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Stephen Wilson Date

Synthesis and Reactivity of Benzo[1,3,2]dithiazole 1,1-dioxides: Implications in Acylative Redox Dehydration

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Synthesis and Reactivity of Benzo[1,3,2]dithiazole 1,1-dioxides: Implications in Acylative Redox Dehydration

By

Stephen Wilson
B.S., University of Richmond, 2012

Advisor: Lanny S. Liebeskind, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
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Master of Science
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Abstract

Synthesis and Reactivity of Benzo[1,3,2]dithiazole 1,1-dioxides: Implications in Acylative Redox Dehydration

By Stephen Wilson

Benzo-1,3,2-dithiazole-1,1-dioxides (BDTs) are novel 5-membered heterocycles bearing an internal sulfur-nitrogen bond and are structurally similar to benzoisothiazolones (BiTs). A new method for the synthesis of these molecules was developed and a series of BDTs were made and studied as potential BiT alternatives in organocatalytic redox-coupled, metal catalyzed dehydrative bond constructions. The BDTs could be synthesized via generation of a sulfenyl chloride from *o*-benzylthiobenzene sulfonamide followed by condensation with the adjacent nitrogen. The BDTs could react with carboxylic acids in a redox dehydration with triphenylphosphine or triethyl phosphite to generate BDT-derived thioesters. This reaction worked well with aliphatic acids and to a lesser extent with aromatic acids. These thioesters could then undergo coupling with boronic acids to give S-arylated products, but the reaction between BDT-derived thioester and amine gave only hydrolysis of the thioester with no desired amide formation. Finally, the reduced form of BDT, the *o*-mercaptobenzene sulfonamide, could be oxidized back to the BDT at temperatures above 100 ^{o}C in the presence of a variety of oxidants. Future work will be de done to assess the utility of BDTs as organocatalysts in redox dehydration reactions as well as explore other alternative applications.

Synthesis and Reactivity of Benzo[1,3,2]dithiazole 1,1-dioxides: Implications in Acylative Redox Dehydration

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Abbreviations

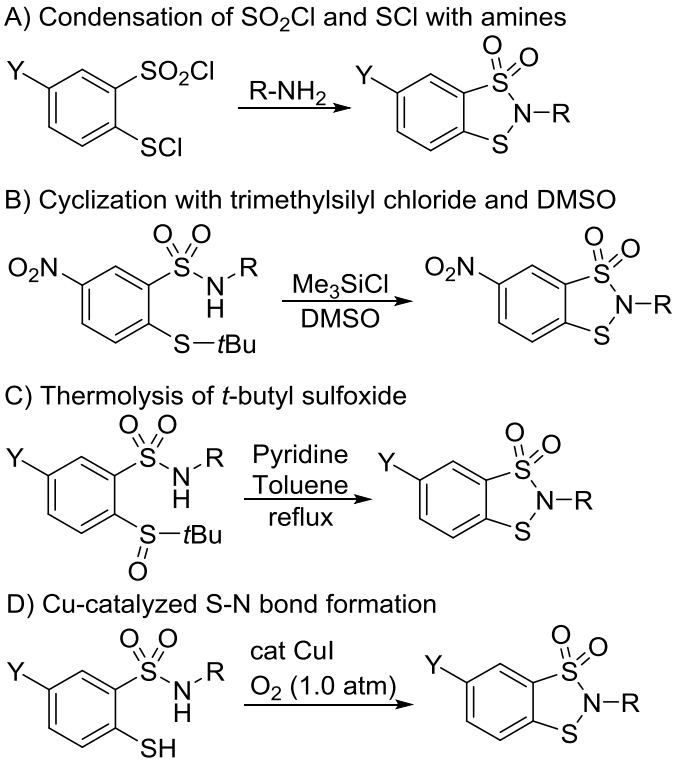
APCI	atmospheric-pressure chemical ionization
Ar	argon
BDT	benzo-1,3,2-dithaizole-1,1-dioxide
BiT	benzoisothiazolone
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bpy	bipyridine
Calcd	calculated
Cbz	carboxybenzyl
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
CuI	copper iodide
CuMeSal	copper(I) 3-methylsalicylate
d	doublet
DCM	dichloromethane
dd	doublet of doublets
DIPEA	N,N-diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d6	deuterated dimethyl sulfoxide
dq	doublet of quartets
ESI	electrospray ionization
EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
h	hour(s)
HCl	hydrochloric acid
HIV	human immunodeficiency virus
HRMS	high resolution mass spectroscopy
Hz	hertz
i-Pr	isopropyl
IR	infrared
J	coupling constant
KOH	potassium hydroxide
lit.	literature
Lys	lysine
M	molarity
m	multiplet
Me	methyl
mg	milligram(s)
$MgSO_4$	magnesium sulfate
MHz	megahertz
mL	milliliter(s)
mmol	millimole(s)

m.p.	melting point
µL	microliter(s)
N	nitrogen
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
NMI	N-methylimidazole
NMR	nuclear magnetic resonance
Nuc	nucleophile
$OP(OEt)_3$	triethylphosphate
Ph	phenyl
PhMe	toluene
PIFA	bis(trifluoroacetoxy)iodobenzene
$P(OEt)_3$	triethylphosphite
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet
rt	room temperature
s	singlet
S	sulfur
sept	septet
sext	sextet
SO_2Cl_2	sulfuryl chloride
δ	chemical shift
t	triplet
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride

Introduction

Benzoisothiazolones (BiTs) are well known 5-membered heterocycles containing an internal sulfur-nitrogen bond and are widely used in pharmaceutical and agricultural industries. In particular, it has been shown that specific BiT derivatives exhibit antifungal and antimicrobial activities,[1,2] can selectively inhibit phosphatase enzymes,[3,4] and possess anti-HIV and anti-cancer properties.[5,6] Because of their biological importance, the synthesis of activity of BiTs has been extensively studied.

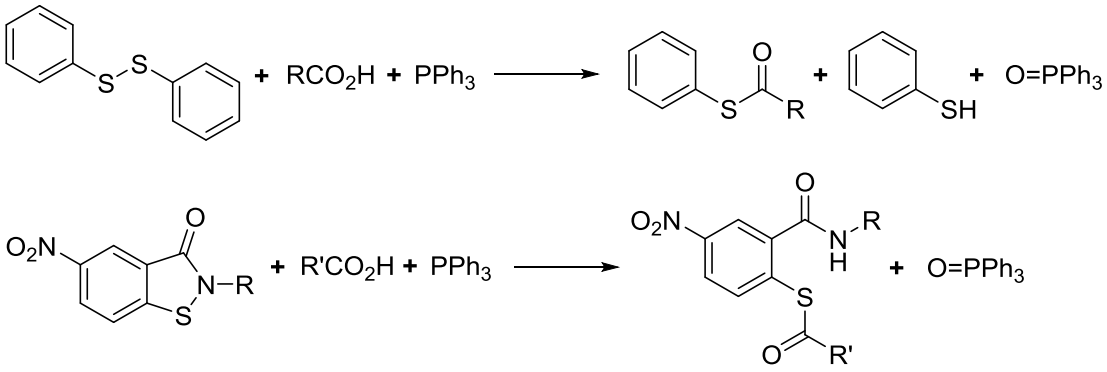
Figure 1. Select methods for the synthesis of benzoisothiazolones



As illustrated in Figure 1, a number of methods to construct benzoisothiazolones have been reported. These methods include: (a) condensation of 2-(chlorocarbonyl)phenyl hypochlorothioite and amine,[7] (b) treatment of 2-(t-butylthio)-5-nitrobenzamide with trimethylsilyl chloride,[8] (c) cyclization of *t*-butyl sulfoxides[9] and (d) copper-catalyzed intramolecular S-N bond formation.[10] While these synthetic methods often involve multiple steps

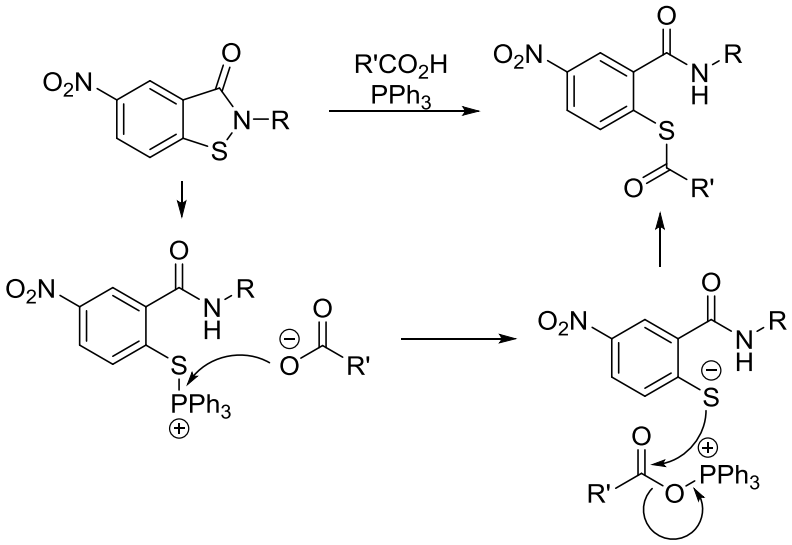
and some wasted reagent, benzoisothiazolones can be obtained in high yields and with a wide variety of structural variation. Further, BiTs are synthetically useful molecules that can react with reducing agents to give *o*-mercaptobenzamides,[11] thiols to give unsymmetrical disulfides,[12,13] as well as a variety of phosphorus, carbon and sulfur nucleophiles to give other products.[11]

Scheme 1. Formation of thioesters as described by Mukaiyama (top) and Srogl (bottom)



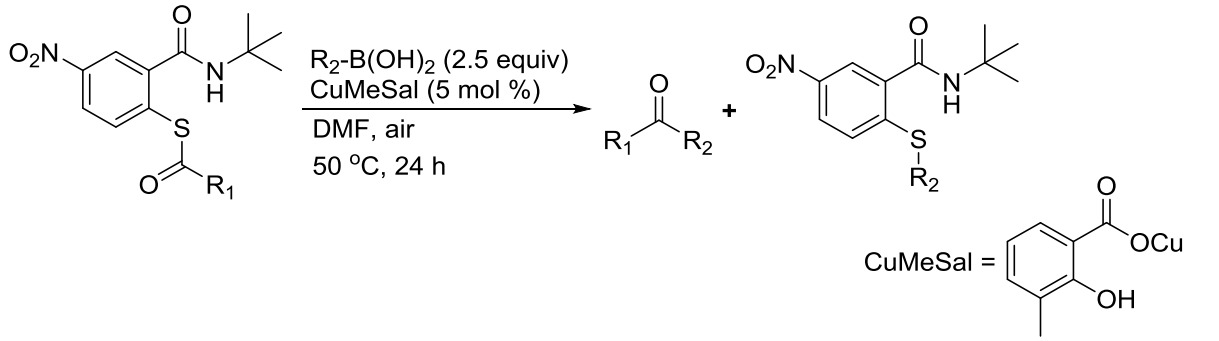
Another interesting transformation of BiTs has been described by Villalbos[8] and then Srogl.[14] In 2008, she reported the conversion of BiTs into thioesters via redox dehydration of carboxylic acids using an organophosphine reductant. This reaction is analogous to the thioesterification of disulfides previously described by Mukaiyama.[15] A direct comparison of these two reactions is given in Scheme 1. Both are redox reactions in which sulfur is reduced to a thiol which goes on to generate thioester by reacting with an acyloxyphosphonium intermediate and resulting in oxidation of a phosphine to phosphine oxide (Scheme 2). The major disadvantage in Mukaiyama's procedure is the loss of half of the disulfide as thiol. The BiT reaction does not suffer from this drawback, and as we will see, the BiT-derived thioesters are valuable starting materials or intermediates in organic synthesis.

Scheme 2. Mechanism for thioesterification of BiTs

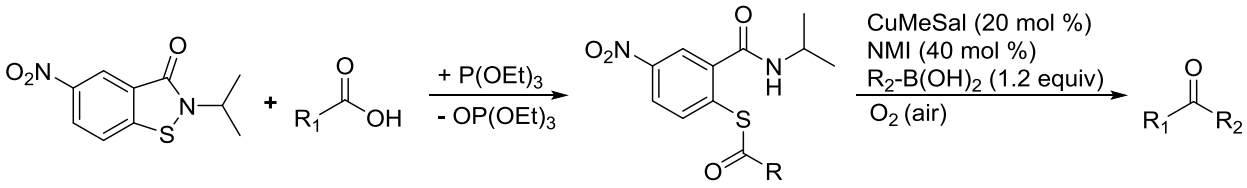


One interesting application in which BiT-derived thioesters are important is the copper catalyzed aerobic ketone synthesis from thioesters and boronic acids as described by Liebeskind.[16] In this reaction, ortho mercaptobenzamides are involved in a coupling reaction with boronic acids to synthesize a variety of peptidyl-based and other synthetically useful ketones (Scheme 3).[17] A major limitation of this procedure is the need for a sacrificial equivalent of boronic acid in order to trap (as a thioether) any thiolate generated under the reaction conditions. This drives the reaction forward by facilitating the release of the copper catalyst that was previously tied up as a stable copper thiolate. As a result, a full equivalent of the S-arylated ortho mercaptobenzoic acid amide is obtained as an undesired side product. In an effort to overcome this limitation, the Liebeskind group became interested in the oxidative recycle of ortho mercaptobenzoic acid amides to BiTs as a way to "internally" trap thiolate without the need for wasted reagents or the production of side products. In recent results from Matthew Lindale[18] this goal was achieved via the use of N-methylimidazole (NMI) as a ligand on copper(I) 3-methylsalicylate (CuMeSal).[19] The overall reaction is shown in Scheme 4.

Scheme 3. Aerobic coupling of thioesters and boronic acids



Scheme 4. Aerobic ketonization with recycle of BiT



The Liebeskind group now envisioned a fully catalytic protocol for dehydrative bond construction by linking thioesterification and the coupling of BiT-derived thioesters, shown in Schemes 2 and 4, through an oxidative recycle of the BiT. This reaction can also be generalized to reaction partners beyond boronic acids and the full catalytic cycle is described in Figure 2. This catalytic cycle takes advantage of BiTs as redox organocatalysts for the construction of amides, esters and ketones. The cycle begins with the generation of a BiT-derived thioester in a Mukaiyama-like dehydration as described above. Results from the Liebeskind lab have also significantly improved this protocol by replacing organophosphine reductants with triethyl phosphite. The use of triethylphosphite both eliminates the need for more reactive organophosphines and dramatically simplifies the reaction workup since P(OEt)$_3$ is converted to water soluble OP(OEt)$_3$ during the reaction. The synthesis of a variety of thioesters synthesized by this method has been described by Leighann Lam.[20] The next step consists of a reaction between the thioester and a nucleophilic reaction partner to generate the acylated product, an ortho-mercaptobenzoic acid amide, and water. The identity of the nucleophilic

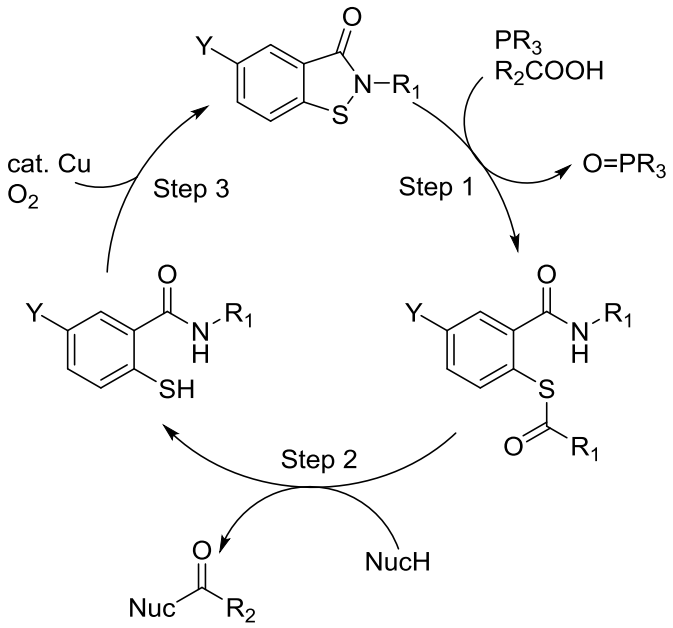
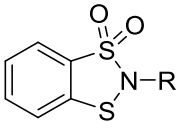


Figure 2. BiT catalyzed redox condensation. The catalytic cycle is composed of 3 steps: 1) Redox dehydration of carboxylic acid to give BiT-derived thioster 2) Generation of a new acyl bond on a nucleophilic reaction partner and 3) Copper catalyzed oxidation of ortho-mercapto benzamide to BiT

reaction partner determines the product outcome (i.e. amine, alcohols and boronic acids will give rise to amides, esters and ketones respectively), making the catalytic cycle generalizable to a wide range of substrates beyond the scope described thus far. The final step of the cycle is copper catalyzed aerobic regeneration of the BiT. To date, a variety of amides have been synthesized using this procedure, and work is underway to extend the utility of this catalytic reaction into making esters and ketones.

Figure 3. Structure of BDT

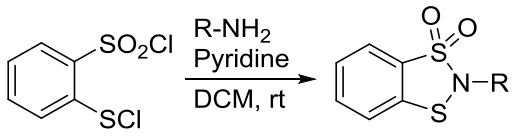


Another class of molecules bearing an internal sulfur-nitrogen bond is benzo-1,3,2-dithiazole-1,1-dioxides, here referred to as BDTs. The structure of the BDT (Figure 3) is analogous to that of BiTs except for the replacement of the amide group with a sulfonamide.

Further, since sulfonamides are stronger electron withdrawing groups, we can predict that the sulfenamide functional group (S-N bond) on the BDT is more electrophilic than that of BiTs and as a result should react more rapidly with nucleophiles. If this is true, then BDTs may be useful redox organocatalysts.

Despite their structural similarities to BiTs, a widely used and versatile molecule, surprisingly little work can be found in the literature on BDTs, and the only known information is described in two patents.[7,21] The first patent discusses the synthesis of 5-nitro-1,3,2-dithiazole-3,3-dioxides, a molecule with the same internal sulfur-nitrogen-sulfur bonds. The second describes the synthesis of N-aryl BDTs from a condensation reaction between 2-(chlorosulfonyl)phenyl hypochlorothioite and amines as shown in Scheme 5. The patent also describes BDTs as potential medicaments but does not give any specific details beyond the synthesis of a small sample of molecules. With relatively little known about BDTs, there is a lot of potential for the discovery of new and interesting chemistry. Here we describe a study of BDTs as potential alternatives to BiTs in some known catalytic systems.

Scheme 5. Condensation of 2-(chlorosulfonyl)phenyl hypochlorothioite with amine



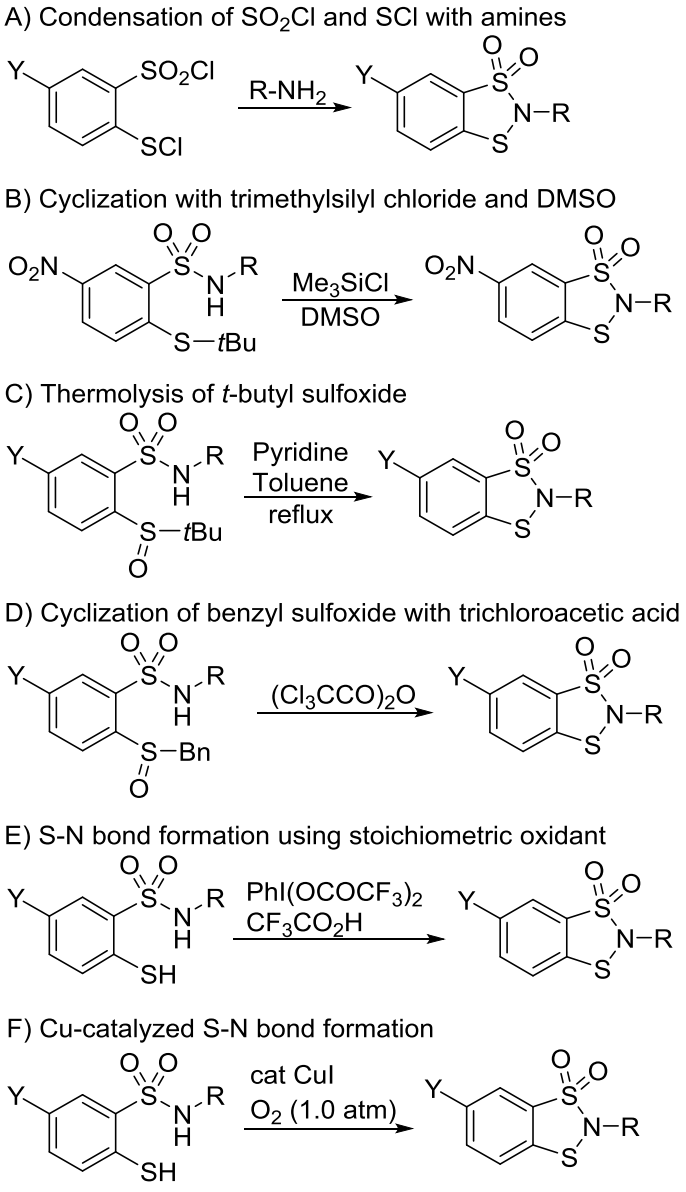
A general synthetic route to BDTs was explored, and the BDTs were then studied as redox organocatalysts in place of BiTs. The study took place in three parts: (1) thioesterification of carboxylic acids with BDTs and both phosphine and phosphite reducing agents, (2) reaction of amines and boronic acids with BDT-derived thioesters and (3) oxidative regeneration of the BDT. If each constituent step is possible with BDTs in place of BiTs, then future studies can be

done to examine the use of BDTs as redox organocatalysts for the synthesis of interesting and useful organic molecules such as amides, ketones and esters.

Results / Discussion

There are a variety of methods we could envision for the successful synthesis of BDTs. The first is the protocol described by Uhlendorf in the patent literature mentioned above.

Figure 4. Proposed methods for the synthesis of benzo-1,3,2-diathiazole-1,1-dioxide



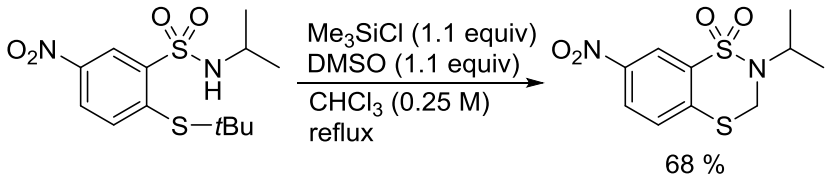
This method will begin with the synthesis of 2-(chlorosulfonyl)phenyl hypochlorothioite. From here, condensation with the appropriate amine should give BDT. Other potential methods are those described for the synthesis of BiTs, and all potential methods are outlined in Figure 4.

Benzo-1,3,2-dithiazole-1,1-dioxide Synthesis

Our studies began with the development of a new procedure for the synthesis of benzo-1,3,2-dithiazole-1,1-dioxides (BDTs). In the only reported literature procedure, a variety of N-aryl BDTs were synthesized by the reaction of 2-(chlorosulfonyl)phenyl hypochlorothioite with the respective amine in the presence of a tertiary amine base.[7] This method is similar to the condensation of 2-(chlorocarbonyl)phenyl hypochlorothioite to form the corresponding BiT (Figure 1a) and the proposed reaction is shown in Figure 4A. However, there is no literature procedure available for the synthesis of the starting sulfonyl/sulfenyl chloride, and obtaining this reagent proved difficult leading us to quickly abandon this route.

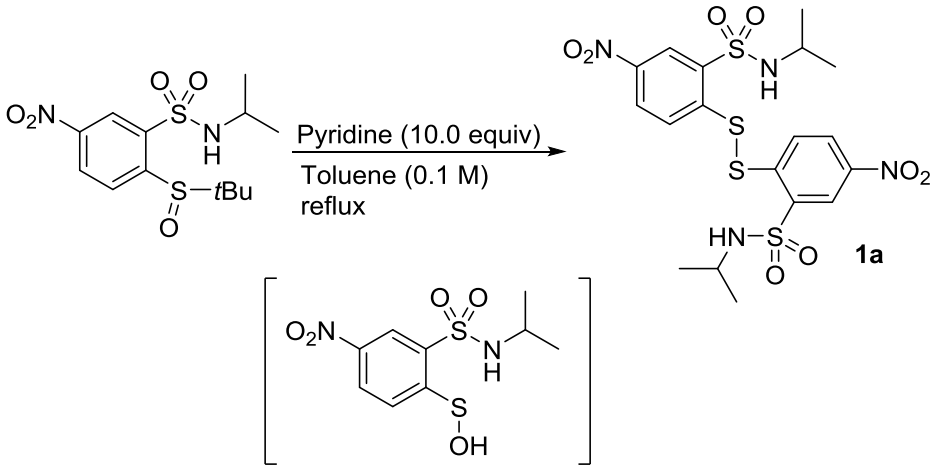
Next, we turned our attention to known procedures for the synthesis of benzisothiazolinone (BiT). In a reaction analogous to one described by Srogl,[14] cyclization of 2-(tert-butylthio)- N-isopropyl-5-nitrobenzenesulfonamide using DMSO in the presence of trimethylsilyl chloride (Figure 4B) was also unsuccessful in producing the desired BDT. At room temperature, no reaction was seen and the starting sulfonamide was re-isolated in quantitative yield. Upon heating the reaction to reflux in chloroform, the only product observed after 2 hours was 2-isopropyl-7-nitro-2,3-dihydrobenzo[e][1,4,2]dithiazine 1,1-dioxide (Scheme 6). This product could arise from the trapping of a thionium intermediate in a reaction Pummerer-like rearrangement. And in fact, the Pummerer rearrangement has been observed as a minor product in some previous BiT syntheses.[9]

Scheme 6. Pummerer rearrangement product from t-butylthiol



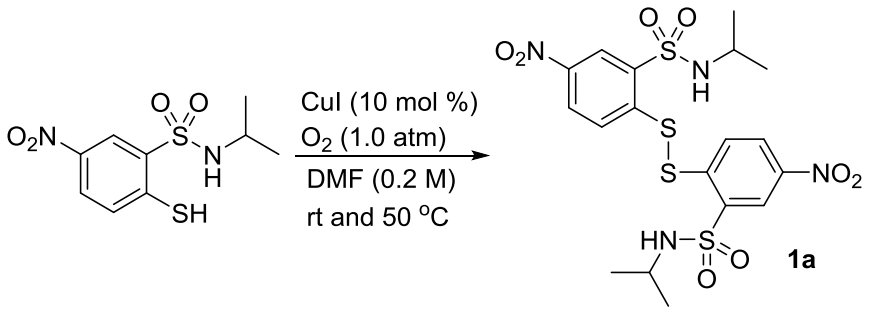
Cyclization of tert-butyl sulfoxides via heating in a pyridine/toluene mixture (Figure 4C) was also unsuccessful. The major product observed upon heating of 2-(tert-butylsulfinyl)-N-isopropyl-5-nitrobenzenesulfonamide with toluene and pyridine was disulfide **1a** (Scheme 7), presumably arising from the rapid disproportionation of an intermediate sulfenic acid formed by loss of isobutene.[9,22] The thermal cyclization of the related benzyl sulfoxide was also unsuccessful and only quantitative recovery of starting material was observed.

Scheme 7. Thermal cyclization of t-butyl sulfoxide to disulfide **1a**



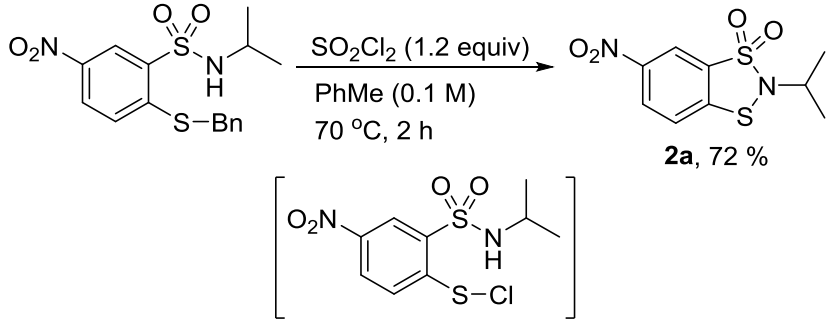
Oxidation of N-isopropyl-2-mercapto-5-nitrobenzenesulfonamide, the reduced form of BDT, in the presence of copper iodide (CuI) while open to air resulted in formation of disulfide **1a** in quantitative yield at room temperature and at 50 ^{o}C (Scheme 8). Attempts at bis(trifluoroacetoxy)iodobenzene-mediated nitrenium formation followed by subsequent ring closure resulted in quantitative recovery of starting material.[23]

Scheme 8. Cu-catalyzed oxidation of o-mercapto benzenesulfonamide to disulfide



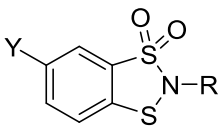
After many failed attempts at synthesizing any BDT, we instead decided to focus on procedures that would generate a sulfenyl halide that could then react in a condensation with the NH of the adjacent sulfonamide. Past research has shown that benzyl thioethers are readily converted to sulfenyl chlorides by chlorination with sulfuryl chloride (SO_2Cl_2).[13] Based on this observation, 2-(benzylthio)-N-isopropyl-5-nitrobenzenesulfonamide was reacted with SO_2Cl_2 as shown in Scheme 9. Gratifyingly, upon cooling of the reaction to 0 °C a yellow precipitate was

Scheme 9. Synthesis of BDT **2a** from benzyl thioether and sulfuryl chloride



obtained and readily recrystallized from ethanol to give clean BDT in 72 percent yield. The reaction was also attempted with other halogenating reagents used in place of SO_2Cl_2, but no improvement in reaction yield was ever observed.

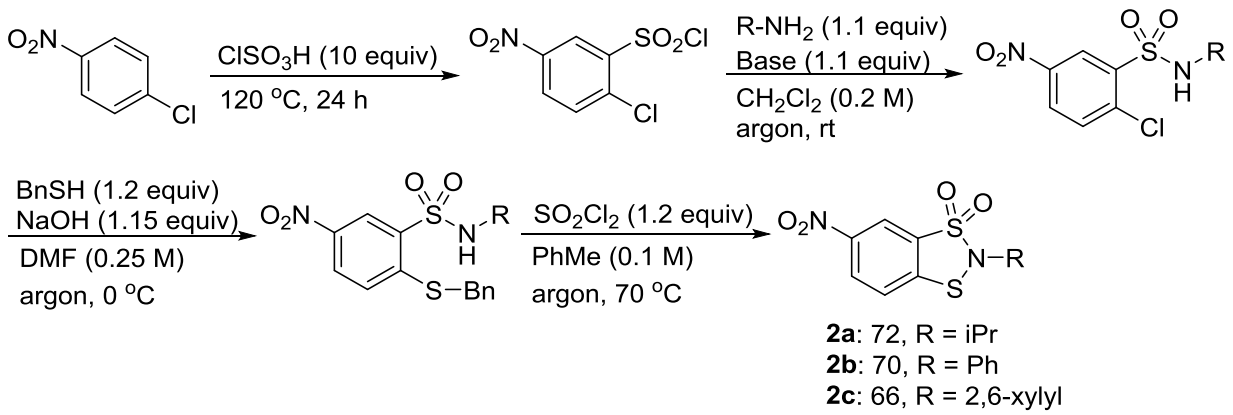
Figure 5. benzo-1,3,2-dithiazole-1,1,-dioxide library



2a : Y = NO_2, R = iPr
2b : Y = NO_2, R = Ph
2c : Y = NO_2, R = 2,6-xylyl
2d : Y = H, R = Ph
2e : Y = H, R = 2,6-xylyl
2f : Y = H, R = iPr

With a successful synthesis of the BDT in hand, a library of six BDTs with different structural variations was proposed to study as potential organocatalysts (Figure 5). A general procedure for the synthesis **2a-2c**, is shown in Scheme 10. Starting from 1-chloro-4-nitrobenzene, chlorosulfonation by heating overnight in the presence of chlorosulfonic acid furnished the desired sulfonyl chloride. While chlorosulfonic acid was used in this procedure, the same product can be obtained using a variety of sulfonating reagents described in the literature.[24,25] The desired sulfonamides were obtained by condensation of sulfonyl chloride and the appropriate amine in the presence of base. Triethylamine, pyridine or excess of the reactant amine are all good potential bases, but for the more acidic sulfonamides (i.e. those derived from aryl amines) pyridine gave the highest yields, presumably due to its slightly less basic nature. Next, aromatic substitution by benzyl thiol in the presence of either sodium or potassium hydroxide at low temperature gave the desired benzyl thioethers in good yield. Finally, oxidative ring-closure was achieved by heating in the presence of SO_2Cl_2 for one hour. As shown in Scheme 10, all of the BDTs were obtained in 66 -72 percent yield from benzyl thioether with formation of disulfide as the only major side reaction. Conducting the ring closure under a dry, inert atmosphere is crucial for N-aryl BDTs **2b** and **2c**, and when the reaction was conducted

Scheme 10. Synthesis of BDTs **2a-2c**

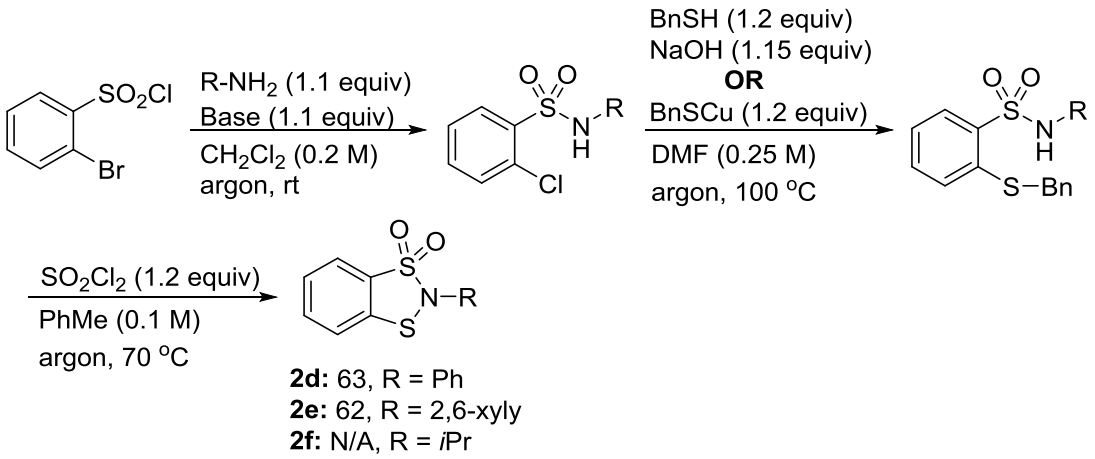


open to air the major product in those reactions was the disulfide with very little BDT formation observed.

Synthesis of aromatic ring-unsubstituted BDTs **2d**-**2f** was achieved under similar conditions (Scheme 11). Starting from commercially available 2-bromobenzenesulfonyl chloride, the desired sulfonamides were obtained by condensation with the appropriate amine and base. The optimal base in this reaction follows the same trend noted above with BDTs **2a**-**2c**. Next, aromatic substitution with benzyl thiol was achieved by heating to temperatures above 100 ^{o}C overnight in the presence of sodium hydroxide. As might be anticipated, the yield of the desired benzyl thioether was lower under these conditions than it was for the 4-nitro BDTs. However, the yield could be improved in some cases by first generating the copper benzyl thiolate by heating benzyl thiol in the presence of copper oxide, then performing the aromatic substitution using the copper salt without any added base. Finally, in the same manner as the 4-nitro BDTs, ring-closure was achieved by heating with SO_2Cl_2 under an inert atmosphere. All BDTs were purified by recrystallization in ethanol with the exception of parent N-isopropyl BDT (**2f**) which was obtained by column chromatography as an oil with impurities that could not be removed.

Due to the low purity of **2f**, it was excluded from further studies. Yields of BDT from benzyl thioether are also reported in Scheme 11.

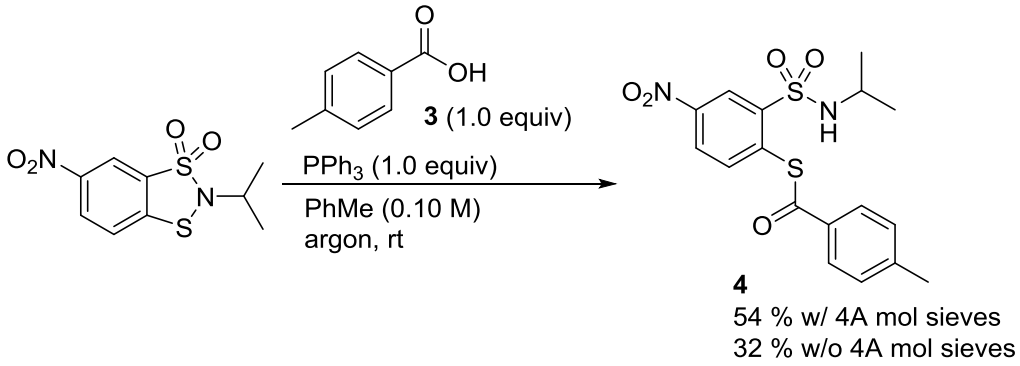
Scheme 11. Synthesis of N-substituted parent BDTs **2d-2f**



Thioesterification of BDT with Triphenylphosphine

The first step in the catalytic cycle using BiTs as organocatalysts for redox dehydration reactions is the formation of thioester from carboxylic acid, BiT and a phosphorous(III) reducing agent (step 1, Figure 2). In order to compare the reactivity of BDTs with that of BiTs, we first studied thioesterification of BDT **2a** with p-toluic acid (**3**) and triphenylphosphine as shown in Scheme 12. Triphenylphosphine was used in preliminary tests in place of the triethylphosphite because the potential for side reactions with the R groups on phosphorus is eliminated with the phosphine.

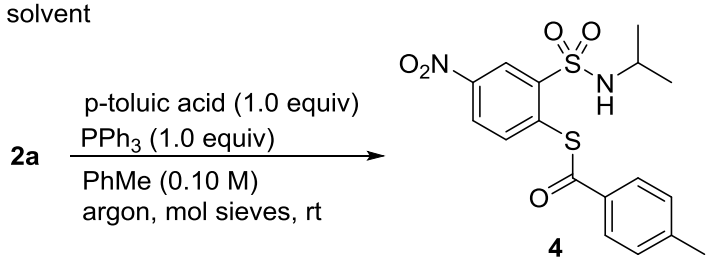
Scheme 12. Synthesis of thioester **4** from triphenylphosphine



The reaction was conducted as follows: the solids (BDT, triphenylphosphine and the carboxylic acid) were added to a small test tube and the tube was capped with a rubber septum and purged with argon. To the solids at room temperature was added toluene and the reaction was stirred and monitored by thin layer chromatography. Upon addition of solvent, an immediate change in color from yellow to orange was noted and within 2 minutes all of the starting materials were consumed. Purification by column chromatography gave the desired thioester in 32 percent yield, with the remainder of the BDT being converted to its reduced thiol form. The significant amount of thiol generated suggested the presence of enough water to quench the phosphonium intermediate that forms during the reaction. And indeed, when the reaction was run with dry toluene (less than 100 ppm water) in the presence of activated molecular sieves, the yield of **4** improved to 54 percent.

Since it was demonstrated that BDTs can react to generate thioester, we next varied solvent and temperature in order to improve the overall yield. The results of this study are shown in Table 1. A clear solvent trend was noted, as the yield improved going from polar to nonpolar

Table 1. Thioester **4** from **1a** and p-toluic acid with varying temperature and solvent



Entry	Solvent	T (C)	Yield (%)
1	DMF	25	13
2	EtOAc	25	25
3	PhMe	25	54
4	DMF	0	10
5	EtOAc	0	18
6	PhMe	0	52
7	PhMe	-20	51

solvents, with the best yield being obtained in toluene and modest to poor yields reported in ethyl acetate and DMF. However, no significant trend was seen in the range of temperatures tested. These results suggest that the best conditions for the reaction are toluene as solvent at room temperature.

With only modest success using aryl carboxylic acid to obtain thioesters, our interest turned to aliphatic carboxylic acids. Previous results with BiT chemistry suggest that aliphatic acids, and in particular amino acids, are better substrates for thioesterification. With this in mind, **2a** was reacted with Boc-protected phenylalanine as shown in Scheme 13. Gratifyingly, the reaction in toluene at room temperature gave an excellent yield of thioester. Consistent with the observations using p-toluic acid, the reaction was complete almost immediately upon addition and still had a corresponding color change from yellow to orange. Further, as noted in Scheme 13, the reaction could be performed with no additional drying precautions without a significant loss in yield.

Scheme 13. Synthesis of thioester **6a** from **5** and triphenylphosphine

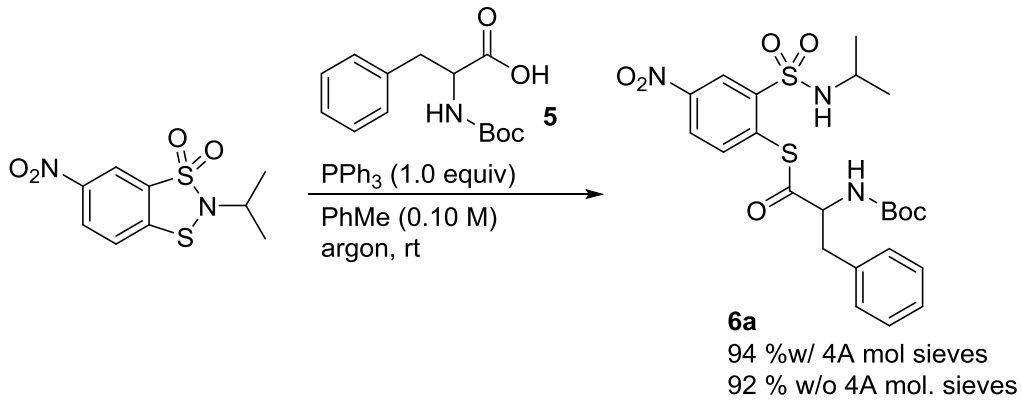
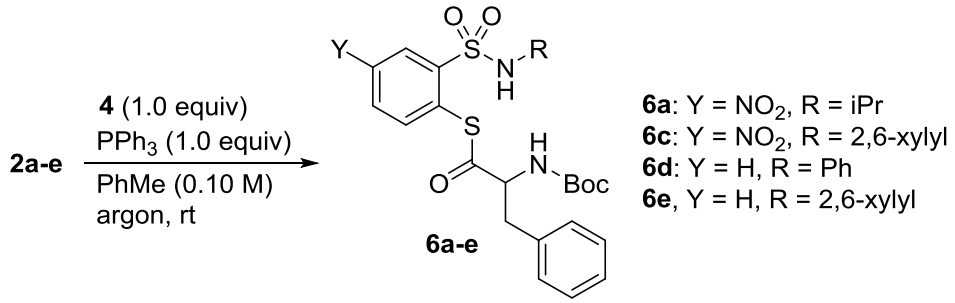


Table 2. Thioester synthesis with BDT, N-Boc-phenylalanine and triphenylphosphine



Entry	BDT	Time (min)	Yield w/ Dry Conditions (%)	Yield w/o Dry Conditions (%)
1	2a	5	94	92
3	2c	<1	86	84
4	2d	10	84	71
5	2e	8	87	74

In order to study the reactivity of BDTs, 2a was compared to 2b, 2c and 2f. Each one was subjected to the best conditions for thioesterification using triphenylphosphine and Boc-protected phenylalanine. The results are shown in Table 2. There is a clear difference in reactivity between the 4-nitro BDTs and the corresponding unsubstituted BDTs. The reaction time for every BDT in the 4-nitro series (**2a** and **2c**) is under 2 minutes, with the N-aryl BDT **2c** giving an almost instantaneous reaction. But, the corresponding parent BDTs (**2d** and **2e**) are much less reactive. Further, there is a clear trend in reactivity based on the nature of the group on nitrogen. Alkyl groups are less reactive than aryl, with the 2,6-dimethylaniline giving the fastest reaction time.

Another interesting result was observed when the reaction was run open to air versus under a dry, inert atmosphere. For the more reactive BDTs, the presence of water seems to have little effect on the yield of thioester, as the yields were unchanged when the reaction was run under dry conditions instead of open to air. However, the less reactive BDTs required dry reaction conditions to optimize the yield. This observation might be explained by the reactivity of the phosphonium intermediates formed during the reaction. The intermediates formed from

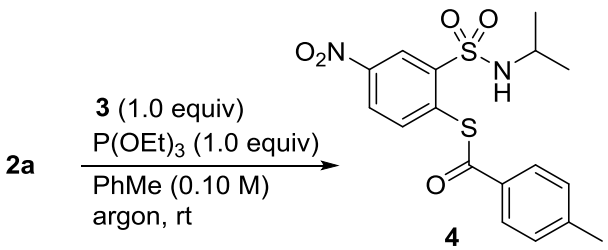
more reactive BDTs go on almost immediately upon forming to give the desired product while the less reactive BDTs give more stable intermediates, allowing more time for water to quench the reaction. This explanation is consistent with the observation that thiol was the major side product from thioesterification of less reactive BDTs.

Thioesterification of BDT with Triethyl Phosphite

With the success of triphenylphosphine as a terminal reductant for the dehydration of carboxylic acids to form BDT-derived thioesters, our attention turned to organophosphites as terminal reductants to replace triphenylphosphine. There are a number of advantages to using phosphites in place of phosphines, including atom economy, cost, and ease of removal. Ease of removal is perhaps the greatest advantage of reagents such as triethylphosphite, since they are oxidized during the reaction to phosphates which are water soluble and easily separated from the reaction by aqueous work-up.

The reaction of p-toluic acid and **2a** was studied first with triethylphosphite as the terminal reductant. To form thioester, triethylphosphite was added slowly to a solution of p-

Table 3. Thioesterification of 1a with p-toluic acid and triethyl phosphite

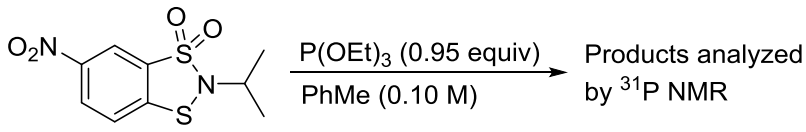


Entry	Solvent	Yield w/ Dry Conditions (%)	Yield w/o Dry Conditions (%)
1	DMF	9	0
2	EtOAc	23	11
3	PhMe	47	26

toluic acid and BDT in various solvents (0.1 M in BDT). The reaction was performed at room temperature, both with and without dry conditions. The results are shown in Table 3. Similar to the reactions with triphenylphosphine, a trend in yield with varying solvent was observed. While some product was observed under dry conditions in toluene, the yield in ethyl acetate was poor and almost no product was observed when run in DMF. Further, yields were significantly lower in all cases when the reaction was run open to air.

Unlike the reactions run with triphenylphosphine, when triethylphosphite was used as reductant, a variety of side products were observed in the crude ^{1}H NMR. Among these products were thiol, disulfide, and a range of products derived from loss of an ethyl group from the phosphite. Based on these results, the best conditions for making BDT-derived thioester from aryl carboxylic acid were in dry toluene under an inert atmosphere. This result is consistent with observations using a triphenylphosphine reductant. However, the yields are much lower with triethylphosphite due to the reactive ethyl groups, and even with dry conditions the yield of desired thioester never exceeded 50 percent.

Scheme 14. Reaction between **1a** and triethyl phosphite



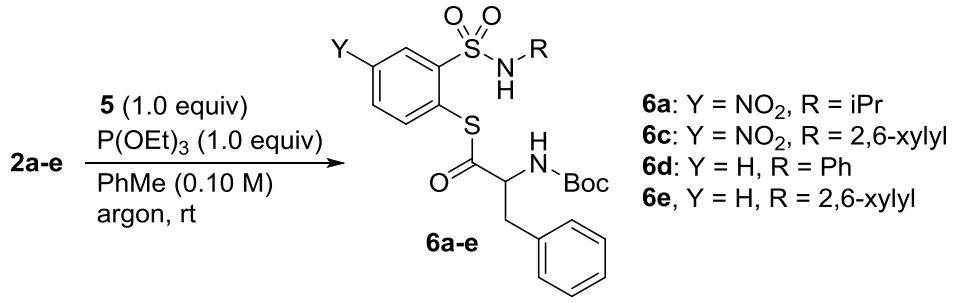
Next, in order further illuminate the cause for such low yields, phosphorous NMR was used to study the reaction of BDT **2a** and triethylphosphite in toluene without any carboxylic acid present (Scheme 14). Amazingly, even without any acid present a rapid color change was observed upon mixing BDT and triethylphosphite with toluene in an NMR tube, and the signal for triethyl phosphite was no longer evident in the ^{31}P NMR. The ^{31}P NMR spectrum instead shows the formation of a range of new products (see spectra attached on page 102). Isolation of

the products giving rise to each signal proved difficult so no characterization was performed, but even so the study still highlights a number of non-productive degradation pathways for the triethylphosphite that can explain the lowered yield of thioester.

While we were able to successfully isolate BDT-derived thioester from aromatic carboxylic acids, the best yields were still very modest and prohibitive for use in the catalytic cycle envisioned in Figure 2. So, with the overall goal being to demonstrate the use of BDTs as organocatalysts in redox dehydration reactions, we next turned to the dehydration of aliphatic carboxylic acids in an effort to improve product yield.

As a direct comparison to triphenylphosphine mediated thioesterification of aliphatic carboxylic acids, we next studied thioesterification of N-Boc-phenylalanine with triethylphosphite. The outcomes from thioesterification of the series of BDTs with N-Boc-phenylalanine are shown in Table 4. As expected, the yield of thioester when the reaction was run open to air was only modest. However, under dry conditions yields were improved for all thioesters although the yields are still considerably better when the reaction is run with triphenylphosphine.

Table 4. Thioester synthesis with BDT, N-Boc-phenylalanine and triethyl phosphite



Entry	BDT	Time (min)	Yield w/ Dry Conditions (%)	Yield w/o Dry Conditions (%)
1	2a	<1	79	41
3	2c	<1	61	32
4	2d	<1	64	28
5	2e	<1	66	23

Finally, in order to demonstrate the importance of running these reactions under the strict exclusion of water, the thioesterification of BDT **2a** with N-Boc-phenylalanine was studied by ^{31}P NMR. The respective NMR spectra are shown in Figure 6. Clean conversion of triethylphosphite to triethylphosphate can be seen in the top spectrum, corresponding to the reaction under dry conditions. Likewise, a number of phosphorous containing products that are not triethyl phosphate can be seen in the bottom spectrum, corresponding to the reaction run open to air. These results further support the conclusion that water is detrimental to the reaction and can give rise to non-productive conversion of the phosphite into a range of undesired side products.

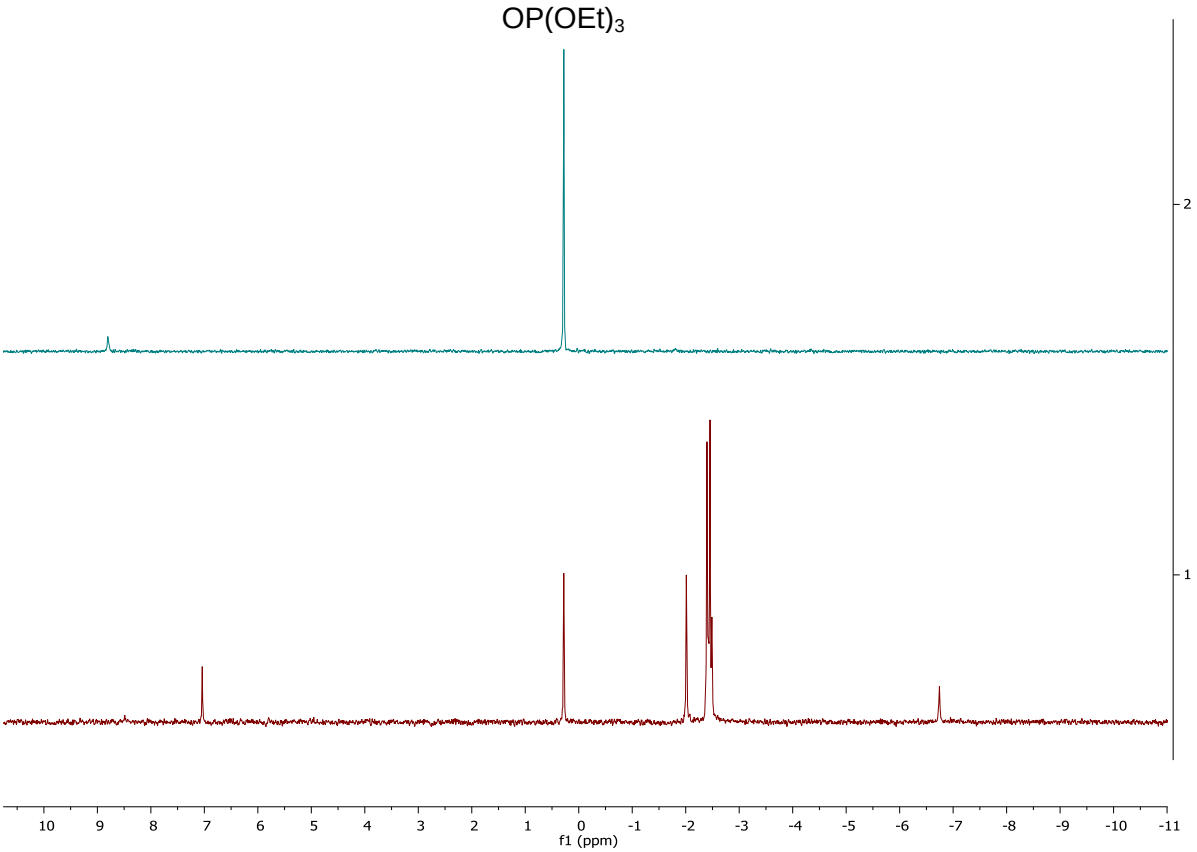


Figure 6. ^{31}P NMR from thioesterification of 1a. Clean conversion of triethyl phosphite to triethylphosphate can be seen when run under dry conditions (top) but a variety of side products form when run open to air (bottom)

Taken together, the results suggest that the dehydration of carboxylic acids in the presence of either triphenylphosphine or triethylphosphite can be optimized to give good yields of BDT-derived thioesters. In the case of aromatic carboxylic acids, thioesters could only be obtained when triphenylphosphine was the reducing agent, while aliphatic acids gave suitable yields with triphenylphosphine and the entire series of BDTs tested as well as with triethylphosphite and less reactive BDT **2a**. As previously discussed, the ideal conditions for thioesterification were in toluene, at room temperature and under a dry, inert atmosphere and reactions are complete within minutes. Having confirmed that BDTs can react to give thioesters in a manner analogous to BiTs, our attention was next turned to the study of the final two steps of the catalytic cycle, namely reaction of BDT-derived thioester to give an acylated product (i.e. amides, esters, ketones) and oxidation of the resulting thiol back to the BDT.

Reaction of BDT-Derived Thioesters

The second step in BDT-catalyzed redox dehydrations (step 2, Figure 2) is the reaction of BDT-derived thioester with a nucleophile to give the desired product by generating a new acyl bond as well as the reduced form of the BDT (*o*-mercaptobenzene sulfonamides will be referred to as “thiol”). As previously discussed, boronic acids, amines and alcohols have all been utilized as nucleophiles with both catalytic and stoichiometric BiT to give ketones, amides and esters respectively. In order to compare the reactivity between BDTs and BiTs and assess the potential of BDTs as organocatalysts, we next examined the reaction of BDT-derived thioesters with both boronic acid and amine.

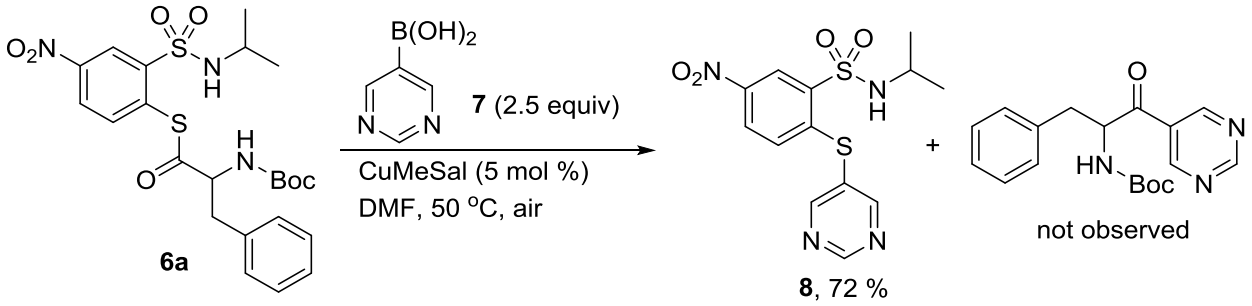
We first sought to study the ketonization of thioester and boronic acid in the presence of a copper catalyst. We began by attempting ketone formation under the conditions for second

generation Liebeskind-Srogl coupling[16] as follows: A dry test tube was charged with thioester **6a**, pyrimidine-5-boronic acid (2.5 equiv), copper(I)-3-methylsalicylate (CuMeSal, 5 mol %) and activated molecular sieves. The solids were taken up in dry DMF (0.10 M) and the reaction was heated in an oil bath at 50 ^{o}C until TLC indicated complete consumption of the starting thioester. Reaction workup involved a basic wash with saturated $NaHCO_3$ to remove unreacted boronic acid and thiol. Products were isolated by column chromatography in a 2:1 mixture of hexanes: ethyl acetate.

The results of the reaction are shown in Scheme 15. As indicated, no ketone was generated during the course of the reaction and the only major product isolated was S-arylated BDT derived from the reaction between thiol and boronic acid. This outcome is noteworthy because it demonstrates a major difference in reactivity between BiTs and BDTs. As described above and reported in the literature[16], BiT-derived thioesters react with boronic acid to give the desired ketone and the S-arylated BiT. These results suggest that BDTs do not give ketone under the same conditions.

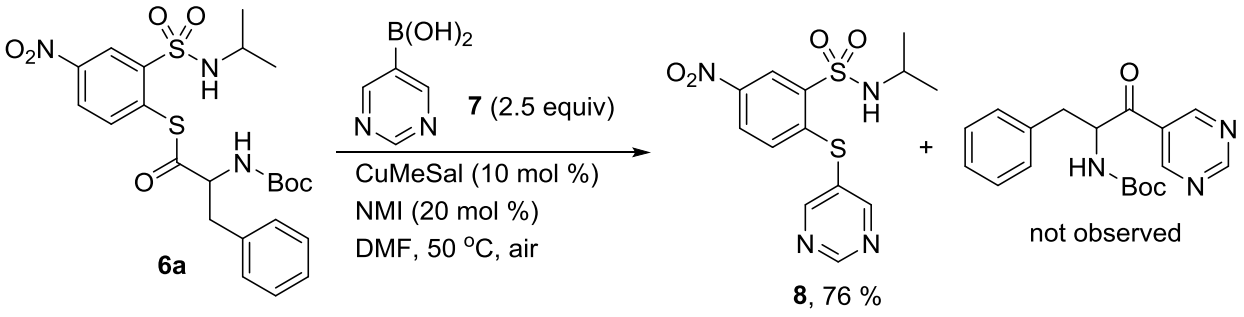
As previously discussed, the addition of NMI as a ligand for copper was effective in preventing S-arylation of BiTs. Accordingly, in an effort to inhibit the generation of S-arylated

Scheme 15. Cu-catalyzed coupling of thioester **5a** and boronic acid **6**

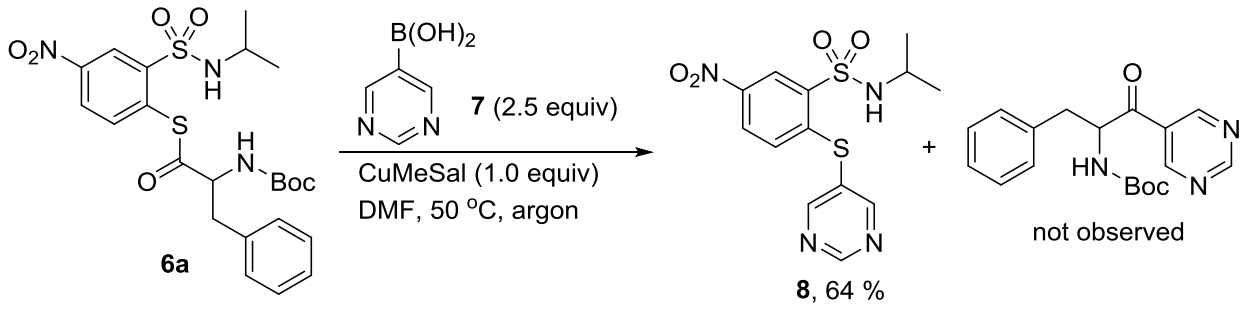


BDT, the above reaction was run in the presence catalytic NMI (Scheme 16). However, even with added ligand no ketone formation was observed and again the major product isolated was S-arylated BDT. Finally, since oxygen in air was thought to be necessary for regeneration of the copper catalyst in Liebeskind-Srogl coupling, the same reaction was run under argon with *stoichiometric* CuMeSal to see if ketone formation was even possible. Surprisingly, even under an inert atmosphere the only product observed was S-arylated BDT (Scheme 17). Coupling of aryl thiols with aryl boronic acids is a known reaction that is typically catalyzed by higher oxidation state copper complexes (Cu^{II}/Cu^{III})[26]. Presumably then, under our reaction conditions disproportionation of Cu^{I} occurs[27] to give a higher oxidation state copper that is capable of catalyzing the coupling reaction, resulting in the formation of S-arylated BDT. Based on these results, BDT-derived thioesters do not react with boronic acids to give ketone, but rather S-arylation occurs to give aryl thioethers as the major product.

Scheme 16. Cu-catalyzed coupling of thioester **6a** and boronic acid **7** with N-methylimidazole

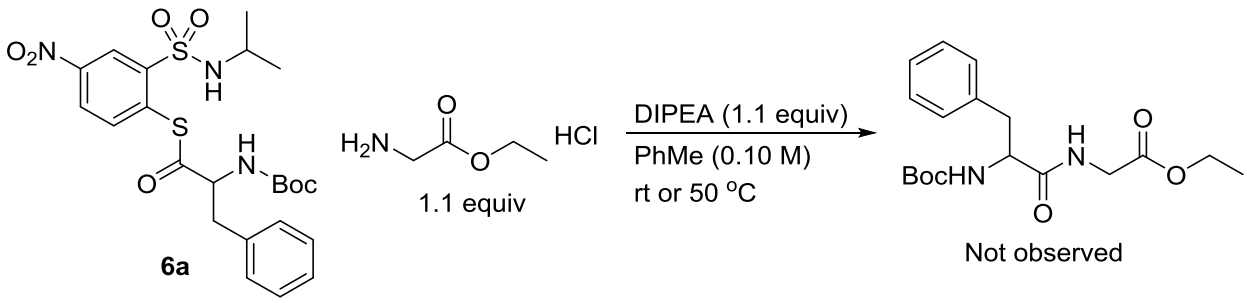


Scheme 17. Coupling of thioester **6a** and boronic acid **7** with stoichiometric copper

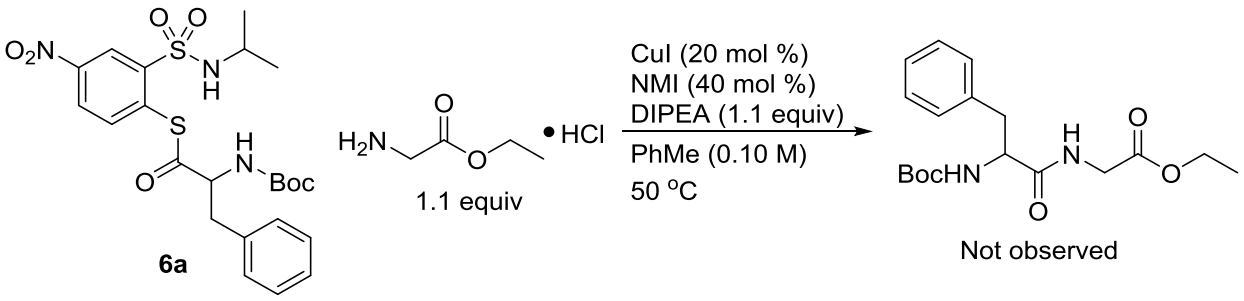


Following the unsuccessful ketonization attempts, we instead turned our attention to amidation by reacting BDT-derived thioesters with amine. Our investigation began by simply taking up thioester in toluene and adding glycine ethyl ester hydrochloride (1.1 equiv) and N,N-diisopropylethylamine (DIPEA, 1.05 equiv) as shown in Scheme 18. Unfortunately at room temperature and 50 °C no reaction occurred and the thioester was quantitatively recovered after acidic workup. Next, in order to facilitate amide formation, the same reaction was run with the addition of a copper catalysts and the result is shown in Scheme 19. As shown, under the same copper catalyzed conditions used for amidation of BiT-derived thioesters, the desired amide was not obtained after running at 50 °C overnight. Instead, only hydrolysis of the thioester was observed. Further, in the presence of copper catalyst the thiol, generated by loss of the acyl group on the thioester, was completely oxidized to disulfide. While no amide was formed, the formation of disulfide was an encouraging result as it implies oxidation of the BDT-based thiol is

Scheme 18. Reaction of thioester **6a** with amine



Scheme 19. Reaction of thioester **6a** with amine under copper catalyzed conditions

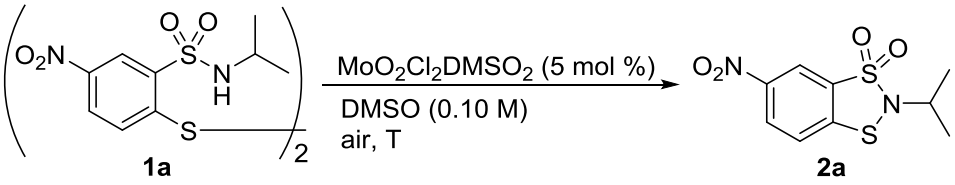


possible and under appropriate conditions the BDT might be regenerated during the reaction. Further work is needed to find appropriate conditions for the generation of amides from BDT-derived thioesters.

Oxidative Recycle of Thiol to BDT

After observing oxidation of the BDT-derived thiol to disulfide under the very mild conditions required for amidation, we next studied conditions for the final step in the catalytic cycle (step 3, Figure 2), the oxidative recycle of the BDT. Since the BiT recycle is believed to occur first by oxidation of thiol to disulfide followed by disproportionation of the disulfide to give BDT and thiol[28], we began our study by simply heating disulfide **1a** in DMF to various temperatures in the presence of a molybdenum catalyst (5 mol %). The molybdenum catalyst used has been previously studied and found to be an excellent catalyst for the oxidation of thiols to disulfides[29]. Table 5 shows the outcome of these reactions. Below 100 ^{o}C (entries 1-3) no or

Table 5. Mo-catalyzed oxidation of disulfide of 1a to BDT at varied temperature

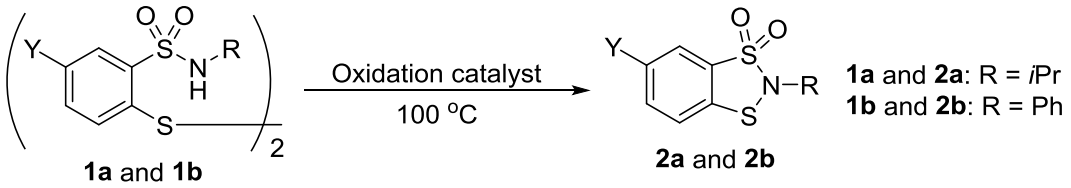


Entry	Temperature (C)	Time (h)	Yield (%)
1	RT	24	0
2	50	24	0
3	80	24	10
4	100	6	92
5	120	2	96

very little reaction was seen and the disulfide was recovered in near quantitative yield in each case. However, at 100 ^{o}C disproportionation begins to occur and after heating for 6 hours at this temperature the BDT was obtained in excellent yield (entry 4). An even faster reaction was observed at 120 ^{o}C and again the BDT was obtained in high yield in only 2 hours (entry 5).

In an effort to lower the temperature of disproportionation, a variety of catalysts were tested under the conditions described in Table 6. Unfortunately, no significant disproportionation took place at temperatures below 100 ^{o}C with any of the catalyst tested, and BDT was only obtained when the reaction was run at high temperature. The best yields were obtained with Mo and CuI/NMI catalysts (entries 1 and 2), but both Pd/C and charcoal also gave good yield of BDT (entries 3 and 4). Finally, to see if there is any difference in the rate and temperature of disproportionation for the more reactive BDTs, **1b** (the disulfide of BDT **2b**) was reacted in the presence of the Mo catalyst at 100 ^{o}C as shown in entry 5. The rate of BDT formation was increased and complete conversion was achieved in only 2 hours with the more reactive BDT. Taken together these results suggest that oxidation under BiT-like conditions only occurs at higher temperature and different conditions or chemical additives may be needed to make the BDT recycle compatible with the other steps of catalytic reaction.

Table 6. Oxidation of disulfide to BDT with different catalysts

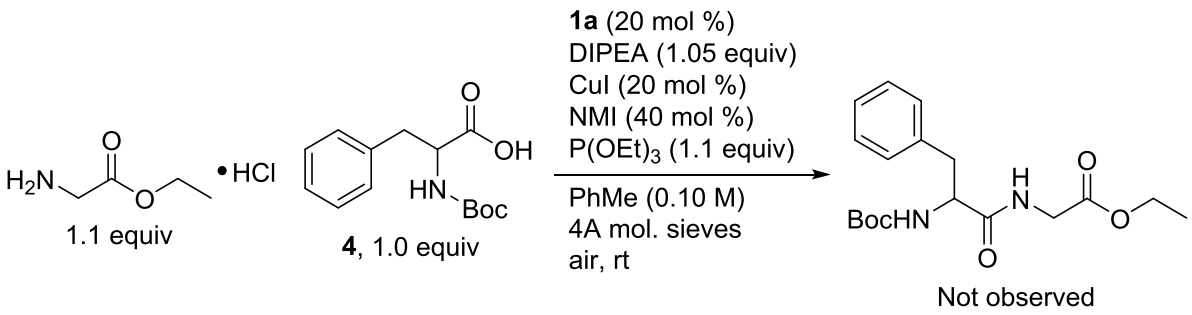


Entry	Disulfide	Catalyst	Catalyst Loading	Time (h)	Yield (%)
1	1a	$MoO_2Cl_2DMSO_2$	5 mol %	6	92
2	1a	CuI/NMI	10 mol %/ 20 mol %	6	87
3	1a	Pd/C	1 weight %	6	89
4	1a	Charcoal	1 weight %	6	79
5	1b	$Mo_2O_2Cl_2DMSO_2$	5 mol %	2	94

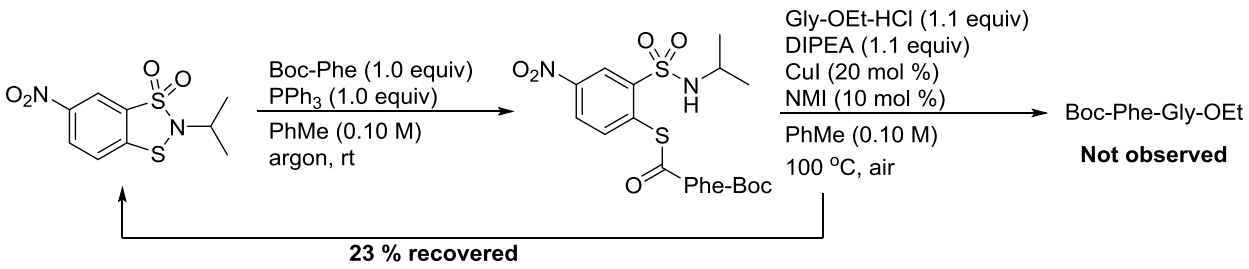
Amidation Using Stoichiometric or Catalytic BDT

We completed our examination of BDTs by attempting a catalytic amidation under the optimal conditions based on our previous results. The catalytic procedure is shown in Scheme 20 and was performed as follows: A dry test tube was charged with BDT **1a**, N-Boc-phenylalanine, glycine ethyl ester hydrochloride, DIPEA, CuI, NMI and activated molecular sieves. The solids were taken up in dry toluene and stirred for 10 minutes before triethyl phosphite (1.0 equiv) was added. The reaction was heated to 100 °C and monitored by TLC. After 8 hours, toluene was evaporated and the crude reaction mixture was analyzed by ^{1}H NMR. Unfortunately, no amidation was observed, and the crude ^{1}H NMR and TLC both show a complex mixture of products.

Scheme 20. Catalytic amidation with BDT **1a**



Scheme 21. Amidation with batch recycle of BDT



Following the unsuccessful catalytic reaction, the potential for amidation through a batch recycle was assessed as shown in Scheme 21. The BDT-derived thioester was made first, and in a one-pot reaction the thioester was exposed to the appropriate amine and CuI/NMI and then heated to 100 ^{o}C. However, after reacting overnight again no amide formation was observed but some BDT could be isolated by column chromatography, albeit in poor yield. These results suggest that more work is needed, particularly on the amidation and BDT recycle step, in order to develop a mild catalytic reaction that can be applied to a variety of dehydrative, acylative chemistry.

Conclusion

A series of BDTs were synthesized through a reaction 2-(benzylthio)benzene sulfonamide with sulfuryl chloride. In a typical reaction, the product yields was moderately high and BDTs could be easily purified by precipitation from the reaction and recrystallization where necessary. The purified BDTs could also be converted to thioesters through a redox dehydration with carboxylic acids and triphenylphosphine or triethyl phosphite. BDT-derived thioesters were synthesized from both aryl and alkyl carboxylic acids. However, the aryl acids gave poor very poor yields with phosphite, and only modest yields with phosphine while aliphatic acids gave modest to good yields with both phosphorus sources. The BDT-derived thioesters could undergo coupling with boronic acid to give S-arylated BDTs, but no ketone formation was observed.

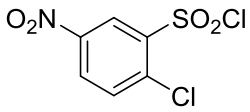
Further, no amidation with amines was observed under the conditions tested in this study. Finally, BDTs could be synthesized from their corresponding disulfide through a disproportionation/oxidation procedure. While attempts to use BDTs in place of BiTs for catalytic dehydrative bond construction were unsuccessful, future work may uncover the conditions necessary to develop a fully catalytic system or delve into other interesting applications of BDT.

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 (CDCl3: 1H = 7.26 ppm, 13C = 77.16 ppm), or deuterated DMSO (DMSO-d6: 1H = 2.50 ppm, 13C = 39.52 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.

Reagents chlorosulfonic acid, pyridine, triethylamine, benzyl thiol, sodium hydroxide, potassium hydroxide, sulfuryl chloride, sodium borohydride, triphenylphosphine and triethyl phosphite were purchased from Alfa Aesar or Sigma-Aldrich. Starting materials 1-chloro-4-nitrobenzene, 2-bromobenzenesulfonyl chloride, isopropylamine, aniline, 2,6-dimethylaniline, N-Boc-Phe, pyrimidine-5-boronic acid and glycine ethyl ester hydrochloride were purchased from Oakwood Chemicals, TCI Chemicals or Sigma-Aldrich.



2-chloro-5-nitrobenzenesulfonyl chloride. To a 250 mL round-bottomed flask equipped with a magnetic stir bar was charged 1-chloro-4-nitrobenzene (20.0 g, 127 mmol) and chlorosulfonic acid (85 mL, 1.27 mol). The flask was equipped with a reflux condenser and carefully heated to 125 ^{o}C for 24 hours while open to air. Then the reaction mixture was cooled to room temperature, poured onto ice, and extracted with DCM (3 x 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated to give a dark brown oil. The oil was taken up in EtOAc (100 mL) and decolorized with activated carbon to give a yellow solution. The product was isolated by crystallization upon addition of hexanes. Yellow solid (20.83 g, 81.0 mmol, 64 % yield); **m.p.** 88 - 89 ^{o}C (lit 89 - 90 ^{o}C)[21]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 2.6, 0.6 Hz, 1H), 8.51 (ddd, *J* = 8.8, 2.6, 0.6 Hz, 1H), 7.89 (dd, *J* = 8.8, 0.6 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.0, 142.0, 139.6, 134.2, 129.9, 125.7

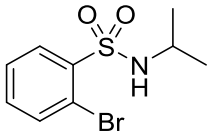
General procedure for sulfonamide synthesis:

Method A via excess amine:

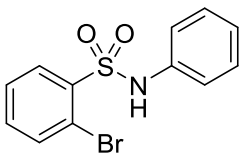
To a round-bottomed flask equipped with a magnetic stir bar was added sulfonyl chloride (1.0 equiv) and DCM (0.50 M) followed by the appropriate amine (3.0 equiv). The reaction was stirred at room temperature until completion as indicated by TLC. Upon completion the reaction was diluted with DCM and washed with saturated sodium bicarbonate. The organic layer was then dried with $MgSO_4$ and concentrated to give product. When necessary, product was purified by recrystallization from appropriate solvent.

Method B via amine and base:

To a round-bottom flask equipped with a magnetic stir bar was added sulfonyl chloride (1.0 equiv), base (1.1 equiv) and DCM (0.50 M). Amine (1.1 equiv) was then added slowly and the reaction stirred at room temperature until completion as indicated by TLC. Upon completion the reaction was diluted with DCM and washed with saturated sodium bicarbonate. The organic layer was then dried with $MgSO_4$ and concentrated to give product. When necessary, product was purified by recrystallization from appropriate solvent.

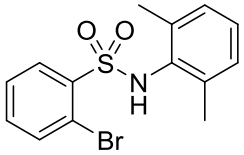


2-bromo-N-isopropylbenzenesulfonamide. Following method A, from 2-bromobenzenesulfonyl chloride (3.00 g, 11.7 mmol) and isopropylamine (2.9 mL, 35.2 mmol) was obtained clean product after recrystallization from ethanol and water. White solid (3.17 g, 11.4 mmol, 97 % yield); **m.p.** 102 - 104 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.71 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.45 (td, *J* = 7.5, 1.3 Hz, 1H), 7.39 (td, *J* = 7.5, 1.9 Hz, 1H), 4.99 (d, *J* = 7.5 Hz, 1H), 3.53 – 3.28 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.8, 135.0, 133.5, 131.3, 127.8, 119.7, 46.6, 23.4; **HRMS** (ESI) Calcd for $C_9H_{13}BrNO_2S$ [M+H$^+$] 277.9845, found 277.9856; **IR** (neat) 3371 cm^{-1}

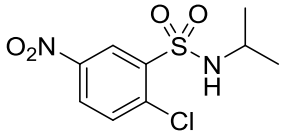


2-bromo-N-phenylbenzenesulfonamide. Following method B, from 2-bromobenzenesulfonyl chloride (5.19 g, 20.3 mmol), pyridine (1.80 mL, 22.3 mmol) and aniline (2.04 mL, 22.3 mmol)

was obtained clean product after recrystallization from ethanol. White solid (5.23 g, 16.8 mmol, 82 % yield); **m.p.** 132 - 134 ^{o}C (lit. 137 - 138 ^{o}C)[30]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.88 (m, 1H), 7.67 – 7.57 (m, 1H), 7.30 – 7.25 (m, 2H), 7.20 – 6.98 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.9, 135.8, 135.1, 134.2, 132.4, 129.5, 127.9, 125.9, 121.8, 119.8; **IR** (neat) 3281 cm^{-1}

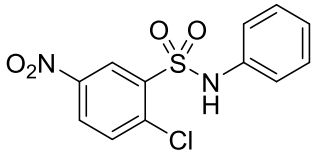


2-bromo-N-(2,6-dimethylphenyl)benzenesulfonamide. Following method B, from 2-bromobenzenesulfonyl chloride (5.00 g, 19.6 mmol), pyridine (6.30 mL, 78.0 mmol) and 2,6-dimethylaniline (2.41 mL, 19.6 mmol) was obtained clean product without further purification. Orange solid (6.27 g, 18.4 mmol, 94 % yield); **m.p.** 159 - 160 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.88 (m, 1H), 7.82 – 7.74 (m, 1H), 7.46 – 7.36 (m, 2H), 7.08 (dd, *J* = 8.4, 6.6 Hz, 1H), 7.00 (d, *J* = 7.1 Hz, 2H), 6.54 (s, 1H), 2.10 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.5, 138.4, 135.0, 133.5, 132.5, 130.4, 128.6, 128.3, 127.8, 120.0, 18.8; **HRMS** (ESI) Calcd for $C_{14}H_{15}BrNO_2S$ [M+H^{+}] 340.0001, found 339.9994; **IR** (neat) 3303 cm^{-1}

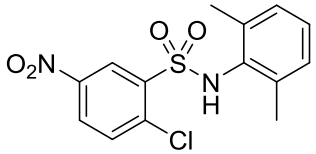


2-chloro-N-isopropyl-5-nitrobenzenesulfonamide. Following method A from 2-chloro-5-nitrobenzenesulfonyl chloride (3.0 g, 11.7 mmol) and isopropylamine (2.9 mL, 35.1 mmol) was obtained clean product after recrystallization. Yellow solid (3.12 g, 11.2 mmol, 94 % yield);

m.p. 170 - 172 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.7 Hz, 1H), 8.33 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 5.05 (d, *J* = 7.9 Hz, 1H), 3.52 (dp, *J* = 7.9, 6.5 Hz, 1H), 1.11 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5, 140.5, 138.3, 133.1, 128.0, 126.3, 47.2, 23.8; **HRMS** (ESI) Calcd for $C_9H_{11}ClNaN_2O_4S$ [M+Na^+] 301.0020, found 301.0022; **IR** (neat) 3283 cm^{-1}



2-chloro-5-nitro-N-phenylbenzenesulfonamide. Following method B from 2-chloro-5-nitrobenzenesulfonyl chloride (3.00 g, 11.7 mmol), pyridine (1.04 mL, 12.9 mmol) and aniline (1.17 mL, 12.9 mmol) was obtained clean product after recrystallization from ethanol and water. Yellow solid (2.95 g, 9.4 mmol, 81 % yield); **m.p.** 168 - 169 ^{o}C; **^{1}H NMR** (600 MHz, CDCl3) δ 8.80 (dd, J = 2.7, 0.8 Hz, 1H), 8.28 (ddd, J = 8.7, 2.7, 0.8 Hz, 1H), 7.69 (dd, J = 8.7, 0.8 Hz, 1H), 7.30 – 7.17 (m, 2H), 7.16 – 7.06 (m, 4H); **^{13}C NMR** (75 MHz, CDCl3) δ 146.4, 138.1, 134.8, 133.0, 129.9, 128.5, 127.2, 126.7, 122.0; **HRMS** (ESI) Calcd for $C_{12}H_{19}ClNaN_2O_4S$ [M+Na^+] 334.9864, found 334.9868; **IR** (neat) 3285 cm^{-1}



2-chloro-N-(2,6-dimethylphenyl)-5-nitrobenzenesulfonamide. Following method B, from 2-chloro-5-nitrobenzenesulfonyl chloride (1.46 g, 5.7 mmol), pyridine (0.55 mL, 6.8 mmol) and 2,6-dimethylaniline (0.84 mL, 6.8 mmol) was obtained clean product after recrystallization from

ethanol and water. Orange solid (1.29 g, 3.8 mmol, 66 % yield); **m.p.** 161 - 162 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.7 Hz, 1H), 8.34 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.18 – 7.07 (m, 1H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.58 (s, 1H), 2.10 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.2, 141.4, 138.3, 138.2, 132.8, 131.8, 128.9, 128.8, 127.8, 125.3, 18.8; **HRMS** (ESI) Calcd for $C_{14}H_{13}ClNaN_2O_4S$ [M+Na^+] 363.0177, found 363.0177; **IR** (neat) 3314 cm^{-1}

General procedure for thioether synthesis:

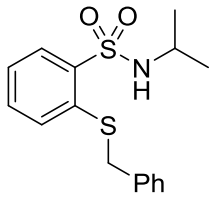
Method A via thiol and base:

To a dry roundbottom flask equipped with magnetic stir bar was added thiol (1.20 equiv) and base (1.15 equiv). The flask was evacuated and backfilled with argon and DMF (0.50 M) was added. Sulfonamide (1.0 equiv) was added and the reaction was adjusted to the appropriate temperature. The reaction was stirred at the same temperature until completion as indicated by TLC. Upon completion, the reaction was cooled in an ice bath and water was added with continued stirring until solid precipitate began to form. The solid was collected by filtration and washed with water to give crude product that was purified by recrystallization from appropriate solvent.

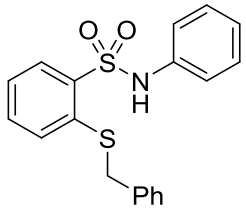
Method B via copper thiolate:

To a roundbottom flask equipped with a magnetic stir bar was added sulfonamide (1.0 equiv), DMF (0.33 M) and copper(I) phenylmethanethiolate (1.1 equiv) prepared as previously described[31] from copper(I) oxide and benyl mercaptan. The reaction mixture was adjusted to 100 ^{o}C in an oil bath and stirred at the same temperature until completion as indicated by TLC. Upon completion the reaction was cooled to room temperature and any undissolved solid was removed

by filtration. The filtrate was then cooled in an ice bath with stirring and water was added until a solid precipitate formed. The solid was collected by filtration and washed with water to give crude product that was purified by recrystallization from the appropriate solvent.

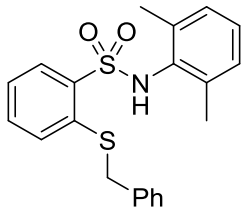


2-(benzylthio)-N-isopropylbenzenesulfonamide. Following general procedure A, from 2-chloro-N-isopropylbenzenesulfonamide (2.07 g, 7.4 mmol), sodium hydroxide (0.34 g, 8.5 mmol) and benzyl mercaptan (1.04 mL, 8.9 mmol) at 100 ^{o}C was obtained clean product after recrystallization from ethyl acetate and hexanes. White solid (1.48 g, 4.6 mmol, 62 % yield); **m.p.** 88 - 90 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.36 – 7.20 (m, 6H), 5.34 (d, *J* = 7.2 Hz, 1H), 4.22 (s, 2H), 3.50 – 3.18 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.5, 136.3, 134.3, 132.4, 132.2, 130.0, 129.1, 128.7, 127.6, 126.7, 46.5, 39.5, 23.4; **HRMS** (ESI) Calcd for $C_{16}H_{20}NO_2S_2$ [M+H^{+}] 322.0930, found 322.0931; **IR** (neat) 3340 cm^{-1}

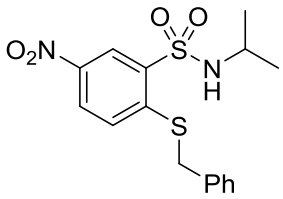


2-(benzylthio)-N-phenylbenzenesulfonamide. Following general procedure A, from 2-bromo-N-phenylbenzenesulfonamide (2.41 g, 7.7 mmol), potassium hydroxide (0.50 g, 8.9 mmol) and benzyl mercaptan (1.09 mL, 9.2 mmol) at 120 ^{o}C was obtained clean product after

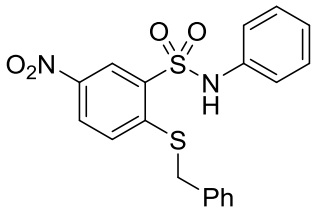
recrystallization from ethanol. White solid (1.66 g, 4.7 mmol, 61 % yield); **m.p.** 116 - 117 ^{o}C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.48 (s, 1H), 7.39 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.37 – 7.22 (m, 6H), 7.18 (td, *J* = 7.6, 1.3 Hz, 1H), 7.12 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.07 – 6.98 (m, 1H), 6.92 (dd, *J* = 8.5, 1.2 Hz, 2H), 4.27 (s, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.2, 136.2, 134.4, 132.8, 132.0, 131.0, 129.1, 129.1, 128.8, 127.7, 126.6, 125.5, 121.9, 39.5; **HRMS** (ESI) Calcd for $C_{19}H_{18}NO_2S_2$ [M+H$^+$] 356.0773, found 356.0767; **IR** (neat) 3254 cm^{-1}



2-(benzylthio)-N-(2,6-dimethylphenyl)benzenesulfonamide. Following general procedure B, from 2-chloro-N-(2,6-dimethylphenyl)benzenesulfonamide (1.06 g, 3.1 mmol) and copper(I) phenylmethanethiolate (0.64 g, 3.4 mmol) was obtained clean product after recrystallization from ethyl acetate and hexanes. Yellow solid (0.77 g, 2.0 mmol, 65 % yield); **m.p.** 148 -149 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 1H), 7.48 – 7.41 (m, 2H), 7.40 – 7.34 (m, 2H), 7.35 – 7.23 (m, 4H), 7.07 (dd, *J* = 8.4, 6.6 Hz, 1H), 6.99 (m, 3H), 4.31 (s, 2H), 2.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.6, 138.1, 136.0, 135.0, 132.9, 132.5, 131.3, 129.1, 129.0, 128.8, 128.6, 127.9, 127.7, 126.6, 39.6, 18.8; **HRMS** (ESI) Calcd for $C_{21}H_{22}NO_2S_2$ [M+H$^+$] 384.1092, found 384.1086; **IR** (neat) 3310 cm^{-1}

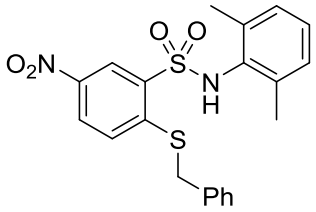


2-(benzylthio)-N-isopropyl-5-nitrobenzenesulfonamide. Following the general procedure A, from 2-chloro-N-isopropyl-5-nitrobenzenesulfonamide (1.40 g, 5.0 mmol), NaOH (0.23 g, 5.8 mmol) and benzyl mercaptan (0.71 mL, 6.0 mmol) at 0 ^{o}C was obtained clean product after recrystallization. Yellow solid (1.73 g, 4.7 mmol, 94 % yield); **m.p.** 135 - 138 ^{o}C; **^{1}H NMR** (600 MHz,$CDCl_3$) δ 8.83 (d, *J* = 2.5 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.43 – 7.27 (m, 5H), 5.14 (d, *J* = 7.6 Hz, 1H), 4.35 (s, 2H), 3.50 – 3.34 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.3, 144.8, 139.4, 134.6, 129.2, 129.0, 128.5, 128.4, 126.5, 125.2, 46.9, 38.2, 23.6; **HRMS** (ESI) Calcd for $C_{16}H_{18}ClNaN_2O_4S_2$ [M+Na^+] 389.0600, found 389.0599; **IR** (neat) 3298 cm^{-1}



2-(benzylthio)-5-nitro-N-phenylbenzenesulfonamide. Following general procedure A, from 2-chloro-5-nitro-N-phenylbenzenesulfonamide (2.13 g, 6.8 mmol), KOH (0.42 g, 7.5 mmol) and benzyl mercaptan (0.96 mL, 8.2 mmol) at 120 ^{o}C was obtained clean product after recrystallization from ethanol and water. Yellow solid (1.93 g, 4.8 mmol, 71 % yield); **m.p.** 159 - 160 ^{o}C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.5 Hz, 1H), 8.17 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.36 – 7.28 (m, 4H), 7.15 (t, *J* = 7.9 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 2H), 4.37 (s, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.3,

144.5, 136.8, 135.2, 134.4, 129.5, 129.1, 128.9, 128.3, 128.3, 126.9, 126.1, 126.0, 121.8, 38.1; **HRMS** (ESI) Calcd for $C_{19}H_{16}ClNaN_2O_4S_2$ [M+Na^+] 423.0444, found 423.0444; **IR** (neat) 3291 cm^{-1}



2-(benzylthio)-N-(2,6-dimethylphenyl)-5-nitrobenzenesulfonamide. Following general procedure A, from 2-chloro-N-(2,6-dimethylphenyl)-5-nitrobenzenesulfonamide (2.50 g, 7.3 mmol), KOH (0.45 g, 8.1 mmol) and benzyl mercaptan (1.03 mL, 8.8 mmol) at 0 ^oC was obtained clean product after recrystallization from ethanol and water. Yellow solid (2.74 g, 6.4 mmol, 87 % yield); **m.p.** 177 - 179 ^oC; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.5 Hz, 1H), 8.25 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.37 – 7.25 (m, 3H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 6.76 (s, 1H), 4.37 (s, 2H), 2.02 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.9, 144.6, 140.1, 138.2, 134.2, 132.0, 129.1, 129.0, 128.8, 128.5, 128.3, 128.0, 126.6, 124.4, 38.3, 18.7; **HRMS** (ESI) Calcd for $C_{21}H_{20}NaN_2O_4S_2$ [M+Na^+] 451.0757, found 451.0756; **IR** (neat) 3305 cm^{-1}

<u>General procedure for BDT synthesis:</u>

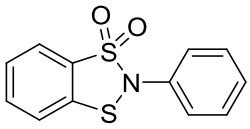
Method A via benzyl thioether:

To a roundbottom flask or test tube equipped with a magnetic stir bar was added thioether (1.0 equiv) and toluene (0.50 M). To the stirred solution at room temperature was added slowly sulfuryl chloride (1.2 equiv). The flask or test tube was then transferred to an oil bath at 75 ^oC for

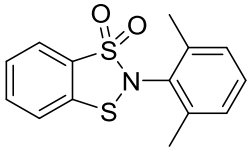
2 hours. Upon completion, the reaction was allowed to cool to room temperature and concentrated to give crude product that was purified by recrystallization from an appropriate solvent.

Method B via disproportionation of disulfide:

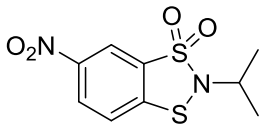
To a round bottom flask equipped with a magnetic stir bar is added disulfide (1.0 equiv), oxidation catalyst (5 mol %) and either DMF or DMSO solvent (0.10 M). The reaction is heated to 100 ^{o}C in an oil bath until completion as indicated by TLC. Upon completion, the reaction was cooled to room temperature and water was added slowly until solid precipitate forms. The crude solid was collected by filtration, washed thoroughly with water and dried overnight to give the desired BDT that was purified by recrystallization from appropriate solvent when needed.



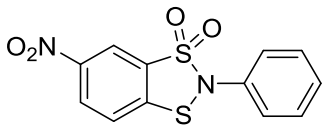
2-phenyl-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide. Following method A, from 2-(benzylthio)-N-phenylbenzenesulfonamide (2.32 g, 6.5 mmol) and sulfuryl chloride (0.63 mL, 7.9 mmol) was obtained clean product after recrystallization from ethanol. Pale yellow solid. (1.08 g, 4.1 mmol, 63 % yield); **m.p.** 152 - 153 ^{o}C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.65 (td, *J* = 7.8, 1.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.43 (td, *J* = 7.6, 0.9 Hz, 1H), 7.36 – 7.27 (m, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.2, 138.8, 133.4, 130.1, 129.3, 128.5, 127.4, 125.7, 124.0, 122.5; **HRMS** (ESI) Calcd for $C_{12}H_{10}NO_2S_2$ [M+H^{+}] 264.0148, found 264.0147



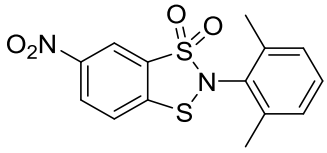
2-(2,6-dimethylphenyl)-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide. Following method A, from 2-(benzylthio)-N-(2,6-dimethylphenyl)benzenesulfonamide (2.40 g, 6.3 mmol) and sulfuryl chloride (0.60 mL, 7.5 mmol) was obtained clean product after recrystallization from toluene. White solid (1.13 g ,3.9 mmol, 62 % yield); **m.p.** 165 -166 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.62 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.49 – 7.37 (m, 2H), 7.20 (dd, *J* = 8.3, 6.8 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 2.26 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.5, 136.9, 134.6, 132.6, 130.8, 129.8, 129.2, 126.8, 122.6, 121.7, 18.8; **HRMS** (ESI) Calcd for $C_{14}H_{13}NO_2S_2$ [M+H^{+}] 292.0466, found 292.0458



2-isopropyl-6-nitro-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide. Following method A, from 2-(benzylthio)-N-isopropyl-5-nitrobenzenesulfonamide (0.83 g, 2.3 mmol) and sulfuryl chloride (0.27 mL, 3.4 mmol) was obtained clean product after recrystallization from ethanol and water. Yellow solid (0.45 g, 1.6 mmol, 72 % yield); **m.p.** 156 - 157 ^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.1 Hz, 1H), 8.43 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 4.37 (hept, *J* = 6.5 Hz, 1H), 1.10 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.5, 146.7, 134.7, 128.0, 123.1, 118.6, 57.1, 19.2; **HRMS** (ESI) Calcd for $C_9H_{10}NaN_2O_4S_2$ [M+Na^{+}] 296.9974, found 296.9973



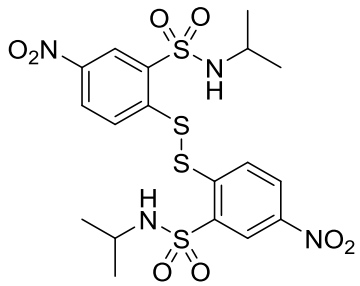
6-nitro-2-phenyl-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide. Following method A, from 2-(benzylthio)-5-nitro-N-phenylbenzenesulfonamide (4.72 g, 11.8 mmol) and sulfuryl chloride (1.14 mL, 14.1 mmol) was obtained clean prodouct after recrystallization from ethanol. Yellow solid (2.55 g, 8.3 mmol, 70 % yield); **m.p.** 234 ^{o}C (decomposed); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.06 – 8.89 (m, 1H), 8.80 (ddd, *J* = 8.5, 2.0, 0.9 Hz, 1H), 8.42 – 8.23 (m, 1H), 7.77 – 7.54 (m, 5H); **^{13}C NMR** (100 MHz, DMSO-d6) δ 152.4, 138.3, 135.8, 132.8, 132.3, 131.9, 131.2, 126.0, 124.6, 120.4; **HRMS** (ESI) Calcd for $C_{12}H_8KN_2O_4S_2$ [M+K^+] 346.8762, found 346.8834



2-(2,6-dimethylphenyl)-6-nitro-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide. Following method A, from 2-(benzylthio)-N-(2,6-dimethylphenyl)-5-nitrobenzenesulfonamide (2.40 g, 5.6 mmol) and sulfuryl chloride (0.54 mL, 6.7 mmol) was obtained clean product after recrystallization from ethanol. Yellow solid (1.23 g, 3.7 mmol, 65 % yield); **m.p.** 239 - 241 ^{o}C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.73 (d, *J* = 2.2 Hz, 1H), 8.53 (dd, *J* = 8.9, 2.2 Hz, 1H), 8.20 (d, *J* = 8.9 Hz, 1H), 7.26 (dd, *J* = 8.3, 6.7 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 2.14 (s, 6H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 146.7, 144.9, 140.2, 134.2, 130.9, 130.5, 129.7, 128.0, 125.5, 118.5, 18.6; **HRMS** (ESI) Calcd for $C_{14}H_{12}NaN_2O_4S_2$ [M+Na^+] 359.0131, found 359.0131

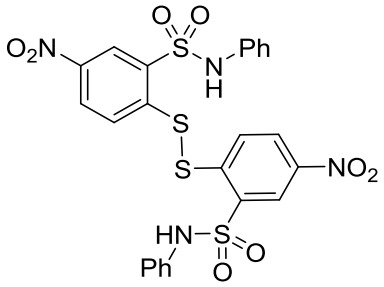
General procedure for reductive ring opening and oxidation to disulfide:

To a dry round bottom flask was added BDT (1.0 equiv) and the flask was evacuated and backfilled with argon. Dry ethanol (0.20 M) was added and the flask cooled in an ice bath. As a solid in one portion was added sodium borohydride (4.0 equiv) and the reaction was stirred in the ice bath until completion as indicated by TLC. Upon completion, the product was precipitated by addition of 1M HCl, collected by filtration, and used as obtained without further purification. The crude thiol (1.0 equiv) was added to a round bottom flask and taken up in DMSO (0.50 M) and $MoO_2Cl_2DMSO_2$ (10 mol %, prepared as previously described[32]) was added to the flask as a solid in one portion. The reaction was stirred at room temperature until completion as indicated by TLC. Upon completion, water was added to the reaction to precipitate the disulfide which was collected by vacuum filtration, washed with water, and dried overnight. When necessary, the product was purified by recrystallization from ethanol or ethanol and water.



6,6'-disulfanediylbis(N-isopropyl-3-nitrobenzenesulfonamide). Following general procedure, from 2-isopropyl-6-nitro-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide (2.00 g, 7.3 mmol), sodium borohydride (1.10 g, 29.2 mmol) and $MoO_2Cl_2DMSO_2$ (0.30 g, 0.7 mmol) was obtained clean product without further purification. Yellow solid (1.53 g, 2.8 mmol, 76 % yield over 2 steps); **m.p.** 184 - 187 ^{o}C; **^{1}H NMR** (400 MHz, DMSO-d6) δ 8.57 (dd, *J* = 2.5, 1.1 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.34 (ddd, *J* = 8.8, 2.5, 1.1 Hz, 1H), 8.01 (dd, *J* = 8.8, 1.1 Hz, 1H), 3.50 – 3.35 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO-d6) δ 146.1, 141.6, 140.0, 128.3,

127.2, 124.3, 45.8, 23.3; **HRMS** (ESI) Calcd for $C_{18}H_{22}NaN_4O_8S_4$ [M+Na^+] 573.0213, found 573.0212; **IR** (neat) 3338, 3292 cm^{-1}

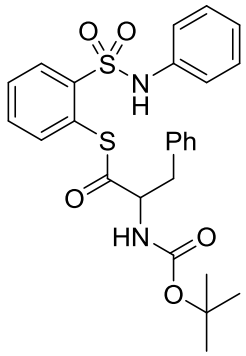


6,6'-disulfanediylbis(3-nitro-N-phenylbenzenesulfonamide). Following general procedure from 6-nitro-2-phenyl-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide (0.20 g, 0.7 mmol), sodium borohydride (0.10 g, 2.6 mmol) and $MoO_2Cl_2DMSO_2$ (0.02 g, 0.1 mmol) was obtained clean product after recrystallization from ethanol. Pale yellow solid (0.11 g, 0.2 mmol, 55 % yield); **m.p**. 255 - 258 ^oC (decomposed); **^{1}H NMR** (600 MHz, DMSO-d_6) δ 11.11 (s, 1H), 8.57 (d, *J* = 2.4 Hz, 1H), 8.17 - 8.00 (m, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 3H); **^{13}C NMR** (151 MHz, DMSO-d6) δ 146.1, 141.8, 137.9, 136.1, 129.6, 128.1, 127.8, 125.2, 125.1, 120.7; **HRMS** (ESI) Calcd for $C_{24}H_{18}NaN_4O_8S_4$ [M+Na^+] 640.9900, found 640.9900; **IR** (neat) 3222 cm^{-1}

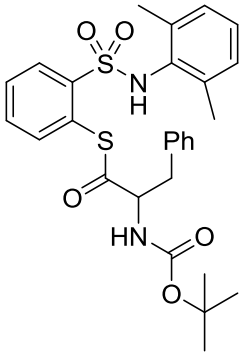
General procedure for thioesterification:

To a dry round bottom flask was added BDT (1.0 equiv), carboxylic acid (1.0 equiv) and 4Å molecular sieves and the flask was evacuated and backfilled with argon. Dry toluene was added followed by either triphenylphosphine or triethylphosphite (1.0 equiv) and the reaction was stirred at room temperature until completion as indicated by TLC. Upon completion toluene was

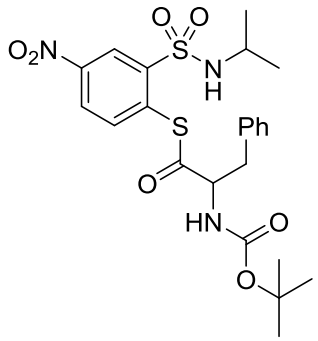
removed under reduced pressure and the crude residue was purified by flash column chromatography on silica gel to give the desired product thioesters.



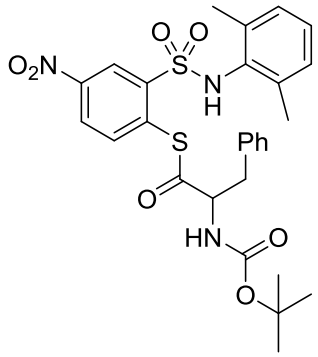
S-(2-(N-phenylsulfamoyl)phenyl) 2-((tert-butoxycarbonyl)amino)-3-phenylpropanethioate. Following general procedure from 2-phenyl-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide (0.05 g, 0.2 mmol), (tert-butoxycarbonyl)-L-phenylalanine (0.05 g, 0.2 mmol) and either triphenylphosphine (0.05 g, 0.2 mmol) or triethylphosphite (0.03 mL, 0.2 mmol) was obtained clean thioester after purification by flash column chromatography on silica gel (3:1, hexanes:EtOAc). White solid (0.09 g, 0.18 mmol, 84 % yield from phosphine; 0.06 g, 0.13 mmol, 64 % yield from phosphite); **m.p.** 108 - 110 ^{o}C; **1H NMR** (400 MHz); **^{13}C NMR** (101 MHz) 198.2, 156.4, 142.5, 139.3, 136.7, 135.2, 132.8, 131.1, 129.9, 129.1, 129.0, 128.9, 127.5, 125.9, 124.7, 121.2, 82.2, 62.2, 37.1, 28.5; **HRMS** (ESI) Calcd for $C_{26}H_{28}N_2O_5S_2$ [M+H$^+$] 513.1518, found 513.1517; **IR** (neat) 3367, 3217, 1714, 1682 cm^{-1}



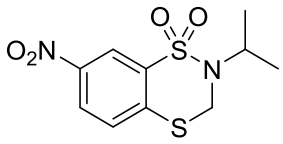
S-(2-(N-(2,6-dimethylphenyl)sulfamoyl)phenyl) 2-((tert-butoxycarbonyl)amino)-3-phenylpropanethioate. Following general procedure from 2-(2,6-dimethylphenyl)-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide (0.06 g, 0.2 mmol), (tert-butoxycarbonyl)-L-phenylalanine (0.05 g, 0.2 mmol) and either triphenylphosphine (0.05 g, 0.2 mmol) or triethylphosphite (0.03 mL, 0.2 mmol) was obtained clean thioester after purification by flash column chromatography on silica gel (4:1, hexanes:EtOAc). White solid (0.09 g, 0.17 mmol, 87 % yield from phosphine; XX g, XX mmol, 66 % yield from phosphite); **m.p.** 97 - 98 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.61 (td, *J* = 7.5, 1.5 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.38 – 7.25 (m, 3H), 7.23 – 7.16 (m, 2H), 7.05 (dd, *J* = 8.7, 6.2 Hz, 1H), 7.01 – 6.96 (m, 2H), 5.11 (d, *J* = 6.3 Hz, 1H), 4.47 (dt, *J* = 8.0, 5.8 Hz, 1H), 3.15 (qd, *J* = 14.2, 6.7 Hz, 2H), 2.09 (s, 6H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.2, 155.9, 139.0, 138.4, 135.2, 133.8, 132.3, 129.9, 129.2, 129.0, 128.9, 128.7, 128.3, 127.7, 127.5, 125.5, 81.6, 61.8, 37.2, 28.3, 19.1; **HRMS** (ESI) Calcd for $C_{28}H_{32}N_2O_5S_2$ [M+H^{+}] 541.1831, found 541.1822; **IR** (neat) 3365, 3242, 1715, 1687 cm^{-1}



S-(2-(N-isopropylsulfamoyl)-4-nitrophenyl) 2-((tert-butoxycarbonyl)amino)-3-phenylpropanethioate. Following general procedure from 2-isopropyl-6-nitro-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide (0.05 g, 0.2 mmol), (tert-butoxycarbonyl)-L-phenylalanine (0.05 g, 0.2 mmol) and either triphenylphosphine (0.05 g, 0.2 mmol) or triethylphosphite (0.03 mL, 0.2 mmol) was obtained clean thioester after purification by flash column chromatography on silica gel (3:1, hexanes:EtOAc). Yellow solid (0.09 g, 0.17 mmol, 94 % yield from phosphine; 0.08 g, 0.16 mmol, 79 % yield from phosphite); **m.p.** 92 - 94 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.94 (d, *J* = 2.5 Hz, 1H), 8.38 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.26 (m, 3H), 7.24 – 7.17 (m, 2H), 6.04 (d, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 5.6 Hz, 1H), 4.36 (dt, *J* = 8.9, 5.2 Hz, 1H), 3.51 (ddt, *J* = 13.0, 7.8, 6.5 Hz, 1H), 3.23 (dd, *J* = 14.2, 4.9 Hz, 1H), 3.14 (dd, *J* = 14.2, 8.9 Hz, 1H), 1.49 (s, 9H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.2, 156.2, 148.0, 146.6, 140.4, 134.9, 133.8, 129.2, 129.1, 127.7, 126.1, 124.5, 82.4, 62.4, 46.8, 36.9, 28.5, 23.8, 22.9; **HRMS** (ESI) Calcd for $C_{23}H_{29}N_3O_7S_2$ [M+H^{+}] 524.1525, found 524.1523; **IR** (neat) 3364, 3253, 1714, 1689 cm^{-1}



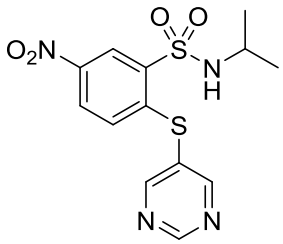
S-(2-(N-(2,6-dimethylphenyl)sulfamoyl)-4-nitrophenyl) 2-((tert-butoxycarbonyl)amino)-3-phenylpropanethioate. Following general procedure from 2-(2,6-dimethylphenyl)-6-nitro-2H-benzo[d][1,3,2]dithiazole 1,1-dioxide (0.07 g, 0.2 mmol), (tert-butoxycarbonyl)-L-phenylalanine (0.05 g, 0.2 mmol) and either triphenylphosphine (0.05 g, 0.2 mmol) or triethylphosphite (0.03 mL, 0.2 mmol) was obtained clean thioester after purification by flash column chromatography on silica gel (3:1, hexanes:EtOAc). Yellow solid (0.09 g, 0.17 mmol, 86 % yield from phosphine; 0.08 g, 0.16 mmol, 61 % yield from phosphite); **m.p.** 112 - 113 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 2.5 Hz, 1H), 8.43 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.43 – 7.28 (m, 3H), 7.25 – 7.18 (m, 2H), 7.10 (dd, *J* = 8.4, 6.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 2H), 5.15 (d, *J* = 6.0 Hz, 1H), 4.48 (dt, *J* = 7.6, 5.8 Hz, 1H), 3.27 – 3.12 (m, 2H), 2.08 (s, 6H), 1.42 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.9, 156.2, 148.1, 147.6, 140.3, 138.3, 135.0, 134.0, 133.2, 129.3, 129.3, 128.7, 128.3, 127.9, 126.3, 123.8, 82.3, 62.3, 37.2, 28.4, 19.3; **HRMS** (ESI) Calcd for $C_{38}H_{31}N_3O_7S_2$ [M+H^{+}] 586.1681, found 586.1701; **IR** (neat) 3383, 3216, 1716, 1689 cm^{-1}



2-isopropyl-7-nitro-2,3-dihydrobenzo[e][1,4,2]dithiazine 1,1-dioxide. In a roundbottom flask, 2-(tert-butylthio)-N-isopropyl-5-nitrobenzenesulfonamide (1.00 g, 3.01 mmol), TMSCl (0.40 g, 3.31 mmol) and DMSO (0.26 g, 3.31 mmol) were taken up in chloroform and refluxed for 2 hours. Upon completion, hexane was added to the reaction until a precipitate formed. The solid was collected by filtration and recrystallized from ethanol and water to give clean product. Yellow solid (0.59 g, 2.05 mmol, 68 % yield); **m.p.** 86 - 88 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.6 Hz, 1H), 8.16 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.37 (d, *J* = 9.2 Hz, 1H), 5.22 (s, 2H), 4.40 – 3.92 (m, 1H), 1.25 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.4, 144.5, 134.1, 129.1, 126.2, 121.4, 121.4, 52.1, 46.4, 20.9, 20.8; **HRMS** (ESI) Calcd for $C_{10}H_{12}N_2O_4S_2$ [M+H^{+}] 289.0317, found 289.0315; **IR** (neat) 3283 cm^{-1}

General procedure for coupling of thioester with boronic acid:

To a dry round bottom flask was added thioester (1.1 equiv), boronic acid (2.5 equiv), copper(I) 3-methylsalicylate (10 mol %) and 4Å molecular sieves. Dry DMF was then added and the reaction was stirred at the appropriate temperature until completion as indicated by TLC. Over the course of the reaction the color of the solution changed from dark red to green. Upon completion, the reaction was diluted with diethyl ether and washed with 1M HCl (2x), saturated sodium bicarbonate (2x), and water (1x). The ether layer was then collected, dried with $MgSO_4$, and concentrated to give crude product that was purified by column chromatography on silica gel to give S-arylated BDT.



N-isopropyl-5-nitro-2-(pyrimidin-5-ylthio)benzenesulfonamide. Following general procedure from S-(2-(N-isopropylsulfamoyl)-4-nitrophenyl) 2-((tert-butoxycarbonyl)amino)-3-phenylpropanethioate (0.04 g, 0.08 mmol), pyrimidine-5-boronic acid (0.03 g, 0.21 mmol), and copper(I) 3-methylsalicylate (0.9 mg, 0.008 mmol)) was obtained S-arylated BDT after purification by flash column chromatography on silica gel (2:1, hexanes:EtOAc). Yellow solid (0.021 g, 0.06 mmol, 72 % yield); **m.p.** 87 – 89 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.93 – 8.79 (m, 3H), 8.17 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 5.22 (d, *J* = 7.9 Hz, 1H), 3.70 – 3.53 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.8, 159.2, 145.7, 143.3, 129.9, 129.4, 128.3, 126.8, 125.2, 46.9, 23.8; **HRMS** (ESI) calcd for $C_{13}H_{14}N_4O_4S_2$ [M+H^{+}] 355.0534, found 355.0529; **IR** (neat) 3276 cm^{-1}

References

(1) Zani, F.; Vicini, P.; Incerti, M. *Eur. J. Med. Chem.* **2004**, *39* (2), 135–140.
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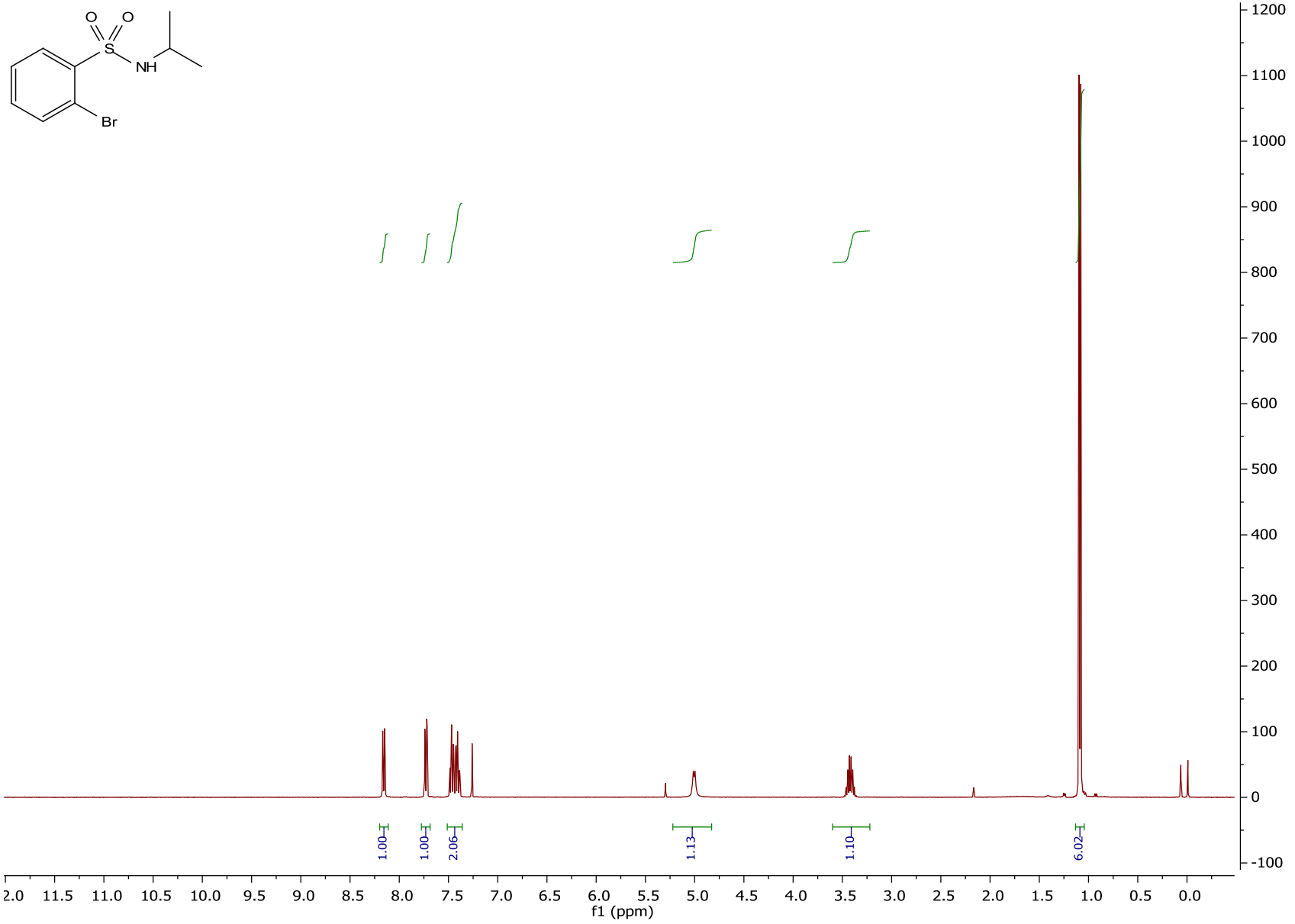
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S
NH
Br
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1100
1000
900
800
700
600
500
400
300
200
100
0
-100
1.00
1.00
2.06
1.13
1.10
6.02
2.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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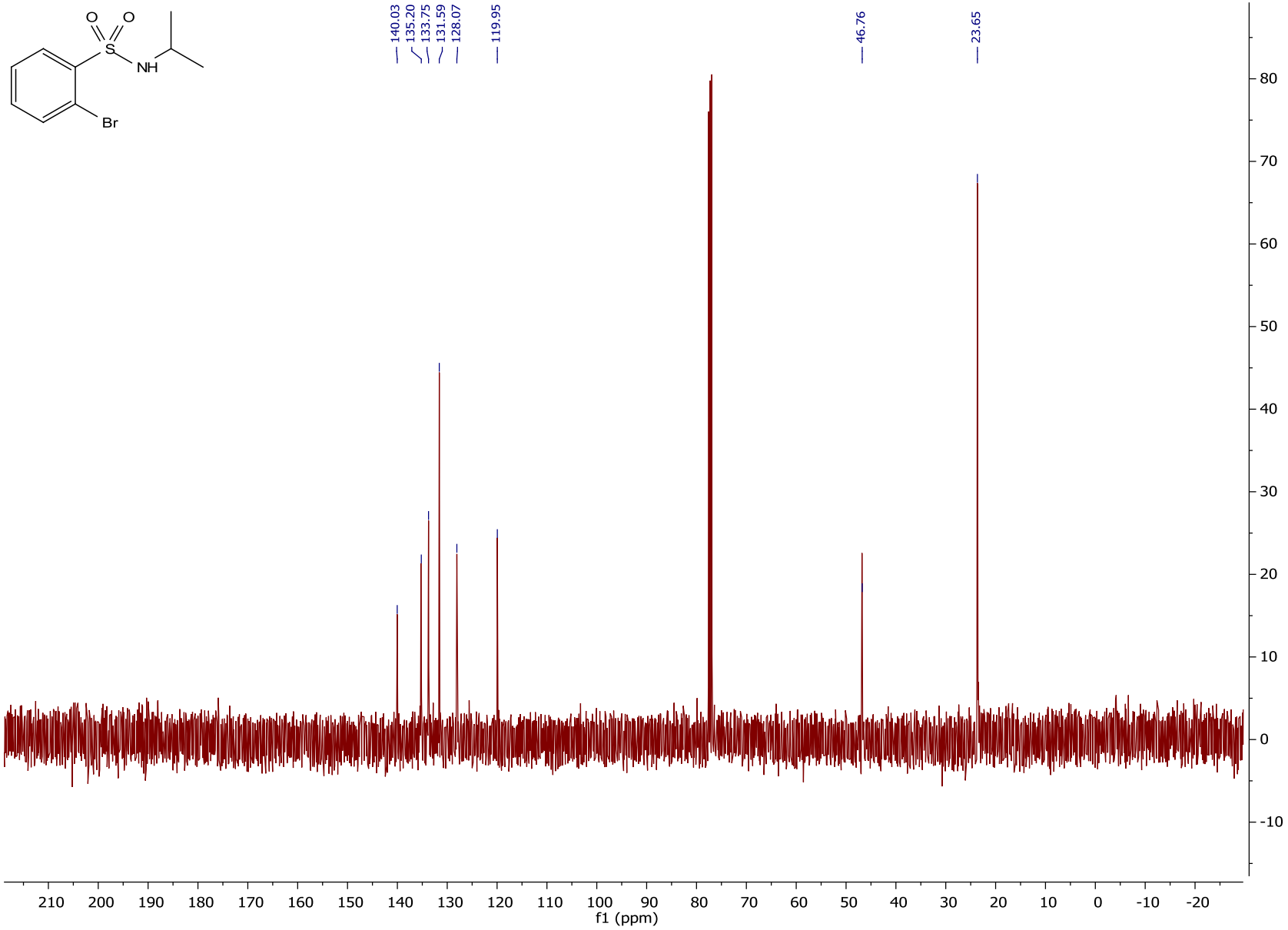
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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135.20
133.75
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128.07
119.95
46.76
23.65
80
70
60
50
40
30
20
10
0
-10
210
200
190
180
170
160
150
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130
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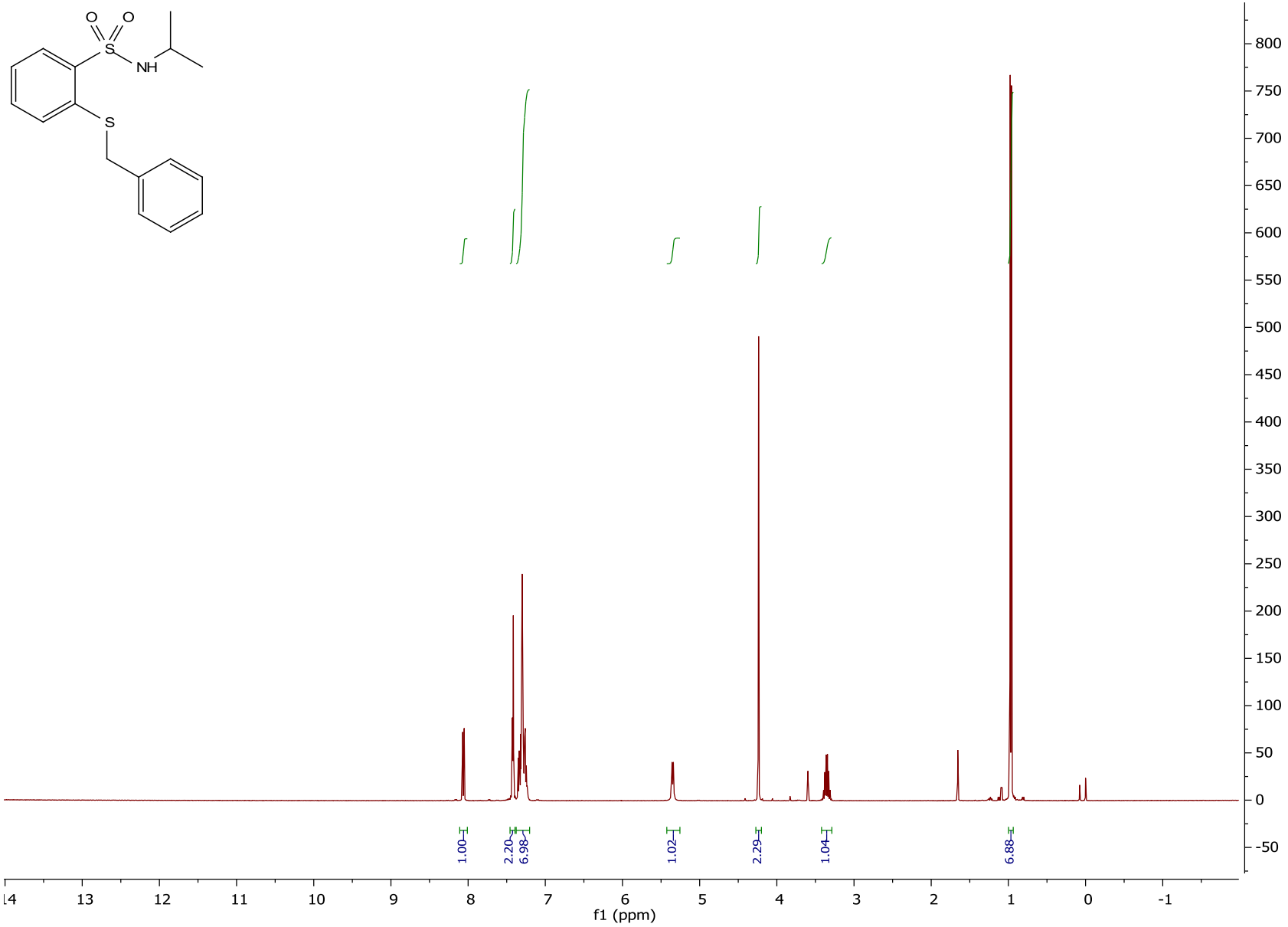
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)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S
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6.98
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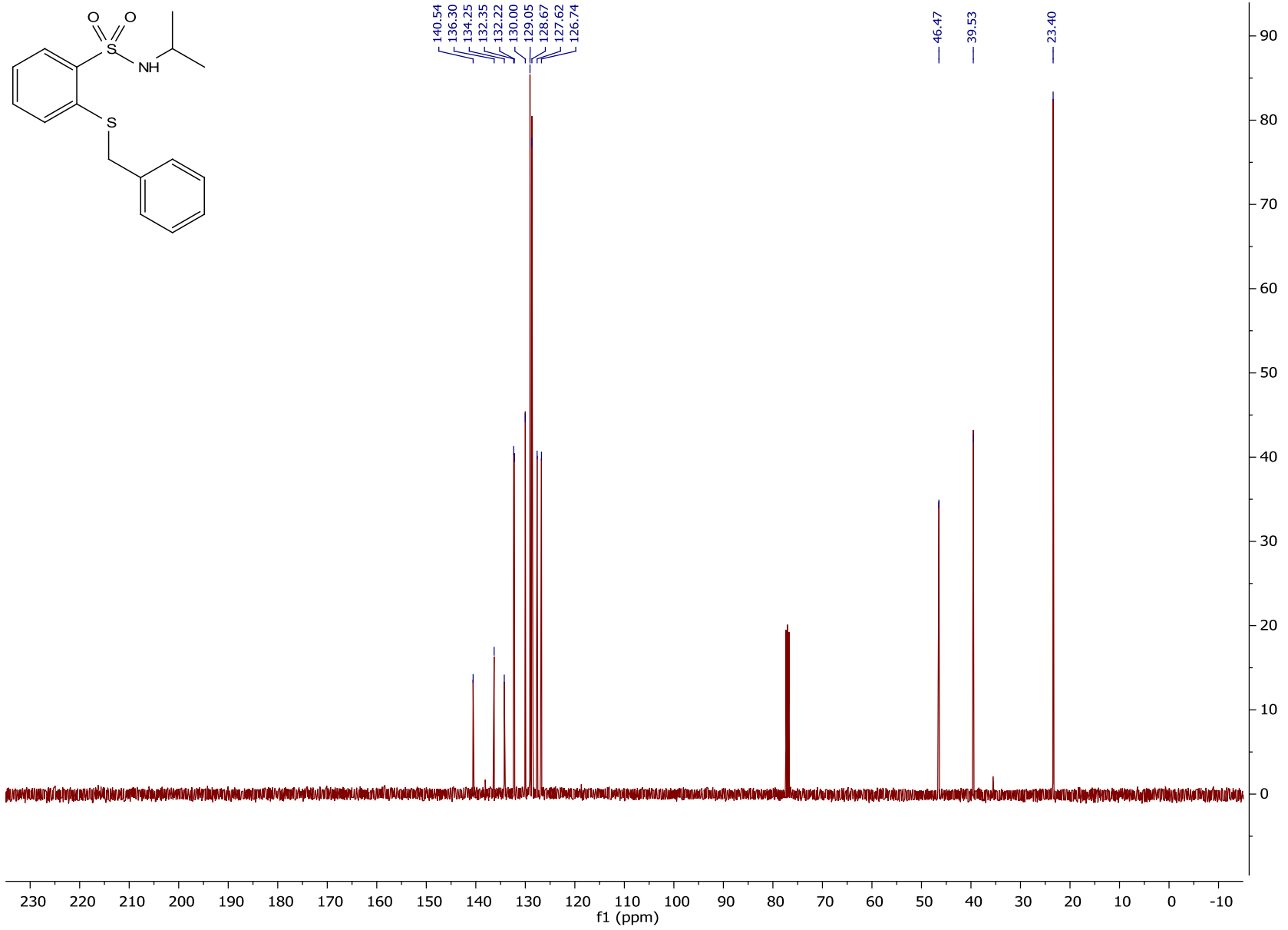
2.29
1.04
6.88
f1 (ppm)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NH
S
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134.25
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128.67
127.62
126.74
46.47
39.53
23.40
90
80
70
60
50
40
30
20
10
0
230
220
210
200
190
180
170
160
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120
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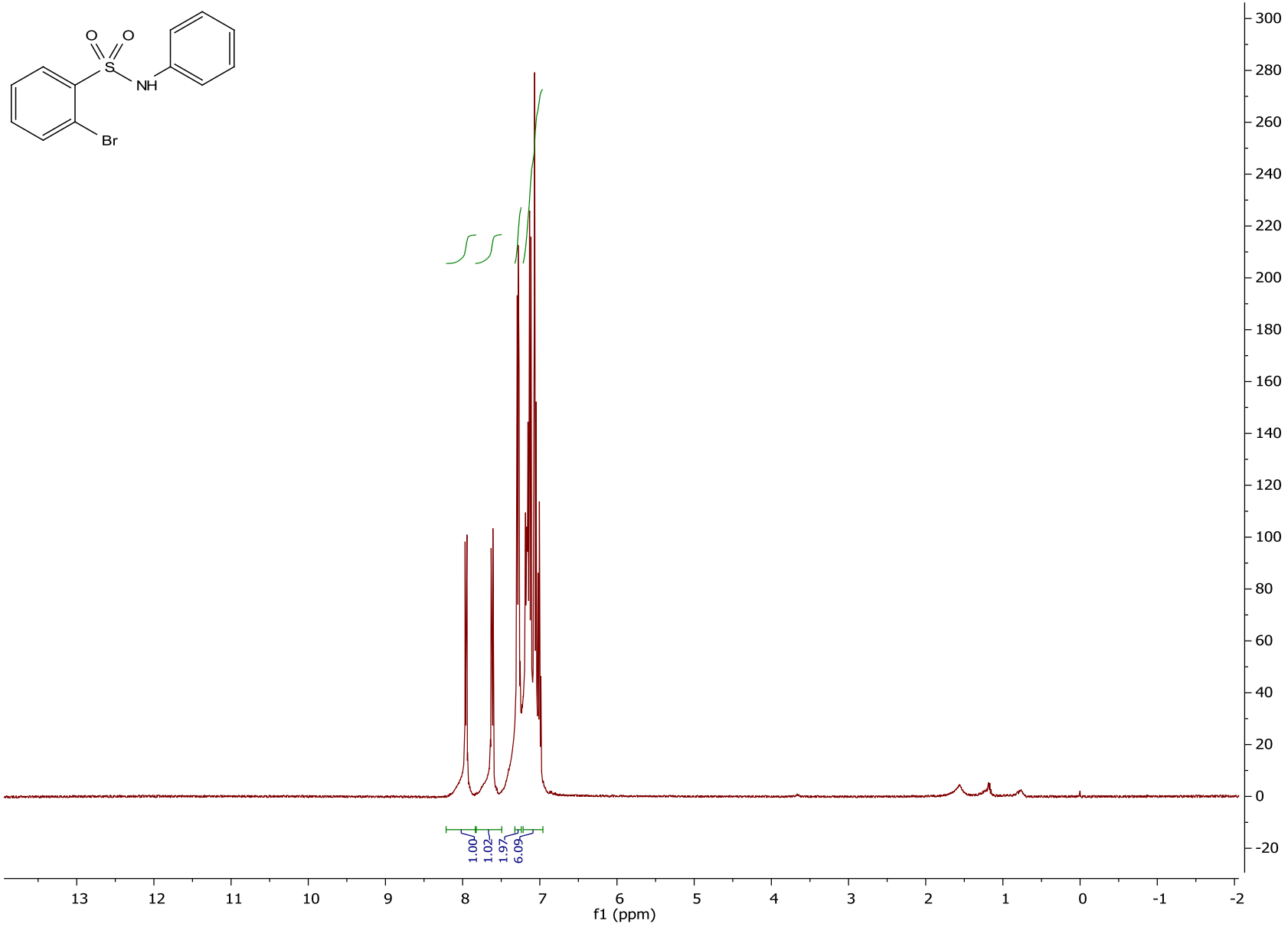
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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S
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Br
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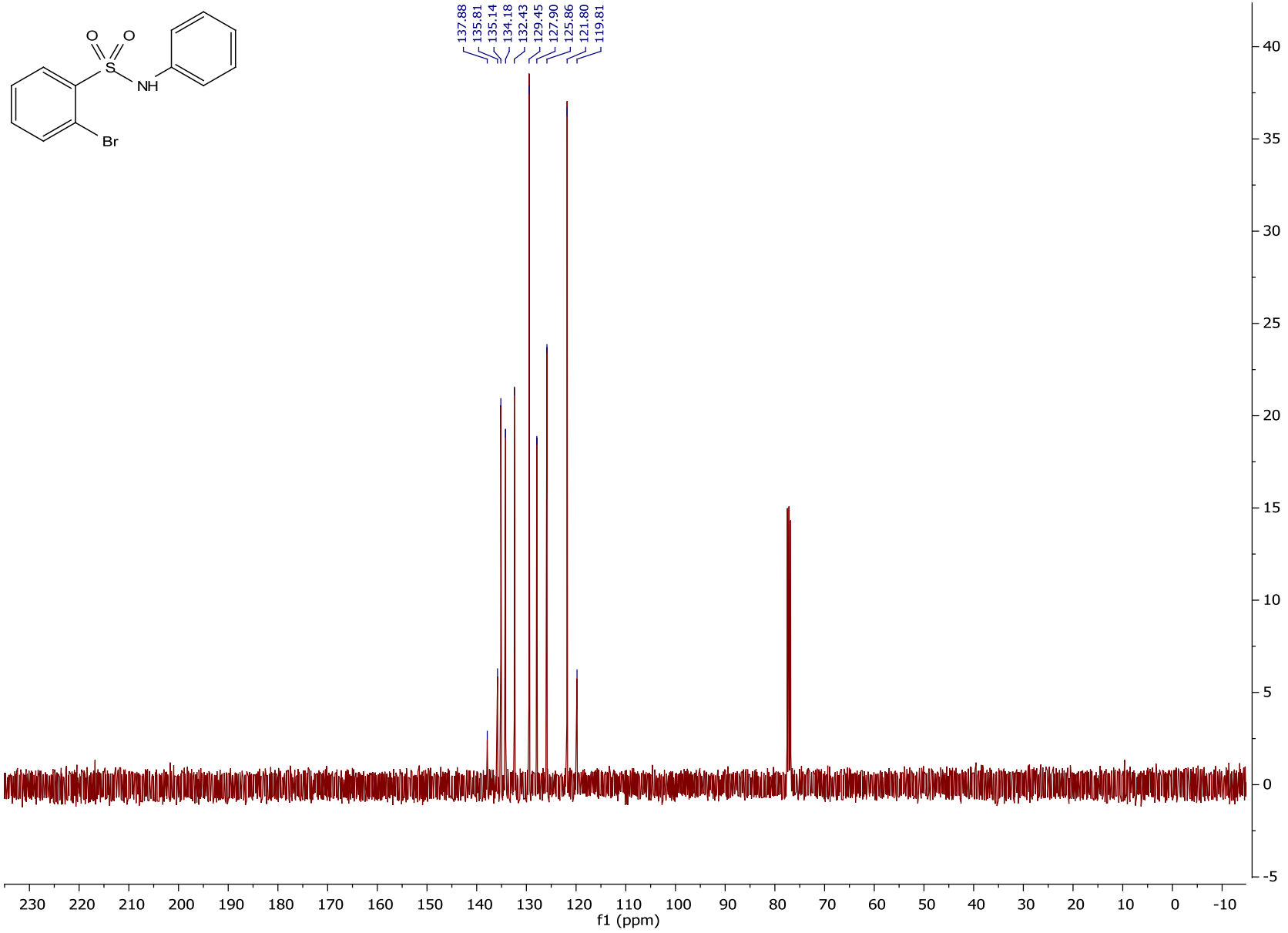
1.02
1.97
6.09
f1 (ppm)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Br
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132.43
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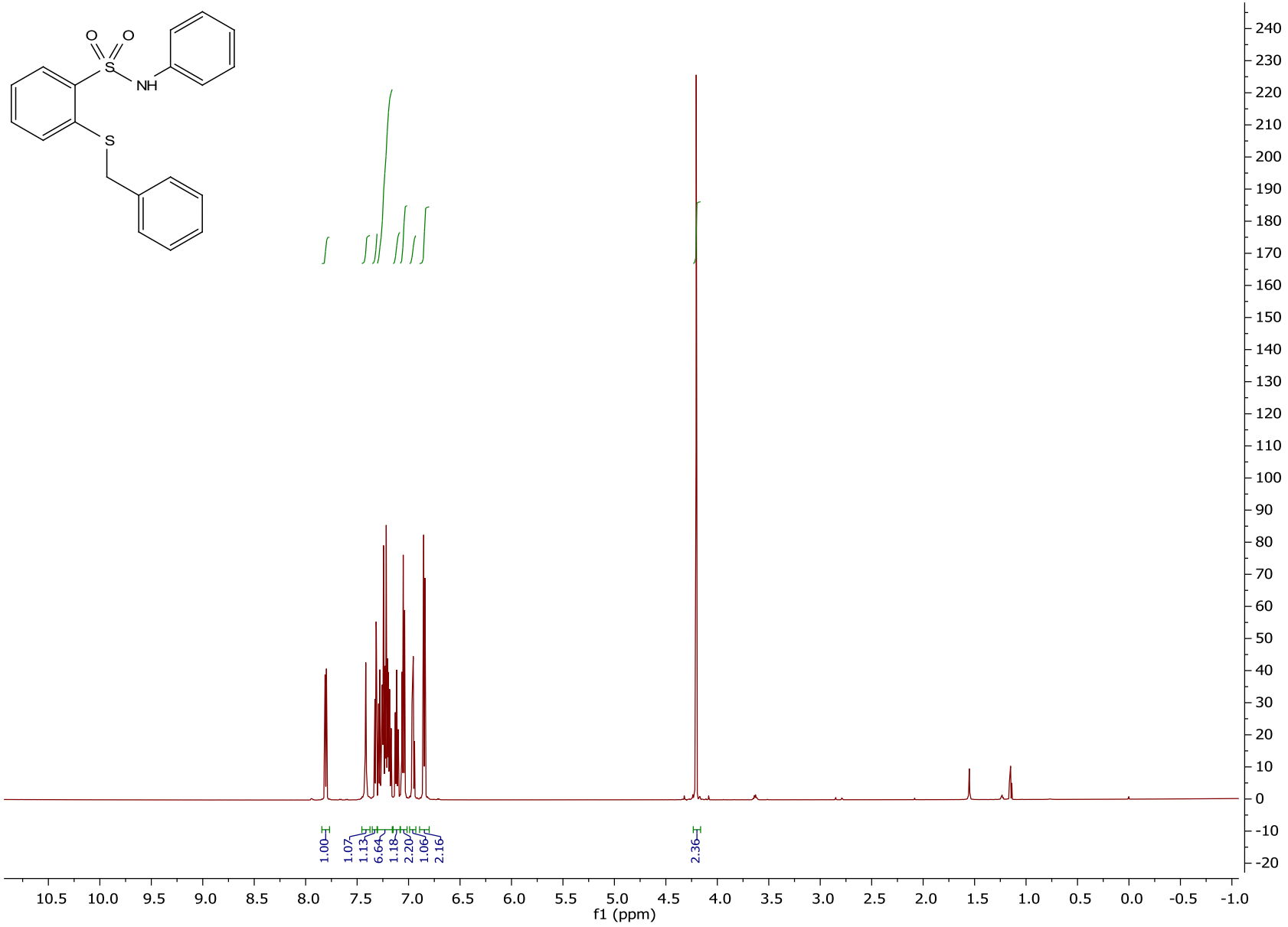
127.90
125.86
121.80
119.81
40
35
30
25
20
15
10
5
0
-5
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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O
S
NH
S
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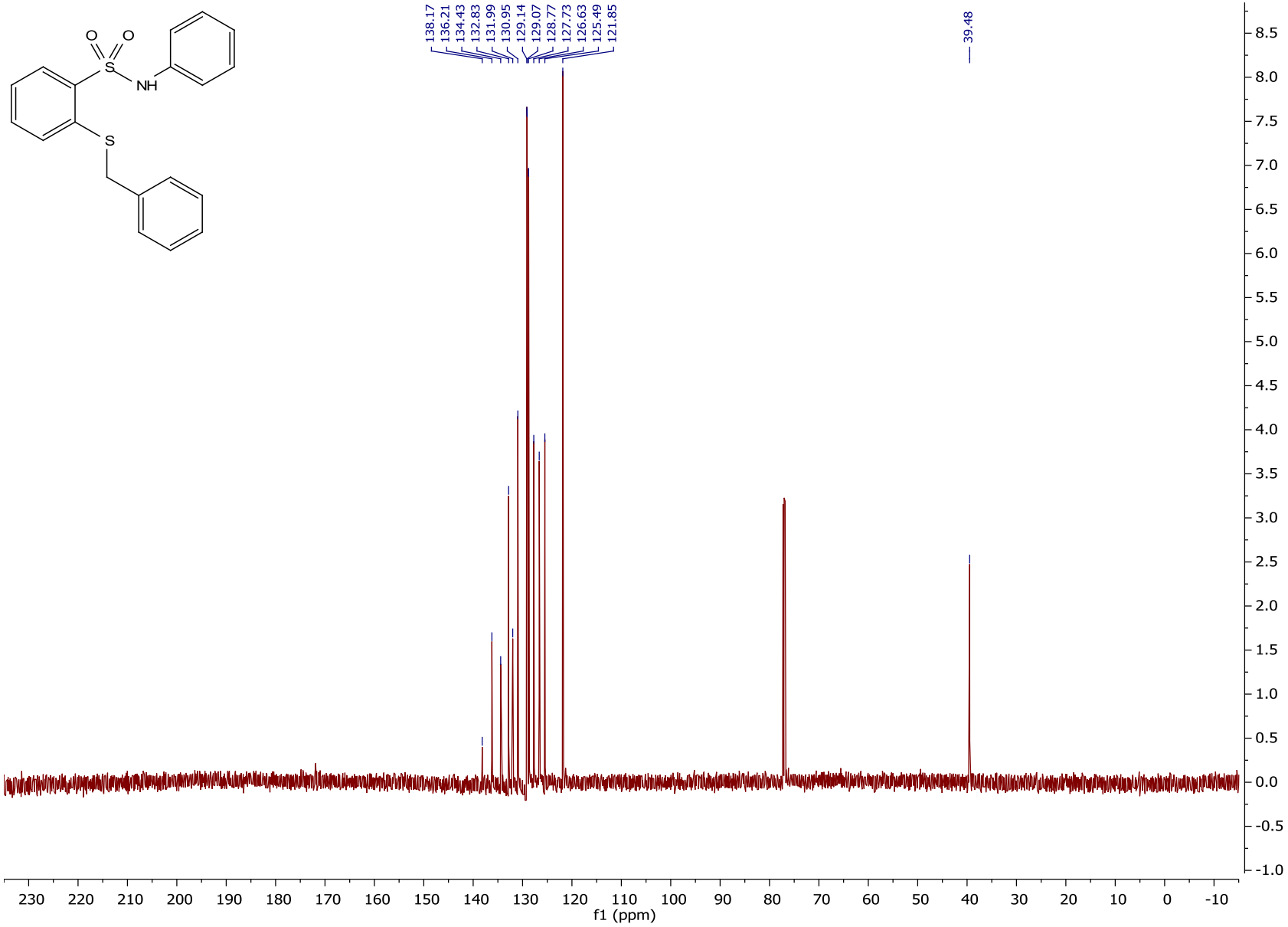
1.13
6.64
1.18
2.20
1.06
2.16
2.36
f1 (ppm)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129.14
129.07
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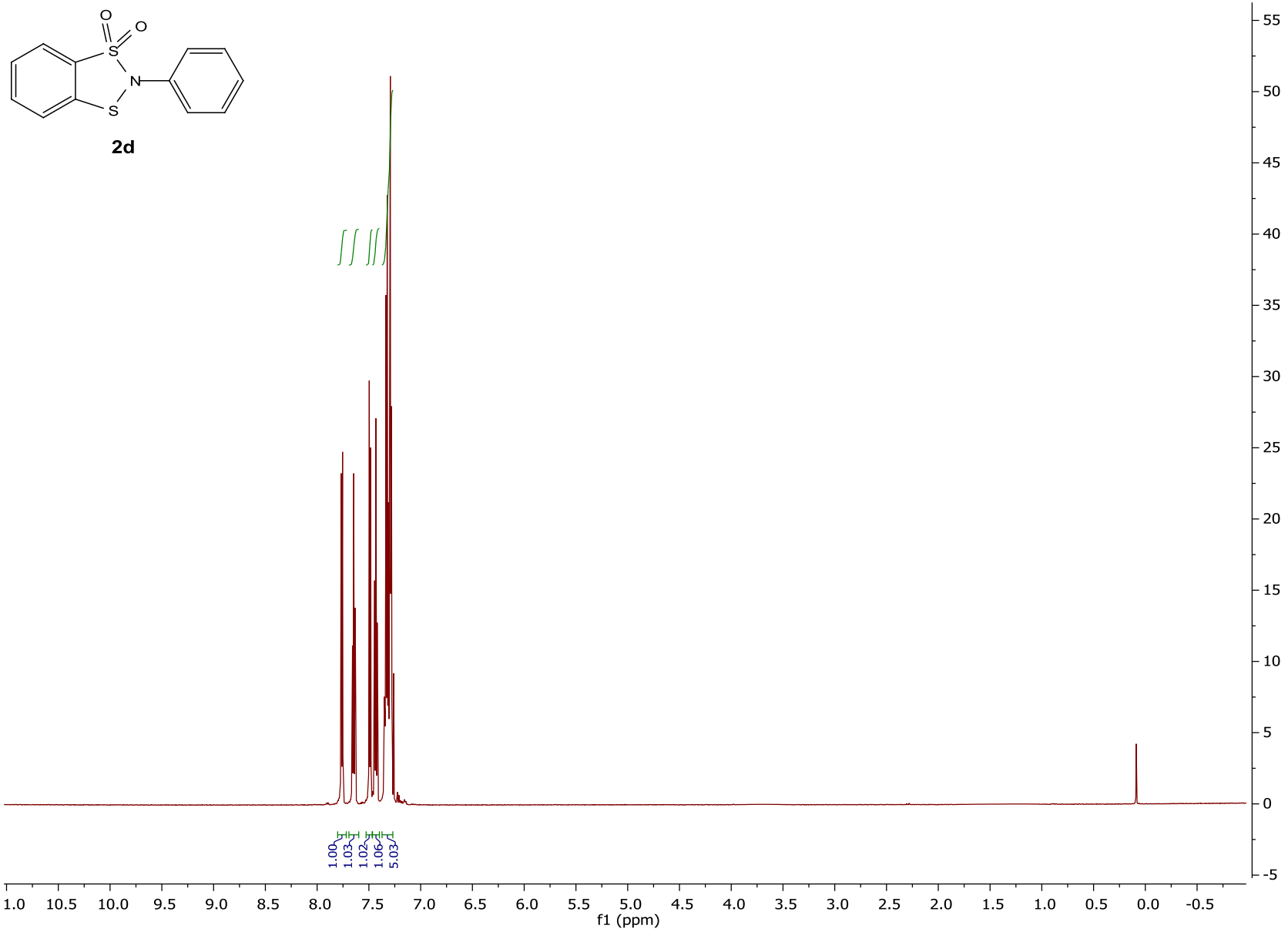
127.73
126.63
125.49
121.85
39.48
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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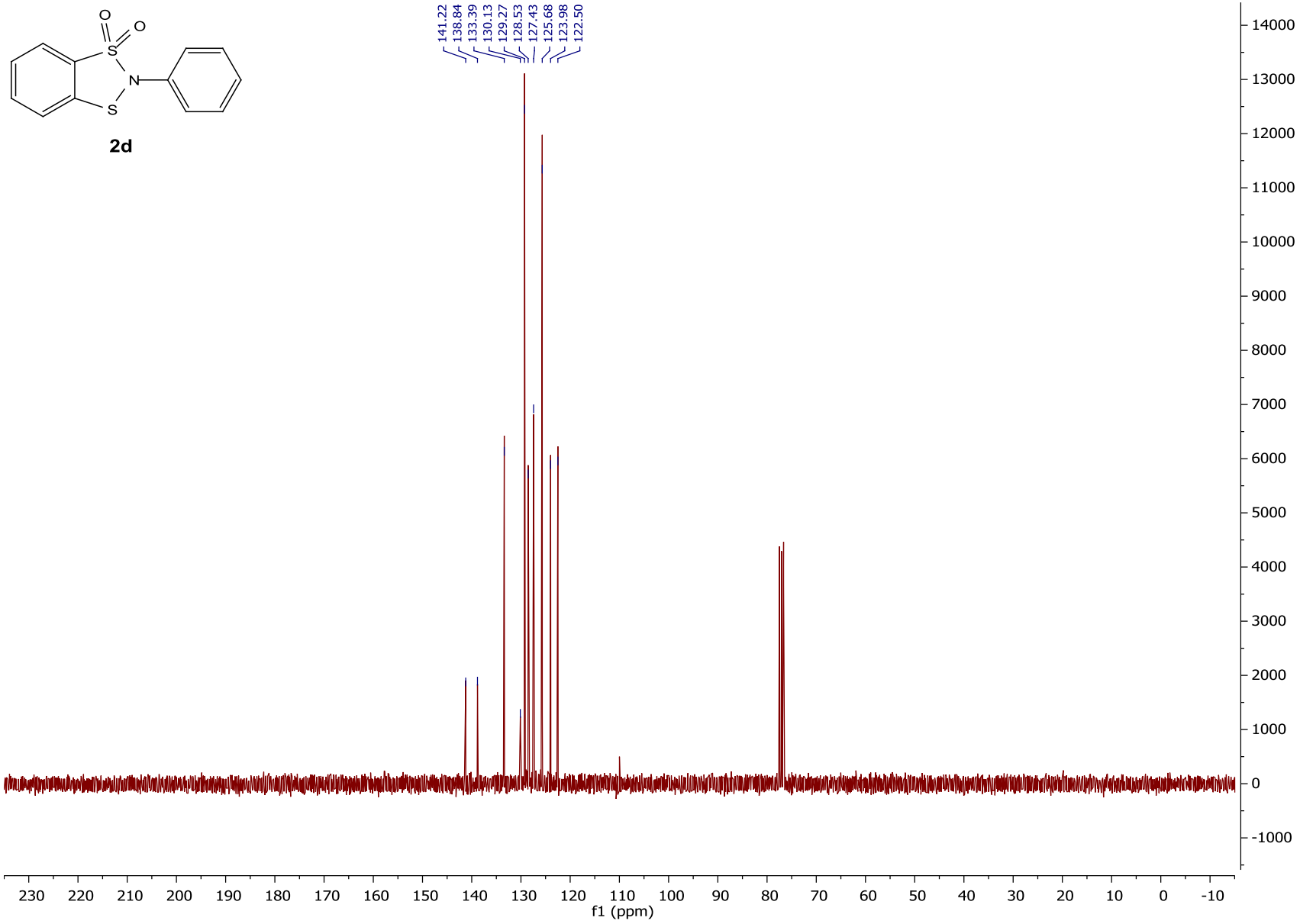
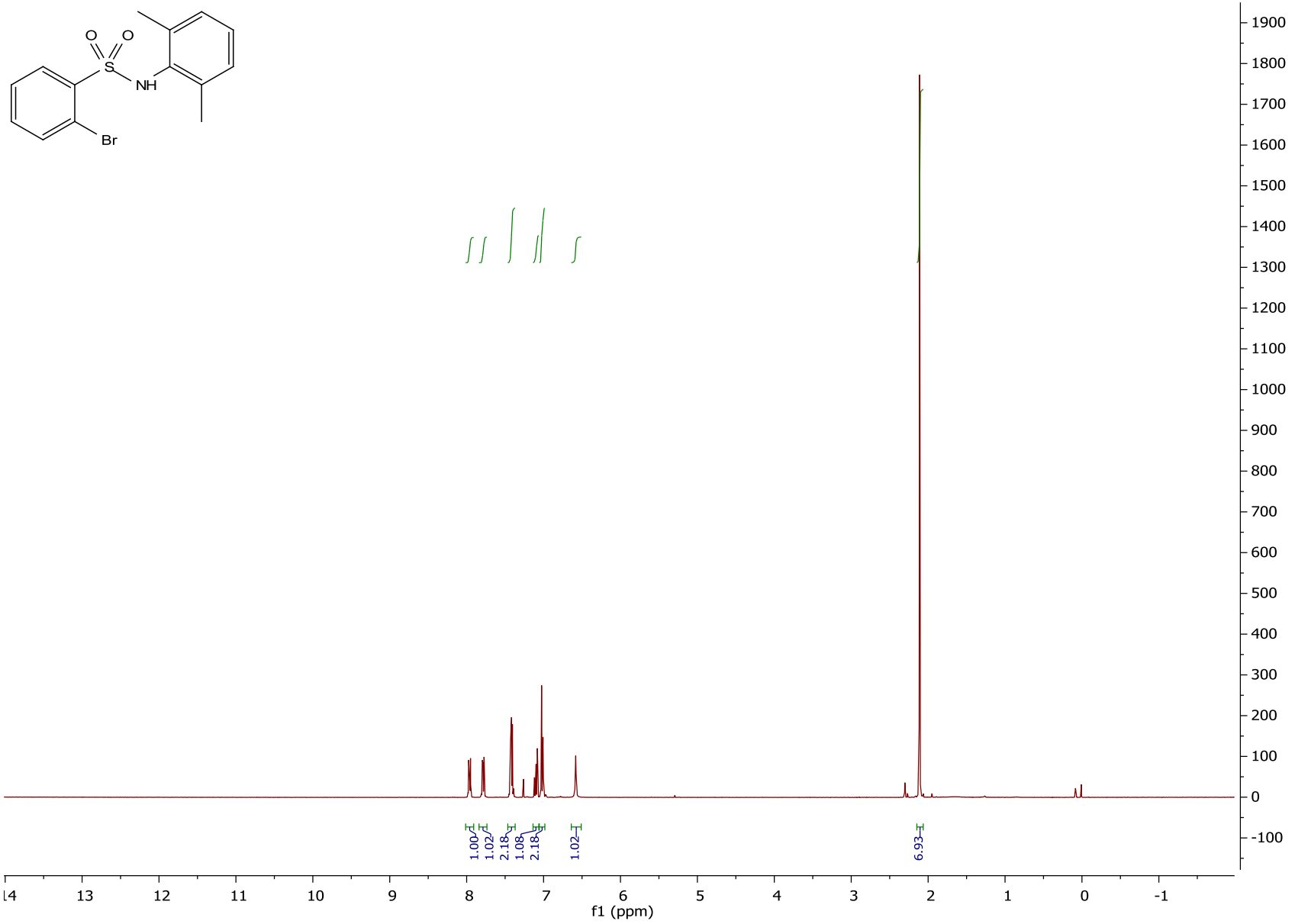
O
S
N
S
2d
1.00
1.03
1.02
1.06
5.03
f1 (ppm)


O
O
S
N
S
2d
141.22
138.84
133.39
130.13
129.27
128.53
127.43
125.68
123.98
122.50
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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S
NH
Br
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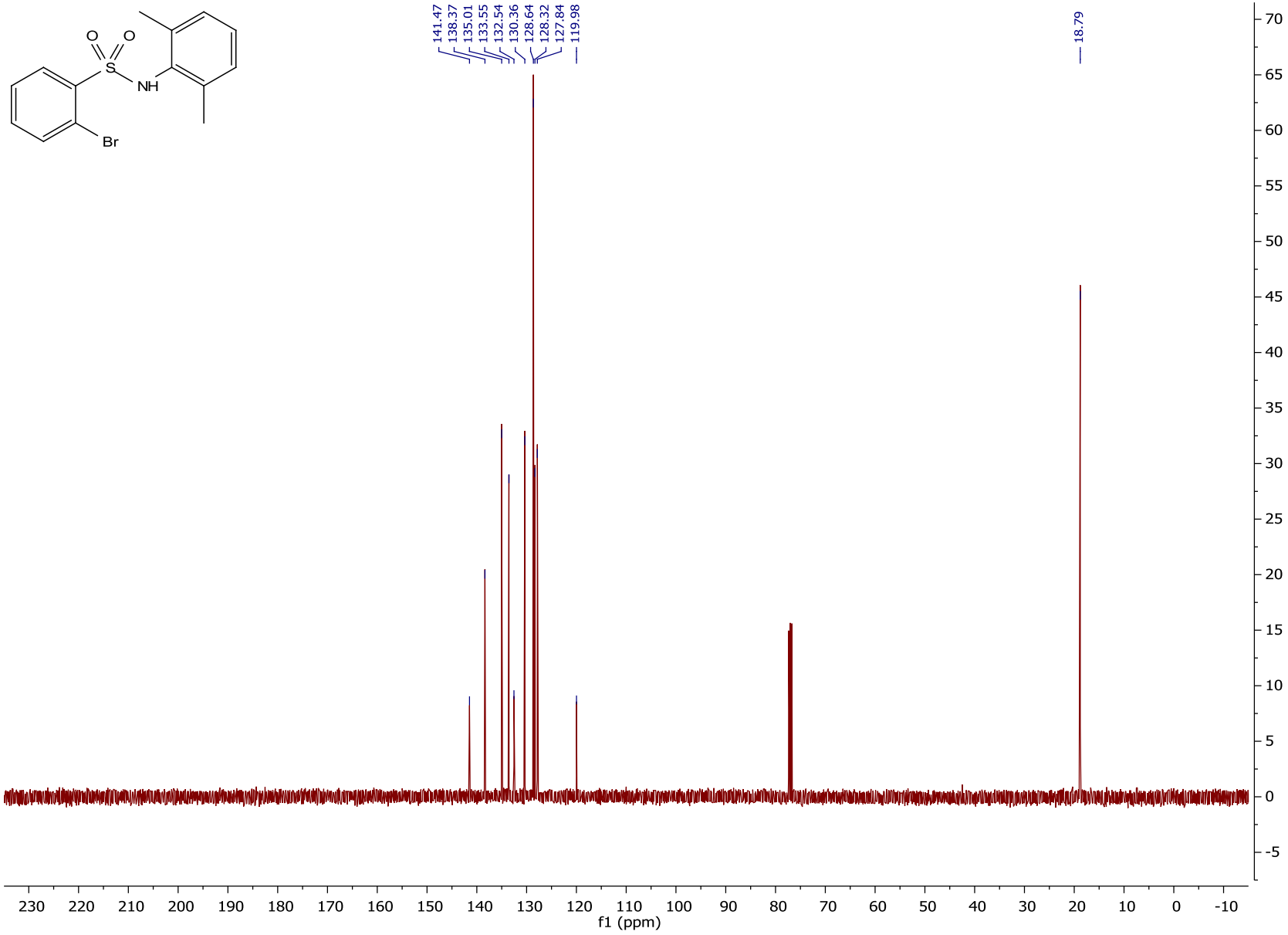
2.18
1.08
2.18
1.02
6.93
f1 (ppm)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S
NH
Br
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132.54
130.36
128.64
128.32
127.84
119.98
18.79
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
230
220
210
200
190
180
170
160
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140
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120
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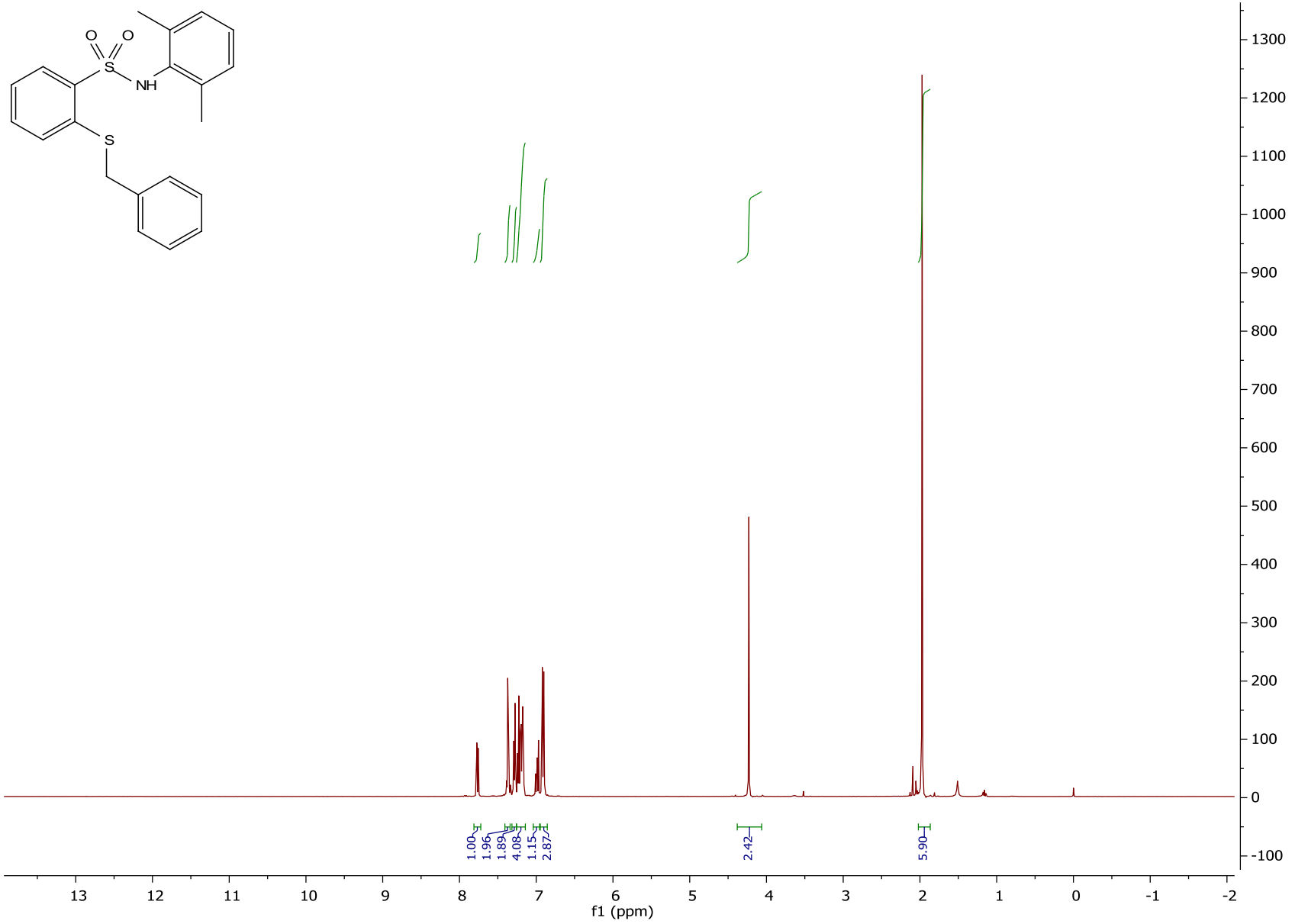
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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S
NH
S
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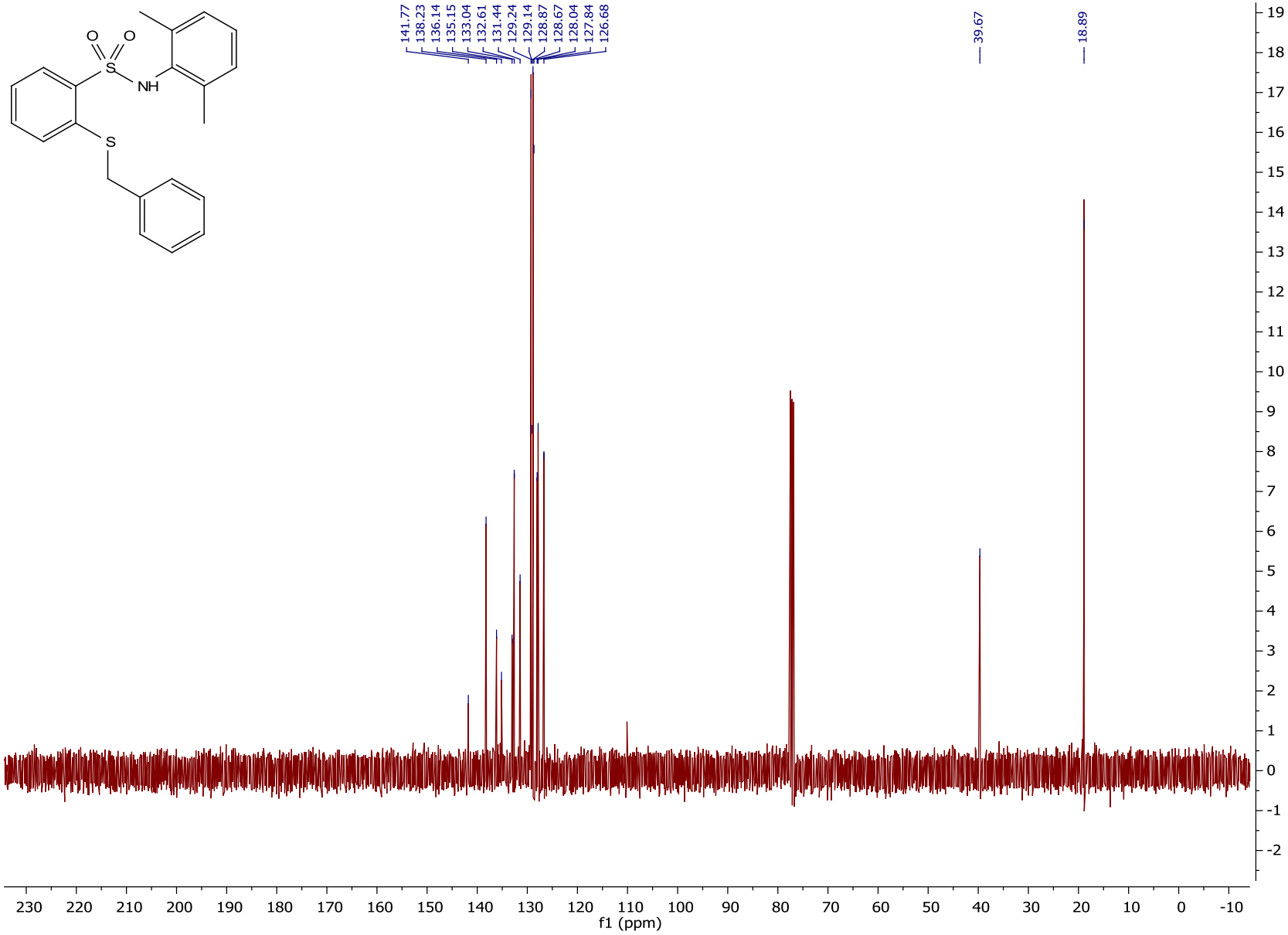
1.96
1.89
4.08
1.15
2.87
2.42
5.90
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100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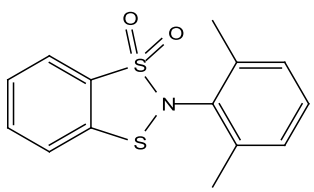
127.84
126.68
39.67
18.89
f1 (ppm)


O
O
S
N
S

2e

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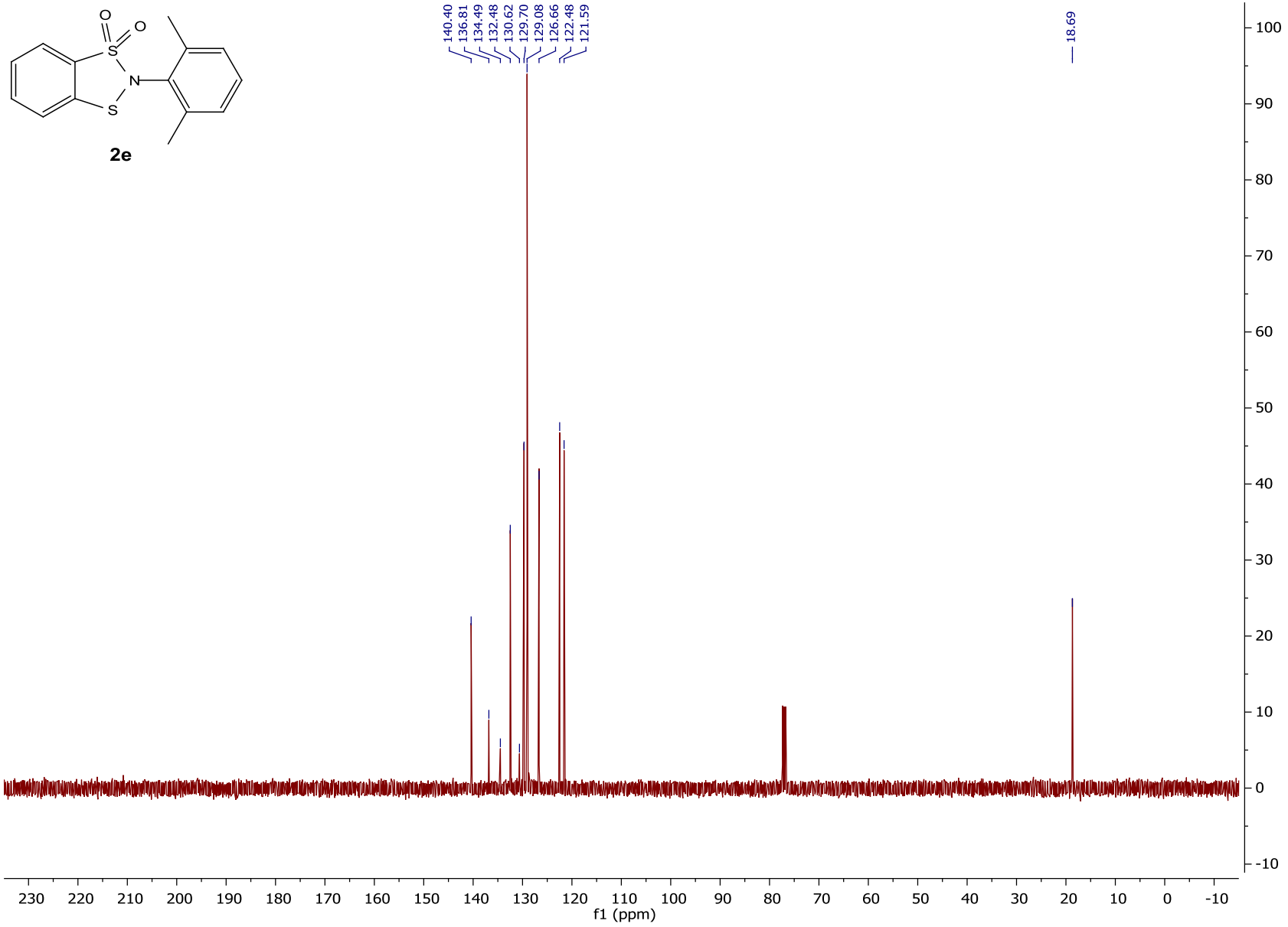
900
800
700
600
500
400
300
200
100
0
1.00
1.17
2.17
1.09
2.08
6.60
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)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O
S
N
S
2e
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129.70
129.08
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122.48
121.59
18.69
100
90
80
70
60
50
40
30
20
10
0
-10
230
220
210
200
190
180
170
160
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140
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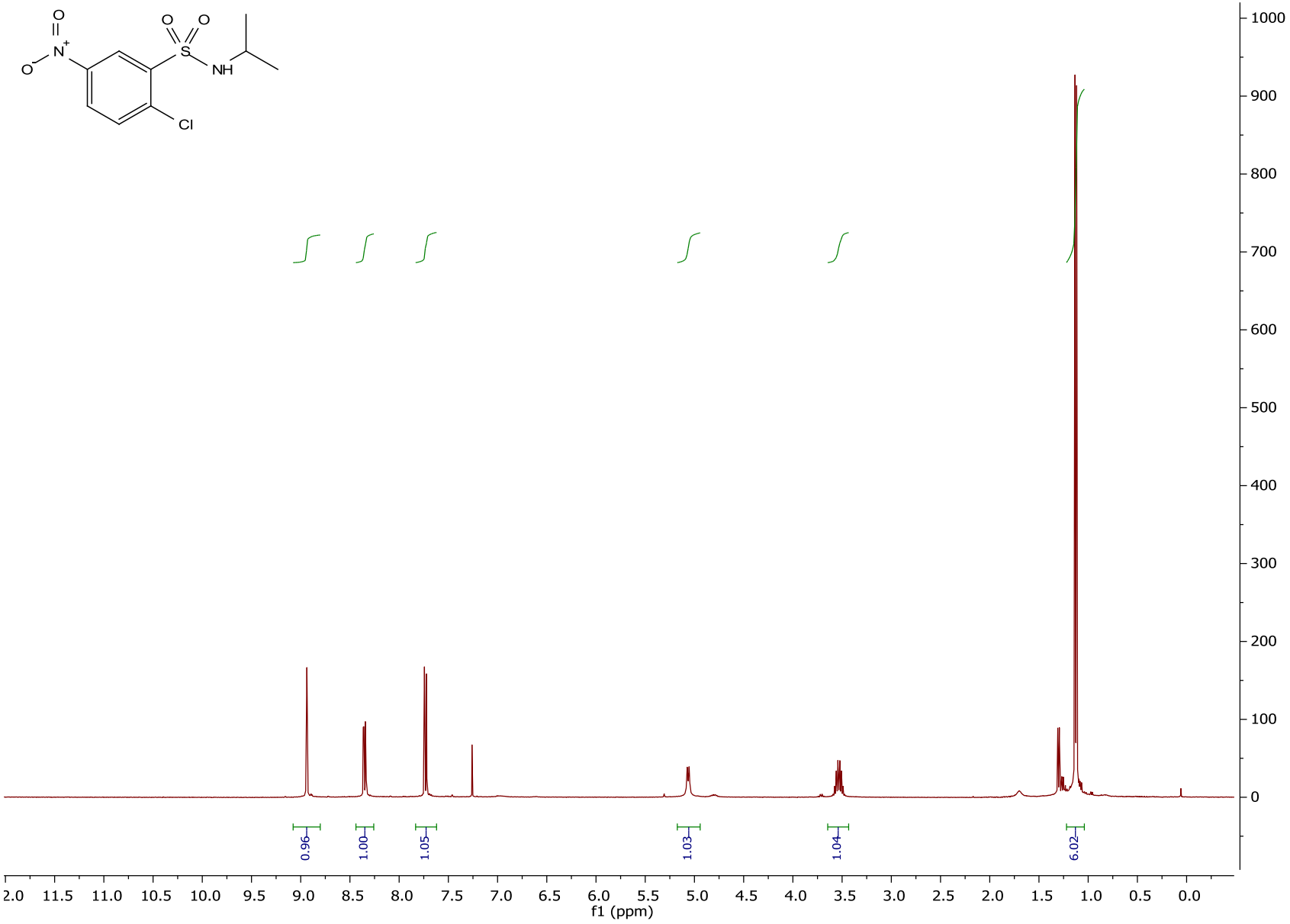
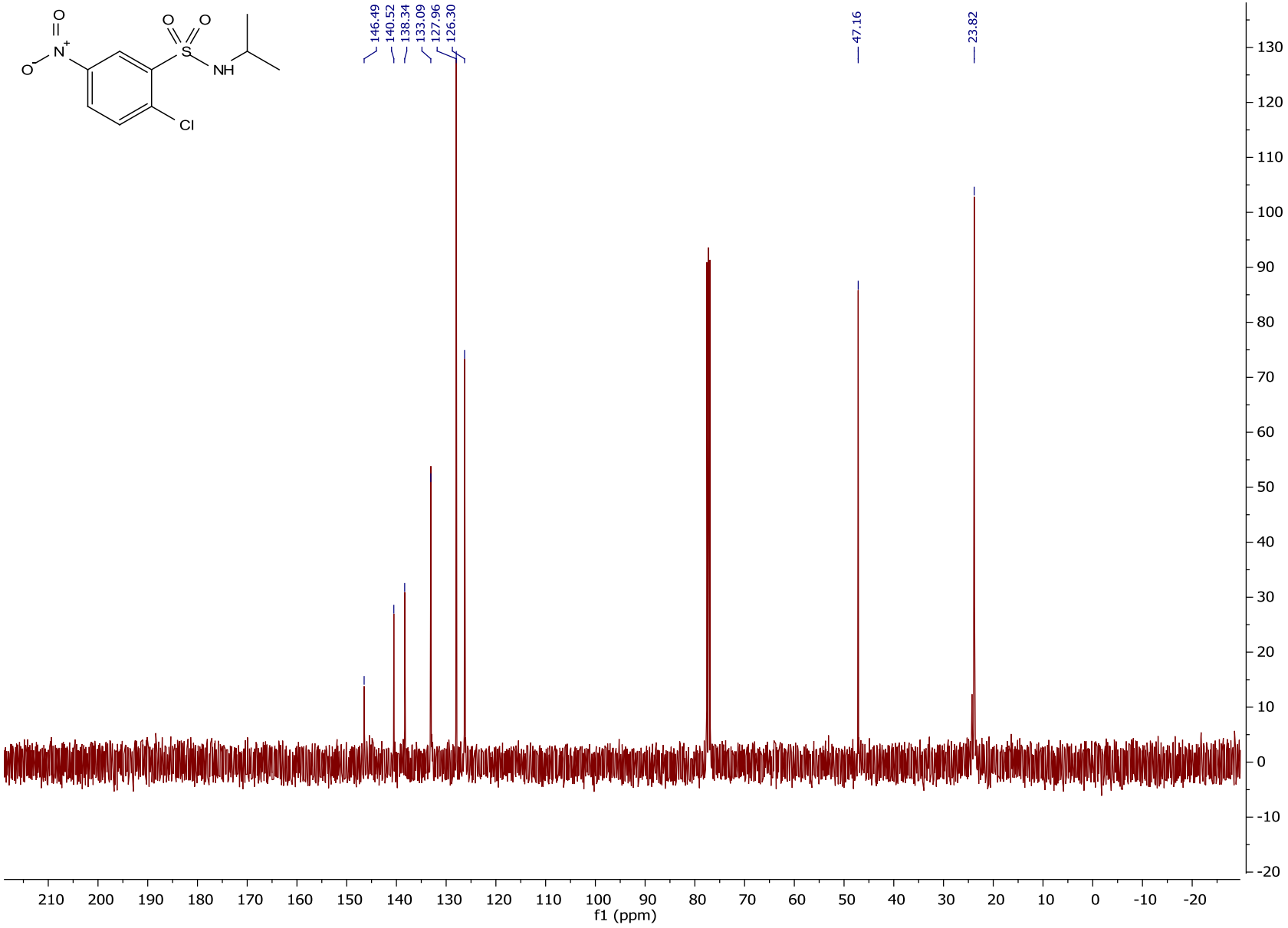
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
N+
O-
O
O
S
NH
Cl
1000
900
800
700
600
500
400
300
200
100
0
0.96
1.00
1.05
1.03
1.04
6.02
2.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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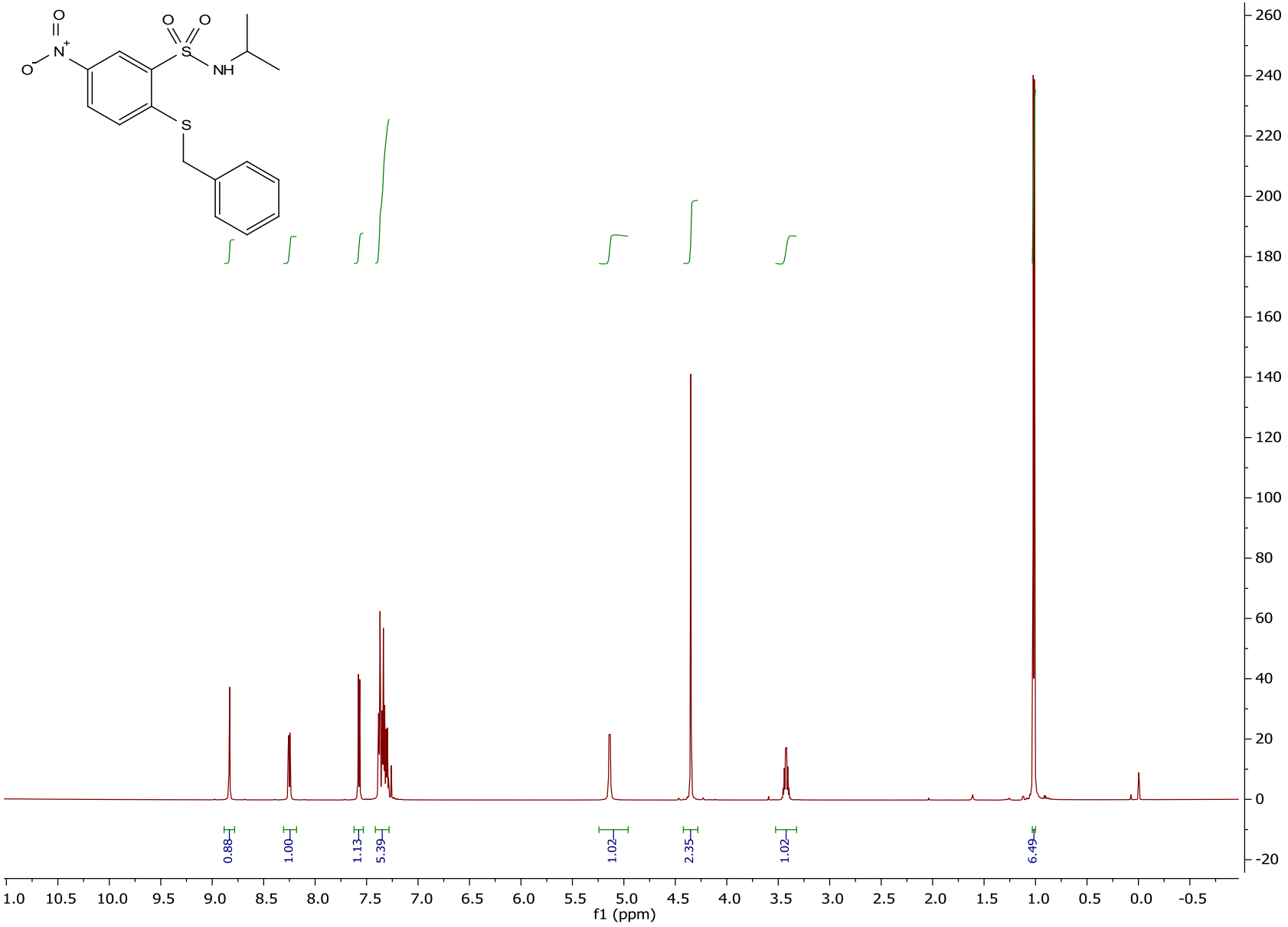
127.96
126.30
47.16
23.82
f1 (ppm)


O
N+
O-
O
O
S
NH
S
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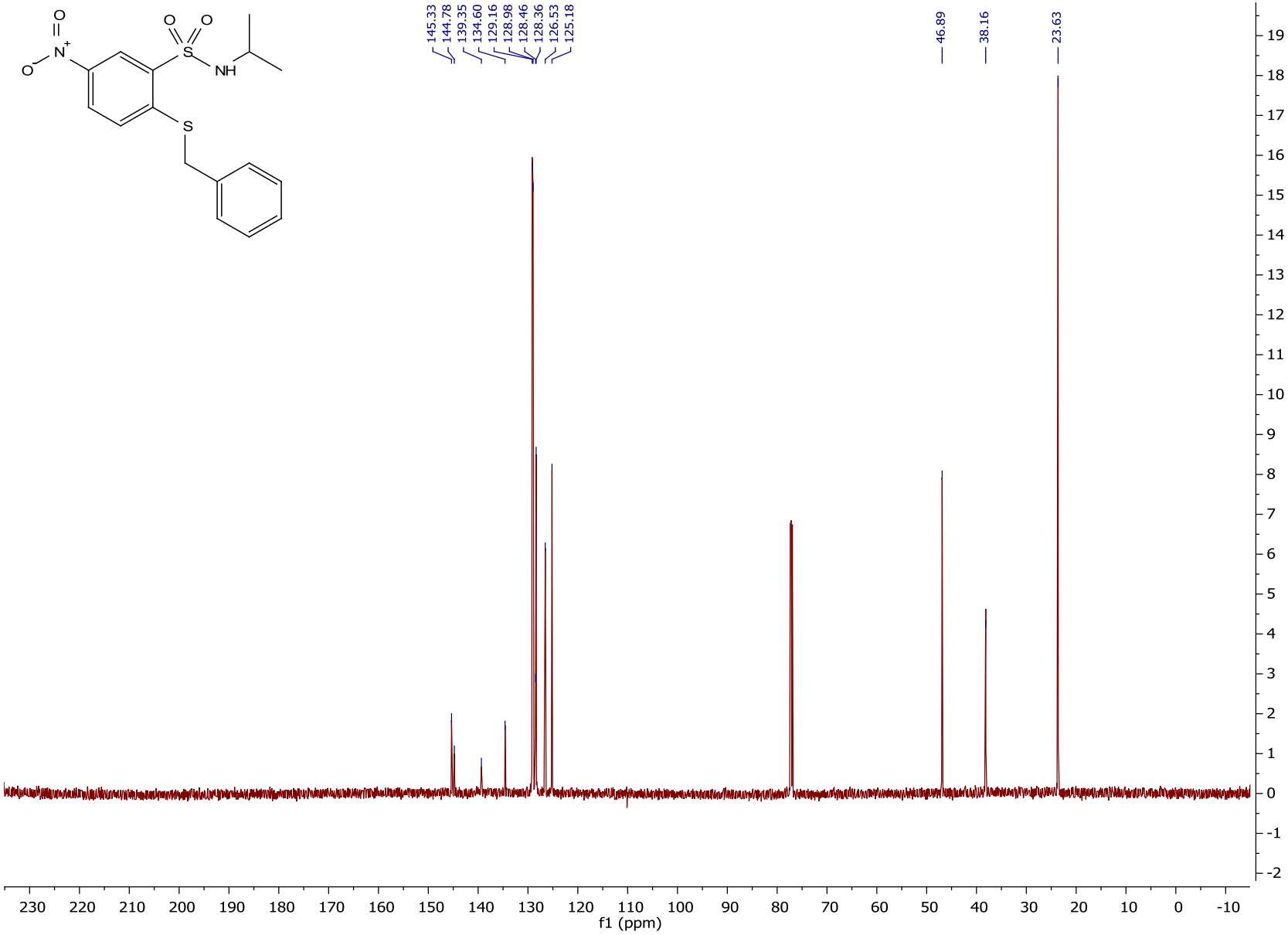
1.00
1.13
5.39
1.02
2.35
1.02
6.49
f1 (ppm)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144.78
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128.36
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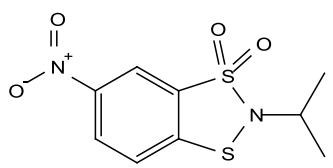
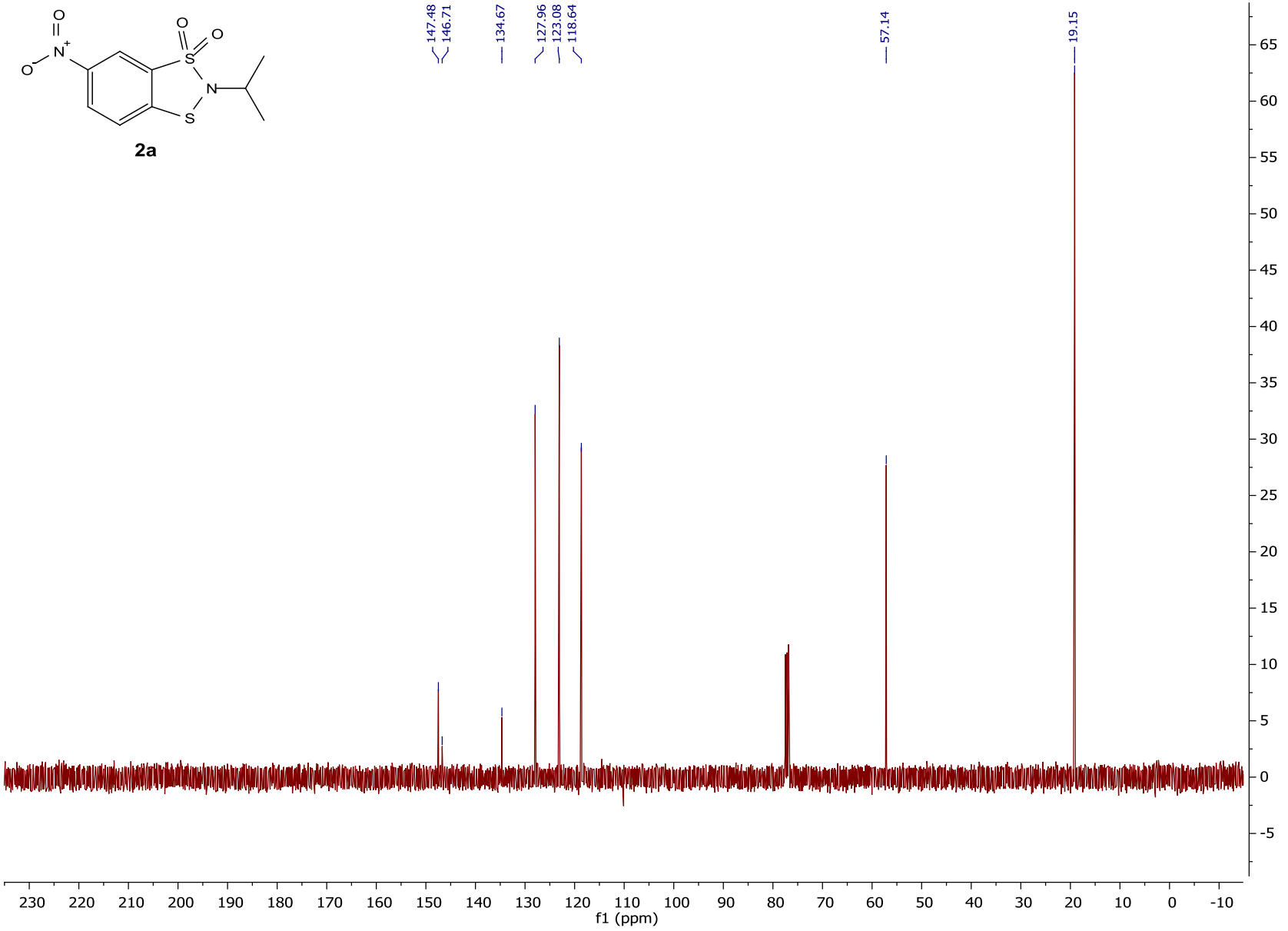
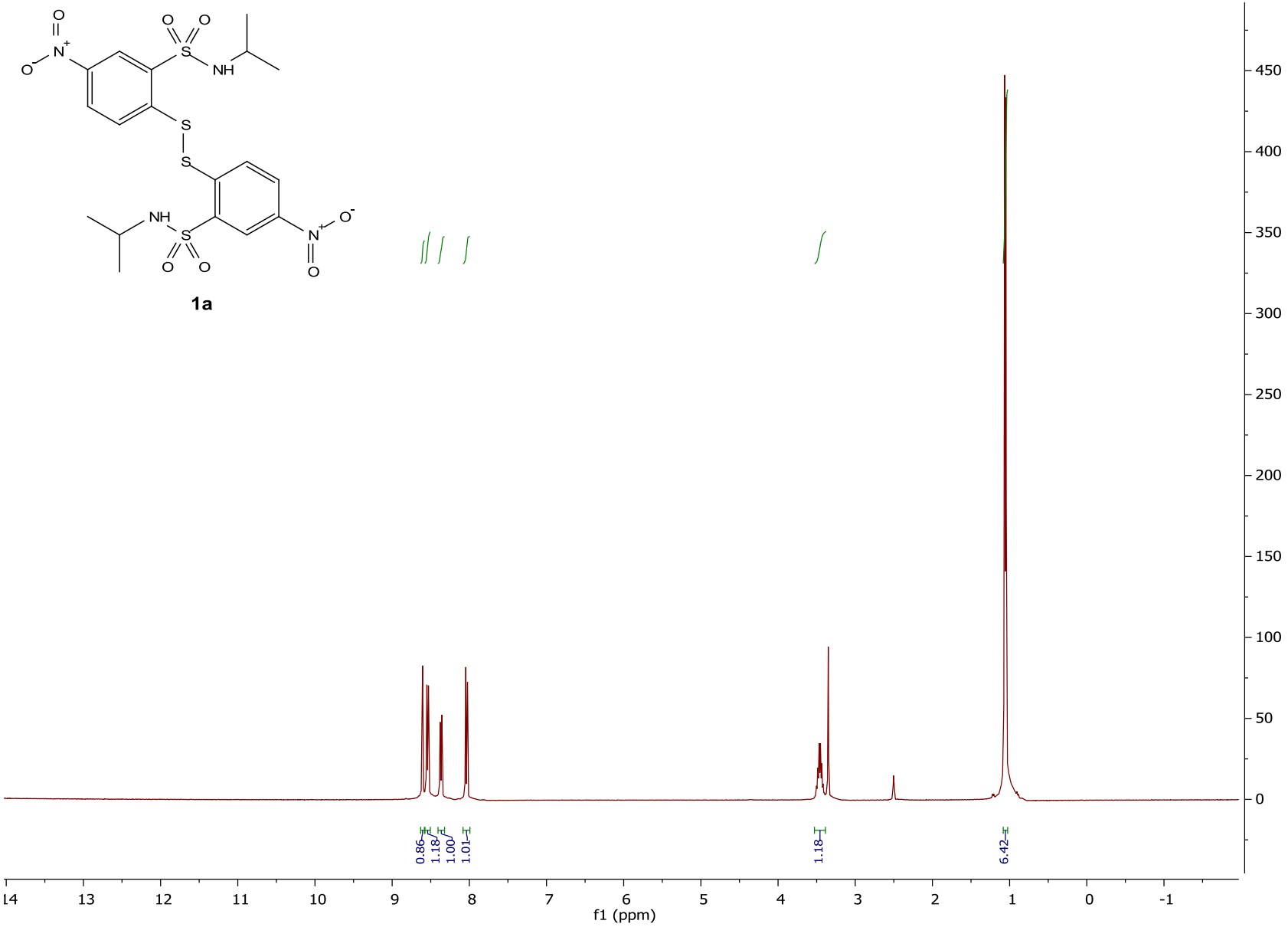
125.18
46.89
38.16
23.63
f1 (ppm)



2a



2a


1a
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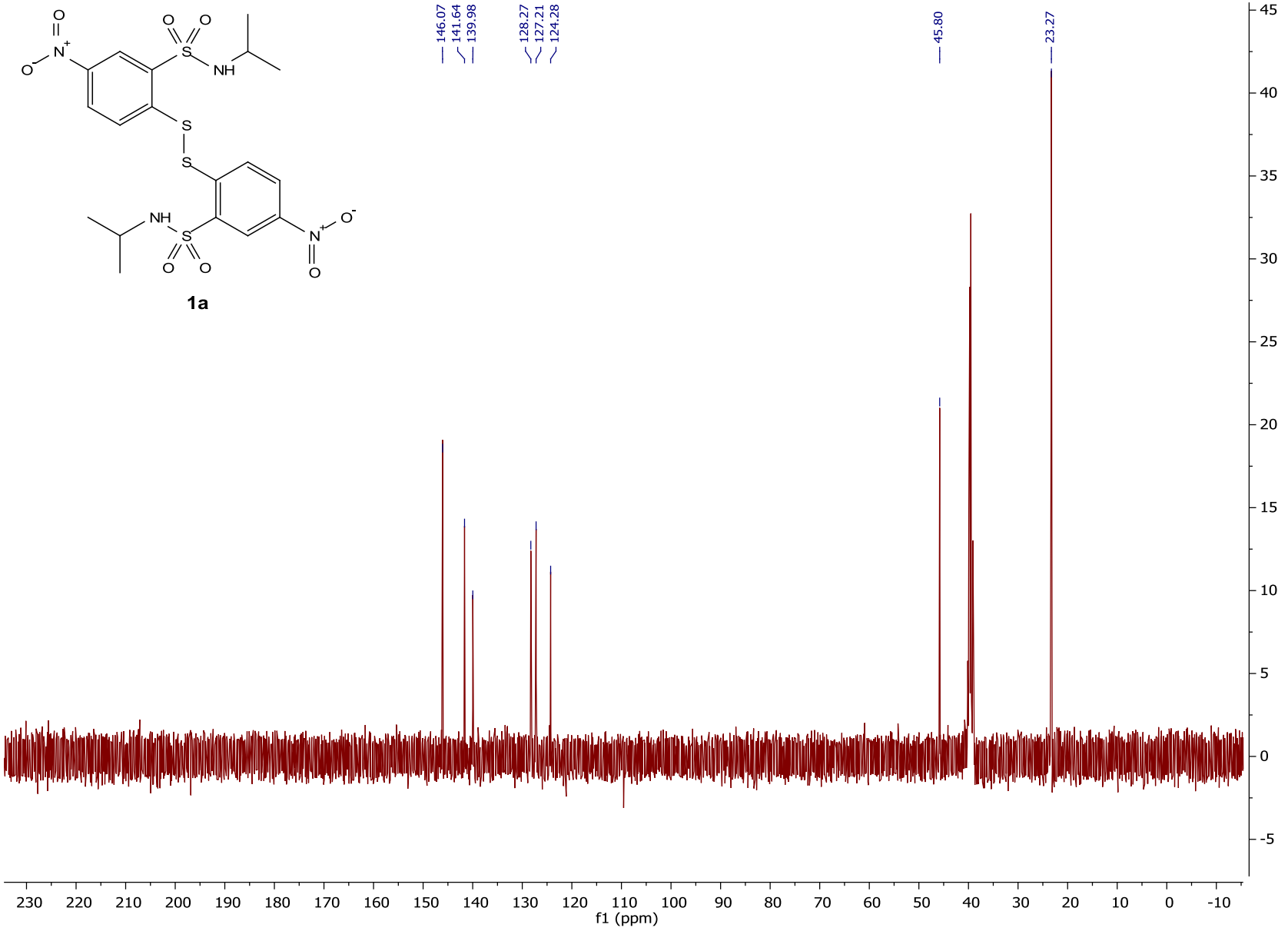
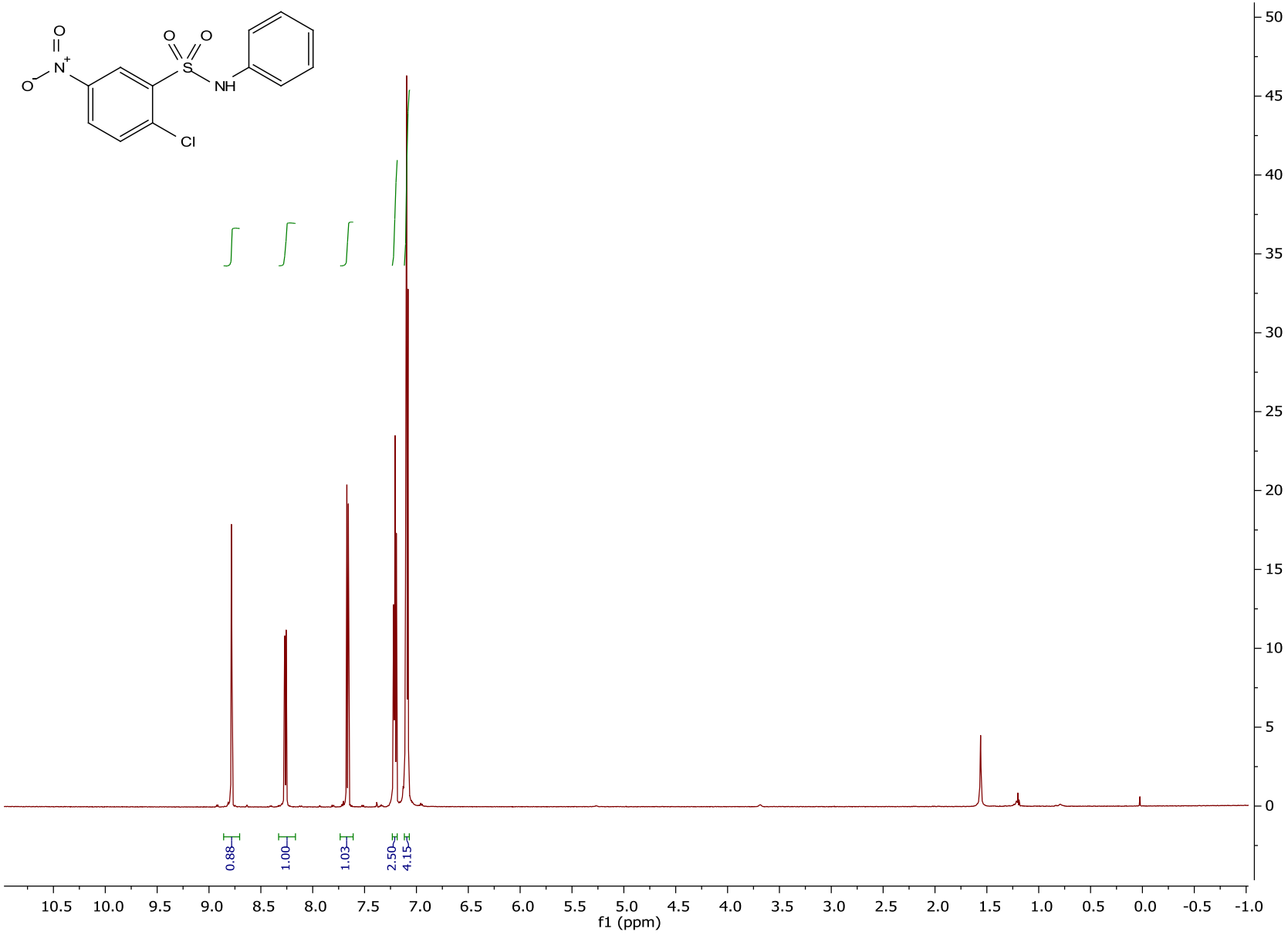
1.18
1.00
1.01
1.18
6.42
f1 (ppm)



1a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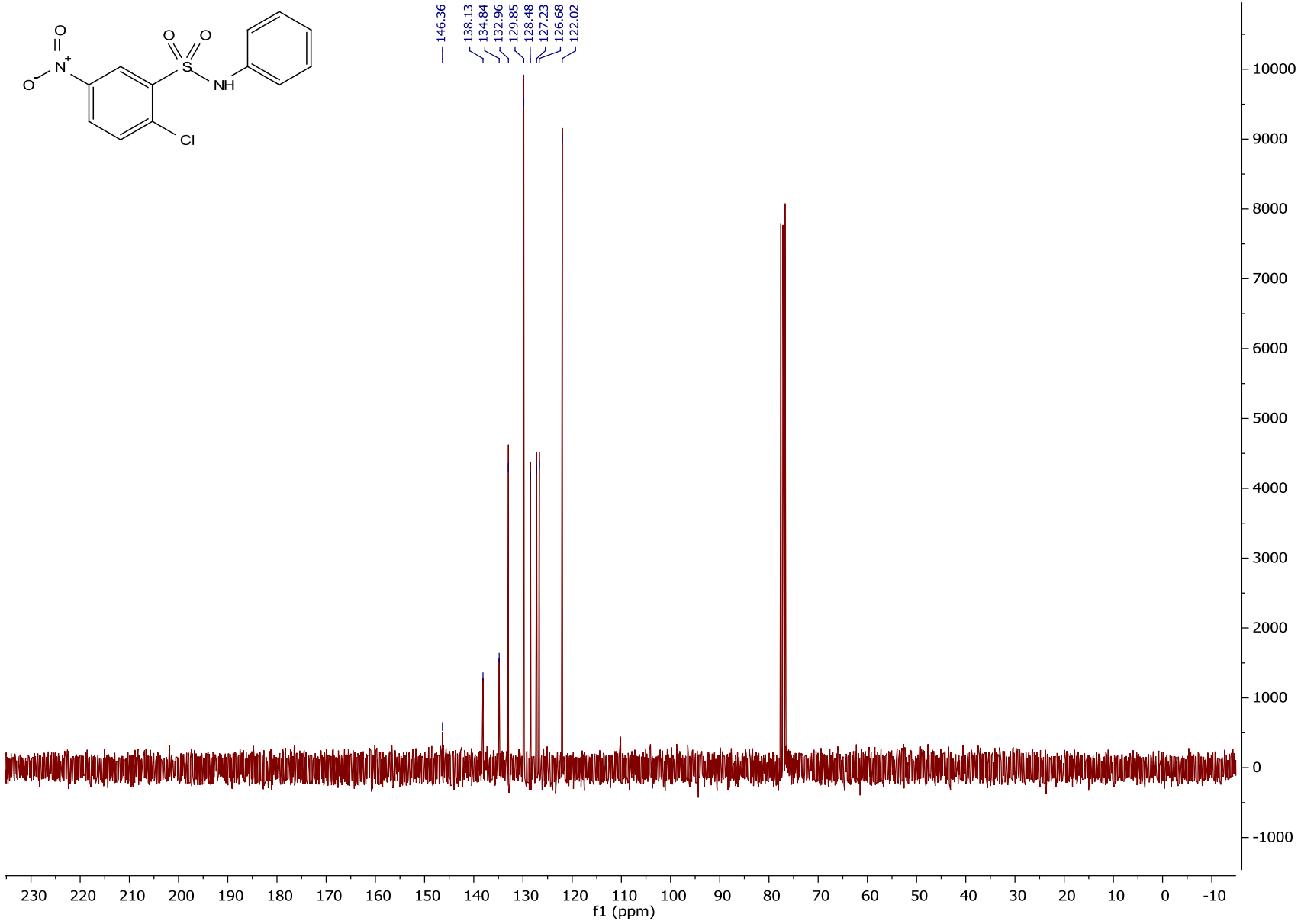
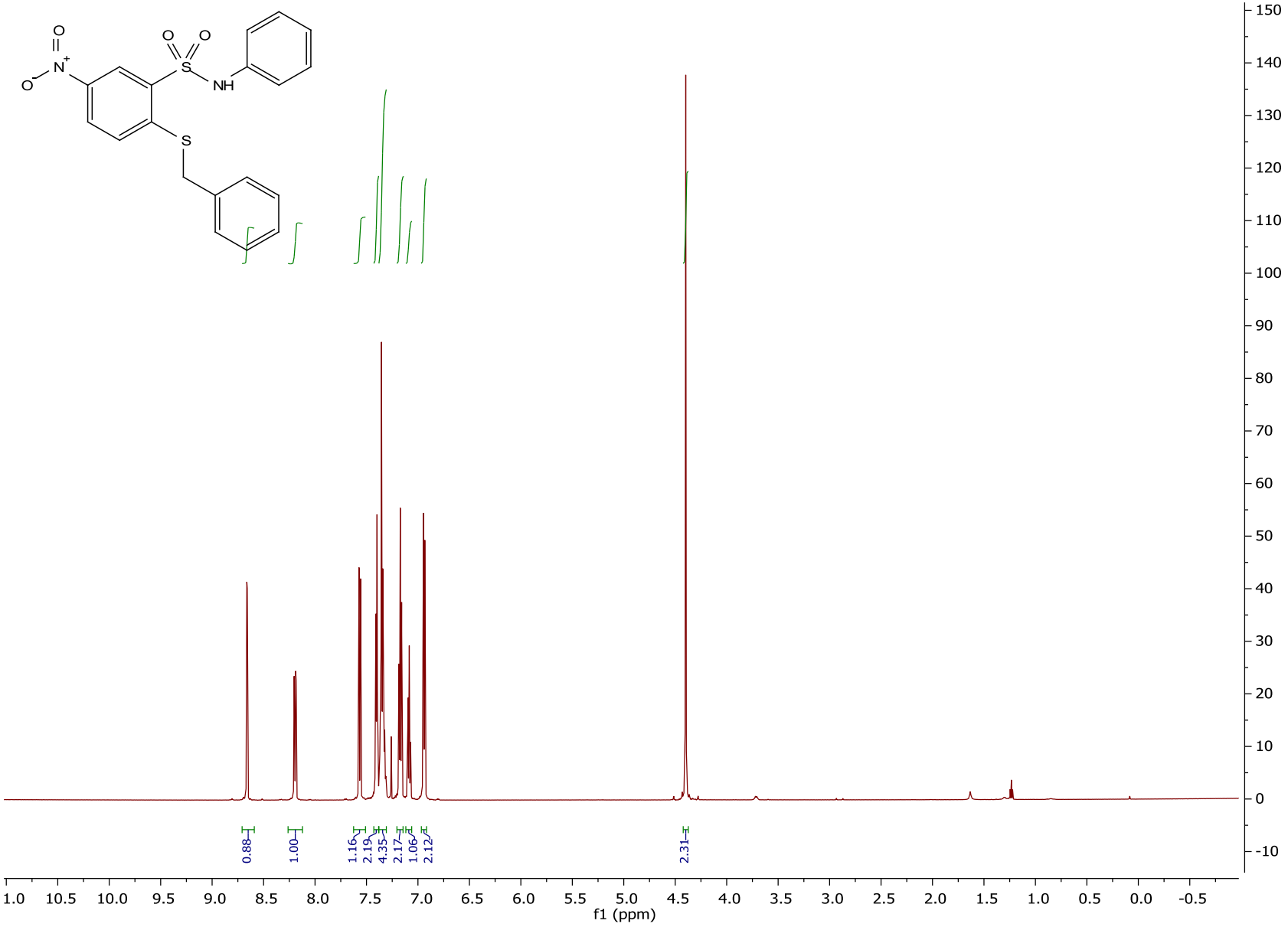
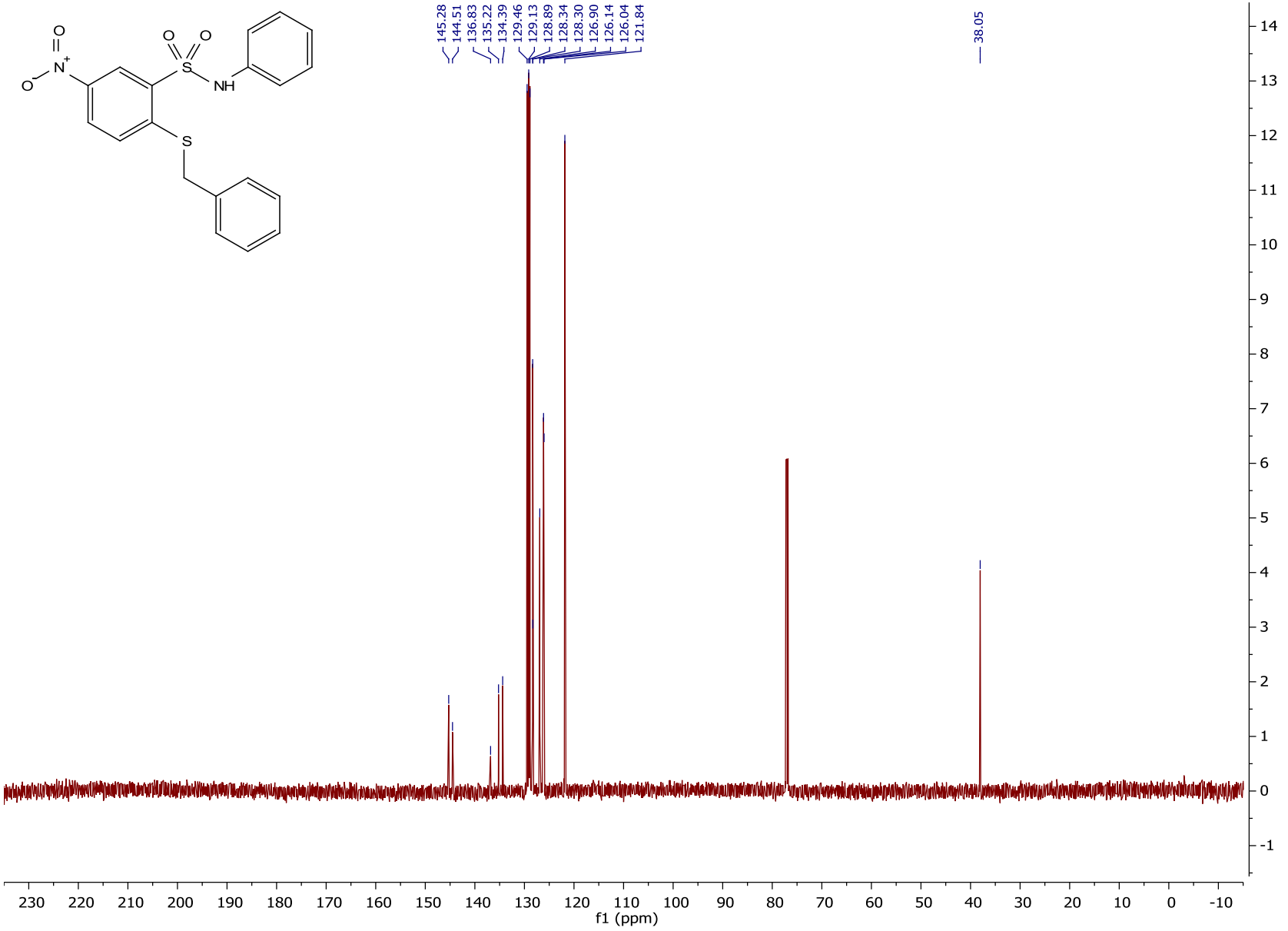
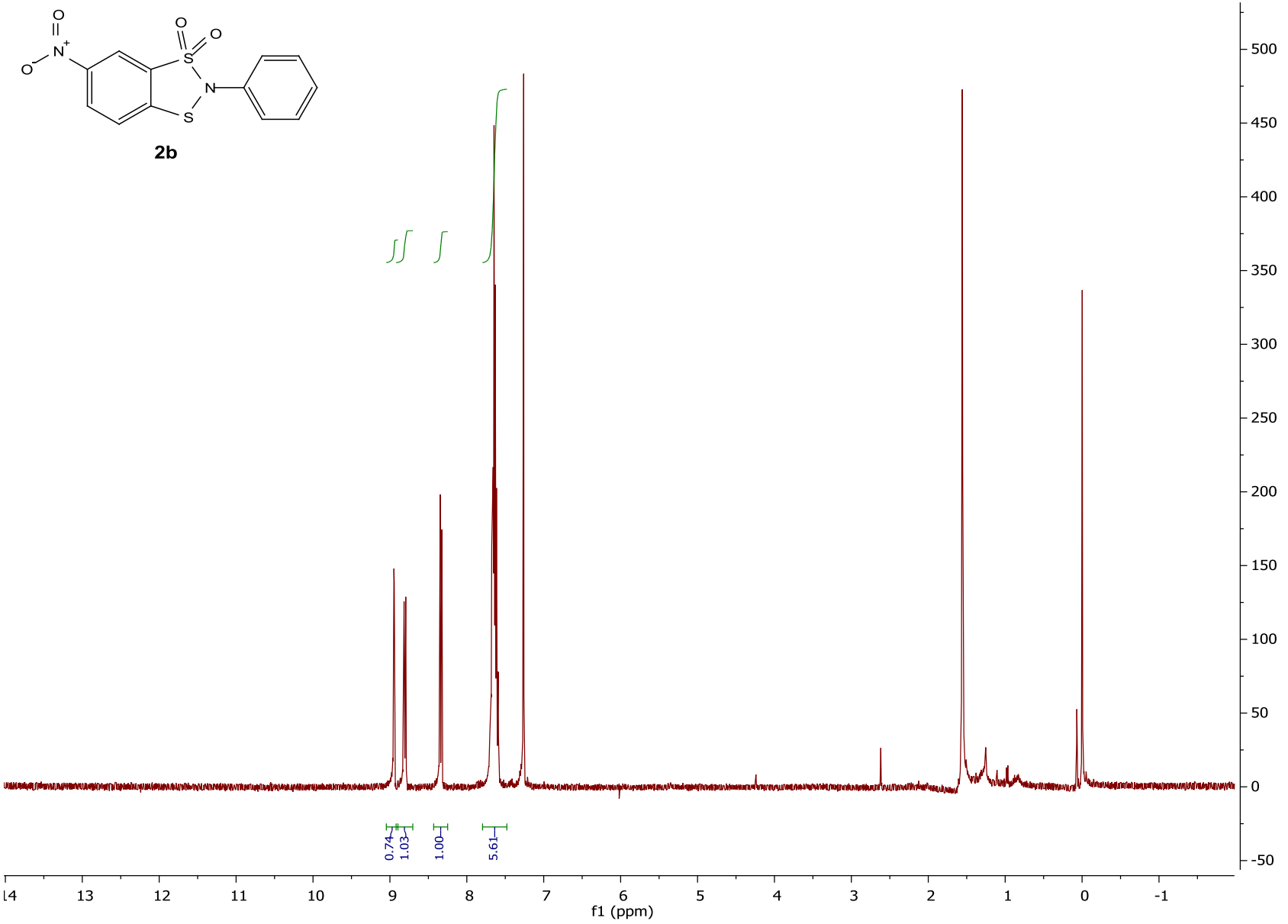
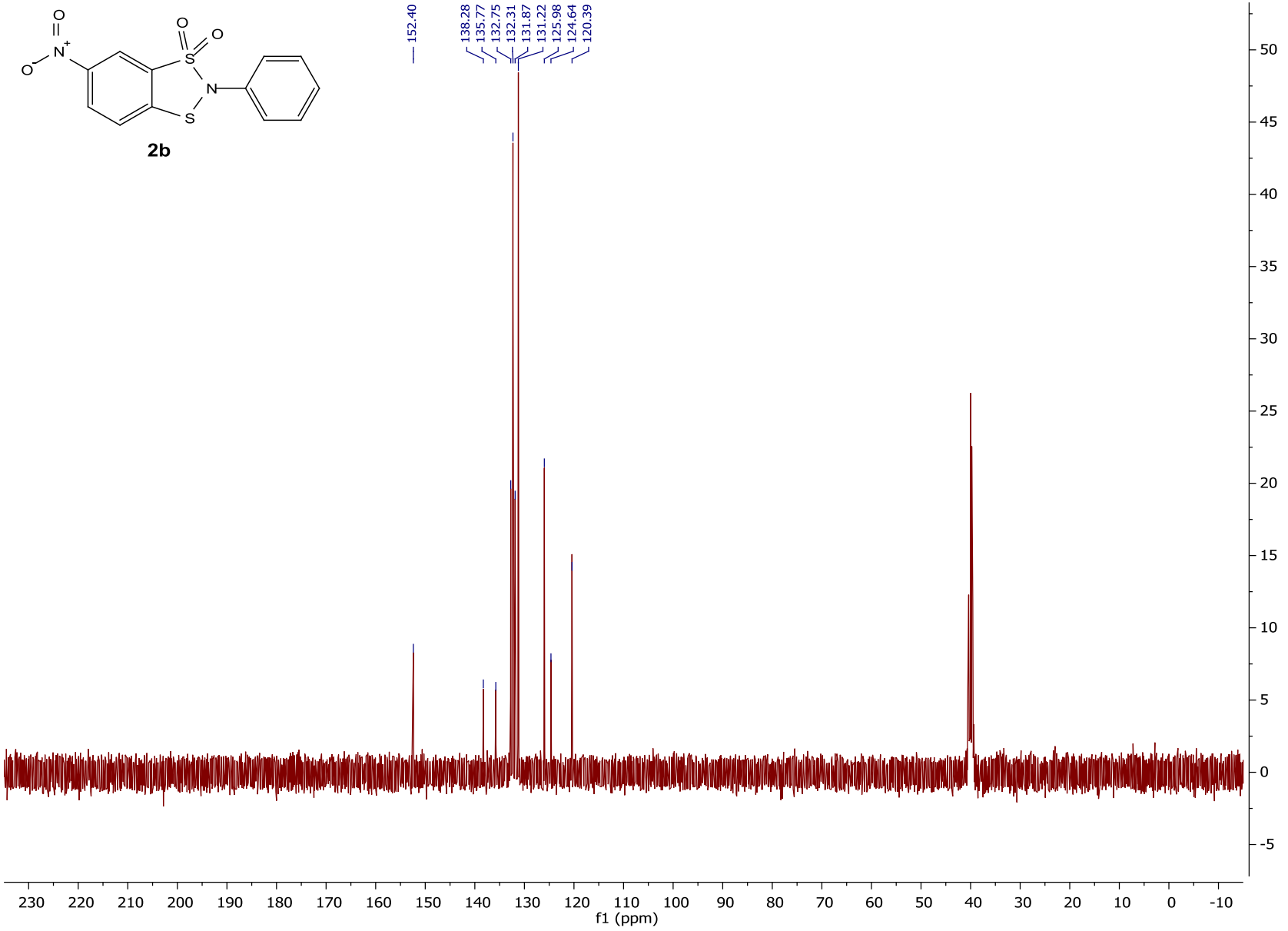
O
N+
O-
O
O
S
NH
Cl
0.88
1.00
1.03
2.50
4.15
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
50 45 40 35 30 25 20 15 10 5 0


146.36
138.13
134.84
132.96
129.85
128.48
127.23
126.68
122.02
O
O
N+
O-
S
O
NH
Cl
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

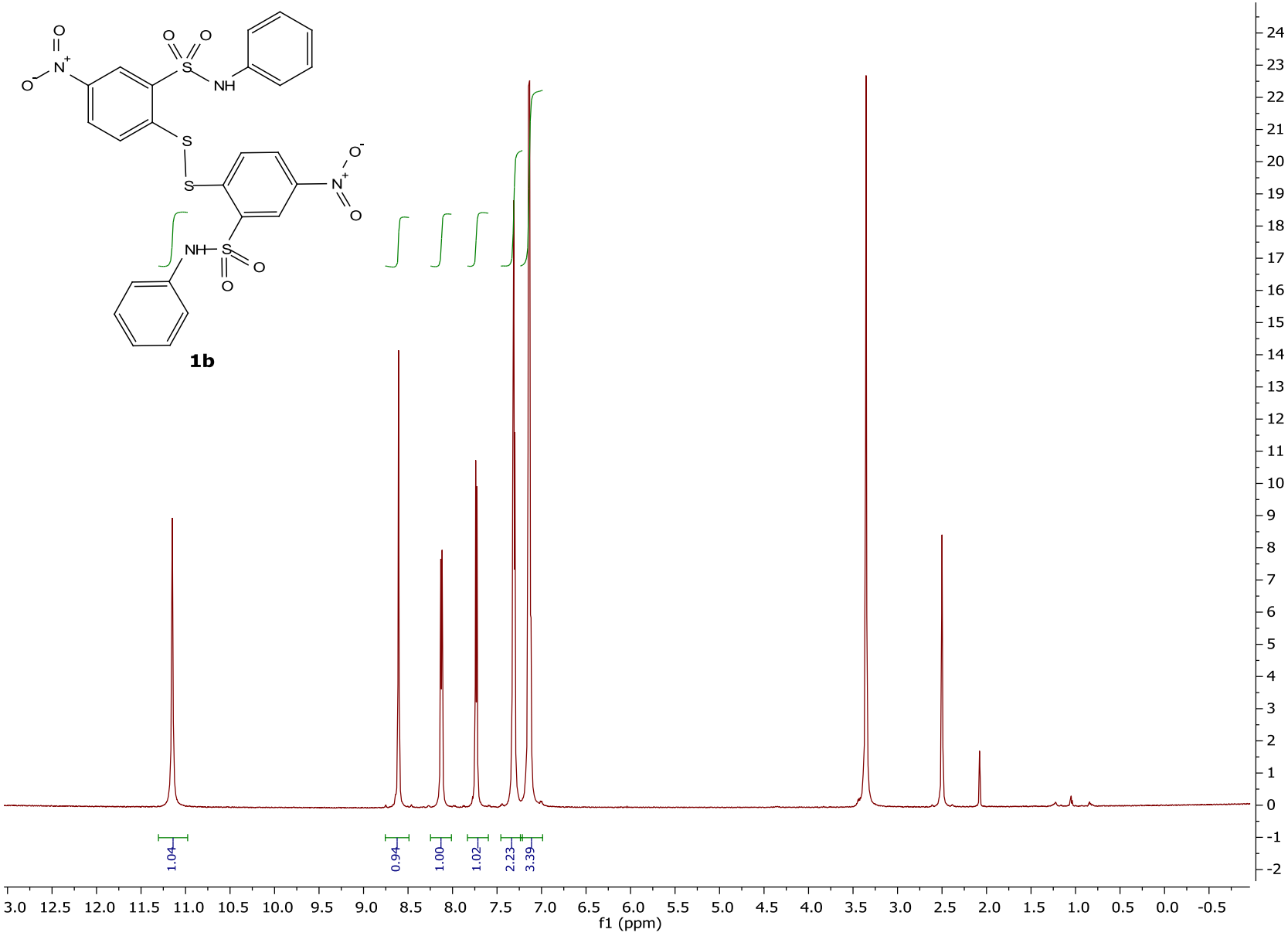

O
N+
O-
O
O
S
NH
S
0.88
1.00
1.16
2.19
4.35
2.17
1.06
2.12
2.31
f1 (ppm)

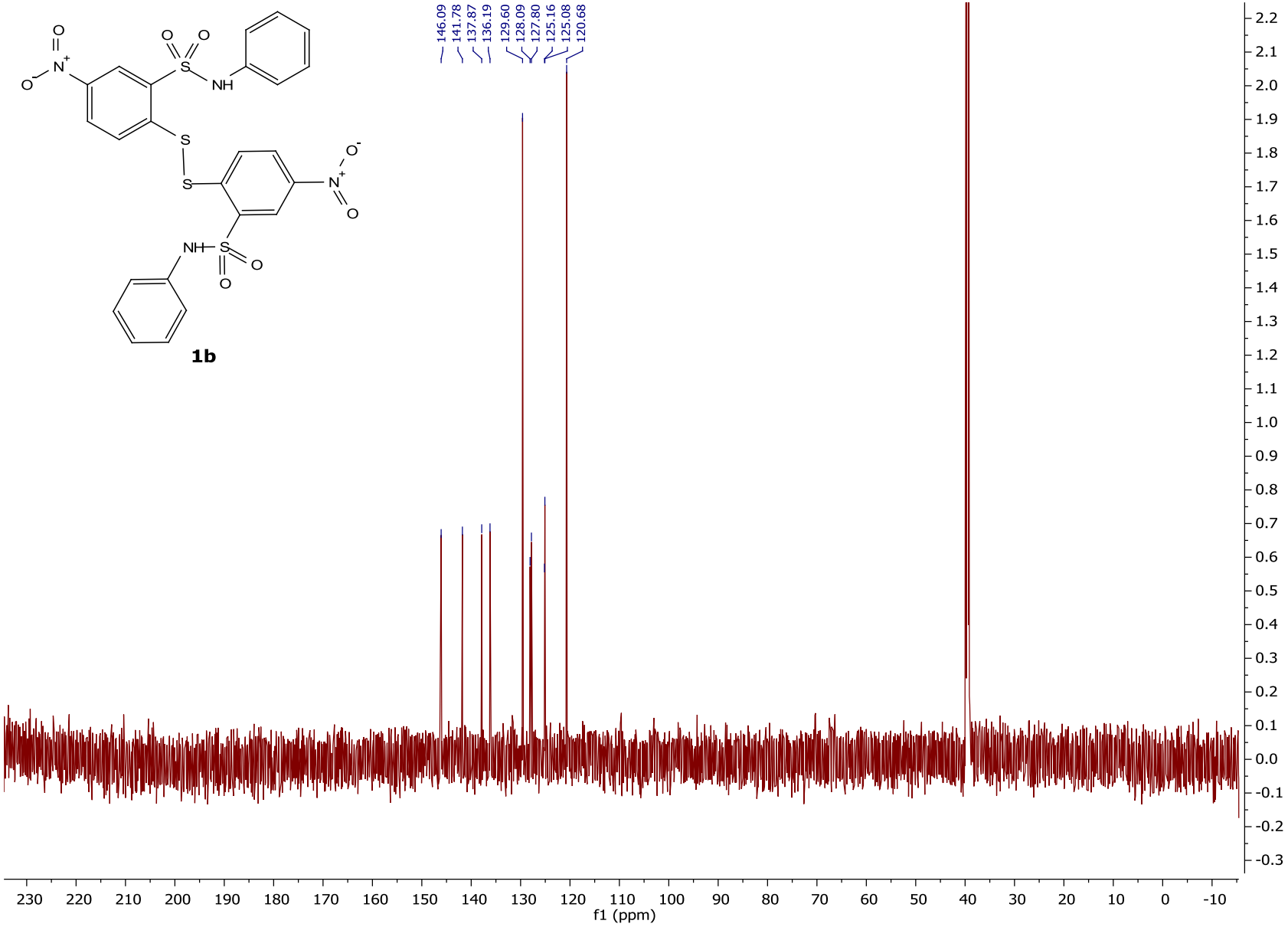

145.28
144.51
136.83
135.22
134.39
129.46
129.13
128.89
128.34
128.30
126.90
126.14
126.04
121.84
38.05
f1 (ppm)


O
N+
O-
O
S
O
N
S
2b
0.74
1.03
1.00
5.61
500
450
400
350
300
250
200
150
100
50
0
-50
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

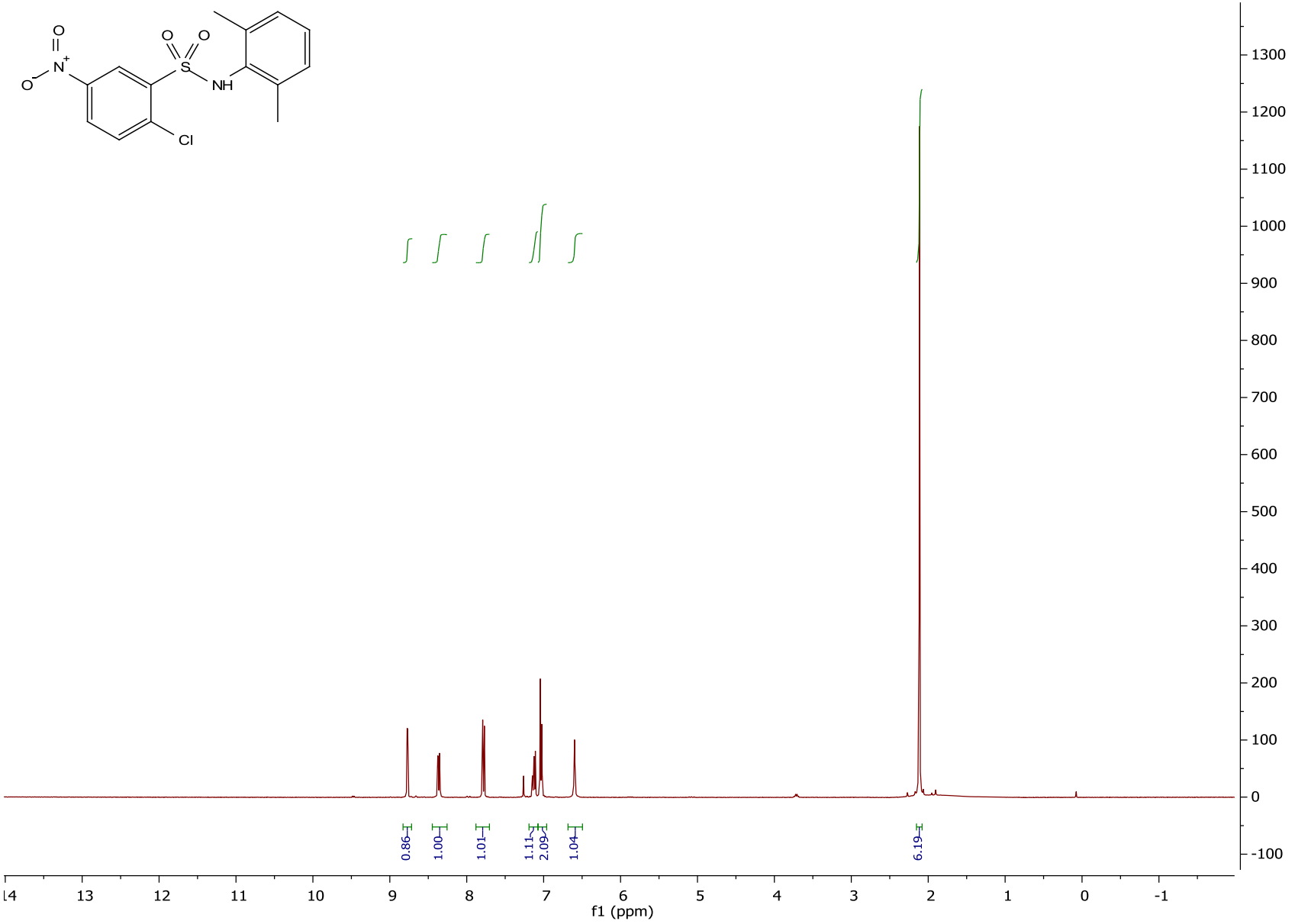

152.40
138.28
135.77
132.75
132.31
131.87
131.22
125.98
124.64
120.39
f1 (ppm)

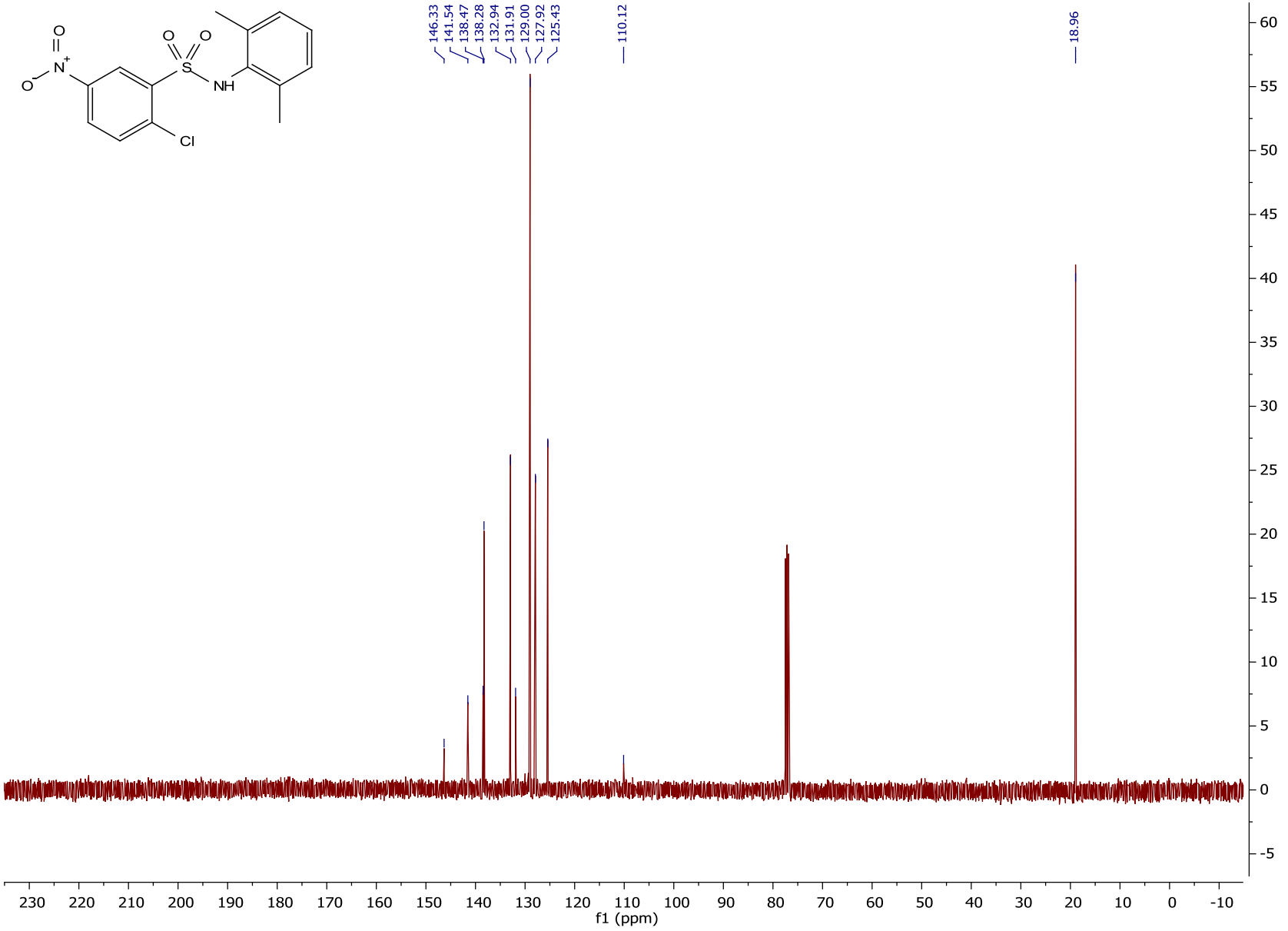
2b

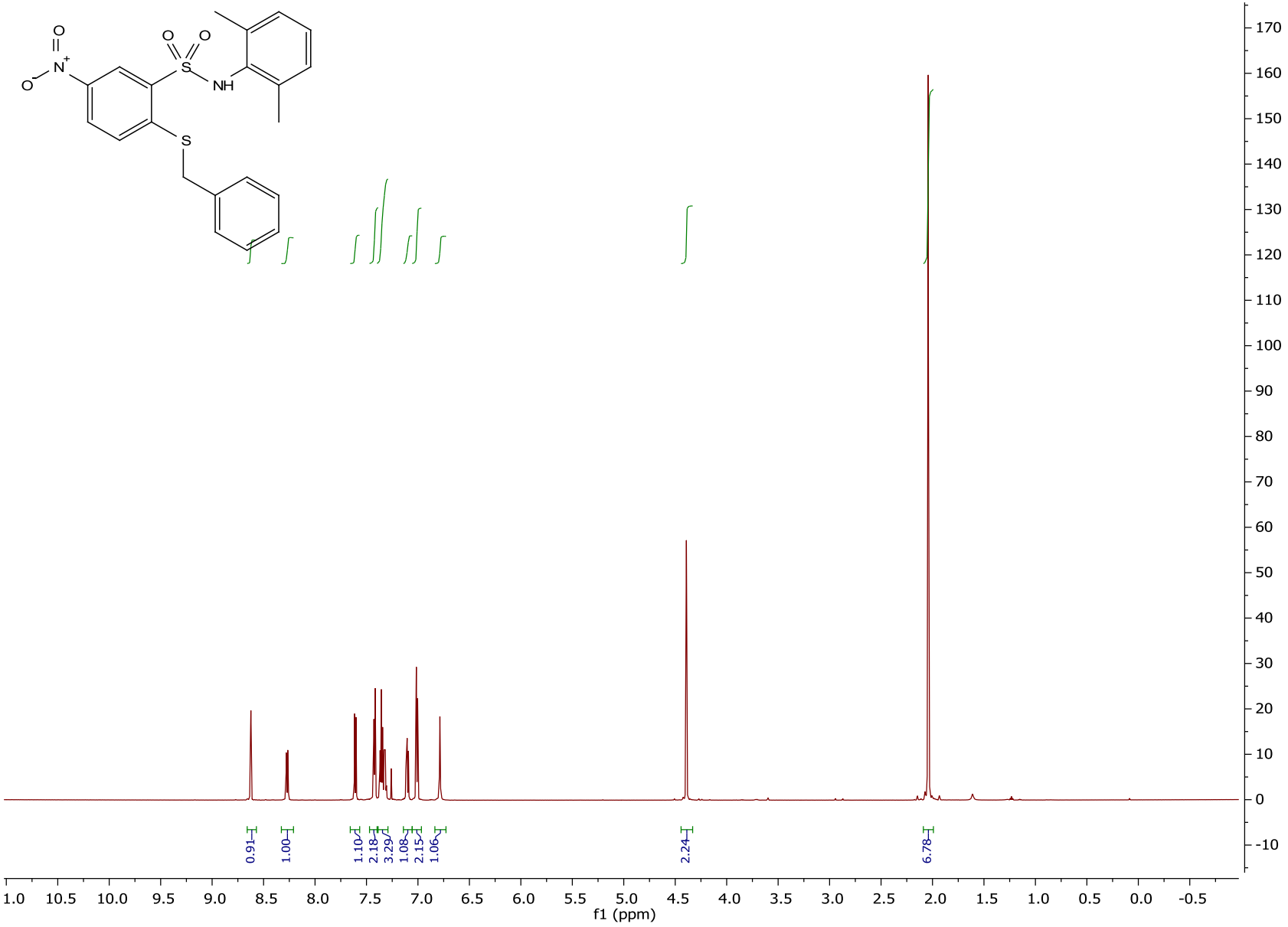

1b
1.04
0.94
1.00
1.02
2.23
3.39
f1 (ppm)

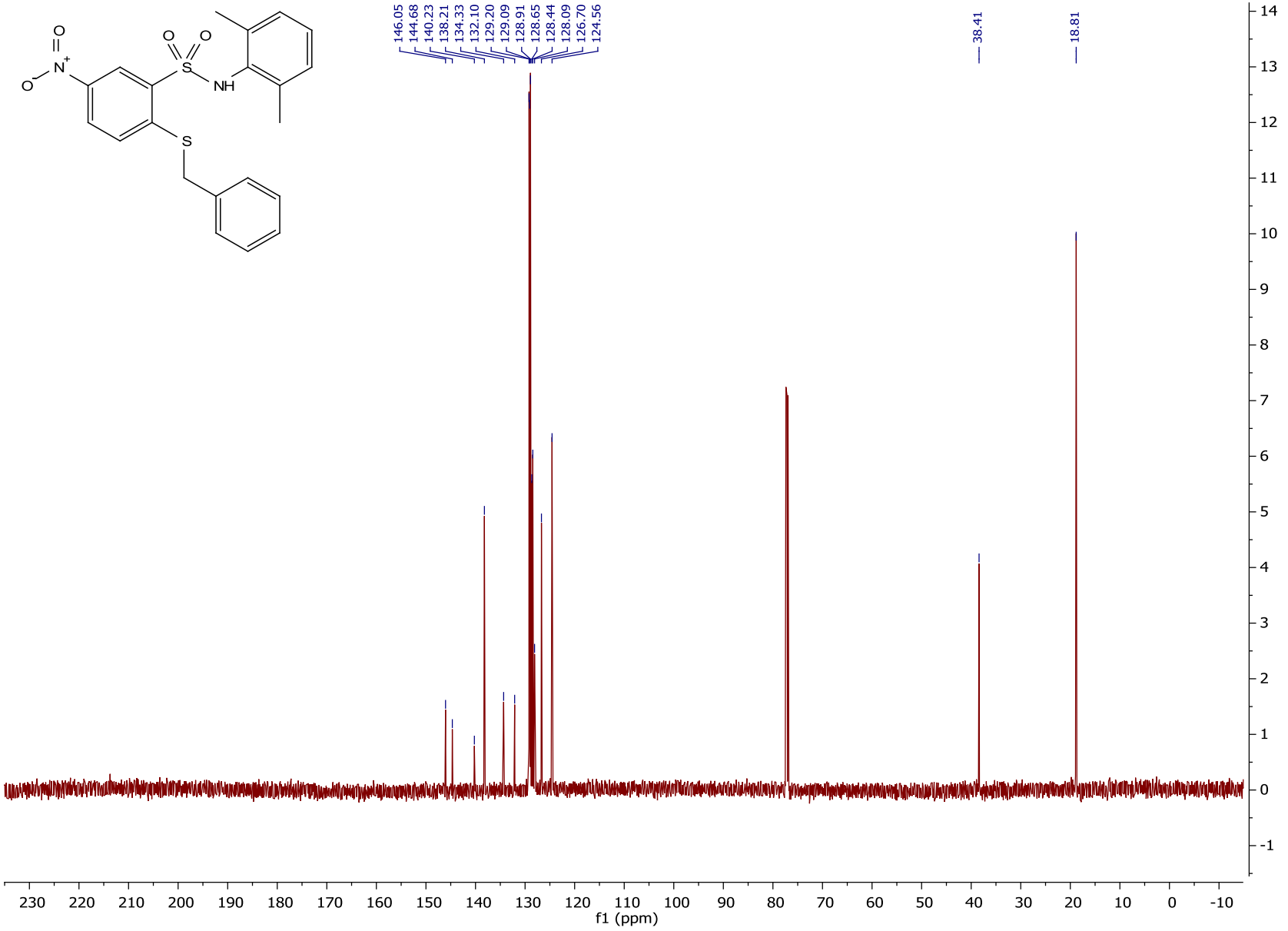

146.09
141.78
137.87
136.19
129.60
128.09
127.80
125.16
125.08
120.68
f1 (ppm)

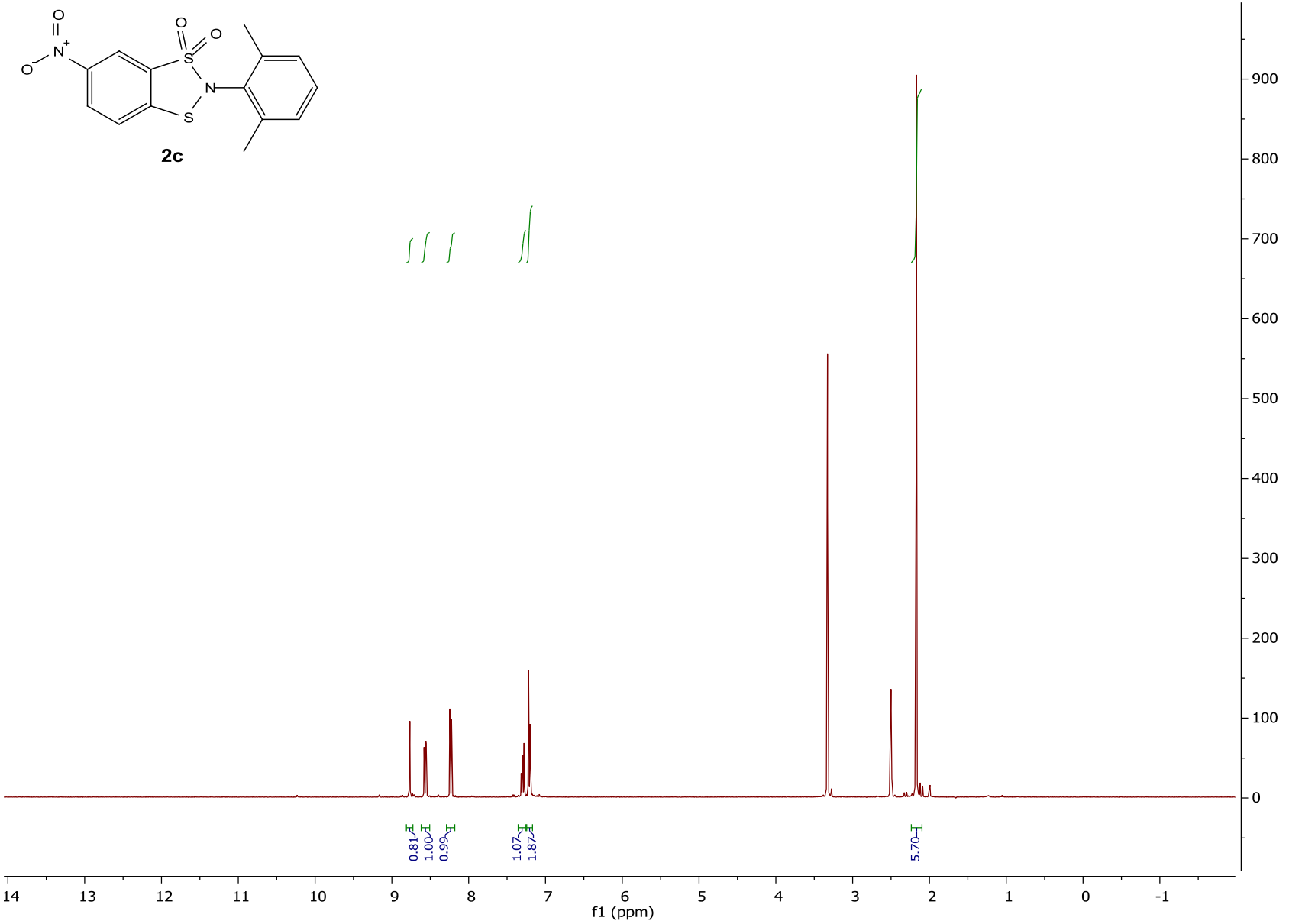
1b

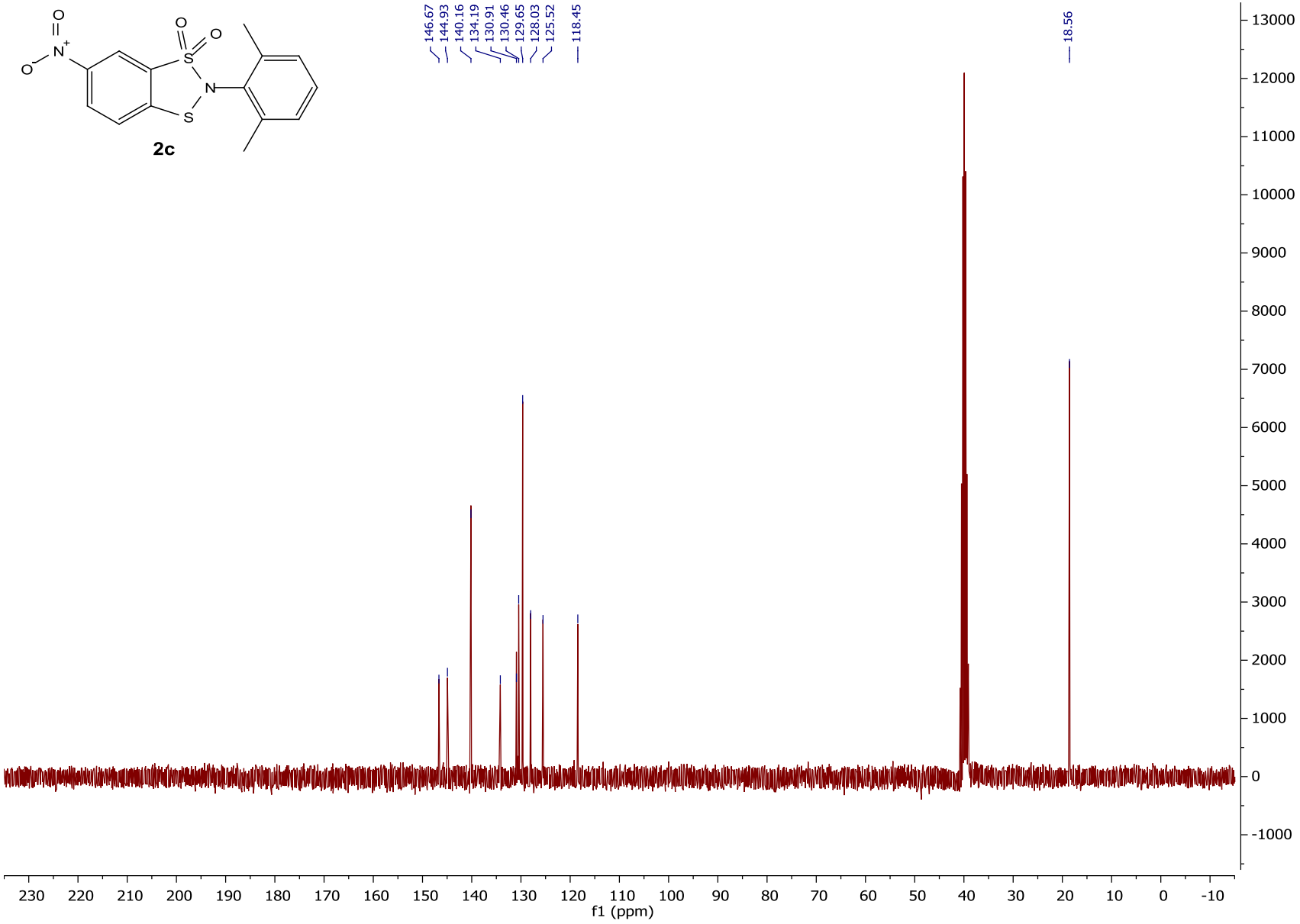

O
O
N+
O-
O
O
S
NH
Cl
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
0.86
1.00
1.01
1.11
2.09
1.04
6.19
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

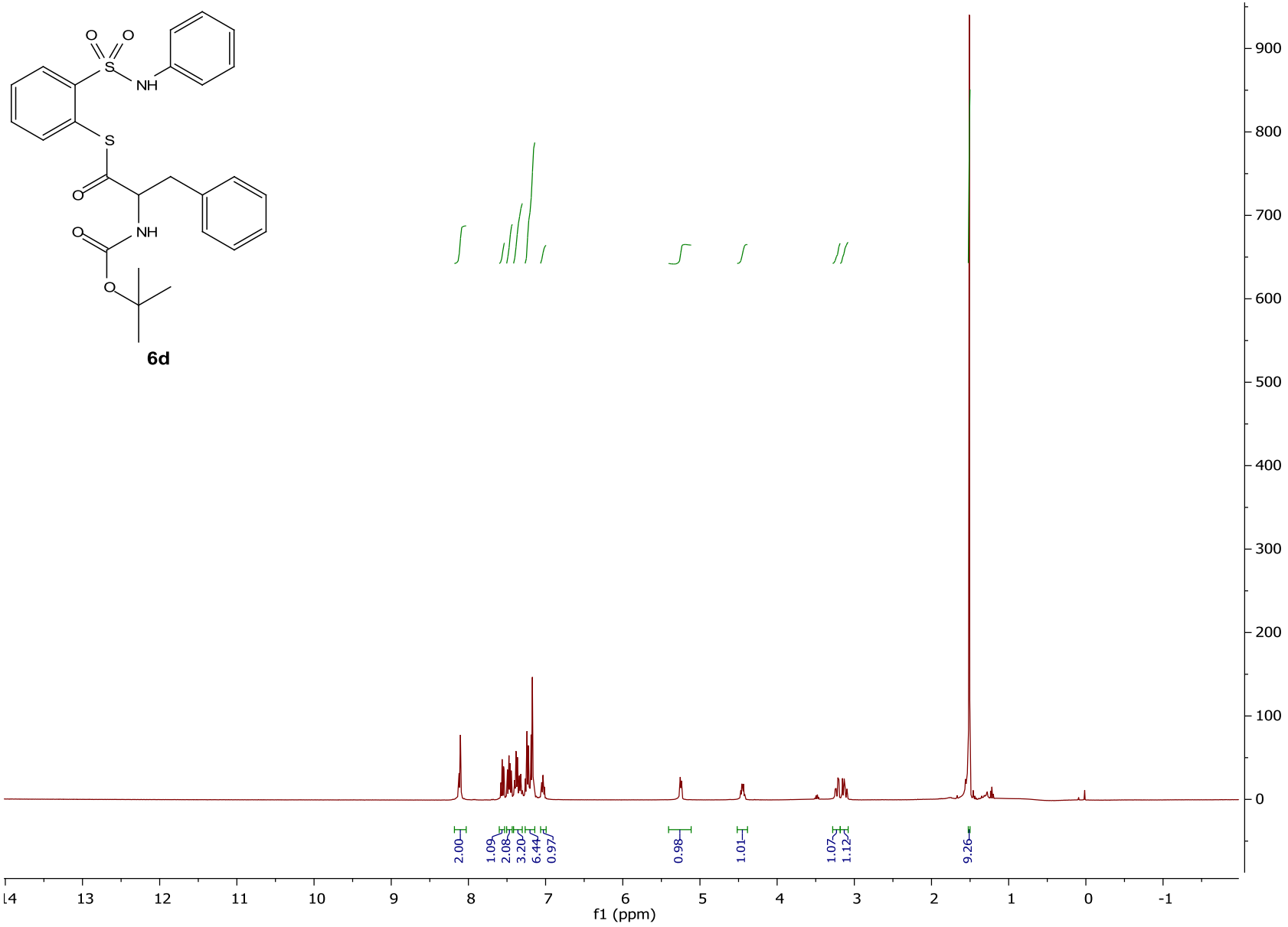

146.33
141.54
138.47
138.28
132.94
131.91
129.00
127.92
125.43
110.12
18.96
f1 (ppm)

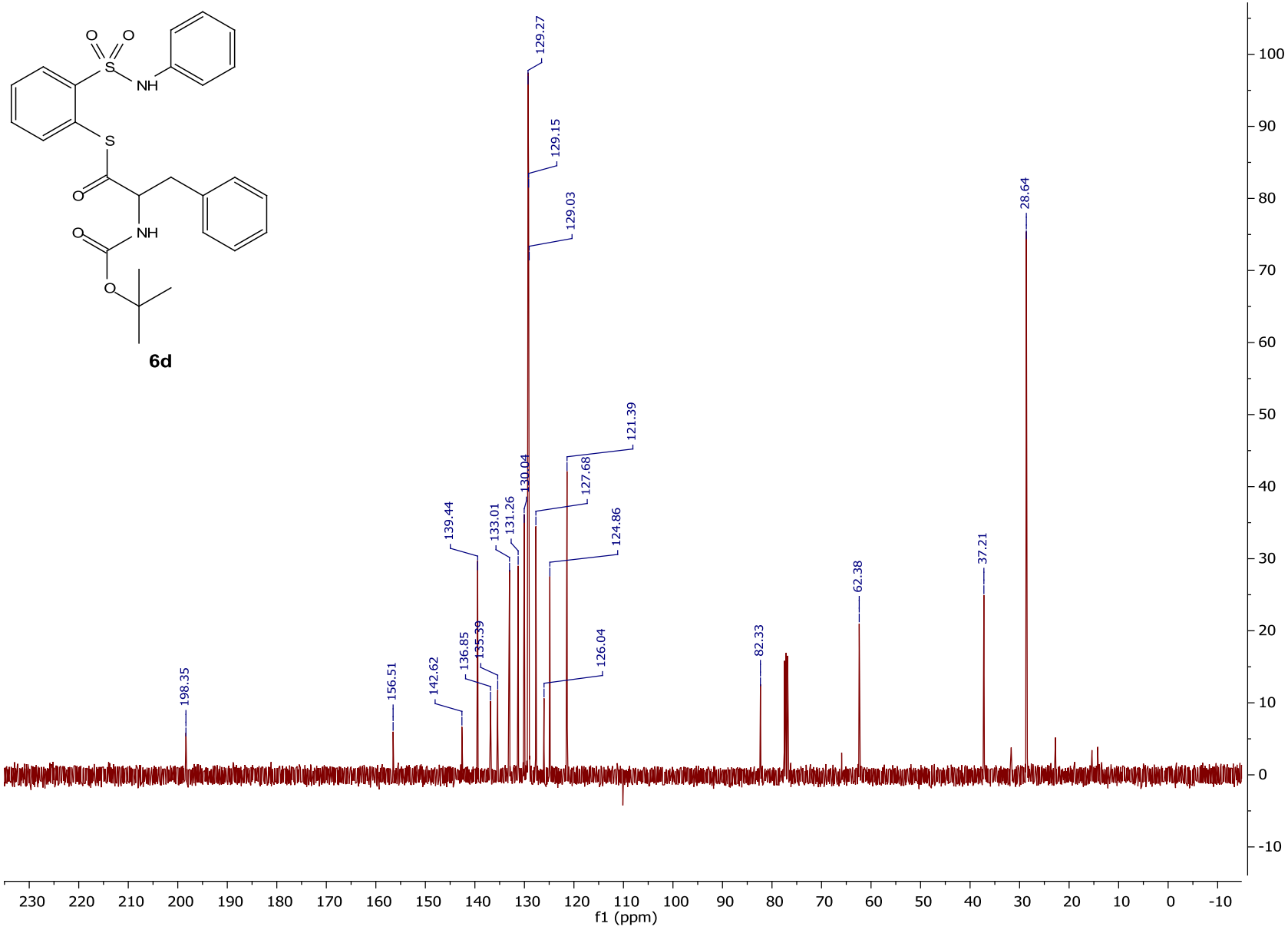

O
O
N+
O-
O
O
S
NH
S
0.91
1.00
1.10
2.18
3.29
1.08
2.15
1.06
2.24
6.78
f1 (ppm)

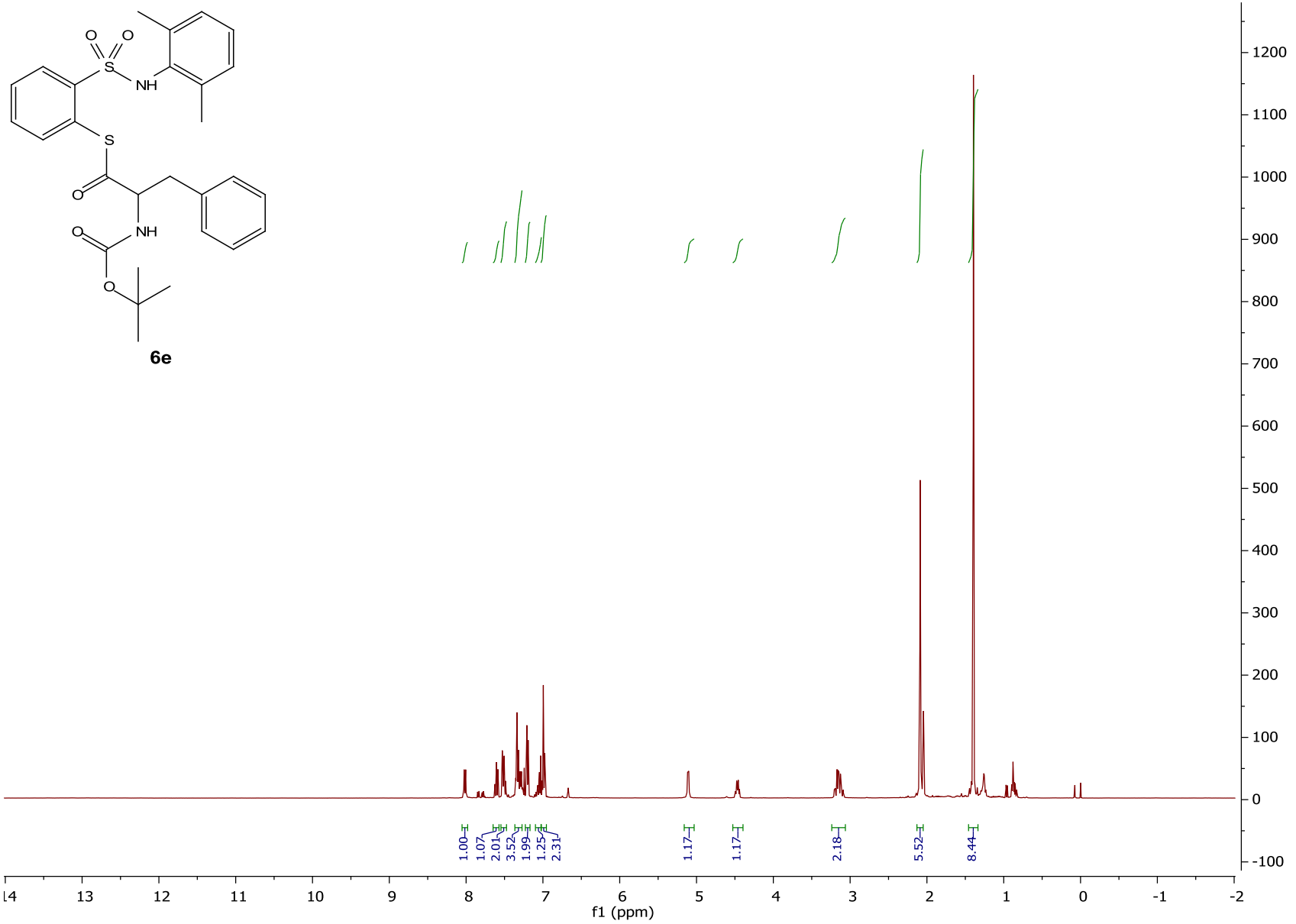

146.05
144.68
140.23
138.21
134.33
132.10
129.20
129.09
128.91
128.65
128.44
128.09
126.70
124.56
38.41
18.81
f1 (ppm)


O
O
N+
O-
O
S
O
N
S
2c
900
800
700
600
500
400
300
200
100
0
0.81
1.00
0.99
1.07
1.87
5.70
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

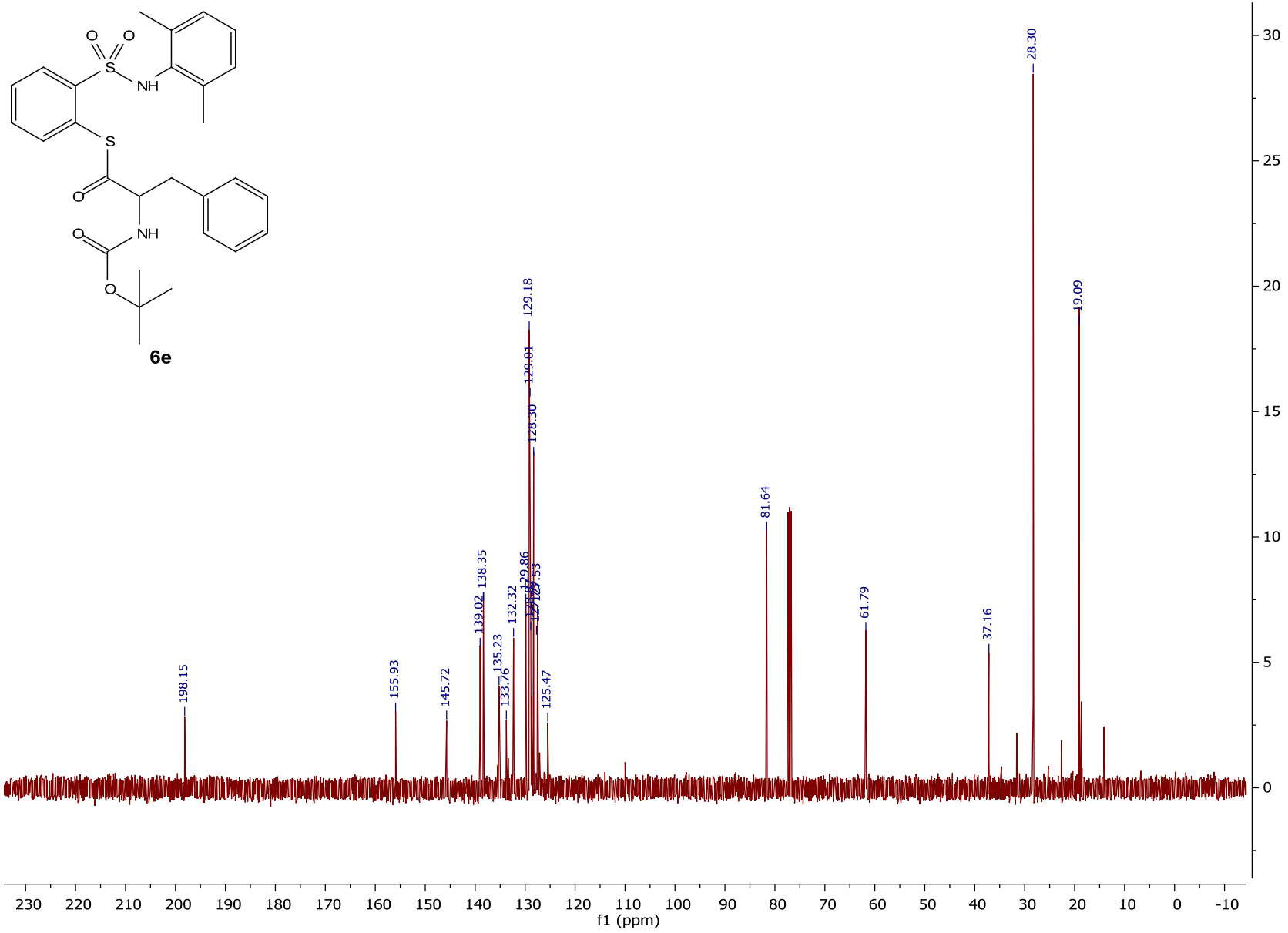

2c
146.67
144.93
140.16
134.19
130.91
130.46
129.65
128.03
125.52
118.45
18.56
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

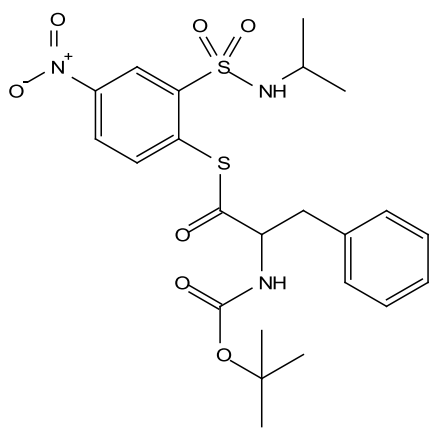

O
O
S
NH
S
O
NH
O
O
6d
900
800
700
600
500
400
300
200
100
0
2.00
1.09
2.08
3.20
6.44
0.97
0.98
1.01
1.07
1.12
9.26
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


O
O
S
NH
S
O
NH
O
O
6d
198.35
156.51
142.62
136.85
135.39
139.44
133.01
131.26
130.04
129.27
129.15
129.03
127.68
121.39
124.86
126.04
82.33
62.38
37.21
28.64
f1 (ppm)

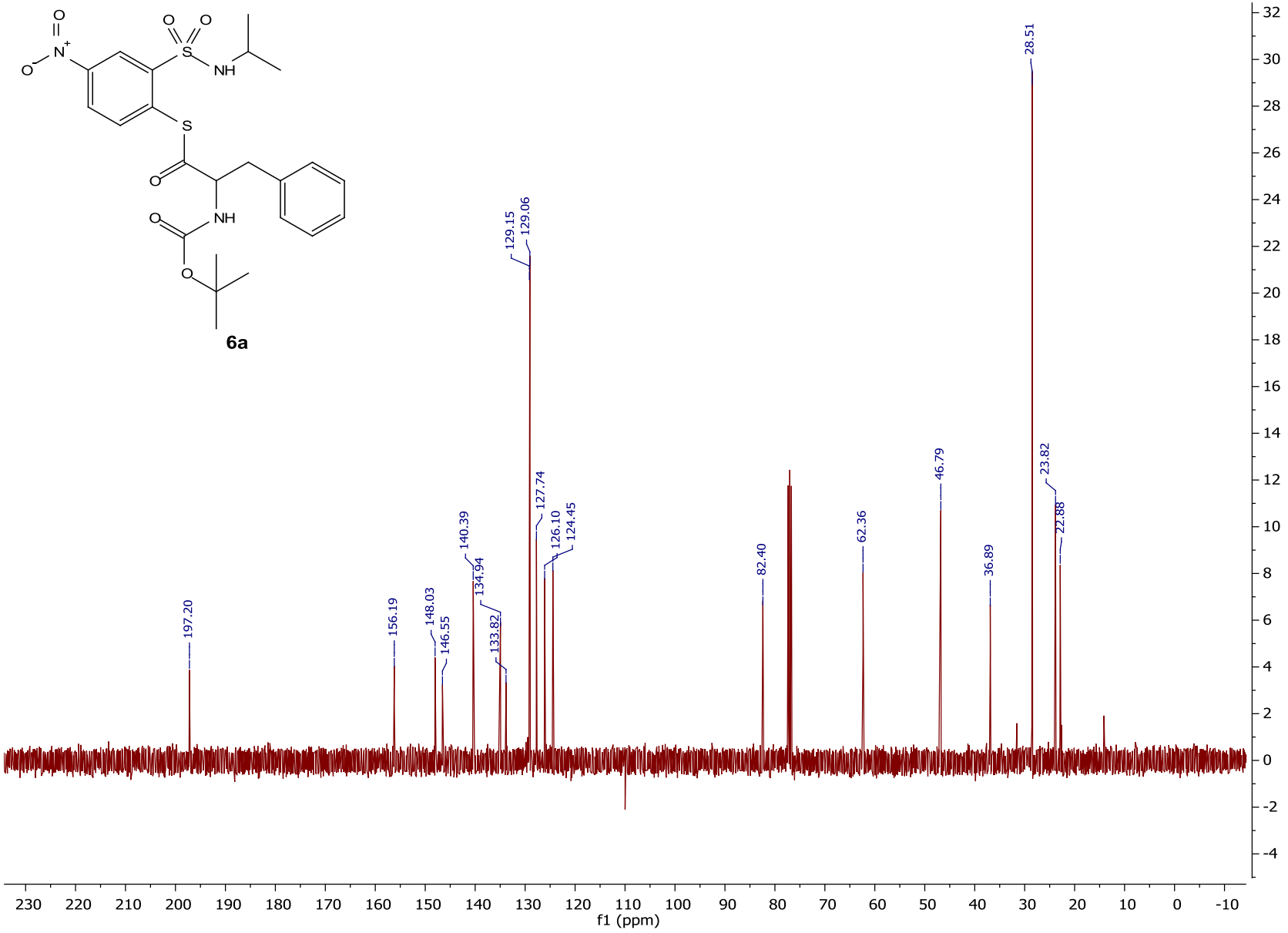

O
O
S
NH
S
O
NH
O
O
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
1.00
1.07
2.01
3.52
1.99
1.25
2.31
1.17
1.17
2.18
5.52
8.44
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

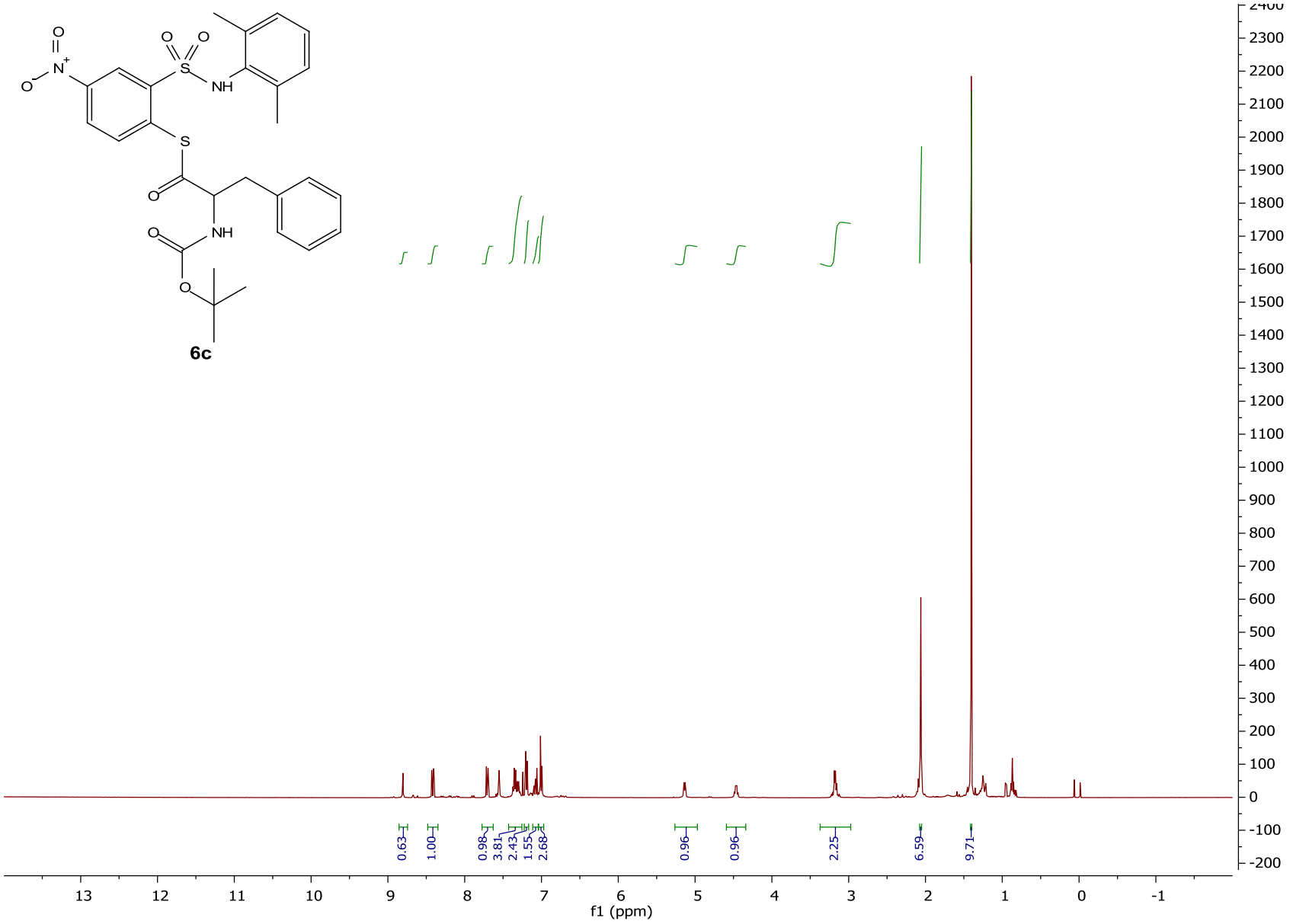
6e

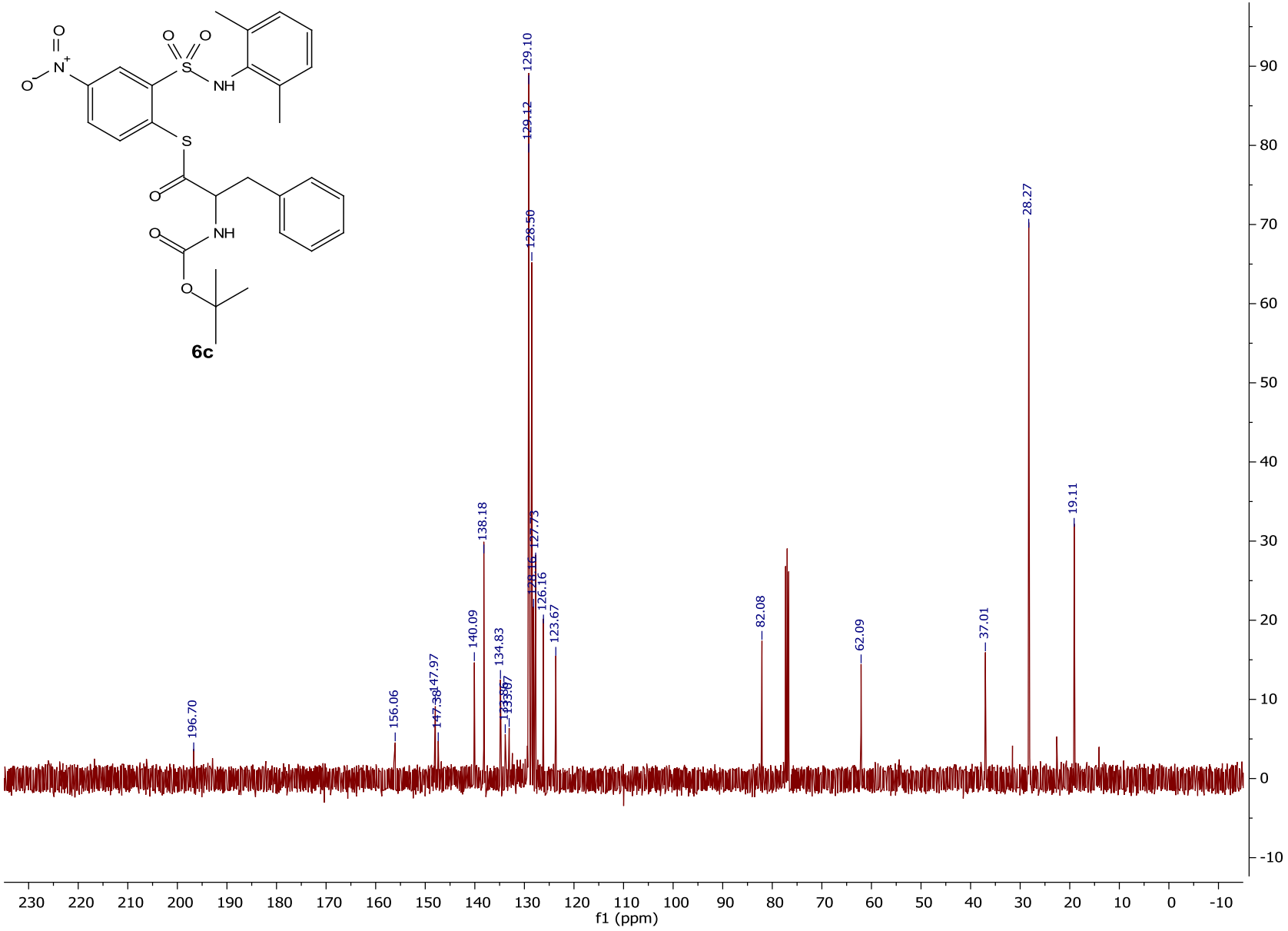

O
O
S
NH
S
O
NH
O
O
6e
198.15
155.93
145.72
139.02
138.35
135.23
133.76
132.32
129.86
129.18
129.01
128.30
125.47
81.64
61.79
37.16
28.30
19.09
f1 (ppm)

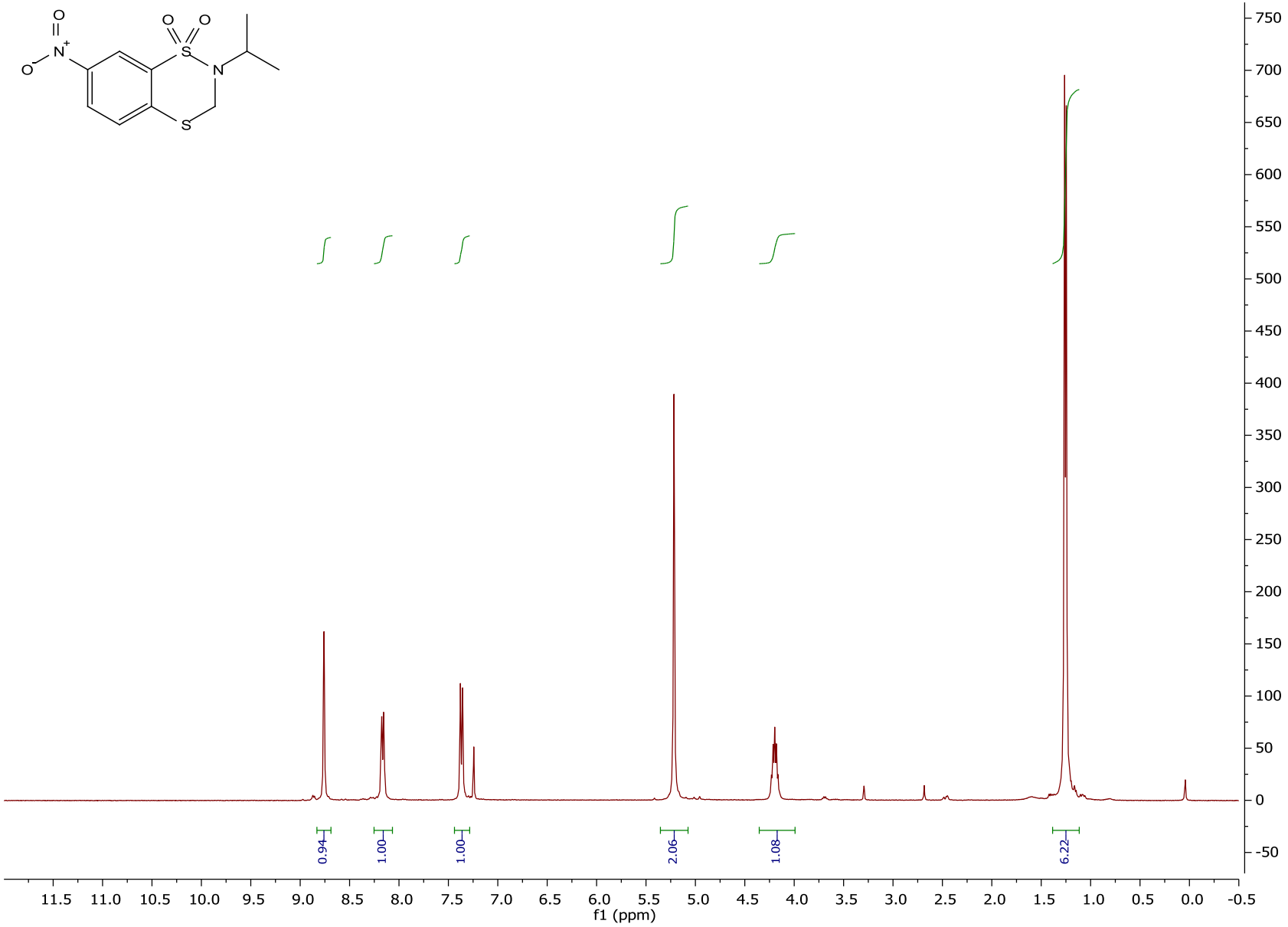


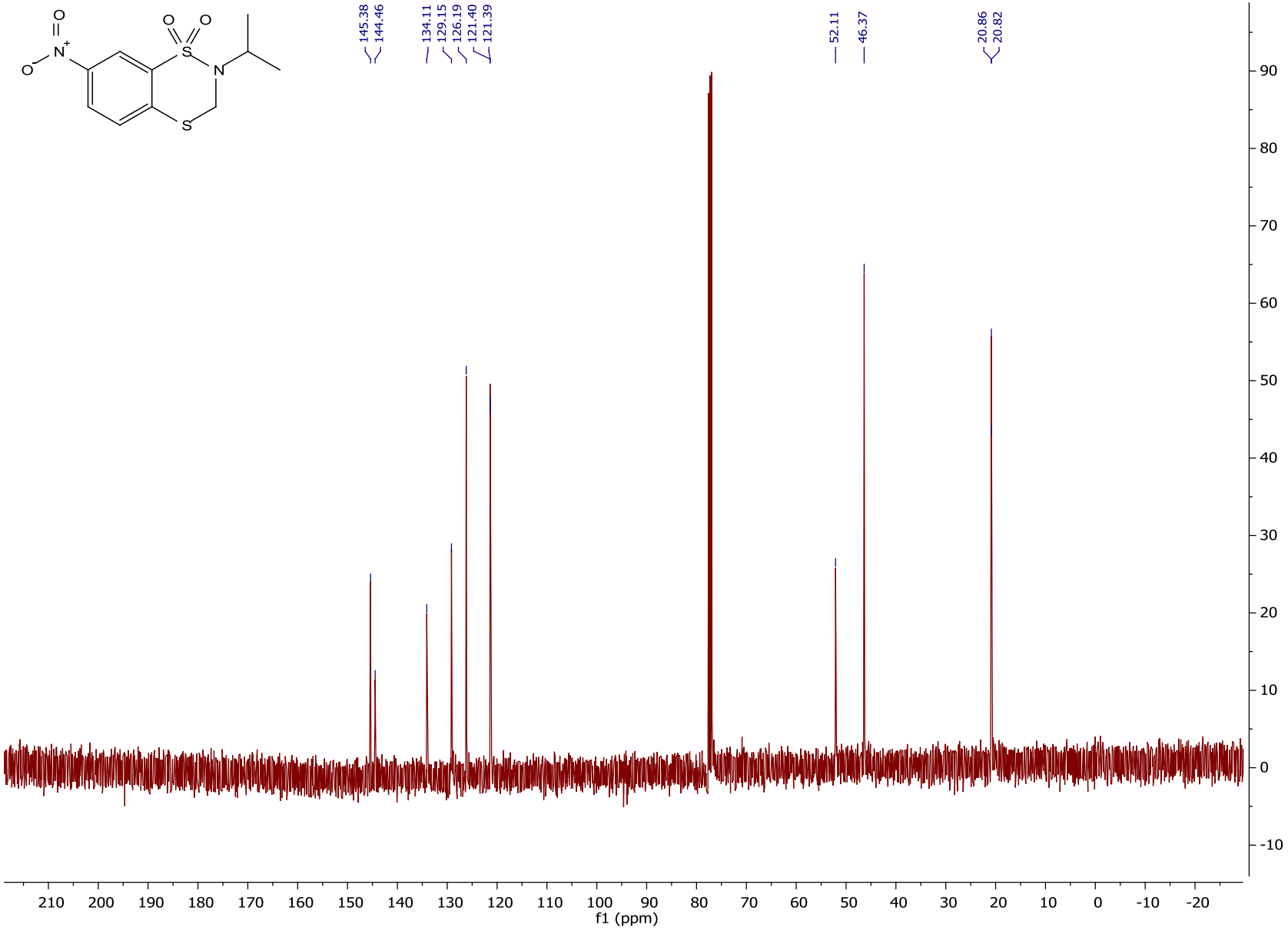
6a

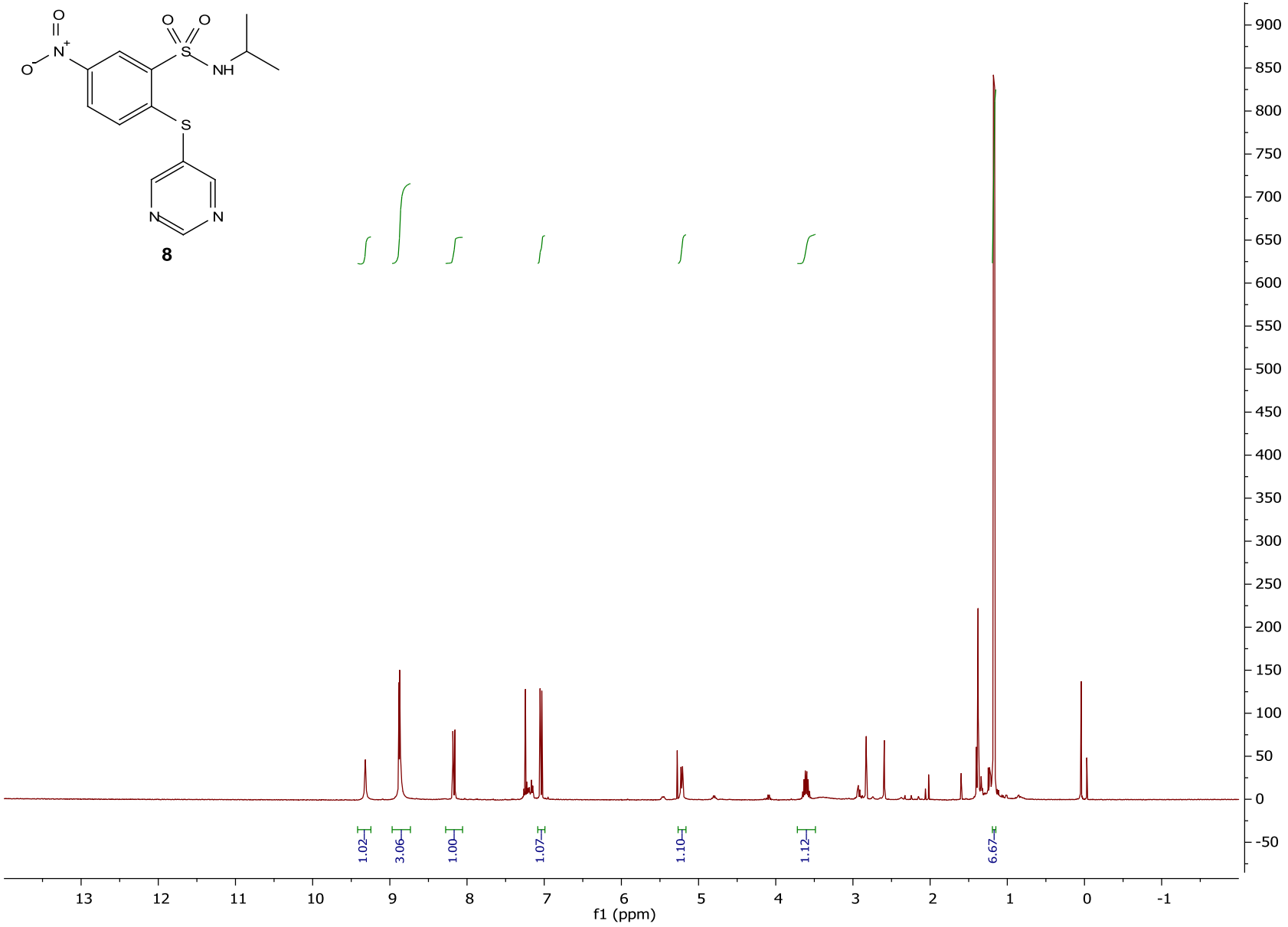

6a
197.20
156.19
148.03
146.55
140.39
134.94
133.82
129.15
129.06
127.74
126.10
124.45
82.40
62.36
46.79
36.89
28.51
23.82
22.88
f1 (ppm)

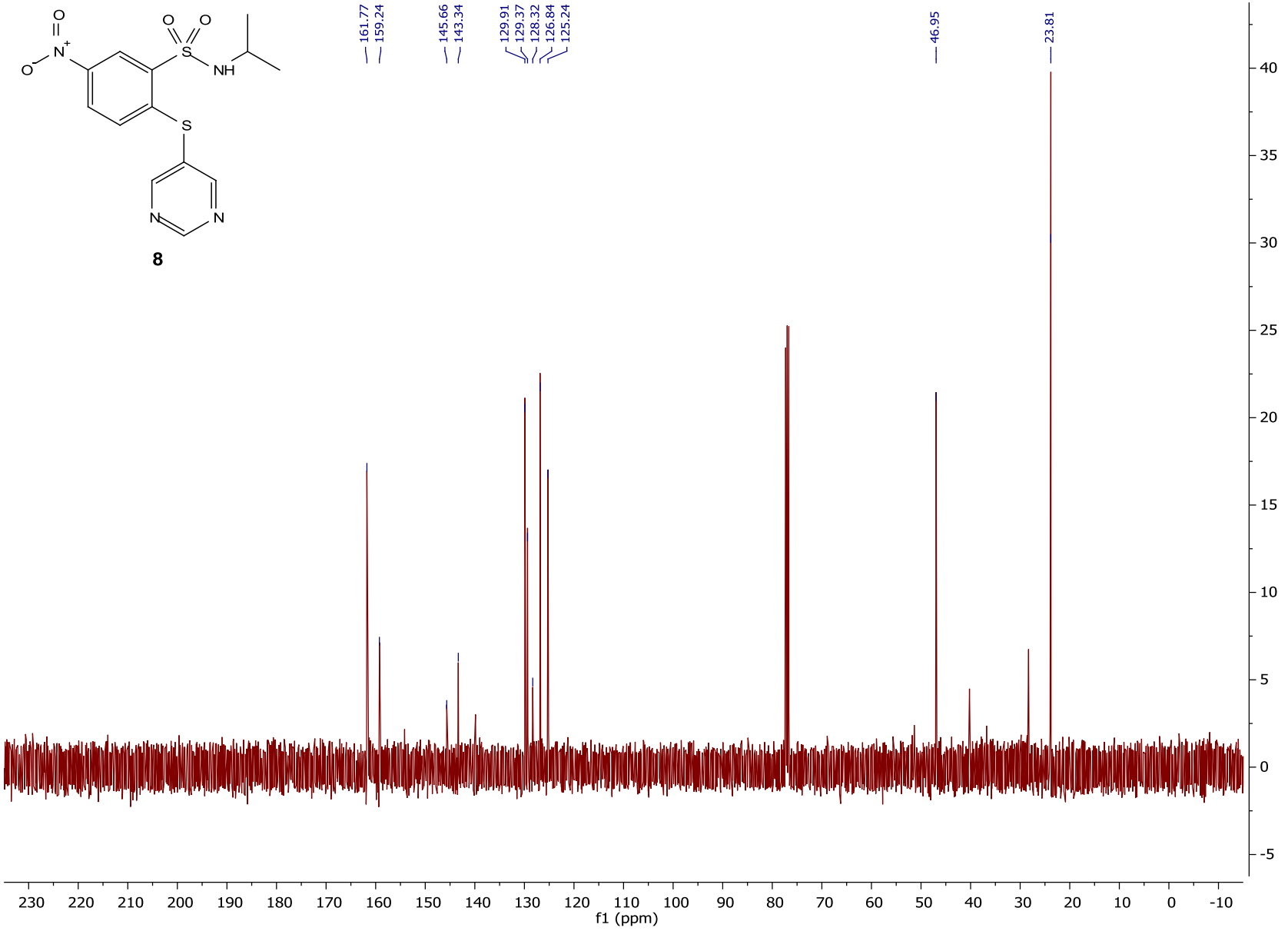

6c
0.63
1.00
0.98
3.81
2.43
1.55
2.68
0.96
0.96
2.25
6.59
9.71
f1 (ppm)


6c
196.70
156.06
147.97
147.38
140.09
138.18
134.83
129.10
129.12
128.50
128.16
127.73
126.16
123.67
82.08
62.09
37.01
28.27
19.11
f1 (ppm)


O
N+
O-
O
O
S
N
S
0.94
1.00
1.00
2.06
1.08
6.22
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
750 700 650 600 550 500 450 400 350 300 250 200 150 100 50 0 -50

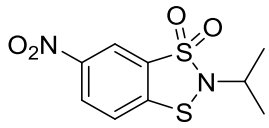

145.38
144.46
134.11
129.15
126.19
121.40
121.39
52.11
46.37
20.86
20.82
f1 (ppm)


8
1.02
3.06
1.00
1.07
1.10
1.12
6.67
f1 (ppm)


161.77
159.24
145.66
143.34
129.91
129.37
128.32
126.84
125.24
46.95
23.81
f1 (ppm)

8

Reaction of BDT and triethylphosphite as analyzed by ^{31}P NMR



$P(OEt)_3$ (0.95 equiv)
PhMe (0.10 M)

Products analyzed by ^{31}P NMR