Design, synthesis, and biological evaluation of *m*-amidophenol derivatives as a new class of antitubercular agents

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Supporting Information

1. Synthesis and Chemical Information Data

Synthesis of methyl 3-methoxy-5-nitrobenzoate (2)

To a solution of methyl 3, 5-dinitrobenzoate (4.520 g, 20 mmol) in dry methanol (50 mL) was added lithium methoxide (2.2 M in methanol, 19 mL). The reaction solution was refluxed under an argon atmosphere for 4 h. After being cooled to room temperature, the solution was acidified with 1M HCl to pH=7 and extracted with ether (50 mL × 2). The combined extracts were washed with ice-cold saturated aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 40:1 ~ 20:1) to give methyl 3-methoxy-5-nitrobenzoate **2** (2.53 g, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.91 (t, J = 2.2 Hz, 1H), 7.88 (m, 1H), 3.98 (s, 3H，CH_3OOC), 3.95 (s, 3H, CH_3O).

Synthesis of (3-methoxy-5-nitrophenyl) methanol (3)

To a solution of **2** (2.53 g, 12.0 mmol) in a mixed solvent (CH_2Cl_2/CH_3OH = 9:1(V/V), 36 mL), was added sodium hydroxide (720 mg, 18.0 mmol). The reaction mixture was stirred at room temperature for 3 h. After the solvent was removed in vacuo, the residue was diluted with water (30 mL). The solution was extracted with diethyl ether (30 mL). The aqueous phase was cooled in an ice-bath, acidified to pH=2–3 with 1M HCl and extracted with AcOEt (30 mL × 2). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. 3-Methoxy-5-nitrobenzoic acid (2.32 g, 11.76 mmol, 98%) was obtained and used directly in next step without further purification. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.80 (s, 1H, COOH), 8.21 (s, 1H), 7.94 (s, 1H), 7.81 (s, 1H), 3.94 (s, 3H, CH_3).

To a suspension of $NaBH_4$ (889.7 mg, 23.52 mmol) in dry THF (20 mL) at 0°C was added a solution of 3-methoxy-5-nitrobenzoic acid (2.32 g, 11.76 mmol) in THF (20 mL) and $BF_3{\cdot}OEt_2$ (3.8 mL, 30.68 mmol). The resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with 1 M HCl (50 mL). The aqueous phase was extracted with dichloromethane (30 mL × 2). The combined organic layer was then washed with saturated aqueous Na_2CO_3, dried over anhydrous $MgSO_4$. After the solvent was evaporated in vacuo, (3-methoxy-5-nitrophenyl) methanol **3** was obtained as an orange solid (1.94 g, 10.6 mmol, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.80 (m, 1H), 7.63 (t, J = 2.2 Hz, 1H), 7.25 (d, J = 0.9 Hz, 1H), 4.77 (s, 2H, CH_2), 3.90 (s, 3H, CH_3).

Synthesis of 1-benzyl-3-methoxy-5-nitrobenzene (4)

3 (1.94 g, 10.6 mmol) and dry benzene (10 mL) were added to a flask equipped with a reflux condenser and a base trap. $AlCl_3$ (2.9 g, 21.2 mmol) in anhydrous CH_2Cl_2 (20 mL) was added portion-wise at 0°C under an argon atmosphere. The reaction mixture was then heated to 80°C and stirred for 5 h. After being cooled to room

temperature, the mixture was poured into cold water (20 mL) and stirred for 30 min. The aqueous phase was extracted with AcOEt (20 mL × 3). The combined organic layer was washed with H_2O (30 mL) and brine (20 mL), and then dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 40:1~10:1) to give 1-benzyl-3-methoxy-5-nitrobenzene **4** (1.35 g, 5.6 mmol, 53%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.56 (t, J = 2.2 Hz, 1H), 7.31 (m, 2H), 7.26 – 7.21 (m, 1H), 7.20 – 7.15 (m, 2H), 7.07 – 7.01 (m, 1H), 4.01 (s, 2H, $ArCH_2Ar$), 3.83 (s, 3H, CH_3).

Synthesis of 3-amino-5-benzylphenol (5)

To a solution of compound **4** (1.35 g, 5.6 mmol) in methylene chloride (10 mL) was added slowly a solution of BBr_3 in dichloromethane (1.0 M, 28 mL, 28 mmol) at -80°C. The resulting red solution was warmed to 0°C and stirred for 12 h. Saturated aqueous sodium bicarbonate (50 mL) was added at 0°C. The solution was extracted with dichloromethane (20 mL × 3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 20:1~5:1) to give 3-benzyl-5-nitrophenol (760 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (m, 1H), 7.55 (t, J = 2.2 Hz, 1H), 7.35 (m, 2H), 7.30 – 7.25 (m, 1H), 7.23 – 7.18 (m, 2H), 7.02 – 6.96 (m, 1H), 4.03 (s, 2H, $ArCH_2Ar$).

A solution of 3-benzyl-5-nitrophenol (760 mg, 3.32 mmol) and 10% Pd/C (152 mg) in a mixed solvent (CH_3OH/CH_2Cl_2 = 1:1(*V*/*V*), 10 mL) was purged with H_2 three times. The reaction mixture was stirred with a balloon of H_2 at room temperature for 4 h. The reaction mixture was filtered and concentrated in vacuo. The 3-amino-5-benzylphenol **5** was obtained and directly used in next step without further purification.

Synthesis of compounds 12a-12c

To a solution of compound **3** (366 mg, 2 mmol) in CH_2Cl_2 (5 mL) was added Celite® (520 mg) and PCC (518 mg, 2.4 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The mixture was concentrated in vacuo. The residue was dissolved in Et_2O (20 mL), filtered through a pad of silica gel and washed with Et_2O (20 mL). The filtrate was concentrated in vacuo to give 3-methoxy-5-nitrobenzaldehyde. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.07 (s, 1H, CHO), 8.29 (m, 1H), 7.98 (t, J = 2.2 Hz, 1H), 7.74 – 7.70 (m, 1H), 3.98 (s, 3H, CH_3).

To a stirred suspension of $CH_3CH_2PPh_3Br$ (445 mg, 1.2 mmol) in THF (4 mL) was added *n*-BuLi in hexane (2.5 M, 0.5 mL) at 0 °C. The mixture was stirred for 30 min. Then a solution of 3-methoxy-5-nitrobenzaldehyde (144.8 mg, 0.8 mmol) in THF (2 mL) was added. The reaction mixture was warmed to room temperature. After HCl (1M, 10 mL) was added, the organic phase was separated. The aqueous phase was extracted with ethyl acetate (20 mL).

The combined organic layer was washed with water, aqueous $NaHCO_3$, brine respectively, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The residue was purified by flash chromatography over silica gel to afford 1-methoxy-3-nitro-5-(prop-1-en-1-yl)benzene **10a.** **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (m, 1H), 7.55 (m, 1H), 7.11 (s, 1H), 6.44 – 5.88 (m, 2H), 3.88 (m, 3H, CH_3O), 1.94 – 1.86 (m, 3H, CH_3).

To a solution of compound **10a** (216 mg, 1.12 mmol) in methylene chloride (4 mL) was added slowly a solution of BBr_3 in dichloromethane (1.0 M, 5.6 mL, 5.6 mmol) at -80°C. The resulting red solution was warmed to 0°C and stirred for 12 h. Saturated aqueous sodium bicarbonate (10 mL) was added at 0°C. The solution was extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 20:1~5:1) to give 3-nitro-5-(prop-1-en-1-yl)phenol.

A solution of 3-nitro-5-(prop-1-en-1-yl)phenol (118 mg, 0.66 mmol) and 10% Pd/C (30 mg) in a mixed solvent (CH_3OH/CH_2Cl_2 = 1:1(*V*/*V*), 2 mL) was purged with H_2 three times. The reaction mixture was stirred with a balloon of H_2 at room temperature for 4 h. The reaction mixture was filtered and concentrated in vacuo. The 3-amino-5-propyl-phenol **11a** was obtained and directly used in next step without further purification.

To solution of 3-amino-5-propyl-phenol **11a** (75.5 mg, 0.5 mmol) and triethylamine (76.3 μL, 0.55 mmol) in THF (2 mL) was added slowly a solution of cyclohexanecarbonyl chloride (80 mg, 0.55 mmol) in THF (1 mL) at 0 °C. After the reaction mixture was stirred for 3 h at room temperature, the reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (15 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After the solvent was removed in vacuo, the crude product was purified by column chromatography (petroleum/EtOAc=20:1~2:1) to afford *N*-(3-hydroxy-5-propylphenyl)cyclohexanecarboxamide **12a** as a white solid (83 mg, 64%). m.p. 178.7–180.1°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.53 (bs, 1H, NH), 9.15 (bs, 1H, OH), 6.98 (s, 1H), 6.83 (s, 1H), 6.24 (s, 1H), 2.39(t, *J* = 8 Hz, 2H), 2.28 (m, 1H, cyclohexyl-CH) , 1.75 (m, 4H), 1.64 (m, 1H), 1.53 (m, 2H), 1.44 – 1.31 (m, 2H), 1.30 – 1.15 (m, 3H), 0.87 (t, *J* = 7.3 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 174.57 (CONH), 157.80 (C-OH), 143.77 (C-NH), 140.70, 110.57, 110.51, 104.38, 45.33 (cyclohexyl-CH), 37.94, 29.63, 25.89, 25.72, 24.28, 14.11 (CH_3); **HRMS (ESI)** calculated for $C_{16}H_{23}NO_2$ $[M-H]^-$: 260.1656, found: 260.1649. Purity: 98.4% (by HPLC).

***N*-(3-hydroxy-5-pentylphenyl)cyclohexanecarboxamide (12b)**

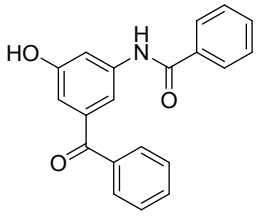
This compound was synthesized via a similar procedure of **12a.** White solid, yield 56%, m.p. 172.2–173.7°C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.55 (bs, 1H, NH), 9.16 (bs, 1H, OH), 6.98 (s, 1H), 6.83 (s, 1H), 6.24 (s, 1H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.28 (m, 1H, cyclohexyl-CH)), 1.74 (m, 4H), 1.64 (d, *J* = 11.5 Hz, 1H), 1.54 – 1.46 (m, 2H), 1.43 – 1.33

(m, 2H), 1.32 – 1.17 (m, 7H), 0.86 (t, *J* = 6.9 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 174.58 (CONH), 157.80 (C-OH), 144.02 (C-NH), 140.72, 110.51, 110.41, 104.29, 45.34 (cyclohexyl-CH), 35.77, 31.33, 30.88, 29.62, 25.89, 25.72, 22.44, 14.37; **HRMS (ESI)** calculated for $C_{18}H_{27}NO_2$ $[M-H]^{\cdot-}$: 288.1969, found: 288.1964. Purity: 98.3% (by HPLC).

***N*-(3-hydroxy-5-isopentylphenyl)cyclohexanecarboxamide (12c)**

This compound was synthesized via a similar procedure of **12a.** Yellow solid, yield 59%, m.p. 170.7–172.6°C; **^{1}H NMR** (400 MHz, CD_3OD) δ 6.97 (t, *J* = 1.9 Hz, 1H), 6.81 (m, 1H), 6.37 (m, 1H), 2.53 – 2.47 (m, 2H), 2.32 (m, 1H, cyclohexyl-CH), 1.83 (m, 4H), 1.71 (d, *J* = 10.9 Hz, 1H), 1.61 – 1.51 (m, 2H), 1.51 – 1.44 (m, 3H), 1.33 (m, 3H),0.94(s, 3H, CH_3),0.92(s, 3H, CH_3); **^{13}C NMR** (101 MHz, CD_3OD) δ 176.24 (CONH), 157.25 (C-OH), 144.56 (C-NH), 139.45, 111.26, 110.71, 104.59, 45.83 (cyclohexyl-CH), 40.44, 33.45, 29.31, 27.33, 25.50, 25.40, 21.50 (CH_3); **HRMS (ESI)** calculated for $C_{18}H_{27}NO_2$ $[M+H]^+$: 290.2115, found: 290.2102. Purity: 99.5% (by HPLC).

Synthesis of *N*-(3-benzoyl-5-hydroxyphenyl)benzamide (14)



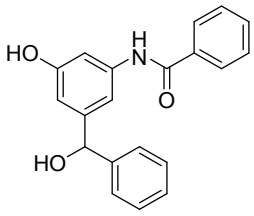
3-Methoxy-5-nitrobenzoic acid (394 mg, 2 mmol) and $SOCl_2$ (286 μL, 4 mmol) was heated at 80 °C for 2 h. After excess $SOCl_2$ was evaporated, benzene (2 mL) and $AlCl_3$ (400 mg, 3 mmol) were added at 0 °C. The mixture was stirred at room temperature overnight. After the addition of ice (5 g), the mixture was filtered. The filtrate was extracted with dichloromethane (10 mL × 2). The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo. 3-Methoxy-5-nitrophenyl)(phenyl)methanone **13** was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.15 (m, 1H), 7.93 (t, *J* = 2.3 Hz, 1H), 7.82 – 7.78 (m, 2H), 7.67 – 7.62 (m, 2H), 7.52 (M, 2H), 3.95 (s, 3H, CH_3O).

To a solution of compound **13** (385 mg, 1.5 mmol) in methylene chloride (4 mL) was added slowly a solution of BBr_3 in dichloromethane (1.0 M, 7.5 mL, 7.5 mmol) at -80°C. The resulting red solution was warmed to 0°C and stirred for 12 h. Saturated aqueous sodium bicarbonate (8 mL) was added at 0°C. The solution was extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 20:1-5:1) to give (3-hydroxy-5-nitrophenyl)(phenyl)methanone (211 mg, 58%).

A solution of (3-hydroxy-5-nitrophenyl)(phenyl)methanone (211 mg, 0.87 mmol) and iron powder (243 mg, 4.4 mmol) in a mixed solvent (AcOH/MeOH/H_2O= 2:2:1(*V/V/V*), 5 mL) was heated at 106 °C for 1 h and then the mixture was stirred at room temperature for 4 h. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 10:1-5:1) to give (3-amino-5-hydroxyphenyl)(phenyl)methanone.

To solution of (3-amino-5-hydroxyphenyl)(phenyl)methanone (106 mg, 0.5 mmol) and triethylamine (76.3 μL, 0.55 mmol) in THF (2 mL) was added slowly a solution of benzoyl chloride (63 μL, 0.55 mmol) in THF (1 mL) at 0 °C. After the reaction mixture was stirred for 3 h at room temperature, the reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (15 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After the solvent was removed in vacuo, the crude product was purified by column chromatography (petroleum/EtOAc=10:1~2:1) to afford **14** as a white solid (111 mg, 70%). m.p. 221.7–222.8°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.36 (bs, 1H, NH), 9.91 (bs, 1H, OH), 7.95 (d, *J* = 7.4 Hz, 2H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.73 (s, 1H), 7.69 (m, 1H), 7.63 (m, 1H), 7.55 (m, 5H), 6.89 (s, 1H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 196.09 (ArCOAr), 166.22 (CONH), 158.06, 140.82, 138.68, 137.73, 135.19, 133.02, 132.16, 130.00, 128.98, 128.85, 128.18, 113.23, 111.97, 111.76; **HRMS (ESI)** calculated for $C_{20}H_{15}NO_3$ $[M+H]^+$: 318.1125, found: 318.1123. Purity: 98.2% (by HPLC).

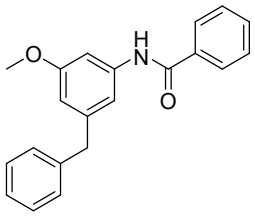
Synthesis of *N*-(3-hydroxy-5-(hydroxy(phenyl)methyl)phenyl)benzamide (15)



To a stirred solution of compound **14** (317 mg, 1 mmol) in methanol (3 mL) was added sodium borohydride (91 mg, 1.2 mmol) in portions at 0°C. The resulting mixture was warmed to room temperature and stirred for 1 h. Excessive sodium borohydride was then quenched with water (10 mL). The solution was extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with water (20 mL × 2) and brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. *N*-(3-Hydroxy-5-(hydroxy(phenyl)methyl)phenyl)benzamide **15** was obtained as a white solid (270 mg, 85%). m.p. 178.4–180.2°C; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.87 (d, *J* = 7.4 Hz, 2H), 7.52 (m, 1H), 7.46 (m, 2H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.22 (m, 2H), 7.14 (s, 1H), 6.65 (s, 1H), 5.69 (s, 1H, ArCHOHAr); **^{13}C NMR** (126 MHz, CD_3OD) δ 167.55 (CONH), 157.44, 146.53, 144.33, 139.35, 134.98, 131.42, 128.20, 127.89, 127.21, 126.88, 126.41, 110.54, 109.60,

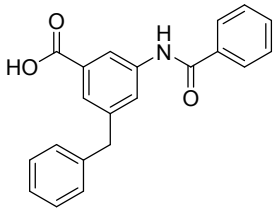
106.91, 75.50 (ArCHOHAr); **HRMS (ESI)** calculated for $C_{20}H_{17}NO_3$ $[M-H]^-$: 318.1136, found: 318.1123. Purity: 99.5% (by HPLC).

Synthesis of *N*-(3-benzyl-5-methoxyphenyl)benzamide (18)



A mixture of **7a** (30.3 mg, 0.1 mmol), iodomethane (9.33 μL, 0.15 mmol) and anhydrous K_2CO_3 (27.6 mg, 0.2 mmol) in acetone (2 mL) was refluxed for 12 h. The mixture was cooled to room temperature. After the solvent was removed in vacuo, the residue was purified by column chromatography over silica gel (hexane/EtOAc = 9:1) to give *N*-(3-Benzyl-5-methoxyphenyl)benzamide **18** as a white solid (22 mg, 69%). m.p. 116.4–117.7°C; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.88 (d, J = 7.5 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.26 (m, 3H), 7.20 (d, J = 7.2 Hz, 2H), 7.16 (t, J = 7.1 Hz, 1H), 7.11 (s, 1H), 6.56 (s, 1H), 3.91 (s, 2H, $ArCH_2Ar$), 3.75 (s, 3H, CH_3O); **^{13}C NMR** (126 MHz, CD_3OD) δ 159.40 (CONH), 152.04, 135.08, 132.83, 131.42, 126.81, 123.34, 120.45, 1120.09, 119.96, 119.10, 117.64, 105.54, 102.51, 96.12, 46.19 (CH_3O), 33.45 ($ArCH_2Ar$); HRMS (ESI) calculated for $C_{21}H_{19}NO_2$ $[M+H]^+$: 318.1489 found: 318.1485. Purity: 98.7% (by HPLC).

Synthesis of 3-benzamido-5-benzylbenzoic acid (19)



To a solution of 3-(methoxycarbonyl)-5-nitrobenzoic acid (2.3 g, 10.0 mmol) in THF (20 mL) was added dropwise BH_3·THF (1 M in THF, 20.0 mmol) at 0°C. After the completion of the addition, the cooling bath was removed and the mixture was stirred at room temperature for 24 h. The excess of borane was quenched by slow addition of saturated aqueous $NaHCO_3$ (15 mL). After the addition of ethyl acetate (40 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL × 2). The combined organic layer was washed with brine (50 mL × 2) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by column chromatography to provide methyl 3-(hydroxymethyl)-5-nitrobenzoate as a white solid (1.3 g, 60%).

3-(Hydroxymethyl)-5-nitrobenzoate (1.3 g, 6.0 mmol) and dry benzene (6 mL) were added to a flask equipped with a reflux condenser and a base trap. $AlCl_3$ (1.2 g, 9 mmol) in anhydrous CH_2Cl_2 (20 mL) was added portion-wise at 0°C under an argon atmosphere. The reaction mixture was then heated to 80°C and stirred for 5 h. After being cooled to room temperature, the mixture was poured into cold water (20 mL) and stirred for 30 min. The aqueous phase was extracted with AcOEt (15 mL × 3). The combined organic layer was washed with H_2O (20 mL) and brine (10 mL), and then dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 20:1~10:1) to give methyl 3-benzyl-5-nitrobenzoate as a red solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 7.39 – 7.30 (m, 4H), 7.29 – 7.21 (m, 1H), 4.23 (s, 2H, $ArCH_2Ar$), 3.92 (s, 3H, $COOCH_3$).

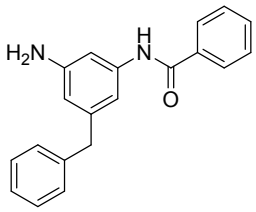
A solution of methyl 3-benzyl-5-nitrobenzoate (542 mg, 2 mmol) and 10% Pd/C (108 mg) in a mixed solvent (CH_3OH/CH_2Cl_2 = 1:1(*V*/*V*), 8 mL) was purged with H_2 three times. The reaction mixture was stirred with a balloon of H_2 at room temperature for 4 h. The reaction mixture was filtered and concentrated in vacuo. The methyl 3-amino-5-benzylbenzoate was obtained and directly used in next step without further purification.

To a solution of methyl 3-amino-5-benzylbenzoate (120 mg, 0.5 mmol) and triethylamine (76.3 µL, 0.55 mmol) in THF (2 mL) was added slowly a solution of benzoyl chloride (63 µL, 0.55 mmol) in THF (1 mL) at 0 °C. After the reaction mixture was stirred for 3 h at room temperature, the reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (15 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After the solvent was removed in vacuo, the crude product was purified by column chromatography (petroleum/EtOAc=40:1~10:1) to afford methyl 3-benzamido-5-benzylbenzoate as a white solid (112 mg, 65%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.42 (s, 1H, NH), 8.35 (s, 1H), 7.99 (m, 3H), 7.61 (m, 2H), 7.55 (m, 2H), 7.33 (m, 2H), 7.30 – 7.20 (m, 3H), 4.05 (s, 2H, $ArCH_2Ar$), 3.87 (s, 3H, $COOCH_3$).

To a solution of methyl 3-benzamido-5-benzylbenzoate (112 mg, 0.33 mmol) in a mixed solvent (CH_2Cl_2/CH_3OH = 9:1(*V*/*V*), 2 mL), was added sodium hydroxide (20 mg, 0.5 mmol). The reaction mixture was stirred at room temperature for 3 h. After the solvent was removed in vacuo, the residue was diluted with water (10 mL). The solution was extracted with diethyl ether (10 mL). The aqueous phase was cooled in an ice-bath, acidified to pH=2–3 with 1M HCl and extracted with AcOEt (10 mL × 2). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford 3-benzamido-5-benzylbenzoic acid as a white solid. m.p. 262.1–263.8°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.9 (s, 1H, COOH), 10.37 (s, 1H, NH), 8.29 (s, 1H), 7.96 (m, 3H), 7.56 (m, 4H), 7.32 (m, 2H), 7.29 – 7.18 (m, 3H), 4.03 (s, 2H, $ArCH_2Ar$); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.88 (COOH), 165.60 (CONH), 142.38, 140.81, 139.47, 134.78, 131.74, 131.34, 128.88, 128.56, 128.34, 127.68, 126.17,

124.83, 124.67, 119.16, 41.13 ($ArCH_2Ar$); HRMS (ESI) calculated for $C_{21}H_{17}NO_3$ $[M+H]^+$: 332.1281 found: 332.1277. Purity: 99.2% (by HPLC).

Synthesis of *N*-(3-amino-5-benzylphenyl)benzamide (20)



To a solution of 3, 5-dinitrobenzoic acid (2.12 g, 10.0 mmol) in THF (20 mL) was added dropwise BH_3·THF (1 M in THF, 20.0 mmol) at 0°C. After the completion of the addition, the cooling bath was removed and the mixture was stirred at room temperature for 24 h. The excess of borane was quenched by slow addition of saturated aqueous $NaHCO_3$ (15 mL). After the addition of ethyl acetate (40 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL × 2). The combined organic layer was washed with brine (50 mL × 2) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by column chromatography to provide (3, 5-dinitrophenyl)methanol as a white solid (970 mg, 49%).

(3, 5-Dinitrophenyl)methanol (970 mg, 4.9 mmol) and dry benzene (5 mL) were added to a flask equipped with a reflux condenser and a base trap.

$AlCl_3$ (978 mg, 7.4 mmol) in anhydrous CH_2Cl_2 (15 mL) was added portion-wise at 0°C under an argon atmosphere. The reaction mixture was then heated to 80°C and stirred for 5 h. After being cooled to room temperature, the mixture was poured into cold water (20 mL) and stirred for 30 min. The aqueous phase was extracted with AcOEt (15 mL × 3). The combined organic layer was washed with H_2O (15 mL) and brine (10 mL), and then dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 20:1~10:1) to give 1-benzyl-3, 5-dinitrobenzene as a red solid.

3-Benzyl-5-nitroaniline was synthesized according to a reported method [1]. To a mixture of 1-benzyl-3, 5-dinitrobenzene (456 mg, 2 mmol) and iron phthalocyanine (FePc) (0.5 mol %) in water/ethanol (*V*/*V*=1:1, 15 mL) was added hydrazine hydrate (200 mg, 4 mmol) was added. The reaction solution was refluxed at 120 °C. After the completion of the reaction as indicated by TLC analysis, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (25 mL × 2). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford 3-Benzyl-5-nitroaniline as a green solid.

To a solution of 3-benzyl-5-nitroaniline (342 mg, 1.5 mmol) and triethylamine (229 μL, 1.65 mmol) in THF (6 mL)

was added slowly a solution of benzoyl chloride (189 μL, 1.65 mmol) in THF (3 mL) at 0 °C. After the reaction mixture was stirred for 3 h at room temperature, the reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (25 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After the solvent was removed in vacuo, the crude product was purified by column chromatography (petroleum/EtOAc=40:1~10:1) to afford *N*-(3-benzyl-5-nitrophenyl)benzamide as a white solid.

A solution of *N*-(3-benzyl-5-nitrophenyl)benzamide (166 mg, 0.5 mmol) and 10% Pd/C (33 mg) in a mixed solvent (CH_3OH/CH_2Cl_2 = 1:1(V/V), 5 mL) was purged with H_2 three times. The reaction mixture was stirred with a balloon of H_2 at room temperature for 4 h. The reaction mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography (petroleum/EtOAc=10:1~2:1) to afford 20 as a white solid. Yield 38%. m.p. 155.3–157.1°C; 1H NMR (500 MHz, DMSO-d_6) δ 9.91 (bs, 1H, NH), 7.91 (d, J = 6.7 Hz, 2H), 7.55 (m, 1H), 7.51 (m, 2H), 7.29 (m, 2H), 7.26 – 7.13 (m, 3H), 6.97 (s, 1H), 6.77 (s, 1H), 6.18 (s, 1H), 5.07 (s, 2H, NH_2), 3.75 (s, 2H, $ArCH_2Ar$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.69 (CONH), 149.34, 142.18, 141.91, 140.22, 135.76, 131.74, 129.16, 128.77, 128.72, 128.06, 126.31, 110.79, 109.57, 104.62, 42.07 ($ArCH_2Ar$); HRMS (ESI) calculated for $C_{20}H_{18}N_2O$ [M+H]+: 303.1492, found: 303.1497. Purity: 97.7% (by HPLC).

2. Mtb-InhA inhibition assay

The expression, isolation and purification of Mtb-InhA were performed as described in the reference.[2] The substrate 2-*trans*-octenoyl coenzyme A (C8-CoA) was synthesized according to the reported procedure.[3-4] The assays were performed via the comparison of the reduction rate of C8-CoA by NADH catalyzed by InhA with or without the tested compound. The percentage of InhA inhibition was measured by monitoring the transformation of NADH to NAD+.[5] Triclosan was used as the positive control. The reaction system consisted of 100 nM InhA, 50 μM inhibitor and 250 μM NADH in the buffer with 30 mM PIPES, 150 mM NaCl and 1 mM EDTA (pH 6.8). After being incubated at 25°C for 5 minutes, C8-CoA was added to the solution and the final concentration was 25 μM. The blank control was performed at the same conditions without the inhibitor. The inhibitory activity against Mtb-InhA was determined by observing the changes of UV absorbance at 340 nm.

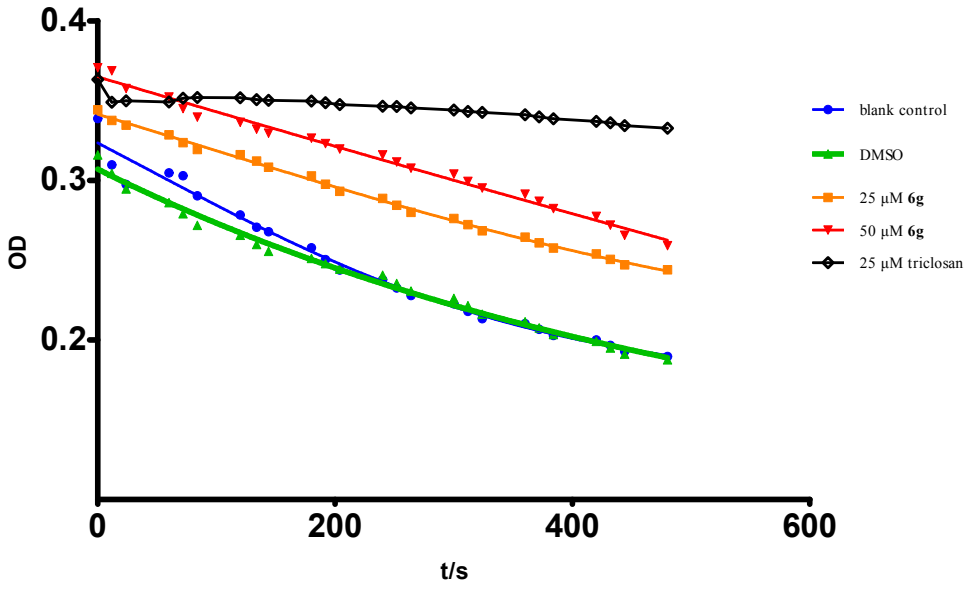


Figure1. Enzyme inhibition experiment of **6g** against Mtb-InhA.

3. References

[1] U. Sharma, P. K. Verma, N. Kumar, V. Kumar, M. Bala, B. Singh, *Chem. Eur. J.* **2011**, *17*, 5903-5907.

[2] X. He, A. Alian, R. Stroud, PDM Ortiz, *J. Med. Chem.* **2006**, *49*, 6308-6323.

[3] S. Parikh, D. P. Moynihan, G. Xiao, P. J. Tonge, *Biochemistry* **1999**, *38*, 13623-13634.

[4] A. Quemard, J. C. Sacchettini, A. Dessen, C. Vilcheze, R. Bittman, W. R. Jr. Jacobs, J. S. Blanchard, *Biochemistry* **1995**, *34*, 8235-824.

[5] A. Chollet, G. Mori, C. Menendez, F. Rodriguez, I. Fabing, M. R. Pasca, J. Madacki, J. Korduláková, P. Constant, A. Quémard, V. B. Génisson, C. Lherbet, M. Baltas, *Eur. J. Med. Chem.* **2015**, *101*, 218-235.

4. Copies of NMR spectra

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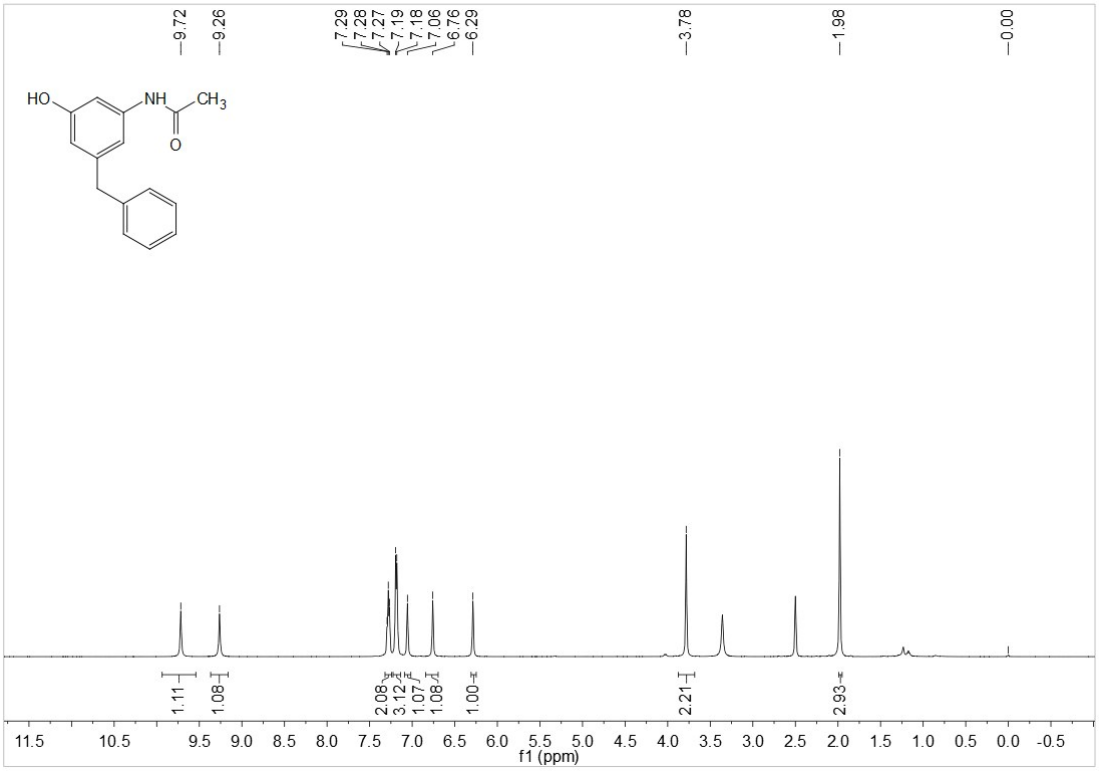

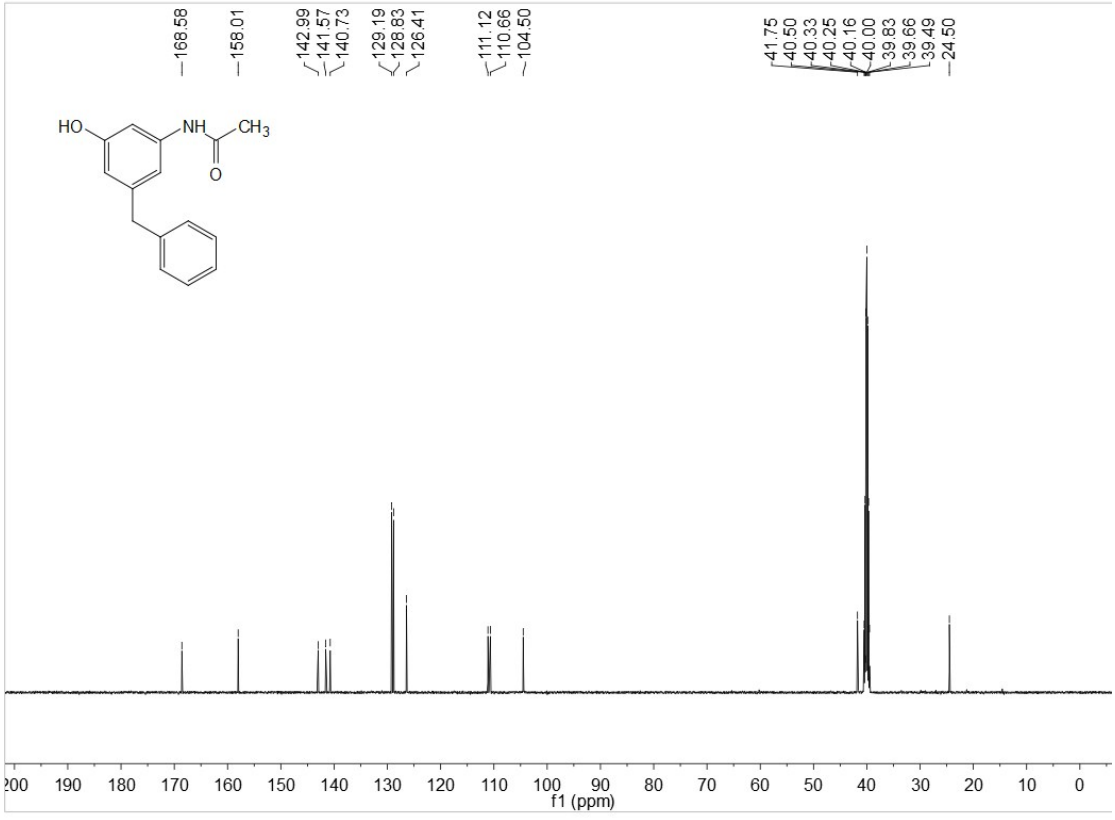

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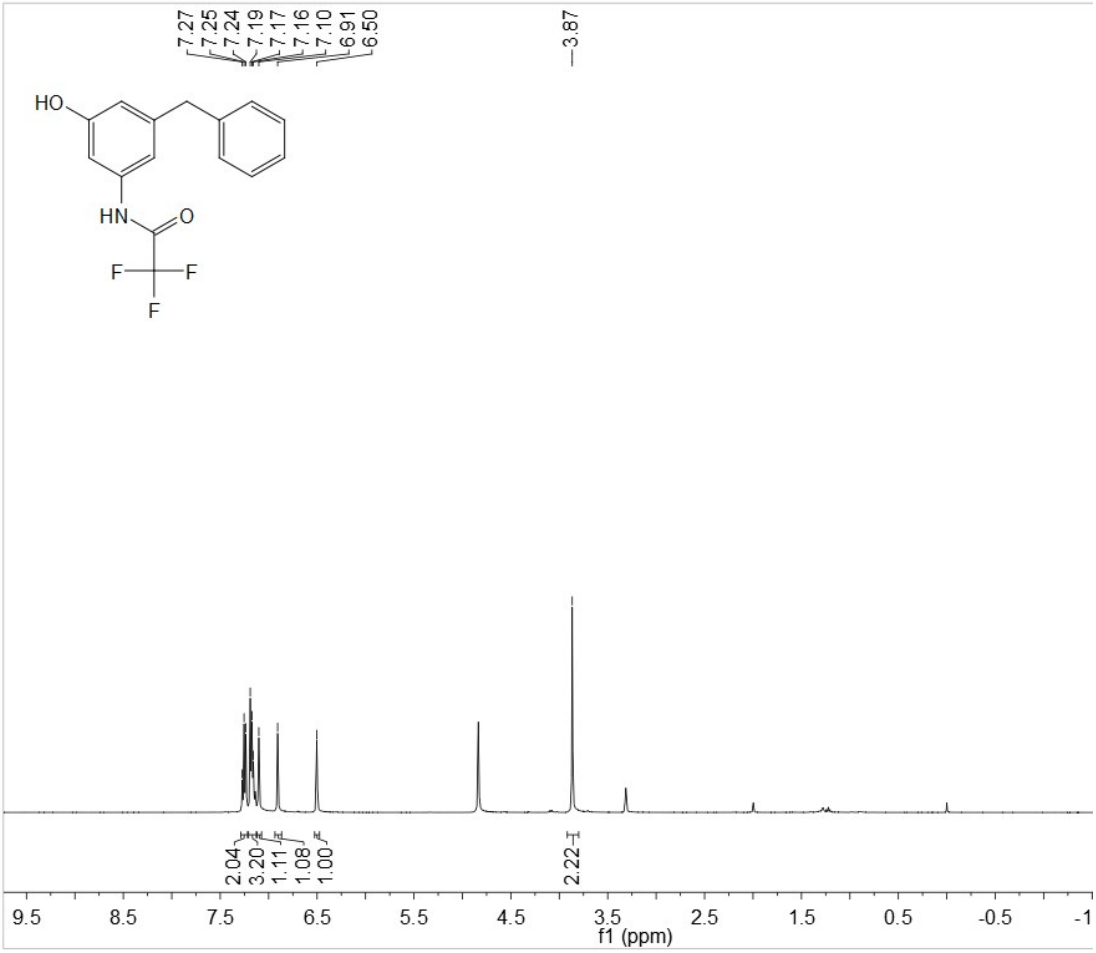
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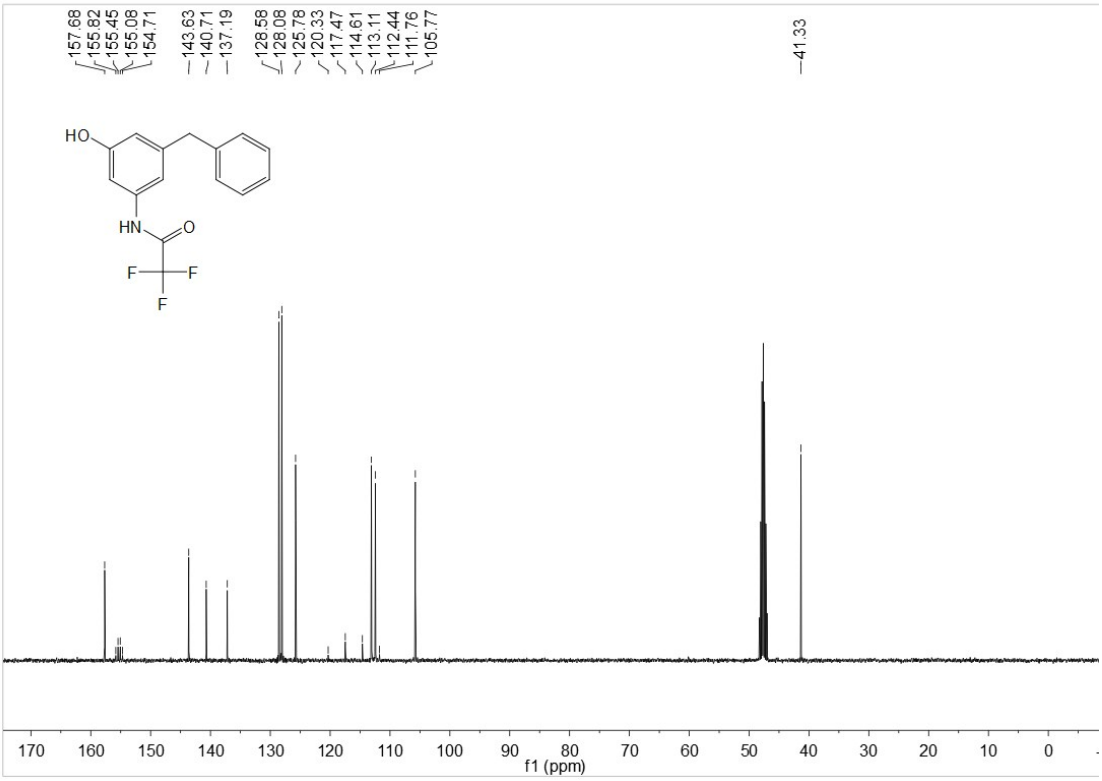
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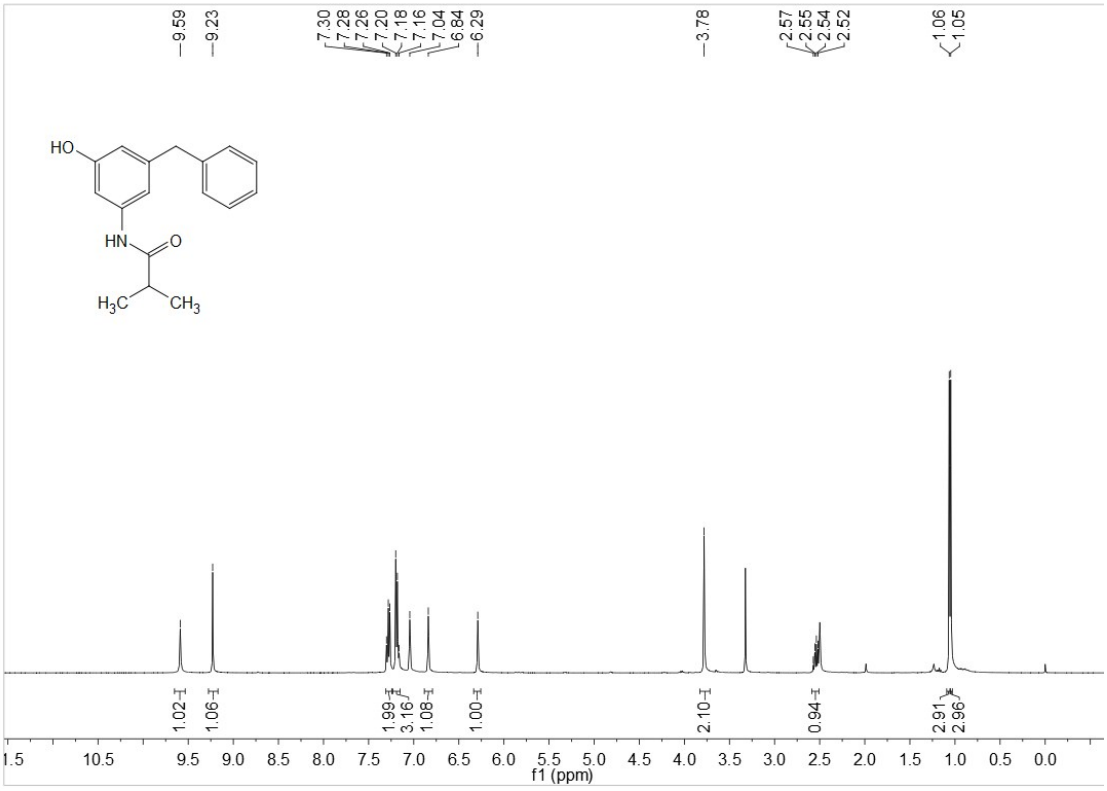
6c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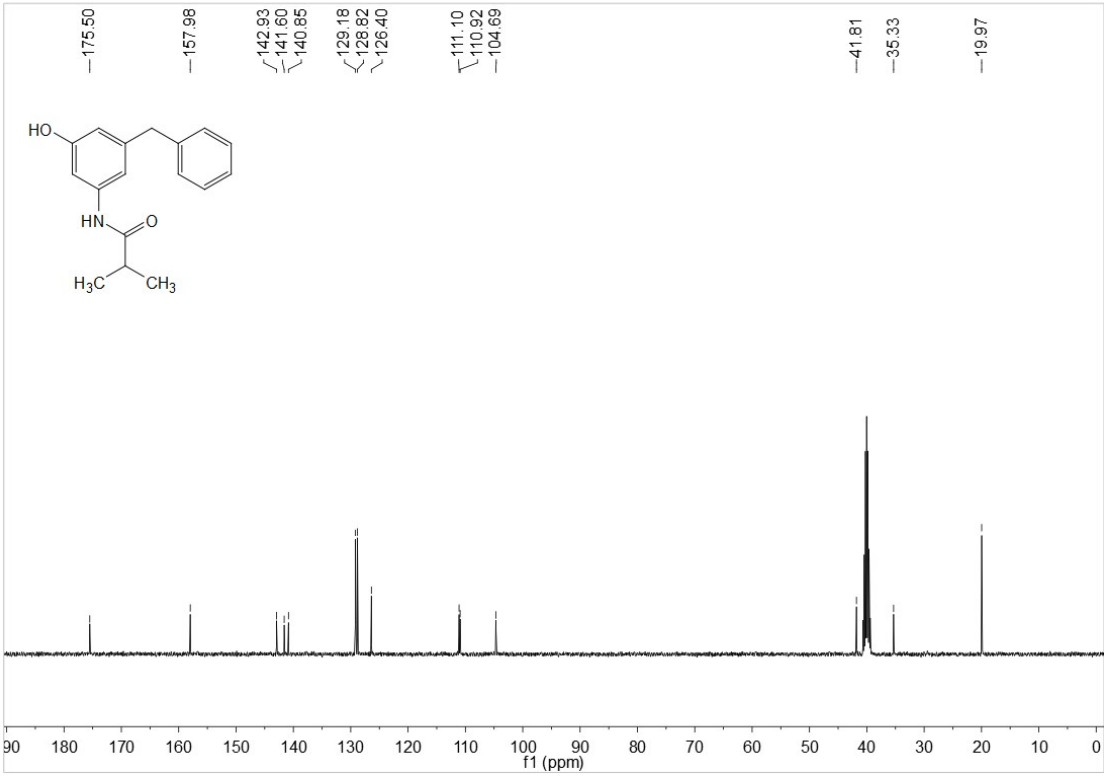
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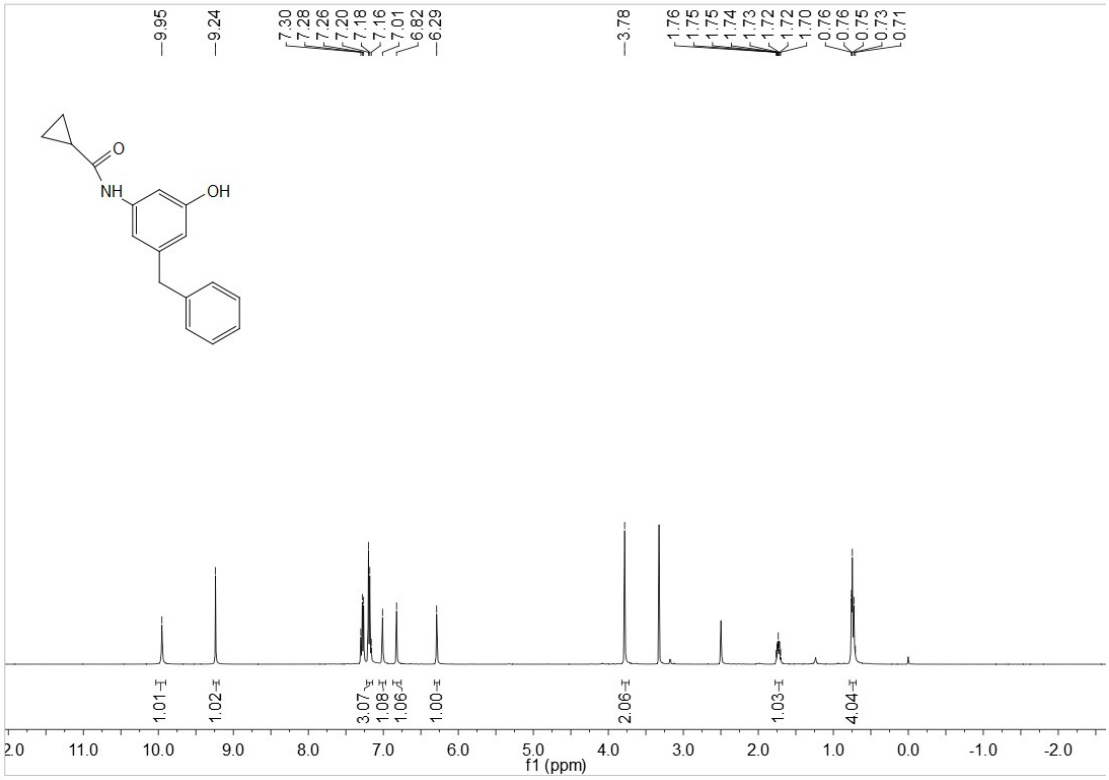
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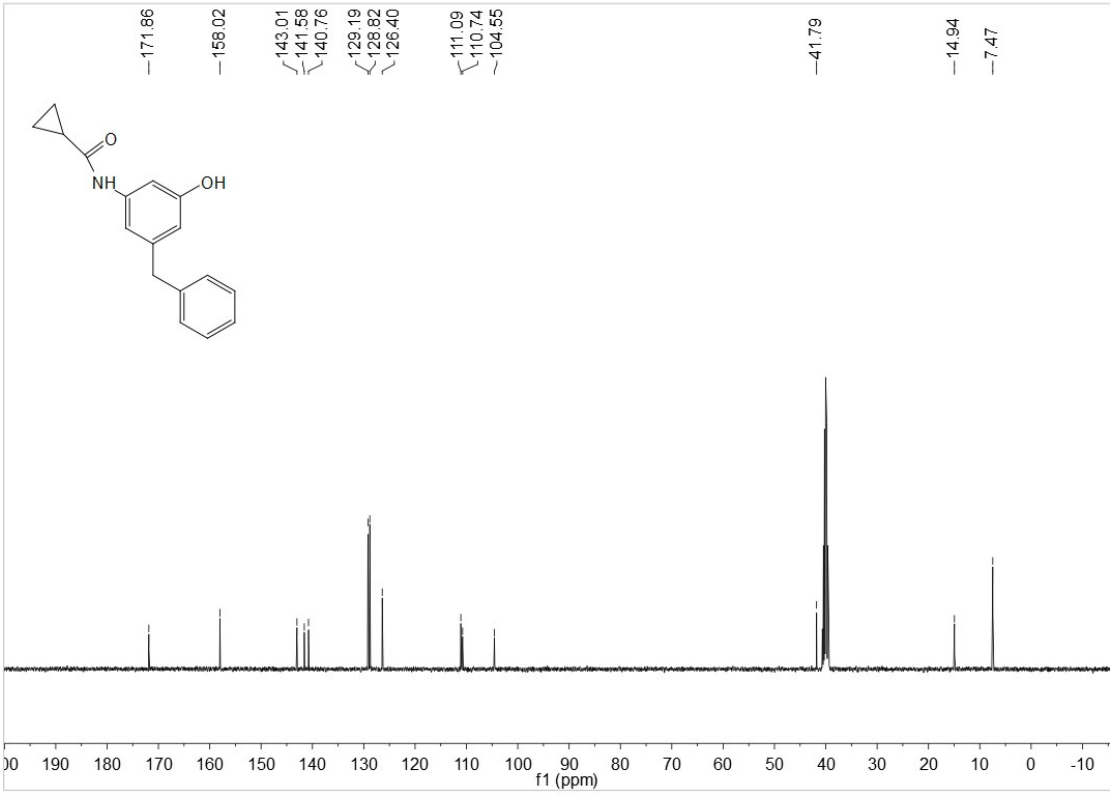
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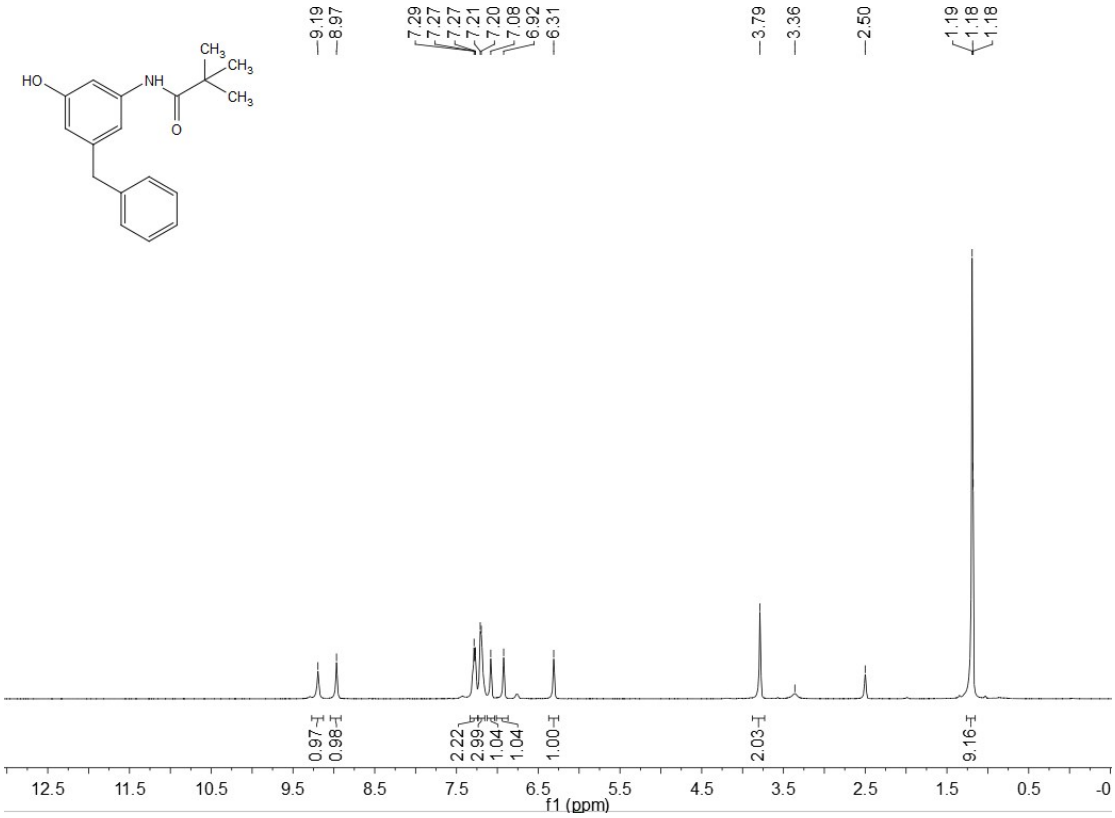
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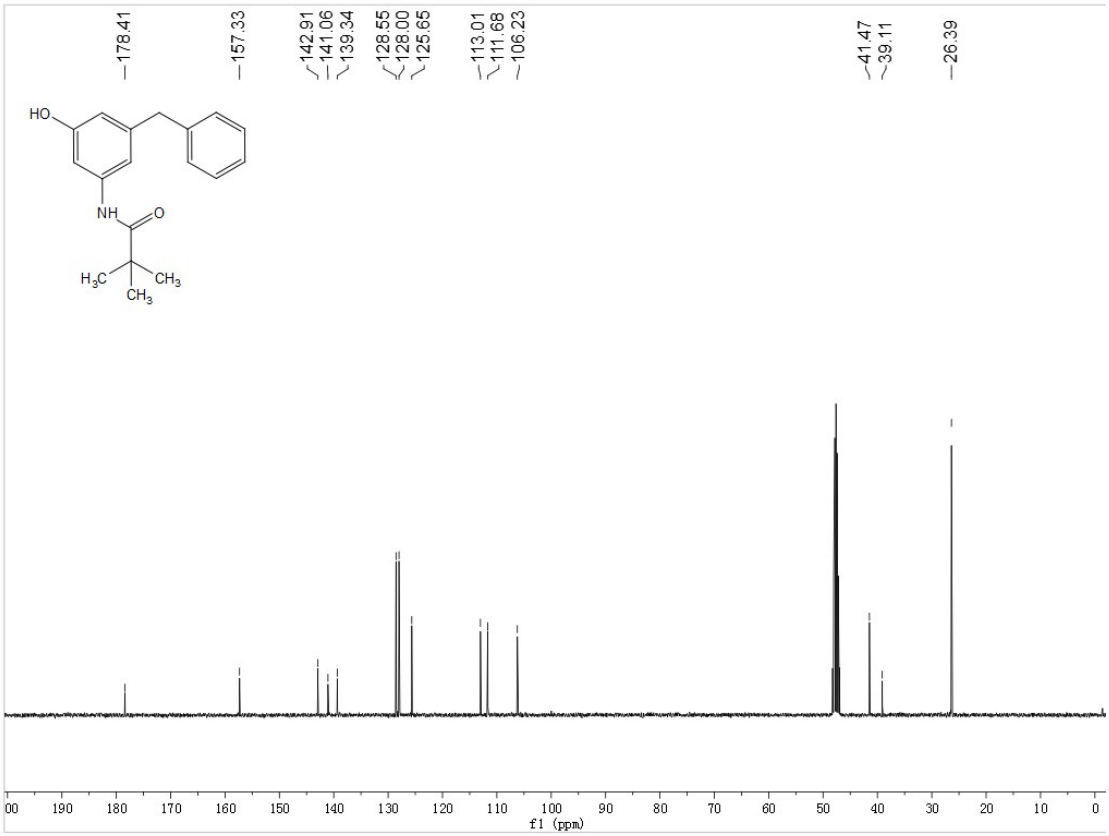
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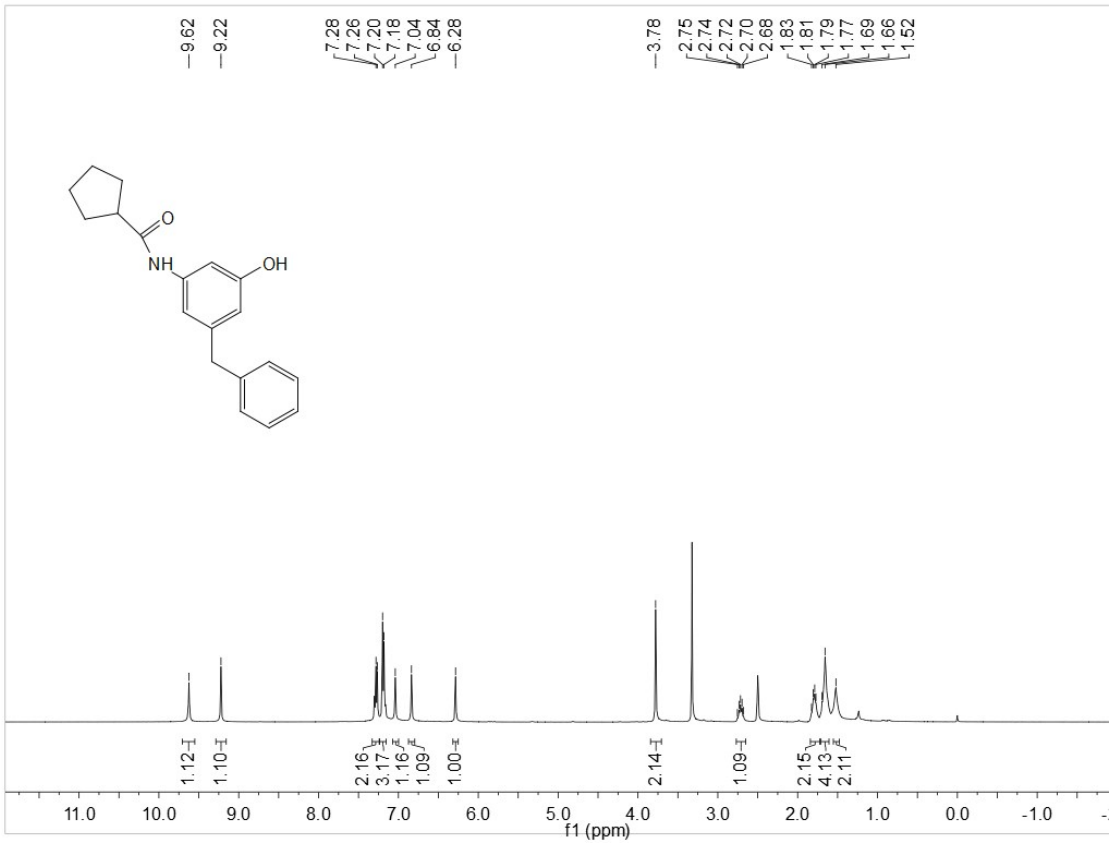
6f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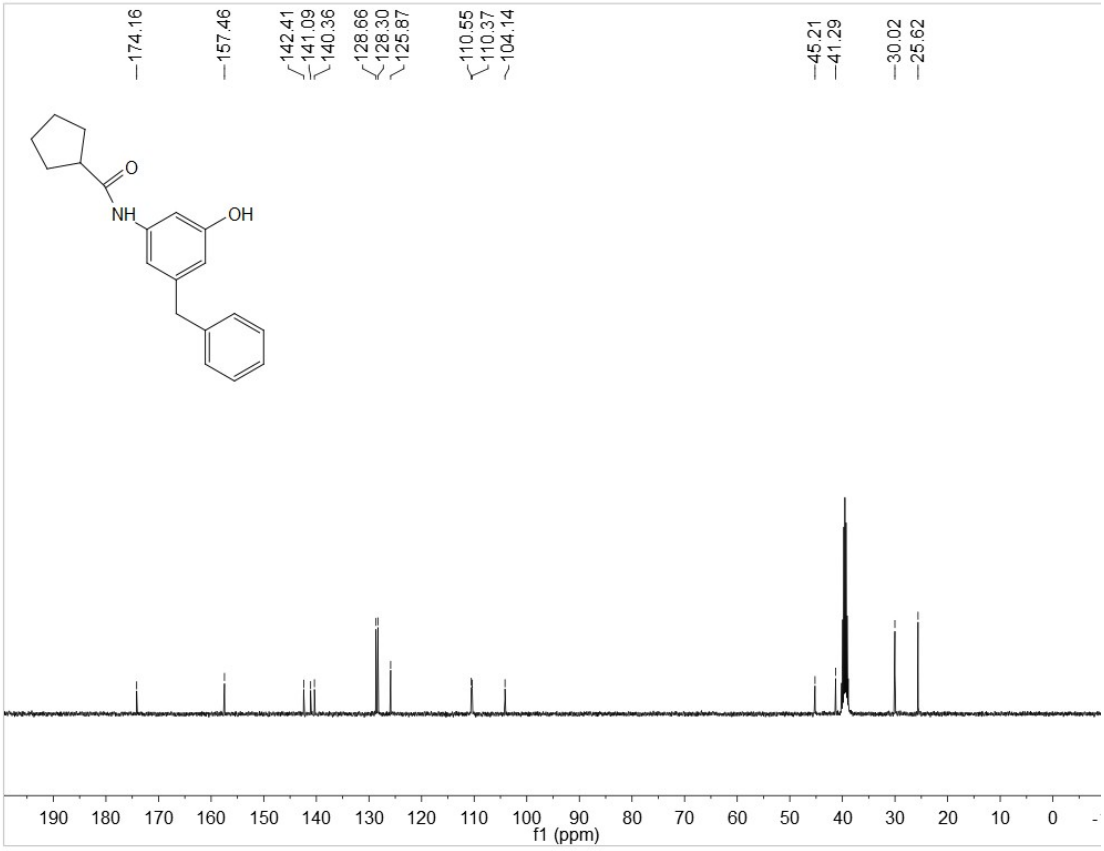
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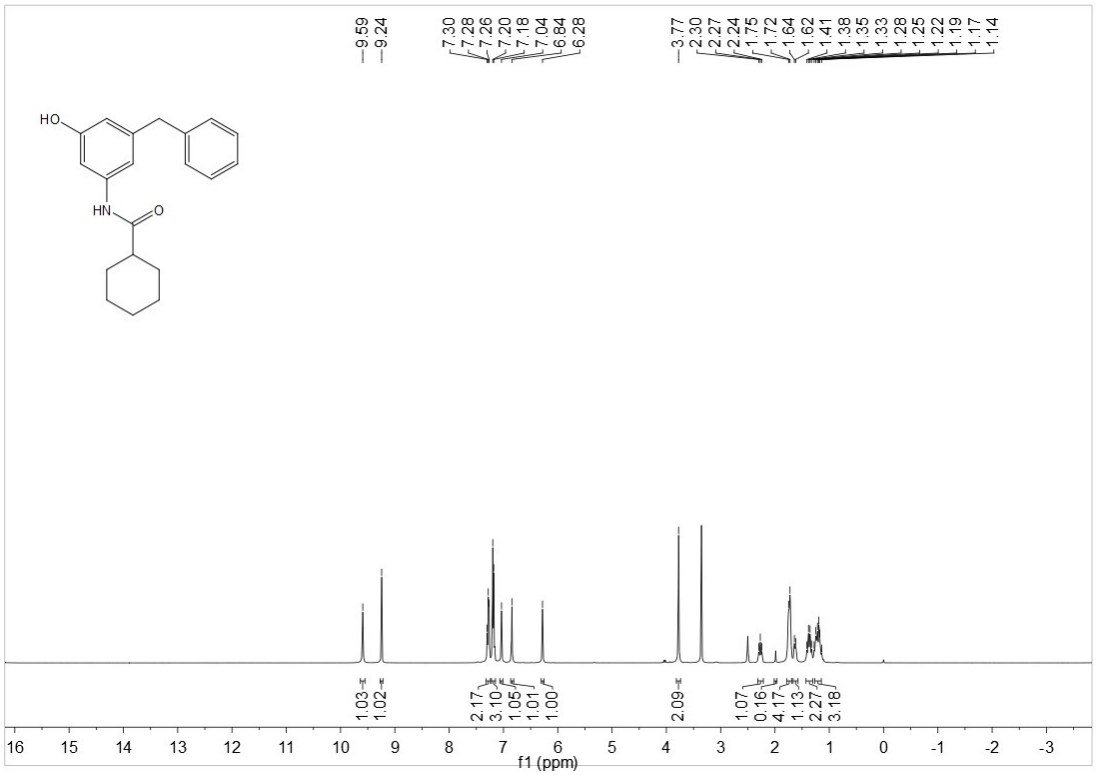
6g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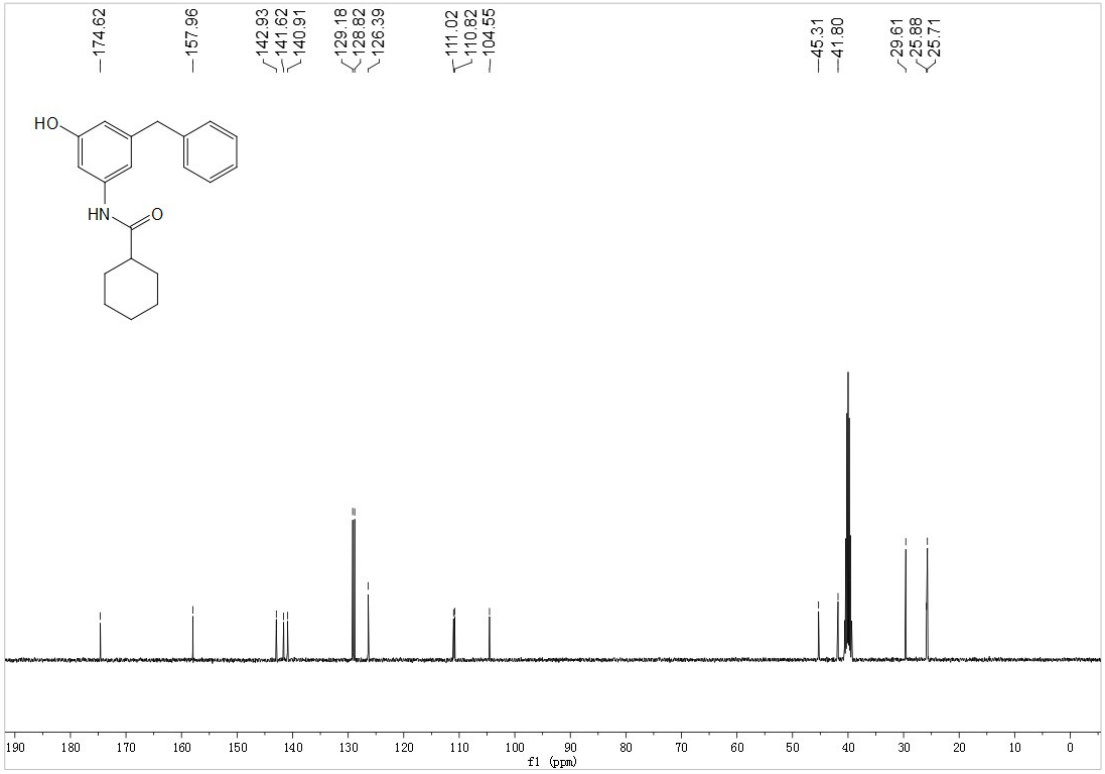
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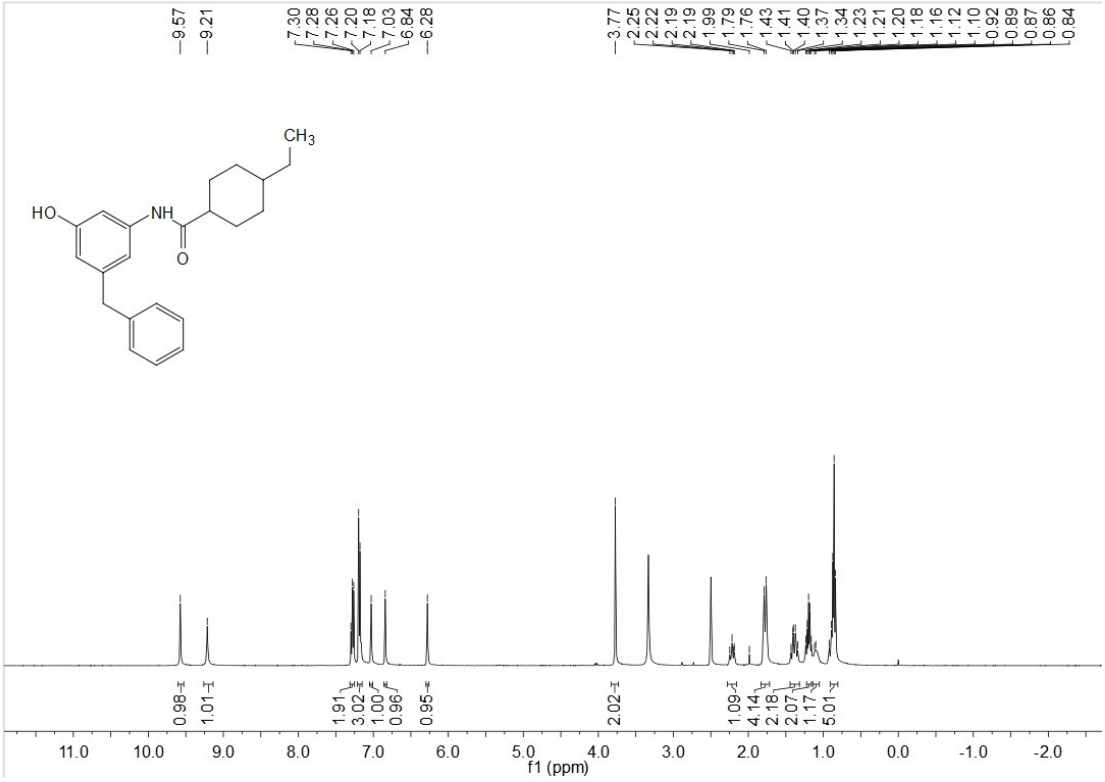
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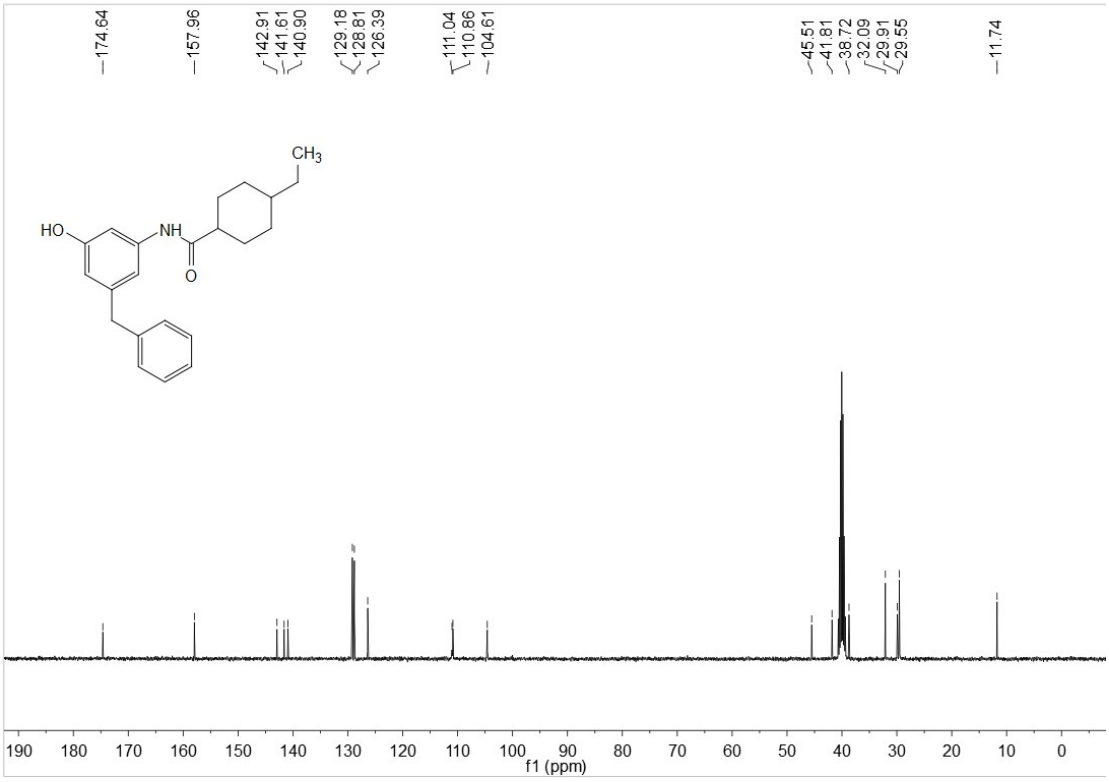
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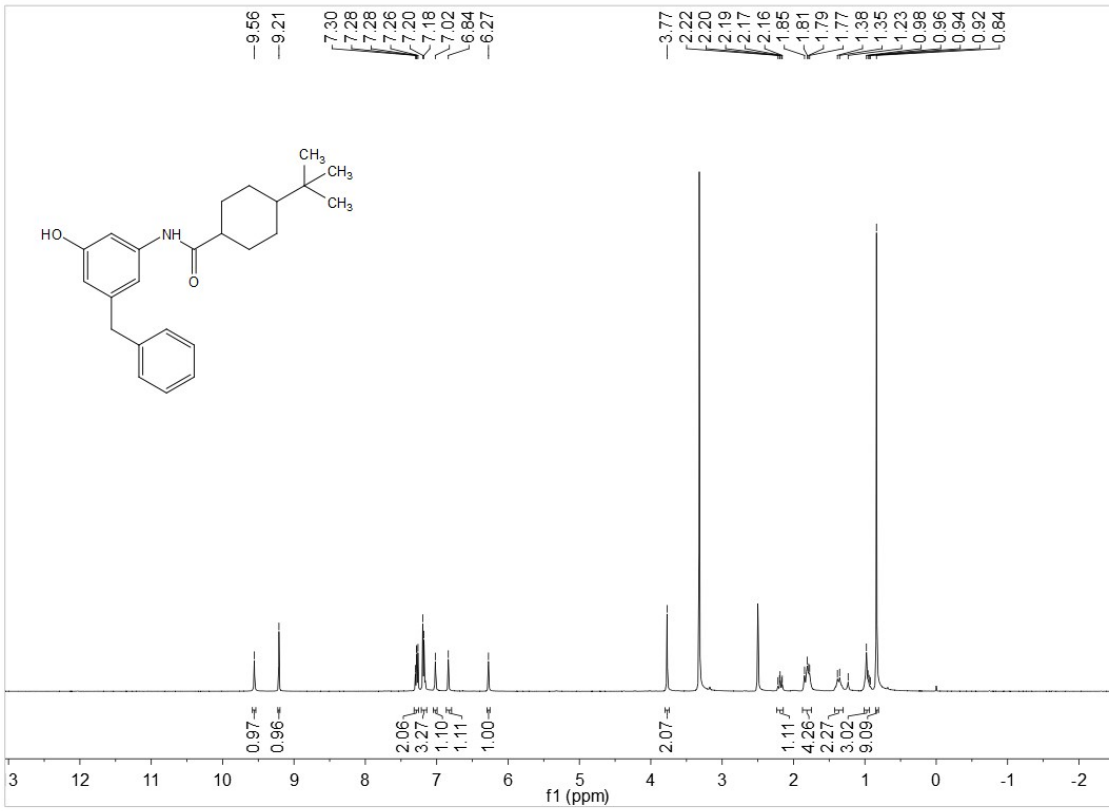
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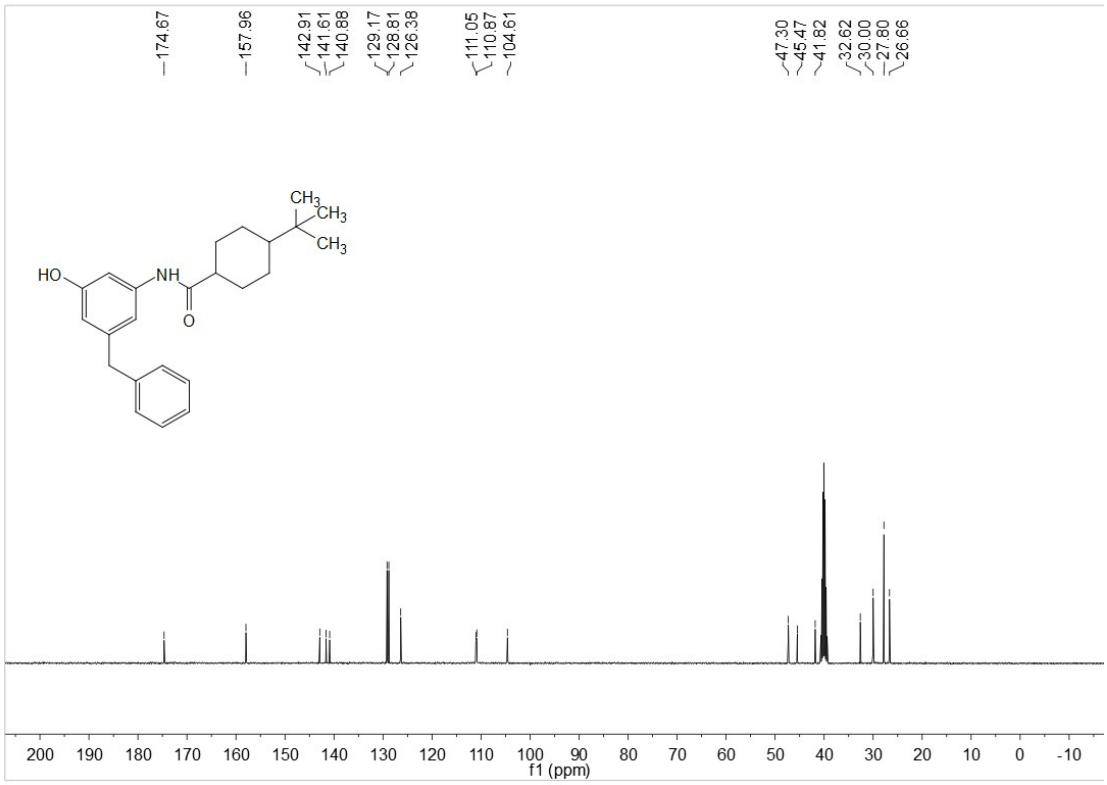
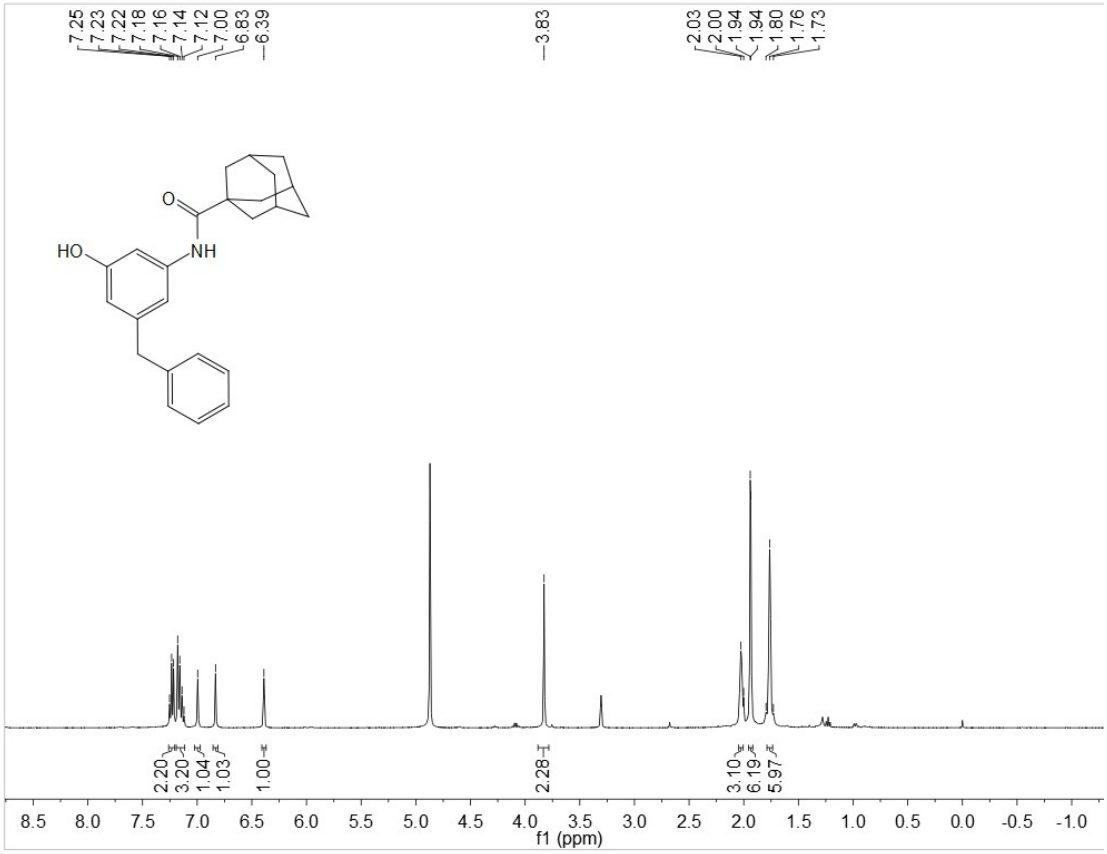
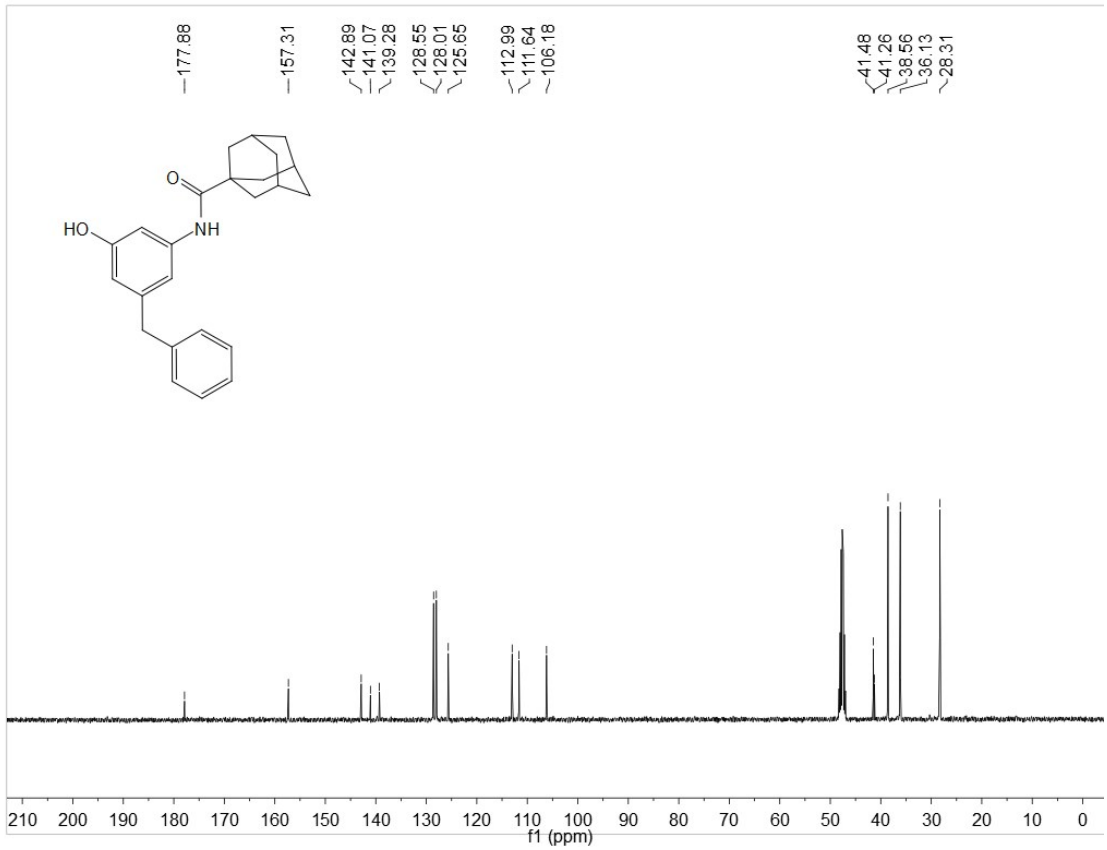
9.09
f1 (ppm)

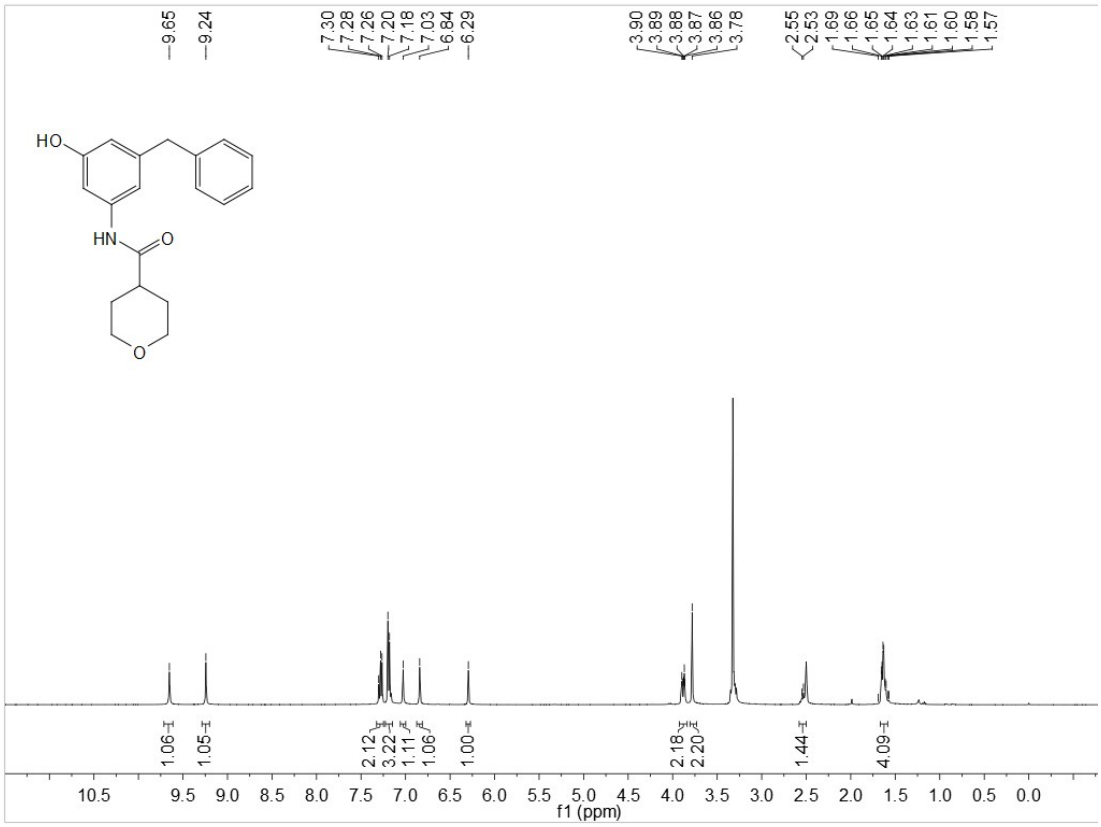

174.67
157.96
142.91
141.61
140.88
129.17
128.81
126.38
111.05
110.87
104.61
47.30
45.47
41.82
32.62
30.00
27.80
26.66
HO
NH
O
CH3
CH3
CH3
f1 (ppm)

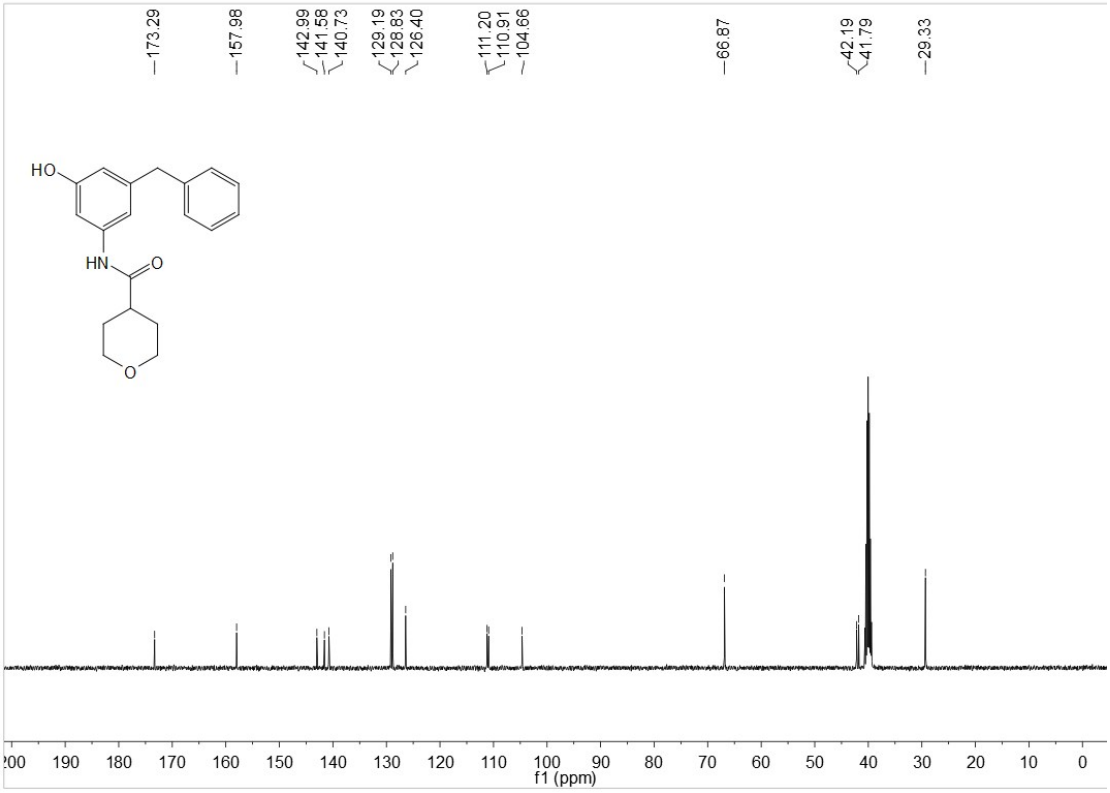
6j


7.25
7.23
7.22
7.18
7.16
7.14
7.12
7.00
6.83
6.39
3.83
2.03
2.00
1.94
1.94
1.80
1.76
1.73
O
NH
HO
2.20
3.20
1.04
1.03
1.00
2.28
3.10
6.19
5.97
f1 (ppm)

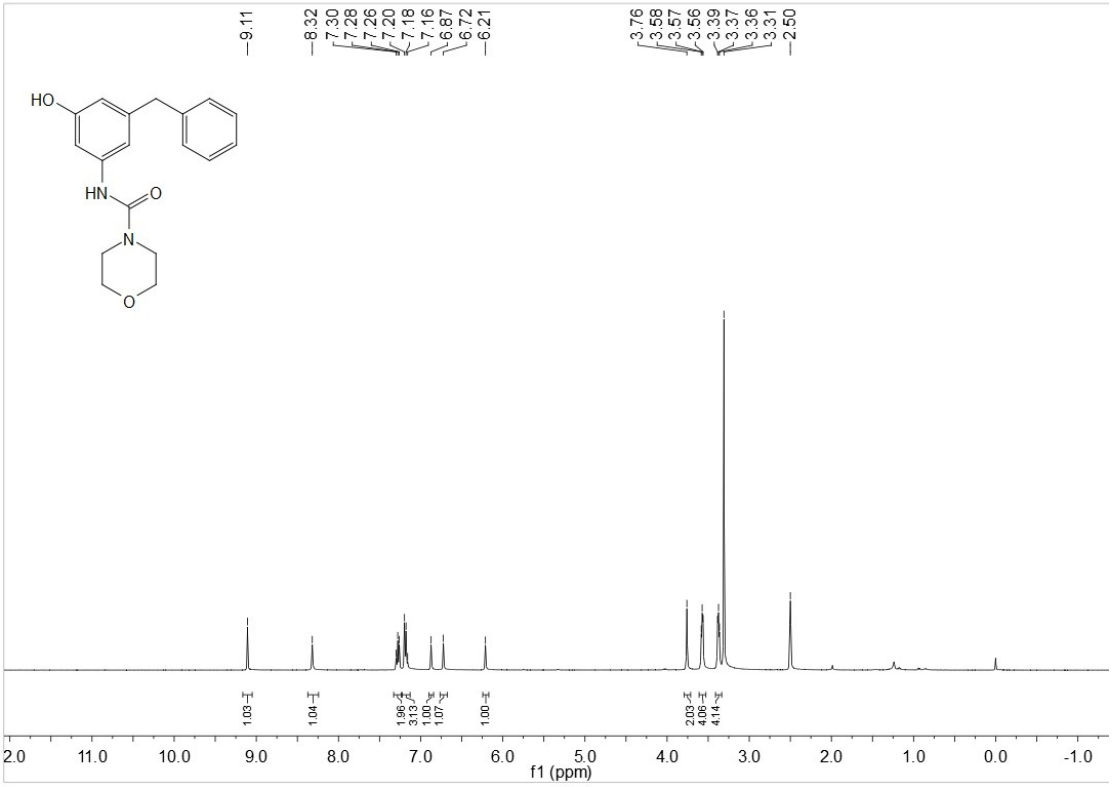

177.88
157.31
142.89
141.07
139.28
128.55
128.01
125.65
112.99
111.64
106.18
41.48
41.26
38.56
36.13
28.31
O
NH
HO
f1 (ppm)

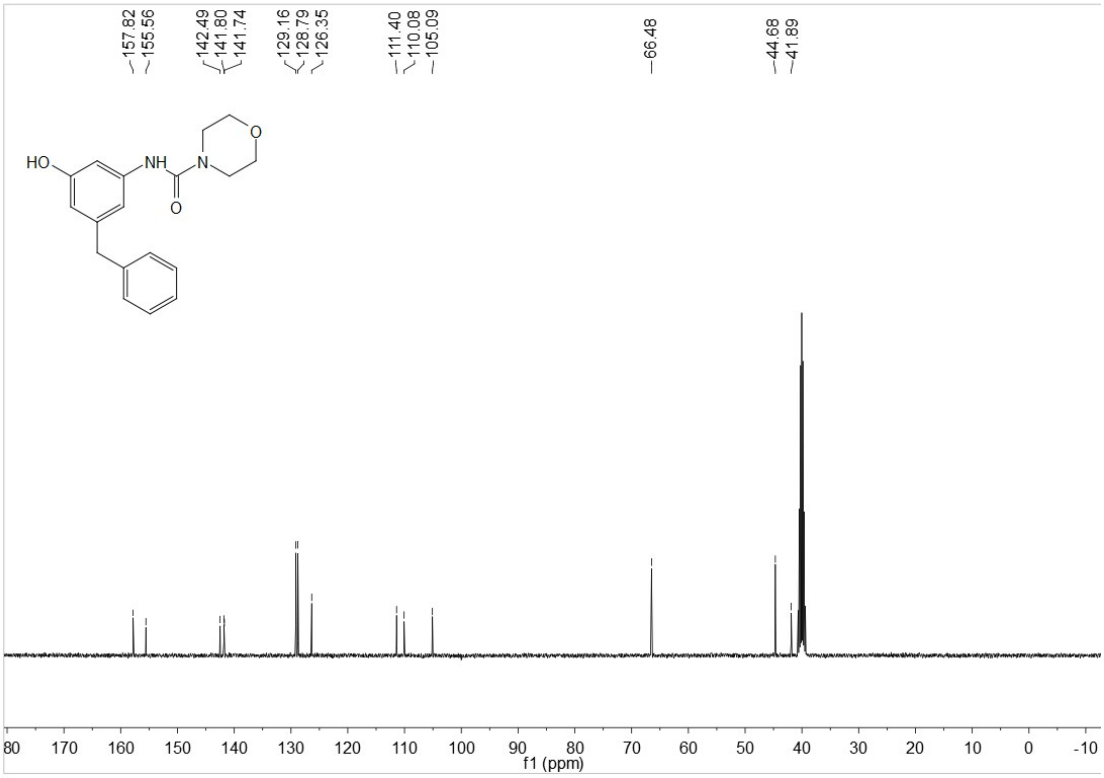
6k


9.65
9.24
7.30
7.28
7.26
7.20
7.18
7.03
6.84
6.29
3.90
3.89
3.88
3.87
3.86
3.78
2.55
2.53
1.69
1.66
1.65
1.64
1.63
1.61
1.60
1.58
1.57
HO
HN
O
O
1.06
1.05
2.12
3.22
1.11
1.06
1.00
2.18
2.20
1.44
4.09
f1 (ppm)

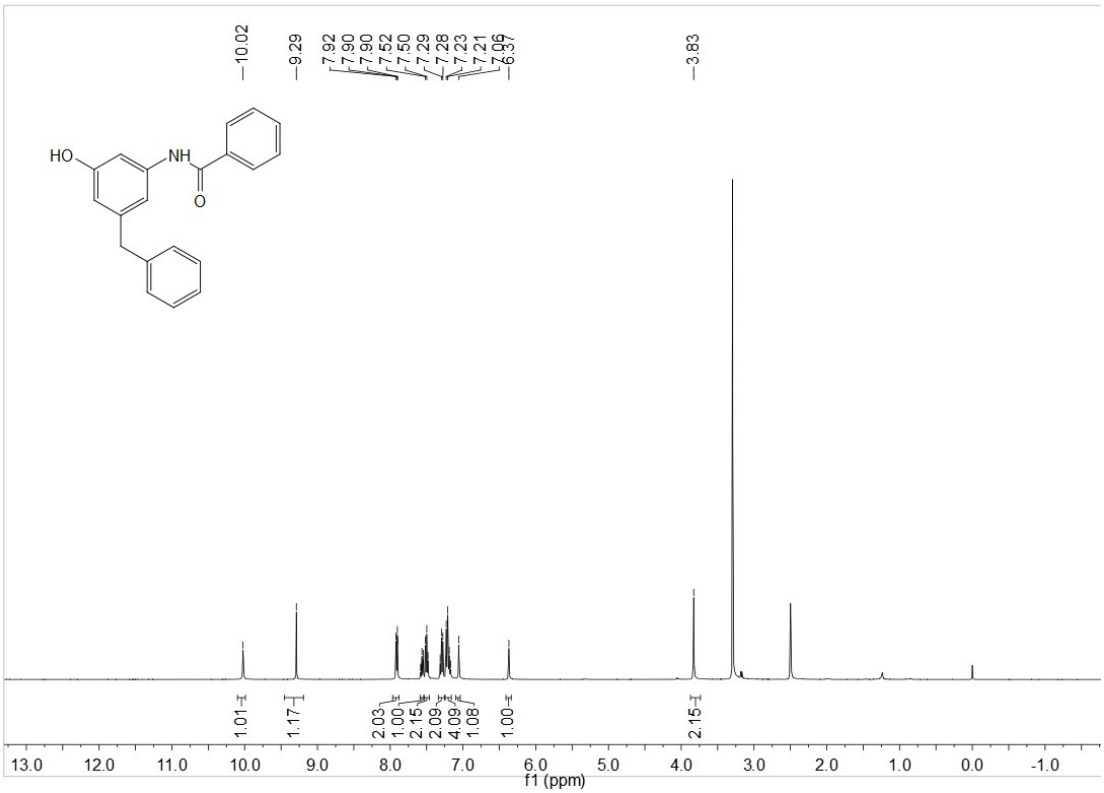

173.29
157.98
142.99
141.58
140.73
129.19
128.83
126.40
111.20
110.91
104.66
66.87
42.19
41.79
29.33
HO
HN
O
O
f1 (ppm)

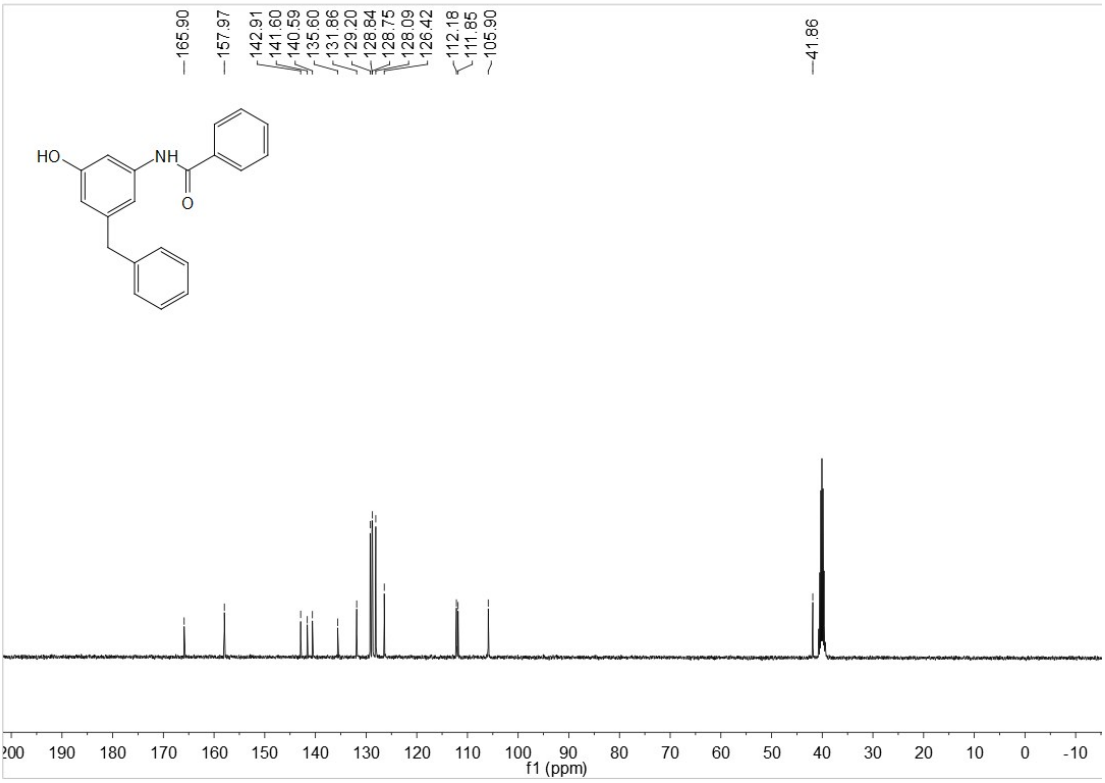
6l


9.11
8.32
7.30
7.28
7.26
7.20
7.18
7.16
6.87
6.72
6.21
3.76
3.58
3.57
3.56
3.39
3.37
3.36
3.31
2.50
HO
HN
O
N
O
1.03
1.04
1.96
3.13
1.00
1.07
1.00
2.03
4.06
4.14
f1 (ppm)

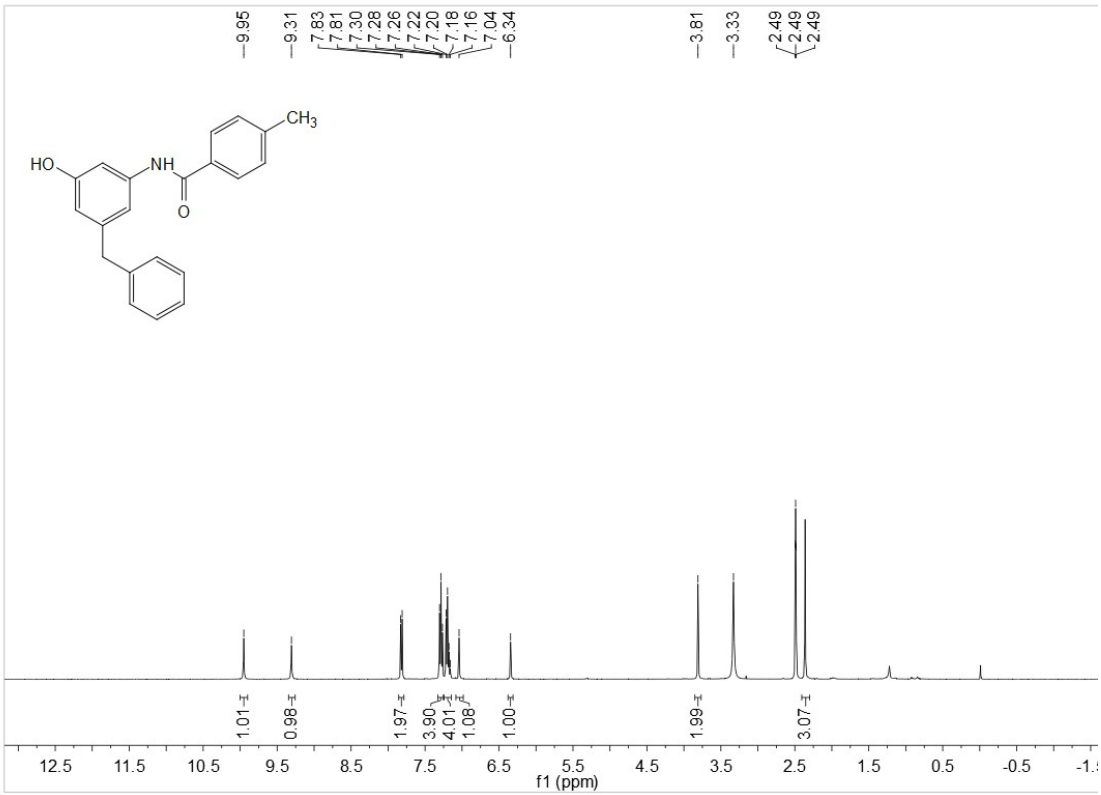

157.82
155.56
142.49
141.80
141.74
129.16
128.79
126.35
111.40
110.08
105.09
66.48
44.68
41.89
HO
NH
O
N
O
f1 (ppm)

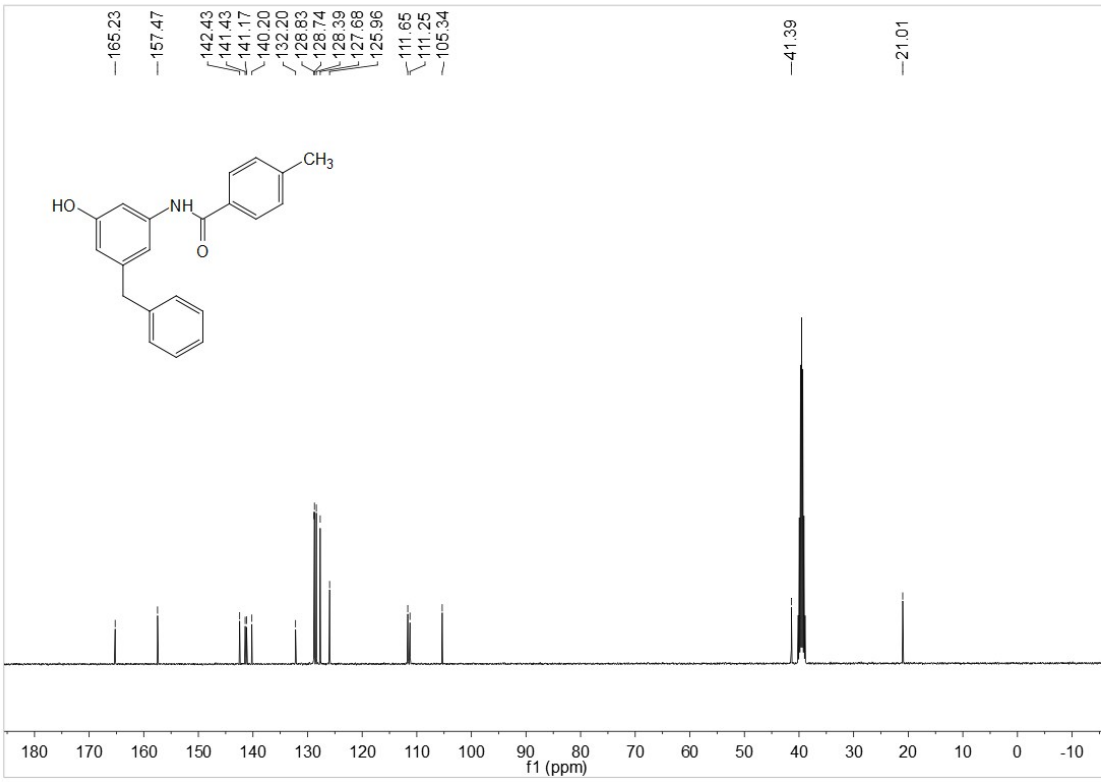
7a


10.02
9.29
7.92
7.90
7.90
7.52
7.50
7.29
7.28
7.23
7.21
7.06
6.97
3.83
HO
NH
O
1.01
1.17
2.03
1.00
2.15
2.09
4.09
1.08
1.00
2.15
13.0 12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0
f1 (ppm)

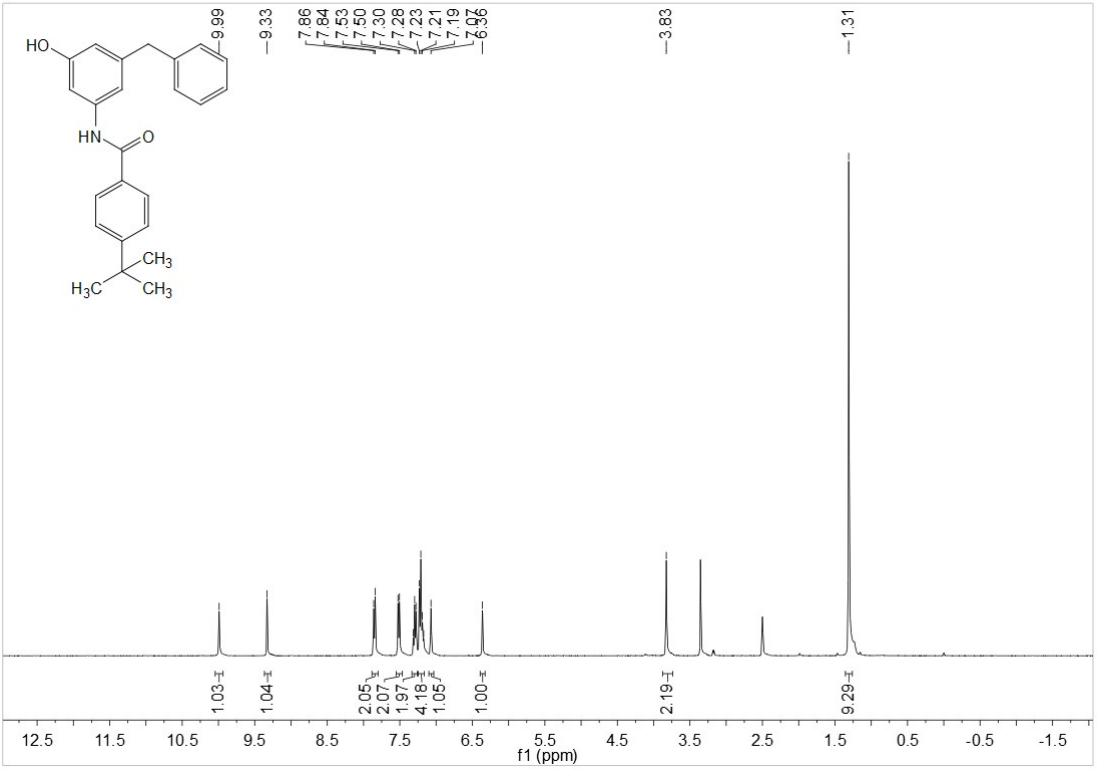

165.90
157.97
142.91
141.60
140.59
135.60
131.86
129.20
128.84
128.75
128.09
126.42
112.18
111.85
105.90
41.86
HO
NH
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

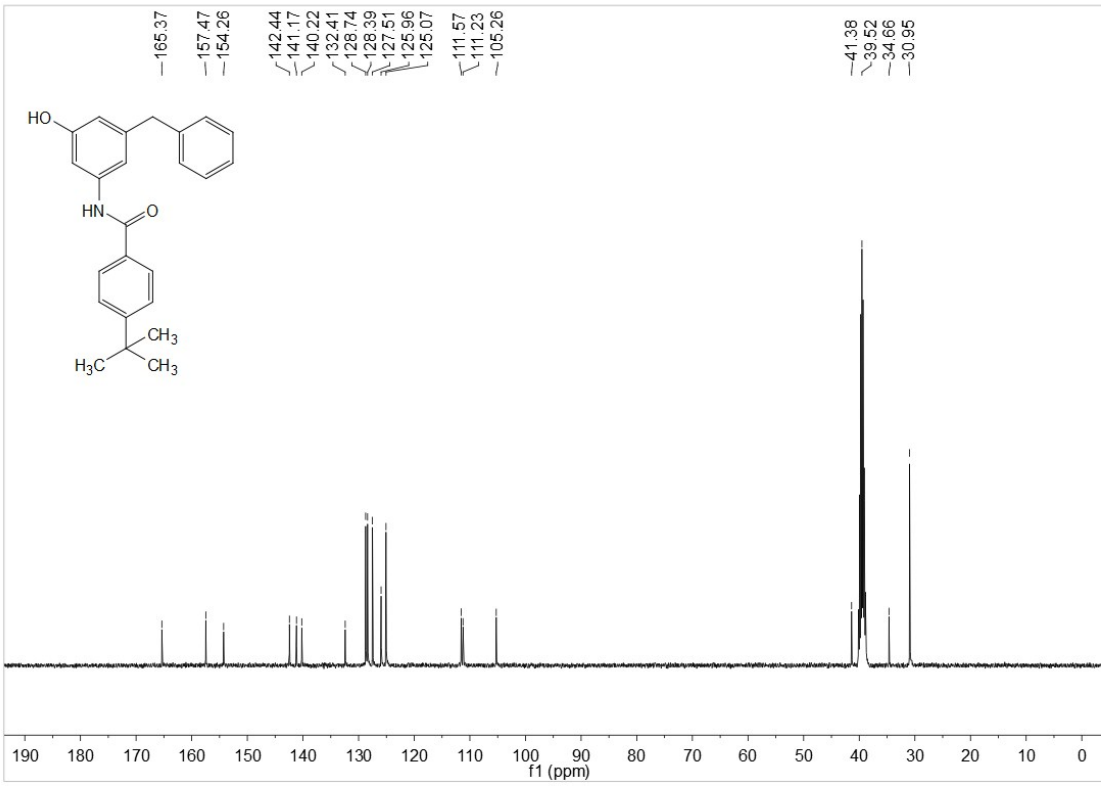
7b


9.95
9.31
7.83
7.81
7.30
7.28
7.26
7.22
7.20
7.18
7.16
7.04
6.34
3.81
3.33
2.49
2.49
2.49
HO
NH
O
CH3
1.01
0.98
1.97
3.90
4.01
1.08
1.00
1.99
3.07
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

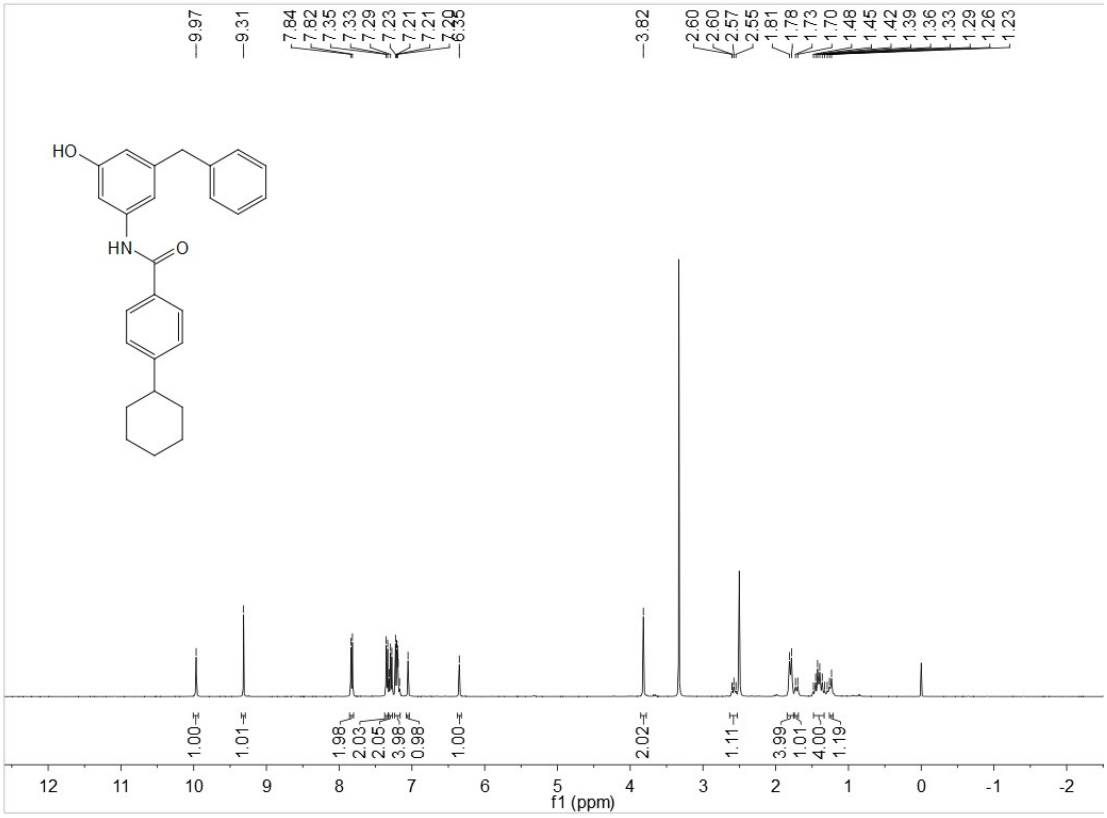

165.23
157.47
142.43
141.43
141.17
140.20
132.20
128.83
128.74
128.39
127.68
125.96
111.65
111.25
105.34
41.39
21.01
HO
NH
O
CH3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

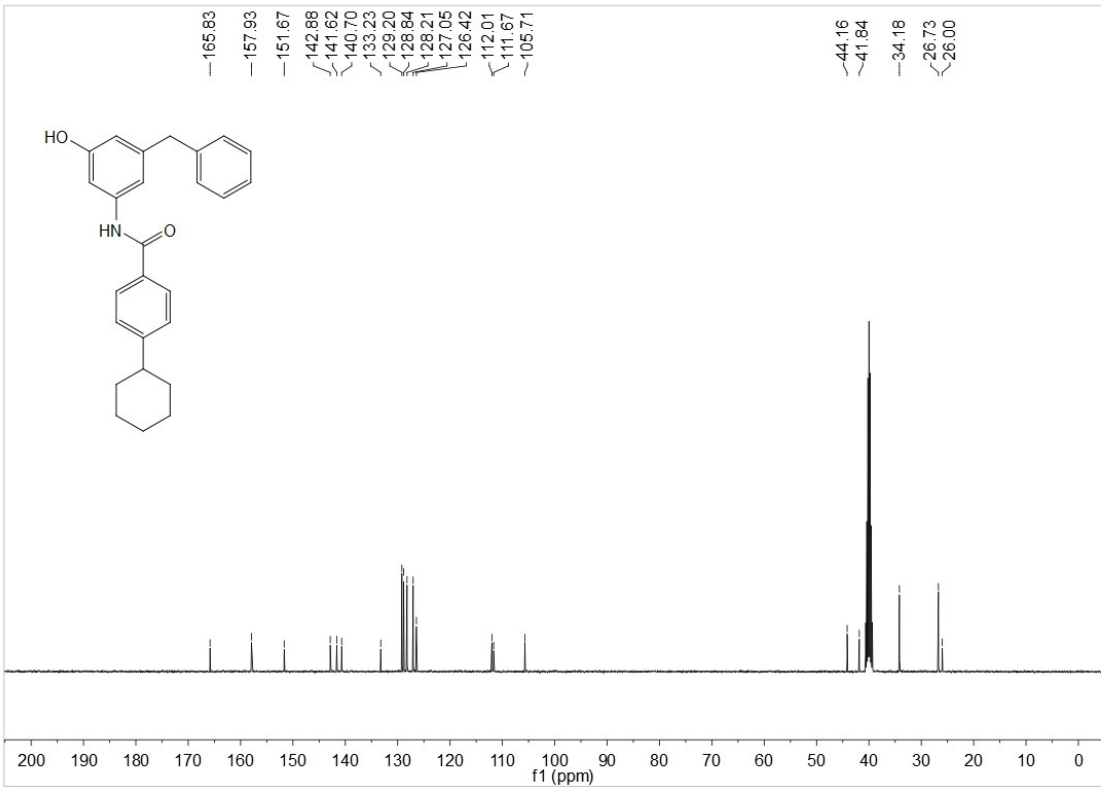
7c


HO
HN
O
CH3
H3C
CH3
9.99
9.33
7.86
7.84
7.53
7.50
7.30
7.28
7.23
7.21
7.19
6.96
6.36
3.83
1.31
1.03
1.04
2.05
2.07
1.97
4.18
1.05
1.00
2.19
9.29
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
f1 (ppm)

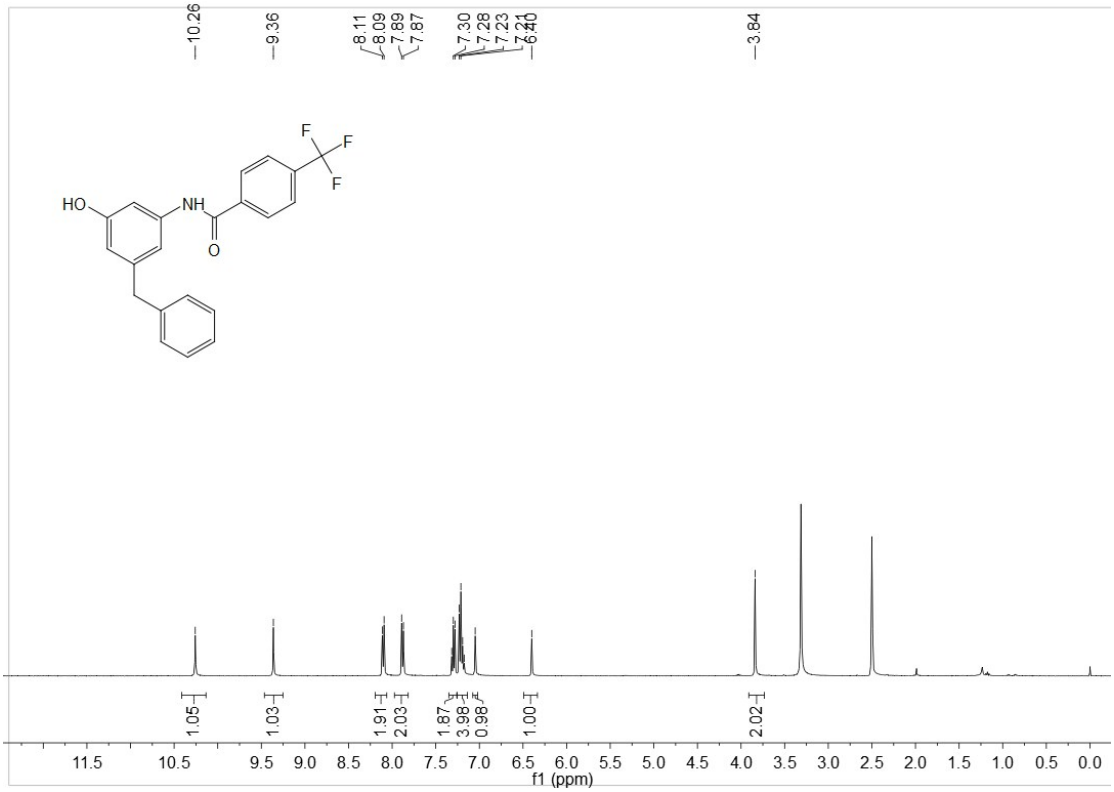

HO
HN
O
CH3
H3C
CH3
165.37
157.47
154.26
142.44
141.17
140.22
132.41
128.74
128.39
127.51
125.96
125.07
111.57
111.23
105.26
41.38
39.52
34.66
30.95
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

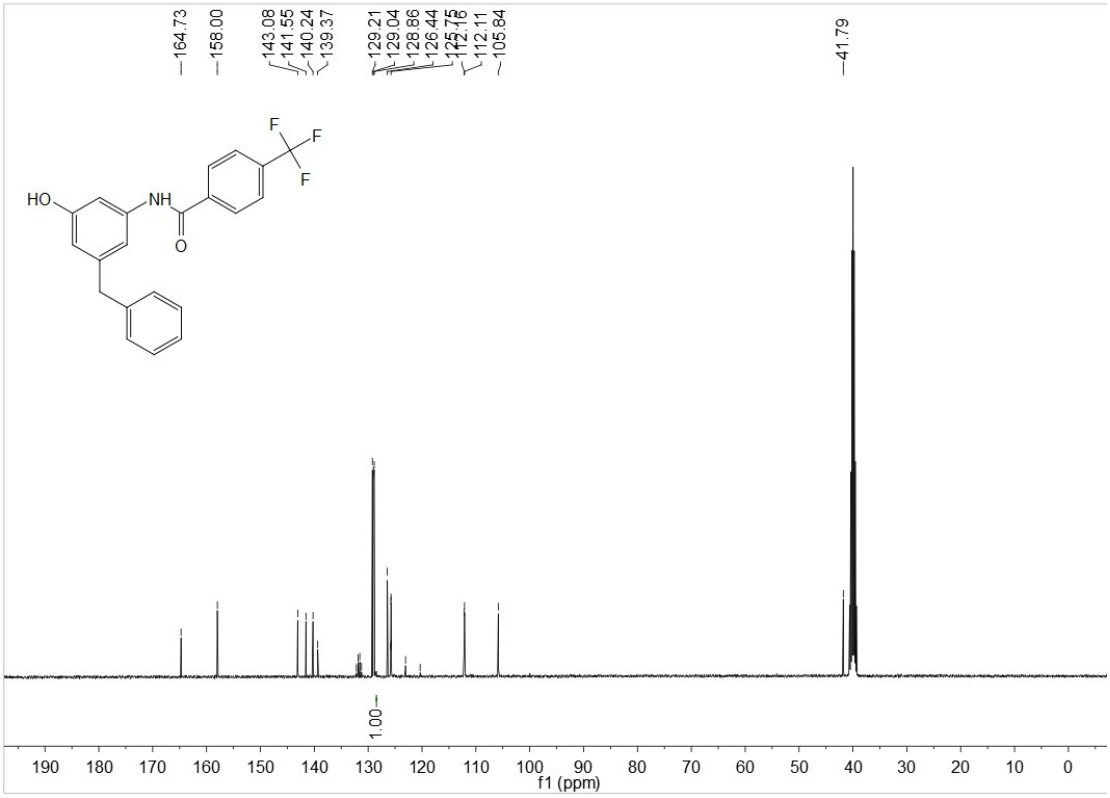
7d


9.97
9.31
7.84
7.82
7.35
7.33
7.29
7.23
7.21
7.21
6.35
3.82
2.60
2.60
2.57
2.55
1.81
1.78
1.73
1.70
1.48
1.45
1.42
1.39
1.36
1.33
1.29
1.26
1.23
HO
HN
O
1.00
1.01
1.98
2.03
2.05
3.98
0.98
1.00
2.02
1.11
3.99
1.01
4.00
1.19
f1 (ppm)

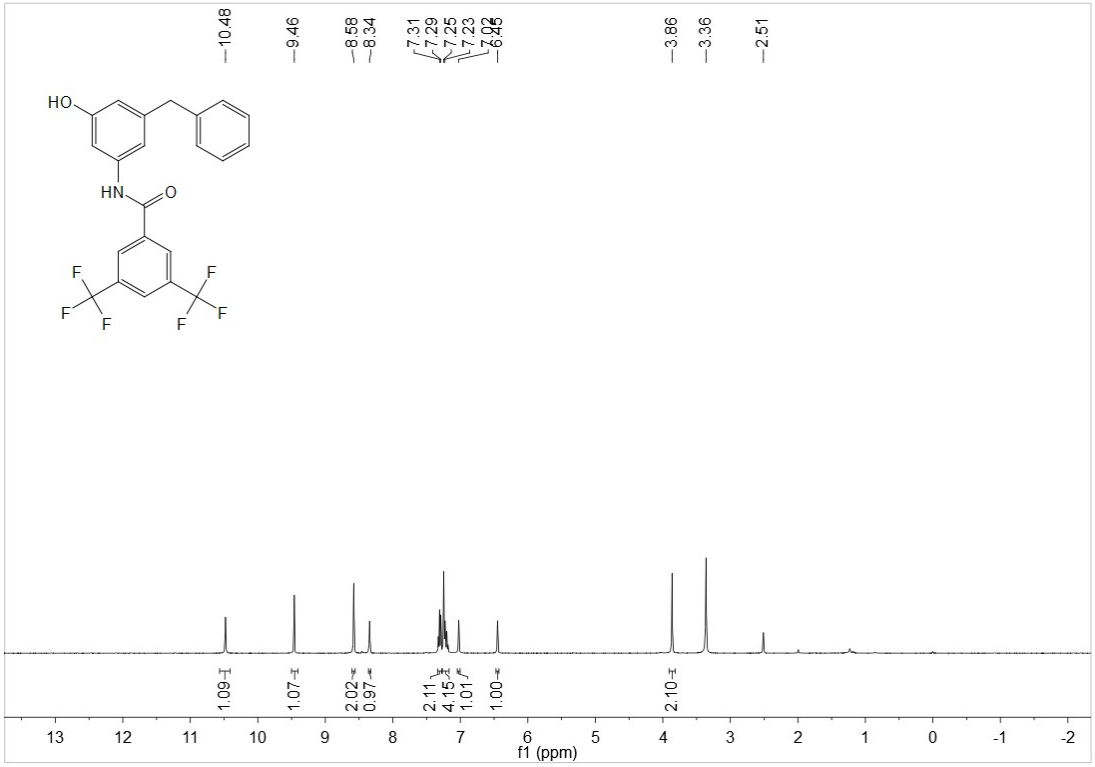

165.83
157.93
151.67
142.88
141.62
140.70
133.23
129.20
128.84
128.21
127.05
126.42
112.01
111.67
105.71
44.16
41.84
34.18
26.73
26.00
HO
HN
O
f1 (ppm)

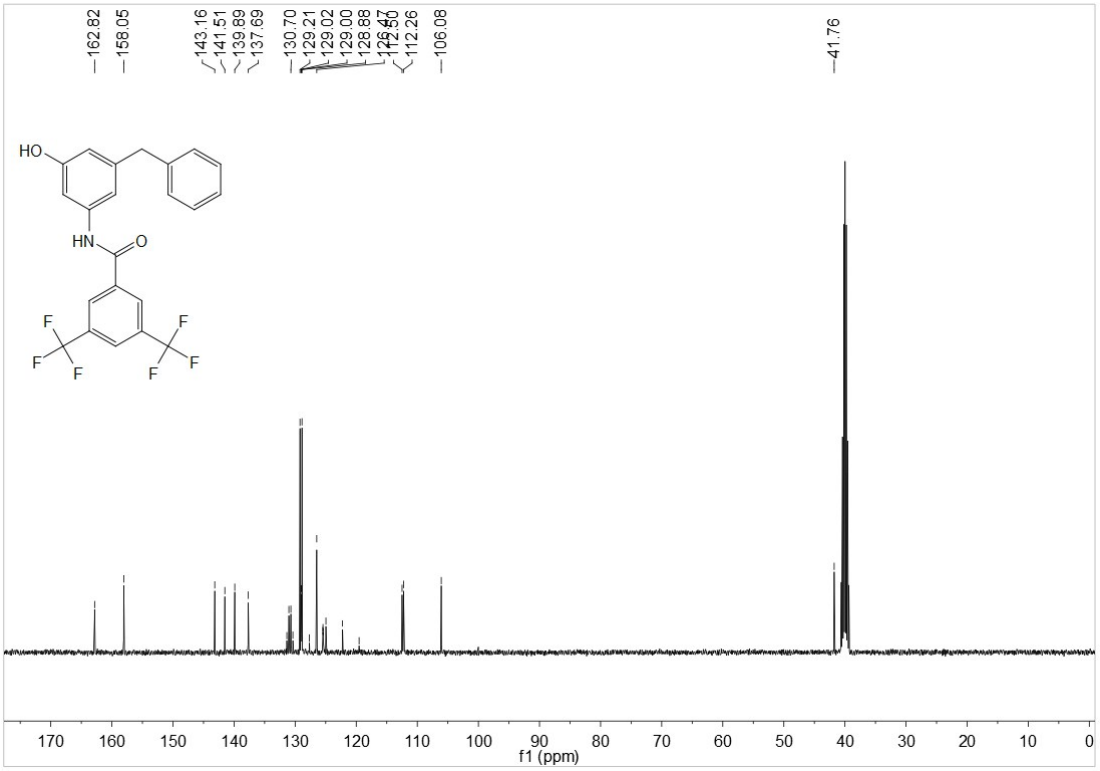
7e


10.26
9.36
8.11
8.09
7.89
7.87
7.30
7.28
7.23
3.84
HO
NH
O
F
F
F
1.05
1.03
1.91
2.03
1.87
3.98
0.98
1.00
2.02
f1 (ppm)

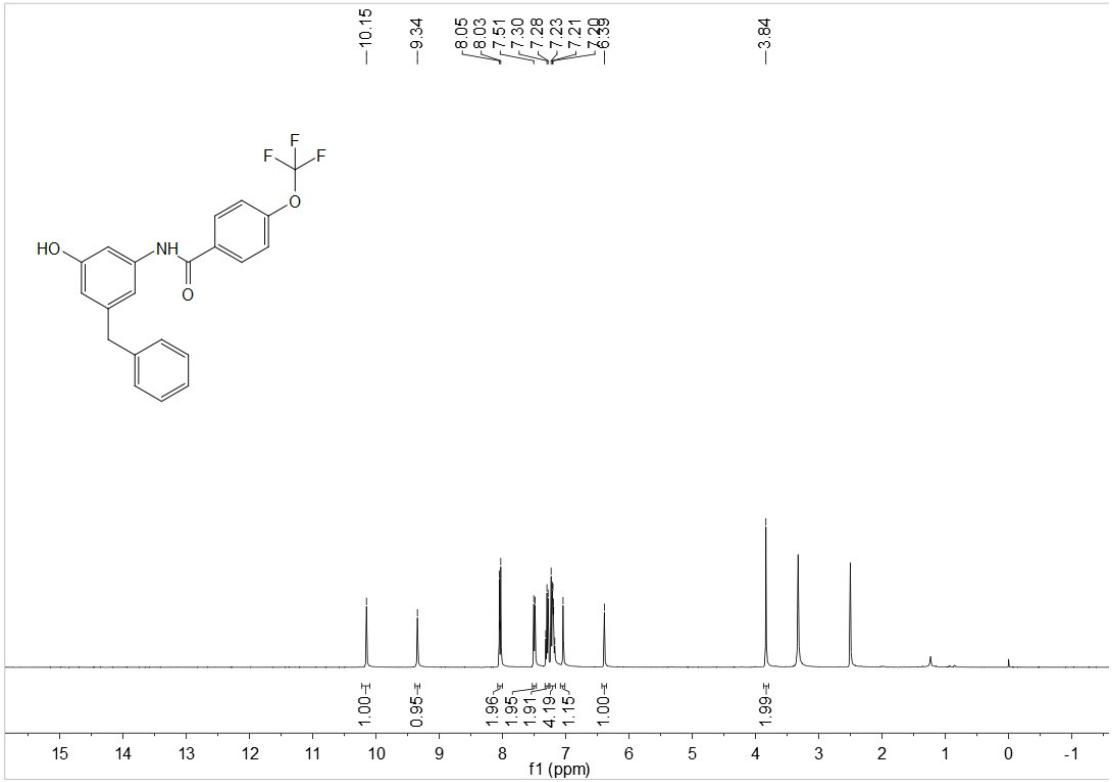

164.73
158.00
143.08
141.55
140.24
139.37
129.21
129.04
128.86
126.44
112.11
105.84
41.79
HO
NH
O
F
F
F
1.00
f1 (ppm)

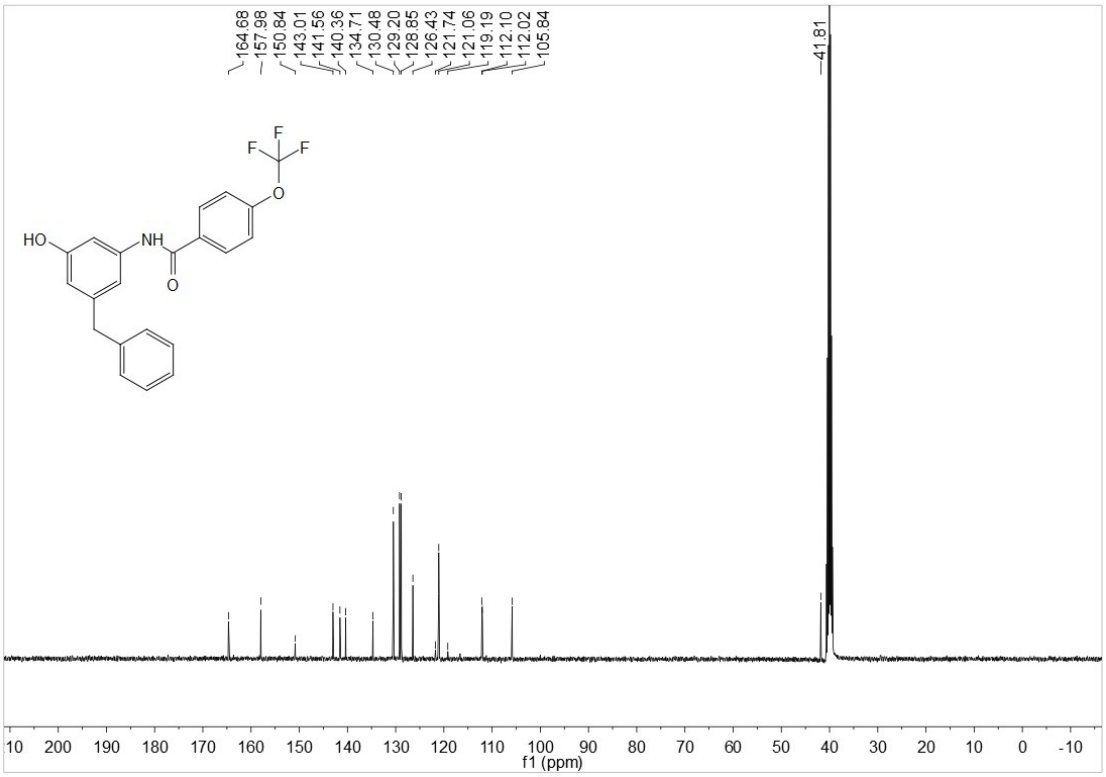
7f


10.48
9.46
8.58
8.34
7.31
7.29
7.25
7.23
6.45
3.86
3.36
2.51
HO
HN
O
F
F
F
F
F
F
1.09
1.07
2.02
0.97
2.11
4.15
1.01
1.00
2.10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

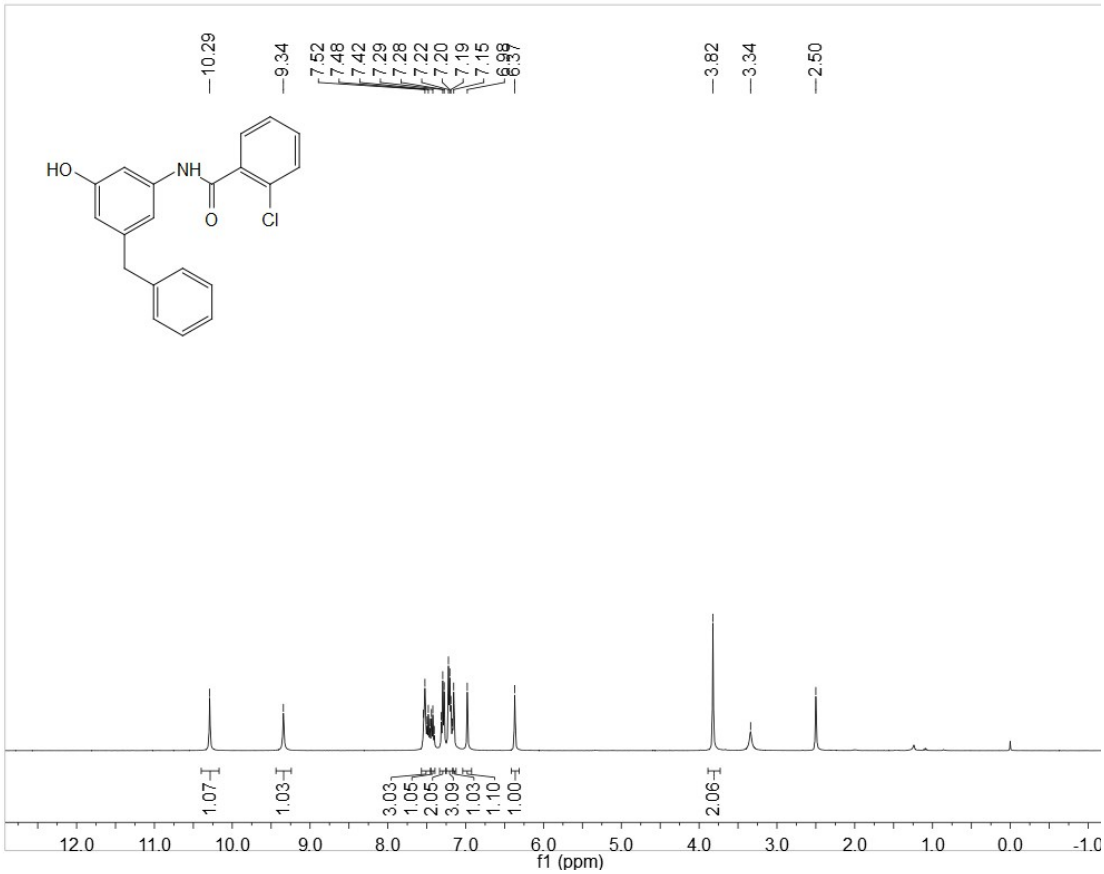

162.82
158.05
143.16
141.51
139.89
137.69
130.70
129.21
129.02
129.00
128.88
112.26
106.08
41.76
HO
HN
O
F
F
F
F
F
F
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

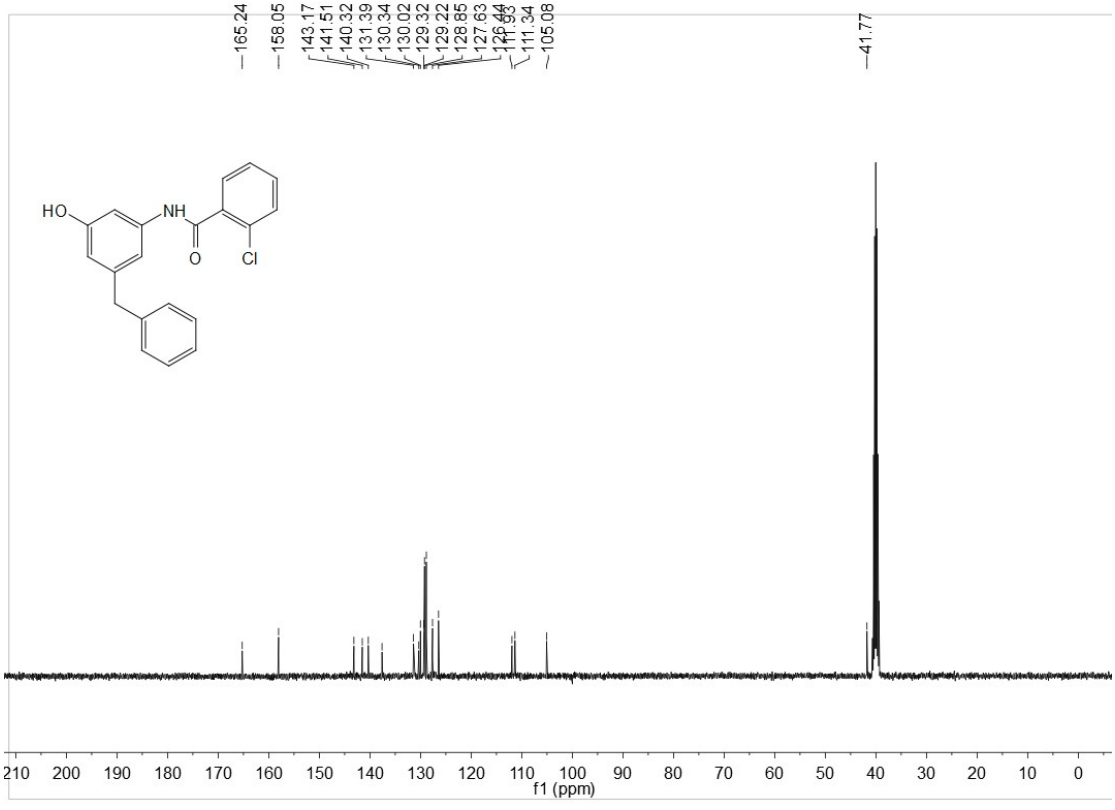
7g


10.15
9.34
8.05
8.03
7.51
7.30
7.28
7.23
7.21
6.39
3.84
F
F
F
O
HO
NH
O
1.00
0.95
1.96
1.95
1.91
4.19
1.15
1.00
1.99
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

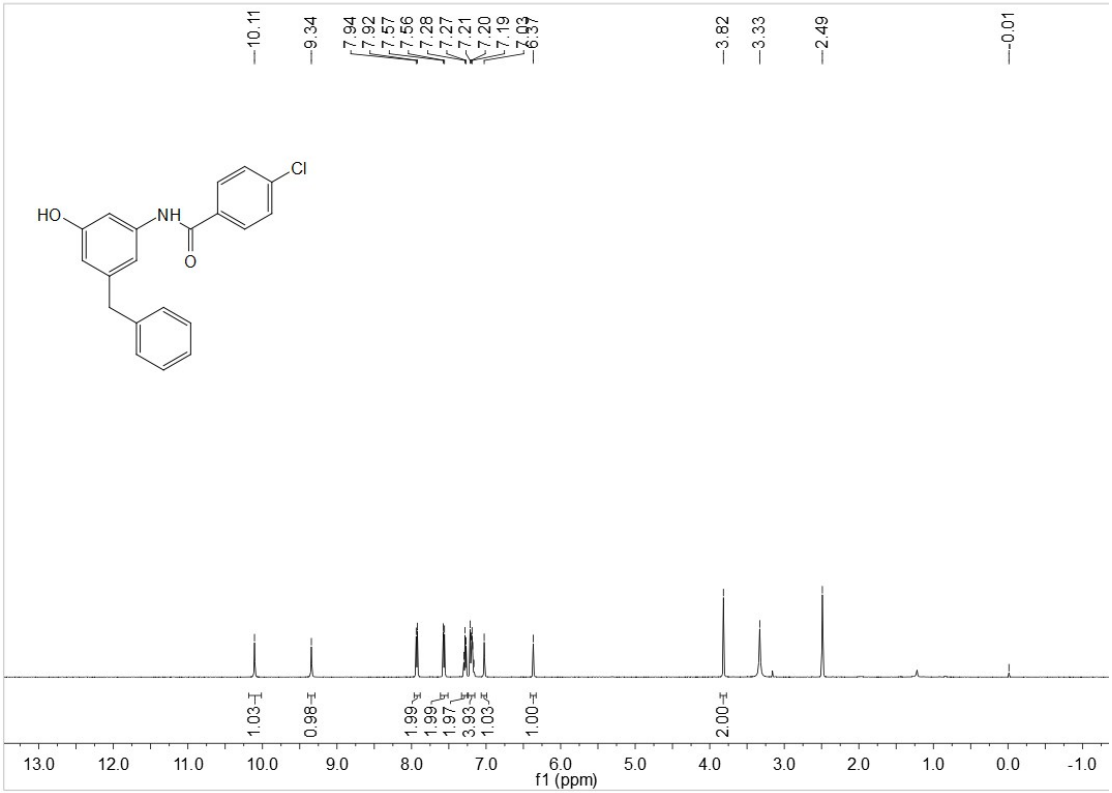

164.68
157.98
150.84
143.01
141.56
140.36
134.71
130.48
129.20
128.85
126.43
121.74
121.06
119.19
112.10
112.02
105.84
41.81
F
F
F
O
HO
NH
O
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

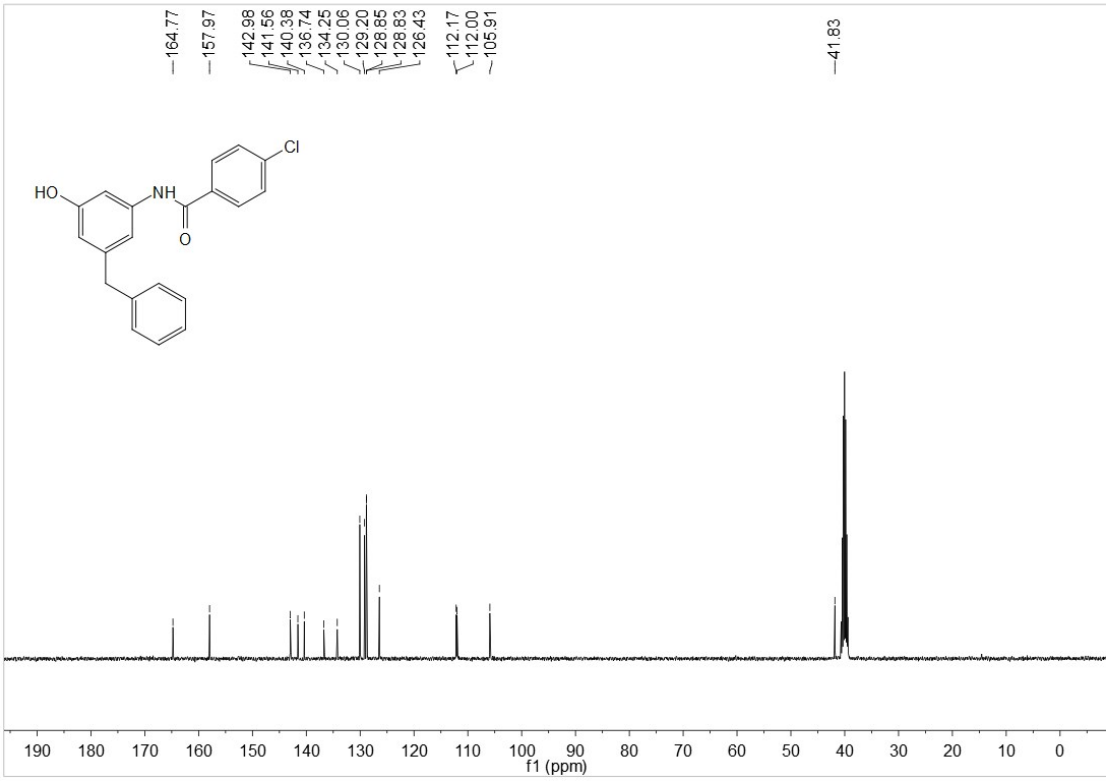
7h


10.29
9.34
7.52
7.48
7.42
7.29
7.28
7.22
7.20
7.19
7.15
6.98
6.97
3.82
3.34
2.50
HO
NH
O
Cl
1.07
1.03
3.03
1.05
2.05
3.09
1.03
1.10
1.00
2.06
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
f1 (ppm)

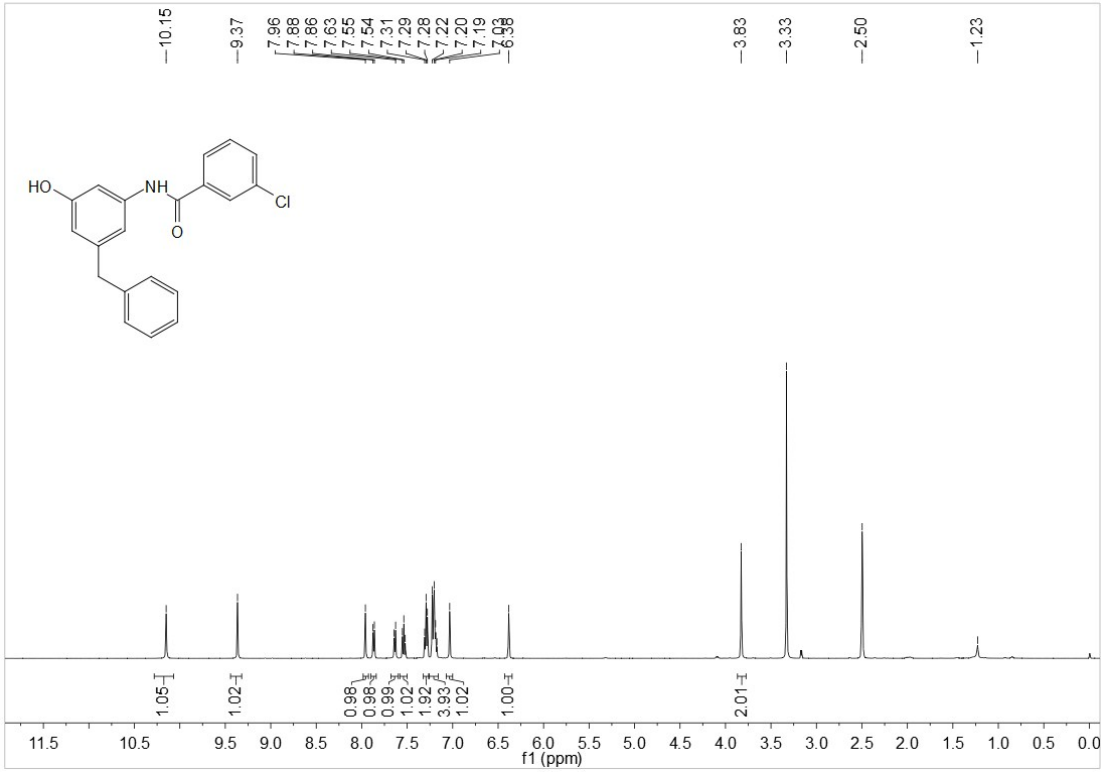

165.24
158.05
143.17
141.51
140.32
131.39
130.34
130.02
129.32
129.22
128.85
127.63
126.44
111.93
111.34
105.08
41.77
HO
NH
O
Cl
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

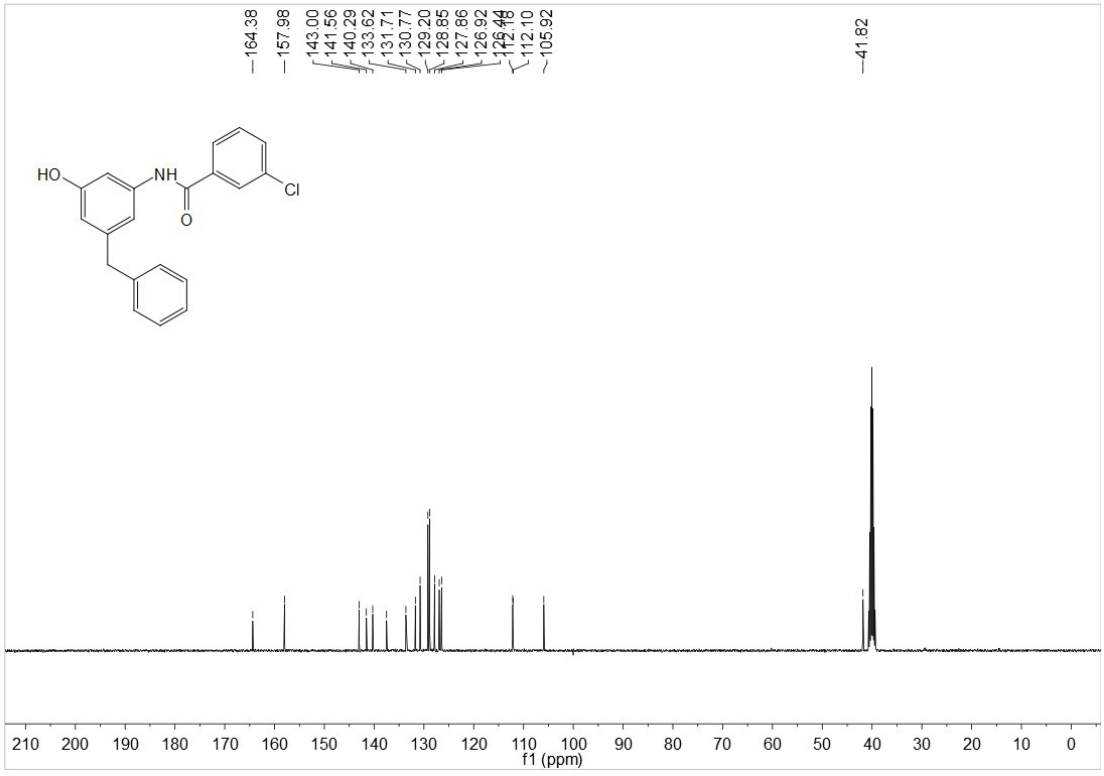
7i


10.11
9.34
7.94
7.92
7.57
7.56
7.28
7.27
7.21
7.20
7.19
6.37
3.82
3.33
2.49
0.01
HO
NH
O
Cl
1.03
0.98
1.99
1.99
1.97
3.93
1.03
1.00
2.00
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
f1 (ppm)

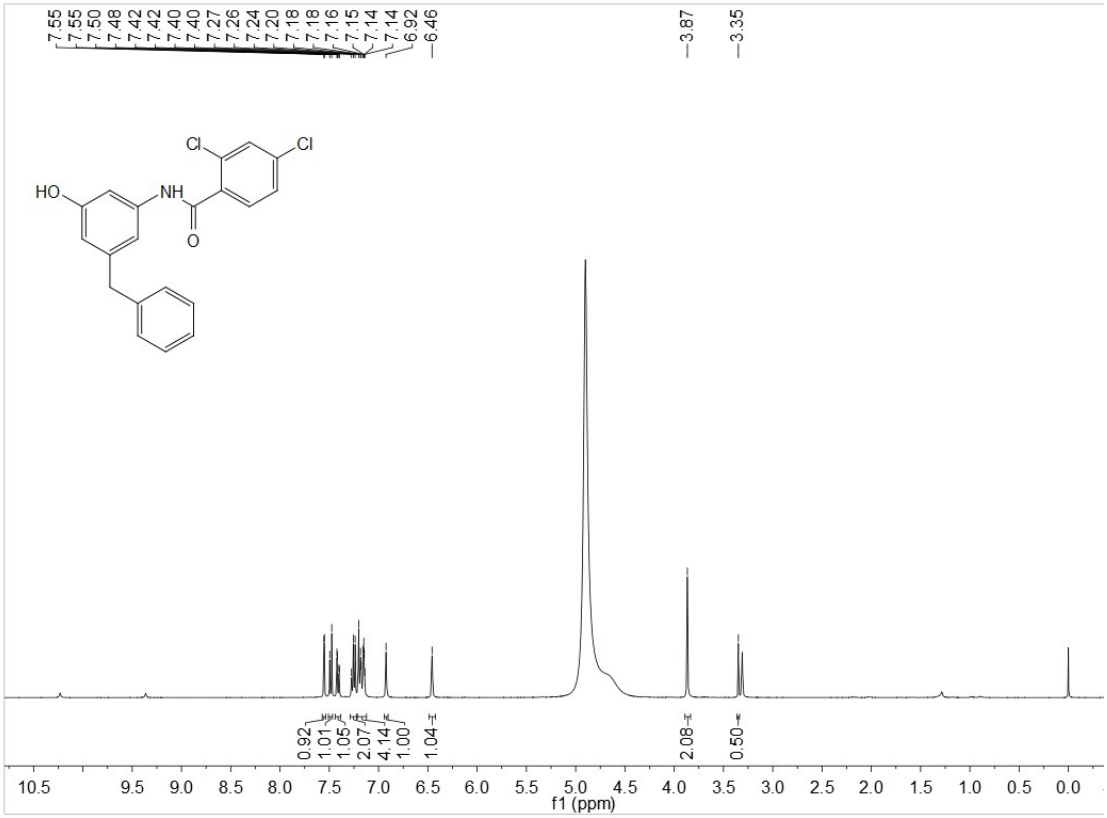

164.77
157.97
142.98
141.56
140.38
136.74
134.25
130.06
129.20
128.85
128.83
126.43
112.17
112.00
105.91
41.83
HO
NH
O
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

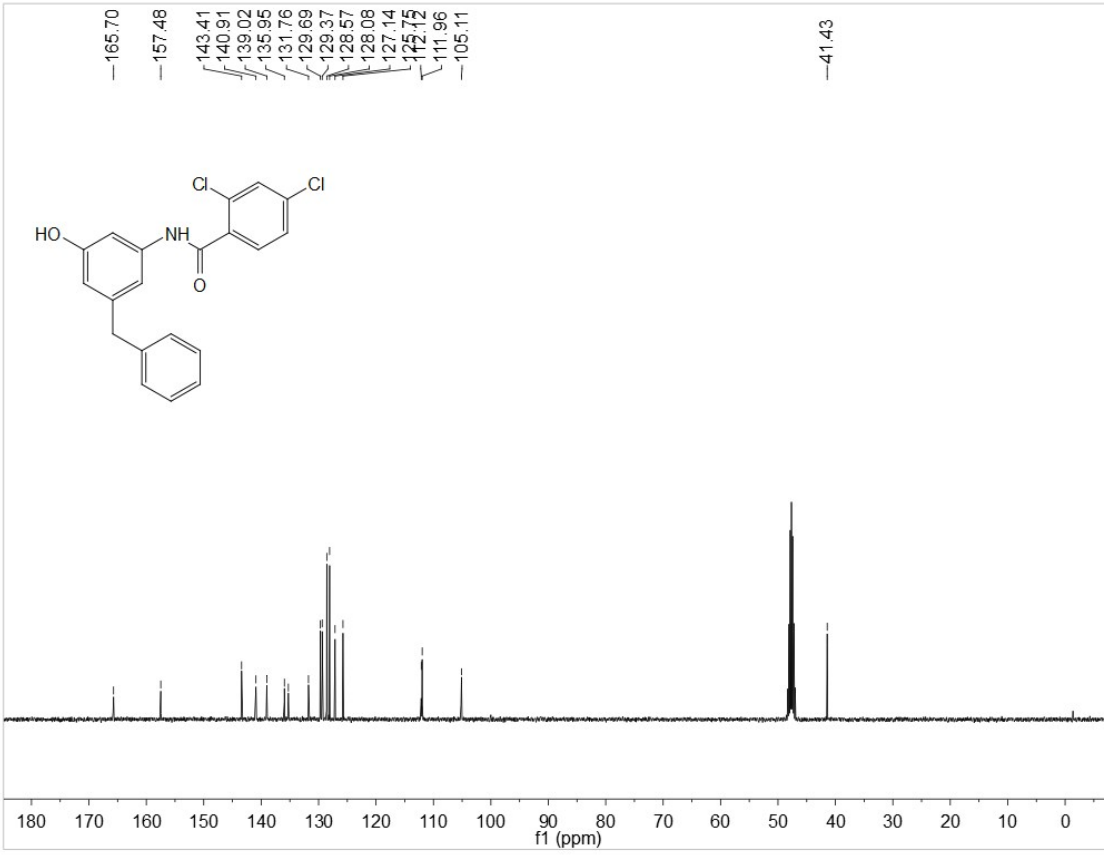
7j


10.15
9.37
7.96
7.88
7.86
7.63
7.55
7.54
7.31
7.29
7.28
7.22
7.20
7.19
7.03
6.98
3.83
3.33
2.50
1.23
HO
NH
O
Cl
1.05
1.02
0.98
0.98
0.99
1.02
1.92
3.93
1.02
1.00
2.01
11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

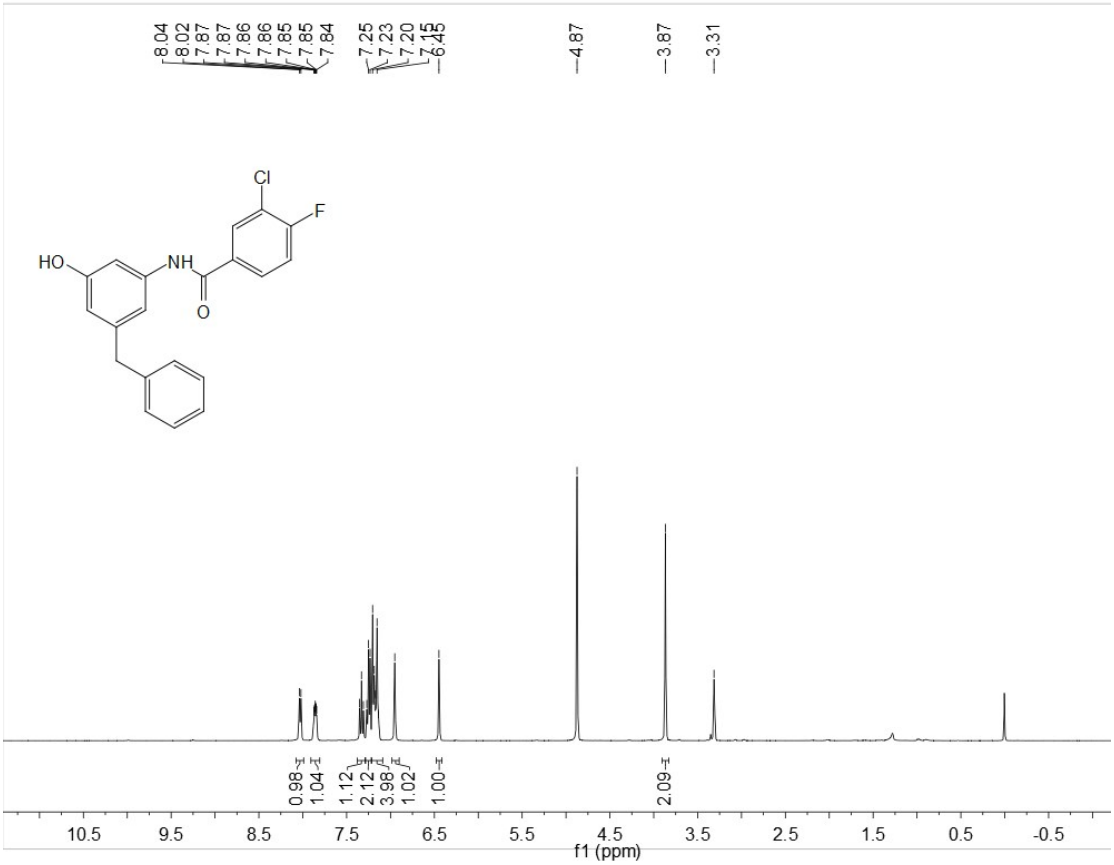

164.38
157.98
143.00
141.56
140.29
133.62
131.71
130.77
129.20
128.85
127.86
126.92
112.10
105.92
41.82
HO
NH
O
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

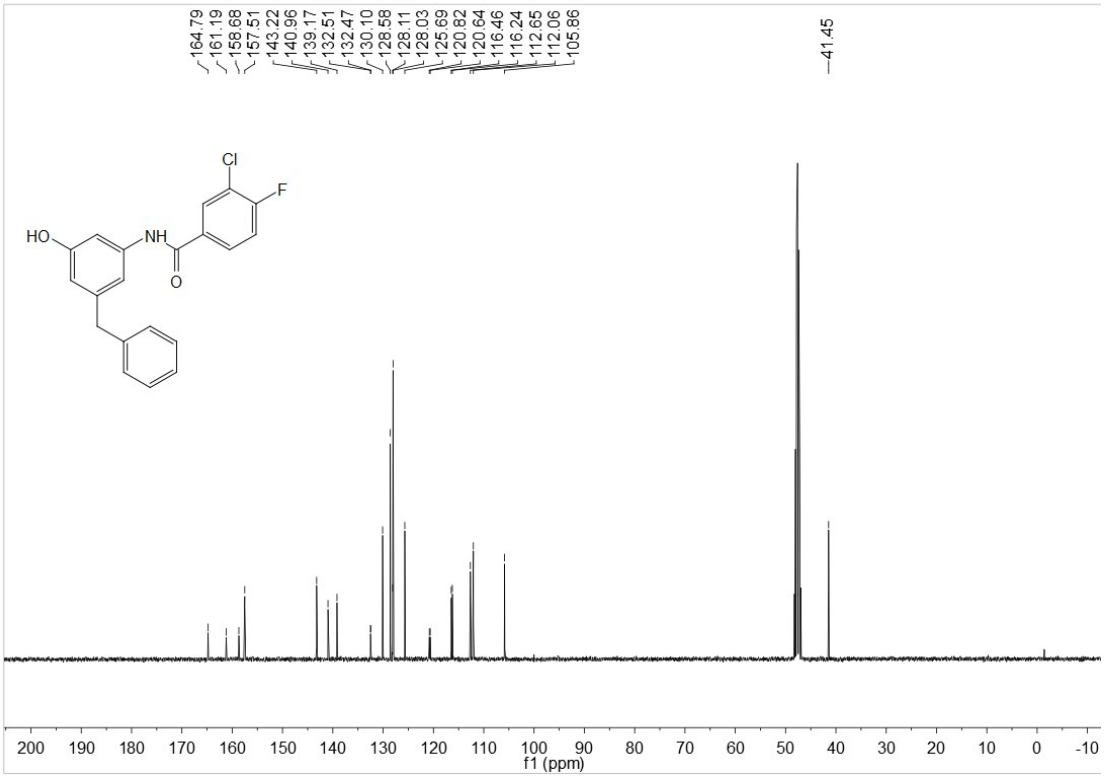
7k


7.55
7.55
7.50
7.48
7.42
7.42
7.40
7.40
7.27
7.26
7.24
7.20
7.18
7.18
7.16
7.15
7.14
7.14
6.92
6.46
3.87
3.35
Cl
Cl
HO
NH
O
0.92
1.01
1.05
2.07
4.14
1.00
1.04
2.08
0.50
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

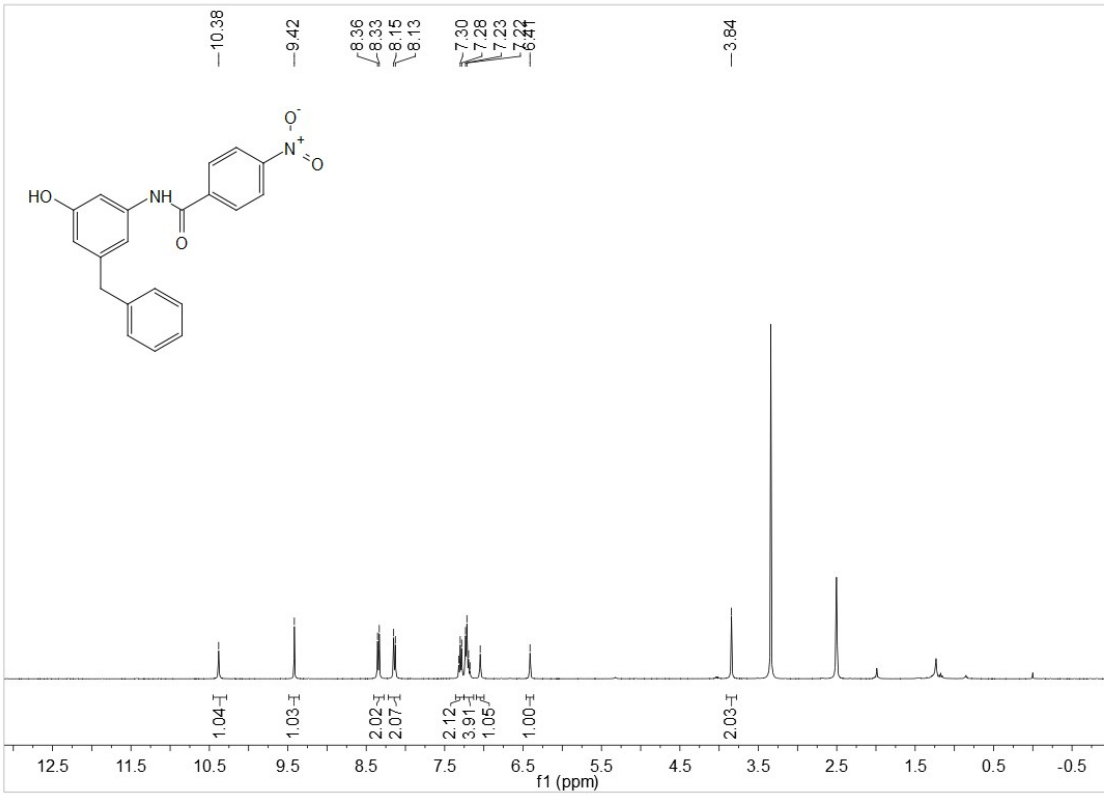

165.70
157.48
143.41
140.91
139.02
135.95
131.76
129.69
129.37
128.57
128.08
127.14
125.75
125.12
111.96
105.11
41.43
Cl
Cl
HO
NH
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

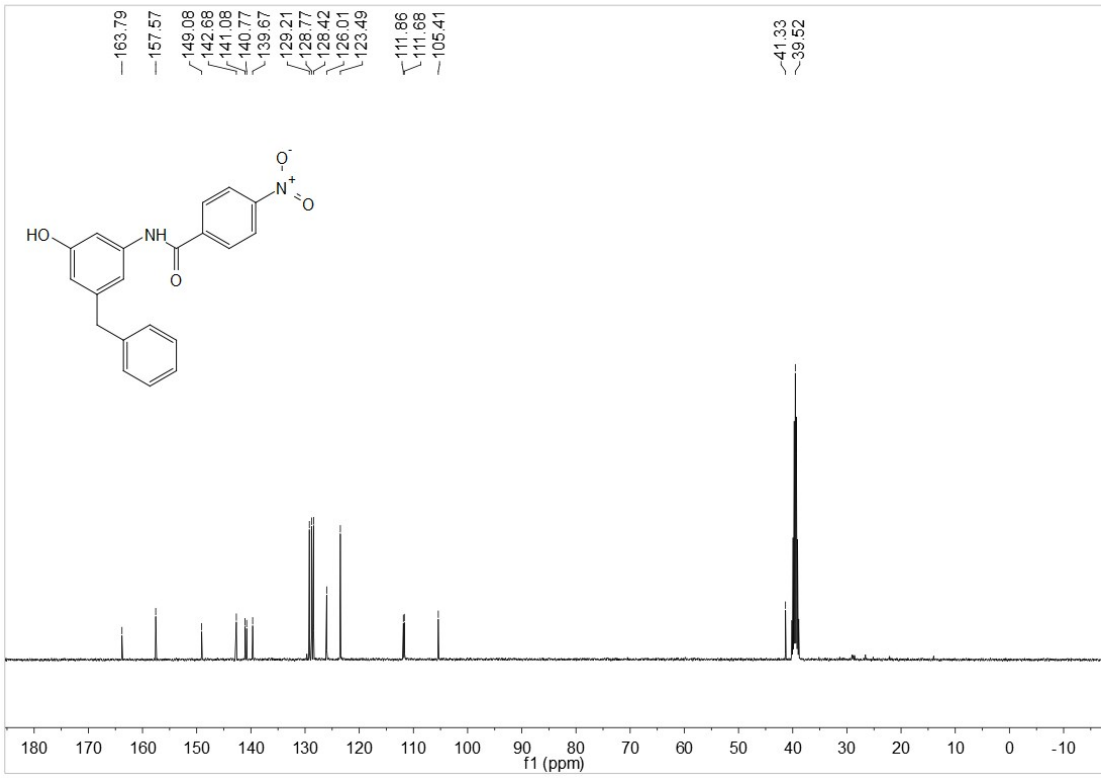
7l


8.04
8.02
7.87
7.87
7.86
7.86
7.85
7.85
7.84
7.25
7.23
7.20
7.15
6.45
4.87
3.87
3.31
Cl
F
HO
NH
O
0.98
1.04
1.12
2.12
3.98
1.02
1.00
2.09
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

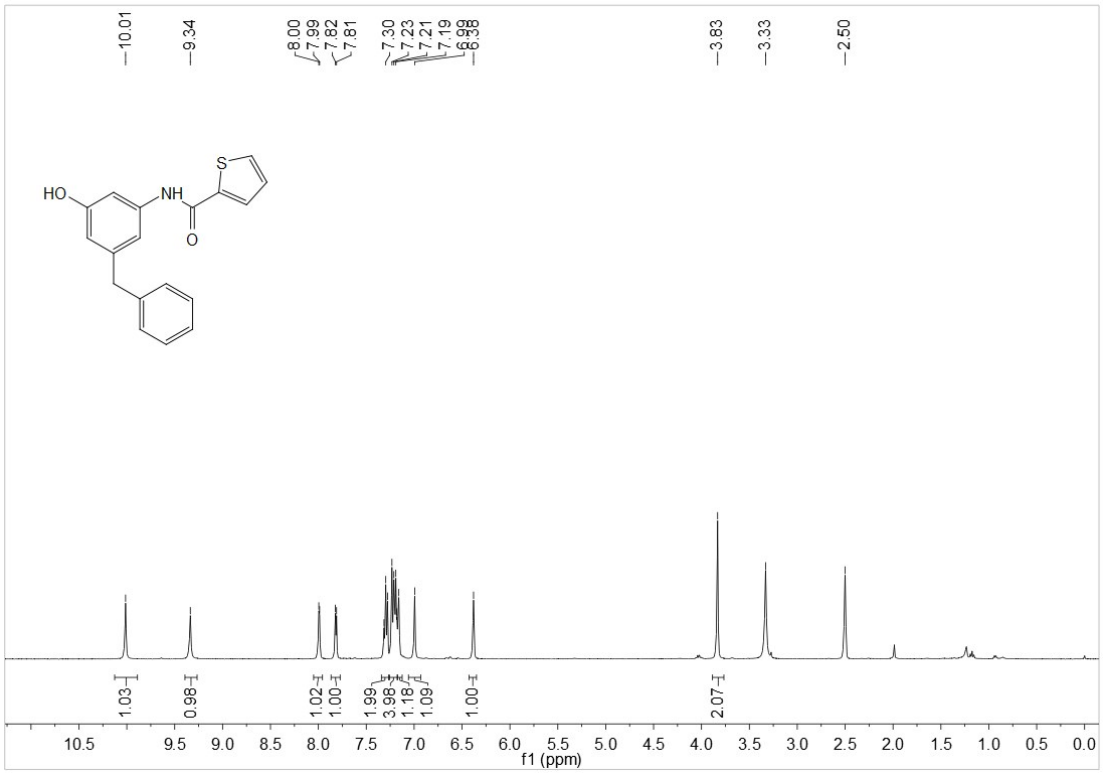

164.79
161.19
158.68
157.51
143.22
140.96
139.17
132.51
132.47
130.10
128.58
128.11
128.03
125.69
120.82
120.64
116.46
116.24
112.65
112.06
105.86
41.45
Cl
F
HO
NH
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

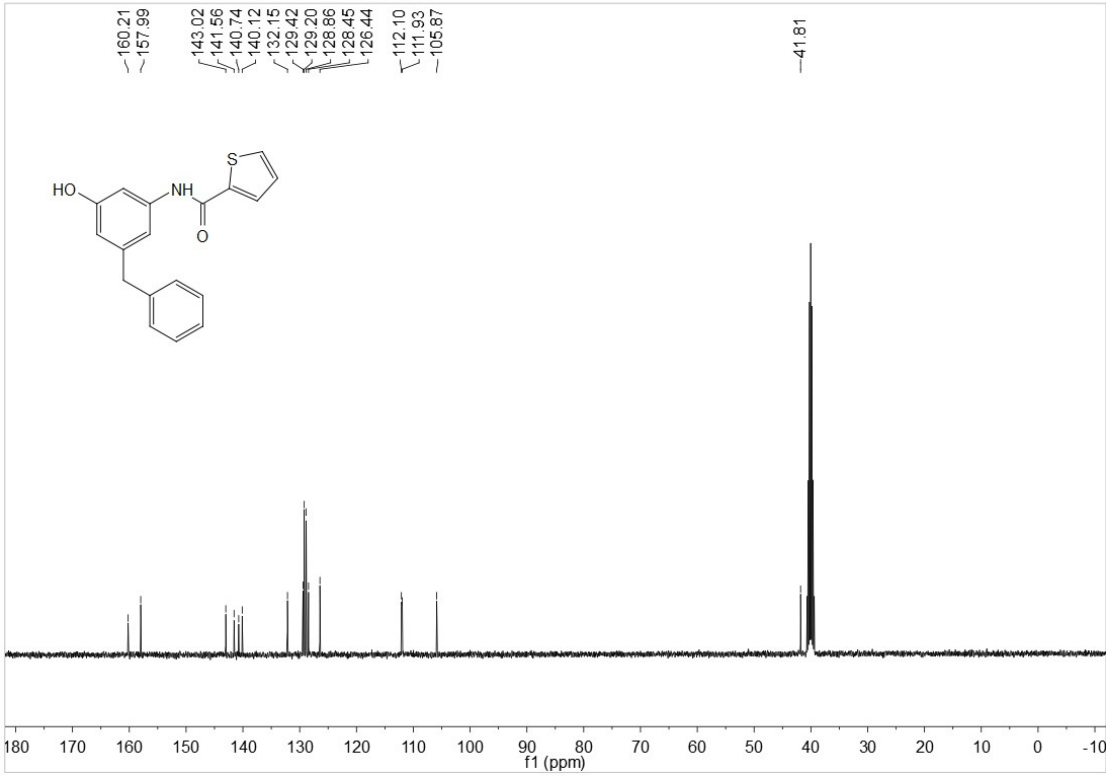
7m


10.38
9.42
8.36
8.33
8.15
8.13
7.30
7.28
7.23
3.84
HO
NH
O
O
N+
O-
1.04
1.03
2.02
2.07
2.12
3.91
1.05
1.00
2.03
f1 (ppm)

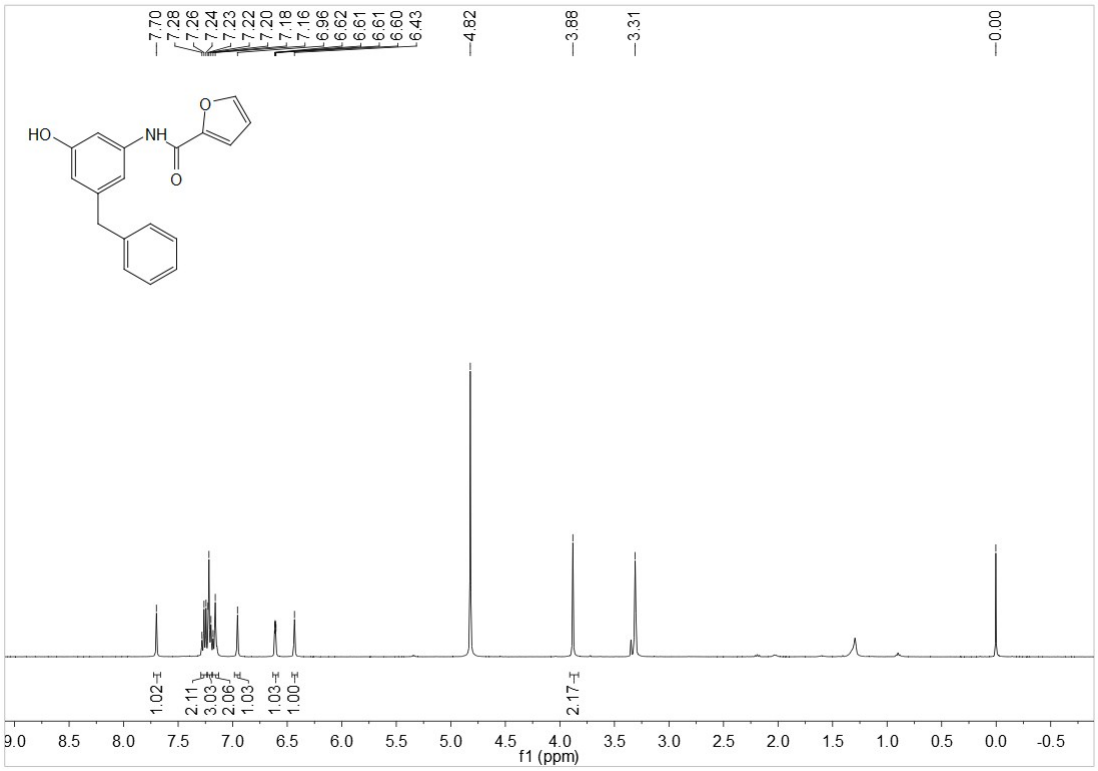

163.79
157.57
149.08
142.68
141.08
140.77
139.67
129.21
128.77
128.42
126.01
123.49
111.86
111.68
105.41
41.33
39.52
HO
NH
O
O
N+
O-
f1 (ppm)

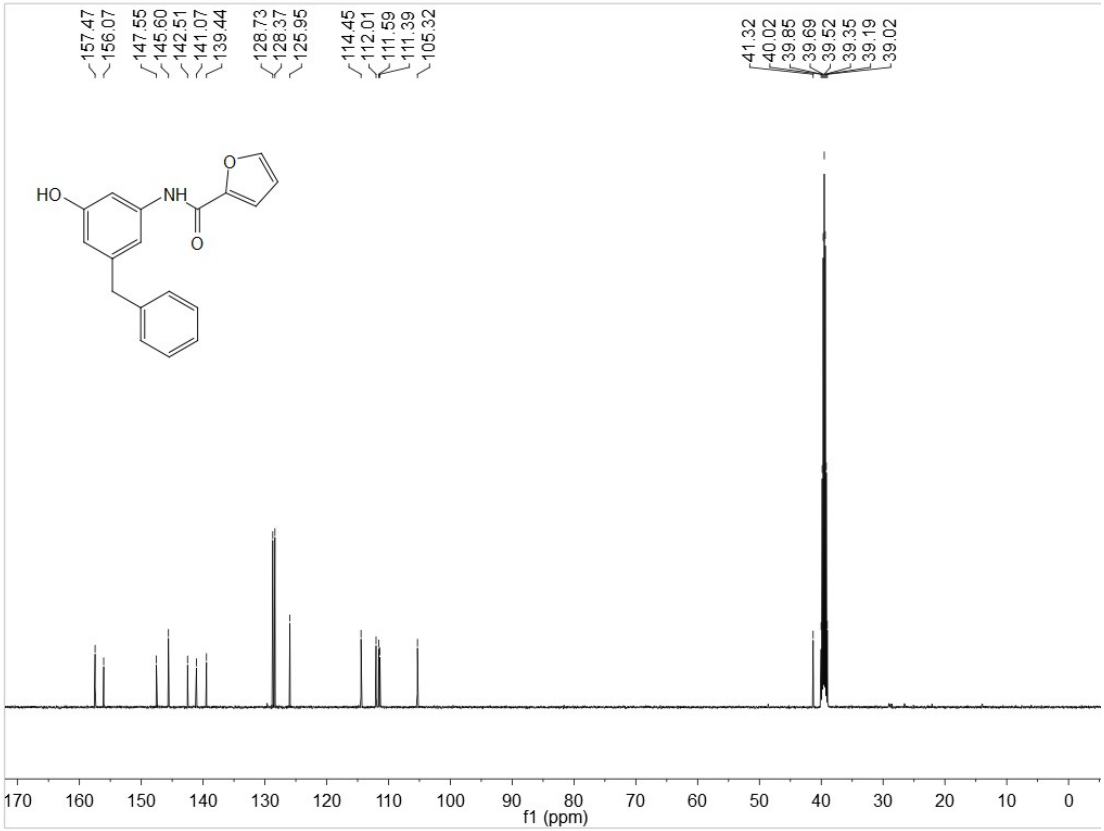
7n


10.01
9.34
8.00
7.99
7.82
7.81
7.30
7.23
7.21
7.19
6.99
6.98
3.83
3.33
2.50
HO
NH
O
S
1.03
0.98
1.02
1.00
1.99
3.98
1.18
1.09
1.00
2.07
f1 (ppm)

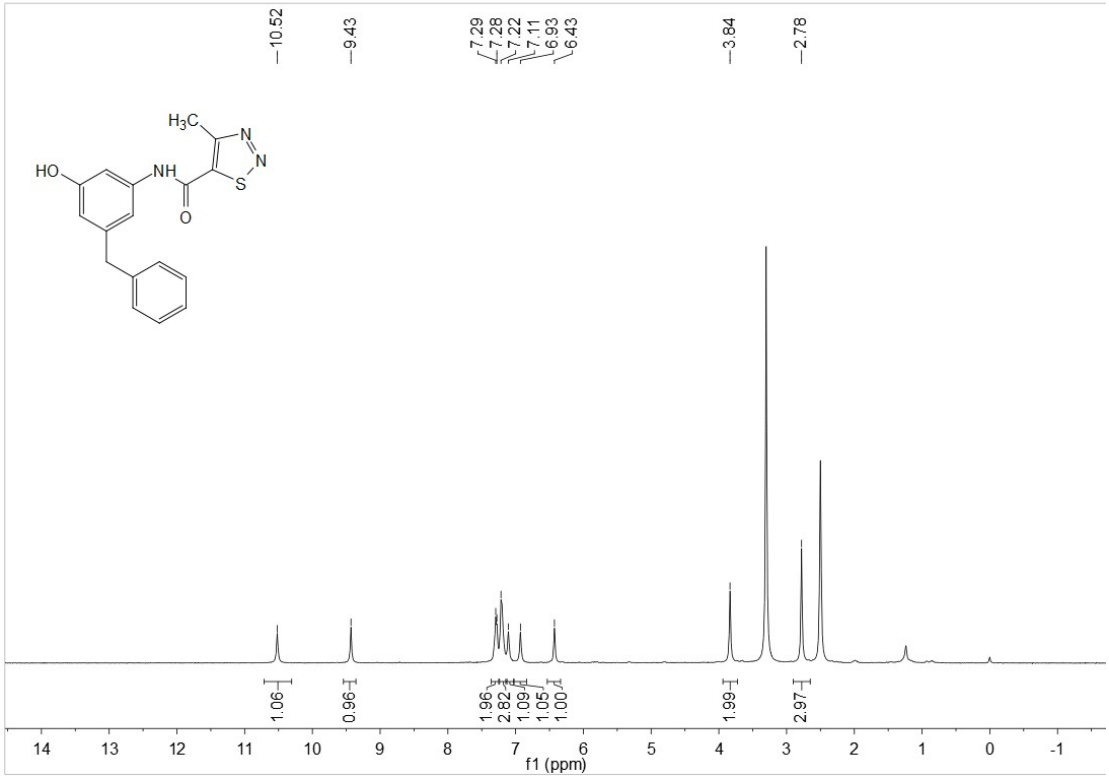

160.21
157.99
143.02
141.56
140.74
140.12
132.15
129.42
129.20
128.86
128.45
126.44
112.10
111.93
105.87
41.81
HO
NH
O
S
f1 (ppm)

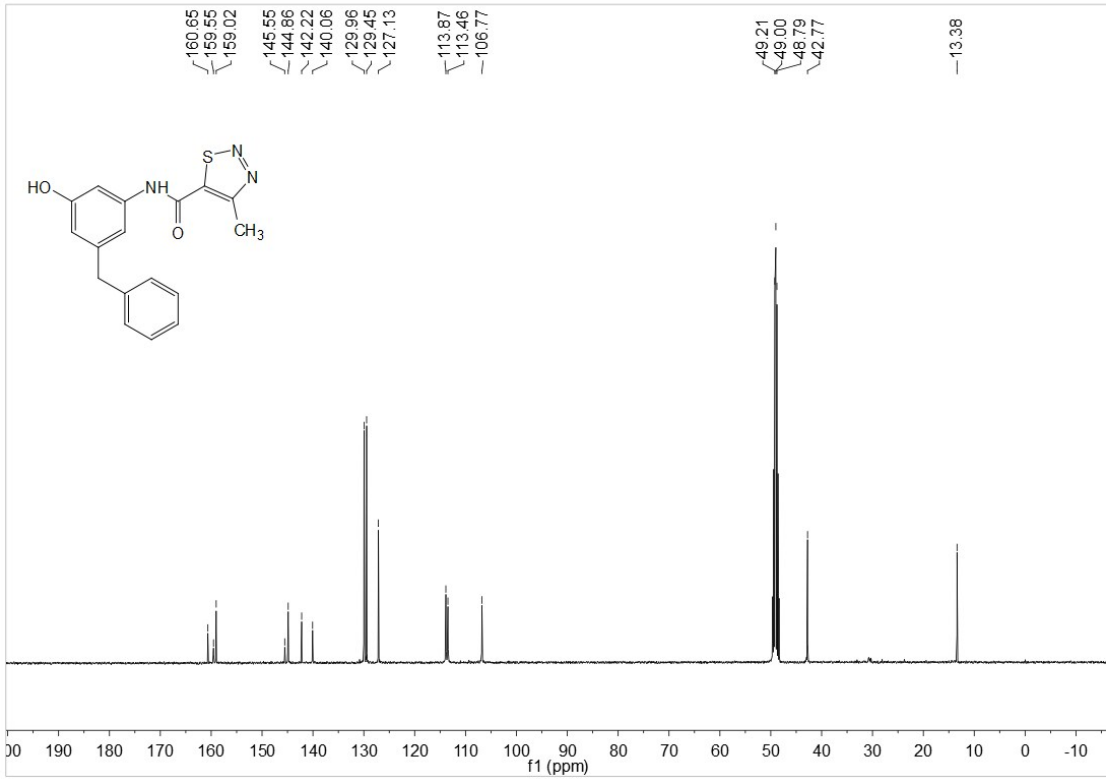
7o


7.70
7.28
7.26
7.24
7.23
7.22
7.20
7.18
7.16
6.96
6.62
6.61
6.61
6.60
6.43
4.82
3.88
3.31
0.00
HO
NH
O
O
1.02
2.11
3.03
2.06
1.03
1.03
1.00
2.17
f1 (ppm)

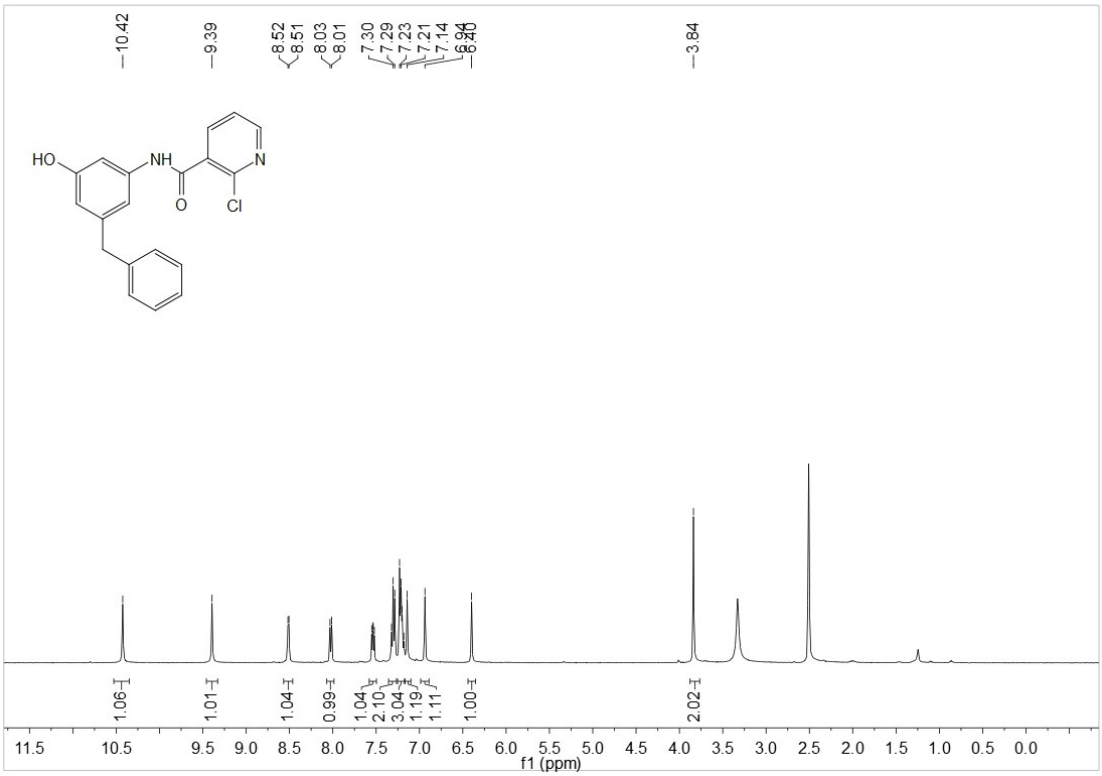

157.47
156.07
147.55
145.60
142.51
141.07
139.44
128.73
128.37
125.95
114.45
112.01
111.59
111.39
105.32
41.32
40.02
39.85
39.69
39.52
39.35
39.19
39.02
HO
NH
O
O
f1 (ppm)

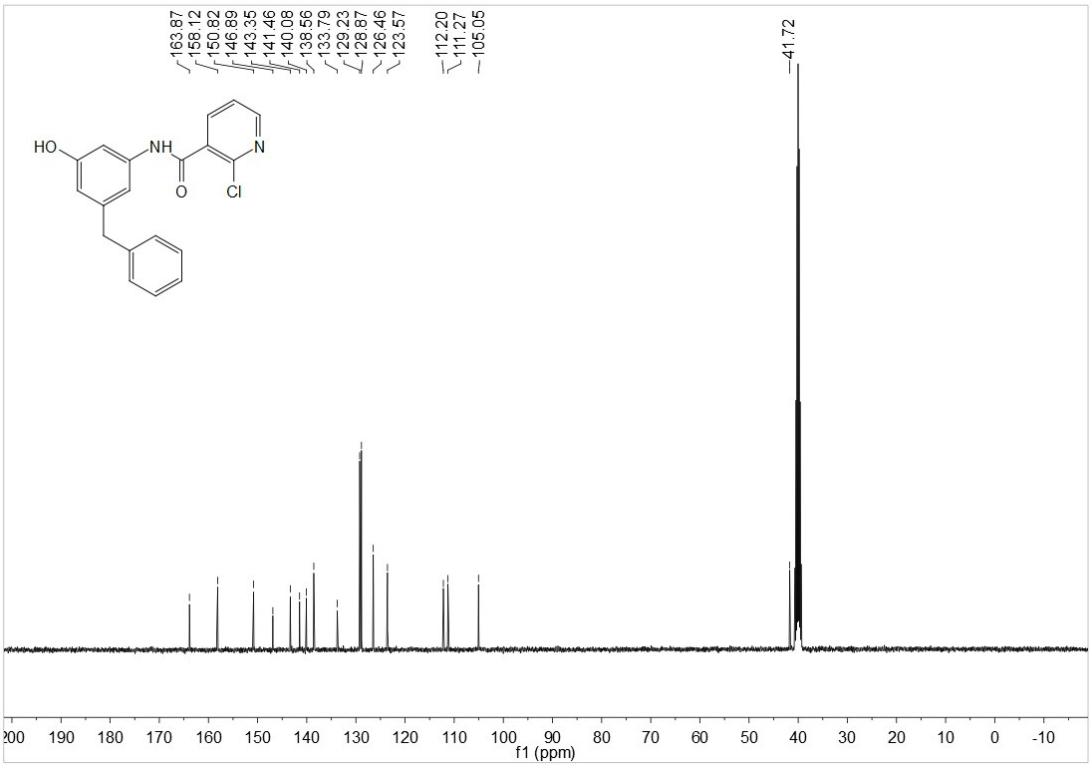
7p


10.52
9.43
7.29
7.28
7.22
7.11
6.93
6.43
3.84
2.78
1.06
0.96
1.96
2.82
1.09
1.05
1.00
1.99
2.97
f1 (ppm)

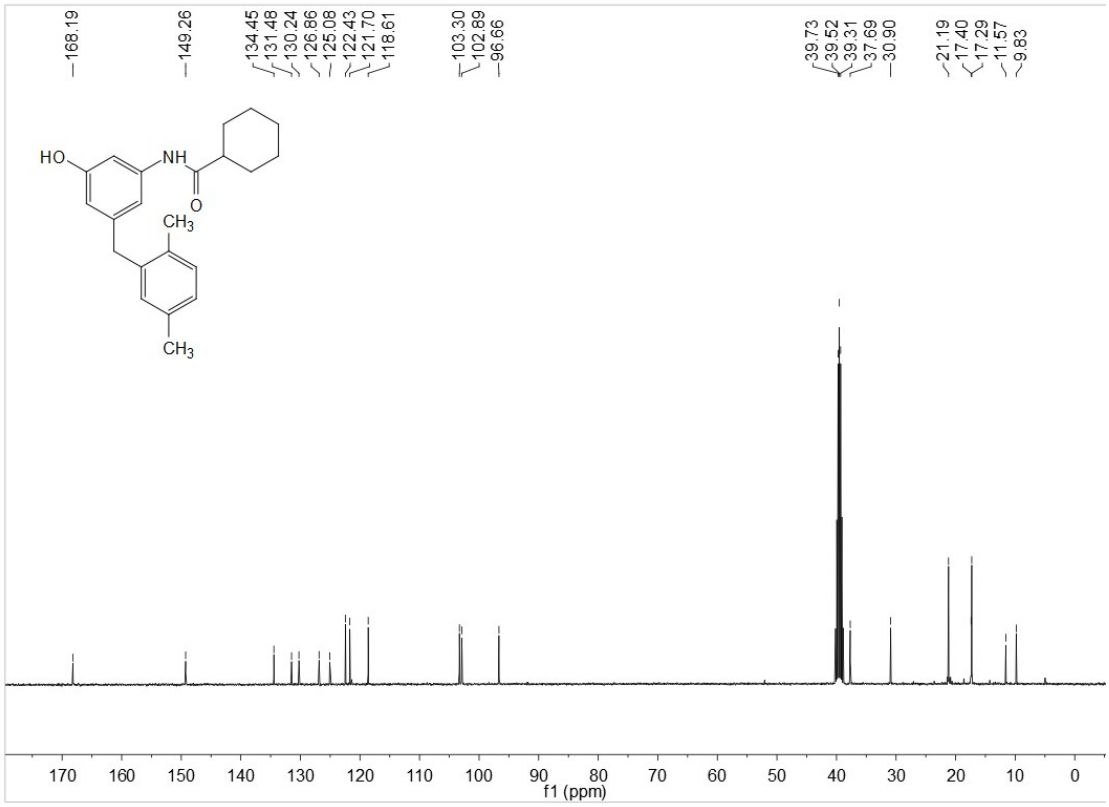

160.65
159.55
159.02
145.55
144.86
142.22
140.06
129.96
129.45
127.13
113.87
113.46
106.77
49.21
49.00
48.79
42.77
13.38
f1 (ppm)

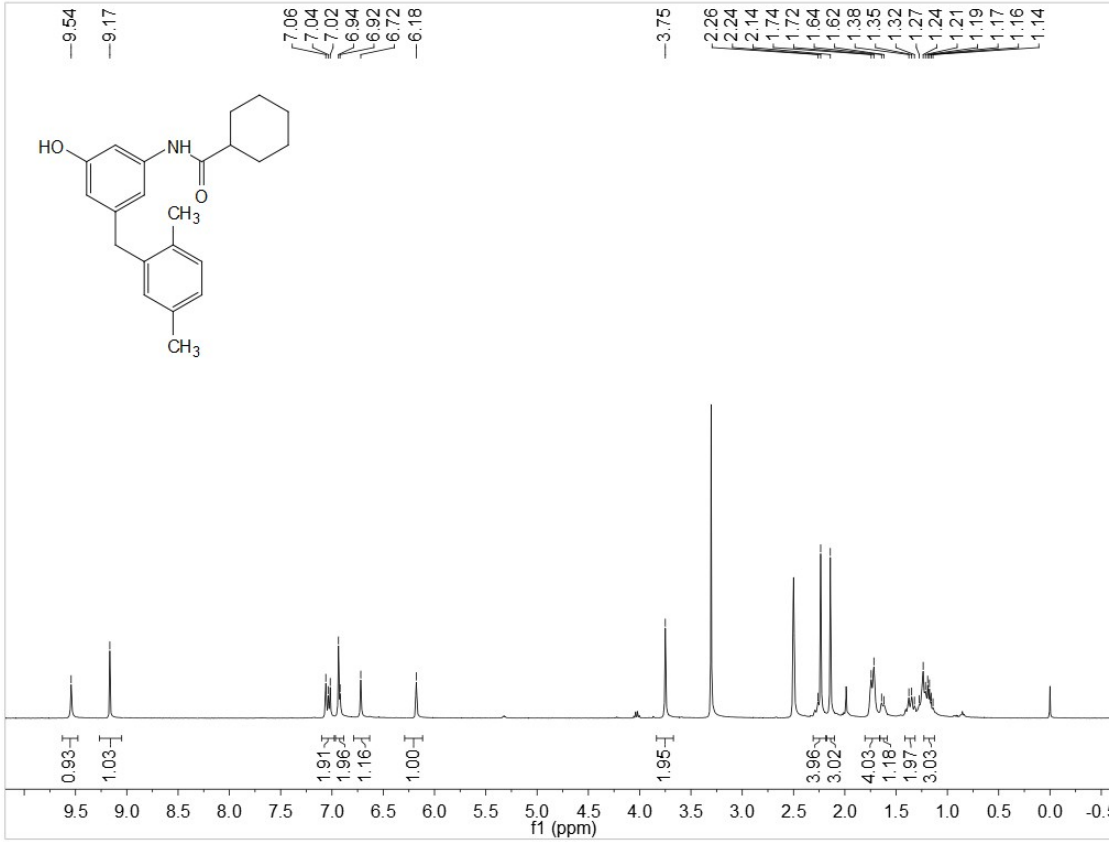
7q


10.42
9.39
8.52
8.51
8.03
8.01
7.30
7.29
7.23
7.21
7.14
6.94
6.40
3.84
HO
NH
O
N
Cl
1.06
1.01
1.04
0.99
1.04
2.10
3.04
1.19
1.11
1.00
2.02
f1 (ppm)

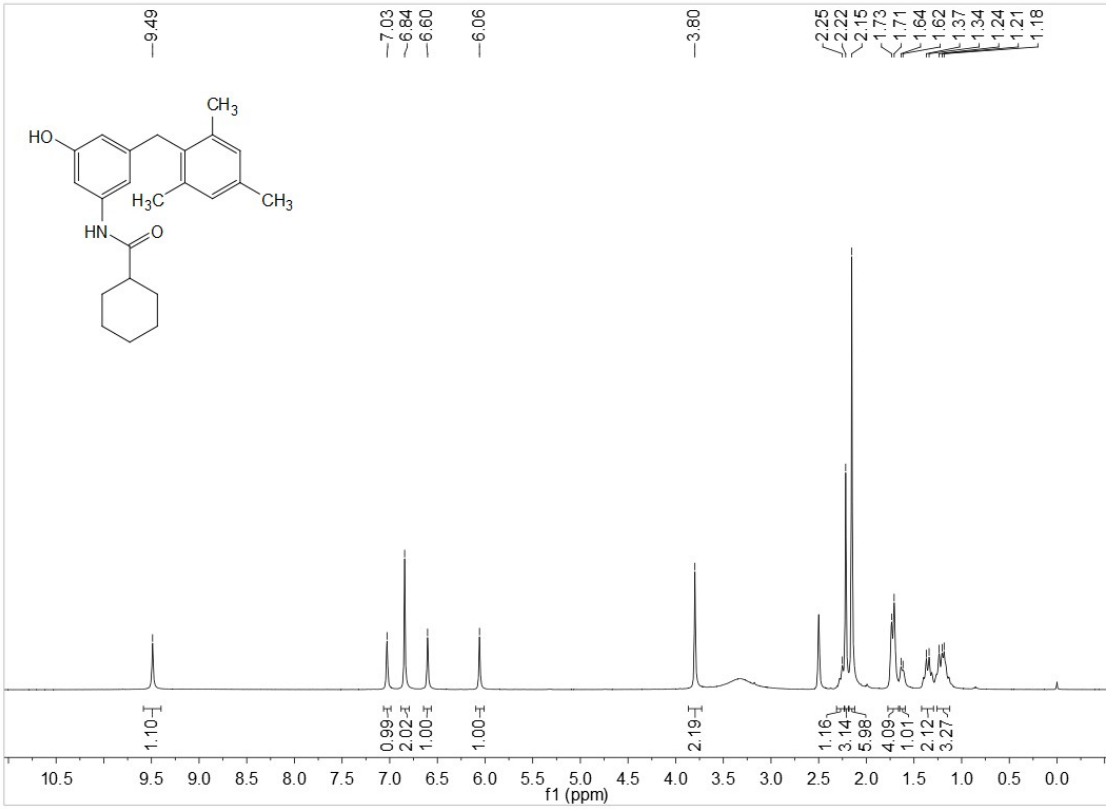

163.87
158.12
150.82
146.89
143.35
141.46
140.08
138.56
133.79
129.23
128.87
126.46
123.57
112.20
111.27
105.05
41.72
HO
NH
O
N
Cl
f1 (ppm)

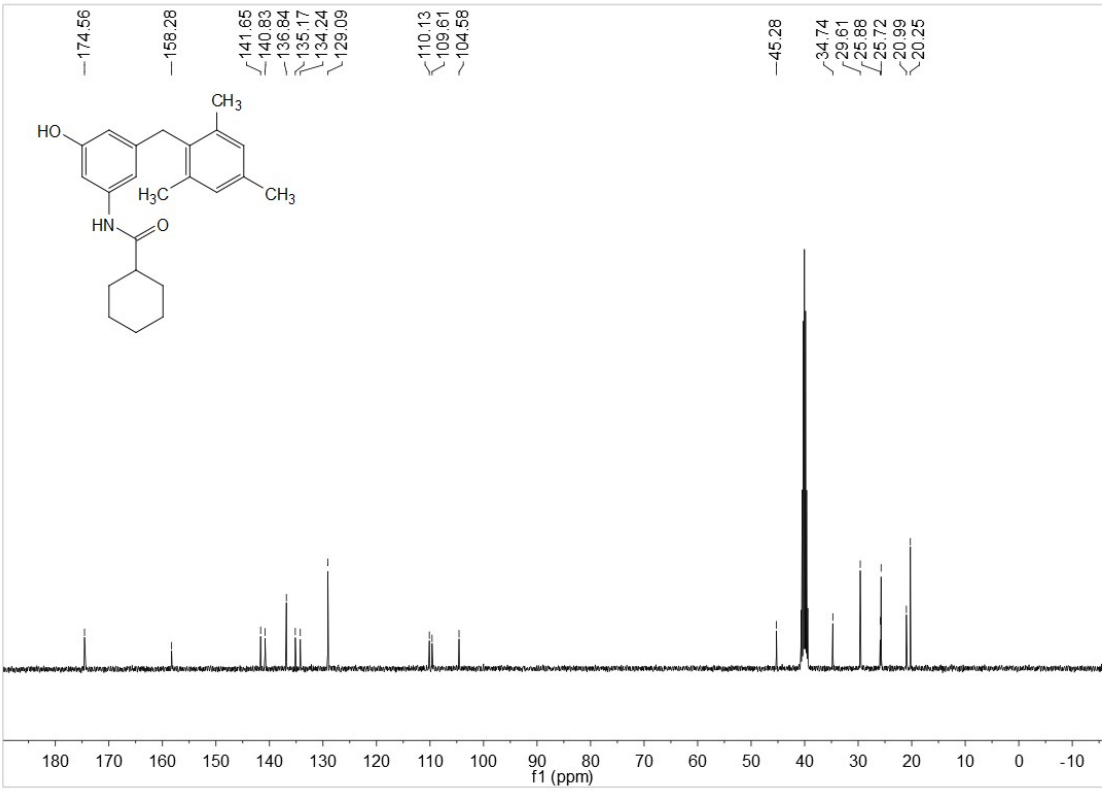
9a


168.19
149.26
134.45
131.48
130.24
126.86
125.08
122.43
121.70
118.61
103.30
102.89
96.66
39.73
39.52
39.31
37.69
30.90
21.19
17.40
17.29
11.57
9.83
HO
NH
O
CH3
CH3
f1 (ppm)

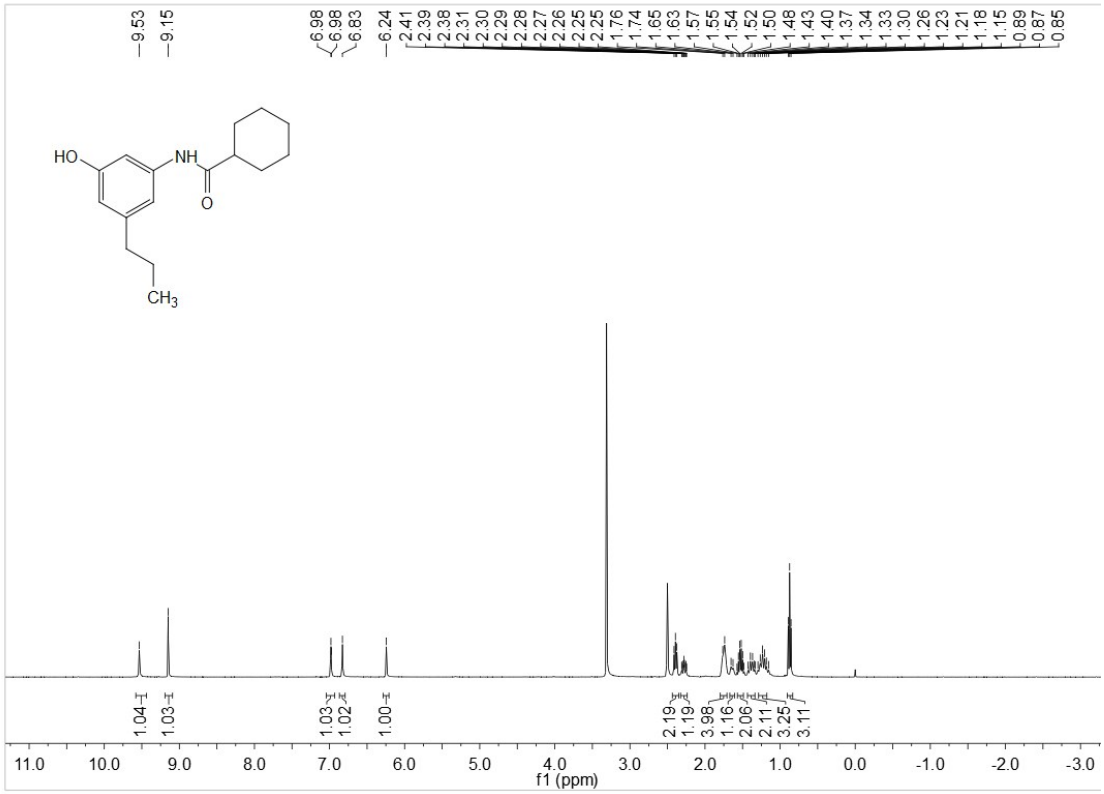

9.54
9.17
7.06
7.04
7.02
6.94
6.92
6.72
6.18
3.75
2.26
2.24
2.14
1.74
1.72
1.64
1.62
1.38
1.35
1.32
1.27
1.24
1.21
1.19
1.17
1.16
1.14
HO
NH
O
CH3
CH3
0.93
1.03
1.91
1.96
1.16
1.00
1.95
3.96
3.02
4.03
1.18
1.97
3.03
f1 (ppm)

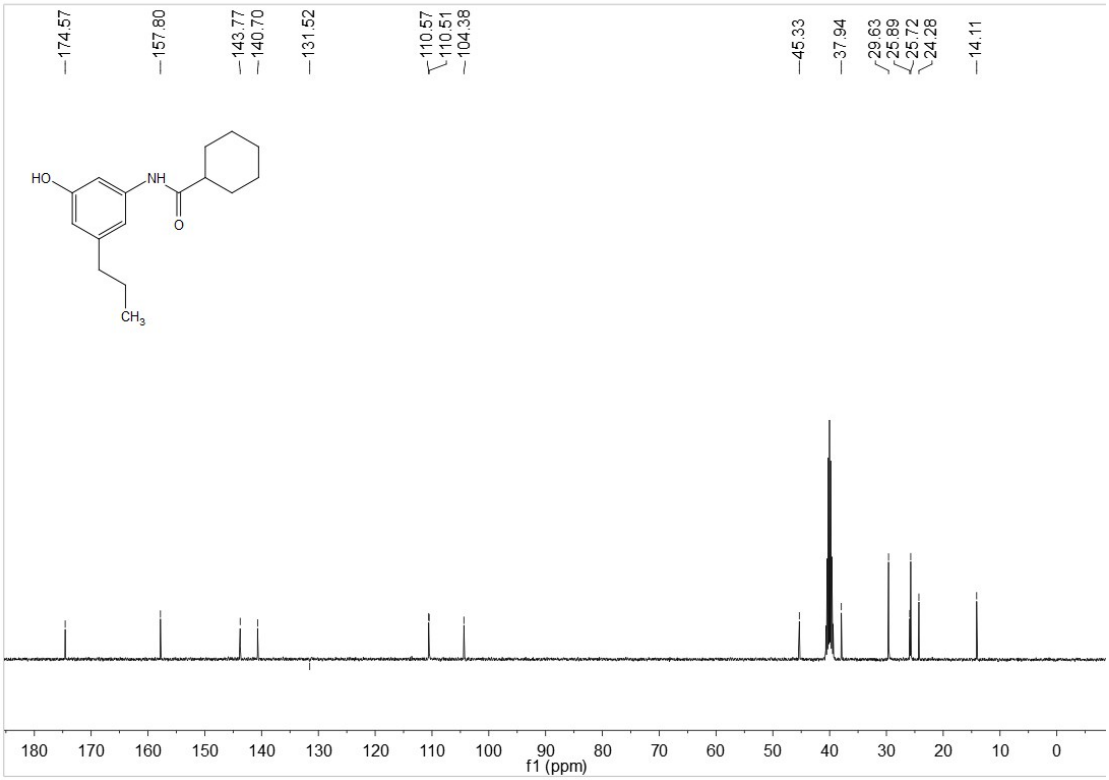
9b


9.49
7.03
6.84
6.60
6.06
3.80
2.25
2.22
2.15
1.73
1.71
1.64
1.62
1.37
1.34
1.24
1.21
1.18
HO
CH3
H3C
CH3
HN
O
1.10
0.99
2.02
1.00
1.00
2.19
1.16
3.14
5.98
4.09
1.01
2.12
3.27
f1 (ppm)

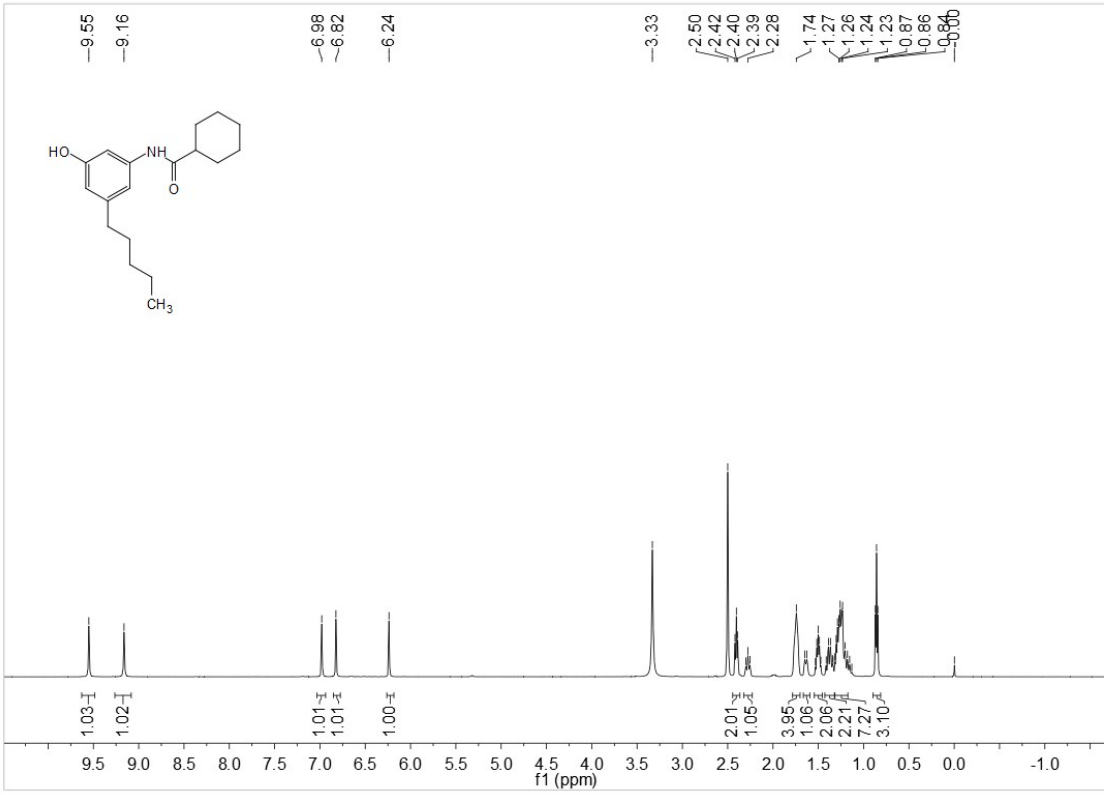

174.56
158.28
141.65
140.83
136.84
135.17
134.24
129.09
110.13
109.61
104.58
45.28
34.74
29.61
25.88
25.72
20.99
20.25
HO
CH3
H3C
CH3
HN
O
f1 (ppm)

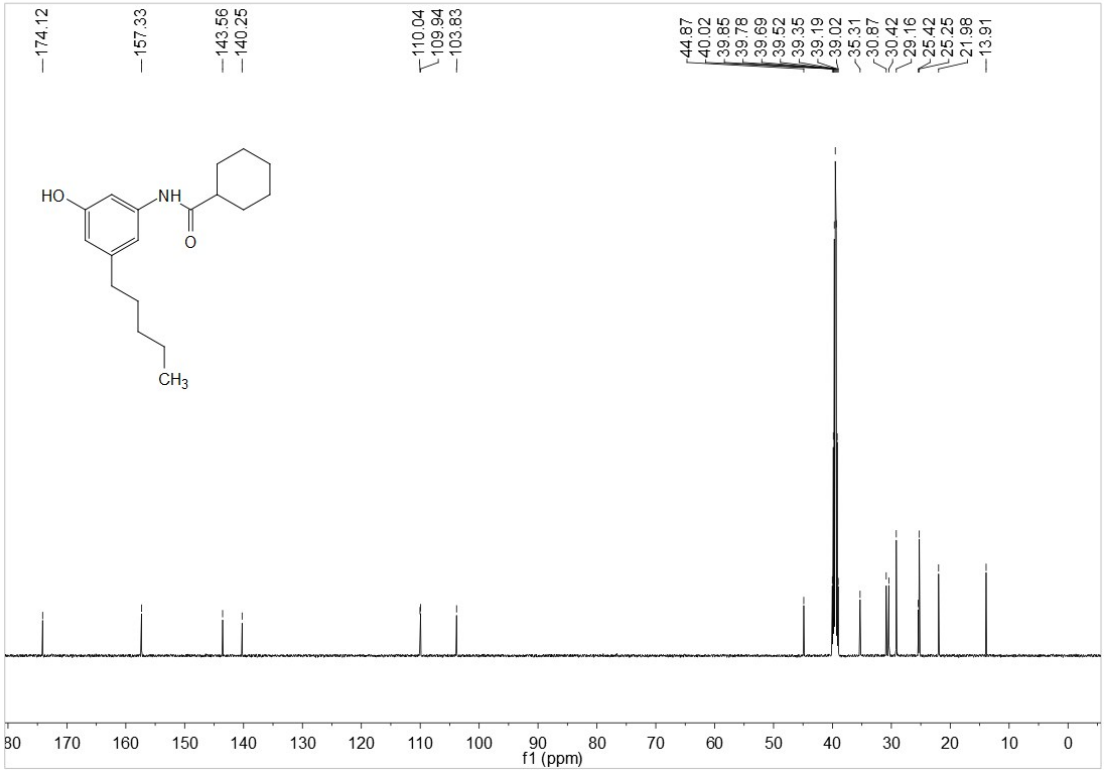
12a


9.53
9.15
6.98
6.98
6.83
6.24
HO
NH
O
CH3
1.04
1.03
1.03
1.02
1.00
2.19
1.19
3.98
1.16
2.06
2.11
3.25
3.11
f1 (ppm)

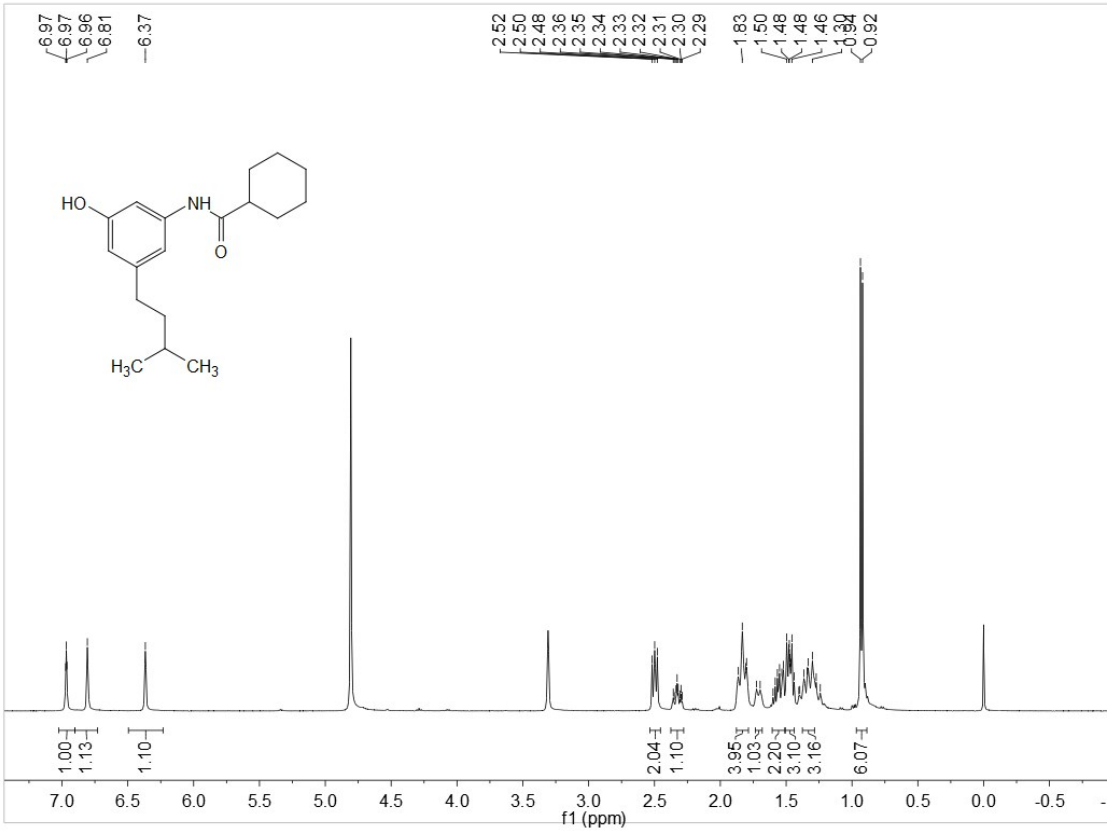

174.57
157.80
143.77
140.70
131.52
110.57
110.51
104.38
45.33
37.94
29.63
25.89
25.72
24.28
14.11
HO
NH
O
CH3
f1 (ppm)

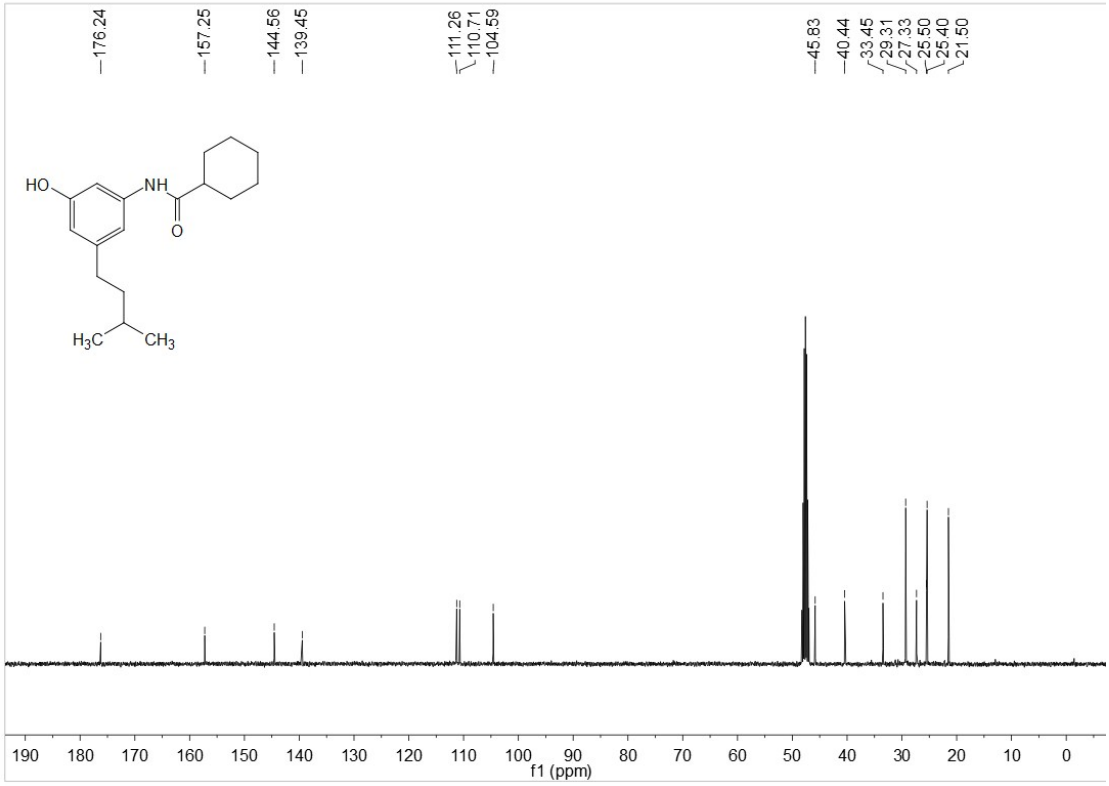
12b


9.55
9.16
6.98
6.82
6.24
3.33
2.50
2.42
2.40
2.39
2.28
1.74
1.27
1.26
1.24
1.23
0.87
0.86
0.84
0.00
HO
NH
O
CH3
1.03
1.02
1.01
1.01
1.00
2.01
1.05
3.95
1.06
2.06
2.21
7.27
3.10
f1 (ppm)

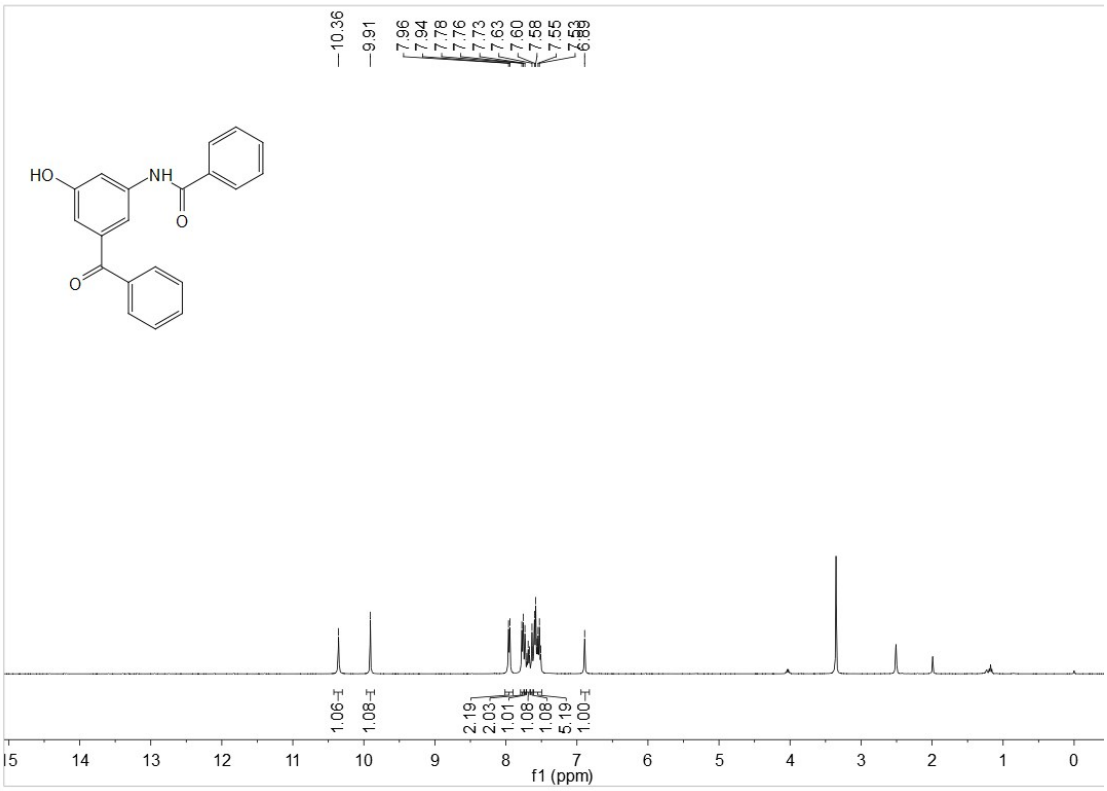

174.12
157.33
143.56
140.25
110.04
109.94
103.83
44.87
40.02
39.85
39.78
39.69
39.52
39.35
39.19
39.02
35.31
30.87
30.42
29.16
25.42
25.25
21.98
13.91
HO
NH
O
CH3
f1 (ppm)

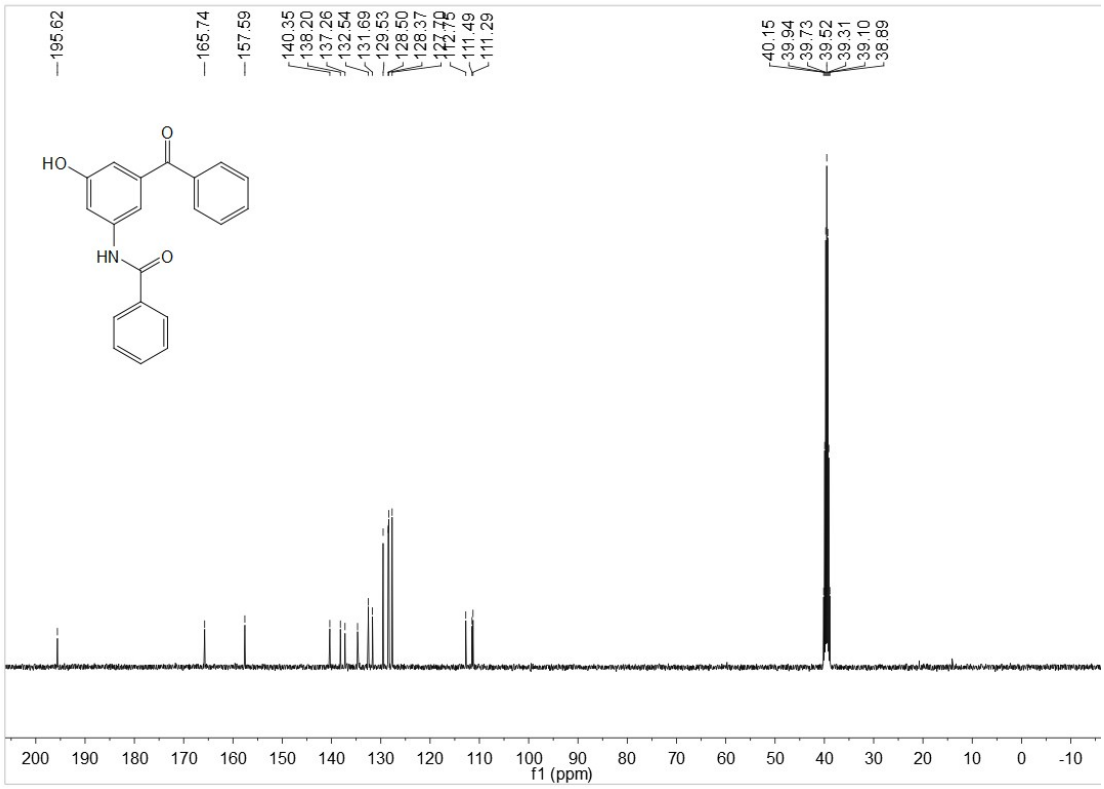
12c


6.97
6.97
6.96
6.81
6.37
2.52
2.50
2.48
2.36
2.35
2.34
2.33
2.32
2.31
2.30
2.29
1.83
1.50
1.48
1.46
0.94
0.92
HO
NH
O
H3C
CH3
1.00
1.13
1.10
2.04
1.10
3.95
1.03
2.20
3.10
3.16
6.07
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

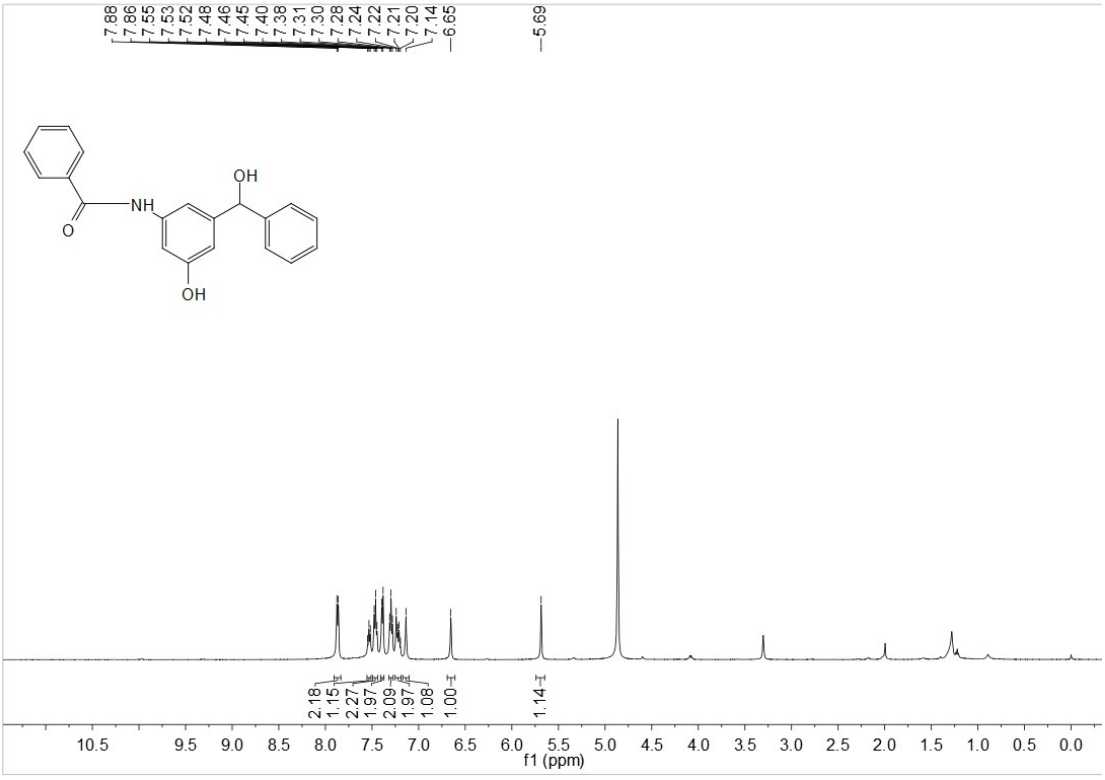

176.24
157.25
144.56
139.45
111.26
110.71
104.59
45.83
40.44
33.45
29.31
27.33
25.50
25.40
21.50
HO
NH
O
H3C
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

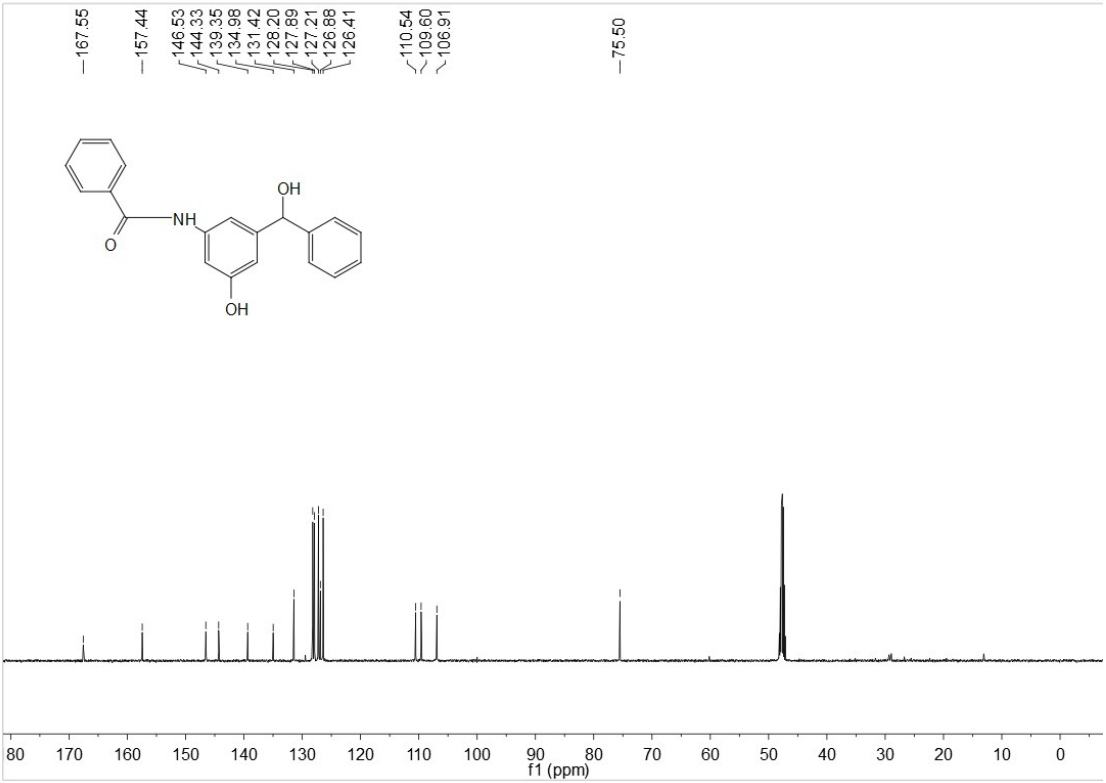
14


10.36
9.91
7.96
7.94
7.78
7.76
7.73
7.63
7.60
7.58
7.55
HO
NH
O
O
1.06
1.08
2.19
2.03
1.01
1.08
1.08
5.19
1.00
f1 (ppm)

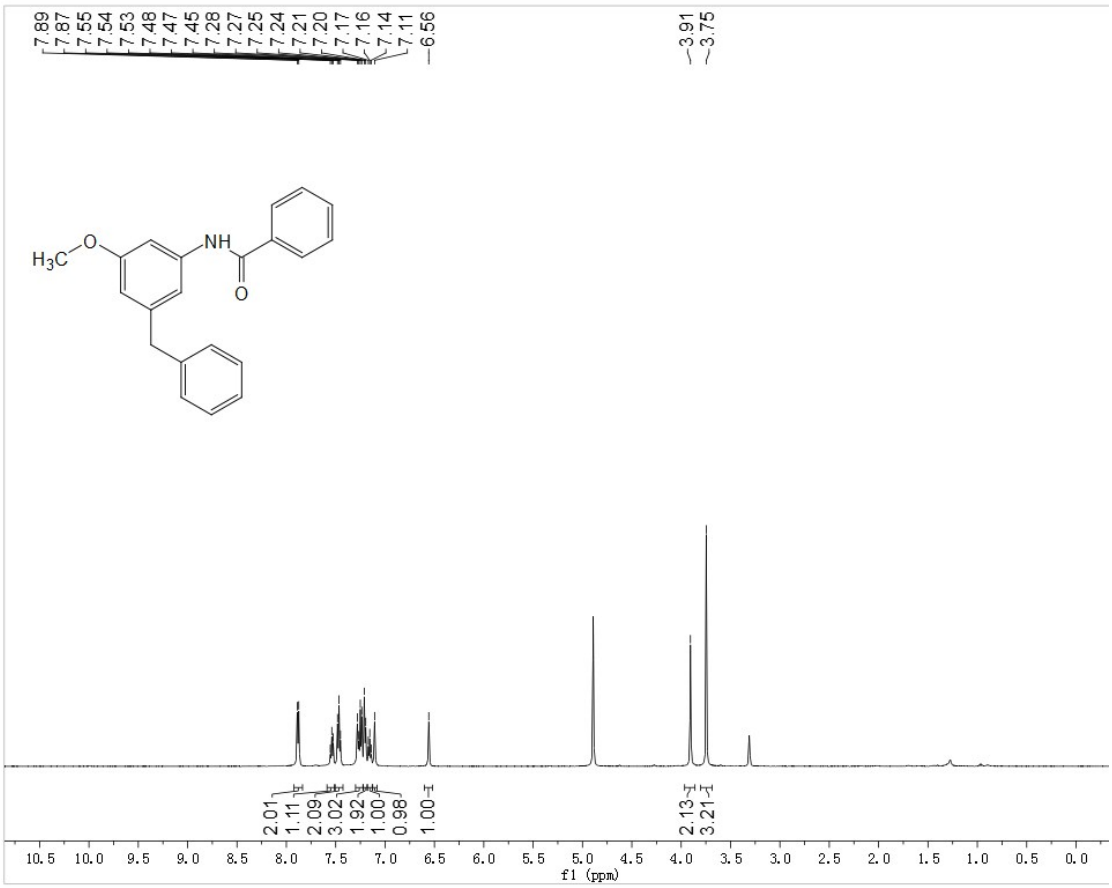

195.62
165.74
157.59
140.35
138.20
137.26
132.54
131.69
129.53
128.50
128.37
111.49
111.29
40.15
39.94
39.73
39.52
39.31
39.10
38.89
HO
O
HN
O
f1 (ppm)

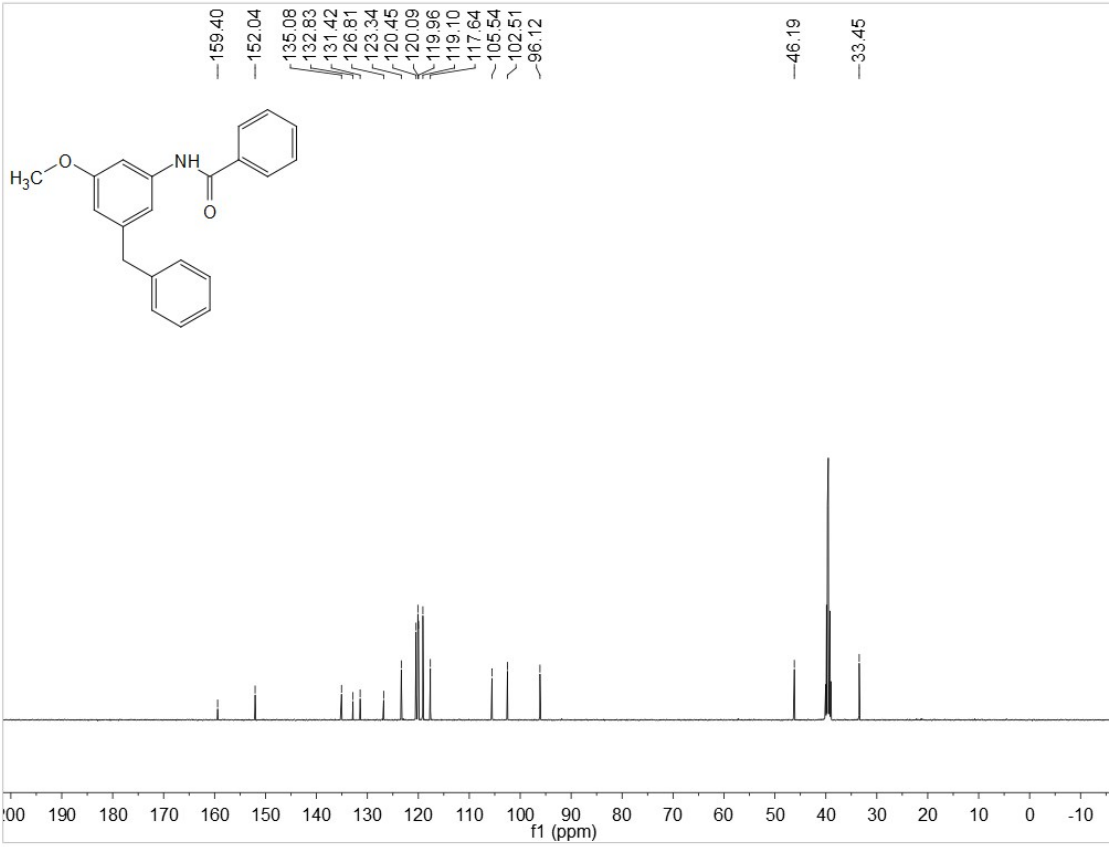
15


7.88
7.86
7.55
7.53
7.52
7.48
7.46
7.45
7.40
7.38
7.31
7.30
7.28
7.24
7.22
7.21
7.20
7.14
6.65
5.69
OH
NH
O
OH
2.18
1.15
2.27
1.97
2.09
1.97
1.08
1.00
1.14
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

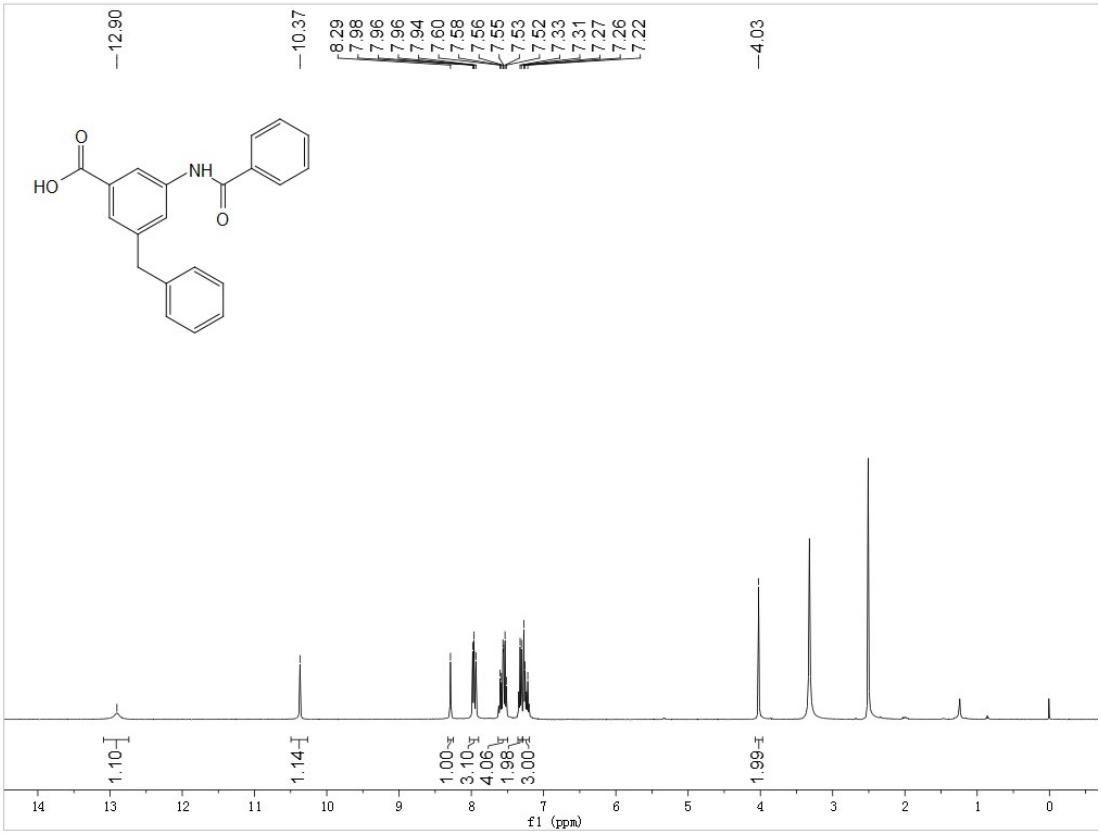

167.55
157.44
146.53
144.33
139.35
134.98
131.42
128.20
127.89
127.21
126.88
126.41
110.54
109.60
106.91
75.50
OH
NH
O
OH
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

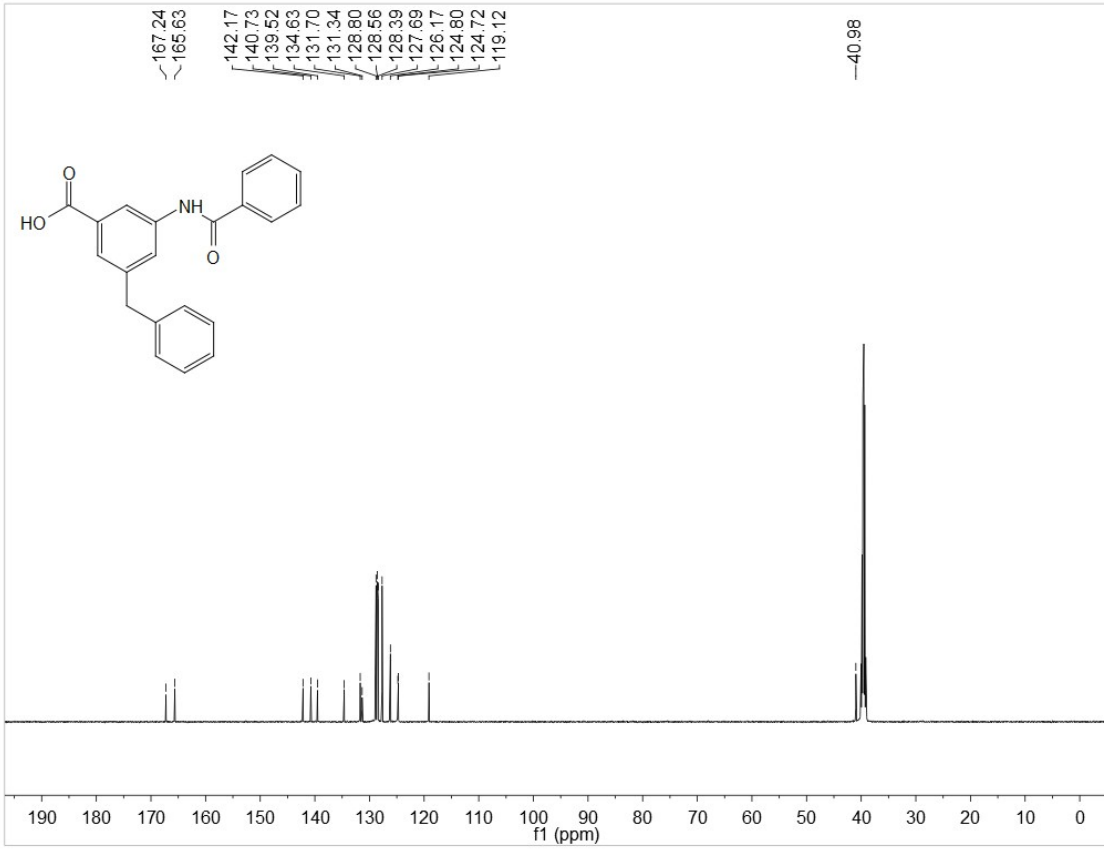
18


7.89
7.87
7.55
7.54
7.53
7.48
7.47
7.45
7.28
7.27
7.25
7.24
7.21
7.20
7.17
7.16
7.14
7.11
6.56
3.91
3.75
H3C
O
NH
O
2.01
1.11
2.09
3.02
1.92
1.00
0.98
1.00
2.13
3.21
f1 (ppm)

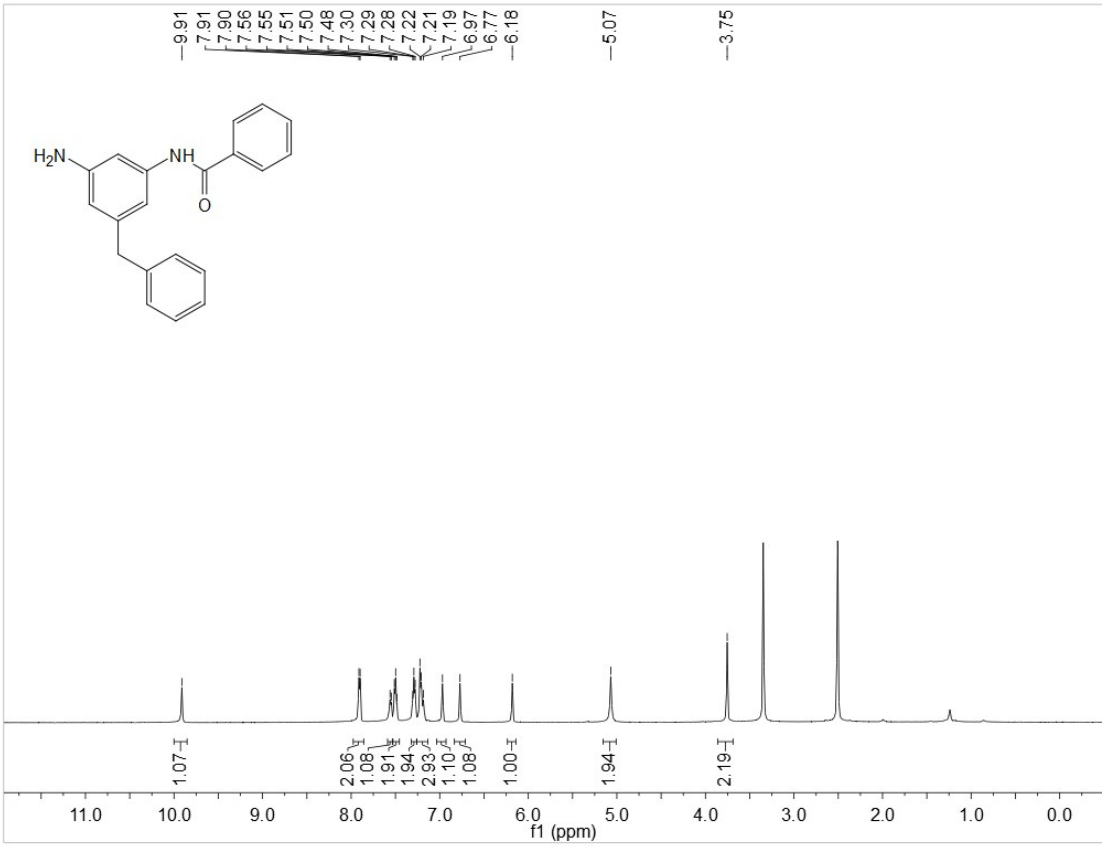

159.40
152.04
135.08
132.83
131.42
126.81
123.34
120.45
120.09
119.96
119.10
117.64
105.54
102.51
96.12
46.19
33.45
H3C
O
NH
O
f1 (ppm)

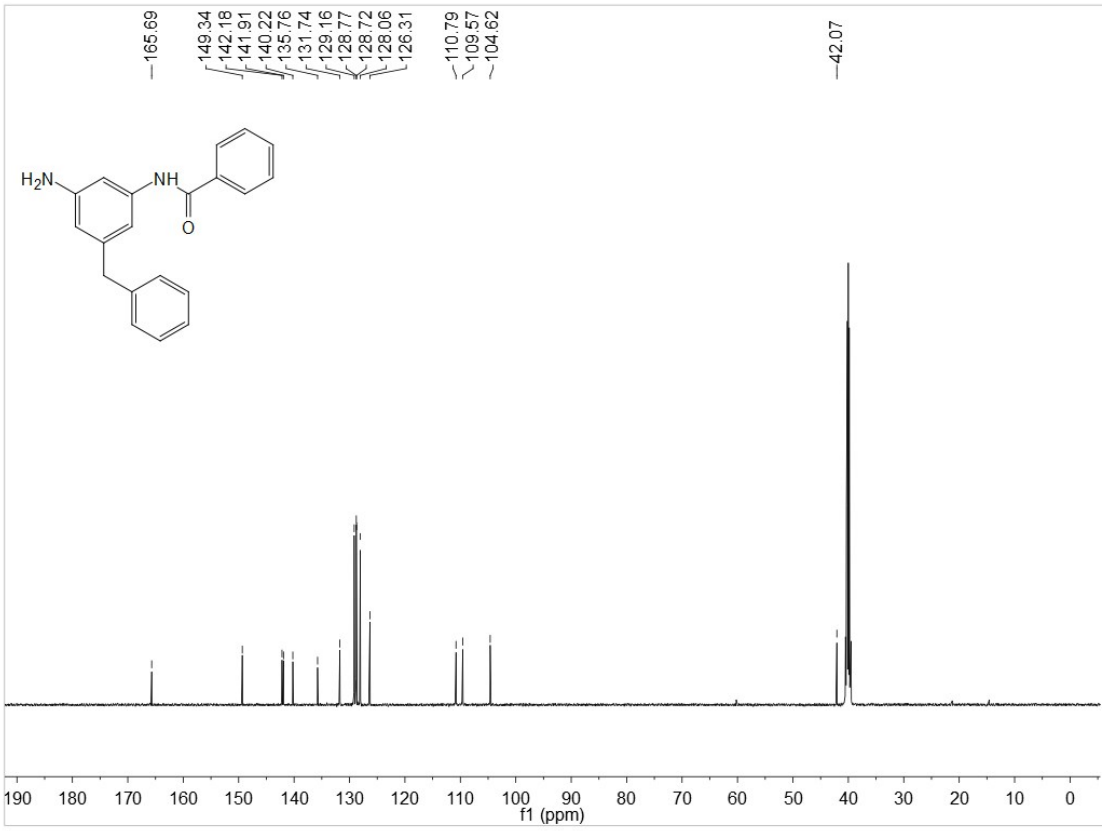
19


12.90
10.37
8.29
7.98
7.96
7.96
7.94
7.60
7.58
7.56
7.55
7.53
7.52
7.33
7.31
7.27
7.26
7.22
4.03
HO
O
NH
O
1.10
1.14
1.00
3.10
4.06
1.98
3.00
1.99
f1 (ppm)


167.24
165.63
142.17
140.73
139.52
134.63
131.70
131.34
128.80
128.56
128.39
127.69
126.17
124.80
124.72
119.12
40.98
HO
O
NH
O
f1 (ppm)

20


9.91
7.91
7.90
7.56
7.55
7.51
7.50
7.48
7.30
7.29
7.28
7.22
7.21
7.19
6.97
6.77
6.18
5.07
3.75
H2N
NH
O
1.07
2.06
1.08
1.91
1.94
2.93
1.10
1.08
1.00
1.94
2.19
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


165.69
149.34
142.18
141.91
140.22
135.76
131.74
129.16
128.77
128.72
128.06
126.31
110.79
109.57
104.62
42.07
H2N
NH
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)