

# Supporting Information

## Identification of Aminopyridazine-derived Anti-neuroinflammatory Agents Effective in an Alzheimer's Mouse Model

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*KEY WORDS: Alzheimer's disease; neuroinflammation; microglia; Morris water maze; anti-neuroinflammatory agent; animal model;*

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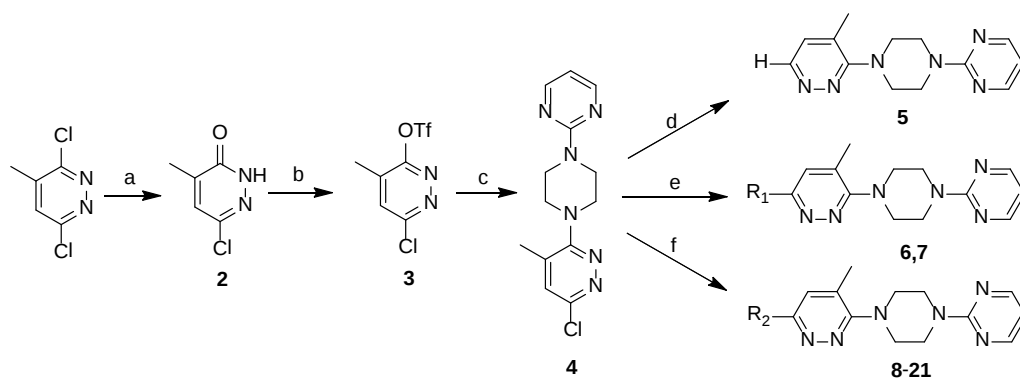
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# 1. Synthesis and characterization of compounds 1b and 4-21

## 1.1. General

Reagents were obtained from commercial sources and were used as received. Dry solvents were obtained according to the standard procedures, and reactions were conducted under dry N<sub>2</sub> unless otherwise noted. The product solutions were evaporated in vacuo using a rotatory evaporator. The reactions were monitored by thin layer chromatography (TLC) using Qing Dao Hai Yang GF254 silica gel plates visualized with ultraviolet (UV) light (254 nm), iodine steam or phosphomolybdic acid (PMA), and column chromatography was performed using silica gel (200-300 mesh). <sup>1</sup>H Nuclear magnetic resonance (NMR) data were acquired with a Bruker NMR AVANCE 400 (400 MHz) and <sup>13</sup>C NMR spectra were recorded using a Bruker NMR AVANCE 500 (500 MHz); all samples were dissolved in CDCl<sub>3</sub> if not stated otherwise. Chemical shifts are given in  $\delta$  relative to tetramethylsilane (TMS) in parts per million (ppm), and coupling constants (*J*) are in hertz (Hz). Low-resolution mass spectra (MS) and compound purity data were acquired on a Waters ZQ LC/MS single quadrupole system equipped with an electrospray ionization (ESI) source, a UV detector (220 nm and 254 nm), and an evaporative light scattering detector (ELSD). High performance liquid chromatography (HPLC) analysis revealed a purity of >95% for all compounds.

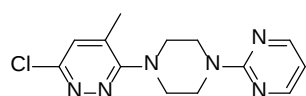
## 1.2. Synthetic route of target compounds



### Scheme 1. Synthesis of target compounds 5-21

Reagents and conditions: (a) acetic acid, reflux (56.5%); (b) trifluoromethanesulfonic anhydride, triethylamine, DCM, -10 °C to 0 °C; (c) 1-(2-pyrimidinyl)piperazine, DMF, 0 °C (76.5% over two steps); (d) H<sub>2</sub>, Pd/C, MeOH, rt, 24 h (64%); (e) R<sub>1</sub>=Me (**6**), MeMgCl, NMP, ferric acetylacetonate, Et<sub>2</sub>O, THF, 0.5 h, rt (76.4%); R<sub>1</sub>=*i*-Pr (**7**), *i*-PrMgCl, NMP, ferric acetylacetonate, Et<sub>2</sub>O, THF, 0.5 h, rt (84.2%); (f) R<sub>2</sub>B(OH)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, DME (31.5-79.9%).

#### 6-chloro-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (**4**)

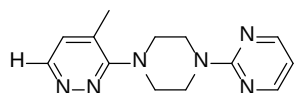


100 g (0.69 mol) of 6-chloro-4-methylpyridazin-3(2*H*)-one, prepared according to the literature<sup>1, 2</sup>, and 211 mL (1.52 mol, 2.2 equiv.) of triethylamine was dissolved in 300 mL of anhydrous dichloromethane in an inert atmosphere. The mixture was kept at -10 °C, and 405 g (1.44 mol, 2.08 equiv.) of trifluoromethanesulfonic anhydride in 200 mL of dichloromethane was added over 2 h. The mixture was allowed to warm to ambient temperature and stirred for an additional 2 h. The reaction was quenched with 500 mL of water, and the organic phase was separated. The organic phase was washed with 1 N HCl (100 mL×2) and brine (100 mL), dried over MgSO<sub>4</sub> and filtered. The solvent was removed in vacuo to afford crude 6-chloro-4-methylpyridazin-3-yl trifluoromethanesulfonate (**3**) as brown oil. The crude product (**3**) was dissolved in DMF (200 mL) and cooled in an ice bath. Triethylamine (115 mL, 0.83 mmol, 1.2 equiv.) was added, followed by 2-(piperazin-1-yl)pyrimidine (136 g, 0.83 mmol, 1.2 equiv.) in DMF (150 mL). The mixture was allowed to warm to room temperature over 1 h and was stirred at this temperature for 18 h. It was diluted with ethyl acetate (500 mL), washed with water (500 mL×2) and brine (200 mL), dried (MgSO<sub>4</sub>), and concentrated under vacuum. The residue was purified by flash chromatography to afford 6-chloro-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (**4**) as a white powder (153 g, 76.5% yield over two steps).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.33 (d, *J* = 4.8 Hz, 2H), 7.21 (d, *J* = 0.4 Hz, 1H), 6.53 (t, *J* = 4.8 Hz, 1H), 3.98 (dd, *J*<sub>1</sub> = 6.8 Hz, *J*<sub>2</sub> = 2.8 Hz, 4H), 3.35 (t, *J* = 4.8 Hz, 4H), 2.35 (d, *J*

= 0.8 Hz, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.0, 161.7, 157.7, 151.3, 134.1, 130.1, 110.3, 49.5, 43.6, 18.1. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{13}\text{H}_{15}\text{ClN}_6$ :  $[\text{M} + \text{H}]^+$ , 291.1120; found, 291.1118.

#### 4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (5)

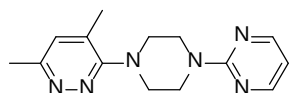


A mixture of 6-chloro-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (**4**, 581 mg, 2.00 mmol) and 10% Pd/C (145 mg, 25 wt %) was hydrogenated with  $\text{H}_2$  at room temperature for 8 h and then filtered through Celite. The filtrate was evaporated, and the residue was purified by flash column chromatography to give 328 mg (64% yield) of compound **5** as a white powder.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.72 (d,  $J$  = 4.8 Hz, 1H), 8.33 (d,  $J$  = 4.4 Hz, 2H), 7.17 (d,  $J$  = 4.8 Hz, 1H), 6.52 (t,  $J$  = 4.4 Hz), 3.98 (t,  $J$  = 5.2 Hz, 4H), 3.37 (t,  $J$  = 5.2 Hz, 4H), 2.35 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.8, 161.8, 157.7, 147.1, 131.0, 129.1, 110.2, 49.5, 43.7, 18.1. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_6$ :  $[\text{M} + \text{H}]^+$ , 257.1509; found, 257.1510.

### 1.3. General procedure the synthesis of compounds **6** and **7**

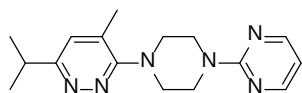
To a solution of 6-chloro-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (**4**, 581 mg, 2.00 mmol) and iron (III) acetylacetonate (50 mg) in tetrahydrofuran (50 mL) was added alkylmagnesium chloride (4.0 mmol) via a syringe at room temperature. The resulting mixture was stirred for 2 h, diluted with ethyl acetate and carefully quenched with a few drops of 10% HCl.<sup>3</sup> The mixture was washed with saturated aqueous  $\text{NaHCO}_3$  solution. The organic layer was dried over  $\text{MgSO}_4$  and concentrated in vacuo. Purification on silica gel afforded compounds **6-7**.

#### 6-dimethyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (6)



76.4% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.32 (d,  $J = 4.8$  Hz, 2H), 7.03 (s, 1H), 6.53 (t,  $J = 4.8$  Hz, 1H), 3.99 (t,  $J = 5.2$  Hz, 4H), 3.32 (t,  $J = 5.2$  Hz, 4H), 2.56 (s, 3H), 2.31 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.2, 161.8, 157.7, 155.4, 131.1, 129.7, 110.1, 49.7, 43.8, 21.3, 17.8. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_6$ :  $[\text{M} + \text{H}]^+$ , 271.1666; found, 271.1663.

#### 6-isopropyl-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (7)



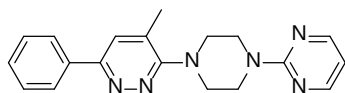
84.2% yield,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.32 (d,  $J = 4.8$  Hz, 2H), 7.05 (s, 1H), 6.50 (t,  $J = 4.8$  Hz, 1H), 3.97 (t,  $J = 5.2$  Hz, 4H), 3.33 (t,  $J = 5.2$  Hz, 4H), 3.15 (m, 1H), 2.33 (s, 3H), 1.32 (d,  $J = 7.2$  Hz, 6H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.6, 162.4, 161.8, 157.7, 131.3, 127.5, 110.1, 49.6, 43.7, 34.0, 22.3, 18.0. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{16}\text{H}_{22}\text{N}_6$ :  $[\text{M} + \text{H}]^+$ , 299.1906; found, 299.1980.

### 1.4. General procedure for the synthesis of compounds 1b, 8-21

Briefly, 600 mg (2.07 mmol) of

3-chloro-4-methyl-6-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (**4**), 277 mg (2.27 mmol) of arylboronic acid, 856 mg (6.20 mmol) of potassium carbonate and 120 mg (0.103 mmol) of tetrakis(triphenylphosphine)palladium were placed in a reaction tube with 6 mL of DME, and the reaction was capped and heated at  $110^\circ\text{C}$  for 48 h.<sup>4</sup> The solution was cooled to ambient temperature and filtered through Celite. The filtrate was concentrated under reduced pressure to give an oily residue. After purification of the crude product by column silica gel chromatography, compounds **1** and **8-21** were obtained.

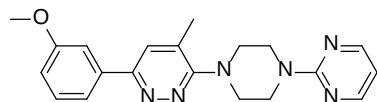
**4-methyl-6-phenyl-3-(4-(pyrimidin-2-yl) piperazin-1-yl)pyridazine (1b)**



50% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.35(d,  $J$  = 4.8 Hz, 2H), 8.03 (d,  $J$  = 9.2 Hz, 2H), 7.60 (s, 1H), 7.48 (m, 3H), 6.54 (t,  $J$  = 4.8 Hz, 1H), 4.02 (t,  $J$  = 5.2 Hz, 4H), 3.44 (t,  $J$  = 5.2 Hz, 4H), 2.43 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.6, 161.8, 157.7, 154.9, 136.4, 131.1, 129.2, 128.8, 126.9, 126.5, 110.2, 49.5, 43.7, 18.5.

High-resolution mass spectra (HRMS) calcd for  $\text{C}_{19}\text{H}_{20}\text{N}_6$ :  $[\text{M} + \text{H}]^+$ , 333.1822; found, 333.1825

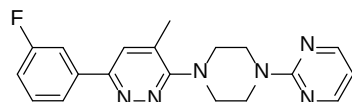
**6-(3-methoxyphenyl)-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (8)**



74.2% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.35 (d,  $J$  = 4.8 Hz, 2H), 7.74 (s, 1H), 7.59 (s, 1H), 7.51 (d,  $J$  = 7.6 Hz, 1H), 7.38 (t,  $J$  = 8.0 Hz, 1H), 6.98 (dd,  $J_1$  = 8.4 Hz,  $J_2$  = 2.4 Hz, 1H), 6.53 (t,  $J$  = 4.8 Hz, 1H), 4.02 (t,  $J$  = 5.2 Hz, 4H), 3.89 (s, 3H), 3.44 (t,  $J$  = 5.2 Hz, 4H), 2.42 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.7, 161.8, 160.1, 157.7, 154.5, 137.8, 132.1, 131.1, 129.7, 127.0, 118.7, 115.8, 111.1, 110.2, 55.4, 49.5, 43.7, 18.5.

High-resolution mass spectra (HRMS) calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_6\text{O}$ :  $[\text{M} + \text{H}]^+$ , 363.1928; found, 363.1929.

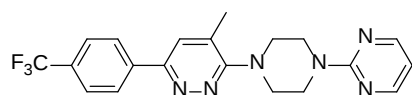
**6-(3-fluorophenyl)-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (9)**



72.3% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.36 (d,  $J$  = 4.8 Hz, 1H), 7.76 (d,  $J$  = 8.0 Hz, 1H), 7.67-7.71 (m, 1H), 7.62, (s, 1H), 7.46-7.51 (m, 1H), 7.13-7.18 (m, 1H), 6.55 (t,  $J$  = 4.8 Hz, 1H), 4.05 (t,  $J$  = 4.8 Hz, 4H), 3.47 (t,  $J$  = 5.2 Hz, 4H), 2.47 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  164.3, 162.8, 162.3, 161.7, 157.8, 153.9, 138.0, 138.0, 132.7, 130.7, 130.6, 128.1, 122.28, 122.26, 116.58, 116.41, 113.8, 113.6, 110.3, 49.5, 43.7, 18.7. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_6\text{O}$ :  $[\text{M} + \text{H}]^+$ ,

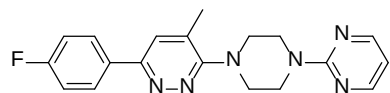
351.1728; found, 351.1729.

**4-methyl-6-(4-(trifluoromethyl)phenyl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (10)**



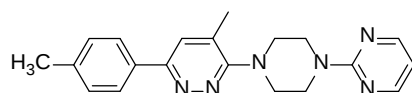
31.5% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.35 (d,  $J$  = 4.8 Hz, 2H), 8.16 (d,  $J$  = 8.0 Hz, 2H), 7.74 (d,  $J$  = 8.4 Hz, 2H), 7.62 (d,  $J$  = 0.8 Hz, 1H), 6.54 (t,  $J$  = 4.8 Hz, 1H), 4.03 (t,  $J$  = 5.2 Hz, 4H), 3.48 (t,  $J$  = 5.2 Hz, 4H), 2.45 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.9, 161.8, 157.8, 153.3, 139.8, 131.2, 131.1, 127.0, 126.7, 125.80, 125.77, 110.3, 49.4, 43.7, 18.6. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_6$ :  $[\text{M} + \text{H}]^+$ , 401.1696; found, 401.1693.

**4-methyl-6-(4-fluorophenyl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (11)**



79.9% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.34 (d,  $J$  = 4.8 Hz, 2H), 8.02 (m, 2H), 7.55 (s, 1H), 7.16 (t,  $J$  = 8.8 Hz, 2H), 6.53 (t,  $J$  = 4.8 Hz, 1H), 4.02 (t,  $J$  = 5.2 Hz, 4H), 3.44 (t,  $J$  = 5.2 Hz, 4H), 2.43 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  164.6, 162.7, 162.5, 161.8, 157.7, 153.9, 132.5, 131.3, 128.3, 128.2, 126.6, 115.9, 115.7, 110.2, 49.5, 43.7, 18.4. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{19}\text{H}_{19}\text{FN}_6$ :  $[\text{M} + \text{H}]^+$ , 351.1728; found, 351.1728.

**4-methyl-6-(p-tolyl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (12)**

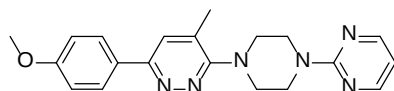


69.2% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.33 (d,  $J$  = 4.8 Hz, 2H), 7.93 (d,  $J$  = 8.0 Hz, 2H), 7.55 (s, 1H), 7.27 (d,  $J$  = 8.4 Hz, 1H), 6.51 (t,  $J$  = 4.8 Hz, 1H), 4.00 (t,  $J$  = 5.2 Hz, 4H), 3.41 (t,  $J$  = 5.2 Hz, 4H), 2.39 (s, 6H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.4, 161.7,

157.7, 154.8, 139.2, 133.6, 131.0, 129.5, 126.5, 126.3, 110.1, 49.5, 43.7, 21.2, 18.3.

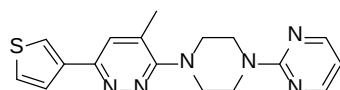
High-resolution mass spectra (HRMS) calcd for  $C_{20}H_{22}N_6$ :  $[M + H]^+$ , 347.1979; found, 347.1979.

**4-methyl-6-(4-methoxyphenyl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (13)**



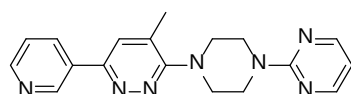
51.5% yield,  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.35 (d,  $J = 4.8$  Hz, 2H), 8.00 (d,  $J = 8.4$  Hz, 2H), 7.54 (s, 1H), 7.01 (d,  $J = 8.4$  Hz, 2H), 6.53 (t,  $J = 4.8$  Hz, 1H), 4.02 (t,  $J = 4.8$  Hz, 4H), 3.87 (s, 3H), 3.42 (t,  $J = 5.2$  Hz, 4H), 2.42 (s, 3H).  $^{13}C$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  162.3, 161.8, 160.7, 157.7, 154.6, 131.2, 129.0, 127.7, 126.3, 114.2, 110.1, 55.3, 49.6, 43.8, 18.4. High-resolution mass spectra (HRMS) calcd for  $C_{20}H_{22}N_6O$ :  $[M + H]^+$ , 363.1928; found, 363.1925.

**4-methyl-6-(thiophen-3-yl)-3-(4-(pyrimidin-2-yl) piperazin-1-yl)pyridazine (14)**



57.2% yield,  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.34 (d,  $J = 4.8$  Hz, 2H), 7.88 (d,  $J = 1.2$  Hz, 1H), 7.77 (d,  $J = 4.8$  Hz, 1H), 7.49 (s, 1H), 7.41 (m, 1H), 6.52 (m, 1H), 4.01 (t,  $J = 5.2$  Hz, 4H), 3.41 (t,  $J = 4.8$  Hz, 4H), 2.40 (s, 3H).  $^{13}C$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  162.3, 161.8, 157.7, 151.5, 138.9, 131.2, 126.7, 126.5, 125.9, 123.0, 110.1, 49.5, 43.7, 18.3. High-resolution mass spectra (HRMS) calcd for  $C_{17}H_{18}N_6S$ :  $[M + H]^+$ , 339.1386; found, 339.1385.

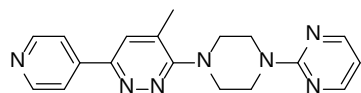
**4-methyl-6-(pyridin-3-yl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (15)**



35.7% yield,  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  9.17 (d,  $J = 1.2$  Hz, 1H), 8.67 (d,  $J = 3.6$  Hz, 1H), 8.43 (d,  $J = 8.0$  Hz, 1H), 8.35 (d,  $J = 4.8$  Hz, 2H), 7.62 (s, 1H), 7.43 (dd,  $J_1 = 12.0$  Hz,

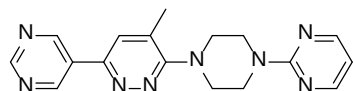
$J_2 = 4.8$  Hz, 1H), 6.54 (t,  $J = 4.8$  Hz, 1H), 4.03 (t,  $J = 4.8$  Hz, 4H), 3.46 (t,  $J = 5.2$  Hz, 4H), 2.45 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.9, 161.8, 157.7, 152.3, 150.2, 147.6, 133.9, 132.2, 131.3, 126.7, 123.8, 110.3, 49.4, 43.7, 18.6. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{18}\text{H}_{19}\text{N}_7$ :  $[\text{M} + \text{H}]^+$ , 334.1775; found, 334.1775.

**4-methyl-6-(pyridin-4-yl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (16)**



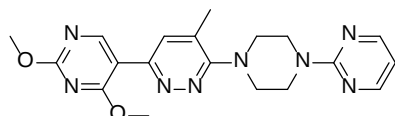
37.4% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.73 (d,  $J = 4.0$  Hz, 2H), 8.35 (d,  $J = 4.8$  Hz, 2H), 7.93 (d,  $J = 6.0$  Hz, 2H), 7.63 (s, 1H), 6.54 (t,  $J = 4.4$  Hz, 1H), 4.02 (t,  $J = 5.2$  Hz, 4H), 3.49 (t,  $J = 5.2$  Hz, 4H), 2.45 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.3, 161.8, 157.7, 152.1, 150.5, 143.7, 130.9, 126.9, 120.4, 110.3, 49.3, 43.6, 29.7, 18.7. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_7$ :  $[\text{M} + \text{H}]^+$ , 334.1775; found, 334.1773.

**4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)-6-(pyrimidin-5-yl)pyridazine (17)**



79.6% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  9.35 (s, 2H), 9.26 (s, 1H), 8.98 (s, 1H), 8.33 (d,  $J = 4.8$  Hz, 2H), 7.60 (s, 1H), 6.53 (t,  $J = 4.8$  Hz, 1H), 4.02 (t,  $J = 4.8$  Hz, 4H), 3.47 (t,  $J = 4.8$  Hz, 4H), 2.45 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.1, 161.7, 158.7, 157.7, 154.4, 149.7, 131.3, 130.0, 126.4, 110.3, 49.3, 43.6, 18.8. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_8$ :  $[\text{M} + \text{H}]^+$ , 335.1727; found, 335.1729.

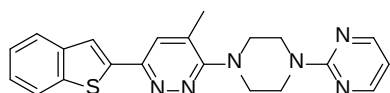
**4-methyl-6-(2,4-dimethoxypyrimidin-5-yl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (18)**



66.7% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  9.01 (s, 1H), 8.34 (d,  $J = 4.8$  Hz, 2H), 7.70 (s, 1H), 6.53 (t,  $J = 4.8$  Hz, 1H), 4.08 (s, 3H), 4.06 (s, 3H), 4.01 (d,  $J = 5.2$  Hz, 4H), 3.43 (d,  $J$

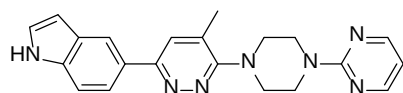
= 5.2 Hz, 4H), 2.41 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.1, 165.3, 162.3, 161.8, 159.2, 157.7, 150.3, 130.2, 132.0, 112.0, 110.2, 55.0, 54.2, 49.4, 43.7, 18.5. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_6\text{O}_2$ :  $[\text{M} + \text{H}]^+$ , 395.1939; found, 395.1937.

**4-methyl-6-(benzothiophen-2-yl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (19)**



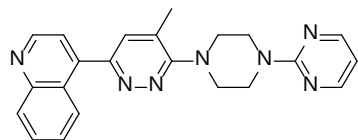
69.7% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.35 (d,  $J$  = 4.4 Hz, 2H), 7.86 (dd,  $J_1$  = 6.0 Hz,  $J_2$  = 2.8 Hz, 1H), 7.77 (dd,  $J_1$  = 5.2 Hz,  $J_2$  = 2.8 Hz, 1H), 7.60 (s, 1H), 7.35 (dd,  $J_1$  = 6.0 Hz,  $J_2$  = 3.2 Hz, 1H), 6.78 (s, 1H), 4.00 (t,  $J$  = 4.8 Hz, 4H), 3.45 (t,  $J$  = 4.8 Hz, 4H), 2.43 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  161.6, 158.6, 157.7, 148.0, 142.6, 140.41, 139.96, 136.4, 124.8, 124.1, 123.8, 122.6, 122.1, 113.5, 110.3, 44.6, 43.2, 21.7. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{21}\text{H}_{20}\text{N}_6\text{S}$ :  $[\text{M} + \text{H}]^+$ , 389.1543; found, 389.1546.

**5-(5-methyl-6-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazin-3-yl)-1H-indole (20)**



78.4% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.39 (br s, 1H), 8.35 (d,  $J$  = 4.8 Hz, 2H), 8.27 (s, 1H), 7.99 (d,  $J$  = 5.2 Hz, 1H), 7.67 (t,  $J$  = 9.6 Hz, 2H), 7.50 (m, 3H), 6.63 (s, 1H), 6.53 (t,  $J$  = 4.8 Hz, 1H), 4.02 (t,  $J$  = 4.8 Hz, 4H), 3.44 (t,  $J$  = 5.2 Hz, 4H), 2.44 (s, 3H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.2, 161.8, 157.7, 156.2, 136.6, 132.0, 131.3, 128.5, 127.0, 125.1, 121.0, 119.2, 111.5, 110.1, 113.4, 50.0, 43.8, 18.4. High-resolution mass spectra (HRMS) calcd for  $\text{C}_{21}\text{H}_{21}\text{N}_7$ :  $[\text{M} + \text{H}]^+$ , 372.1931; found, 372.1933.

**4-(5-methyl-6-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazin-3-yl)quinolone (21)**



35% yield,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  9.33 (s, 1H), 8.53(s, 1H), 8.36 (d,  $J = 4.8$  Hz, 2H), 8.09 (t,  $J_1 = 6.0$  Hz,  $J_2 = 4.8$ Hz, 1H), 7.7-7.5 (m, 3H), 6.92 (s, 1H), 6.56 (t,  $J = 4.8$  Hz, 1H), 4.04 (t,  $J = 5.6$  Hz, 4H), 3.87 (t,  $J_1 = 5.6$  Hz,  $J_2 = 4.8$  Hz, 4H), 2.08 (s, 3H)  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  161.7, 159.7, 157.8, 153.0, 151.2, 143.6, 138.5, 134.7, 130.8, 128.7, 128.4, 128.0, 127.4, 124.5, 112.8, 110.3, 44.7, 43.4, 19.6.

High-resolution mass spectra (HRMS) calcd for  $\text{C}_{22}\text{H}_{21}\text{N}_7$ :  $[\text{M} + \text{H}]^+$ , 384.1931; found, 384.1934.

## 2. In vitro assay protocols

### 2.1. Cell culture condition

Microglia cell-based assays for the concentration-dependent activity of the compounds were performed as previously described.<sup>5-9</sup> The murine microglial cell line BV-2 (Cell Resource Center of Chinese Academy Of Medical Science, Beijing, China ) was cultured at 37°C, 7%  $\text{CO}_2$  in  $\alpha$ MEM containing 10% fetal calf serum (Hyclone, UT, U.S.), 100 U/ml penicillin, and 100  $\mu\text{g}/\text{ml}$  streptomycin (Gibco, CA, U.S.).

### 2.2. Inhibition activity of IL-1 $\beta$ synthesis

Two days prior to treatment, the cells were trypsinized and plated in 96-well plates at a density of  $2 \times 10^4$  cells/well. After 48 h, the cells were rinsed with PBS, and 80  $\mu\text{l}$  of serum-free MEM was added. For each drug, one 96-well plate was used and ten different experimental conditions were tested (six wells per each condition): (1) control cells in plain  $\alpha$ MEM; (2) cells treated with media containing LPS (100 ng/ml); (3–9) cells treated with LPS (100 ng/ml)+one of seven different concentrations of

drug; and (10) cells treated with the highest concentration of drug in the absence of LPS. The drugs and LPS solutions were added to the BV-2 cells sequentially. The drug solutions (10  $\mu$ l) were added to the cells first, and then 10  $\mu$ l of a 1  $\mu$ g/ml LPS solution was added to all wells except for (1) and (10), where 10  $\mu$ l media was added. The cells were incubated for 16 h at 37°C. The levels of IL-1 $\beta$  in cell lysates were measured by ELISA (R&D systems, MN, U.S.) according to the manufacturers' instructions.

### **3. In vivo studies of compound 14<sup>10</sup>**

#### **3.1. Materials and methods**

##### **3.1.1. Materials**

Compound **14** was dissolved in 0.5% carboxymethylcellulose (CMC)-saline solution to the desired 2.5 mg/kg concentration. Donepezil (Eisai Pharmaceutical, Suzhou, China) was used as the positive control drug in this study. A $\beta$ <sub>1-42</sub> (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in sterile saline (0.9% NaCl) at a concentration of 1 mM, then sealed and stored at -20 °C. A $\beta$ <sub>1-42</sub> was incubated at 37 °C for 5 days before the injection to aggregate.

##### **3.1.2. Animals**

Healthy male Kunming mice (8 weeks old; body weight, 18 - 22 g at the start of experiments; Experimental Animal Center of Shenyang Pharmaceutical University, Shenyang, China) were used throughout the study. Animals were housed in a room maintained at a controlled temperature (23 $\pm$ 1 °C) and relative humidity of 45 $\pm$ 15% with a 12 h light/12 h dark cycle and were provided ad libitum access to standard laboratory food and water. Behavioral experiments were performed in a sound-attenuated and air-regulated experimental room to which mice were habituated

for  $\geq 1$  h. All animal studies were performed in strict accordance with the National Institutes of Health Guide for the use and care of laboratory animals and the guidelines established by the Chinese Society of Laboratory Animal Sciences.

### **3.2. Treatment**

Mice were randomly divided into four groups (n=10/group). The A $\beta$  model group received intracerebroventricular (i.c.v.) injection of 3  $\mu$ l of aggregated A $\beta_{1-42}$  (equivalent to 410 pmol/mouse). The mice were anesthetized with 3.5% chloral hydrate (i.p.) and fixed on a stereotactic instrument (Narishige, Tokyo, Japan). A $\beta_{1-42}$  was implanted into the right ventricle (A, -0.5 mm; L, 1 mm from the bregma; V, 3 mm from the skull). As a control, the sham-operated group of mice were injected i.c.v. with the vehicle (saline) only. The vehicle itself failed to induce any behavioral and neurochemical changes. The A $\beta$ +compound **14** (2.5 mg/kg body weight) group consisted of A $\beta$  model mice with per oral (p.o.) administration of compound **14** at 2.5 mg/kg. The A $\beta$  + donepezil (0.65 mg/kg) group was given p.o. donepezil at 0.65 mg/kg. The A $\beta$  model group and sham-operated group also received p.o. administration of the same volume of 0.5% CMC-saline solution. All compounds were administered at a volume of 0.1 ml/10 g body weight once a day from the day of i.c.v. A $\beta$  until the end of behavioral testing.

### **3.3. Morris water maze tests**

The experiment was carried out 9-13 days after the A $\beta_{1-42}$  injection. The apparatus was a circle water tank (100 cm diameter and 44 cm height), divided into four equal quadrants. During testing, the tank was filled with water ( $23 \pm 1$  °C). A transparent platform was set inside the tank and its top was submerged 1 cm below the water surface in the center of one among the four quadrants of the maze in the reference memory test. The movements of the animals in the tank were monitored with a video tracking system (purchased from Chinese Academy of Medical Sciences).

### **3.3.1. Reference memory tests**

The reference memory test was conducted three times a day for 4 consecutive days. In each trial, the mouse was placed in the water at one of the three starting positions that were equally spaced around the rim of the tank. The sequence of the positions was selected randomly. If the mouse found the platform within 60 s, it was allowed to remain there for 10 s and then returned to its home cage. If the mouse could not find the platform within 60 s, the trial was terminated and a maximum score of 60 s was assigned. The swimming distance, escape latency and swimming speed to the platform were recorded by a computer.

### **3.3.2. Probe tests**

After the 12th reference memory test training trial on day 13 after the A $\beta$ <sub>1-42</sub> injection, the platform was removed from the pool and each mouse underwent a 60 s spatial probe trial. The swimming percentage of path length and the time spent in the target quadrant where the platform was located during training were recorded.

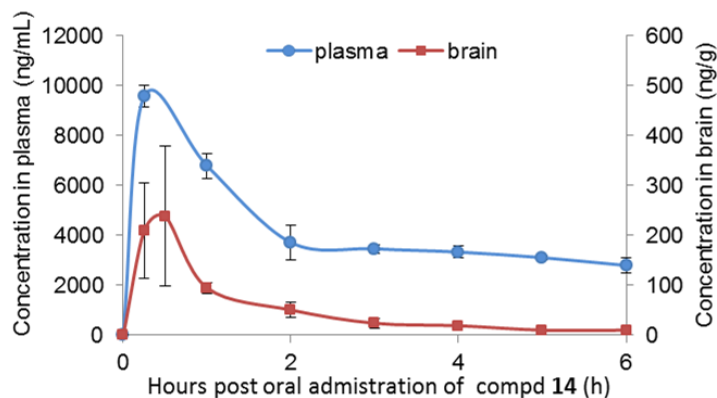
## **3.4. Statistical analysis**

All analyses were performed using IBM SPSS Statistics 17.0 software. All data are expressed as the means  $\pm$  S.E.M.. Significant differences among the experimental groups were tested using one-way analysis of variance ANOVA followed by the Bonferroni test. Escape latency and swimming distance in the Morris water maze were determined by two-way ANOVA with repeated measures (trial blocks). Values of  $P < 0.05$  were considered statistically significant.

## **4. Brain uptake assay**

Compound 14 was administered to mice (20g-30g) by oral gavage using 2.5mg/kg compound in 0.5% carboxymethylcellulose vehicle. At 0, 15, 30, 60, 120, 180, 240, 300, 360 min after administration, blood was collected in heparinized tubes from anesthetized animals and plasma obtained by centrifugation. After perfusion, brains

were immediately harvested, weighed and homogenized in 0.1% formic acid and deproteinized with ice-cold acetonitrile. The obtained mixture was then centrifuged to remove precipitated protein, and the brain homogenate supernatants were further diluted with 0.1% formic acid. The plasma samples were acidified with 0.1% formic acid. The solid phase extraction followed by HPLC analysis was used to quantify the amount of compound in the plasma and brain supernatants with compound 14 used as an internal standard.



**Figure S1.** Brain and plasma level of compound 14 after single dose oral administration of 2.5mg/kg. (●, concentration of compound in plasma, ng/mL; ■, concentration of compound 14 in brain, ng/g)

## 5. References

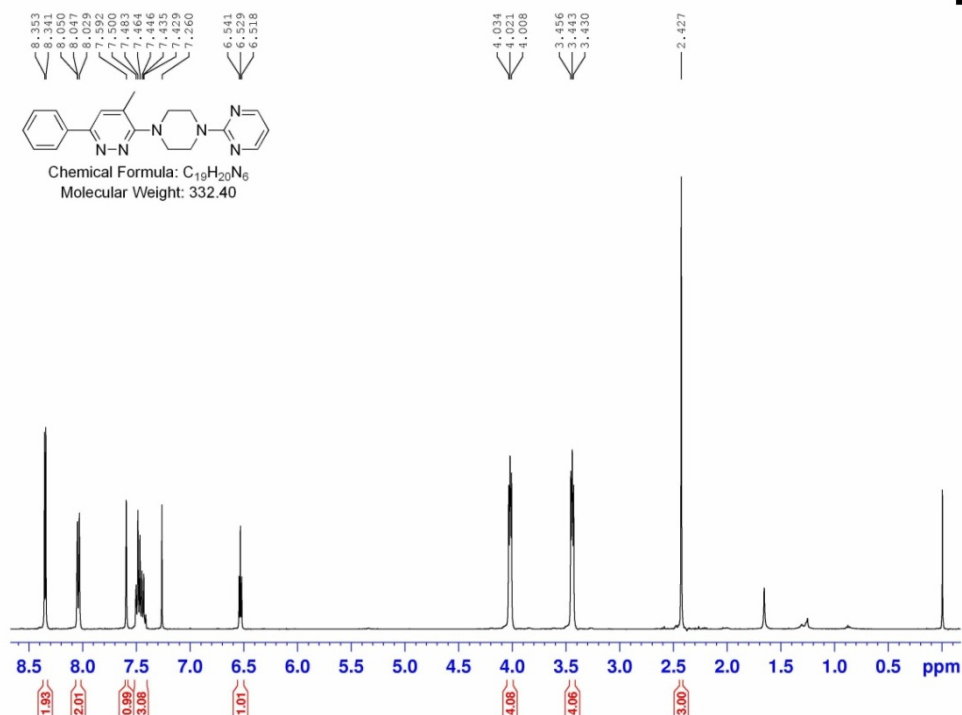
1. Johnston, K. A.; Allcock, R. W.; Jiang, Z.; Collier, I. D.; Blakli, H.; Rosair, G. M.; Bailey, P. D.; Morgan, K. M.; Kohno, Y.; Adams, D. R., Concise routes to pyrazolo[1,5-a]pyridin-3-yl pyridazin-3-ones. *Organic & Biomolecular Chemistry* **2008**, 6, (1).
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- 3-amino-6-phenyl-pyridazine derivative as a new synthetic antineuroinflammatory compound. *Journal of Medicinal Chemistry* **2002**, 45, (3), 563-566.
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## 6. NMR spectra of compounds 1b, 4-21

### 4-methyl-6-phenyl-3-(4-(pyrimidin-2-yl) piperazin-1-yl)pyridazine (1b)

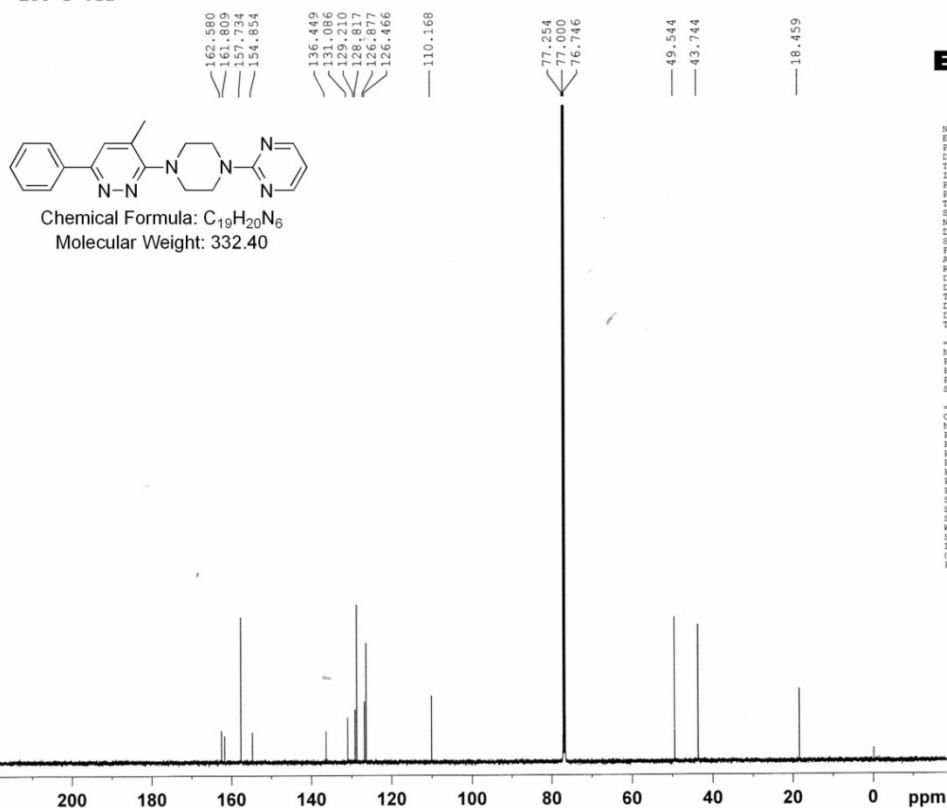
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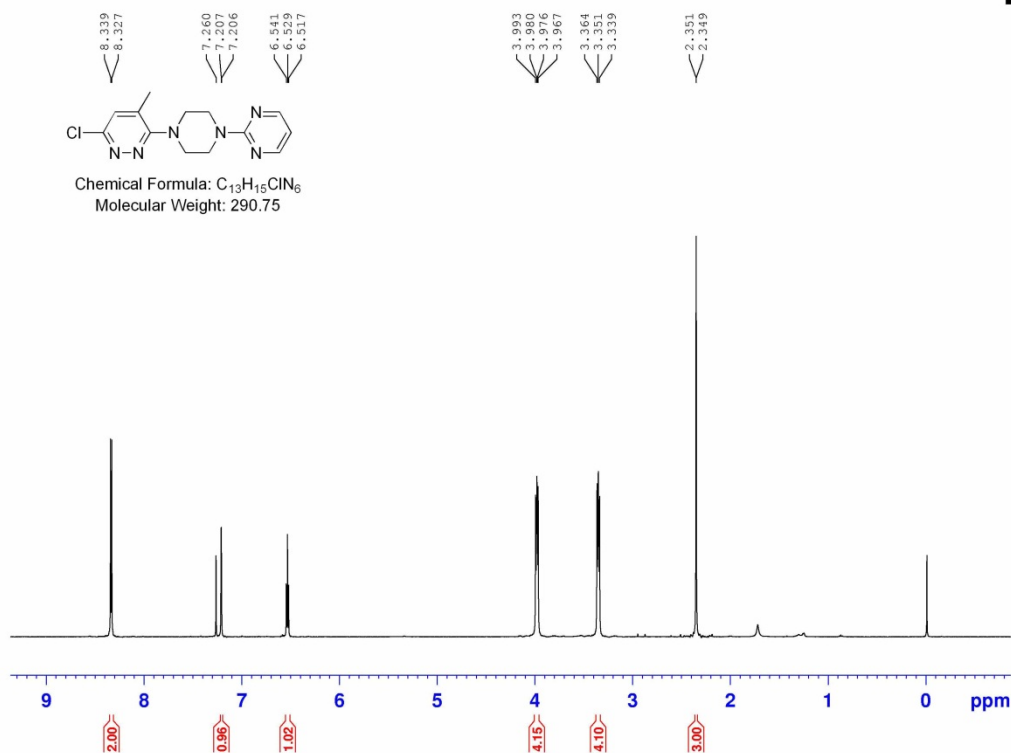
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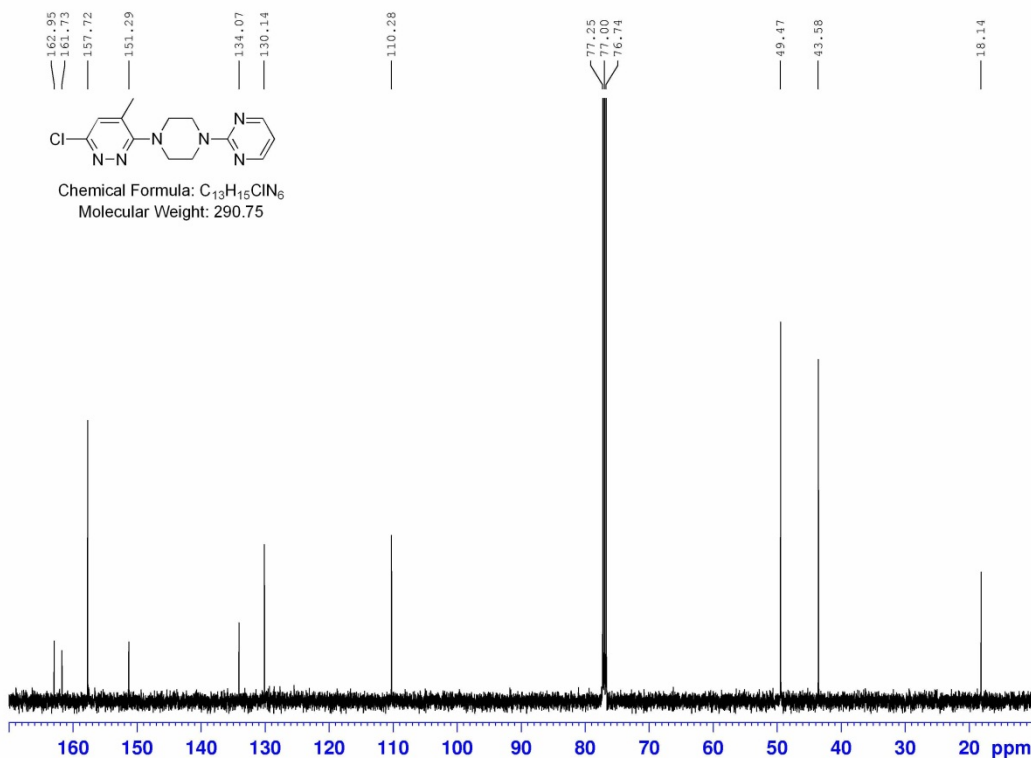
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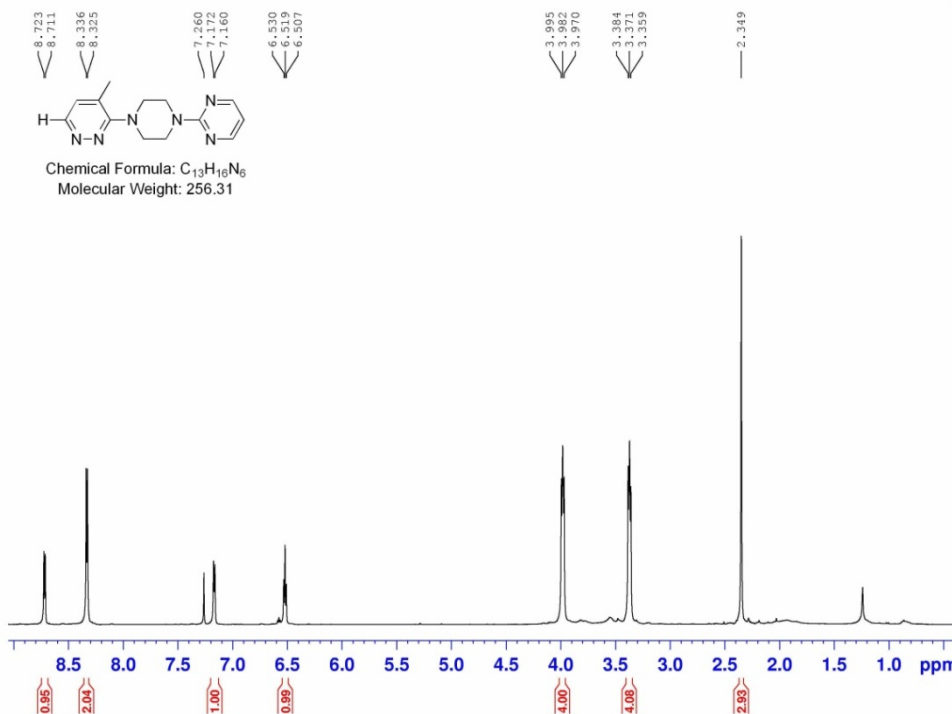
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PC 1.40

# 4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (5)

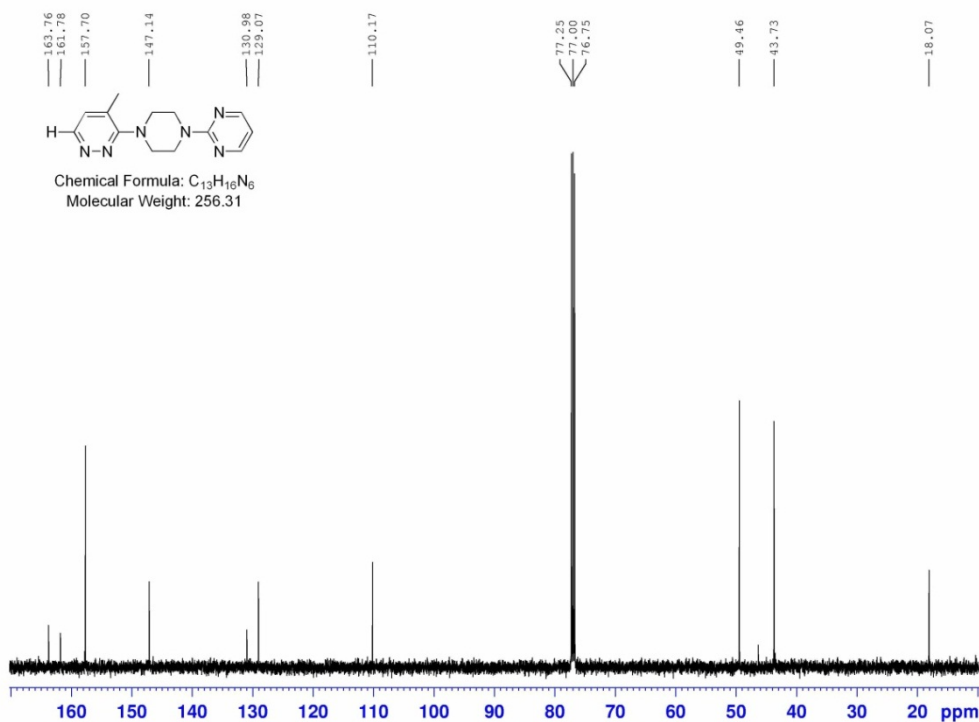
ZW-2-387



NAME ZW-2-387  
EXPNO 11  
PROCNO 1  
Date\_ 20111109  
Time 11.16  
INSTRUM spect  
PROBHD 5 mm PARBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl<sub>3</sub>  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 181  
LW 60.400 usec  
DE 6.50 usec  
TE 297.4 K  
D1 1.0000000 sec  
TD0 1

----- CHANNEL f1 -----  
NUC1 1H  
P1 14.50 usec  
PL1 0.00 dB  
PL1W 10.87646866 W  
SF01 400.1324710 MHz  
S1 32768  
SF 400.1300092 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

ZW-2-387



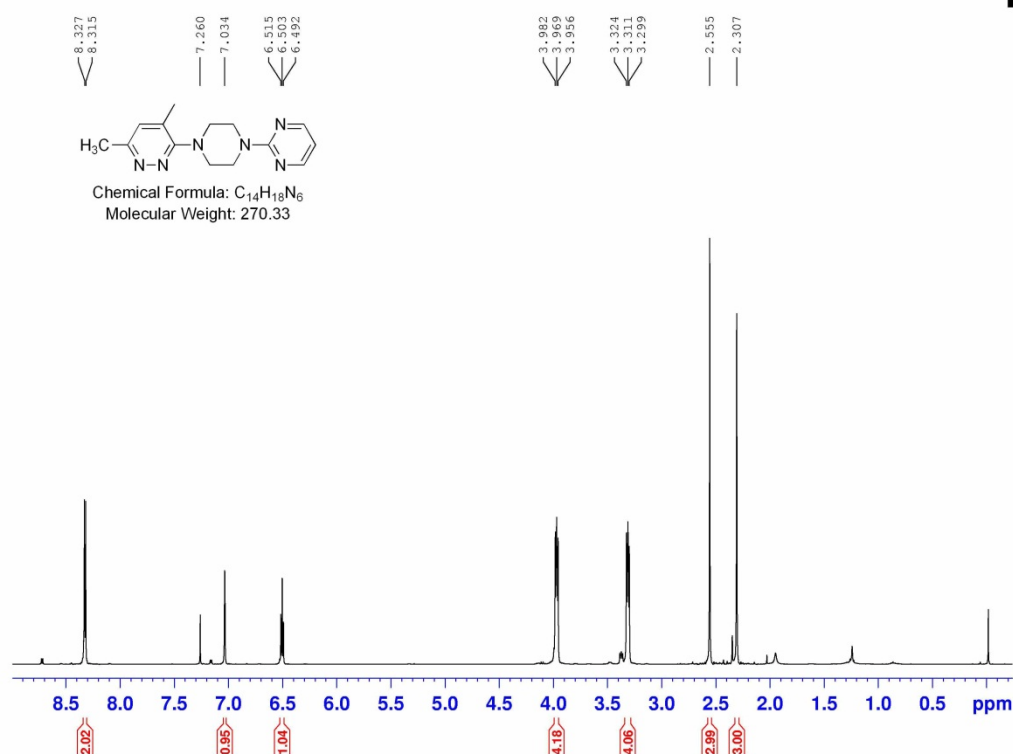
NAME ZW-2-387  
EXPNO 1  
PROCNO 1  
Date\_ 20111111  
Time 23.12  
INSTRUM spect  
PROBHD 5 mm PARBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl<sub>3</sub>  
NS 89  
DS 2  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010348 sec  
RG 201  
LW 16.800 usec  
DE 6.50 usec  
TE 296.1 K  
D1 2.0000000 sec  
D11 0.0300000 sec  
TD0 1

----- CHANNEL f1 -----  
NUC1 13C  
P1 11.57 usec  
PL1 0.00 dB  
PL1W 89.39463043 W  
SF01 125.7703643 MHz

----- CHANNEL f2 -----  
CPDPRG2 waltz1616  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.50 dB  
PL12 17.40 dB  
PL13 17.40 dB  
PL2W 13.02359581 W  
PL3W 0.42143536 W  
SF02 500.1320005 MHz  
S1 32768  
SF 125.7577966 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

# 6-dimethyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (6)

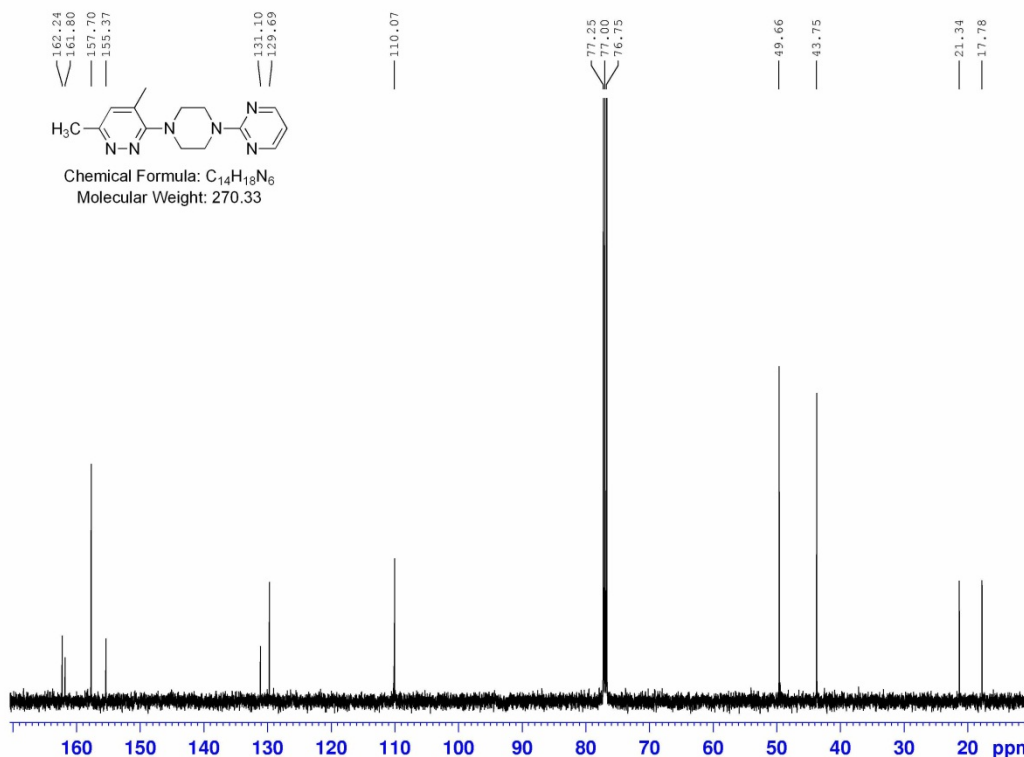
LSR-4-157



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NAME      LSR-4-157
EXPNO     1
PROCNO    1
Date_     20120507
Time      21.20
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zg30
TD         65536
SOLVENT    CDCl3
NS         16
DS         2
SWH         8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         114
DW         60.400 usec
DE         6.50 usec
TE         273.2 K
D1         1.00000000 sec
TD0
===== CHANNEL f1 =====
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300000 MHz
WDW        EM
SSB         0
LB         0.30 Hz
GB         0
PC         1.00
    
```

LSR-4-157

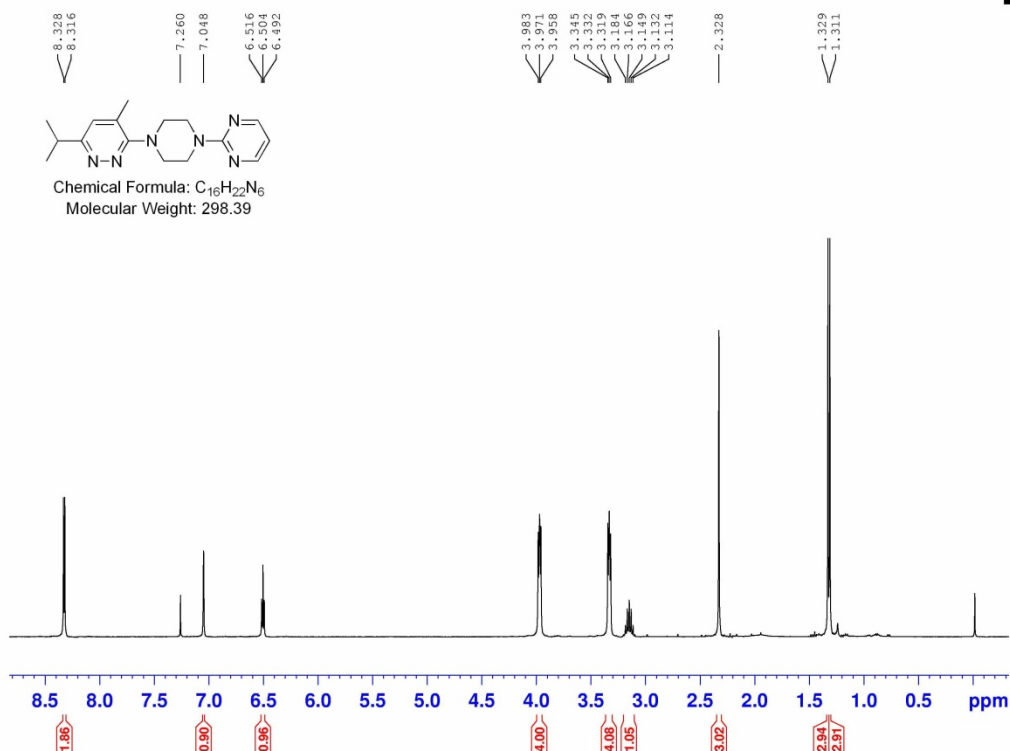


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NAME      LSR-4-157
EXPNO     1
PROCNO    1
Date_     20111227
Time      22.41
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zgpg30
TD         65536
SOLVENT    CDCl3
NS         104
DS         4
SWH         29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010548 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         297.6 K
D1         2.00000000 sec
D11        0.03000000 sec
TD0        1
===== CHANNEL f1 =====
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463043 W
SFO1       125.7703643 MHz
===== CHANNEL f2 =====
CPDPRG2    waltz16
NUC2       1H
PCPD2      80.00 usec
PL2        2.50 dB
PL12       17.40 dB
PL13       17.40 dB
PL2W       13.02359581 W
PL12W      0.42143336 W
PL13W      0.42143336 W
SFO2       500.1320000 MHz
SI         32768
SF         125.7577954 MHz
WDW        EM
SSB         0
LB         1.00 Hz
GB         0
PC         1.40
    
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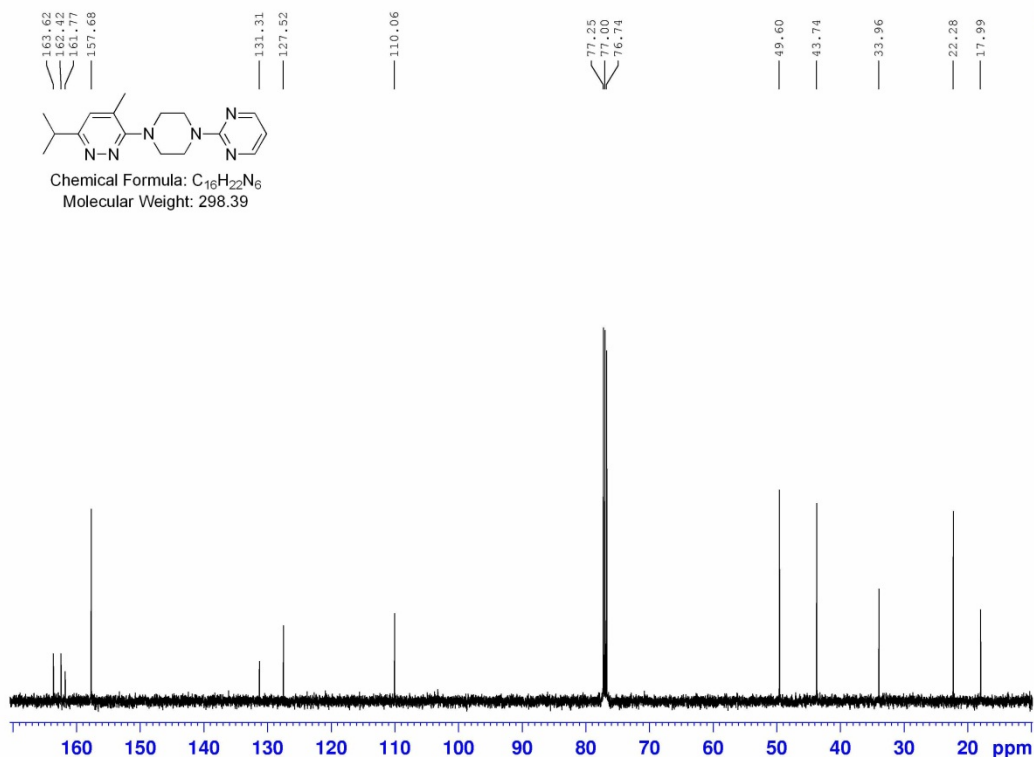
# 6-isopropyl-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (7)

ZW-2-395



NAME ZW-2-395  
EXPNO 13  
PROCNO 1  
Date\_ 20111109  
Time 11:30  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl<sub>3</sub>  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126514 Hz  
AQ 3.9584243 sec  
RG 90.5  
DW 60.400 usec  
DE 6.50 usec  
TE 297.4 K  
D1 1.0000000 sec  
TDO  
----- CHANNEL f1 -----  
NUC1 1H  
P1 14.50 usec  
PL1 0.00 dB  
PL1W 10.87646866 W  
SFO1 400.1324710 MHz  
SI 32768  
SF 400.1300093 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

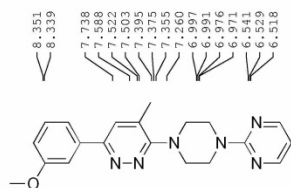
ZW-2-395



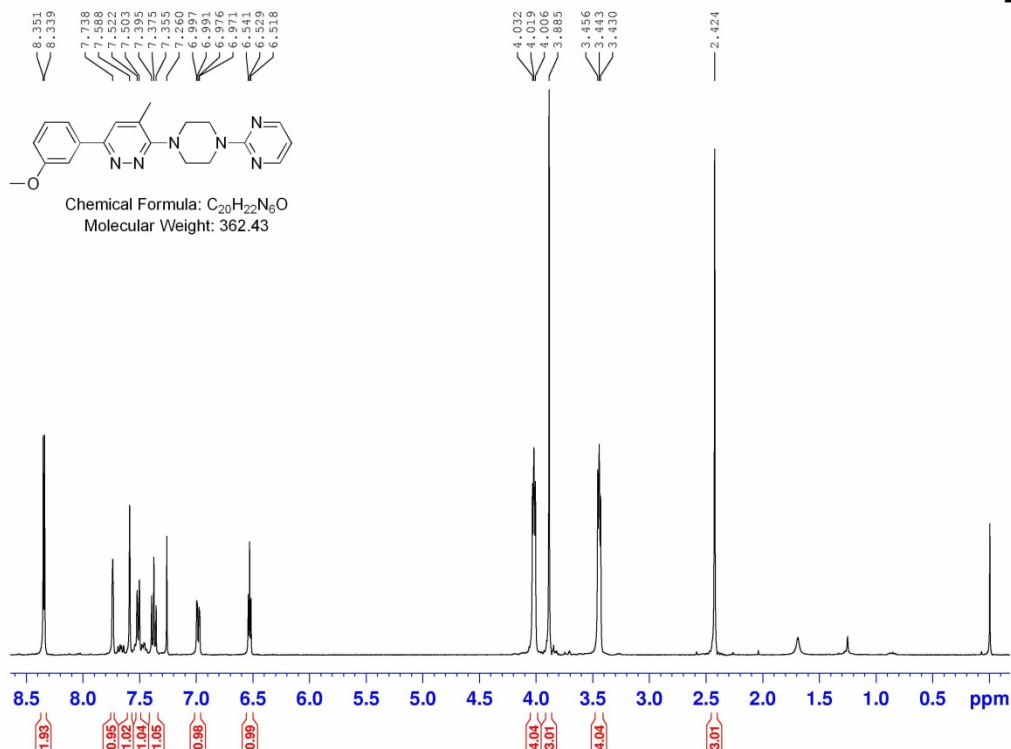
NAME ZW-2-395  
EXPNO 1  
PROCNO 1  
Date\_ 20111111  
Time 23:21  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl<sub>3</sub>  
NS 86  
DS 2  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 295.9 K  
D1 2.0000000 sec  
D11 0.0300000 sec  
TDO 1  
----- CHANNEL f1 -----  
NUC1 13C  
P1 11.57 usec  
PL1 0.00 dB  
PL1W 83.39463043 W  
SFO1 125.7703643 MHz  
----- CHANNEL f2 -----  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.50 dB  
PL12 17.40 dB  
PL13 17.40 dB  
PL2W 13.02359581 W  
PL12W 0.42143536 W  
PL13W 0.42143536 W  
SFO2 500.1320093 MHz  
SI 32768  
SF 125.7577976 MHz  
WDW RM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

# 6-(3-methoxyphenyl)-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (8)

ZGF-2-029



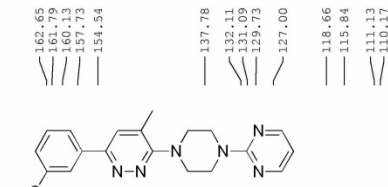
Chemical Formula:  $C_{20}H_{22}N_6O$   
Molecular Weight: 362.43



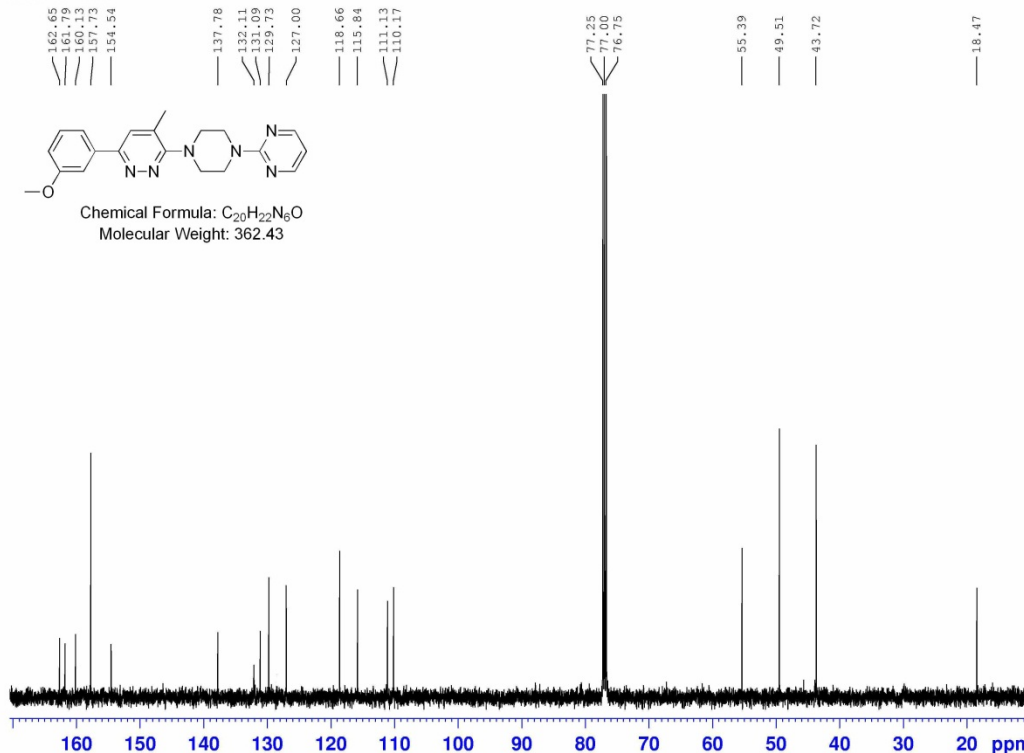
```

NAME      ZGF-2-029
EXPNO     1
PROCNO    1
Date_     20111109
Time      11.44
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zg30
TD         65536
SOLVENT    CDCl3
NS         16
DS         2
SWH        8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         228.1
DW         60.400 usec
DE         6.50 usec
TE         297.3 K
D1         1.00000000 sec
TD0        1
===== CHANNEL f1 =====
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300038 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
    
```

ZGF-2-029



Chemical Formula:  $C_{20}H_{22}N_6O$   
Molecular Weight: 362.43

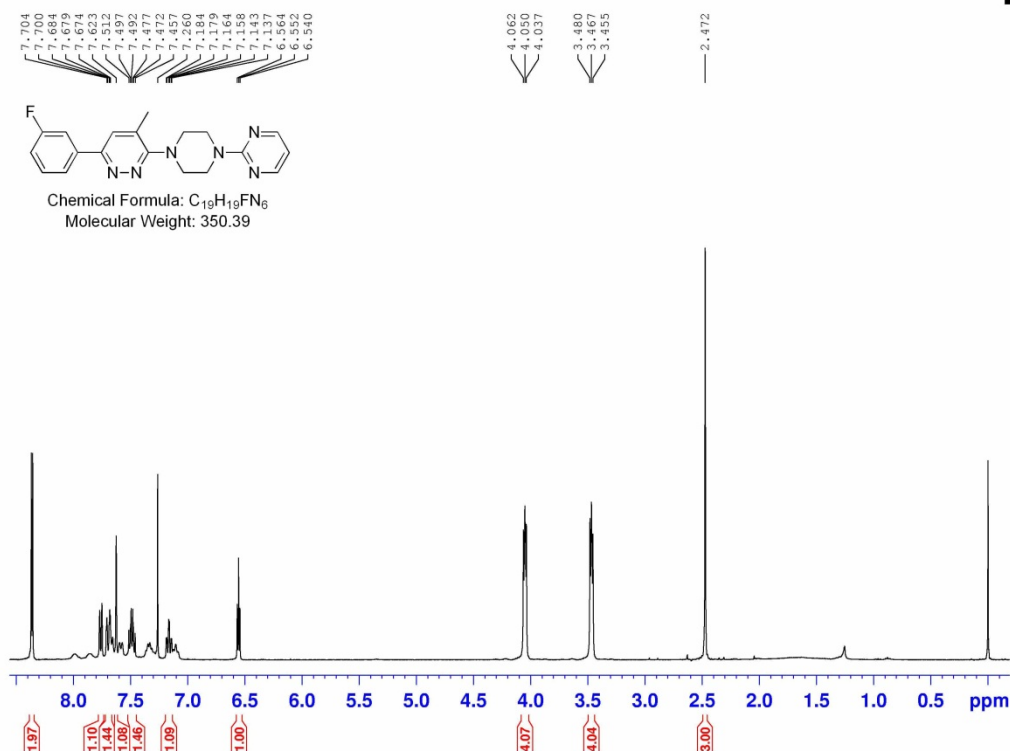


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NAME      ZGF-2-029
EXPNO     1
PROCNO    1
Date_     20111111
Time      23.35
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zgpg30
TD         65536
SOLVENT    CDCl3
NS         120
DS         2
SWH        29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010348 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         296.2 K
D1         2.00000000 sec
D11        0.03000000 sec
TD0        1
===== CHANNEL f1 =====
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463943 W
SFO1       125.7703643 MHz
===== CHANNEL f2 =====
CPDPRG2    waltz16
NUC2       1H
PCPD2      80.00 usec
PL2        2.50 dB
PL12       17.40 dB
PL13       17.40 dB
PL2W       13.02359581 W
PL12W      0.42143336 W
PL13W      0.42143336 W
SFO2       500.1320095 MHz
SI         32768
SF         125.7577956 MHz
WDW        RM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
    
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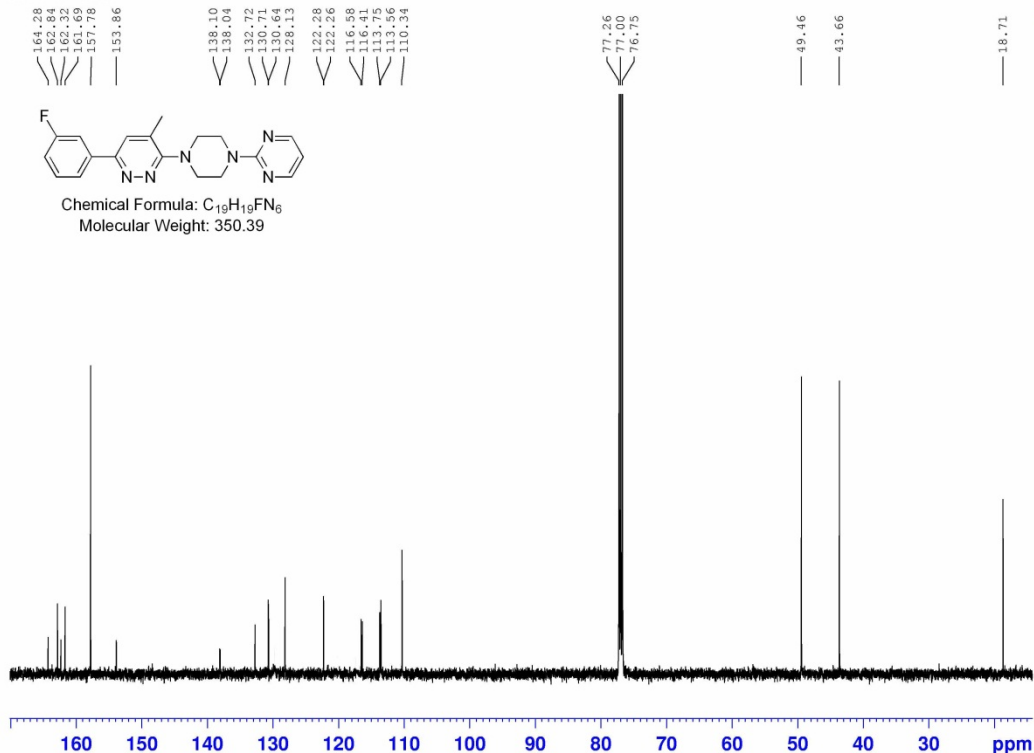
# 6-(3-fluorophenyl)-4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (9)

ZGF-6-033



NAME ZGF-6-033  
EXPNO 16  
PROCNO 1  
Date\_ 20111109  
Time 12.52  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 256  
DW 60.400 usec  
DE 6.50 usec  
TE 297.4 K  
D1 1.00000000 sec  
TDO  
----- CHANNEL f1 -----  
NUC1 1H  
P1 14.50 usec  
PL1 0.00 dB  
PL1W 10.8764686 W  
SFO1 400.1324710 MHz  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

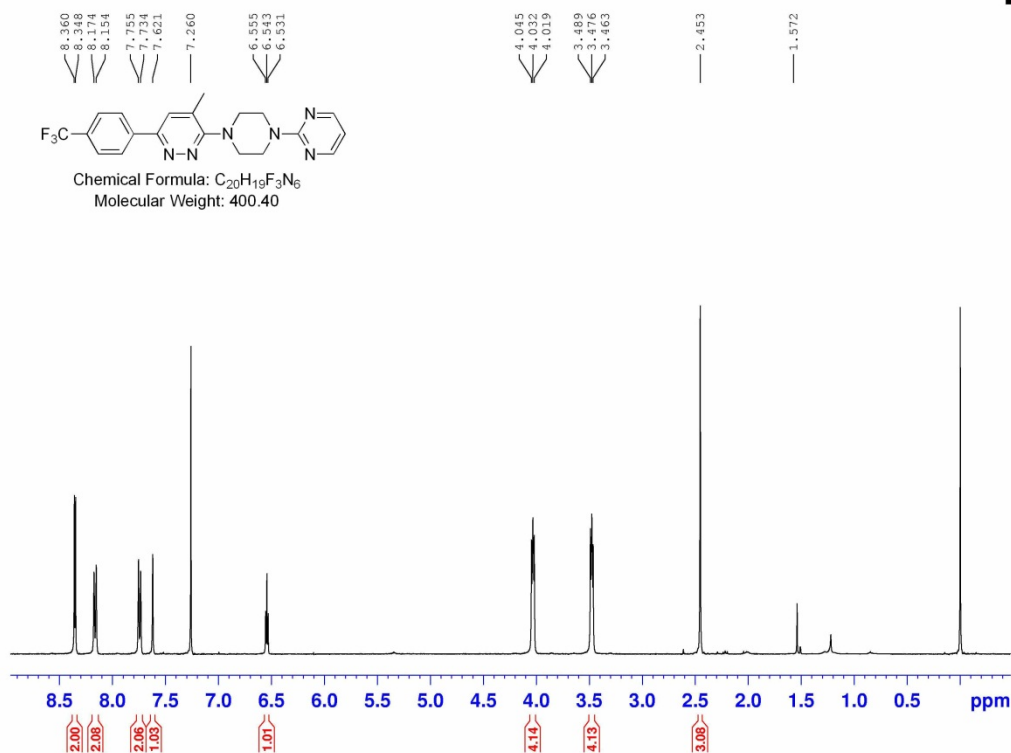
ZGF-6-033



NAME ZGF-6-033  
EXPNO 1  
PROCNO 1  
Date\_ 20111112  
Time 0.17  
INSTRUM Spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 1000  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 296.5 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TDO 1  
----- CHANNEL f1 -----  
NUC1 13C  
P1 11.57 usec  
PL1 0.00 dB  
PL1W 83.39463043 W  
SFO1 125.7703643 MHz  
----- CHANNEL f2 -----  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.50 dB  
PL12 17.40 dB  
PL13 17.40 dB  
PL2W 13.02359581 W  
PL12W 0.42143536 W  
PL13W 0.42143536 W  
SFO2 500.1320000 MHz  
SI 32768  
SF 125.7577936 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

# 4-methyl-6-(4-(trifluoromethyl)phenyl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (10)

LSR-5-154

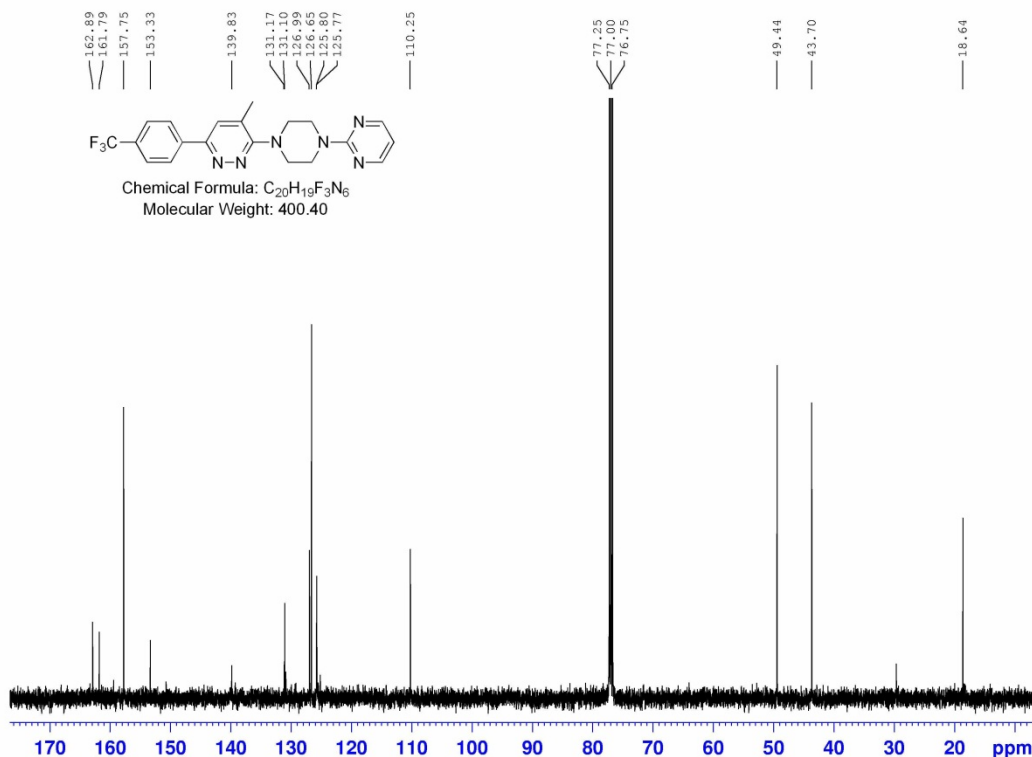


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NAME      LSR-5-154
EXPNO     1
PROCNO    1
Date_     20120507
Time      21.02
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zg30
TD         65536
SOLVENT    CDCl3
NS         16
DS         2
SWH        8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         362
DW         60.400 usec
DE         6.50 usec
TE         273.2 K
D1         1.00000000 sec
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LSR-5-154

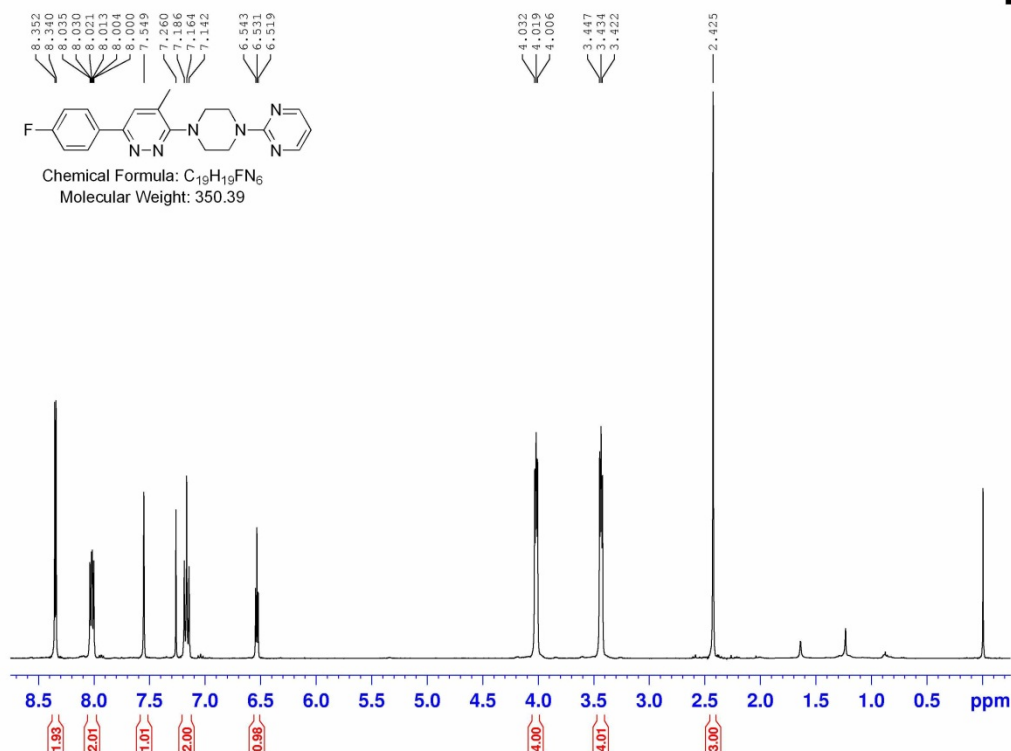


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NAME      LSR-5-154
EXPNO     1
PROCNO    1
Date_     20111227
Time      23.43
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zgpg30
TD         65536
SOLVENT    CDCl3
NS         223
DS         4
SWH        29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010548 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         297.7 K
D1         2.00000000 sec
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# 4-methyl-6-(4-fluorophenyl)-3-(4-(pyrimidin-2-yl) piperazin-1-yl)pyridazine (11)

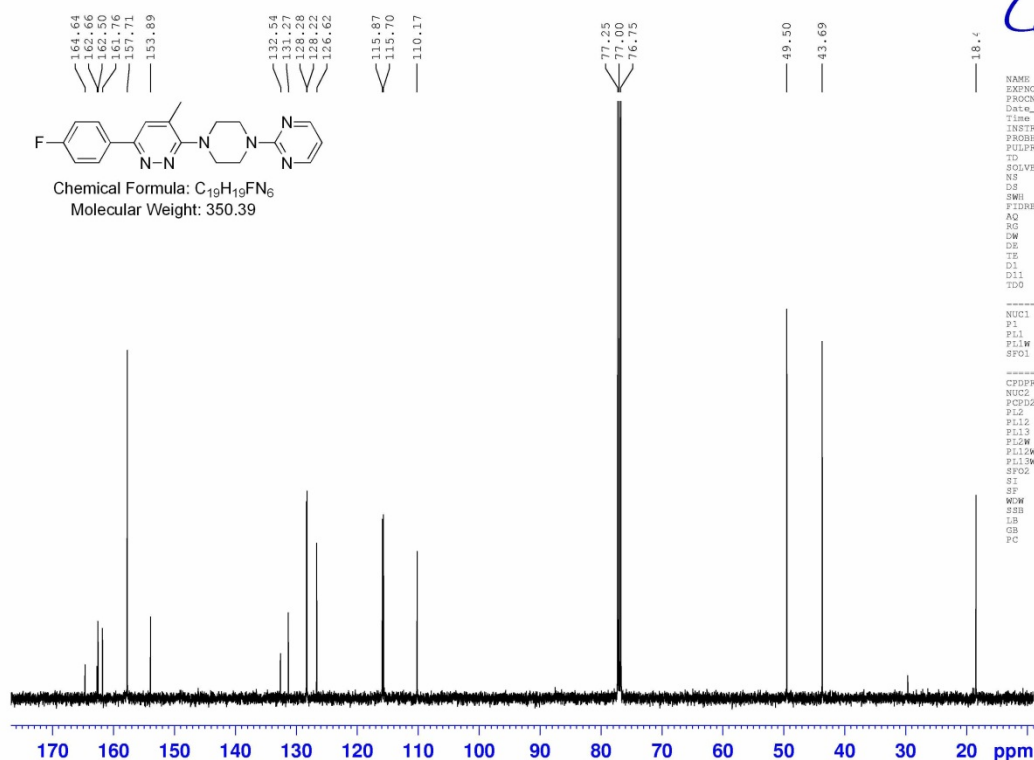
LSR-5-157



```

NAME      LSR-5-157
EXPNO     1
PROCNO    1
Date_     20120507
Time      21.08
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zg30
TD         65536
SOLVENT    CDCl3
NS         16
DS         2
SWH         8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         256
DW         60.400 usec
DE         6.50 usec
TE         273.2 K
D1         1.00000000 sec
TDO
===== CHANNEL f1 =====
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300000 MHz
WDW        EM
SSB         0
LB         0.30 Hz
GB         0
PC         1.00
    
```

LSR-5-157

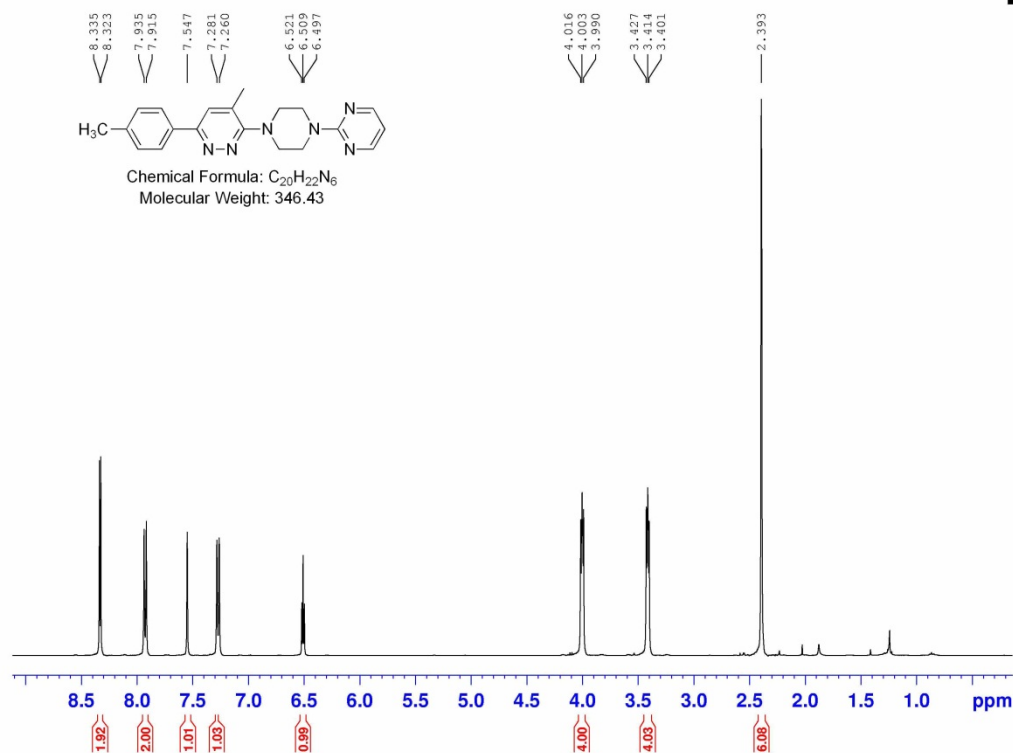


```

NAME      LSR-5-157
EXPNO     1
PROCNO    1
Date_     20111228
Time      15.32
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zgpg30
TD         65536
SOLVENT    CDCl3
NS         129
DS         2
SWH         29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010548 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         297.1 K
D1         2.00000000 sec
D11        0.03000000 sec
TDO
===== CHANNEL f1 =====
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463043 W
SFO1       125.7703643 MHz
===== CHANNEL f2 =====
CPDPRG2    waltz16
NUC2       1H
PCPD2      80.00 usec
PL2        2.50 dB
PL12       17.40 dB
PL13       17.40 dB
PL2W       13.02359581 W
PL12W      0.42143336 W
PL13W      0.42143336 W
SFO2       500.1320000 MHz
SI         32768
SF         125.7577972 MHz
WDW        RM
SSB         0
LB         1.00 Hz
GB         0
PC         1.40
    
```

# 4-methyl-6-(p-tolyl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (12)

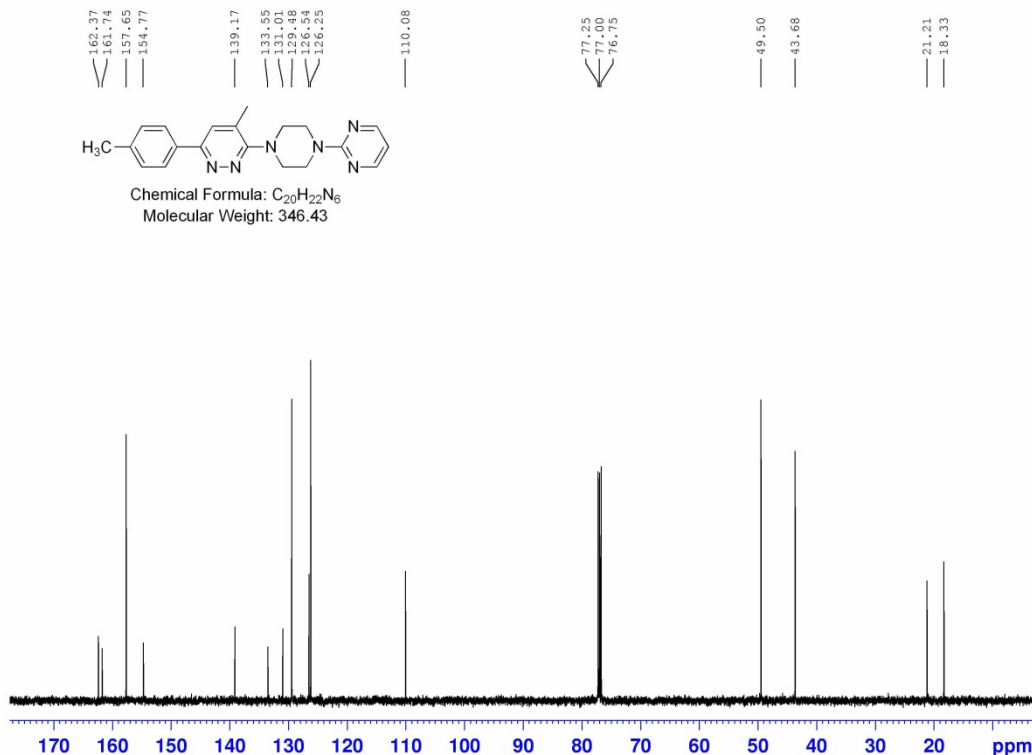
LH-1-079



```

NAME      LH-1-079
EXPNO     1
PROCNO    1
Date_     20120507
Time      21.33
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zg30
TD          65536
SOLVENT    CDCl3
NS          16
DS          2
SWH         8278.146 Hz
FIDRES      0.126314 Hz
AQ          3.9584243 sec
RG          71.8
DW          60.400 usec
DE          6.50 usec
TE          273.2 K
D1          1.00000000 sec
TDO         0
===== CHANNEL f1 =====
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300102 MHz
WDW        EM
SSB         0
LB          0.30 Hz
GB          0
PC          1.00
    
```

LH-1-079

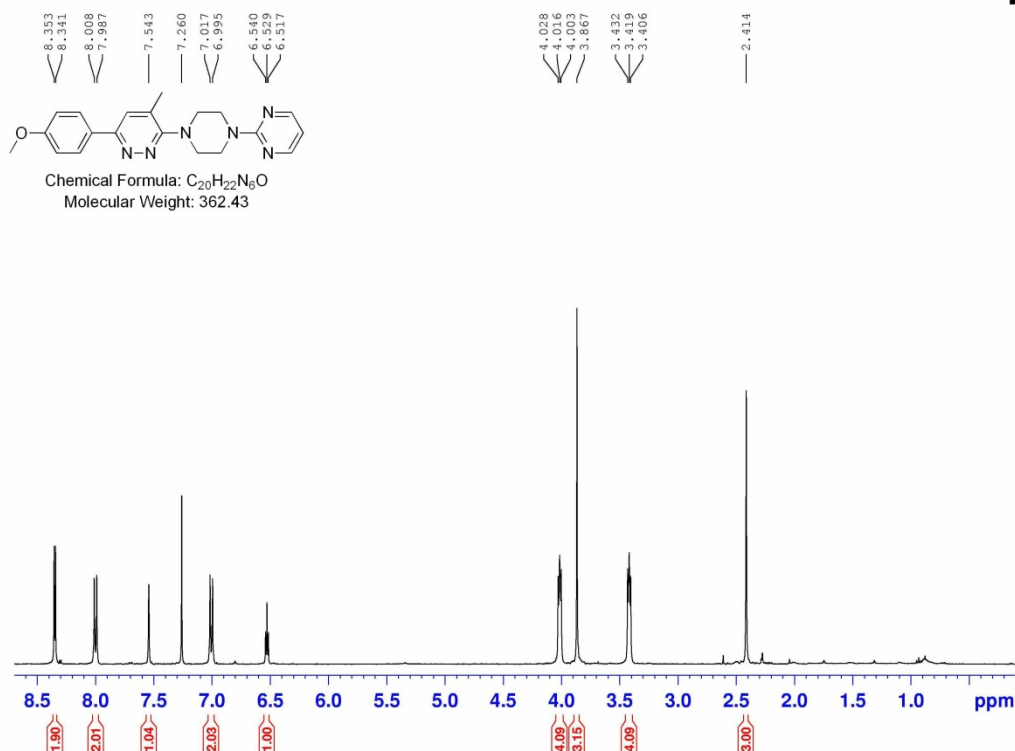


```

NAME      LH-1-079
EXPNO     1
PROCNO    1
Date_     20111227
Time      22.16
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zgpg30
TD          65536
SOLVENT    CDCl3
NS          64
DS          4
SWH         29761.904 Hz
FIDRES      0.454131 Hz
AQ          1.1010548 sec
RG          203
DW          16.800 usec
DE          6.50 usec
TE          297.7 K
D1          2.00000000 sec
D11        0.03000000 sec
TDO         1
===== CHANNEL f1 =====
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463043 W
SFO1       125.7703643 MHz
===== CHANNEL f2 =====
CPDPRG2    waltz16
NUC2        1H
PCPD2       80.00 usec
PL2         2.50 dB
PL12        17.40 dB
PL13        17.40 dB
PL2W       13.02359581 W
PL12W       0.42143536 W
PL13W       0.42143536 W
SFO2       500.1320093 MHz
SI         32768
SF         125.7578017 MHz
WDW        RM
SSB         0
LB          1.00 Hz
GB          0
PC          1.40
    
```

# 4-methyl-6-(4-methoxyphenyl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (13)

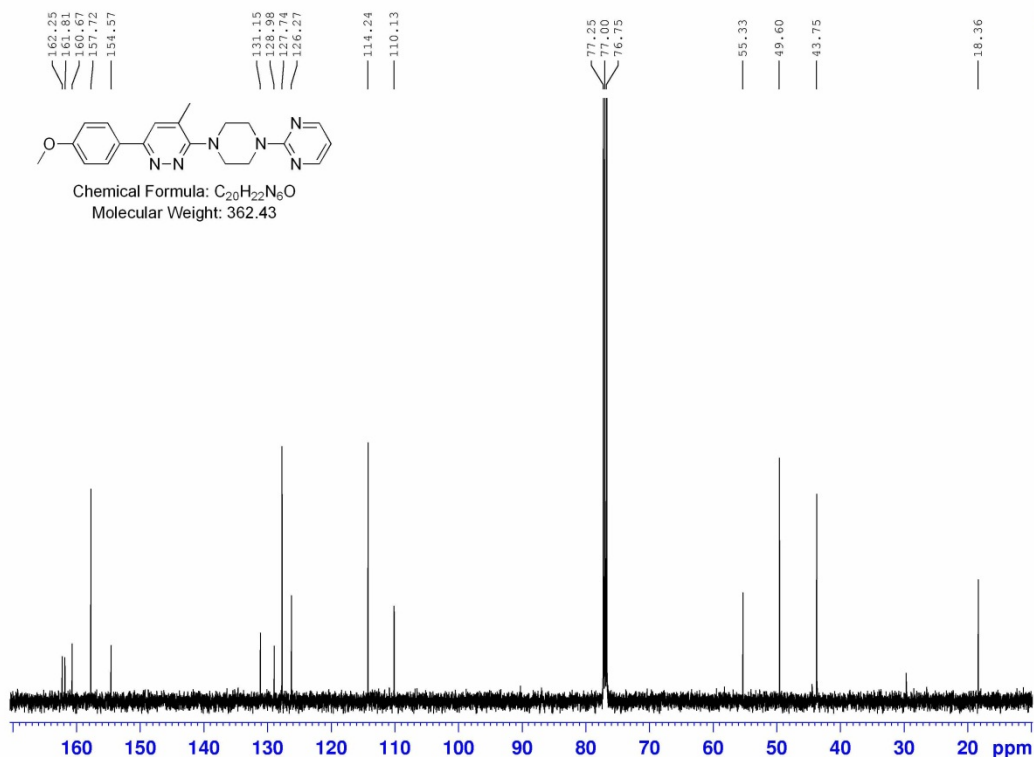
LH-1-083



NAME LH-1-083  
EXPNO 70  
PROCNO 1  
Date\_ 20120507  
Time 21.27  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 322.5  
DW 60.400 usec  
DE 6.50 usec  
TE 297.2 K  
D1 1.00000000 sec  
TDO

CHANNEL f1  
NUC1 1H  
P1 14.50 usec  
PL1 0.00 dB  
PL1W 10.8764686 W  
SFO1 400.1324710 MHz  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

LH-1-083



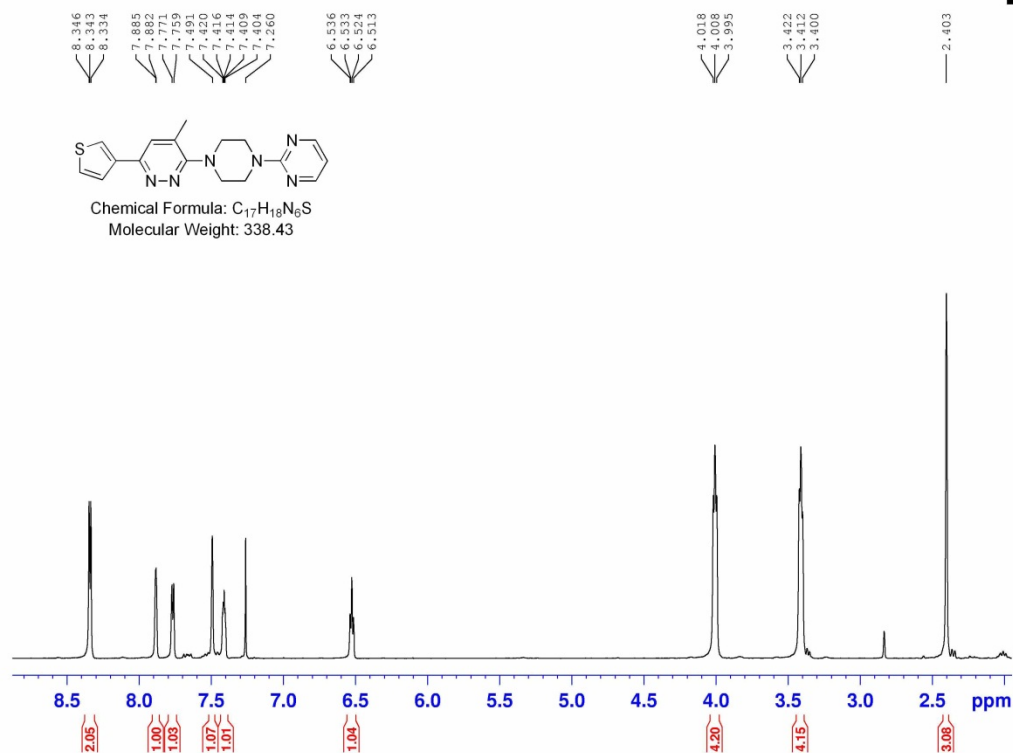
NAME LH-1-083  
EXPNO 1  
PROCNO 1  
Date\_ 20111227  
Time 22.29  
INSTRUM Spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 136  
DS 2  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 297.2 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TDO 1

CHANNEL f1  
NUC1 13C  
P1 11.57 usec  
PL1 0.00 dB  
PL1W 83.39463043 W  
SFO1 125.7703643 MHz

CHANNEL f2  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.50 dB  
PL12 17.40 dB  
PL13 17.40 dB  
PL2W 13.02359581 W  
PL12W 0.42143536 W  
PL13W 0.42143536 W  
SFO2 500.1320000 MHz  
SI 32768  
SF 125.7577949 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

# 4-methyl-6-(thiophen-3-yl)-3-(4-(pyrimidin-2-yl) piperazin-1-yl)pyridazine (14)

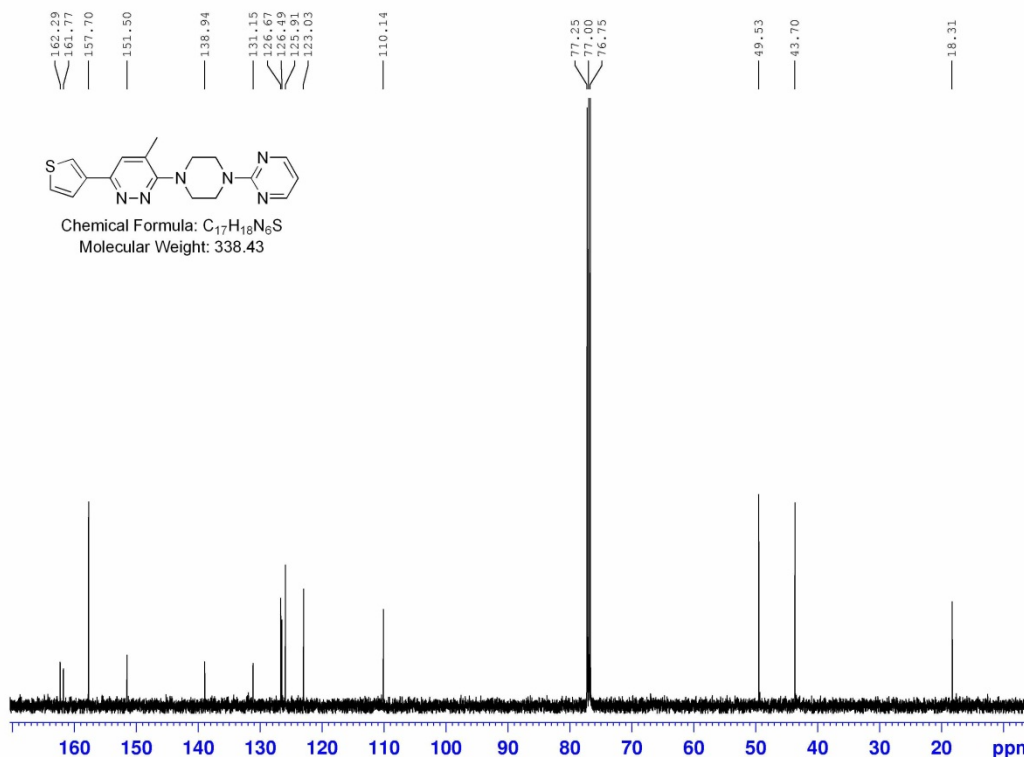
LH-1-069



```

NAME      LH-1-069
EXPNO     1
PROCNO    1
Date_     20120508
Time      9.44
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         2
SWH        8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         228.1
DW         60.400 usec
DE         6.50 usec
TE         673.2 K
D1         1.0000000 sec
TDO        0
===== CHANNEL f1 =====
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300000 MHz
WDW        EM
SSB         0
LB         0.30 Hz
GB         0
PC         1.00
    
```

LH-1-069

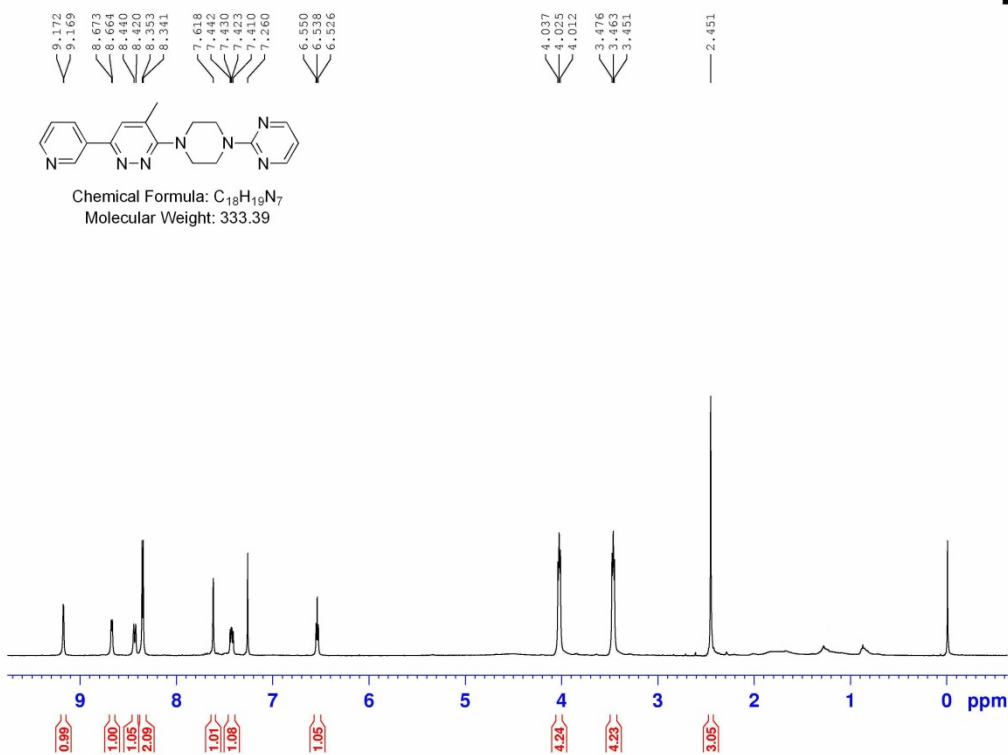


```

NAME      LH-1-069
EXPNO     1
PROCNO    1
Date_     20111227
Time      22.22
INSTRUM   Spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         64
DS         2
SWH        29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010548 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         298.0 K
D1         2.0000000 sec
D11        0.0300000 sec
TDO        1
===== CHANNEL f1 =====
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463043 W
SFO1       125.7703643 MHz
===== CHANNEL f2 =====
CPDPRG2   waltz16
NUC2       1H
PCPD2      80.00 usec
PL2        2.50 dB
PL12       17.40 dB
PL13       17.40 dB
PL2W       13.02359581 W
PL12W      0.42143536 W
PL13W      0.42143536 W
SFO2       500.1320000 MHz
SI         32768
SF         125.7577971 MHz
WDW        RM
SSB         0
LB         1.00 Hz
GB         0
PC         1.40
    
```

# 4-methyl-6-(pyridin-3-yl)-3-(4-(piperazin-1-yl)pyridazine (15)

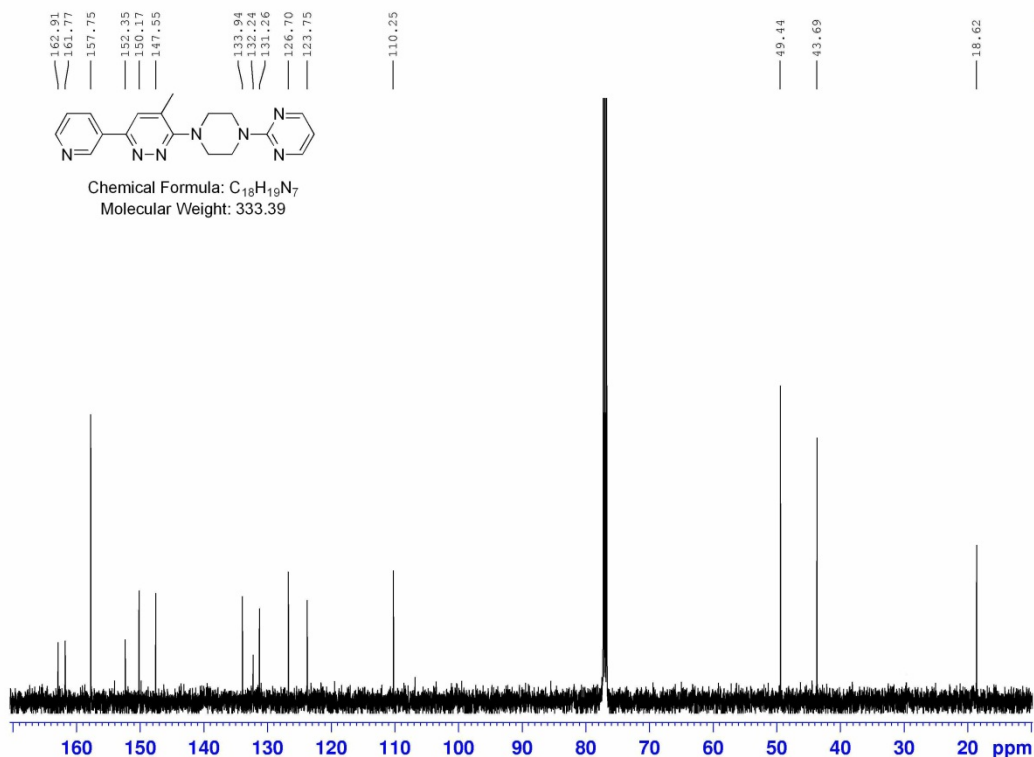
ZGF-6-040



```

NAME      ZGF-6-040
EXPNO     1
PROCNO    1
Date_     20111109
Time      12.37
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zg30
TD         65536
SOLVENT    CDCl3
NS         16
DS         2
SWH        8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         256
DW         60.400 usec
DE         6.50 usec
TE         297.4 K
D1         1.00000000 sec
TDO
----- CHANNEL f1 -----
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300930 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
    
```

ZGF-6-040

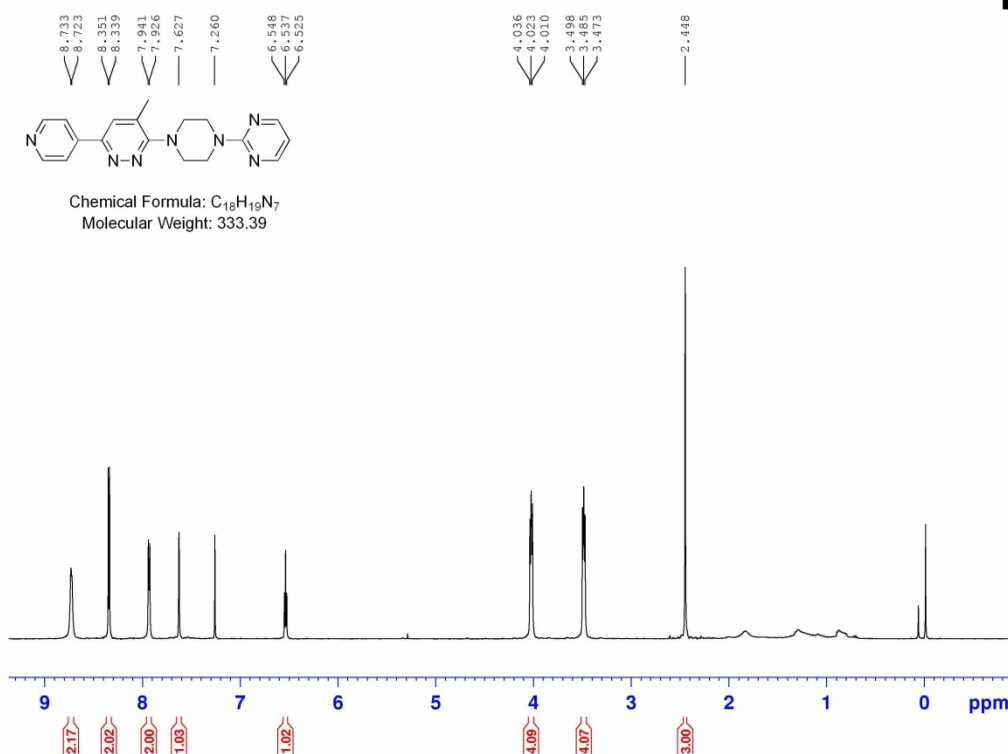


```

NAME      ZGF-6-040
EXPNO     1
PROCNO    1
Date_     20111111
Time      23.44
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zgpg30
TD         65536
SOLVENT    CDCl3
NS         263
DS         4
SWH        29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010548 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         296.2 K
D1         2.00000000 sec
D11        0.03000000 sec
TDO        1
----- CHANNEL f1 -----
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463043 W
SFO1       125.7703643 MHz
----- CHANNEL f2 -----
CPDPRG2    waltz16
NUC2       1H
PCPD2      80.00 usec
PL2        2.50 dB
PL12       17.40 dB
PL13       17.40 dB
PL2W       13.02359581 W
PL12W      0.42143336 W
PL13W      0.42143336 W
SFO2       500.1320093 MHz
SI         32768
SF         125.7577944 MHz
WDW        RM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
    
```

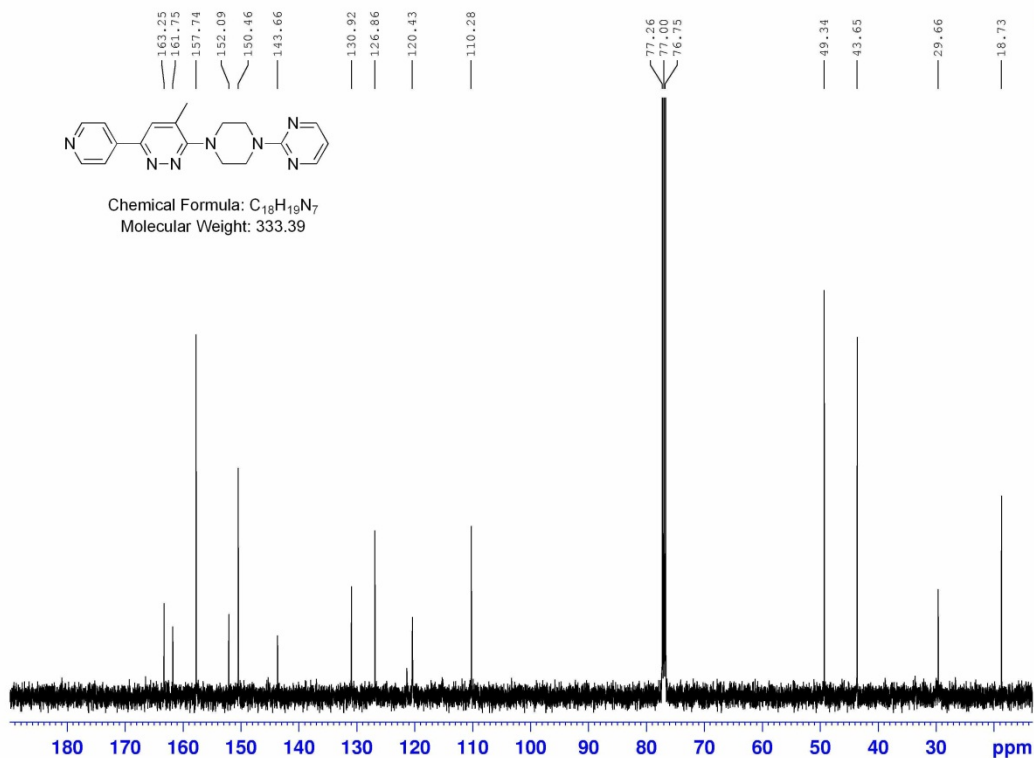
# 4-methyl-6-(pyridin-4-yl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (16)

ZGF-6-036



NAME ZGF-6-036  
EXPNO 17  
PROCNO 1  
Date\_ 20111109  
Time 12.45  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 181  
DW 60.400 usec  
DE 6.50 usec  
TE 297.5 K  
D1 1.00000000 sec  
TDO  
----- CHANNEL f1 -----  
NUC1 1H  
P1 14.50 usec  
PL1 0.00 dB  
PL1W 10.87646866 W  
SFO1 400.1324710 MHz  
SI 32768  
SF 400.1300092 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

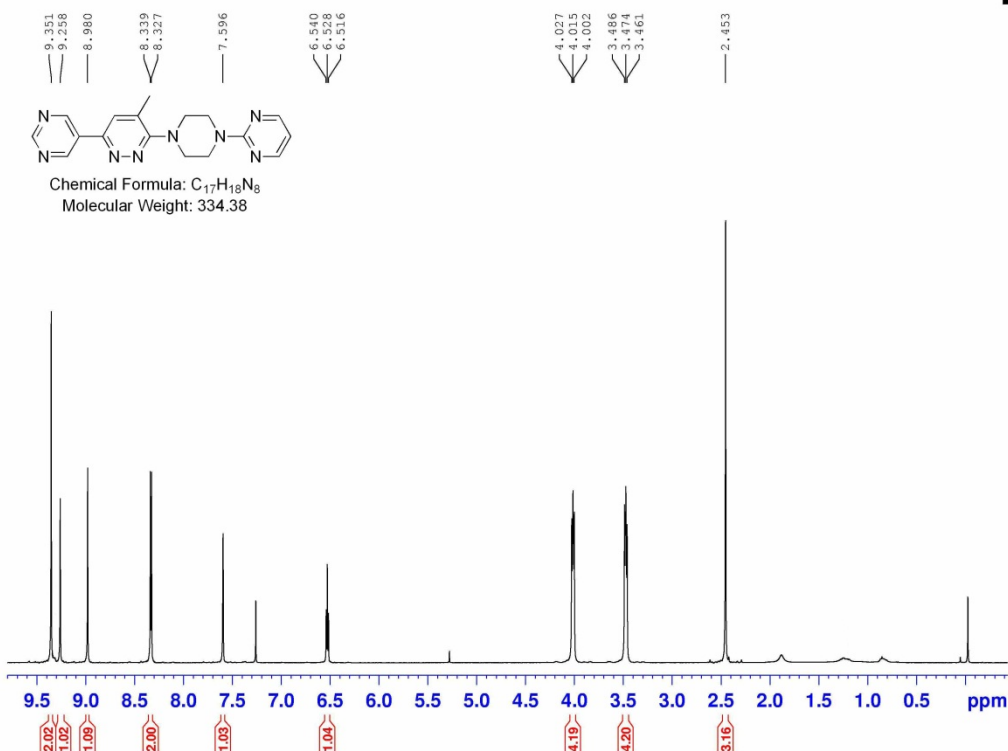
ZGF-6-036



NAME ZGF-6-036  
EXPNO 1  
PROCNO 1  
Date\_ 20111112  
Time 0.02  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 206  
DS 2  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 296.2 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TDO 1  
----- CHANNEL f1 -----  
NUC1 13C  
P1 11.57 usec  
PL1 0.00 dB  
PL1W 83.39463043 W  
SFO1 125.7703643 MHz  
----- CHANNEL f2 -----  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.50 dB  
PL12 17.40 dB  
PL13 17.40 dB  
PL2W 13.02359581 W  
PL12W 0.42143336 W  
PL13W 0.42143336 W  
SFO2 500.1320093 MHz  
SI 32768  
SF 125.7577955 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

# 4-methyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)-6-(pyrimidin-5-yl)pyridazine (17)

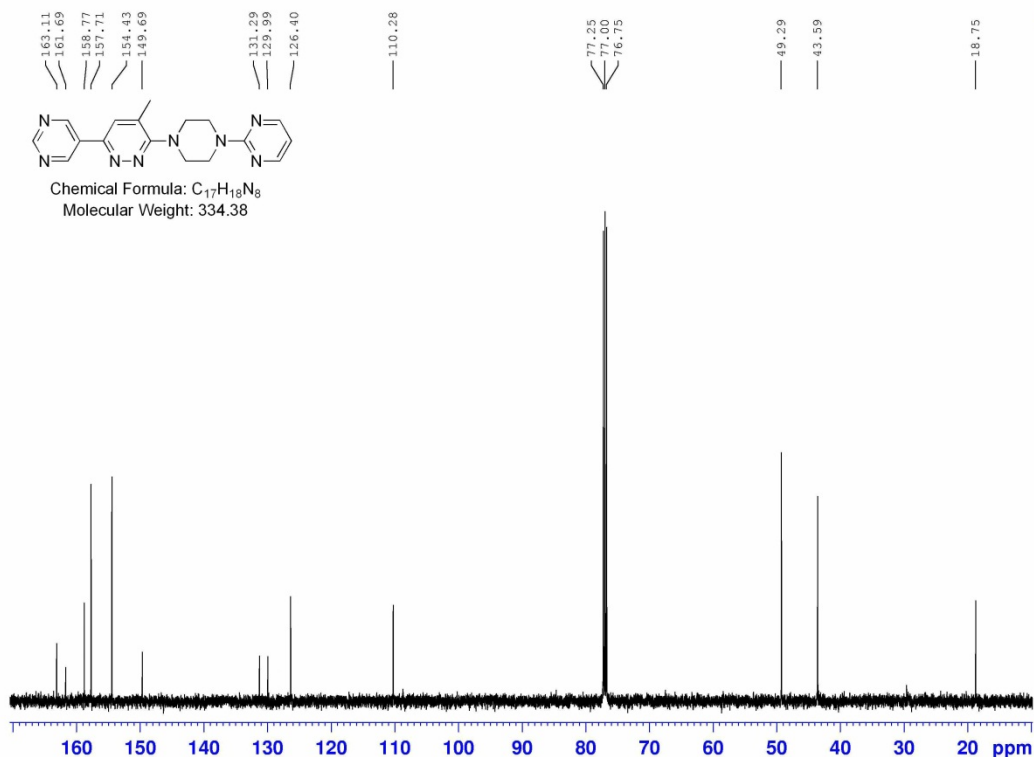
ZW-2-399



```

NAME      ZW-2-399
EXPNO     14
PROCNO    1
Date_     20111109
Time      11.38
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zg30
TD         65536
SOLVENT    CDCl3
NS         16
DS         2
SWH         8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         114
DW         60.400 usec
DE         6.50 usec
TE         297.4 K
D1         1.00000000 sec
TD0
===== CHANNEL f1 =====
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300092 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
    
```

ZW-2-399

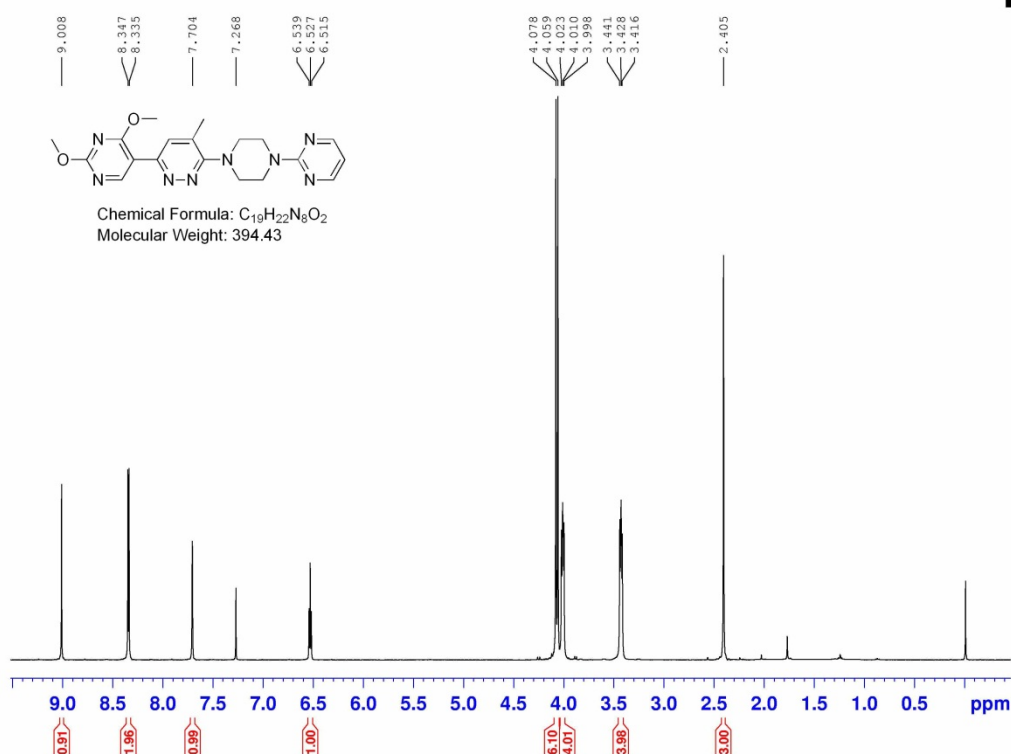


```

NAME      ZW-2-399
EXPNO     1
PROCNO    1
Date_     20111111
Time      23.31
INSTRUM    spect
PROBHD     5 mm PABBO BB-
PULPROG    zgpg30
TD         65536
SOLVENT    CDCl3
NS         72
DS         2
SWH         29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010548 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         296.9 K
D1         2.00000000 sec
D11        0.03000000 sec
TD0        1
===== CHANNEL f1 =====
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463943 W
SFO1       125.7703643 MHz
===== CHANNEL f2 =====
CPDPRG2    waltz16
NUC2       1H
PCPD2      80.00 usec
PL2        2.50 dB
PL12       17.40 dB
PL13       17.40 dB
PL2W       13.02359581 W
PL12W      0.42143536 W
PL13W      0.42143536 W
SFO2       500.1320098 MHz
SI         32768
SF         125.7577986 MHz
WDW        RM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
    
```

# 4-methyl-6-(2,4-dimethoxypyrimidin-5-yl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (18)

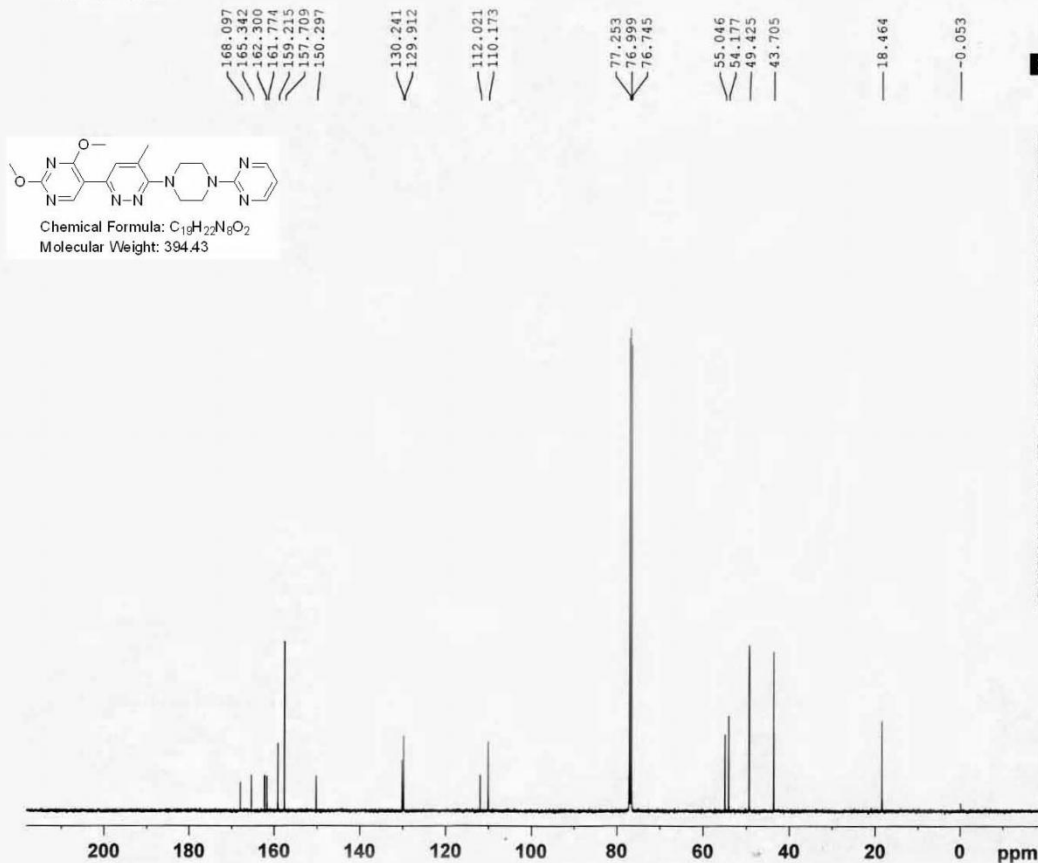
ZCS-2-062



```

NAME      ZCS-2-062
EXPNO     1
PROCNO    1
Date_     20120510
Time      11.09
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         2
SWH        8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         128
DW         60.400 usec
DE         6.50 usec
TE         297.0 K
D1         1.00000000 sec
TD0
===== CHANNEL f1 =====
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300057 MHz
WDW        EM
SSB         0
LB         0.30 Hz
GB         0
PC         1.00
    
```

ZCS-2-062

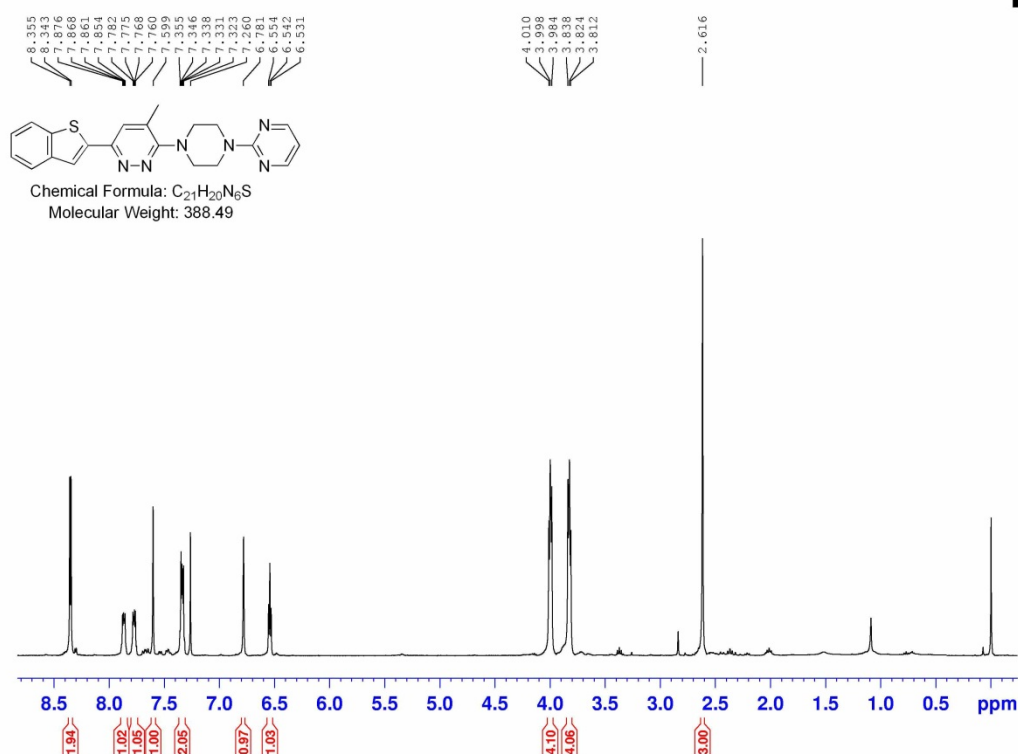


```

NAME      ZCS-2-062
EXPNO     1
PROCNO    1
Date_     20120510
Time      12.54
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         1024
DS         4
SWH        25761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010549 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         297.0 K
D1         2.00000000 sec
D11        0.03000000 sec
TD0        1
===== CHANNEL f1 =====
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463043 W
SFO1       125.7703643 MHz
===== CHANNEL f2 =====
CPDPRG2   waltz16
NUC2       1H
PCPD2     80.60 usec
PL2        2.50 dB
PL12       17.40 dB
PL13       17.40 dB
PL2W       13.02359581 W
PL12W      5.42143536 W
PL13W      5.42143536 W
SFO2       500.1320005 MHz
SI         32768
SF         125.7577960 MHz
WDW        EM
SSB         0
LB         1.00 Hz
GB         0
PC         1.40
    
```

# 4-methyl-6-(benzothiophen-2-yl)-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine (19)

LSR-5-187

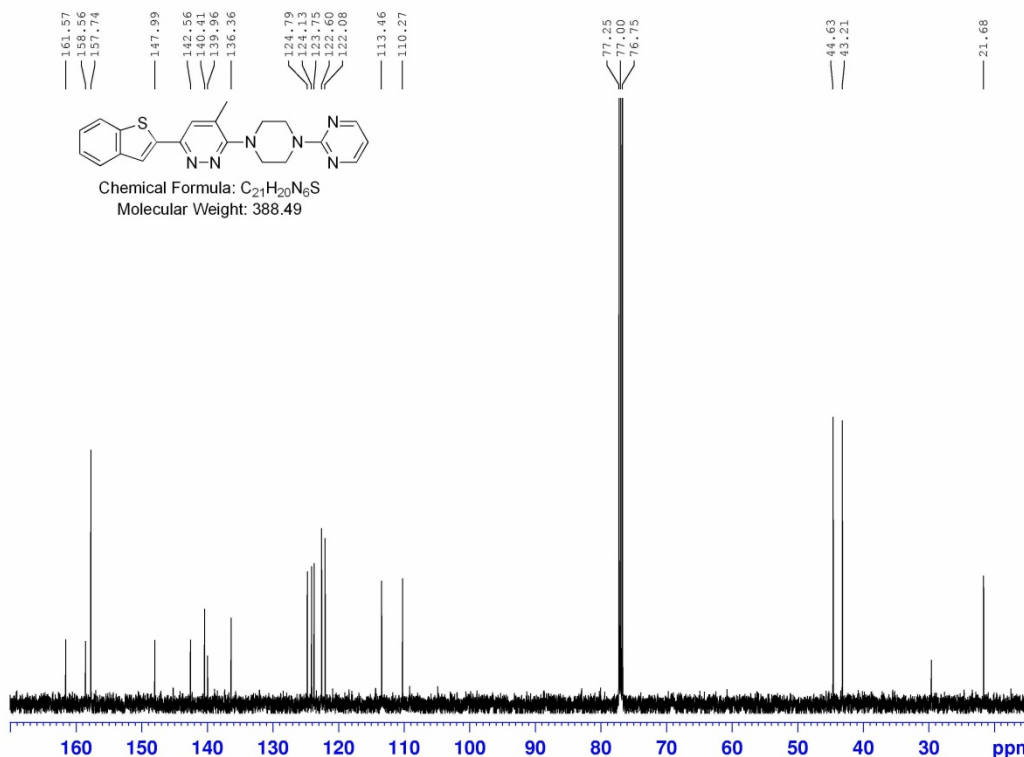


```

NAME      LSR-5-187
EXPNO     74
PROCNO    1
Date_     20120507
Time      21.51
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         2
SWH        8278.146 Hz
FIDRES     0.126314 Hz
AQ         3.9584243 sec
RG         256
DW         60.400 usec
DE         6.50 usec
TE         273.2 K
D1         1.00000000 sec
TDO        0

===== CHANNEL f1 =====
NUC1       1H
P1         14.50 usec
PL1        0.00 dB
PL1W       10.87646866 W
SFO1       400.1324710 MHz
SI         32768
SF         400.1300000 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
    
```

LSR-5-187



```

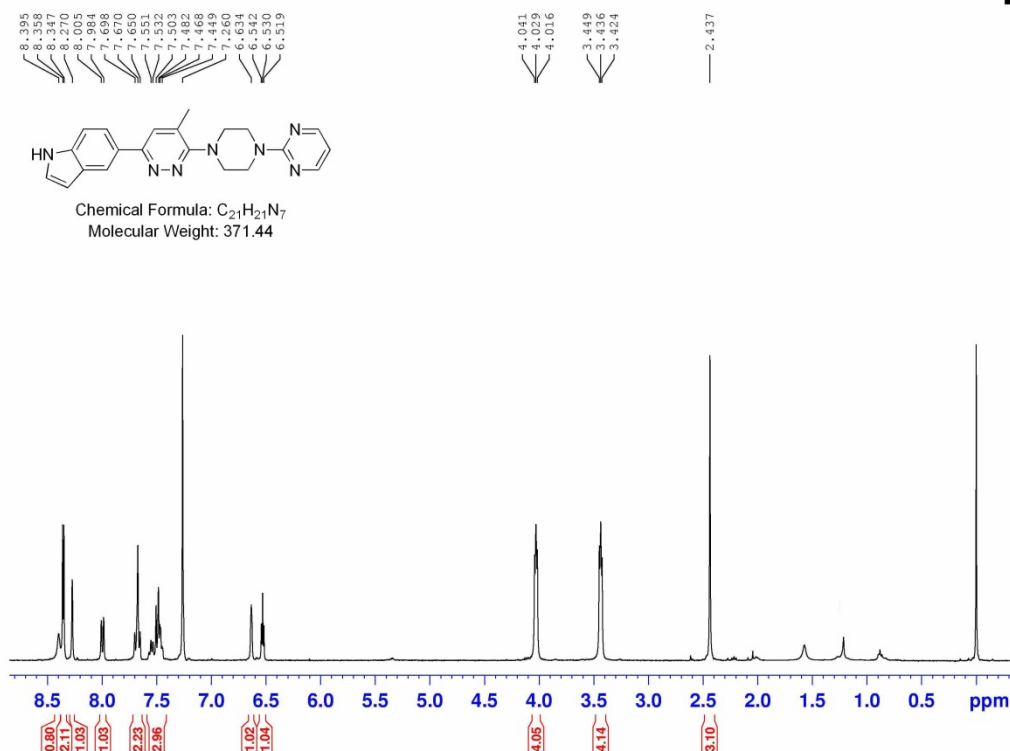
NAME      LSR-5-187
EXPNO     1
PROCNO    1
Date_     20111227
Time      22.50
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         64
DS         4
SWH        29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010548 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         297.5 K
D1         2.00000000 sec
D11        0.03000000 sec
TDO        1

===== CHANNEL f1 =====
NUC1       13C
P1         11.57 usec
PL1        0.00 dB
PL1W       83.39463043 W
SFO1       125.7703643 MHz

===== CHANNEL f2 =====
CPDPRG2   waltz16
NUC2       1H
PCPD2     80.00 usec
PL2        2.50 dB
PL12       17.40 dB
PL13       17.40 dB
PL2W       13.02359581 W
PL12W      0.42143336 W
PL13W      0.42143336 W
SFO2       500.1320000 MHz
SI         32768
SF         125.7577984 MHz
WDW        RM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
    
```

# 5-(5-methyl-6-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazin-3-yl)-1H-indole (20)

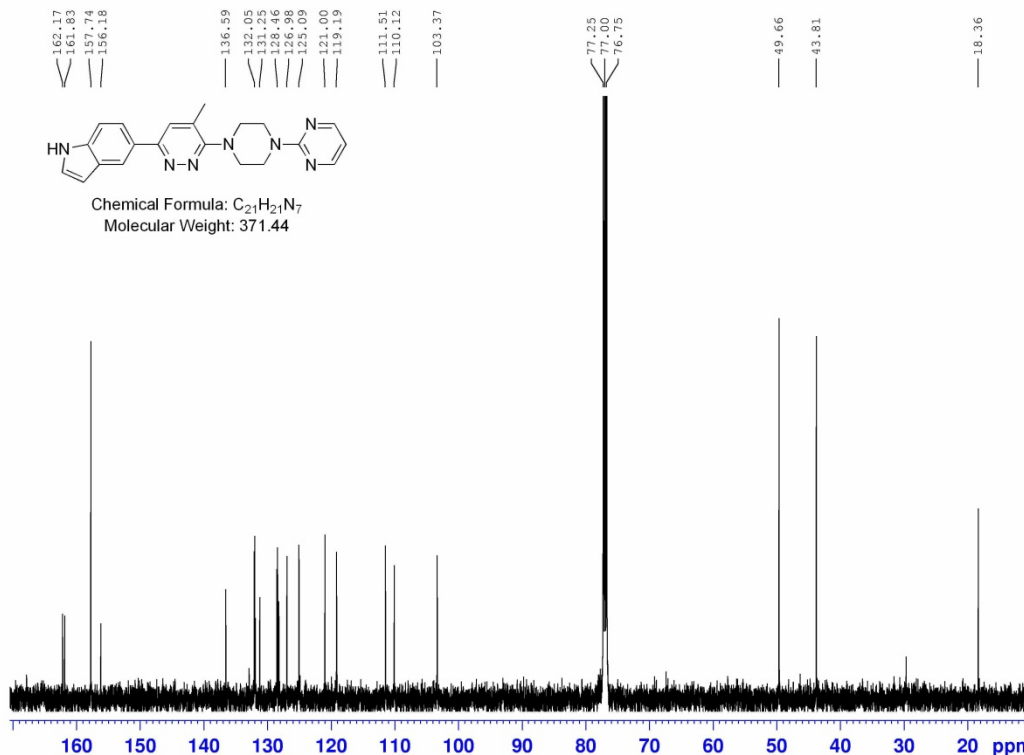
LSR-5-136



NAME LSR-5-136  
EXPNO 73  
PROCNO 1  
Date\_ 20120507  
Time 21.43  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 322.5  
DW 60.400 usec  
DE 6.50 usec  
TE 673.2 K  
D1 1.00000000 sec  
TDO

CHANNEL f1  
NUC1 1H  
P1 14.50 usec  
PL1 0.00 dB  
PL1W 10.87646866 W  
SFO1 400.1324710 MHz  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

LSR-5-136



NAME LSR-5-136  
EXPNO 1  
PROCNO 1  
Date\_ 20111227  
Time 22.59  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 845  
DS 2  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 297.2 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TDO 1

CHANNEL f1  
NUC1 13C  
P1 11.57 usec  
PL1 0.00 dB  
PL1W 83.39463043 W  
SFO1 125.7703643 MHz

CHANNEL f2  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.50 dB  
PL12 17.40 dB  
PL13 17.40 dB  
PL2W 13.02359581 W  
PL12W 0.42143536 W  
PL13W 0.42143536 W  
SFO2 500.1320000 MHz  
SI 32768  
SF 125.7577940 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

