Electronic Supporting Information

Development of Madelung-Type Indole Synthesis Using Copper-Catalyzed Amidation/Condensation Strategy

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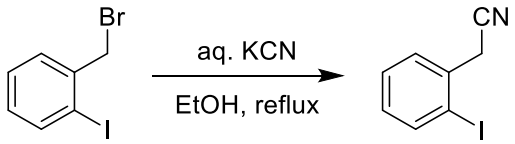
Materials.

Unless otherwise noted, commercially available materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification (distillation and recrystallization). Flash column chromatography was performed with Kanto silica gel 60 N (spherical, neutral, 63–210 mesh). Reactions were monitored by thin-layer chromatography on precoated plates of silica gel (Merck Silica gel 60 F254).

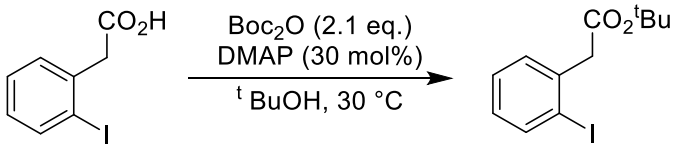
2-(2-iodophenyl)acetonitrile（1a）



To 1-(bromomethyl)-2-iodobenzene (2.97 g, 10 mmol) in EtOH (20 mL) was added a solution of KCN (782 mg, 12 mmol) in water (0.1 mL) at room temperature. The reaction mixture was stirred for 2 hour at 80 °C and it was partitioned between Et_2O and water. The aqueous layer was extracted three times with E_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under a reduced pressure. Purification by column chromatography afforded 2-(2-iodophenyl)acetonitrile (2.19 g, 9.0 mmol) as yellow oil.

Obtained as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.82 (1H, s), 7.04–7.06 (m, 1H), 7.39–7.42 (m, 1H), 7.53–7.55 (m, 1H), 7.87–7.89 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 30.1, 99.2, 117.3, 129.1, 129.2, 130.0, 133.4, 139.9. LRMS (EI) *m/z*: 243 (M^+), 116 (M^+–127). HRMS: Calcd. for C_8H_6IN: 242.9545. Found: 242.9559. IR (neat, cm^{-1}): 3055, 2978, 2920, 2246, 1465, 1437, 1410 1017, 745 cm^{-1}.

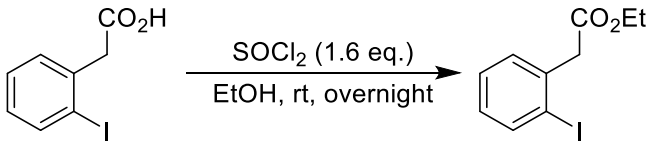
tert-butyl 2-(2-iodophenyl)acetate (1b)



DMAP (184 mg, 1.5 mmol) was added to a solution of 2-(2-iodophenyl)acetic acid (1.31 g, 5 mmol), Boc_2O (2.3 g, 10.5 mmol) in *tert*-butanol (15 mL). The reation mixture was stirred at 30 °C for 3 h. The solvent was evaporated and the residue was dissolved in Et_2O and washed with brine, the organic layer was then dried over Mg_2SO_4. The solvent was evaporated under reduced pressure. Purification by column chromatography afforded the tert-butyl 2-(2-iodophenyl)acetate as colorless oil (1.46 g, 4.6 mmol).

Obtained as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.46 (s, 9H), 3.69 (s, 2H), 6.90–6.95 (m, 1H), 7.24–7.31 (m, 2H), 7.81–7.83 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 28.2, 47.5, 81.2, 101.2, 128.4, 128.7, 130.7, 138.5, 139.5, 169.8. LRMS (EI) *m/z*: 318 (M^+), 217 (M^+–101). HRMS: Calcd. for $C_{12}H_{15}O_2I$: 318.01167. Found: 317.01062. IR (neat, cm^{-1}): 3064, 2978, 2930, 1729, 1588, 1565, 1467, 1456, 1437, 1415, 1393, 1368, 1337, 1275, 1257, 1225, 1142, 1107, 1047, 1014, 954, 939, 926, 880, 855, 828, 746, 735 cm^{-1}.

ethyl 2-(2-iodophenyl)acetate (1c)

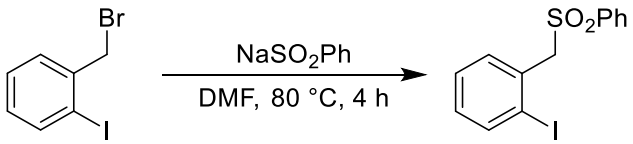


To a 0 °C solution of (2-iodophenyl) acetic acid (1.31 g, 5 mmol) in ethanol (30 mL) was added thionyl chloride (0.58 mL, 8 mmol). The reaction mixture was allowed to warm up to room temperature and was stirred for 15 h. The solvent was evaporated under reduced pressure. Purification by column chromatography afforded ethyl 2-(2-iodophenyl)acetate (1.30 g, 99 %).

Obtained as colorless prisms (mp. 44–45 °C). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.27 (t, *J* = 7.3 Hz, 3H), 3.78 (s, 2H), 4.18 (q, *J* = 7.3 Hz, 2H), 6.93–6.97 (m, 1H), 7.26–7.33 (m, 2H),

7.84 (d, *J* = 8.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 14.3, 46.4, 61.1, 101.1, 128.5, 128.9, 130.7, 138.0, 139.6, 170.5. LRMS (EI) *m/z*: 290 (M^+), 217 (M^+–73). HRMS: Calcd. for $C_{10}H_{11}O_2I$: 357.9804. Found: 289.9810. IR (neat, cm^{-1}): 3060, 2980, 2935, 2905, 1730, 1587, 1565, 1466, 1437, 1413, 1368, 1334, 1293, 1275, 1244, 1214, 1156, 1107, 1096, 1047, 1028, 1014, 925, 884, 860, 829, 756, 732 cm^{-1}.

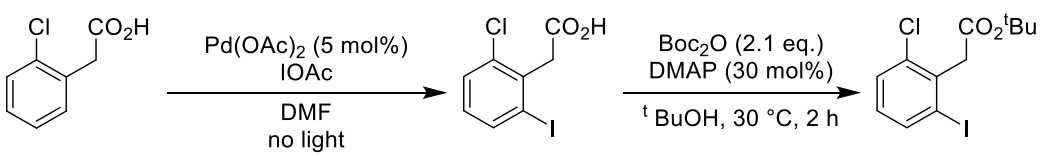
1-iodo-2-((phenylsulfonyl)methyl)benzene (1d)



A DMF solution (10 mL) of 2-idobenzyl bromide (1.48 g, 5 mmol) and $PhSO_2Na$ (1.5 g, 9.1 mmol) was heated at 80 °C for 2 h. The mixture was poured on ice-water and stirred vigorously. The precipitate was filtered, washed with water and dried. in *vacuo*. The crude was recrystallized from CH_2Cl_2 and hexane and 1-iodo-2-((phenylsulfonyl)methyl)benzene was obtained as colorless crystals (1.24g, 3.47 mmol).

Obtained as colorless prisms (Recrystallized from CH_2Cl_2/hexane, mp. 133–134 °C). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 4.59 (s, 2H), 6.98–7.03 (m, 1H), 7.33–7.37 (m, 1H), 7.44–7.51 (m, 3H), 7.61–7.66 (m, 3H), 7.72–7.75 (m, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 66.2, 102.4, 128.6, 129.1, 129.2, 130.5, 131.9, 132.3, 134.1, 138.3, 139.9. LRMS (EI) *m/z*: 358 (M^+), 217 (M^+–141). HRMS: Calcd. for $C_{13}H_{11}O_2SI$: 357.9525. Found: 357.9518. IR (neat, cm^{-1}): 2977, 2929, 1582, 1562, 1471, 1449, 1435, 1414, 1308, 1292, 1286, 1242, 1166, 1147, 1096, 1084, 1071, 1046, 1026, 1011, 997, 949, 931, 823, 777, 757, 728 cm^{-1}.

tert-butyl 2-(2-chloro-6-iodophenyl)acetate (1e)

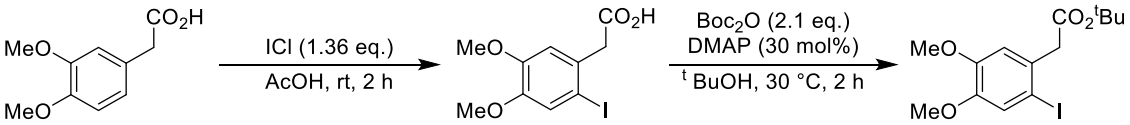


2-(2-chloro-6-iodophenyl)acetic acid was obtained as reference[1]. 2-(2-chlorophenyl)acetic acid (1.7 g, 10 mmol), Pd(OAc) (113 mg, 5 mol%), $PhI(OAc)_2$ (2.4 g, 7.5 mmol) and I_2 (1.9 g, 7.5 mmol) were dissolved in 30 mL anhydrous DMF under air. The mixture was stirred at 60 °C for 12 h in the dark. After the reaction mixture cooled to room temperature, another batch of $PhI(OAc)_2$ (2.4 g, 7.5 mmol) and I_2 (1.9 g, 7.5 mmol) was added under air. And then the reaction mixture was stirred at 60 °C for another 12 h in the dark. To the reaction mixture was added third batch of $PhI(OAc)_2$ (1.6 g, 5.0 mmol) and I_2 (1.27 g, 0.5 mmol) under air after cooling to room temperature, and stirred for another 12 h at in the dark. After cooling to room temperature, the mixture was filtered through a pad of Celite®. The filtrate was extracted three times with CH_2Cl_2 and washed with brine. The organic solvent was concentrated under reduced pressure and the residue was subjected to column chromatography to give 2-(2-chloro-6-iodophenyl)acetic acid as a white solid.

DMAP (37 mg, 0.3 mmol) was added to a solution of 2-(2-chloro-6-iodophenyl)acetic acid. (296 mg, 1 mmol), Boc_2O (458 mg, 2.1 mmol) in *tert*-butanol (5 mL). The reation mixture was stirred at 30 °C for 3 h. The solvent was evaporated and the residue was dissolved in Et_2O and washed with brine, the organic layer was then dried over Mg_2SO_4. The solvent was evaporated under reduced pressure. Purification by column chromatography afforded the tert-butyl 2-(2-chloro-6-iodophenyl)acetate as colorless oil (277 mg, 0.78 mmol).

Obtained as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.46 (s, 9H), 4.00 (s, 2H), 6.87 (t, *J* = 5.5 Hz), 7.36 (d, *J* = 5.5 Hz, 1H), 7.74 (d, *J* = 5.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 28.14, 45.9, 81.5, 102.3, 123.0 (2C), 134.7, 136.6, 138.2, 168.5. LRMS (EI) *m/z*: 352 (M^+). HRMS: Calcd. for $C_{10}H_{11}{}^{35}ClIO_2$: 351.97270. Found: 351.96939. IR (neat, cm^{-1}): 2978, 2931, 1733, 1576, 1554, 1477, 1456, 1430, 1417, 1393, 1368, 1331, 1280, 1255, 1226, 1148, 1055, 929, 871, 828, 773, 747, 721 cm^{-1}.

tert-butyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate (1f)

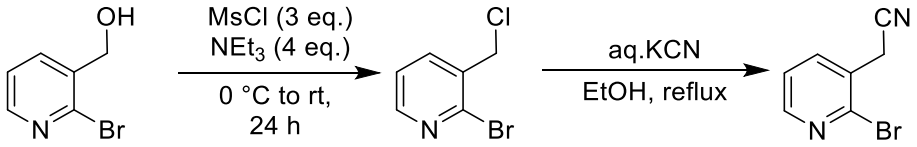


Iodine monochloride (2.2 g, 13.6 mmol) was dissolved in AcOH (50 mL) and added to a stirred solution of 2-(3,4-dimethoxyphenyl)acetic acid (1.96 g, 10 mmol) in AcOH (50 mL), keeping stirring at room temperature for 2h. The reaction was poured into 10 % $Na_2S_2O_3$ aq. until the purple color was discharged to yellow. Vigorous stirring and slow addition H_2O led to the precipitation of a white solid, that was collected by filtration and thoroughly washed with H_2O. The filter cake was recrystallized from MeOH/H_2O and dried in *vacuo* (2.3 g, 7.1 mmol).

DMAP (73 mg, 0.6 mmol) was added to a solution of 2-(2-chloro-6-iodophenyl)acetic acid. (644 mg, 2 mmol), Boc_2O (917 mg, 4.2 mmol) in *tert*-butanol (10 mL). The reation mixture was stirred at 30 °C for 3 h. The solvent was evaporated and the residue was dissolved in Et_2O and washed with brine, the organic layer was then dried over Mg_2SO_4. The solvent was evaporated under reduced pressure. Purification by column chromatography afforded the tert-butyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate as yellow oil (277 mg, 0.78 mmol).

Obtained as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.47 (s, 9H), 3.63 (s, 2H), 3.848 (s, 3H), 3.853 (s, 3H), 6.80 (s, 1H), 7.23 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 28.2, 47.0, 56.0, 56.2, 81.2, 89.0, 113.4, 121.8, 130.9, 148.5, 149.3, 170.2. LRMS (EI) *m/z*: 378 (M^+), 322 (M^+–56), 277 (M^+–101). HRMS: Calcd. for $C_{14}H_{19}IO_4$: 378.0328. Found: 378.0327. IR (neat, cm^{-1}):3003, 2975, 2934, 2839, 1727, 1597, 1506, 1464, 1456, 1440, 1417, 1392, 1379, 1368, 1327, 1304, 1274, 1256, 1214, 1162, 1142, 1028, 969, 951, 930, 863, 849, 780, 753, 733, 703 cm^{-1}.

2-(2-bromopyridin-3-yl)acetonitrile (1h)

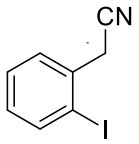


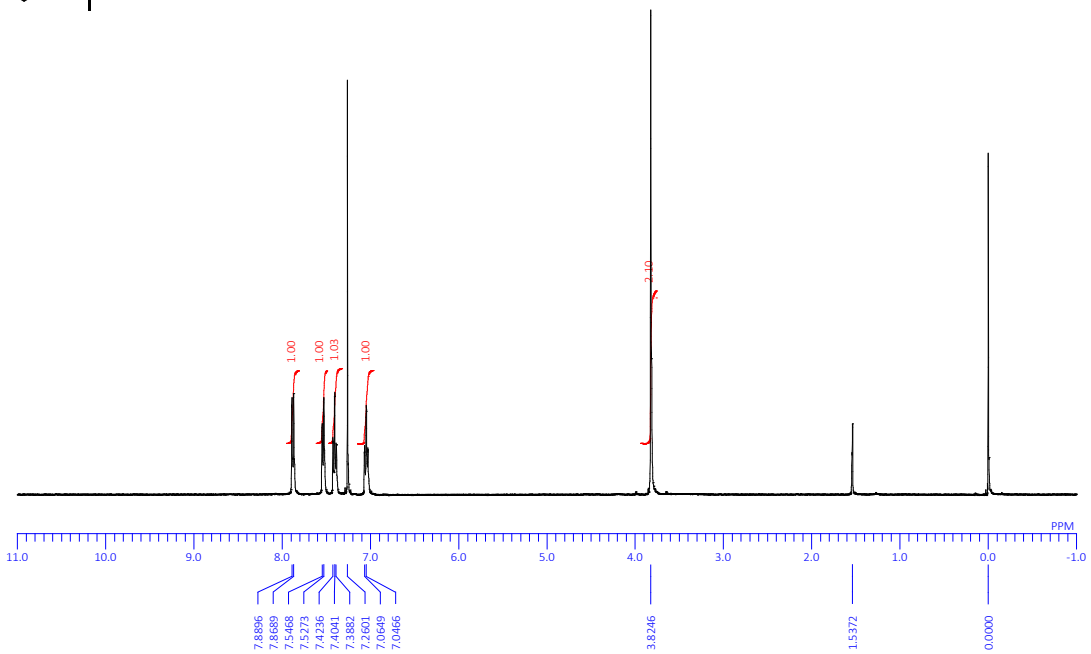
Methanesulfonyl chloride (1.1 mL, 14.1 mmol) was added dropwise to a solution of (2-bromopyridin-3-yl) methanol (886 mg, 4.7 mmol) and triethylamine (2.62 mL, 18.8 mmol) in dichloromethane (20 mL) under argon at 0 °C. The solution was stirred for 24 h. The mixture was concentrated then extracted three times with diethylether. The organic layer was concentrated under reduced pressure. Purification by column chromatography 2-bromo-3-(chloromethyl)pyridine (884 mg, 4.28 mmol).

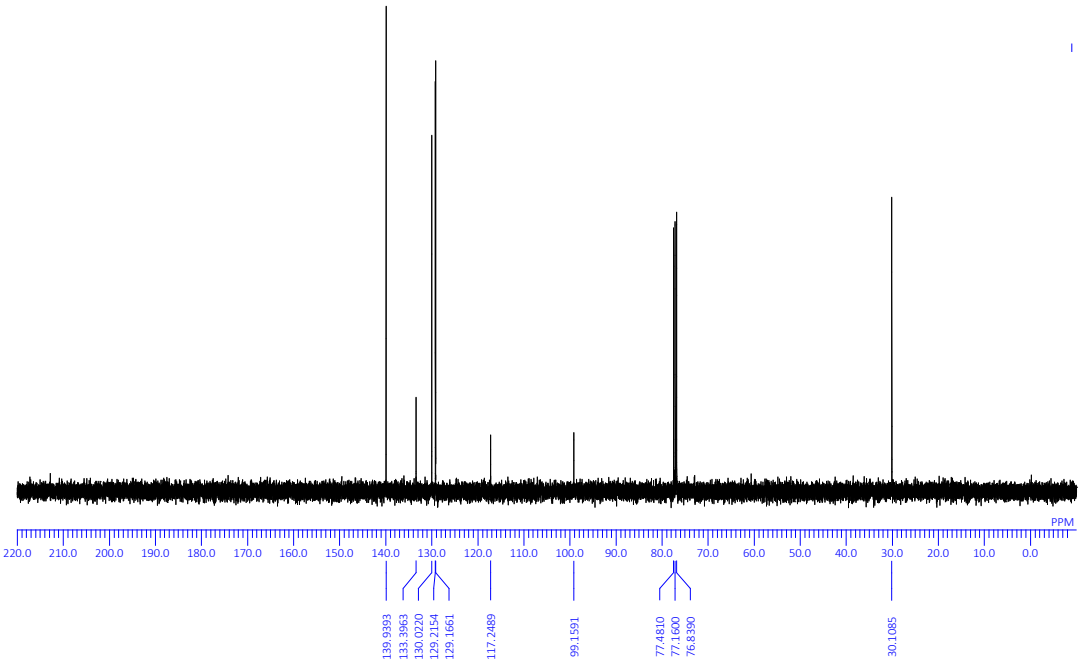
To 2-bromo-3-(chloromethyl)pyridine (826 mg, 4 mmol) in EtOH (10 mL) was added a solution of KCN (320 mg, 4.9 mmol) in water at room temperature. The reaction mixture was stirred for 2 hour at 80 °C and it was partitioned between Et_2O and water. The aqueous layer was extracted with E_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under a reduced pressure. Purification by column chromatography afforded 2-(2-bromopyridin-3-yl)acetonitrile (556 mg, 2.87 mmol).

Obtained as colorless prisms (Recrystallized from AcOEt/hexane, mp. 88–89 °C). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.87 (s, 2H), 7.35–7.38 (m, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 8.38 (d, *J* = 4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 24.3, 116.0, 123.4, 127.9, 137.8, 143.2, 149.8. LRMS (EI) *m/z*: 196 (M^+), 117 (M^+–79). HRMS: Calcd. for $C_7H_5{}^{79}BrN_2$: 195.96361. Found: 195.96384. IR (neat, cm^{-1}): 2944, 2917, 2257, 2238, 1574, 1563, 1419, 1404, 1180, 1121, 1071, 1054, 961, 926, 909, 837, 802, 742 cm^{-1}.

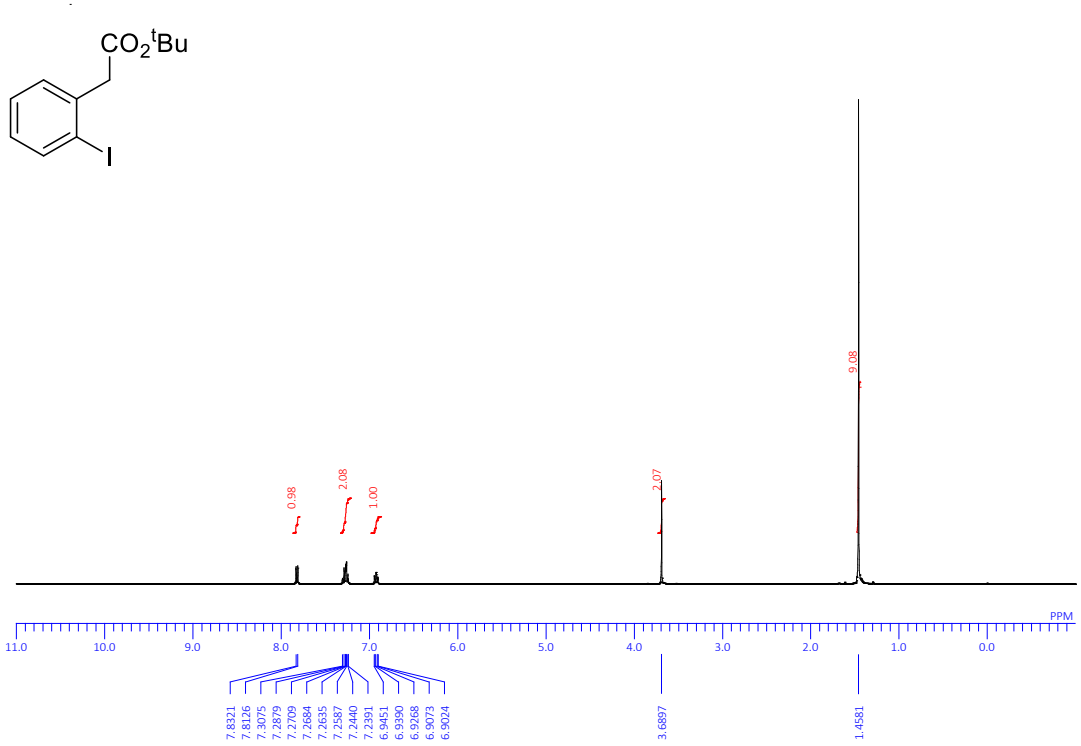
2-(2-iodophenyl)acetonitrile（1a）

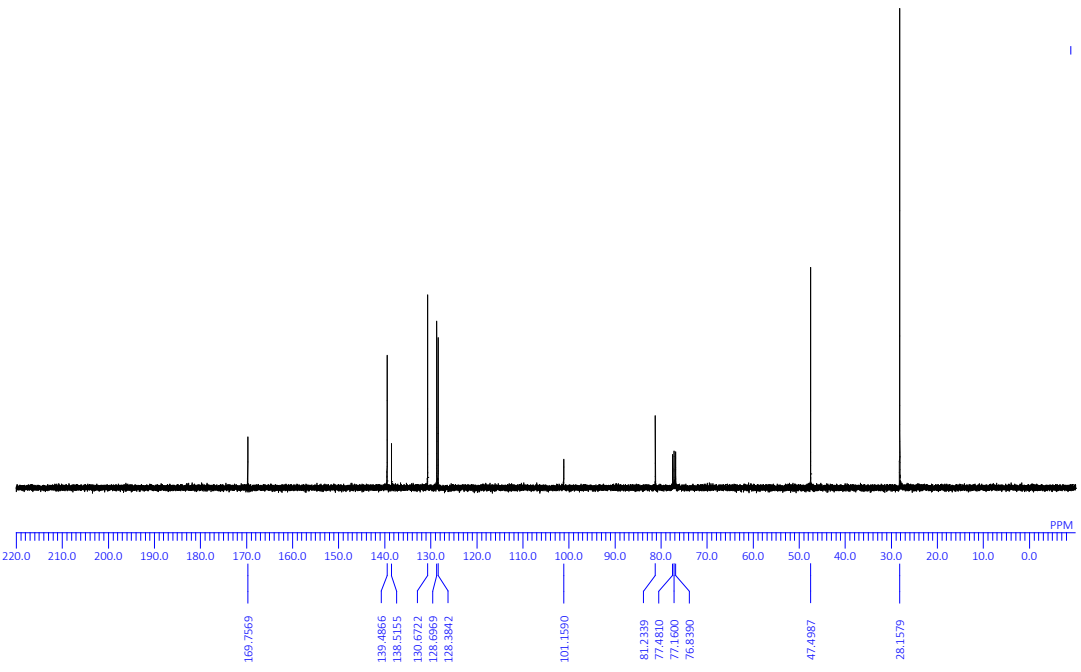




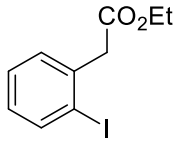


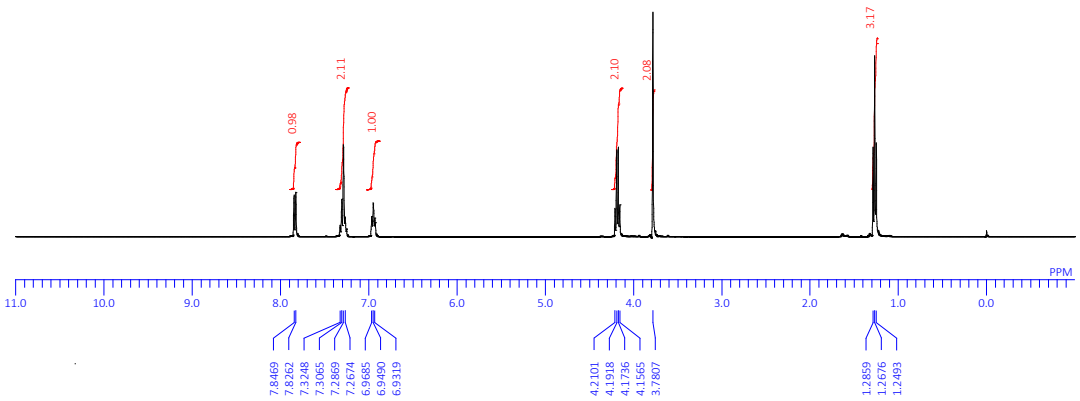
tert-butyl 2-(2-iodophenyl)acetate (1b)

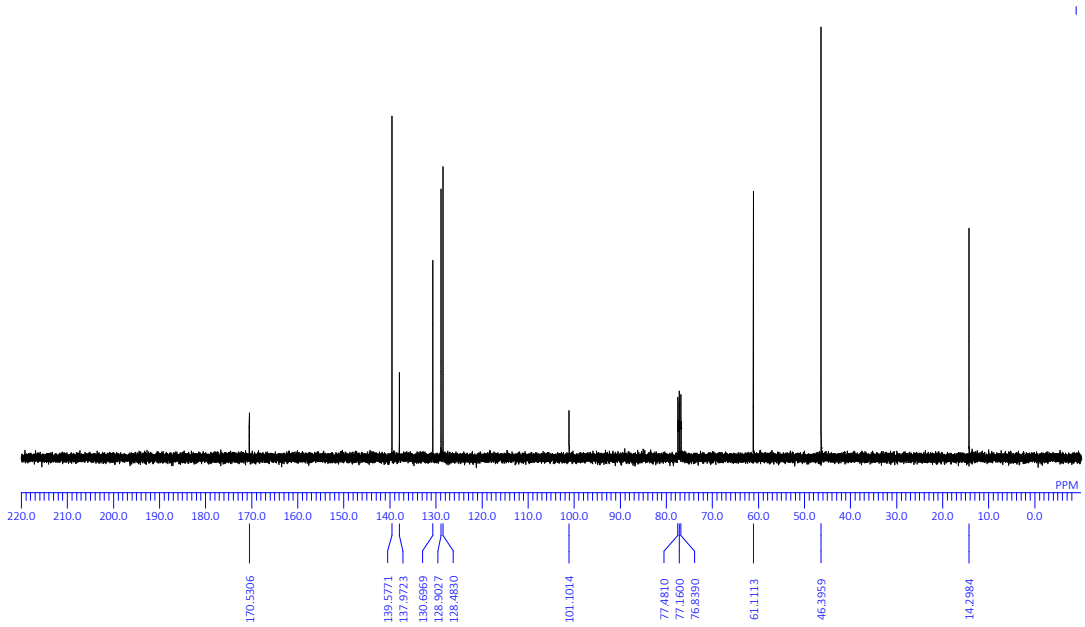




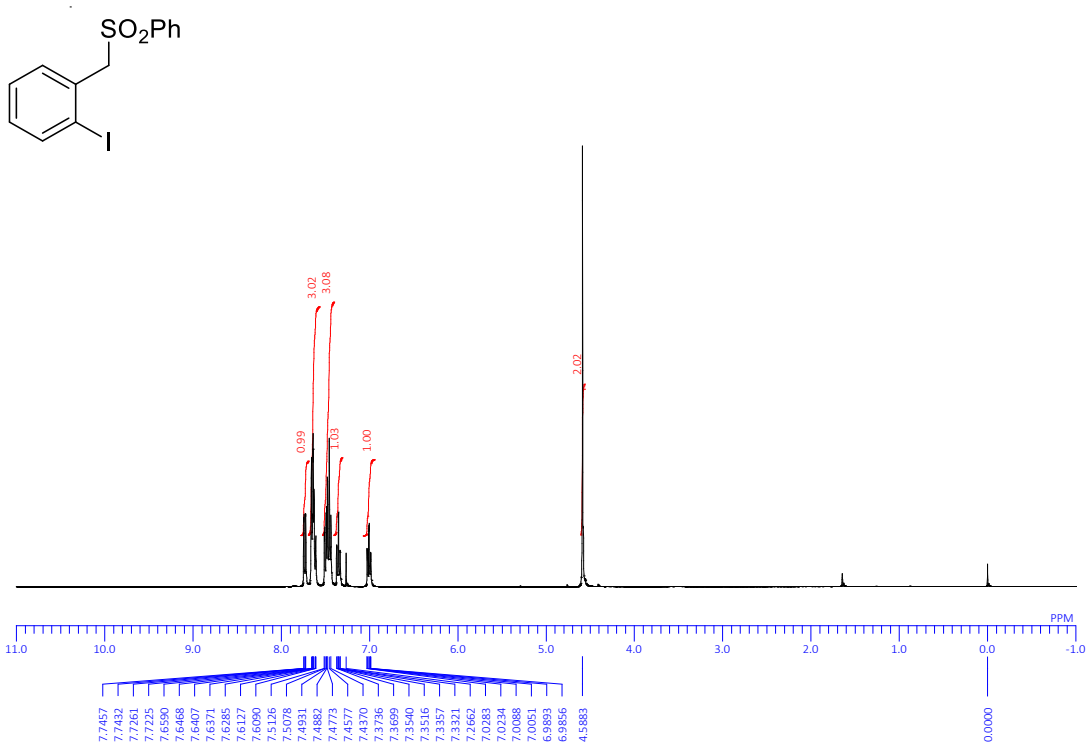
ethyl 2-(2-iodophenyl)acetate (1c)

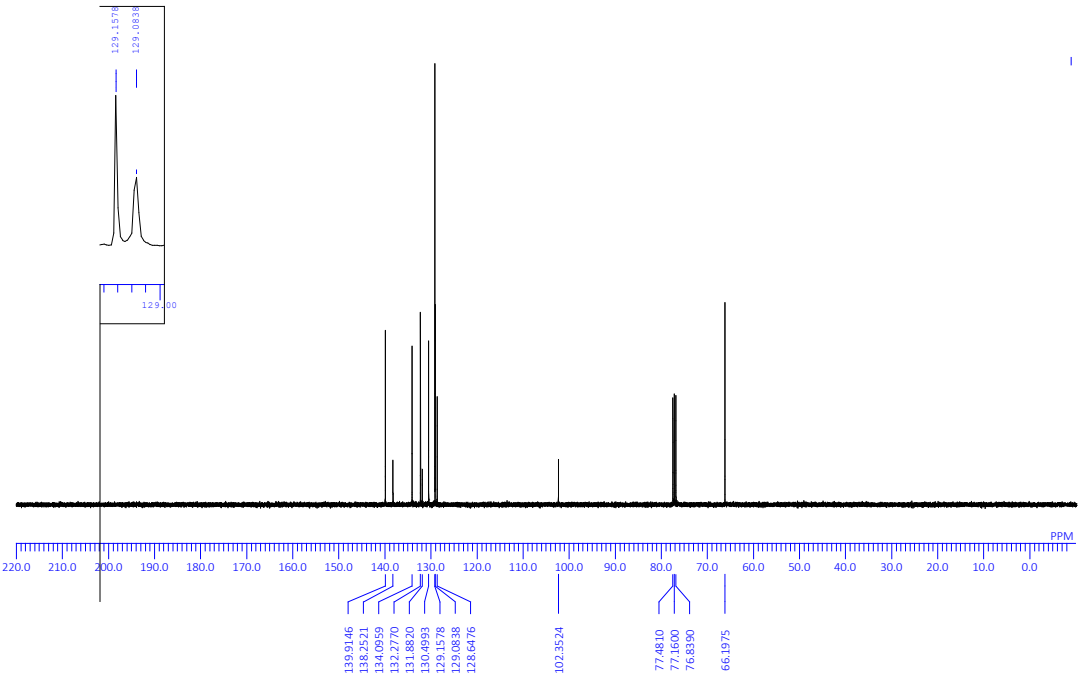




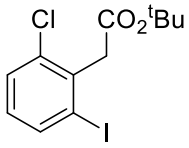


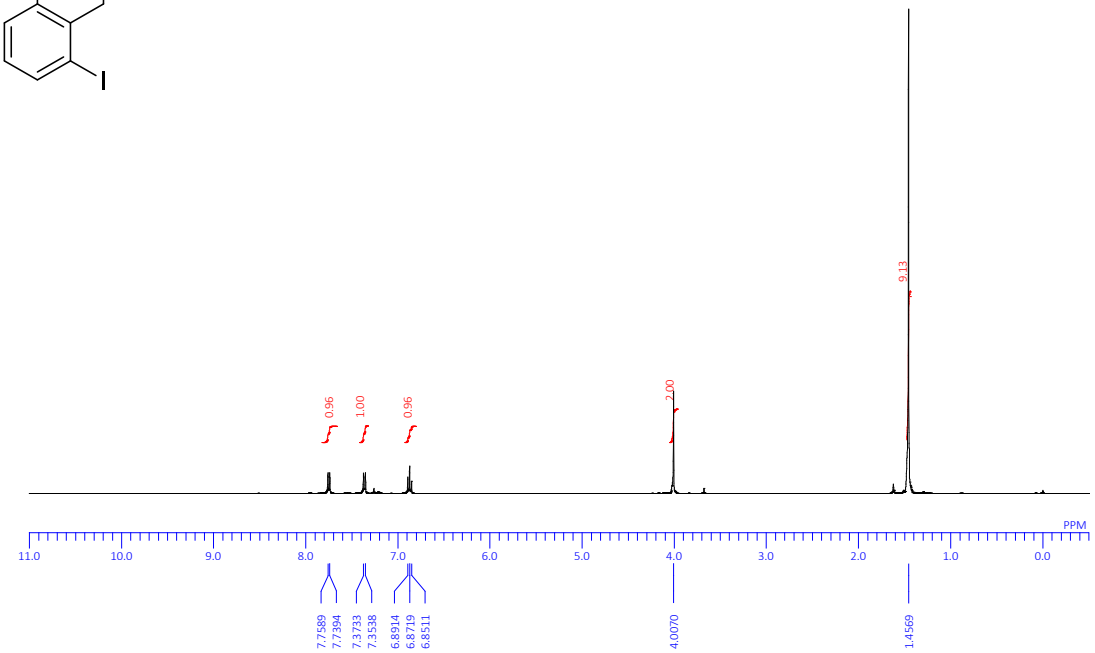
1-iodo-2-((phenylsulfonyl)methyl)benzene (1d)

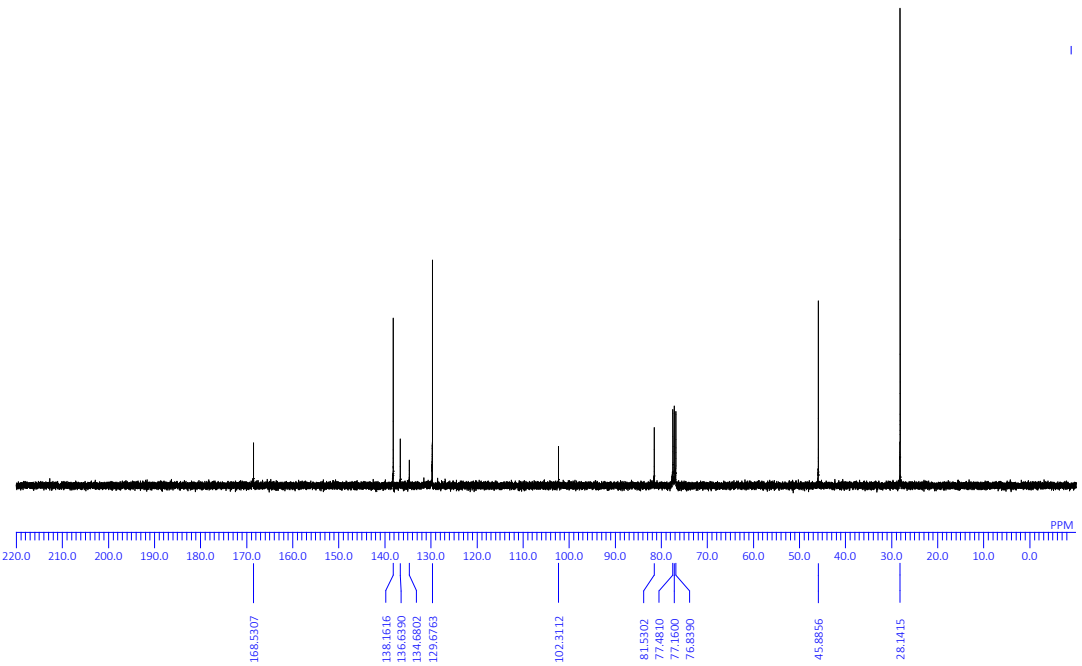




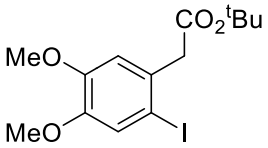
tert-butyl 2-(2-chloro-6-iodophenyl)acetate (1e)

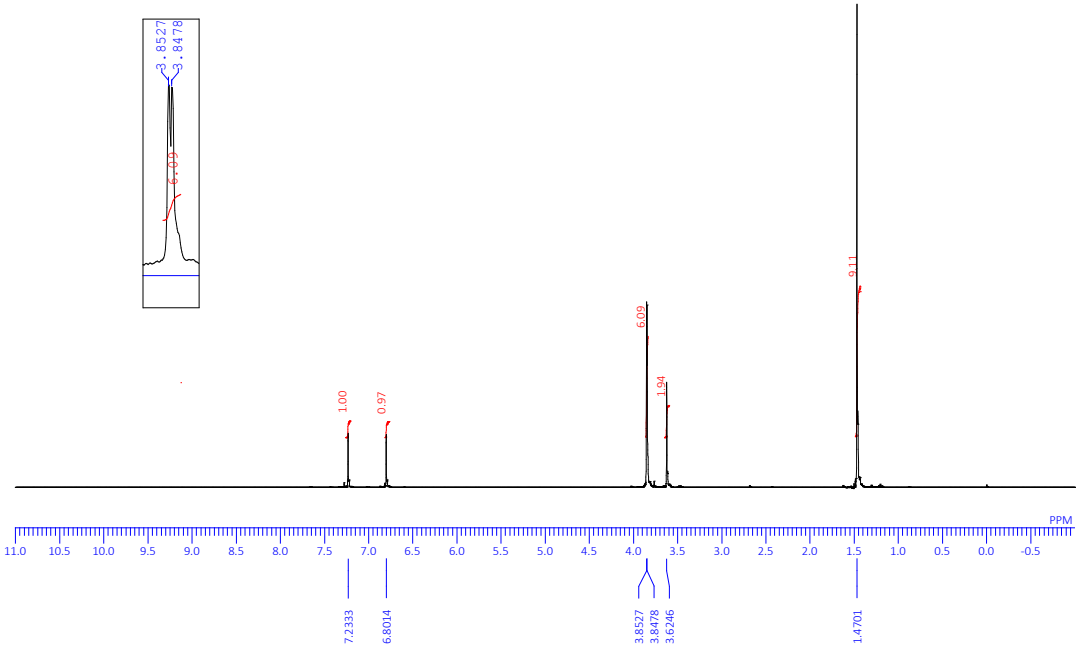


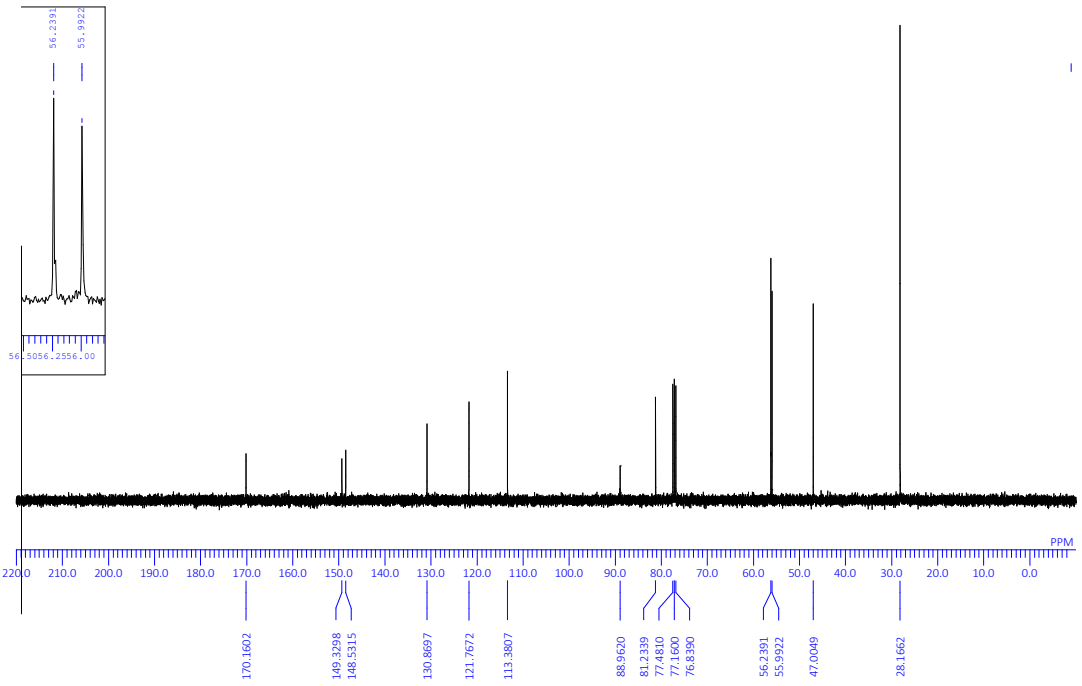




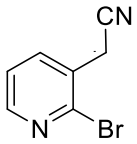
tert-butyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate (1f)

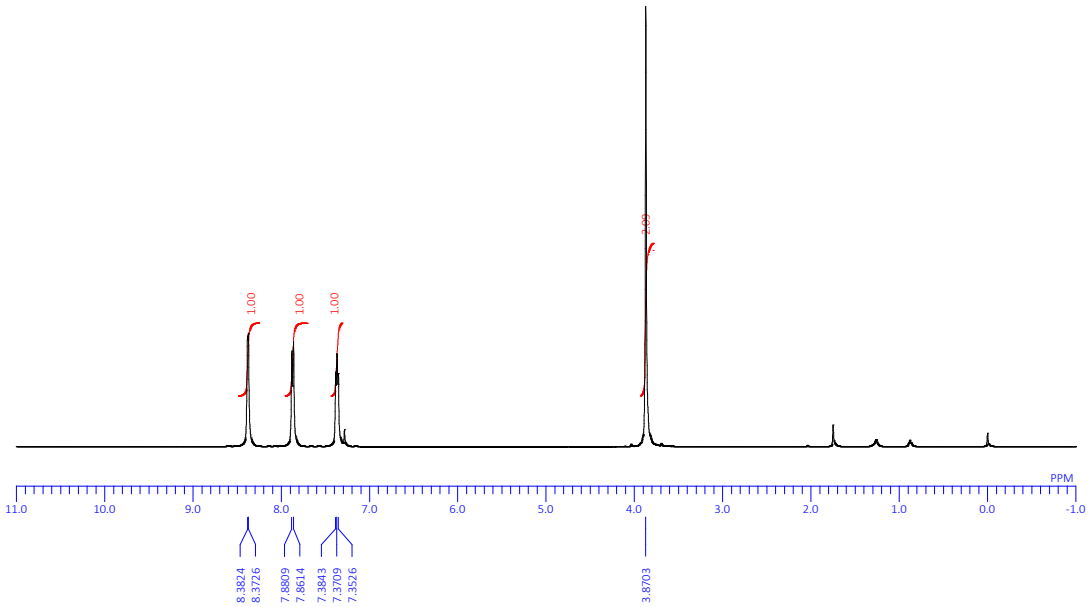


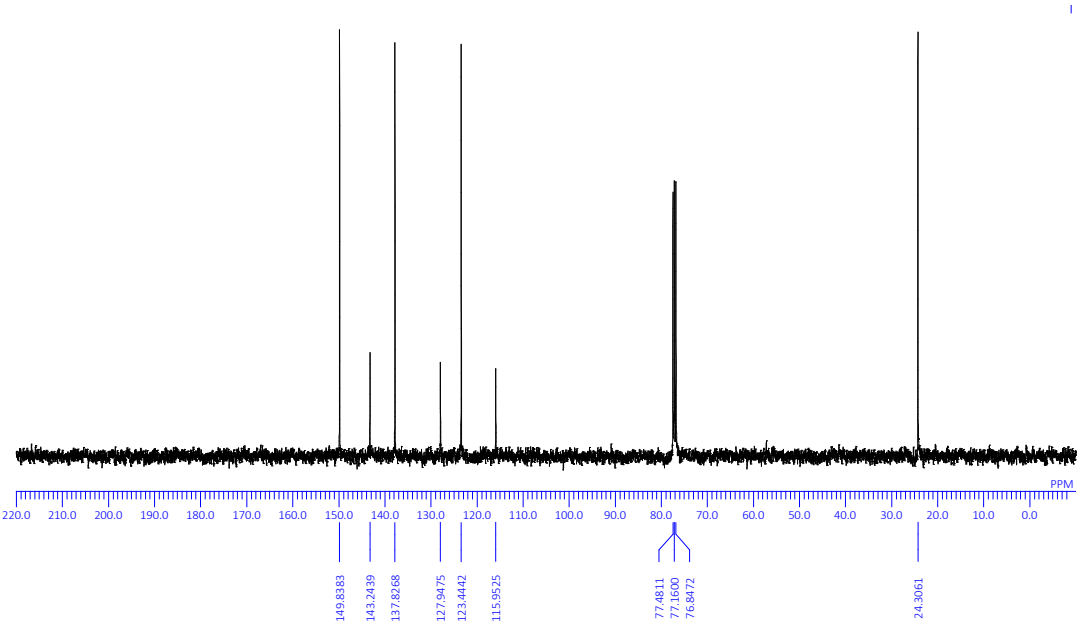




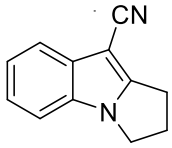
2-(2-bromopyridin-3-yl)acetonitrile (1h)

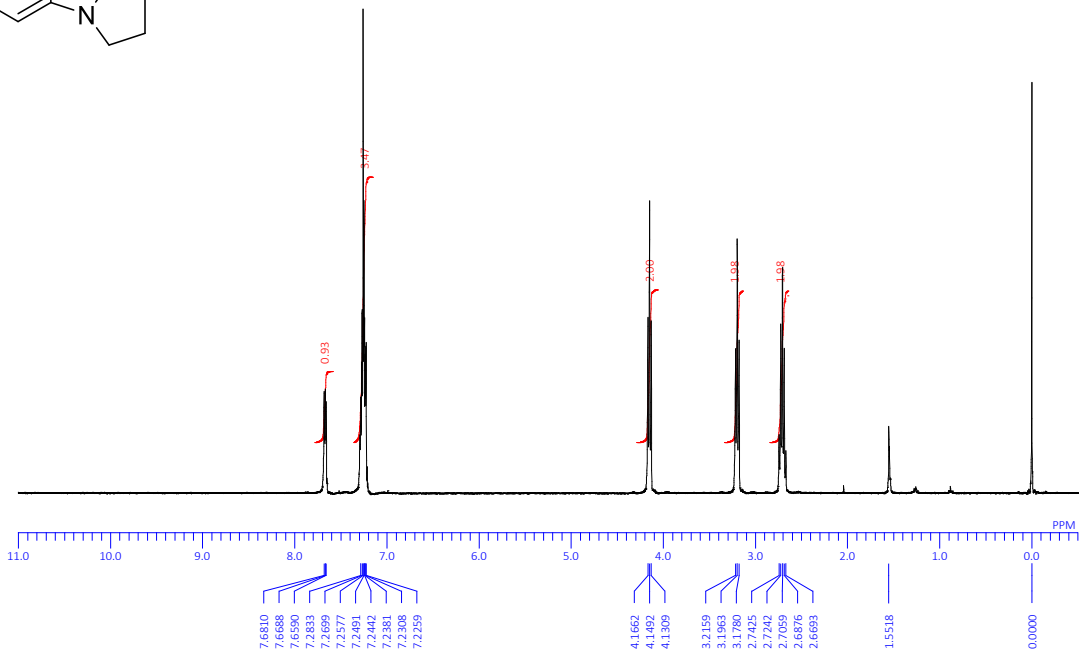


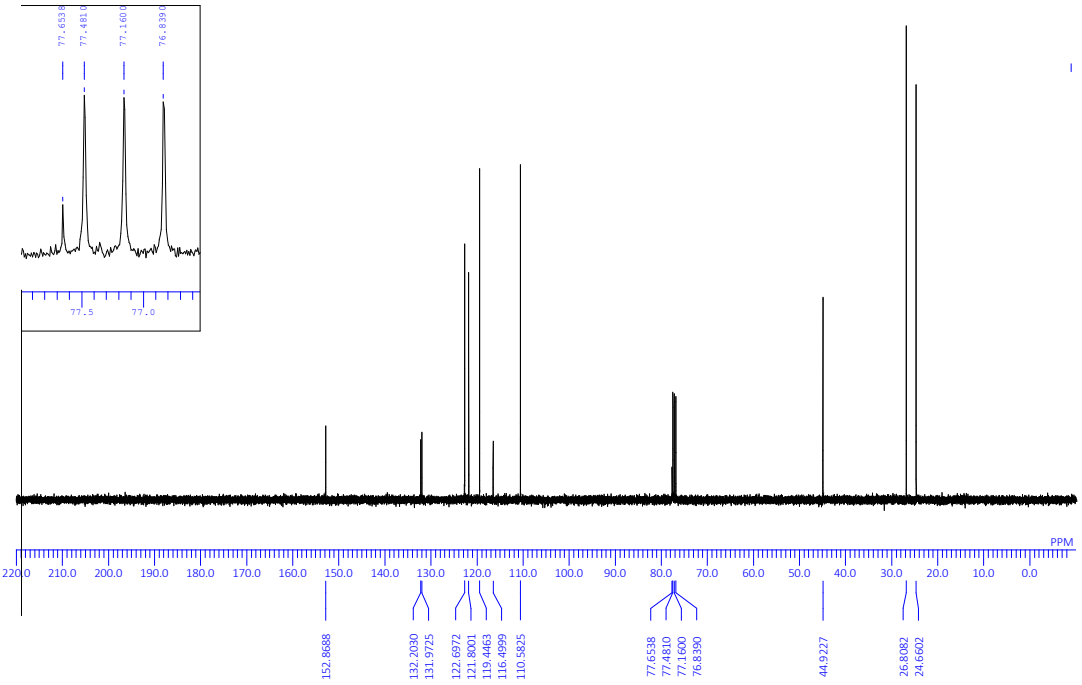




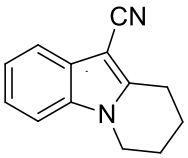
2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbonitrile (3aa)

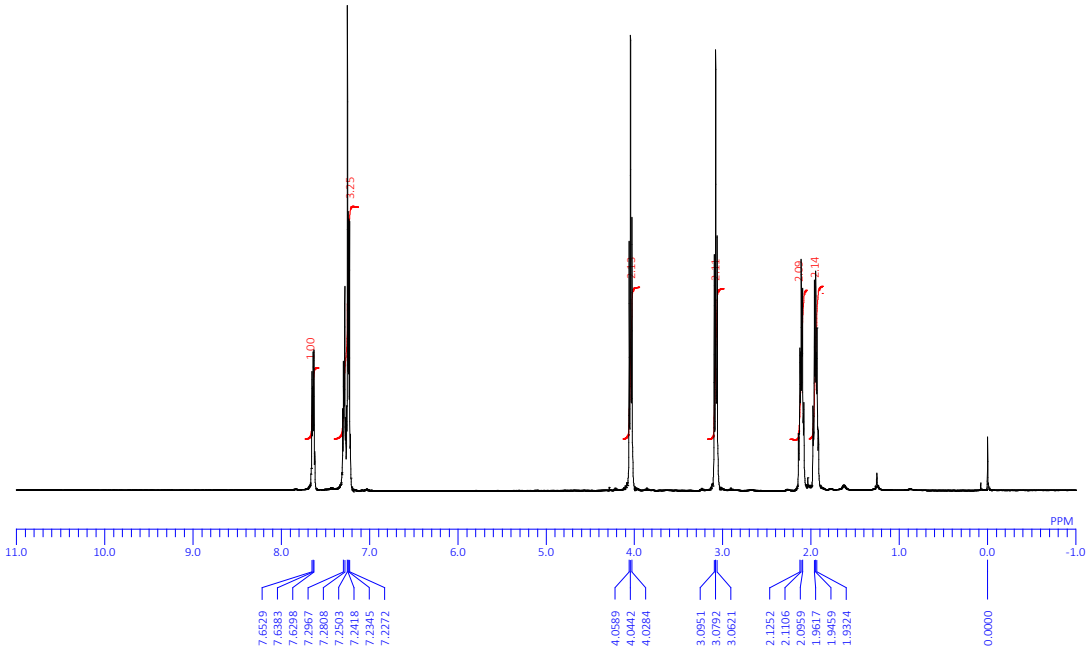


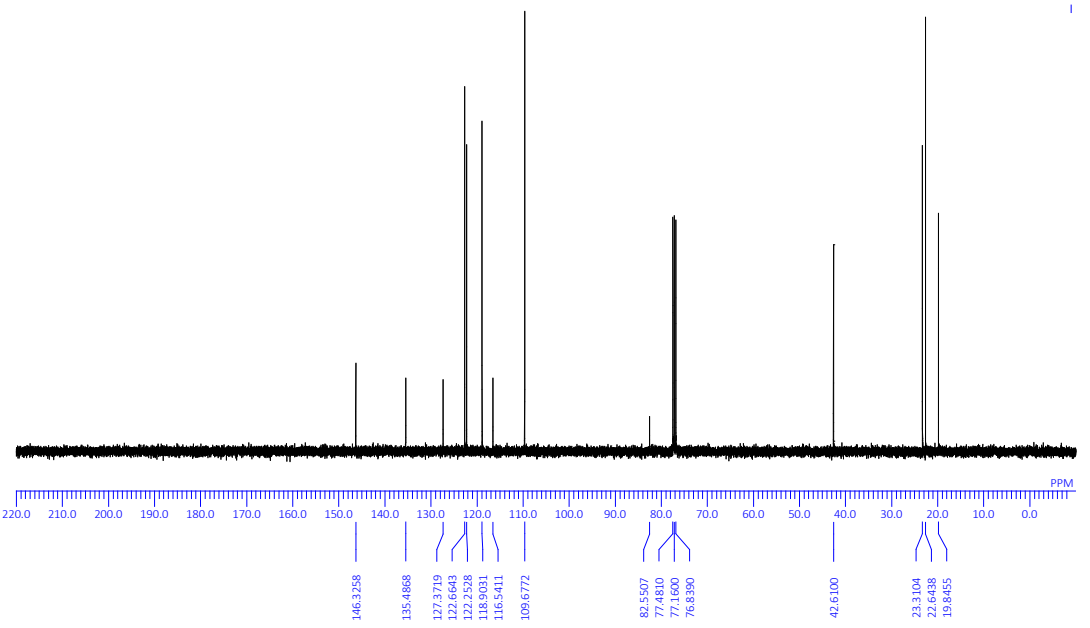




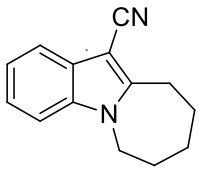
6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carbonitrile (3ab)

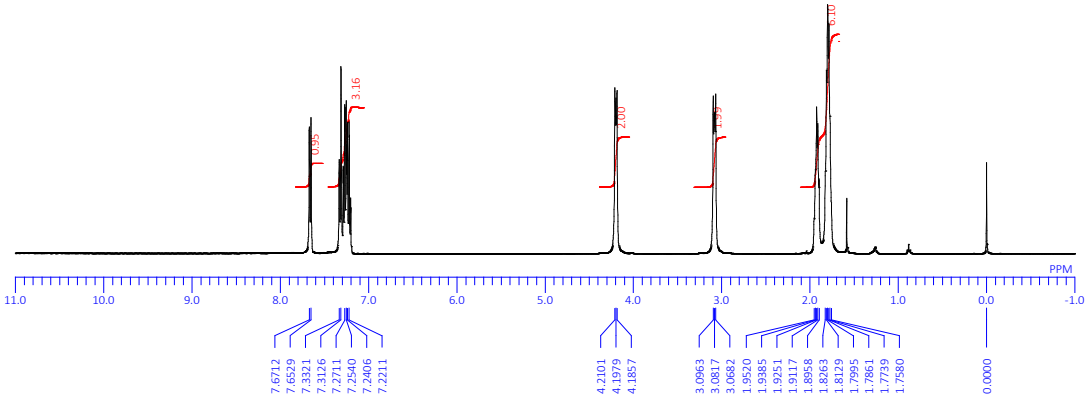


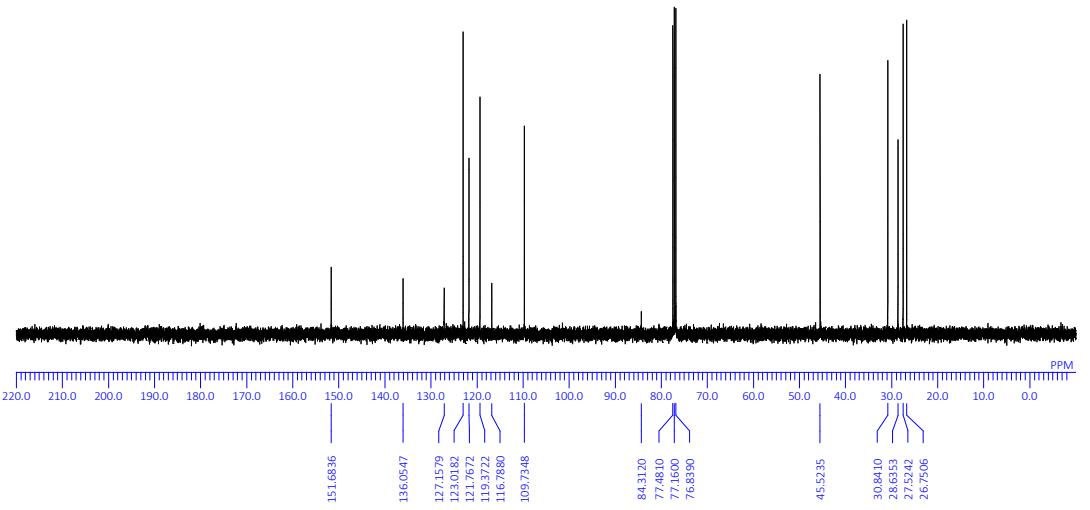




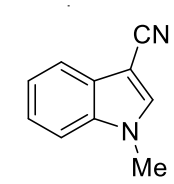
7,8,9,10-tetrahydro-6H-azepino[1,2-a]indole-11-carbonitrile(3ac)

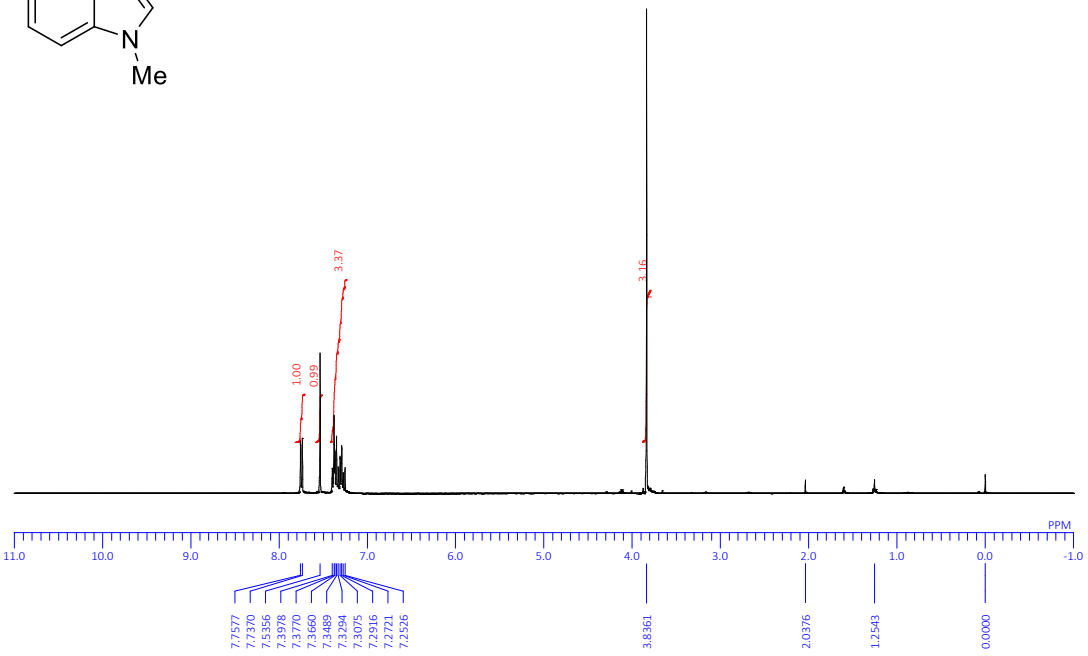


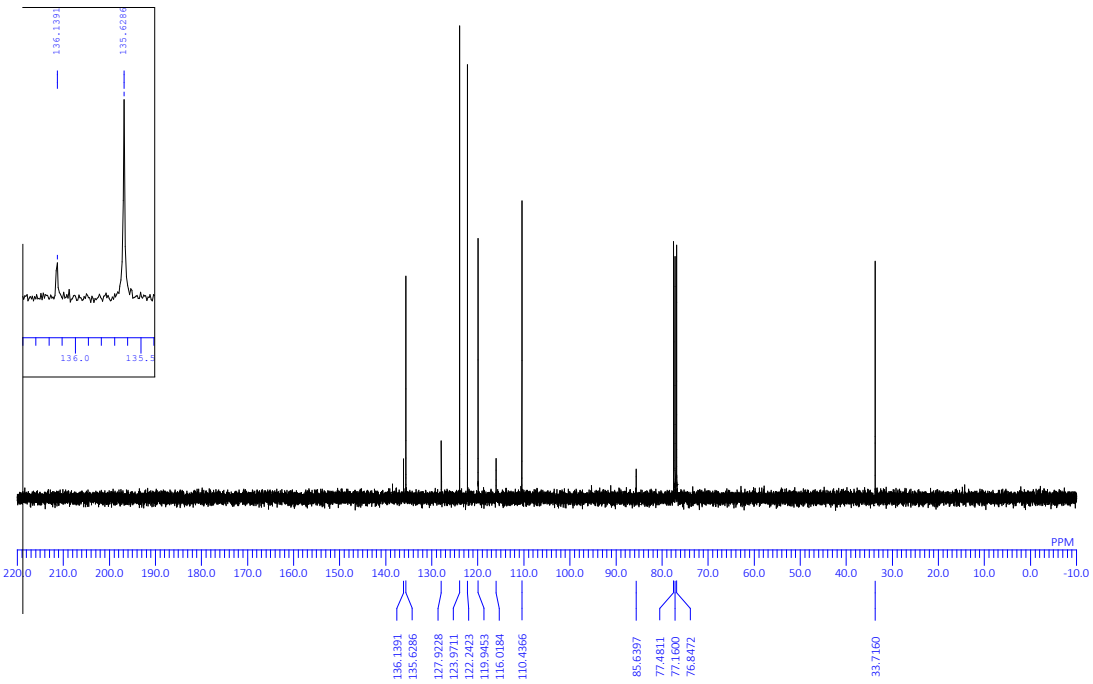




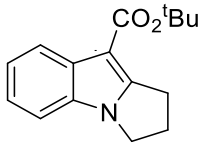
1-methyl-indole-3-carbonitrile (3ad)

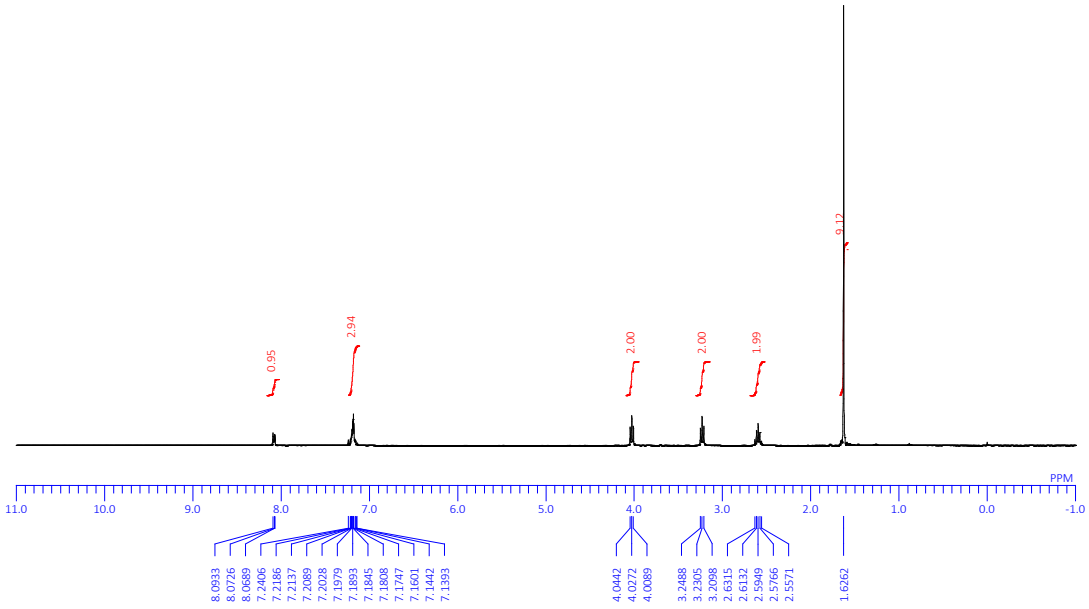


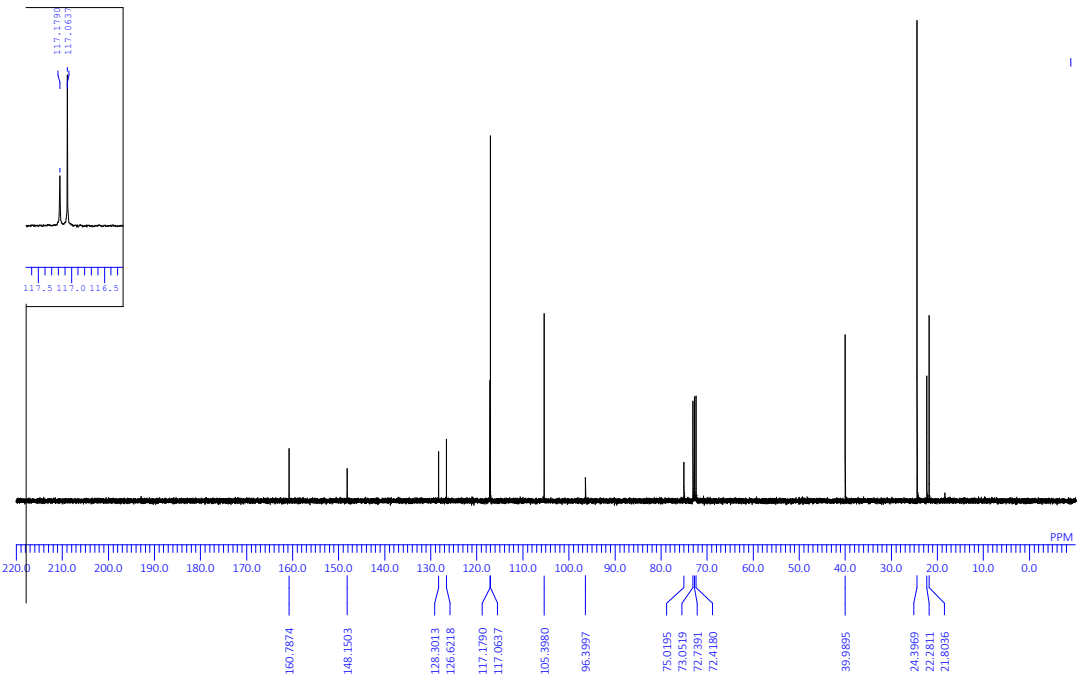




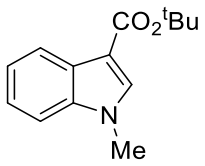
tert-butyl 2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate (3ba)

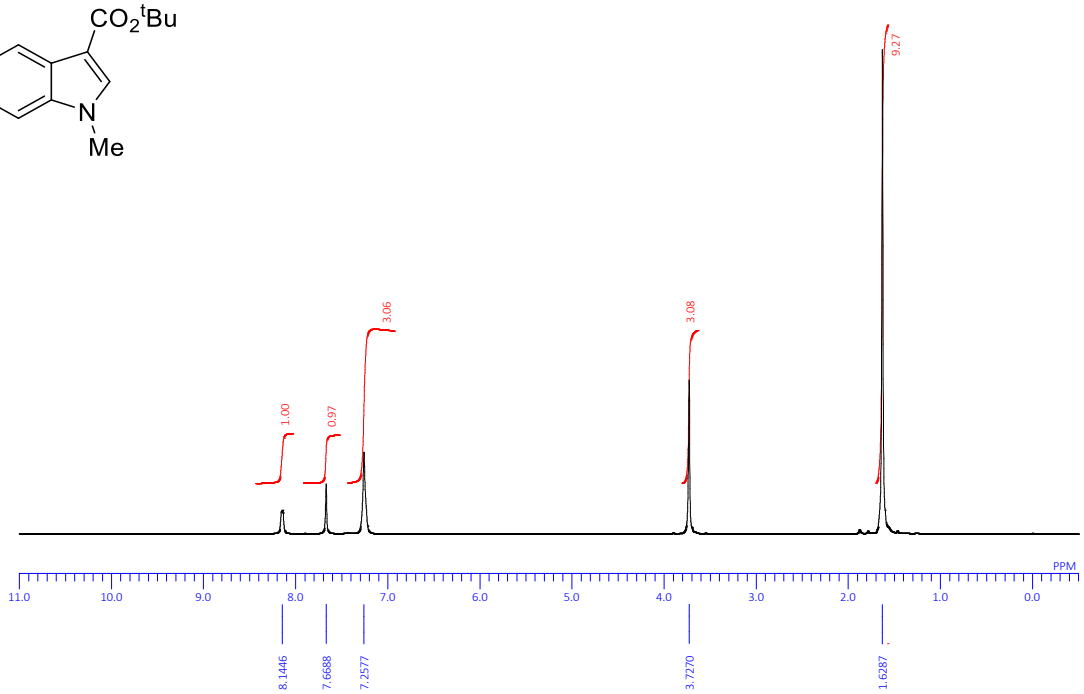


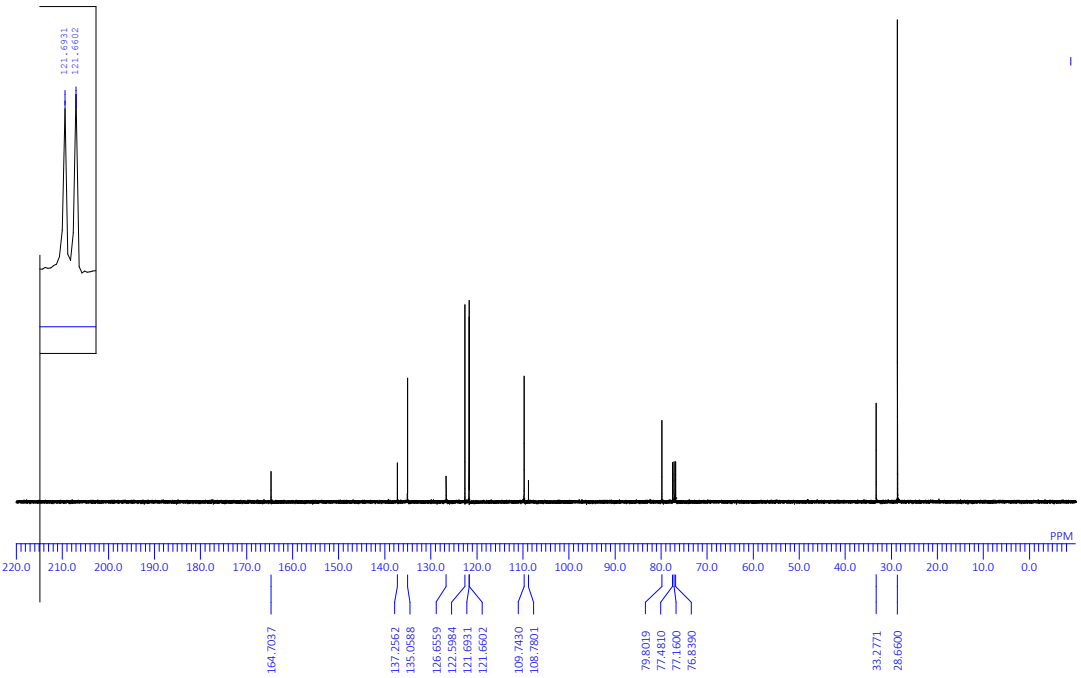




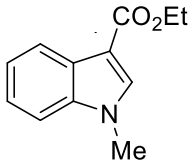
tert-butyl 1-methyl-1H-indole-3-carboxylate (3bd)

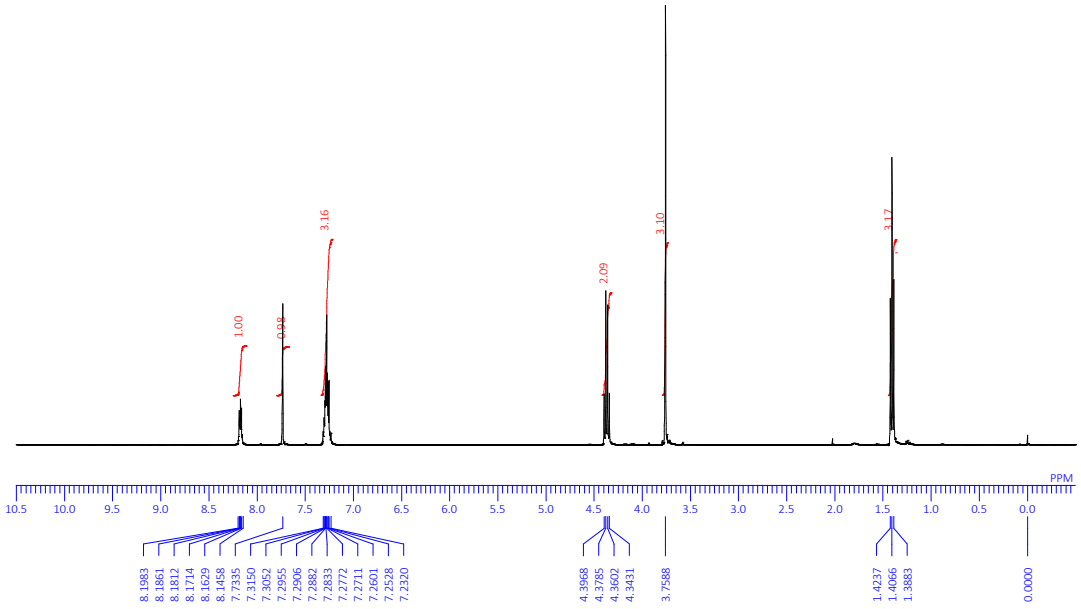


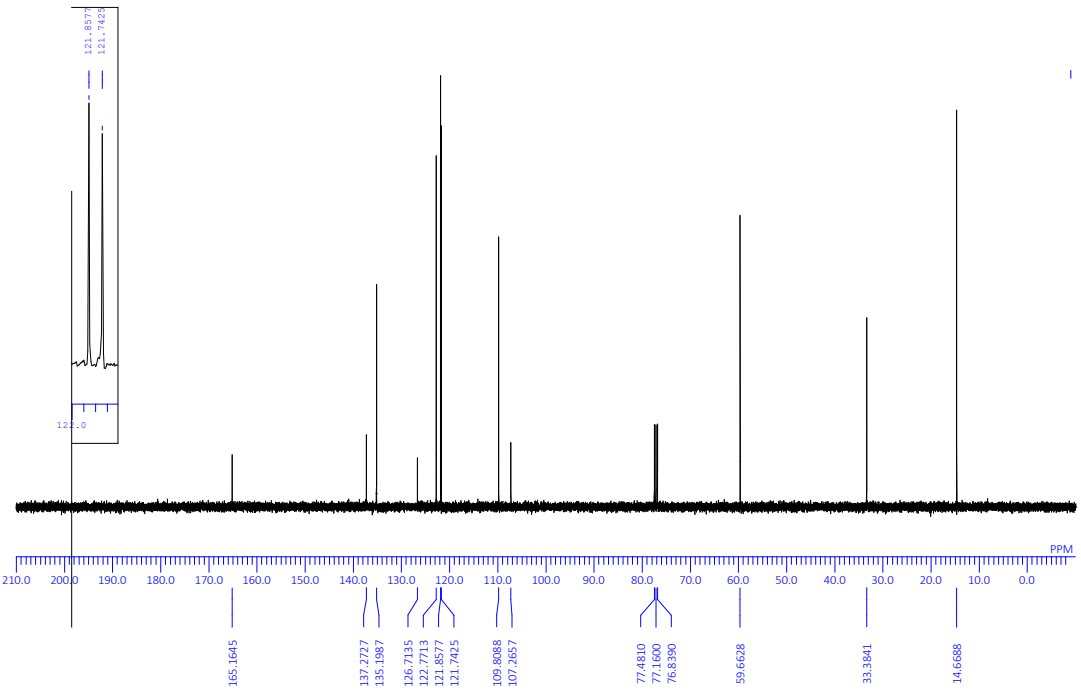




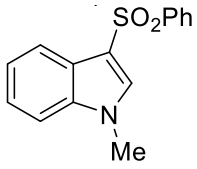
ethyl 1-methyl-1H-indole-3-carboxylate (3ca)

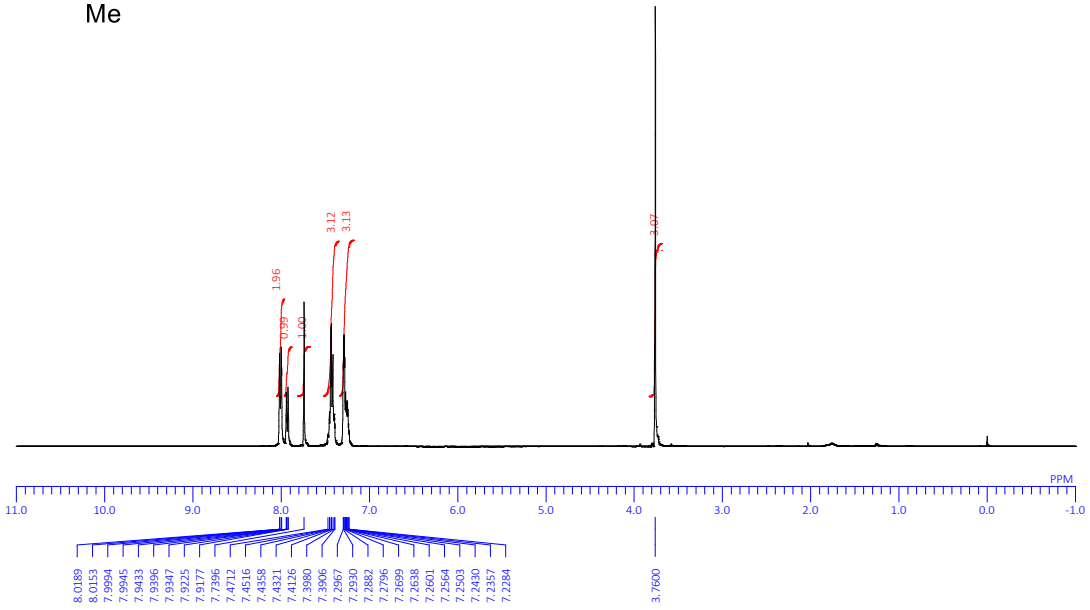


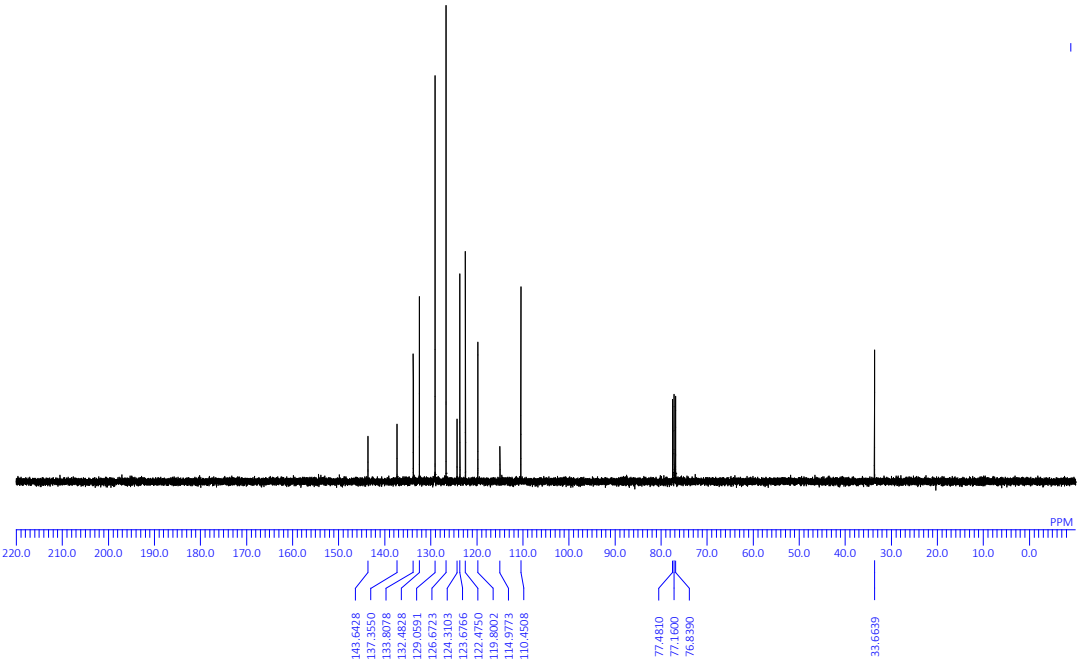




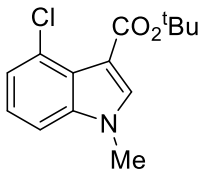
1-methyl-3-(phenylsulfonyl)-1H-indole (3dd)

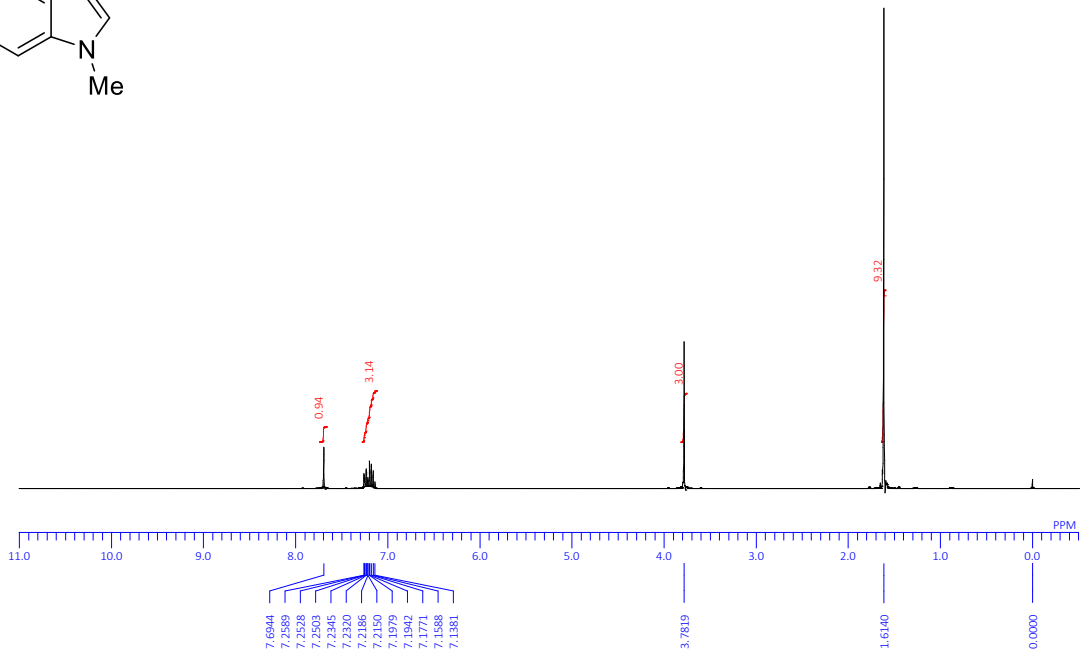


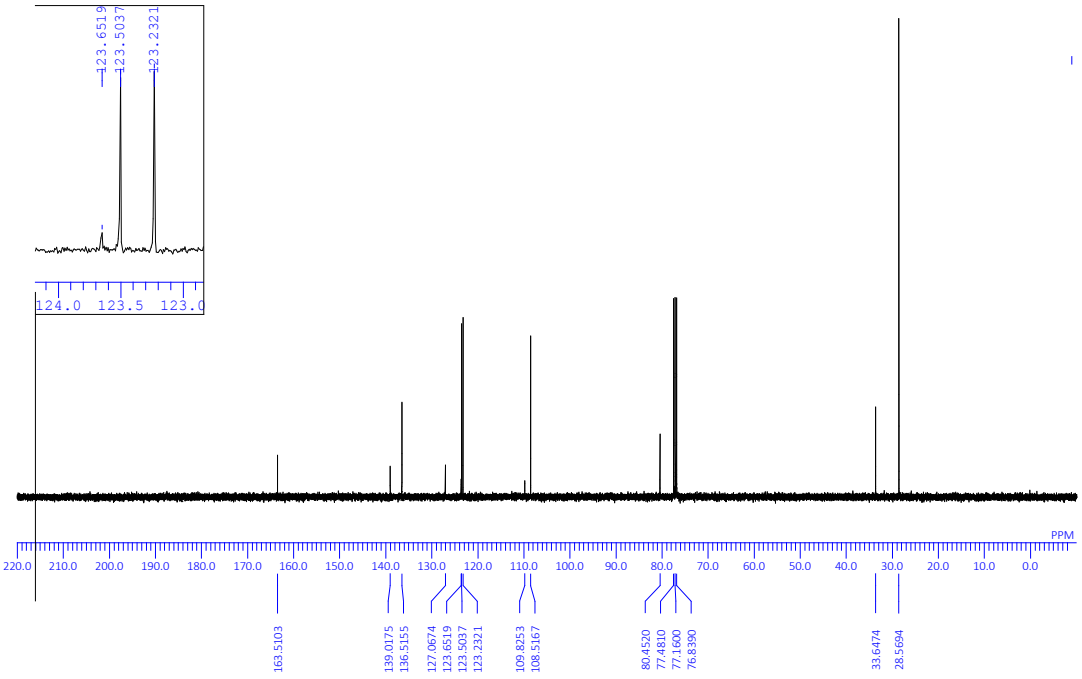




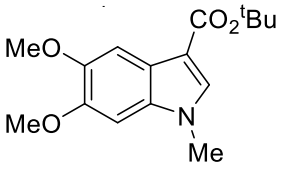
tert-butyl 4-chloro-1-methyl-1H-indole-3-carboxylate (3ed)

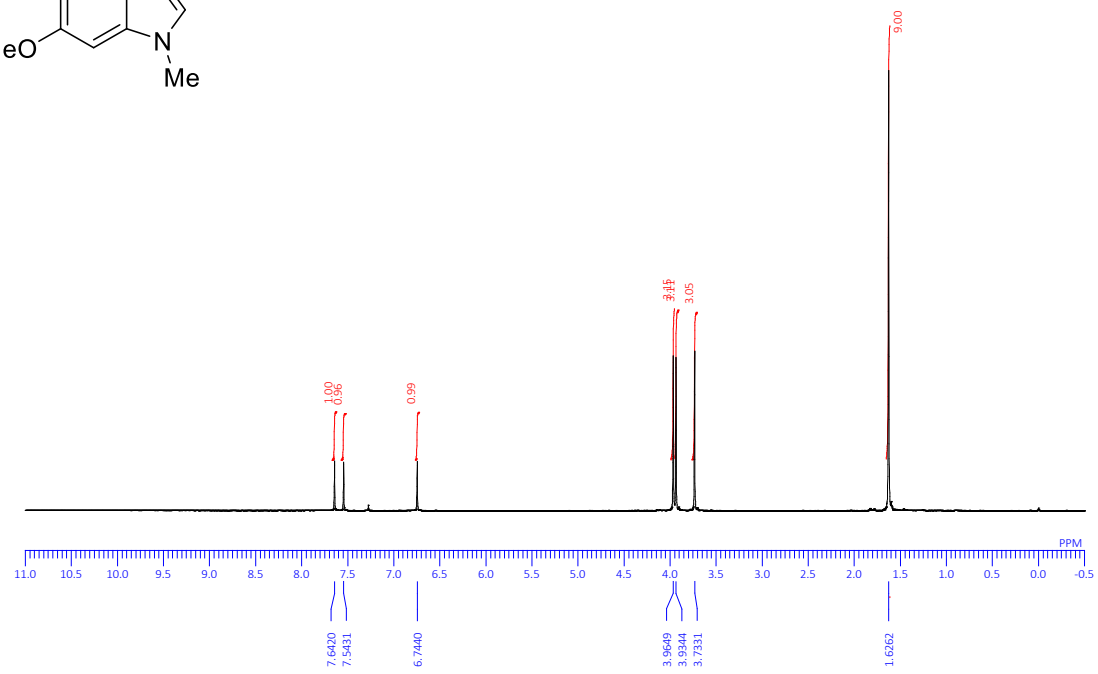


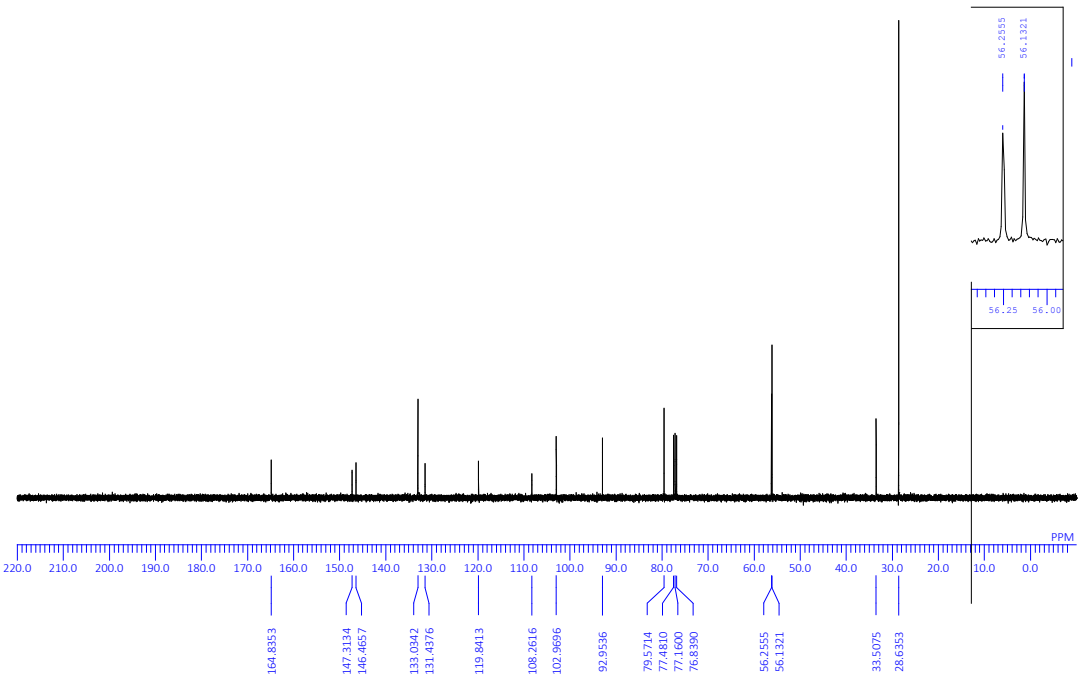




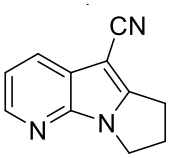
tert-butyl 5,6-dimethoxy-1-methyl-1H-indole-3-carboxylate (3fd)

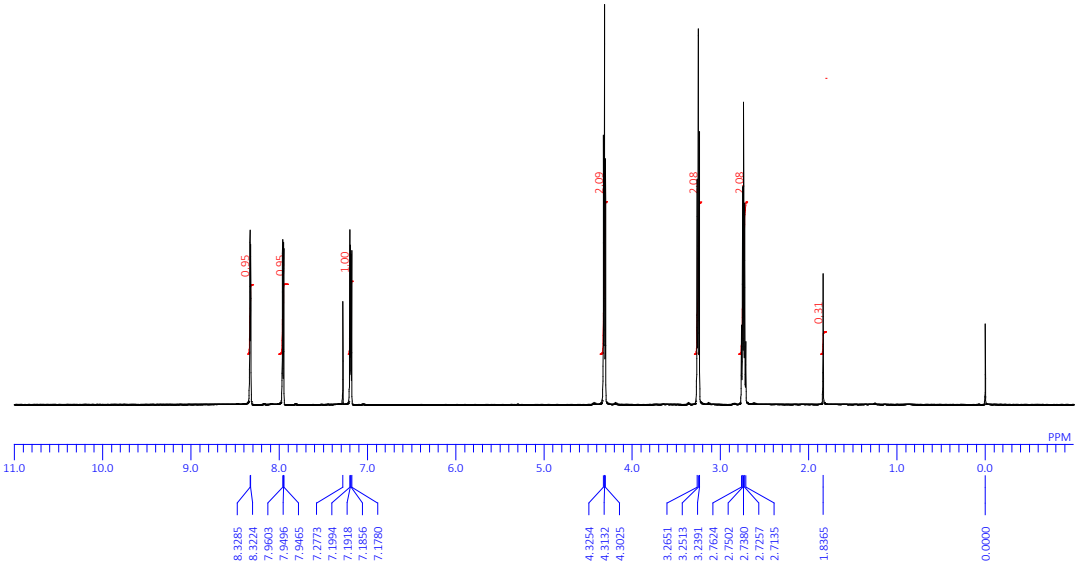


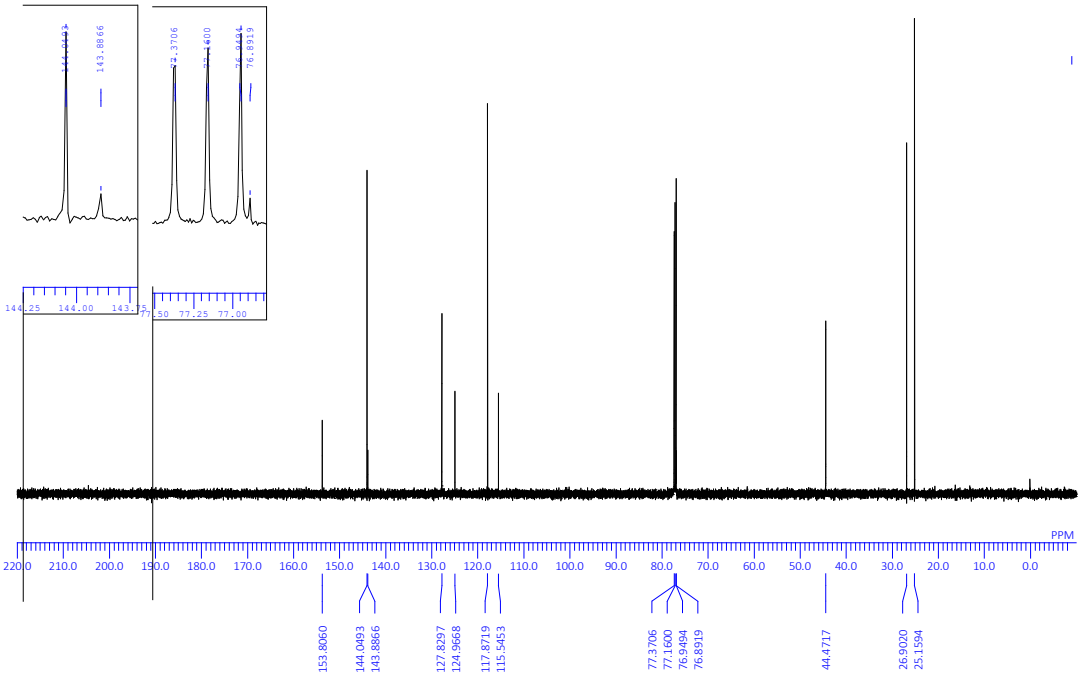




7,8-dihydro-6H-pyrido[3,2-b]pyrrolizine-5-carbonitrile (3ha)







2-(2-(2-oxopyrrolidin-1-yl)phenyl)acetonitrile (4aa)