Supporting Information

Terphenyl-based Small-Molecule Inhibitors of Programmed Cell Death-1/Programmed Death-Ligand 1 Protein−Protein Interaction

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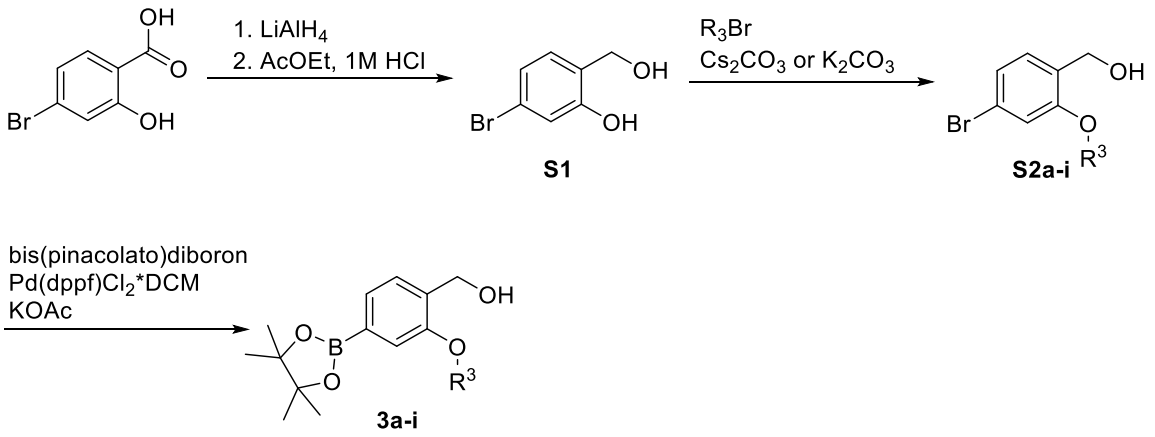
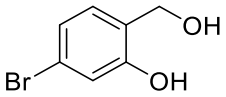
CONTENT

1. PREPARATION OF PHENYLBORONIC ACID PINACOL ESTERS



1.1. Preparation of 4-bromo-2-hydroxymethylbenzyl alcohol (S1):



$LiAlH_4$ (2.28 g, 60.0. mmol, 4.0 equiv) in anhydrous diethyl ether was placed in a round-bottom flask and cooled down in ice bath. Then 4-bromo-2-hydroxybenzoic acid (3.26 g, 15.0 mmol, 1 equiv) dissolved in anhydrous diethyl ether was added dropwise to this mixture. The reaction was stirred at RT overnight, after this time it was quenched with ethyl acetate/water and then acidified with 1 M HCl, followed by extraction with ethyl acetate. Organic phases were combined, dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:2) giving final product **S1** with 73.9% (2.25 g) yield. Compound **S1** was previously described in a patent application.[1]

R_f = 0.53 (SiO_2, hexane/ethyl acetate 1:2); **^{1}H NMR** (600 MHz, DMSO-d_6) δ [ppm]: 9.85 (s, 1H), 7.24 (d, J = 8.1 Hz, 1H), 6.97 (dd, J = 8.0, 2.0 Hz, 1H), 6.94 (d, J = 1.9 Hz, 1H), 4.44 (s, 2H); **^{13}C NMR** (151 MHz, DMSO-d_6) δ [ppm]: 155.7, 129.4, 128.8, 121.9, 119.8, 117.5, 58.2; **IR (ATR)** [cm^{-1}]: 3419, 3142, 2360, 1588, 1405, 1256; **LC-MS (DAD/ESI):** t_R = 4.11 min, calcd for C_7H_7Br (*m/z*): $[M-H]^-$ 200.96, found: $[M-H]^-$ 200.90.

1.2. General procedure for Williamson alkylation leading to alkoxy intermediates S2a-i:

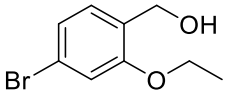
5-Bromo-2-(hydroxymethyl)phenol (**S1**), appropriate alkyl halide, Cs_2CO_3 or K_2CO_3 and anhydrous DMF were placed in a round-bottom flask. The reaction mixture was heated at 85ºC for 16 h. When it was completed water was added and extraction with ethyl acetate follows. Organic phases were combined, dried over anhydrous $MgSO_4$ and evaporated. Crude products

were purified by flash chromatography (SiO_2, hexane/ethyl acetate) giving final products **S1a-i** with 91-43% yield.

(4-Bromo-2-methoxyphenyl)methanol (S2a)

Compound **S2a** was purchased from Sigma-Aldrich.

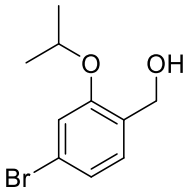
(4-Bromo-2-ethoxyphenyl)methanol (S2b)



5-Bromo-2-(hydroxymethyl)phenol (**S1**) (0.50 g, 2.46 mmol, 1.0 equiv), bromoethane (0.82 ml, 2.71 mmol, 1.1 equiv), Cs_2CO_3 (1.20 g, 3.69 mmol, 1.5 equiv). Product **S2b** was obtained as colourless solid with 91.0% (0.52 g) yield. Compound **S2b** was previously characterized in patent application.[2]

R_f = 0.46 (SiO_2, hexane/ethyl acetate 1:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ [ppm]: 7.07 (d, J = 7.9 Hz, 1H), 6.99 (dd, J = 8.0, 1.7 Hz, 1H), 6.92 (d, J = 1.6 Hz, 1H), 4.56 (s, 2H), 4.00 (q, J = 7.0 Hz, 2H), 2.13 (s_{broad}, 1H), 1.37 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ [ppm]: 157.3, 129.7, 128.3, 123.5, 121.9, 114.7, 64.0, 61.6, 14.8; **IR (ATR)** [cm^{-1}]: 3486, 2985, 1414, 1351, 1242, 1145; **LC-MS (DAD/ESI):** t_R = 5.96 min, calcd for $C_9H_{11}BrO_2$ (*m/z*): $[M\text{-}H_2O+H]^+$ 213.00, found: $[M\text{-}H_2O+H]^+$ 212.99; **HRMS (ESI):** Calcd for $C_9H_{11}BrO_2$ (*m/z*): $[M+Na]^+$ 252.9835, found: $[M+Na]^+$ 252.9835

(4-Bromo-2-isopropoxyphenyl)methanol (S2c)

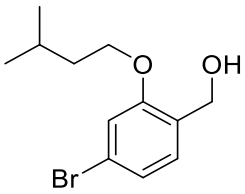


5-Bromo-2-(hydroxymethyl)phenol (**S1**) (0.69 g, 3.40 mmol, 1.0 equiv), 2-bromopropane (0.64 ml, 6.80 mmol, 2.0 equiv), Cs_2CO_3 (2.21 g, 6.80 mmol, 2.0 equiv). Product **S2c** was obtained as light yellow oil with 62.0% (0.52 g) yield. Compound **S2c** was previously described in literature.[3]

R_f = 0.24 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ [ppm]: 7.14 (d, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0, 1.8 Hz, 1H), 7.01 (d, J = 1.7 Hz, 1H), 4.61 (s, 2H), 4.60-4.56 (m, 1H), 1.37 (d, J = 6.1 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ [ppm]: 156.5, 130.0, 129.2, 123.5, 12.0, 116.1, 70.9, 62.0, 22.2; **IR (ATR)** [cm^{-1}]: 3343, 2977, 2930, 1592, 1484, 1402, 1238, 1122, 1109,

1042, 960, 879; **LC-MS (DAD/ESI)**: t_r = 6.48 min, calcd for $C_{10}H_{13}BrO_2$ (*m/z*): $[M-H_2O+H]^+$ 227.01, found: $[M-H_2O+H]^+$ 227.02; **HRMS (ESI):** Calcd for $C_{10}H_{13}BrO_2$ (*m/z*): $[M+Na]^+$ 266.9991, found: $[M+Na]^+$ 266.9991

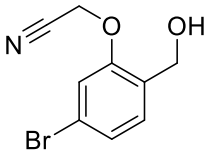
(4-Bromo-2-isopentyloxyphenyl)methanol (S2d)



5-Bromo-2-(hydroxymethyl)phenol (**S1**) (0.43 g, 2.12 mmol, 1.0 equiv), 1-bromo3-methylbutane (0.51 ml, 4.24 mmol, 2.0 equiv), Cs_2CO_3 (1.38 g, 4.24 mmol, 2.0 equiv). Product **S2d** was obtained as yellow oil with 51.6% (0.30 g) yield.

R_f = 0.29 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.15 (d, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 4.63 (s, 2H), 4.02 (t, *J* = 6.6 Hz, 2H), 1.87-1.77 (m, 1H), 1.71 (q, *J* = 6.7 Hz, 2H), 0.98 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 157.5, 129.7, 128.3, 123.5, 122.0, 114.6, 66.8, 61.8, 37.8, 25.2, 22.5; **IR (ATR)** [cm^{-1}]: 3335, 2956, 2931, 2871, 1593, 1490, 1404, 1386, 1241, 1044, 1016, 835, 806; **LC-MS (DAD/ESI)**: t_r = 7.88 min, calcd for $C_{12}H_{17}BrO_2$ (*m/z*): $[M-H_2O+H]^+$ 255.04, found: $[M-H_2O+H]^+$ 255.13; **HRMS (ESI):** Calcd for $C_{12}H_{17}BrO_2$ (*m/z*): $[M+Na]^+$ 295.0304, found: $[M+Na]^+$ 295.0305

2-(5-Bromo-2-(hydroxymethyl)phenoxy)acetonitrile (S2e)

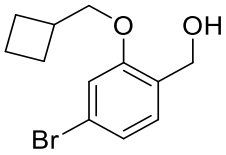


5-Bromo-2-(hydroxymethyl)phenol (**S1**) (0.50 g, 2.46 mmol, 1.0 equiv), bromoacetonitrile (0.34 ml, 4.92 mmol, 2.0 equiv), Cs_2CO_3 (0.68 g, 4.92 mmol, 2.0 equiv). Product **S2e** was obtained as light yellow solid with 42.7% (0.25 g) yield.

R_f = 0.32 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.31 (d, *J* = 8.1 Hz, 1H), 7.25 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.08 (d, *J* = 1.7 Hz, 1H), 4.82 (s, 2H), 4.67 (s, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 154.6, 130.5, 129.5, 126.5, 122.0, 115.5, 114.6, 60.3, 54.1; **IR (ATR)** [cm^{-1}]: 372, 3109, 3074, 2983, 2927, 2876, 2071, 1597, 1487, 1409, 1222, 1049, 851; **LC-MS (DAD/ESI)**: t_r = 4.72 min, calcd for $C_9H_8BrNO_2$ (*m/z*): $[M-H_2O+H]^+$ 223.97, found: [M-

$H_2O+H]^+$ 224.03; **HRMS (ESI):** Calcd for $C_9H_8BrNO_2$ (*m/z*): $[M+Na]^+$ 263.9631, found: $[M+Na]^+$ 263.9633

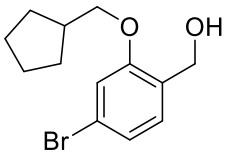
(4-Bromo-2-(cyclobutylmethoxy))methanol (S2f)



5-Bromo-2-(hydroxymethyl)phenol (**S1**) (1.00 g, 4.90 mmol, 1.0 equiv), (bromomethyl)cyclobutane (1.10 ml, 9.80 mmol, 2.0 equiv), K_2CO_3 (1.35 g, 9.80 mmol, 2.0 equiv). Product **S2f** was obtained as light yellow oil with 59.4% (0.79 g) yield.

R_f = 0.32 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.14 (d, *J* = 8.0, 1H), 7.07 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 4.63 (s, 2H), 3.96 (d, *J* = 6.6 Hz, 2H), 2.83-2.75 (m, 1H), 2.18-2.12 (m, 2H), 2.04-1.92 (m, 2H), 1.90-1.83 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 157.7, 129.8, 128.5, 123.6, 122.1, 114.9, 72.4, 61.8, 34.5, 24.9, 18.7; **IR (ATR)** [cm^{-1}]: 3323, 2975, 2935, 2864, 1593, 1488, 1403, 1237, 1045, 1013, 873; **LC-MS (DAD/ESI)**: t_r = 7.59 min, calcd for $C_{12}H_{15}BrN_2$ (*m/z*): $[M-H_2O+H]^+$ 253.07, found: $[M-H_2O+H]^+$ 253.02; **HRMS (ESI):** Calcd for $C_{12}H_{15}BrO_2$ (*m/z*): $[M+Na]^+$ 293.0148, found: $[M+Na]^+$ 293.0148

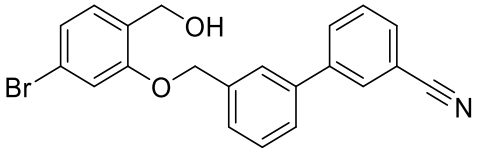
(4-Bromo-2-(cyclopentylmethoxy))methanol (S2g)



5-Bromo-2-(hydroxymethyl)phenol (**S1**) (0.62 g, 3.07 mmol, 1.0 equiv), (bromomethyl)cyclopentane (0.55 ml, 4.29 mmol, 1.4 equiv), Cs_2CO_3 (2.00 g, 6.13 mmol, 2.0 equiv). Product **S2g** was obtained as light yellow oil with 62.8% (0.55 g) yield.

R_f = 0.32 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.14 (d, *J* = 7.9 Hz, 1H), 7.07 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 4.64 (s, 2H), 3.88 (d, *J* = 6.9 Hz, 2H), 2.44-2.33 (m, 1H), 1.90-1.83 (m, 2H), 1.69-1.56 (m, 4H), 1.39-132 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 157.7, 129.8, 128.4, 123.6, 122.1, 114.8, 72.7, 61.9, 39.1, 29.6, 25.6; **IR (ATR)** [cm^{-1}]: 3335, 2952, 2866, 1593, 1489, 1404, 1238, 1028, 875; **LC-MS (DAD/ESI)**: t_r = 8.14 min, calcd for $C_{13}H_{17}BrO_2$ (*m/z*): $[M-H_2O+H]^+$ 267.04, found: $[M-H_2O+H]^+$ 267.16; **HRMS (ESI):** Calcd for $C_{13}H_{17}BrO_2$ (*m/z*): $[M+Na]^+$ 307.0304, found: $[M+Na]^+$ 307.0305

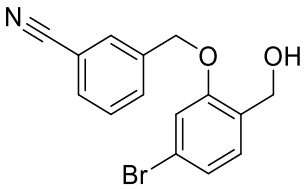
3'-((5-bromo-2-(hydroxymethyl)phenoxy)methyl)-[1,1'-biphenyl]-3-carbonitrile (S2h)



5-Bromo-2-(hydroxymethyl)phenol (**S1**) (0.45 g, 2.2 mmol, 1.0 equiv), 3'-(chloromethyl)-[1,1'-biphenyl]-3-carbonitrile (0.51 g, 2.2 mmol, 1.0 equiv), Cs_2CO_3 (1.43 g, 4.4 mmol, 2 equiv). Product **S2h** was obtained as light-yellow oil with 44.4% (0.38 g) yield.

R_f = 0.48 (SiO_2, hexane/ethyl acetate 1:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ [ppm]: 7.84 (t, *J* = 1.5 Hz, 1H), 7.80 (m, 1H), 7.62 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.59 (s_{broad}, 1H), 7.55-7.49 (m, 3H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.11-7.09 (m, 2H), 5.12 (s, 2H), 4.68 (s, 2H), 2.34 (s, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ [ppm]: 156.8, 141.9, 139.5, 137.2, 131.6, 131.0, 130.7, 129.8, 129.8, 129.7, 128.7, 127.4, 127.1, 126.1, 124.2, 121.9, 118.8, 115.2, 113.0, 70.2, 61.0; **IR (ATR)** [cm^{-1}]:3273, 3059, 2920, 2231, 1592, 1491, 1243, 1053, 774; **LC-MS (DAD/ESI)**: t_r = 7.83 min, calcd for $C_{21}H_{16}BrNO_2$ (*m/z*): $[M-H_2O+H]^+$ 376.04, found: $[M-H_2O+H]^+$ 376.15; **HRMS (ESI):** Calcd for $C_{21}H_{16}BrNO_2$ (*m/z*): $[M+Na]^+$ 416.0257, found: $[M+Na]^+$ 416.0255

3-((5-Bromo-2-(hydroxymethyl)phenoxy)methyl)benzonitrile (S2i)



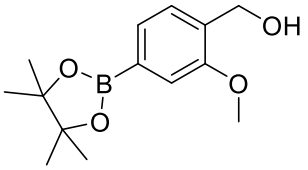
5-Bromo-2-(hydroxymethyl)phenol (**S1**) (1.0 g, 5.0 mmol, 1.0 equiv), 3-cyanobenzyl bromide (1.15 g, 5,9 mmol, 1.2 equiv), K_2CO_3 (1.03 g, 1.03 mmol, 1.5 equiv) Product **S2i** was obtained as colourless solid with 68.4% (1.09 g) yield. The product was recrystallized from cyclohexane/ethyl acetate mixture.

R_f = 0.64 (SiO_2, hexane/ethyl acetate 1:1); **^{1}H NMR** (600 MHz, DMSO-d_6) δ [ppm]: 7.91 (s, 1H), 7.81 (d, *J* = 12.3, 7.9 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 1.7 Hz, 1H), 7.17 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.22 (s, 2H), 5.14 (t, *J* = 5.6 Hz, 1H), 4.51 (d, 5.6 Hz, 2H); **^{13}C NMR** (151 MHz, DMSO-d_6) δ [ppm]: 155.5, 138.6, 132.1, 131.7, 130.7, 130.4, 129.8, 128.8, 123.4, 119.9, 118.7, 114.7, 111.5, 68.3; **IR (ATR)** [cm^{-1}]: 3288, 2922, 2230, 1594, 1489, 1400, 1054; **LC-MS (DAD/ESI)**: t_r = 6.56 min, calcd for $C_{15}H_{12}BrNO_2$ (*m/z*): $[M-H_2O+H]^+$ 300.00, found: $[M-H_2O+H]^+$ 300.06; **HRMS (ESI):** Calcd for $C_{15}H_{12}BrNO_2$ (*m/z*): $[M+Na]^+$ 339.9944, found: $[M+Na]^+$ 339.9941.

1.3. General procedure for Miyaura borylation (3a-i)

Bis(pinacolato)diboron, anhydrous potassium acetate, appropriate bromoaryl **S2a-i,** and anhydrous dioxane were placed in a two-neck round-bottom flask under argon atmosphere. The mixture was deoxygenated by rinsing with argon for half an hour, then Pd(dppf)Cl_2 dichloromethane complex was added. The reaction mixture was heated at 80°C, using a preheated bath, for three hours and after this time the progression of reaction was controlled using TLC analysis (SiO_2, hexane/ethyl acetate, 4:1). If the conversion was completed water was added and extraction with ethyl acetate followed. Organic phases were combined, dried over anhydrous $MgSO_4$ and evaporated. Crude products were purified by column chromatography (SiO_2, hexane/ethyl acetate) giving final boranes **3a-i** with 64.0-99.0% yield.

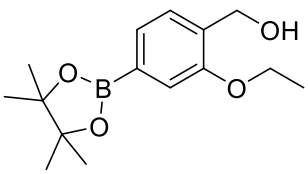
(2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3a)



(4-Bromo-2-methoxyphenyl)methanol (**S2a**) (2.17 g, 10.0 mmol, 1.0 equiv), bis(pinacoloato)diboran (2.79 g, 11.0 mmol, 1.1 equiv), anhydrous potassium acetate (2.94 g, 30.0 mmol, 3.0 equiv), Pd(dppf)Cl_2 complex with dichloromethane (0.41 g, 0.5 mmol, 0.05 equiv). Product **3a** was obtained as colourless solid with quantitative (2.61 g) yield. Product **3a** was crystallized from a cyclohexane/ethyl acetate mixture. The compound was previously described in the literature.[4]

R_f = 0.46 (SiO_2, hexane/ethyl acetate 1:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ [ppm]: 7.42 (d, J = 7.3 Hz, 1H), 7.30-7.28 (m, 2H), 4.70 (s, 2H), 3.91 (s, 4H), 1.35 (s, 12H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ [ppm]: 157.0, 132.4, 128.1, 127.7, 115.7, 84.0, 62.3, 55.5, 25.0; **IR (ATR)** [cm^{-1}]: 3287, 2979, 1402, 1353; **HRMS (ESI):** Calcd for $C_{14}H_{21}BO_4$ (*m/z*): $[M+Na]^+$ 287.1425, found: $[M+Na]^+$ 287.1429

(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3b)

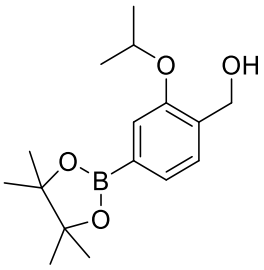


(4-Bromo-2-ethoxyphenyl)methanol (**S2b**) (0.42 g, 1.81 mmol, 1.0 equiv), bis(pinacoloato)diboran (0.55 g, 2.17 mmol, 1.2 equiv), anhydrous potassium acetate (0.53 g,

5.43 mmol, 3.0 equiv), Pd(dppf)Cl_2 complex with dichloromethane (0.07 g, 0.09 mmol, 0.05 equiv). Product **3b** was obtained as colourless oil with 81.0% (0.41 g) yield. Compounds was previously described in patent application.[5]

R_f = 0.46 (SiO_2, hexane/ethyl acetate 1:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.39 (m, 1H), 7.28 (m, 2H), 4.70 (s, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 2.44 (s_{broad}, 1H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.34 (s, 12H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 156.4, 132.3, 128.0, 127.5, 116.6, 83.9, 63.6, 62.6, 24.9, 15.0; **IR (ATR)** [cm^{-1}]: 3486, 2985, 1414, 1351, 1242, 1145; **HRMS (ESI):** Calcd for $C_{15}H_{23}BO_4$ (*m/z*): $[M+Na]^+$ 301.1582, found: $[M+Na]^+$ 301.1582

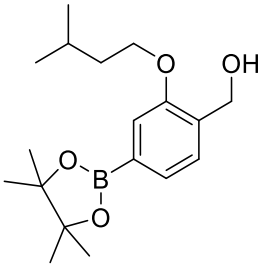
(2-Isopropoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3c)



(4-Bromo-2-isopropoxyphenyl)methanol (**S2c**) (0.51 g, 2.10 mmol, 1.0 equiv), bis(pinacoloato)diboran (0.59 g, 2.31 mmol, 1.1 equiv), anhydrous potassium acetate (0.62 g, 6.30 mmol, 3.0 equiv), Pd(dppf)Cl_2 complex with dichloromethane (0.05 g, 0.06 mmol, 0.03 equiv). Product **3c** was obtained as colourless oil with 64.0% (0.39 g) yield.

R_f = 0.19 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.30 (d, *J* = 7.3 Hz, 1H), 7.23 (s, 1H), 7.19 (d, H = 7.3 Hz, 1H), 4.67 (hept, *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 1.29 (d, *J* = 6.1 Hz, 6H), 1.27 (s, 12H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 155.5, 133.4,128.3, 127.5, 118.3, 84.0, 70.3, 62.8, 25.0, 22.4; **HRMS (ESI):** Calcd for $C_{16}H_{25}BO_4$ (*m/z*): $[M+Na]^+$ 315.1738, found: $[M+Na]^+$ 315.1741

(2-Isopentoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3d)

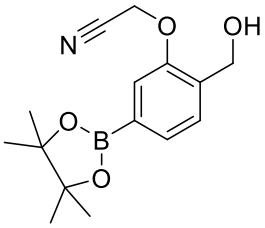


(4-Bromo-2-isopentoxyphenyl)methanol (**S2d**) (0.29 g, 1.09 mmol, 1.0 equiv), bis(pinacoloato)diboran (0.30 g, 1.30 mmol, 1.1 equiv), anhydrous potassium acetate (0.32 g,

3.27 mmol, 3.0 equiv), Pd(dppf)Cl_2 complex with dichloromethane (0.03 g, 0.03 mmol, 0.03 equiv). Product **3d** was obtained as colourless oil with 68.4% (0.35 g) yield.

R_f = 0.25 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.40 (d, *J* = 7.3 Hz, 1H), 7.29-7.27 (m, 2H), 4.70 (s, 2H) 4.10 (t, *J* = 6.5 Hz, 2H), 1.84 (sept, *J* = 6.8 Hz, 1H), 1.71 (q, *J* = 6.6 Hz, 2H), 1.35 (s, 12H), 0.98 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 156.6, 132.4, 128.0, 127.6, 116.5, 84.0, 66.5, 62.7, 38.3, 25.4, 25.0, 22.7; **IR (ATR)** [cm^{-1}]: 3445, 2977, 2930, 1410, 1353, 1235, 1145; **HRMS (ESI):** Calcd for $C_{18}H_{29}BO_4$ (*m/z*): $[M+Na]^+$ 343.2051, found: $[M+Na]^+$ 343.2052

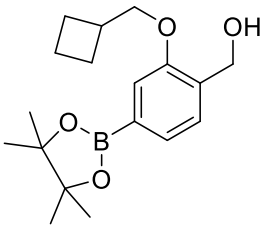
2-(2-Hydroxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)acetonitrile (3e)



2-(5-Bromo-2-(hydroxymethyl)phenoxy)acetonitrile (**S2e**) (0.49 g, 2.04 mmol, 1.0 equiv), bis(pinacoloato)diboran (0.57 g, 2.24 mmol, 1.1 equiv), anhydrous potassium acetate (0.60 g, 6.12 mmol, 3.0 equiv), Pd(dppf)Cl_2 complex with dichloromethane (0.05 g, 0.06 mmol, 0.03 equiv). Product **3e** was obtained as light-yellow solid with 96.6% (0.57 g) yield.

R_f = 0.30 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.56 (d, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.31 (s, 1H), 4.88 (s, 2H), 4.75 (s, 2H), 1.35 (s, 12 H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 153.8, 133.4, 130.1, 128.7, 117.0, 115.2, 84.3, 61.0, 53.9, 25.0; **IR (ATR)** [cm^{-1}]: 3320, 2983, 2937, 1410, 1351, 1237, 1143, 1050, 852; **HRMS (ESI):** Calcd for $C_{15}H_{20}BNO_4$ (*m/z*): $[M+Na]^+$ 312.1378, found: $[M+Na]^+$ 312.1381.

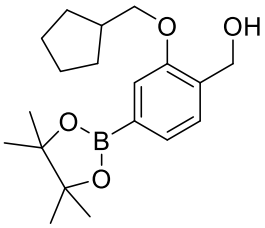
(2-(Cyclobutylmethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3f)



(4-Bromo-2-(cyclobutylmethoxy))methanol (**S2f**) (0.78 g, 2.9 mmol, 1.0 equiv), bis(pinacoloato)diboran (0.81 g, 3.19 mmol, 1.1 equiv), anhydrous potassium acetate (0.85 g, 8.70 mmol, 3.0 equiv), Pd(dppf)Cl_2 complex with dichloromethane (0.07 g, 0.09 mmol, 0.03 equiv). Product **3f** was obtained as colourless oil with 71.6% (0.66 g) yield.

R_f = 0.26 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.40 (d, *J* = 7.4 Hz, 1H), 7.28-7.26 (m, 2H), 4.70 (s, 2H), 4.06 (d, *J* = 6.6 Hz, 2H), 2.84-2.76 (m, 1H), 2.19-2.11 (m, 2H), 2.03-1.84 (m, 4H), 1.35 (s, 12H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 156.8, 132.5, 128.1, 127.6, 116.7, 84.0, 72.2, 62.8, 34.8, 29.8, 25.0, 25.0, 18.8; **IR (ATR)** [cm^{-1}]: 3417, 2977, 2933, 2861, 1409, 1354, 1233, 1145, 855; **HRMS (ESI):** Calcd for $C_{18}H_{27}BO_4$ (*m/z*): $[M+Na]^+$ 341.1895, found: $[M+Na]^+$ 341.1899

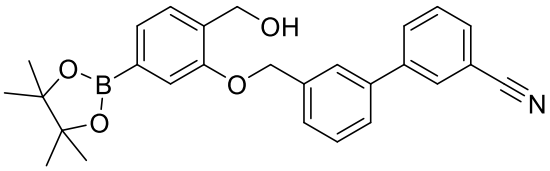
(2-(Cyclopentylmethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (3g)



(4-Bromo-2-(cyclopentylmethoxy))methanol (**S2g**) (0.50 g, 1.75 mmol, 1.0 equiv), bis(pinacoloato)diboran (0.49 g, 1,93 mmol, 1.1 equiv), anhydrous potassium acetate (0.52 g, 5.25 mmol, 3.0 equiv), Pd(dppf)Cl_2 complex with dichloromethane (0.04 g, 0.05 mmol, 0.03 equiv). Product **3g** was obtained as colourless oil with 97.5% (0.55 g) yield.

R_f = 0.26 (SiO_2, hexane/ethyl acetate 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* [ppm]: 7.39 (d, *J* = 7.3 Hz, 1H), 7.28-7.25 (m, 2H), 4.70 (s, 2H), 3.96 (d, *J* = 6.9 Hz, 2H), 2.41-2.36 (m, 1H), 1.89-1.82 (m, 2H), 1.68-1.58 (m, 4H), 1.39-1.35 (m, 2H), 1.34 (s, 12H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* [ppm]: 156.3, 132.4, 128.0, 127.6, 116.5, 84.0, 72.3, 62.8, 39.3, 29.7, 25.6, 25.0; **IR (ATR)** [cm^{-1}]: 3435, 2956, 2866, 1410, 1354, 1238, 1146, 1051, 855; **HRMS (ESI):** Calcd for $C_{19}H_{29}BO_4$ (*m/z*): $[M+Na]^+$ 355.2051, found: $[M+Na]^+$ 355.2053

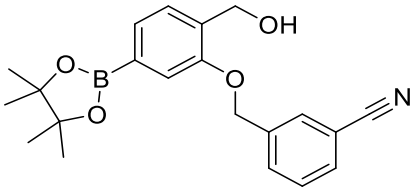
3'-((2-(Hydroxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)methyl)-[1,1'-biphenyl]-3-carbonitrile (3h)



3'-((5-Bromo-2-(hydroxymethyl)phenoxy)methyl)-[1,1'-biphenyl]-3-carbonitrile (**S2h**) (0.50 g, 1.27 mmol, 1.0 equiv), bis(pinacoloato)diboran (0.48 g, 1.90 mmol, 1.5 equiv), anhydrous potassium acetate (0.37 g, 3.81 mmol, 3.0 equiv), Pd(dppf)Cl_2 complex with dichloromethane (0.05 g, 0.06 mmol, 0.05 equiv). Product **3h** was obtained as colourless solid with 92.0% (0.52 g) yield.

R_f = 0.46 (SiO_2, hexane/ethyl acetate 1:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ [ppm]: 7.87 (t, J = 1.6 Hz, 1H), 7.81 (m, 1H), 7.65-7.63 (m, 2H), 7.56-7.48 (m, 4H), 7.47 (d, J = 7.3 Hz, 1H), 7.43 (s, 1H), 7.35 (d, J = 7.3 Hz, 1H), 5.21 (s, 2H), 4.76 (s, 2H), 2.38 (s_{broad}, 1H), 1.35 (s, 12H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ [ppm]: 155.9, 142.1, 139.3, 138.0, 132.7, 131.6, 130.9, 130.7, 129.7, 129.6, 128.1, 128.0, 127.5, 126.9, 126.3, 118.8, 116.9, 113.1, 84.0, 69.9, 62.0, 24.9; **IR (ATR)** [cm^{-1}]: 3471, 2977, 2230, 1408, 1352, 1144; **HRMS (ESI)**: Calcd for $C_{27}H_{28}BNO_4$ (*m/z*): $[M+Na]^+$ 464.2004, found: $[M+Na]^+$ 464.2008

3-((2-(Hydroxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)methyl)benzonitrile (3i)



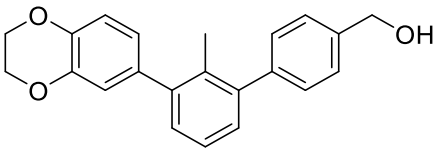
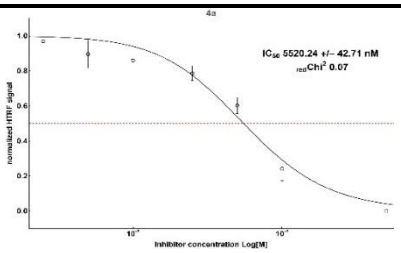
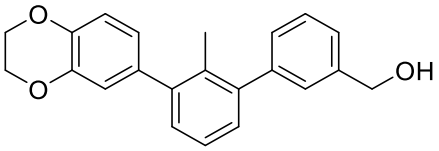
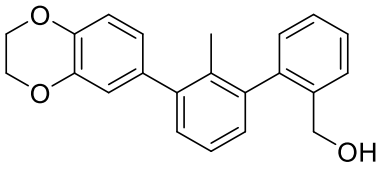
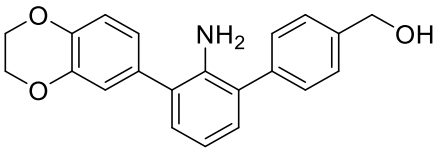
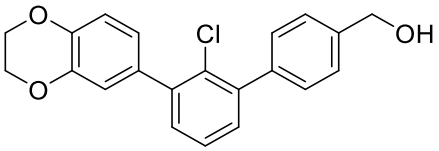
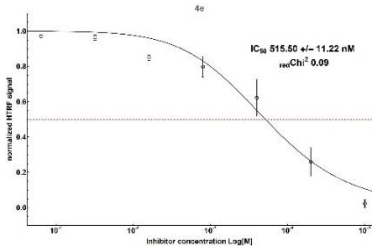
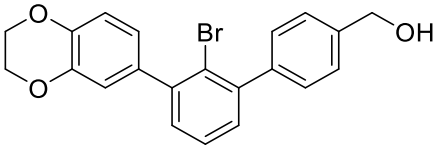
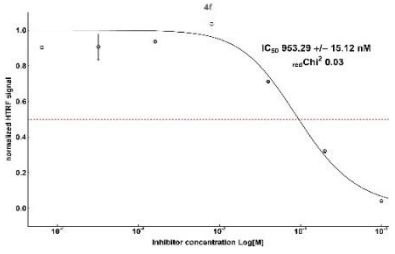
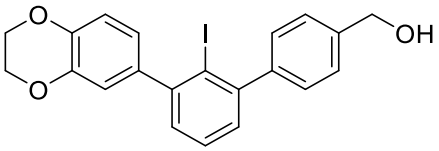
3-((5-Bromo-2-(hydroxymethyl)phenoxy)methyl)benzonitrile (**S2i**) **(**0.95 g, 3.0 mmol, 1.0 equiv), bis(pinacoloato)diboran (0.84 g, 3.3 mmol, 1.1 equiv), anhydrous potassium acetate (0.88 g, 9.0 mmol, 3.0 eq.), Pd(dppf)Cl_2 complex with dichloromethane (0.12 g, 0.15 mmol, 0.05 equiv). Product **3i** was obtained as colourless solid with 76.1% (0.83 g) yield. Product **3i** was crystallized from cyclohexane/ethyl acetate mixture.

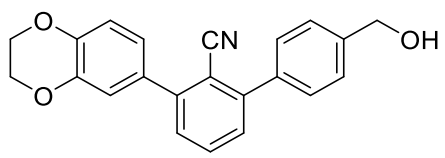
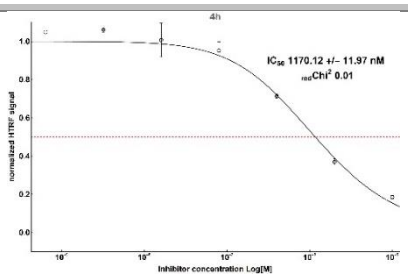
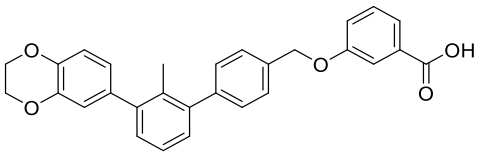
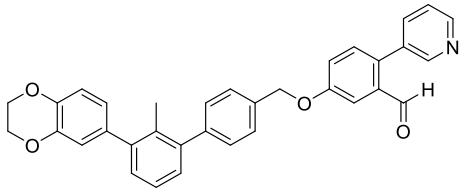
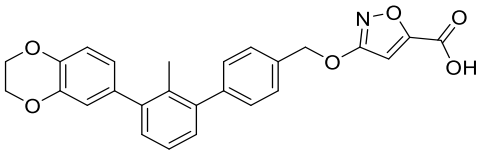
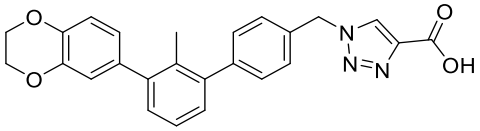
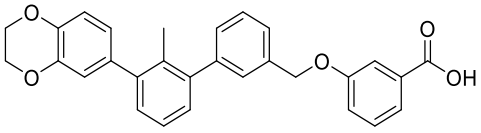
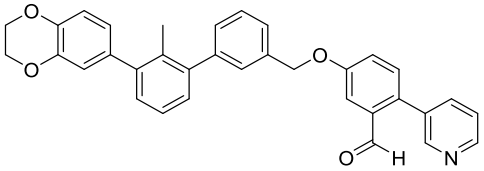
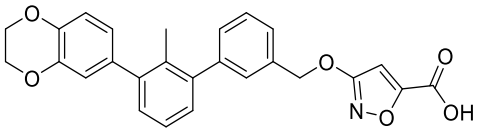
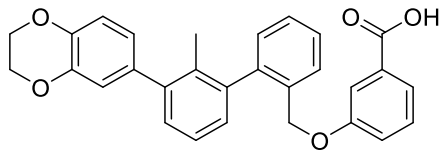
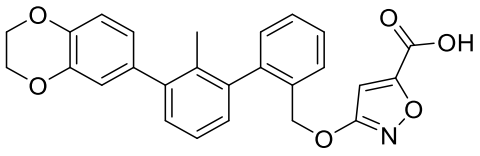
R_f = 0.63 (SiO_2, hexane/ethyl acetate 1:1); **^{1}H NMR** (600 MHz, DMSO-d_6) δ [ppm]: 7.93 (s, 1H), 7.83 (d, J = 13.5, 7.8 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.24 (s, 1H), 5.20 (s, 2H), 5.30 (t, J = 5.5 Hz, 1H), 4.60 (d, J = 5.0 Hz, 2H), 1.30 (s, 12H); **^{13}C NMR** (151 MHz, DMSO-d_6) δ [ppm]: 154.3, 139.1, 134.5, 132.0, 131.5, 130.6, 129.7,

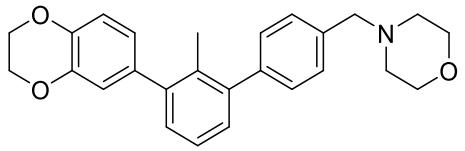
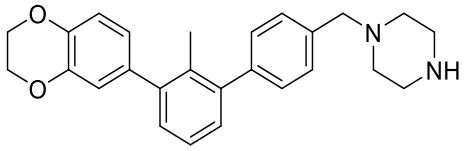
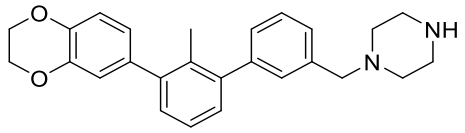
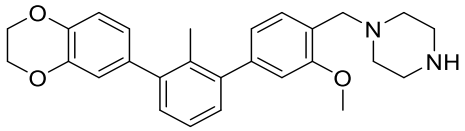
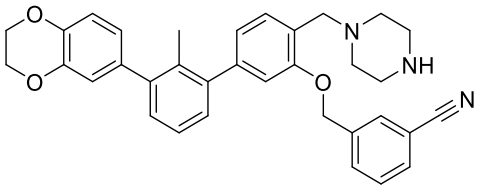
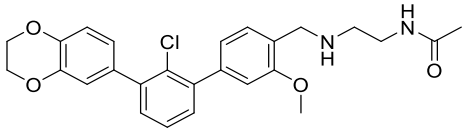
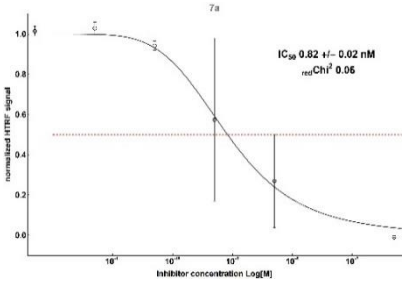
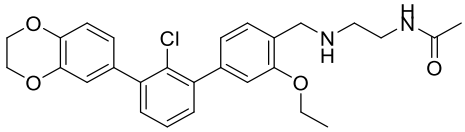
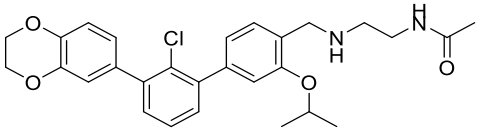
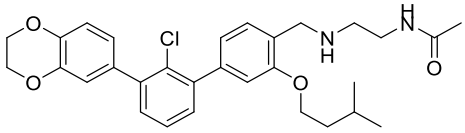
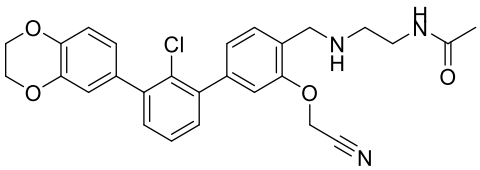
127.4, 126.5, 118.8, 116.1, 111.4, 83.7, 67.9, 58.0, 24.7; **IR (ATR)** [cm^{-1}]: 3435, 2980, 2227, 1571, 1509, 1405, 1351, 1238, 1141, 1064, 968, 924, 853, 785, 683; **HRMS (ESI):** Calcd for $C_{21}H_{24}BNO_4$ (*m/z*): $[M+Na]^+$ 388.1691, found: $[M+Na]^+$ 388.1696

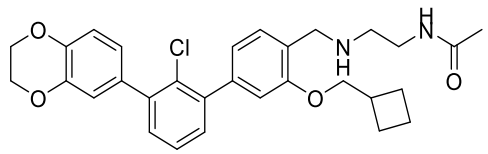
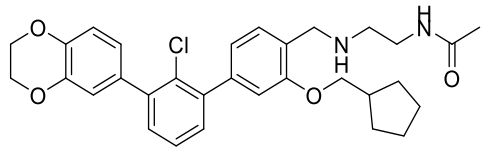
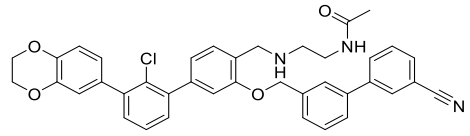
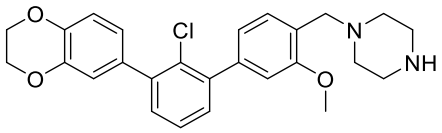
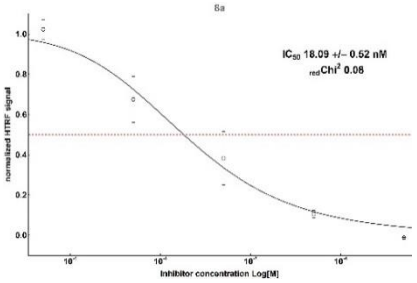
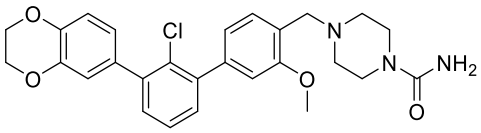
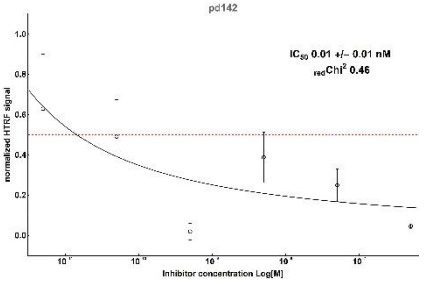
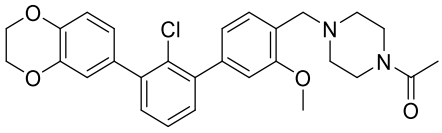
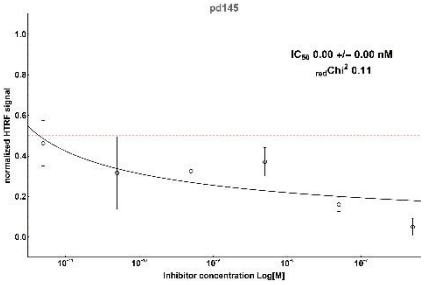
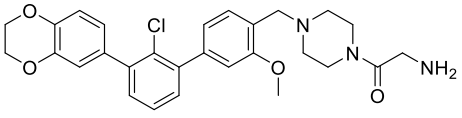
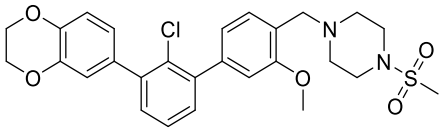
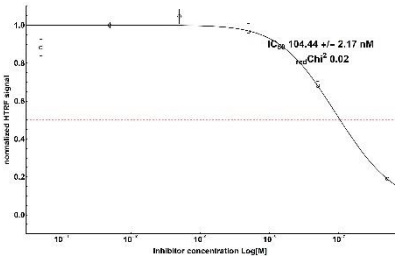
2. SUPPRORTING FIGURES AND TABLES

Table S1. Structures and HTRF data for obtained compounds

No	Structure	% of undissociated complex at 5 μM	IC_{50}	
			Determined [μM]	Plot
4a		42	**5.52±0.04**	
4b		88	-	--
4c		98	-	-
4d		73	-	-
4e		1	**0.51±0.01**	
4f		15	**0.95±0.02**	
4g		56	-	-

4h		21	**1.17±0.12**	
5b		71 at 50 µM	-	-
5d		65 at 50 µM	-	-
5f		90	-	-
5h		100	-	-
5j		90	-	-
5l		95 at 50 µM	-	-
5n		77	-	-
5p		87 at 50 µM	-	-
5r		100	-	-

6a		55	-	-
6b		5	-	-
6c		56	-	-
		% of undissociated complex at 5 nM	**Determined [nM]**	
6d		63	-	-
6e		88	-	-
7a		0	**0.82±0.02**	
7b		5	-	-
7c		5	-	-
7d		65	-	-
7e		1	-	-

7f		53	-	-
7g		76	-	-
7h		100	-	-
8a		38	**18.09±0.09**	
8b		28	-	
8c		40	-	
8d		5	-	-
8e		88	**104.44±2.17**	

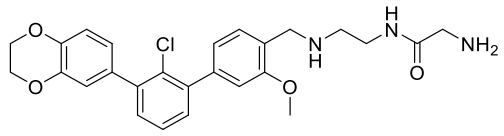
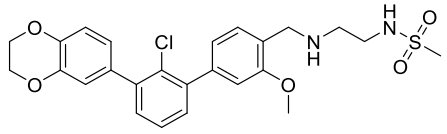
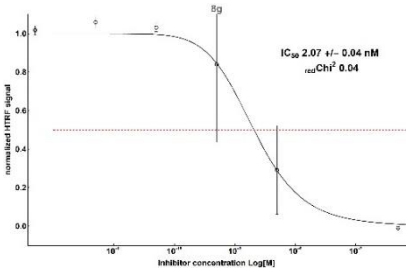
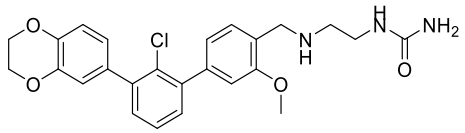
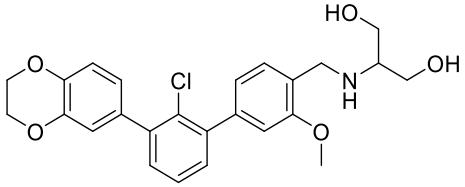
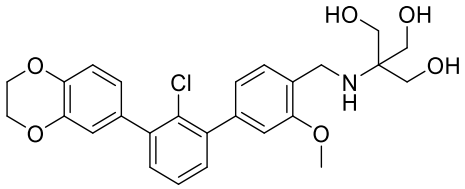
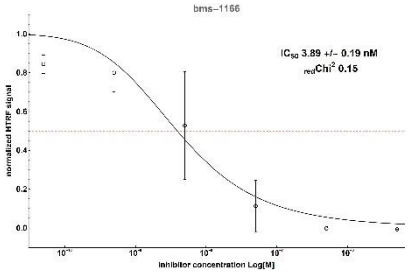
8f		8	-	-
8g		32	**2.07±0.04**	
8h		6	-	-
8i		0	-	-
8j		0	-	-
BMS-1166		53	**3.89±0.19**	

Table S2. Data collection and refinement statistics (molecular replacement)

Data collection	
Wavelength (Å)	0.9184
Space group	P 1 21 1
Cell dimensions	
a, b, c (Å)	67.09 75.25 74.35
α, β, γ (o)	90.0 96.29 90.0
Resolution range (Å)	47.01 - 2.30 (2.42- 2.30)
Rmerge	0.119 (3.196)
I/σI	15.00 (1.0)
Completeness (%)	99.0 (98.7)
Redundancy	13.4 (13.0)
Total reflections	217995 (21254)
CC1/2	1.0 (0.77)
Refinement statistics	
No. reflections	32189 (3143)
*R*work/*R*free	0.246/0.290
	(0.425/0.471)
Wilson B-factor	53.15
No. atoms	5360
Protein	5216
Water	42
Ramachandran favoured (%)	91.94
Ramachandran allowed (%)	7.18
Ramachandran outliers (%)	0.88
B-factors	56.60
Protein	56.24
Water	52.59
R.m.s deviations	
Bond lengths (Å)	0.011
Bond angles (o)	1.11

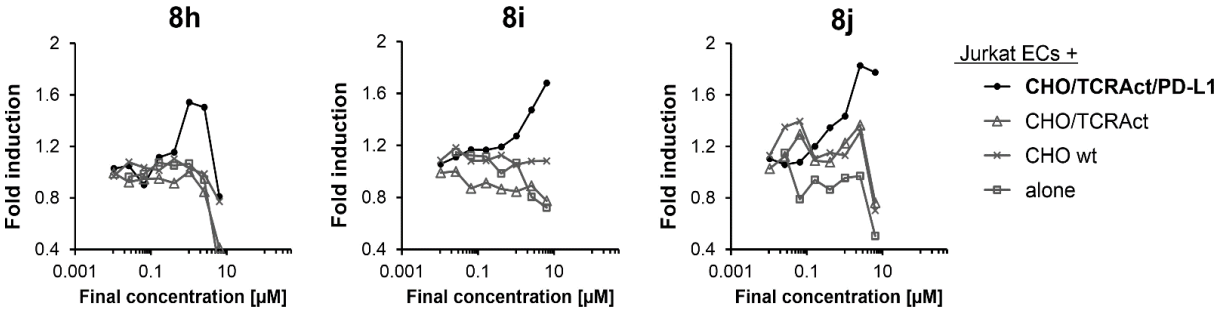
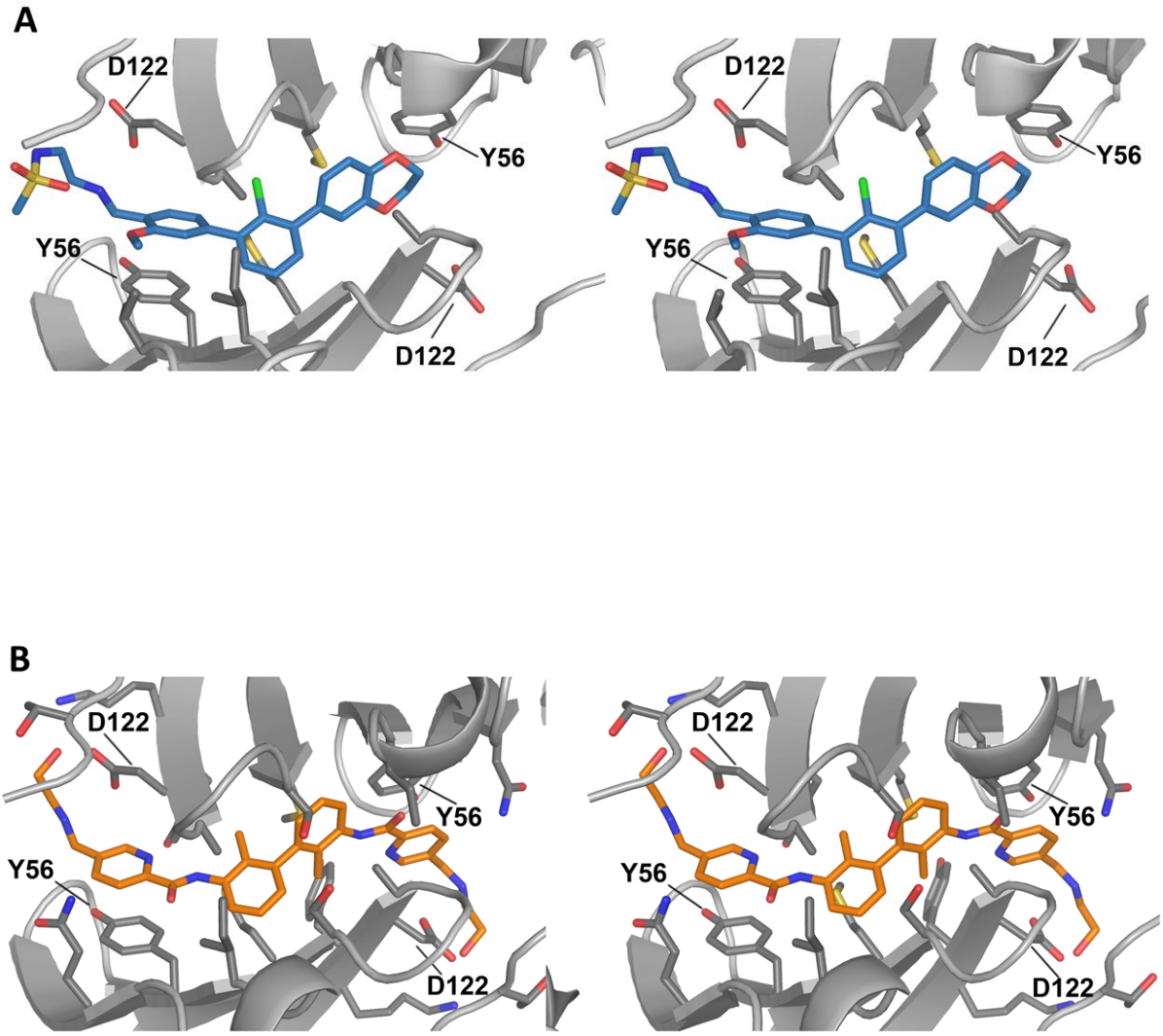
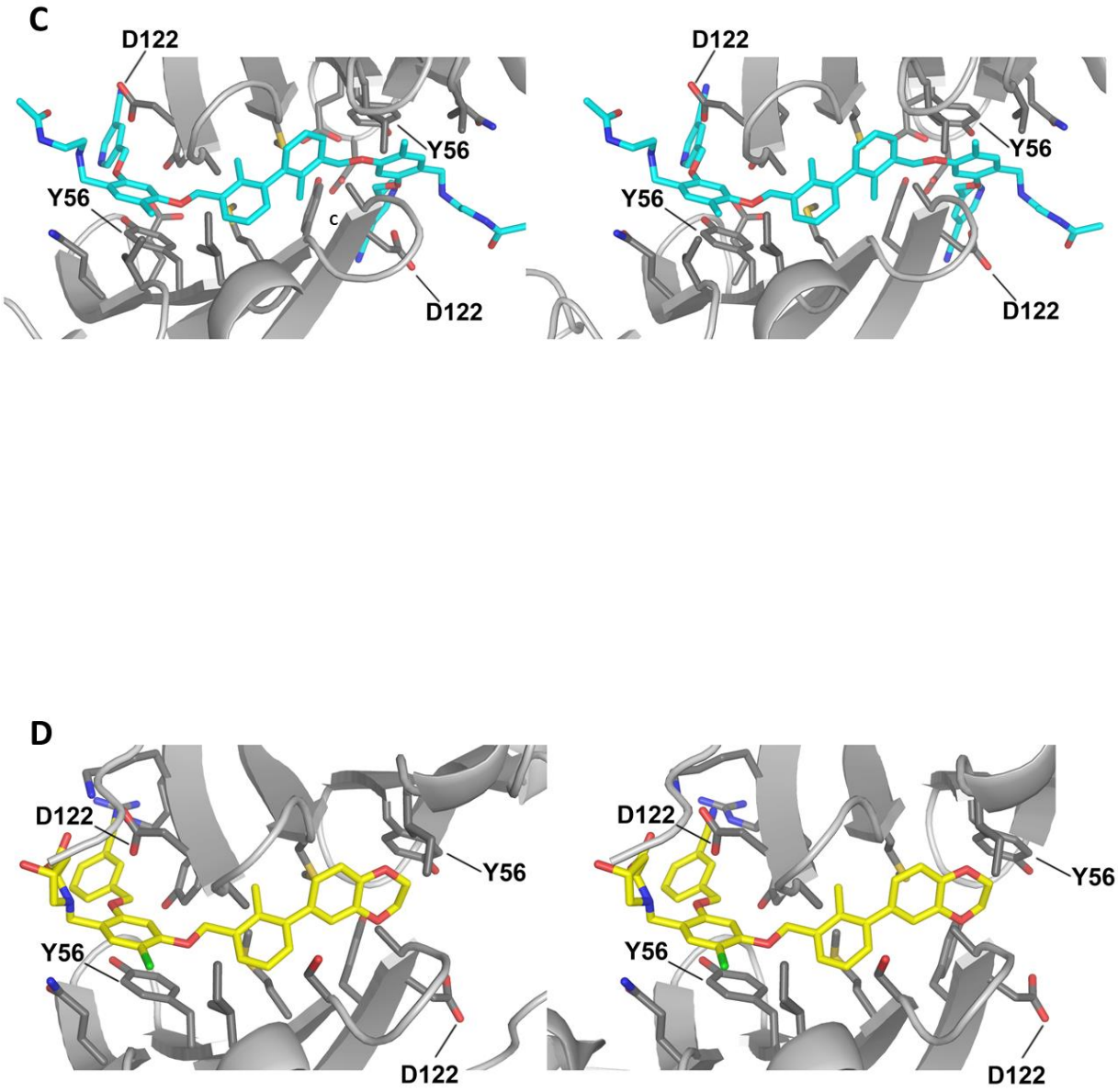
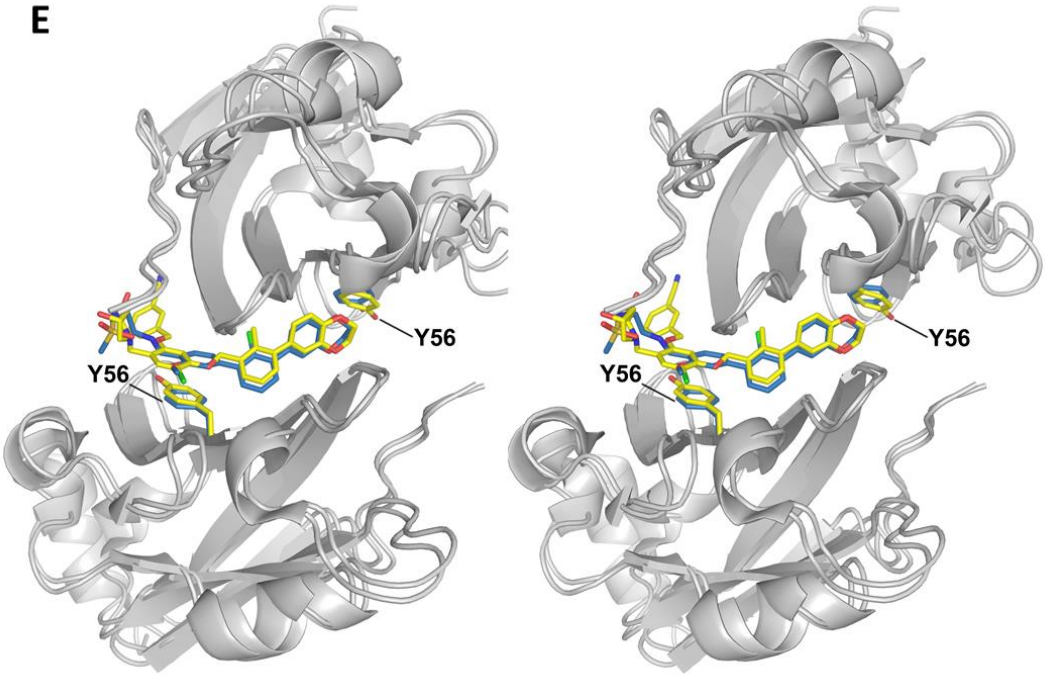
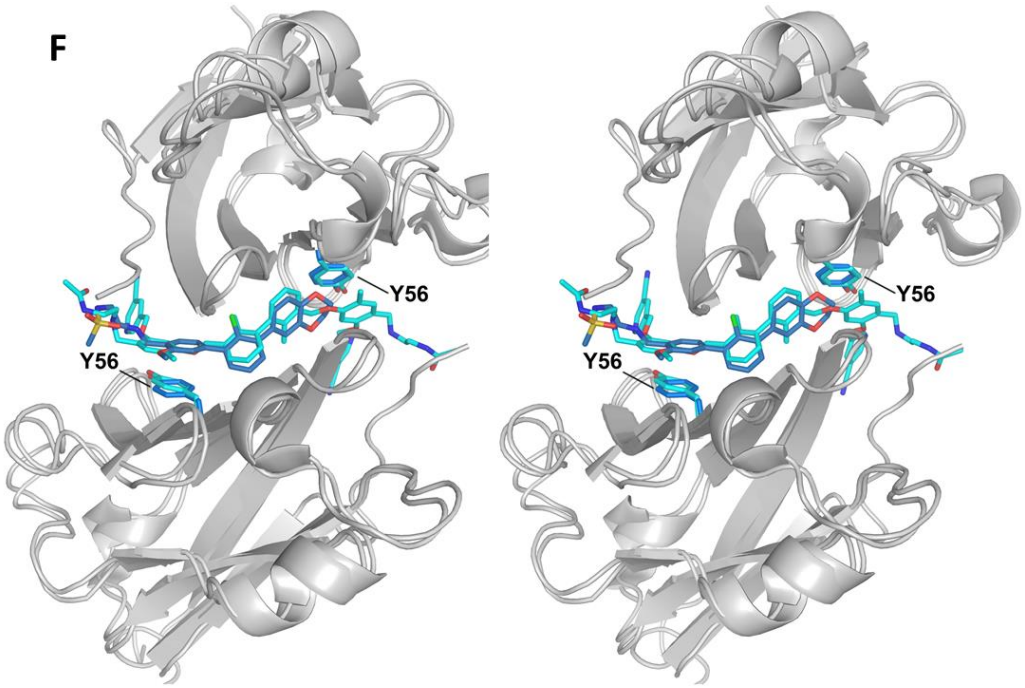


Figure S1. Terphenyl compounds **8h**, **8i**, and **8j** bioactivity requires the presence of PD-L1 in the ICB assay. Results of the Immune Checkpoint Blockade (ICB) assay, where **8h**, **8i**, and **8j** were used to restore the activation of effector Jurkat-ECs. Jurkat-ECs were either kept alone, or contacted with one of the following cell lines: wild type CHO K1 cells (CHO wt), CHO K1 cells expressing TCR Activator (CHO/TCRAct), or CHO K1 cells expressing TCR Activator and PD-1 receptor (CHO/TCRAct/PD-1). The cells were incubated with the indicated concentrations of the compounds for 6 hours and luminescence was measured as an indicator of TCR-dependent activation of Jurkat-ECs. The graphs present fold induction of the luminescence signal relative to DMSO-treated cells. Increased activation of Jurkat-ECs is observed only when the cells were contacted with PD-L1-expressing CHO/TCRAct/PD-L1 cells.


A
D122
Y56
Y56
D122
D122
Y56
Y56
D122
B
D122
Y56
Y56
D122
D122
Y56
Y56
D122


C
D122
Y56
Y56
D122
D122
Y56
Y56
D122
D
D122
Y56
Y56
D122
D122
Y56
Y56
D122


E
Y56
Y56
Y56
Y56


F
Y56
Y56
Y56
Y56

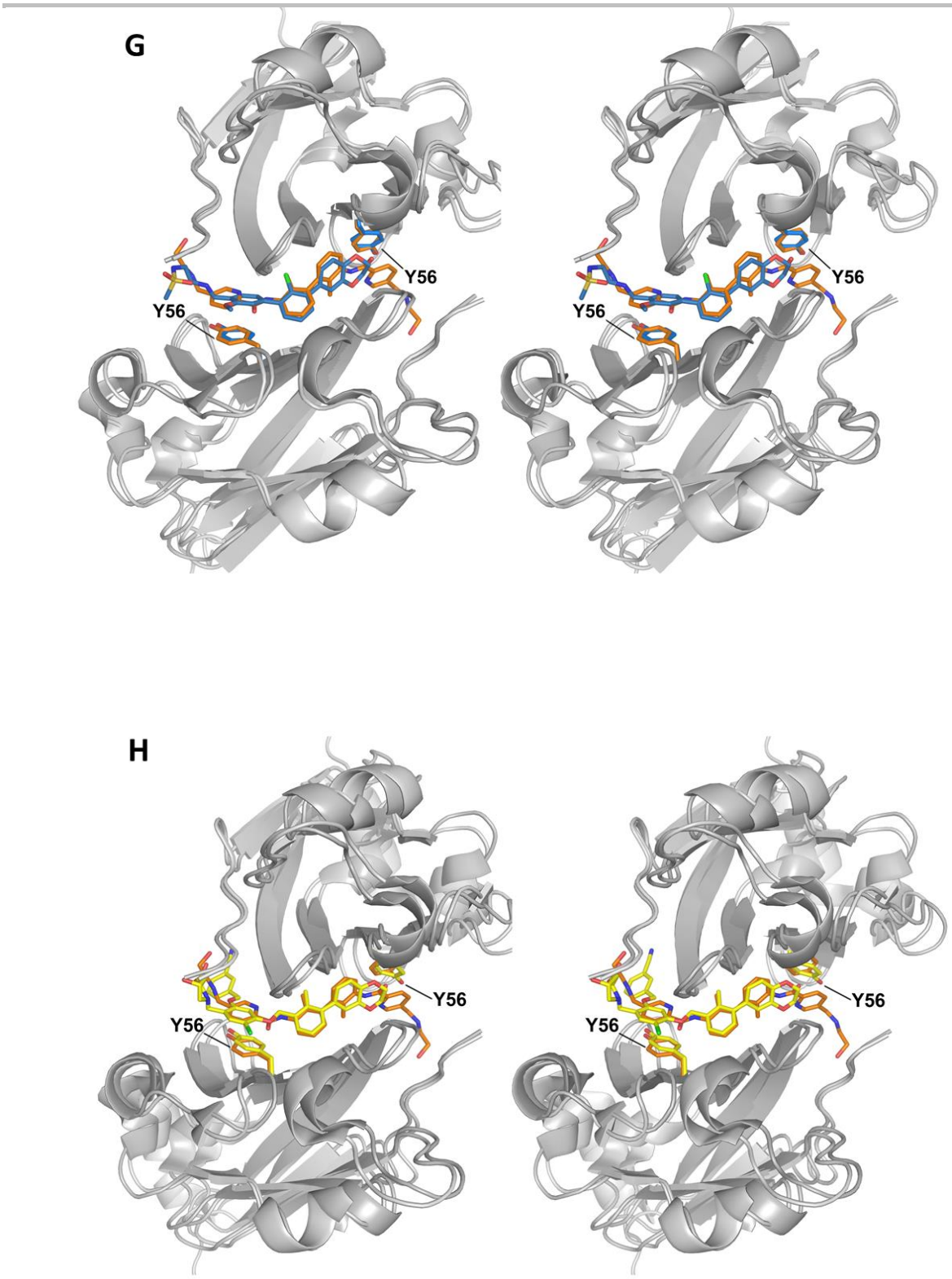
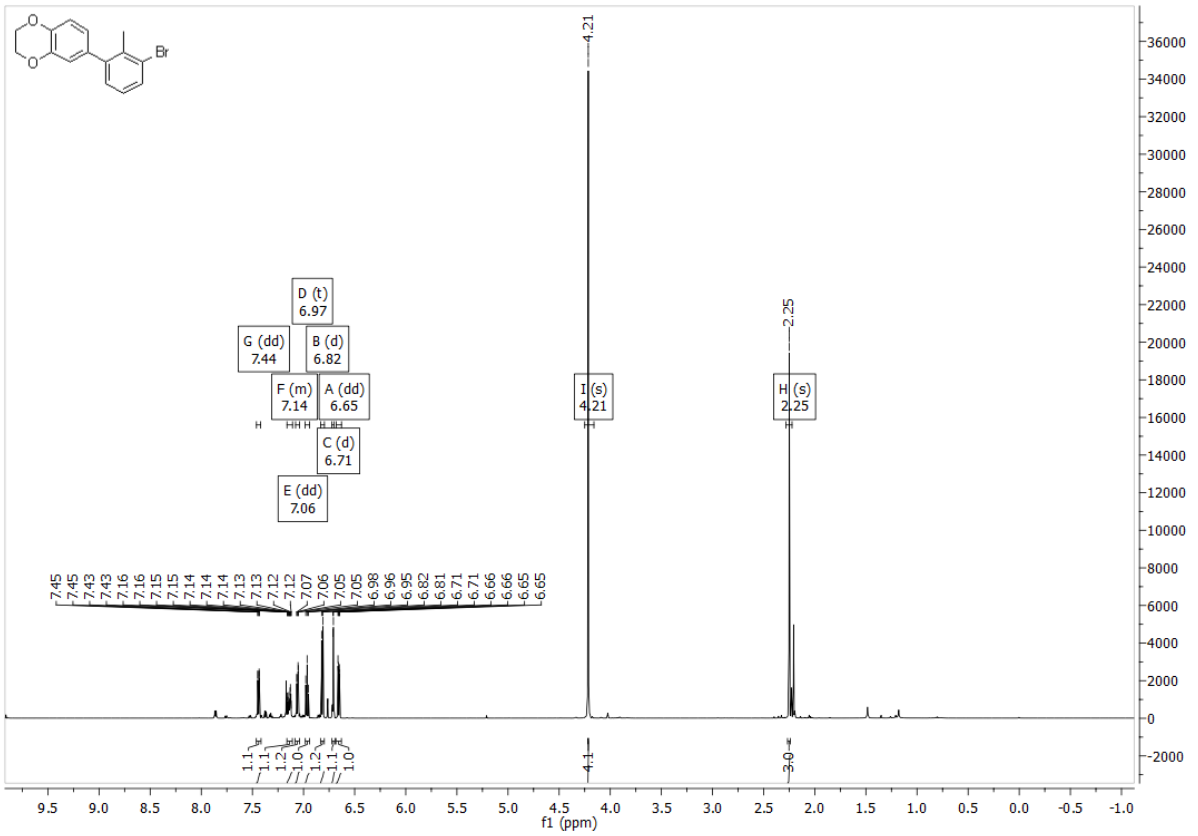
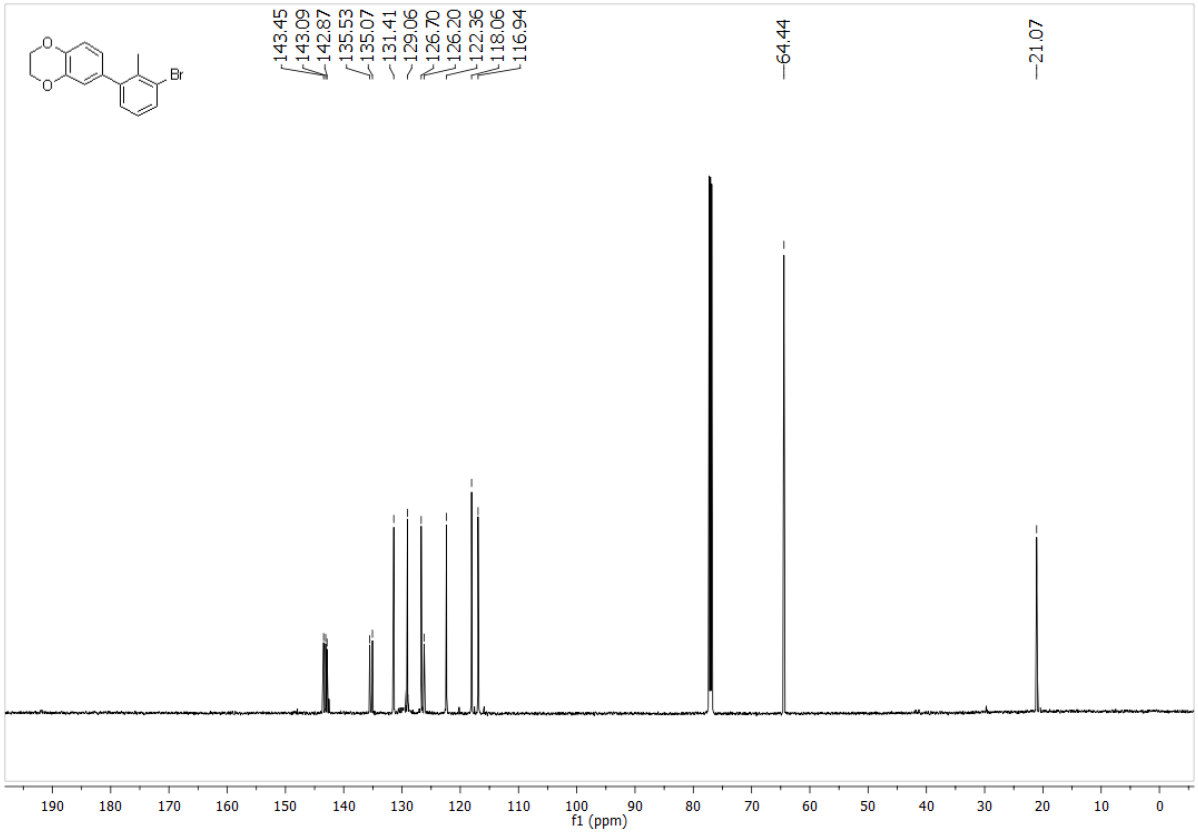


Figure S2. Comparison of the terphenyl-based with biphenyl-based inhibitor structures. (A-D) The stereoviews of detailed interactions of **8g** (blue), **ARB-272572 - Compound A** (orange), the C2-symmetric inhibitor (cyan) and **BMS-1166** (yellow) with the PD-L1 molecules. (E) Superposition of the **8g**/PD-L1 (blue) and **BMS-1166**/PD-L1 (yellow) structures (stereoview). (F) Superposition of the **8g**/PD-L1 (blue) and the C2-symmetric inhibitor/PD-L1 (cyan) structures (stereoview). (G) Superposition of the **8g**/PD-L1 (blue) and **ARB-272572**/PD-L1 (orange) structures (stereoview). (H) Superposition of the **BMS-1166**/PD-L1 (yellow) and **ARB-272572**/PD-L1 (orange) structures (stereoview).

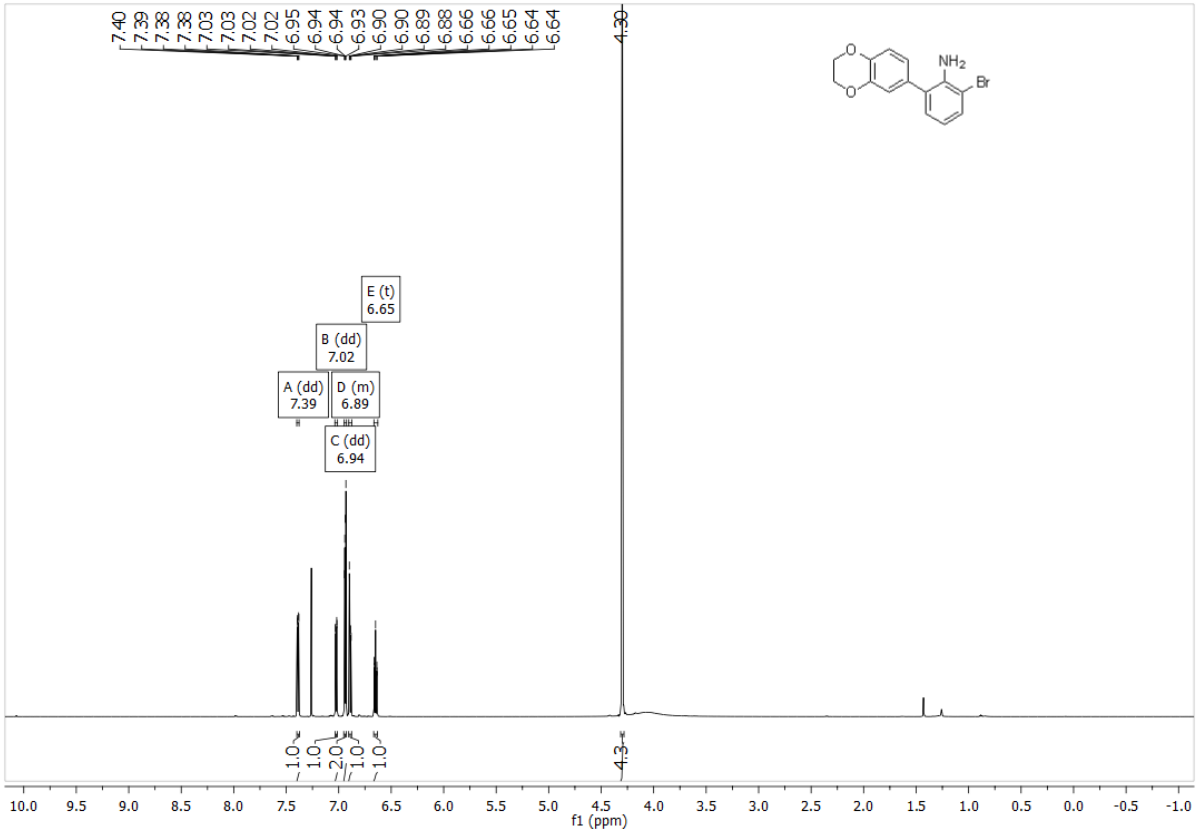
3. COPIES OF NMR SPECTRA

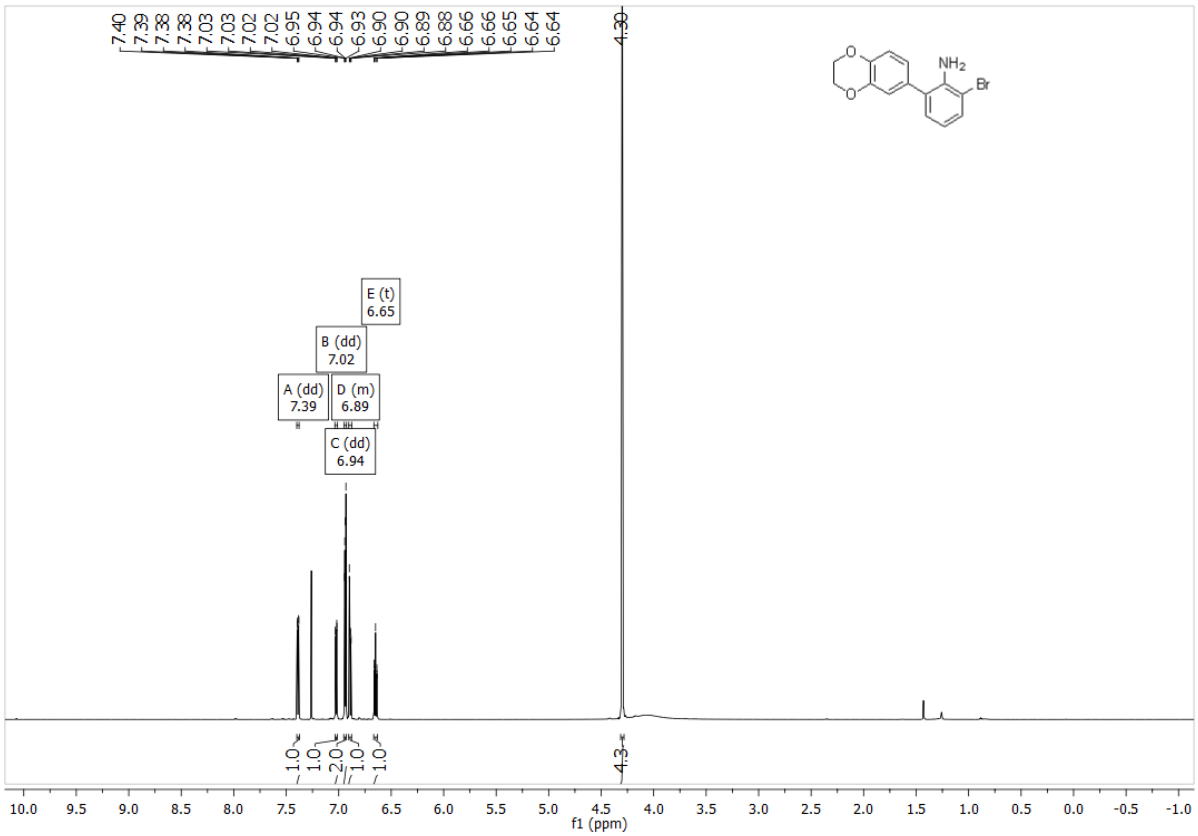
2a. 6-(3-Bromo-2-methylphenyl)-1,4-benzodioxane



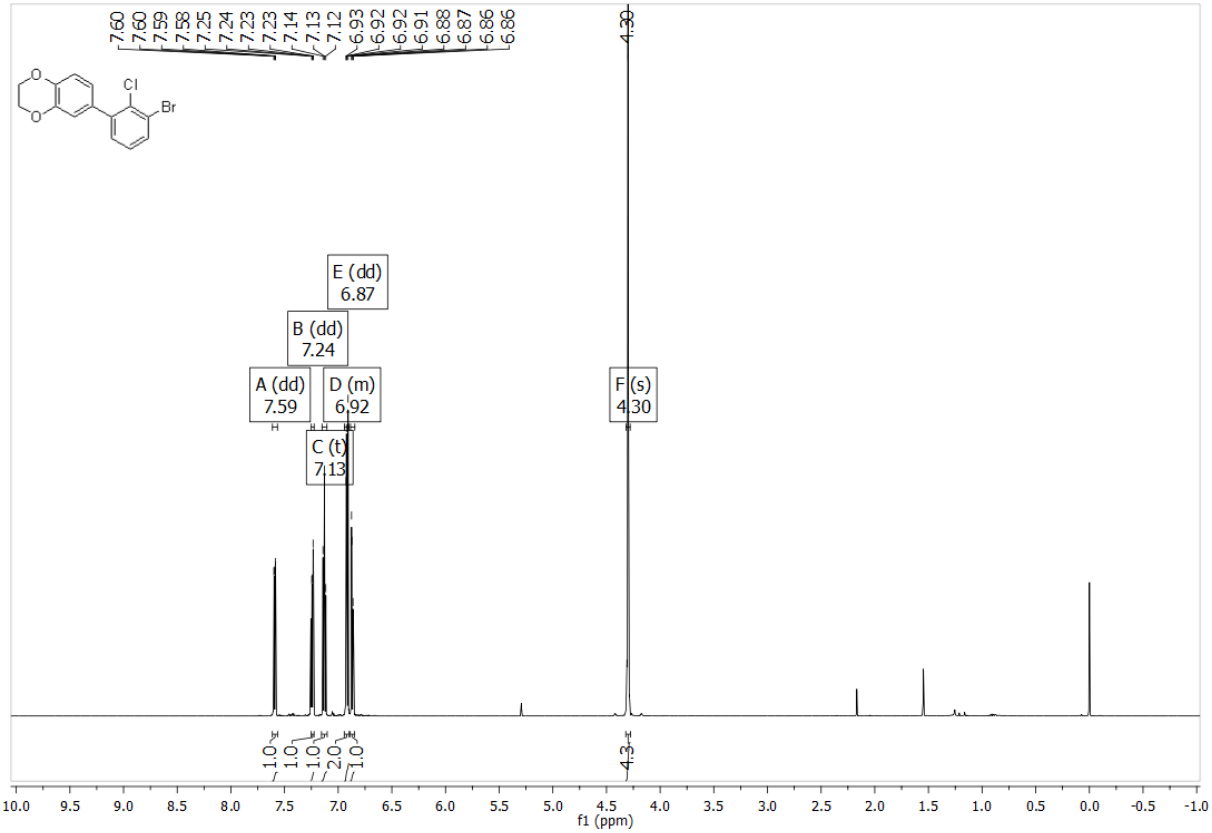


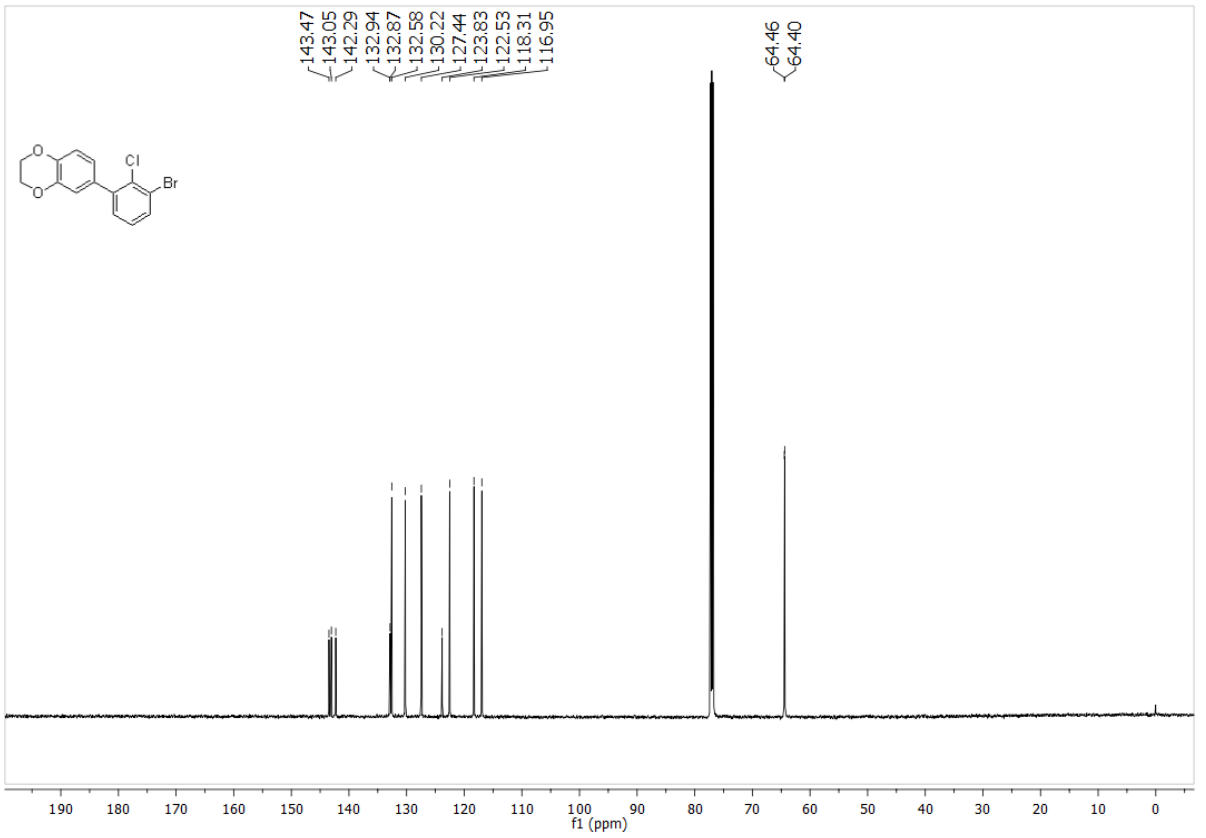
2b. 6-(2-Amino-3-bromophenyl)-1,4-benzodioxane



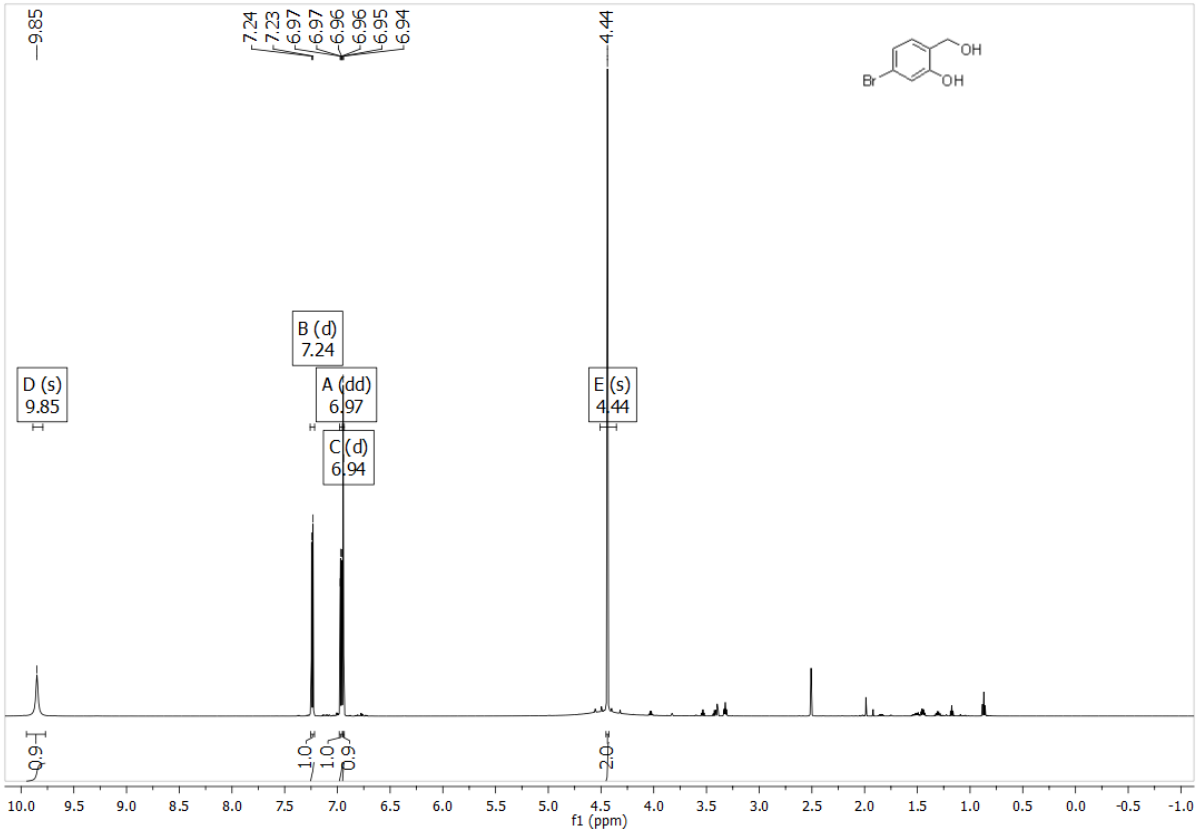


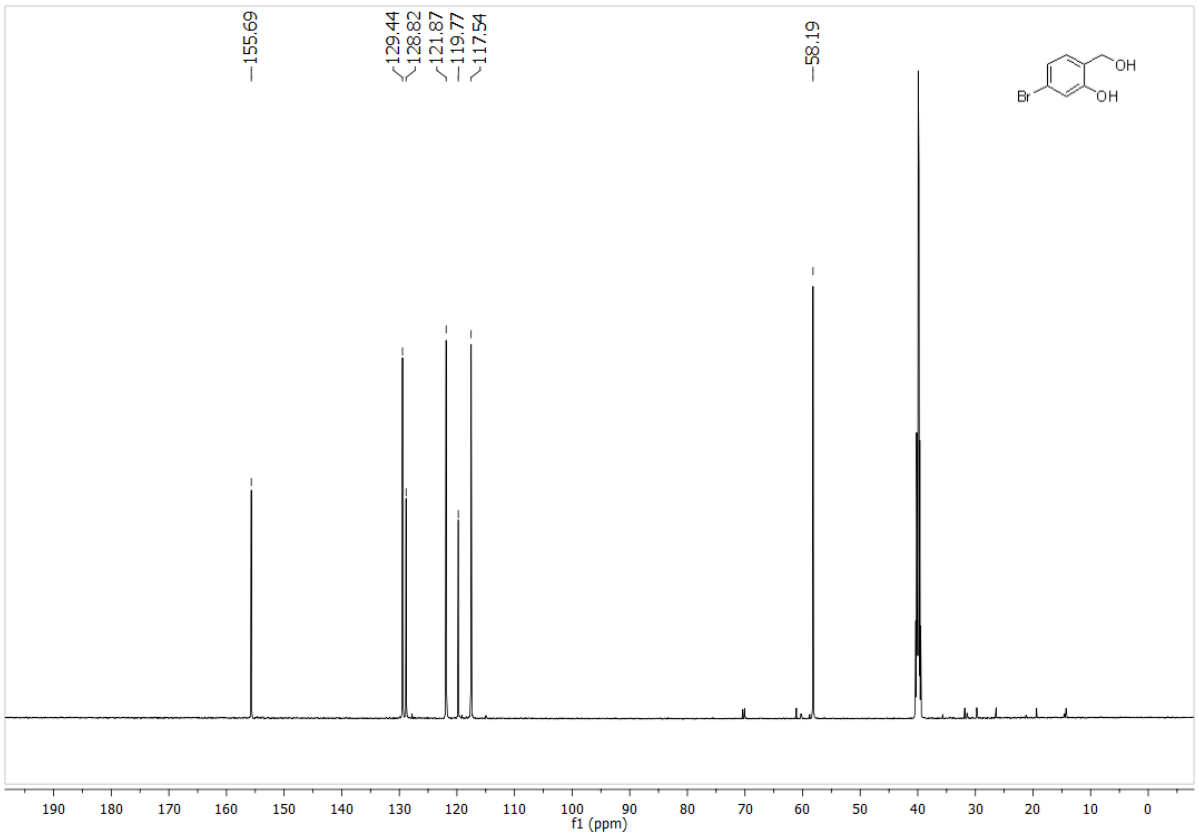
2c. 6-(3-Bromo-2-chlorophenyl)-1,4-benzodioxane



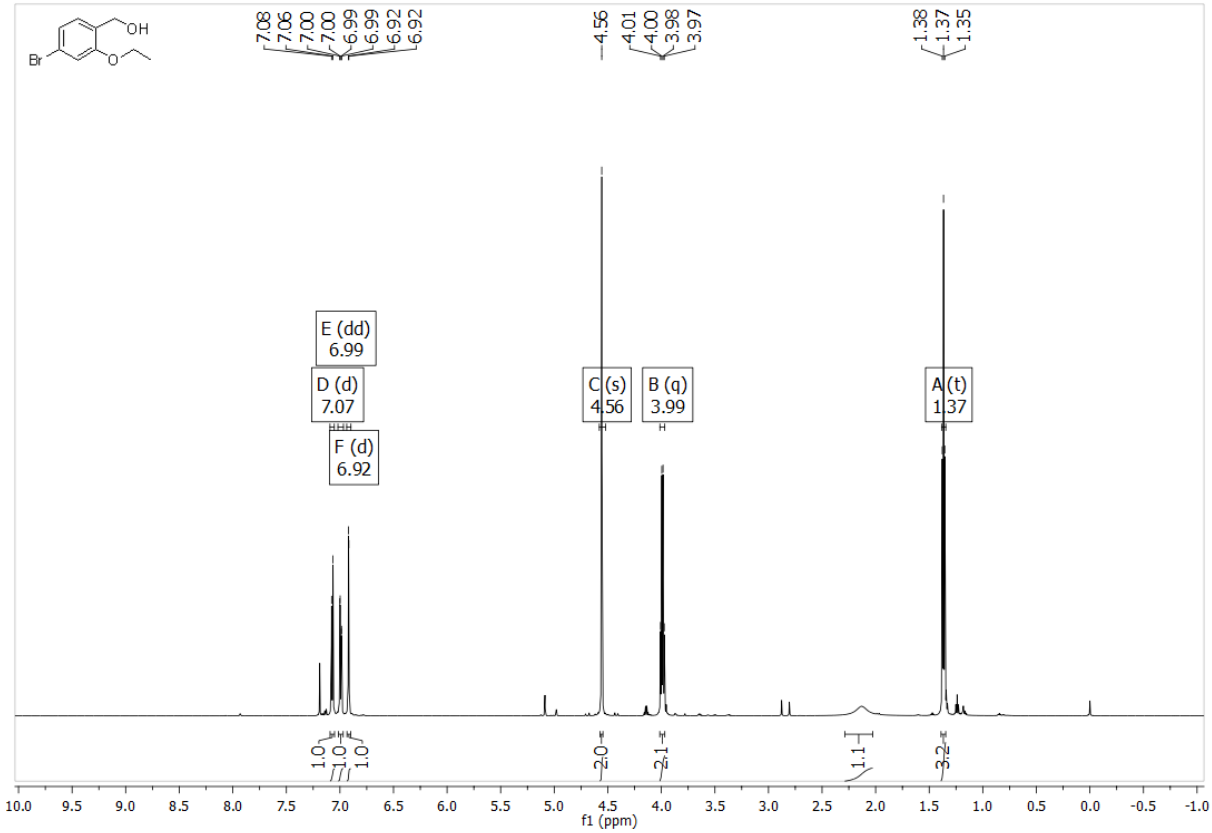


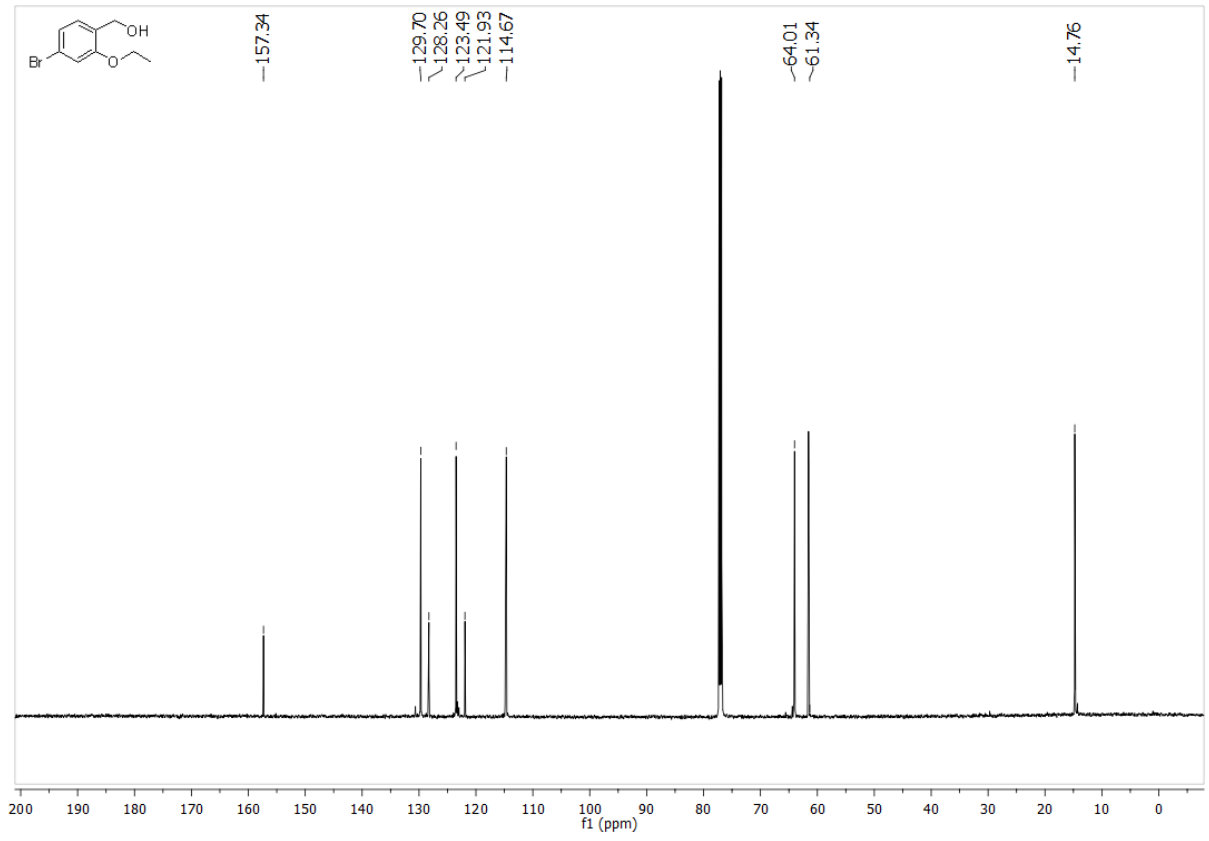
I-O. 4-bromo-2-hydroxymethylbenzyl alkohol



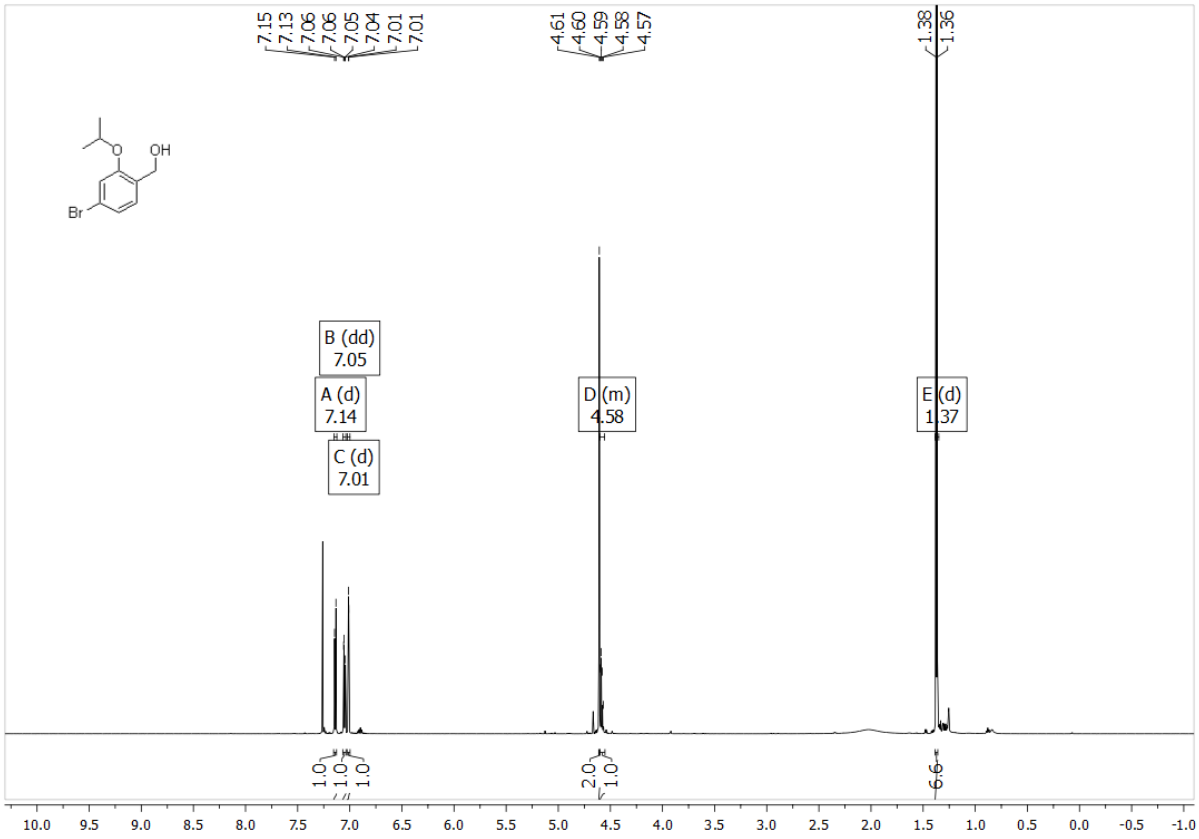


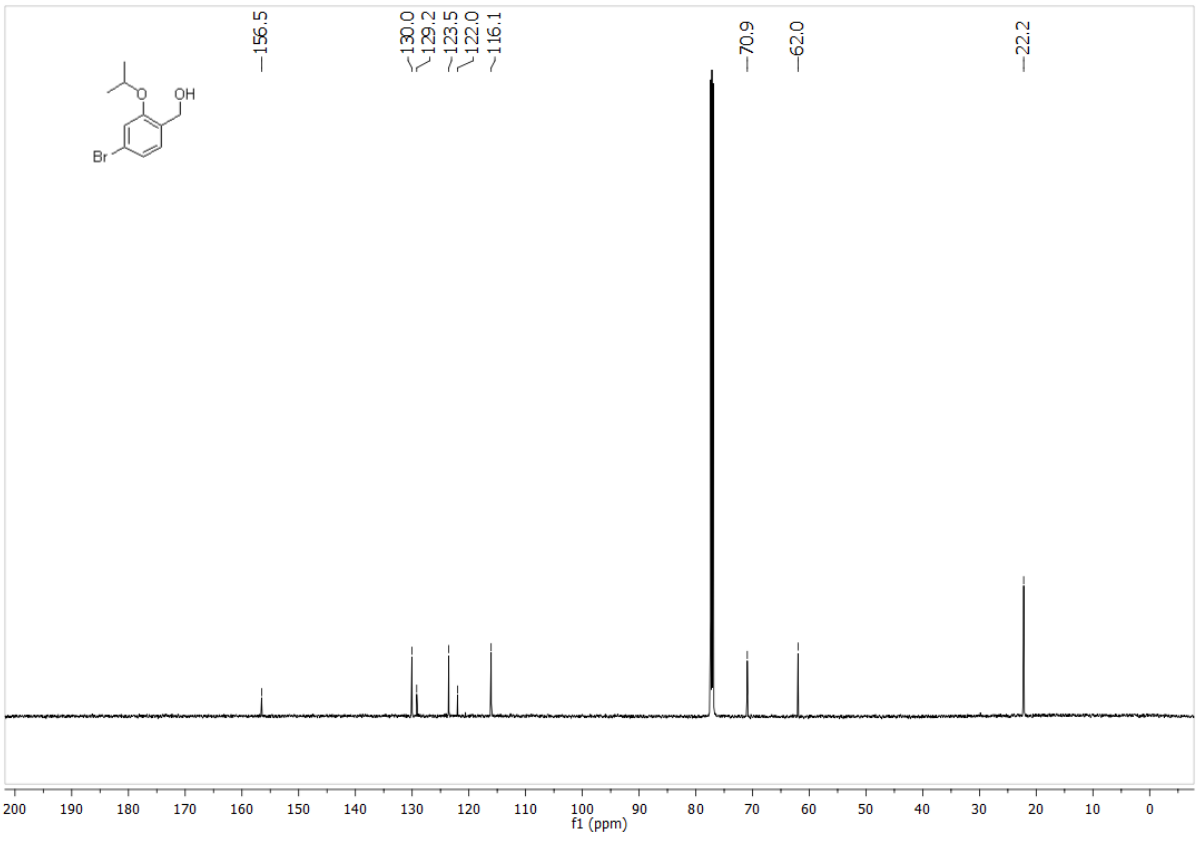
Ib. (4-Bromo-2-ethoxyphenyl)methanol



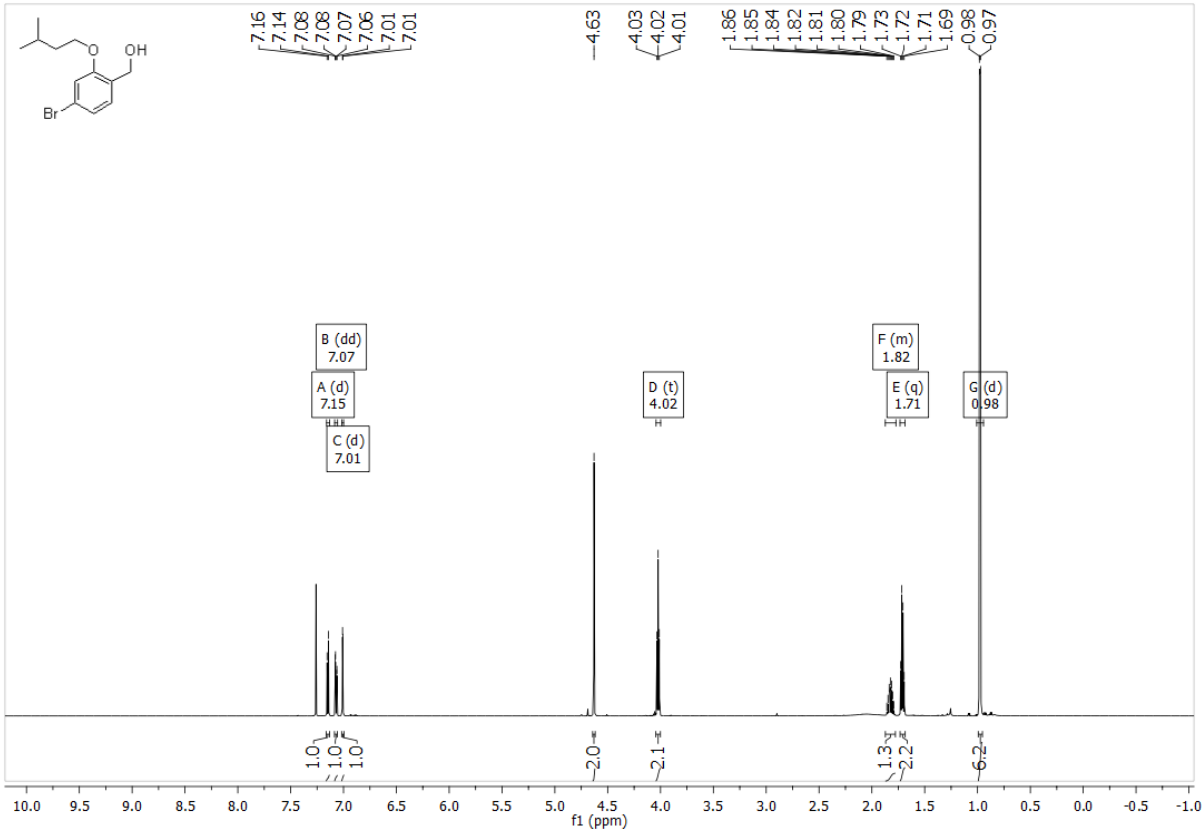


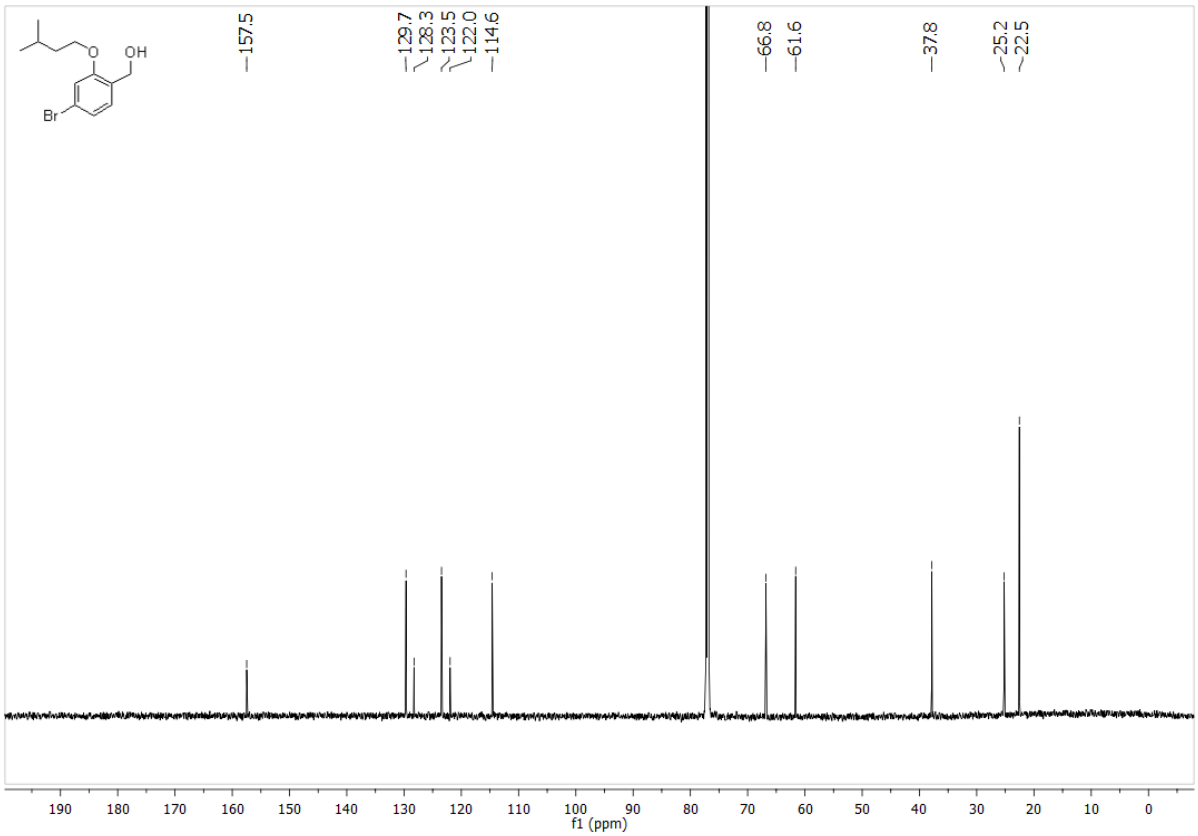
Ic. (4-Bromo-2-isopropoxyphenyl)methanol



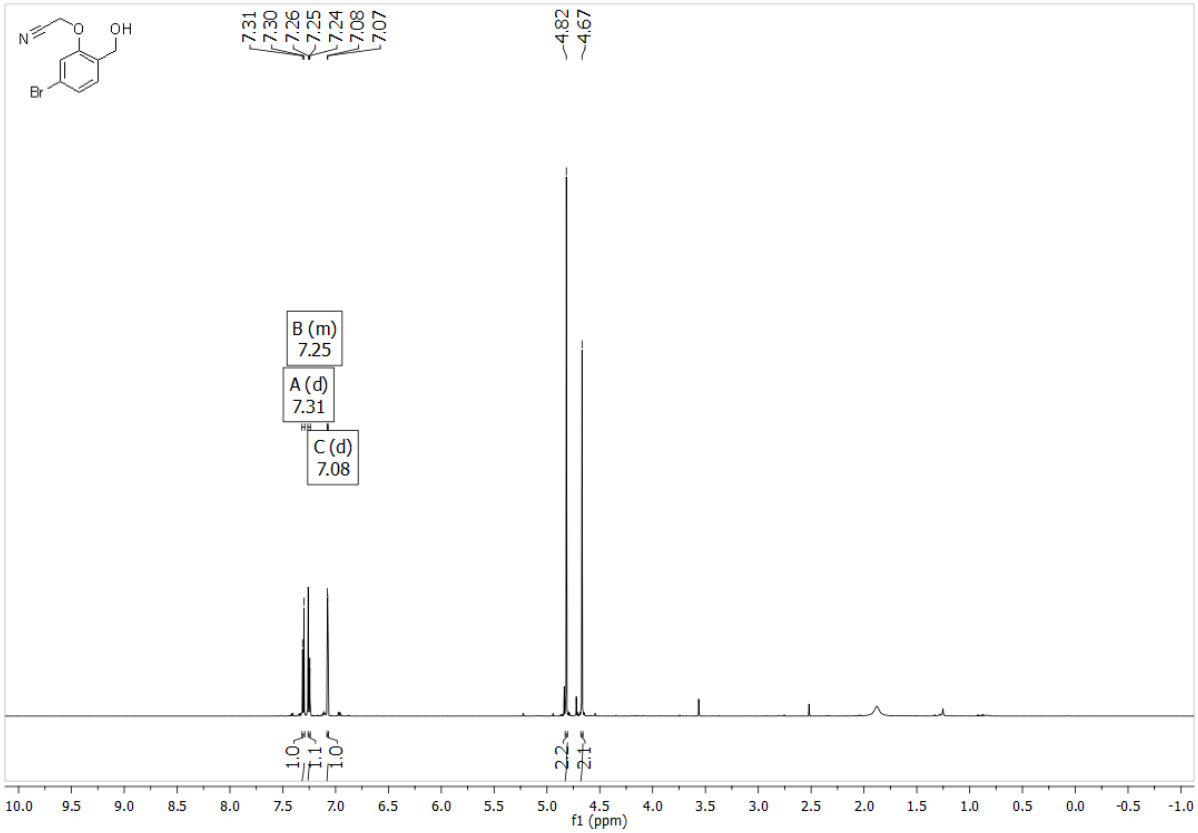


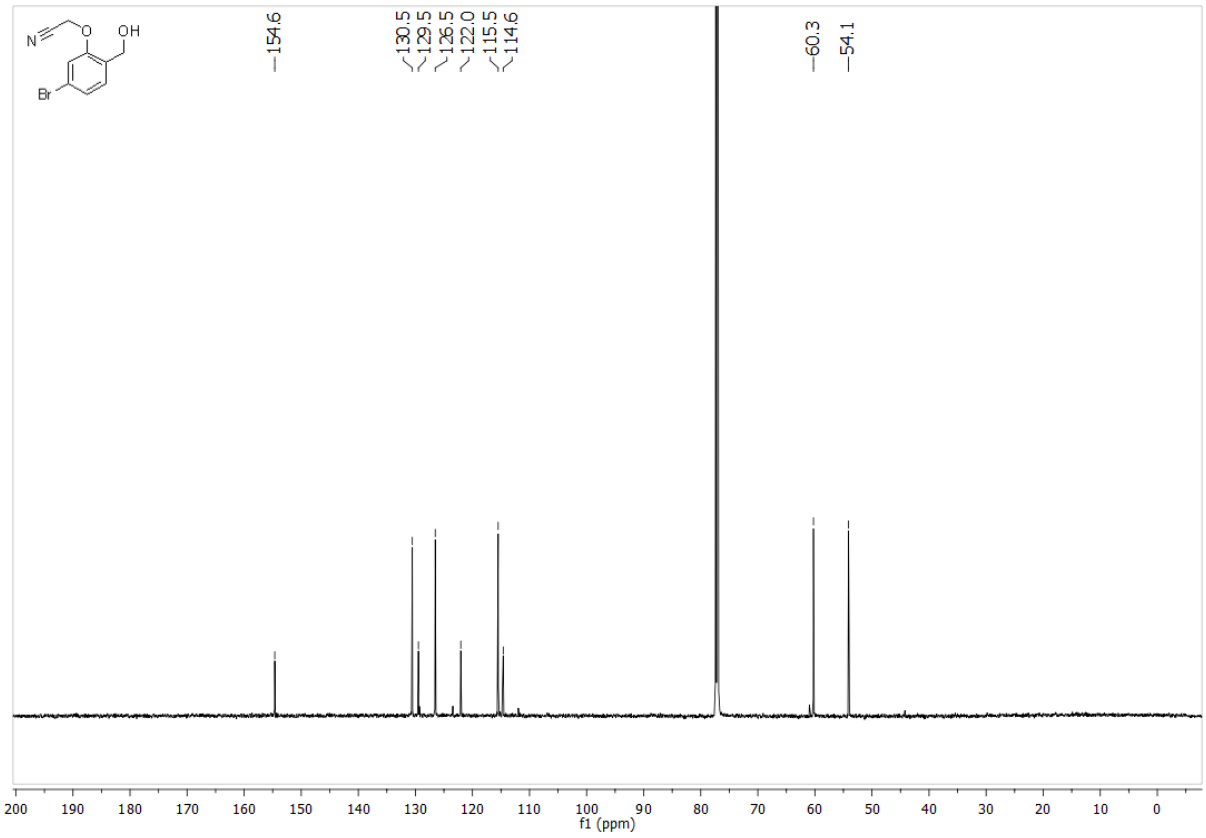
Id. (4-Bromo-2-isopentyloxyphenyl)methanol



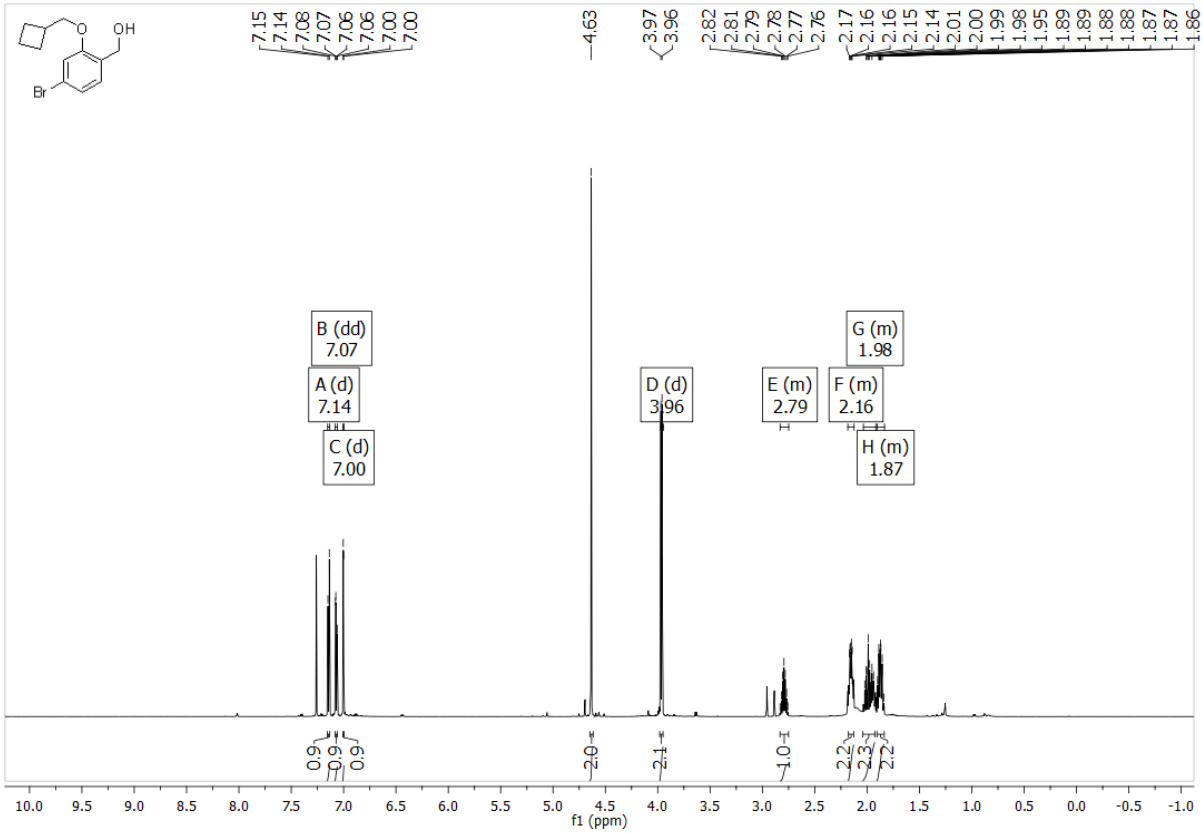


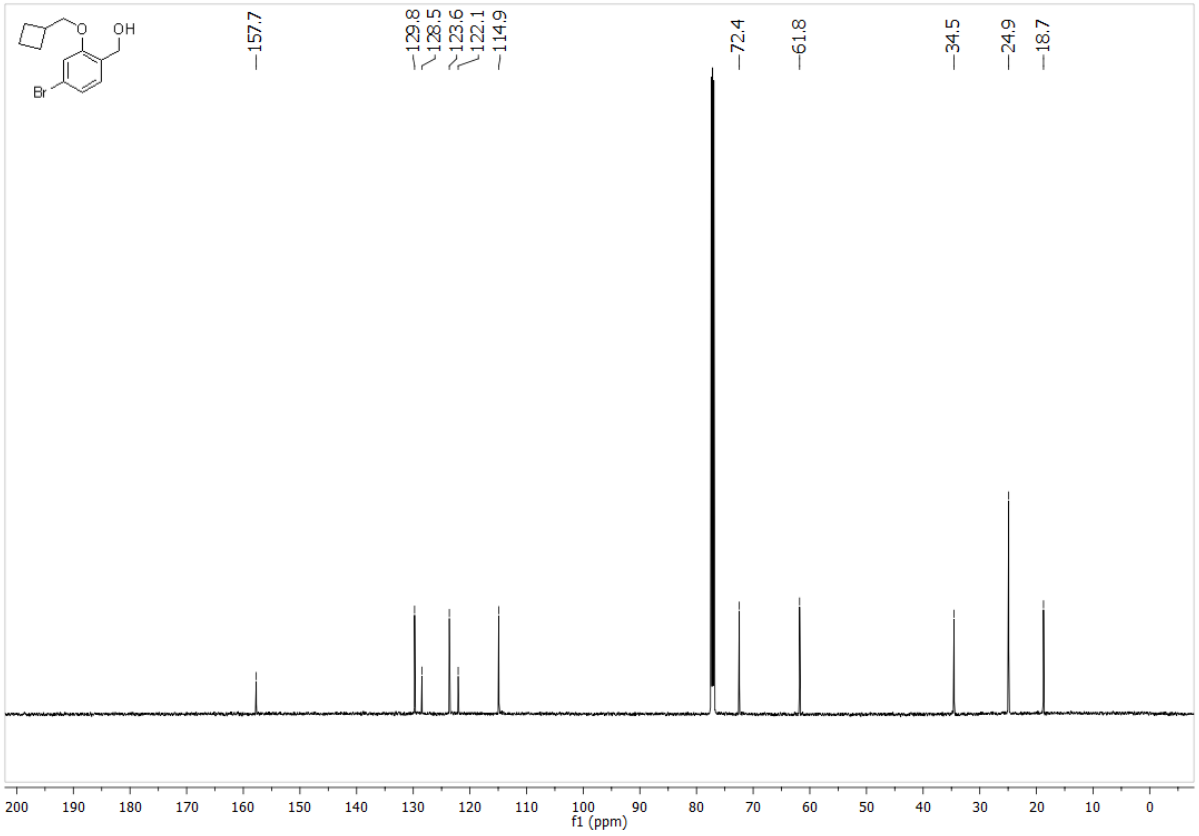
Ie. 2-(5-Bromo-2-(hydroxymethyl)phenoxy)acetonitrile



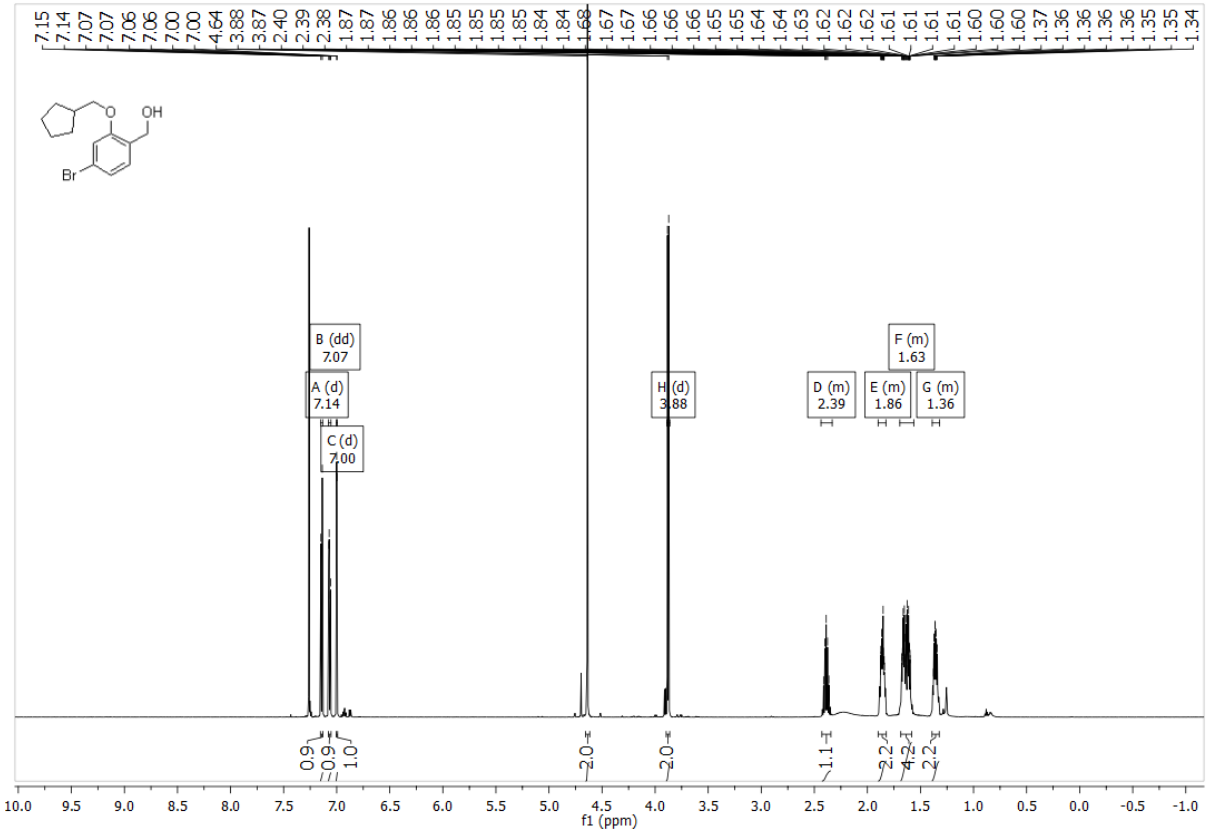


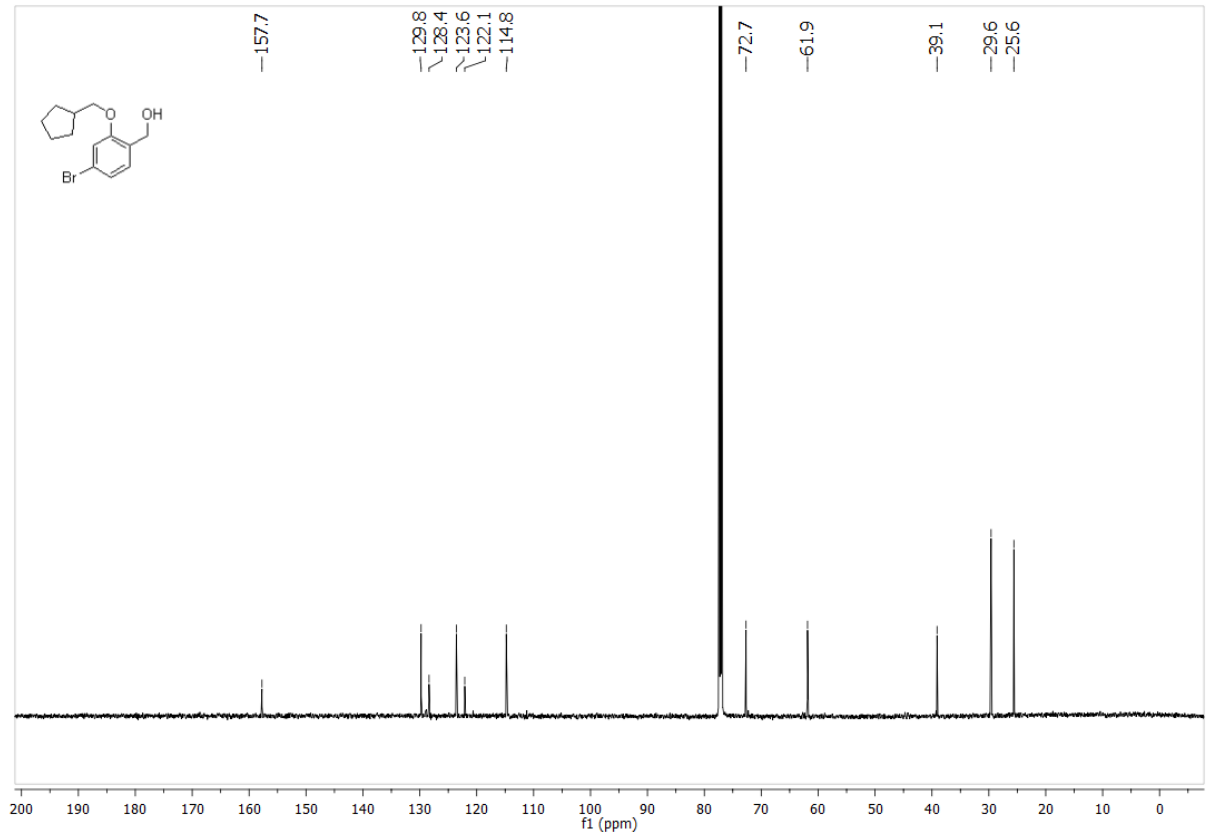
If. (4-Bromo-2-(cyclobutylmethoxy))methanol



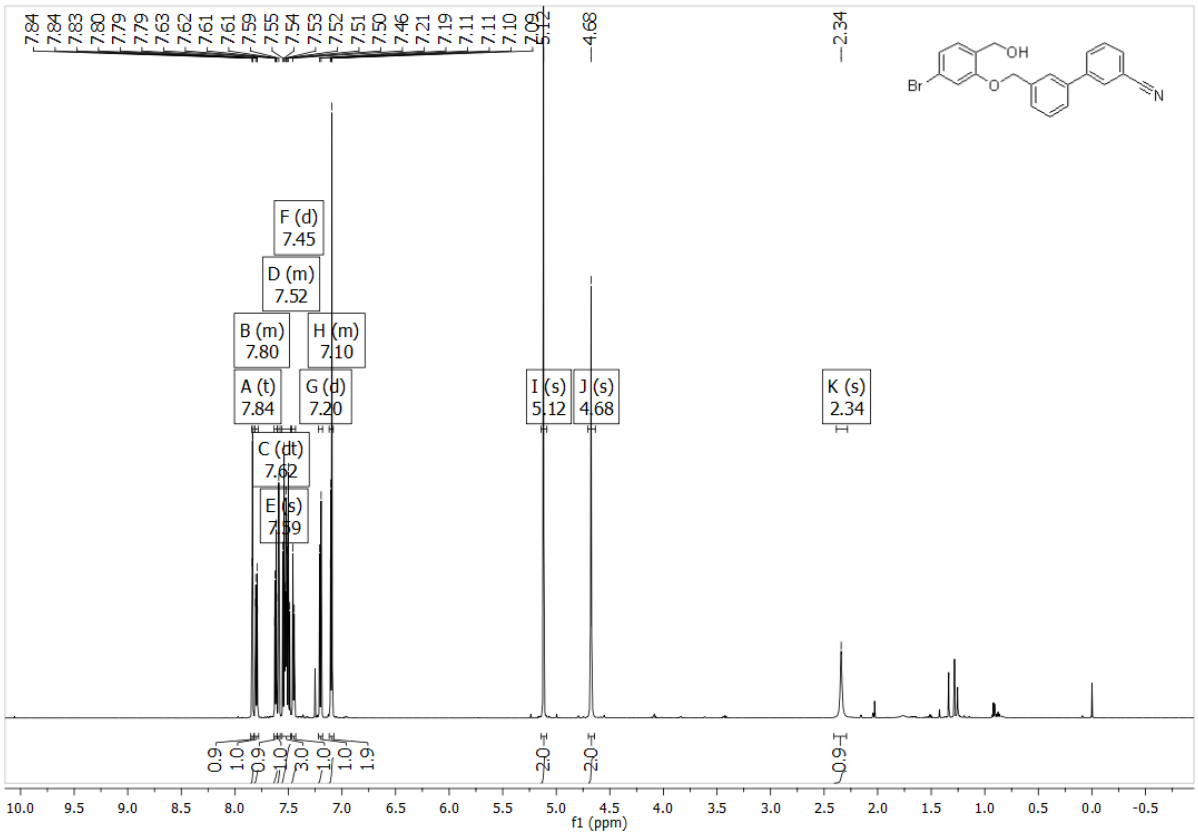


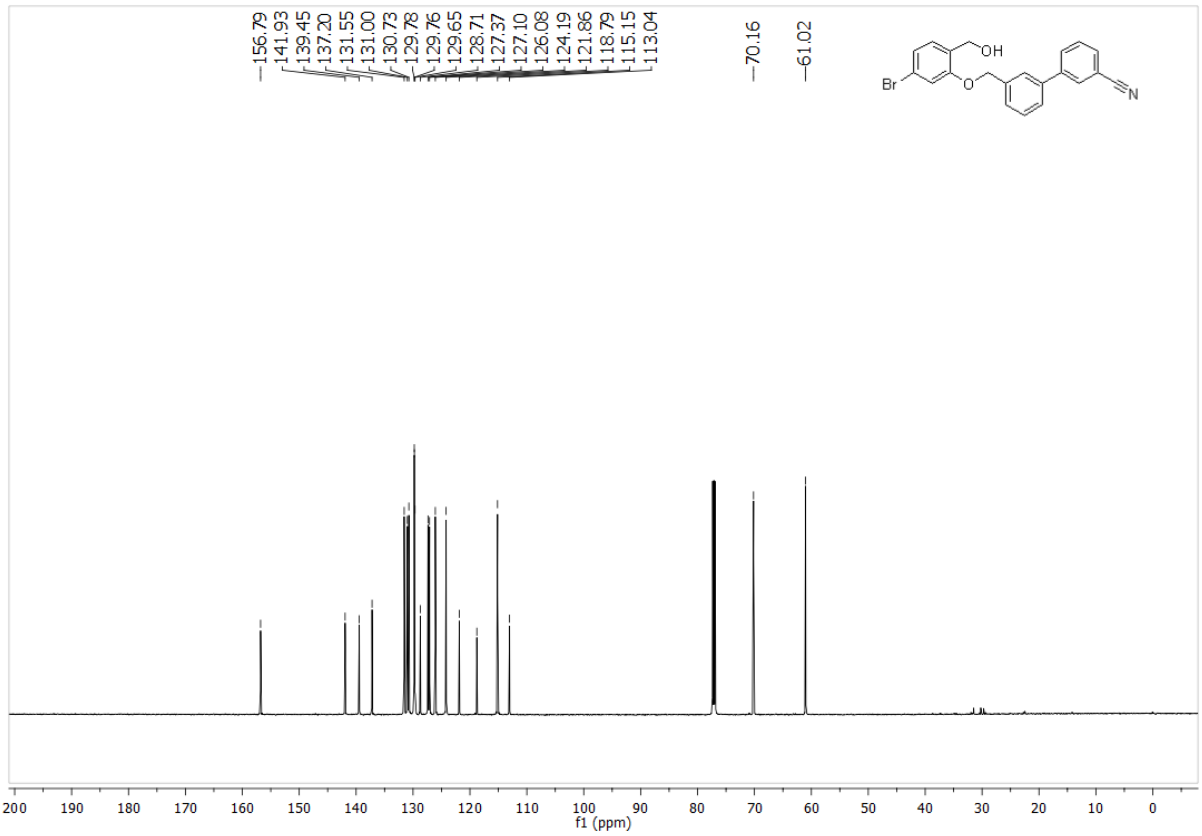
Ig. (4-Bromo-2-(cyclopentylmethoxy))methanol



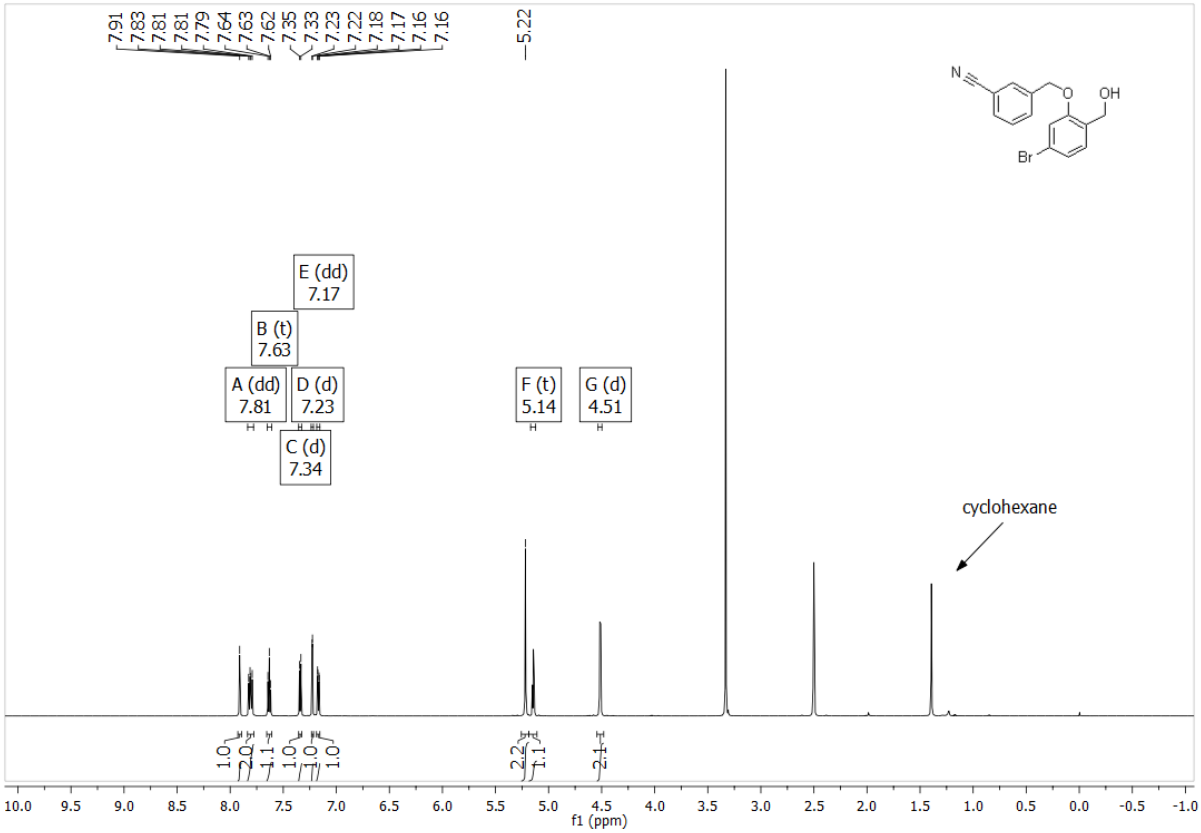


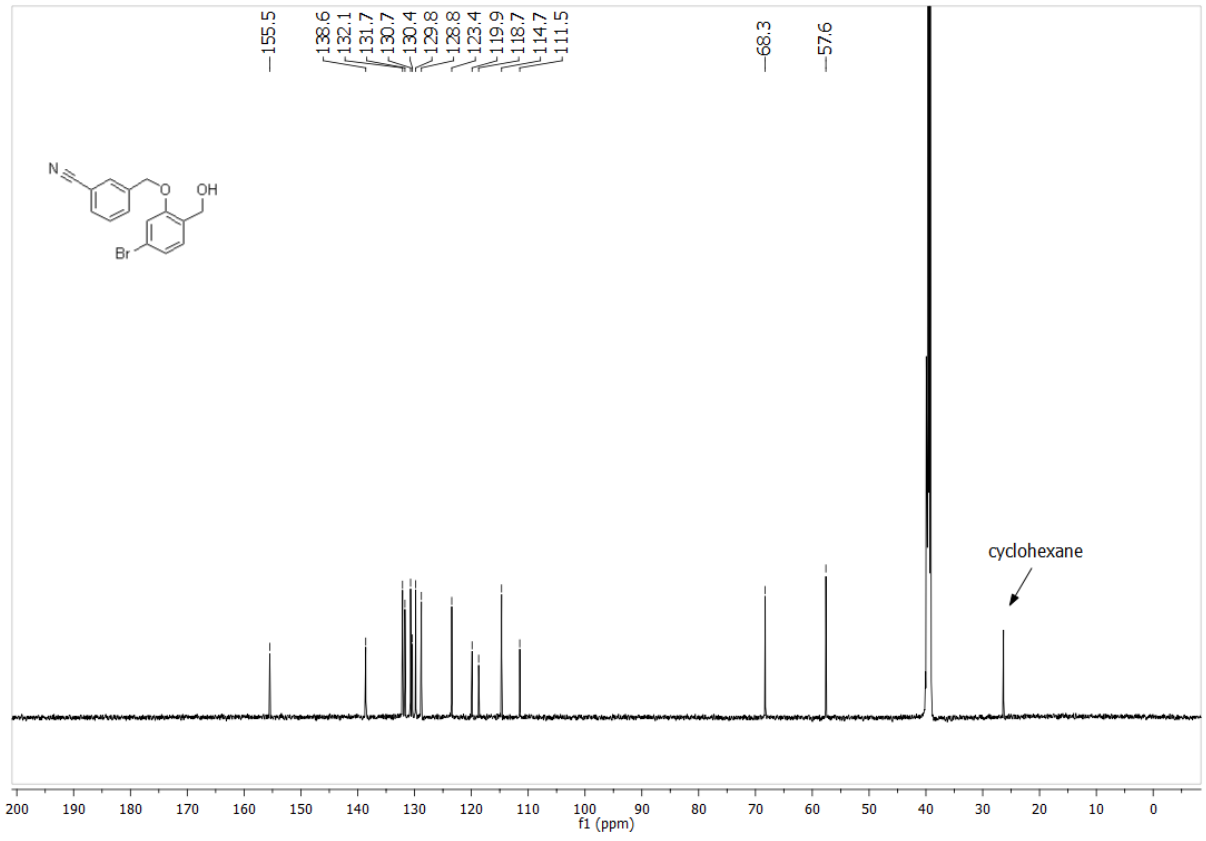
Ih. 3'-((5-bromo-2-(hydroxymethyl)phenoxy)methyl)-[1,1'-biphenyl]-3-carbonitrile



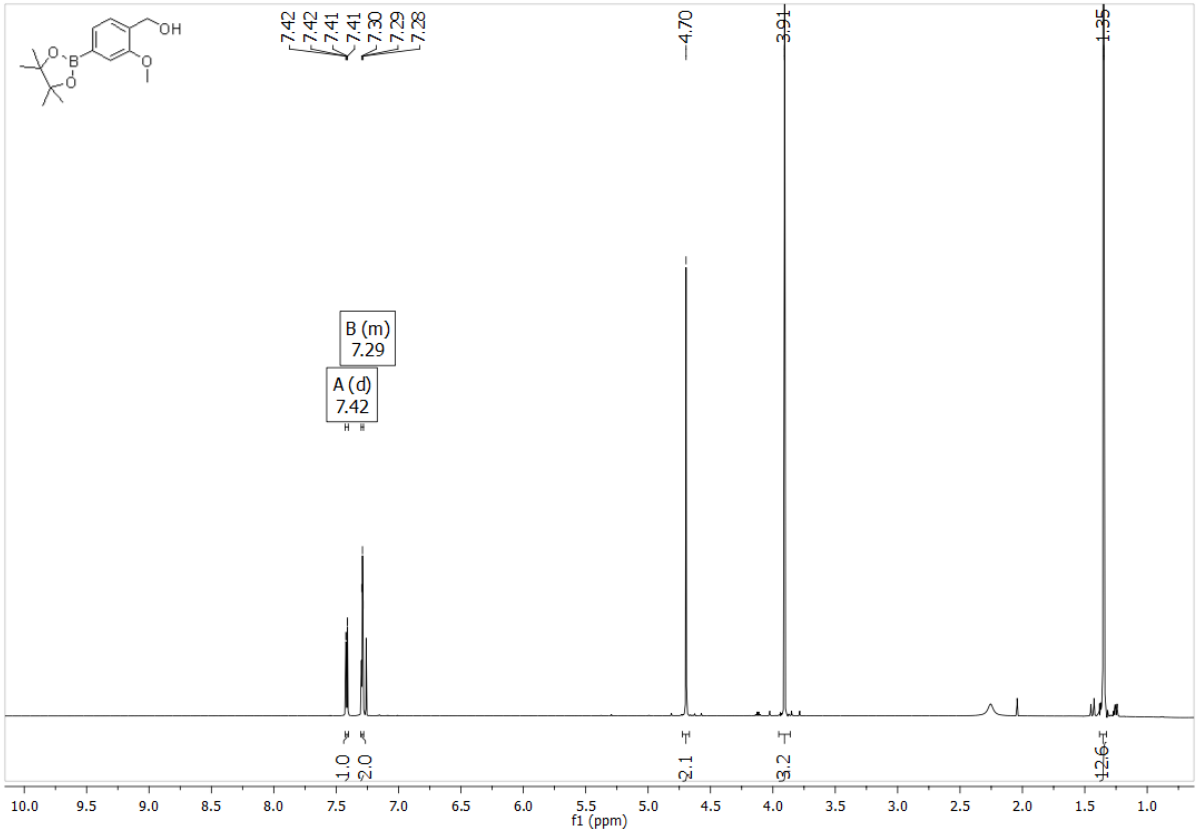


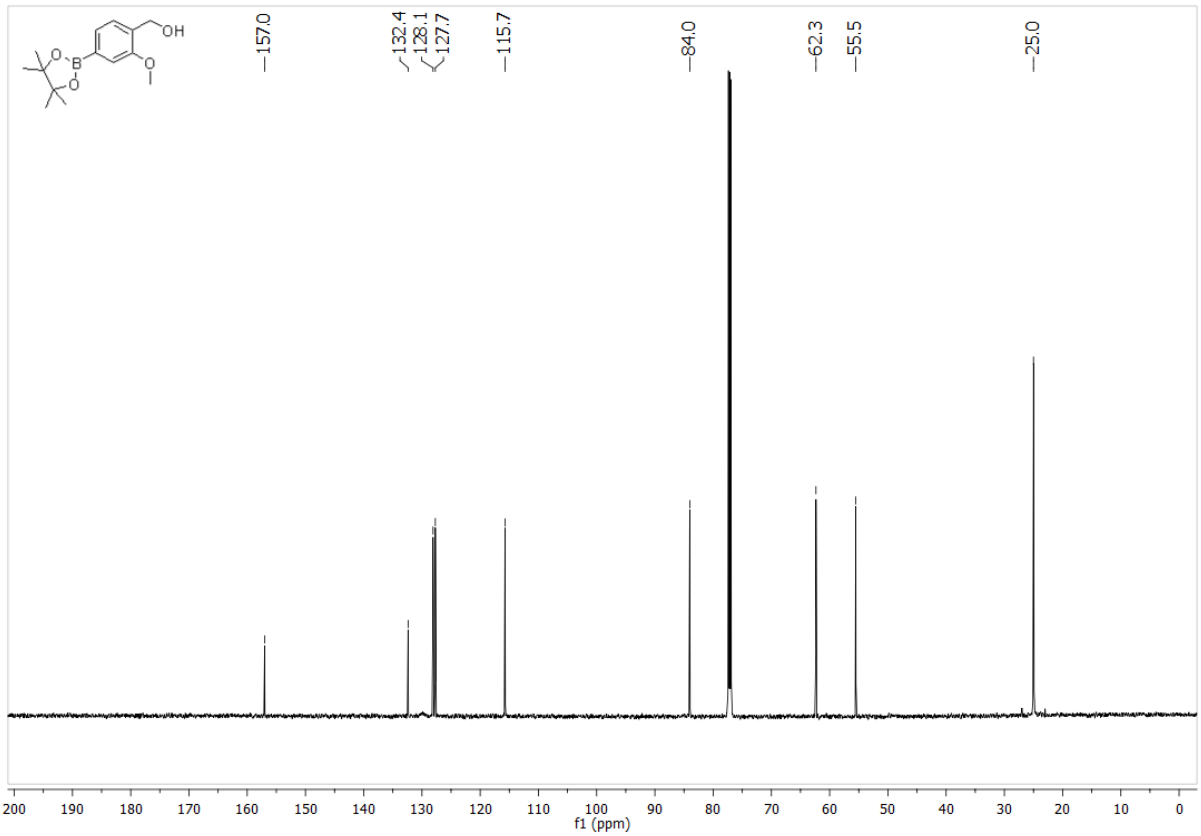
Ii. 3-((5-Bromo-2-(hydroxymethyl)phenoxy)methyl)benzonitrile



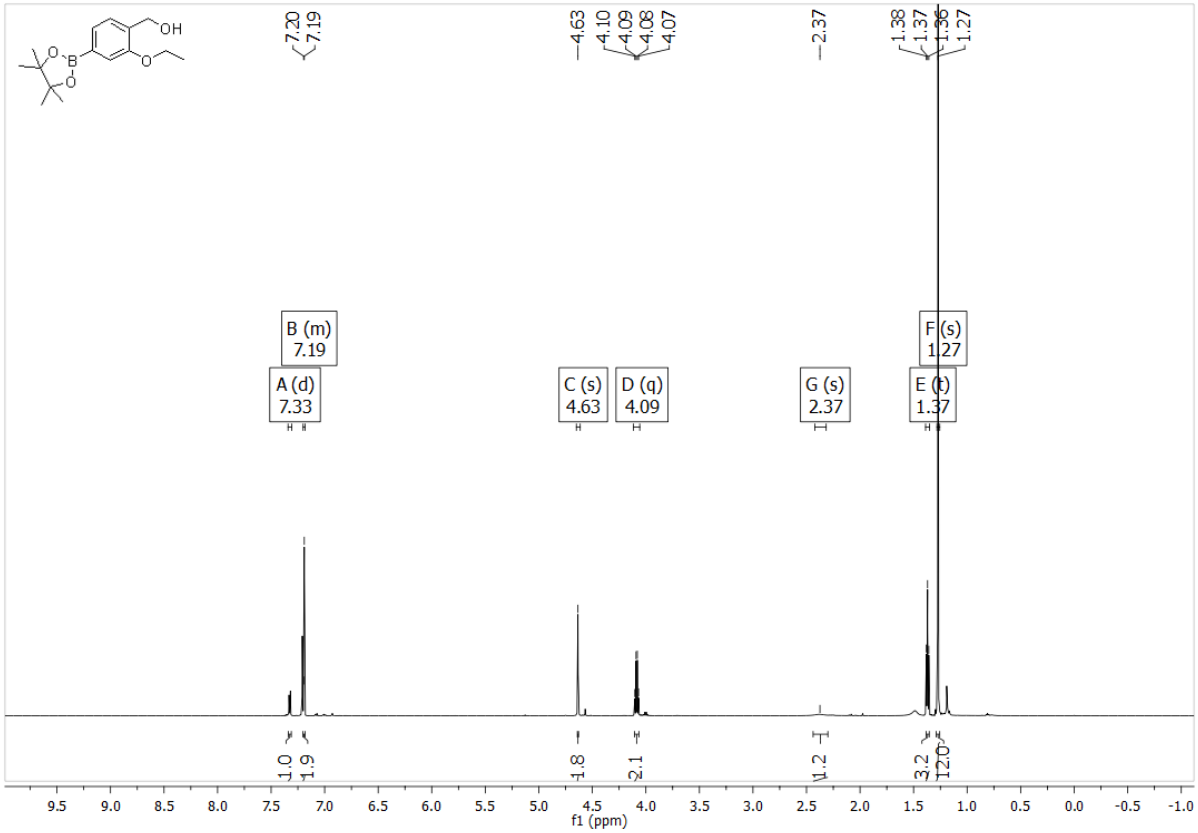


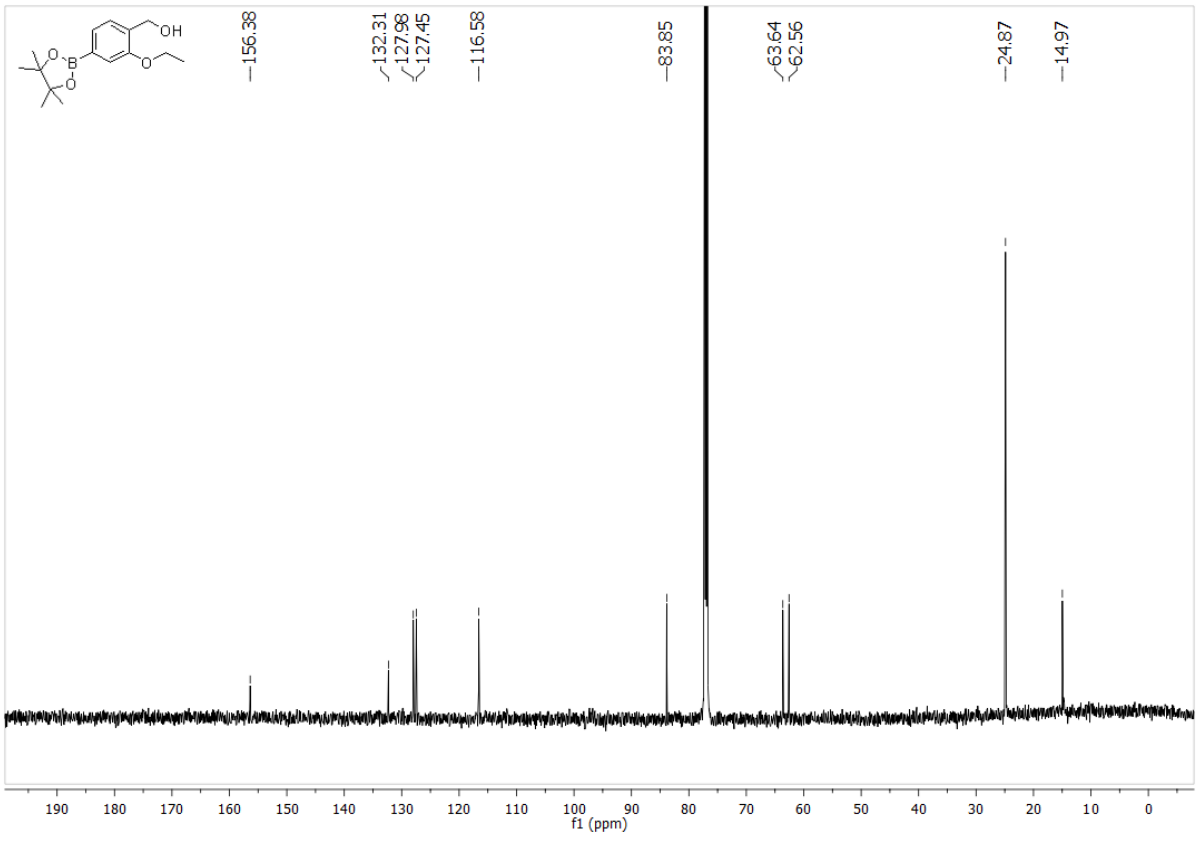
3a. (2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



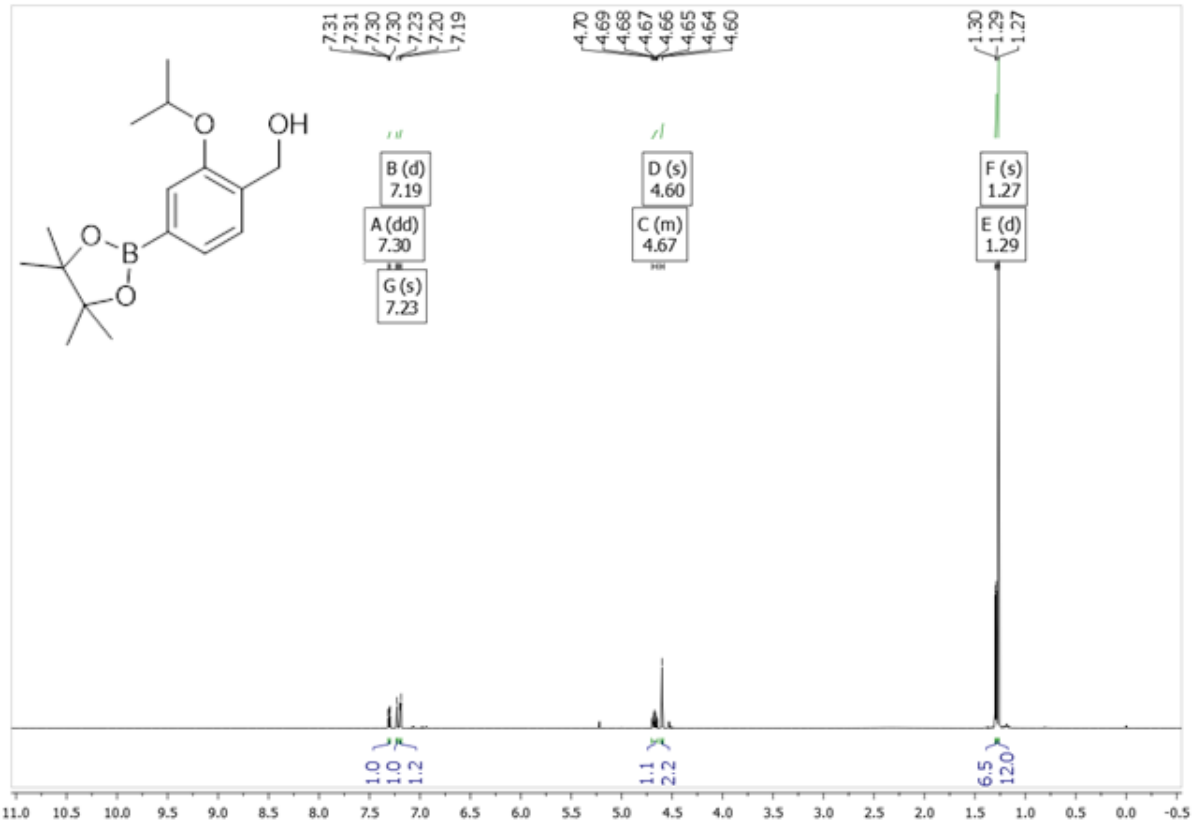


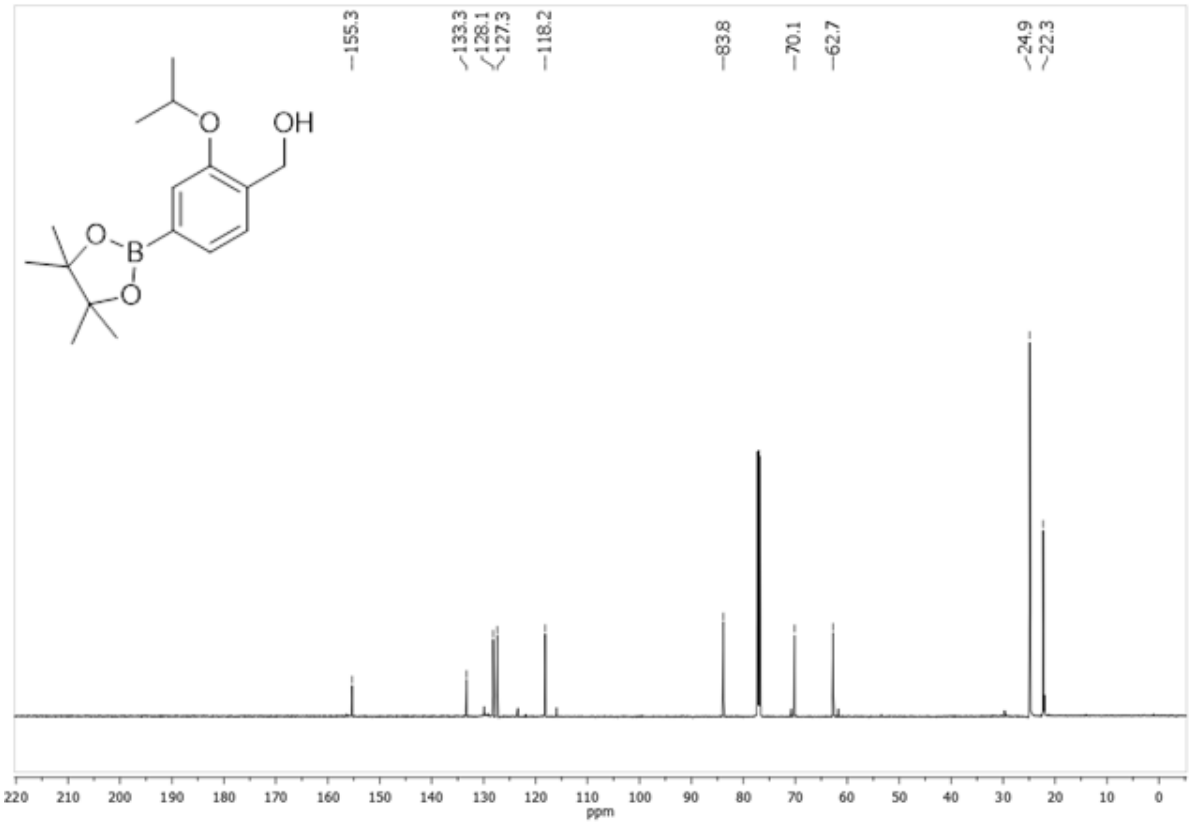
3b. (2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



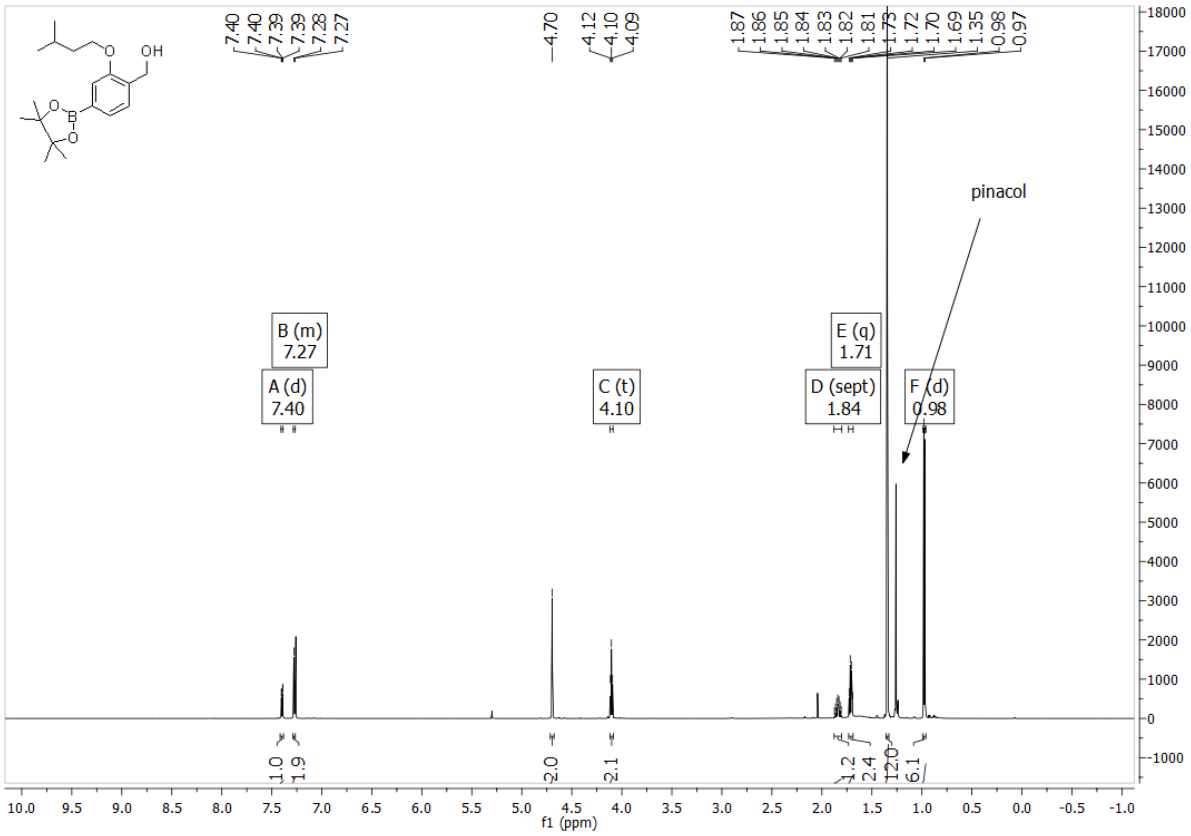


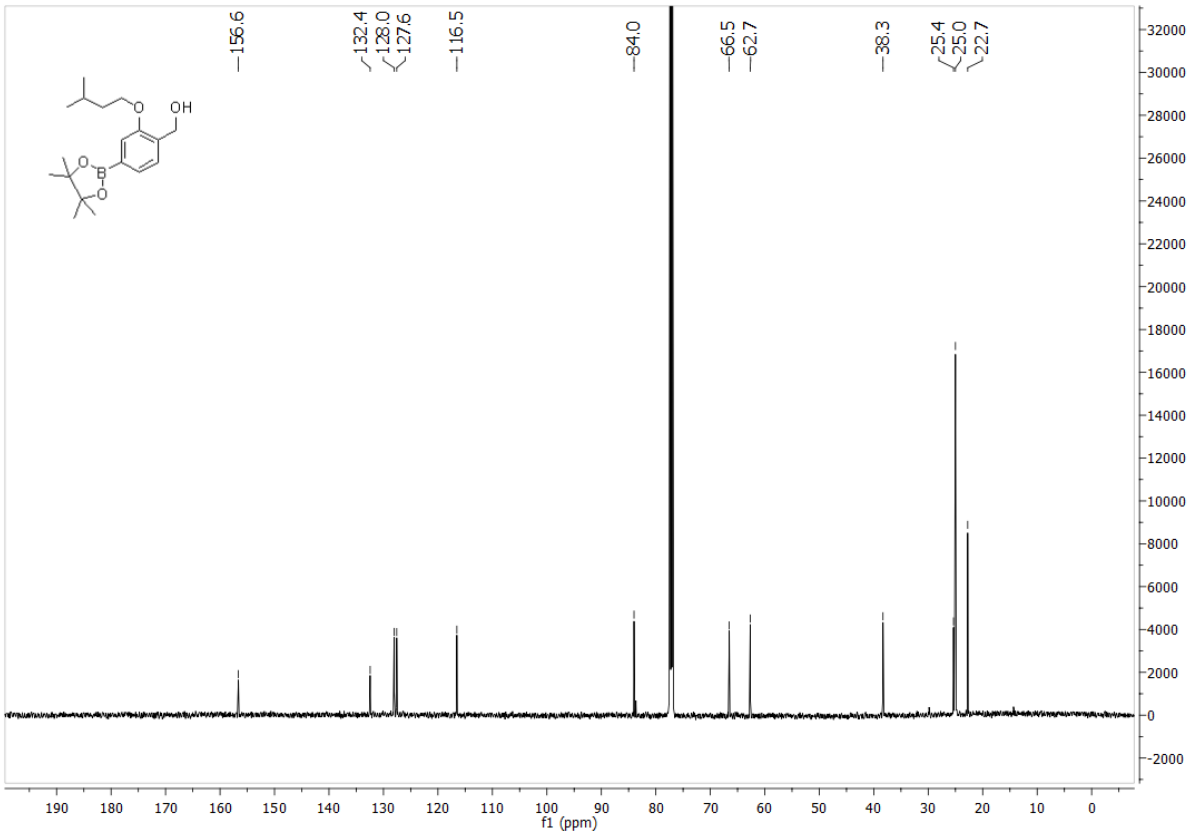
3c. (2-Isopropoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



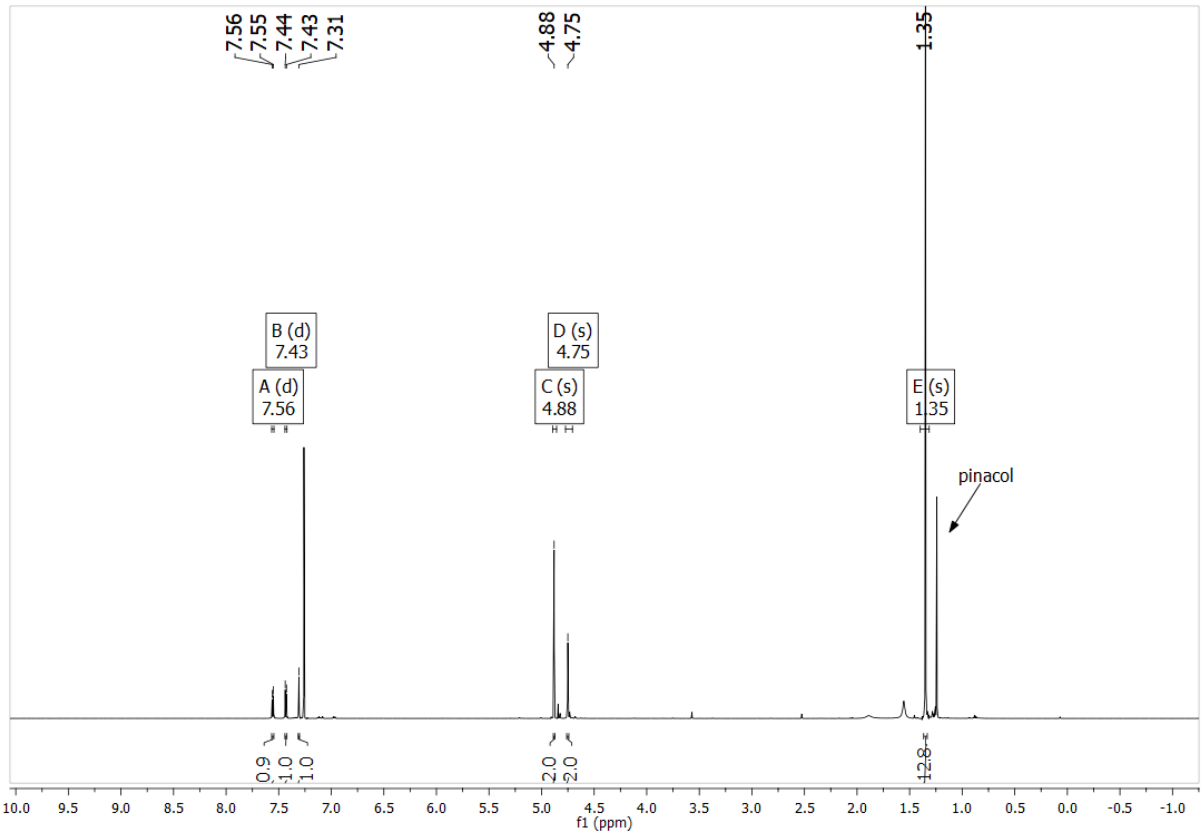


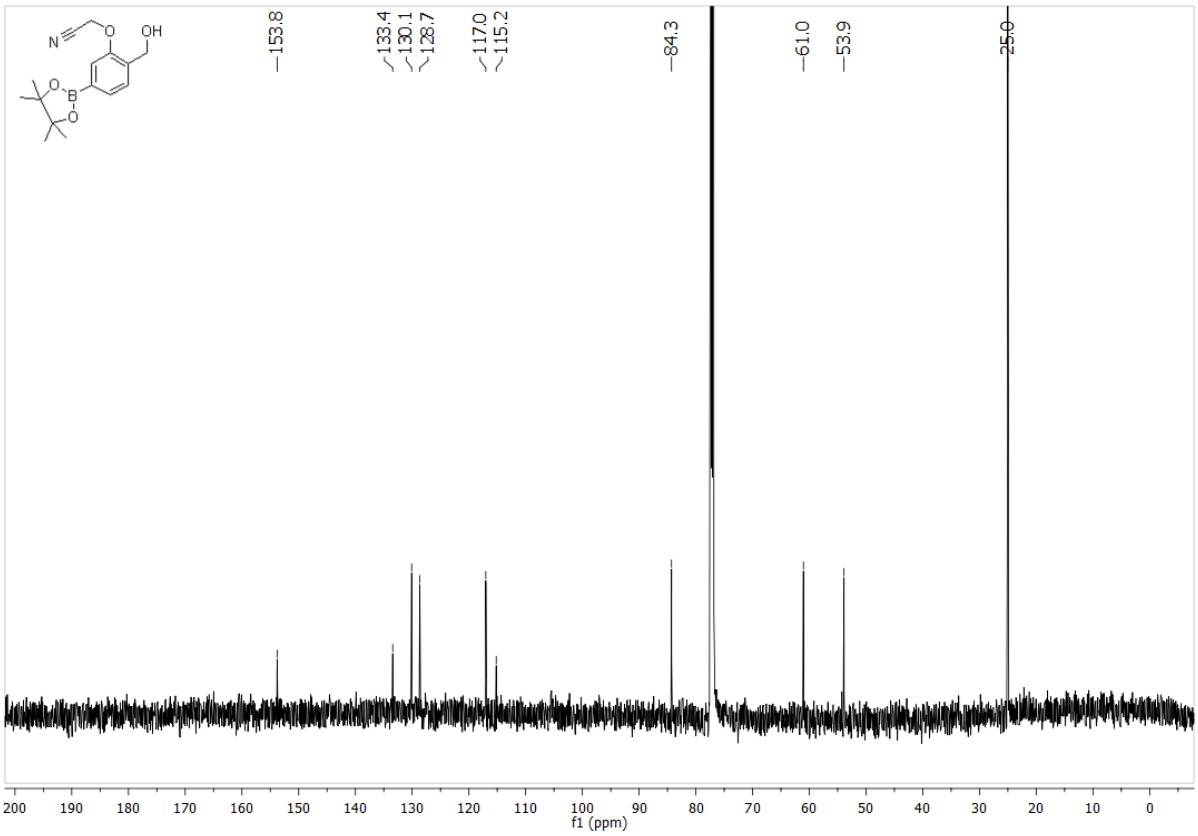
3d. (2-Isopentoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



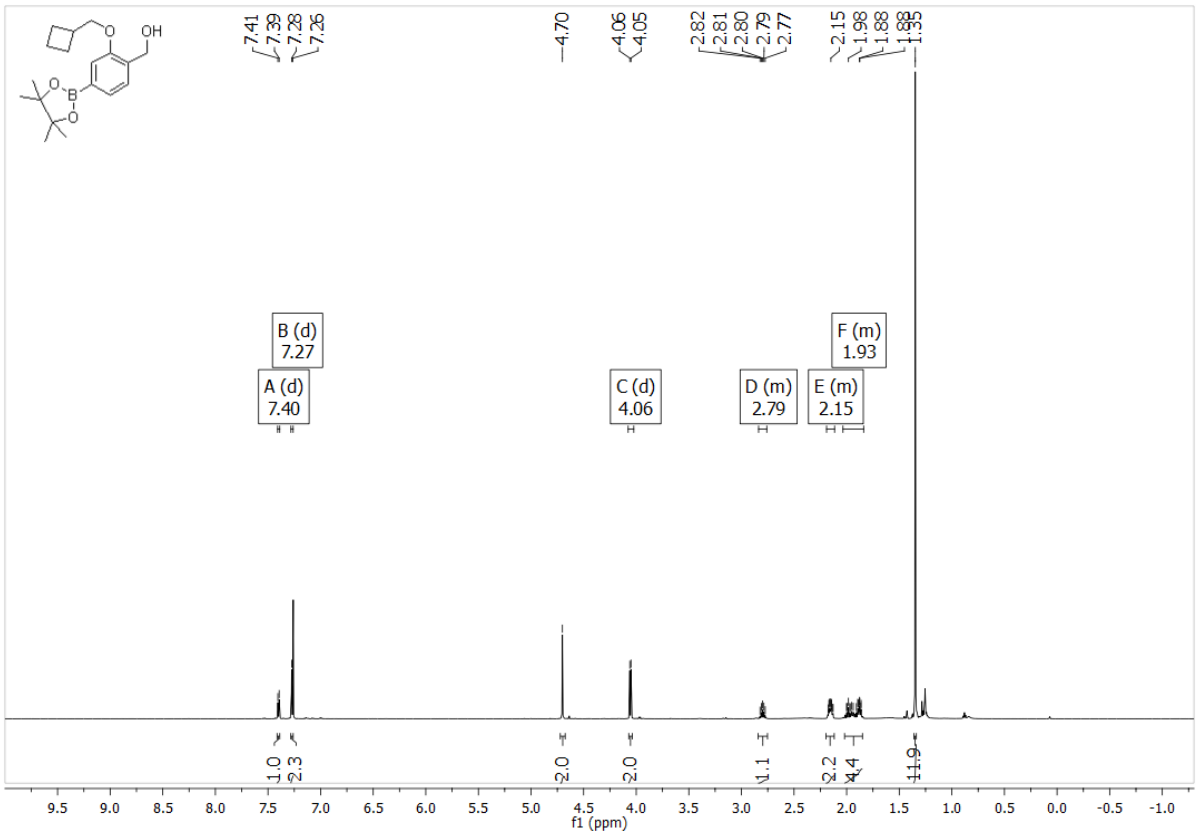


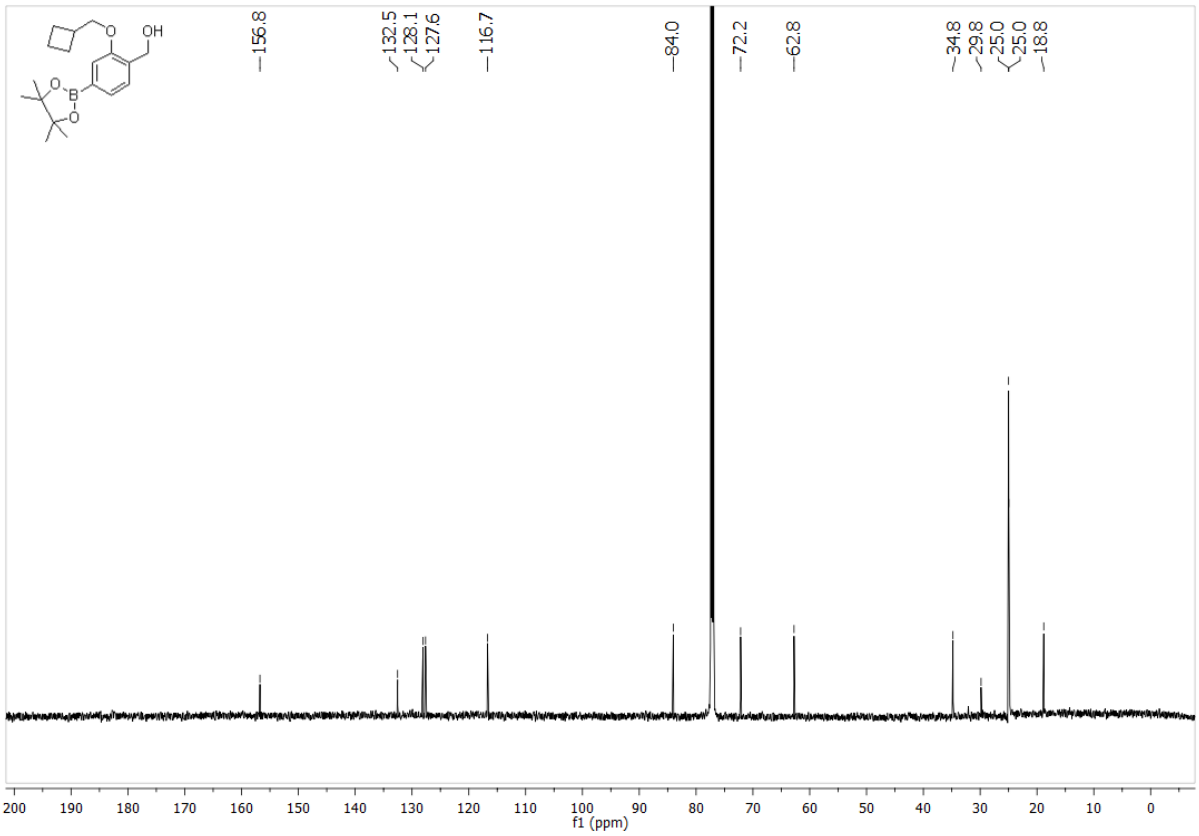
3e. 2-(2-Hydroxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)acetonitrile



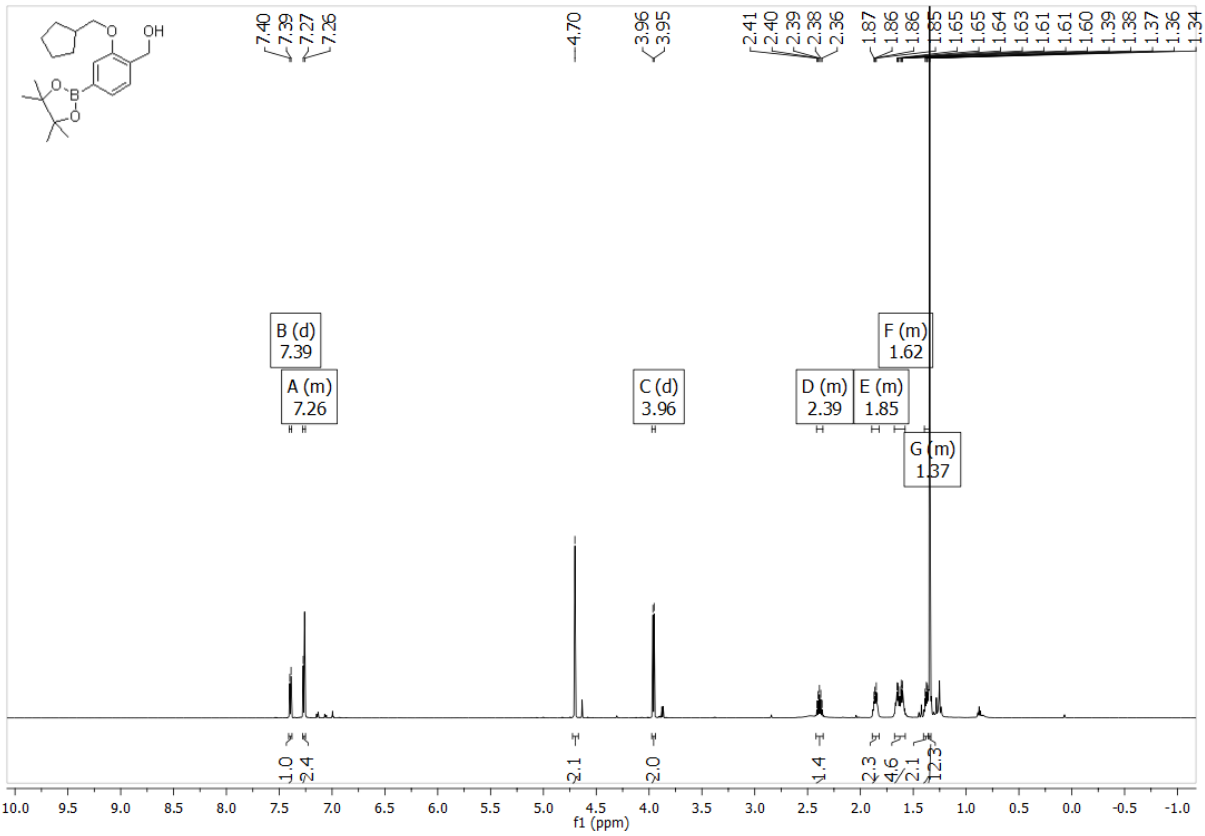


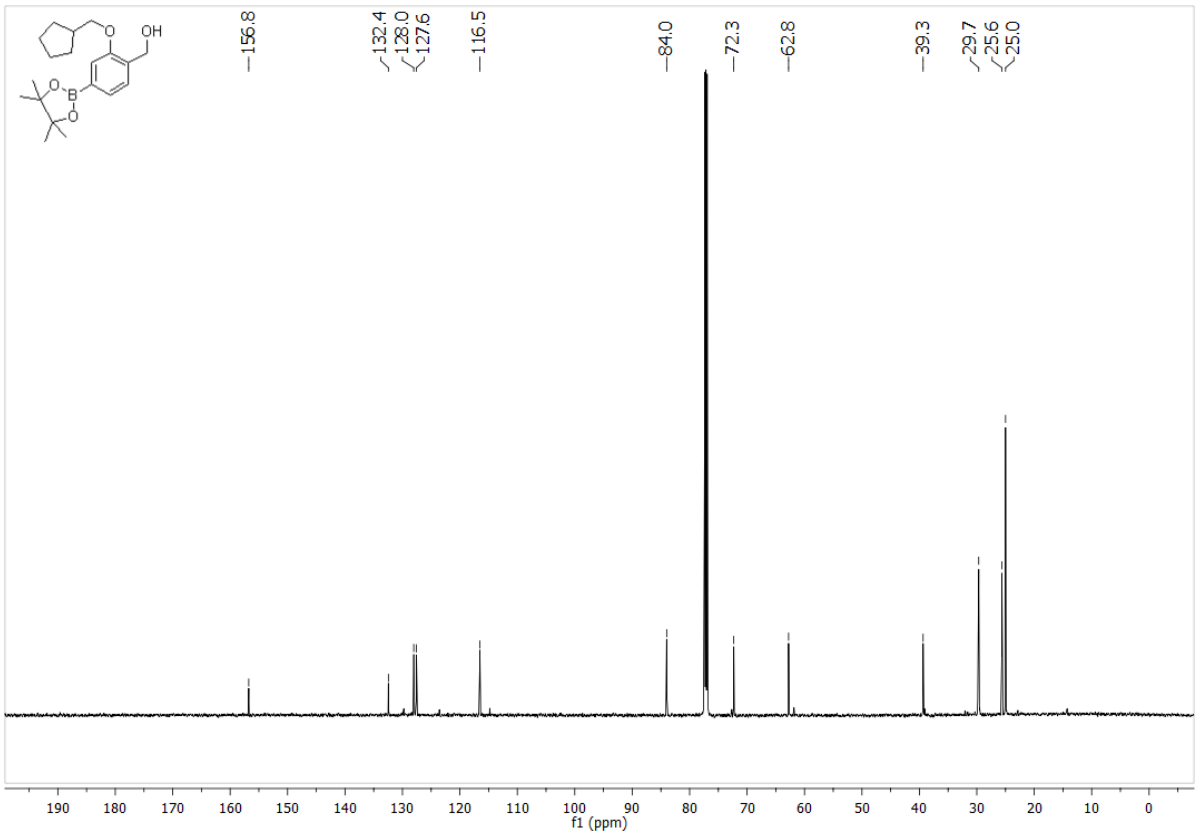
3f. (2-(Cyclobutylmethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



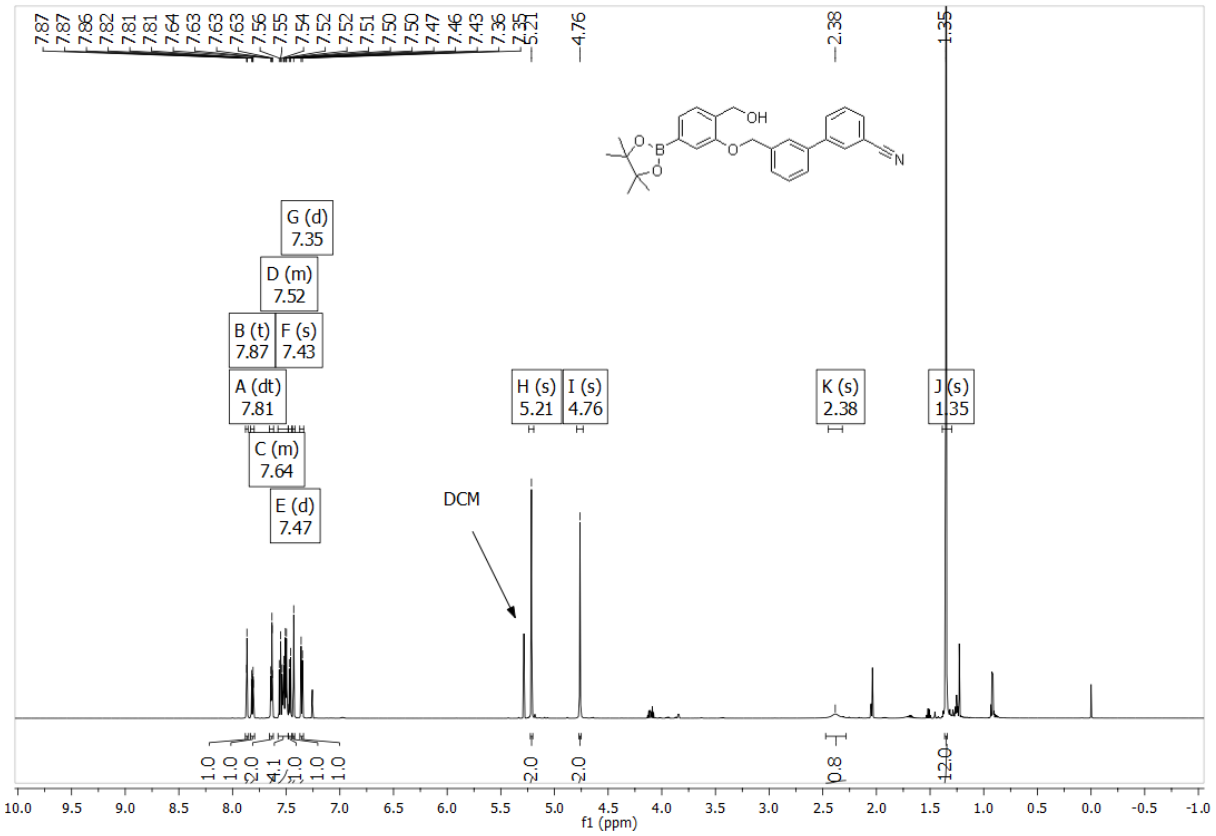


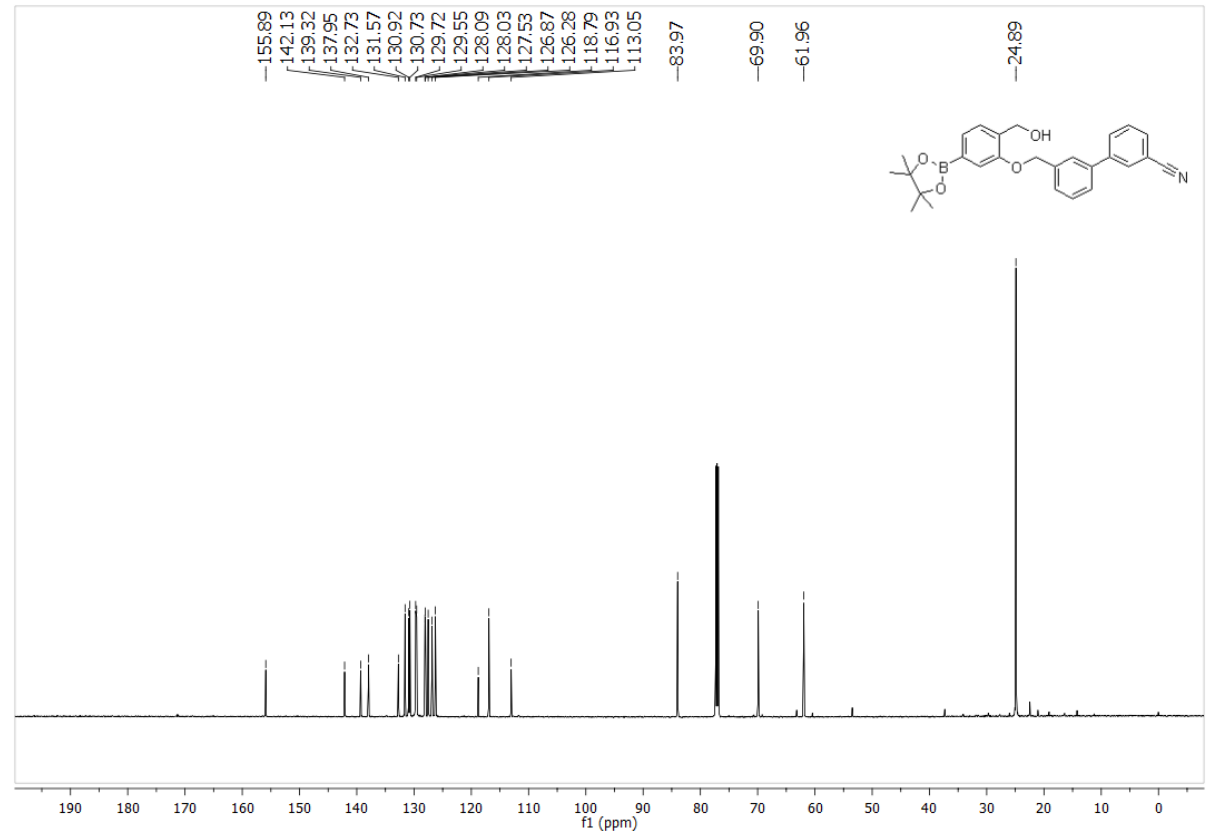
3g. (2-(Cyclopentylmethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



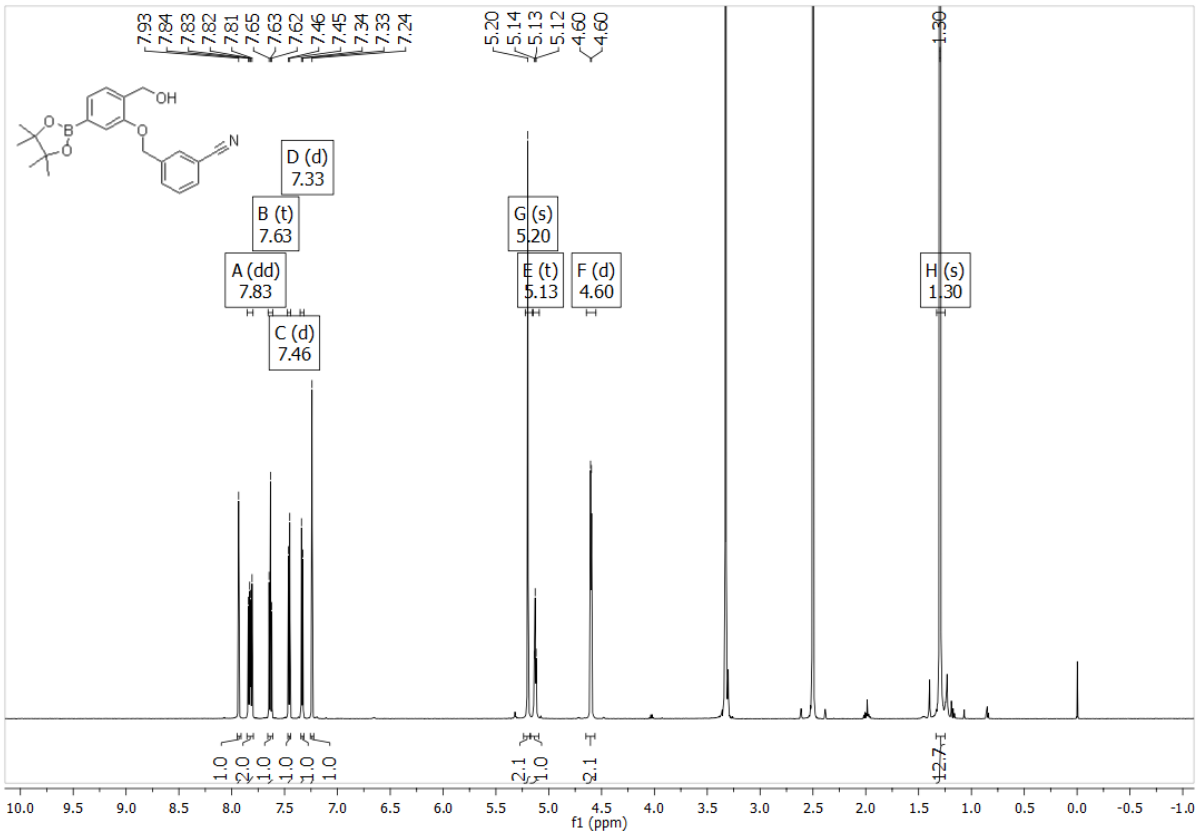


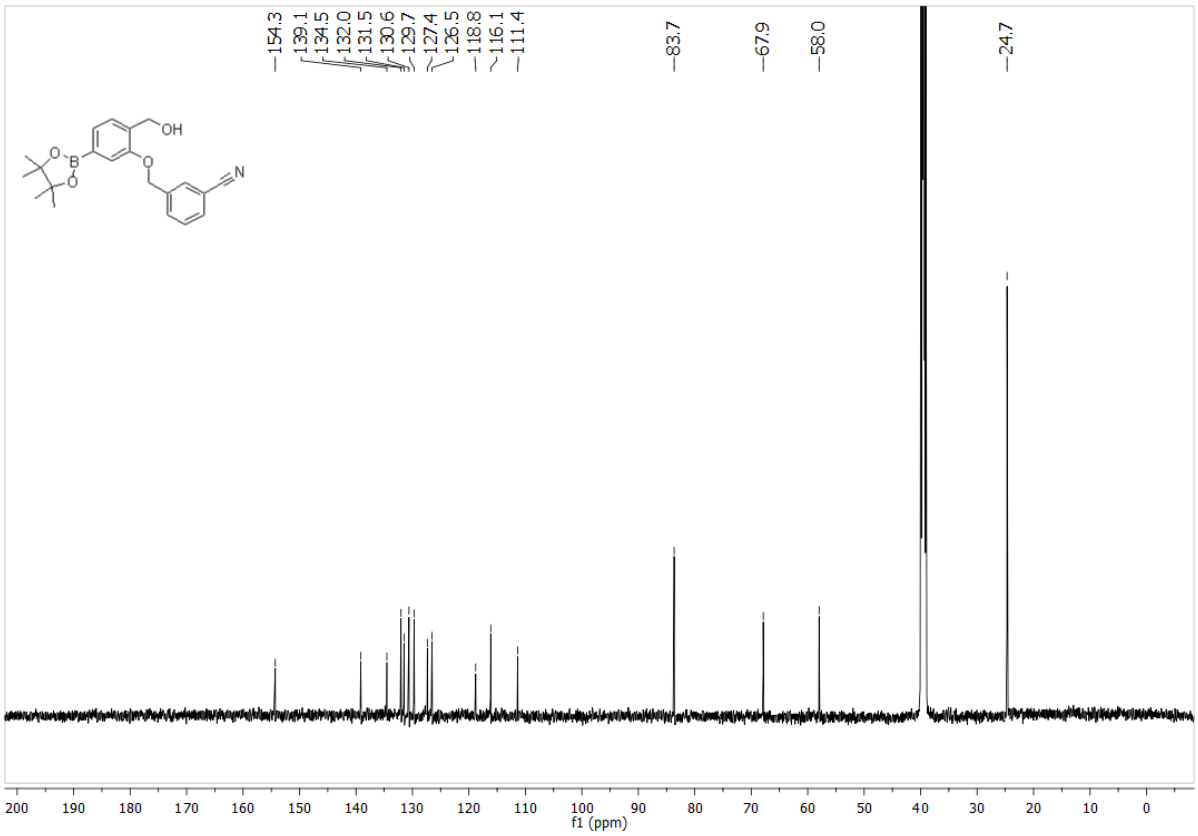
3h. 3'-((2-(Hydroxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)methyl)-[1,1'-biphenyl]-3-carbonitrile



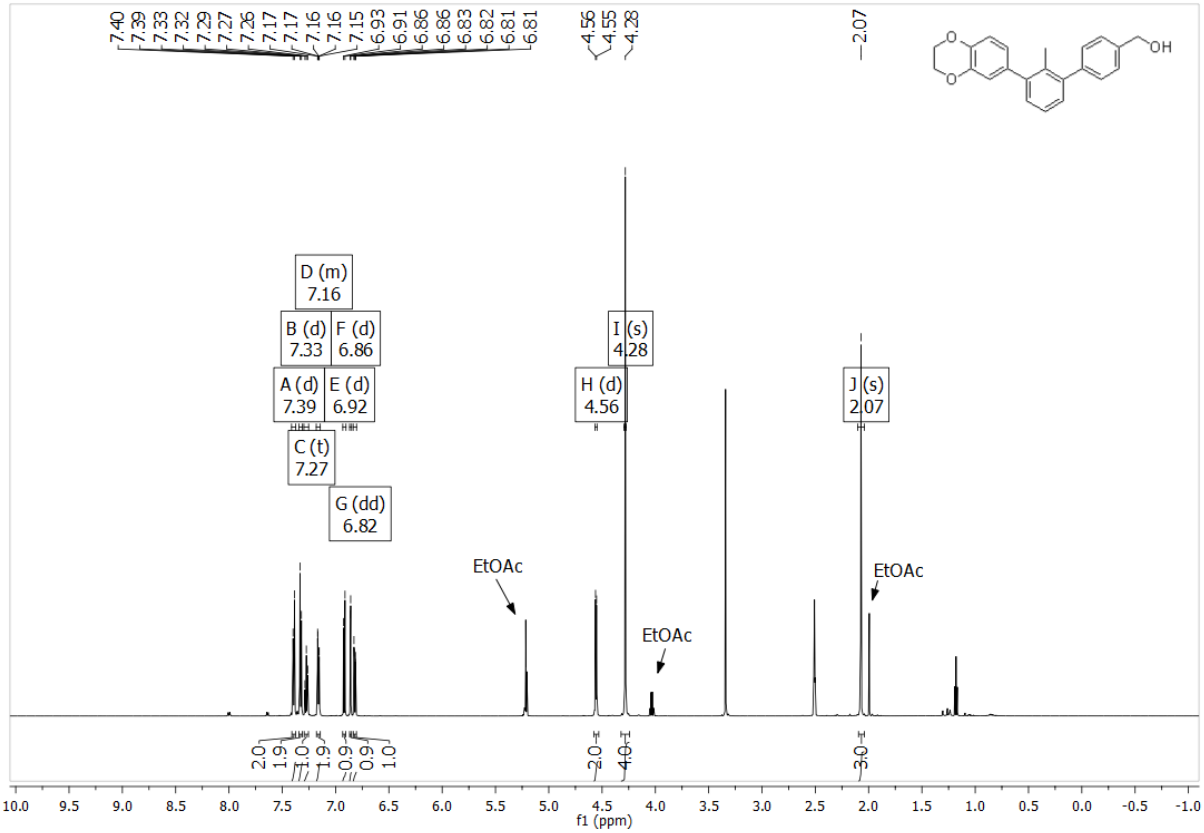


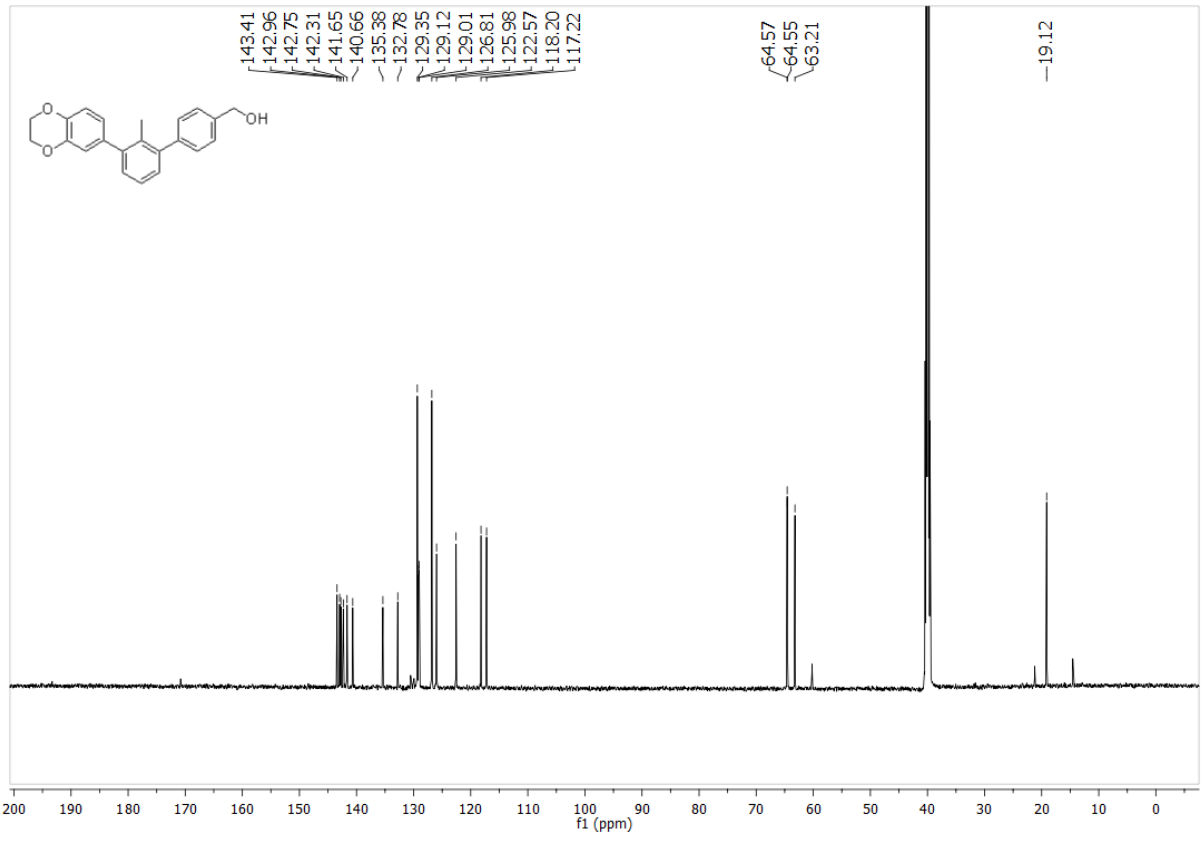
3i. 3-((2-(Hydroxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)methyl)benzonitrile



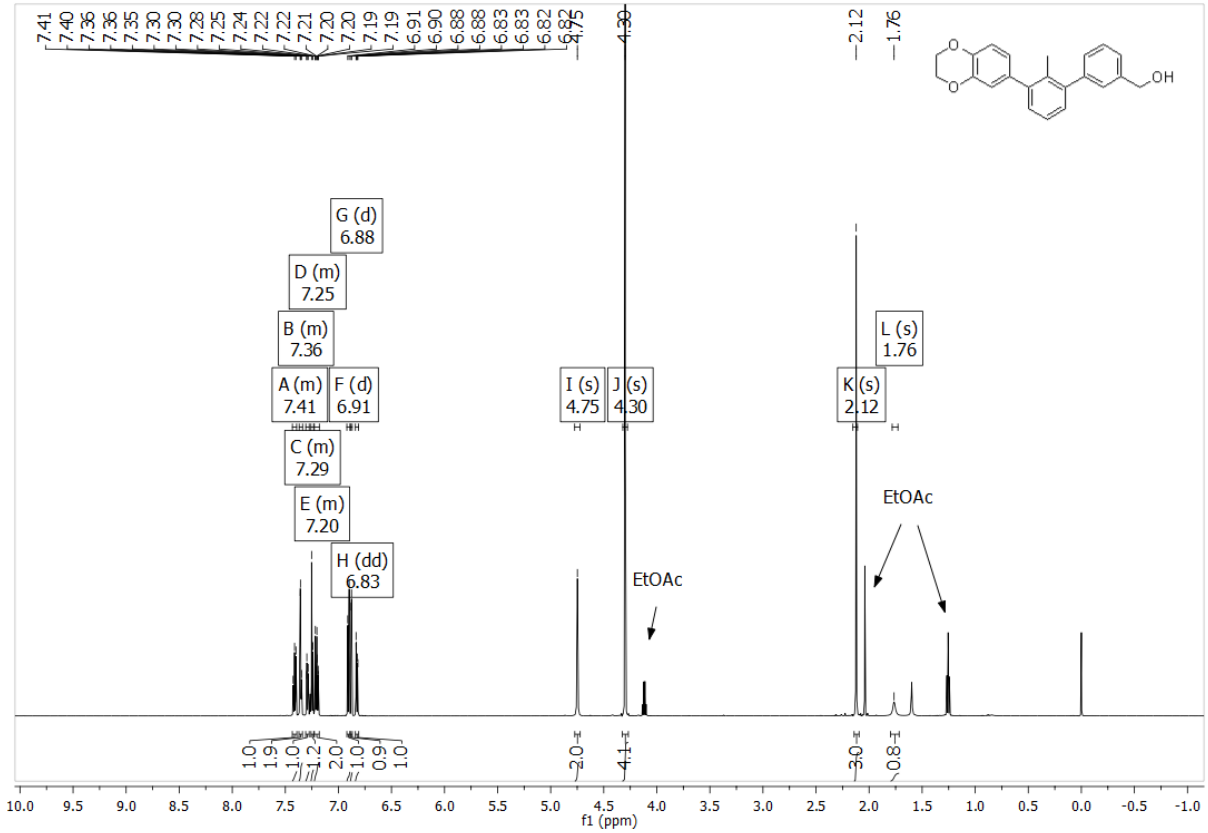


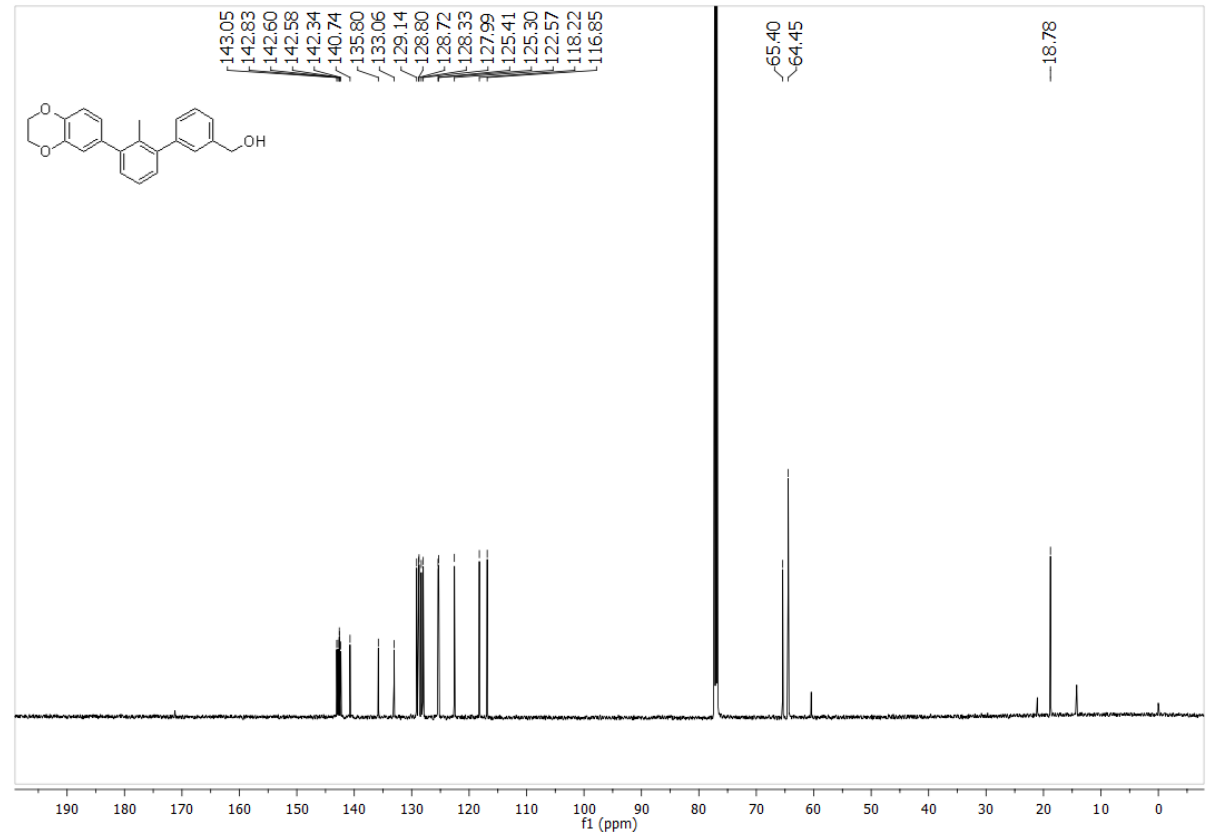
4a. (3'-(Benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methanol



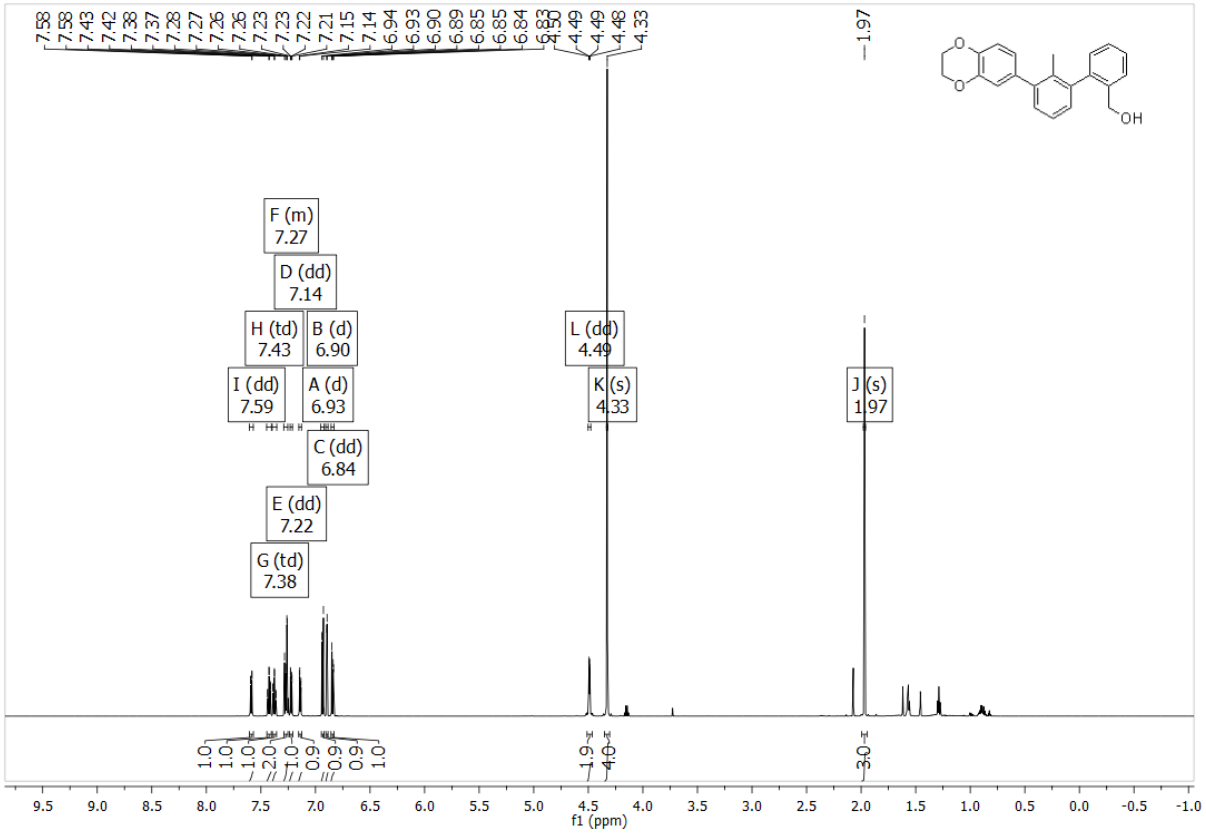


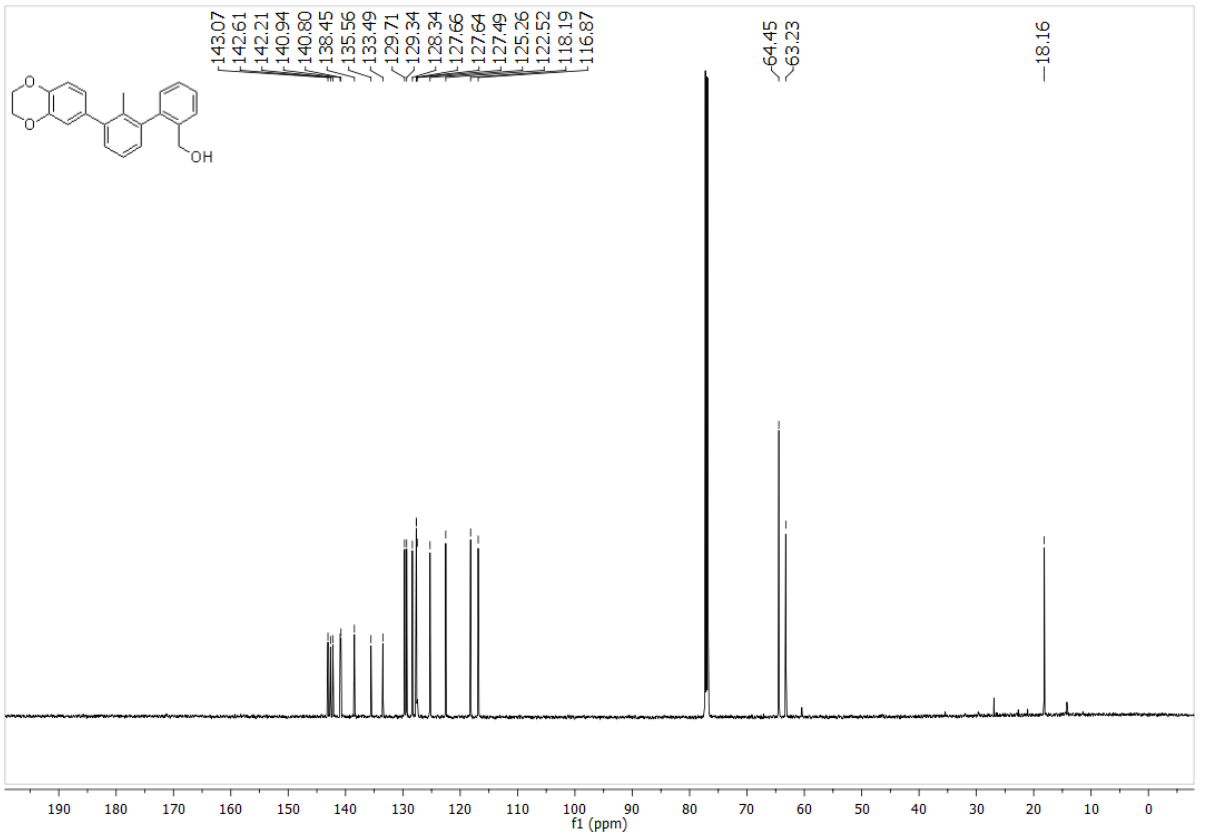
4b. (3'-(Benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methanol



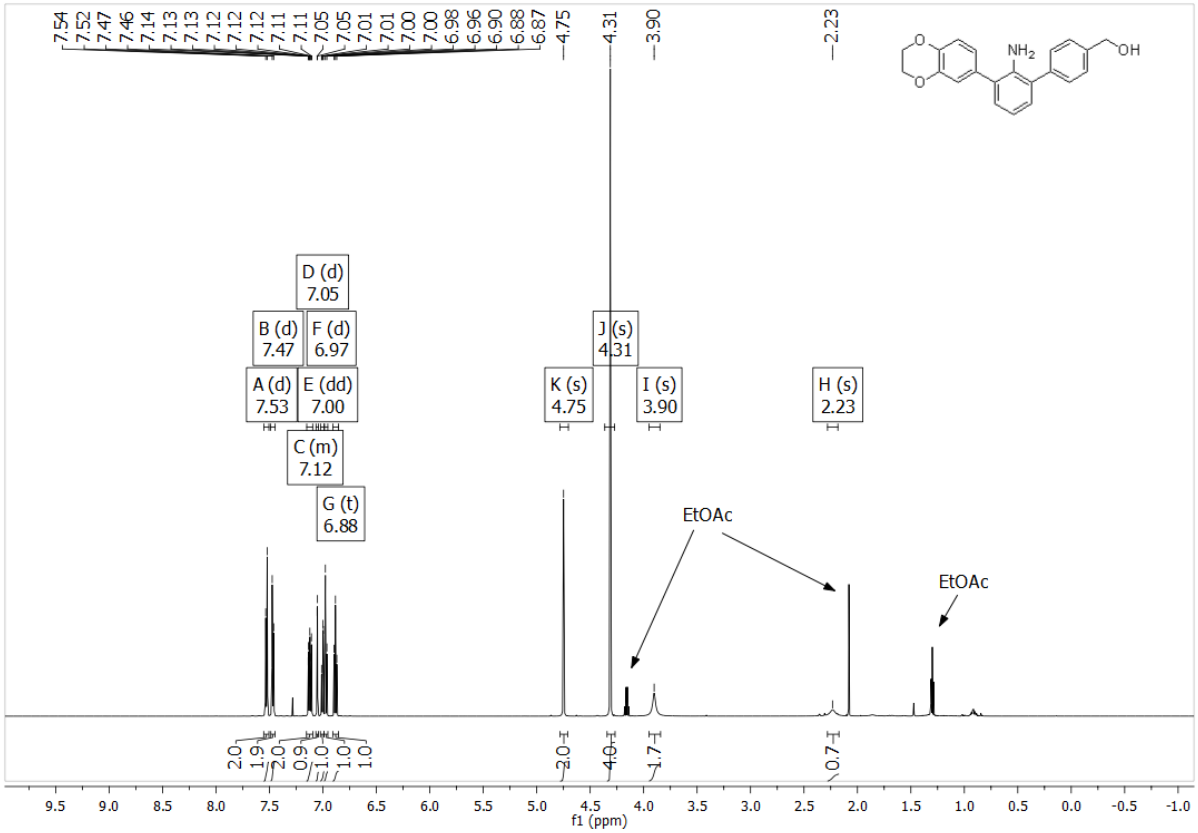


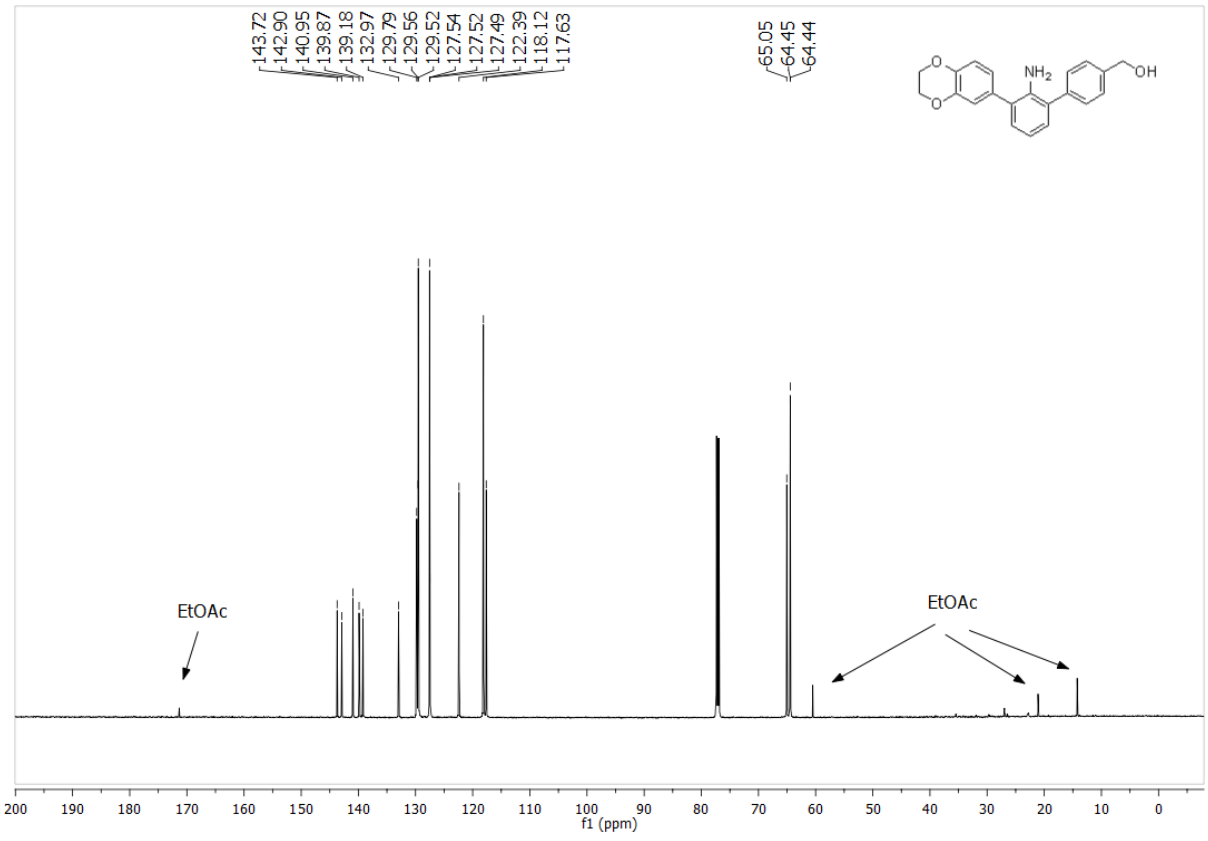
4c. (3'-(Benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)methanol



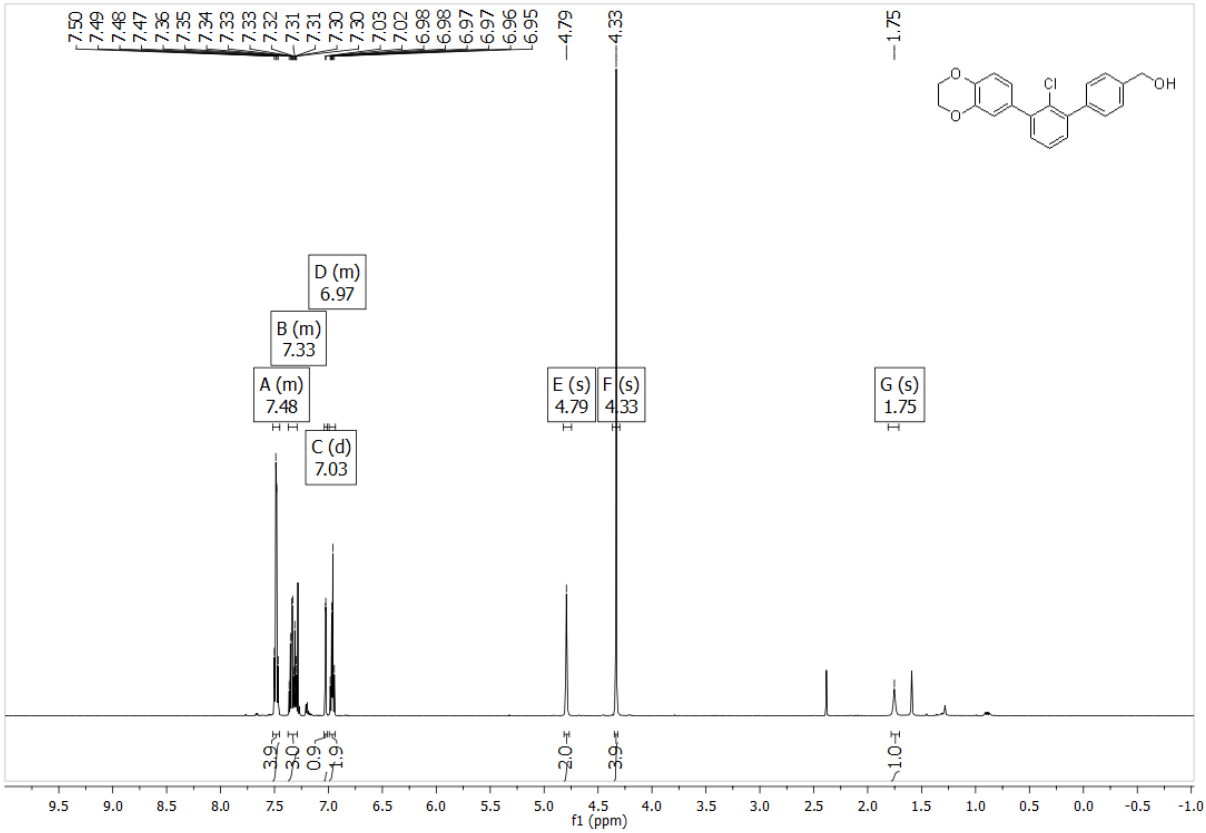


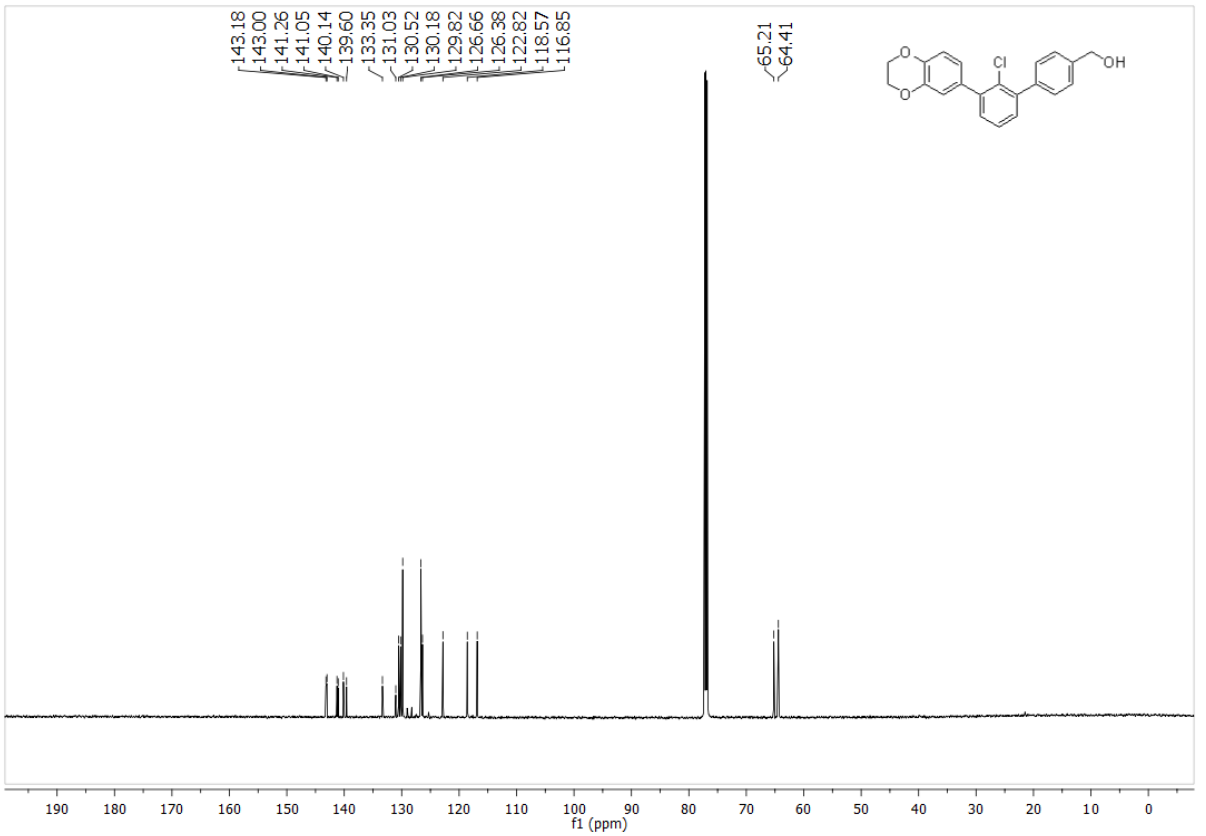
4d. (2'-Amino-3'-(benzo-1,4-dioxan-6-yl)-[1,1'-biphenyl]-4-yl)methanol



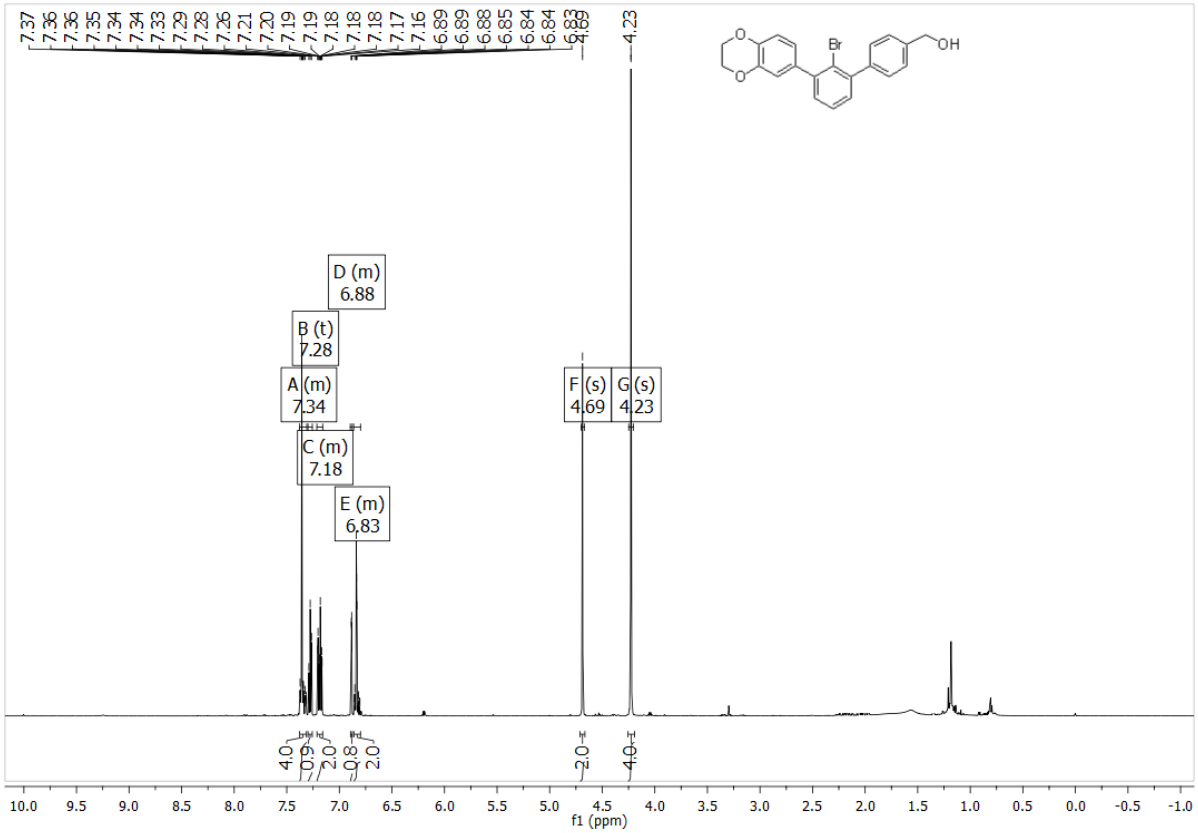


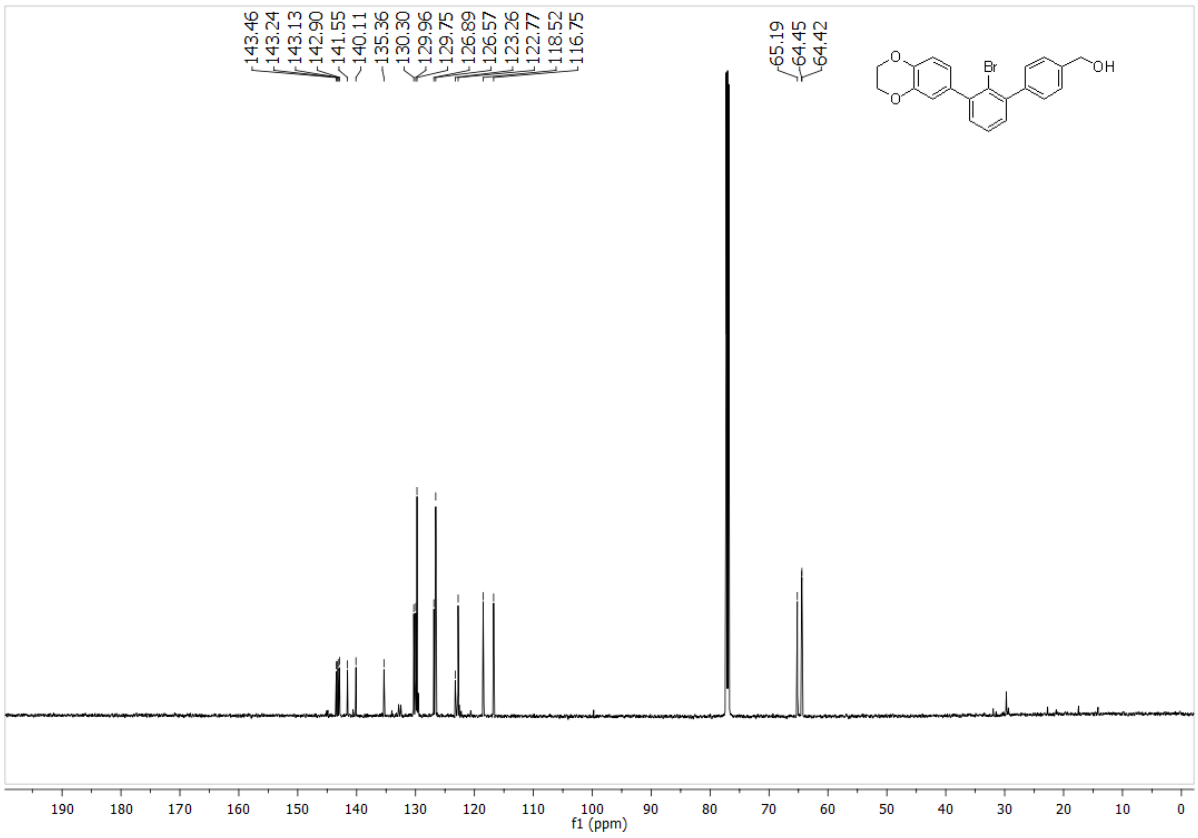
4e. (3'-(Benzo-1,4-dioxan-6-yl)-2'-chloro-[1,1'-biphenyl]-4-yl)methanol



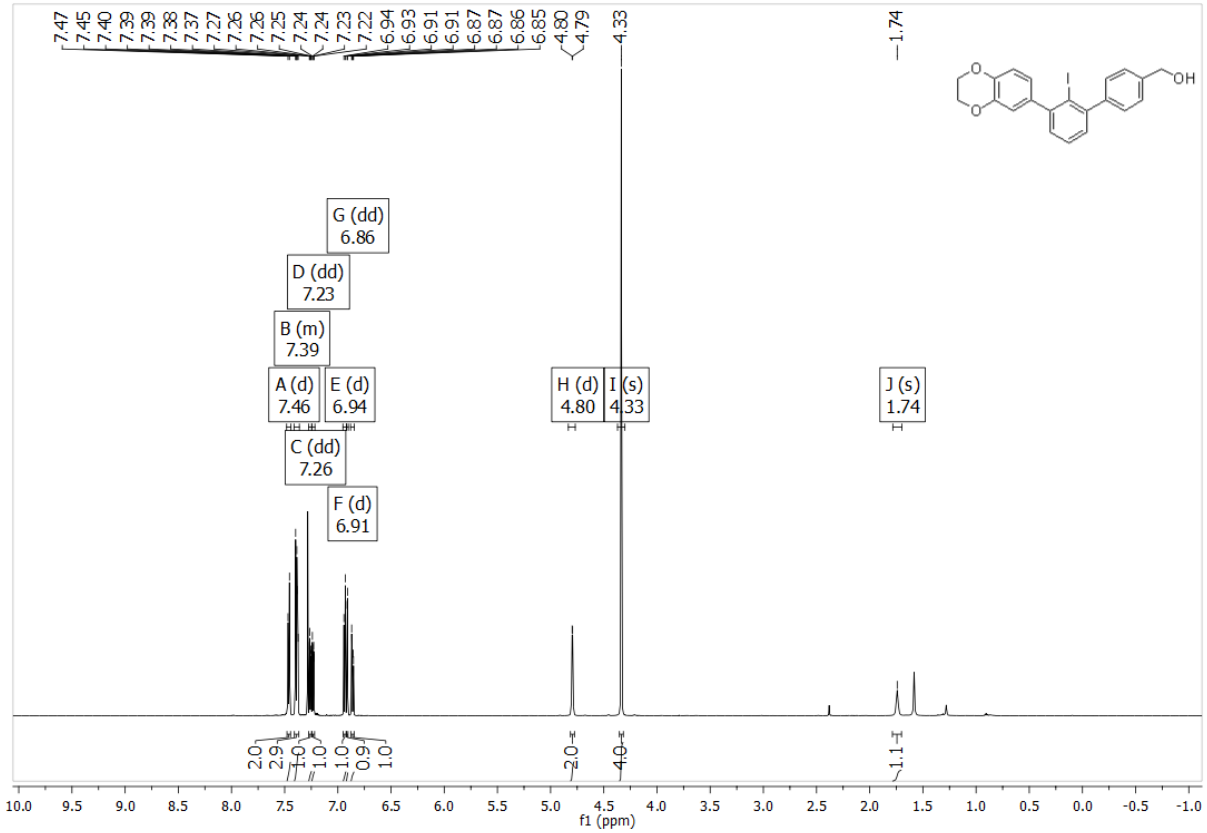


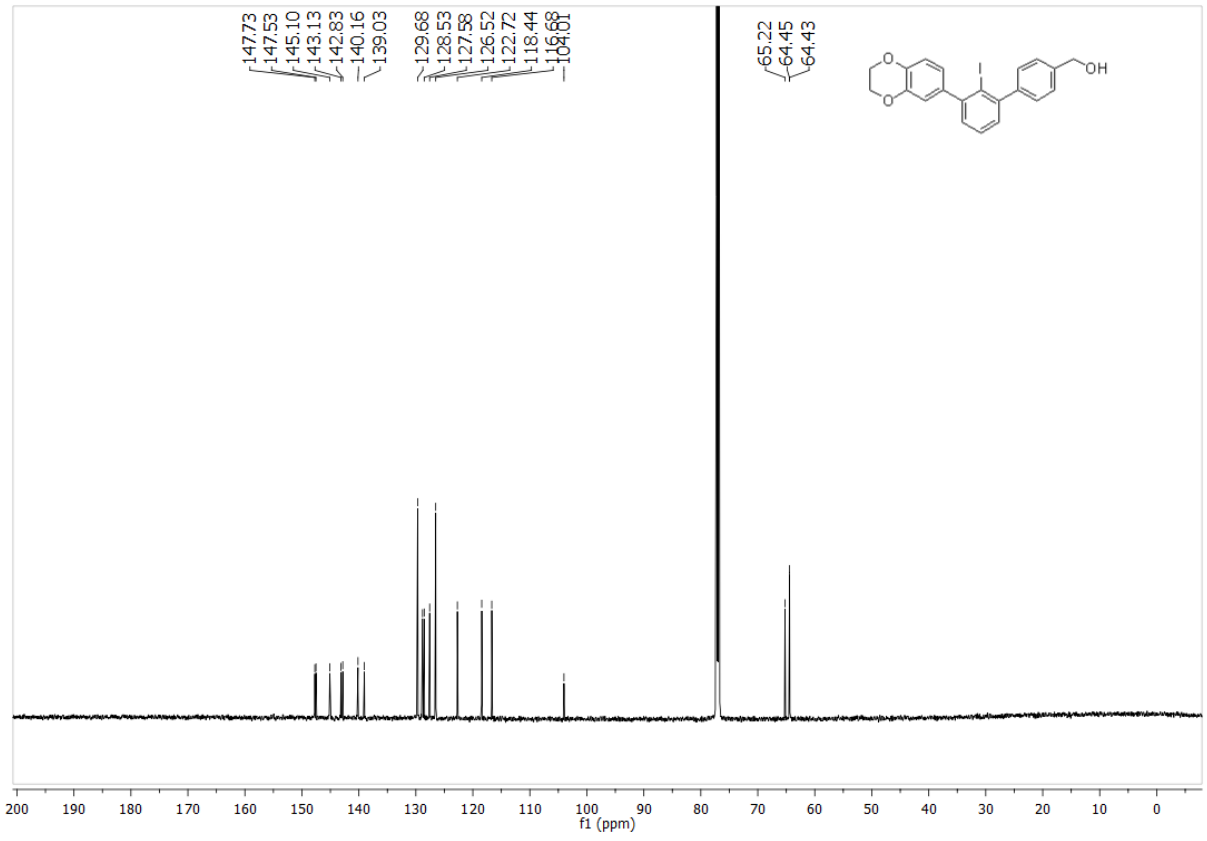
4f. (2'-Bromo-3'-(benzo-1,4-dioxan-6-yl)-[1,1'-biphenyl]-4-yl)methanol



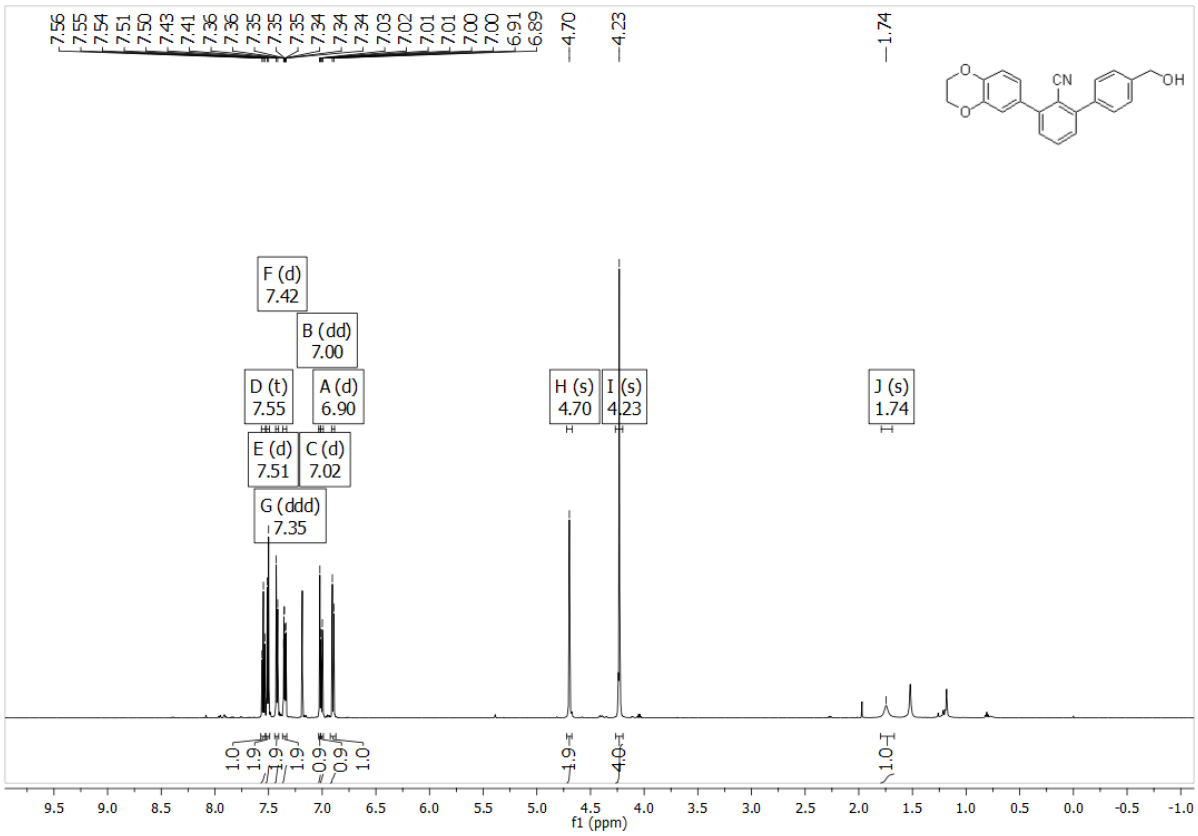


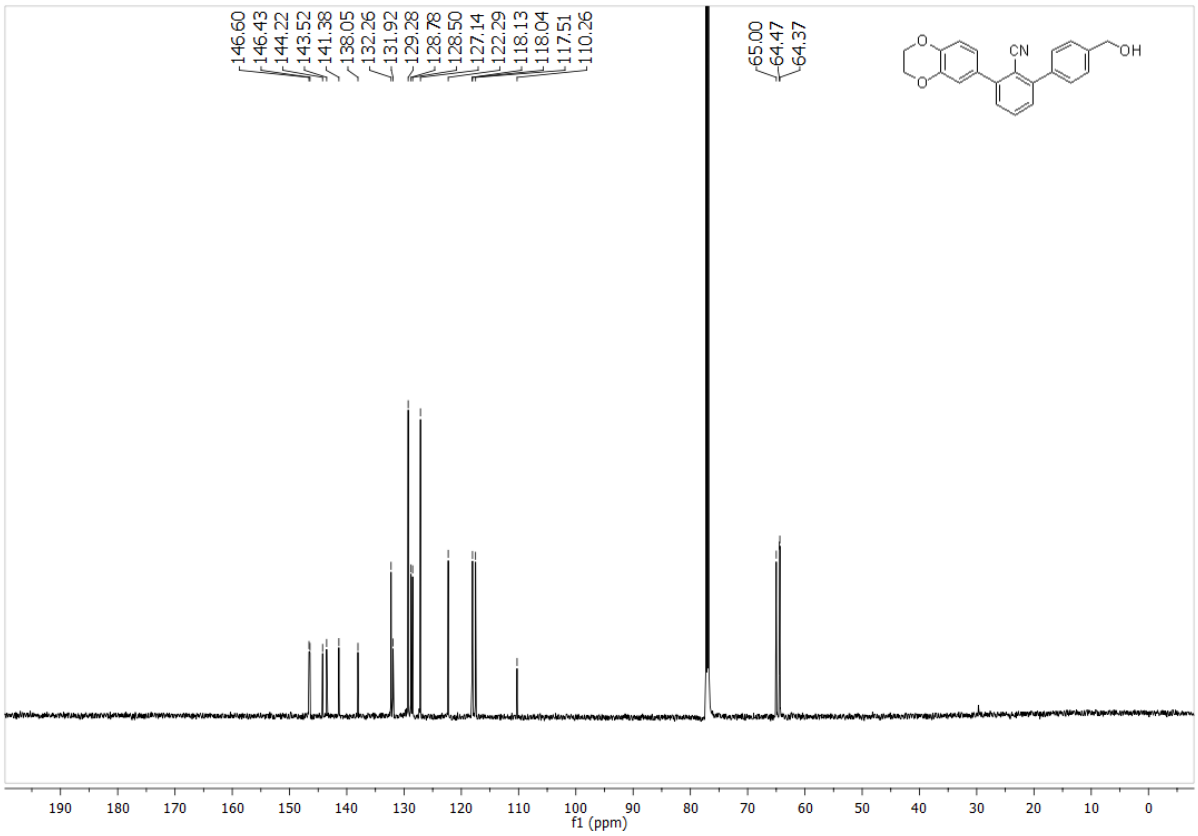
4g. (3'-(Benzo-1,4-dioxan-6-yl)-2'-iodo-[1,1'-biphenyl]-4-yl)methanol



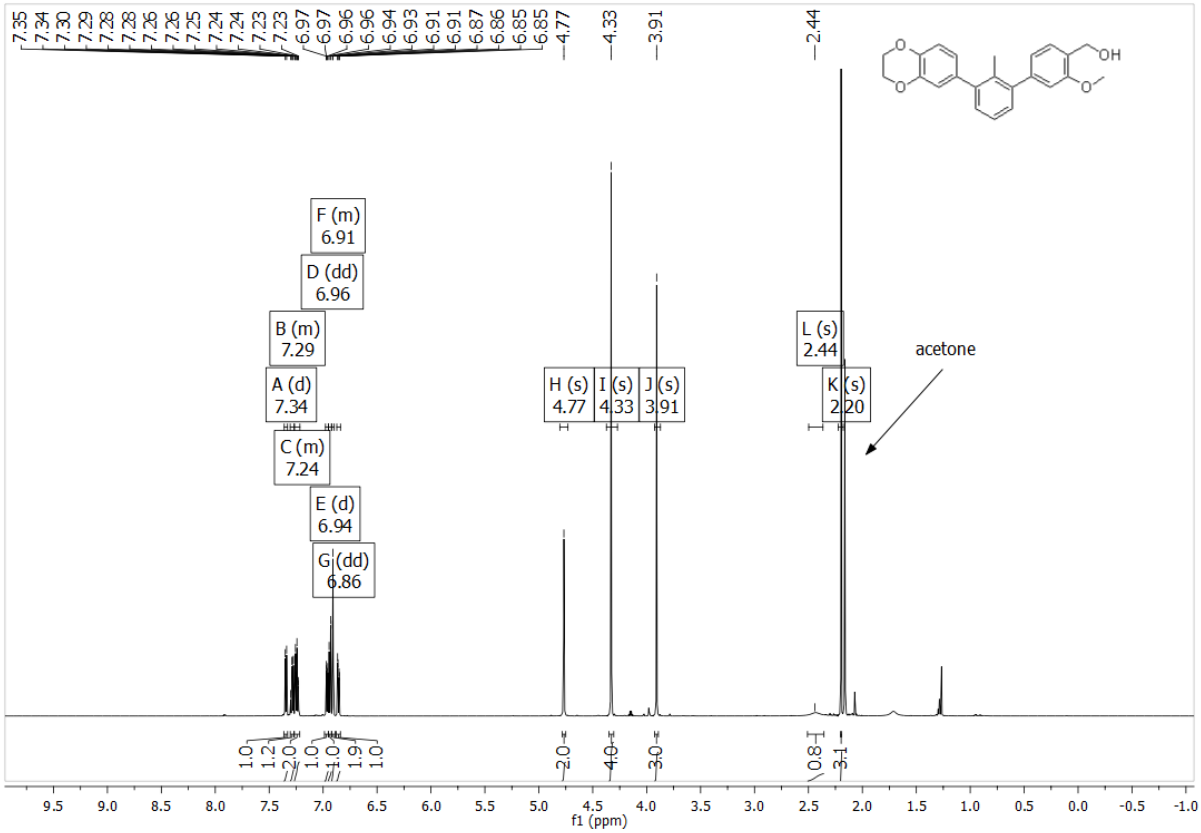


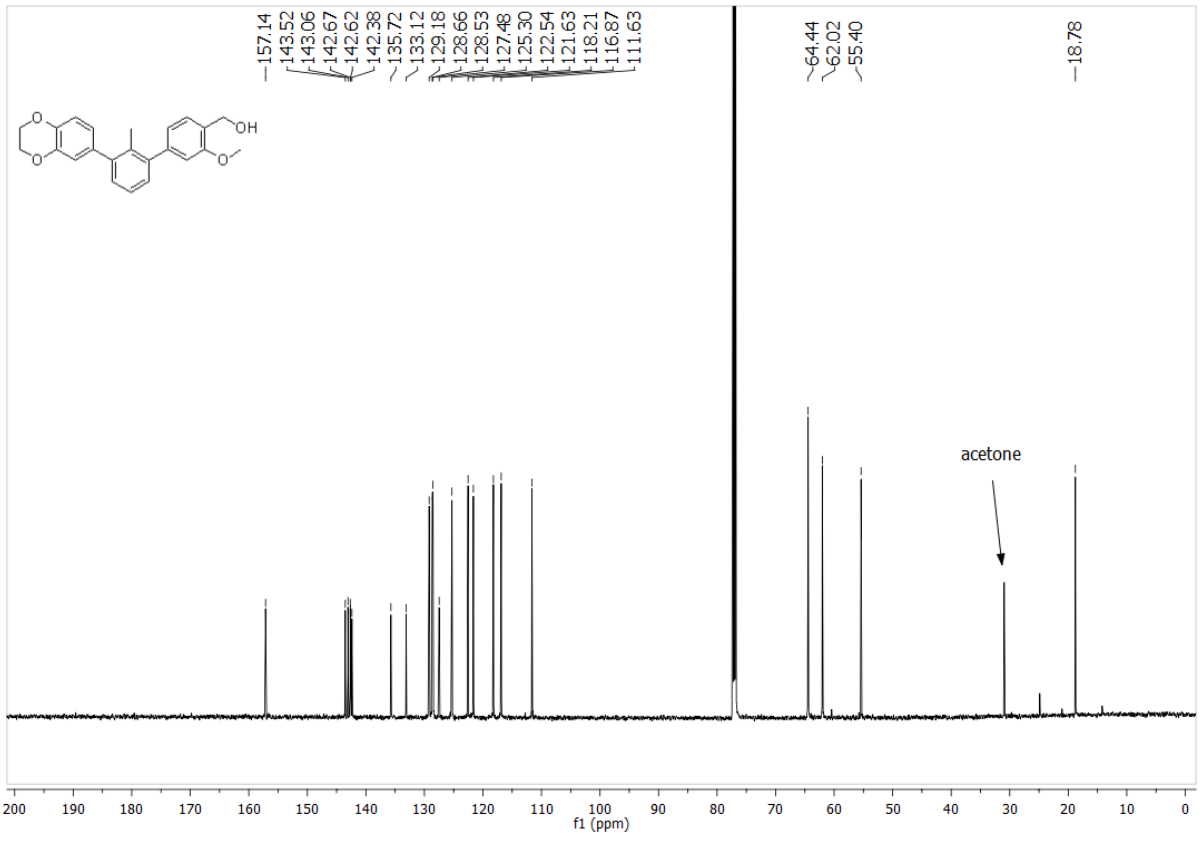
4h. 3-(3'-(Benzo-1,4-dioxan-6-yl)-4'-(hydroxymethyl)-[1,1'-biphenyl]-2-carbonitrile



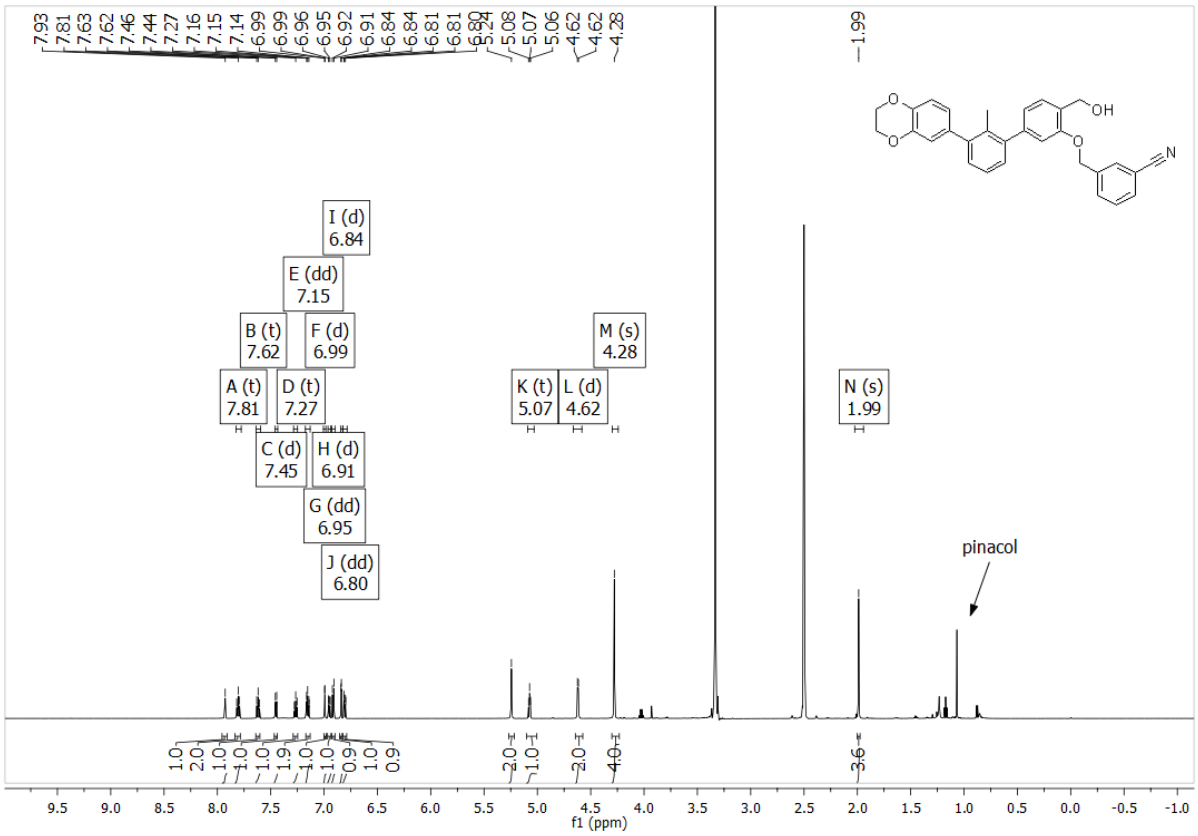


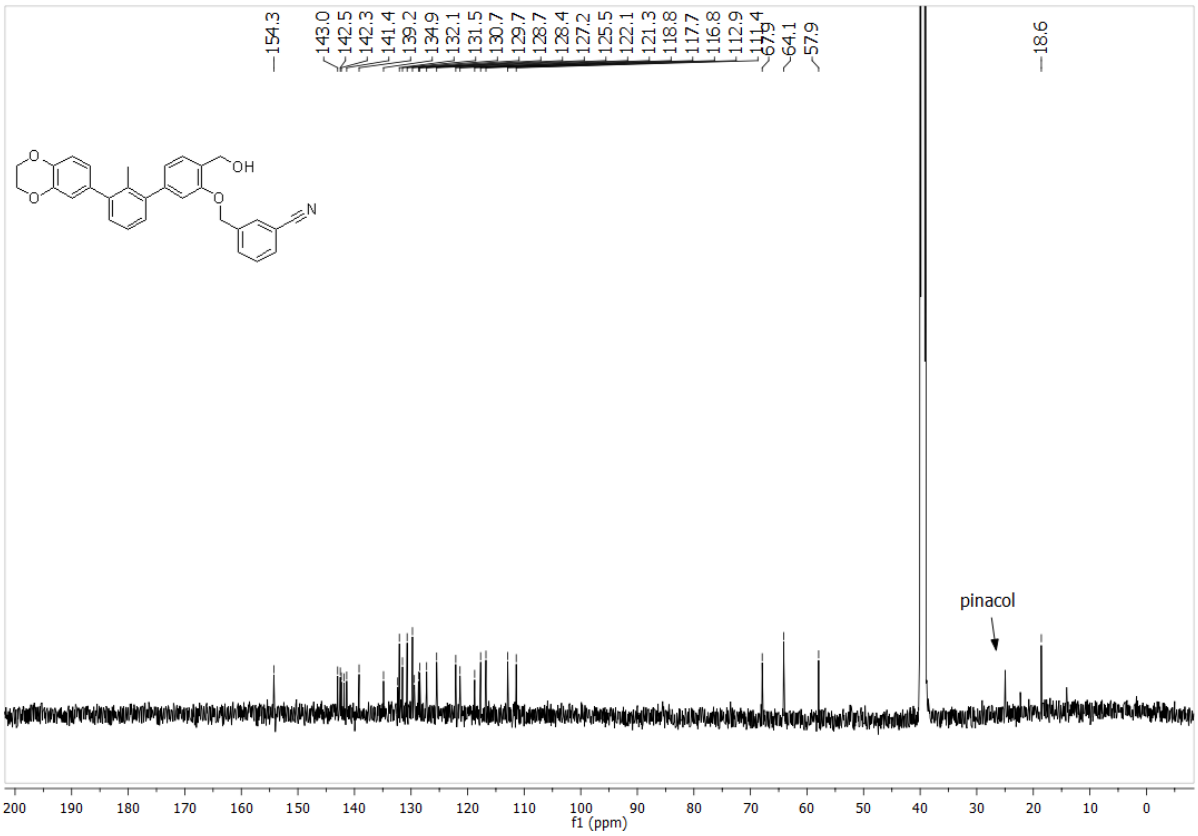
4i. (3'-(Benzo-1,4-dioxan-6-yl)-3-methoxy-2'-methyl-[1,1'-biphenyl]-4-yl)methanol



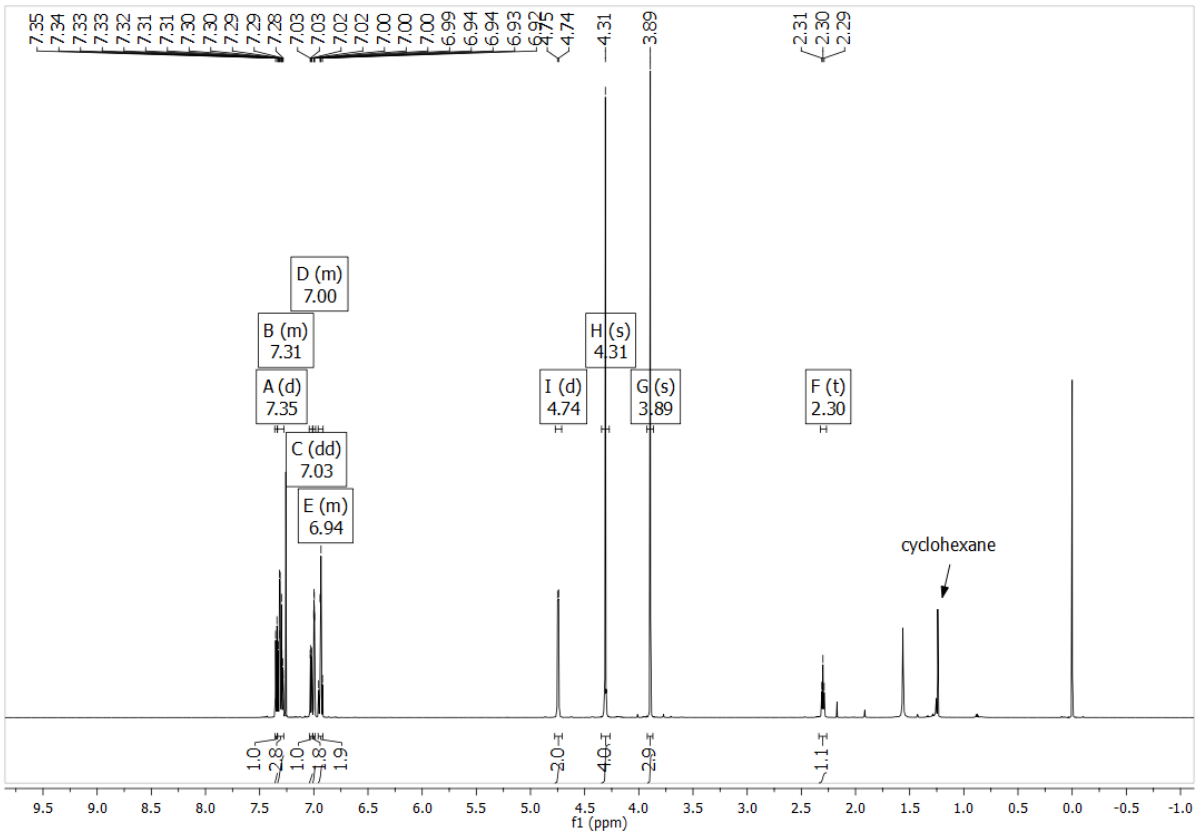


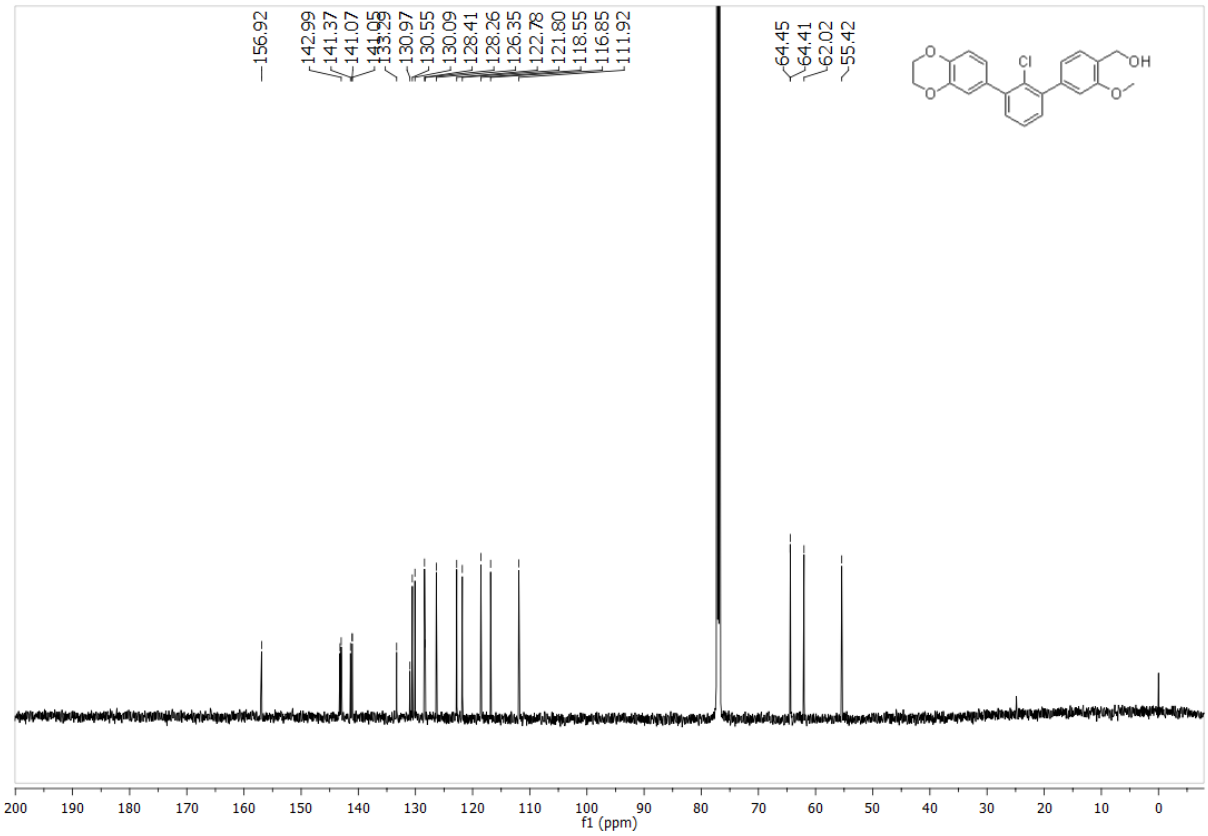
4j. 3-(((3'-(Benzo-1,4-dioxan-6-yl)-4-(hydroxymethyl)-2'-methyl-[1,1'-biphenyl]-3-yl)oxy)methyl)benzonitrile



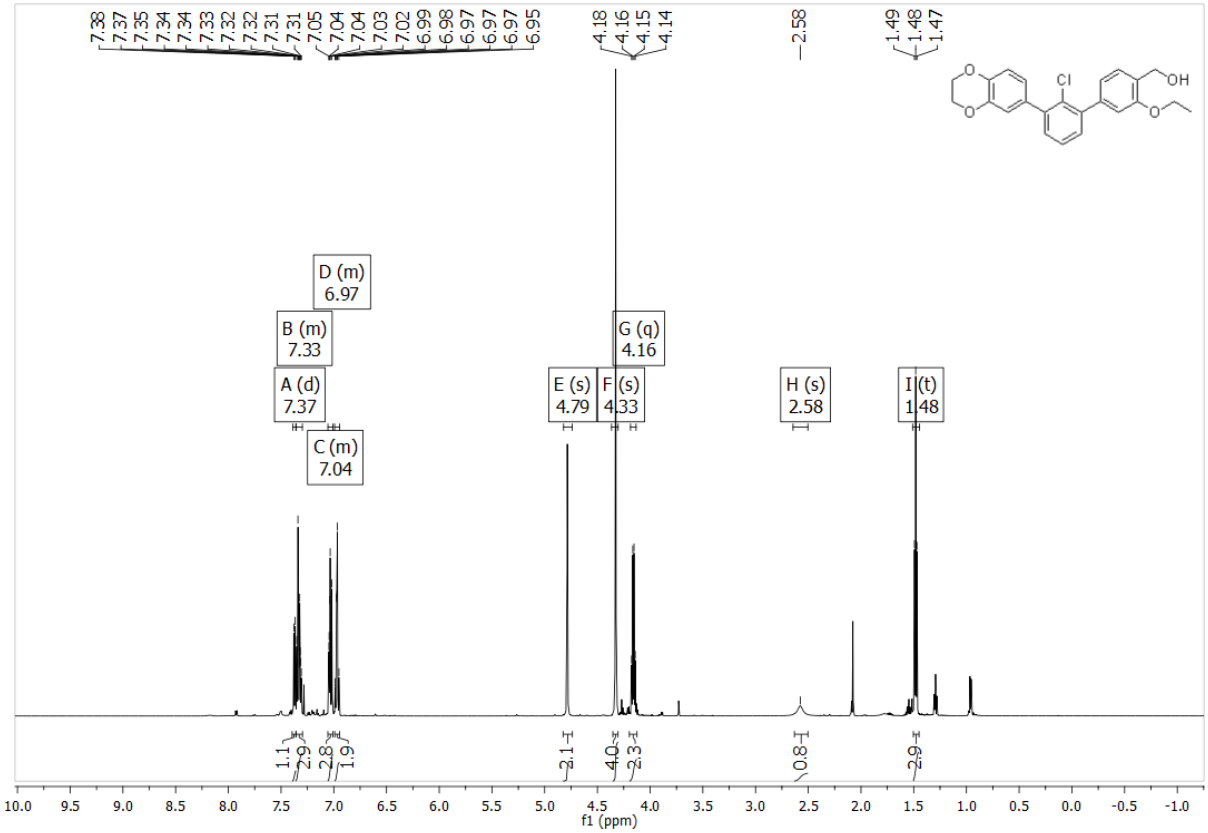


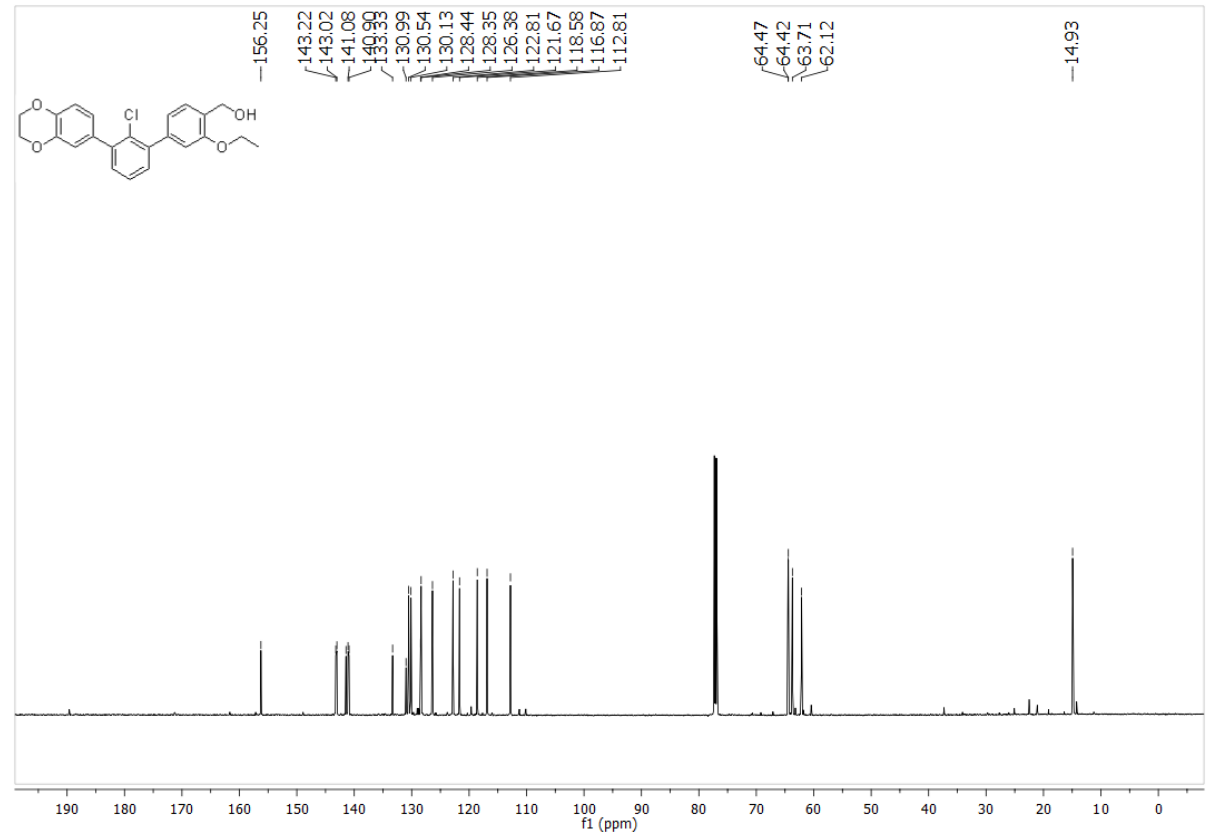
4k. (2'-Chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methanol



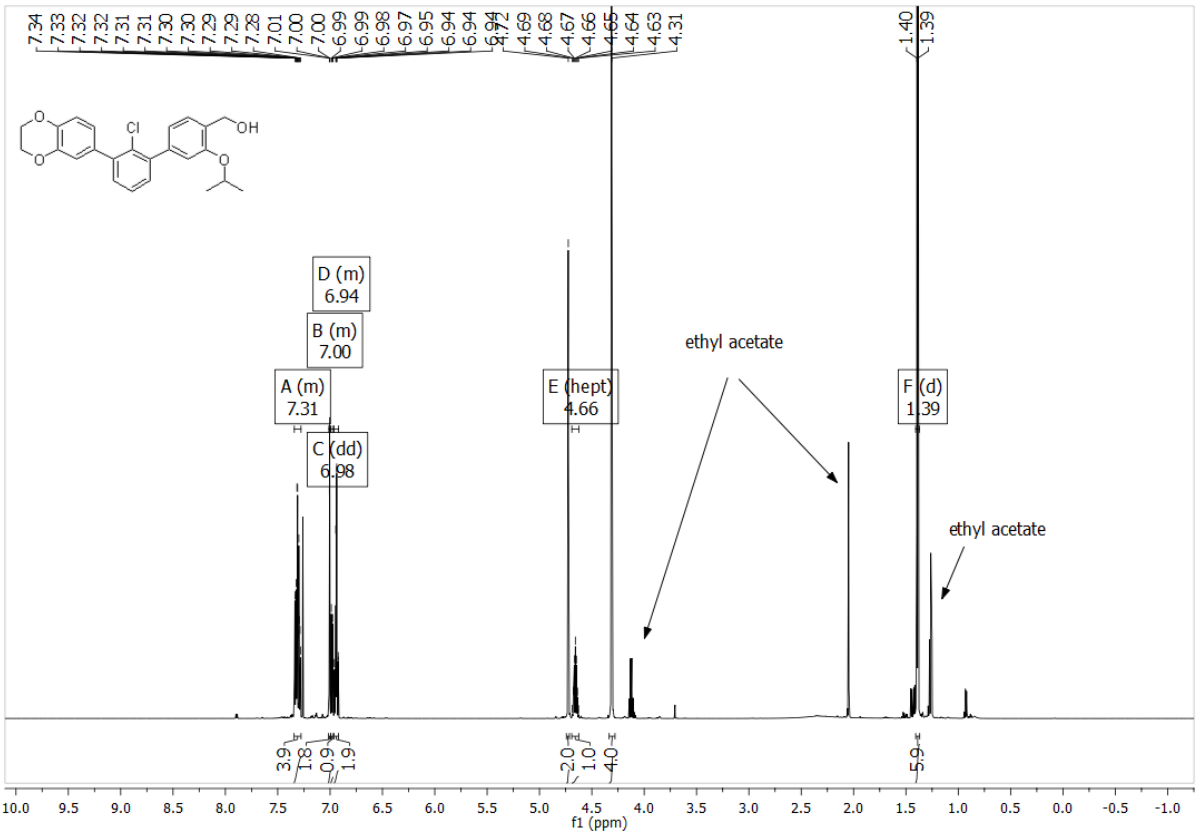


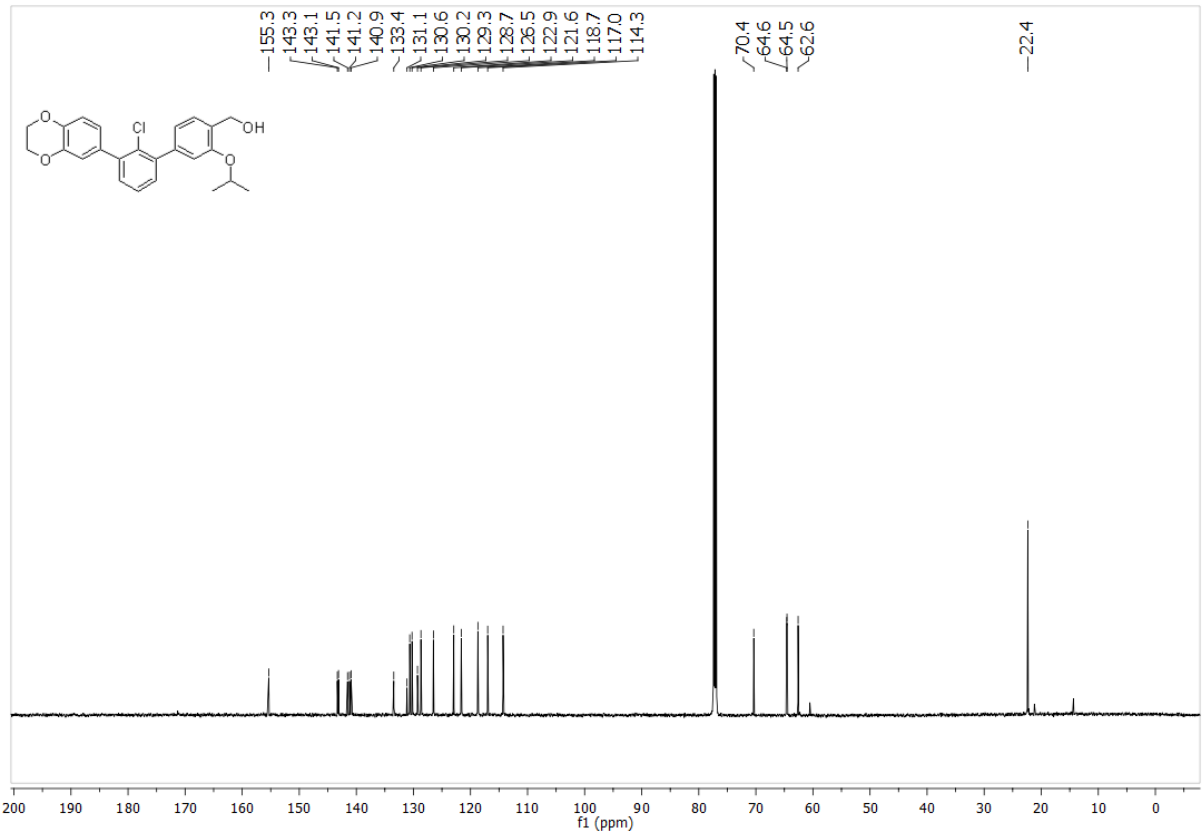
4l. (2'-Chloro-3'-(benzo-1,4-dioxan-6-yl)-3-ethoxy-[1,1'-biphenyl]-4-yl)methanol



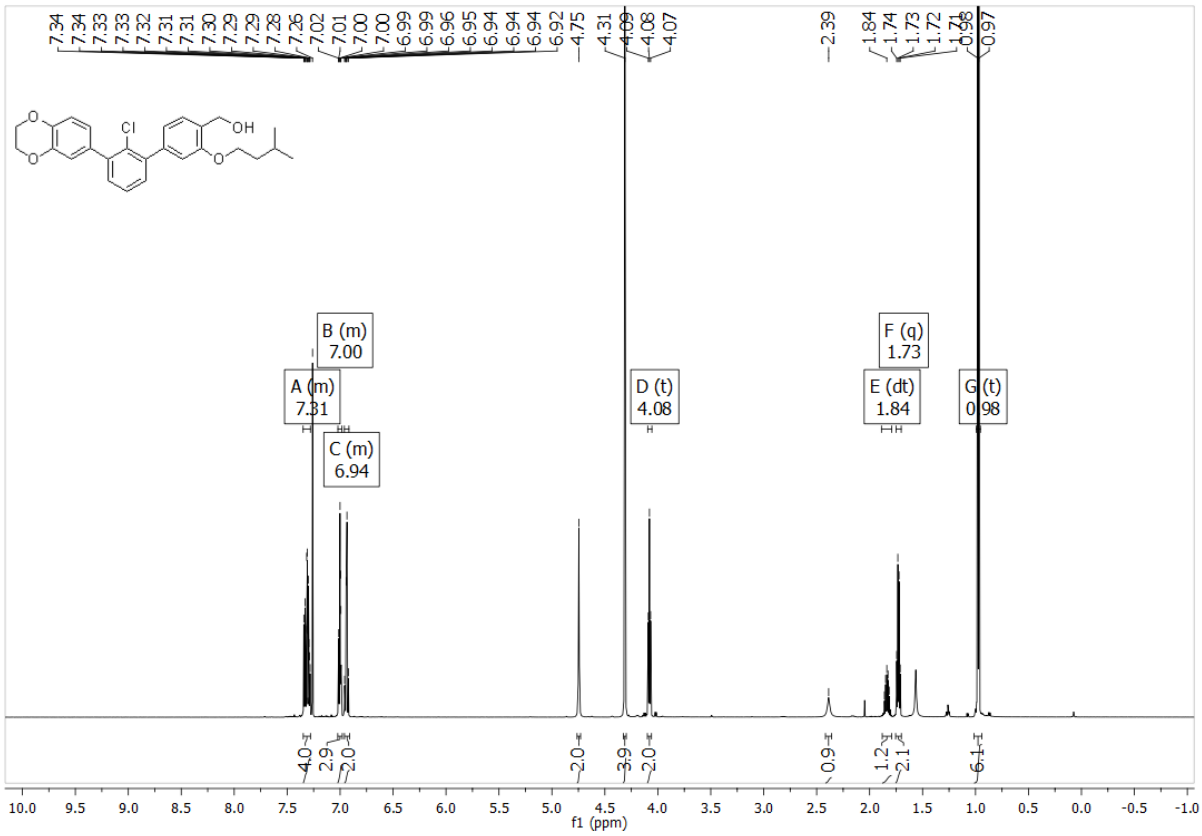


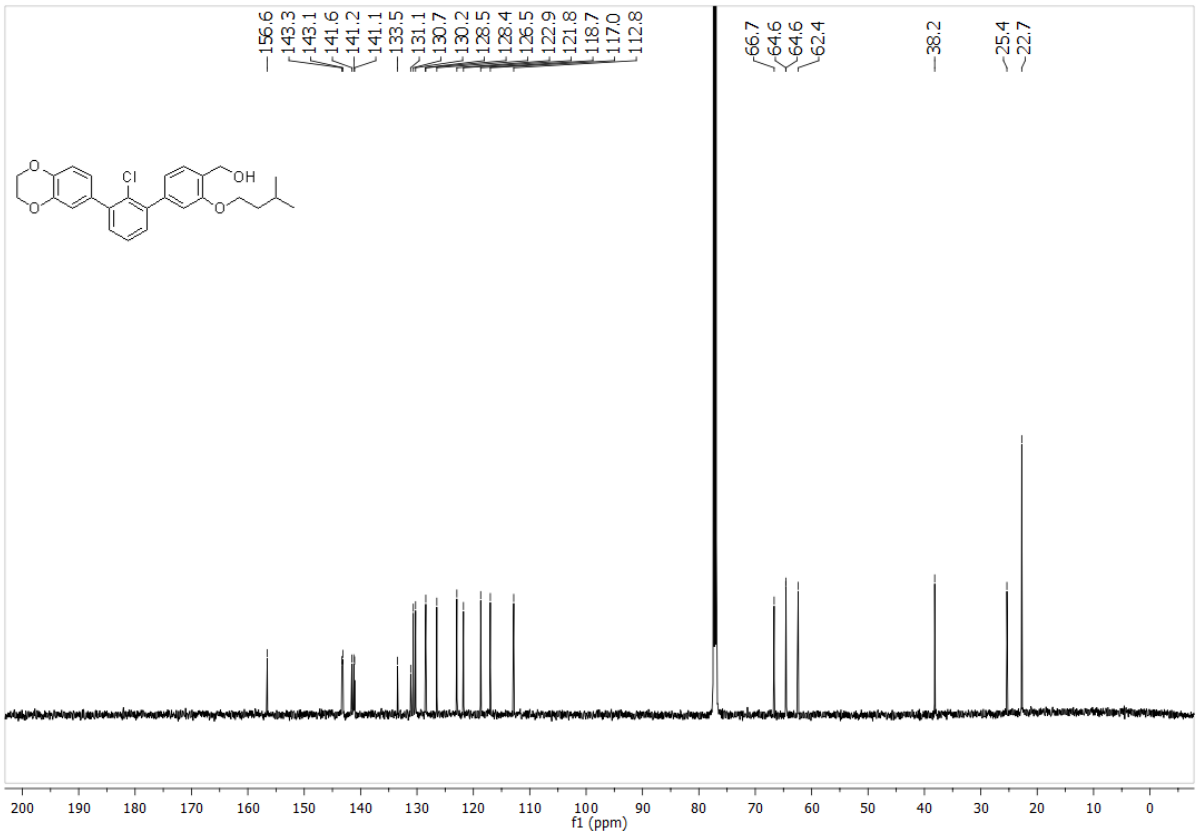
4m. (3'-(Benzo-1,4-dioxan-6-yl)-2'-chloro-3-isopropoxy-[1,1'-biphenyl]-4-yl)methanol



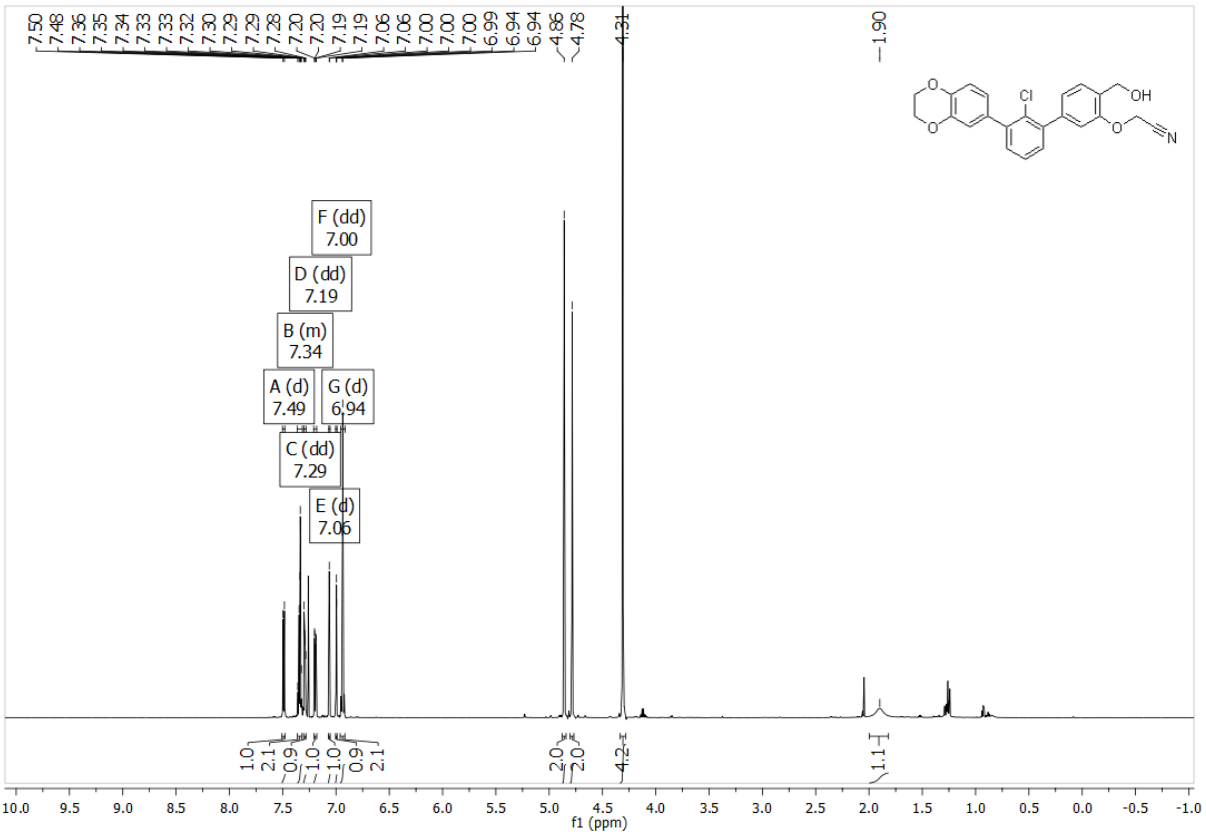


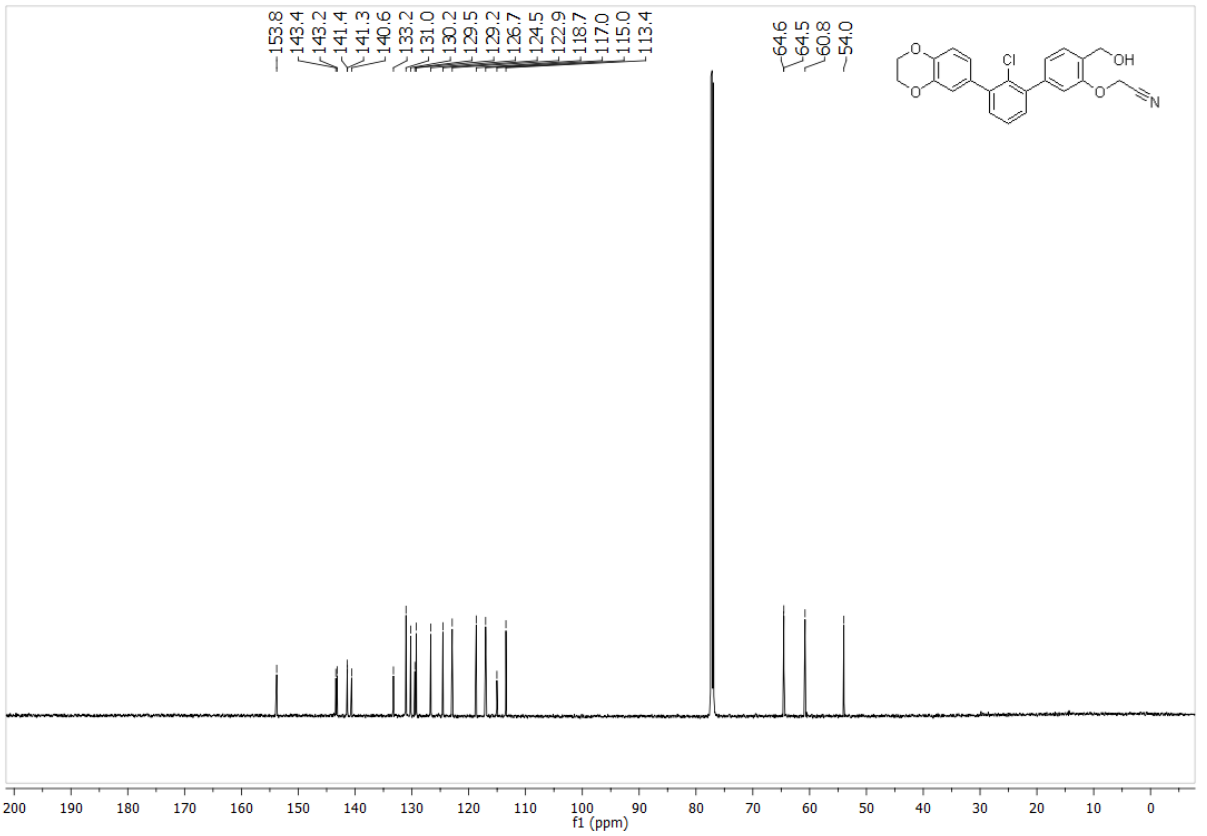
4n. (3'-(benzo-1,4-dioxan-6-yl)-2’-chloro-3-isopentyloxy-[1,1'-biphenyl]-4-yl)methanol



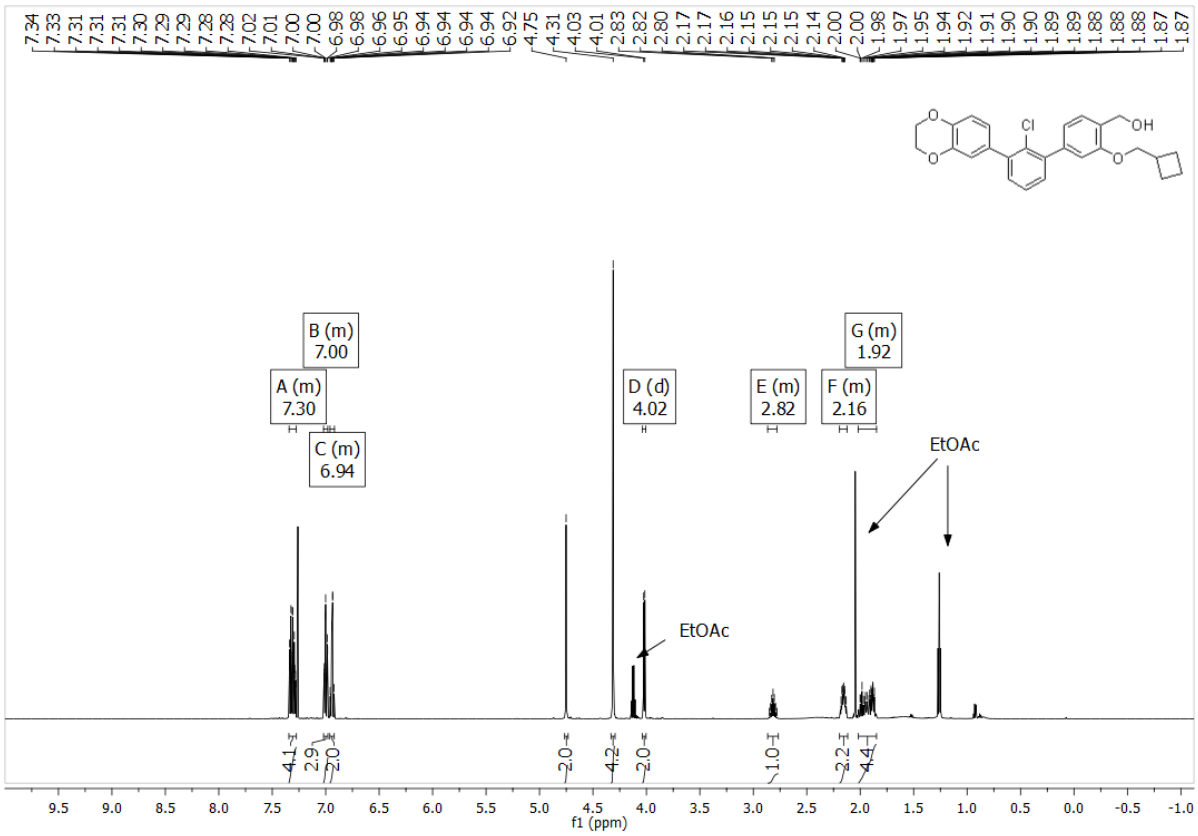


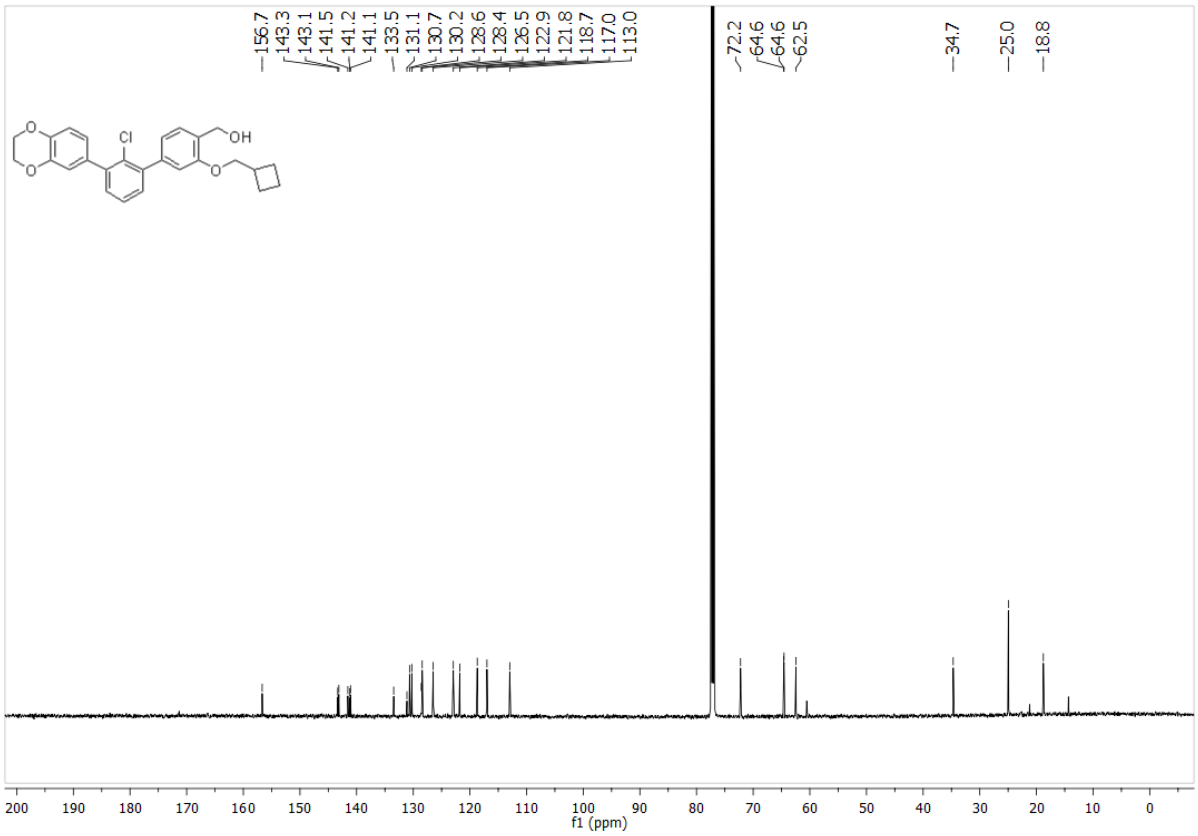
4o. 2-((3'-(Benzo-1,4-dioxan-6-yl)-2'-chloro-4-(hydroxymethyl)-[1,1'-biphenyl]-3-yl)oxy)acetonitrile



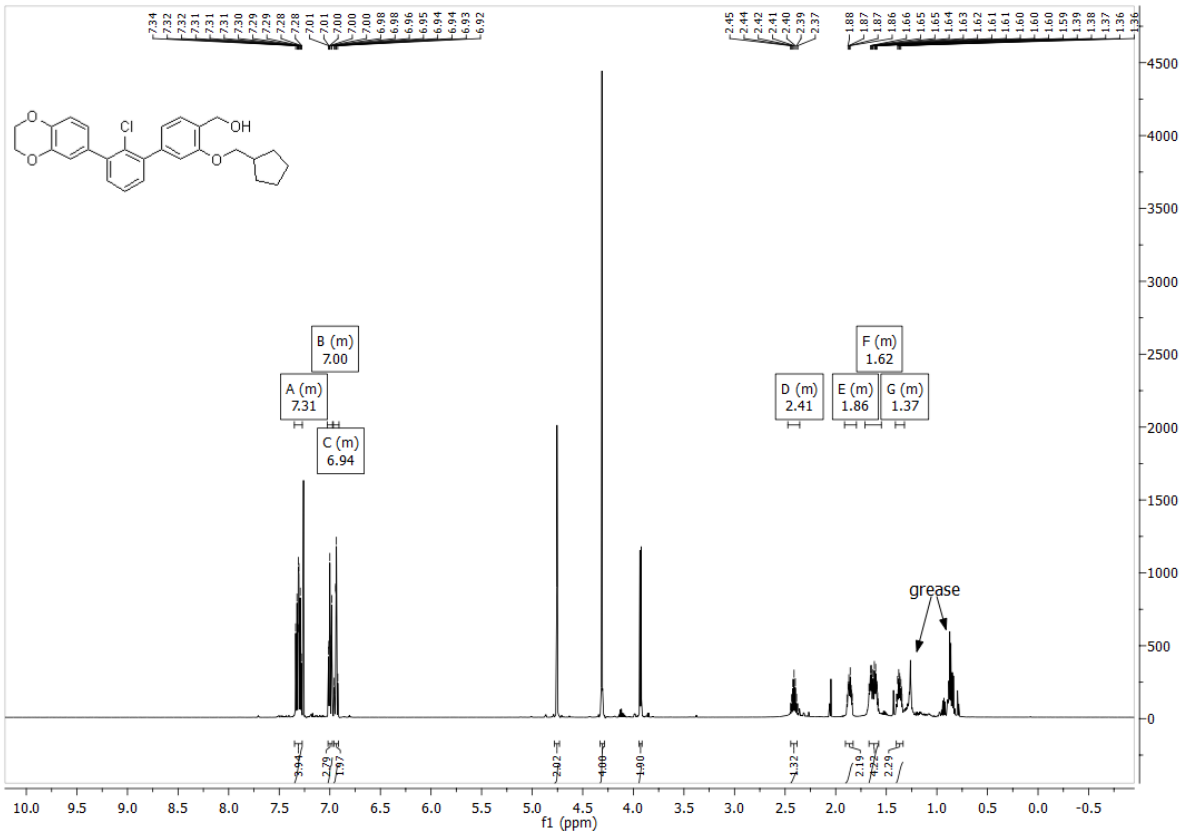


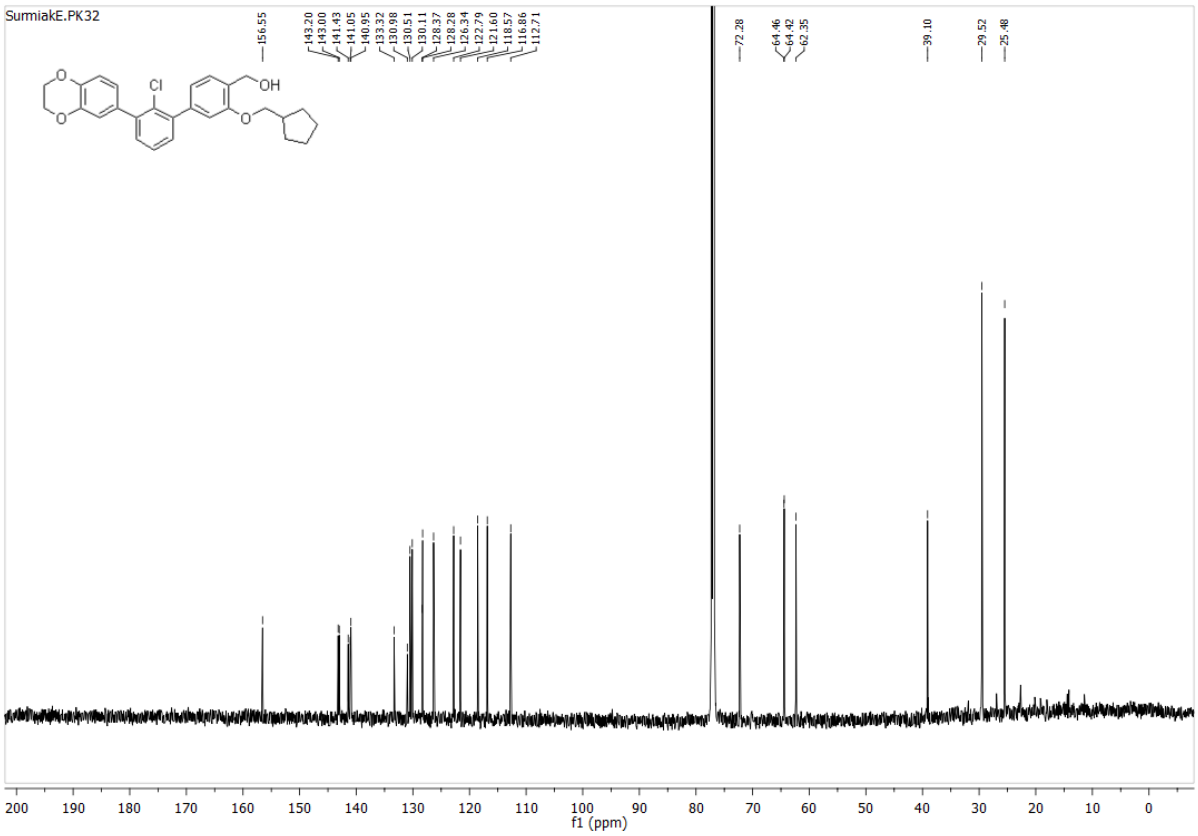
4p.(3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-cyclobutylmethoxy-[1,1'-biphenyl]-4-yl)methanol



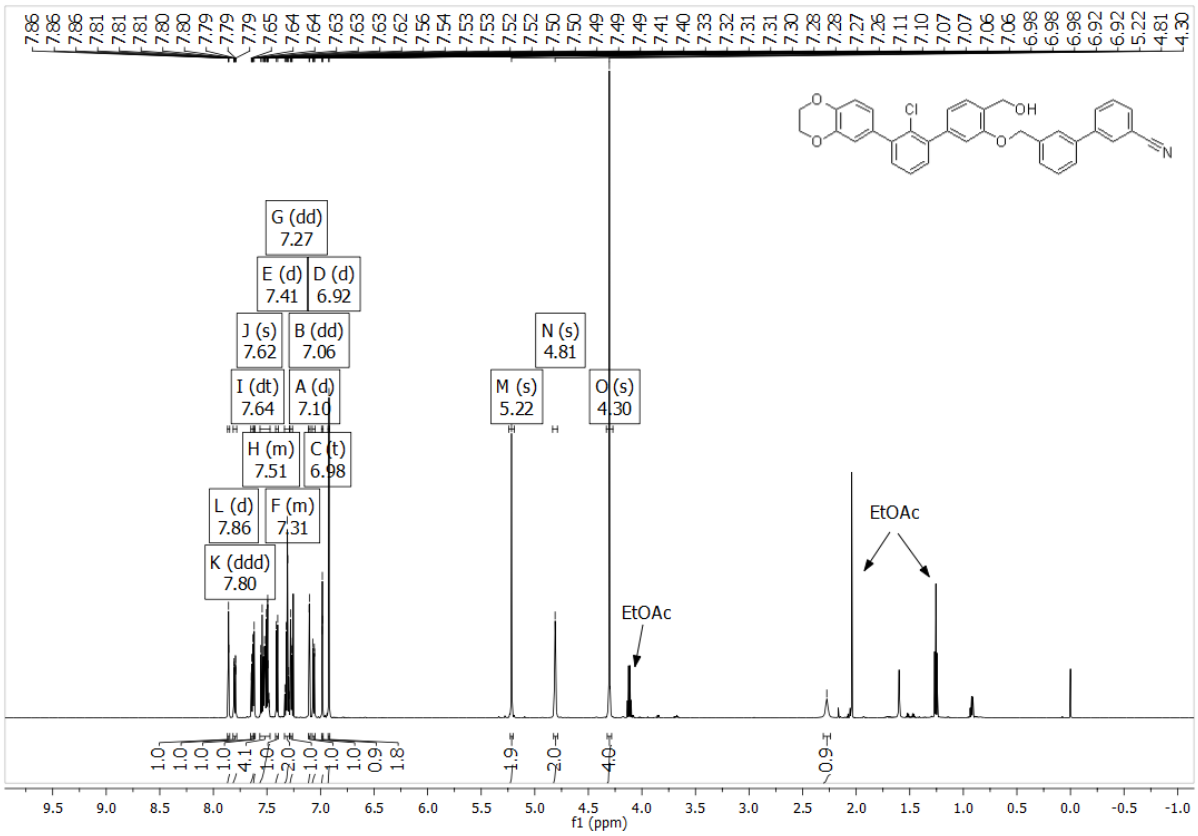


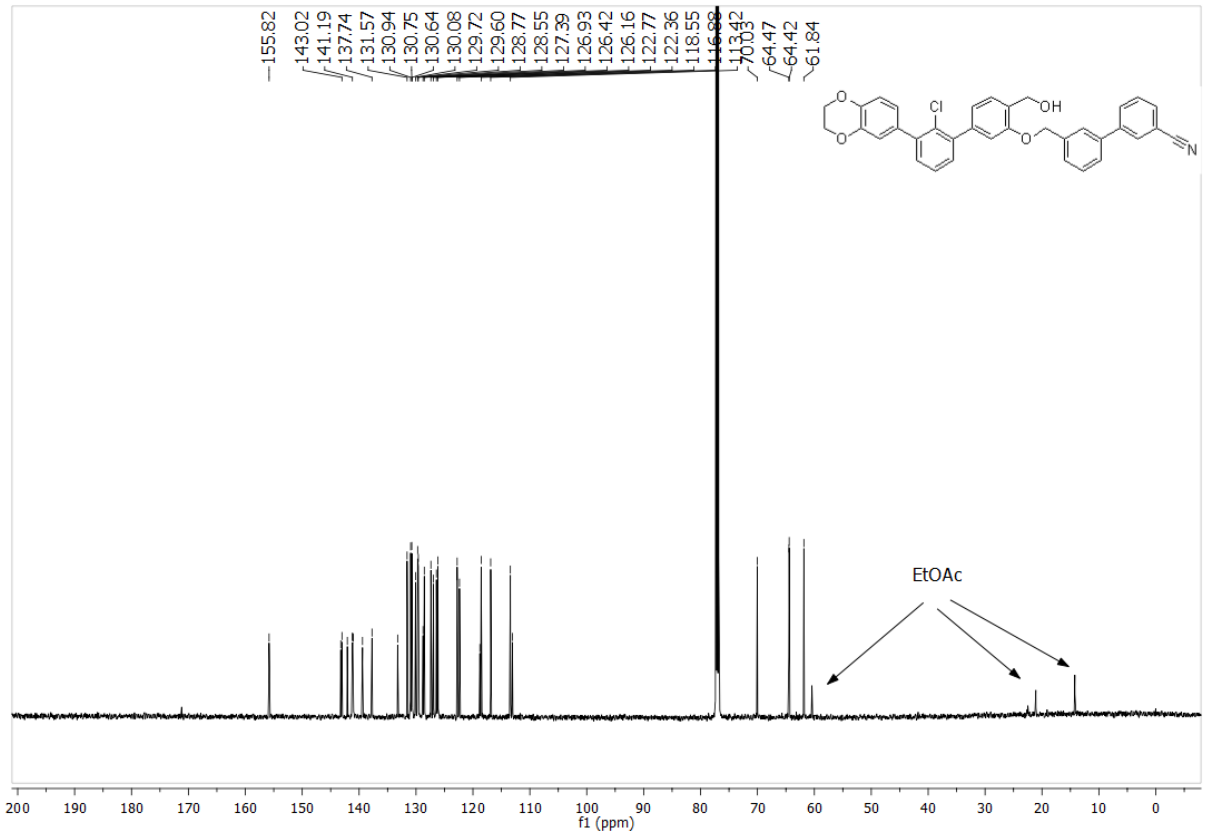
4q. (3'-(Benzo-1,4-dioxan-6-yl)-2’-chloro-3-cyclopentylmethoxy-[1,1'-biphenyl]-4-yl)methanol



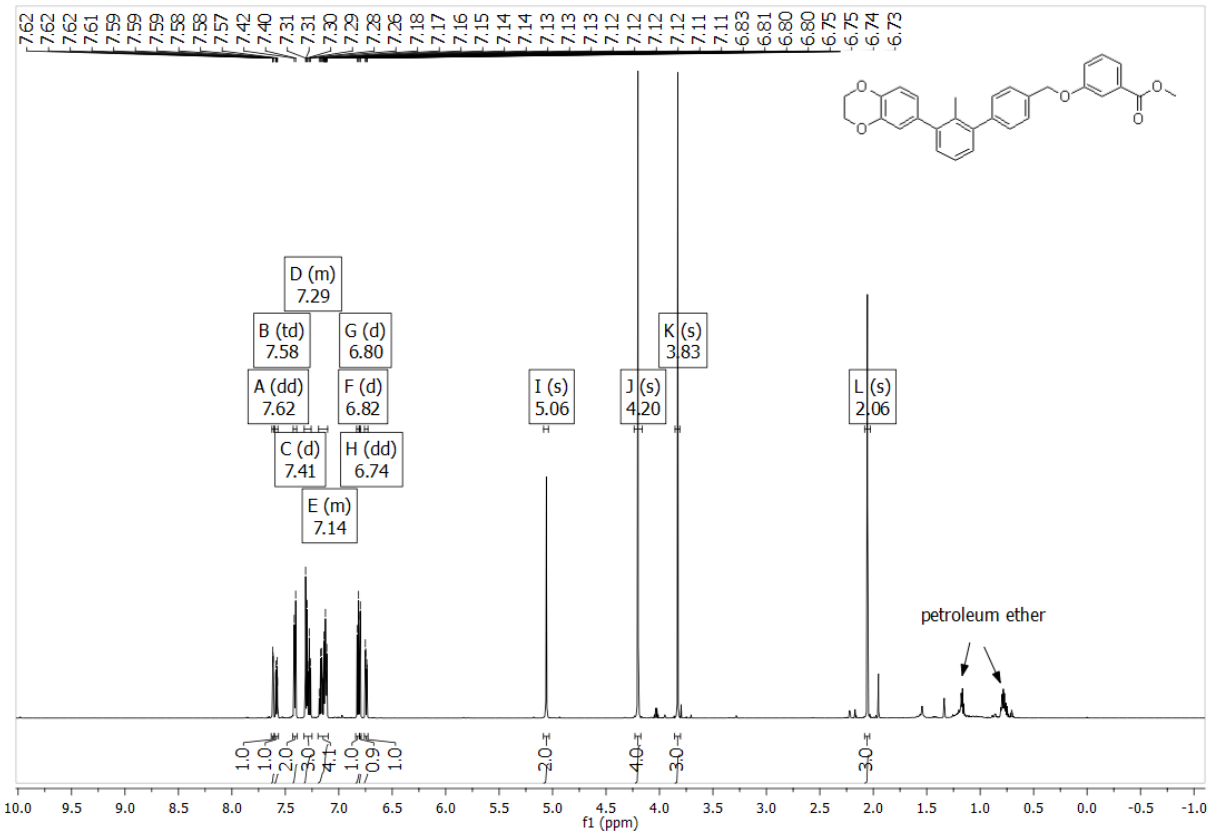


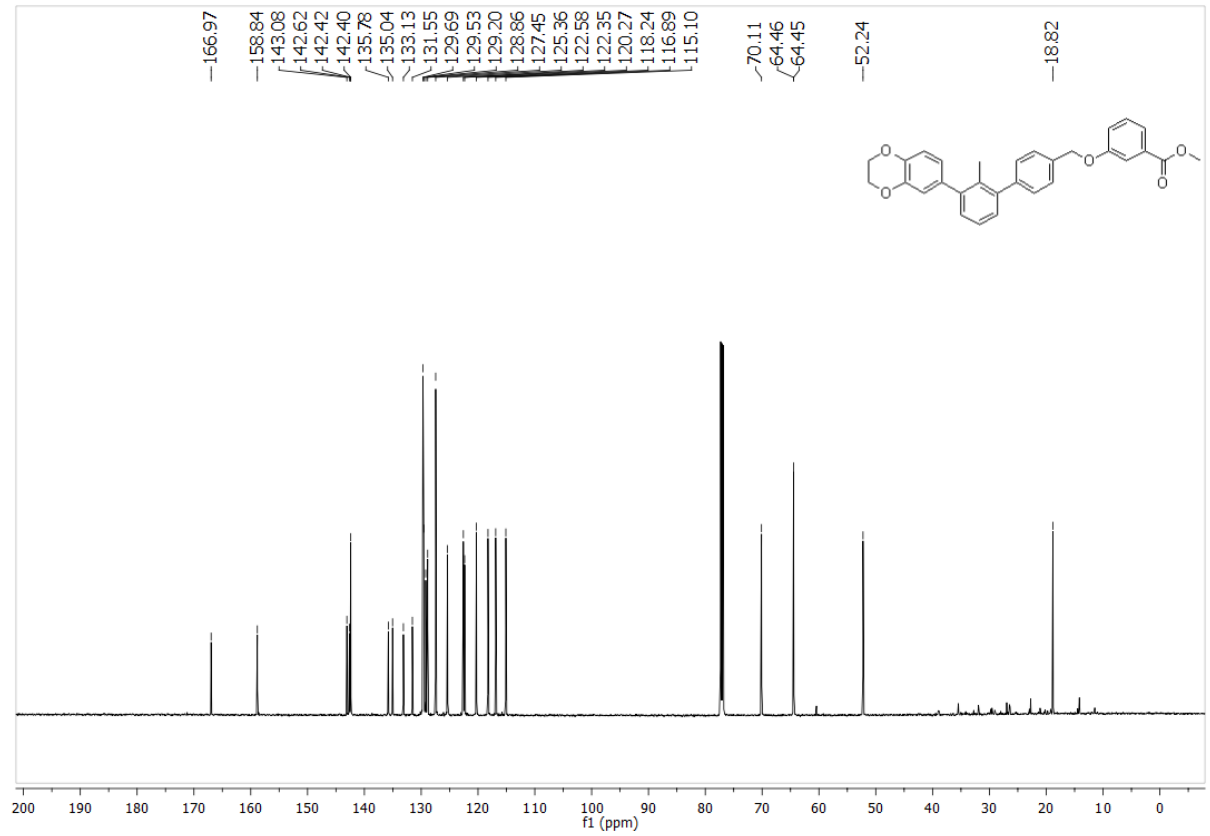
4r. 3'-(((2'-Chloro-3'-(benzo-1,4-dioxan-6-yl)-4-(hydroxymethyl)-[1,1'-biphenyl]-3-yl)oxy)methyl)-[1,1'-biphenyl]-3-carbonitrile



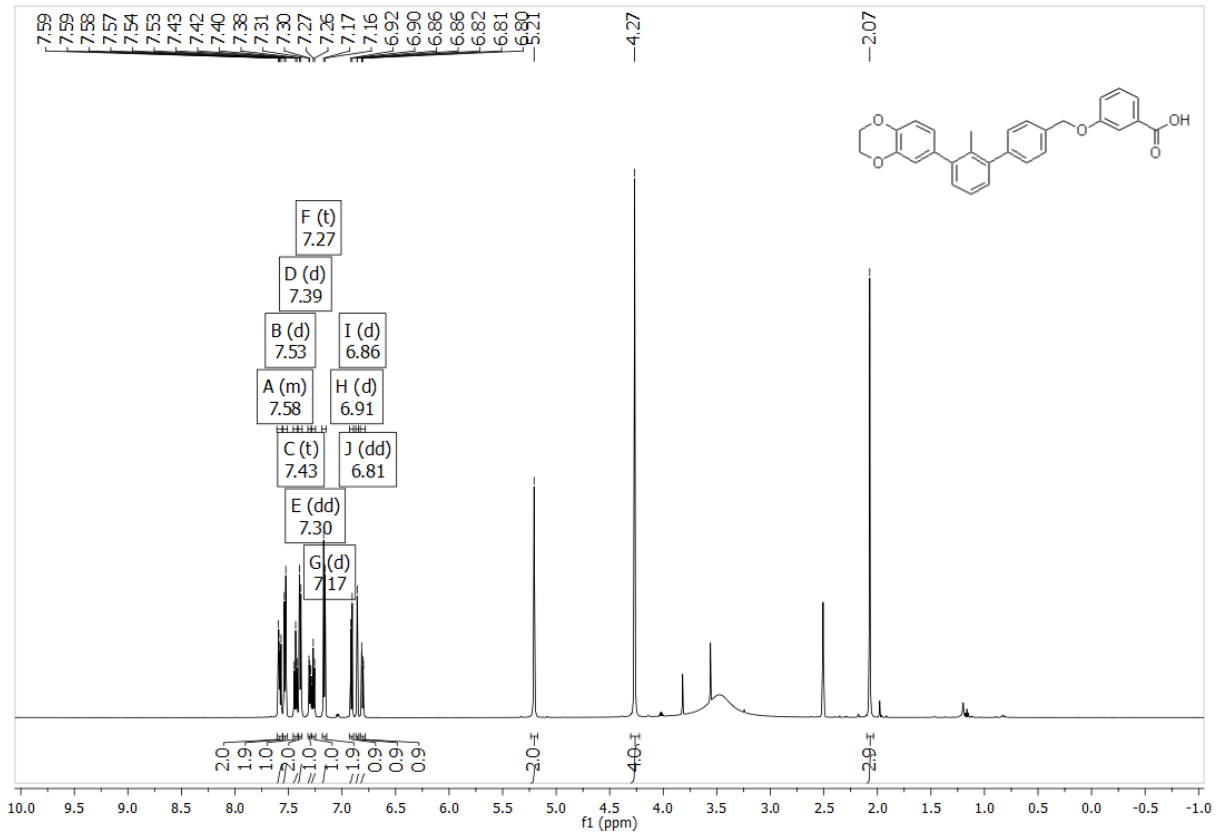


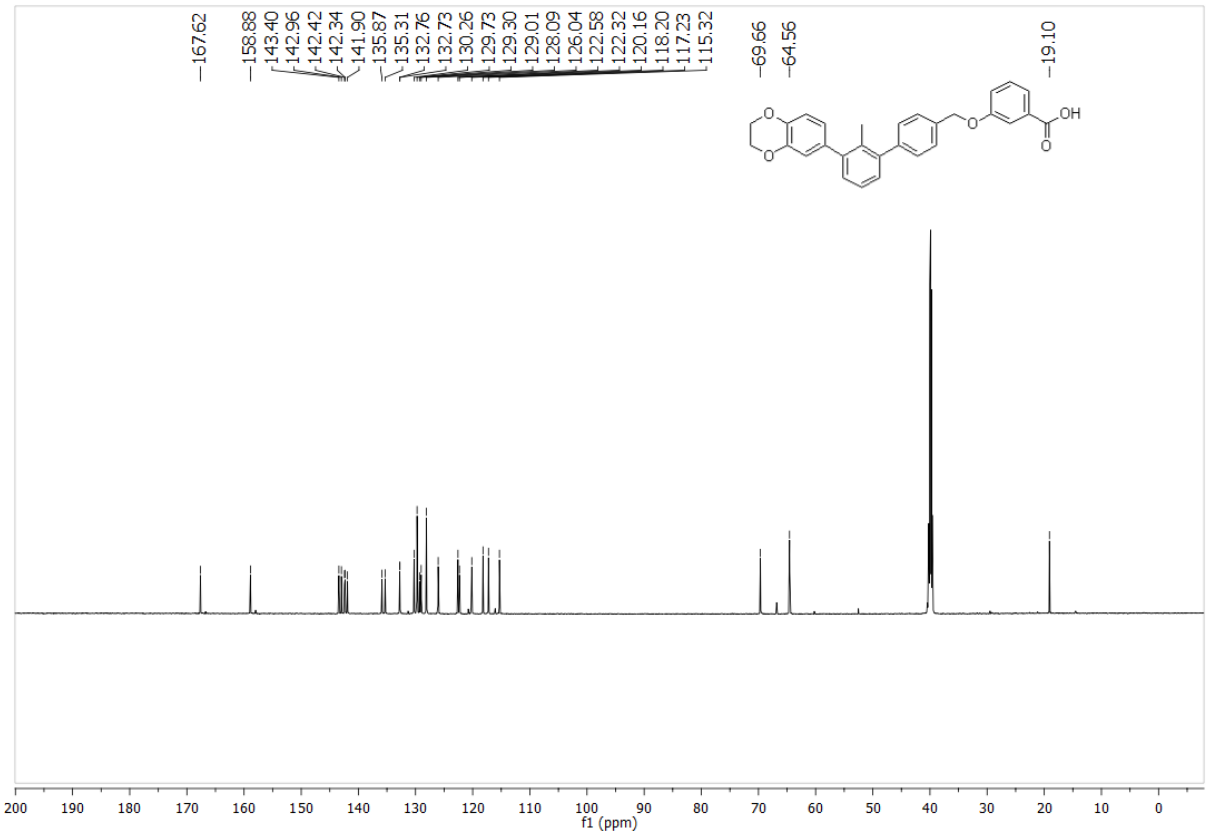
5a. methyl 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)benzoate



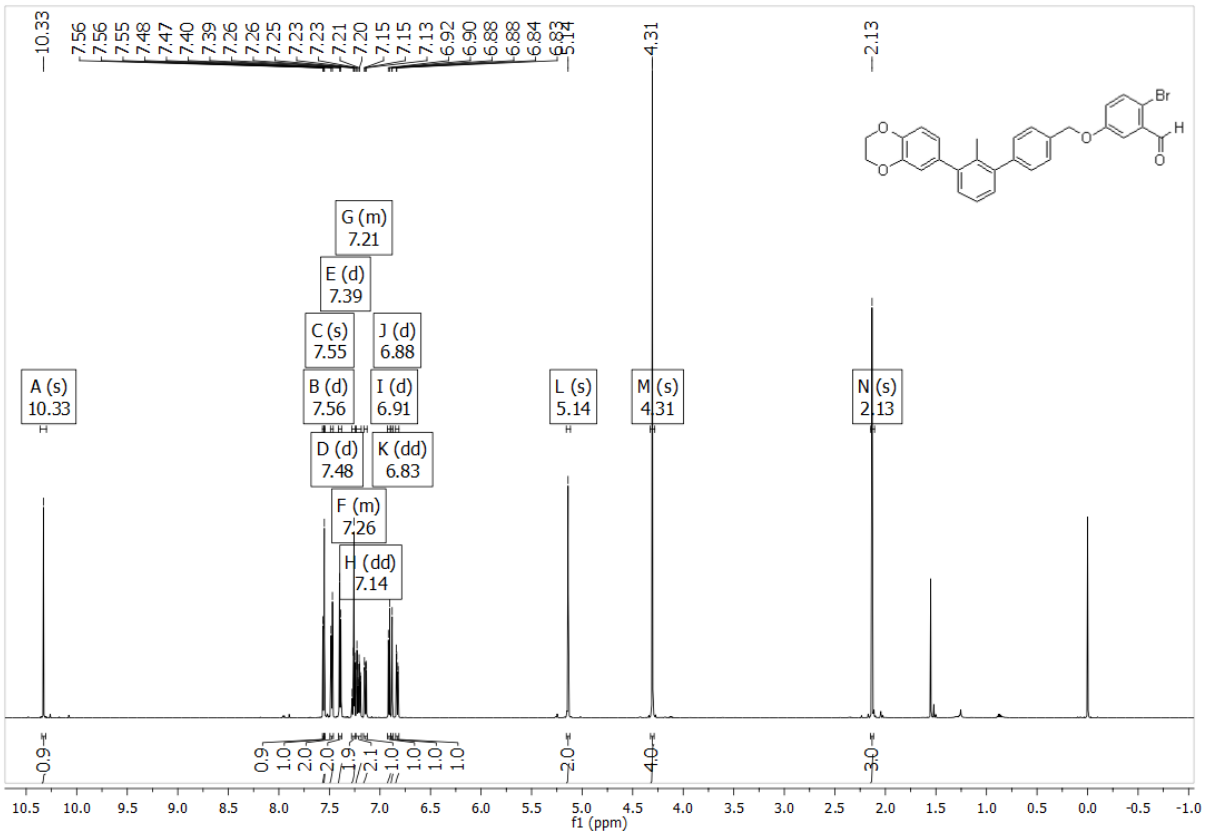


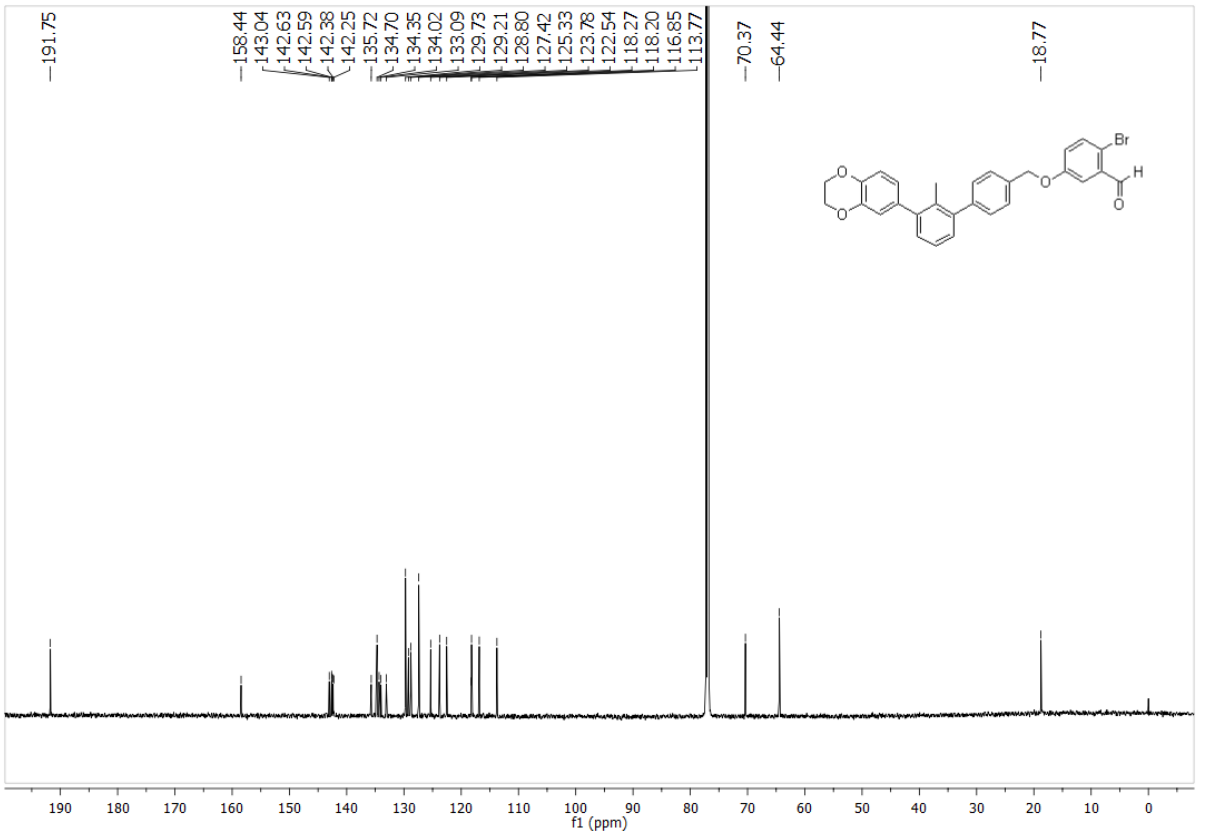
5b. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)benzoic acid



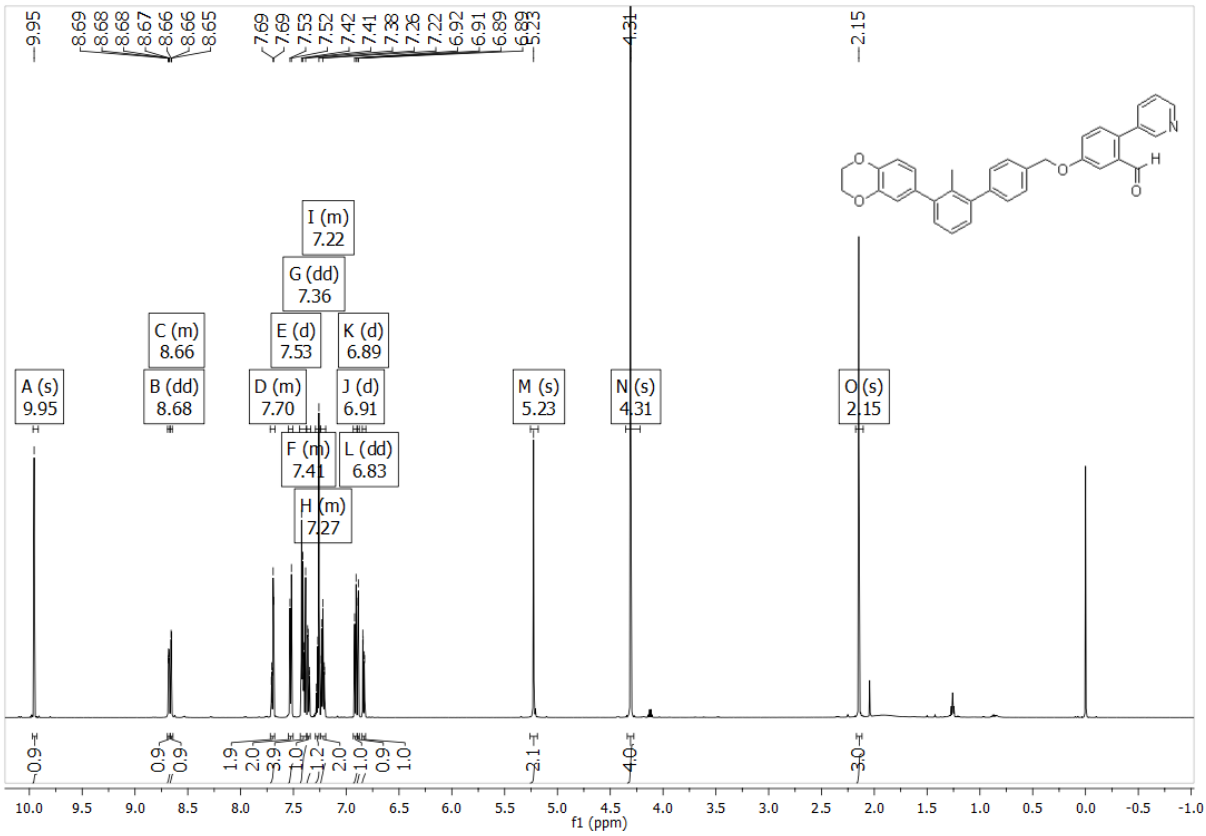


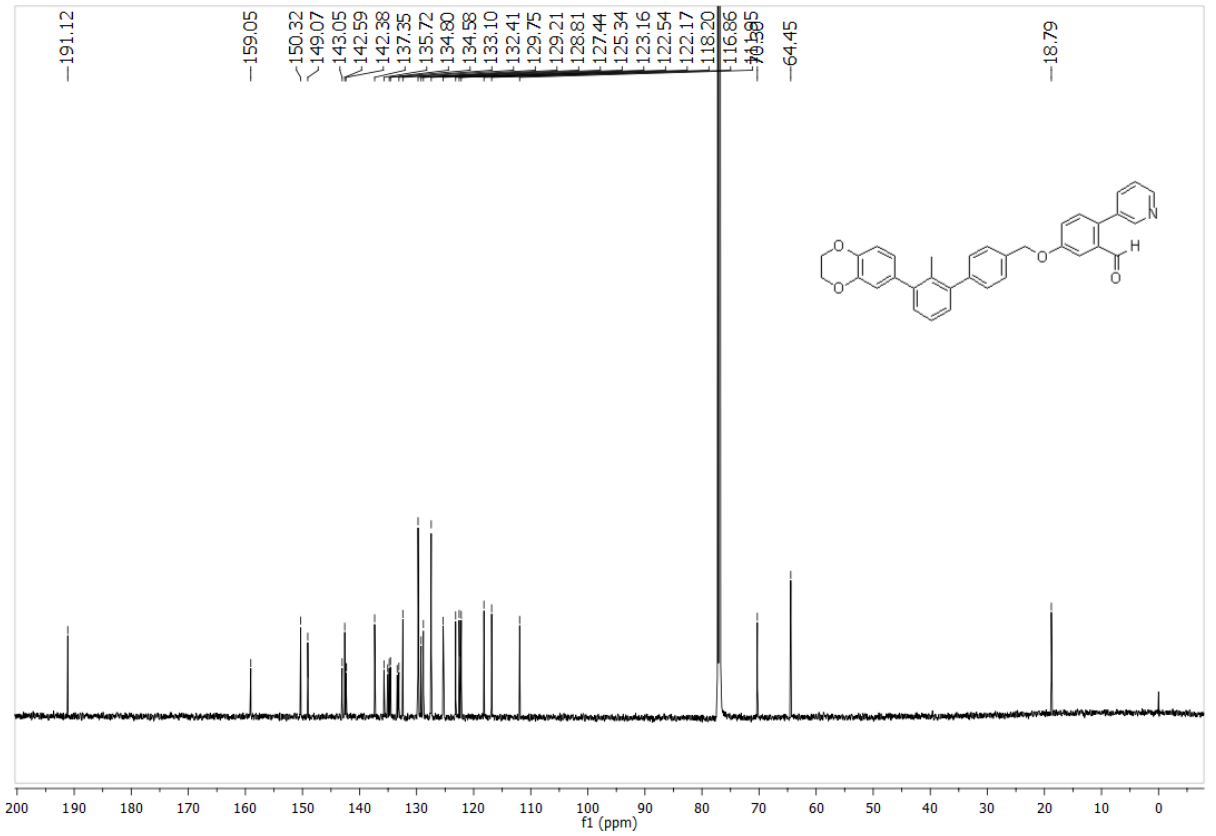
5c. 2-Bromo-5-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)benzaldehyde



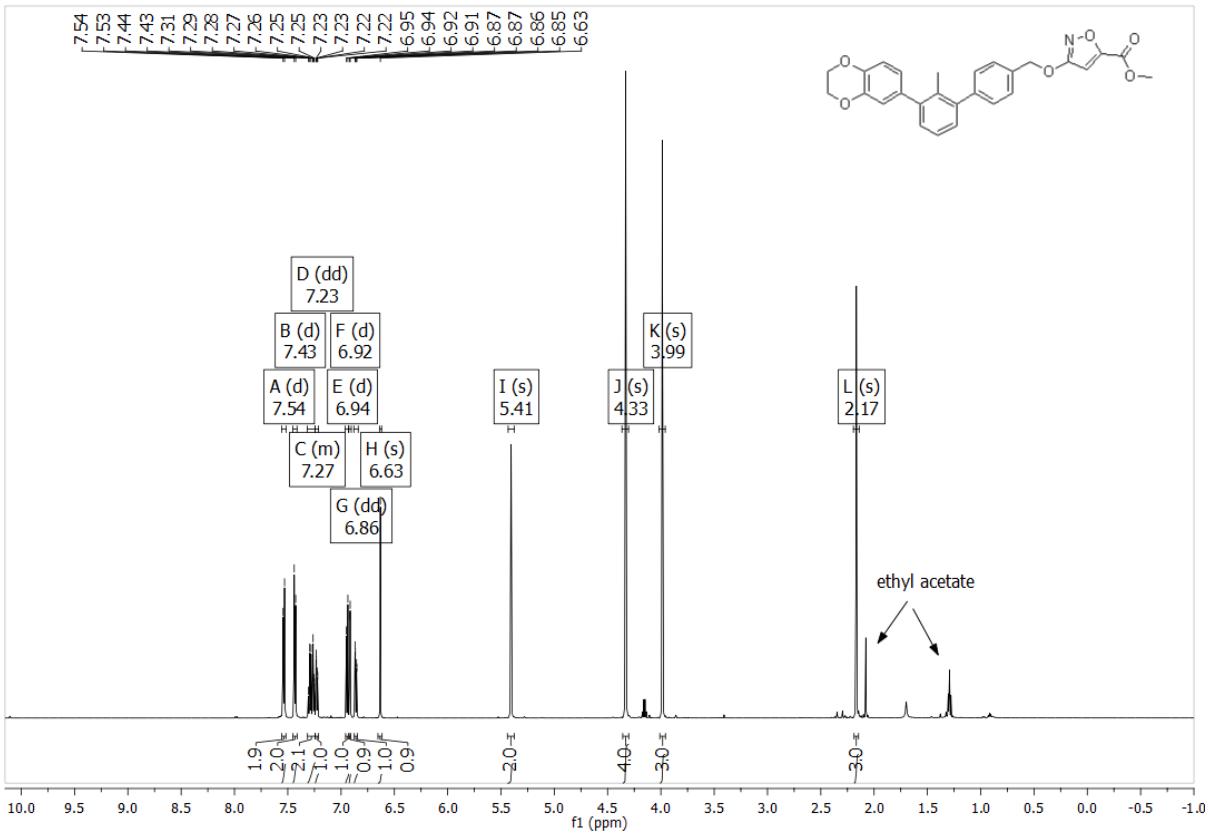


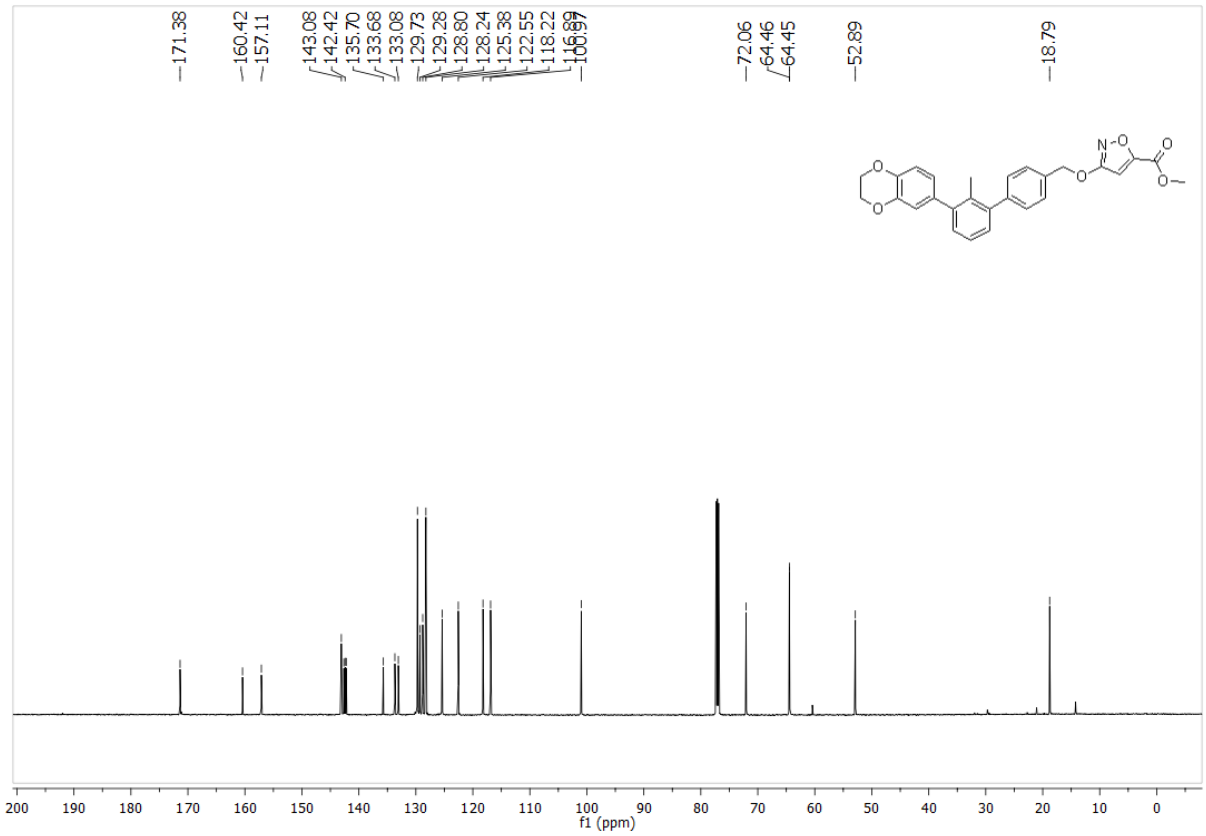
5d. 5-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)-2-(pyridin-3-yl)benzaldehyde



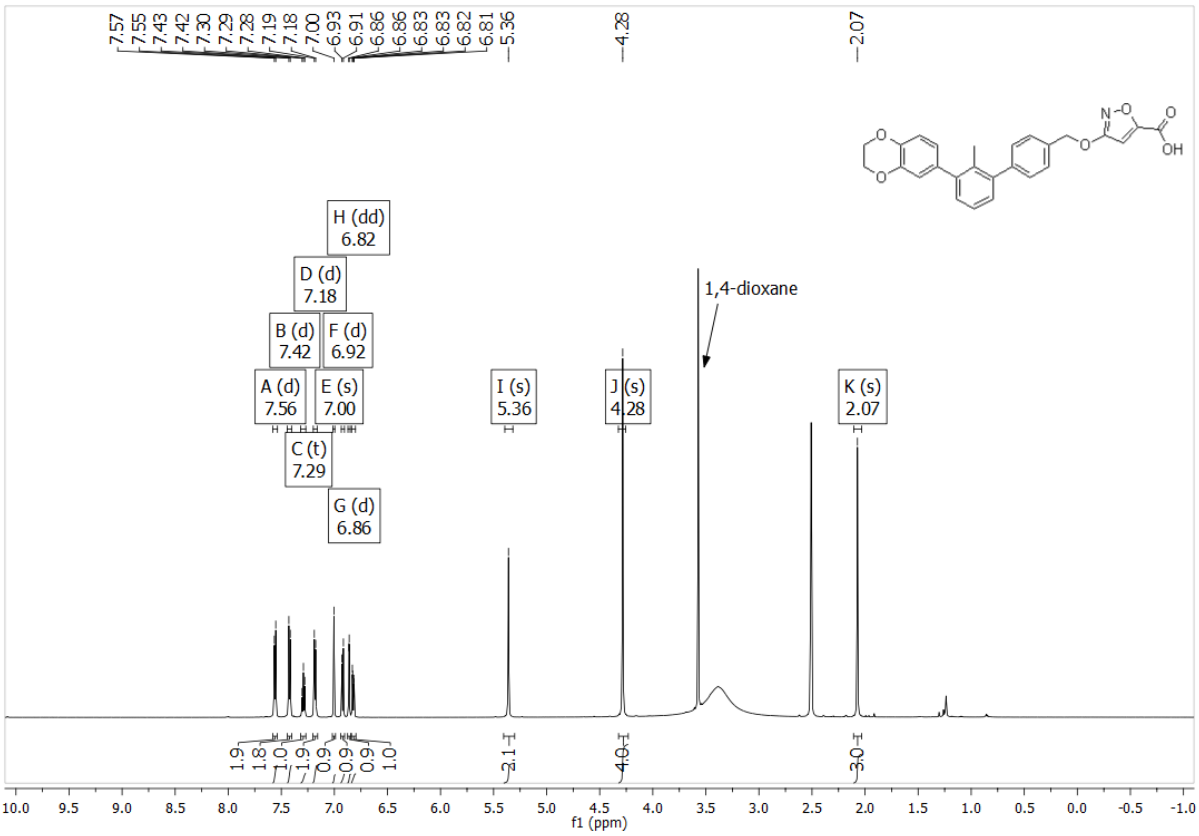


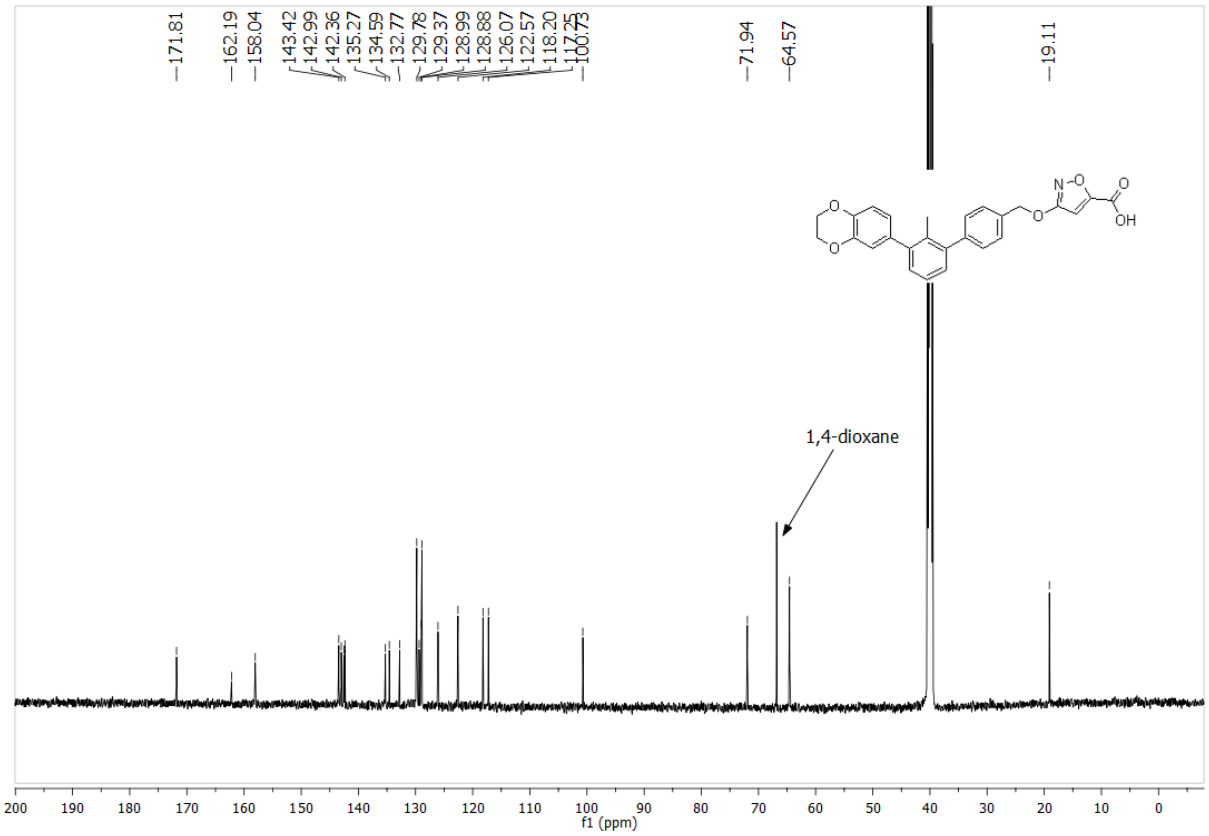
5e. methyl 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)isoxazole-5-carboxylate



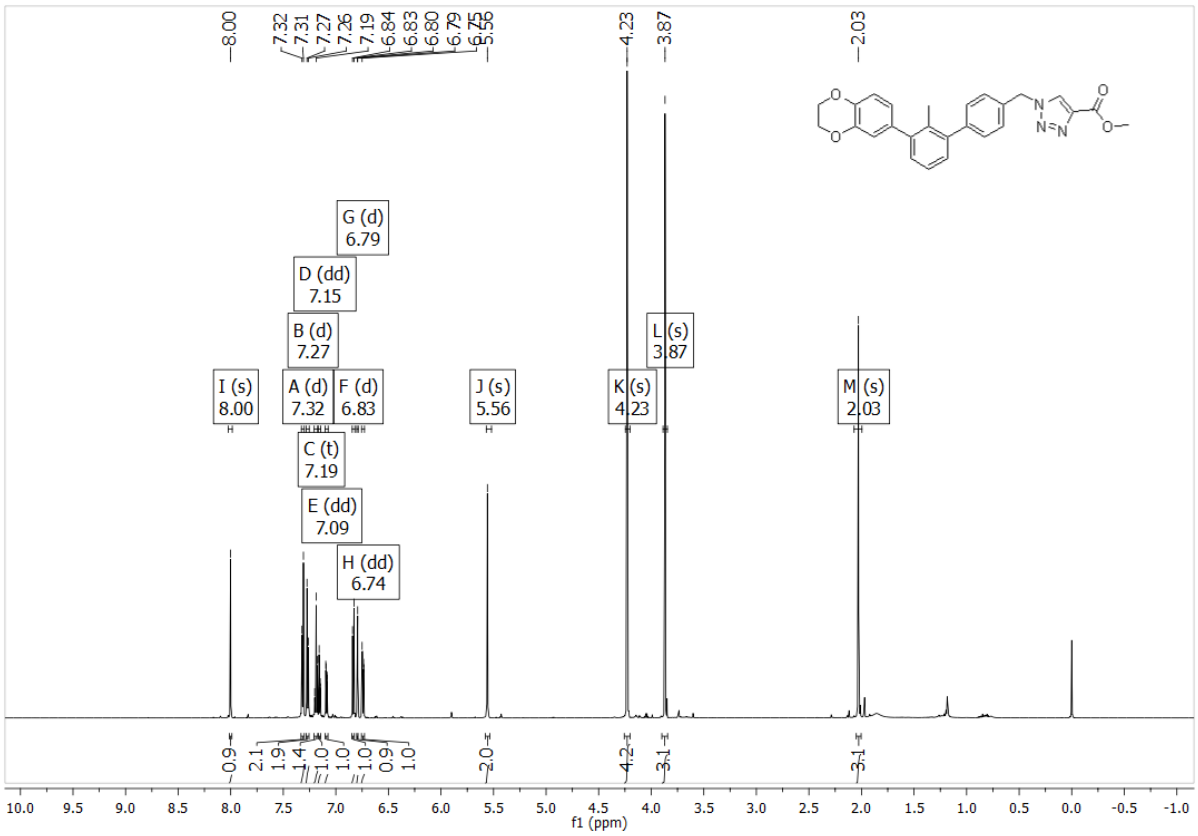


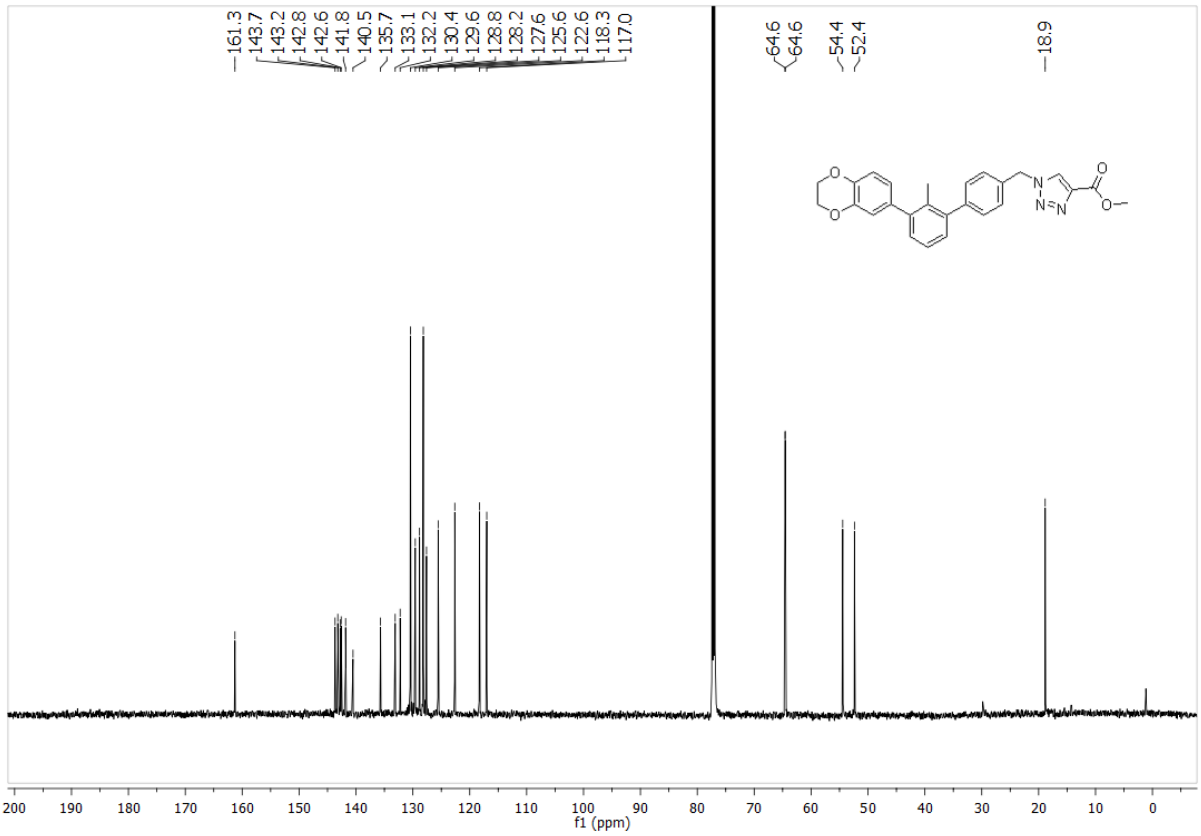
5f. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)isoxazole-5-carboxylic acid



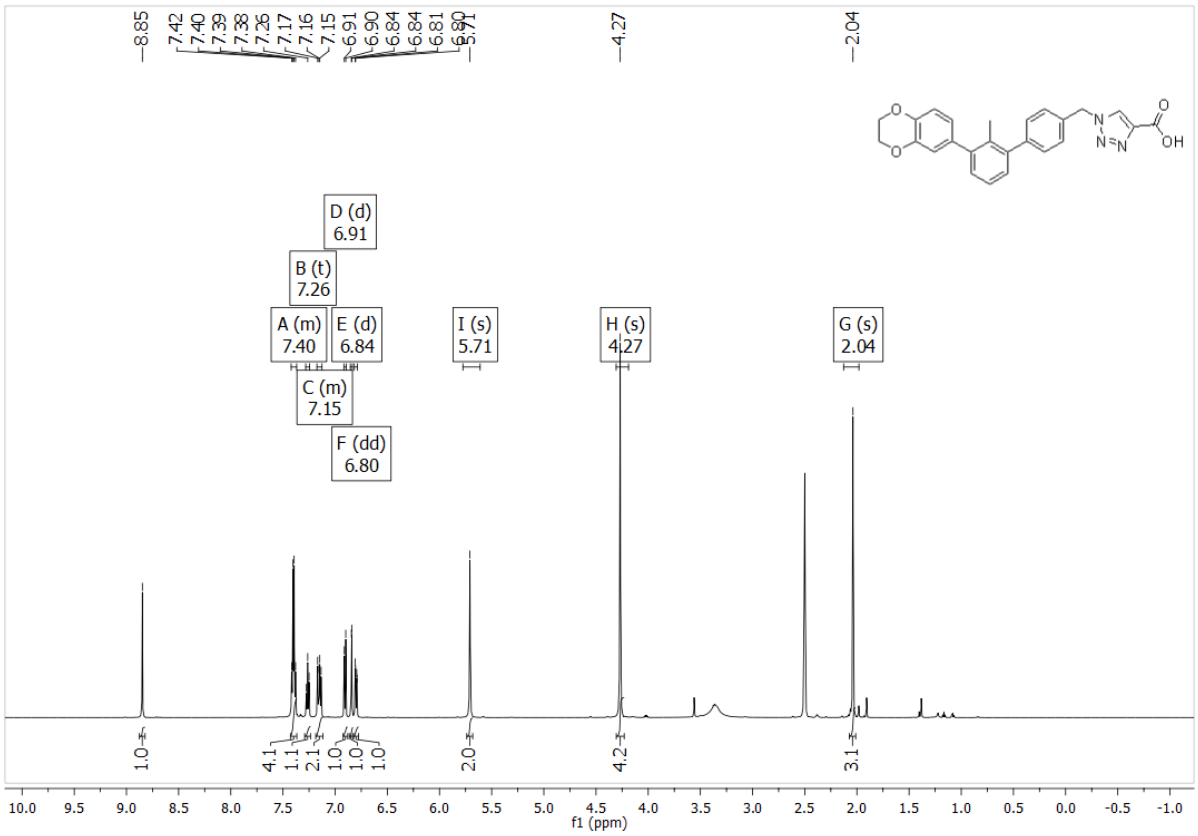


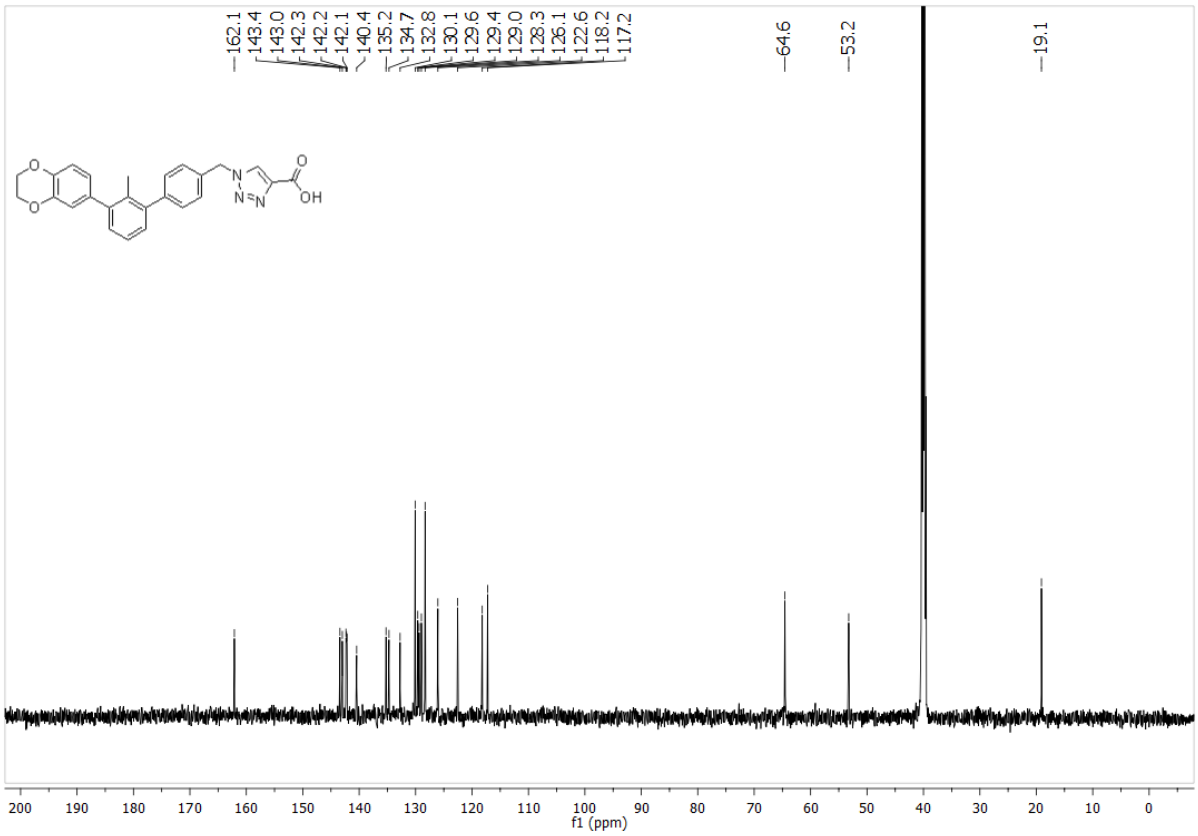
5g. Methyl 1-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)-1H-1,2,3-triazole-4-carboxylate



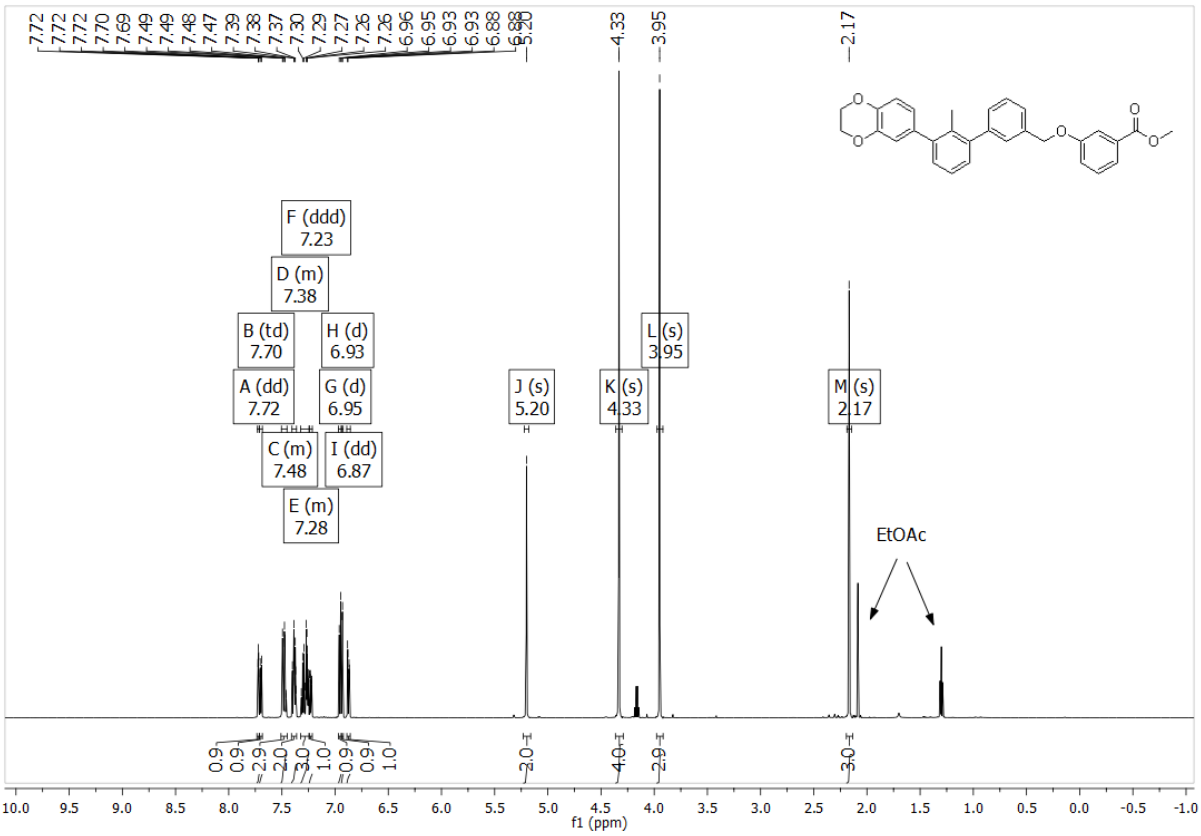


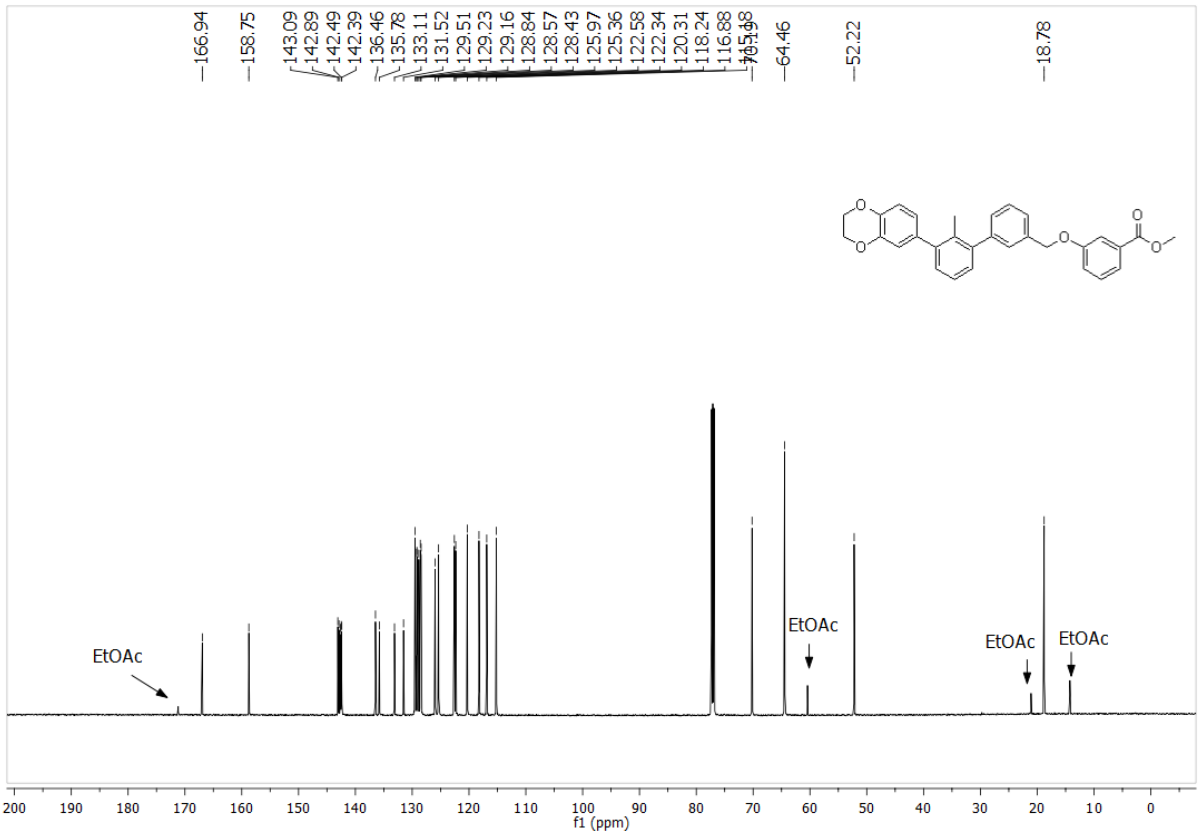
5h. 1-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid



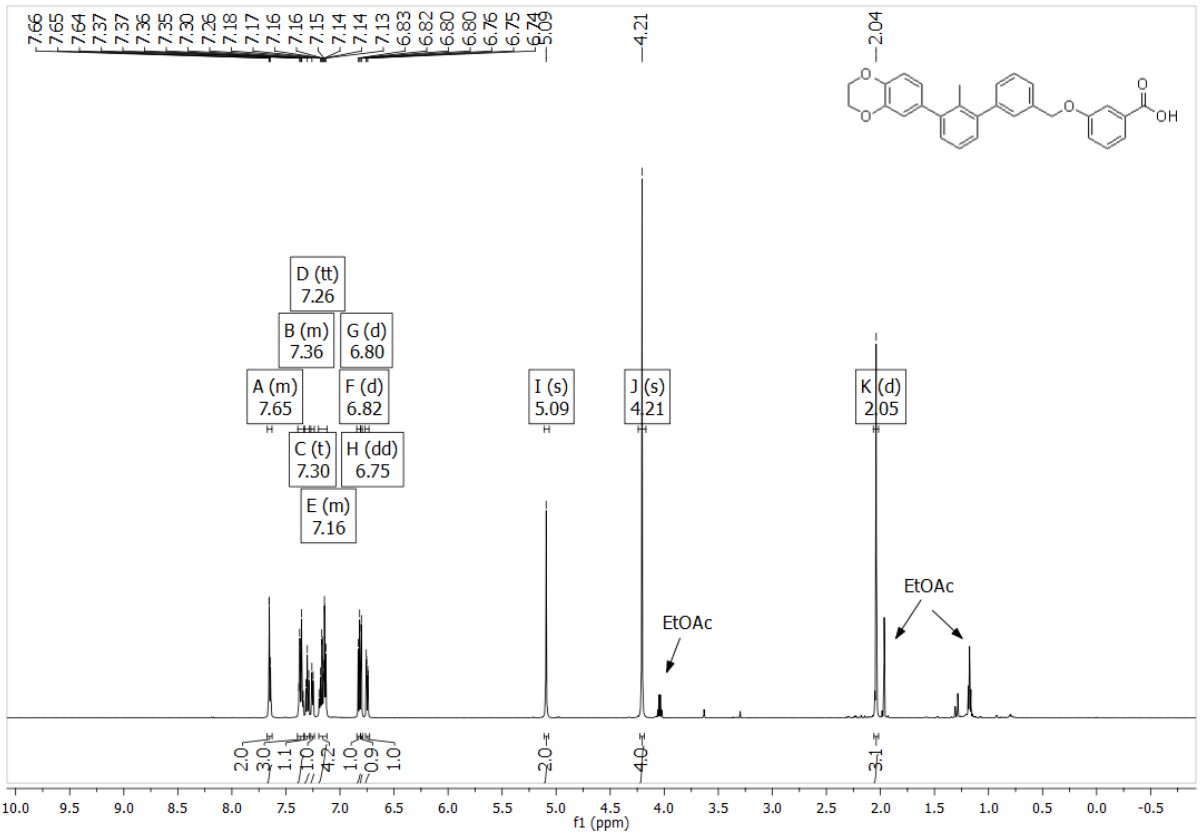


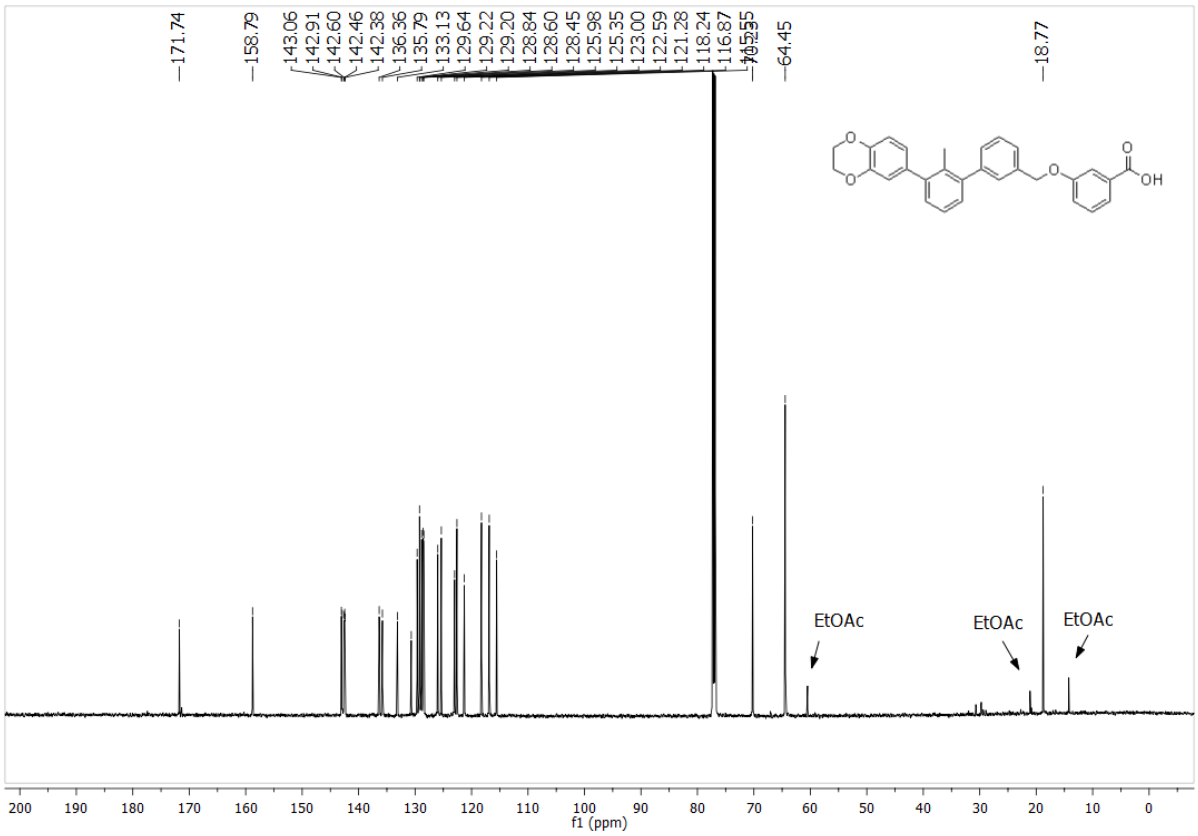
5i. methyl 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)benzoate



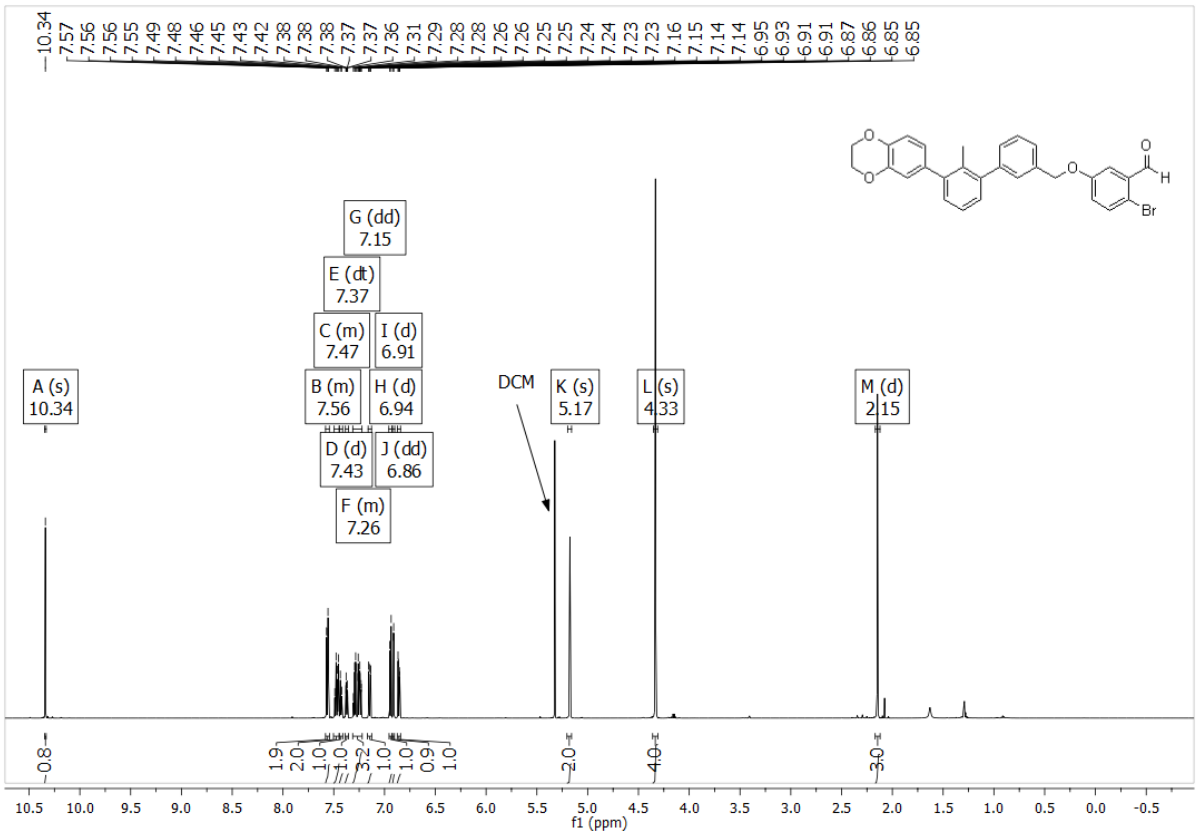


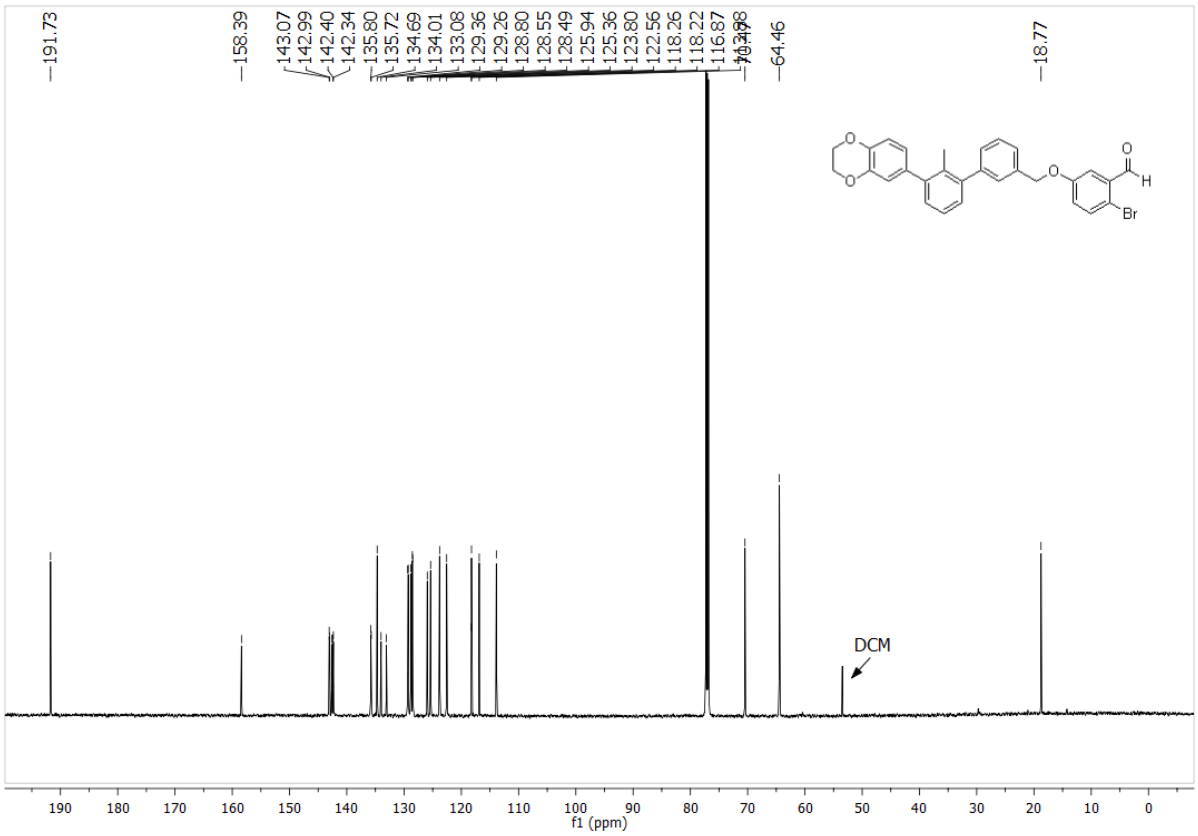
5j. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)benzoic acid



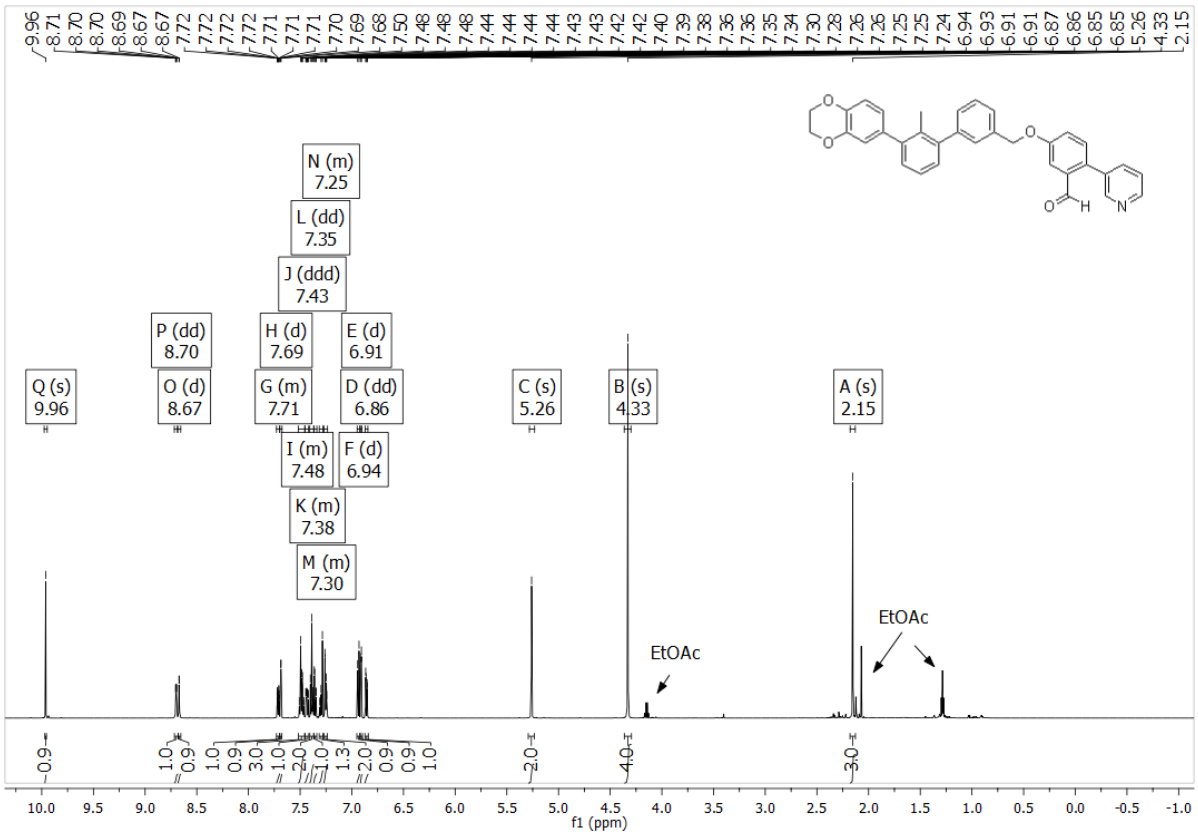


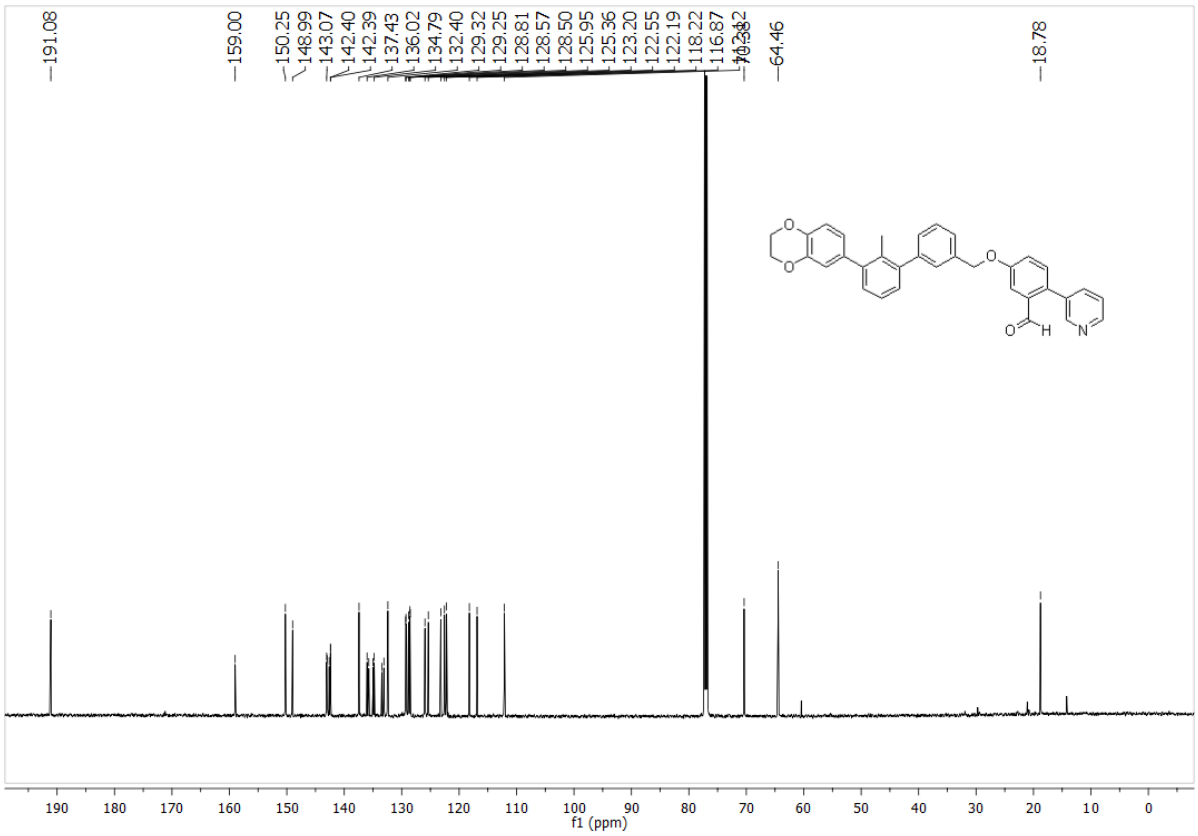
5k. 2-bromo-5-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)benzaldehyde



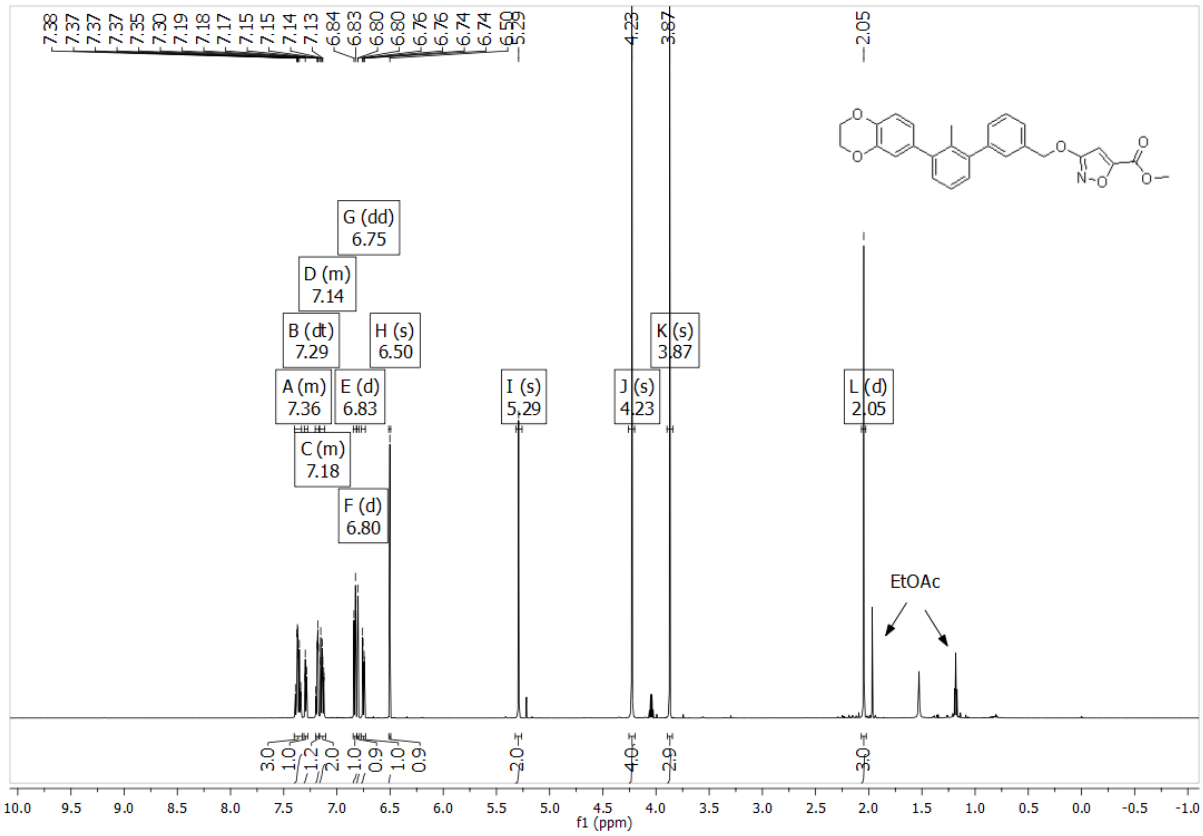


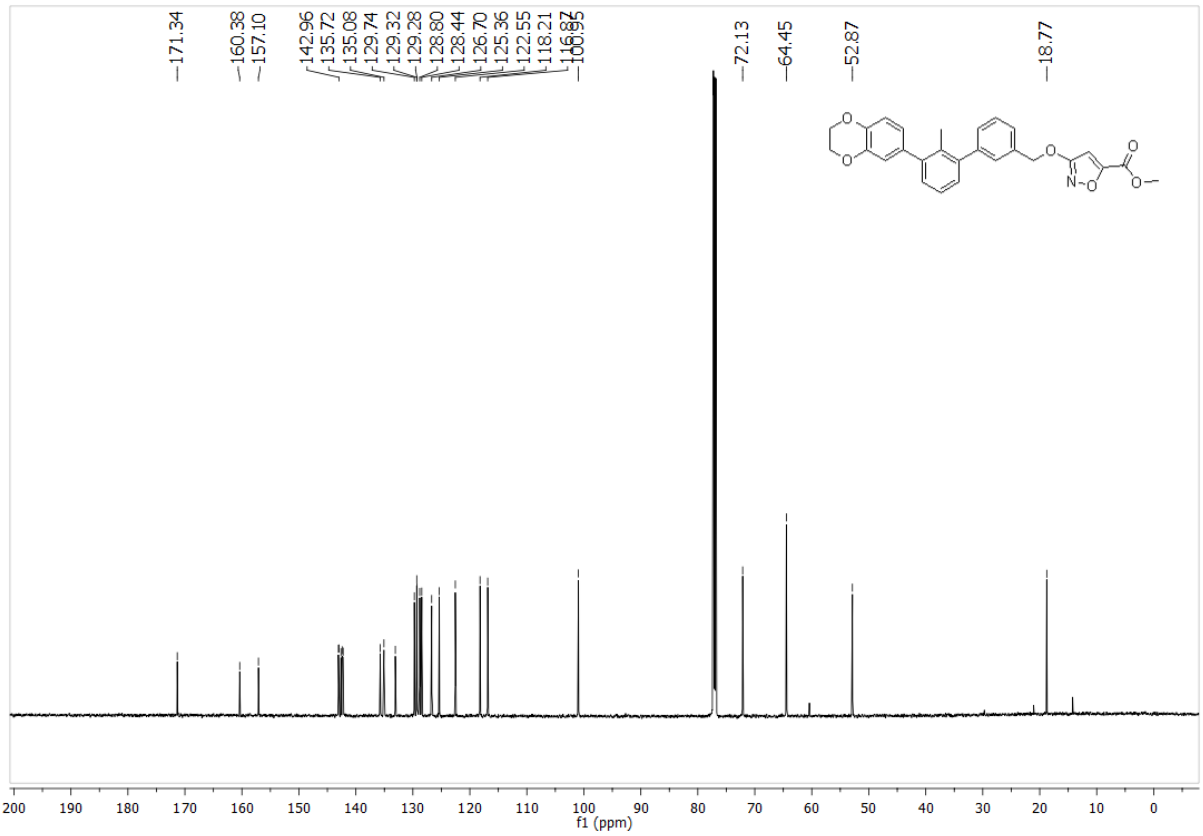
5l. 5-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)-2-(pyridin-3-yl)benzaldehyde



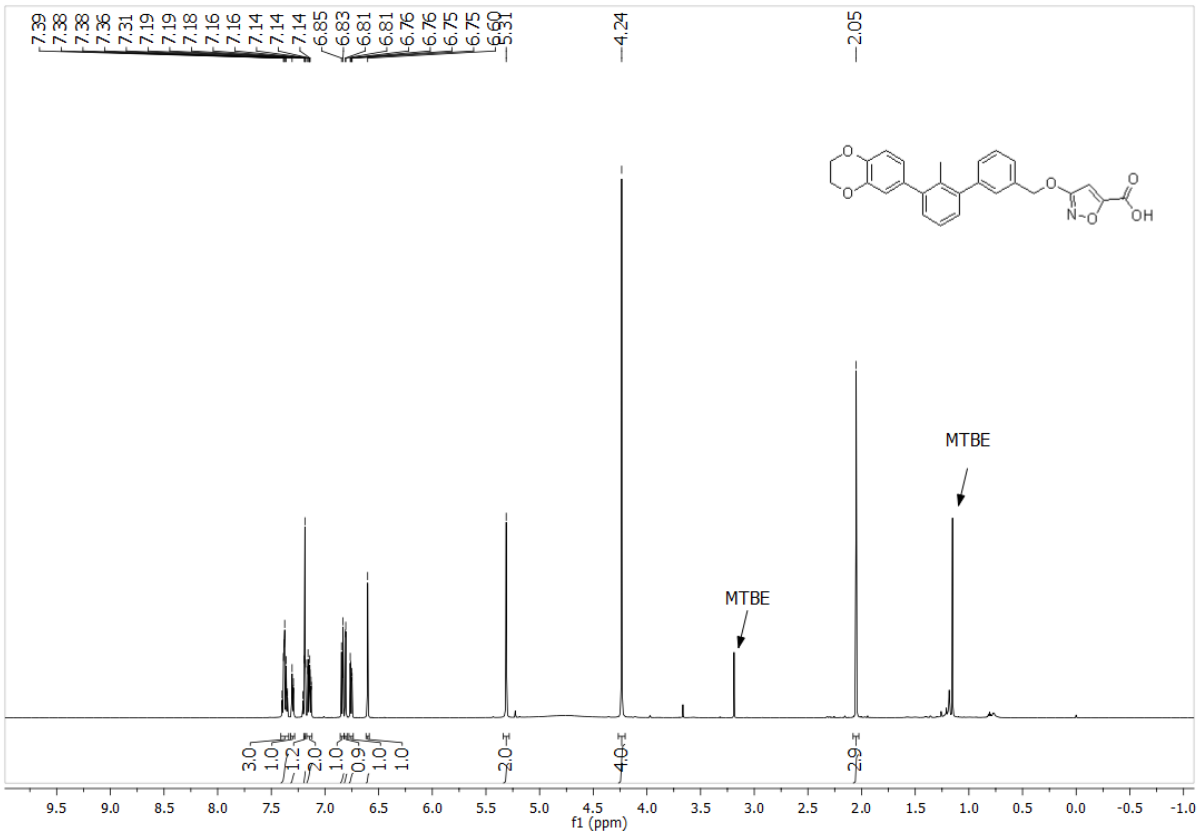


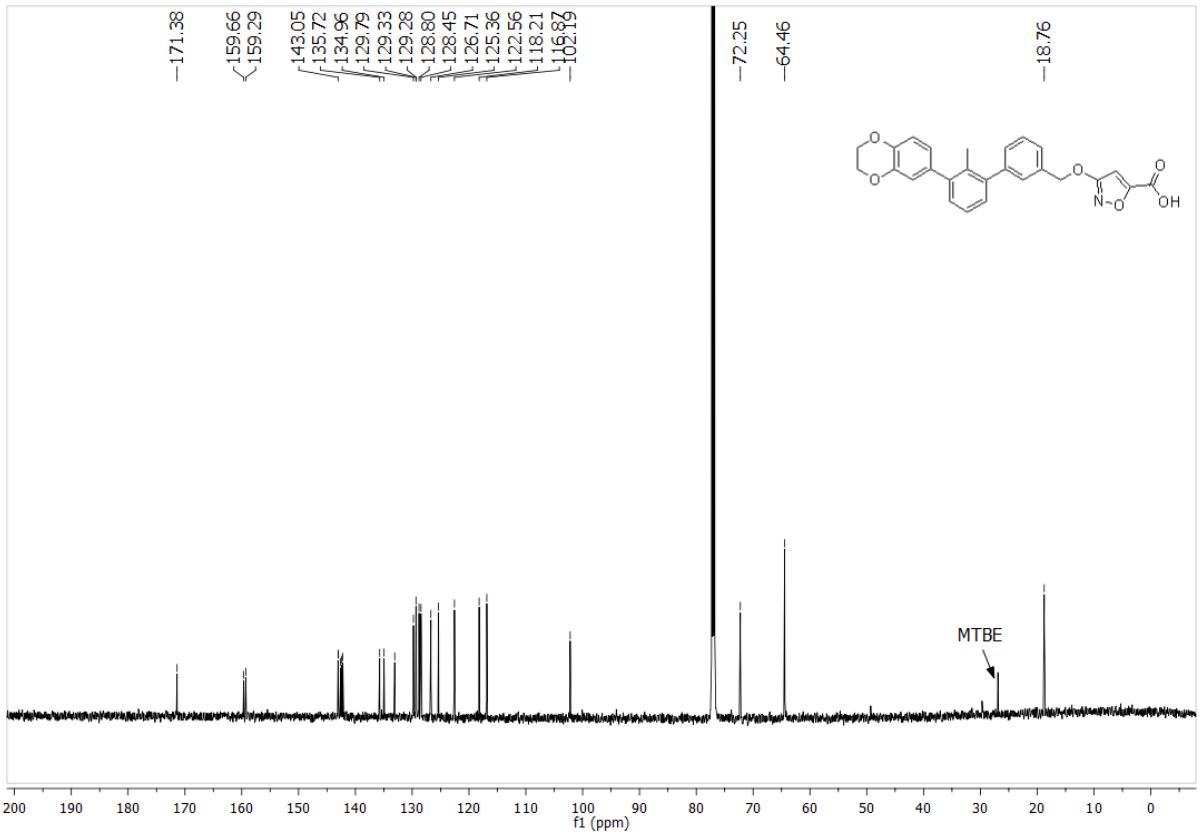
5m. methyl 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)isoxazole-5-carboxylate



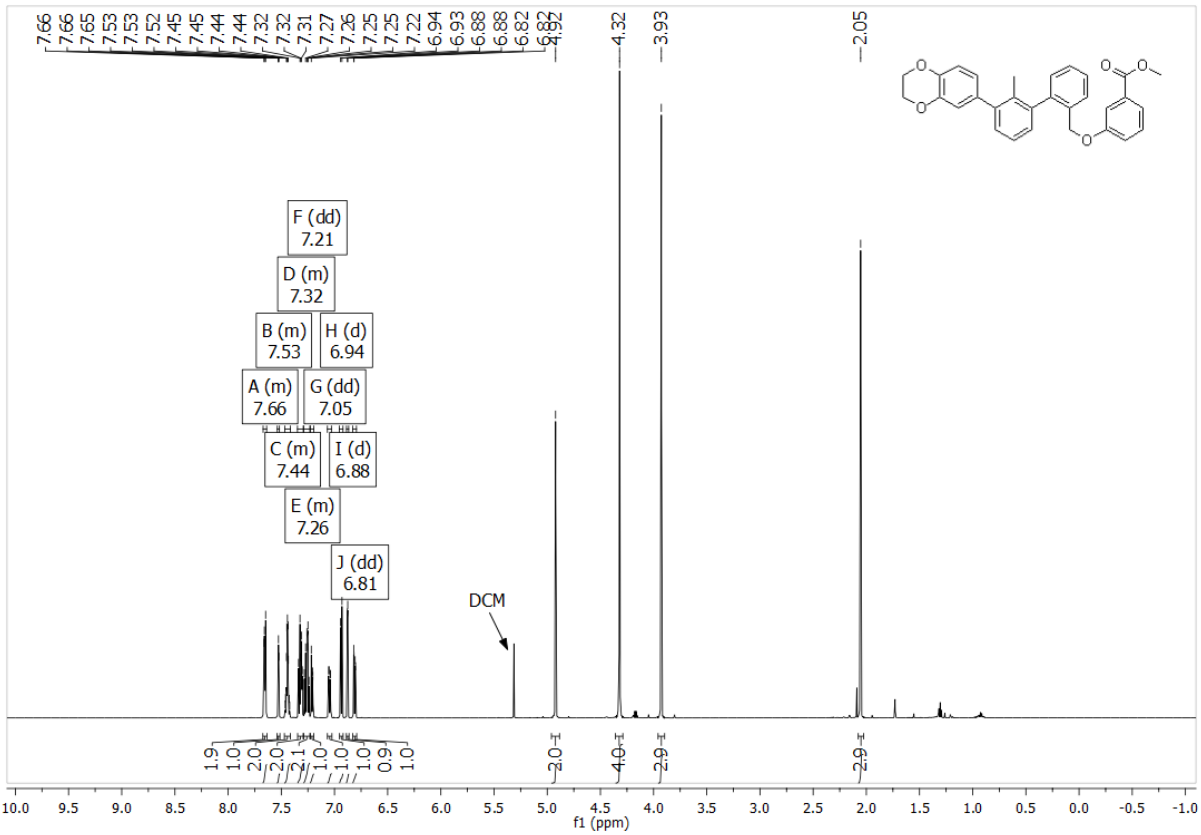


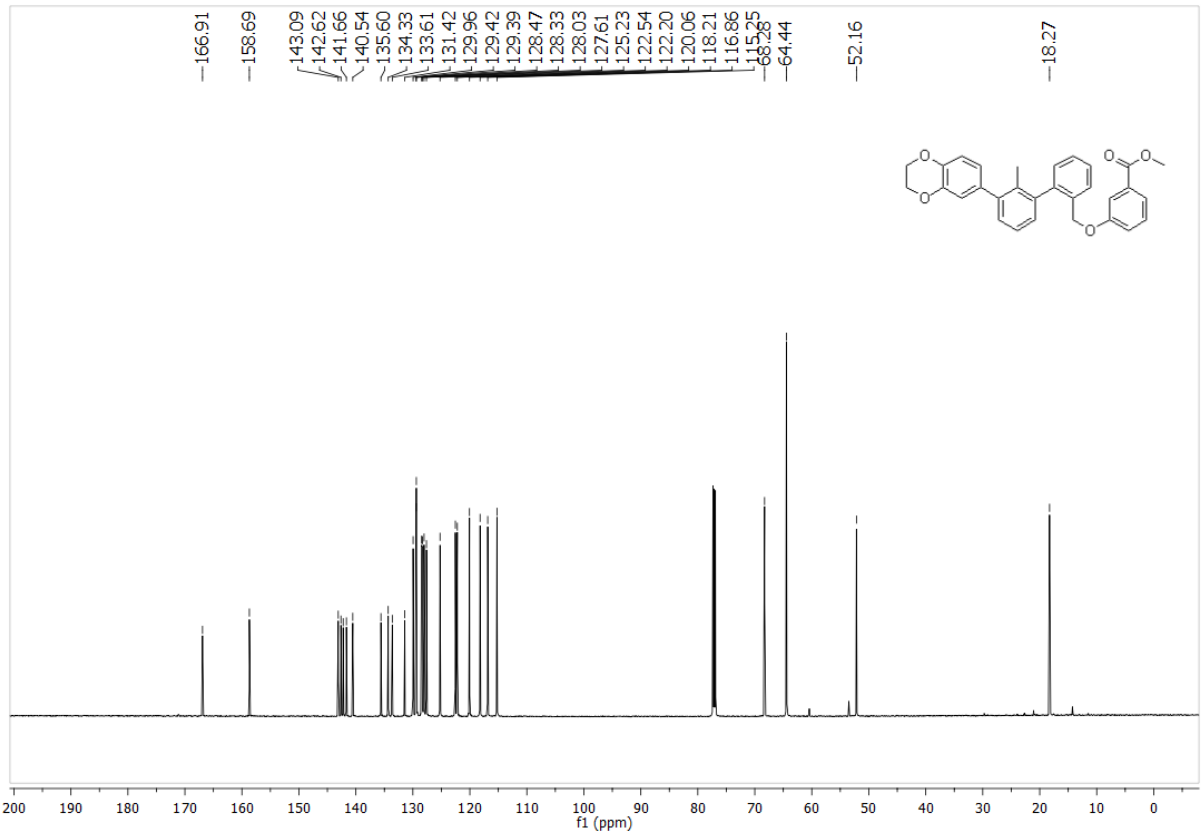
5n. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)isoxazole-5-carboxylic acid



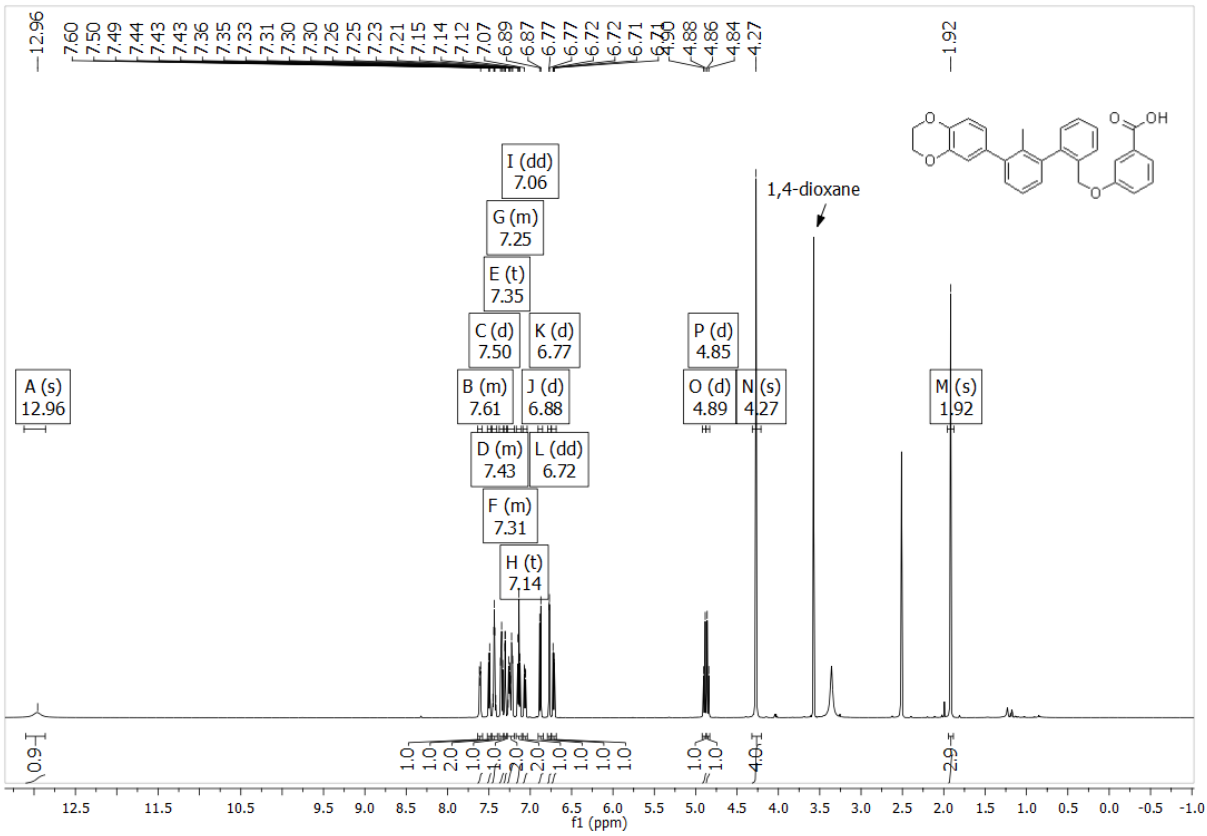


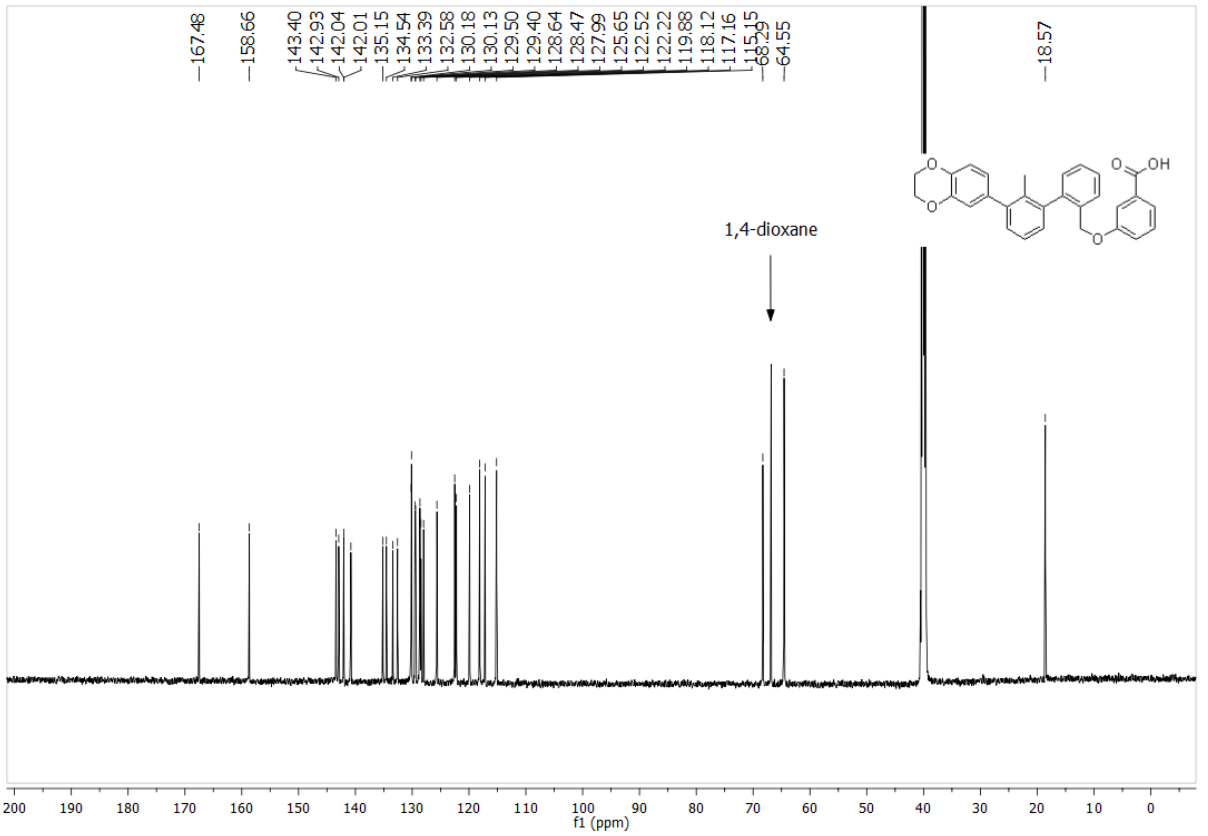
5o. methyl 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)methoxy)benzoate



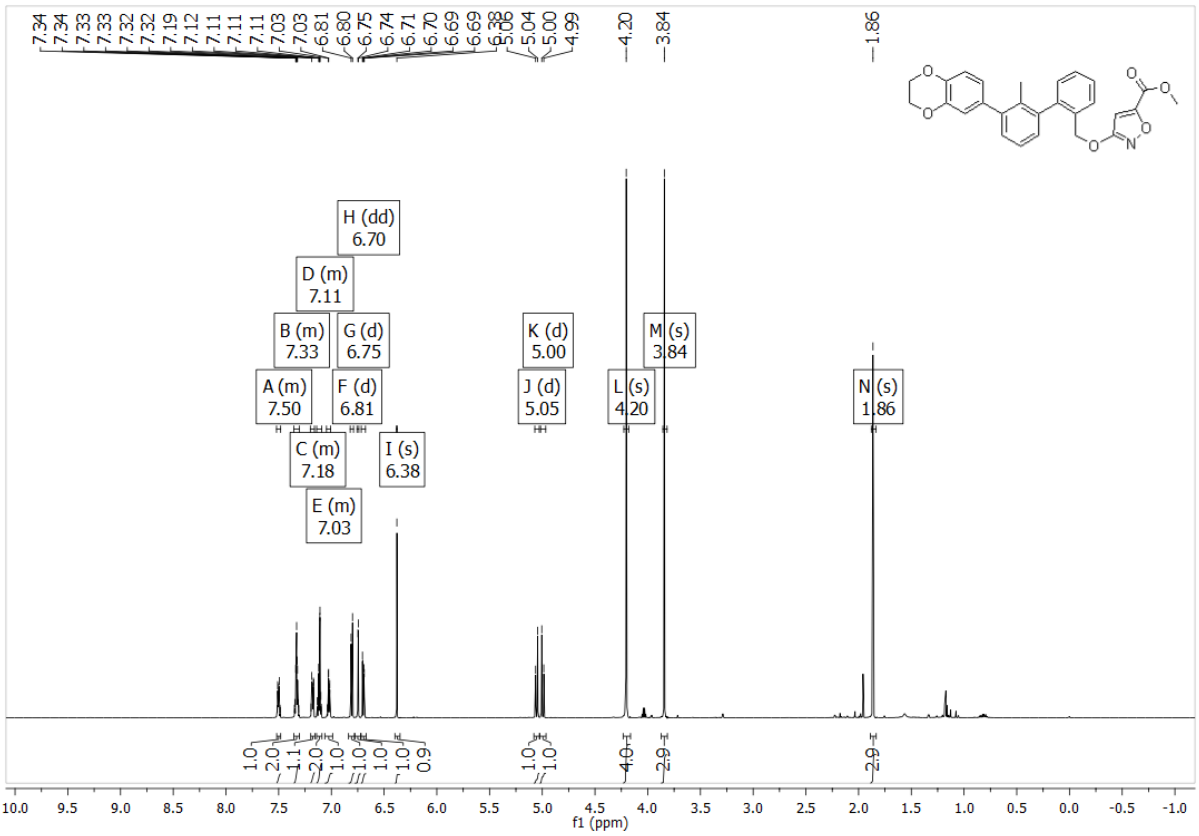


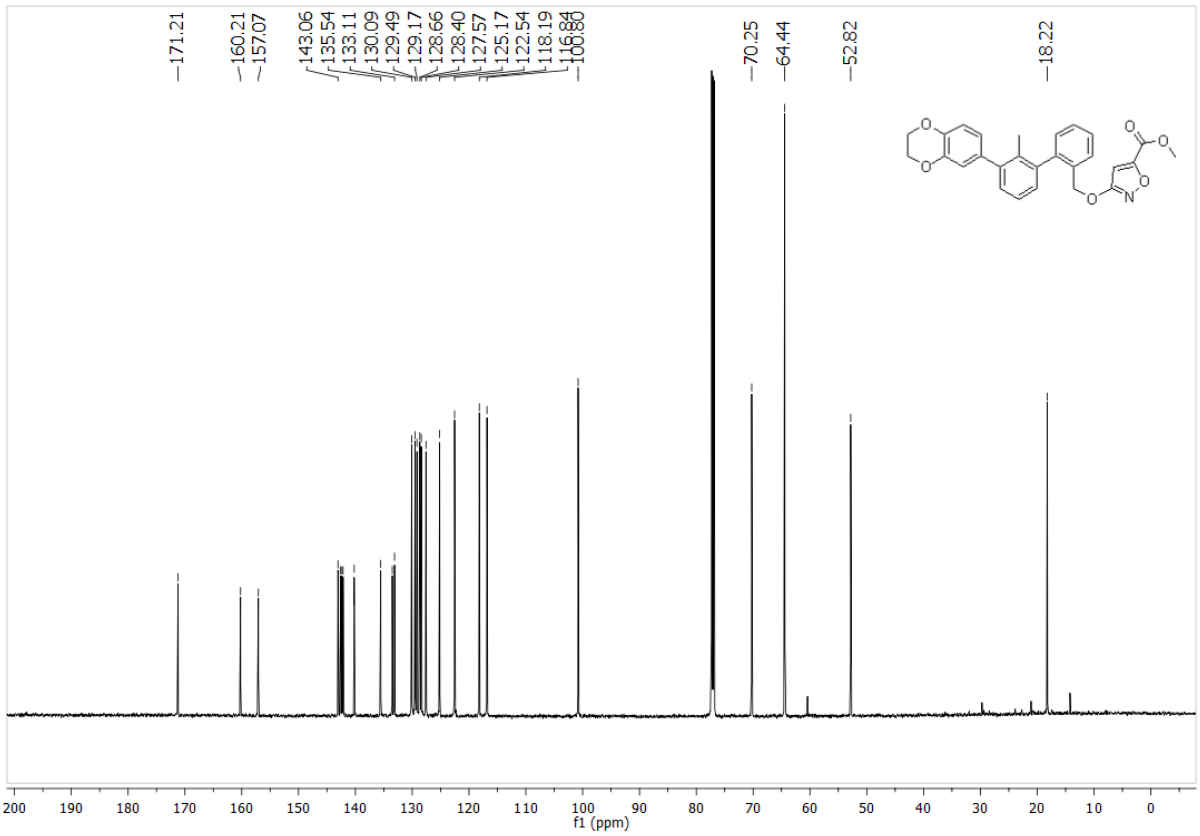
5p. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)methoxy)benzoic acid



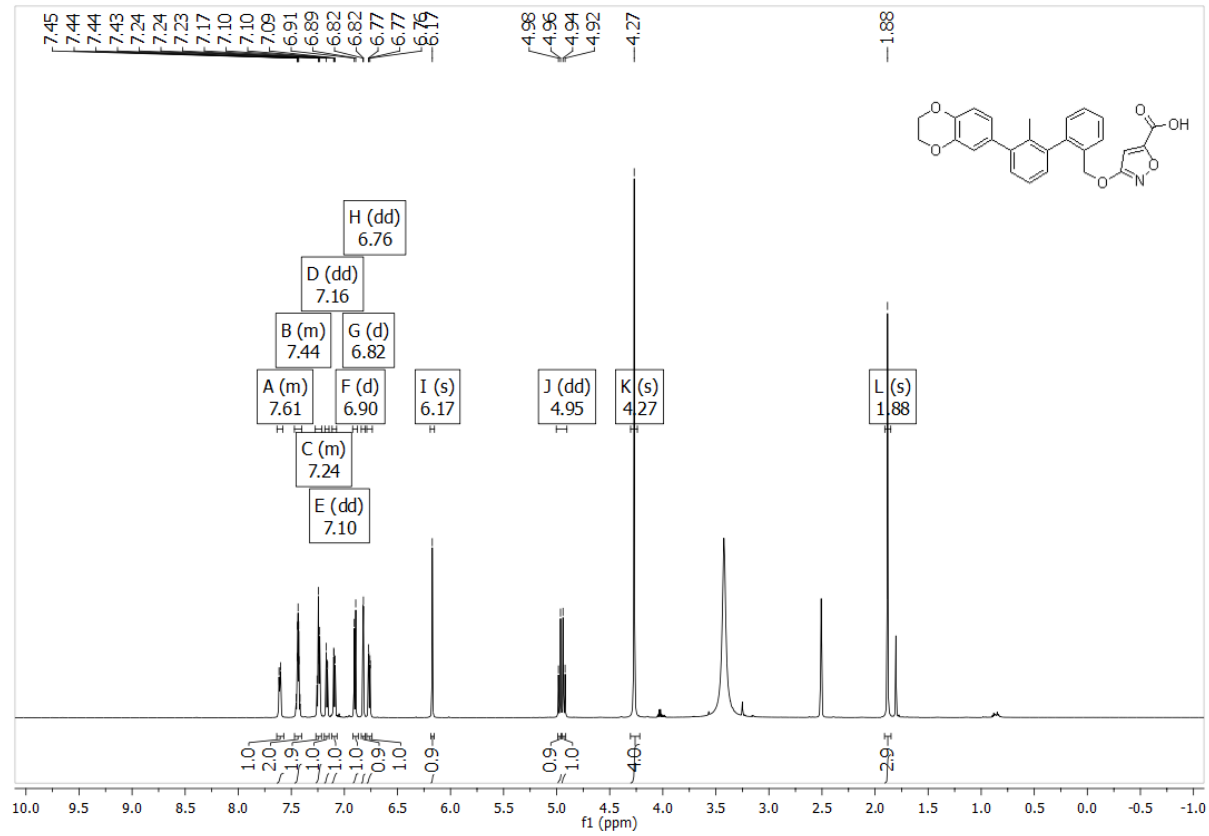


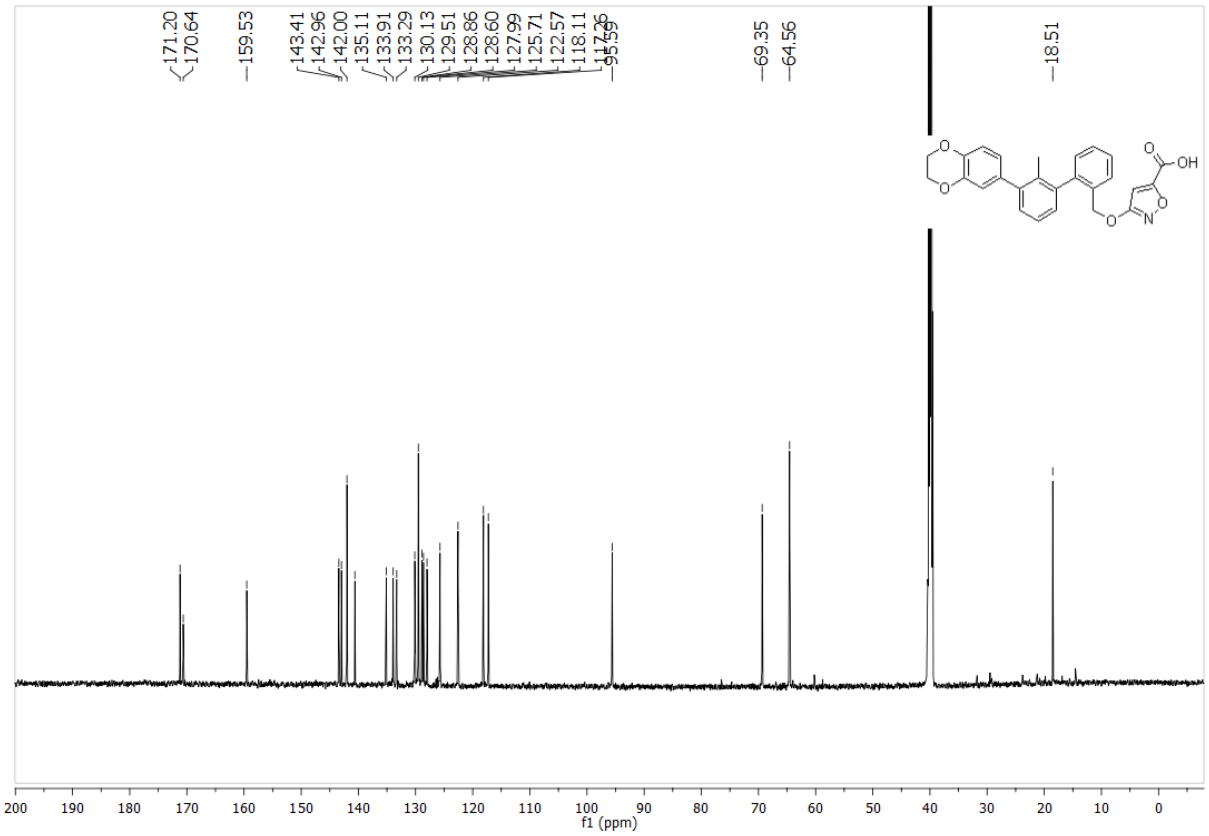
5q. methyl 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)methoxy)isoxazole-5-carboxylate



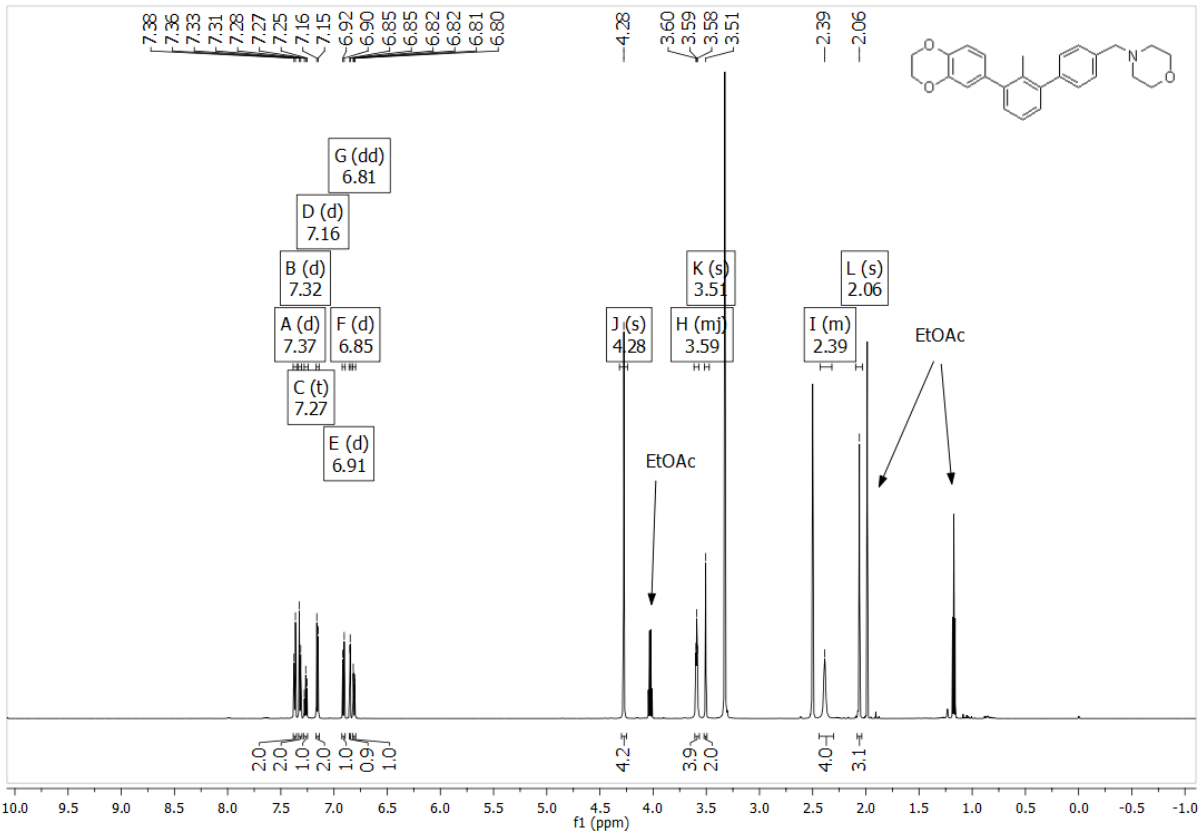


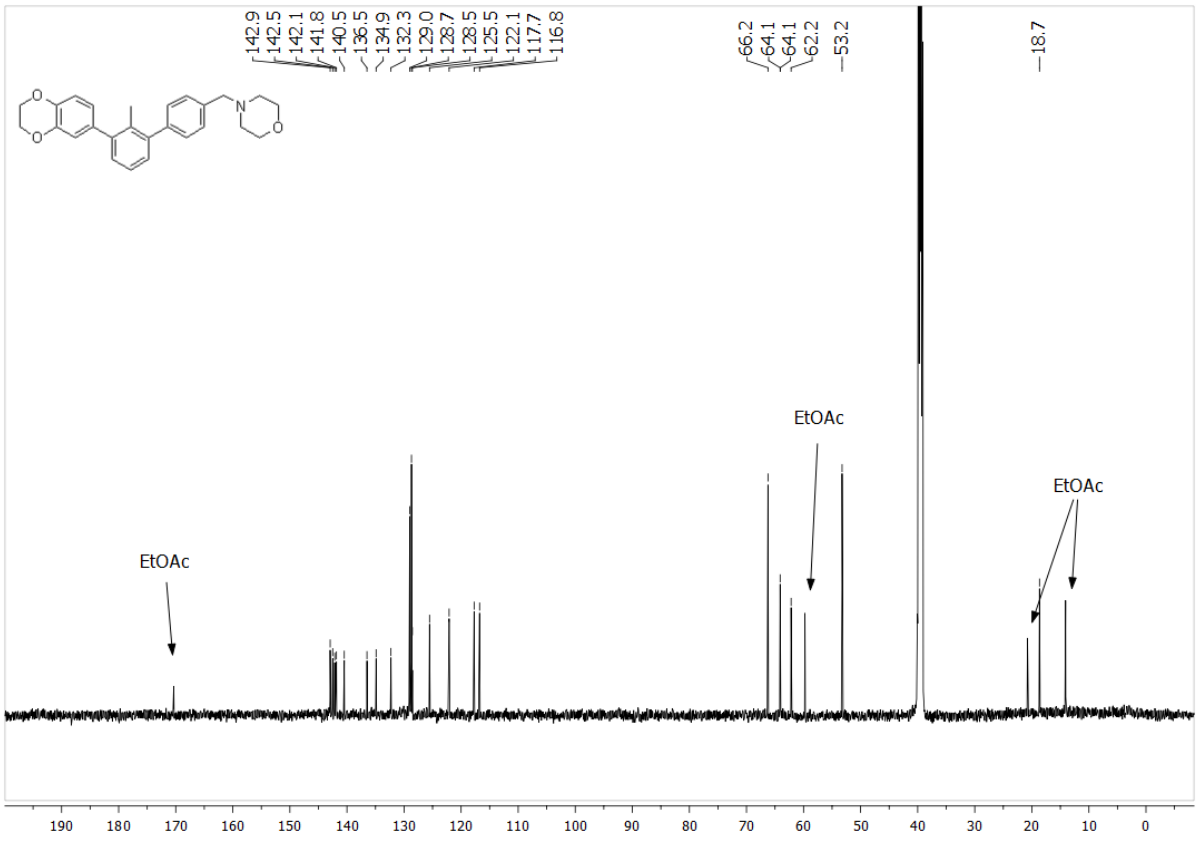
5r. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)methoxy)isoxazole-5-carboxylic acid



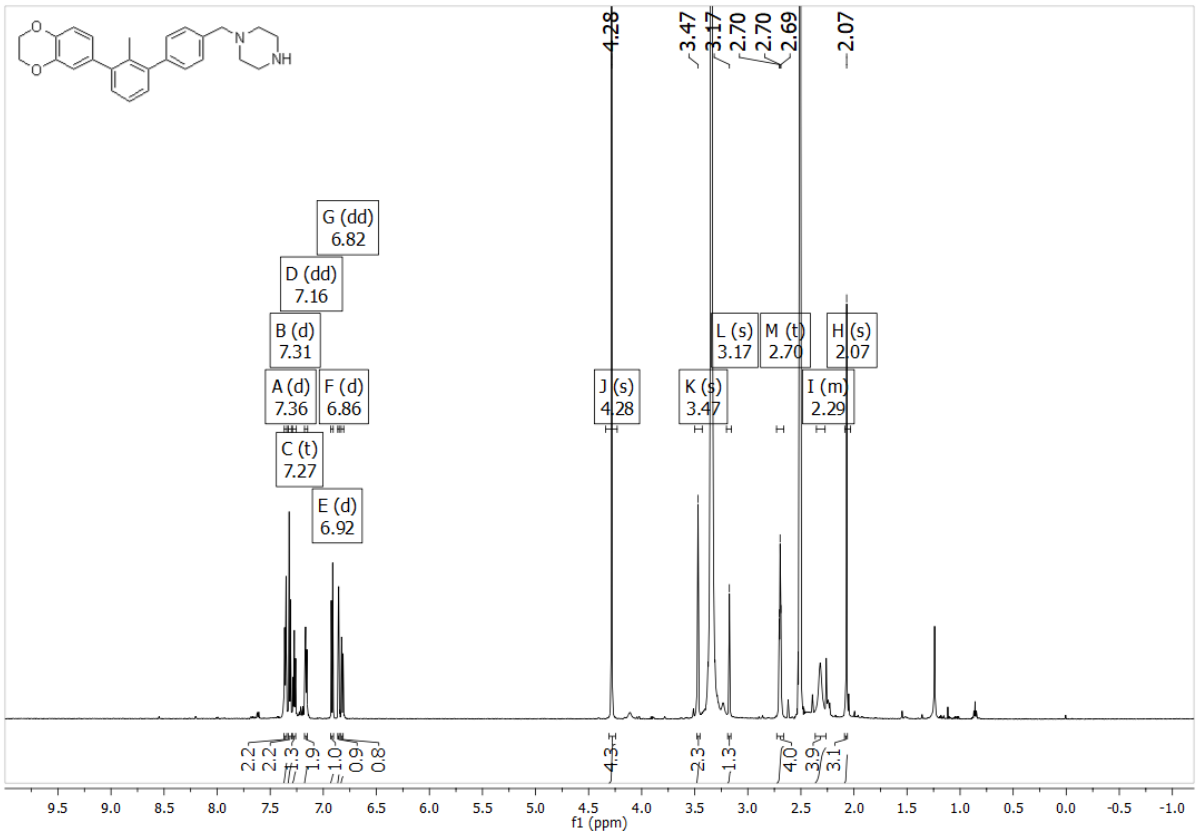


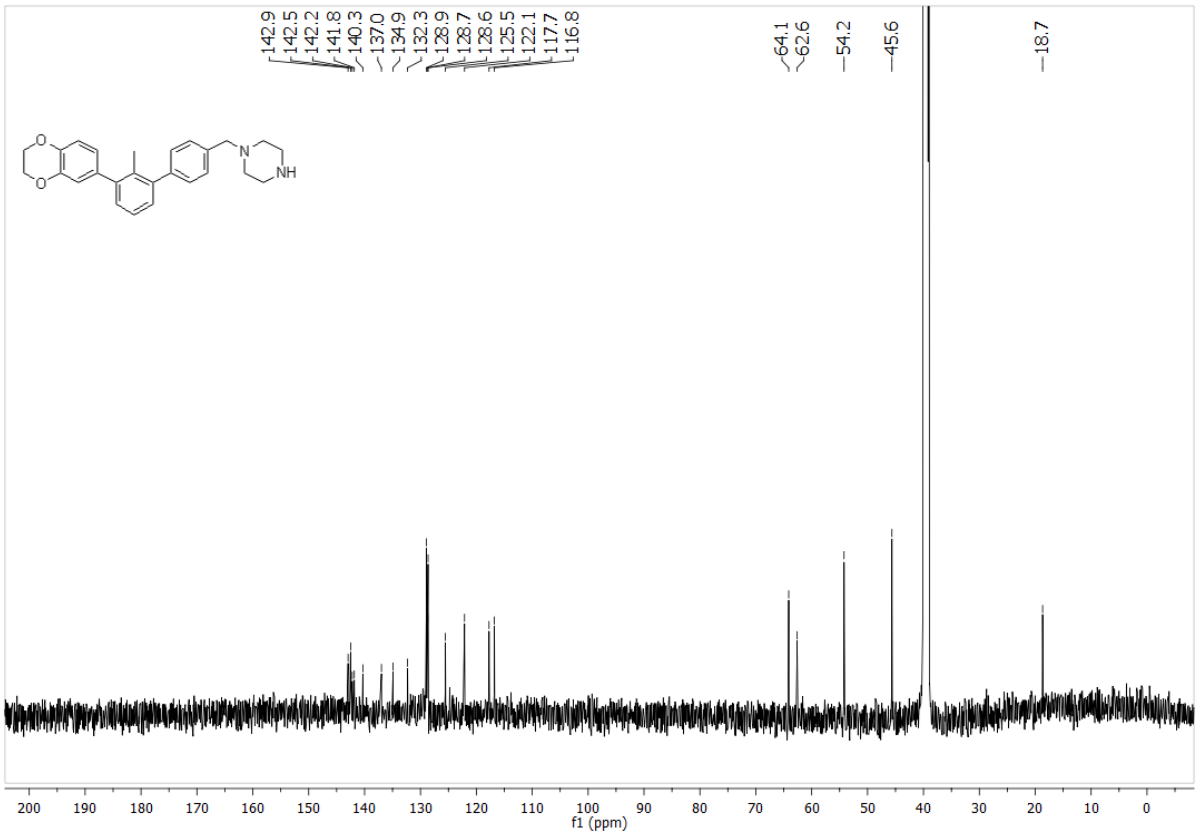
6a. 4-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)morpholine



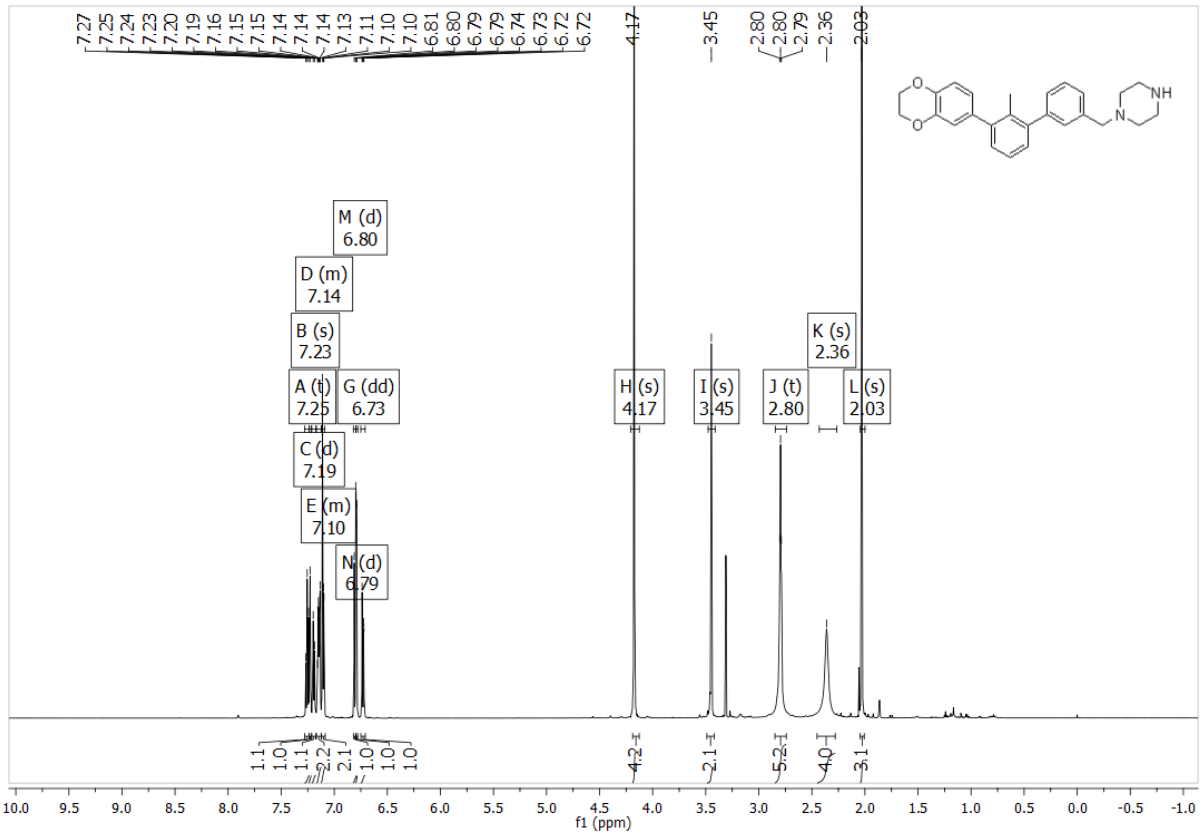


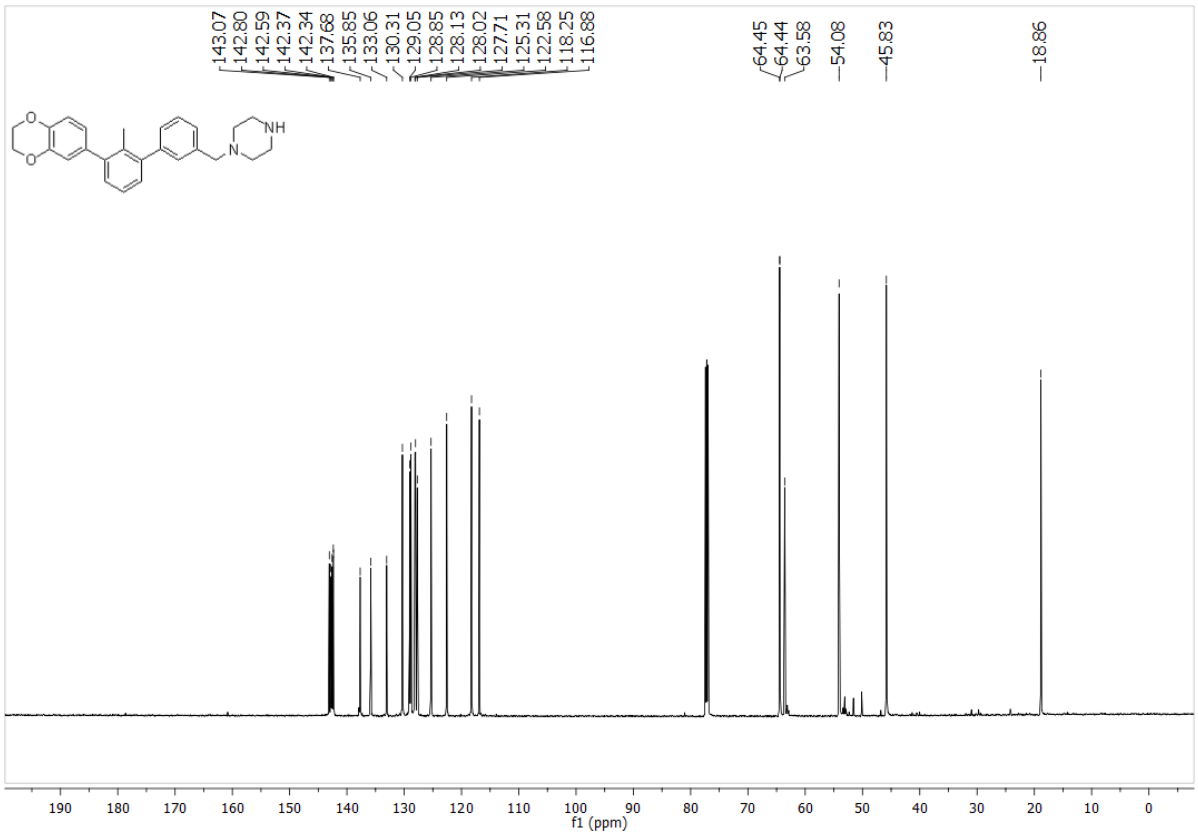
6b. 4-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)piperazine



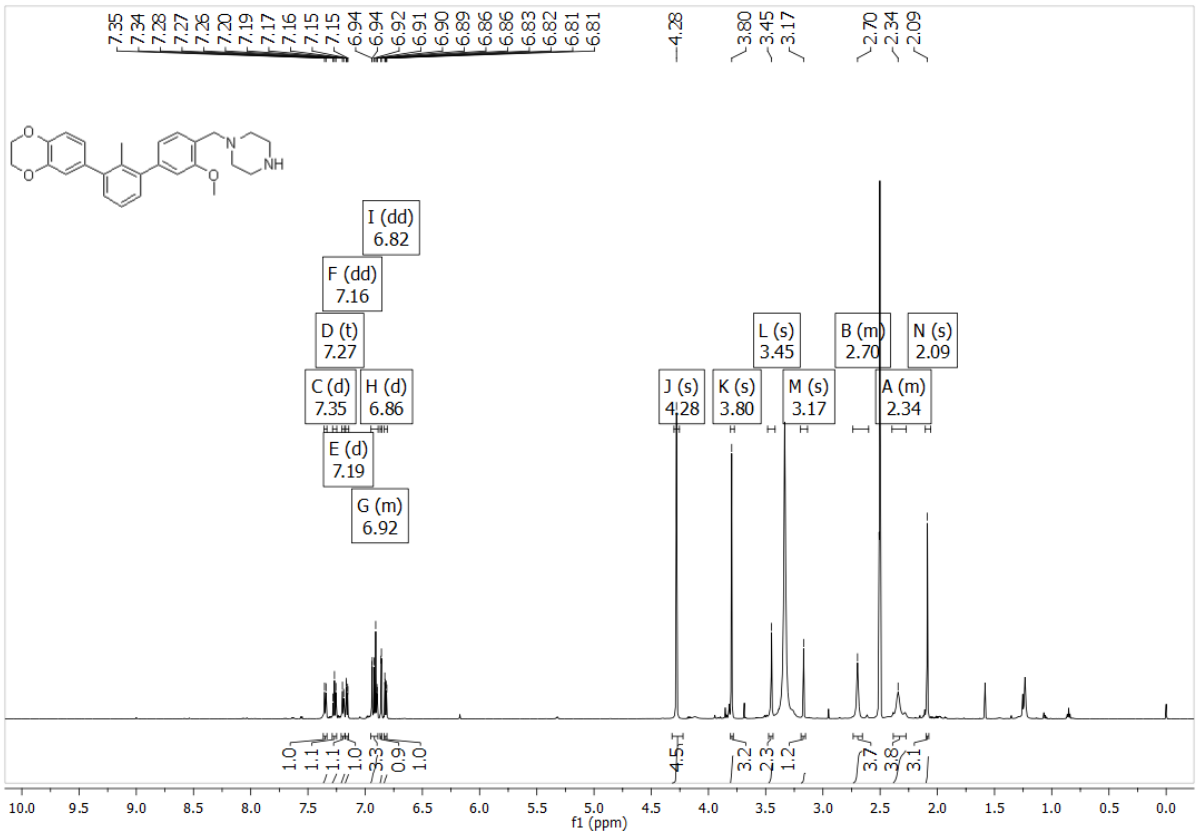


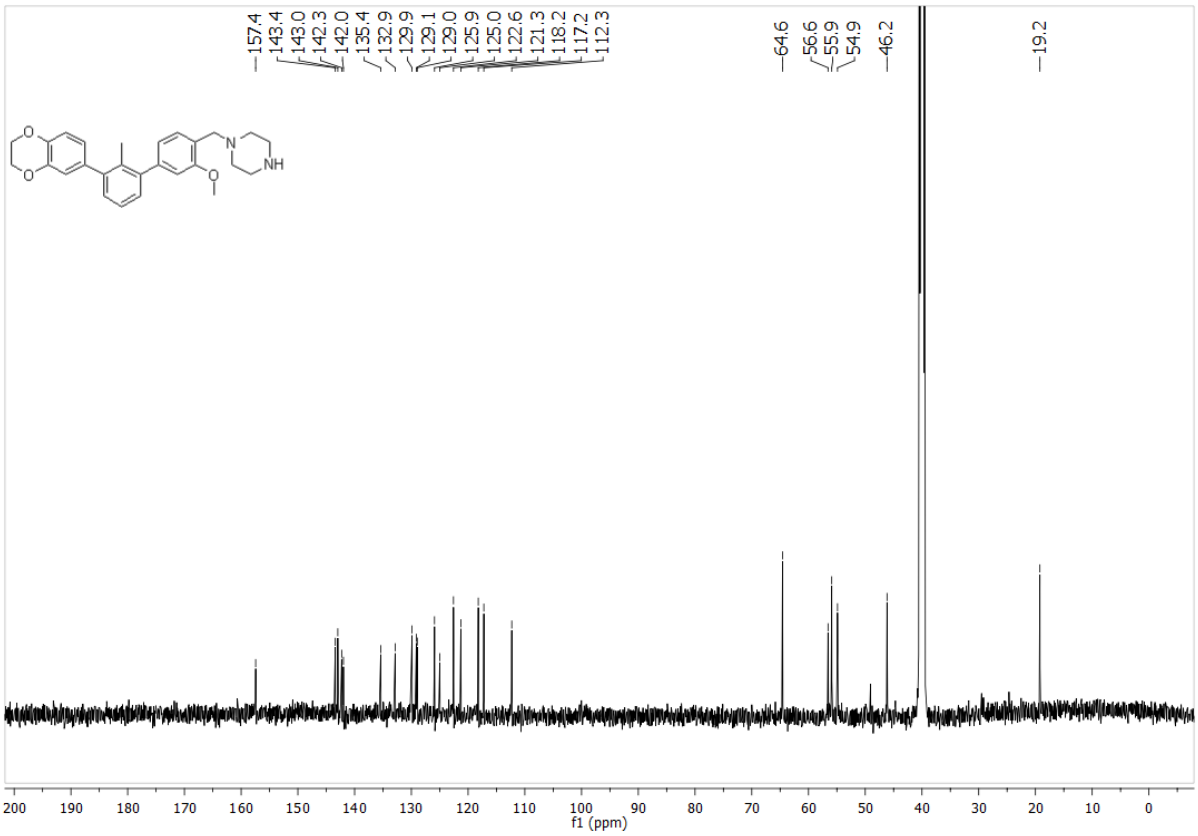
6c. 1-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methyl)piperazine



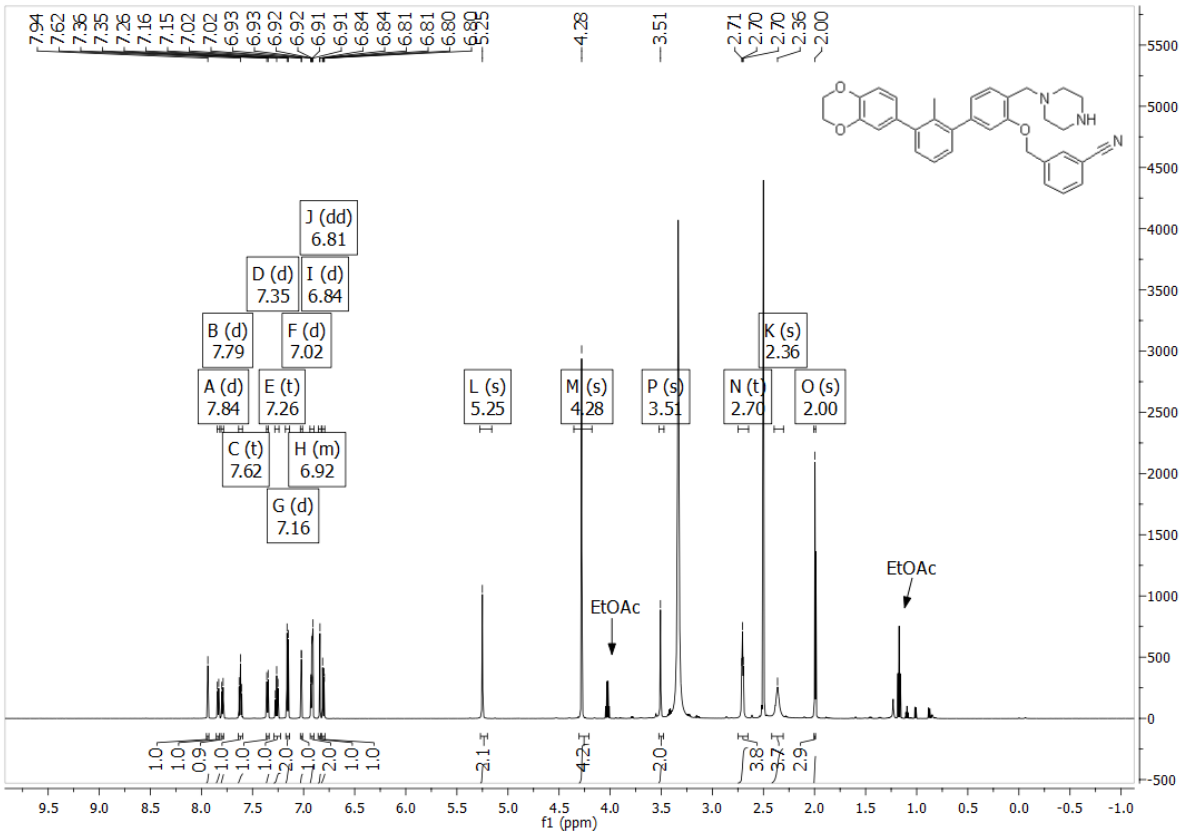


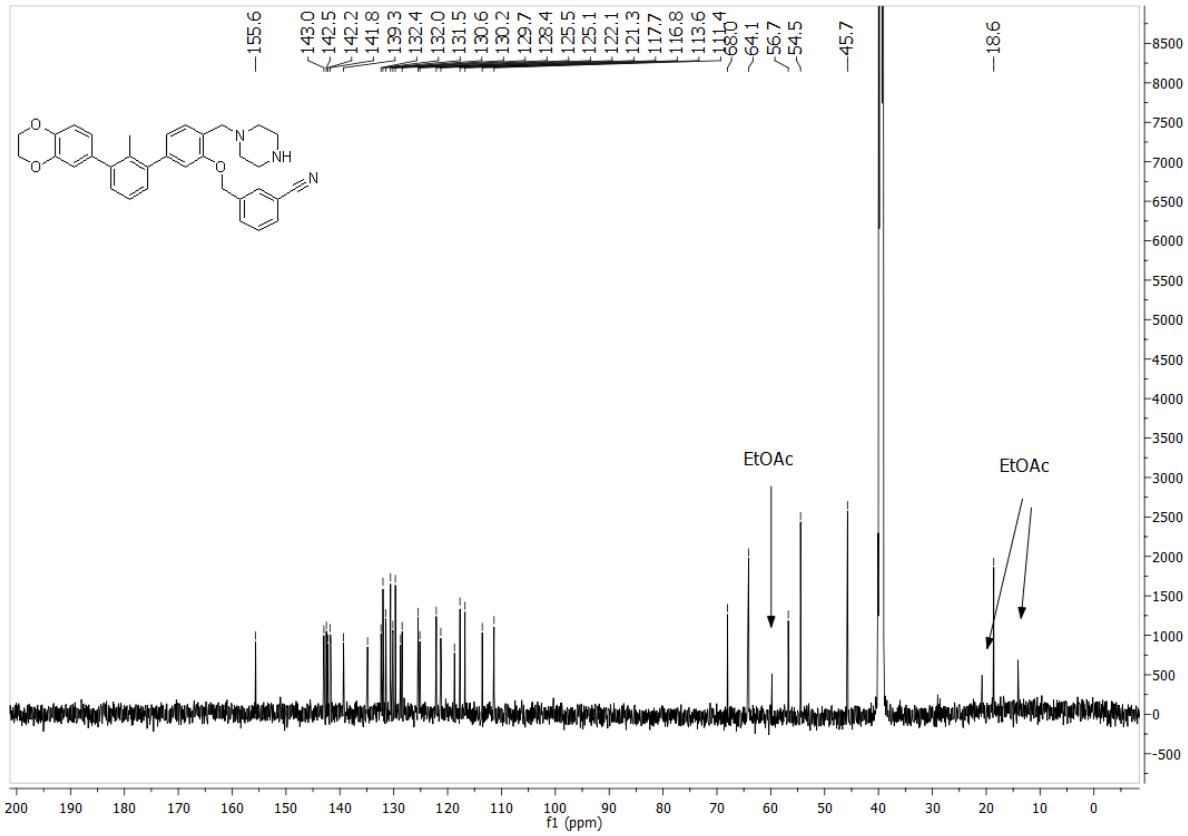
6d. 1-((3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)piperazine



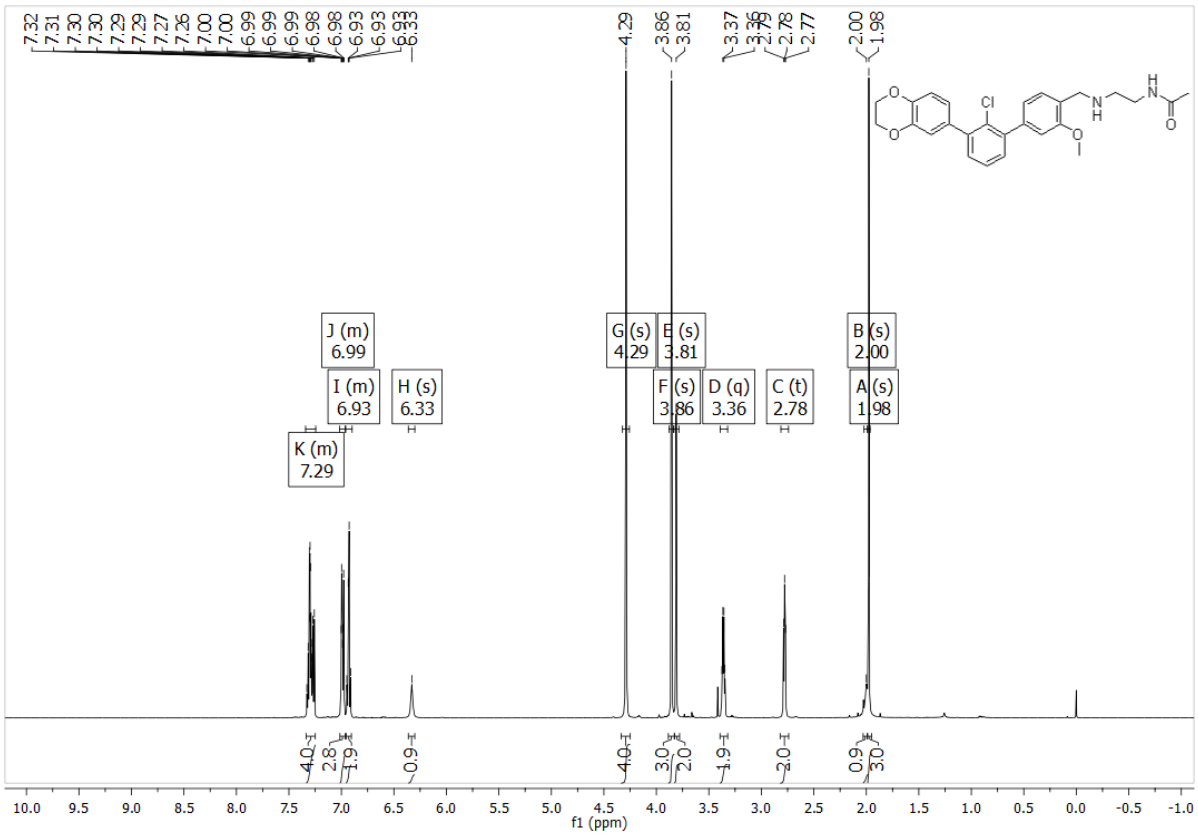


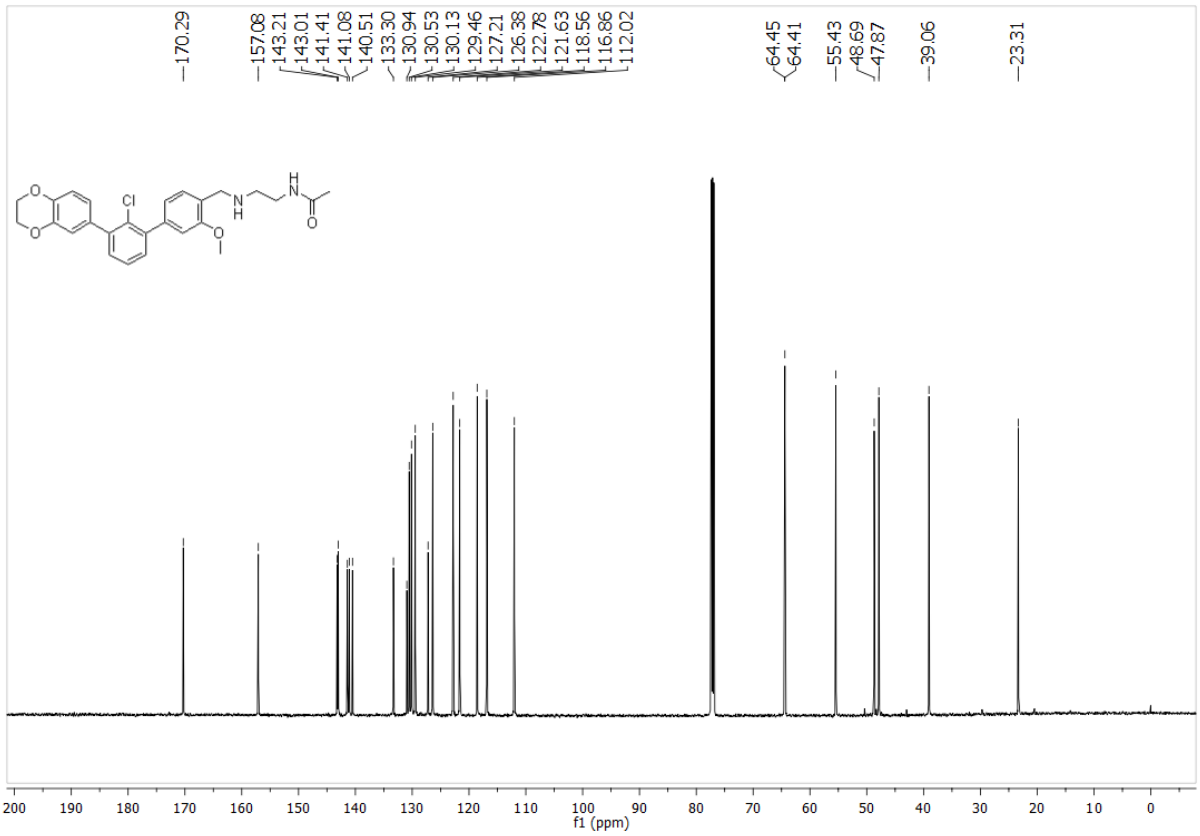
6e. 3-(((3'-(2,3-benzo-1,4-dioxan-6-yl)-2'-methyl-4-(piperazin-1-ylmethyl)-[1,1'-biphenyl]-3-yl)oxy)methyl)benzonitrile



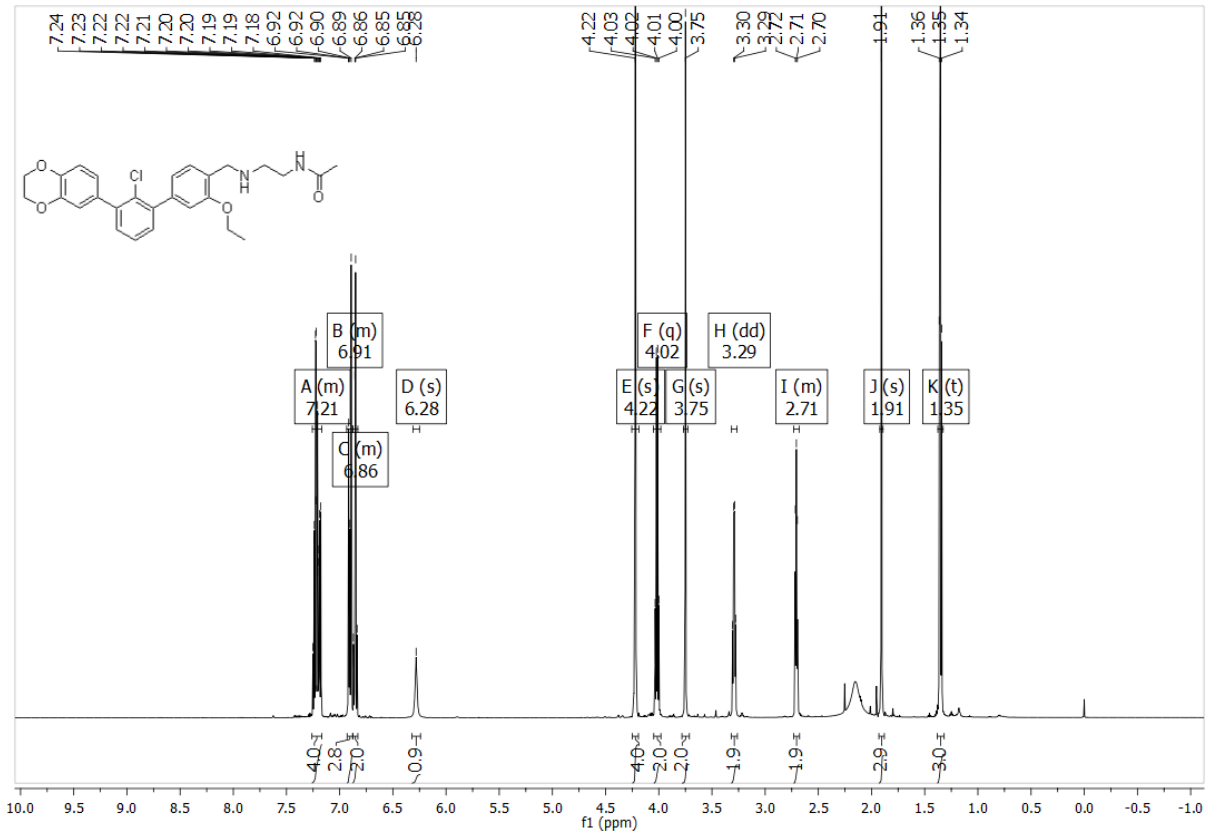


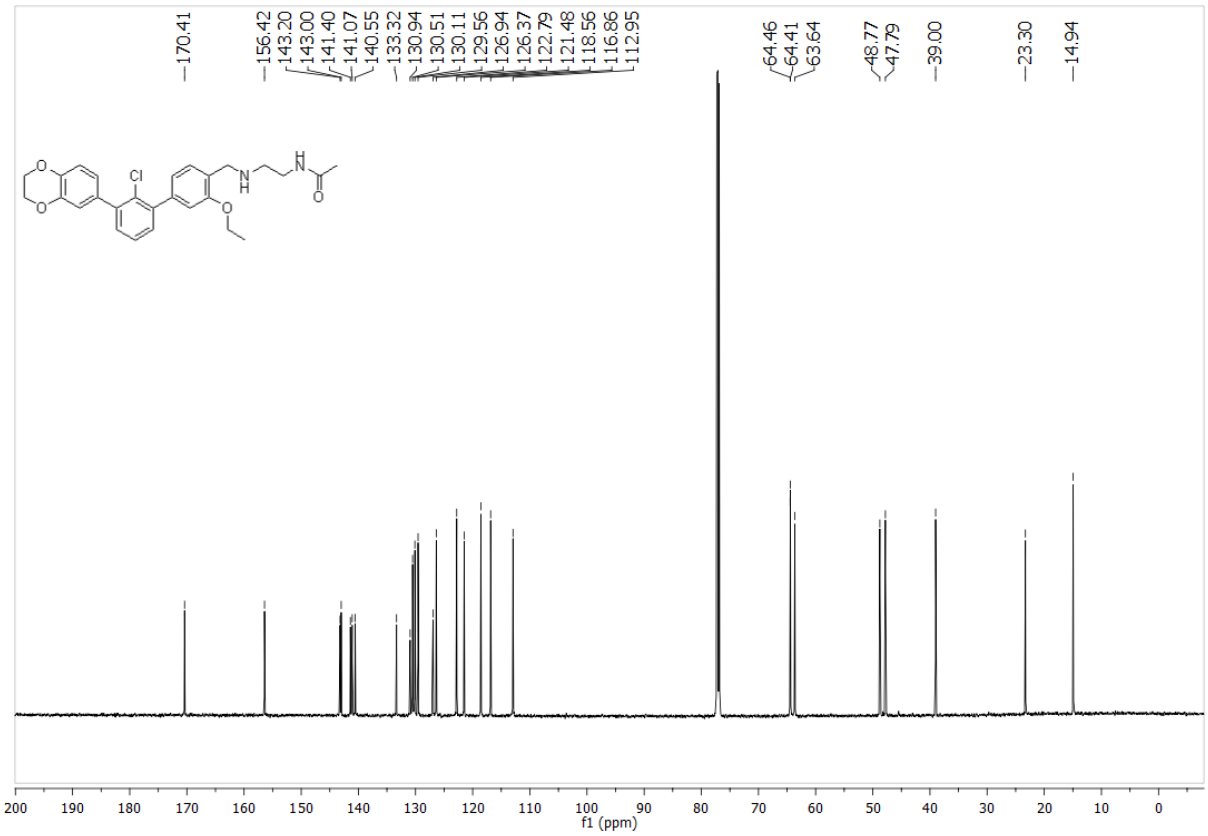
7a. N-(2-(((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



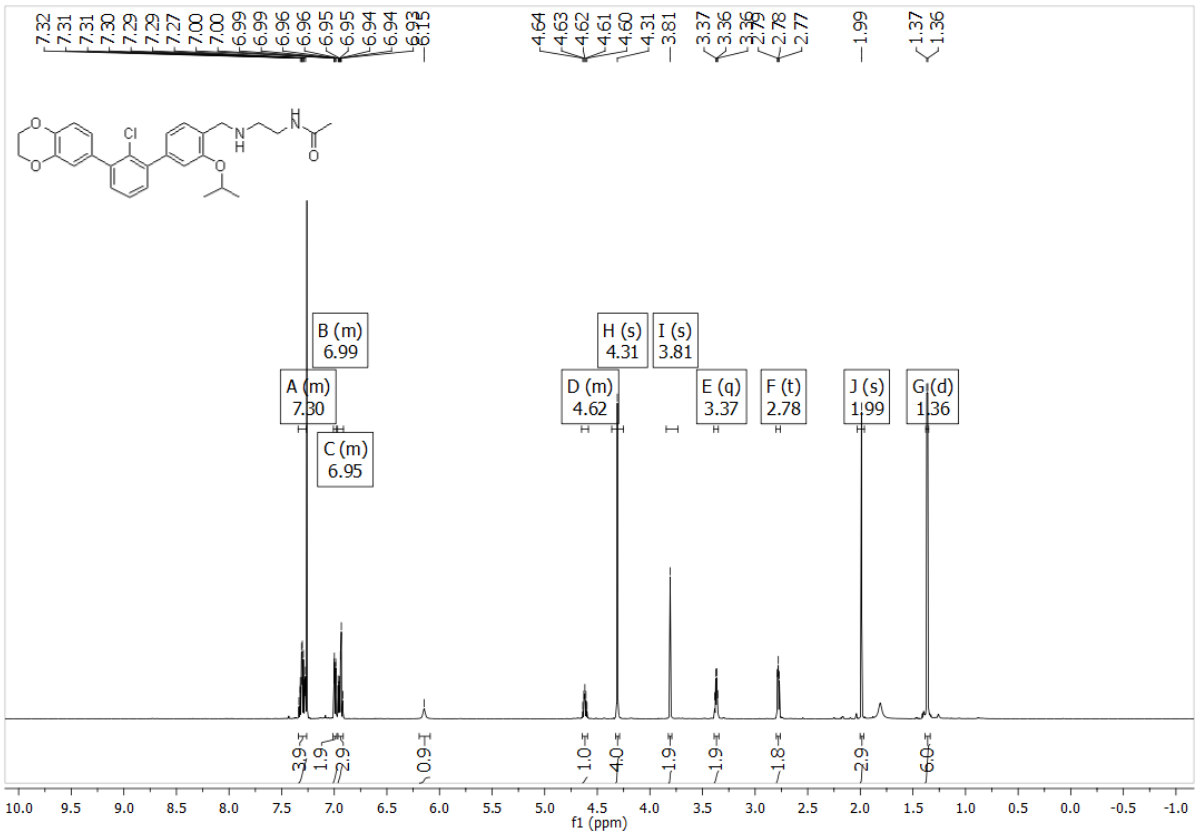


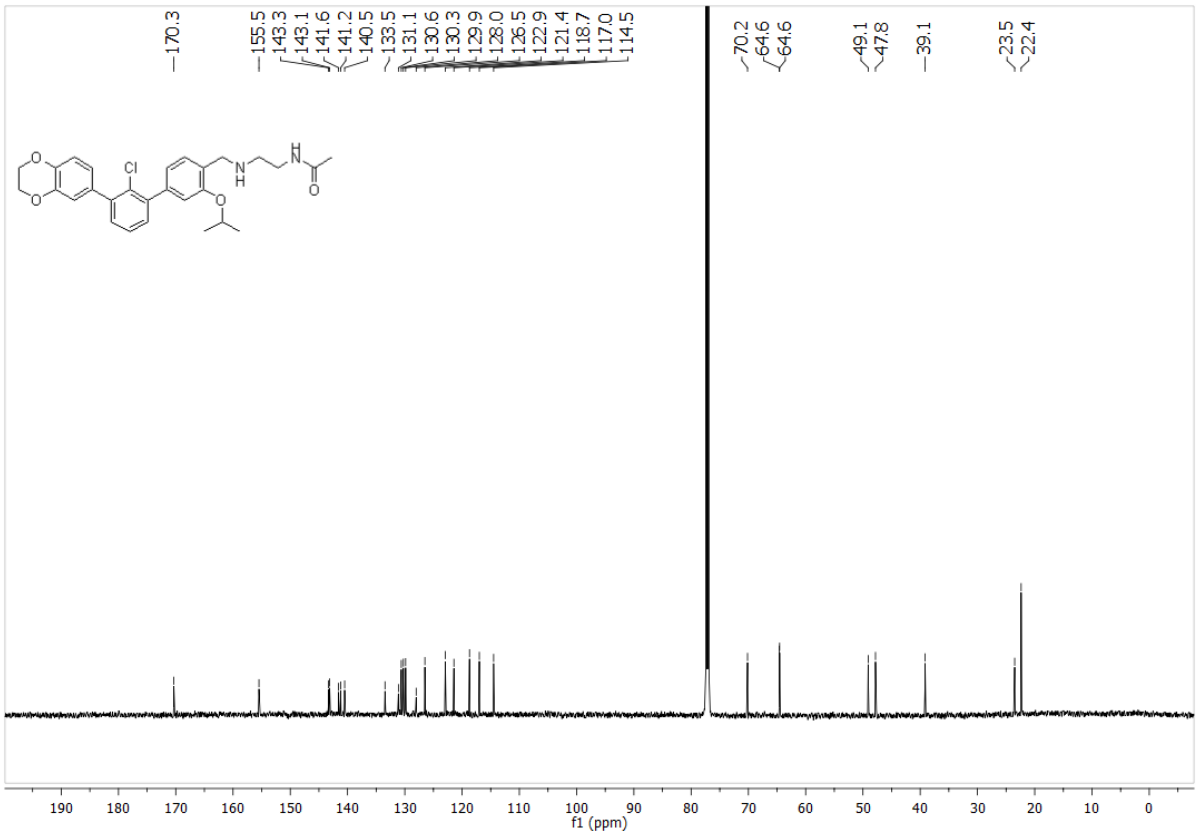
7b. N-(2-((((benzo-1,4-dioxan-6-yl)-2'-chloro-3'-3-ethoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



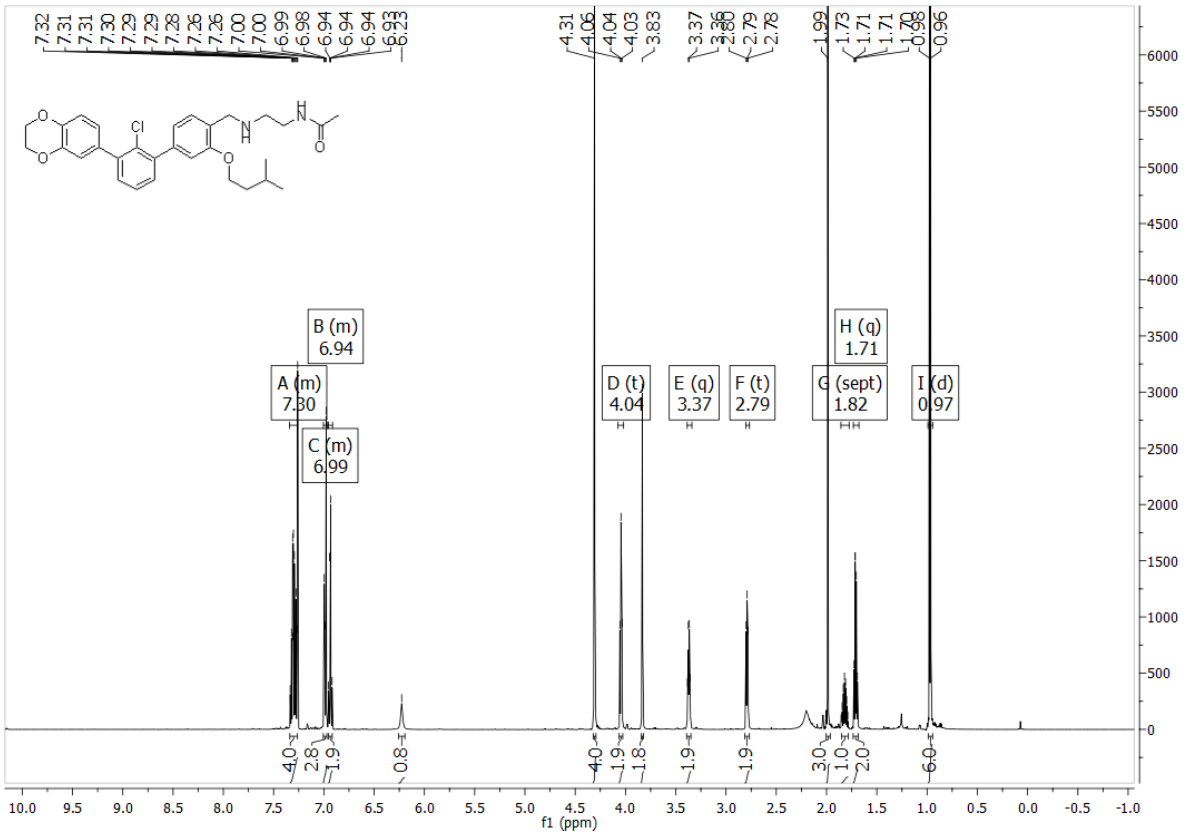


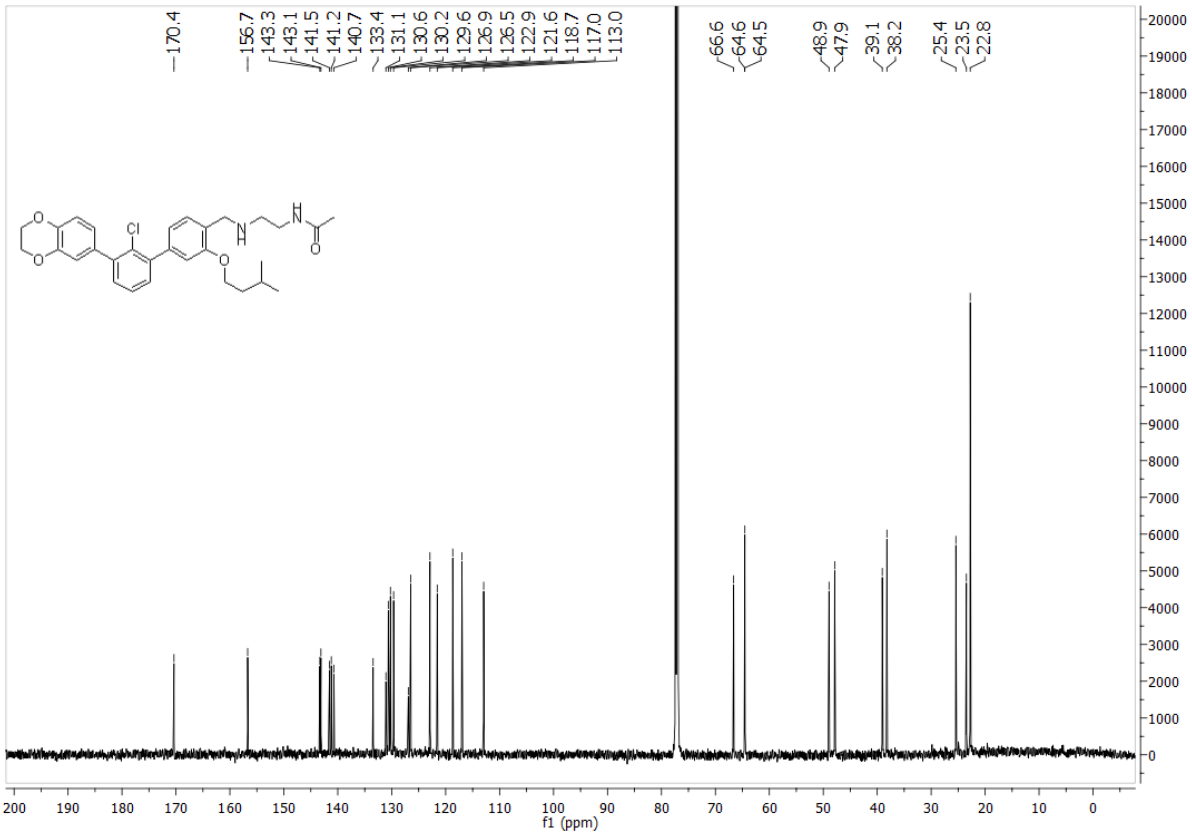
7c. N-(2-(((2'-chloro-3-((3'-cyano-[1,1'-biphenyl]-3-yl)isopropoxy)-3'-(benzo-1,4-dioxan-6-yl)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



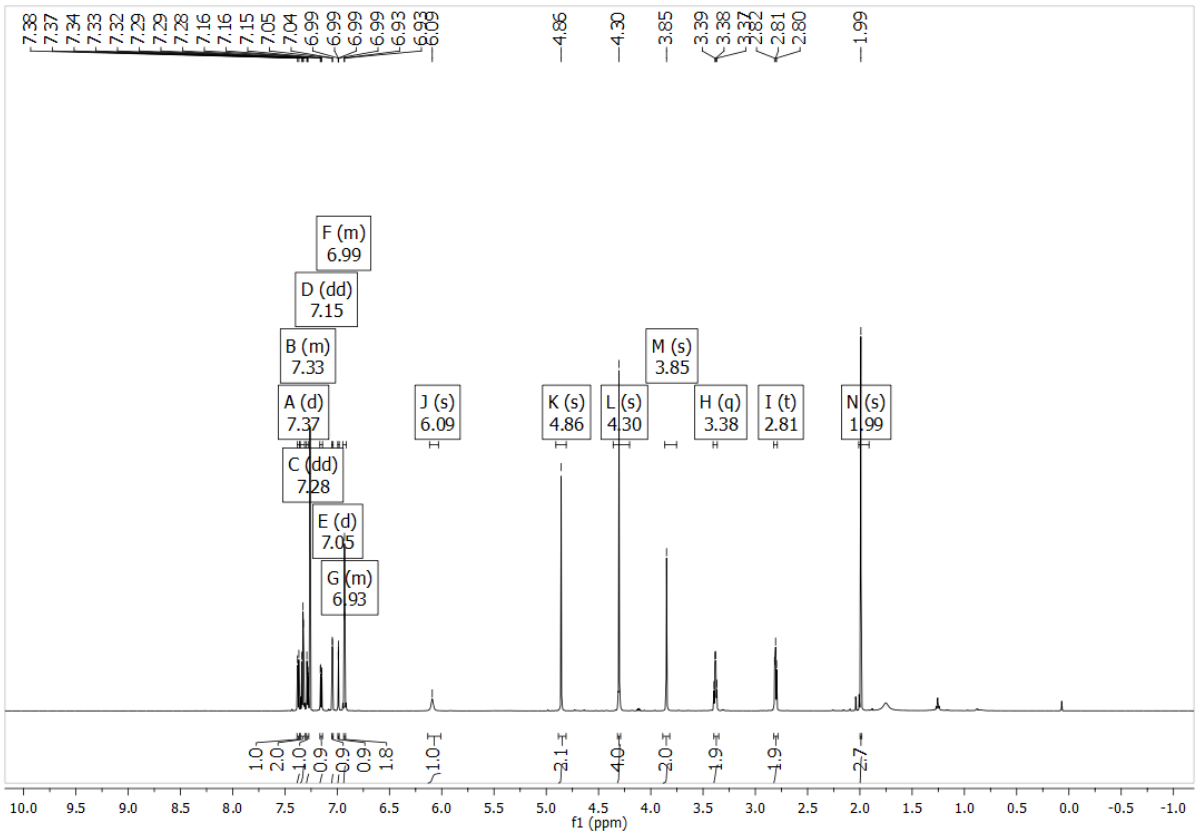


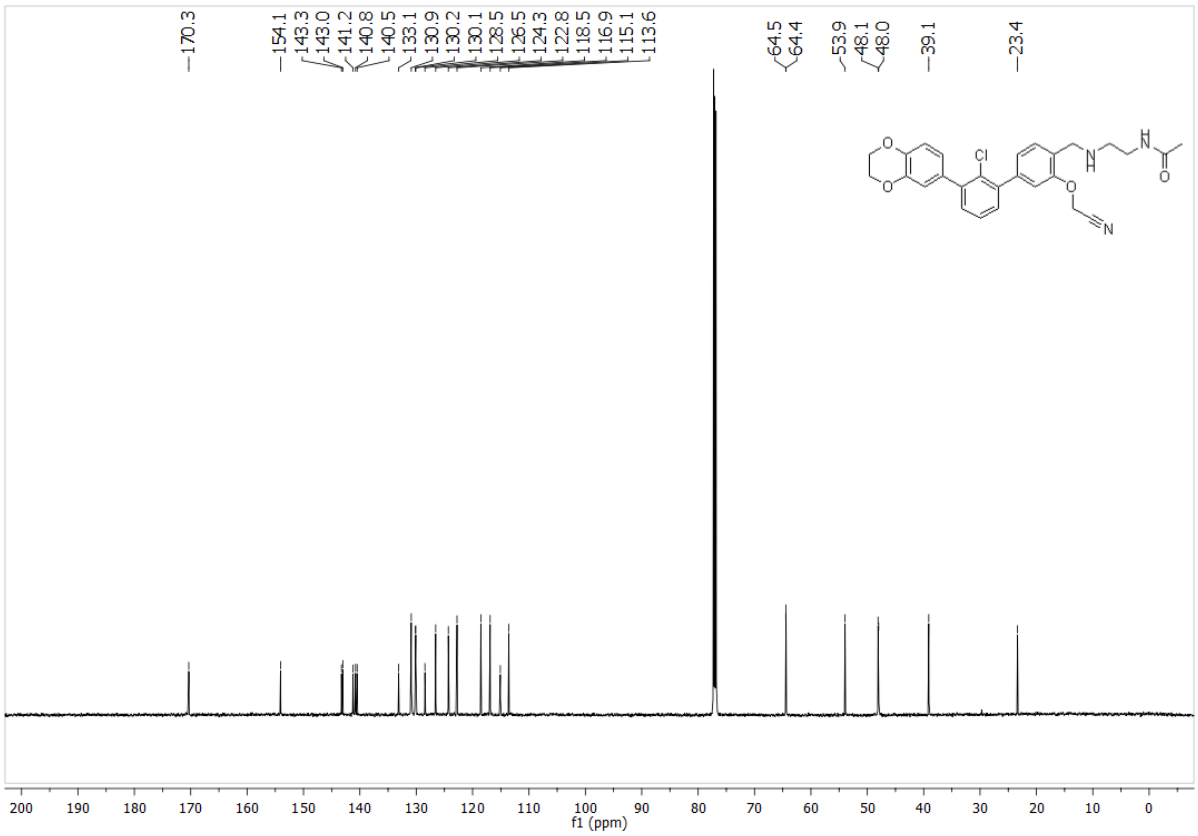
7d. N-(2-(((2'-chloro-3-((3'-cyano-[1,1'-biphenyl]-3-yl)isopentyloxy)-3'-(benzo-1,4-dioxan-6-yl)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



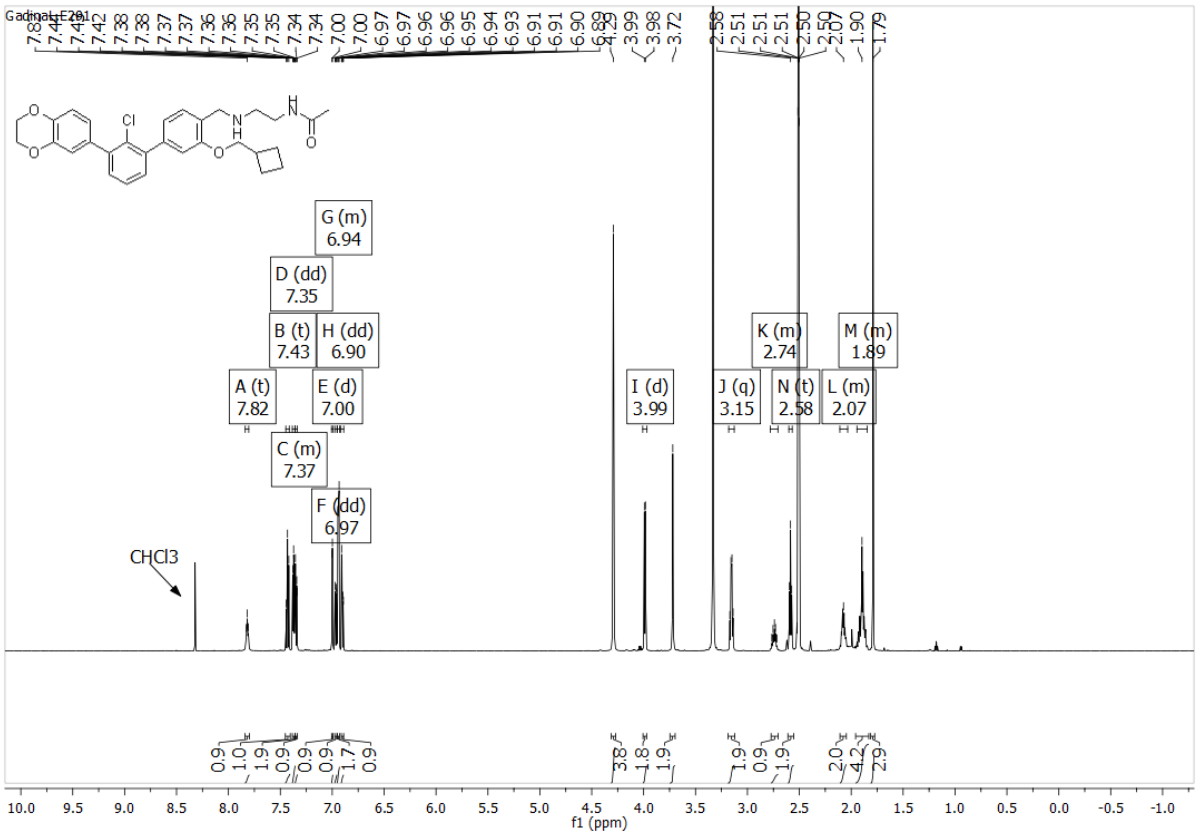


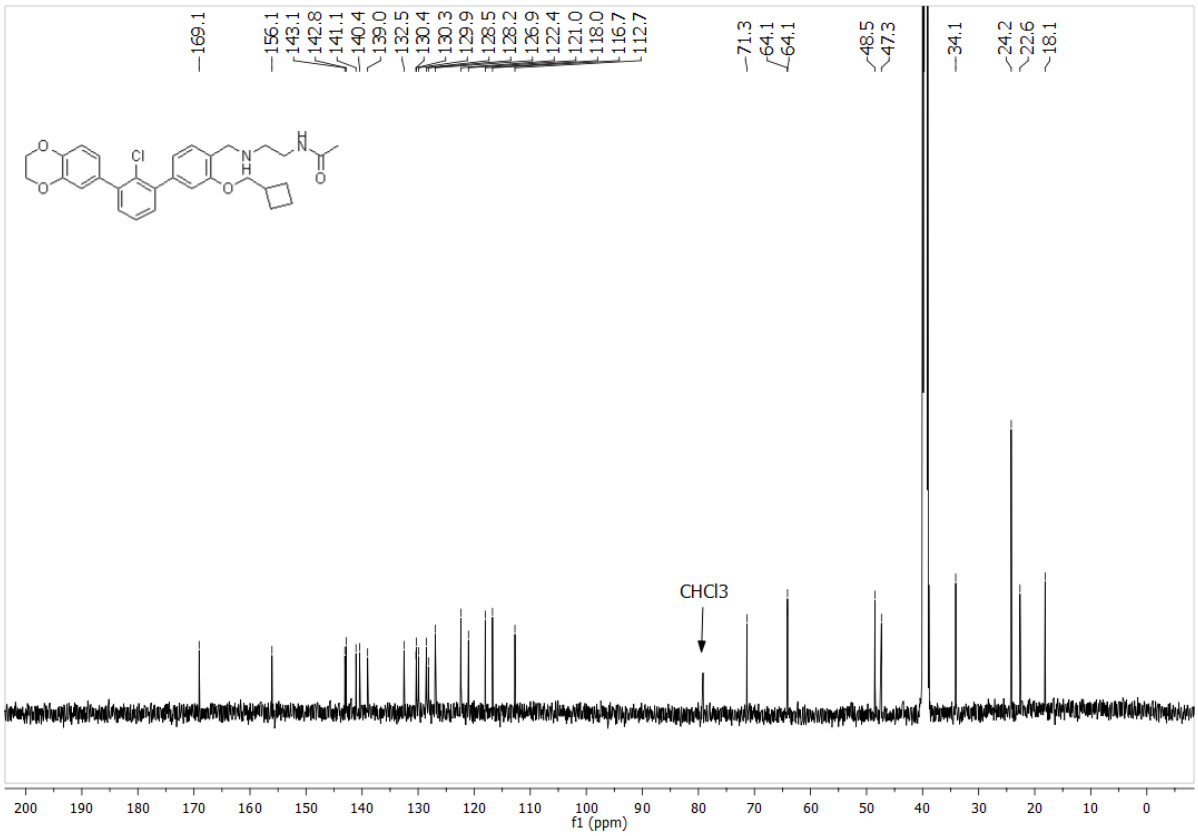
7e. N-(2-(((3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-(cyanomethoxy)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



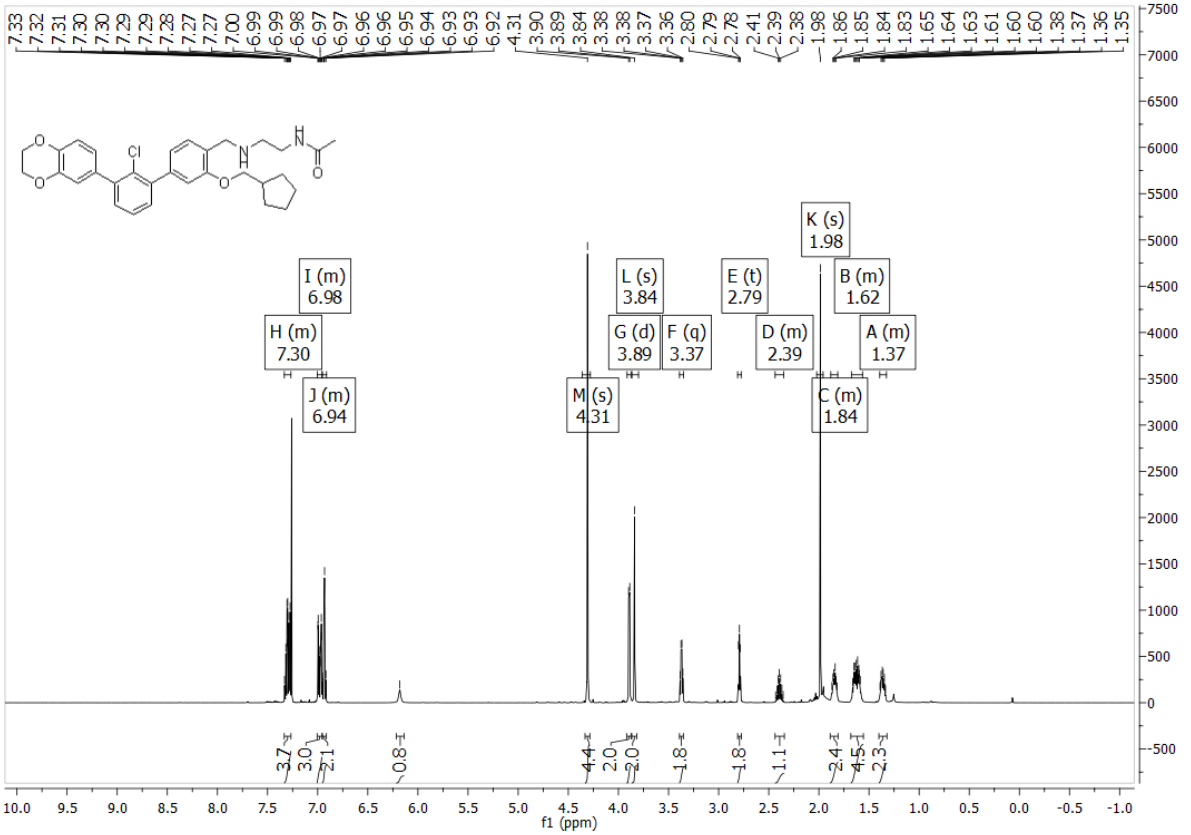


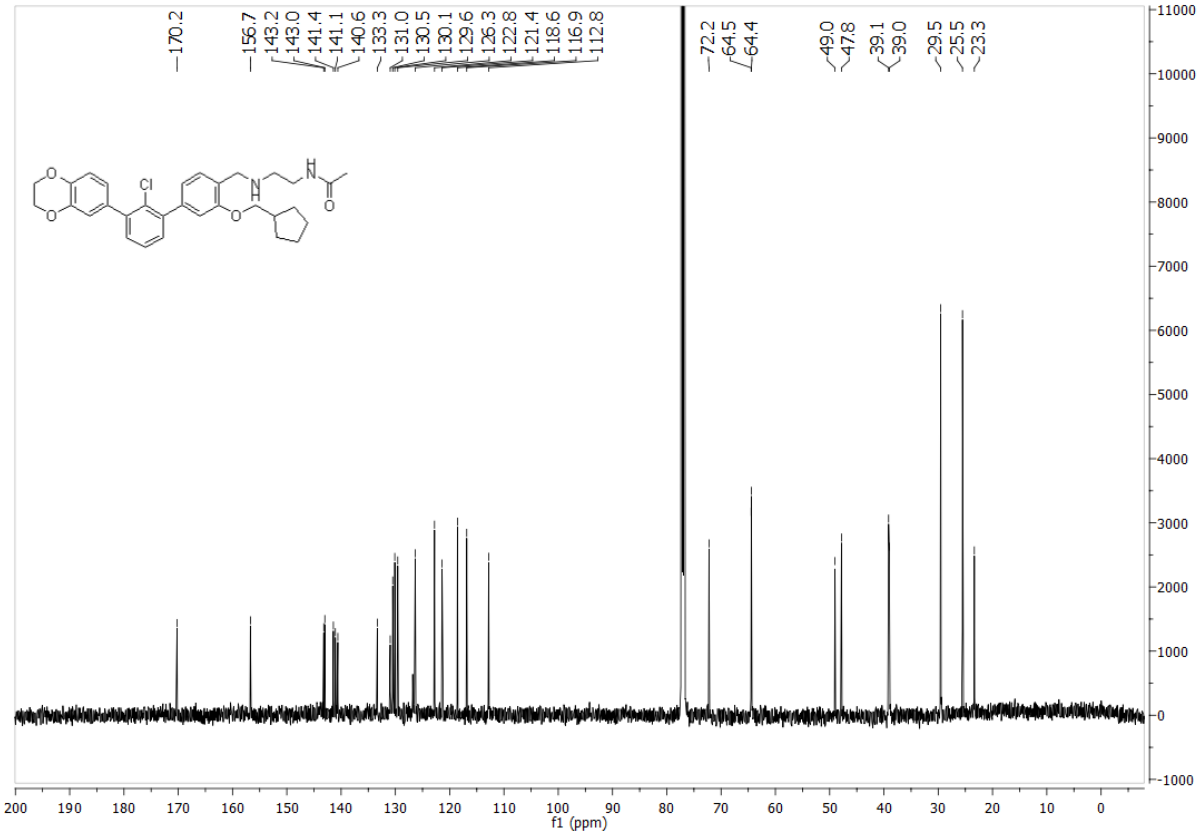
7f. N-(2-(((3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-(cyclobutylmethoxy)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



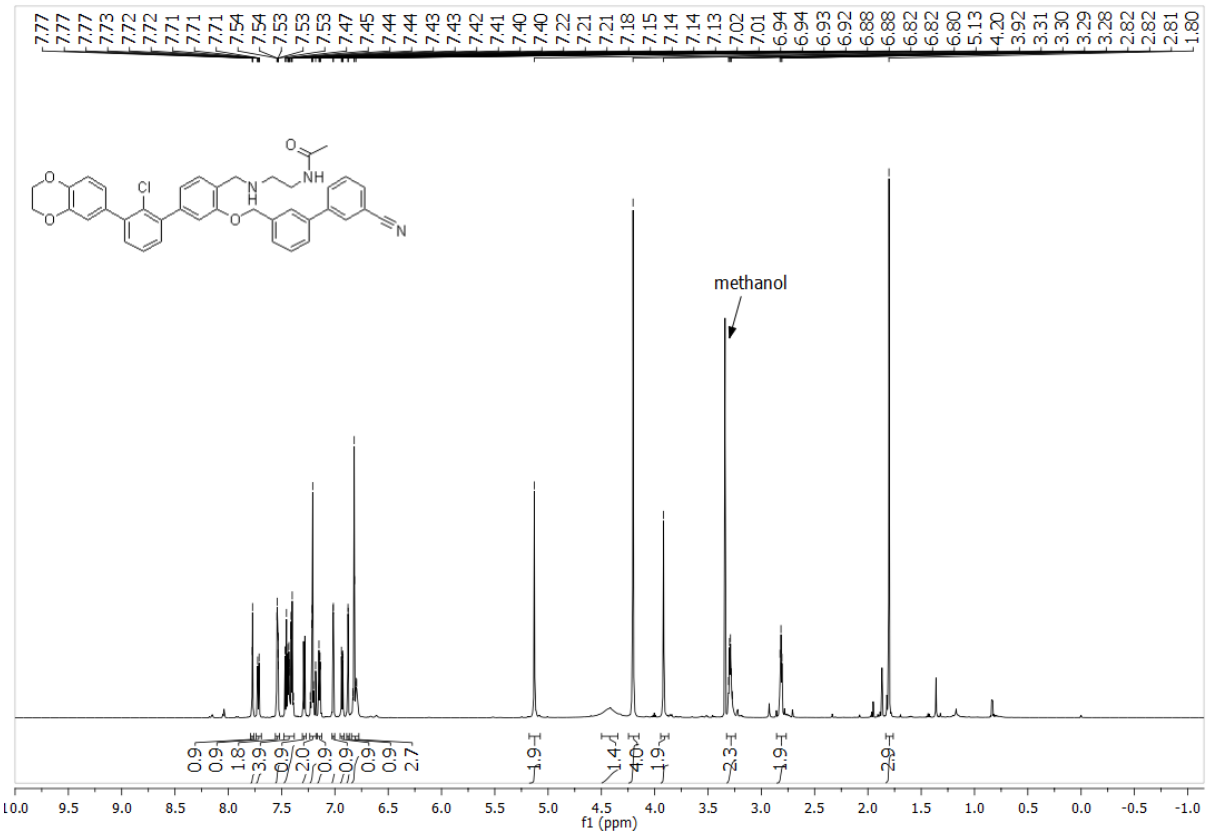


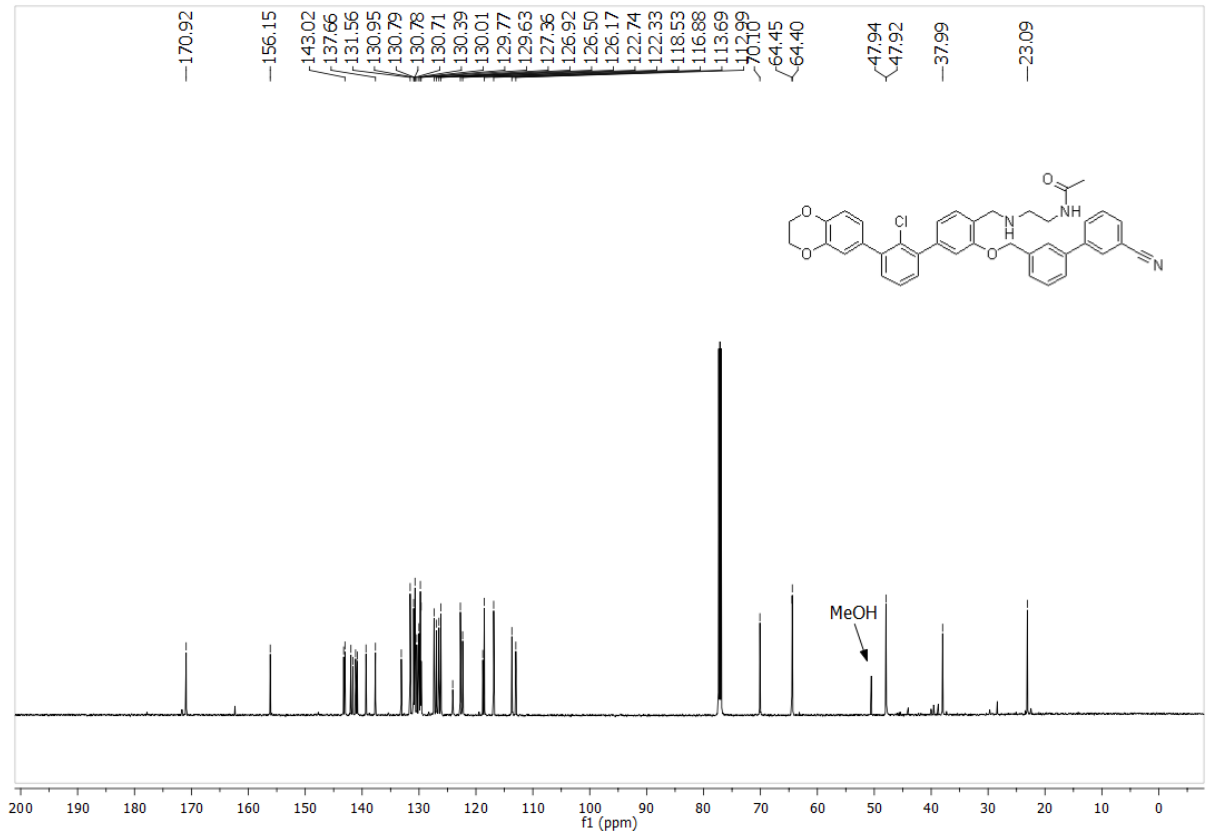
7g. N-(2-(((3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-(cyclopentylmethoxy)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



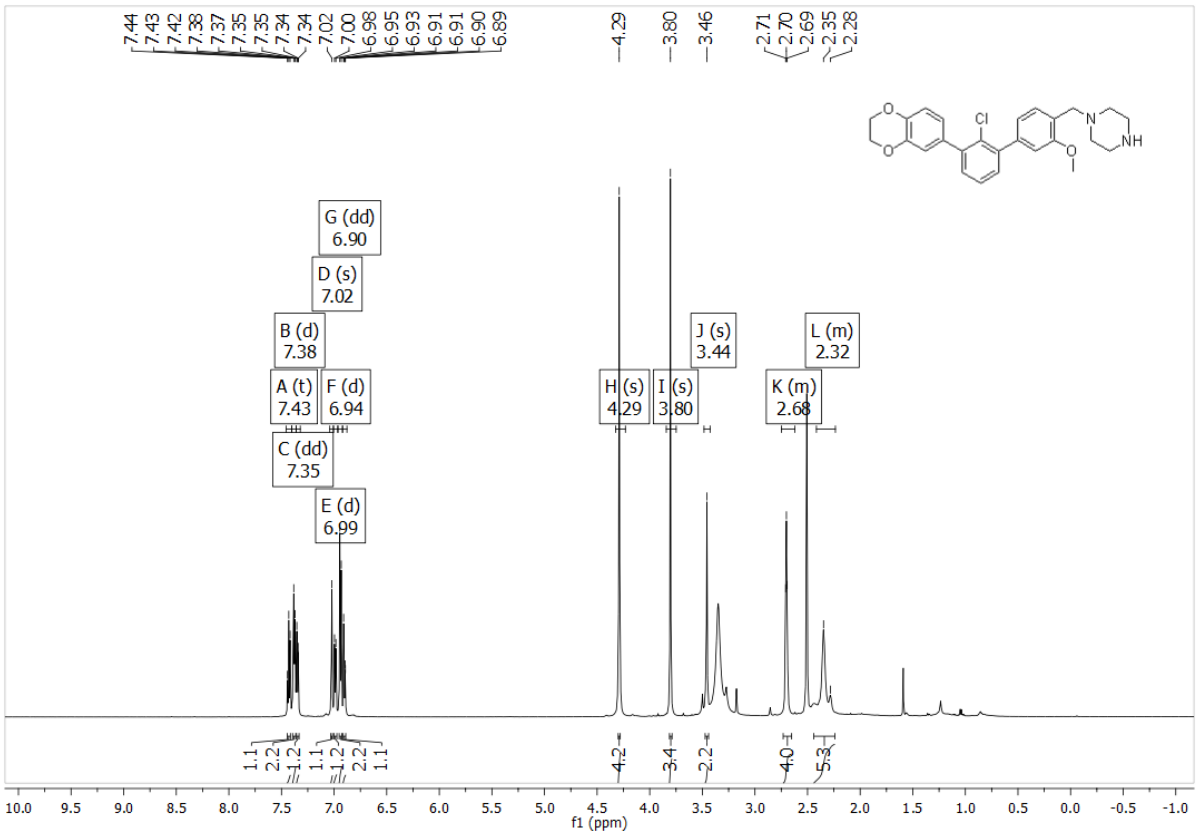


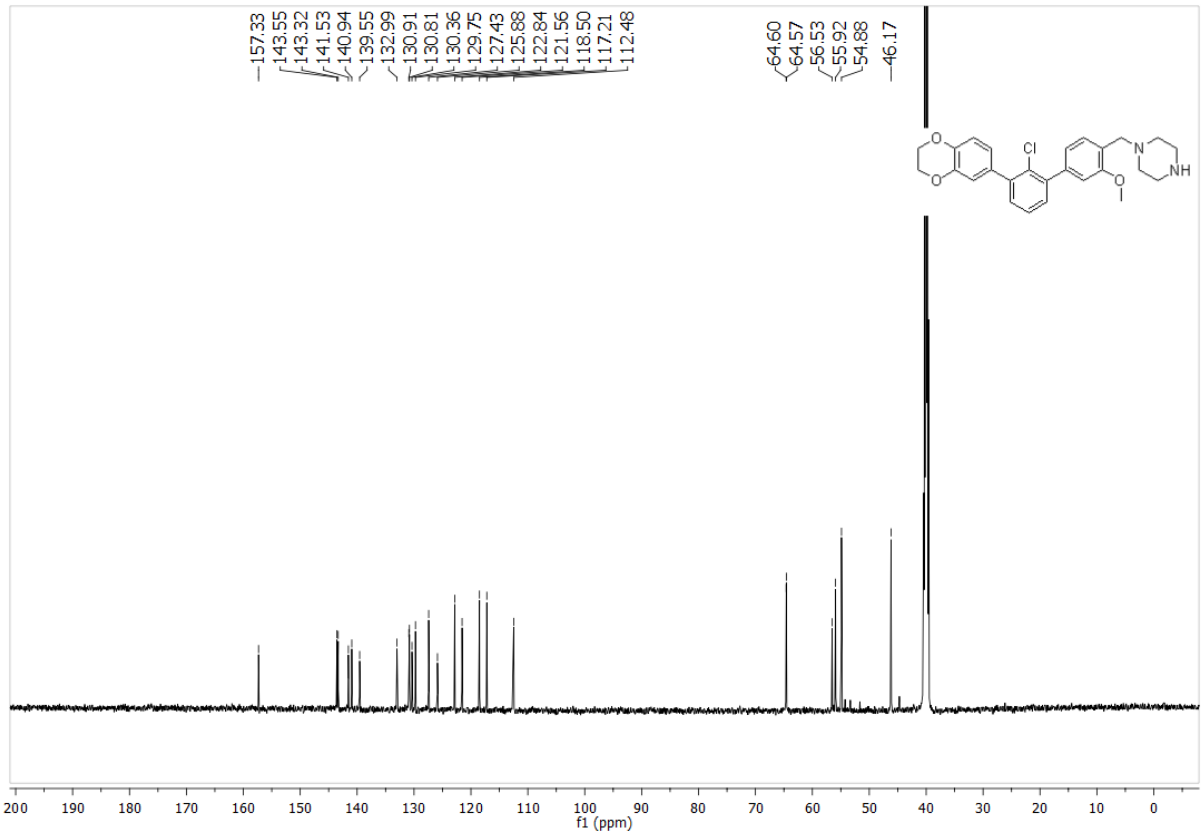
7h. N-(2-(((3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-((3'-cyano-[1,1'-biphenyl]-3-yl)methoxy)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



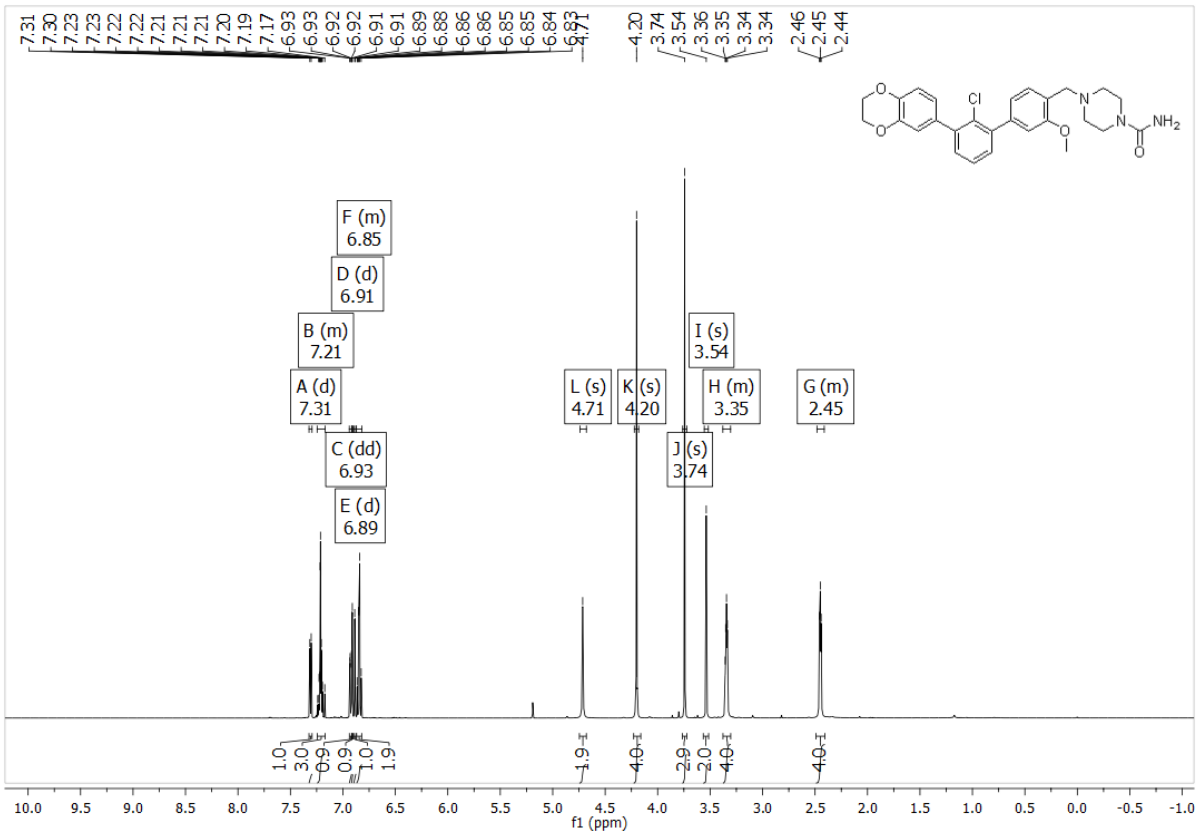


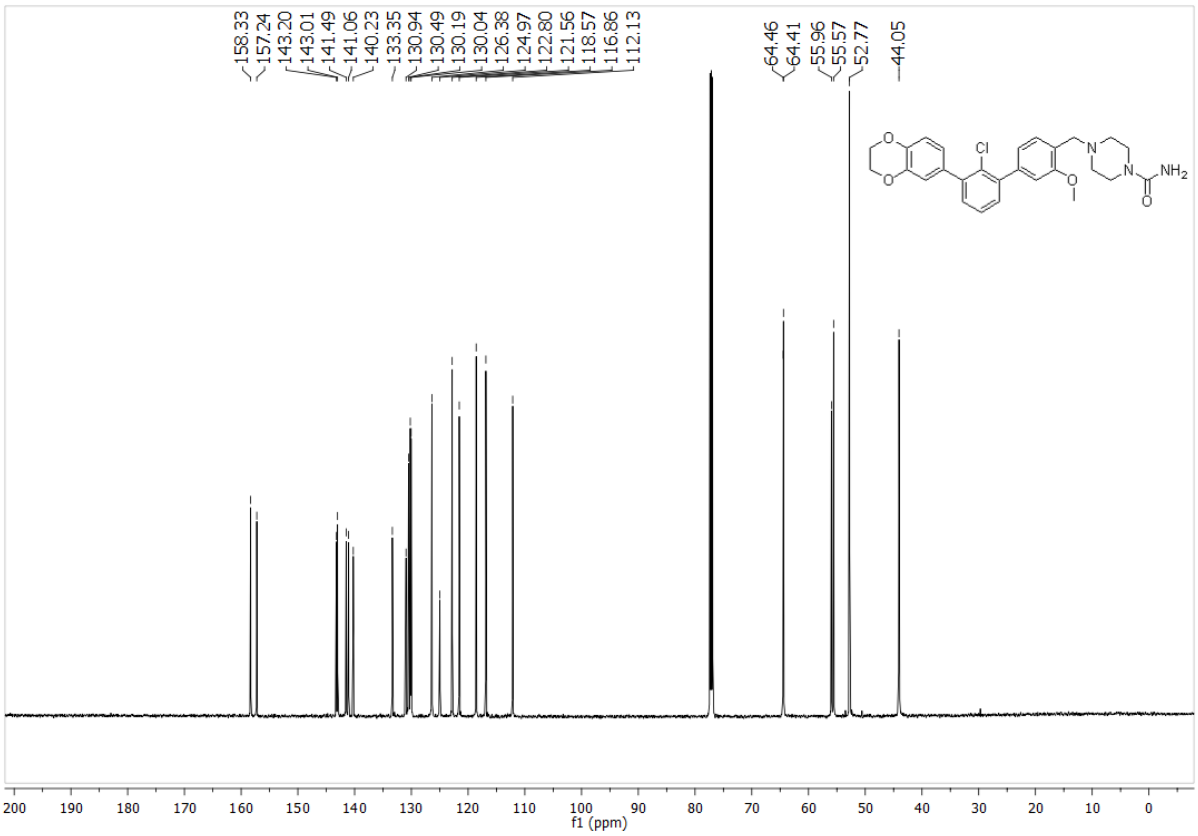
8a. 1-((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)piperazine



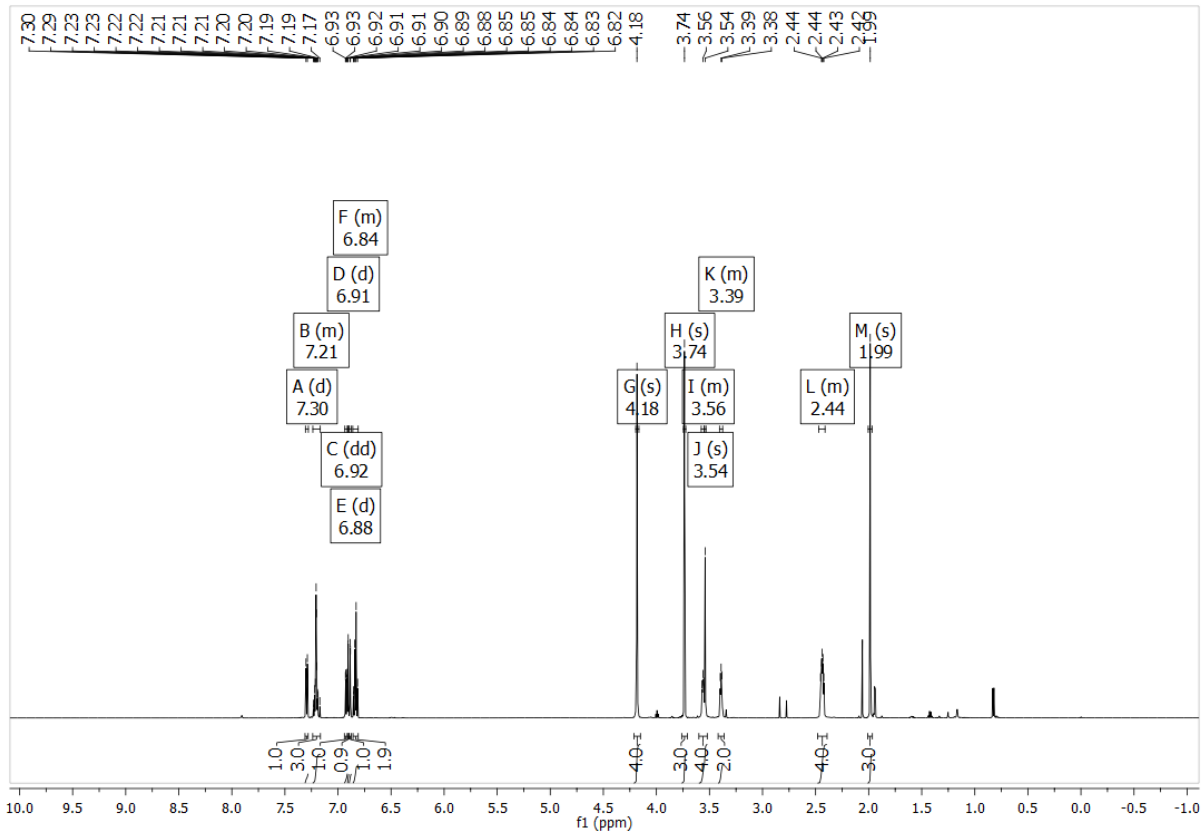


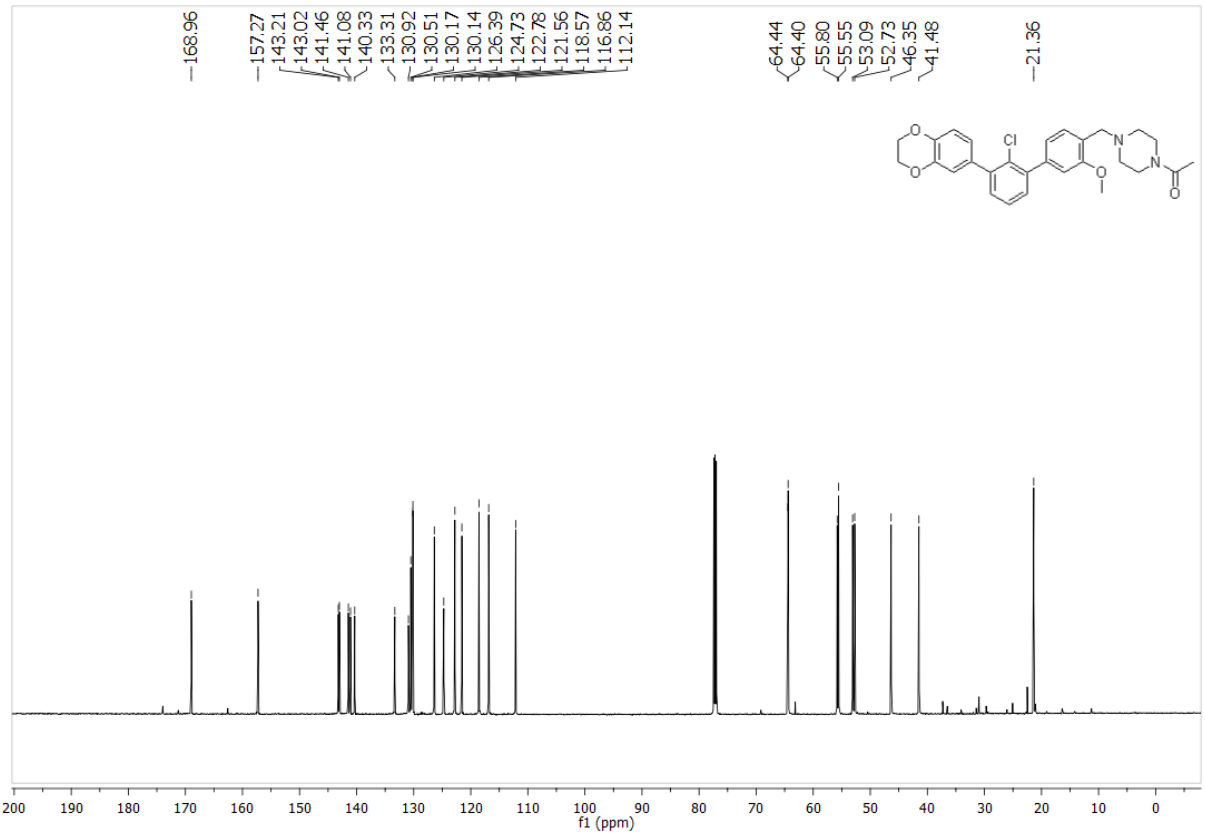
8b. 4-((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)piperazine-1-carboxamide



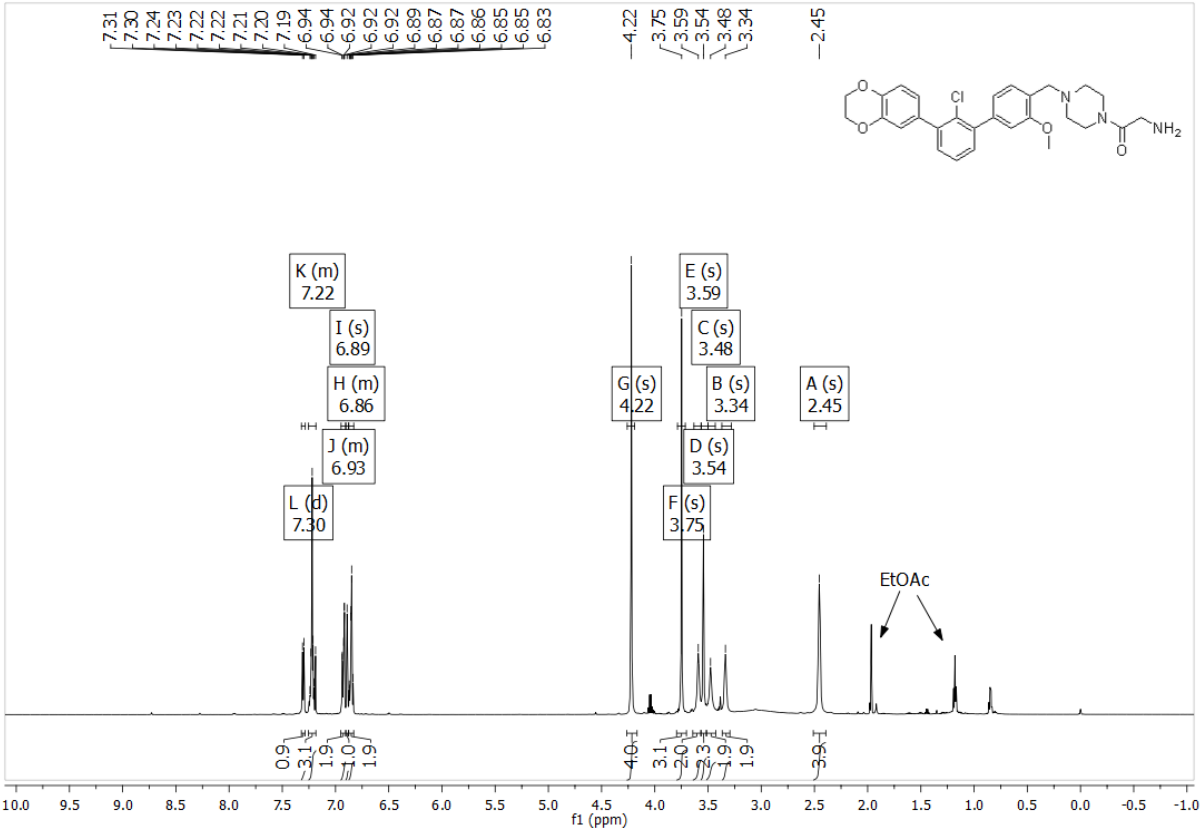


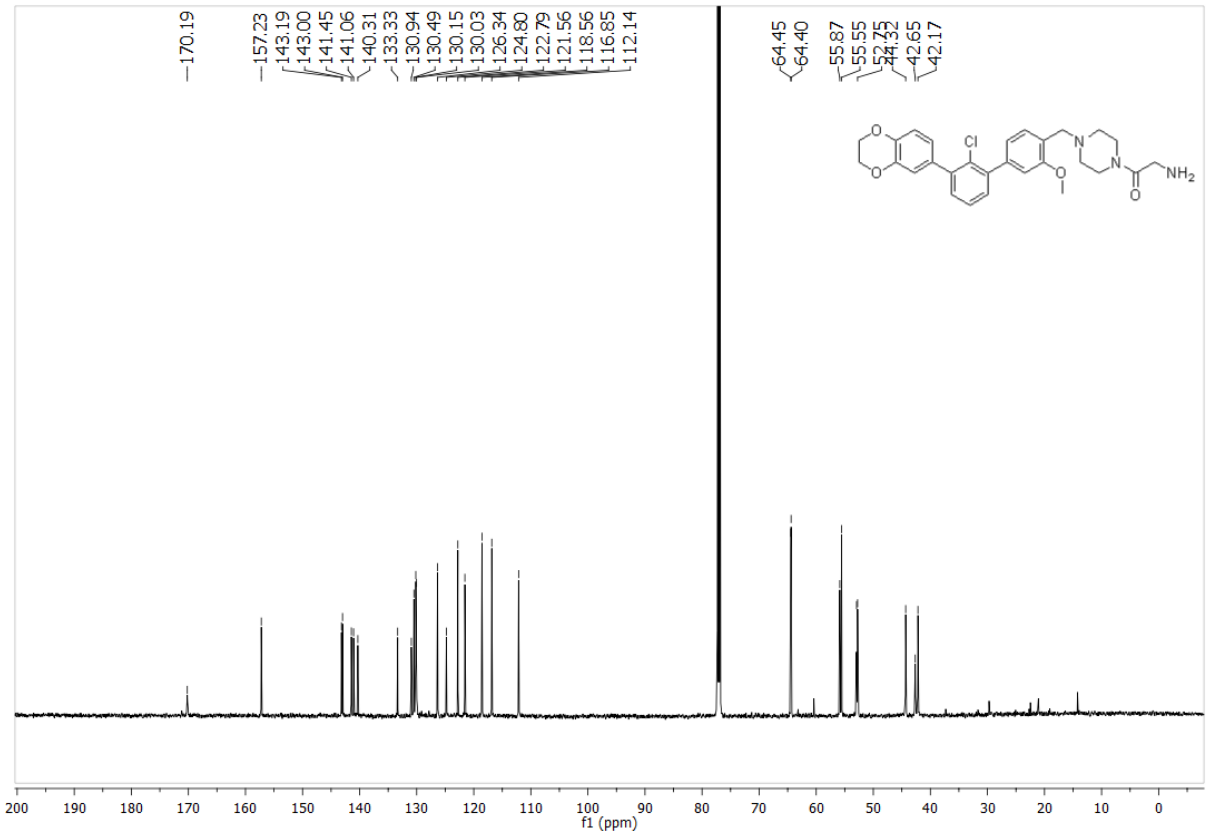
8c. 1-(4-((2'-Chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)piperazin-1-yl)ethan-1-one



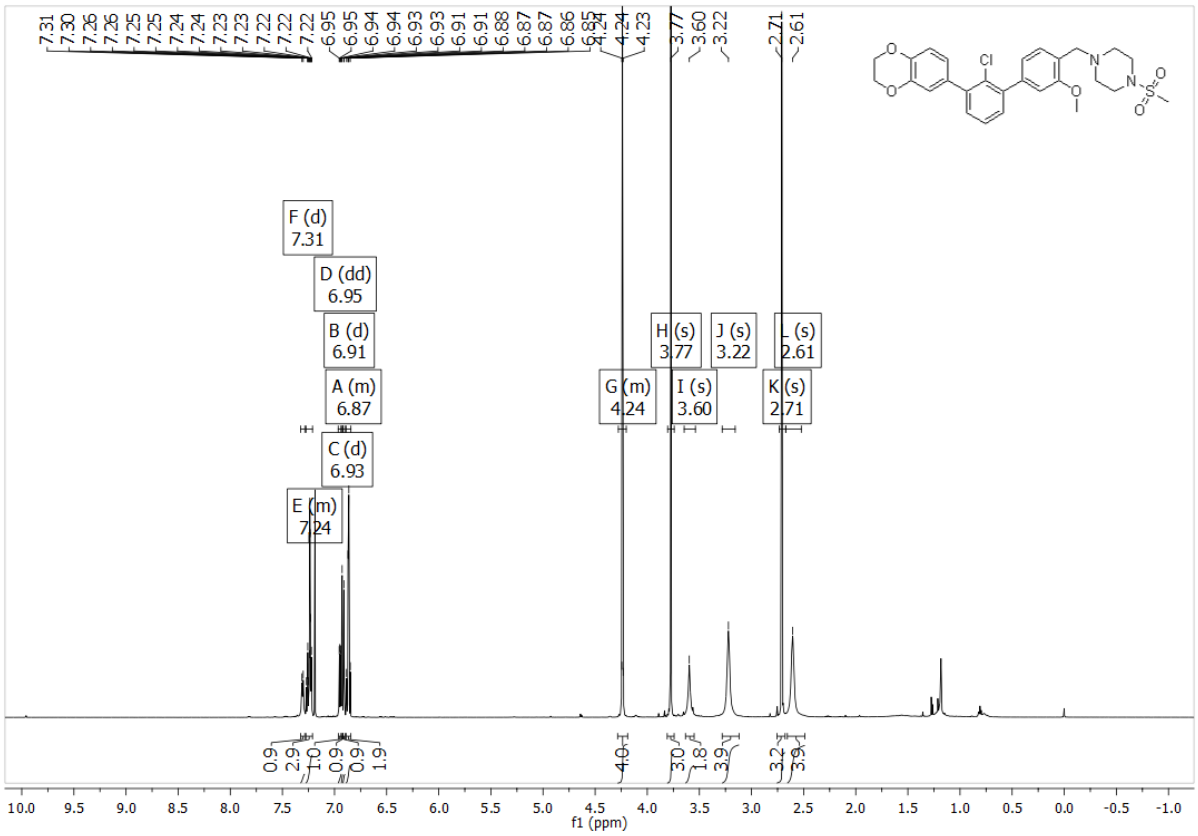


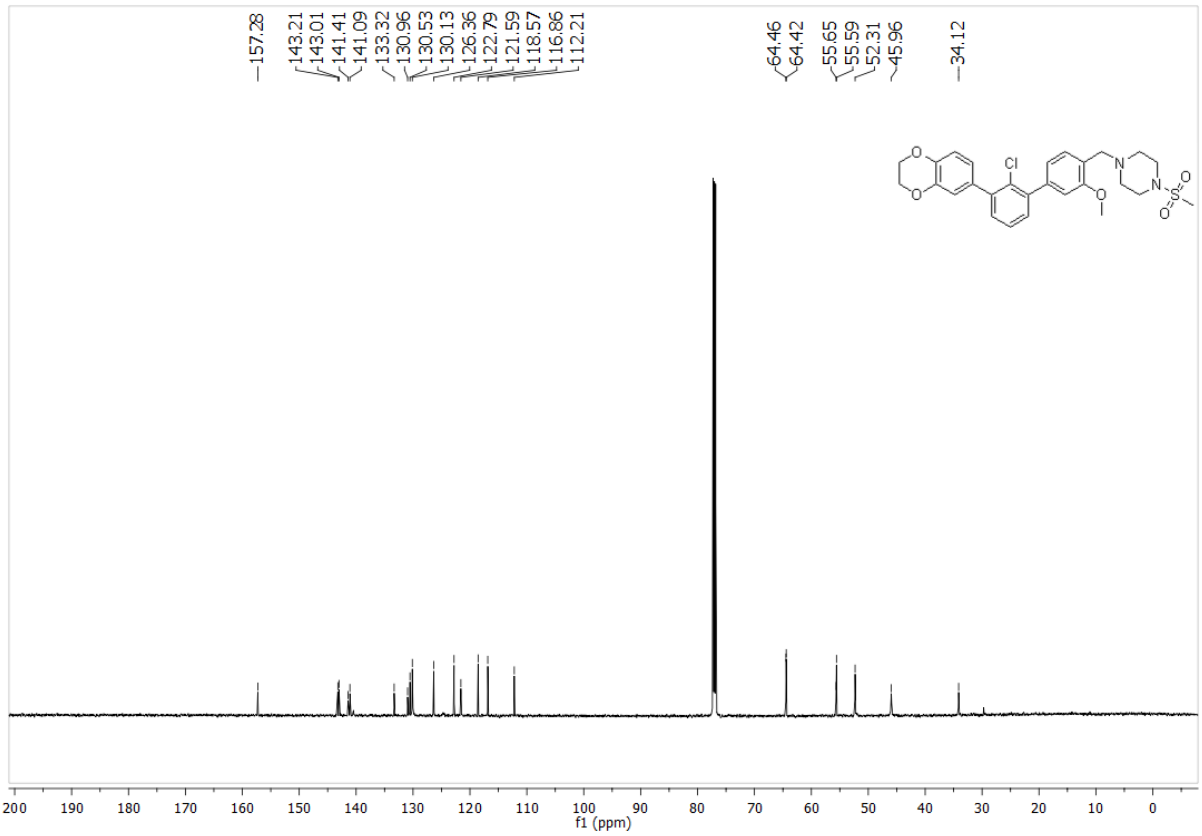
8d. 2-amino-1-(4-((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)piperazin-1-yl)ethan-1-one



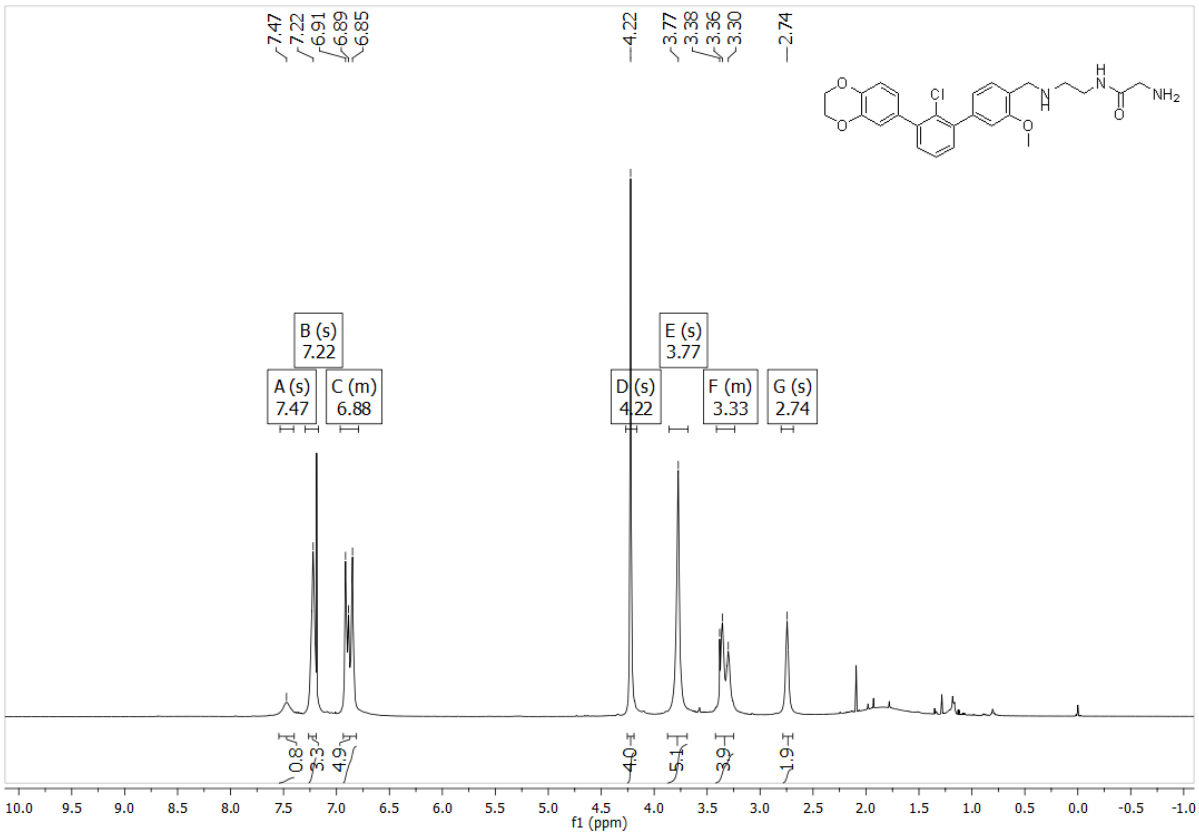


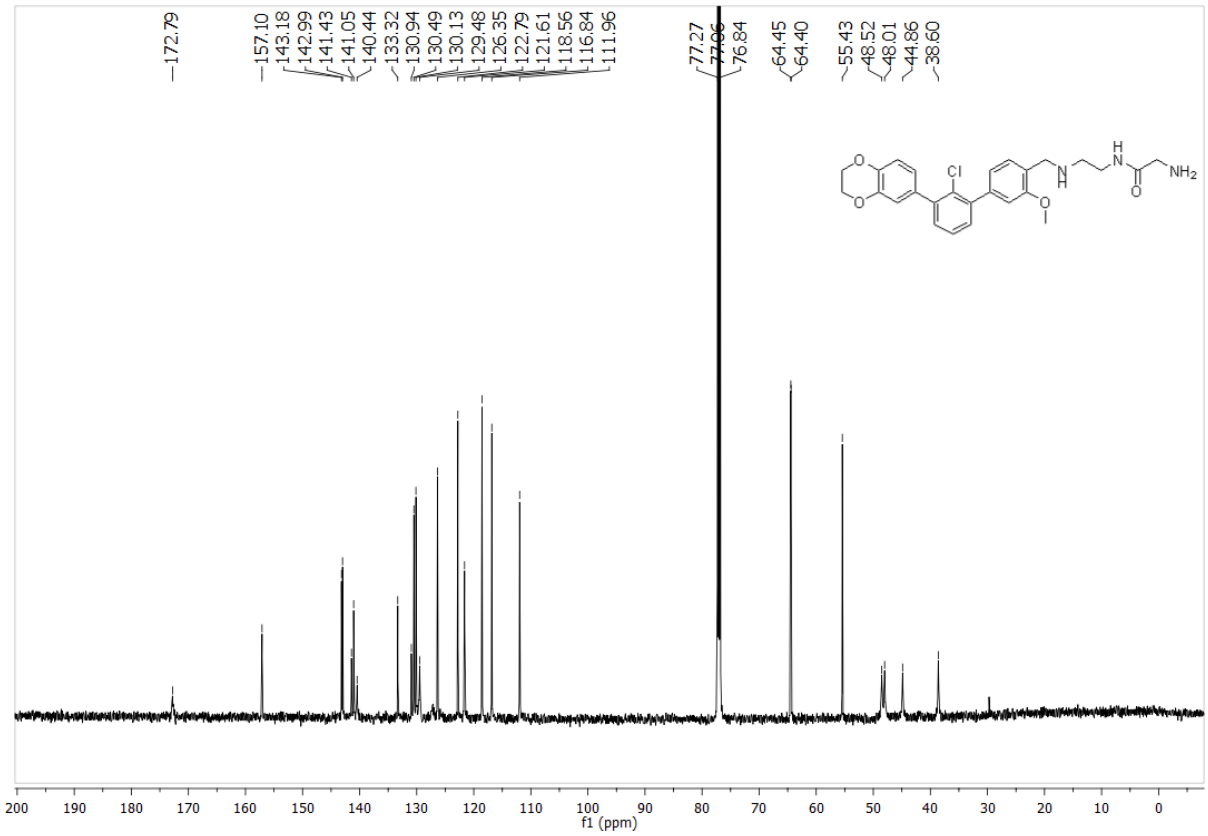
8e. 1-((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)-4-(methylsulfonyl)piperazine



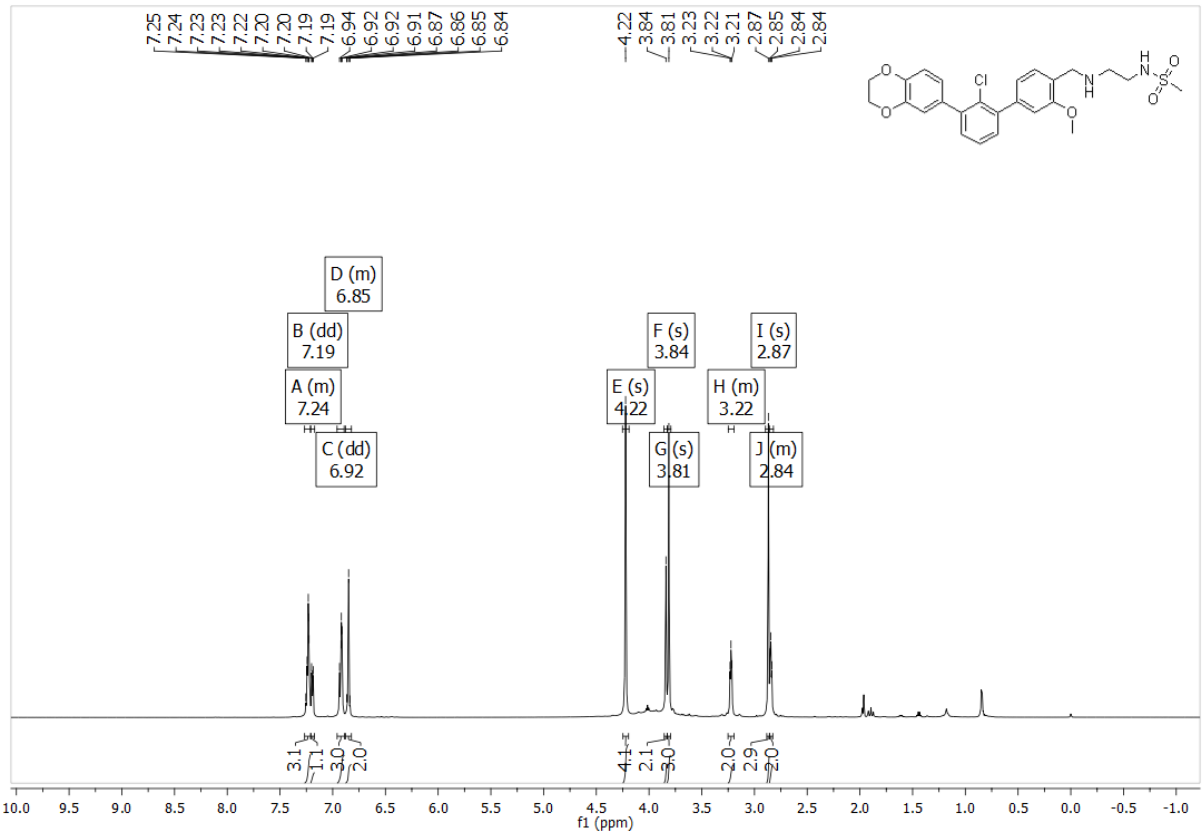


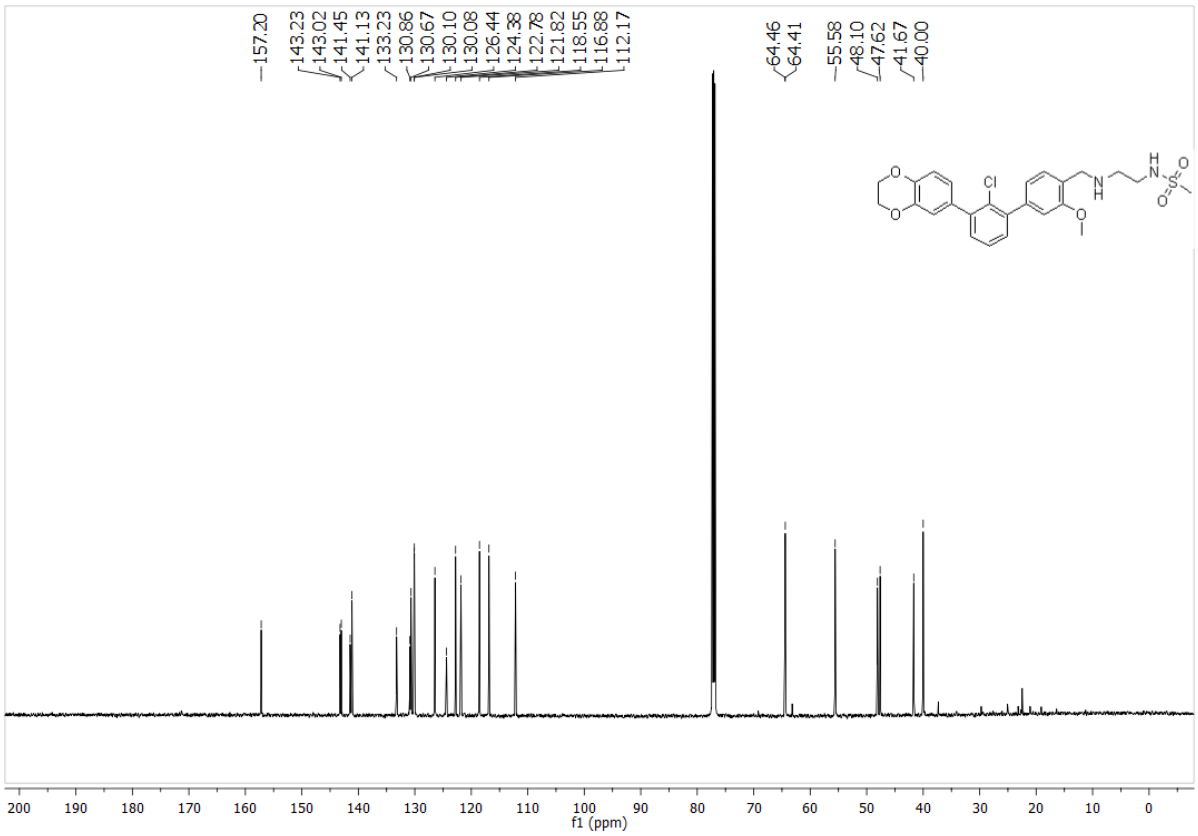
8f. 2-amino-N-(2-(((benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



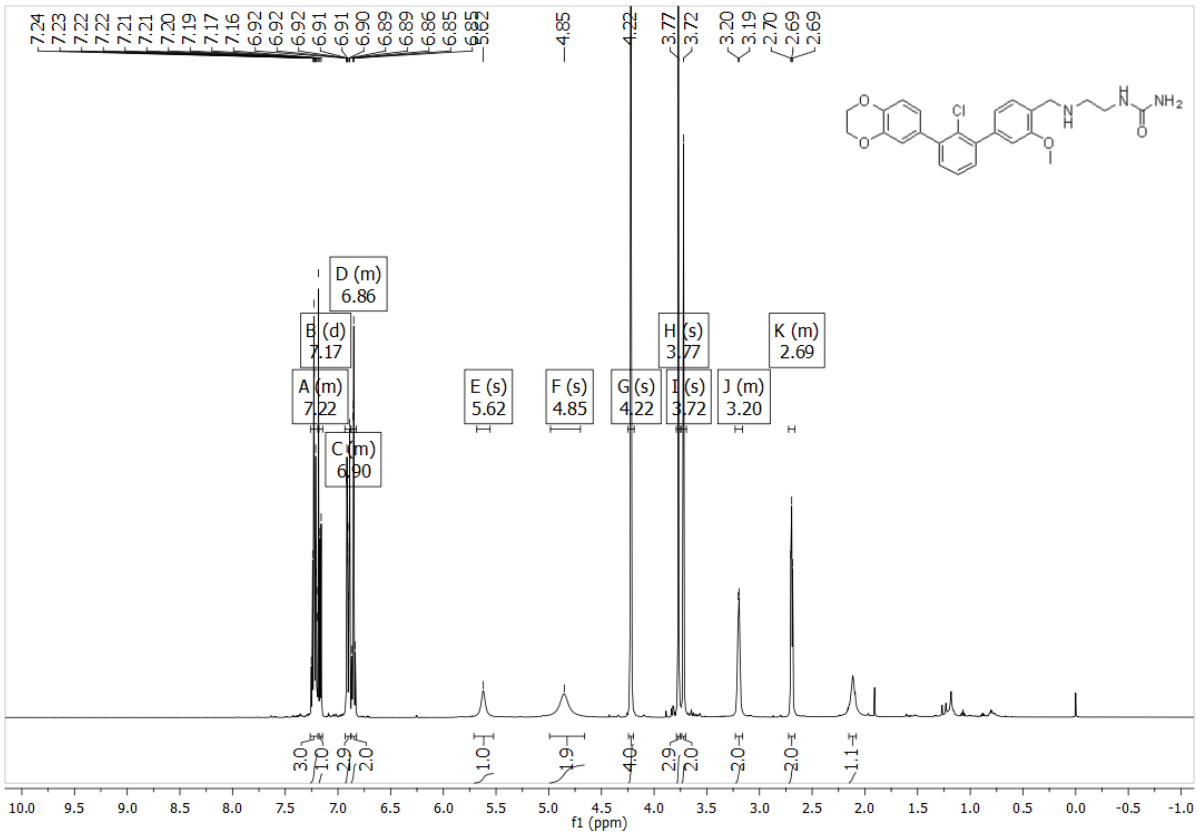


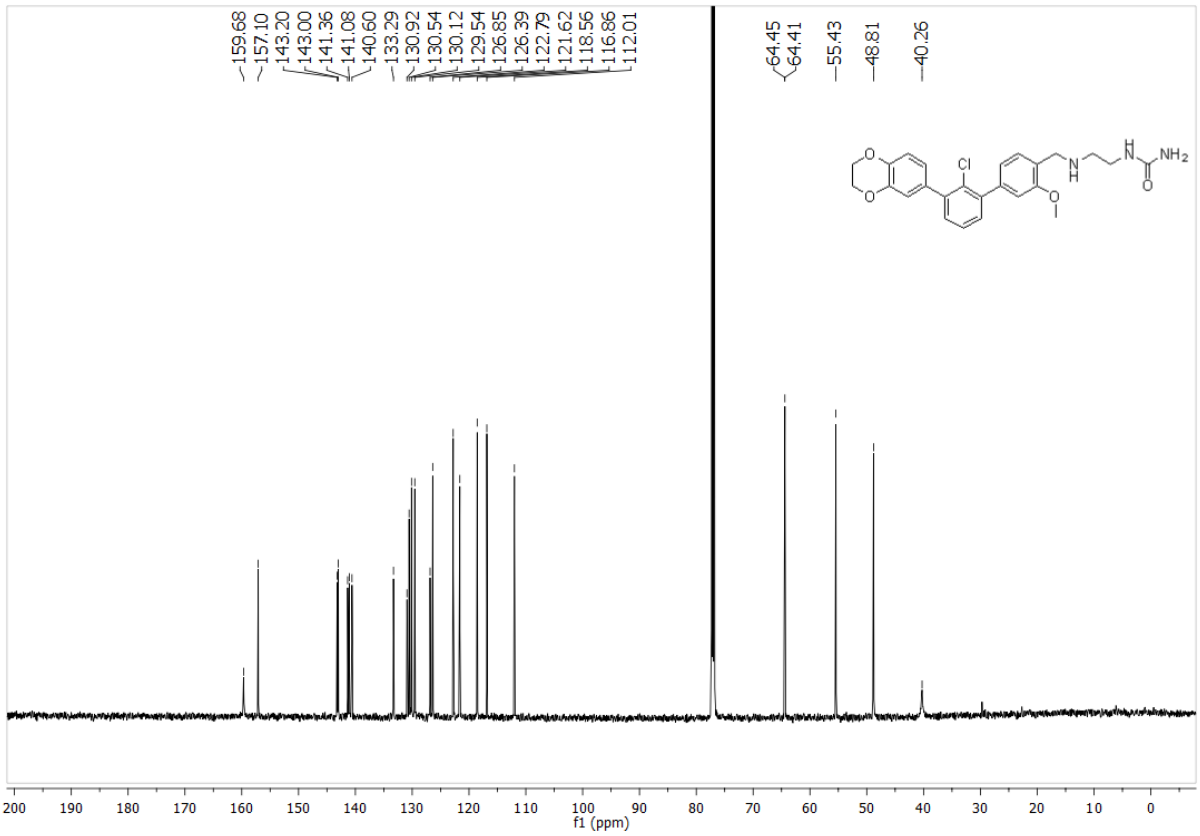
8g. N-(2-(((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)methanesulfonamide



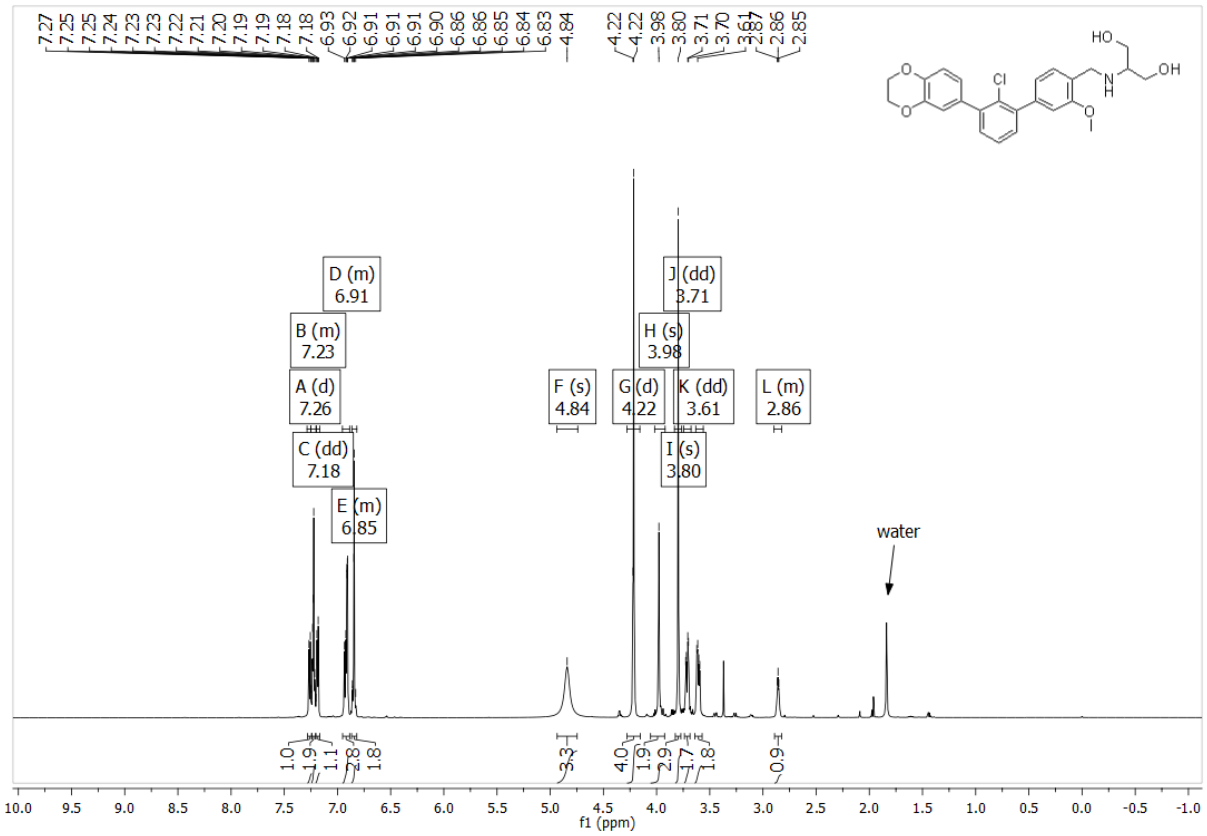


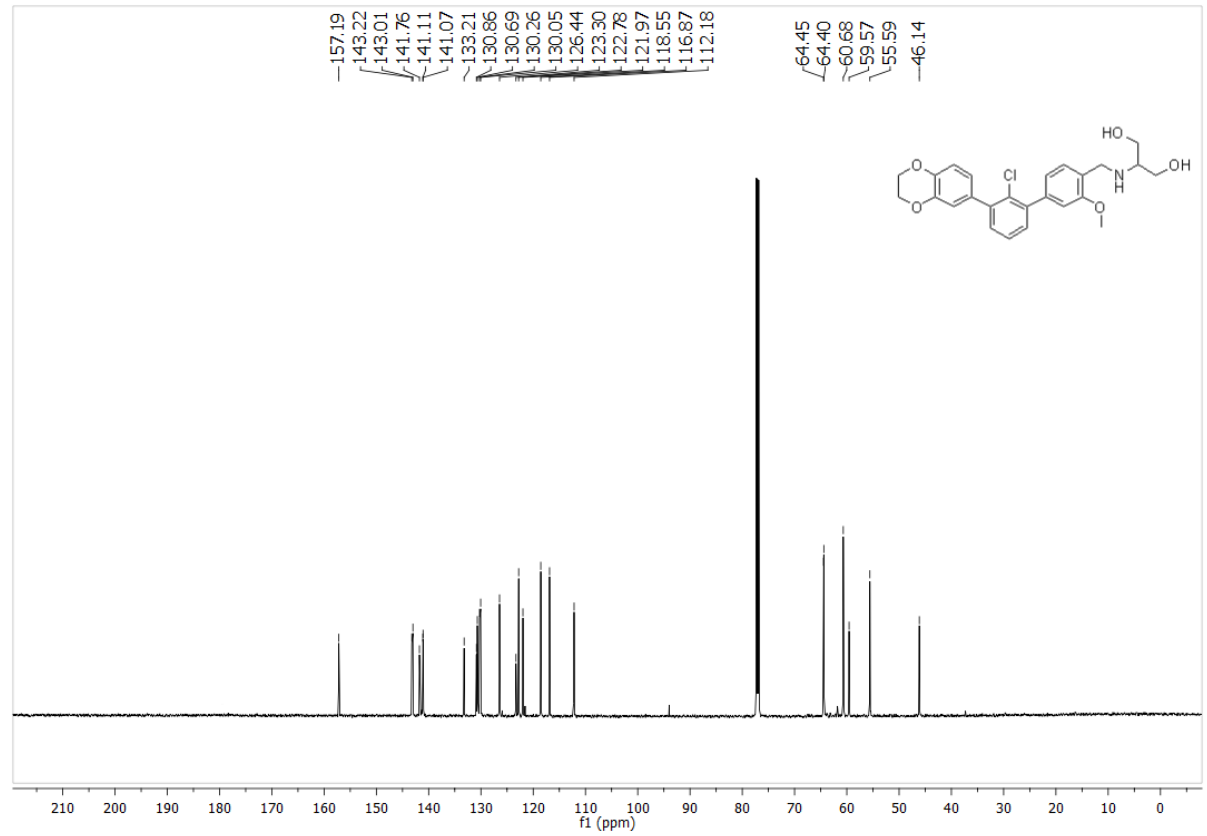
8h. 1-(2-(((2'-Chloro-3'-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)urea



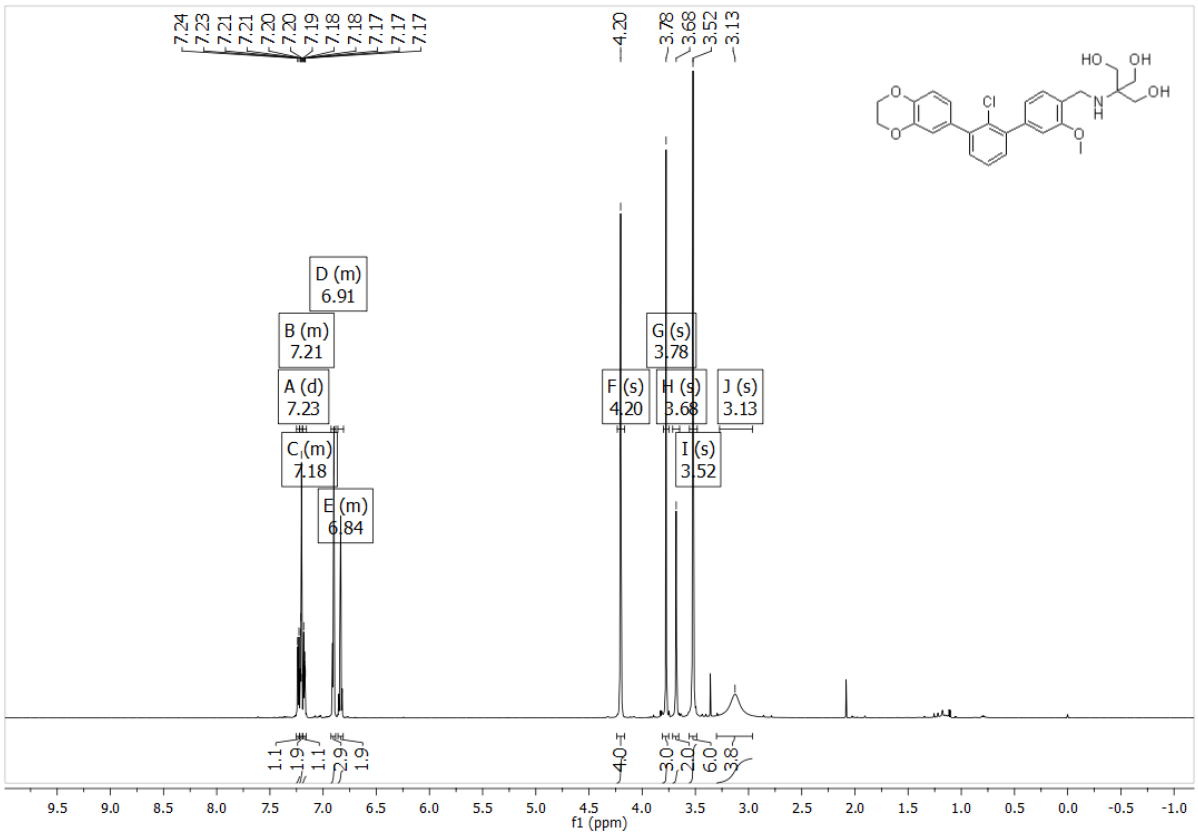


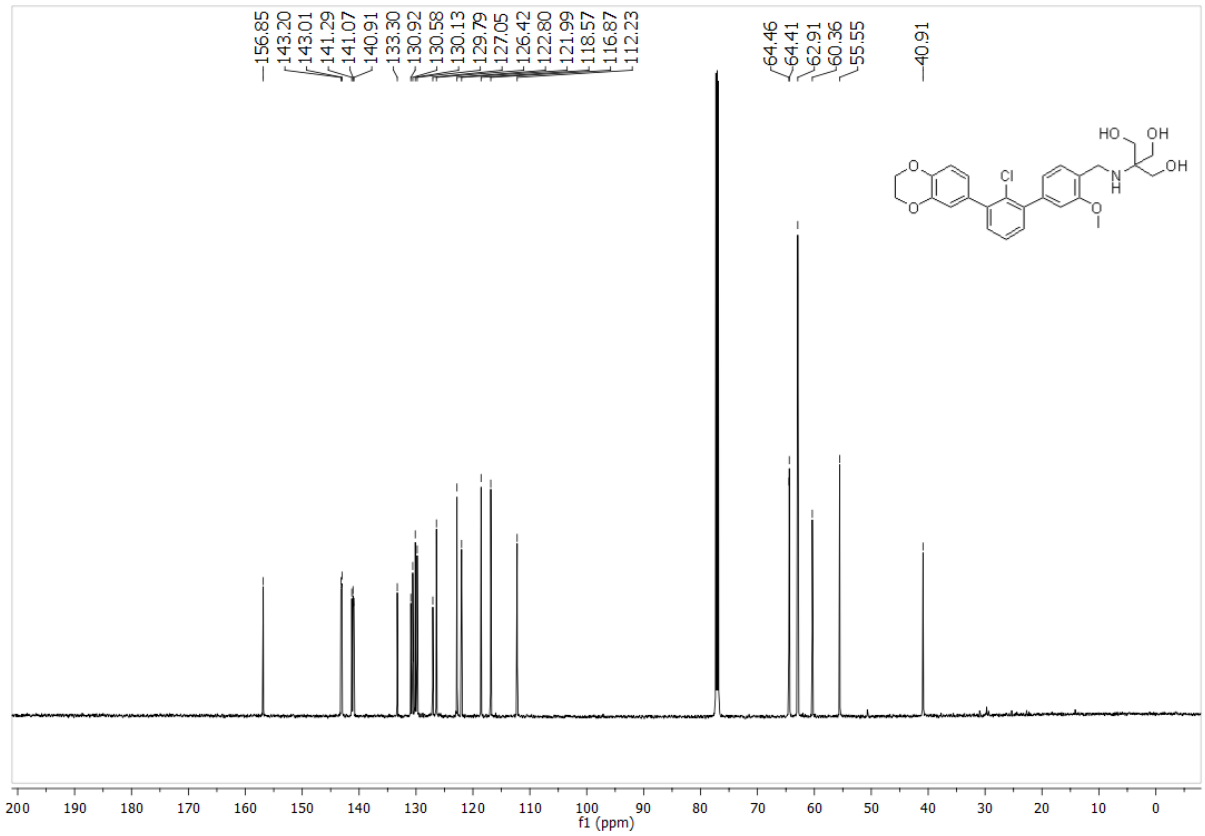
8i. 2-(((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)propane-1,3-diol





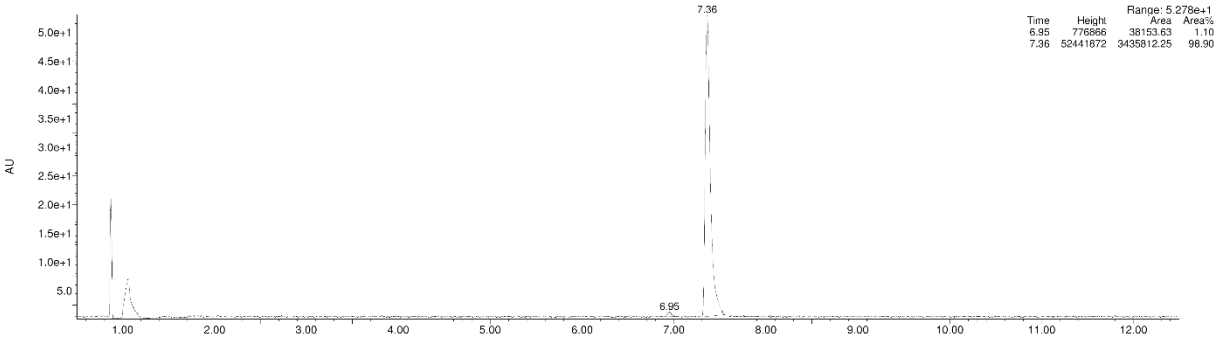
8j. 2-(((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)-2-(hydroxymethyl)propane-1,3-diol



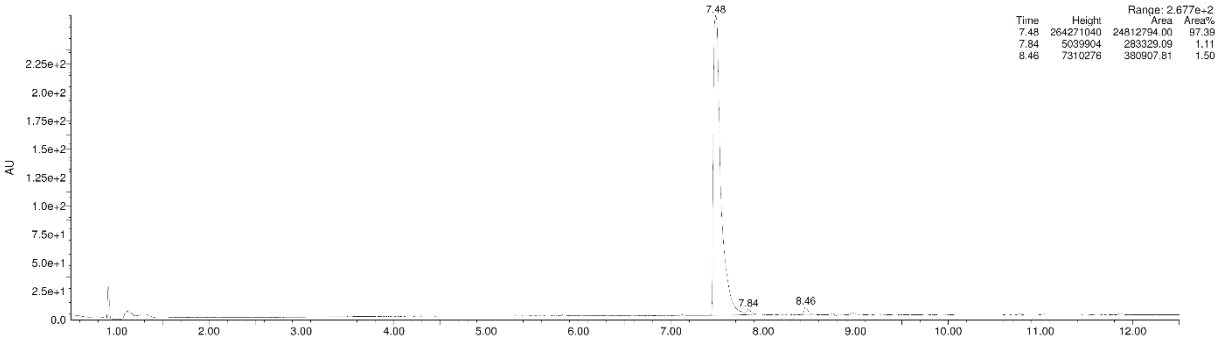


4. COPIES OF LCMS OF FINAL COMPOUNDS

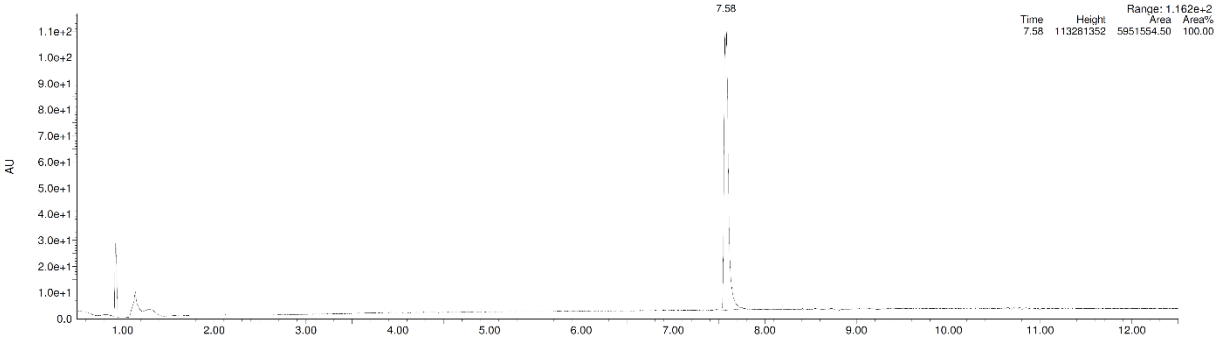
4a. (3'-(Benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methanol



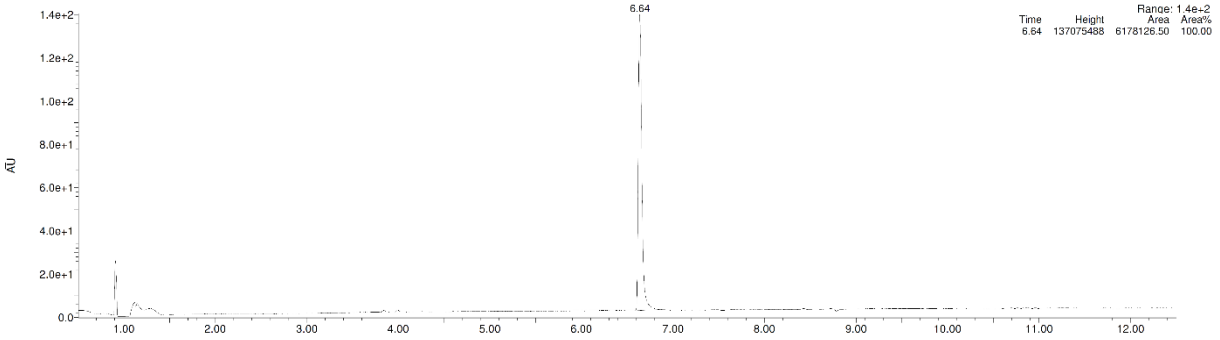
4b. (3'-(Benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methanol



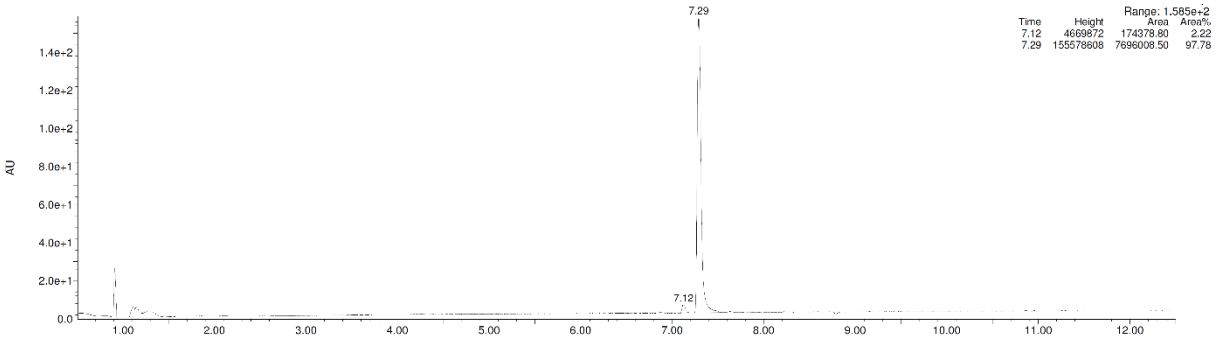
4c. (3'-(Benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)methanol



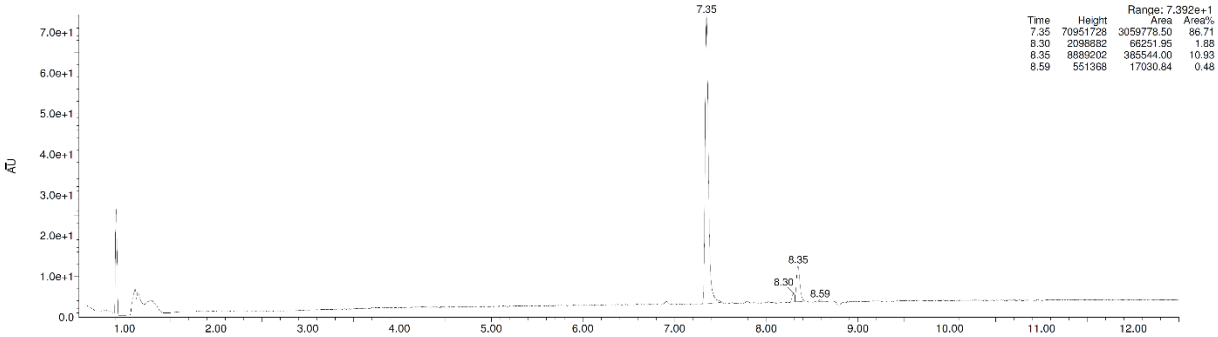
4d. (2'-Amino-3'-(benzo-1,4-dioxan-6-yl)-[1,1'-biphenyl]-4-yl)methanol



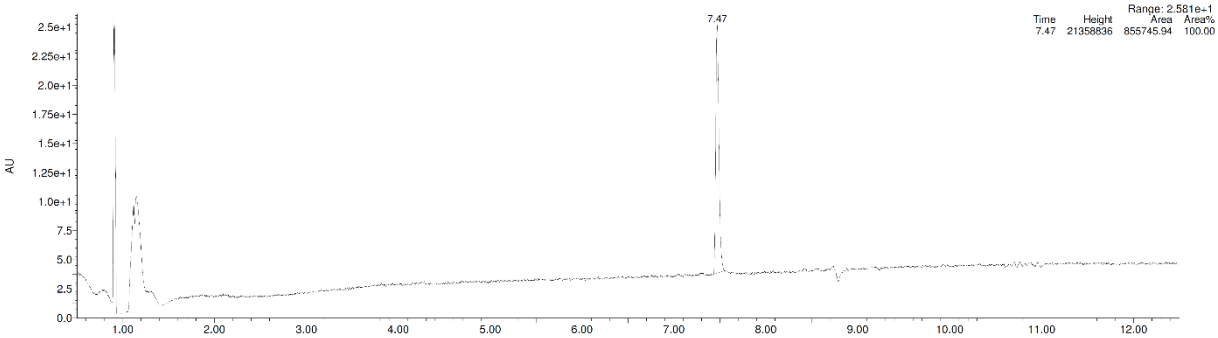
4e. (3'-(Benzo-1,4-dioxan-6-yl)-2'-chloro-[1,1'-biphenyl]-4-yl)methanol



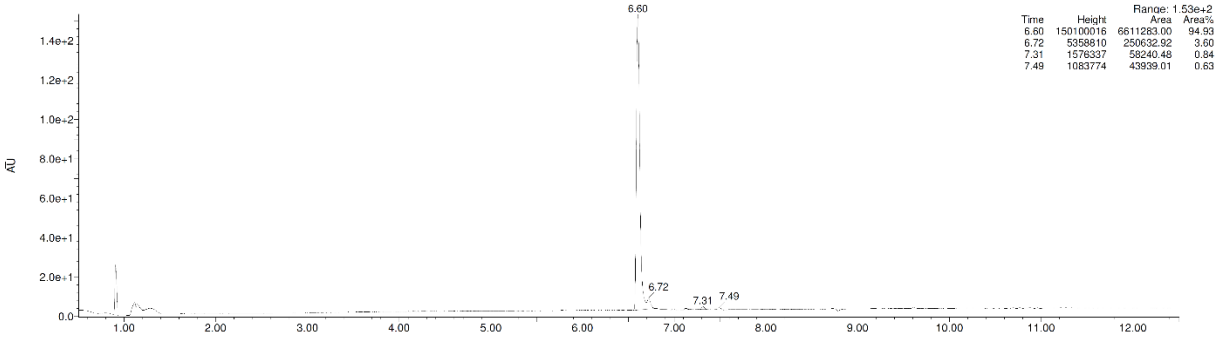
4f. (2'-Bromo-3'-(benzo-1,4-dioxan-6-yl)-[1,1'-biphenyl]-4-yl)methanol



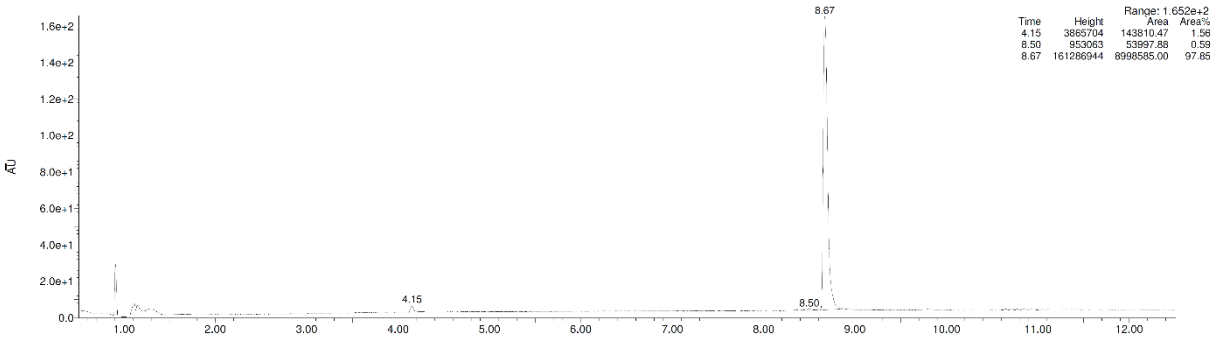
4g. (3'-(Benzo-1,4-dioxan-6-yl)-2'-iodo-[1,1'-biphenyl]-4-yl)methanol



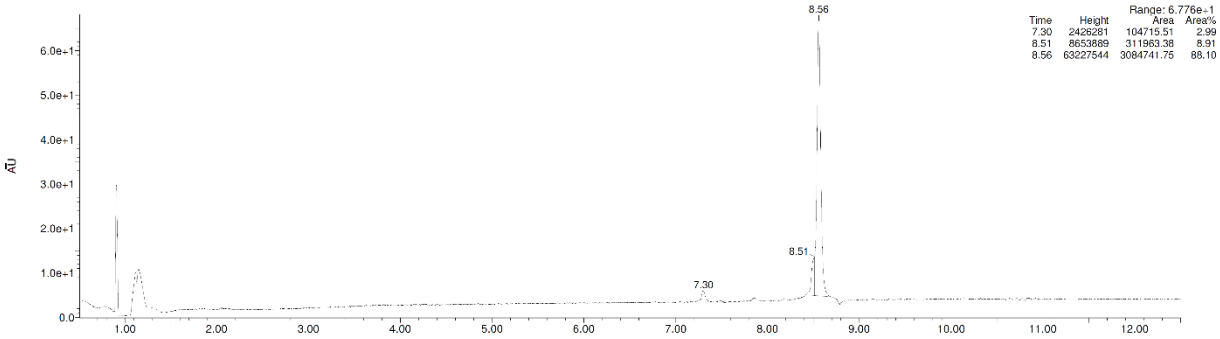
4h. 3-(3'-(Benzo-1,4-dioxan-6-yl)-4'-(hydroxymethyl)-[1,1'-biphenyl]-2-carbonitrile



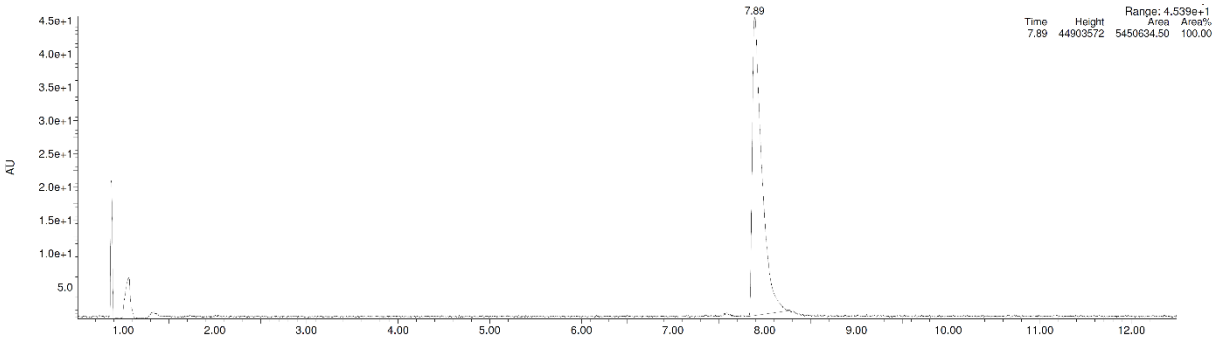
5b. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)benzoic acid



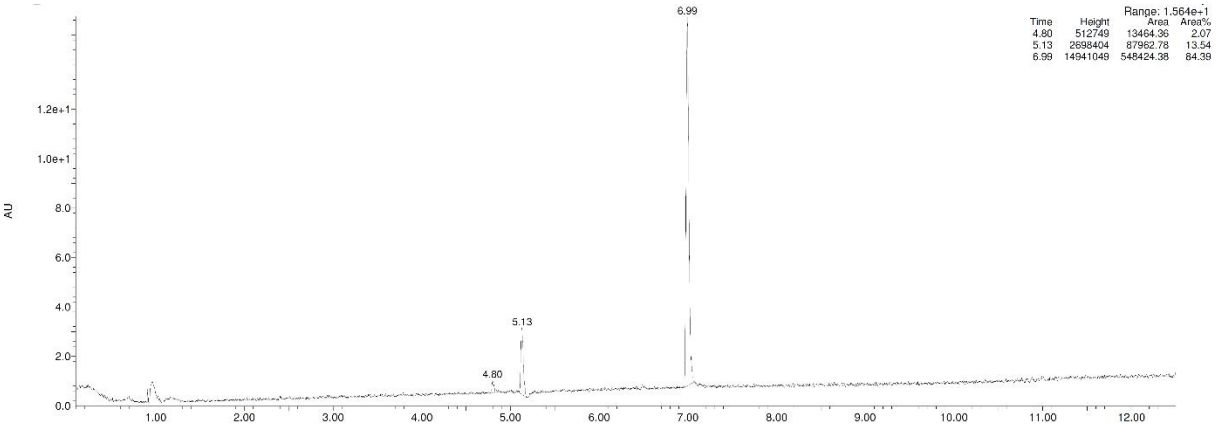
5d. 5-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)-2-(pyridin-3-yl)benzaldehyde



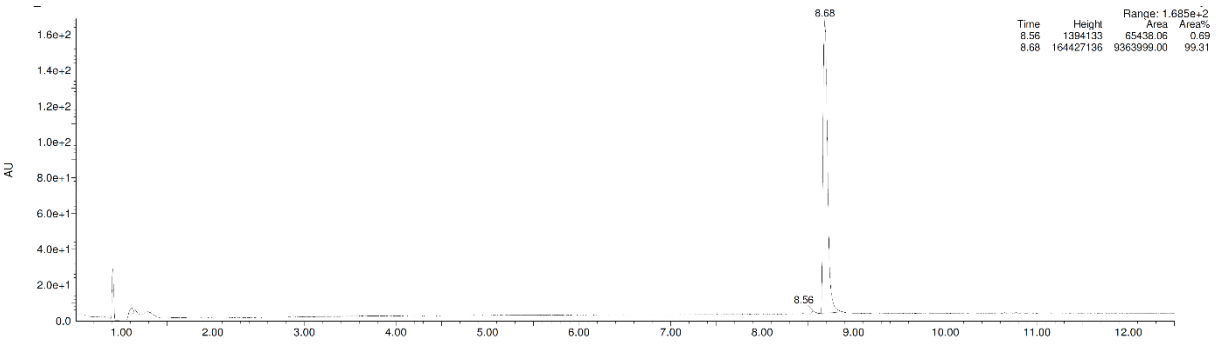
5f. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methoxy)isoxazole-5-carboxylic acid



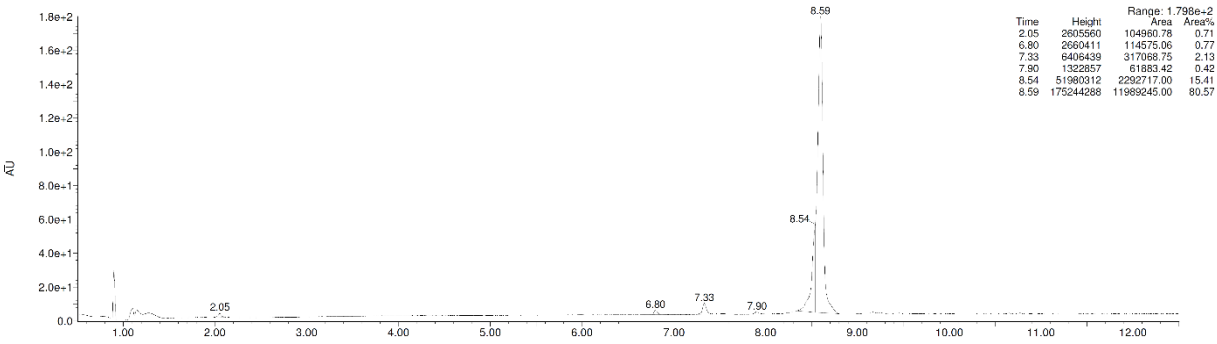
5h. 1-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid



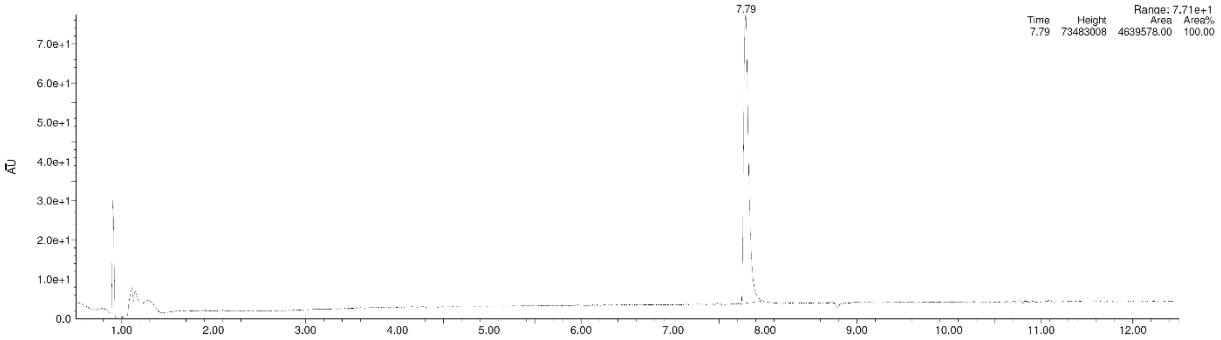
5j. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)benzoic acid



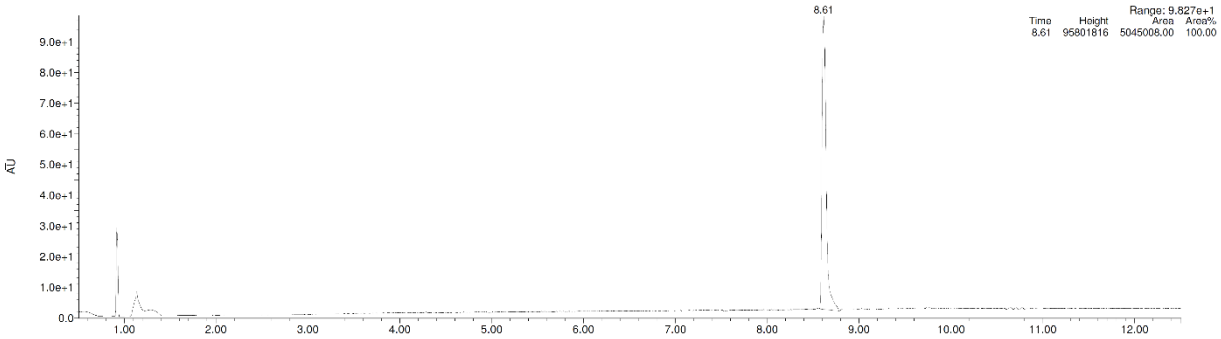
5l. 5-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)-2-(pyridin-3-yl)benzaldehyde



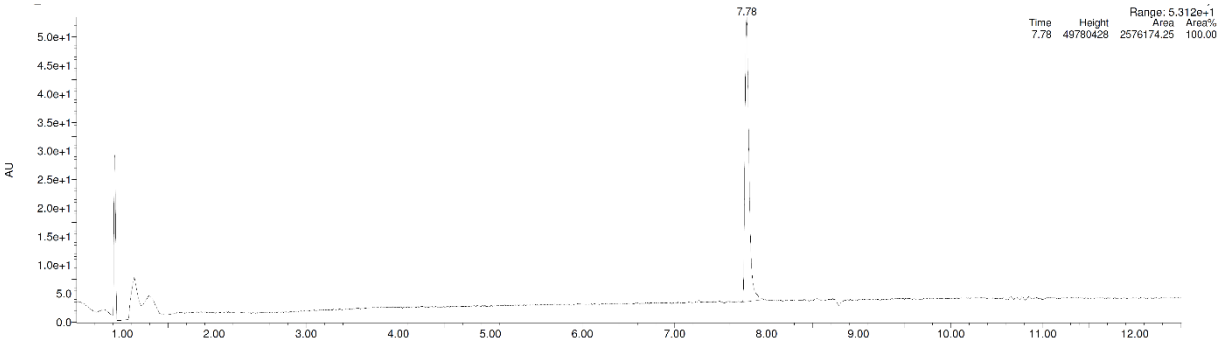
5n. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methoxy)isoxazole-5-carboxylic acid



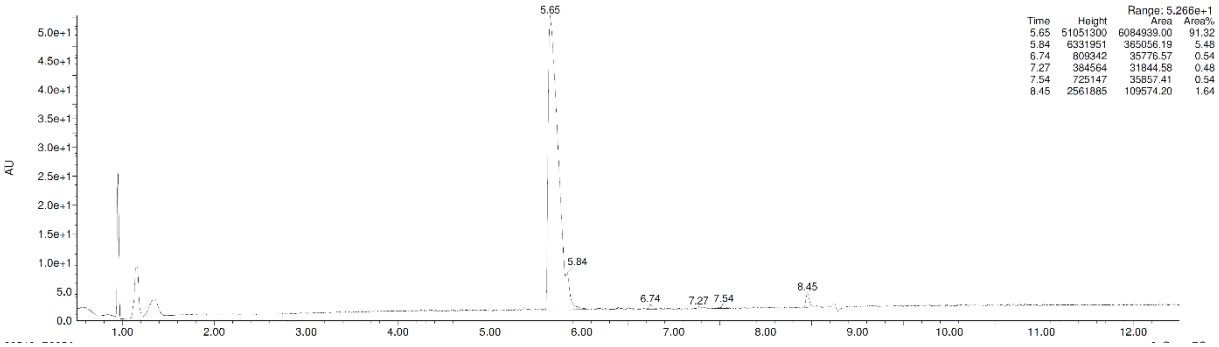
5p. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)methoxy)benzoic acid



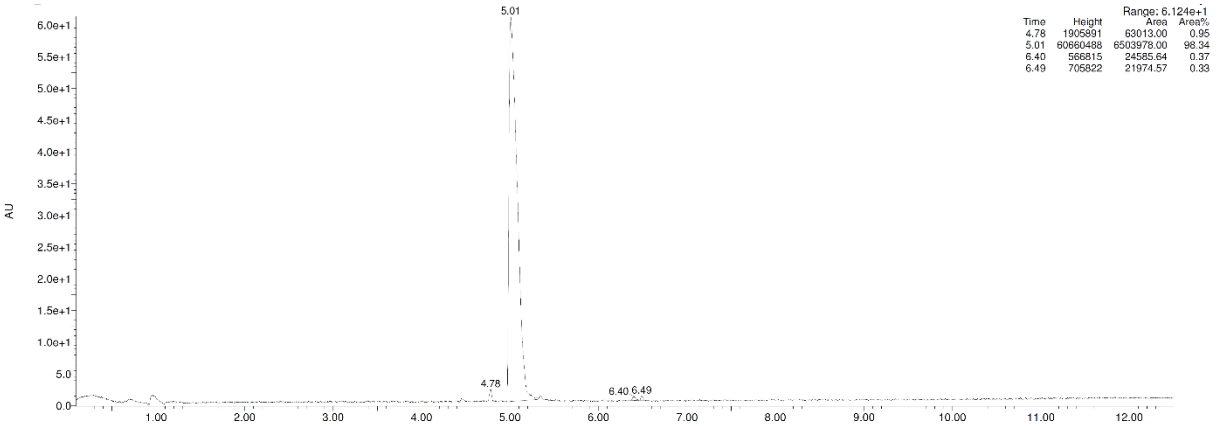
5r. 3-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)methoxy)isoxazole-5-carboxylic acid



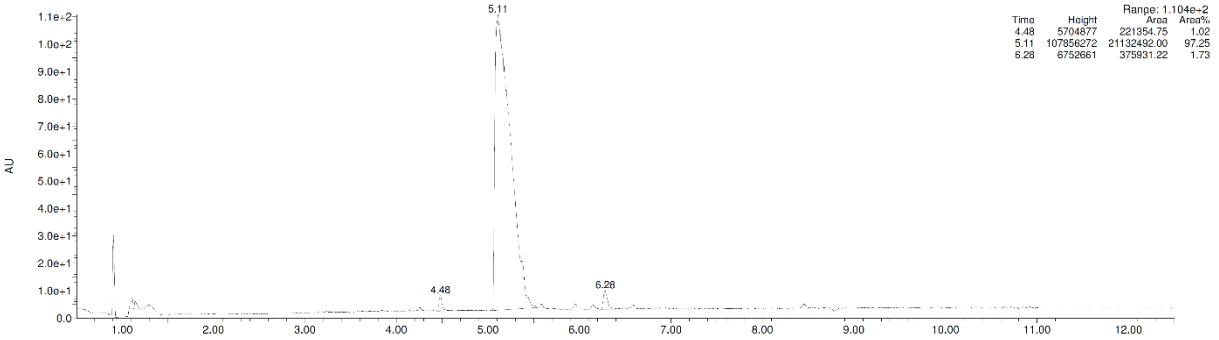
6a. 4-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)morpholine



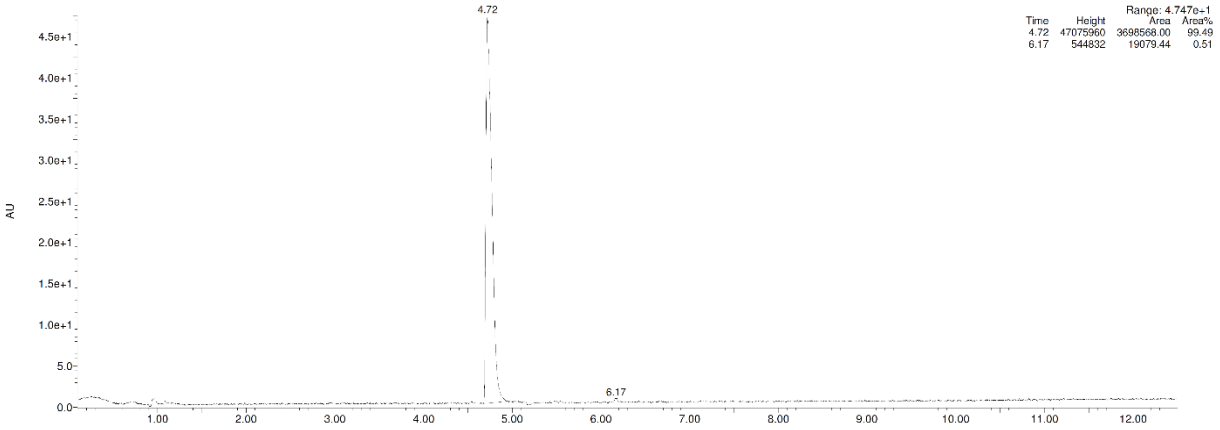
6b. 4-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)piperazine



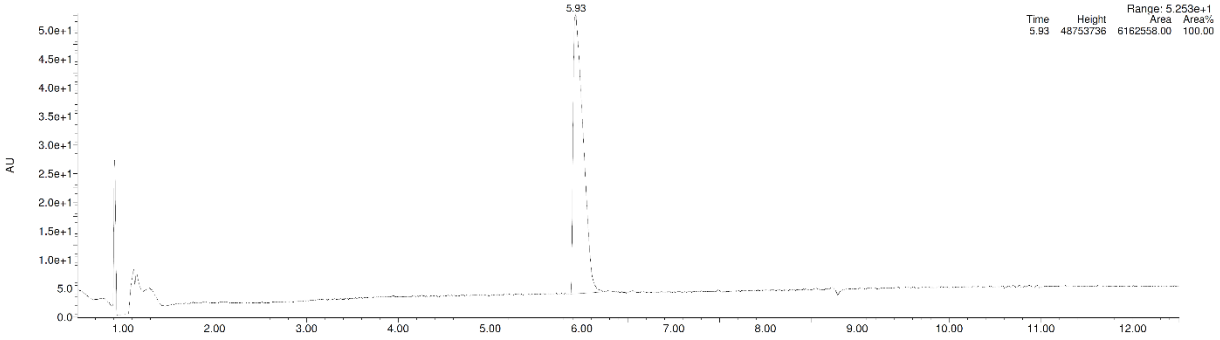
6c. 1-((3'-(benzo-1,4-dioxan-6-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)methyl)piperazine



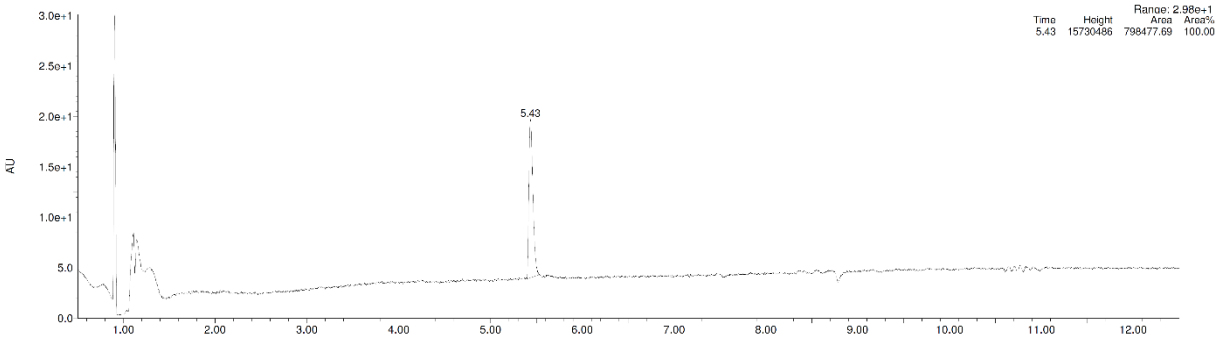
6d. 1-((3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-2'-methyl-[1,1'-biphenyl]-4-yl)methyl)piperazine



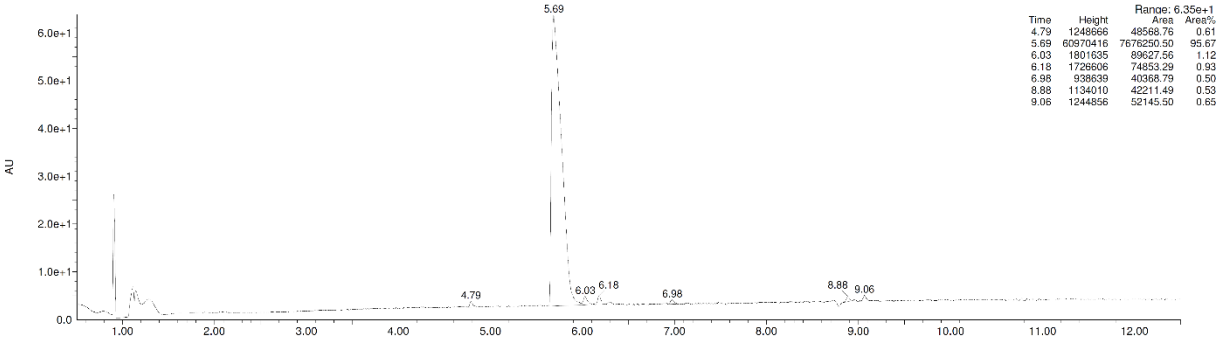
6e. 3-(((3'-(2,3-benzo-1,4-dioxan-6-yl)-2'-methyl-4-(piperazin-1-ylmethyl)-[1,1'-biphenyl]-3-yl)oxy)methyl)benzonitrile



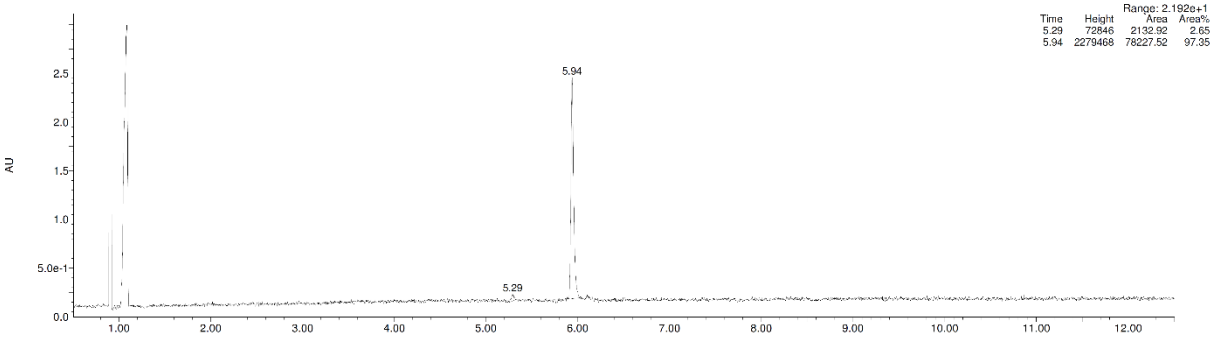
7a. N-(2-(((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



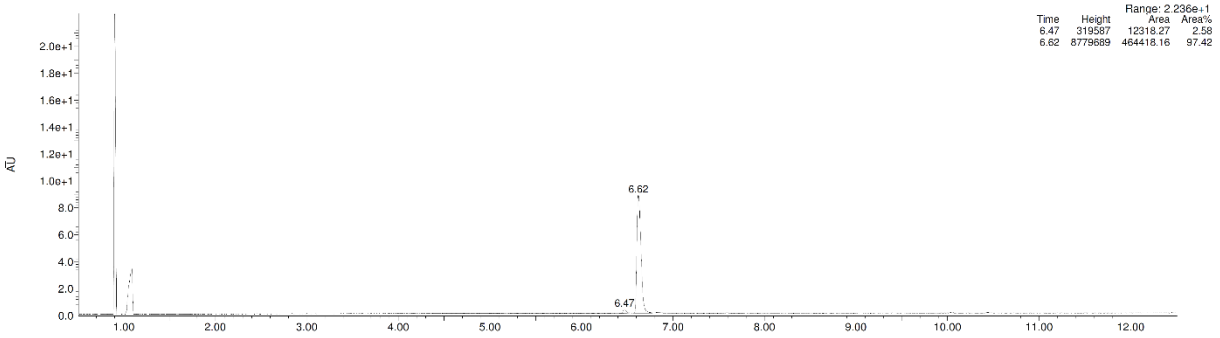
7b. N-(2-((((benzo-1,4-dioxan-6-yl)-2'-chloro-3'-3-ethoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



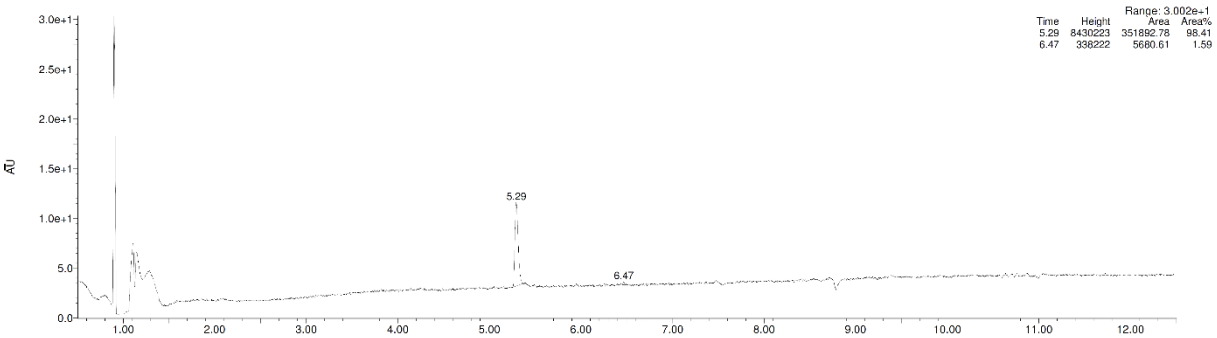
7c. N-(2-(((2'-chloro-3-((3'-cyano-[1,1'-biphenyl]-3-yl)isopropoxy)-3'-(benzo-1,4-dioxan-6-yl)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



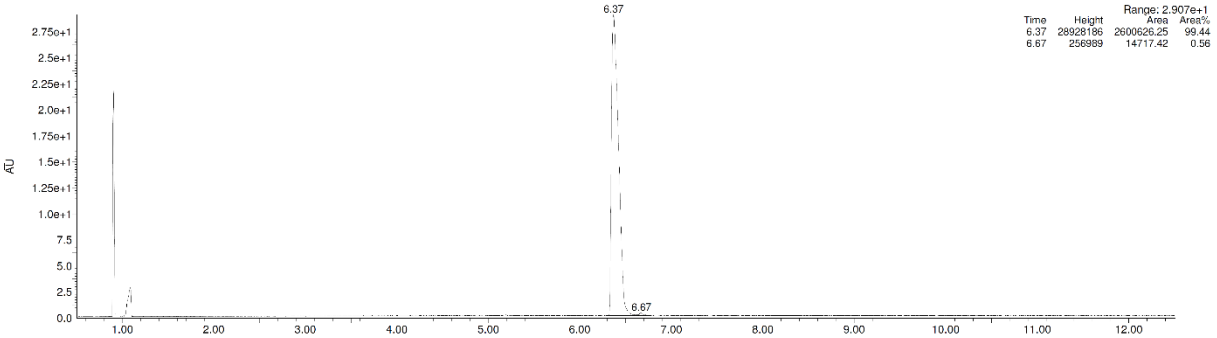
7d. N-(2-(((2'-chloro-3-((3'-cyano-[1,1'-biphenyl]-3-yl)isopentyloxy)-3'-(benzo-1,4-dioxan-6-yl)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



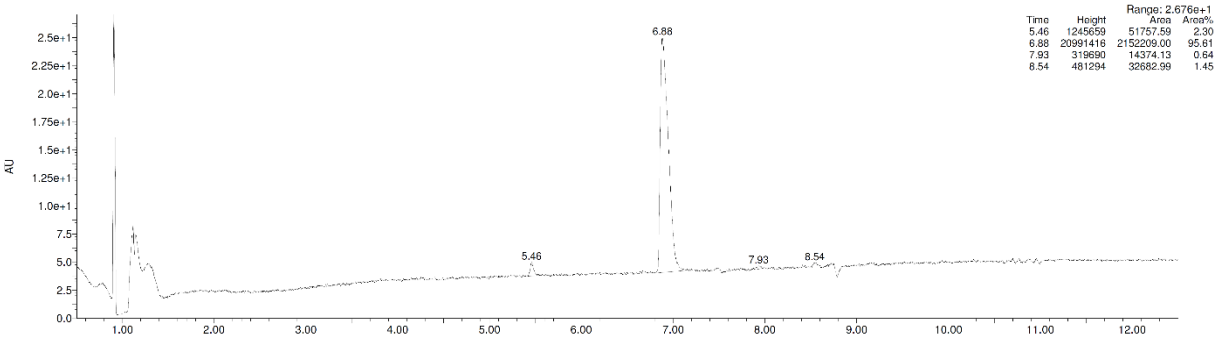
7e. N-(2-(((3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-(cyanomethoxy)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



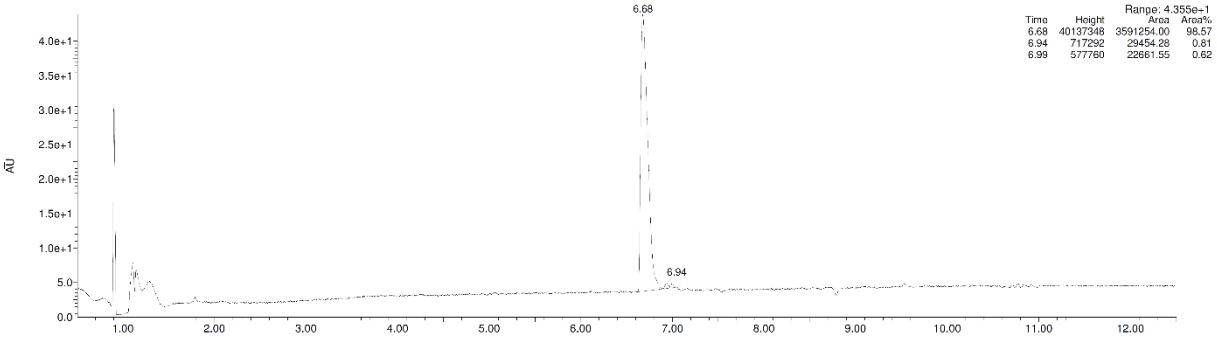
7f. N-(2-(((3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-(cyclobutylmethoxy)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



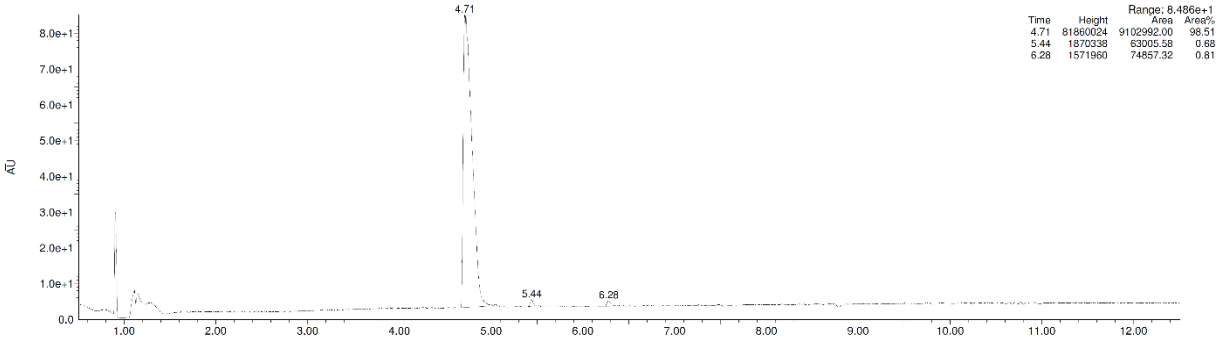
7g. N-(2-(((3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-(cyclopentylmethoxy)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



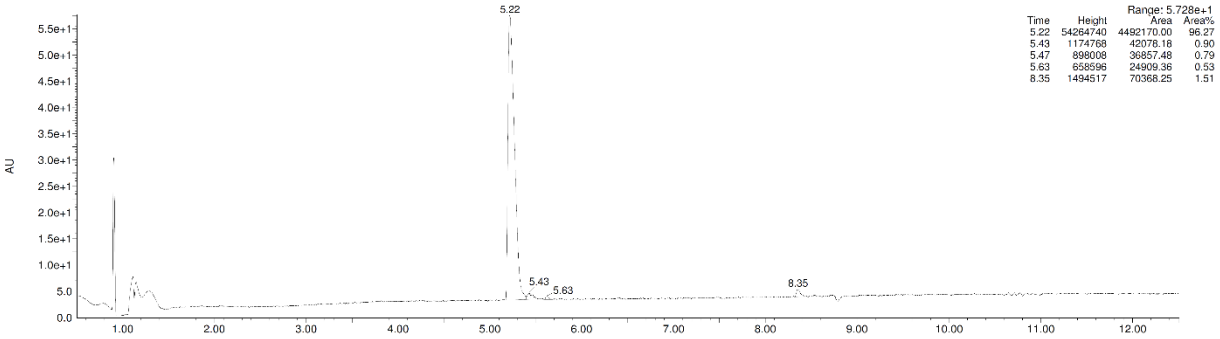
7h. N-(2-(((3'-(benzo-1,4-dioxan-6-yl)-2'-chloro-3-((3'-cyano-[1,1'-biphenyl]-3-yl)methoxy)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



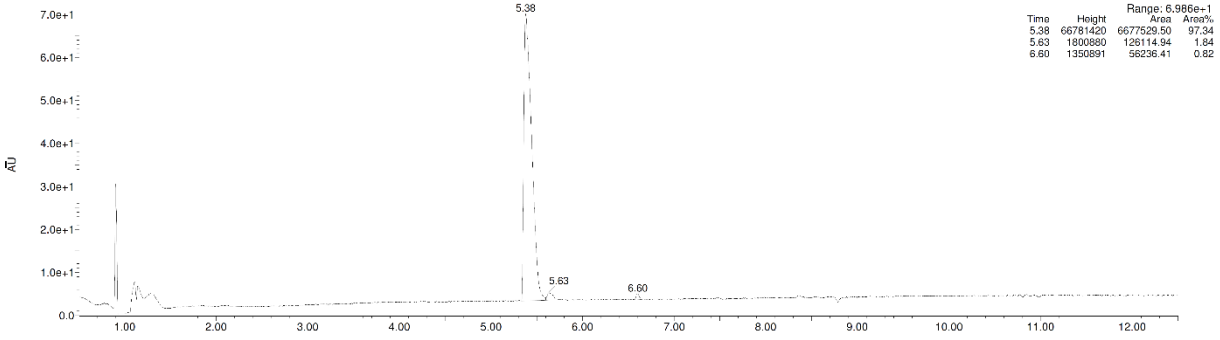
8a. 1-((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)piperazine



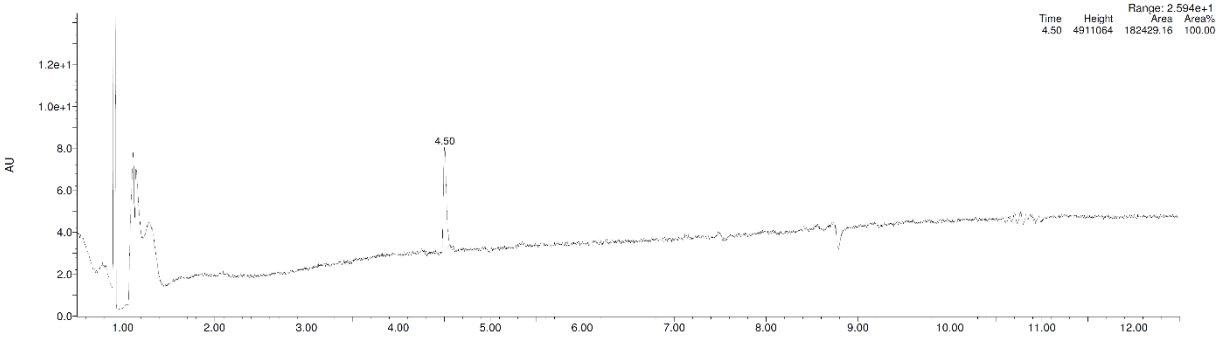
8b. 4-((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)piperazine-1-carboxamide



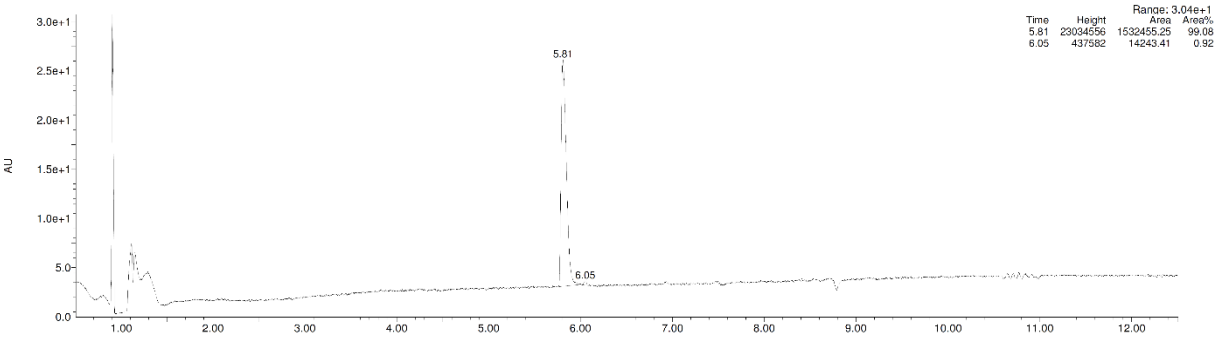
8c. 1-(4-((2'-Chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)piperazin-1-yl)ethan-1-one



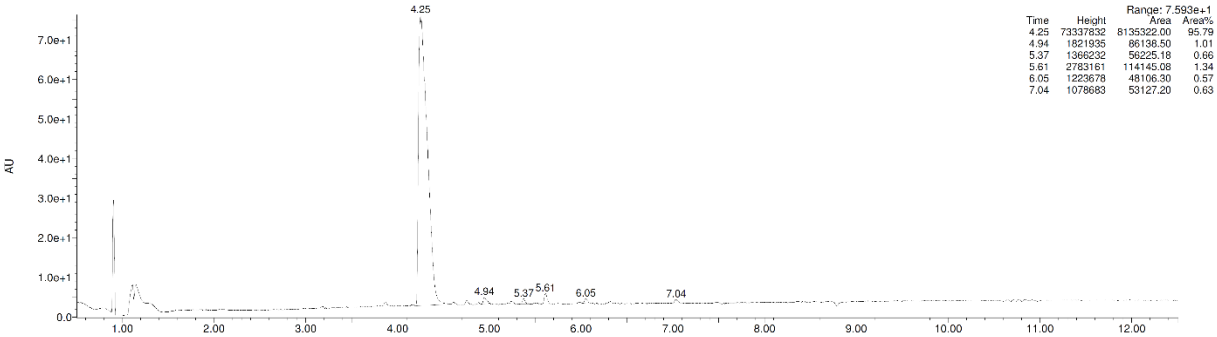
8d. 2-amino-1-(4-((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)piperazin-1-yl)ethan-1-one



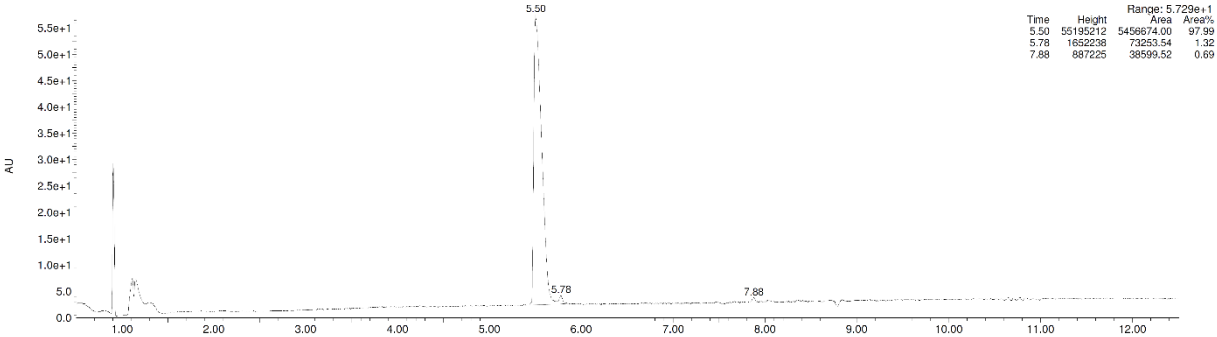
8e. 1-((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)-4-(methylsulfonyl)piperazine



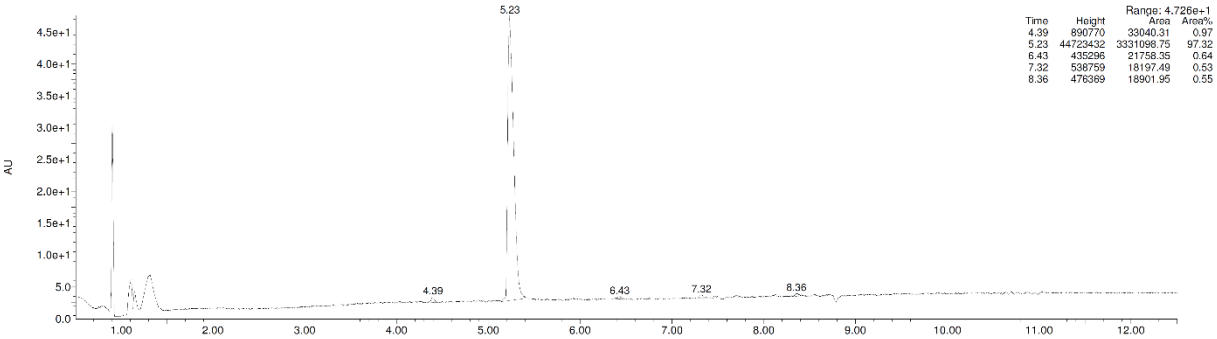
8f. 2-amino-N-(2-(((benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)acetamide



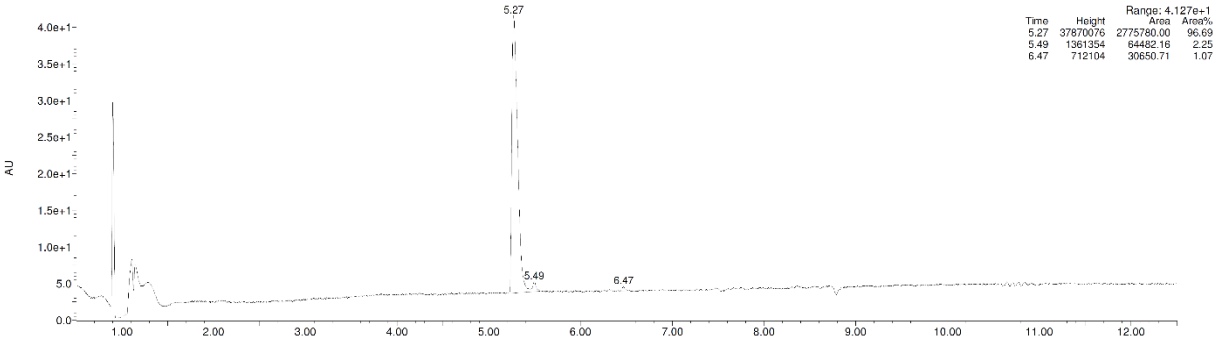
8g. N-(2-(((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)methanesulfonamide



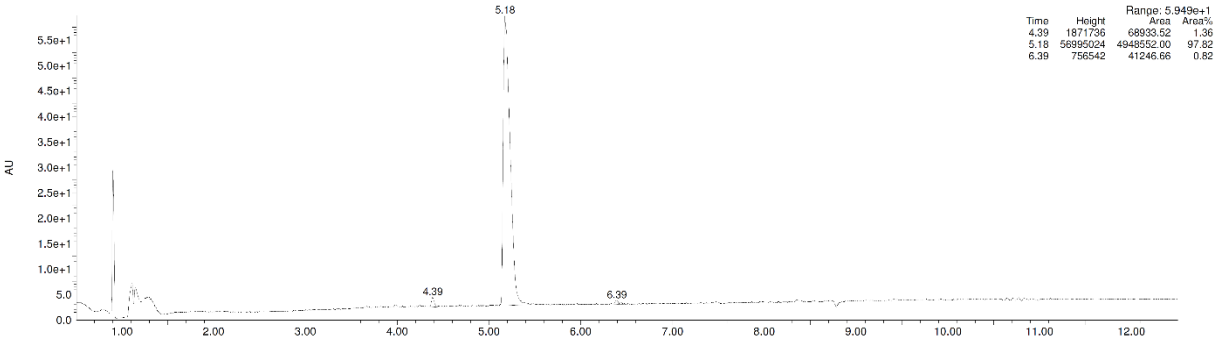
8h. 1-(2-(((2'-Chloro-3'-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)urea



8i. 2-(((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)propane-1,3-diol



8j. 2-(((2'-chloro-3'-(benzo-1,4-dioxan-6-yl)-3-methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)-2-(hydroxymethyl)propane-1,3-diol



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