

1 Restoring and enhancing the potency of existing antibiotics against drug-resistant
2 Gram-negative bacteria through the development of potent small-molecule
3 adjuvants
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12 This SI file includes:

13 Figs. S1 to S4

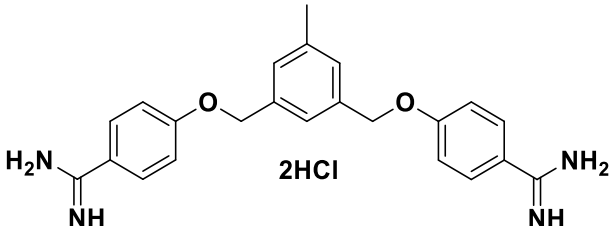
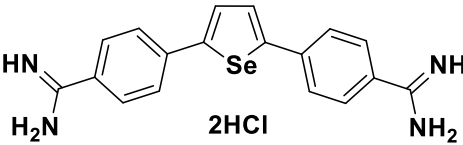
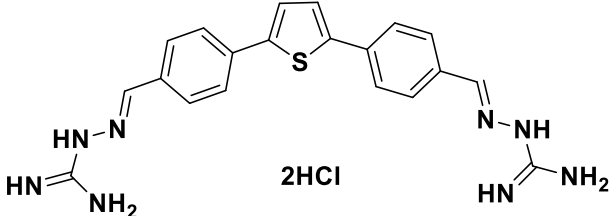
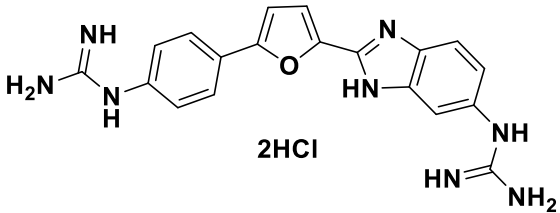
14 Tables S1 to S9

15 Scheme S1 to S2

16 ¹H NMR and ¹³C NMR spectra for all synthesized compounds
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32 Tables, figures and schemes

Table S1. Activity and cytotoxicity comparison of lead bacterial sensitizer			
Compound Name	Structure	Sensitization fold	IC ₅₀ on mammalian cells
DB2560 (MD-100)		32 ^a	100 μM
DB1213		32 ^a	50 μM
DB1079		64 ^b	12 μM
DB704		16 ^a	100 μM
Sensitization fold was tested on <i>E.coli</i> using rifampicin as antibiotic. a: 10 μg/ml bacterial sensitizer was used; b: 5 μg/ml bacterial sensitizer was used; IC ₅₀ was tested on HEK293 and NIH3T3 cells.			

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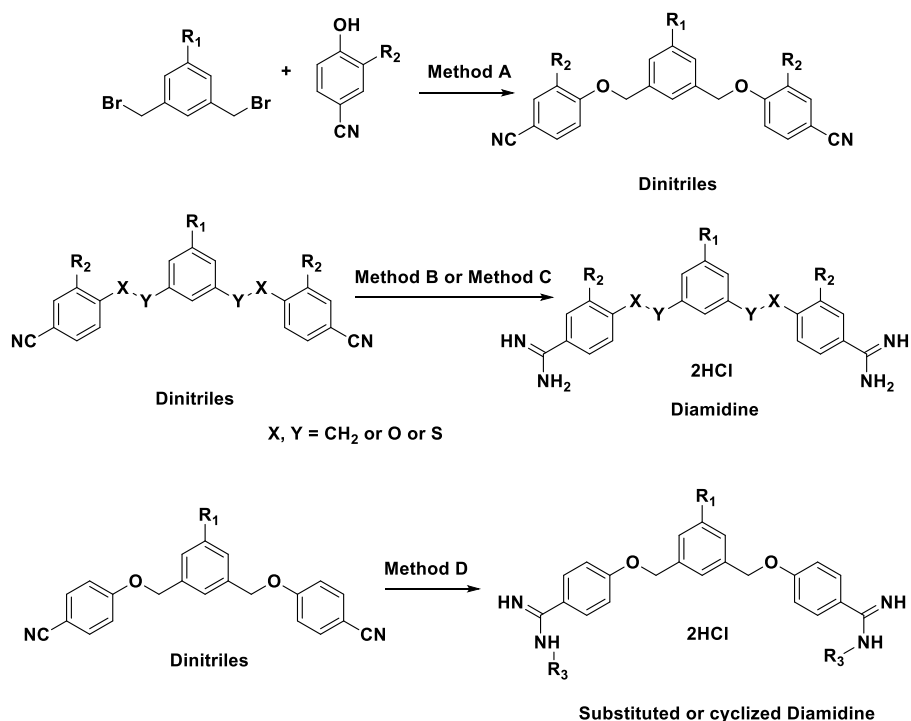
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42 **Scheme S1. General synthetic methods for diamidine compounds**



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44 **General procedures for the preparation of dinitriles (Method A)**

45 A mixture of 1,3-bis (bromomethyl)-benzene/substituted benzene (5 mmol), 4-

46 hydroxybenzonitrile or 4-hydroxy substituted benzonitrile (10 mmol) and anhydrous K₂CO₃ (2.07

47 g, 15 mmol) in 10 mL DMF was heated at 45 °C for 4 h. Then the reaction mixture was diluted

48 with ice water (70 mL) and stirred for 30 min. The white precipitate was filtered, washed with

49 water, and dried in air. Then the white solid was dissolved in organic solvent (75 mL) (DCM,

50 methanol or THF). The organic phase was dried over anhydrous MgSO₄. MgSO₄ was then filtered

51 and the supernatant was concentrated with rotavapor to afford crude product. The crude product

52 was then triturated with hexane, filtered and dried *in vacuum* to yield white solid in 80-90% yield.

53 **General procedures for diamidines as dihydrochloride salt (Method B)**

54 To a cold and stirred suspension of dinitrile (1 mmol) in 15 mL dry THF was added 6.0

55 mL (6 mmol) of LiN(TMS)₂ (1M in THF). The reaction was stirred for 24 h at r.t. Then the mixture

56 was cooled and acidified with saturated ethanolic-HCl to form a white solid. The mixture was
57 stirred for 2 h, after which all solvents were removed under vacuum to afford a crude product. The
58 crude product was then diluted with ether and the mixture was filtered to obtain a white solid. The
59 white solid was then diluted with 10 mL ice water, basified with 2M NaOH to afford a white
60 precipitate. The white precipitate was then filtered, washed with water and dried in air. The solid
61 was suspended in anhydrous ethanol (15 mL) and 5 mL saturated ethanolic HCl for 6 h. Then
62 ethanol was distilled off and the product was triturated with dry ether and filtered. The solid was
63 dried *in vacuum* at 80 °C for 12 h to yield (65-75%) diamidine dihydrochloride as white solid.

64 **General procedures for diamidines as dihydrochloride salt (Method C)**

65 Dinitrile (1 mmol) was added to anhydrous EtOH saturated with hydrogen chloride (20 mL)
66 at 0 °C in a dry flask. The reaction mixture was then sealed, slowly warmed to ambient temperature,
67 and stirred for 7 days. Ethanol was removed using rotary evaporator. Anhydrous diethyl ether (20
68 mL) was added to the reaction mixture and the precipitated imidate ester dihydrochloride was
69 filtered off and dried under high vacuum. Ammonia gas (using a cylinder) was passed through
70 imidate ester in EtOH (10 mL) and stirred for a day. The reaction mixture was concentrated *in*
71 *vacuum*. Then anhydrous ether was added, and the product was filtered and dried under vacuum.
72 The diamidine was converted to its dihydrochloride salt by stirring the diamidine with saturated
73 ethanolic HCl (2 mL) for 2-3h. The solvent was removed, and the solid was dried *in vacuum* at 80
74 °C for 12 h to yield final product (65-75%).

75 **General procedure for the preparation of substituted diamidine or cyclized diamidine as** 76 **dihydrochloride salts (Method D)**

77 The nitrile compound was added to anhydrous EtOH saturated with hydrogen chloride at
78 0 °C in a dry flask. The reaction mixture was then sealed, slowly warmed to ambient temperature,
79 and stirred until the nitrile compound was no longer detectable by TLC. The reaction mixture was
80 diluted with anhydrous ether. The precipitated imidate ester dihydrochloride was filtered off under
81 nitrogen and dried under high vacuum. The imidate was then reacted immediately with 2.5
82 equivalents of the appropriate amine in EtOH for 24h. The reaction mixture was concentrated *in*
83 *vacuum*. Then ether was added, and the product was filtered. The solid was suspended in 10 mL
84 ice-water and basified with 2M NaOH. The resulting white precipitate was filtered, washed with
85 water, and air dried. The free base was converted to its dihydrochloride salt using saturated
86 ethanolic HCl as white solid, which was dried *in vacuum* at 80 °C for 12 h to yield final product
87 (65-75%).

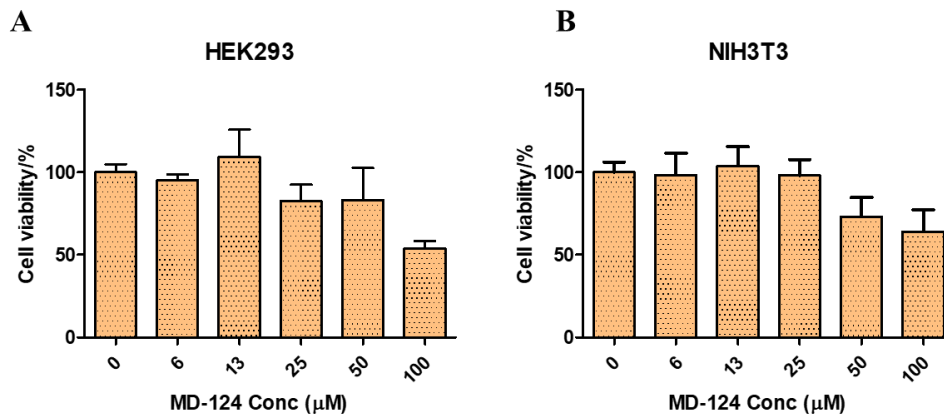
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Table S2A. MD-124 sensitizes wild-type <i>E. coli</i> (ATCC 25922) towards various antibiotics			
Antibiotics (AB)	MIC of AB (µg/ml) only	MIC of AB (µg/ml) with 5 µg/ml MD-124	Sensitization fold with 5 µg/ml MD-124
Rifampicin	10	0.019	512
Rifapentine	25	0.8	32
Rifaximin	12.5	0.2	64
Clarithromycin	50	0.2	256
Erythromycin	50	0.4	128
Azithromycin	6.2	0.4	16
Novobiocin	100	1.6	64
Clindamycin	200	3.2	64
Fusidic acid	>200	6.25	>32
Polymyxin B	1.2	0.04	32
Chloramphenicol	12.5	1.6	8
Trovafloxacin	0.05	0.0015	32
Besifloxacin	0.1	0.0125	8
Moxifloxacin	0.05	0.0062	8
Levofloxacin	0.05	0.0062	8
Ciprofloxacin	0.05	0.0125	4
Nafcillin	>300	75	>4
Cloxacillin	>300	75	>4
Meropenem	0.063	0.063	1
Tetracycline	1.2	0.6	2
Trimethoprim	2.5	1.25	2

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Table S2B. MD-124 sensitizes wild-type <i>E. coli</i> (ATCC 10536) towards rifampicin		
MD-124 Conc (µg/ml)	MIC of rifampicin in the presence of MD-124 (µg/ml)	Sensitization fold
4	0.62	16
5	0.16	64
6	0.04	256
7	0.04	256
MIC of rifampicin on wild-type <i>E. coli</i> is 10 µg/ml.		

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95 **Figure S1.** Cytotoxicity test of MD-124 on HEK293 cells (A) and NIH3T3 cells (B). Cells were
96 incubated with various concentrations of MD-124 at 37 °C with an atmosphere of 5% CO₂ for 24
97 h, then cell viability was determined by CCK-8. Values are means ± SD. n = 3.

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Table S3. MD-124 overcomes Gram-negative ESKAPE bacterial drug-resistance.					
	MIC of Rifampicin only	MIC of MD-124 only	MIC of rifampicin with 5 µg/ml MD-124	MIC of rifampicin with 7 µg/ml MD-124	FIC
<i>A. baumannii</i>	5	25	0.04	0.01	0.14
<i>K. pneumoniae</i>	40	25	0.64	0.32	0.15
NDM-1 <i>E. coli</i>	10	50	0.02	0.0024	0.09
MCR-1 <i>E. coli</i>	5	12.5	0.016	0.08	0.37
MDR <i>K. pneumoniae</i>	>160	>50	10	0.16	< 0.16
MDR <i>S. Typhimurium</i>	20	>50	1.25	0.04	< 0.16
Concentration unit for rifampicin and MD-124: µg/ml					

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Table S4. MD-124 sensitizes wild-type <i>A. baumannii</i> towards various antibiotics			
Antibiotics (AB)	MIC of AB (µg/ml) only	MIC of AB (µg/ml) with 5 µg/ml MD-124	Sensitization fold with 5 µg/ml MD-124
Rifampicin	5	0.04	128
Clarithromycin	25	0.4	64
Novobiocin	25	0.8	32
Fusidic acid	50	0.4	128
Clindamycin	100	12.5	8
Polymyxin B	1.6	0.04	4
Chloramphenicol	100	25	4
Ciprofloxacin	0.05	0.0125	4
Trimethoprim	25	12.5	2
Tetracycline	1.2	0.6	2
Trovafloxacin	0.032	0.016	2
Kanamycin	12.5	0.62	2
Nafcillin	200	100	2
MIC of MD-124 on <i>A. baumannii</i> is 25 µg/ml.			

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Table S5. MD-124 sensitizes wild-type <i>K. pneumoniae</i> towards various antibiotics			
Antibiotics (AB)	MIC of AB (µg/ml) only	MIC of AB (µg/ml) with 5 µg/ml MD-124	Sensitization fold with 5 µg/ml MD-124
Rifampicin	40	0.016	252
Clarithromycin	200	0.8	252
Novobiocin	200	6.4	32
Chloramphenicol	>100	1.6	>64
Clindamycin	>200	25	>8
Fusidic acid	100	25	4
MIC of MD-124 on <i>K. pneumoniae</i> is 25 µg/ml.			

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Table S6. NDM-1-expressing <i>E.coli</i> exhibits drug-resistance towards β-lactam antibiotics		
Antibiotics	MIC on wild-type <i>E.coli</i> (µg/ml)	MIC on NDM-1-expressing <i>E.coli</i> (µg/ml)
Ampicillin	6	> 300
Ceftazidime	< 0.2	> 6.25
Meropenem	0.03	12.5

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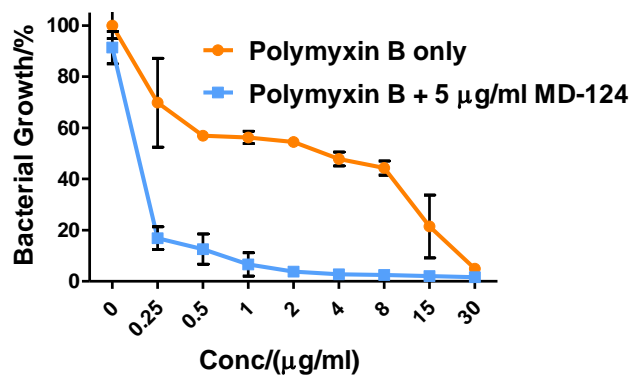
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Table S7. MD-124 sensitizes on NDM-1-expressing <i>E.coli</i> towards various antibiotics			
Antibiotics (AB)	MIC of AB ($\mu\text{g/ml}$) only	MIC of AB ($\mu\text{g/ml}$) with 5 $\mu\text{g/ml}$ MD-124	Sensitization fold with 5 $\mu\text{g/ml}$ MD-124
Rifampicin	10	0.02	512
Clarithromycin	25	0.4	64
Novobiocin	50	1.6	32
Clindamycin	200	3.2	64
Trovaflaxacin	0.025	0.0008	32
Chloramphenicol	12.5	1.6	8
Polymyxin B	2.5	0.32	8
Tetracycline	12.5	3.2	4
Meropenem	12.5	6.2	2
Ampicillin	>300	300	>1
MIC of MD-124 on NDM-1-expressing <i>E. coli</i> is 50 $\mu\text{g/ml}$.			

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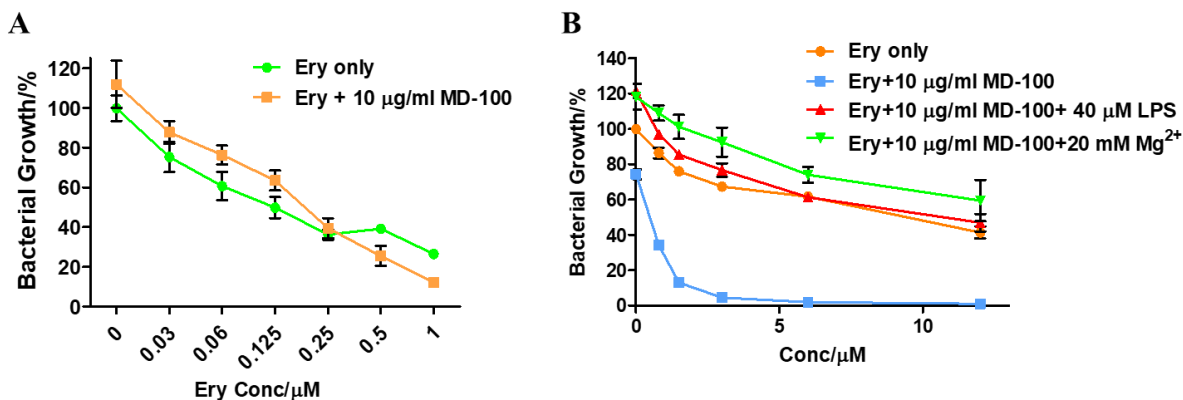
Table S8. MD-124 sensitizes on <i>mcr-1</i>-expressing <i>E.coli</i> towards various antibiotics			
<i>Antibiotics (AB)</i>	<i>MIC of AB ($\mu\text{g/ml}$) only</i>	MIC of AB ($\mu\text{g/ml}$) with 5 $\mu\text{g/ml}$ MD-124	Sensitization fold with 5 $\mu\text{g/ml}$ MD-124
Rifampicin	5	0.16	32
Clarithromycin	25	0.2	128
Polymyxin B	30	0.93	32
The MIC of polymyxin B on this <i>mcr-1</i> -expressing <i>E. coli</i> strain is 30 $\mu\text{g/ml}$. MIC of MD-124 on this <i>mcr-1</i> -expressing <i>E. coli</i> is 12.5 $\mu\text{g/ml}$.			

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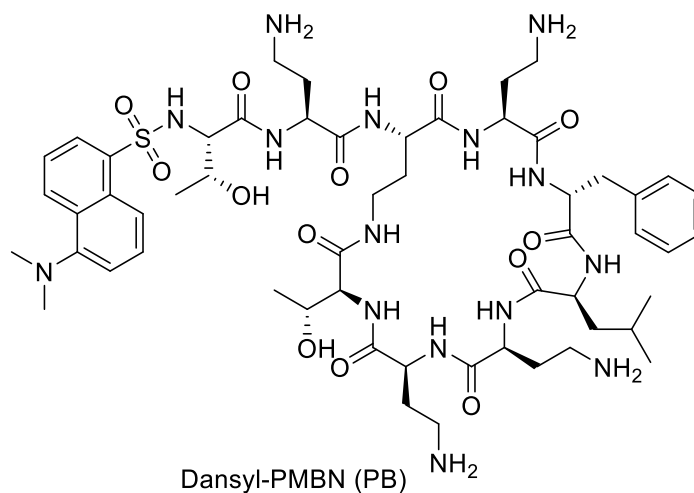


144 **Figure S2.** 5 µg/ml MD-124 sensitizes *mcr-1*- expressing *E. coli* towards polymyxin B. *E. coli*
 145 was cultured with the polymyxin B at various concentrations in the presence or absence of 5 µg/ml
 146 MD-124 for 24 h at 37 °C. Then bacterial growth density was determined by measuring OD₆₀₀.
 147 Values are means ± SD. n = 3.

Table S9. MIC of various antibiotics on MDR <i>K. pneumoniae</i> and MDR <i>S. Typhimurium</i>		
Antibiotics (AB)	MIC of AB (µg/ml) on MDR <i>K. pneumoniae</i>	MIC of AB (µg/ml) on MDR <i>S. Typhimurium</i>
Rifampicin	>160	40
Erythromycin	>160	>160
Clarithromycin	>160	>160
Novobiocin	>160	>160
Clindamycin	>160	>160
Polymyxin B	5	10
Chloramphenicol	>160	80
Trimethoprim	>160	>160
Tetracycline	20	160
Trovafloxacin	20	20
Moxifloxacin	40	40
Kanamycin	>160	20
Ampicillin	>160	>160
Methicillin	>160	>160



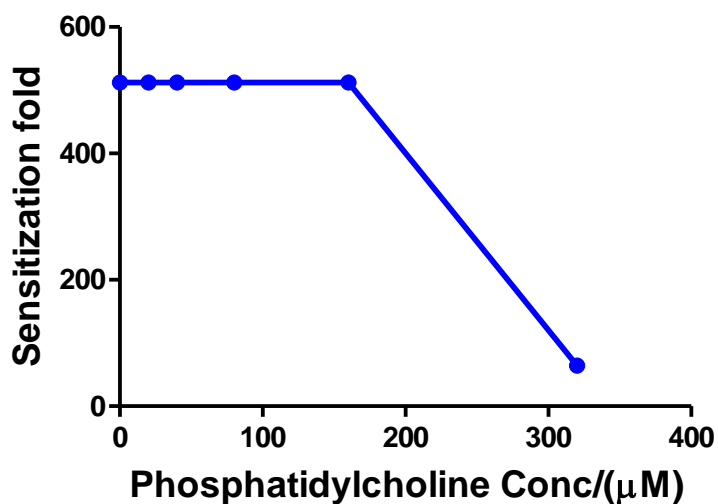
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 150 **Figure S3.** Molecular mechanism study of bacterial sensitizers. **A**, MD-100 failed to sensitize *E.*
 151 *coli* strain NR698 towards erythromycin, a strain with outer membrane “leaky” phenotype. 10
 152 µg/ml MD-100 sensitized wild-type *E. coli* towards erythromycin for 32-fold (The comparison
 153 between the blue and orange line in **Figure b**). *E. coli* NR698 was cultured with the antibiotic at
 154 various concentrations in the presence or absence of bacterial sensitizer for 24 h at 37 °C. Then
 155 bacterial growth density was determined by measuring OD₆₀₀. **B**, LPS and high concentration of
 156 Mg²⁺ decreased the sensitization ability of MD-100. *E. coli* was treated with 10 µg/ml MD-100
 157 and erythromycin combination in the presence and absence of 40 µM LPS for 24 h at 37 °C. Then
 158 the growth density/% was calculated based on OD₆₀₀. *E. coli* was treated with 10 µg/ml MD-100
 159 and erythromycin combination in the presence and absence of 20 mM Mg²⁺ for 24 h at 37 °C, then
 160 the growth density/% was calculated based on OD₆₀₀. Values are means ± SD. n = 3.



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 166 **Scheme S2.** Structure of Dansyl-PMBN (PB)

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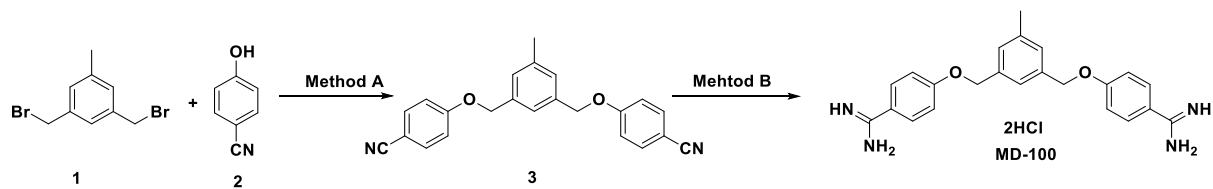
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169 **Figure S4.** The effect of phosphatidylcholine on MD-124 sensitization activity. *E. coli* was treated
170 with 10 μM MD-124 (about 5 μg/ml) and rifampicin combination with varying concentrations of
171 phosphatidylcholine (from 0 to 320 μM) for 24 h at 37 °C, then the OD₆₀₀ was measured and the
172 sensitization folds were calculated as mentioned above. All results were of triplicates.

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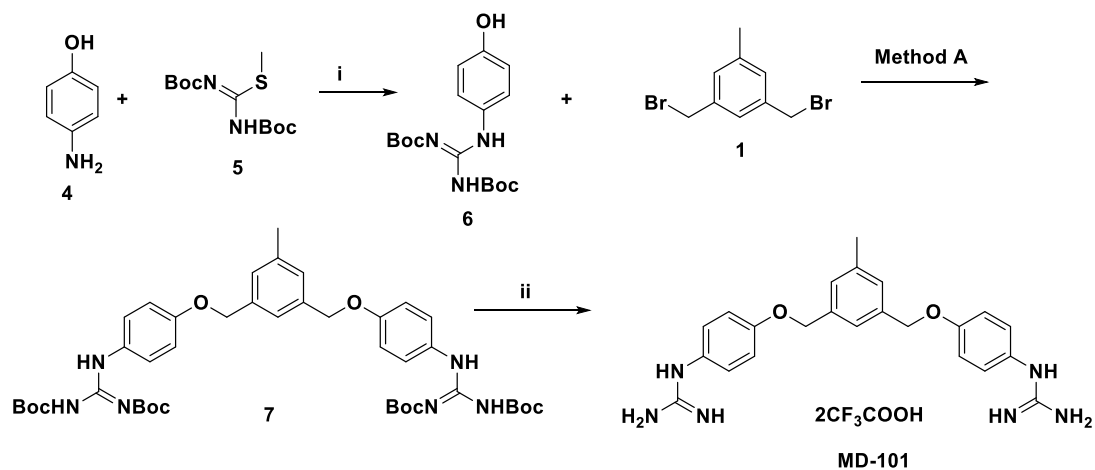
174 **Synthesis of MD-100**



176 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))dibenzonitrile (3).* Reaction
 177 of 1,3-bis (bromomethyl)-5-methylbenzene (**1**, 1.38 g, 5 mmol) and 4-hydroxybenzonitrile (**2**, 1.19
 178 g, 10 mmol) in the presence of anhydrous K_2CO_3 (2.07 g, 15 mmol) in 10 mL DMF yielded 1, 3-
 179 bis (4-cyano-phenoxy methyl)-5-methyl-benzene as white solid (**3**, 1.58 g, 90%) using method A.
 180 1H NMR ($CDCl_3$): δ 7.59 (d, $J = 8.8$ Hz, 4H), 7.26 (s, 1H), 7.22 (s, 2H), 7.02 (d, $J = 8.8$ Hz, 4H),
 181 5.09 (s, 4H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 161.9, 139.3, 136.4, 134.1, 128.3, 123.7, 119.2,
 182 115.6, 104.3, 70.1, 21.4. HRMS calcd for $C_{23}H_{18}N_2O_2Na$ $[M+Na]^+$: 377.1266, found: 377.1269.

183 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))dibenzimidamide*
 184 *dihydrochloride (MD-100).* **3** (0.354 g, 1 mmol) was converted to **MD-100** as brown solid
 185 following method B (**MD-100**, 0.33 g, 71%). 1H NMR ($DMSO-d_6$): δ 9.24 (s, 4H), 8.90 (s, 4H),
 186 7.82 (d, $J = 8.8$ Hz, 4H), 7.34 (s, 1H), 7.25 (s, 2H), 7.20 (d, $J = 8.8$ Hz, 4H), 5.18 (s, 4H), 2.32 (s,
 187 3H). ^{13}C NMR ($DMSO-d_6$): δ 165.0, 162.9, 138.6, 136.9, 130.5, 128.5, 124.6, 120.0, 115.5, 69.9,
 188 21.2. HRMS calcd for $C_{23}H_{25}N_4O_2$ $[M+H]^+$: 389.1972, found: 389.1976.

189 **Synthesis of MD-101**



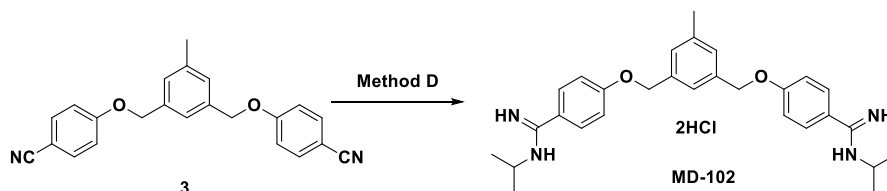
190 i) 0 °C , 10 min, HgCl₂, 20 h ii) TFA, DCM, rt, 2h.

191 *Synthesis of p-[N', N''-Di(Boc)guanidino]phenol (6).* p-aminophenol (**4**, 1.64 g, 15.0 mmol) and
 192 N,N'-Di(Boc)-S-methylisothiourea (**5**, 2.90 g, 10.0 mmol) were stirred in THF (100 mL) for 10
 193 minutes after which the reaction was cooled to 0°C. HgCl₂ (2.99 g, 11.0 mmol) was added slowly
 194 to this solution and stirred for 20 h. The reaction mixture was concentrated and purified with
 195 column chromatography using 5:1 Hexane: EA as eluant to give p-[N', N''-
 196 Di(Boc)guanidino]phenol (**6**) as a white solid (3.16 g, 60%).¹ ¹H NMR (CDCl₃): δ 11.61 (s, 1H),
 197 9.96 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.58 (d, *J* = 8.8 Hz, 2 H), 1.53 (s, 9 H), 1.44 (s, 9 H). ¹³C
 198 NMR (CDCl₃): δ 156.1, 155.7, 153.3, 126.7, 116.4, 84.0, 80.4, 28.3, 28.2. HRMS calcd for
 199 C₁₇H₂₆N₃O₅ [M+H]⁺: 352.1872, found 352.1863.

200 *Synthesis of 1,1'-((((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(4,1-
 201 phenylene))diguanidine di(trifluoroacetate).* Reaction of 1,3-bis (bromomethyl)-5-methylbenzene
 202 (**1**, 0.36 g, 1.3 mmol), p-[N',N''-Di(Boc)guanidino]phenol (**6**, 1.0 g, 2.84 mmol) and K₂CO₃ (0.54
 203 g, 3.9 mmol) yielded 1,3-Bis -5-methylbenzene (**7**) as white solid (0.74 g, 70%) using method A.
 204 Compound **7** (32 mg, 0.039 mmol) in DCM (2 mL) was treated with TFA (1 mL) for 2 h The
 205 solvent was removed in vacuo to yield 1,3-Bis -5-methylbenzene di(trifluoroacetate) (**MD-101**)

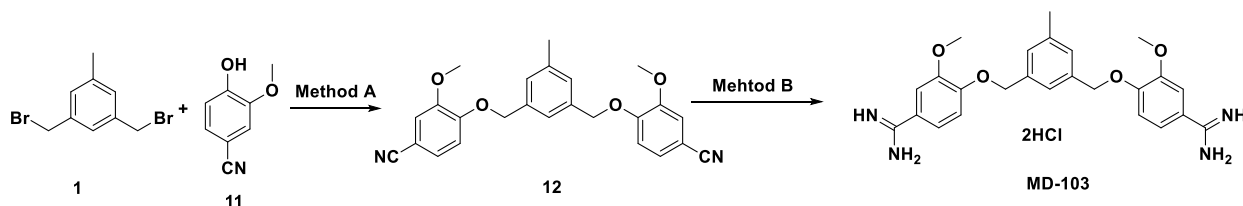
206 salt as a white solid (**MD-101**, 20 mg, 80%). ¹H NMR (MeOD): δ 7.33 (s, 1H), 7.23 (s, 2H), 7.22-
207 7.20 (m, 4H), 7.09- 7.07 (m, 4H), 5.09 (s, 4H), 2.36 (s, 3H). ¹³C NMR (MeOD): δ 159.8, 158.5,
208 139.8, 138.7, 128.8, 128.8, 128.6, 124.8, 117.2, 71.1, 21.4. HRMS calcd for C₂₃H₂₇N₆O₂ [M+H]⁺:
209 419.2195, found 419.2212.

210 Synthesis of MD-102



212 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(N-*
213 *isopropylbenzimidamide) dihydrochloride (MD-102).* Dinitrile (**3**, 0.35 g, 1 mmol) was converted
214 to **MD-102** by the reaction with isopropyl amine (0.15 g, 2.5 mmol) in ethanol (10 mL) at r.t. for
215 24h as pale yellow solid using general method D (**MD-102**, 0.27 g, 50%). ¹H NMR (DMSO-d₆):
216 δ 9.43 (d, *J* = 8.0 Hz, 2H), 9.33 (s, 2H), 8.99 (s, 2H), 7.73 (d, *J* = 8.8 Hz, 4H), 7.36 (s, 1H), 7.27
217 (s, 2H), 7.21 (d, *J* = 8.8 Hz, 4H), 5.20 (s, 4H), 4.09-4.04 (m, 2H), 2.34 (s, 3H), 1.26 (d, *J* = 6.4
218 Hz, 12H). ¹³C NMR (DMSO-d₆): δ 162.1, 161.2, 138.1, 136.7, 130.3, 128.1, 124.3, 121.2, 114.9,
219 69.5, 54.9, 44.9, 21.3, 21.0. HRMS calcd for C₂₉H₃₈N₄O₂ [M+2H]²⁺/2: 237.1492, found 237.1482.

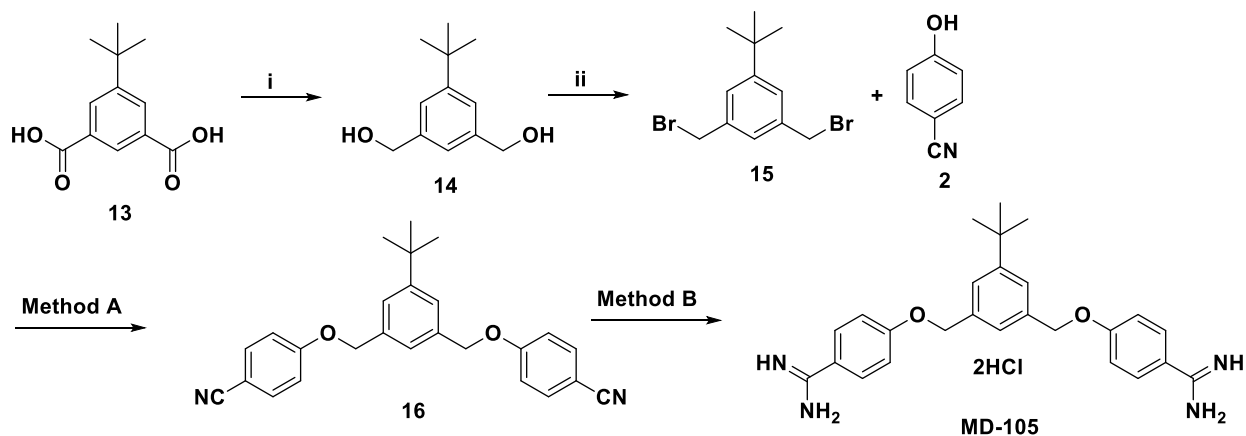
220 Synthesis of MD-103



222 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(3-methoxybenzotrile)*
223 **(12)**. Reaction of 1,3-bis (bromomethyl)-5-methylbenzene (**1**, 1.4 g, 5 mmol) and 4-hydroxy- 2-
224 methoxybenzotrile (**11**, 1.37 g, 10 mmol) the presence of anhydrous K₂CO₃ (2.07 g, 15 mmol)
225 in 10 mL DMF yielded 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(3-
226 methoxybenzotrile) as white solid (**12**, 1.57 g, 76%) following method A. ¹H NMR (DMSO-d₆):
227 δ 7.41-7.39 (m, 4H), 7.30 (s, 1H), 7.24 (s, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 5.15 (s, 4H), 3.80 (s, 6H),
228 2.33 (s, 3H). ¹³C NMR (DMSO-d₆): δ 151.8, 149.2, 138.0, 136.5, 128.5, 126.3, 124.6, 119.2, 114.7,
229 113.4, 102.9, 69.9, 56.0, 21.0. HRMS calcd for C₂₅H₂₃N₂O₄[M+H]⁺: 415.1652, found 415.1643.

230 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(3-methoxybenzimidamide)*
231 *dihydrochloride (MD-103)*. Dinitrile (**12**, 0.41 g, 1 mmol) was converted to yield 4,4'-(((5-methyl-
232 1,3-phenylene)bis(methylene))bis(oxy))bis(3-methoxybenzimidamide) dihydrochloride as brown
233 solid following method B (**MD-103**, 0.39 g, 76%). ¹H NMR (DMSO-d₆): δ 9.27 (s, 4H), 8.97 (s,
234 4H), 7.49 - 7.48 (m, 4H), 7.33 (s, 1H), 7.26 - 7.24 (m, 4H), 5.18 (s, 4H), 3.86 (s, 6H), 2.34 (s, 3H).
235 ¹³C NMR (DMSO-d₆): δ 164.7, 152.3, 148.81, 138.1, 136.7, 128.5, 124.7, 121.9, 119.5, 112.8,
236 111.6, 70.0, 56.1, 21.0. HRMS calcd for C₂₅H₃₀N₄O₄ [M+2H]²⁺/2: 225.1128, found 225.1119.

237 **Synthesis of MD-105**



238 (i) LiAlH₄, THF, 0 °C - rt, overnight (ii) PBr₃, CH₂Cl₂, 0 °C - r.t., 4h.

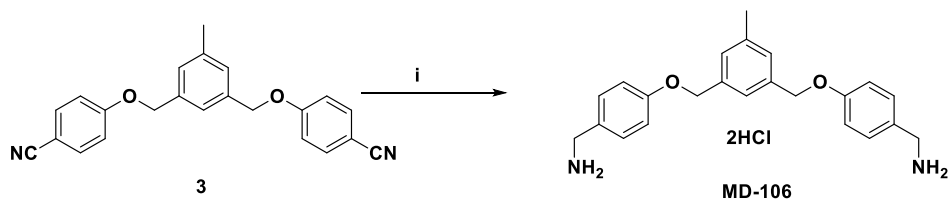
239 *Synthesis of diol (5-(tert-butyl)-1,3-phenylene)dimethanol (14).* 5-tert-butylisophthalic acid (13, 4
 240 g, 18 mmol) in THF (100 mL) was added dropwise under ice-bath condition to a solution of lithium
 241 aluminium hydride (1.5 g, 38mmol) in THF (100 mL). The reaction was stirred for 1 h at 0 °C,
 242 after which the reaction was heated at 60 °C for 24 h. The reaction was monitored by TLC. Upon
 243 completion, the reaction mixture was cooled to 0 °C and quenched with methanol and water. The
 244 quenched reaction was filtered through celite and washed with EtOAc (100 mL). The combined
 245 organic solvent was removed under reduced pressure and was extracted with EtOAc (3 × 100 mL),
 246 dried over MgSO₄ and concentrated to give the required diol (5-(tert-butyl)-1,3-
 247 phenylene)dimethanol (14, 3.2 g, 94%). ¹H NMR (CDCl₃): δ 7.32 (s, 2H), 7.19 (s, 1H), 4.69 (s,
 248 4H), 1.33 (s, 6H). ¹³C NMR (CDCl₃): δ 152.2, 141.1, 123.6, 123.1, 65.7, 34.9, 31.5. HRMS calcd
 249 for C₁₂H₁₇O[M- H₂O]⁺: 177.1274, found 177.1274.

250 *Synthesis of 1, 3-bis (4-cyano-phenoxy methyl)- 5-(tert-butyl)benzene (16).* PBr₃ (2.5 mL, 26 mmol)
 251 was added dropwise to a solution of diol (5-(tert-butyl)-1,3-phenylene)dimethanol (14, 2.3 g,
 252 11.8mmol) in DCM at 0°C. The reaction mixture was stirred at room temperature for 4 h and then
 253 quenched with ice water. The solution was extracted with CH₂Cl₂ (3 × 100 mL), dried over MgSO₄

254 and concentrated to give the required dibromo compound (1,3-bis(bromomethyl)-5-(tert-
 255 butyl)benzene) as a white solid (**15**, 3.4 g, 90%). Reaction of 1,3-bis(bromomethyl)-5-(tert-
 256 butyl)benzene (**15**, 1.6 g, 5 mmol) and 4-hydroxybenzonitrile (**2**, 1.19 g, 10 mmol) yielded dinitrile
 257 compound as white solid (**16**, 1.54 g, 78%) using method A. ¹H NMR (DMSO-d₆): δ 7.79 -7.78
 258 (m, 4H), 7.48 (s, 2H), 7.36 (s, 1H), 7.20 - 7.18 (m, 4H), 5.20 (s, 4H), 1.29 (s, 9H). ¹³C NMR
 259 (CDCl₃): δ 161.8, 151.3, 136.1, 134.2, 124.8, 119.1, 115.9, 103.0, 69.9, 34.5, 31.1. HRMS calcd
 260 for C₂₆H₂₅N₂O₂[M+H]⁺: 397.1911, found 397.1912.

261 *Synthesis of 4,4'-(((5-(tert-butyl)-1,3-phenylene)bis(methylene))bis(oxy))dibenzimidamide*
 262 *dihydrochloride (MD-105)*. 1, 3-bis (4-cyano-phenoxy methyl)- 5-(tert-butyl)benzene (**16**, 0.370
 263 g, 1 mmol) was converted to yielded 4,4'-(((5-(tert-butyl)-1,3-
 264 phenylene)bis(methylene))bis(oxy))dibenzimidamide dihydrochloride as brown solid following
 265 method B (**MD-105**, 0.35 g, 70%). ¹H NMR (DMSO-d₆): δ 9.42 (s, 4H), 9.21 (s, 4H), 7.94 (d, *J* =
 266 8.4 Hz, 4H), 7.49 (s, 2H), 7.39 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 4H), 5.23 (s, 4H), 1.28 (s, 9H). ¹³C
 267 NMR (DMSO-d₆): δ 165.7, 163.5, 152.5, 137.0, 131.0, 125.6, 120.3, 116.1, 70.7, 35.2, 31.8.
 268 HRMS calcd for C₂₆H₃₁N₄O₂[M+H]⁺: 431.2442, found 431.2425.

269 **Synthesis of MD-106**

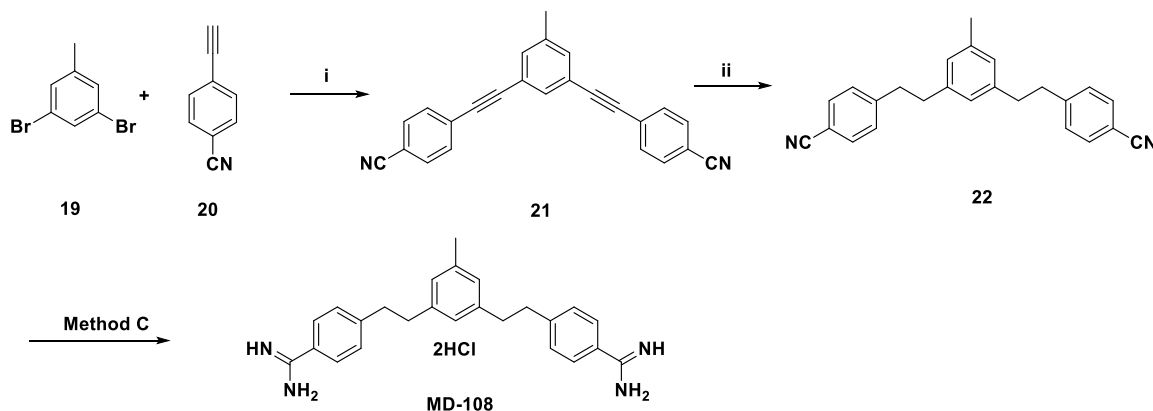


(i) LiAlH₄, THF, 0°C - rt, 16 h.

271 *Synthesis of (((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(4,1-*
 272 *phenylene))dimethanamine dihydrochloride (MD-106)*. A solution of 1, 3-bis (4-cyano-phenoxy

273 methyl-5-methyl-benzene (**3**, 1.0 g, 2.8 mmol) in THF (20 mL) was added dropwise to a
 274 suspension of LiAlH₄ (0.32 g, 7.4 mmol) in THF under argon gas at 0 °C and the mixture was
 275 stirred at room temperature for 16 h. The reaction was quenched with addition of H₂O (5 mL) at 0
 276 °C followed by addition of 16% NaOH solution (2 mL). The mixture was stirred at room
 277 temperature for around 2 hours after which it was filtered through celite. The solution was then
 278 concentrated *in vacuo* to obtain the free diamine. The product residue was then dissolved in ethanol
 279 followed by addition of HCl in ethanol (2 mL) for salt formation. The reaction mixture was
 280 evaporated *in vacuo* followed by ether precipitation to obtain the product as a green solid. (**MD-**
 281 **106**, 1.0 g, 87%). ¹H NMR (DMSO-d₆): δ 8.45 (s, 6H), 7.43 (d, *J* = 8.4 Hz, 4H), 7.32 (s, 1H), 7.22
 282 (s, 2H), 7.03 (d, *J* = 8.4 Hz, 4H), 5.09 (s, 4H), 2.32 (s, 3H). ¹³C NMR (DMSO-d₆): δ 158.4, 137.9,
 283 137.2, 130.5, 127.8, 126.2, 124.3, 114.8, 69.2, 41.6, 21.0. HRMS calcd for C₂₃H₂₇N₂O₂ [M+H]⁺:
 284 363.2079, found 363.2067.

285 Synthesis of MD-108



286 (i) 3 mol% Pd(PPh₃)₄, 6 mol% sodium ascorbate, 1 mol% CuSO₄, 1:1 Et₃N; DMSO (ii) H₂,
 Pd/C, MeOH, overnight.

287 Synthesis of 4,4'-((5-methyl-1,3-phenylene)bis(ethyne-2,1-diyl))dibenzonitrile (**21**). 3,5-
 288 dibromotoluene (**19**, 0.98 g, 3.9 mmol) was dissolved with 1:1 DMF-Et₃N (6 mL). To this solution,

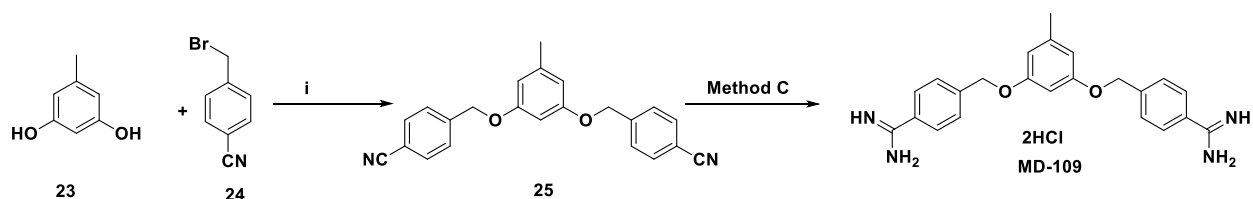
289 3 mole% Pd(PPh₃)₄ and 4-ethynylbenzonitrile (1 g, 7.8 mmol) were added and the mixture was
290 stirred for 5 minutes. Further, 6 mol% sodium ascorbate solution, 1 mol% CuSO₄ solution in DMF
291 were added to the reaction mixture and stirred for 4 h at 80 °C.² The reaction mixture was extracted
292 with ethyl acetate followed by ammonium chloride and brine wash. The combined organic layer
293 was dried over anhydrous Na₂SO₄ and then concentrated in vacuo. The product was purified using
294 column chromatography and obtained using 5:1 hexane: ethyl acetate system as a white solid (**21**,
295 0.67 g, 50%).² ¹H NMR (CDCl₃): δ 7.66 - 7.59 (m, 8H), 7.55 (s, 1H), 7.38 (s, 2H), 2.38 (s, 3H).
296 ¹³C NMR (CDCl₃): δ 38.9, 133.1, 132.3, 132.2, 128.1, 122.8, 118.6, 111.9, 92.9, 88.3, 21.2.
297 HRMS-calcd for C₂₅H₁₄N₂Na[M+Na]⁺: 365.1055 found 365.1068.

298 *Synthesis of 4,4'-((5-methyl-1,3-phenylene)bis(ethane-2,1-diyl))dibenzonitrile (22)*. To 10% Pd/C
299 in THF (30 mL) under argon gas was added 4,4'-((5-methyl-1,3-phenylene)bis(ethyne-2,1-
300 diyl))dibenzonitrile (**21**, 0.5 g, 1.46 mmol). The argon gas was exchanged for H₂ gas and the
301 reaction mixture was stirred overnight. The reaction mixture was quenched with CH₂Cl₂ and
302 filtered through celite. Extraction was carried out with CH₂Cl₂ followed by washing with H₂O. The
303 combined organic layer was dried over anhydrous Na₂SO₄ and then concentrated under vacuum to
304 give the product as a pale-yellow solid (**22**, 0.45 g, 87.6%). ¹H NMR (CDCl₃): δ 7.56 (d, *J* = 8.4
305 Hz, 4H), 7.24 (d, *J* = 8.4 Hz, 4H), 6.81 (s, 2H), 6.67 (s, 1H), 2.95 - 2.90 (m, 4H), 2.85 - 2.81 (m,
306 4H), 2.29 (s, 3H). ¹³C NMR (CDCl₃): δ 147.5, 141.0, 138.4, 132.3, 129.4, 127.3, 125.8, 119.2,
307 110.0, 38.1, 37.3, 21.5. HRMS calcd for C₂₅H₂₃N₂[M+H]⁺: 351.1856 found 351.1846.

308 *Synthesis of 4,4'-((5-methyl-1,3-phenylene)bis(ethane-2,1-diyl))dibenzimidamide dihydrochloride*
309 (**MD-108**). Dinitrile compound (**21**, 0.35 g, 1 mmol) was converted to 4,4'-((5-methyl-1,3-
310 phenylene)bis(ethane-2,1-diyl))dibenzimidamide dihydrochloride (**MD-108**) as white solid
311 following method B (**MD-108**, 0.32 g, 70%). ¹H NMR (DMSO-d₆): δ 9.34 (s, 4H), 9.12 (s, 4H),

312 7.78 (d, $J = 8.4$ Hz, 4H), 7.49 (d, $J = 8.4$ Hz, 4H), 6.94 (s, 1H), 6.90 (s, 2H), 2.98 - 2.94 (m, 4H),
313 2.85 - 2.81 (m, 4H), 2.24 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 165.5, 148.4, 141.0, 137.3, 129.1, 128.2,
314 126.9, 125.6, 125.5, 36.9, 36.6, 21.1. HRMS calcd for $\text{C}_{25}\text{H}_{30}\text{N}_4$ $[\text{M}+2\text{H}]^{2+}/2$: 193.1230, found
315 193.1222.

316 Synthesis of MD-109

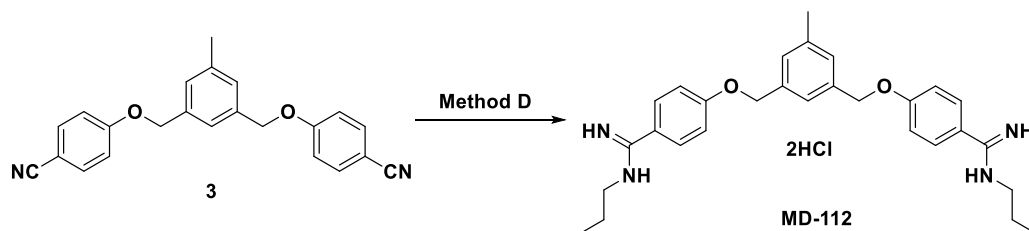


317 i) K_2CO_3 , DMF, rt, overnight.

318 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(oxy))bis(methylene))dibenzonitrile (25).* A
319 mixture of orcinol (**23**, 0.5 g, 4.1 mmol), 4-cyanobenzyl bromide (**24**, 1.65 g, 8.4 mmol) and
320 anhydrous K_2CO_3 (1.66 g, 12 mmol) in 10 mL DMF was stirred at room temperature overnight.
321 Then the reaction mixture was diluted with ice water (70 mL) and stirred for 30 min. The yellow
322 precipitate was filtered, washed with water, and dried in air. Then the yellow solid was dissolved
323 in a DCM (100 mL), dried over anhydrous MgSO_4 , filtered and concentrated with rotavapor. The
324 crude product was triturated with hexane and the precipitate was filtered, which was then dried *in*
325 *vacuo* to yield 4,4'-(((5-methyl-1,3-phenylene)bis(oxy))bis(methylene))dibenzonitrile as a yellow
326 solid (**25**, 0.97 g, 66.5%). ^1H NMR (CDCl_3): δ 7.68 (d, $J = 8.4$ Hz, 4H), 7.53 (d, $J = 8.4$ Hz, 4H),
327 6.43 (d, $J = 2.0$ Hz, 2H), 6.39 (t, $J = 2.0$ Hz, 1H), 5.08 (s, 4H), 2.30 (s, 3H). ^{13}C NMR (CDCl_3): δ
328 159.5, 142.5, 140.9, 132.5, 127.7, 118.8, 111.9, 108.7, 99.5, 69.0, 22.0. HRMS calcd for
329 $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 377.1266, found 377.1283.

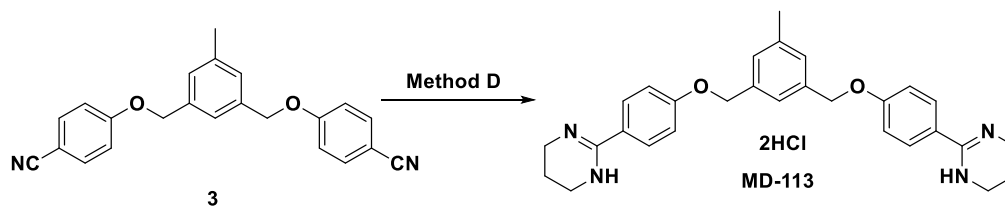
330 Synthesize of 4,4'-(((5-methyl-1,3-phenylene)bis(oxy))bis(methylene))dibenzimidamide
331 dihydrochloride (**MD-109**). Dinitrile (**25**, 0.33 g, 0.93 mmol) was converted to 4,4'-(((5-methyl-
332 1,3-phenylene)bis(oxy))bis(methylene))dibenzimidamide dihydrochloride as white solid
333 following method C (**MD-109**, 0.3 g, 75%). ¹H NMR (DMSO-d₆): δ 9.45 (s, 4H), 9.25 (s, 4H), 7.86
334 (d, *J* = 7.6 Hz, 4H), 7.64 (d, *J* = 7.6 Hz, 4H), 6.50 (s, 1H), 6.48 (s, 2H), 5.20 (s, 4H), 2.23 (s, 3H).
335 ¹³C NMR (DMSO-d₆): δ 165.5, 159.1, 143.4, 140.0, 128.4, 127.6, 127.3, 108.3, 99.3, 68.3, 21.5.
336 HRMS calcd for C₂₃H₂₅N₄O₂ [M+H]⁺: 389.1978, found 389.1960.

337 Synthesis of MD-112



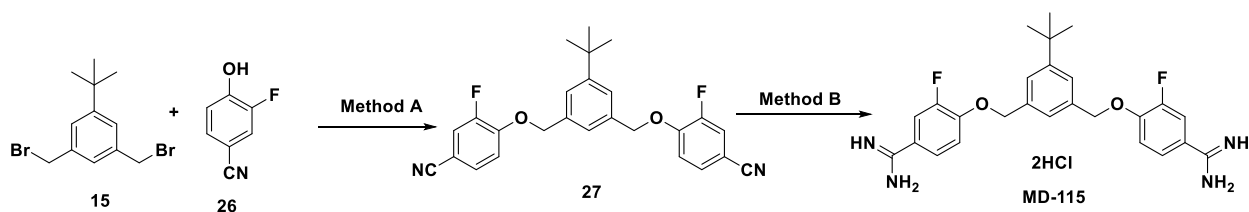
339 Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(oxy))bis(methylene))bis(N-propylbenzimidamide)
340 dihydrochloride (**MD-112**). Dinitrile (**3**, 0.35 g, 0.98 mmol) was converted to 4,4'-(((5-methyl-
341 1,3-phenylene)bis(oxy))bis(methylene))bis(N-propylbenzimidamide) dihydrochloride (**MD-112**)
342 by the reaction with *n*-propylamine (0.14 g, 2.45 mmol) in ethanol (10 mL) at 49 °C for 24 h as
343 white solid following method D (0.37 g, 70%). ¹H NMR (DMSO-d₆): δ 9.90 (s, 2H), 9.53 (s, 2H),
344 9.18 (s, 2H), 7.79 (d, *J* = 8.4 Hz, 4H), 7.63 (d, *J* = 8.4 Hz, 4H), 6.50 – 6.48 (m, 3H), 5.19 (s, 4H),
345 3.41 - 3.36 (m, 2H), 2.23 (s, 3H), 1.68-1.63 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 6H). ¹³C NMR (DMSO-
346 d₆): δ 162.5, 159.1, 142.7, 140.2, 128.5, 128.3, 127.6, 108.3, 99.7, 68.3, 44.2, 21.5, 20.9, 11.2.
347 HRMS- calcd for C₂₉H₃₇N₄O₂ [M+H]⁺: 473.2917, found 473.2940.

348 Synthesis of MD-113



349
 350 *Synthesis of 2,2'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(4,1-*
 351 *phenylene))bis(1,4,5,6-tetrahydropyrimidine) dihydrochloride (MD-113).* Dinitrile (**3**, 0.4 g, 1.12
 352 mmol) was converted to 2,2'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(4,1-
 353 phenylene))bis(1,4,5,6-tetrahydropyrimidine) dihydrochloride (**MD-113**) by the reaction with
 354 1,3-diaminopropane (0.25 g, 3.4 mmol) in ethanol (10 mL) at 140 °C as white solid following
 355 method D (**MD-113**, 0.48 g, 75%). ¹H NMR (DMSO-d₆): δ 10.23 (s, 4H), 7.82 (d, *J* = 8.0 Hz,
 356 4H), 7.63 (d, *J* = 8.0 Hz, 4H), 6.51 (s, 1H), 6.48 (s, 2H), 5.19 (s, 4H), 3.48 – 3.37 (m, 8H), 2.23 (s,
 357 3H), 1.98-1.95 (m, 4H). ¹³C NMR (DMSO-d₆): δ 159.1, 158.5, 142.6, 139.9, 128.0, 127.6, 127.6,
 358 108.3, 99.2, 68.3, 38.7, 21.4, 17.7. HRMS calcd for C₂₉H₃₃N₄O₂ [M+H]⁺: 469.2604, found
 359 469.2617.

360 Synthesis of BW-MD-115

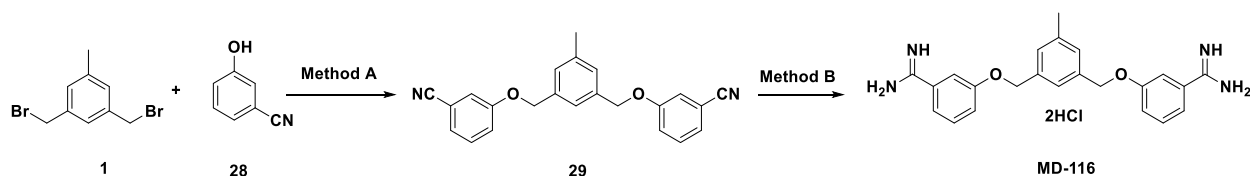


361
 362 *Synthesis of 4,4'-(((5-(tert-butyl)-1,3-phenylene)bis(methylene))bis(oxy))bis(3-fluorobenzonitrile)*
 363 *(27).* Reaction of 1,3-bis(bromomethyl)-5-(tert-butyl)benzene (**15**, 1.5g, 4.7mmol) and 2-fluoro-
 364 4-hydroxybenzonitrile (**26**, 1.3 g, 9.4 mmol) yielded 4,4'-(((5-(tert-butyl)-1,3-
 365 phenylene)bis(methylene))bis(oxy))bis(3-fluorobenzonitrile) as white solid (**27**, 1.52 g, 75%)
 366 using method A. ¹H NMR (DMSO-d₆): δ 7.85 (dd, *J* = 11.2, 1.6 Hz, 2H), 7.68-7.66 (m, 2H), 7.50

367 (s, 2H), 7.44 (t, $J = 8.8$ Hz, 2H), 7.36 (s, 1H), 5.29 (s, 4H), 1.29 (s, 9H). ^{13}C NMR (DMSO- d_6): δ
 368 153.4, 151.8 (d, $J_{\text{C-F}} = 186$ Hz), 151.0, 135.6, 129.7 (d, $J_{\text{C-F}} = 4$ Hz), 125.0, 123.9, 120.0 (d, $J_{\text{C-F}}$
 369 = 21 Hz), 118.0 (d, $J_{\text{C-F}} = 3$ Hz), 115.4 (d, $J_{\text{C-F}} = 3$ Hz), 104.6 (d, $J_{\text{C-F}} = 9$ Hz), 71.5, 35.0, 31.4.
 370 HRMS calcd for $\text{C}_{26}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 455.1547, found 455.1541.

371 *Synthesis of 4,4'-(((5-(tert-butyl)-1,3-phenylene)bis(methylene))bis(oxy))bis(3-*
 372 *fluorobenzimidamide) dihydrochloride (MD-115).* Dinitrile (**27**, 0.35 g, 0.8 mmol) was converted
 373 to 4,4'-(((5-(tert-butyl)-1,3-phenylene)bis(methylene))bis(oxy))bis(3-fluorobenzimidamide)
 374 dihydrochloride (**MD-115**) as brown solid following method B (0.30 g, 70.1%). ^1H NMR (DMSO-
 375 d_6): δ 9.49 (s, 4H), 9.26 (s, 4H), 7.90 (dd, $J = 12.4, 2.4$ Hz, 2H), 7.81-7.79 (m, 2H), 7.52-7.50 (m,
 376 4H), 7.39 (s, 1H), 5.31 (s, 4H), 1.28 (s, 9H). ^{13}C NMR (DMSO- d_6): δ 164.0, 152.3, 151.0 (d, $J_{\text{C-F}}$
 377 = 11 Hz), 150.8 (d, $J_{\text{C-F}} = 177$ Hz), 136.0, 126.0 (d, $J_{\text{C-F}} = 3$ Hz), 125.2, 124.9, 120.0 (d, $J_{\text{C-F}} = 7$
 378 Hz), 116.3 (d, $J_{\text{C-F}} = 20$ Hz), 115.3, 70.9, 34.6, 31.2. HRMS calcd for $\text{C}_{26}\text{H}_{29}\text{F}_2\text{N}_4\text{O}_2$ [$\text{M}+\text{H}$] $^+$:
 379 467.2272, found 467.2271.

380 Synthesis of MD-116

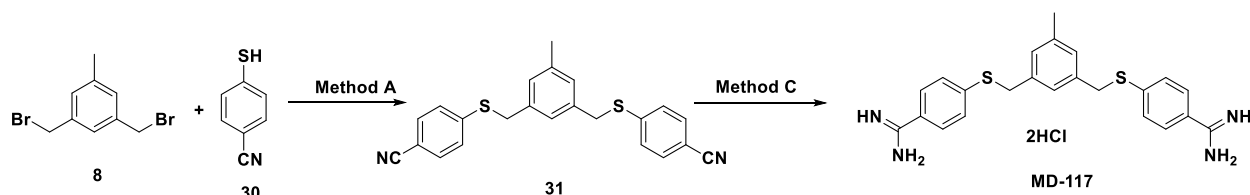


382 *Synthesis of 3,3'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))dibenzonitrile (29).*
 383 Reaction of 1,3-bis (bromomethyl)-5-methylbenzene (**1**, 2.13 g, 7.7 mmol) and 3-cyanophenol (**28**,
 384 2.05 g, 17 mmol) yielded 3,3'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))dibenzonitrile
 385 as white solid (**29**, 2.6 g, 91%) using method A. ^1H NMR (CDCl_3): δ 7.38-7.36 (m, 2H), 7.27-7.25
 386 (m, 3H), 7.22-7.19 (m, 6H), 5.06 (s, 4H), 2.41 (s, 3H). ^{13}C NMR (CDCl_3): δ 158.8, 139.3, 136.6,

387 130.6, 128.3, 125.0, 123.6, 120.2, 118.8, 117.9, 113.4, 70.2, 21.5. HRMS calcd for
388 $C_{23}H_{18}N_2O_2Na[M+Na]^+$: 377.1266, found 377.1250.

389 *Synthesis of 3,3'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))dibenzimidamide*
390 *dihydrochloride (MD-116)*. Dinitrile (**29**, 0.32 g, 0.9 mmol) was converted to 3,3'-(((5-methyl-
391 1,3-phenylene)bis(methylene))bis(oxy))dibenzimidamide dihydrochloride (**MD-116**) as white
392 solid using method B (0.32 g, 76%). 1H NMR (DMSO- d_6): δ 9.40 (s, 4H), 9.07 (s, 4H), 7.53 (t, J
393 = 8.0 Hz, 2H), 7.47 (s, 2H), 7.41-7.34 (m, 5H), 7.26 (s, 2H), 5.16 (s, 4H), 2.33 (s, 3H). ^{13}C NMR
394 (DMSO- d_6): δ 165.6, 158.7, 138.5, 137.0, 130.8, 129.5, 128.5, 124.6, 120.7, 120.5, 114.5, 69.9,
395 21.2. HRMS calcd for $C_{23}H_{25}N_4O_2 [M+H]^+$: 389.1978, found 389.1980.

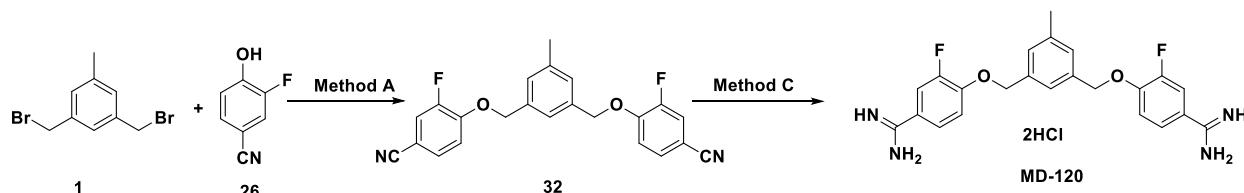
396 **Synthesis of MD-117**



398 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(sulfanediy))dibenzonitrile (31)*.
399 Reaction of 1,3-bis (bromomethyl)-5-methylbenzene (**8**, 0.93 g, 3.3 mmol) and 4-
400 mercaptobenzonitrile (**30**, 1.0 g, 7.3 mmol) yielded 4,4'-(((5-methyl-1,3-
401 phenylene)bis(methylene))bis(sulfanediy))dibenzonitrile as white solid (1.12 g, 85%), using
402 method A. 1H NMR (CDCl $_3$): δ 7.50 (d, J = 8.4 Hz, 4H), 7.28 (d, J = 8.4 Hz, 4H), 7.14 (s, 1H),
403 7.08 (s, 2H), 4.13 (s, 4H), 2.32 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 144.3, 139.0, 136.2, 132.1, 128.9,
404 127.1, 126.1, 118.7, 108.4, 36.7, 21.2. HRMS calcd for $C_{23}H_{19}N_2S_2 [M+H]^+$: 387.0984, found
405 387.1003.

406 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(sulfanediyl))dibenzimidamide*
 407 *dihydrochloride (MD-117)*. Dinitrile (**31**, 0.30 g, 0.74 mmol) was converted to 4,4'-(((5-methyl-
 408 1,3-phenylene)bis(methylene))bis(sulfanediyl))dibenzimidamide dihydrochloride (**MD-117**) as
 409 green solid following method C (**MD-117**, 0.19 g, 50%). ¹H NMR (DMSO-d₆): δ 9.30 (s, 4H),
 410 9.03 (s, 4H), 7.74 (d, *J* = 8.4 Hz, 4H), 7.51 (d, *J* = 8.4 Hz, 4H), 7.31 (s, 1H), 7.16 (s, 2H), 4.33
 411 (s, 4H), 2.26 (s, 3H). ¹³C NMR (DMSO-d₆): δ 164.9, 144.8, 138.1, 136.8, 128.6, 128.5, 126.5,
 412 126.3, 124.1, 35.0, 20.9. HRMS calcd for C₂₃H₂₅N₄S₂ [M+H]⁺: 421.1521, found 421.1532.

413 **Synthesis of MD-120**

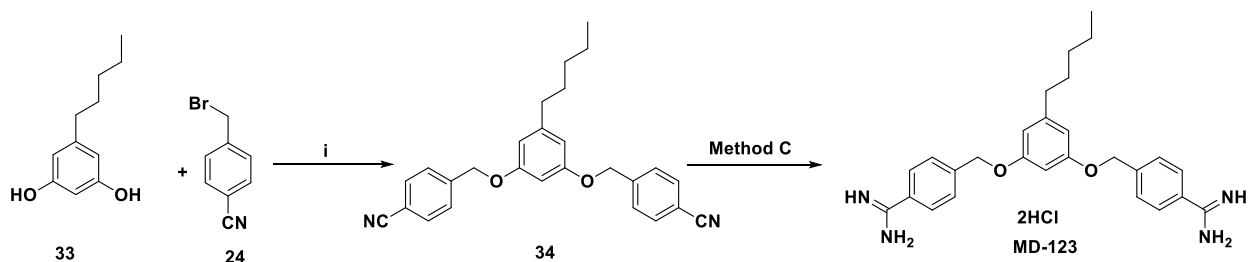


415 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(3-fluorobenzonitrile) (32)*.
 416 Reaction of 1,3-bis (bromomethyl)-5-methylbenzene (**1**, 0.99 g, 3.6 mmol) and 3-fluoro-4-
 417 hydroxybenzotrile (**26**, 1.1 g, 7.9 mmol) yielded 4,4'-(((5-methyl-1,3-
 418 phenylene)bis(methylene))bis(oxy))bis(3-fluorobenzonitrile) as white solid (**32**, 1.12 g, 80%),
 419 using method A. ¹H NMR (CDCl₃): δ 7.40 - 7.37 (m, 4H), 7.28 (s, 1H), 7.23 (s, 2H), 7.04 (t, *J* =
 420 8.4 Hz, 2H), 5.17 (s, 4H), 2.40 (s, 3H). ¹³C NMR (CDCl₃): δ 152.2 (d, *J*_{C-F} = 242 Hz), 150.9 (d, *J*_{C-}
 421 _F = 4 Hz), 139.5, 135.9, 129.7 (d, *J*_{C-F} = 4 Hz), 128.5, 123.6, 120.0 (d, *J*_{C-F} = 21 Hz), 118.0 (d, *J*_{C-}
 422 _F = 2 Hz), 115.3 (d, *J*_{C-F} = 2 Hz), 104.6 (d, *J*_{C-F} = 8 Hz), 71.1, 21.5. HRMS calcd for
 423 C₂₃H₁₆F₂N₂O₂Na [M+Na]⁺: 413.1078, found 413.1087.

424 *Synthesis of 4,4'-(((5-methyl-1,3-phenylene)bis(methylene))bis(oxy))bis(3-fluorobenzimidamide)*
 425 *dihydrochloride (MD-120)*. Dinitrile (**32**, 0.35 g, 0.9 mmol) was converted to 4,4'-(((5-methyl-

426 1,3-phenylene)bis(methylene))bis(oxy))bis(3-fluorobenzimidamide) dihydrochloride as white
 427 solid following method B (**MD-120**, 0.32 g, 72%). ¹H NMR (DMSO-d₆): δ 9.42 (s, 4H), 9.24 (s,
 428 4H), 7.90 (dd, *J* = 12.0, 2.0 Hz, 2H), 7.78-7.76 (m, 2H), 7.49 (t, *J* = 8.8 Hz, 2H), 7.38 (s, 1H), 7.29
 429 (s, 2H), 5.30 (s, 4H), 2.35 (s, 3H). ¹³C NMR (DMSO-d₆): δ 163.8, 150.9 (d, *J*_{C-F} = 244 Hz), 150.6
 430 (d, *J*_{C-F} = 10 Hz), 138.3, 136.2, 128.5, 125.8 (d, *J*_{C-F} = 3 Hz), 124.5, 119.8 (d, *J*_{C-F} = 7 Hz), 116.1
 431 (d, *J*_{C-F} = 21 Hz), 151.0, 70.3, 20.9. HRMS calcd for C₂₃H₂₃F₂N₄O₂ [M+H]⁺: 425.1789, found
 432 425.1777.

433 Synthesis of MD-123



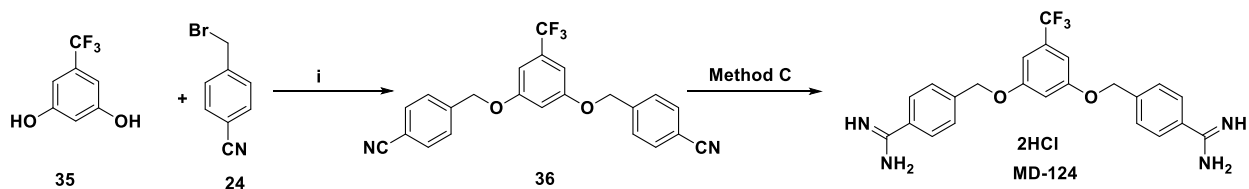
434 i) K₂CO₃, DMF, rt, overnight.

435 *Synthesis of 4,4'-(((5-butyl-1,3-phenylene)bis(oxy))bis(methylene))dibenzonitrile (34)*. A mixture
 436 of olivetol (**33**, 1.4 g, 8.2 mmol), 4-cyanobenzyl bromide (**24**, 3.53 g, 18 mmol) and anhydrous
 437 K₂CO₃ (3.4 g, 24.6 mmol) in 100 mL DMF was stirred at room temperature overnight. Then the
 438 reaction mixture was diluted with ice water (50 mL) and extracted with ethyl acetate (3 x 100 mL)
 439 followed by water and brine wash. The combined organic layer is dried over anhydrous Na₂SO₄,
 440 filtered, concentrated in vacuum to yield 4,4'-(((5-butyl-1,3-
 441 phenylene)bis(oxy))bis(methylene))dibenzonitrile (**34**) as an orange solid (**34**, 3.2 g, 95.0%). ¹H
 442 NMR (CDCl₃): δ 7.67 (d, *J* = 8.4 Hz, 4H), 7.53 (d, *J* = 8.4 Hz, 4H), 6.44 (d, *J* = 2.0 Hz, 2H), 6.40
 443 (t, *J* = 2.0 Hz, 1H), 5.09 (s, 4H), 2.56 – 2.52 (m, 2H), 1.60 - 1.57 (m, 2H), 1.33 - 1.27 (m, 4H),
 444 0.89 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (CDCl₃): δ 159.4, 146.0, 142.5, 132.5, 127.7, 118.8, 111.8,

445 108.0, 99.5, 69.0, 36.3, 31.5, 31.0, 22.6, 14.1. HRMS calcd for C₂₇H₂₆N₂O₂Na [M+Na]⁺: 433.1892,
446 found 433.1873.

447 *Synthesis of 4,4'-((5-pentyl-1,3-phenylene)bis(ethane-2,1-diyl))dibenzimidamide dihydrochloride*
448 **(MD-123)**. Dinitrile (**34**, 0.32 g, 0.78 mmol) was converted to 4,4'-((5-pentyl-1,3-
449 phenylene)bis(ethane-2,1-diyl))dibenzimidamide dihydrochloride **(MD-123)** as white solid
450 following method C (**MD-123**, 0.32 g, 80%). ¹H NMR (DMSO-d₆): δ 9.47 (s, 4H), 9.28 (s, 4H),
451 7.87 (d, *J* = 8.4 Hz, 4H), 7.65 (d, *J* = 8.4 Hz, 4H), 6.51 (t, *J* = 2.0 Hz, 1H), 6.48 (d, *J* = 2.0 Hz,
452 2H), 5.20 (s, 4H), 2.50 - 2.46 (m, 2H), 1.55 - 1.52 (m, 2H), 1.29 - 1.20 (m, 4H), 0.84 (t, *J* = 6.8
453 Hz, 3H). ¹³C NMR (DMSO-d₆): δ 165.4, 159.1, 145.0, 143.4, 128.3, 127.7, 127.3, 107.6, 99.6,
454 68.3, 35.4, 30.9, 30.4, 22.0, 14.0. HRMS calcd for C₂₇H₃₃N₄O₂[M+H]⁺: 445.2604, found 445.2624.

455 **Synthesis of MD-124**

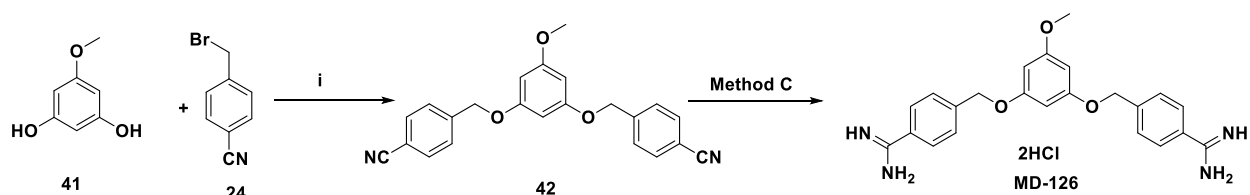


456 i) K₂CO₃, DMF, rt, overnight.

457 *Synthesis of 4,4'-(((5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(methylene))dibenzimidamide*
458 *dihydrochloride (MD-124)*. A mixture of 5-(Trifluoromethyl)-1,3-diol (**35**, 0.7 g, 4.2 mmol), 4-
459 cyanobenzyl bromide (**24**, 1.80 g, 9.21 mmol) and anhydrous K₂CO₃ (1.73 g, 12.6 mmol) in 20
460 mL DMF was stirred at room temperature overnight. Then the reaction mixture was diluted with
461 ice water (50 mL) and stirred for 30 min. The grey precipitate was filtered, washed with water,
462 and dried in air. Then the yellow solid was dissolved in a dichloromethane (100 mL), dried over
463 anhydrous Na₂SO₄, filtered, concentrated *in vacuum* to afford crude product. The crude product
464 was triturated with hexane, filtered and dried *in vacuum* to yield dinitrile intermediate compound

465 **36** as a grey solid (1.48 g, 87.0%). Dinitrile (**36**, 0.35 g, 0.85 mmol) was converted to 4,4'-(((5-
 466 (trifluoromethyl)-1,3-phenylene)bis(oxy))bis(methylene))dibenzimidamide dihydrochloride as
 467 pale-yellow solid following method C (**MD-124**, 0.3 g, 70%). ¹H NMR (DMSO-d₆): δ 9.43 (s, 4H),
 468 9.20 (s, 4H), 7.87 (d, *J* = 8.4 Hz, 4H), 7.68 (d, *J* = 8.4 Hz, 4H), 7.03 (s, 1H), 6.99 (s, 2H), 5.32
 469 (s, 4H). ¹³C NMR (DMSO-d₆): δ 165.4, 159.7, 142.5, 131.1 (q, *J*_{C-F} = 32 Hz), 128.4, 127.8, 127.6
 470 (q, *J*_{C-F} = 240 Hz), 122.4, 105.9, 104.2, 68.9. HRMS calcd for C₂₃H₂₂F₃N₄O₂ [M+H]⁺: 443.1695,
 471 found 443.1687.

472 Synthesis of MD-126



473 i) K₂CO₃, DMF, rt, overnight.

474 *Synthesis of 4,4'-(((5-methoxy-1,3-phenylene)bis(oxy))bis(methylene))dibenzonitrile (42).* A
 475 mixture of 5-methoxyresorcinol (**41**, 1.22 g, 8.7 mmol), 4-cyanobenzyl bromide (**24**, 3.74 g, 18
 476 mmol) and anhydrous K₂CO₃ (3.6 g, 26.02 mmol) in 100 mL DMF was stirred at room temperature
 477 overnight. Then the reaction mixture was diluted with ice water (50 mL) and extracted with ethyl
 478 acetate (3 x 100 mL) followed by water and brine wash. The combined organic layer is dried over
 479 anhydrous Na₂SO₄, filtered, concentrated with rotavapor and purified with column
 480 chromatography using 5:1 hexane: EA as elution buffer to yield of 4,4'-(((5-methoxy-1,3-
 481 phenylene)bis(oxy))bis(methylene))dibenzonitrile (**42**) as a white solid (**42**, 2.94 g, 71.0%). ¹H
 482 NMR (CDCl₃): δ 7.64 (d, *J* = 8.4 Hz, 4H), 7.51 (d, *J* = 8.4 Hz, 4H), 6.18 (t, *J* = 2.0 Hz, 1H), 6.16
 483 (d, *J* = 2.0 Hz, 2H), 5.06 (s, 4H), 3.75 (s, 3H). ¹³C NMR (CDCl₃): δ 161.8, 160.3, 142.3, 132.6,

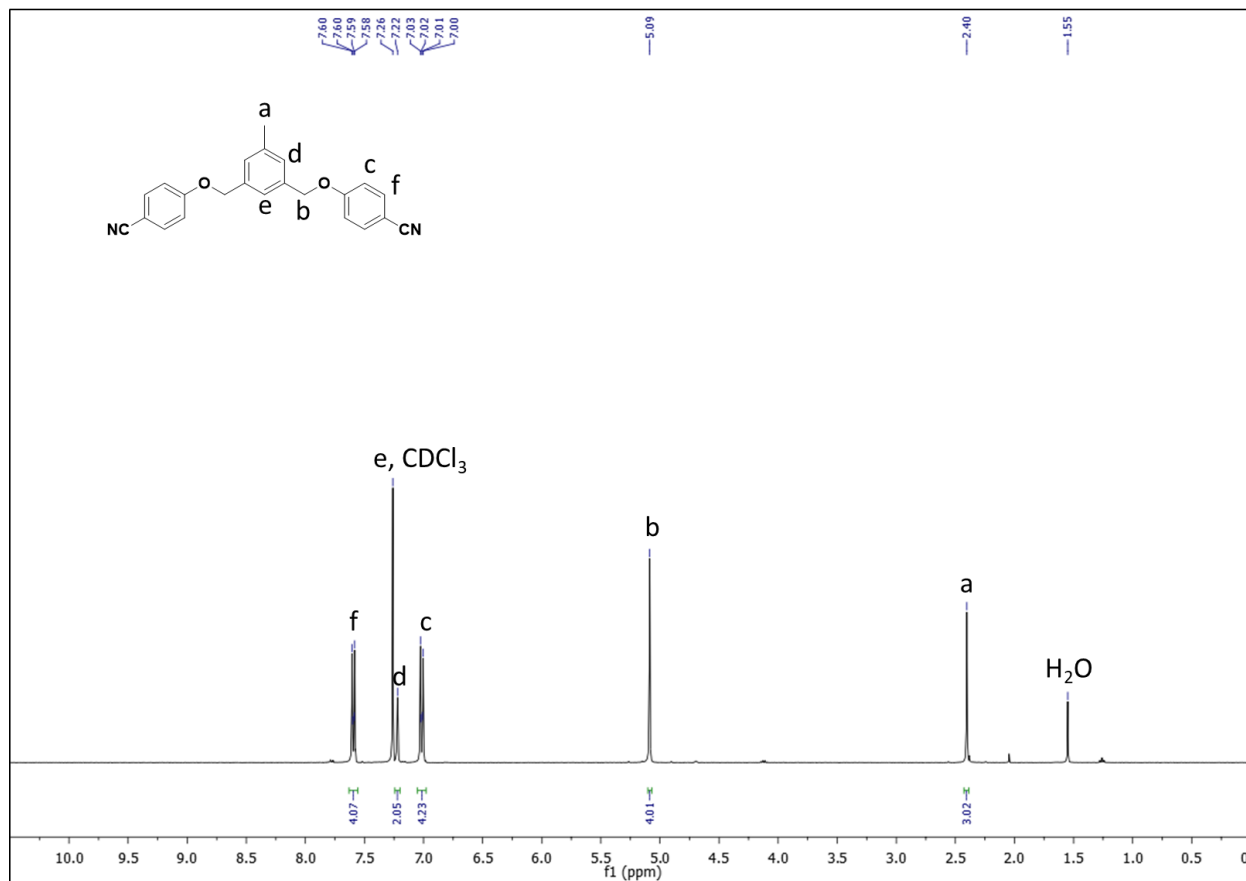
484 127.7, 118.8, 111.9, 94.7, 94.5, 69.11, 55.6. HRMS calcd for C₂₃H₁₈N₂O₃Na [M+Na]⁺: 393.1215,
485 found 393.1201.

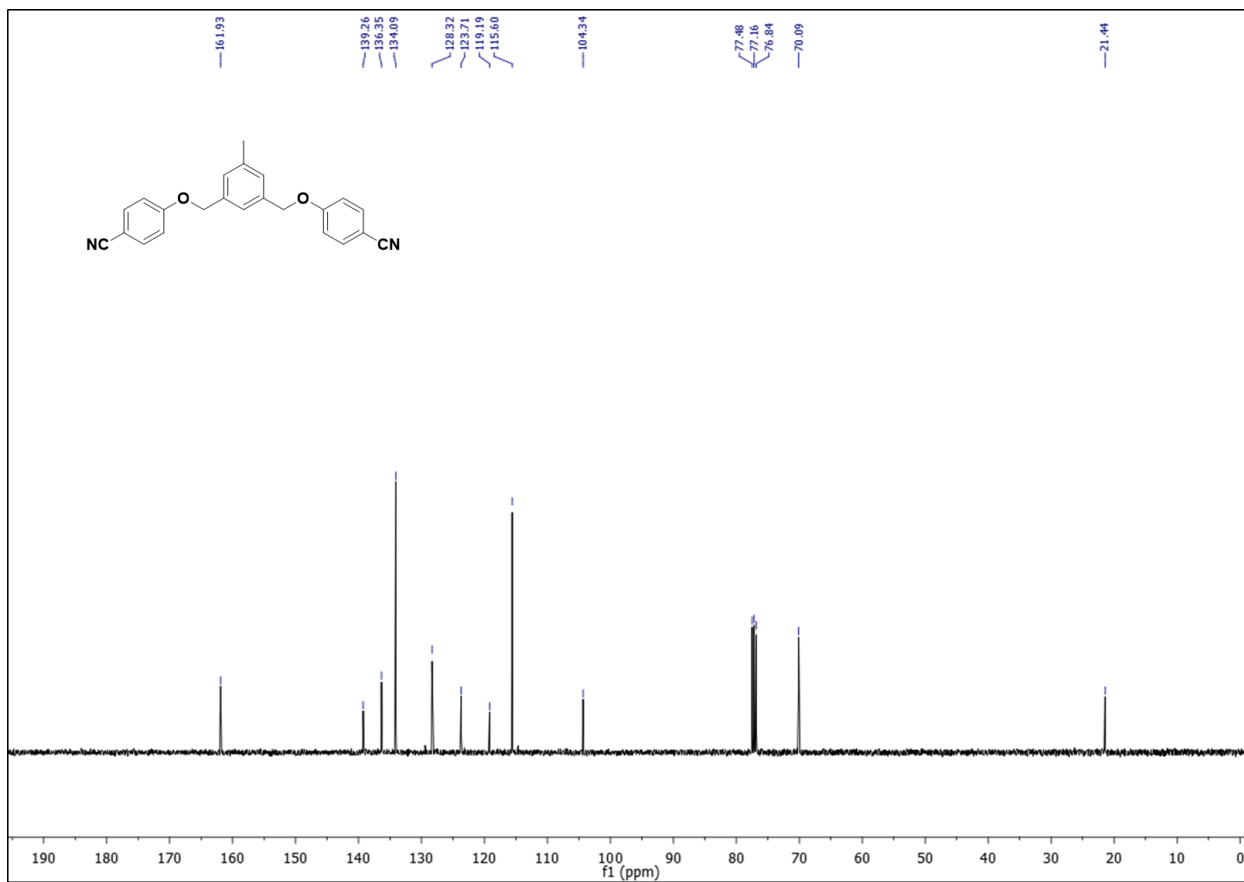
486 *Synthesis of 4,4'-(((5-methoxy-1,3-phenylene)bis(oxy))bis(methylene))dibenzimidamide*
487 *dihydrochloride (MD-126)*. Dinitrile (**42**, 0.37 g, 0.99 mmol) was converted to 4,4'-(((5-methoxy-
488 1,3-phenylene)bis(oxy))bis(methylene))dibenzimidamide dihydrochloride as yellow solid
489 following method C (**MD-126**, 0.35 g, 75%) using ammonia gas. ¹H NMR (DMSO-d₆): δ 9.44 (s,
490 4H), 9.23 (s, 4H), 7.86 (d, *J* = 8.0 Hz, 4 H), 7.65 (d, *J* = 8.0 Hz, 4 H), 6.31 (s, 1H), 6.22 (s, 2H),
491 5.21 (s, 4 H), 3.70 (s, 3 H). ¹³C NMR (DMSO-d₆): δ 165.4, 161.2, 159.8, 143.2, 128.3, 127.6, 94.7,
492 94.1, 68.4, 55.3. HRMS calcd for C₂₃H₂₅N₄O₃ [M+H]⁺: 405.1927, found 405.1923.

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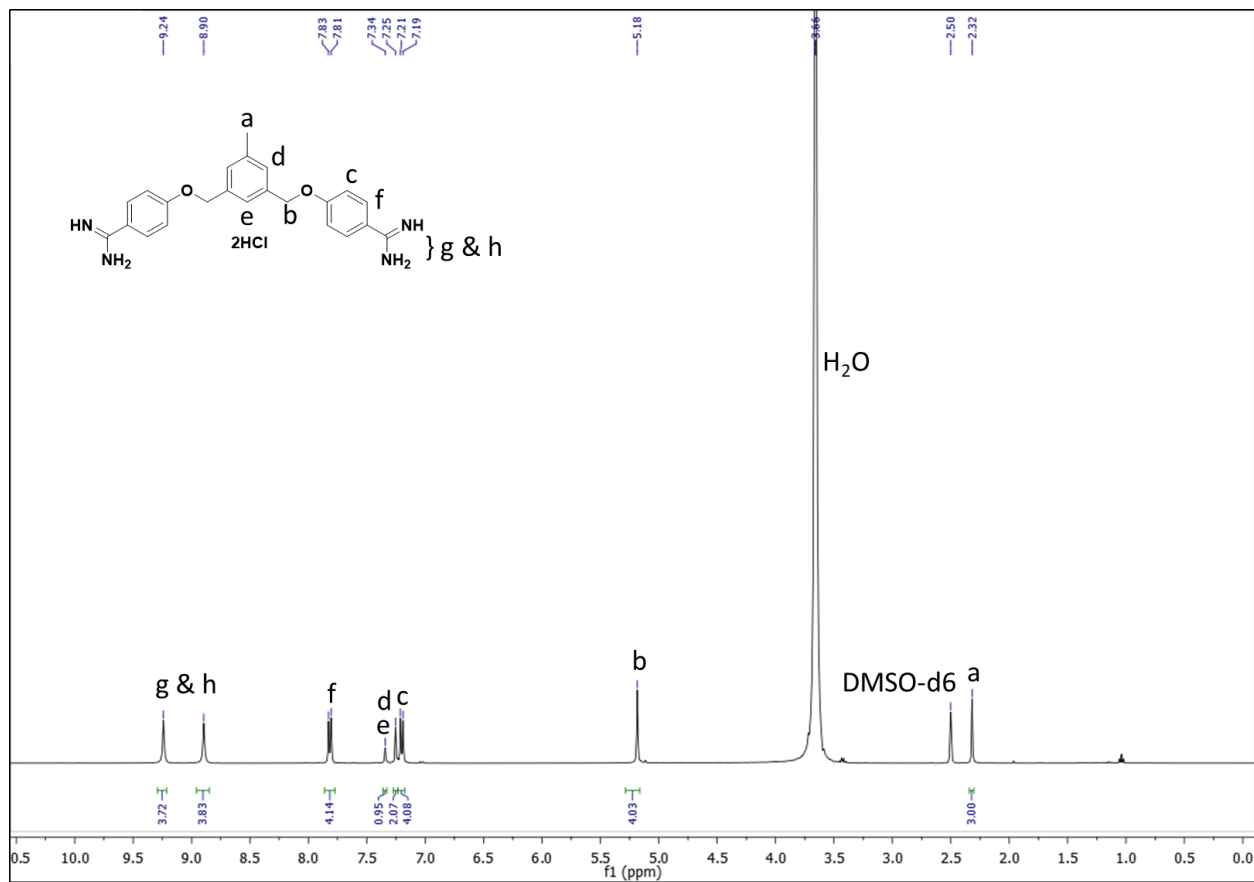
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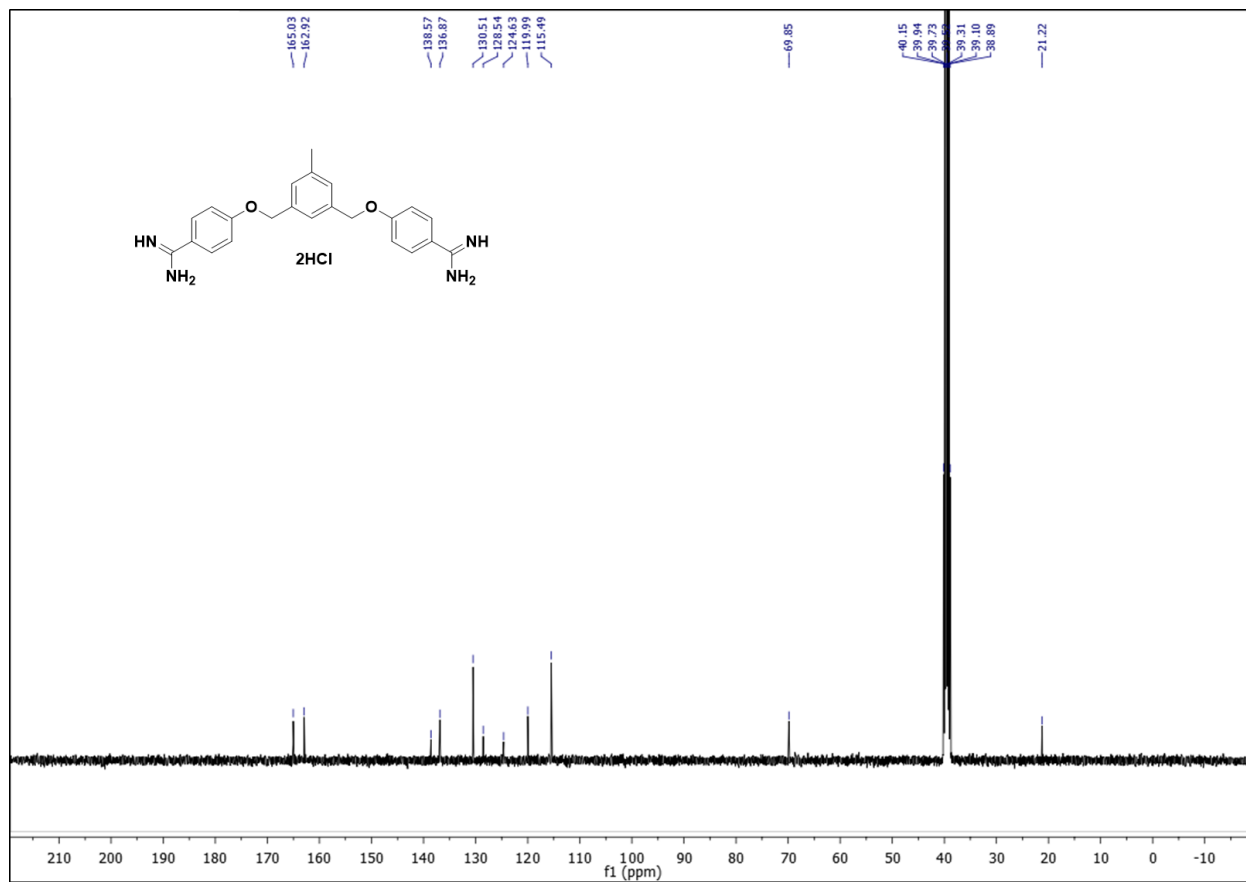
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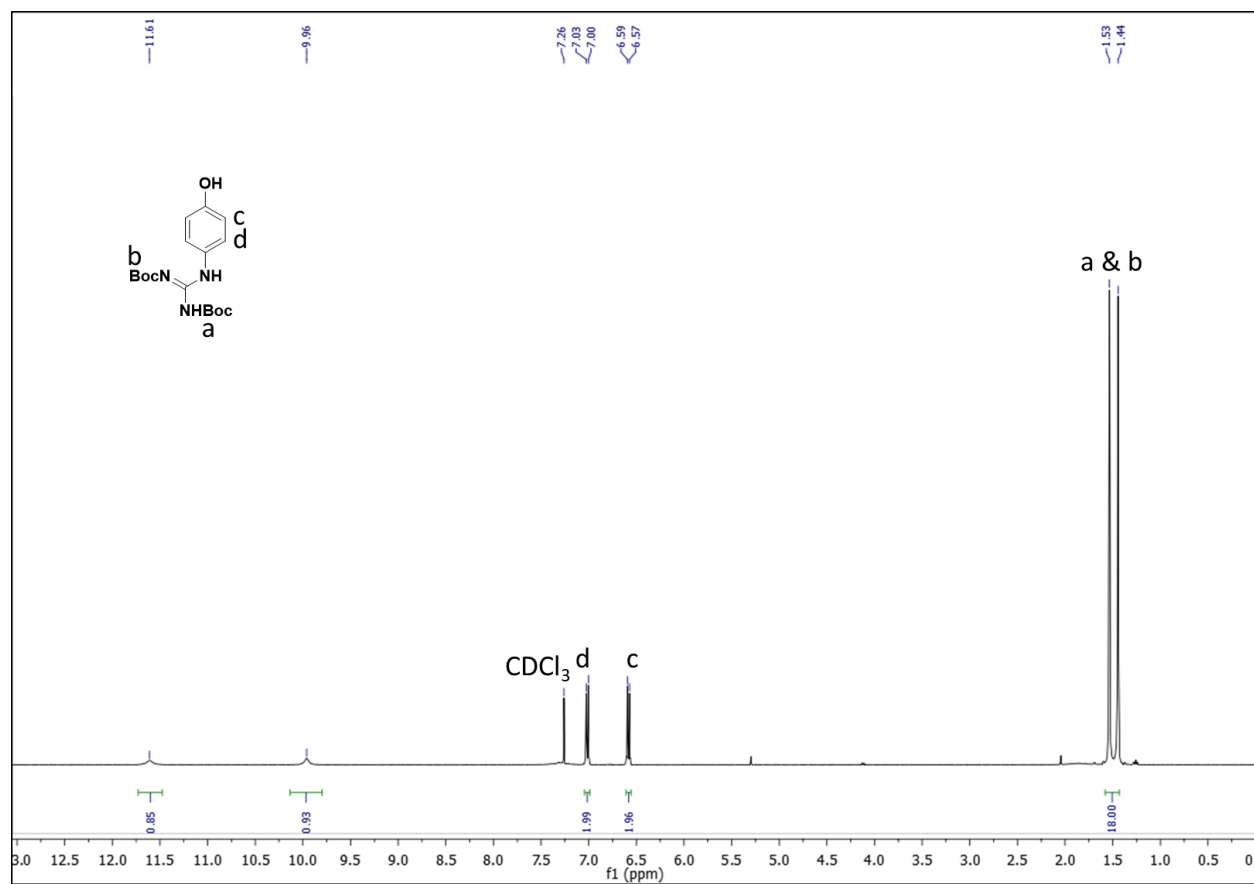
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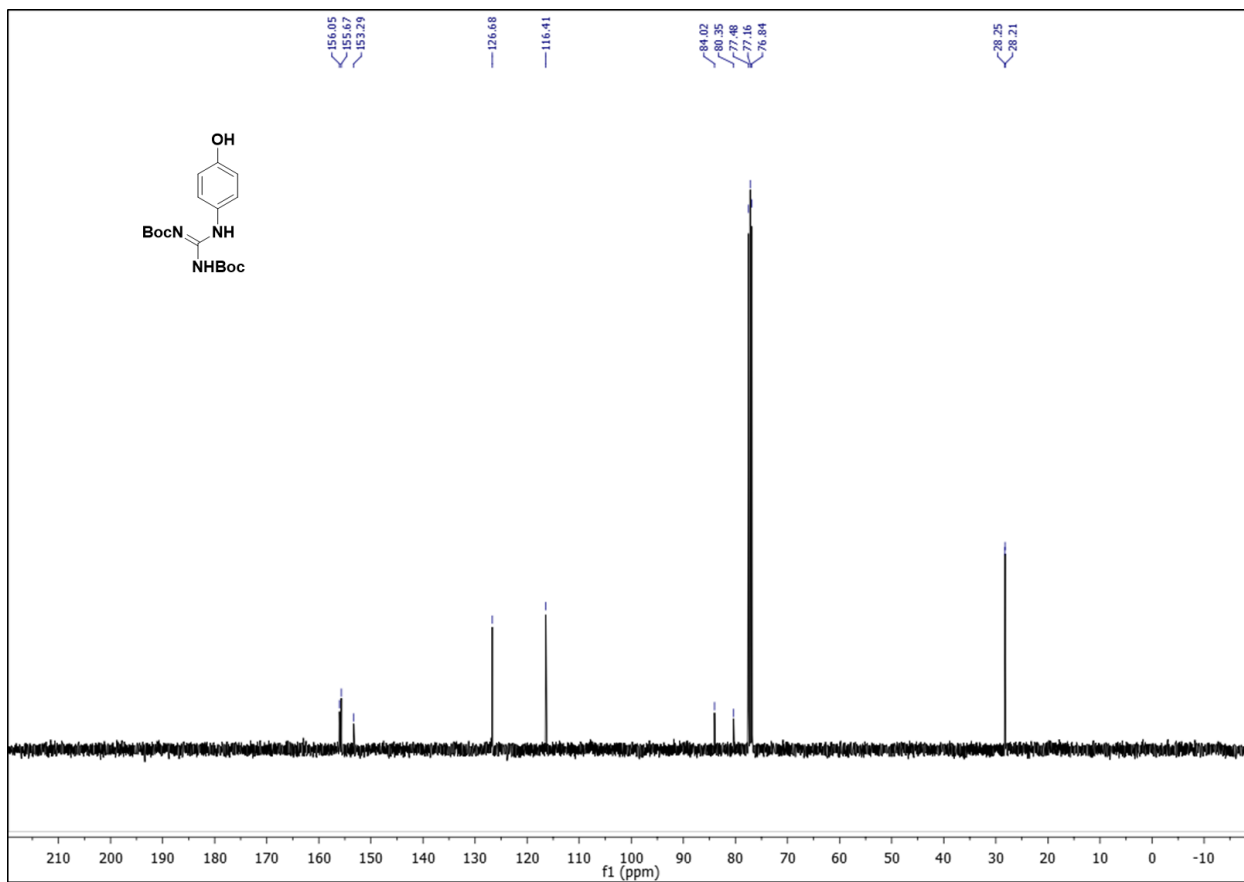
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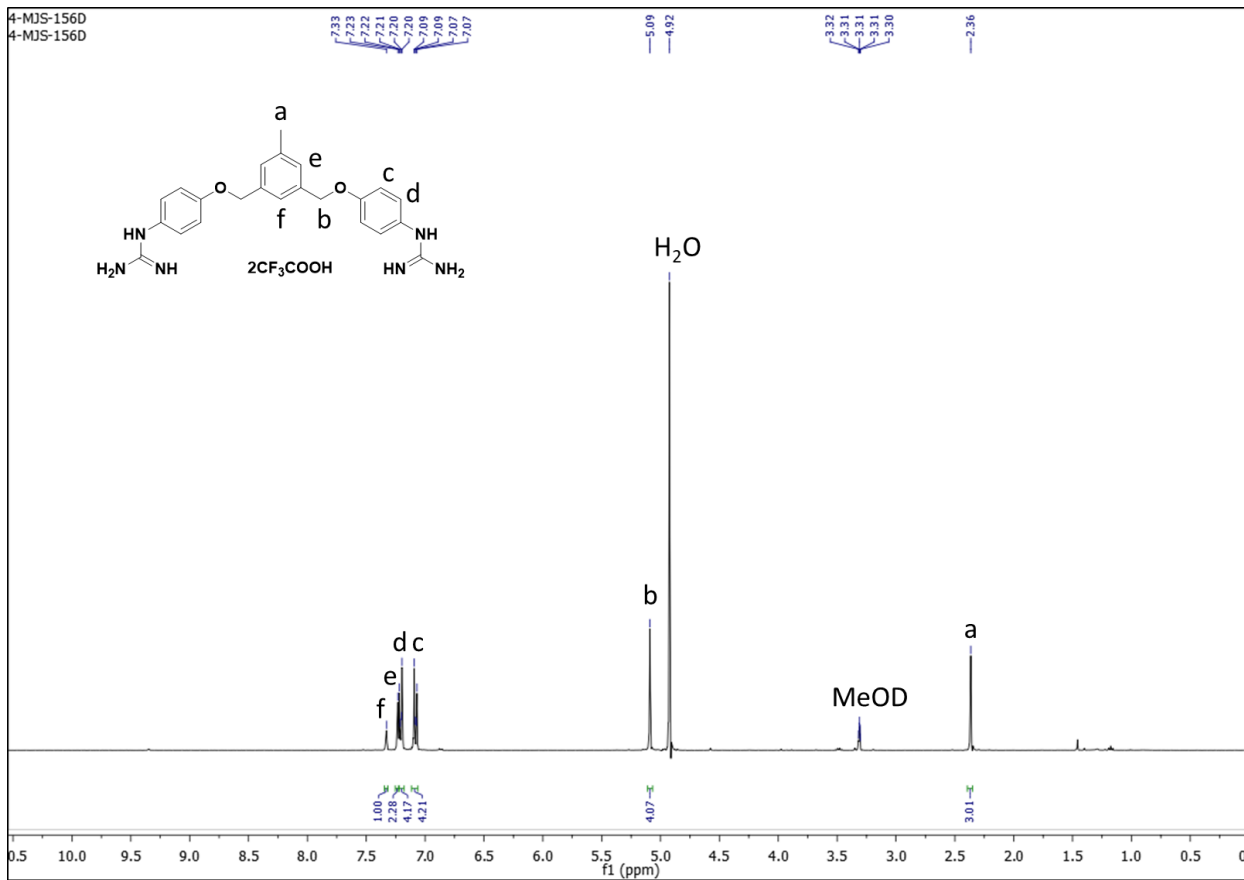
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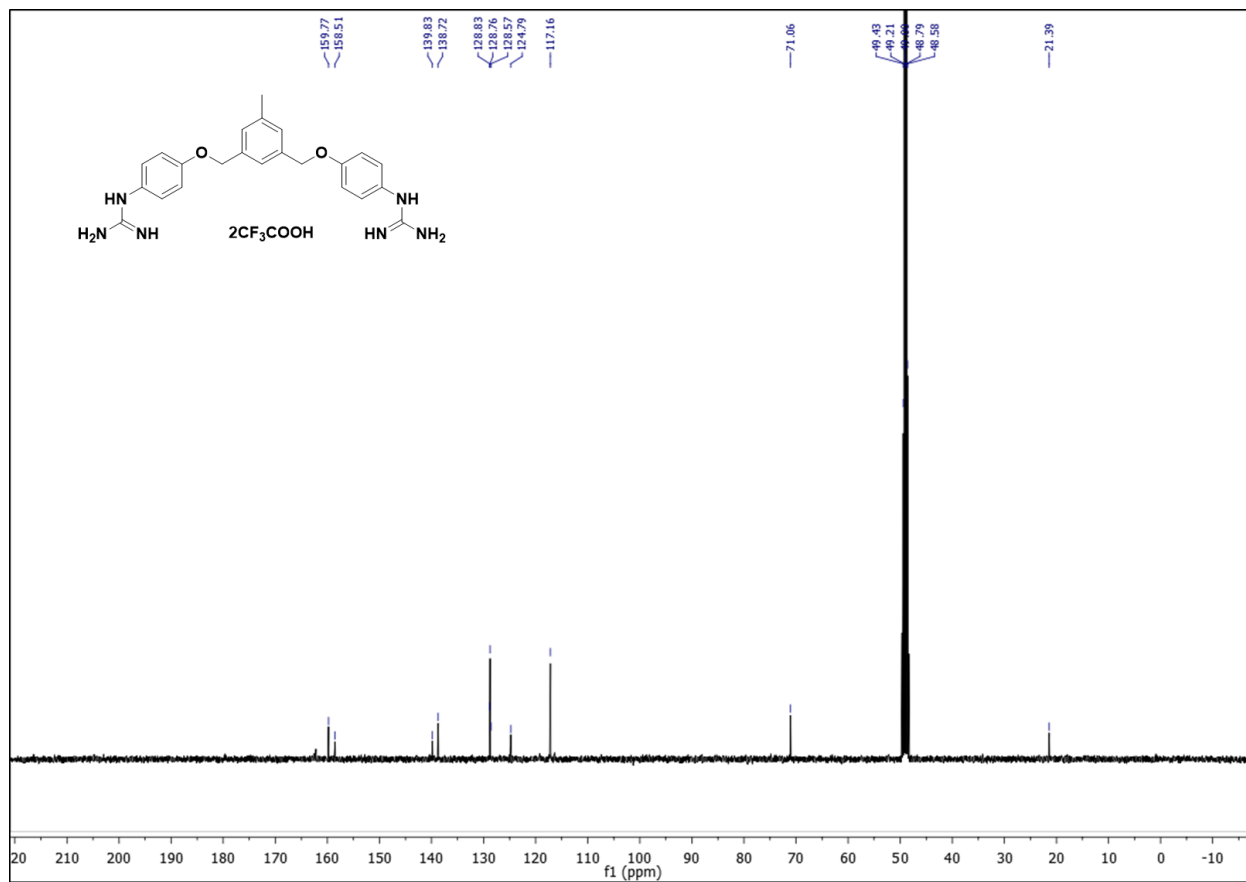


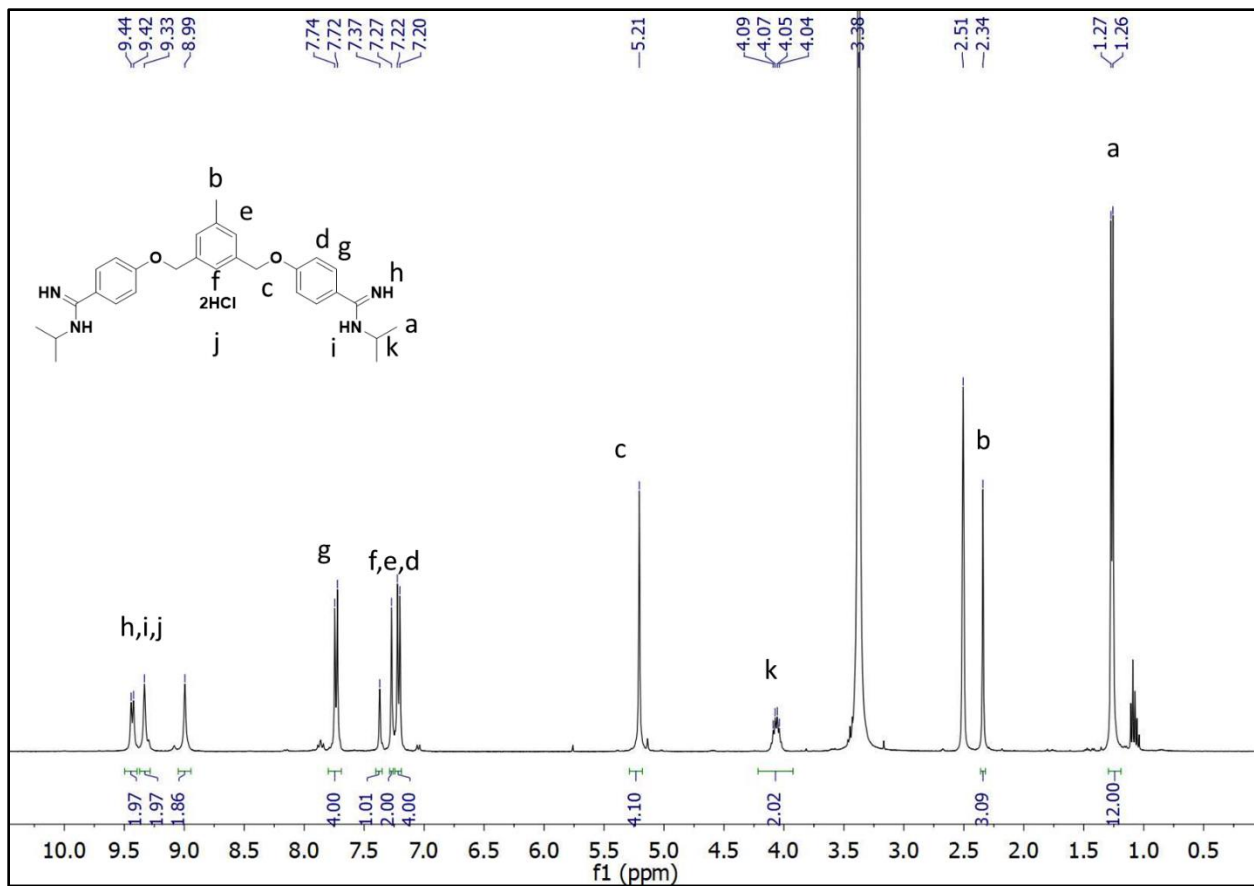
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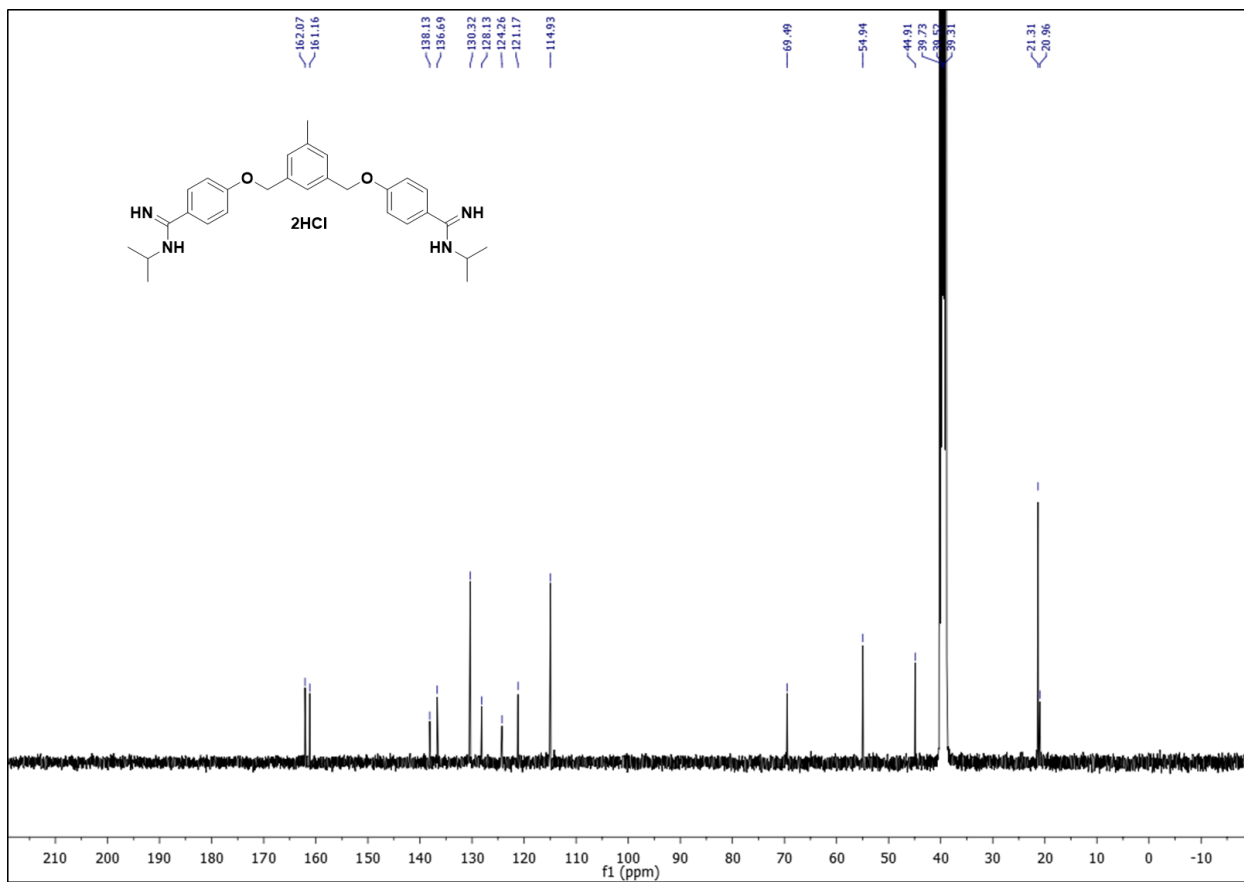
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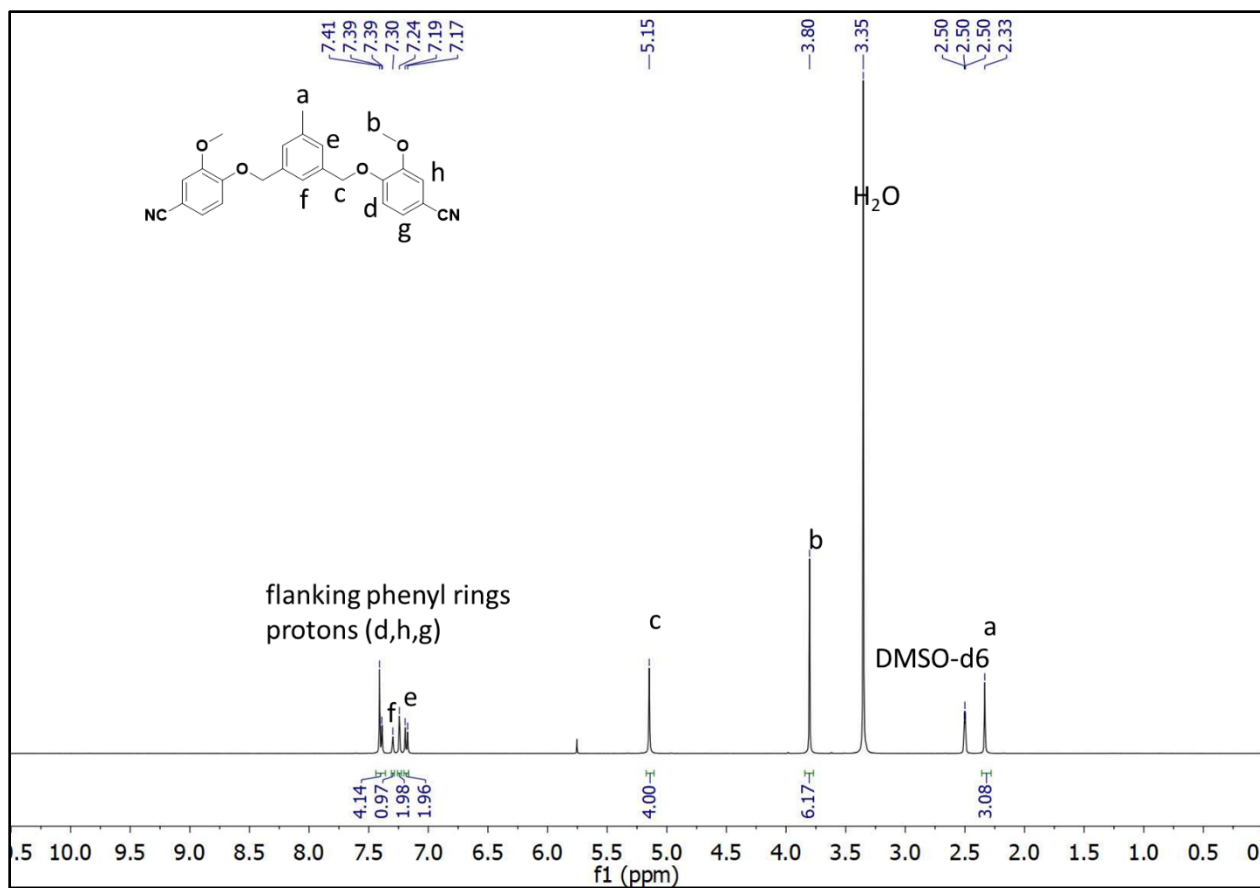
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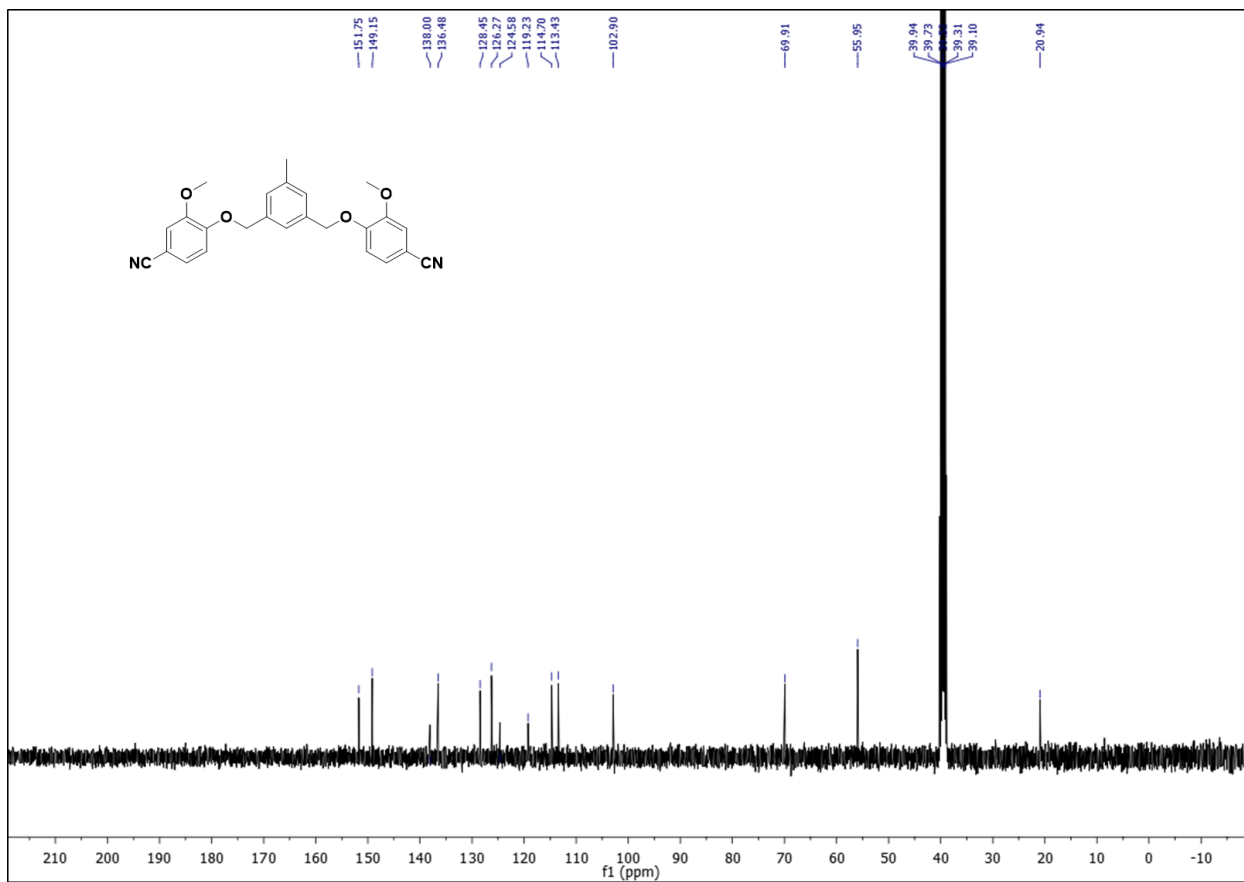
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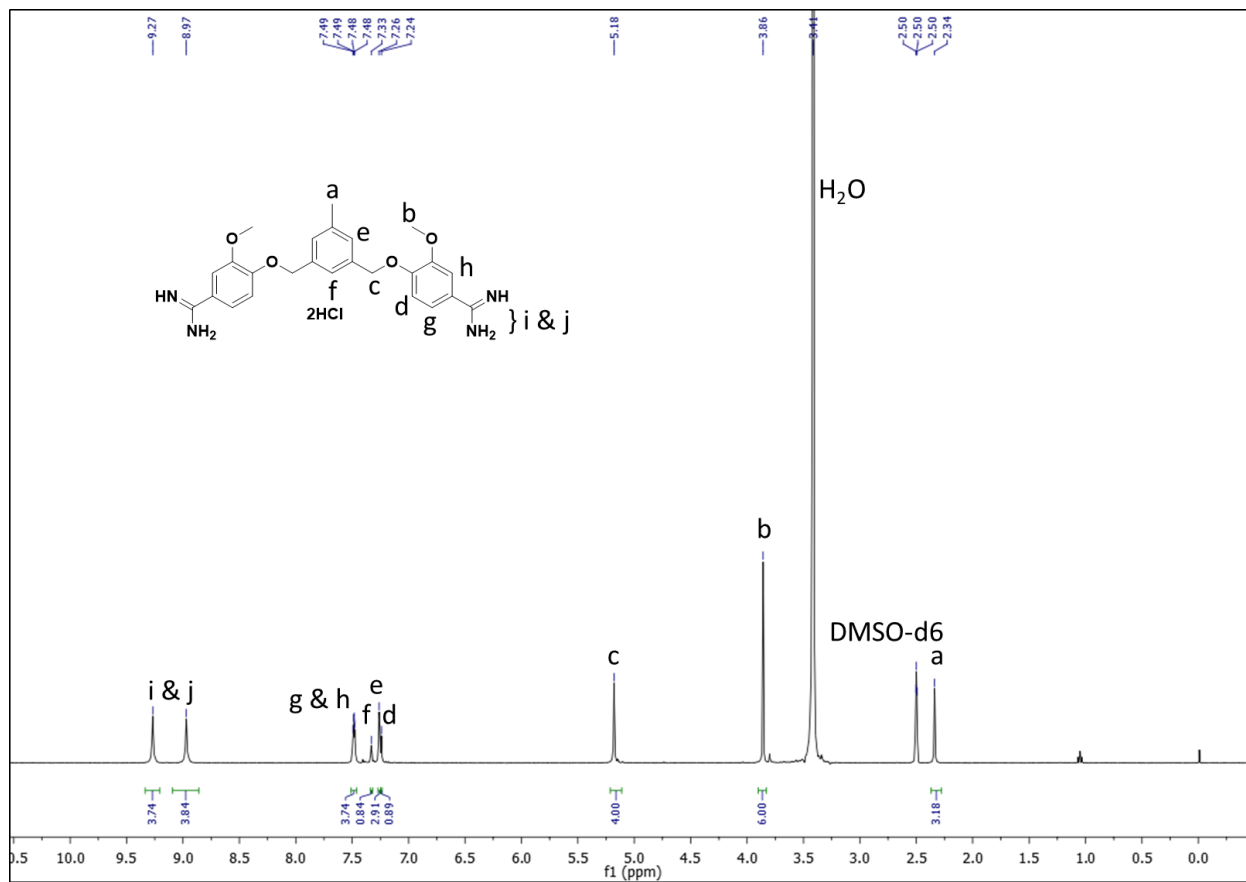
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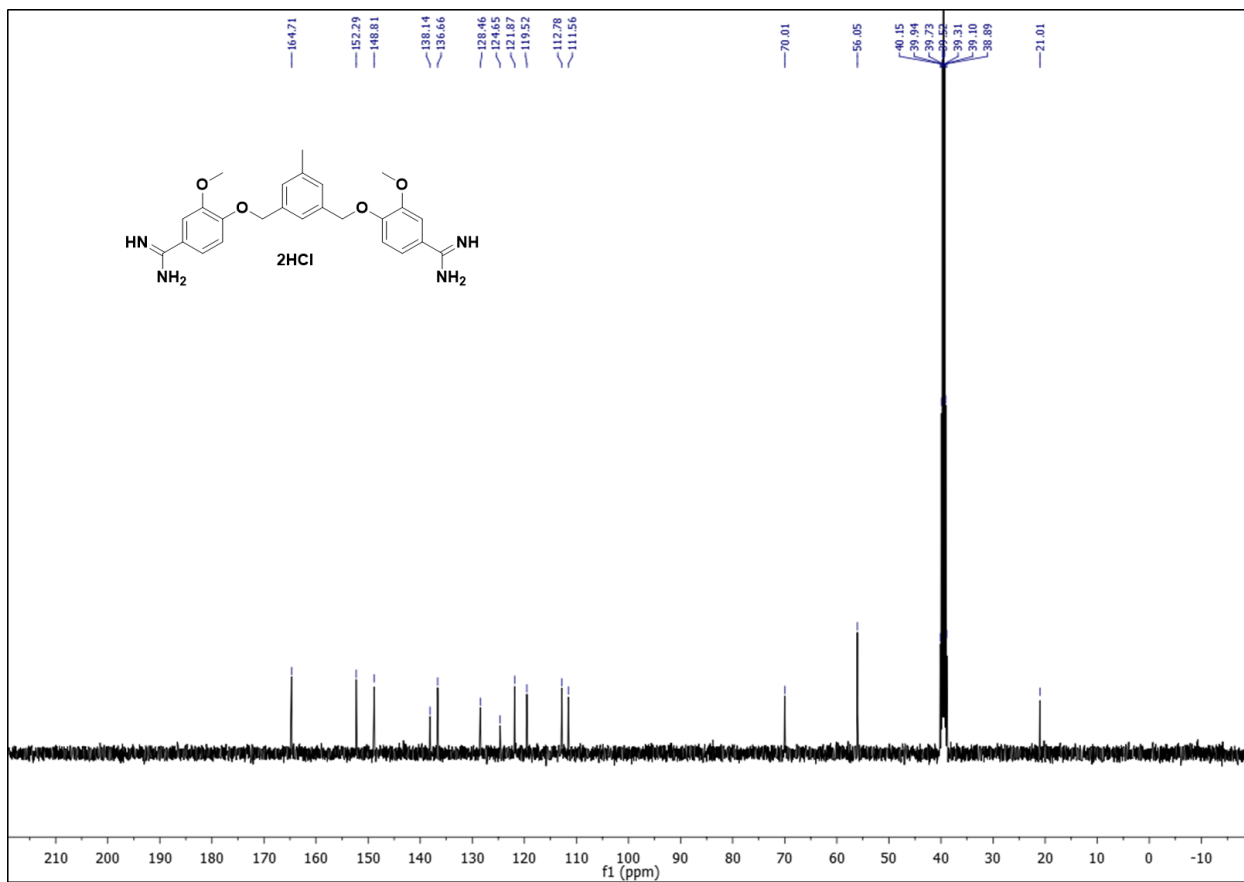
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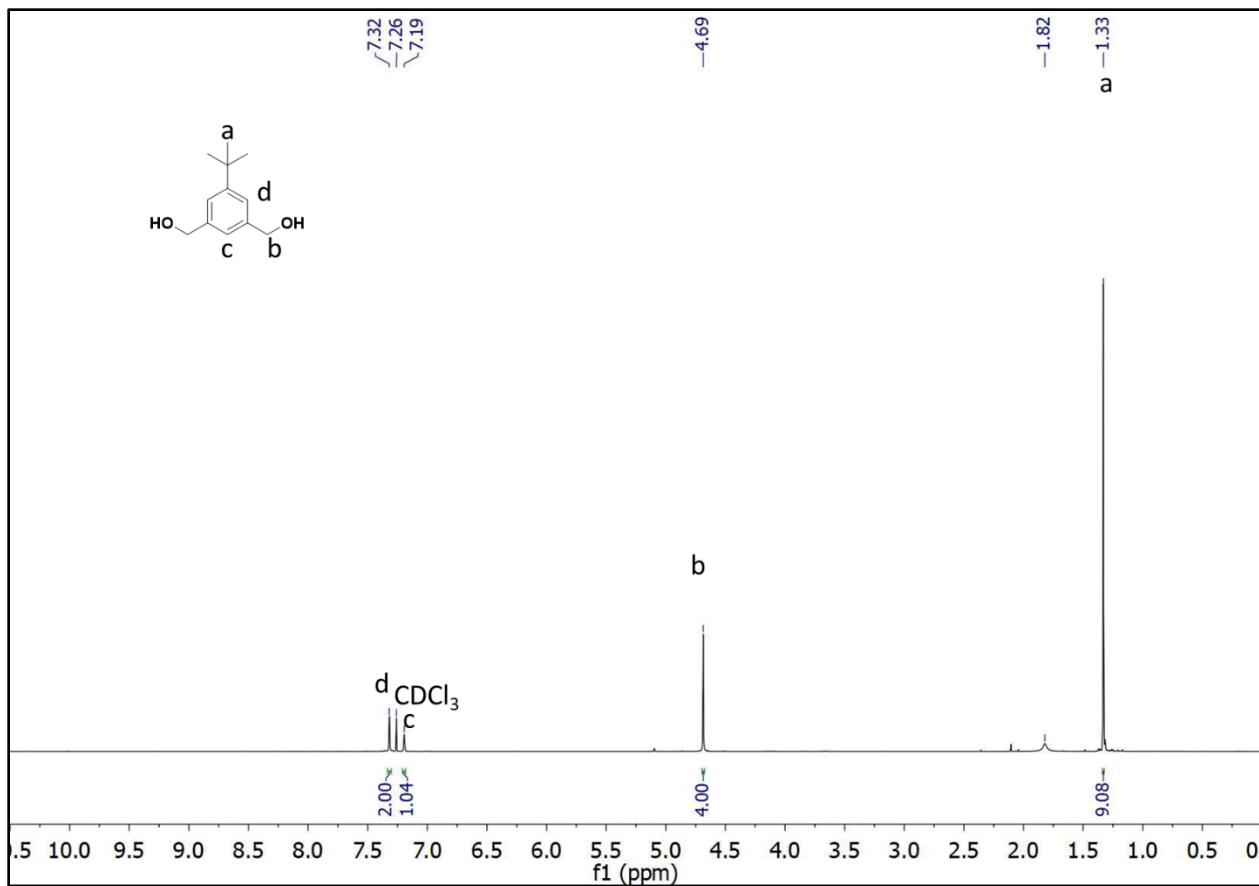
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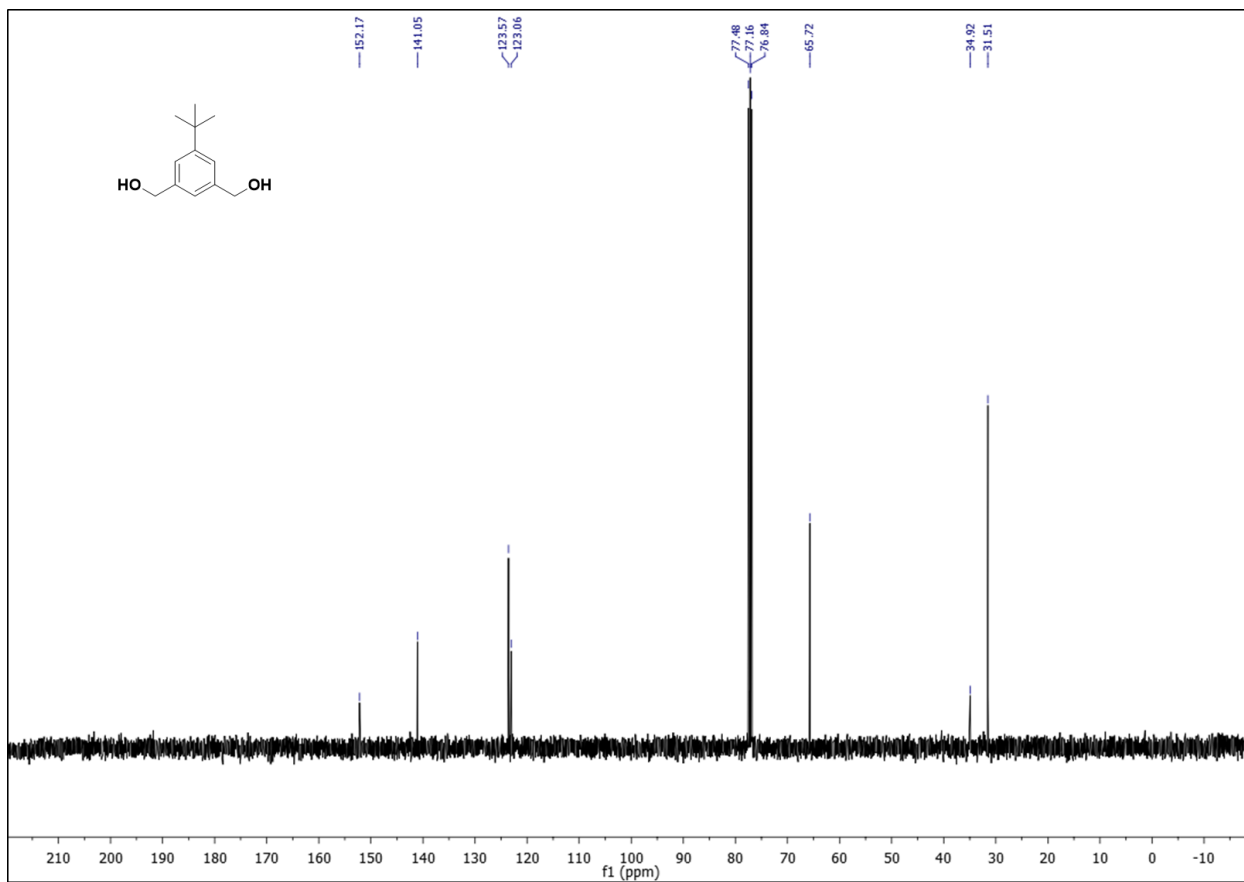
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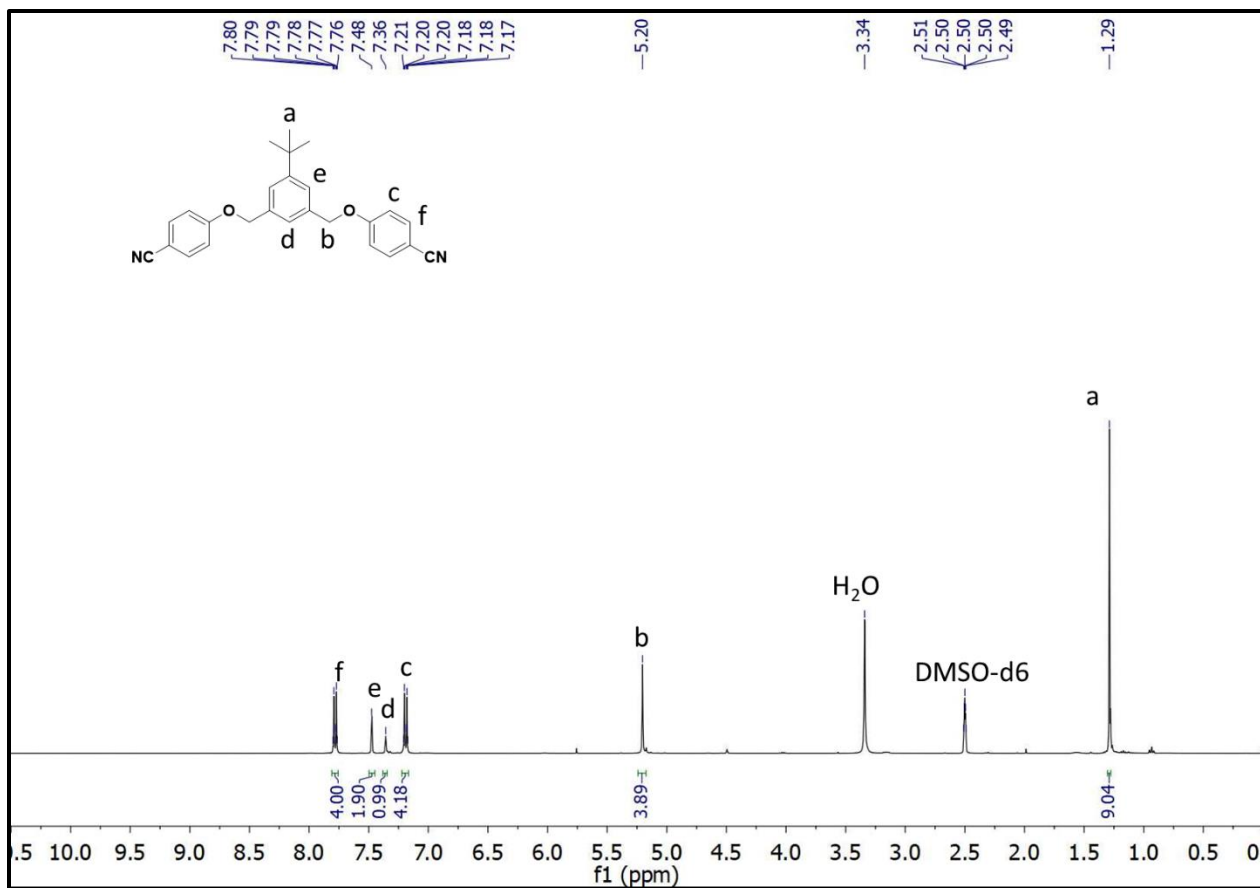
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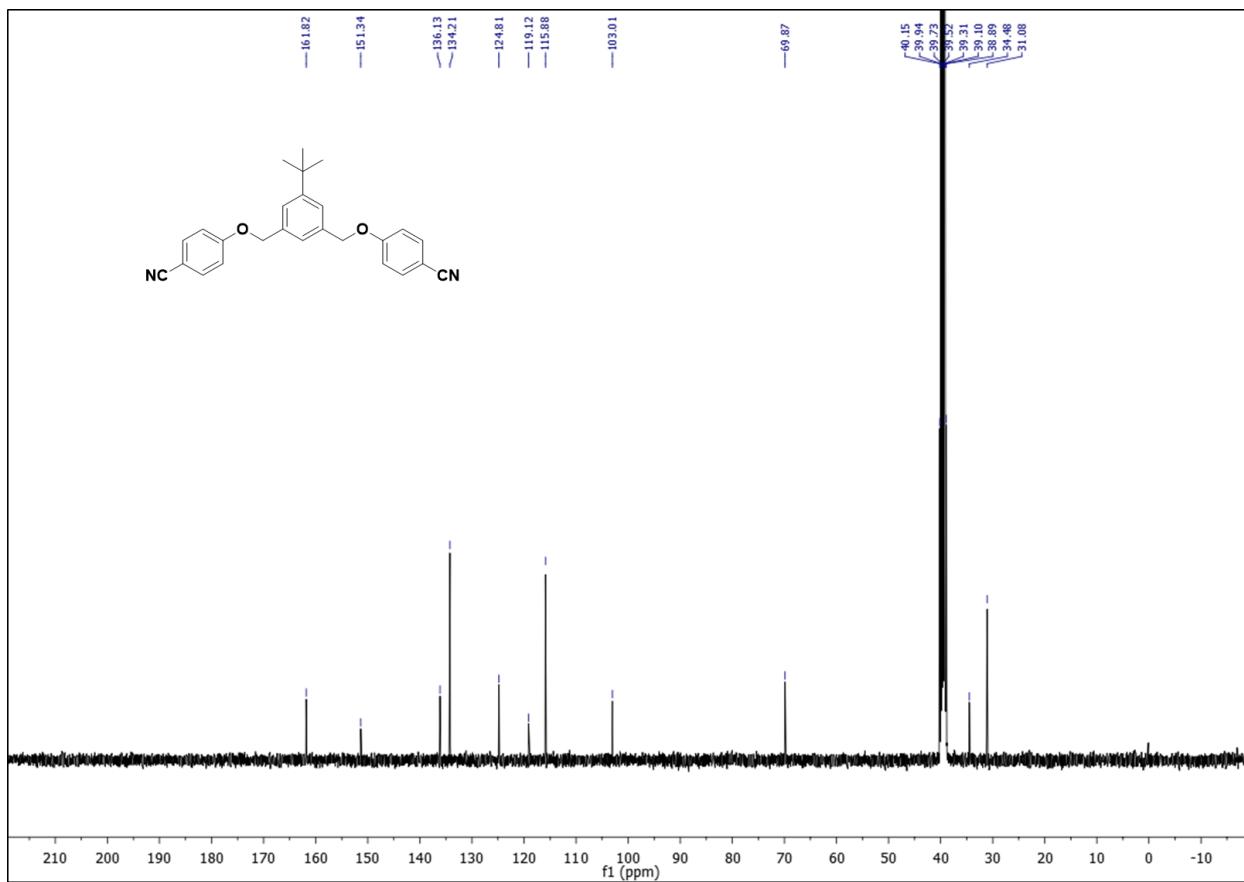
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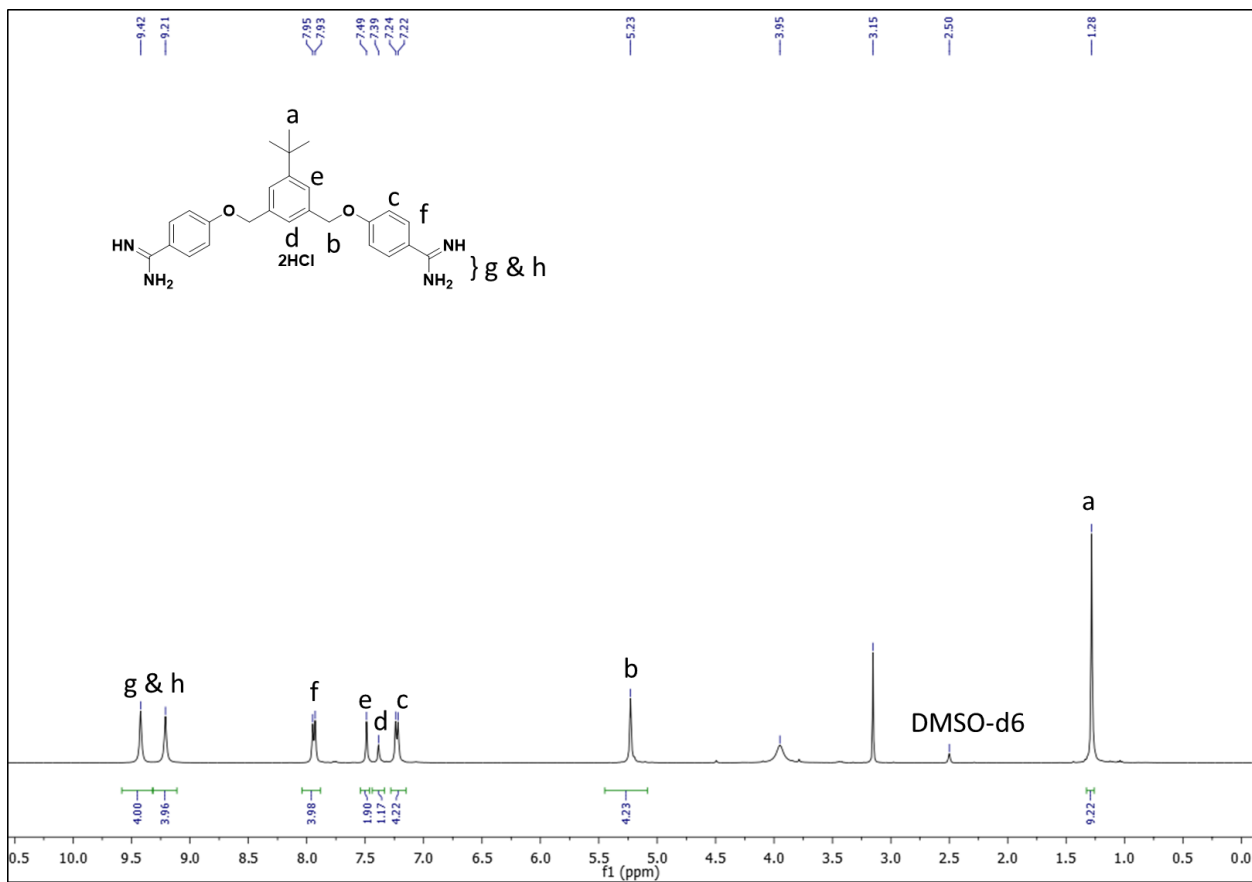
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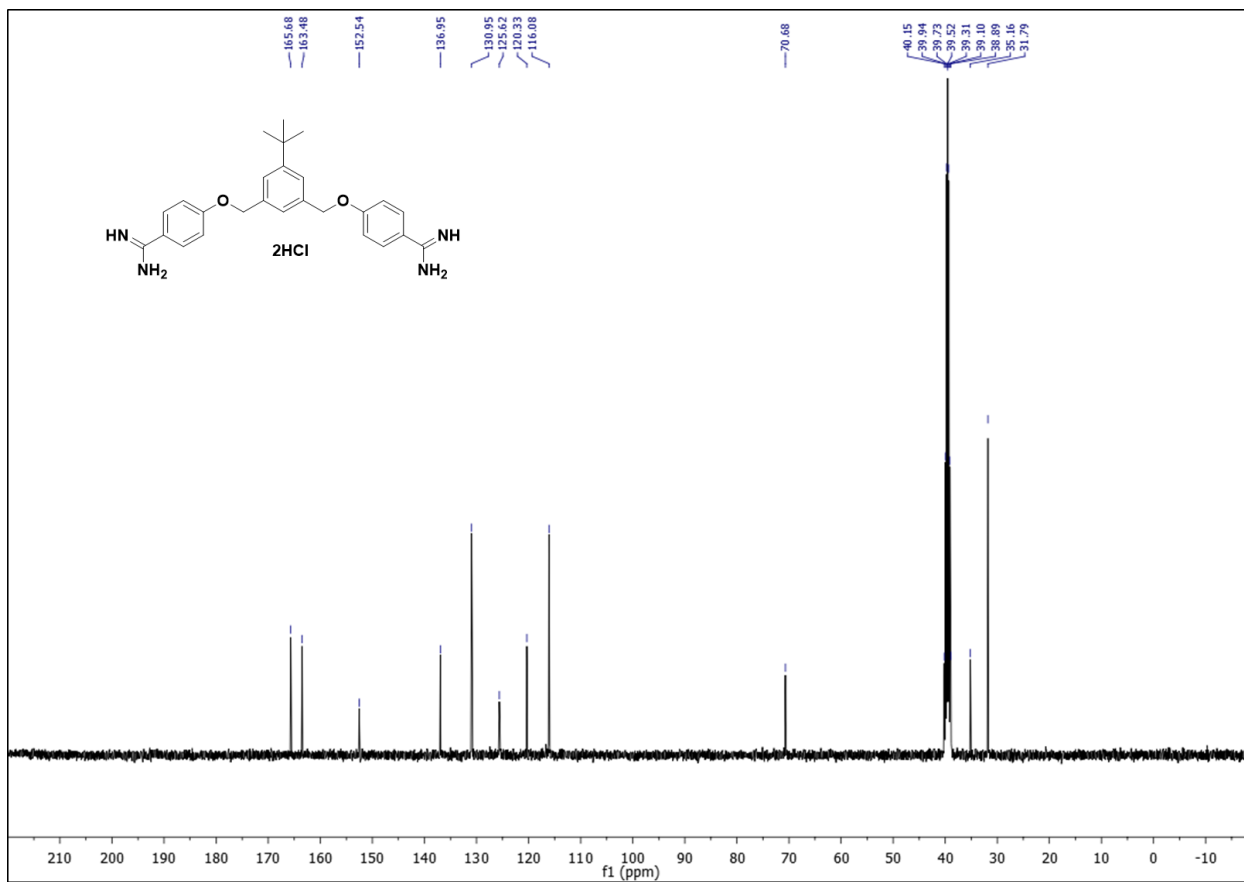
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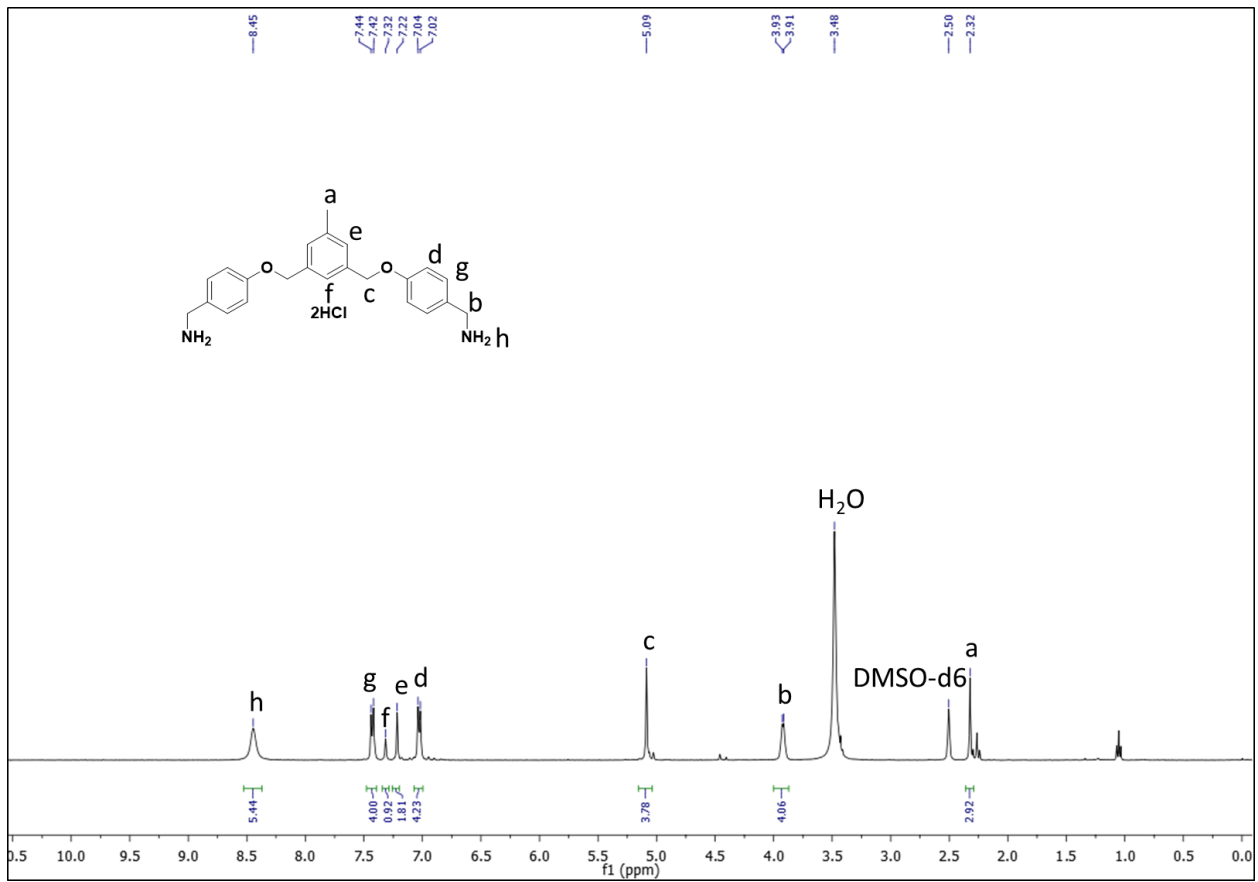
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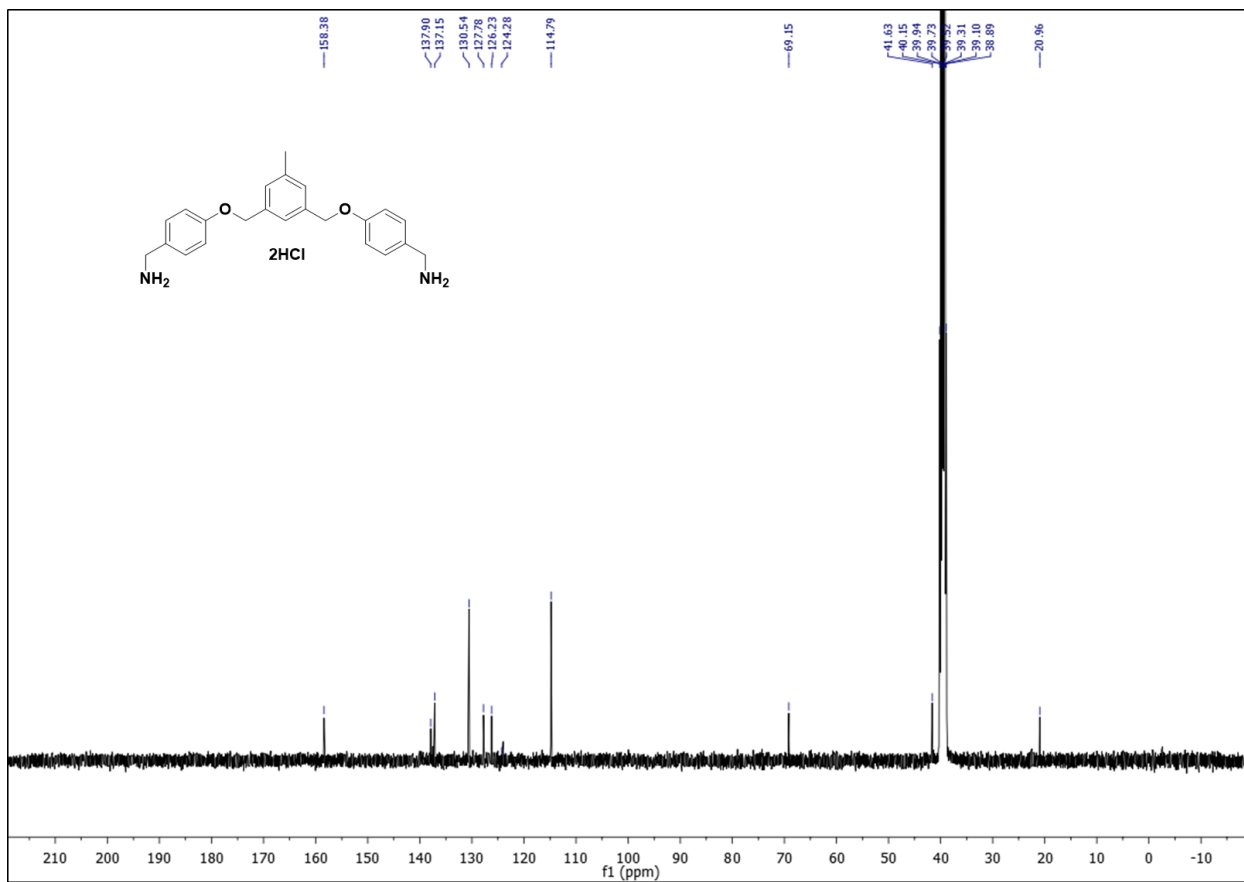
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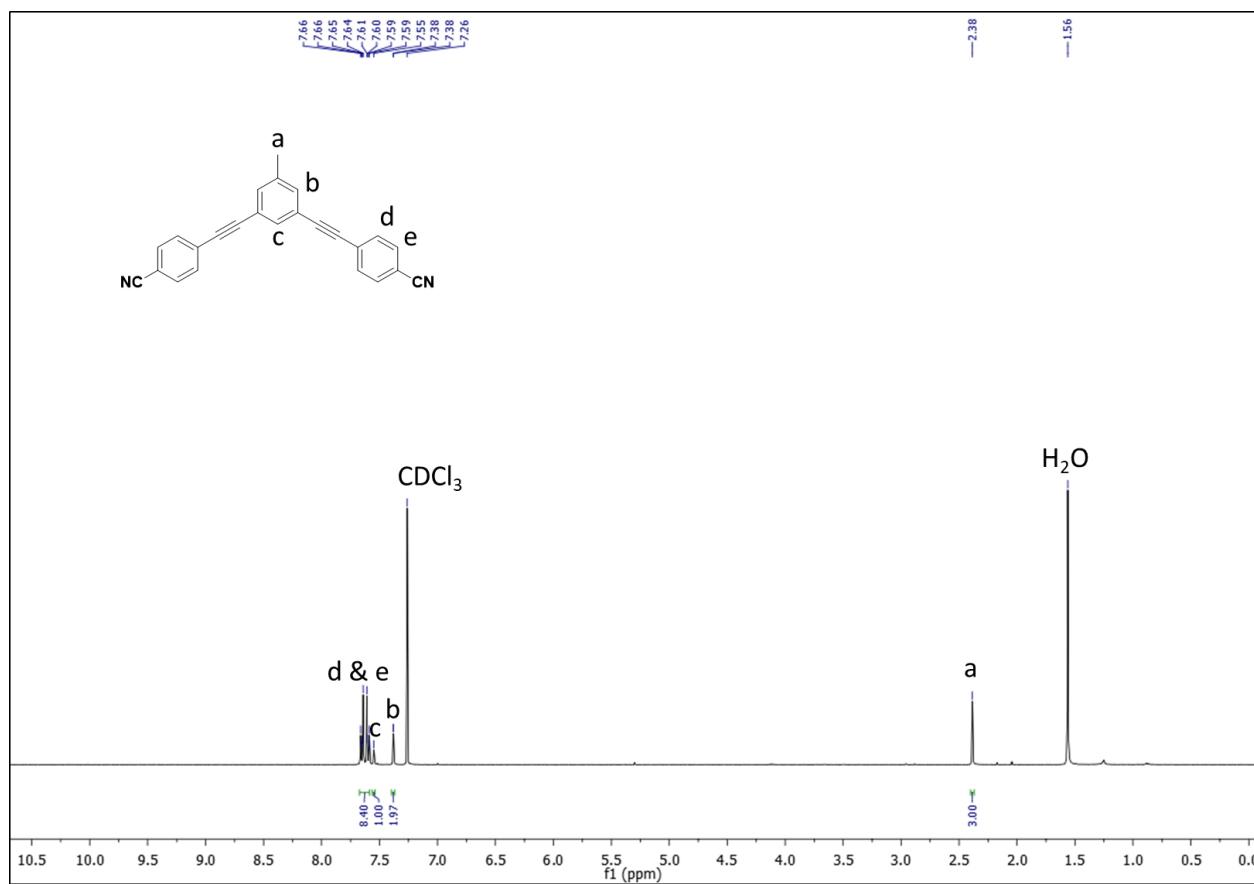
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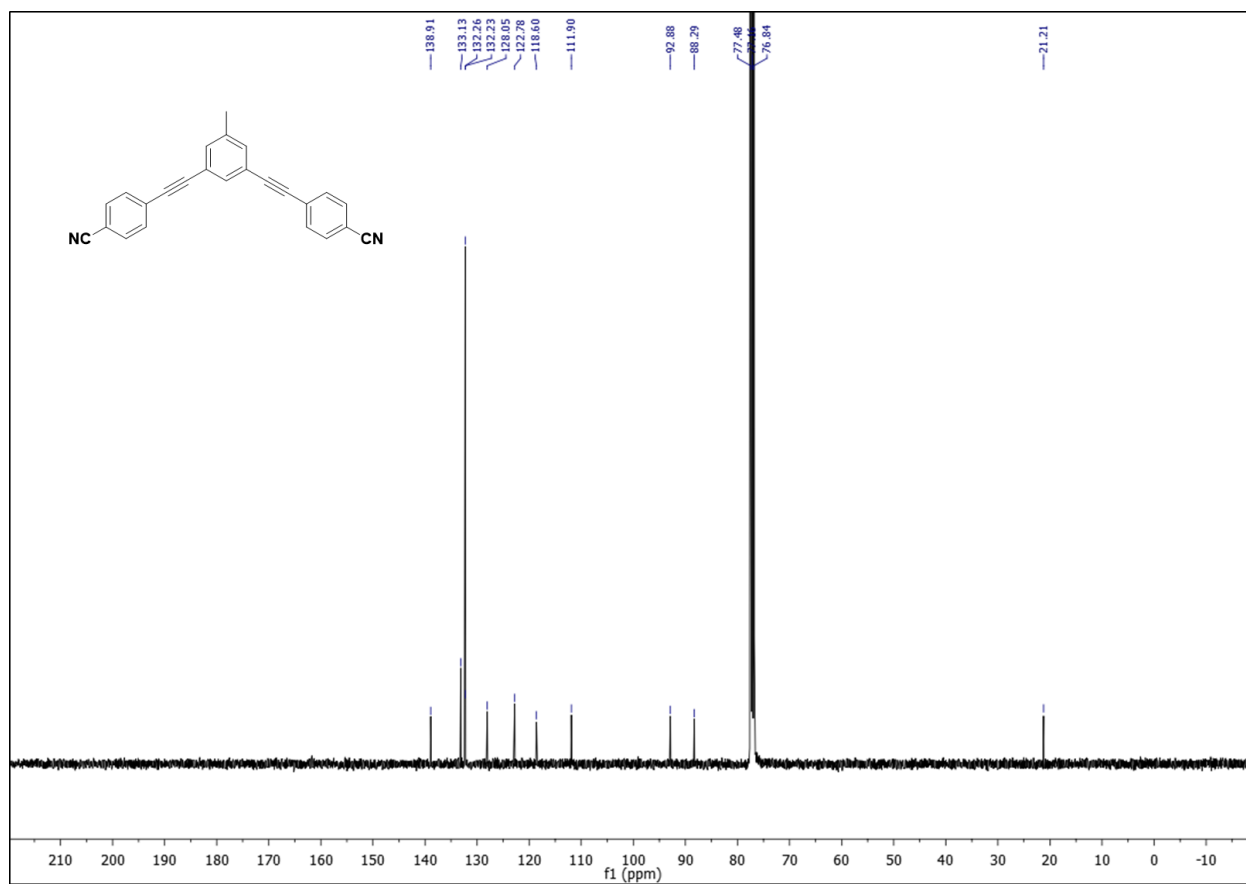
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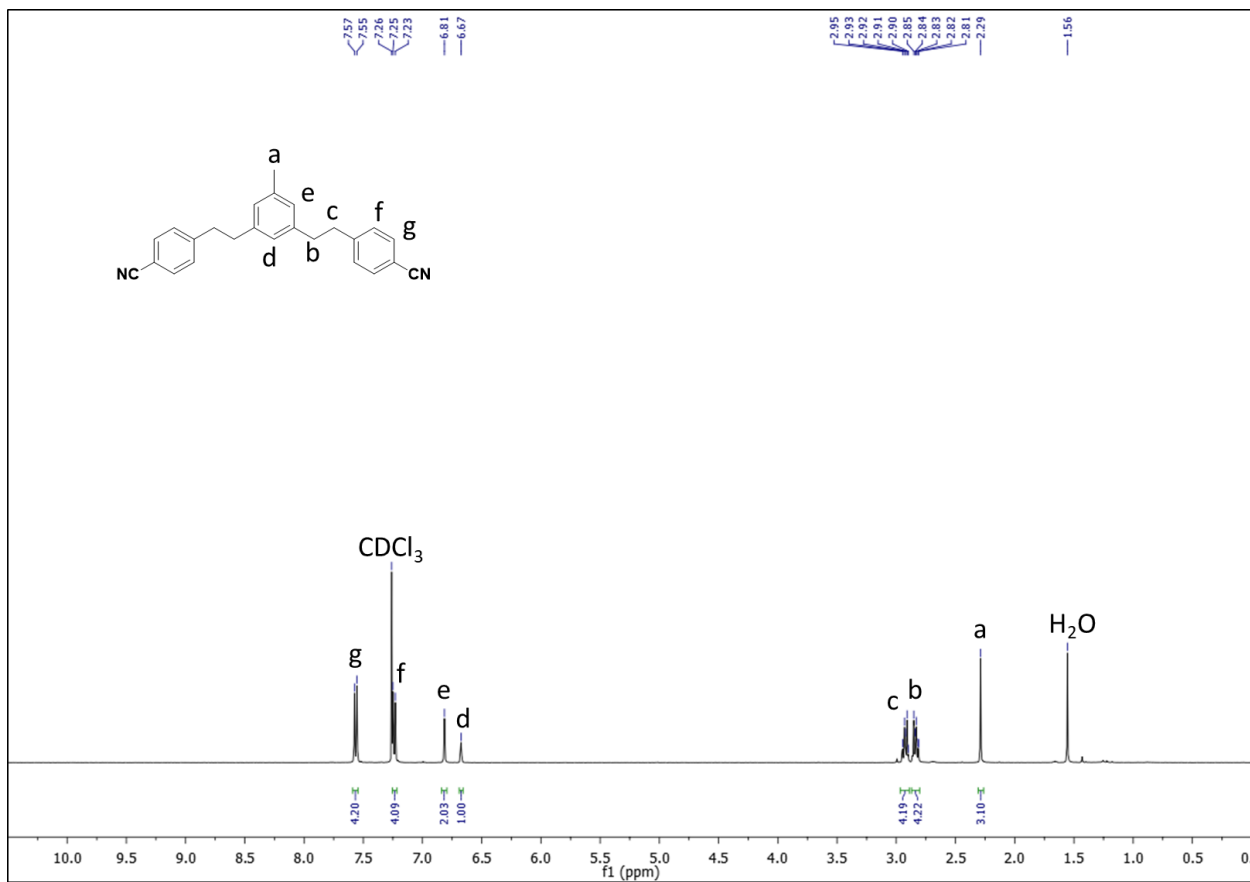
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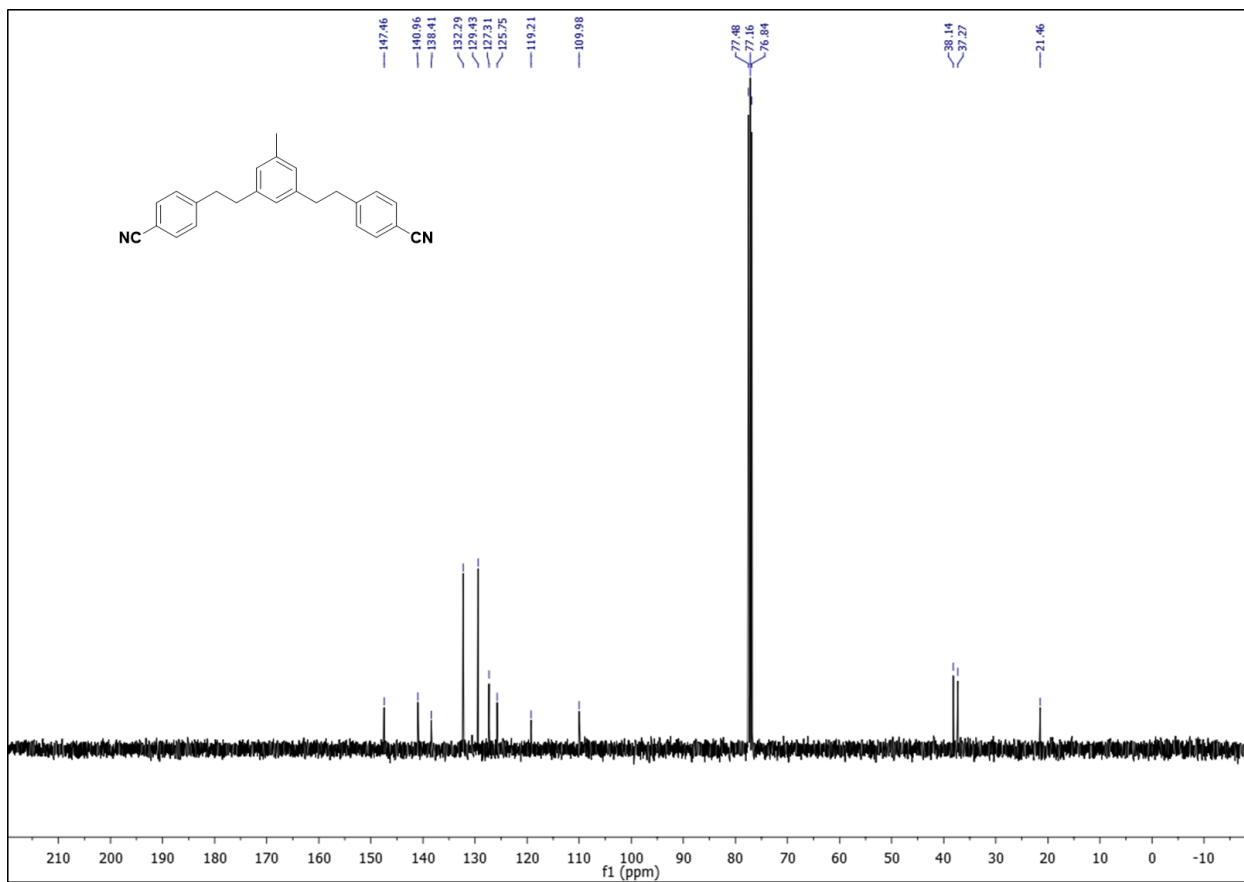
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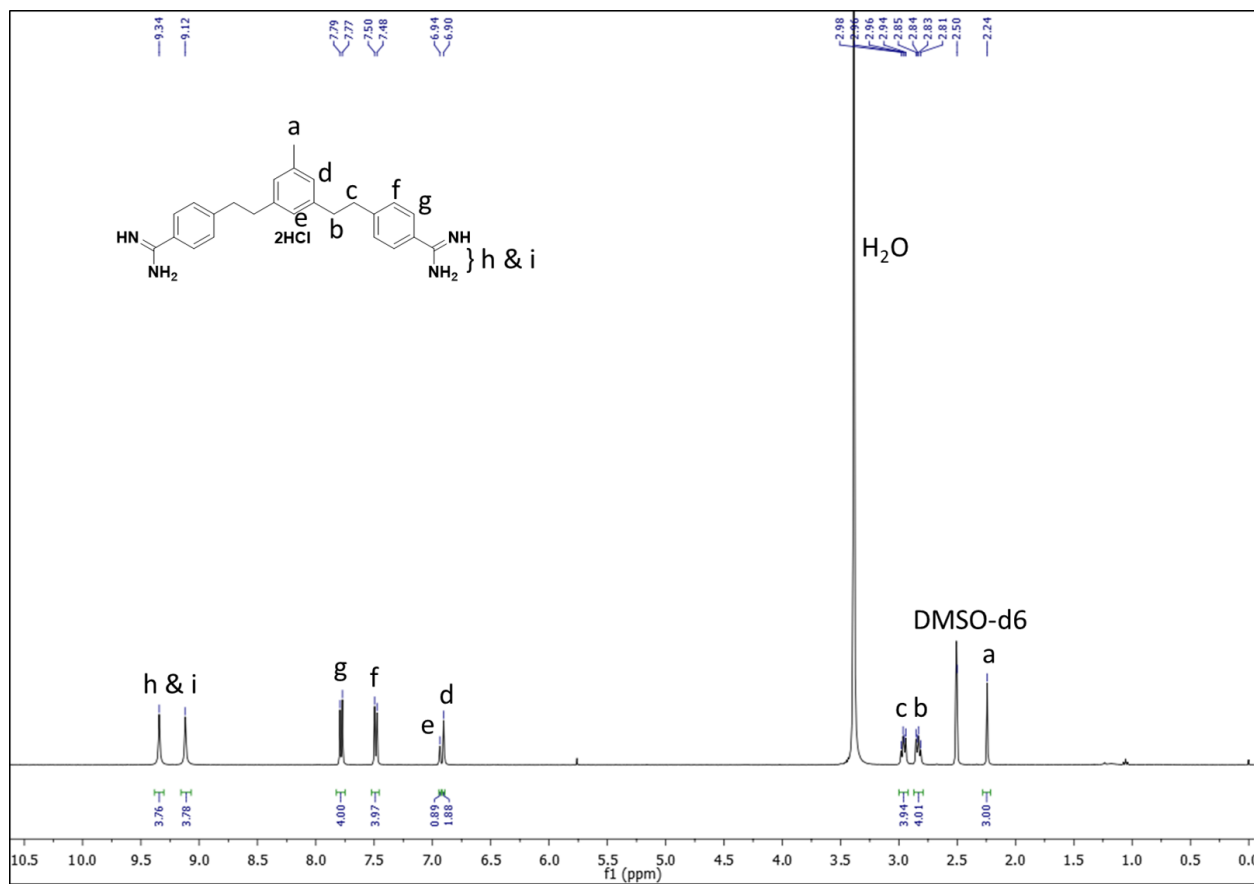
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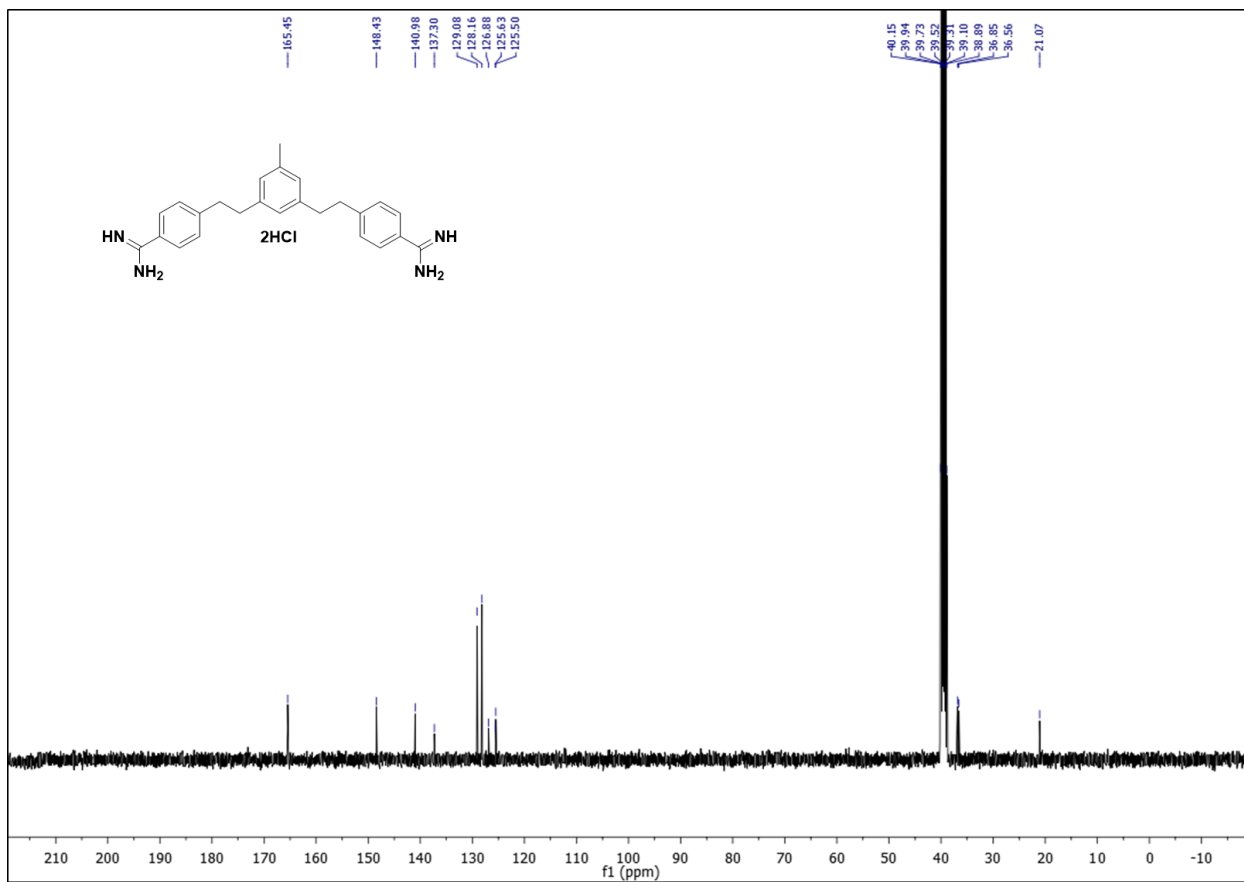
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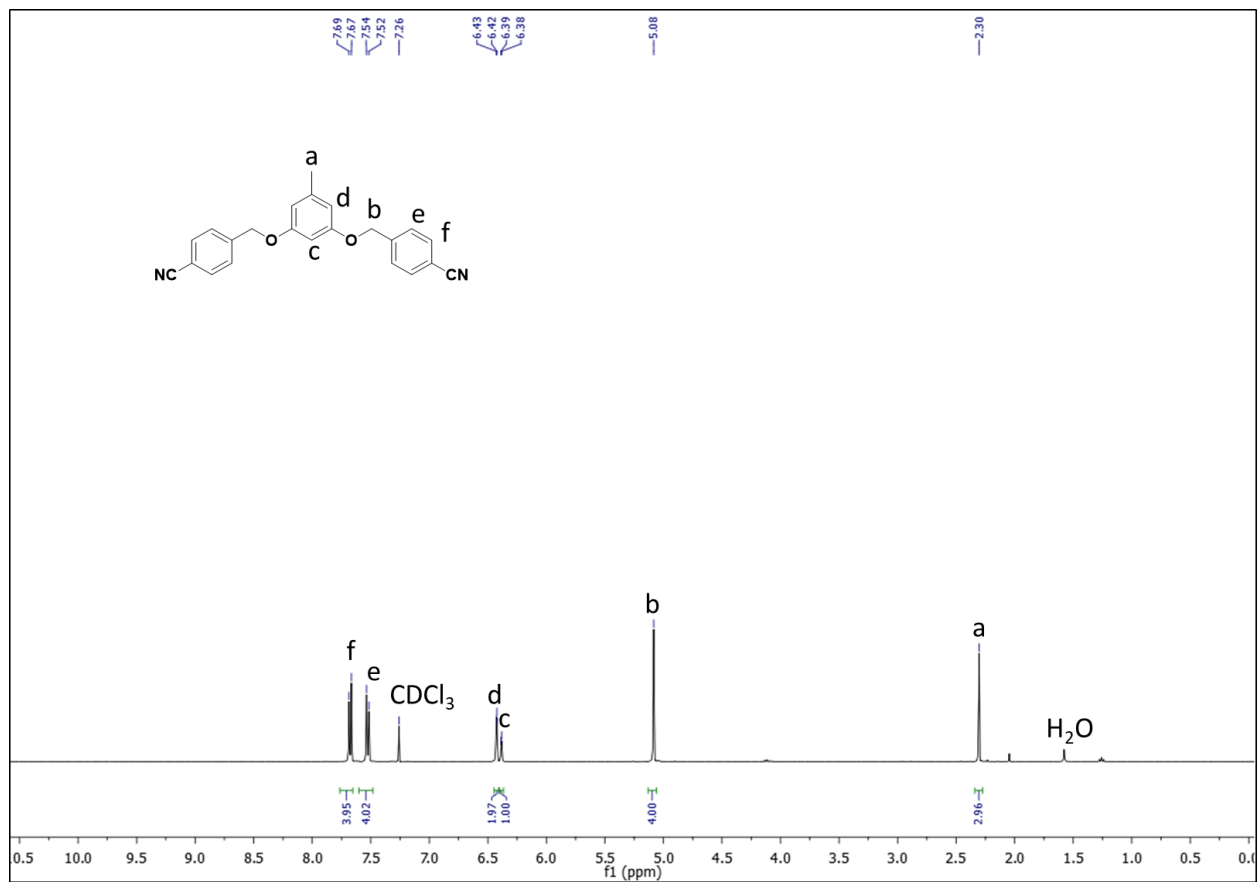
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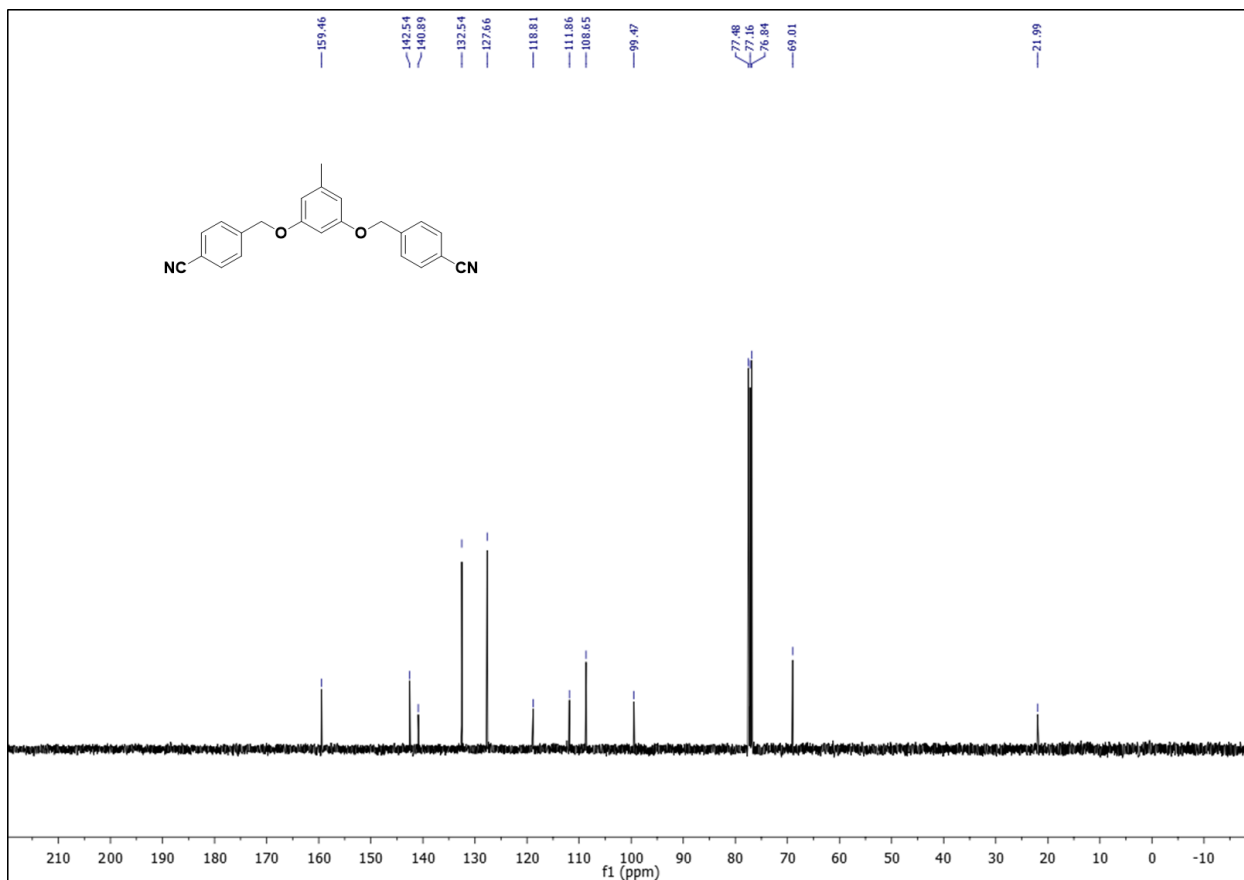
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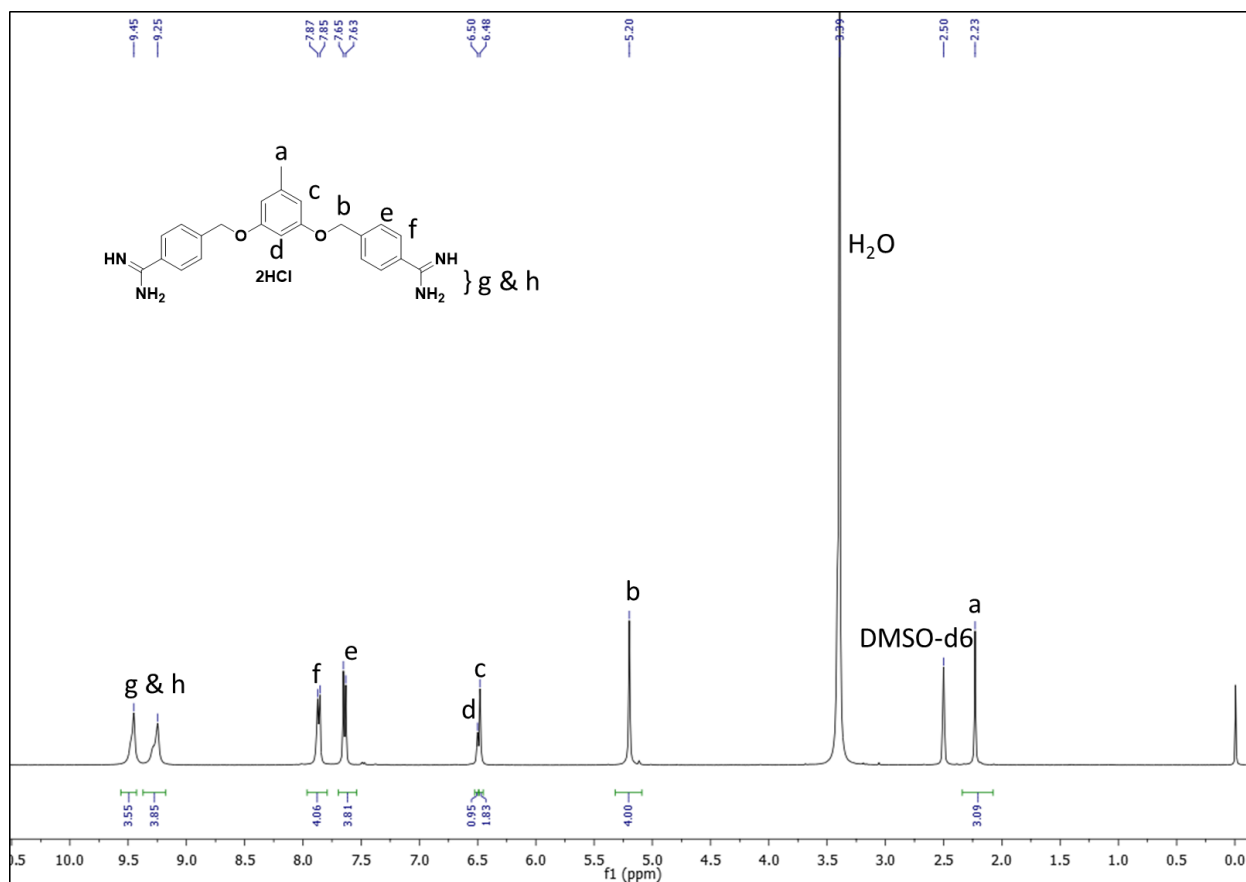
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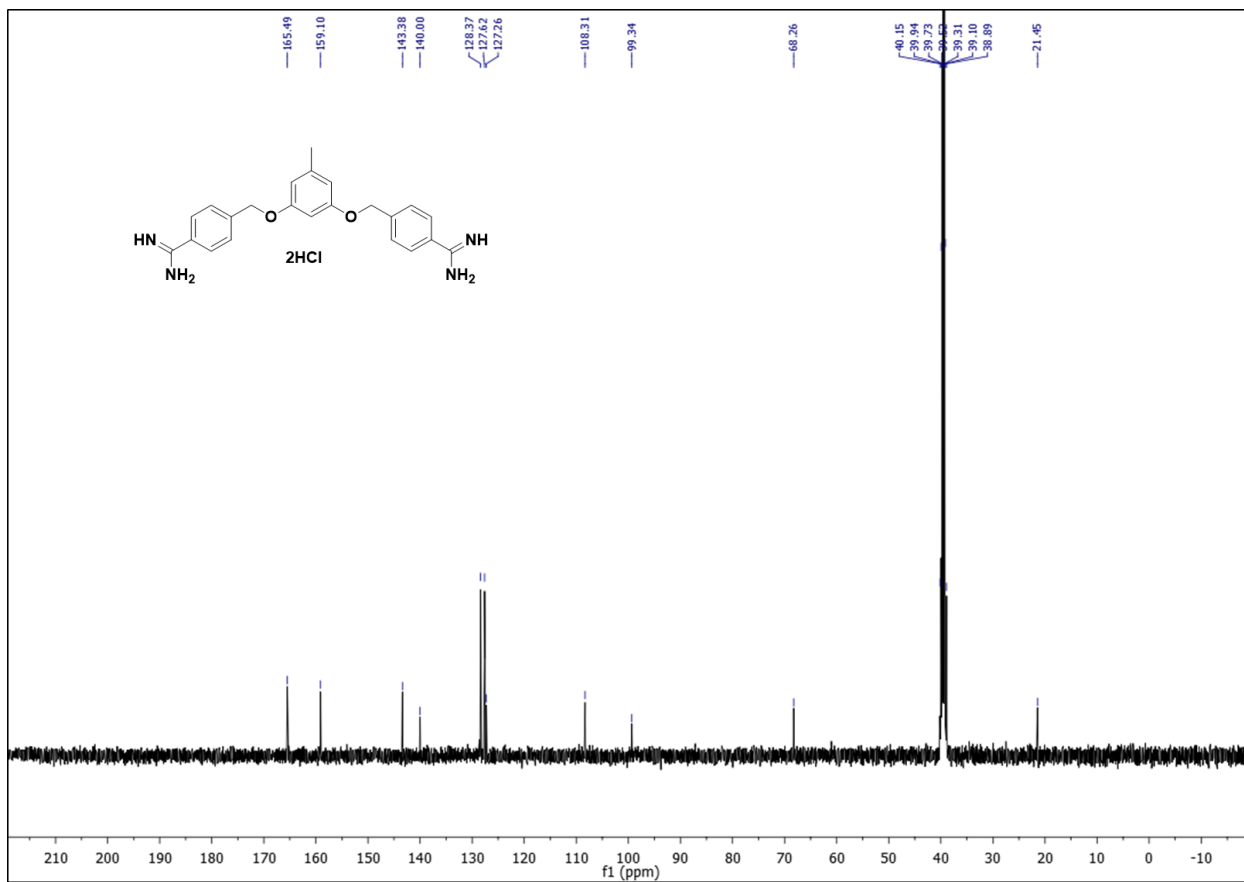
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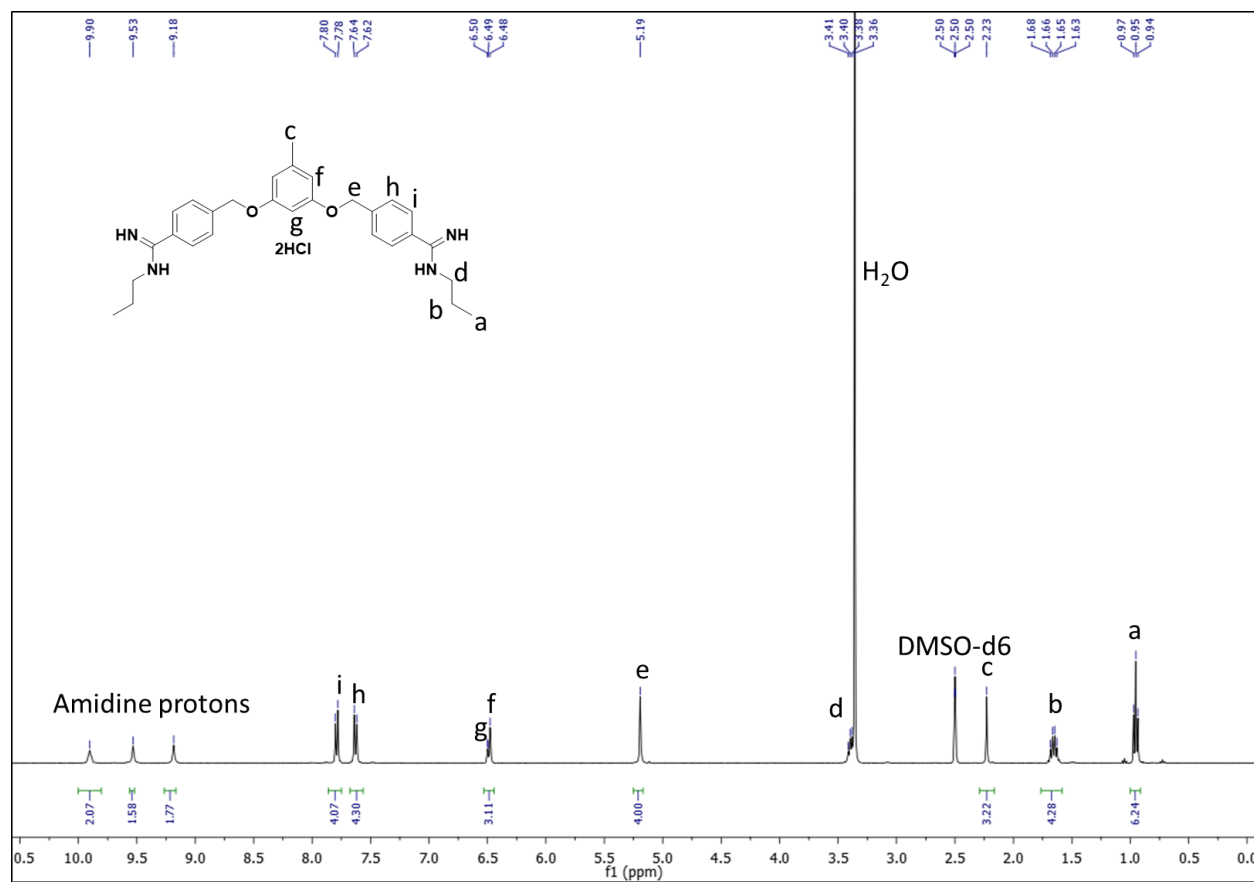
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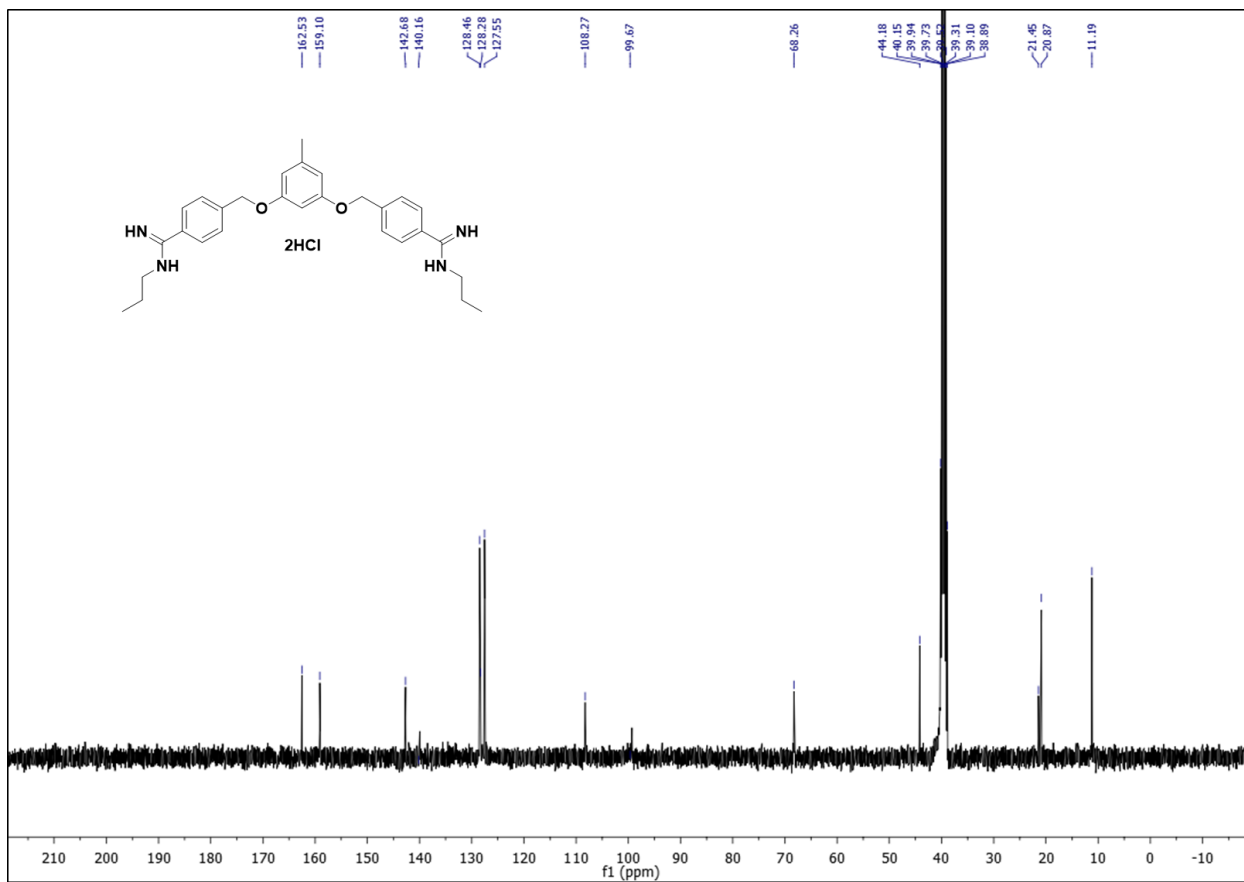
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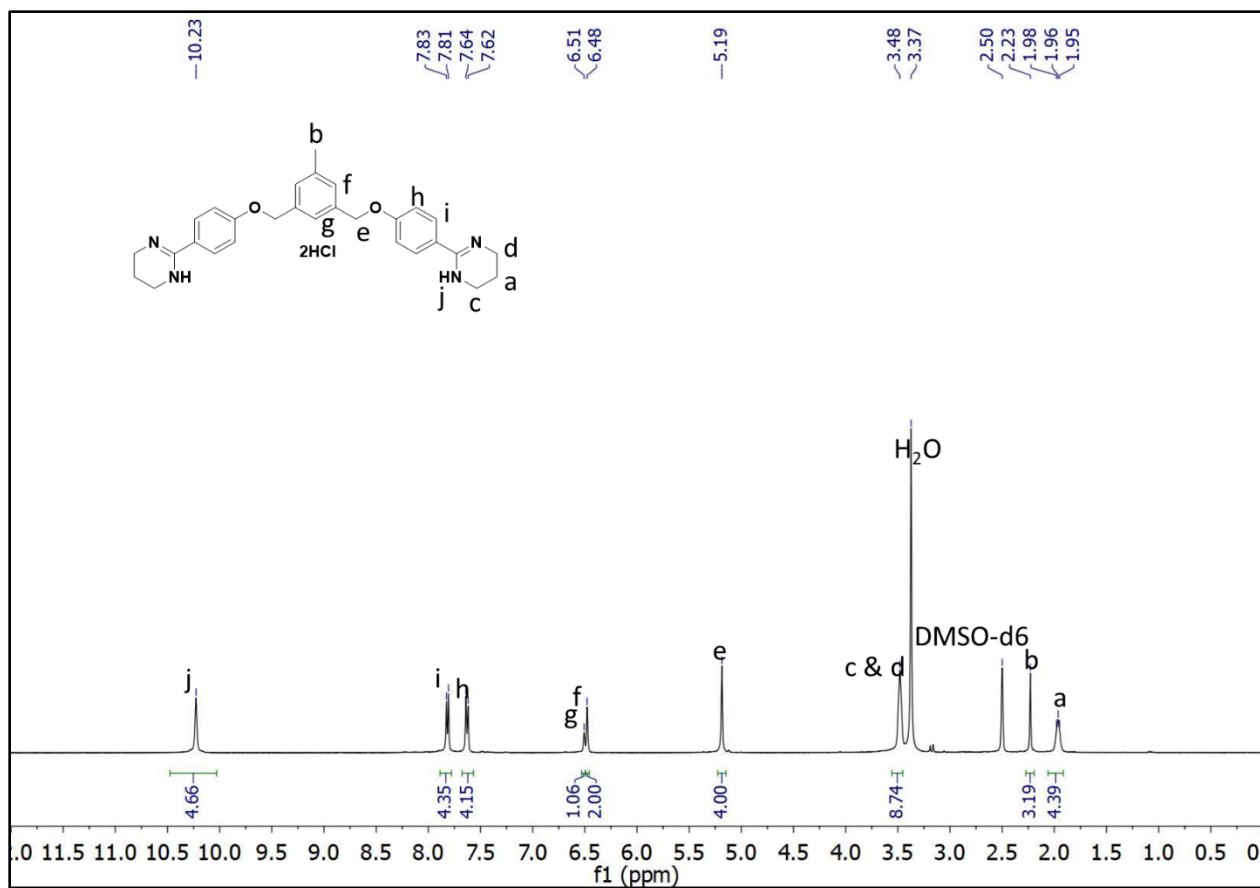
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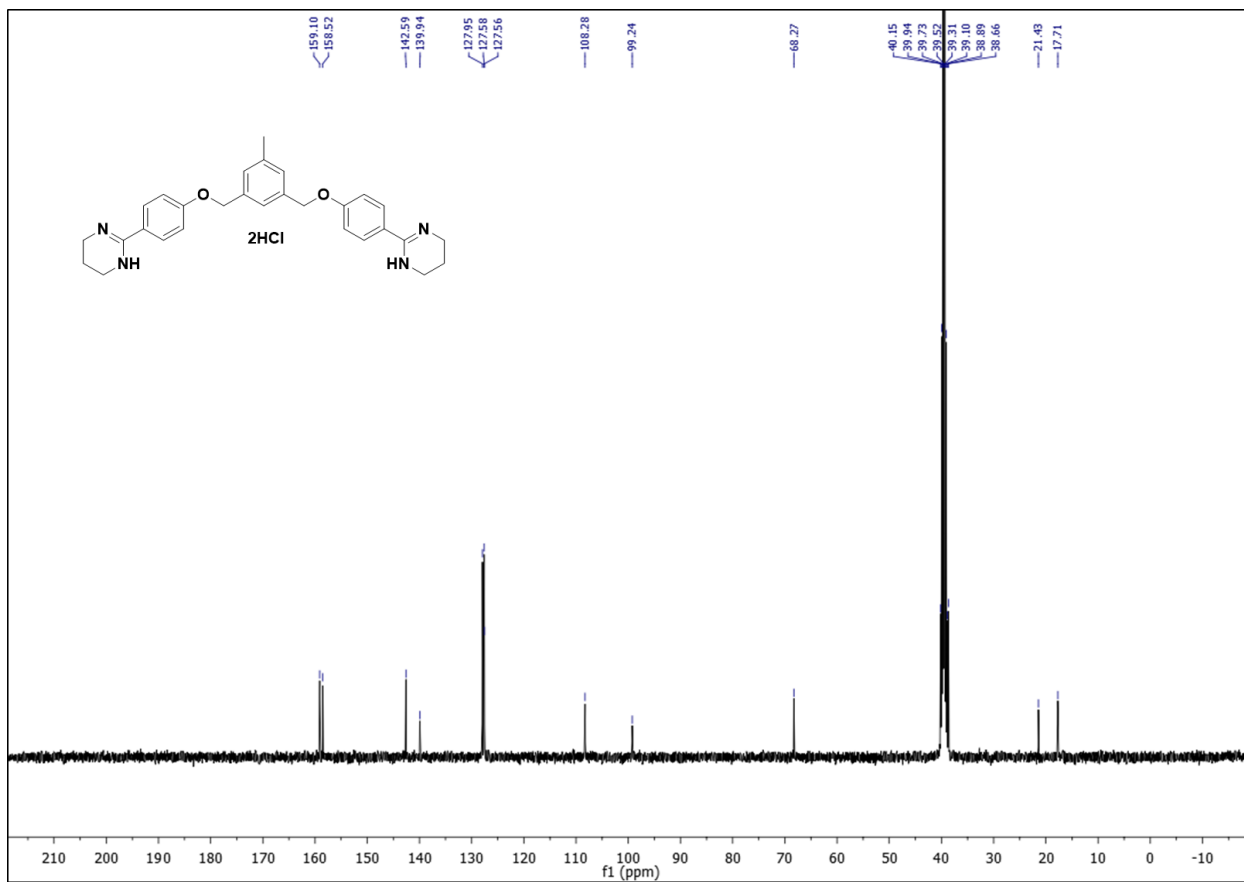
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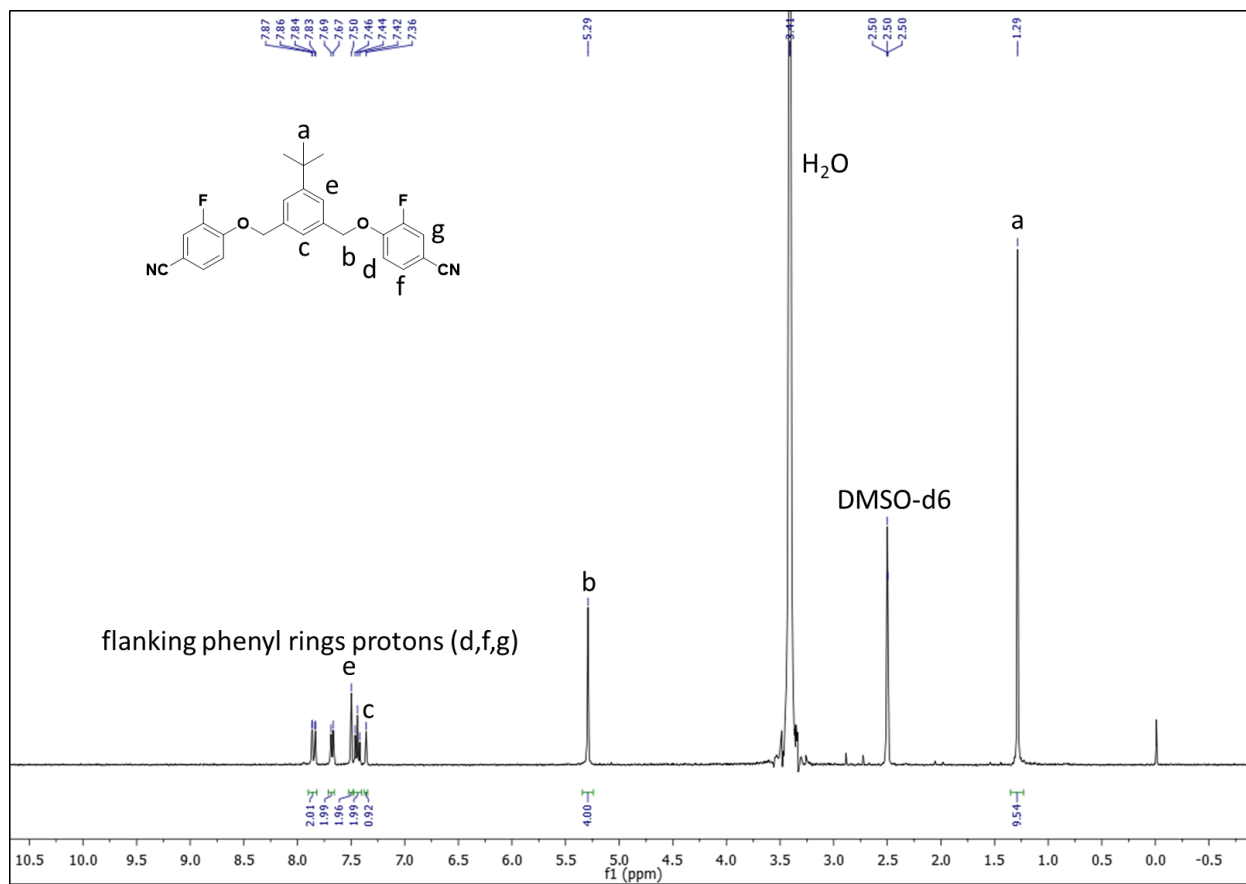
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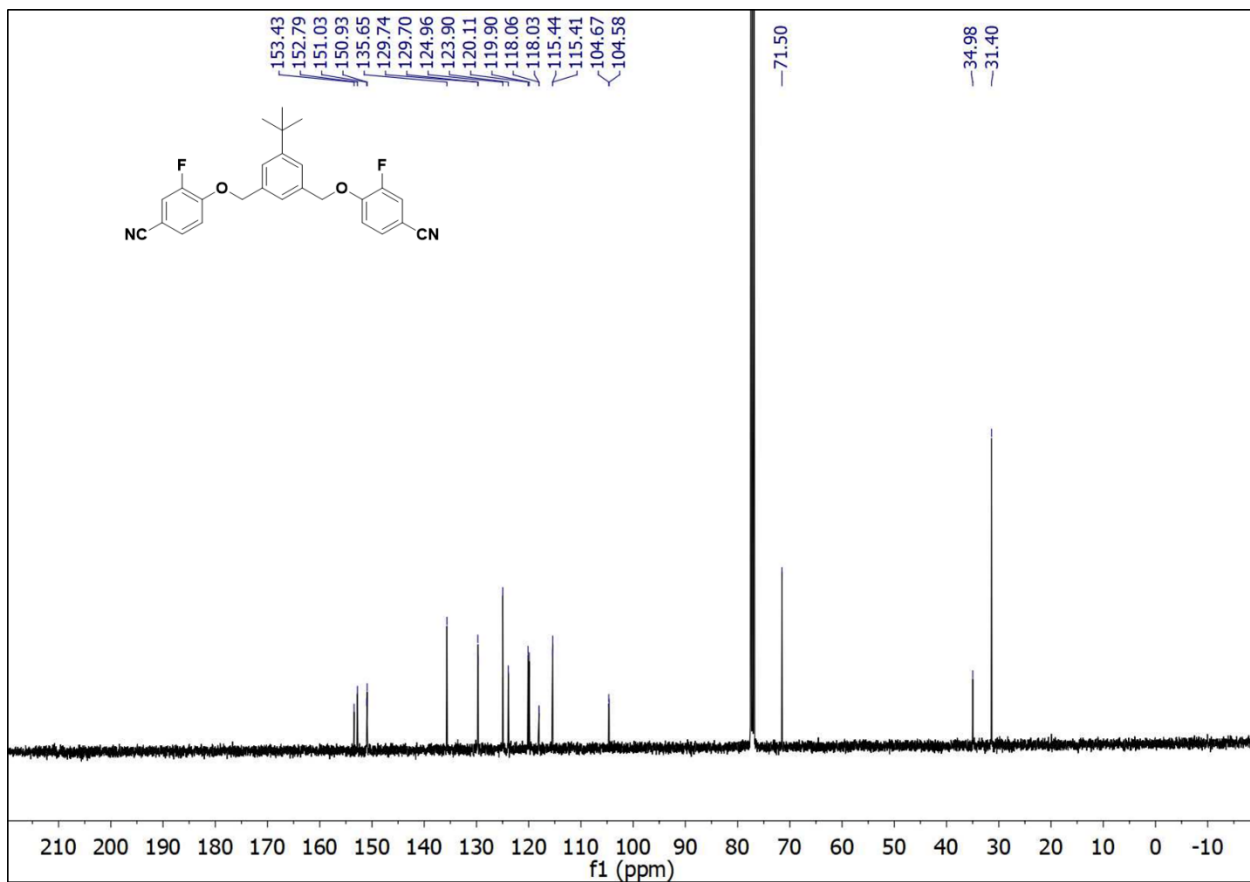
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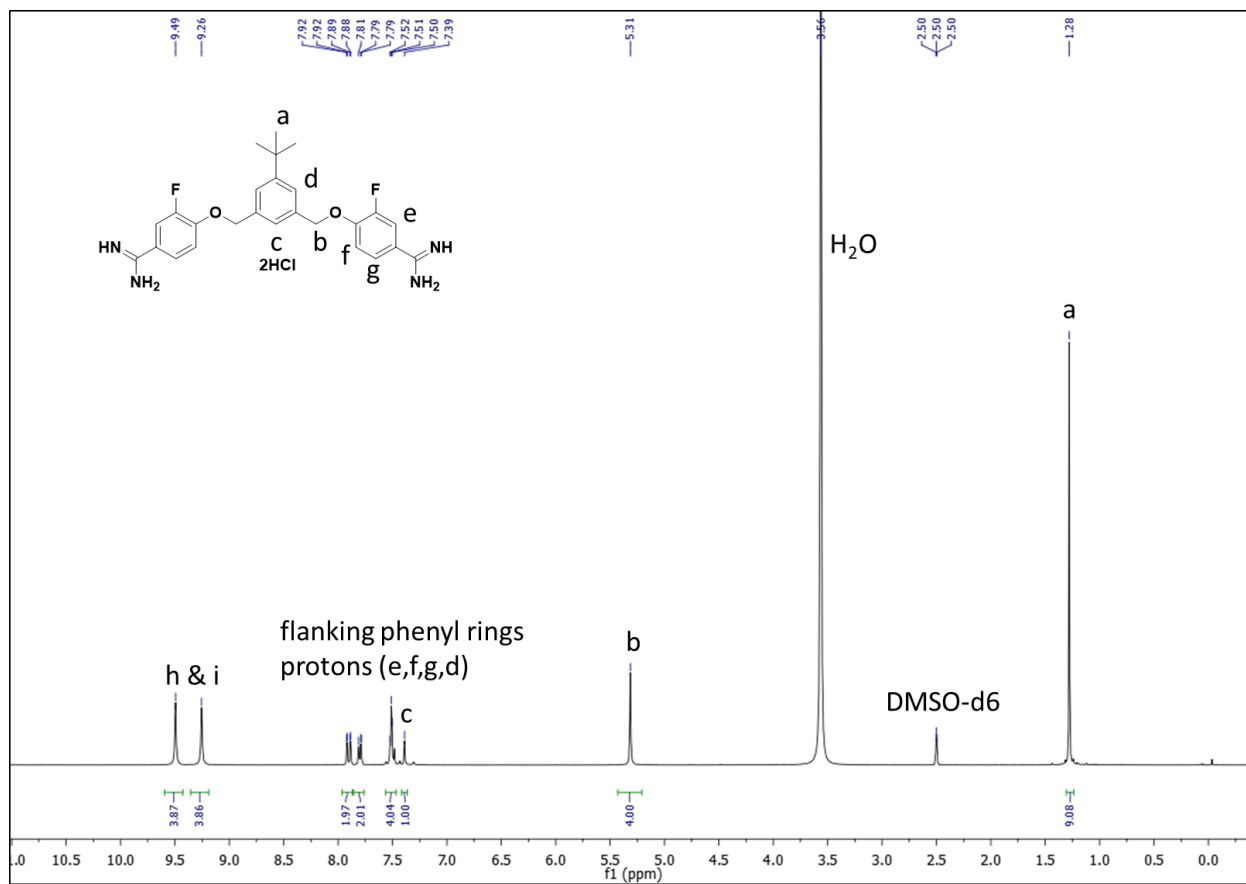
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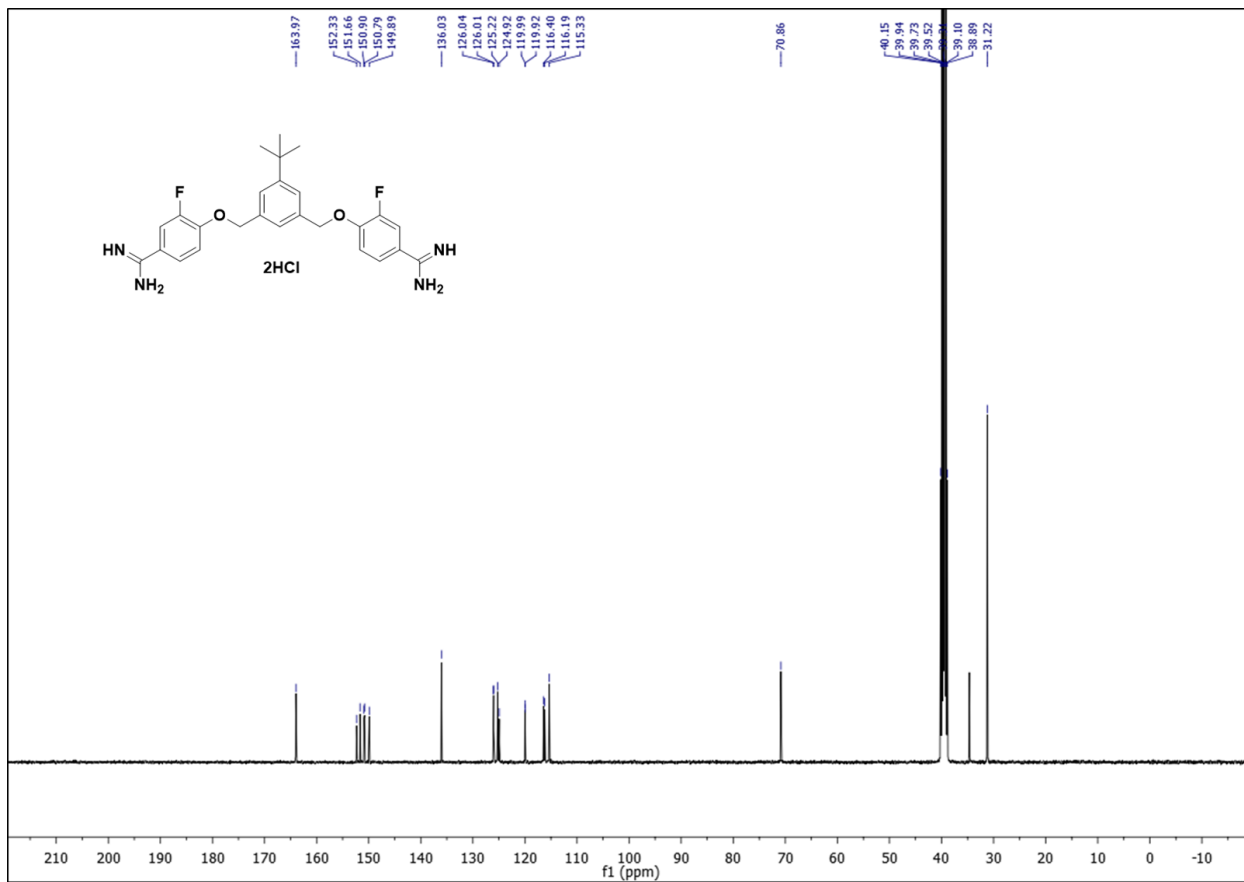
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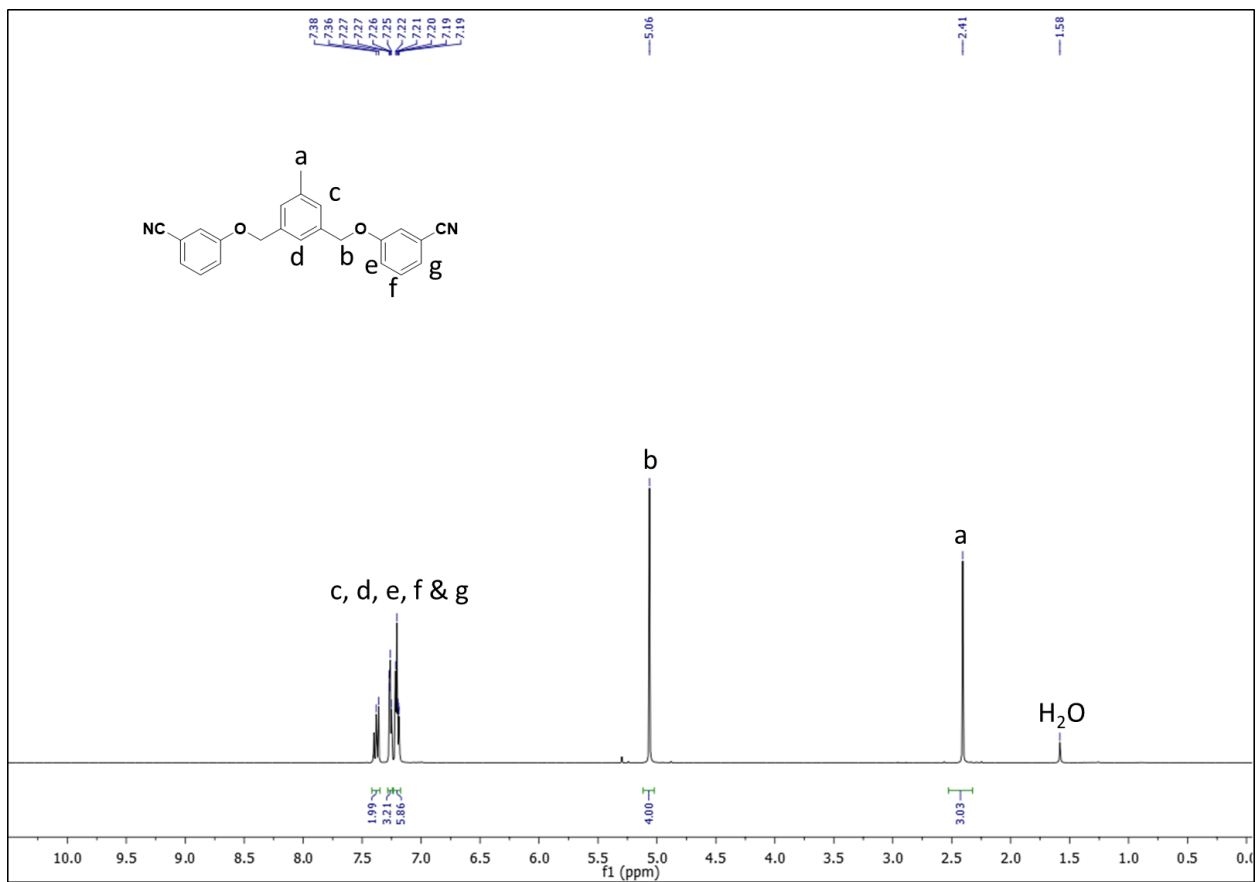
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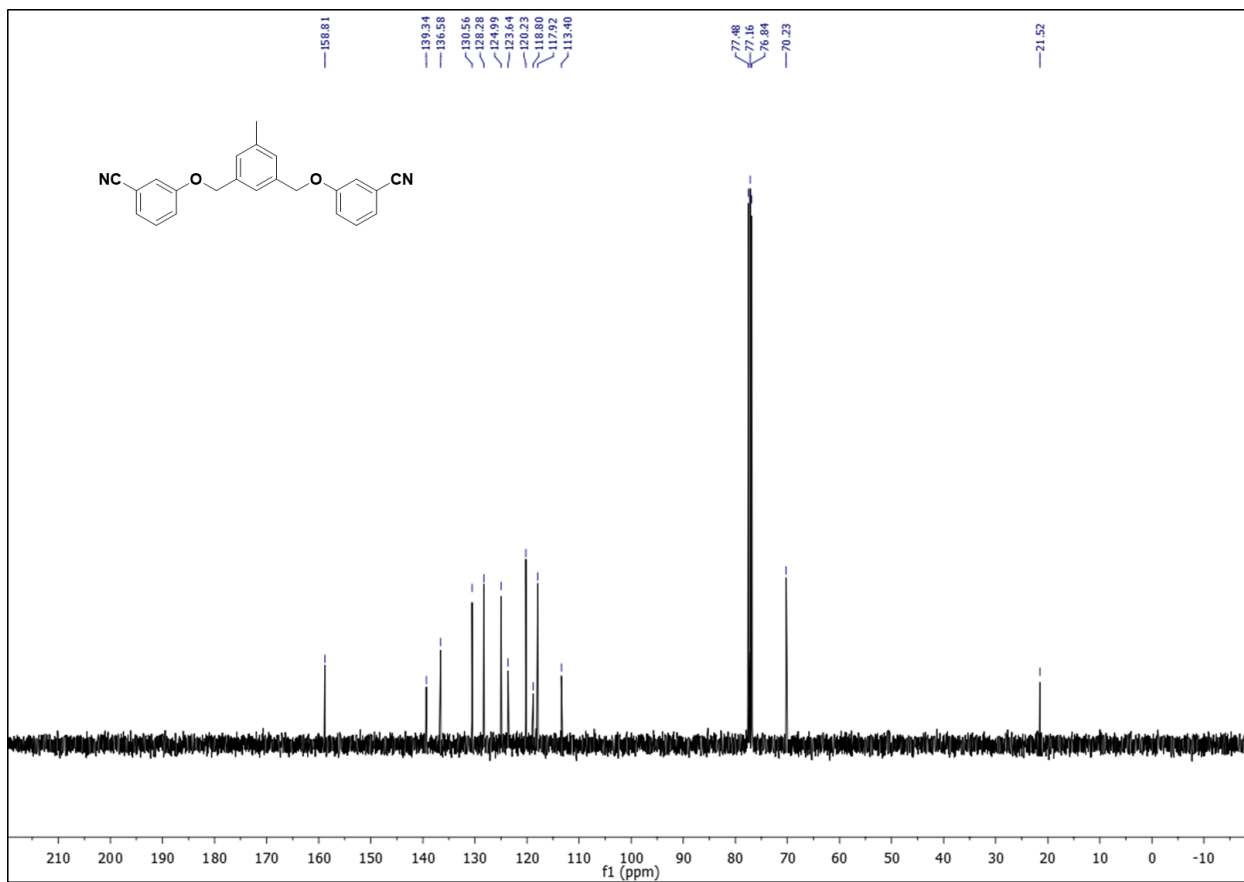
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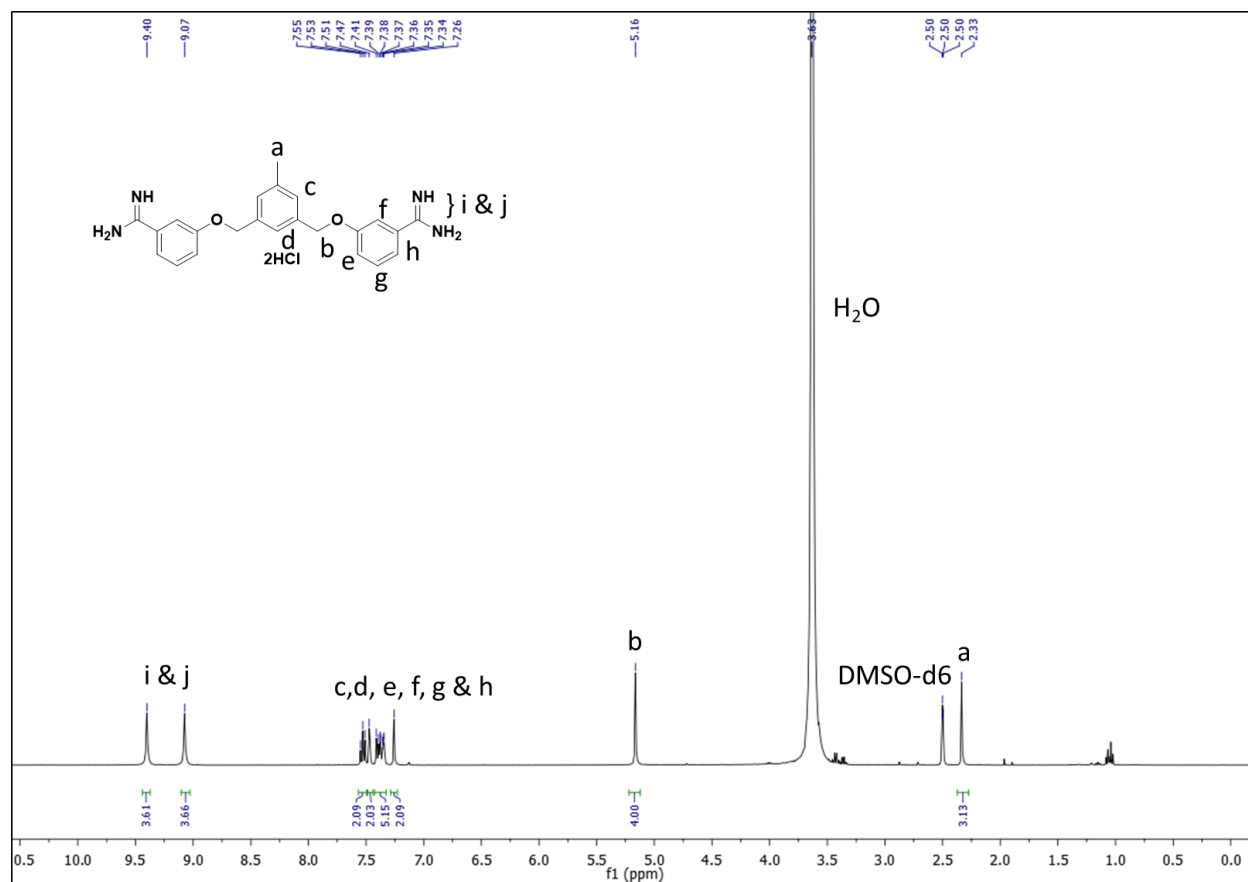
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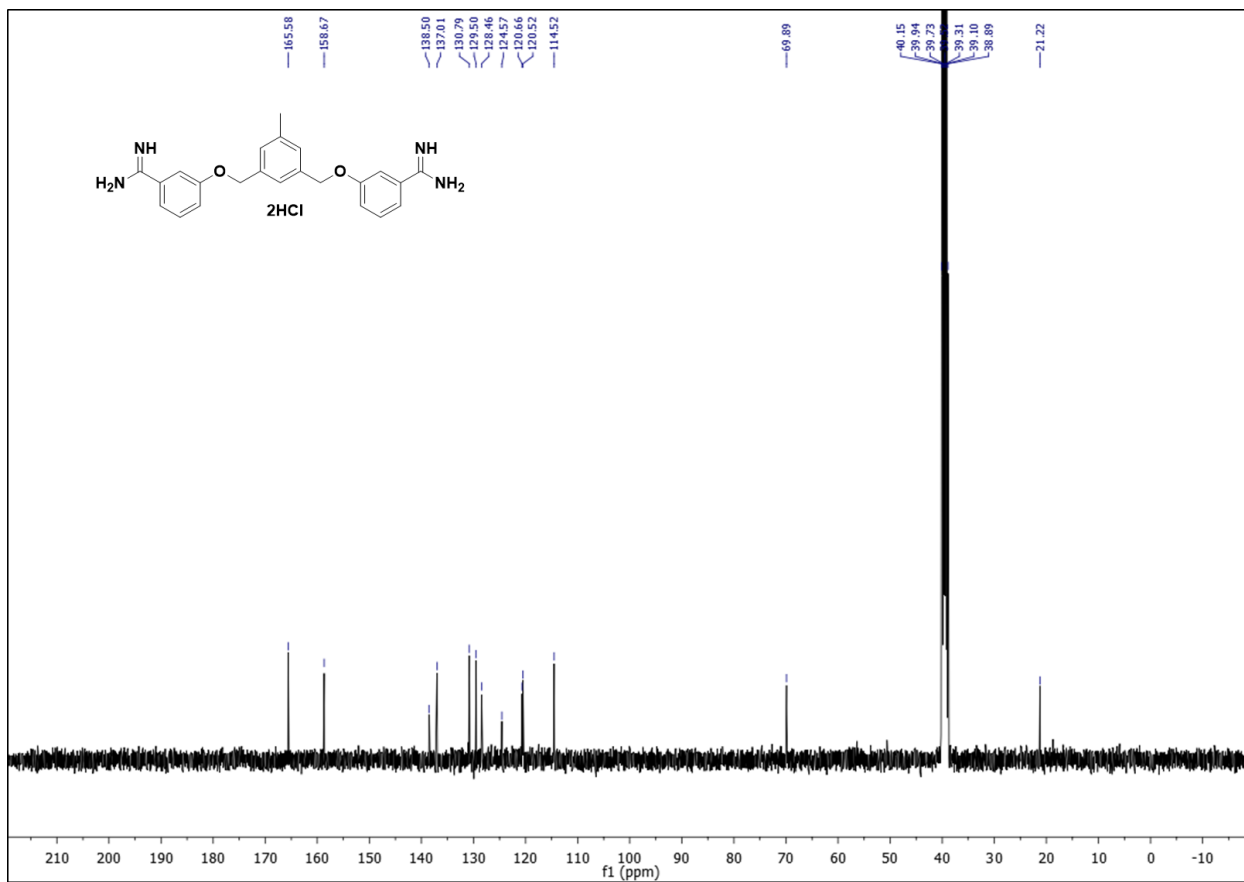
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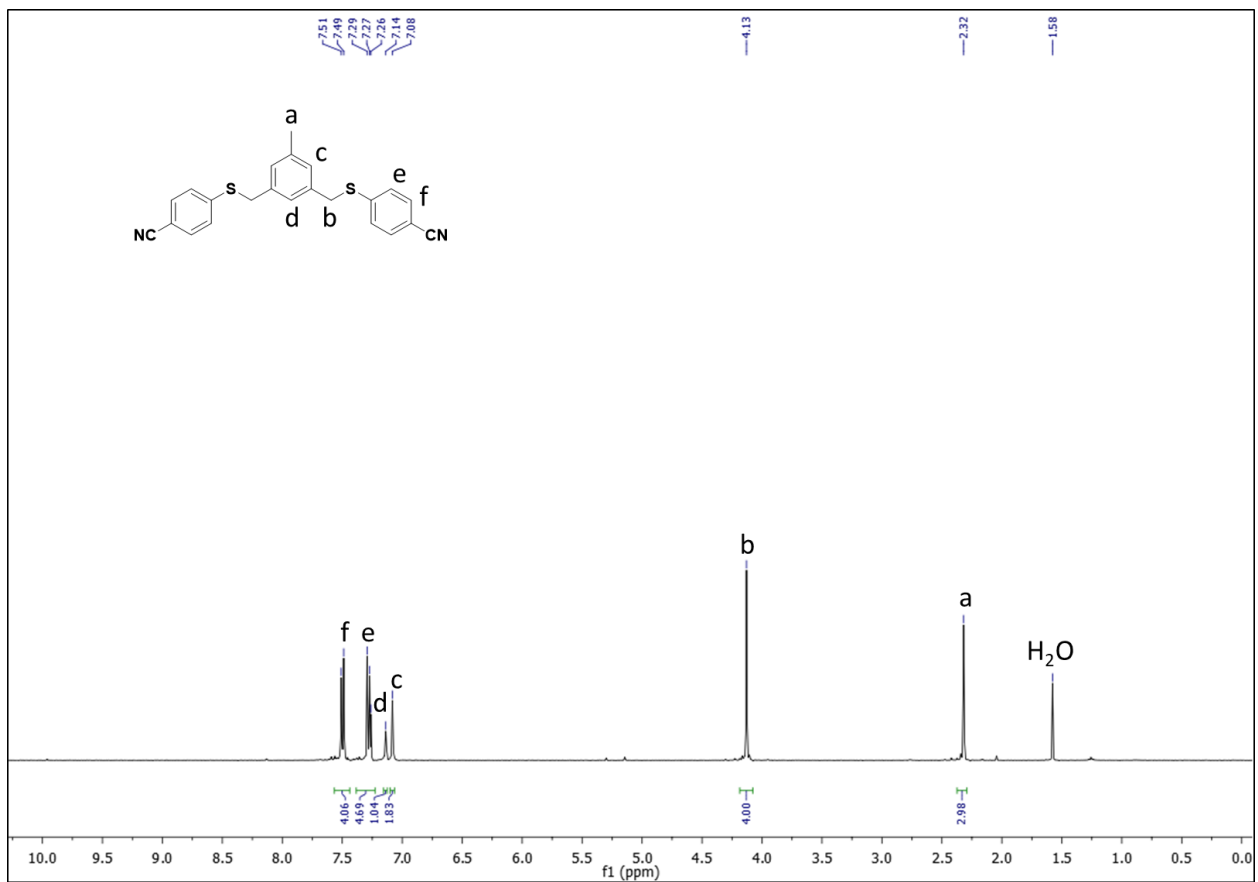
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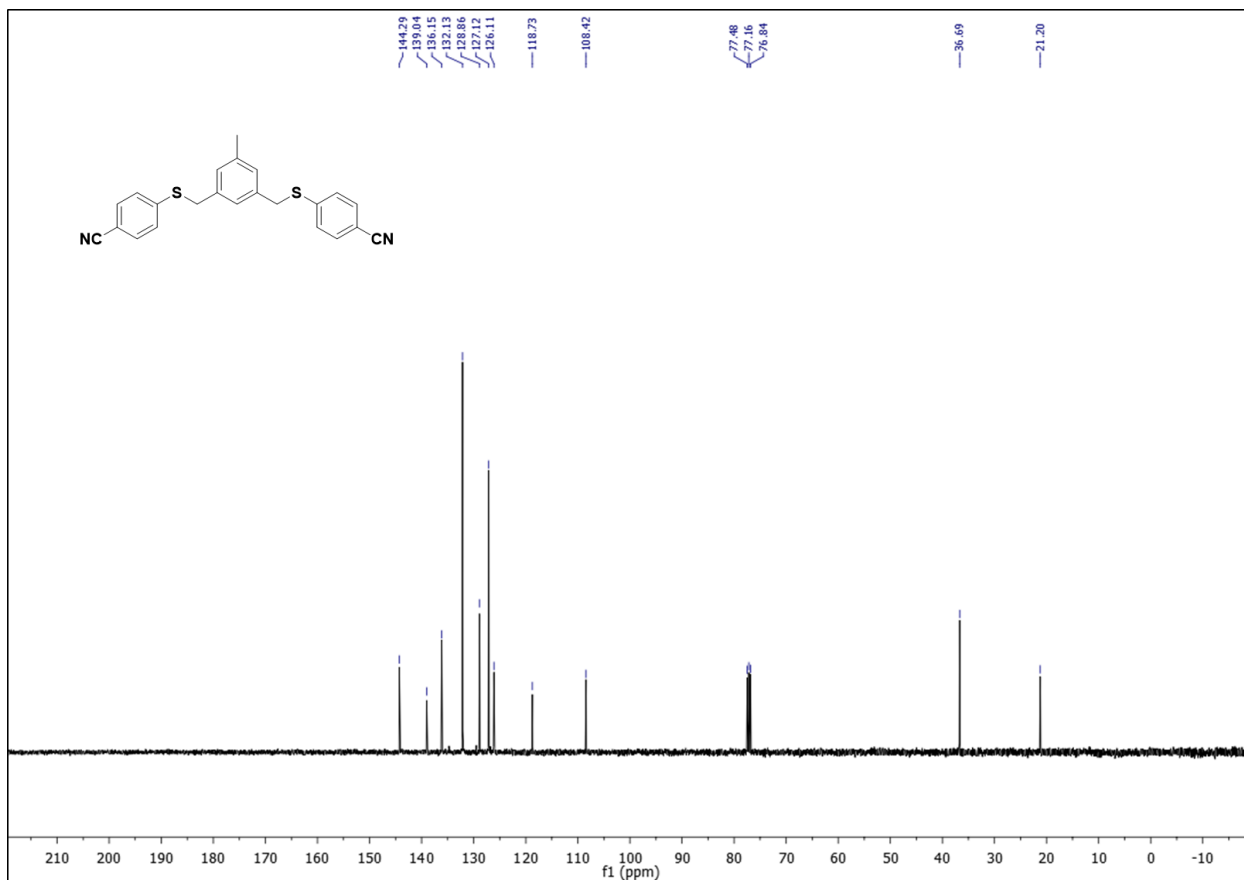
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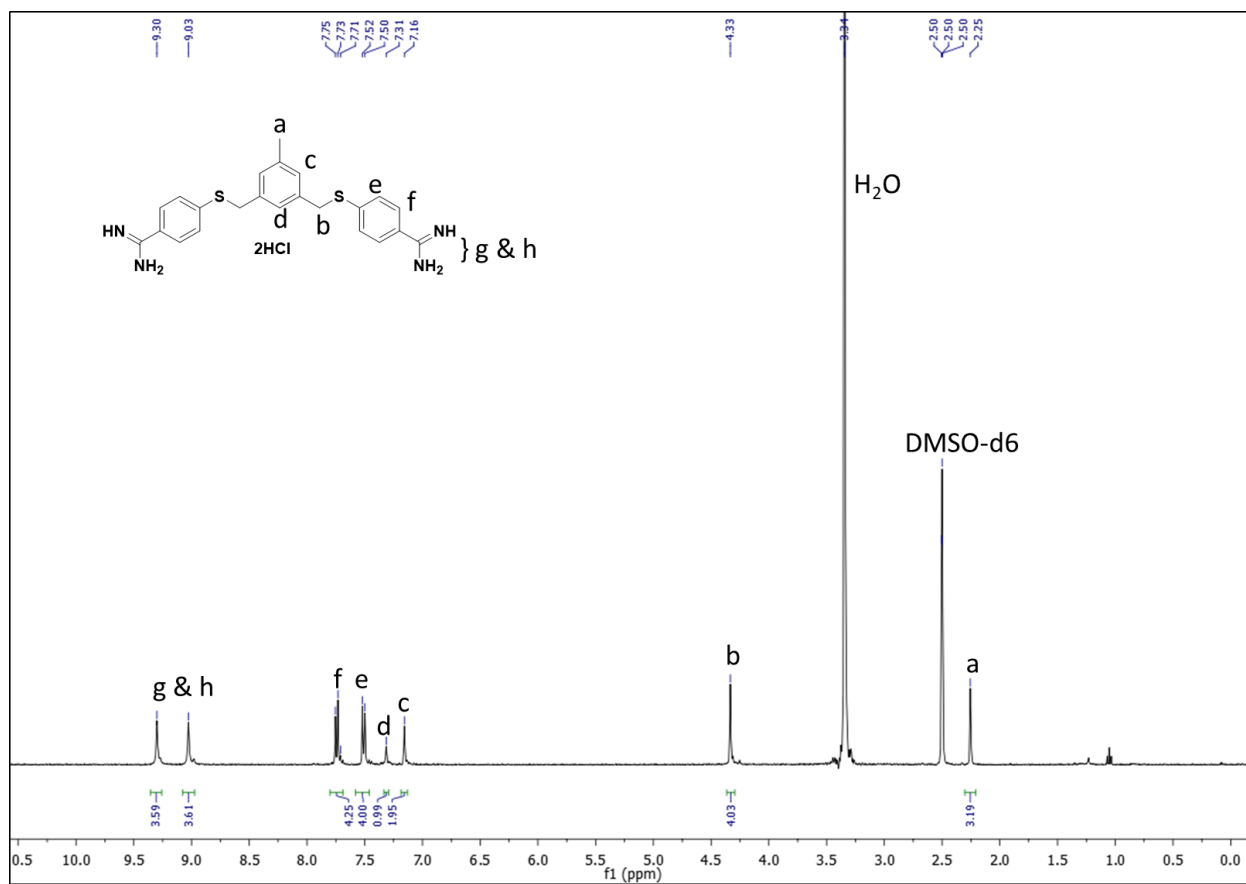
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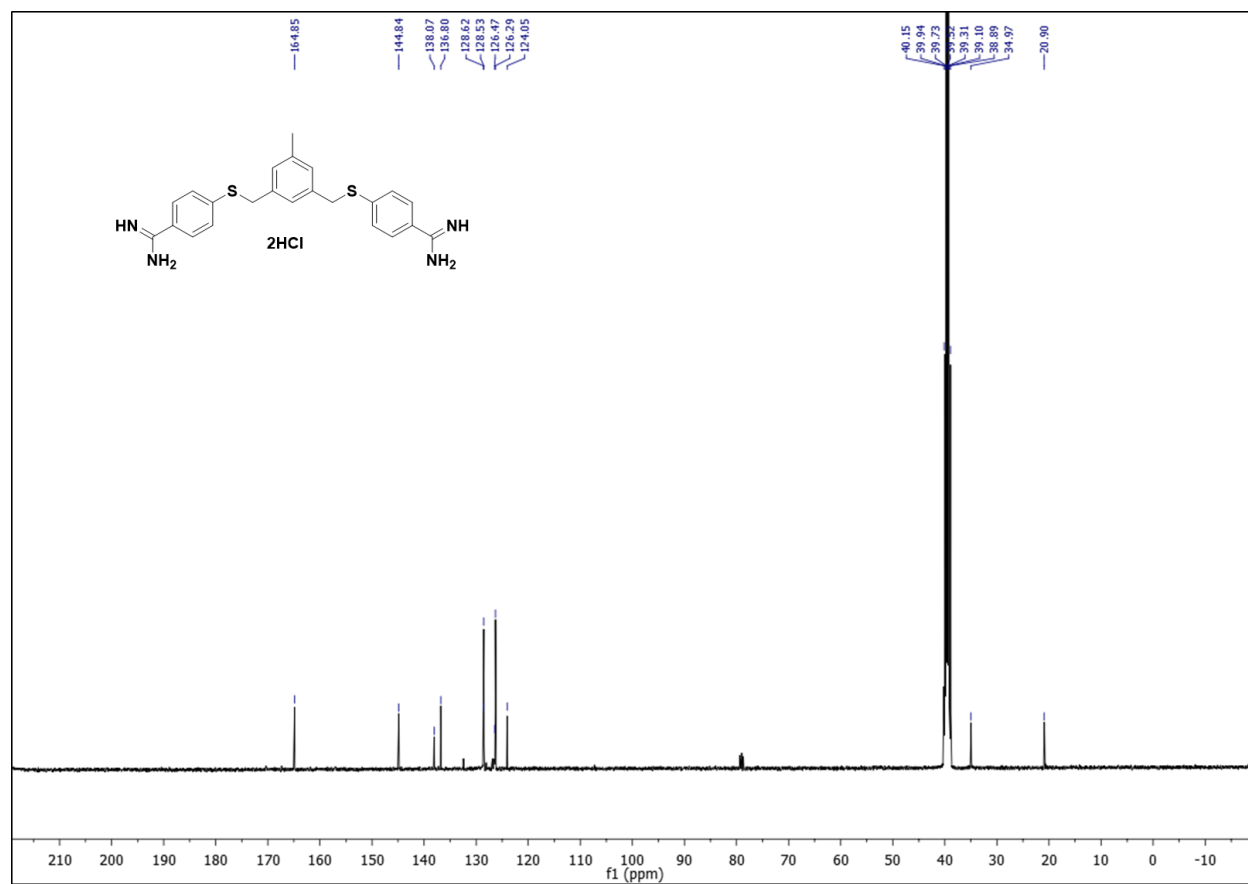
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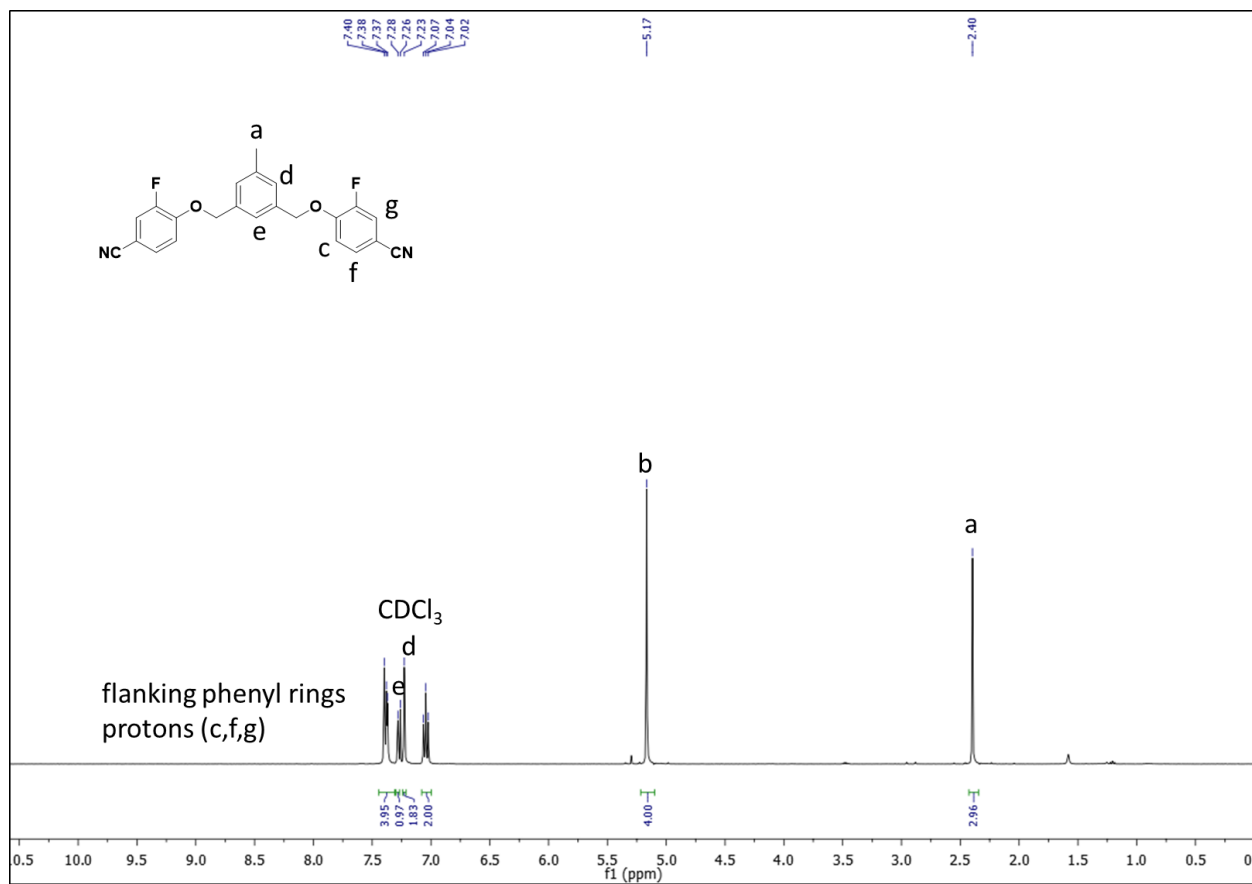
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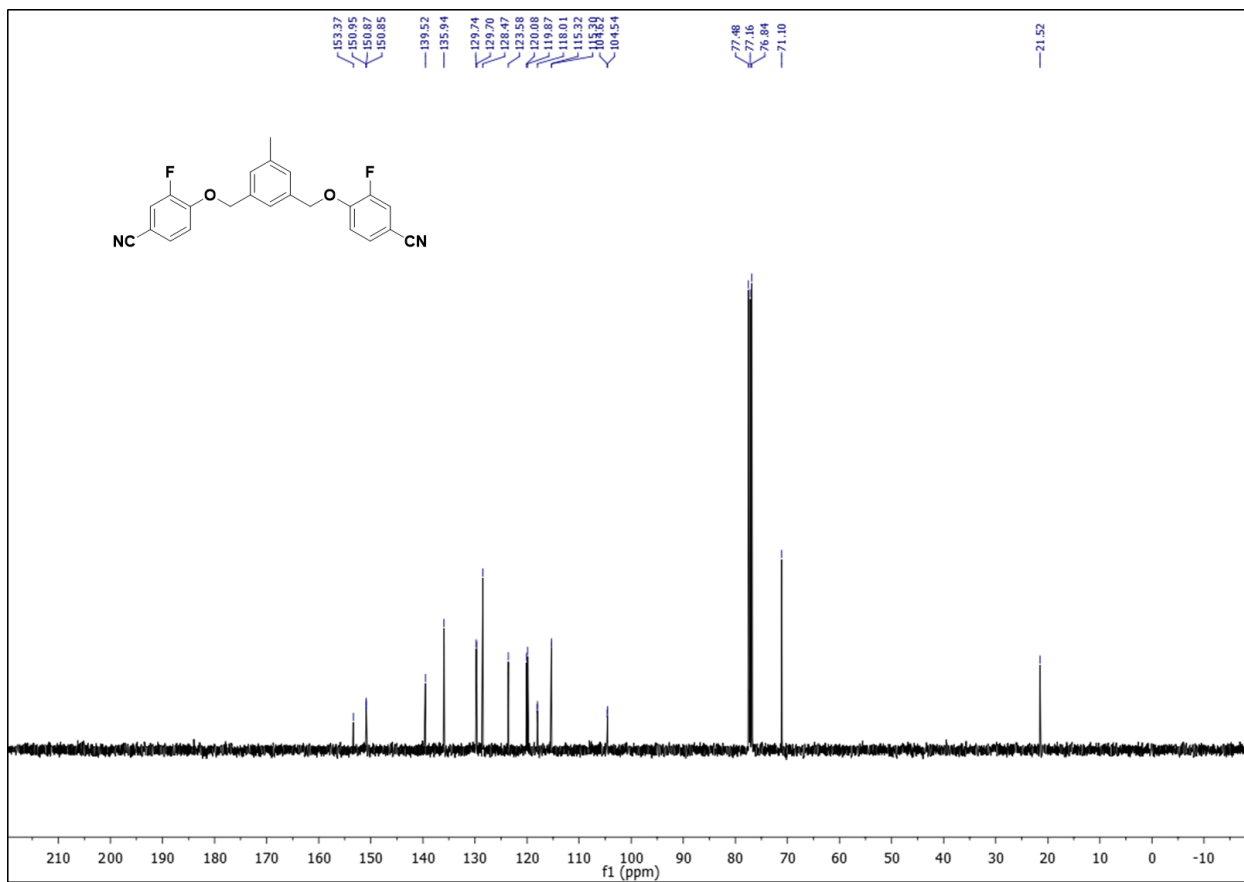
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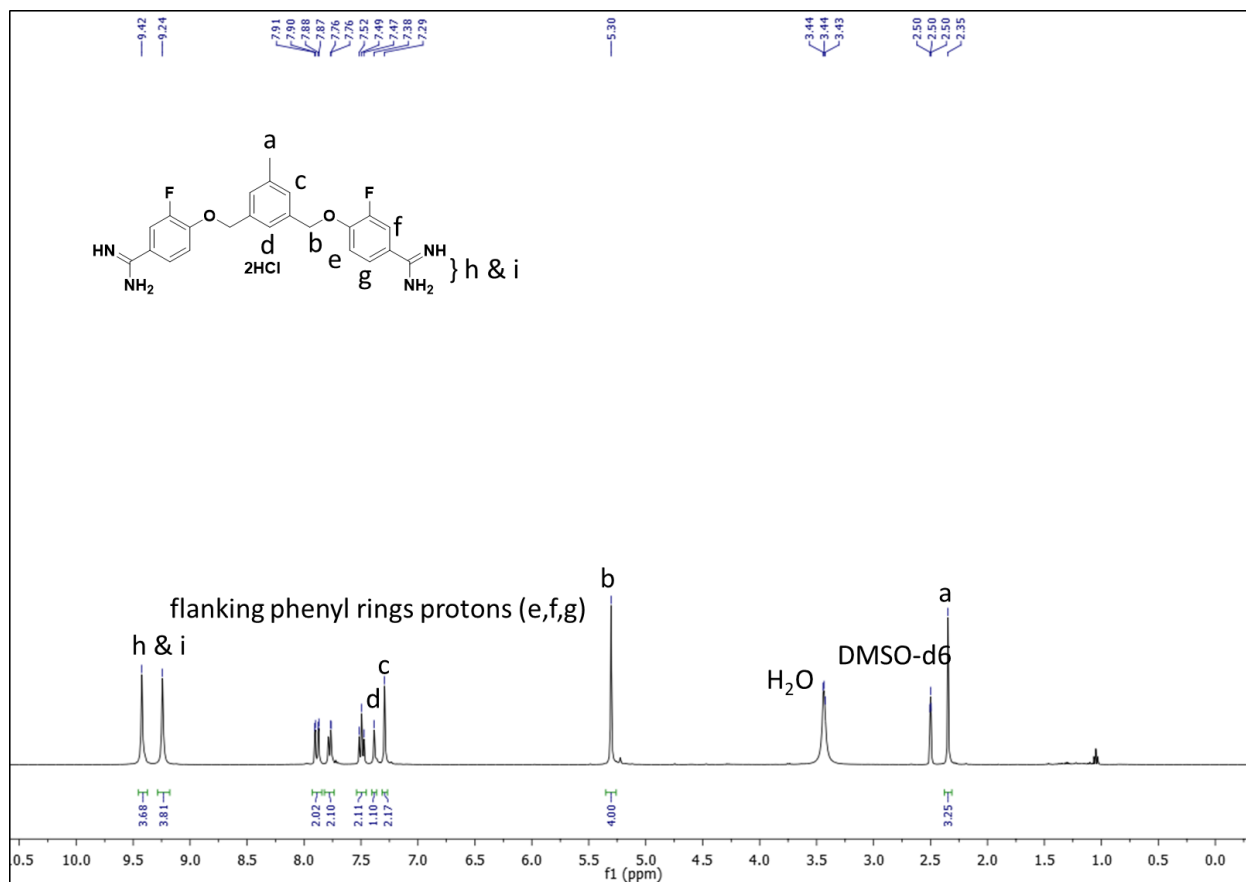
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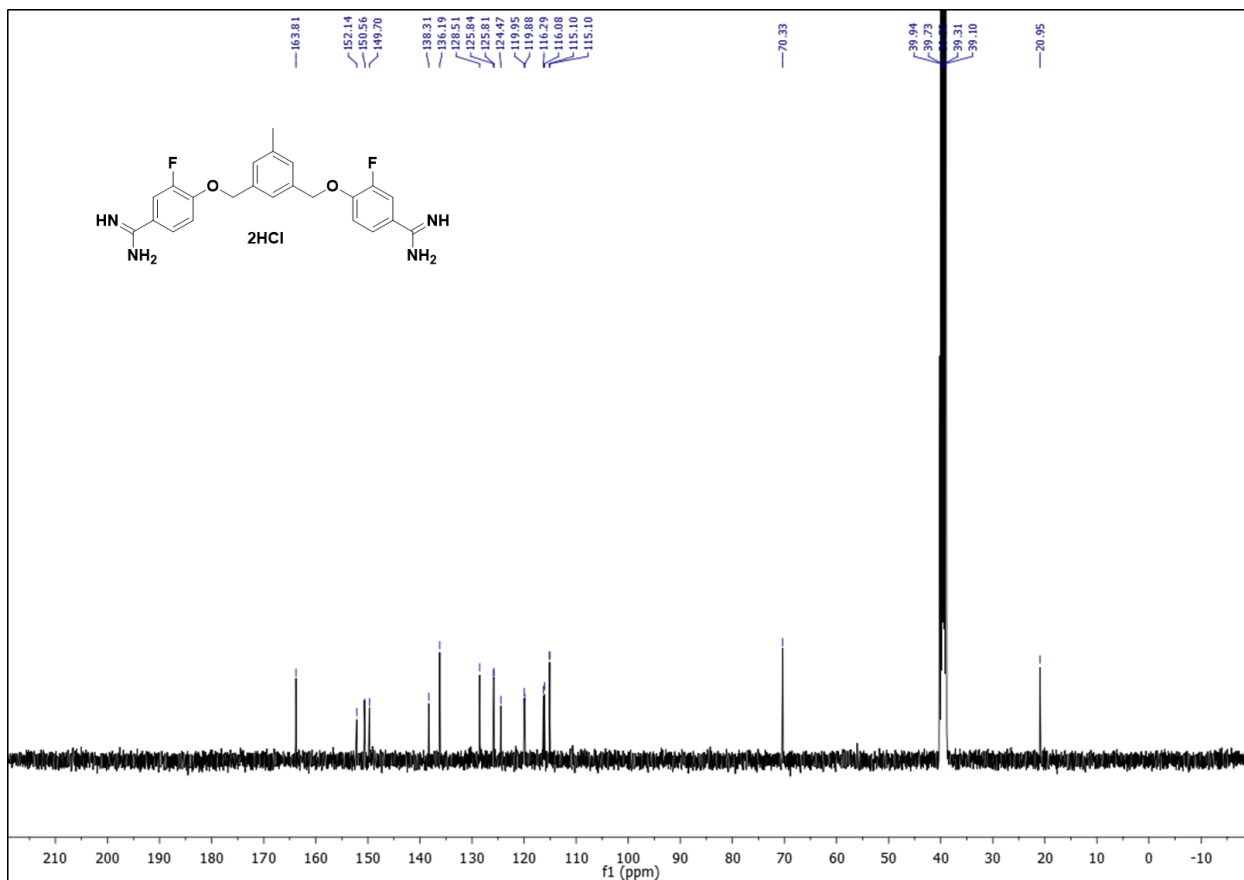
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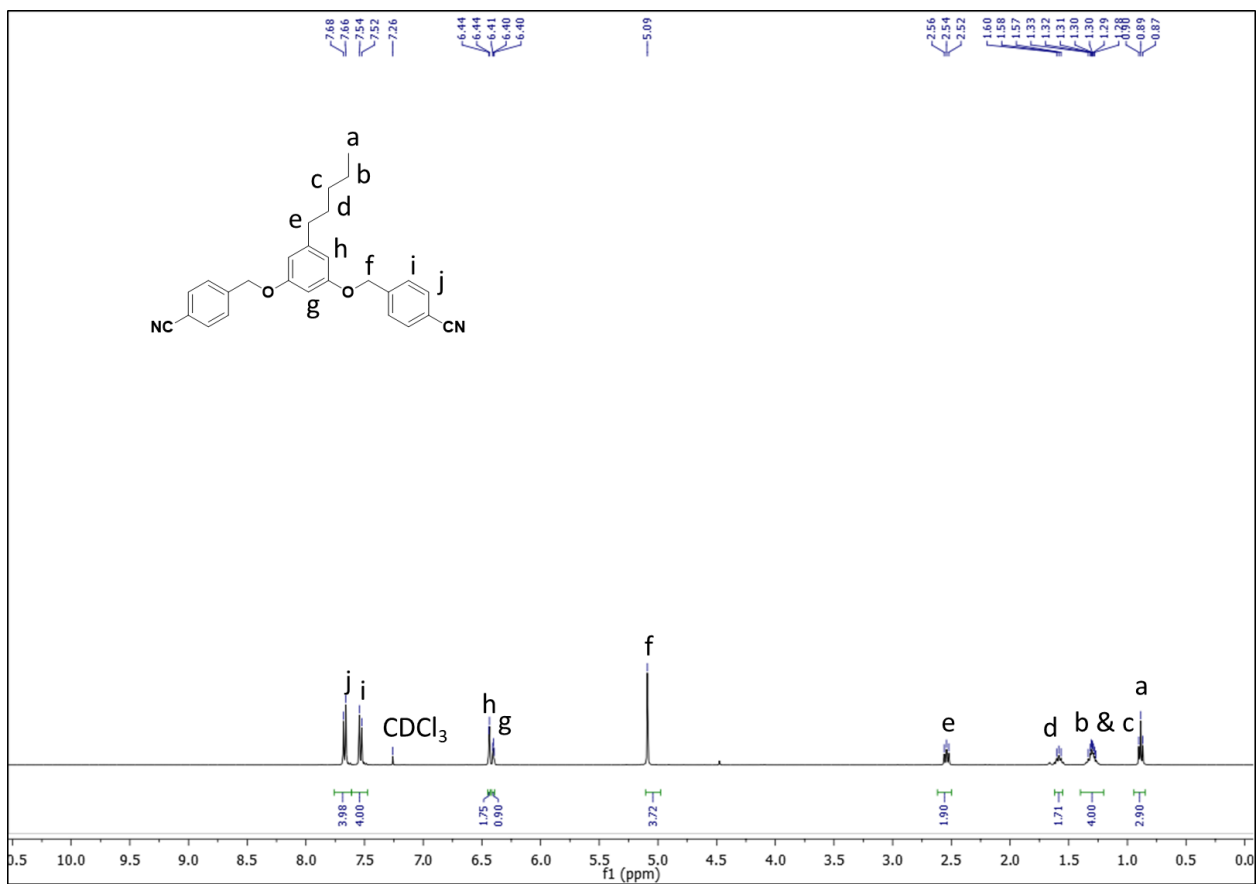
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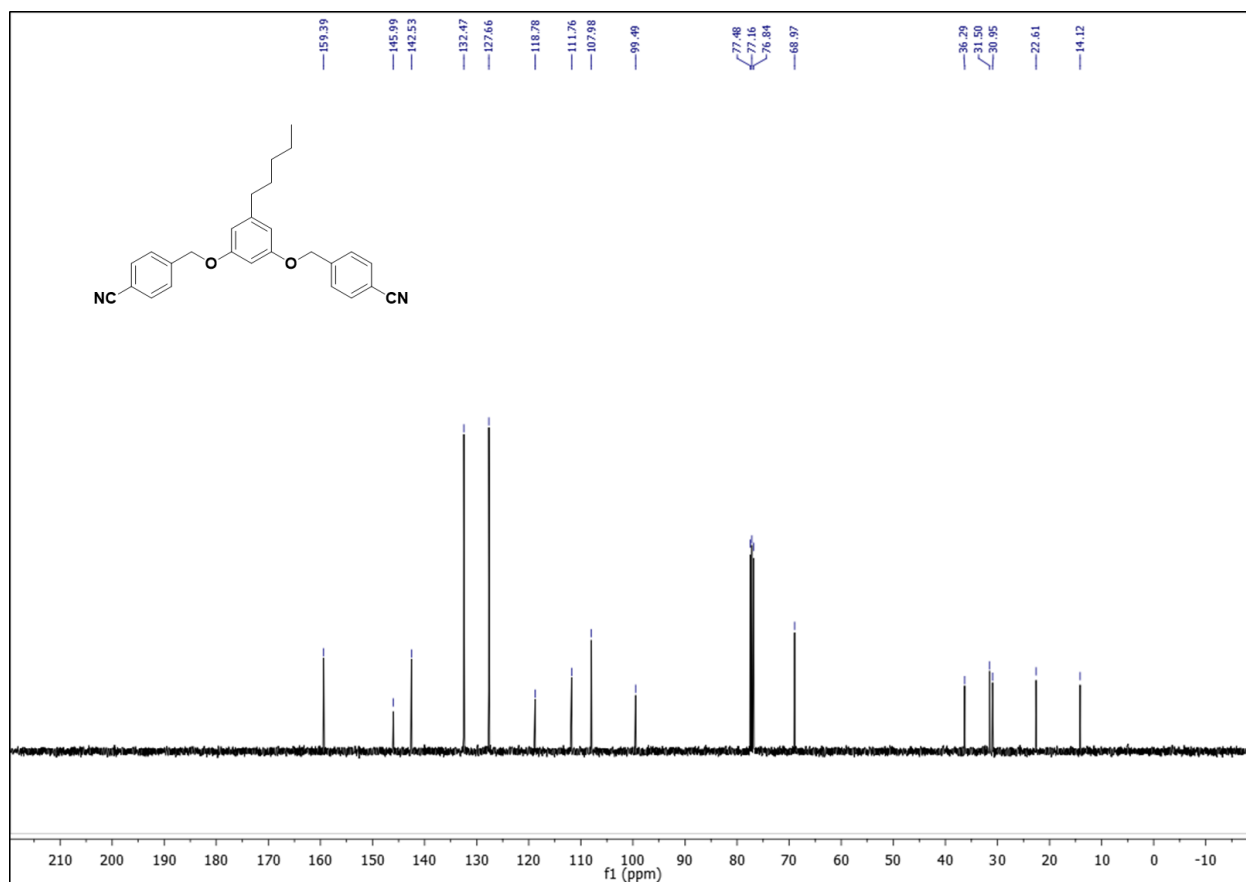
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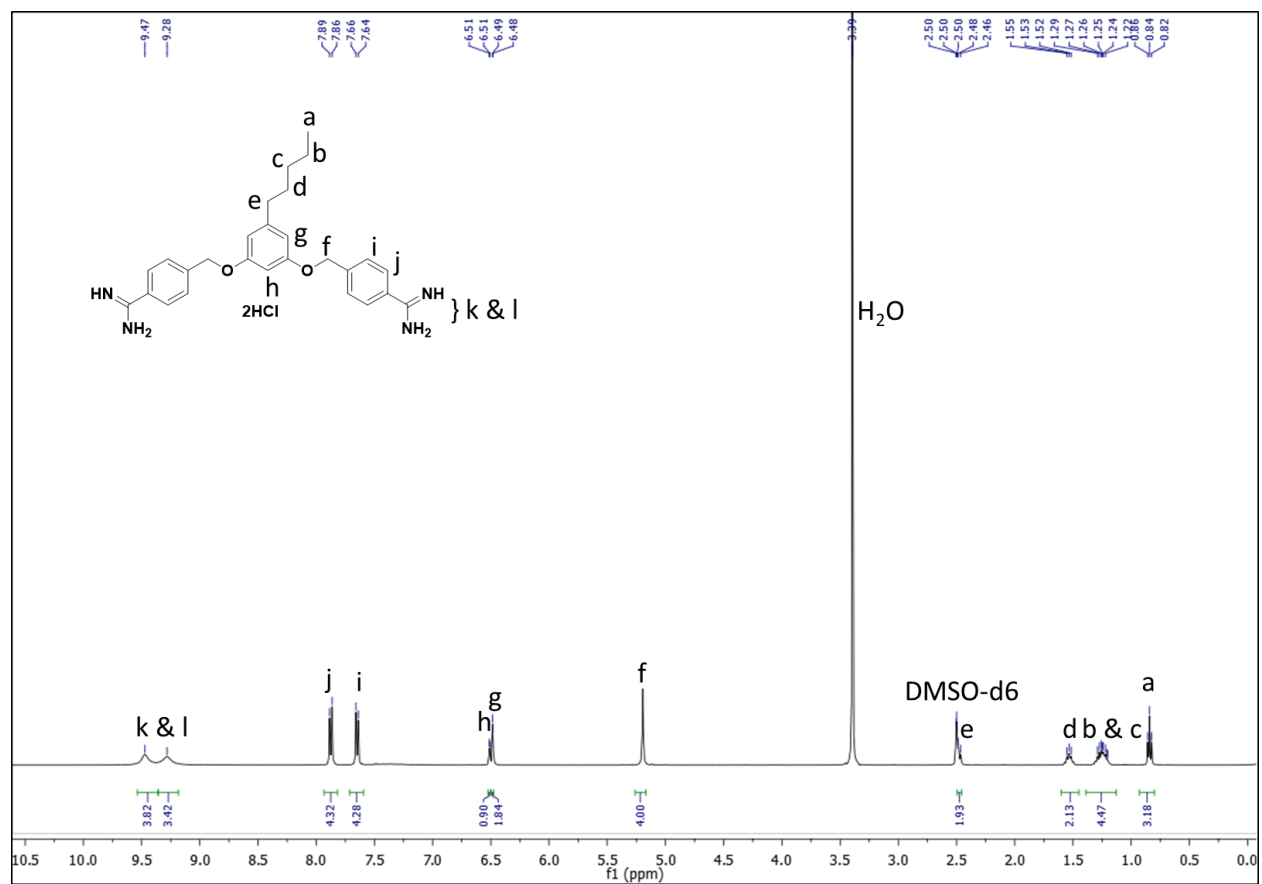
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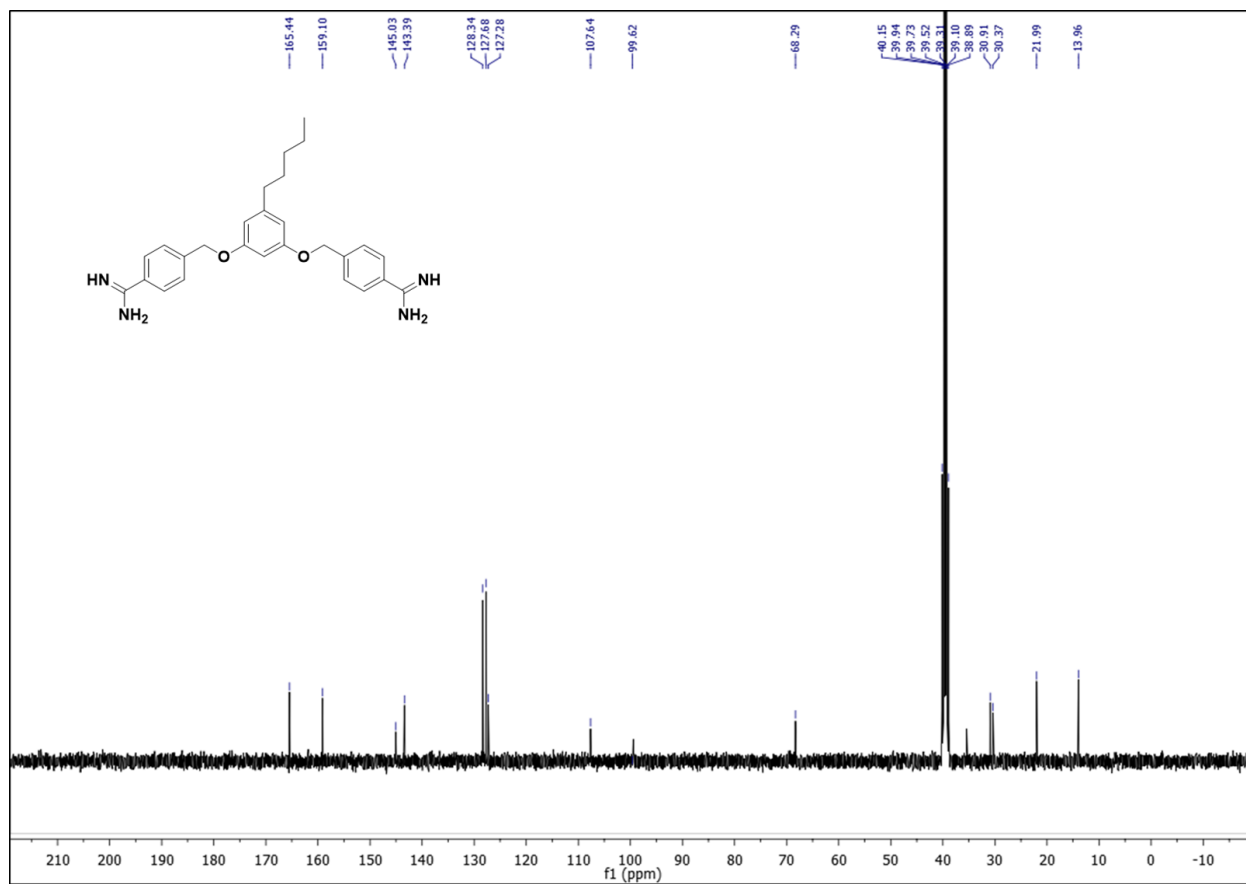
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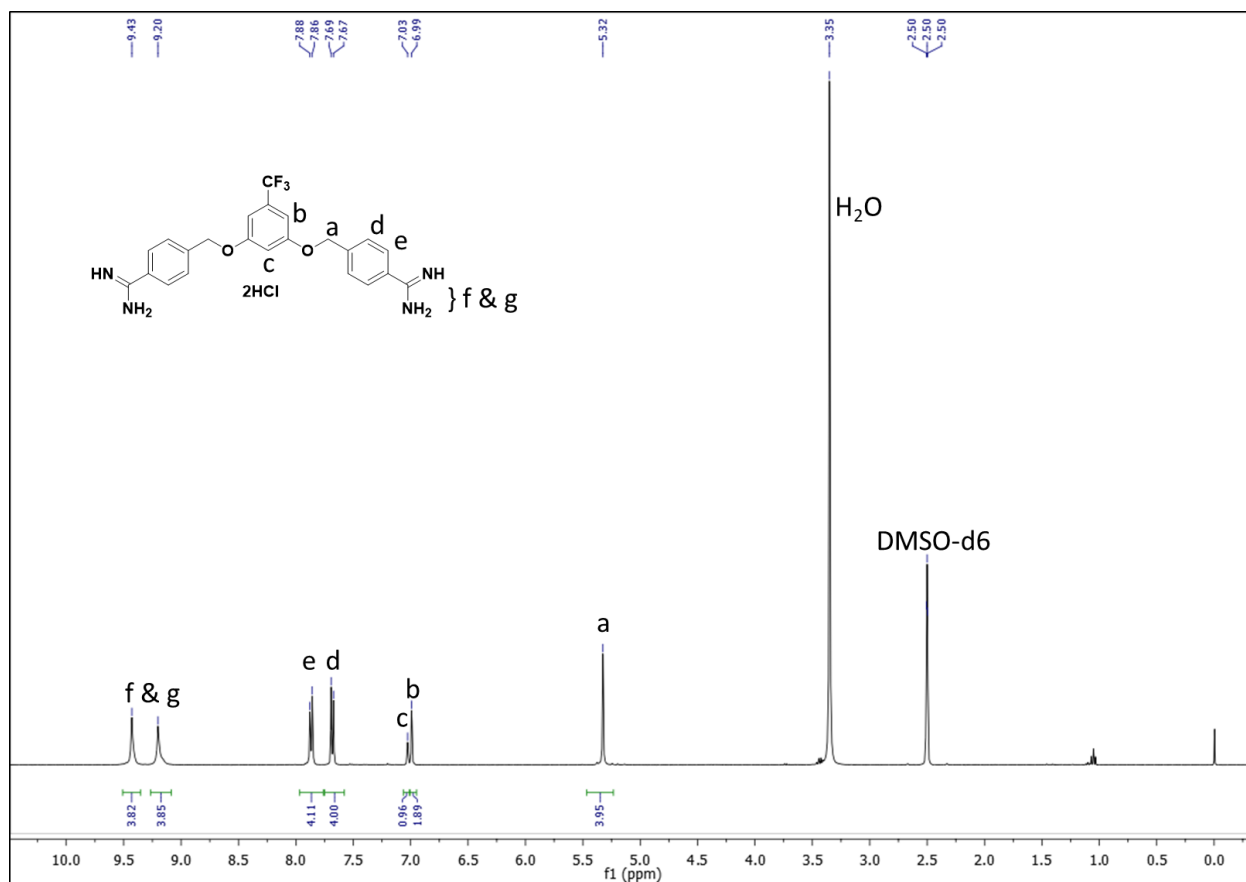
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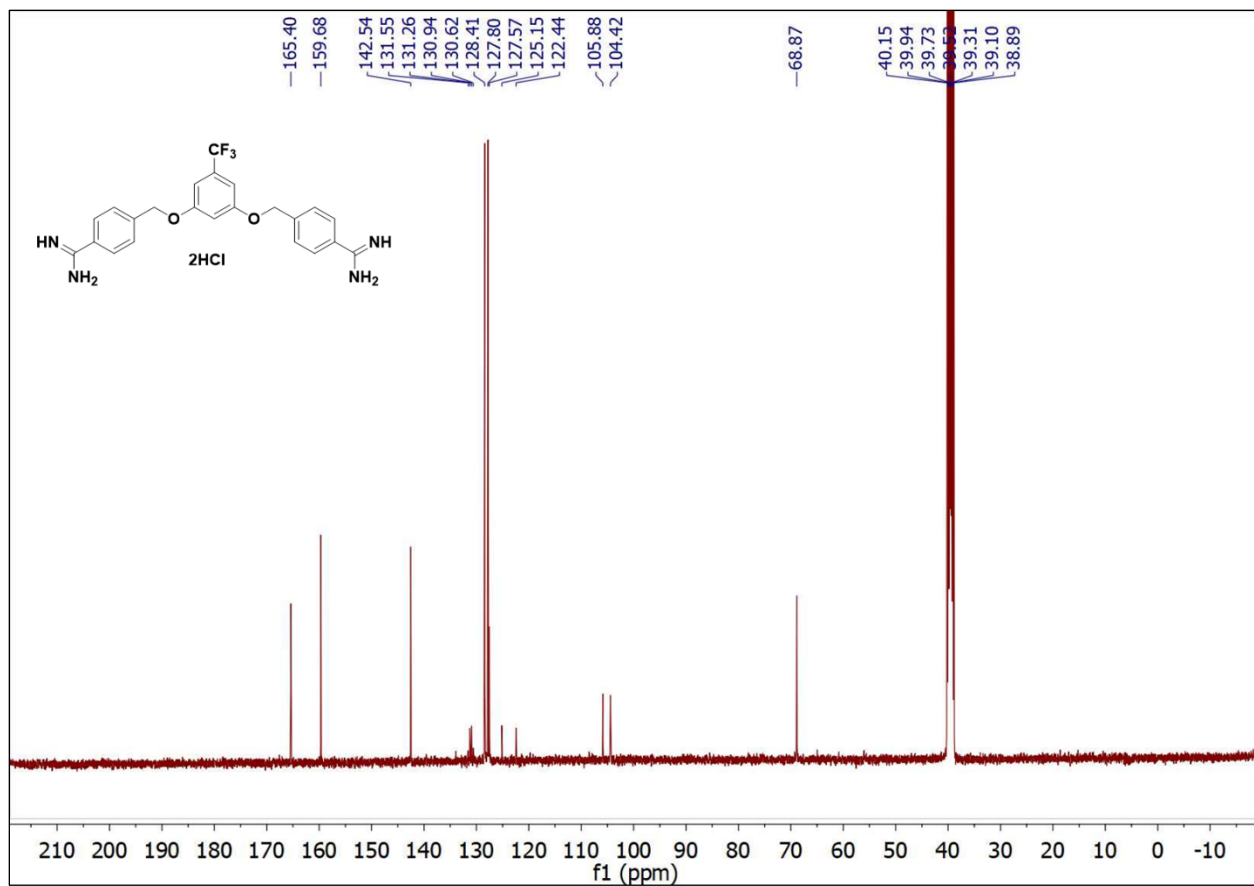
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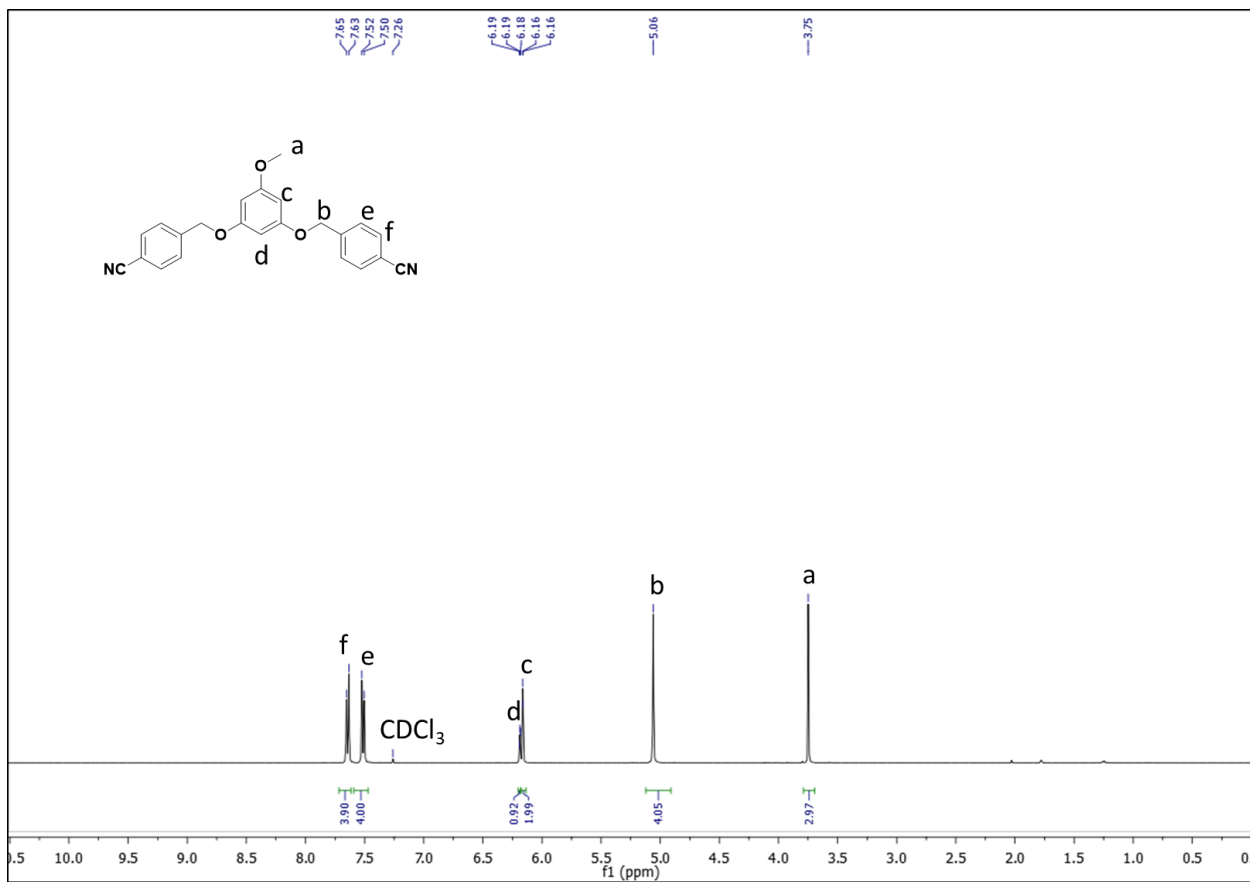
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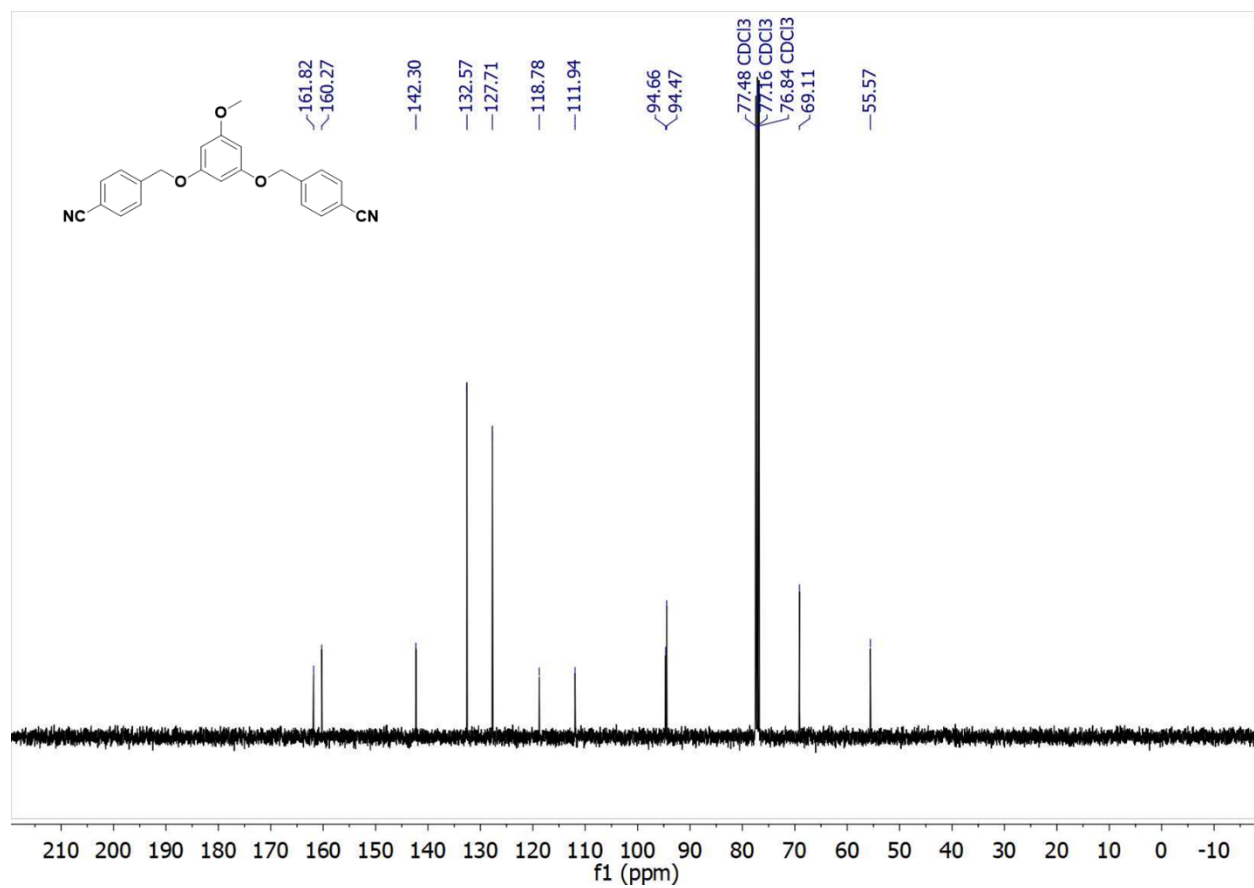
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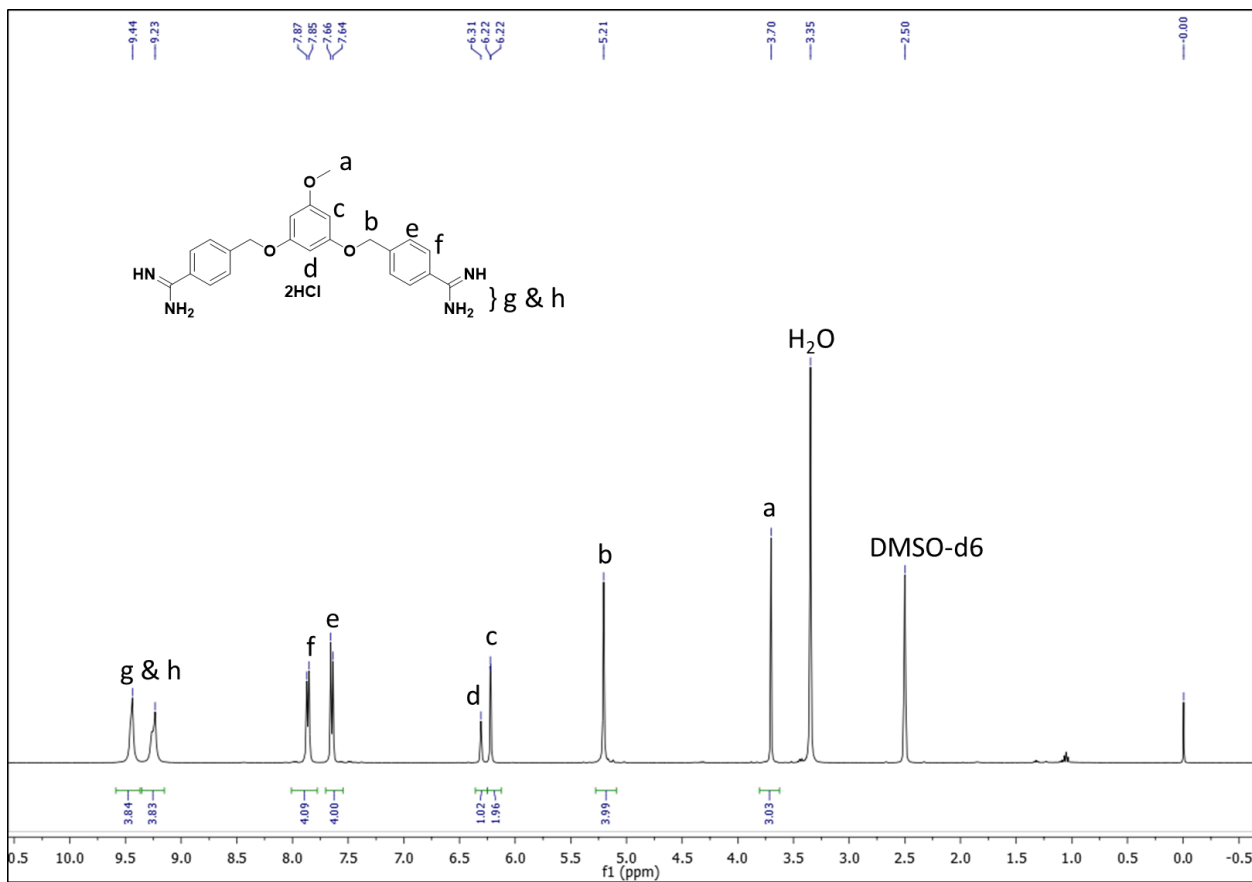
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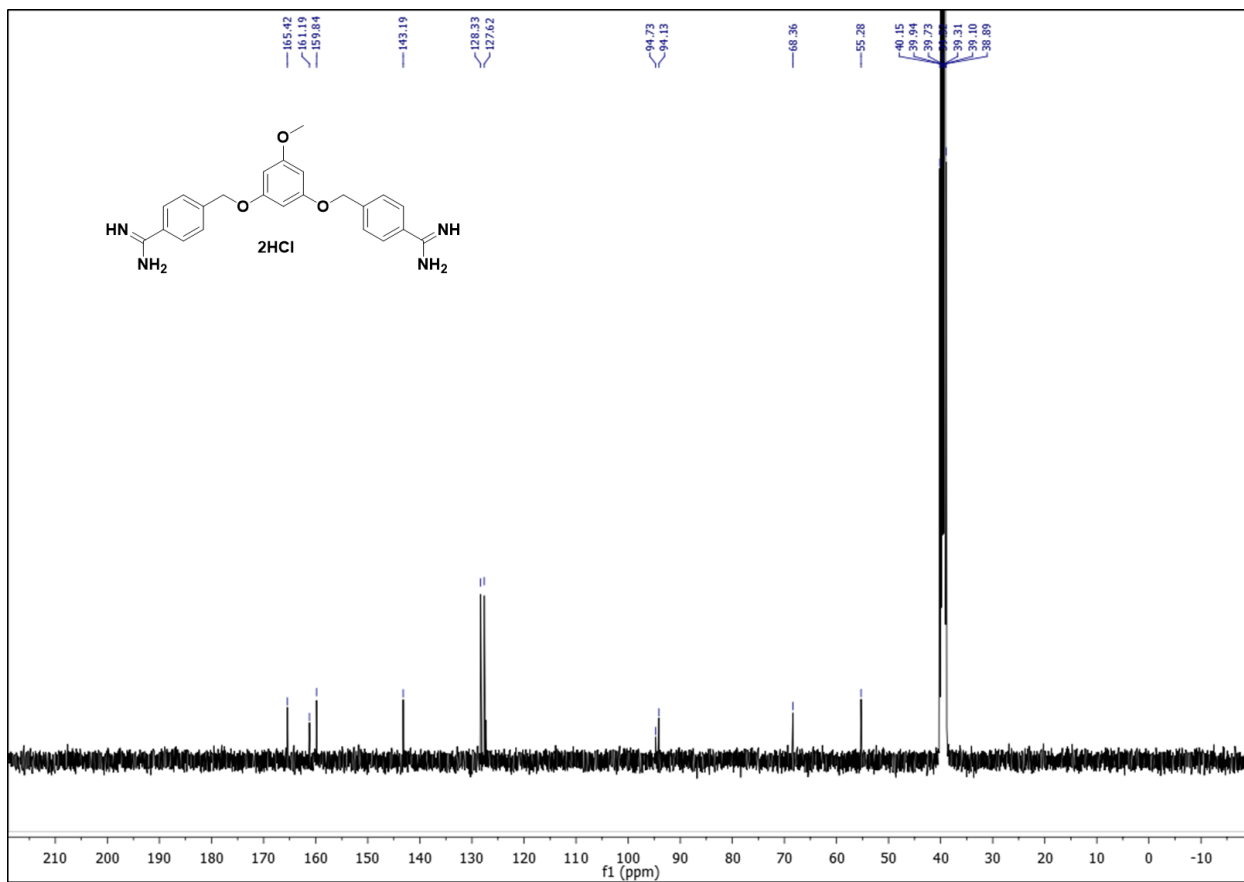
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