Mimicry of a β-Hairpin Turn by a Nonpeptidic Laterally-Flexible Foldamer

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Supporting Information

1. General Methods

1.1. Solvents and Reagents

Reagents were purchased from Sigma Aldrich (St. Louis) and used without further purification. Reactions were carried out under an argon atmosphere in oven-dried glassware. Anhydrous solvents dimethylformamide (DMF), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), dioxane, and methanol (MeOH) were purchased from Sigma Aldrich (St. Louis) and used without further purification.

1.2. Spectroscopy

^1H and ^{13}C NMR spectroscopy was carried out on a Bruker AVANCE-III-600 MHz (150 MHz carbon) spectrometer running TopSpin™ software. Chemical shifts are given in parts per million (ppm) and are referenced against tetramethylsilane (TMS) or residual solvent internal standards. Coupling constants (*J*) are given in Hertz (Hz). Multiplicity is abbreviated as follows: s = singlet, br = broad, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, q = quartet, dq = doublet of quartet, qn = quintet, sept = septet, m = multiplet. Compound names are generated following IUPAC nomenclature using ChemDraw™ Professional (CambridgeSoft). High resolution mass spectra (HRMS) were acquired on an Agilent 6224 Accurate-Mass TOF LC/MS using an atmospheric pressure chemical ionization (APCI) source or electrospray ionization (ESI) source. X-ray structural determinations were performed on a Bruker AXS SMART APEXII single crystal diffractometer equipped with an Oxford Cryosystems 700 plus cooler.

2. General Procedures

2.1. General Procedure (a) – amide coupling

Carboxylic acid (1.0 eq), diisopropylethylamine (DIPEA, 3.0 eq), and N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU, 1.1 eq) were dissolved in dimethylformamide (DMF) at approximately 0.1 M and stirred at room temperature under argon for 5 minutes. Amine (1.0 eq) is then added and the reaction is stirred 4 h at room temperature under argon. Upon completion, the mixture was poured into 100 mL ethyl acetate and washed twice with 100 mL 1 M $NaHSO_4$, three times with 75 mL 5% $NaHCO_3$, and once with 100 mL saturated NaCl. The organic layer was then dried and filtered over a $MgSO_4$/ Celite™ plug and concentrated *in vacuo*. The residue was purified by recrystallization or trituration from CH_2Cl_2/hexanes unless specified otherwise.

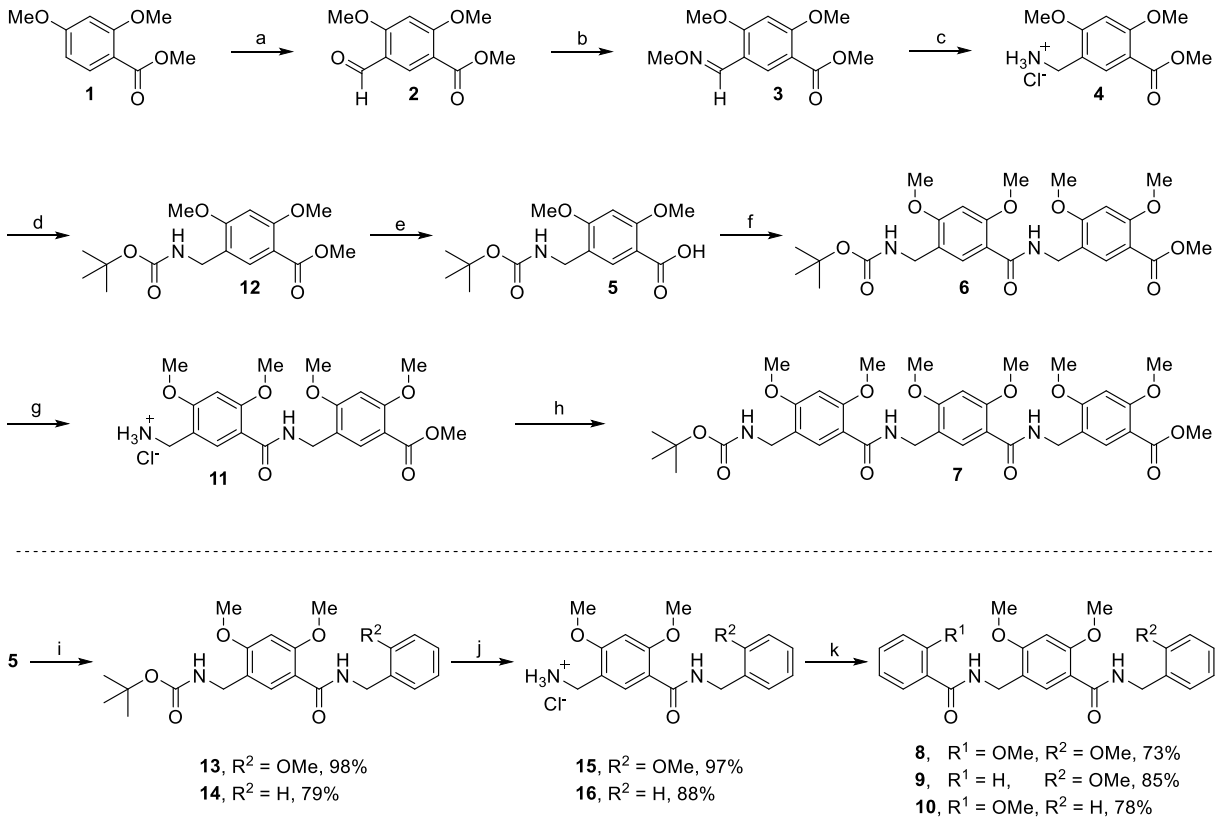
2.2. General Procedure (b) – *tert*-butylcarbamate deprotection

The *tert*-butylcarbamate (Boc) protected amine was dissolved in anhydrous dioxane at approximately 0.1 M. HCl in dioxane (4.0 M, 20 eq) was then added and the reaction stirred at

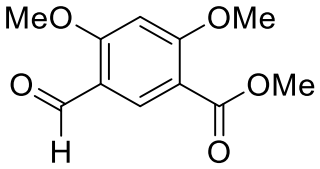
room temperature for 2 h under argon. The product was then precipitated with cold CH_2Cl_2, filtered, and washed with CH_2Cl_2 to give the analytically pure product.

3. Procedures

3.1. Synthetic Procedures



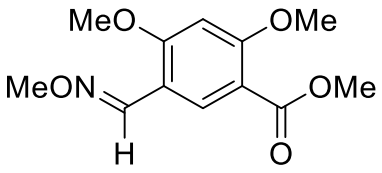
a) $CHCl_2OMe$, $TiCl_4$, CH_2Cl_2, 69%; b) $MeONH_3Cl$, pyridine, 50 °C, 97%; c) H_2, Pd/C, MeOH, HCl, 94%; d) Boc_2O, DIPEA, DMF, 90%; e) LiOH, THF, H_2O, 96%; f) **4**, HBTU, DIPEA, DMF, 80%; g) HCl, dioxane, 97%; h) **4**, HBTU, DIPEA, DMF, 73%; i) HBTU, DIPEA, DMF, 98% (**13**), 79% (**14**); j) HCl, dioxane, 97% (**15**), 88% (**16**); k) HBTU, DIPEA, DMF, (**8**) 73%, (**9**) 85%, (**10**) 78%.



methyl 5-formyl-2,4-dimethoxybenzoate (2)

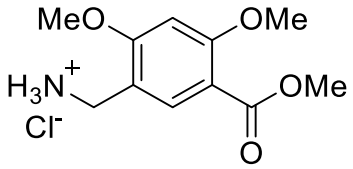
To a stirred solution of methyl 2,4-dimethoxybenzoate (9.0 g, 46 mmol) and dichloromethyl methyl ether (12.5 mL, 138 mmol) in dichloromethane (100 mL) at 0 °C was added dropwise titanium (IV) chloride (20 mL, 184 mmol) in dichloromethane (20 mL) and stirred for 2 h at 0 °C, then for 16 h at room temperature. The reaction mixture was then poured into 1 M hydrochloric acid (100 mL) containing 50 g of crushed ice and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organic layers were washed with 5% sodium bicarbonate (1 x 100 mL) and brine (1 x 100

mL) and filtered over Celite™ and magnesium sulfate. The crude product is then purified by recrystallization from dichloromethane and hexane to give the title compound **2** as a white solid (7.12 g, 69%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 10.29 (s, 1H), 8.42 (s, 1H), 6.48 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.88 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 187. 6, 165.97, 165.87, 165.0, 134.2, 117.9, 112.8, 94.9, 56.4, 55.9, 51.9. HRMS (APCI$^+$): Calcd for $C_{11}H_{13}O_5^+$ $[M+H]^+$ 225.0757, found 225.0756.



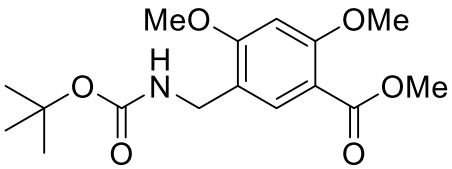
methyl 2,4-dimethoxy-5-((methoxyimino)methyl)benzoate (3)

Methyl 5-formyl-2,4-dimethoxybenzoate **2** (7.0 g, 31.2 mmol) and methoxyamine hydrochloride (3.9 g, 47 mmol) were suspended in pyridine (100 mL) and stirred at 60 °C for 1 h. The reaction mixture was then poured into ethyl acetate (150 mL) and washed with 1 M sodium bisulfate (5 x 100 mL), 5% sodium bicarbonate (2 x 100 mL), and brine (1 x 100 mL), filtered over Celite™ and magnesium sulfate, and the solvent was removed *in vacuo* to give the title compound **3** as a mixture of E and Z isomers as a white solid (7.7 g, 97%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.34-8.32 (m, 2H), 6.45 (m, 1H), 4.01-3.96 (m, 6H), 3.93-3.91 (m, 3H), 3.89-3.87 (m, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 165.6, 162.5, 161.6, 143.6, 130.6, 113.1, 112.5, 95.1, 61.9, 56.2, 55.9, 51.8. HRMS (APCI$^+$): Calcd for $C_{12}H_{16}NO_5^+$ $[M+H]^+$ 254.1023, found 254.1024.



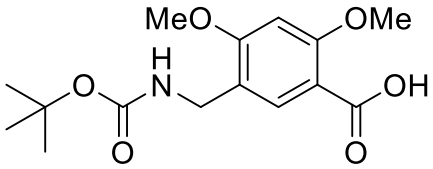
methyl 5-(aminomethyl)-2,4-dimethoxybenzoate hydrochloride (4)

Methyl 2,4-dimethoxy-5-((methoxyimino)methyl)benzoate **3** (7.7 g, 30 mmol), palladium on activated carbon (1.6 g, 10% by mass) and concentrated hydrochloric acid (12.7 mL, 12 M) were dissolved in methanol (100 mL) and placed under an atmosphere of hydrogen for 16 h. The reaction mixture was filtered over Celite™ and concentrated *in vacuo*. The resulting slurry was triturated with cold dichloromethane and the product was filtered to give the hydrochloride salt of title compound **4** as an off-white solid (7.5 g, 94%). ^{1}H-NMR (600 MHz, CD_3OD): δ 7.90 (s, 1H), 6.79 (s, 1H), 4.07 (s, 2H), 4.04 (s, 3H), 3.97 (s, 3H), 3.85 (s, 3H). ^{13}C-NMR (150 MHz, CD_3OD): δ 166.0, 162.9, 162.6, 134.4, 112.7, 111.0, 95.7, 55.69, 55.60, 51.0, 38.3. HRMS (APCI$^+$): Calcd for $C_{11}H_{13}O_4^{\bullet+}$ $[M-NH_2]^{\bullet+}$ 209.0808, found 209.0809.



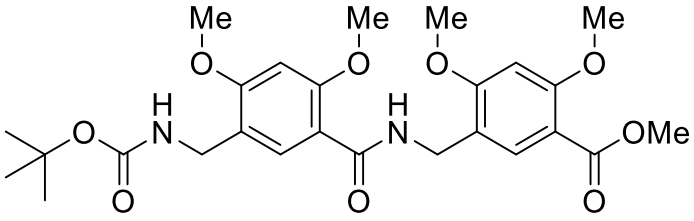
methyl 5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzoate (11)

Di-*tert*-butyl dicarbonate (1.9 mL, 8.25 mmol) was added to a solution of methyl 5-(aminomethyl)-2,4-dimethoxybenzoate hydrochloride **4** (1.8 g, 6.9 mmol) and diisopropylethylamine (6 mL, 35 mmol) in DMF (20 mL) and stirred at room temperature for 16 h. The reaction mixture was then poured into ethyl acetate (100 mL) and washed with 1 M sodium bisulfate (3 x 75 mL), 5% sodium bicarbonate (3 x 75 mL), and brine (1 x 75 mL), filtered over Celite™ and magnesium sulfate, and concentrated *in vacuo*. The product was triturated with cold hexane and dried to give the title compound **11** as a white powder (2.01 g, 90%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.82 (s, 1H), 6.46 (s, 1H), 4.92 (br, 1H), 4.26 (br, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 1.47 (s, 9H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 165.9, 161.9, 161.2, 155.8, 133.1, 118.9, 111.3, 95.3, 79.3, 56.3, 55.6, 51.7, 39.6, 28.4. HRMS (APCI$^+$): Calcd for $C_{12}H_{16}NO_6^+$ $[M\text{-}tBu+H]^+$ 270.0972, found 270.0972.



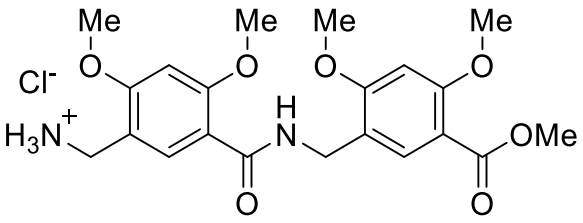
5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzoic acid (5)

An aqueous solution of lithium hydroxide (62 mL, 1M) was added to ethyl 5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzoate **11** (2.01 g, 6.18 mmol) in THF (50 mL) and stirred 6 h at room temperature. The reaction mixture was then concentrated *in vacuo* and the remaining aqueous solution was acidified with 1 M hydrochloric acid and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (1x 50 mL) and filtered over Celite™ and magnesium sulfate to give the title compound **5** as a white powder (1.85 g, 96%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 10.60 (br, 1H), 8.03 (s, 1H), 6.49 (s, 1H), 4.93 (s, 1H), 4.28 (d, 2H, J = 5.0 Hz), 4.08 (s, 3H), 3.94 (s, 3H), 1.46 (s, 9H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 165.4, 162.6, 159.4, 155.7, 133.4, 121.3, 109.5, 94.6, 79.5, 56.9, 55.9, 39.2, 28.4. HRMS (APCI$^+$): Calcd for $C_{11}H_{12}NO_6^+$ $[M\text{-}tBu+H]^+$ 256.0816, found 256.0814.



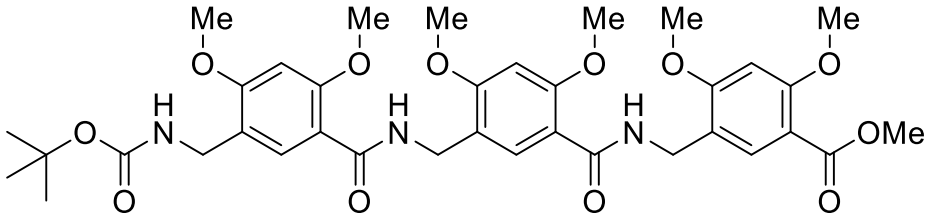
methyl 5-((5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzamido)methyl)-2,4-dimethoxybenzoate (6)

According to general procedure (a): 5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzoic acid **5** (623 mg, 2.0 mmol) and methyl 5-(aminomethyl)-2,4-dimethoxybenzoate hydrochloride **4** (575 mg, 2.2 mmol) gave the title compound **6** as an off-white solid (889 mg, 86%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.09 (br, 1H), 7.90 (s, 1H), 6.49 (s, 1H), 6.43 (s, 1H), 4.86 (br, 1H), 4.59 (d, J = 5.5 Hz, 2H), 4.29 (d, J = 4.4 Hz, 2H), 3.96 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 1.46 (s, 9H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 165.9, 164.8, 161.8, 161.1, 160.8, 158.3, 155.7, 132.8, 132.5, 119.9, 119.0, 113.8, 111.3, 95.3, 94.6, 79.2, 56.32, 56.19, 55.6, 51.7, 39.4, 38.4, 28.4. HRMS (APCI$^+$): Calcd for $C_{26}H_{35}N_2O_9^+$ $[M+H]^+$ 519.2337, found 519.2330.



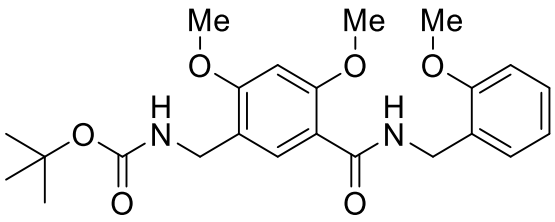
methyl 5-((5-(aminomethyl)-2,4-dimethoxybenzamido)methyl)-2,4-dimethoxybenzoate hydrochloride (12)

According to the general procedure (b): methyl 5-((5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzamido)methyl)-2,4-dimethoxybenzoate **6** (250 mg, 0.48 mmol) gave the title compound **12** as a white powder (212 mg, 97%). ^{1}H-NMR (600 MHz, d$_6$-DMSO): δ 8.46 (t, J = 6.1 Hz, 1H), 8.07 (br. s., 3H), 7.93 (s, 1H), 7.63 (s, 1H), 6.80 (s, 1H), 6.74 (s, 1H), 4.40 (d, J = 6.1 Hz, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.93 (s, 2H), 3.87 (s, 3H), 3.72 (s, 3H). ^{13}C-NMR (150 MHz, d$_6$-DMSO): δ 165.7, 164.0, 161.1, 160.7, 160.1, 159.3, 133.4, 130.7, 118.8, 113.8, 110.4, 96.3, 95.9, 56.5, 56.2, 56.1, 56.0, 51.5, 37.4, 37.1. HRMS (APCI$^+$): Calcd for $C_{21}H_{27}N_2O_7^+$ $[M+H]^+$ 419.1813, found 419.1807.



methyl 5-((5-((5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzamido)methyl)-2,4-dimethoxybenzamido)methyl)-2,4-dimethoxybenzoate (7)

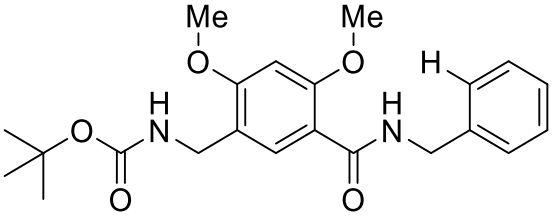
According to the general procedure (a): 5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzoic acid **5** (100 mg, 0.32 mmol) and methyl 5-((5-(aminomethyl)-2,4-dimethoxybenzamido)methyl)-2,4-dimethoxybenzoate hydrochloride **12** (146 mg, 0.32 mmol) gave the title compound **7** as an off-white solid (167 mg, 73%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.15-8.12 (m, 3H), 8.08 (s, 1H), 7.88 (s, 1H), 6.49 (s, 1H), 6.48 (s, 1H), 6.44 (s, 1H), 4.89 (br, 1H), 4.61 (d, J = 4.4 Hz, 2H), 4.58 (d, J = 5.1 Hz, 2H), 4.26 (br, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 1.46 (s, 10H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 166.0, 165.0, 161.9, 161.1, 160.89, 160.81, 158.6, 158.3, 132.9, 132.1, 119.8, 118.9, 113.67, 113.54, 111.3, 95.3, 94.76, 94.65, 56.33, 56.23, 55.72, 55.63, 51.7, 38.5, 38.3, 28.5. HRMS (APCI$^+$): Calcd for $C_{36}H_{46}N_3O_{12}^+$ $[M+H]^+$ 712.3076, found 712.3071.



tert-butyl (2,4-dimethoxy-5-((2-methoxybenzyl)carbamoyl)benzyl)carbamate (13)

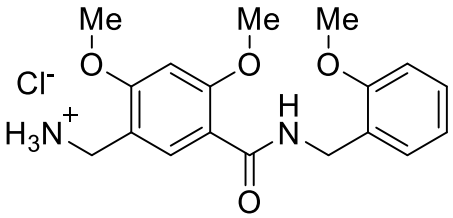
According to the general procedure (a): 5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzoic acid **5** (300 mg, 0.96 mmol) and 2-methoxybenzylamine (138 μL, 1.06 mmol) gave the title compound

13 as an off-white solid (409 mg, 99%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.23 (br. t, J = 5.2 Hz, 1H), 8.13 (s, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.28 - 7.25 (m, 1H), 6.94 (t, J = 7.4 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.44 (s, 1H), 4.85 (br. s., 1H), 4.68 (d, J = 5.7 Hz, 2H), 4.30 (br. s., 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 1.47 (s, 9H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 164.8, 160.7, 158.4, 157.5, 155.7, 132.6, 129.3, 128.5, 127.1, 120.7, 119.9, 113.9, 110.2, 94.6, 79.2, 56.2, 55.6, 55.3, 39.3, 28.4. HRMS (APCI$^+$): Calcd for $C_{23}H_{31}N_2O_6^+$ $[M+H]^+$ 431.2177, found 431.2170.



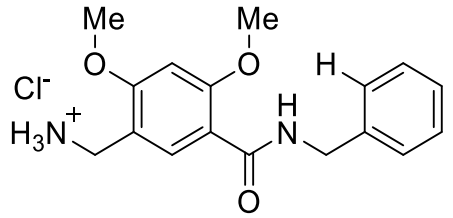
tert-butyl (5-(benzylcarbamoyl)-2,4-dimethoxybenzyl)carbamate (14)

According to the general procedure (a): 5-(((tert-butoxycarbonyl)amino)methyl)-2,4-dimethoxybenzoic acid **5** (100 mg, 0.32 mmol) and benzylamine (39 µL, 0.38 mmol) gave the title compound **14** as an off-white solid (101 mg, 79%).^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.06 (t, J = 5.0 Hz, 1H), 7.39 - 7.26 (m, 5H), 6.45 (s, 1H), 4.88 (br. s., 1H), 4.69 (d, J = 5.7 Hz, 2H), 4.31 (br. s., 1H), 3.96 (s, 3H), 3.91 (s, 3H), 1.47 (s, 9H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 165.1, 160.9, 158.4, 155.7, 139.0, 132.6, 128.6, 127.5, 127.2, 120.0, 113.5, 94.6, 79.3, 56.2, 55.6, 43.7, 39.4, 28.4. HRMS (APCI$^+$): Calcd for $C_{22}H_{29}N_2O_5^+$ $[M+H]^+$ 401.2071, found 401.2067.



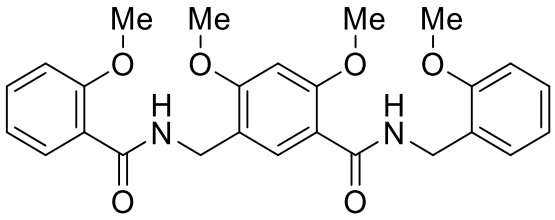
5-(aminomethyl)-2,4-dimethoxy-N-(2-methoxybenzyl)benzamide hydrochloride (15)

According to the general procedure (b): tert-butyl (2,4-dimethoxy-5-((2-methoxybenzyl)carbamoyl)benzyl)carbamate **13** (400 mg, 0.93 mmol) gave the title compound **15** as an off-white solid (330 mg, 97%). ^{1}H-NMR (600 MHz, d_6-DMSO): δ 8.49 (m, J = 6.1 Hz, 1H), 8.14 - 8.01 (m, 3H), 7.96 (s, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.80 (s, 1H), 4.48 (d, J = 6.1 Hz, 2H), 4.02 (s, 3H), 3.96 - 3.91 (m, 5H), 3.87 (s, 3H). ^{13}C-NMR (150 MHz, d_6-DMSO): δ 164.4, 161.2, 159.9, 157.2, 134.0, 128.5, 128.0, 127.4, 120.6, 114.3, 114.2, 110.9, 96.4, 57.0, 56.7, 55.8, 38.8, 37.5. HRMS (APCI$^+$): Calcd for $C_{18}H_{23}N_2O_4^+$ $[M+H]^+$ 331.1652, found 331.1649.



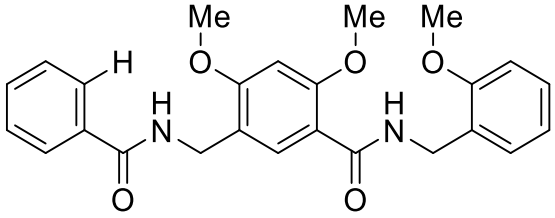
5-(aminomethyl)-N-benzyl-2,4-dimethoxybenzamide hydrochloride (16)

According to the general procedure (b): tert-butyl (5-(benzylcarbamoyl)-2,4-dimethoxybenzyl)carbamate **14** (100 mg, 0.25 mmol) gave the title compound **16** as an off-white powder (69 mg, 88%). ^{1}H-NMR (600 MHz, d_6-DMSO): δ 8.59 (t, J = 6.0 Hz, 1H), 8.09 (br. s, 3H), 7.94 (s, 1H), 7.36 - 7.21 (m, 5H), 6.79 (s, 1H), 4.52 (d, J = 6.1 Hz, 2H), 4.00 (s, 3H), 3.96 - 3.91 (m, 5H). ^{13}C-NMR (150 MHz, d_6-DMSO): δ 164.7, 161.1, 159.9, 140.4, 133.9, 128.7, 127.5, 127.1, 114.4, 114.2, 96.3, 56.9, 56.7, 43.0, 37.5. HRMS (APCI$^+$): Calcd for $C_{17}H_{21}N_2O_3^+$ $[M+H]^+$ 301.1547, found 301.1558.



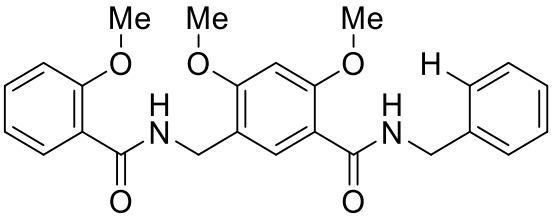
2,4-dimethoxy-5-((2-methoxybenzamido)methyl)-N-(2-methoxybenzyl)benzamide (8)

According to general procedure (a): 5-(aminomethyl)-2,4-dimethoxy-N-(2-methoxybenzyl)benzamide hydrochloride **15** (200 mg, 0.55 mmol) and 2-methoxybenzoic acid (83 mg, 0.55 mmol) gave the title compound **8** as a white powder (185 mg, 73%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.28 - 8.17 (m, 4H), 7.42 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 7.3 Hz, 1H), 7.28 - 7.25 (m, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.48 (s, 1H), 4.69 - 4.64 (m, 4H), 3.96 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 165.1, 164.9, 160.8, 158.3, 157.6, 157.5, 132.6, 132.4, 132.3, 129.3, 128.5, 127.0, 121.8, 121.2, 120.7, 119.7, 113.9, 111.3, 110.2, 94.7, 56.2, 56.1, 55.7, 55.3, 39.3, 38.4. HRMS (APCI$^+$): Calcd for $C_{26}H_{29}N_2O_6^+$ $[M+H]^+$ 465.2020, found 465.2020.



5-(benzamidomethyl)-2,4-dimethoxy-N-(2-methoxybenzyl)benzamide (9)

According to general procedure (a): 5-(aminomethyl)-2,4-dimethoxy-N-(2-methoxybenzyl)benzamide hydrochloride **15** (100 mg, 0.27 mmol) and benzoic acid (33.3 mg, 0.27 mmol) gave the title compound **9** as a white powder (101 mg, 85%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.24 - 8.19 (m, 2H), 7.75 (d, J = 7.0 Hz, 2H), 7.49 - 7.44 (m, 1H), 7.43 - 7.38 (m, 2H), 7.33 (dd, J = 1.6, 7.4 Hz, 1H), 7.28 - 7.23 (m, 1H), 6.95 - 6.87 (m, 2H), 6.46 (s, 1H), 6.39 (br. s., 1H), 4.65 (d, J = 5.7 Hz, 2H), 4.62 (d, J = 5.1 Hz, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 167.3, 164.9, 160.9, 158.5, 157.5, 134.7, 133.1, 131.2, 129.3, 128.5, 128.5, 127.0, 126.9, 120.7, 119.0, 113.8, 110.2, 94.7, 56.2, 55.7, 55.3, 39.3, 38.9. HRMS (APCI$^+$): Calcd for $C_{25}H_{27}N_2O_5^+$ $[M+H]^+$ 435.1914, found 435.1920.



N-benzyl-2,4-dimethoxy-5-((2-methoxybenzamido)methyl)benzamide (10)

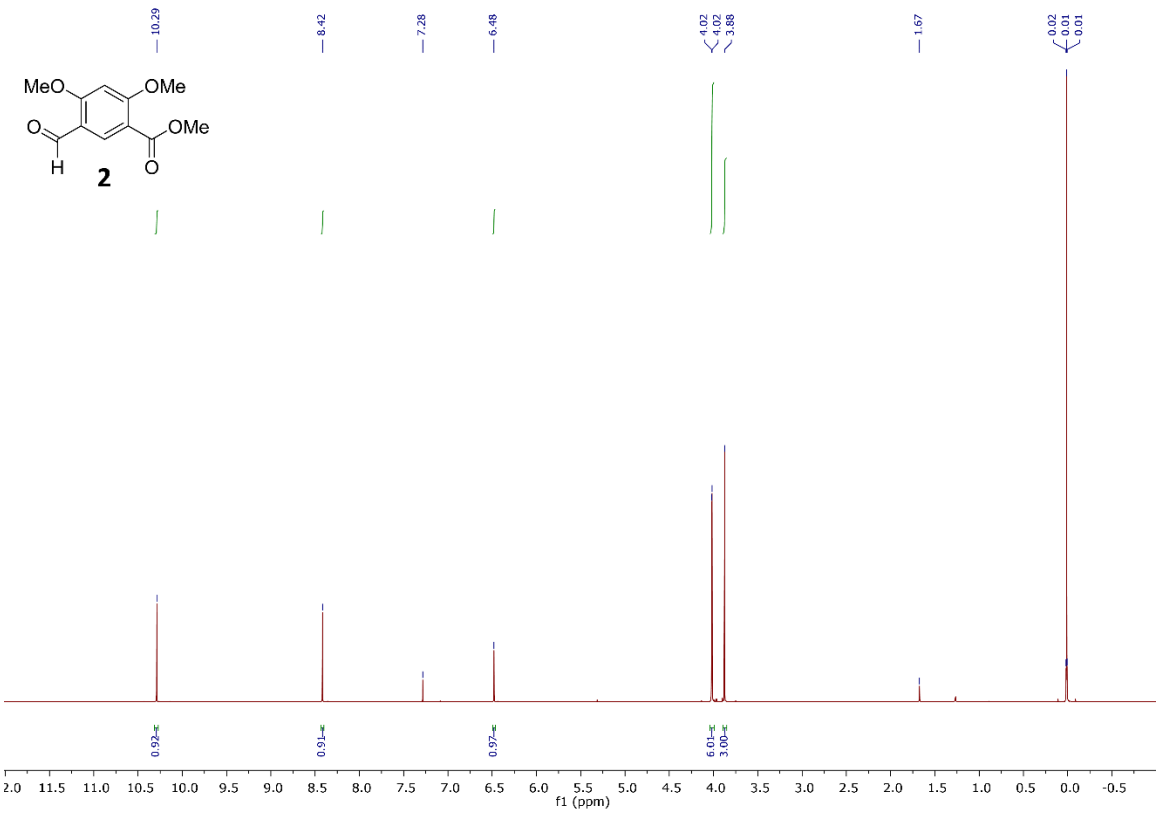
According to general procedure (a): 5-(aminomethyl)-N-benzyl-2,4-dimethoxybenzamide hydrochloride **16** (65 mg, 0.19 mmol) and 2-methoxybenzoic acid (29.4 mg, 0.19 mmol) gave the title compound **10** as a white powder (65 mg, 78%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.29 - 8.22 (m, 3H), 8.03 (t, J = 5.0 Hz, 1H), 7.45 - 7.40 (m, 1H), 7.37 - 7.31 (m, 5H), 7.09 - 7.04 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.47 (s, 1H), 4.68 - 4.64 (m, 4H), 3.98 (s, 3H), 3.93 (s, 3H), 3.93 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 165.2, 165.1, 160.9, 158.3, 157.6, 139.0, 132.6, 132.4, 132.3, 128.6, 127.5, 127.2, 121.8, 121.2, 119.9, 113.6, 111.3, 94.6, 56.2, 56.1, 55.7, 43.7, 38.4. HRMS (APCI$^+$): Calcd for $C_{25}H_{27}N_2O_5^+$ $[M+H]^+$ 435.1914, found 435.1914.

3.2. NMR Solvent Polarity Procedure

Stock solutions of 10 mM **8**, **9**, or **10** were prepared in $CDCl_3$ and d_6-DMSO and mixed to give samples of solvent ratio 0.2, 0.4, 0.5, 0.6, 0.8 and 1.0. NMR spectra were recorded and the chemical shift of amide protons were plotted as a function of solvent ratio.

4. NMR Spectra

4.1. 1D NMR Spectra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6.48
4.02
4.02
3.88
1.67
0.02
0.01
0.01
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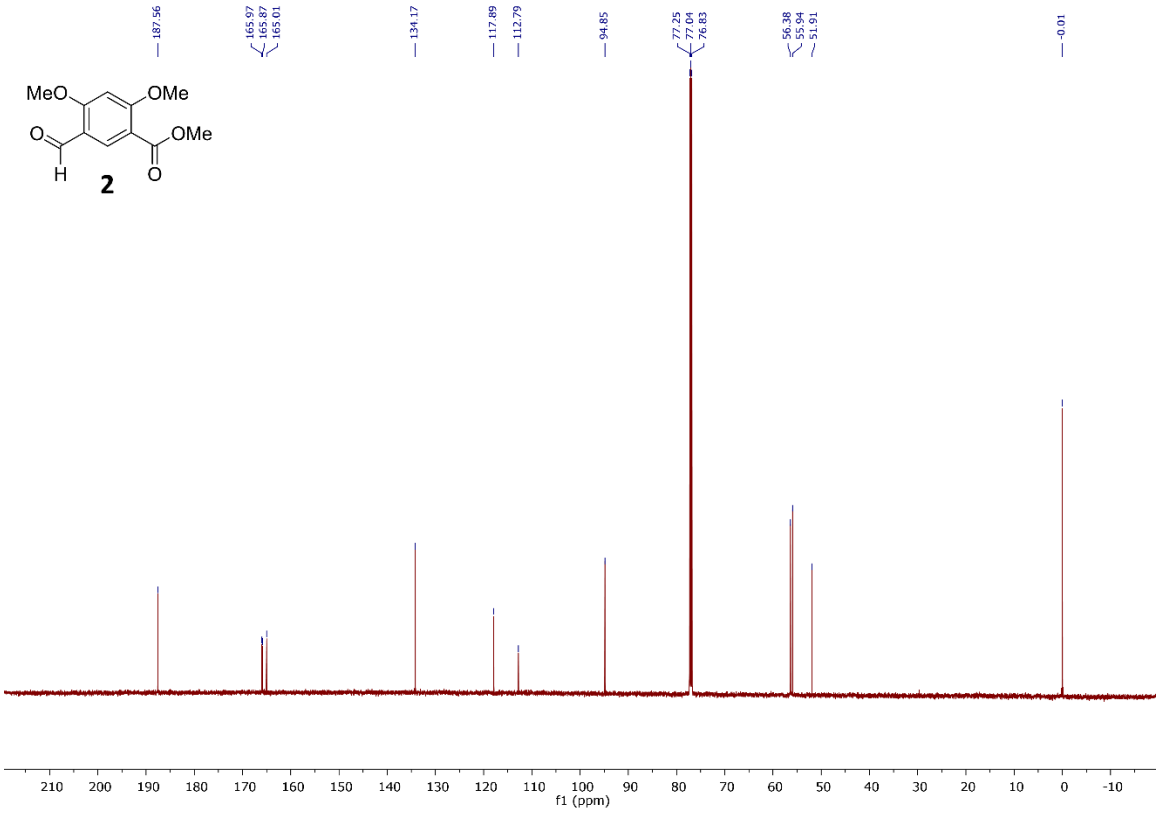
OMe
O
OMe
H
O
2
0.92
0.91
0.97
6.01
3.00
f1 (ppm)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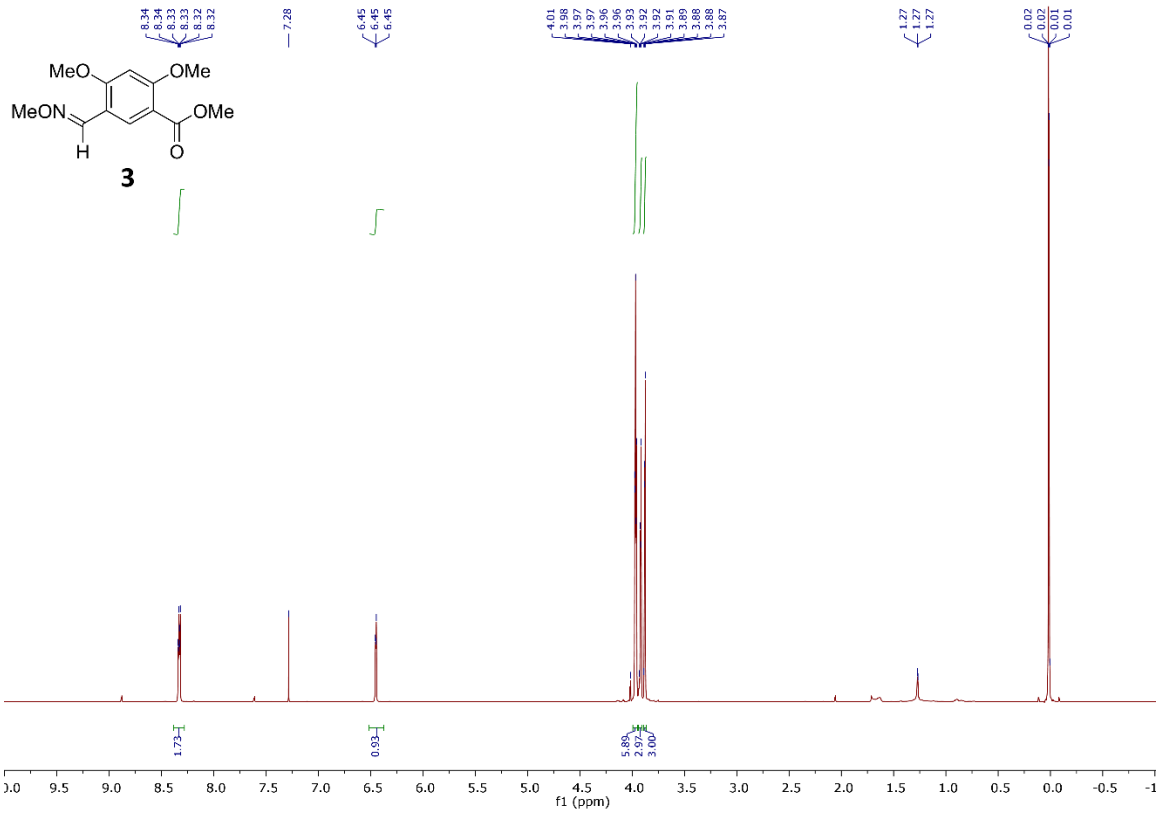
165.97
165.87
165.01
134.17
117.89
112.79
94.85
77.25
77.04
76.83
56.38
55.94
51.91
-0.01
MeO
OMe
O
OMe
H
O
2
f1 (ppm)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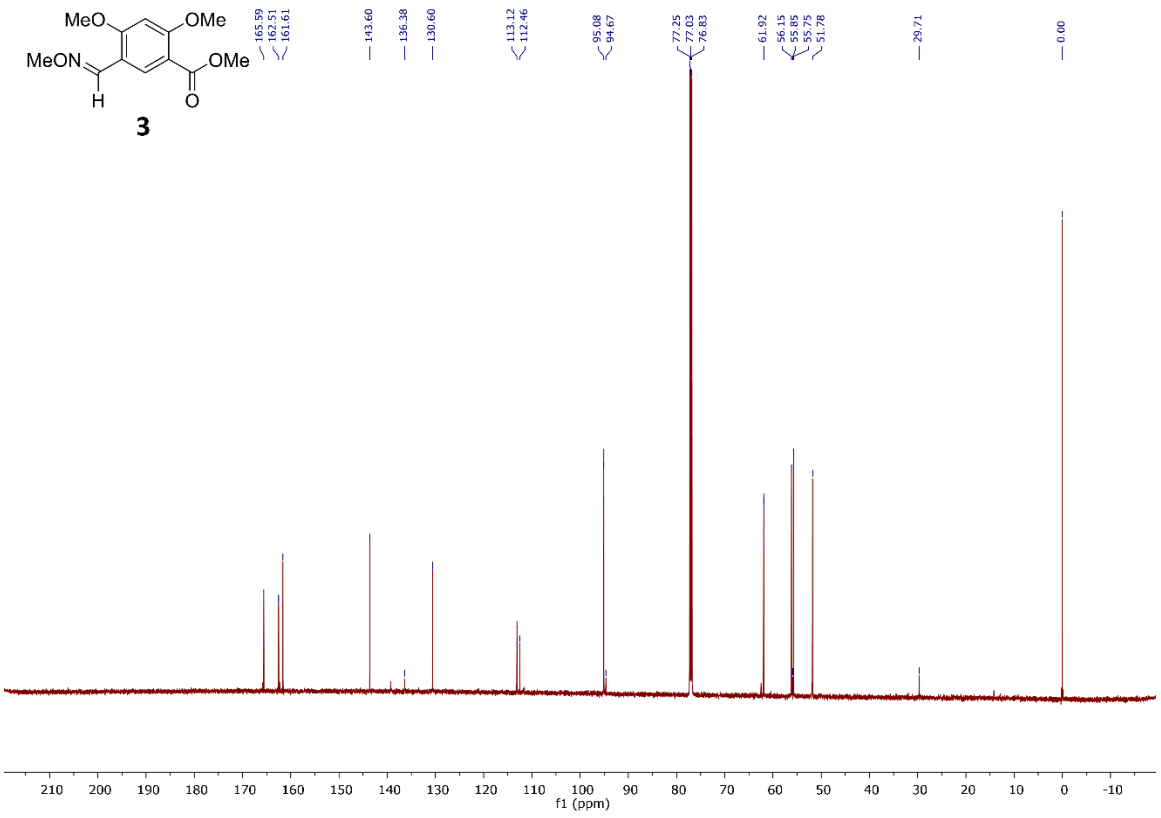
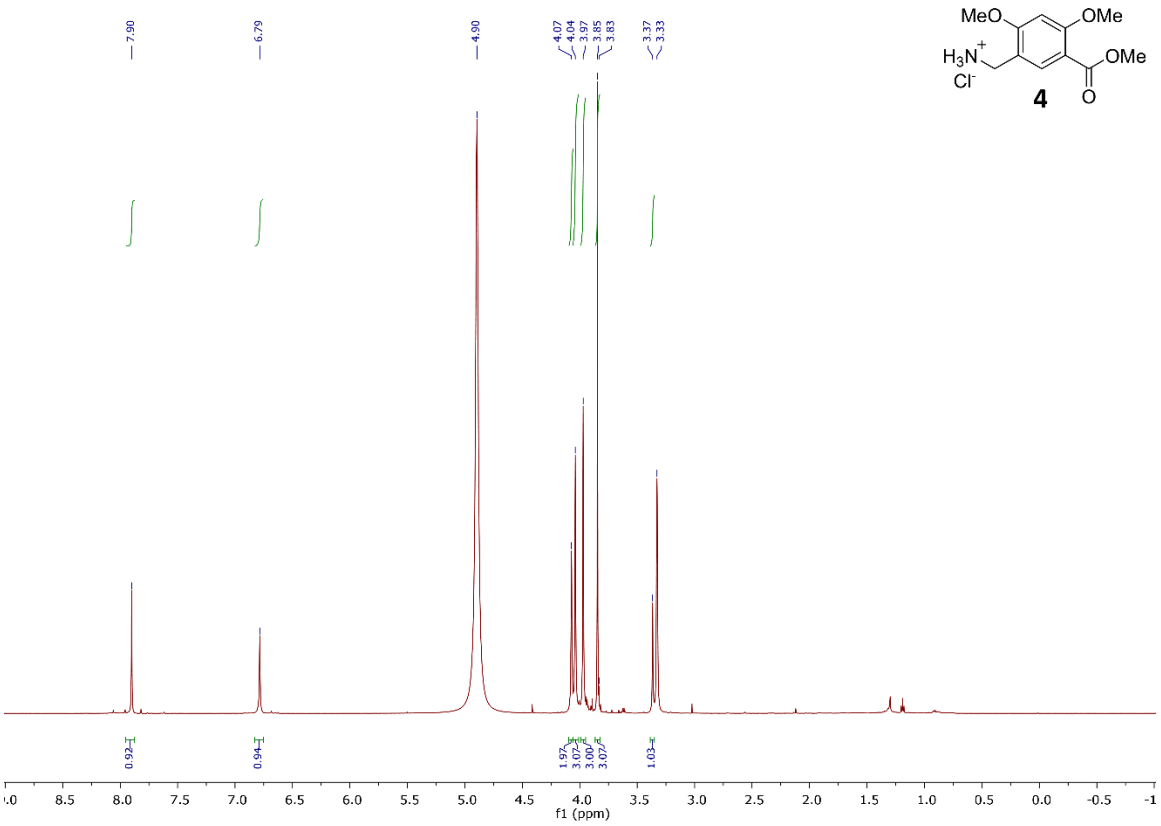
OMe
MeON
OMe
H
O
3
8.34
8.34
8.33
8.33
8.32
8.32
7.28
6.45
6.45
6.45
4.01
3.98
3.97
3.97
3.96
3.96
3.93
3.92
3.91
3.91
3.89
3.88
3.88
3.87
1.27
1.27
1.27
0.02
0.02
0.01
0.01
1.73
0.93
5.89
2.97
3.00
f1 (ppm)


MeO
OMe
MeON
OMe
H
O
3
165.59
162.51
161.61
143.60
136.38
130.60
113.12
112.46
95.08
94.67
77.25
77.03
76.83
61.92
56.15
55.85
55.75
51.78
29.71
0.00
f1 (ppm)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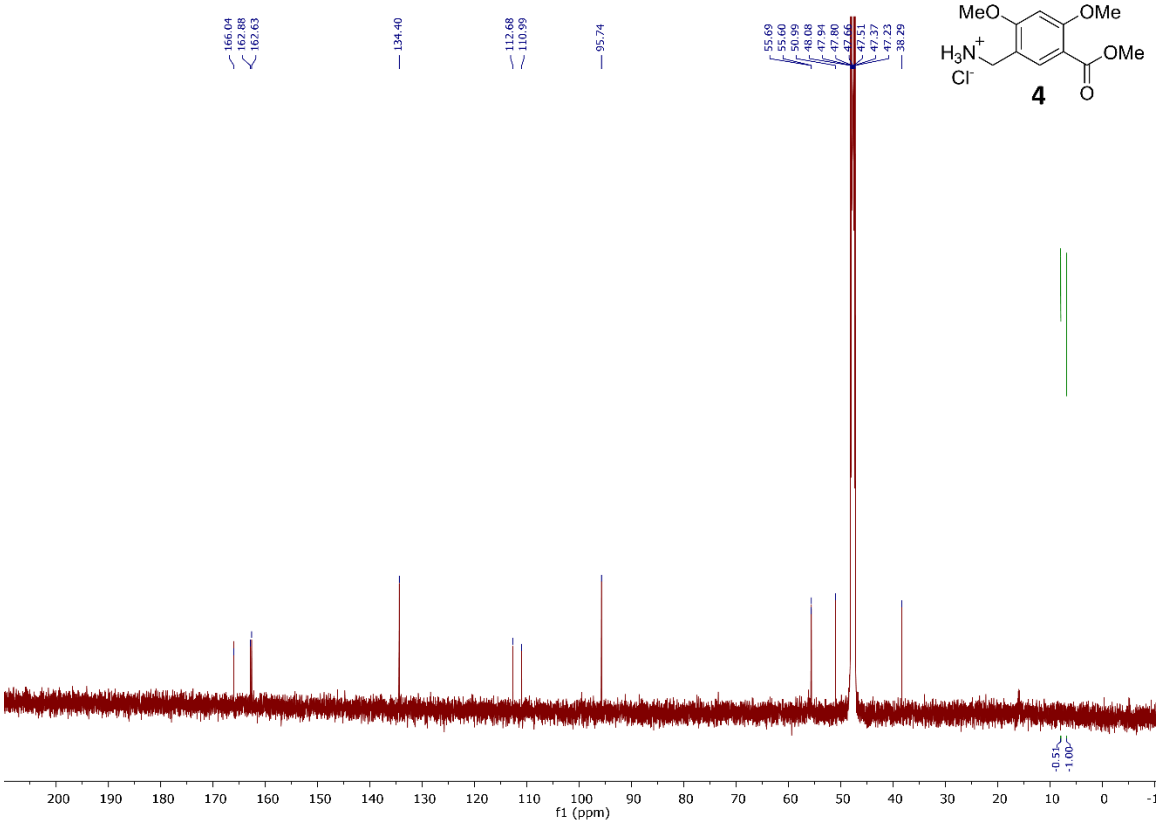
6.79
4.90
4.07
4.04
3.97
3.85
3.83
3.37
3.33
0.92
0.94
1.97
3.07
3.00
3.07
1.03
f1 (ppm)
MeO
OMe
H3N+
Cl-
OMe
O
4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112.68
110.99
95.74
55.69
55.60
50.99
48.08
47.94
47.80
47.66
47.51
47.37
47.23
38.29
0.51
1.00
f1 (ppm)
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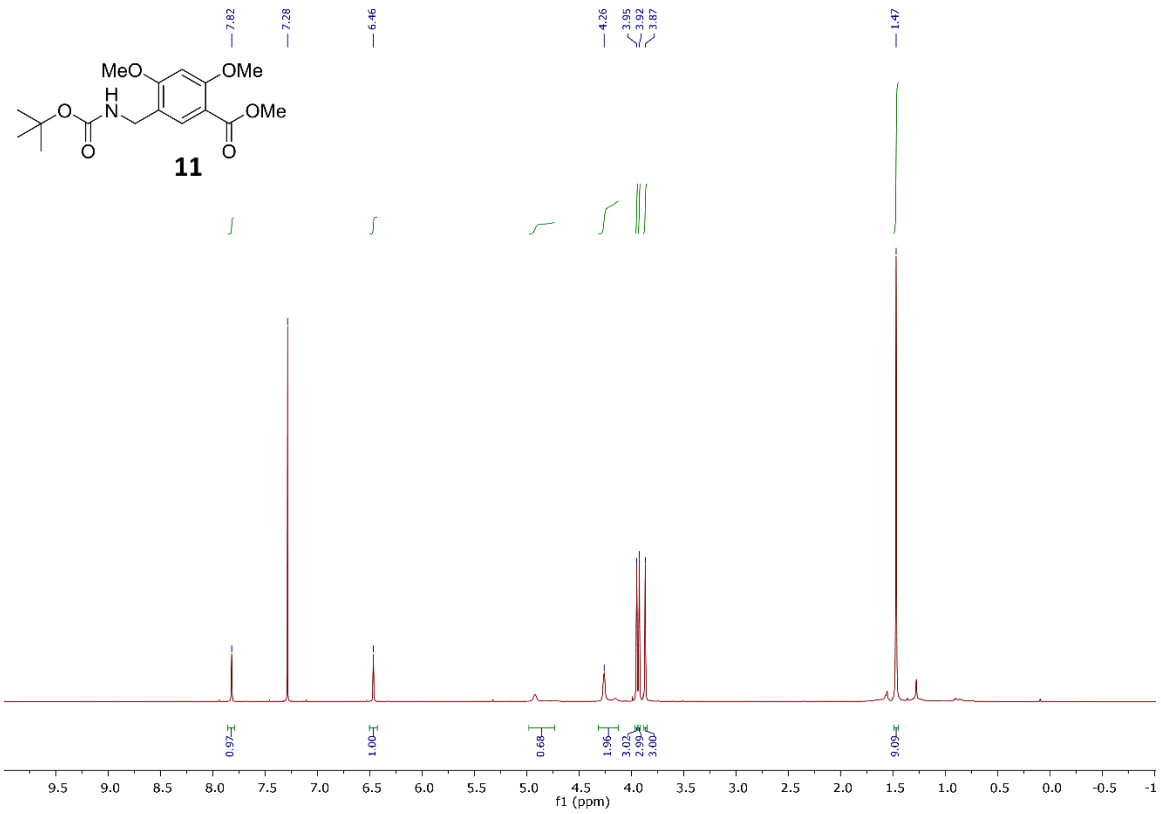
OMe
H3N+
Cl-
OMe
O
4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7.28
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4.26
3.95
3.92
3.87
1.47
MeO
OMe
OMe
H
N
O
O
O
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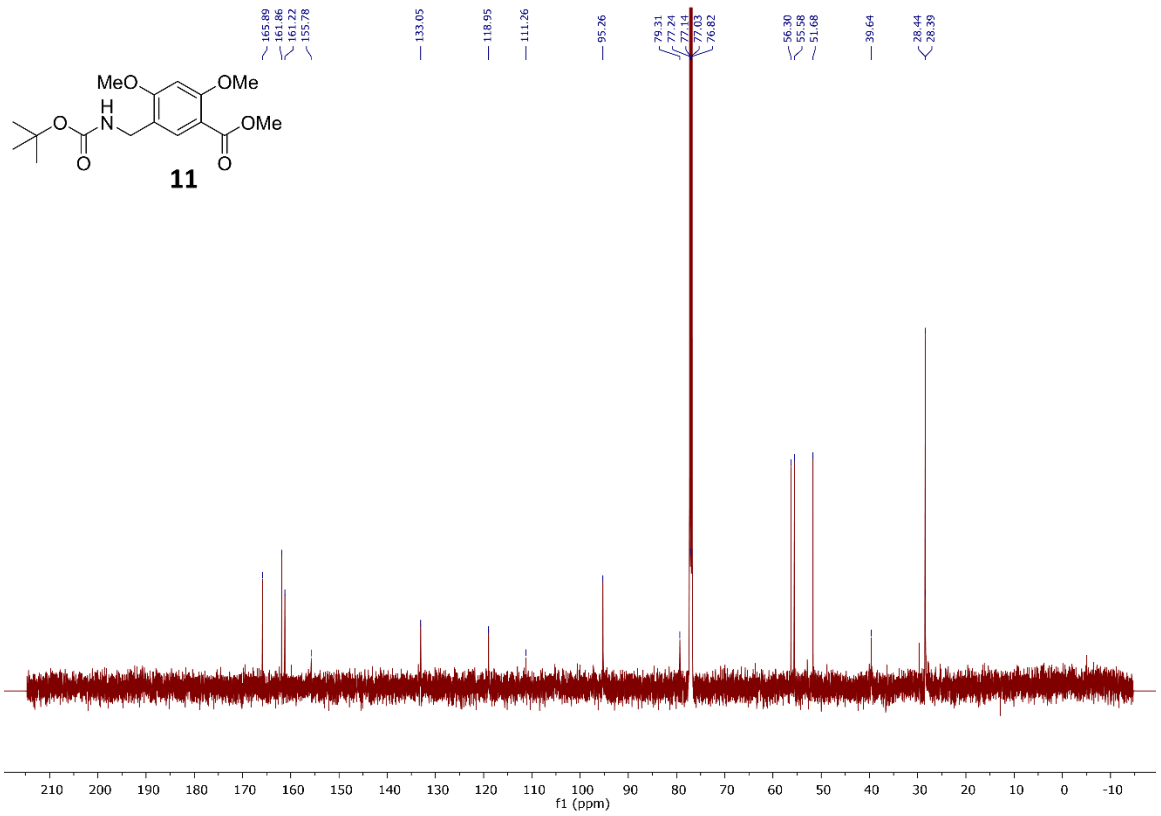
0.97
1.00
0.68
1.96
3.02
2.99
3.00
9.09
f1 (ppm)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118.95
111.26
95.26
79.31
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77.14
77.03
76.82
56.30
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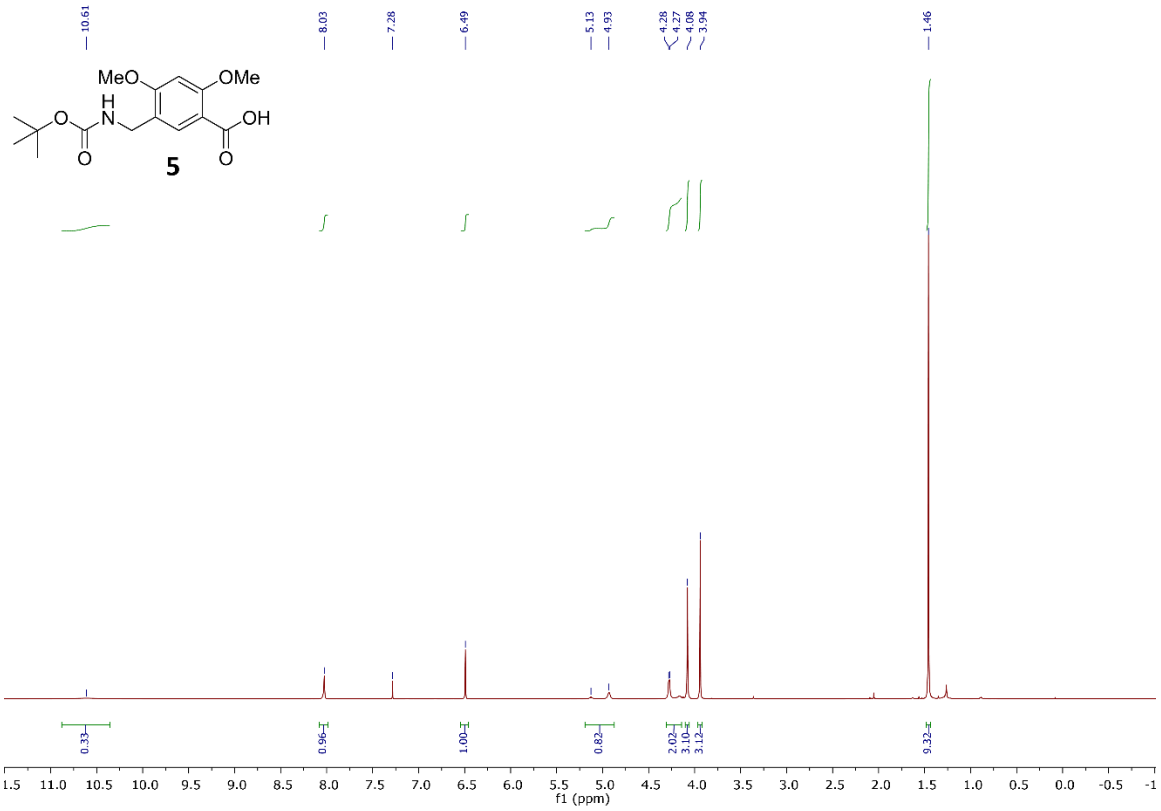
OMe
H
N
O
O
O
11
f1 (ppm)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7.28
6.49
5.13
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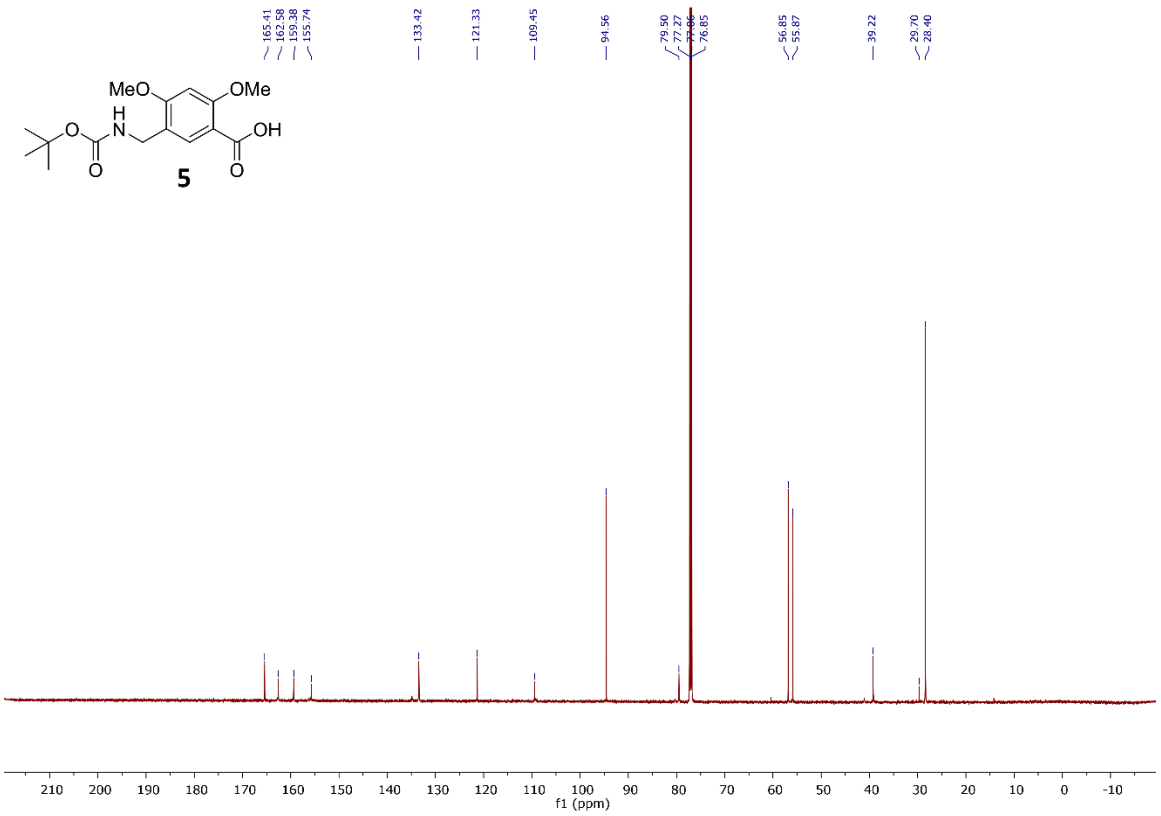
4.28
4.27
4.08
3.94
1.46
MeO
OMe
H
N
O
OH
O
O
5
0.33
0.96
1.00
0.82
2.02
3.10
3.12
9.32
f1 (ppm)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121.33
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55.87
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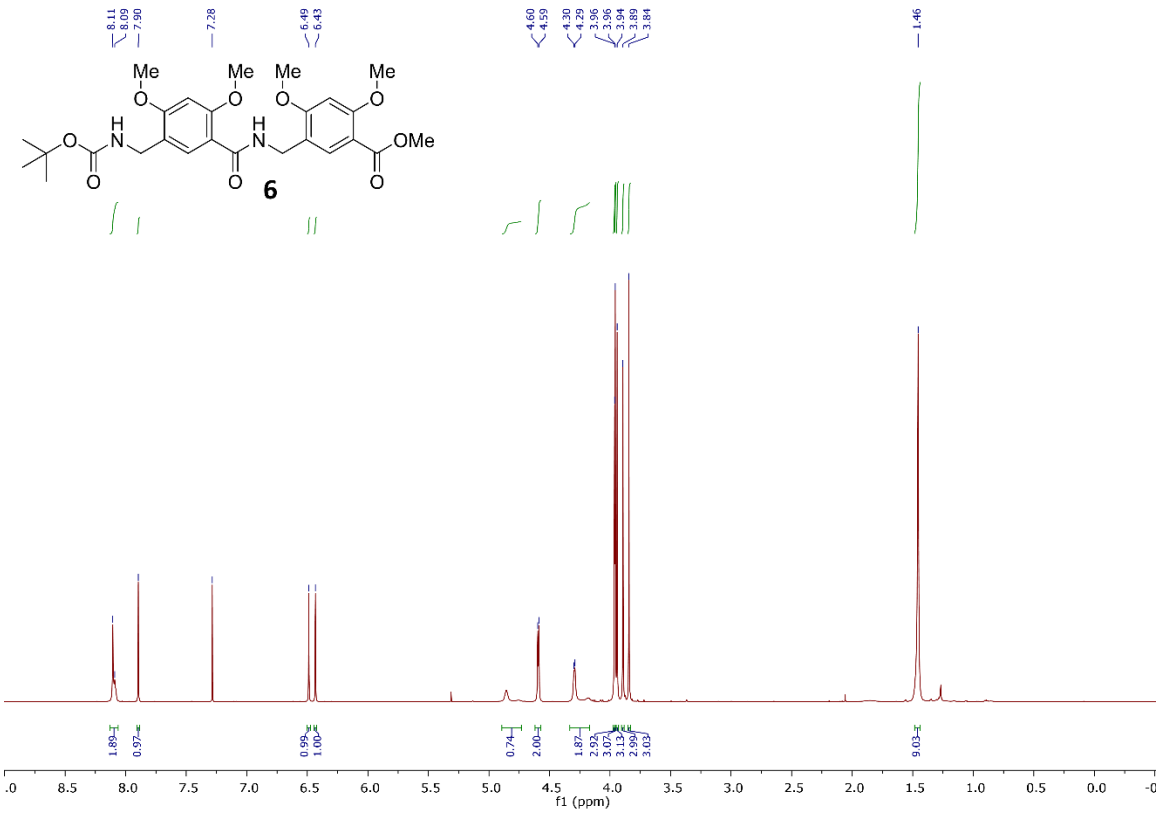
29.70
28.40
MeO
OMe
H
N
O
OH
O
O
5
f1 (ppm)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6.49
6.43
4.60
4.59
4.30
4.29
3.96
3.96
3.94
3.89
3.84
1.46
Me
Me
Me
Me
O
O
O
O
H
N
H
N
O
O
O
O
OMe
6
1.89
0.97
0.99
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2.00
1.87
2.92
3.07
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2.99
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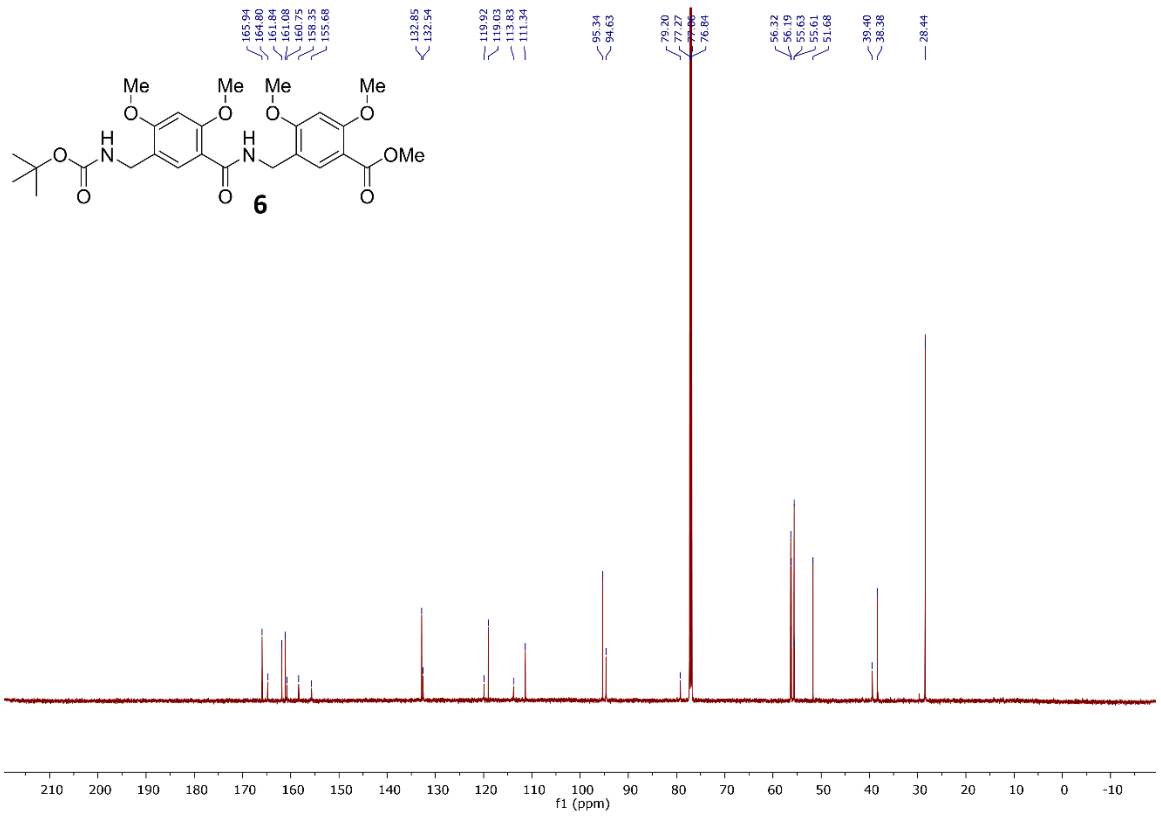
9.03
f1 (ppm)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155.68
132.85
132.54
119.92
119.03
113.83
111.34
95.34
94.63
79.20
77.27
76.84
56.32
56.19
55.63
55.61
51.68
39.40
38.38
28.44
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Me
Me
Me
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O
O
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H
N
H
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O
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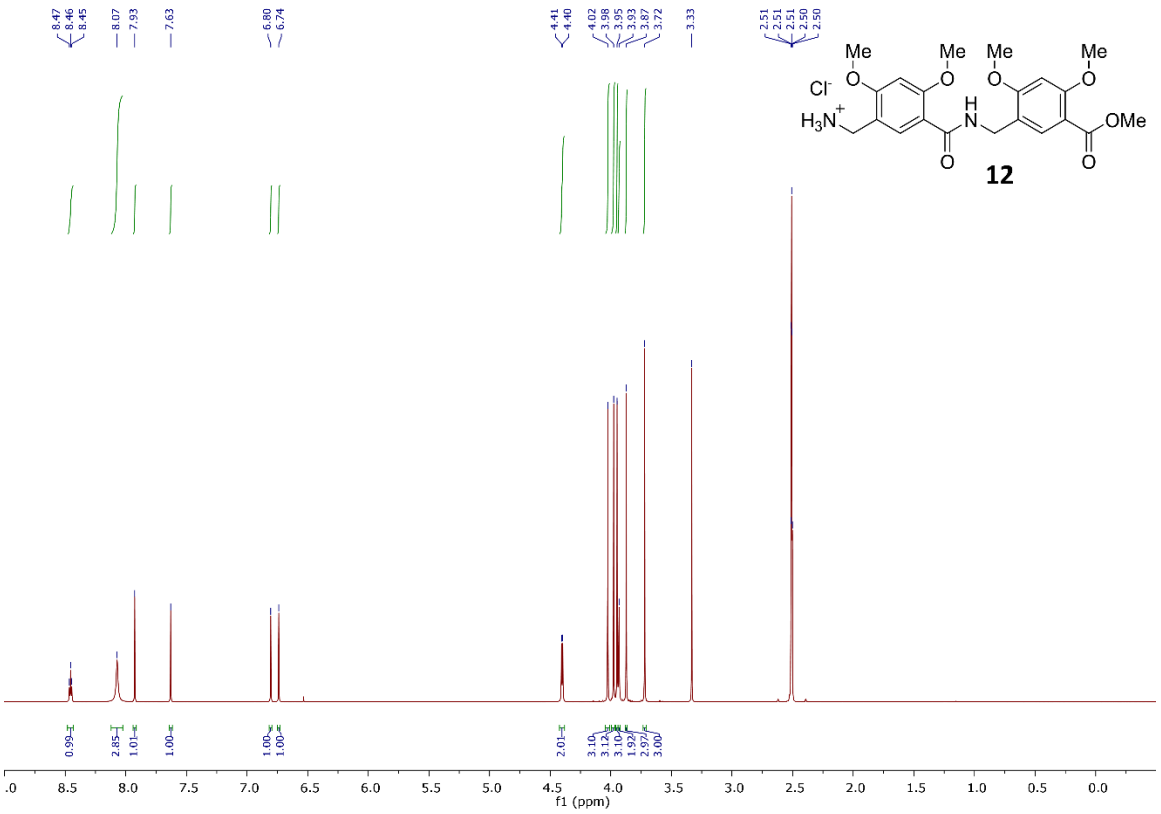
OMe
6
f1 (ppm)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6.74
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4.02
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3.87
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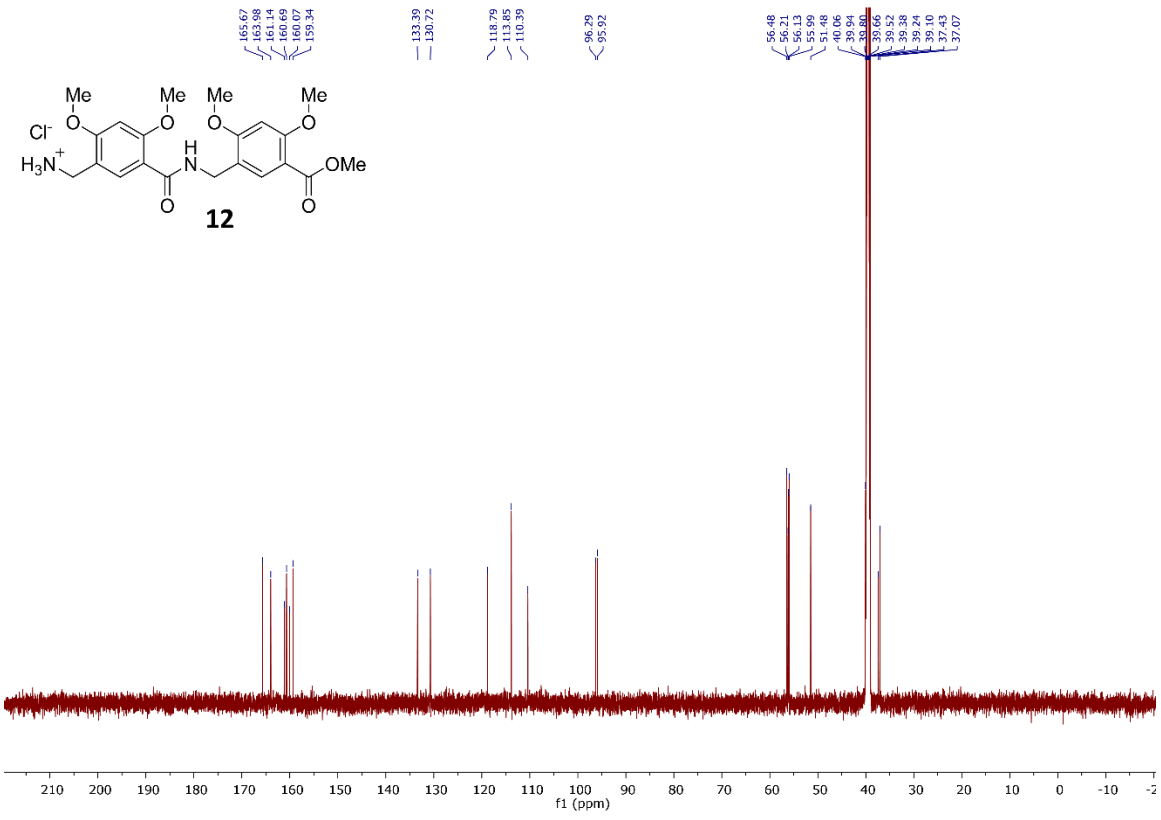
2.51
2.51
2.50
2.50
Me
Me
Me
Me
Cl⁻
H3N+
H
N
OMe
O
12
0.99
2.85
1.01
1.00
1.00
1.00
2.01
3.10
3.12
3.10
1.92
2.97
3.00
f1 (ppm)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56.13
55.99
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40.06
39.94
39.80
39.66
39.52
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39.24
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Me
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H3N+
H
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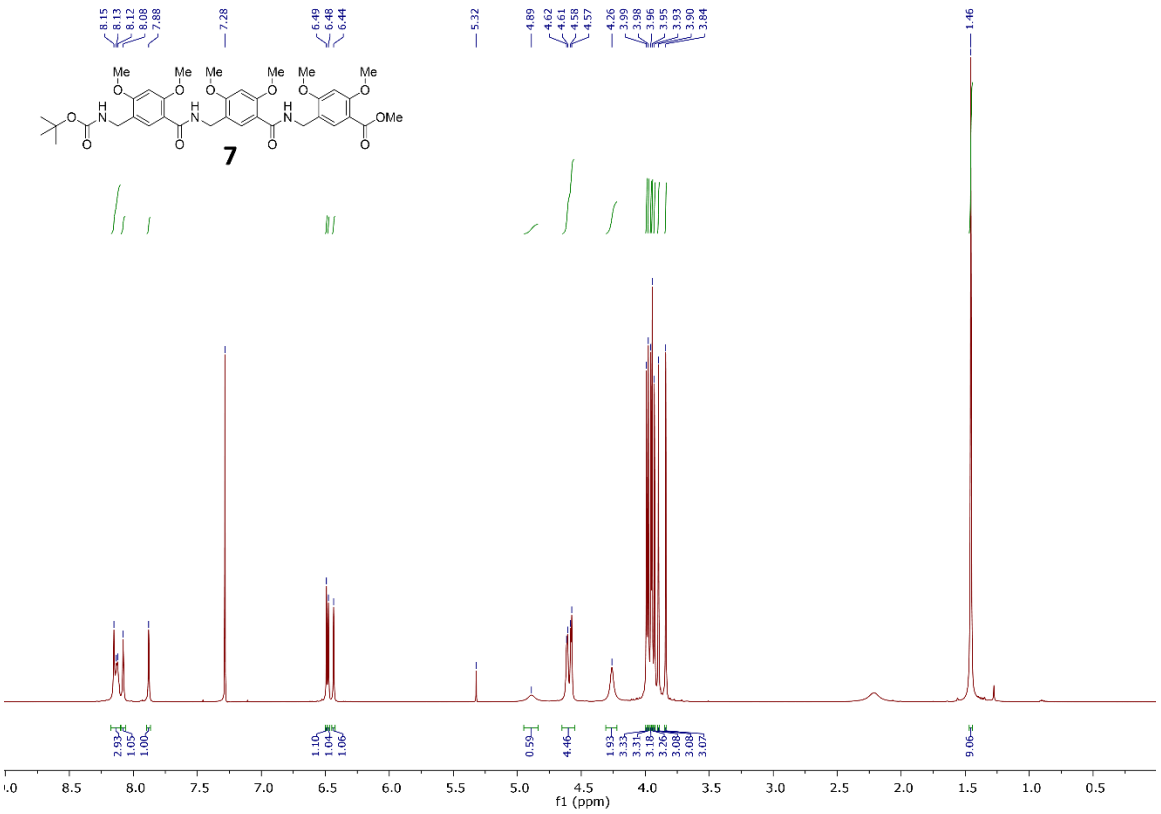
O
12
f1 (ppm)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3.93
3.90
3.84
1.46
Me
OMe
7
2.93
1.05
1.00
1.10
1.04
1.06
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3.31
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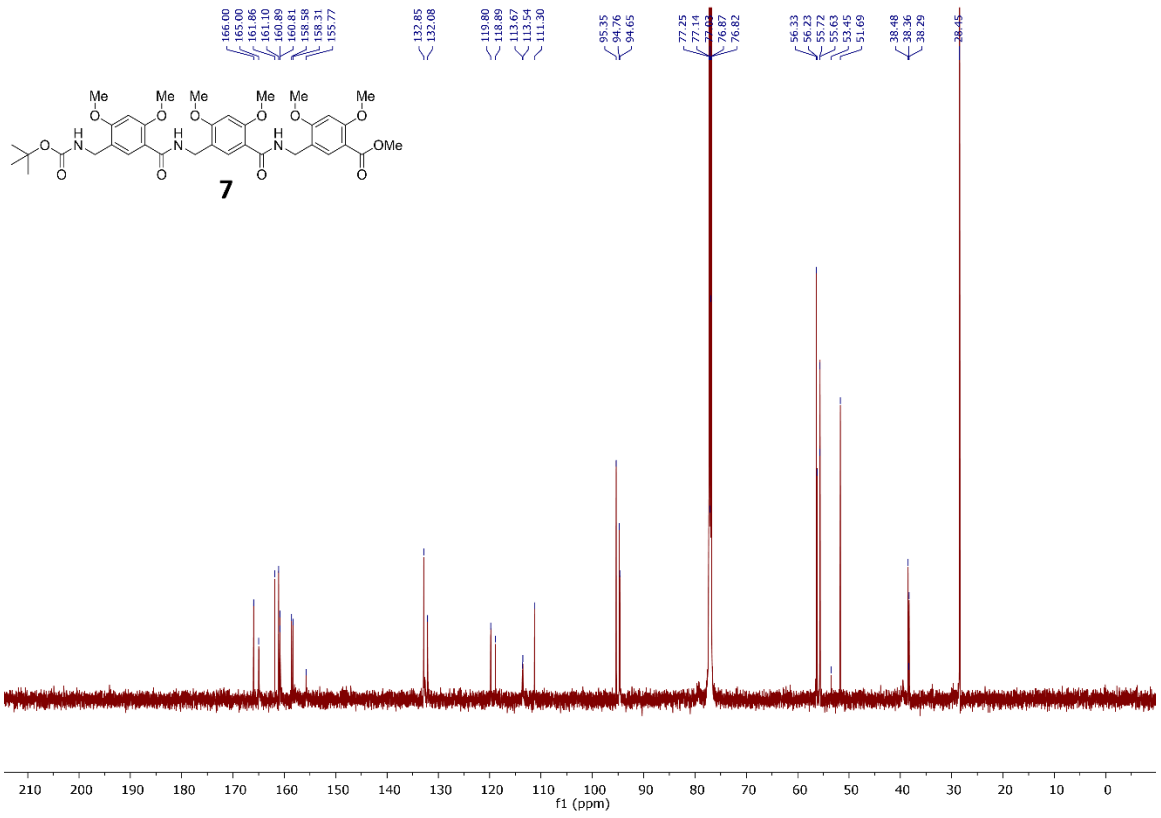
9.06
f1 (ppm)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132.08
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113.67
113.54
111.30
95.35
94.76
94.65
77.25
77.14
77.03
76.87
76.82
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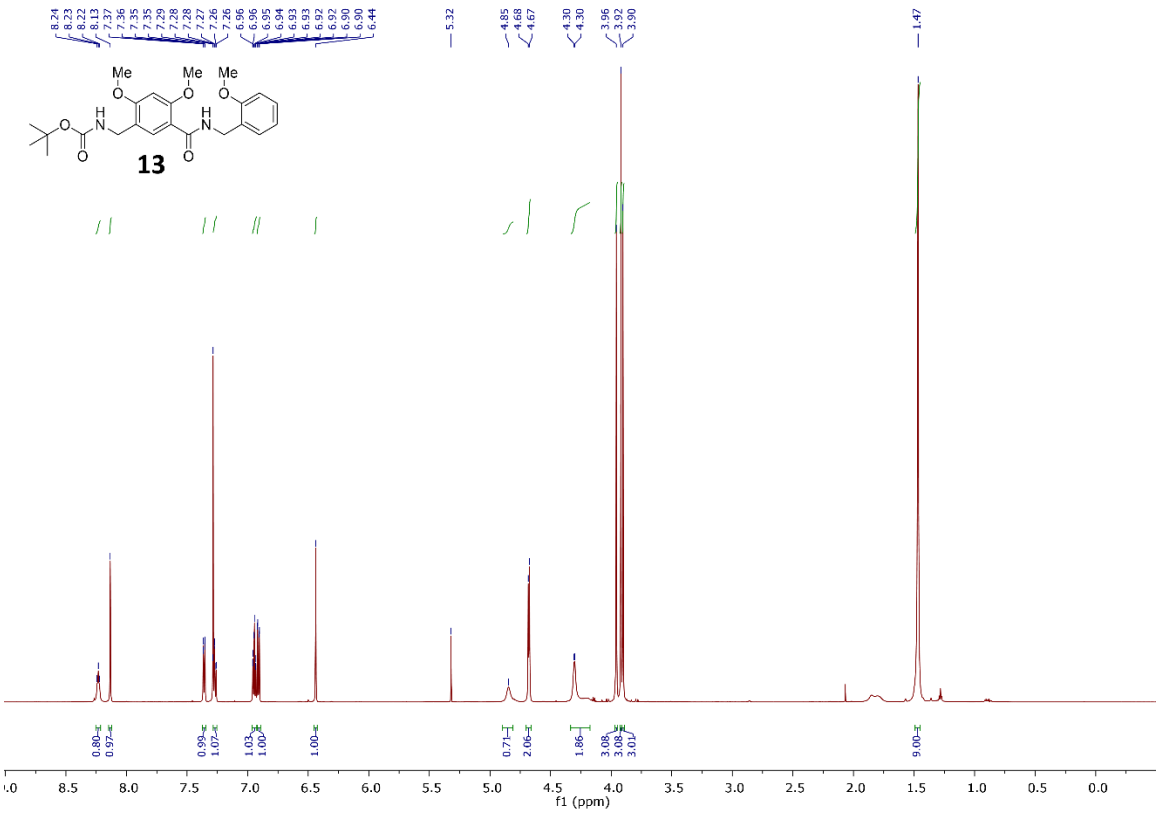
f1 (ppm)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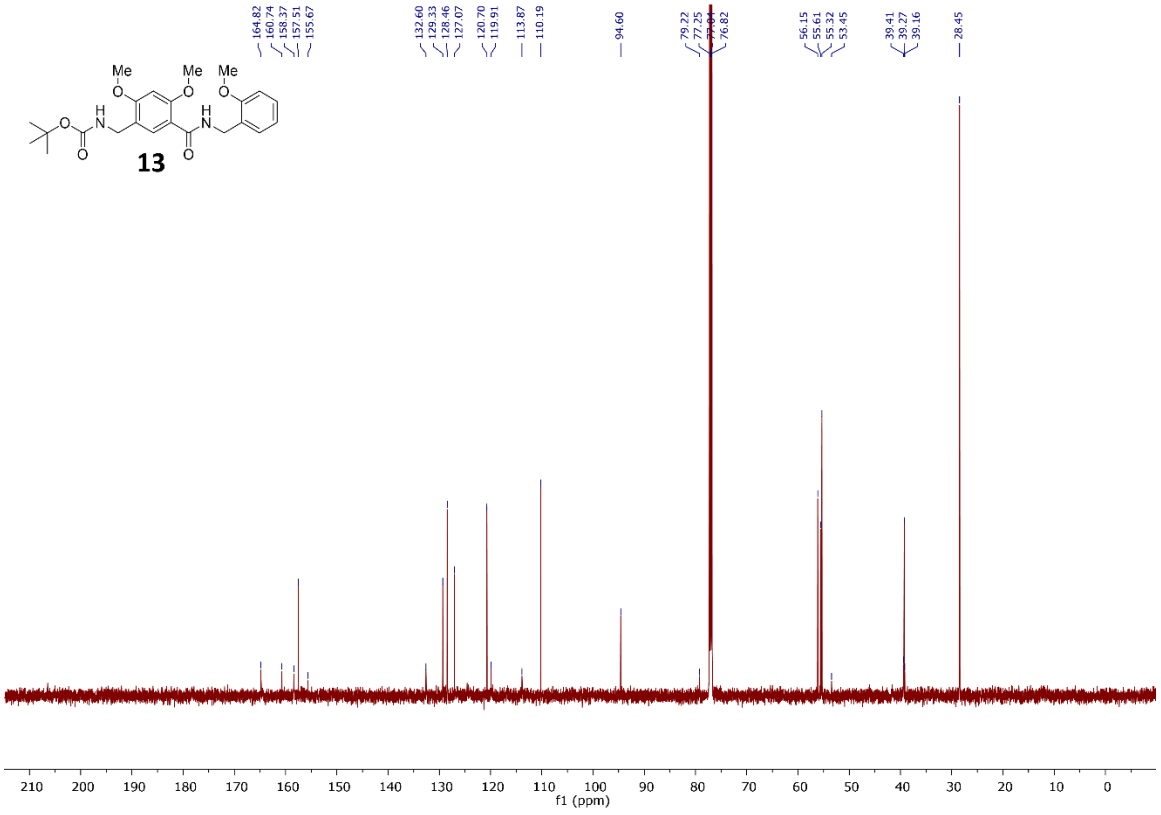
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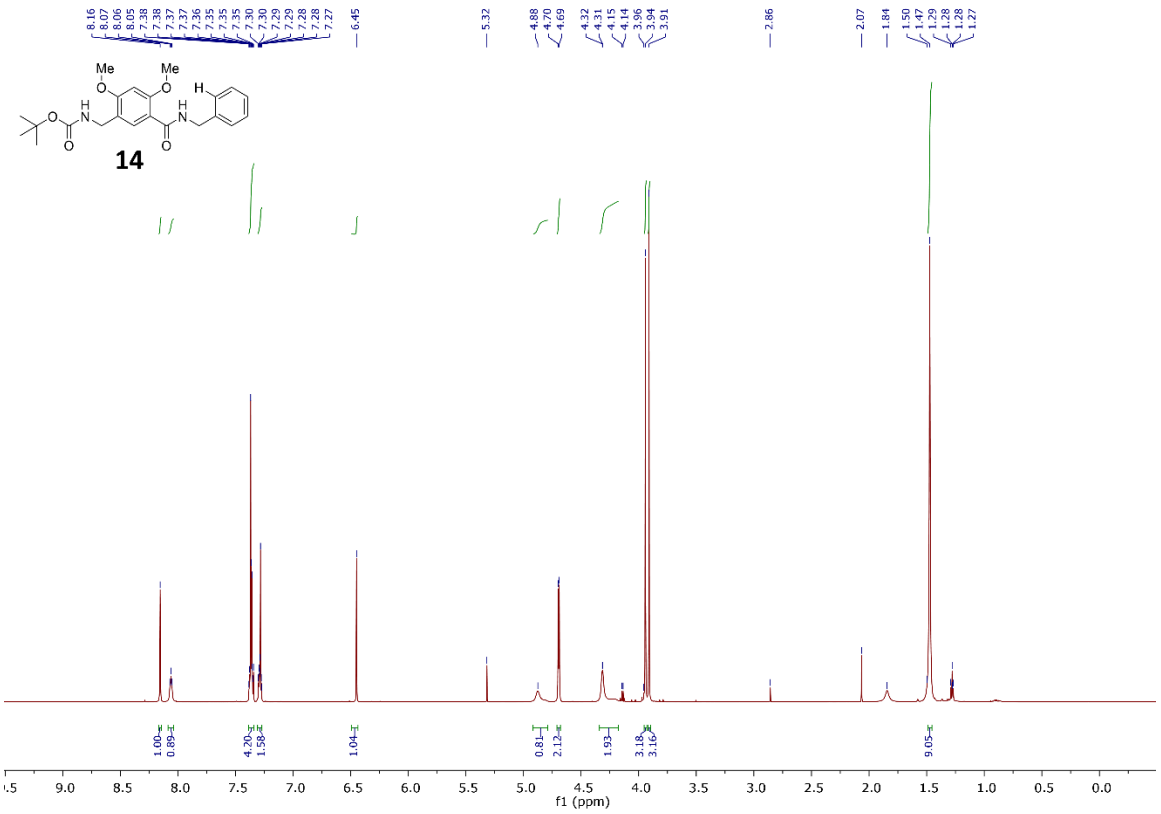
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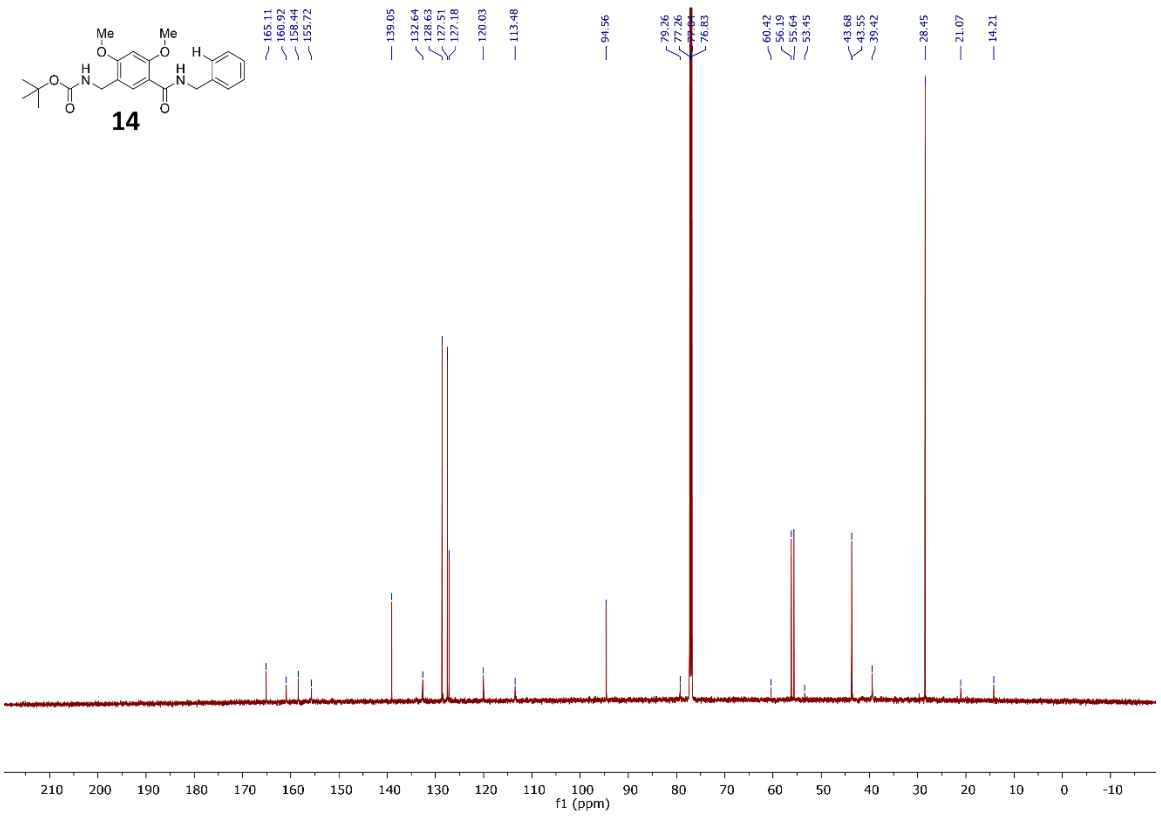
f1 (ppm)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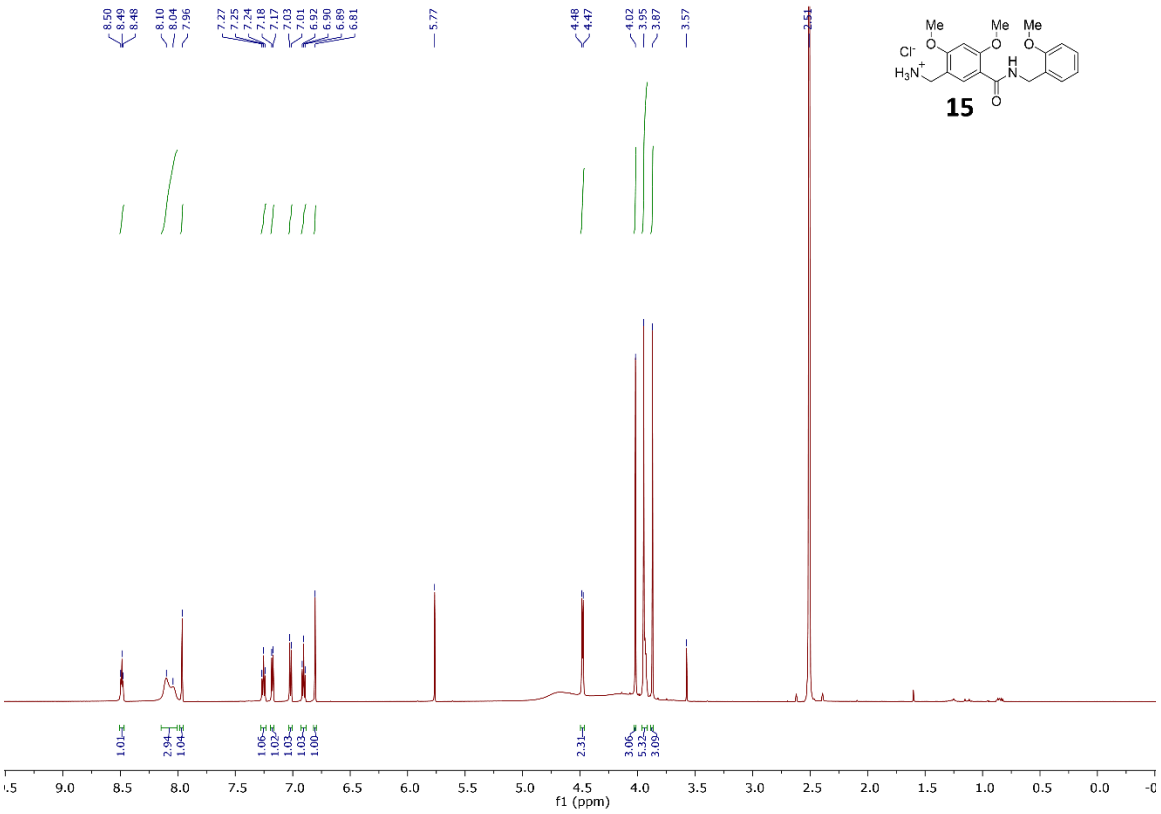
21.07
14.21
Me
Me
H
14
f1 (ppm)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2.94
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1.03
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1.00
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3.06
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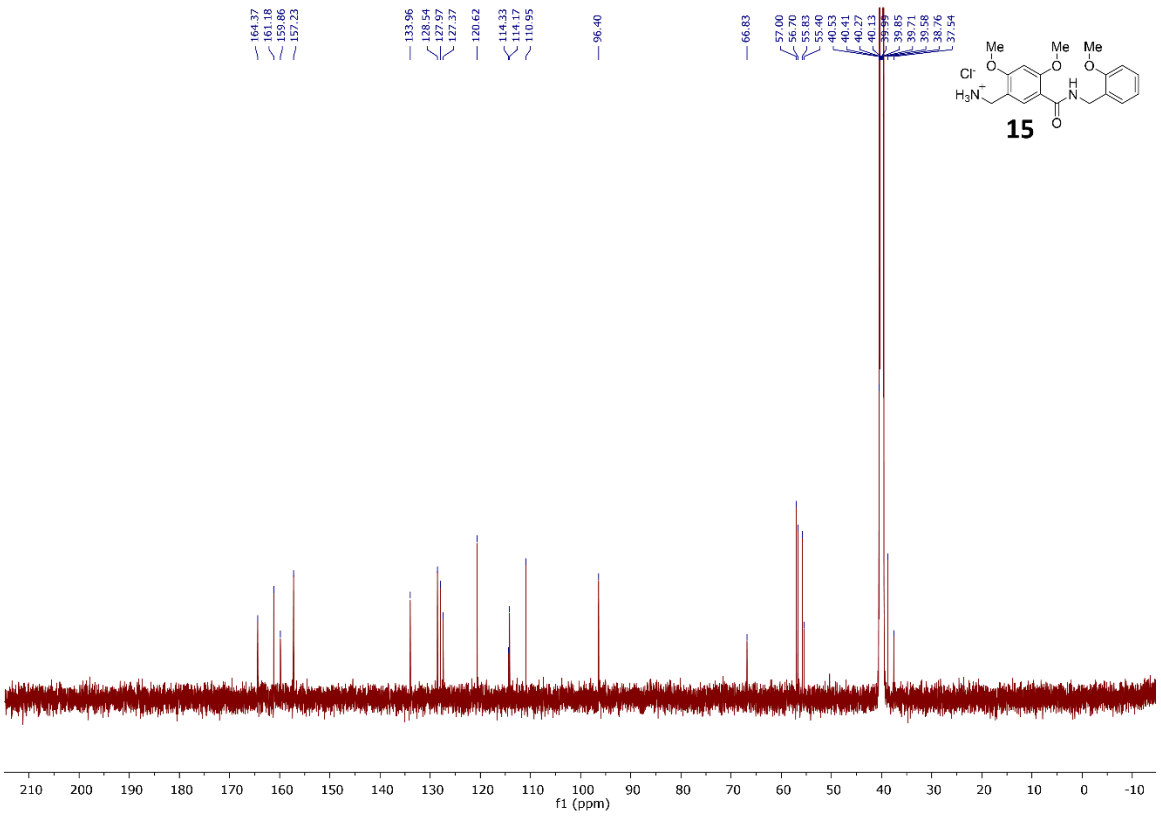
3.09
f1 (ppm)
15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120.62
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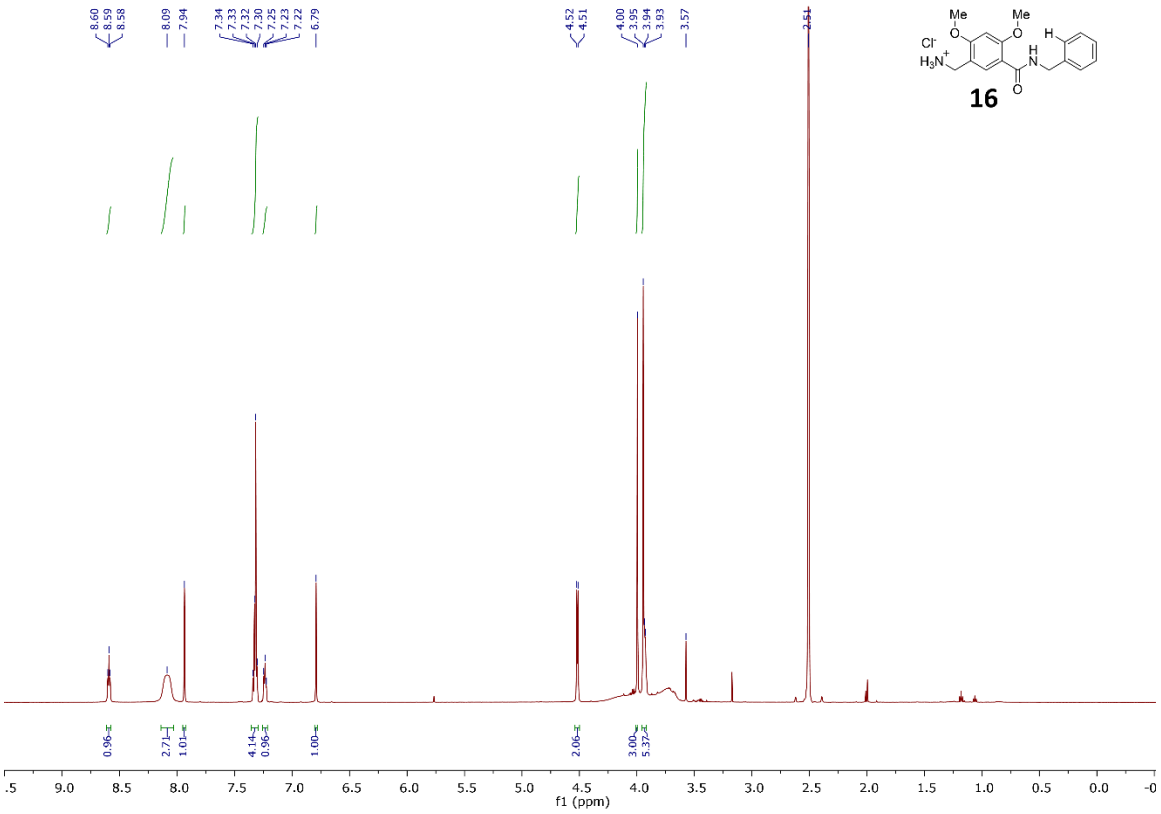
40.41
40.27
40.13
39.99
39.85
39.71
39.58
39.44
39.30
37.54
f1 (ppm)
15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Cl⁻
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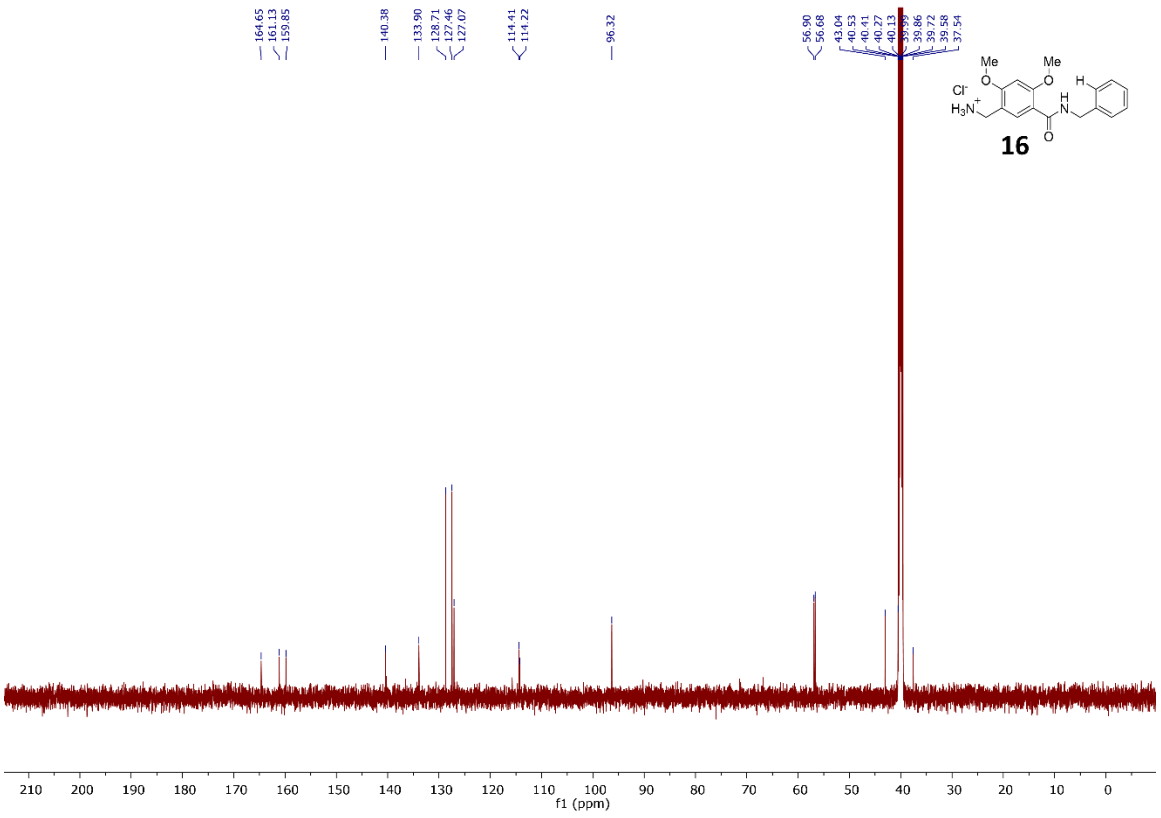
H
N
O
16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43.04
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40.27
40.13
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Cl⁻
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H
N
O
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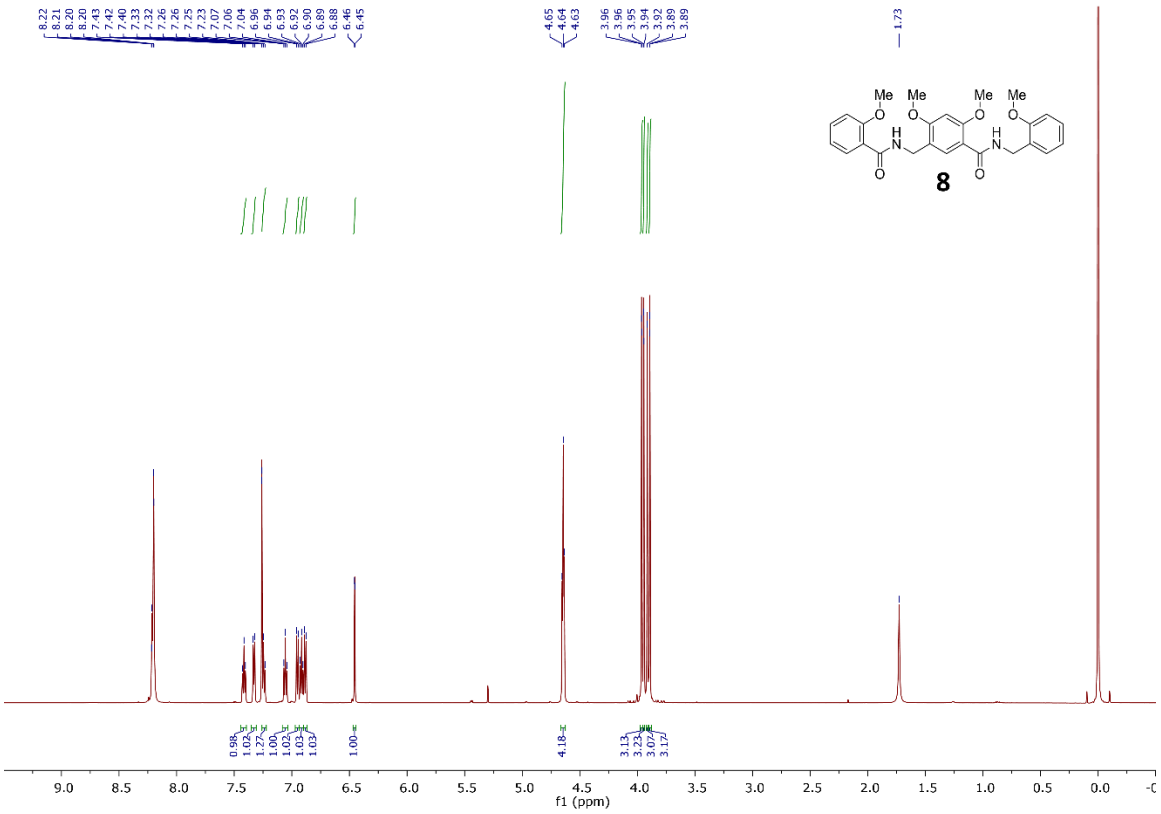
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7.23
7.07
7.06
7.04
6.96
6.94
6.93
6.92
6.90
6.89
6.88
6.46
6.45
4.65
4.64
4.63
3.96
3.96
3.95
3.94
3.92
3.89
3.89
1.73
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Me
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Me
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H
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O
O
O
8
0.98
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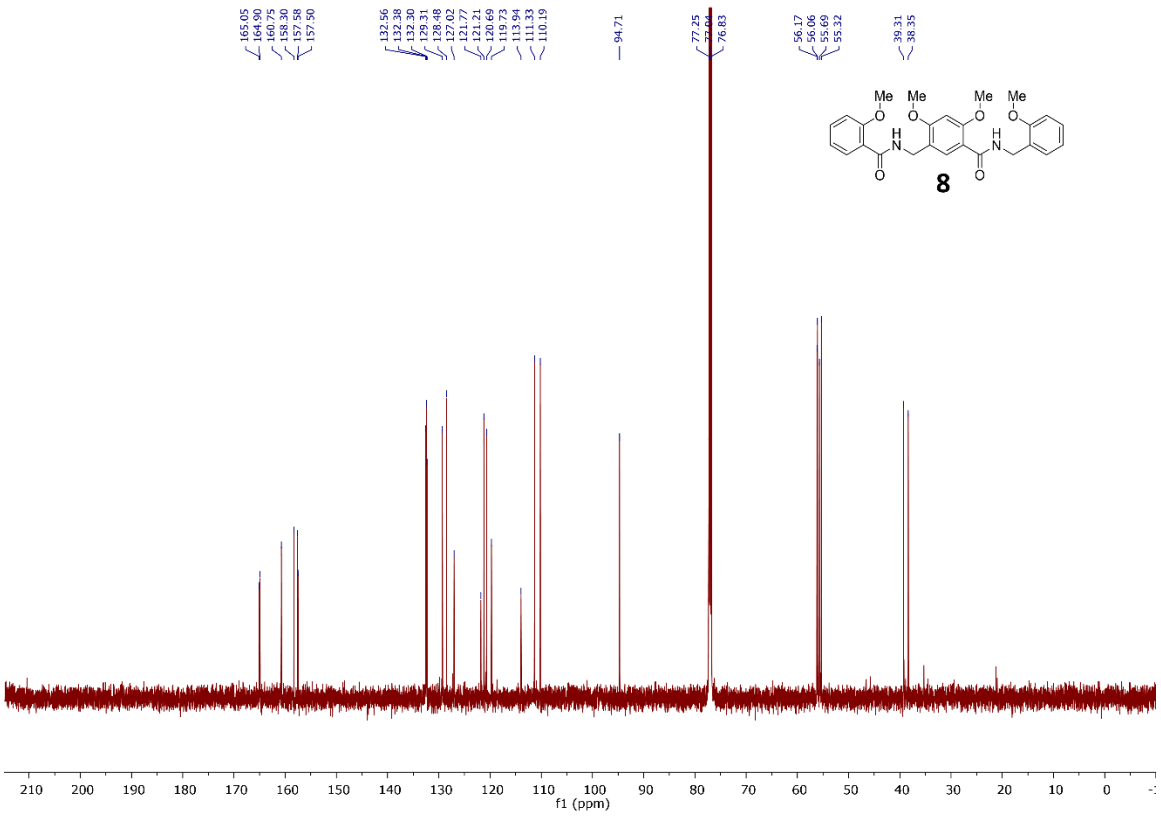
f1 (ppm)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77.25
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76.83
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56.06
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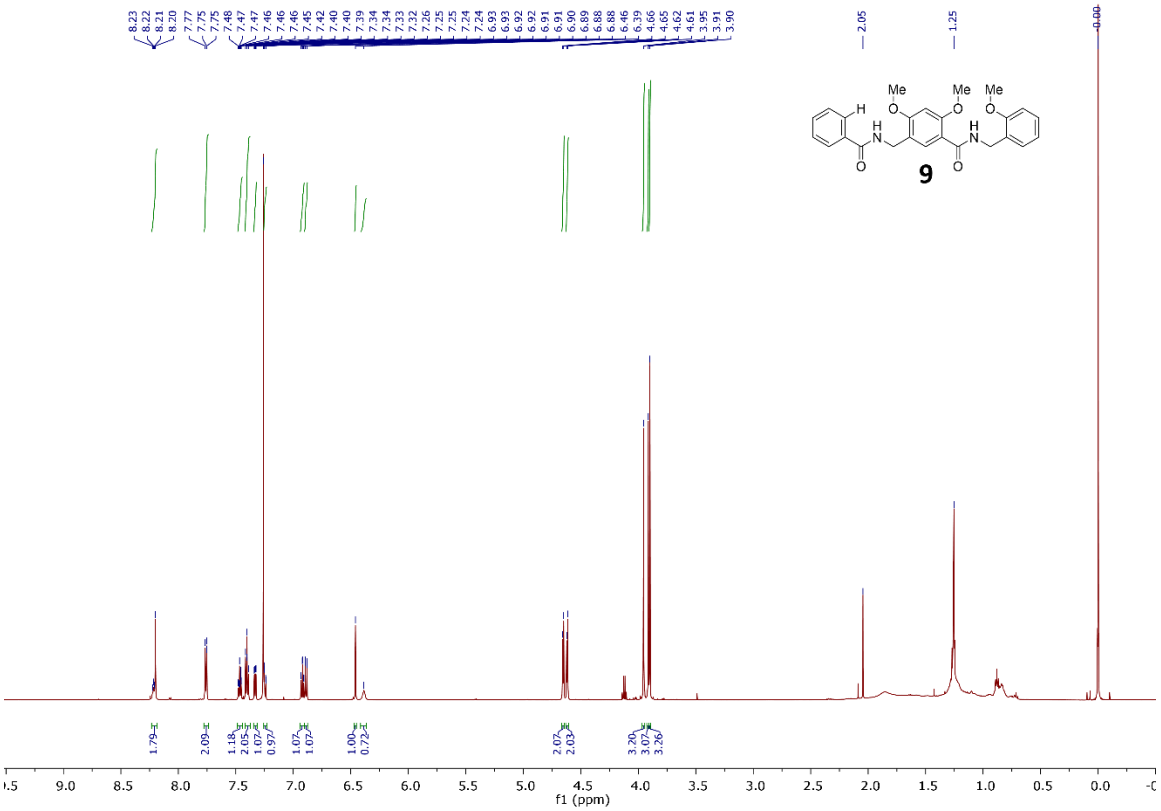
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Me
Me
H
N
H
N
O
O
O
O
O
9
1.79
2.09
1.18
2.05
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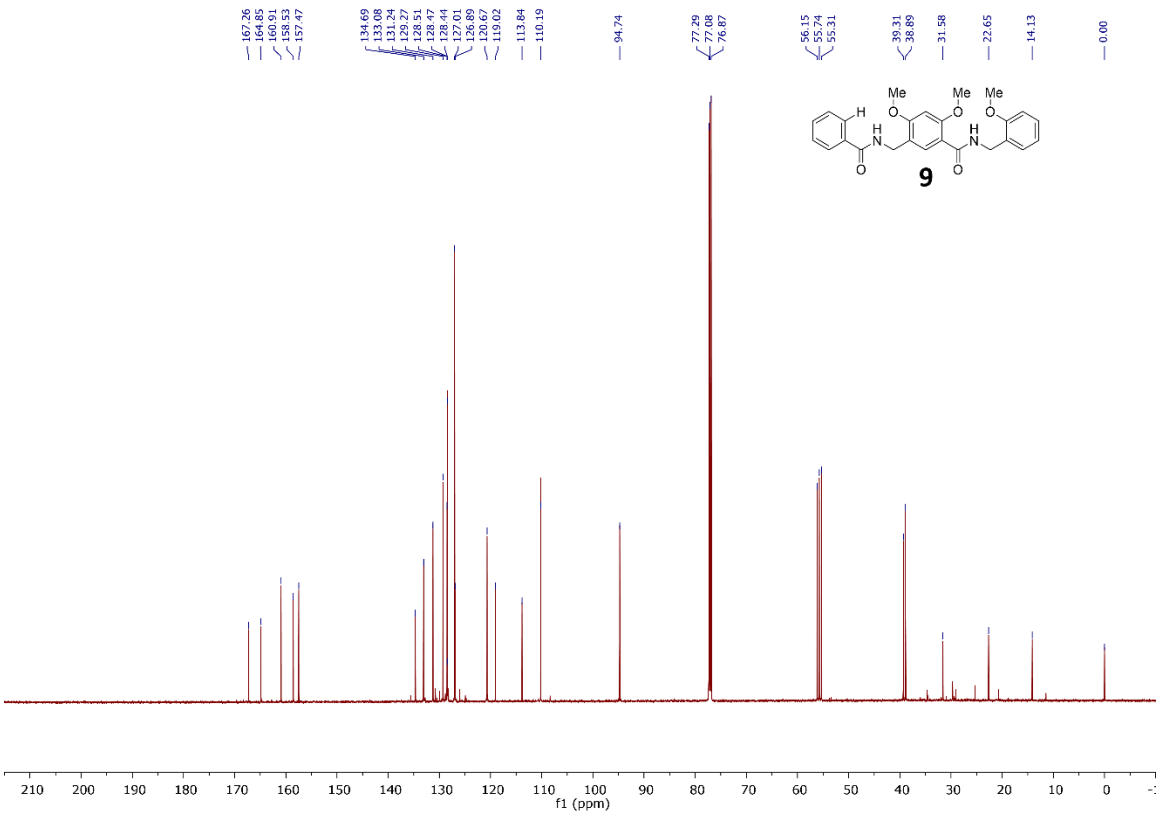
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O
O
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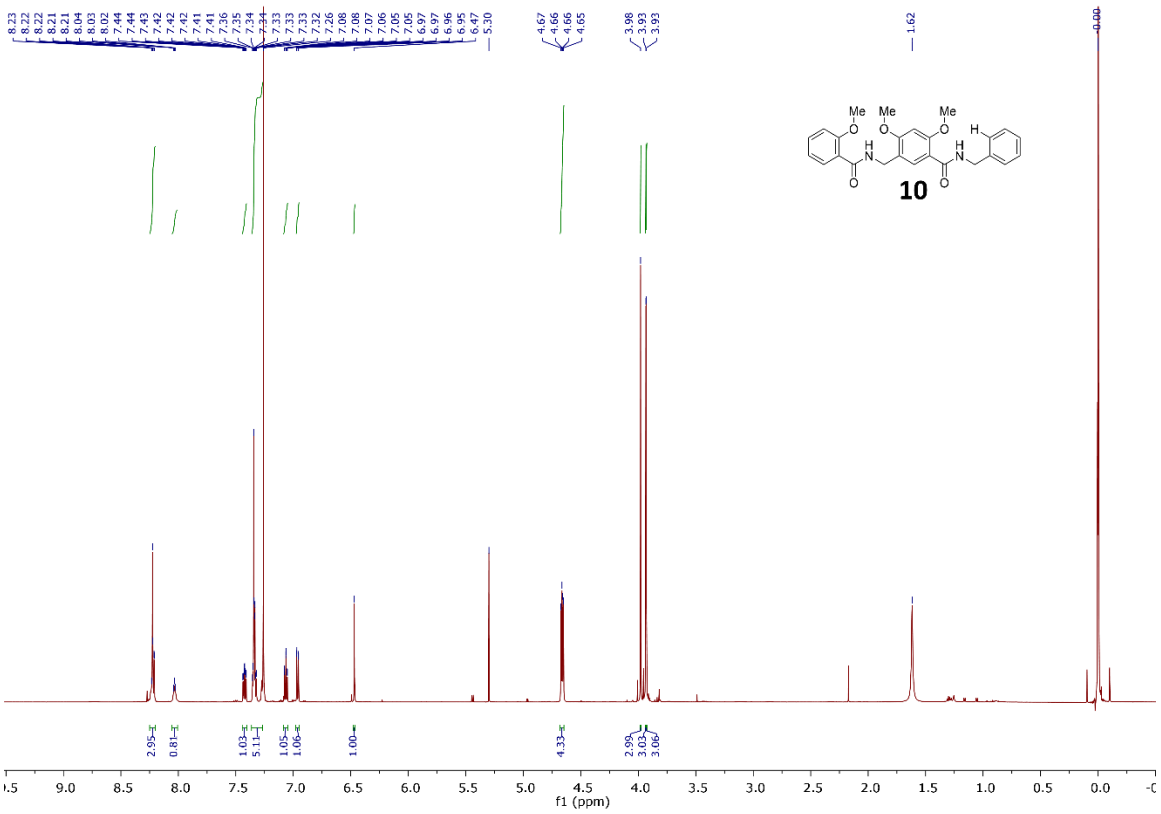
O
O
9
f1 (ppm)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4.67 4.66 4.66 4.65
3.98 3.93 3.93
1.62
0.00
Me Me Me
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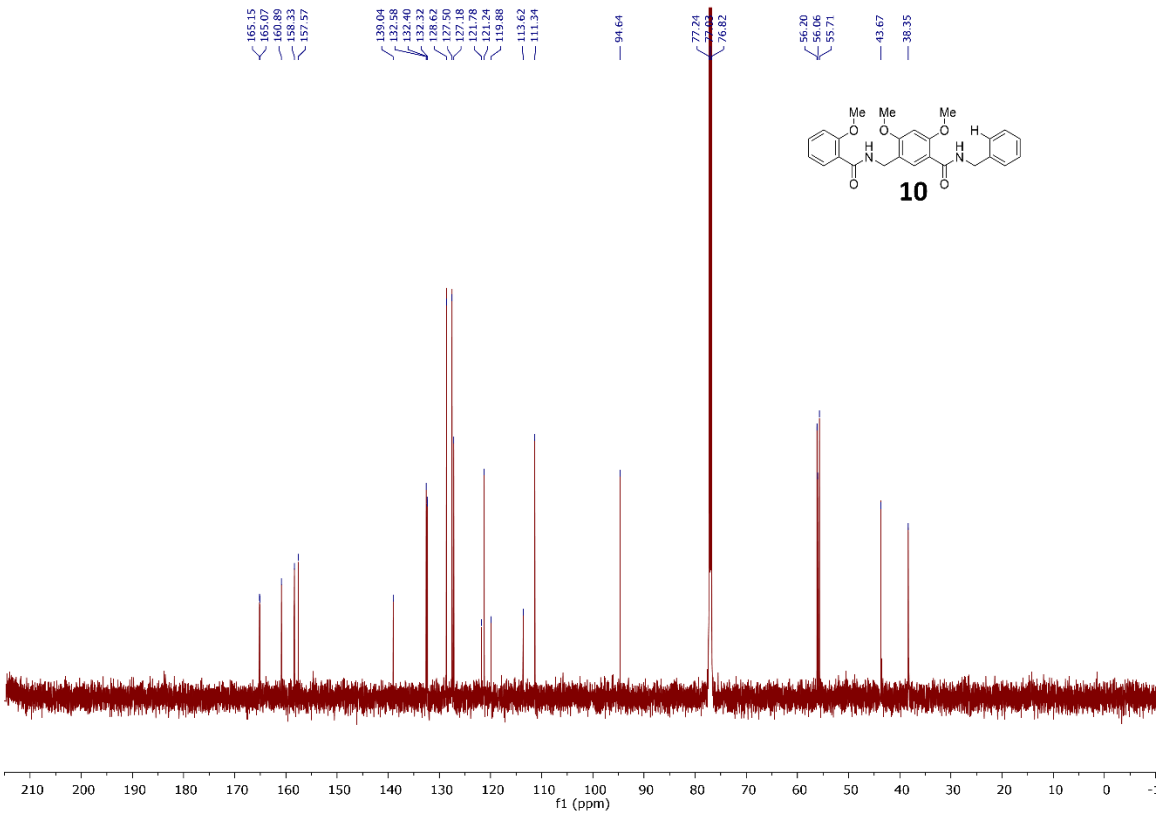
H
H N N H
O O
10
2.95 0.81 1.03 5.11 1.05 1.06 1.00 4.33 2.99 3.03 3.06
f1 (ppm)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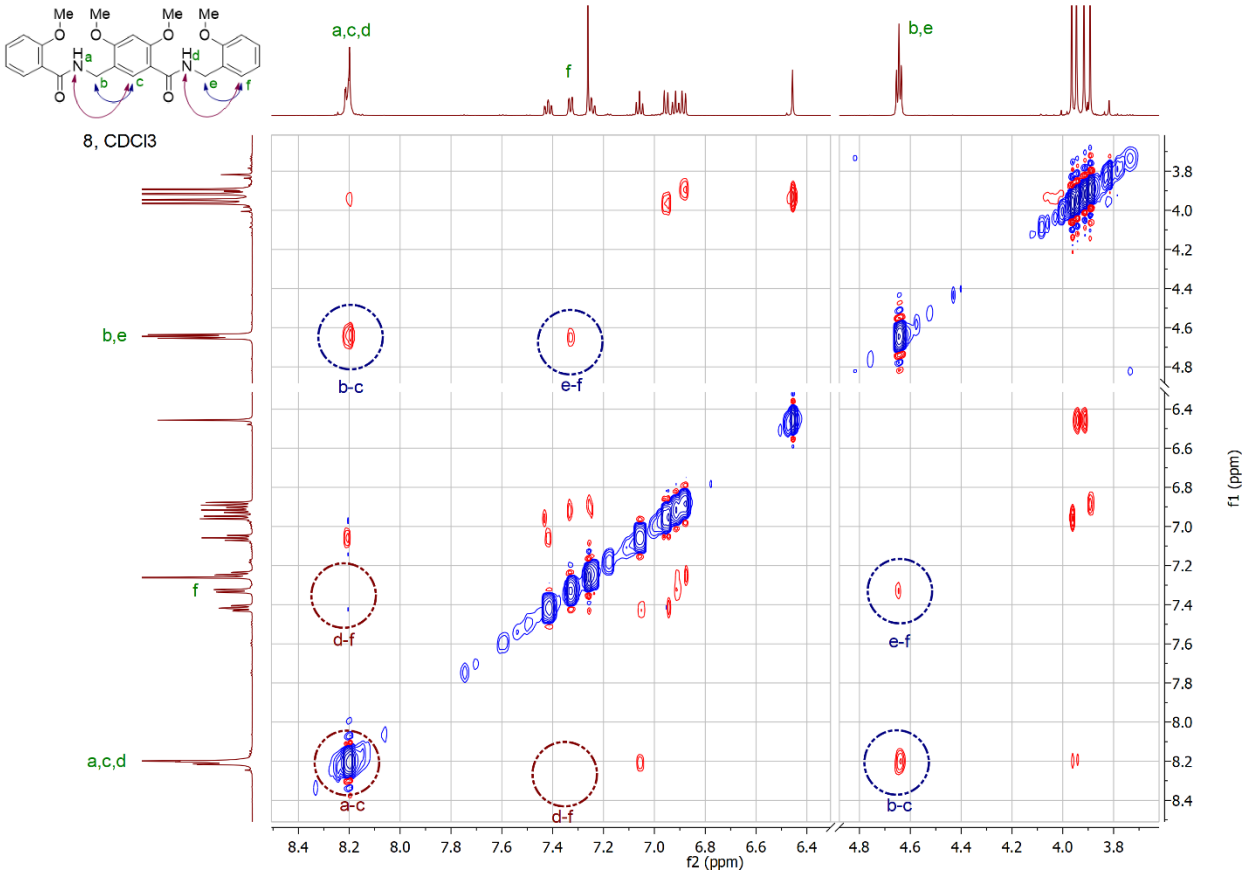
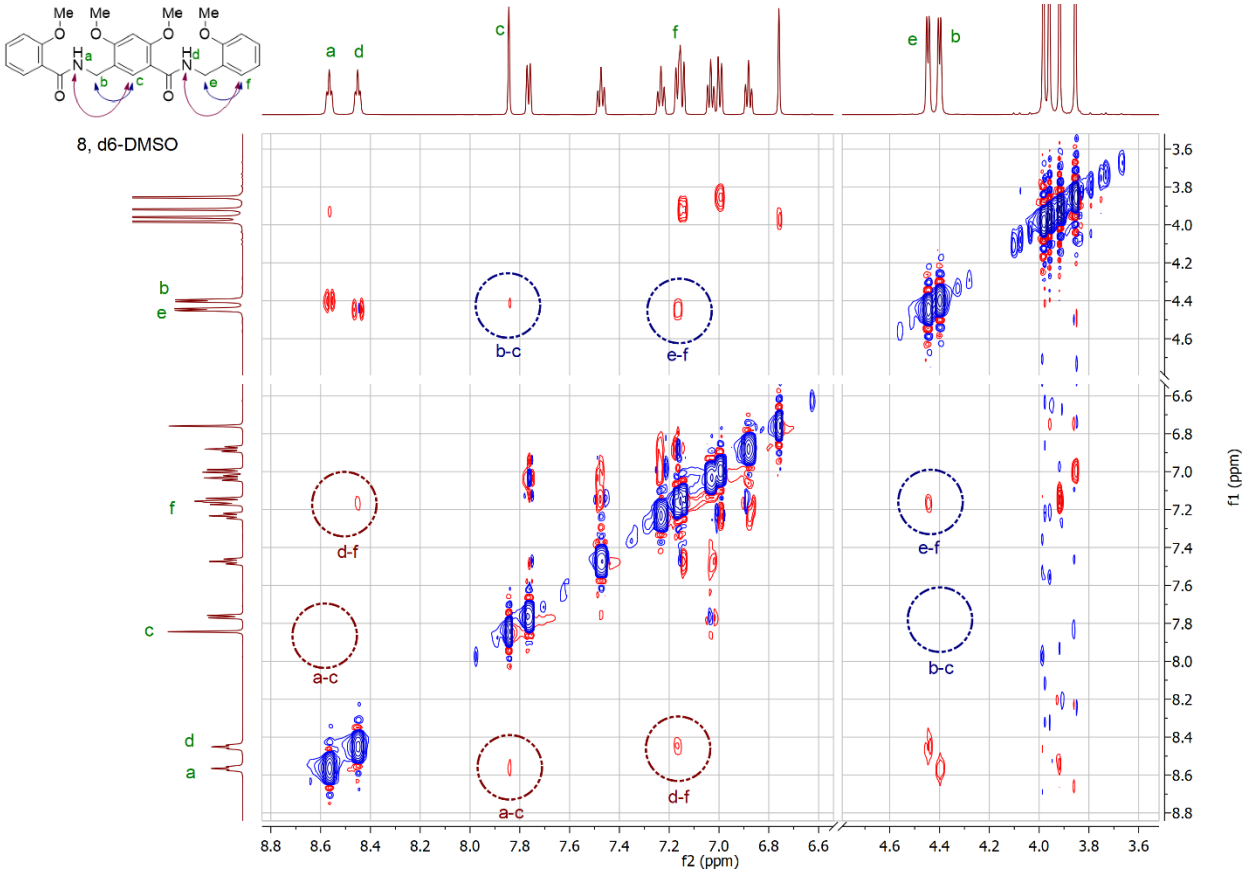
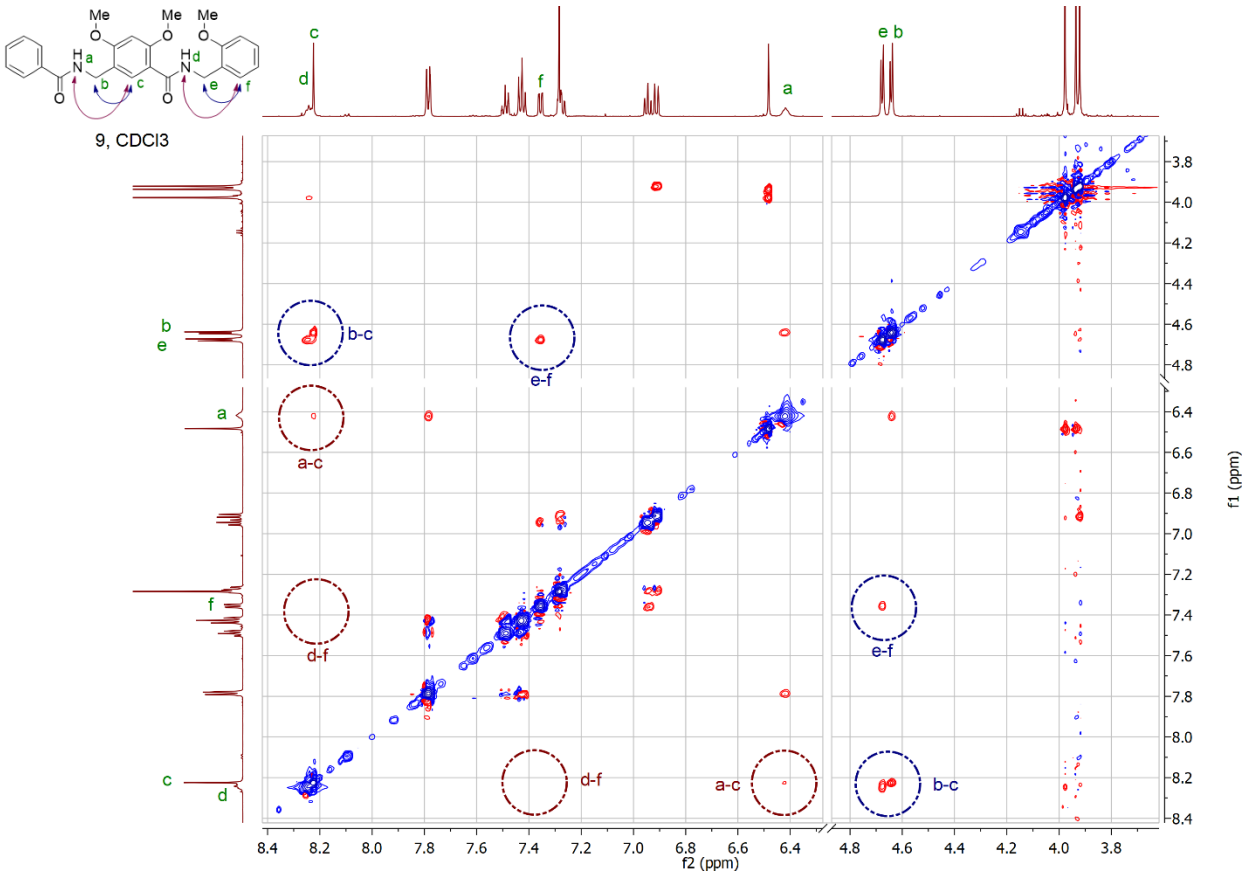
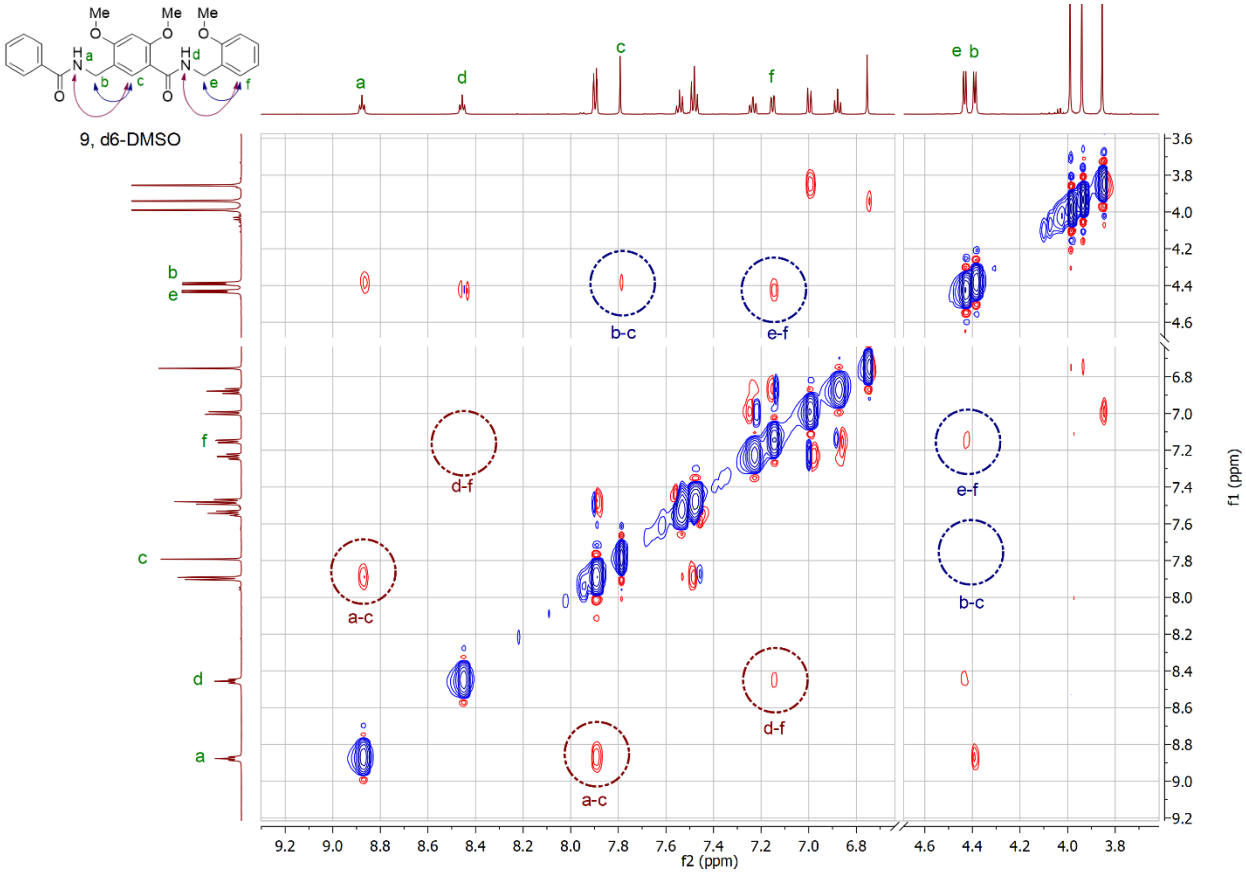
139.04 132.58 132.40 128.32 128.02 127.50 127.18 121.78 121.24 119.88
113.62 111.34
94.64
77.24 77.03 76.82
56.20 56.06 55.71
43.67
38.35
Me Me Me
O O O
H
H N N H
O O
10
f1 (ppm)

4.2. 2D NMR Spectra






Me
Me
Me
H
a
N
b
c
d
e
f
O
9, CDCl3
b-c
e-f
a-c
d-f
f2 (ppm)
f1 (ppm)


Me
Me
Me
H
a
N
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c
d
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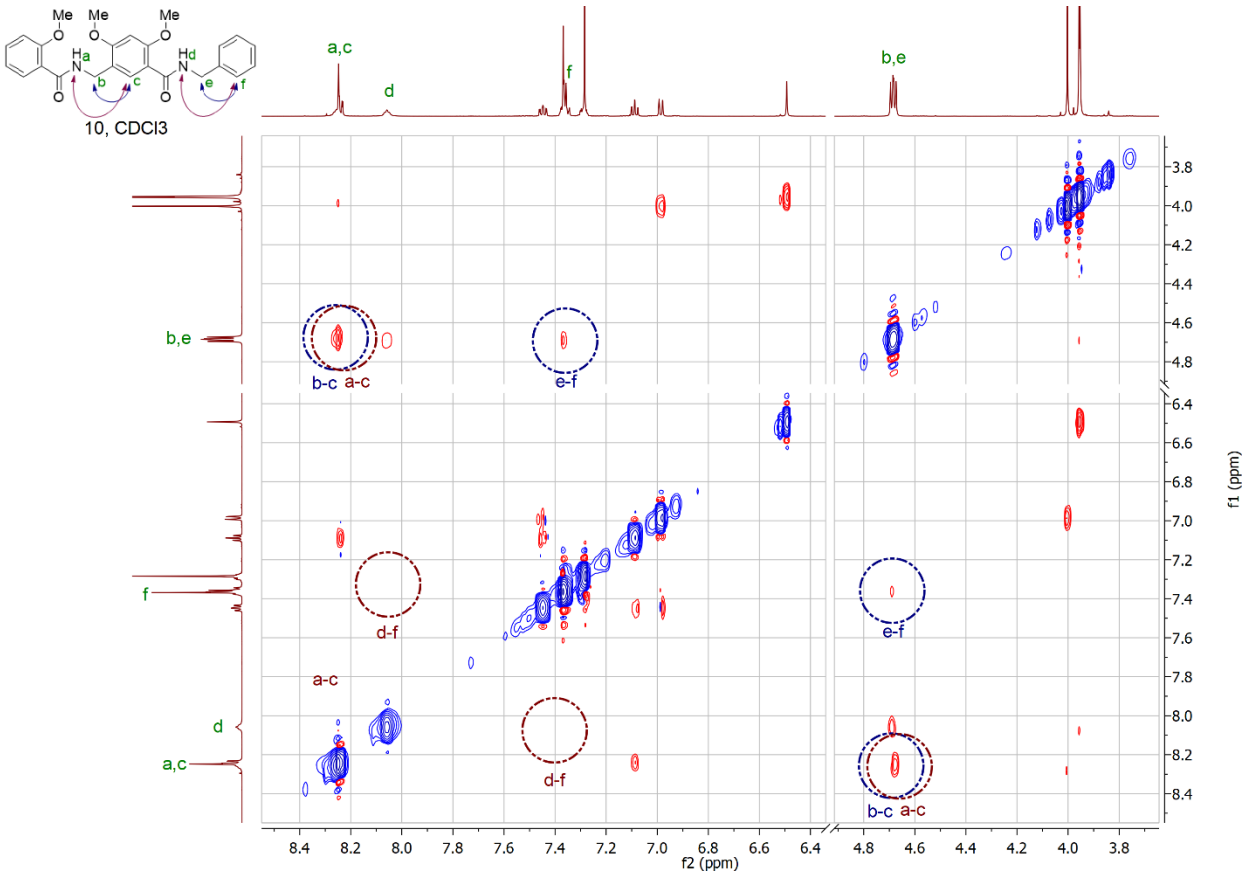
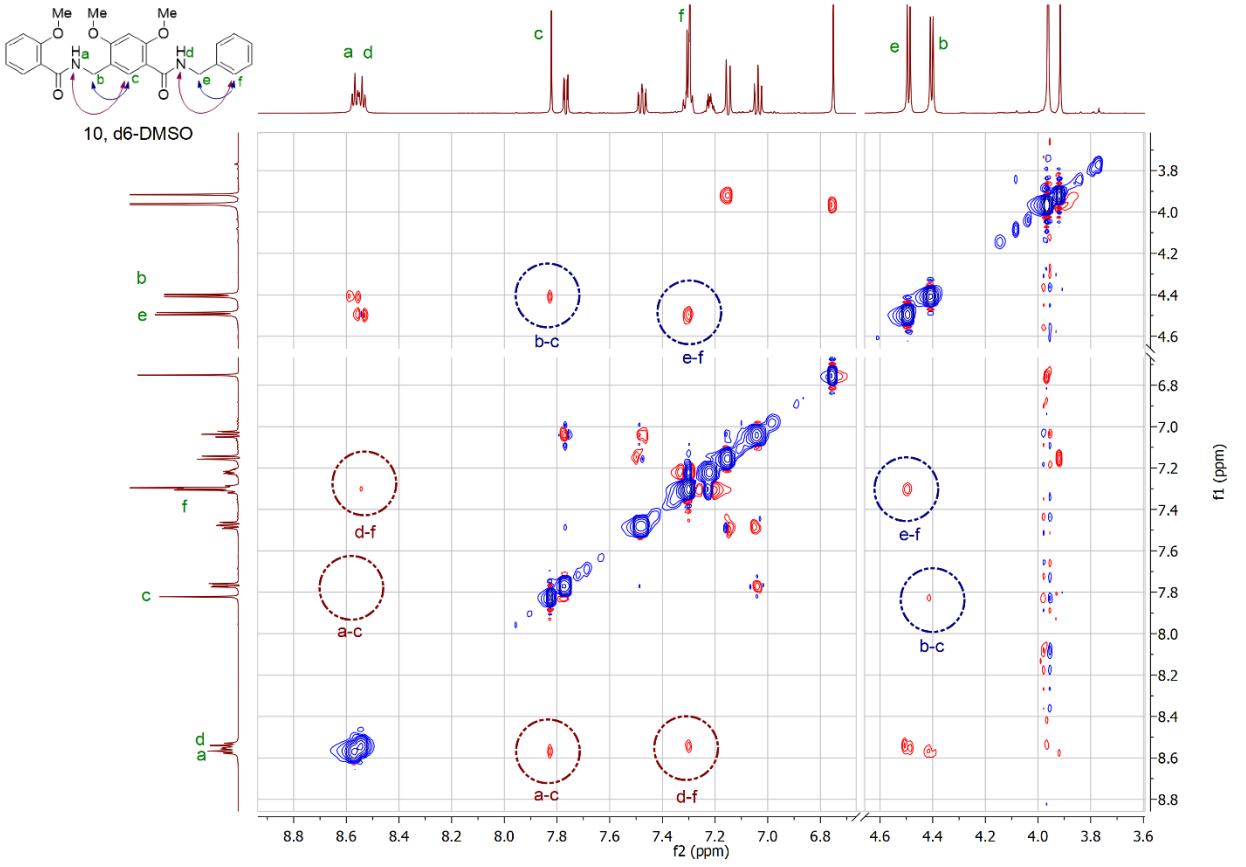
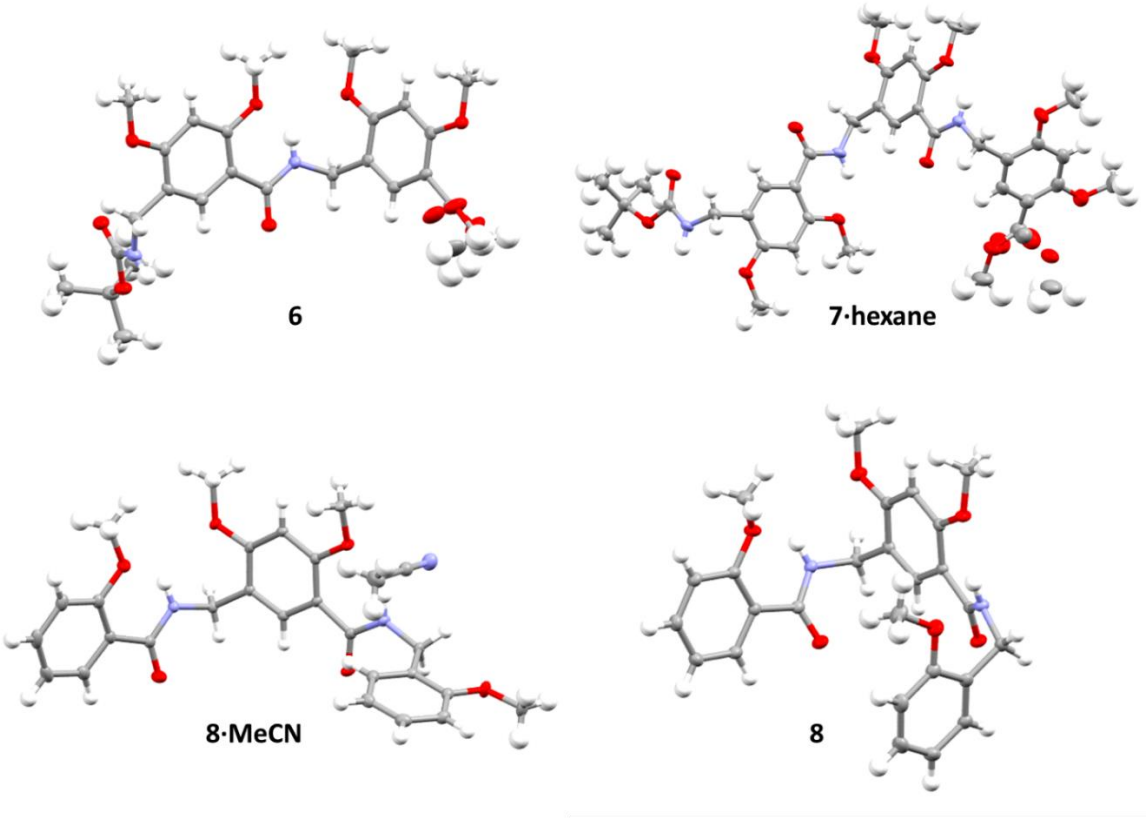
f
O
9, d6-DMSO
b-c
e-f
d-f
a-c
f2 (ppm)
f1 (ppm)


10, CDCl3
a,c
d
f
b,e
b-c a-c
e-f
d-f
a-c
f1 (ppm)
f2 (ppm)


10, d6-DMSO
a d
c
f
e
b
b-c
e-f
d-f
a-c
f1 (ppm)
f2 (ppm)

5. X-Ray Crystallographic Analysis



Crystals of **6**, **7**, and **8** suitable for diffraction experiments were grown by slow evaporation from a solution of the respective compound dissolved in a mixture of methylene chloride and hexane; **8·MeCN** was obtained from a solution of **8** in acetonitrile. X-ray intensity data of complex **6**, **7·hexane**, **8** and **8·MeCN** were recorded on a Bruker D8 APEX-II CCD system equipped with a sealed Mo X-ray tube, a graphite monochromator, and a 0.5 mm MonoCap collimator. All datasets were collected at 100 K, which was controlled by an Oxford Cryosystems 700+ Cooler. The datasets of **6** and **7·hexane** were acquired with the ϕ/ω scan method, and **8** and **8·MeCN** with the ϕ/ω scan method. All datasets were processed with the INTEGRATE program of the APEX2 software for reduction and cell refinement[S1]. Multi-scan absorption corrections were applied by the SCALE program for the area detector. All structures were solved by intrinsic phasing methods (SHELXT)[S2] and the structure models were completed and refined using the full-matrix least-square methods on F^2 (SHELXL)[S3]. Non-hydrogen atoms in the structures were refined with anisotropic displacement parameters. Hydrogen atoms on carbons were placed in idealized positions (C-H = 0.95-1.00 Å) and included as riding with *U*iso(H) = 1.2 or 1.5 *U*eq(non-H). Hydrogen atoms on nitrogens were found from the difference Fourier electron density maps and refined isotropically. One of the OMe groups in **6** and **7·hexane** is disordered, and their geometries and atomic displacement parameters were refined with necessary constraints and

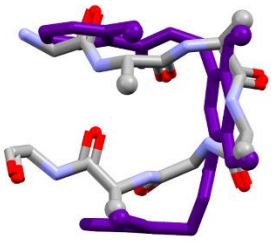
restraints. The crystal of **6** is a two-component twin. The second twin domain is related to the first one via a two-fold rotation along the [100] direction. The refinement on the twin data revealed that the minor domain contributed 31.4% to the overall intensity. In the structure of **7·hexane**, no suitable model of hexane could be defined due to the severe disorder so its contribution was treated by the program PLATON/SQUEEZE[S4]. The selected crystallographic parameters of four structures were listed in Table S1. The crystallographic information files (CIFs) including the HKL and RES data were deposited to the Cambridge Crystallographic Data Centre (CCDC). The reference numbers are listed in the Table S1.

Table S1. Selected crystal data for complex **6**, **7·hexane**, **8** and **8·MeCN**.

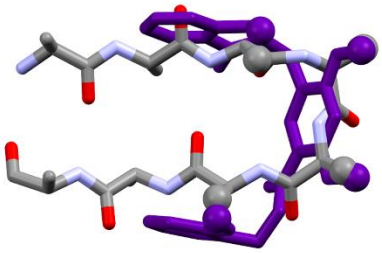
Complex	**6**	**7·hexane**	**8**	**8·MeCN**
X-ray code	17adh1h_twin5	17adh2h_sq	17adh9h	17adh8h
CCDC no.	1828445	1828448	1828446	1828447
Formula	$C_{26}H_{34}N_2O_9$	$C_{36}H_{45}N_3O_{12}$	$C_{26}H_{28}N_2O_6$	$C_{28}H_{31}N_3O_6$
Formula weight	518.55	711.75	460.50	505.56
Crystal habit	colorless plate	colorless plate	colorless rod	colorless block
Crystal size (mm)	0.02 × 0.16 × 0.37	0.02 × 0.13 × 0.45	0.10 × 0.18 × 0.54	0.20 × 0.50 × 0.54
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic
Space group (no.)	$P2_1/c$ (14)	$P\bar{1}$ (2)	$P\bar{1}$ (2)	$P\bar{1}$ (2)
***a* (Å)**	6.8984(6)	7.7667(10)	8.1703(5)	8.0883(5)
***b* (Å)**	22.5587(19)	13.9113(17)	11.1885(7)	11.3907(8)
***c* (Å)**	16.7574(14)	17.914(2)	13.5345(9)	13.8858(9)
α (°)	90	90.3087(15)	74.5027(12)	81.2009(13)
β (°)	93.9850(10)	98.9994(15)	79.0850(10)	83.7877(11)
γ (°)	90	90.9951(15)	77.1703(11)	82.7997(11)
***V* (Å^3)**	2601.5(4)	1911.3(4)	1151.30(13)	1249.11(14)
Z	4	2	2	2
***D*$_c$ (g cm^{-3})**	1.324	1.237	1.340	1.344
μ (mm^{-1})	0.100	0.093	0.096	0.095
***F*(000)**	1104	756	492	536
Total reflections	17823	24867	24918	26978
Unique reflections	11220	7024	5720	6208
***R*$_{int}$**	0.0732	0.0660	0.0260	0.0222
GOF	1.036	1.029	1.050	1.054
***R*$_1$[a] [*I* > 2σ(*I*)]**	0.0566	0.0577	0.0410	0.0399
***wR*$_2$[b] (all data)**	0.1409	0.1393	0.1152	0.1114

[a] $R_1 = \sum ||F_o|-|F_c|| / \sum |F_o|$; [b] $wR_2 = \{ \sum [w(F_o^2-F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2}$

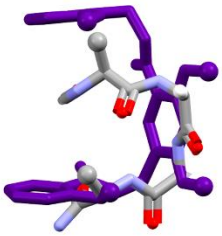
6. β-Hairpin Overlay by Turn Subtype



PDB: 1K5U; Type I
8-pt Cα-O Cβ-Me RMSD = 1.24 Å



PDB: 1FTH; Type II
8-pt Cα-O Cβ-Me RMSD = 1.11 Å



PDB: 1KKO; Type I′
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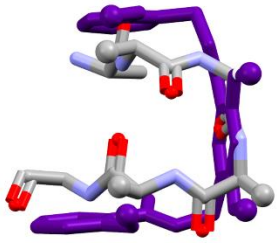

PDB: 1UXA; Type II′
8-pt Cα-O Cβ-Me RMSD = 1.16 Å

7. References

[S1] APEX2 (version 2014.11.0). Program for Bruker CCD X-ray Diffractometer Control and Data Analysis BAI, Madison, WI, (2014).

[S2] G. M. Sheldrick (2014). SHELXT - Integrated space-group and crystal-structure determination. *Acta Crystallogr. Sect. A*, **2014**, *71*, 3-8.

[S3] G. M. Sheldrick (2008). A short history of SHELX. *Acta Crystallogr. Sect. A*, **2008**, *64*, 112-122.

[S4] PLATON. A. L. Spek *Acta*. *Crystallogr*. *Sect. C*, **2015**, *71*, 9-18.