New Preparation of TMPZnCl·LiCl by Zn Insertion into TMPCl. Application to the Functionalization of Dibromodiazines

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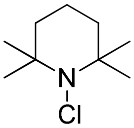
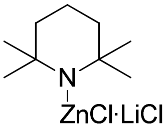
General All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be > 95 % pure as determined by 1H-NMR (25 °C) and capillary GC. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.25 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR) or *d6*-DMSO (δ 2.49 ppm for ^1H NMR and δ 39.5 ppm for ^{13}C NMR). Column chromatographical purifications were performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not indicated otherwise. TMPH, TMPCl and liquid acid chlorides were distilled prior to use.

Preparation of TMPCl (4)



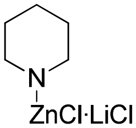
This compound was prepared from commercially available TMPH and aqueous sodium hypochlorite according to the procedure reported by Rabalais *et al.*[1]

Preparation of the reagent TMPZnCl·LiCl:



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (3.18 g, 75 mmol) dried for 5 min at 400 °C (heat gun) in high vacuum and then zinc powder (6.5 g, 100 mmol) was added and again dried for 5 min at 400 °C (heat gun) in high vacuum. THF (10 ml) was added and the zinc activated with *i*Bu_2AlH (0.07 mL, 0.5 mmol). After 5 min of stirring the zinc was further activated with 1,2-dibromoethane (0.22 mL, 0.5 mmol) and the reaction mixture was heated until ebullition occured. After cooling to 25 °C, trimethylsilyl chloride (0.06 mL, 0.01 mmol) and I_2 (0.5 mL, 1 M in THF, 0.5 mmol) were added and the mixture was cooled to 0 °C. 1-Chloro-2,2,6,6-tetramethylpiperidine (8.75 g, 50 mmol) was diluted with THF to a total volume of 30 mL and added via syringe pump at a rate of 0.25 mL/min. After the addition the reaction was stirred for further 30 minutes. Then the excess of zinc was allowed to sediment and the solution titrated with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.15 M in THF (92%) was obtained.

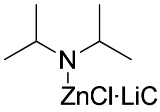
Preparation of the reagent piperidyl-ZnCl·LiCl:



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (3.18 g, 75 mmol) dried for 5 min at 400 °C (heat gun) in high vacuum and then zinc powder (6.5 g, 100 mmol) was added and again dried for 5 min at 400 °C (heat gun) in high vacuum. THF (10 ml) was added and the zinc activated with *i*Bu_2AlH (0.07 mL, 0.5 mmol). After 5 min of stirring the zinc was further activated with 1,2-dibromoethane (0.22 mL, 0.5 mmol) and the reaction mixture was heated until ebullition occured. After cooling to 25 °C, trimethylsilyl chloride (0.06 mL, 0.01 mmol) and I_2 (0.5 mL, 1 M in THF, 0.5 mmol) were added and the mixture was cooled to 0 °C. 1-Chloro-piperidine[2] (5.98 g, 50 mmol) was diluted with THF to a total volume of 30 mL and added via syringe pump at a rate of 0.25 mL/min. After the addition the reaction was stirred for further 30 minutes. Then the excess of zinc was allowed to sediment and the solution titrated with benzoic acid using 4-

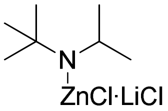
(phenylazo)diphenylamine as indicator. A concentration of 0.53 M in THF (42%) was obtained.

Preparation of the reagent Diisopropylamino-ZnCl·LiCl:



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (3.18 g, 75 mmol) dried for 5 min at 400 °C (heat gun) in high vacuum and then zinc powder (6.5 g, 100 mmol) was added and again dried for 5 min at 400 °C (heat gun) in high vacuum. THF (10 ml) was added and the zinc activated with *i*Bu$_2$AlH (0.07 mL, 0.5 mmol). After 5 min of stirring the zinc was further activated with 1,2-dibromoethane (0.22 mL, 0.5 mmol) and the reaction mixture was heated until ebullition occured. After cooling to 25 °C, trimethylsilyl chloride (0.06 mL, 0.01 mmol) and I_2 (0.5 mL, 1 M in THF, 0.5 mmol) were added and the mixture was cooled to 0 °C. 1-Chloro-diisopropylamine[3] (6.78 g, 50 mmol) was diluted with THF to a total volume of 30 mL and added via syringe pump at a rate of 0.25 mL/min. After the addition the reaction was stirred for further 30 minutes. Then the excess of zinc was allowed to sediment and the solution titrated with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.55 M in THF (44%) was obtained.

Preparation of the reagent tertButylisopropylamino-ZnCl·LiCl:



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (3.18 g, 75 mmol) dried for 5 min at 400 °C (heat gun) in high vacuum and then zinc powder (6.5 g, 100 mmol) was added and again dried for 5 min at 400 °C (heat gun) in high vacuum. THF (10 ml) was added and the zinc activated with *i*Bu$_2$AlH (0.07 mL, 0.5 mmol). After 5 min of stirring the zinc was further activated with 1,2-dibromoethane (0.22 mL, 0.5 mmol) and the reaction mixture was heated until ebullition occured. After cooling to 25 °C, trimethylsilyl chloride (0.06 mL, 0.01 mmol) and I_2 (0.5 mL, 1 M in THF, 0.5 mmol) were added and the mixture was cooled to 0 °C. 1-Chloro-tertbutylisopropylamine[4] (7.48 g, 50 mmol) was diluted with THF to a total volume of 30 mL and added via syringe pump at a rate of 0.25 mL/min. After the addition the reaction was stirred for further 30 minutes. Then the excess of zinc was allowed to sediment and the solution titrated with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.66 M in THF (53%) was obtained.

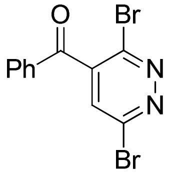
Typical procedure for the zincation of dibromodiazines with TMPZnCl·LiCl (TP 1):

A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding dibromodiazines (2.0 mmol) in dry THF (2 mL) as well as 50 μL of tetradecane (internal standard for GC analysis). After setting the desired temperature (Table 1), the zinc base (1.1 mmol) was added dropwise and stirred at the same temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure for the Pd-catalyzed cross-coupling reaction of organozinc reagents (TP 2):

In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the heteroaromatic bromide or iodide (1 mmol) was dissolved in THF (1.0 mL) and the Pd-source (0.02 mmol, 2 mol%) was added. Then, the phosphineligand (0.04 mmol, 4 mol%) was added. After the addition of the corresponding zinc reagent (0.80 mmol, 0.8 equiv), the reaction mixture was stirred for the given time at the indicated temperature until GC-analysis showed full conversion.

Synthesis of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (7a)



According to **TP 1**, the metalation of 3,6-dibromopyridazine (**5a**; 476 mg, 2 mmol) was completed within 15 min at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.28 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 9:1) to give **7a** (588 mg, 86%) as a colorless solid.

m.p.: 148.8 – 149.9 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.39 (s, 1 H), 7.92 – 7.88 (m, 2 H), 7.81 – 7.76 (m, 1 H), 7.62 –7.58 (m, 2 H).

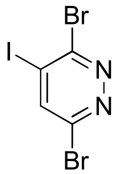
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 189.8, 148.0, 143.3, 142.0, 135.4, 133.7, 131.4, 130.2, 129.3.

MS (70 eV, EI) *m/z* (%): 343 (7), 341 (13), 339 (6) [M$^+$], 199 (3), 105 (100), 77 (43), 50 (5), 43 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061, 1663, 1656, 1591, 1490, 1451, 1342, 1320, 1305, 1250, 1169, 1162, 1128, 1086, 1077, 1023, 999, 960, 943, 911, 854, 809, 799, 748, 713, 695, 687, 652 .

HRMS (EI) for **$C_{11}H_6Br_2N_2O$** (339.8847): 339.8841.

Synthesis of 3,6-dibromo-4-iodopyridazine (7b)



According to **TP 1**, the metalation of 3,6-dibromopyridazine (**5a**; 476 mg, 2 mmol) was completed within 15 min at 25 °C. The reaction mixture was cooled to 0 °C, then a solution of iodine (761 mg, 3 mmol) dissolved in THF (6 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 49:1) to give **7b** (515 mg, 71%) as a colorless solid.

m.p.: 154.9 – 156.2 °C.

^{1}H-NMR (DMSO-d$_6$, 300 MHz) δ: 8.67 (s, 1 H).

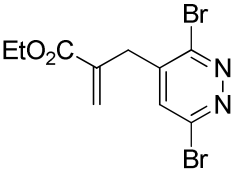
^{13}C-NMR (DMSO-d$_6$, 75 MHz) δ: 154.8, 145.5, 142.8, 112.2.

MS (70 eV, EI) *m/z* (%): 365 (43), 363 (100) [M$^+$], 361 (43), 210 (34), 208 (82), 206 (35), 129 (39), 127 (43), 126 (30), 77 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3085, 1725, 1668, 1587, 1563, 1528, 1496, 1469, 1419, 1396, 1321, 1286, 1260, 1190, 1160, 1146, 1091, 1074, 1038, 1028, 997, 962, 937, 881, 830, 811, 769, 745, 727, 670, 657.

HRMS (EI) for $\mathbf{C_4HBr_2IN_2}$ (361.7551): 361.7687.

Synthesis of ethyl 2-((3,6-dibromopyridazin-4-yl)methyl)acrylate (7c)



According to **TP 1**, the metalation of 3,6-dibromopyridazine (**5a**; 476 mg, 2 mmol) was completed within 15 min at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate (463 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 9:1) to give **7c** (513 mg, 73%) as a colorless solid.

m.p.: 60.4 – 61.4 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.45 (s, 1 H), 6.47 (s, 1 H), 5.74 (d, *J*=0.6 Hz, 1 H), 4.20 (q, *J*=7.2 Hz, 2 H), 3.70 (s, 2 H), 1.27 (t, *J*=7.2 Hz, 3 H).

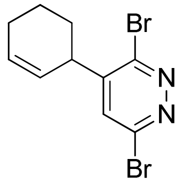
^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 165.5, 150.9, 147.4, 143.1, 134.8, 132.6, 129.9, 61.5, 36.8, 14.1.

MS (70 eV, EI) *m/z* (%): 348 (2) [M$^+$], 305 (11), 271 (20), 243 (95), 241 (100), 177 (16), 161 (11), 117 (17), 90 (14), 85 (15), 71 (20), 63 (12), 57 (27), 55 (11), 43 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3059, 2978, 1707, 1632, 1553, 1465, 1371, 1360, 1326, 1306, 1290, 1221, 1207, 1146, 1123, 1078, 1024, 1017, 969, 944, 888, 858, 822, 747, 729, 677.

HRMS (EI) for $\mathbf{C_{10}H_{10}Br_2N_2O_2}$ (347.9109): 347.9108.

Synthesis of 3,6-dibromo-4-(cyclohex-2-en-1-yl)pyridazine (7d)



According to **TP 1**, the metalation of 3,6-dibromopyridazine (**5a**; 476 mg, 2 mmol) was completed within 15 min at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (463 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 19:1) to give **7d** (485 mg, 76%) as a colorless solid.

m.p.: 50.4 – 51.4 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 7.62 (s, 1 H), 6.08 – 6.02 (m, 1 H), 5.63 – 5.57 (m, 1 H), 3.64 – 3.57 (m, 1 H), 2.09 – 1.97 (m, 3 H), 1.60 – 1.48 (m, 3 H).

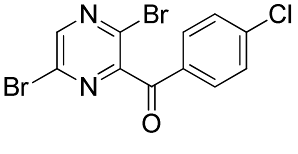
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 150.9, 149.2, 147.8, 132.0, 131.4, 125.4, 39.2, 27.7, 24.2, 19.6.

MS (70 eV, EI) *m/z* (%): 319 (29), 317 (56), 315 (30) [M$^+$], 302 (11), 263 (18), 239 (15), 157 (41), 130 (15), 102 (22), 81 (22), 79 (16), 77 (17), 67 (13), 61 (15), 57 (13), 53 (10), 45 (13), 43 (100), 40 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3023, 2922, 2859, 2829, 1548, 1493, 1455, 1444, 1427, 1391, 1351, 1339, 1321, 1299, 1288, 1274, 1248, 1115, 1085, 1076, 1056, 1038, 1016, 992, 910, 878, 844, 819, 758, 747, 723, 681, 664.

HRMS (EI) for **$C_{10}H_{10}Br_2N_2$** (315.9211): 315.9208.

Synthesis of (4-chlorophenyl)(3,6-dibromopyrazin-2-yl)methanone (7e)



According to **TP 1**, the metalation of 2,5-dibromopyrazine (**5b**; 476 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (0.31 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 4:1) to give **7e** (596 mg, 79%) as an off white solid.

m.p.: 130.8 – 132.8 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) *δ*: 8.95 (s, 1 H), 7.96 (dt, *J*=9.0, 2.4, Hz, 2 H), 7.67 (dt, *J*=9.0, 2.4, 2 H)

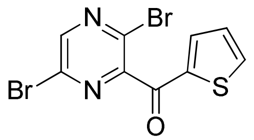
^{13}C-NMR (DMSO-d$_6$, 100 MHz) *δ*: 189.2, 151.2, 149.3, 140.4, 138.3, 135.0, 132.3, 132.1, 129.4.

MS (70 eV, EI) *m/z* (%): 377 (5), 375 (8) [M$^+$], 139 (8), 138 (100), 111 (30), 75 (12), 44 (7), 43 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3116, 3061, 1663, 1656, 1590, 1583, 1490, 1451, 1342, 1320, 1304, 1249, 1168, 1162, 1127, 1086, 1078, 1022, 999, 960, 943, 911, 855, 808, 798, 748, 711, 695, 686.

HRMS (EI) for **$C_{11}H_5Br_2ClN_2O$** (373.8547): 373.8464.

Synthesis of (3,6-dibromopyrazin-2-yl)(thiophen-2-yl)methanone (7f)



According to **TP 1**, the metalation of 2,5-dibromopyrazine (**5b**; 476 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and thiophene-2-carbonyl chloride (0.26 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **7f** (450 mg, 65%) as an off white solid.

m.p.: 106.2 – 108.7 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) *δ*: 8.60 (s, 1 H), 7.84 (d, *J* = 4.1 Hz, 1 H), 7.65 (d, *J* = 3.3 Hz, 1 H), 7.22–7.16 (m, 1 H).

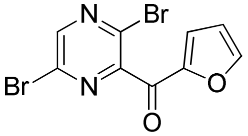
^{13}C-NMR (CDCl$_3$, 75 MHz) *δ*: 181.4, 151.1, 148.3, 140.8, 137.6, 137.2, 136.9, 136.1, 128.7.

MS (70 eV, EI) *m/z* (%): 348 (13), 346 (7) [M$^+$], 319 (2), 112 (6), 110 (100), 83 (6), 56 (3), 45 (2).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3090, 2920, 1633, 1509, 1410, 1403, 1376, 1368, 1350, 1256, 1237, 1175, 1168, 1156, 1131, 1085, 1059, 1039, 946, 916, 907, 858, 802, 759, 743, 682.

HRMS (EI) for **$C_9H_4Br_2N_2OS$** (345.8411): 345.8408.

Synthesis of (3,6-dibromopyrazin-2-yl)(furan-2-yl)methanone (7g)



According to **TP 1**, the metalation of 2,5-dibromopyrazine (**5b**; 476 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and thiophene-2-carbonyl chloride (0.26 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **7g** (352 mg, 53%) as an off white solid.

m.p.: 139.2 – 140.4 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.95 (s, 1 H), 8.24 (dd, *J*=1.6, 0.8 Hz, 1 H), 7.58 (dd, *J*=3.7, 0.6 Hz, 1 H), 6.85 – 6.84 (m, 1 H).

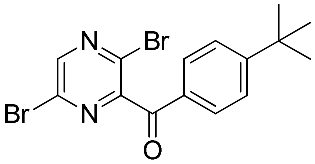
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 176.4, 151.0, 150.3, 149.6, 149.4, 138.1, 135.2, 125.6, 113.6.

MS (70 eV, EI) *m/z* (%): 333 (11), 331 (25) [M$^+$], 329 (12), 305 (12), 303 (26), 301 (13), 96 (13), 95 (54), 94 (100), 43 (65).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3125, 3069, 1648, 1558, 1500, 1460, 1403, 1376, 1361, 1282, 1238, 1167, 1153, 1135, 1081, 1058, 1032, 964, 918, 904, 880, 801, 773, 743, 657.

HRMS (EI) for **$C_9H_4Br_2N_2O_2$** (329.8640): 329.8587.

Synthesis of (4-(tert-butyl)phenyl)(3,6-dibromopyrazin-2-yl)methanone (7h)



According to **TP 1**, the metalation of 2,5-dibromopyrazine (**5b**; 476 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 4-(*tert*-butyl)benzoyl chloride (0.31 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 4:1) to give **7h** (567 mg, 71%) as a colorless oil.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) *δ*: 8.94 (s, 1 H), 7.84 (dt, *J*=8.8, 2.0 Hz, 2 H), 7.61 (dt, *J*=8.8, 2.0 Hz, 2 H), 1.31 (s, 9 H).

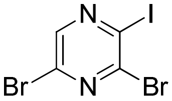
^{13}C-NMR (DMSO-d$_6$, 100 MHz) *δ*: 189.7, 158.7, 152.1, 149.0, 138.4, 134.9, 131.1, 130.3, 126.2, 35.2, 30.6.

MS (70 eV, EI) *m/z* (%): 399 (19), 397 (39), 395 (20) [M^+], 384 (45), 382 (95), 380 (45), 264 (20), 236 (27), 162 (90), 161 (100), 146 (32), 118(48), 115 (26), 91 (30), 77 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961, 2903, 2867, 1670, 1602, 1565, 1462, 1410, 1365, 1313, 1250, 1171, 1134, 1107, 1048, 952, 907, 849, 817, 775, 723, 705, 652.

HRMS (EI) for **$C_{15}H_{14}Br_2N_2O$** (395.9473): 395.9462.

Synthesis of 3,5-dibromo-2-iodopyrazine (7i)



According to **TP 1**, the metalation of 2,6-dibromopyrazine (**5c**; 476 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to 0 °C, then a solution of iodine (761 mg, 3 mmol) dissolved in THF (6 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 9:1) to give **7i** (604 mg, 83%) as a colorless solid.

m.p.: 115.6 – 117.6 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) *δ*: 8.68 (s, 1 H).

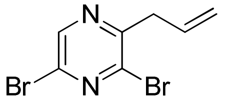
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 147.1, 145.3, 136.7, 123.9.

MS (70 eV, EI) *m/z* (%): 365 (41), 363 (100), 361 (41) [M$^+$], 238 (45), 236 (87), 234 (46), 184 (16), 177 (13), 129 (17), 126 (29), 77 (13), 71 (11), 57 (18), 43 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1782, 1496, 1477, 1374, 1344, 1294, 1261, 1255, 1192, 1162, 1136, 1120, 1103, 1022, 1010, 893, 803, 734.

HRMS (EI) for **$C_4HBr_2IN_2$** (361.7551): 361.7563.

Synthesis of 2-allyl-3,5-dibromopyrazine (7j)



According to **TP 1**, the metalation of 2,6-dibromopyrazine (**5c**; 476 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and allylbromide (0.21 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 19:1) to give **7i** (499 mg, 90%) as a colorless oil.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.82 (s, 1 H), 6.03 – 5.93 (m, 1 H), 5.15 – 5.12 (m, 1 H), 5.13 (dq, *J*=28.0, 1.6 Hz, 1 H), 3.65 (dt, *J*=6.43, 1.56 Hz, 2 H)

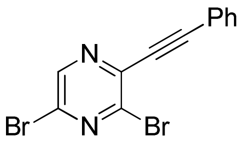
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 154.1, 145.9, 145.2, 139.2, 135.4, 132.9, 117.9.

MS (70 eV, EI) *m/z* (%): 278 (52), 277 (100), 275 (24) [M$^+$], 274 (55), 251 (13), 198 (10), 118 (20), 91 (10), 90 (14), 57 (16), 43 (14), 40 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1638, 1525, 1501, 1428, 1407, 1367, 1328, 1309, 1262, 1246, 1210, 1174, 1142, 1123, 1082, 1047, 989, 919, 898, 858, 849, 782, 711.

HRMS (EI) for **$C_7H_6Br_2N_2$** (275.8898): 275.8872.

Synthesis of 3,5-dibromo-2-(phenylethynyl)pyrazine (7k)



According to **TP 1**, the metalation of 2,6-dibromopyrazine (**5c**; 476 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and (bromoethynyl)benzene[5] (434 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 19:1) to give **7k** (502 mg, 74%) as an off white solid.

m.p.: 128.7 – 130.2 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.59 (s, 1 H), 7.62 – 7.66 (m, 2 H), 7.46 – 7.36 (m, 3 H).

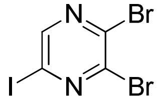
^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 145.0, 141.3, 140.0, 136.1, 132.2, 130.1, 128.6, 121.1, 98.5, 85.1.

MS (70 eV, EI) *m/z* (%): 335 (1) [M$^+$], 88 (5), 73 (5), 70 (10), 61 (14), 60 (5), 45 (13), 43 (100), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2222, 1568, 1486, 1440, 1415, 1330, 1270, 1192, 1169, 1158, 1119, 1069, 1055, 1020, 997, 916, 897, 871, 775, 759, 689, 653.

HRMS (EI) for **$C_{12}H_6Br_2N_2$** (335.8898): 335.88925.

Synthesis of 2,3-dibromo-5-iodopyrazine (7l)



According to **TP 1**, the metalation of 2,3-dibromopyrazine (**5d**; 476 mg, 2 mmol) was completed within 12 h at 50 °C. The reaction mixture was cooled to 0 °C, then a solution of iodine (761 mg, 3 mmol) dissolved in THF (6 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 19:1) to give **7l** (514 mg, 71%) as a colorless solid.

m.p.: 117.5 – 119.9 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.72 (s, 1 H).

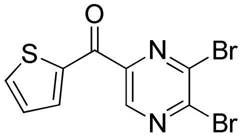
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 146.8, 146.2, 137.0, 122.9.

MS (70 eV, EI) *m/z* (%): 365 (3), 363 (1) [M$^+$], 321 (24), 319 (73), 317 (68), 194 (25), 190 (100), 165 (25), 163 (19), 69 (12), 57 (49), 56 (18), 55 (17), 44 (26), 43 (16), 41 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1496, 1477, 1374, 1345, 1292, 1263, 1195, 1172, 1137, 1113, 1093, 1029, 1015, 894, 810, 800, 737.

HRMS (EI) for **$C_4HBr_2IN_2$** (363.7766): 363.7538.

Synthesis of (5,6-dibromopyrazin-2-yl)(thiophen-2-yl)methanone (7m)



According to **TP 1**, the metalation of 2,3-dibromopyrazine (**5d**; 476 mg, 2 mmol) was completed within 12 h at 50 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 2.2 mL, 2.247mmol) and thiophene-2-carbonyl chloride (0.26 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 4:1) to give **7m** (527 mg, 76%) as an off white solid.

m.p.: 144.5 – 146.9 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 9.00 (s, 1 H), 8.26 (dd, *J*=3.9, 1.3 Hz, 1 H), 8.22 (dd, *J*=4.9, 1.2 Hz, 1 H), 7.34 (dd, *J*=4.9, 3.9 Hz, 1 H).

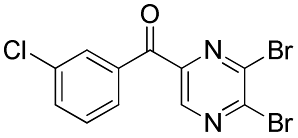
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 180.3, 146.2, 146.0, 142.9, 140.6, 139.3, 138.4, 137.5, 128.8.

MS (70 eV, EI) *m/z* (%): 347 (18), 345 (9) [M^+], 319 (4), 111 (100), 83 (6), 57 (2), 56 (2), 33 (2).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3111, 1636, 1601, 1530, 1507, 1500, 1407, 1356, 1313, 1264, 1227, 1215, 1187, 1158, 1141, 1071, 1048, 1042, 1028, 936, 930, 897, 864, 802, 775, 767, 739, 717.

HRMS (EI) for **$C_9H_4Br_2N_2OS$** (345.8411): 345.8409.

Synthesis of (3-chlorophenyl)(5,6-dibromopyrazin-2-yl)methanone (7n)



According to **TP 1**, the metalation of 2,3-dibromopyrazine (**5d**; 476 mg, 2 mmol) was completed within 12 h at 50 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 3-chlorobenzoyl chloride (0.27 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 9:1) to give **7n** (424 mg, 56%) as a colorless solid.

m.p.: 155.9 – 157.2 °C.

^{1}H-NMR (DMSO-d$_6$, 300 MHz) *δ*: 8.94 (s, 1 H), 8.09 (t, *J*=1.80 Hz, 1 H), 8.02 – 7.97 (m, 1 H), 7.64 – 7.59 (m, 1 H), 7.46 (t, *J*=8.02 Hz, 1 H).

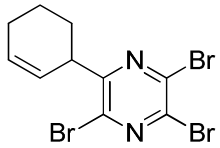
^{13}C-NMR (DMSO-d$_6$, 75 MHz) *δ*: 188.2, 146.8, 143.3, 141.4, 136.4, 134.8, 133.9, 130.7, 129.8, 129.0.

MS (70 eV, EI) *m/z* (%): 373 (1) [M^+], 138 (12), 111 (5), 88 (5), 73 (5), 70 (10), 61 (14), 45 (11), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3085, 1720, 1667, 1587, 1563, 1528, 1496, 1469, 1418, 1395, 1320, 1259, 1190, 1170, 1160, 1145, 1090, 1074, 1038, 1028, 997, 970, 961, 937, 881, 829, 810, 769, 746, 727, 670, 657.

HRMS (EI) for **$C_{11}H_5Br_2ClN_2O$** (373.8457): 373.8438.

Synthesis of 2,3,5-tribromo-6-(cyclohex-2-en-1-yl)pyrazine (7o)



According to **TP 1**, the metalation of 2,3,5-tribromopyrazine (**5e**; 634 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (463 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 19:1) to give **7o** (437 mg, 55%) as an off white solid.

m.p.: 70.9 – 72.8 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) *δ*: 5.95 – 5.78 (m, 1 H), 5.61 (dd, *J*=10.0, 1.3 Hz, 1 H), 3.83 (dt, *J*=5.4, 2.7 Hz, 1 H), 2.11 – 1.94 (m, 3 H), 1.81 (td, *J*=10.2, 5.1 Hz, 1 H), 1.69 – 1.52 (m, 2 H).

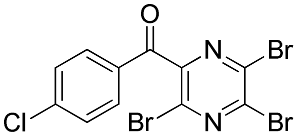
^{13}C-NMR (DMSO-d$_6$, 100 MHz) *δ*: 158.6, 140.2, 137.7, 137.0, 128.8, 126.3, 40.1, 27.3, 24.0, 20.7.

MS (70 eV, EI) *m/z* (%): 399 (16), 397 (42), 395 (47), 393 (19) [M$^+$], 370 (16), 368 (46), 366 (50), 364 (15), 356 (15), 354 (16), 343 (36), 341 (39), 331 (45), 329 (41), 318 (51), 316 (100), 314 (53), 288 (16), 81 (16), 79 (22), 77 (28), 67 (93), 57 (16), 53 (19), 43 (31), 41 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3023, 2945, 2897, 2830, 1683, 1493, 1448, 1429, 1355, 1313, 1255, 1185, 1174, 1142, 1130, 1080, 1055, 1015, 931, 897, 863, 810, 720.

HRMS (EI) for **$C_{10}H_9Br_3N_2$** (393.8316): 393.8311.

Synthesis of (4-chlorophenyl)(3,5,6-tribromopyrazin-2-yl)methanone (7p)



According to **TP 1**, the metalation of 2,3,5-tribromopyrazine (**5e**; 634 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (0.27 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 9:1) to give **7p** (598 mg, 66%) as a yellowish solid.

m.p.: 156.9 – 159.8 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) *δ*: 8.00 (dt, *J*=8.97, 2.24 Hz, 2 H), 7.68 (dt, *J*=9.06, 2.29 Hz, 2 H).

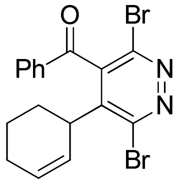
^{13}C-NMR (DMSO-d$_6$, 400 MHz) *δ*: 188.9, 148.9, 143.0, 141.0, 140.5, 132.9, 132.5, 132.2, 129.4.

MS (70 eV, EI) *m/z* (%): 452 (1) [M$^+$], 139 (100), 111 (19), 75 (9), 70 (5), 61 (8), 45 (7), 43 (60).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2921, 2852, 1678, 1585, 1571, 1504, 1486, 1404, 1355, 1279, 1240, 1180, 1165, 1140, 1090, 1069, 1012, 956, 843, 823, 768, 752, 729, 685, 667.

HRMS (EI) for **$C_{11}H_4Br_3ClN_2O$** (451.7562): 451.7569.

Synthesis of (3,6-dibromo-5-(cyclohex-2-en-1-yl)pyridazin-4-yl)(phenyl)methanone (8a)



According to **TP 1**, the metalation of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**7a**; 342 mg, 1 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 0.05 mL, 0.05 mmol) and 3-bromocyclohexene (193 mg, 1.2 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 9:1) to give **8a** (335 mg, 72%) as a colorless solid.

m.p.: 56.9 – 59.8 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.87 – 7.58 (m, 3 H), 7.55 – 7.45 (m, 2 H), 5.59 – 5.43 (m, 1 H), 5.17 – 5.02 (m, 1 H), 3.92 – 3.66 (m, 1 H), 1.99 – 1.42 (m, 1 H).

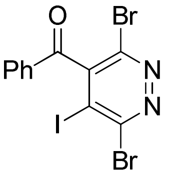
^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 190.9, 144.5, 144.3, 135.9, 135.0, 134.5, 131.3, 129.7, 129.2, 129.0, 129.0, 124.7, 41.6, 24.5, 24.0, 21.7.

MS (70 eV, EI) *m/z* (%): 422 (13), 420 (8) [M^+], 165 (12), 127 (12), 125 (11), 113 (17), 111 (26), 109 (14), 105 (55), 99 (22), 97 (36), 95 (19), 91 (12), 85 (59), 83 (36), 81 (23), 79 (14), 77 (61), 71 (76), 69 (40), 61 (16), 57 (100), 55 (47), 43 (63), 41 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3024, 2925, 2860, 2829, 1671, 1594, 1581, 1495, 1448, 1324, 1227, 1221, 1177, 1141, 1073, 1037, 1000, 955, 910, 804, 783, 770, 759, 706, 684, 661.

HRMS (EI) for **$C_{17}H_{14}Br_2N_2O$** (419.9473): 419.9480.

Synthesis of (3,6-dibromo-5-iodopyridazin-4-yl)(phenyl)methanone (8b)



According to **TP 1**, the metalation of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**7a**; 342 mg, 1 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -20 °C, then a solution of iodine (381 mg, 1.5 mmol) dissolved in THF (3 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 9:1) to give **8b** (314 mg, 67%) as a colorless solid.

m.p.: 230.9 – 232.1 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 7.98 (d, *J*=7.2 Hz, 2 H), 7.80 (t, *J*=7.4 Hz, 1 H), 7.62 (t, *J*=7.73 Hz, 2 H).

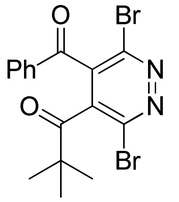
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 191.2, 156.0, 147.8, 140.1, 135.7, 131.6, 130.0, 129.7, 110.8.

MS (70 eV, EI) *m/z* (%): 467 (12), 465 (5) [M$^+$], 105 (100), 77 (46), 50 (5), 42 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1667, 1590, 1580, 1494, 1456, 1449, 1318, 1311, 1297, 1227, 1180, 1169, 1161, 1096, 1054, 1025, 998, 955, 938, 809, 795, 761, 735, 705, 680, 658.

HRMS (EI) for **$C_{11}H_5Br_2IN_2O$** (465.7813): 465.7802.

Synthesis of 1-(5-benzoyl-3,6-dibromopyridazin-4-yl)-2,2-dimethylpropan-1-one (8c)



According to **TP 1**, the metalation of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**7a**; 342 mg, 1 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol) and pivaloyl chloride (145 mg, 1.2 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 4:1) to give **8c** (244 mg, 57%) as a colorless solid.

m.p.: 116.8 – 119.9 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 7.90 (dd, *J*=8.5, 1.3 Hz, 2 H), 7.80 (tt, *J*=7.5, 1.3 Hz, 1 H), 7.59 (dd, *J*=8.3, 7.5 Hz, 2 H), 1.12 (s, 9 H).

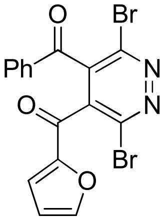
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 207.6, 190.4, 143.4, 142.2, 140.7, 137.0, 136.1, 133.6, 130.4, 129.5, 44.0, 26.9.

MS (70 eV, EI) *m/z* (%): 423 (1) [M$^+$], 376 (43), 371 (50), 369 (100), 2351 (25), 233 (23), 209 (10), 77 (40), 56 (94), 43 (11), 41 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2923, 1795, 1691, 1667, 1592, 1478, 1463, 1447, 1396, 1368, 1361, 1320, 1270, 1232, 1165, 1146, 1049, 1025, 995, 955, 841, 821, 800, 774, 756, 705, 683, 669.

HRMS (EI) for **$C_{16}H_{14}Br_2N_2O_2$** (423.9422): 423.9427.

Synthesis of (5-benzoyl-3,6-dibromopyridazin-4-yl)(furan-2-yl)methanone (8d)



According to **TP 1**, the metalation of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**7a**; 342 mg, 1 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol) and pivaloyl chloride (145 mg, 1.2 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 4:1) to give **8d** (271 mg, 62%) as an off white solid.

m.p.: 173.3 – 174.1 °C

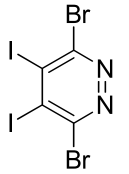
^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.16 (dd, *J*=1.7, 0.8 Hz, 1 H), 7.88 (dt, *J*=6.9, 1.5 Hz, 2 H), 7.76 – 7.71 (m, 2 H), 7.56 – 7.52 (m, 2 H), 6.79 (dd, *J*=3.80, 1.66 Hz, 1 H).

^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 189.3, 175.0, 151.6, 149.4, 144.0, 143.6, 139.2, 137.6, 135.8, 135.8, 133.5, 130.2, 129.3, 114.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1671, 1646, 1595, 1561, 1505, 1449, 1396, 1385, 1330, 1318, 1304, 1238, 1142, 1082, 1047, 1037, 1019, 1000, 983, 903, 883, 822, 805, 784, 772, 726, 705, 682, 668.

HRMS (ESI) for **$C_{16}H_9Br_2N_2O_3^+$** (434.8902): 434.8974.

Synthesis of 3,6-dibromo-4,5-diiodopyridazine (8e)



According to **TP 1**, the metalation of 3,6-dibromo-4,5-diiodopyridazine (**7b**; 364 mg, 1 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -20 °C, then a solution of iodine (381 mg, 1.5 mmol) dissolved in THF (3 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 19:1) to give **8e** (361 mg, 74%) as a yellowish solid.

m.p.: 143.3 – 145.7 °C

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: .

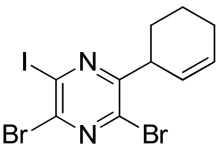
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 152.0, 127.1.

MS (70 eV, EI) *m/z* (%): 492 (49), 489 (100) [M^+], 487 (50), 336 (22), 334 (46), 332 (24), 255 (11), 253 (39), 209 (32), 207 (68), 205 (35), 176 (14), 128 (15), 126 (56), 57 (10), 42 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 2925, 2870, 1661, 1503, 1476, 1427, 1402, 1321, 1272, 1261, 1217, 1139, 1118, 1043, 984, 919, 890, 886, 859, 783, 723, 701, 654.

HRMS (EI) for **$C_4{}^{79}Br{}^{81}Br{}^{127}I_2N_2$** (489.6518): 489.6492.

Synthesis of 2,6-dibromo-3-(cyclohex-2-en-1-yl)-5-iodopyrazine (8f)



According to **TP 1**, the metalation of 3,5-dibromo-2-iodopyrazine (**7i**; 364 mg, 1 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -40 °C, then CuCN•2LiCl (1 M in THF, 0.05 mL, 0.05 mmol) and 3-bromocyclohexene (193 mg, 1.2 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$.. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 19:1) to give **8f** (312 mg, 70%) as a colorless solid.

m.p.: 64.4 – 65.8 °C

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.97 – 5.88 (m, 1 H), 5.67 – 5.60 (m, 1 H), 3.94 – 3.85 (m, 1 H), 2.16 – 2.03 (m, 3 H), 1.95 – 1.84 (m, 1 H), 1.80 – 1.65 (m, 2 H).

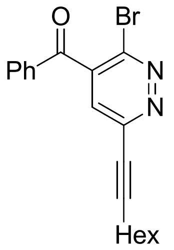
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 159.6, 143.6, 138.0, 129.6, 125.9, 119.9, 40.7, 27.8, 24.5, 21.2.

MS (70 eV, EI) *m/z* (%): 443 (7) [M^+], 377 (7), 177 (10), 70 (13), 67 (13), 61 (18), 57 (14), 45 (16), 43 (100), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3018, 2947, 2886, 2829, 1449, 1428, 1352, 1336, 1312, 1287, 1252, 1240, 1195, 1174, 1138, 1127, 1079, 1051, 1040, 988, 930, 896, 859, 804, 723.

HRMS (EI) for **$C_{10}H_9Br_2IN_2$** (441.8177): 441.8171.

Synthesis of 3-bromo-6-(oct-1-yn-1-yl)pyridazin-4-yl)(phenyl)methanone (9a)



According to **TP 2** (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**7a**; 342 mg, 1.00 mmol, in 1 mL THF) was reacted with 1-octyne (0.18 mL, 1.20 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 4 mol%), CuI (19 mg, 10 mol%) and NEt_3 (0.55 ml, 4 mmol). After 3 h at 50 °C, the reaction mixture was quenched with sat. aq Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 9:1) to give **9a** (298 mg, 80%) as a yellowish solid.

m.p.: 44.4 – 45.8 °C

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 8.06 (s, 1 H), 7.87 – 7.83 (m, 2 H), 7.77 (tt, *J*=7.5, 1.2 Hz, 1 H), 7.61 – 7.56 (m, 2 H), 2.54 (t, *J*=6.9 Hz, 2 H), 1.63 – 1.53 (m, 2 H), 1.47 – 1.37 (m, 2 H), 1.32 – 1.25 (m, 4 H), 0.89 – 0.83 (m, 3 H).

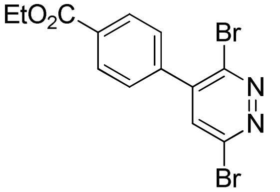
^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 190.6, 147.4, 141.3, 139.6, 135.2, 133.9, 130.1, 129.3, 129.2, 98.4, 76.8, 30.7, 27.9, 27.4, 21.9, 18.6, 13.9.

MS (70 eV, EI) *m/z* (%): 370 (6) [M^+], 314 (18), 312 (19), 301 (13), 299 (12), 291 (9), 104 (100), 77 (57).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3053, 2931, 2857, 2229, 1667, 1595, 1579, 1450, 1378, 1338, 1247, 1183, 1157, 1078, 999, 908, 858, 793, 757, 711, 701, 684, 669.

HRMS (EI) for **$C_{19}H_{19}BrN_2O$** (370.0681): 370.0681.

Synthesis of ethyl 4-(3,6-dibromopyridazin-4-yl)benzoate (9b)



According to **TP 2** 3,6-dibromo-4-iodopyridazine (**7b**; 364 mg, 1.00 mmol, in 1 mL THF) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide[6] (0.80 mmol), $Pd(dba)_2$ (28 mg, 2 mol%) and $P(2\text{-furyl})_3$ (23 mg, 4 mol%). After 3 h at 25 °C, the reaction mixture was quenched with sat. aq Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 4:1) to give **9b** (173 mg, 56%) as a colorless solid.

m.p.: 135.7 – 136.8 °C

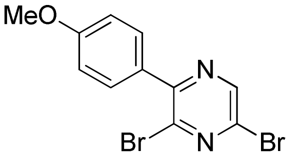
^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.18 (s, 1 H), 8.08 (dt, *J*=8.5, 1.8, 2 H), 7.72 (dt, *J*=8.5, 1.8 Hz, 2 H), 4.35 (q, *J*=7.1 Hz, 2 H), 1.33 (t, *J*=7.12 Hz, 3 H).

^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 165.1, 148.2, 147.7, 143.6, 139.0, 133.2, 130.9, 129.6, 129.1, 61.1, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2987, 1706, 1609, 1551, 1472, 1447, 1409, 1344, 1321, 1275, 1234, 1184, 1127, 1113, 1104, 1039, 1026, 1016, 1012, 903, 863, 823, 775, 748, 713, 703.

HRMS (ESI) for **$C_{13}H_{11}Br_2N_2O_2^+$** (384.9109): 384.9181.

Synthesis of 3,5-dibromo-2-(4-methoxyphenyl)pyrazine (9c)



According to **TP 2** 3,5-dibromo-2-iodopyrazine (**7i**; 364 mg, 1.00 mmol, in 1 mL THF) was reacted with 4-methoxyphenylzinc iodide[6] (0.80 mmol), Pd(dba)$_2$ (28 mg, 2 mol%) and P(2-furyl)$_3$ (23 mg, 4 mol%). After 3 h at 25 °C, the reaction mixture was quenched with sat. aq Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 4:1) to give **9c** (136 mg, 49%) as a colorless solid.

m.p.: 173.3 – 174.1 °C

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.63 (s, 1 H), 7.74 (dt, *J*=9.4, 2.8 Hz, 2 H), 7.00 (dt, *J*=9.4, 2.8 Hz, 2 H), 3.87 (s, 3 H).

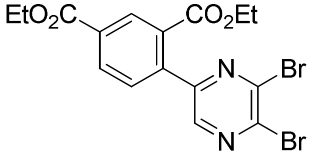
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.9, 153.3, 144.7, 137.6, 135.3, 131.0, 128.2, 113.7, 55.4.

MS (70 eV, EI) *m/z* (%): 345 (30), 343 (72), 341 (30) [M^+], 264 (38), 177 (14), 161 (12), 133 (19), 83 (10), 71 (14), 70 (14), 69 (10), 61 (18), 57 (23), 55 (12), 45 (12), 43 (100), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1671, 1646, 1595, 1561, 1505, 1449, 1396, 1385, 1330, 1318, 1304, 1238, 1142, 1082, 1047, 1037, 1019, 1000, 983, 903, 883, 822, 805, 784, 772, 726, 705, 682, 668.

HRMS (EI) for **$C_{11}H_8Br_2N_2O$** (341.9003): 341.8998.

Synthesis of diethyl 4-(5,6-dibromopyrazin-2-yl)isophthalate (9d)



According to **TP 2** 2,3-dibromo-5-iodopyrazine (**7l**; 364 mg, 1.00 mmol, in 1 mL THF) was reacted with 2,4-bis(ethoxycarbonyl)phenylzinc bromide[6] (0.80 mmol), Pd(dba)$_2$ (28 mg, 2 mol%) and P(2-furyl)$_3$ (23 mg, 4 mol%). After 6 h at 25 °C, the reaction mixture was quenched with sat. aq Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 2:1) to give **9d** (290 mg, 79%) as a colorless solid.

m.p.: 135.3 – 137.1 °C

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.88 (s, 1 H), 8.33 (dd, *J*=1.8, 0.4 Hz, 1 H), 8.25 (dt, *J*=8.1, 1.9 Hz, 1 H), 7.92 (dd, *J*=8.1, 0.5 Hz, 1 H), 4.38 (q, *J*=7.0 Hz, 2 H), 4.18 (q, *J*=7.0 Hz, 2 H), 1.35 (t, *J*=7.1 Hz, 3 H), 1.09 (t, *J*=7.1 Hz, 3 H).

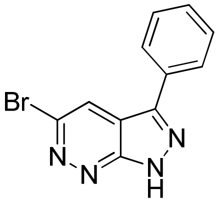
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 166.7, 164.9, 151.6, 142.8, 141.6, 141.2, 138.7, 132.5, 132.3, 131.7, 131.4, 130.6, 61.9, 61.9, 14.5, 14.2.

MS (70 eV, EI) *m/z* (%): 455 (2) [M$^+$], 430 (7), 428 (12), 426 (7), 412 (10), 70 (12), 61 (16), 45 (15), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2903, 1709, 1569, 1537, 1483, 1445, 1391, 1302, 1277, 1261, 1232, 1167, 1147, 1123, 1109, 1092, 1044, 1032, 1016, 926, 853, 827, 791, 771, 754, 726, 702, 670.

HRMS (EI) for **$C_{16}H_{14}Br_2N_2O_4$** (455.9320): 455.9305.

Synthesis of 5-bromo-3-phenyl-1H-pyrazolo[3,4-c]pyridazine (10a)



A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**7a**; 342 mg, 1.00 mmol) in EtOH (10 mL). $N_2H_4 \cdot H_2O$ (0.3 mL, 3 mmol) was added in one portion and the resulting mixture was refluxed for 30 min. After cooling to 25 °C CH_2Cl_2 (100 mL) was added and the organic layer was washed with brine (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH giving **10a** as a yellow solid (205 mg, 75%).

m.p.: 258.3 – 259.4 °C

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.84 (d, *J*=0.8 Hz, 1 H), 8.08 (d, *J*=8.0 Hz, 2 H), 7.53 (t, *J*=7.6 Hz, 2 H), 7.45 (td, *J*=7.3, 1.2 Hz, 1 H).

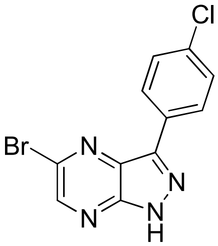
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 155.4, 142.3, 137.9, 131.2, 129.1, 129.0, 126.6, 123.7, 116.1.

MS (70 eV, EI) *m/z* (%): 275 (98), 273 (100) [M$^+$], 140 (45), 104 (10), 77 (14), 64 (15), 43 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3091, 2994, 2919, 1583, 1509, 1456, 1432, 1388, 1287, 1253, 1187, 1139, 1064, 1002, 926, 909, 880, 830, 796, 756, 742, 688, 666.

HRMS (EI) for **$C_{11}H_7BrN_4$** (273.9854): 273.9722.

Synthesis of 5-bromo-3-(4-chlorophenyl)-1H-pyrazolo[3,4-b]pyrazine (10b)



A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension of (4-chlorophenyl)(3,6-dibromopyrazin-2-yl)methanone (**7e**; 376 mg, 1.00 mmol) in EtOH (10 mL). $N_2H_4 \cdot H_2O$ (0.3 mL, 3 mmol) was added in one portion and the resulting mixture was refluxed for 30 min. After cooling to 25 °C CH_2Cl_2 (100 mL) was added and the organic layer was washed with brine (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH giving **10b** as a yellow solid (260 mg, 84%).

m.p.: 246.3 – 248.5 °C

^{1}H-NMR (DMSO-d$_6$, 300 MHz) δ: 8.76 (s, 1 H), 8.30 (dt, *J*=8.9, 2.5 Hz, 2 H), 7.60 (dt, *J*=8.9, 2.6 Hz, 2 H).

^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 145.6, 144.6, 140.2, 135.0, 133.8, 131.2, 130.6, 129.5, 128.0.

MS (70 eV, EI) *m/z* (%): 311 (5), 309 (23), 307 (15) [M$^+$], 58 (33), 43 (100), 42 (8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3177, 3138, 3015, 1812, 1583, 1570, 1513, 1463, 1440, 1365, 1333, 1302, 1287, 1210, 1185, 1111, 1085, 1016, 996, 936, 907, 837, 829, 790, 775, 756, 699, 664.

HRMS (EI) for **$C_{11}H_6BrClN_4$** (307.9464): 307.9458.

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[2] Socha, A. M.; Tan, N. Y.; Sello, J. K.; Laplante, K. L. *Bioorg. Med. Chem.* **2010**, *18*, 7193.

[3] Kolodiazhnyi, O. I.; Golovatyi, O. R. *Phosphorus, Sulfur and Silicon Relat. Elem.* **1995**, *102*, 133.

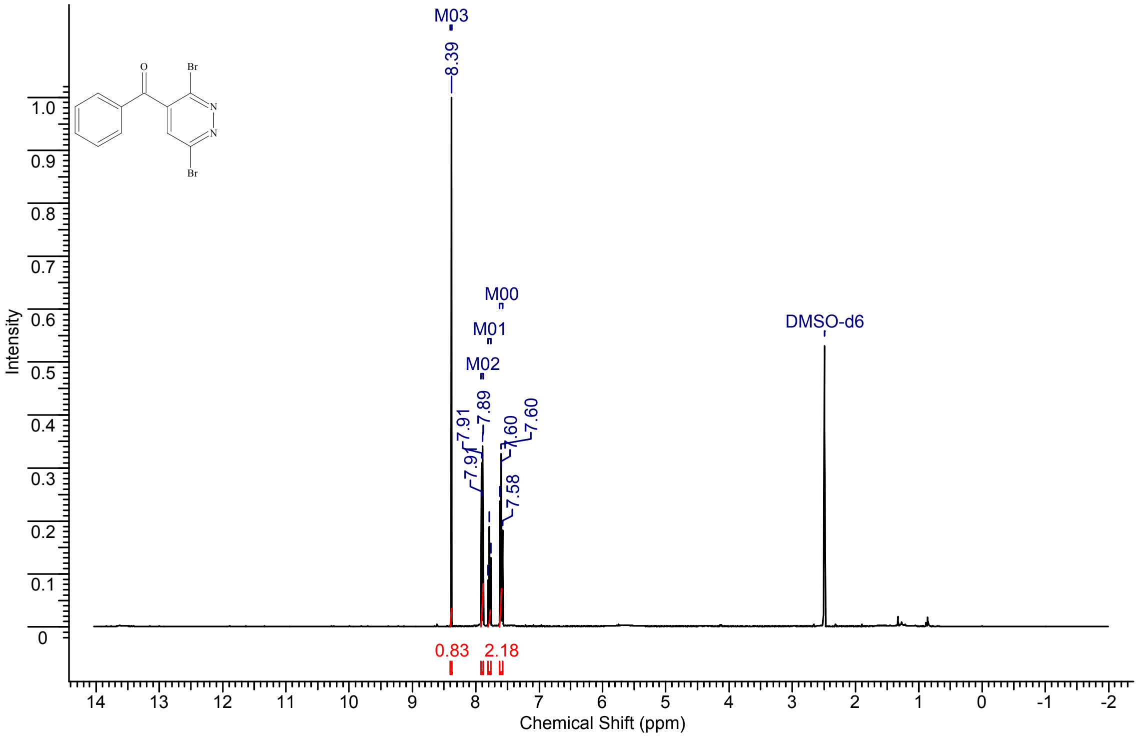
[4] prepared according to: Smith, K.; Butters, M.; Nay, B. *Tetrahedron Lett.* **1988**, *29*, 1319.

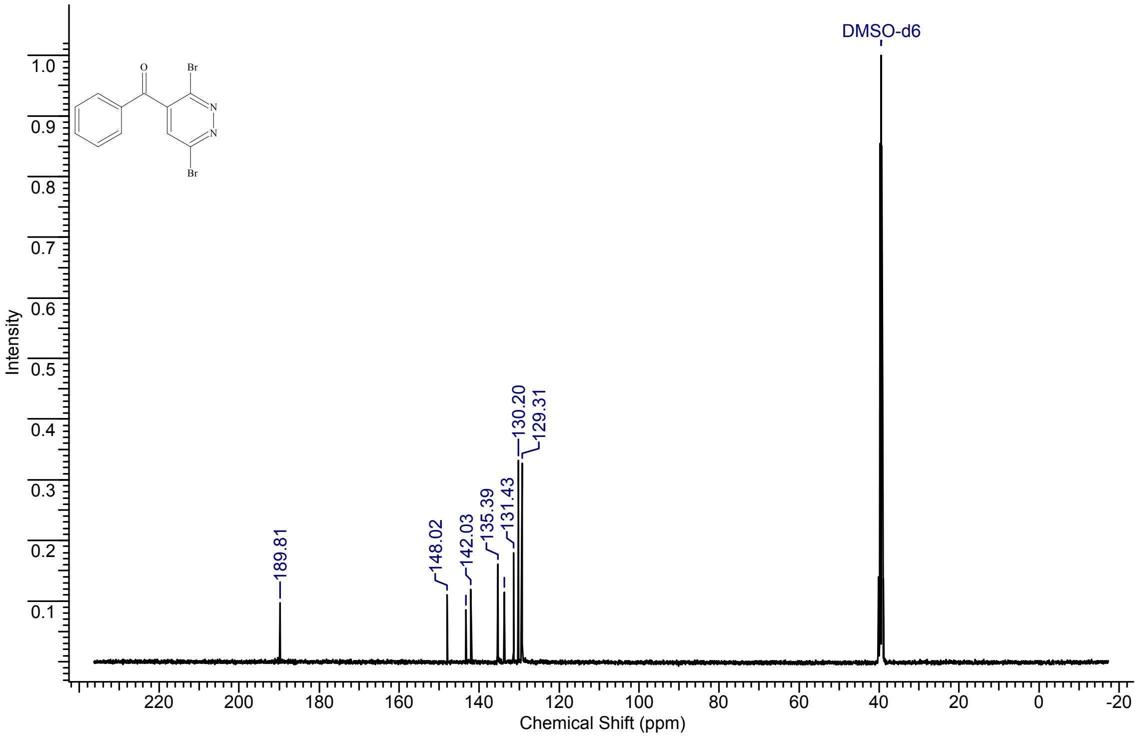
[5] Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841

[6] Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem.* **2006**, *118*, 6186; *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

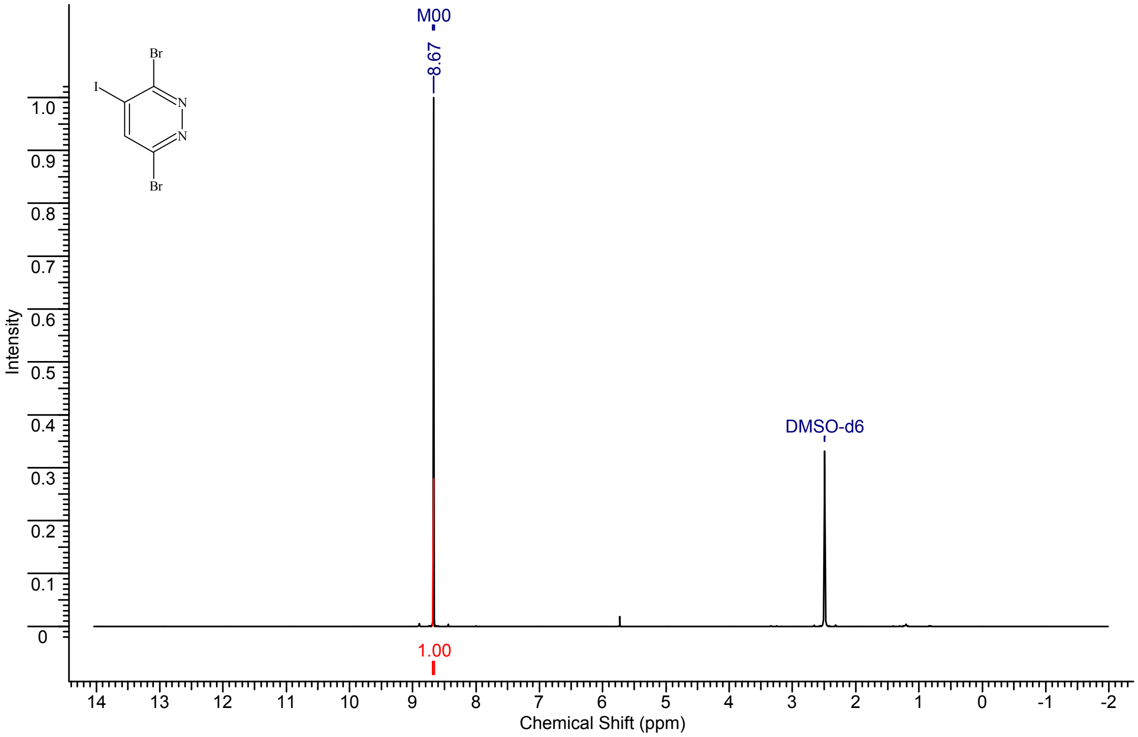
NMR Spectras:

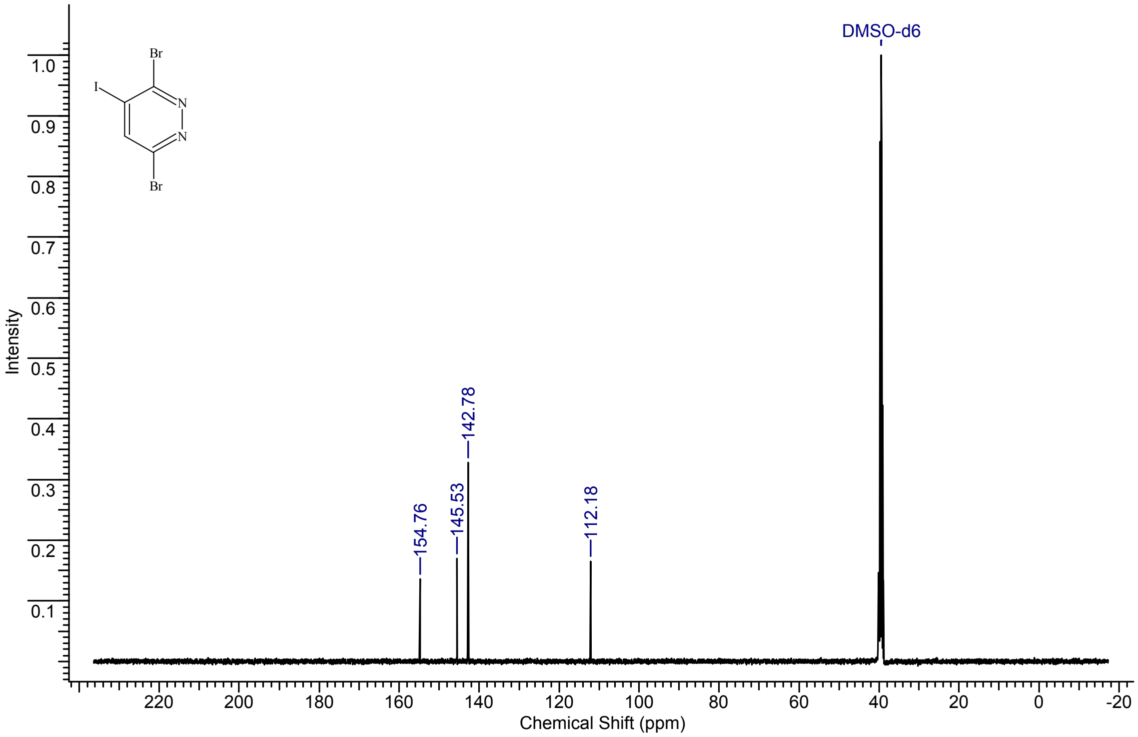
(3,6-dibromopyridazin-4-yl)(phenyl)methanone (7a)



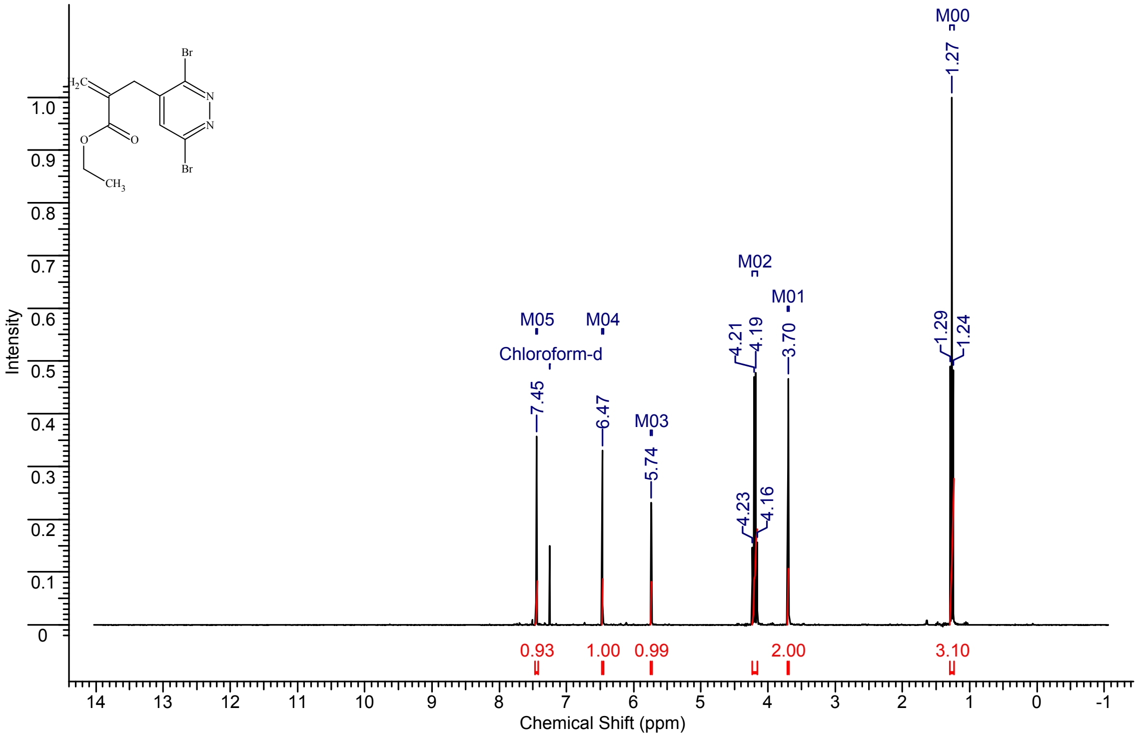


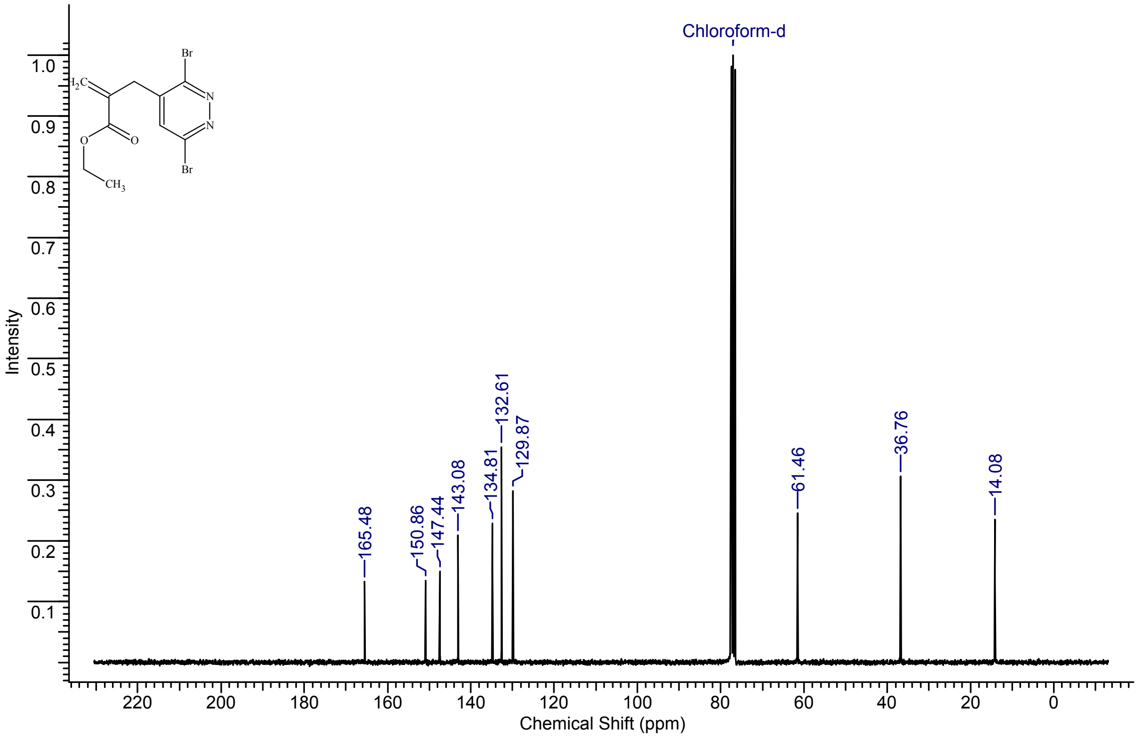
3,6-dibromo-4-iodopyridazine (7b)



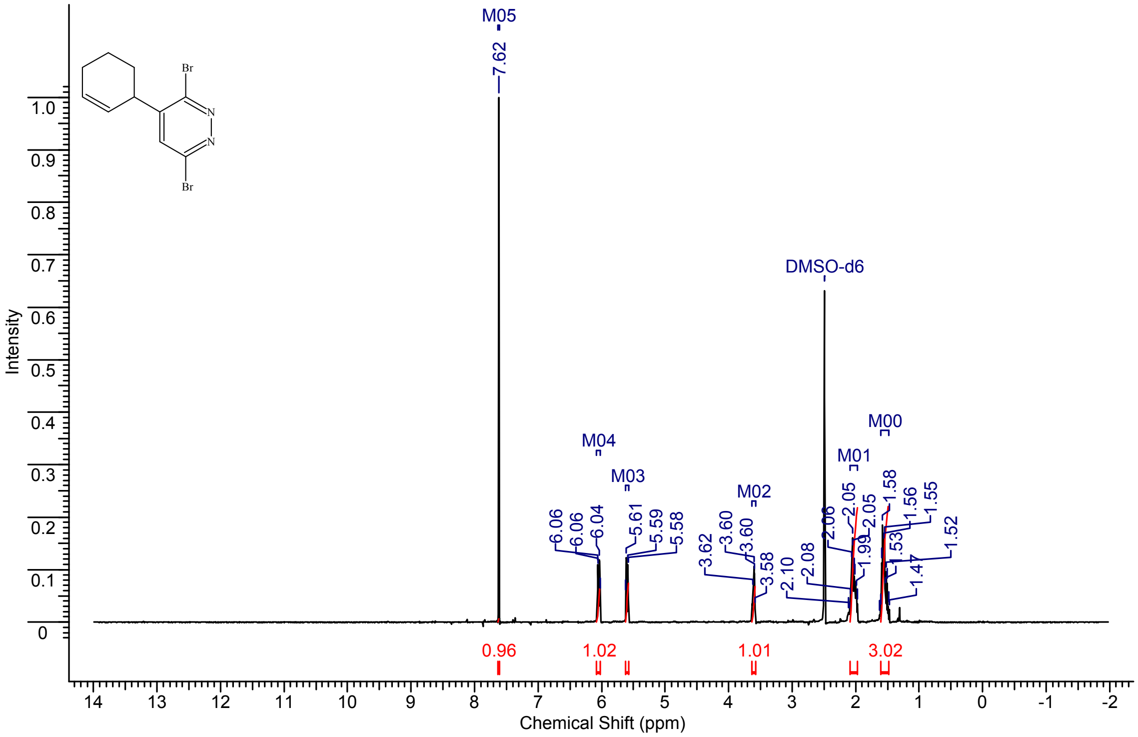


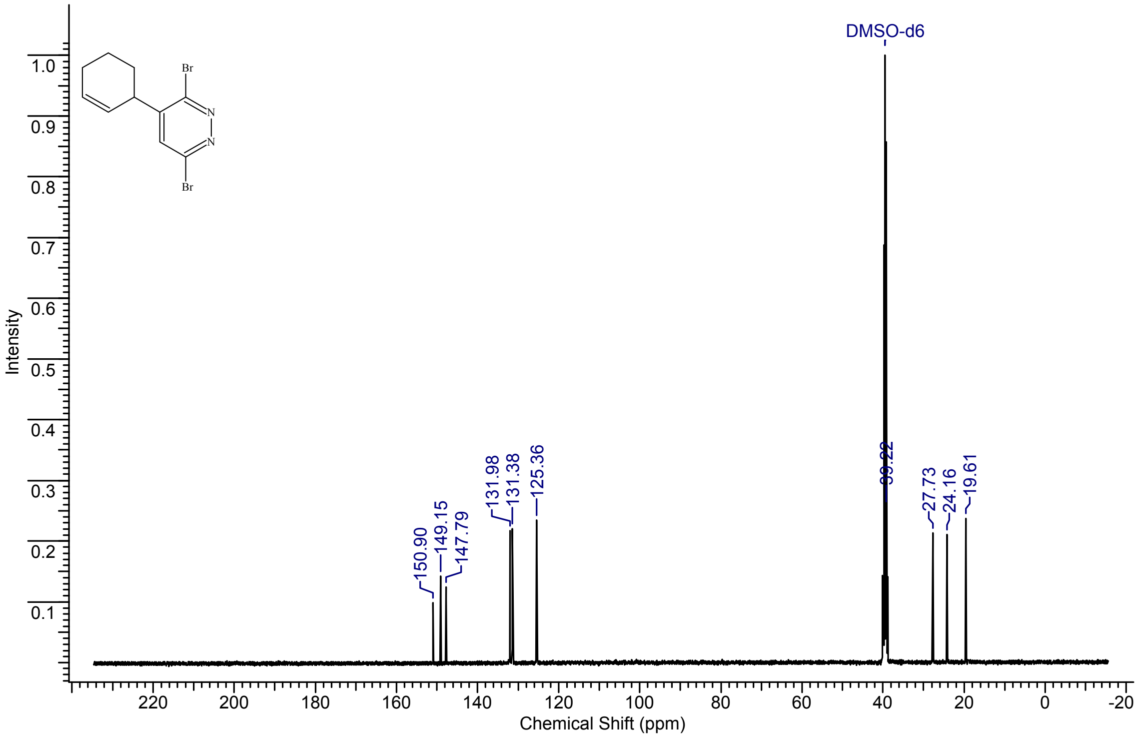
ethyl 2-((3,6-dibromopyridazin-4-yl)methyl)acrylate (7c)



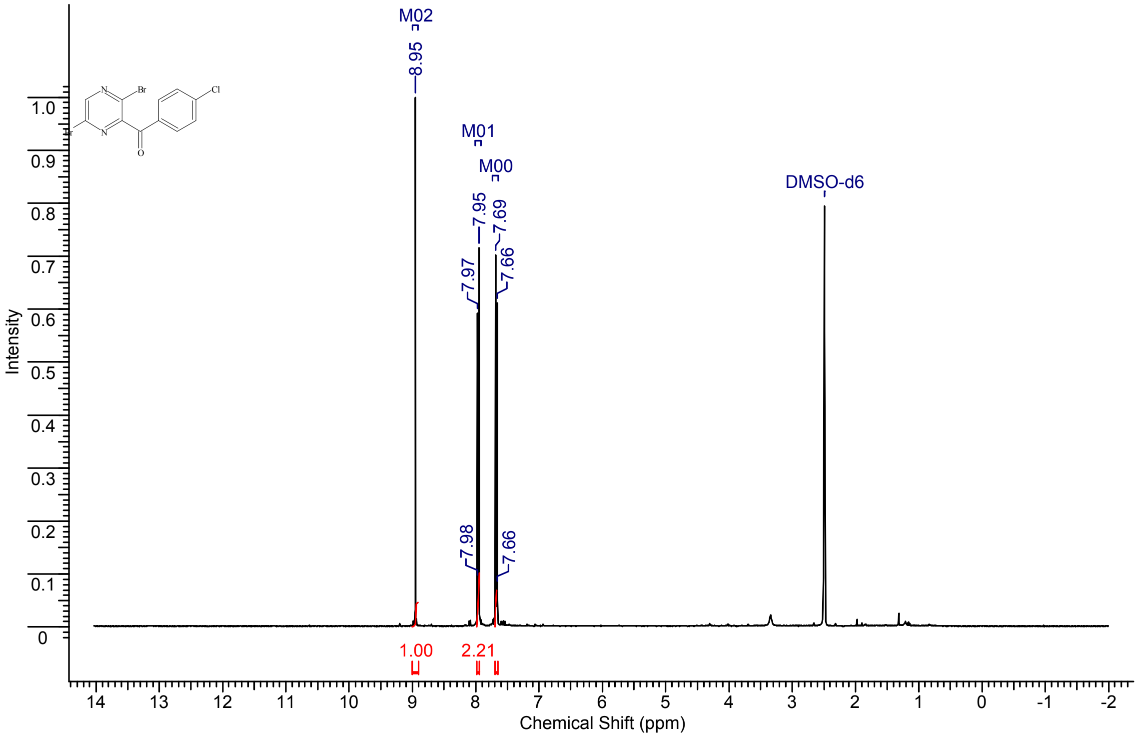


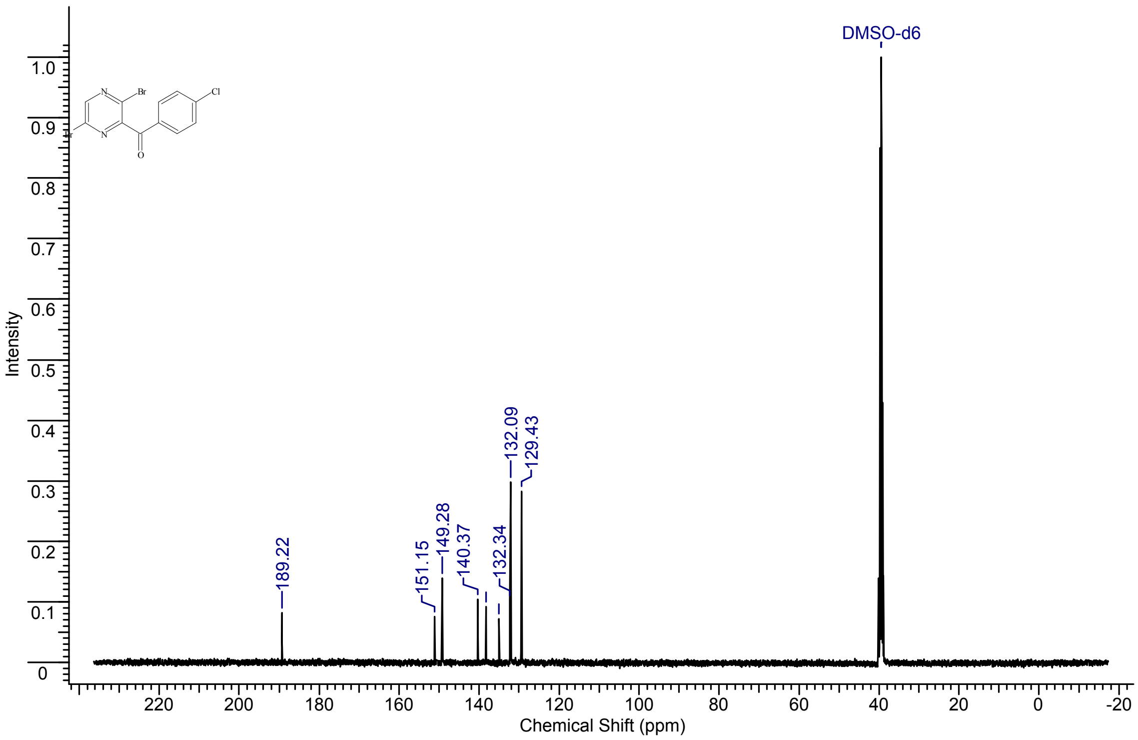
3,6-dibromo-4-(cyclohex-2-en-1-yl)pyridazine (7d)



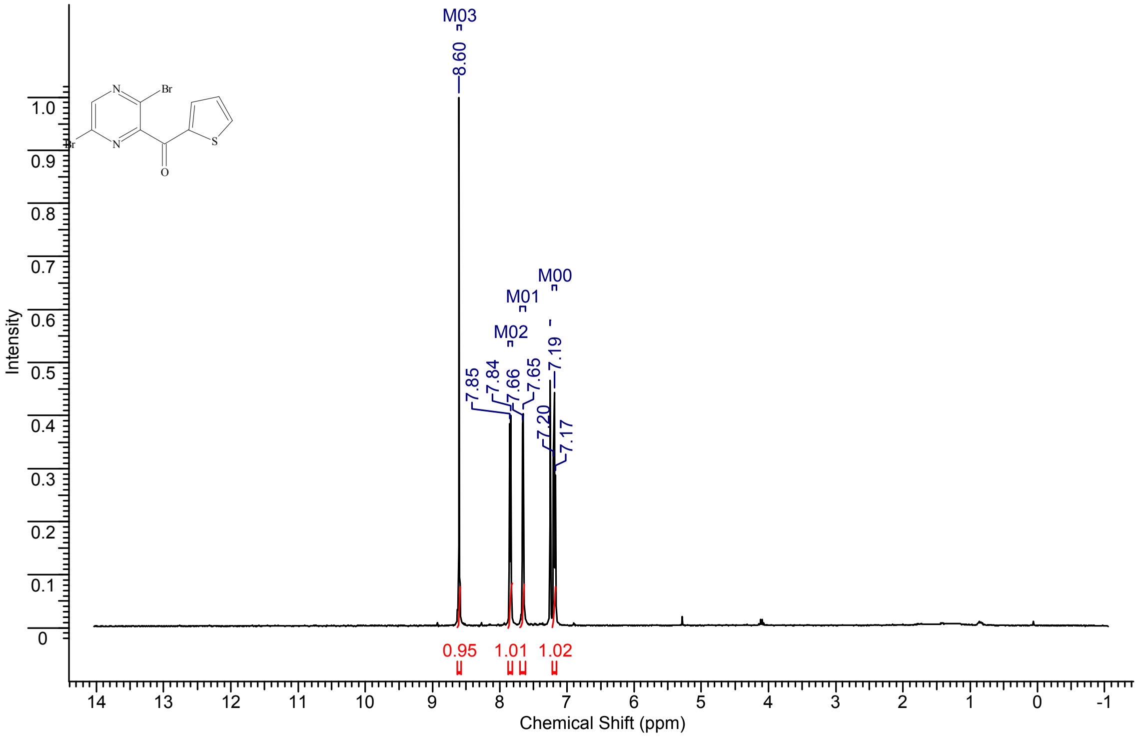


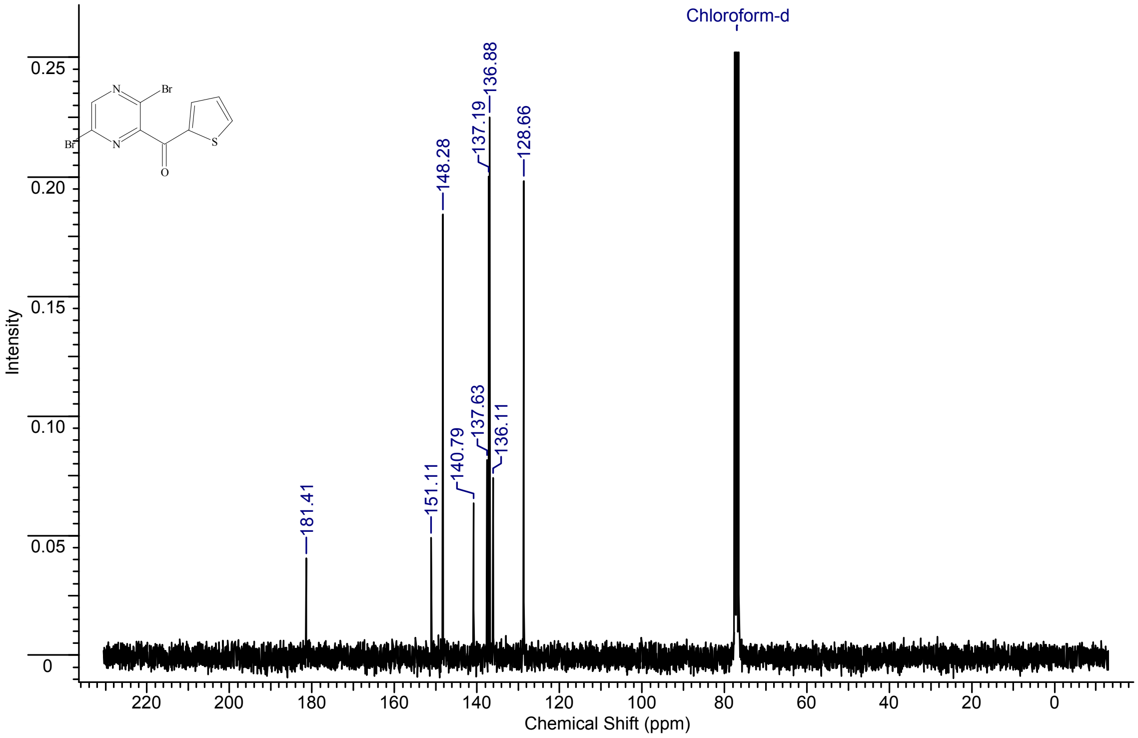
(4-chlorophenyl)(3,6-dibromopyrazin-2-yl)methanone (7e)



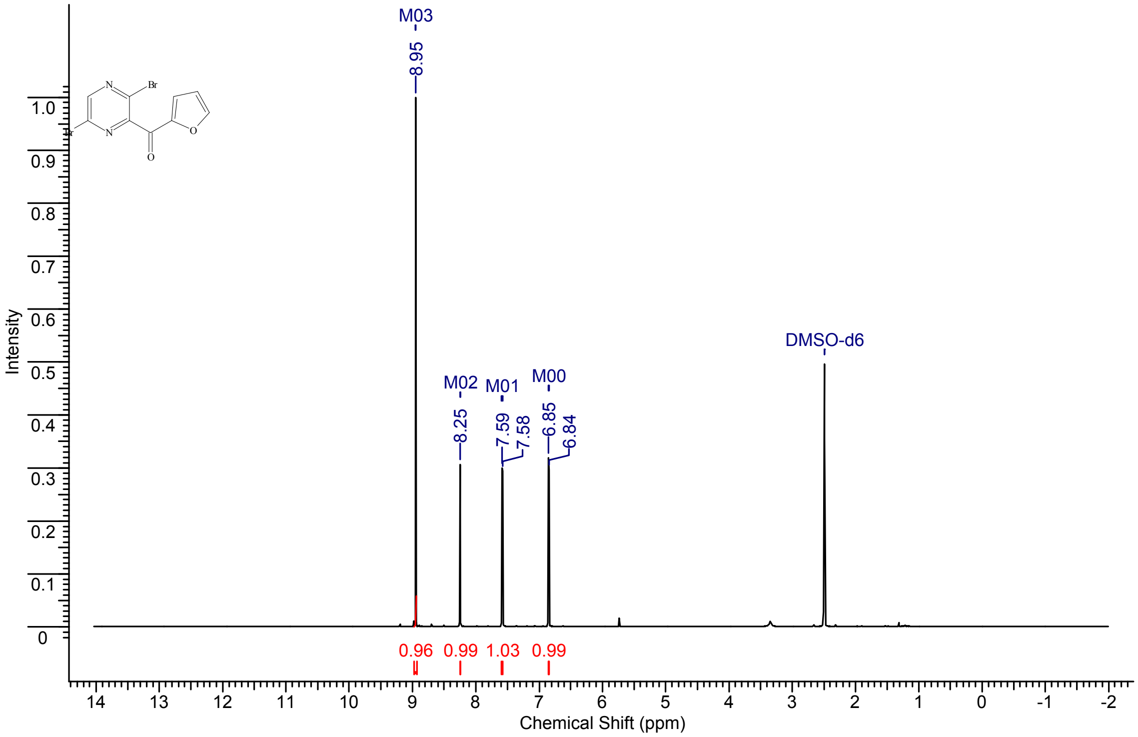


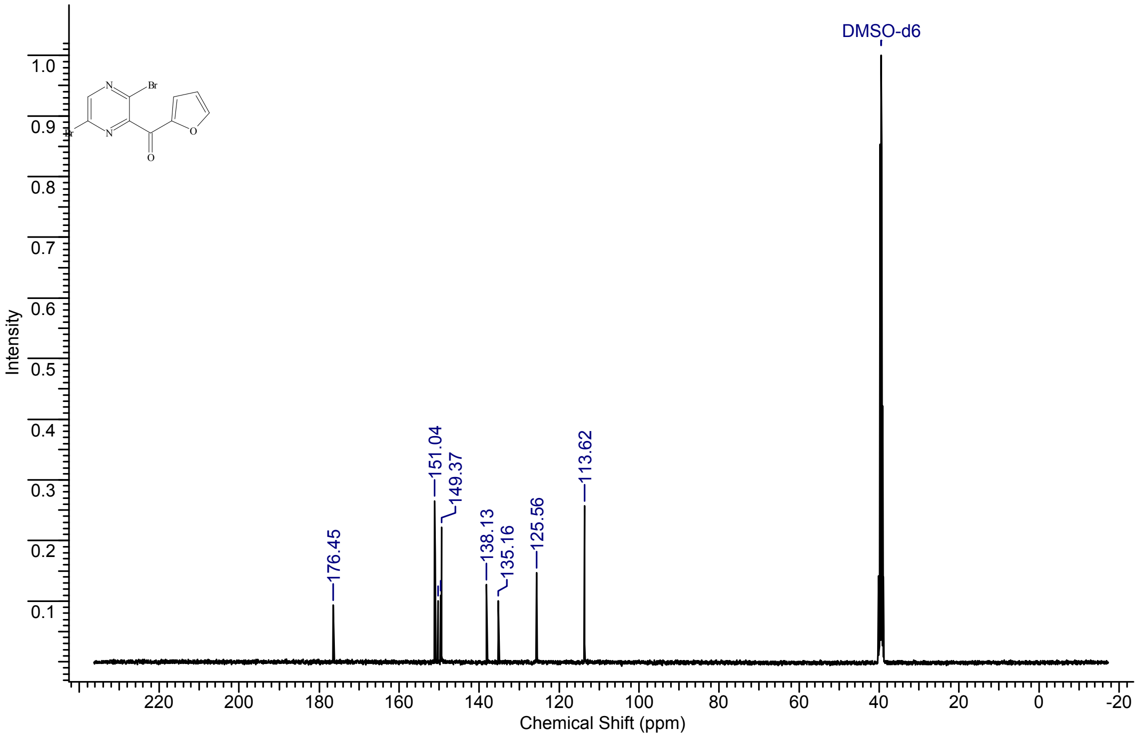
(3,6-dibromopyrazin-2-yl)(thiophen-2-yl)methanone (7f)



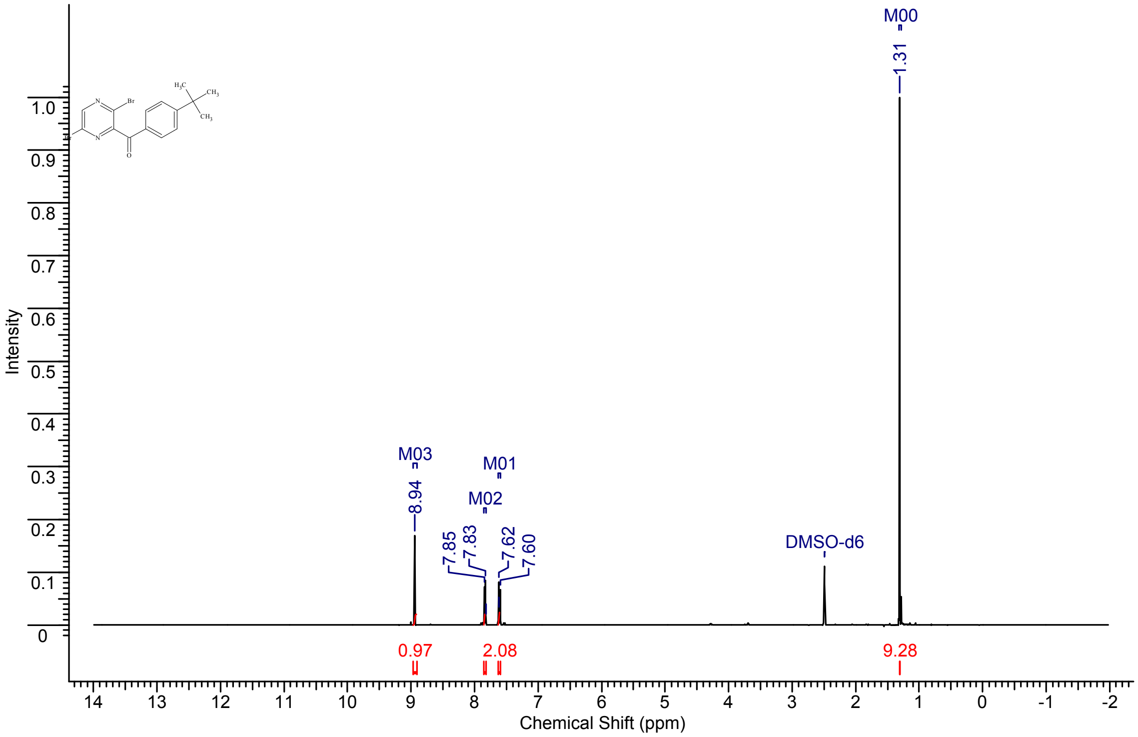


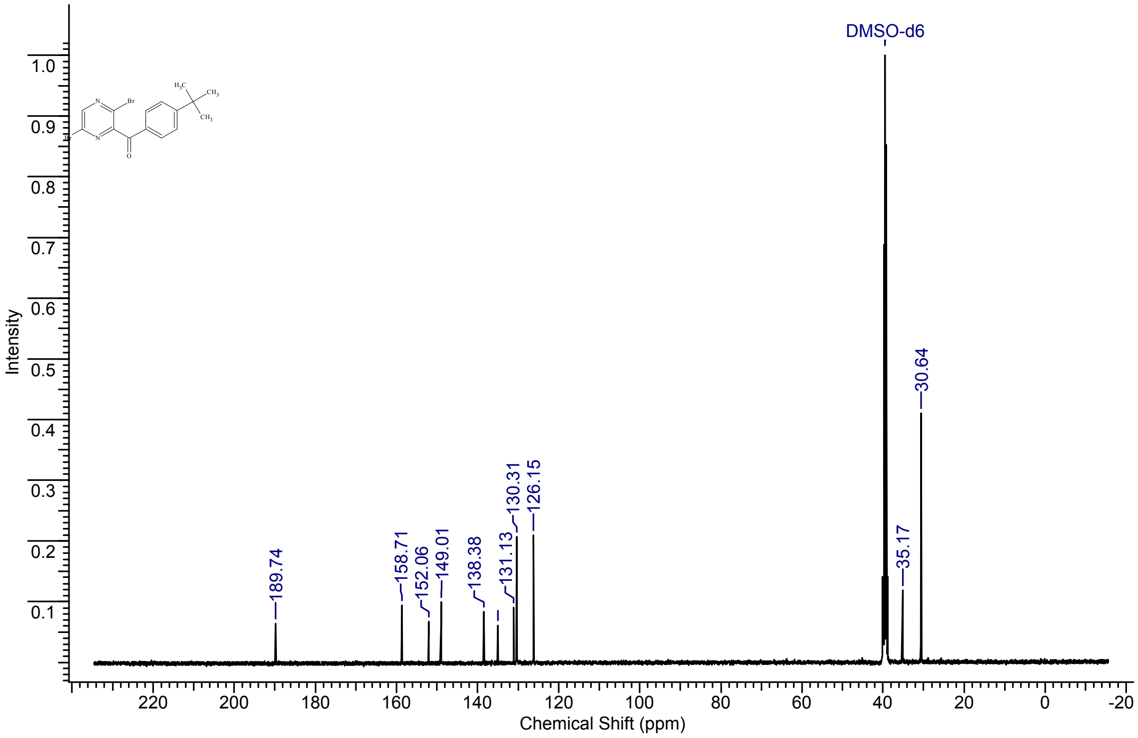
(3,6-dibromopyrazin-2-yl)(furan-2-yl)methanone (7g)



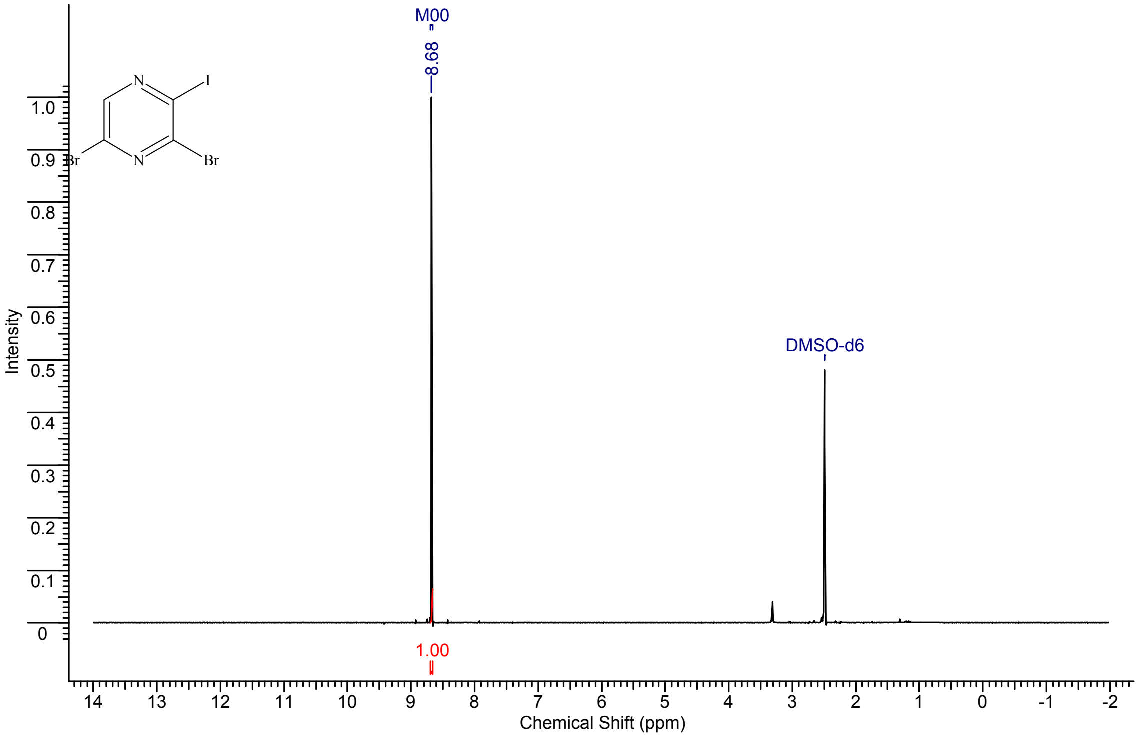


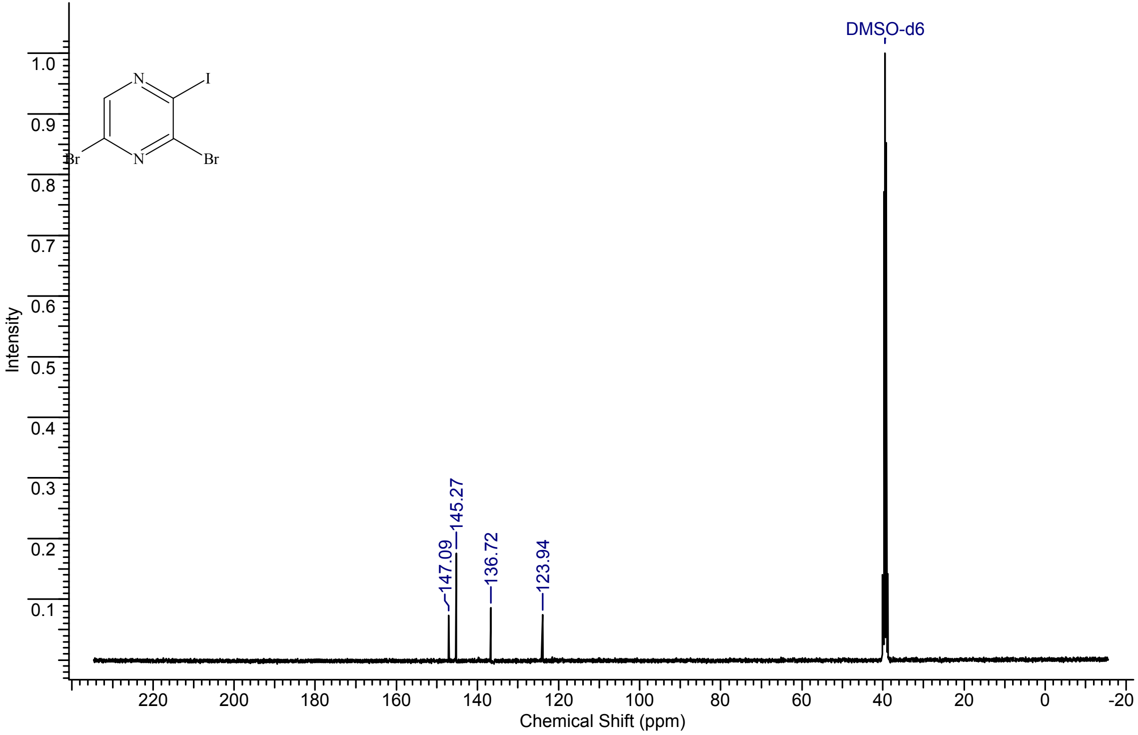
(4-(tert-butyl)phenyl)(3,6-dibromopyrazin-2-yl)methanone (7h)



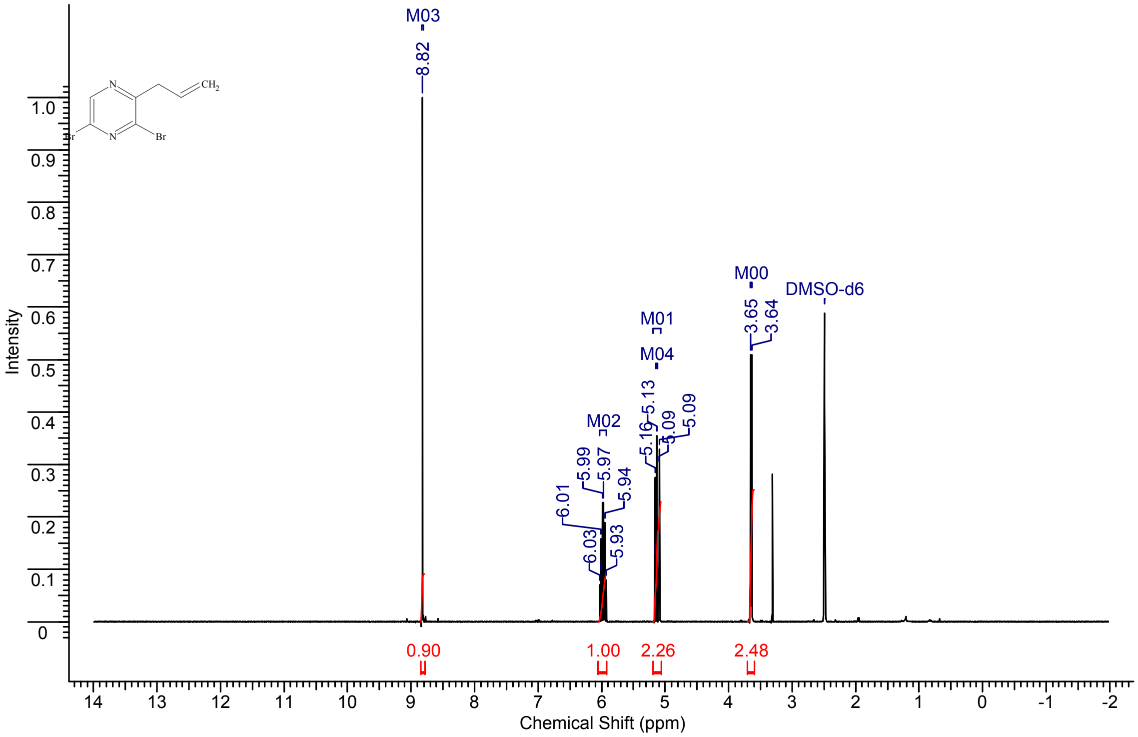


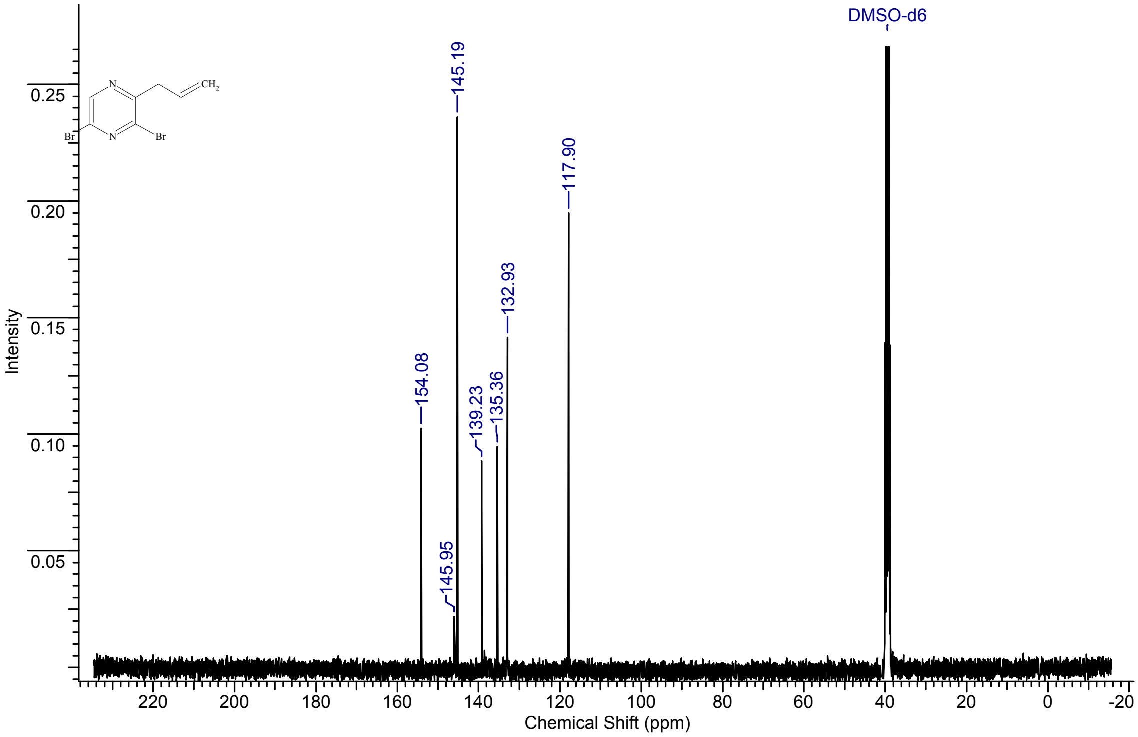
3,5-dibromo-2-iodopyrazine (7i)



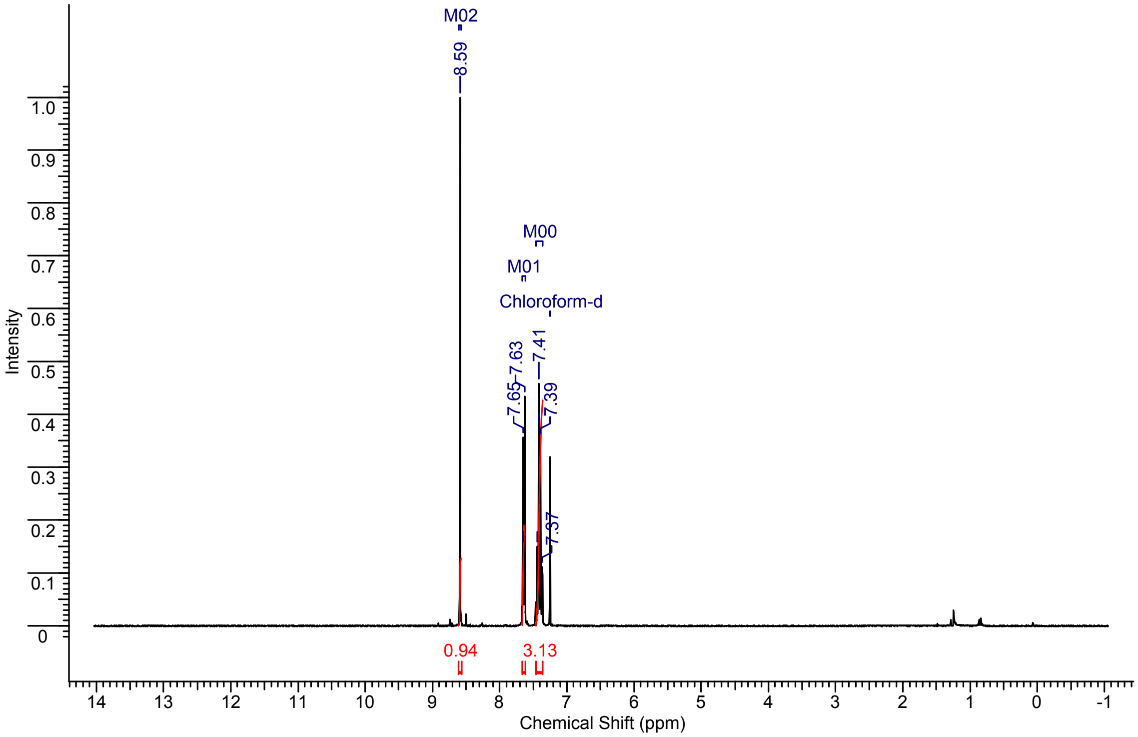


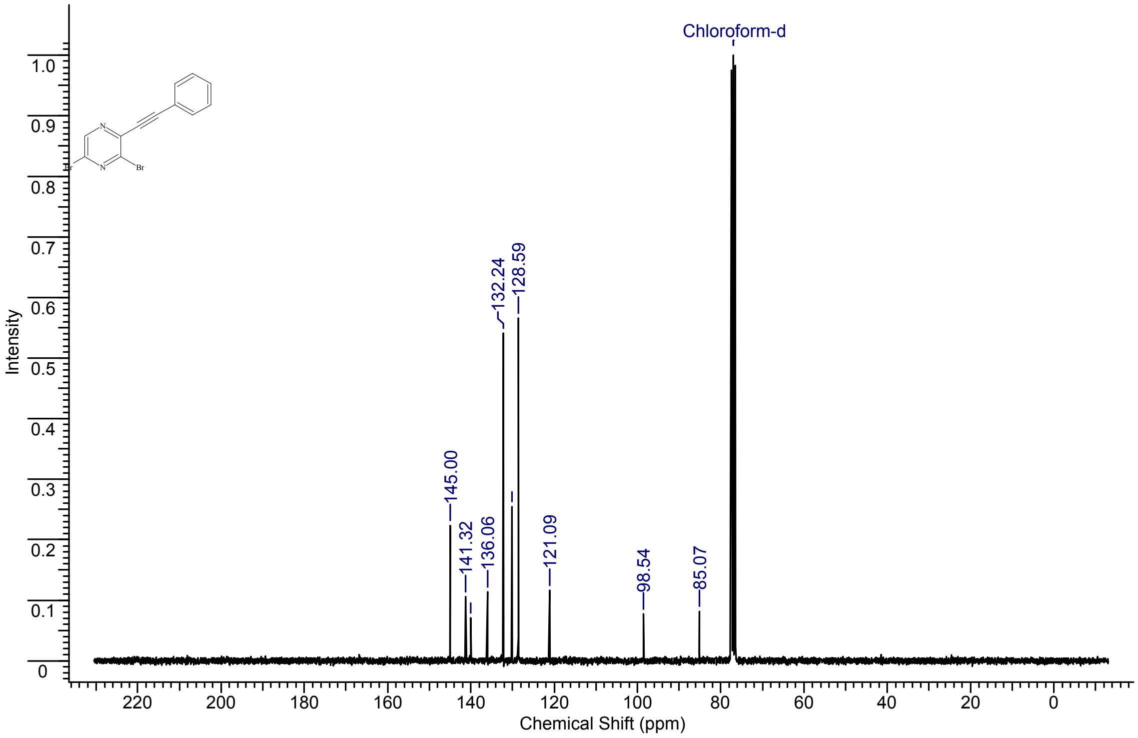
2-allyl-3,5-dibromopyrazine (7j)



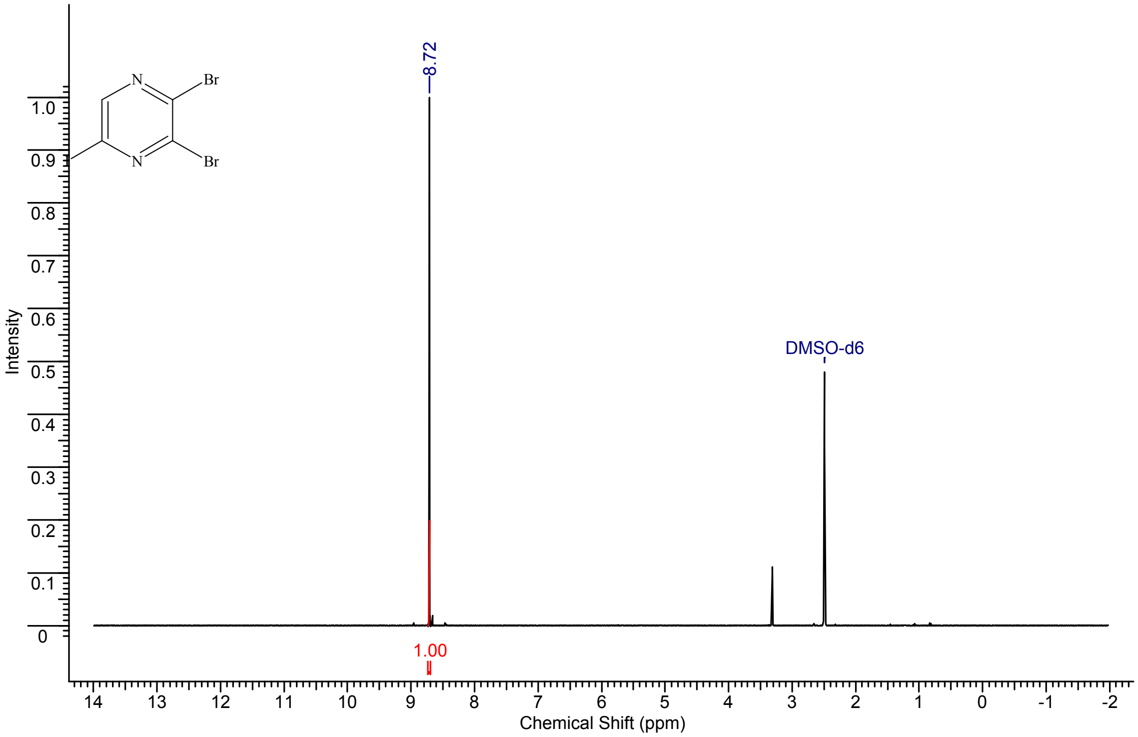


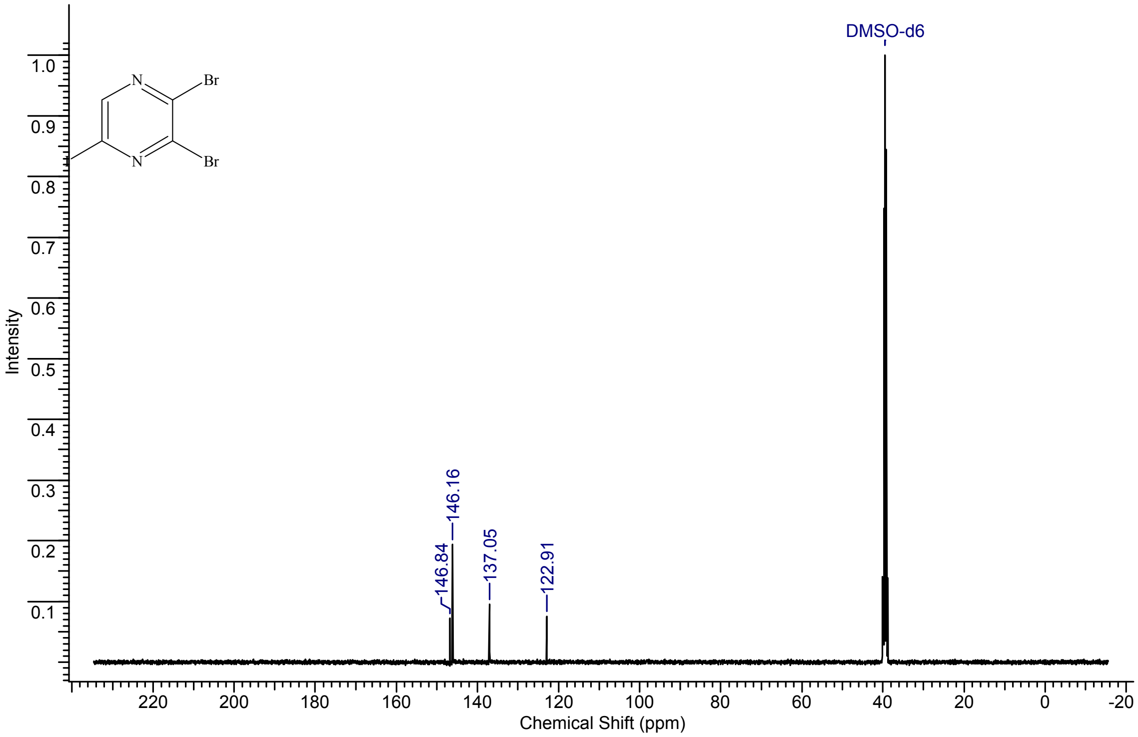
3,5-dibromo-2-(phenylethynyl)pyrazine (7k)



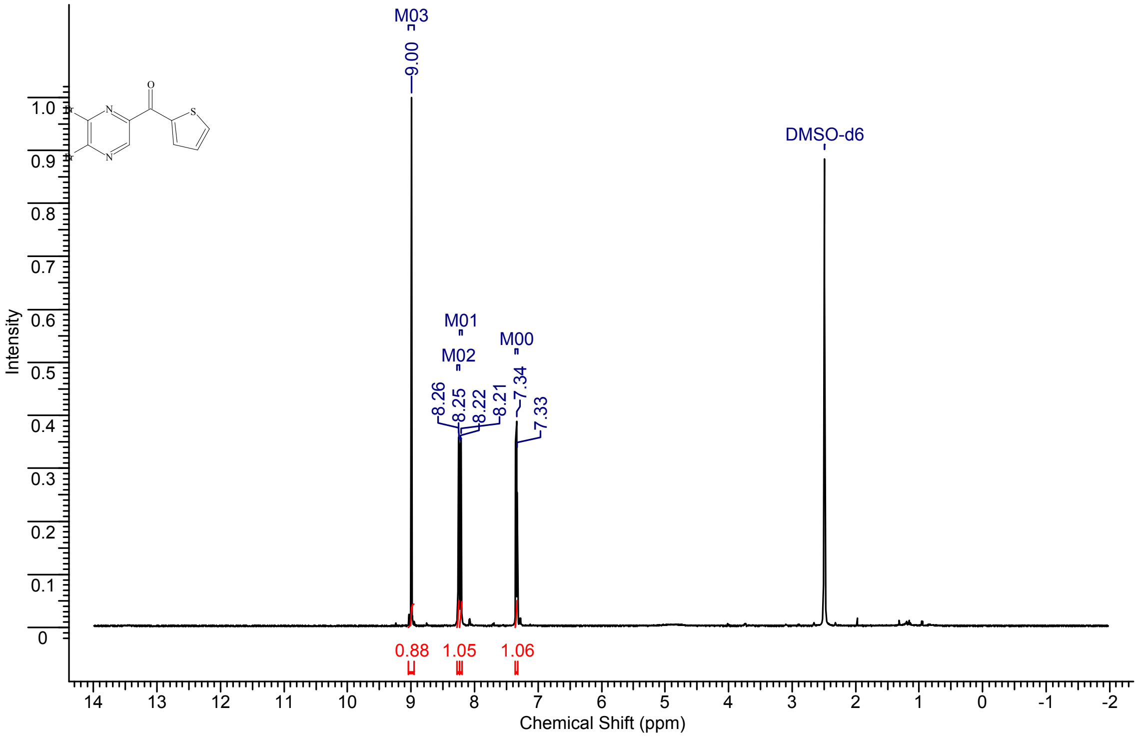


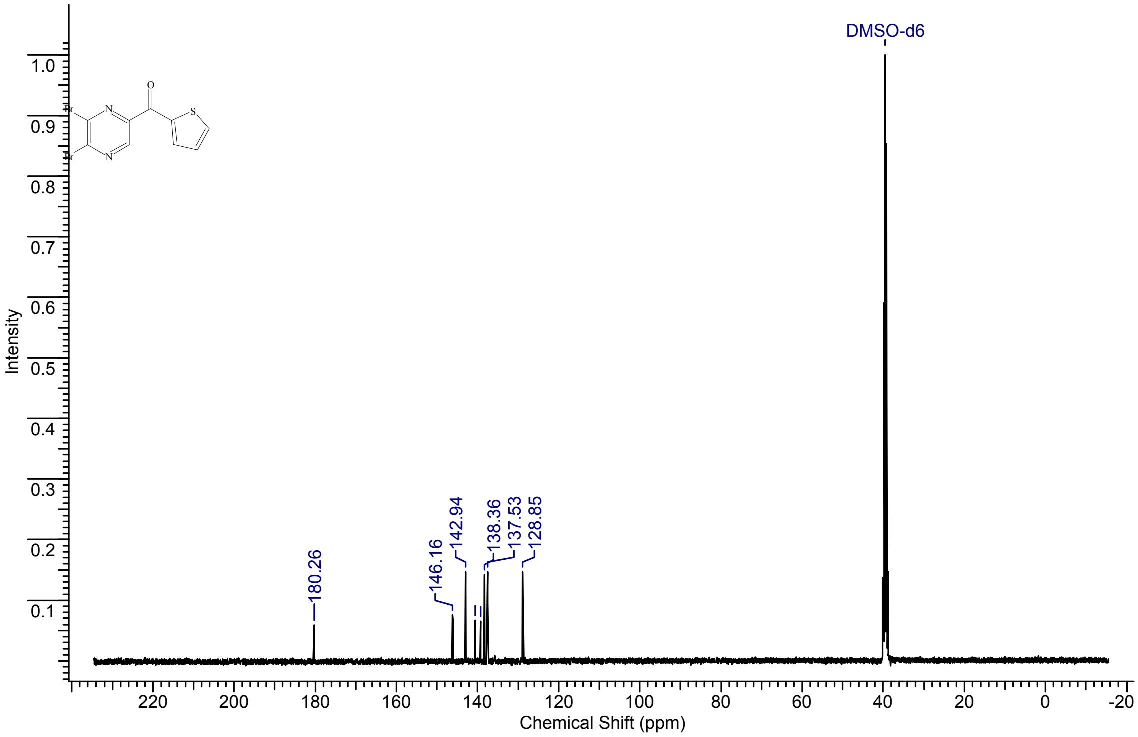
2,3-dibromo-5-iodopyrazine (7l)



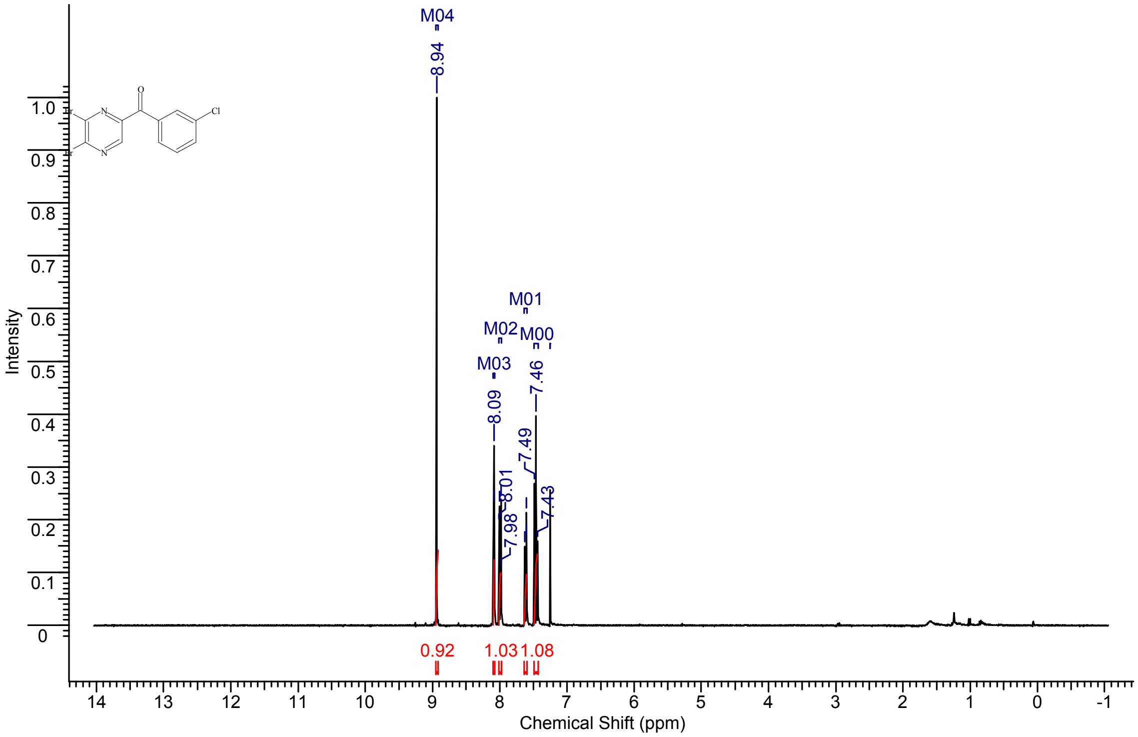


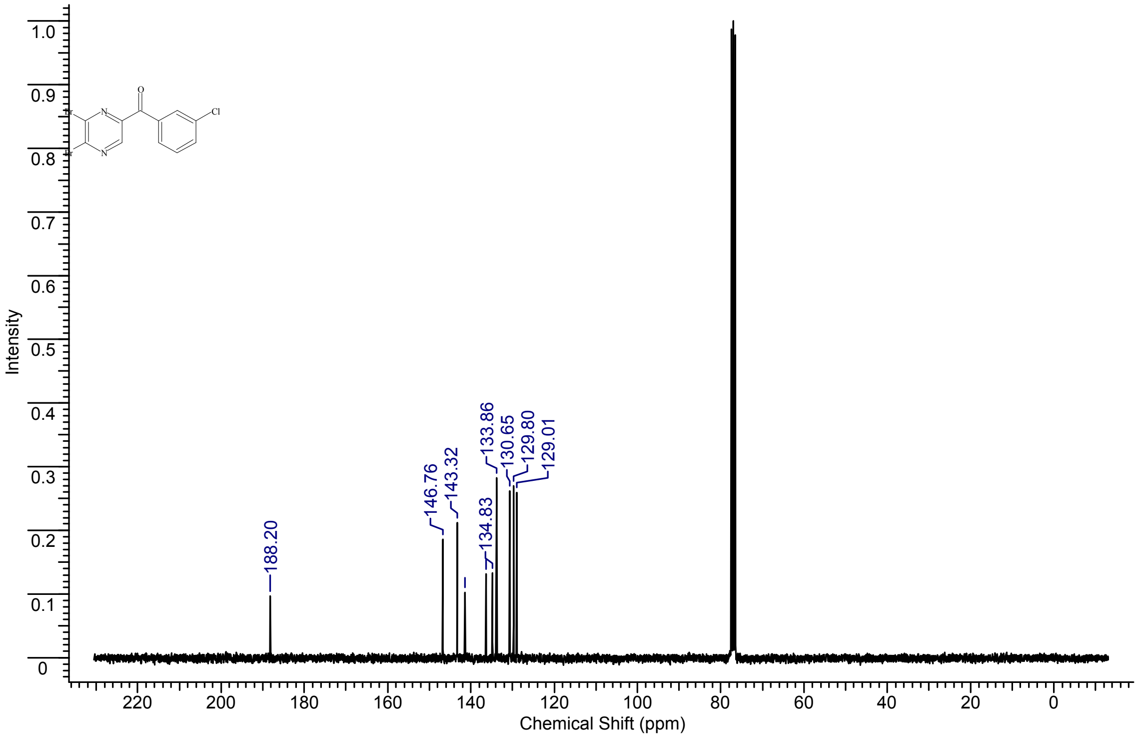
(5,6-dibromopyrazin-2-yl)(thiophen-2-yl)methanone (7m)



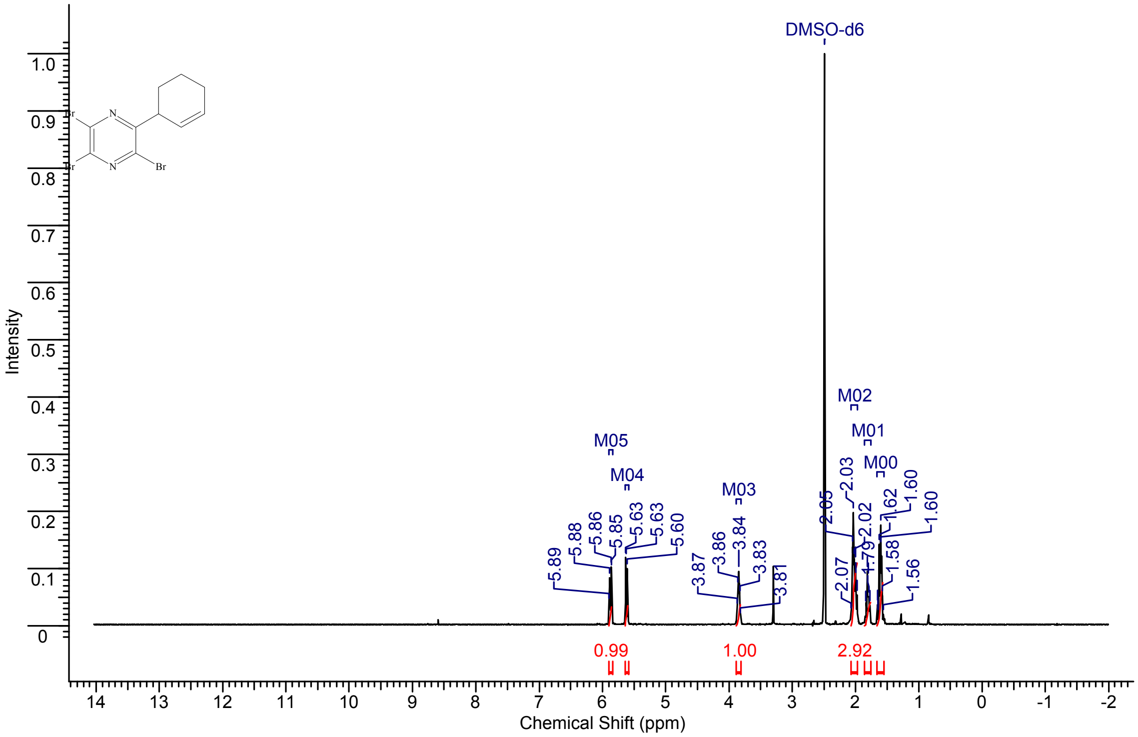


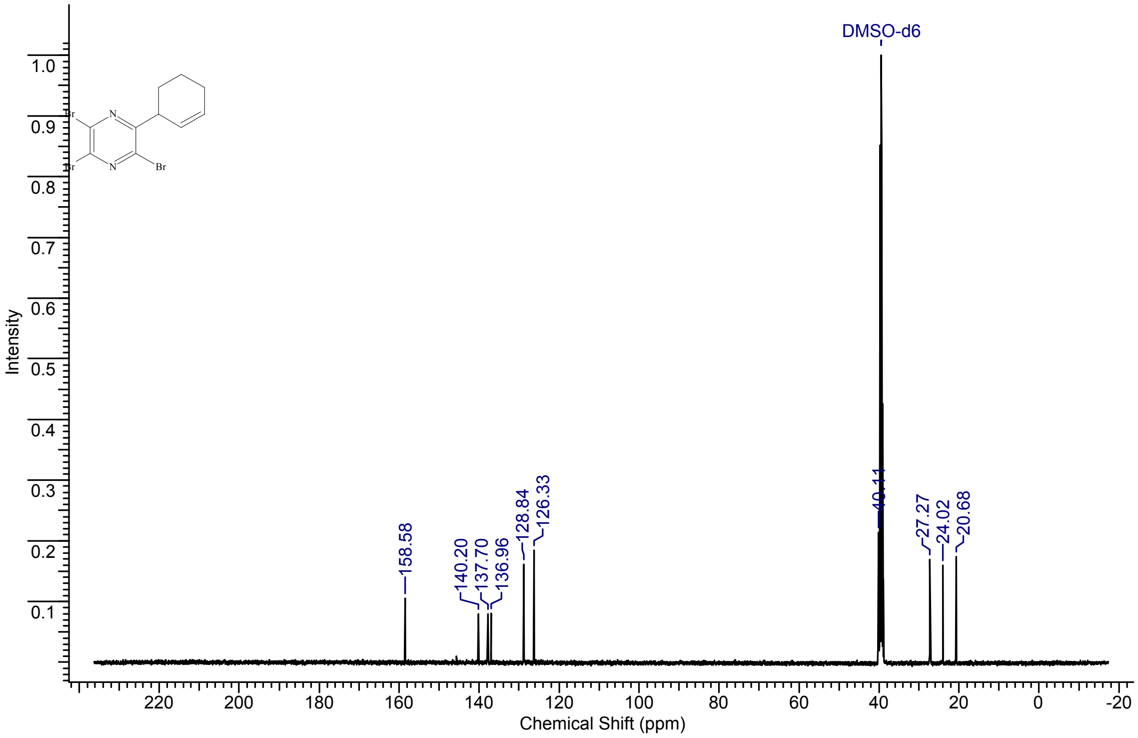
(3-chlorophenyl)(5,6-dibromopyrazin-2-yl)methanone (7n)



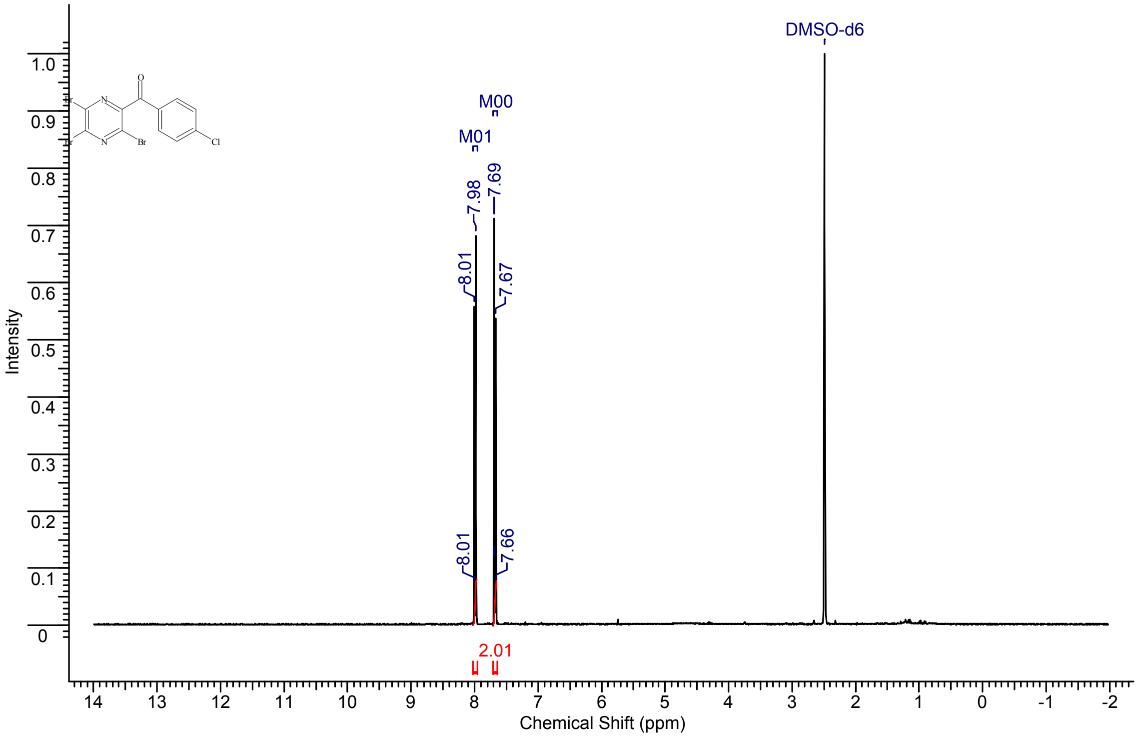


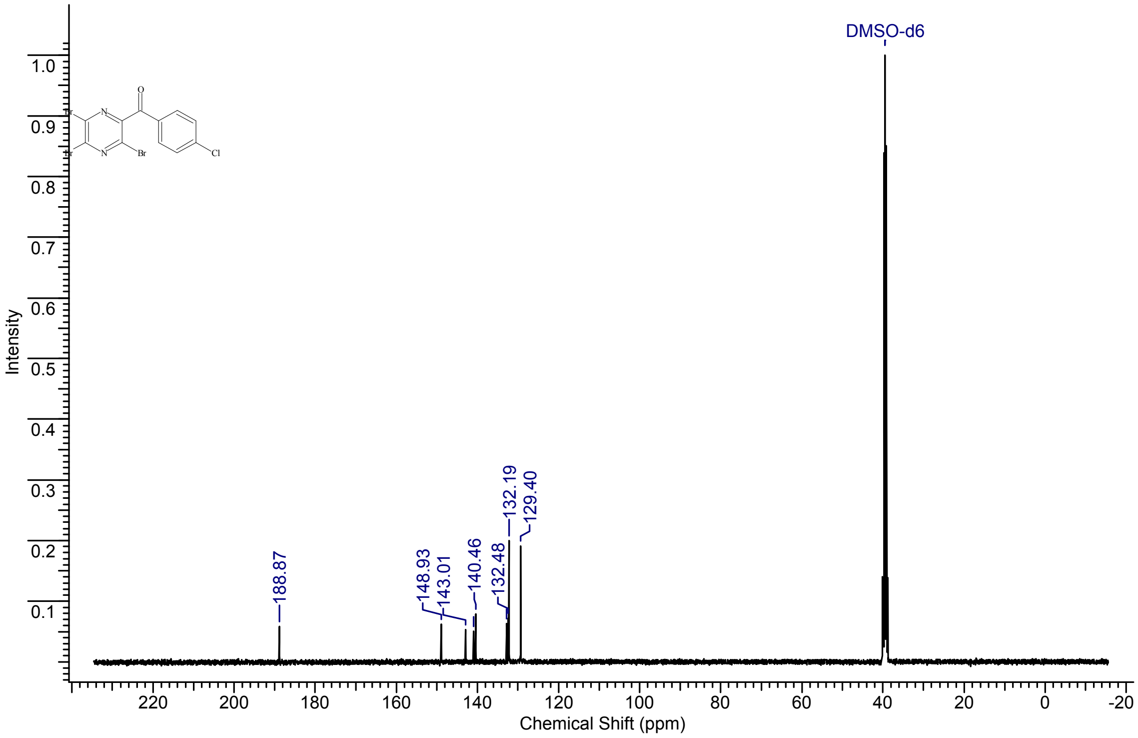
2,3,5-tribromo-6-(cyclohex-2-en-1-yl)pyrazine (7o)



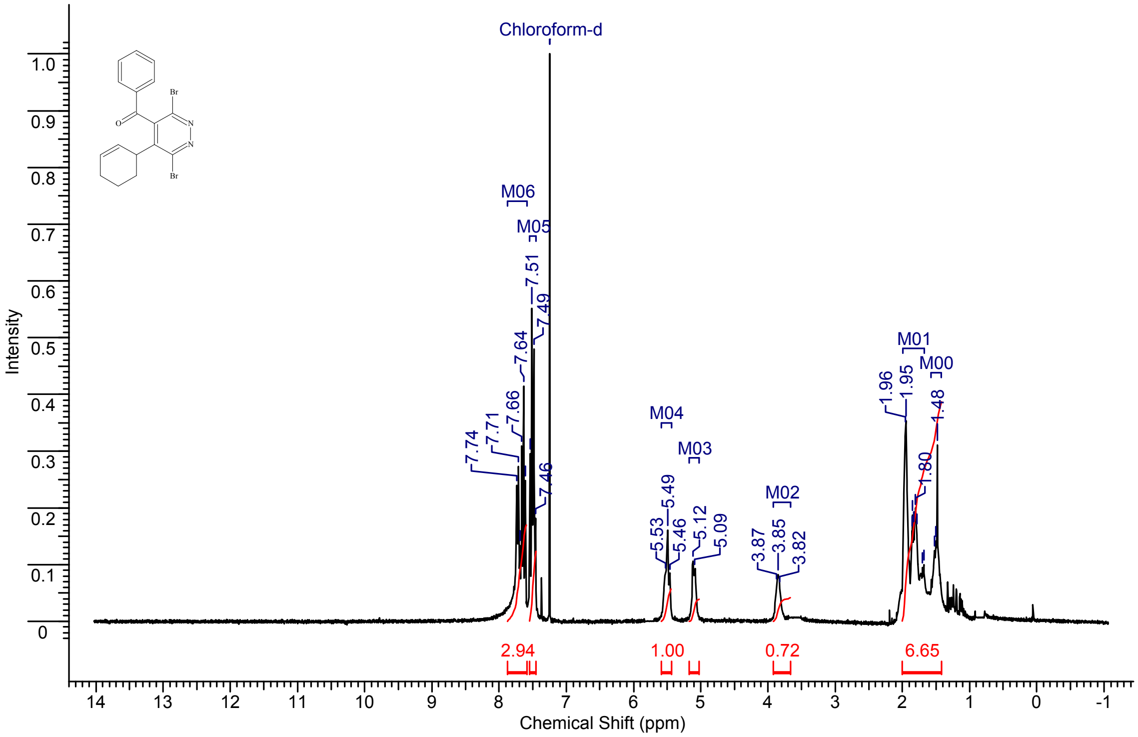


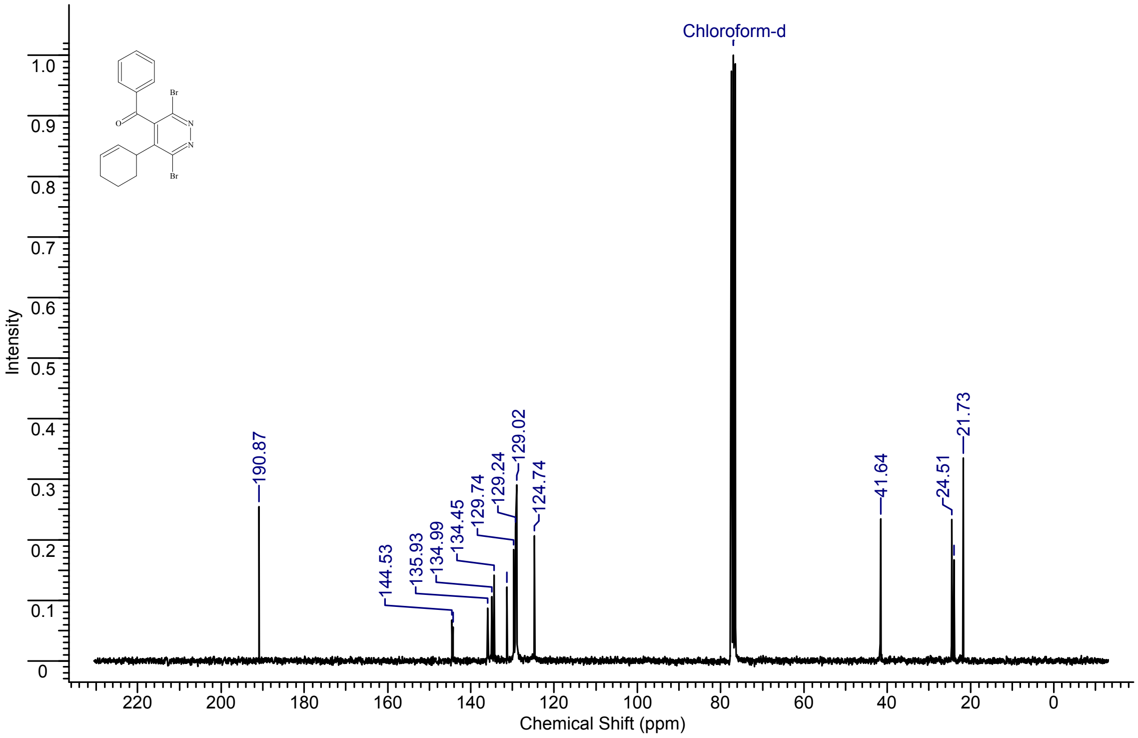
(4-chlorophenyl)(3,5,6-tribromopyrazin-2-yl)methanone (7p)



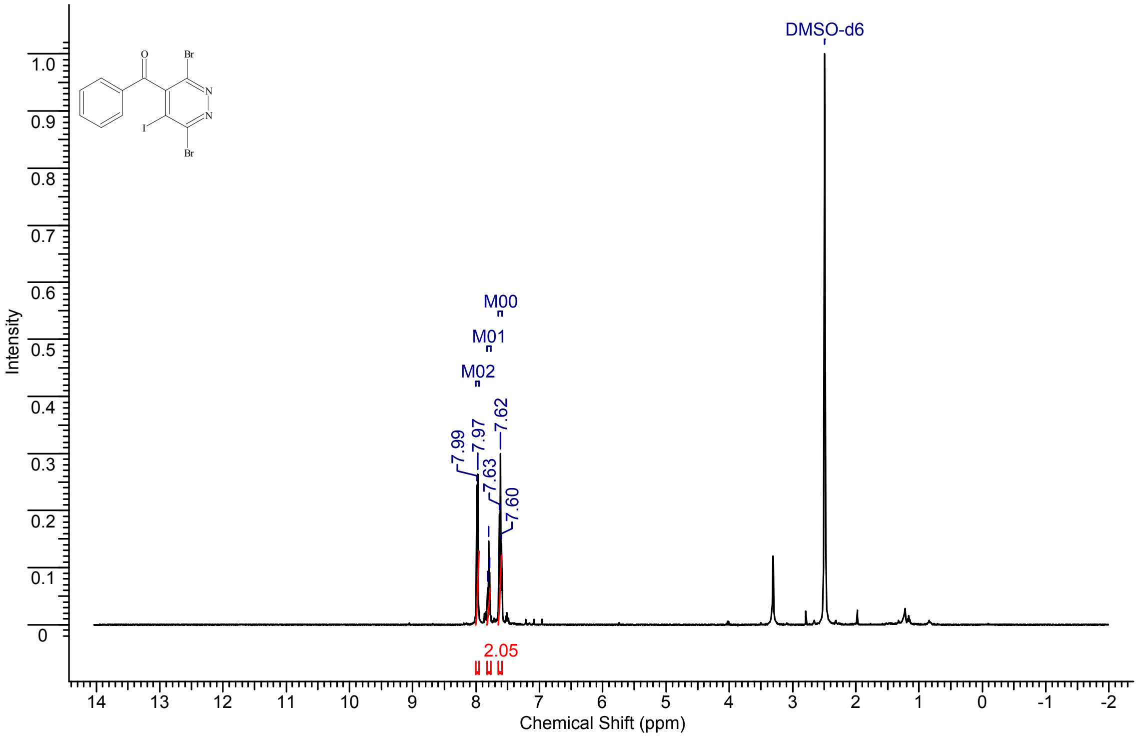


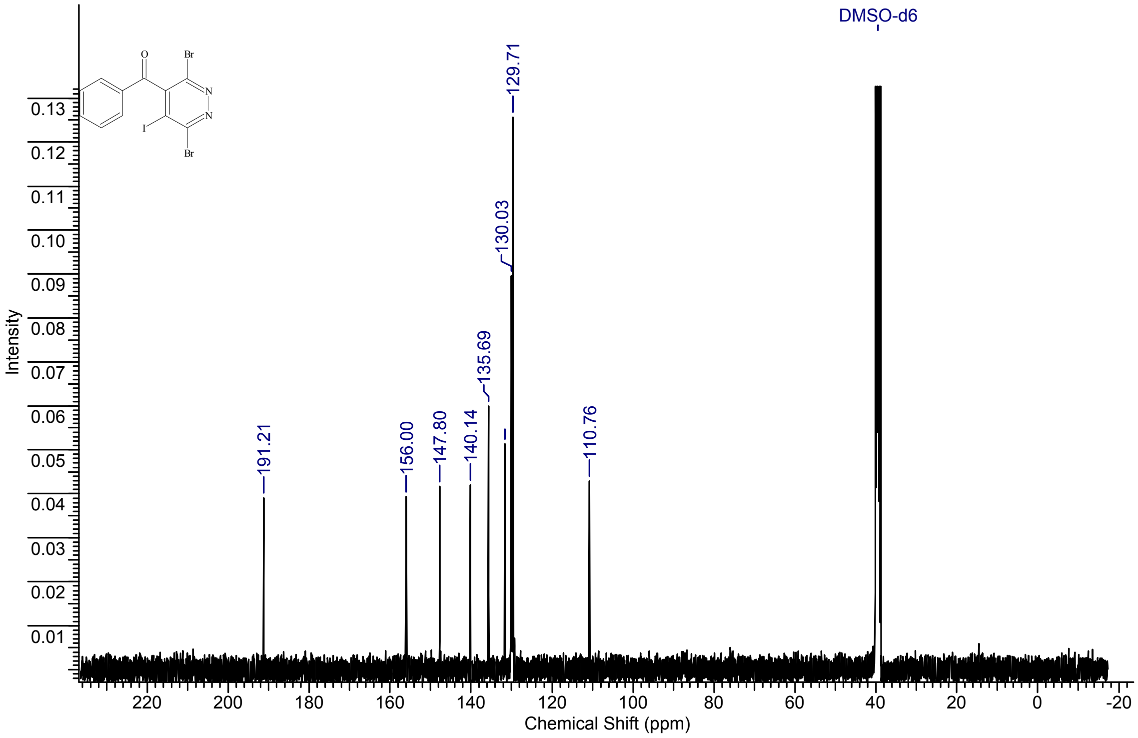
(3,6-dibromo-5-(cyclohex-2-en-1-yl)pyridazin-4-yl)(phenyl)methanone (8a)



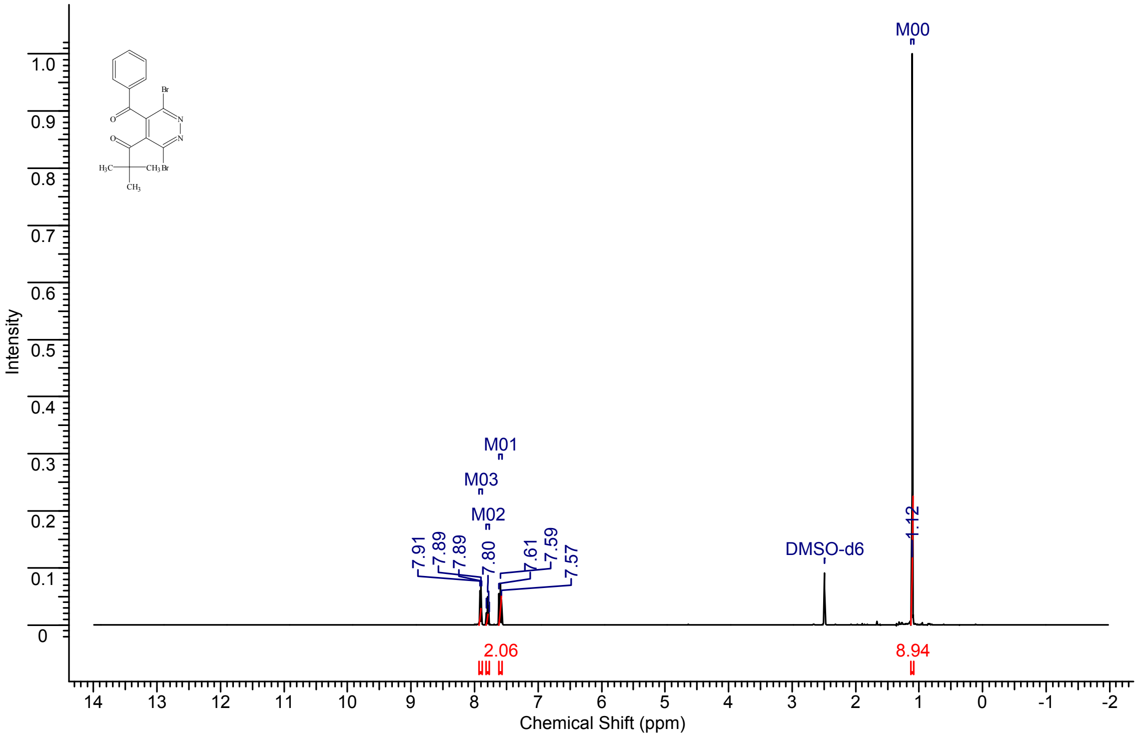


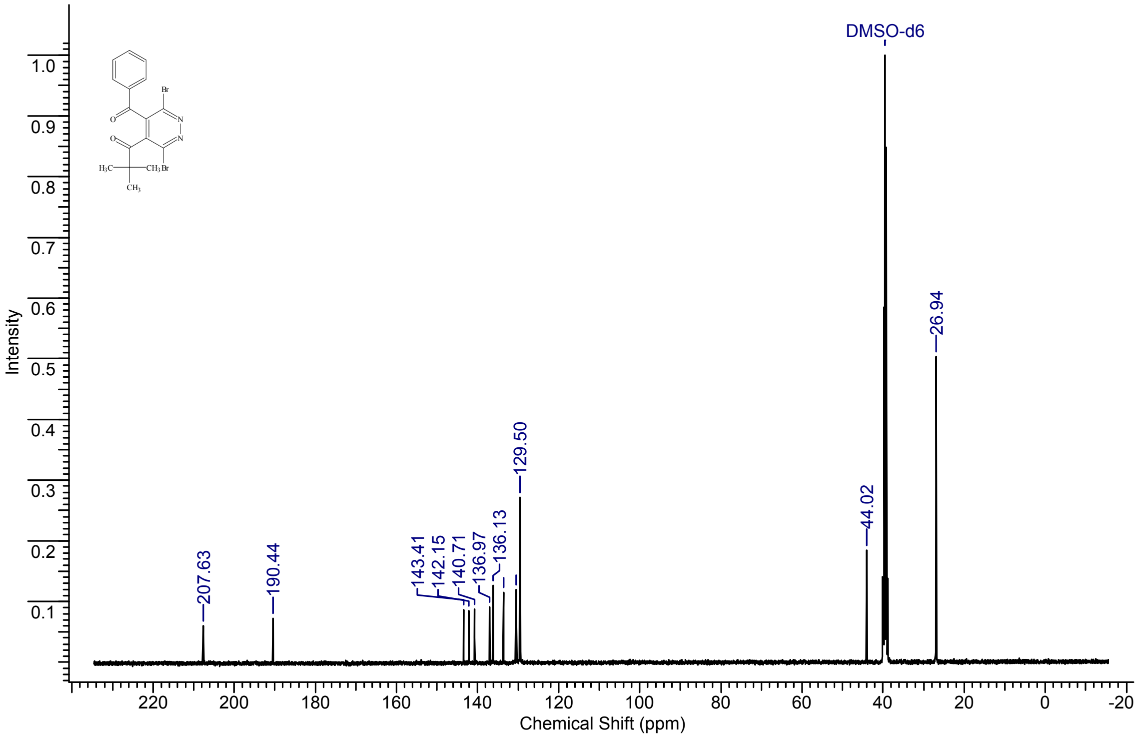
(3,6-dibromo-5-iodopyridazin-4-yl)(phenyl)methanone (8b)



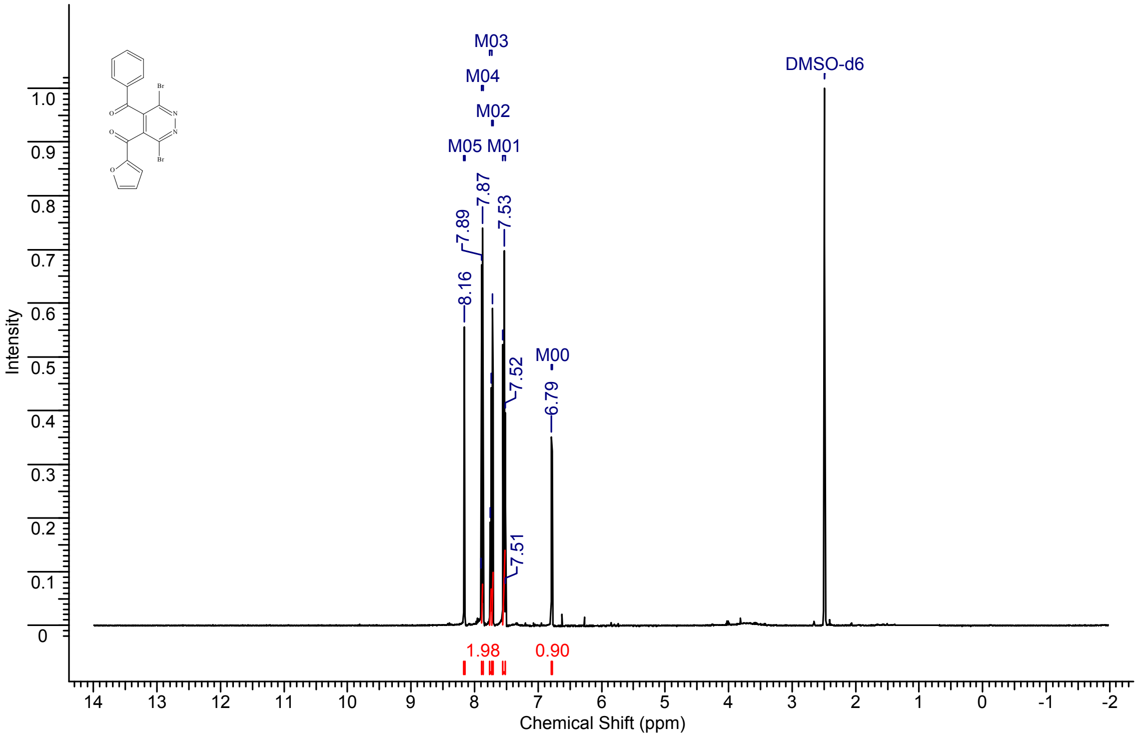


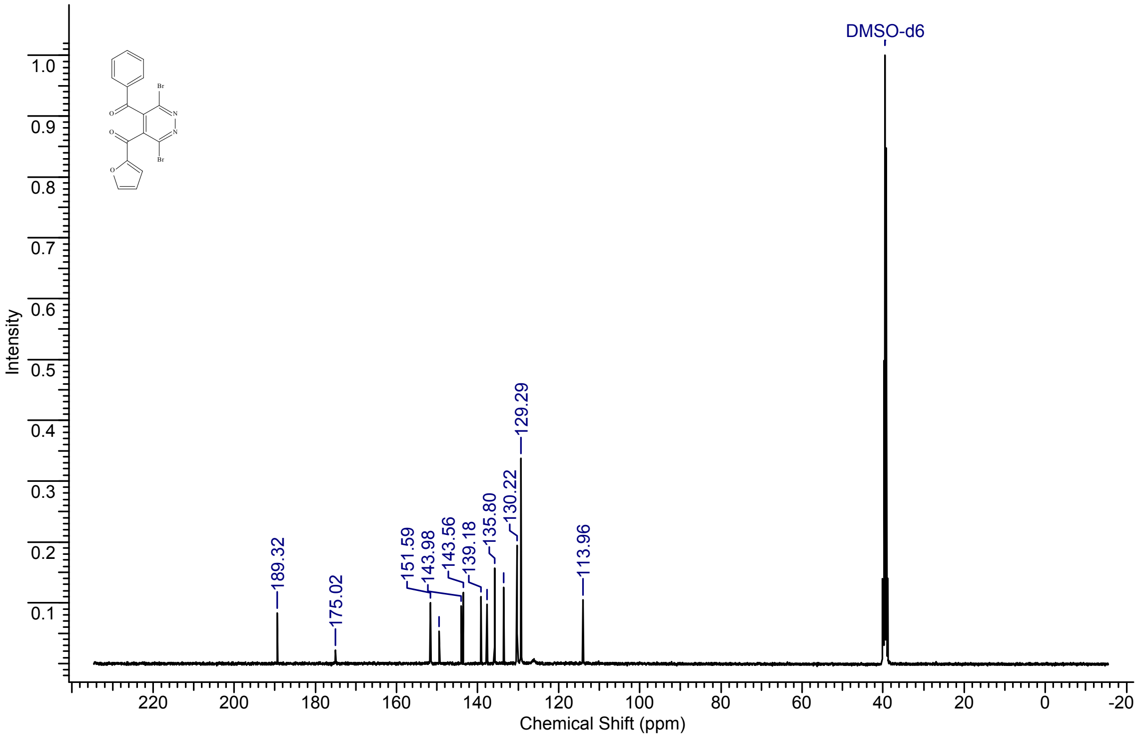
1-(5-benzoyl-3,6-dibromopyridazin-4-yl)-2,2-dimethylpropan-1-one (8c)



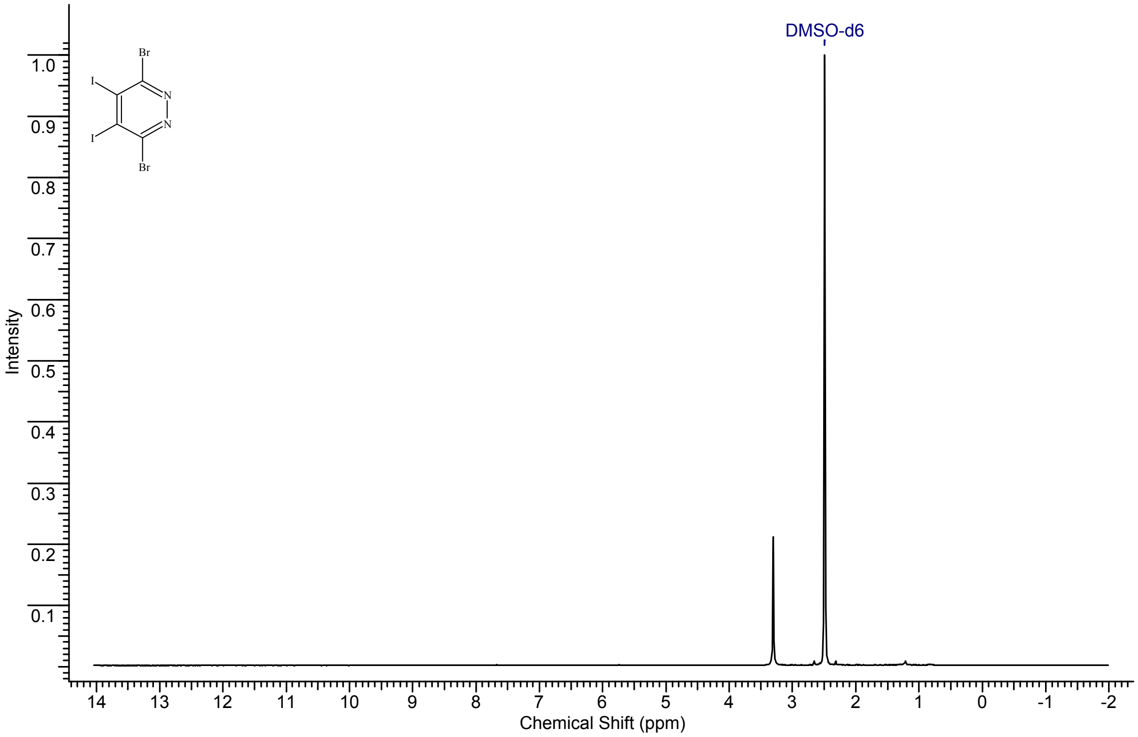


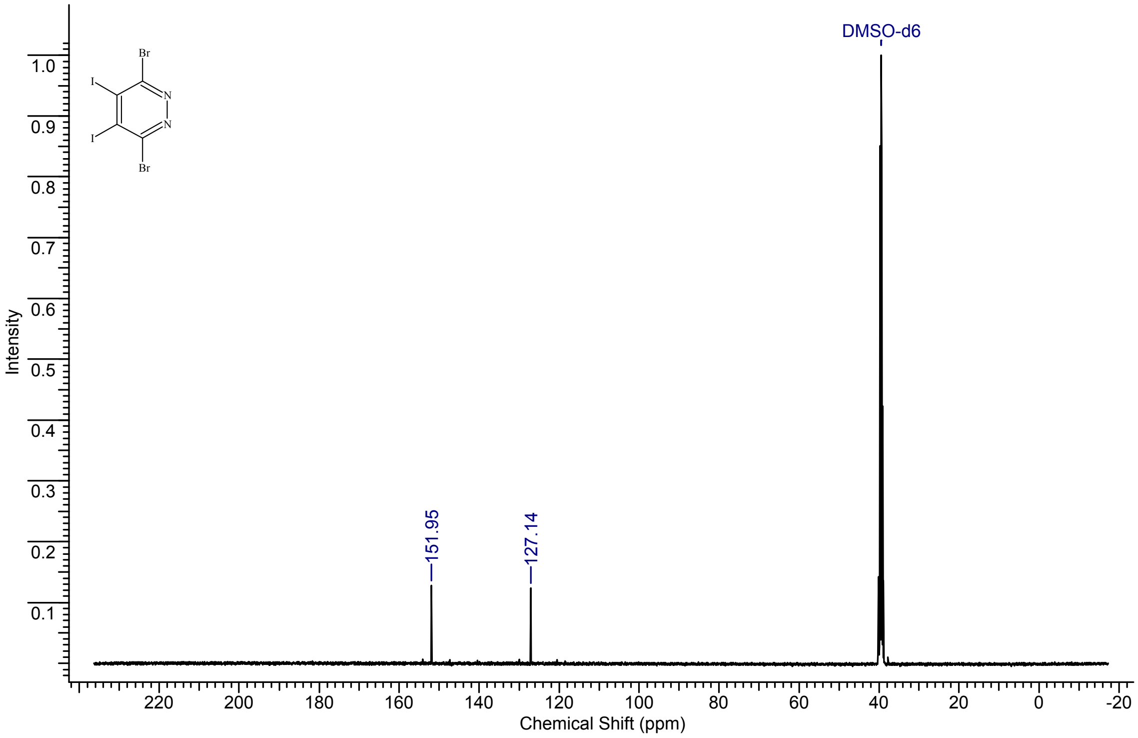
(5-benzoyl-3,6-dibromopyridazin-4-yl)(furan-2-yl)methanone (8d)



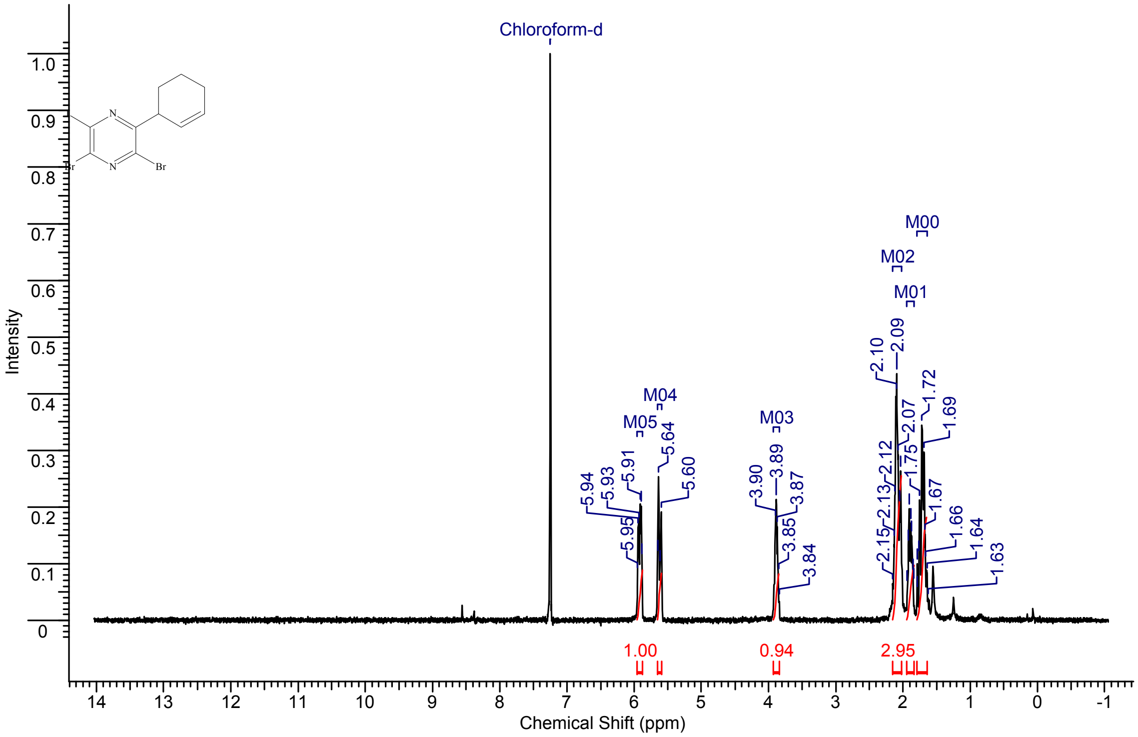


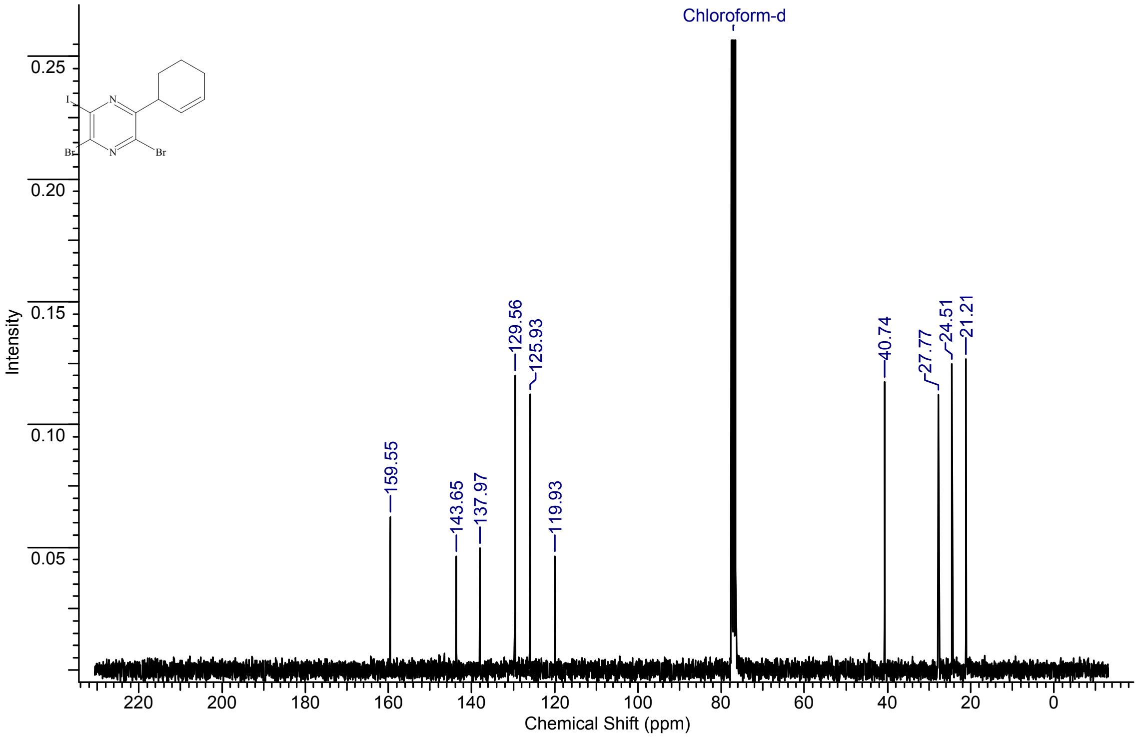
3,6-dibromo-4,5-diiodopyridazine (8e)



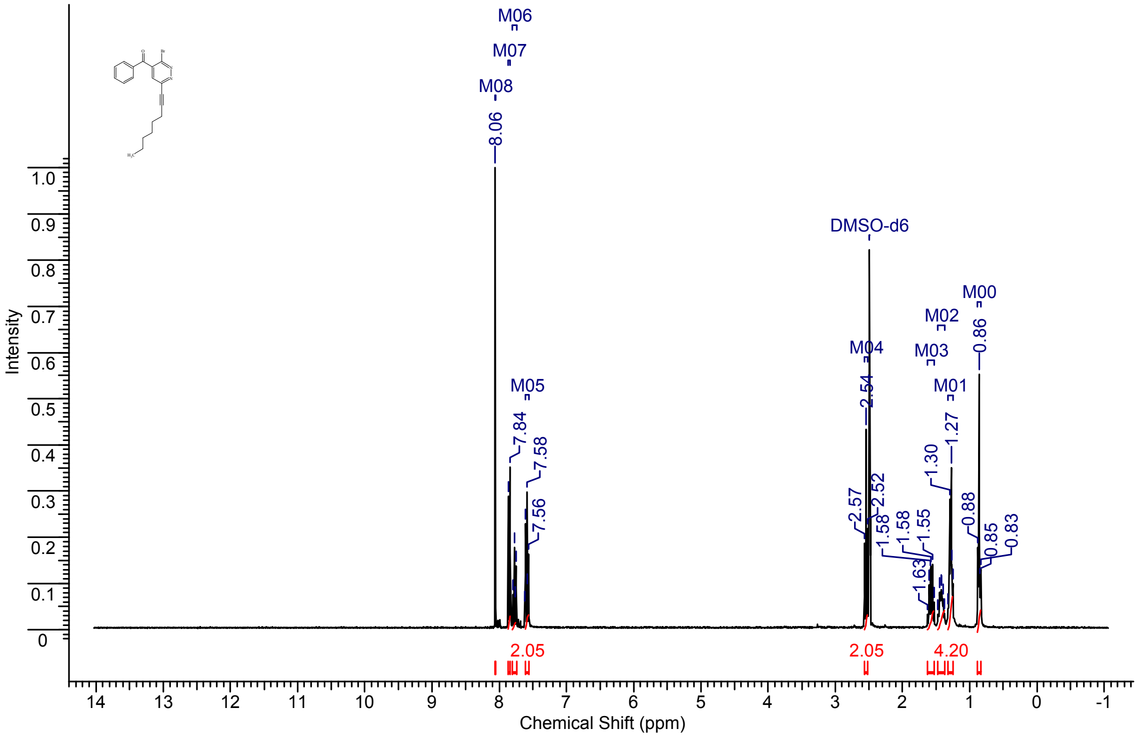


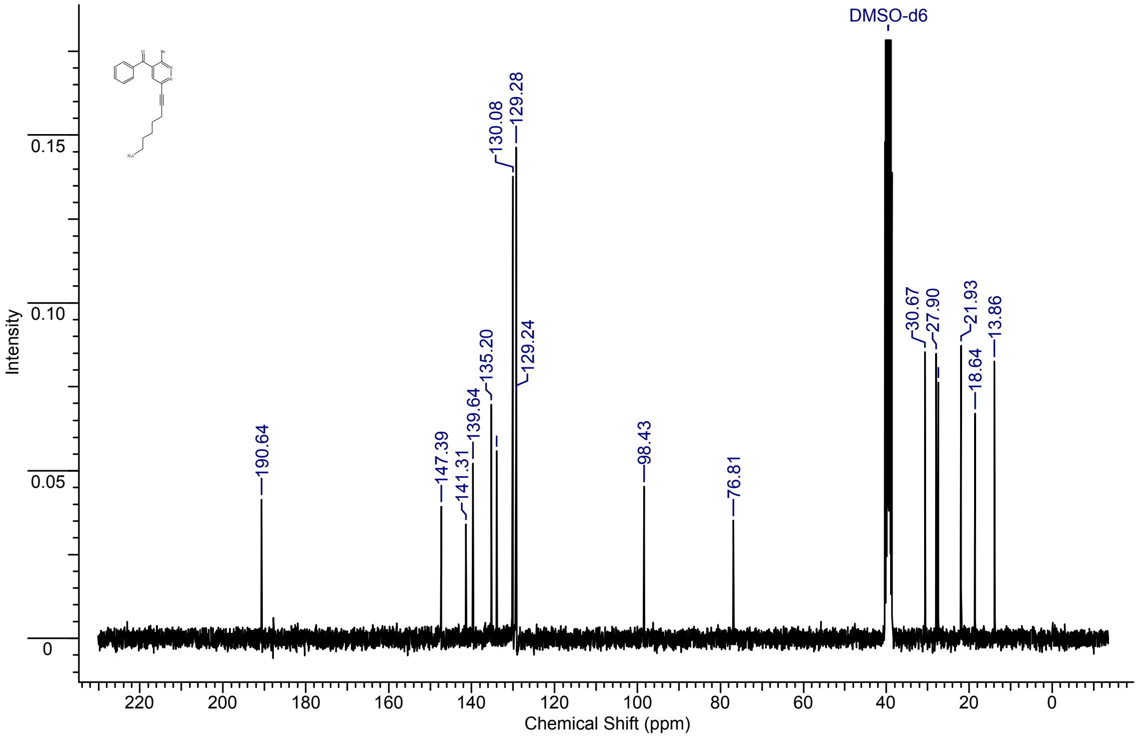
2,6-dibromo-3-(cyclohex-2-en-1-yl)-5-iodopyrazine (8f)



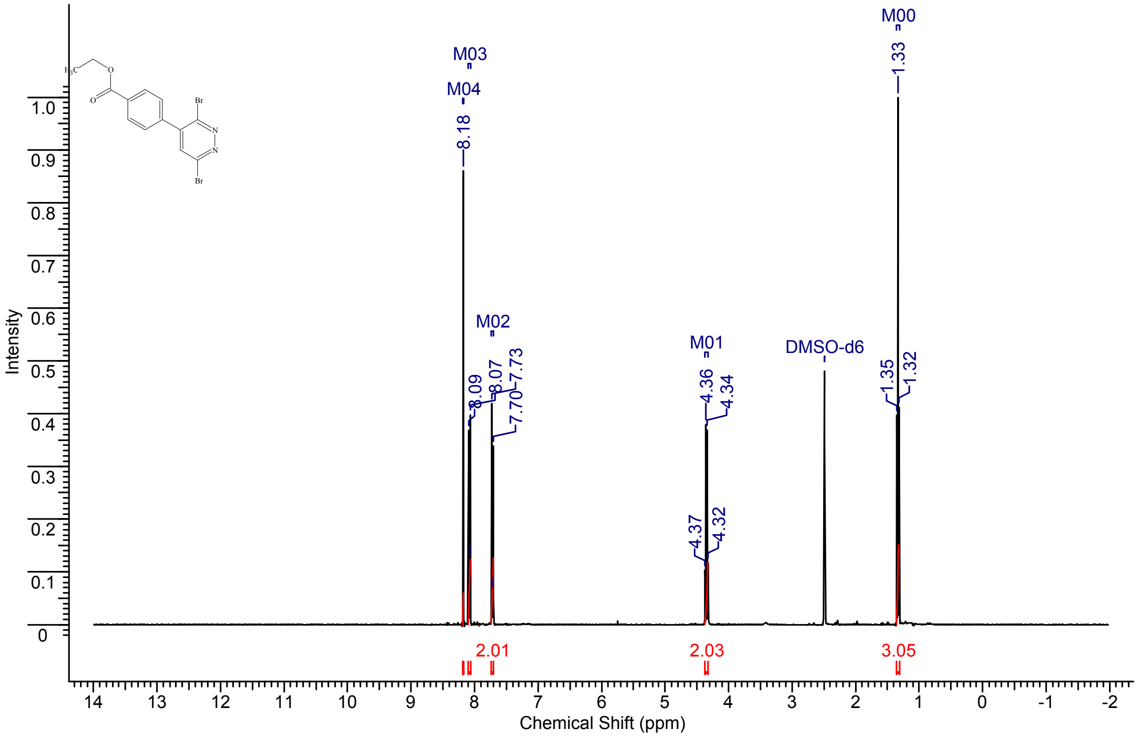


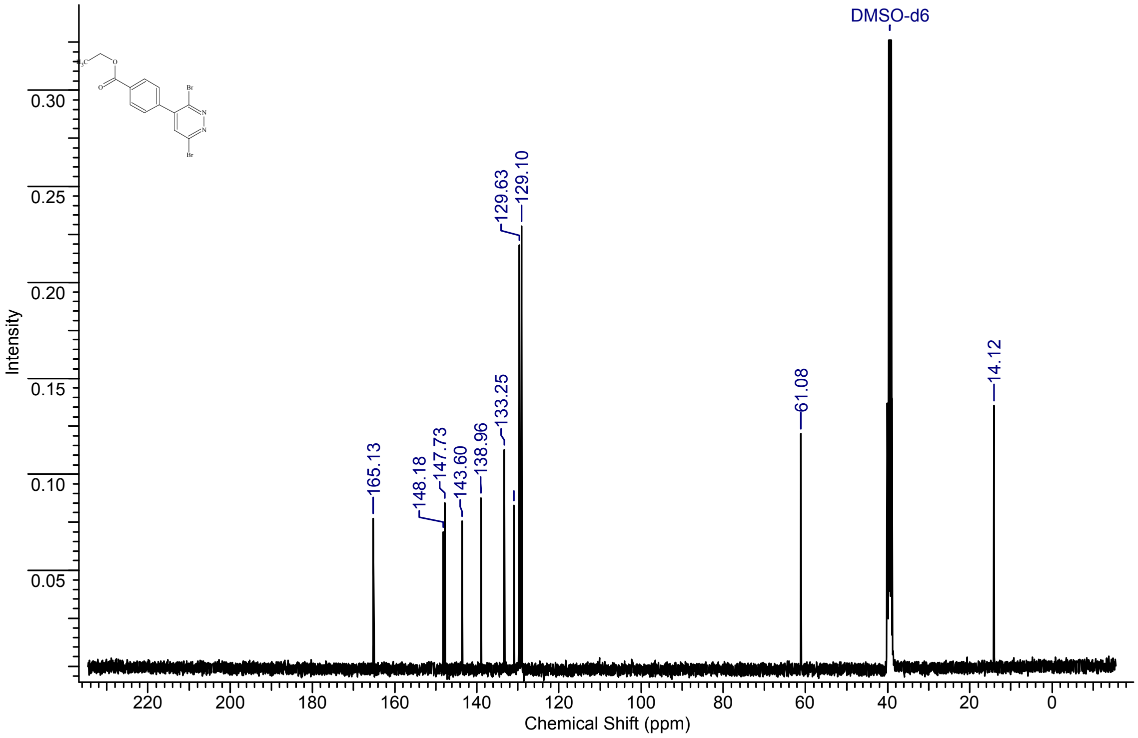
3-bromo-6-(oct-1-yn-1-yl)pyridazin-4-yl)(phenyl)methanone (9a)



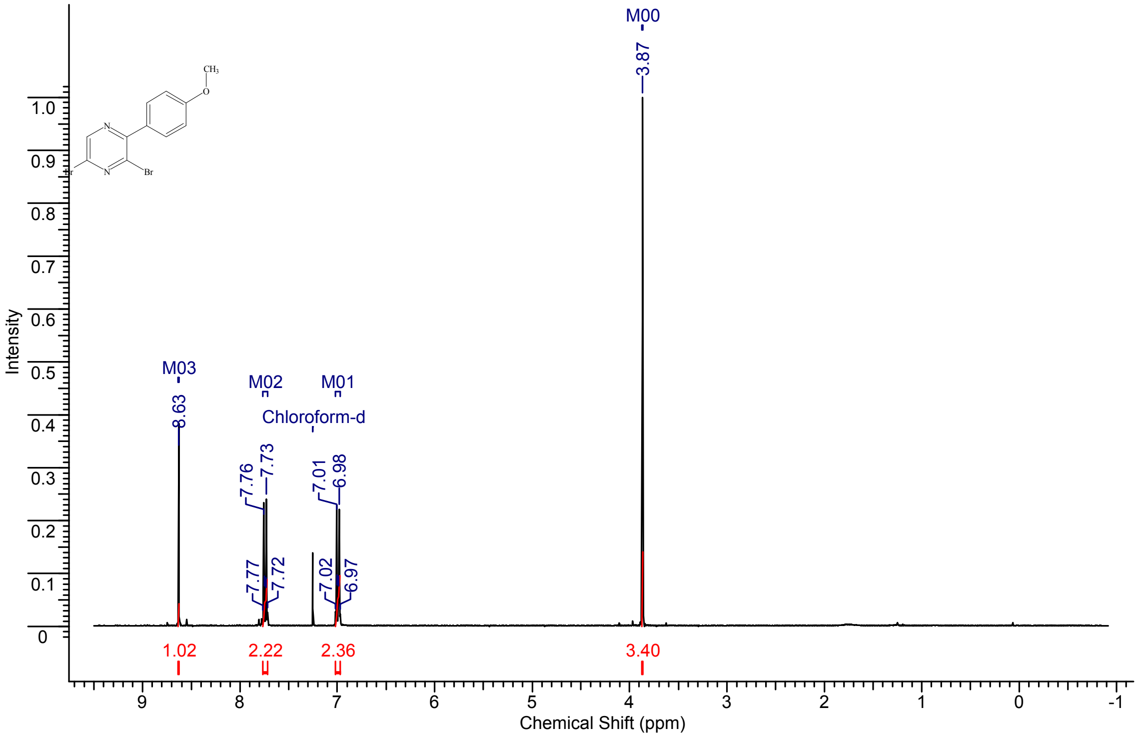


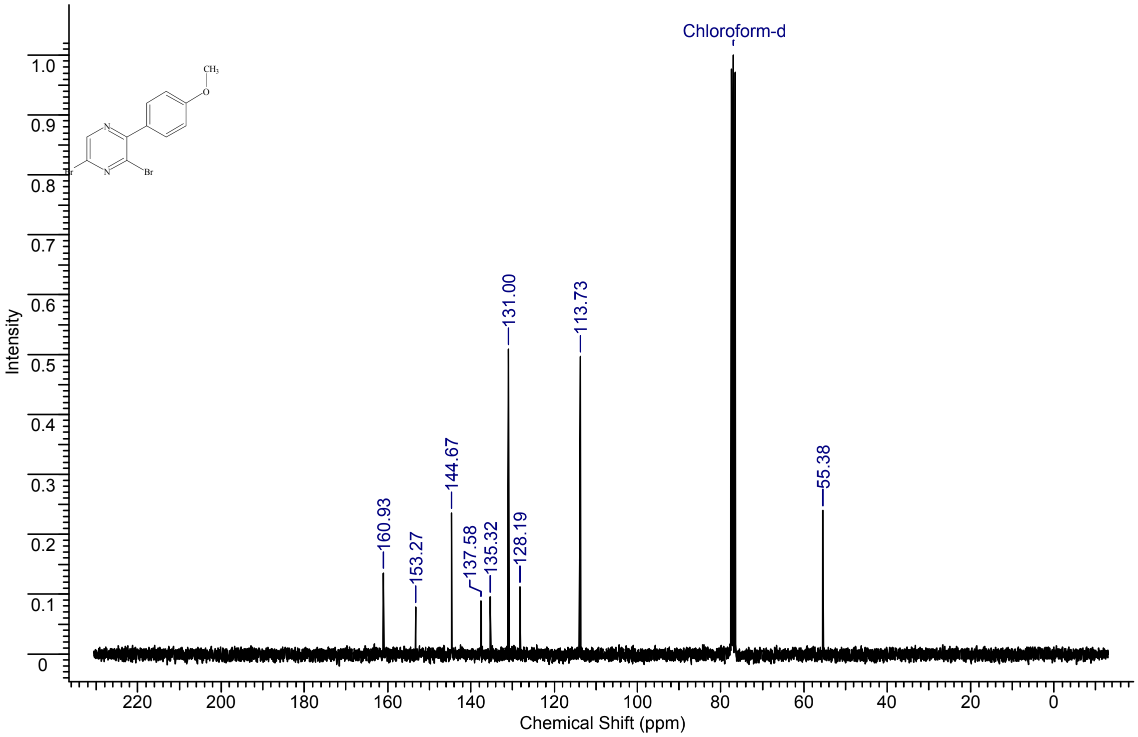
ethyl 4-(3,6-dibromopyridazin-4-yl)benzoate (9b)



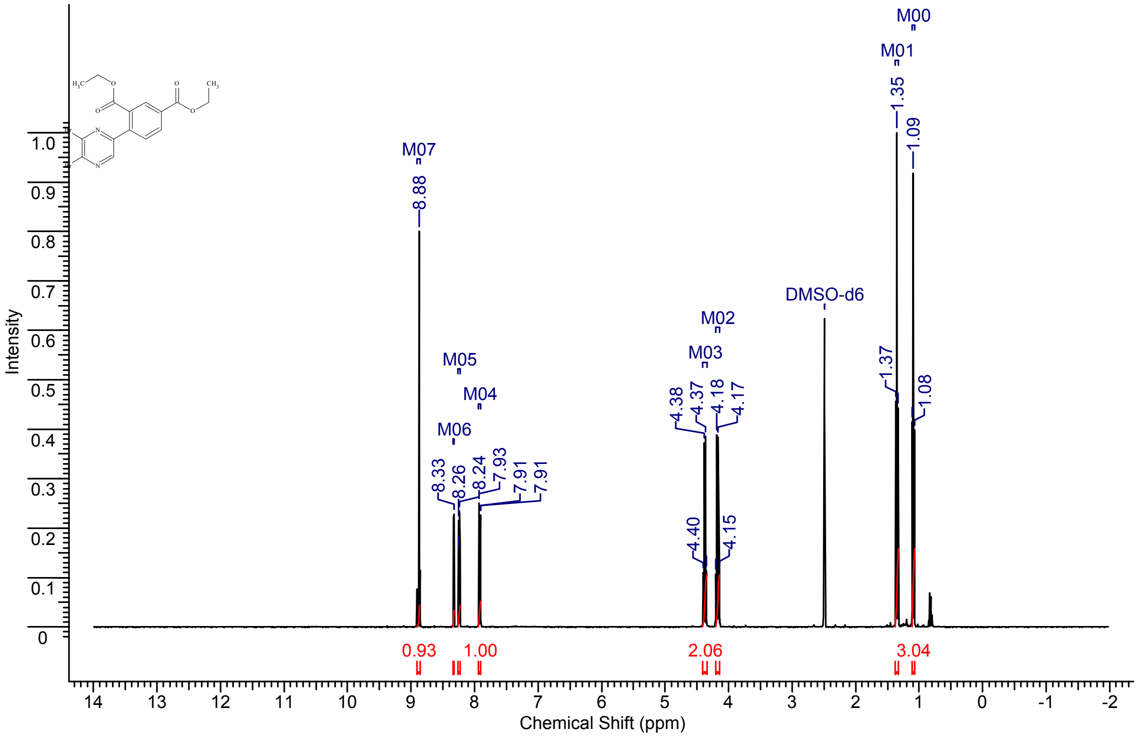


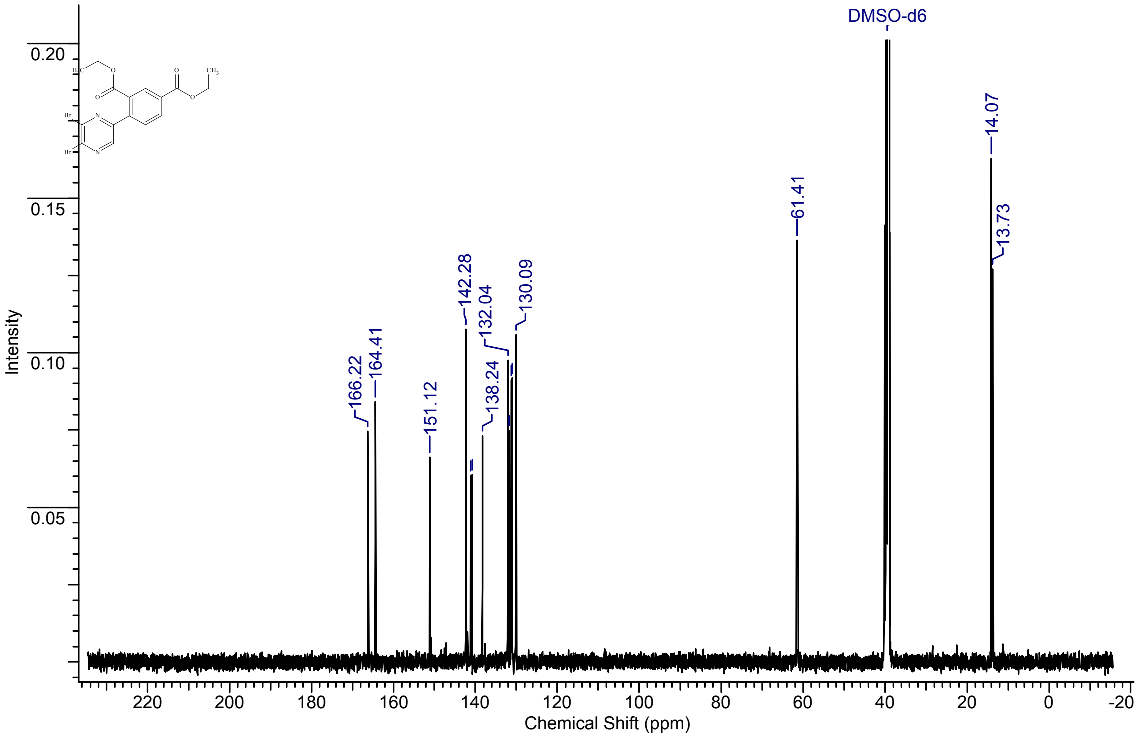
3,5-dibromo-2-(4-methoxyphenyl)pyrazine (9c)



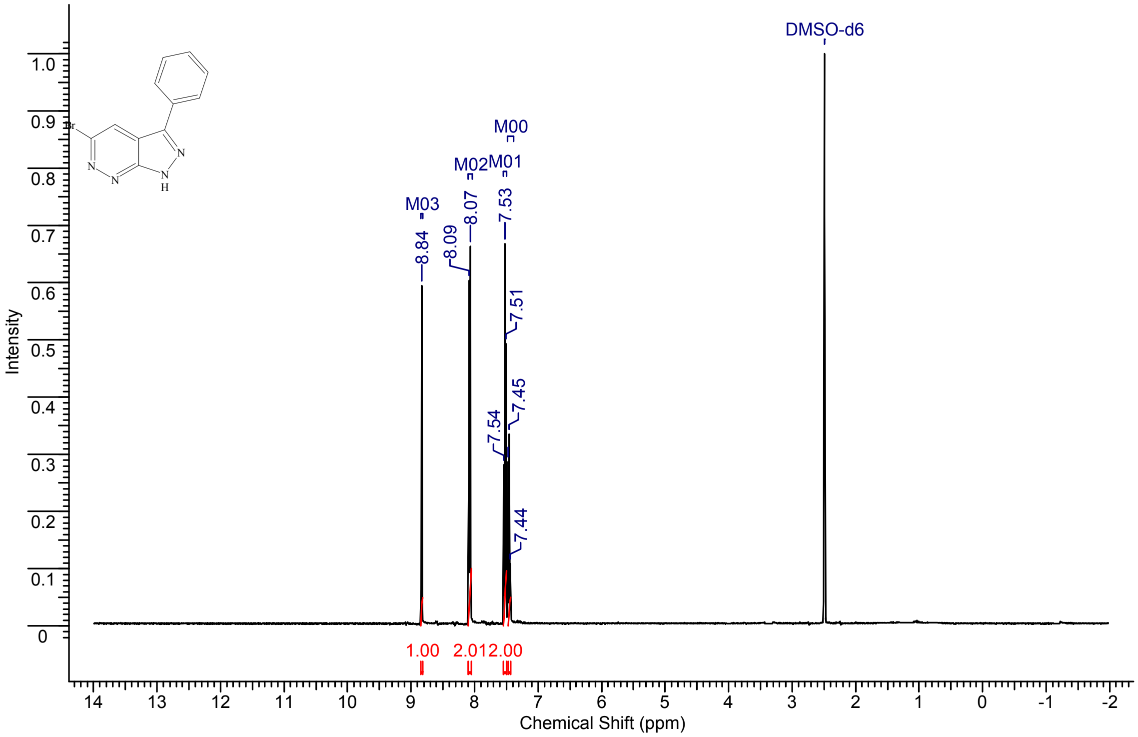


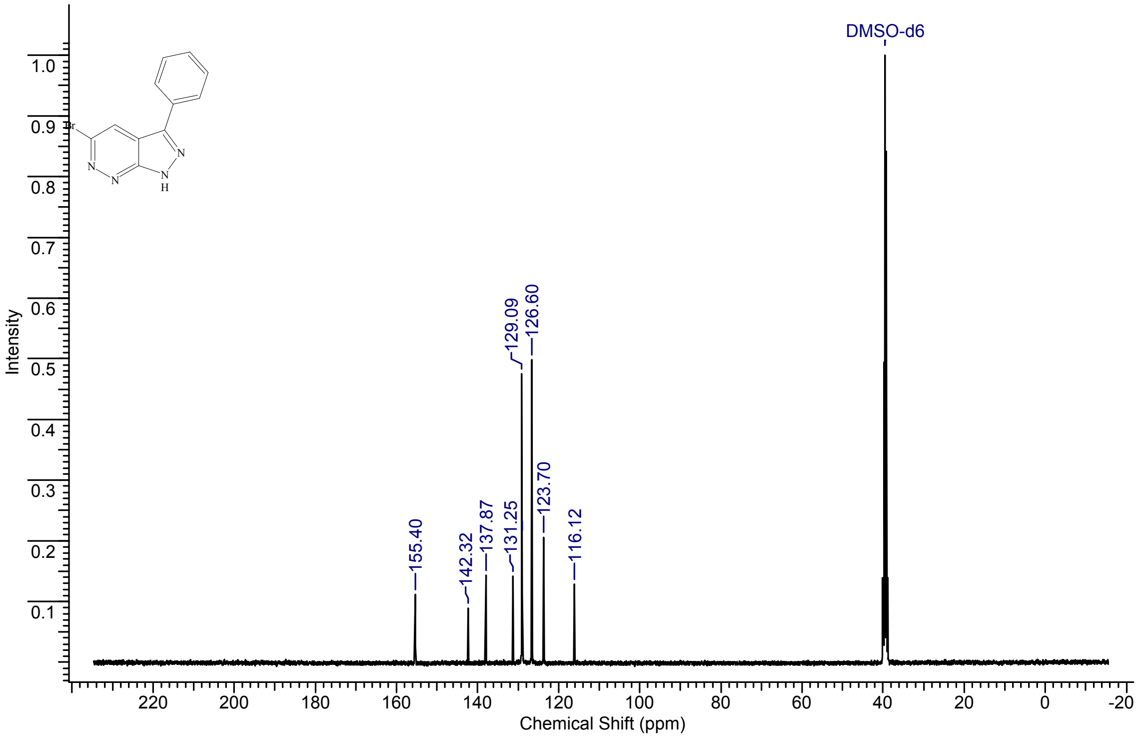
diethyl 4-(5,6-dibromopyrazin-2-yl)isophthalate (9d)





5-bromo-3-phenyl-1H-pyrazolo[3,4-c]pyridazine (10a)





5-bromo-3-(4-chlorophenyl)-1H-pyrazolo[3,4-b]pyrazine (10b)