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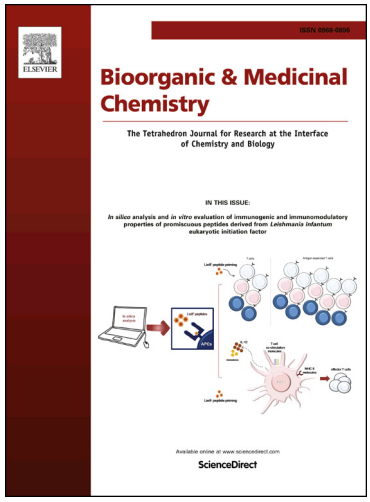

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PII: S0968-0896(17)32116-8
DOI: https://doi.org/10.1016/j.bmc.2017.11.036
Reference: BMC 14088

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 30 October 2017
Revised Date: 22 November 2017
Accepted Date: 23 November 2017

Please cite this article as: Yeon, S.K., Choi, J.W., Park, J-H., Lee, Y.R., Kim, H.J., Shin, S.J., Jang, B.K., Kim, S., Bahn, Y.S., Han, G., Lee, Y.S., Pae, A.N., Park, K.D., Synthesis and Evaluation of Biaryl Derivatives for Structural Characterization of Selective Monoamine Oxidase B Inhibitors toward Parkinson's Disease Therapy, *Bioorganic & Medicinal Chemistry* (2017), doi: https://doi.org/10.1016/j.bmc.2017.11.036

Synthesis and Evaluation of Biaryl Derivatives for Structural Characterization of Selective Monoamine Oxidase B Inhibitors toward Parkinson's Disease Therapy

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Abstract

Benzyloxyphenyl moiety is a common structure of highly potent, selective and reversible inhibitors of monoamine oxidase B (MAO-B), safinamide and sembragiline. We synthesized 4-(benzyloxy)phenyl and biphenyl-4-yl derivatives including halogen substituents on the terminal aryl unit. In addition, we modified the carbon linker between amine group and the biaryl linked unit. Among synthesized compounds, **12c** exhibited the most potent and selective MAO-B inhibitory effect (hMAO-B IC_{50}: 8.9 nM; >10,000-fold selectivity over MAO-A) as a competitive inhibitor. In addition, **12c** showed greater MAO-B inhibitory activity and selectivity compared to well-known MAO-B inhibitors such as selegiline, safinamide and sembragiline. In the MPTP-induced mouse model of Parkinson's disease (PD), **12c** significantly protected the tyrosine hydroxylase (TH)-immunopositive DAergic neurons and attenuated the PD-associated behavioral deficits. This study suggests characteristic structures as a MAO-B inhibitor that may provide a good insight for the development of therapeutic agents for PD.

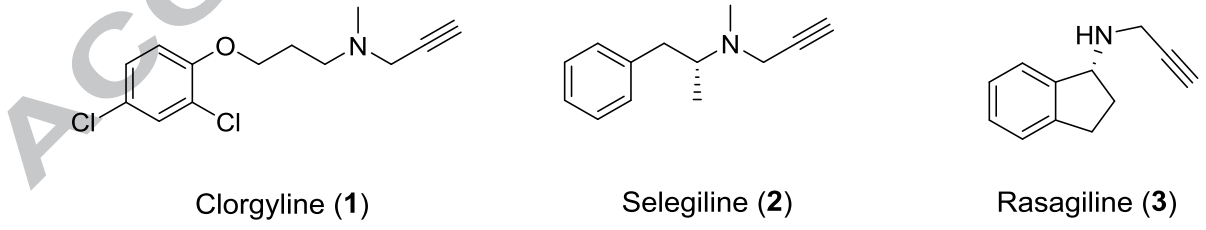
Keywords

Benzyloxyphenyl derivatives, MAO-B inhibitor, MPTP mouse model, Parkinson's disease

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder characterized by marked motor deficits such as resting tremor, bradykinesia, rigidity and postural instability.[1] These motor symptoms are mostly associated with dopamine (DA) depletion caused by a profound loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc). However, the exact mechanisms causing neurodegeneration are not yet known.[2-4]

Recently, several studies have reported that the expression level of monoamine oxidase B (MAO-B) in human brain increases with age, and activity is highly increased in the substantia nigra of PD patients.[5,6] MAOs are localized on the outer membrane of mitochondria, particularly in the liver and brain, and catalyze the oxidative deamination of monoamine neurotransmitters such as dopamine.[7] In addition, the reaction catalyzed by MAOs result in the production of hydrogen peroxide (H_2O_2) which causes oxidative stress and neuronal cell death.[8,9] There are two isoforms, MAO-A and MAO-B. MAO-A is localized in catecholaminergic neurons and selectively inhibited by low concentrations of clorgyline (**1**), whereas MAO-B is abundant in serotonergic neurons and astrocytes, and selectively inhibited by potent inhibitors selegiline (**2**) and rasagiline (**3**) (**Fig. 1**).[10-12]

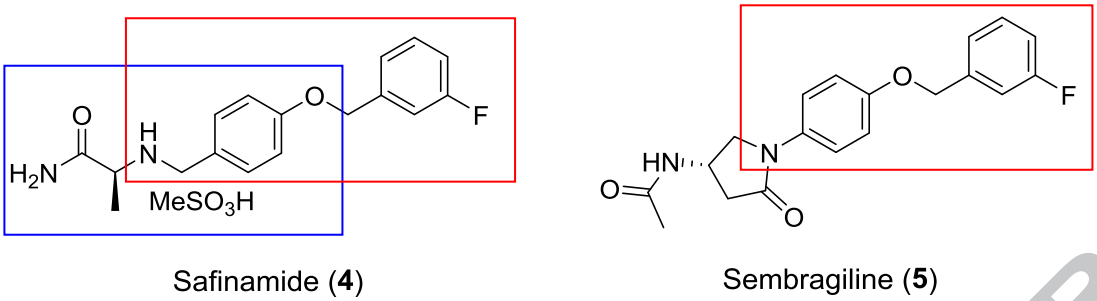


Clorgyline (**1**) Selegiline (**2**) Rasagiline (**3**)

Fig. 1. Chemical structures of irreversible MAO-B inhibitors

Selegiline and rasagiline, selective and potent MAO-B inhibitors, are the most widely used drugs for the therapy of PD by either mono-therapy or in combination with the levodopa, the dopamine

prodrug, resulting in the increase of dopamine.[13,14] However, selegiline and rasagiline are irreversible MAO-B inhibitors and showed undesirable adverse effects in long term treatment of PD such as hallucinations and headaches. Recent studies have been shown that the irreversibility of MAO-B inhibition may contribute short-lived action.[15] Accordingly, the development of selective and reversible MAO-B inhibitors could reduce undesirable adverse effects and maintain the effectiveness in long-term use for the treatment of neurodegenerative diseases. Recently, safinamide (**4**, Xadago™, **Fig. 2**), a highly selective and reversible MAO-B inhibitor, was approved for the treatment of mild-to-late PD patients as an add-on therapy to stable dose of levodopa alone or in combination with other PD medications.[16] However, safinamide may cause disadvantageous effects due to other biological properties such as selective sodium channel blockade, calcium channel modulation, and inhibition of stimulated release of glutamate.[17-20] Sembragiline (**5**, RG-1577, **Fig. 2**) is another potent reversible MAO-B inhibitor for the treatment of Alzheimer's disease (AD). MAO-B activity is linked to the production of reactive oxygen species (ROS) that can cause neuronal damage. Sembragiline was expected to slow progression of neurodegeneration by reducing oxidative stress. However, it failed to demonstrate benefit of the primary endpoint in clinical trial phase 2.[21,22] Interestingly, two recent potent and selective MAO-B inhibitors have common moieties, ((3-fluorobenzyl)oxy)phenyl group (**Fig. 2**, red box).



Safinamide (**4**) Sembragiline (**5**)

Fig. 2. Chemical structures of reversible MAO-B inhibitors.

In this study, we asked if compounds conforming to the biaryl linked unit exhibited MAO-B inhibitory activity. First, we synthesized substituted (4-(benzyloxy)phenyl)-methylammonium chlorides. Next, we modified the carbon linker between amine group and the biaryl linked unit (**Fig.3.**). In addition, we prepared biphenyl-4-yl derivatives wherein the aryl linker (X) is a single bond (**Fig.3.**). We reported that the substituted (4-(benzyloxy)phenyl)-ethylammonium chlorides exhibited potent and selective MAO-B inhibitory activities. One of the compounds with the highest potency was further evaluated for in vivo efficacy in the MPTP-induced mouse model of PD.

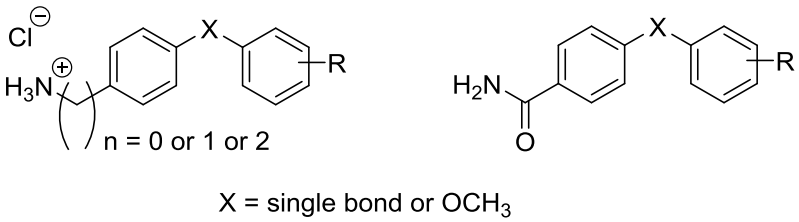


Fig. 3. Representative chemical structures of biaryl derivatives.

Recently, some biaryl derivatives in our study have been reported their biological activities such as anticonvulsant activity[23] and trace amine-associated receptor agonist effects[24]. However, this is the

first report to propose structural features for the excellent activity of MAO-B inhibitors by variously modifying the biaryl linker and the carbon linker. Thus, this study can provide insight into the development of new potential MAO-B inhibitors for PD therapy.

Results and Discussion

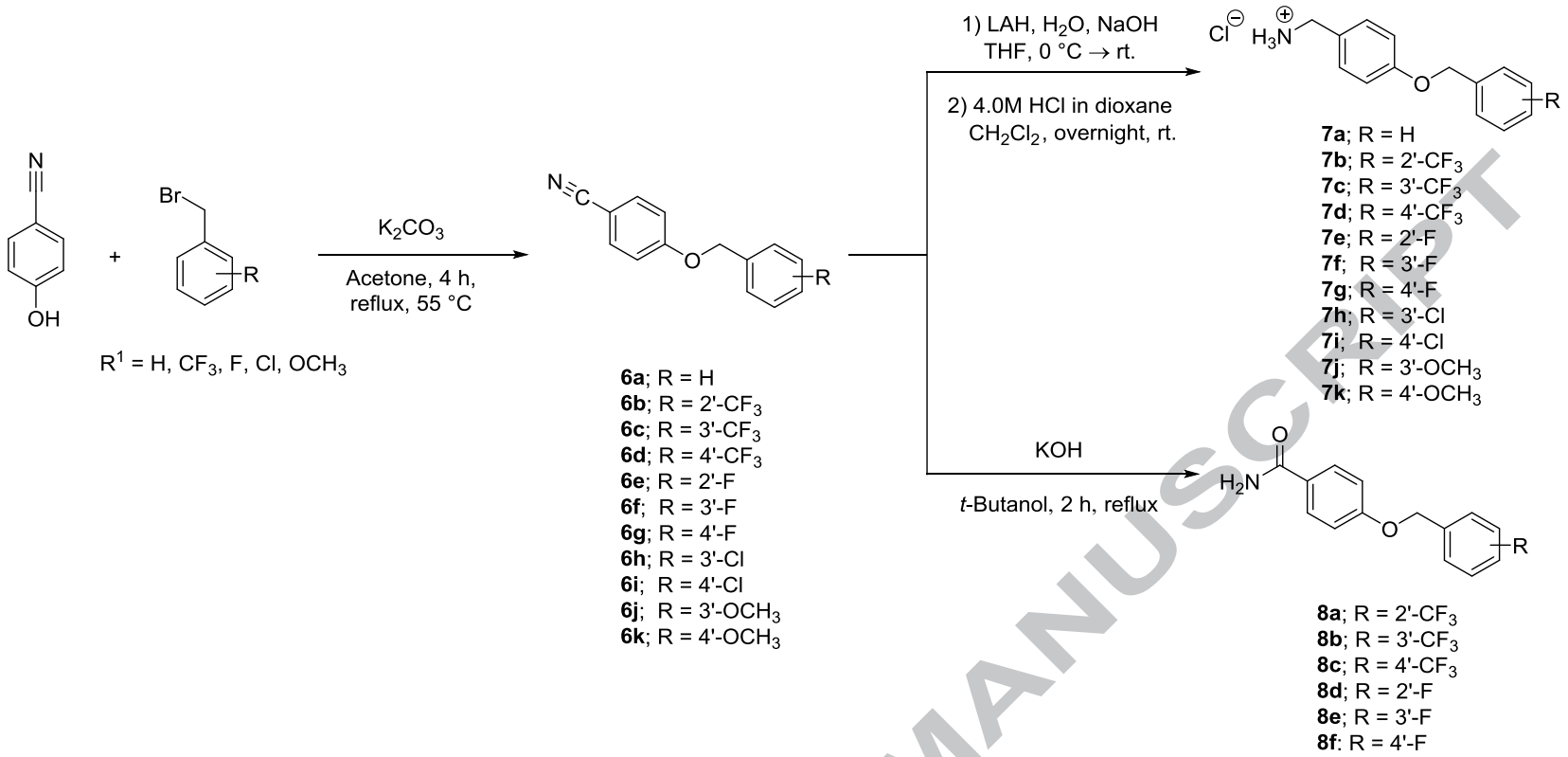
2.1. Selection of compounds

According to recent literature, safinamide (**4**) has emerged as a new therapeutic agent for the treatment of PD through MAO-B inhibition. We divided safinamide into two parts (the blue and the red boxes in Fig. 2) to determine the part that affected the MAO-B inhibitory effects. We found that (4-((3-fluorobenzyl)oxy)phenyl)methanaminium chloride (**7f**) corresponding to the red box showed much potent than compound **15** corresponding to blue box (IC_{50} hMAO-B = 0.926 μM vs >10 μM). Sembragiline (**5**, RG-1577), a reversible MAO-B inhibitor, has a ((3-fluorobenzyl)oxy)phenyl group in common with safinamide. We observed that 4-((3-fluorobenzyl)oxy)benzenaminium chloride (**10e**) corresponding to the red box in **5** inhibited MAO-B activity. Accordingly, we prepared 4-(benzyloxy)phenyl and biphenyl-4-yl derivatives which included various substituents on the terminal aryl unit. We also modified the carbon linker between amine group and the biaryl linked unit.

2.2. Synthesis

Compounds **7** and **8** were prepared in two steps (Scheme 1). Using a slightly modified method from the previous method, we prepared the Williamson ether coupled products **6** by treating 4-cyanophenol with the appropriate substituted benzyl bromide and potassium carbonate (K_2CO_3). Lithium aluminum hydride ($LiAlH_4$) reduction of the nitrile group in **6a-6k** afforded the amines,

which were immediately converted to the corresponding aminium chlorides **7a**-**7k**. The conversion of nitriles (**6a**-**6k**) to amides by partial hydrolysis with KOH afforded benzamide derivatives **8a**-**8f**. To prepare 4-nitrophenoxy benzene derivatives **9a**-**9f**, we synthesized 4-nitrophenol and the appropriate substituted benzyl bromide using the similar method above except reaction solvent (DMF) (Scheme 2). 4-nitrophenoxy benzene derivatives **9a**-**9f** were reduced to benzenaminium chlorides **10a**-**10f** by platinum (II) oxide under hydrogen gas (Scheme 2). Compounds **11** were prepared by Williamson ether coupling using *tert*-butyl (4-hydroxyphenethyl)carbamate and the substituted benzyl bromide. Deprotection of boc-group by 4.0M hydrogen chloride in dioxane gave ethanaminium chlorides **12a**-**12j** (Scheme 3). The (biphenyl-4-yl)ethanaminum chlorides were prepared using Suzuki coupling of *N*-boc-2-(4-bromophenyl)ethylamine (**13**) with the appropriate, commercially available substituted aryl boronic acids to give the boc-protected amines, which then were immediately deprotected and converted to their hydrochloride salts **14a**-**14j** using HCl (Scheme 4).

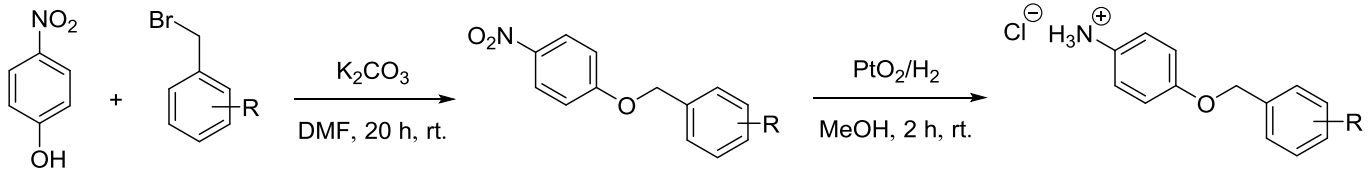


6a; R = H
6b; R = 2'-CF_3
6c; R = 3'-CF_3
6d; R = 4'-CF_3
6e; R = 2'-F
6f; R = 3'-F
6g; R = 4'-F
6h; R = 3'-Cl
6i; R = 4'-Cl
6j; R = 3'-OCH_3
6k; R = 4'-OCH_3

7a; R = H
7b; R = 2'-CF_3
7c; R = 3'-CF_3
7d; R = 4'-CF_3
7e; R = 2'-F
7f; R = 3'-F
7g; R = 4'-F
7h; R = 3'-Cl
7i; R = 4'-Cl
7j; R = 3'-OCH_3
7k; R = 4'-OCH_3

8a; R = 2'-CF_3
8b; R = 3'-CF_3
8c; R = 4'-CF_3
8d; R = 2'-F
8e; R = 3'-F
8f: R = 4'-F

Scheme 1. General Procedure for Substituted (Benzyloxyphenyl)methanaminium Chlorides and Substituted (Benzyloxy)benzamides.

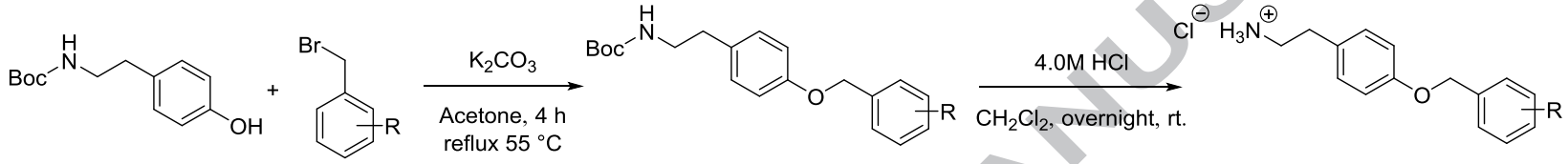


R^1 = CF_3, F

9a; R = 2'-CF_3
9b; R = 3'-CF_3
9c; R = 4'-CF_3
9d; R = 2'-F
9e; R = 3'-F
9f; R = 4'-F

10a; R = 2'-CF_3
10b; R = 3'-CF_3
10c; R = 4'-CF_3
10d; R = 2'-F
10e; R = 3'-F
10f; R = 4'-F

Scheme 2. General Procedure for Substituted (Benzyloxy)benzenaminium Chlorides.

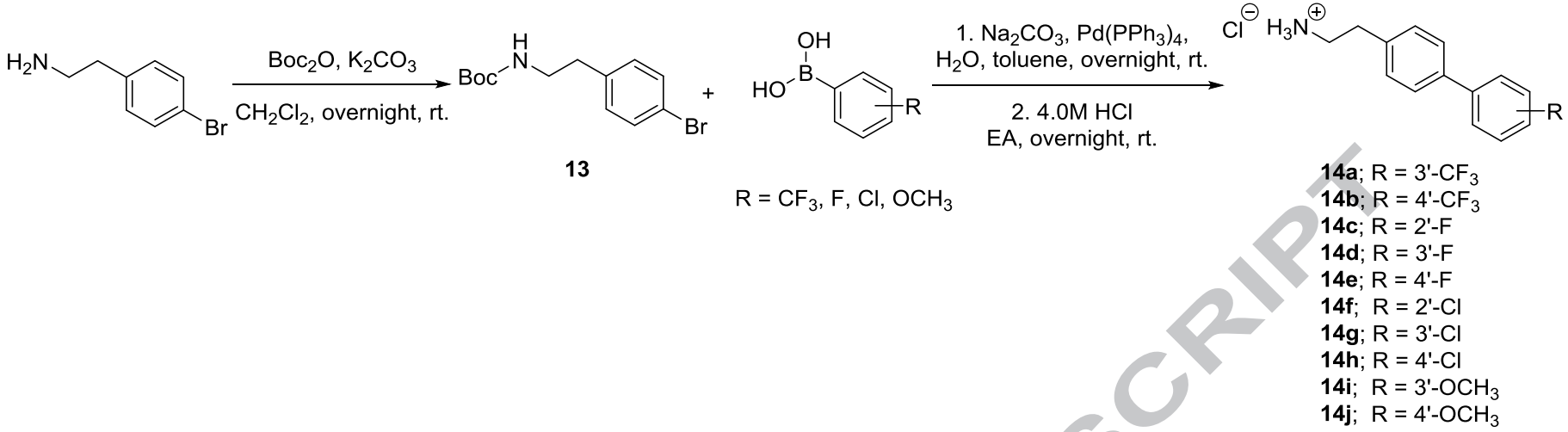


R = CF_3, F, Cl

11a; R = 2'-CF_3
11b; R = 3'-CF_3
11c; R = 4'-CF_3
11d; R = 2'-F
11e; R = 3'-F
11f; R = 4'-F
11g; R = 2'-Cl
11h; R = 3'-Cl
11i; R = 4'-Cl
11j; R = 3'-OCH_3

12a; R = 2'-CF_3
12b; R = 3'-CF_3
12c; R = 4'-CF_3
12d; R = 2'-F
12e; R = 3'-F
12f; R = 4'-F
12g; R = 2'-Cl
12h; R = 3'-Cl
12i; R = 4'-Cl
12j; R = 3'-OCH_3

Scheme 3. General Procedure for Substituted (Benzyloxyphenyl)ethanaminium Chlorides.



Scheme 4.

General Procedure for Substituted (Biphenyl)ethanaminium Chlorides.

2.3. Inhibitory Activities of the Synthesized Compounds against Monoamine Oxidase B

The synthesized compounds were evaluated for inhibitory activities of human MAO-A and MAO-B using recombinant enzymes. The enzyme inhibition assay on test compounds was performed using Amplex Red reagents and the inhibitory activity was determined by spectrophotometrically measuring the resorufin formation at 570 nm. The inhibitory potencies (IC_{50} values) for all synthesized compounds are summarized in Table 1, with comparative values of the positive controls, selegiline, safinamide and sembragiline.

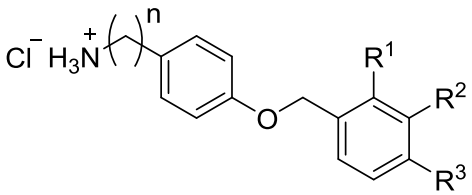
First, we prepared 11 (benzyloxyphenyl)methanaminium chlorides with various functional groups on the terminal aryl ring (Table 1, compounds **7**). The first set of compounds **7** contained methylamine hydrochloride groups at one end of the biaryl linked unit. Compound **7f**, which is the biaryl linked unit of safinamide (the red box on the left in **Fig. 2**), exhibited moderate MAO-B inhibitory activity (IC_{50} = 0.926 μM). We introduced a variety of electron-withdrawing groups and electron-donating group into the terminal aryl ring (**7a-7k**). We observed that the two groups did not exhibit significant activity differences, but most of them showed moderate inhibitory activities (IC_{50}: 0.136 μM ~ 0.926 μM).

Next, we changed the number of carbon atoms between the amine group and the biaryl linked unit of compound **7** from one to zero (**10**) and two (**12**). Compound **10e**, which is the biaryl linked unit of sembragiline (the red box on the right in **Fig. 2**), has lower MAO-B inhibitory activity (IC_{50} = 2.483 μM) than compound **7f**. All compound **10**, in which no carbon was present between the amine groups and the biaryl linked units, exhibited lower inhibitory activity (IC_{50}: 0.402 μM ~ >10 μM) than compound **7** having one carbon at the corresponding position. We investigated whether adding one carbon to this position of compound **7** improved MAO-B inhibitory activities. Interestingly, this modification resulted in dramatic improvement of inhibitory activity in most compounds (IC_{50}: 0.009 μM ~ 0.396 μM). For the CF_3-substituted compounds **12a-12c**, we found that the 4'-CF_3 derivative

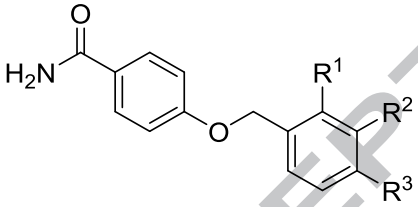
12c was more potent than the corresponding 2'- and 3'-CF_3 derivatives **12a** and **12b** (**12c**, IC_{50} = 0.009 μM; **12a**, IC_{50} =1.803 μM; **12b**, IC_{50} = 0.110 μM). A similar trend on the inhibitory activities of 2', 3', and 4' regioisomers was observed in the F- or Cl-substituted compounds **12d**-**12i**. In addition, we modified the methanaminum chloride group of compound **7** to an amide group, and found that the substitution with the amide group did not significantly affect MAO-B inhibitory activity.

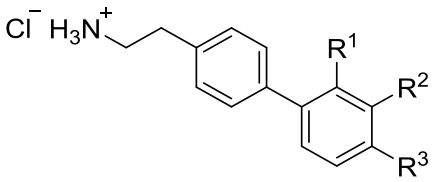
Finally, we prepared (biphenyl-4-yl)ethanaminium chlorides **14a-14j** wherein the aryl linker is a single bond. In this case, the compounds substituted with bulky electron-withdrawing groups (CF_3 and OCF_3) exhibit far superior inhibitory activity than the F- or Cl-substituted compounds **14c**-**14h**. In particular, 4'-CF_3 derivatives **14b** showed much better MAO-B inhibitory activities than 4'-F and 4'-Cl derivatives **14e** and **14h** (**14b**, IC_{50} = 0.041 μM; **14e**, IC_{50} = 6.806 μM; **14h**, IC_{50} = 0.625 μM).

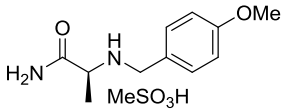
Table 1. Inhibitory effects of the synthesized compounds against hMAOs.



Compd	n	R^1	R^2	R^3	MAO-B (IC_{50}, μM)[a]	MAO-A (IC_{50}, μM)	SI[b]
7a	1	H	H	H	3.225±0.06	>100	>31
7b	1	CF_3	H	H	3.146±0.40	>100	>32
7c	1	H	CF_3	H	0.387±0.08	>100	>250
7d	1	H	H	CF_3	0.136±0.01	>100	>730
7e	1	F	H	H	1.462±0.19	>100	>68
7f	1	H	F	H	0.926±0.03	>100	>100
7g	1	H	H	F	0.452±0.07	>100	>220
7h	1	H	Cl	H	0.257±0.02	>100	>380
7i	1	H	H	Cl	0.440±0.02	>30	>68
7j	1	H	OMe	H	0.175±0.01	>30	>170
7k	1	H	H	OMe	0.283±0.02	>100	>350
10a	0	CF_3	H	H	>10	>100	nd[e]
10b	0	H	CF_3	H	1.507±0.03	>100	>66
10c	0	H	H	CF_3	0.402±0.02	>100	>240
10d	0	F	H	H	>10	>30	nd[e]
10e	0	H	F	H	2.483±0.07	>100	>40
10f	0	H	H	F	3.324±0.11	>100	>30
12a	2	CF_3	H	H	1.803±0.12	>100	>55
12b	2	H	CF_3	H	0.110±0.02	>100	>900
12c	2	H	H	CF_3	0.009±0.001	>100	>11000
12d	2	F	H	H	0.396±0.02	>10	>25
12e	2	H	F	H	0.193±0.01	>100	>510
12f	2	H	H	F	0.109±0.01	>100	>910
12g	2	Cl	H	H	2.849±0.07	>10	>3.5
12h	2	H	Cl	H	0.062±0.01	>100	>1600
12i	2	H	H	Cl	0.059±0.01	>100	>1600
12j	2	H	OMe	H	0.305±0.03	>10	>33





Compd	R^1	R^2	R^3	MAO-B (IC_{50}, μM)[a]	MAO-A (IC_{50}, μM)	SI[b]
8a	CF_3	H	H	2.023±0.20	>100	>49
8b	H	CF_3	H	1.108±0.17	>100	>90
8c	H	H	CF_3	0.642±0.09	>100	>150
8d	F	H	H	1.055±0.07	>100	>95
8e	H	F	H	1.550±0.05	>100	>65
8f	H	H	F	0.271±0.01	>100	>360
Clorgyline[c] (1)				>1	0.008±0.001	nd[e]
Selegiline[d] (2)				0.011±0.001	1.5±0.02	>130
Safinamide[d] (4)				0.017±0.002	>100	>5800
Sembragiline[d] (5)				0.016±0.001		nd[e]
15				>10	>10	nd[e]

Compd	R^1	R^2	R^3	MAO-B (IC_{50}, μM)[a]	MAO-A (IC_{50}, μM)	SI[b]
14a	H	CF_3	H	1.568±0.04	>10	>6.4
14b	H	H	CF_3	0.041±0.02	>10	>240
14c	F	H	H	>10	>10	nd[e]
14d	H	F	H	>10	>10	nd[e]
14e	H	H	F	6.806±0.09	>10	>1.5
14f	Cl	H	H	8.340±0.12	>10	>1.2
14g	H	Cl	H	2.110±0.07	>10	>4.7
14h	H	H	Cl	0.625±0.05	>10	>16
14i	H	OMe	H	5.003±0.23	>10	>1.9
14j	H	H	OMe	5.757±0.19	>10	>1.7

[a]Inhibition data are reported as IC_{50} (μM) ± SEM.
[b]SI = selectivity index, the selectivity for the MAO-B isoform and is given as the ratio of IC_{50}(MAO-A)/IC_{50}(MAO-B).
[c]Positive controls (MAO-A inhibitor); clorgyline: irreversible inhibitor
[d]Positive controls (MAO-B inhibitor); selegiline: irreversible inhibitor, (*S*)-safinamide & sembragiline: reversible inhibitor.
[e]nd: not determined
.

2.4. Mode of MAO-B inhibition of 12c

To examine the interaction mode of MAO-B inhibition, the most potent compound **12c** was evaluated in substrate-dependent kinetic experiments, and both the corresponding progression curves and the Linewever-Burk plots were generated. The initial rates of the MAO-B-catalyzed oxidation of benzylamine at seven different substrate concentrations in the absence and in the presence of three different concentrations of **12c** were measured. The results are depicted in **Fig. 4**. The Lineweaver-Burk plots for different concentration of **12c** were linear and intersected at the *y*-axis. Using GraphPad Prism, the maximal velocity (V_{max}), the Michaelis constant (K_m) and the inhibition constant (K_i) were calculated (V_{max} = 5.864e^{+7}, K_m = 4.093^{-4} and Ki = 6.88e^{-9}). These results indicate that **12c** is a competitive MAO-B inhibitor. (**Fig. 4**)

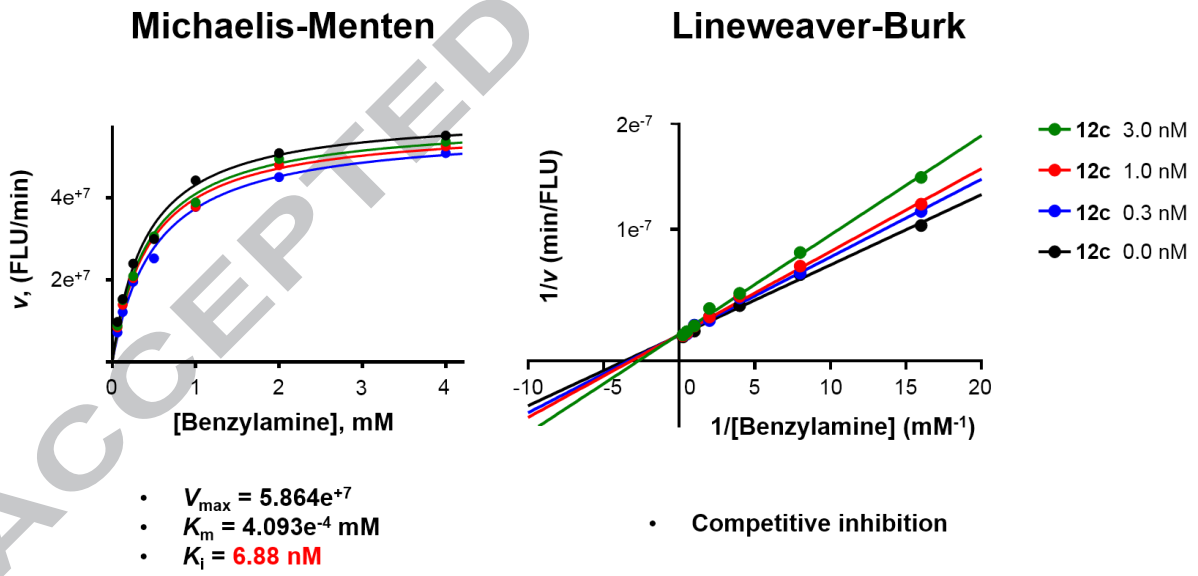


Fig. 4. Mode of **12c** with the binding site of MAO-B. The catalytic rates were measured at different concentrations of benzylamine (0.065, 0.125, 0.25, 0.5, 1, 2 and 4 mM) in the absence and in the presence of different concentrations (0.3, 1 and 3 nM) of **12c**. In the Lineweaver-Burk plot, the reciprocal MAO-B inhibitory activity was plotted against the reciprocal substrate concentration. The maximal velocity (V_{max}), the Michaelis constant (K_m) and the inhibition constant (K_i) were calculated

(V_{max} = 5.864e^{+7}, K_m = 4.093^{-4} and Ki = 6.88e^{-9}) using Sigma plot®.

2.5. Alleviative effect of compound 12c in MPTP-induced motor impairment

To verify *in vivo* efficacy of the compound **12c** as a MAO-B inhibitor, we conducted an animal model for Parkinson's disease generated by MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, administration. The dyskinesia in Parkinson's disease occurs when MPP^+, 1-methyl-4-phenylpyridinium, is converted by MAO-B in glia cells, cause the death of dopamine(DA)ergic neurons in substantia nigra pars compacta (SNpc). We conducted treatment of compound **12c** (30 mg/kg, *p.o.* injection) for 3 consecutive days including before and after MPTP administration (4 injections of MPTP, 2 h intervals; 20 mg/kg, *i.p.* injection), and assessed whether treatment can restore motor ability (**Fig. 5A**). Commonly, transient weight loss is observed in the acute injection method of MPTP.[25] As shown in **Fig. 5B**, MPTP-treated mice showed weight loss compared to saline-treated control mice. In the case of treatment with compound **12c**, the weight loss was restored more rapidly. In coat-hanger experiment, MPTP-induced mouse showed a falling or slipping to the first hanging position on the base of coat hanger (score 2.0 ± 0.58). In contrast to the vehicle-treated control mouse climbing to the top of the central vertical handle (score 4.75 ± 0.25). In comparison, the compound **12c** oral administrated mice recovered ascending ability to reach a stable position (score 3.83 ± 0.40) (**Fig. 5C**). Similarly, we found that mice treated with compound **12c** though a vertical grid test showed significant improvement in motor impairment by measuring the total time spent on the test, the time of rotation at the top of the grid and time to go down (**Fig. 5D**). These results indicate that oral administration of compound **12c** can inhibit MAO-B activity in the brain and alleviates the MPTP-induced motor dysfunction.

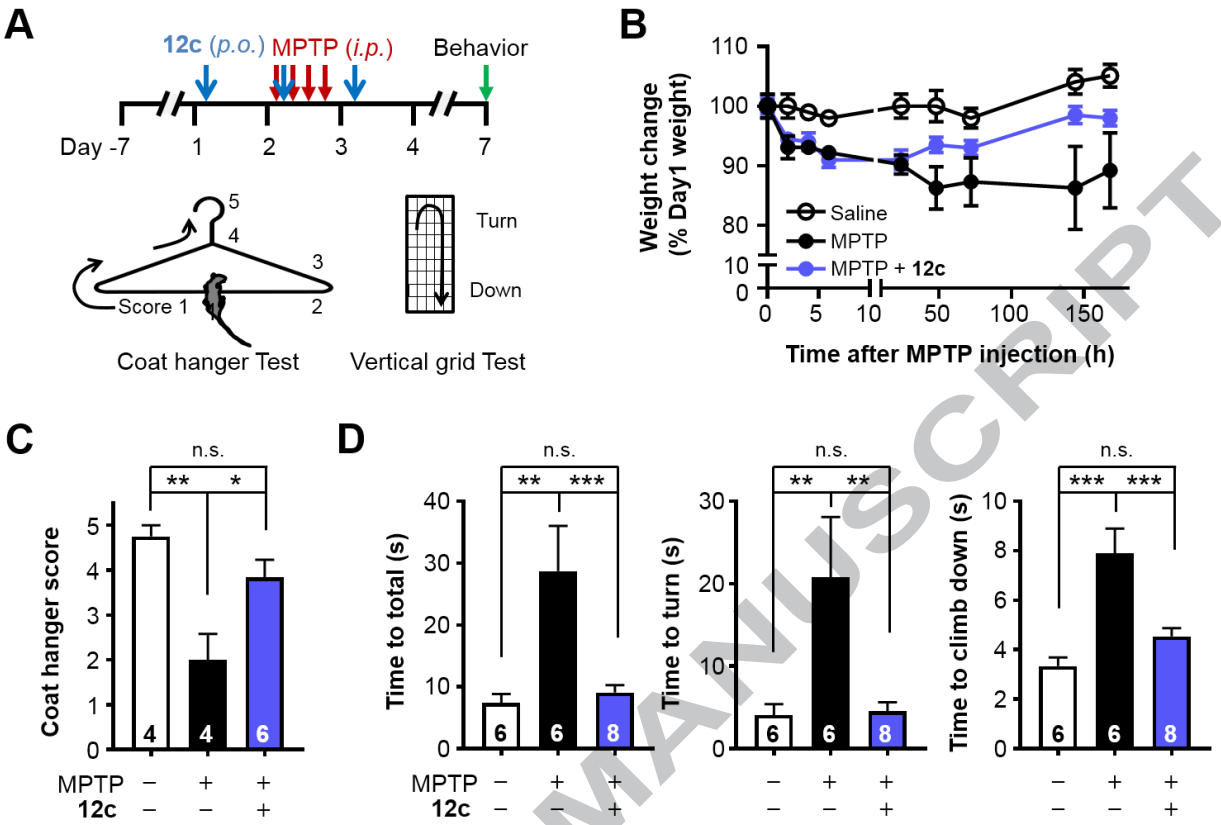


Fig. 5. Alleviation in MPTP-induced motor impairment by **12c** oral treatment A) The experimental protocol of MPTP treatment (20 mg/kg, *i.p.*) with or without **12c** compound (30 mg/kg, *p.o.*). Score diagram in coat hanger test and schematic diagram of vertical grid test. B) Weight change curve over time by MPTP treatment. C) Coat hanger score (F = 9.094, p = 0.005), D) Total time taken in vertical grid test (left, F = 10.87, $p < 0.001$), time to turn at the top of the grid (middle, F = 7.384, p = 0.003) and time to climb down (right, F = 15.55, $P < 0.001$). ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, and n.s., not significant (One-way ANOVA with *Tukey's* test), *n* refers to the number of mice. Data are means±s.e.m.

2.6. Protection against reduction of MPTP-induced tyrosine hydroxylase (TH)-positive dopamine neurons by oral treatment of compound 12c

To determine whether the recovery of motor ability by compound **12c** was due to the protection of

DAergic neurons, we measured the amount of tyrosine hydroxylase (TH) by immunohistochemistry (**Fig. 6A**). TH is an enzyme involved in the synthesis of dopamine in DAergic neurons of SNpc. Thus, TH-positive neurons are considered markers of DAergic neurons. The number of TH-positive DAergic neurons in SNpc was significantly reduced by MPTP, whereas the number of TH-positive DAergic neurons in compound **12c**-treated group was reduced by only 38%. Moreover, although a sharp decrease in TH-immunoreactive fiber density was observed in striatum of MPTP treated mice (7% compared to vehicle-treated mice by density measurement analysis), the decrease was also prevented in mice administered with compound **12c** (**Fig. 6B**).

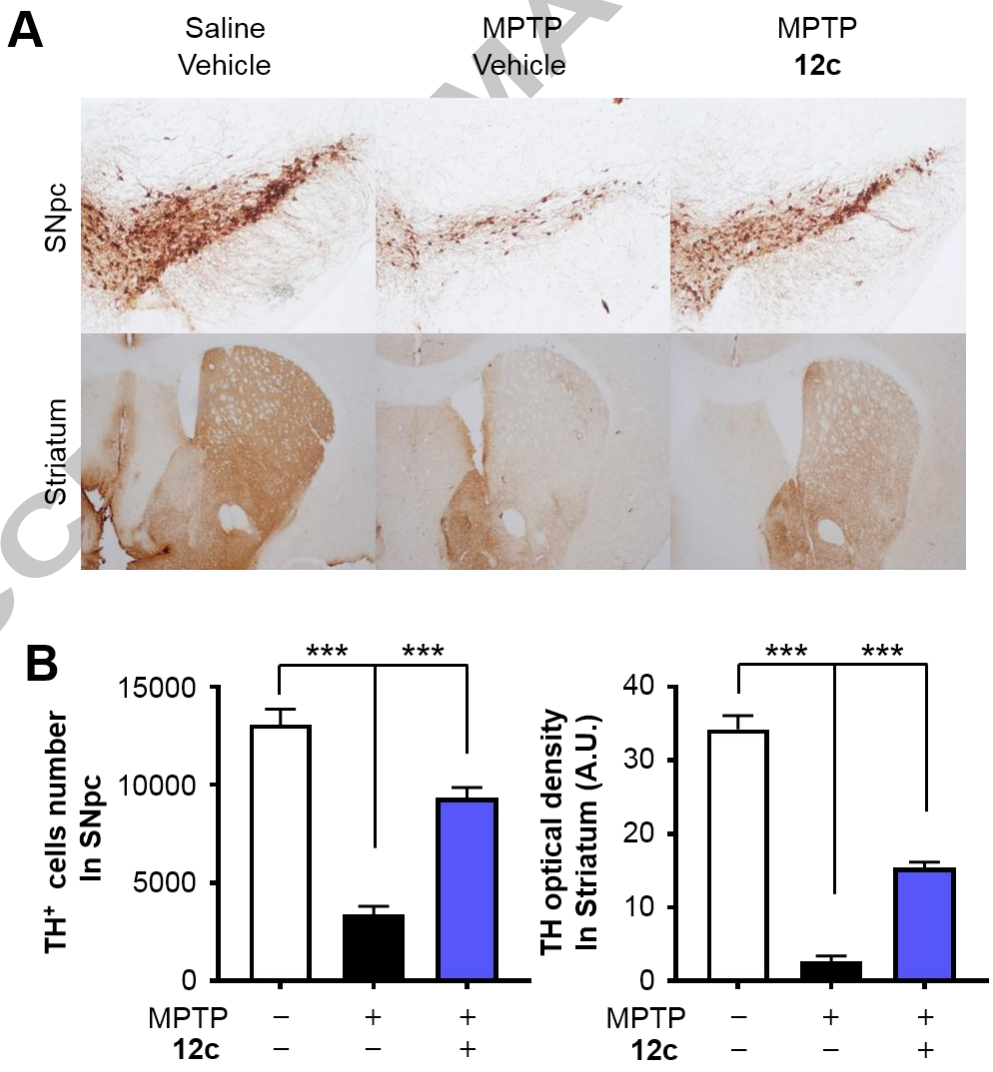


Fig. 6. Protection in MPTP-induced Tyrosine hydroxylase (TH) positive cell reduction by **12c** oral treatment A) Representative images of immunostaining was conducted with TH on SNpc (substantia nigra pars compacta) and striatum sections. B) Left, TH-immuno-positive cells in SNpc were counted (F = 63.31, p < 0.001), right, The TH-immuno-positive fibers in the striatum were quantitated by optical density (F = 196, p < 0.001). ***p < 0.001 (One-way ANOVA with *Tukey's* test). Data are means±s.e.m.

Conclusion

In this study, we synthesized a series of 4-(benzyloxy)phenyl and biphenyl-4-yl derivatives by modifying the benzyloxyphenyl moiety, a common structure of potent, selective, and reversible MAO-B inhibitors such as safinamide and sembragiline. Significant activity was observed for many of these compounds. Comparison of CF_3 substituted aryl regioisomers (2', 3', and 4') on the terminal aryl ring demonstrated that 4'-CF_3 derivatives exhibited the most potent inhibitory activity against MAO-B. The compound with the highest potency (**12c**) significantly protected the tyrosine hydroxylase (TH)-immunopositive DAergic neurons and attenuated the PD-associated behavioral deficits in the MPTP-induced mouse model of PD. In conclusion, we present a potent and selective MAO-B inhibitor with structural features that can be a good starting point for development of therapeutic agents for PD.

Experimental Section

General Methods. NMR spectra were obtained at either 400 MHz (^{1}H) and 100 MHz (^{13}C) or 300 MHz(^{1}H) and 75 MHz (^{13}C) using TMS as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS). Reactions were monitored by analytical thin-layer chromatography (TLC) plates (Merck, Cat # 1.05715) and analyzed with 254 nm light. The reactions were purified by column chromatography using silica gel (Merck, Cat # 1.07734& 1.09385). All chemicals and solvents were reagent grade and used as obtained from commercial sources without further purification. Yields reported are for purified products and were not optimized. Compounds were checked by ^{1}H and ^{13}C NMR.

General procedure for the preparation of (4-(benzyloxy)phenyl)methanaminium chloride derivatives (Method A). To a THF (400 mL) solution of $LiAlH_4$ (3.0 equiv) was added a THF (30 mL) solution of the 4-(benzyloxy)benzonitrile derivative dropwise at 0 °C. The reaction mixture was stirred at room temperature (16 h). Distilled water (4 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (2 mL, 15% w/w), then distilled water (4 mL) again. The product mixture was stirred at room temperature (1-2 h) for quenching the reaction, and was filtered through celite. The filtered solution was concentrated in vacuo. The product residue was dissolved in CH_2Cl_2, and 4.0M HCl in dioxane was added dropwise for salt formation. The product mixture was evaporated in vacuo and washed with EtOAc and *n*-hexane.

General procedure for the preparation of 4-(benzyloxy)benzamide derivatives (Method B). To a 4-(benzyloxy)benzonitrile derivative dissolved in *tert*-butanol was added potassium hydroxide and reflux for 2 h. After the reaction is completed, product mixture is extracted with EtOAc and brine

(200 mL x 3). Organic layer is dried with sodium sulfate. The residue is recrystallized.

General procedure for the preparation of 4-(benzyloxy)benzenaminium chloride (Method C). To a 1-(benzyloxy)-4-nitrobenzene derivative dissolved in MeOH was added Platinum (II) oxide. The reaction mixture was stirred for 1-2 h under H_2 gas at room temperature. The product mixture was filtered through celite and evaporated in vacuo. To a product residue dissolved in EtOAc was added 4.0M HCl in dioxane for salt formation. The product is washed with MeOH and ether.

General procedure for the preparation of 2-(4-(benzyloxy)phenyl)ethan-1-aminium chloride (Method D). To a *tert*-butyl (4-(benzyloxy)phenethyl)carbamate derivative dissolved in CH_2Cl_2 was added 4.0M HCl in dioxane and stirred for overnight at room temperature. After the reaction, the product mixture was evaporated in vacuo and washed with EtOAc and *n*-hexane.

General Procedure for the preparation of 2-([1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride derivatives (Method E). A mixture of *N*-boc-2-(4-bromophenyl)ethylamine, the desired arylboronic acid (a-m) (1.2 equiv), tetrakis(triphenylphosphine)palladium(0) (0.04 equiv), Na_2CO_3 (5 equiv) in degassed toluene/H_2O (5/2) was refluxed for 18 h. The reaction mixture was filtered through celite and concentrated in vacuo. The resulting residue was dissolved in in EtOAc (200 mL), washed with H_2O (200 mL× 2) and brine (200 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on SiO_2.

Preparation of (4-(benzyloxy)phenyl)methanaminium chloride (7a). Using Method A, **6a** (0.50 g,

2.4 mmol), $LiAlH_4$ (0.27 g, 7.2 mmol), and NaOH (0.2 mL) gave **7a** as a white solid (0.60 g, 100%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.91 (s, C**H**$_2$NH$_3$), 5.13 (s, OC**H**$_2$), 7.03 (d, J = 8.6 Hz, 2 Ar**H**), 7.29-7.35 (m, 1 Ar**H**), 7.36-7.41 (m, 3 Ar**H**), 7.41-7.46 (m, 3 Ar**H**), 8.40 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 41.5 (**C**H$_2$NH$_2$), 69.2 (O**C**H$_2$), 114.8, 126.3, 127.7, 128.4, 130.5, 130.7, 137.0 (11 Ar**C**), 158.3 (1 Ar**C**).

Preparation of (4-((2-(trifluoromethyl)benzyl)oxy)phenyl)methanaminium chloride (7b). Using Method A, **6b** (1.50 g, 5.4 mmol), $LiAlH_4$ (0.62 g, 16.2 mmol), and NaOH (0.6 mL) gave **7b** as a white solid (0.52 g, 34%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.95 (s, C**H**$_2$NH$_3$), 5.25 (s, OC**H**$_2$), 7.05 (d, J = 8.6 Hz, 2 Ar**H**), 7.42 (d, J = 8.6 Hz, 2 Ar**H**), 7.57-7.62 (m, 1 Ar**H**), 7.69-7.78 (m, 2 Ar**H**), 7.78-7.83 (m, 1 Ar**H**), 8.24 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 41.6 (**C**H$_2$NH$_2$), 66.3 (O**C**H$_2$), 114.7, 124.3 (**C**F$_3$, q, $J_{C\text{-}F}$ = 275.5 Hz), 126.2, 126.9 (q, $J_{C\text{-}F}$ = 31.7 Hz), 128.8, 130.5, 130.7, 132.8, 134.8 (11 Ar**C**), 158.1 (1 Ar**C**).

Preparation of (4-((3-(trifluoromethyl)benzyl)oxy)phenyl)methanaminium chloride (7c). Using Method A, **6c** (0.50 g, 1.8 mmol), $LiAlH_4$ (0.20 g, 5.4 mmol), and NaOH (0.2 mL) gave **7c** as a white solid (0.20 g, 40%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.94 (s, C**H**$_2$NH$_3$), 5.24 (s, OC**H**$_2$), 7.07 (d, J = 8.7 Hz, 2 Ar**H**), 7.40 (d, J = 8.6 Hz, 2 Ar**H**), 7.61-7.67 (m, 1 Ar**H**), 7.68-7.73 (m, 1 Ar**H**), 7.74-7.78 (m, 1 Ar**H**), 7.80-7.82 (m, 1 Ar**H**), 8.13 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 41.6 (**C**H$_2$NH$_2$), 68.3 (O**C**H$_2$), 114.8, 124.0, 124.2 (**C**F$_3$, q, $J_{C\text{-}F}$ = 270.5 Hz), 124.6, 126.5, 129.2 (q, $J_{C\text{-}F}$ = 31.3 Hz), 129.6, 130.6, 131.6, 138.6 (11 Ar**C**), 158.1 (1 Ar**C**).

Preparation of (4-((4-(trifluoromethyl)benzyl)oxy)phenyl)methanaminium chloride (7d). Using

Method A, **6d** (0.3 g, 1.1 mmol), $LiAlH_4$ (0.12 g, 3.2 mmol), and NaOH (0.12 mL) gave **7d** as a white solid (0.18 g, 59%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.93 (s, C**H**$_2$NH$_3$), 5.26 (s, OC**H**$_2$), 7.06 (d, J = 8.5 Hz, 2 Ar**H**), 7.41 (d, J = 8.5 Hz, 2 Ar**H**), 7.63-7.79 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 41.5 (**C**H$_2$NH$_2$), 68.2 (O**C**H$_2$), 114.8, 124.2 (**C**F$_3$, q, $J_{C\text{-}F}$ = 271.6 Hz), 125.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 126.5, 127.9, 128.3 (q, $J_{C\text{-}F}$ = 31.5 Hz), 130.6, 141.9 (11 Ar**C**), 158.0 (1 Ar**C**).

Preparation of (4-((2-fluorobenzyl)oxy)phenyl)methanaminium chloride (7e). Using Method A, **6e** (0.50 g, 2.2 mmol), $LiAlH_4$ (0.25 g, 6.6 mmol), and NaOH (0.2 mL) gave **7e** as a white crystalline (0.08 g, 16%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.92 (s, C**H**$_2$NH$_3$), 5.15 (s, OC**H**$_2$), 7.05 (d, J = 8.5 Hz, 2 Ar**H**), 7.20-7.30 (m, 2 Ar**H**), 7.38-7.46 (m, 3 Ar**H**), 7.55 (t, J = 7.6 Hz, 1 Ar**H**), 8.40 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 41.6 (**C**H$_2$NH$_2$), 63.6 (O**C**H$_2$), 114.7, 115.4 (d, $J_{C\text{-}F}$ = 20.7 Hz), 123.7 (d, $J_{C\text{-}F}$ = 14.3 Hz), 124.5, 126.7, 130.4, 130.5, 130.6, 130.7 (10 Ar**C**), 158.2 (1 Ar**C**), 160.4 (1 Ar**C**, d, $J_{C\text{-}F}$ = 244.7 Hz).

Preparation of (4-((3-fluorobenzyl)oxy)phenyl)methanaminium chloride (7f). Using Method A, **6f** (3.00 g, 13.2 mmol), $LiAlH_4$ (1.50 g, 39.6 mmol), and NaOH (2.4 mL) gave **7f** as a white solid (2.70 g, 89%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.92 (s, C**H**$_2$NH$_3$), 5.16 (s, OC**H**$_2$), 7.01-7.07 (m, 2 Ar**H**), 7.11-7.19 (m, 1 Ar**H**), 7.24-7.30 (m, 2 Ar**H**), 7.37-7.47 (m, 3 Ar**H**), 8.13 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.6 (**C**H$_2$NH$_2$), 68.3 (O**C**H$_2$), 114.1 (d, $J_{C\text{-}F}$ = 21.7 Hz), 114.3, 114.5, 114.6, 123.3, 123.4, 128.3, 130.4 (d, $J_{C\text{-}F}$ = 8.2 Hz), 140.2 (10 Ar**C**), 156.8 (1 Ar**C**), 162.2 (1 Ar**C**, d, $J_{C\text{-}F}$ = 244.7 Hz).

Preparation of (4-((4-fluorobenzyl)oxy)phenyl)methanaminium chloride (7g). Using Method A, **6g** (1.00 g, 4.4 mmol), $LiAlH_4$ (0.50 g, 13.2 mmol), and NaOH (0.40 mL) gave **7g** as a white solid (1.0 g, 97%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.92 (s, C**H**$_2$NH$_3$), 5.11 (s, OC**H**$_2$), 7.00-7.09 (m, 2 Ar**H**), 7.16-7.29 (m, 2 Ar**H**), 7.50-7.65 (m, 4 Ar**H**), 8.45 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 45.0 (**C**H$_2$NH$_2$), 68.4 (O**C**H$_2$), 114.5, 115.2 (d, $J_{C\text{-}F}$ = 21.2 Hz), 128.2, 129.8 (d, $J_{C\text{-}F}$ = 8.2 Hz), 133.5, 136.5, 156.8 (11 Ar**C**), 161.7 (1 Ar**C**, d, $J_{C\text{-}F}$ = 242.0 Hz).

Preparation of (4-((3-chlorobenzyl)oxy)phenyl)methanaminium chloride (7h). Using Method A, **6h** (0.40 g, 1.6 mmol), $LiAlH_4$ (0.19 g, 4.9 mmol), and NaOH (0.16 mL) gave **7h** as a white solid (0.20 g, 50%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.94 (s, C**H**$_2$NH$_3$), 5.26 (s, OC**H**$_2$), 7.03-7.10 (m, 2 Ar**H**), 7.36-7.43 (m, 2 Ar**H**), 7.62-7.80 (m, 4 Ar**H**), 8.15 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 42.1 (**C**H$_2$NH$_2$), 68.8 (O**C**H$_2$), 115.3, 125.8, 125.8, 126.5, 127.0, 128.2, 128.4, 128.6, 129.0, 129.4, 131.1, 142.4, 158.5 (12 Ar**C**).

Preparation of (4-((4-chlorobenzyl)oxy)phenyl)methanaminium chloride (7i). Using Method A, **6i** (0.40 g, 1.6 mmol), $LiAlH_4$ (0.19 g, 4.9 mmol), and NaOH (0.16 mL) gave **7i** as a white solid (0.16 g, 39%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.93 (s, C**H**$_2$NH$_3$), 5.14 (s, OC**H**$_2$), 7.01-7.07 (m, 2 Ar**H**), 7.36-7.42 (m, 2 Ar**H**), 7.44-7.49 (m, 4 Ar**H**), 8.20 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 42.1 (**C**H$_2$NH$_2$), 68.8 (O**C**H$_2$), 115.3, 126.9, 128.9, 129.9, 131.0, 132.8, 136.5, 158.6 (12 Ar**C**).

Preparation of (4-((3-methoxybenzyl)oxy)phenyl)methanaminium chloride (7j). Using Method A, **6j** (1.00 g, 4.2 mmol), $LiAlH_4$ (0.48 g, 12.5 mmol), and NaOH (0.4 mL) gave **7j** as a white solid

(0.37 g 37%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.75 (s, OC**H**$_3$), 3.92 (s, C**H**$_2$NH$_3$), 5.10 (s, OC**H**$_2$), 6.85-6.91 (m, 1 Ar**H**), 6.97-7.06 (m, 4 Ar**H**), 7.26-7.33 (m, 1 Ar**H**), 7.38-7.44 (m, 2 Ar**H**), 8.35 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 42.0 (**C**H$_2$NH$_2$), 55.1 (O**C**H$_3$), 69.0 (O**C**H$_2$), 113.1, 113.2, 114.6, 114.8, 119.7, 127.3, 128.3, 129.6, 130.4, 138.6, 158.2, 159.4 (12 Ar**C**).

Preparation of (4-((4-methoxybenzyl)oxy)phenyl)methanaminium chloride (7k). Using Method A, **6k** (0.30 g, 1.3 mmol), $LiAlH_4$ (0.14 g, 3.8 mmol), and NaOH (0.12 mL) gave **7k** as a white solid (0.25 g, 71%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.75 (s, OC**H**$_3$), 3.93 (s, C**H**$_2$NH$_3$), 5.09 (s, OC**H**$_2$), 6.90-7.06 (m, 4 Ar**H**), 7.32-7.43 (m, 4 Ar**H**), 8.26 ((s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 42.1 (**C**H$_2$NH$_2$), 55.6 (O**C**H$_3$), 69.4 (O**C**H$_2$), 114.3, 115.3, 126.5, 129.3, 129.9, 131.0, 159.5, 162.3 (12 Ar**C**).

Preparation of 4-((2-(trifluoromethyl)benzyl)oxy)benzamide (8a). Using Method B, **6b** (0.50 g, 1.8 mmol) and potassium hydroxide (0.76 g, 13.5 mmol) gave **8a** as a baige solid (0.47 g, 89%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.33 (s, OC**H**$_2$), 6.98-7.05 (m, 2 Ar**H**), 7.41-7.48 (m, 1 Ar**H**), 7.55-7.61 (m, 1 Ar**H**), 7.69-7.75 (m, 2 Ar**H**), 7.77-7.83 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 66.8 (O**C**H$_2$), 114.6, 120.7, 124.8 (**C**F$_3$, q, $J_{C\text{-}F}$ = 272.2 Hz), 126.7 (q, $J_{C\text{-}F}$ = 5.7 Hz), 127.0, 127.5 (q, $J_{C\text{-}F}$ = 30.3 Hz), 127.6, 127.9, 128.9, 129.3, 129.9, 131.1, 133.3, 135.0 (11 Ar**C**), 160.8 (1 Ar**C**), 167.8 (**C**(O)).

Preparation of 4-((3-(trifluoromethyl)benzyl)oxy)benzamide (8b). Using Method B, **6c** (0.20 g, 0.7 mmol) and potassium hydroxide (0.30 g, 5.4 mmol) gave **8b** as a white solid (0.19 g, 91%): R_f =

0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.28 (s, OC**H**$_2$), 7.06-7.14 (m, 2 Ar**H**), 7.16-7.27 (m, 1 Ar**H**), 7.62-7.70 (m, 1 Ar**H**), 7.70-7.76 (m, 1 Ar**H**), 7.77-7.82 (m, 1 Ar**H**), 7.82-7.93 (m, 2 Ar**H,** C(O)N**H**$_2$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 68.4 (O**C**H$_2$), 114.3, 124.1, 124.1, 124.2 (**C**F$_3$, q, $J_{C\text{-}F}$ = 270.7 Hz), 124.6, 127.0, 129.2 (q, $J_{C\text{-}F}$ = 29.2 Hz), 129.6, 131.7, 138.3 (11 Ar**C**), 160.4 (1 Ar**C**), 167.4 (**C**(O)).

Preparation of 4-((4-(trifluoromethyl)benzyl)oxy)benzamide (8c). Using Method B, **6d** (0.30 g, 1.1 mmol) and potassium hydroxide (0.45 g, 8.1 mmol) gave **8c** as a brown solid (0.29 g, 92%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.30 (s, OC**H**$_2$), 7.05-7.14 (m, 2 Ar**H**), 7.16-7.27 (m, 1 Ar**H**), 7.66-7.74 (m, 2 Ar**H**), 7.76-7.82 (m, 2 Ar**H**), 7.82-7.90 (m, 1 Ar**H,** C(O)N**H**$_2$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 68.9 (O**C**H$_2$), 114.7, 124.7 (**C**F$_3$, q, $J_{C\text{-}F}$ = 272.0 Hz), 125.8, 125.8, 127.4, 128.5, 128.9 (q, $J_{C\text{-}F}$ = 31.6 Hz), 129.9, 142.1 (11 Ar**C**), 160.8 (1 Ar**C**), 167.8 (**C**(O)).

Preparation of 4-((2-fluorobenzyl)oxy)benzamide (8d). Using Method B, **6e** (0.50 g, 2.2 mmol) and potassium hydroxide (0.93 g, 16.5 mmol) gave **8d** as a brown powder (0.50 g, 93%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.20 (s, OC**H**$_2$), 7.06-7.11 (m, 2 Ar**H**), 7.18-7.30 (m, 3 Ar**H**), 7.40-7.48 (m, 1 Ar**H**), 7.55-7.61 (m, C(O)N**H**H), 7.83-7.89 (m, 2Ar**H**, C(O)NH**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 63.6 (O**C**H$_2$), 114.1, 115.4 (d, $J_{C\text{-}F}$ = 20.8 Hz), 123.4, 123.6, 124.5, 124.6, 126.9, 129.4, 130.5 (d, $J_{C\text{-}F}$ = 8.3 Hz), 130.8, 130.8, 160.4 (d, $J_{C\text{-}F}$ = 244.9 Hz), 160.5 (12 Ar**C**), 167.3 (**C**(O)).

Preparation of 4-((3-fluorobenzyl)oxy)benzamide (8e). Using Method B, **6f** (2.0 g, 8.8 mmol) and

potassium hydroxide (3.70 g, 66.0 mmol) gave **8e** as a beige crystalline (1.89 g, 88%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.19 (s, OC**H**$_2$), 7.04-7.10 (m, 2 Ar**H**), 7.13-7.26 (m, 2 Ar**H**), 7.27-7.34 (m, 2 Ar**H**), 7.40-7.48 (m, 1 Ar**H**), 7.83-7.90 (m, 1 Ar**H,** C(O)N**H**$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 68.5 (O**C**H$_2$), 114.3, 114.4, 114.7 (d, $J_{C\text{-}F}$ = 20.8 Hz), 123.6, 126.9, 129.4, 130.5 (d, $J_{C\text{-}F}$ = 8.2 Hz), 139.7, 139.7, 160.4, 162.2 (d, $J_{C\text{-}F}$ = 242.2 Hz) (12 Ar**C**), 167.38 (**C**(O)).

Preparation of 4-((4-fluorobenzyl)oxy)benzamide (8f). Using Method B, **6g** (0.3 g, 1.3 mmol) and potassium hydroxide (0.56 g, 9.9 mmol) gave **8f** as a white crystalline (0.32 g, 98%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.14 (s, OC**H**$_2$), 7.02-7.08 (m, 2 Ar**H**), 7.15-7.26 (m, 3 Ar**H**), 7.47-7.55 (m, 2 Ar**H**), 7.80-7.87 (m, 1 Ar**H,** C(O)N**H**$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 69.0 (O**C**H$_2$), 114.7, 115.7 (d, $J_{C\text{-}F}$ = 21.2 Hz), 127.2, 129.8, 130.5 (d, $J_{C\text{-}F}$ = 8.2 Hz), 133.4, 161.0, 162.3 (d, $J_{C\text{-}F}$ = 242.3 Hz) (12 Ar**C**), 167.8 (**C**(O)).

Preparation of 4-((2-(trifluoromethyl)benzyl)oxy)benzenaminium chloride (10a). Using Method C, **9a** (0.20 g, 0.7 mmol), platinum oxide, (0.016 g, 0.7 mmol), and 4.0M hydrogen chloride gave **10a** as a white powder (0.11 g, 53%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.25 (s, OC**H**$_2$), 7.09-7.14 (m, 2 Ar**H**), 7.29-7.34 (m, 2 Ar**H**), 7.57-7.63 (m, 1 Ar**H**), 7.70-7.79 (m, 2 Ar**H**), 7.79-7.83 (m, 1 Ar**H**), 10.02 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 67.0 (O**C**H$_2$), 116.1, 124.7 (**C**F$_3$, q, $J_{C\text{-}F}$ = 272.1 Hz), 125.0, 125.4, 126.6, 126.7, 127.4 (q, $J_{C\text{-}F}$ = 30.3 Hz), 129.3, 131.1, 133.3, 135.0, 157.9 (12 Ar**C**).

Preparation of 4-((3-(trifluoromethyl)benzyl)oxy)benzenaminium chloride (10b). Using Method

C, **9b** (0.20 g, 0.7 mmol), platinum oxide, (0.016 g, 0.7 mmol), and 4.0M hydrogen chloride gave **10b** as a white powder (0.13 g, 63%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.24 (s, OC**H**$_2$), 7.12-7.17 (m, 2 Ar**H**), 7.30-7.36 (m, 2 Ar**H**), 7.62-7.84 (m, 4 Ar**H**), 10.13 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 68.6 (O**C**H$_2$), 115.8, 124.2 (**C**F$_3$, q, $J_{C\text{-}F}$ = 270.9 Hz), 124.1, 124.5, 124.6, 124.7, 129.2 (q, $J_{C\text{-}F}$ = 31.4 Hz), 129.6, 131.7, 138.3, 157.5 (12 Ar**C**).

Preparation of 4-((4-(trifluoromethyl)benzyl)oxy)benzenaminium chloride (10c). Using Method C, **9c** (0.20 g, 0.7 mmol), platinum oxide, (0.016 g, 0.7 mmol), and 4.0M hydrogen chloride gave **10c** as a white powder (0.15 g, 72%): R_f = 0.00 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.26 (s, OC**H**$_2$), 7.11-7.16 (m, 2 Ar**H**), 7.30-7.35 (m, 2 Ar**H**), 7.65-7.70 (m, 2 Ar**H**), 7.75-7.80 (m, 2 Ar**H**), 10.15 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 69.1 (O**C**H$_2$), 116.2, 124,7 (**C**F$_3$, q, $J_{C\text{-}F}$ = 270.5 Hz), 125.0, 125.3, 125.8 (q, $J_{C\text{-}F}$ = 3.8 Hz), 128.5, 128.8 (q, $J_{C\text{-}F}$ = 31.4 Hz), 142.1, 157.9 (12 Ar**C**).

Preparation of 4-((2-fluorobenzyl)oxy)benzenaminium chloride (10d). Using Method C, **9d** (0.15 g, 0.6 mmol), platinum oxide, (0.012 g, 0.06 mmol), and 4.0M hydrogen chloride gave **10d** as a white solid (0.04 g, 30%): R_f = 0.59 (5% CH_2Cl_2/MeOH): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.10 (s, OC**H**$_2$), 7.08-7.14 (m, 2 Ar**H**), 7.19-7.26 (m, 2 Ar**H**), 7.29-7.35 (m, 2 Ar**H**), 7.47-7.54 (m, 2 Ar**H**) 10.19 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 68.8 (O**C**H$_2$), 115.3 (d, $J_{C\text{-}F}$ = 21.3 Hz), 115.3, 115.5, 115.7, 115.7, 123.4, 123.6, 124.5, 124.6, 124.7, 130.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 130.5, 130.6, 130.7, 130.8, 133.0, 157.6, 157.6, 160.4 (d, $J_{C\text{-}F}$ = 245.0 Hz) (12 Ar**C**).

Preparation of 4-((3-fluorobenzyl)oxy)benzenaminium chloride (10e). Using Method C, **9e** (0.10

g, 0.4 mmol) and platinum oxide, (0.008 g, 0.04 mmol), and 4.0M hydrogen chloride gave **10e** as a white solid (0.38 g, 71%): R_f = 0.33 (EtOAc 1 : *n*-Hexane 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.15 (s, OC**H**$_2$), 7.09-7.20 (m, 3 Ar**H**), 7.26-7.34 (m, 4 Ar**H**), 7.41-7.48 (m, 1Ar**H**), 10.06 (s, N**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 68.6 (O**C**H$_2$), 114.2 (d, $J_{C\text{-}F}$ = 21.8 Hz), 114.7 (d, $J_{C\text{-}F}$ = 20.8 Hz), 115.7, 123.5, 123.5, 124.5, 124.7, 130.5 (d, $J_{C\text{-}F}$ = 8.3 Hz), 139.6, 139.7, 161.9, 162.2 (d, $J_{C\text{-}F}$ = 242.2 Hz) (12 Ar**C**).

Preparation of 4-((4-fluorobenzyl)oxy)benzenaminium chloride (10f). Using Method C, **9f** (0.10 g, 0.4 mmol), platinum oxide, (0.008 g, 0.04 mmol), and 4.0M hydrogen chloride gave **10f** as a white solid (0.04 g, 30%): R_f = 0.59 (5% CH_2Cl_2/MeOH): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.10 (s, OC**H**$_2$), 7.08-7.13 (m, 2 Ar**H**), 7.19-7.26 (m, 2 Ar**H**), 7.26-7.31 (m, 2Ar**H**), 7.47-7.53 (m, 2 Ar**H**), 9.93 (s, N**H**$_3$) ; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 68.8 (O**C**H$_2$), 115.3 (d, $J_{C\text{-}F}$ = 21.3 Hz), 115.7, 124.4, 124.6, 130.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 132.9, 157.6, 161.8 (d, $J_{C\text{-}F}$ = 242.4 Hz) (12 Ar**C**).

Preparation of 2-(4-((2-(trifluoromethyl)benzyl)oxy)phenyl)ethan-1-aminium chloride (12a). Using Method D, **11a** (0.50 g, 1.3 mmol) and 4.0M HCl in dioxane (2.3 g, 63.0 mmol) gave **12a** as a white cotton form (0.38 g, 90%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.77-2.84 (m, NH_3C**H$_2$**CH_2), 2.96-3.03 (m, NH_3CH_2C**H$_2$**), 5.20 (s, OC**H$_2$**), 6.98-7.04 (m, 2 Ar**H**), 7.18-7.23 (m, 2 Ar**H**), 7.62-7.83 (m, 4 Ar**H**), 7.86 (s, N**H**$_3$**);** ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.5 (NCH_2**C**CH_2), 66.6 (O**C**H$_2$), 115.3, 124.8 (**C**F$_3$, q, $J_{C\text{-}F}$ = 272.9 Hz), 126.5, 126.7, 127.3 (q, $J_{C\text{-}F}$ = 30.3 Hz), 129.2, 130.3, 130.5, 130.8, 133.3, 135.5, 157.3 (12 Ar**C**).

Preparation of 2-(4-((3-(trifluoromethyl)benzyl)oxy)phenyl)ethan-1-aminium chloride (12b). Using Method D, **11b** (0.50 g, 1.3 mmol) and 4.0M HCl in dioxane (2.3 g, 63.0 mmol) gave **12b** as a

white crystalline (0.35 g, 84%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.73-2.83 (m, $NH_3C\mathbf{H}_2CH_2$), 2.91-3.02 (m, $NH_3CH_2C\mathbf{H}_2$), 5.20 (s, $OC\mathbf{H}_2$), 6.90-7.02 (m, 2 Ar**H**), 7.13-7.21 (m, 2 Ar**H**), 7.60-7.82 (m, 4 Ar**H**), 7.86 (s, $N\mathbf{H}_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.2 ($N\mathbf{C}H_2\mathbf{C}H_2$), 68.4 ($O\mathbf{C}H_2$), 115.1, 124.0, 124.3 ($\mathbf{C}F_3$, q, $J_{C\text{-}F}$ = 270.5 Hz), 124.6, 129.3 (q, $J_{C\text{-}F}$ = 31.6 Hz), 129.7, 129.9, 131.7, 138.8, 157.0 (12 Ar**C**).

Preparation of 2-(4-((4-(trifluoromethyl)benzyl)oxy)phenyl)ethan-1-aminium chloride (12c). Using Method D, **11c** (0.50 g, 1.3 mmol) and 4.0M HCl in dioxane (2.3 g, 63.0 mmol) gave **12c** as a white cotton form (0.35 g, 84%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.75-2.83 (m, $NH_3C\mathbf{H}_2CH_2$), 2.93-3.01(m, $NH_3CH_2C\mathbf{H}_2$), 5.22 (s, $OC\mathbf{H}_2$), 6.93-7.01 (m, 2 Ar**H**), 7.14-7.21 (m, 2 Ar**H**), 7.61-7.69 (m, 2 Ar**H**), 7.73-7.79 (m, 2 Ar**H**), 7.90 (s, $N\mathbf{H}_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 32.5 ($N\mathbf{C}H_2\mathbf{C}H_2$), 68.7 ($O\mathbf{C}H_2$), 115.4, 120.6, 124.7 ($\mathbf{C}F_3$, q, $J_{C\text{-}F}$ = 270.4 Hz), 125.7, 125.8, 128.3, 128.4, 128.6, 128.8, 129.0 (q, $J_{C\text{-}F}$ = 31.5 Hz), 130.2, 130.3, 142.6, 157.3 (12 Ar**C**); HPLC purity: 10.6 min, > 98% at 254 & 280 nm; LRMS $(M + H)^+$ (ESI^+) 296.1 $[M + H]^+$ (calcd for $C_{16}H_{16}F_3NOH^+$ 296.1).

Preparation of 2-(4-((2-fluorobenzyl)oxy)phenyl)ethan-1-aminium chloride (12d). Using Method D, **11d** (0.90 g, 2.6 mmol) and 4.0M HCl in dioxane (3.91 mL, 15.6 mmol) gave **12d** as a white solid (0.73 g, 99%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.84-3.00 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 5.12 (s, $OC\mathbf{H_2}$), 7.00 (d, J = 8.5 Hz, 2 Ar**H**), 7.53-7.57 (m, 6 Ar**H**), 8.24 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.5 ($N\mathbf{C}H_2\mathbf{C}H_2$), 64.0 ($O\mathbf{C}H_2$), 115.3, 115.8 (d, $J_{C\text{-}F}$ = 21.0 Hz), 124.4 (d, $J_{C\text{-}F}$ = 14.5 Hz), 125.0 (d, $J_{C\text{-}F}$ = 3.4 Hz), 130.2. 130.3, 130.8 (d, $J_{C\text{-}F}$ = 8.2 Hz), 131.1 (d, $J_{C\text{-}F}$ = 4.0 Hz), 157.5, 160.8 (d, $J_{C\text{-}F}$ = 244.5 Hz) (12 Ar**C**).

Preparation of 2-(4-((3-fluorobenzyl)oxy)phenyl)ethan-1-aminium chloride (12e). Using Method D, **11e** (0.20 g, 0.6 mmol) and 4.0M HCl in dioxane (1.01 mL, 29.0 mmol) gave **12e** as a white powder (0.16 g, 100%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.77-3.02 (m, $NH_3C\mathbf{H}_2C\mathbf{H}_2$), 5.12 (s, $OC\mathbf{H}_2$), 6.89-7.01 (m, 2 Ar**H**), 7.07-7.22 (m, 3 Ar**H**), 7.23-7.31 (m, 2 Ar**H**), 7.38-7.49 (m, 1 Ar**H**), 8.04 (s, $N\mathbf{H}_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.1 ($N\mathbf{C}H_2\mathbf{C}H_2$), 68.3 ($O\mathbf{C}H_2$), 114.1 (d, $J_{C\text{-}F}$ = 21.7 Hz), 114.5 (d, $J_{C\text{-}F}$ = 20.7 Hz), 114.9, 123.4, 129.7, 130.5 (d, $J_{C\text{-}F}$ = 8.2 Hz), 140.1, 140.2, 156.9, 162.2 (d, $J_{C\text{-}F}$ = 242.0 Hz) (12 Ar**C**).

Preparation of 2-(4-((4-fluorobenzyl)oxy)phenyl)ethan-1-aminium chloride (12f). Using Method D, **11f** (0.50 g, 1.5 mmol) and 4.0M HCl in dioxane (2.50 mL, 72.4 mmol) gave **12f** as a white cotton form (0.40 g, 98%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.80-3.01 (m, $NH_3C\mathbf{H}_2C\mathbf{H}_2$), 5.06 (s, $OC\mathbf{H}_2$), 6.90-7.00 (m, 2 Ar**H**), 7.10-7.30 (m, 4 Ar**H**), 7.44-7.55 (m, 2 Ar**H**), 8.22 (s, $N\mathbf{H}_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.5 ($NH\mathbf{C}H_2\mathbf{C}H_2$), 68.9 ($O\mathbf{C}H_2$), 115.4, 115.7 (d, $J_{C\text{-}F}$ = 21.2 Hz), 130.1, 130.2, 130.3 (d, $J_{C\text{-}F}$ = 8.2 Hz), 133.8, 133.9, 157.5, 162.2 (d, $J_{C\text{-}F}$ = 241.8 Hz) (12 Ar**C**).

Preparation of 2-(4-((2-chlorobenzyl)oxy)phenyl)ethan-1-aminium chloride (12g). Using Method D, **11g** (1.15 g, 3.2 mmol) and 4.0M HCl in dioxane (4.77 mL, 19.1 mmol) gave **12g** as a white solid (0.95 g, 99%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.85-3.00 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 5.14 (s, $OC\mathbf{H_2}$), 7.00 (d, J = 8.3 Hz, 2 Ar**H**), 7.21 (d, J = 8.2 Hz, 2 Ar**H**), 7.38-7.40 (m, 2 Ar**H**), 7.50-7.60 (m, 2 Ar**H**), 8.26 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.5 ($N\mathbf{C}H_2\mathbf{C}H_2$), 67.3 ($O\mathbf{C}H_2$), 115.3, 127.8, 128.9, 129.8, 130.2, 130.3, 130.4, 130.5, 133.0, 134.8,

157.5 (12 Ar**C**).

Preparation of 2-(4-((3-chlorobenzyl)oxy)phenyl)ethan-1-aminium chloride (12h). Using Method D, **11h** (0.50 g, 1.4 mmol) and 4.0M HCl in dioxane (2.4 mL, 69.1 mmol) gave **12h** as a white powder (0.39 g, 95%): R_f = 0.25 (15% CH_2Cl_2/MeOH): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.79-3.01 (m, $NH_3C\mathbf{H}_2C\mathbf{H}_2$), 5.11 (s, $OC\mathbf{H}_2$), 6.93-7.00 (m, 2 Ar**H**), 7.15-7.23 (m, 2 Ar**H**), 7.33-7.48 (m, 3 Ar**H**), 7.49-7.54 (m, 1 Ar**H**), 8.17 (s, $N\mathbf{H}_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.5 ($NH\mathbf{C}H_2\mathbf{C}H_2$), 68.7 ($O\mathbf{C}H_2$), 115.4, 126.5, 127.6, 128.1, 130.2, 130.3, 130.8, 133.6, 140.3, 157.4 (12 Ar**C**).

Preparation of 2-(4-((4-chlorobenzyl)oxy)phenyl)ethan-1-aminium chloride (12i). Using Method D, **11i** (0.50 g, 1.4 mmol) and 4.0M HCl in dioxane (2.4 mL, 69.1 mmol) gave **12i** as a white powder (0.39 g, 94%): R_f = 0.25 (15% CH_2Cl_2/MeOH): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.80-3.00 (m, $NH_3C\mathbf{H}_2C\mathbf{H}_2$), 5.08 (s, $OC\mathbf{H}_2$), 6.93-6.99 (m, 2 Ar**H**), 7.15-7.21 (m, 2 Ar**H**), 7.42-7.50 (m, 4 Ar**H**), 8.18 (s, $N\mathbf{H}_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.0 ($NH\mathbf{C}H_2\mathbf{C}H_2$), 68.3 ($O\mathbf{C}H_2$), 114.9, 128.4, 129.4, 129.7, 132.3, 136.2, 156.9, 161.8 (12 Ar**C**).

Preparation of 2-(4-((3-methoxybenzyl)oxy)phenyl)ethan-1-aminium chloride (12j). Using Method D, **11j** (1.20 g, 3.4 mmol) and 4.0M HCl in dioxane (5.04 mL, 20.2 mmol) gave **12j** as a white solid (0.92 g, 93%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.81-2.96 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 3.75 ($OC\mathbf{H_3}$), 5.06 (s, $OC\mathbf{H_2}$), 6.87-7.01 (m, 5 Ar**H**), 7.16-7.19 (m, 2 Ar**H**), 7.27-7.33 (m, 1 Ar**H**), 8.16 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.1 ($N\mathbf{C}H_2\mathbf{C}H_2$), 55.0 ($O\mathbf{C}H_3$), 69.0 ($O\mathbf{C}H_2$), 113.1, 114.9, 119.6, 129.5, 129.7, 138.7, 157.1, 159.3 (12 Ar**C**).

Preparation of 2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14a). Using Method E, **13** (1.00 g, 3.3 mmol), 3-(trifluoromethyl)phenylboronic acid (0.76 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.1 mmol), Na_2CO_3 (1.77 g, 16.7 mmol) in toluene/H_2O (33 ml/13.3 ml), followed by 4.0 M HCl in dioxane (2.50 ml, 10.0 mmol) gave **14a** as a white solid (0.57 g, 56%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.98-3.10 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 7.42 (d, J = 8.2 Hz, 2 Ar**H**), 7.69-7.74 (m, 4 Ar**H**), 7.95-8.00 (m, 2 Ar**H**), 8.31 (s, N$\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.0 (N$\mathbf{C}H_2\mathbf{C}H_2$), 123.4 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.4 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.7 (**C**F_3, q, $J_{C\text{-}F}$ = 270.9 Hz), 127.6, 129.9, 130.2 (q, $J_{C\text{-}F}$ = 31.4 Hz), 130.5, 131.1, 137.4, 138.1, 141.4 (12 Ar**C**).

Preparation of 2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14b). Using Method E, **13** (0.50 g, 1.7 mmol), 4-(trifluoromethyl)phenylboronic acid (0.38 g, 2.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.08 g, 0.1 mmol), Na_2CO_3 (0.89 g, 8.3 mmol) in toluene/H_2O (16 ml/6.6 ml), followed by 4.0 M HCl in dioxane (1.25 ml, 5.0 mmol) gave **14b** as a white solid (0.28 g, 56%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.01-3.11 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 7.44 (d, J = 8.1 Hz, 2 Ar**H**), 7.71-7.91 (m, 6 Ar**H**), 8.37 (s, N$\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 33.0 (N$\mathbf{C}H_2\mathbf{C}H_2$), 124.8 (**C**$F_3$, q, $J_{C\text{-}F}$ = 270.1 Hz), 126.2 (q, $J_{C\text{-}F}$ = 3.8 Hz), 127.6, 127.7, 128.2 (q, $J_{C\text{-}F}$ = 31.7 Hz), 129.9, 137.4, 138.4, 144.3 (12 Ar**C**).

Preparation of 2-(2'-fluoro-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14c). Using Method E, **13** (1.00 g, 3.3 mmol), 2-fluorophenylboronic acid (0.56 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.1 mmol) and Na_2CO_3 (1.77 g, 16.7 mmol) in toluene/H_2O (33 ml/13.3 ml), followed by 4.0 M HCl in dioxane (2.50 ml, 10.0 mmol) gave **14c** as a white solid (0.36 g, 43%); R_f = 0.00 (EtOAc 9 : acetone 1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.89-

3.09 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 7.24-7.52 (m, 8 Ar**H**), 8.32 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.1 ($N\mathbf{C}H_2\mathbf{C}H_2$), 116.6 (d, $J_{C\text{-}F}$ = 22.4 Hz), 120.3, 125.4 (d, $J_{C\text{-}F}$ = 3.5 Hz), 129.4, 129.5, 129.9 (d, $J_{C\text{-}F}$ = 8.2 Hz), 131.1 (d, $J_{C\text{-}F}$ = 3.3 Hz), 131.5, 131.9, 137.5 (d, $J_{C\text{-}F}$ = 21.9 Hz), 159.6 (d, $J_{C\text{-}F}$ = 244.2 Hz) (12 Ar**C**).

Preparation of 2-(3'-fluoro-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14d). Using Method E, **13** (1.00 g, 3.3 mmol), 3-fluorophenylboronic acid (0.56 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.1 mmol), Na_2CO_3 (1.77 g, 16.7 mmol) in toluene/H_2O (33 ml/13.3 ml), followed by 4.0 M HCl in dioxane (2.50 ml, 10.0 mmol) gave **14d** as a white solid (0.52 g, 62%); R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.98-3.09 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 7.17-7.52 (m, 6 Ar**H**), 7.68 (d, J = 8.0 Hz, 2 Ar**H**), 8.34 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.0 ($N\mathbf{C}H_2\mathbf{C}H_2$), 113.6 (d, $J_{C\text{-}F}$ = 21.8 Hz), 114.5 (d, $J_{C\text{-}F}$ = 20.9 Hz), 123.0 (d, $J_{C\text{-}F}$ = 2.4 Hz), 127.4, 129.8, 131.3 (d, $J_{C\text{-}F}$ = 8.5 Hz), 137.6 (d, $J_{C\text{-}F}$ = 2.1 Hz), 137.9, 142.8 (d, $J_{C\text{-}F}$ = 7.7 Hz), 163.2 (d, $J_{C\text{-}F}$ = 241.7 Hz) (12 Ar**C**).

Preparation of 2-(4'-fluoro-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14e). Using Method E, **13** (1.00 g, 3.3 mmol), 4-fluorophenylboronic acid (0.56 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.1 mmol), Na_2CO_3 (1.77 g, 16.7 mmol) in toluene/H_2O (33 ml/13.3 ml), followed by 4.0 M HCl in dioxane (2.50 ml, 10.0 mmol) gave **14e** as a white solid (0.84 g, 67%); R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.96-3.08 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 7.27-7.31 (m, 2 Ar**H**), 7.37 (d, J = 8.1 Hz, 2 Ar**H**), 7.60-7.71 (m, 4 Ar**H**), 8.30 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.0 ($N\mathbf{C}H_2\mathbf{C}H_2$), 116.2 (d, $J_{C\text{-}F}$ = 21.2 Hz), 127.3, 129.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.7, 136.8 (d, $J_{C\text{-}F}$ = 3.1 Hz), 137.2, 138.0, 162.3 (d, $J_{C\text{-}F}$ = 242.7 Hz) (12 Ar**C**).

Preparation of 2-(2'-chloro-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14f). Using Method E, **13** (1.00 g, 3.3 mmol), 2-chlorophenylboronic acid (0.63 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.1 mmol) and Na_2CO_3 (1.77 g, 16.7 mmol) in toluene/H_2O (33 ml/13.3 ml), followed by 4.0 M HCl in dioxane (2.50 ml, 10.0 mmol) gave **14f** as a white solid (0.47 g, 53%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.90-3.11 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 7.24-7.64 (m, 8 Ar**H**), 8.33 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.0 ($N\mathbf{C}H_2\mathbf{C}H_2$), 129.0, 129.7, 136.8, 137.2, 138.0, 162.3 (12 Ar**C**).

Preparation of 2-(3'-chloro-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14g). Using Method E, **13** (1.00 g, 3.3 mmol), 3-chlorophenylboronic acid (0.63 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.1 mmol), Na_2CO_3 (1.77 g, 16.7 mmol) in toluene/H_2O (33 ml/13.3 ml), followed by 4.0 M HCl in dioxane (2.50 ml, 10.0 mmol) gave **14g** as a white solid (0.84 g, 67%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.93-3.09 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 7.25-7.82 (m, 8 Ar**H**), 8.33 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.1 ($N\mathbf{C}H_2\mathbf{C}H_2$), 128.0, 129.0, 129.4, 129.6, 129.7, 129.9, 130.3, 131.5, 131.7, 131.9, 137.6, 140.0 (12 Ar**C**).

Preparation of 2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14h). Using Method E, **13** (1.50 g, 5.0 mmol), 4-chlorophenylboronic acid (0.94 g, 6.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.23 g, 0.2 mmol), Na_2CO_3 (2.65 g, 25.0 mmol) in toluene/H_2O (50 ml/20 ml), followed by 4.0 M HCl in dioxane (3.75 ml, 15.0 mmol) gave **14h** as a white solid (0.94 g, 69%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.99-

3.06 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 7.37-7.77 (m, 8 Ar**H**), 8.31 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 33.0 ($N\mathbf{C}H_2\mathbf{C}H_2$), 127.3, 128.7, 129.3, 129.8, 132.7, 137.6, 137.7, 139.1 (12 Ar**C**).

Preparation of 2-(3'-methoxy-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14i). Using Method E, **13** (1.00 g, 3.3 mmol), 3-methoxyphenylboronic acid (0.61 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.1 mmol), Na_2CO_3 (1.77 g, 16.7 mmol) in toluene/H_2O (33 ml/13.3 ml), followed by 4.0 M HCl in dioxane (2.50 ml, 10.0 mmol) gave **4i** as a white solid (0.47 g, 53%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.93-3.07 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 3.79 ($OC\mathbf{H_3}$), 7.01 (d, J = 8.7 Hz, 1 Ar**H**), 7.33 (d, J = 8.1 Hz, 2 Ar**H**), 7.56-7.60 (m, 4 Ar**H**), 8.27 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 33.0 ($N\mathbf{C}H_2\mathbf{C}H_2$), 55.6 ($\mathbf{C}H_3$), 114.8, 126.8, 128.1, 129.7, 132.7, 136.3, 138.7, 159.3 (OAr**C**) (12 Ar**C**).

Preparation of 2-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethan-1-amine hydrochloride (14j). Using Method E, **13** (1.00 g, 3.3 mmol), 4-methoxyphenylboronic acid (0.61 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.1 mmol), Na_2CO_3 (1.77 g, 16.7 mmol) in toluene/H_2O (33 ml/13.3 ml), followed by 4.0 M HCl in dioxane (2.50 ml, 10.0 mmol) gave **14j** as a white solid (0.52 g, 58%): R_f = 0.00 (EtOAc 9 : acetone 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.02-3.05 (m, $NH_3C\mathbf{H_2}C\mathbf{H_2}$), 3.82 ($OC\mathbf{H_3}$), 6.93 (d, J = 8.1 Hz, 1 Ar**H**), 7.18-7.23 (m, 2 Ar**H**), 7.35-7.40 (m, 3 Ar**H**), 7.64 (d, J = 6.8 Hz, 2 Ar**H**), 8.37 (s, $N\mathbf{H_3}$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 33.0 ($N\mathbf{C}H_2\mathbf{C}H_2$), 55.6 ($\mathbf{C}H_3$), 112.5, 113.4, 119.3, 127.4, 129.7, 130.4, 137.4, 138.9, 141.9, 160.2 (OAr**C**) (12 Ar**C**).

Monoamine oxidase (MAO) enzyme assay

The MAO enzyme inhibitory activity of the compounds was evaluated according to the method described previously.[6] The MAO activity was carried out with a fluorescence-based method by measuring the effects of the compounds on the production of H_2O_2 from substrate (MAO-A: *p*-tyramine, MAO-B: benzylamine, Sigma-Aldrich, Co., Louis, USA) using 10-acetyl-3,7-dihydroxyphenoxazine (Amplex® Red, Molecular Probes, Eugene, Oregon, USA). The test compounds in final concentrations ranged from 10^{-5} μM to 10 μM with recombinant hMAO-A or hMAO-B (Sigma-Aldrich, Co., Louis, USA) in 100 μL of aqueous 50 mM of sodium phosphate buffer (pH 7.4) were preincubated for 15 min 37 °C in a black-clear bottom 96 well assay plate (Costar®, Corning, NY, USA). The reaction was performed by adding 200 μM Amplex red, 2U/mL horseradish peroxidase (Sigma-Aldrich, Co., Louis, USA) and 2 mM *p*-tyramine for hMAO-A or 2 mM benzylamine (Sigma-Aldrich, Co., Louis, USA) for hMAO-B in 100 μL of aqueous 50 mM of sodium phosphate buffer (pH 7.4) (final volume of 200 μL). After 20 min of incubation at 37 °C, the assay was quantified with a multi-mode microplate reader (SpectraMax®i3, Molecular Device, CA, USA) based on the generated fluorescence of resorufin (excitation: 545 nm, emission: 590 nm). The IC_{50} values of the compounds were determined in quadruplicate from the dose response inhibition curves using SigmaPlot software version 13.0 as the mean ± S.E.M.

Kinetic studies of MAO-B inhibition

To investigate the interaction mode of compound **12c**, the type of enzyme inhibition was determined by Michaelis-Menten kinetic experiment. The catalytic rates of human MAO-B enzyme were measured at seven different concentrations of substrate benzylamine (0.065, 0.125, 0.25, 0.5, 1, 2, and 4 mM) in the absence and in the presence of three different concentrations (0.3, 1, and 3 nM) of compound **12c**. The corresponding progression curves and the Lineweaver-Burk plots were generated using GraphPad Prism (GraphPad software). In addition, the maximal velocity (V_{max}), the

Michaelis constant (K_m) and the inhibition constant (K_i) were calculated using SigmaPlot software version 13.0.

Generation of the mouse model of Parkinson's disease induced by MPTP

All mice were housed in a temperature and humidity controlled environment with a 12 h light-dark cycle and were free to consume food and water. All animal care and handling was performed in accordance with the instructions of the KIST Institutional Animal Care and Use Committee (Seoul, Korea). For animal experiments, 10-week-old male C57Bl/6 mice weighing 23−25 g were used. All MPTP experiments used acute administration consisting of intraperitoneal injection of MPTP-HCl (M0896, Sigma-Aldrich, 2 mg/mL in saline, 20 mg/kg for one injection) at 2 h intervals. The mice (n = 5−8 per group) were orally administrated with compound **12c** suspended in 12.5% of mixture Castor oil with ethanol in the same ratio in distilled water at 30 mg/kg body weight per day for 24 h per 3 consecutive days. See also **Fig. 4A.**

Behavior test

The vertical grid test was performed as described in the previous study.[4] A mouse was gently placed inside of the device 3 cm away from the top facing upward. All mice were habituated twice a day for two consecutive days prior to MPTP administration. This test was performed 6 days after MPTP administration, and all experimental sessions were video recorded for time measurement. For the coat-hanger test, the triangular-shaped coat-hanger consisted of a horizontal steel wire (diameter: 3 mm, length: 40 cm, height: 20 cm) with two diagonal side-bars (length: 20 cm; inclination: 35° from the horizontal axis). The mice were placed in a dangling posture in the middle of the horizontal wire. The motor coordination was rated (0) If the mouse fell off the hanger, (1) lifted both limbs, (2) reached one of the ends of the hanger, (3) rose above the diagonal edge, (4) reached the top corner of

triangle, and (5) reached the handle of coat-hanger. See also **Fig. 4A.** This assessment is a single test that lasts for 3 minutes or when the mouse falls off the wire or reach the hanger handle.

Immunostaining for TH

For histological analysis, the mice were anesthetized with 2% avertin (20 μg/g, *i.p.*) and perfused with 0.9% saline, and fixed by perfusion with 4% paraformaldehyde (PFA). The isolated brain post-fixed with 4% PFA for overnight at 4 ℃ and immersed in 30% sucrose solution for over 48 h. Cornal sections for striatum and SNpc were cut at 25 μm in a cryostat and kept in tissue stock solution Glycerol, ethelene glycol, DW and 0.2 M PB (3:3:3:1, v/v/v/v). After further washing with PBS, the sections were immunostained with DAB staining kit (TL-060-QHD, Thermo). The sections were incubated for 10 min in a 4% hydrogen peroxide block, washed three times with PBS, incubated for 10 min in an Protein Block Serum-Free (X0909, DAKO), then washed again. The sample was then immunostained with a mixture of primary antibodies against TH (1:500, p40101-0, Pel-freez) in a blocking solution (0.3% Triton-X, 2% Protein Block Serum-Free in 0.1 M PBS) overnight at 4 ℃ on a shaker. After washing three times with PBS, the section were incubated in HRP Polymer Quanto for 1 h and washed 4 times with PBS. And the sections were immersed in the mixture of DAB+ substrate buffer (K3468, DAKO) at 1:10 ratio. Finally, the sections were mounted. A series of bright field images were obtained by Olympus microscope with 4X magnification. The optical density of the TH stained striatum was determined in the equivalent frame range, with optical density in the corpus callosum used as a reference. The results were expressed as the average of all sections. Cell counting with the 20 X magnification images were performed using the cell counting tool in Image J.

Data analysis

Data is expressed as mean ± S.E.M. Comparisons of three or more groups were analyzed through

one-way ANOVA and *Turkey's* multiple comparison tests. Statistical analysis was carried out using PRISM (GraphPad Software). $p < 0.05$ was considered statistically significant.

Abbreviations

AD, Alzheimer's disease; DA, dopamine; DAergic: dopaminergic; hMAO-A, human monoamine oxidase A; hMAO-B, human monoamine oxidase B; HRP, horseradish peroxidase; IC_{50}: the half maximal inhibitory concentration; i.p., intraperitoneal; K_i, inhibition constant; K_m, Michaelis constant; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PBS, phosphate buffer saline; PD, Parkinson's disease; PFA, paraformaldehyde; *p.o.*, peroral; ROS, reactive oxygen species; S.E.M, standard error of mean; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase; V_{max}, maximal velocity.

Acknowledgements

This study was supported by the National Research Council of Science & Technology (NST) grant by the Korea government (MSIP) (No. CRC-15-04-KIST) and Main Research Program (E0164503-01) of the Korea Food Research Institute (KFRI). We thank Elija Lee for the careful review of the manuscript.

Supplementary data

Supplementary data (experimental procedures for intermediates and ^{1}H and ^{13}C NMR spectra for all final compounds (**7**, **8**, **10**, **12**, **14**) associated with this article can be found, in the

online version, at http://dx.doi.org

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Supplementary Data

Synthesis and Evaluation of Biaryl Derivatives for Structural Characterization of Selective Monoamine Oxidase B Inhibitors toward Parkinson's Disease Therapy

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Supplementary Experiments

General procedure for the preparation of 4-(benzyloxy)benzonitrile derivatives (Method A). A solution mixture of benzylbromide derivative, 4-cyanophenol (1.0–1.2 equiv) and K_2CO_3 (4.0 equiv) was heated in acetone (200–400 mL) at 50-60 °C of reflux (4 h). The reaction mixture was evaporated in vacuo, and the resulted residue was diluted in CH_2Cl_2 (300 mL), then extracted with distilled H_2O (300 mL × 2). The combined organic layer was dried (Na_2SO_4) and evaporated in vacuo.

General procedure for the preparation of 1-(benzyloxy)-4-nitrobenzene derivatives (Method B). To a 4-nitrophenol dissolved in DMF was added potassium carbonate and benzyl bromide derivative. The reaction mixture was stirred for overnight at room temperature. After the reaction, the product mixture was extracted by EtOAc and distilled water. Organic layer was dried over sodium sulfate and recrystallized.

General procedure for the preparation of *tert*-butyl (4-(benzyloxy)phenethyl)carbamate derivatives (Method C). To a *N*-Boc-tyramine dissolved in acetone was added benzyl bromide derivative and potassium carbonate. The reaction mixture was refluxed at 50-60 °C for 4 h. After the reaction, the reaction mixture was filtered, and filtered solution was evaporated in vacuo. The product residue was purified by column chromatography.

Preparation of 4-(benzyloxy)benzonitrile (6a). Using Method A, 4-cyanophenol (2.00 g, 16.8 mmol), benzyl bromide (2.89 mL, 25.7 mmol), and K_2CO_3 (9.29 g, 67.2 mmol) gave **6a** as a white solid (3.27 g, 93%): R_f = 0.31 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.21 (s, OC**H**$_2$), 7.19 (d, J = 8.8 Hz, 2 Ar**H**), 7.32-7.38 (m, 1 Ar**H**), 7.38-7.43 (m, 2 Ar**H**), 7.44-7.48 (m, 2 Ar**H**), 7.78 (d, J = 8.8 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 69.7 (O**C**H$_2$), 103.0 (Ar**C**-CN), 115.9 (2 Ar**C**), 119.1 (**C**N), 127.9, 128.1, 128.5, 134.5, 136.1 (8 Ar**C**), 161.8 (OAr**C**).

Preparation of 4-((2-(trifluoromethyl)benzyl)oxy)benzonitrile (6b). Using Method A, 4-cyanophenol (1.00 g, 8.4 mmol), 2-(trifluoromethyl)benzyl bromide (1.28 mL, 8.4 mmol), and K_2CO_3 (4.64 g, 33.6 mmol) gave **6b** as a white solid (1.63 g, 70%): R_f = 0.39 (EtOAc 1 : *n*-hexane 5): mp 67-68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.33 (s, OC**H**$_2$), 7.20 (d, J = 8.8 Hz, 2 Ar**H**), 7.59-7.64 (m, 1 Ar**H**), 7.71-7.77 (m, 2 Ar**H**), 7.78-7.84 (m, 3 Ar**H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 66.5

(O**C**H_2), 104.8 (Ar**C**-CN), 115.6, 119.1 (**C**N), 124.4 (q, J_{C-F} = 272.0 Hz), 126.3 (**C**F_3), 127.8, 127.6 (q, J_{C-F} = 30.9 Hz), 128.4, 128.8, 132.4, 134.2, 134.3 (8 Ar**C**), 161.6 (OAr**C**).

Preparation of 4-((3-(trifluoromethyl)benzyl)oxy)benzonitrile (6c). Using Method A, 4-cyanophenol (0.30 g, 2.5 mmol), 3-(trifluoromethyl)benzyl bromide (0.40 mL, 2.5 mmol), and K_2CO_3 (1.39 g, 10.1 mmol) gave **6c** as a white solid (0.64 g, 91%): R_f = 0.31 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.32 (s, OC**H**$_2$), 7.21 (d, J = 8.8 Hz, 2 Ar**H**), 7.62-7.68 (m, 1 Ar**H**), 7.70-7.75 (m, 1 Ar**H**), 7.76-7.82 (m, 3 Ar**H**), 7.82-7.86 (m, 1 Ar**H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 69.5 (O**C**H_2), 104.8 (Ar**C**-CN), 115.7, 119.1 (**C**N), 124.0 (q, J_{C-F} = 265.3 Hz), 124.2 (**C**F_3), 124.3, 130.7, 131.3 (q, J_{C-F} = 32.3 Hz), 134.2 (10 Ar**C**), 161.7 (OAr**C**).

Preparation of 4-((4-(trifluoromethyl)benzyl)oxy)benzonitrile (6d). Using Method A, 4-cyanophenol (0.30 g, 2.5 mmol), 4-(trifluoromethyl)benzyl bromide (0.40 mL, 2.5 mmol), and K_2CO_3 (1.39 g, 10.1 mmol) gave **6d** as a white solid (0.40, 57%): R_f = 0.27 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.33 (s, OC**H**$_2$), 7.20 (d, J = 8.8 Hz, 2 Ar**H**), 7.65-7.70 (m, 2 Ar**H**), 7.75-7.82 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 69.2 (O**C**H_2), 103.8 (Ar**C**-CN), 116.4 (1 Ar**C**), 119.5 (**C**N), 124.8 (q, J_{C-F} = 270.5 Hz), 125.8 (q, J_{C-F} = 3.7 Hz), 125.9, 128.6, 129.0 (q, J_{C-F} = 31.5 Hz), 134.7, 141.5 (10 Ar**C**), 162.0 (OAr**C**).

Preparation of 4-((2-fluorobenzyl)oxy)benzonitrile (6e). Using Method A, 4-cyanophenol (1.00 g, 8.4 mmol), 2-fluorobenzyl bromide (1.90 g, 10.1 mmol), and K_2CO_3 (4.64 g, 33.6 mmol) gave **6e** as a white powder (1.61 g, 84%): R_f = 0.50 (EtOAc 1 : *n*-hexane 3): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.24 (s, OC**H**$_2$), 7.19-7.31 (m, 4 Ar**H**), 7.41-7.49 (m, 1 Ar**H**), 7.54-7.60 (m, 1 Ar**H**), 7.77-7.82 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 64.1 (O**C**H_2), 103.3 (Ar**C**-CN), 115.5 (d, J_{C-F} = 20.8 Hz), 115.8, 119.1 (**C**N), 122.9, 123.1, 124.6, 130.8 (d, J_{C-F} = 8.0 Hz), 130.9, 134.3 (9 Ar**C**), 160.5 (d, J_{C-F} = 244.2 Hz), 161.6 (OAr**C**).

Preparation of 4-((3-fluorobenzyl)oxy)benzonitrile (6f). Using Method A, 4-cyanophenol (4.00 g, 33.6 mmol), 3-fluorobenzyl bromide (4.18 mL, 33.6 mmol), and K_2CO_3 (18.60 g, 134.3 mmol) gave **6f** as a white solid (7.25 g, 95%): R_f = 0.47 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.23 (s, OC**H**$_2$),7.14-7.22 (m, 3 Ar**H**), 7.28-7.32 (m, 2 Ar**H**), 7.45 (q, J = 7.6 Hz, 14.1 Hz, 1 Ar**H**), 7.79 (d, J = 8.8 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 68.8 (O**C**H_2), 103.2 (Ar**C**-CN), 114.4,

114.6, 114.9 (d, $J_{C\text{-}F}$ = 20.9 Hz), 115.9, 119.1 (**C**N), 123.8, 130.6 (d, $J_{C\text{-}F}$ = 8.3 Hz), 134.3, 139.1 (10 Ar**C**), 161.6 (OAr**C**), 162.2 (d, $J_{C\text{-}F}$ = 242.4 Hz).

Preparation of 4-((4-fluorobenzyl)oxy)benzonitrile (6g). Using Method A, 4-cyanophenol (1.00 g, 8.39 mmol), 4-fluorobenzyl bromide (1.05 mL, 8.39 mmol), and K_2CO_3 (4.64 g, 33.56 mmol) gave **6g** as a white solid (1.86 g, 97%): R_f = 0.26 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.19 (s, OC**H**$_2$), 7.16-7.27 (m, 4 Ar**H**), 7.49-7.55 (m, 2 Ar**H**), 7.78 (d, J = 8.8 Hz, 2 Ar**H**);^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.9 (O**C**H$_2$), 103.1 (1 Ar**C**), 115.4 (d, $J_{C\text{-}F}$ = 21.4 Hz), 119.1 (**C**N), 130.3 (d, $J_{C\text{-}F}$ = 8.3 Hz), 132.4, 134.2 (4 Ar**C**), 161.7 (1 Ar**C**), 161.9 (d, $J_{C\text{-}F}$ = 242.7 Hz).

Preparation of 4-((3-chlorobenzyl)oxy)benzonitrile (6h). Using Method A, 4-cyanophenol (1.00 g, 8.4 mmol), 3-chlorobenzyl bromide (2.07 g, 10.1 mmol), and K_2CO_3 (4.64 g, 33.6 mmol) gave **6h** as a white crystalline (1.63 g, 80%): R_f = 0.33 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.22 (s, OC**H**$_2$), 7.16-7.22 (m, 2 Ar**H**), 7.40-7.45 (m, 3 Ar**H**), 7.52-7.55 (m, 1 Ar**H**), 7.75-7.81 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 68.7 (O**C**H$_2$), 103.2 (Ar**C**-CN), 115.9, 119.1 (**C**N), 126.3, 127.5, 128.0, 130.4, 133.2, 134.2, 138.7 (10 Ar**C**), 161.5 (OAr**C**).

Preparation of Preparation of 4-((4-chlorobenzyl)oxy)benzonitrile (6i). Using Method A, 4-cyanophenol (1.00 g, 8.4 mmol), 4-chlorobenzyl bromide (1.72 g, 8.4 mmol), and K_2CO_3 (4.64 g, 33.6 mmol) gave **6i** as a white solid (1.96 g, 96%): R_f = 0.20 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.21 (s, OC**H**$_2$), 7.18 (d, J = 8.9 Hz, 2 Ar**H**), 7.45-7.52 (m, 4 Ar**H**), 7.78 (d, J = 8.8 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.8 (O**C**H$_2$), 103.2 (Ar**C**-CN), 115.9, 119.1 (**C**N), 128.5, 129.7, 132.7, 134.2 (Ar**C**-Cl), 135.2 (10 Ar**C**), 161.6 (OAr**C**).

Preparation of 4-((3-methoxybenzyl)oxy)benzonitrile (6j). Using Method A, 4-cyanophenol (1.00 g, 8.4 mmol), 3-methoxybenzyl bromide (1.18 mL, 8.4 mmol), and K_2CO_3 (4.64 g, 36.6 mmol) gave **6j** as a white solid (2.00 g, 100%): R_f = 0.32 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.76 (s, OC**H**$_3$), 5.18 (s, OC**H**$_2$), 6.89-6.94 (m, 1 Ar**H**), 7.00-7.04 (m, 2 Ar**H**), 7.18 (d, J = 8.8 Hz, 2 Ar**H**), 7.31 (t, J = 8.1 Hz, 1 Ar**H**), 7.77 (d, J = 8.8 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.1 (O**C**H$_3$), 69.5 (O**C**H$_2$), 103.0 (Ar**C**-CN), 113.3, 113.5, 115.9, 119.1 (**C**N), 119.9, 129.7, 134.2, 137.7 (9 Ar**C**), 159.4 (Ar**C**-OCH$_2$), 161.7 (Ar**C**-OCH$_3$).

Preparation of 4-((4-methoxybenzyl)oxy)benzonitrile (6k). Using Method A, 4-cyanophenol (0.50 g, 4.2 mmol), 4-methoxybenzyl bromide (0.43 mL, 4.2 mmol), and K_2CO_3 (2.32 g, 16.8 mmol) gave **6k** as a white solid (0.65 g, 70%): R_f = 0.27 (EtOAc 1 : *n*-hexane 3): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.76 (s, OC**H**$_3$), 5.11 (s, OC**H**$_2$), 6.91-6.99 (m, 2 Ar**H**), 7.13-7.20 (m, 2 Ar**H**), 7.36-7.43 (m, 2 Ar**H**), 7.73-7.80 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 55.6 (O**C**H$_3$), 70.0 (O**C**H$_2$), 103.3 (Ar**C**-CN), 114.4, 116.4, 119.6 (**C**N), 128.5, 130.2, 134.6, 159.7 (Ar**C**-OCH$_2$), 162.3 (Ar**C**-OCH$_3$).

Preparation of 1-((4-nitrophenoxy)methyl)-2-(trifluoromethyl)benzene (9a). Using Method B, 4-nitrophenol (0.50 g, 3.6 mmol), 2-(trifluoromethyl)benzyl bromide (1.03 g, 4.3 mmol), and potassium carbonate (1.98 g, 14.4 mmol) gave **9a** as a white powder (0.58 g, 54%): R_f = 0.26 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.38 (s, OC**H**$_2$), 7.22-7.28 (m, 2 Ar**H**), 7.60-7.66 (m, 1 Ar**H**), 7.72-7.85 (m, 3 Ar**H**), 8.21-8.27 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 67.2 (O**C**H$_2$), 115.3, 124.3 (q, $J_{C\text{-}F}$ = 275.1 Hz), 126.0, 126.3, 126.4, 127.2 ((q, $J_{C\text{-}F}$ = 30.3 Hz), 129.2, 131.0, 132.9, 133.7, 141.3 (10 Ar**C**), 163.2 (OAr**C**).

Preparation of 1-((4-nitrophenoxy)methyl)-3-(trifluoromethyl)benzene (9b). Using Method B, 4-nitrophenol (0.50 g, 3.6 mmol), 3-(trifluoromethyl)benzyl bromide (1.03 g, 4.3 mmol), and potassium carbonate (1.98 g, 14.4 mmol) gave **9b** as a white powder (0.98 g, 91%): R_f = 0.27 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.38 (s, OC**H**$_2$), 7.24-7.30 (m, 2 Ar**H**), 7.65-7.71 (m, 1 Ar**H**), 7.73-7.77 (m, 1 Ar**H**), 7.79-7.83 (m, 1 Ar**H**), 7.86-7.89 (m, 1 Ar**H**), 8.22-8.28 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 69.2 (O**C**H$_2$), 115.4, 124.1 (q, $J_{C\text{-}F}$ = 268.2 Hz), 124.3, 124.3, 124.9, 124.9, 129.3 (q, $J_{C\text{-}F}$ = 31.5 Hz), 129.7, 131.9, 137.5, 141.1 (10 Ar**C**), 163.3 (OAr**C**).

Preparation of 1-((4-nitrophenoxy)methyl)-4-(trifluoromethyl)benzene (9c). Using Method B, 4-nitrophenol (0.50 g, 3.6 mmol), 4-(trifluoromethyl)benzyl bromide (1.03 g, 4.3 mmol), and potassium carbonate (1.98 g, 14.4 mmol) gave **9c** as a white powder (0.61 g, 57%): R_f = 0.27 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.39 (s, OC**H**$_2$), 7.22-7.28 (m, 2 Ar**H**), 7.68-7.72 (m, 2 Ar**H**), 7.76-7.81 (m, 2 Ar**H**), 8.21-8.26 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 69.2 (O**C**H$_2$), 115.4, 124.1 (q, $J_{C\text{-}F}$ = 265.8 Hz), 125.4, 125.5, 128.2, 128.7 (q, $J_{C\text{-}F}$ = 31.7 Hz), 140.9 (10 Ar**C**), 141.2 (Ar**C**-NO$_2$), 163.3 (OAr**C**).

Preparation of 1-fluoro-2-((4-nitrophenoxy)methyl)benzene (9d). Using Method B, 4-nitrophenol (0.30 g, 2.2 mmol), 2-fluorobenzyl bromide (0.32 mL, 2.6 mmol), and potassium carbonate (1.19 g,

8.6 mmol) gave **9d** as a white solid (0.38 g, 71%): R_f = 0.40 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.31 (s, OC**H**$_2$), 7.23-7.32 (m, 4 Ar**H**), 7.46 (q, J = 13.8 Hz, 1 Ar**H**), 7.59 (t, J = 7.5 Hz, 1 Ar**H**), 8.23 (d, J = 9.1 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 64.6 (O**C**H$_2$), 115.3, 115.5 (d, $J_{C\text{-}F}$ = 20.8 Hz), 122.7, 122.9, 124.7, 125.9, 130.9 (d, $J_{C\text{-}F}$ = 8.1 Hz), 141.1 (11 Ar**C**), 160.5 (d, $J_{C\text{-}F}$ = 245.0 Hz), 163.4 (OAr**C**).

Preparation of 1-fluoro-3-((4-nitrophenoxy)methyl)benzene (9e). Using Method B, 4-nitrophenol (0.20 g, 1.4 mmol), 3-fluorobenzyl bromide (0.21 mL, 1.7 mmol), and potassium carbonate (0.80 g, 5.8 mmol) gave **9e** as a white solid (0.31 g, 89%): R_f = 0.43 (EtOAc 1 : *n*-hexane 5): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.39 (s, OC**H**$_2$), 7.23-7.34 (m, 3 Ar**H**), 7.35-7.48 (m, 2 Ar**H**), 7.57-7.68 (m, 1 Ar**H**), 8.40-8.50 (m, 2 Ar**H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 69.9 (O**C**H$_2$), 114.3, 114.5, 115.0, 115.5 (d, $J_{C\text{-}F}$ = 21.0 Hz), 122.9, 126.1, 130.5 (d, $J_{C\text{-}F}$ = 8.1 Hz), 138.2, 138.2, 142.0 (11 Ar**C**), 163.1 (d, $J_{C\text{-}F}$ = 245.4 Hz), 163.5 (OAr**C**).

Preparation of 1-fluoro-4-((4-nitrophenoxy)methyl)benzene (9f). Using Method B, 4-nitrophenol (0.30 g, 2.2 mmol), 4-fluorobenzyl bromide (0.32 mL, 2.6 mmol), and potassium carbonate (1.19 g, 8.6 mmol) gave **9f** as a pale yellow solid (0.38 g, 71%): R_f = 0.33 (EtOAc 1 : *n*-hexane 3): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.29 (s, OC**H**$_2$), 7.16-7.26 (m, 3 Ar**H**), 7.30-7.35 (m, 2 Ar**H**), 7.42-7.50 (m, 1 Ar**H**), 8.22 (d, J = 9.2 Hz, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 69.4 (O**C**H$_2$), 115.3, 115.4 (d, $J_{C\text{-}F}$ = 21.2 Hz), 125.9, 130.3 (d, $J_{C\text{-}F}$ = 8.3 Hz), 132.2, 141.0 (11 Ar**C**), 162.0 (d, $J_{C\text{-}F}$ = 242.7 Hz), 163.5 (OAr**C**).

Preparation of *tert*-butyl (4-((2-(trifluoromethyl)benzyl)oxy)phenethyl)carbamate (11a). Using Method C, *N*-Boc-tyramine (0.50 g, 2.1 mmol), 2-(trifluoromethyl)benzyl bromide (0.60 g, 2.5 mmol), and potassium carbonate (1.17 g, 8.4 mmol) gave **11a** as a white solid (0.79 g, 94%): R_f = 0.47 (EtOAc 1: *n*-Hexane 3): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.36 (s, C(C**H**$_3$)$_3$), 2.56-2.66 (m, NHC**H**$_2$CH$_2$), 3.03-3.13 (m, NHCH$_2$C**H**$_2$), 5.20 (s, OC**H**$_2$), 6.82-6.95 (m, 3 Ar**H**), 7.07-7.15 (m, 2 Ar**H**), 7.52-7.61 (m, 1 Ar**H**), 7.67-7.82 (m, 3 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 28.2 (C(**C**H$_3$)$_3$), 34.7 (NHCH$_2$**C**H$_2$), 41.7 (NH**C**H$_2$CH$_2$), 66.1 (O**C**H$_2$), 77.5 (**C**(CH$_3$)$_3$), 114.6, 124.3 (q, $J_{C\text{-}F}$ = 272.2 Hz), 126.1, 126.8 (q, $J_{C\text{-}F}$ = 30.3 Hz), 128.6, 129.7, 130.3, 12.1, 132.8, 135.2, 155.5 (13 Ar**C**), 156.5 (**C**(O)C(CH$_3$)$_3$).

Preparation of *tert*-butyl (4-((3-(trifluoromethyl)benzyl)oxy)phenethyl)carbamate (11b). Using Method C, *N*-Boc-tyramine (0.50 g, 2.1 mmol), 3-(trifluoromethyl)benzyl bromide (0.60 g, 2.5 mmol), and potassium carbonate (1.17 g, 8.4 mmol) gave **11b** as a white solid (0.84 g, 100%): R_f = 0.47 (EtOAc 1: *n*-Hexane 3): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.36 (s, C(C**H**$_3$)$_3$), 2.59-2.64 (m, NHC**H**$_2$CH$_2$), 3.05-3.12 (m, NHCH$_2$C**H**$_2$), 5.18 (s, OC**H**$_2$), 6.85 (t, J = 5.5 Hz, 1 Ar**H**), 6.92-6.97 (m, 2 Ar**H**), 7.09-7.14 (m, 2 Ar**H**), 7.61-7.82 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 28.2 (C(**C**H$_3$)$_3$), 34.6 (NHCH$_2$**C**H$_2$), 41.7 (NH**C**H$_2$CH$_2$), 68.3 (O**C**H$_2$), 77.4 (**C**(CH$_3$)$_3$), 114.7, 124.2 (q, $J_{C\text{-}F}$ = 270.2 Hz), 125.3, 127.9, 128.2 (q, $J_{C\text{-}F}$ = 31.4 Hz), 129.6, 131.9, 142.2, 155.5 (13 Ar**C**), 156.4 (**C**(O)C(CH$_3$)$_3$).

Preparation of *tert*-butyl (4-((4-(trifluoromethyl)benzyl)oxy)phenethyl)carbamate (11c). Using Method C, *N*-Boc-tyramine (0.50 g, 2.1 mmol), 4-(trifluoromethyl)benzyl bromide (0.60 g, 2.5 mmol), and potassium carbonate (1.17 g, 8.4 mmol) gave **11c** as a white solid (0.85 g, 100%): R_f = 0.38 (EtOAc 1: *n*-Hexane 3): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.35 (s, C(C**H**$_3$)$_3$), 2.61 (t, J = 7.5 Hz, NHC**H**$_2$CH$_2$), 3.08 (q, J = 7.9 Hz, NHCH$_2$C**H**$_2$), 5.19 (s, OC**H**$_2$), 6.85 (t, J = 5.4 Hz, 1 Ar**H**), 6.91-6.96 (m, 2 Ar**H**), 7.08-7.14 (m, 2 Ar**H**), 7.63-7.78 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 28.2 (C(**C**H$_3$)$_3$), 34.2 (NHCH$_2$**C**H$_2$), 41.7 (NH**C**H$_2$CH$_2$), 68.2 (O**C**H$_2$), 77.4 (**C**(CH$_3$)$_3$), 114.7, 124.2 (q, $J_{C\text{-}F}$ = 270.2 Hz), 125.3, 127.9, 128.2 (q, $J_{C\text{-}F}$ = 31.4 Hz), 129.6, 131.9, 142.2, 155.5 (13 Ar**C**), 156.4 (**C**(O)C(CH$_3$)$_3$).

Preparation of tert-butyl (4-((2-fluorobenzyl)oxy)phenethyl)carbamate (11d). Using Method C, *N*-Boc-tyramine (1.00 g, 4.2 mmol), 2-fluorobenzyl bromide (0.53 ml, 4.4 mmol) and potassium carbonate (2.33 g, 16.8 mmol) gave **11d** as a white solid (0.97 g, 66%); R_f = 0.48 (EtOAc 1: *n*-hexane 3); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.43 (s, C(C**H**$_3$)$_3$), 2.73 (t, J = 6.8 Hz, NHCH$_2$C**H$_2$**), 7.06-7.17 (m, 4 Ar**H**), 7.28-7.33 (m, 1 Ar**H**), 7.50 (t, J = 7.2 Hz, 1 Ar**H**); ^{13}C NMR (75 MHz, CDCl$_3$) δ 28.4 (C(**C**H$_3$)$_3$), 35.4 (NHCH$_2$**C**H$_2$), 42.0 (NH**C**H$_2$CH$_2$), 63.8 (O**C**H$_2$), 79.2 (**C**(CH$_3$)$_3$), 115.0, 115.2, 115.5, 124.2, 115.0, 115.3 (d, $J_{C\text{-}F}$ = 21.1 Hz), 124.2 (d, $J_{C\text{-}F}$ = 3.6 Hz), 124.3 (d, $J_{C\text{-}F}$ = 14.1 Hz), 129.6 (d, $J_{C\text{-}F}$ = 5.8 Hz), 129.7 (d, $J_{C\text{-}F}$ = 1.4 Hz), 129.8, 131.6, 155.9 (**C**(O)), 158.8 (OAr**C**) (12 Ar**C**).

Preparation of *tert*-butyl (4-((3-fluorobenzyl)oxy)phenethyl)carbamate (11e). Using Method C, *N*-Boc-tyramine (0.50 g, 2.1 mmol), 3-fluorobenzyl bromide (0.39 mL, 3.2 mmol), and potassium carbonate (1.17 g, 8.4 mmol) gave **11e** as a white solid (0.29 g, 40%): R_f = 0.34 (EtOAc 1: *n*-Hexane 3): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.36 (s, C(C**H**$_3$)$_3$), 2.57-2.65 (m, NHC**H**$_2$CH$_2$), 3.03-3.13 (m,

$NHCH_2C\mathbf{H}_2$), 5.09 (s, $OC\mathbf{H}_2$), 6.84 (t, J = 5.3 Hz, N**H**), 6.89-6.96 (m, 2 Ar**H**), 7.07-7.19 (m, 3 Ar**H**), 7.23-7.30 (m, 2 Ar**H**), 7.39-7.48 (m, 1 Ar**H**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.7 ($C(\mathbf{C}H_3)_3$), 35.1 ($NH\mathbf{C}H_2CH_2$), 42.2 ($NHCH_2\mathbf{C}H_2$), 68.7 ($O\mathbf{C}H_2$), 77.9 ($\mathbf{C}(CH_3)_3$), 114.5 (d, $J_{C\text{-}F}$ = 21.6 Hz), 114.8, 115.1, 123.8, 123.8, 130.1, 130.9 (d, $J_{C\text{-}F}$ = 8.3 Hz), 132.3, 140.7, 140.8 (10 Ar**C**), 156.0 (**C**(O)), 157.0 (OAr**C**), 162.7 (d, $J_{C\text{-}F}$ = 242.1 Hz).

Preparation of *tert*-butyl (4-((4-fluorobenzyl)oxy)phenethyl)carbamate (11f). Using Method C, *N*-Boc-tyramine (0.50 g, 2.1 mmol), 4-fluorobenzyl bromide (0.31 mL, 2.5 mmol), and potassium carbonate (1.17 g, 8.4 mmol) gave **11f** as a white solid (0.71 g, 97%): R_f = 0.23 (EtOAc 1: *n*-Hexane 3): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.36 (s, $C(C\mathbf{H}_3)_3$), 2.58-2.66 (m, $NHC\mathbf{H}_2CH_2$), 3.04-3.14 (m, $NHCH_2C\mathbf{H}_2$), 5.04 (s, $OC\mathbf{H}_2$), 6.84 (t, J = 5.4 Hz, N**H**), 6.89-6.96 (m, 2 Ar**H**), 7.07-7.13 (m, 2 Ar**H**), 7.16-7.26 (m, 2 Ar**H**), 7.45-7.52 (m, 2 Ar**H**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.2 ($C(\mathbf{C}H_3)_3$), 34.6 ($NH\mathbf{C}H_2CH_2$), 41.7 ($NHCH_2\mathbf{C}H_2$), 68.4 ($O\mathbf{C}H_2$), 77.4 ($\mathbf{C}(CH_3)_3$), 114.6, 115.2 (d, $J_{C\text{-}F}$ = 21.2 Hz), 129.5, 129.8 (d, $J_{C\text{-}F}$ = 8.2 Hz), 131.7, 133.4, 133.5 (11 Ar**C**), 155.5 (**C**(O)), 156.6 (OAr**C**), 161.7 (d, $J_{C\text{-}F}$ = 242.1 Hz).

Preparation of tert-butyl (4-((2-chlorobenzyl)oxy)phenethyl)carbamate (11g). Using Method C, *N*-Boc-tyramine (1.00 g, 4.2 mmol), 2-chlorobenzyl bromide (0.57 ml, 4.4 mmol) and potassium carbonate (2.33 g, 16.9 mmol) gave **11g** as a white solid (1.19 g, 78%); R_f = 0.47 (EtOAc 1: *n*-Hexane 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, $C(C\mathbf{H}_3)_3$), 2.73 (t, J = 6.9 Hz, $NHCH_2C\mathbf{H_2}$), 3.33-3.35 (m, $NHC\mathbf{H_2}CH_2$), 4.55 (br s, BocN**H**), 5.14 (s, $OC\mathbf{H_2}$), 6.93 (d, J = 8.3 Hz, 2 Ar**H**), 7.11 (d, J = 8.3 Hz, 2 Ar**H**), 7.23-7.30 (m, 2 Ar**H**), 7.38-7.40 (m, 1 Ar**H**), 7.54-7.56 (m, 1 Ar**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4 ($C(\mathbf{C}H_3)_3$), 35.4 ($NHCH_2\mathbf{C}H_2$), 42.0 ($NH\mathbf{C}H_2CH_2$), 67.2 ($O\mathbf{C}H_2$), 79.2 ($\mathbf{C}(CH_3)_3$), 127.0, 128.8, 129.0, 129.4, 129.8, 131.6, 132.2, 132.6, 134.9, 155.9 (**C**(O)), 157.2 (OAr**C**) (12 Ar**C**).

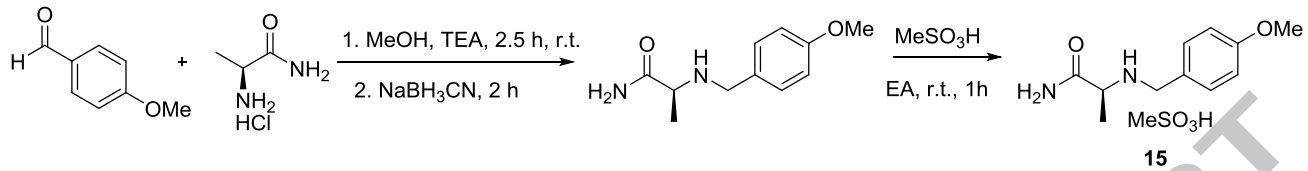
Preparation of *tert*-butyl (4-((3-chlorobenzyl)oxy)phenethyl)carbamate (11h). Using Method C, *N*-Boc-tyramine (0.50 g, 2.1 mmol), 3-chlorobenzyl bromide (0.41 mL, 3.2 mmol), and potassium carbonate (1.17 g, 8.4 mmol) gave **11h** as a white solid (0.68 g, 93%): R_f = 0.40 (EtOAc 1: *n*-Hexane 3): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.36 (s, $C(C\mathbf{H}_3)_3$), 2.58-2.66 (m, $NHC\mathbf{H}_2CH_2$), 3.03-3.13 (m, $NHCH_2C\mathbf{H}_2$), 5.09 (s, $OC\mathbf{H}_2$), 6.84 (t, J = 5.4 Hz, N**H**), 6.89-6.96 (m, 2 Ar**H**), 7.07-7.14 (m, 2 Ar**H**), 7.35-7.44 (m, 3 Ar**H**), 7.48-7.52 (m, 1 Ar**H**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.7 ($C(\mathbf{C}H_3)_3$), 35.1

(NH**C**H_2CH_2), 42.2 (NHCH$_2$**C**H$_2$), 68.7 (O**C**H$_2$), 77.9 (**C**(CH$_3$)$_3$), 115.1, 126.5, 127.6, 128.1, 130.1, 130.8, 132.3, 133.6 (Ar**C**-Cl), 140.4 (10 Ar**C**), 156.0 (**C**(O)), 156.9 (OAr**C**).

Preparation of *tert*-butyl (4-((4-chlorobenzyl)oxy)phenethyl)carbamate (11i). Using Method C, *N*-Boc-tyramine (0.50 g, 2.1 mmol), 4-chlorobenzyl bromide (0.41 mL, 3.2 mmol), and potassium carbonate (1.17 g, 8.4 mmol) gave **11i** as a white solid (0.70 g, 96%): R_f = 0.34 (EtOAc 1: *n*-Hexane 3): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.36 (s, C(C**H**$_3$)$_3$), 2.58-2.66 (m, NHC**H**$_2$CH$_2$), 3.04-3.14 (m, NHCH$_2$C**H**$_2$), 5.06 (s, OC**H**$_2$), 6.84 (t, J = 5.4 Hz, N**H**), 6.88-6.95 (m, 2 Ar**H**), 7.07-7.13 (m, 2 Ar**H**), 7.41-7.50 (m, 4 Ar**H**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.2 (C(**C**H$_3$)$_3$), 34.6 (NH**C**H$_2$CH$_2$), 41.7 (NHCH$_2$**C**H$_2$), 68.3 (O**C**H$_2$), 77.4 (**C**(CH$_3$)$_3$), 114.6, 128.4, 129.3, 129.56, 131.7, 132.3 (Ar**C**-Cl), 136.3 (10 Ar**C**), 155.5 (**C**(O)), 156.5 (OAr**C**).

Preparation of tert-butyl (4-((3-methoxybenzyl)oxy)phenethyl)carbamate (11j). Using Method C, *N*-Boc-tyramine (1.00 g, 4.2 mmol), 3-methoxybenzyl bromide (0.71 ml, 5.1 mmol) and potassium carbonate (2.33 g, 16.9 mmol) gave **11j** as a white solid (1.31 g, 87%); R_f = 0.40 (EtOAc 1: *n*-Hexane 3); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.43 (s, C(C**H**$_3$)$_3$), 2.72 (t, J = 6.9 Hz, NHCH$_2$C**H$_2$**), 3.32-3.34 (m, NHC**H$_2$**CH$_2$), 3.81 (s, OC**H$_3$**), 4.56 (br s, BocN**H**), 5.01 (s, OC**H$_2$**), 6.84-6.93 (m, 3Ar**H**), 7.00 (d, J = 7.3 Hz, 2Ar**H**), 7.10 (d, J = 8.4 Hz, 2Ar**H**), 7.25-7.32 (m, 1Ar**H**); ^{13}C NMR (75 MHz, CDCl$_3$) δ 28.4 (C(**C**H$_3$)$_3$), 35.4 (NHCH$_2$**C**H$_2$), 42.0 (NH**C**H$_2$CH$_2$), 55.3 (O**C**H$_3$), 70.0 (O**C**H$_2$), 79.2 (**C**(CH$_3$)$_3$), 112.9 (12Ar**C**), 113.5, 115.0, 119.6, 129.7, 129.8, 131.4, 138.8, 155.9 (**C**(O)), 157.5(OAr**C**), 159.9 (CH$_3$OAr**C**) (12 Ar**C**).

Preparation of *N*-boc-2-(4-bromophenyl)ethylamine (13). To a solution of 4-bromophenethylamine (5.00 g, 25.0 mmol), potassium carbonate (5.18 g, 37.5 mmol) in CH_2Cl_2 (125 ml) was stirred for 15 min at room temperature, and boc anhydride was added (6.04 mL, 26.3 mmol). After 16 h, the reaction mixture was washed with H_2O (125 mL × 3) and brine (75 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was washed with *n*-hexane and gave **13** as a white solid (6.63 g, 88%); R_f = 0.50 (EtOAc 1: *n*-Hexane 3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43 (s, C(C**H**$_3$)$_3$), 2.75 (t, J = 6.6 Hz, NHCH$_2$C**H$_2$**), 3.34-3.35(m, NHC**H$_2$**CH$_2$), 7.06 (d, J = 8.0 Hz, 2 Ar**H**), 7.42 (d, J = 8.2 Hz, 2 Ar**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.4 (C(**C**H$_3$)$_3$), 35.7 (NHCH$_2$**C**H$_2$), 41.6 (NH**C**H$_2$CH$_2$), 79.3 (**C**(CH$_3$)$_3$), 120.2, 130.6, 131.6, 138.0 (6 Ar**C**), 155.8 (**C**(O)).



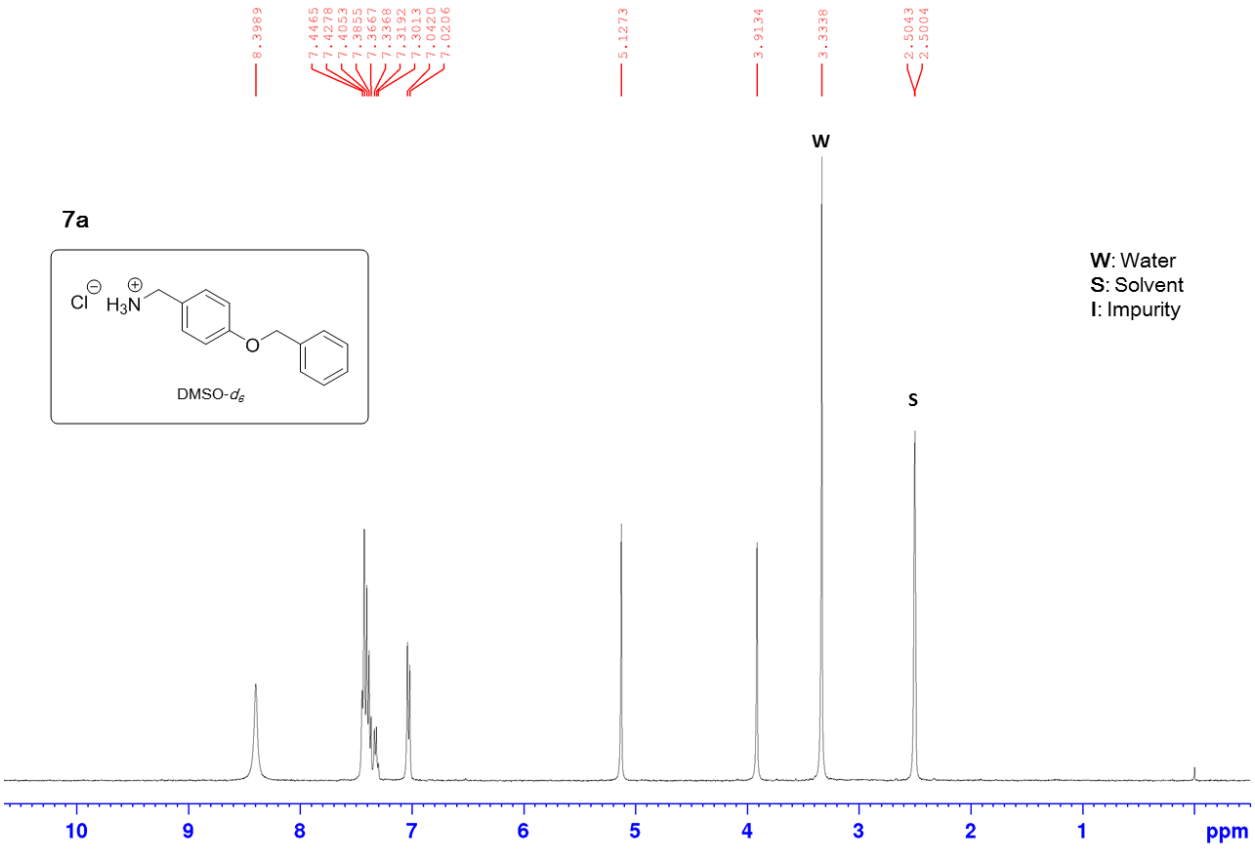
15

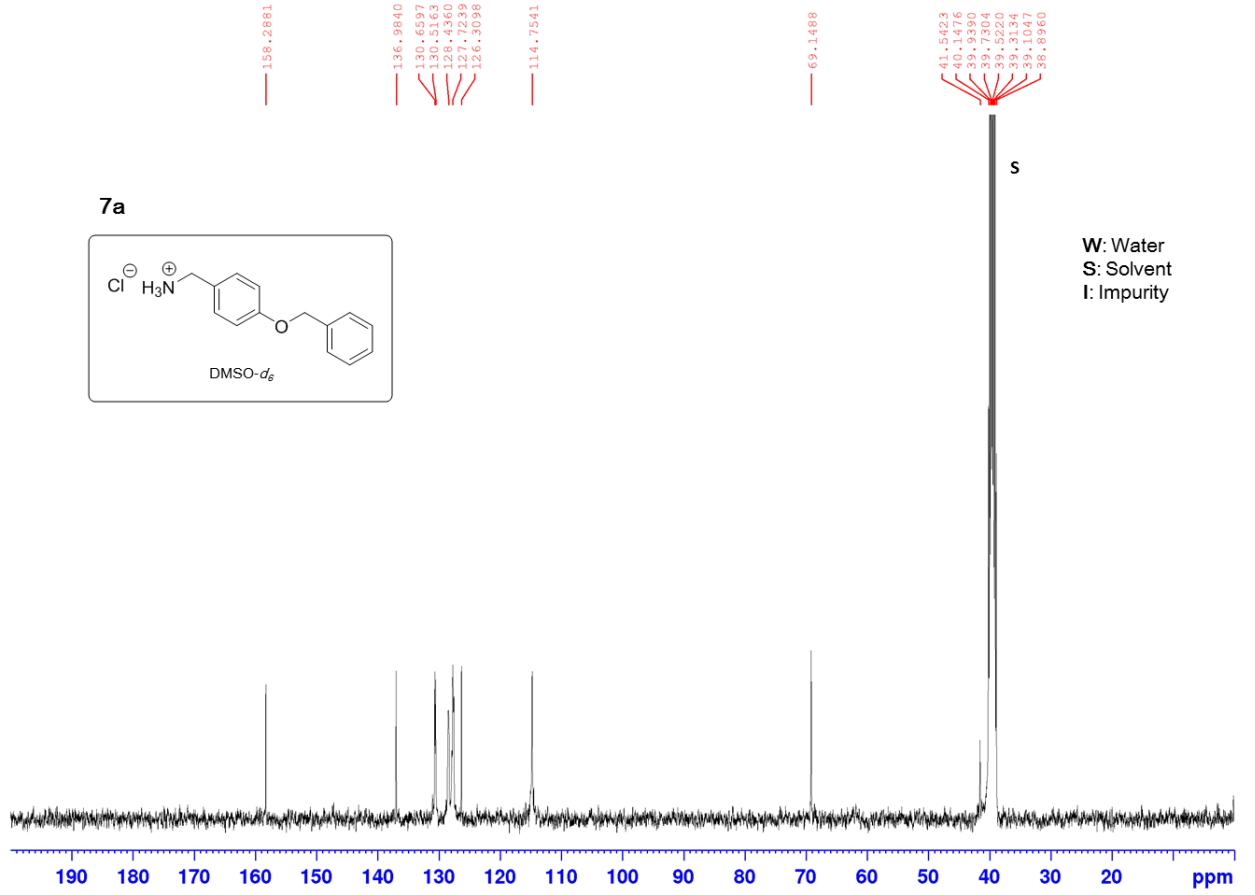
Scheme S1. Synthetic Procedure for Compound **15**.

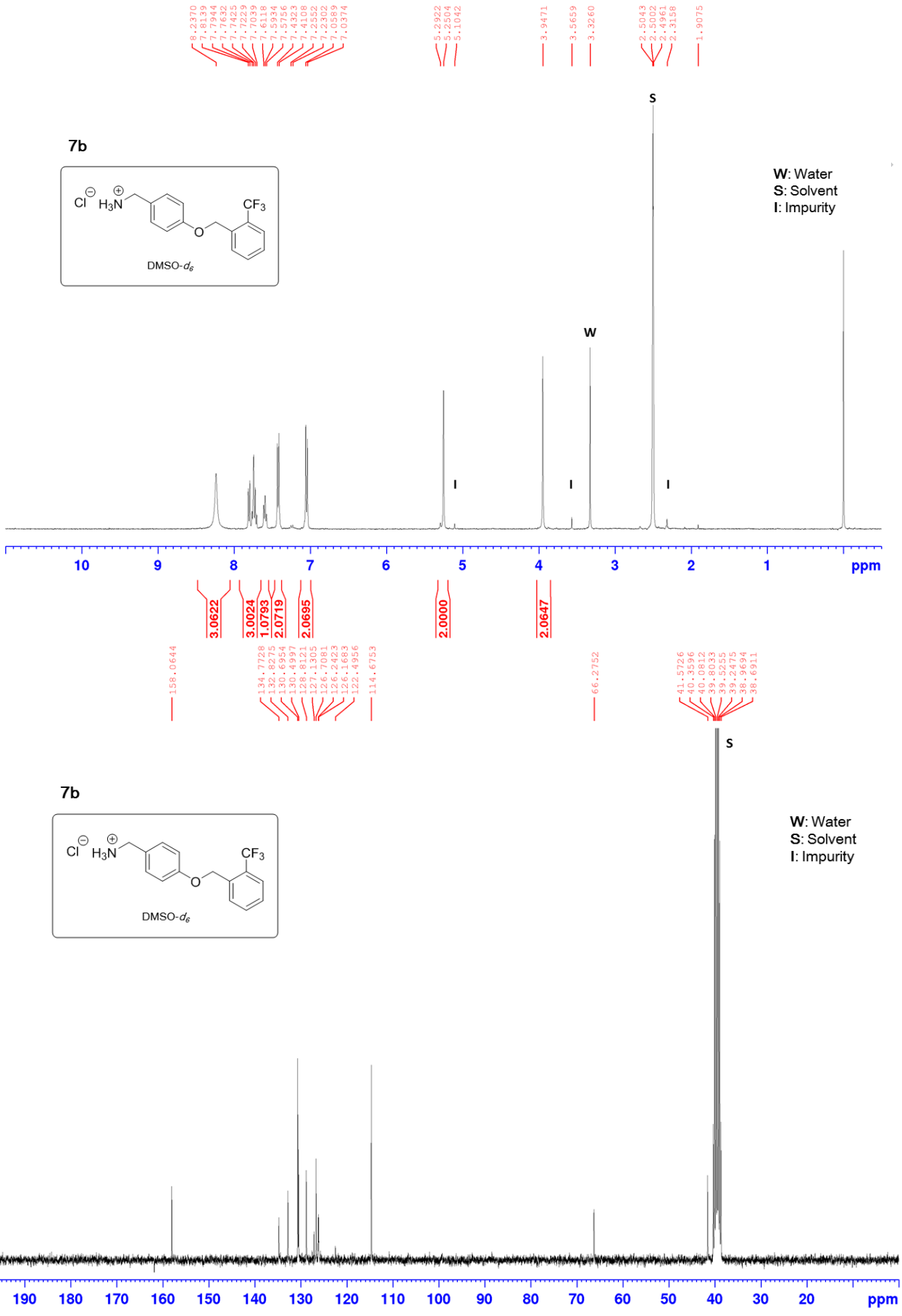
Preparation of (S)-2-((4-methoxybenzyl)amino)propanamide methanesulfonate (15).

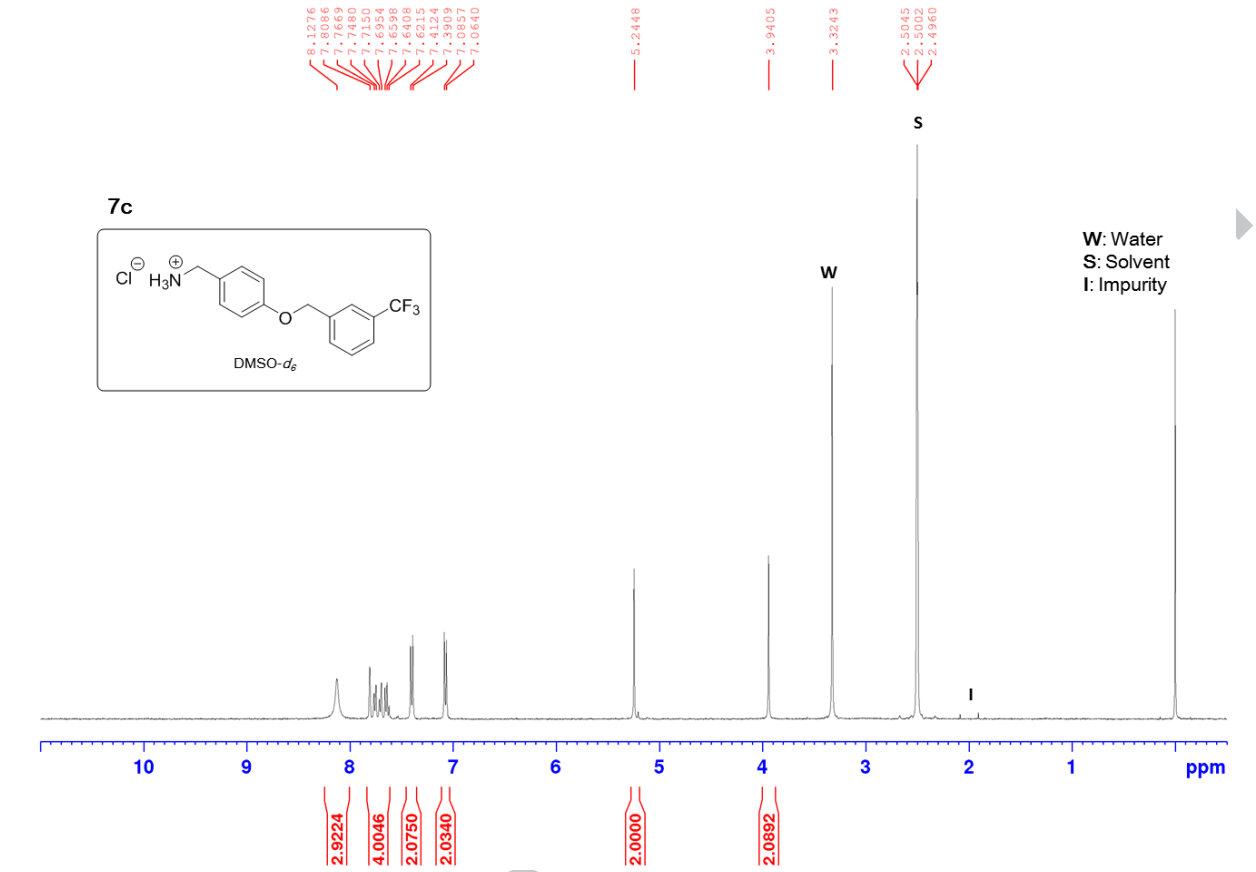
To MeOH solution (4 mL) of L-alanine amide hydrochloride (0.69 g, 5.5 mmol), trimethylamine (0.90 mL, 6.4 mmol) was added. The reaction mixture was stirred for 15 min at room temperature and then treated with *p*-anisaldehyde (0.45 mL, 3.7 mmol) at room temperature. After 2.5 h, the reaction mixture was concentrated in vacuo. The resulting residue was dissolved in EtOAc (20 mL) and washed (10 mL × 2) with brine (10 mL × 2). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. To crude mixture, MeOH (4 mL) solution and sodium cyanoborohydride (0.92 g, 14.7 mmol) were added. The reaction mixture was stirred at room temperature (2 h). The reaction mixture was concentrated in vacuo. The resulting residue was dissolved in EtOAc (20 mL) and washed (10 mL × 2) with brine (10 mL × 2). The organic layer was dried with anhydrous Na_2SO_4 and then concentrated in vacuo. The residue was purified by column chromatography with SiO_2 and gave (S)-2-((4-methoxybenzyl)amino)propanamide as a white solid (0.31 g, 40%); R_f = 0.12 (only EtOAc); mp: 111-112 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 1.11 (d, J = 6.88 Hz, C**H**$_3$), 2.31 (br s, N**H**), 2.98 (q, J = 6.88 Hz, CH_3C**H**), 3.47 (d, J = 13.1 Hz, C**H**$_2$), 3.60 (d, J = 13.1 Hz, C**H**$_2$), 3.72 (s, OC**H**$_3$), 6.86 (d, J = 8.56 Hz, 2 Ar**H**), 6.97 (br s, C(O)N**H**H), 7.23 (d, J = 8.52 Hz, 2 Ar**H**), 7.30 (br s, C(O)NH**H**); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.7 (**C**H_2), 52.0, 55.3, 57.6, 114.0, 129.2, 131.7, 158.8 (6 Ar**C**), 178.4 (**C**O).

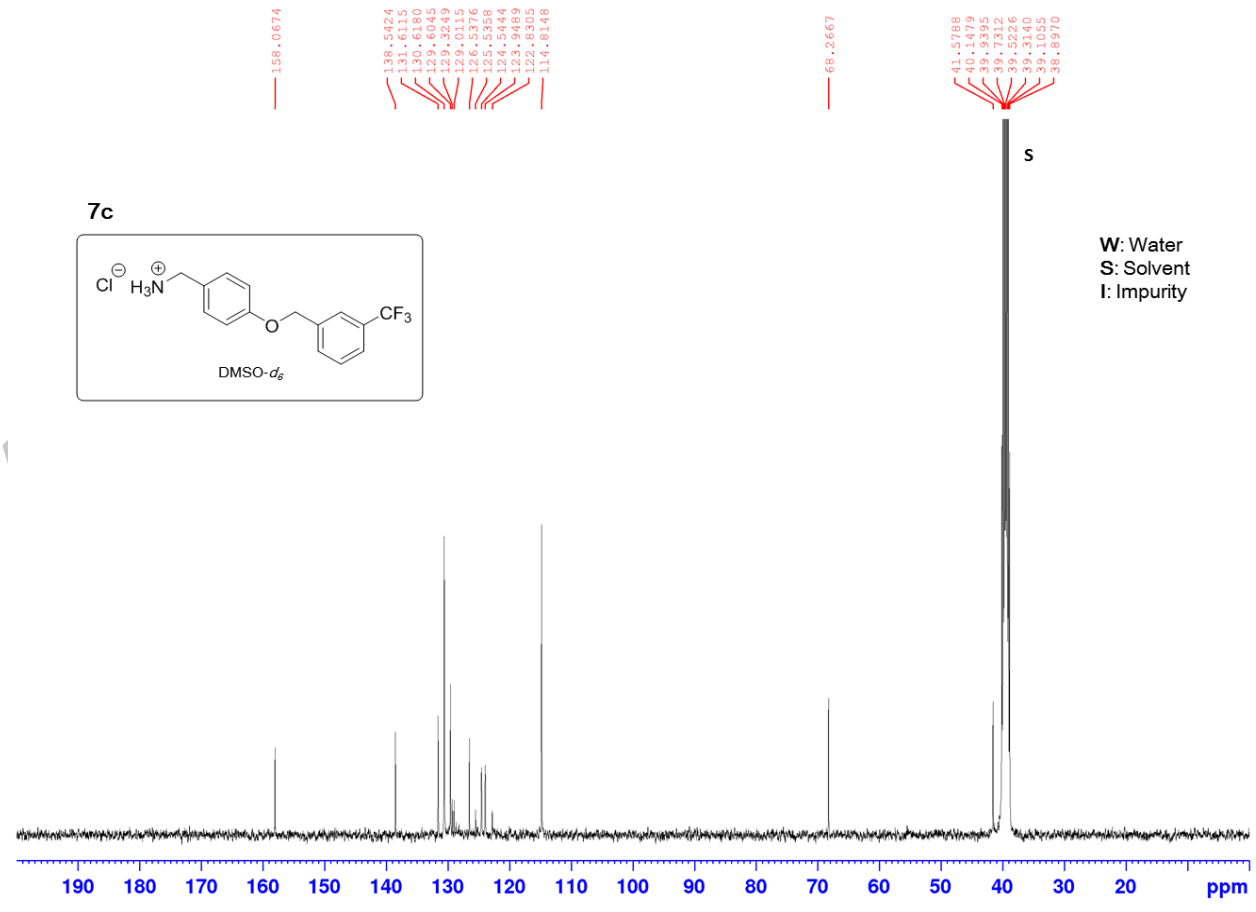
Methanesulfonic acid (0.08 mL, 1.2 mmol) was added to a solution of (*S*)-2-((4-methoxybenzyl)amino)propanamide (0.20 g, 1.0 mmol) in EtOAc (2 mL) at 60 ^oC. After 1 h, the reaction mixture was cooled until room temperature and then filtered in vacuo and washed with EtOAc. The filtercake was dried without further purification and gave **15** as a white solid (0.28 g, 95%); mp: 202–203 ^oC ^1H NMR (400 MHz, DMSO-d_6) δ 1.42 (d, J = 6.92 Hz, C**H**$_3$$SO_3^-$), 2.39 (s, C**H**$_3$), 3.72–3.82 (m, CH_3C**H**, OC**H**$_3$), 4.03 (s, C**H**$_2$), 6.99 (J = 8.44 Hz, 2Ar**H**), 7.41 (J = 8.48 Hz, 2Ar**H**), 7.62 (s, C(O)N**H**H), 7.93 (s, C(O)NH**H**), 9.03 (br s, N**H**$_2^+$); ^{13}C NMR (75 MHz, DMSO-d_6) 16.4, 48.5, 54.7, 55.7, 114.5, 123.9, 132.1, 160.2, 171.0 (**C**O, 6 Ar**C**, **C**H_2, **C**H_3SO_3H).

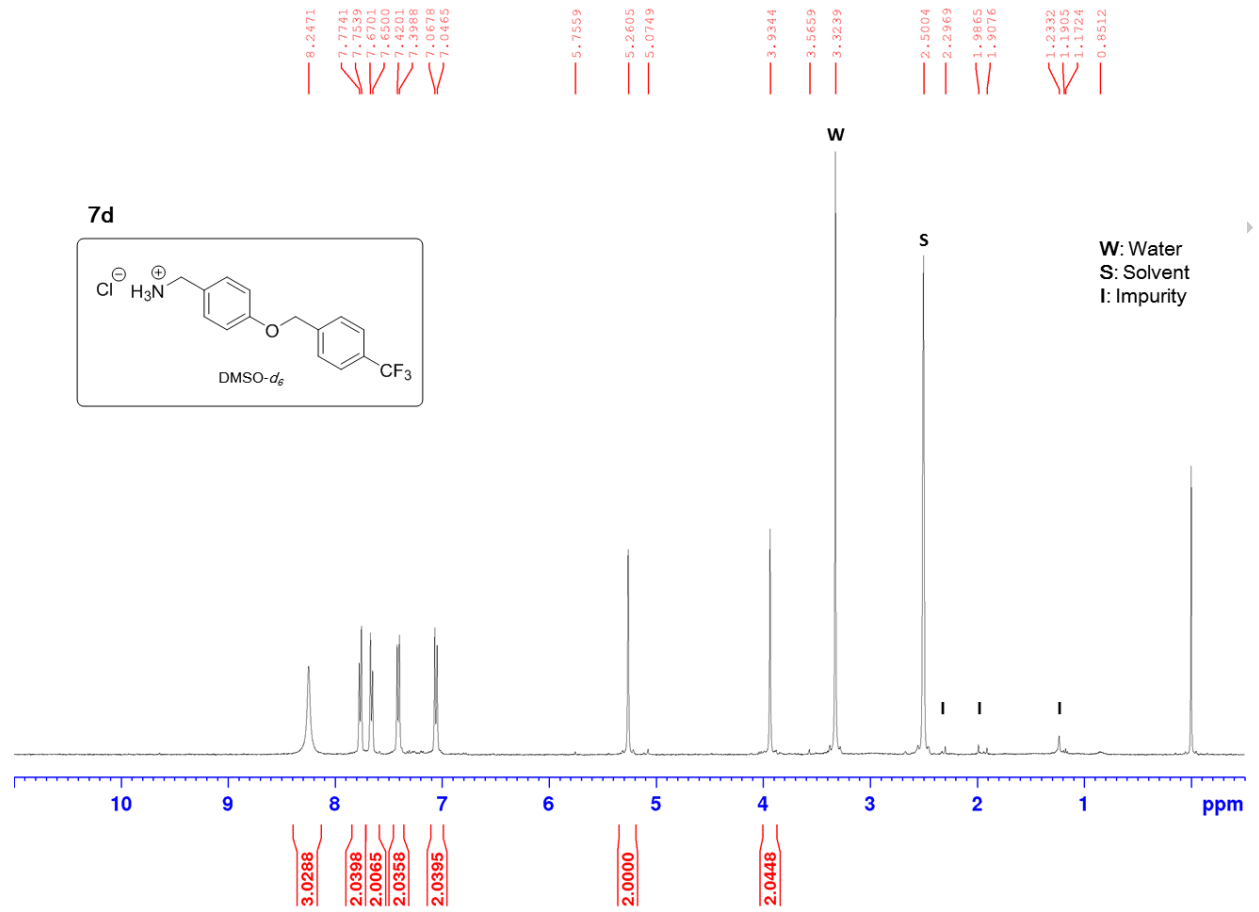


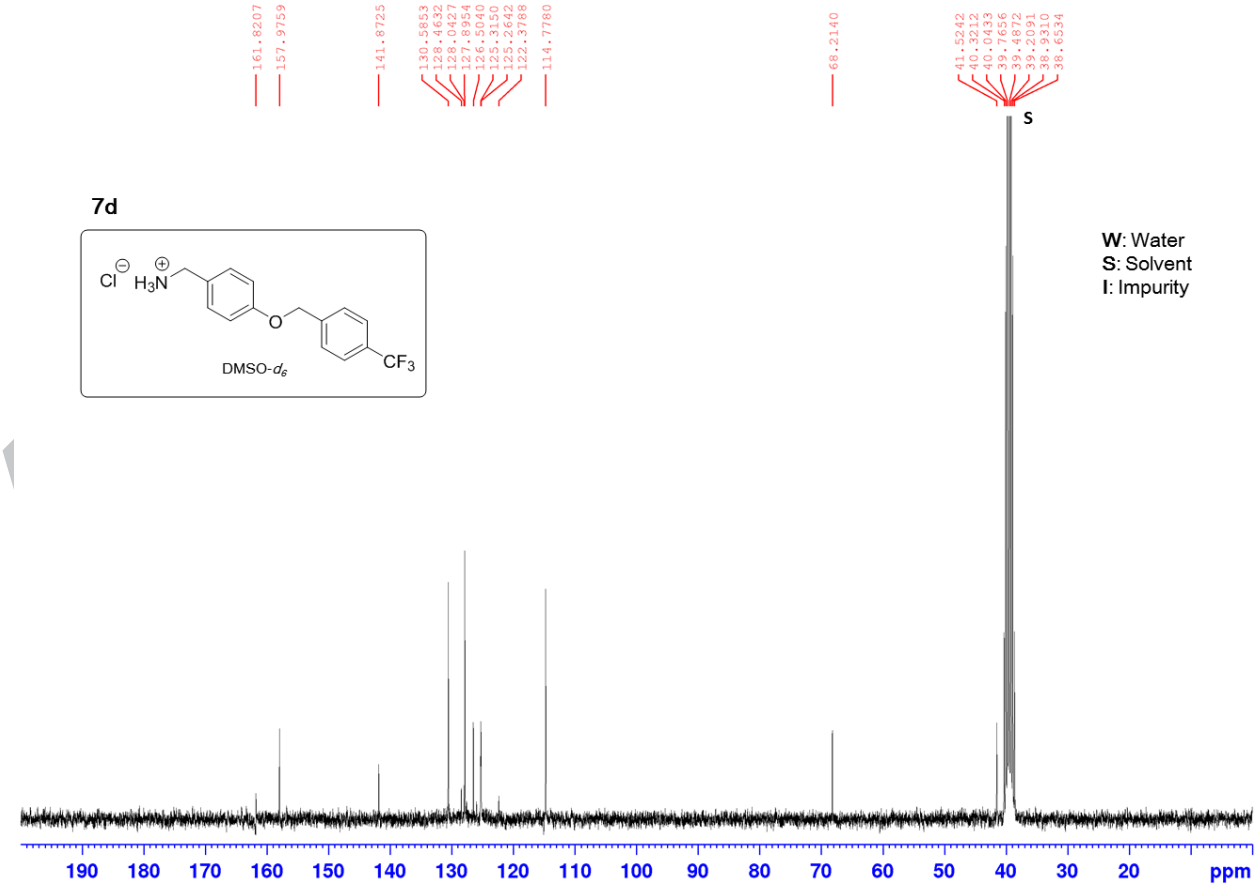












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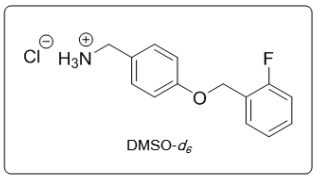

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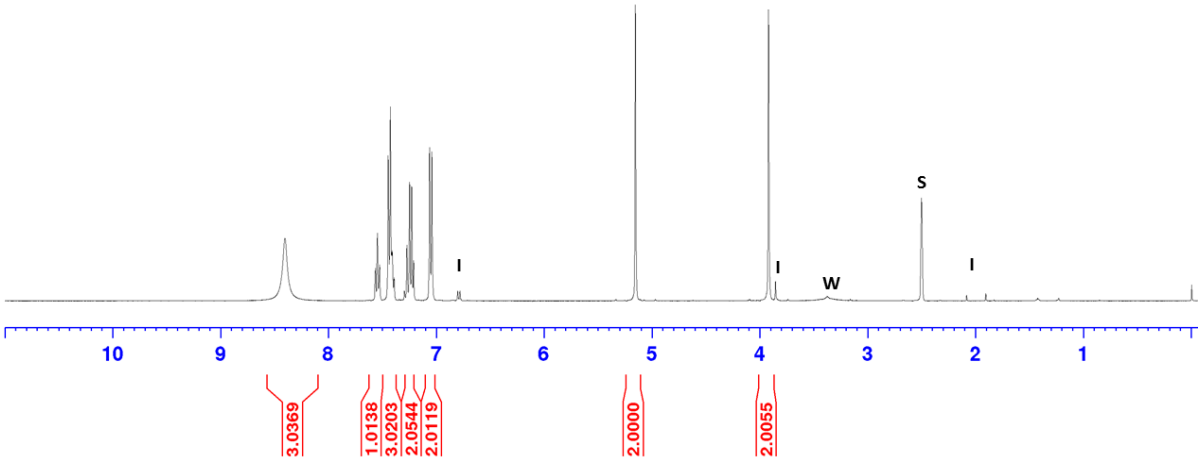
S: Solvent
I: Impurity



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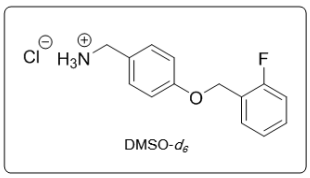

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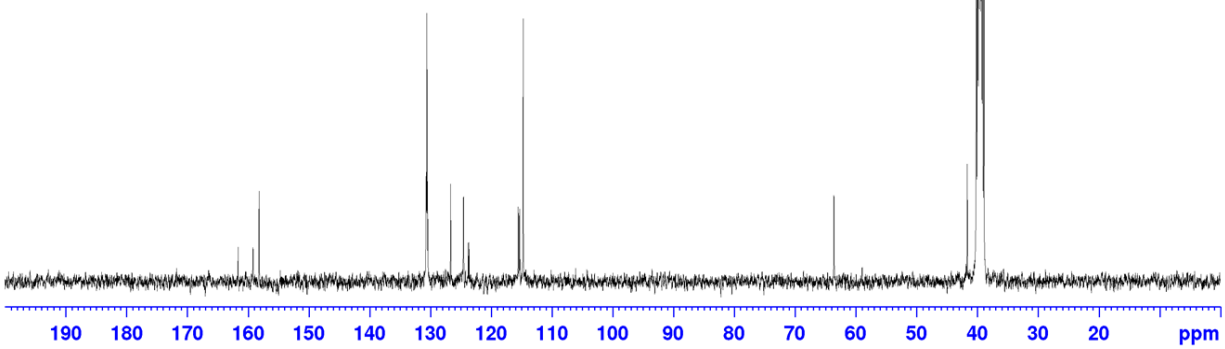
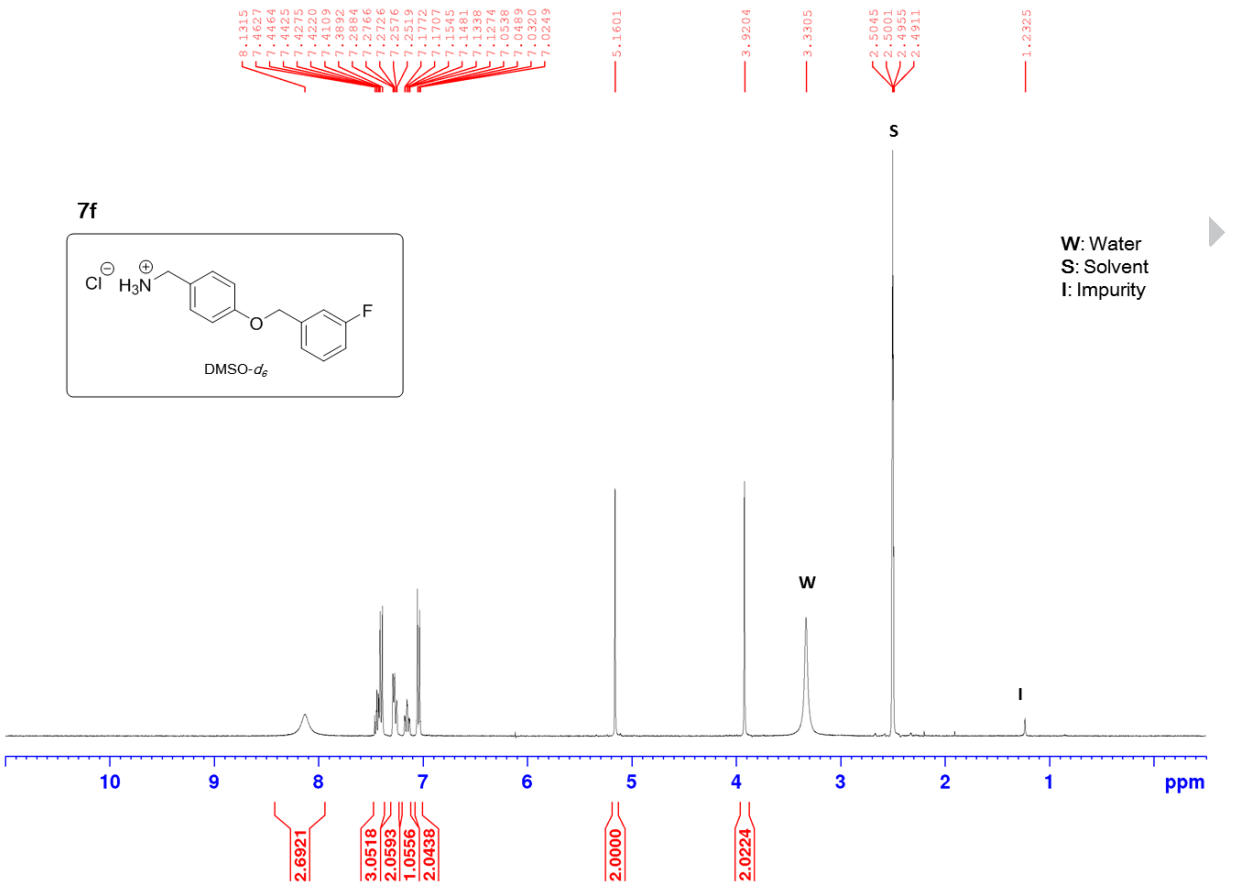
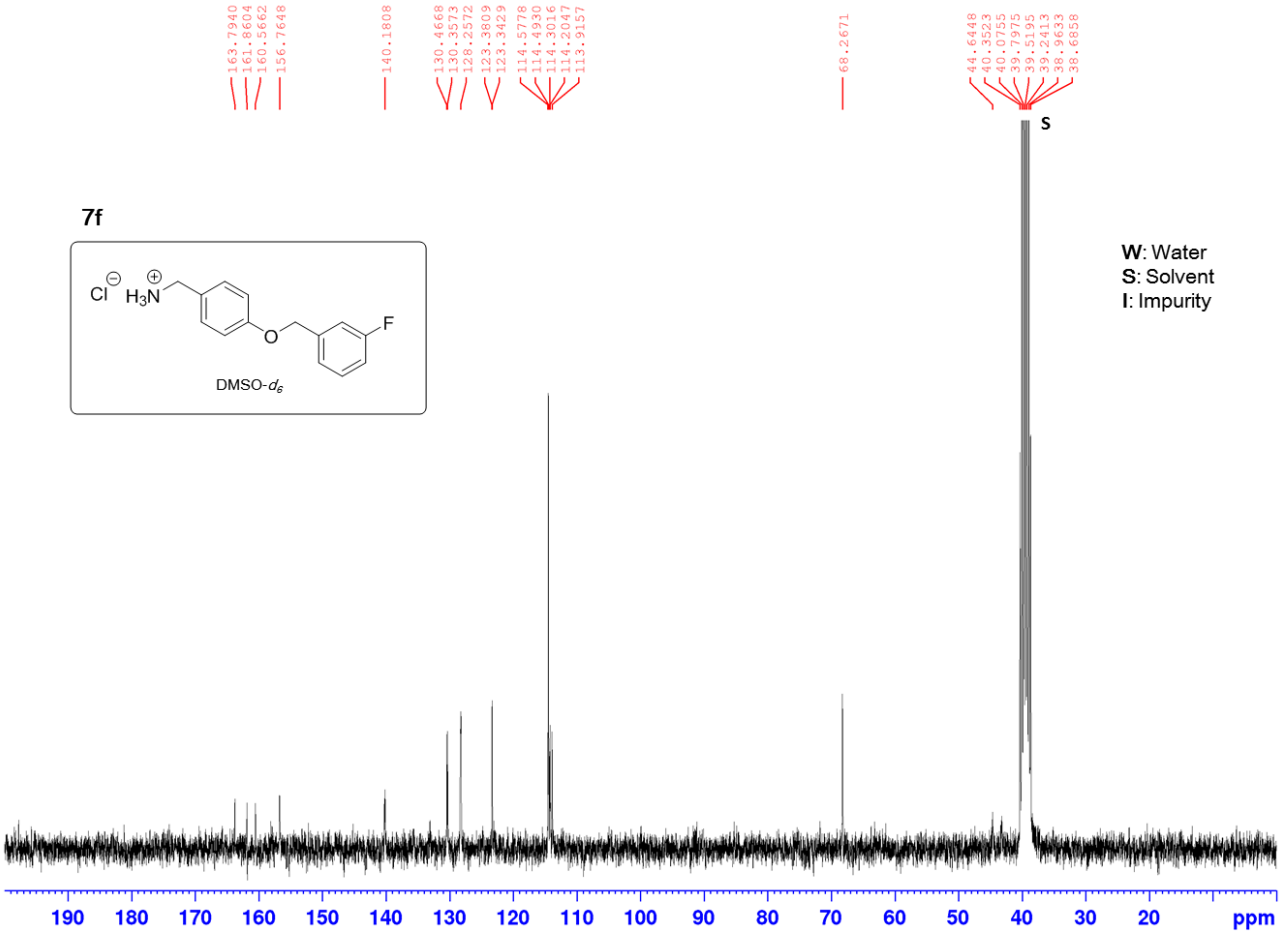
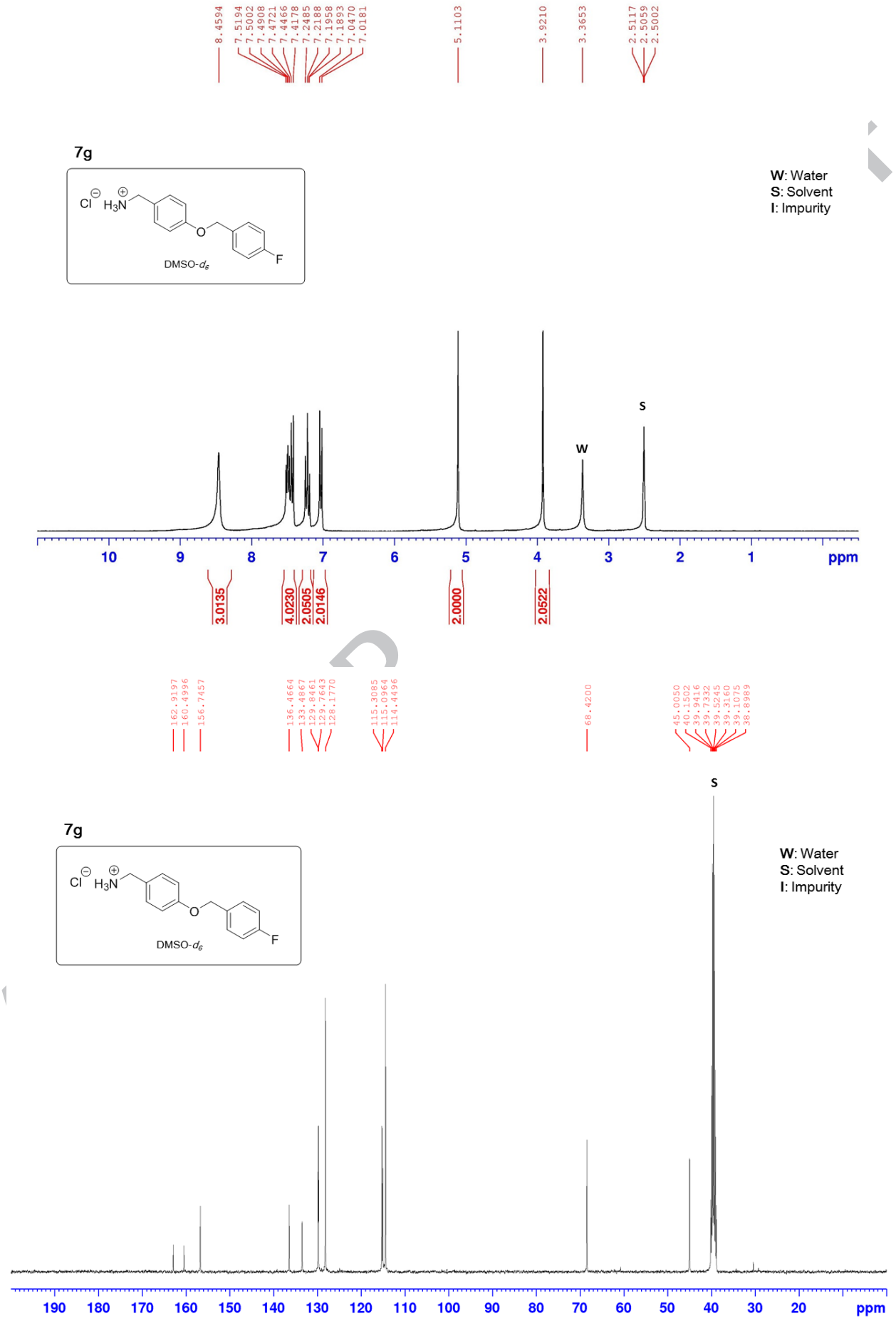
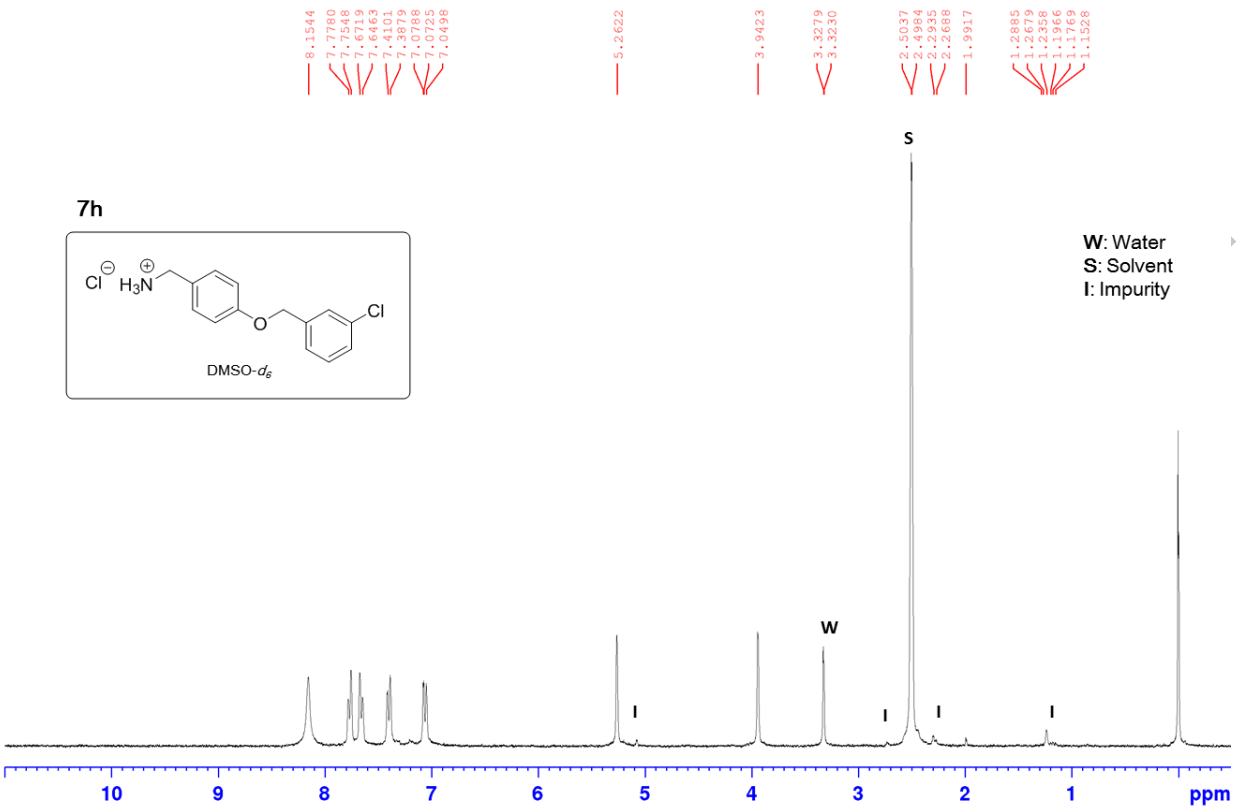
S: Solvent
I: Impurity

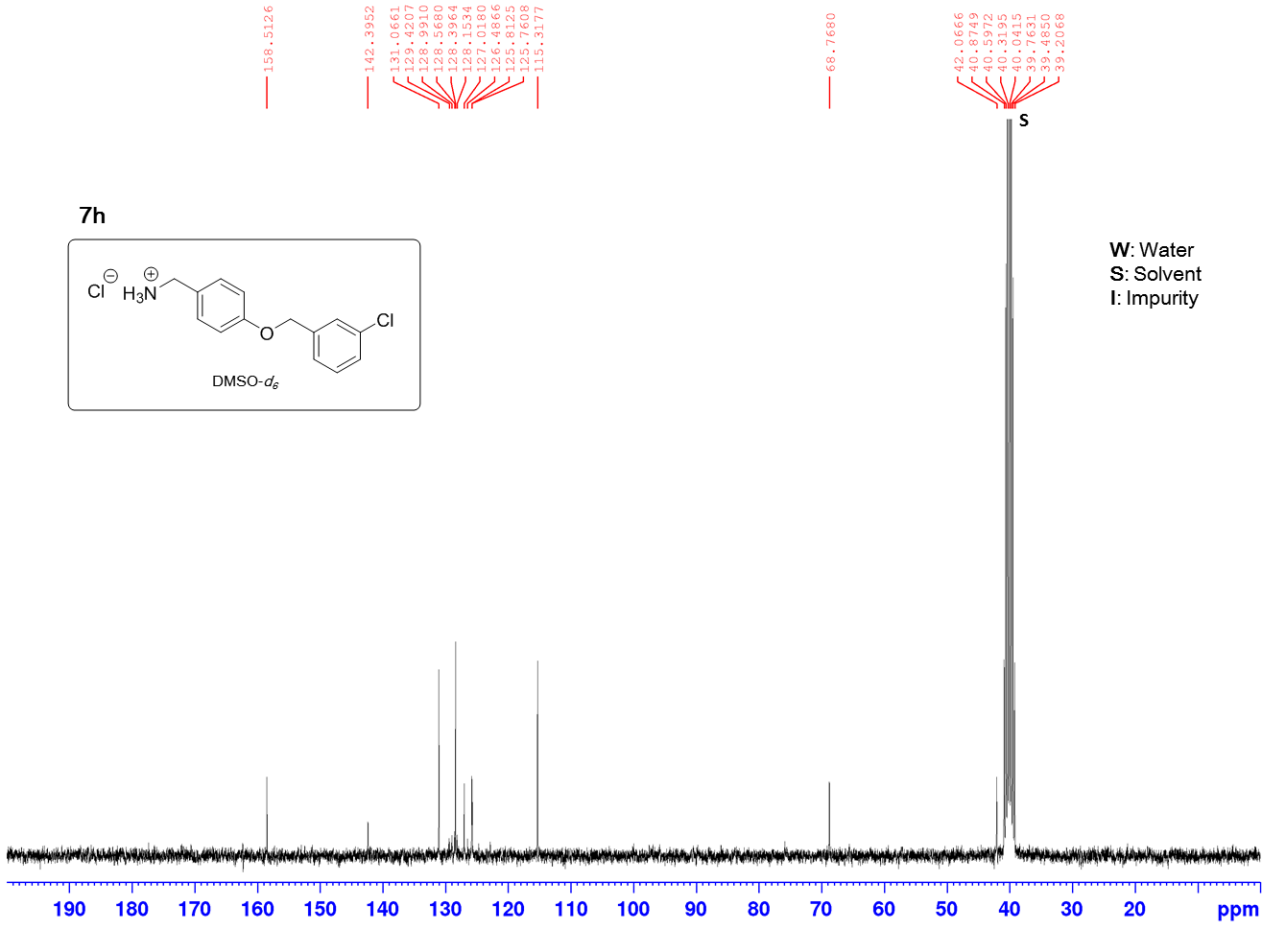


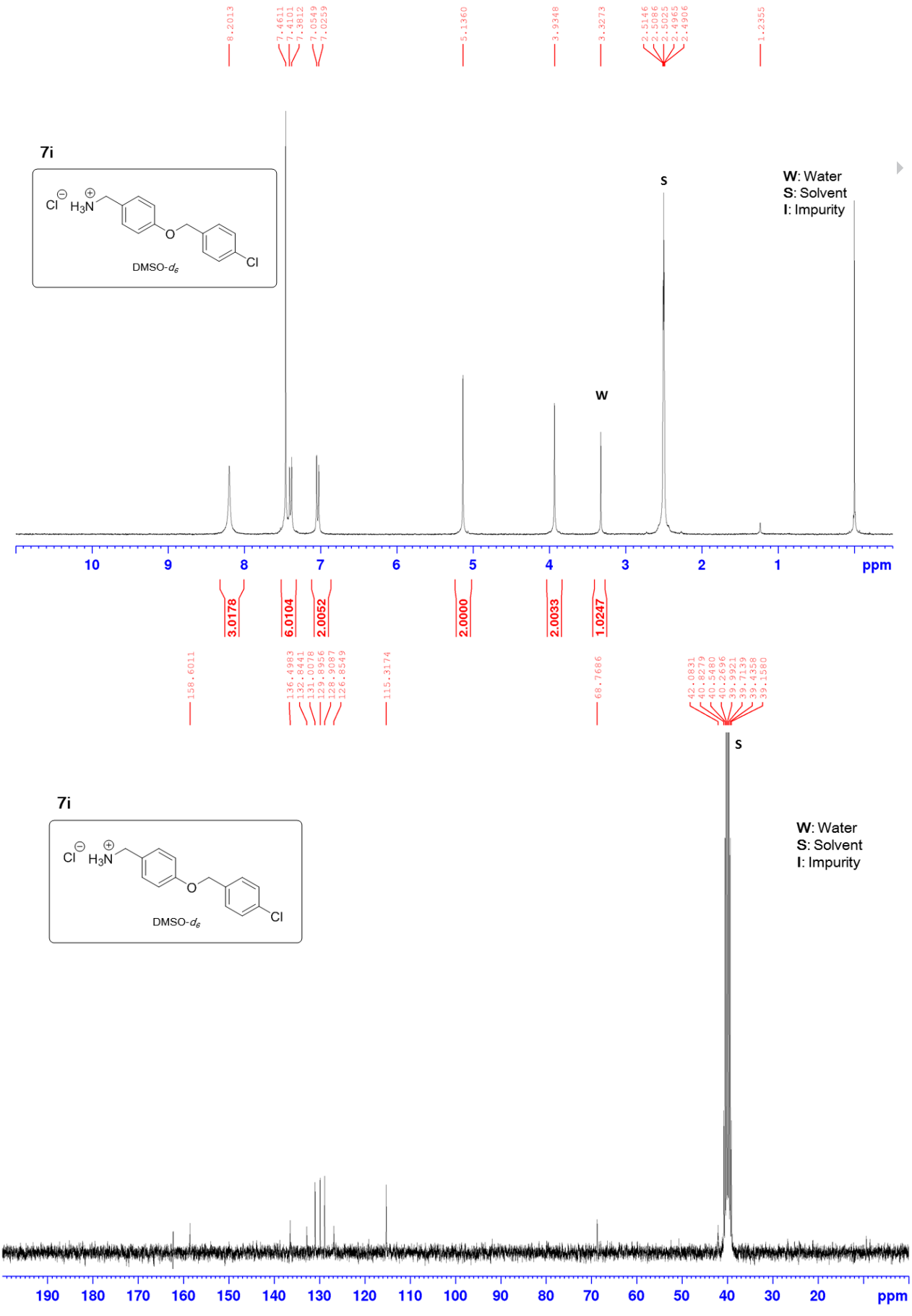


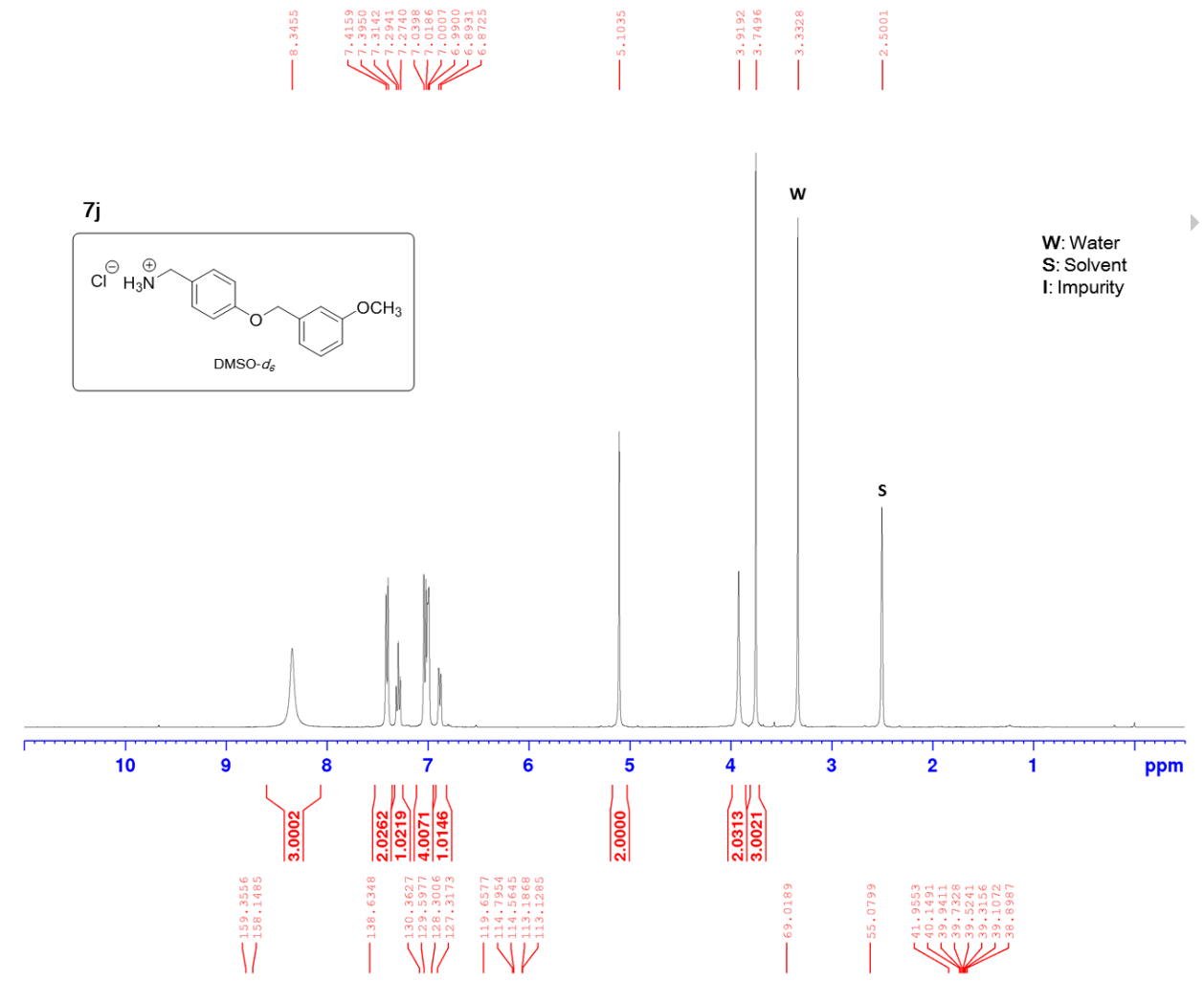


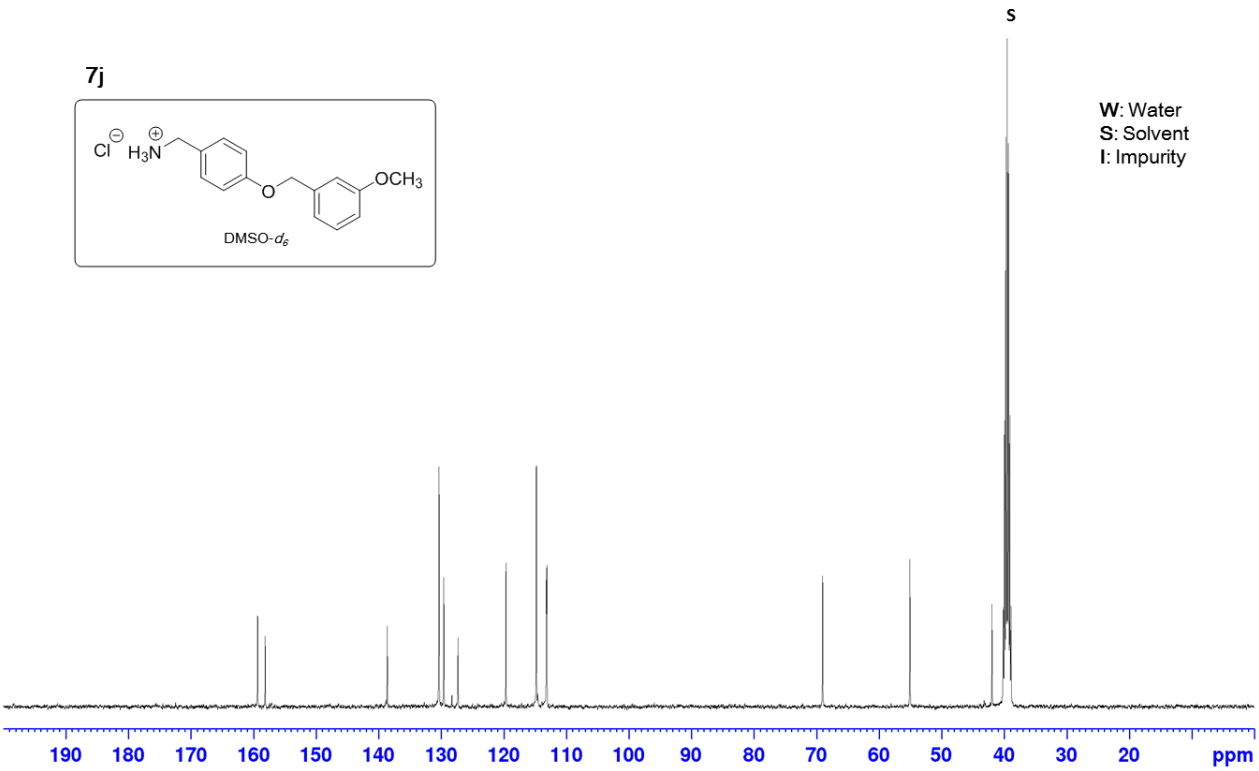


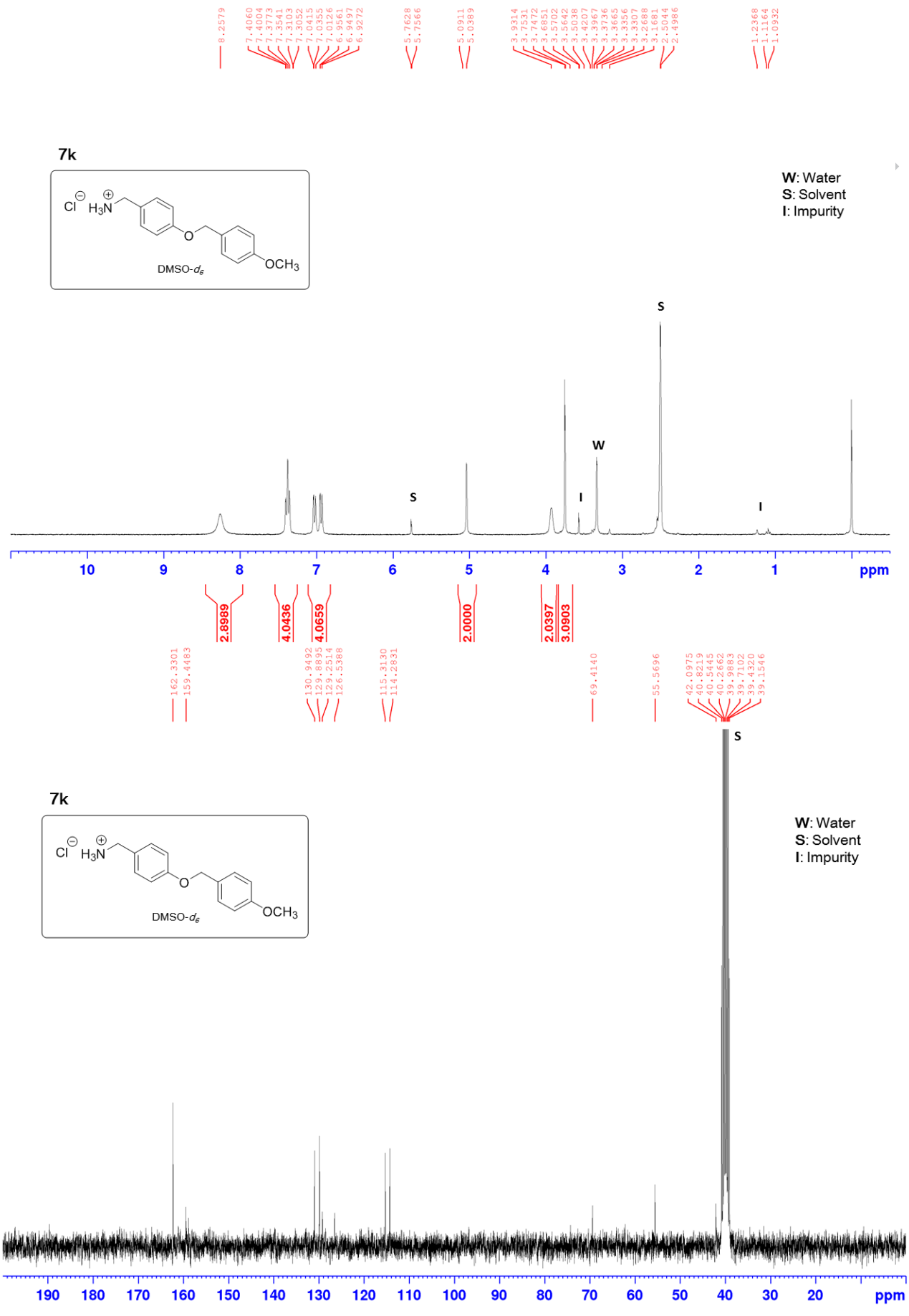


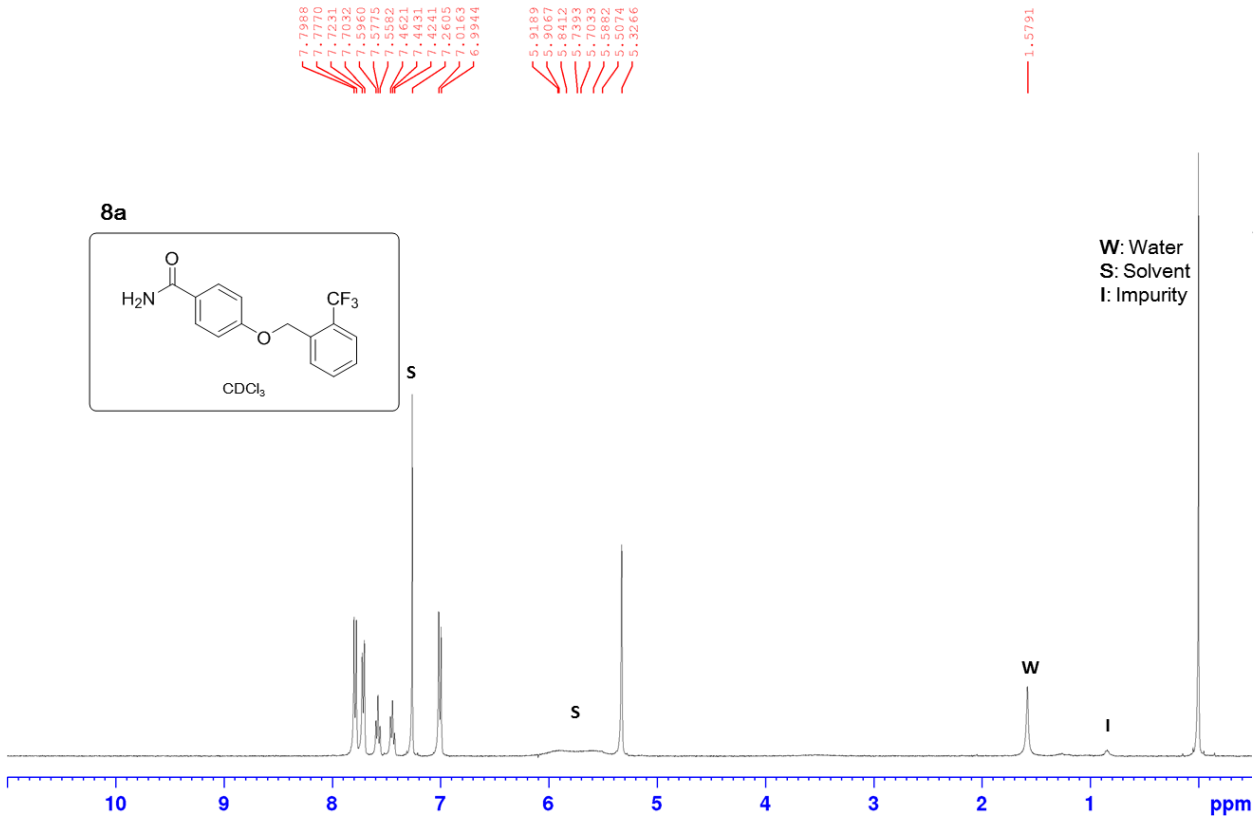


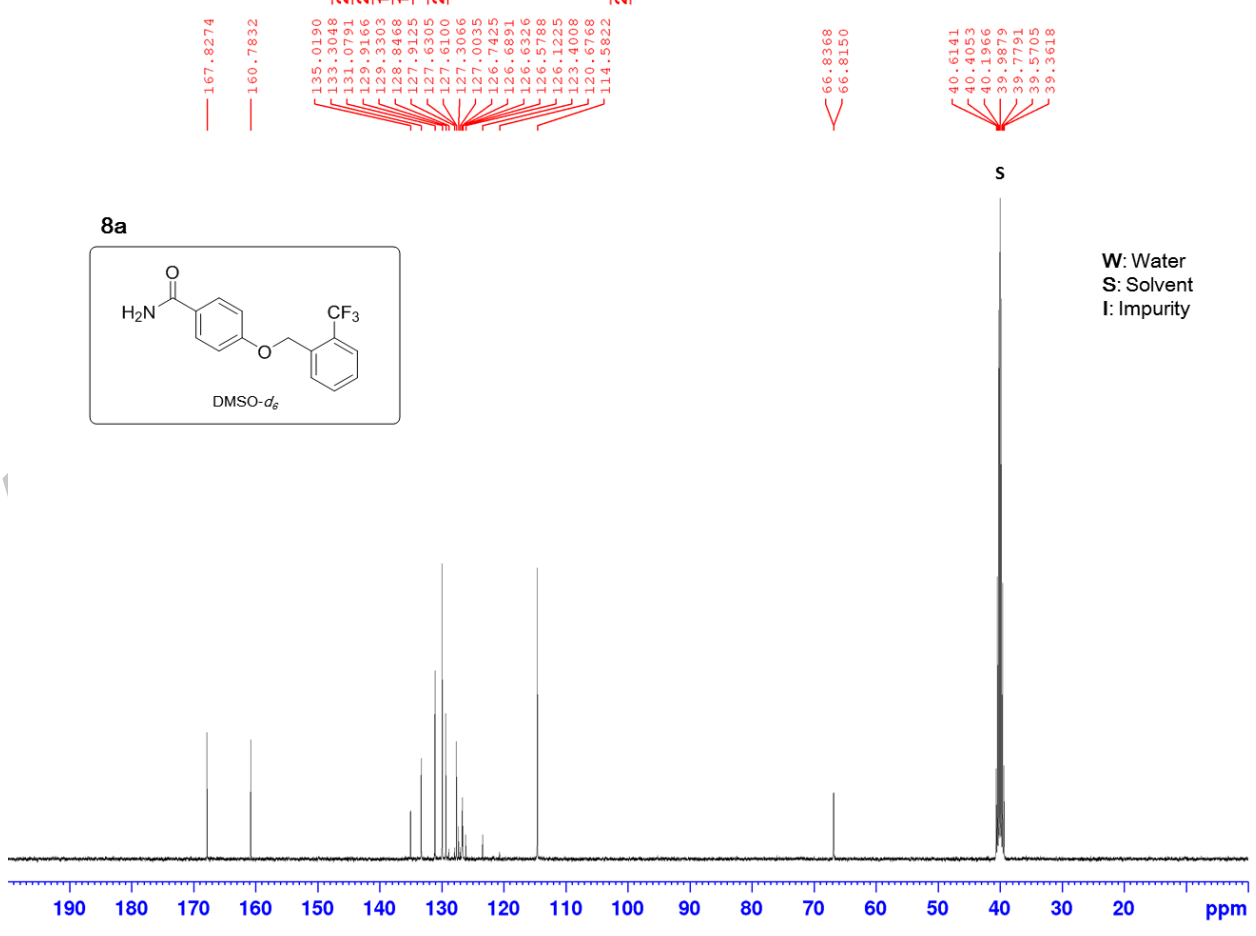


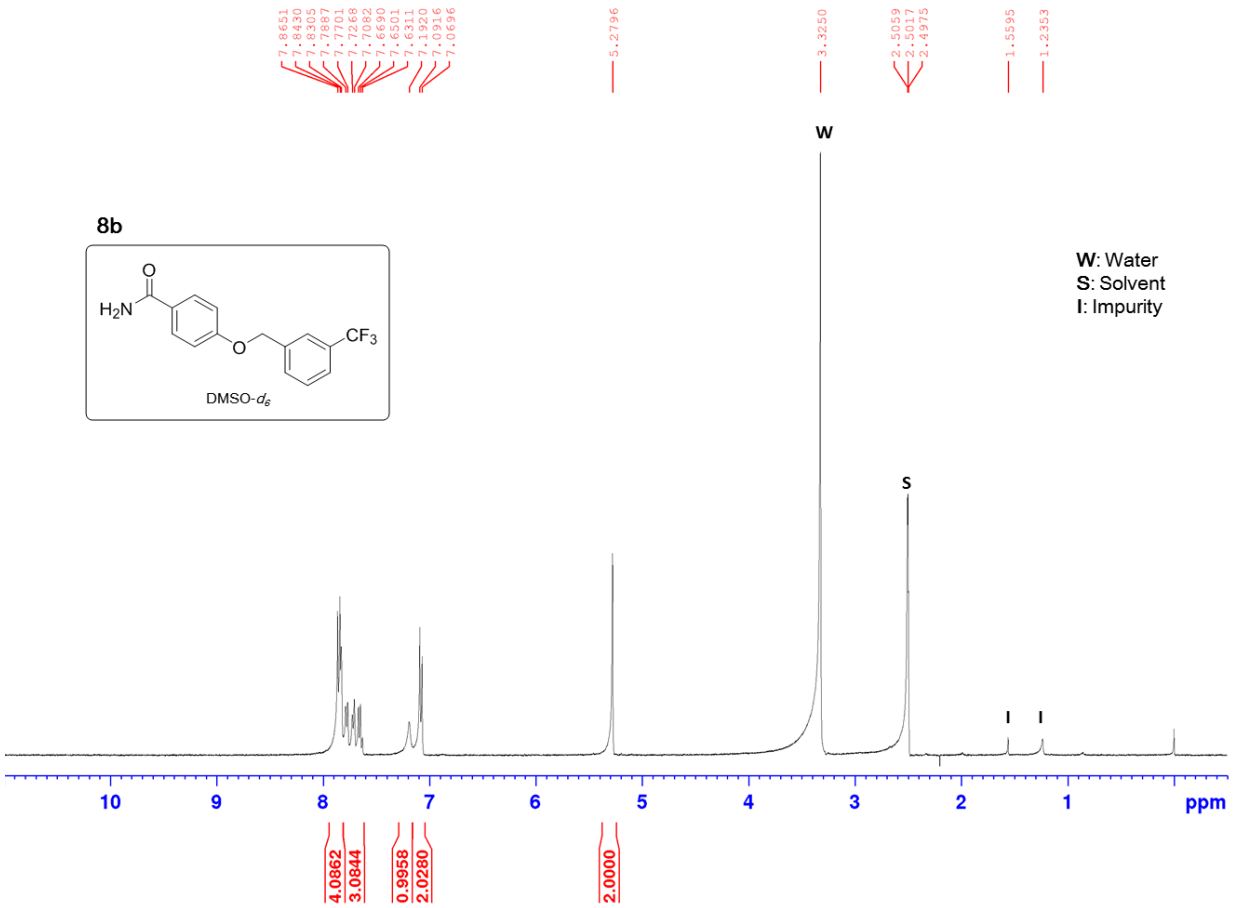


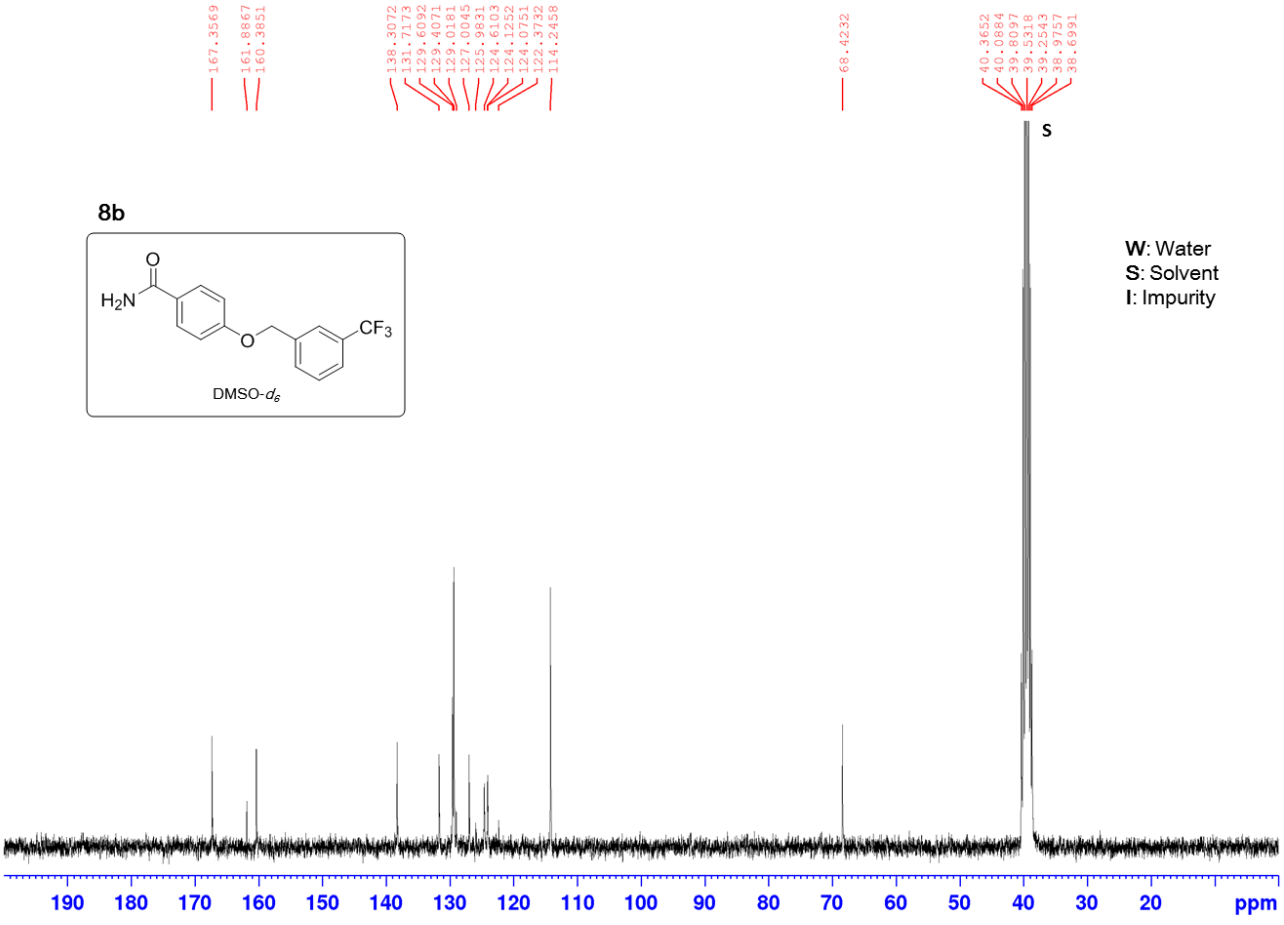


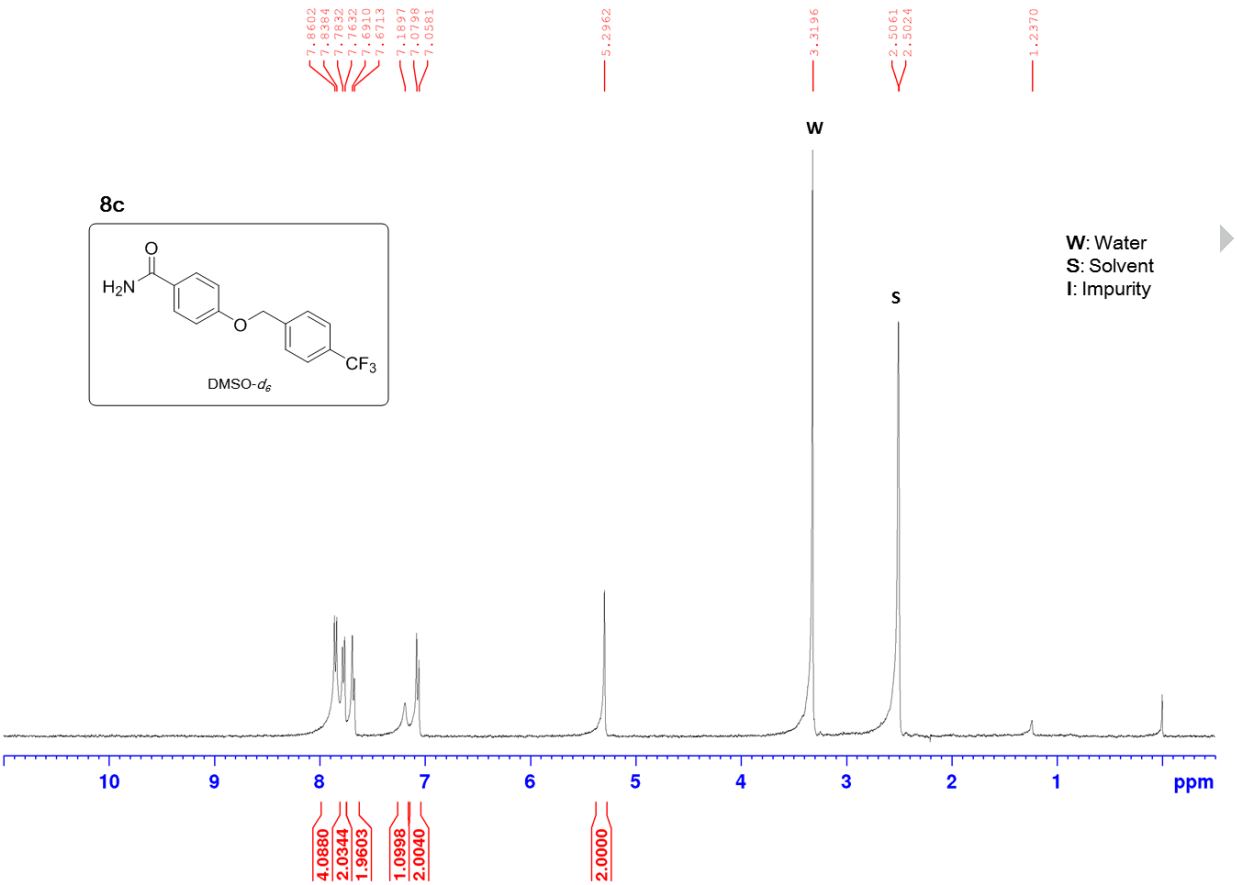


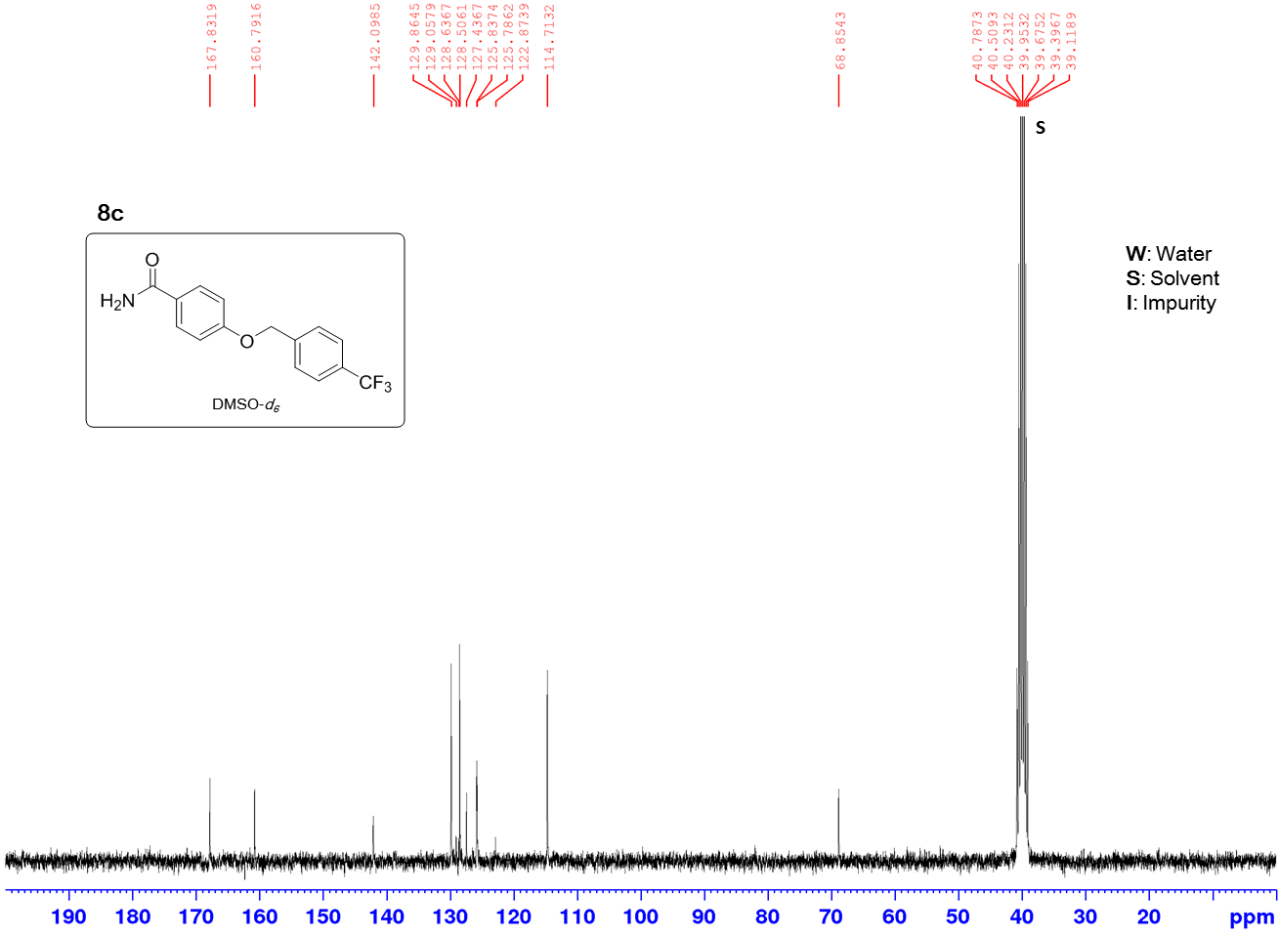












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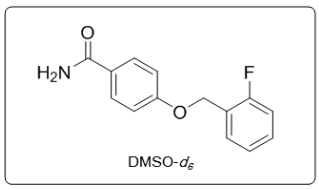

W: Water
S: Solvent
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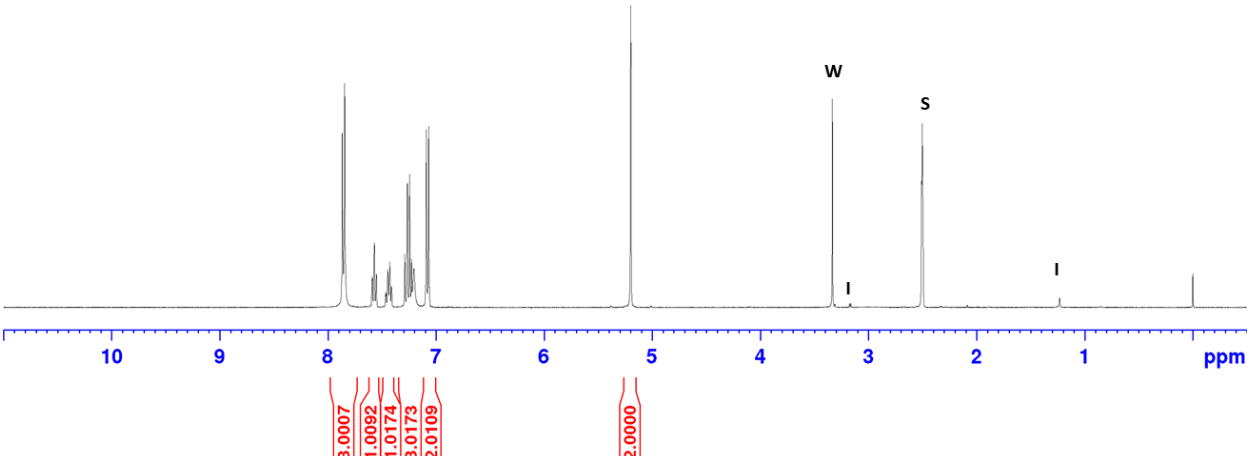

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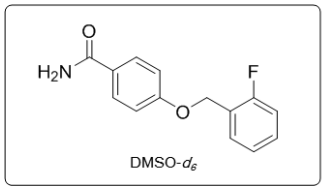

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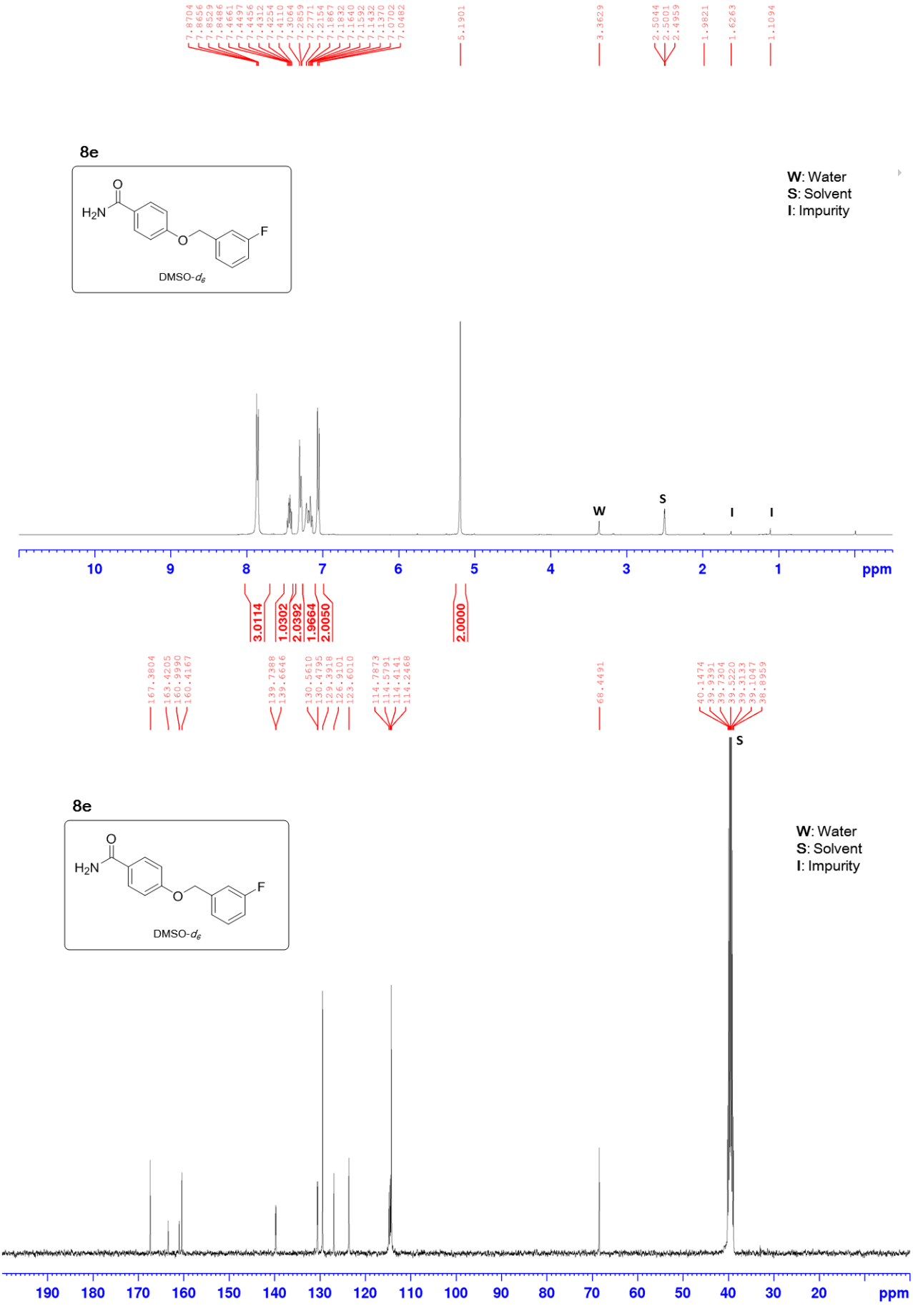

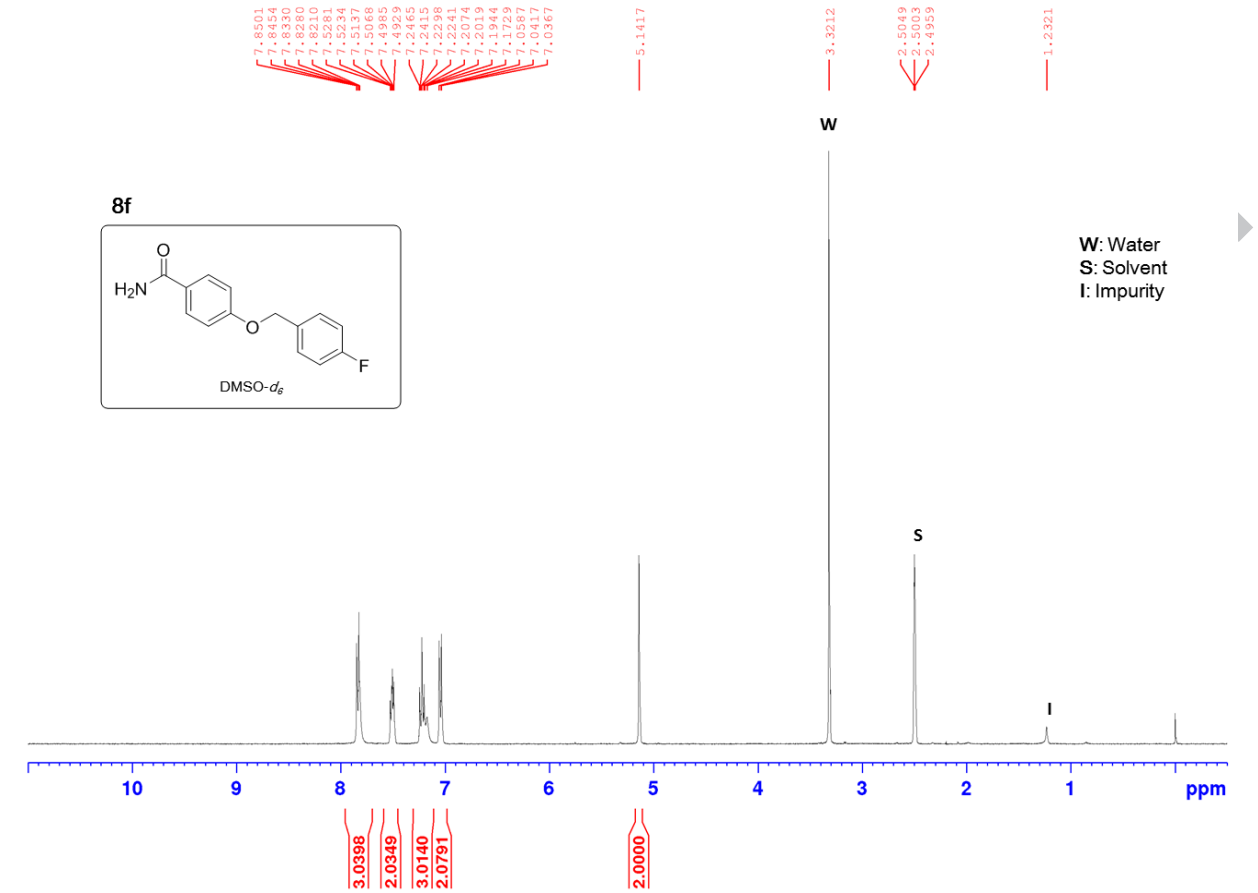

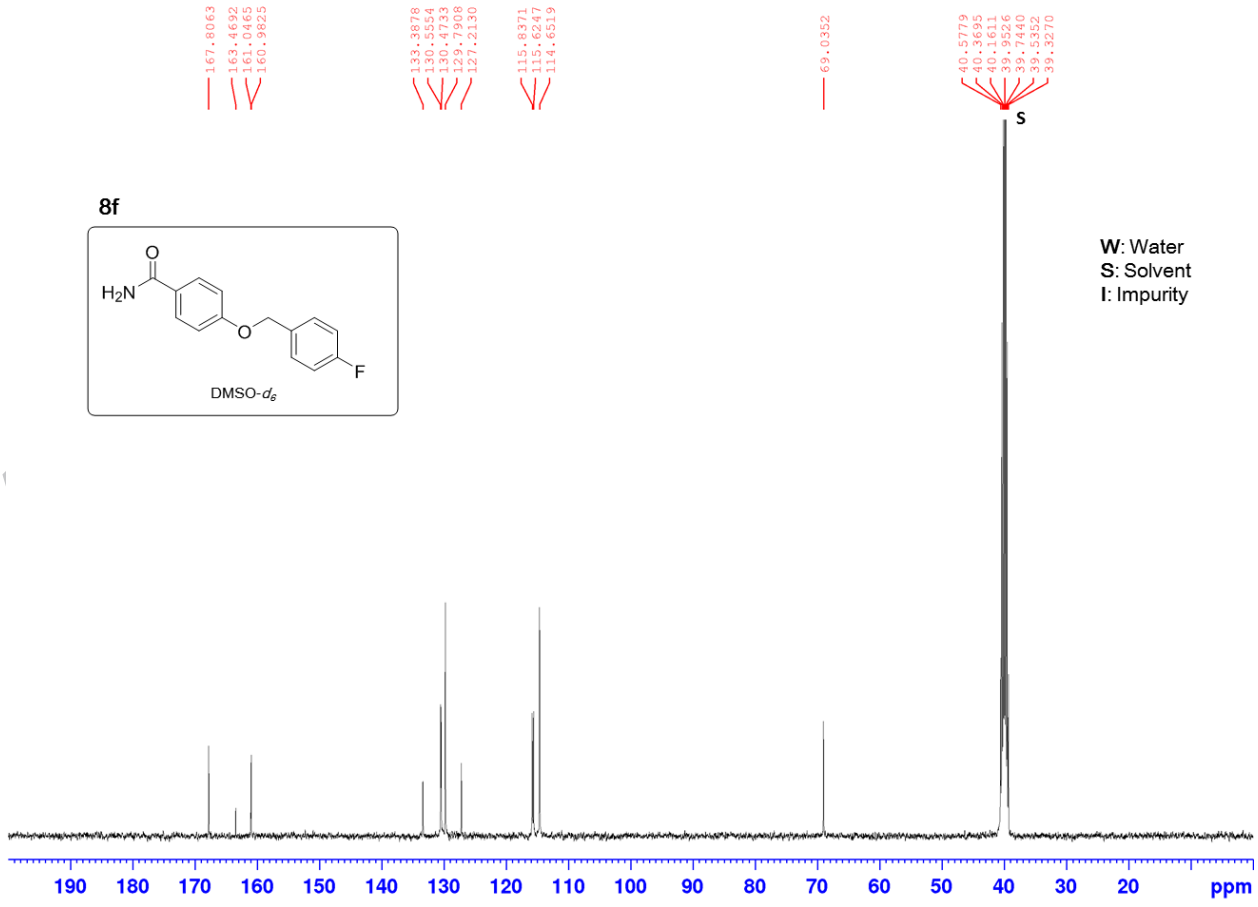

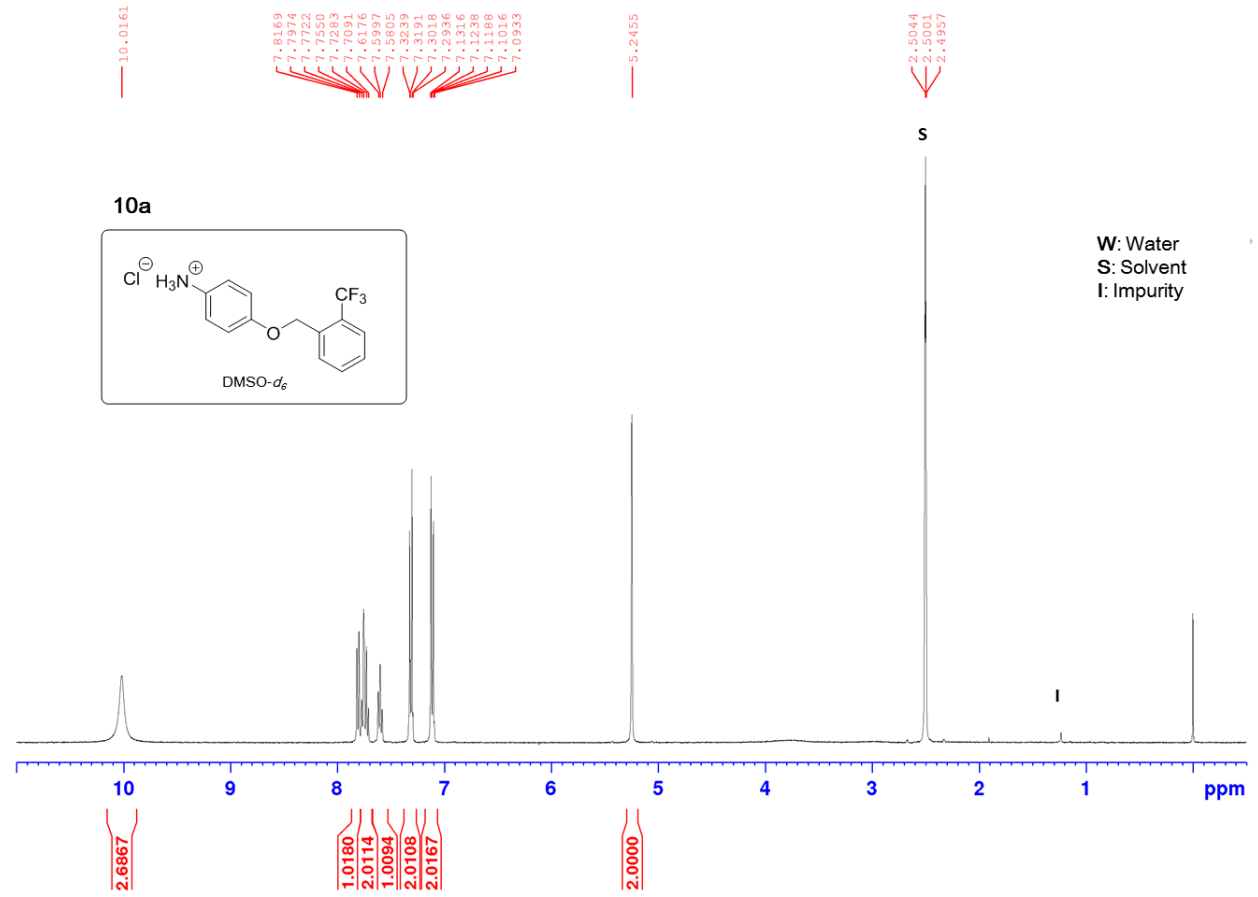

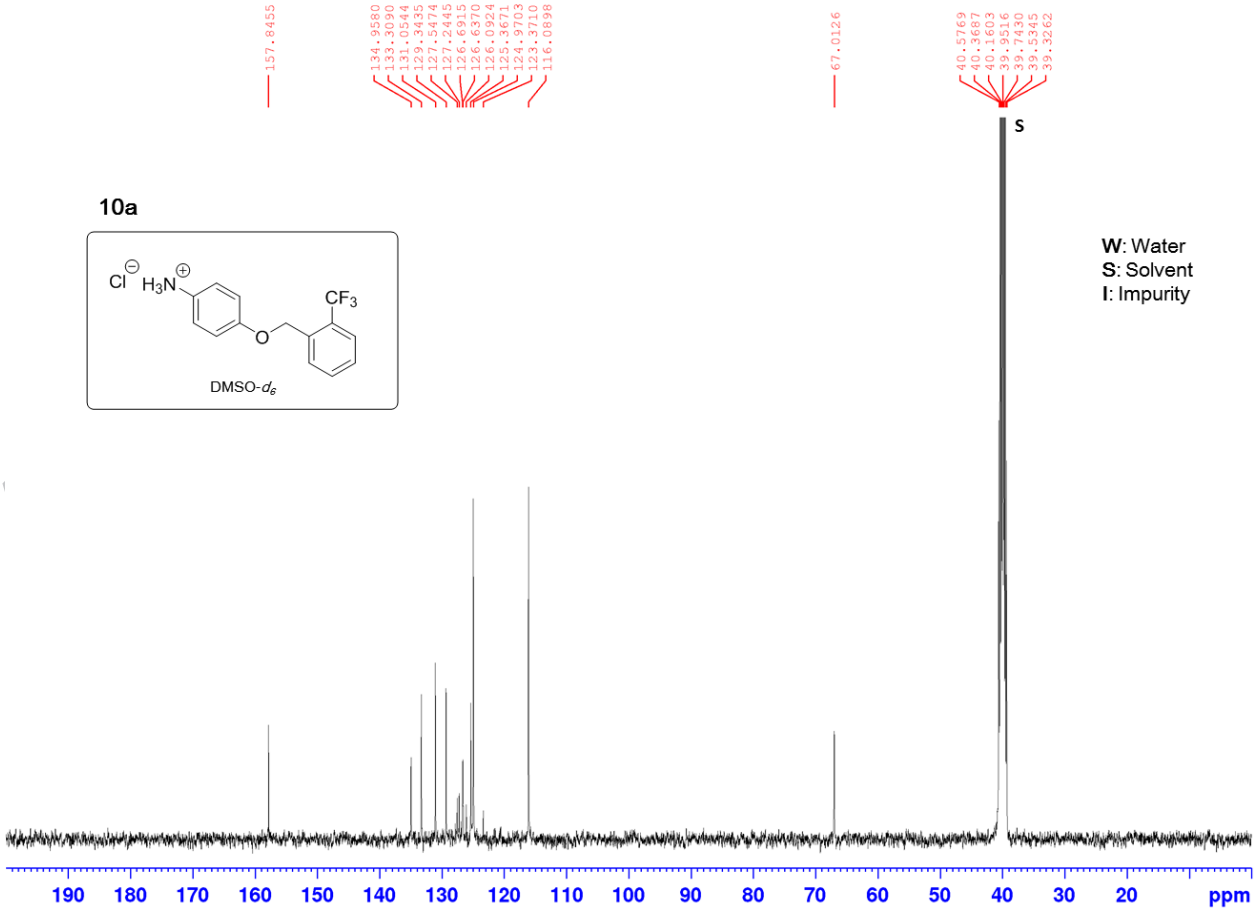

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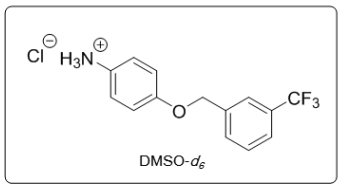

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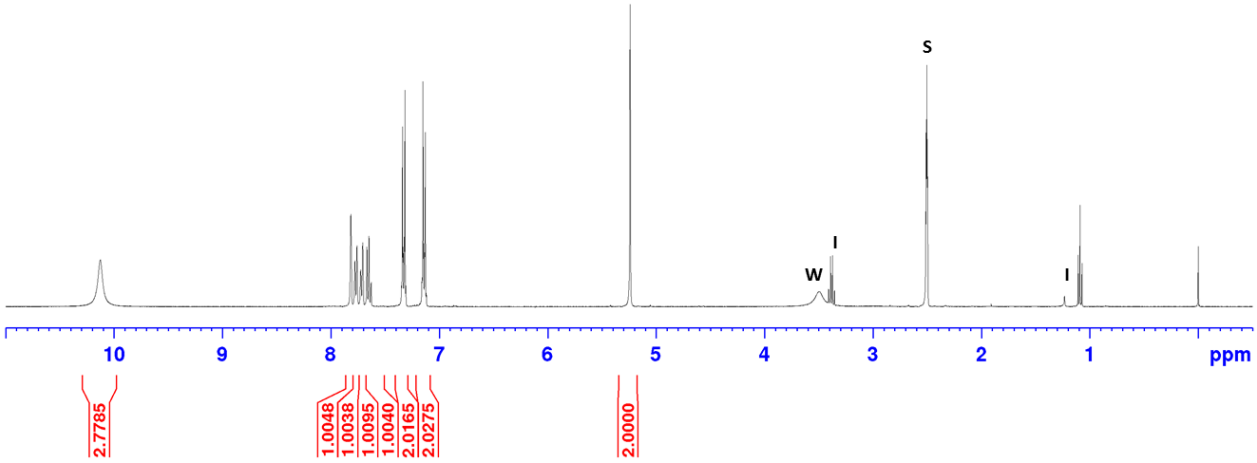

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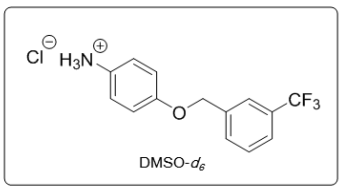

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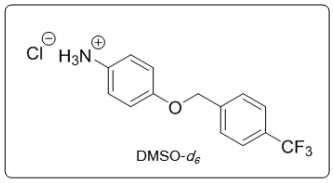

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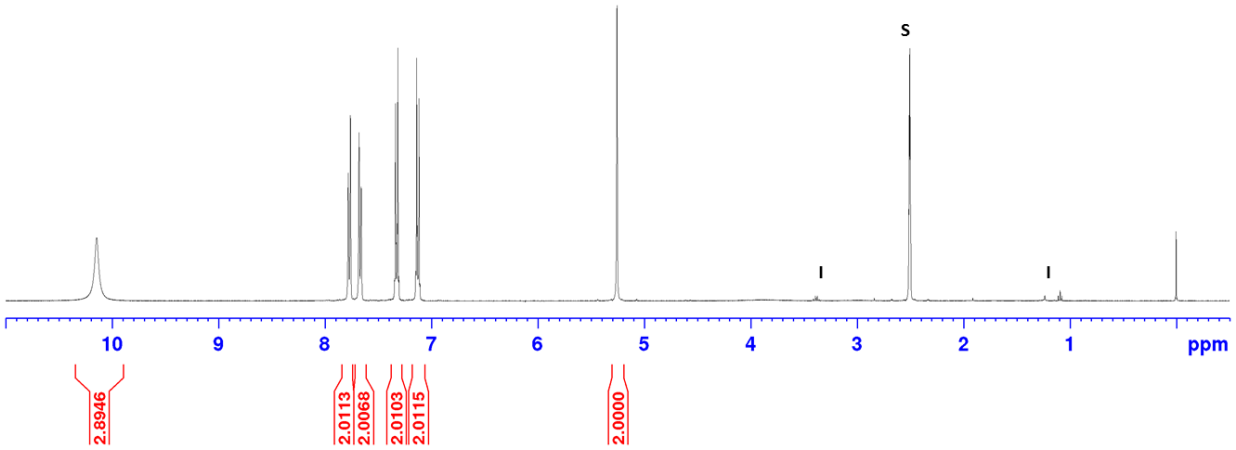

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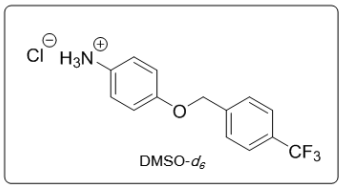

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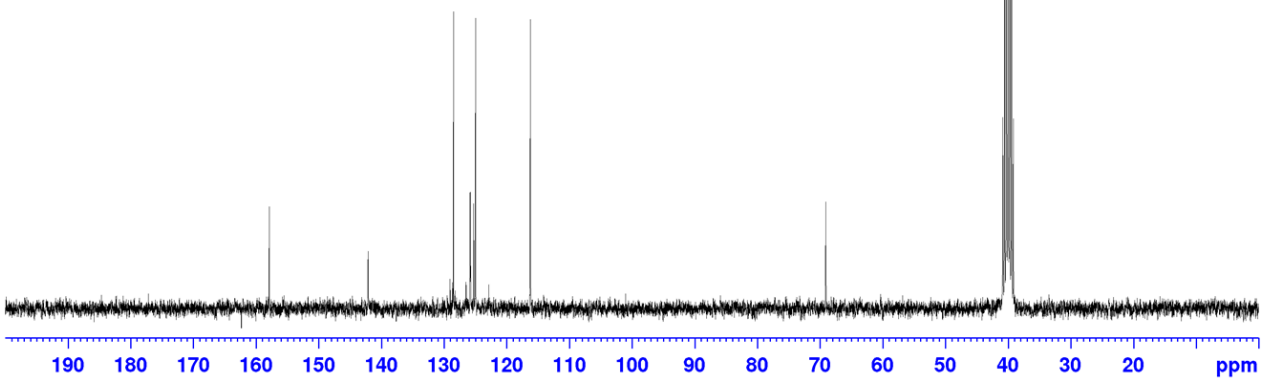

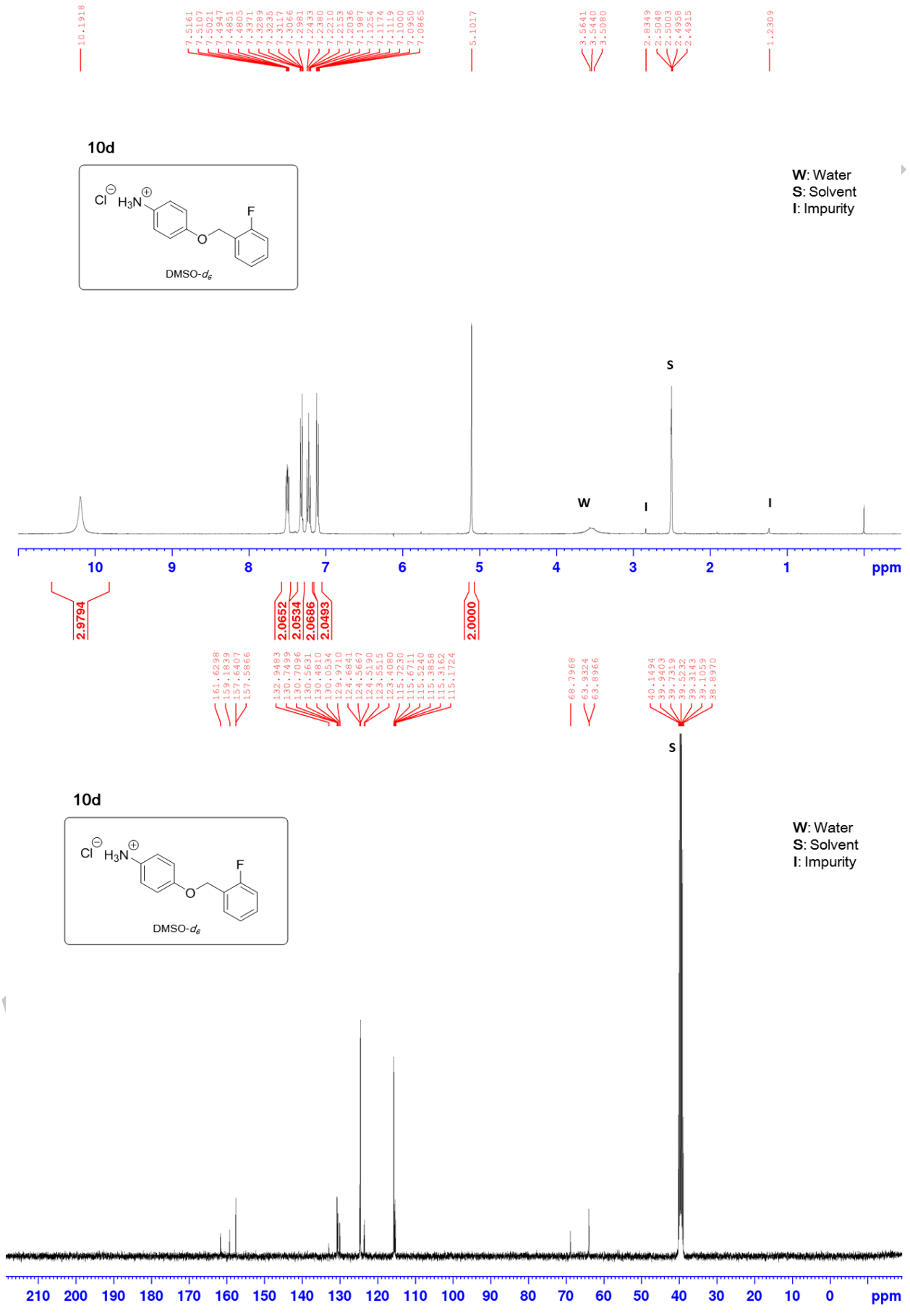

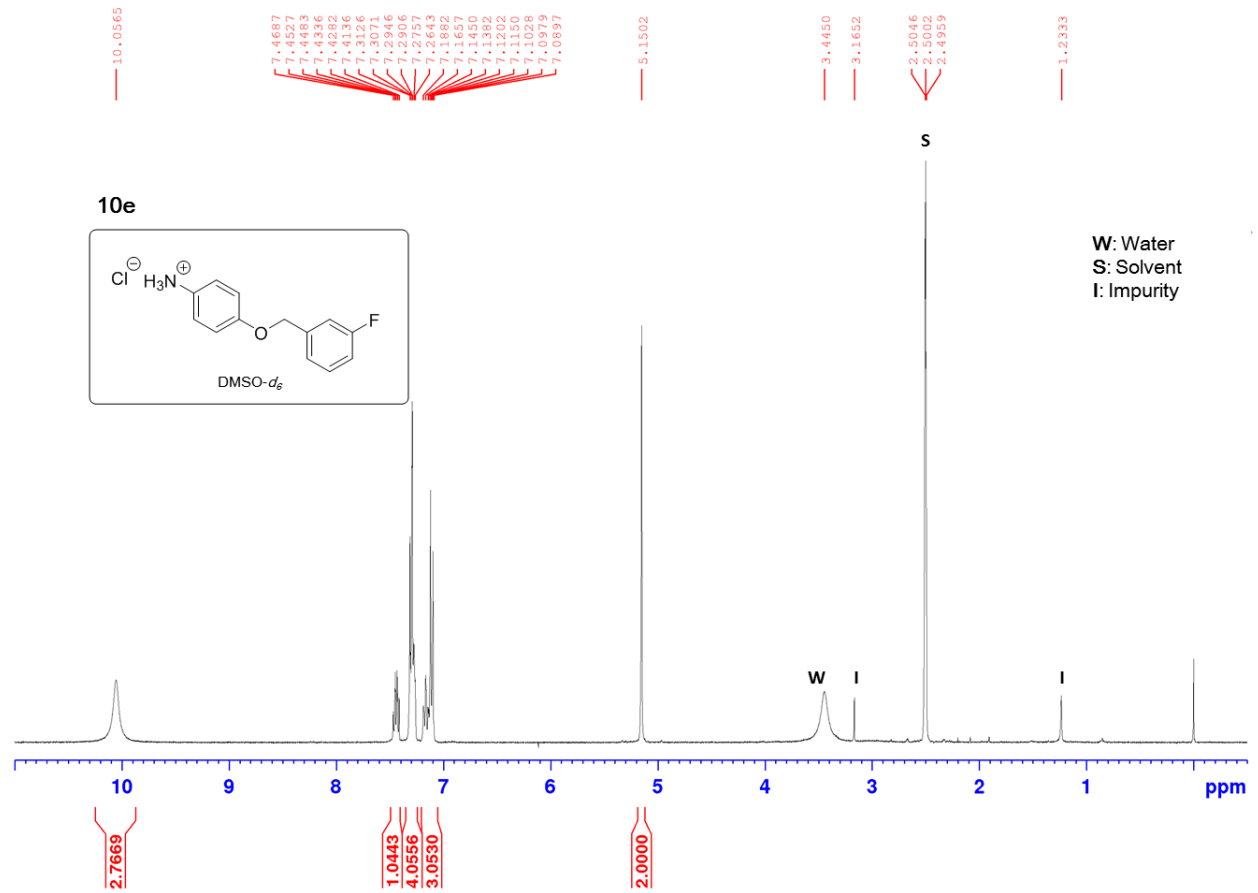

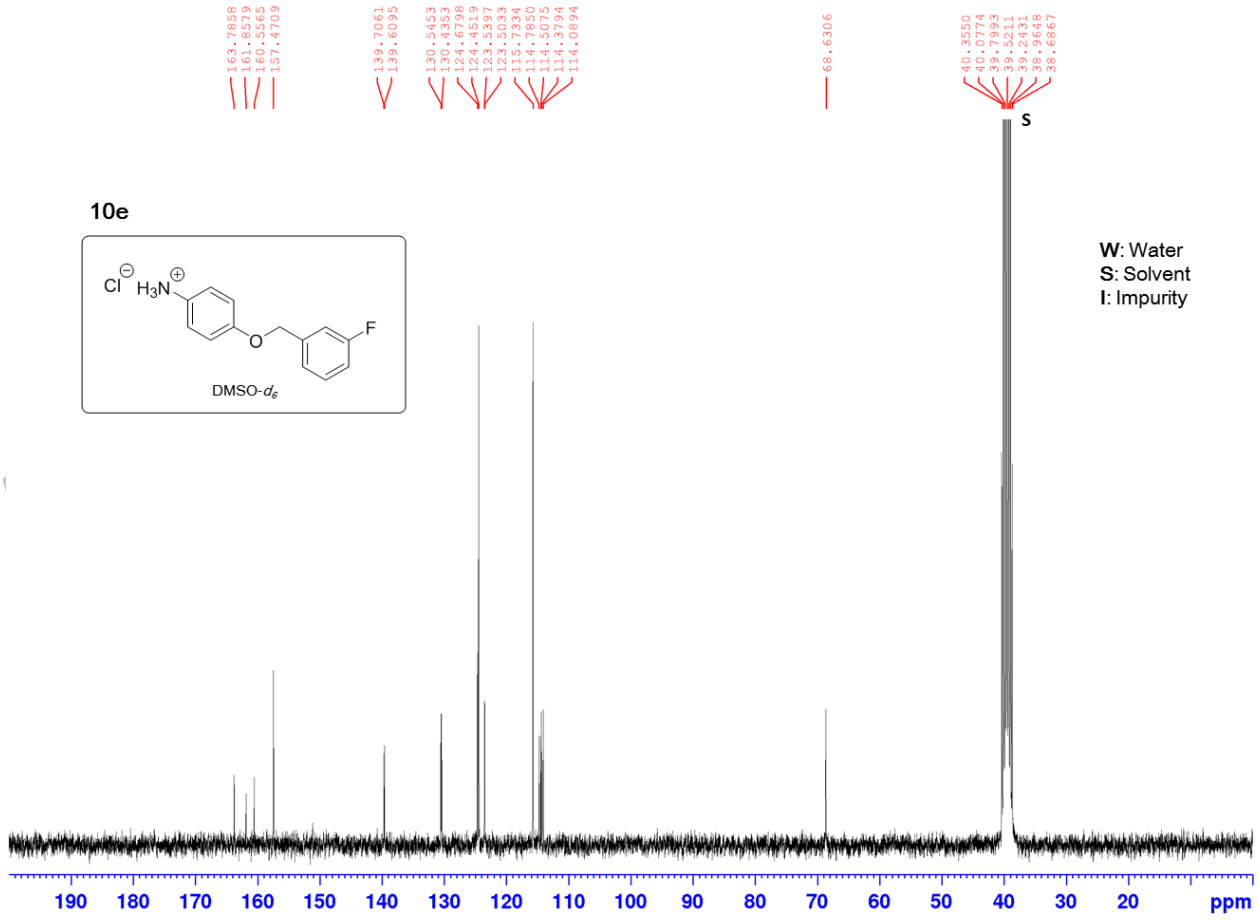

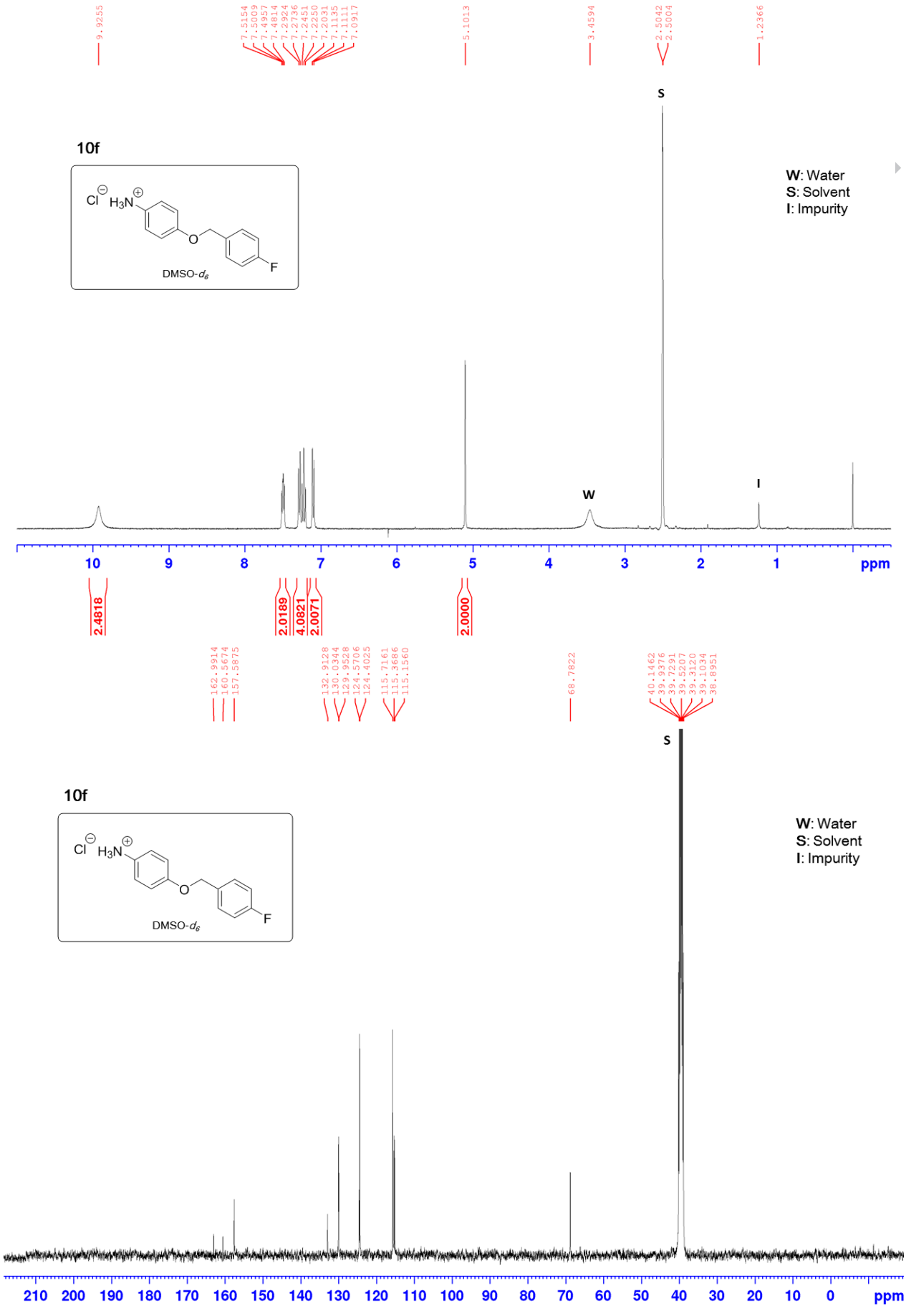

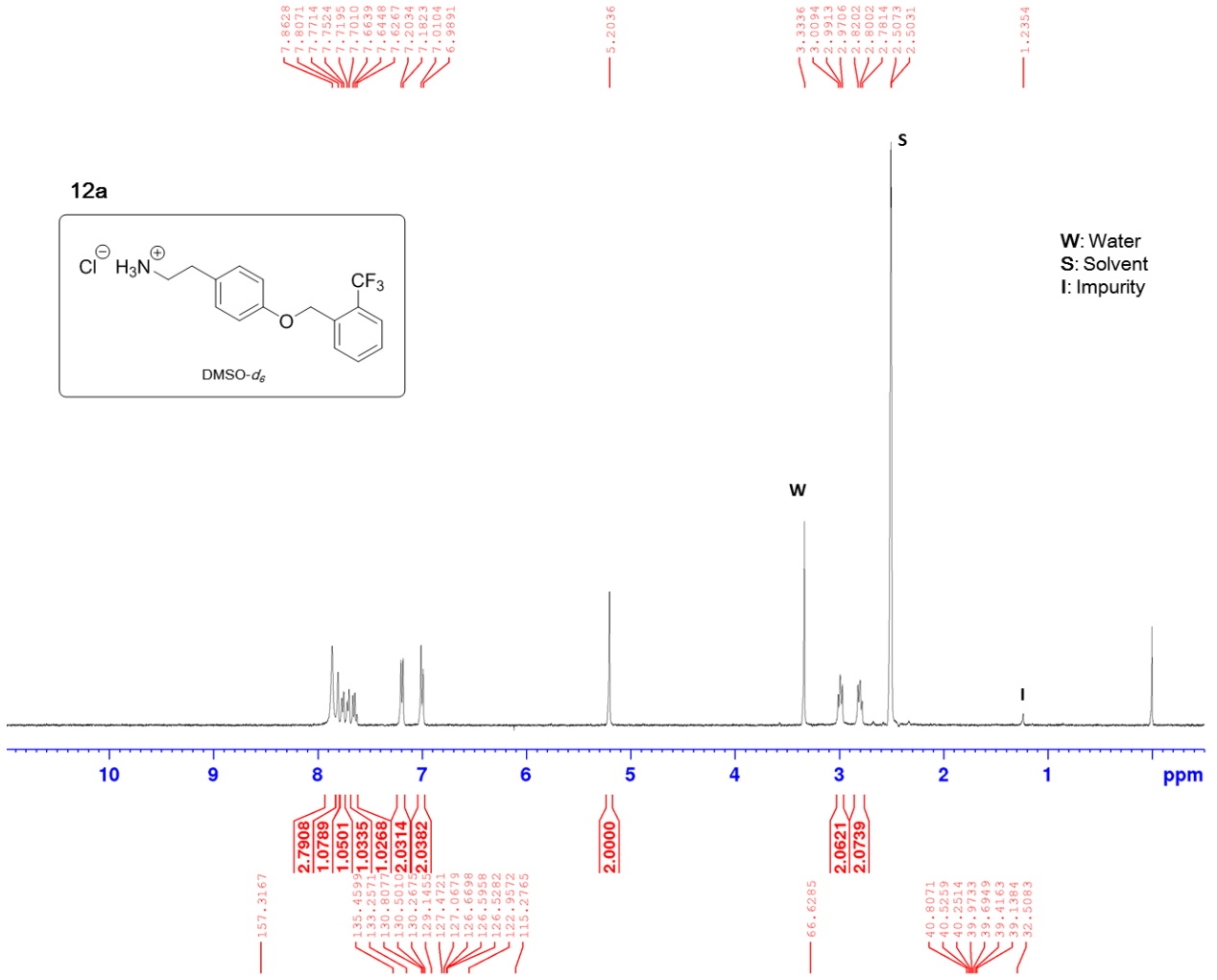

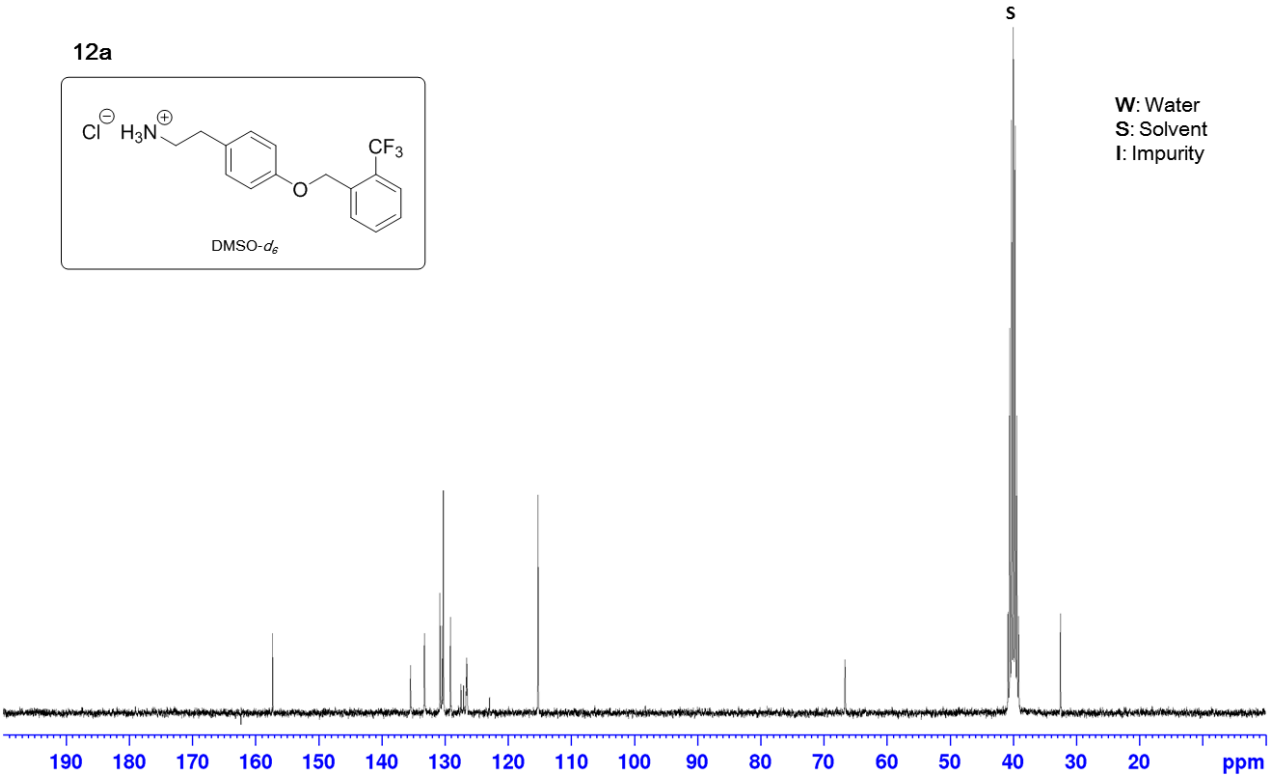

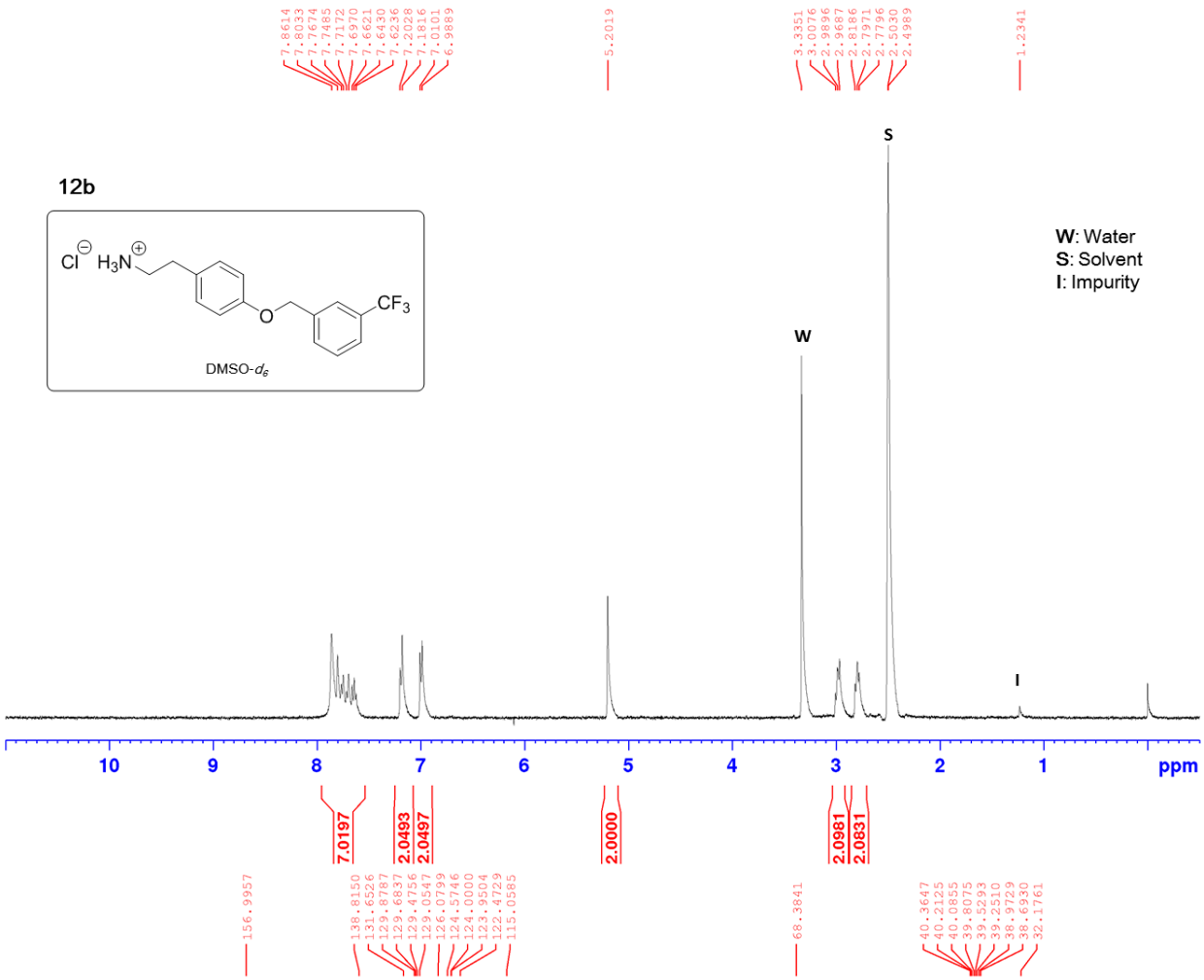

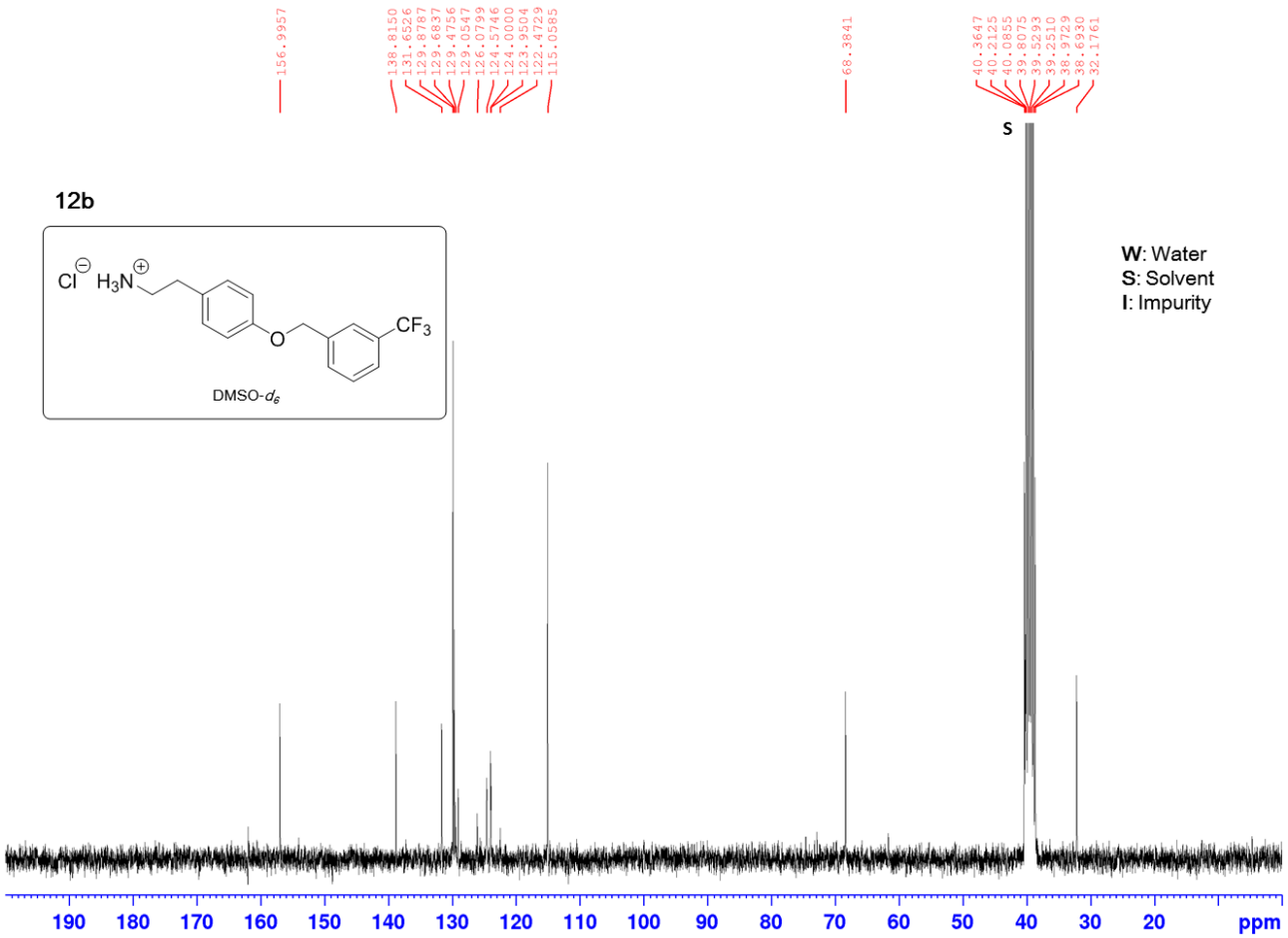

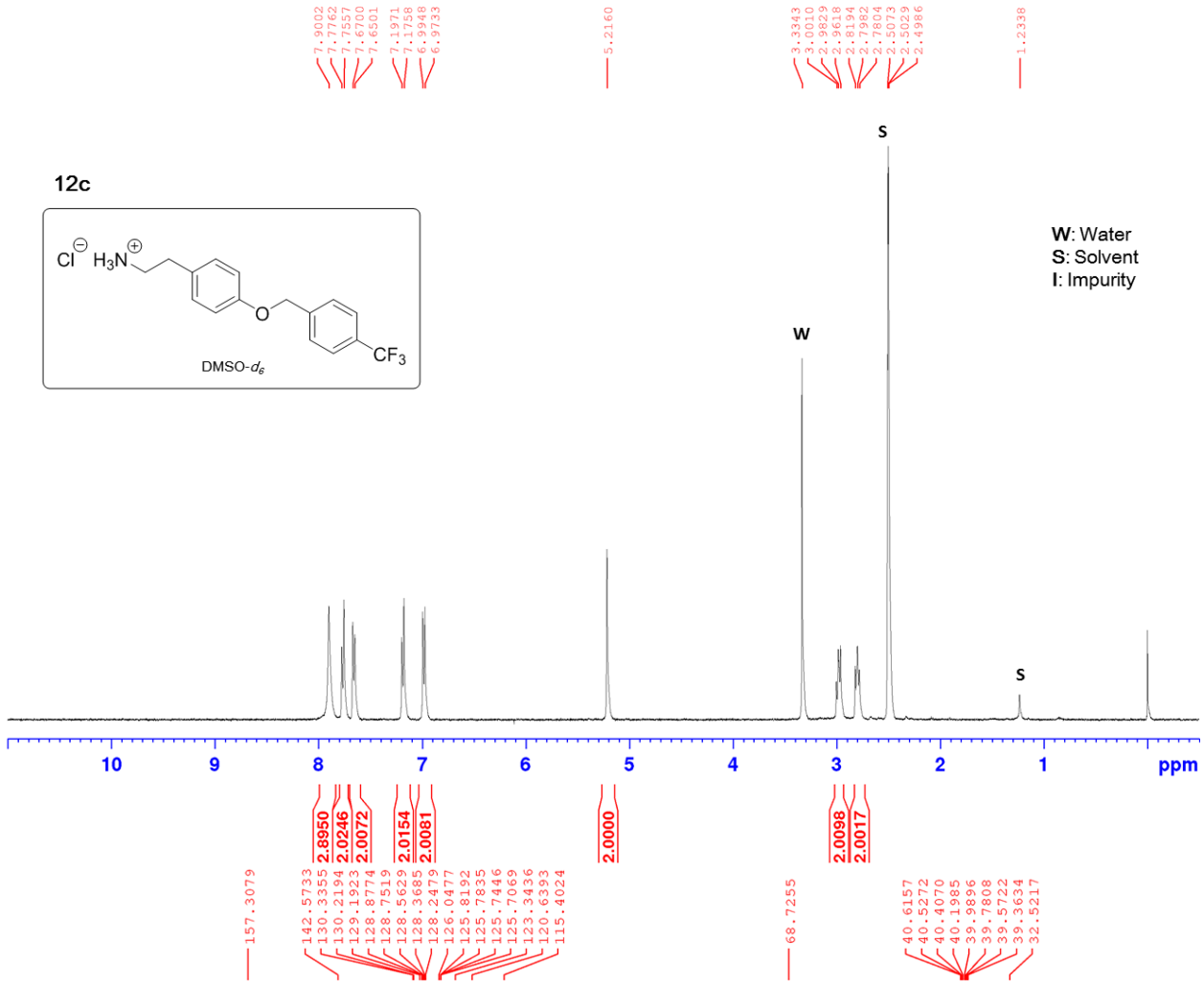

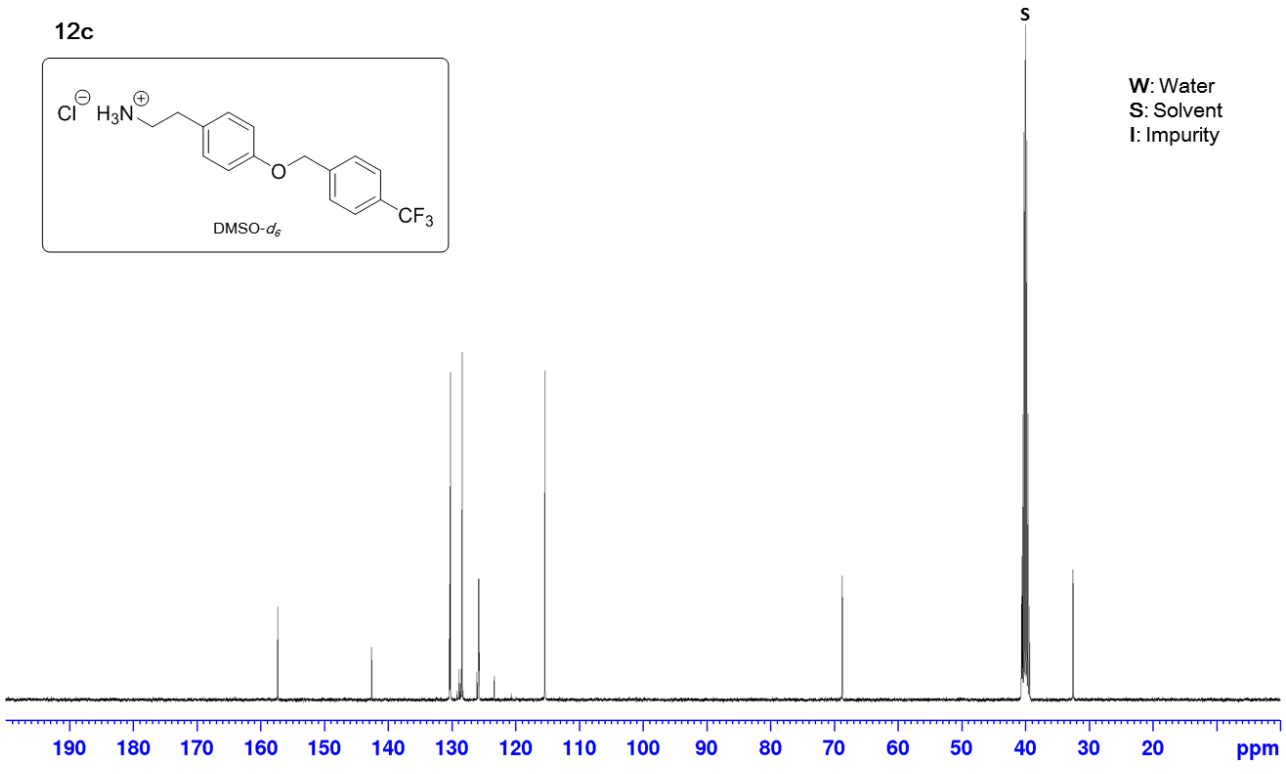

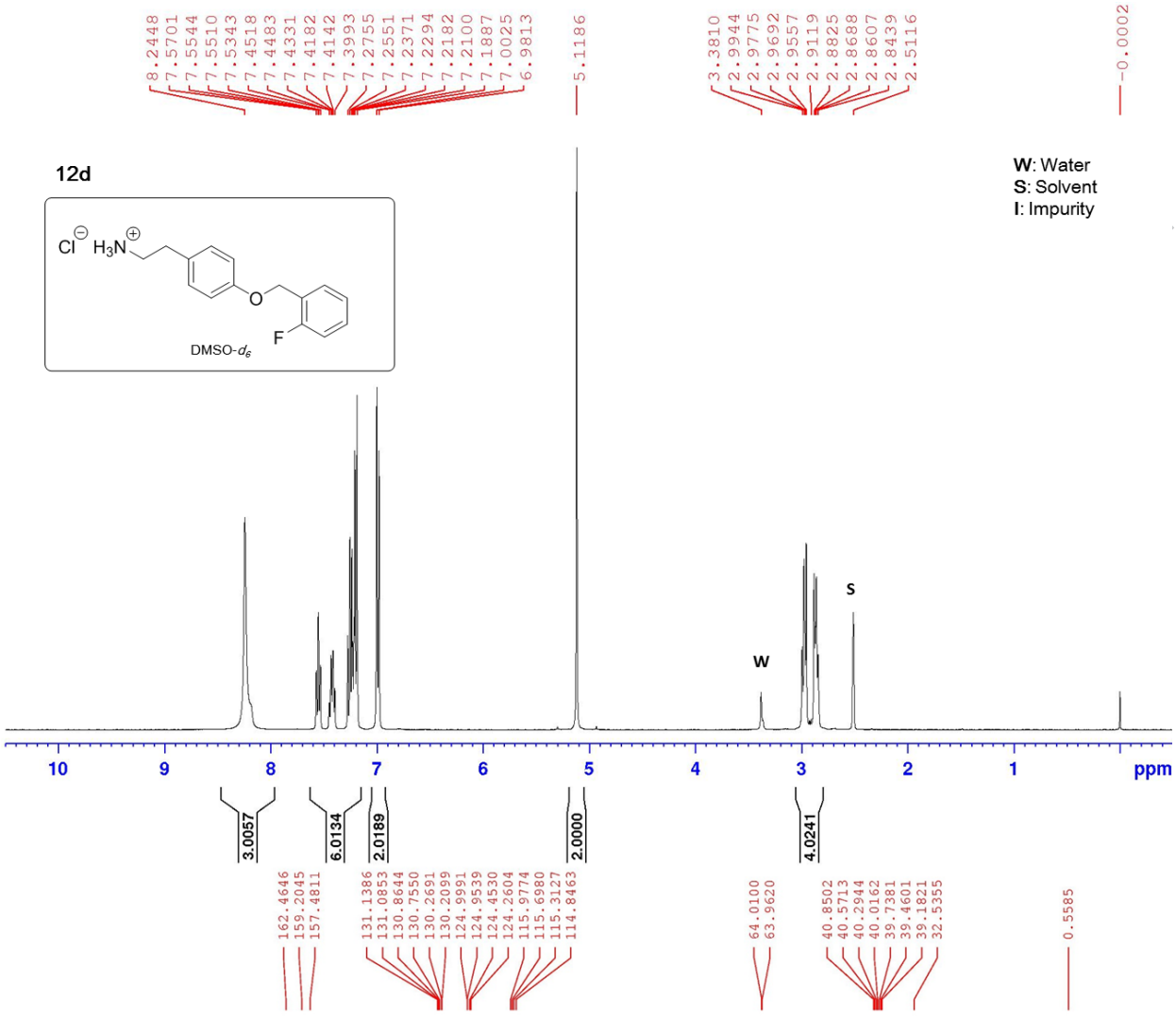

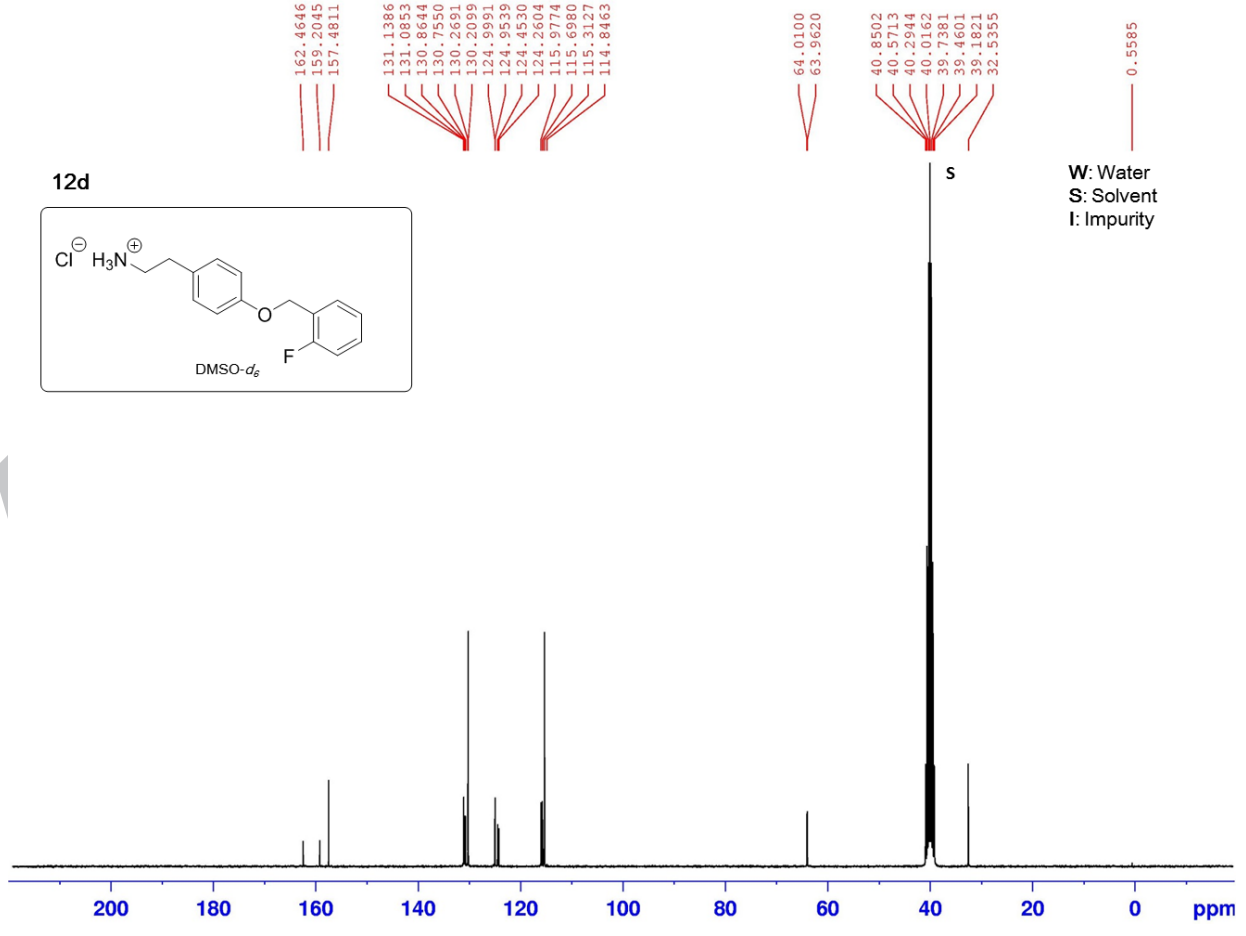

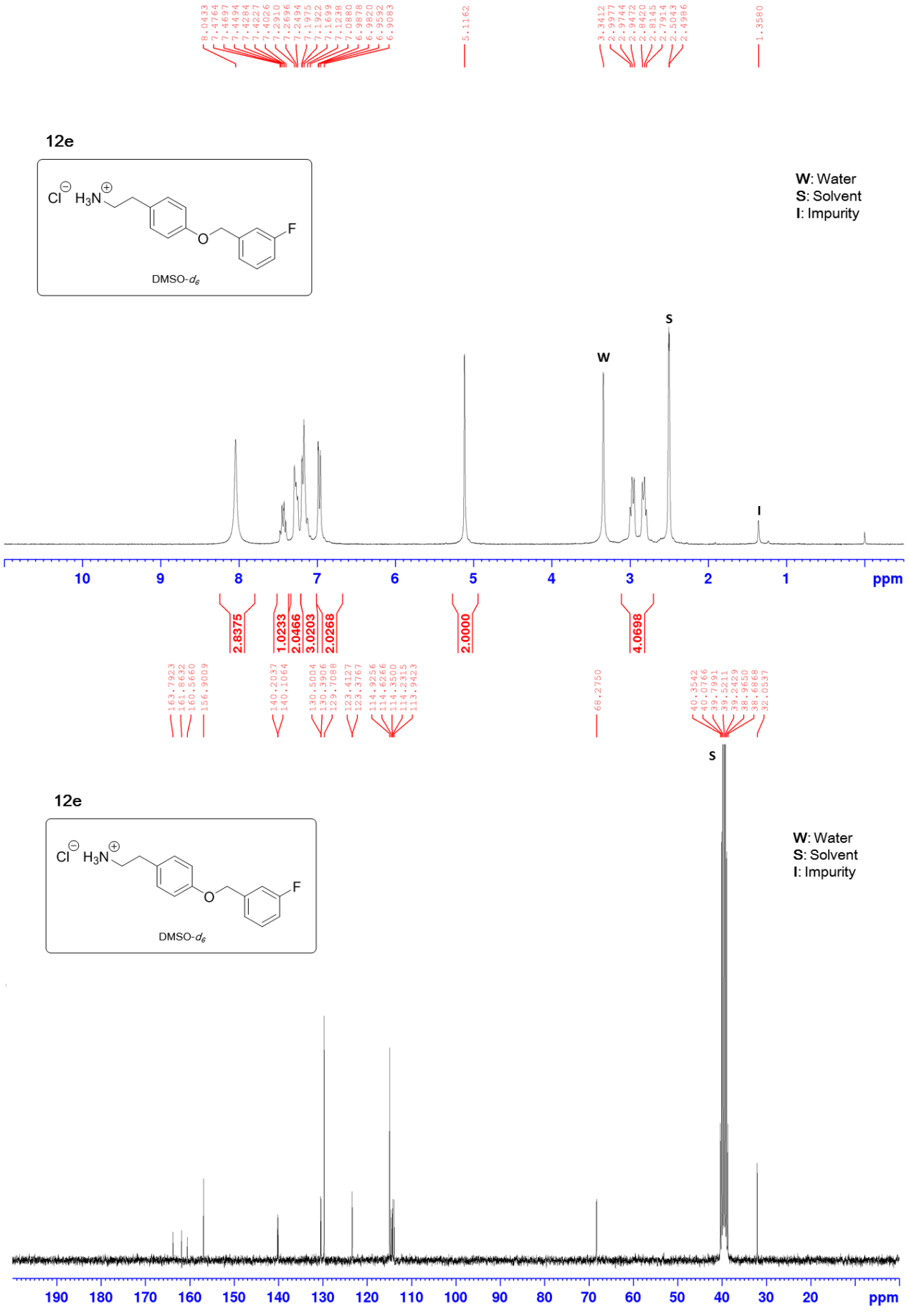

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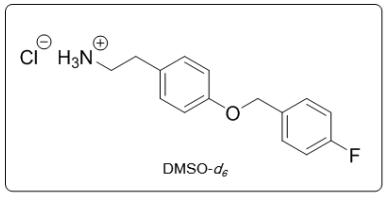

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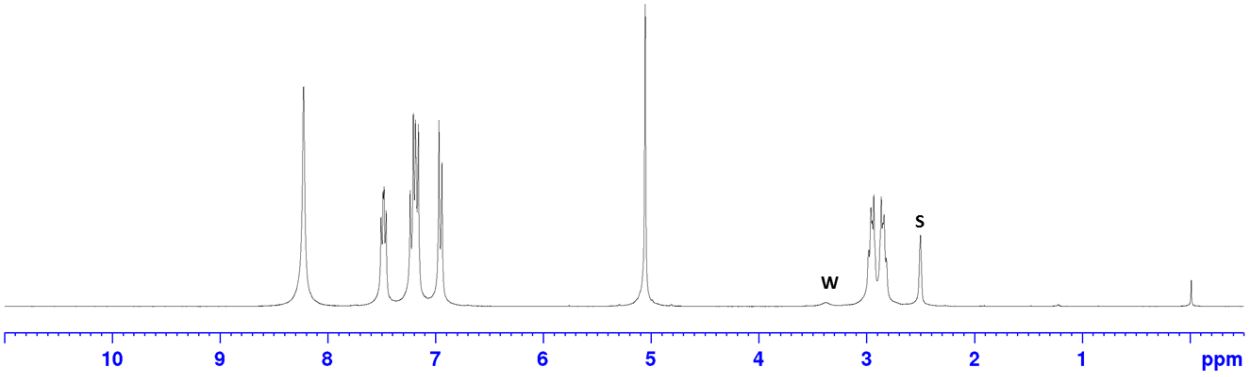

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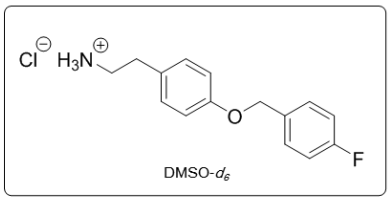

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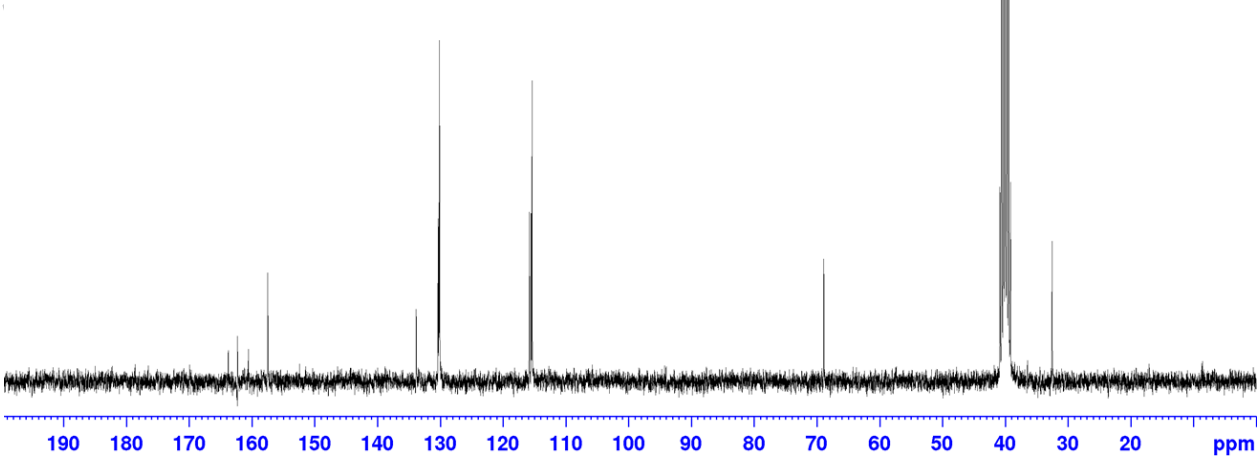

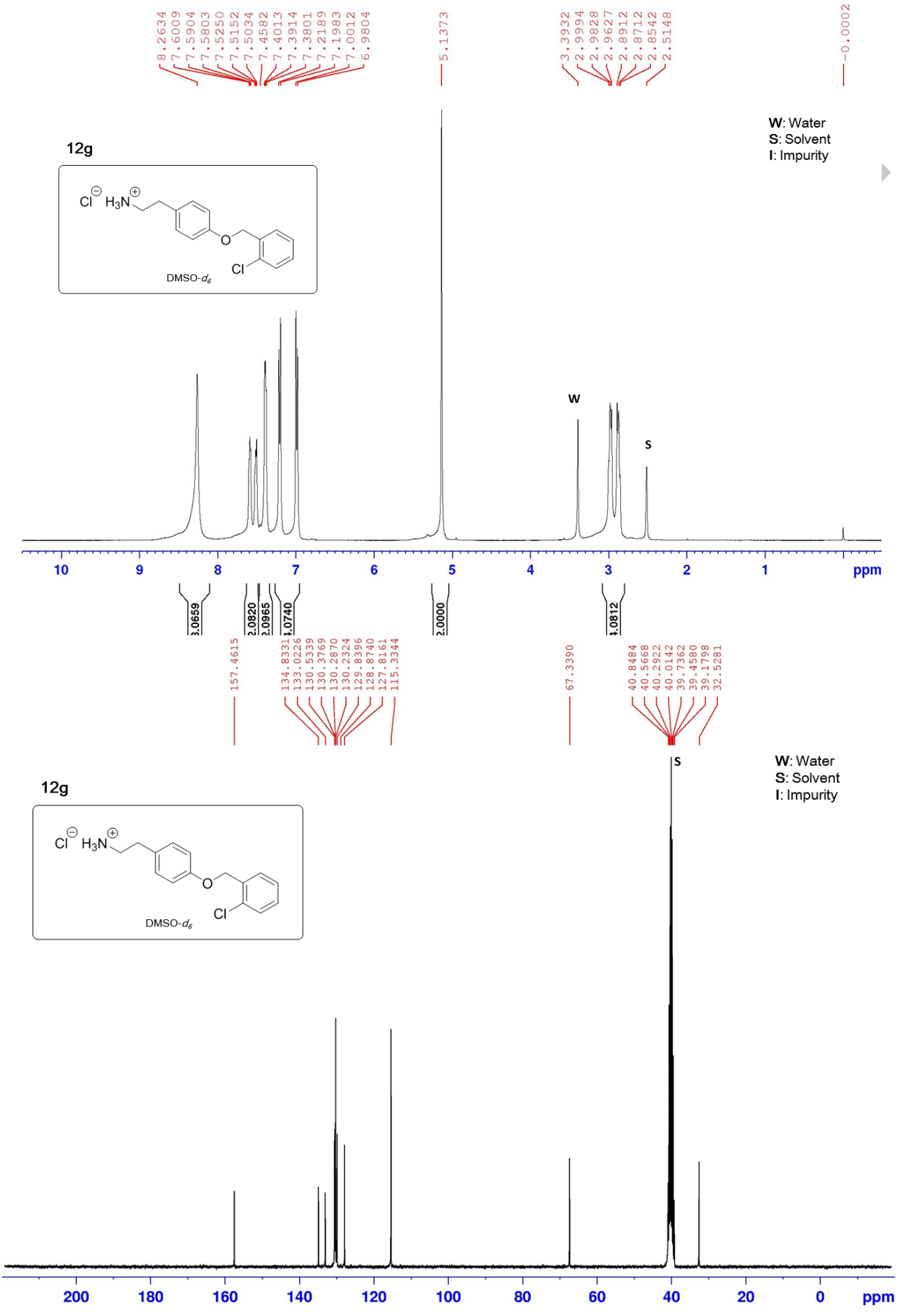

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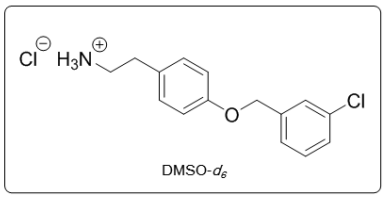

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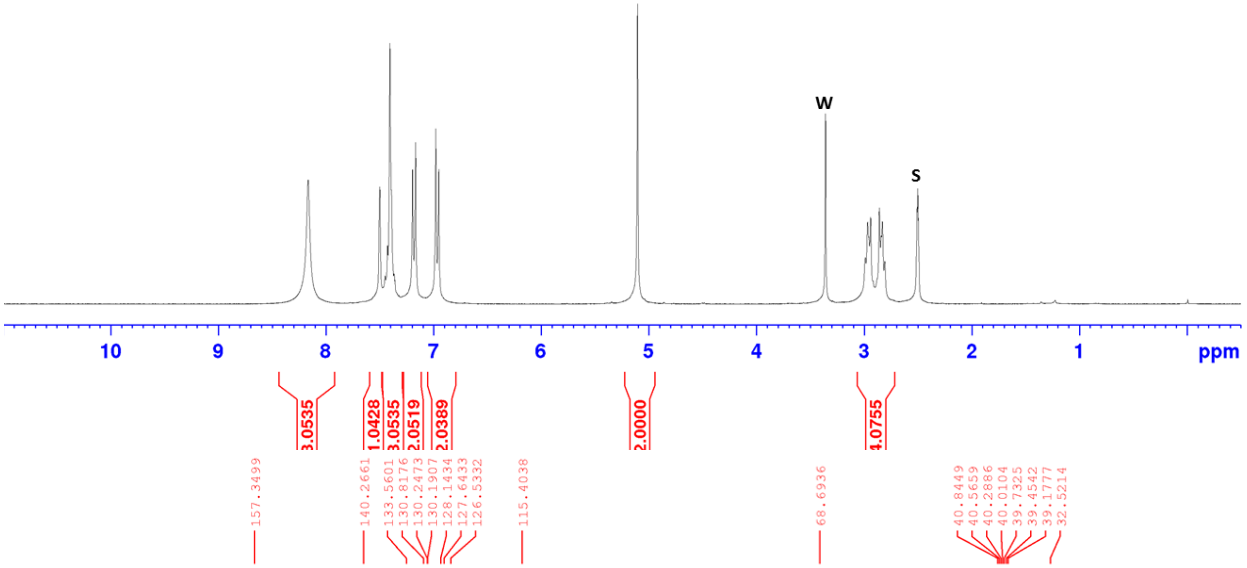

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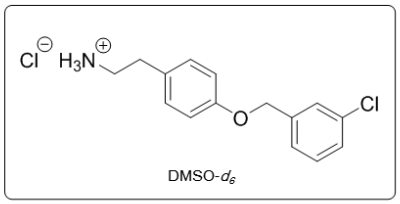
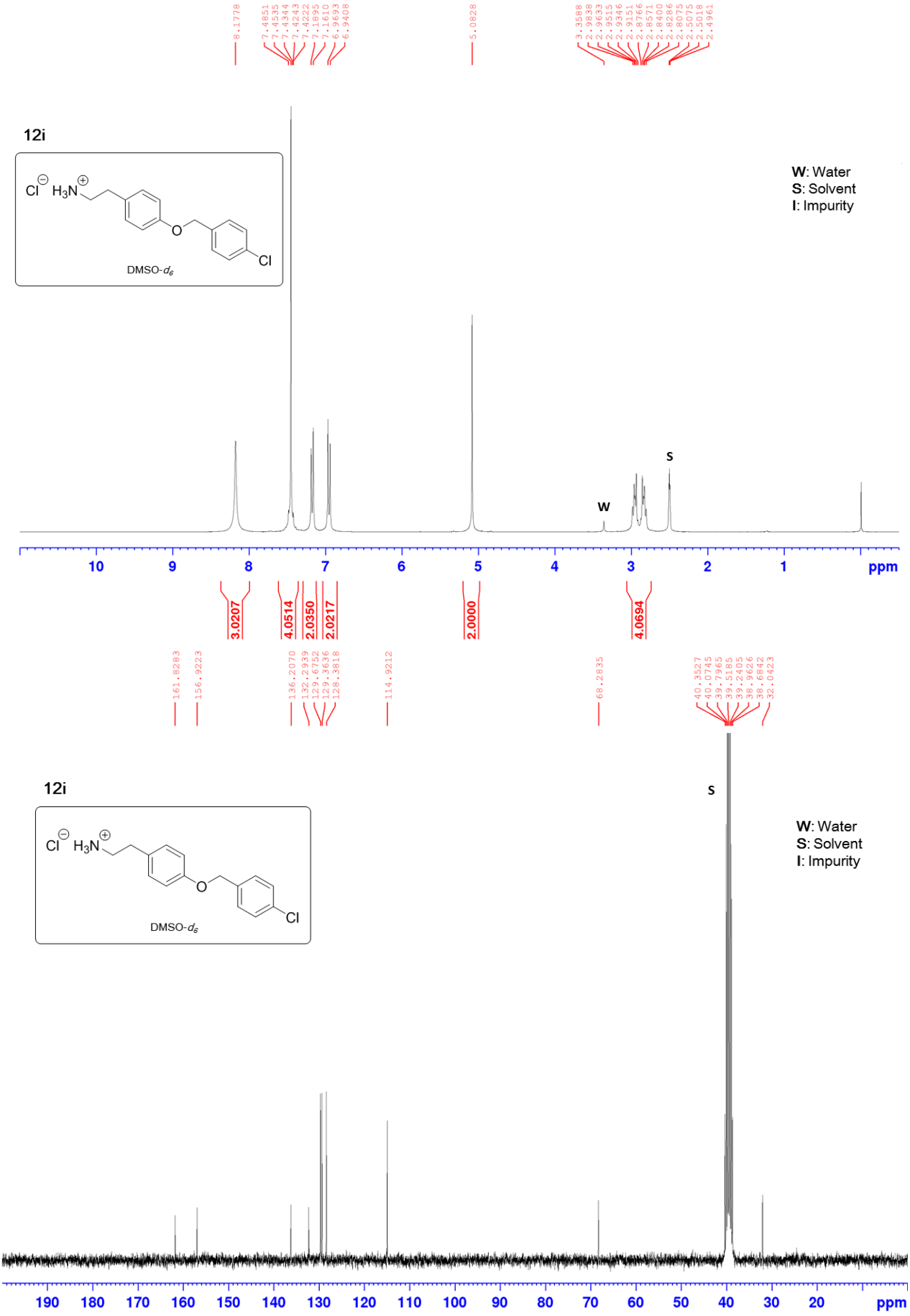
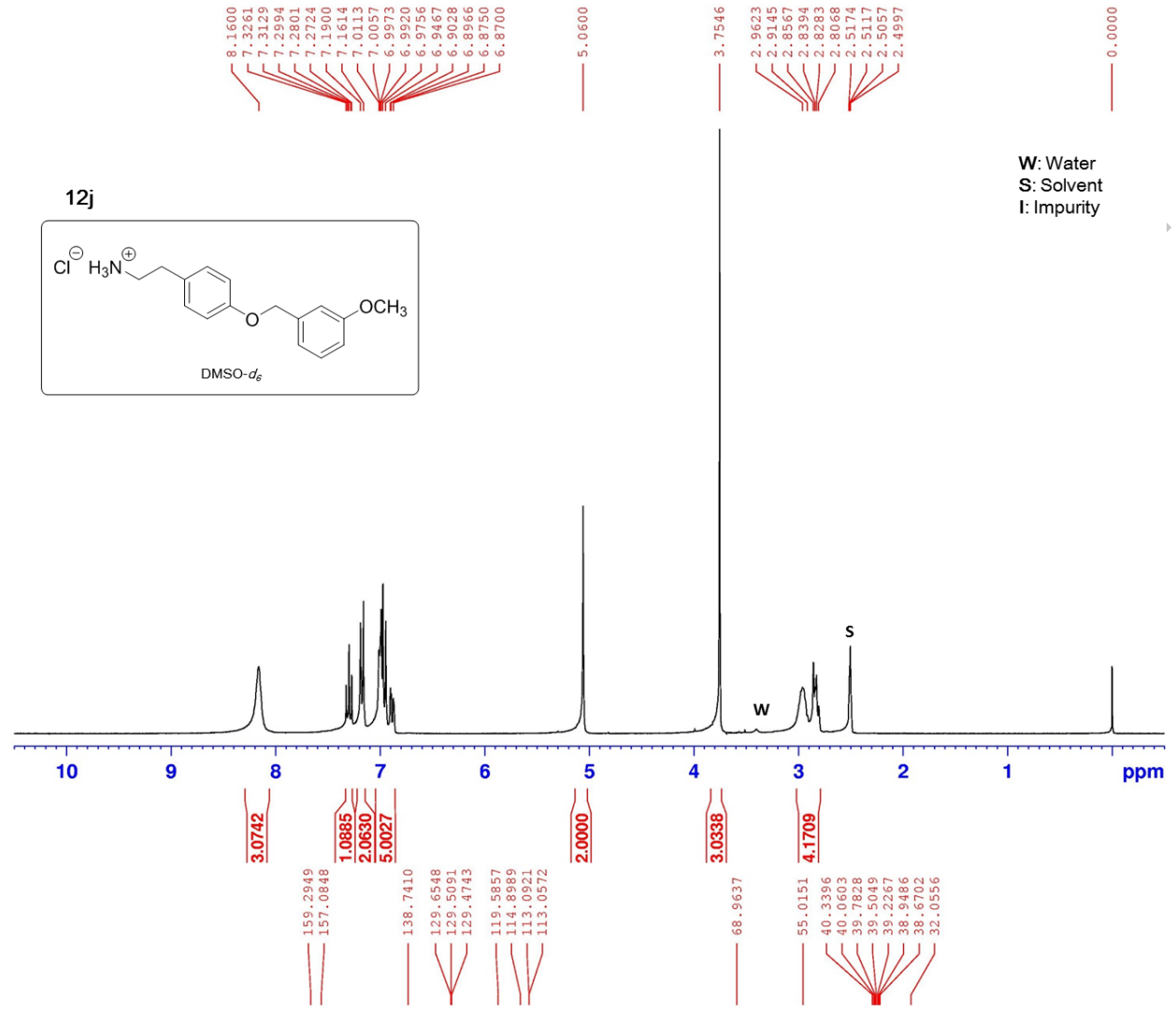
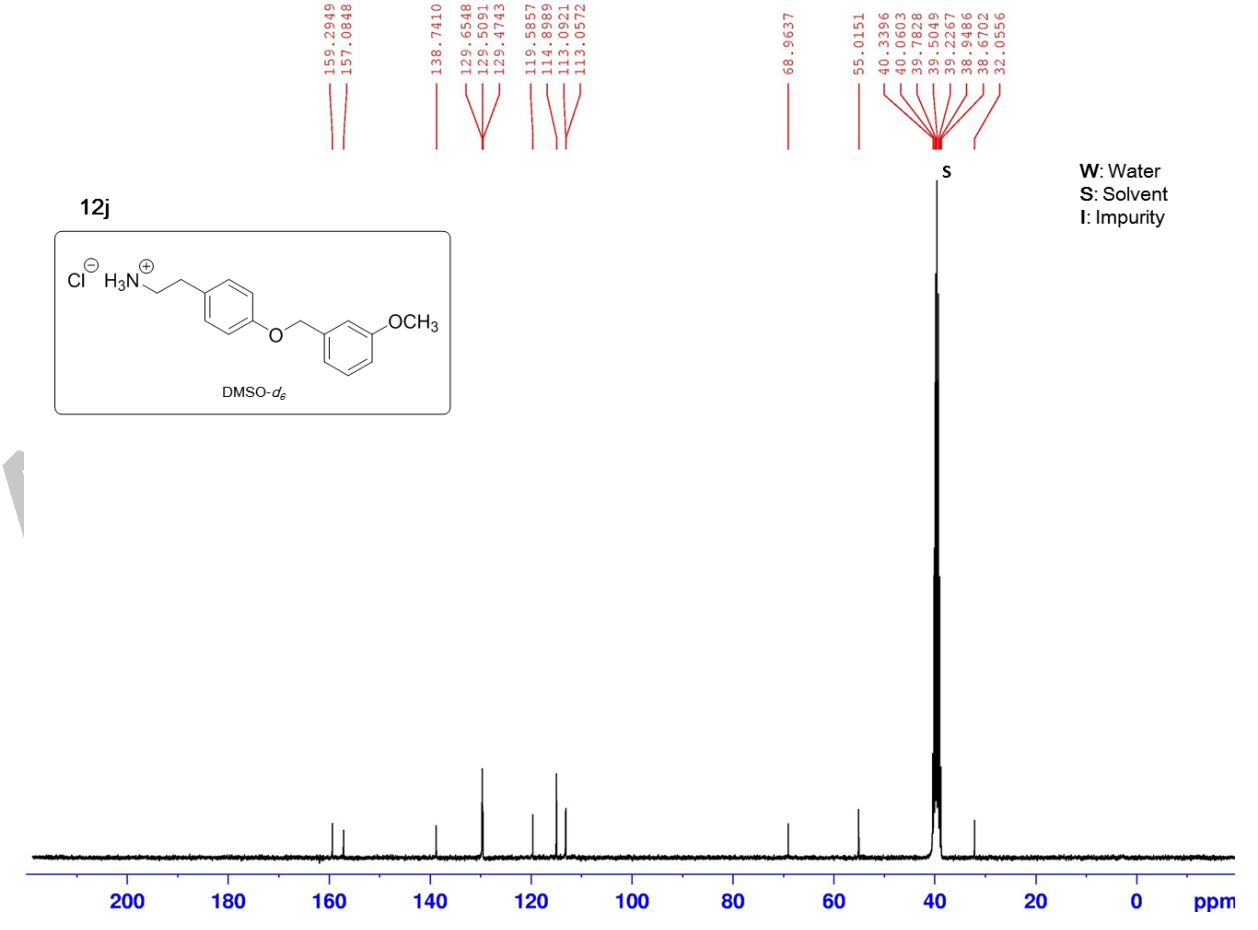
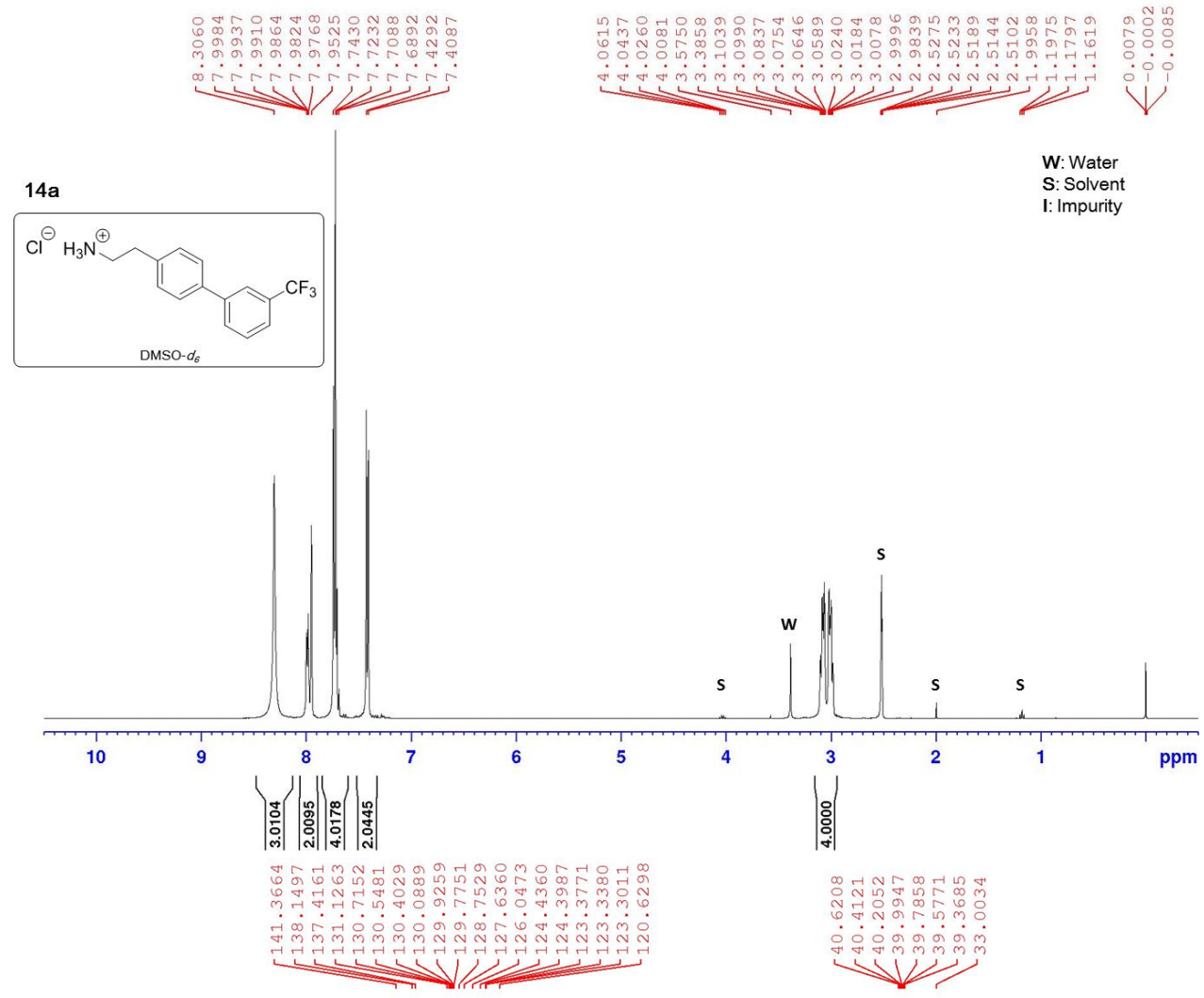
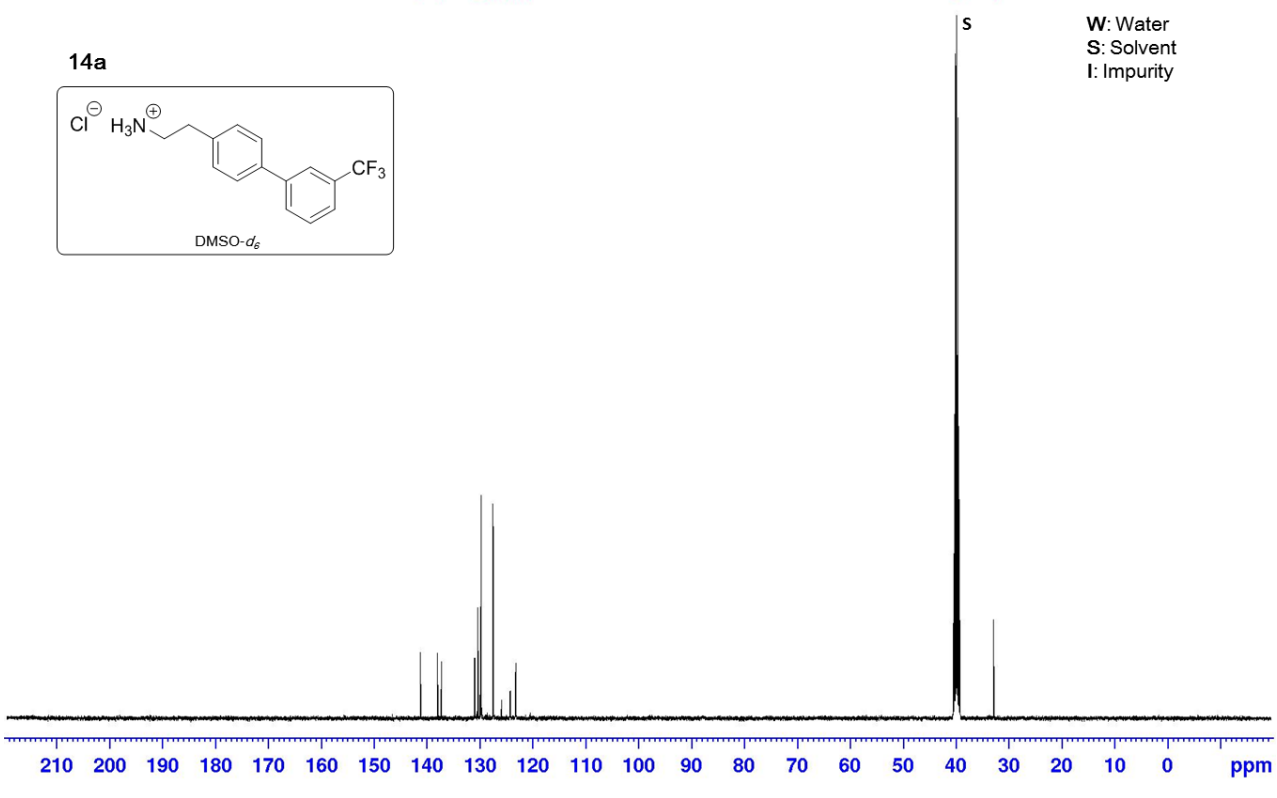


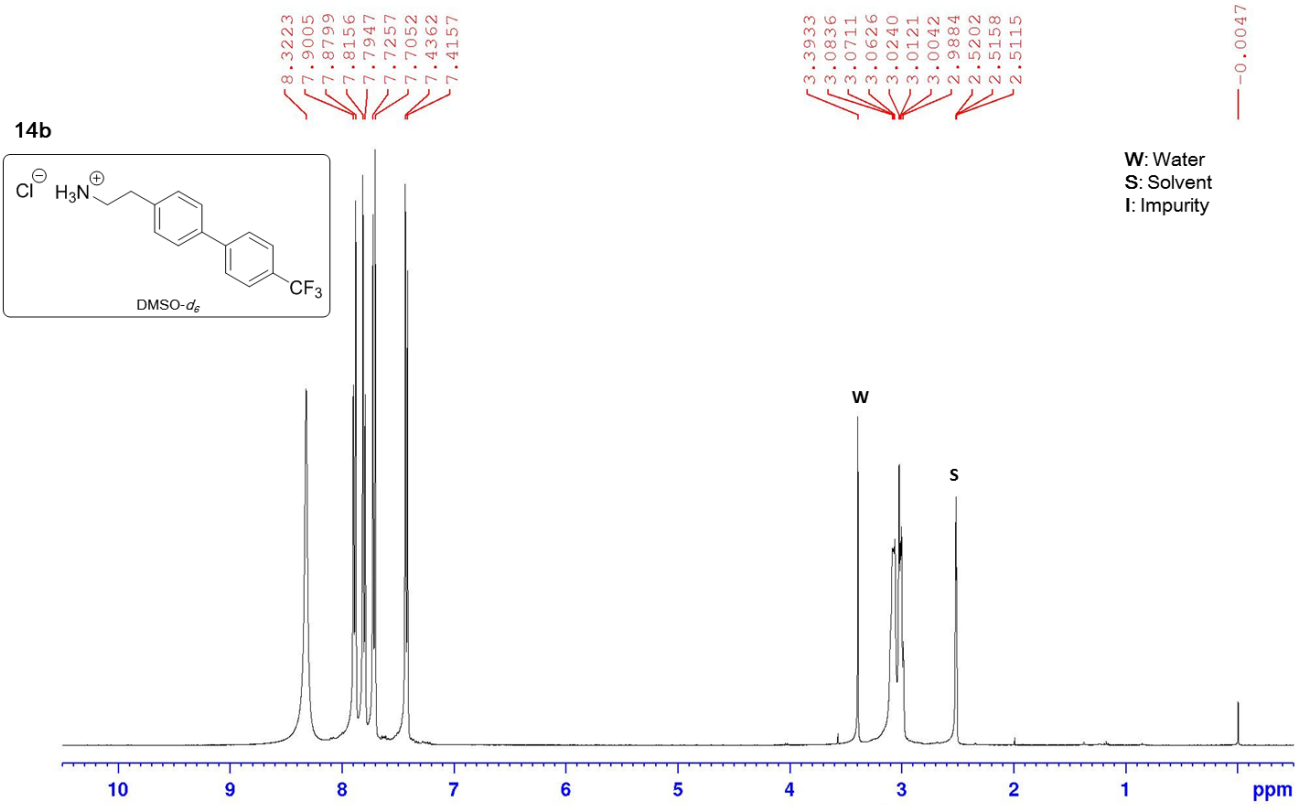


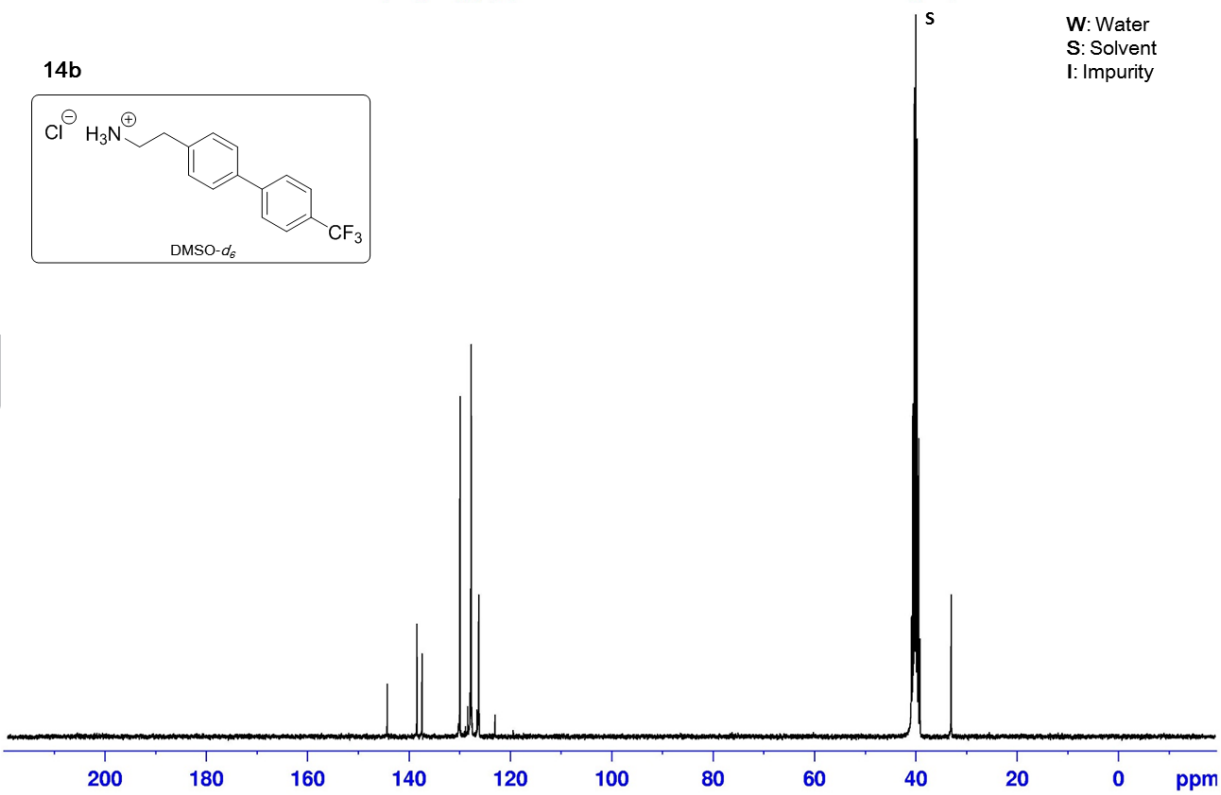


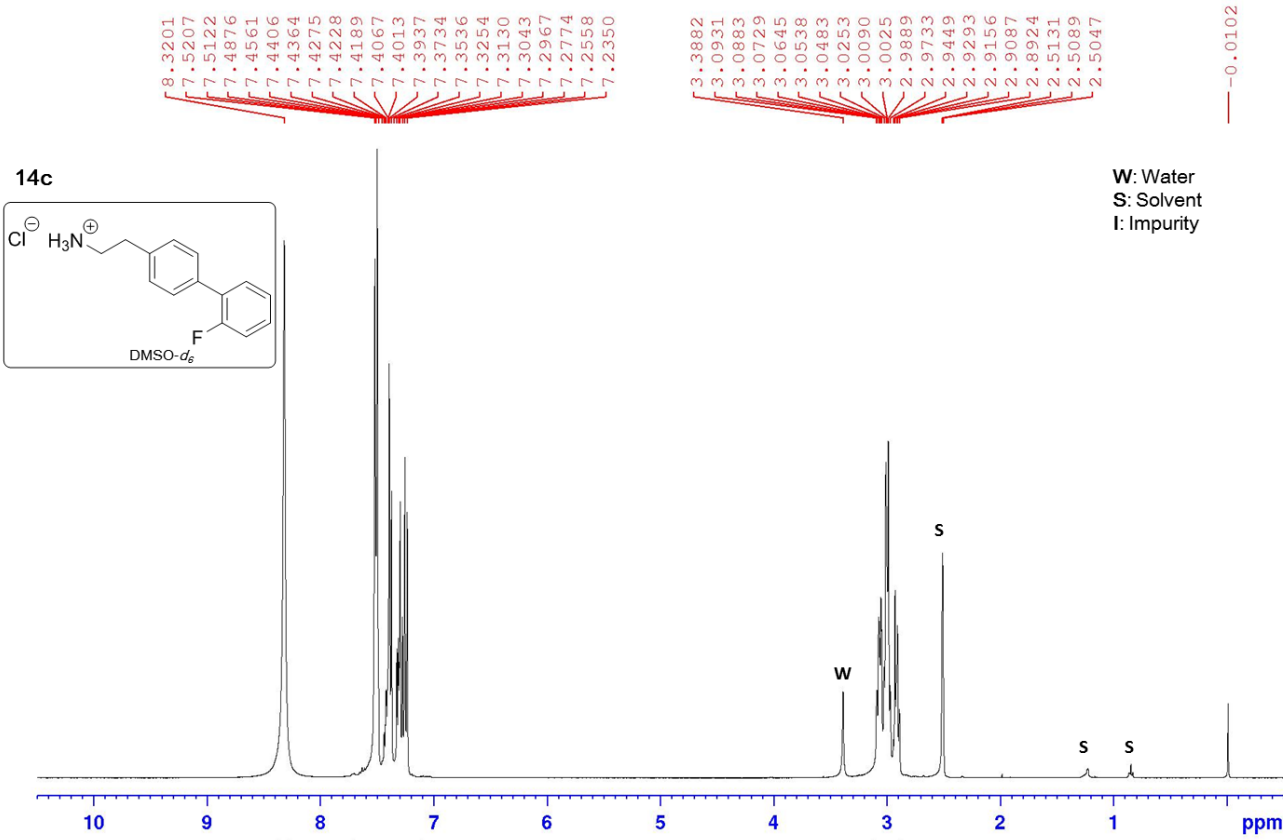


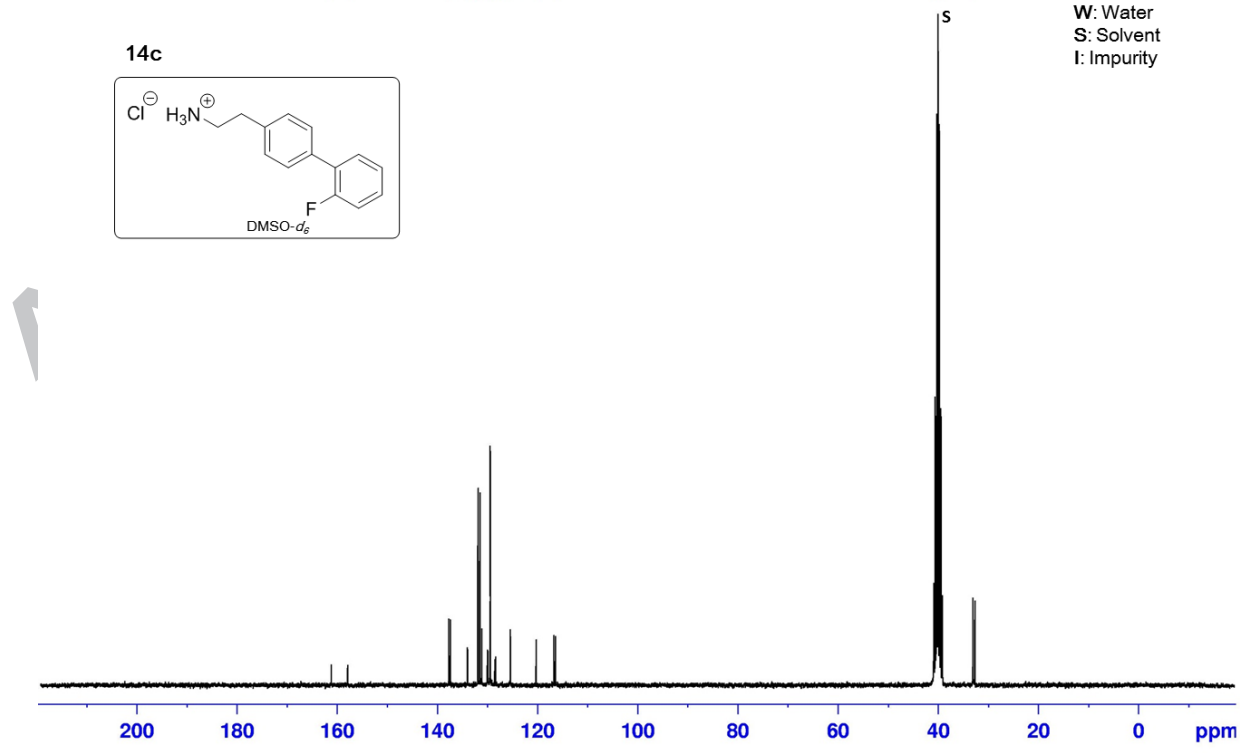


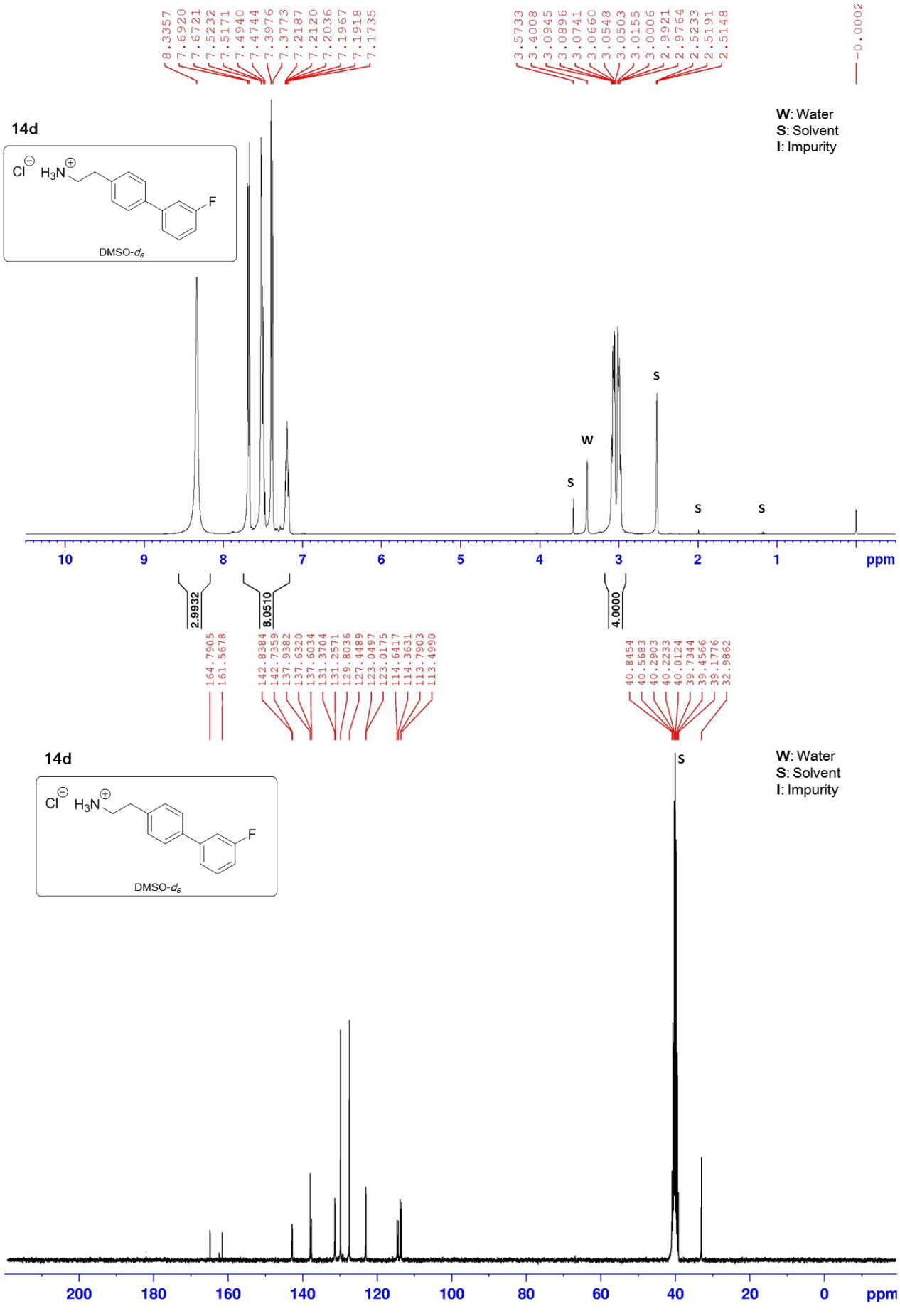


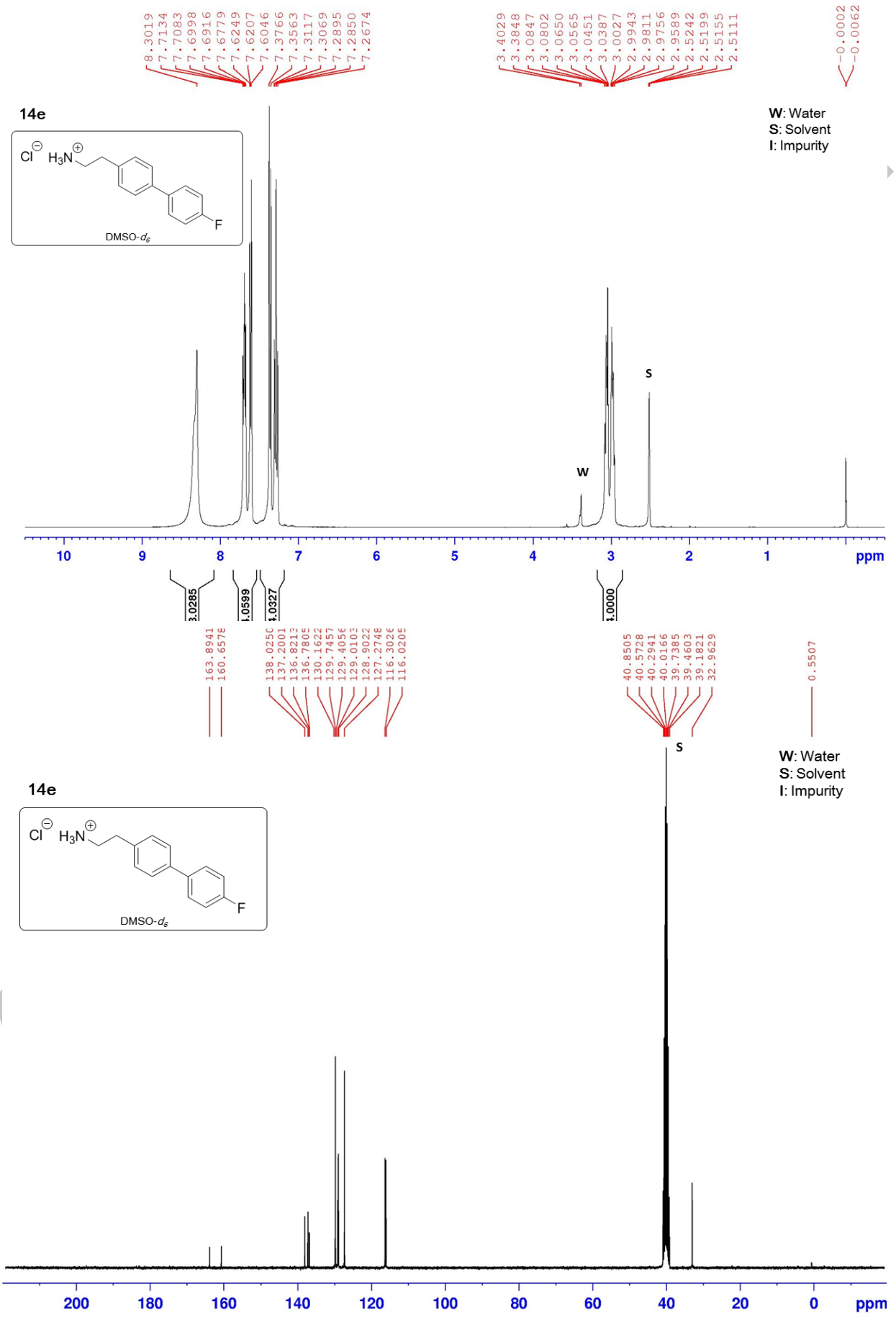


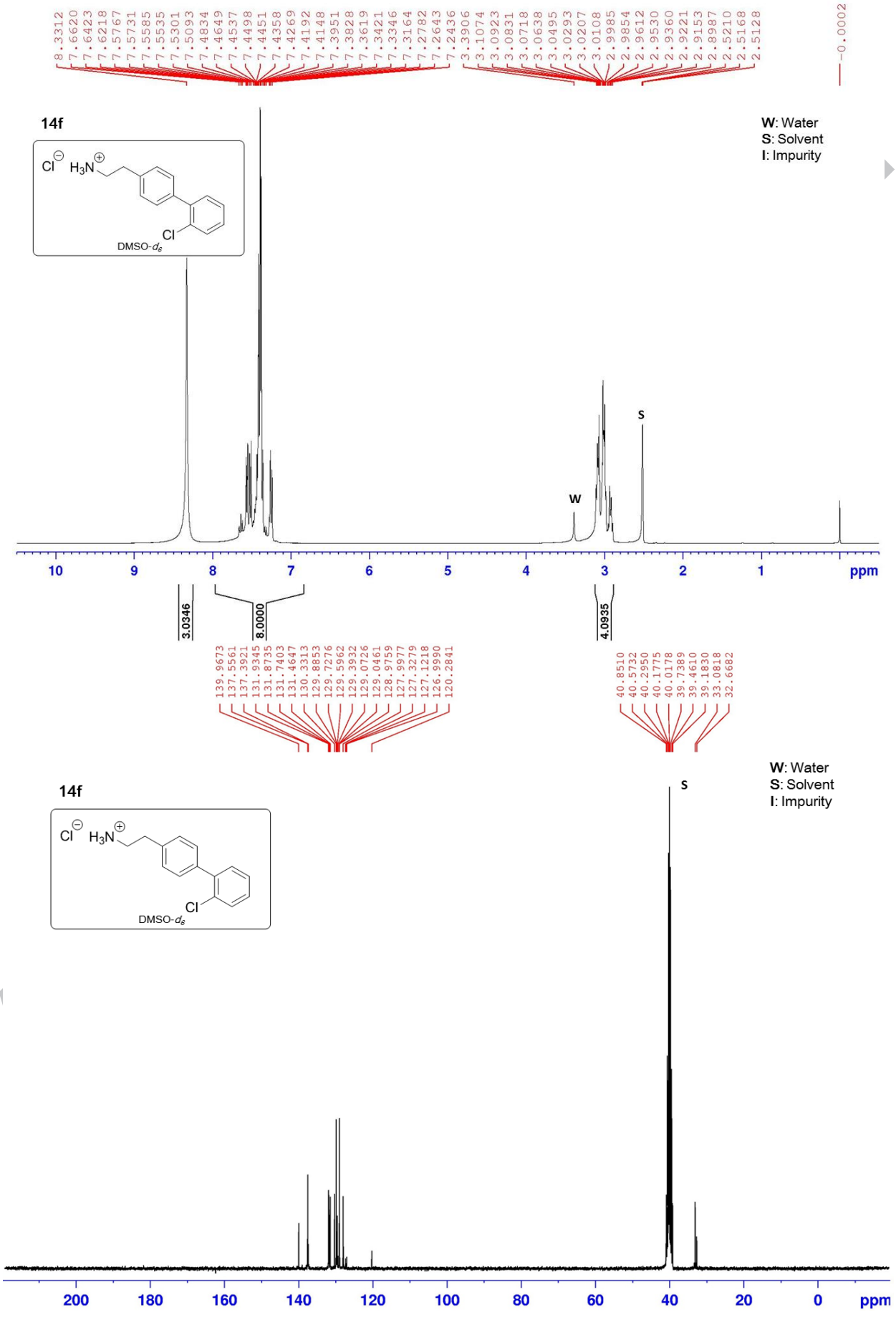


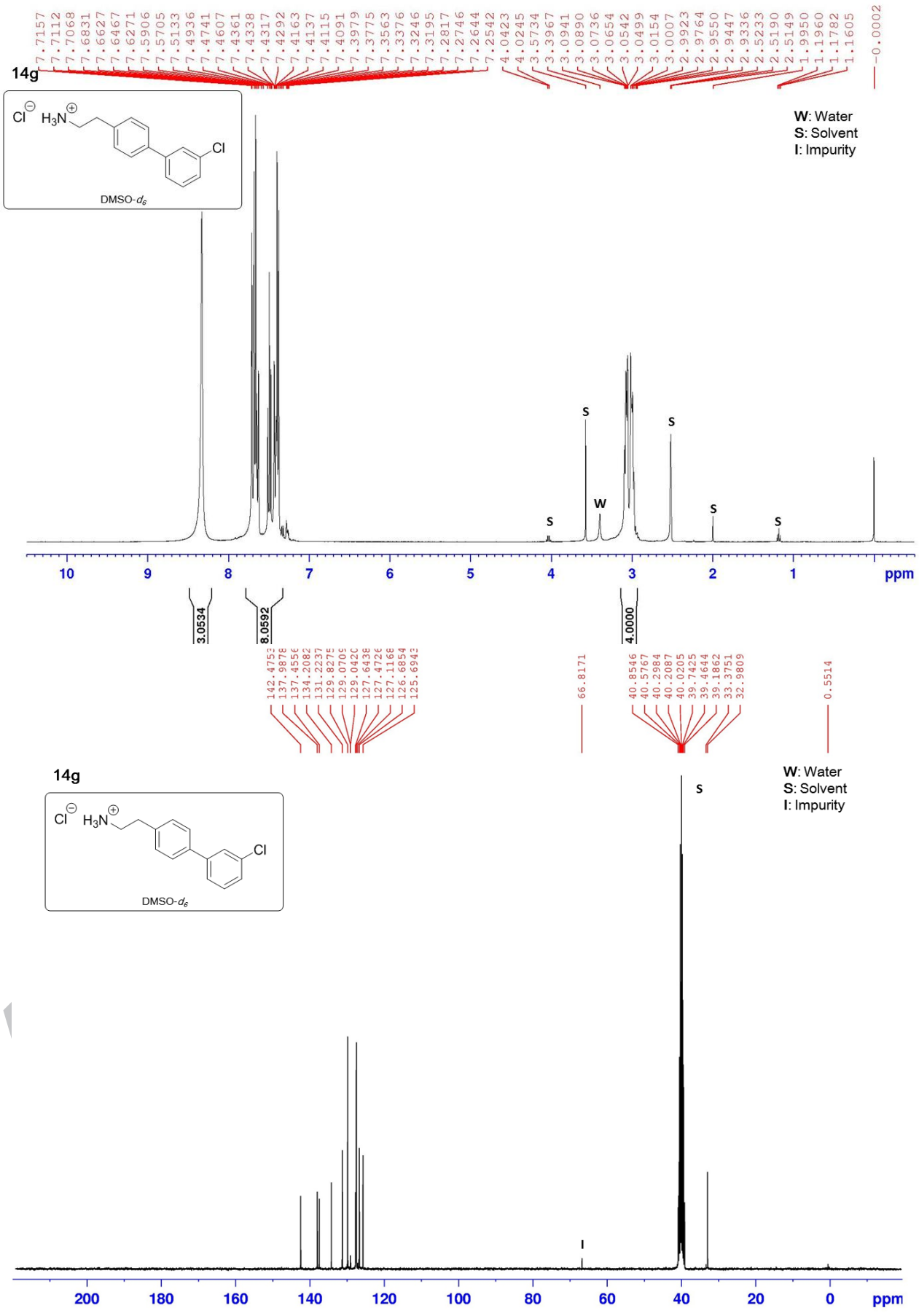


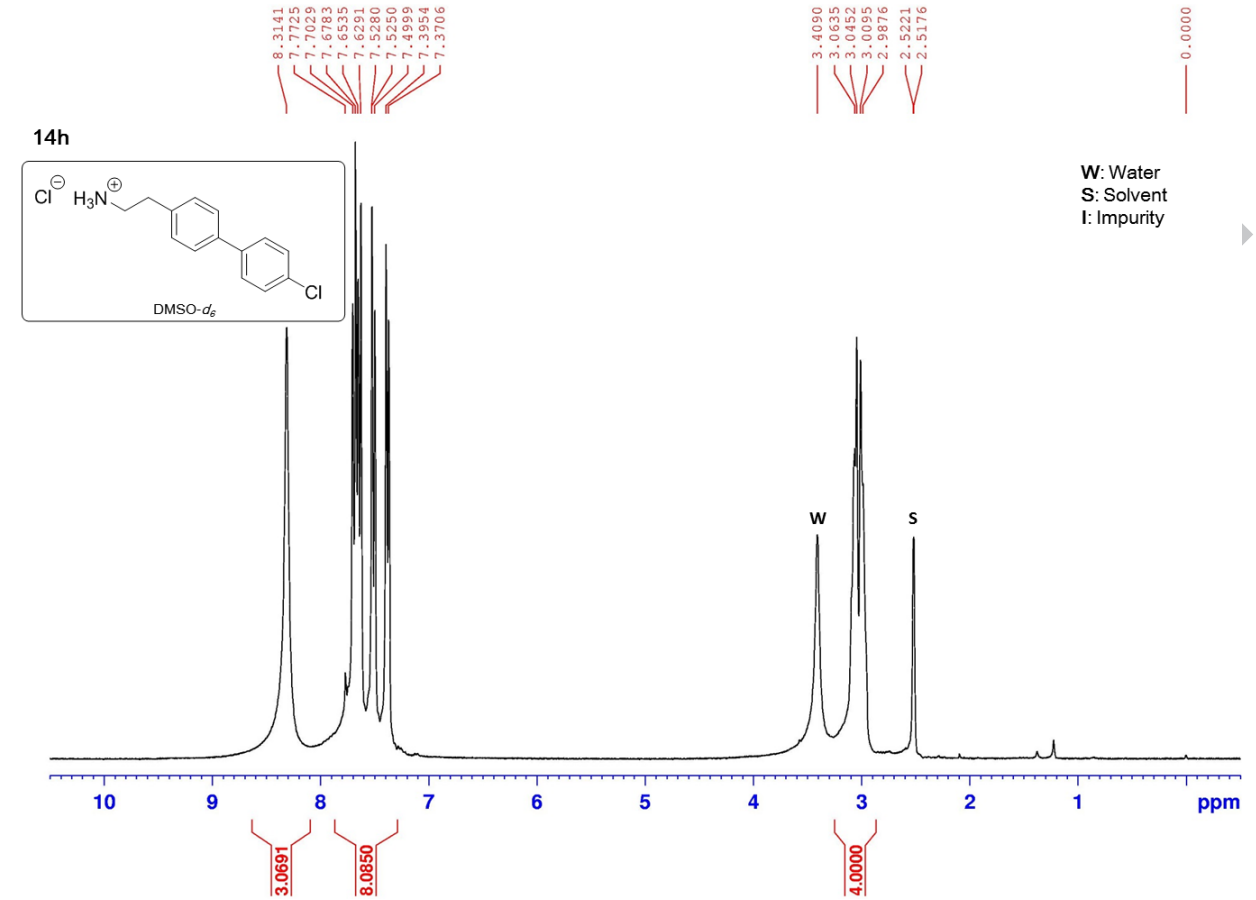


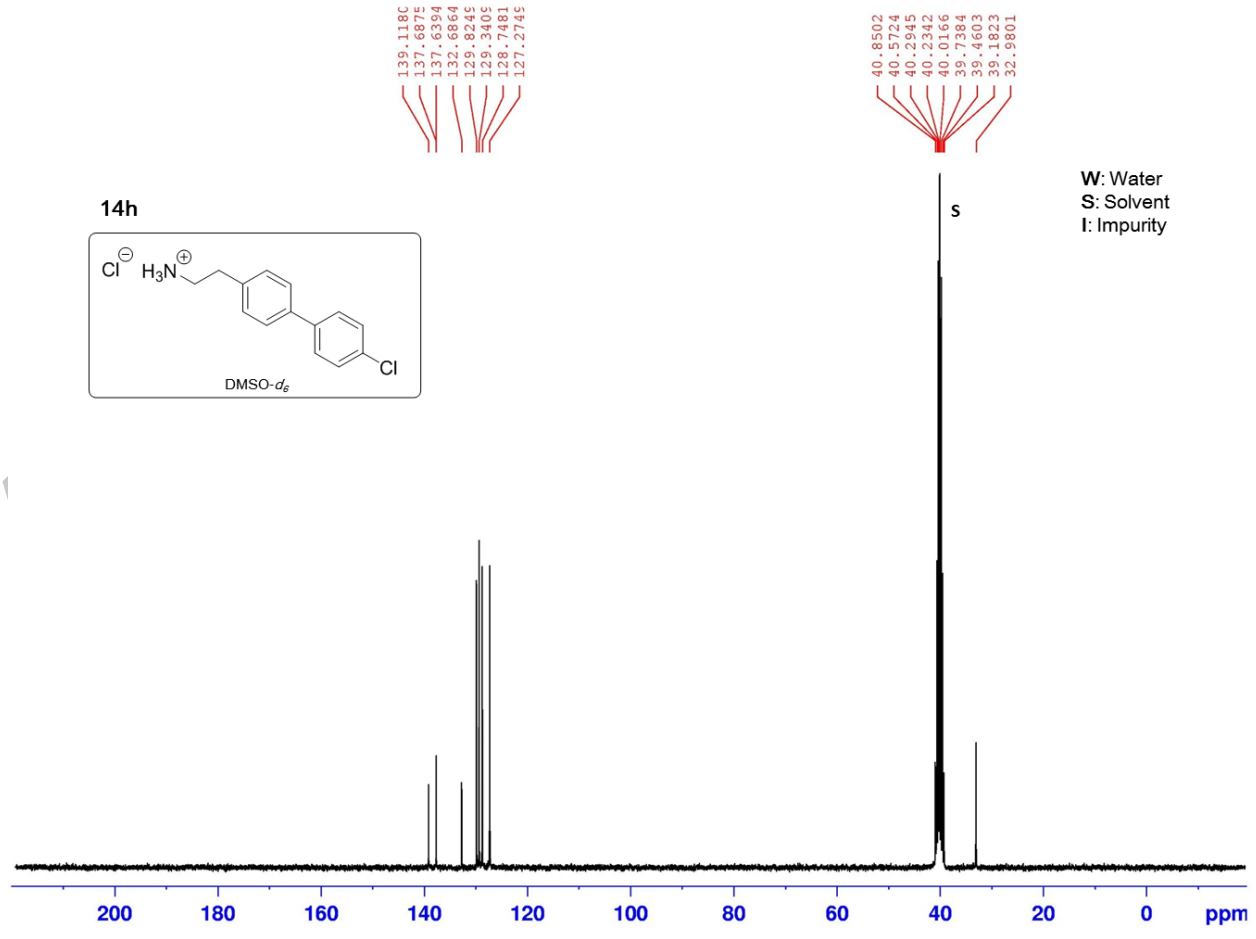


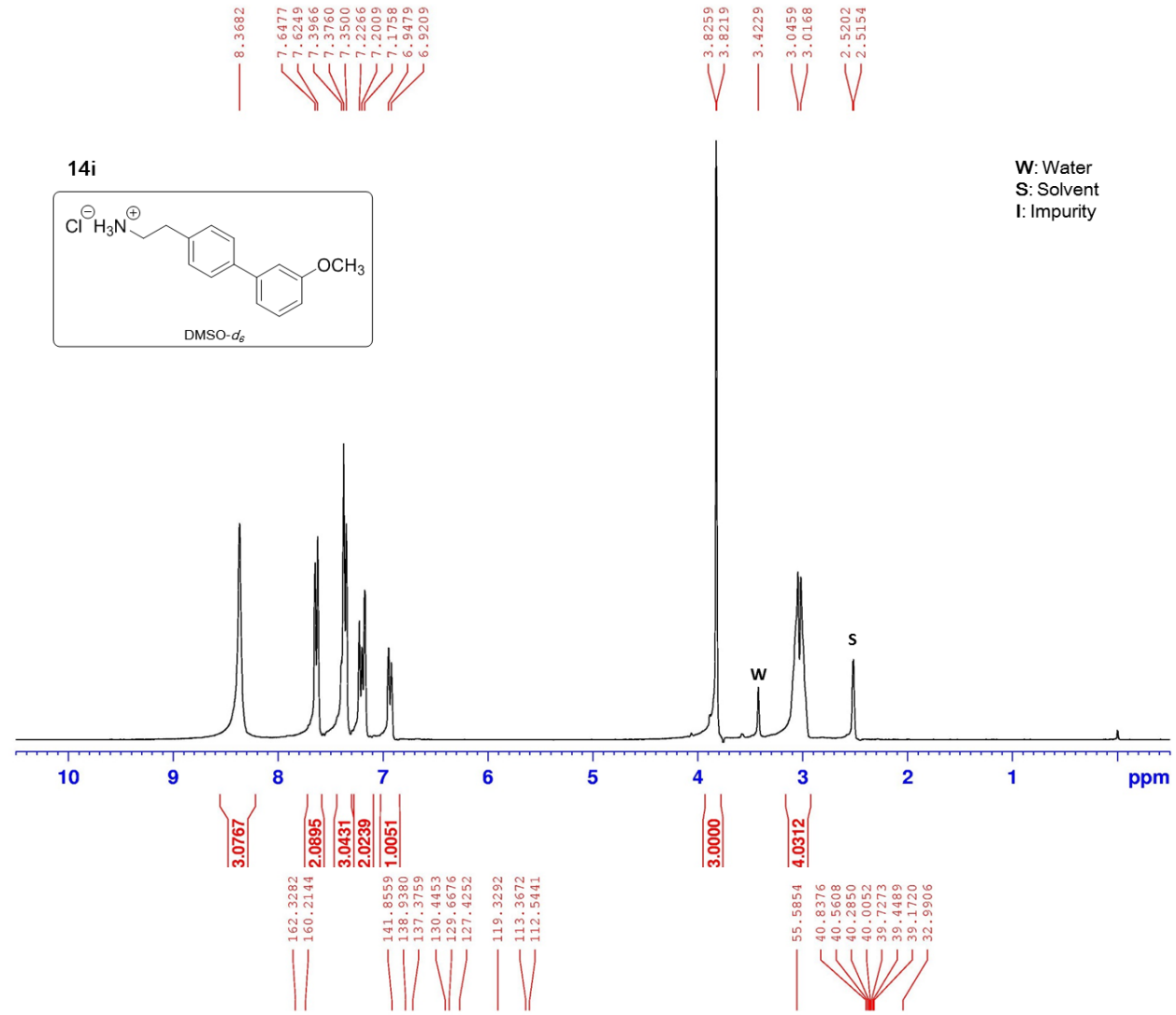


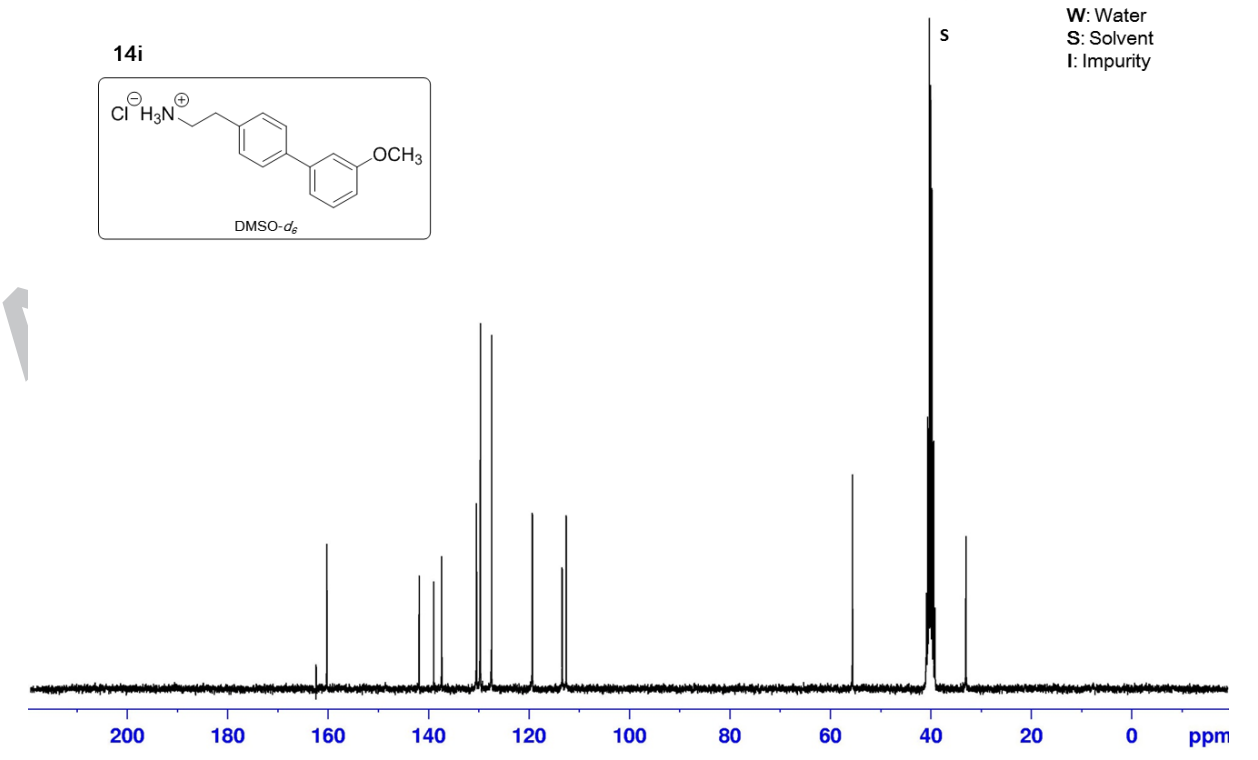


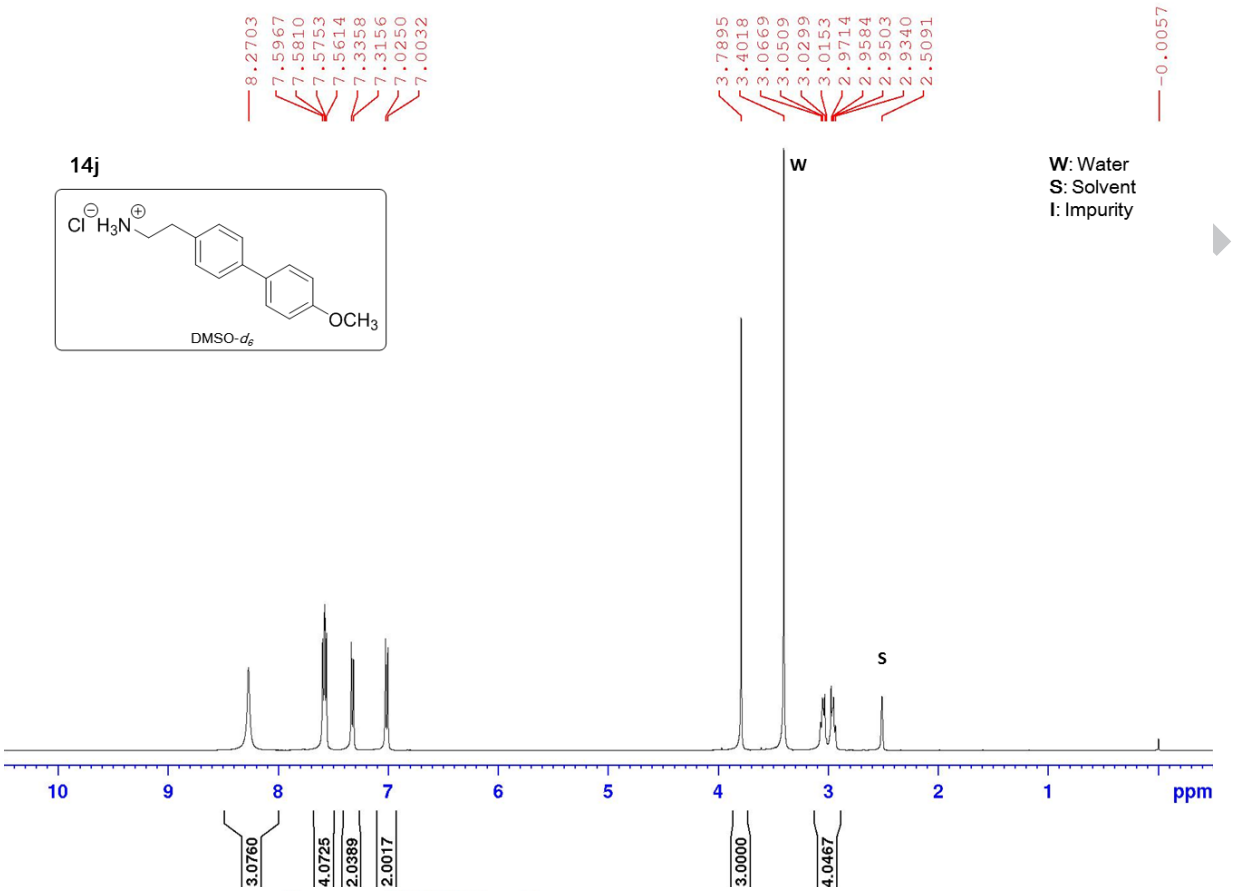


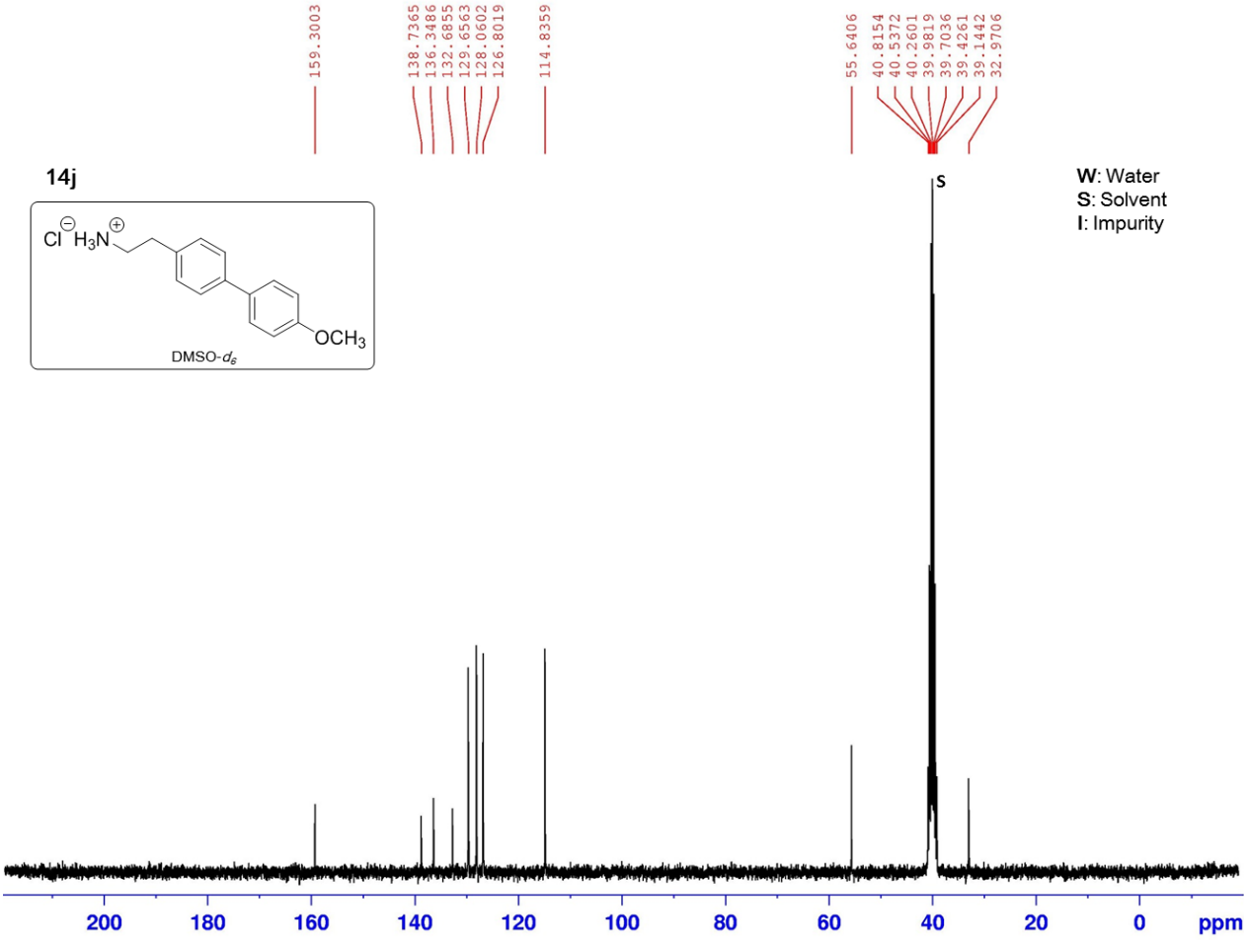


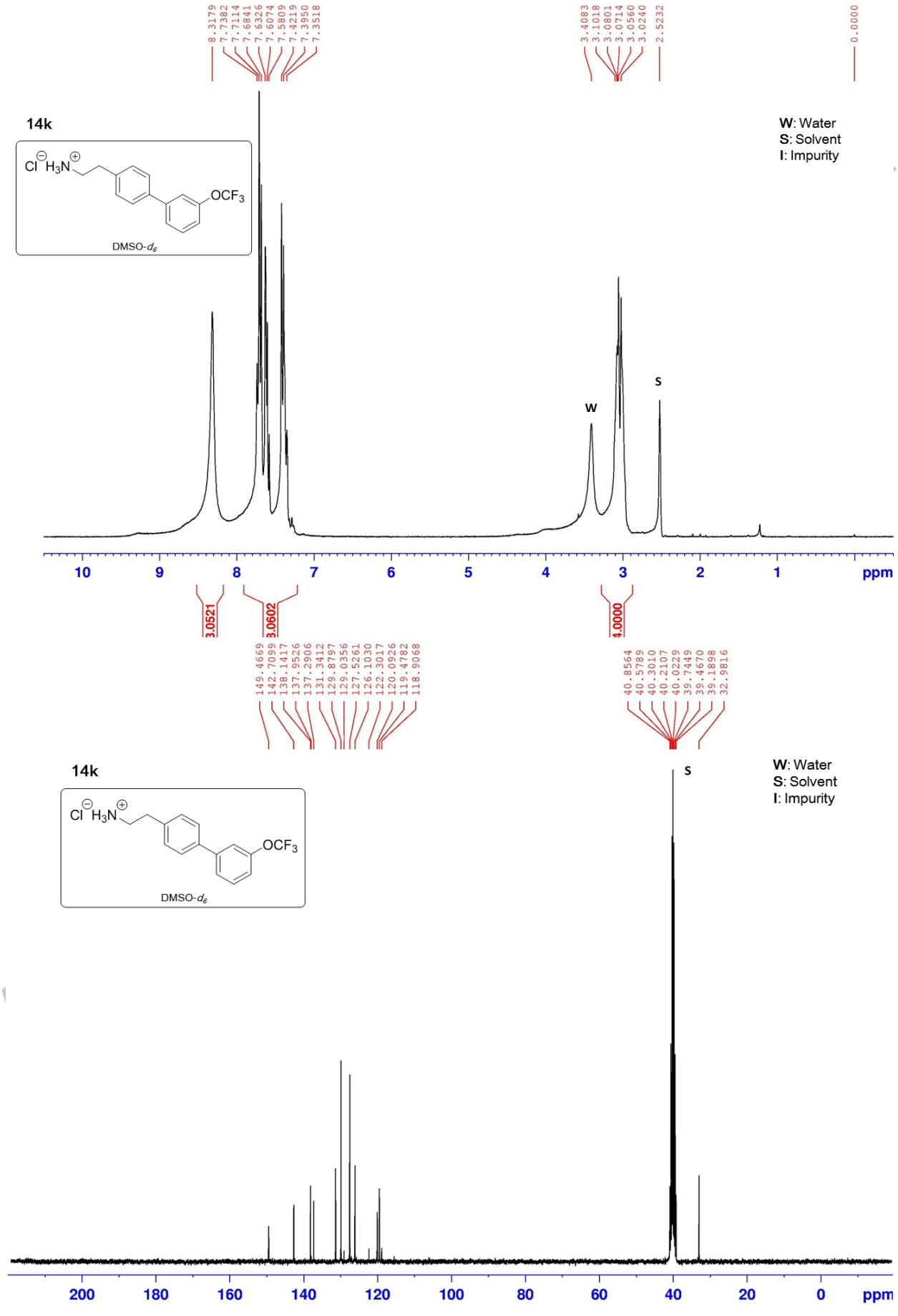


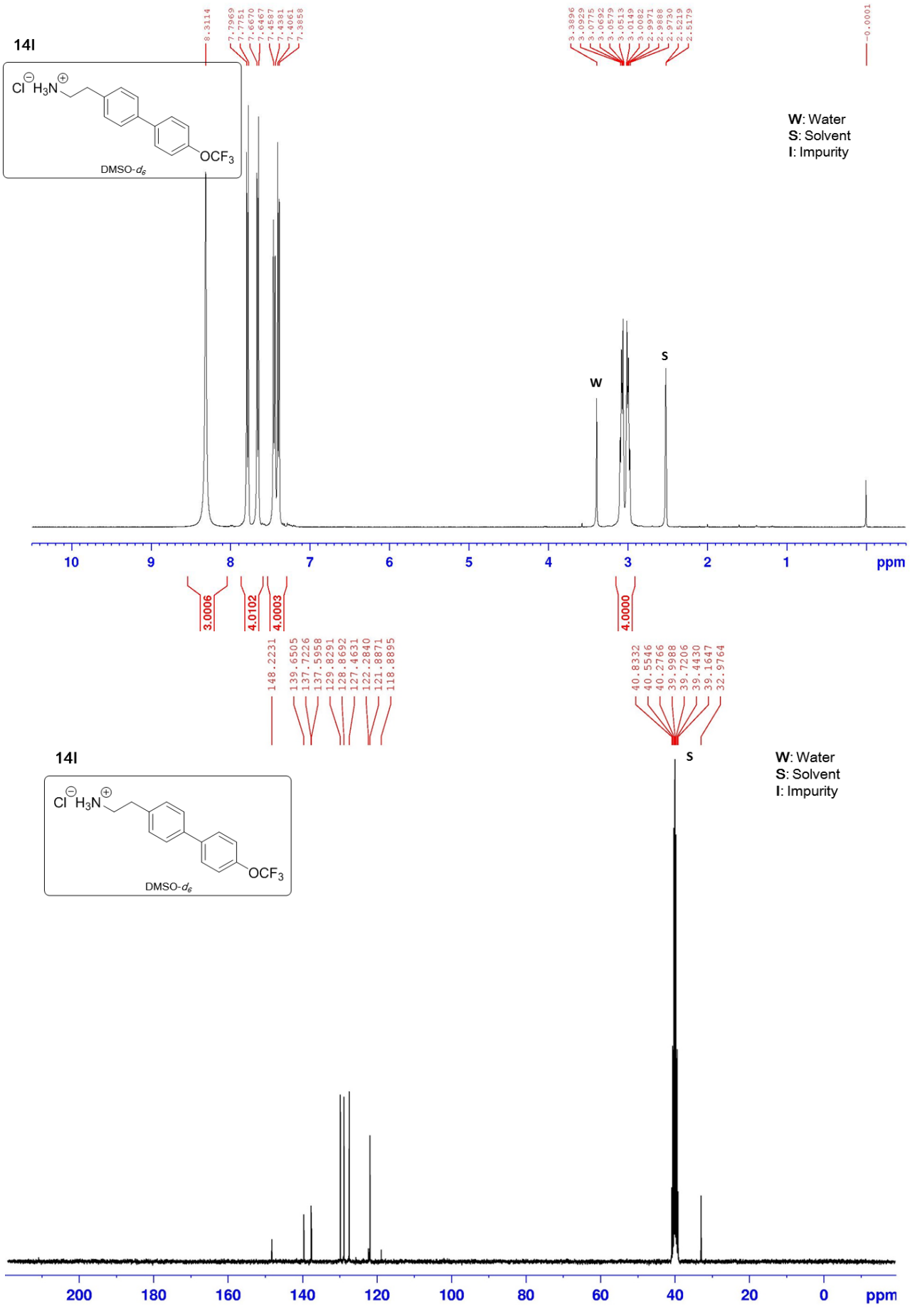


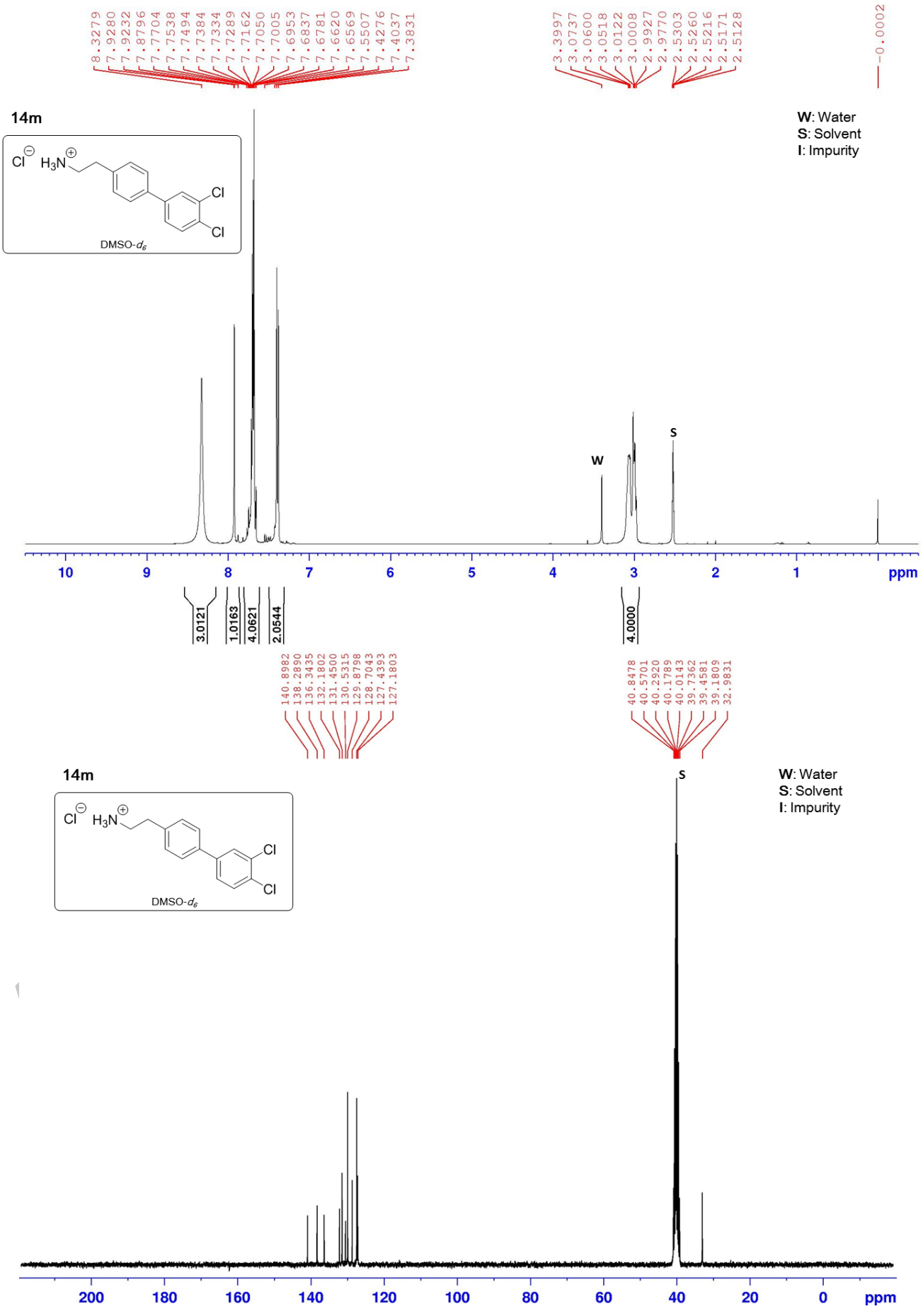


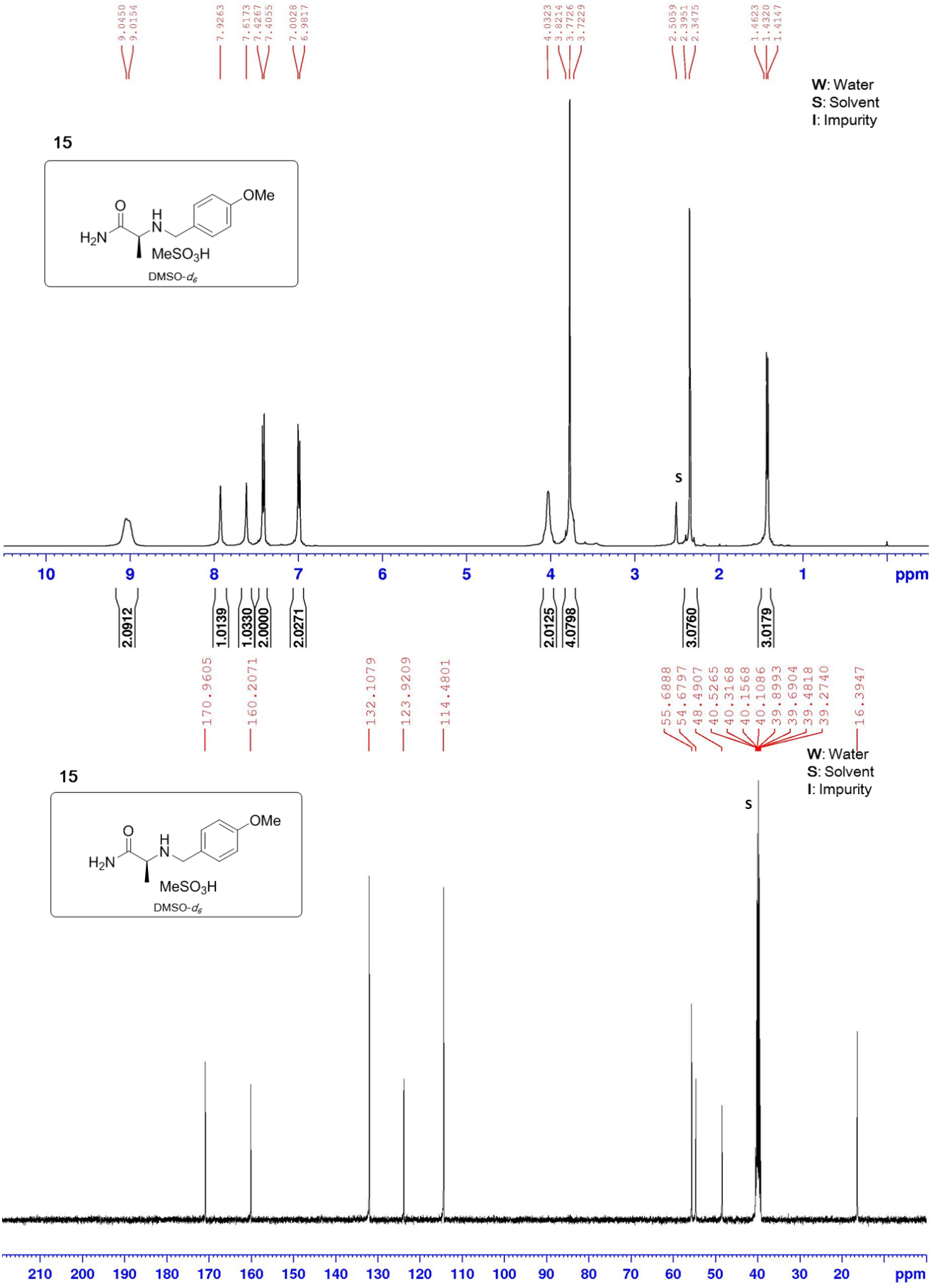












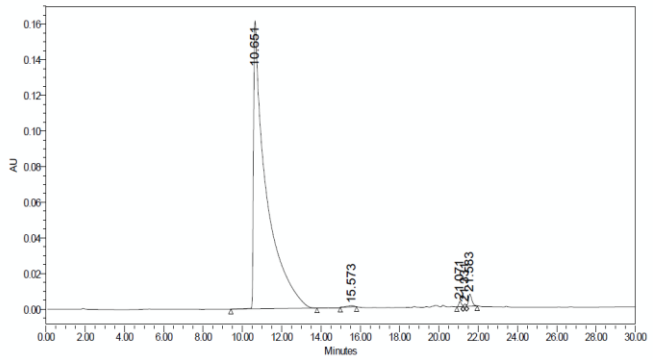
Purity of Compound 12c

Analytical HPLC was performed using a Waters e2695 system equipped with the following columns: Capcell Pak® colulmn (4.6 × 75 mm; 3μm). HPLC data were recorded using following methods: H_2O/MeCN, 90/10 → 50/50 in 15 min, + 50/50 → 0/100 in 5 min + 10 min isocratic, flow rate of 0.75 mL/min, λ = 254, 280 nm.

HPLC purity: 10.6 min, > 98% at 254 & 280 nm

SAMPLE INFORMATION

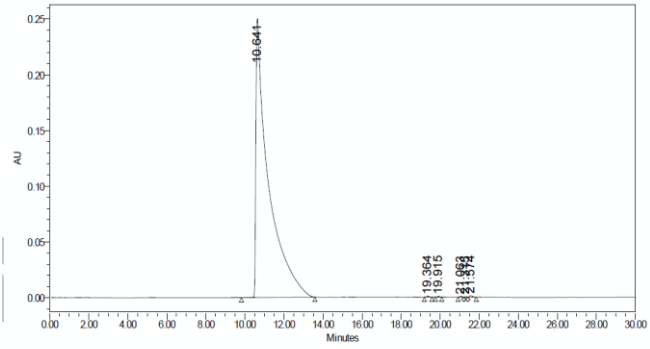
Sample Name:	Unk	Acquired By:	System
Sample Type:	Unknown	Sample Set Name	1524_075
Vial:	2	Acq. Method Set:	75mm method_including
Injection #:	1	Processing Method	1
Injection Volume:	15.00 ul	Channel Name:	W2489 ChA
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	W2489 ChA 254nm
Date Acquired:	11/20/2017 7:58:32 PM KST		
Date Processed:	11/20/2017 8:36:10 PM KST		



	RT	Area	% Area	Height
1	10.651	7189792	98.11	161691
2	15.573	18104	0.25	701
3	21.071	26845	0.37	2903
4	21.331	11230	0.15	1276
5	21.583	82587	1.13	6827

SAMPLE INFORMATION

Sample Name:	Unk	Acquired By:	System
Sample Type:	Unknown	Sample Set Name	1524_075
Vial:	2	Acq. Method Set:	75mm method_including
Injection #:	1	Processing Method	1
Injection Volume:	15.00 ul	Channel Name:	W2489 ChB
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	W2489 ChB 280nm
Date Acquired:	11/20/2017 7:58:32 PM KST		
Date Processed:	11/20/2017 8:37:20 PM KST		



	RT	Area	% Area	Height
1	10.641	11092680	99.69	251238
2	19.364	8164	0.07	831
3	19.915	4316	0.04	613
4	21.063	6000	0.05	673
5	21.315	3356	0.03	390
6	21.574	13126	0.12	1143

The low-resolution mass spectrum was performed on an API 3200 LC/MS/MS system (SCIEX).

LRMS (M + H)+ (ESI+) 296.1 [M + H]+ (calcd for C16H16F3NOH+ 296.1).