Picomolar Inhibitors of HIV Reverse Transcriptase Featuring Bicyclic Replacement of a Cyanovinylphenyl Group

Won-Gil Lee,[†] Ricardo Gallardo-Macias,[†] Kathleen M. Frey,[‡] Krasimir A. Spasov,[‡] Mariela Bollini,[†] Karen S. Anderson,[‡,*] and William L. Jorgensen[†,*]

Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107, and the Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06520-8066

Supporting Information

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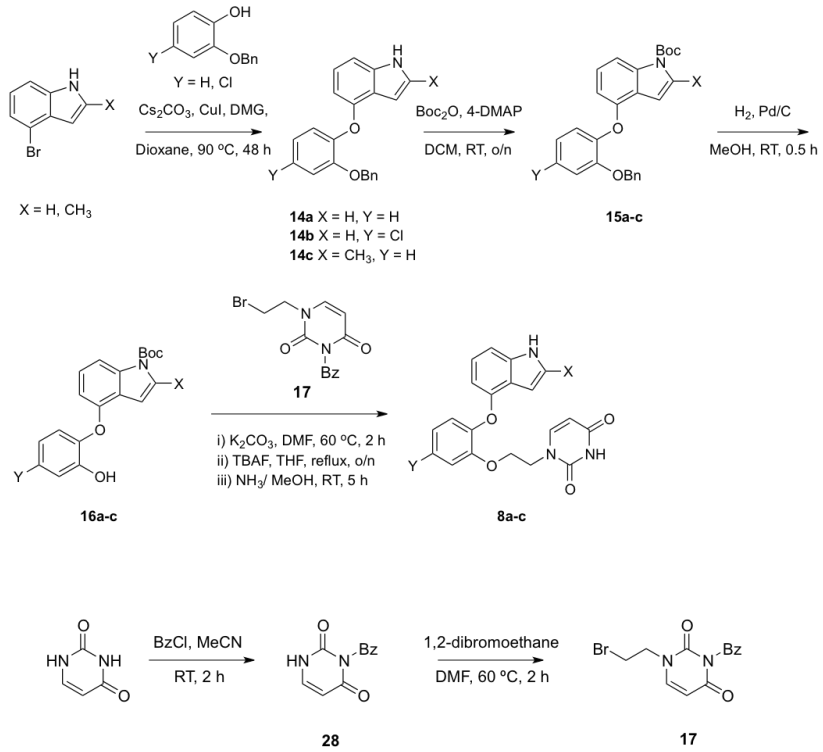
1. General Information

NMR spectra were recorded on a Agilent (800 MHz), and Bruker Avance DRX-500 (500 MHz) and DRX-400 (400 MHz) instruments. Column chromatography was carried out using CombiFlash over redisep column cartridges employing Merck silica gel (Kieselgel 60, 63-200 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. Mass determination were performed using electrospray ionization on water Micromass ZQ (LC-MS) and on an Agilent Technologies 6890N (GC-MS). HRMS (ESI-TOF) analyses were performed on Waters Xevo QTOF equipped with Z-spray electrospray ionization source. HPLC analyses were performed on a Waters 2487 dual λ abosrbance detector with a Waters 1525 binary pump and a Phenomenex Luna 5μ C18(2) 250 x 4.6 mm column.

2. 1. Synthesis of Compounds 8 a-c

Scheme 1.1



Step 1[1]

A solution of indole (1.0 equiv), phenol (1.3 equiv), Cs_2CO_3 (1.5 euqiv), CuI (0.1 equiv) and *N*,*N*-dimethylglycine hydrochloride (0.3 equiv) in dry dioxane (5.0 mL per indole intermediate) was stirred at 90–100 ºC under N_2 atmosphere in a sealed tube for 48 h. The reaction was cooled down, quenched with brine, and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **14a–c**.

4-(2-(benzyloxy)phenoxy)-1H-indole (**14a**) (42%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, br, 1H), 7.24 (s, 4H), 7.13 (d, *J* = 3.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.06 – 7.03 (m, 4H), 6.93 – 6.89 (m, 1H), 6.56 – 6.55 (m, 2H), 5.14 (s, 2H). GC-MS (ES) for $C_{21}H_{17}NO_2$ $[M]^+$ 315.

4-(2-(benzyloxy)-4-chlorophenoxy)-1H-indole (14b) (23%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, br, 1H), 7.24 (s, 4H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.15 – 7.13 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 2.5 Hz, 1H), 6.93 (s, 1H), 6.93 (s, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.52 (t, *J* = 3.0 Hz, 1H), 5.12 (s, 2H). GC-MS (ES) for $C_{21}H_{16}ClNO_2$ $[M]^+$ 349.

4-(2-(benzyloxy)phenoxy)-2-methyl-1H-indole (14c) (23%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, br, 1H), 7.28 – 7.26 (m, 4H), 7.24 - 7.23 (m, 2H), 7.04 (t, *J* = 1.2 Hz, 1H), 7.03 (d, *J* = 1.2 Hz, 1H), 7.01 (s, 1H), 6.98 (s, 1H), 6.57 (d, *J* = 0.8 Hz, 1H), 6.54 (d, *J* = 0.8 Hz, 1H), 6.17 – 6.16 (m, 1H), 5.16 (s, 2H), 2.41 (s, 3H). GC-MS (ES) for $C_{21}H_{19}NO_2$ $[M]^+$ 329.

Step 2[2]

To a solution of phenoxyindole (1.0 equiv) and 4-dimethylaminopyridine (1.5 equiv) in dry THF (5.0 mL per mmol phenoxyindole) at 0 ºC was added a solution of Boc_2O (1.5 equiv) in dry THF (3.0 mL per mmol Boc_2O). After addition, the reaction was stirred at room temperature overnight. The reaction mixture was quenched with brine and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **15a–c**.

***tert*-butyl 4-(2-(benzyloxy)phenoxy)-1H-indole-1-carboxylate (15a)** (21%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 3.5 Hz, 1H), 7.25 – 7.23 (m, 3H), 7.20 – 7.18 (m, 3H), 7.09 – 7.06 (m, 1H), 7.05 – 7.01 (m, 2H), 6.94 – 6.91 (m, 1H), 6.63 (d, *J* = 10.5 Hz, 1H), 6.64 (s, 1H), 5.10 (s, 2H), 1.69 (s, 9H). GC-MS (ES) for $C_{26}H_{25}NO_4$ $[M]^+$ 415.

***tert*-butyl 4-(2-(benzyloxy)-4-chlorophenoxy)-1H-indole-1-carboxylate (15b)** (53%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 4 Hz, 1H), 7.25 – 7.24 (m, 4H), 7.18 – 7.16 (m, 2H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.62 – 6.60 (m, 2H), 5.07 (s, 2H), 1.68 (s, 9H). GC-MS (ES) for $C_{26}H_{24}ClNO_4$ $[M]^+$ 449.

***tert*-butyl 4-(2-(benzyloxy)phenoxy)-2-methyl-1H-indole-1-carboxylate (15c)** (42%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.25 – 7.24 (m, 5H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.04 – 7.02 (m, 2H), 6.91 (s, 1H), 6.90 – 6.88 (m, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.36 (s, 1H), 5.12 (s, 2H), 2.53 (s, 3H), 1.69 (s, 9H). GC-MS (ES) for $C_{27}H_{27}NO_4$ $[M]^+$ 429.

Step 3

To a solution of *t*-butyl phenoxyindole carboxylate (1.0 equiv) in dry MeOH: THF (1:1, 8.0 mL per mmol indole) was added Pd over carbon (0.15 equiv). The reaction mixture was purged with N_2 three times, then a H_2 ballon was attached, and the reaction was stirred at room temperature until completion. The crude was filtered, concentrated by rotary evaporation, and purified by column chromatography to give **16a–c**.

***tert*-butyl 4-(2-hydroxyphenoxy)-1H-indole-1-carboxylate (16a)** (53%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 3.6 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.09 – 7.03 (m, 2H), 6.83 – 6.77 (m, 3H), 6.55(d, *J* = 4.0 Hz, 1H), 5.71 (s, 1H), 1.68 (s, 9H). GC-MS (ES) for $C_{19}H_{19}NO_4$ $[M]^+$ 325.

***tert*-butyl 4-(4-chloro-2-hydroxyphenoxy)-1H-indole-1-carboxylate (16b)** (77%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 3.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.79 – 6.75 (m, 3H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.53 (d, *J* = 3.6 Hz, 1H), 5.76 (s, 1H), 1.68 (s, 9H). GC-MS (ES) for $C_{19}H_{18}ClNO_4$ $[M]^+$ 359.

***tert*-butyl 4-(2-hydroxyphenoxy)-2-methyl-1H-indole-1-carboxylate (16c)** (90%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.29 (s, 1H), 7.15 (td, *J* = 8.0, 1.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.02 – 6.98 (m, 1H), 6.78 – 6.75(m, 2H), 6.28 (s, 1H), 5.68 (s, 1H), 2.56 (s, 3H), 1.68 (s, 9H). GC-MS (ES) for $C_{20}H_{21}NO_4$ $[M]^+$ 339.

Step 4[2, 3]

A solution of phenol (1.0 equiv) and K_2CO_3 (1.2 equiv) in dry DMF (4.0 mL per mmol phenol) were stirred at room temperature for 1 h. After this period, a solution of 1-(2-bromoethyl)pyrimidine-2,4(1H,3H)-dione (1.2 equiv) in dry DMF (4.0 mL per mmol phenol) was added. The reaction mixture was stirred at 60 ºC for 2 h and then at room

temperature overnight. The reaction was quenched with brine and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in dry THF and TBAF (5.0 equiv, 1.0M solution in THF) were added and stirred at reflux under N_2 atmosphere overnight. The crude was cooled down, quenched with saturated NH_4Cl, and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo and the crude was taken to the next reaction. To a solution of crude product in dry MeOH (3.0 mL) was added 3.0 mL of NH_4OH and the reaction was stirred at room temperature until completion. The crude reaction was concentrated by rotary evaporation and purified by column chromatography to give **8a–c**. Further purification was performed by HPLC (5-100% of water with 0.1% trifluoroacetic acid (TFA) (A) and 10:1 acetonitrile:water with 0.1% TFA(B)).

1-(2-(2-((1H-indol-4-yl)oxy)phenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (8a) (10%) ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.82 (s, br, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.22 – 7.19 (m, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.04 – 7.00 (m, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 4.99 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.23 (t, *J* = 4.4 Hz, 2H), 3.92 (t, *J* = 4.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.91, 150.82, 149.85, 148.98, 145.81, 125.40, 124.93, 122.56, 122.26, 114.50, 114.28, 109.79, 107.52, 105.88, 103.82, 103.58, 101.19, 66.80, 48.14. HR-MS (ES) calcd for $C_{20}H_{17}N_3O_4$ $[M+1]^+$ 364.1219 found 364.1255.

1-(2-(2-((1H-indol-4-yl)oxy)-5-chlorophenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (8b) (30 %) ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 4.0 Hz, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.0 (d, *J* = 8.5 Hz, 1H), 6.96 (dd, *J* = 8.5, 2.0Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.6 (d, *J* = 4.0 Hz, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 4.89 (d, *J* = 8.0 Hz, 1H), 4.14 (t, *J* = 4.5 Hz, 2H), 3.86 (t, *J* = 4.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) δ 152.53, 152.36, 150.99, 147.41, 127.54, 126.38, 125.98, 124.23, 123.09, 116.42, 111.01, 110.68, 108.41, 106.68, 104.85, 101.50, 68.16. HR-MS (ES) calcd for $C_{20}H_{16}ClN_3O_4$ $[M+1]^+$ 398.0829 found 398.0851

1-(2-(2-((2-methyl-1H-indol-4-yl)oxy)phenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (8c) (30 %) ^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (d, *J* = 8.5 Hz, 1H), 7.14 – 7.08 (m,

1H), 7.06 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.99 – 6.93 (m, 3H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.33 (s, 1H), 6.28 (d, *J* = 8.0 Hz, 1H), 4.92 (d, *J* = 8.0, 1H), 4.14 (t, *J* = 4.5 Hz, 2H), 3.86 (t, *J* = 4.5 Hz, 2H), 2.54 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 151.91, 151.71, 151.46, 147.59, 146.25, 139.70, 138.26, 126.55, 124.69, 123.31, 123.12, 116.10, 111.22, 108.75, 105.38, 101.43, 68.08, 17.28. HR-MS (ES) calcd for $C_{21}H_{19}N_3O_4$ $[M+1]^+$ 378.1454 found 378.1470.

Synthesis of Compound 17

Step 1

Triethylamine (4.5 mmol) and benzoyl chloride (4.5 mmol) were added to a solution of uracil (3.0 mmol) in acetonitrile (15 mL) and the mixture was stirred for 2 h. The reaction mixture was poured into brine (20 mL) and extracted with ethyl acetate (2 x 30 mL). The organic layer was sequentially washed with brine, dried over anhydrous Na_2SO_4, and concentration by rotary evaporation. After completion, the reaction mixture was concentrated by rotary evaporation and purified by column chromatography to give **28**.

3-benzoylpyrimidine-2,4(1*H*,3*H*)-dione (28) (43%) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.61 (s, 1H), 7.96 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 2H), 5.75 (d, *J* = 7.7 Hz, 1H). LC-MS (ES) for $C_{11}H_9N_2O_3$ $[M+1]^+$ 316.98.

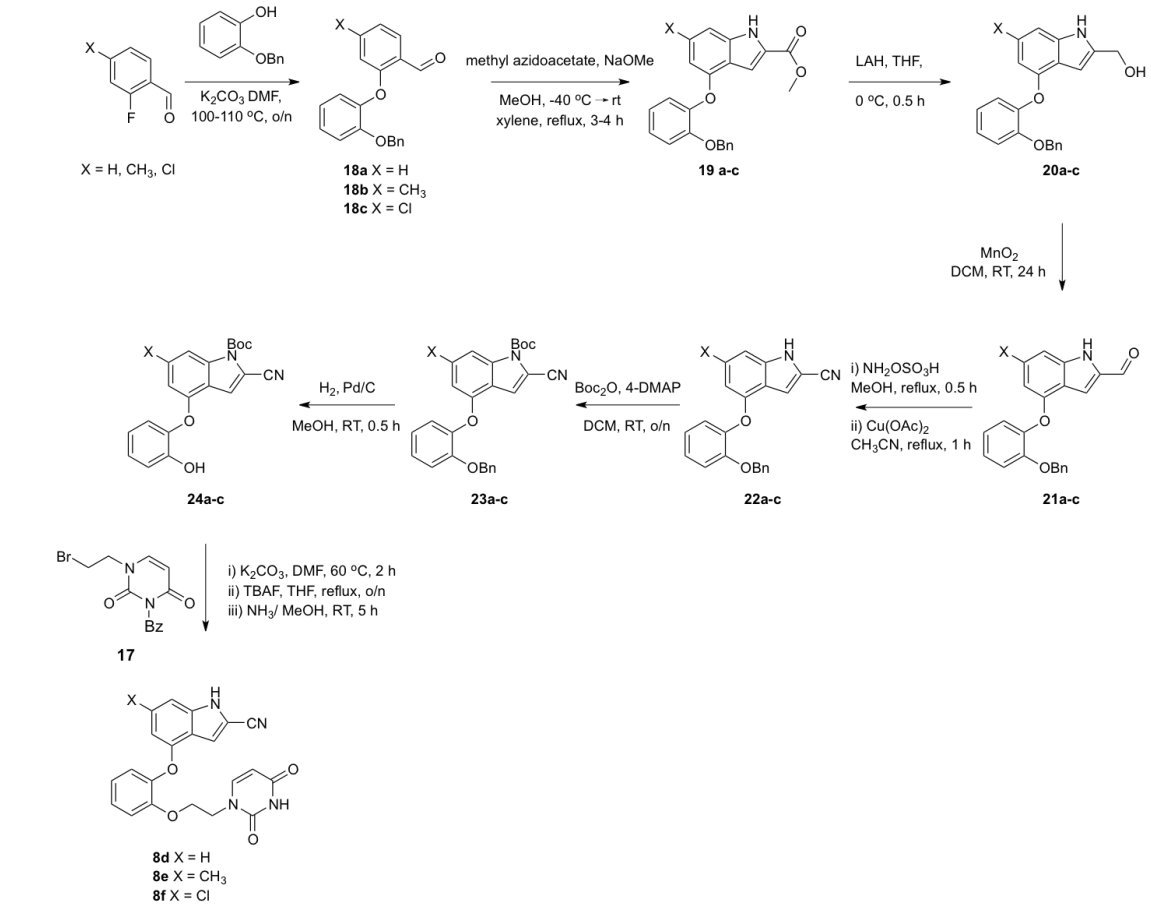
Step 2

1,2-dibromoethane (3.3 mmol), and K_2CO_3 (2.0 mmol) were added to a solution of **28** (1.3 mmol) in dry DMF (10 mL) and the mixture was stirred for 3 h at 60 ºC to complete the reaction. The reaction mixture was poured into brine (20 mL) and extracted with ethyl acetate (2 x 25 mL). The organic layer was sequentially washed with brine, dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **17**.

3-benzoyl-1-(2-bromoethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**17**) (37%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H), 7.73 – 7.66 (m, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 5.86 (d, *J* = 8.0 Hz, 1H), 4.19 (t, *J* = 5.7 Hz, 2H), 3.72 (t, *J* = 5.7 Hz, 2H). LC-MS (ES) for $C_{13}H_{11}BrN_2O_3$ $[M+1]^+$ 323.90.

2. 2. Representative synthesis of Compounds 8 d-f

Scheme 1.2



Step 1

A solution of benzylaldehyde (1.0 equiv), 2-benzyloxyphenol (1.0 equiv), and K_2CO_3 (1.5 equiv) in dry DMF (3.0 mL per mmol benzyaldehyde) were stirred at 100–110 ºC under N_2 atmosphere overnight. The reaction was cooled down, quenched with 1N HCl, and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was

dried over anhydrous Na_2SO_4, concentrated by rotary evaporation and purified by column chromatography to give **18a–c**.

2-(2-(benzyloxy)phenoxy)benzaldehyde (18a) (69%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.91 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.25 (d, *J* = 2.4 Hz, 2H), 7.19 – 7.15 (m, 2H), 7.14 – 7.10 (m, 4H), 7.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.01 (td, *J* = 7.8, 1.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.06 (s, 2H). GC-MS (ES) for $C_{20}H_{16}O_3$ $[M]^+$ 304.

2-(2-(benzyloxy)phenoxy)-4-methylbenzaldehyde (18b) (46%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.58 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.26 (m, 3H), 7.18 – 7.13 (m, 4H), 7.07 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.01 (td, *J* = 7.5, 1.5 Hz, 1H), 6.93 (d, *J* = 7.0 Hz, 1H), 6.53 (s, 1H), 5.06 (s, 2H), 2.28 (s, 3H). GC-MS (ES) for $C_{21}H_{18}O_3$ $[M]^+$ 318.

2-(2-(benzyloxy)phenoxy)-4-chlorobenzaldehyde (18c) (60%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.26 (m, 4H), 7.21 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.09 – 7.07 (m, 1H), 7.05 (t, *J* = 0.8 Hz, 1H), 7.03 (s, 1H), 6.69 (d, *J* = 1.2 Hz, 1H), 5.05 (s, 2H). GC-MS (ES) for $C_{20}H_{15}ClO_3$ $[M]^+$ 338.

Step 2[4]

To a stirred solution of (benzyloxy)phenoxybenzaldehyde (1.0 equiv) and methyl 2-azidoacetate (4.0 equiv) in dry MeOH (4.0 mL per mmol benzaldehyde) under N_2 atmosphere at -40 ºC, was added a solution of 25% sodium methoxide (4.0 equiv) dropwise. The reaction was stirred at -40 ºC for 2 h, and then to 0 ºC for 2 h. After this time, the reaction mixture was allowed to warm to room temperature and stirred overnight. The crude reaction was concentrated in vacuo, quenched with water, and extracted with dry xylenes (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The above solution was added dropwise to a stirring solution of dry xylene and stirred at reflux for 4 h under N_2 atmosphere. The crude reaction was cooled down, quenched with water, and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **19a–c**.

methyl 4-(2-(benzyloxy)phenoxy)-1H-indole-2-carboxylate (19a) (62%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, br, 1H), 7.31 – 7.30 (m, 1H), 7.22 – 7.21 (m, 4H), 7.17 – 7.16 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.09 – 7.07 (m, 1H), 7.05 (dd, *J* = 6.4, 1.2 Hz, 1H), 6.97 – 6.93 (m, 1H), 6.47 (d, *J* = 6.8 Hz, 1H), 5.10 (s, 2H), 3.92 (s, 3H). GC-MS (ES) for $C_{23}H_{19}NO_4$ $[M]^+$ 373.

methyl 4-(2-(benzyloxy)phenoxy)-6-methyl-1H-indole-2-carboxylate (19b) (46%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (s, br, 1H), 7.44 – 7.42 (m, 2H), 7.31 – 7.24 (m, 4H), 7.18 – 7.16 (m, 1H), 7.14 – 7.12 (m, 1H), 7.10 (s, 1H), 7.00 – 6.98 (m, 1H), 6.92 (d, *J* = 1.5 Hz, 1H), 6.36 (s, 1H), 5.12 (s, 2H), 3.91 (s, 3H), 2.30 (s, 3H). GC-MS (ES) for $C_{24}H_{21}NO_4$ $[M]^+$ 387.

methyl 4-(2-(benzyloxy)phenoxy)-6-chloro-1H-indole-2-carboxylate (19c) (47%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, br, 1H), 7.30 (d, *J* = 1.5 Hz, 1H), 7.23 – 7.22 (m, 4H), 7.15 – 7.14 (m, 5H), 7.09 (s, 1H), 6.99 (td, *J* = 7.5, 1.5 Hz, 1H), 6.37 (s, 1H), 5.07 (s, 2H), 3.93 (s, 3H). GC-MS (ES) for $C_{23}H_{18}ClNO_4$ $[M]^+$ 407.

Step 3[5]

A solution of the methyl 4-(2-(benzyloxy)phenoxy)-1H-indole-2-carboxylate (1.0 equiv) in dry THF was added to a solution of LAH (3.0 equiv) in dry THF at 0 ºC and stirred for 30 min at 0 ºC. The reaction was quenched by adding water (3.0 mL) dropwise (very slowly), then aq. 20% NaOH (3.0 mL), and water (5.0 mL) dropwise. Afterwards, a solution of DCM: MeOH (8:1, 25 mL) was added and the slurry was stirred at room temperature for 1 h. The crude reaction was filtered and the organic layer was dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **20a–c**.

(4-(2-(benzyloxy)phenoxy)-1H-indol-2-yl)methanol (20a) (51%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, br, 1H), 7.23 (d, *J* = 1.2 Hz, 4H), 7.08 (d, *J* = 4.4 Hz, 1H), 7.06 (s, 1H), 7.05 – 7.03 (m, 2H), 7.02 – 7.00 (m, 1H), 6.92 – 6.88 (m, 2H), 6.56 (dd, *J* = 6.8, 1.2 Hz, 1H), 6.38 (d, *J* = 1.6 Hz, 1H), 5.13 (s, 2H), 4.78 (s, 2H). GC-MS (ES) for $C_{22}H_{19}NO_3$ $[M]^+$ 345.

(4-(2-(benzyloxy)phenoxy)-6-methyl-1H-indol-2-yl)metanol (20b) (37%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, br, 1H), 7.42 (s, 1H), 7.25 (s, 3H), 7.14 – 7.12 (m, 1H), 7.03 (td, *J* = 8.0, 1.5 Hz, 2H), 6.94 (td, *J* = 8.0, 1.5 Hz, 1H), 6.91 – 6.89 (m, 1H), 6.39 (s, 1H), 5.14 (s, 2H), 4.75 (s, 2H), 2.37 (s, 3H). GC-MS (ES) for $C_{23}H_{21}NO_3$ $[M]^+$ 359.

(4-(2-(benzyloxy)phenoxy)-6-chloro-1H-indol-2-yl)metanol (20c) (43%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, br, 1H), 7.42 (s, 1H), 7.25 – 7.22 (m, 4H), 7.19 – 7.18 (m, 2H), 7.11 – 7.07 (m, 2H), 7.06 (s, 1H), 7.03 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.97 – 6.93 (m, 1H), 6.39 – 6.38 (m, 1H), 5.09 (s, 2H), 4.76 (s, 2H). GC-MS (ES) for $C_{22}H_{18}ClNO_3$ $[M]^+$ 379.

Step 4[5]

To a solution of (4-(2-(benzyloxy)phenoxy)-1H-indol-2-yl)methanol (1.0 equiv) in dry DCM (5.0 mL per mmol indole) was added MnO_2 (5.0 equiv) and the reaction was stirred at room temperature for 24 h under N_2 atmosphere. The crude was filtered through celite and the organic layer was concentrated in vacuo to yield **21a–c**.

4-(2-(benzyloxy)phenoxy)-1H-indole-2-carbaldehyde (21a) (82%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.92 (s, br, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.20 – 7.19 (m, 3H), 7.16 – 7.13 (m, 2H), 7.12 – 7.09 (m, 3H), 7.07 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.99 (td, *J* = 7.5, 1.5 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 5.07 (s, 2H). GC-MS (ES) for $C_{22}H_{17}NO_3$ $[M]^+$ 343.

4-(2-(benzyloxy)phenoxy)-6-methyl-1H-indole-2-carbaldehyde (21b) (86%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.79 (s, br, 1H), 7.26 – 7.25 (m, 2H), 7.15 – 7.13 (m, 4H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 7.0 Hz, 1H), 6.89 (s, 1H), 6.27 (s, 1H), 5.09 (s, 2H), 2.36 (s, 3H). GC-MS (ES) for $C_{23}H_{19}NO_3$ $[M]^+$ 357.

4-(2-(benzyloxy)phenoxy)-6-chloro-1H-indole-2-carbaldehyde (21c) (66%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.91 (s, br, 1H), 7.33 (dd, *J* = 2.0, 0.5 Hz, 1H), 7.22 – 7.20 (m, 3H), 7.19 (s, 1H), 7.18 (s, 1H), 7.12 – 7.10 (m, 2H), 7.09 (t, *J* = 1.5 Hz, 1H), 7.07 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.02 (td, *J* = 7.8, 1.5 Hz, 1H), 6.36 (d, *J* = 1.5 Hz, 1H), 5.06 (s, 2H). GC-MS (ES) for $C_{22}H_{16}ClNO_3$ $[M]^+$ 377.

Step 5[6]

A solution of 4-(2-(benzyloxy)phenoxy)-1H-indole-2-carbaldehyde (1.0 equiv) in dry MeOH (7.5 mL per mmol indole) and hydroxylamine-*O*-sulfonic acid (2.0 equiv) was stirred at room temperature for 15 min and then heated at reflux for 30 min. The reaction mixture was cooled down and concentrated in vacuo. The residue was triturated with water, filtered, and the slurry was dissolved in ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Afterwards, the crude product was diluted in dry CH_3CN (10 mL per mmol indole) and anhydrous $Cu(OAc)_2$ (0.1 equiv) was added to the above solution and stirred at reflux for 1 h. The crude reaction was then cooled down and concentrated in vacuo. After that, the crude product was extracted with ether (3 x 15 mL) and the organic layer was washed with aq. 5% H_2SO_4 (3 x 10 mL), washed with water, dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **22a–c**.

4-(2-(benzyloxy)phenoxy)-1H-indole-2-carbonitrile (22a) (38%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, br, 1H), 7.24 – 7.20 (m, 5H), 7.14 – 7.11 (m, 4H), 7.07 (t, *J* = 9.0 Hz, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 5.06 (s, 2H). GC-MS (ES) for $C_{22}H_{16}N_2O_2$ $[M]^+$ 340.

4-(2-(benzyloxy)phenoxy)-6-methyl-1H-indole-2-carbonitrile (22b) (19%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, br, 1H), 7.23 – 7.22 (m, 3H), 7.14 – 7.11 (m, 4H), 7.10 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.97 (td, *J* = 7.5, 1.0 Hz, 1H), 6.87 (s, 1H), 6.32 (s, 1H), 5.07 (s, 2H), 2.35 (s, 3H). GC-MS (ES) for $C_{23}H_{18}N_2O_2$ $[M]^+$ 354.

4-(2-(benzyloxy)phenoxy)-6-chloro-1H-indole-2-carbonitrile (22c) (40%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, br, 1H), 7.24 – 7.22 (m, 5H), 7.13 – 7.10 (m, 2H), 7.07 – 7.06 (m, 2H), 7.04 (dd, *J* = 10.0, 1.6 Hz, 1H), 7.01 – 6.99 (m, 1H), 6.40 (d, *J* = 1.6 Hz, 1H), 5.05 (s, 2H). GC-MS (ES) for $C_{22}H_{15}ClN_2O_2$ $[M]^+$ 374.

Step 6

To a solution of 4-(2-(benzyloxy)phenoxy)-1H-indole-2-carbonitrile (1.0 equiv) and 4-Dimethylamino pyridine (1.5 equiv) in dry THF (20 mL per mmol indole) at 0 ºC was

added a solution of Boc_2O (1.5 equiv) in dry THF (10 mL per mmol indole). After addition, the crude reaction was stirred at room temperature overnight. The reaction was quenched with brine and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **23a–c**.

***tert*-butyl 4-(2-(benzyloxy)phenoxy)-2-cyano-1H-indole-1-carboxylate (23a)** (80%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 1H), 7.42 (s, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.23 – 7.22 (m, 3H), 7.15 (td, *J* = 7.5, 1.5 Hz, 1H), 7.11 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.09 – 7.07 (m, 2H), 7.05 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.98 (td, *J* = 8.0, 1.0 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.02 (s, 2H), 1.74 (s, 9H). GC-MS (ES) for $C_{27}H_{24}N_2O_4$ $[M]^+$ 440.

***tert*-butyl 4-(2-(benzyloxy)phenoxy)-2-cyano-6-methyl-1H-indole-1-carboxylate (23b)** (74%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.34 (s, 1H), 7.24 – 7.23 (m, 4H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.12 – 7.09 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.41 (s, 1H), 5.04 (s, 2H), 2.38 (s, 3H), 1.73 (s, 9H). GC-MS (ES) for $C_{28}H_{26}N_2O_4$ $[M]^+$ 454.

***tert*-butyl 4-(2-(benzyloxy)phenoxy)-6-chloro-2-cyano-1H-indole-1-carboxylate (23c)** (80%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.40 (s, 1H), 7.24 – 7.23 (m, 3H), 7.19 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.16 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.10 – 7.08 (m, 2H), 7.06 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.01 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.51 (d, *J* = 1.5 Hz, 1H), 5.01 (s, 2H), 1.73 (s, 9H). GC-MS (ES) for $C_{27}H_{23}ClN_2O_4$ $[M]^+$ 474.

Step 7

To a solution of *t*-butyl phenoxyindole carboxylate (1.0 equiv) in dry MeOH: THF (1:1, 25 mL per mmol indole) was added Pd over carbon (0.2 equiv). The reaction mixture was purged with N_2 three times, then a H_2 balloon was attached, and the reaction was stirred at room temperature until completion. The crude was filtered, concentrated by rotary evaporation, and purified by column chromatography to give **24a–c**.

***tert*-butyl 2-cyano-4-(2-hydroxyphenoxy)-1H-indole-1-carboxylate (24a)** (71%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.11 – 7.08

(m, 2H), 6.88 – 6.85 (m, 2H), 6.76 (d, J = 8.0 Hz, 1H), 5.47 (s, br, 1H), 1.73 (s, 9H). GC-MS (ES) for $C_{20}H_{18}N_2O_4$ $[M]^+$ 350.

***tert*-butyl 2-cyano-4-(2-hydroxyphenoxy)-6-methyl-1H-indole-1-carboxylate (24b)** (60%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.32 (s, 1H), 7.11 – 7.08 (m, 2H), 6.87 – 6.86 (m, 2H), 6.59 (s, 1H), 5.47 (s, br, 1H), 2.42 (s, 3H), 1.73 (s, 9H). GC-MS (ES) for $C_{21}H_{20}N_2O_4$ $[M]^+$ 364.

***tert*-butyl 6-chloro-2-cyano-4-(2-hydroxyphenoxy)-1H-indole-1-carboxylate (24c)** (74%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.39 (t, J = 1.0 Hz, 1H), 7.18 – 7.15 (m, 1H), 7.11 (d, J = 8.0, 1.5 Hz, 1H), 6.96 – 6.92 (m, 2H), 6.71 (d, J = 1.5 Hz, 1H), 5.35 (s, 1H), 1.74 (s, 9H). GC-MS (ES) for $C_{20}H_{17}ClN_2O_4$ $[M]^+$ 384.

Step 8

A solution of phenol (1.0 equiv) and K_2CO_3 (1.2 equiv) in dry DMF (4.0 mL per mmol phenol) were stirred at rt for 1 hr. Then, a solution of 1-(2-bromoethyl)pyrimidine-2,4(1H,3H)-dione (1.2 equiv) in dry DMF (4.0 mL per mmol phenol) was added and the reaction mixture was stirred at 60 ºC for 2 h and then at room temperature. After overnight, the crude reaction was quenched with brine and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in dry THF and TBAF (5.0 equiv, 1.0M solution in THF) was added and stirred at reflux under N_2 atmosphere overnight. The crude was cooled down, quenched with saturated NH_4Cl, and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude was taken to next reaction. To a solution of crude product in dry MeOH (3.0 mL) was added 3.0 mL of a NH_4OH and the crude reaction was stirred at room temperature until reaction completion. The crude reaction was by rotary evaporation and purified column chromatography to give **8d–f**. Further purification was performed by HPLC (5-100% of water with 0.1% trifluoroacetic acid (TFA) (A) and 10:1 acetonitrile:water with 0.1% TFA(B)) to afford final product.

4-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethoxy)phenoxy)-1H-indole-2-carbonitrile (8d) (10%) ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.50 (s, 1H), 11.12 (s, 1H),

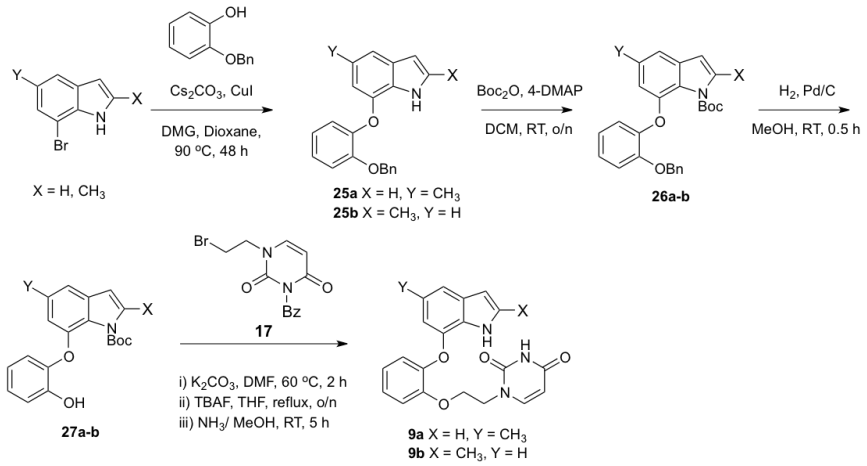
7.32 (s, 1H), 7.22 – 7.20 (m, 2H), 7.19 (s, 1H), 7.14 – 7.11 (m, 1H), 7.10 (d, J = 4.0 Hz, 2H), 6.84 (d, J = 7.5 Hz, 1H), 6.13 (d, J = 9.0 Hz, 1H), 4.79 (dd, J = 8.0, 2.0 Hz, 1H), 4.14 (t, J = 6.0 Hz, 2H), 3.83 (t, J = 5.0 Hz, 2H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 163.36, 157.74, 157.59, 150.71, 150.12, 145.55, 143.03, 138.85, 129.38, 126.42, 126.13, 122.53, 121.84, 117.26, 114.59, 114.53, 110.27, 106.41, 105.16, 103.74, 99.83, 66.12, 46.99. HR-MS (ES) calcd for $C_{21}H_{16}N_4O_4$ $[M+1]^+$ 389.1250 found 389.1247.

4-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethoxy)phenoxy)-6-methyl-1H-indole-2-carbonitrile (**8e**) (10%) ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.34 (s, 1H), 11.15 (s, 1H), 7.25 (s, 1H), 7.23 – 7.21 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 7.02 (td, J = 5.0, 1.0 Hz, 1H), 6.89 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 5.97 (s, 1H), 4.78 (dd, J = 8.0, 2.0 Hz, 1H), 4.15 (t, J = 5.0 Hz, 2H), 3.84 (t, J = 5.0 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 163.39, 157.81, 157.67, 151.34, 150.74, 150.19, 145.55, 139.17, 136.51, 126.13, 122.53, 121.89, 115.37, 114.73, 144.66, 110.31, 106.06, 104.42, 99.81, 66.16, 47.13, 21.69. HR-MS (ES) calcd for $C_{22}H_{18}N_4O_4$ $[M+1]^+$ 403.1407 found 403.1395.

6-chloro-4-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethoxy)phenoxy)-1H-indole-2-carbonitrile (**8f**). (8%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 11.12 (s, 1H), 7.39 (d, J = 1.2 Hz, 1H), 7.25 (d, J = 1.6 Hz, 1H), 7.22 (dd, J = 7.5, 1.2 Hz, 1H), 7.15 (s, 1H), 7.13 (s, 1H), 7.09 – 7.05 (m, 1H), 6.88 (d, J = 8.0 Hz, 1H), 5.99 (d, J = 1.2 Hz, 1H), 4.76 (dd, J = 7.8, 2.4 Hz, 1H), 4.17 (t, J = 4.8 Hz, 2H), 3.85 (t, J = 4.8 Hz, 2H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 163.27, 157.85, 157.70, 152.28, 150.67, 150.07, 145.38, 142.04, 138.48, 130.64, 126.93, 122.85, 121.99, 115.93, 114.67, 110.54, 106.10, 99.73, 66.07, 47.05. HR-MS (ES) calcd for $C_{21}H_{15}ClN_4O_4$ $[M+1]^+$ 423.0861 found 423.0847.

3. Synthesis of Compounds 9a-b

Scheme 1.3



Step 1

7-(2-(benzyloxy)phenoxy)-5-methyl-1H-indole (25a) Following step 1 in the synthetic scheme 1.1, **25a**, from 7-bromo-5-methyl-1*H*-indole, was obtained after column chromatography. (47%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, br, 1H), 7.42 – 7.42 (m, 4H), 7.27 – 7.26 (m, 2H), 7.09 – 7.07 (m, 4H), 6.94 (d, *J* = 1.0 Hz, 1H), 6.50 (s, 1H), 6.47 (t, *J* = 2.5 Hz, 1H), 5.12 (s, 2H), 2.37 (s, 3H). GC-MS (ES) for $C_{22}H_{19}NO_2$ $[M]^+$ 329.

7-(2-(benzyloxy)phenoxy)-2-methyl-1H-indole (25b) Following step 1 in the synthetic scheme 1.1 **25b**, from 7-bromo-2-methyl-1*H*-indole, was obtained after column chromatography. (84%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, br, 1H), 7.28 – 7.27 (m, 4H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.08 – 7.07 (m, 2H), 6.94 (s, 1H), 6.93 – 6.92 (m, 1H), 6.89 (td, *J* = 8.0, 1.5 Hz, 1H), 6.84 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.23 (d, *J* = 2.0 Hz, 1H), 5.12 (s, 2H), 2.37 (s, 3H). GC-MS (ES) for $C_{21}H_{19}NO_2$ $[M]^+$ 329.

Step 2

***tert-butyl* 7-(2-(benzyloxy)phenoxy)-5-methyl-1H-indole-1-carboxylate (26a)** Following step 2 in the synthetic scheme 1.1 **26a**, from **25a**, was obtained after column chromatography. (53%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.8 Hz, 1H), 7.26 –

7.22 (m, 5H), 7.08 (s, 1H), 6.98 – 6.96 (m, 2H), 6.87 (t, *J* = 2.8 Hz, 2H), 6.60 (s, 1H), 6.48 (d, *J* = 3.6 Hz, 1H), 5.13 (s, 2H), 2.31 (s, 3H), 1.46 (s, 9H). GC-MS (ES) for $C_{27}H_{27}NO_4$ $[M]^+$ 429.

***tert*-butyl 7-(2-(benzyloxy)phenoxy)-2-methyl-1H-indole-1-carboxylate (26b)** Following step 2 in the synthetic scheme 1.1 **26b**, from **25b**, was obtained after column chromatography. (61%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.0 Hz, 1H), 7.24 – 7.23 (m, 2H), 7.18 – 7.13 (m, 4H), 7.04 – 7.03 (m, 1H), 7.01 (s, 1H), 6.99 (s, 1H), 6.96 – 6.95 (m, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.29 (d, *J* = 1.0 Hz, 1H), 5.10 (s, 2H), 2.50 (s, 3H), 1.48 (s, 9H). GC-MS (ES) for $C_{27}H_{27}NO_4$ $[M]^+$ 429.

Step 3

***tert*-butyl 7-(2-hydroxyphenoxy)-5-methyl-1H-indole-1-carboxylate (27a)** Following step 3 in the synthetic scheme 1.1 **27a**, from **26a**, was obtained after column chromatography. (21%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.25 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.07 (dd, *J* = 7.3, 1.5 Hz, 1H), 6.87 (td, *J* = 8.3, 1.5Hz, 1H), 6.71 (s, 1H), 6.42 (s, 1H), 2.19 (s, 3H), 1.53 (s, 9H). GC-MS (ES) for $C_{20}H_{21}NO_4$ $[M]^+$ 339.

***tert*-butyl 7-(2-hydroxyphenoxy)-2-methyl-1H-indole-1-carboxylate (27b)** Following step 3 in the synthetic scheme 1.1 **27b**, from **26b**, was obtained, after column chromatography. (63%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.15 (dd, *J* = 7.75, 1.0 Hz, 1H), 7.07 – 7.06 (m, 1H), 7.05 (t, *J* = 2.0 Hz, 1H), 6.91 (td, *J* = 7.8, 2.0 Hz, 1H), 6.87 (td, *J* = 7.5, 1.5 Hz, 1H), 6.68 (dd, *J* = 8.0, 0.5 Hz, 1H), 6.31 (d, *J* = 1.0 Hz, 1H), 5.46 (s, 1H), 2.52 (s, 3H), 1.60 (s, 9H). GC-MS (ES) for $C_{20}H_{21}NO_4$ $[M]^+$ 339.

Step 4

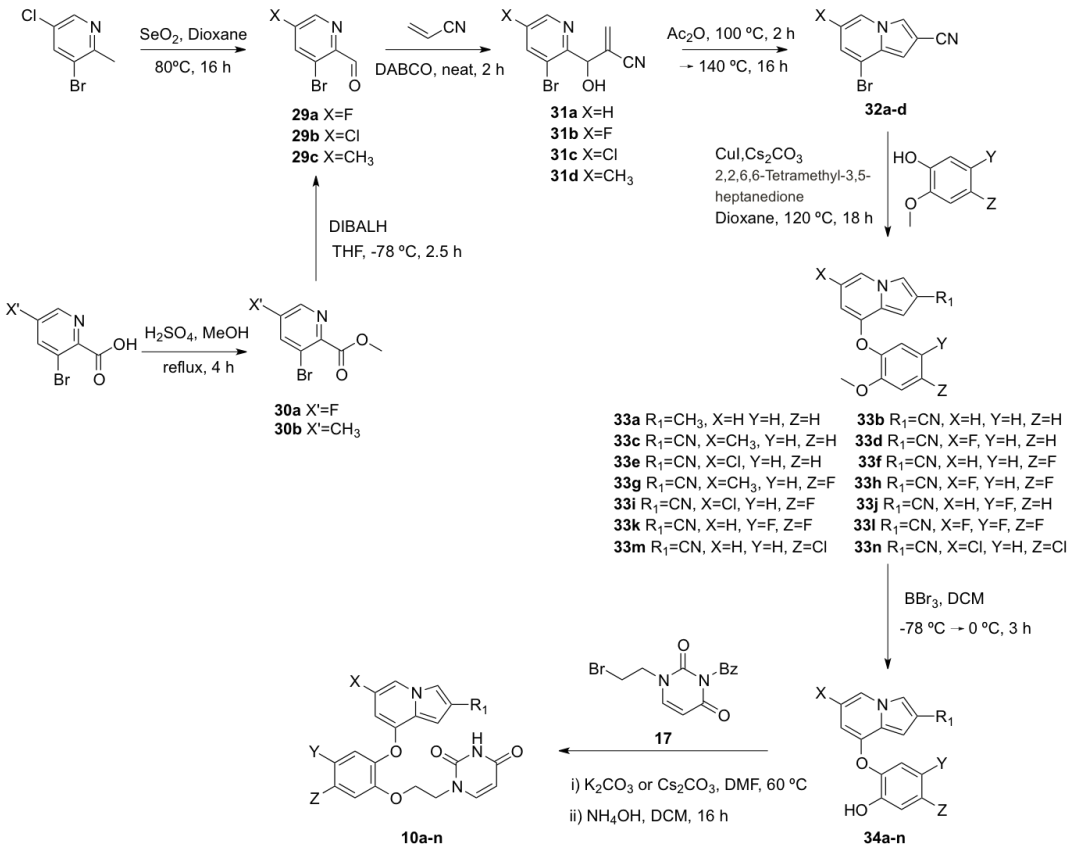
1-(2-(2-((5-methyl-1H-indol-7-yl)oxy)phenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (9a) Following step 4 in the synthetic scheme 1.1 **9a**, from **27a**, was obtained after column chromatography. Further purification was performed by HPLC (5-100% of water with 0.1% trifluoroacetic acid (TFA) (A) and 10:1 acetonitrile:water with 0.1% TFA (B)) to afford final product. (8%) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (s,br, 1H), 7.28 (d,

J = 7.5 Hz, 1H), 7.11 (td, *J* = 8.0, 1.5 Hz, 2H), 7.06 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.93 (td, *J* = 8.0, 1.5 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.75 (s, 1H), 6.52 (s, br, 1H), 6.25 (s, 1H), 5.26 (dd, *J* = 7.5, 2.0 Hz, 1H), 4.16 (t, *J* = 5.0 Hz, 2H), 3.92 (t, *J* = 5.0 Hz, 2H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.73, 150.83, 149.26, 145.84, 145.62, 144.37, 136.61, 134.35, 129.40, 124.34, 121.73, 120.08, 119.73, 116.16, 114.88, 100.33, 66.38, 20.53. HR-MS (ES) calcd for $C_{21}H_{19}N_3O_4$ $[M+1]^+$ 378.1454 found 378.1470.

1-(2-(2-((2-methyl-1H-indol-7-yl)oxy)phenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (9b) Following step 4 in the synthetic scheme 1.1 **9b**, from **27b**, was obtained after column chromatography. Further purification was performed by HPLC (5-100% of water with 0.1% trifluoroacetic acid (TFA) (A) and 10:1 acetonitrile:water with 0.1% TFA) to afford final product. (20 %). ^{1}H NMR (500 MHz, Acetone-d_6) δ 10.23 (s, br, 1H), 9.84 (s, br, 1H), 7.15 – 7.14 (m, 3H), 7.05 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.00 – 6.96 (m, 1H), 6.80 (t, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.27 (dd, *J* = 7.5, 0.5 Hz, 1H), 6.23 – 6.22 (m, 1H), 4.91 (d, *J* = 7.5 Hz, 1H), 4.20 (t, *J* = 5.0 Hz, 2H), 3.83 (t, *J* = 5.0 Hz, 2H), 2.47 (d, *J* = 0.5 Hz, 3H).^{13}C NMR (125 MHz, Acetone-d_6) δ163.80, 151.15, 146.33, 145.67, 144.35, 125.84, 122.63, 122.22, 119.98, 115.46, 114.64, 114.61, 106.45, 101.17, 67.59, 48.52, 13.44. HR-MS (ES) calcd for $C_{21}H_{19}N_3O_4$ $[M+1]^+$ 378.1454 found 378.1456.

4. 1. Synthesis of Compounds 10a–n

Scheme 2.1



Step A1

A mixture of SeO_2 (16 mmol) in dioxane (20 mL) was pre-heated over 80 °C, then a solution of 3-bromo-5-chloro-2-methylpyridine (4.0 mmol) in dioxane (5.0 mL) was added. After stirring at 80 °C for 16 h, the reaction mixture was cooled and filtered. The filtrate was concentrated by rotary evaporation, and purified by column chromatography to give **29b**.

3-bromo-5-chloropicolinaldehyde (**29b**) (76%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.81 (s, 1H), 7.69 (s, 1H). LC-MS (ES) for $C_6H_3BrClNO$ $[M+1]^+$ 220.99.

Step B1

A mixture of the corresponding 3-bromopicolinic acid (1.0 equiv) and sulfonic acid (10 equiv) in MeOH (2.0 mL per mmol pyridine) was heated at reflux for 4 h. The reaction mixture was cooled in ice bath and neutralized with 2N aq. Na_2CO_3 solution. The aqueous layer was extracted with ethyl acetate, and the combined organic solution was dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **30a**–**b**.

methyl 3-bromo-5-fluoropicolinate (**30a**) (76%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4 Hz, 1H), 7.72 (dd, *J* = 4.0, 8.0 Hz, 1H), 3.94 (s, 3H). LC-MS (ES) for $C_7H_5BrFNO_2$ $[M+1]^+$ 235.06.

methyl 3-bromo-5-methylpicolinate (**30b**) (92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.33 (m, 1H), 7.77 (dd, *J* = 1.8, 0.8 Hz, 1H), 3.93 (s, 3H), 2.33 (s, 3H). LC-MS (ES) for $C_8H_8BrNO_2$ $[M+1]^+$ 230.98.

Step B2

A solution of the corresponding methyl picolinate (1.0 equiv) in THF (1.0 mL per mmol picolinate) was cooled to -78 °C. After 10 min, diisobutylaluminum hydride (1.5 equiv, 1.0 M in THF) was added dropwise over 40 min and stirred for an additional 2.5 h at -78 °C. After which it was quenched by MeOH and diluted with 1N aq. $NaHCO_3$ solution. The aqueous solution was extracted with ethyl acetate, and the combined organic solution was dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **29a** and **29c**.

3-bromo-5-fluoropicolinaldehyde (**29a**) (86%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.57 (d, *J* = 2.4 Hz, 1H), 7.78 – 7.70 (m, 1H). LC-MS (ES) for $C_6H_3BrFNO_2$ $[M+1]^+$ 220.33.

3-bromo-5-methylpicolinaldehyde (**29c**) (89%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.51 (s, 1H), 7.79 (s, 1H), 2.37 (s, 3H). LC-MS (ES) for C_7H_6BrNO $[M+1]^+$ 201.01.

Step 2

A mixture of the corresponding pyridine-2-carbaldehydes (1.0 equiv), acrylonitrile (10 equiv) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (1.1 equiv) was stirred for 1.5 h at room temperature, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **31a–d**.

2-((3-bromopyridin-2-yl)(hydroxy)methyl)acrylonitrile (**31a**) (82%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 4.7, 1.2 Hz, 1H), 7.95 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.27 (dd, *J* = 8.0, 4.7 Hz, 1H), 6.14 (dd, *J* = 22.0, 0.6 Hz, 2H), 5.55 (d, *J* = 8.0 Hz, 1H), 5.23 (d, *J* = 8.0 Hz, 1H). LC-MS (ES) for $C_9H_6BrClN_2O$ $[M+1]^+$ 238.98.

2-((3-bromo-5-fluoropyridin-2-yl)(hydroxy)methyl)acrylonitrile (**31b**) (86%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.0 Hz, 1H), 7.69 (dd, *J* = 4.0, 8.0 Hz, 1H), 6.05 (s, 2H), 5.48 (d, *J* = 8.0 Hz, 1H), 4.78 (d, *J* = 8.0 Hz, 1H). LC-MS (ES) for $C_9H_6BrFN_2O$ $[M+1]^+$ 258.97.

2-((3-bromo-5-chloropyridin-2-yl)(hydroxy)methyl)acrylonitrile (**31c**) (64%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 6.10 (d, *J* = 0.9 Hz, 2H), 5.47 (d, *J* = 8.0 Hz, 1H), 4.77 (d, *J* = 8.0 Hz, 1H). LC-MS (ES) for $C_9H_6BrClN_2O$ $[M+1]^+$ 274.94.

2-((3-bromo-5-methylpyridin-2-yl)(hydroxy)methyl)acrylonitrile (**31d**) (86%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 6.05 (d, *J* = 0.6 Hz, 2H), 5.42 (d, *J* = 7.9 Hz, 1H), 5.13 (d, *J* = 8.0 Hz, 1H), 2.31 (S, 3H). LC-MS (ES) for $C_{10}H_9BrN_2O$ $[M+1]^+$ 253.00.

Step 3[7]

A solution of the corresponding pyridine intermediate (1.0 equiv) in acetic anhydride (1.0 mL per mmol of pyridine intermediate) was heated at 100 ºC for 2 h. After this time, the reaction mixture was heated at 140 ºC for 7 h or overnight. The solution was cooled to room temperatura, then a solution of sodium bicarbonate was added at 0 ºC, and stirred for 30 min. Ethyl acetate was added and the organic layer was extracted and washed with brine, dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified

column by chromatography to give **32a–d**.

8-bromoindolizine-2-carbonitrile (**32a**) (86%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.61 – 6.30 (m, 1H). LC-MS (ES) for $C_9H_5BrN_2$ $[M+1]^+$ 220.12.

8-bromo-6-fluoroindolizine-2-carbonitrile (**32b**) (48%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.66 (s, 1H), 7.02 (s, 1H), 6.85 (s, 1H). LC-MS (ES) for $C_9H_4BrFN_2$ $[M+1]^+$ 240.07.

8-bromo-6-chloroindolizine-2-carbonitrile (**32c**) (48%) ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.61 – 8.58 (m, 1H), 8.27 (d, *J* = 1.7 Hz, 1H), 7.30 (d, *J* = 1.5 Hz, 1H), 7.00 (s, 1H). LC-MS (ES) for $C_9H_4BrClN_2$ $[M+1]^+$ 256.22.

8-bromo-6-methylindolizine-2-carbonitrile (**32d**) (65%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.57 (m, 2H), 6.87 (d, *J* = 0.9 Hz, 1H), 6.73 (s, 1H), 2.17 (s, 3H). LC-MS (ES) for $C_{10}H_7BrN_2$ $[M+1]^+$ 236.04.

Step 4

A mixture of the corresponding indolizine intermediate (1.0 equiv), the corresponding catechol (2.5 equiv), Cs_2CO_3 (2.2 equiv), CuI (0.2 equiv) and 2,2,6,6-tetramethyl-3,5-heptanedione (0.4 equiv) in dioxane (1.0 mL per mmol indolizine) in a sealed tube was heated at 120 ºC under nitrogen atmosphere for 18 h. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **33a-n**.

8-(2-methoxyphenoxy)-2-methylindolizine (**33a**) (87%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 1H), 7.23 – 7.12 (m, 2H), 7.09 – 6.99 (m, 1H), 6.93 – 6.88 (m, 1H), 6.63 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.17 – 6.10 (m, 2H), 3.78 (s, 3H), 2.10 (s, 3H). LC-MS (ES) for $C_{16}H_{15}NO_2$ $[M+1]^+$ 254.12.

8-(2-methoxyphenoxy)indolizine-2-carbonitrile (**33b**) (40%) ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.61 (d, *J* = 6.9 Hz, 1H), 7.09 – 7.01 (m, 2H), 6.47 (t, *J* = 7.2 Hz, 1H), 3.69 (3H, s). LC-MS (ES) for $C_{16}H_{12}N_2O_2$ $[M+1]^+$ 265.24

8-(2-methoxyphenoxy)-6-methylindolizine-2-carbonitrile (**33c**) (84%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 2.0 Hz, 1H), 7.34 (s, 1H), 7.19 – 7.13 (m, 1H), 7.03 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.93 (td, *J* = 8.0, 1.6 Hz, 1H), 6.80 (s, 1H), 5.65 (s 1H), 3.75 (s, 3H), 2.05 (s, 3H). LC-MS (ES) for $C_{17}H_{14}N_2O_2$ $[M+1]^+$ 279.11.

6-fluoro-8-(2-methoxyphenoxy)indolizine-2-carbonitrile (**33d**) (51%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 2.0 Hz, 1H), 7.49 (ddd, *J* = 4.0, 1.7, 0.9 Hz, 1H), 7.09 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.08 – 7.03 (m, 1H), 7.00 – 6.91 (m, 3H), 5.71 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.74 (s, 3H). LC-MS (ES) for $C_{16}H_{11}FN_2O_2$ $[M+1]^+$ 283.10.

6-chloro-8-(2-methoxyphenoxy)indolizine-2-carbonitrile (**33e**) (57%) ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.61 – 7.59 (m, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.02 – 6.91 (m, 4H), 6.79 (d, *J* = 1.5 Hz, 1H), 5.52 (s, 1H), 3.74 (s, 3H). LC-MS (ES) for $C_{16}H_{11}ClN_2O_2$ $[M+1]^+$ 299.06.

8-(4-fluoro-2-methoxyphenoxy)indolizine-2-carbonitrile (**33f**) (76%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 6.9 Hz, 1H), 6.90 (dd, *J* = 8.9, 5.2 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.69 (dd, *J* = 8.8, 5.2 Hz, 1H), 6.18 (t, *J* = 7.2 Hz, 1H), 5.93 (d, *J* = 7.2 Hz, 1H), 3.88 (s, 3H). LC-MS (ES) for $C_{16}H_{11}FN_2O_2$ $[M+1]^+$ 283.07.

8-(4-fluoro-2-methoxyphenoxy)-6-methylindolizine-2-carbonitrile (**33g**) (79%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 1.7 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.00 (dd, *J* = 8.8, 5.7 Hz, 1H), 6.83 – 6.78 (m, 1H), 6.71 (dd, *J* = 10.1, 2.8 Hz, 1H), 6.62 (ddd, *J* = 8.8, 7.9, 2.9 Hz, 1H), 3.73 (s, 3H), 2.05 (s, 3H). LC-MS (ES) for $C_{17}H_{13}FN_2O_2$ $[M+1]^+$ 297.10.

6-fluoro-8-(4-fluoro-2-methoxyphenoxy)indolizine-2-carbonitrile (**33h**) (51%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 1.7 Hz, 1H), 7.51 (ddd, *J* = 4.1, 1.7, 0.9 Hz, 1H), 7.05 (dd, *J* = 8.8, 5.7 Hz, 1H), 6.95 (dd, *J* = 1.5, 0.9 Hz, 1H), 6.72 (dd, *J* = 10.0, 2.8 Hz, 1H), 6.65 (ddd, *J* = 8.8, 7.8, 2.9 Hz, 1H), 5.68 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.72 (s, 3H). LC-MS (ES) for $C_{16}H_{10}F_2N_2O_2$ $[M+1]^+$ 301.09.

6-chloro-8-(4-fluoro-2-methoxyphenoxy)indolizine-2-carbonitrile (**33i**) (50%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 2H), 7.04 (dd, *J* = 8.8, 5.7 Hz, 1H), 6.93 (s, 1H), 6.78 – 6.61 (m, 2H), 5.68 (d, *J* = 1.3 Hz, 1H), 3.72 (s, 3H). LC-MS (ES) for $C_{15}H_{10}ClFN_2O_2$ $[M+1]^+$ 317.05.

8-(5-fluoro-2-methoxyphenoxy)indolizine-2-carbonitrile (**33j**) (41%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 6.9 Hz, 1H), 6.94 – 6.84 (m, 2H), 6.83 (s, 1H), 6.78 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.43 (t, *J* = 7.2 Hz, 1H), 5.89 (d, *J* = 7.4 Hz, 1H), 3.74 (s, 3H). LC-MS (ES) for $C_{16}H_{11}FN_2O_2$ $[M+1]^+$ 283.06.

8-(4,5-difluoro-2-methoxyphenoxy)indolizine-2-carbonitrile (**33k**) (50%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 7.0 Hz, 1H), 6.97 (dd, *J* = 10.2, 7.9 Hz, 1H), 6.89 (s, 1H), 6.85 (dd, *J* = 11.6, 7.4 Hz, 1H), 6.46 (t, *J* = 7.2 Hz, 1H), 5.85 (d, *J* = 7.4 Hz, 1H), 3.76 (s, 3H). LC-MS (ES) for $C_{16}H_{10}F_2N_2O_2$ $[M+1]^+$ 301.08.

8-(4,5-difluoro-2-methoxyphenoxy)-6-fluoroindolizine-2-carbonitrile (**33l**) (55%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.7 Hz, 1H), 7.54 (ddd, *J* = 4.1, 1.7, 0.9 Hz, 1H), 6.99 (dd, *J* = 10.0, 7.8 Hz, 1H), 6.95 – 6.91 (m, 1H), 6.83 (dd, *J* = 11.5, 7.3 Hz, 1H), 5.72 (dd, *J* = 9.8, 1.7 Hz, 1H), 3.71 (s, 3H). LC-MS (ES) for $C_{16}H_9F_3N_2O_2$ $[M+1]^+$ 319.08.

8-(4-chloro-2-methoxyphenoxy)indolizine-2-carbonitrile (**33m**) (74%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 6.9 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.81 (s, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 6.82 (d, *J* = 1.2 Hz, 1H), 6.27 (t, *J* = 7.2 Hz, 1H), 5.98 (d, *J* = 7.4 Hz, 1H), 3.86 (s, 3H). LC-MS (ES) for $C_{15}H_9ClN_2O_2$ $[M+1]^+$ 285.49.

6-chloro-8-(4-chloro-2-methoxyphenoxy)indolizine-2-carbonitrile (**33n**) (73%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 1.8 Hz, 1H), 7.31 (dd, *J* = 1.4, 1.0 Hz, 1H), 7.01 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.78 – 6.72 (m, 2H), 6.34 (d, *J* = 1.5 Hz, 1H), 5.47 (d, *J* = 1.8 Hz, 1H), 3.70 (s, 3H). LC-MS (ES) for $C_{16}H_{10}Cl_2N_2O_2$ $[M+1]^+$ 334.10.

Step 5

A solution of BBr_3 (2.5 equiv, 1.0M in DCM) was added dropwise to a solution of the corresponding diether intermediate (1.0 equiv) in anhydrous DCM (1.0 mL per mmol

diether intermediate) under N_2 atmosphere at -78 °C. The reaction mixture was stirred for an additional 3h at 0 ºC. After this period, the solution was quenched with ice water, and the organic layer washed with water. The organic layer was dried over anhydrous Na_2SO_4, concentration by rotary evaporation, and purified by column chromatography to give **34a-n**.

2-((2-methylindolizin-8-yl)oxy)phenol (**34a**) (64%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 1H), 7.10 – 6.92 (m, 4H), 6.60 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.17 – 6.09 (m, 3H), 2.08 (s, 3H). LC-MS (ES) for $C_{15}H_{13}NO_2$ $[M+1]^+$ 240.01.

8-(2-hydroxyphenoxy)indolizine-2-carbonitrile (**34b**) (94%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.0 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.47 (t, *J* = 7.2 Hz, 1H). LC-MS (ES) for $C_{15}H_{10}N_2O_2$ $[M+1]^+$ 250.21

8-(2-hydroxyphenoxy)-6-methylindolizine-2-carbonitrile (**34c**) (40%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.9 Hz, 1H), 7.32 (s, 1H), 7.02 – 6.93 (m, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 8.0 Hz, 1H), 6.68 (s, 1H), 5.79 (s 1H), 5.35 (s, 1H), 2.00 (s, 3H). LC-MS (ES) for $C_{16}H_{12}N_2O_2$ $[M+1]^+$ 265.20.

6-fluoro-8-(2-hydroxyphenoxy)indolizine-2-carbonitrile (**34d**) (57%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.0 Hz, 1H), 7.51 (ddd, *J* = 4.0, 1.7, 0.9 Hz, 1H), 7.26 – 7.17 (m, 1H), 6.95 (td, *J* = 8.3, 1.5 Hz, 2H), 6.86 – 6.78 (m, 2H), 5.87 (dd, *J* = 9.7, 1.7 Hz, 1H), 5.25 (s, 1H). LC-MS (ES) for $C_{15}H_9FN_2O_2$ $[M+1]^+$ 269.02.

6-chloro-8-(2-hydroxyphenoxy)indolizine-2-carbonitrile (**34e**) (41%) ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.60 – 7.57 (m, 1H), 7.59 (d, *J* = 1.7 Hz, 1H), 7.02 – 6.91 (m, 4H), 6.82 (d, *J* = 1.0 Hz, 1H), 5.83 (s, 1H), 5.53 (br, 1H). LC-MS (ES) for $C_{15}H_9ClN_2O_2$ $[M+1]^+$ 285.25.

8-(4-fluoro-2-hydroxyphenoxy)indolizine-2-carbonitrile (**34f**) (52%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 7.0 Hz, 1H), 6.93 (dd, *J* = 9.0, 5.3 Hz, 1H), 6.86 – 6.82 (m, 1H), 6.77 (dd, *J* = 9.4, 2.9 Hz, 1H), 6.71 (dd, *J* = 8.8, 5.2 Hz, 1H), 6.20 (t, *J* = 7.2 Hz, 1H), 5.98 (d, *J* = 7.4 Hz, 1H), 5.41 (s, 1H). LC-MS (ES) for $C_{15}H_9FN_2O_2$ $[M+1]^+$ 269.00.

8-(4-fluoro-2-hydroxyphenoxy)-6-methylindolizine-2-carbonitrile (**34g**) (45%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.6 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.05 (dd, *J* = 8.8, 5.7 Hz, 1H), 6.83 – 6.78 (m, 1H), 6.60 – 6.56 (m, 2H), 5.81 (s, 1H), 5.43(s, 1H), 2.05 (s, 3H). LC-MS (ES) for $C_{16}H_{11}FN_2O_2$ $[M+1]^+$ 283.09.

6-fluoro-8-(4-fluoro-2-hydroxyphenoxy)indolizine-2-carbonitrile (**34h**) (52%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.6 Hz, 1H), 7.60 (ddd, *J* = 4.0, 1.6, 0.9 Hz, 1H), 7.11 (dd, *J* = 8.8, 5.7 Hz, 1H), 6.91 (dd, *J* = 1.6, 0.9 Hz, 1H), 6.70 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.64 (ddd, *J* = 8.8, 7.8, 2.9 Hz, 1H), 5.72 (dd, *J* = 10.0, 1.7 Hz, 1H), 5.42 (s, 1H). LC-MS (ES) for $C_{15}H_8F_2N_2O_2$ $[M+1]^+$ 287.03.

6-chloro-8-(4-fluoro-2-hydroxyphenoxy)indolizine-2-carbonitrile (**34i**) (49%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.57 (m, 1H), 7.52 (d, *J* = 1.6 Hz, 1H), 6.89 (dd, *J* = 8.9, 5.4 Hz, 1H), 6.82 (d, *J* = 1.0 Hz, 1H), 6.70 (dt, *J* = 9.3, 2.6 Hz, 1H), 6.53 (ddt, *J* = 8.9, 7.9, 2.9 Hz, 1H), 5.83 (d, *J* = 1.3 Hz, 1H), 5.53 (br, 1H). LC-MS (ES) calcd for $C_{15}H_8ClFN_2O_2$ $[M+1]^+$ 303.29.

8-(5-fluoro-2-hydroxyphenoxy)indolizine-2-carbonitrile (**34j**) (61%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 6.98 (q, J = 4.4 Hz, 1H), 6.80 – 6.76 (m, 2H), 6.69 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.49 (t, *J* = 7.4 Hz, 1H), 6.13 (d, *J* = 7.4 Hz, 1H), 5.19 (s, 1H). LC-MS (ES) for $C_{15}H_9FN_2O_2$ $[M+1]^+$ 269.08.

8-(4,5-difluoro-2-hydroxyphenoxy)indolizine-2-carbonitrile (**34k**) (68%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 1.4 Hz, 1H), 7.56 (s, 1H), 6.85 – 6.69 (m, 3H), 6.40 (t, *J* = 7.3 Hz, 1H), 5.96 (d, *J* = 7.4 Hz, 1H), 5.63 (s, 1H). LC-MS (ES) for $C_{16}H_{10}F_2N_2O_2$ $[M+1]^+$ 301.09.

8-(4,5-difluoro-2-hydroxyphenoxy)-6-fluoroindolizine-2-carbonitrile (**34l**) (76%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.6 Hz, 1H), 7.62 (d, *J* = 3.2 Hz, 1H), 6.96 – 6.84 (m, 3H), 5.98 (dd, *J* = 9.4, 1.7 Hz, 1H), 5.23 (S, 1H). LC-MS (ES) for $C_{15}H_7F_3N_2O_2$ $[M+1]^+$ 305.05.

8-(4-chloro-2-hydroxyphenoxy)indolizine-2-carbonitrile (**34m**) (33%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 1.6 Hz, 1H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.05 (d, *J* = 2.4 Hz,

1H), 6.87 (s, 1H), 6.84 – 6.79 (m, 2H), 6.47 (t, *J* = 7.2 Hz, 1H), 6.05 (d, *J* = 7.4 Hz, 1H), 5.39 (s, 1H). LC-MS (ES) for $C_{14}H_7ClN_2O_2$ $[M+1]^+$ 271.57.

6-chloro-8-(4-chloro-2-hydroxyphenoxy)indolizine-2-carbonitrile (**34n**) (39%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 1.6 Hz, 1H), 7.38 (dd, *J* = 1.4, 1.0 Hz, 1H), 7.06 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.67 (d, *J* = 1.5 Hz, 1H), 5.74 (d, *J* = 1.5 Hz, 1H), 5.23 (s, 1H). LC-MS (ES) for $C_{15}H_8Cl_2N_2O_2$ $[M+1]^+$ 320.09.

Step 6

17 (1.2 equiv) and K_2CO_3 (2.0 equiv) were added to a solution of the corresponding catechol aryl ether intermediate (1.0 equiv) in anhydrous DMF (1.0 mL per mmol catechol aryl ether intermediate) and the mixture was stirred for 3 h at 60 ºC to complete the reaction. The reaction mixture was poured into brine and extracted with ethyl acetate. The organic layer was sequentially washed with brine, dried over anhydrous Na_2SO_4, and concentration by rotary evaporation. The crude product was dissolved in DCM (0.5 mL per mmol catechol diether intermediate) and NH_4OH (0.5 mL per mmol catechol aryl ether intermediate) were added. The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was concentrated by rotary evaporation and purified by column chromatography to give **10a-n**.

1-(2-(2-((2-methylindolizin-8-yl)oxy)phenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (**10a**) (36%) ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.89 – 9.70 (m, 1H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.38 (d, *J* = 0.7 Hz, 1H), 7.31 – 7.11 (m, 3H), 7.09 – 7.01 (m, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.45 (s, 1H), 6.26 (s, 1H), 5.69 – 5.56 (m, 1H), 4.84 – 4.64 (m, 1H), 4.30 – 4.17 (m, 2H), 4.04 – 3.87 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.29, 158.44, 150.60, 149.95, 145.73, 143.75, 140.21, 134.36, 125.50, 122.62, 122.25, 119.35, 115.10, 111.53, 101.12, 96.83, 66.26, 47.98, 21.24. HRMS (ES) calcd for $C_{21}H_{19}N_3O_4$ $[M+1]^+$ 378.1271, found 378.1270.

8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethoxy)phenoxy)indolizine-2-carbonitrile (**10b**) (51 %) ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.81 (s, 1H), 8.19 (d, *J* = 1.7 Hz, 1H), 7.96 (d, *J* = 7.0 Hz, 1H), 7.40 – 7.02 (m, 4H), 7.02 – 6.78 (m, 2H), 6.56 (t, *J* = 7.2 Hz, 1H), 5.78 (d, *J* = 7.4 Hz, 1H), 4.71 (d, *J* = 7.9 Hz, 1H), 4.33 – 4.19 (m, 2H),

4.07 – 3.95 (m, 2H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 163.67, 151.51, 150.91, 146.29, 143.16, 128.41, 127.75, 123.89, 122.75, 120.99, 120.49, 116.66, 115.16, 113.59, 101.06, 100.68, 99.57, 97.52, 67.16, 48.58. HR-MS (ES) calcd for $C_{21}H_{16}N_4O_4$ $[M+1]^+$ 389.1245, found 389.1247.

8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)-6-methylindolizine-2-carbonitrile (**10c**) (36%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.27 (d, *J* = 1.7 Hz, 1H), 7.83 – 7.76 (m, 1H), 7.39 – 7.24 (m, 3H), 7.12 (td, *J* = 7.9, 1.7 Hz, 1H), 7.04 – 6.95 (m, 2H), 5.58 (s, 1H), 4.70 (dd, *J* = 7.8, 2.2 Hz, 1H), 4.24 (t, *J* = 4.9 Hz, 2H), 3.95 (t, *J* = 4.8 Hz, 2H), 2.06 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.27, 150.65, 150.08, 148.71, 145.56, 141.48, 126.90, 125.68, 122.82, 122.03, 121.86, 119.63, 117.58, 116.54, 114.50, 101.68, 100.04, 99.46, 95.02, 65.86, 47.26, 17.91. HR-MS (ES) calcd for $C_{22}H_{18}N_4O_4$ $[M+1]^+$ 403.1406, found 403.1368.

8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)-6-fluoroindolizine-2-carbonitrile (**10d**) (65%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.37 (d, *J* = 1.6 Hz, 1H), 8.26 (d, *J* = 3.9 Hz, 1H), 7.44 – 7.28 (m, 3H), 7.21 – 7.09 (m, 2H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.75 (dd, *J* = 10.1, 1.6 Hz, 1H), 4.71 (d, *J* = 7.8 Hz, 1H), 4.25 (t, *J* = 4.8 Hz, 2H), 3.97 (t, *J* = 4.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.62, 154.69, 152.84, 151.02, 150.24, 146.01, 141.29, 127.91, 125.01, 123.23, 122.29, 116.43, 114.89, 107.42, 107.07, 102.12, 99.76, 96.43, 93.04, 66.20, 47.55. HR-MS (ES) calcd for $C_{21}H_{15}FN_4O_4$ $[M+1]^+$ 407.1156, found 407.1114.

8-(4-chloro-2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)indolizine-2-carbonitrile (**10e**) (41%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 1.0 Hz, 1H), 7.06 – 7.00 (m, 3H), 6.97 (d, *J* = 2.1 Hz, 1H), 6.92 (s, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 5.53 (d, *J* = 1.3 Hz, 1H), 4.63 (dd, *J* = 7.9, 2.2 Hz, 1H), 4.15 (t, *J* = 4.7 Hz, 2H), 3.92 (t, *J* = 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.11, 150.82, 150.65, 150.09, 145.33, 140.59, 133.02, 125.91, 124.53, 123.08, 121.85, 119.71, 118.03, 115.80, 115.42, 110.54, 102.68, 101.10, 98.40, 66.76, 48.85. HR-MS (ES) calcd for $C_{21}H_{15}ClN_4O_4$ $[M+1]^+$ 423.0860, found 423.0862.

8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4-fluorophenoxy)indolizine-2-carbonitrile (**10f**) (33%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 8.34 (d, *J* = 1.5 Hz, 1H), 7.98 (d, *J* = 6.9 Hz, 1H), 7.26 (ddd, *J* = 26.6, 9.7, 4.3 Hz, 2H), 7.01 (s, 1H), 6.97 – 6.84 (m, 2H), 6.54 (t, *J* = 7.2 Hz, 1H), 5.73 (d, *J* = 7.4 Hz, 1H), 4.66 (dd, *J* = 7.8, 1.6 Hz, 1H), 4.20 (t, *J* = 4.8 Hz, 2H), 3.90 (t, *J* = 4.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.25, 158.88, 150.95, 150.64, 149.32, 145.55, 137.78, 126.64, 123.84, 120.32, 120.22, 116.40, 112.63, 107.67, 102.72, 100.11, 99.52, 98.58, 95.57, 66.31, 46.83. HR-MS (ES) calcd for $C_{21}H_{15}FN_4O_4$ $[M+1]^+$ 407.1156, found 407.1139.

8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4-fluorophenoxy)-6-methylindolizine-2-carbonitrile (**10g**) (50%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.26 (d, *J* = 1.7 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.30 (ddd, *J* = 19.4, 9.7, 4.4 Hz, 2H), 7.04 – 6.86 (m, 3H), 5.60 (s, 1H), 4.66 (dd, *J* = 7.8, 2.2 Hz, 1H), 4.25 (t, *J* = 4.8 Hz, 2H), 3.95 (t, *J* = 4.8 Hz, 2H), 2.06 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.64, 161.43, 159.50, 151.51, 151.02, 149.13, 145.84, 138.09, 125.95, 124.18, 122.43, 120.02, 116.91, 108.11, 103.18, 101.87, 100.42, 99.86, 95.43, 66.68, 47.43, 18.28. HR-MS (ES) calcd for $C_{22}H_{17}FN_4O_4$ $[M+1]^+$ 421.1312, found 421.1277.

8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4-fluorophenoxy)-6-fluoroindolizine-2-carbonitrile (**10h**) (46%) ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.82 (s, 1H), 8.21 (d, *J* = 1.7 Hz, 1H), 8.08 (ddd, *J* = 4.6, 1.8, 0.9 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1H), 7.31 (ddd, *J* = 10.1, 8.1, 1.5 Hz, 1H), 7.14 (td, *J* = 7.7, 1.5 Hz, 1H), 7.10 (dd, *J* = 1.6, 0.9 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 5.76 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.72 (dd, *J* = 7.9, 2.1 Hz, 1H), 4.32 (t, *J* = 4.9 Hz, 2H), 4.04 (t, *J* = 4.9 Hz, 2H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 163.19, 153.59, 151.05, 150.87, 145.84, 141.98, 127.94, 125.75, 123.44, 122.40, 121.48, 115.84, 114.77, 107.17, 106.83, 102.09, 100.09, 93.08, 92.86, 66.58, 48.17. HR-MS (ES) calcd for $C_{21}H_{14}F_2N_4O_4$ $[M+1]^+$ 425.1061, found 425.1058.

6-chloro-8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4-fluorophenoxy)indolizine-2-carbonitrile (**10i**) (41%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.60 (s, 1H), 7.08 (dd, *J* = 8.6, 5.6 Hz, 1H), 6.93 (s, 1H), 6.72 (ddt, *J* = 12.3, 6.5, 2.8 Hz, 3H), 6.61 (d, *J* = 7.9 Hz, 1H), 5.52 (d, *J* = 1.2 Hz,

1H), 4.60 (dd, *J* = 7.9, 2.1 Hz, 1H), 4.14 (t, *J* = 4.7 Hz, 2H), 3.92 (t, *J* = 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.55, 162.00, 150.70, 150.17, 150.00, 144.98, 137.46, 125.63, 124.00, 121.52, 119.26, 117.50, 115.48, 108.92, 102.58, 102.27, 100.64, 100.44, 97.94, 66.23, 48.45. HR-MS (ES) calcd for $C_{21}H_{14}ClFN_4O_4$ $[M+1]^+$ 441.0766, found 441.0755.

8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-5-fluorophenoxy)indolizine-2-carbonitrile (**10j**) (37%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 6.9 Hz, 1H), 6.89 (dd, *J* = 6.3, 1.4 Hz, 2H), 6.86 – 6.80 (m, 2H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.34 (t, *J* = 7.2 Hz, 1H), 5.66 (d, *J* = 7.4 Hz, 1H), 4.70 (d, *J* = 7.9 Hz, 1H), 4.11 (t, *J* = 4.7 Hz, 2H), 3.91 (t, *J* = 4.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.15, 158.39,156.42, 150.56, 149.47, 146.46, 145.21, 127.08, 120.03, 119.00, 115.91, 115.15, 112.94, 112.62, 111.03, 100.96, 100.77, 99.16, 97.37, 67.05, 48.42. HR-MS (ES) calcd for $C_{21}H_{15}FN_4O_4$ $[M+1]^+$ 407.1156, found 407.1134.

8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4,5-difluorophenoxy)indolizine-2-carbonitrile (**10k**) (48%) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.39 (d, *J* = 1.7 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 1H), 7.58 (ddd, *J* = 28.5, 11.6, 8.0 Hz, 2H), 7.04 (s, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.60 (t, *J* = 7.2 Hz, 1H), 5.89 (d, *J* = 7.4 Hz, 1H), 4.75 (d, *J* = 7.8 Hz, 1H), 4.23 (t, *J* = 4.9 Hz, 2H), 3.94 (t, *J* = 4.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.25, 150.63, 148.90, 146.83, 146.76, 145.53, 126.44, 120.68, 120.31, 116.35, 112.55, 112.48, 112.32, 104.30, 104.12, 100.09, 99.57, 99.13, 95.64, 66.83, 46.83. HR-MS (ES) calcd for $C_{21}H_{15}FN_4O_4$ $[M+1]^+$ 425.1061, found 425.1044.

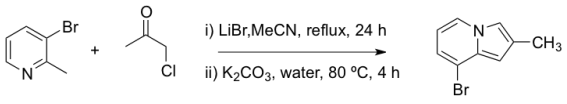
8-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4,5-difluorophenoxy)-6-fluoroindolizine-2-carbonitrile (**10l**) (48%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.77 (d, *J* = 1.8 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.11 – 7.07 (m, 1H), 6.99 (s, 1H), 6.92 – 6.91 (m, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 5.58 (dd, *J* = 9.4, 1.8 Hz, 1H), 4.75 (d, *J* = 7.6 Hz, 1H), 4.19 (t, *J* = 4.3 Hz, 2H), 3.99 (t *J* = 4.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.70, 154.94, 153.05, 150.28, 144.91, 124.82, 120.32, 115.43, 112.80, 112.65, 106.77,

106.44, 104.35, 104.17, 102.34, 100.79, 97.89, 93.16, 92.91, 67.09, 48.39. HR-MS (ES) calcd for $C_{21}H_{13}F_3N_4O_4$ $[M+1]^+$ 443.0967, found 443.0935.

8-(4-chloro-2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)indolizine-2-carbonitrile (**10m**) (39%) ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.14 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 6.9 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.83 – 6.72 (m, 2H), 6.34 (t, *J* = 7.2 Hz, 1H), 5.58 (d, *J* = 7.4 Hz, 1H), 4.51 (dd, *J* = 7.8, 2.2 Hz, 1H), 4.02 (t, *J* = 4.9 Hz, 2H), 3.69 (t, *J* = 4.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.27, 150.71, 150.65, 148.91, 145.55, 140.64, 130.50, 126.60, 123.98, 121.46, 120.56, 120.28, 116.36, 114.82, 112.60, 100.13, 99.59, 99.19, 95.62, 66.35, 46.83. HR-MS (ES) calcd for $C_{21}H_{15}ClN_4O_4$ $[M+1]^+$ 423.0860, found 423.0838.

6-chloro-8-(4-chloro-2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)indolizine-2-carbonitrile (**10n**) (38%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.37 (d, *J* = 1.7 Hz, 1H), 8.27 (d, *J* = 4.0 Hz, 1H), 7.40 (dd, *J* = 8.8, 5.8 Hz, 1H), 7.35 – 7.27 (m, 1H), 7.18 (s, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.01 – 6.92 (m, 1H), 5.90 – 5.78 (m, 1H), 4.69 (d, *J* = 7.5 Hz, 1H), 4.27 (t, *J* = 4.6 Hz, 2H), 3.97 (t, *J* = 4.6 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.08, 151.31, 150.51, 146.90, 146.68, 130.19, 125.72, 124.02, 123.65, 122.11, 120.45, 119.70, 115.88, 115.79, 113.13, 113.01, 105.32, 100.81, 97.71, 67.17, 47.31. HR-MS (ES) calcd for $C_{21}H_{14}Cl_2N_4O_4$ $[M+1]^+$ 458.0470, found 458.0438.

Synthesis of Compound 35



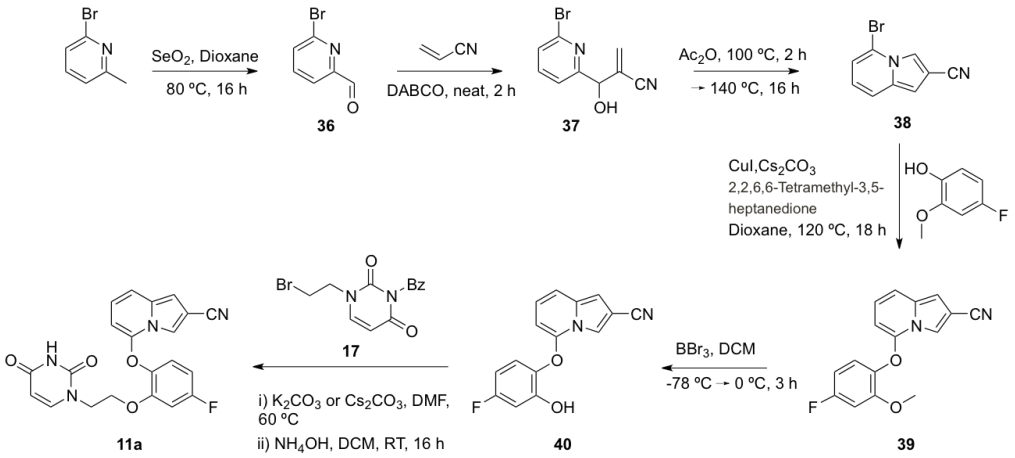
35

8-bromo-2-methylindolizine (**35**). A mixture of cloroacetone (17 mmol), LiBr (17 mmol) in acetonitrile (10 mL) was stirred at room temperature for 15 min. Then, a solution of 2-bromo-3-methylpyridine (19 mmol) in acetonitrile (10 mL) was added and

the resulting mixture was heated at reflux for 24 h. The mixture was cooled to room temperature and the solvent was removed under reduce pressure. The residue was diluted with water extracted with diethylether. The aqueous was treated with K_2CO_3 (96 mmol) and heated at 80 ºC for 2 h. The mixture was cooled to room temperature and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **35**. (34 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, J = 6.9, 0.8 Hz, 1H), 7.20 – 7.07 (m, 1H), 6.83 (dd, J = 7.1, 0.7 Hz, 1H), 6.40 (s, 1H), 6.25 (t, J = 7.0 Hz, 1H), 2.39 (s, 3H). LC-MS (ES) for C_9H_8BrN $[M+1]^+$ 209.11.

5. Synthesis of Compound 11a

Scheme 2.2



Step 1

6-bromopicolinaldehyde (36) Following step A1 in the synthetic scheme 2.1 from 2-bromo-6-methylpyridine was obtained **36** after column chromatography. (71%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.84 (dd, J = 7.8, 1.5 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.70 (dd, J = 7.7, 1.4 Hz, 1H). LC-MS (ES) for C_6H_4BrNO $[M+1]^+$ 187.37.

Step 2

2-((6-bromopyridin-2-yl)(hydroxy)methyl)acrylonitrile (**37**) Following step 2 in the synthetic scheme 2.1 from **36** was obtained **37** after column chromatography. (84%) ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 6.20 (d, *J* = 1.4 Hz, 2H), 5.22 (s, 1H), 4.37 (s, 1H). LC-MS (ES) for $C_9H_7BrN_2O$ $[M+1]^+$ 240.04.

Step 3

5-bromoindolizine-2-carbonitrile (**38**) Following step 2 in the synthetic scheme 2.1 from **37** was obtained **38** after column chromatography. (84%) ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 6.20 (d, *J* = 1.4 Hz, 2H), 5.22 (s, 1H), 4.37 (s, 1H). LC-MS (ES) for $C_9H_7BrN_2O$ $[M+1]^+$ 240.04.

Step 4

5-(4-fluoro-2-methoxyphenoxy)indolizine-2-carbonitrile (**39**) Following step 3 in the synthetic scheme 2.1 from **38** was obtained **39** after column chromatography. (30%) ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 6.75 – 6.69 (m, 2H), 6.69 – 6.63 (m, 1H), 6.61 (s, 1H), 6.56 (td, *J* = 7.0, 1.2 Hz, 1H), 3.70 (s, 3H). LC-MS (ES) for $C_{16}H_{11}FN_2O_2$ $[M+1]^+$ 283.01.

Step 5

5-(4-fluoro-2-hydroxyphenoxy)indolizine-2-carbonitrile (**40**) Following step 4 in the synthetic scheme 2.1 from **39** was obtained **40** after column chromatography. (37%) ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.09 (d, *J* = 9.1 Hz, 1H), 7.01 (dd, *J* = 9.0, 5.3 Hz, 1H), 6.79 (dd, *J* = 9.3, 2.9 Hz, 1H), 6.71 – 6.66 (m, 2H), 6.56 (td, *J* = 7.0, 1.2 Hz, 1H), 5.62 (s, 1H). LC-MS (ES) for $C_{15}H_9FN_2O_2$ $[M+1]^+$ 269.07.

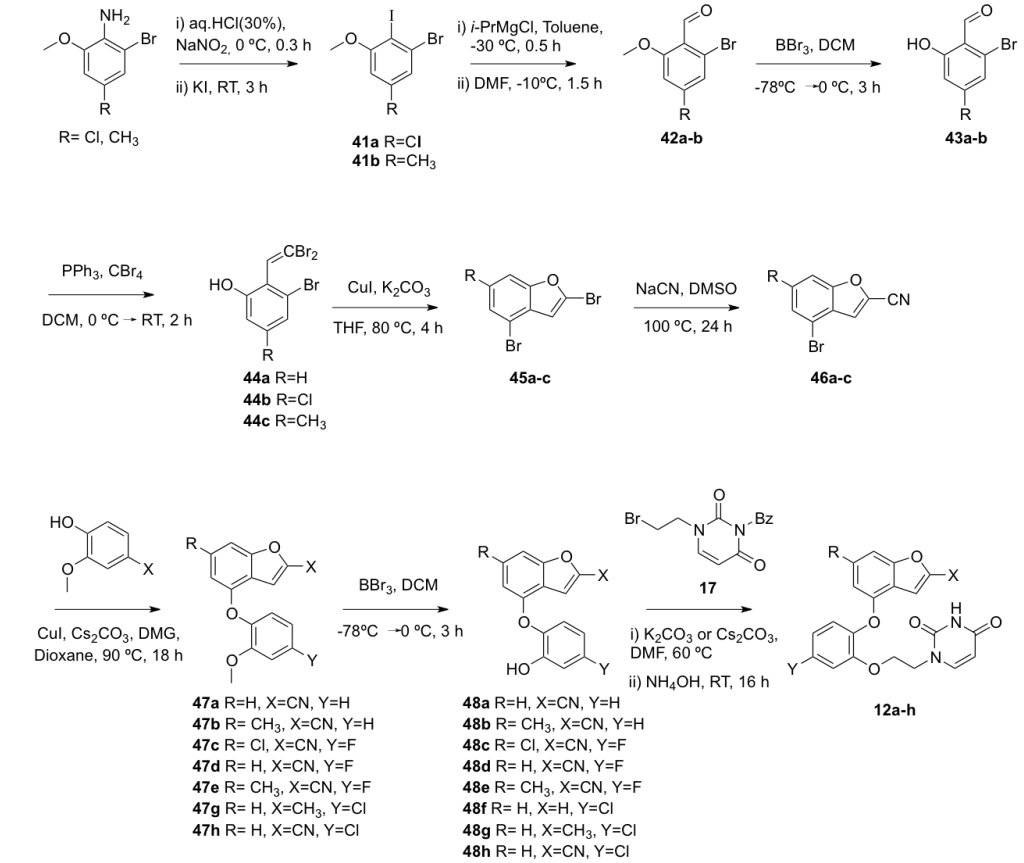
Step 6

5-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4-fluorophenoxy)indolizine-2-carbonitrile (**11a**) Following step 6 in the synthetic scheme 2.1 from **40** was obtained **11a** after column chromatography. (29%) ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.3 Hz, 1H), 7.78 (s, 1H), 7.16 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.07 (d, *J*

= 9.0 Hz, 1H), 6.77 – 6.67 (m, 3H), 6.66 – 6.56 (m, 1H), 6.24 (d, *J* = 7.9 Hz, 1H), 5.46 (d, *J* = 6.8 Hz, 1H), 4.69 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.10 (t, *J* = 4.6 Hz, 2H), 3.85 (t, *J* = 4.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.85, 159.79, 157.87, 156.65, 151.38, 151.15, 146.46, 144.08, 142.41, 139.81, 134.98, 128.86, 121.44, 120.34, 116.37, 116.09, 106.46, 101.82, 101.10, 68.89, 48.72. HR-MS (ES) calcd for $C_{21}H_{15}FN_4O_4$ $[M+1]^+$ 407.1156, found 407.1129.

6. Synthesis of Compounds 12 a-h

Scheme 3.1



Step1

The mixture of the corresponding aniline (1.0 equiv), and 50% aq. HCl (30%) in acetonitrile was cooled to 0 °C, then a solution of $NaNO_2$ (1.5 equiv) in H_2O (5.0 mL per

mmol aniline) was added and stirred for 20 min. Then, a solution of KI (2.0 equiv) in H_2O (2.0 mL per mmol KI) was added dropwise to the above solution. After addition, the dark brown solid was started to precipitate and the mixture was allowed to warm to room temperature and stirred for an additional 3 h. The result solid was filtered, washed with 1N aq. HCl solution, and dried to give the corresponding iodobenzene intermediate **41a-b**.

1-bromo-5-chloro-2-iodo-3-methoxybenzene (**41a**) (91%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 2.1 Hz, 1H), 3.81 (s, 3H). LC-MS (ES) for $C_7H_5BrClIO$ $[M+1]^+$ 348.06.

1-bromo-2-iodo-3-methoxy-5-methylbenzene (**41b)** (83%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 6.62 (s, 1H), 3.78 (s, 3H), 2.29 (s, 3H). LC-MS (ES) for C_8H_8BrIO $[M+1]^+$ 327.44.

Step 2

A solution of the corresponding iodobenzene intermediate (1.0 equiv) in toluene (5.0 mL per iodoaryl intermediate) was cooled to a temperature of -30 ºC. Then, a solution of isopropyl magnesium chloride (1.5 equiv, 2.0 M in THF) was added slowly over 0.5 h. A clear brown solution was obtained. Stirring was continued for 1 h. Anhydrous DMF (4.0 equiv) was added slowly over 5 min, the temperature of the reaction mixture increased to -19 ºC. The reaction mixture was warmed to 0 ºC over 1 h. The reaction was quenched into saturated aqueous NH_4Cl, and allowed to warm to room temperature. Ethyl acetate and water were added and the layers were separated. The organic layer was washed with brine, concentrated by rotary evaporator, and purified by column chromatography to give **42a-b**.

2-bromo-4-chloro-6-methoxybenzaldehyde (**42a**) (91%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 1H), 10.19 (d, *J* = 0.5 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 1H), 6.91 (dd, *J* = 1.9, 0.6 Hz, 2H). LC-MS (ES) for $C_7H_4BrClO_2$ $[M+1]^+$ 235.98.

2-bromo-6-hydroxy-4-methylbenzaldehyde (**42b**) (86%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 9.72 (s, 1H), 7.61 (s, 1H), 6.84 (s, 1H), 2.35 (s, 4H). LC-MS (ES) for $C_8H_7BrO_2$ $[M+1]^+$ 215.83.

Step 3

A solution of BBr_3 (2.5 equiv, 1.0M in DCM) was added dropwise to a solution of the corresponding benzaldehyde intermediate (1.0 equiv) in DCM (5.0 mL per mmol bezaldehyde intermediate) under N_2 at -78 ºC. The reaction mixture was stirred for an additional 3 h at 0 ºC. After this period, the solution was quenched with ice water, and the organic layer was washed with water. The organic solvent was concentrated by rotary evaporation and purified by column chromatography to give **43a-b**.

2-bromo-4-chloro-6-hydroxybenzaldehyde (**43a)** (73%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 1H), 10.19 (d, *J* = 0.5 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 1H), 6.91 (dd, *J* = 1.9, 0.6 Hz, 2H). LC-MS (ES) for $C_7H_4BrClO_2$ $[M+1]^+$ 235.98.

2-bromo-6-hydroxy-4-methylbenzaldehyde (**43b**) (88%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 9.72 (s, 1H), 7.61 (s, 1H), 6.84 (s, 1H), 2.35 (s, 4H). LC-MS (ES) for $C_8H_7BrO_2$ $[M+1]^+$ 215.83.

Step 4[8]

The mixture of the corresponding aldehyde intermediate (1.0 equiv) and CBr_4 (3.0 equiv) in DCM (5.0 mL per mmol aldehyde intermediate) was cooled to 0 ºC. After 20 min, PPh_3 (3.0 equiv) in DCM (5.0 mL per PPh_3) was added dropwise over 30 min and stirred for an additional 1 h at 0 °C. After which it was allowed to warm to room temperature and stirred for an additional 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution. The phases were then separated, and the aqueous layer was extracted with DCM. The combined organic layer was concentrated by rotary evaporation and purified by column chromatography to give **44a-c**.

3-bromo-2-(2,2-dibromovinyl)phenol (**44a)** (62%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.09 – 7.03 (m, 2H), 6.83 (d, *J* = 1.2 Hz, 1H), 5.04 (s, 1H). LC-MS (ES) for $C_8H_5Br_3O$ $[M+1]^+$ 357.27

3-bromo-5-chloro-2-(2,2-dibromovinyl)phenol (**44b**) (43%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.14 (d, *J* = 1.9 Hz, 1H), 6.86 (d, *J* = 1.9 Hz, 1H), 5.15 (s, 1H). LC-MS (ES) for $C_8H_4Br_3ClO$ $[M+1]^+$ 392.00.

3-bromo-2-(2,2-dibromovinyl)-5-methylphenol (**44c**) (46%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.39 (s, 1H), 6.66 (s, 1H), 4.89 (s, 1H), 2.26 (s, 3H). LC-MS (ES) for $C_9H_7Br_3O$ $[M+1]^+$ 371.46.

Step 5[8]

K_3PO_4 (2.0 equiv) and CuI (0.1 equiv) were added to a solution of the corresponding gem-dibromoolefin (1.0 equiv) in THF (3.0 mL per mmol of gem-dibromoolefin intermediate). The flask was flushed with nitrogen for 5 min and the vial sealed and placed in a pre-heated oil bath at 80 ºC. The vial was stirred for 4 h, after which it was allowed to cool to room temperature. The contents were filtered over a pad of silica gel, washing with ethyl acetate. The resulting solution was concentrated by rotary evaporation and purified by column chromatography to give **45a-c**.

2,4-dibromobenzofuran (**45a**) (85%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 0.9 Hz, 1H). LC-MS (ES) for $C_8H_4Br_2O$ $[M+1]^+$ 276.71.

2,4-dibromo-6-chlorobenzofuran (**45b**) (90%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 6.69 (s, 1H). LC-MS (ES) for $C_8H_3Br_2ClO$ $[M+1]^+$ 311.12.

2,4-dibromo-6-methylbenzofuran (**45c)** (85%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.36 (s, 1H), 6.66 (d, *J* = 0.9 Hz, 1H), 2.50 (s, 3H). LC-MS (ES) for $C_9H_6Br_2O$ $[M+1]^+$ 290.64.

Step 6[9]

Sodium cyanide (1.5 equiv) was added to a solution of the corresponding dibromobenzofuran intermediate (1.0 equiv) in dry DMSO (3.0 mL per mmol of Benzofuran intermediate) under N_2 at 100 ºC for 24 h, quenched with saturated NH_4Cl solution and diluted with ethyl acetate. The organic layer was separated and washed with

water, dried by rotary evaporation, and purified by column chromatography to give **46a-c**.

4-bromobenzofuran-2-carbonitrile (**46a**) (35%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 3H), 7.32 (dd, *J* = 8.4, 7.7 Hz, 1H). LC-MS (ES) for C_9H_4BrNO $[M+1]^+$ 222.90.

4-bromo-6-chlorobenzofuran-2-carbonitrile (**46b**) (29%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.39 (d, *J* = 0.9 Hz, 1H), 7.28 (d, *J* = 1.8 Hz, 1H). LC-MS (ES) for $C_9H_3BrClNO$ $[M+1]^+$ 257.31.

4-bromo-6-methylbenzofuran-2-carbonitrile (**46c**) (38%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.38 (s, 1H), 7.30 (d, *J* = 0.9 Hz, 1H), 2.47 (s, 3H). LC-MS (ES) for $C_{10}H_6BrNO$ $[M+1]^+$ 236.88.

Step 7

A mixture of the corresponding benzofuran intermediate (1.0 equiv), the corresponding catechol (2.5 equiv), Cs_2CO_3 (2.2 equiv), CuI (0.2 equiv), *N,N*-dimethyl glycine hydrochloride (0.4 equiv) in dioxane (5.0 mL per mmol benzofuran intermediate) in a sealed tube was heated to 90 ºC under N_2 atmosphere for 18 h. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography to give **47a-e** and **47g-h**.

4-(2-methoxyphenoxy)benzofuran-2-carbonitrile (**47a**) (53%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 0.9 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.99 (td, *J* = 7.9, 1.5 Hz, 2H), 6.91 (td, *J* = 7.7, 1.5 Hz, 1H), 6.53 (dd, *J* = 8.0, 0.6 Hz, 1H), 3.73 (s, 3H). LC-MS (ES) for $C_{16}H_{11}NO_3$ $[M+1]^+$ 266.08.

4-(2-methoxyphenoxy)-6-methylbenzofuran-2-carbonitrile (**47b**) (71%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.23 (d, *J* = 0.9 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.75 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.66 (s, 1H) 6.64 – 6.59 (m, 2H), 3.69 (s, 3H), 2.39 (s, 3H). LC-MS (ES) for $C_{17}H_{13}NO_3$ $[M+1]^+$ 280.07.

6-chloro-4-(2-methoxyphenoxy)benzofuran-2-carbonitrile (**47c**) (59%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 1.5 Hz, 1H), 7.36 (d, *J* = 0.9 Hz, 1H), 7.24 – 7.13 (m, 2H), 7.06 – 6.95 (m, 2H), 6.45 (d, *J* = 1.5 Hz, 1H), 3.72 (s, 3H). LC-MS (ES) for $C_{16}H_{10}ClNO_3$ $[M+1]^+$ 300.52.

4-(4-fluoro-2-methoxyphenoxy)benzofuran-2-carbonitrile (**47d**) (67%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 0.9 Hz, 1H), 7.37 (t, *J* = 8.2 Hz, 1H), 7.33 (s, 1H), 7.30 – 7.27 (m, 2H), 7.02 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.64 (dd, *J* = 8.0, 0.6 Hz, 1H), 3.77 (s, 3H). LC-MS (ES) for $C_{16}H_{10}FNO_3$ $[M+1]^+$ 284.10.

4-(4-fluoro-2-methoxyphenoxy)-6-methylbenzofuran-2-carbonitrile (**47e**) (34%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.20 (d, *J* = 0.8 Hz, 1H), 6.81 – 6.74 (m, 2H), 6.69 (dd, *J* = 10.1, 2.8 Hz, 1H), 6.56 (ddd, *J* = 8.7, 7.9, 2.9 Hz, 1H), 3.74 (s, 3H), 2.40 (s, 3H). LC-MS (ES) for $C_{17}H_{12}FNO_3$ $[M+1]^+$ 297.74.

4-(4-chloro-2-methoxyphenoxy)-2-methylbenzofuran (**47g**) (48%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 1H), 7.20 – 7.04 (m, 1H), 6.99 (dd, *J* = 5.2, 2.2 Hz, 1H), 6.91 – 6.77 (m, 2H), 6.63 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.39 – 6.18 (m, 1H), 3.85 (s, 3H), 2.42 (s, 3H). LC-MS (ES) for $C_{16}H_{13}ClO_3$ $[M+1]^+$ 289.21.

4-(4-chloro-2-methoxyphenoxy)benzofuran-2-carbonitrile (**47h**) (52%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 0.9 Hz, 1H), 7.26 (t, *J* = 8.2 Hz, 1H), 7.14 (dt, *J* = 8.4, 0.8 Hz, 1H), 6.98 (dd, *J* = 8.8, 5.7 Hz, 1H), 6.71 (dd, *J* = 10.1, 2.8 Hz, 1H), 6.62 (ddd, *J* = 8.8, 7.8, 2.9 Hz, 1H), 6.44 (dd, *J* = 8.0, 0.6 Hz, 1H), 3.70 (s, 3H). LC-MS (ES) for $C_{16}H_{10}ClNO_3$ $[M+1]^+$ 390.12.

Step 8

A solution of BBr_3 (2.5 equiv, 1.0M in DCM) was added dropwise to a solution of the corresponding diether intermediate (1.0 equiv) in DCM (3.0 mL per mmol diether intermediate) under N_2 at -78 ºC. The reaction mixture was stirred for an additional 3 h or overnight at 0 ºC. After this period, the solution was quenched with ice water, the organic layer washed with water and dried over Na_2SO_4. The organic solvent was concentrated by rotary evaporation and purified by column chromatography to give **48a-h**.

4-(2-hydroxyphenoxy)benzofuran-2-carbonitrile (**48a**) (87%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.24 (dt, *J* = 8.4, 0.7 Hz, 1H), 7.11 – 7.00 (m, 2H), 6.88 – 6.79 (m, 2H), 6.73 (dd, *J* = 8.0, 0.6 Hz, 1H), 5.43 (s, 1H). LC-MS (ES) for $C_{15}H_9NO_3$ $[M+1]^+$ 252.02.

4-(2-hydroxyphenoxy)-6-methylbenzofuran-2-carbonitrile (**48b**) (61%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.26 (d, *J* = 0.9 Hz, 1H), 7.05 (s, 1H), 7.02 – 6.94 (m, 2H), 6.75 (ddd, *J* = 8.1, 7.1, 2.0 Hz, 1H), 6.60 (dd, *J* = 8.1, 1.3 Hz, 1H), 5.50 (s, 1H), 2.36 (s, 3H). LC-MS (ES) for $C_{16}H_{11}NO_3$ $[M+1]^+$ 265.82.

6-chloro-4-(2-hydroxyphenoxy)benzofuran-2-carbonitrile (**48c**) (60%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 0.9 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.15 – 7.09 (m, 1H), 7.04 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.91 (td, *J* = 8.4, 1.7 Hz, 2H), 6.69 (d, *J* = 1.5 Hz, 1H), 5.25 (s, 1H). LC-MS (ES) for $C_{15}H_8ClNO_3$ $[M+1]^+$ 286.29.

4-(4-fluoro-2-hydroxyphenoxy)benzofuran-2-carbonitrile (**48d**) (69%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 1.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.02 – 6.94 (m, 3H), 6.66 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.33 (s, 1H). LC-MS (ES) for $C_{15}H_8FNO_3$ $[M+1]^+$ 270.08.

4-(4-fluoro-2-hydroxyphenoxy)-6-methylbenzofuran-2-carbonitrile (**48e**) (72%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.24 (d, *J* = 0.9 Hz, 1H), 6.97 (s, 1H), 6.74 (dd, *J* = 9.3, 2.9 Hz, 1H), 6.59 (dd, *J* = 8.9, 5.3 Hz, 1H), 6.47 (ddd, *J* = 8.9, 8.1, 3.0 Hz, 1H), 5.60 (s, 1H), 2.35 (s, 3H). LC-MS (ES) for $C_{16}H_{10}FNO_3$ $[M+1]^+$ 283.96.

2-(benzofuran-4-yloxy)-5-chlorophenol (48f) (43%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 6.79 – 6.78 (m, 2H), 6.66 (s, 1H), 5.74 (s, 1H). GC-MS (ES) for $C_{14}H_9ClO_3$ $[M]^+$ = 260.

5-chloro-2-((2-methylbenzofuran-4-yl)oxy)phenol (48g) (82%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.15 (t, *J* = 8.1 Hz, 1H), 7.06 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.85 – 6.64 (m, 3H), 6.21 (d, *J* = 0.8 Hz, 1H), 5.76 (d, *J* = 13.8 Hz, 1H), 2.55 – 2.29 (m, 3H). LC-MS (ES) for $C_{15}H_{11}ClO_3$ $[M+1]^+$ 275.11.

4-(4-chloro-2-hydroxyphenoxy)benzofuran-2-carbonitrile (**48h**) (64%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 2H), 7.27 (dt, *J* = 8.5, 0.8 Hz, 1H), 7.05 (dd, *J* = 2.1, 0.5 Hz, 1H), 6.80 – 6.78 (m, 2H), 6.73 (dd, *J* = 8.0, 0.6 Hz, 1H), 5.44 (s, 1H). LC-MS (ES) for $C_{15}H_8ClNO_3$ $[M+1]^+$ 285.73.

Step 9

17 (1.5 equiv) and K_2CO_3 (2.0 equiv) were added to a solution of the corresponding catechol aryl ether intermediate (1.0 equiv) in DMF (1.0 mL per mmol aryl ether intermediate) and the mixture was stirred for 3 h at 60 ºC to complete the reaction. The reaction mixture was poured into brine and extracted with ethyl acetate. The organic layer was sequentially washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude product was dissolved in DCM (1.0 mL per mmol catechol diether intermediate) and aq. NH_4OH (30%) (0.5 mL per mmol catechol aryl ether intermediate) were added. The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was concentrated by rotary evaporation and purified by column chromatography to give **12a-h**.

4-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)benzofuran-2-carbonitrile (**12a**) (41%) ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.80 (s, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.35 – 7.21 (m, 4H), 7.11 (ddd, *J* = 7.9, 7.3, 1.7 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.51 (dd, *J* = 8.0, 0.5 Hz, 1H), 4.99 (d, *J* = 7.9 Hz, 1H), 4.31 – 4.23 (m, 2H), 3.99 – 3.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.30, 160.57, 156.62, 152.69, 150.69, 150.01, 145.27, 143.78, 127.22, 126.14, 122.60, 122.52, 118.49, 114.19, 108.06, 106.09, 104.81, 101.36, 99.99, 66.69, 48.21. HR-MS (ES) calcd for $C_{21}H_{15}N_3O_5$ $[M+1]^+$ 390.1090, found 390.1093.

4-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)-6-methylbenzofuran-2-carbonitrile (**12b**) (47%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.37 (s, 1H), 7.18 (d, *J* = 0.8 Hz, 1H), 7.11 – 7.03 (m, 1H), 6.96 – 6.87 (m, 3H), 6.82 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.72 (s, 1H), 5.22 (dd, *J* = 7.9, 2.1 Hz, 1H), 4.17 (t, *J* = 4.6 Hz, 2H), 3.95 (t, *J* = 4.6 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.81, 153.42, 151.79, 150.46, 149.38, 145.37, 130.51, 127.55, 125.09, 124.02, 122.76, 120.75,

118.14, 114.82, 113.66, 111.79, 107.64, 106.33, 101.35, 66.92, 48.31, 17.37. HR-MS (ES) calcd for $C_{22}H_{17}N_3O_5$ $[M+1]^+$ 404.1168, found 404.1163.

6-chloro-4-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)benzofuran-2-carbonitrile (**12c**) (53%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.33 (d, *J* = 0.9 Hz, 1H), 7.21 (d, *J* = 1.5 Hz, 1H), 7.10 – 6.94 (m, 4H), 6.60 (d, *J* = 7.9 Hz, 1H), 6.36 (d, *J* = 1.5 Hz, 1H), 5.05 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.16 (t, *J* = 4.7 Hz, 2H), 3.89 (t, *J* = 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.44, 153.86, 149.72, 149.39, 145.20, 144.95, 134.16, 127.27, 127.15, 126.43, 125.21, 119.45, 117.12, 114.71, 114.44, 111.72, 110.79, 109.79, 100.56, 66.79, 47.15. HR-MS (ES) calcd for $C_{21}H_{14}ClN_3O_5$ $[M+1]^+$ 424.0700, found 424.0682.

4-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4-fluorophenoxy)benzofuran-2-carbonitrile (**12d**) (52%) ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.81 (br, 1H), 7.92 (d, *J* = 0.9 Hz, 1H), 7.46 (t, *J* = 8.2 Hz, 1H), 7.37 (s, 1H), 7.38 – 7.32 (m, 2H), 7.13 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.60 – 6.56 (m, 1H), 5.01 (d, *J* = 7.9 Hz, 1H), 4.34 (t, *J* = 4.0 Hz, 2H), 3.99 (t, *J* = 4.0 Hz, 2H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 163.07, 157.41, 152.91, 151.70, 150.99, 145.48, 142.50, 131.39, 130.00, 126.90, 124.12, 122.17, 116.82, 116.62, 115.50, 110.56, 108.63, 106.46, 100.70, 67.26, 47.78. HR-MS (ES) calcd for $C_{21}H_{14}FN_3O_5$ $[M+1]^+$ 408.0996, found 408.0977.

4-(2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)-4-fluorophenoxy)-6-methylbenzofuran-2-carbonitrile (**12e**) (63%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.37 (s, 1H), 7.17 (d, *J* = 0.8 Hz, 1H), 6.84 (dd, *J* = 8.7, 5.6 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.70 – 6.61 (m, 3H), 5.16 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.13 (t, *J* = 4.7 Hz, 2H), 3.92 (t, *J* = 4.7 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.24, 161.84, 152.75, 150.56, 149.43, 149.23, 143.99, 131.00, 127.60, 126.32, 124.60, 122.91, 121.03, 117.04, 112.66, 110.74, 107.61, 105.32, 100.43, 65.80, 47.12, 16.35. HR-MS (ES) calcd for $C_{22}H_{16}FN_3O_5$ $[M+1]^+$ 422.1074, found 422.1066.

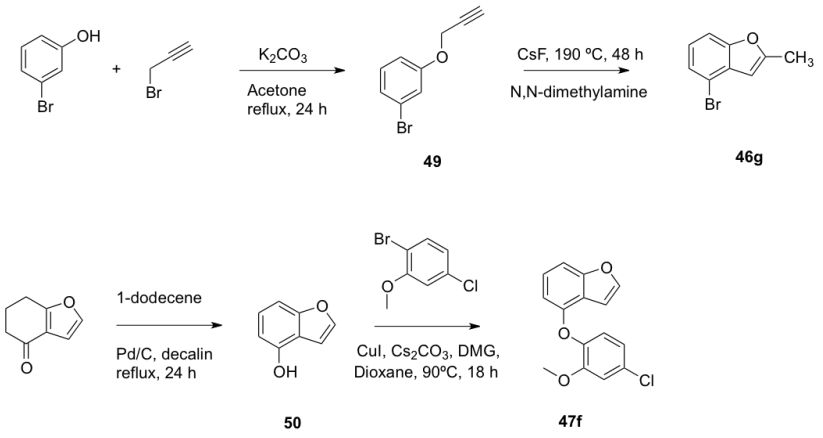
1-(2-(2-(benzofuran-4-yloxy)-5-chlorophenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (12f) (10%) ^{1}H NMR (500 MHz, CD_3OD) δ 7.66 (d, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 2.5 Hz,

1H), 7.13 (s, 1H), 7.06 (t, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.97 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.70 (dd, *J* = 2.3, 0.5 Hz, 1H), 6.34 (d, *J* = 8.0 Hz, 1H), 4.88 (d, *J* = 8.0 Hz, 1H), 4.14 (t, *J* = 5.0 Hz, 2H), 3.87 (t, *J* = 5.0 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) δ 158.12, 153.53, 152.8, 152.44, 147.41, 145.89, 131.78, 125.94, 124.38, 123.05, 116.21, 108.49, 107.07, 104.59, 101.41, 67.98. HR-MS (ES) calcd for $C_{20}H_{15}ClN_2O_5$ $[M+1]^+$ 399.0669, found 399.0630.

1-(2-(5-chloro-2-((2-methylbenzofuran-4-yl)oxy)phenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (**12g**) (78%) ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.90 (m, 1H), 7.63 – 7.39 (m, 1H), 7.27 (dd, *J* = 4.3, 2.3 Hz, 1H), 7.22 – 7.02 (m, 3H), 7.02 – 6.85 (m, 2H), 6.63 – 6.32 (m, 2H), 5.06 (d, *J* = 8.1 Hz, 1H), 4.32 (dd, *J* = 8.7, 4.7 Hz, 2H), 4.16 – 3.89 (m, 2H), 2.45 (2, *3*H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.40, 149.95, 145.27, 140.79, 126.13, 122.71, 122.68, 122.25, 119.17, 114.54, 111.33, 101.30, 97.12, 77.29, 77.03, 76.78, 66.70, 48.27, 21.34. HR-MS (ES) calcd for $C_{21}H_{17}ClN_2O_5$ $[M+1]^+$ 413.0826, found 413.0808.

4-(4-chloro-2-(2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)ethoxy)phenoxy)benzofuran-2-carbonitrile (**12h**) (47%) ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.80 (br, 1H), 7.92 (s, 1H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.29 (dd, *J* = 8.8, 5.8 Hz, 1H), 7.14 (dd, *J* = 10.4, 2.9 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.88 (ddd, *J* = 8.8, 8.2, 2.9 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 7.9 Hz, 1H), 4.32 (t, *J* = 4.0 Hz, 2H), 3.99 (t, *J* = 4.0 Hz, 2H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 157.42, 153.28, 145.45, 129.99, 128.05, 126.81, 126.78, 124.07, 123.69, 116.65, 115.67, 108.16, 107.42, 106.19, 104.96, 103.09, 101.14, 100.67, 99.94, 67.17, 47.76. HR-MS (ES) calcd for $C_{21}H_{14}ClN_3O_5$ $[M+1]^+$ 424.0700, found 424.0696.

Synthesis of Compounds 46g and 47f



Step A1

To a solution of 3-bromophenol (23 mmol), propargyl bromide (27 mmol) in acetone (40 mL), K_2CO_3 (27 mmol) was added and the mixture was stirred at reflux for 24 h. After this period, the mixture was allowed to cool to room temperature, the solid was filtered, the acetone was concentrated by rotary evaporation, and purified by column chromatography to give **49**.

Synthesis of 1-bromo-3-(prop-2-yn-1-yloxy)benzene (**49**) (92%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (t, *J* = 5 Hz, 1H), 4.80 (s, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.16 – 7.29 (m, 2H), 7.33 (s, 1H). LC-MS (ES) for C_9H_7BrO $[M+1]^+$ 212.93.

Step A2

To a solution of **49** (21 mmol) in *N, N*-diethylaniline (30 mL), cesium fluoride (11 mmol) was added and the mixture was heated at 190 °C for 24 h. After cooling, the suspension was diluted with ethyl acetate (100 mL) and washed with dil HCl (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation and purified column chromatography to give 4-bromo-2-methylbenzofuran (**46g**, 87%) and 6-bromo-2-methylbenzofuran (13%). The resulting mixture was purified by reverse phase HPLC using 10:1 acetonitrile: water with 0.1% TFA (B) for 22 min followed by 3 min at 100% B, to give compound **46g** (26 %).

4-bromo-2-methylbenzofuran (**46g**) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 3H), 6.80 (s, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.33 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H). LC-MS (ES) for C_9H_7BrO $[M+1]^+$ 212.33.

Step B1

To a solution of 6,7-Dihydro-4(5*H*)-benzofuranone (11 mmol), 1-dodecene (14 mmol), Pd/C (1.0 g) in dry decalin (20 mL) was stirred at reflux under N_2 atmosphere for 24 h. The reaction was cooled down, quenched with EtOH (15 mL), filtered, and concentrated in vacuo. The product was purified by column chromatography to give **50**.

benzofuran-4-ol (50) (32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.12 (s, 1H), 6.86 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.64 (dd, *J* = 6.8, 1.6 Hz, 1H), 5.64 (s, 1H). GC-MS (ES) for $C_8H_6O_2$ $[M]^+$ 134.

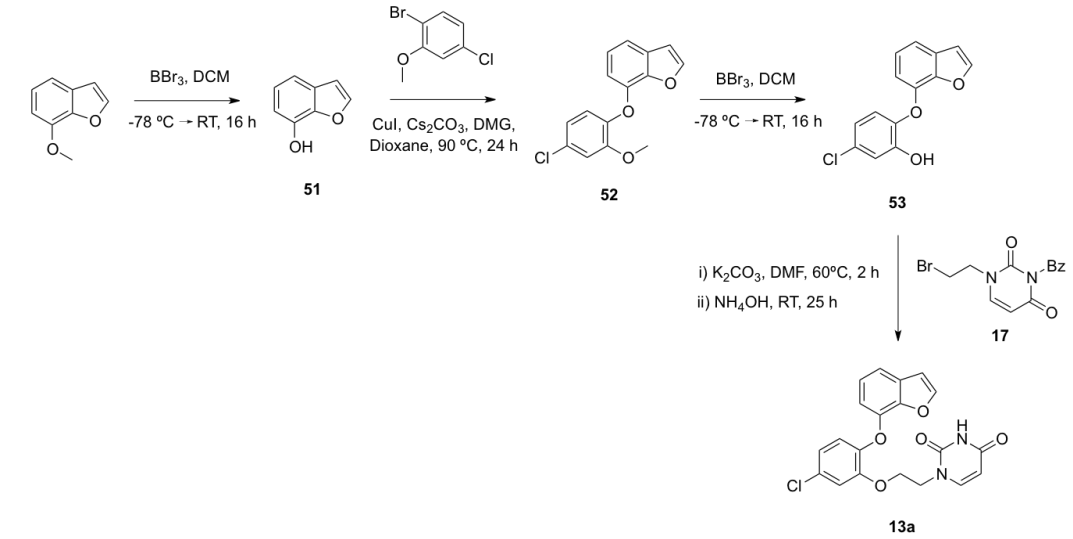
Step B2

To a solution of benzofuran-4-ol (2.0 mmol), 2-bromo-5-chloroanisole (2.6 mmol), Cs_2CO_3 (3.0 mmol), CuI (0.2 mmol) and *N*,*N*-dimethylglycine hydrochloride (0.6 mmol) in dry dioxane were stirred at 90-100 ºC under N_2 atmosphere for 24 h. The reaction was cooled down, quenched with brine, and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography to give **47f**.

4-(4-chloro-2-methoxyphenoxy)Benzofuran (47f) (33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.0 Hz, 1H), 7.24 (s, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 1.2 Hz, 1H), 6.89 – 6.88 (m, 2H), 6.72 – 6.71 (m, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 3.84 (s, 3H). GC-MS (ES) for $C_{15}H_{11}ClO_3$ $[M]^+$ = 274.

7. Synthesis of Compound 13a

Scheme 3.2



Step1

To a stirred solution of 7-methoxybenzofuran (3.3 mmol)) in dry DCM (5.0 mL) at -78 ºC under N_2 atmosphere was added BBr_3 (3.0 mmol) (1.0M solution in DCM) and then the reaction was allowed to stir overnight at room temperature. The crude reaction was quenched with ice water and extracted with DCM (3 x 5.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography to give **51**.

benzofuran-7-ol (51) (42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 7 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 5.43 (s, 1H). GC-MS (ES) for $C_8H_6O_2$ $[M]^+$ 134.

Step 2

Synthesis of 7-(4-chloro-2-methoxyphenoxy)Benzofuran (52). Following step A2 in the synthetic scheme 1.2 from **51** to give **52** (20%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.88 – 6.85 (m, 2H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H). GC-MS (ES) for $C_{15}H_{11}ClO_3$ $[M]^+$ = 274.

Step 3

To a stirred solution of 7-(4-chloro-2-methoxyphenoxy)benzofuran (**52**, 0.2 mmol) in dry DCM (5.0 mL) at -78 ºC under N_2 atmosphere was added BBr_3 (3.0 mmol, 1.0M solution in DCM) and then the reaction was allowed to stir overnight at room temperature. The crude reaction was quenched with ice water and extracted with DCM (3 x 5.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography to give **53**.

2-(benzofuran-7-yloxy)-5-chlorophenol (53) (100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.78 – 6.77 (m, 2H), 5.86 (s, 1H). GC-MS (ES) for $C_{14}H_9ClO_3$ $[M]^+$ = 260.

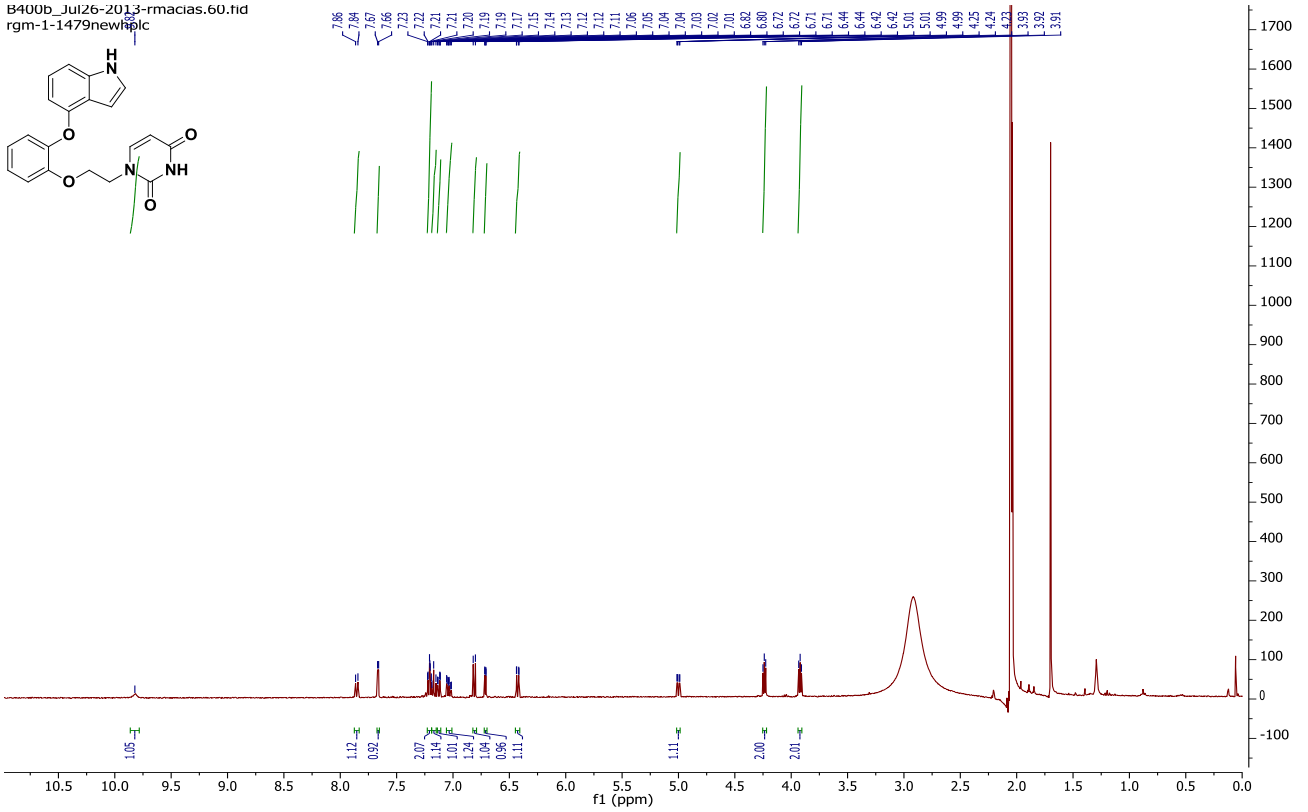
Step 4

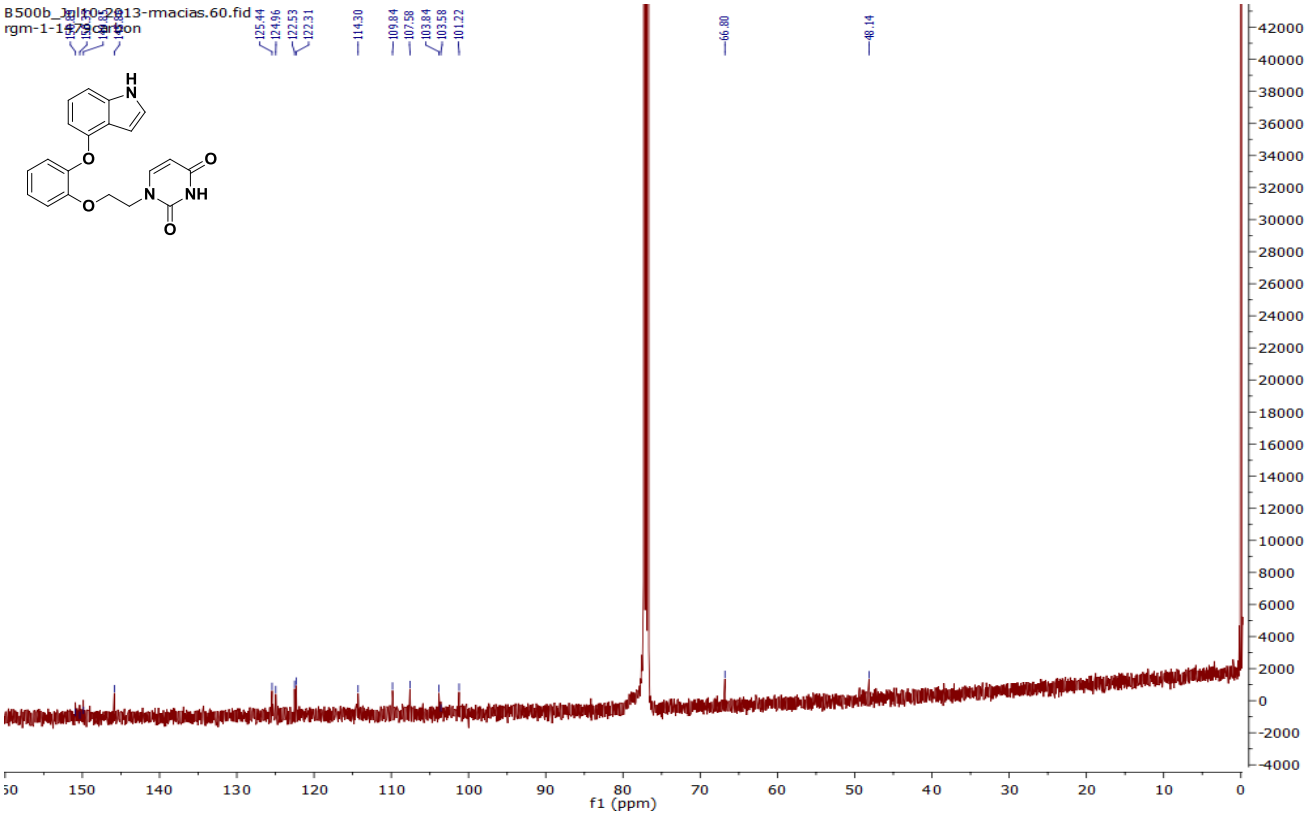
A solution of 2-(benzofuran-7-yloxy)-5-chlorophenol (**53**, 1.0 mmol) and K_2CO_3 (1.1 mmol) in dry DMF (2.0 mL) were stirred at room temperature for 1 h. Then, a solution of 1-(2-bromoethyl)pyrimidine-2,4(1H,3H)-dione (**17**, 1.1 mol) in dry DMF (2.0 mL) was added and the reaction mixture was stirred at 60 ºC for 2 h and then at room temperature for overnight. The crude reaction was quenched with brine and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in dry MeOH (3.0 mL) and then 3.0 mL of NH_4OH was added. The crude reaction was stirred at room temperature until completion. Then, the crude reaction was concentrated in vacuo and the product purified by column chromatography to give **13a**. Further purification was performed by HPLC (5-100% of water with 0.1% trifluoroacetic acid (TFA) (A) and 10:1 acetonitrile:water with 0.1% TFA(B)).

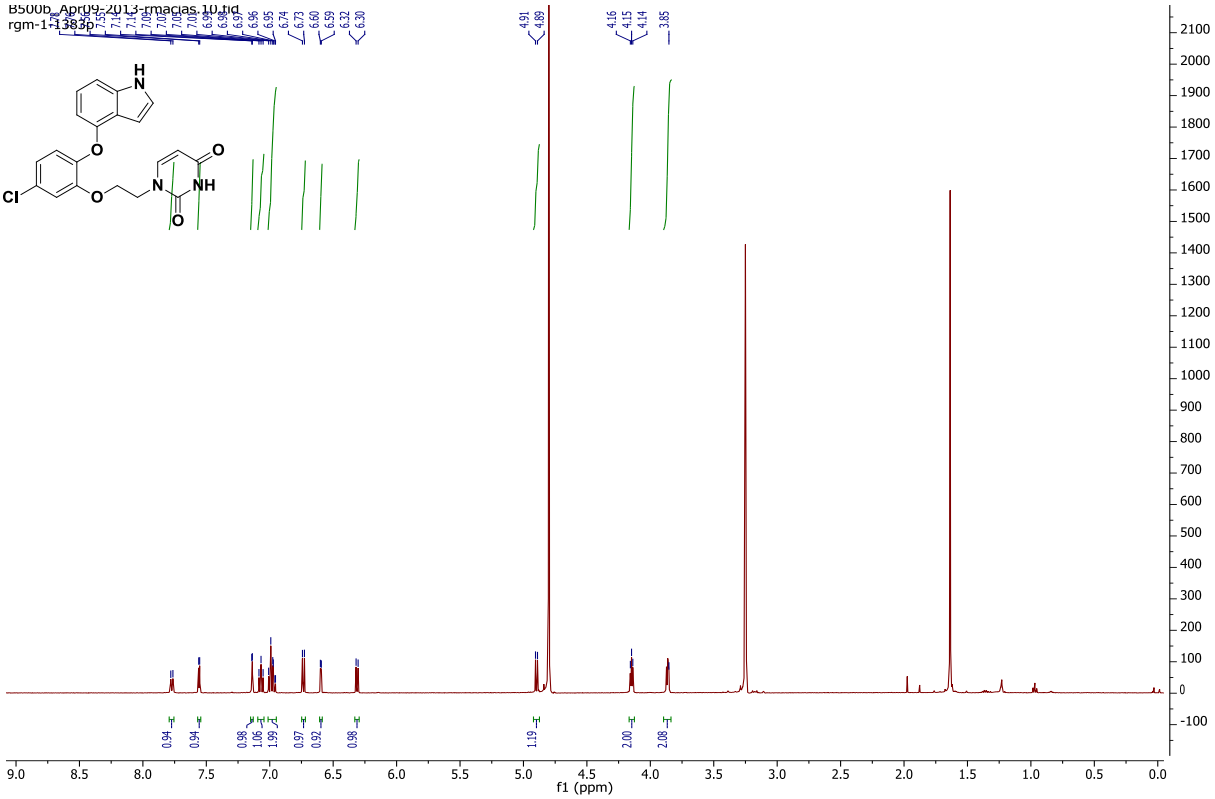
1-(2-(2-(benzofuran-7-yloxy)-5-chlorophenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (13a) (10%) ^{1}H NMR (800 MHz, CD_3OD) δ 7.75 (d, *J* = 2.4 Hz, 1H), 7.27 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.98 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.87 – 6.86 (m, 2H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.97 (d, *J* =

7.2 Hz, 1H), 4.20 (t, *J* = 4.8 Hz, 2H), 3.92 (t, *J* = 4.8 Hz, 2H). ^{13}C NMR (200 MHz, CD_3OD) δ 166.48, 152.52, 152.18, 147.98, 146.9, 144.26, 131.6, 131.5, 124.49, 123.6, 122.97, 116.73, 116.29, 111.55, 108.14, 101.39, 68.10. HR-MS (ES) calcd for $C_{20}H_{15}ClN_2O_5$ $[M+1]^+$ 399.0785, found 399.0663.

8. ^{1}H and ^{13}C NMR spectra



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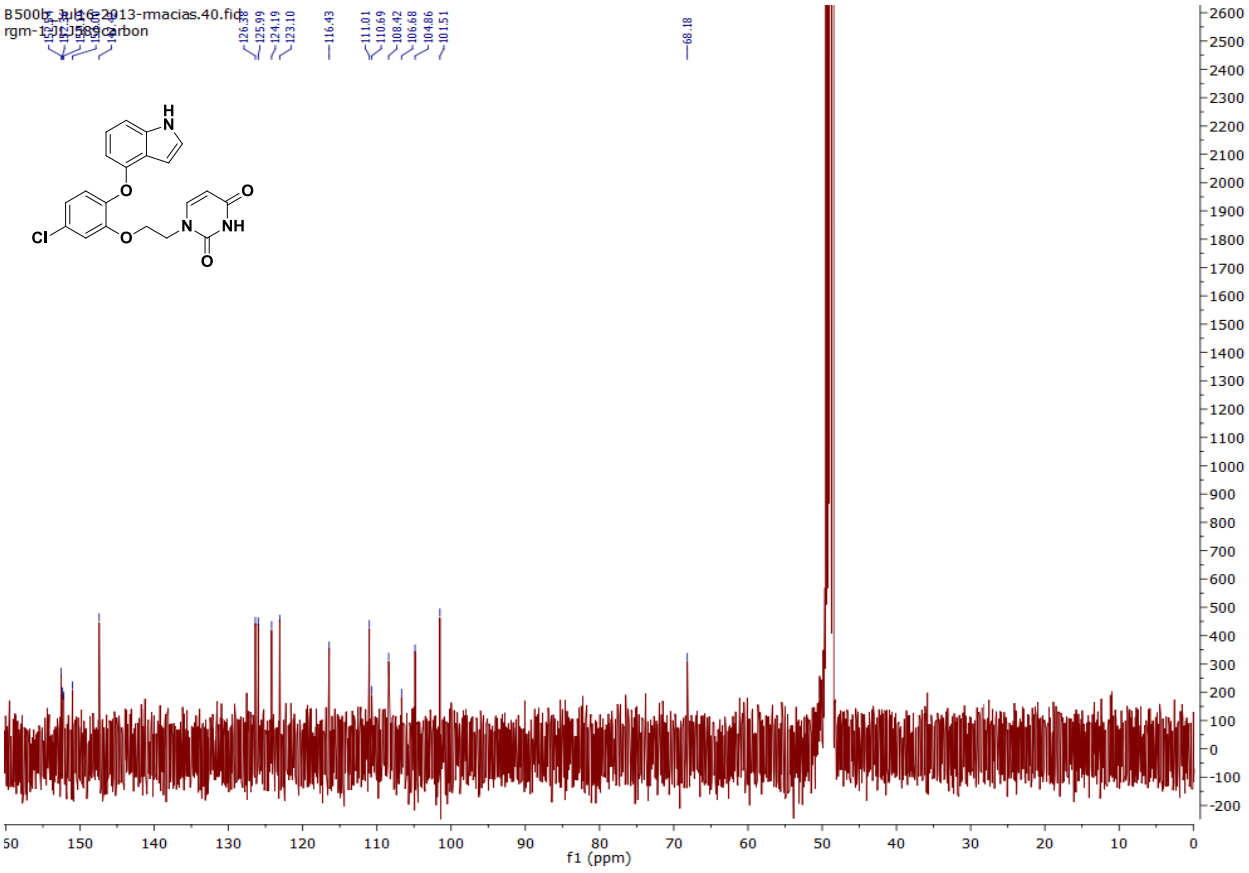
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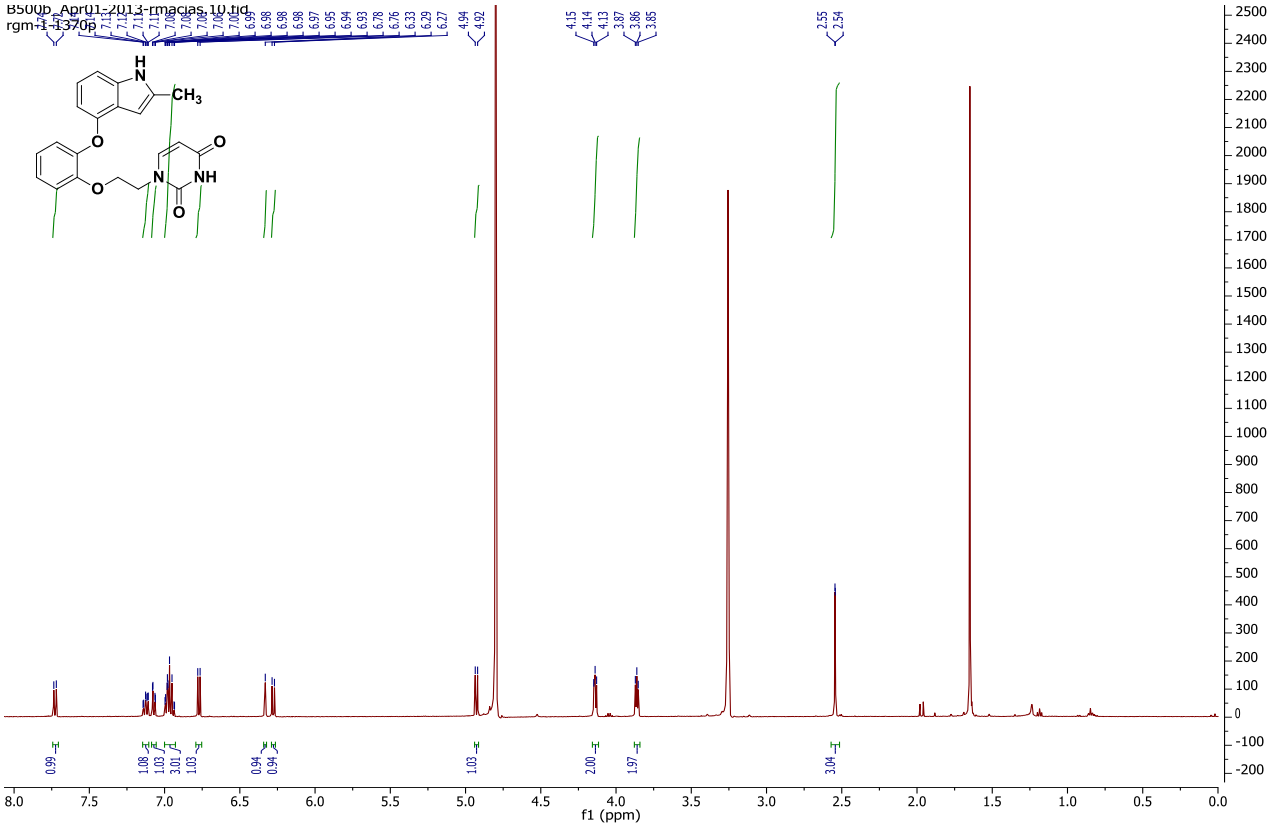
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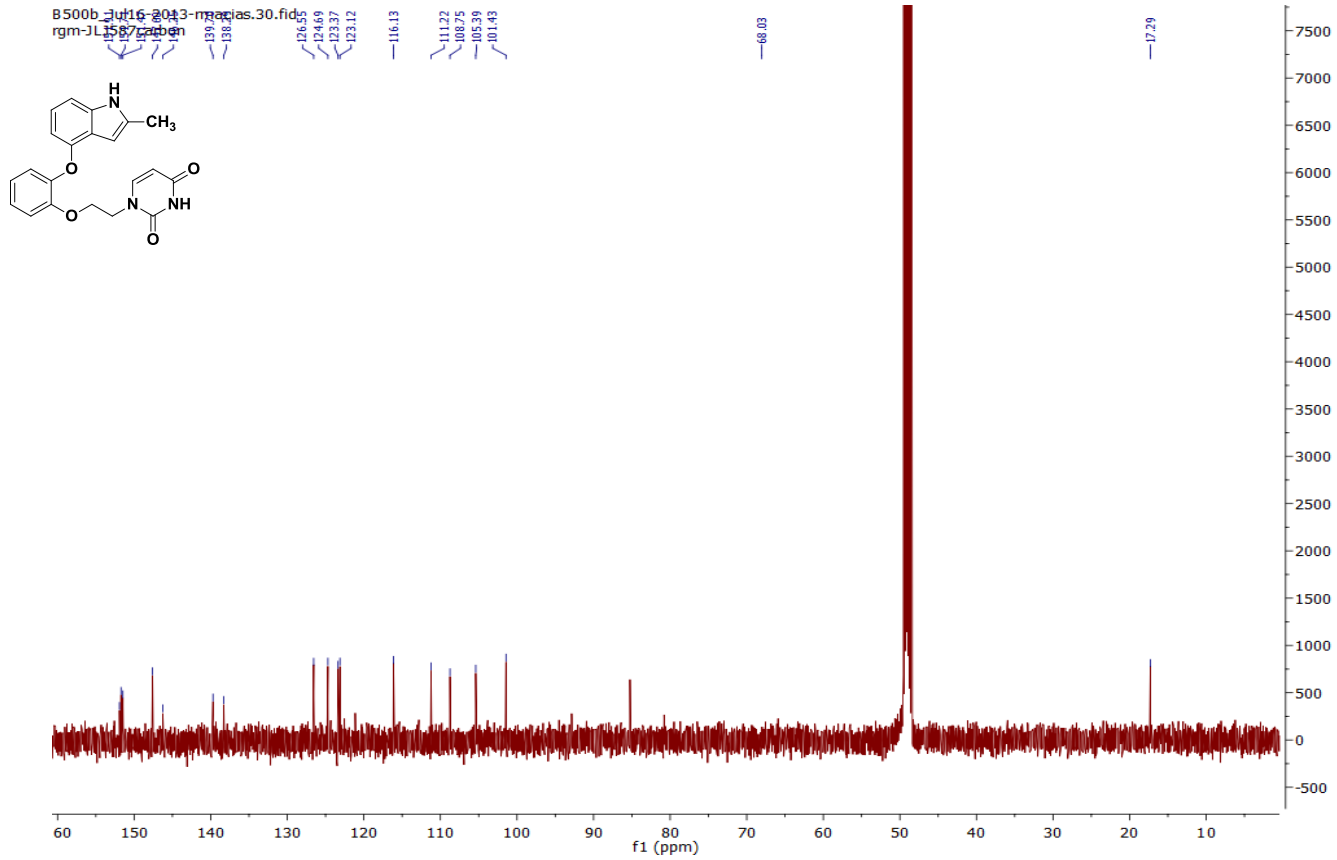
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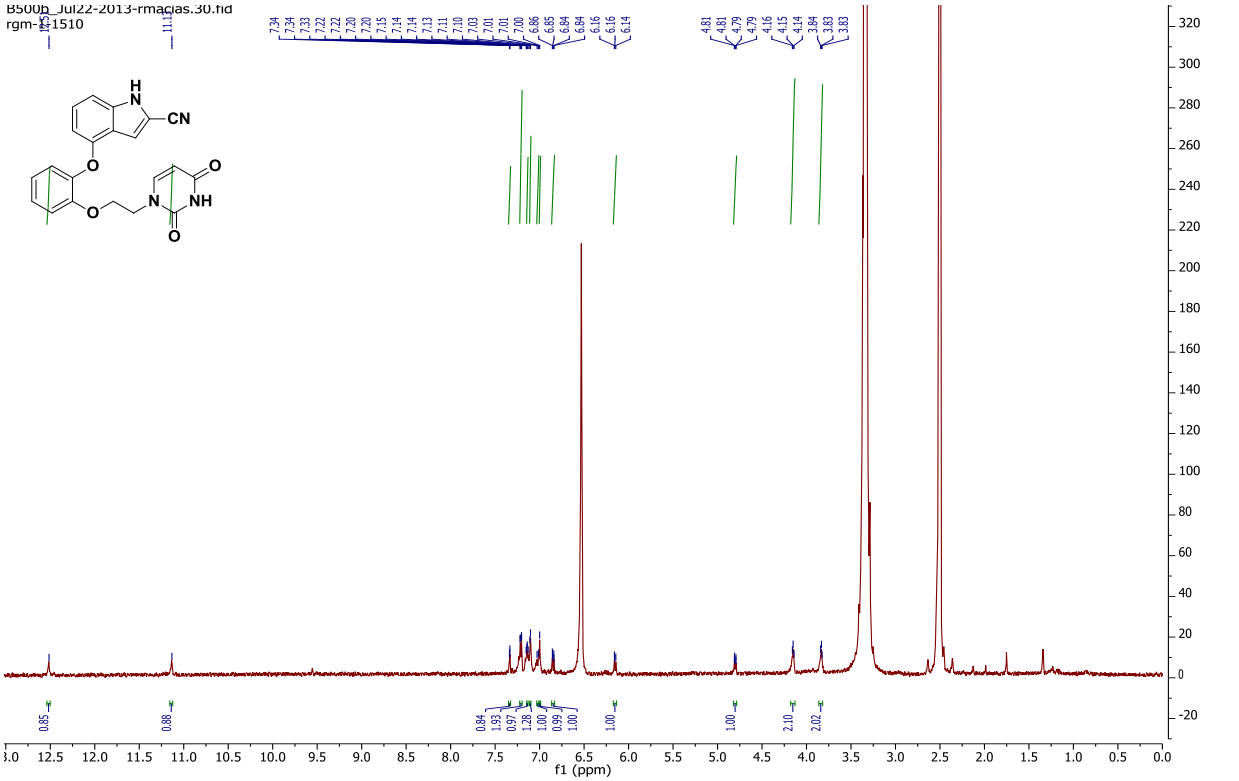
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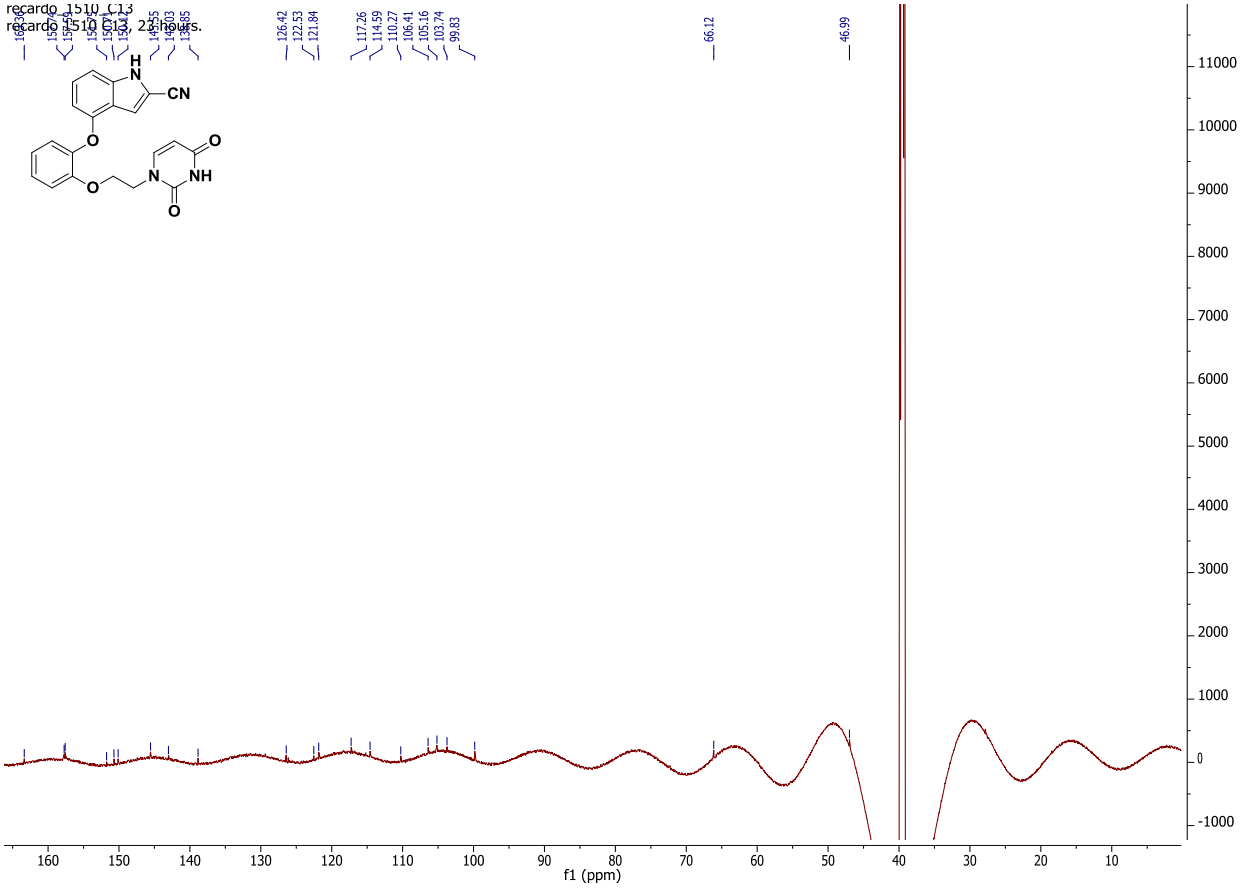
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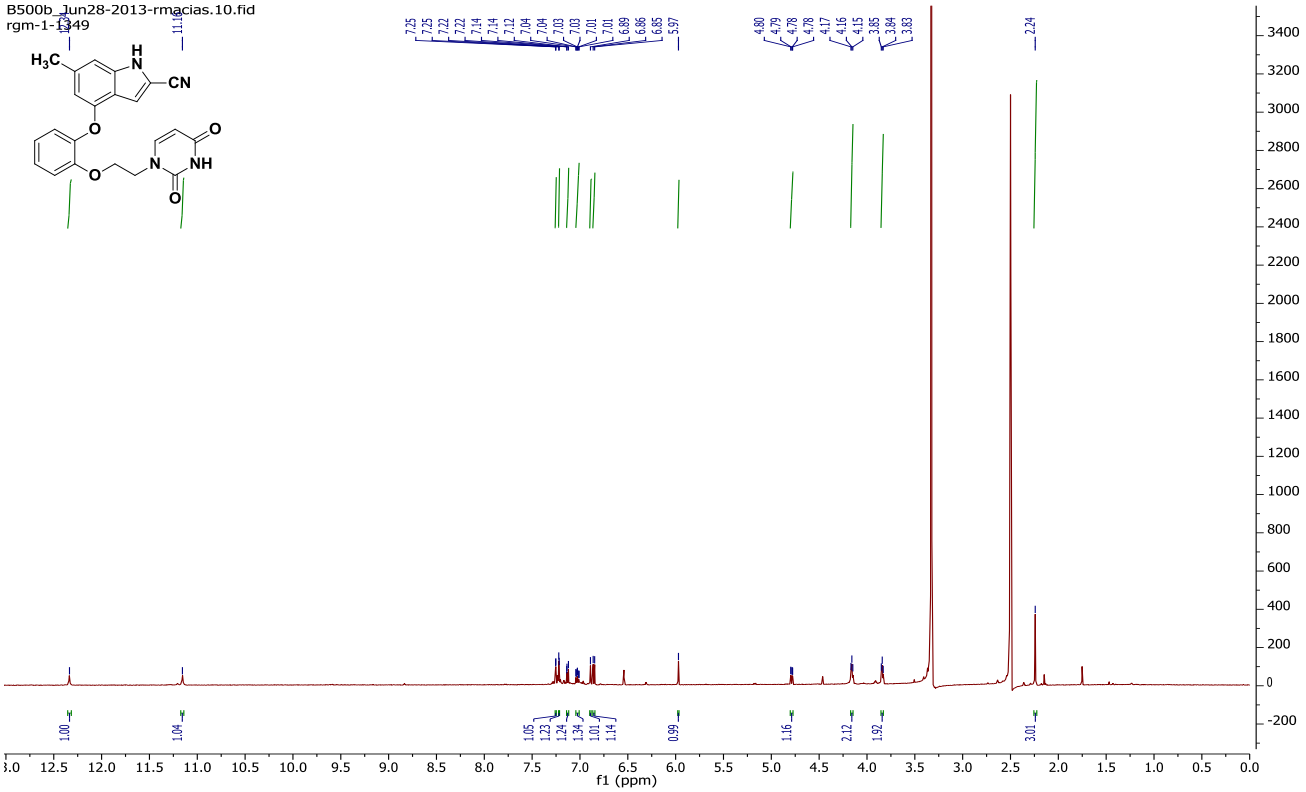
f1 (ppm)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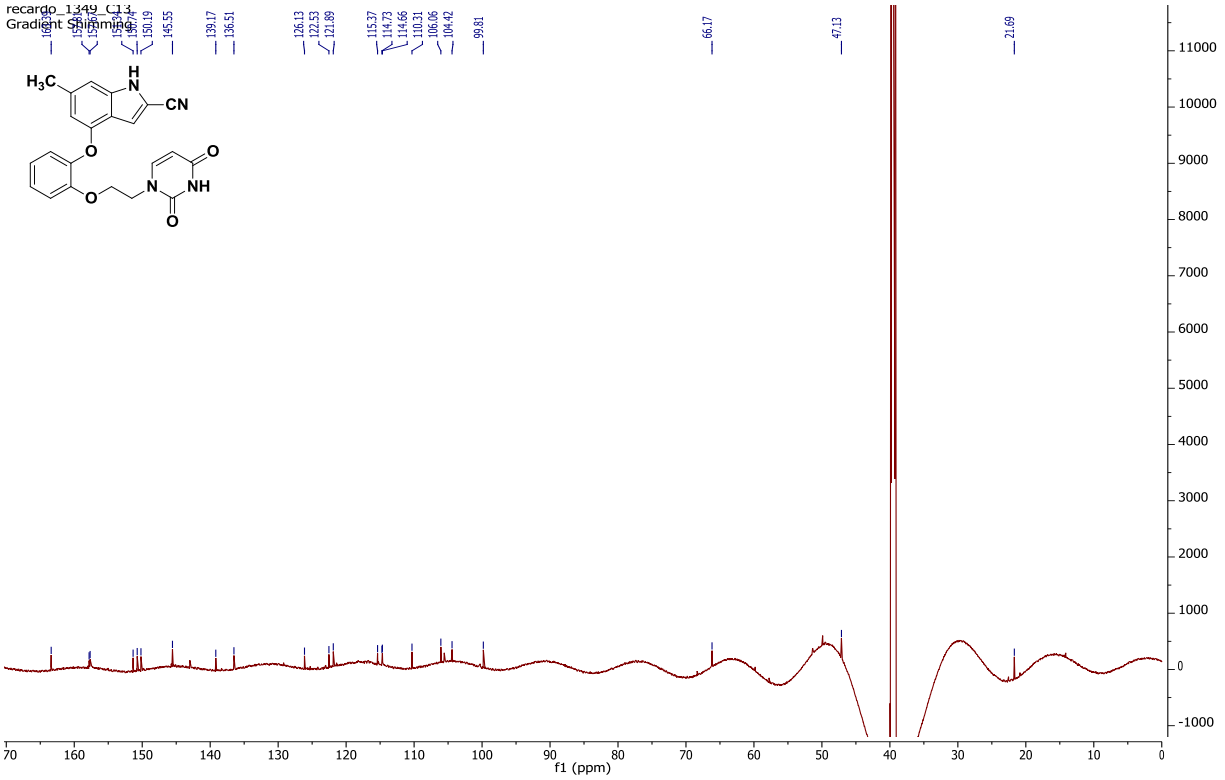
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Gradient Shimming
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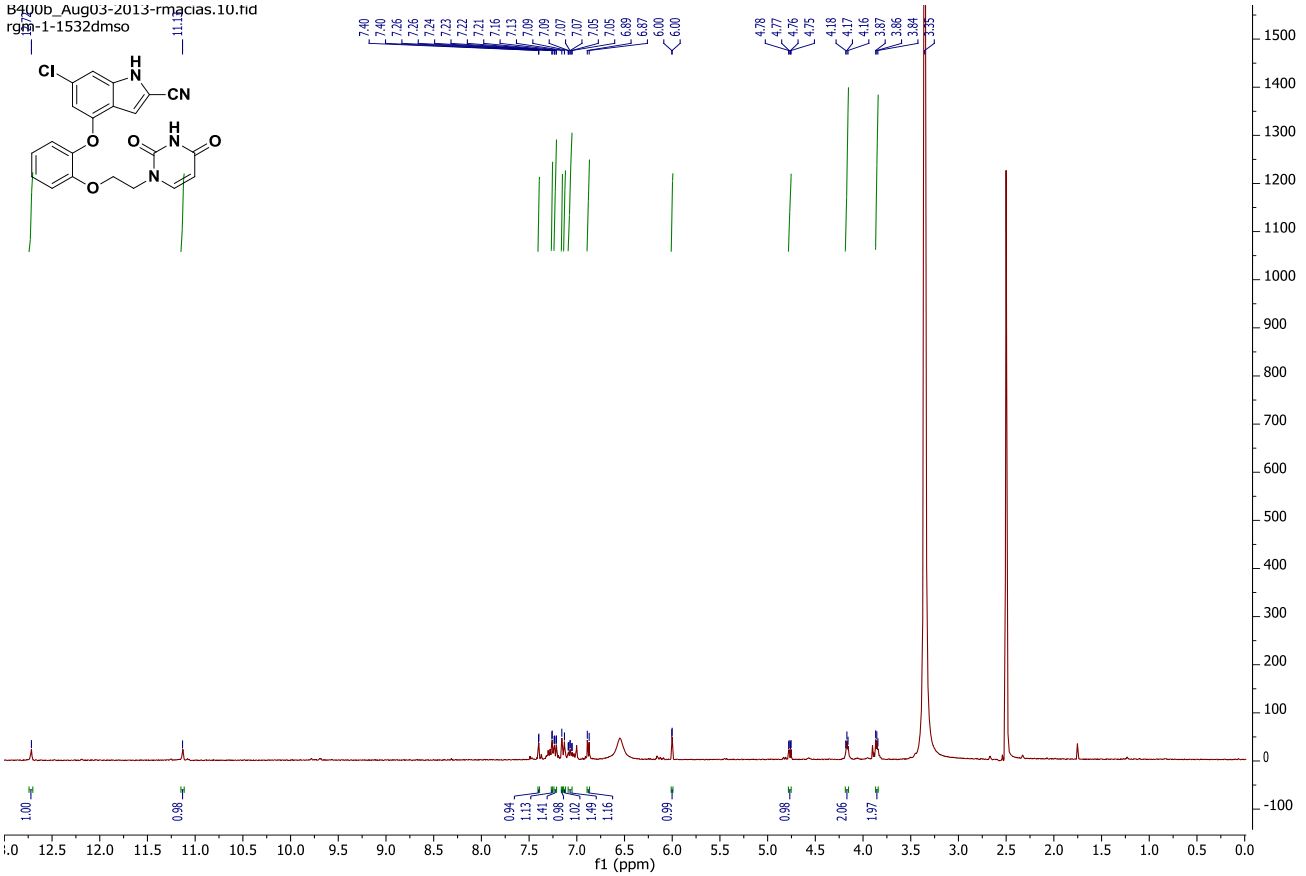
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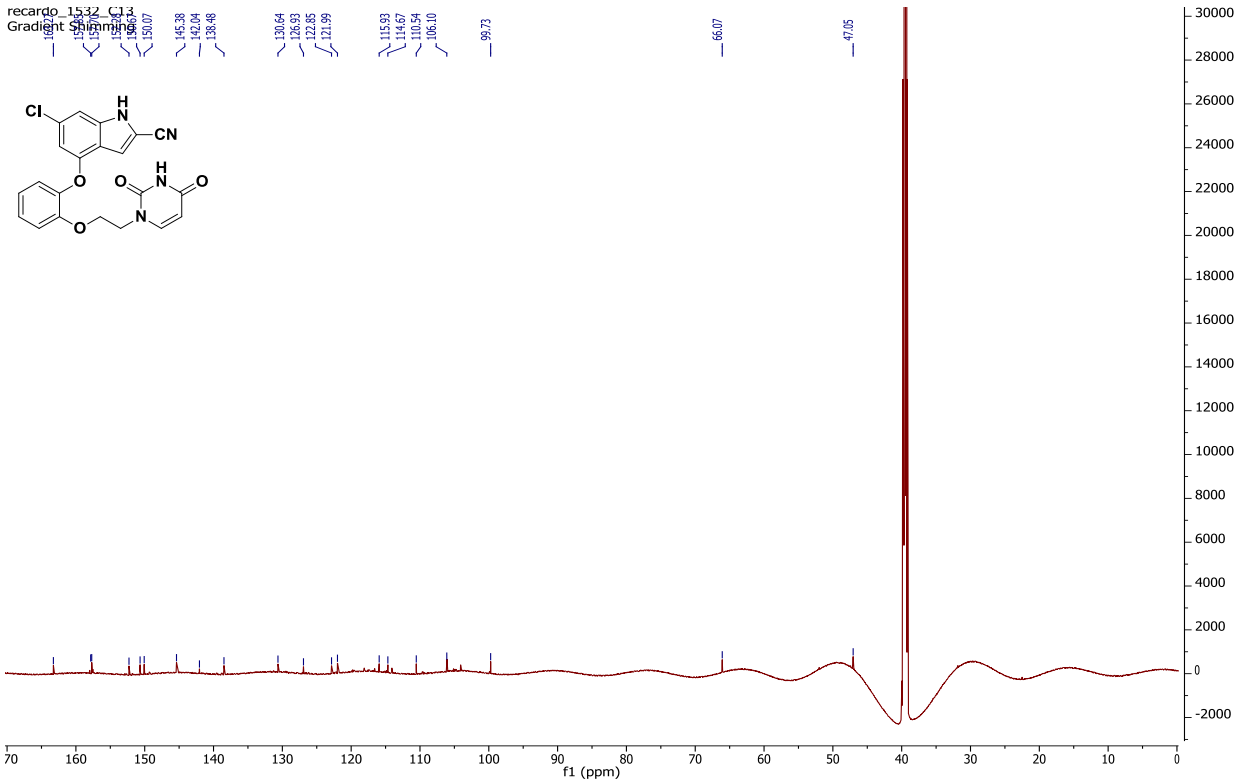
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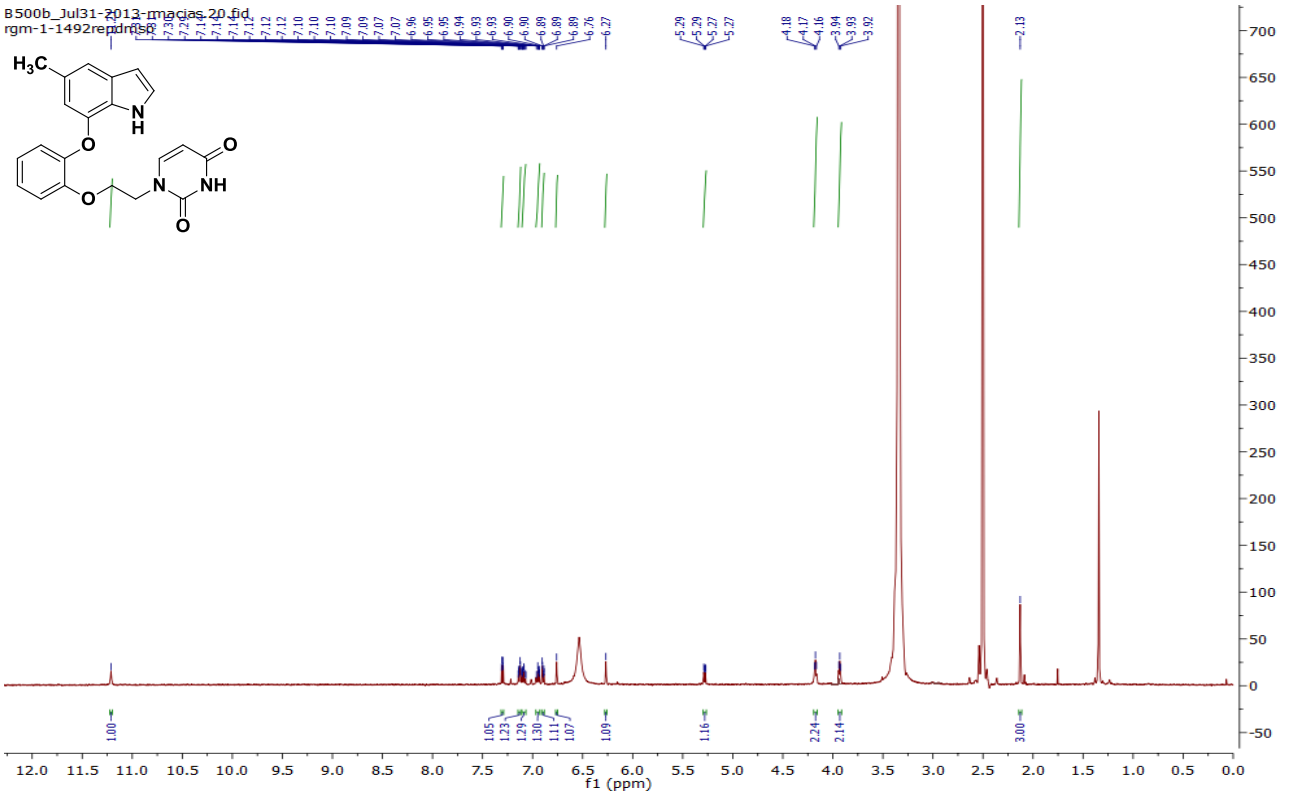
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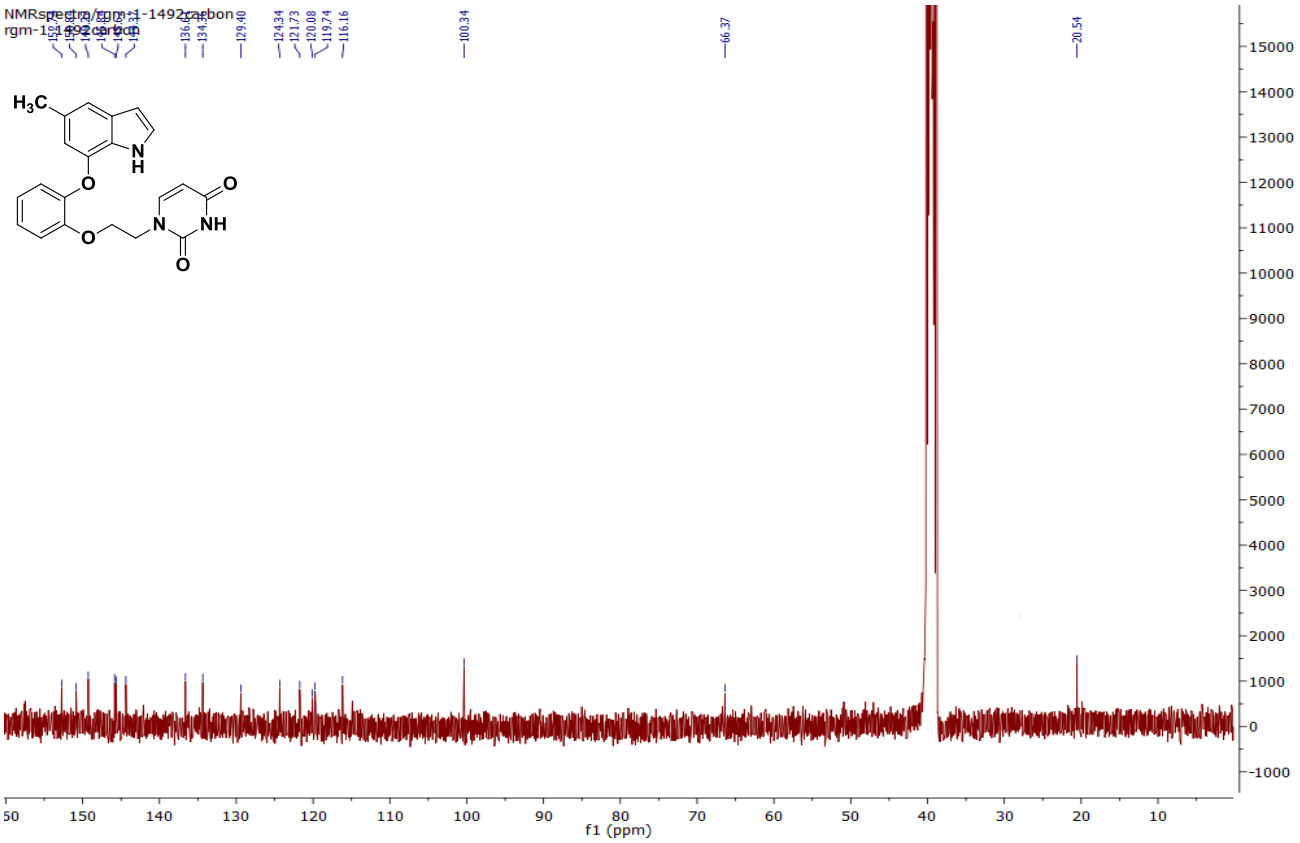
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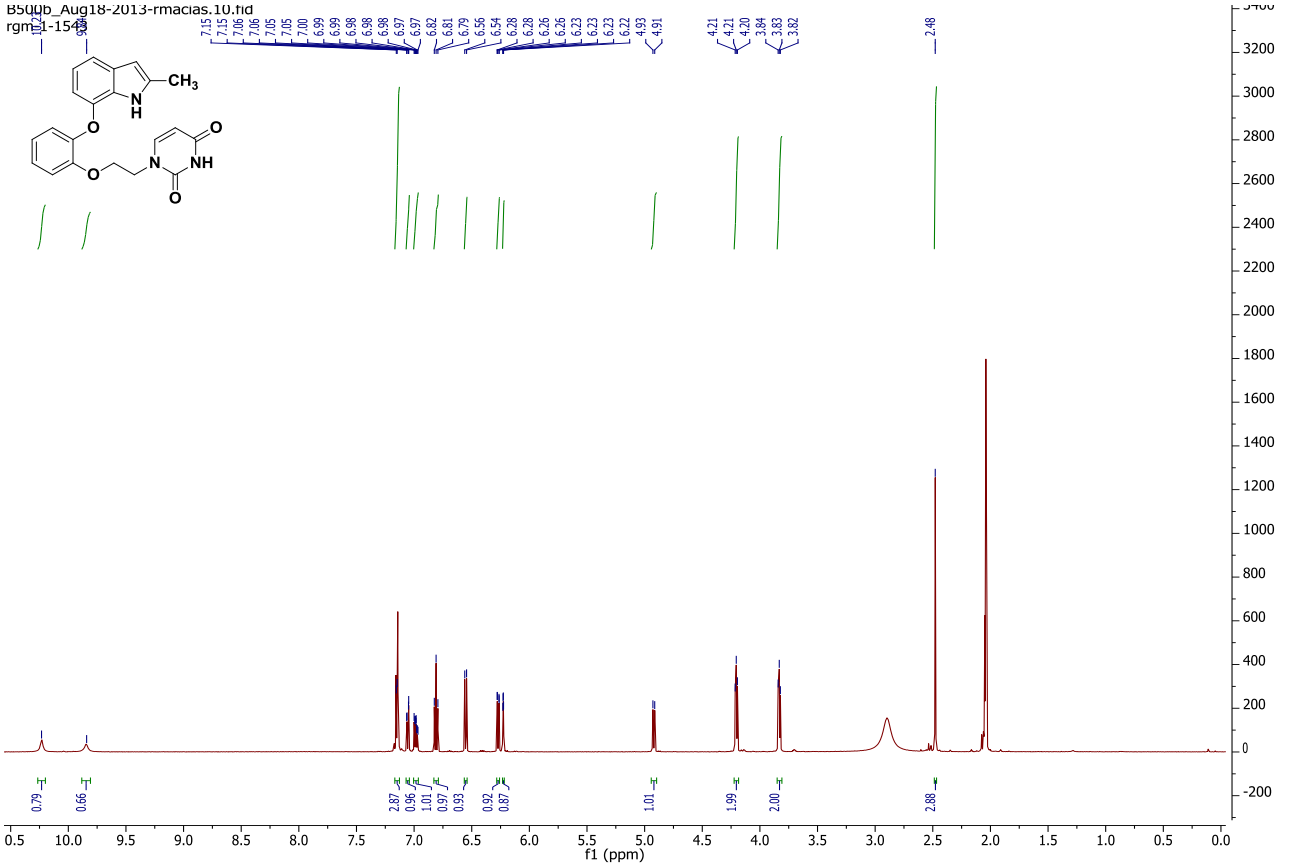
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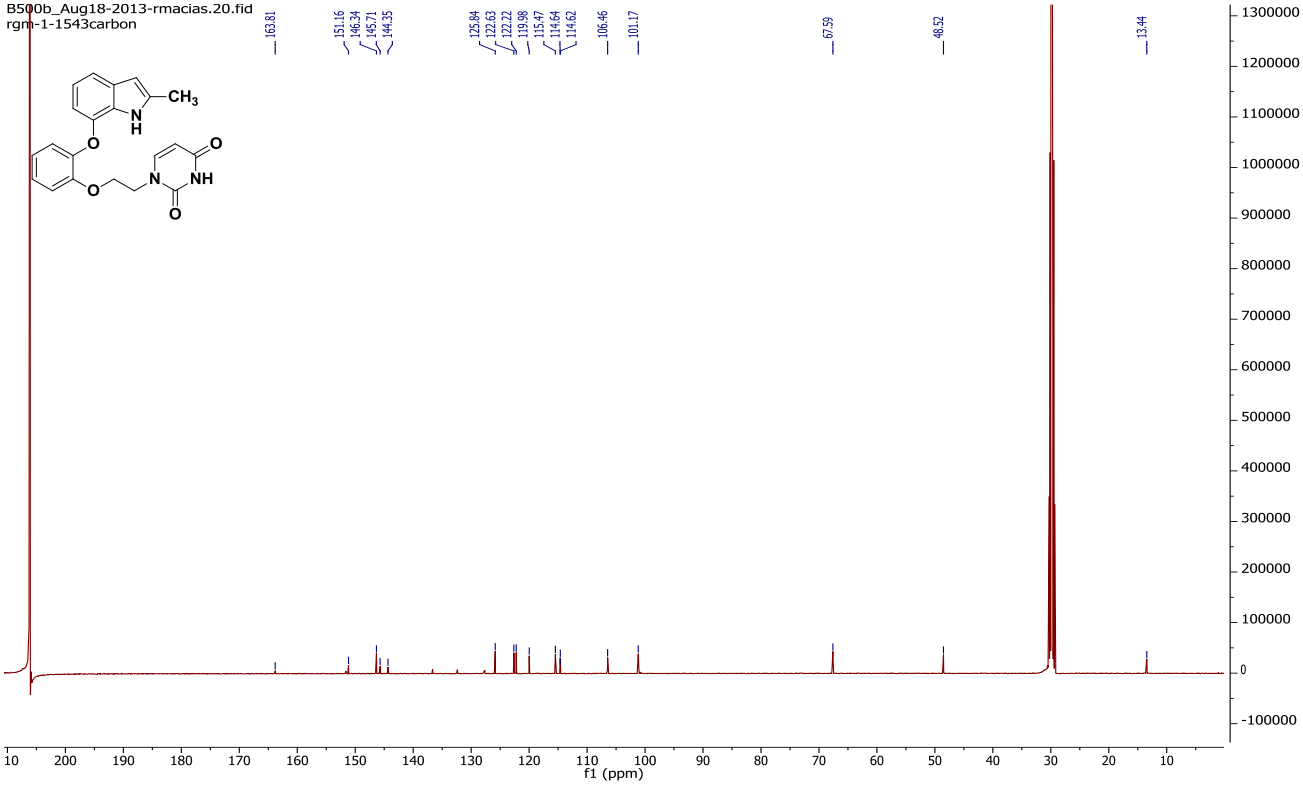
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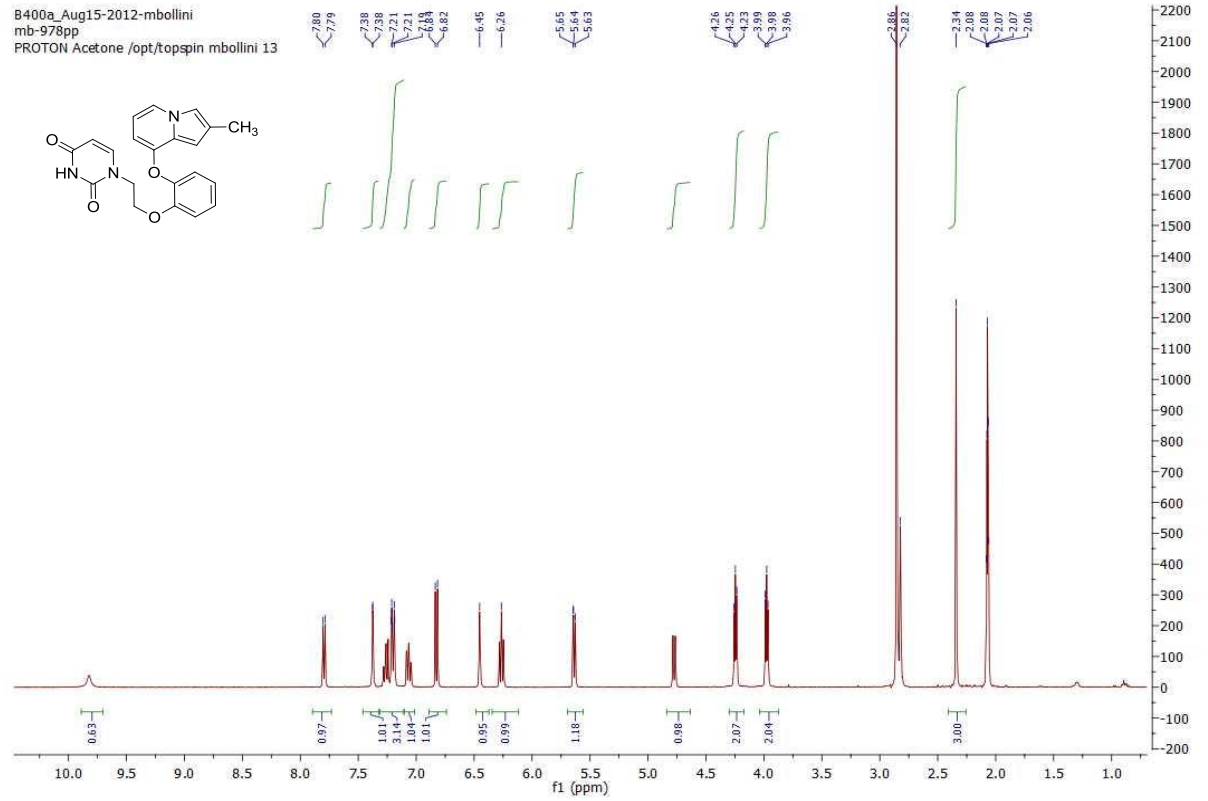
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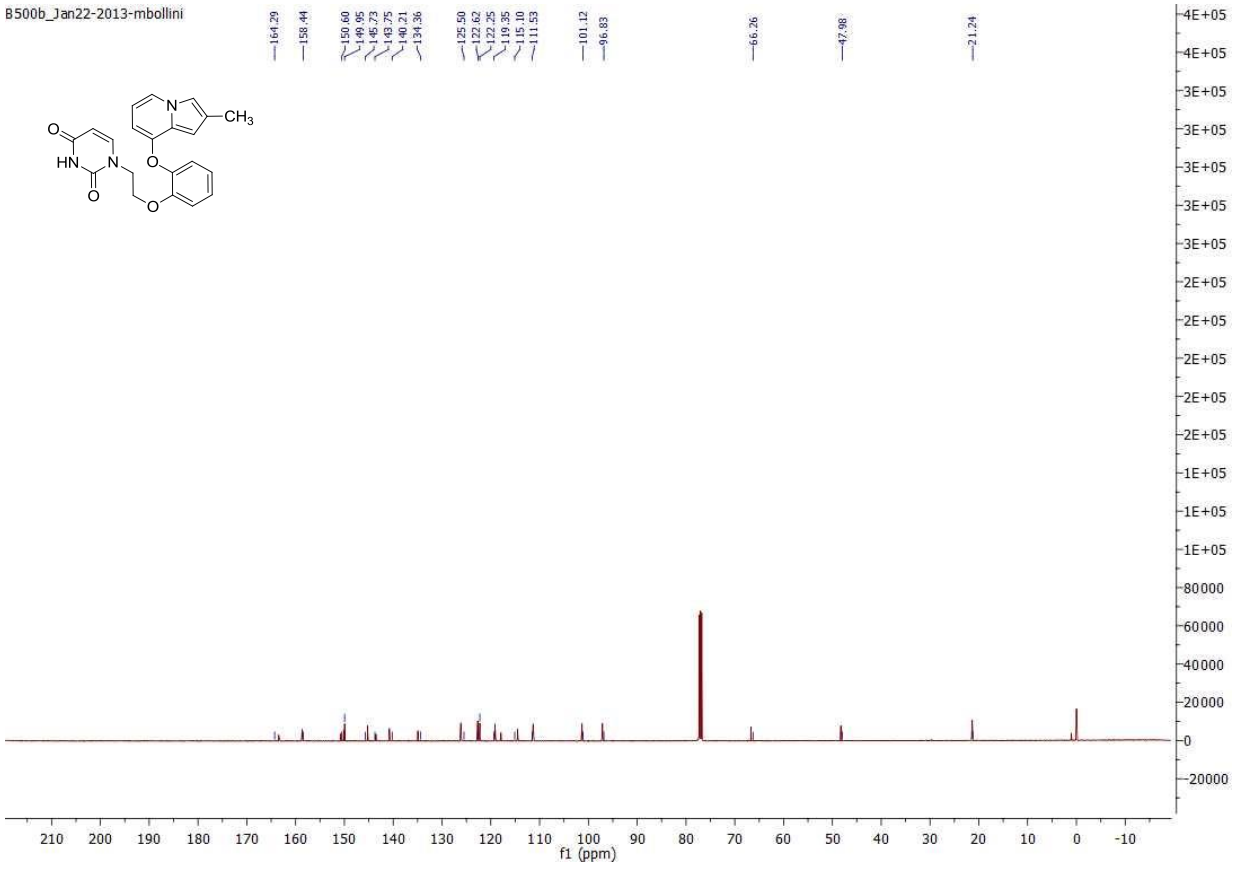
f1 (ppm)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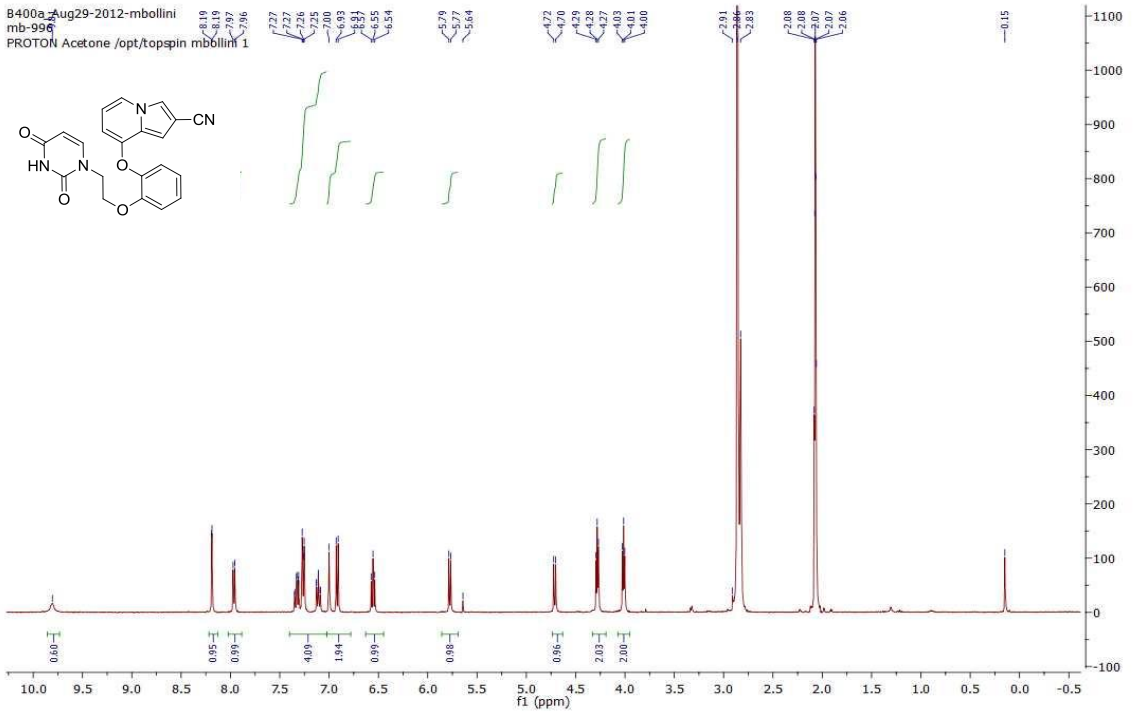
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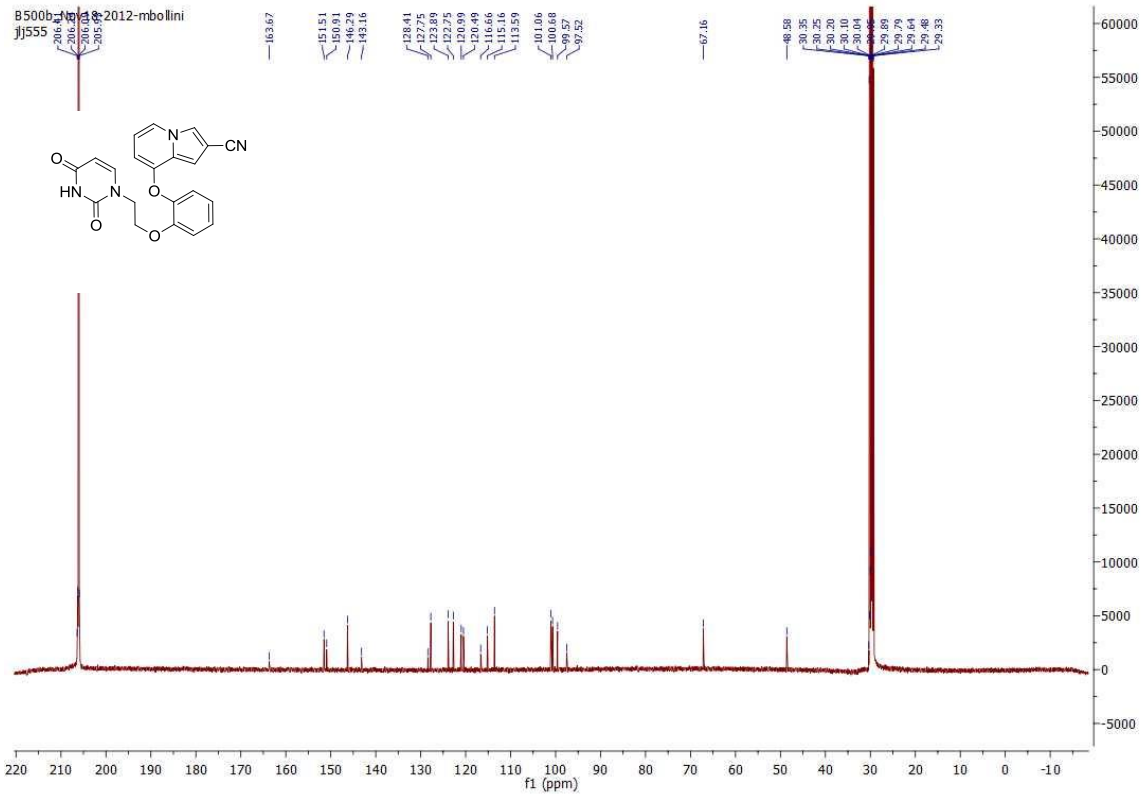
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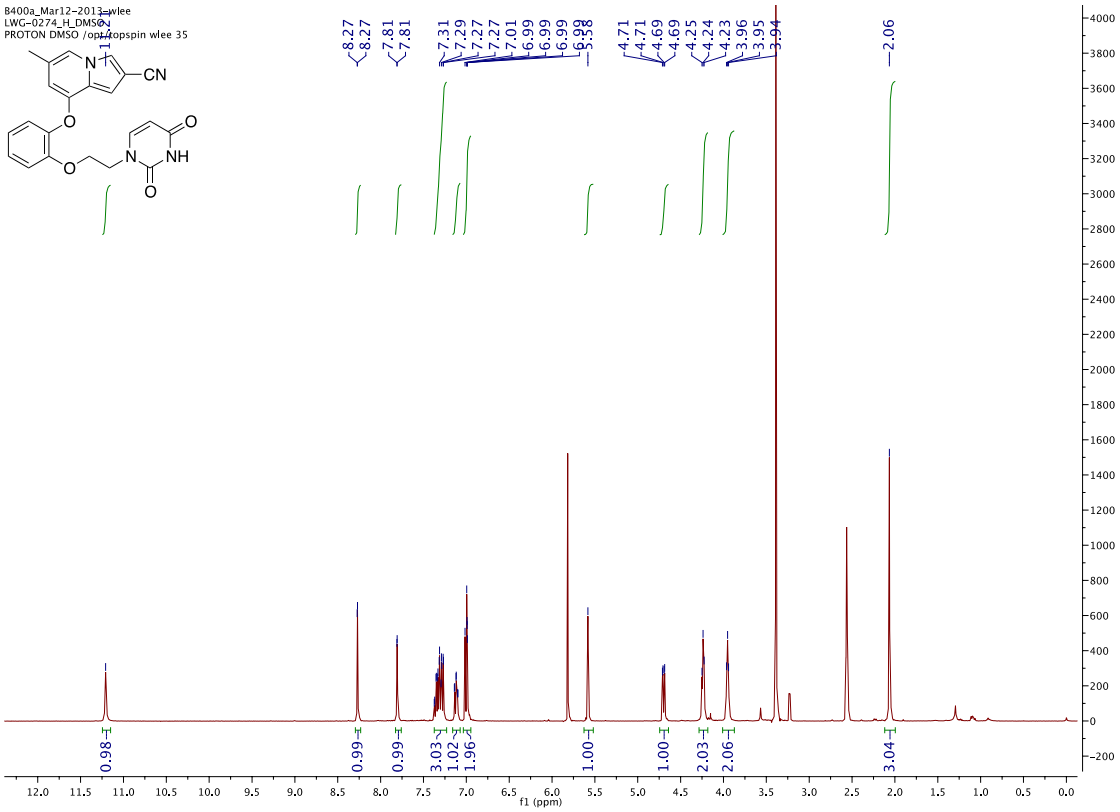
B400a_Mar12-2013-wlee
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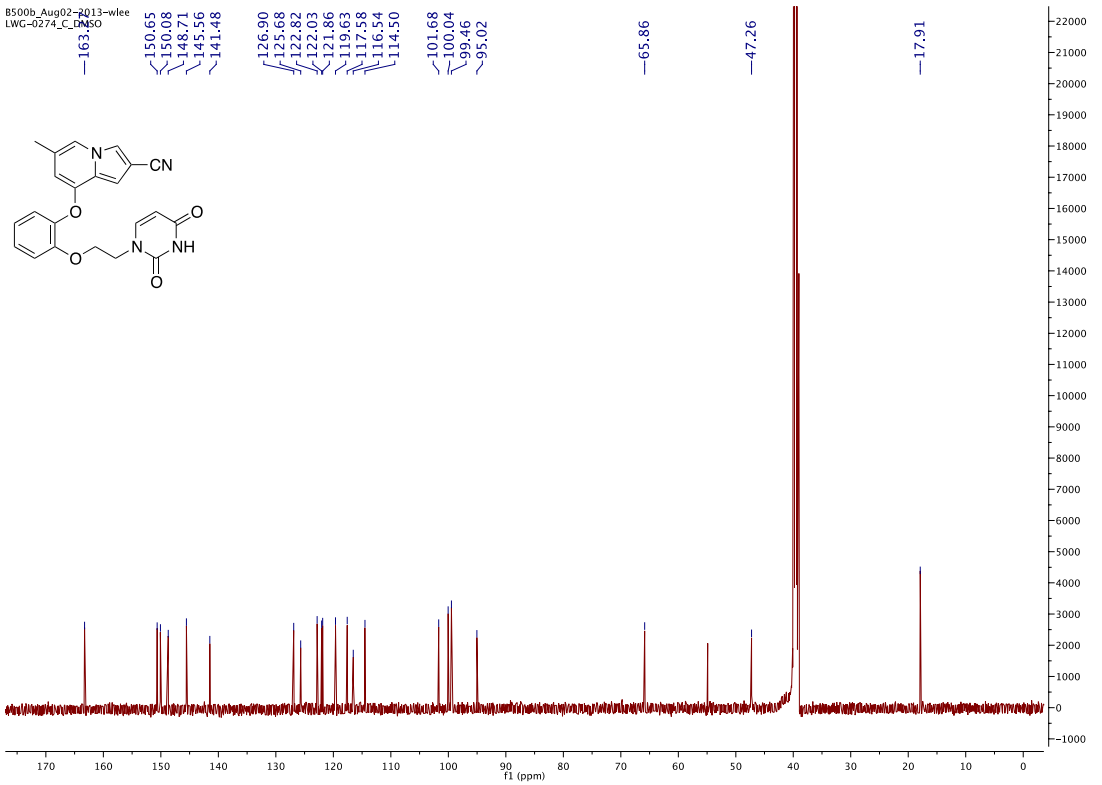
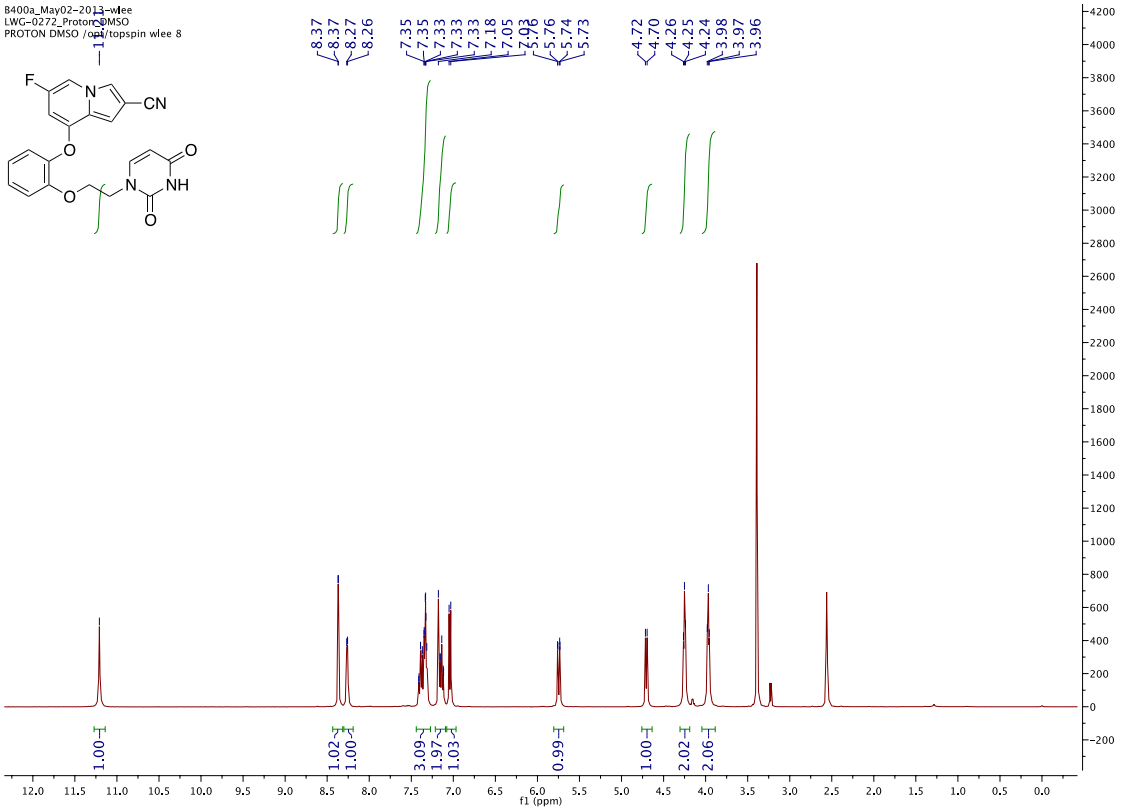
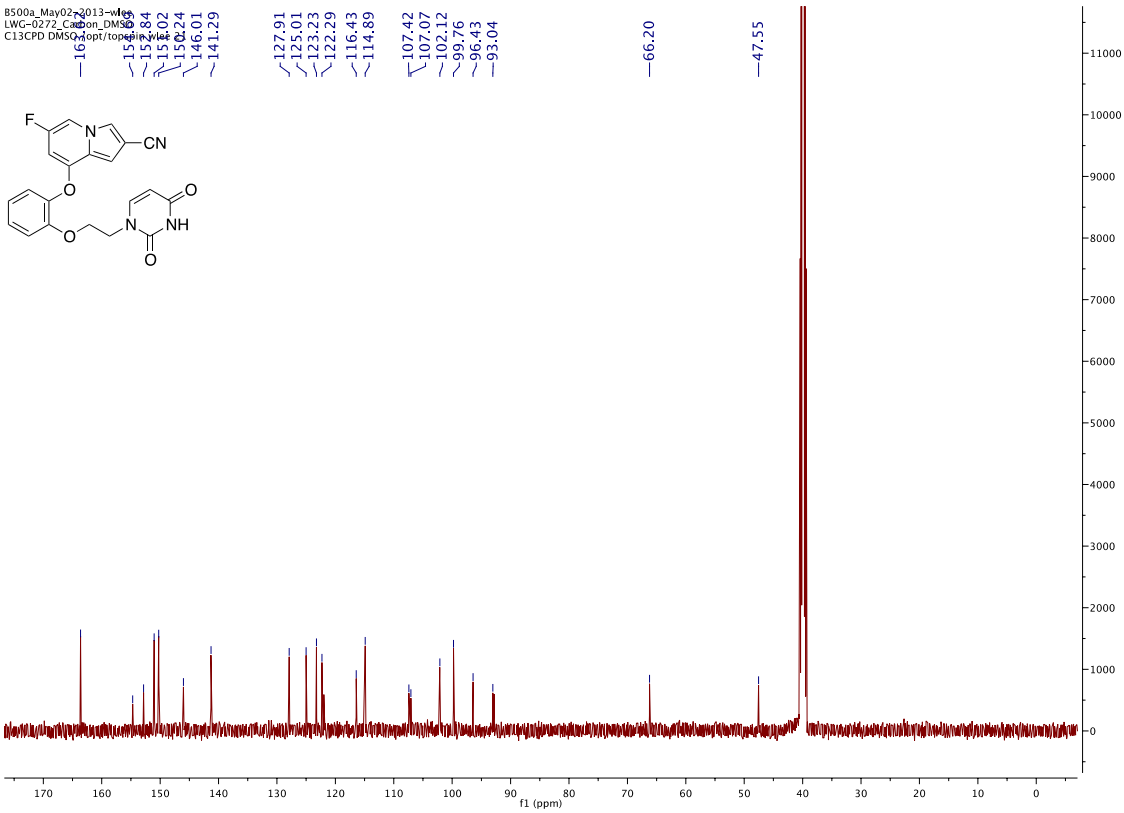
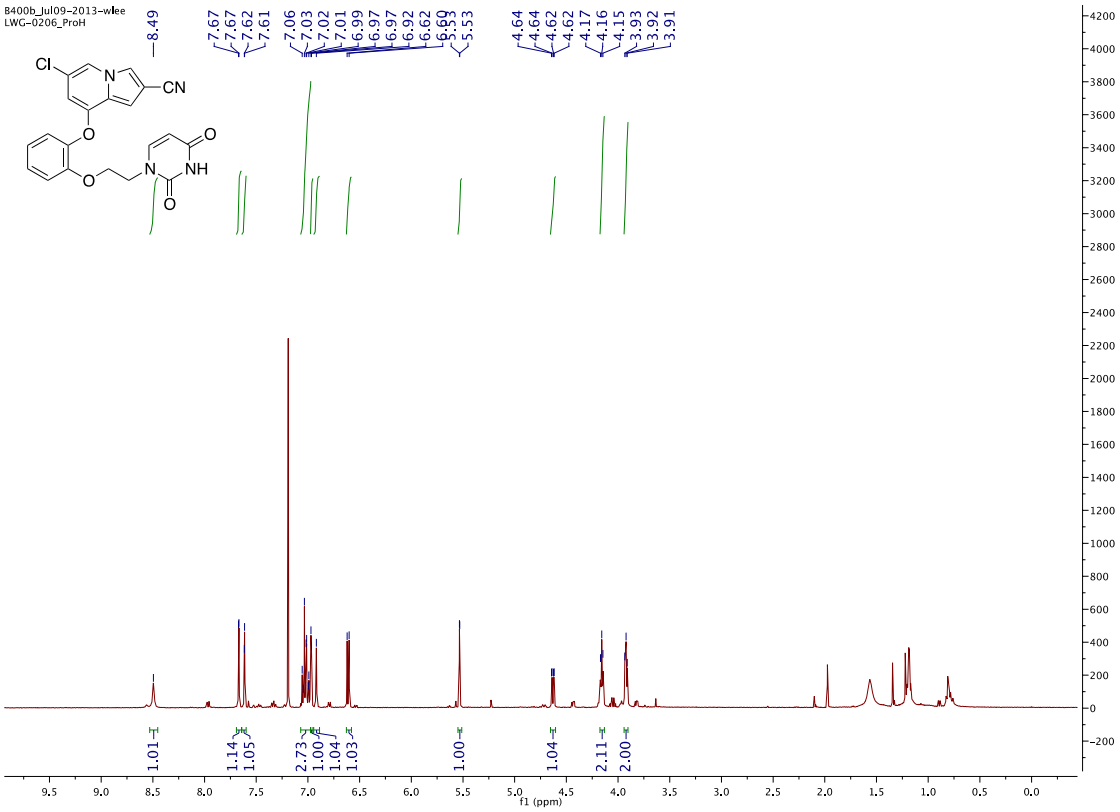
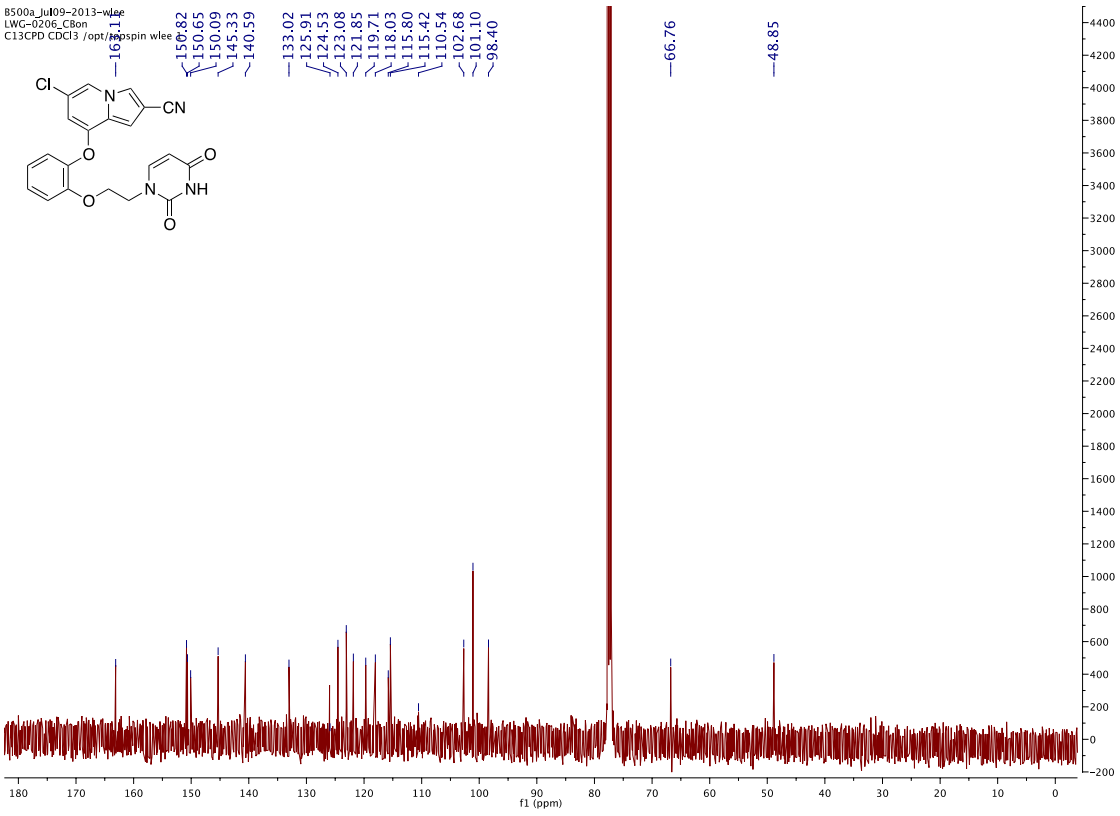
4.71
4.71
4.69
4.69
4.25
4.24
4.23
3.96
3.95
3.94
2.06
0.98
0.99
0.99
3.03
1.02
1.96
1.00
1.00
2.03
2.06
3.04
f1 (ppm)

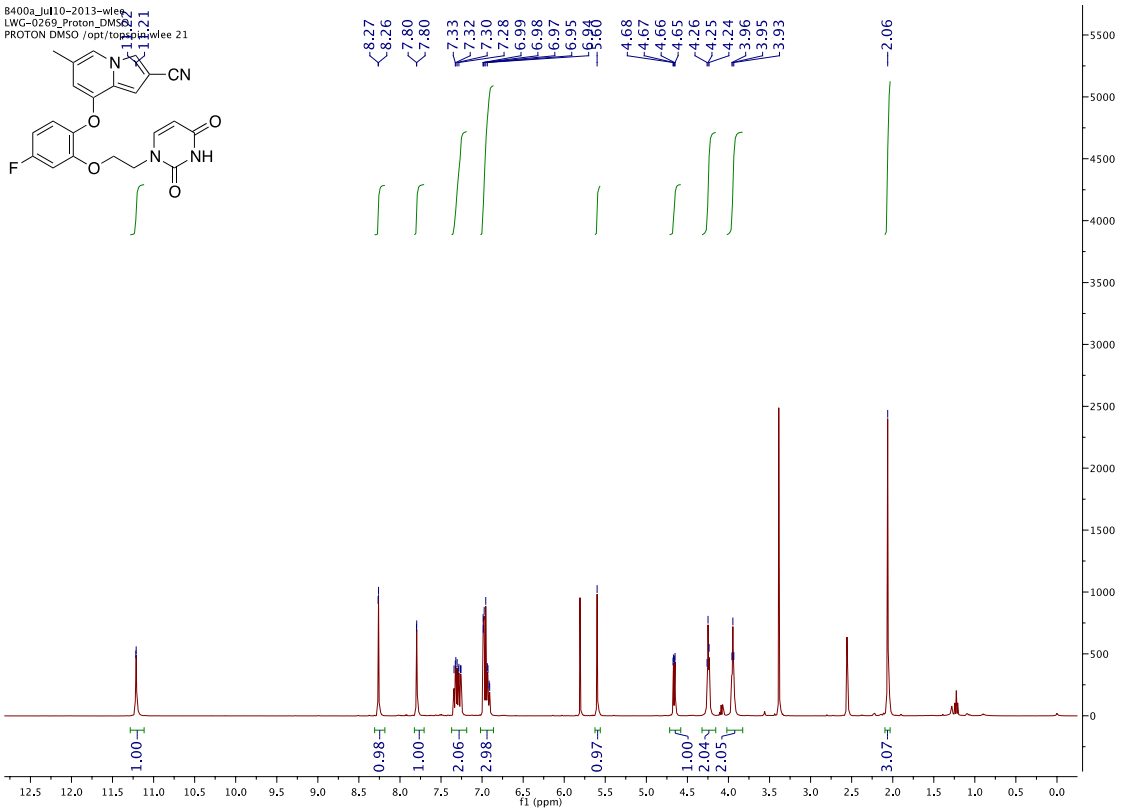

B500b_Aug02-2013-wlee
LWG-0274_C_DMSO
163.1
150.65
150.08
148.71
145.56
141.48
126.90
125.68
122.82
122.03
121.86
119.63
117.58
116.54
114.50
101.68
100.04
99.46
95.02
65.86
47.26
17.91
f1 (ppm)

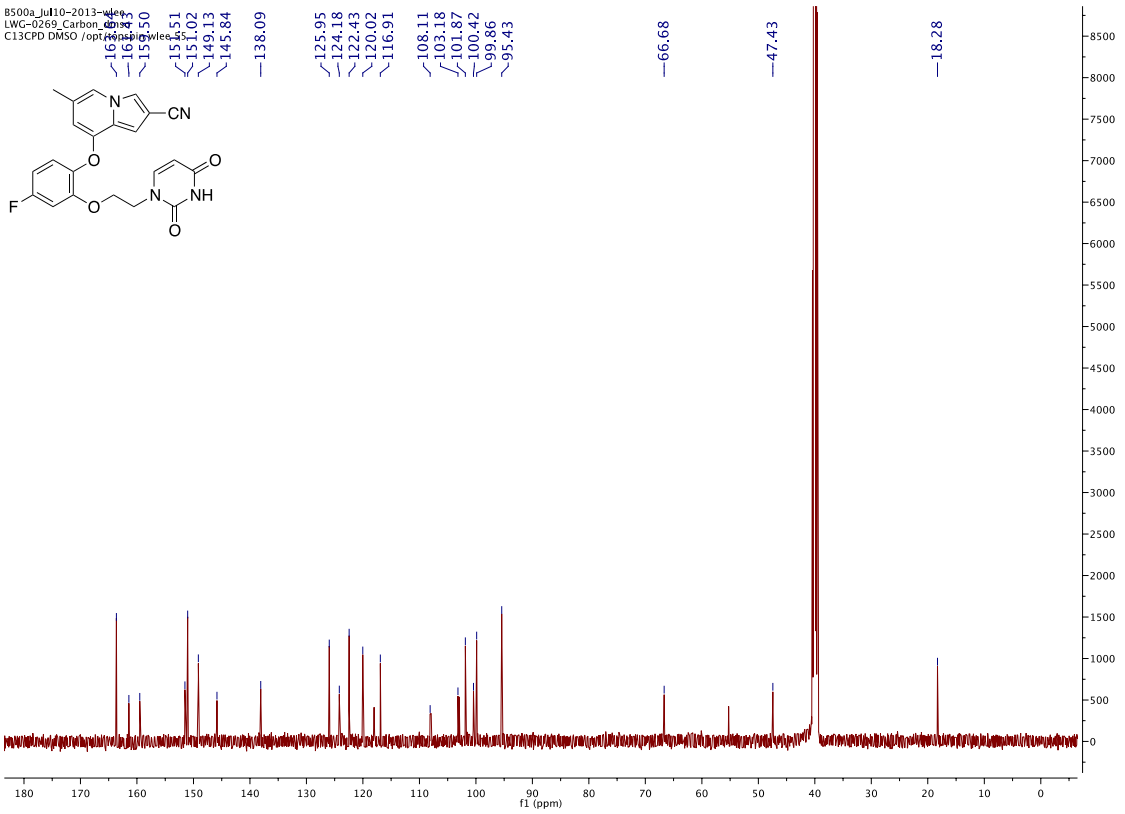

B400a_May02-2013-wlee
LWG-0272_Proton_DMSO
PROTON DMSO /opt/topspin wlee 8
8.37
8.37
8.27
8.26
7.35
7.35
7.33
7.33
7.33
7.18
7.05
5.76
5.74
5.73
4.72
4.70
4.26
4.25
4.24
3.98
3.97
3.96
1.00
1.02
1.00
3.09
1.97
1.03
0.99
1.00
2.02
2.06
f1 (ppm)

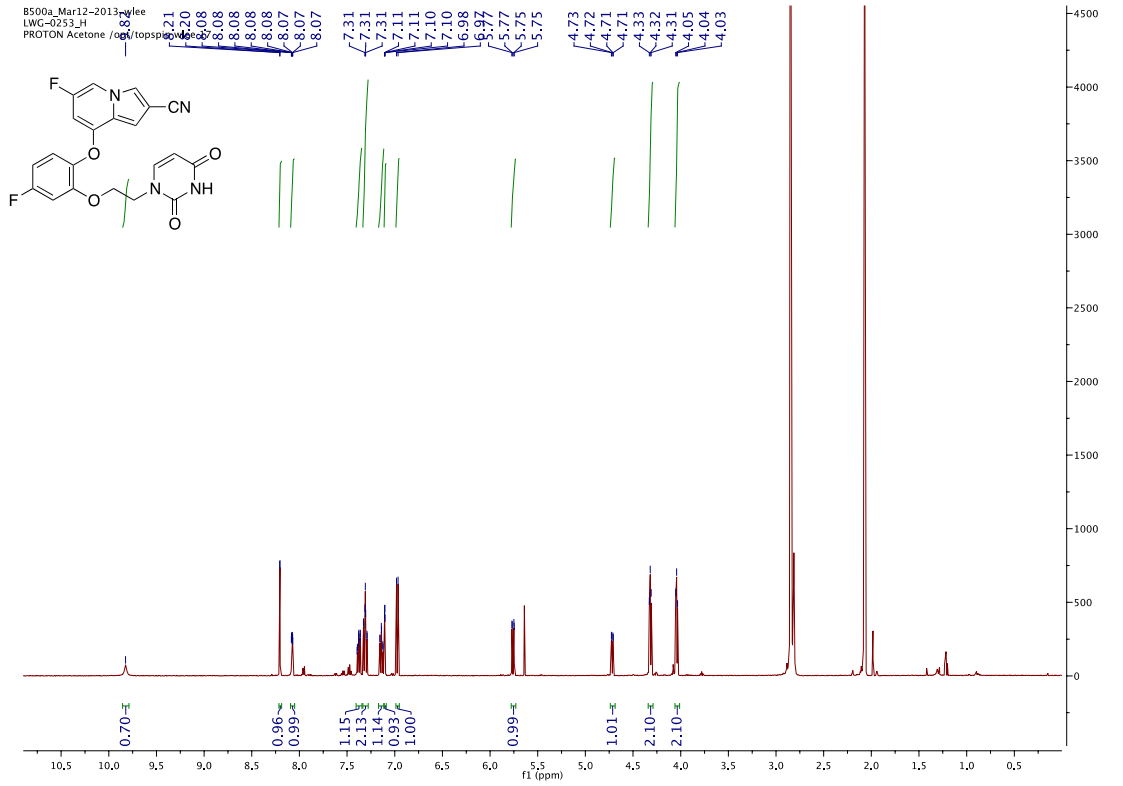

B500a_May02-2013-wlee
LWG-0272_Carbon_DMSO
C13CPD DMSO /opt/topspin wlee
163.72
152.84
152.02
150.24
146.01
141.29
127.91
125.01
123.23
122.29
116.43
114.89
107.42
107.07
102.12
99.76
96.43
93.04
66.20
47.55
f1 (ppm)

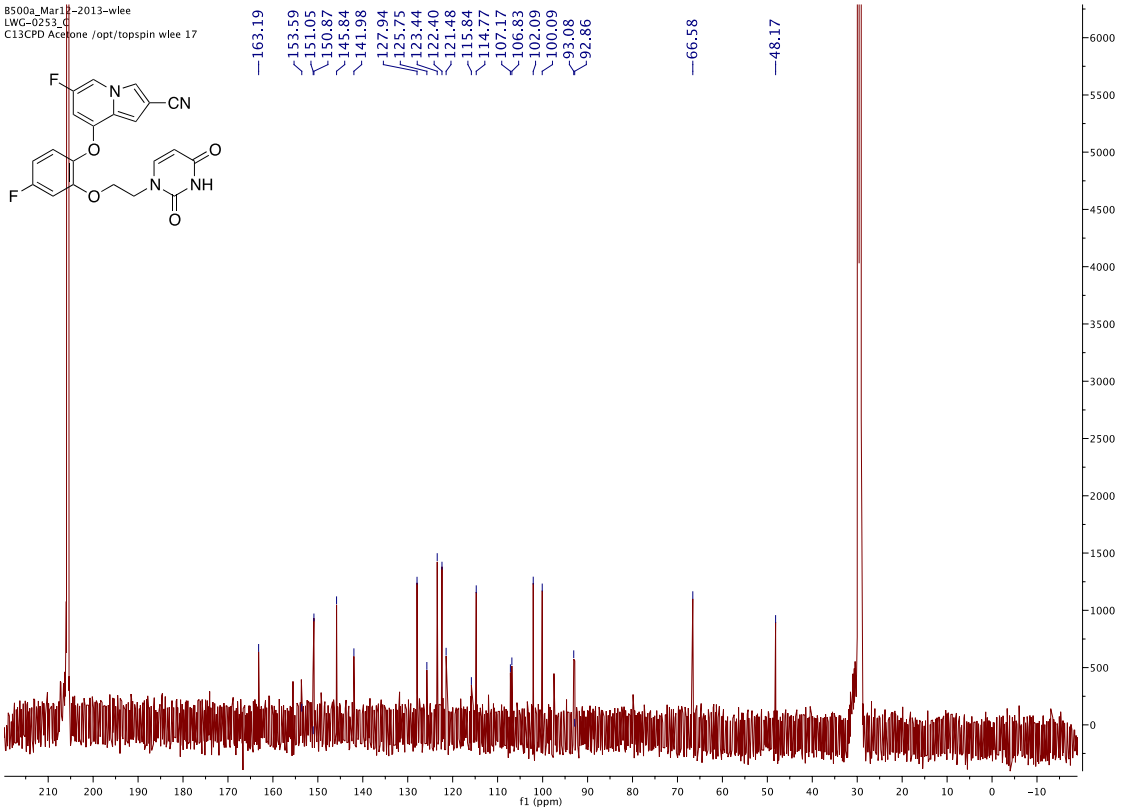

B400b_Jul09-2013-wlee
LWG-0206_ProH
8.49
7.67
7.67
7.62
7.61
7.06
7.03
7.02
7.01
6.99
6.97
6.92
6.62
6.60
5.53
5.53
4.64
4.64
4.62
4.62
4.17
4.16
4.15
3.93
3.92
3.91
Cl
N
CN
O
O
N
NH
O
O
1.01
1.14
1.05
2.73
1.00
1.04
1.03
1.00
1.04
2.11
2.00
f1 (ppm)

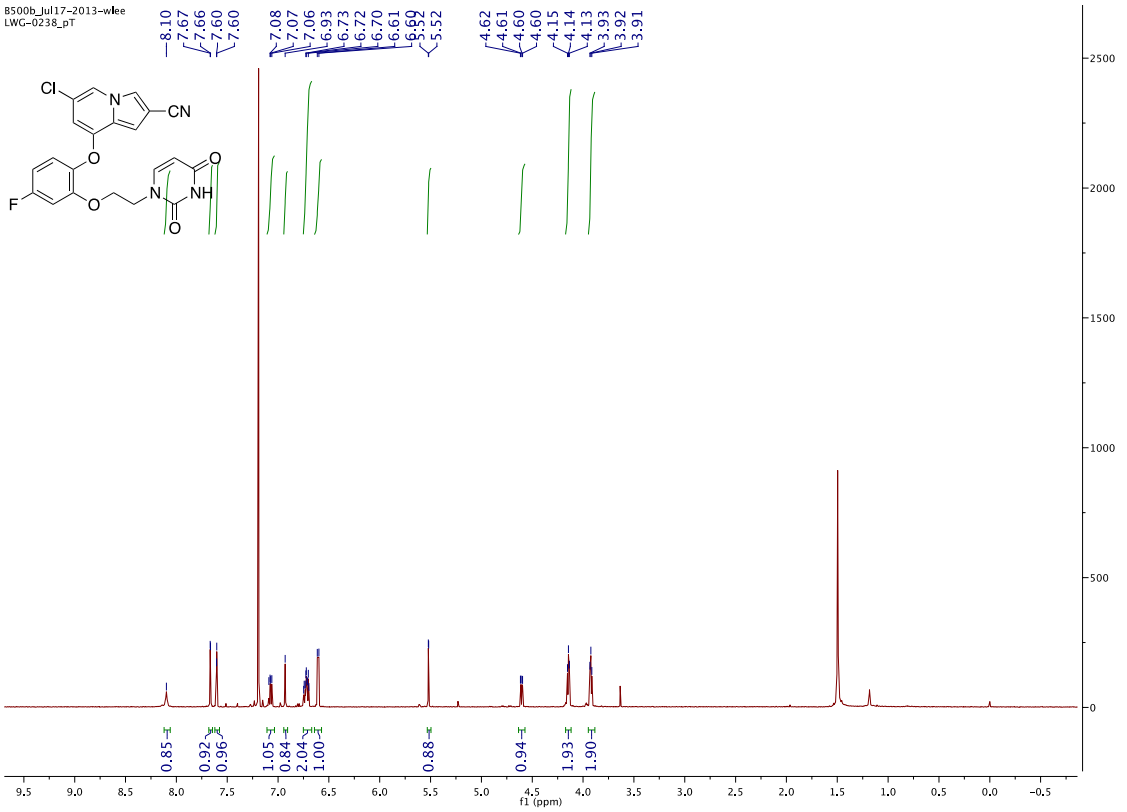

B500a_Jul09-2013-wlee
LWG-0206_CBon
C13CPD CDCl3 /opt/topspin wlee
161.11
150.82
150.65
150.09
145.33
140.59
133.02
125.91
124.53
123.08
121.85
119.71
118.03
115.80
115.42
110.54
102.68
101.10
98.40
66.76
48.85
Cl
N
CN
O
O
N
NH
O
O
f1 (ppm)

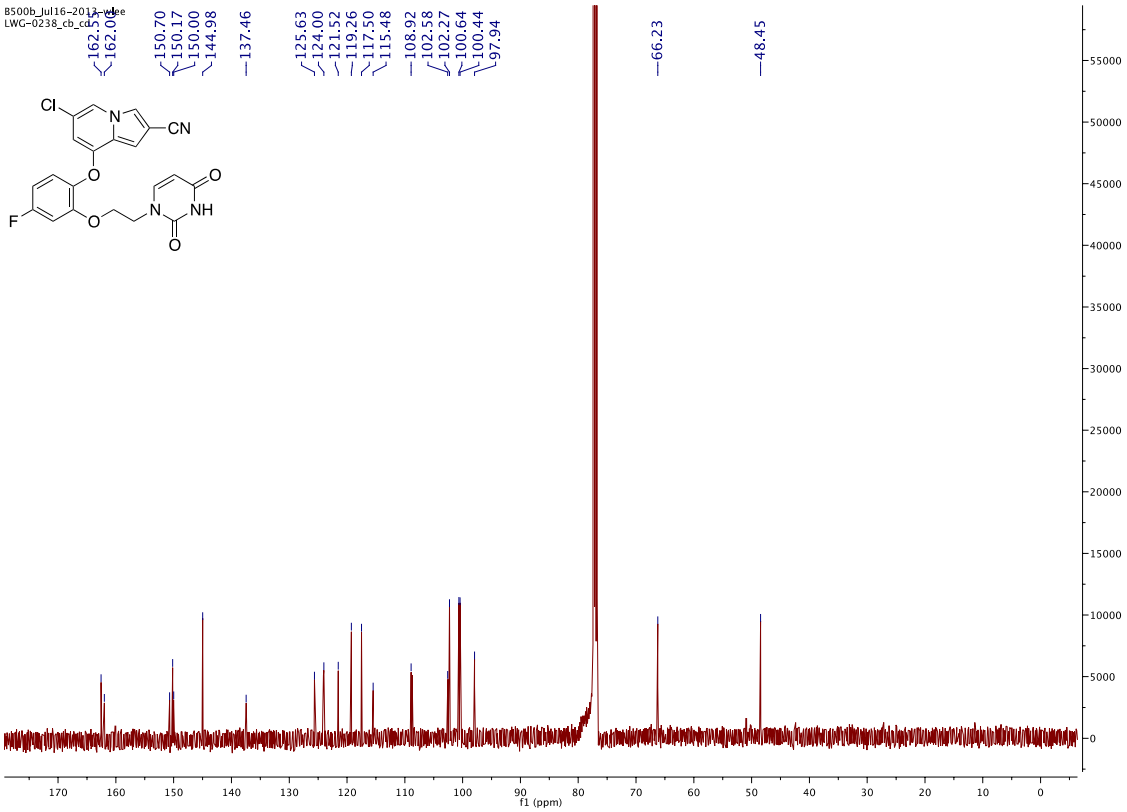

B400a_Jul10-2013-wlee
LWG-0269_Proton_DMSO
PROTON DMSO /opt/topspin/wlee 21
11.22
11.21
8.27
8.26
7.80
7.80
7.33
7.32
7.30
7.28
6.99
6.98
6.97
6.95
6.94
5.60
4.68
4.67
4.66
4.65
4.26
4.25
4.24
3.96
3.95
3.93
2.06
CN
O
F
N
NH
1.00
0.98
1.00
2.06
2.98
0.97
1.00
2.04
2.05
3.07
f1 (ppm)

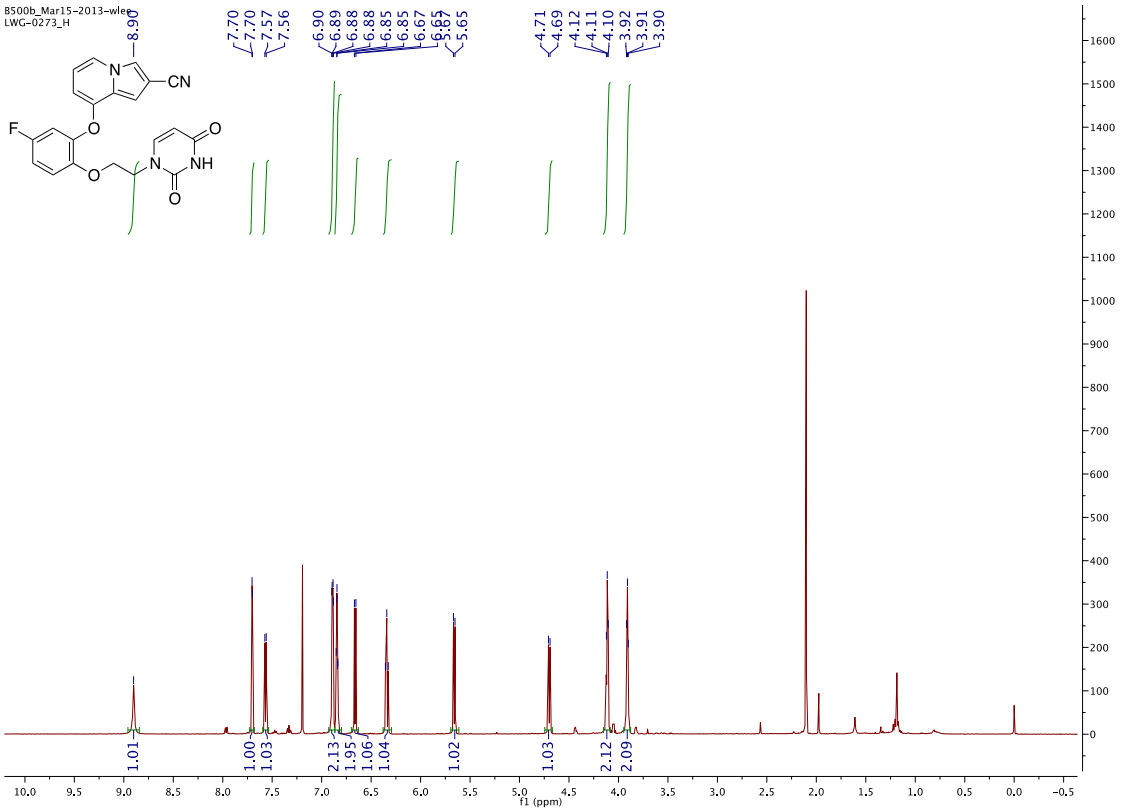

B500a_Jul10-2013-wlee
LWG-0269_Carbon_dmso
C13CPD DMSO /opt/topspin/wlee 55
162.43
160.43
155.50
151.51
151.02
149.13
145.84
138.09
125.95
124.18
122.43
120.02
116.91
108.11
103.18
101.87
100.42
99.86
95.43
66.68
47.43
18.28
CN
O
F
N
NH
f1 (ppm)

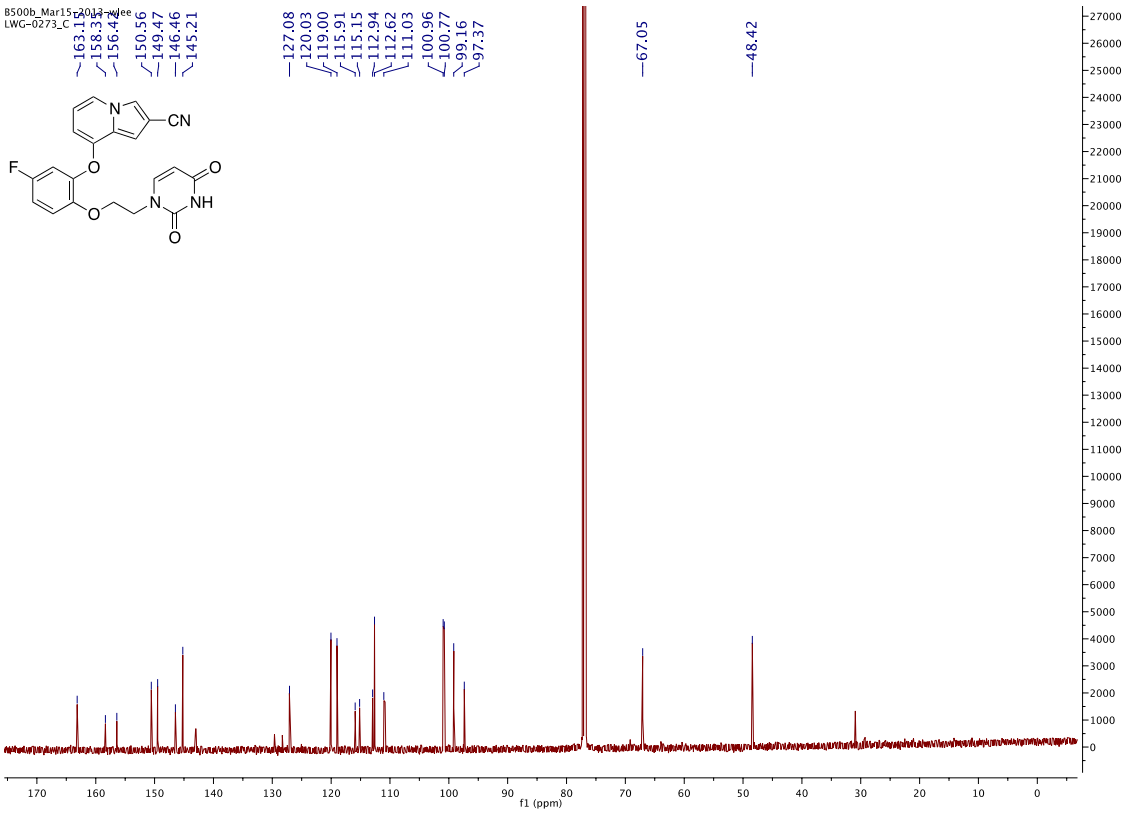

B500a_Mar12-2013_wlee
LWG-0253_H
PROTON Acetone /opt/topspin wlee 17
9.88
8.21
8.20
8.08
8.08
8.08
8.08
8.08
8.07
8.07
8.07
7.31
7.31
7.31
7.11
7.11
7.10
7.10
6.98
6.97
5.77
5.75
5.75
4.73
4.72
4.71
4.71
4.33
4.32
4.31
4.05
4.04
4.03
F
N
CN
O
F
O
O
N
NH
O
0.70
0.96
0.99
1.15
2.13
1.14
0.93
1.00
0.99
1.01
2.10
2.10
f1 (ppm)

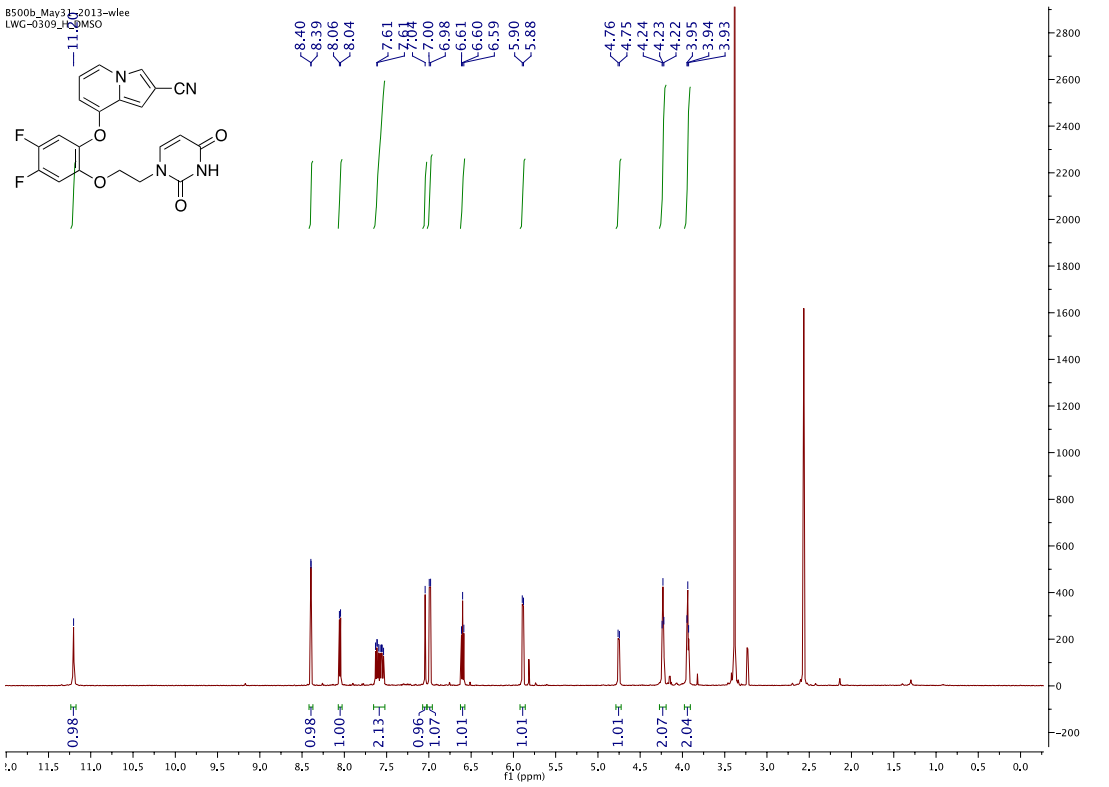

B500a_Mar12-2013_wlee
LWG-0253_C
C13CPD Acetone /opt/topspin wlee 17
163.19
153.59
151.05
150.87
145.84
141.98
127.94
125.75
123.44
122.40
121.48
115.84
114.77
107.17
106.83
102.09
100.09
93.08
92.86
66.58
48.17
F
N
CN
O
F
O
O
N
NH
O
f1 (ppm)

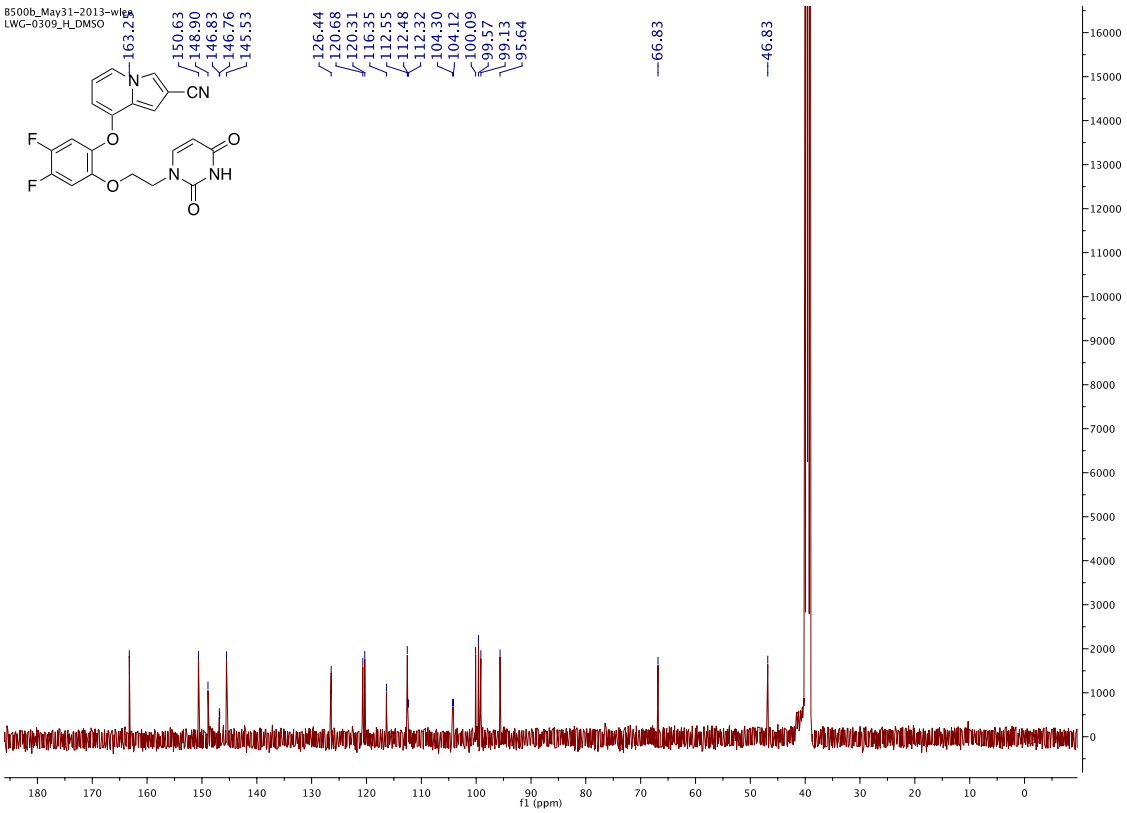

B500b_Jul17-2013-wlee
LWG-0238_pT
8.10
7.67
7.66
7.60
7.60
7.08
7.07
7.06
6.93
6.73
6.72
6.70
6.61
6.59
6.52
5.52
4.62
4.61
4.60
4.60
4.15
4.14
4.13
3.93
3.92
3.91
0.85
0.92
0.96
1.05
0.84
2.04
1.00
0.88
0.94
1.93
1.90
f1 (ppm)

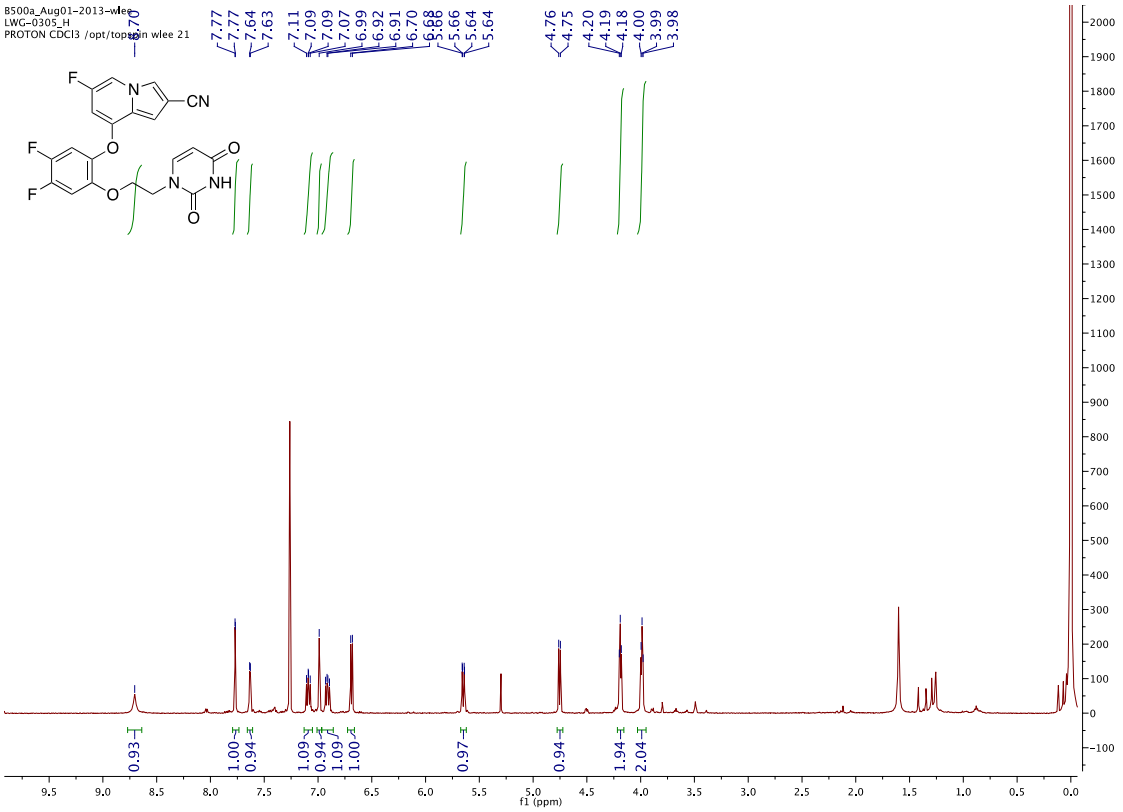

B500b_Jul16-2013-wlee
LWG-0238_cb_cd3
162.51
162.08
150.70
150.17
150.00
144.98
137.46
125.63
124.00
121.52
119.26
117.50
115.48
108.92
102.58
102.27
100.64
100.44
97.94
66.23
48.45
f1 (ppm)

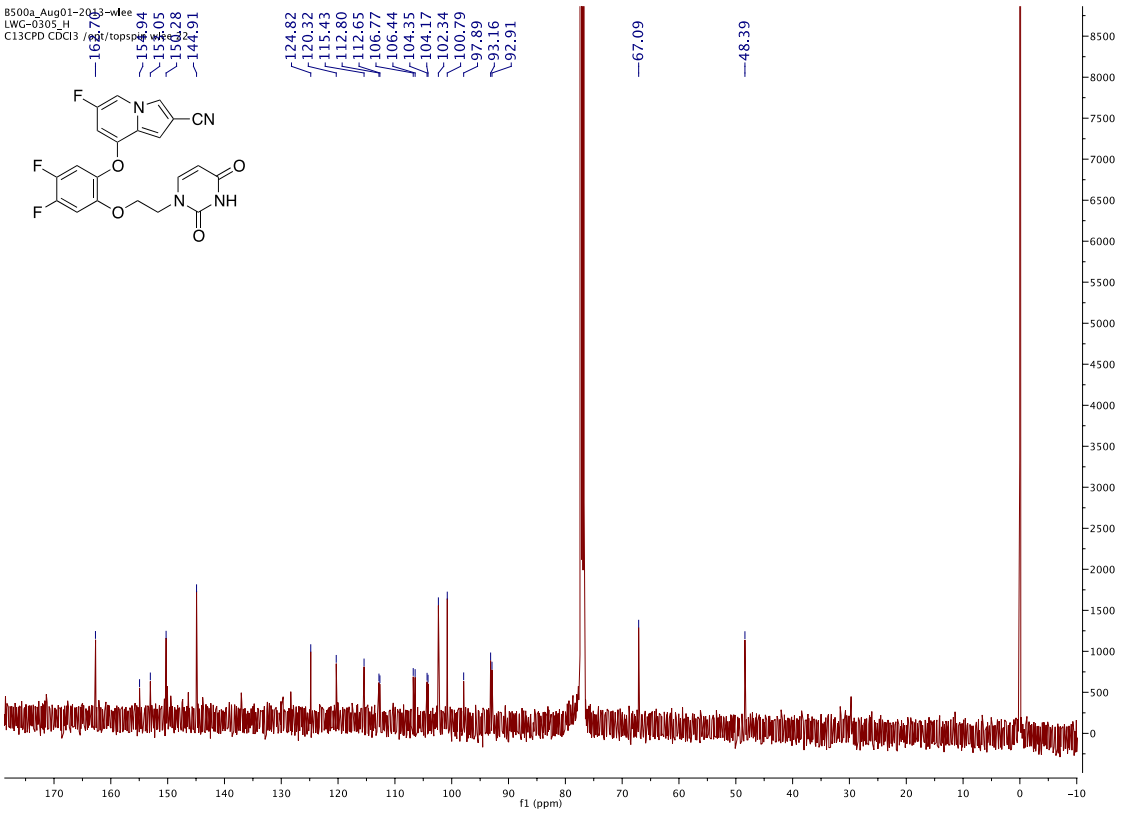

B500b_Mar15-2013-wlee
LWG-0273_H
8.90
7.70
7.70
7.57
7.56
6.90
6.89
6.88
6.88
6.85
6.85
6.67
6.65
5.67
5.65
4.71
4.69
4.12
4.11
4.10
3.92
3.91
3.90
CN
F
O
N
NH
1.01
1.00
1.03
2.13
1.95
1.06
1.04
1.02
1.03
2.12
2.09
f1 (ppm)

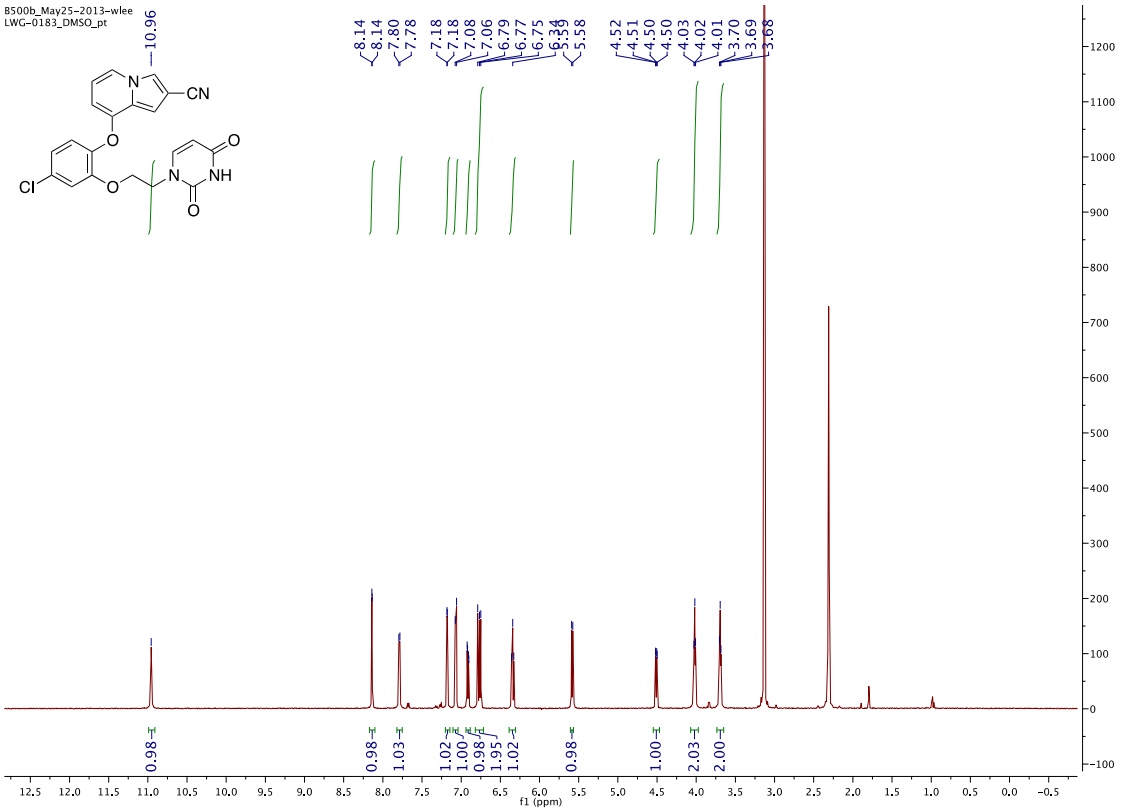

B500b_Mar15-2013-wlee
LWG-0273_C
163.13
158.35
156.42
150.56
149.47
146.46
145.21
127.08
120.03
119.00
115.91
115.15
112.94
112.62
111.03
100.96
100.77
99.16
97.37
67.05
48.42
CN
F
O
N
NH
f1 (ppm)

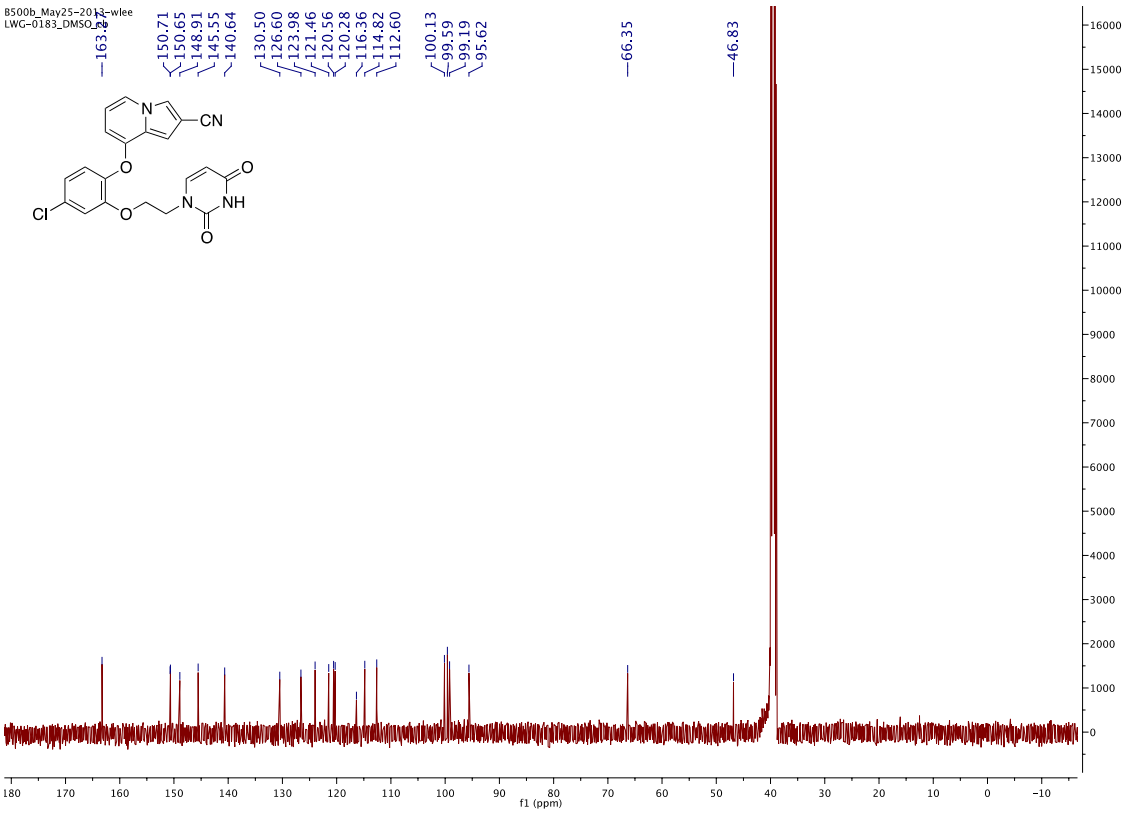

B500b_May31-2013-wlee
LWG-0309_H_DMSO
11.07
8.40
8.39
8.06
8.04
7.61
7.61
7.04
7.00
6.98
6.61
6.60
6.59
5.90
5.88
4.76
4.75
4.24
4.23
4.22
3.95
3.94
3.93
CN
F
F
O
O
N
NH
O
0.98
0.98
1.00
2.13
0.96
1.07
1.01
1.01
1.01
2.07
2.04
f1 (ppm)

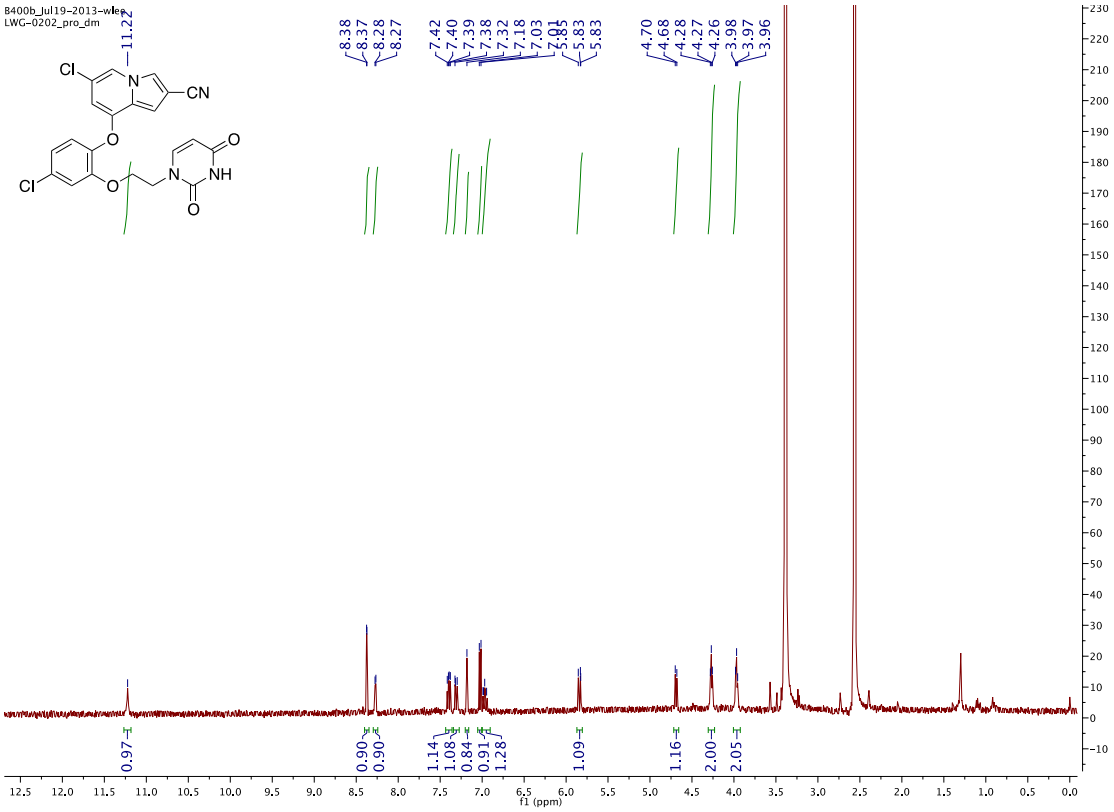

B500b_May31-2013-wlee
LWG-0309_H_DMSO
163.25
150.63
148.90
146.83
146.76
145.53
126.44
120.68
120.31
116.35
112.55
112.48
112.32
104.30
104.12
100.09
99.57
99.13
95.64
66.83
46.83
CN
F
F
O
O
N
NH
O
f1 (ppm)

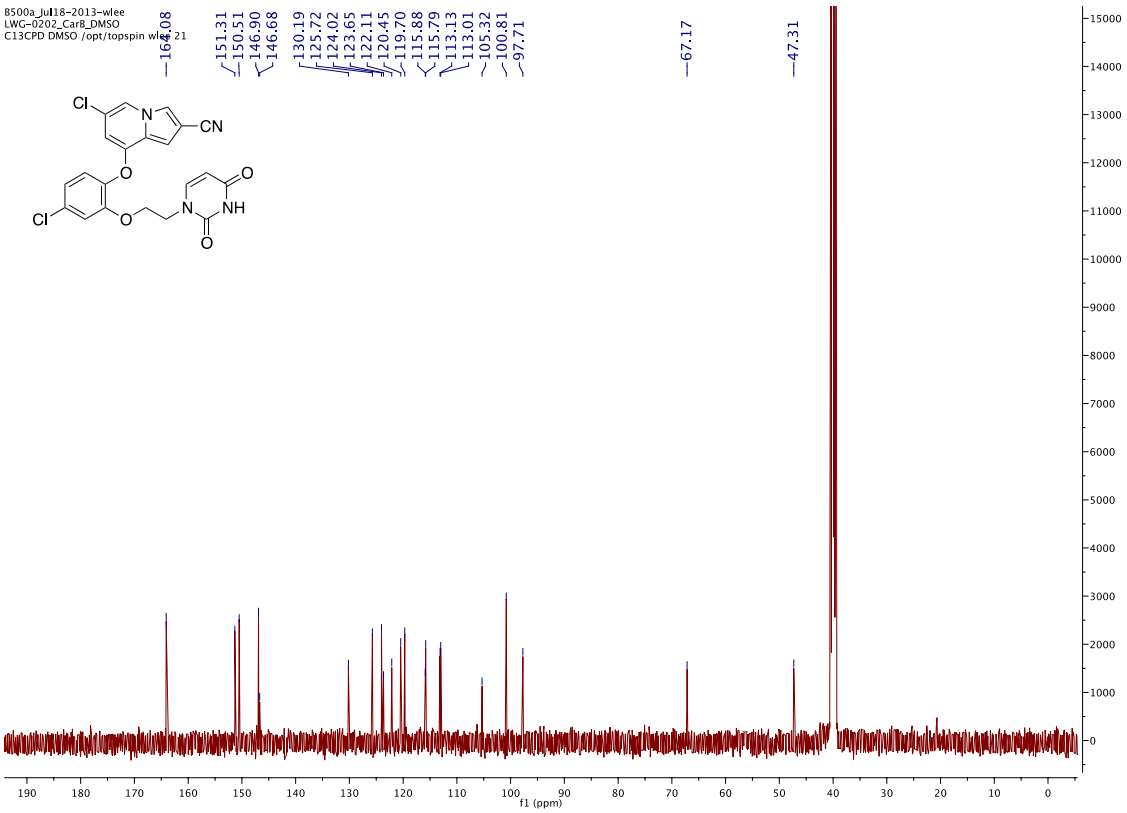

B500a_Aug01-2013-wlee
LWG-0305_H
PROTON CDCl3 /opt/topspin wlee 21
7.77
7.77
7.64
7.63
7.11
7.09
7.09
7.07
6.99
6.92
6.91
6.70
5.66
5.64
5.64
4.76
4.75
4.20
4.19
4.18
4.00
3.99
3.98
0.93
1.00
0.94
1.09
0.94
1.09
1.00
0.97
0.94
1.94
2.04
f1 (ppm)

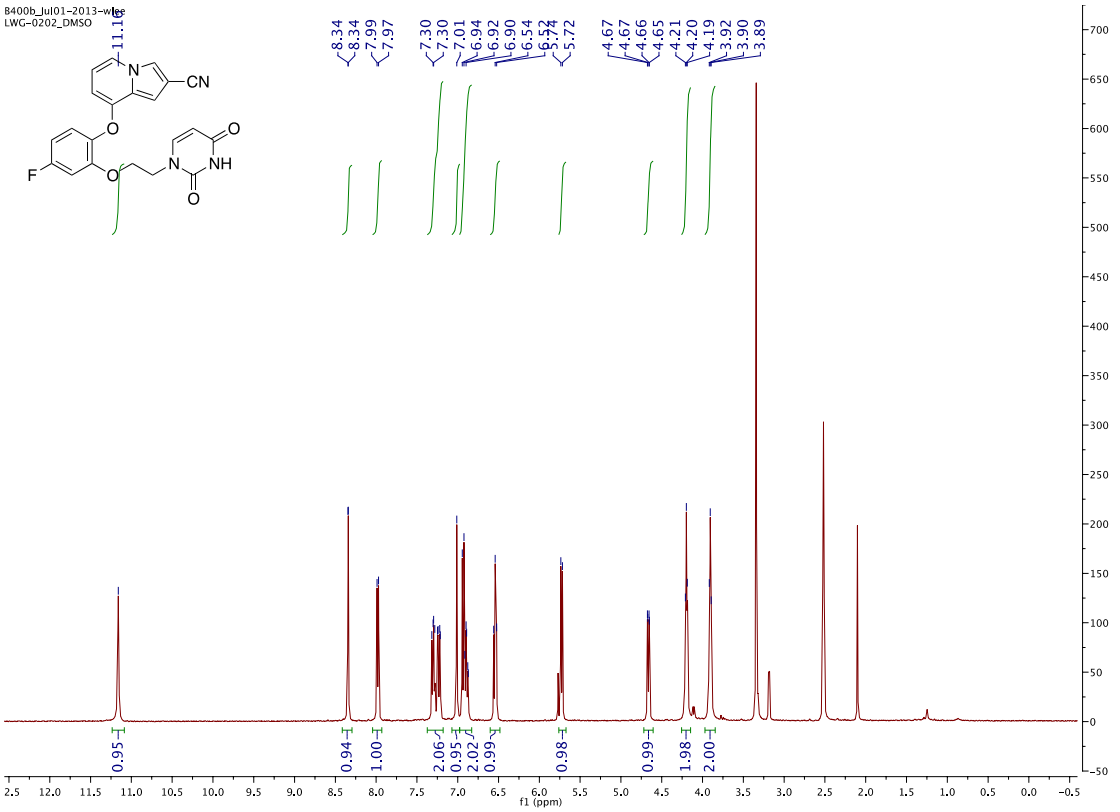

B500a_Aug01-2013-wlee
LWG-0305_H
C13CPD CDCl3 /opt/topspin wlee 22
163.70
154.94
153.05
152.28
144.91
124.82
120.32
115.43
112.80
112.65
106.77
106.44
104.35
104.17
102.34
100.79
97.89
93.16
92.91
67.09
48.39
f1 (ppm)

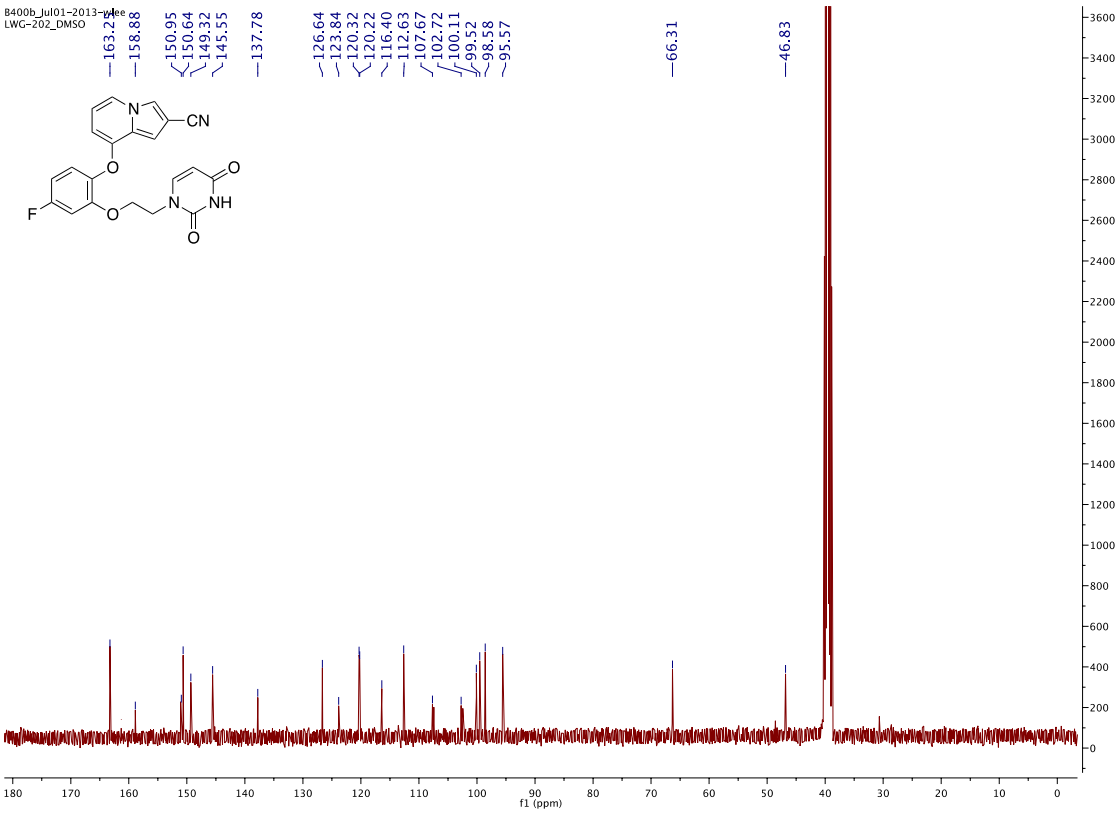

B500b_May25-2013-wlee
LWG-0183_DMSO_pt
10.96
8.14
8.14
7.80
7.78
7.18
7.18
7.08
7.06
6.79
6.77
6.75
6.34
5.59
5.58
4.52
4.51
4.50
4.50
4.03
4.02
4.01
3.70
3.69
3.68
0.98
0.98
1.03
1.02
1.00
0.98
1.95
1.02
0.98
1.00
2.03
2.00
f1 (ppm)

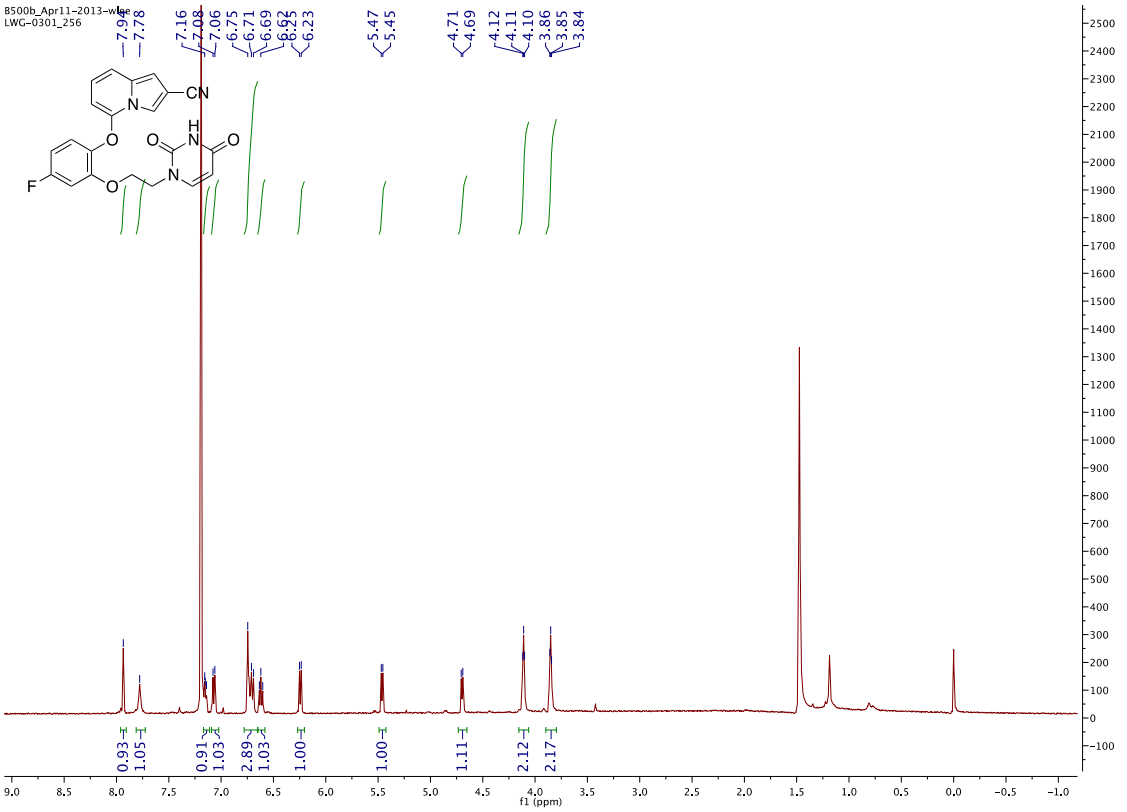

B500b_May25-2013-wlee
LWG-0183_DMSO_pt
163.42
150.71
150.65
148.91
145.55
140.64
130.50
126.60
123.98
121.46
120.56
120.28
116.36
114.82
112.60
100.13
99.59
99.19
95.62
66.35
46.83
f1 (ppm)

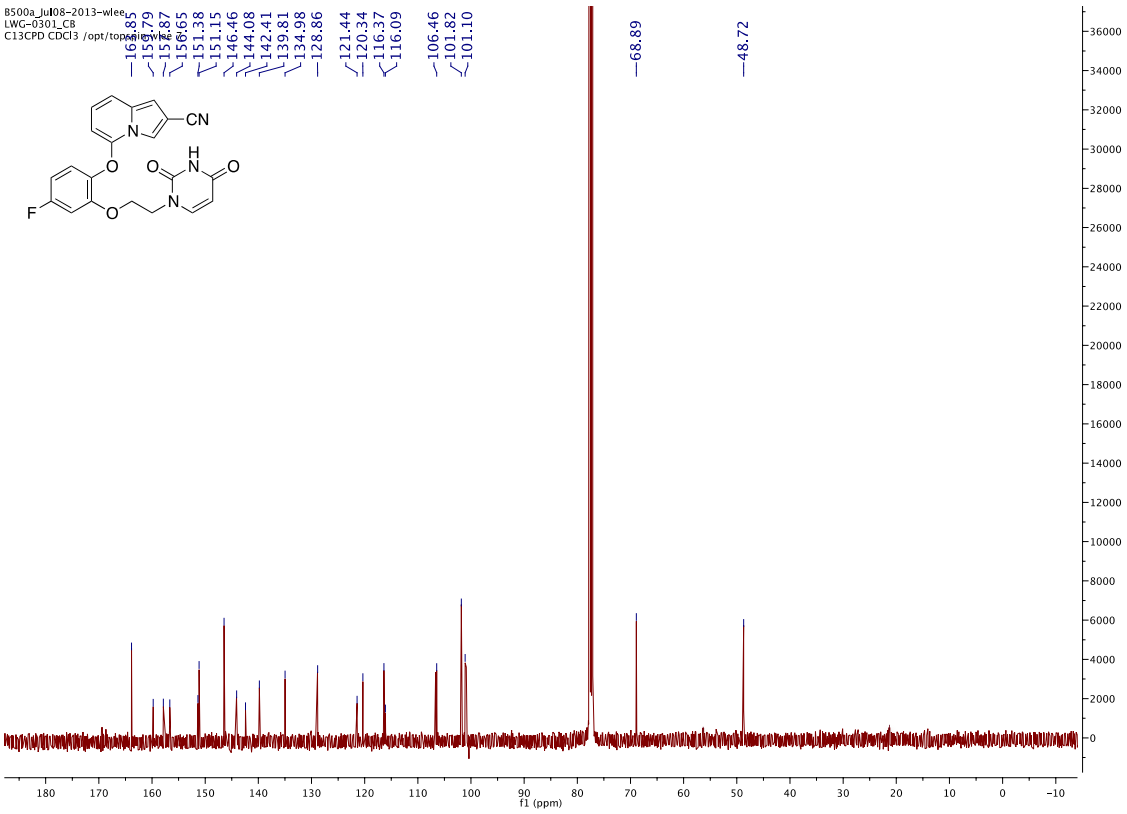

B400b_Jul19-2013-wlee
LWG-0202_pro_dm
11.22
8.38
8.37
8.28
8.27
7.42
7.40
7.39
7.38
7.32
7.18
7.03
7.01
5.85
5.83
5.83
4.70
4.68
4.28
4.27
4.26
3.98
3.97
3.96
0.97
0.90
0.90
1.14
1.08
0.84
0.91
1.28
1.09
1.16
2.00
2.05
f1 (ppm)

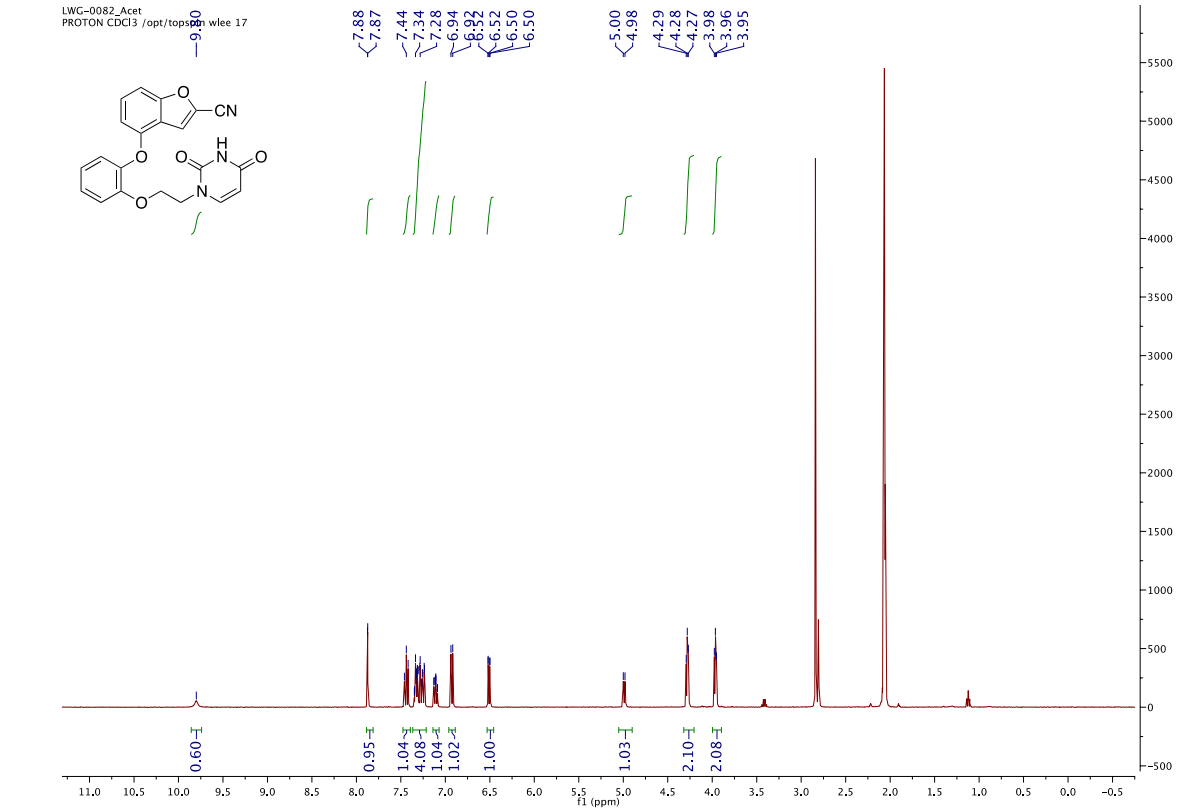

B500a_Jul18-2013-wlee
LWG-0202_Car8_DMSO
C13CPD DMSO /opt/topspin wlee 21
163.08
151.31
150.51
146.90
146.68
130.19
125.72
124.02
123.65
122.11
120.45
119.70
115.88
115.79
113.13
113.01
105.32
100.81
97.71
67.17
47.31
f1 (ppm)

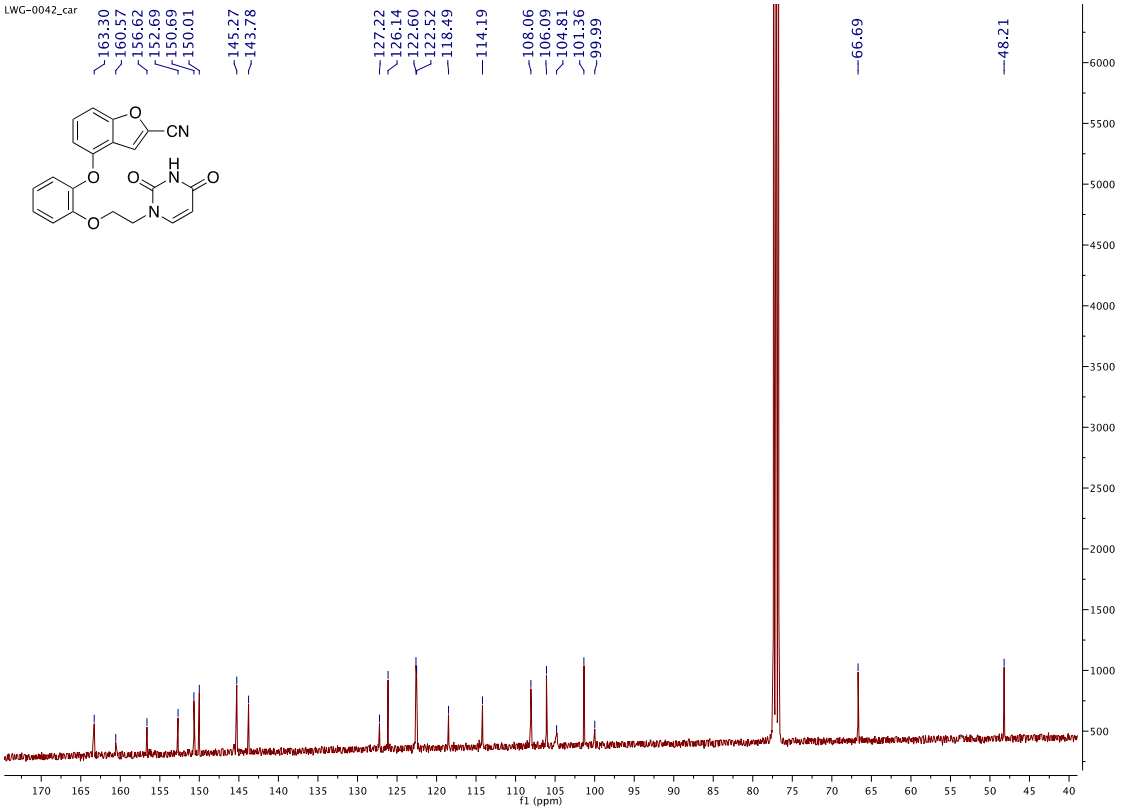

B400b_Jul01-2013-wlee
LWG-0202_DMSO
11.16
8.34
8.34
7.99
7.97
7.30
7.30
7.01
6.94
6.92
6.90
6.54
6.52
5.74
5.72
4.67
4.67
4.66
4.65
4.21
4.20
4.19
3.92
3.90
3.89
0.95
0.94
1.00
2.06
0.95
2.02
0.99
0.98
0.99
1.98
2.00
f1 (ppm)


B400b_Jul01-2013-wlee
LWG-202_DMSO
163.24
158.88
150.95
150.64
149.32
145.55
137.78
126.64
123.84
120.32
120.22
116.40
112.63
107.67
102.72
100.11
99.52
98.58
95.57
66.31
46.83
f1 (ppm)


B500b_Apr11-2013-wlee
LWG-0301_256
7.94
7.78
7.16
7.08
7.06
6.75
6.71
6.69
6.62
6.23
5.47
5.45
4.71
4.69
4.12
4.11
4.10
3.86
3.85
3.84
0.93
1.05
0.91
1.03
2.89
1.03
1.00
1.00
1.11
2.12
2.17
f1 (ppm)


B500a_Jul08-2013-wlee
LWG-0301_CB
C13CPD CDCl3 /opt/topspin/wlee
163.85
159.79
157.87
156.65
151.38
151.15
146.46
144.08
142.41
139.81
134.98
128.86
121.44
120.34
116.37
116.09
106.46
101.82
101.10
68.89
48.72
f1 (ppm)


LWG-0082_Acet
PROTON CDCl3 /opt/topspin wlee 17
9.80
7.88
7.87
7.44
7.34
7.28
6.94
6.92
6.52
6.50
6.50
5.00
4.98
4.29
4.28
4.27
3.98
3.96
3.95
CN
H
O
N
0.60
0.95
1.04
4.08
1.04
1.02
1.00
1.03
2.10
2.08
f1 (ppm)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160.57
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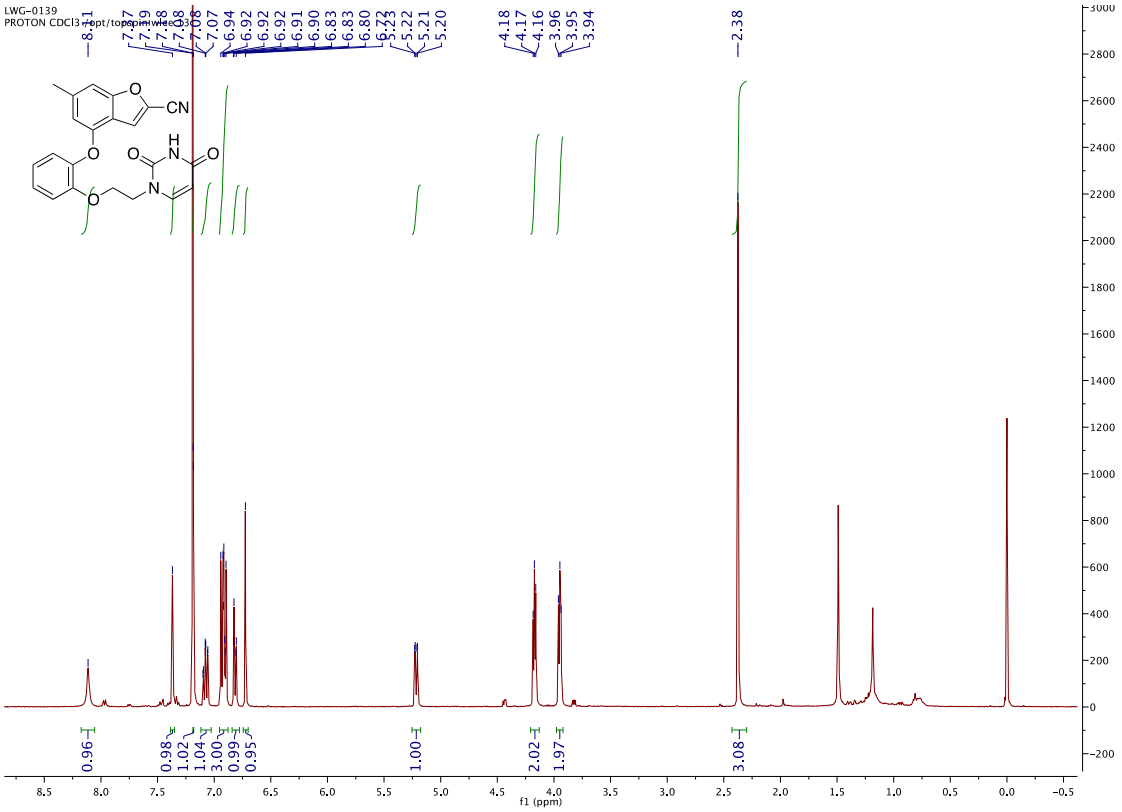
152.69
150.69
150.01
145.27
143.78
127.22
126.14
122.60
122.52
118.49
114.19
108.06
106.09
104.81
101.36
99.99
66.69
48.21
CN
H
O
N
f1 (ppm)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7.77
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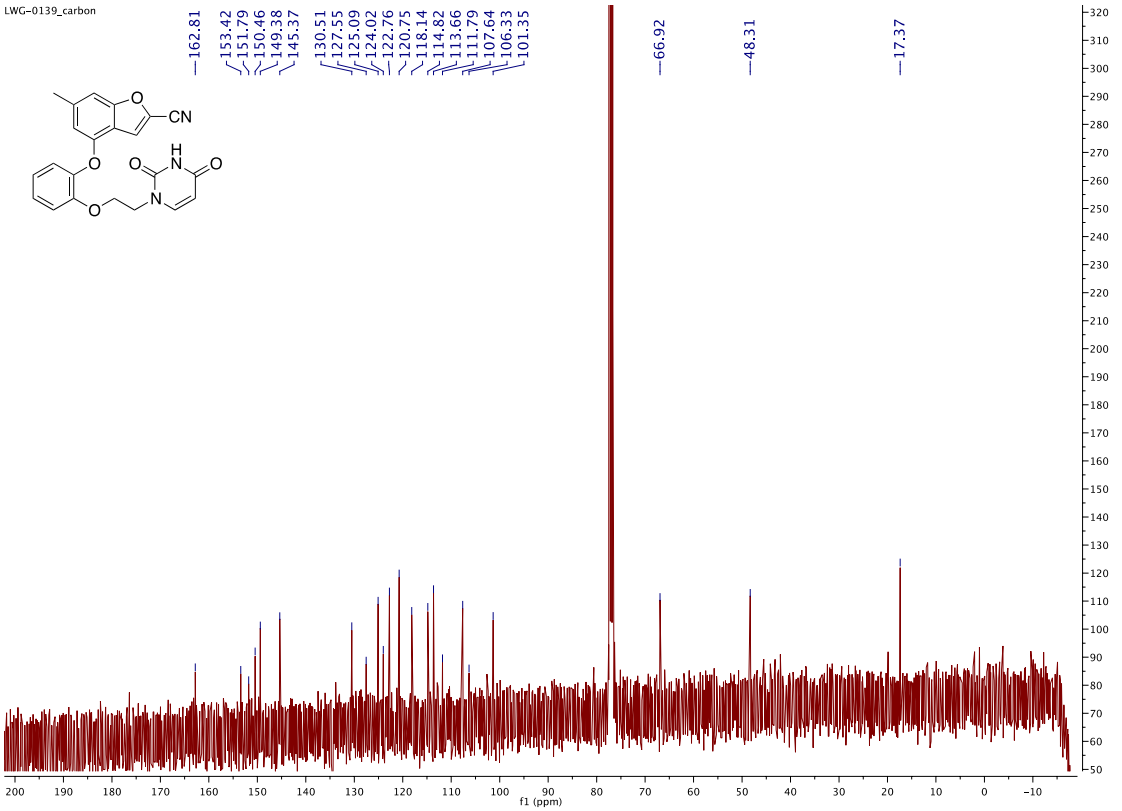
7.38
7.08
7.07
6.94
6.92
6.92
6.92
6.91
6.90
6.83
6.83
6.80
5.23
5.22
5.21
5.20
4.18
4.17
4.16
3.96
3.95
3.94
2.38
0.96
0.98
1.02
1.04
3.00
0.99
0.95
1.00
2.02
1.97
3.08
f1 (ppm)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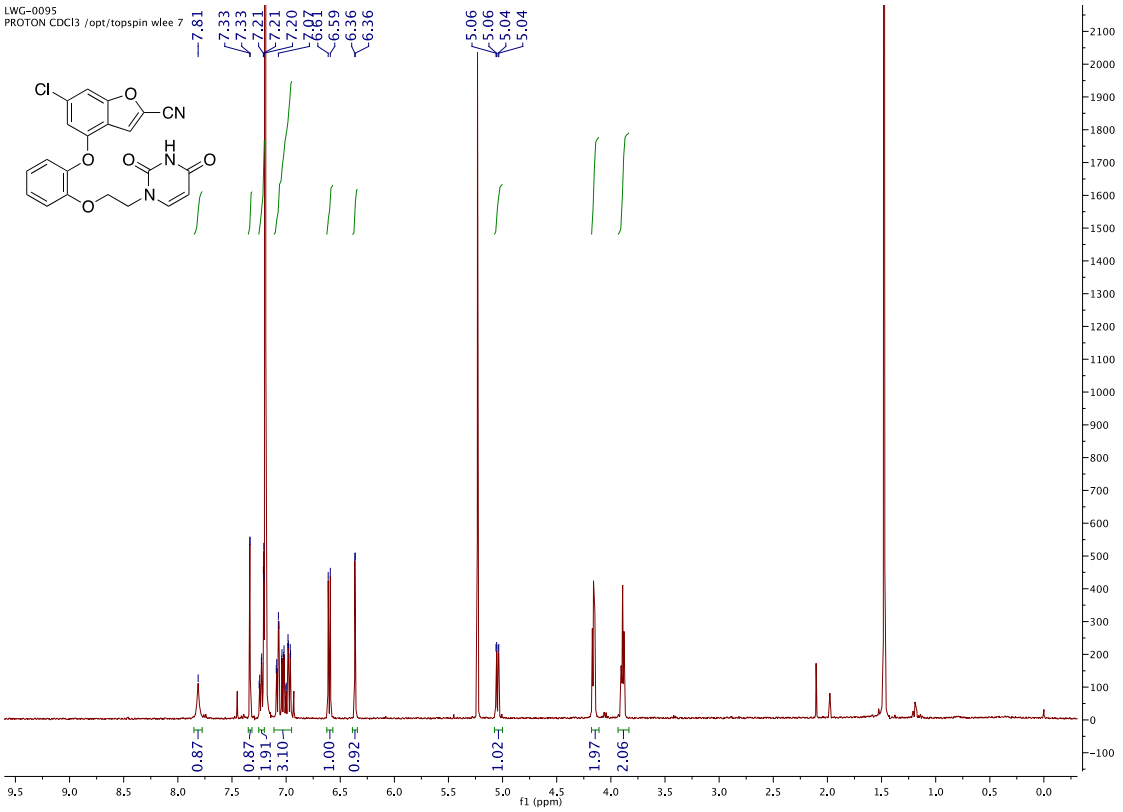
101.35
66.92
48.31
17.37
f1 (ppm)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PROTON CDCl3 /opt/topspin wlee 7
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7.33
7.33
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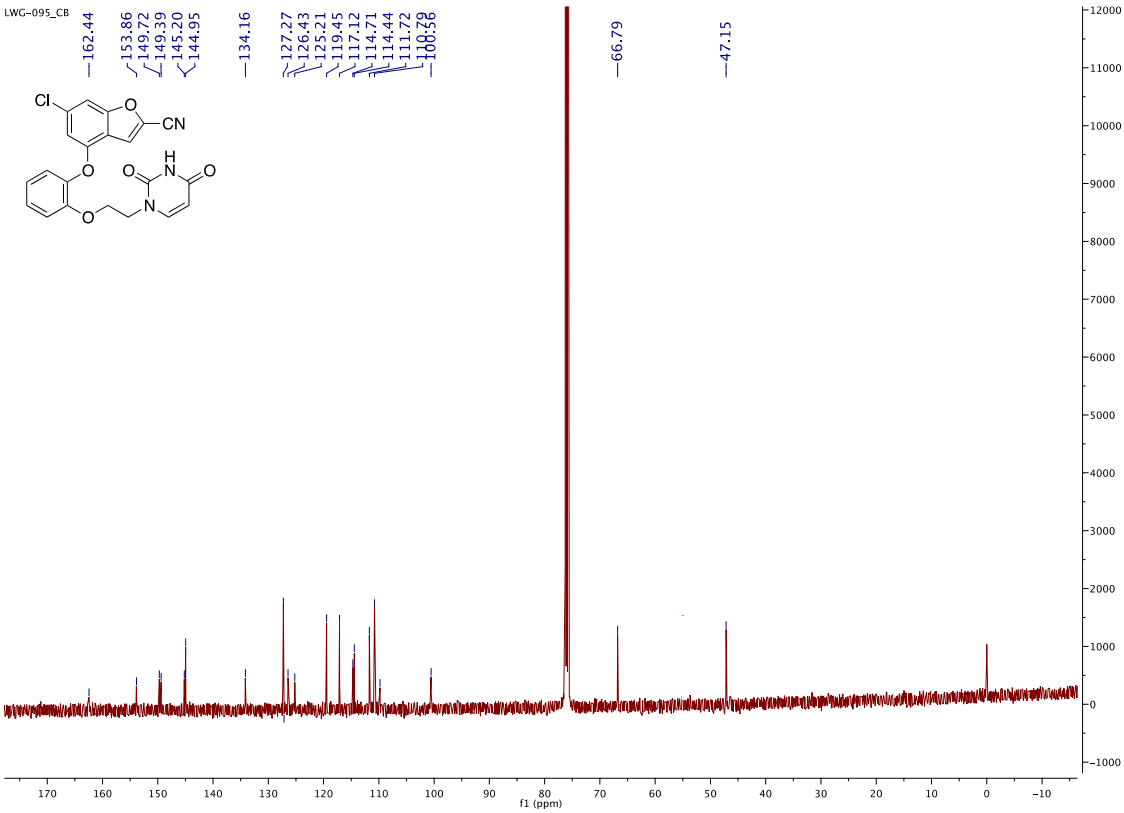
7.20
7.07
6.81
6.59
6.36
6.36
5.06
5.06
5.04
5.04
0.87
0.87
1.91
3.10
1.00
0.92
1.02
1.97
2.06
f1 (ppm)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110.79
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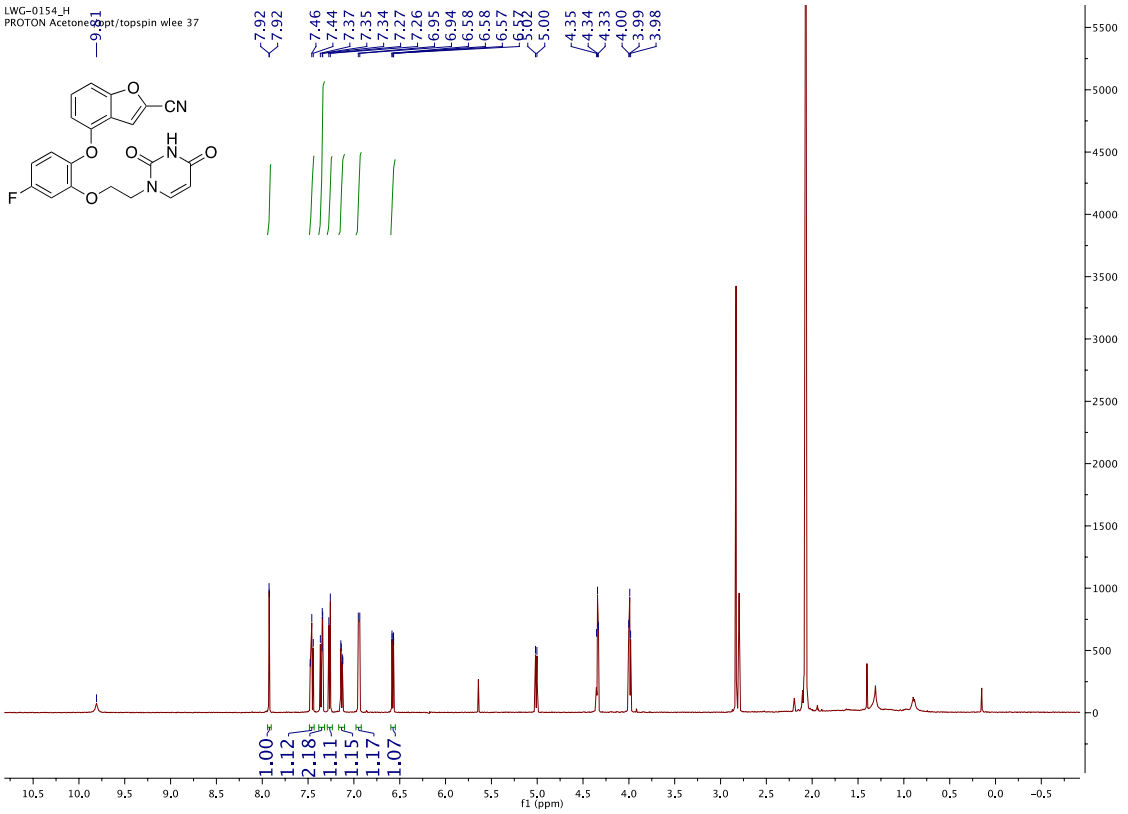
47.15
f1 (ppm)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7.92
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7.35
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7.27
7.26
6.95
6.94
6.58
6.58
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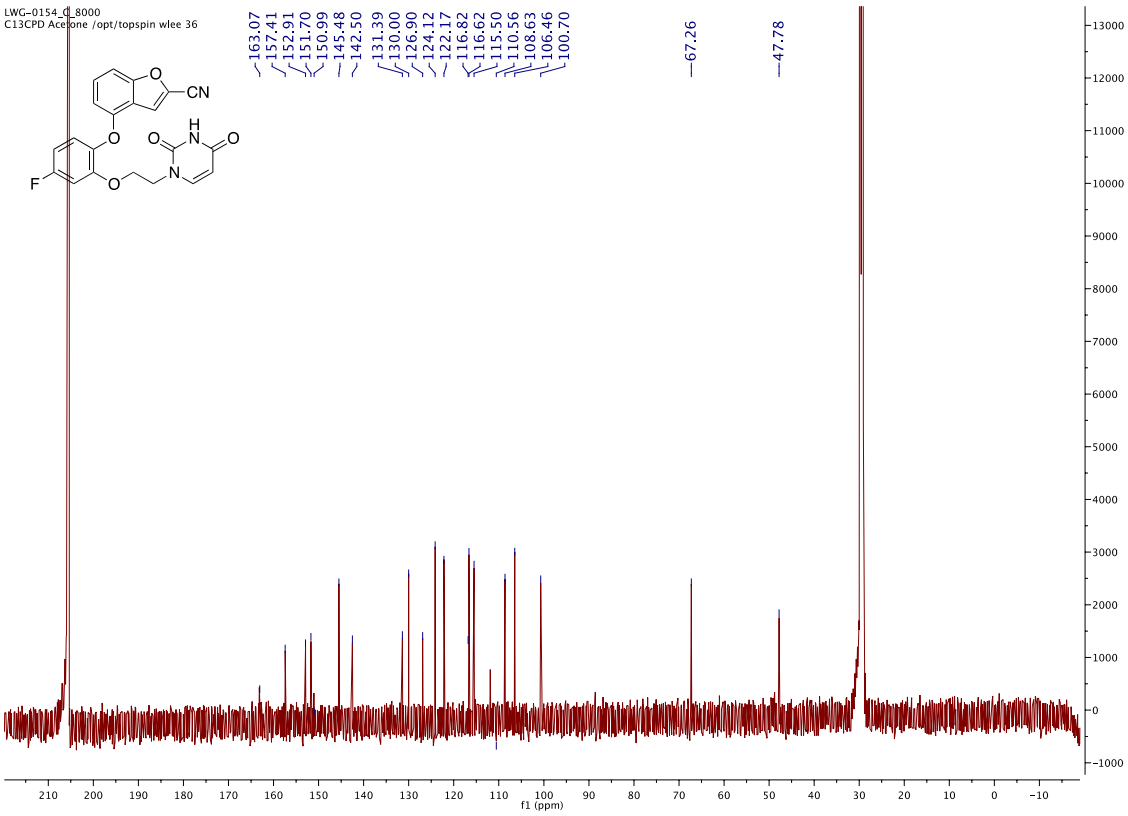
1.11
1.15
1.17
1.07
f1 (ppm)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151.70
150.99
145.48
142.50
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130.00
126.90
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115.50
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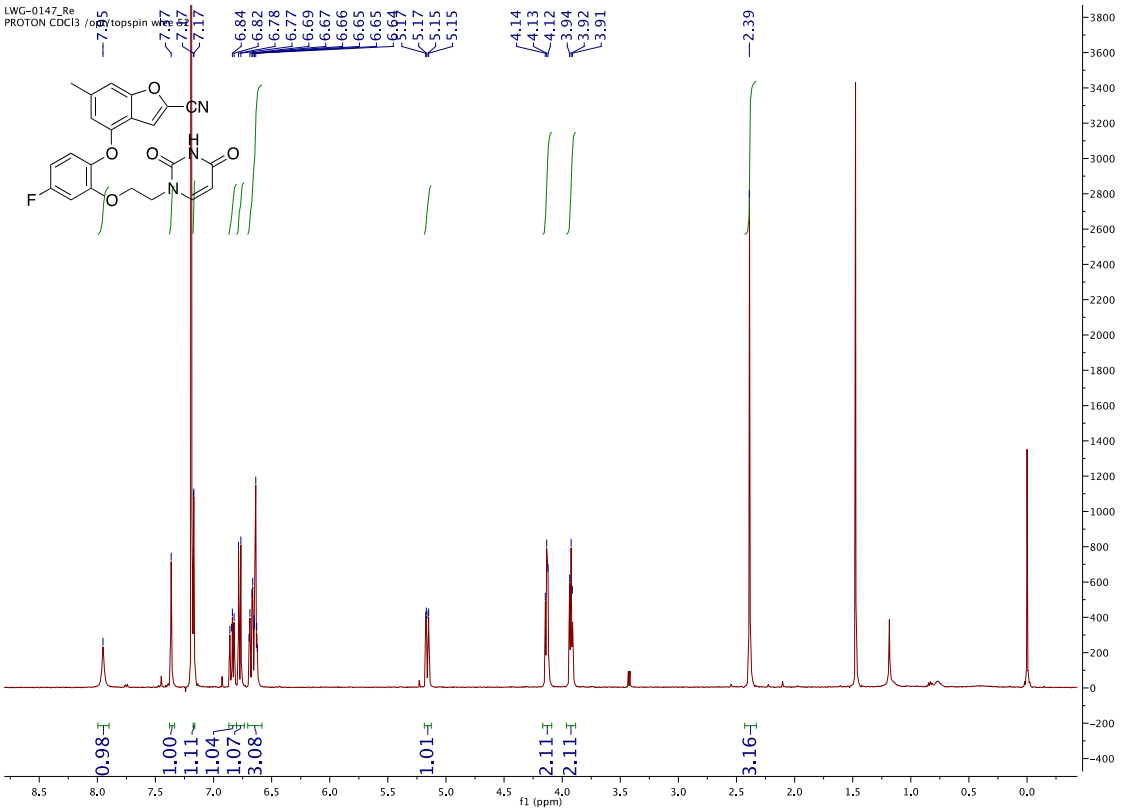
108.63
106.46
100.70
67.26
47.78
f1 (ppm)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7.37
7.37
7.17
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6.82
6.78
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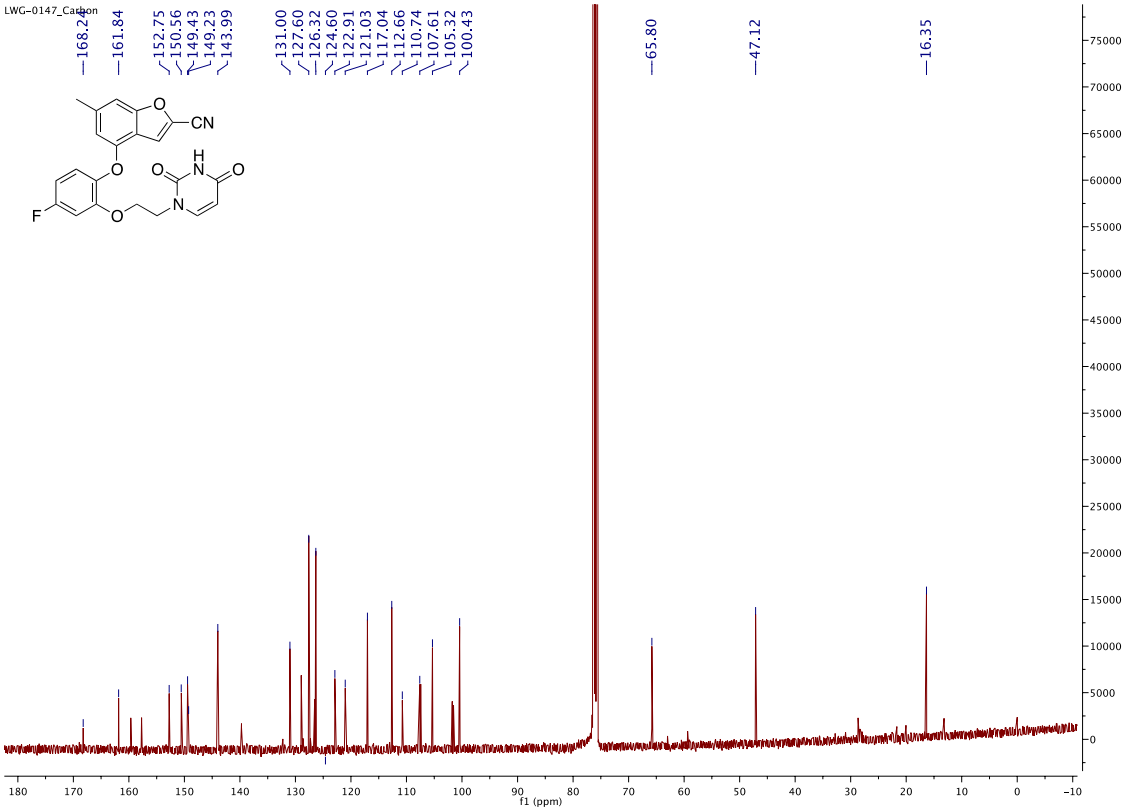
6.67
6.66
6.65
6.65
6.64
5.17
5.15
5.15
4.14
4.13
4.12
3.94
3.92
3.91
2.39
0.98
1.00
1.11
1.04
1.07
3.08
1.01
2.11
2.11
3.16
f1 (ppm)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152.75
150.56
149.43
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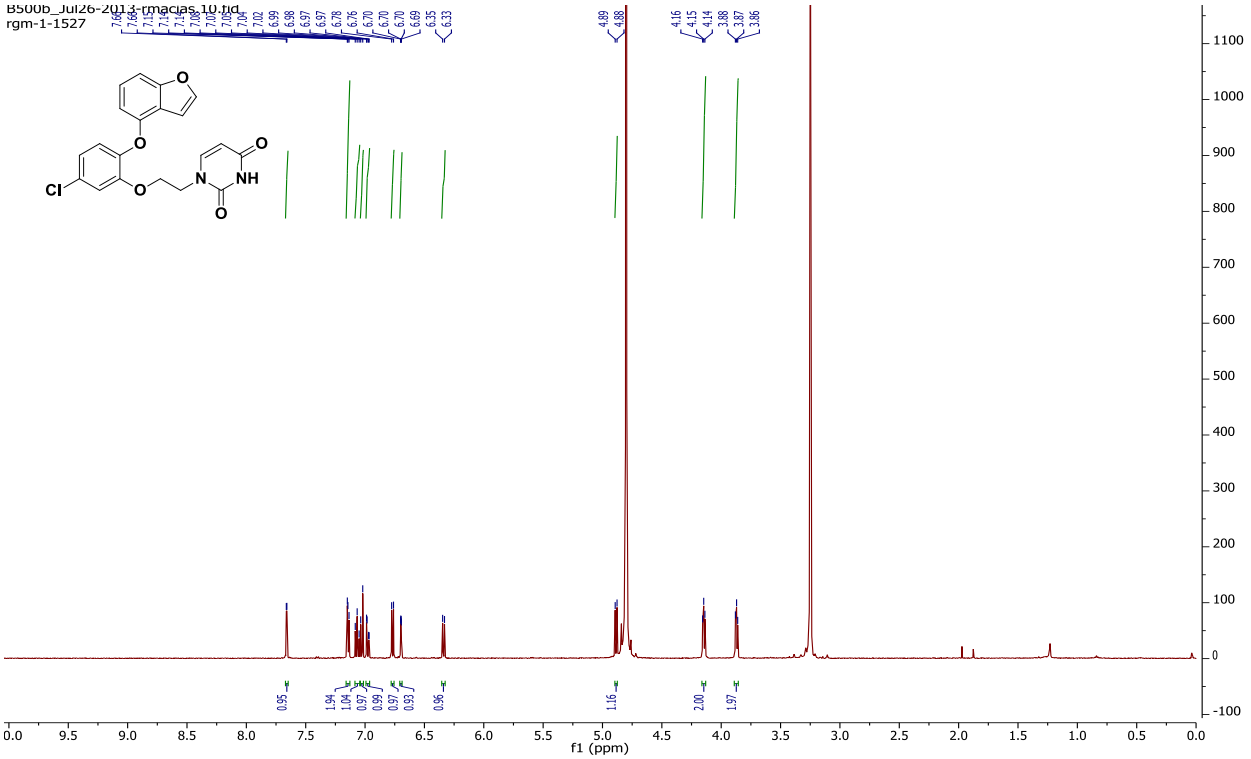
143.99
131.00
127.60
126.32
124.60
122.91
121.03
117.04
112.66
110.74
107.61
105.32
100.43
65.80
47.12
16.35
f1 (ppm)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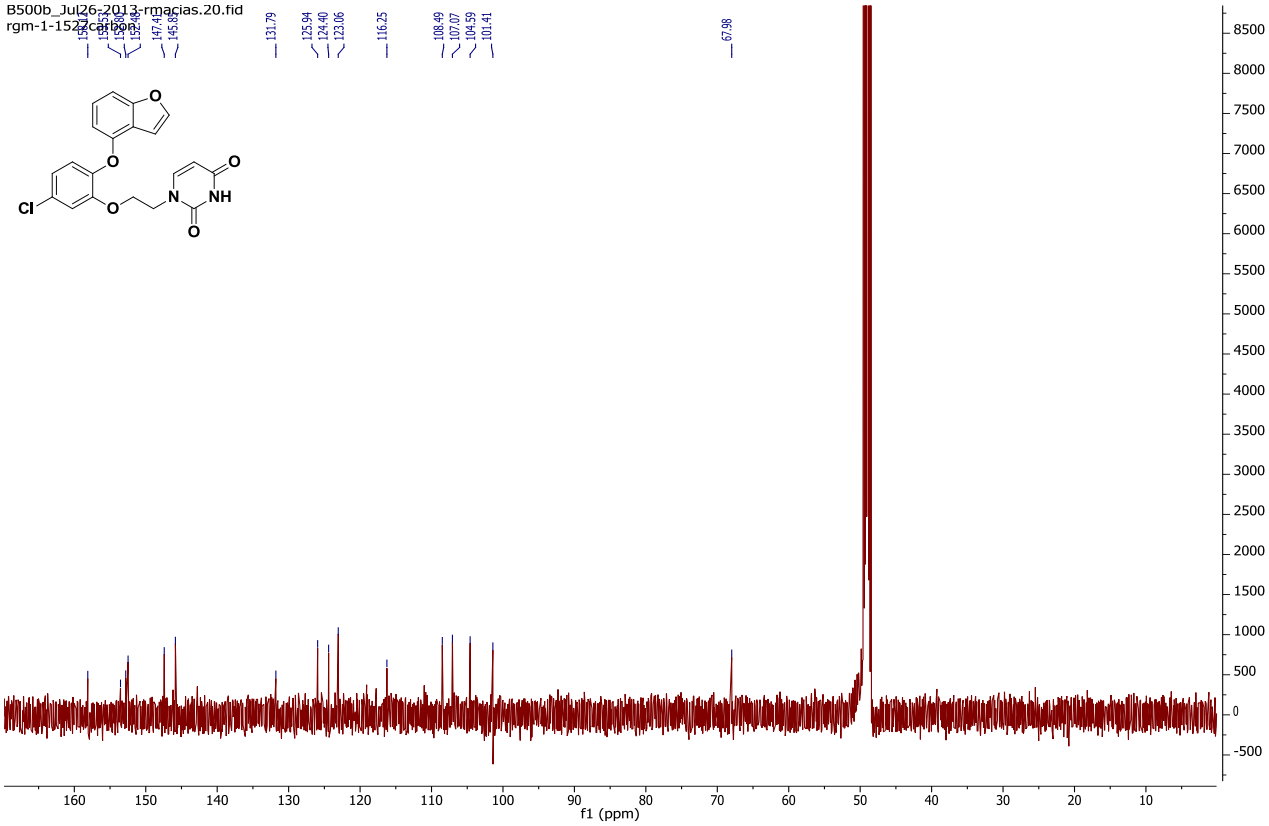
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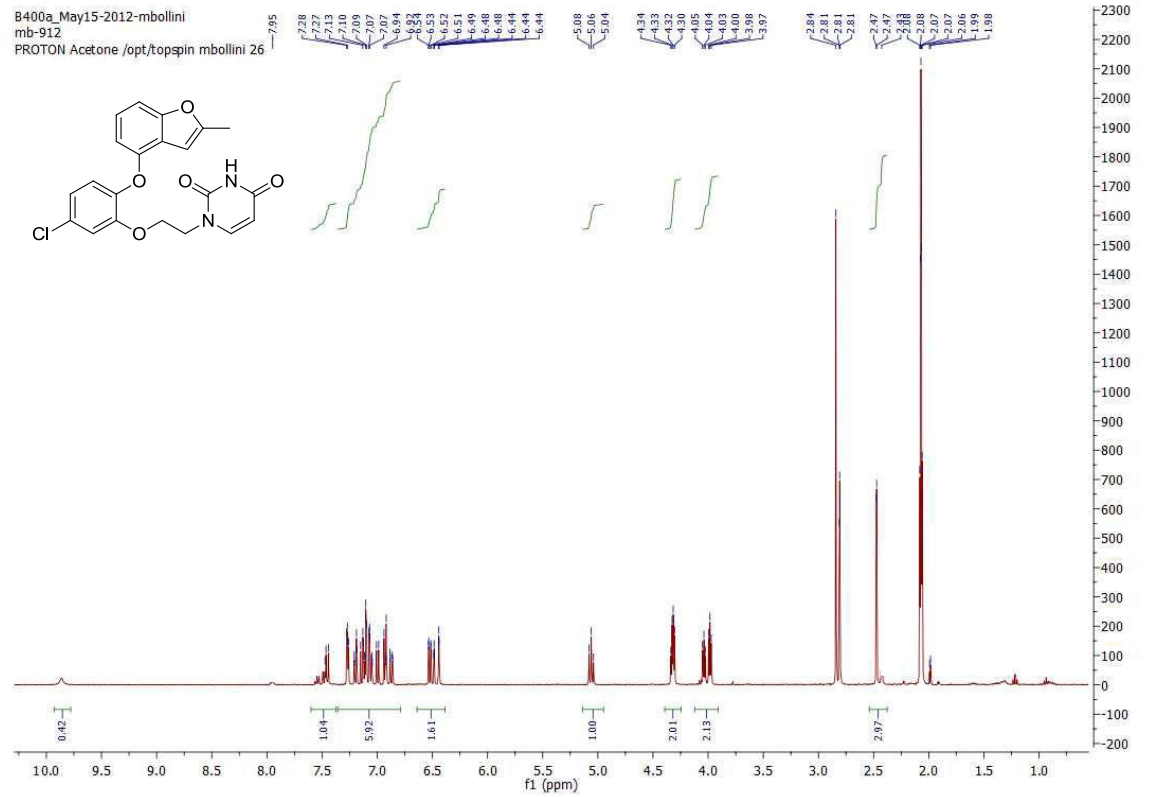
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mb-912
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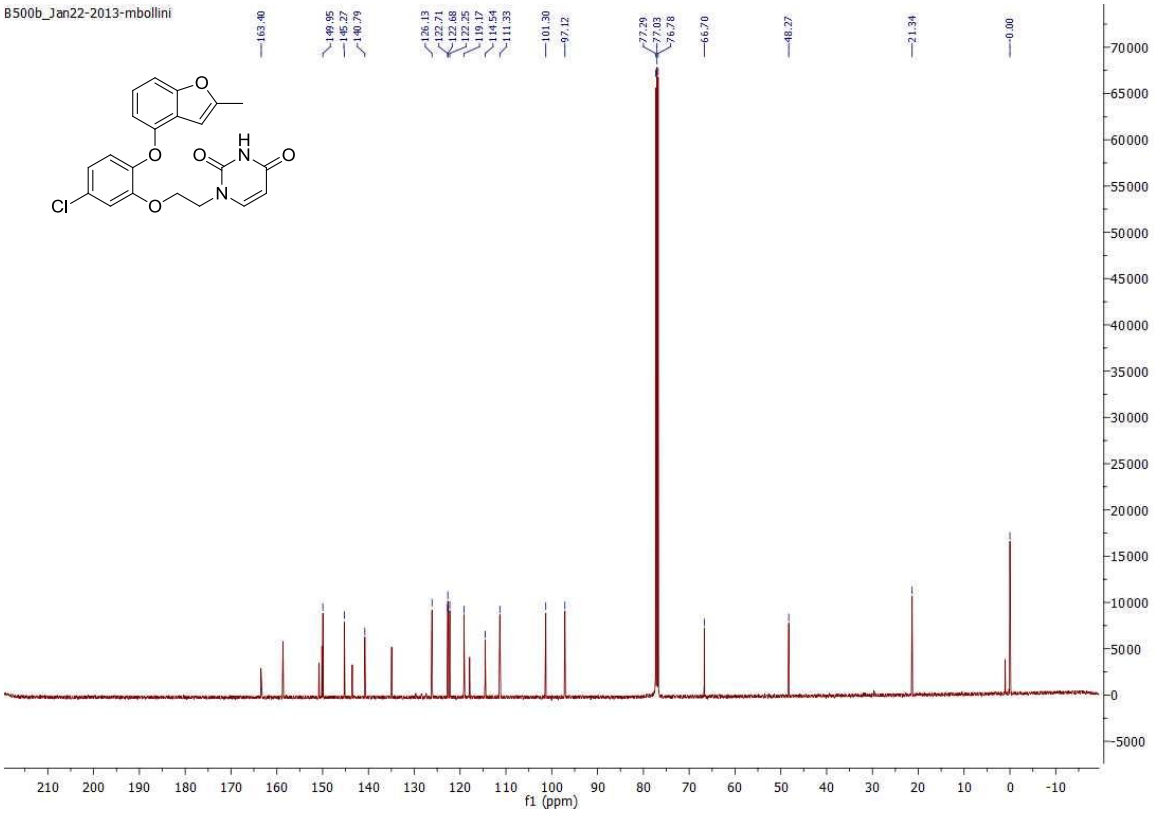
f1 (ppm)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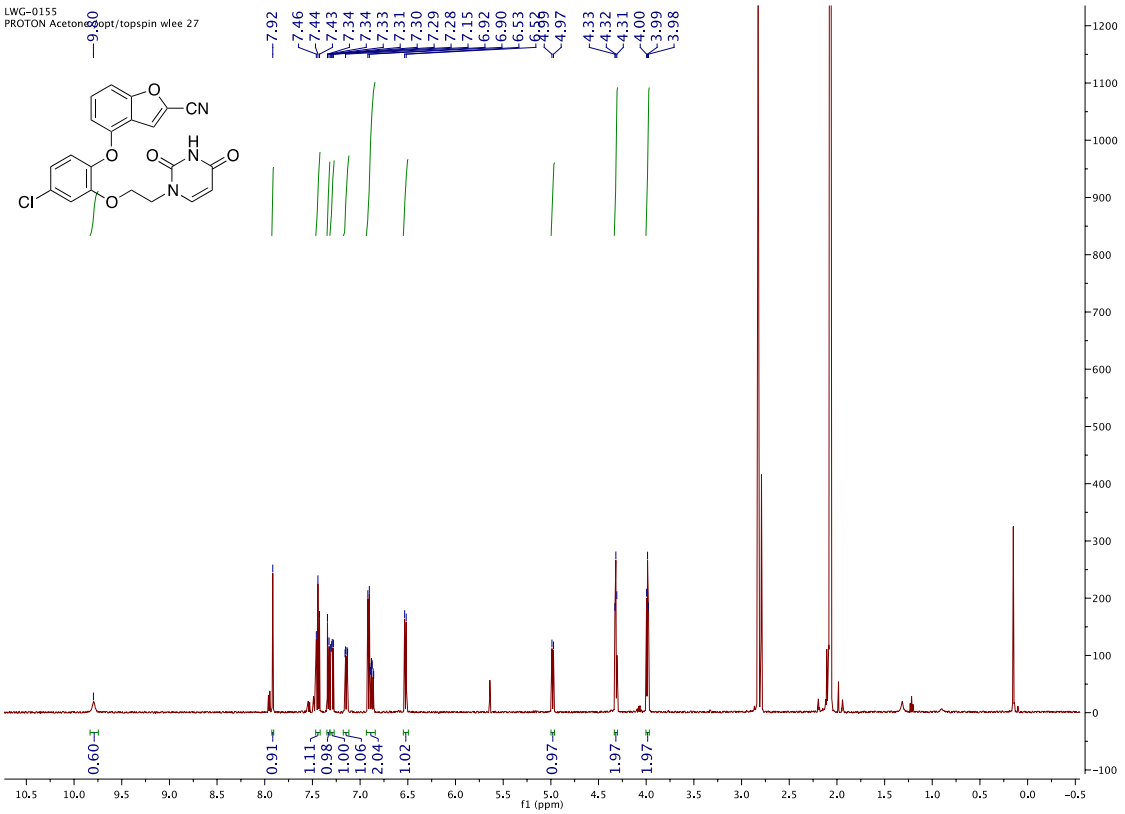
f1 (ppm)


LWG-0155
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9.80
7.92
7.46
7.44
7.43
7.34
7.34
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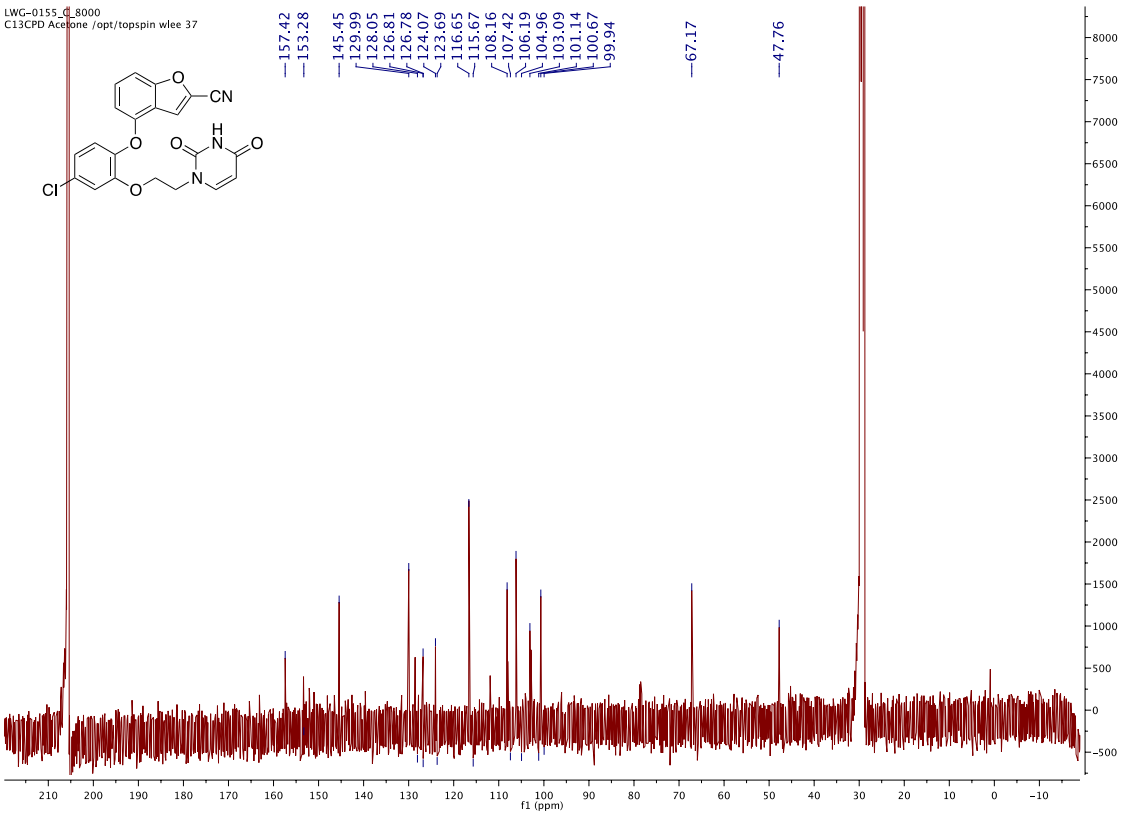
7.31
7.30
7.29
7.28
7.15
6.92
6.90
6.53
4.97
4.33
4.32
4.31
4.00
3.99
3.98
0.60
0.91
1.11
0.98
1.00
1.06
2.04
1.02
0.97
1.97
1.97
f1 (ppm)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157.42
153.28
145.45
129.99
128.05
126.81
126.78
124.07
123.69
116.65
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108.16
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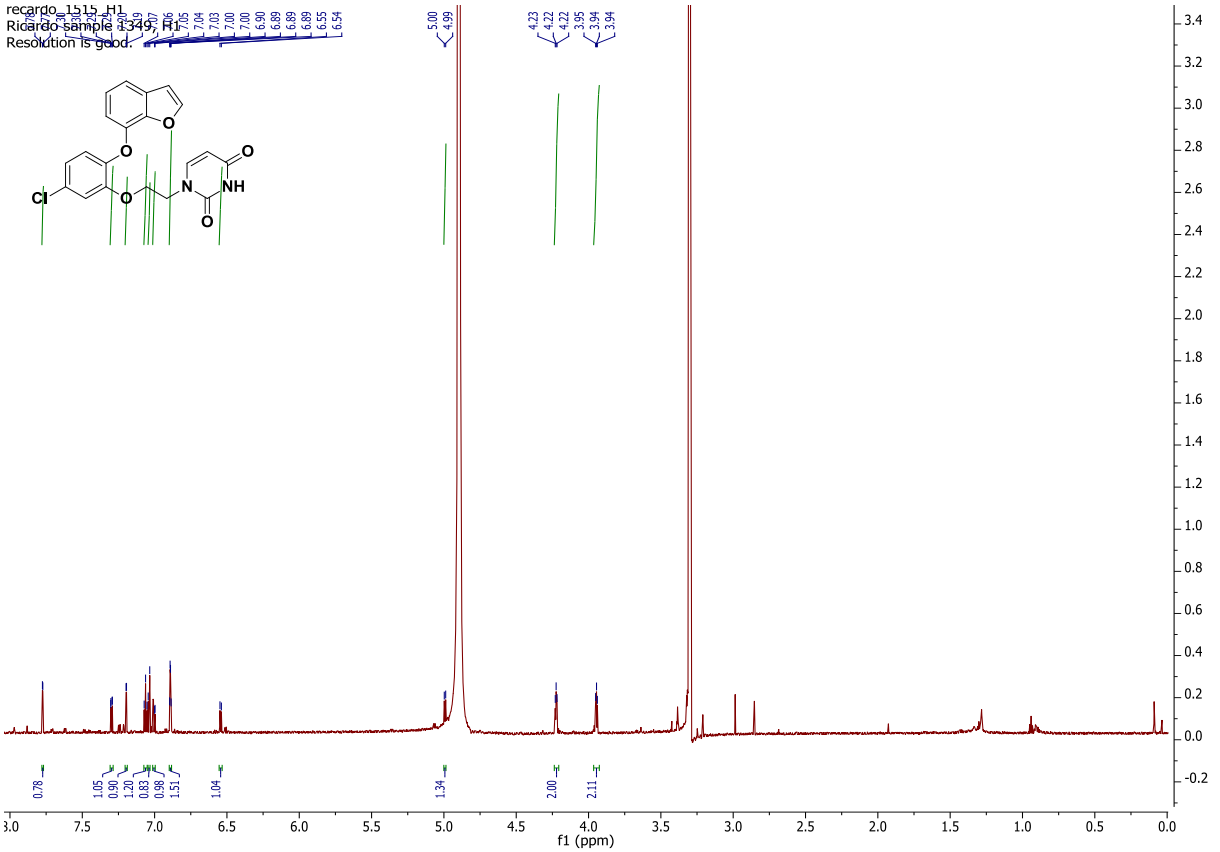
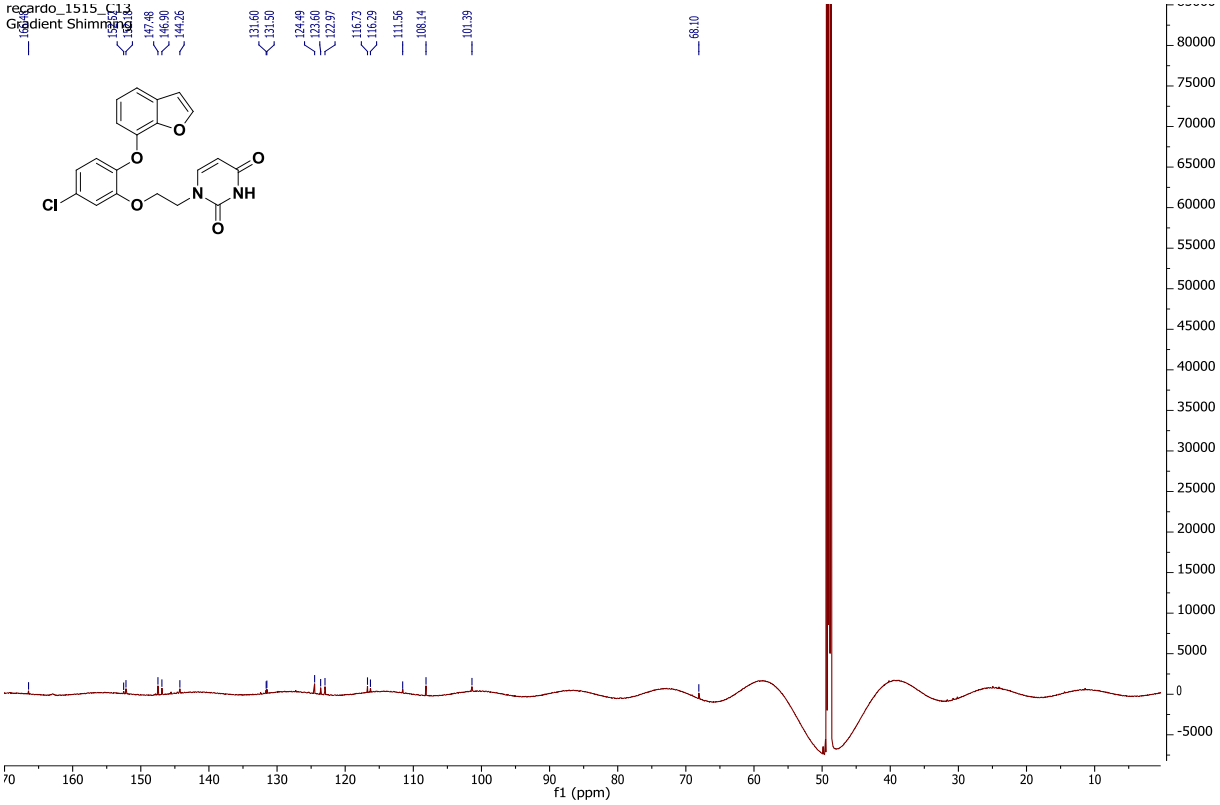
103.09
101.14
100.67
99.94
67.17
47.76
f1 (ppm)


recardo_1515_H1
Ricardo sample 1349, H1
Resolution is good.
f1 (ppm)


recardo_1515_C13
Gradient Shimming
f1 (ppm)

9. References - Synthesis

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10. Protein Crystallography

Materials and Methods

Recombinant RT52A enzyme was expressed and purified to homogeneity using methods described previously.[1,2] Crystals of RT52A in complex with **10b** (aka **JLJ555)** were prepared using similar methods as the catechol diether complexes.[1] The final optimized condition for crystal growth consisted of 12.5% (w/v) PEG 8,000, 100 mM ammonium sulfate, 15 mM magnesium sulfate, 5 mM spermine, and 50 mM MES pH 6.0. Crystals were transferred to a cryo-solution containing 27% (v/v) ethylene glycol and flash cooled with liquid nitrogen.

Diffraction data for the best crystals were collected at Brookhaven NSLS on beam line X29A. High-resolution data sets for the best diffracting crystals were collected, indexed, integrated, and scaled into the C2 space group using HKL2000.[3] In order to obtain phases, molecular replacement was performed with Phaser[4] using a previously determined RT:**3** (PDB code: **4H4M**) as the search model.[2] The program Coot[5] was used for model building into the electron density. Maximum-likelihood restrained refinement in Phenix[6] was used to refine the structure after each cycle of model building until acceptable *R*-factors, geometry statistics (ideal rmsd for bonds and angles), and Ramachandran statistics were achieved. Iterative build, composite omit electron density maps were generated using Phenix Autobuild.[7]

Data Collection and Refinement Statistics

Complex	RT: **10b** (**JLJ555**)
PDB Code	**4MFB**
Resolution Limit, Å	2.88
X-Ray Source	NSLS X29A
Wavelength, Å	1.075
Space group	C2
No. molecules in asymmetric unit	1
Unit cell, a,b,c in Å (α,β,γ, in °)	a=223.56, b=69.39, c=104.79 (α=90, β=106.04, γ=90)
Resolution range, Å	36.6-3.10
Last Shell, Å	2.93-2.88
R-sym (last shell)	0.067 (0.479)
Completeness, % (last shell, %)	99.0 (91.2)
No. of Reflections (Unique Reflections)	130654 (35128)
Redundancy (last shell)	3.7 (3.4)
Avg. I/σ (last shell)	28.3 (2.2)
Total Number of Atoms (Protein/Inhibitor/Solvent)	7877 (7831/29/17)
R-free, R-factor	0.2694, 0.2368
RMS deviation bond lengths, Å (angles, °)	0.003 (0.770)
Avg. B-factor, Å^2 (Total/Protein/Inhibitor/Solvent, Å^2)	63.46 (76.0/53.08/48.82)
Ramachandran Favored, Allowed, Outliers, %	97, 2.7, 0.3

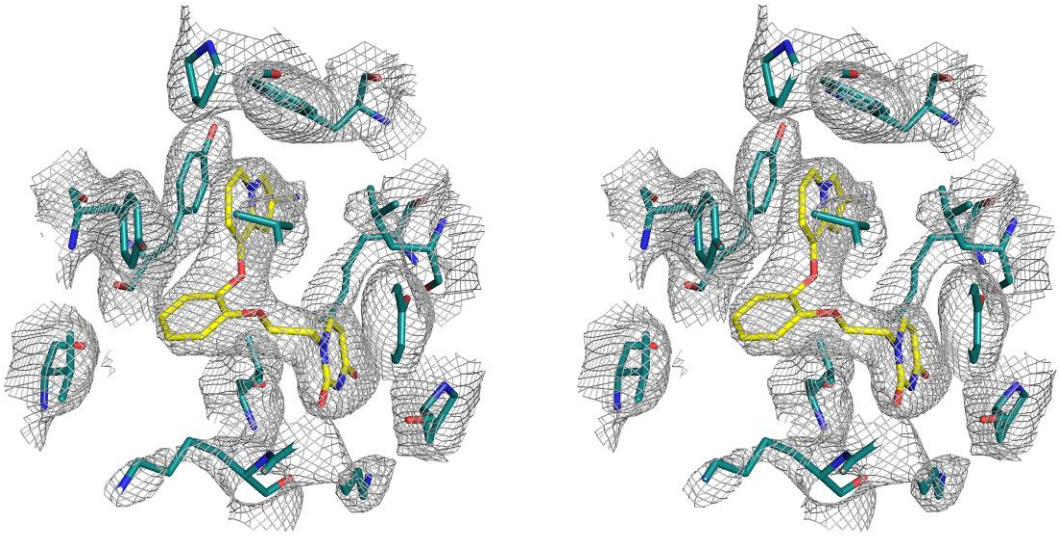

Figure S1. Stereoview of the final $2F_o$-F_c electron density (contour level of 1.0σ) showing the non-nucleoside binding pocket for the RT:**10b** complex.

11. References – Protein Crystallography

(1) Frey, K. M.; Bollini, M.; Mislak, A. C.; Cisneros, J. A.; Gallardo-Macias, R.; Jorgensen, W. L.; Anderson, K. S. *J. Am. Chem. Soc.* **2012**, *134*, 19501-19503.
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(4) Mccoy, A. J.; Grosse-Kunstleve, R. W.; Adams, P. D.; Winn, M. D.; Storoni, L. C.; Read, R. J. *J. Appl. Crystallogr.* **2007**, *40*, 658-674.
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12. Complete Citation for Reference 22

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.