liebeskind group: solid reagents (1.0 equiv each of B*i*T and acid) were placed in a dry test tube that was

then back-flushed with argon. Dry EtOAc (0.16 M) and triethylphosphite (1.0 equiv) were added, and the mixture was stirred at room temperature until TLC indicated complete consumption of the starting B*i*T. Reaction workup involved a basic wash with saturated $NaHCO_3$ solution to remove any unreacted carboxylic acid. Upon concentration of the organic layer, an oil was obtained. To purify the product, the crude product was dissolved in a minimum amount of dichloromethane and then carefully layered with hexane. After sitting undisturbed for several hours, pure thioester crystallized as a solid.

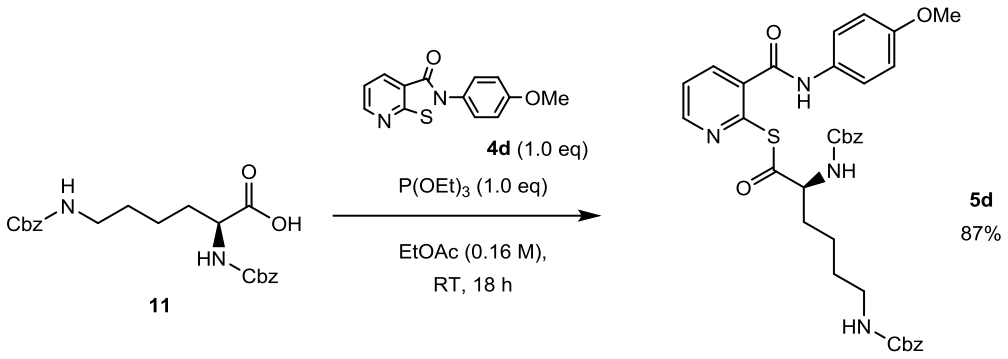
With the same B*i*T and procedure, Cbz-Lys(Cbz)-L-OH (**11**) was converted into its thioester in 76% yield (**5c**) (Scheme 15). The reactions were run at slightly elevated temperatures (50°C) and were complete in less than 5 hours. Pure product was obtained after work-up and trituration without any need for column chromatography.

Scheme 15. Synthesis of thioesters **5a** and **5c**



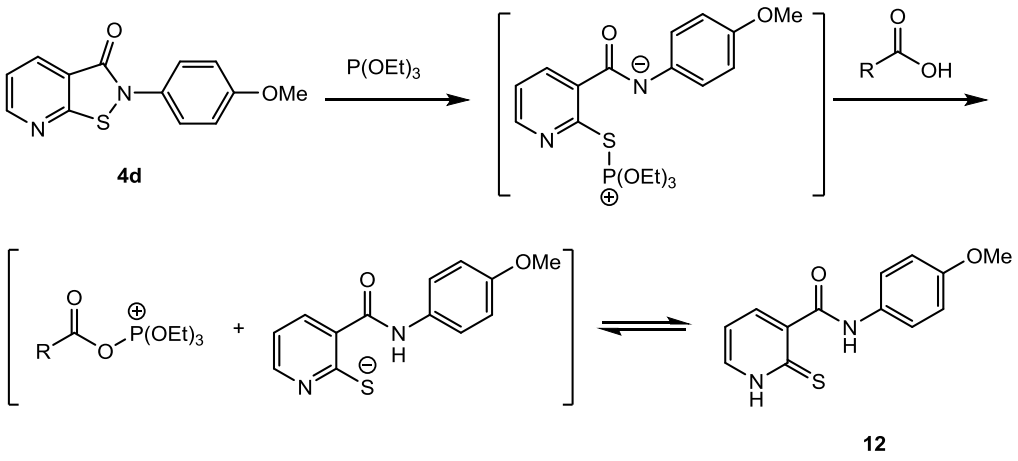
With reaction mildness being a goal, the serine and lysine thioesters were also repeated using an N-aryl B*i*T in place of the N-isopropyl B*i*T on the assumption that the more electron-deficient S—N bond would enable reactions to be carried out at room temperature. One of the first thioesters made with 2-(4-methoxyphenyl)isothiazolo[5,4-b]pyridin-3(2H)-one (**4d**) was that derived from lysine. No trouble was encountered here – after stirring the reaction overnight and a subsequent workup, the product **5d** was obtained in 87% yield (Scheme 16).

Scheme 16. Synthesis of thioester **5d**



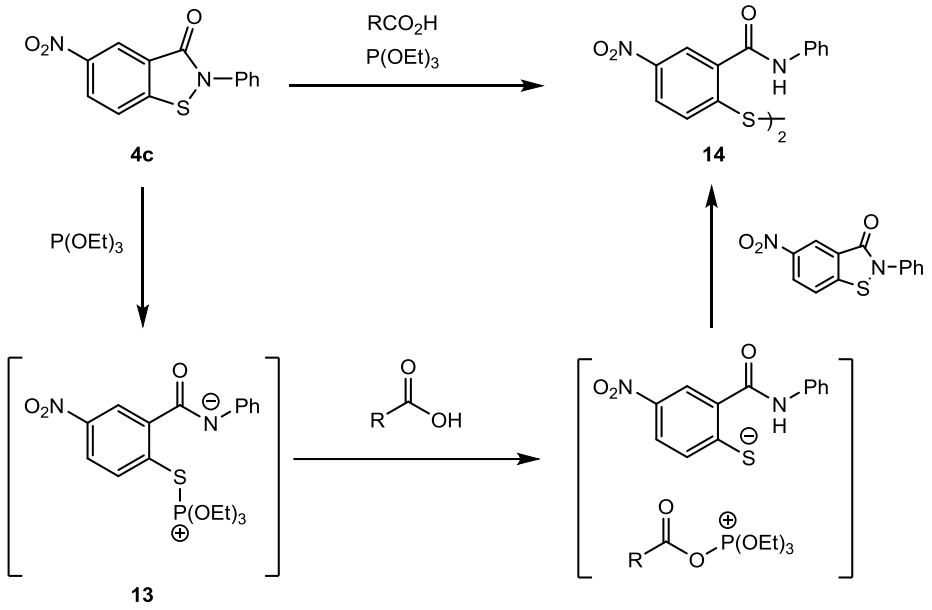
Unfortunately, preparation of the thioester derived from N-Cbz-L-serine and B*i*T **4d** proved to be more troublesome. Despite multiple attempts at its synthesis, no thioester was ever obtained with this combination of reactants. Instead, the thione (**12**) was recovered (Scheme 17), most likely in a manner similar to that observed by Mukaiyama with his self-trapping disulfides.[10] In those cases, the thiolate that is liberated after displacement from the phosphonium ion thermodynamically tautomerizes to the thione form and is then less likely to attack the acyloxyphosphonium intermediate to form thioester. The product's infrared spectrum showed signals at 1555 cm^{-1} and 1510 cm^{-1}, a result that is consistent with those of Katritzky who found that 2-thiopyridines preferentially tautomerize into the thione form by a factor of $10^{4.5}$ and exhibit IR bands at 1540 cm^{-1} and 1540 cm^{-1}.[11] No peak was seen around the 2500 cm^{-1} region which would indicate the presence of a thiol group. The thione was further confirmed via NMR and mass spectrometry data.

Scheme 17. Formation of thione **12**

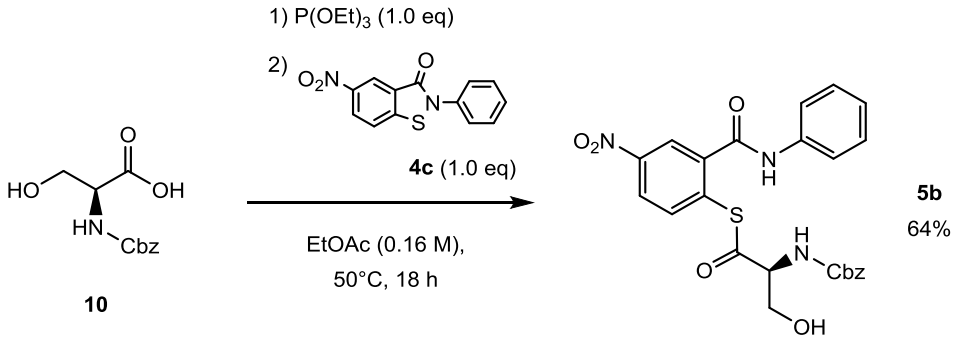


Combining the 5-NO_2 B*i*T **4c** with N-Cbz-serine proved to be slightly better. The thioester **5b** was formed in 49% yield and some disulfide formation was observed (**14**, 20% yield; See Scheme 18 for the mechanism of formation of the disulfide). The earlier success in forming N-Cbz-serine thioester **5a** suggested that the amino acid's free hydroxyl group is not problematic, thereby leading us to believe that the origin of the lower yield of thioester **5c** might reside in the structure of the B*i*T. It is likely that the N-phenyl functional group makes the S—N bond of B*i*T **4c** particularly reactive such that it rapidly intercepts the thiolate intermediate **13** shown in the lower half of Scheme 18 and facilitates the formation of disulfide **14** (which competes with thioester formation). Therefore, the reaction was redone where the B*i*T **4c** was added last, portionwise, into a solution of Cbz-L-serine and triethylphosphite to decrease the concentration of B*i*T in the solution. This time the thioester yield was 64% (Scheme 19).

Scheme 18. Mechanism for disulfide formation from **4c**

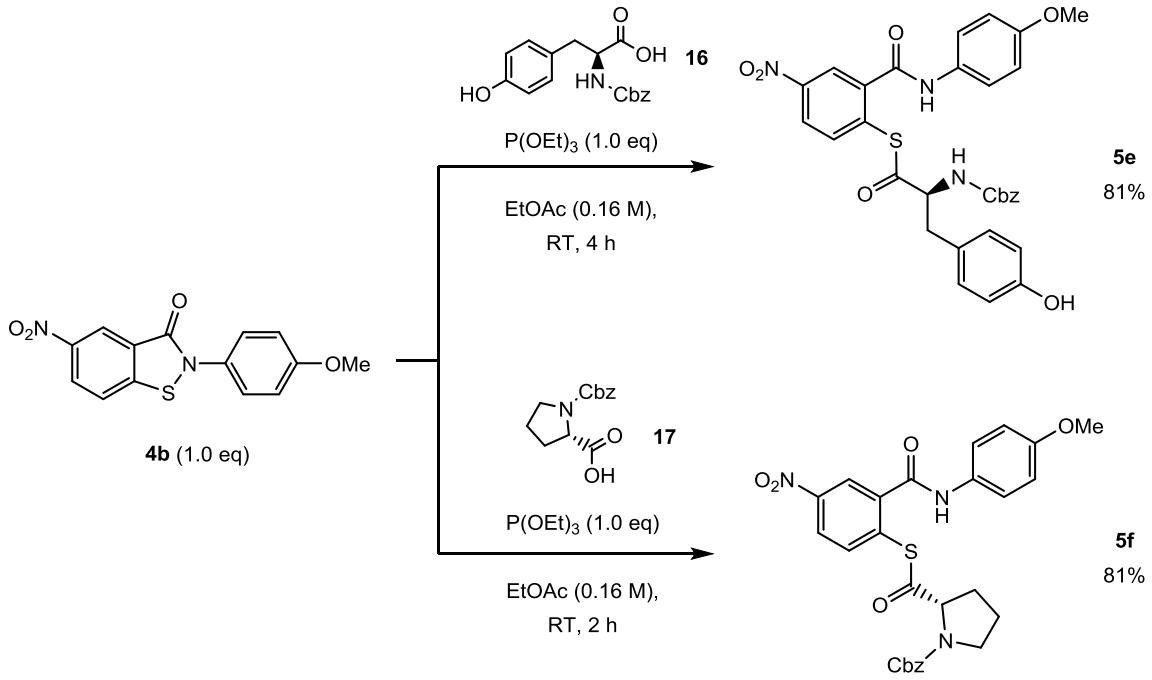


Scheme 19. Synthesis of thioester **5b**



Nevertheless, the difficulty encountered with the pyridyl-derived B*i*T's discouraged their further use. For the remaining two amino acids that were studied, we turned to the less reactive B*i*T, 2-(4-methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one (**4b**). At room temperature, Cbz-L-Tyr (**16**) and Cbz-L-Pro (**17**) both successfully produced thioesters upon reaction with triethylphosphite and **4b**, each in 81% yields within 4 hours (**5e, 5f**) (Scheme 20).

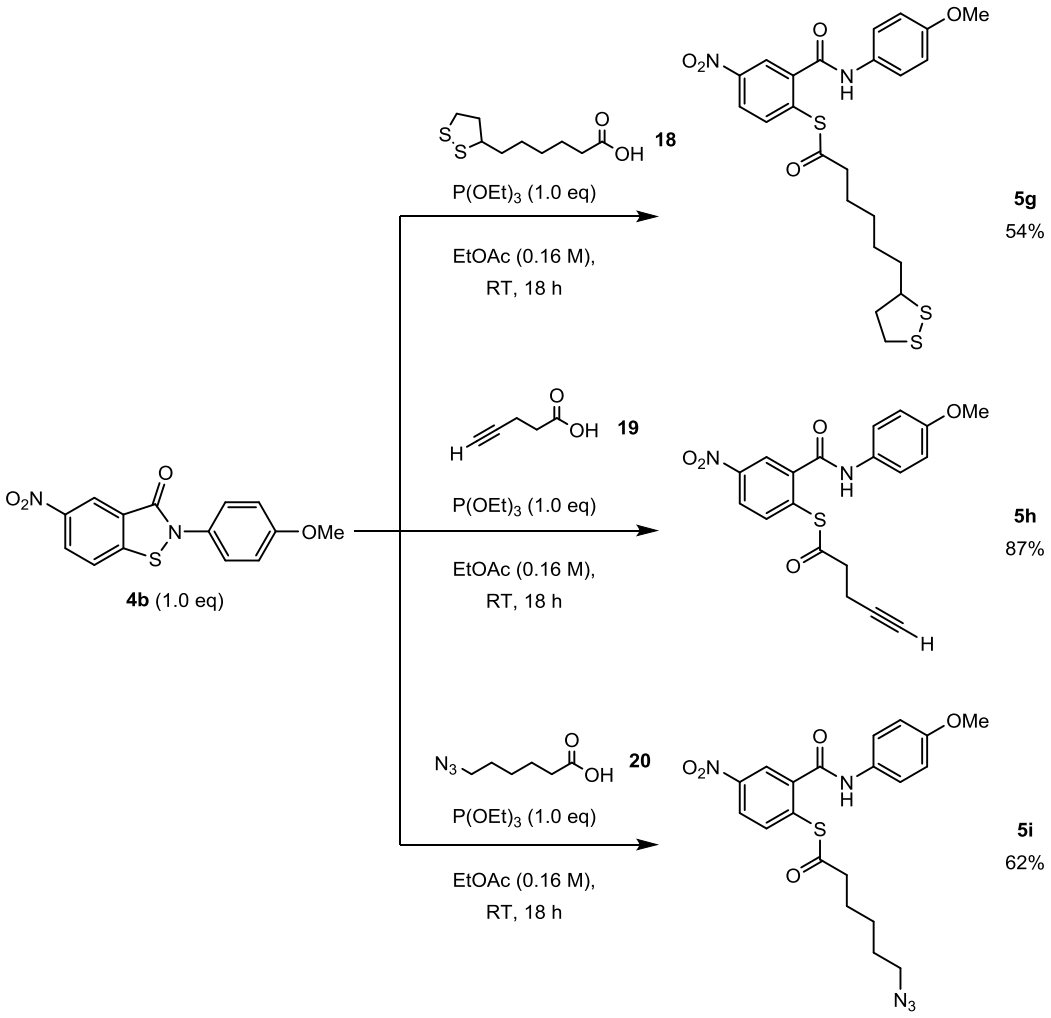
Scheme 20. Synthesis of thioesters **5e** and **5f**



Expanding the Thioester Library

With the success of the amino acids, our interest then turned to exploring in a modest fashion the scope of the reaction (Scheme 21). Lipoic acid **18** was subjected to thioester formation from B*i*T **4b**, and although the yield was low (54%), pure thioester (**5g**) was obtained. Notably, the disulfide bond of lipoic acid remained unbroken which attests to the mildness of the reaction conditions. A terminal alkyne, 4-pentynoic acid **19**, was another acid of interest and product was obtained in high yield (**5h,** 87%). Good results were also obtained using 6-azidohexanoic acid **20** (**5i**, 62%); the azide did not undergo a Staudinger reaction with the triethylphosphite, but rather survived the reaction conditions intact.

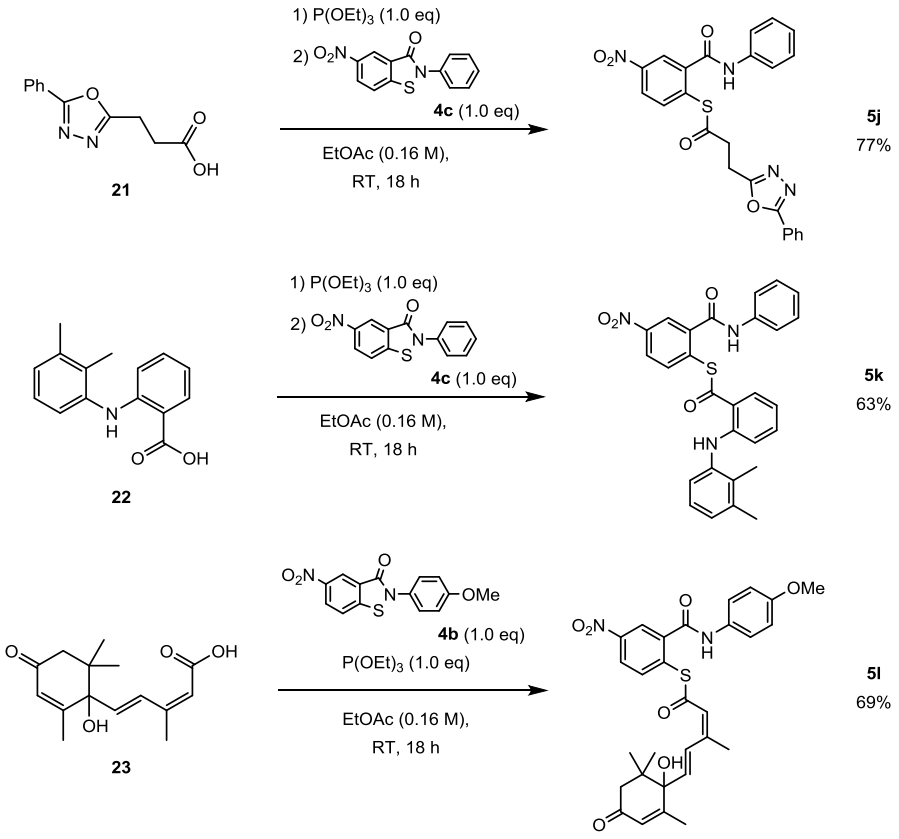
Scheme 21. Synthesis of thioesters **5g**-**5i**



Other interesting carboxylic acids explored included 3-(5-phenyl-1,3,4-oxadiazol-2-yl) propanoic acid (**21**), mefenamic acid (**22**), and abscisic acid (**23**) (Scheme 22). Acid **21** was chosen for study on account of its oxadiazole functional group - it easily formed thioester **5j** in 77% yield from B*i*T **4c**. Mefenamic acid, an anti-inflammatory drug, smoothly reacted with B*i*T **4c** to give pure thioester (**5k**) in good yield (63%) after trituration. The highly conjugated abscisic acid also met expectations and produced thioester **5l** in 69% yield from B*i*T **4b**. Once again, the formation of both thioesters **5j** and **5k**, which utilized the troublesome N-phenyl B*i*T **4c,** required that the B*i*T be added

last, portionwise, to a solution of triethylphosphite and the carboxylic acid in order to obtain acceptable thioester yields.

Scheme 22. Synthesis of thioesters **5j**-**5l**

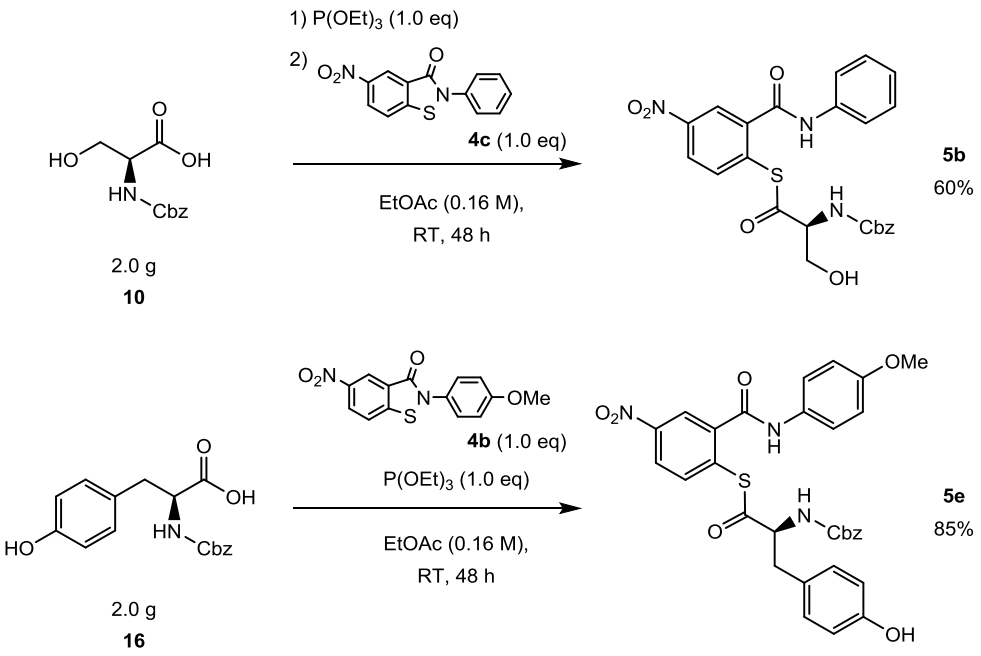


Large-Scale Thioester Synthesis

Having confirmed through various examples of carboxylic acids that the B*i*T / $P(OEt)_3$ system was indeed useful for the synthesis of thioesters, attention was next turned to testing the reaction on a larger scale. All previous attempts had been carried out using a 75 mg B*i*T scale. This time, two thioester reactions using Cbz-L-Tyr (**5e**) and Cbz-L-Ser (**5b**) were repeated on a 2.0 g scale with BiTs **4c** and **4b** respectively (Scheme 23). The reactions were monitored by TLC over several days at which point the thioester was observed precipitating out of the solution. When the B*i*T was no longer detected, the

reaction mixture was extracted with saturated $NaHCO_3$ solution and brine and triturated. Both of the N-protected amino acids gave favorable results in line with their small-scale counterparts. The large-scale tyrosine reaction gave 85% yield versus 81% in the small-scale, while the serine reaction gave 60% yield compared to the small-scale's 64%.

Scheme 23. Large-scale thioester syntheses

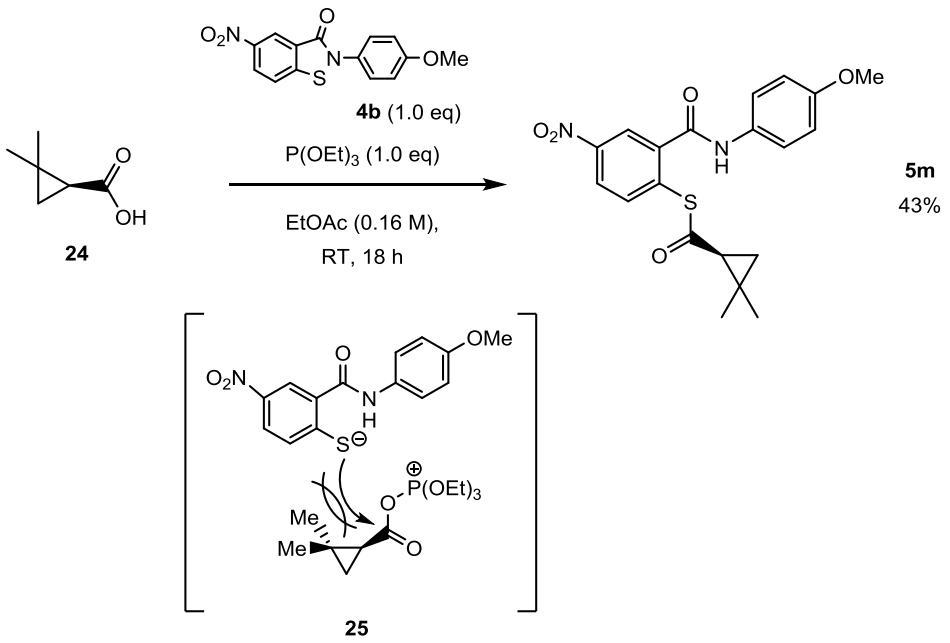


Thioester Synthesis from Sterically Hindered Carboxylic Acids

Sterically hindered acids were another source of interest for probing the scope of our thioester synthesis. Featuring a carboxylic acid group directly adjacent to geminal methyl groups in a three-membered ring, (S)-(+)-2,2-dimethylcyclopropane carboxylic acid (**24** in Scheme 24) was one such example. This was paired with the N-*p*-C_6H_4OMe B*i*T (**4b**) that had thus far given good results (Scheme 24). Unsurprisingly, the yield of thioester was lower than usual (**5m**, 43%), probably due to the methyl groups hindering the thiolate from easily approaching the acyl phosphorous intermediate (see intermediate

25 in Scheme 24). An increase in the reaction concentration from 0.16 M to 0.30 M did not significantly affect the yield (38%).

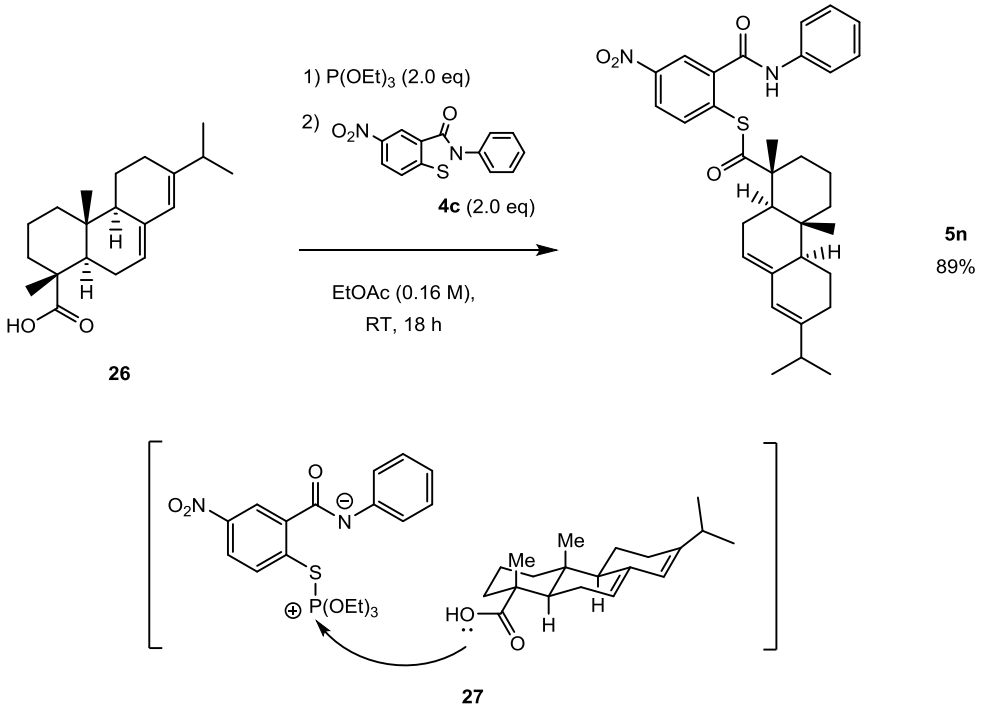
Scheme 24. Synthesis of thioester **5m**



Formation of the thioester derived from abietic acid **26** and B*i*T **4c** was also troublesome. The acid features a large, tri-cyclic structure with two axial methyl groups near the carbonyl group and gave a low 30% yield of thioester (**5n**). It was hypothesized that the methyl groups made it difficult for the carboxylate group to approach the phosphonium complex, particularly with the B*i*T's N-aryl group positioned directly above (see structure **27** in Scheme 25). Following the lesson learned from the serine thioester derived from the same B*i*T, we experimented with adding the B*i*T last, portionwise. Unfortunately, the yield was unchanged (32%). Increasing the equivalents of both B*i*T and $P(OEt)_3$ from 1.0 equiv to 1.5 equiv also showed little improvement in the yield of thioester (36%). However, upon combining both methods (increasing reagent

equivalence to 1.5 and addition of the B*i*T last), a modest increase in yield of the thioester was observed (52%). Further increasing the B*i*T and triethylphosphite to 2.0 equiv produced the thioester in 89% yield.

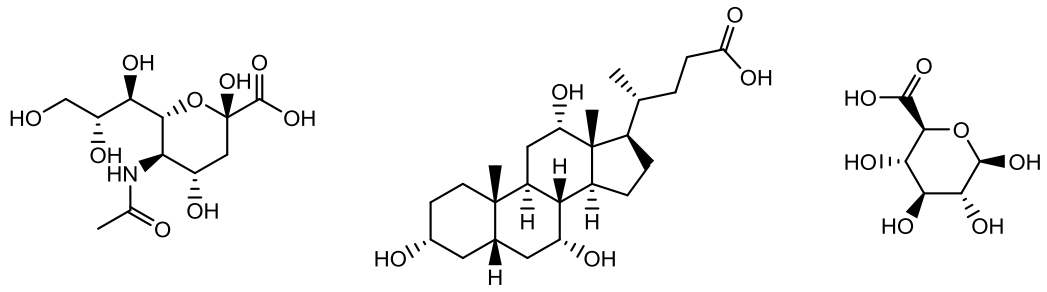
Scheme 25. Synthesis of thioester **5n**



Unsuccessful Thioesters

Among the carboxylic acids studied, a few never successfully gave thioester. Sialic acid (**28**), cholic acid (**29**), and glucuronic acid (**30**) were three that failed to yield the desired product (Figure 2). All possess multiple hydroxyl groups and are most soluble in water or in the case of glucuronic acid, acetic acid. Thus, the failure of reaction might be due to the low solubility of the acids in the reaction solvents used. Although the thioester reactions were attempted in both EtOAc and DMF, it was observed that the carboxylic acids never fully dissolved.

Figure 2. Unsuccessful carboxylic acids



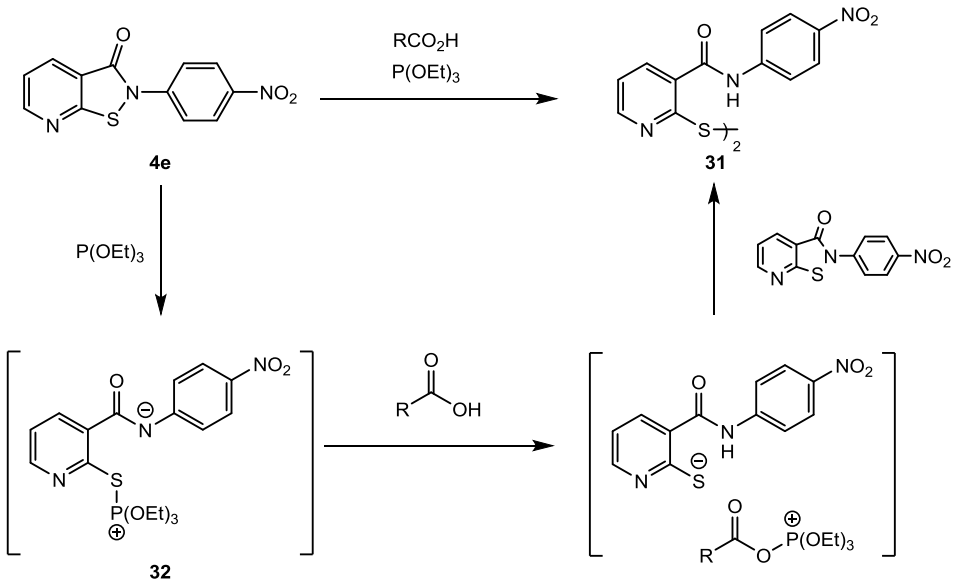
28 **29** **30**

An Unsuccessful Benzoisothiazolone

Failures in generating thioesters were encountered not only with some of the carboxylic acids explored, but also with one of the B*i*T's chosen for study. 2-(4-Nitrophenyl)isothiazolo[5,4-b]pyridin-3(2H)-one (**4e** – see Scheme 26 for structure) never produced any thioester, no matter which carboxylic acid it was paired with. Initially, exploratory reactions with B*i*T **4e** were attempted in EtOAc, but when the B*i*T failed to dissolve, the solvent was switched to DMF. In DMF, the B*i*T dissolved into a clear yellow solution within half an hour upon addition of $P(OEt)_3$. However, when the two reagents were mixed in the presence of the amino acid Cbz-Lys(Cbz)-L-OH (**11**) (which worked well with both an N-alkyl B*i*T (**4a**) as well as a 2-pyridyl B*i*T (**4d**)), no thioester was generated. Instead, the disulfide (**31**) derived from B*i*T **4e** was produced in 55% yield (confirmed with mass spectrometry). When the B*i*T failed to produce thioester even with an acid as simple as *p*-toluic acid, it was eventually concluded that the electron-withdrawing capabilities of the N-p-NO_2Ph group caused the S—N bond of the B*i*T to become so reactive that disulfide was formed before the carboxylic acid had a chance to add into the acyl phosphonium ion (**32**, Scheme 26), much in the same manner

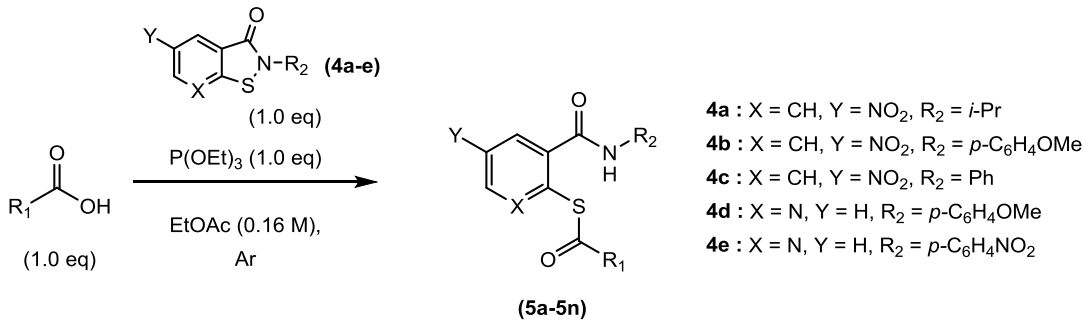
as shown in Scheme 18 with the N-phenyl B*i*T **4c**. Thus, this B*i*T was set aside. Should further studies be done with this B*i*T, lower temperatures may be one variable to explore to slow the rate of the undesired reaction.

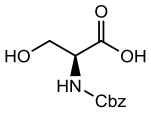
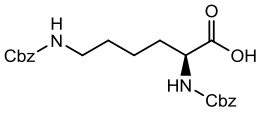
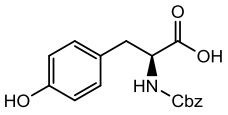
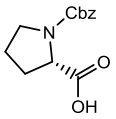
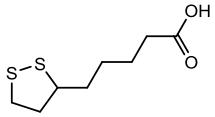
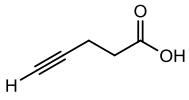
Scheme 26. Formation of disulfide from **4e**



Troubles aside, a total of fourteen different thioesters were successfully synthesized using the B*i*T / $P(OEt)_3$ system (Table 1).

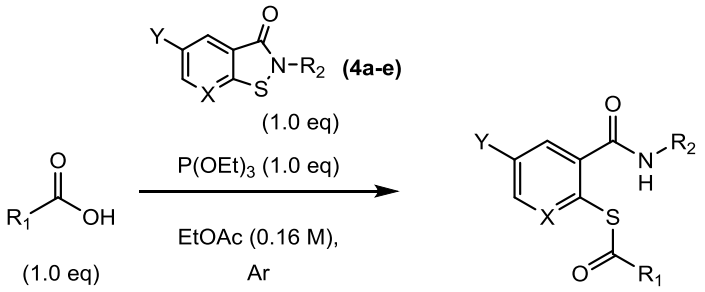
Table 1. Thioester synthesis with benzoisothiazolone and triethylphosphite



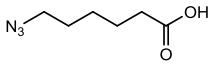
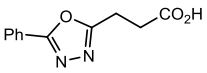
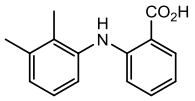
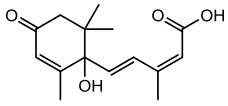
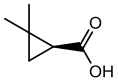
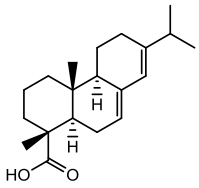
Entry	Carboxylic Acid	BiT	Temperature (°C)	Time (h)	Yield
5a		**4a**	50°C	3	69%
5b*		**4c**	RT	18	64%
5c		**4a**	50°C	5	76%
5d		**4d**	RT	18	87%
5e		**4b**	RT	4	81%
5f		**4b**	RT	2	81%
5g		**4b**	RT	1.3	54%
5h		**4b**	RT	18	87%

** BiT added last portionwise to solution of carboxylic acid and $P(OEt)_3$*

Table 1 (cont). Thioester synthesis with benzoisothiazolone and triethylphosphite



4a : X = CH, Y = NO_2, R_2 = *i*-Pr
4b : X = CH, Y = NO_2, R_2 = *p*-C_6H_4OMe
4c : X = CH, Y = NO_2, R_2 = Ph
4d : X = N, Y = H, R_2 = *p*-C_6H_4OMe
4e : X = N, Y = H, R_2 = *p*-$C_6H_4NO_2$

Entry	Carboxylic Acid	B*i*T	Temperature (°C)	Time (h)	Yield
5i		**4b**	RT	18	62%
5j*		**4c**	RT	18	77%
5k*		**4c**	RT	18	63%
5l		**4b**	RT	18	69%
5m		**4b**	RT	18	43%
5n**		**4c**	RT	18	89%

** BiT added last portionwise to solution of carboxylic acid and $P(OEt)_3$ ** 2.0 eq of BiT and $P(OEt)_3$ used, BiT added last portionwise to solution of carboxylic acid and $P(OEt)_3$*

Conclusion

A series of structurally diverse thioesters were synthesized through a redox dehydration reaction with carboxylic acids using a benzoisothiazolone / $P(OEt)_3$ system. In a typical reaction, product yield was moderately high and no purification other than a basic wash and trituration were necessary to produce pure product, thereby demonstrating an improvement over the past triorganophosphine-based systems. Future work will delve into expanding the library of B*i*Ts and optimizing the reaction conditions towards a catalytic system for the formation of amides, peptides, ketones, and esters.

Experimental

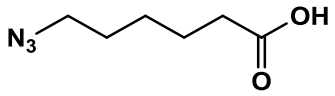
General Methods

^{1}H and ^{13}C NMR were recorded on Inova 400, VNMR 400, or Inova 600 spectrometers relative to tetramethylsilane in deuterated chloroform ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm), deuterated DMSO (DMSO-d_6: ^{1}H = 2.50 ppm, ^{13}C = 39.52 ppm), deuterated acetone (acetone-d_6: : ^{1}H = 2.05 ppm, ^{13}C = 29.84, 206.26 ppm), or deuterated trifluoroacetic acid (CF_3CO_2D: ^{1}H = 11.50 ppm, ^{13}C = 116.60, 164.20 ppm) as noted. Spectral data are reported in the following order: chemical shift (δ); multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), sept (septet), m (multiplet); coupling constants, J (Hz); integration. Infrared spectra were recorded on a Nicolet 510 FT-IR spectrometer. Uncalibrated melting points were taken on a *Thomas-Hoover* melting point apparatus in open capillary tubes. ESI or APCI high resolution mass spectrometry was carried out on new compounds. Solvents for reactions and chromatography were reagent grade and used as received. Where indicated, dry solvents were obtained via drying with 4 Å molecular sieves overnight. Reactions requiring inert atmospheres were carried out in flame-dried glassware under argon. Brine refers to a saturated solution of NaCl.

Reagents sodium azide, $SOCl_2$, triethylamine, *t*-butylthiol, sodium hydroxide, potassium hydroxide, and 77% *m*-CPBA were purchased from Sigma-Aldrich. Starting materials mefenamic acid, N-Cbz-L-tyrosine, (S)-(+)-2,2-dimethylcyclopropane carboxylic acid, N-Cbz-L-serine, N-Cbz-L-proline, 6-bromo-hexanoic acid, 2-chloronicotinic acid, *p*-nitroaniline, isopropylamine, 2-chloro-5-nitrobenzoic acid, aniline,

p-anisidine. 4-pentynoic acid, abietic acid, Cbz-L-Lys(Cbz)-OH, (±)-abscisic acid, 3-(5-phenyl-1,3,4-oxadiazol-2-yl)propanoic acid, and lipoic acid were purchased from TCI Chemicals, Alfa Aesar, Santa-Cruz Biotechnology, Inc., or Sigma-Aldrich.

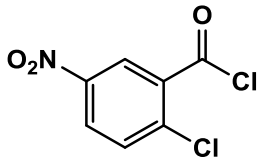
Experimental Procedure



6-Azidohexanoic acid.[25]

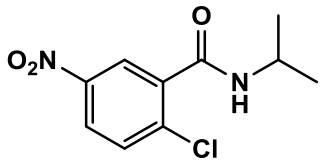
A solution of 6-bromo-hexanoic acid (1.4 g, 7.2 mmol) and sodium azide (0.9 g, 14.4 mmol) in 2.4 mL dry DMF was heated in an oil bath set at 85 °C for 4 hours under Ar. The solution was quenched with 0.1 M aqueous HCl (4 mL), unreacted azide filtered off, and the filtrate extracted twice with dichloromethane (4 mL each). The combined dichloromethane layers were then washed twice with water (10 mL each), dried with anhydrous $MgSO_4$, and concentrated to give a tan-colored oil (0.54 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 (t, *J*=6.8 Hz, 2 H) 2.37 (t, *J*=7.4 Hz, 2 H) 1.56 - 1.72 (m, 4 H) 1.38 - 1.48 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 51.2, 33.8, 28.5, 26.1, 24.1. IR (neat, cm^{-1}): 2938, 2090, 1703.

5-Nitro Benzoisothiazolones:



2-Chloro-5-nitrobenzoyl chloride.[23] **(1)**

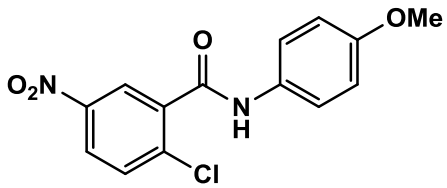
In a dry flask, 32.5 g (161 mmol) of 2-chloro-5-nitro benzoic acid in 100 mL of $SOCl_2$ was heated to reflux overnight under Ar. After cooling and concentrating, hexane (30 mL) was added and the mixture was allowed to stand at room temperature for 2 hours. The resulting precipitate was filtered and washed with hexanes to give 34.7 g (99%) of the acid chloride as pale yellow crystals, mp 59-60 °C (lit. 56-58 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.91 (d, *J* = 2.6 Hz, 1H), 8.38 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8, 146.3, 140.2, 134.1, 132.9, 128.5, 128.0. IR (neat, cm^{-1}): 1780.



2-Chloro-N-isopropyl-5-nitrobenzamide.[23] **(2a)**

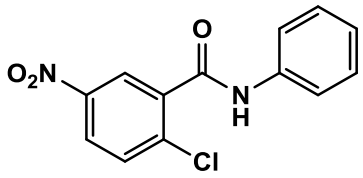
To isopropylamine (0.78 mL, 9.5 mmol) in 8.0 mL of dry pyridine was added 2-chloro-5-nitrobenzoyl chloride **1** (1.6 g, 7.3 mmol) at 0 °C portionwise. After stirring at room temperature for 6 hours open to air, 16 mL of ice-cold water was added and the resulting precipitate was filtered and washed three times with cold 10% aqueous AcOH. Pure benzamide was obtained as an orange-colored solid (1.6 g, 90%), mp 183-184°C (lit. 186-186.5 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, *J* = 2.7 Hz, 1H), 8.19 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 5.97 (s, 1H), 4.31 (sept, *J* = 6.4 Hz, 1H), 1.30 (d, *J*

= 6.6 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.5, 146.7, 137.6, 137.0, 131.5, 125.6, 125.2, 42.8, 22.7. IR (neat, cm^{-1}): 3267, 2972, 1648.



2-Chloro-N-(4-methoxyphenyl)-5-nitrobenzamide.[26] **(2b)**

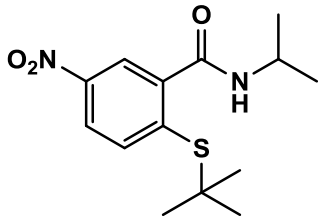
To *p*-anisidine (9.0 mL, 76 mmol) and triethylamine (13.0 mL, 93 mmol) in 100 mL of dichloromethane was added 2-chloro-5-nitrobenzoyl chloride **1** (17 g, 76 mmol) at 0 °C portionwise. After stirring at room temperature overnight open to air, the mixture was diluted with water (100 mL), extracted with EtOAc, dried with anhydrous $MgSO_4$, and concentrated to give 22.4 g (94%) of pure benzamide as white flakes, mp 155-157 °C (lit. 151-153°C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.7 Hz, 1H), 8.24 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.82 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2, 157.4, 146.7, 137.7, 136.8, 131.7, 130.0, 126.0, 125.5, 122.4, 114.5, 55.7. IR (neat, cm^{-1}): 3258, 1657.



2-Chloro-5-nitro-N-phenylbenzamide.[23] **(2c)**

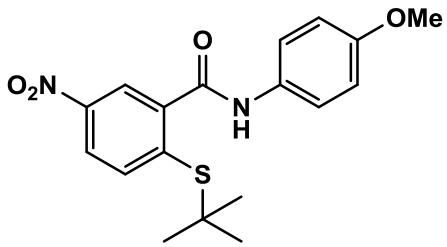
To aniline (7.2 mL, 79 mmol) and triethylamine (13.3 mL, 95 mmol) in 100 mL of dichloromethane was added 2-chloro-5-nitrobenzoyl chloride **1** (17.4 g, 79 mmol) at 0 °C portionwise. After stirring at room temperature overnight open to air, the mixture was filtered and the collected precipitate washed with water. After recrystallization with

EtOAc, pure benzamide was obtained in the form of cream-colored crystals (19.5 g, 93%), mp 156-157 °C (lit. 158.5-159 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.7 Hz, 1H), 8.26 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.86 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.3, 146.8, 137.7, 137.0, 136.6, 131.7, 129.4, 126.1, 125.7, 125.5, 120.5. IR (neat, cm^{-1}): 3268, 1660.



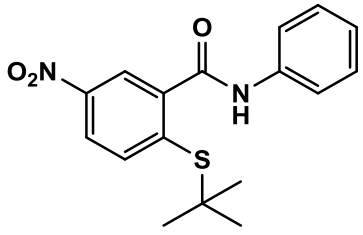
2-(Tert-butylthio)-N-isopropyl-5-nitrobenzamide.[23] **(3a)**

To *t*-butyl thiol (0.89 mL, 7.9 mmol) and NaOH (0.29 g, 7.3 mmol) in 10 mL of DMF was added 2-chloro-N-isopropyl-5-nitrobenzamide **2a** (1.60 g, 6.6 mmol) portionwise at 0 °C. After stirring at room temperature for 4 hours open to air, an extra 0.2 equiv of *t*-butyl thiol was added and the mixture stirred for an additional 0.5 hour. Cold 10% aqueous AcOH (30 mL) was slowly added and the resulting precipitate filtered and washed with water to give 1.7 g (85%) of pure thioether as an orange solid, mp 150-152 °C (lit. 151-151.5 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.34 (s, 1H), 4.29 (sept, *J* = 7.6 Hz, 1H), 1.33 (s, 9H), 1.30 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 148.2, 142.5, 139.8, 137.8, 125.4, 123.9, 50.3, 42.7, 31.2, 22.7. IR (neat, cm^{-1}): 3272, 2976, 1633.



2-(Tert-butylthio)-N-(4-methoxyphenyl)-5-nitrobenzamide. (3b)

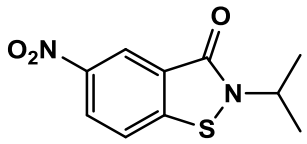
To *t*-butyl thiol (9.5 mL, 84 mmol) and NaOH (3.1 g, 77 mmol) in 250 mL of DMF was added 2-chloro-N-(4-methoxyphenyl)-5-nitrobenzamide **2b** (21.4 g, 70 mmol) portionwise at 0 °C. After stirring at room temperature for 3 hours open to air, an extra 0.5 equiv of *t*-butyl thiol was added and the mixture stirred for an additional 0.5 hour. Cold 10% aqueous AcOH (600 mL) was slowly added and the resulting precipitate filtered and washed with water to give 24.1 g (96%) of pure thioether as a yellow solid, mp 139-140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.96 (s, 1H), 8.23 (td, *J* = 8.7, 2.2 Hz, 1H), 7.82 – 7.77 (m, 1H), 7.59 (t, *J* = 8.6 Hz, 2H), 6.93 (t, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 156.9, 148.54, 141.8, 140.6, 137.3, 130.7, 126.2, 124.4, 121.9, 114.5, 55.6, 50.9, 31.1. IR (neat, cm^{-1}): 3233, 1655. HRMS (ESI) Calcd for $C_{18}H_{21}N_2O_4S$ ($M+H^+$): 361.1222. Found: 361.1218.



2-(Tert-butylthio)-5-nitro-N-phenylbenzamide.[23] (3c)

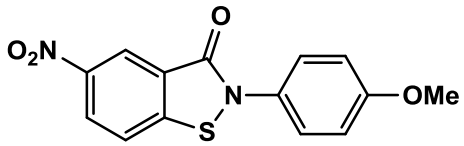
To *t*-butyl thiol (9.6 mL, 85 mmol) and NaOH (3.1 g, 77 mmol) in 250 mL of DMF was added 2-chloro-5-nitro-N-phenylbenzamide **2c** (19.5 g, 71 mmol) portionwise at 0 °C. After stirring at room temperature for 3 hours open to air, an extra 0.5 equiv of *t*-butyl

thiol was added and the mixture stirred for an additional 0.5 hour. Cold 10% aqueous AcOH (600 mL) was slowly added and the resulting precipitate filtered and washed with water to give 22.6 g (95%) of pure thioether in the form of an orange solid, mp 142-143 °C (lit. 142-145 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.99 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1, 148.6, 141.6, 140.7, 137.6, 137.3, 129.4, 126.3, 125.1, 124.6, 120.3, 51.0, 31.0. IR (neat, cm^{-1}): 3235, 1655.



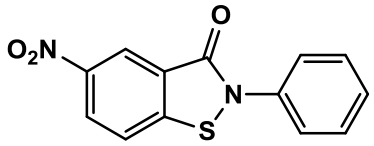
2-isopropyl-5-nitrobenzo[d]isothiazol-3(2H)-one.[23] **(4a)**

To 2-(tert-butylthio)-N-isopropyl-5-nitrobenzamide **3a** (2.0 g, 6.6 mmol) and dry DMSO (1.3 mL, 10.0 mmol) in dry dichloromethane (20 mL) was added TMSCl (1.1 mL, 8.7 mmol). After stirring at room temperature under Ar overnight, hexane (30 mL) was added and the resulting precipitate filtered and washed with hexane. The crude product was recrystallized with EtOH to give 1.35 g (85%) of the benzoisothiazolone as yellow crystals, mp 169-170 °C (lit. 164-165 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.86 (d, *J*=3.5 Hz, 1 H), 8.43 (dt, *J*=8.8, 2.2 Hz, 1 H), 7.72 (d, *J*=8.8 Hz, 1 H), 4.99 (sept, *J*=6.6 Hz, 1 H), 1.44 (d, *J*=6.6 Hz, 6 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.6, 146.3, 146.1, 126.2, 126.0, 122.6, 121.5, 46.9, 22.3. IR (neat, cm^{-1}): 1647.



2-(4-Methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one. (4b)

To 2-(tert-butylthio)-N-(4-methoxyphenyl)-5-nitrobenzamide **3b** (23.7 g, 66 mmol) and dry DMSO (7.0 mL, 99 mmol) in dry dichloromethane (160 mL) was added TMSCl (16.7 mL, 132 mmol). After stirring at room temperature under Ar overnight, the resulting yellow precipitate was filtered and washed with diethyl ether. The crude product was recrystallized with DMF to give 18.1 g (91%) of the benzoisothiazolone as bright yellow crystals, mp 236-238 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.57 (d, J = 2.3 Hz, 1H), 8.53 (dd, J = 8.9, 2.3 Hz, 1H), 8.32 (d, J = 8.9 Hz, 1H), 7.57 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 162.2, 158.6, 146.9, 145.8, 128.8, 127.0, 126.3, 124.9, 123.8, 121.2, 114.7, 55.5. IR (neat, cm^{-1}): 1665. HRMS (ESI) Calcd for $C_{14}H_{11}N_2O_4S$ ($M+H^+$): 303.0440. Found: 303.0436.

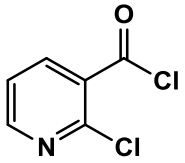


5-Nitro-2-phenylbenzo[d]isothiazol-3(2H)-one.[27] **(4c)**

To 2-(tert-butylthio)-5-nitro-N-phenyl-benzamide **3c** (21.7 g, 66 mmol) and dry DMSO (7.0 mL, 99 mmol) in dry dichloromethane (130 mL) was added TMSCl (16.7 mL, 132 mmol). After stirring at room temperature under Ar overnight, the resulting precipitate was filtered and washed with diethyl ether. The crude product was recrystallized with DMF to give 15.6 g (87%) of the benzoisothiazolone as dark yellow crystals, mp 229-230 °C (lit. 221-223 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.56 (d, J = 2.1 Hz, 1H), 8.52

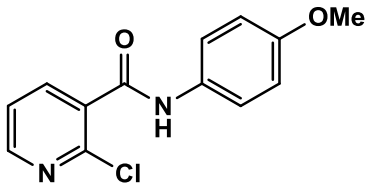
(dd, *J* = 8.9, 2.0 Hz, 1H), 8.33 (d, *J* = 8.9 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 162.1, 146.8, 145.8, 136.5, 129.6, 127.6, 126.5, 125.1, 124.7, 123.9, 121.3. IR (neat, cm^{-1}): 1645.

2-Pyridyl Benzoisothiazolones:



2-Chloronicotinoyl chloride.[28] **(6)**

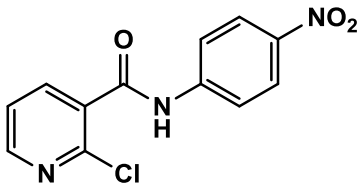
A solution of 2-chloronicotinic acid (3.0 g, 19 mmol) in 70 mL of $SOCl_2$ was heated to reflux for 3 hours under Ar. After concentration, the crude oil was layered with hexane and allowed to sit at room temperature for 4 hrs to crystallize. Pale peach-colored crystals were obtained (2.6 g, 78%), mp 40-41 °C (lit. 39-42 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.53 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.21 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.51 (dd, *J* = 7.6, 4.8 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.9, 151.8, 147.9, 140.2, 128.2, 123.2. IR (neat, cm^{-1}): 1703.



2-Chloro-N-(4-methoxyphenyl)nicotinamide. (7a)

A solution of 2-chloronicotinoyl chloride **6** (1.0 g, 5.7 mmol), *p*-anisidine (0.70 g, 5.7 mmol), and triethylamine (1.6 mL, 11 mmol) in 40 mL of dry THF was stirred at room temperature under Ar overnight. Ethyl acetate was added and the mixture extracted twice

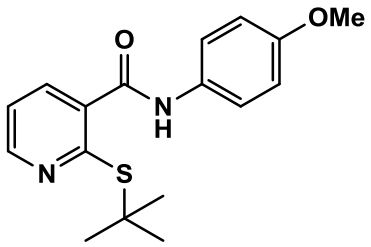
with a saturated $NaHCO_3$ solution, once with water and brine, dried with $MgSO_4$, and finally concentrated to give a purple-grey solid. The crude product was recrystallized using a mix of EtOAc and hexane to give 1.1 g of the amide as purple-grey needles (76%), mp 130-132 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.52 (dd, J = 4.8, 1.8 Hz, 1H), 8.06 (dd, J = 7.5, 1.8 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.55 (dd, J = 7.5, 4.8 Hz, 1H), 6.94 (d, J = 8.9 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.1, 155.8, 150.4, 146.5, 138.2, 133.3, 131.8, 123.2, 121.1, 114.0, 55.2. IR (neat, cm^{-1}) 3236, 1658. HRMS (ESI) Calcd for $C_{13}H_{12}ClN_2O_2$ ($M+H^+$): 263.0587. Found: 263.0584.



2-Chloro-N-(4-nitrophenyl)nicotinamide. (7b)

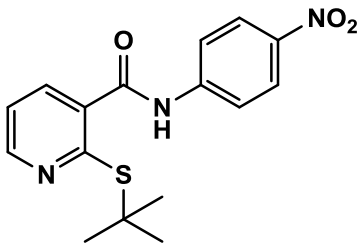
A solution of 2-chloronicotinoyl chloride **6** (2.6 g, 15 mmol), *p*-nitroaniline (2.1 g, 15 mmol), and triethylamine (4.1 mL, 30 mmol) in 70 mL of dry THF was stirred at room temperature under Ar overnight. Ethyl acetate was added and the mixture extracted twice with a saturated $NaHCO_3$ solution, once with water and brine, dried with $MgSO_4$, and finally concentrated to give a yellow solid. Ten milliliters of EtOAc were added and the undissolved solids filtered off and washed with hexane. The crude solid was then recrystallized using a mixture of EtOAc and hexane to give 2.1 g of the amide as bright yellow crystals (66%), mp 208-209 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (dd, J = 4.8, 1.9 Hz, 1H), 8.29 (d, J = 9.2 Hz, 2H), 8.16 (dd, J = 7.5, 1.9 Hz, 1H), 7.95 (d, J = 9.1 Hz, 2H), 7.60 (dd, J = 7.5, 4.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.3, 151.0,

146.4, 144.7, 142.9, 138.4, 132.5, 125.1, 123.3, 119.5. IR (neat, cm^{-1}): 3029, 1687. HRMS (ESI) Calcd for $C_{12}H_9ClN_3O_3$ ($M+H^+$): 278.0332. Found: 278.0331.



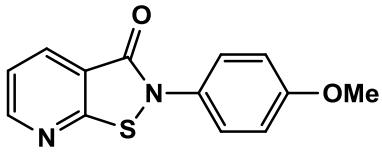
2-(Tert-butylthio)-N-(4-methoxyphenyl)nicotinamide. (8a)

Potassium hydroxide (0.14 g, 2.5 mmol) and *t*-butylthiol (0.31 mL, 2.7 mmol) were dissolved in 5 mL of DMF and cooled to 0 °C. 2-Chloro-N-(4-methoxyphenyl)-nicotinamide **7a** (0.6 g, 2.3 mmol) was then added portionwise and the solution stirred at room temperature open to air overnight. Cold 10% aqueous AcOH (30 mL) was added and the resulting precipitate filtered off and washed with cold water. The crude product was then recrystallized using a mixture of EtOAc and hexane to give 0.50 g (69%) of the thioether as purple-grey needles, mp 164-165 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.61 – 8.53 (m, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.24 (dd, *J* = 7.4, 4.9 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.6, 156.9, 155.6, 149.3, 135.1, 133.5, 132.2, 121.0, 119.4, 113.9, 55.2, 47.5, 30.5. IR (neat, cm^{-1}) 3325, 1657. HRMS (ESI) Calcd for $C_{17}H_{21}N_2O_2S$ ($M+Na^+$): 339.1143. Found: 339.1138.



2-(Tert-butylthio)-N-(4-nitrophenyl)nicotinamide. (8b)

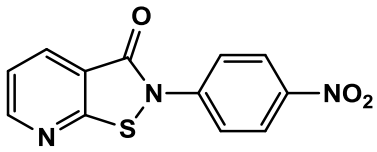
Sodium hydroxide (0.33 g, 8.3 mmol) and *t*-butylthiol (1.0 mL, 9.1 mmol) were dissolved in 12 mL of DMF and cooled to 0 °C. 2-Chloro-N-(4-nitrophenyl)nicotinamide **7b** (2.1 g, 7.6 mmol) was then added portionwise and the solution stirred at room temperature open to air overnight. Cold 10% aqueous AcOH (25 mL) was added and the resulting precipitate filtered off and washed with cold water. The crude product was then recrystallized using a mixture of EtOAc and hexane to give 2.3 g (93%) of the thioether as pale yellow crystals, mp 288-290°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.66 (d, *J* = 4.7 Hz, 1H), 8.28 (d, *J* = 9.0 Hz, 3H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.31 – 7.27 (m, 1H), 1.57 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.8, 156.8, 150.0, 145.1, 142.7, 135.5, 132.7, 125.0, 119.5, 119.4, 47.9, 30.5. IR (neat, cm^{-1}): 3260, 2960, 1664. HRMS (ESI) Calcd for $C_{16}H_{18}N_3O_3S$ ($M+H^+$): 332.1069. Found: 332.1062.



2-(4-Methoxyphenyl)isothiazolo[5,4-b]pyridin-3(2H)-one. (4d)

2-(Tert-butylthio)-N-(4-methoxyphenyl)nicotinamide **8a** (75 mg, 0.24 mmol) was dissolved in 5 mL of dry DCM and cooled to 0 °C. Forty five miligrams (0.26 mmol) of 77% *m*-CPBA was then added portionwise and the reaction stirred under Ar at 0 °C and monitored with TLC. Upon complete consumption of the starting thioether, the solution

was washed with a saturated solution of $NaHCO_3$ as well as brine, dried with $MgSO_4$, and concentrated to give a white solid. Without any further purification, the crude sulfoxide was refluxed in a mixture of dry toluene (0.3 M) and pyridine (0.8 M) for 1 hour under Ar. The solution was then washed with 10% aqueous AcOH, extracted with EtOAc and water, dried with $MgSO_4$, and concentrated to give a white solid. The solid was recrystallized using a mixture of EtOAc and hexane to give pure benzoisothiazolone as white needles (31 mg, 51%), mp 165-166 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.91 (dd, J = 4.7, 1.7 Hz, 1H), 8.37 (dd, J = 7.9, 1.7 Hz, 1H), 7.63 – 7.52 (m, 3H), 7.08 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.9, 161.0, 158.6, 154.5, 135.2, 128.7, 127.2, 121.8, 118.8, 114.7, 55.5. IR (neat, cm^{-1}) 1660. HRMS (ESI) Calcd for $C_{13}H_{11}N_2O_2S$ ($M+H^+$): 259.0541. Found: 259.0535.



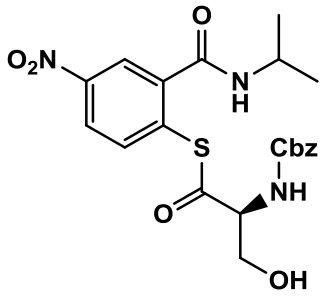
2-(4-Nitrophenyl)isothiazolo[5,4-b]pyridin-3(2H)-one. (4e)

2-(Tert-butylthio)-N-(4-nitrophenyl) nicotinamide **8b** (65 mg, 0.20 mmol) was dissolved in 8 mL of dry DCM and cooled to 0 °C. Forty eight miligrams (0.22 mmol) of 77% *m*-CPBA was then added portionwise and the reaction stirred under Ar at 0 °C and monitored with TLC. Upon complete consumption of the starting thioether, the solution was washed with a saturated solution of $NaHCO_3$ as well as brine, dried with $MgSO_4$, and concentrated to give a pale yellow solid. Without any further purification, the crude sulfoxide was refluxed in a mixture of dry toluene (0.3 M) and pyridine (0.8 M) for 1 hour under Ar, whereupon a yellow solid precipitated out of the solution. The solid was filtered off and washed with EtOAc to give pure benzoisothiazolone (50 mg, 93%), mp

300-302 °C. ^{1}H NMR (600 MHz, CF_3CO_2D) δ 9.21 – 9.04 (m, 2H), 8.37 (d, *J* = 9.0 Hz, 2H), 8.07 – 7.96 (m, 1H), 7.83 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (151 MHz, CF_3CO_2D) δ 163.4, 157.3, 149.7, 149.6, 147.8, 141.9, 128.5, 127.7, 126.9, 126.0. IR (neat, cm^{-1}) 1684. HRMS (APCI) Calcd for $C_{12}H_8N_3O_3S$ ($M+H^+$): 274.0286. Found: 274.0288.

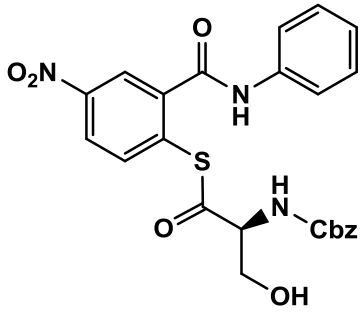
General procedure for thioesters:

In a procedure developed by Mr. Matthew G. Lindale of the Liebeskind laboratory, to a dry test tube was added benzoisothiazolone (1.0 equiv) and the carboxylic acid (1.0 equiv). After backflushing the text tube three times with Ar, dry EtOAc (0.16 M) and $P(OEt)_3$ (1.0 equiv) were added, and the mixture stirred at either 50 °C or room temperature under Ar. After stirring overnight or until TLC indicated complete consumption of starting reagents, the mixture was quenched with saturated $NaHCO_3$ solution and extracted twice with EtOAc, washed with H_2O and brine, dried with $MgSO_4$, and concentrated. The crude thioester was then purified either through trituration with dichloromethane and hexane (dissolving crude product in minimum dichloromethane and layering with hexane) or via column chromatography.



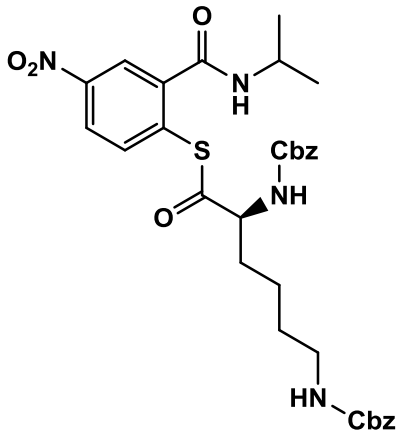
S-(2-(Isopropylcarbamoyl)-4-nitrophenyl)-(S)-2-(((benzyloxy)carbonyl)amino)-3-hydroxy propanethioate. (5a)

The general procedure was employed using 2-isopropyl-5-nitrobenzo[d]isothiazol-3(2H)-one **4a** (0.10 g, 0.42 mmol), N-Cbz-L-serine (0.10 g, 0.42 mmol), and $P(OEt)_3$ (72 μL, 0.42 mmol) in 2.9 mL of dry EtOAc and was stirred at 50 °C for 3 hours. After trituration, pure thioester was obtained as an orange solid (134 mg, 69%), mp 141-143 °C. $[\alpha]_D^{20}$ -44 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.34 (s, 6H), 6.29 (s, 2H), 5.14 (s, 2H), 4.47 – 4.41 (m, 1H), 4.20 – 4.07 (m, 2H), 3.77 (d, *J* = 10.4 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 166.2, 156.2, 148.2, 141.1, 138.0, 136.0, 134.6, 128.7, 128.4, 128.2, 124.9, 122.9, 67.5, 63.4, 63.2, 42.9, 22.6, 22.5. IR (neat, cm^{-1}): 3271, 3077, 1683, 1635, 1518. HRMS (APCI) Calcd for $C_{21}H_{24}N_3O_7S$ ($M+H^+$): 462.1335. Found: 462.1332.



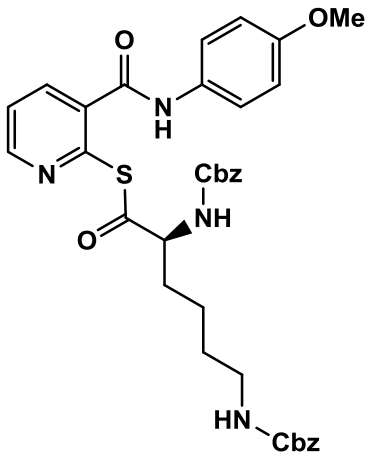
S-(4-Nitro-2-(phenylcarbamoyl)phenyl)(S)-2-(((benzyloxy)carbonyl)amino)-3-hydroxy propanethioate. (5b)

To a dry test tube was added N-Cbz-L-serine (66 mg, 0.28 mmol), and $P(OEt)_3$ (51 μL, 0.28 mmol) in 1.8 mL of dry EtOAc. 5-Nitro-2-phenylbenzo[d]isothiazol-3(2H)-one **4c** (75 mg, 0.28 mmol) was added portionwise and the solution stirred at room temperature under Ar overnight. The general work-up procedure was followed and the crude product triturated with dichloromethane and hexane to give 87 mg (64%) of the thioester as a cream-colored solid, mp 142-144 °C. $[\alpha]_D^{20}$ -20 (*c* 0.6, acetone); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 7.85 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.42 – 7.29 (m, 7H), 7.21 (t, *J* = 7.4 Hz, 1H), 5.98 (d, *J* = 8.1 Hz, 1H), 5.17 (s, 2H), 4.41 (d, *J* = 7.4 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.69 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 196.7, 163.7, 156.2, 147.3, 141.7, 138.6, 137.4, 136.7, 134.6, 128.8, 128.4, 127.9, 127.8, 124.4, 124.2, 122.8, 120.1, 66.0, 64.3, 61.1. IR (neat, cm^{-1}): 3291, 3078, 1708, 1643, 1527. HRMS (ESI) Calcd for $C_{24}H_{21}N_3O_7SNa$ ($M+Na^+$): 518.0998. Found: 518.0999.



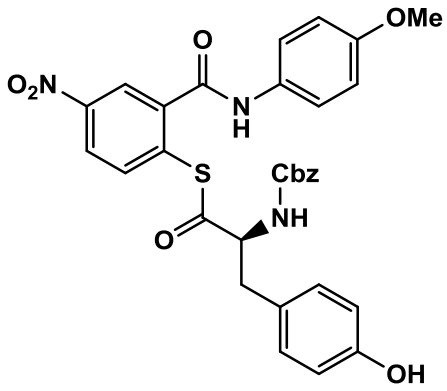
S-(2-(isopropylcarbamoyl)-4-nitrophenyl)-(S)-2,6-bis(((benzyloxy)carbonyl)amino) hexane thioate. (5c)

The general procedure was employed using 2-isopropyl-5-nitrobenzo[d]isothiazol-3(2H)-one **4a** (86 mg, 0.36 mmol), Cbz-L-Lys(Cbz)-OH (0.15 g, 0.36 mmol), and $P(OEt)_3$ (62 μL, 0.36 mmol) in 2.3 mL of dry EtOAc and was stirred at 50 °C for 5 hours. After trituration, pure thioester was obtained as a bright yellow solid (176 mg, 76%), mp 159-160 °C. $[\alpha]_D^{20}$ -19 (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, *J* = 7.6 Hz, 1H), 8.34 – 8.26 (m, 2H), 8.18 (d, *J* = 2.6 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.43 – 7.22 (m, 12H), 5.10 (s, 2H), 4.99 (s, 2H), 4.23 – 4.13 (m, 1H), 4.00 (d, *J* = 6.8 Hz, 1H), 2.97 (s, 1H), 1.69 (s, 2H), 1.38 (s, 4H), 1.13 (dd, *J* = 6.6, 2.6 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.3, 164.3, 156.2, 156.1, 147.2, 142.5, 137.4, 137.3, 136.7, 134.2, 128.4, 128.34, 128.0, 127.8, 127.7, 123.9, 122.3, 66.0, 65.1, 61.6, 41.2, 30.7, 30.5, 28.9, 22.5, 22.1. IR (neat, cm^{-1}): 3321, 3282, 2952, 1738, 1703, 1683, 1634, 1524. HRMS (APCI) Calcd for $C_{32}H_{37}N_4O_8S$ ($M+H^+$): 637.2332. Found: 637.2334.



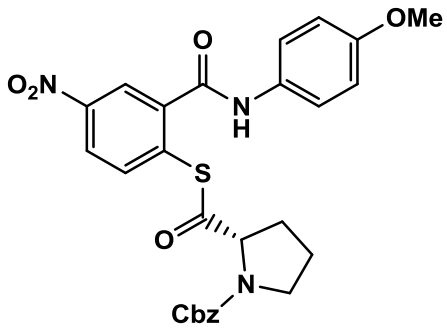
S-(3-((4-Methoxyphenyl)carbamoyl)pyridin-2-yl)(S)-2,6-bis(((benzyloxy)carbonyl) amino) hexanethioate. (5d)

The general procedure was employed using 2-(4-methoxyphenyl)isothiazolo [5,4-b]pyridin-3(2H)-one **4d** (75 mg, 0.29 mmol), Cbz-L-Lys(Cbz)-OH (0.12 g, 0.29 mmol), and $P(OEt)_3$ (50 μL, 0.29 mmol) in 1.8 mL of dry EtOAc and was stirred at room temperature overnight. After trituration, pure thioester was obtained as a yellow-white solid (0.17 g, 87%), mp 236-238 °C. $[\alpha]_D^{20}$ -4.2 (*c* 0.6, DMSO); ^{1}H NMR (600 MHz, acetone-d_6) δ 13.26 (s, 1H), 8.82 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.41 – 7.34 (m, 8H), 7.32 – 7.27 (m, 2H), 7.16 (t, *J* = 6.8 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.58 (s, 1H), 6.38 (s, 1H), 5.09 (d, *J* = 12.7 Hz, 2H), 5.04 (s, 2H), 3.80 (s, 3H), 3.20 – 3.11 (m, 1H), 2.88 – 2.79 (m, 4H), 1.60 – 1.46 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 199.1, 164.1, 161.4, 156.1, 155.6, 150.9, 147.9, 141.9, 141.6, 138.9, 137.3, 136.7, 136.6, 132.0, 131.5, 128.4, 127.8, 124.0, 121.2, 114.2, 113.8, 65.8, 65.1, 61.6, 55.2, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.1, 30.6, 28.9, 22.9, 22.5. IR (neat, cm^{-1}): 3323, 2937, 1827, 1688, 1528. HRMS (ESI) Calcd for $C_{35}H_{37}N_4O_7S$ ($M+H^+$): 657.2383. Found: 657.2396.



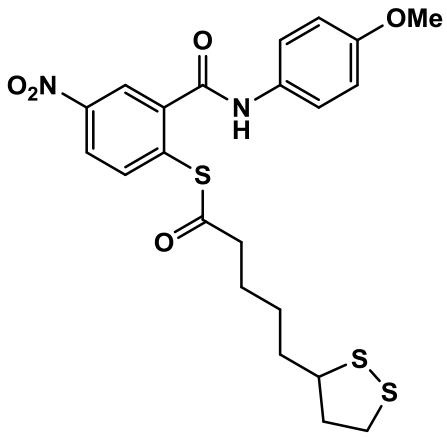
S-(2-((4-Methoxyphenyl)carbamoyl)-4-nitrophenyl)-(S)-2-(((benzyloxy)carbonyl) amino)-3-(4-hydroxyphenyl)propanethioate. (5e)

The general procedure was employed using 2-(4-methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one **4b** (85 mg, 0.28 mmol), N-Cbz-L-tyrosine (89 mg, 0.28 mmol), and $P(OEt)_3$ (48 μL, 0.28 mmol) in 1.8 mL of dry EtOAc and was stirred at room temperature for 4 hours. After trituration, pure thioester was obtained as a yellow solid (135 mg, 81%), mp 173-175 °C. $[\alpha]_D^{20}$ -24 (*c* 1.7, acetone); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.26 (s, 1H), 8.43 (s, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 8.3 Hz, 2H), 4.98 (s, 2H), 4.37 (s, 1H), 3.73 (s, 3H), 2.98 – 2.93 (m, 1H), 2.79 – 2.72 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 197.5, 163.3, 156.1, 156.0, 155.9, 147.3, 142.1, 137.5, 136.7, 134.6, 131.8, 130.1, 128.4, 127.8, 127.4, 126.8, 124.3, 122.8, 121.5, 115.1, 113.9, 65.7, 63.5, 55.2, 35.6. IR (neat, cm^{-1}): 3456, 3292, 1690, 1649, 1512. HRMS (APCI) Calcd for $C_{31}H_{28}N_3O_8S$ ($M+H^+$): 602.1597. Found: 602.1594.



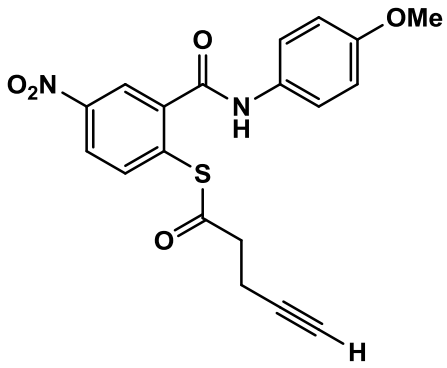
Benzyl-(S)-2-(((2-((4-methoxyphenyl)carbamoyl)-4-nitrophenyl)thio)carbonyl) pyrrolidine-1-carboxylate. (5f)

The general procedure was employed using 2-(4-methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one **4b** (89 mg, 0.29 mmol), N-Cbz-L-proline (73 mg, 0.29 mmol), and $P(OEt)_3$ (51 μL, 0.29 mmol) in 1.8 mL of dry EtOAc and was stirred at room temperature for 2 hours. After extraction and work-up, the crude product was purified via column chromatography to give 130 mg (81%) of the thioester as a bright yellow solid, mp 74-76 °C. $[\alpha]_D^{20}$ -82 (*c* 0.1, $CHCl_3$); ^{1}H NMR (1 : 0.99 rotamer ratio, 600 MHz, $CDCl_3$) δ 8.49 and 8.45 (each d, *J* = 2.2 Hz, 1H), 8.26 and 8.18 (each dd, *J* = 8.5, 2.3 Hz, 1H), 7.80 – 7.67 (overlapping s and m, 4H total), 7.51 – 7.46 (each d, *J* = 8.9 Hz, 2H), 7.38 – 7.27 (overlapping m, 10H total), 6.90 – 6.83 (overlapping m, 4H total), 5.18 – 5.06 (overlapping m, 4H total), 4.56 - 4.50 (each d, *J* = 6.0 Hz, 1H), 3.79 (overlapping s, 6H total), 3.63 (overlapping s, 2H total), 3.54 – 3.48 (each m, 1H), 2.21 – 2.10 (overlapping m, 2H total), 1.98 – 1.86 (overlapping m, 4H total), 1.81 (overlapping s, 2H total). ^{13}C NMR (two rotamers, 151 MHz, $CDCl_3$) δ 200.6, 199.8, 163.8, 157.0, 155.4, 154.4, 148.5, 143.3, 143.0, 138.0, 137.8, 136.3, 133.2, 133.1, 130.5, 128.6, 128.3, 128.0, 124.7, 123.5, 123.2, 122.0, 121.5, 114.4, 67.7, 67.5, 66.9, 66.4, 55.6, 47.5, 47.1, 31.7, 30.7, 24.2, 23.4. IR (neat, cm^{-1}): 3264, 2955, 1702, 1604, 1509, 1344. HRMS (APCI) Calcd for $C_{27}H_{26}N_3O_7S$ ($M+H^+$): 536.1491. Found: 536.1487.



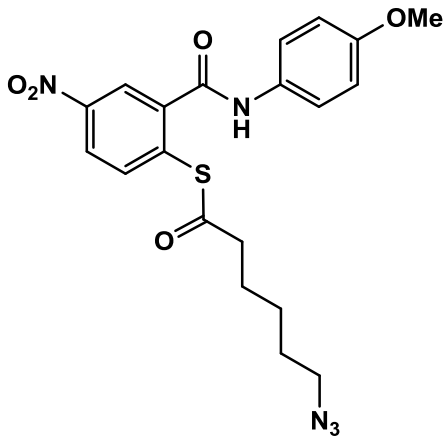
2-(6-(1,2-dithiolan-3-yl)-2-oxohexyl)-N-(4-methoxyphenyl)-5-nitrobenzamide. (5g)

The general procedure was employed using 2-(4-methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one (75 mg, 0.25 mmol), lipoic acid (51 mg, 0.25 mmol), and $P(OEt)_3$ (43 μL, 0.25 mmol) in 1.6 mL of dry EtOAc and was stirred at room temperature overnight. After trituration, pure thioester was obtained as a yellow solid (66 mg, 54%), mp 115-117 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.3 Hz, 1H), 8.30 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.49 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 3.40 (p, *J* = 6.5 Hz, 1H), 3.19 – 3.12 (m, 1H), 3.12 – 3.05 (m, 1H), 2.69 (t, 2H), 2.39 (dq, *J* = 12.5, 6.4 Hz, 1H), 1.84 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.66 (dq, *J* = 14.6, 7.2 Hz, 2H), 1.57 (s, 2H), 1.50 – 1.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 164.0, 157.2, 148.5, 142.9, 137.7, 133.3, 130.5, 124.9, 123.4, 121.9, 114.5, 56.2, 55.7, 44.1, 40.4, 38.7, 34.7, 28.6, 25.5. IR (neat, cm^{-1}): 3294, 1689, 1514. HRMS (APCI) Calcd for $C_{22}H_{25}N_2O_5S_3$ ($M+H^+$): 493.0926. Found 493.0923.



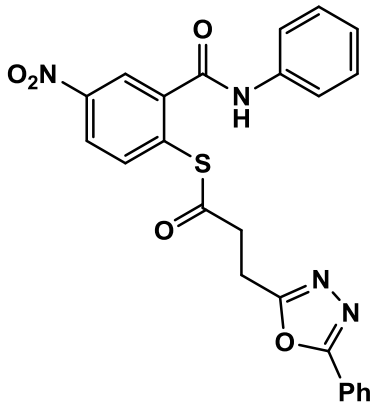
S-(2-((4-Methoxyphenyl)carbamoyl)-4-nitrophenyl) pent-4-ynethioate. (5h)

The general procedure was employed using 2-(4-methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one **4b** (75 mg, 0.25 mmol), 4-pentynoic acid (24 mg, 0.25 mmol), and $P(OEt)_3$ (42 μL, 0.25 mmol) in 1.6 mL of dry EtOAc and was stirred at room temperature overnight. After trituration, pure thioester was obtained as a yellow solid (83 mg, 87%), mp 184-186 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.5 Hz, 1H), 8.32 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.62 (s, 1H), 7.49 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 2.93 (t, *J* = 7.1 Hz, 2H), 2.53 (td, *J* = 7.1, 2.5 Hz, 2H), 1.88 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.4, 163.3, 155.9, 147.2, 141.4, 137.2, 134.0, 131.7, 124.4, 122.9, 121.5, 113.9, 82.3, 72.1, 55.2, 42.0, 13.9. IR (neat, cm^{-1}): 3305, 3270, 1708, 1646. HRMS (ESI) Calcd for $C_{19}H_{17}N_2O_5S$ ($M+H^+$): 385.0858. Found: 385.0857.



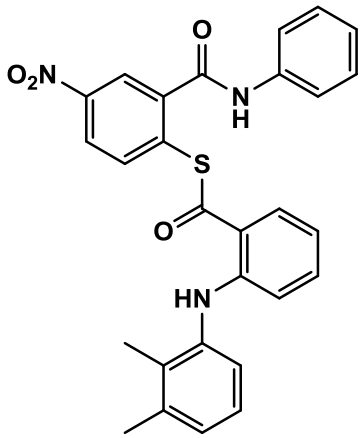
S-(2-((4-Methoxyphenyl)carbamoyl)-4-nitrophenyl) 6-azidohexanethioate. (5i)

The general procedure was employed using 2-(4-methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one **4b** (75 mg, 0.25 mmol), 6-azidohexanoic acid (0.39 mg, 0.25 mmol), and $P(OEt)_3$ (43 μL, 0.25 mmol) in 1.6 mL of dry EtOAc and was stirred at room temperature overnight. After trituration, pure thioester was obtained as a yellow solid (68 mg, 62%), mp 95-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.3 Hz, 1H), 8.30 (dd, *J* = 9.4, 2.5 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.60 (s, 1H), 7.48 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 3.14 (t, *J* = 6.8 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.69 – 1.60 (m, 2H), 1.52 – 1.44 (m, 2H), 1.40 – 1.30 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 194.7, 163.3, 155.8, 147.3, 141.7, 137.3, 134.1, 131.8, 124.3, 122.8, 121.3, 113.9, 55.2, 50.4, 43.2, 27.8, 25.2, 24.6. IR (neat, cm^{-1}): 3302, 2093, 1643, 1513. HRMS (ESI) Calcd for $C_{20}H_{22}N_5O_5S$ ($M+H^+$): 444.1342. Found: 444.1341.



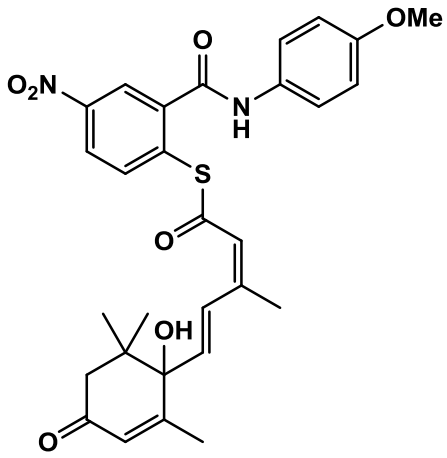
S-(4-Nitro-2-(phenylcarbamoyl)phenyl) 3-(5-phenyl-1,3,4-oxadiazol-2-yl)propane-thioate. (5j)

To a dry test tube was added 3-(5-phenyl-1,3,4-oxadiazol-2-yl)propanoic acid (60 mg, 0.28 mmol), and $P(OEt)_3$ (47 μL, 0.28 mmol) in 1.6 mL of dry EtOAc. 5-Nitro-2-phenylbenzo[d]isothiazol-3(2H)-one **4c** (75 mg, 0.28 mmol) was added portionwise and the solution stirred at room temperature under Ar overnight. The general work-up procedure was followed and the crude product triturated to give the thioester as an orange solid (0.10 g, 77%), mp 128-130 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.30 – 8.24 (m, 1H), 7.97 (d, *J* = 7.7 Hz, 3H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 3.31 (t, *J* = 7.0 Hz, 2H), 3.24 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.6, 165.2, 164.6, 163.9, 148.4, 142.4, 137.8, 137.3, 132.8, 132.0, 129.4, 129.2, 126.9, 125.4, 125.0, 123.7, 123.3, 120.2, 39.7, 21.0. IR (neat, cm^{-1}): 3305, 1716, 1652. HRMS (ESI) Calcd for $C_{24}H_{19}N_4O_5S$ ($M+H^+$): 475.1076. Found: 475.1072.



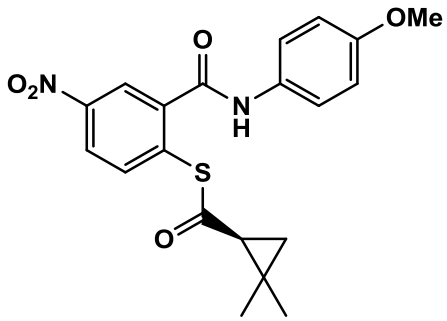
S-(4-Nitro-2-(phenylcarbamoyl)phenyl) 2-((2,3-dimethylphenyl)amino)benzothioate. (5k)

To a dry test tube was added mefenamic acid (67 mg, 0.28 mmol) and $P(OEt)_3$ (47 μL, 0.28 mmol) in 1.6 mL of dry EtOAc. 5-Nitro-2-phenylbenzo[d]isothiazol-3(2H)-one **4c** (75 mg, 0.28 mmol) was added portionwise and the solution stirred at room temperature under Ar overnight. The general work-up procedure was followed and the crude product triturated to give 87 mg (63%) of the thioester as orange needles (87 mg, 63%), mp 120-122 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.62 (d, *J* = 2.5 Hz, 1H), 8.35 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.19 (s, 1H), 8.02 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.34 – 7.23 (m, 3H), 7.15 – 7.10 (m, 2H), 7.05 (dd, *J* = 25.0, 7.5 Hz, 2H), 6.72 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 2.32 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.4, 164.2, 148.9, 148.7, 144.4, 138.8, 138.6, 137.5, 137.4, 136.3, 133.0, 131.2, 129.3, 128.0, 126.4, 125.1, 124.9, 124.1, 123.9, 120.0, 116.9, 116.6, 114.7, 20.7, 14.2. IR (neat, cm^{-1}): 3320, 3068, 1639, 1657. HRMS (ESI) Calcd for $C_{28}H_{24}N_3O_4S$ ($M+H^+$): 498.1488. Found: 498.1483.



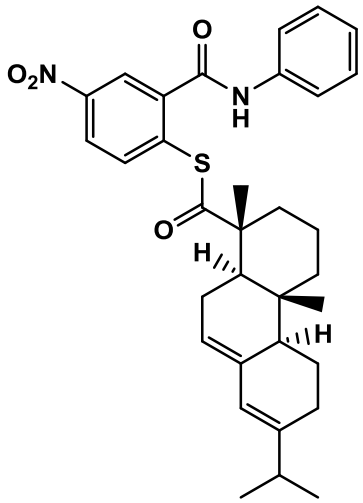
S-(2-((4-Methoxyphenyl)carbamoyl)-4-nitrophenyl)(2Z,4E)-5-(1-hydroxy-2,6,6-trimethyl-4-oxocyclohex-2-en-1-yl)-3-methylpenta-2,4-dienethioate. (5l)

The general procedure was employed using 2-(4-methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one **4b** (75 mg, 0.25 mmol), (±)-abscisic acid (0.66 mg, 0.25 mmol), and $P(OEt)_3$ (43 μL, 0.25 mmol) in 1.6 mL of dry EtOAc and was stirred at room temperature overnight. After trituration, pure thioester was obtained as an orange solid (94 mg, 69%), mp 176-179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.5 Hz, 1H), 8.32 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.82 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 15.8 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.29 (d, *J* = 15.9 Hz, 1H), 6.08 (s, 1H), 5.91 (s, 1H), 3.80 (s, 3H), 2.43 (d, *J* = 17.1 Hz, 1H), 2.28 (d, *J* = 17.2 Hz, 1H), 2.04 (s, 3H), 1.85 (s, 3H), 1.08 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 197.1, 183.2, 163.4, 155.8, 151.2, 147.2 141.8, 141.8, 137.4, 134.5, 131.7, 127.6, 126.1, 124.1, 122.6, 122.2, 121.4, 113.9, 78.4, 55.2, 49.3, 41.3, 24.2, 23.2, 20.6, 18.7. IR (neat, cm^{-1}): 3409, 3330, 3023, 1682, 1662, 1652. HRMS (ESI) Calcd for $C_{29}H_{31}N_2O_7S$ ($M+H^+$): 551.1852. Found: 551.1848.



S-(2-((4-Methoxyphenyl)carbamoyl)-4-nitrophenyl) (S)-2,2-dimethylcyclopropane-1-carbo thioate. (5m)

The general procedure was employed using 2-(4-methoxyphenyl)-5-nitrobenzo[d]iso thiazol-3(2H)-one **4b** (75 mg, 0.25 mmol), (S)-(+)-2,2-dimethylcyclopropane carboxylic acid (29 μL, 0.25 mmol), and $P(OEt)_3$ (43 μL, 0.25 mmol) in 1.6 mL of dry EtOAc and was stirred at room temperature overnight. After work-up, the crude product was purified via column chromatography and then triturated with dichloromethane and hexane to give 43 mg (43%) of the thioester as a pale yellow solid, mp 120-123 °C. $[\alpha]_D^{20}$ +125 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.5 Hz, 1H), 8.30 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 2.00 (dd, *J* = 7.8, 5.3 Hz, 1H), 1.35 (t, *J* = 4.9 Hz, 1H), 1.20 (s, 3H), 1.11 – 1.07 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.6, 164.0, 157.1, 148.3, 142.9, 137.8, 133.8, 130.5, 124.7, 123.5, 121.9, 114.4, 55.7, 36.8, 29.2, 26.9, 25.8, 18.7. IR (neat, cm^{-1}): 3290, 1687, 1649. HRMS (ESI) Calcd for $C_{20}H_{21}N_2O_5S$ ($M+H^+$): 401.1171. Found: 401.1169.

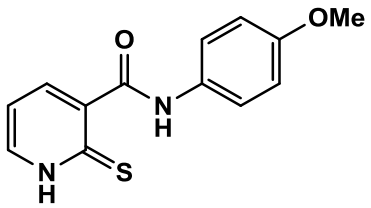


S-(2-((4-Methoxyphenyl)carbamoyl)-4-nitrophenyl)(1R,4aR,4bR,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthrene-1-carbothioate. (5n)

To a dry test tube was added abietic acid (50 mg, 0.17 mmol), and $P(OEt)_3$ (57 μL, 0.33 mmol) in 1.6 mL of dry EtOAc. 5-Nitro-2-phenylbenzo[d]isothiazol-3(2H)-one **4c** (90 mg, 0.33 mmol) was added portionwise and the solution stirred at room temperature under Ar overnight. The general work-up procedure was followed and the crude product purified through column chromatography to give pure thioester as a yellow solid (82 mg, 89%), mp 142-144 °C. $[\alpha]_D^{20}$ +8.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 5.69 (s, 1H), 5.05 (s, 1H), 2.25 – 2.19 (m, 1H), 2.09 – 2.01 (m, 2H), 1.95 – 1.83 (m, 3H), 1.81 – 1.68 (m, 4H), 1.63 – 1.51 (m, 3H), 1.34 (s, 3H), 1.27 – 1.14 (m, 2H), 1.04 – 1.00 (m, 6H), 0.79 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.1, 164.2, 148.5, 145.5, 143.9, 138.1, 137.3, 135.4, 133.9, 129.2, 125.1, 124.7, 123.4, 122.4, 120.0, 120.0, 55.7, 50.9, 46.2, 38.4, 38.1, 35.0, 27.5, 25.5, 22.6, 21.5, 21.0, 18.2, 17.4, 14.4. IR (neat, cm^{-1}): 2931, 1688, 1524. HRMS (ESI) Calcd for $C_{33}H_{39}N_2O_4S$ ($M+H^+$): 559.2631. Found: 559.2655.

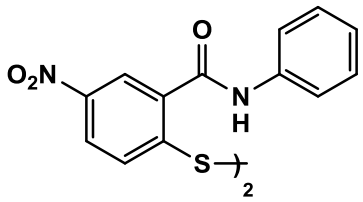
Experimental Data

Benzoisothiazolone By-Products:



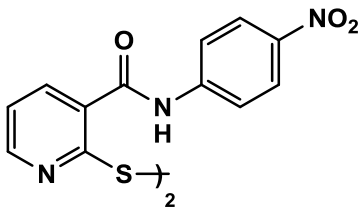
N-(4-nitrophenyl)-2-thioxo-1,2-dihydropyridine-3-carboxamide. (12)

Orange solid, mp 235-236 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.18 (s, 1H), 12.86 (s, 1H), 8.54 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 5.9 Hz, 1H), 7.63 (d, J = 8.9 Hz, 2H), 7.09 (t, J = 6.8 Hz, 1H), 6.95 (d, J = 8.9 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.3, 161.4, 155.7, 141.9, 141.5, 133.3, 131.5, 121.1, 114.2, 114.2, 55.2. IR (neat, cm^{-1}): 3026, 1643, 1247; HRMS (ESI) Calcd for $C_{13}H_{13}N_2O_2S$ (M+H$^+$): 261.0698. Found: 261.0691.



6,6'-Disulfanediylbis(3-nitro-N-phenylbenzamide). (14)

White solid**,** mp 258-260 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.90 (s, 2H), 8.76 (s, 2H), 8.37 (d, J = 8.9 Hz, 2H), 7.95 (d, J = 9.5 Hz, 2H), 7.77 (d, J = 7.7 Hz, 4H), 7.42 (t, J = 7.2 Hz, 4H), 7.19 (t, J = 7.3 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.8, 145.6, 145.4, 138.3, 134.2, 128.9, 127.2, 126.1, 124.6, 123.6, 120.6. IR (neat, cm^{-1}): 3300, 1642. HRMS (ESI) Calcd for $C_{26}H_{19}N_4O_6S_2$ (M+H$^+$): 547.0746. Found: 547.0744.



2-(Methylthio)-N-(4-nitrophenyl)nicotinamide. **(31)**

Yellow solid, mp 289-290 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 2H), 8.43 (d, *J* = 7.6 Hz, 2H), 8.26 (d, *J* = 9.1 Hz, 4H), 8.04 (d, *J* = 5.6 Hz, 2H), 7.94 (d, *J* = 9.3 Hz, 4H), 7.08 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.5, 163.2, 144.5, 142.7, 141.9, 141.7, 133.7, 125.2, 119.5, 114.1. IR (neat, cm^{-1}): 2926, 1672. HRMS (ESI) Calcd for $C_{24}H_{17}N_6O_6S_2$ ($M+H^+$): 549.0651. Found: 549.0659.

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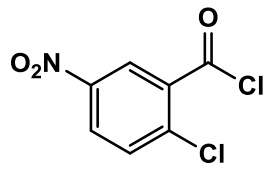

1

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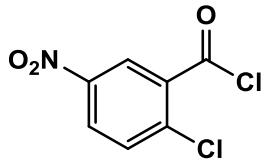
151 MHz



1

$CDCl_3$
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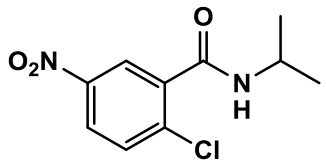
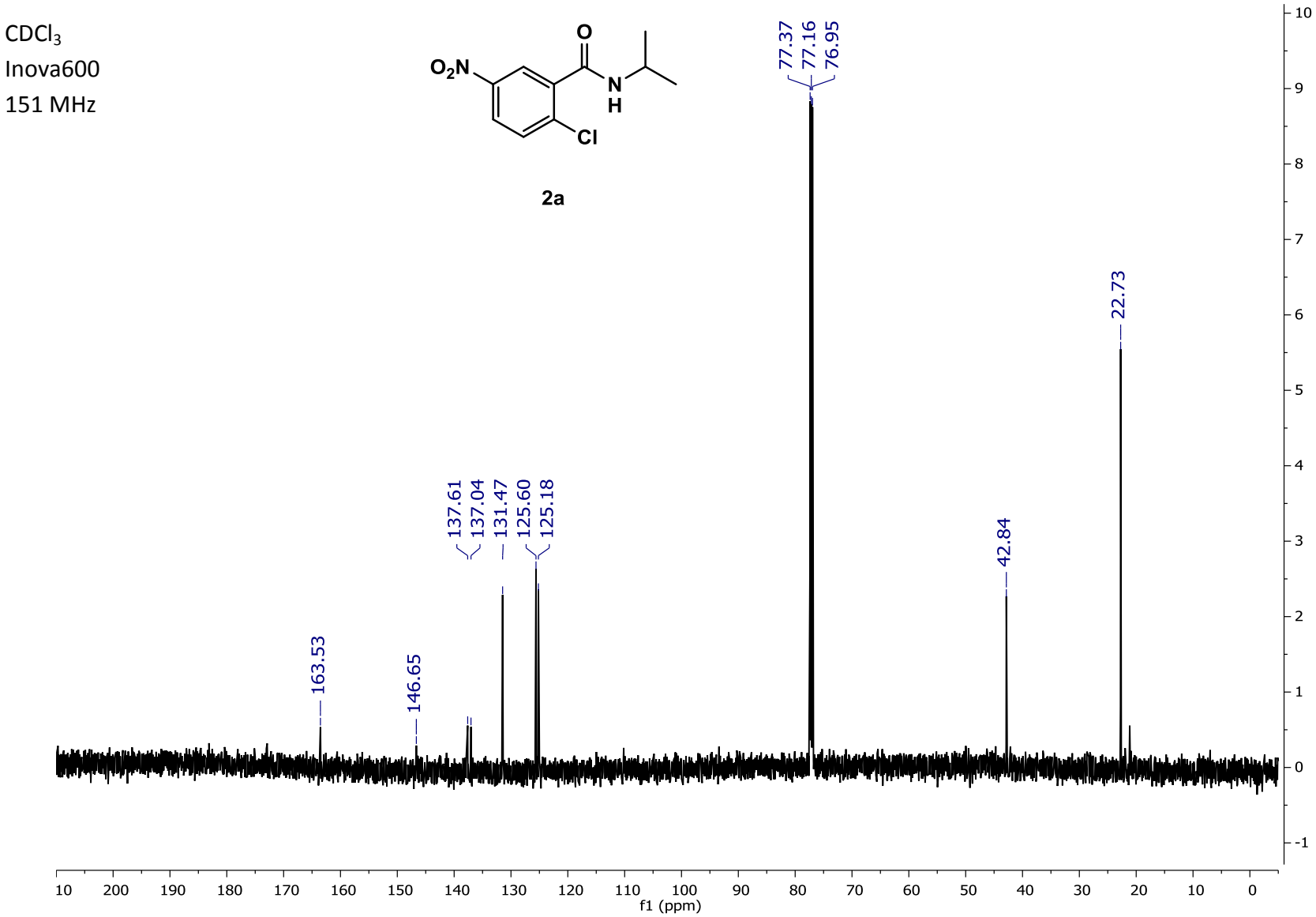
600 MHz



2a


CDCl3
Inova600
151 MHz
O2N
O
N
H
Cl
2a
77.37
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76.95
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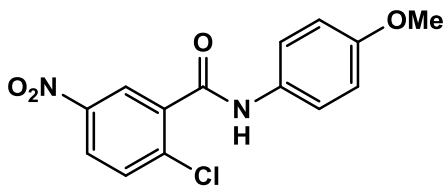
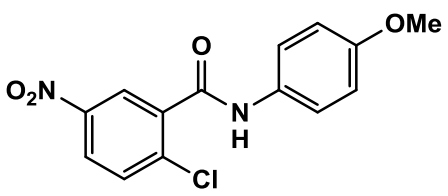
137.04
131.47
125.60
125.18
42.84
22.73
f1 (ppm)

$CDCl_3$
Inova600
600 MHz



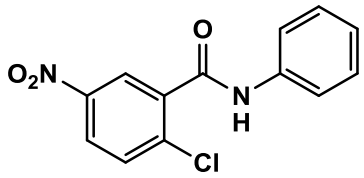
2b

$CDCl_3$
Inova600
151 MHz



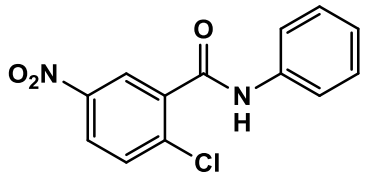
2b

$CDCl_3$
Inova600
600 MHz



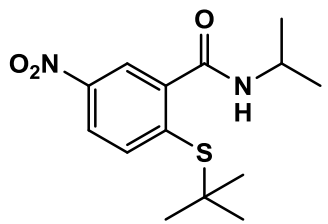
2c

$CDCl_3$
Inova600
151 MHz



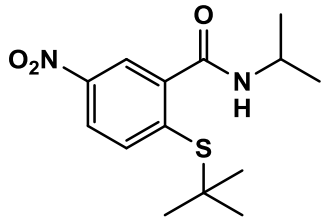
2c

$CDCl_3$
Inova600
600 MHz



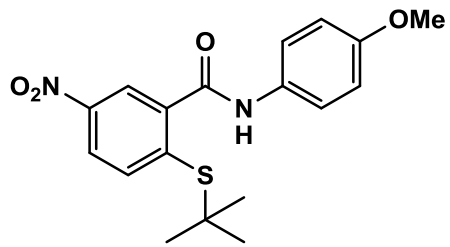
3a

$CDCl_3$
Inova600
151 MHz



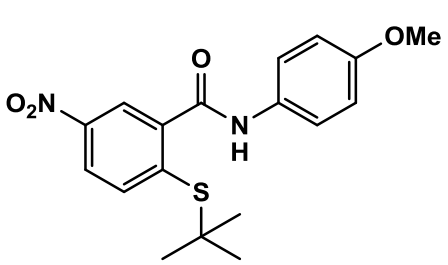
3a

$CDCl_3$
Inova600
600 MHz



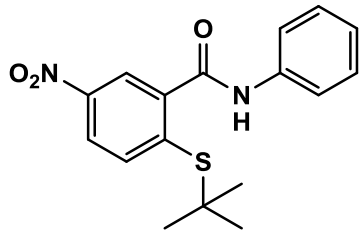
3b

$CDCl_3$
Inova600
151 MHz

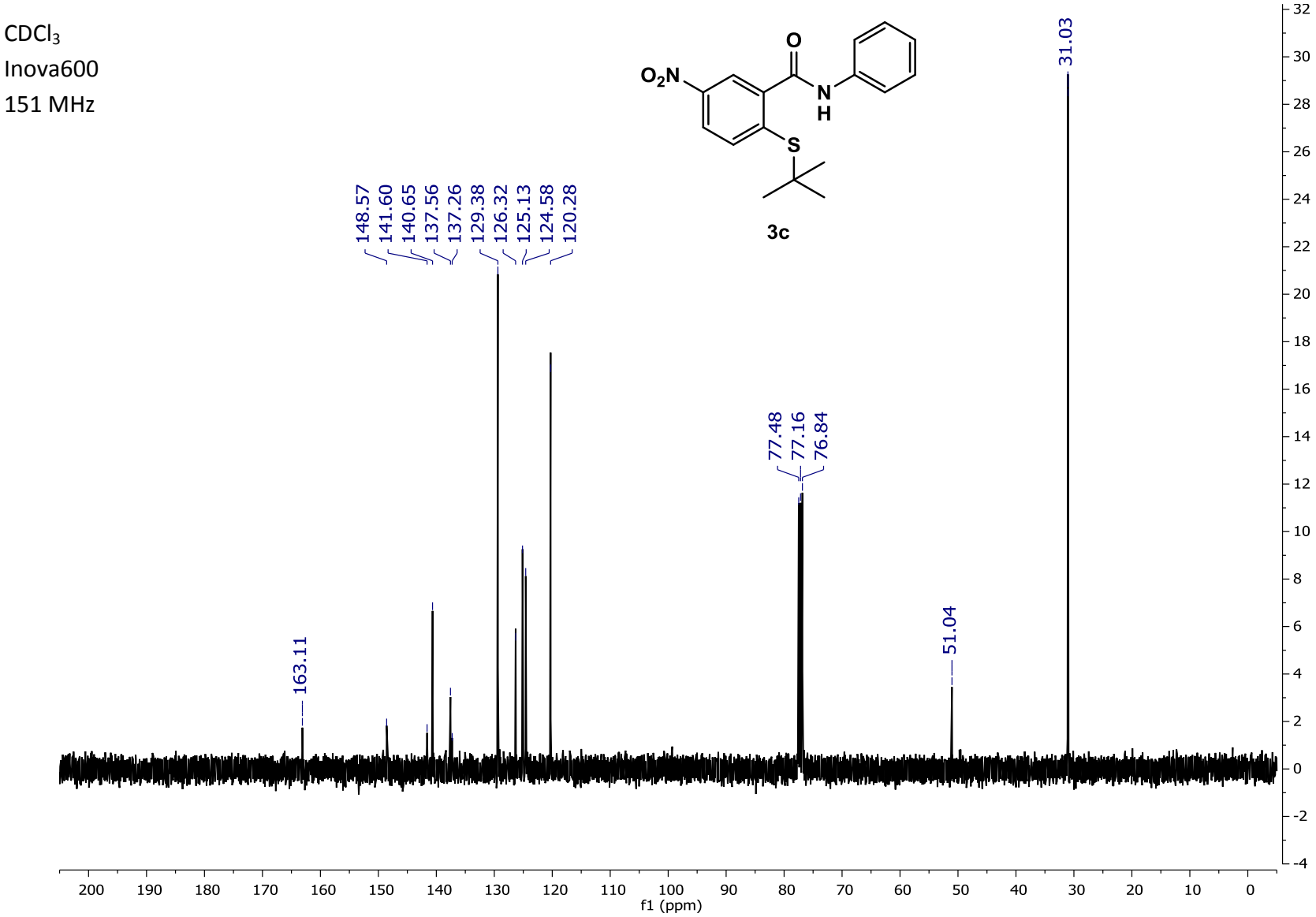


3b

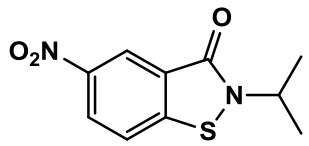
$CDCl_3$
Inova600
600 MHz



3c

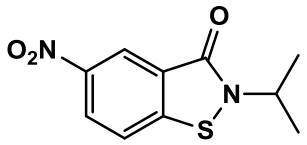

CDCl3
Inova600
151 MHz
O2N
O
N
H
S
3c
148.57
141.60
140.65
137.56
137.26
129.38
126.32
125.13
124.58
120.28
163.11
77.48
77.16
76.84
51.04
31.03
f1 (ppm)

$CDCl_3$
Inova600
600 MHz



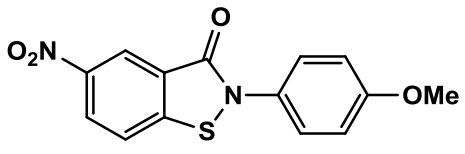
4a

$CDCl_3$
Inova600
151 MHz



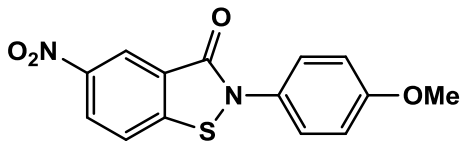
4a

DMSO-d_6
Inova600
600 MHz



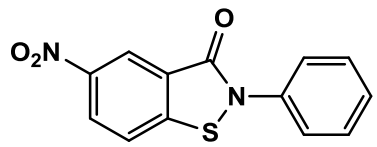
4b

DMSO-d_6
Inova600
151 MHz



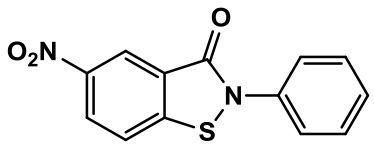
4b

DMSO-d_6
Inova600
600 MHz



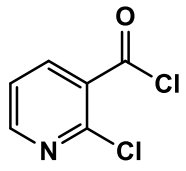
4c

DMSO-d_6
Inova600
151 MHz



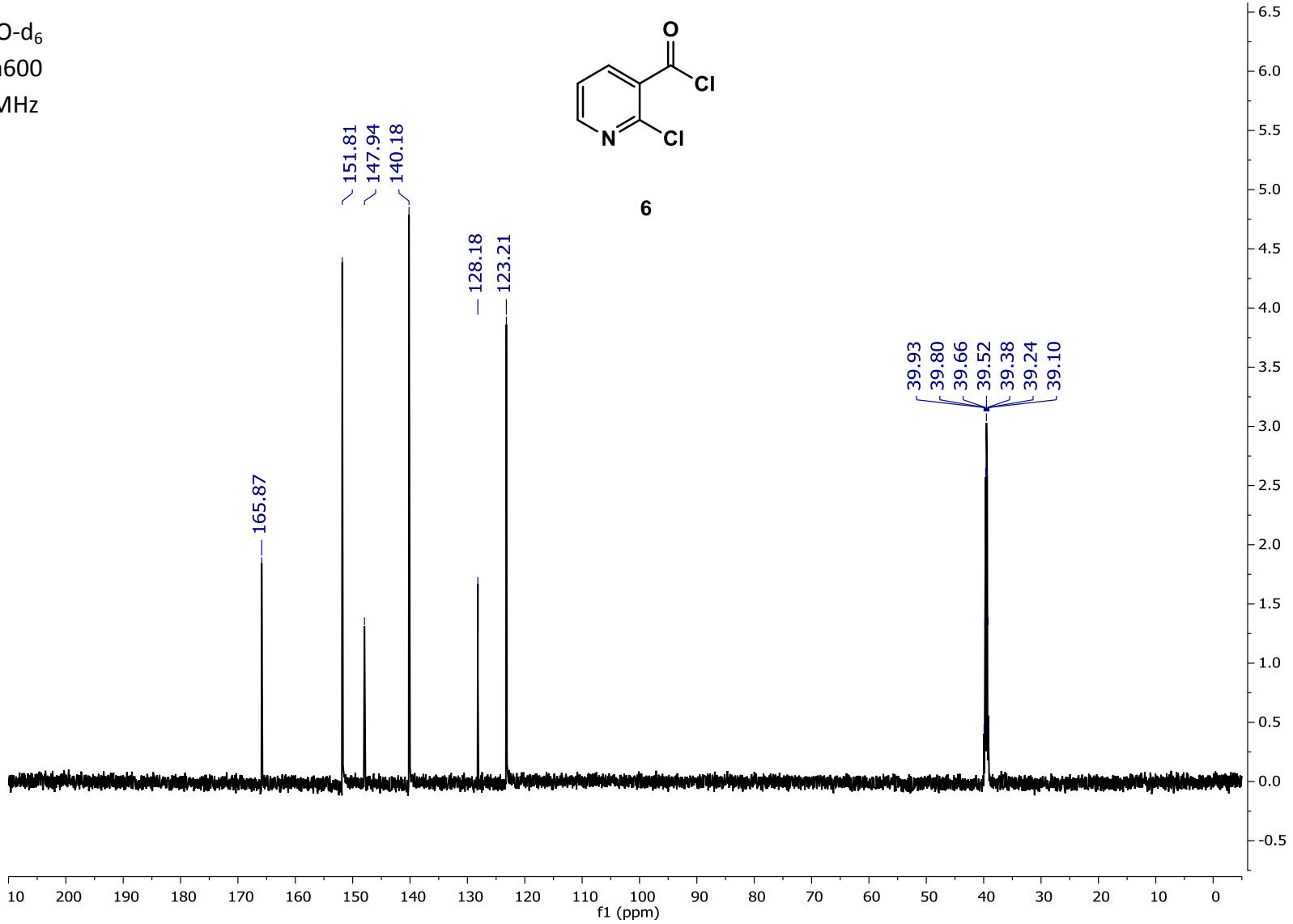
4c

DMSO-d_6
Inova600
600 MHz

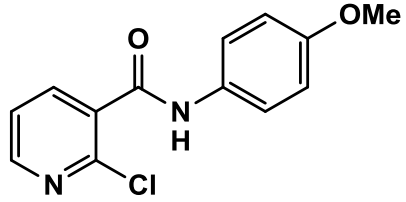


6

DMSO-d_6
Inova600
151 MHz

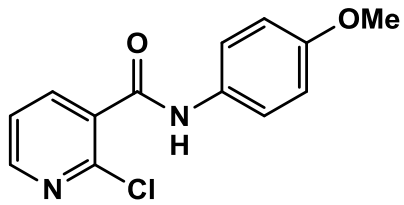


DMSO-d_6
Inova600
600 MHz



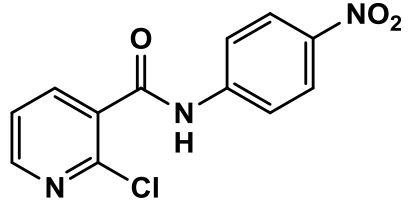
7a

DMSO-d_6
Inova600
151 MHz



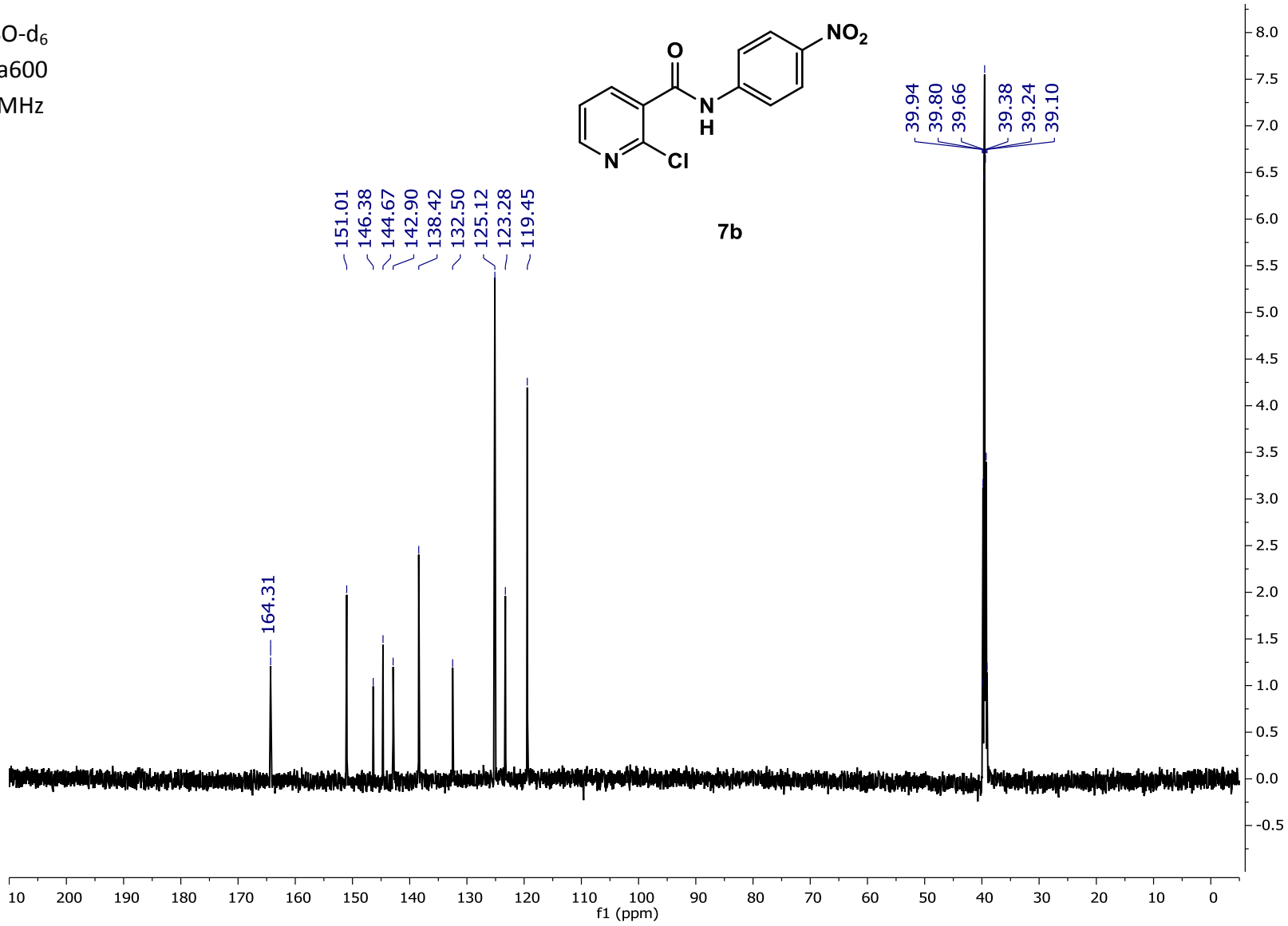
7a

DMSO-d_6
Inova600
600 MHz

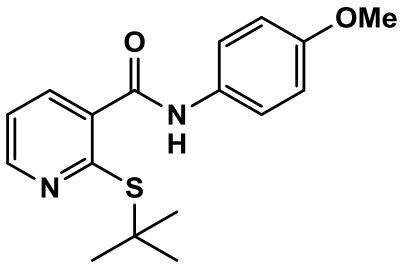


7b

DMSO-d_6
Inova600
151 MHz

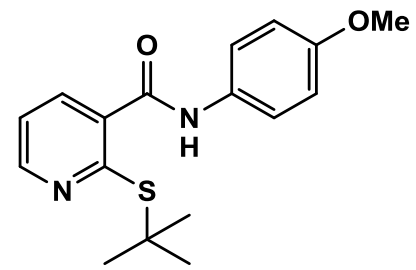


DMSO-d_6
Inova600
600 MHz

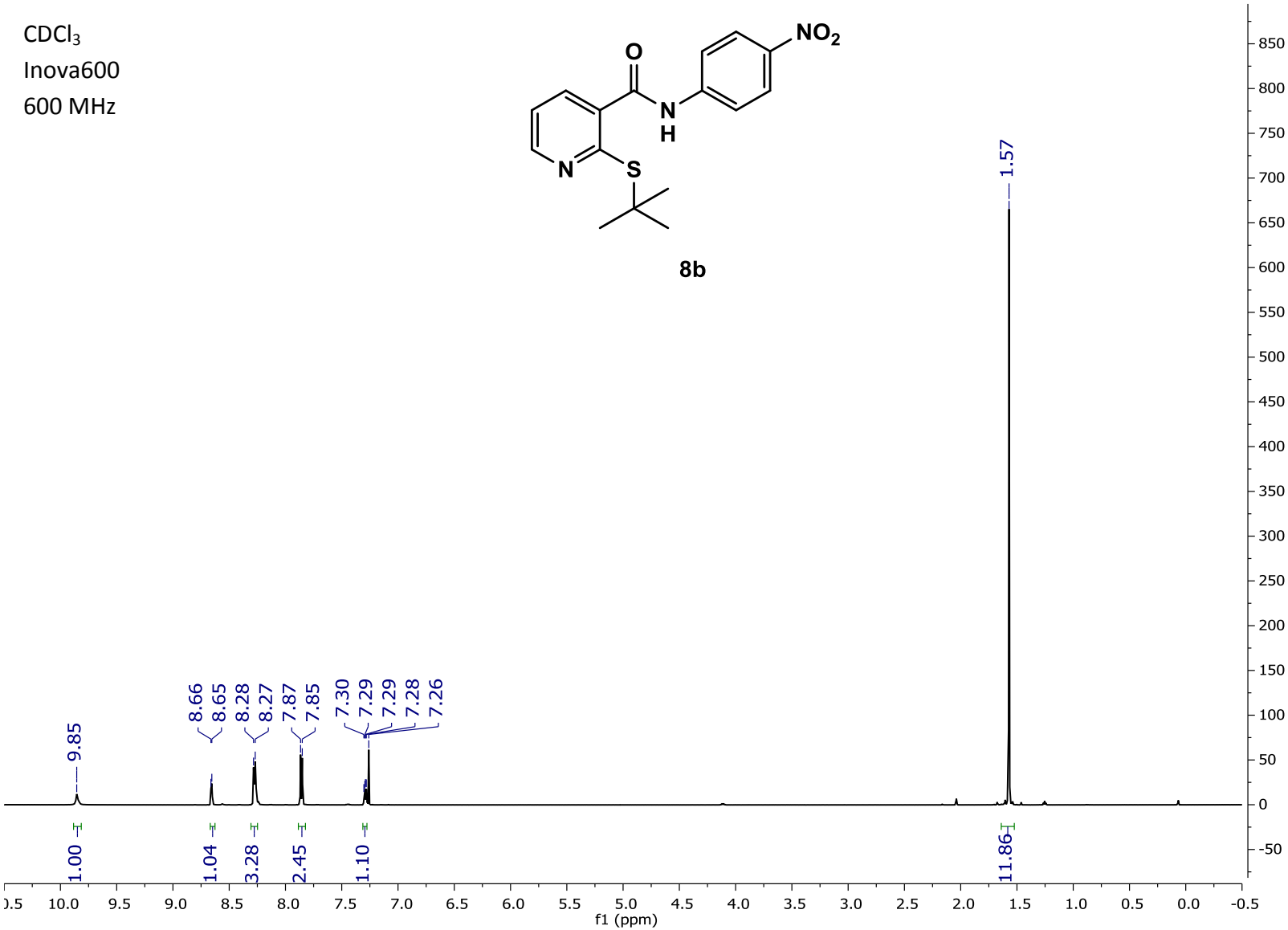


8a

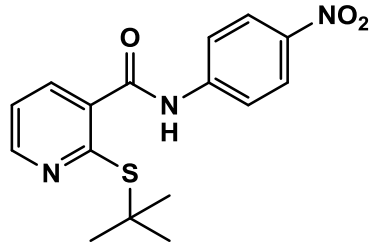
DMSO-d_6
Inova600
151 MHz



8a

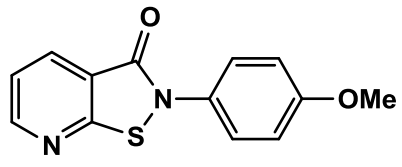

CDCl3
Inova600
600 MHz
O
N
H
N
S
NO2
8b
9.85
8.66
8.65
8.28
8.27
7.87
7.85
7.30
7.29
7.29
7.28
7.26
1.57
1.00
1.04
3.28
2.45
1.10
11.86
f1 (ppm)

DMSO-d_6
Inova600
151 MHz



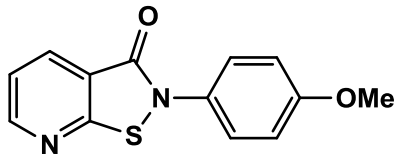
8b

DMSO-d_6
Inova600
600 MHz



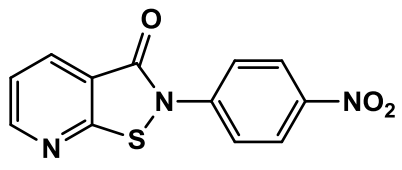
4d

DMSO-d_6
Inova600
151 MHz



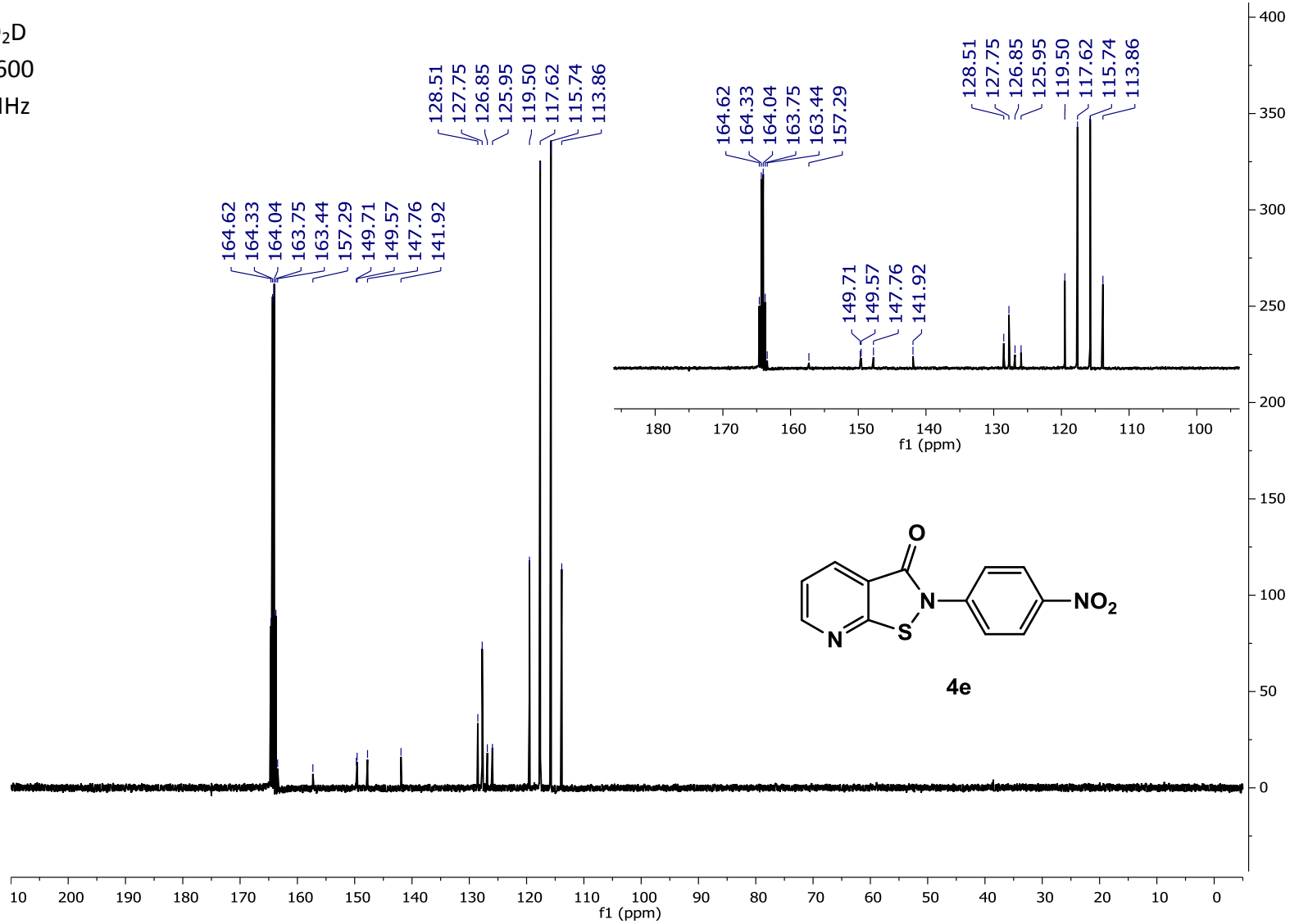
4d

CF_3CO_2D
Inova600
600 MHz

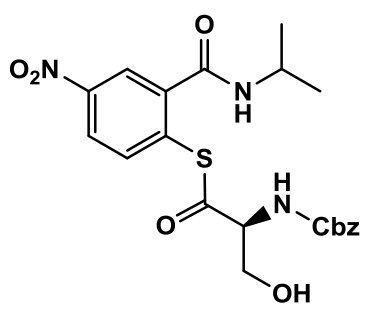


4e

CF_3CO_2D
Inova600
151 MHz

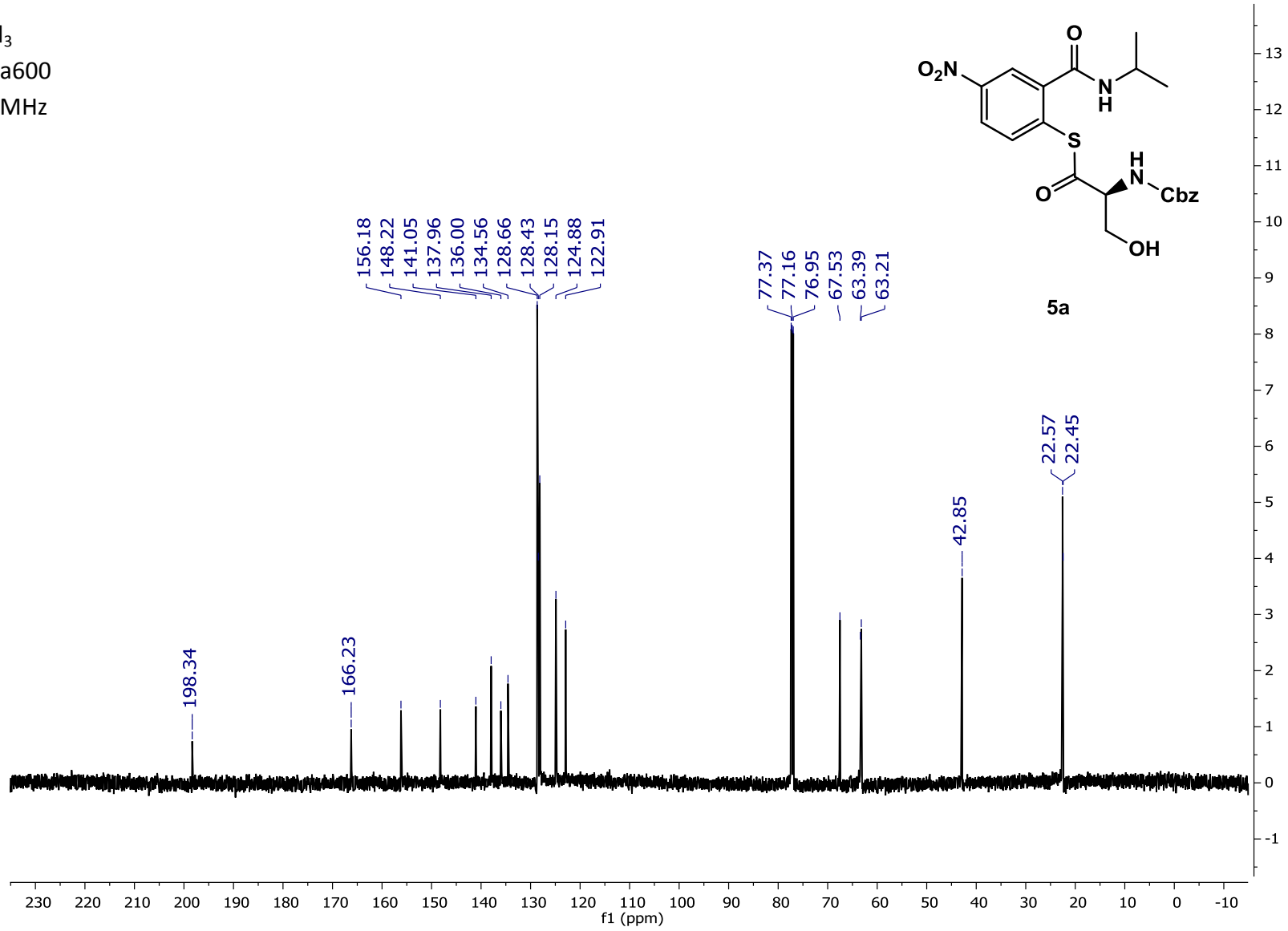


$CDCl_3$
Inova600
600 MHz

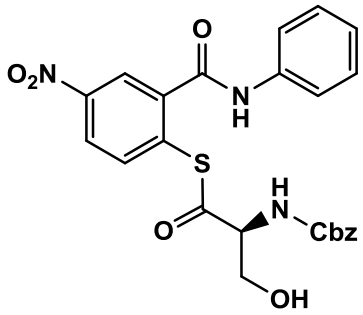


5a

$CDCl_3$
Inova600
151 MHz

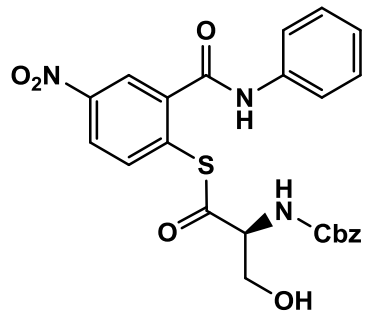


$CDCl_3$
Inova600
600 MHz



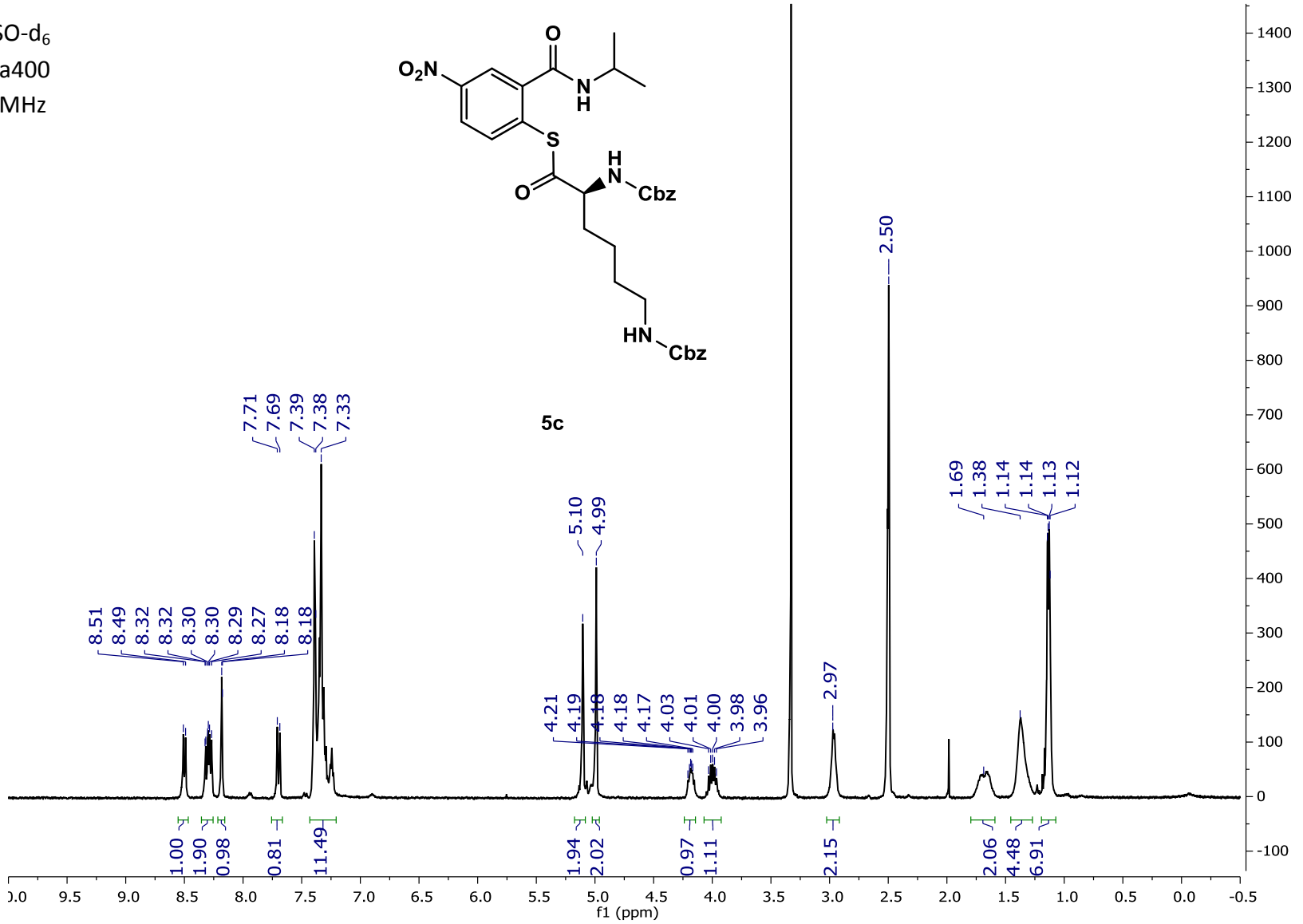
5b

DMSO-d_6
Inova600
151 MHz

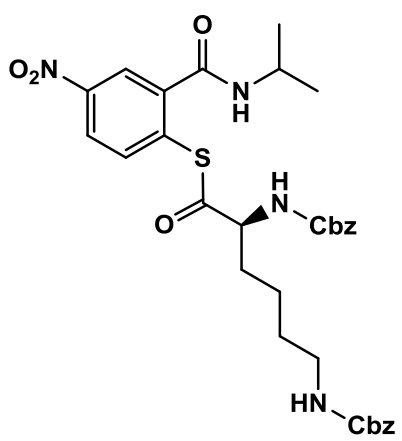


5b

DMSO-d_6
Inova400
400 MHz

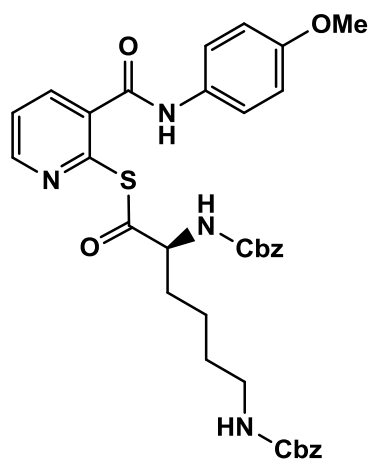


DMSO-d_6
Inova400
100 MHz



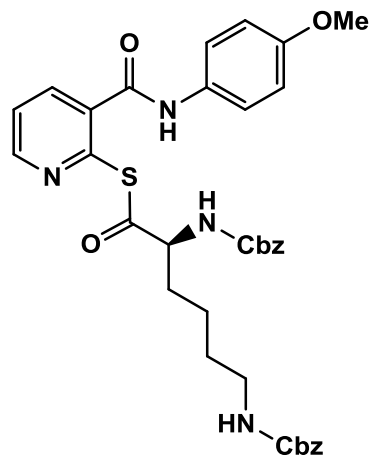
5c

Acetone-d_6
Inova600
600 MHz



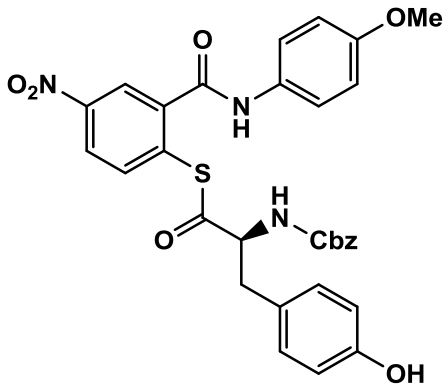
5d

DMSO-d_6
Inova600
151 MHz



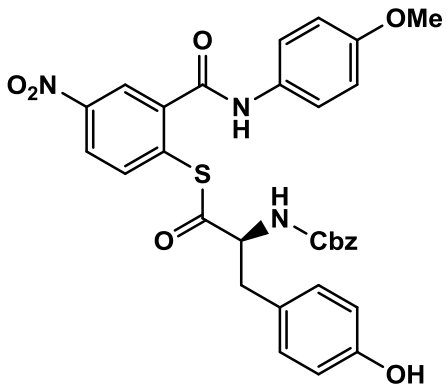
5d

DMSO-d_6
Inova600
600 MHz



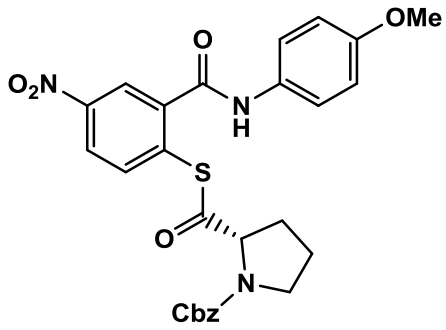
5e

DMSO-d_6
Inova600
151 MHz

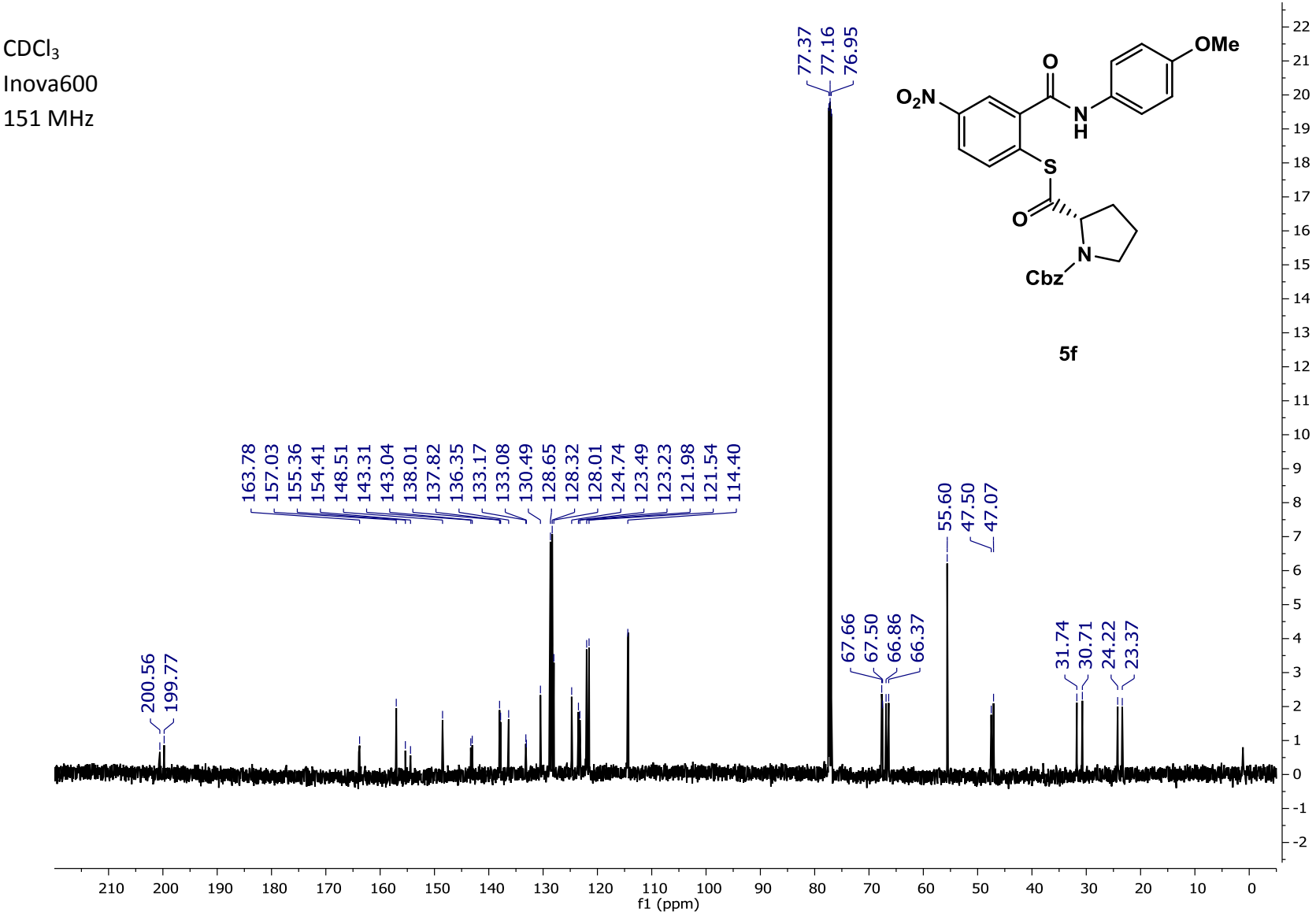


5e

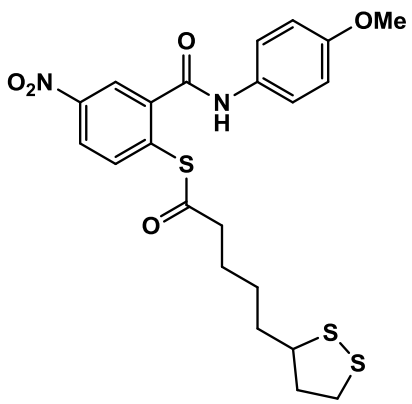
$CDCl_3$
Inova600
600 MHz



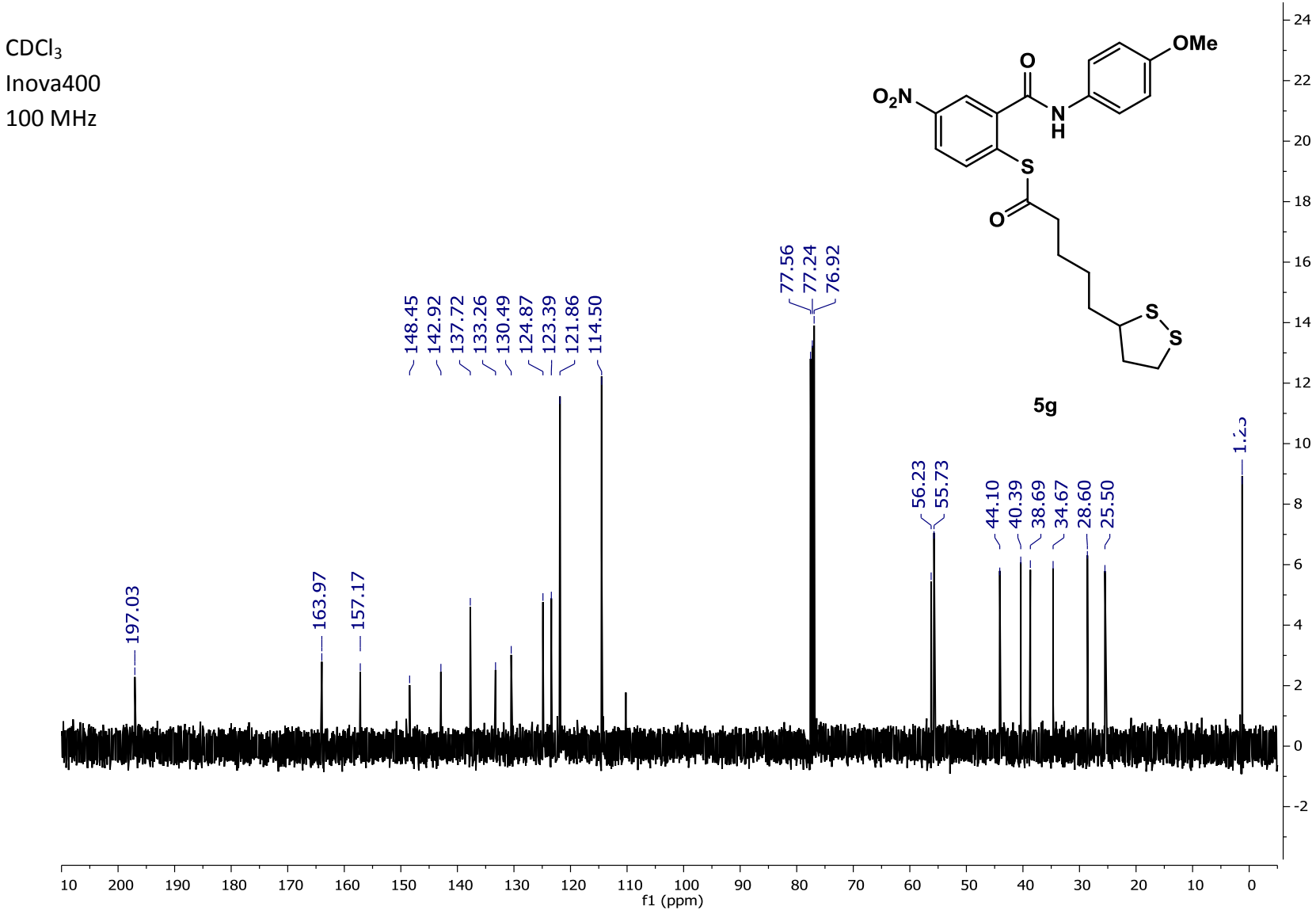
5f

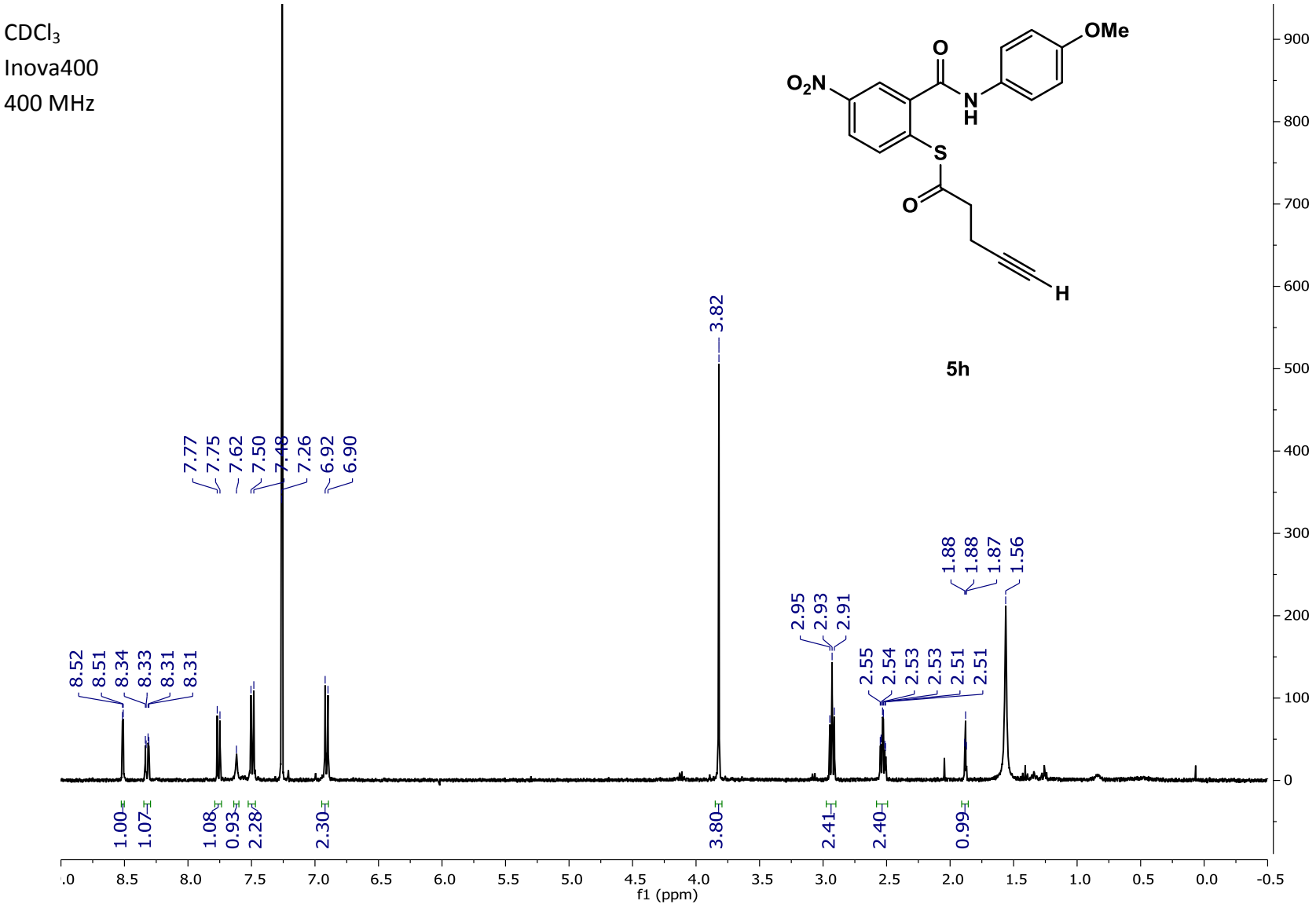

CDCl3
Inova600
151 MHz
77.37
77.16
76.95
163.78
157.03
155.36
154.41
148.51
143.31
143.04
138.01
137.82
136.35
133.17
133.08
130.49
128.65
128.32
128.01
124.74
123.49
123.23
121.98
121.54
114.40
55.60
47.50
47.07
67.66
67.50
66.86
66.37
31.74
30.71
24.22
23.37
200.56
199.77
O2N
O
N
H
OMe
S
O
N
Cbz
5f
f1 (ppm)

$CDCl_3$
Inova600
600 MHz

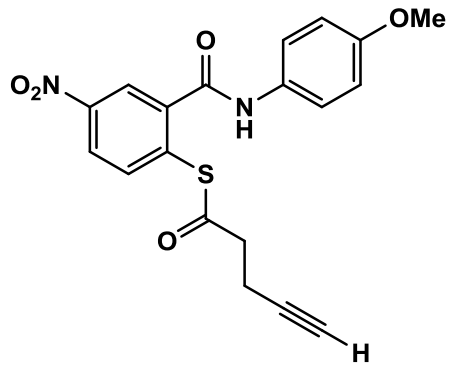


5g

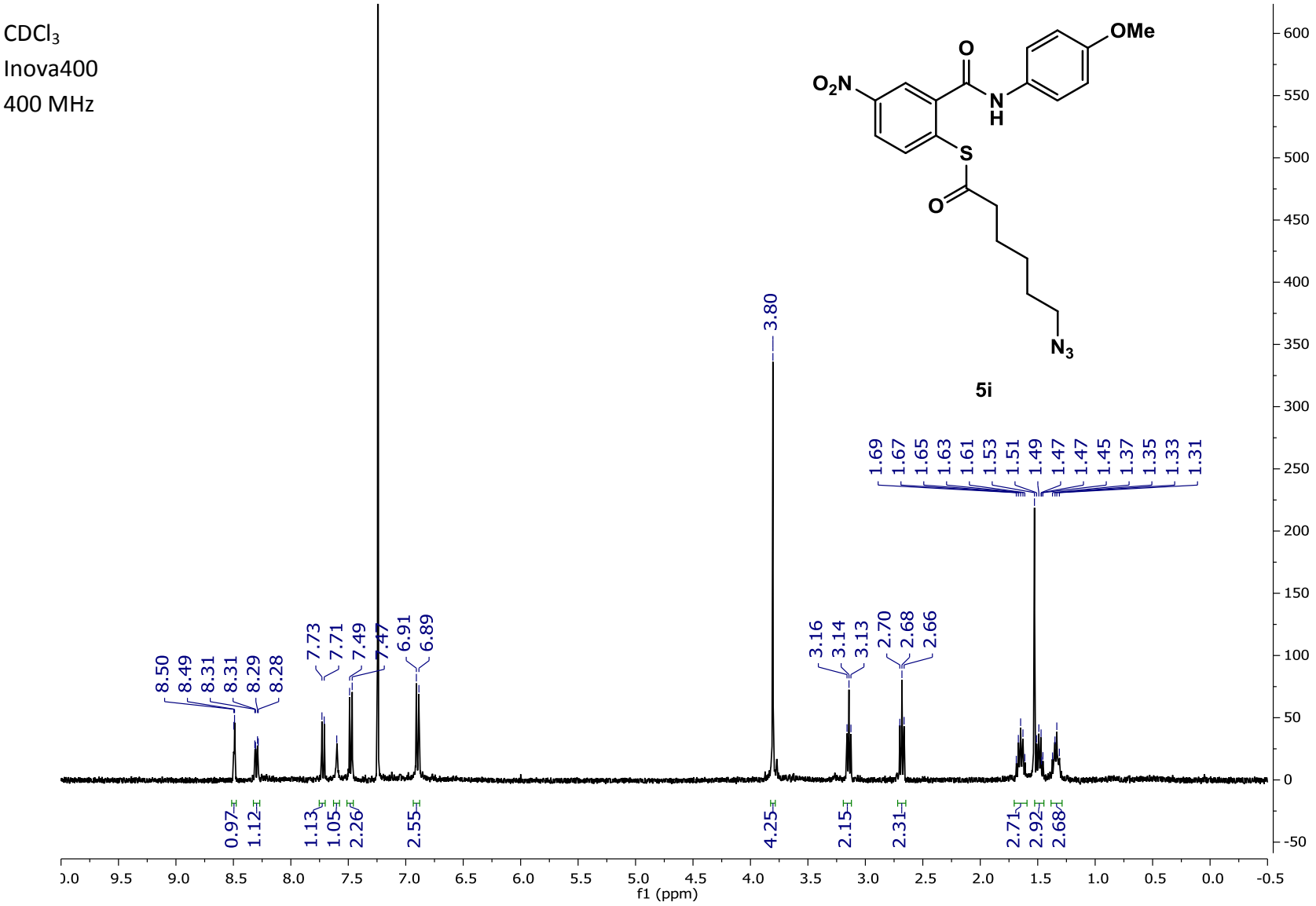

CDCl3
Inova400
100 MHz
O2N
O
N
H
OMe
S
O
S
S
5g
197.03
163.97
157.17
148.45
142.92
137.72
133.26
130.49
124.87
123.39
121.86
114.50
77.56
77.24
76.92
56.23
55.73
44.10
40.39
38.69
34.67
28.60
25.50
f1 (ppm)


CDCl3
Inova400
400 MHz
O2N
O
N
H
OMe
S
O
H
5h
8.52
8.51
8.34
8.33
8.31
8.31
7.77
7.75
7.62
7.50
7.48
7.26
6.92
6.90
3.82
2.95
2.93
2.91
2.55
2.54
2.53
2.53
2.51
2.51
1.88
1.88
1.87
1.56
1.00
1.07
1.08
0.93
2.28
2.30
3.80
2.41
2.40
0.99
f1 (ppm)

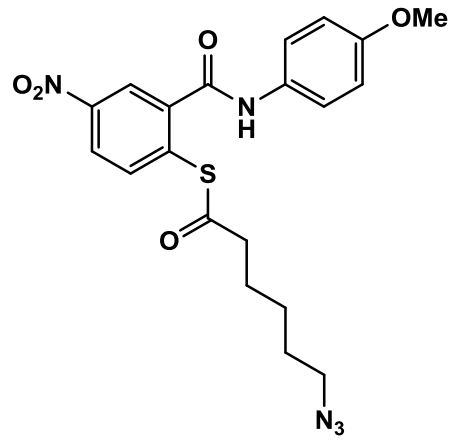
DMSO-d_6
Inova600
151 MHz



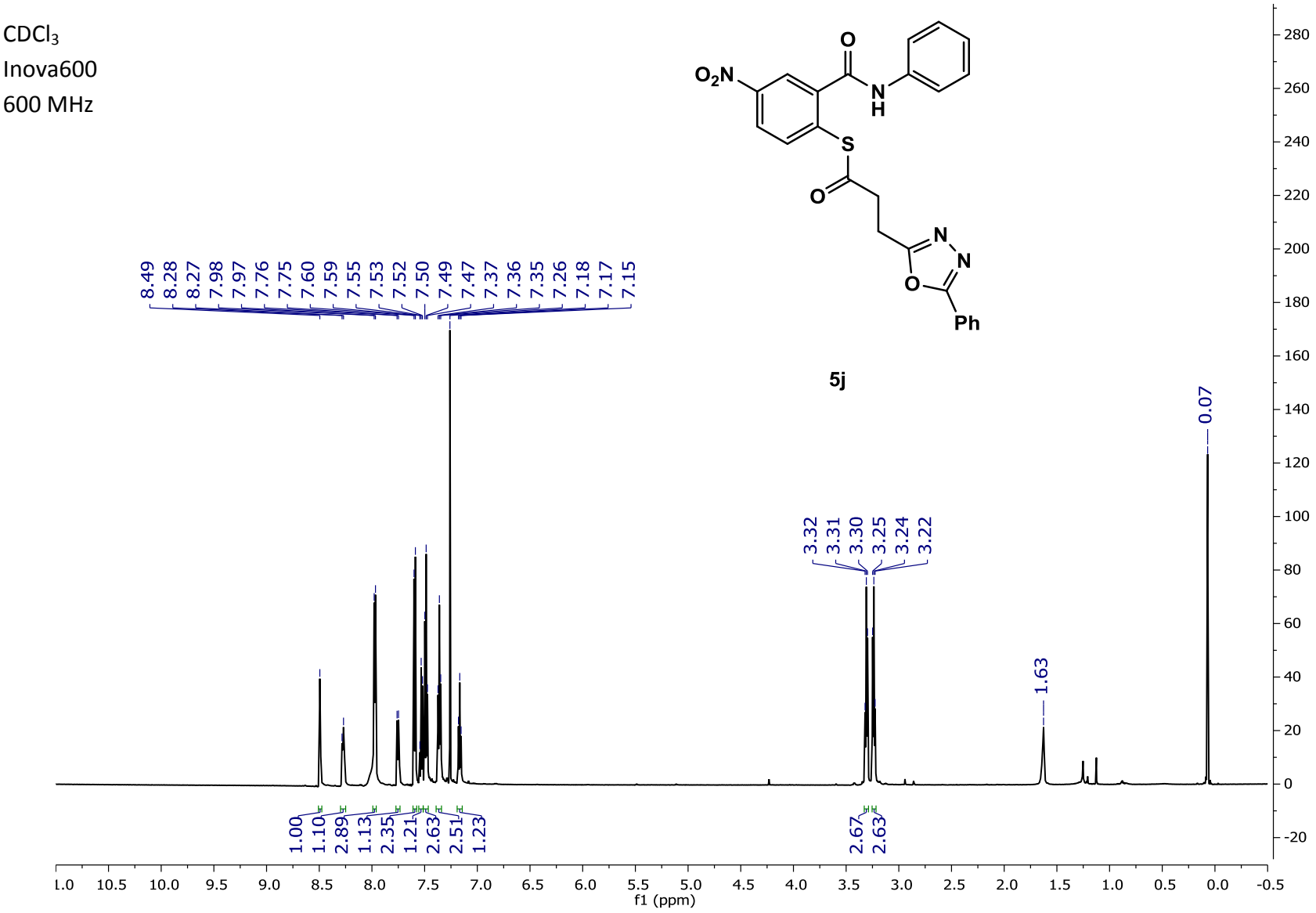
5h


CDCl3
Inova400
400 MHz
O2N
O
N
H
OMe
S
O
N3
5i
8.50
8.49
8.31
8.31
8.29
8.28
7.73
7.71
7.49
7.47
6.91
6.89
3.80
3.16
3.14
3.13
2.70
2.68
2.66
1.69
1.67
1.65
1.63
1.61
1.53
1.51
1.49
1.47
1.47
1.45
1.37
1.35
1.33
1.31
0.97
1.12
1.13
1.05
2.26
2.55
4.25
2.15
2.31
2.71
2.92
2.68
f1 (ppm)

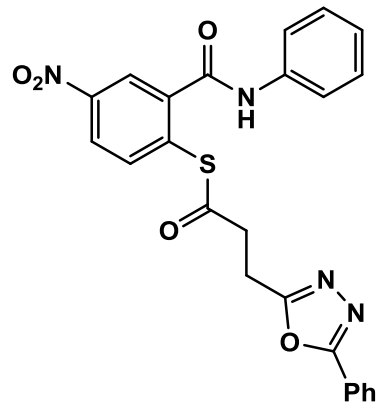
DMSO-d_6
Inova600
151 MHz



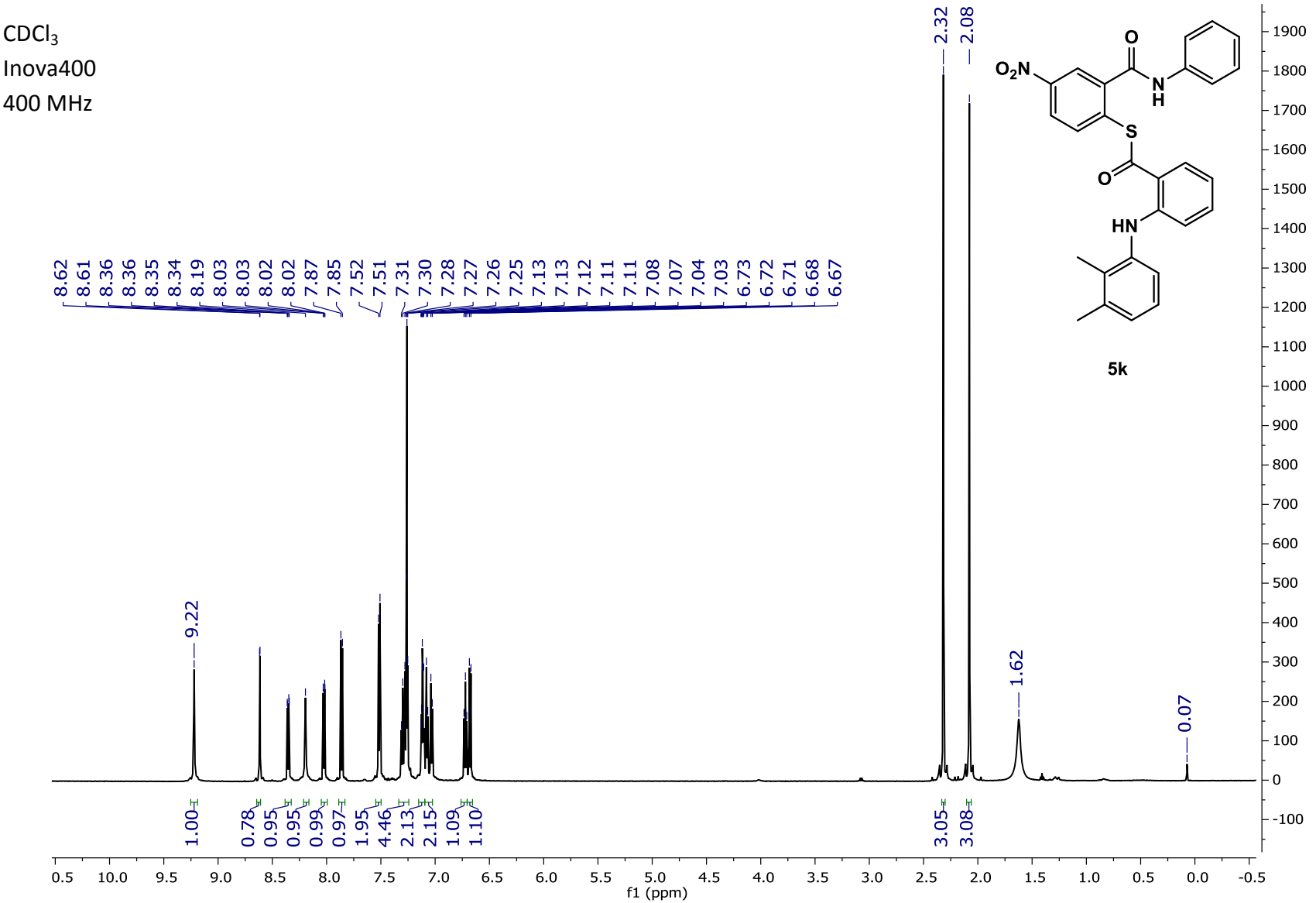
5i

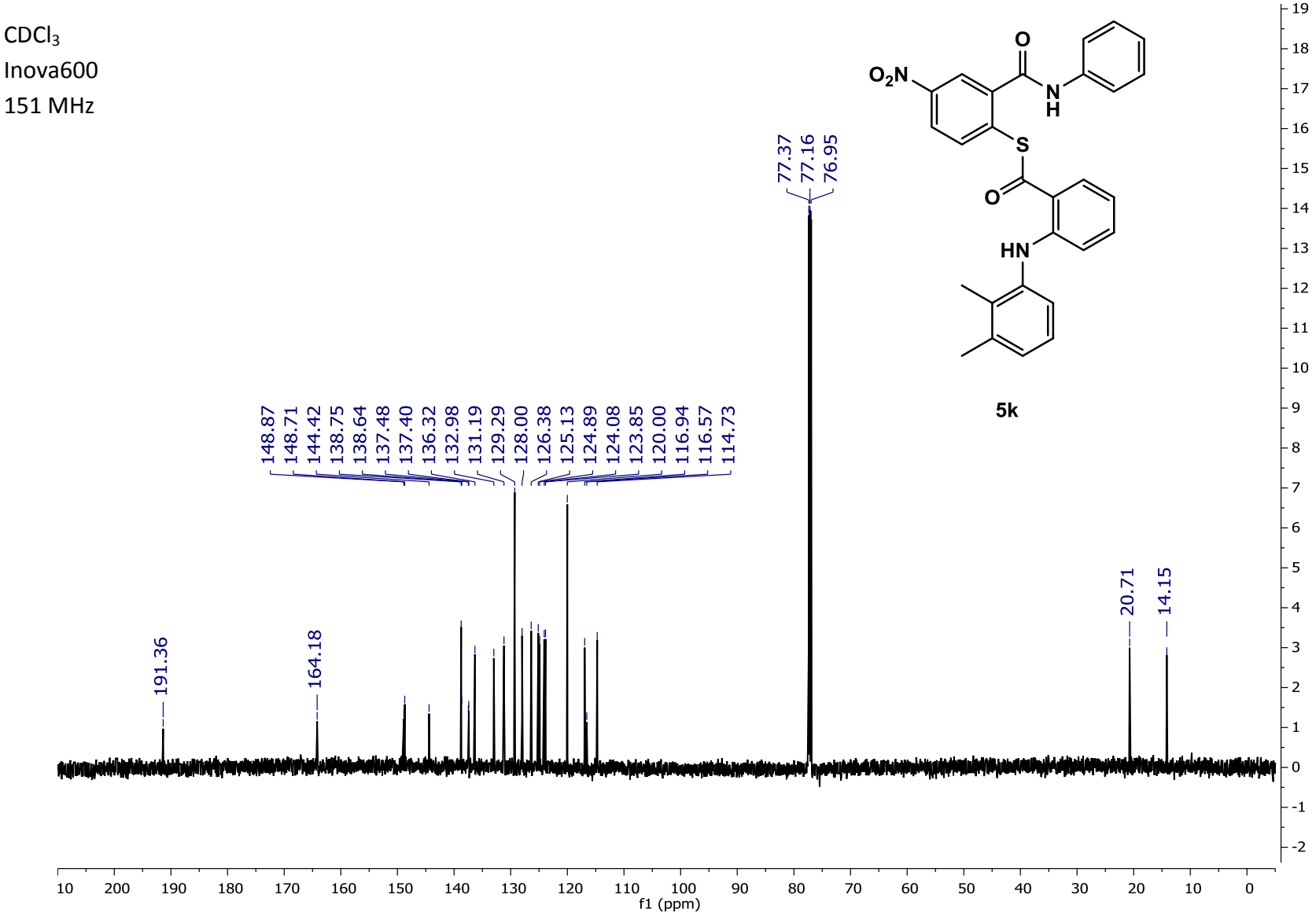

CDCl3
Inova600
600 MHz
O2N
O
N
H
S
O
N
N
O
Ph
5j
8.49
8.28
8.27
7.98
7.97
7.76
7.75
7.60
7.59
7.55
7.53
7.52
7.50
7.49
7.47
7.37
7.36
7.35
7.26
7.18
7.17
7.15
3.32
3.31
3.30
3.25
3.24
3.22
1.63
0.07
1.00
1.10
2.89
1.13
2.35
1.21
2.63
2.51
1.23
2.67
2.63
f1 (ppm)

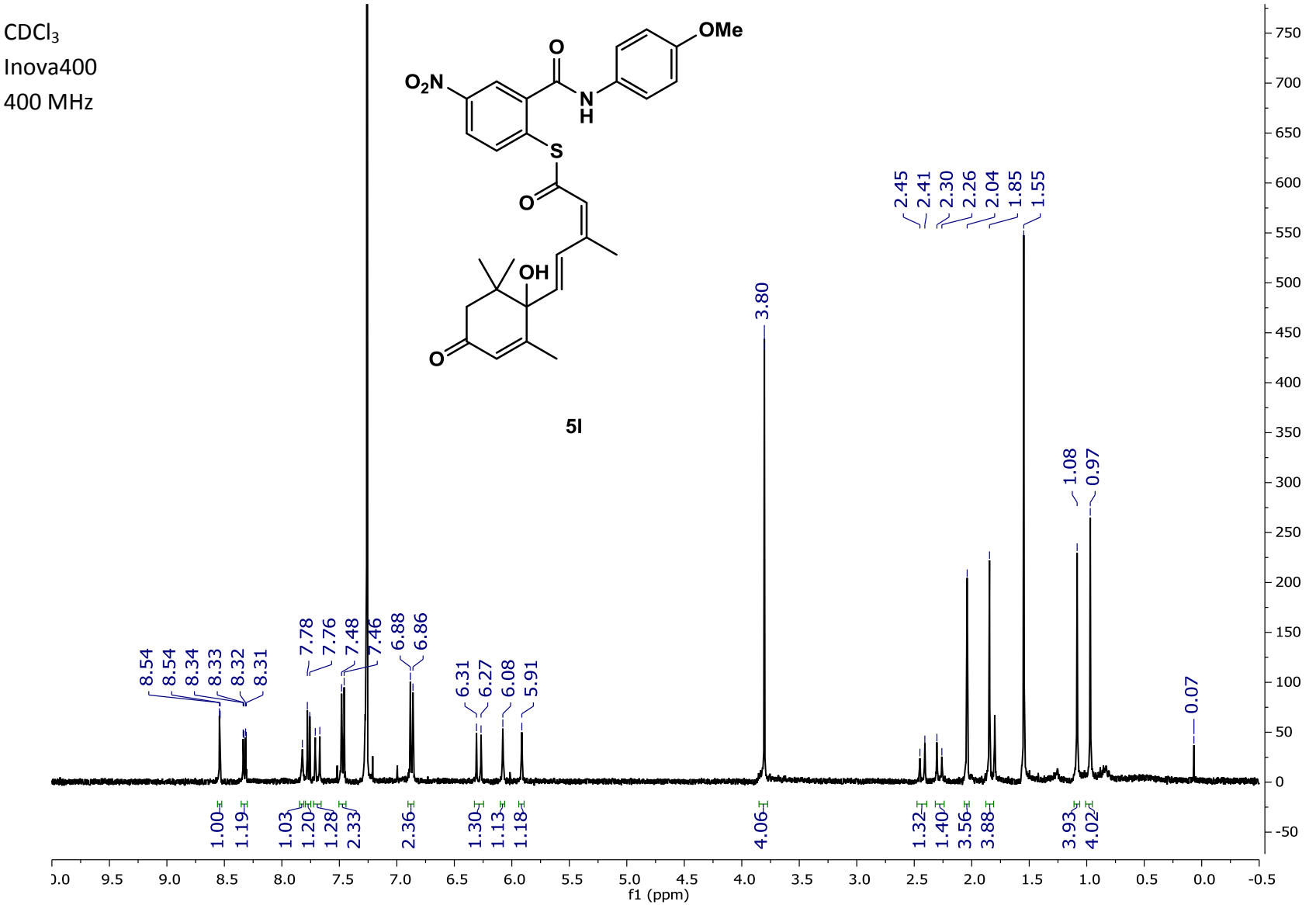
$CDCl_3$
Inova600
151 MHz



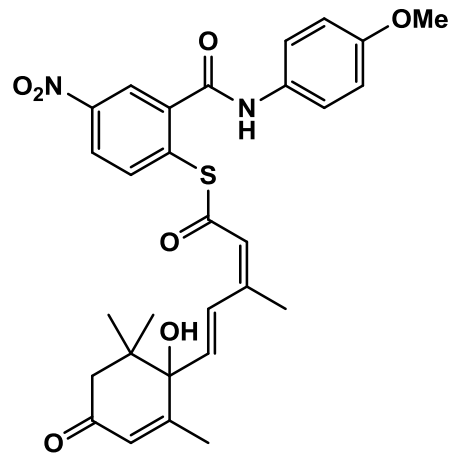
5j


CDCl3
Inova400
400 MHz
5k
f1 (ppm)

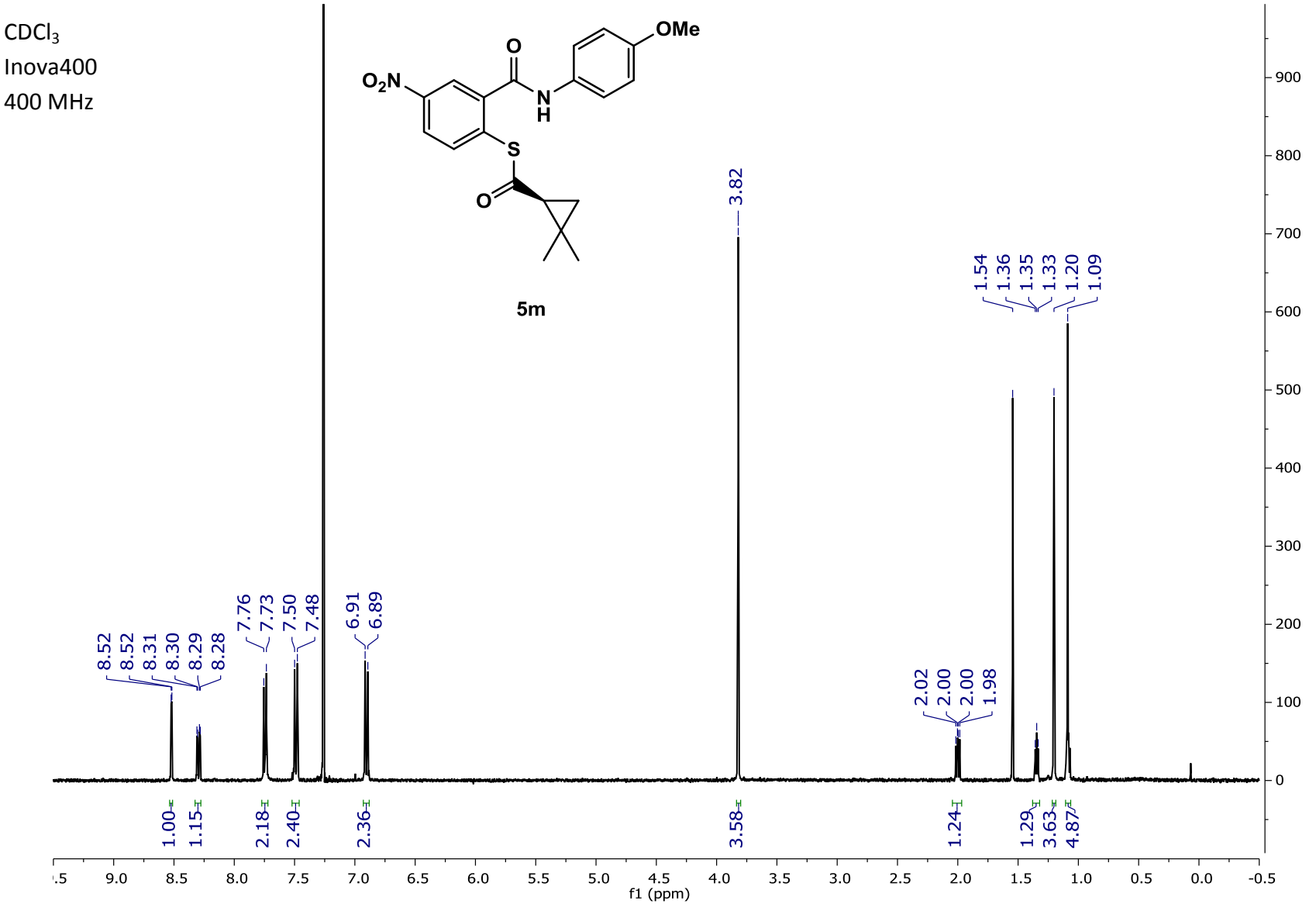

CDCl3
Inova600
151 MHz
O2N
O
N
H
S
O
HN
5k
77.37
77.16
76.95
148.87
148.71
144.42
138.75
138.64
137.48
137.40
136.32
132.98
131.19
129.29
128.00
126.38
125.13
124.89
124.08
123.85
120.00
116.94
116.57
114.73
191.36
164.18
20.71
14.15
f1 (ppm)


CDCl3
Inova400
400 MHz
O2N
O
N
H
OMe
S
O
OH
O
5l
8.54
8.54
8.34
8.33
8.32
8.31
7.78
7.76
7.48
7.46
6.88
6.86
6.31
6.27
6.08
5.91
3.80
2.45
2.41
2.30
2.26
2.04
1.85
1.55
1.08
0.97
0.07
1.00
1.19
1.03
1.20
1.28
2.33
2.36
1.30
1.13
1.18
4.06
1.32
1.40
3.56
3.88
3.93
4.02
f1 (ppm)

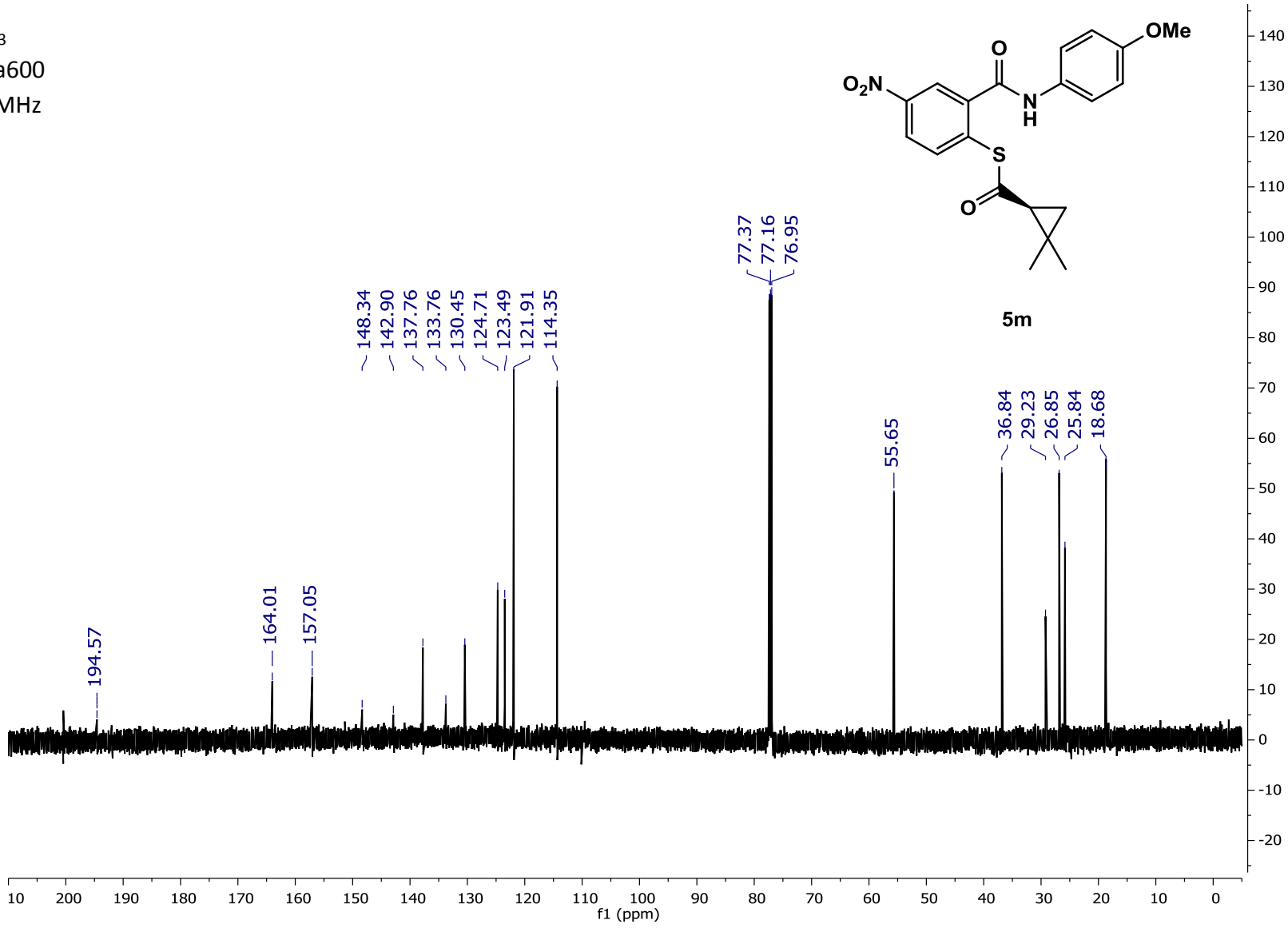
DMSO-d_6
Inova600
151 MHz



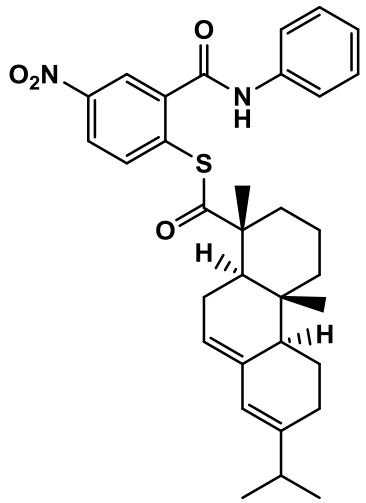
5l


CDCl3
Inova400
400 MHz
O2N
O
N
H
OMe
S
O
5m
8.52
8.52
8.31
8.30
8.29
8.28
7.76
7.73
7.50
7.48
6.91
6.89
3.82
1.54
1.36
1.35
1.33
1.20
1.09
2.02
2.00
2.00
1.98
1.00
1.15
2.18
2.40
2.36
3.58
1.24
1.29
3.63
4.87
f1 (ppm)

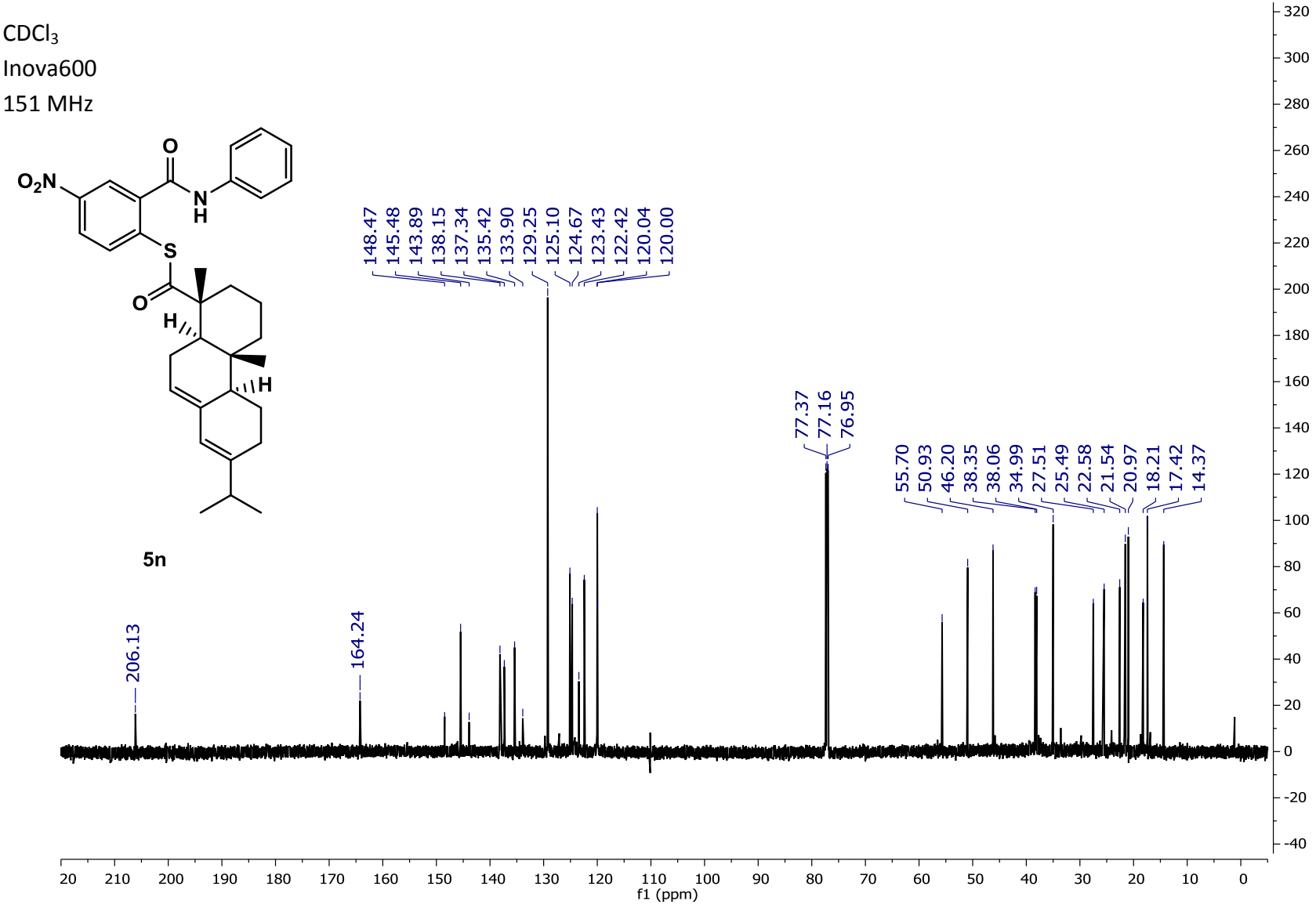
$CDCl_3$
Inova600
151 MHz



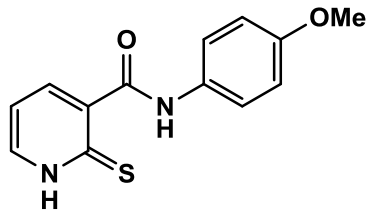
$CDCl_3$
Inova600
600 MHz



5n

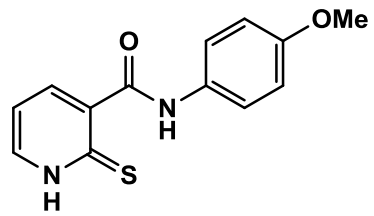

CDCl3
Inova600
151 MHz
O2N
O
N
H
S
O
H
H
5n
148.47
145.48
143.89
138.15
137.34
135.42
133.90
129.25
125.10
124.67
123.43
122.42
120.04
120.00
77.37
77.16
76.95
55.70
50.93
46.20
38.35
38.06
34.99
27.51
25.49
22.58
21.54
20.97
18.21
17.42
14.37
206.13
164.24
f1 (ppm)

DMSO-d_6
Inova400
400 MHz



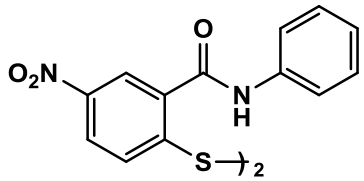
12

DMSO-d_6
Inova600
151 MHz



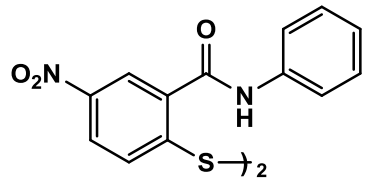
12

DMSO-d_6
Inova600
600 MHz



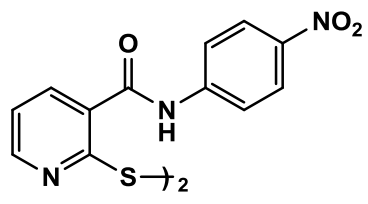
14

DMSO-d_6
Inova600
151 MHz



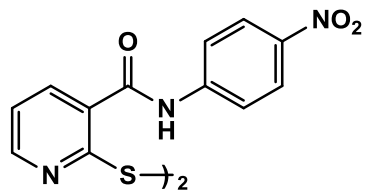
14

DMSO-d_6
Inova400
400 MHz



31

DMSO-d_6
Inova600
151 MHz



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