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Novel aminobenzoboroxoles as potential anti-cancer agents

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NOVEL AMINOBENZOBOROXOLES AS POTENTIAL ANTI-CANCER AGENTS

by

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Dedication

I would like to dedicate this manuscript to Priti Mahendrakumar Gandhi

Acknowledgments

I would like to express my appreciation to Prof. Subash Jonnalagadda for his guidance and help throughout this research. The skills and knowledge that I have gained are things that I will take with me into my next professional endeavour. I look forward to whatever challenges that come my way knowing that I am prepared to take them on. I would also like to thank Dr. Suman Pathi for his kind support through this journey.

Abstract

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NOVEL AMINOBENZOBOROXOLES AS POTENTIAL ANTI-CANCER AGENTS
2017-2018
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Master of Science in Pharmaceutical Sciences

Boronic acids are a promising class of compounds due to their wide range of applications in medicinal and materials chemistry, and as coupling agents in organic synthesis. B-hydroxy-1,2-oxaborolanes (benzoboroxoles) are categorized as cyclic boronic acid derivatives and they are very important organic molecules because of their metabolic stability and their ability to undergo important C-C bond forming reactions such as Suzuki cross coupling. Several of these cyclic boronic acids are found to have promising pharmacological properties as antifungal, antimalarial and anti-inflammatory agents. However, based on the literature reports, synthesis of highly functionalized benzoboroxoles is typically cumbersome and not very conducive for large-scale synthesis.

This thesis details our efforts on the development of novel synthetic methodologies for the synthesis of functionalized benzoboroxoles as potential therapeutic agents. We initiated the synthesis of novel benzoboroxoles starting from 2-formylphenylboronic acid employing reactions such as Baylis-Hillman reaction, Passerini reaction, aldol reaction, and reductive amination. Further functionalization of these benzoboroxoles was achieved via nitrosation and amidation protocols. The biological evaluation of these synthetic derivatives showed excellent promise as anti-cancer agents.

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Chapter 1

Introduction

Boronic Acids

Organoboron compounds in general and boronic acids in particular have been underutilized in medicinal chemistry, as there is a misconception among the scientific community that the boron compounds are in general toxic. Owing to their impressive chemical and biological profile, boronic acids and boronate esters have been utilized as valuable synthons for cross-coupling[1], homologation[2], aldol, and catalytic allylboration[3] reactions to name a few. Boronic acids also find utility in medicinal chemistry as chemotherapeutic[4] and radiotherapeutic (BNCT) agents[5].

Aminoboronic Acids

Aminoboronic acids **1** are ideal bioisosteric replacements for amino acids **2** owing to their comparable stereoelectronic properties and hence they find several applications in peptidomimetics[6]. Boronic acid is a six electron species, hence it is a strong electrophile and forms a stable "ate" complex **3** when it interacts with nucleophiles such as hydroxyl termini of enzymes. Carboxylic acids produce an unstable tetrahedral carbonyl addition intermediate **4** under similar conditions (**Figure 1**). The stable bond formation between boronic acids and enzymes leads to their reversible inhibition, accordingly the former acts as an excellent pharmacophore in pharmaceutical chemistry. This mechanism of action resulted in the FDA approval for bortezomib **5** (Velcade®, **Figure 2**) as an anti-cancer drug for the treatment of multiple myeloma[7]. This event marked a new beginning into the use of organoboron compounds for drug discovery. Buoyed by the success of

bortezomib, large-scale biological screening of boronated compounds was carried out and based on these studies, a second-generation drug ixazomib **6** (Ninlaro®) was also approved recently by the FDA for the treatment of multiple myeloma[8]. Ixazomib citrate **7**, is an orally bioavailable prodrug form of ixazomib which is also used clinically as it undergoes hydrolysis to release the free boronic acid under physiological conditions (**Figure 2**).

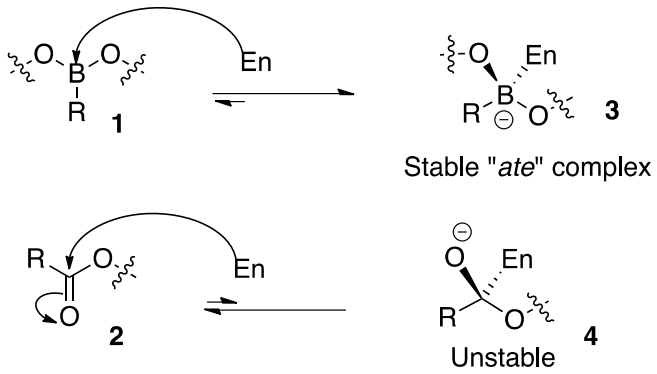


Figure 1. Mechanism of drug action for boronic acids.

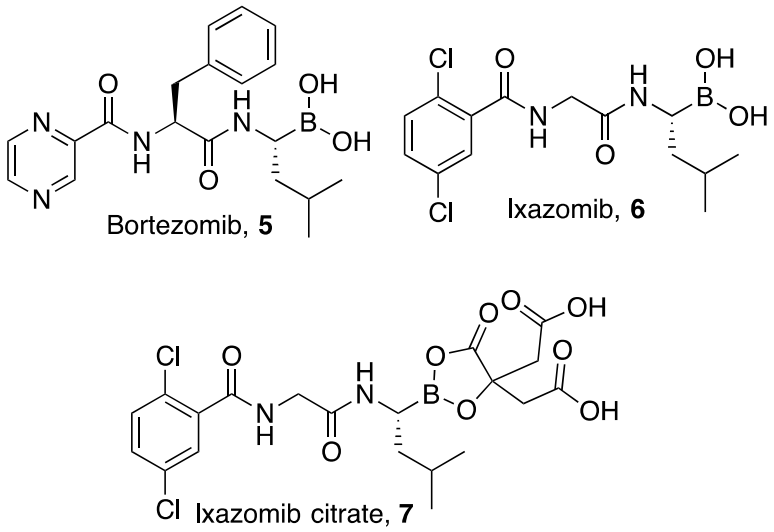


Figure 2. Boronic acids in clinical use.

Benzoboroxoles

Benzoboroxoles (or benzoxaboroles) **8** are one such class of cyclic boronic acid hemiester analogs that have found applications in medicinal, materials, and polymer chemistry because of their unusual chemical stability and ideal physicochemical properties[9]. First synthesized by Torsell[10] in 1957, and later explored briefly by Snyder,[11] this class of boron compounds remained dormant for several decades until the approval of two drugs tavaborole **9**[12] (for the treatment of onychomycosis) and crisaborole **10**[13] (for the topical treatment of atopic dermatitis) (**Figure 3**). The excellent *anti*-fungal activity of tavaborole is attributable to the inhibition of Leucyl-tRNA synthetase, while the inhibition of the enzyme phosphodiesterase-4 leads to the anti-inflammatory activity of crisaborole.

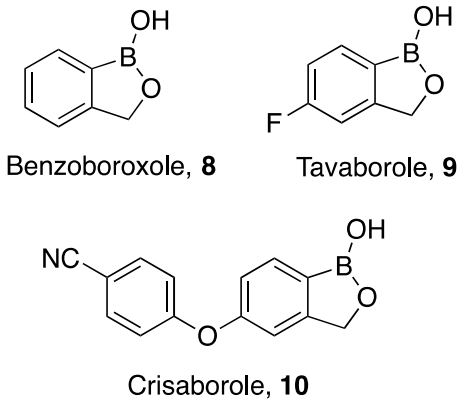


Figure 3. Benzoboroxoles in clinical use.

Owing to our long-standing interest in boron chemistry[14], our group has been working on the functionalization of benzoboroxoles as therapeutic agents. We demonstrated the utility of Baylis-Hillman reaction[15] using *o*-boronobenzaldehyde **11** for the formation of functionalized benzoboroxoles **12-13** with activated olefins such as methyl acrylate, acrylonitrile, methyl vinyl ketone, acrolein and cyclohex-2-enone.[16] Benzoboroxole-based esters **14** were obtained via the reaction of functionalized allylic bromides with the aldehyde **11** under Barbier allylation conditions.[16] Benzoboroxole-based ketones and esters (**15** and **16**) were obtained via aldol condensation of boronoaldehyde **11** with acetophenone and dimethyl malonate respectively (**Figure 1**, paths d-e).[17] Our group was also successful in carrying out Passerini reaction[18] of aldehyde **11** with isonitriles to furnish the benzoboroxole amides **7** (**Figure 4**).[19]

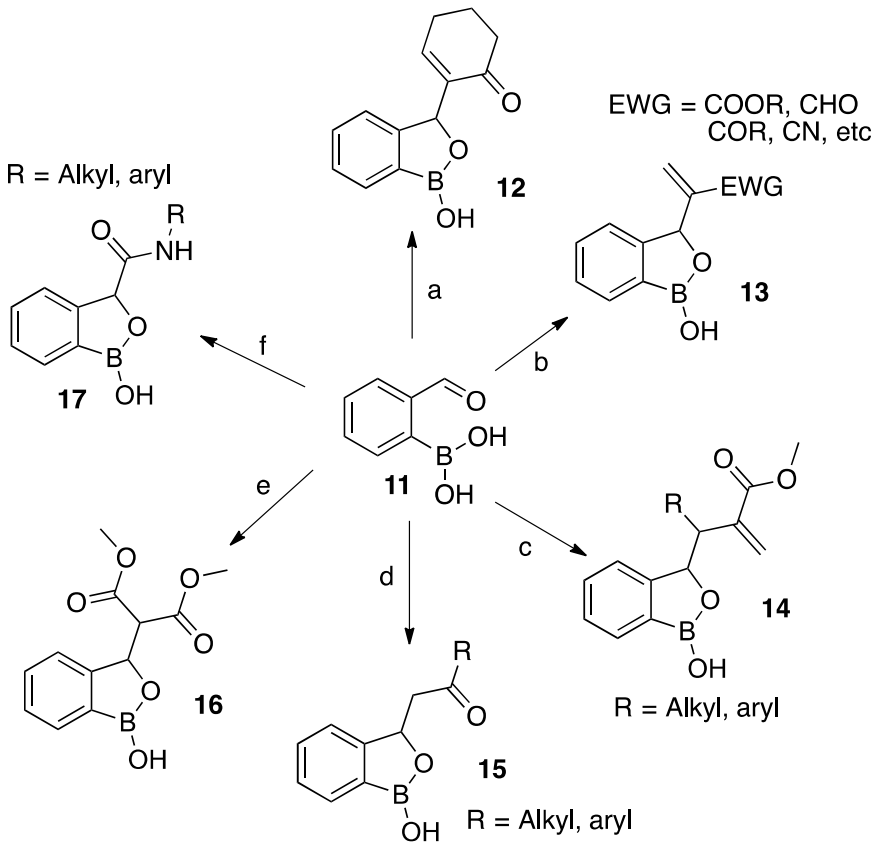


Figure 4. Diverse functionalization of benzoboroxoles.

Applications of Benzoboroxoles in Medicinal Chemistry

There have been several reports on the applications of benzoboroxoles in medicinal chemistry. Most notable are their uses as anti-fungal agents (tavaborole)[12] and anti-inflammatory agents (crisaborole).[13] Other applications of these molecules are noted below.

Anti-Tubercular agents. Our group described a simple synthesis of 6-amino-7-bromobenzoboroxole **20**. This analog showed promising activity against *Mycobacterium tuberculosis* H376Rv. This compound **20** was obtained in four steps via reduction of *o*-formylphenylboronic acid **11** with sodium borohydride followed by electrophilic

nitration of benzoboroxole **8**, reduction, and monobromination. We were also able to prepare dibrominated benzoboroxole derivative **21** (**Figure 5**).[20]

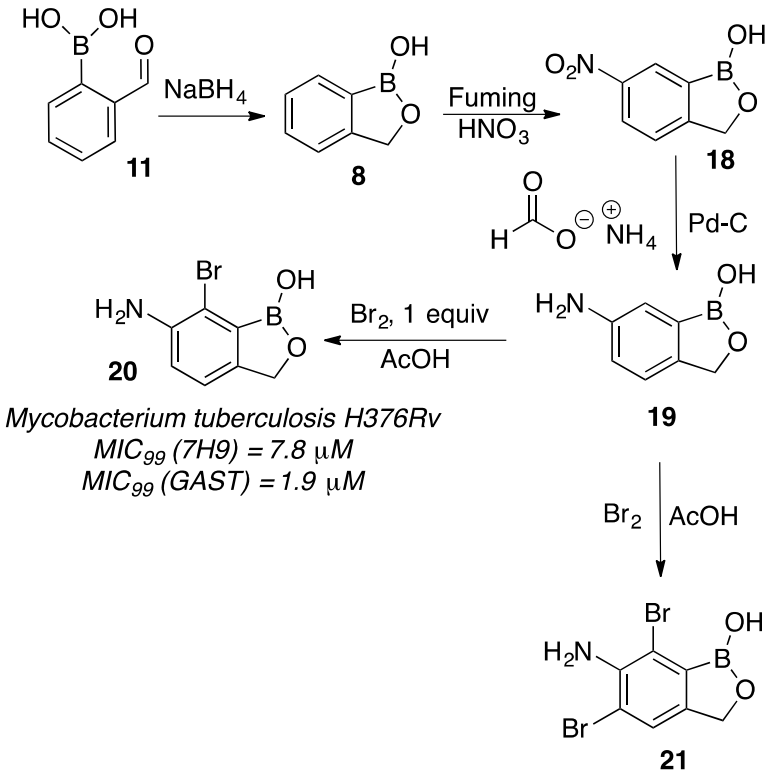


Figure 5. Preparation of benzoboroxoles as anti-tubercular agents.

Benzoboroxoles **22-24** exhibited excellent activity against *M. tuberculosis* (**Figure 6**)[21]. These compounds were prepared using standard aromatic ring chemistry.

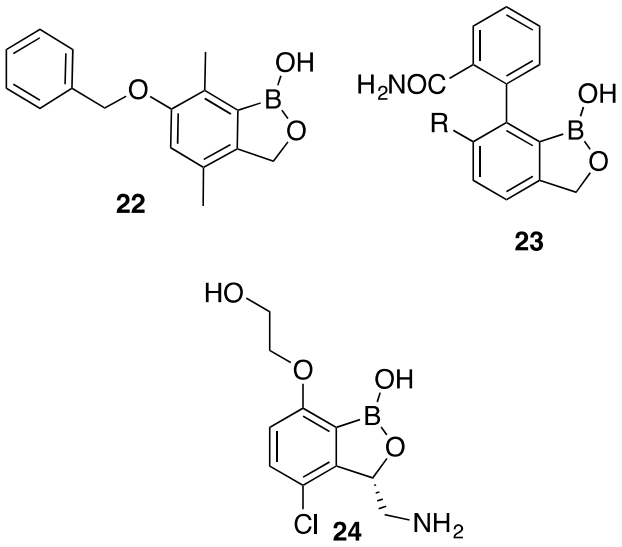


Figure 6. Benzoboroxoles in preclinical development as anti-tubercular agents.

Anti-Malarial agents. 6-Aryloxy-7-alkylbenzoboroxoles **25** and **26** showed impressive *in vitro* and *in vivo* biological activity against *Plasmodium falciparum* thus demonstrating their potential as *anti*-malarial agents (**Figure 7**)[22].

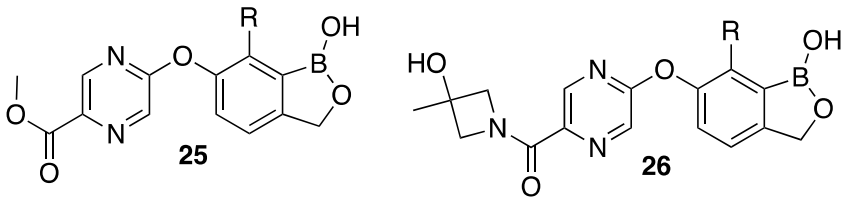
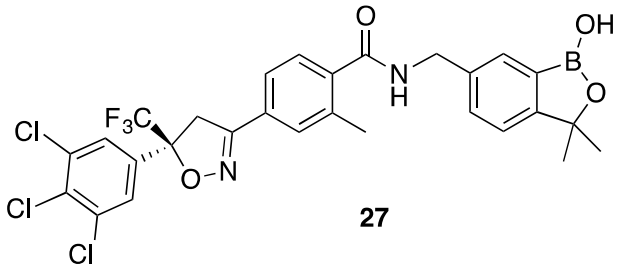


Figure 7. Benzoboroxoles in preclinical development as anti-malarial agents.

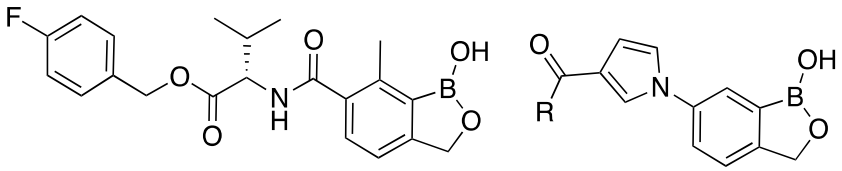
Ectoparasiticidic agents. Isoxazoline-based benzoboroxoles **27** exhibited potential as long acting animal ectoparasiticide against dog ticks and cat fleas.



27

Figure 8. Benzoboroxoles in preclinical development as ectoparasiticidic agents.

Anti-Trypanosomiasis agents. A valine amide substituted benzoboroxole **28** expressed activity against two protozoan parasites are primarily responsible for African trypanosomiasis in animals namely *Trypanosoma congolense* and *T. vivax*. 6-Pyrrolobenzoboroxole **29** was identified as a lead candidate for human African trypanosomiasis or sleeping sickness (**Figure 9**).[23]



28 **29**

Figure 9. Benzoboroxoles in preclinical development as anti-trypanosomiasis agents.

Miscellaneous applications. A clarithromycin-benzoboroxole conjugate **30** proved to be a more potent derivative than the parent drug clarithromycin against gram-positive bacterial strains.[24] Similarly, amphotericin benzoboroxole conjugates **31a-b** showed very good antifungal activity against *Candida albicans, Cryptococcus humicolus, Aspergillus niger,* and *Fusarium oxysoprum*.[25] Thiadiazolyloxy benzoboroxole derivative **32** is a potent inhibitor of serine β-lactamase[26] and 3-aminomethylbenzoboroxole **33** is an effective inhibitor of human protozoan pathogens *Toxoplasma* and *Cryptosporidium* (**Figure 10**).[27]

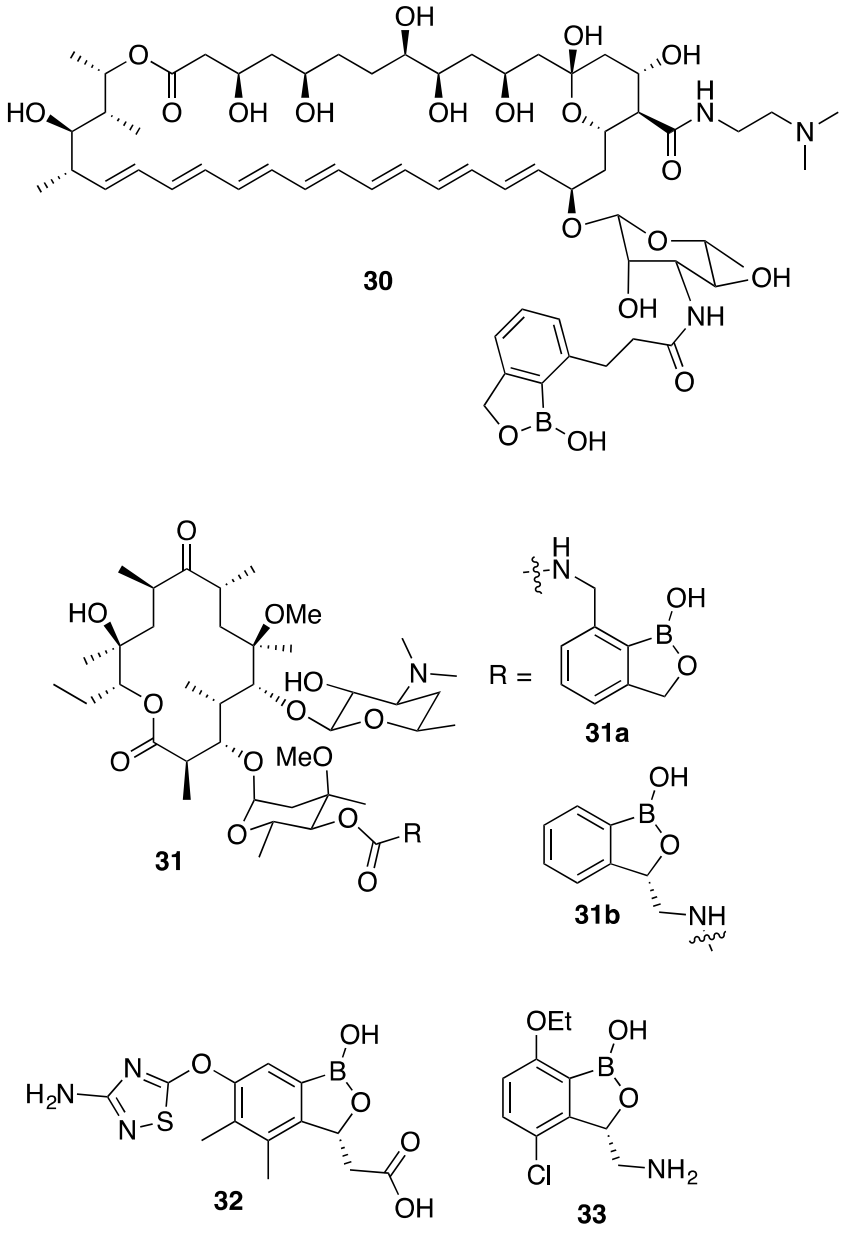


Figure 10. Miscellaneous medicinal applications of benzoboroxoles.

In addition to the analogs mentioned above, several other benzoboroxole derivatives with *anti*-inflammatory[28], and *anti*-viral (HCV protease)[29] activities have also been developed. In addition to the applications in medicinal chemistry, benzoboroxoles

and their derivatives have also been extensively utilized as hydrogels, and for oligosaccharide detection.[30]

Apart from boronic acids and benzoboroxoles, carboranes are another class of boron compounds that have attracted significant attention because of their applications as chemo- and radiotherapeutic agents.[31] BODIPY (boron-dipyrromethene), a valuable fluorophore, is a family of fluorescent boron compounds that have found imaging applications because of their stability and higher quantum yields under physiological conditions.[32] The other uses of boron compounds include their use as electrochemical sensors for recognition of anions and small molecules,[33] use of boron based polymers for the development of thermoresponsive hydrogels, HIV barrier gels, nanoparticles and block copolymers for drug delivery applications.[34]

Chapter 2

Reductive Amination for the Preparation of Benzoboroxoles

In this project, we envisioned the preparation of aromatic ring-functionalized benzoboroxoles while leaving the benzylic carbon unbranched on the oxaborole ring so as to improve the biological efficacy. Herein, we provide an account of our synthetic and biological evaluation results.[35]

Preparation of Aminobenzoboroxole

We started synthesis of precursor aminobenzoboroxole **19** in three steps starting from 2-formylphenylboronic acid **11**. In the first step, reduction of 2-formylphenylboronic acid **11** was carried out with $NaBH_4$ in methanol at 0 °C to yield benzoboroxole **8** in 87% yield (**Figure 11**). The formation of boroxole ring was confirmed by ^{1}H-NMR spectrum, which showed a characteristic signal at δ 4.80 (2H) corresponding to the benzylic methylene protons.

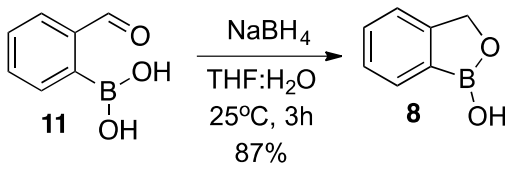


Figure 11. Preparation of benzoboroxole.

In the second step, nitration of benzoboroxole **8** was carried out with fuming nitric acid to afford 6-nitrobenzoboroxole **18** as white solid in 68% yield.[11b,36] Further, 6-nitrobenzoboroxole underwent reduction with zinc and hydrochloric acid to result in the formation of 6-aminobenzoboroxole **19** as pale yellow solid in 78% yield (**Figure 12**). A detailed ^{1}H-NMR comparative analysis of nitrobenzoboroxole and aminobenzoboroxole revealed an upfield shift of C-7 proton signal from δ 8.57 (1H) to δ 7.00 (1H), thus confirming the formation of 6-aminobenzoboroxole. None of these compounds required any chromatographic purification and the compounds could be readily obtained upon workup by simple acid-base manipulations.

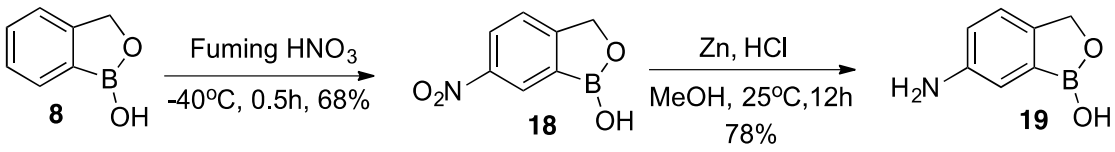


Figure 12. Preparation of 6-aminobenzoboroxole.

Preparation of *N*-Benzylaminobenzoboroxole

After synthesizing 6-aminobenzoboroxole **19**, we attempted the reductive amination of benzaldehyde with **19** in methanol at room temperature, and complete conversion of amine to imine **34** was observed after stirring for 3 h. Sodium borohydride was then added to the reaction mixture at room temperature and stirred for 2 h to affect reduction of the imine. Our initial efforts of isolating the product **35** proved difficult and the standard work up with ethyl acetate and water after evaporation of ethanol did not

furnish the product *N*-benzylaminobenzoboroxole **35**. The product was obtained after acidification with dilute HCl to pH 1 and work up with ethyl acetate, albeit in low yields (~30%). The isolation step was eventually successful after careful neutralization of the aqueous solution to a neutral pH, at which point, the product started precipitating out of the solution and *N*-benzylaminobenzoboroxole **35** was obtained in 82% yield. The solid was then filtered and dried over vacuum to obtain analytically pure product **35** (**Figure 13**). The ^{1}H-NMR analysis revealed a signal at δ 4.26 (2H) as a doublet corresponding to benzylic methylene protons adjacent to the amine and a triplet at δ 6.20 (1H) corresponding to the secondary amine proton thus confirming the formation of *N*-benzylaminobenzoboroxole **35**.

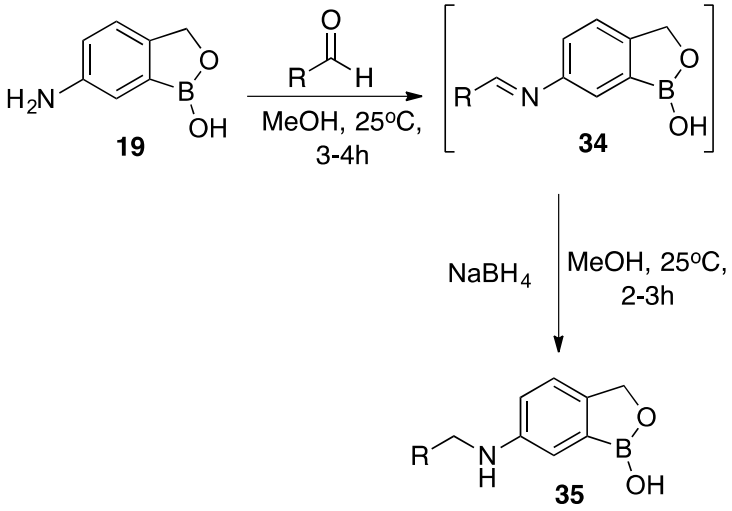


Figure 13. Preparation of *N*-alkylaminobenzoboroxoles via reductive amination.

To evaluate the efficiency of this methodology, variety of aldehydes substituted with electron withdrawing as well as electron donating groups were subjected to

reductive amination with 6-aminobenzoboroxole **19**. All of these aldehydes readily reacted with **19** at room temperature and complete formation of the imine was observed in all these cases within 3-4 h. The imines were then subjected to $NaBH_4$ reduction to afford the products **35a-m** in 72-85% overall yields (**Figure 14**). As expected, imine formation was observed to be relatively faster with electron withdrawing group substituted aldehydes and slightly better yields of the product were observed in these cases (**Figure 14**). All the compounds **35a-m** were characterized using NMR and mass spectrometric analyses.

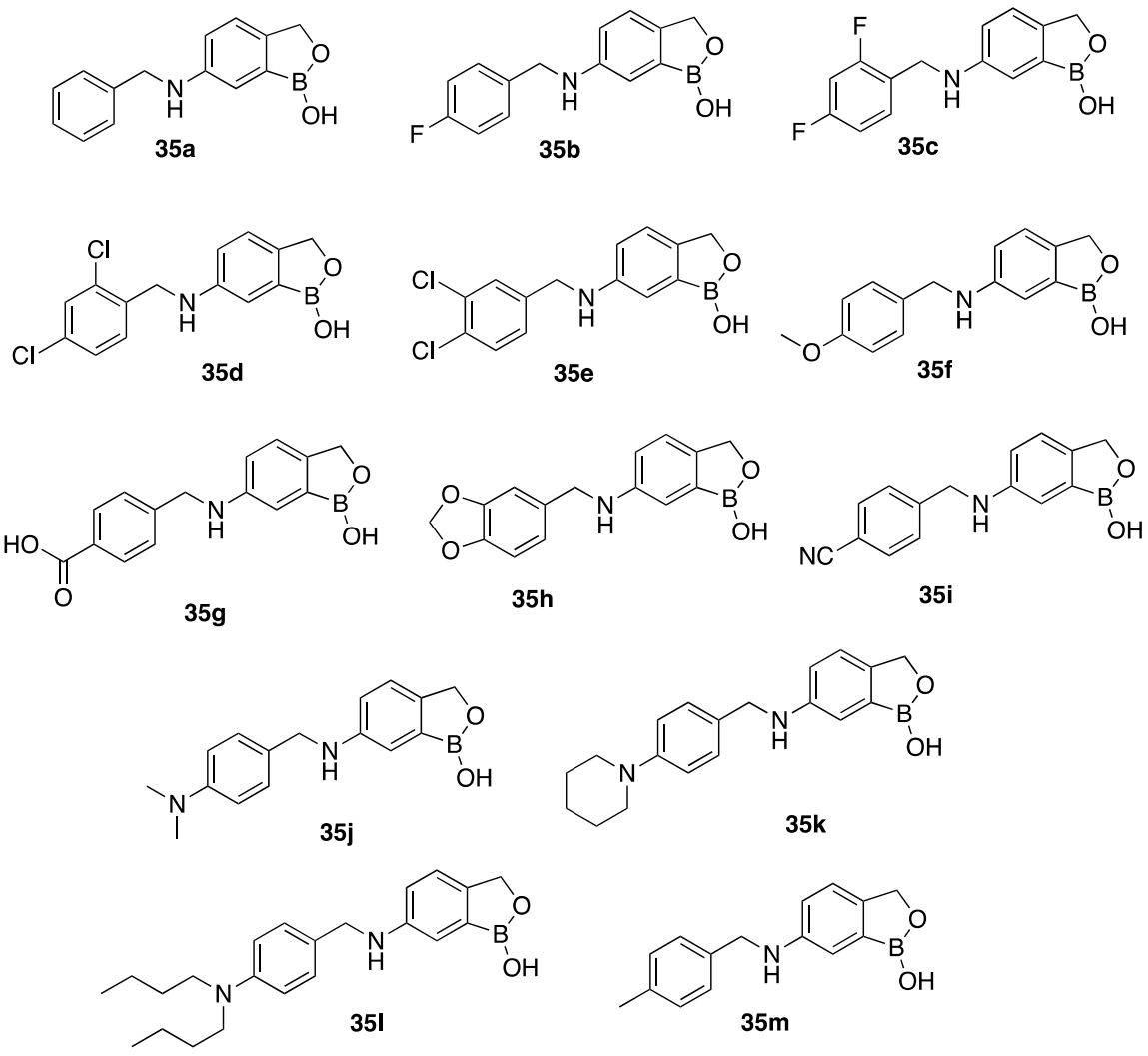


Figure 14. Reductive amination for the preparation of aminobenzoboroxoles.

Preparation of Aminobenzoboroxole-Flutamide Hybrid

Using the reductive amination strategy, an aminobenzoboroxole-flutamide hybrid congener **39** was also synthesized. The condensation of 4-nitro-3-trifloromethylaniline **36** with *p*-formylbenzoic acid in the presence of $POCl_3$ yielded the amido aldehyde **38** in 72% yield. The aldehyde **38** was then subjected to reductive amination with 6-aminobenzoboroxole **19** under standard conditions in a one-pot procedure as described

above to obtain the target compound **39** (**Figure 15**).

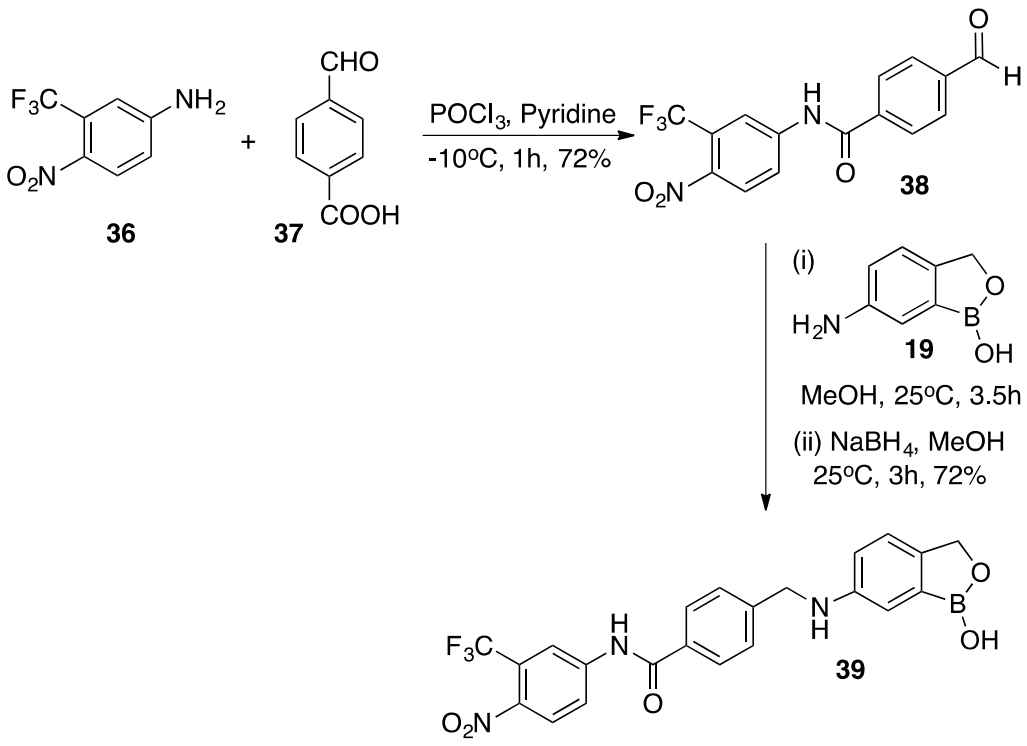


Figure 15. Preparation of aminobenzoboroxole-flutamide hybrid.

Preparation of Chloroquinoline-Aminobenzoboroxole Conjugate

A chloroquinoline-aminobenzoboroxole conjugate **42** was also synthesized in a similar manner starting from 2-chloroquinoline carbaldehyde **41.** The aldehyde **41** was synthesized from acetanilide **40** under Vilsmeier-Haack formylation conditions using $POCl_3$ and DMF. The condensation of aldehyde **41** with aminobenzoboroxole **19** followed by the reduction with $NaBH_4$ yielded the target compound **42** in 81% yield.

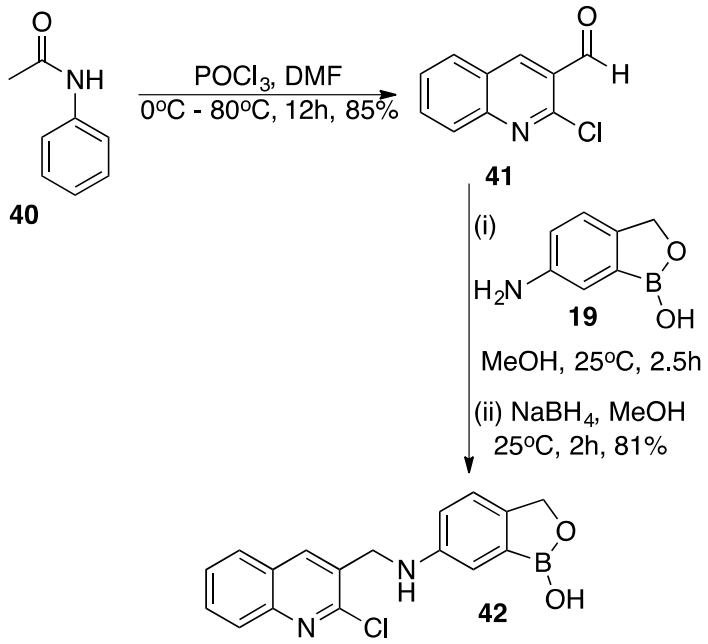


Figure 16. Preparation of chloroquinoline-aminobenzoboroxole conjugate.

Preparation of *N*-Nitrosoaminobenzoboroxoles

Nitrosoamines and nitrosoureas[37] are of interest for the treatment of various types of cancers and compounds such as lomustine and carmustine are prescribed as DNA alkylating drugs in chemotherapy. To demonstrate the robustness of the benzoboroxole moiety, some of the representative secondary amines **35** reported above were subjected to nitrosation. All of the compounds readily reacted with sodium nitrite and HCl in acetonitrile/water solvent system and the corresponding *N*-nitrosoaminobenzoboroxoles **43a-f** precipitated out of the reaction within 1-2 h (**Figures 17-18**). The products were obtained in high yields and were characterized by standard analytical techniques. A detailed ^{1}H-NMR comparative analysis of aminobenzoboroxole **35** and *N*-nitrosoaminobenzoboroxole **43a** revealed a downfield shift of benzylic methylene

protons adjacent to the amine from δ 4.26 (d, 2H) to δ 5.33 (s, 2H) as well as the disappearance of the secondary amine signal, thus confirming the formation of *N*-nitrosoaminobenzoboroxole **43a**.

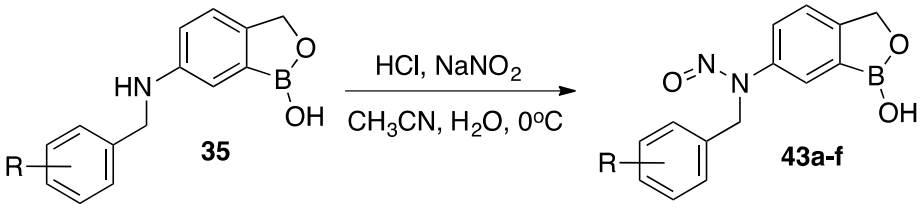


Figure 17. Preparation of *N*-nitrosoaminobenzoboroxoles.

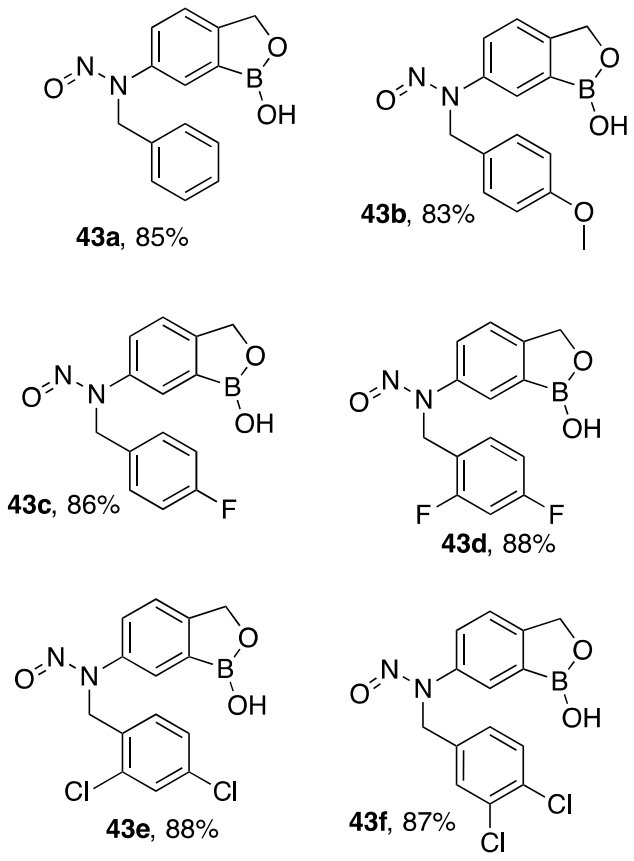


Figure 18. N-nitrosoaminobenzoboroxoles.

Preparation of Aminobenzoboroxole-Based Urea Derivatives

The aminobenzoboroxoles **35** were further reacted with phenyl, cyclohexyl, and 2-chloroethyl isocyanates in dioxane to furnish the urea derivatives **44a-f** in 79-84% yields (**Figures 19-20**). The pure products were obtained upon the removal of solvent and addition of cold water. The products were filtered, dried, and characterized by IR, NMR, and mass spectrometry. In the case of cyclohexyl isocyanate and 2-chloroethyl isocyanate, the products had to be further triturated with hexane under sonication to remove traces of unreacted starting material or other by products.

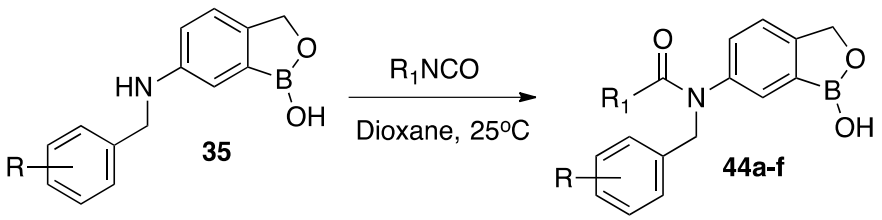


Figure 19. Preparation of aminobenzoboroxole-based urea derivatives.

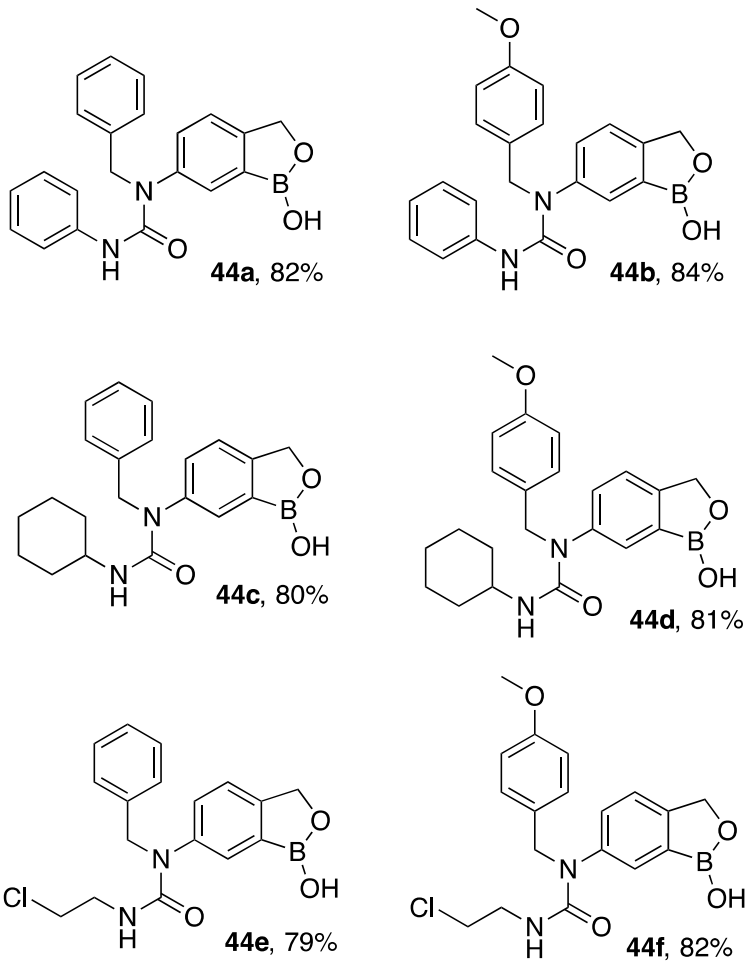


Figure 20. Aminobenzoboroxole-based urea derivatives.

After synthesizing the nitrosamine (**43**) and urea based benzoboroxoles (**44**), we attempted to extend our efforts to synthesize *N*-nitrosourea derivatives of benzoboroxoles. However, our efforts towards the nitrosation of phenylureas **44** did not materialize and a complex mixture of products was observed (**Figure 21**).

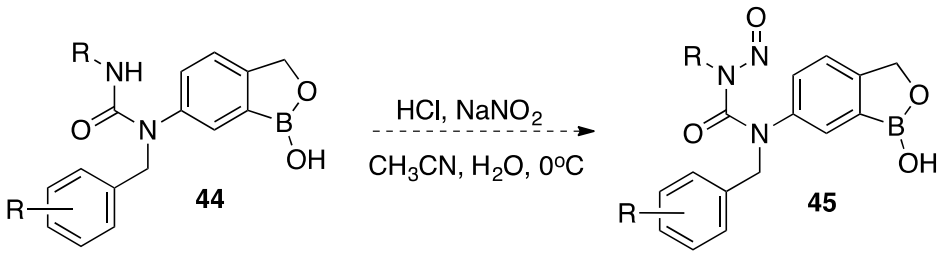


Figure 21. Preparation of *N*-nitrosourea derivatives of benzoboroxoles.

Biological Evaluation of Aminobenzoboroxoles

After synthesizing the functionalized aminobenzoboroxoles, these molecules were evaluated for their general cytotoxicity against breast cancer cell lines (MDA-MB-231) and pancreatic cancer cell lines (MIAPaCa-2). While most of the compounds tested were not found to exhibit any significant cytotoxicity at 12.5 and 50 μM concentration, couple of derivatives **42** and **44b** showed activity against MIAPaCa-2 cell lines at 12.5 μM concentration (Tables 1-3).

Table 1

Cell Viability of Aminobenzoboroxoles on Cancer Cell Lines.

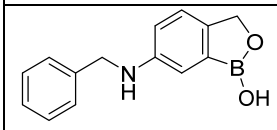
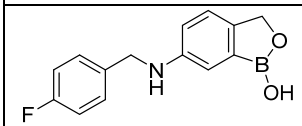
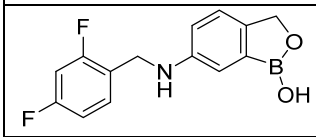
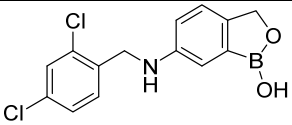
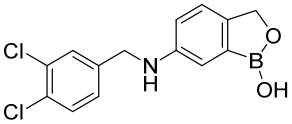
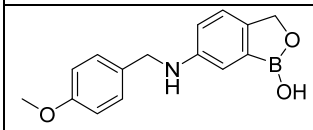
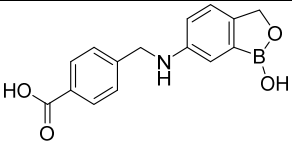
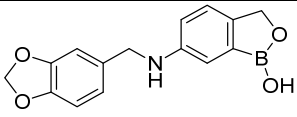
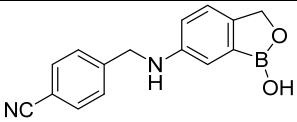
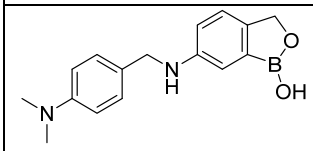
Compound structure	MIAPaCa-2		MDA-MB-231	
	50mM	12.5mM	50mM	12.5mM
 **35a**	34.5	76.6	80.2	73.7
 **35b**	73.6	87.2	91.7	84.0
 **35c**	63.9	90.9	90.0	80.2
 **35d**	65.8	86.4	75.7	75.2
 **35e**	62.6	95.3	68.7	69.2
 **35f**	37.9	51.8	90.0	90.2
 **35g**	80.6	71.3	123.6	100.1
 **35h**	69.0	88.9	101.7	88.5
 **35i**	47.0	80.8	109.2	77.7
 **35j**	78.4	72.1	71.1	97.6

Table 1 (continued)

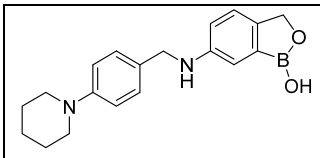
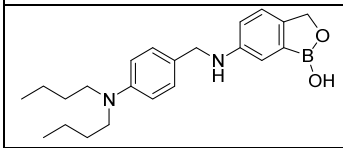
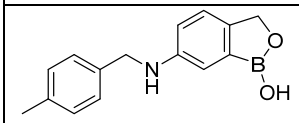
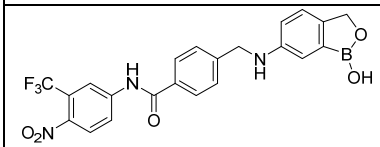
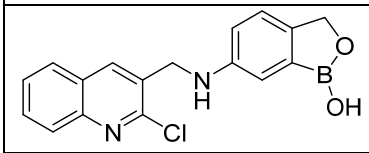
 **35k**	49.5	92.0	90.7	93.9
 **35l**	58.2	89.1	102.6	106.5
 **35m**	45.9	57.2	82.8	84.1
 **39**	77.7	85.8	49.5	112.0
 **42**	28.6	28.2	44.8	44.3
Control	100.0	100.0	100.0	100.0

Table 2

Cell Viability of N-Nitrosoaminobenzoboroxoles on Cancer Cell Lines.

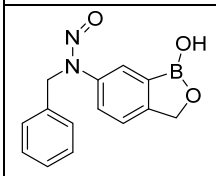
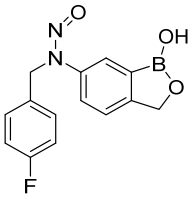
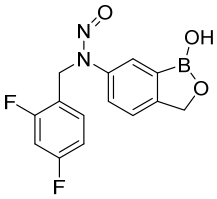
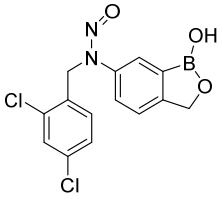
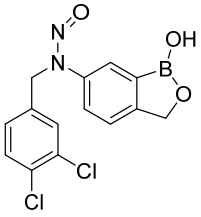
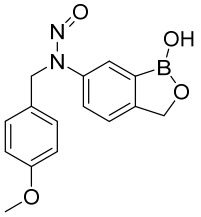
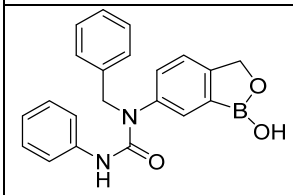
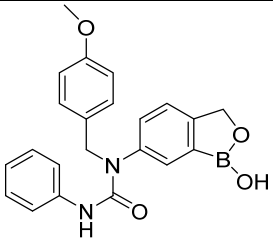
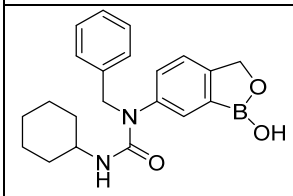
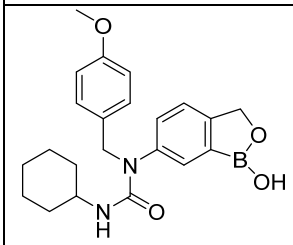
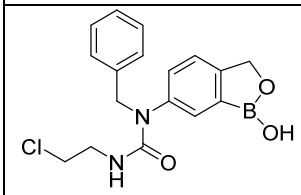
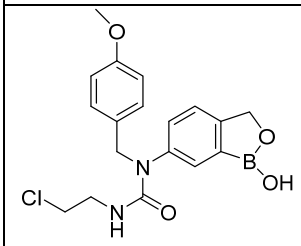
Compound structure	MIAPaca		MDA-MB-231	
	50mM	12.5mM	50mM	12.5mM
 **43a**	51.5	83.5	115.3	120.7
 **43b**	62.8	77.7	107.9	128.3
 **43c**	70.5	70.3	125.6	121.7
 **43d**	69.5	95.7	106.1	133.7
 **43e**	59.9	84.8	146.0	121.5
 **43f**	61.0	83.0	123.2	118.7
Control	100.0	100.0	100.0	100.0

Table 3

Cell Viability of Aminobenzoboroxole-based Ureas on Cancer Cell Lines.

Compound structure	MIAPaca		MDA-MB-231	
	50mM	12.5mM	50mM	12.5mM
 **44a**	30.0	49.6	47.0	115.9
 **44b**	17.5	22.4	53.9	63.0
 **44c**	39.4	64.8	127.6	80.9
 **44d**	25.1	45.5	60.8	96.3
 **44e**	61.8	103.9	100.9	134.8
 **44f**	60.4	74.9	63.2	95.8
Control	100.0	100.0	100.0	100.0

The IC_{50} values for the two most active derivatives **42** and **44b** were found to be 11.5 μM and 11.9 μM respectively in human breast cancer cell lines MDA-MB-231. Similarly, the IC_{50} values for these compounds were determined to be 8.3 μM and 2.7 μM respectively in human pancreatic cancer cell lines MIAPaCa-2 (**Figure 22**).

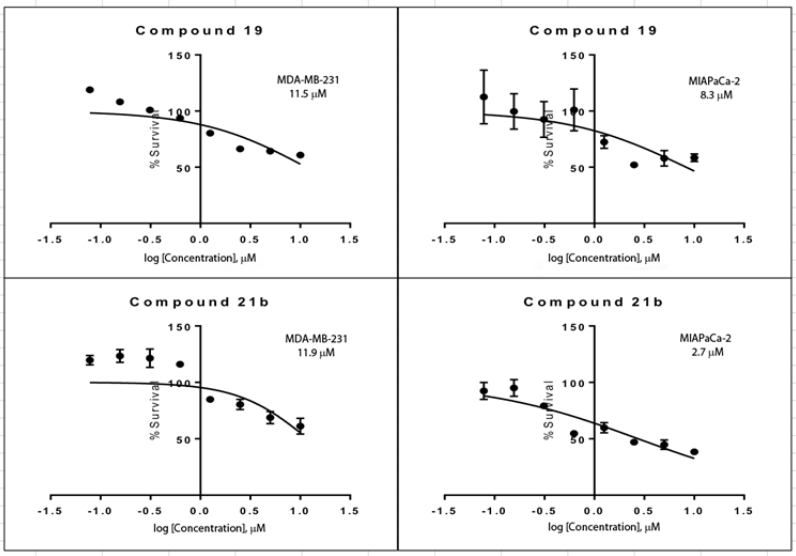


Figure 22. In vitro Anti-cancer evaluation of aminobenzoboroxoles.

Conclusions

We have developed a method for the preparation of 6-aminobenzoboroxoles using zinc/acetic acid reduction of 6-nitrobenzoboroxole. The aminobenzoboroxoles were further utilized for reductive amination of a variety of aldehydes. Further, the resulting *N*-alkylaminobenzoboroxoles have also been transformed into *N*-benzoboroxolylureas as well as *N*-nitroso-aminobenzoboroxoles. The initial cell based biological evaluation of these molecules has shown some promise and we have been able to identify various leads for future development as anti-cancer agents.

Chapter 3

Experimental Procedures

Materials

2-Formylphenylboronic acid was purchased from AK Scientific, Inc. All other reactants were of reagent grade, purchased from Acros Organics, Alfa Aesar and Sigma Aldrich, and used without further purification. All solvents were used without further drying or purification and were of ACS grade purchased from Fisher Scientific.

Instrumentation

Nuclear Magnetic Spectroscopy (NMR) NMR spectra were produced using the Varian 400 MHz spectrophotometer. The instrument was maintained at 25^{o} C operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. The deuterated solvent ($CDCl_3$, DMSO-d_6) used for each respective spectrum is referenced to the appropriate literature peak shift.

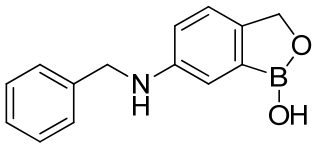
Procedure for the Preparation of 6-Aminobenzoboroxole

6-Nitrobenzoboroxole (400 mg, 2.23 mmol) was stirred in methanol (15 mL) under sonication until a white turbid solution was obtained. The solution was cooled to 0 °C and conc. HCl (2.5 mL) was added. After stirring the reaction mixture for 20 min, Zinc powder (1.62 g, 25.0 mmol) was added in three portions at 0 – 5 °C. The reaction mixture was stirred overnight at room temperature and was filtered through a celite pad. The filtrate was concentrated in vacuo, and the crude mixture was stirred in ethyl acetate (20 mL) for 10 min to dissolve the bright red residue. The resulting solution was neutralized with 1 M aq. K_2CO_3 and extracted with ethyl acetate (2 X 10 mL). The combined organic extract was washed with brine (1 X 10 mL), dried over Na_2SO_4, and

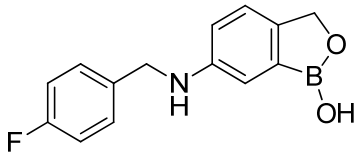
concentrated under vacuum to furnish pure 6-aminobenzoboroxole as a pale yellow powder (260 mg, 78%). The spectral information matched very well with literature data.

Procedure for the Reductive Amination of Aldehydes

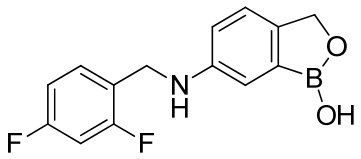
To a stirred solution of 6-aminobenzoboroxole (1.34 mmol) in 5 mL of methanol was added aryl aldehyde (1.34 mmol) at room temperature and stirred for 2 hours. Upon complete consumption of the reactants (TLC), sodium borohydride (2.01 mmol) was added in portions and stirred for 2 hours. After completion of the reaction as indicated by TLC, methanol was removed *in vacuo* and the residue was dissolved in water (5 mL). The solution was neutralized to pH 7 with 10% HCl to effect precipitation. The resulting solid was filtered, washed with water, and dried under vaccum to afford 6-*N*-benzylaminobenzoboroxoles in good yields. This procedure was utilized for the preparation of secondary amines **35a-m**.



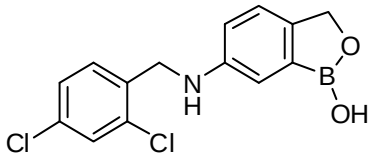
6-(Benzylamino)benzo[c][1,2]oxaborol-1(3H)-ol:Pale cream solid; yield: 82%; mp 123 – 125 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.89 (s, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.18 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.84 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.20 (brs, 1H), 4.79 (s, 2H), 4.26 (s, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 148.5, 142.2, 141.0, 129.0, 127.8, 127.2, 122.1, 117.2, 113.0, 70.2, 47.3; IR (neat): 3398, 3294, 1524, 1436, 1299, 988, 807, 735 cm^{-1}; ESI – MS: *m/z*, 254 $[M+CH_3]^+$.



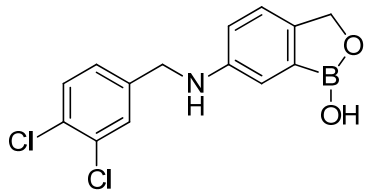
6-((4-Fluorobenzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol:Pale cream solid; yield: 79%; mp 136 – 138 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.89 (s, 1H), 7.36 (t, J = 8.8Hz, 2H), 7.11 (t, J = 8.8 Hz, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.84 (s, 1 H), 6.73 (d, J = 8.8 Hz, 1H), 6.21 (t, J = 8.8 Hz 1H) 4.80 (s, 2H), 4.24 (d J = 5.2 Hz, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 161.7 (d, J = 241.7 Hz), 148.2, 142.3, 137.1 (d, J = 2.8 Hz), 129.6 (d, J = 8.0 Hz), 122.1, 117,2, 115.6 (d, J = 21.2 Hz), 112.9, 70.2, 46.6; IR (neat): 3413, 3245, 1508, 1372, 1216, 989, 821, 753 cm^{-1}; ESI – MS: *m/z*, 272 $[M+CH_3]^+$.



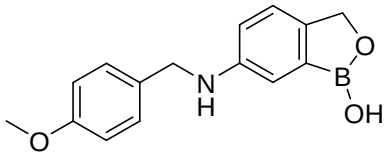
6-((2,4-Difluorobenzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol:Yellow solid; yield: 81%; mp 135 – 137 °C; ^{1}H-NMR (400 MHz, DMSO – d_6): δ 8.90 (s, 1H), 7.37 (m, 1H), 7.19 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.00 (m, 1H), 6.83 (s, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.16 (brs, 1H), 4.80 (s, 2H), 4.25 (d, J = 5.2 Hz, 1H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 161.9 (dd, J = 244.6, 12.4 Hz), 160.9 (dd, J = 246.6, 12.3 Hz), 148.0, 142.6, 130.9 (dd, J = 9.5, 6.4 Hz), 123.8 (dd, J = 15.3, 3.5 Hz), 122.3, 117.2, 112.8, 111.9 (dd, J = 20.9, 2.9 Hz), 104.3 (t, J = 25.8 Hz), 70.2, 46.0; IR (neat): 3398, 3265, 1523, 1235, 1012, 875, 739 cm^{-1}; ESI – MS: *m/z*, 290 $[M+CH_3]^+$.



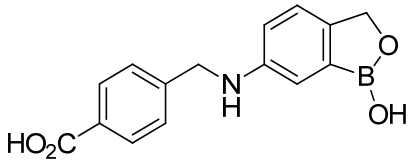
6-((2,4-Dichlorobenzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol:Pale cream solid; yield: 80%; mp 106 – 108 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.91 (s, 1H), 7.60 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.32 (t, J = 6.0 Hz, 1H), 4.80 (s, 2H), 4.30 (d, J = 6.0 Hz, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 147.8, 142.7, 137.0, 133.7, 132.6, 130.5, 129.3, 128.0, 122.4, 117.3, 112.6, 70.2, 44.8; IR (neat): 3412, 3295, 1286, 1320, 989, 815, 760 cm^{-1}; ESI – MS: *m/z*, 322 $[M+CH_3]^+$.



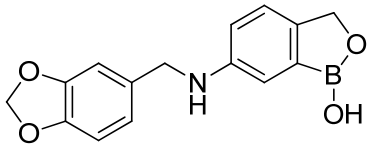
6-((3,4-Dichlorobenzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol: Cream solid; yield: 78%; mp 128 – 130 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.90 (s, 1H), 7.57 (s, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.32 (t, J = 5.6 Hz, 1H), 4.79 (s, 2H), 4.27 (d, J = 5.2 Hz, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 147.9, 142.7, 142.6, 131.6, 131.1, 129.6, 129.5, 128.1, 122.3, 117.3, 113.1, 70.2, 46.2; IR (neat): 3412, 3289, 1489, 1121, 975, 826, 720 cm^{-1}; ESI – MS: *m/z*, 322 $[M-H+CH_3]^+$.



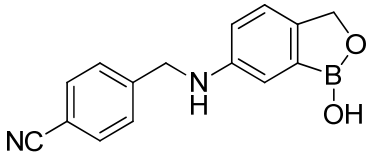
6-((4-methoxybenzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol:Pale yellow solid; yield: 76%; mp 130 – 132 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.88 (s, 1H), 7.25 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.83 (s, 1H), 6.72 (dd, J = 2.4, 8.4 Hz, 1H), 6.11 (t, J = 6.0 Hz, 1H), 4.78 (s, 2H), 4.17 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 158.7, 148.5, 142.1, 132.7, 129.0, 122.1, 117.3, 114.4, 113.0, 70.2, 55.7, 46.8; IR (neat): 3298, 2983, 1526, 1437, 1238, 1172, 769 cm^{-1}; ESI – MS: *m/z*, 283 $[M-H+CH_3]^+$.



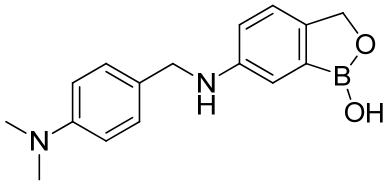
4-(((1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)amino)methyl)benzoic acid: Pale yellow solid; yield: 85%; mp 221 – 223 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 12.78 (s, 1H), 8.89 (s, 1H), 7.87 (d, J = 6.4 Hz, 2H), 7.44 (d, J = 6.4 Hz, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.81 (s, 1H), 6.72 (d, J = 8.4 Hz, 2H), 6.36 (bs, 1H), 4.79 (s, 2H), 4.34 (s, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 167.9, 148.2, 146.6, 142.4, 130.1, 129.8, 127.7, 122.2, 117.3, 113.0, 70.2, 47.2; IR (neat): 3412, 3278, 1682, 1483, 1289, 984, 817, 753 cm^{-1}; ESI-MS: *m/z*, 298 $[M+CH_3]^+$.



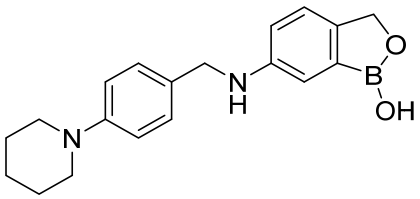
6-((Benzo[d][1,3]dioxol-5-ylmethyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol:Cream solid; yield: 77%; mp 136 – 138 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.89 (s, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.88 (s, 1H), 6.82 (m, 3H), 6.72 (d, J = 8.0 Hz, 1H), 6.14 (t, J = 5.6 Hz, 1H), 5.94 (s, 2H), 4.75 (s, 2H), 4.15 (d, J = 5.6 Hz, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 148.3, 148.0, 146.5, 142.3, 135.0, 122.1, 120.8, 117.3, 113.1, 108.7, 108.3, 101.4,70.2, 47.1; IR (neat): 3413, 3289. 1525, 1316, 1256, 974, 774 cm^{-1}; ESI – MS: *m/z*, 298 $[M+CH_3]^+$.



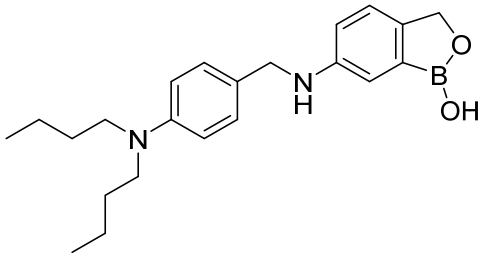
4-(((1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)amino)methyl)benzonitrile:Cream solid; yield: 82%; mp 141 – 143 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.89 (s, 1H), 7.76 (d, J = 6.0 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 1.6 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.37 (t, J = 8.88 Hz 1H), 4.79 (s, 2H), 4.36 (d, J = 6.0 Hz, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 148.0, 147.5, 142.6, 132.9, 128.6, 122.3, 119.7, 117.2, 113.0, 110.0, 70.2, 47.0; IR (neat): 3398, 3265, 2224, 1587, 1387, 974, 819, 725 cm^{-1}; ESI – MS: *m/z*, 279 $[M+CH_3]^+$.



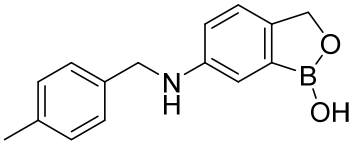
6-((4-(Dimethylamino)benzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol: Pale cream solid; yield: 74%; mp 122 – 124 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.90 (s, 1H), 7.16 (d, J = 7.6 Hz, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.86 (s, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 2H), 6.01 (t, J = 5.6 Hz, 1H), 4.80 (s, 2H), 4.13 (d, J = 5.6 Hz, 2H), 3.34 (s, 6H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 150.2, 148.6, 142.0, 128.7, 128.2, 122.0, 117.3, 113.2, 113.0, 70.3, 47.0; IR (neat): 3357, 3258, 1612, 1443, 1316, 1042, 915, 821, 726 cm^{-1}; ESI – MS: *m/z*, 298 $[M\text{-}H+CH_3]^+$.



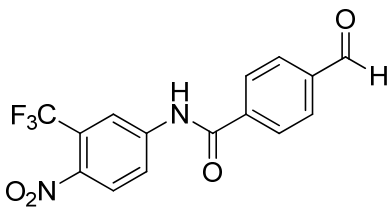
6-((4-(Piperidin-1-yl)benzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol: Orange solid; yield: 73%; mp 65 – 67 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.88 (s, 1H), 7.15 (d, J = 8.8 Hz, 3H), 6.85 (q, 4H), 4.78 (s, 2H), 4.12 (t, 3H), 3.30 (m, 4H), 3.04 (m, 6H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 151.3, 148.6, 142.0, 130.7, 128.6, 122.6, 117.3, 116.6, 112.9 70.2, 50.5, 46.9, 26.0, 24.6; IR (neat): 3413, 3278, 2930, 1512, 1231, 1129, 808, 724 cm^{-1}; ESI – MS: *m/z*, 336 $[M\text{-}H+CH_3]^+$.



6-((4-(Dibutylamino)benzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol: Pale yellow solid; yield: 78%; mp 94 – 96 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.88 (s, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.8 Hz, 1H), 6.86 (s, 1H), 6.73 (d, J = 8.8 Hz, 1H), 6.54 (d, J = 8.0 Hz, 2H), 5.93 (t, J = 5.4 Hz, 1H), 4.79 (s, 2H), 4.06 (d, J = 5.6 Hz, 2H), 3.19 (t, J = 7.0 Hz, 4H), 1.43 (m, 4H), 1.27 (m, 4H), 0.87 (m, 6H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 148.7, 147.4, 141.9, 129.1, 126.7, 122.0, 117.2, 112.9, 112.1, 70.3, 50.7, 47.0, 29.7, 20.4, 14.6; IR (neat): 3429, 3298, 2928, 2895, 1517, 1298, 1187, 988, 768 cm^{-1}; ESI – MS: *m/z*, 381 $[M+CH_3]^+$.



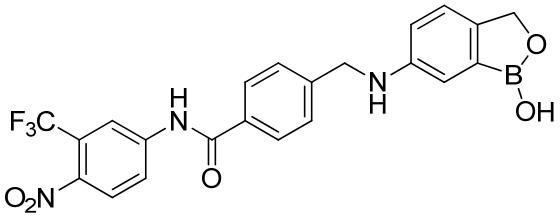
6-((4-methylbenzyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol: Pale yellow solid; yield: 71%; mp 148-150 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.87 (s, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 7.6 Hz, 2H), 7.02 (d, J = 8.2 Hz, 1H), 6.81 (s, 1H), 6.71 (d, J = 7.5 Hz, 1H), 6.14 (br s, 1H), 4.77 (s, 2H), 4.19 (d, J = 5.5 Hz, 2H), 2.22 (s, 3H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 148.40, 142.1, 137.8, 136.2, 129.5, 127.7, 125.2, 122.1, 117.2, 112.9, 70.2, 47.1, 21.3. IR (neat): 3431, 3289, 2926, 2898, 1521, 1194, 982, 771 cm^{-1}; ESI – MS: *m/z*, 267 $[M-H+CH_3]^+$.



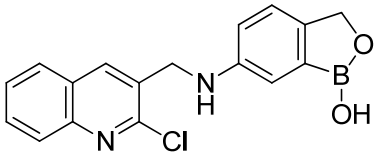
Procedure for the Preparation of Aldehyde 38

$POCl_3$ (136 mL, 1.46 mmol) was added to a solution of 4-formylbenzoic acid **37** (200 mg, 1.33 mmol) and 4-nitro-3-(trifluoromethyl) aniline **36** (247 mg, 1.20 mmol) in pyridine (5 mL) at -10 °C dropwise and the reaction was stirred 1 h at the same temperature. Upon completion (TLC), the reaction was quenched with cold water and extracted with ethyl acetate (2 X 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ solution (1 X 10 mL), brine (1 X 10 mL), and dried over anhydrous Na_2SO_4. The ethyl acetate was concentrated in vacuo and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 2:8) to yield aldehyde (292 mg, 72%) as pale yellow solid. M.P 185 – 187 °C;

^{1}H – NMR (400 MHz, DMSO – d_6): δ 11.12 (s, 1H), 10.10 (s, 1H), 8.43 (s, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 193.5, 166.2, 155.0, 144.3, 142.5, 139.2, 139.1, 130.3, 130.2, 129.3, 128.2, 124.1, 119.2; IR (neat): 3483, 3370, 2956, 1720, 1680, 1524, 1331, 1139, 1042, 749 cm $^{-1}$; ESI – MS: *m/z*, 339 $[M+H]^+$.



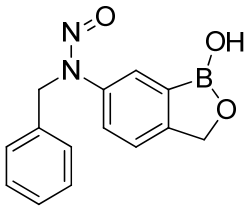
4-(((1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)amino)methyl)-N-(4-nitro-3-(trifluoromethyl)phenyl)benzamide: Yellow solid; yield: 72%; mp 117 – 119 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 10.91 (s, 1H), 8.89 (s, 1H), 8.44 (s, 1H), 8.29 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 6.8 Hz, 2H), 7.51 (d, J = 6.8 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.83 (s, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.36 (s, 1H), 4.79 (s, 2H), 4.37 (d, J = 5.6 Hz, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 167.0, 148.2, 146.2, 144.8, 142.4, 132.8, 128.7, 128.3, 127.7, 123.8, 122.2, 119.0, 117.3, 113.1, 70.2, 47.1; IR (neat): 3418, 3279, 1689, 1539, 1289, 1089, 859, 728 cm^{-1}; ESI – MS: *m/z*, 487 $[M+H+CH_3]^+$.



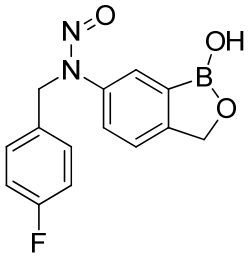
6-(((2-Chloroquinolin-3-yl)methyl)amino)benzo[c][1,2]oxaborol-1(3H)-ol: Yellow solid; yield: 81%; mp 209 – 211 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 8.87 (s, 1H), 8.24 (s, 1H), 7.95(d, J = 6.8 Hz, 1H), 7.75 (t, J = 6.8 Hz, 1H), 7.59 (t, J = 7.6 Hz 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 8.0 Hz, 2H), 6.41 (s, 1H), 4.80 (s, 2H), 4.45 (d, J = 8.0 Hz, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 150.3, 148.0, 146.8, 142.9, 137.2, 132.0, 131.0, 128.5, 128.2, 128.0, 127.8, 122.4, 117.5, 112.8, 70.2, 45.5; IR (neat): 3398, 3218, 2928, 1523, 1140, 978, 756 cm^{-1}; ESI – MS: *m/z*, 338 $[M-H+CH_3]^+$.

Procedure for the Preparation of *N*-Nitrosoaminobenzoboroxoles

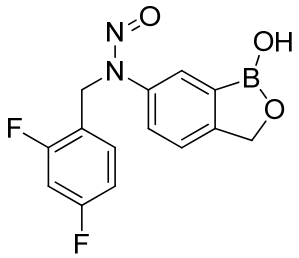
6-*N*-benzylaminobenzoboroxole (0.37 mmol) was dissolved in a 1:2 mixture of acetonitrile and water (3 mL) and the reaction mixture was cooled to 0 °C. HCl (1.86 mmol) was added dropwise and the mixture was stirred for 30 min at 0 °C. $NaNO_2$ (0.2 mL, 2 M solution, 0.4 mmol) was added drop wise and the reaction was stirred for 1.5 h, during this time, *N*-nitrosoamine gradually started precipitating out as a pale yellow solid. After completion of the reaction (TLC), the solid was filtered, washed with distilled water, and dried under *vaccu* to obtain 6-*N*-nitroso-*N*-(benzyl)amino-benzoboroxoles in good yields. This procedure was utilized for the preparation of secondary amines **43a-f**.



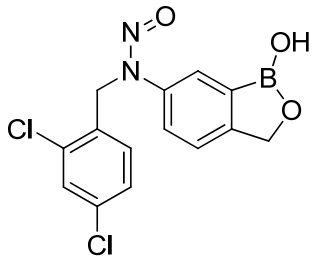
N-benzyl-N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)nitrous amide: Yellow solid; yield: 85%; mp 108 – 110 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.29 (s, 1H), 7.89 (s, 1H), 7.73 (m, 1H), 7.52 (m, 1H), 7.21 – 7.28 (m, 3H), 7.05 (m, 2H), 5.33 (s, 2H), 5.00 (s, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 153.7, 140.9, 135.2, 129.4, 128.0, 127.7, 123.5, 123.3, 122.5, 70.5, 47.4; IR (neat): 2923, 1437, 1369, 1120, 977, 937, 749 cm^{-1}; ESI – MS: *m/z*, 282 $[M-H+CH_3]^+$.



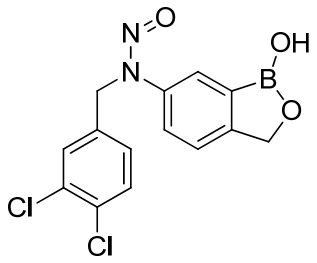
N-(4-fluorobenzyl)-N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)nitrous amide:Yellow solid; yield: 86%; mp 121 – 123 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.31 (s, 1H), 7.88 (s, 1H), 7.73 (d, J = 6.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 6.8 Hz, 4H), 5.32 (s, 1H), 5.01 (s, 1H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 162.0 (d, J = 243.6 Hz), 153.8, 140.7, 131.4 (d, J = 3.1 Hz), 129.9 (d, J = 8.3 Hz), 123.7, 123.4, 122.6, 116.2 (d, J = 21.6 Hz), 70.5, 46.8; IR (neat): 2985, 1454, 1384, 1217, 1120, 978, 814, 757 cm^{-1}; ESI – MS: *m/z*, 300 $[M-H+CH_3]^+$.



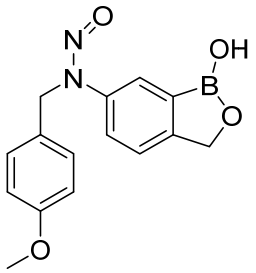
N-(2,4-difluorobenzyl)-N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)nitrous amide:Brownish solid; yield: 88%; mp 125 – 127 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.31 (s, 1H), 7.87 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.20 (m, 1H), 7.10 (m, 1H), 6.98 (m, 1H), 5.31 (s, 2H), 5.01 (s, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): ^{13}C NMR (100 MHz, DMSO –d_6): δ 162.36 (dd, J = 246.8, 12.6 Hz), 160.62 (dd, J = 248.9, 12.8 Hz), 154.0, 140.4, 131.56 (dd, J = 10.0, 5.4 Hz), 124.2, 123.3, 123.2, 118.37 (dd, J = 15.0, 3.7 Hz), 112.37 (d, J = 21.5 Hz), 104.80 (t, J = 25.9 Hz),70.5, 41.7; IR (neat): 2923, 1507, 1440, 1116, 980, 927, 778 cm^{-1}; ESI – MS: *m/z*, 318 $[M\text{-}H+CH_3]^+$.



N-(2,4-dichlorobenzyl)-N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)nitrous amide:Brownish solid; yield: 88%; mp 121 – 123 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.31 (s, 1H), 7.85 (d, J = 1.6 Hz, 1H), 7.72 (dd, J = 8.0 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.33 (dd, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 5.32 (s, 2H), 5.01 (s, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 154.0, 140.4, 133.7, 133.6, 131.4, 130.9, 129.8, 128.3, 124.0, 123.3 122.9, 70.5, 45.6; IR (neat): 2927, 1438, 1133, 977, 830 cm^{-1}; ESI – MS: *m/z*, 350 $[M-H+CH_3]^+$.



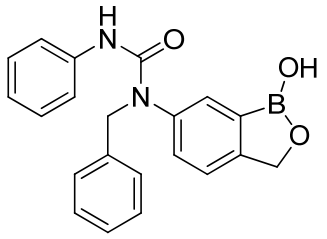
N-(3,4-dichlorobenzyl)-N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)nitrous amide:Yellow solid; yield: 87%; mp 144 – 147 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.30 (s, 1H), 7.88 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.33 (s, 2H), 5.02 (s, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 153.9, 140.6, 136.3, 131.9, 131.6, 130.8, 129.9, 127.9, 123.6, 123.4, 122.5, 70.5, 46.6; IR (neat): 3298, 1436, 1289, 1121, 975, 826, 720 cm^{-1}; ESI – MS: *m/z*, 350 $[M-H+CH_3]^+$.



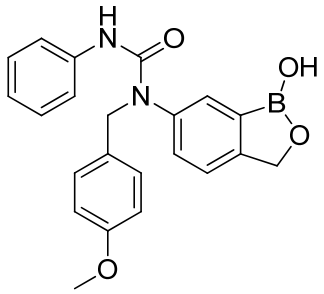
N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-N-(4-methoxybenzyl)nitrous amide:Yellow solid; yield: 83%; mp 110 – 112 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.30 (s, 1H), 7.87 (d, J = 1.6 Hz, 1H), 7.72 (dd, J = 2.0, 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.26 (s, 2H), 5.00 (s, 2H), 3.67 (s, 3H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 159.2, 153.7, 140.8, 129.3, 127.0, 123.7, 123.3, 122.7, 114.8, 70.4, 55.7, 46.7; IR (neat): 2928, 1453, 1404, 1179, 1124, 787 cm^{-1}; ESI – MS: m/z, 312 $[M-H+CH_3]^+$.

Procedure for the Synthesis of *N*-Benzoboroxolyl Ureas

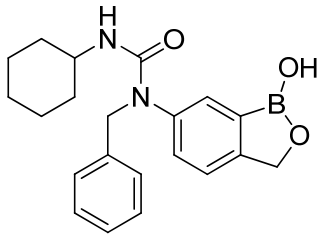
2-Chloroethyl isocyanate (0.37 mmol) was added to the solution of 6-*N*-(benzyl)aminobenzoboroxole (0.37 mmol) in dioxane (3 mL) and the reactionwas stirred overnight at room temperature. After completion of the reaction (TLC), the solvent was removed in vacuo and the residue was diluted with deionized water. The resulting solid was filtered, washed with water, and dried under vaccum. The crude solid was triturated with hexane under sonication to obtain the pure urea derivatives in good yield.



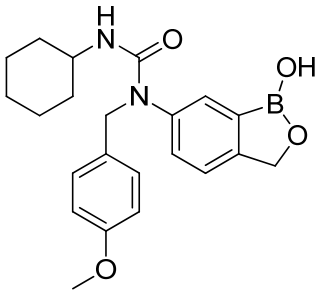
1-Benzyl-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-3-phenylurea:Pale cream solid; yield: 82%; mp 116 – 118 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.16 (s, 1H), 8.00 (s, 1H),7.54 (s, 1H), 7.16 – 7.40 (m, 10H), 6.91 (t, *J* = 8.4 Hz, 2H), 4.94 (s, 2H), 4.90 (s, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): *δ* 155.6, 152.5, 141.7, 140.7, 139.3, 130.6, 129.9, 129.5, 129.0, 128.9, 128.2, 127.6, 123.1, 122.8, 120.6, 118.9, 70.5, 67.0, 53.5; IR (neat): 3320, 1641, 1524, 1439, 1210, 825, 759 cm^{-1}; ESI – MS: *m/z*, 371 $[M-H+CH_3]^+$.



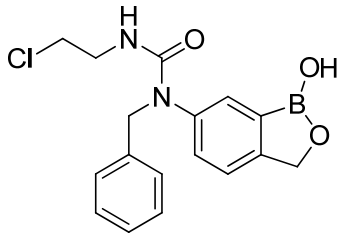
1-(1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1-(4-methoxybenzyl)-3-phenylurea:Pale brown solid; yield: 84%; mp 104 – 106 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.17 (s, 1H), 7.94 (s, 1H), 7.51 (s, 1H), 7.38 (m, 3H), 7.26 (d, J = 8.4 Hz, 1H), 7.12-7.21 (m, 4H), 6.92 (t, J = 7.17 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 4.82 (s, 2H), 4.98 (s, 2H), 3.68 (s, 3H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 159.0, 155.6, 152.5, 141.6, 140.7, 131.1, 130.7, 130.0, 129.6, 129.5, 128.9, 123.1, 122.7, 120.6, 114.4, 70.5, 67.0, 55.6, 52.9; IR (neat): 2928, 1640, 1512, 1405, 1241, 1208, 974, 747 cm^{-1}; ESI – MS: *m/z*, 401 $[M-H+CH_3]^+$.



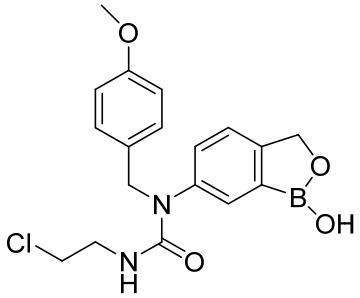
1-Benzyl-3-cyclohexyl-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)urea: Pale cream solid; yield: 80%; mp 125 – 127 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.18 (s,1H), 7.48 (s,1H), 7.35 (d, J = 7.6 Hz, 2H), 7.18 – 7.29 (m, 5H), 5.34 (d, J = 8.0 Hz, 1H), 4.94 (s, 2H), 4.82 (s, 2H), 3.48 (m, 1H), 1.50 – 1.71 (m, 4H), 0.97 – 1.24 (m, 6H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 156.9, 152.3, 141.9, 139.8, 130.8, 130.0, 128.9, 128.1, 127.4, 123.1, 70.4, 53.1, 50.0, 33.4, 25.6; IR (neat): 3295, 1654, 1434, 1289, 1021, 834, 745 cm^{-1}; ESI – MS: *m/z*, 378 $[M-H+CH_3]^+$.



3-Cyclohexyl-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1-(4-methoxybenzyl) urea: Off white solid; yield: 81%; mp 156 – 158 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.16 (s, 1H), 7.42 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.0 Hz, 2H), 5.23 (d, J = 8.4 Hz, 1H), 4.92 (s, 2H), 4.71 (s, 2H), 3.67 (s, 3H), 3.44 (m, 1H), 1.48 – 1.68 (m, 4H), 0.97 – 1.24 (m, 6H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 158.8, 156.8, 152.3, 141.8, 131.6, 130.9, 130.2, 129.5, 123.0, 114.3, 55.6, 49.9, 34.0, 33.4, 25.8, 25.5; IR (neat): 2923, 1623, 1513, 1480, 1250, 1064, 731 cm^{-1}; ESI – MS: *m/z*, 408 $[M\text{-}H+CH_3]^+$.



1-Benzyl-3-(2-chloroethyl)-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)urea:Pale cream solid; yield: 79%; mp 138 – 140 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.18 (s,1H), 7.46 (s,1H), 7.36 (d, J = 8.4 Hz,1H), 7.16 – 7.27 (m, 6H), 6.00 (t, J = 5.6 Hz, 1H), 4.93 (s, 2H), 4.79 (s, 2H), 3.54 (t, J = 6.4 Hz, 2H), 3.31 (m, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 157.5, 152.9, 141.3, 139.5, 131.2, 130.6, 128.9, 128.2, 127.5, 123.3, 70.5, 53.3, 44.1, 42.9; IR (neat): 3214, 2913, 1635, 1554, 1323, 1158, 876, 715 cm^{-1}; ESI – MS: *m/z*, 358 $[M-H+CH_3]^+$.



3-(2-chloroethyl)-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1-(4-methoxybenzyl) urea: Colorless solid; yield: 82%; mp 125 – 127 °C; ^{1}H – NMR (400 MHz, DMSO – d_6): δ 9.18 (s, 1H), 7.42 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 1.6, 8.4 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.92 (t, J = 5.6 Hz, 1H), 4.93 (s, 2H), 4.71 (s, 2H), 3.68 (s, 3H), 3.53 (t, J = 6.4 Hz, 2H), 3.28-3.30 (m, 2H); ^{13}C – NMR (100 MHz, DMSO – d_6): δ 158.8, 157.4, 152.9, 141.2, 131.4, 130.7(2C), 129.6 (2C), 123.2, 114.3 (2C), 70.5, 55.6, 52.6, 44.1, 42.9; IR (neat): 3244, 2932, 1640, 1594, 1301, 1178, 736 cm^{-1}; ESI – MS: *m/z*, 388 $[M\text{-}H+CH_3]^+$.

Cell Viability Assay

Human pancreatic cancer MIAPaCa-2 cells were purchased from ATCC and were maintained in D-MEM supplemented with 10% FBS, 2.5% horse serum, and 1% Penicillin Streptomycin in a humidified atmosphere of 5% CO2 at 37 °C. Human breast cancer MDA-MB-231 cells were purchased from ATCC and were maintained in D-MEM supplemented with 10% FBS and 1% Penicillin Streptomycin in a humidified atmosphere of 5% CO2 at 37 °C. Cells were seeded in 96 well plates at a density of 5 X 104 cells/mL, incubated for 18e24 h, then exposed to benzoboroxoles 1-21 at 50 mM and 12.5 mM concentrations in duplicate for 72 h. DMSO was added as a negative control. To determine the cell viability, MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) was dissolved in PBS solution (5 mg/mL) and 10 mL was added to each well and incubated. After 4 h, 100 mL of SDS (sodium dodecyl sulfate) solution (1 g in 10 mL of 0.01 N HCl) was added to solubilize formazan precipitate and incubated for an additional 4 h. The absorbance of each well was then measured using a microplate reader at 570 nm. The absorbance of control wells was defined as 100% viability and all of the tested compounds were expressed as percentage relative to the control.

Chapter 4

Spectral Characterization

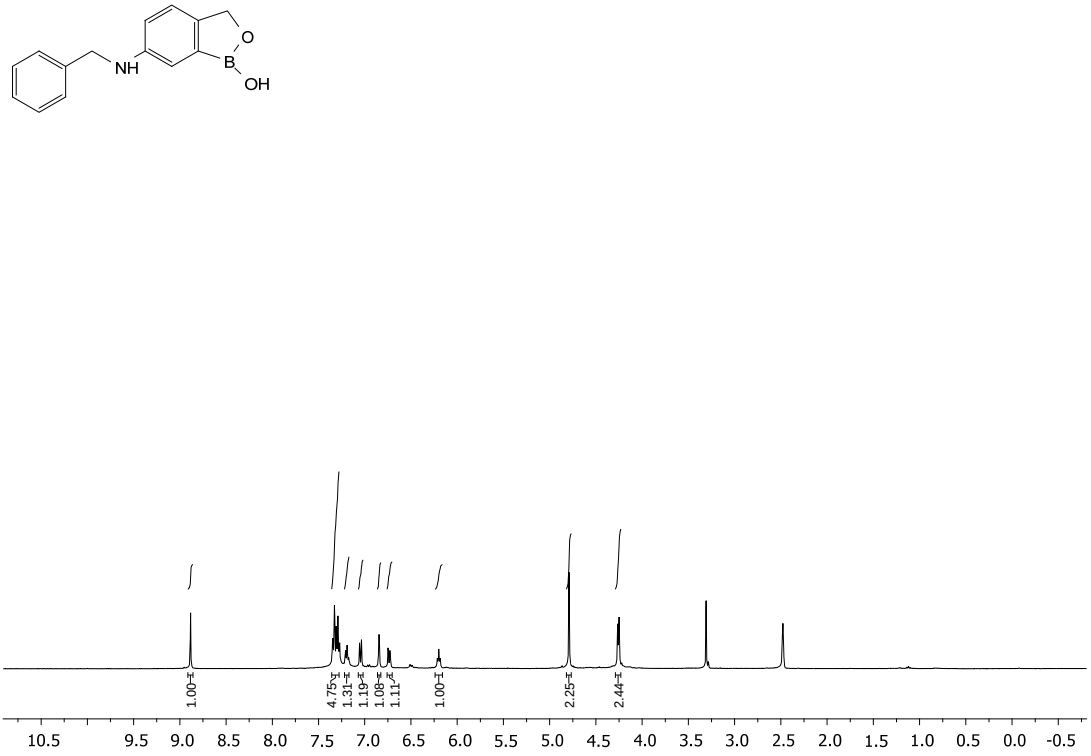


Figure 23. 400 MHz ^{1}H NMR of compound 35a in dmso

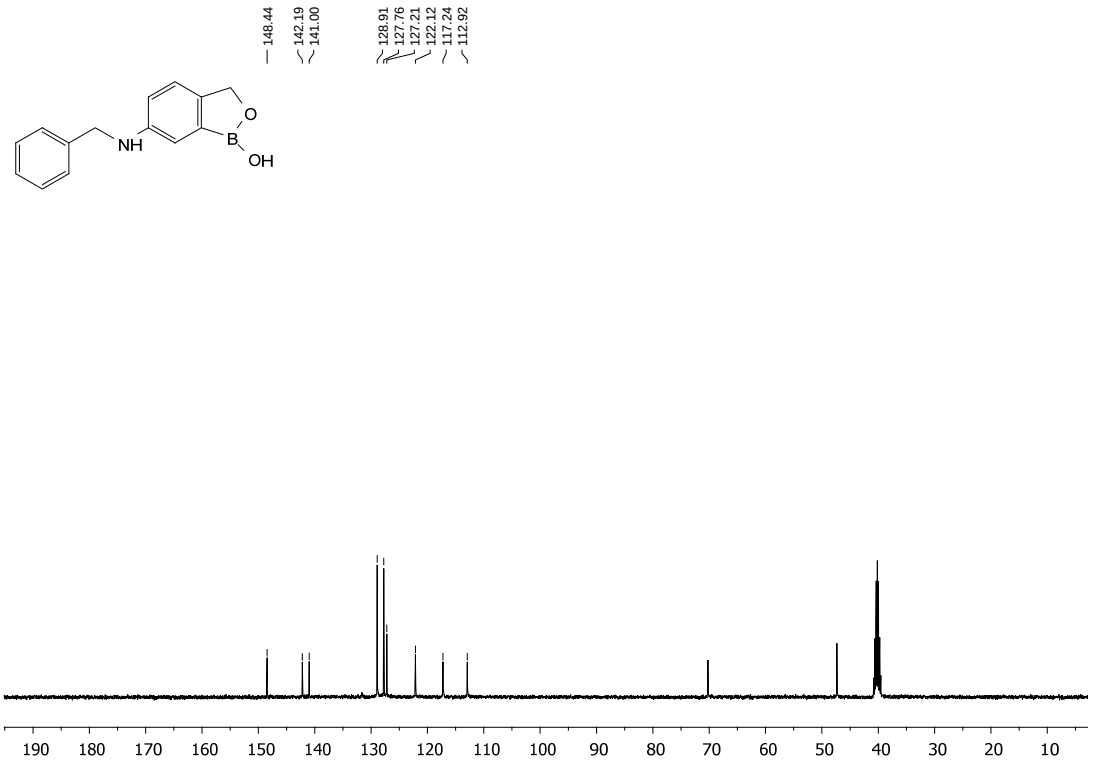


Figure 24. 100 MHz ^{13}C NMR of compound 35a in dmso

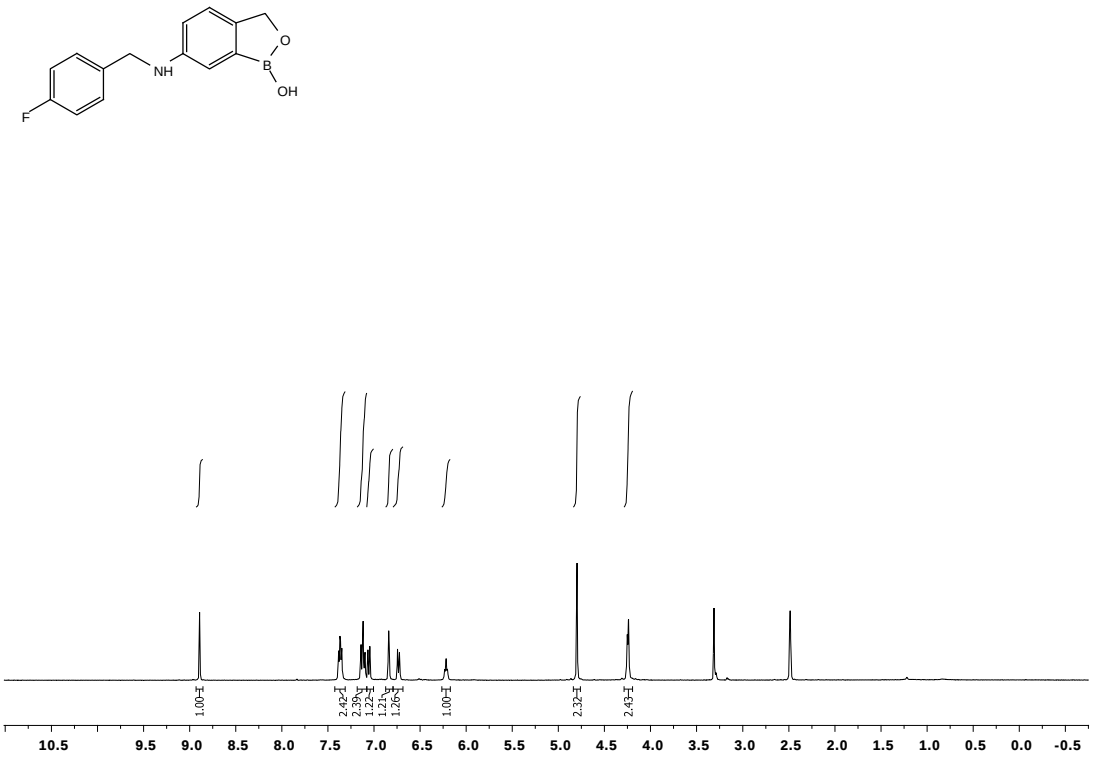


Figure 25. 400 MHz ^{1}H NMR of compound 35b in dmso

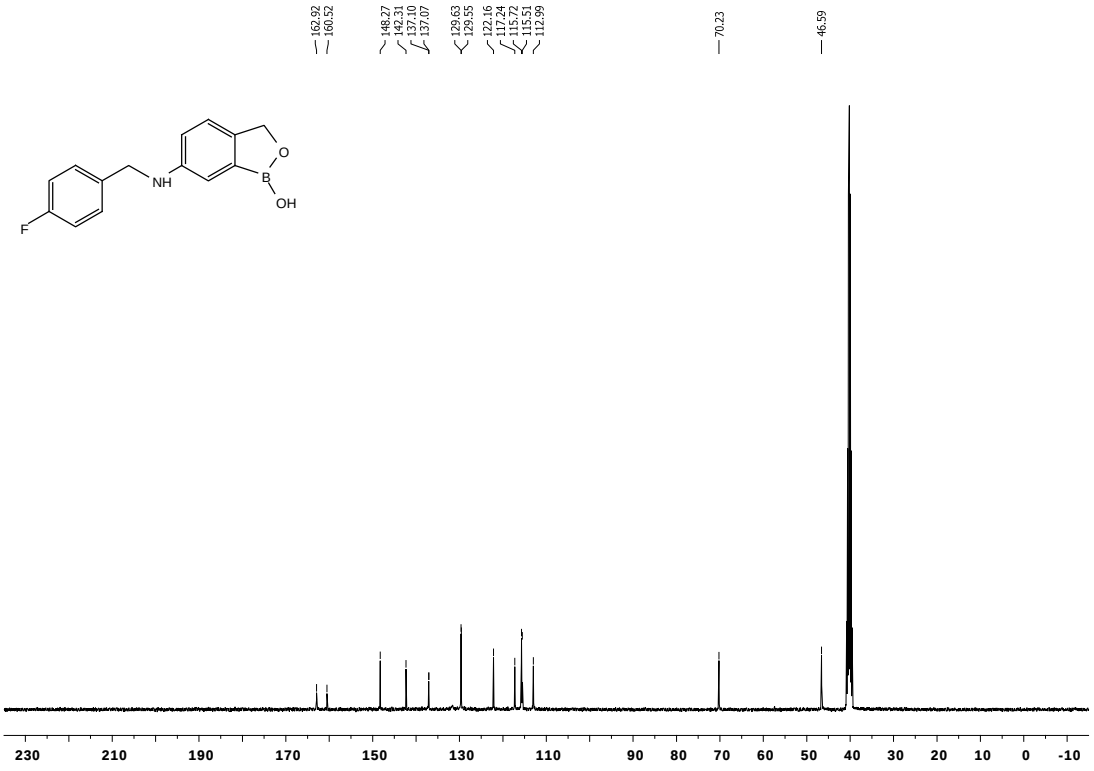


Figure 26. 100 MHz ^{13}C NMR of compound 35b in dmso

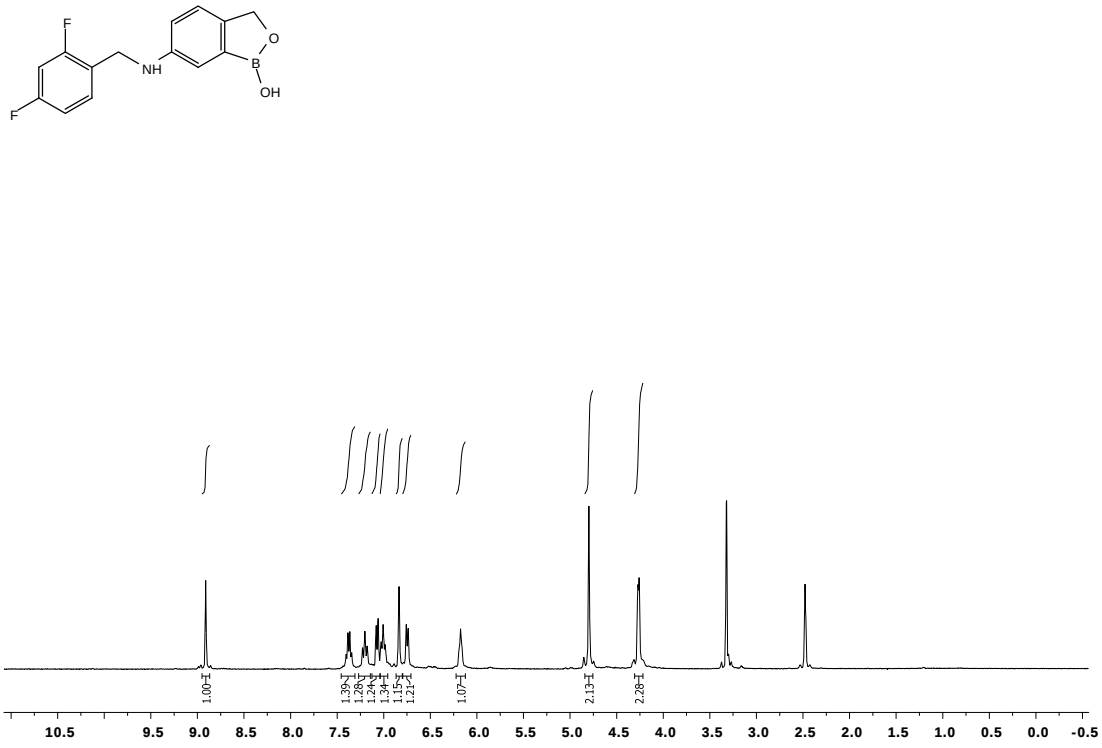


Figure 27. 400 MHz ^{1}H NMR of compound 35c in dmso

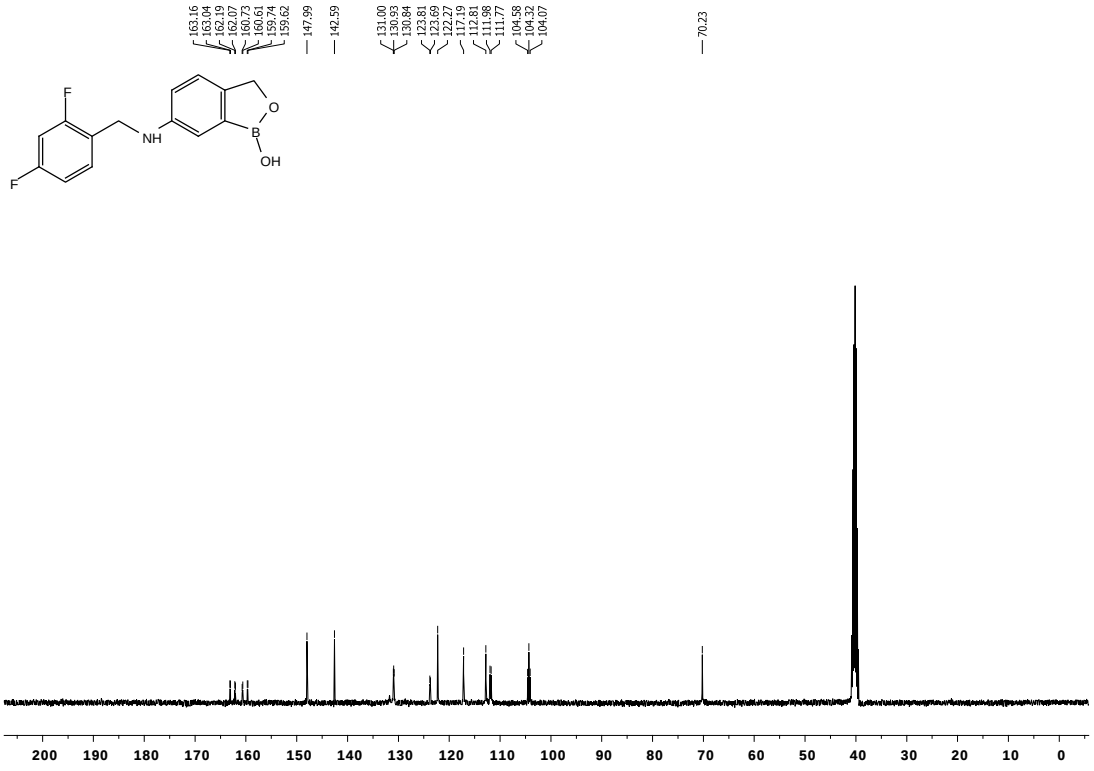


Figure 28. 100 MHz ^{13}C NMR of compound 35c in dmso

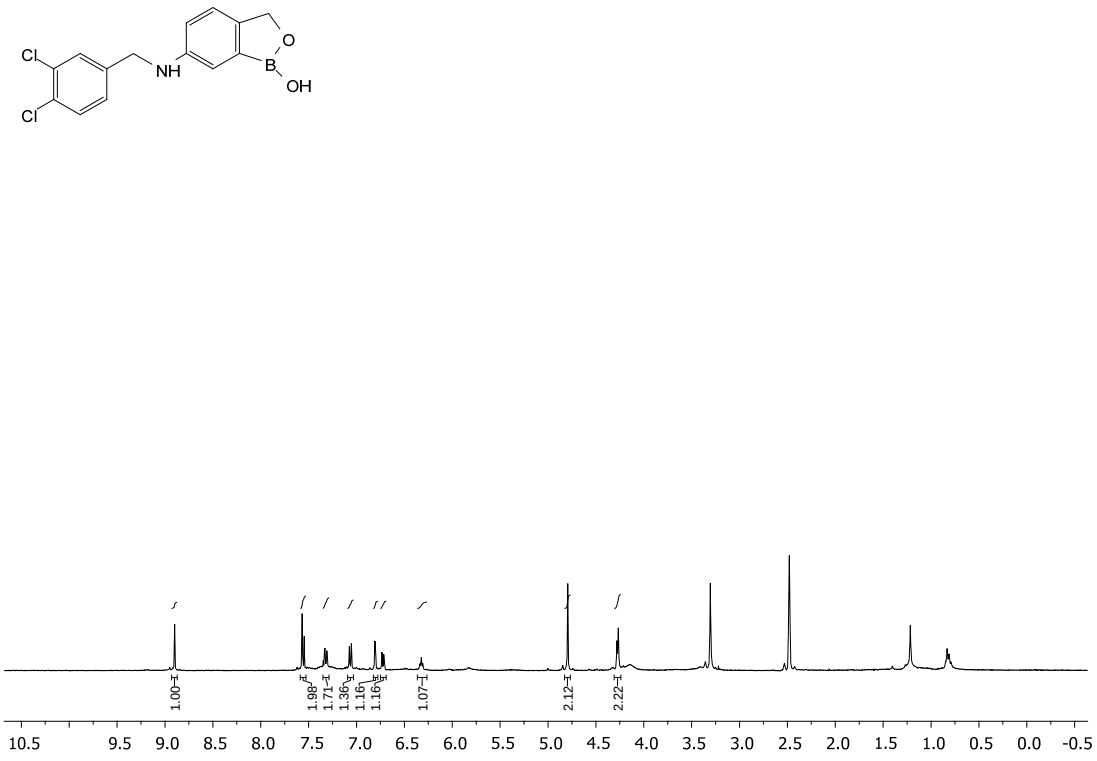


Figure 29. 400 MHz ^{1}H NMR of compound 35e in dmso

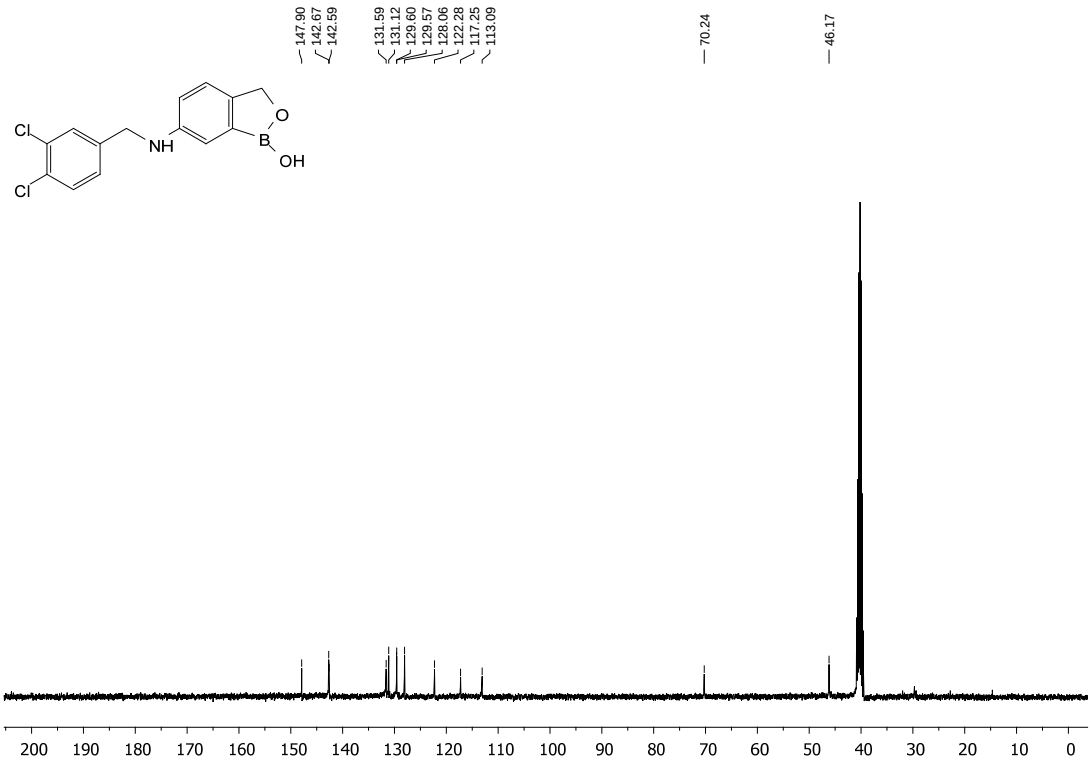


Figure 30. 100 MHz ^{13}C NMR of compound 35e in dmso

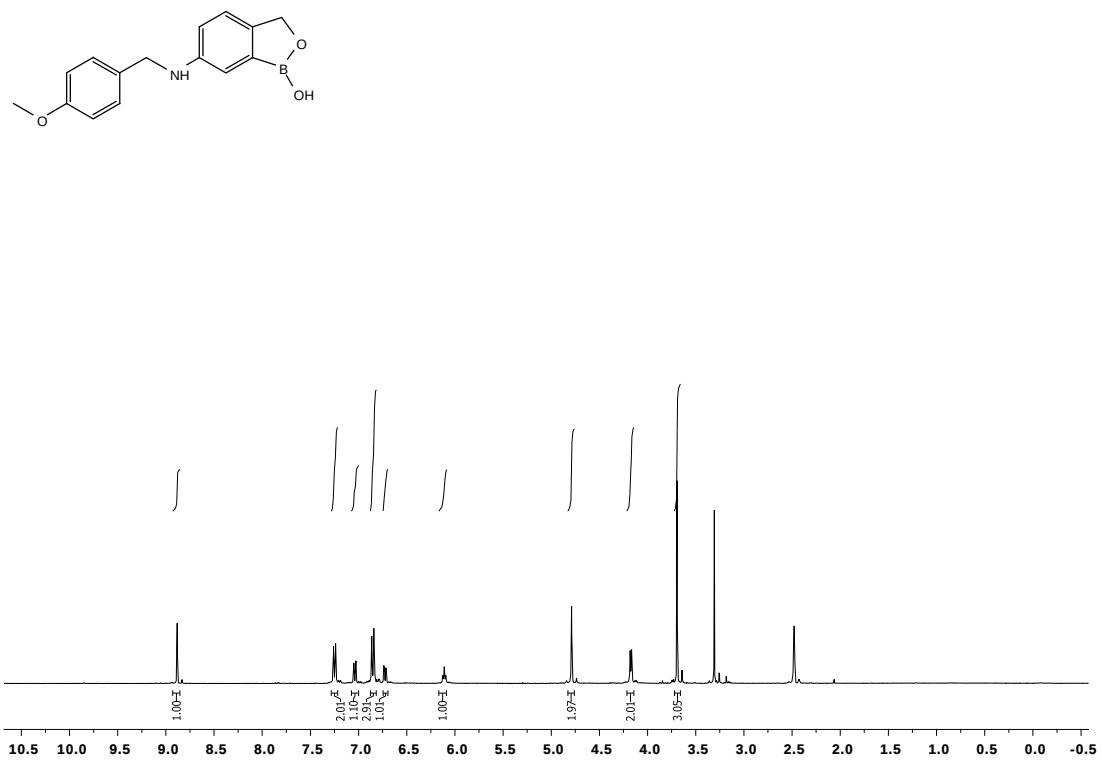


Figure 31. 400 MHz ^{1}H NMR of compound 35f in dmso

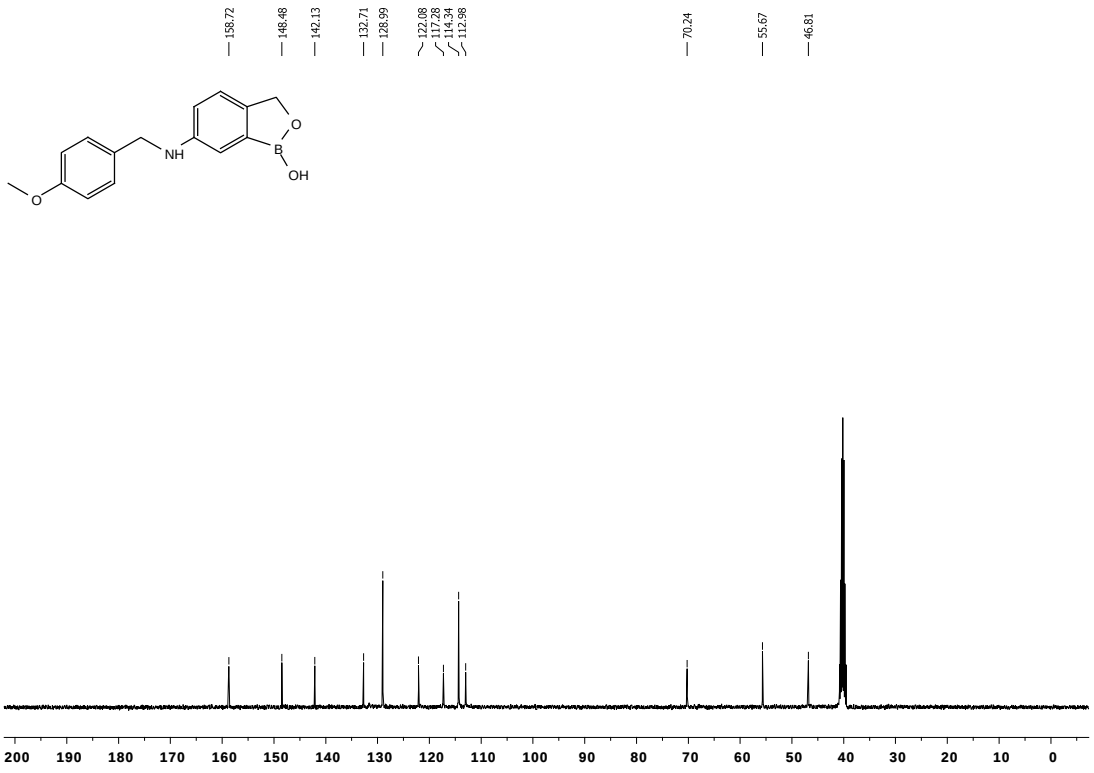


Figure 32. 100 MHz ^{13}C NMR of compound 35f in dmso

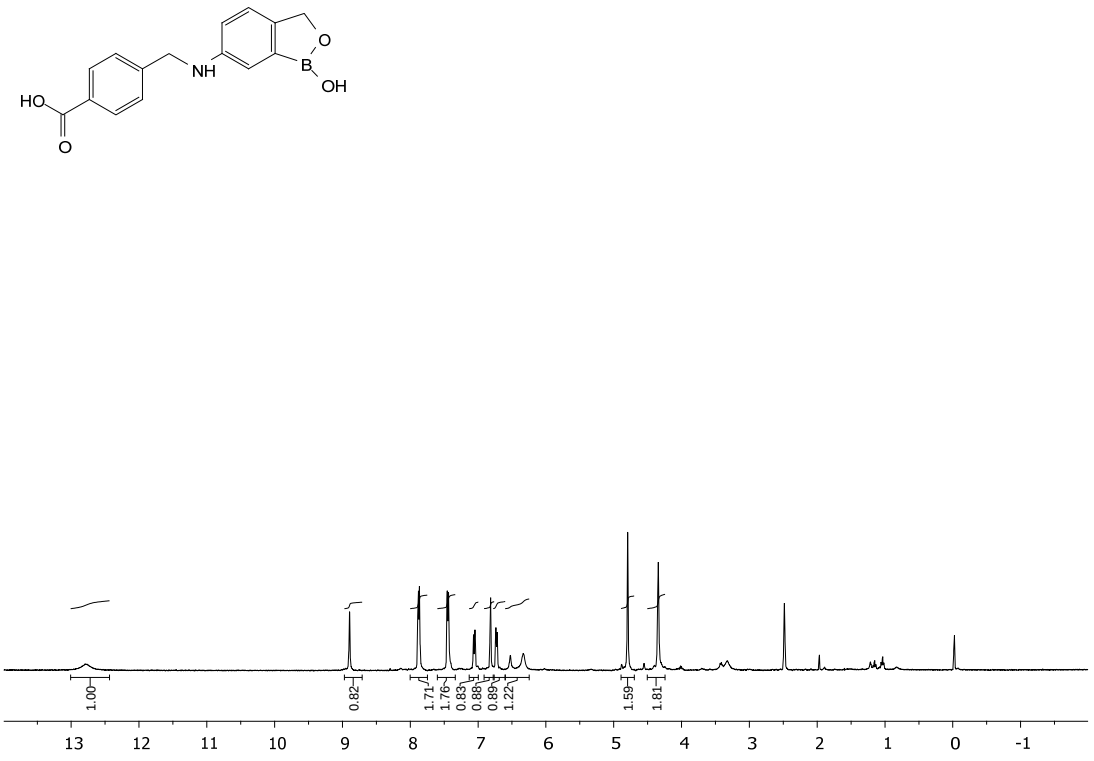


Figure 33. 400 MHz ^{1}H NMR of compound 35g in dmso

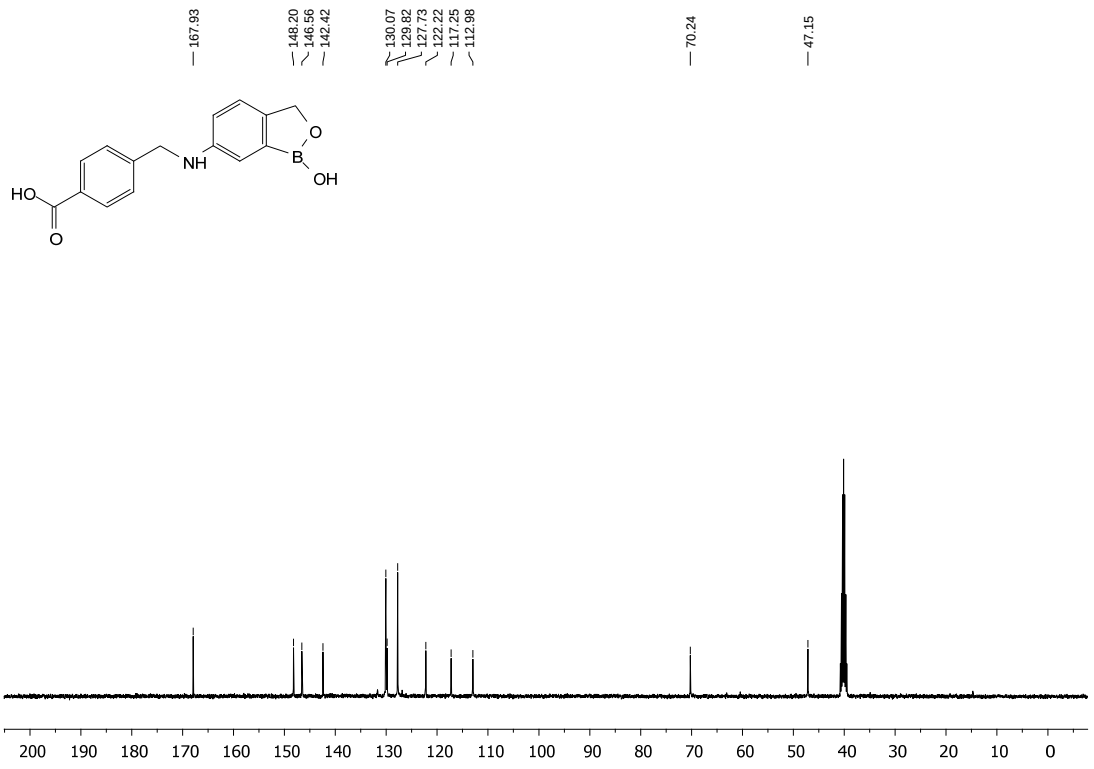


Figure 34. 100 MHz ^{13}C NMR of compound 35g in dmso

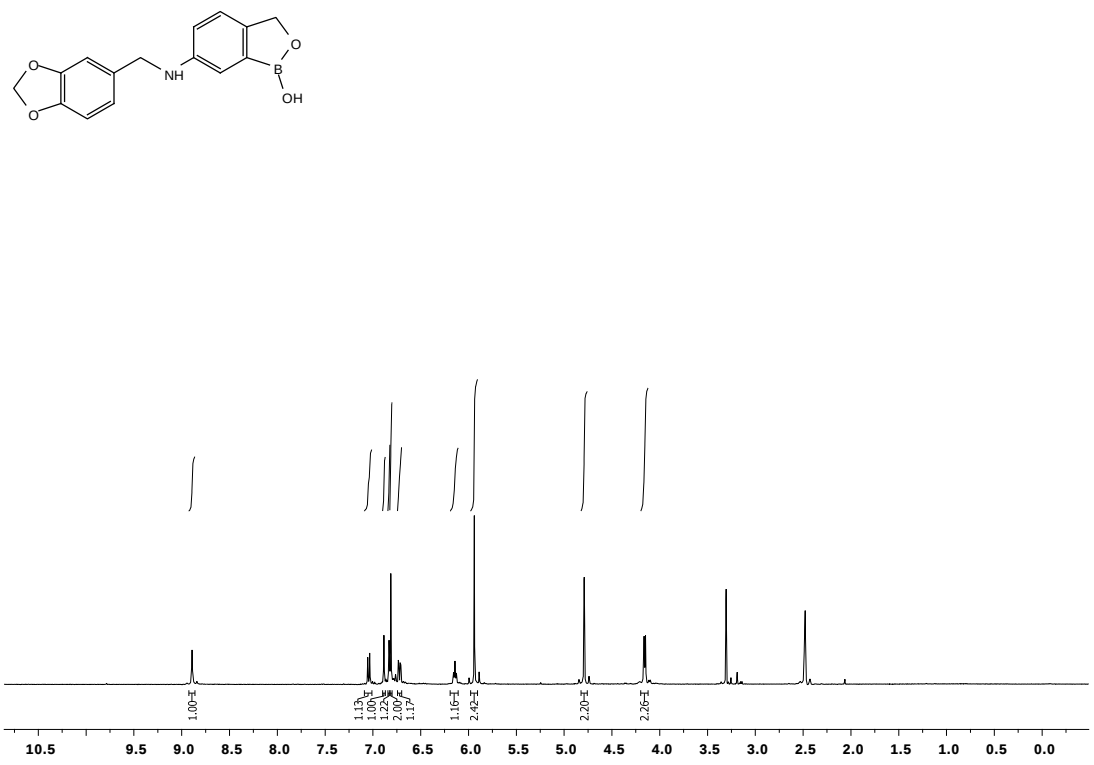


Figure 35. 400 MHz ^{1}H NMR of compound 35h in dmso

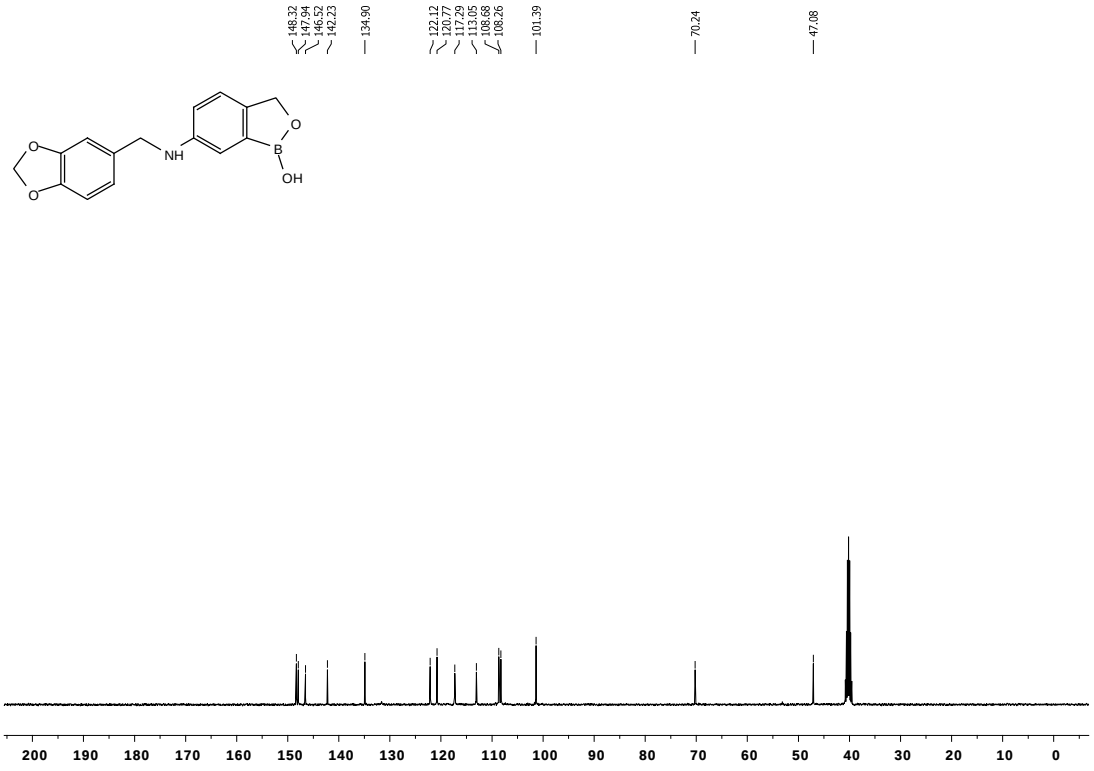


Figure 36. 100 MHz ^{13}C NMR of compound 35h in dmso

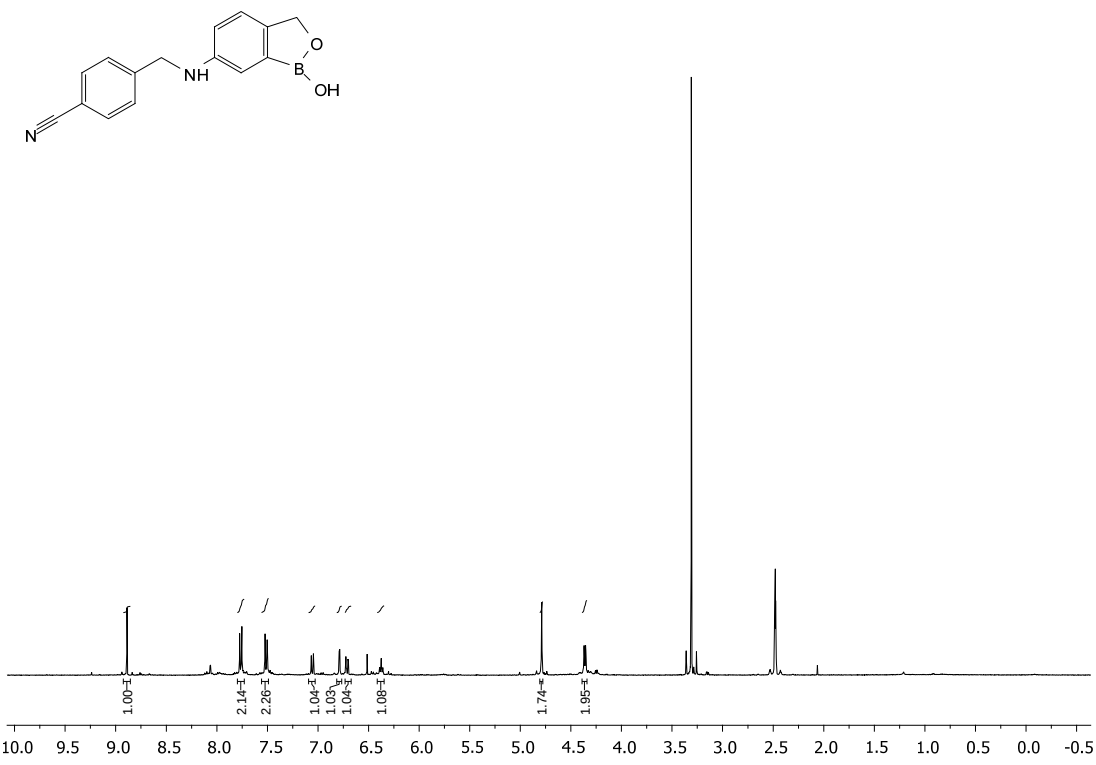


Figure 37. 400 MHz ^{1}H NMR of compound 35i in dmso

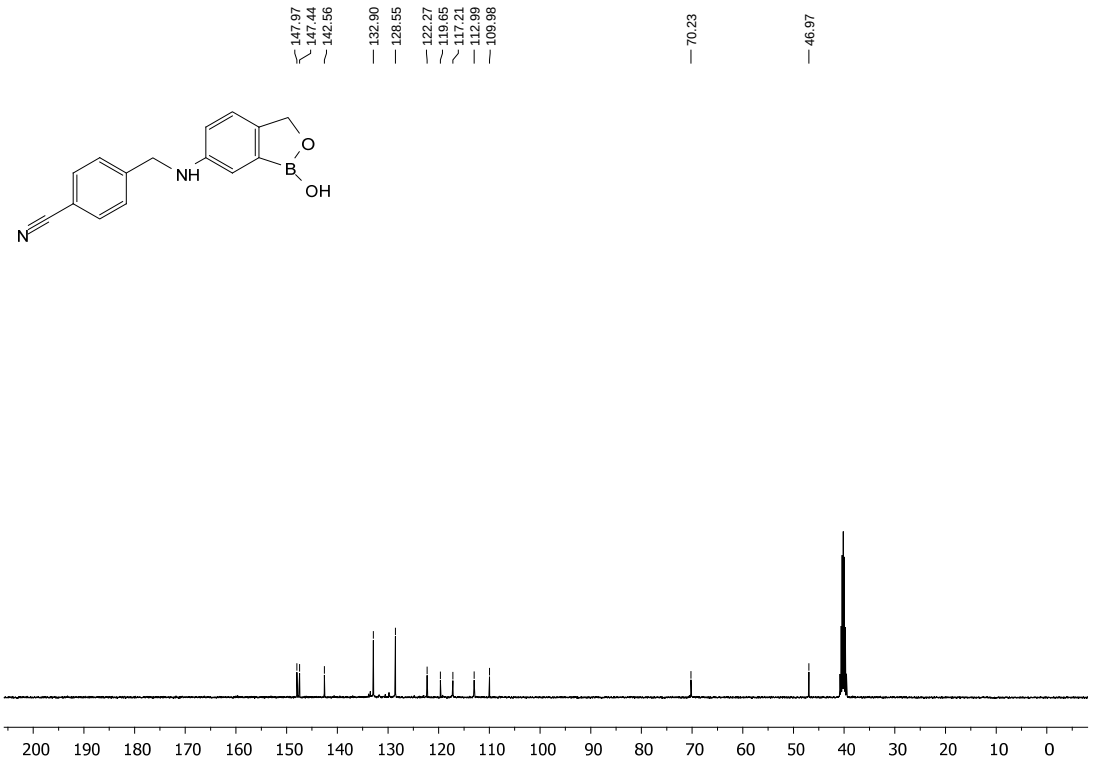


Figure 38. 100 MHz ^{13}C NMR of compound 35i in dmso

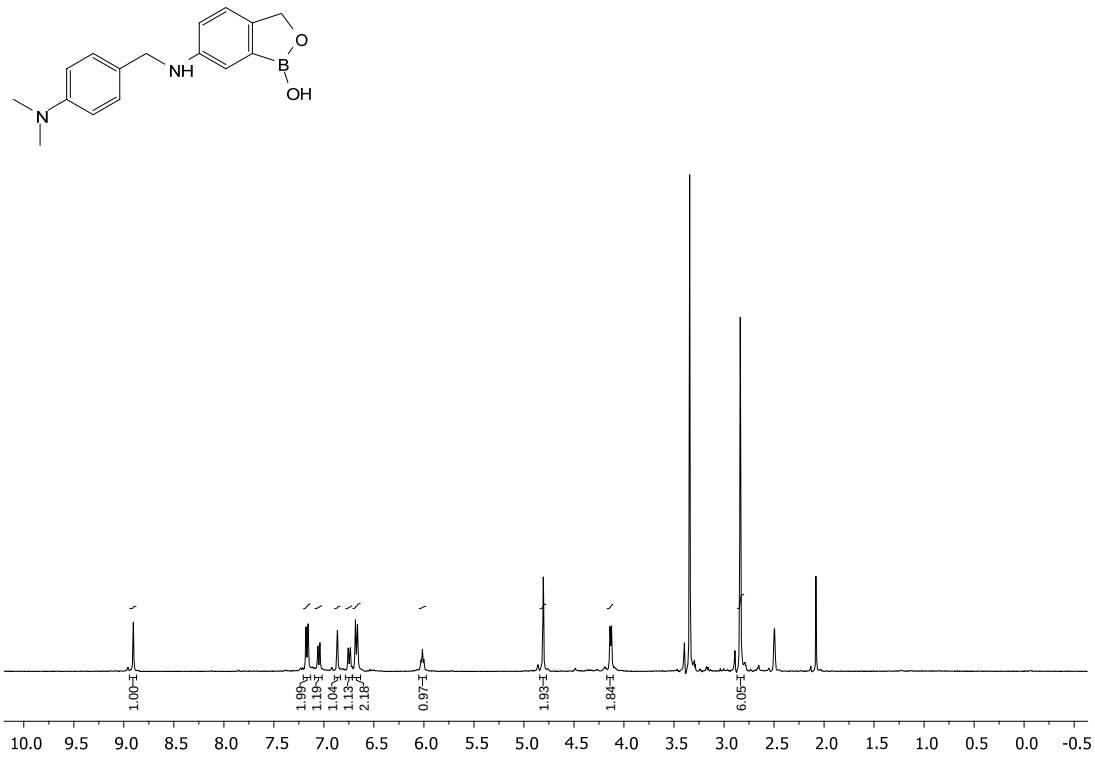


Figure 39. 400 MHz ^{1}H NMR of compound 35j in dmso

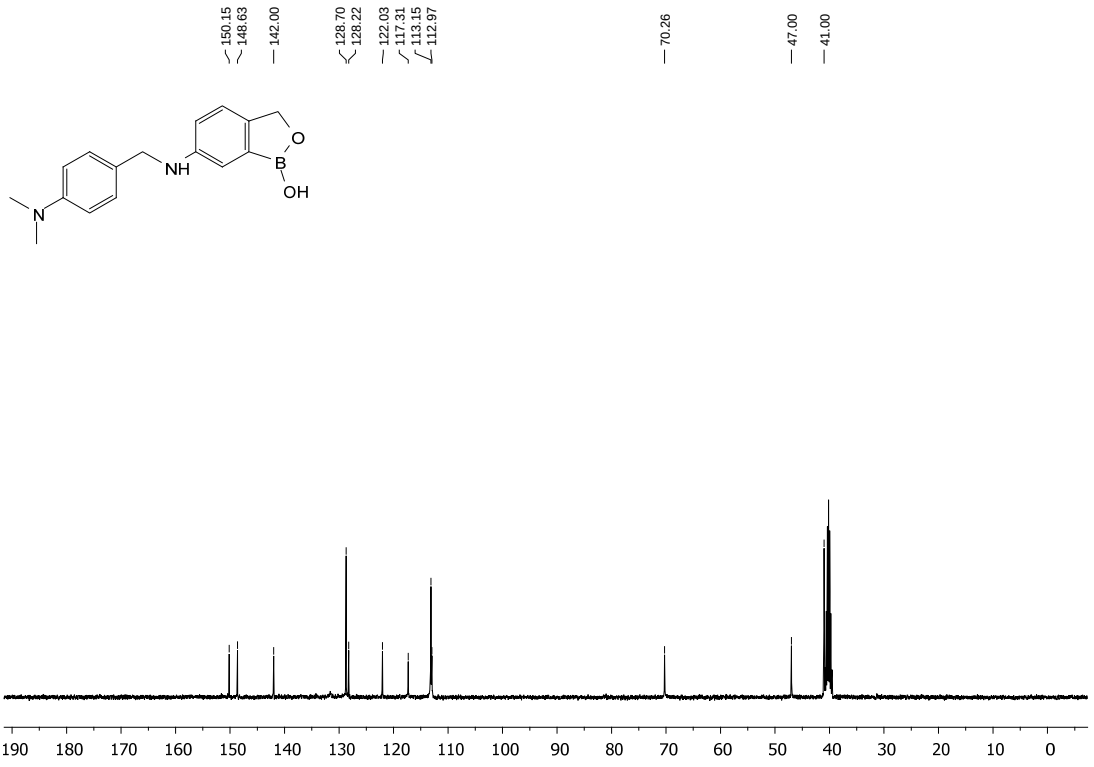


Figure 40. 100 MHz ^{13}C NMR of compound 35j in dmso

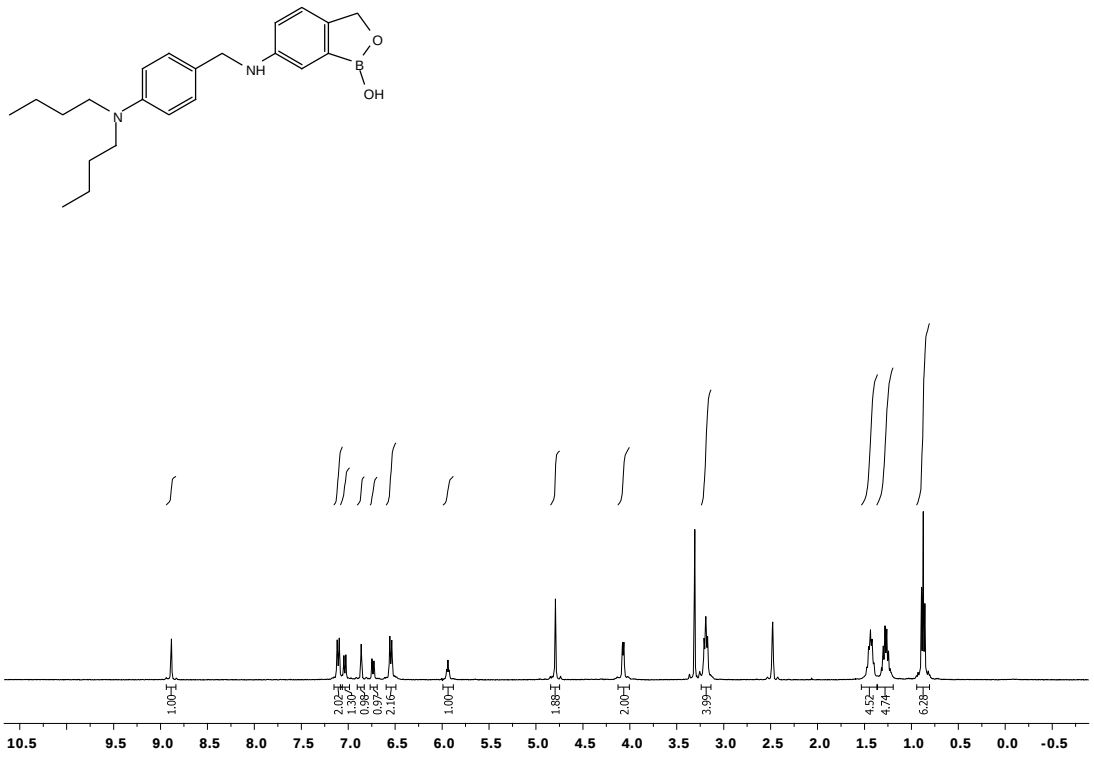


Figure 41. 400 MHz ^{1}H NMR of compound 35l in dmso

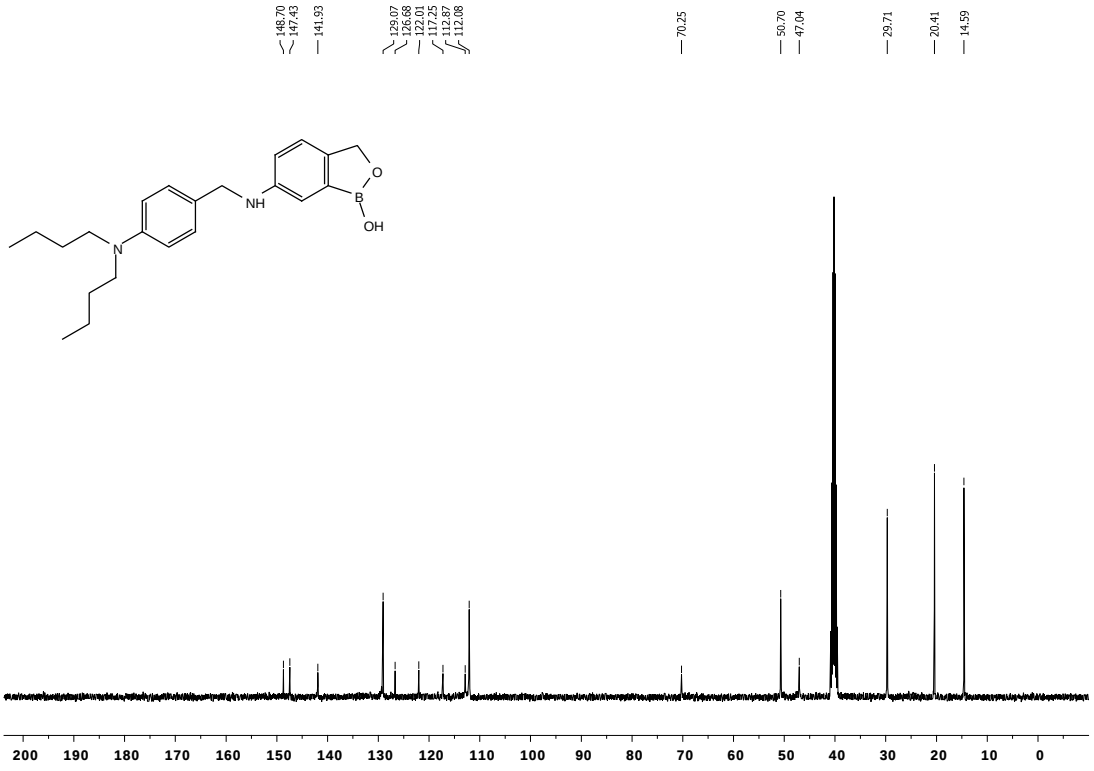


Figure 42. 100 MHz ^{13}C NMR of compound 35l in dmso

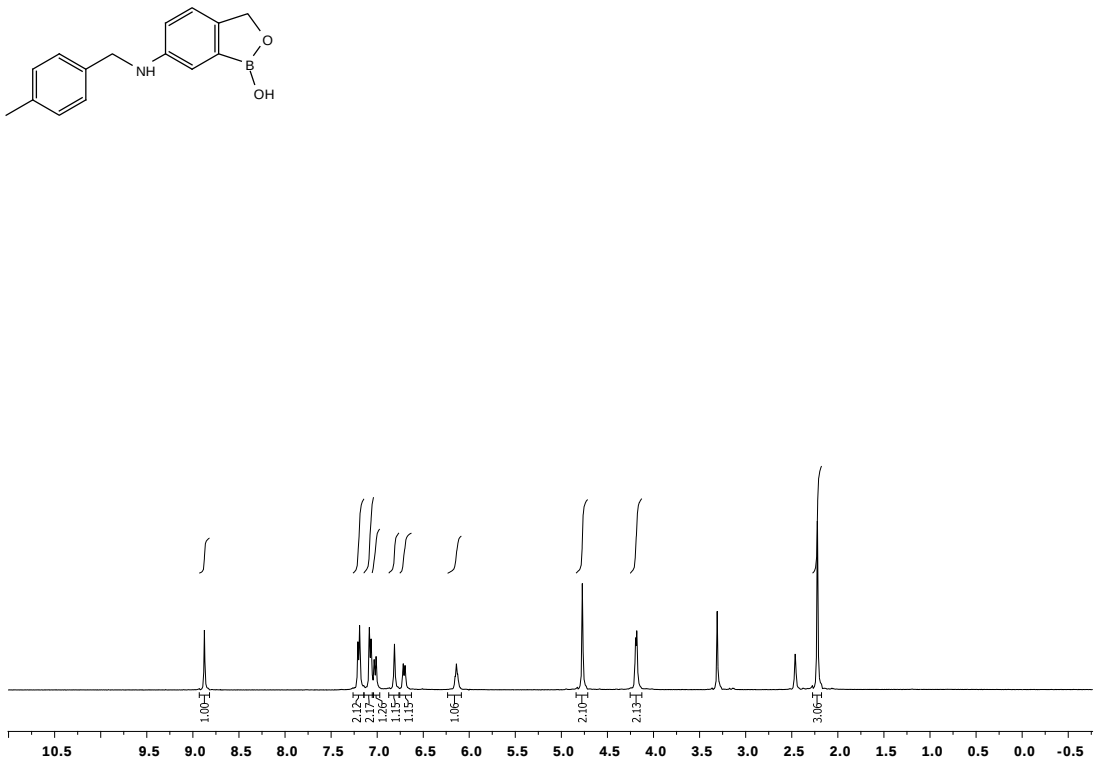


Figure 43. 400 MHz ^{1}H NMR of compound 35m in dmso

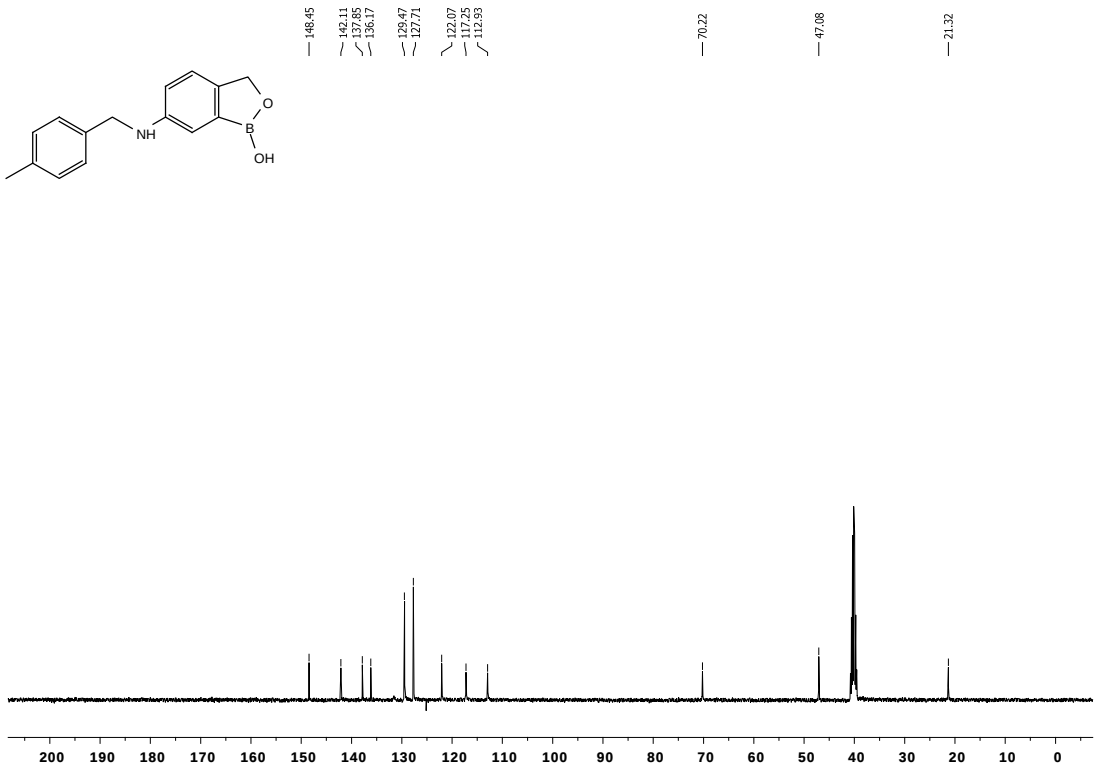


Figure 44. 100 MHz ^{13}C NMR of compound 35m in dmso

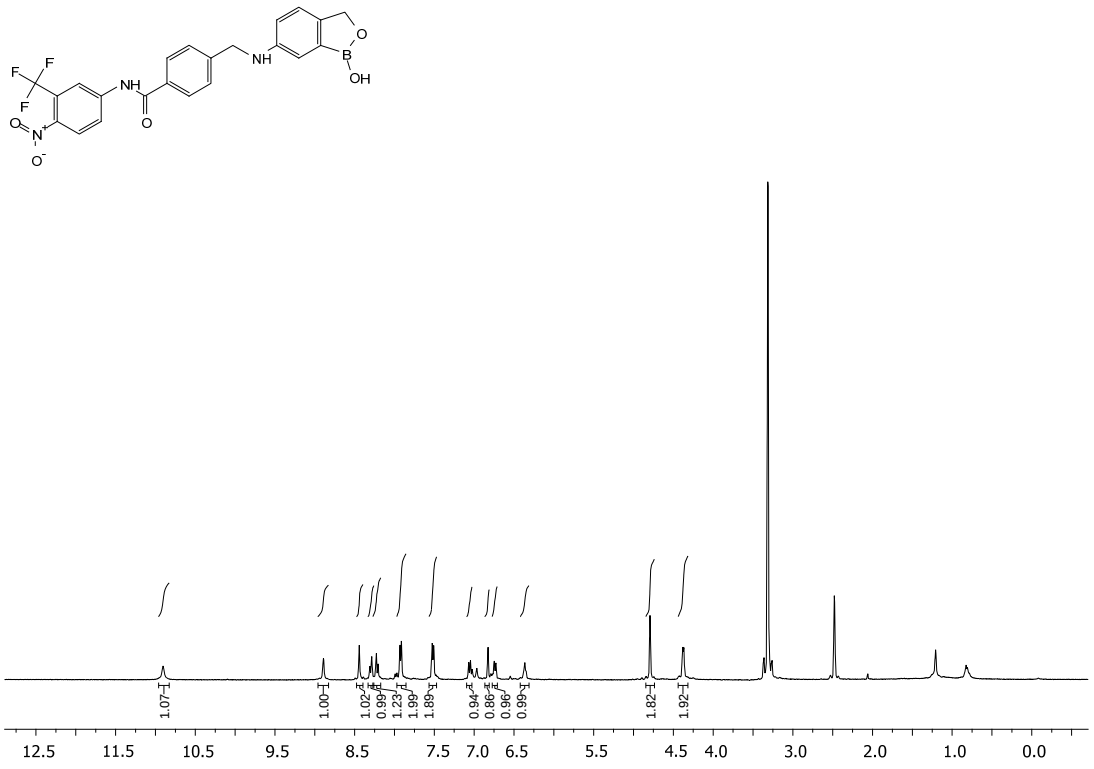


Figure 45. 400 MHz ^{1}H NMR of compound 39 in dmso

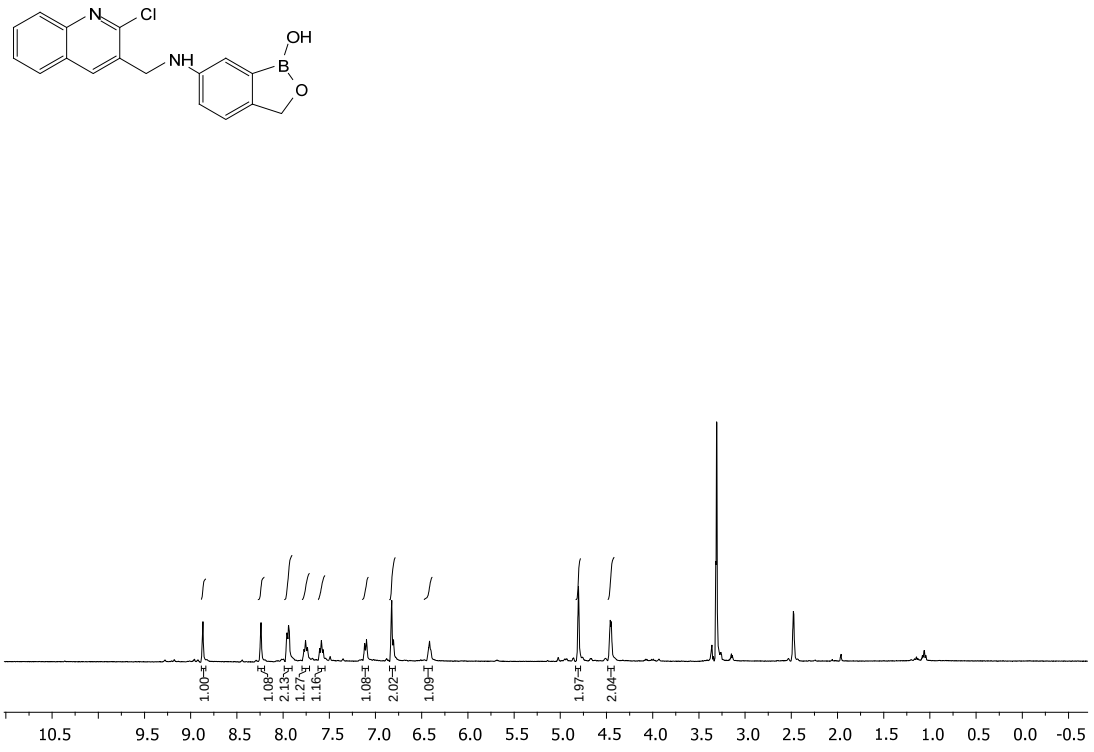


Figure 46. 400 MHz ^{1}H NMR of compound 42 in dmso

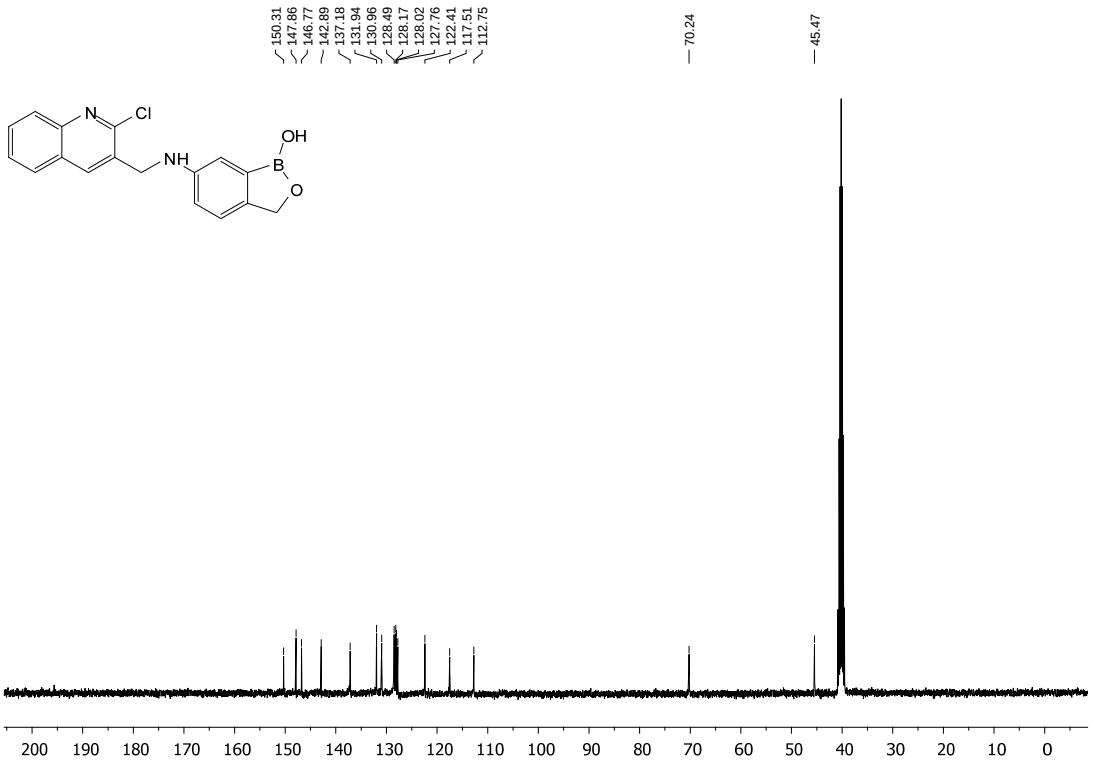


Figure 47. 100 MHz ^{13}C NMR of compound 42 in dmso

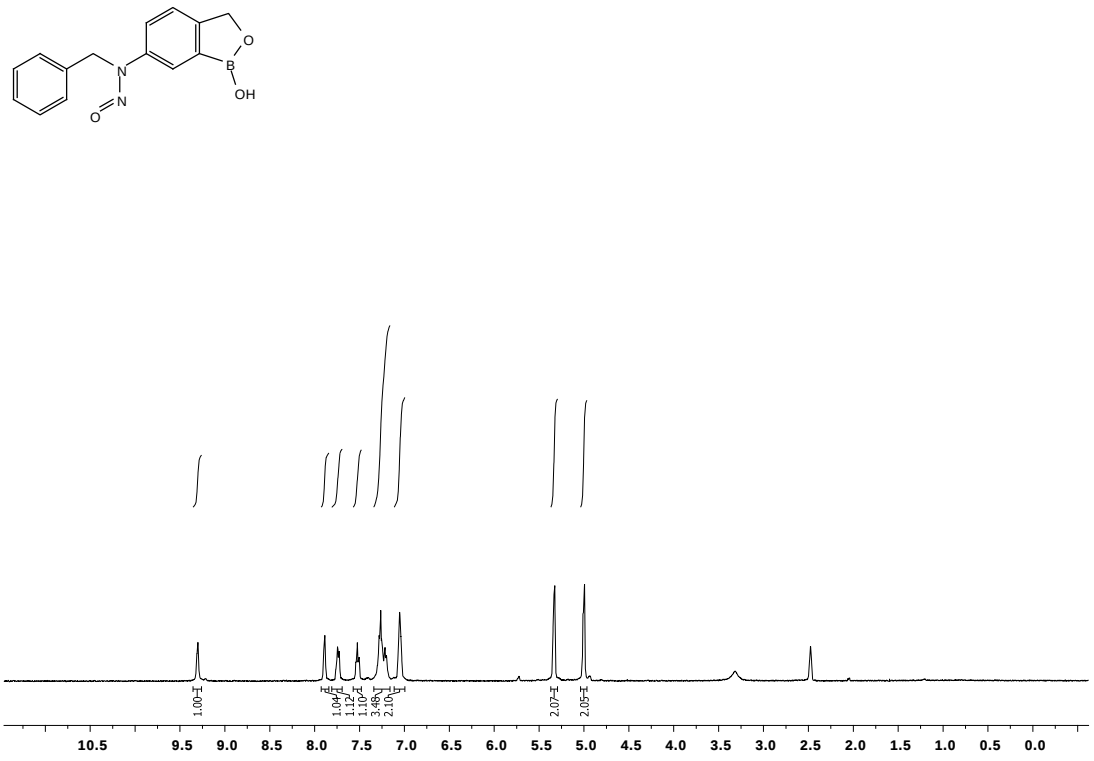


Figure 48. 400 MHz ^{1}H NMR of compound 43a in dmso

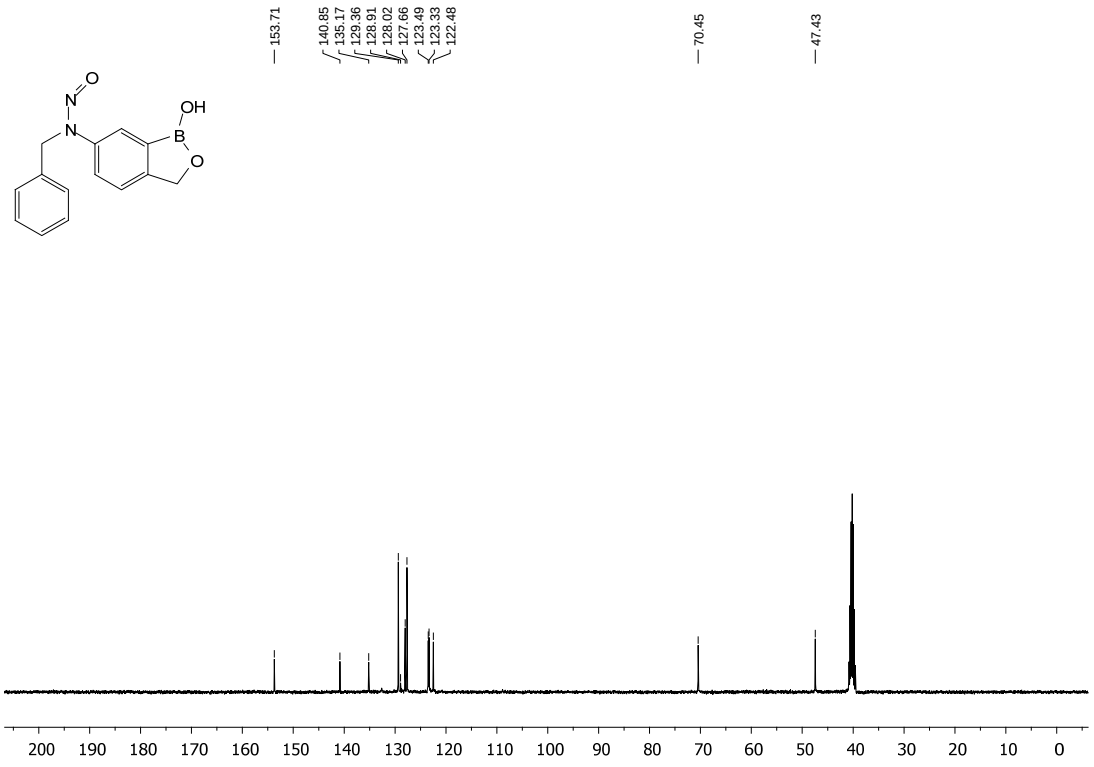


Figure 49. 100 MHz ^{13}C NMR of compound 43a in dmso

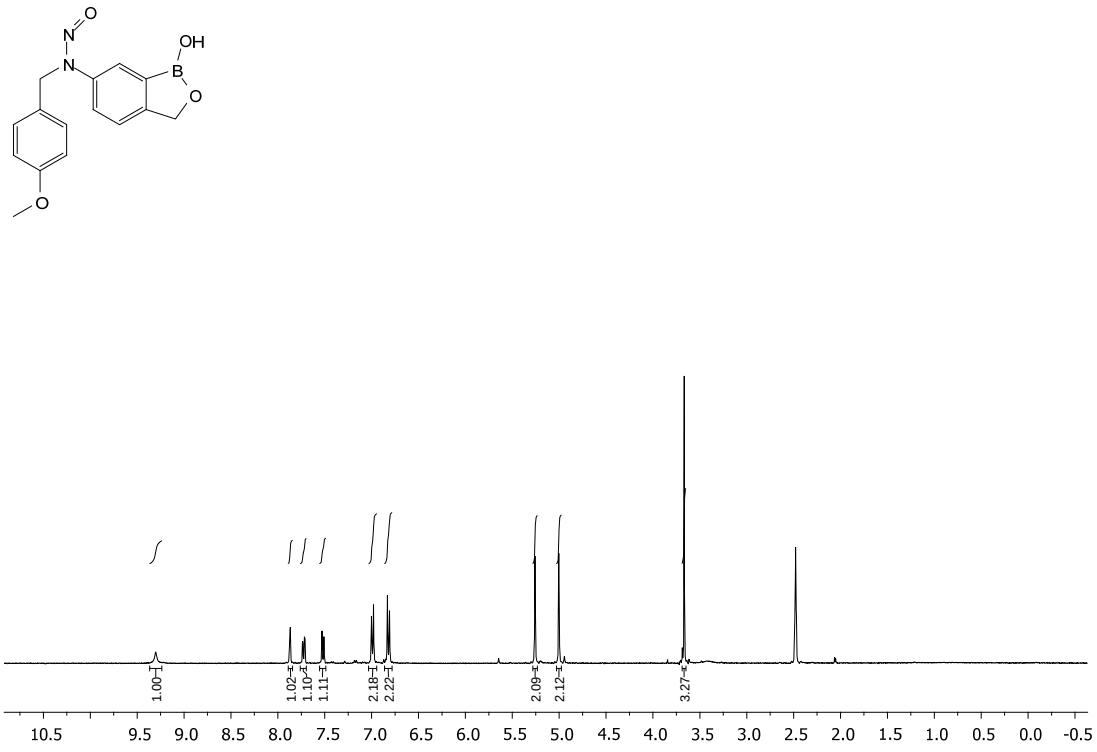


Figure 50. 400 MHz ^{1}H NMR of compound 43b in dmso

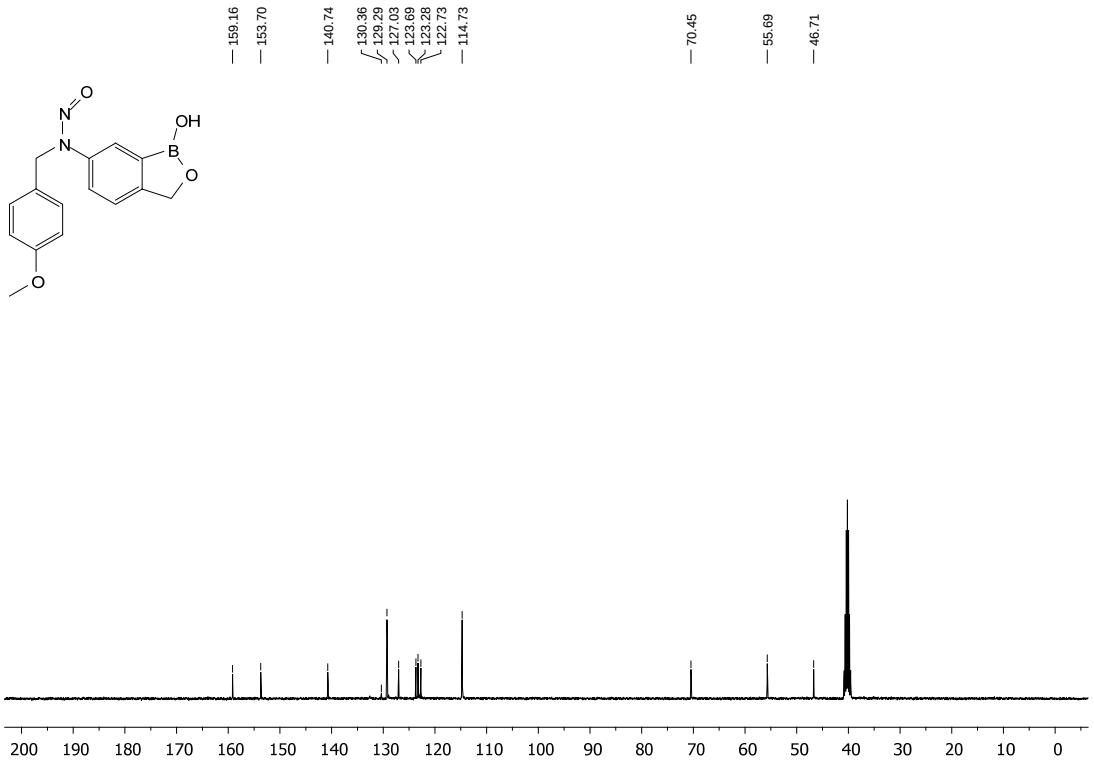


Figure 51. 100 MHz ^{13}C NMR of compound 43b in dmso

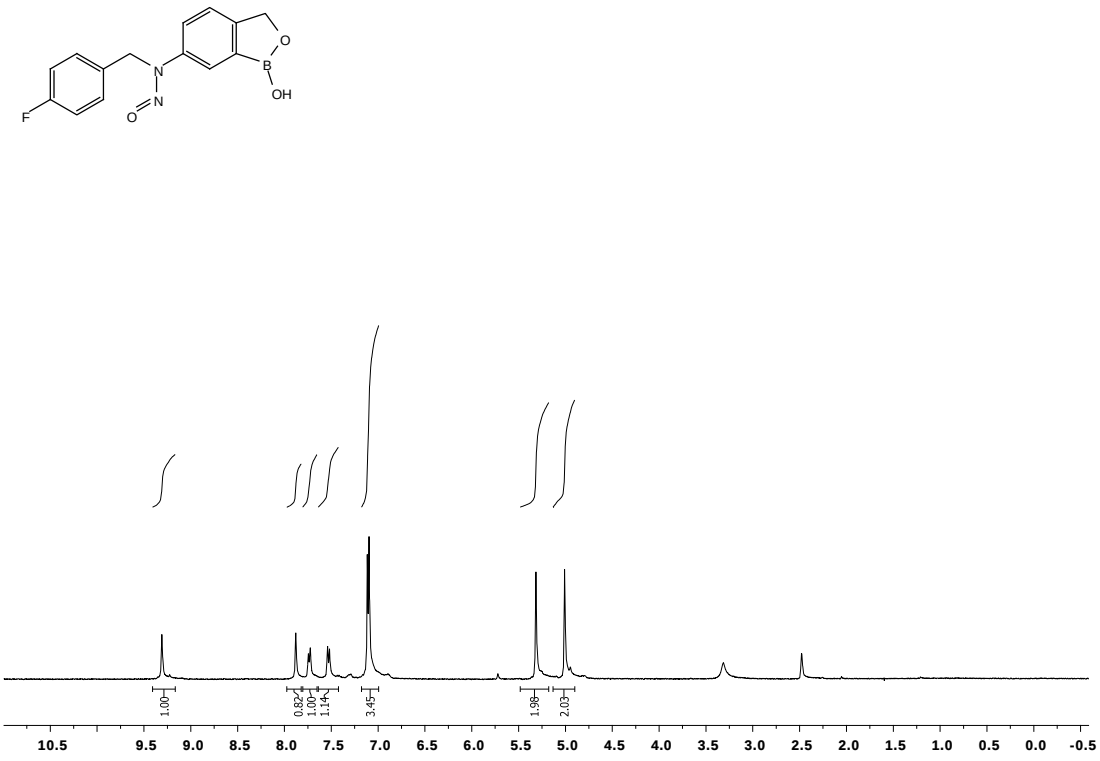


Figure 52. 400 MHz ^{1}H NMR of compound 43c in dmso

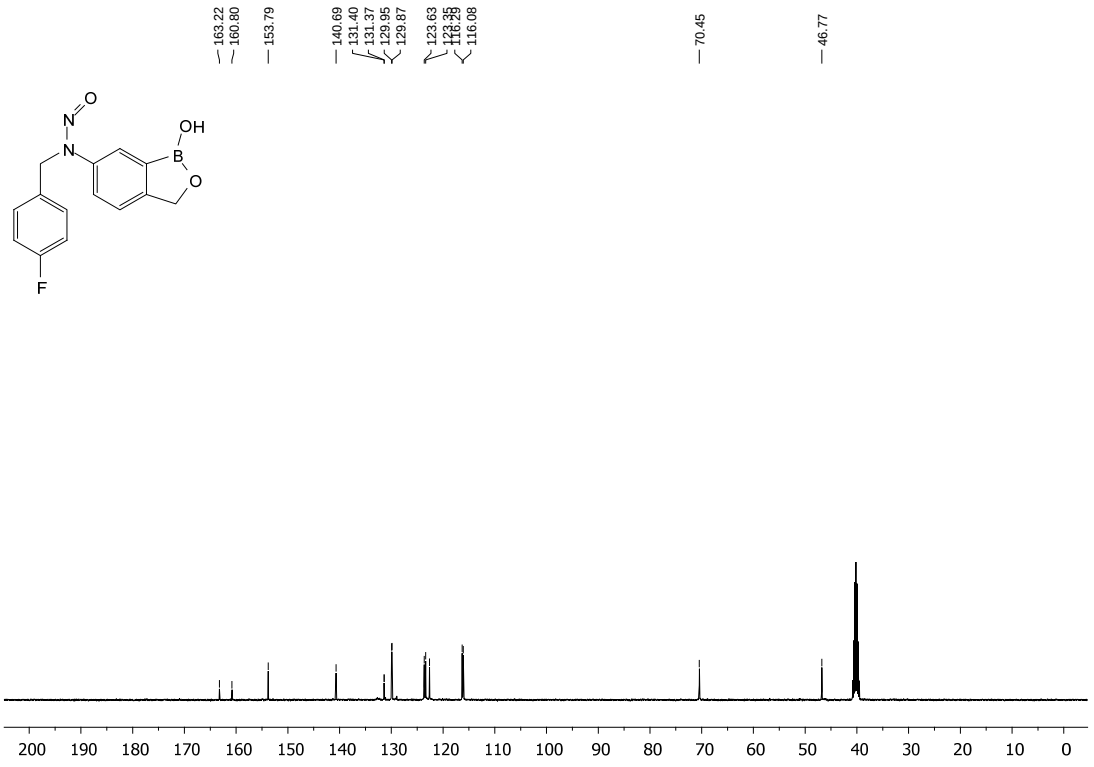


Figure 53. 100 MHz ^{13}C NMR of compound 43c in dmso

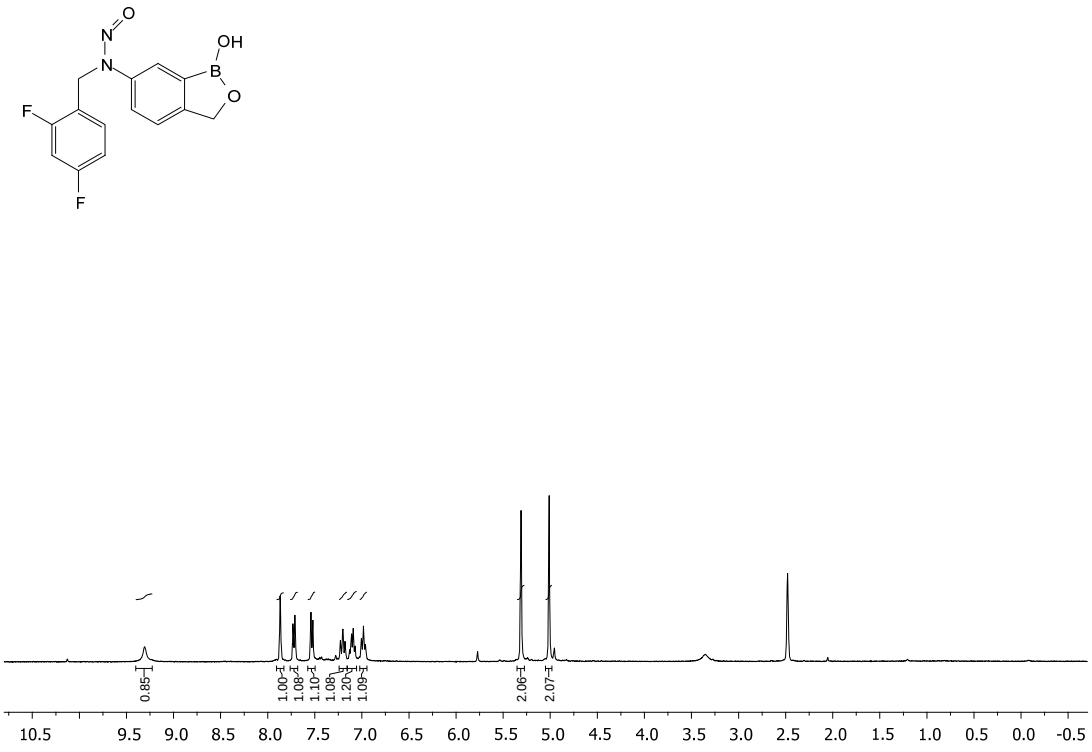


Figure 54. 400 MHz ^{1}H NMR of compound 43d in dmso

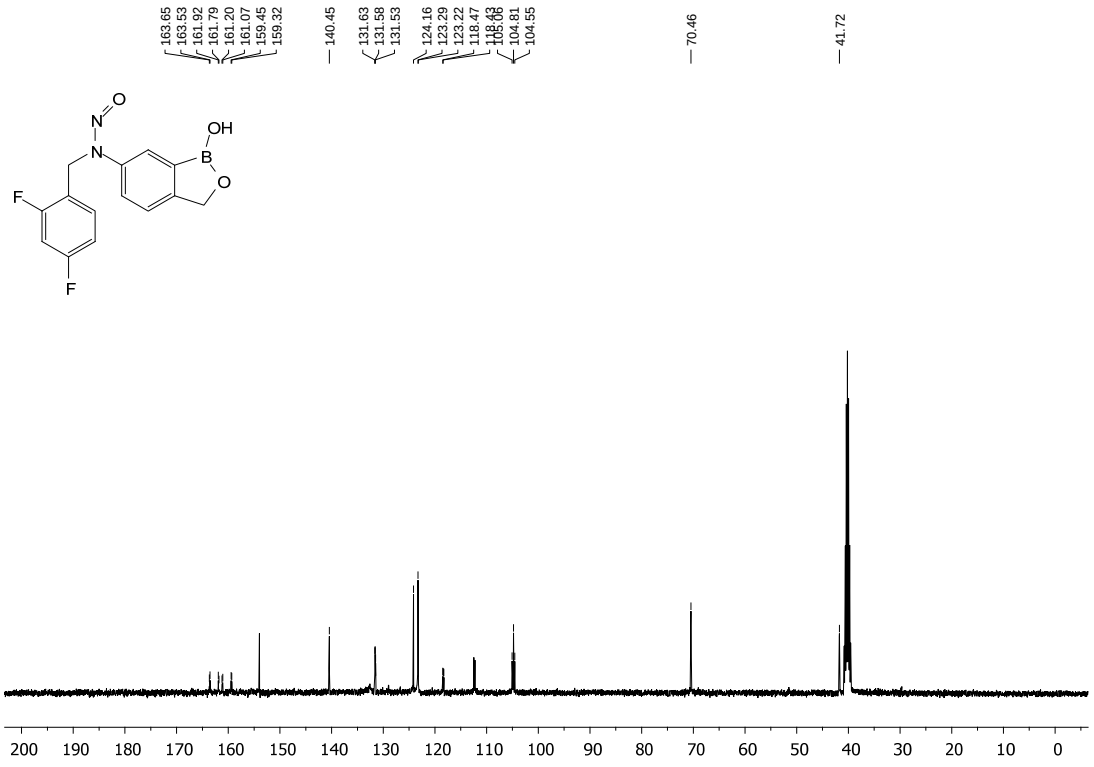


Figure 55. 100 MHz ^{13}C NMR of compound 43d in dmso

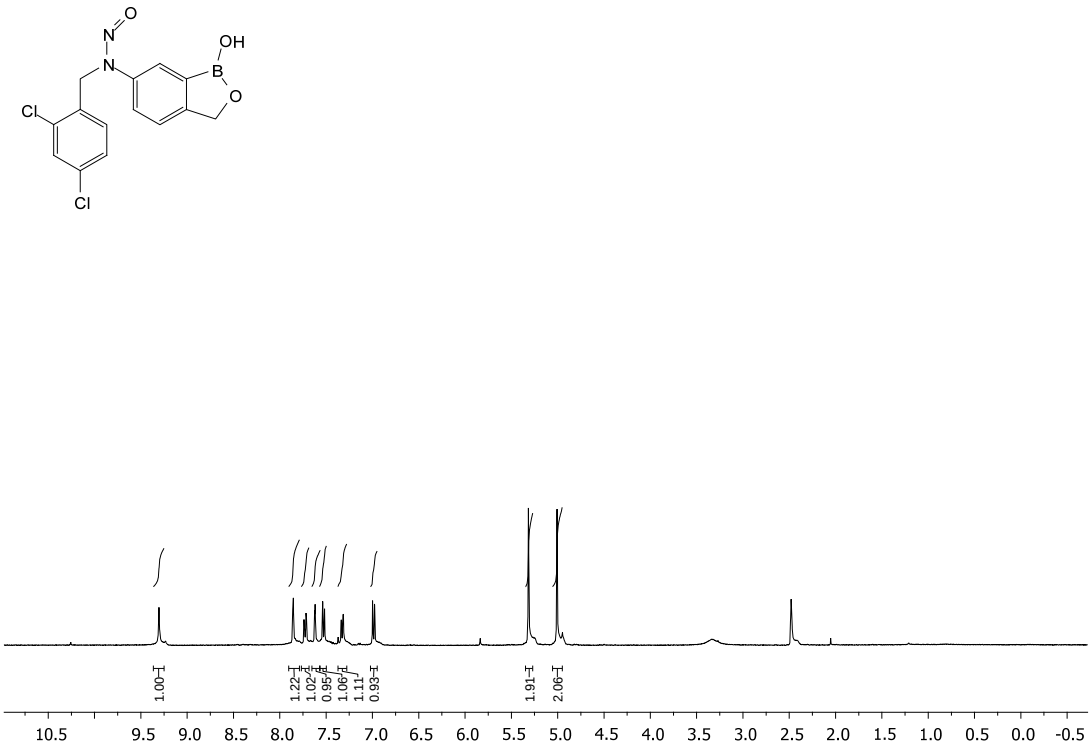


Figure 56. 400 MHz ^{1}H NMR of compound 43e in dmso

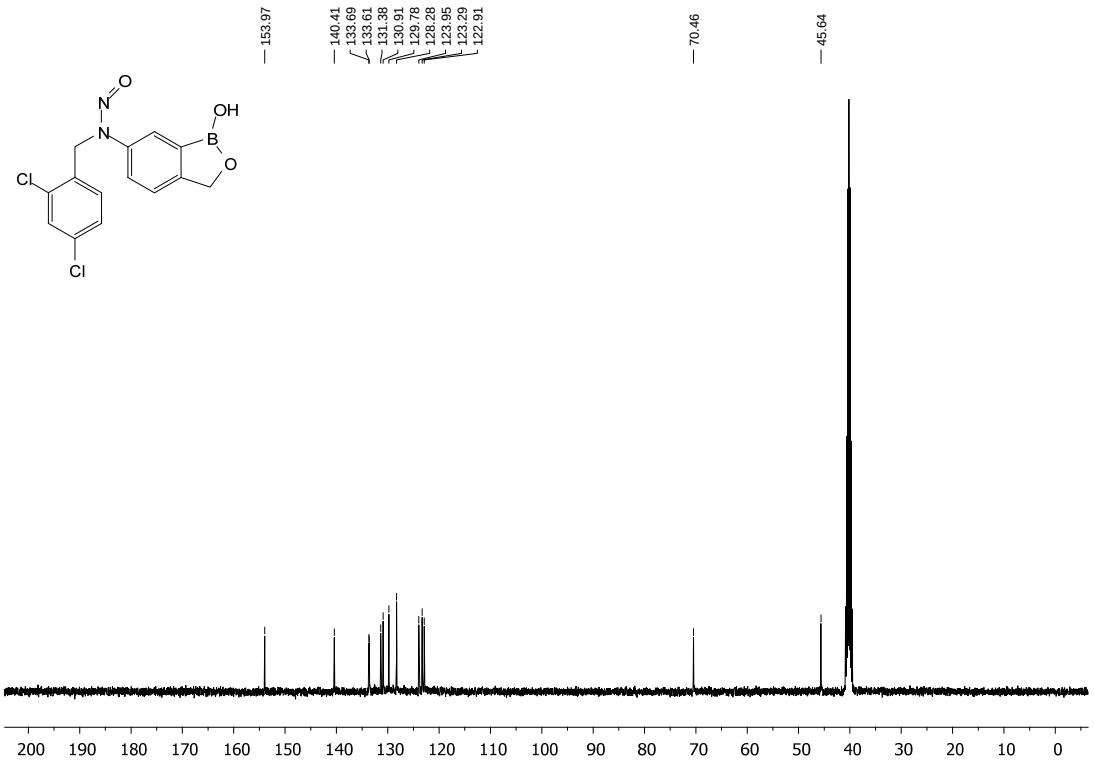


Figure 57. 100 MHz ^{13}C NMR of compound 43e in dmso

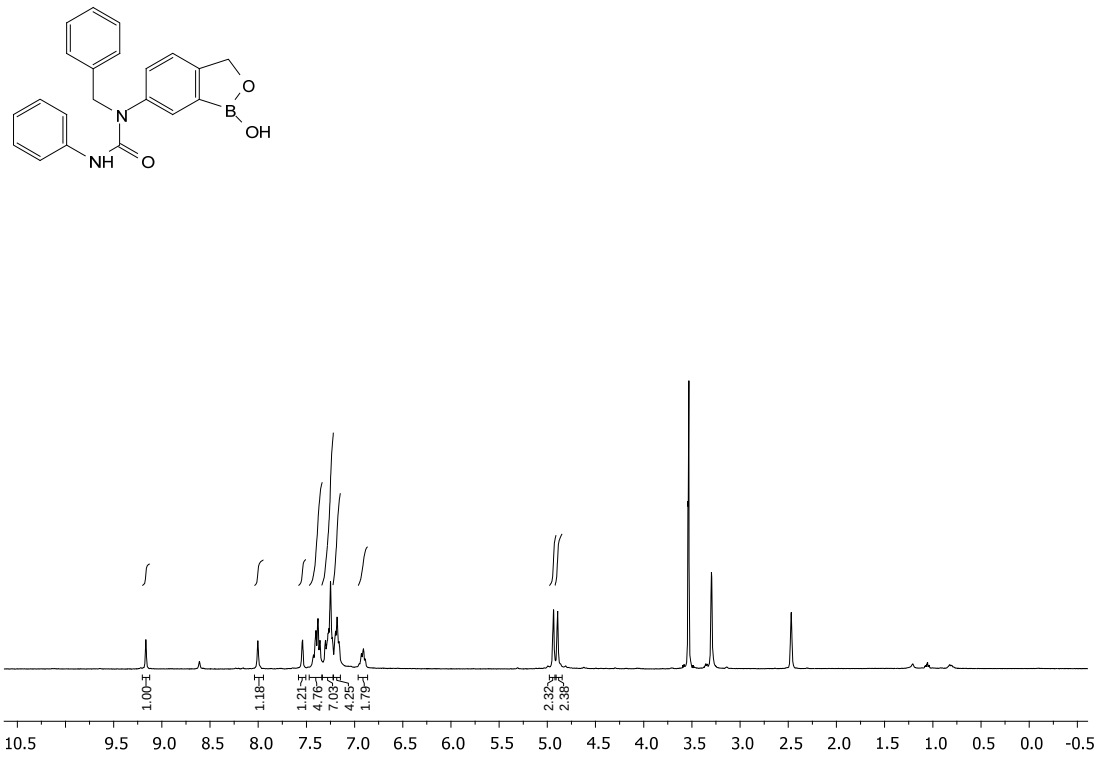


Figure 58. 400 MHz ^{1}H NMR of compound 44a in dmso

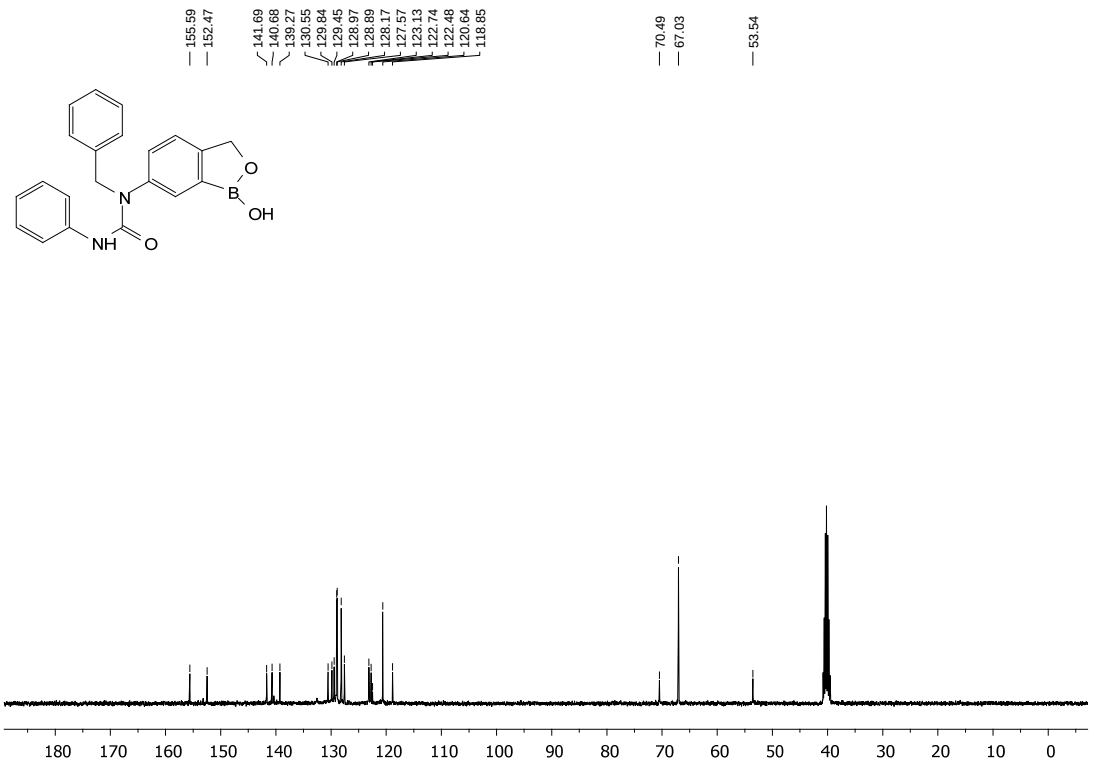


Figure 59. 100 MHz ^{13}C NMR of compound 44a in dmso

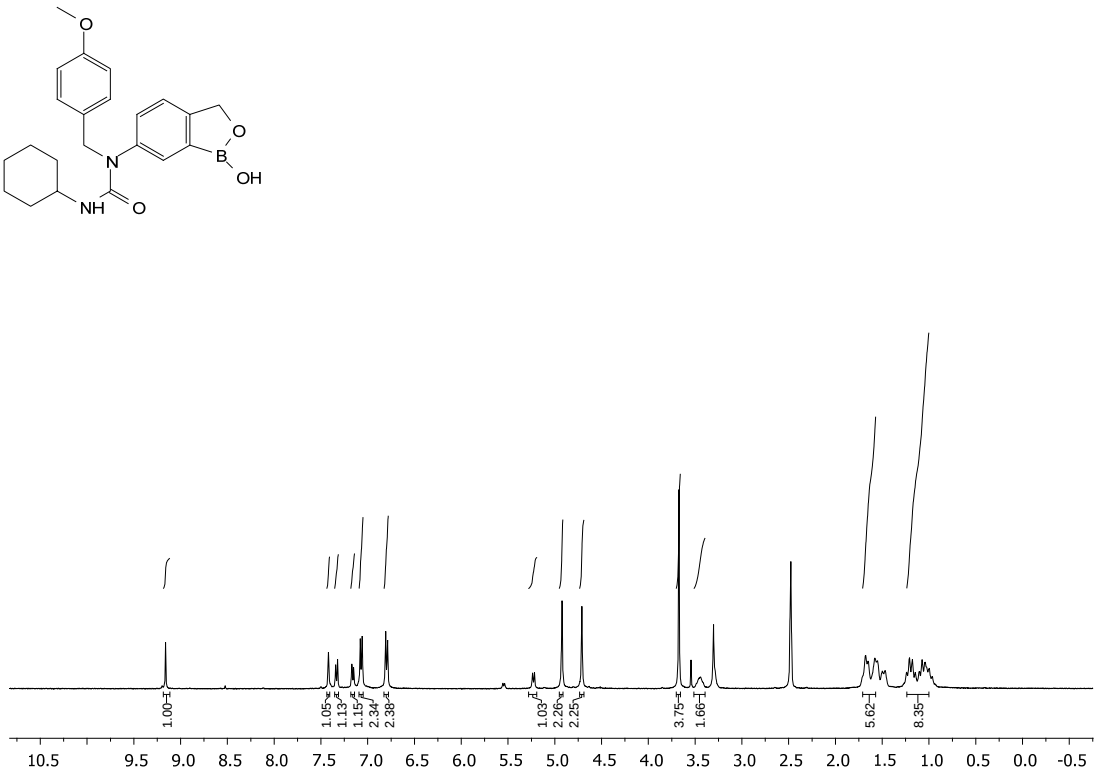


Figure 60. 400 MHz ^{1}H NMR of compound 44d in dmso

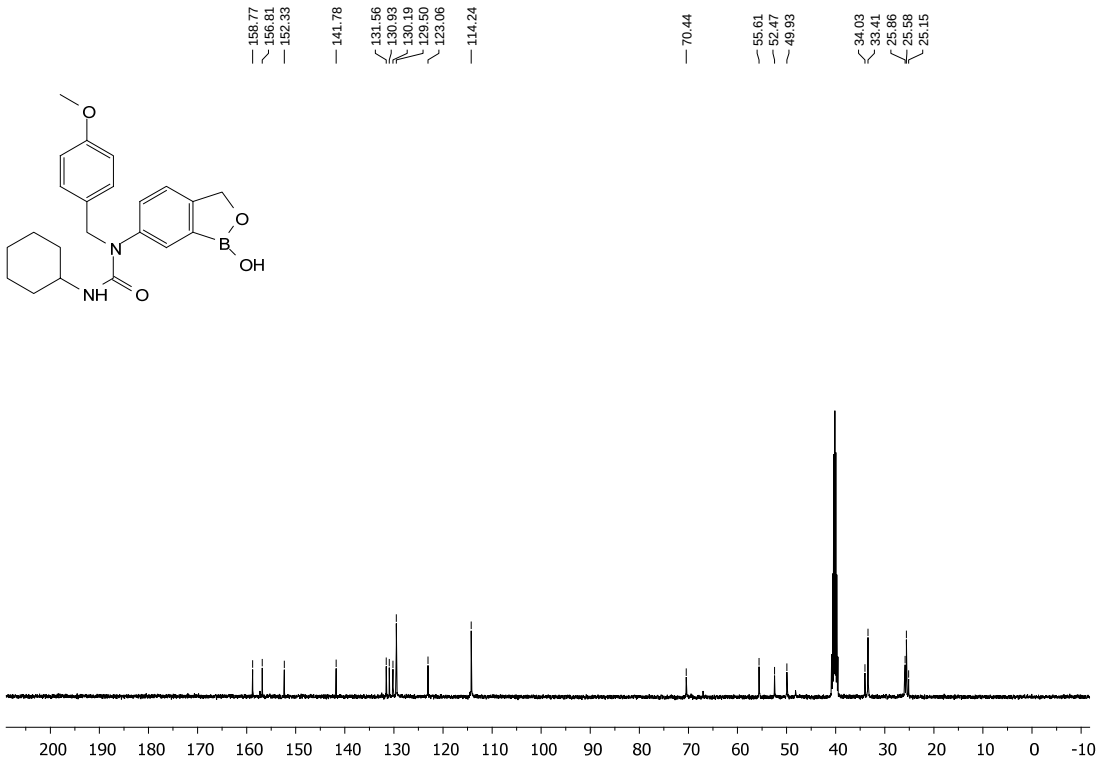


Figure 61. 100 MHz ^{13}C NMR of compound 44d in dmso

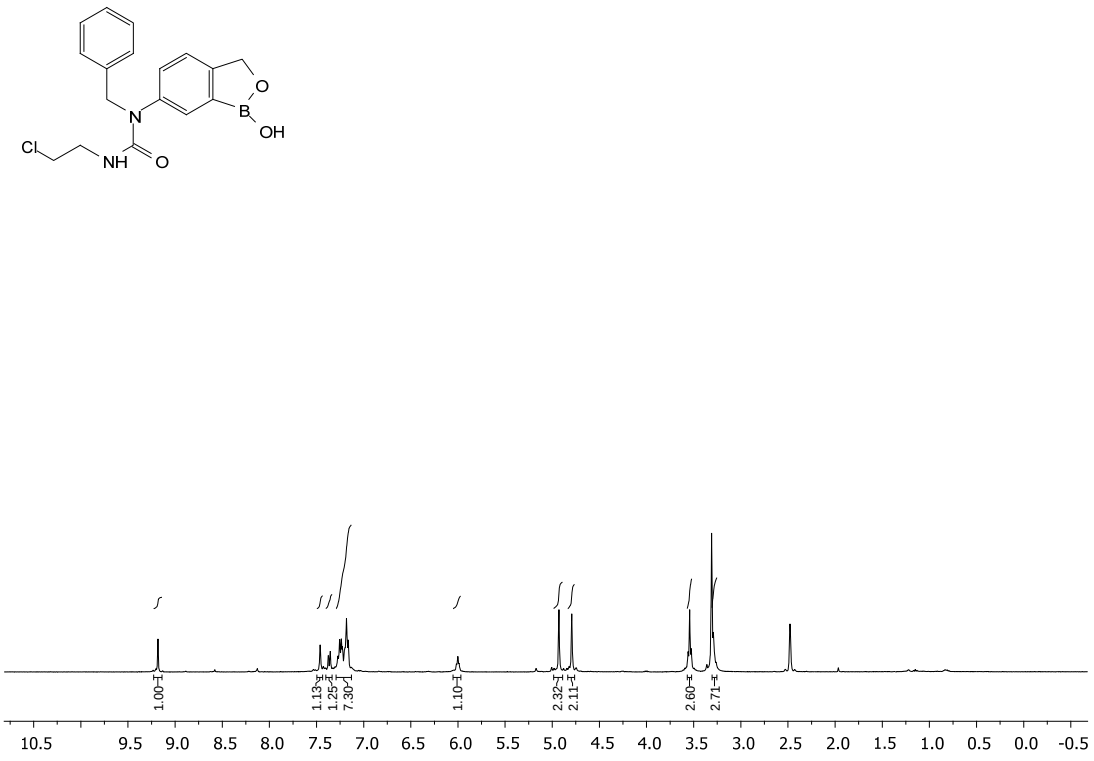


Figure 62. 400 MHz ^{1}H NMR of compound 44e in dmso

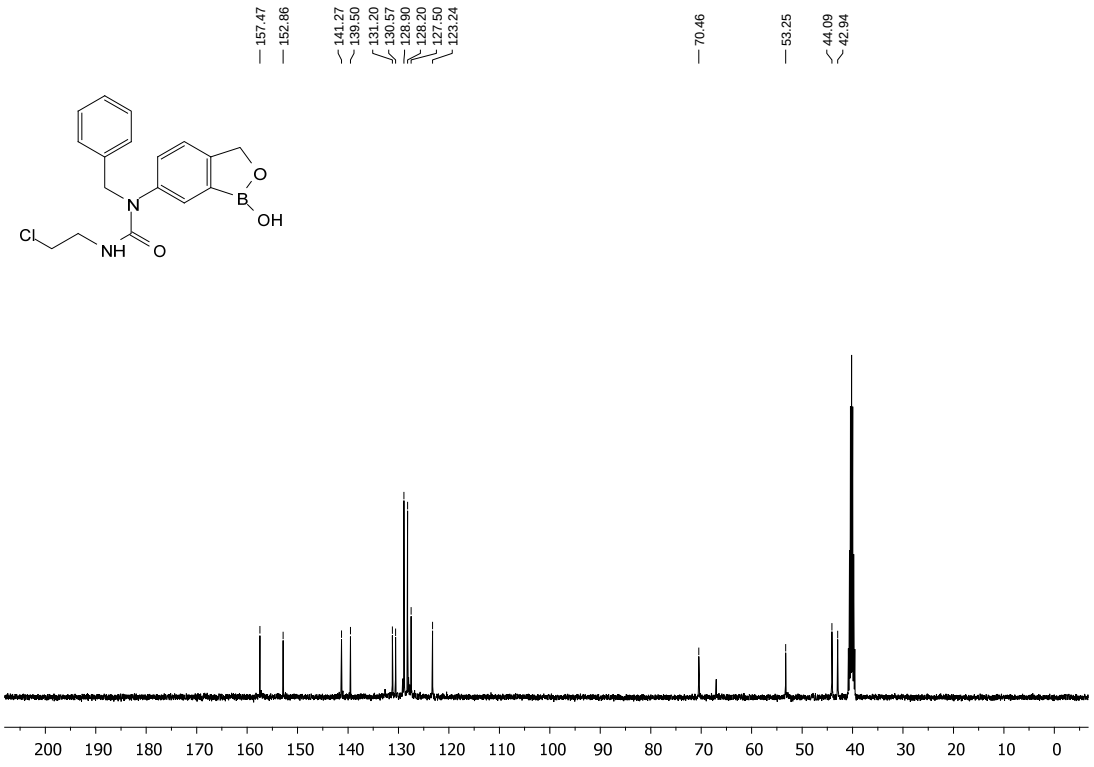


Figure 63. 100 MHz ^{13}C NMR of compound 44e in dmso

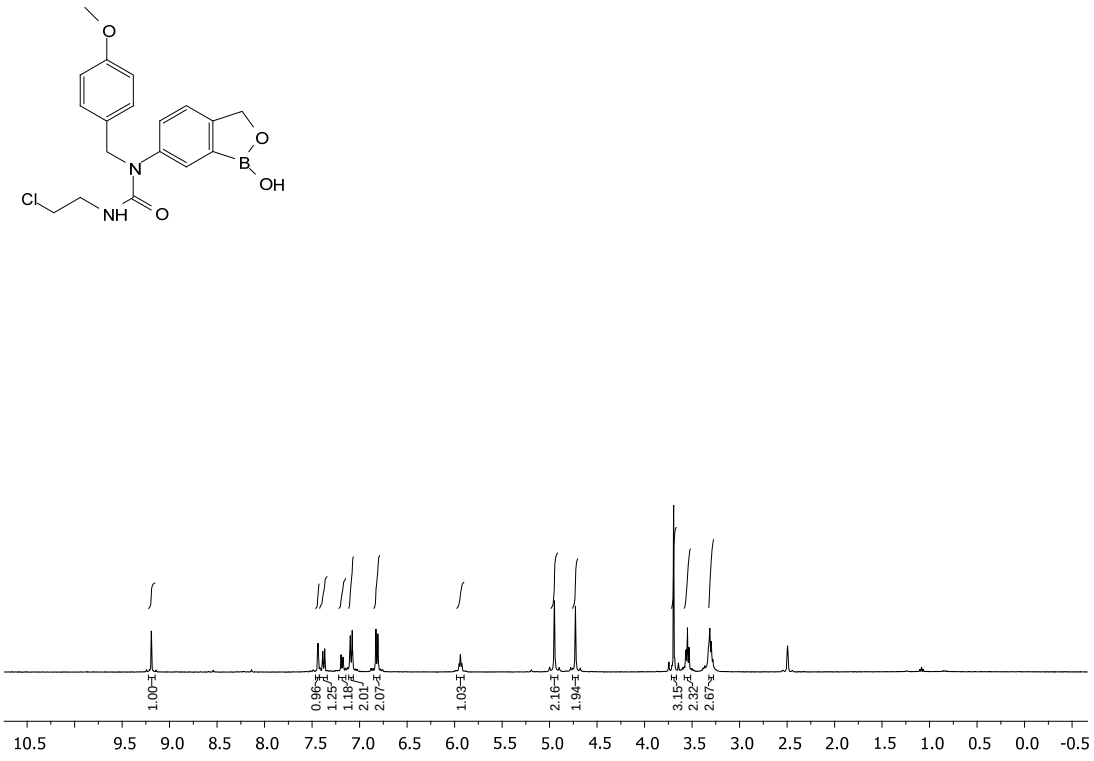


Figure 64. 400 MHz ^{1}H NMR of compound 44f in dmso

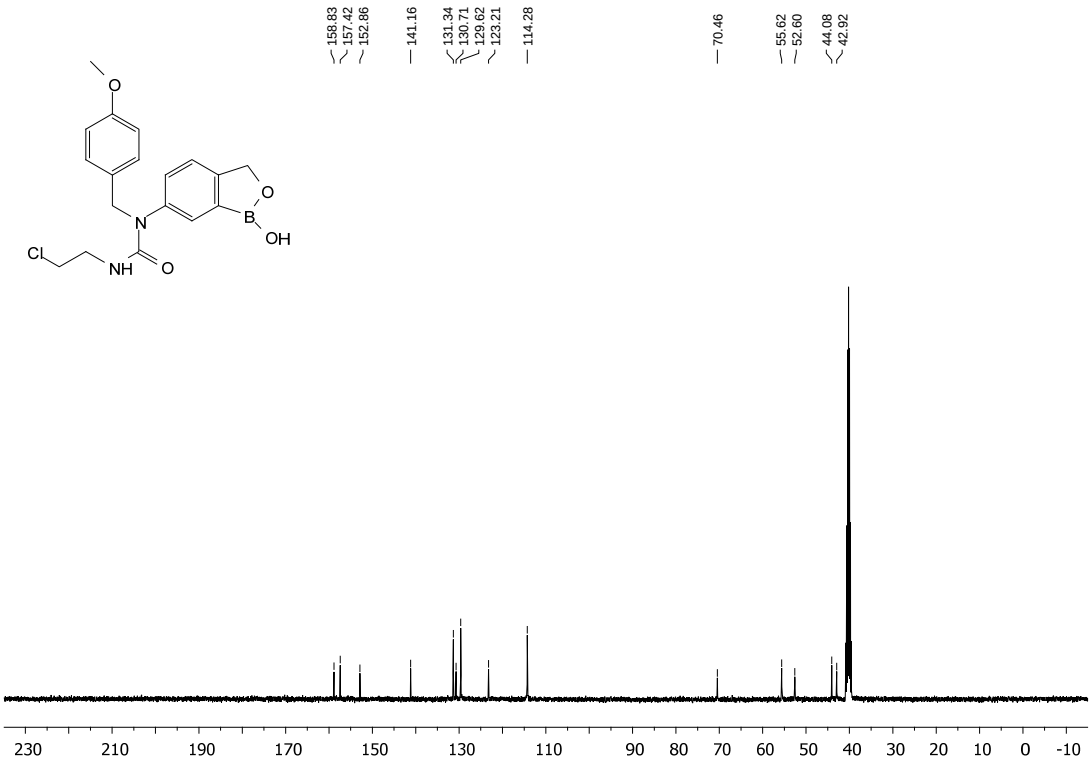


Figure 65. 100 MHz ^{13}C NMR of compound 44f in dmso

References

1. [a] Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem Rev* **2015**, *115*, 9587-9652.

   [b] Jonnalagadda, S. C.; Corsello, M. A.; Hetzell, B. R.; Mereddy, V. R. in "*Boron Science: New Technologies & Applications*" Ed. Hosmane, N. R. CRC Press. pp 741-805, **2012.**

   [c] Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem Rev* **2011**, *111*, 1417-1492.

   [d] Dembitsky, V. M.; Abu-Ali, H.; Srebnik, M. in *Studies in Inorganic Chemistry: Contemporary Aspects of Boron: Chemistry and Biological Applications.* Eds. Abu-Ali, H.; Dembitsky, V. M.; Srebnik, M. Elsevier, pp. 119-297, **2006**.

   [e] Suzuki, A.; Brown, H. C. *Organic Syntheses via Boranes: Volume 3 Suzuki Coupling,* Aldrich Chemical Company, **2003**.

   [f] Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633-9695.

   [g] Suzuki, A. in *Metal-Catalyzed Cross-Couplings Reactions*, Ed. Diederich, F.; Stang, P. J., Wiley-VCH, Weinheim, pp. 49-97, **1998**.

   [h] Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457-2483.

2. [a] Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535-1551.

   [b] Thomas, S.P. French, R.M. Jheengut, V. Aggarwal, V.K. *Chem. Rec.* **2009**, *9*, 24-39.

3. [a] Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774–7854.

   [b] Jonnalagadda, S. C.; Kumar, J. S.; Cirri, A.; Mereddy, V. R. in "*Boron Science: New Technologies & Applications*" Ed. Hosmane, N. R. CRC Press. pp 639–674, **2012.**

   [c] Bubnov, Y. N.; Gurskii, M. E.; Erdyakov, S. Y.; Kizas, O. A.; Kolomnikova, G. D.; Kuznetsov, N. Y.; Potapova, T. V.; Varzatskii, O. A.; Voloshin, Y. Z. *J. Organomet. Chem.* **2009**, *694*, 1754–1763.

   [d] Hall, D. G. *Pure Appl. Chem.* **2008**, *80*, 913-927.

   [e] Kennedy, J. W. J.; Hall, D. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4732–4739.

   [f] Denmark, S. E. Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793.

[g] Brown, H. C.; Ramahcandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1-19.

[h] Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.

[i] Roush WR. "*Allyl organometallics*" In: *Comprehensive Organic Synthesis*. Trost, B. M.; Fleming, I.; Heathcock, C. H. Ed. Vol. 2. Pergamon; Oxford: **1991**. pp. 1–53.

4. [a] Yang, F.; Zhu, M.; Zhang, J.; Zhou, H. *MedChemComm.* **2018,** Article ASAP.

[b] Lesnikowski, Z. J. *Expert Opin. Drug Discov.* **2016**, *11*, 569-578.

[c] Andres, P.; Ballano, G.; Calaza, M. I.; Cativiela, C. *Chem. Soc. Rev.* **2016**, *45*, 2291-2307.

[d] Baker, S. J.; Tomsho, J. W.; Benkovic, S. J. *Chem. Soc. Rev.* **2011**, *40*, 4279-4285.

[e] Trippier, P. C.; McGuigan, C. *MedChemComm.* **2010**, *1*, 183-198.

[f] Baker, S. J.; Ding, C. Z.; Akama, T.; Zhang, Y. K.; Hernandez, V.; Xia, Y. *Future Med. Chem.* **2009**, *1*, 1275-1288.

[g] Yang, W.; Gao, X.; Wang, B. *Boronic Acids*; Hall, D. H. Ed.; Wiley, pp 481-512, **2005**.

[h] Dembitsky, V. M.; Srebnik, M. *Tetrahedron* **2003**, *59*, 579-593.

[i] Yang, W.; Gao, X.; Wang, B. *Med. Res. Rev.* **2003**, *23*, 346-368.

5. [a] Kabalka, G.; Yao, M.-L. *Anti-Cancer Agents in Med.Chem.* **2006**, *6*, 111-125.

[b] Barth, R. F.; Coderre, J. A.; Vicente, M. G.; Blue, T. E. *Clin. Cancer Res.* **2005**, *11*, 3987-4002.

[c] Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515-1562.

6. Borissenko, L.; Groll, M. *Chem. Rev.* **2007**, *107*, 687-717.

7. [a] Chen, D.; Frezza, M.; Schmitt, S.; Kanwar, J.; P. Dou, Q. *Current Cancer Drug Targets* **2011**, *11*, 239-253.

[b] Yang, H.; Zonder, J. A.; Dou, Q. P. *Expert Opin Investig Drugs* **2009**, *18*, 957-971.

[c] Utecht, K. N.; Kolesar, J. *Am J Health Syst Pharm* **2008**, *65*, 1221-1231.

[d] Chauhan, D.; Hideshima, T.; Anderson, K. C. *Br J Cancer* **2006**, *95*, 961-965.

[e] Jackson, G.; Einsele, H.; Moreau, P.; Miguel, J. S. *Cancer Treat Rev* **2005**, *31* 591-602.

[f] Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velankar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T. H.; Neuteboom, S. T.; Richardson, P.; Palladino, M. A.; Anderson, K. C. *Cancer Cell* **2005**, *8*, 407-19.

[g] Bross, P. F.; Kane, R.; Farrell, A. T.; Abraham, S.; Benson, K.; Brower, M. E.; Bradley, S.; Gobburu, J. V.; Goheer, A.; Lee, S-L.; Leighton, J.; Liang, C. Y.; Lostritto, R. T.; McGuinn, W. D.; Morse, D. E.; Rahman, A.; Rosario, L. A.; Verbois, S. L.; Williams, G.; Wang, Y-C.; Pazdur, R. *Clin. Cancer Res.* **2004**, *10*, 3954-3964.

[h] Richardson, P. G.; Hideshima, T.; Anderson, K. C. *Cancer Control* **2003**, *10*, 361-369.

[i] Kane, R. C. *The Oncologist* **2003**, *8*, 508-513.

[j] Adams, J.; Ma, Y-T.; Stein, R.; Baevsky, M.; Grenier, L.; Plamondon, L., U.S. Pat. Appl. Publ., **1998**, US5780454A 19980714,.

8. [a] Schlafer, D.; Shah, K. S.; Panjic, E. H.; Lonial, S. *Expert Opin Drug Saf* **2017**, *16*, 167-183.

[b] Shirley, M. *Drugs* **2016**, *76*, 405-411.

[c] Muz, B.; Ghazarian, R. N.; Ou, M.; Luderer, M. J.; Kusdono, H. D.; Azab, A. K. *Drug Des Devel Ther* **2016**, *10*, 217-226.

[d] Offidani, M.; Corvatta, L.; Gentili, S.; Maracci, L.; Leoni, P. *Expert Rev Anticancer Ther* **2016**, *16*, 21-32.

[e] Richardson, P. G.; Moreau, P.; Laubach, J. P.; Gupta, N.; Hui, A. M.; Anderson, K. C.; San Miguel, J. F.; Kumar, S. *Future Oncol* **2015**, *11*, 1153-1168.

[f] Gentile, M.; Offidani, M.; Vigna, E.; Corvatta, L.; Recchia, A. G.; Morabito, L.; Morabito, F.; Gentili, S. *Expert Opin Investig Drugs* **2015**, *24*, 1287-98.

9. [a] Adamczyk-Wozniak, A.; Borys, K. M.; Sporzynski, A. *Chem. Rev.* **2015**, *115*, 5224-5247.

[b] Liu, C. T.; Tomsho, J. W.; Benkovic, S. J. *Bioorg. Med. Chem.* **2014**, *22*, 4462-4473.

[c] Adamczyk-Woźniak, A.; Cyrański, M. K.; Żubrowska, A.; Sporzyński, A. *J. Organomet. Chem.* **2009**, *694*, 3533-3541.

10. Torsell, K. *Ark. Kemi.* **1957**, *10*, 507-511.

11. [a] Cummings, W. M. Cox, C. H. Snyder, H. R. *J. Org. Chem.* **1969**, *34*, 1669-1674.

[b] Tschampel, P. Snyder, H.R. *J. Org. Chem.* **1964**, *29*, 2168-2172.

[c] Lennarz, W. J. Snyder, H. R. *J. Am. Chem. Soc.* **1960**, *82*, 2172-2175.

[d] Snyder, H. R. Reedy, A. J. Lennarz, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 835-838.

12. [a] Gupta, A. K.; Versteeg, S. G. *Expert Rev. Clin. Pharmacol.* **2016**, *9*, 1145-1152.

[b] Jinna, S.; Finch, J. *Drug Des. Devel. Ther.* **2015**, *9*, 6185-90.

[c] Gupta, A. K.; Daigle, D. *Expert Rev. Anti. Infect. Ther.* **2014**, *12*, 735-42.

[d] Alley, M. R.; Baker, S. J.; Beutner, K. R.; Plattner, J. *Expert Opin. Investig. Drugs* **2007**, *16*, 157-67.

[e] Rock, F. L.; Mao, W.; Yaremchuk, A.; Tukalo, M.; Crepin, T.; Zhou, H.; Zhang, Y. K.; Hernandez, V.; Akama, T.; Baker, S. J.; Plattner, J. J.; Shapiro, L.; Martinis, S. A.; Benkovic, S. J.; Cusack, S.; Alley, M. R. *Science* **2007**, *316*, 1759-61.

[f] Baker, S. J.; Zhang, Y. K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R.; Sanders, V.; Plattner, J. J. *J. Med. Chem.* **2006**, *49*, 4447-4450.

13. [a] Paton, D. M. *Drugs Today* **2017**, *53*, 239-245.

[b] Jarnagin, K.; Chanda, S.; Coronado, D.; Ciaravino, V.; Zane, L. T.; Guttman-Yassky, E.; Lebwohl, M. G. *J. Drugs Dermatol.* **2016**, *15*, 390-396.

[c] Zane, L. T.; Chanda, S.; Jarnagin, K.; Nelson, D. B.; Spelman, L.; Gold, L. S. *Immunotherapy* **2016**, *8*, 853-866.

[d] Zhang, Y. K.; Plattner, J. J.; Akama, T.; Baker, S. J.; Hernandez, V. S.; Sanders, V.; Freund, Y.; Kimura, R.; Bu, W.; Hold, K. M.; Lu, X. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2270-2274.

[e] Akama, T.; Baker, S. J.; Zhang, Y. K.; Hernandez, V.; Zhou, H.; Sanders, V.; Freund, Y.; Kimura, R.; Maples, K. R.; Plattner, J. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2129-2132.

[f] Nazarian, R.; Weinberg, J. M. *Curr. Opin. Investig. Drugs* **2009**, *10*, 1236-1242.

14. [a] Tekkam, S.; Alam, M. A.; Just, M. J.; Berry, S. M.; Johnson, J. L.; Jonnalagadda, S. C.; Mereddy, V. R. *Anti-Cancer Agents in Med. Chem.* **2013**, *13*, 1514-1530.

[b] Jonnalagadda, S. C.; Verga, S. R.; Patel, P. D.; Reddy, A. V.; Srinivas, T.; Scott, P. M.; Mereddy, V. R. *Appl. Organomet. Chem.* **2009**, *10*, 294-300.

[c] Jonnalagadda, S. C.; Cruz, J. S.; Connell, R. J.; Scott, P. M.; Mereddy, V. R. *Tetrahedron Lett.* **2009**, *50*, 4314-4317.

[d] Reddy, V. J.; Chandra, J. S.; Reddy, M. V. R. *Org. Biomol. Chem.* **2007**, *5*, 889-891.

[e] Ramachandran, P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2004**, *45*, 1011-1013.

15 [a] Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev*. **2012**; *41*, 68-78.

[b] Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674.

[c] Declerck, V.; Martinez, J.; Lamaty F. *Chem. Rev.* **2009**, *109*, 1-48.

[d] Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev*. **2007**; *26*, 1581-1588.

[e] Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891.

[f] Ciganek, E. *Organic Reactions*, **1997**, *51*, 201-350.

[g] Basavaiah, D.; Rao P. D.; Hyma, R. S. *Tetrahedron*, **1996**, *52*, 8001-8062.

16. Kumar, J. S.; Bashian, C. M.; Corsello, M. A.; Jonnalagadda, S. C.; Mereddy, V. R. *Tetrahedron Lett.* **2010**, *51*, 4482-4485.

17. Kumar, J. S.; Alam, M. A.; Gurrapu, S.; Nelson, G.; Williams, M.; Corsello, M. A.; Johnson, J. L.; Jonnalagadda, S. C.; Mereddy, V. R. *J. Heterocycl. Chem.* **2013**, *50*, 814-820.

18 [a] Domling, A. *Chem. Rev.* **2006**, *106*, 17–89.

[b] Banfi, L.; Riva, R. *Organic Reactions* **2005**, *65*, 1-140.

[c] Domling, A.; Ugi, I. *Angew Chem. Int. Ed.* **2000**, *39*, 3168-3210.

19. Kumar, J. S.; Jonnalagadda, S. C.; Mereddy, V. R. *Tetrahedron Lett.* **2010**, *51*, 779-782.

20. Alam, M. A.; Arora, K.; Gurrapu, S.; Jonnalagadda, S. K.; Nelson, G. L.; Kiprof, P.; Jonnalagadda, S. C.; Mereddy, V. R. *Tetrahedron* **2016**, *72*, 3795-3801.

21. [a] Korkegian, A.; O'Malley, T.; Xia, Y.; Zhou, Y.; Carter, D. S.; Sunde, B.; Flint, L.; Thompson, D.; Ioerger, T. R.; Sacchettini, J.; Alley, M. R. K.; Parish, T. *Tuberculosis* **2018**, *108*, 96-98.

[b] Li, X.; Hernandez, V.; Rock, F. L.; Choi, W.; Mak, Y. S. L.; Mohan, M.; Mao, W.; Zhou, Y.; Easom, E. E.; Plattner, J. J.; Zou, W.; Perez-Herran, E.; Giordano, I.; Mendoza-Losana, A.; Alemparte, C.; Rullas, J.; Angulo-Barturen, I.; Crouch, S.; Ortega, F.; Barros, D.; Alley, M. R. K. *J. Med. Chem.* **2017**, *60*, 8011-8026.

[c] Patel, N.; O'Malley, T.; Zhang, Y. K.; Xia, Y.; Sunde, B.; Flint, L.; Korkegian, A.; Ioerger, T. R.; Sacchettini, J.; Alley, M. R. K.; Parish, T. *Antimicrob. Agents Chemother.* **2017**, *61*, e01205-17.

22. [a] Zhang, Y. K.; Plattner, J. J.; Easom, E. E.; Jacobs, R. T.; Guo, D.; Freund, Y. R.; Berry, P.; Ciaravino, V.; Erve, J. C. L.; Rosenthal, P. J.; Campo, B.; Gamo, F. J.; Sanz, L. M.; Cao, J. *J. Med. Chem.* **2017**, *60*, 5889-5908.

[b] Zhang, Y. K.; Plattner, J. J.; Easom, E. E.; Jacobs, R. T.; Guo, D.; Sanders, V.; Freund, Y. R.; Campo, B.; Rosenthal, P. J.; Bu, W.; Gamo, F. J.; Sanz, L. M.; Ge, M.; Li, L.; Ding, J.; Yang, Y. *J. Med. Chem.* **2015**, *58*, 5344-5354.

[c] Zhang, Y.-K.; Plattner, J. J.; Easom, E. E.; Liu, L.; Retz, D. M.; Ge, M.; Zhou, H.-H. *J. Labelled Compd. Radiopharm.* **2012**, *55*, 201-205.

[d] Zhang, Y. K.; Plattner, J. J.; Freund, Y. R.; Easom, E. E.; Zhou, Y.; Ye, L.; Zhou, H.; Waterson, D.; Gamo, F. J.; Sanz, L. M.; Ge, M.; Li, Z.; Li, L.; Wang, H.; Cui, H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1299-1307.

[e] Zhang, Y.-K.; Plattner, J. J.; Easom, E. E.; Waterson, D.; Ge, M.; Li, Z.; Li, L.; Jian, Y. *Tetrahedron Lett.* **2011**, *52*, 3909-3911.

[f] Zhang, Y. K.; Plattner, J. J.; Freund, Y. R.; Easom, E. E.; Zhou, Y.; Gut, J.; Rosenthal, P. J.; Waterson, D.; Gamo, F. J.; Angulo-Barturen, I.; Ge, M.; Li, Z.; Li, L.; Jian, Y.; Cui, H.; Wang, H.; Yang, J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 644-651.

23. [a] Akama, T.; Zhang, Y. K.; Freund, Y. R.; Berry, P.; Lee, J.; Easom, E. E.; Jacobs, R. T.; Plattner, J. J.; Witty, M. J.; Peter, R.; Rowan, T. G.; Gillingwater, K.; Brun, R.; Nare, B.; Mercer, L.; Xu, M.; Wang, J.; Liang, H. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 6-10.

[b] Wu, P.; Zhang, J.; Meng, Q.; Nare, B.; Jacobs, R. T.; Zhou, H. *Eur. J. Med. Chem.* **2014**, *81*, 59-75.

[c] Qiao, Z.; Wang, Q.; Zhang, F.; Wang, Z.; Bowling, T.; Nare, B.; Jacobs, R. T.; Zhang, J.; Ding, D.; Liu, Y.; Zhou, H. *J. Med. Chem.* **2012**, *55*, 3553-3557.

[d] Jacobs, R. T.; Plattner, J. J.; Nare, B.; Wring, S. A.; Chen, D.; Freund, Y.; Gaukel, E. G.; Orr, M. D.; Perales, J. B.; Jenks, M.; Noe, R. A.; Sligar, J. M.; Zhang, Y. K.; Bacchi, C. J.; Yarlett, N.; Don, R. *Future Med Chem* **2011**, *3*, 1259-1278.

[e] Jacobs, R. T.; Nare, B.; Wring, S. A.; Orr, M. D.; Chen, D.; Sligar, J. M.; Jenks, M. X.; Noe, R. A.; Bowling, T. S.; Mercer, L. T.; Rewerts, C.; Gaukel, E.; Owens, J.; Parham, R.; Randolph, R.; Beaudet, B.; Bacchi, C. J.; Yarlett, N.; Plattner, J. J.; Freund, Y.; Ding, C.; Akama, T.; Zhang, Y. K.; Brun, R.; Kaiser, M.; Scandale, I.; Don, R. *PLoS Negl Trop Dis* **2011**, *5*, e1151.

[f] Ding, D.; Meng, Q.; Gao, G.; Zhao, Y.; Wang, Q.; Nare, B.; Jacobs, R.; Rock, F.; Alley, M. R.; Plattner, J. J.; Chen, G.; Li, D.; Zhou, H. *J. Med. Chem.* **2011**, *54*, 1276-1287.

[g] Brun, R.; Don, R.; Jacobs, R. T.; Wang, M. Z.; Barrett, M. P. *Future Microbiol* **2011**, *6*, 677-691.

[h] Ding, D.; Zhao, Y.; Meng, Q.; Xie, D.; Nare, B.; Chen, D.; Bacchi, C. J.; Yarlett, N.; Zhang, Y. K.; Hernandez, V.; Xia, Y.; Freund, Y.; Abdulla, M.; Ang, K. H.; Ratnam, J.; McKerrow, J. H.; Jacobs, R. T.; Zhou, H.; Plattner, J. J. *ACS Med Chem Lett* **2010**, *1*, 165-169.

[i] Barrett, M. P. *Curr Opin Infect Dis* **2010**, *23*, 603-608.

24. Lapa, G. B.; Mirchink, E. P.; Isakova, E. B.; Preobrazhenskaya, M. N. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 452-456.

25. Tevyashova, A. N.; Korolev, A. M.; Trenin, A. S.; Dezhenkova, L. G.; Shtil, A. A.; Polshakov, V. I.; Savelyev, O. Y.; Olsufyeva, E. N. *J. Antibiot.* **2016**, *69*, 549-560.

26. McKinney, D. C.; Zhou, F.; Eyermann, C. J.; Ferguson, A. D.; Prince, D. B.; Breen, J.; Giacobbe, R. A.; Lahiri, S.; Verheijen, J. C. *ACS Infect. Dis.* **2015**, *1*, 310-316.

27. [a] Palencia, A.; Bougdour, A.; Brenier-Pinchart, M. P.; Touquet, B.; Bertini, R. L.; Sensi, C.; Gay, G.; Vollaire, J.; Josserand, V.; Easom, E.; Freund, Y. R.; Pelloux, H.; Rosenthal, P. J.; Cusack, S.; Hakimi, M. A. *EMBO Mol. Med.* **2017**, *9*, 385-394.

[b] Palencia, A.; Liu, R. J.; Lukarska, M.; Gut, J.; Bougdour, A.; Touquet, B.; Wang, E. D.; Li, X.; Alley, M. R.; Freund, Y. R.; Rosenthal, P. J.; Hakimi, M. A.; Cusack, S. *Antimicrob. Agents Chemother.* **2016**, *60*, 5817-5827.

28. [a] Akama, T.; Dong, C.; Virtucio, C.; Freund, Y. R.; Chen, D.; Orr, M. D.; Jacobs, R. T.; Zhang, Y. K.; Hernandez, V.; Liu, Y.; Wu, A.; Bu, W.; Liu, L.; Jarnagin, K.; Plattner, J. J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5870-5873.

[b] Akama, T.; Virtucio, C.; Dong, C.; Kimura, R.; Zhang, Y. K.; Nieman, J. A.; Sharma, R.; Lu, X.; Sales, M.; Singh, R.; Wu, A.; Fan, X. Q.; Liu, L.; Plattner, J. J.; Jarnagin, K.; Freund, Y. R. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1680-1683.

29. [a] Li, X.; Zhang, S.; Zhang, Y. K.; Liu, Y.; Ding, C. Z.; Zhou, Y.; Plattner, J. J.; Baker, S. J.; Bu, W.; Liu, L.; Kazmierski, W. M.; Duan, M.; Grimes, R. M.; Wright, L. L.; Smith, G. K.; Jarvest, R. L.; Ji, J. J.; Cooper, J. P.; Tallant, M. D.; Crosby, R. M.; Creech, K.; Ni, Z. J.; Zou, W.; Wright, J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2048-2054.

[b] Li, X.; Zhang, Y. K.; Liu, Y.; Zhang, S.; Ding, C. Z.; Zhou, Y.; Plattner, J. J.; Baker, S. J.; Liu, L.; Bu, W.; Kazmierski, W. M.; Wright, L. L.; Smith, G. K.; Jarvest, R. L.; Duan, M.; Ji, J. J.; Cooper, J. P.; Tallant, M. D.; Crosby, R. M.; Creech, K.; Ni, Z. J.; Zou, W.; Wright, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7493-7497.

[c] Ding, C. Z.; Zhang, Y. K.; Li, X.; Liu, Y.; Zhang, S.; Zhou, Y.; Plattner, J. J.; Baker, S. J.; Liu, L.; Duan, M.; Jarvest, R. L.; Ji, J.; Kazmierski, W. M.; Tallant, M. D.; Wright, L. L.; Smith, G. K.; Crosby, R. M.; Wang, A. A.; Ni, Z. J.; Zou, W.; Wright, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7317-7322.

30. [a] Chen, Y.; Wang, W.; Wu, D.; Nagao, M.; Hall, D. G.; Thundat, T.; Narain, R. *Biomacromolecules* **2018**, Article ASAP.

[b] Wang, J.; Gao, Z.; Qi, W.; Zhao, Y.; Zhang, P.; Lin, M.; Li, Z.; Chen, G.; Jiang, M. *ACS Biomaterials Science & Engineering* **2017**, Article ASAP.

[c] Wuttke, A.; Geyer, A. *J. Pept. Sci.* **2017**, *23*, 549-555.

[d] Sun, P.; Tian, S.; Lin, M.; Chen, G. *Science China Chemistry* **2017**, *61*, 71-75.

[e] Diaz-Dussan, D.; Nakagawa, Y.; Peng, Y. Y.; Sanchez, C. L. V.; Ebara, M.; Kumar, P.; Narain, R. *Acs Macro Letters* **2017**, *6*, 768-774.

[f] Wang, Y. N.; Li, L.; Kotsuchibashi, Y.; Vshyvenko, S.; Liu, Y.; Hall, D.; Zeng, H. B.; Narain, R. *Acs Biomaterials Science & Engineering* **2016**, *2*, 2315-2323.

[g] Sene, S.; McLane, J.; Schaub, N.; Begu, S.; Mutin, P. H.; Ligon, L.; Gilbert, R. J.; Laurencin, D. *J. Mat. Chem. B* **2016**, *4*, 257-272.

[h] L. Rowe, G. El Khoury, C.R. Lowe, J. Mol. Recognit. **2016**, *29*, 232-238.

[i] C.M. Leenders, G. Jansen, M.M. Frissen, R.P. Lafleur, I.K. Voets, A.R. Palmans, E.W. Meijer, Chem. Eur. J. 22 (2016) 4608-4615.

[j] S. Lascano, K.-D. Zhang, R. Wehlauch, K. Gademann, N. Sakai, S. Matile, Chem. Sci. 7 (2016) 4720-4724.

[k] J.P. Couturier, E. Wischerhoff, R. Bernin, C. Hettrich, J. Koetz, M. Sutterlin, B. Tiersch, A. Laschewsky, Langmuir 32 (2016) 4333-4345.

[l] W. Zhu, X. Chai, B. Wang, Y. Zou, T. Wang, Q. Meng, Q. Wu, Chem. Commun. 51 (2015) 9608-11.

[m] K.D. Zhang, S. Matile, Angew. Chem. Int. Ed. Engl. 54 (2015) 8980-8983.

[n] S. Sene, S. Bégu, C. Gervais, G. Renaudin, A. Mesbah, M.E. Smith, P.H. Mutin, A. van der Lee, J.-M. Nedelec, C. Bonhomme, D. Laurencin, Chem. Mater. 27 (2015) 1242-1254.

[o] H. Lu, Y. Wang, L. Li, Y. Kotsuchibashi, R. Narain, H. Zeng, ACS Appl. Mater. Interfaces 7 (2015) 27176-27187.

[p] Y. Kotsuchibashi, M. Ebara, T. Sato, Y. Wang, R. Rajender, D.G. Hall, R. Narain, T. Aoyagi, J. Phys. Chem. B 119 (2015) 2323-2329.

[q] E.S. Jeong, C. Park, K.T. Kim, Polymer Chem. 6 (2015) 4080-4088.

[r] J.P. Couturier, M. Sutterlin, A. Laschewsky, C. Hettrich, E. Wischerhoff, Angew. Chem. Int. Ed. Engl. 54 (2015) 6641-6644.

31. For general reviews on carboranes, please refer:

[a] Hosmane, N. S. *Boron Science: New Technologies & Applications*, CRC Press. **2012**.

[b] Issa, F.; Kassiou, M.; Rendina, L. M. *Chem. Rev.* **2011**, *111*, 5701-5722.

[c] Hosmane, N. S.; Maguire, J. A. *Organometallics* **2005**, *24*, 1356-1389.

[e] Hosmane, N. S. *Pure Appl. Chem.* **2003**, *75*, 1219-1229.

[f] Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173-230.

[g] Saxena, A. K.; Maguire, J. A.; Hosmane, N. S. *Chem. Rev.* **1997**, *97*, 2421-2461.

[h] Saxena, A. K.; Hosmane, N. S. *Chem. Rev.* **1993**, *93*, 1081-1124.

32. For general reviews BODIPY, please refer:

[a] Kowada, K.; Maeda, H.; Kikuchi, K. *Chem. Soc. Rev.* **2015**, *44*, 4953-4972.

[b] Das, B. C.; Thapa, P.; Karki, R.; Schinke, C.; Das, S.; Kambhampati, S.; Banerjee, S. K.; Veldhuizen, P. V.; Verma, A.; Weiss, L. M.; Evans, T. *Future Med. Chem.* **2013**, *5*, 653-676.

[c] Kamkaew, A.; Lim, S. H.; Lee, H. B.; Kiew, L. V.; Chung, L. Y.; Burgess, K. *Chem. Soc. Rev.* **2013**, *42*, 77-88.

[d] Boens, N.; Leen, V.; Dehaen, W. *Chem. Soc. Rev.* **2012**, *41*, 1130-1172.

[e] Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891-4932.

33. For general reviews on this topic, please refer:

[a] Sun, X.; Zhai, W.; Fossey, J. S.; James, T. D. *Chem. Commun.* **2016**, *52*, 3456-3469.

[b] Anzai, J-I. *Mater. Sci. Eng., C* **2016**, *67*, 737-746.

[c] Li, M.; Zhu, W.; Marken, F.; James, T. D. *Chem. Commun.* **2015**, *51*, 2005-2020.

[d] Kubo, Y.; Nishiyabu, R.; James, T. D.; *Chem. Commun.* **2015**, *51*, 1106-1123.

[e] Nishiyabu, R.; Kubo, Y.; James, T. D.; Fossey, J. S. *Chem. Commun.* **2011**, *47*, 1106-1123.

[f] Nishiyabu, R.; Kubo, Y.; James, T. D.; Fossey, J. S. *Chem. Commun.* **2011**, *47*, 1124-1150.

[g] Galbraith, E.; James, T. D. *Chem. Soc. Rev.* **2010**, *39*, 3831-3842.

[h] Yan, J.; Fang, H.; Wang, B. *Med. Res. Rev.* **2005**, *25*, 490-520.

34. For general reviews on this topic, please refer:

[a] Brooks, W. L. A.; Sumerlin, B. S. *Chem. Rev.* **2016**, *116*, 1375-1397.

[b] Cambre, J. N.; Sumerlin, B. S. *Polymer* **2011**, *52*, 4631-4643.

35. Suman, P.; Patel, B. P.; Kasibotla, A. V.; Solano, L. N.; Jonnalagadda, S. C. *J. Organomet. Chem.* **2015**, *798*, 125-131.

36 [a] Lin, M.; Chen, G.; Jiang, M., *Polymer Chemistry* **2014**, *5*, 234-240.

[b] Fu, Z.; He, J.; Tong, A.; Xie, Y.; Wei, Y., *Synthesis* **2013**, *45*, 2843-2852.

[c] Sanders, V.; Maples, K.; Plattner, J. J.; Bellinger-Kawahara, C.; U.S. Pat. Appl. 20070286822 2007.

37 [a] Madelmont, J. C.; Godenche, D.; Parry, D.; Duprat, J.; Chabard, J. L.; Plagne, R.; Athe, G. M.; Meynie, G. *J. Med. Chem*. **1985**, *28*, 1346-1350.

[b] Bartsch, H.; Montesano, R.; *Carcinogenesis* **1984,** *5,* 1381-1393.

[c] Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1981**, *46*, 5309-5321.