Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Electronic Supplementary Information

Regioselective construction of pyridazine and tetrahydrocinnoline derivatives via [4+2] cycloaddition-elimination with α-halogeno hydrazones and enaminones

Liancheng Duan[a], Xin Wang[a], Yucheng Gu[b], Yunlei Hou*[a] and Ping Gong*[a]

[a] School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenhe District, Shenyang, 110016, China.

Email: houyunlei901202@163.com and gongpinggp@126.com.

[b] Syngenta Jealott's Hill International Research Center, Bracknell, Berkshire RG42 6EY, U.K.

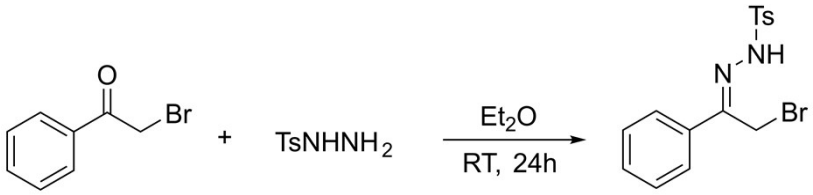
Table of Contents

1. General information

Unless otherwise noted, all reagents and solvents were obtained from commercial sources and used without further purification. Solvents were dried using standard methods and distilled before use. All the reactions were conducted in oil bath and monitored by thin-layer chromatography (TLC) using GF254 silica gel-coated TLC plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 600MHz in deuterated solvents containing TMS as an internal reference standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, J, are reported in hertz (Hz). HRMS analysis was performed on a Q-TOF mass analyzer using the ESI ionization method. Purification by flash column chromatography was performed over silica gel (200−300 mesh) and neutral alumina (200−300 mesh).

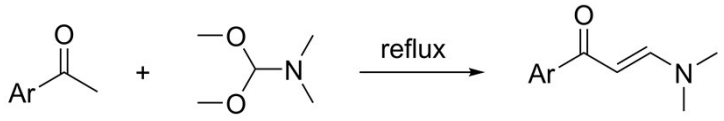
2. General procedure

2.1 Representative procedure for the synthesis of 1



2-BroMoacetophenone (4.0g, 20 mmol) and 4-Methylbenzenesulfonhydrazide (3.7g, 20 mmol) were stirred in ether (50 mL) at RT for 24 h. After this time the product had precipitated as a white solid, which was collected and dried to give hydrazone as a white powder. Other hydrazones were synthesized according to the above procedures.[1]

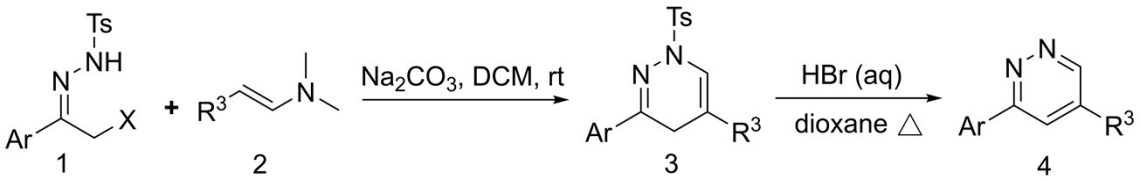
2.2 Representative procedure for the synthesis of 2



Aryl ketones (Acetophenone, 2.4g, 20 mmol) and N,N-dimethylformamide dimethyl acetal (DMF-DMA) (4.8g, 40 mmol) were refluxed until the starting materials were consumed, as determined by thin-

layer chromatography (TLC), then left to cool to room temperature, the precipitate was collected by filtration, and recrystallized from ethanol. Compounds **2n–2p** were prepared by literature procedures.[2]

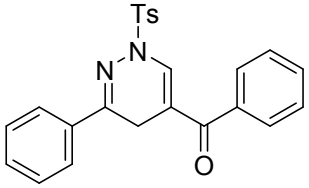
2.3 Representative procedure for compounds 3 and 4



Corresponding α-halogeno hydrazone **1** (**1a**, 0.37g, 1.0 mmol), enaminone **2** (**2a**, 0.18g, 1.0 mmol), and Na_2CO_3 (0.22g, 2.0 mmol) were added to a 10 mL round-bottom flask in DCM (5 mL), the reaction mixture was stirred at room temperature and monitored by TLC until completion. The solvent was then evaporated and the residue was purified by column chromatography on silica gel (PE: DCM =1:1) to afford corresponding dihydropyridazine product **3** (**3aa**).

To a solution of **3** (**3aa**, 0.13g, 0.3 mmol) in 3 mL dioxane was added 3 mL of hydrobromic acid (40 wt% solution in water) and the reaction mixture was heated to 100 ℃ for the appropriate time (checked by TLC, 1-2 h). The mixture was cooled to room temperature and the solution was basified with saturated Na_2CO_3. The resulting mixture was extracted with DCM (3 × 5 mL), the combined organic layer was dried over anhydrous Na_2SO_4, the solvent was then evaporated and the residue was purified by column chromatography on neutral alumina (PE: EA =2:1) to afford pyridazine derivatives as desired product **4** (**4aa**).

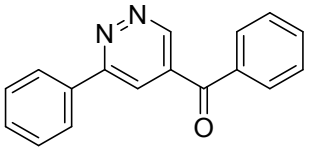
3. Characterization of products



3aa

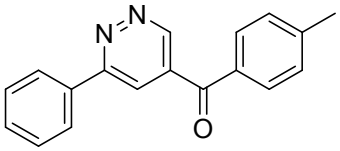
Phenyl(6-phenyl-2-tosyl-2,5-dihydropyridazin-4-yl)methanone (3aa): White solid; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.89 (d, J = 8.3 Hz, 2H), 7.82 – 7.78 (m, 2H), 7.70 – 7.65 (m, 2H), 7.65 – 7.62 (m, 2H), 7.60 (t, J = 7.4 Hz, 2H), 7.54 – 7.47 (m, 5H), 3.53 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (151

MHz, DMSO-d_6) δ 193.17, 151.72, 146.13, 137.91, 134.68, 134.02, 132.87, 132.27, 131.41, 130.67, 129.07, 129.05, 128.91, 128.45, 126.69, 112.40, 22.18, 21.53. HRMS (ESI-Q-TOF, m/z) calcd for $C_{24}H_{21}N_2O_3S$ $[M + H]^+$: 417.1267, found $[M + H]^+$: 417.1259.



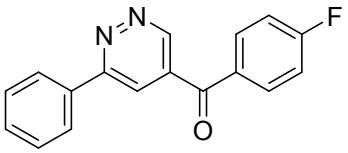
4aa

Phenyl(6-phenylpyridazin-4-yl)methanone (4aa): White solid; m.p 108.5–111.1℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.41 (d, J = 1.6 Hz, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.26 – 8.20 (m, 2H), 7.92 (d, J = 7.4 Hz, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.66 – 7.56 (m, 5H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.71, 159.11, 148.29, 135.97, 135.92, 135.42, 134.68, 130.85, 130.56, 129.49, 129.44, 127.59, 123.24. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{13}N_2O$ $[M + H]^+$: 261.1022, found $[M + H]^+$: 261.1012.



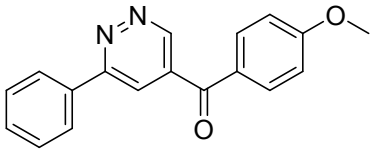
4ab

(6-phenylpyridazin-4-yl)(p-tolyl)methanone (4ab): White solid; m.p 170.5–172.8℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.39 (d, J = 1.9 Hz, 1H), 8.36 (d, J = 1.9 Hz, 1H), 8.23 (dd, J = 7.6, 2.0 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.59 (m, 3H), 7.43 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.20, 159.06, 148.27, 145.46, 136.24, 135.93, 132.94, 130.84, 130.72, 130.02, 129.48, 127.58, 123.14, 21.69. HRMS (ESI-Q-TOF, m/z) calcd for $C_{18}H_{15}N_2O$ $[M + H]^+$: 275.1179, found $[M + H]^+$: 275.1168.



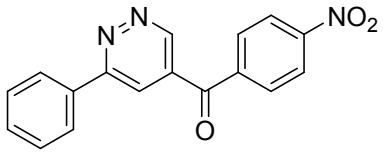
4ac

(4-fluorophenyl)(6-phenylpyridazin-4-yl)methanone (4ac): Light yellow solid; m.p 124.0–125.8℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.41 (d, J = 1.7 Hz, 1H), 8.39 (d, J = 1.7 Hz, 1H), 8.26 – 8.20 (m, 2H), 8.01 (dd, J = 8.6, 5.5 Hz, 2H), 7.63 – 7.56 (m, 3H), 7.45 (t, J = 8.8 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.36, 166.83, 165.15, 159.10, 148.24, 135.90, 135.84, 133.74, 133.67, 132.26, 132.24, 130.86, 129.47, 127.59, 123.22, 116.66, 116.51. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{12}FN_2O$ $[M + H]^+$: 279.0928, found $[M + H]^+$: 279.0923.



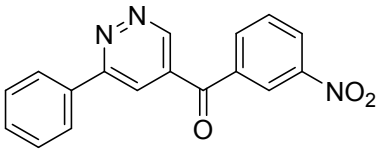
4ad

(4-methoxyphenyl)(6-phenylpyridazin-4-yl)methanone (4ad): White solid; m.p 131.4–133.0℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.38 (d, J = 1.9 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H), 8.25 – 8.21 (m, 2H), 7.93 – 7.87 (m, 2H), 7.62 – 7.56 (m, 3H), 7.16 – 7.12 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 191.94, 164.52, 159.00, 148.26, 136.65, 135.97, 133.12, 130.82, 129.47, 128.26, 127.58, 122.98, 114.81, 56.16. HRMS (ESI-Q-TOF, m/z) calcd for $C_{18}H_{15}N_2O_2$ $[M + H]^+$: 291.1128, found $[M + H]^+$: 291.1123.



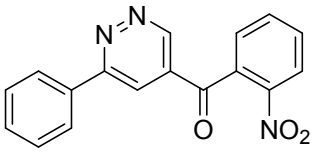
4ae

(4-nitrophenyl)(6-phenylpyridazin-4-yl)methanone (4ae): Yellow solid; m.p 187.9–189.8℃; purity: 97.3%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.45 (d, J = 1.9 Hz, 1H), 8.41 (d, J = 8.8 Hz, 2H), 8.40 (d, J = 1.9 Hz, 1H), 8.24 – 8.20 (m, 2H), 8.17 – 8.13 (m, 2H), 7.62 – 7.57 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.91, 159.25, 150.64, 148.27, 140.38, 135.80, 134.82, 131.91, 130.94, 129.51, 127.61, 124.34, 123.59. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{12}N_3O_3$ $[M + H]^+$: 306.0873, found $[M + H]^+$: 306.0873, $[M + H]^+$: 306.0872.



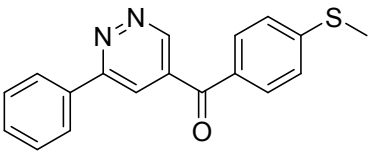
4af

(3-nitrophenyl)(6-phenylpyridazin-4-yl)methanone (4af): Yellow solid; m.p 159.1–161.4℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.47 (d, J = 1.9 Hz, 1H), 8.61 – 8.57 (m, 2H), 8.43 (d, J = 1.9 Hz, 1H), 8.32 (m, J = 7.8, 1.2 Hz, 1H), 8.24 – 8.21 (m, 2H), 7.93 – 7.89 (m, 1H), 7.60 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.34, 159.28, 148.38, 148.34, 136.83, 136.58, 135.82, 134.85, 131.20, 130.94, 129.51, 128.45, 127.62, 124.74, 123.51. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{12}N_3O_3$ [M + H]$^+$: 306.0873, found [M + H]$^+$: 306.0880.



4ag

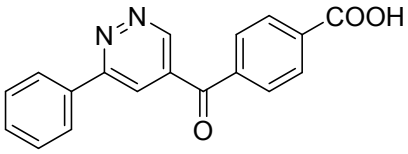
(2-nitrophenyl)(6-phenylpyridazin-4-yl)methanone (4ag): Yellow solid; m.p 112.3–114.5℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.38 (d, J = 8.2 Hz, 1H), 8.27 (s, 1H), 8.21 – 8.14 (m, 2H), 8.03 (t, J = 7.4 Hz, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.58 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.77, 160.06, 147.41, 146.54, 135.70, 135.54, 133.54, 133.05, 132.65, 131.00, 129.68, 129.47, 127.69, 125.50, 122.59. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{12}N_3O_3$ [M + H]$^+$: 306.0873, found [M + H]$^+$: 306.0867.



4ah

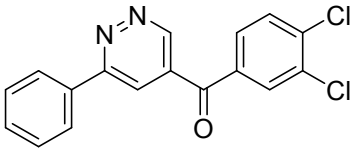
(4-(methylthio)phenyl)(6-phenylpyridazin-4-yl)methanone (4ah): White solid; m.p 152.5–153.9℃; purity: 97.1%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.39 (d, J = 1.9 Hz, 1H), 8.36 (d, J = 1.9 Hz, 1H), 8.25 – 8.21 (m, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.61 – 7.56 (m, 3H), 7.45 (d, J = 8.6 Hz, 2H), 2.57 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.52, 159.04, 148.28, 147.82, 136.24, 135.93, 131.47, 131.01, 130.84,

129.47, 127.59, 125.40, 123.12, 14.24. HRMS (ESI-Q-TOF, m/z) calcd for $C_{18}H_{15}N_2OS$ $[M + H]^+$: 307.0990, found $[M + H]^+$: 307.0895.



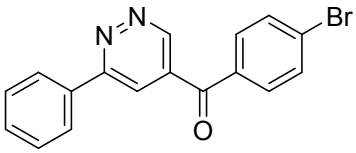
4ai

4-(6-phenylpyridazine-4-carbonyl)benzoic acid (4ai): Light yellow solid; m.p 243.1–245.2℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.45 (s, 1H), 9.44 (d, J = 1.8 Hz, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.23 (dd, J = 7.4, 2.0 Hz, 2H), 8.14 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H), 7.62 – 7.56 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.49, 166.89, 159.19, 148.27, 138.61, 135.87, 135.61, 135.42, 130.89, 130.72, 130.11, 129.49, 127.62, 123.41. HRMS (ESI-Q-TOF, m/z) calcd for $C_{18}H_{11}N_2O_3$ $[M - H]^-$: 303.0775, found $[M - H]^-$: 303.0770.



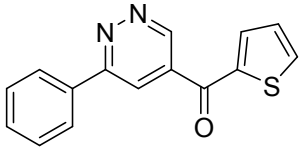
4aj

(3,4-dichlorophenyl)(6-phenylpyridazin-4-yl)methanone (4aj): Light yellow solid; m.p 162.1–164.4℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.42 (d, J = 1.9 Hz, 1H), 8.41 (d, J = 1.9 Hz, 1H), 8.23 (dd, J = 7.5, 1.9 Hz, 2H), 8.11 (d, J = 1.8 Hz, 1H), 7.92 – 7.83 (m, 2H), 7.62 – 7.55 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.04, 159.18, 148.20, 137.36, 135.88, 135.85, 135.04, 132.43, 131.96, 131.66, 130.90, 130.61, 129.48, 127.60, 123.43. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{11}Cl_2N_2O$ $[M + H]^+$: 329.0243, found $[M + H]^+$: 329.0233.



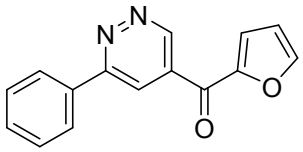
4ak

(4-bromophenyl)(6-phenylpyridazin-4-yl)methanone (4ak): White solid; m.p 186.6–190.2℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.42 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 1.9 Hz, 1H), 8.23 (dd, J = 7.4, 2.0 Hz, 2H), 7.84 (s, 4H), 7.62 – 7.55 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.98, 159.12, 148.25, 135.87, 135.51, 134.53, 132.50, 132.47, 130.88, 129.48, 128.91, 127.60, 123.31. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{12}BrN_2O$ $[M + H]^+$: 339.0128, found $[M + H]^+$: 339.0122.



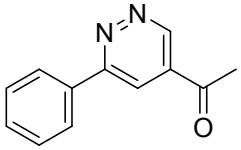
4al

(6-phenylpyridazin-4-yl)(thiophen-2-yl)methanone (4al): White solid; m.p 130.8–132.7℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.49 (s, 1H), 8.27 (dd, J = 13.4, 4.6 Hz, 3H), 7.94 (s, 1H), 7.59 (s, 3H), 7.35 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 185.31, 159.24, 147.89, 142.01, 138.24, 138.22, 136.03, 135.91, 130.86, 129.91, 129.47, 127.65, 122.87. HRMS (ESI-Q-TOF, m/z) calcd for $C_{15}H_{11}N_2OS$ $[M + H]^+$: 267.0587, found $[M + H]^+$: 267.0582.



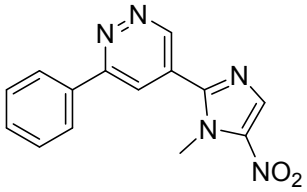
4am

Furan-2-yl(6-phenylpyridazin-4-yl)methanone (4am): Light yellow solid; m.p 116.3–118.5℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.52 (d, J = 1.8 Hz, 1H), 8.51 (d, J = 1.8 Hz, 1H), 8.29 – 8.20 (m, 3H), 7.69 (d, J = 3.6 Hz, 1H), 7.60 (q, J = 5.5 Hz, 3H), 6.88 (dd, J = 3.6, 1.5 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 179.35, 159.34, 150.98, 150.47, 148.00, 135.92, 135.29, 130.86, 129.49, 127.62, 123.94, 123.08, 113.87. HRMS (ESI-Q-TOF, m/z) calcd for $C_{15}H_{11}N_2O_2$ $[M + H]^+$: 251.0815, found $[M + H]^+$: 251.0807.



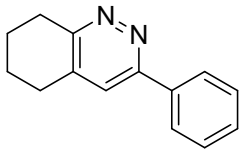
4an

1-(6-phenylpyridazin-4-yl)ethan-1-one (4an): White solid; m.p 96.3–97.9℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.52 (d, J = 1.9 Hz, 1H), 8.53 (d, J = 1.9 Hz, 1H), 8.30 – 8.24 (m, 2H), 7.61 (q, J = 7.5, 6.8 Hz, 3H), 2.76 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 198.17, 160.01, 147.26, 135.89, 133.60, 130.88, 129.49, 127.57, 122.39, 27.70. HRMS (ESI-Q-TOF, m/z) calcd for $C_{12}H_{11}N_2O$ [M + H]$^+$: 199.0866, found [M + H]$^+$: 199.0858.



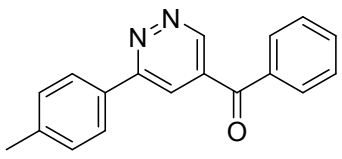
4ao

5-(1-methyl-5-nitro-1H-imidazol-2-yl)-3-phenylpyridazine (4ao): Light yellow solid; m.p 162.5–164.5℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.56 (d, J = 1.9 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.36 (s, 1H), 8.28 – 8.23 (m, 2H), 7.61 (q, J = 6.9, 6.5 Hz, 3H), 4.10 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.83, 149.18, 146.91, 141.23, 135.88, 133.34, 130.90, 129.50, 128.20, 127.63, 123.60, 35.84. HRMS (ESI-Q-TOF, m/z) calcd for $C_{14}H_{12}N_5O_2$ [M + H]$^+$: 282.0986, found [M + H]$^+$: 282.0979.



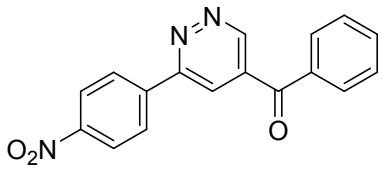
4ap

3-phenyl-5,6,7,8-tetrahydrocinnoline (4ap): Light gery solid; m.p 83.1–85.3℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (d, J = 7.2 Hz, 2H), 7.89 (s, 1H), 7.52 (m, 3H), 3.05 (t, J = 6.4 Hz, 2H), 2.85 (t, J = 6.3 Hz, 2H), 1.89 (m, 2H), 1.78 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.33, 156.42, 137.96, 136.83, 129.87, 129.27, 126.92, 123.96, 29.64, 27.74, 22.40, 21.75. HRMS (ESI-Q-TOF, m/z) calcd for $C_{14}H_{15}N_2$ [M + H]$^+$: 211.1230, found [M + H]$^+$: 211.1220.



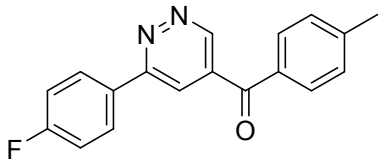
4aq

Phenyl(6-(p-tolyl)pyridazin-4-yl)methanone (4aq): Light yellow solid; m.p 117.4–118.8℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (d, J = 1.9 Hz, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.13 (d, J = 8.2 Hz, 2H), 7.93 – 7.88 (m, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 7.8 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.75, 159.01, 148.03, 140.70, 135.88, 135.44, 134.64, 133.11, 130.53, 130.08, 129.42, 127.44, 122.83, 21.29. HRMS (ESI-Q-TOF, m/z) calcd for $C_{18}H_{15}N_2O$ $[M + H]^+$: 275.1179, found $[M + H]^+$: 275.1176.



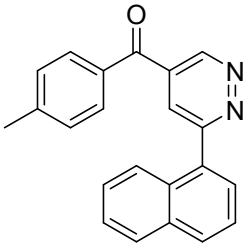
4ar

(6-(4-nitrophenyl)pyridazin-4-yl)(phenyl)methanone (4ar): Light yellow solid; m.p 201.9–204.1℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.51 (d, J = 1.9 Hz, 1H), 8.56 (d, J = 1.9 Hz, 1H), 8.53 – 8.50 (m, 2H), 8.44 – 8.40 (m, 2H), 7.93 (dd, J = 8.2, 1.1 Hz, 2H), 7.81 – 7.77 (m, 1H), 7.66 – 7.62 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.42, 157.49, 149.10, 149.00, 141.95, 136.16, 135.32, 134.78, 130.63, 129.46, 129.02, 124.49, 124.27. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{12}N_3O_3$ $[M + H]^+$: 306.0873, found $[M + H]^+$: 306.0874.



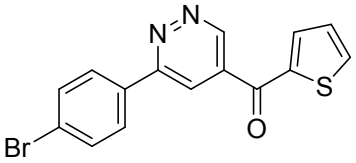
4as

(6-(4-fluorophenyl)pyridazin-4-yl)(p-tolyl)methanone (4as): White solid; m.p 152.6–154.2℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.38 (d, J = 1.9 Hz, 1H), 8.38 (d, J = 1.9 Hz, 1H), 8.33 – 8.28 (m, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.42 (m, 4H), 2.44 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.15, 164.90, 163.25, 158.14, 148.21, 145.48, 136.27, 132.91, 132.45, 132.43, 130.73, 130.02, 129.96, 123.03, 116.51, 116.37, 21.69. HRMS (ESI-Q-TOF, m/z) calcd for $C_{18}H_{14}FN_2O$ $[M + H]^+$: 293.1085, found $[M + H]^+$: 293.1075.



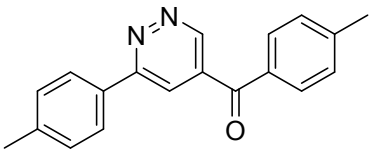
4at

(6-(naphthalen-1-yl)pyridazin-4-yl)(p-tolyl)methanone (4at): White solid; m.p 139.8–141.8℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.53 (d, J = 1.9 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.11 – 8.05 (m, 3H), 7.86 (d, J = 8.1 Hz, 2H), 7.81 – 7.77 (m, 1H), 7.72 – 7.66 (m, 1H), 7.65 – 7.56 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.07, 161.37, 148.23, 145.38, 135.65, 134.91, 133.79, 132.96, 130.72, 130.31, 129.97, 128.95, 128.84, 127.49, 127.33, 126.74, 125.88, 125.42, 21.68. HRMS (ESI-Q-TOF, m/z) calcd for $C_{22}H_{17}N_2O$ $[M + H]^+$: 325.1335, found $[M + H]^+$: 325.1336.



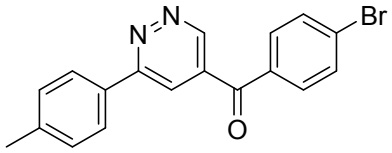
4au

(6-(4-bromophenyl)pyridazin-4-yl)(thiophen-2-yl)methanone (4au): White solid; m.p 180.1–182.3℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.49 (s, 1H), 8.53 (s, 1H), 8.32 – 8.25 (m, 1H), 8.22 (d, J = 7.7 Hz, 2H), 7.94 (s, 1H), 7.80 (d, J = 7.6 Hz, 2H), 7.35 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 185.21, 158.35, 148.12, 141.97, 138.35, 138.31, 136.08, 135.13, 132.44, 129.93, 129.69, 124.74, 122.92. HRMS (ESI-Q-TOF, m/z) calcd for $C_{15}H_{10}BrN_2OS$ $[M + H]^+$: 344.9692, found $[M + H]^+$: 344.9682.



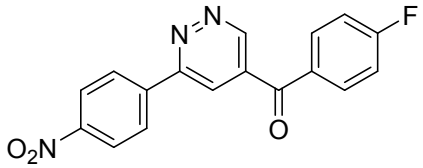
4av

P-tolyl(6-(p-tolyl)pyridazin-4-yl)methanone (4av): White solid; m.p 164.4–166.2℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.35 (d, J = 1.9 Hz, 1H), 8.31 (d, J = 1.9 Hz, 1H), 8.13 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.25, 158.97, 148.01, 145.43, 140.69, 136.18, 133.12, 132.95, 130.69, 130.08, 130.01, 127.44, 122.74, 21.69, 21.29. HRMS (ESI-Q-TOF, m/z) calcd for $C_{19}H_{17}N_2O$ $[M + H]^+$: 289.3500, found $[M + H]^+$: 289.1335, $[M + H]^+$: 289.1327.



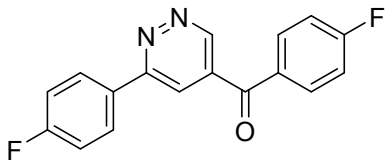
4aw

(4-bromophenyl)(6-(p-tolyl)pyridazin-4-yl)methanone (4aw): Light yellow solid; m.p 192.7–194.5℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.34 (s, 1H), 8.13 (d, J = 7.0 Hz, 2H), 7.83 (s, 4H), 7.39 (d, J = 6.8 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.03, 159.02, 148.00, 140.75, 135.47, 134.54, 133.06, 132.49, 132.44, 130.08, 128.89, 127.46, 122.90, 21.30. HRMS (ESI-Q-TOF, m/z) calcd for $C_{18}H_{13}BrN_2ONa$ $[M + Na]^+$: 375.0103, found $[M + Na]^+$: 375.0089.



4ax

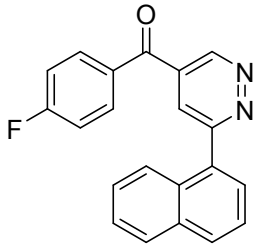
(4-fluorophenyl)(6-(4-nitrophenyl)pyridazin-4-yl)methanone (4ax): Light yellow solid; m.p 196.5–198.6℃; purity: 97.1%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.51 (d, J = 1.7 Hz, 1H), 8.57 (d, J = 1.7 Hz, 1H), 8.52 (d, J = 8.8 Hz, 2H), 8.42 (d, J = 8.8 Hz, 2H), 8.03 (dd, J = 8.6, 5.5 Hz, 2H), 7.46 (t, J = 8.7 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.09, 166.90, 165.22, 157.48, 149.06, 149.02, 141.93, 136.05, 133.83, 133.77, 132.17, 129.02, 124.49, 124.26, 116.68, 116.54. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{11}FN_3O_3$ $[M + H]^+$: 324.0779, found $[M + H]^+$: 324.0782.



4ay

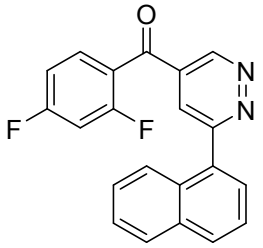
.

(4-fluorophenyl)(6-(4-fluorophenyl)pyridazin-4-yl)methanone (4ay): Light yellow solid; m.p 145.1–146.8℃; purity: 97.5%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.40 (d, J = 1.7 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.30 (dd, J = 8.7, 5.5 Hz, 2H), 8.05 – 7.97 (m, 2H), 7.44 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.31, 166.85, 165.16, 164.91, 163.27, 158.17, 148.18, 135.88, 133.76, 133.69, 132.42, 132.40, 132.23, 132.21, 130.03, 129.97, 123.11, 116.66, 116.51, 116.37. HRMS (ESI-Q-TOF, m/z) calcd for $C_{17}H_{11}F_2N_2O$ $[M + H]^+$: 297.0834, found $[M + H]^+$: 297.0828.



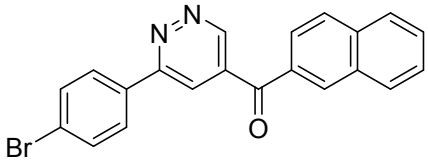
4az

(4-fluorophenyl)(6-(naphthalen-1-yl)pyridazin-4-yl)methanone (4az): Light yellow solid; m.p 163.3–166.6℃; purity: 97.2%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.65 – 9.42 (m, 1H), 8.13 (d, J = 8.4 Hz, 2H), 8.10 – 8.01 (m, 4H), 7.79 (d, J = 6.9 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.61 (m, 2H), 7.45 (t, J = 8.7 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.24, 166.78, 165.09, 161.39, 148.20, 135.32, 134.89, 133.78, 133.74, 133.68, 132.30, 132.28, 130.72, 130.33, 128.96, 128.84, 127.50, 127.40, 126.75, 125.88, 125.43, 116.62, 116.47. HRMS (ESI-Q-TOF, m/z) calcd for $C_{21}H_{13}FN_2ONa$ $[M + Na]^+$: 351.0904, found $[M + Na]^+$: 351.0894.



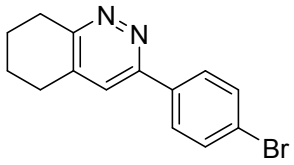
4ba

(2,4-difluorophenyl)(6-(naphthalen-1-yl)pyridazin-4-yl)methanone (4ba): Light yellow solid; m.p 117.1–118.6℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.18 – 8.11 (m, 2H), 8.08 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.95 (q, J = 7.4 Hz, 1H), 7.76 (d, J = 6.5 Hz, 1H), 7.69 (t, J = 7.4 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.52 (t, J = 9.5 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 189.81, 161.75, 147.68, 135.27, 134.75, 134.50, 134.48, 134.43, 134.41, 133.76, 130.68, 130.38, 128.89, 127.55, 127.11, 126.76, 125.88, 125.17, 121.50, 121.48, 121.43, 121.40, 113.07, 113.05, 112.93, 112.91, 106.05, 105.88, 105.70. HRMS (ESI-Q-TOF, m/z) calcd for $C_{21}H_{13}F_2N_2O$ $[M + H]^+$: 347.0990, found $[M + H]^+$: 347.0983.



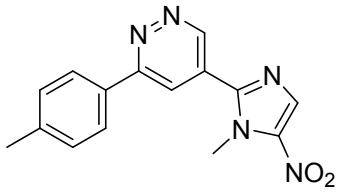
4bb

(6-(4-bromophenyl)pyridazin-4-yl)(naphthalen-2-yl)methanone (4bb): White solid; m.p 145.4–147.2℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.46 (d, J = 1.7 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.42 (d, J = 1.7 Hz, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.73 – 7.66 (m, 2H), 7.64 (t, J = 7.7 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 195.19, 158.51, 148.80, 136.78, 135.08, 134.34, 133.98, 132.59, 132.45, 130.66, 129.62, 129.13, 128.74, 127.30, 125.60, 125.16, 124.73, 123.68. HRMS (ESI-Q-TOF, m/z) calcd for $C_{21}H_{14}BrN_2O$ $[M + H]^+$: 389.0284, found $[M + H]^+$: 389.0274.



4bc

3-(4-bromophenyl)-5,6,7,8-tetrahydrocinnoline (4bc): Light grey solid; m.p 150.4–152.3℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.07 (d, J = 8.5 Hz, 2H), 7.93 (s, 1H), 7.73 (d, J = 8.5 Hz, 2H), 3.04 (t, J = 6.4 Hz, 2H), 2.85 (t, J = 6.3 Hz, 2H), 1.89 (m, 2H), 1.78 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.64, 155.42, 138.27, 135.94, 132.26, 128.94, 124.05, 123.63, 29.60, 27.74, 22.32, 21.68. HRMS (ESI-Q-TOF, m/z) calcd for $C_{14}H_{14}BrN_2$ $[M + H]^+$: 289.0335, found $[M + H]^+$: 289.0328.



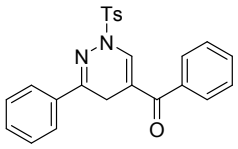
4bd

5-(1-methyl-5-nitro-1H-imidazol-2-yl)-3-(p-tolyl)pyridazine (4bd): Light yellow solid; m.p 216.3–218.3℃; purity >99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.52 (d, J = 1.9 Hz, 1H), 8.49 (d, J = 1.9 Hz, 1H), 8.36 (s, 1H), 8.15 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.09 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.72, 148.92, 146.97, 141.20, 140.77, 133.33, 133.06, 130.11, 128.14, 127.48, 123.23, 35.83, 21.31. HRMS (ESI-Q-TOF, m/z) calcd for $C_{15}H_{14}N_5O_2$ $[M + H]^+$: 296.1142, found $[M + H]^+$: 296.1147.

4. References

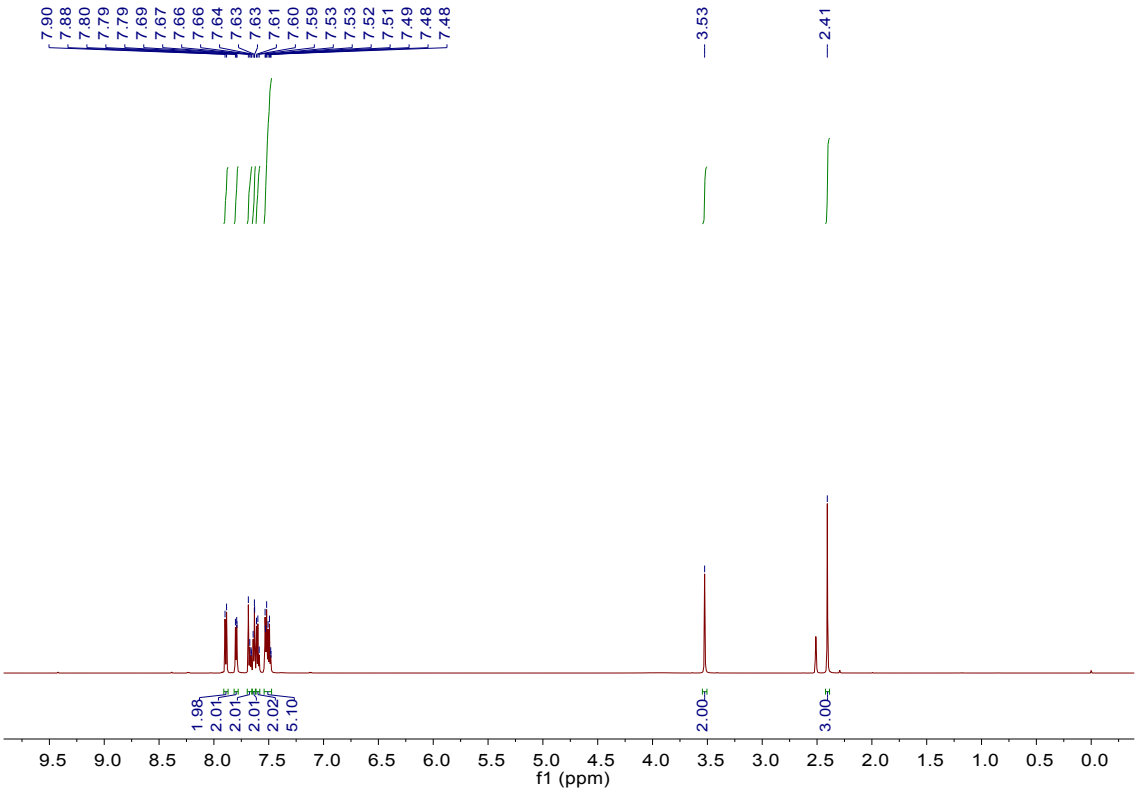
1 a) J.-R. Chen, W.-R. Dong, M. Candy, F.-F. Pan, and M. Jörres, C. Bolm, *J. Am. Chem. Soc*. 2012, **134**, 6924; b) M. S. South, T. L. Jakuboski, M. D. Westmeyer, and D. R. Dukesherer, *J. Org. Chem*. 1996, **61**, 8921.

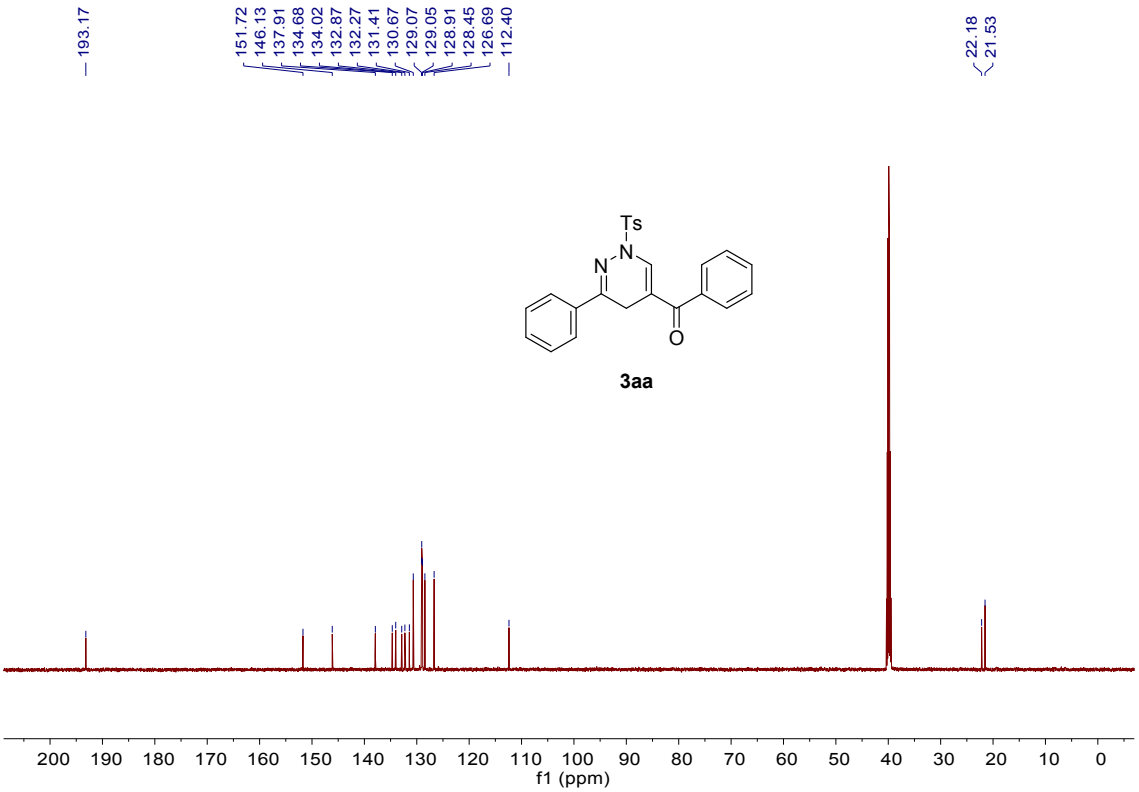
2 a) F. Ma, J. Liu, T. Zhou, M. Lei, J. Chen, X. Wang, Y. Zhang, X. Shen, L. Hu, *European Journal of Medicinal Chemistry*. 2018, **152**, 307; b) J. D. Albright, R. G. Shepherd, *Journal of Heterocyclic Chemistry*. 1973, **10**, 899; c) N. Jebli, W. Debrouwer, J. K. E. T. Berton, K. V. Hecke, C.V. Stevens, S. Touil, *Synlett*. 2017, **28**, 1160.



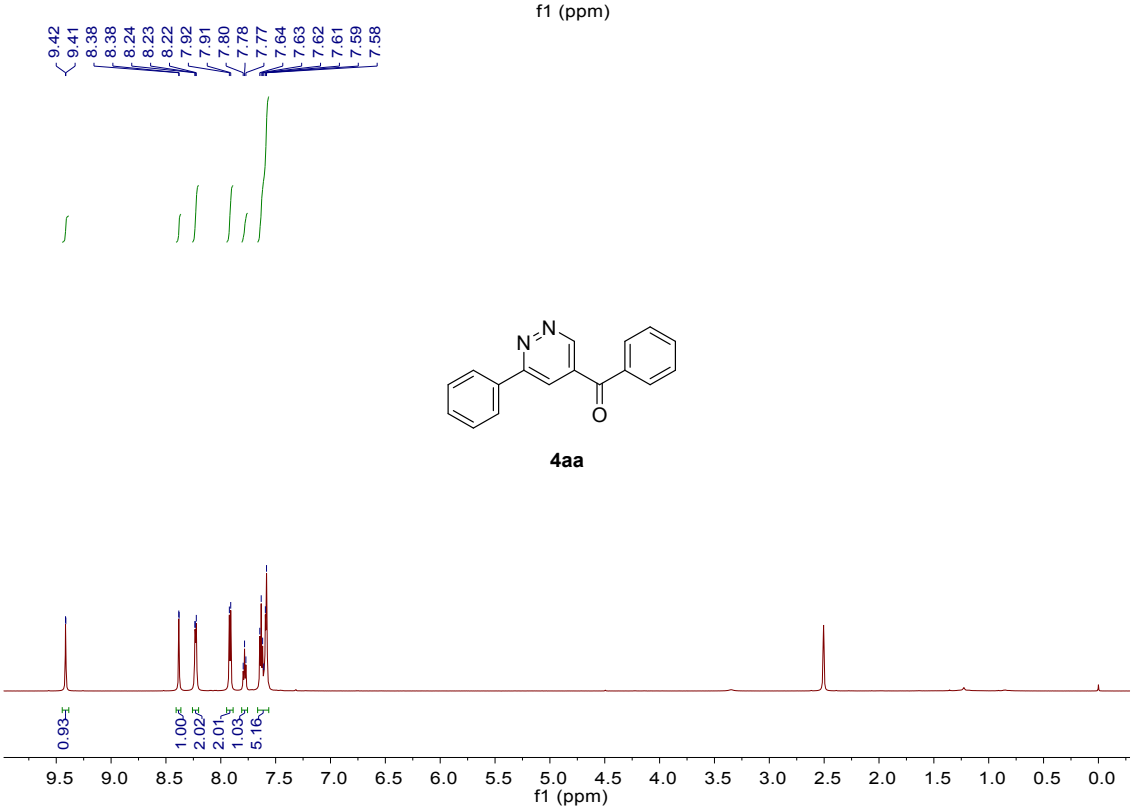
3aa

5. NMR spectra of the products

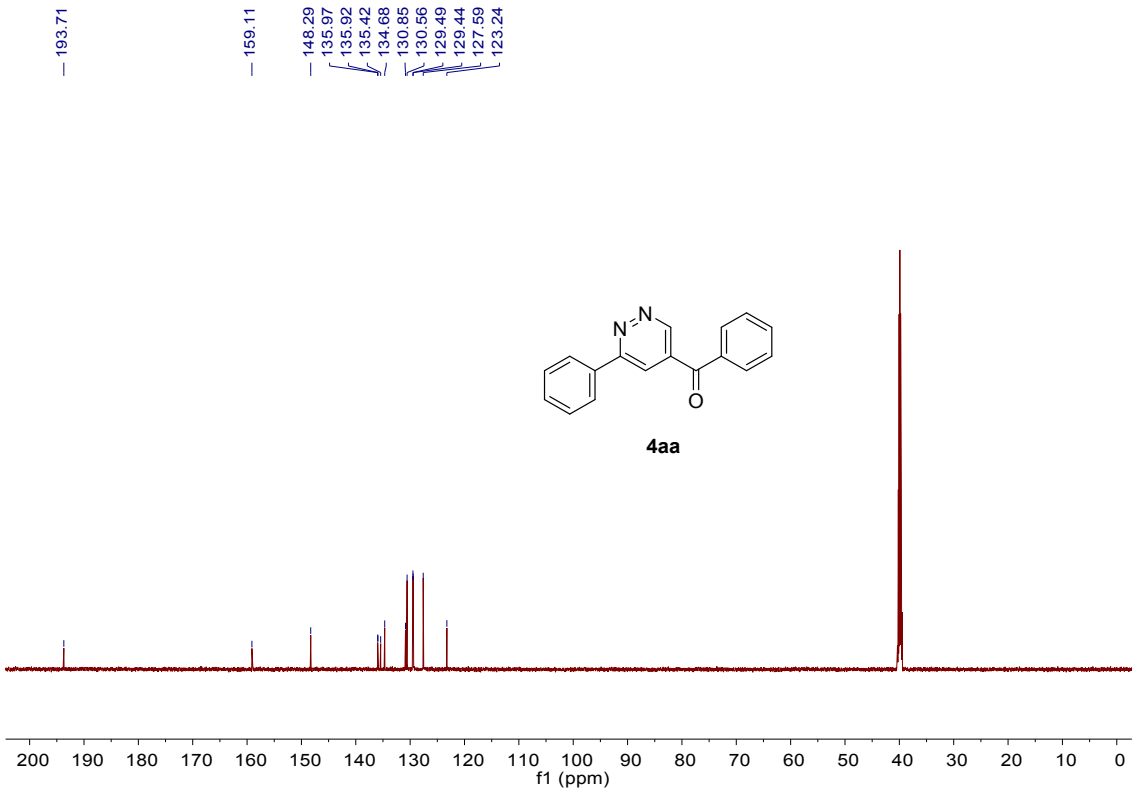



193.17
151.72
146.13
137.91
134.68
134.02
132.87
132.27
131.41
130.67
129.07
129.05
128.91
128.45
126.69
112.40
22.18
21.53
Ts
N
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

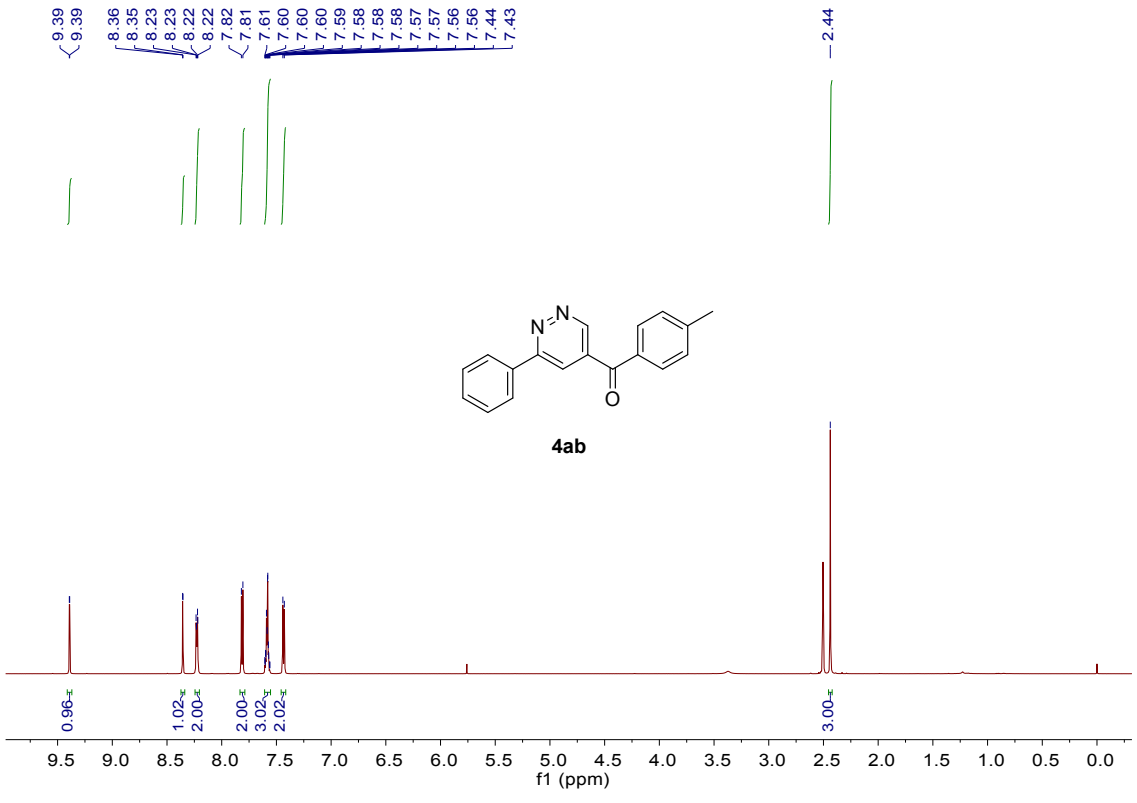
3aa


9.42
9.41
8.38
8.38
8.24
8.23
8.22
7.92
7.91
7.80
7.78
7.77
7.64
7.63
7.62
7.61
7.59
7.58
N
N
O
0.93
1.00
2.02
2.01
1.03
5.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

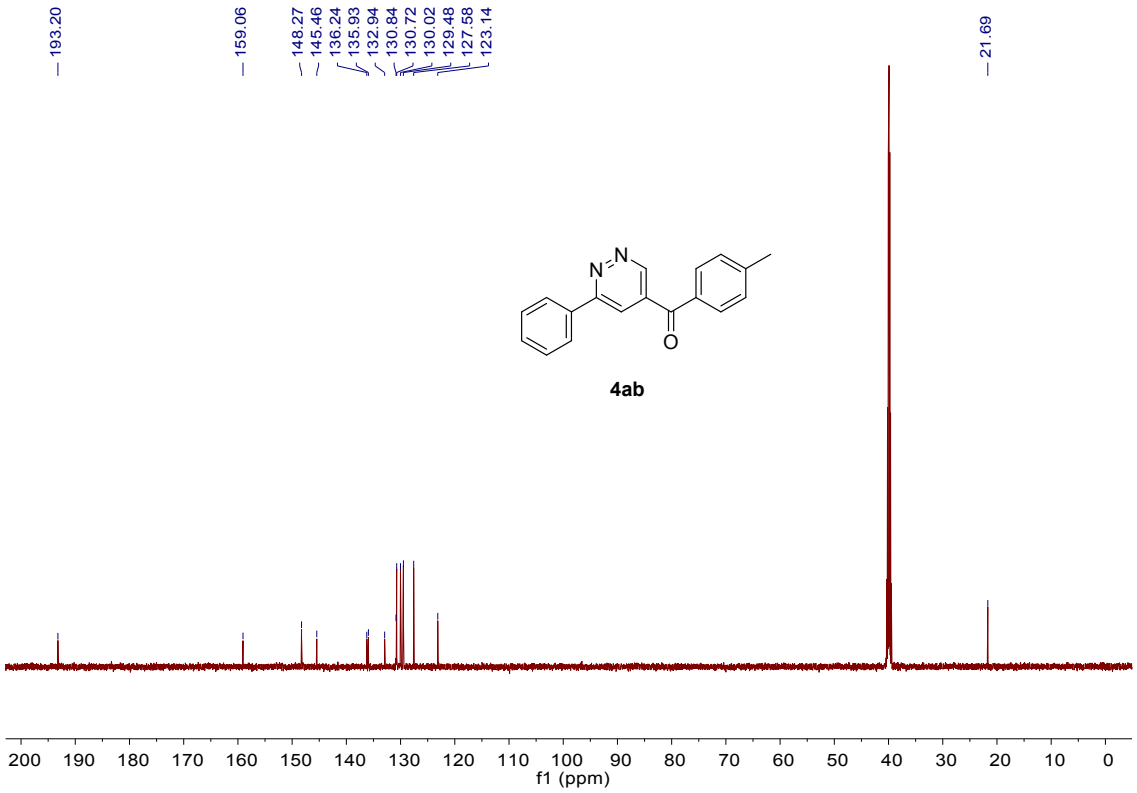
4aa


193.71
159.11
148.29
135.97
135.92
135.42
134.68
130.85
130.56
129.49
129.44
127.59
123.24
N
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

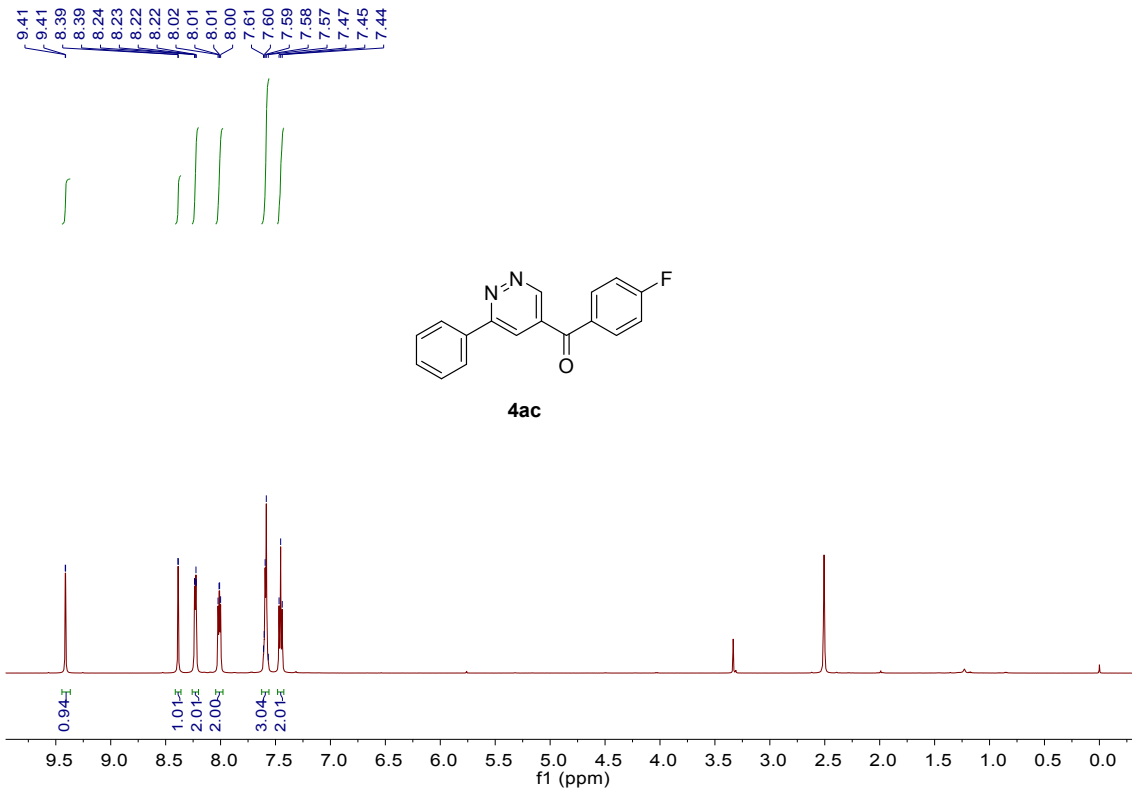
4aa


9.39
9.39
8.36
8.35
8.23
8.23
8.22
8.22
7.82
7.81
7.61
7.60
7.60
7.60
7.59
7.58
7.58
7.58
7.57
7.57
7.56
7.56
7.44
7.43
2.44
N
N
O
0.96
1.02
2.00
2.00
3.02
2.02
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

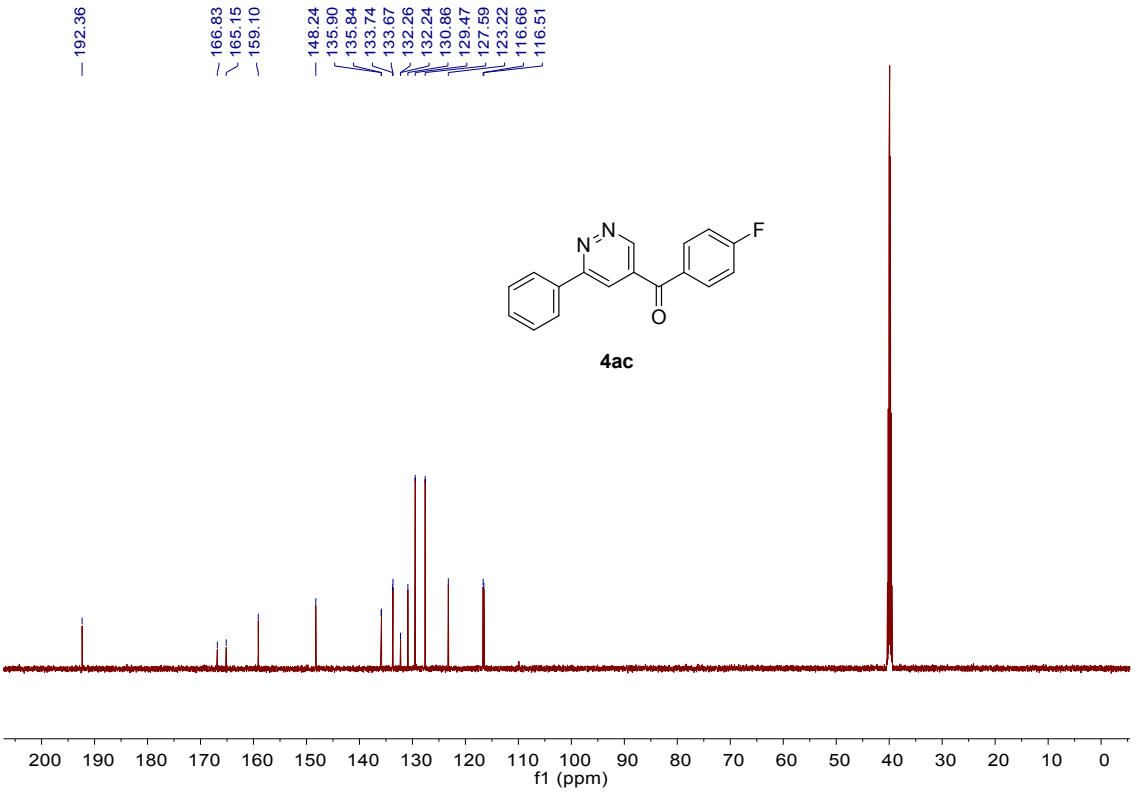
4ab


193.20
159.06
148.27
145.46
136.24
135.93
132.94
130.84
130.72
130.02
129.48
127.58
123.14
21.69
N
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

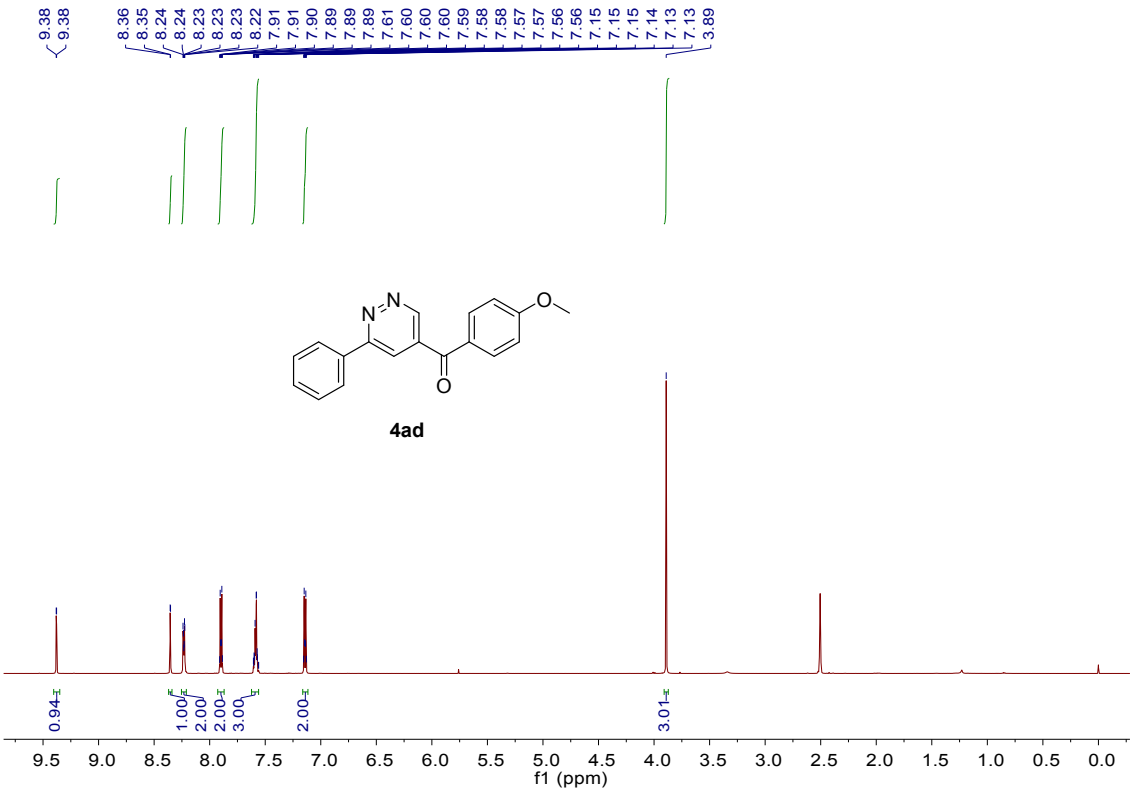
4ab


9.41
9.41
8.39
8.39
8.24
8.23
8.22
8.22
8.02
8.01
8.01
8.00
7.61
7.60
7.59
7.58
7.57
7.47
7.45
7.44
N
N
F
O
0.94
1.01
2.01
2.00
3.04
2.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

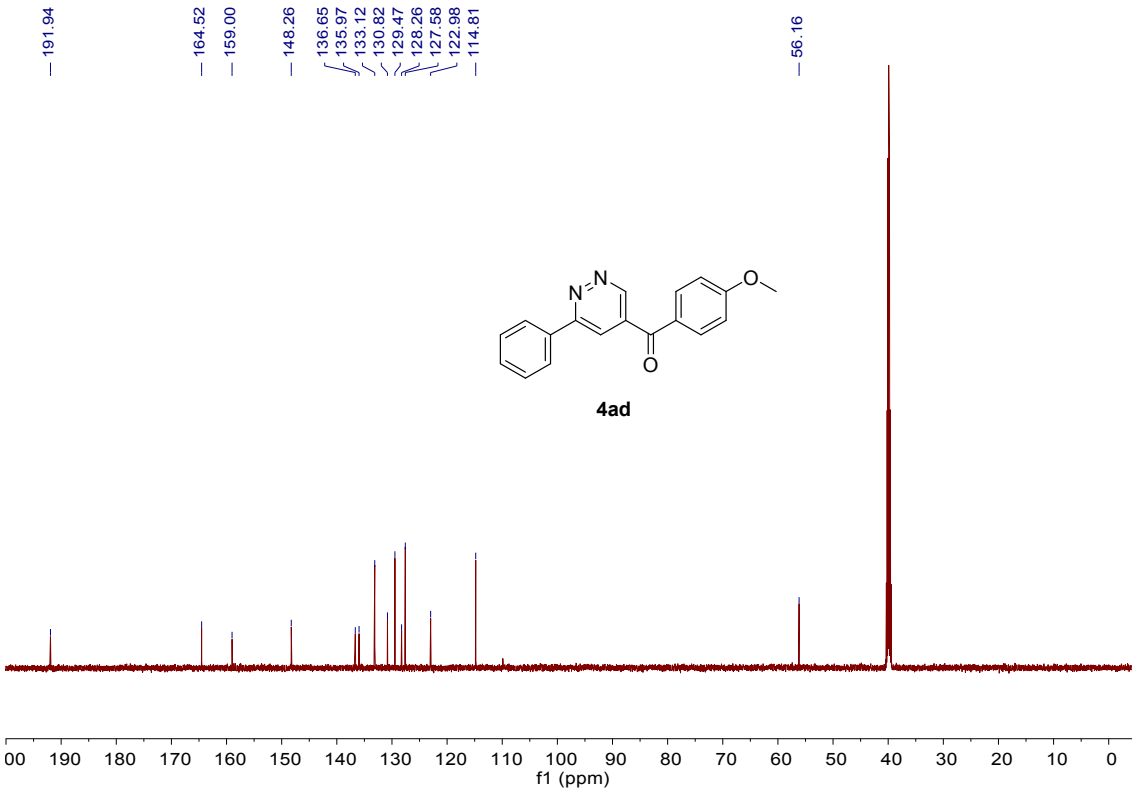
4ac


192.36
166.83
165.15
159.10
148.24
135.90
135.84
133.74
133.67
132.26
132.24
130.86
129.47
127.59
123.22
116.66
116.51
N
N
F
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

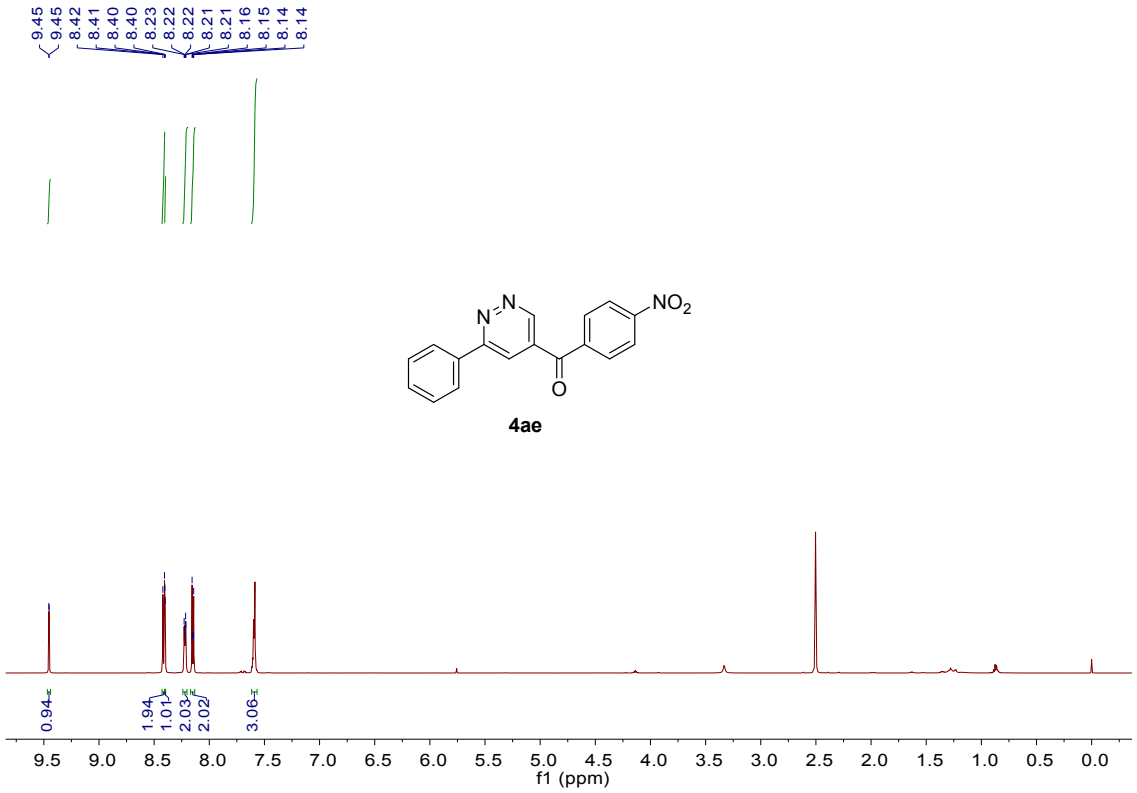
4ac


9.38
9.38
8.36
8.35
8.24
8.24
8.23
8.23
8.23
8.22
7.91
7.91
7.90
7.89
7.89
7.89
7.61
7.60
7.60
7.60
7.59
7.58
7.58
7.57
7.57
7.56
7.56
7.15
7.15
7.15
7.14
7.13
7.13
3.89
N
N
O
O
0.94
1.00
2.00
2.00
3.00
2.00
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

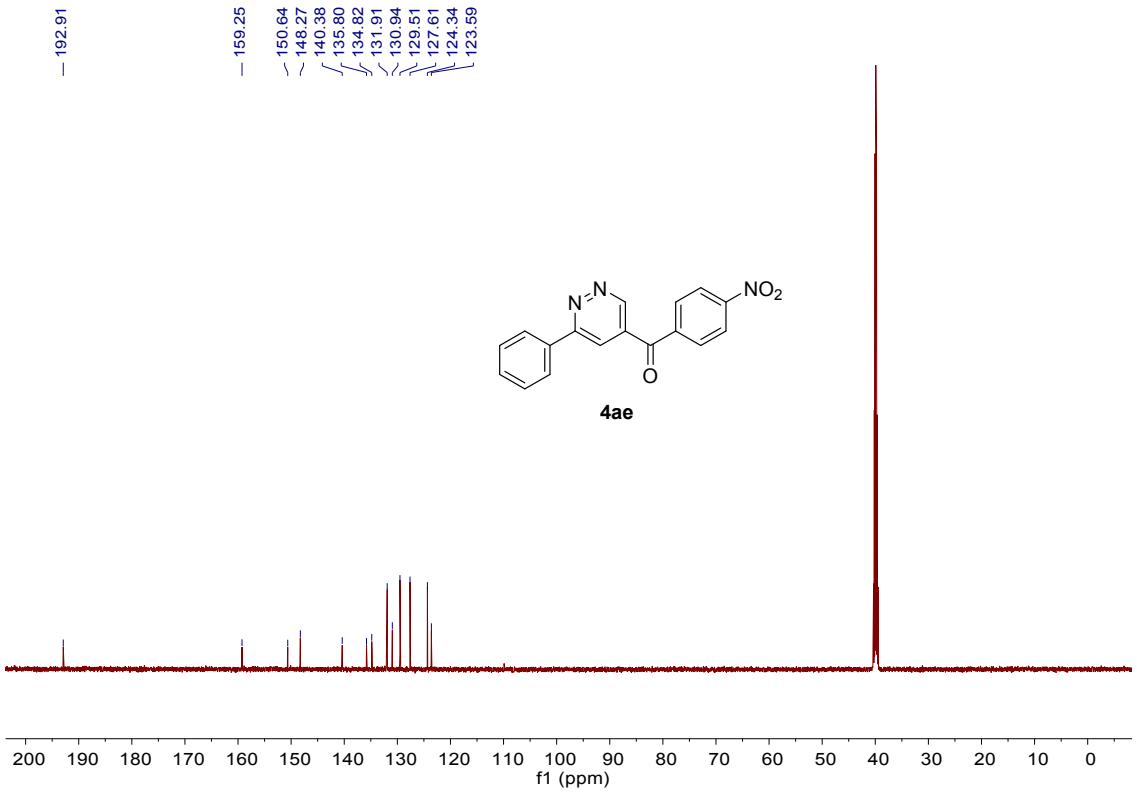
4ad

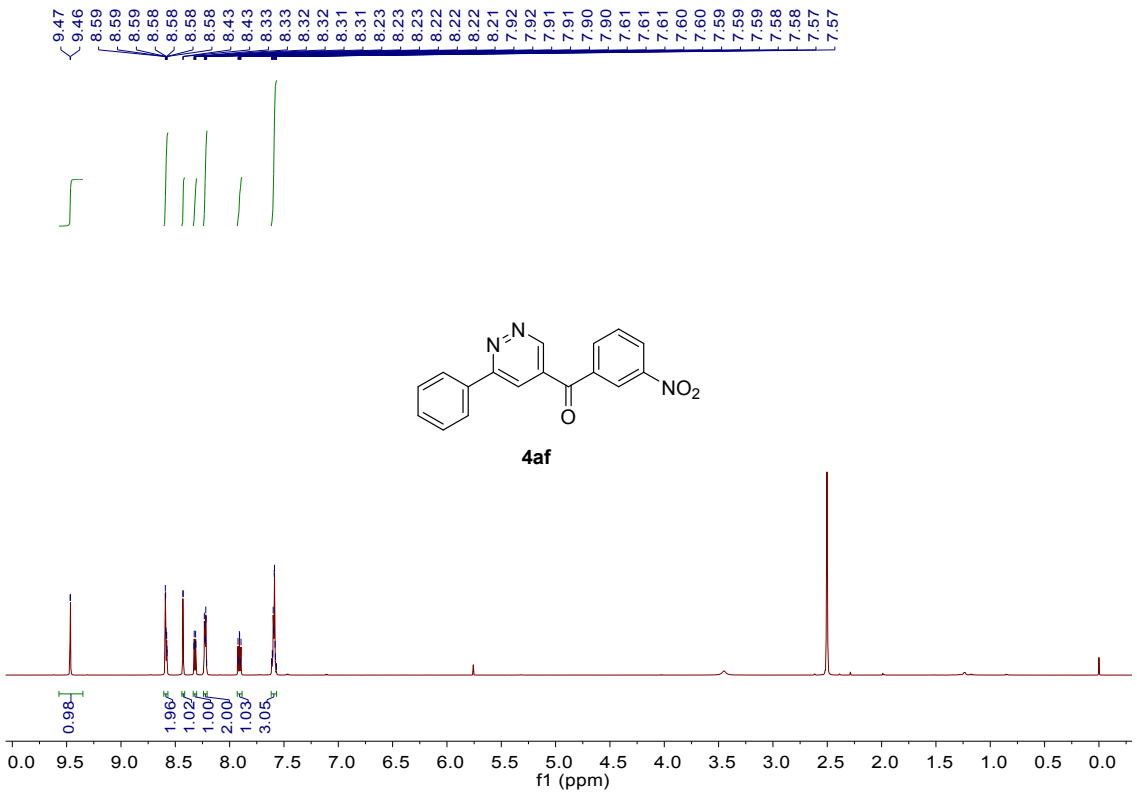

191.94
164.52
159.00
148.26
136.65
135.97
133.12
130.82
129.47
128.26
127.58
122.98
114.81
56.16
N
N
O
O
f1 (ppm)

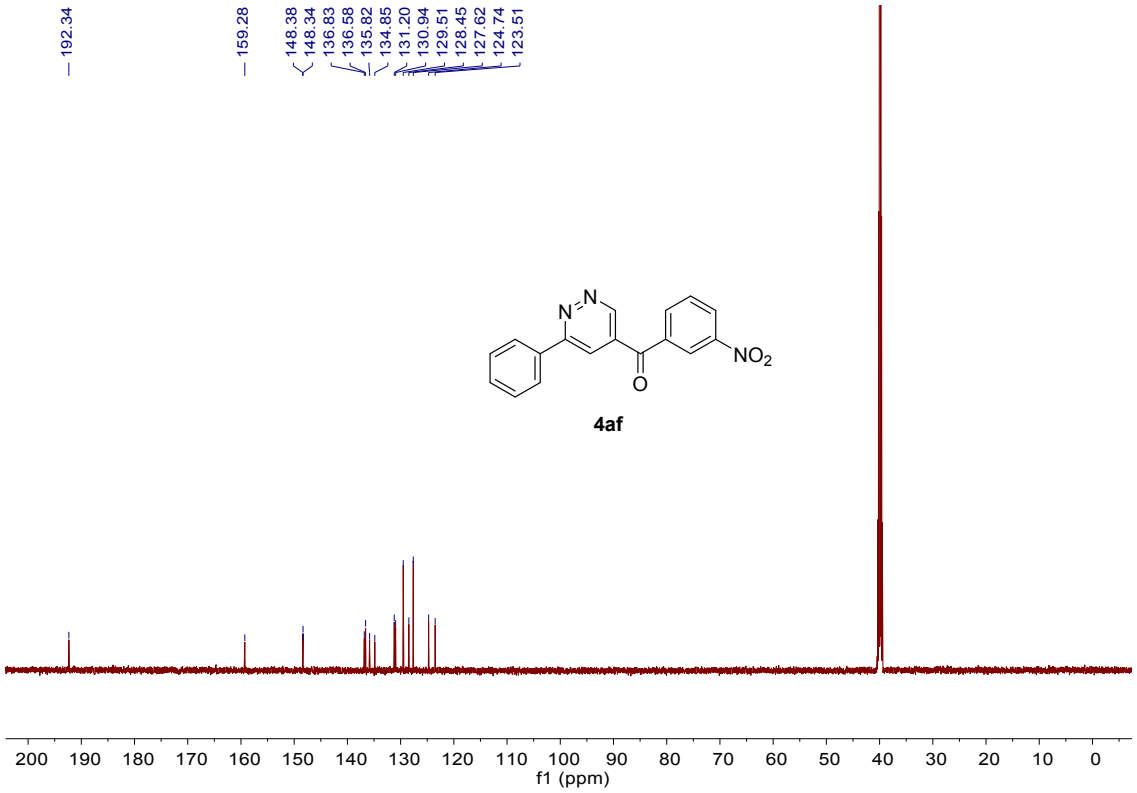
4ad


9.45
9.45
8.42
8.41
8.40
8.40
8.23
8.22
8.22
8.21
8.21
8.16
8.15
8.14
8.14
N
N
NO2
O
0.94
1.94
1.01
2.03
2.02
3.06
f1 (ppm)

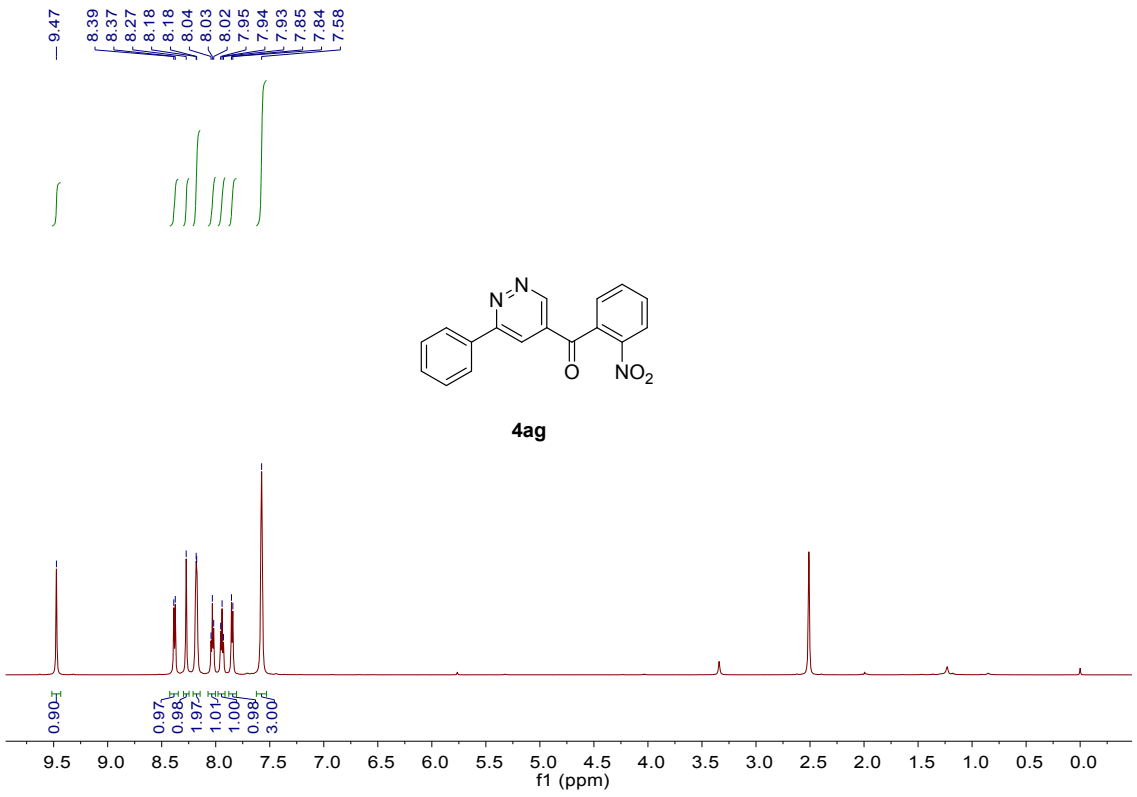
4ae


192.91
159.25
150.64
148.27
140.38
135.80
134.82
131.91
130.94
129.51
127.61
124.34
123.59
N
N
NO2
O
4ae
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

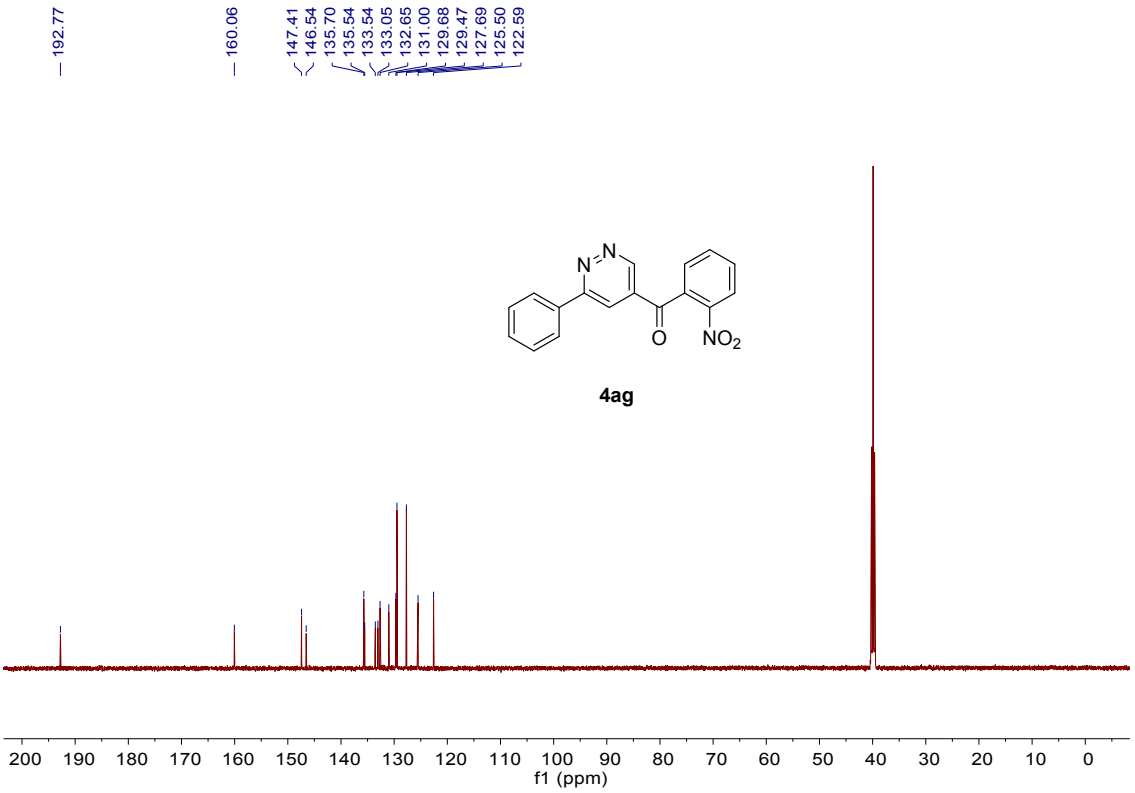

9.47
9.46
8.59
8.59
8.59
8.58
8.58
8.58
8.58
8.58
8.43
8.43
8.33
8.33
8.32
8.32
8.31
8.31
8.23
8.23
8.22
8.22
8.22
8.21
7.92
7.92
7.91
7.91
7.90
7.90
7.61
7.61
7.61
7.60
7.60
7.59
7.59
7.59
7.58
7.58
7.57
7.57
N
N
NO2
O
4af
0.98
1.96
1.02
1.00
2.00
1.03
3.05
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


192.34
159.28
148.38
148.34
136.83
136.58
135.82
134.85
131.20
130.94
129.51
128.45
127.62
124.74
123.51
N
N
O
NO2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

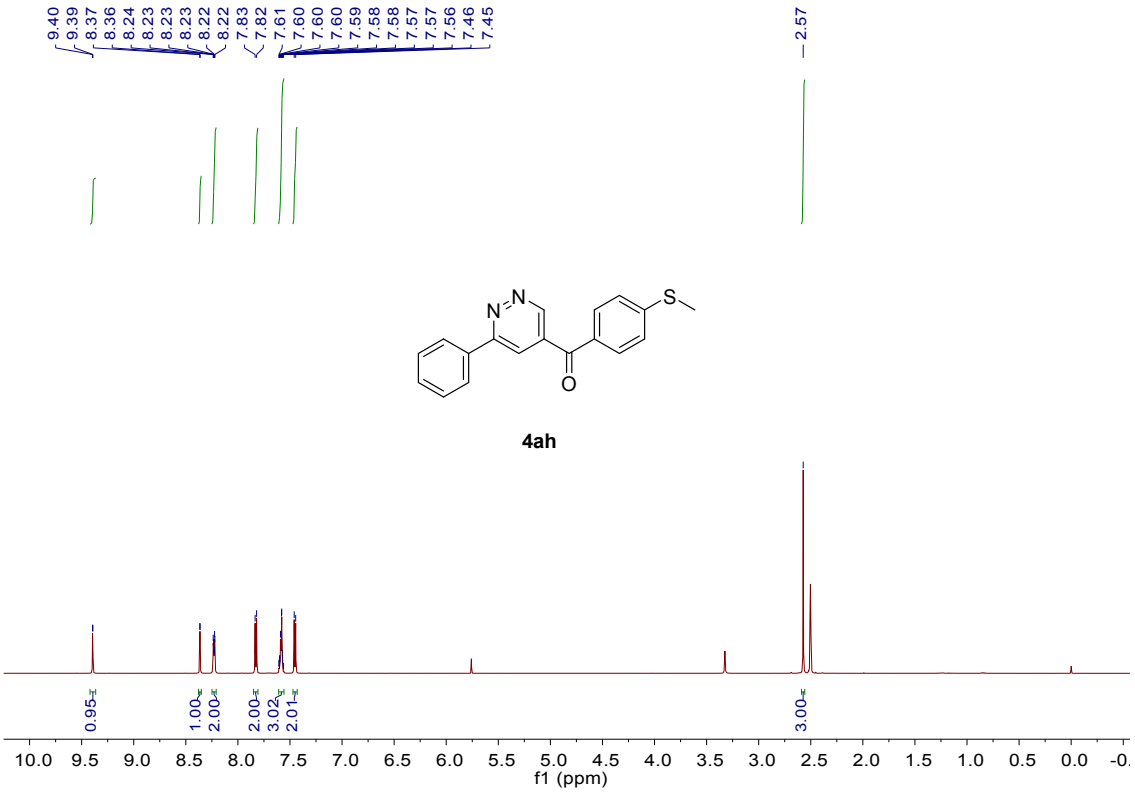
4af


9.47
8.39
8.37
8.27
8.18
8.18
8.04
8.03
8.02
7.95
7.94
7.93
7.85
7.84
7.58
N
N
O
NO2
0.90
0.97
0.98
1.97
1.01
1.00
0.98
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

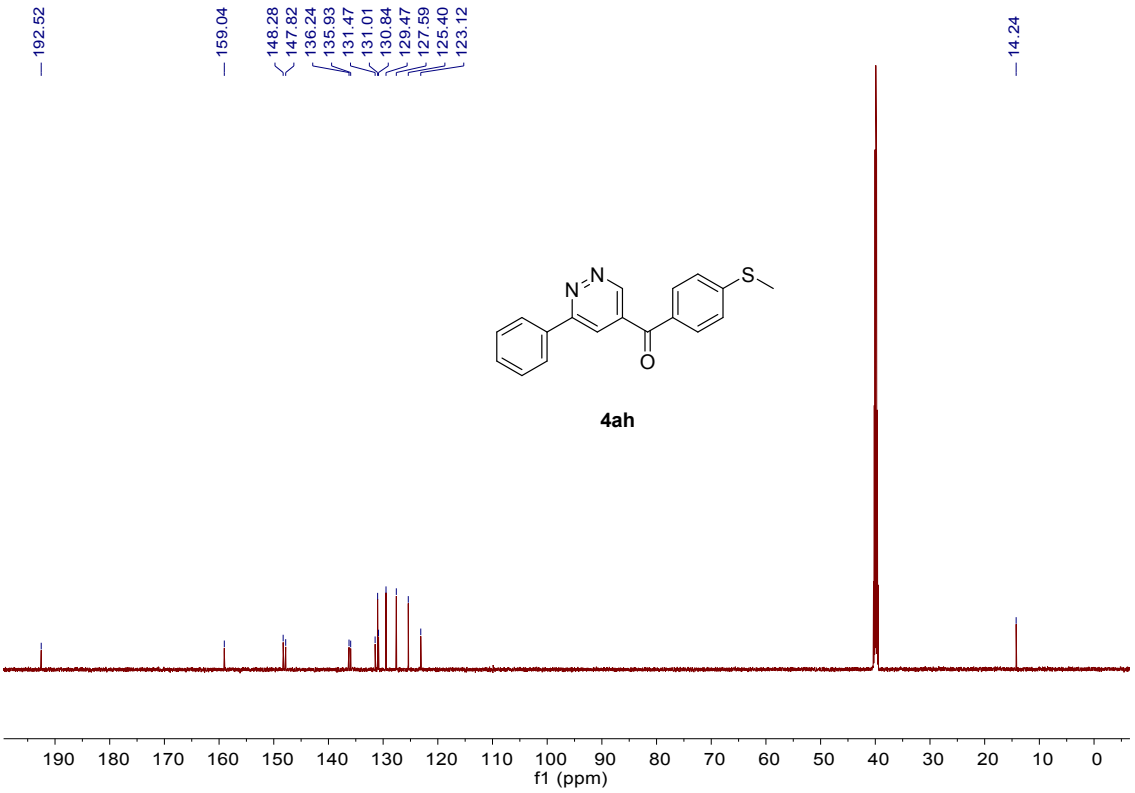
4ag


192.77
160.06
147.41
146.54
135.70
135.54
133.54
133.05
132.65
131.00
129.68
129.47
127.69
125.50
122.59
N
N
O
NO2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

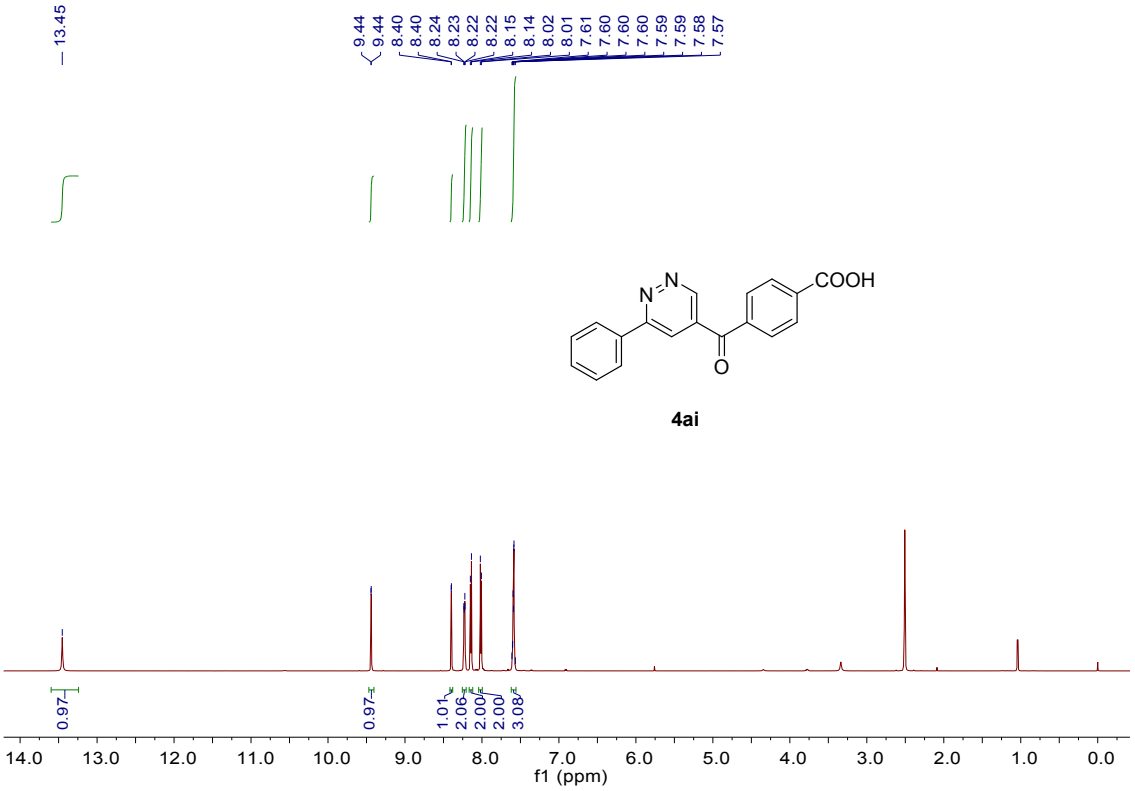
4ag


9.40
9.39
8.37
8.36
8.24
8.23
8.23
8.23
8.22
8.22
7.83
7.82
7.61
7.60
7.60
7.60
7.59
7.58
7.58
7.57
7.57
7.56
7.46
7.45
2.57
N
N
S
O
0.95
1.00
2.00
2.00
3.02
2.01
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

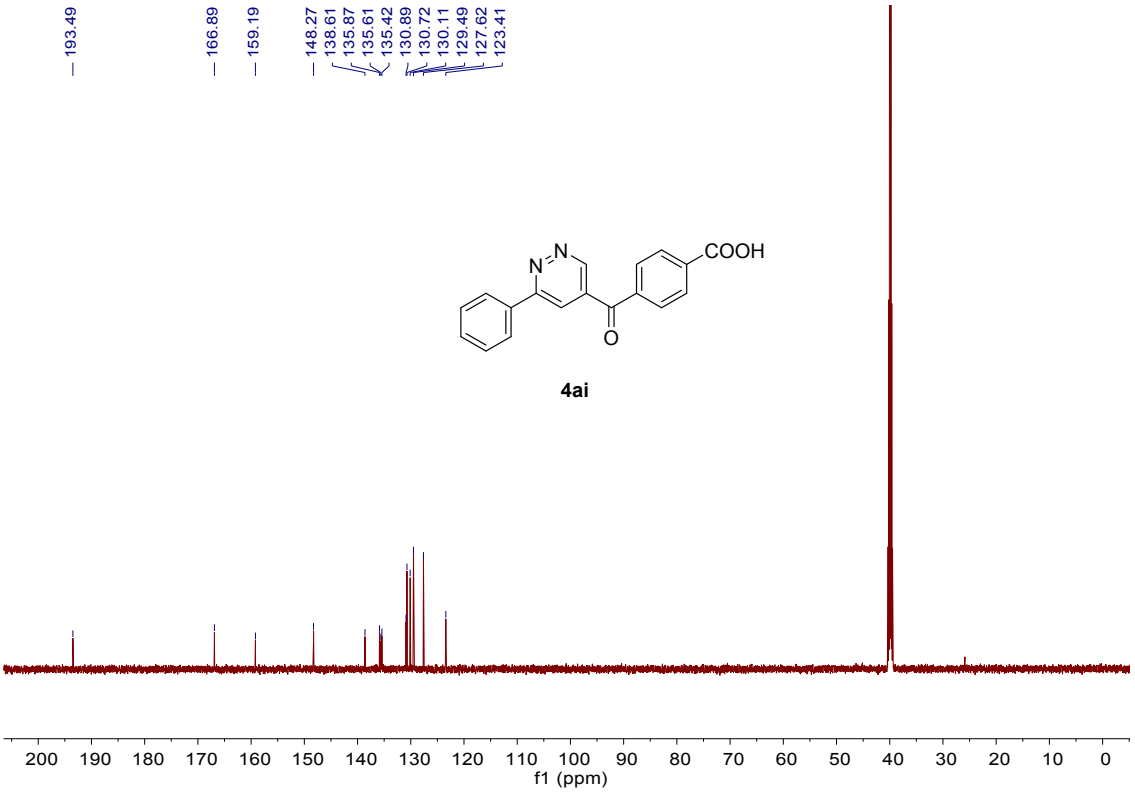
4ah


192.52
159.04
148.28
147.82
136.24
135.93
131.47
131.01
130.84
129.47
127.59
125.40
123.12
14.24
N
N
S
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

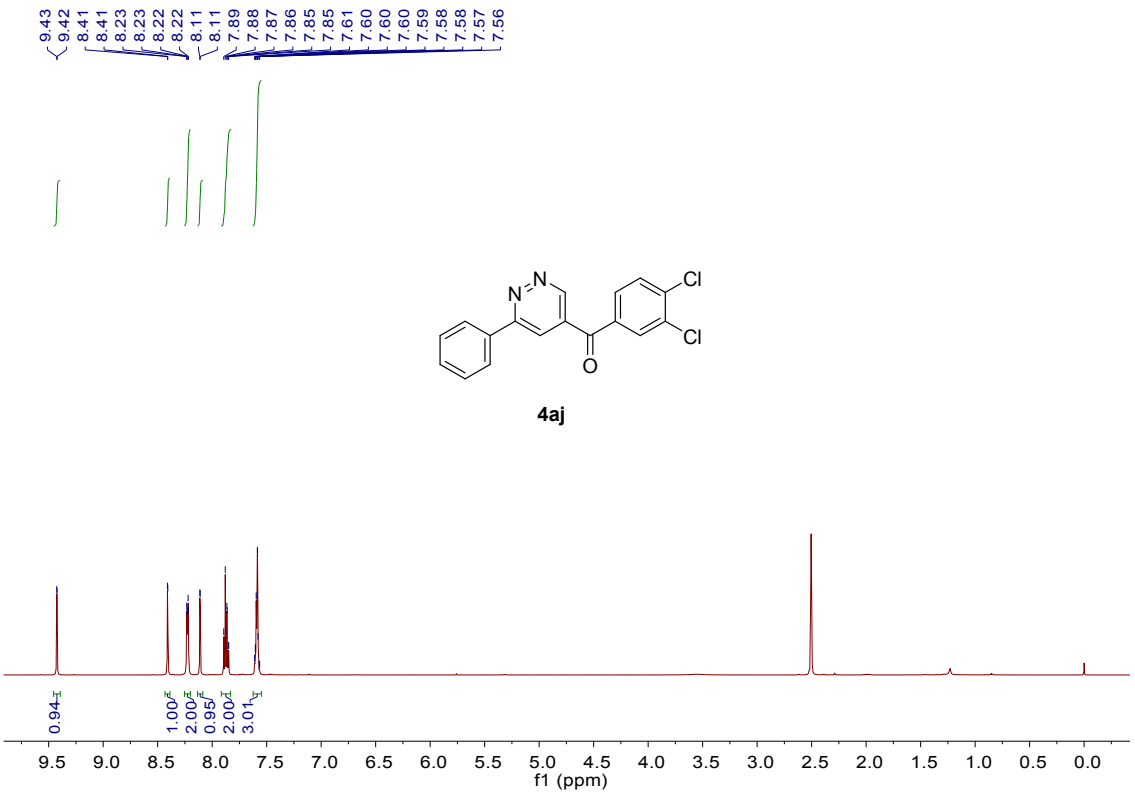
4ah


13.45
9.44
9.44
8.40
8.40
8.24
8.23
8.22
8.22
8.15
8.14
8.02
8.01
7.61
7.60
7.60
7.60
7.59
7.59
7.58
7.57
N
N
COOH
O
0.97
0.97
1.01
2.06
2.00
2.00
3.08
14.0 13.0 12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

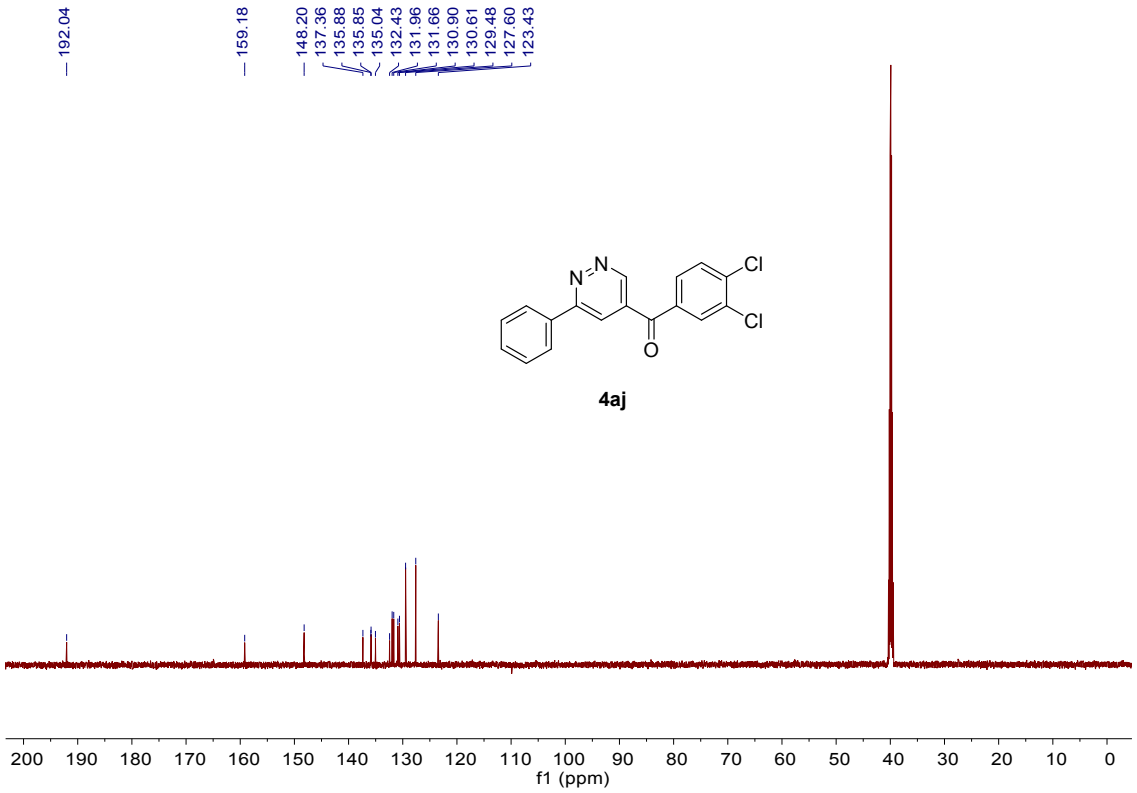
4ai


193.49
166.89
159.19
148.27
138.61
135.87
135.61
135.42
130.89
130.72
130.11
129.49
127.62
123.41
N
N
COOH
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

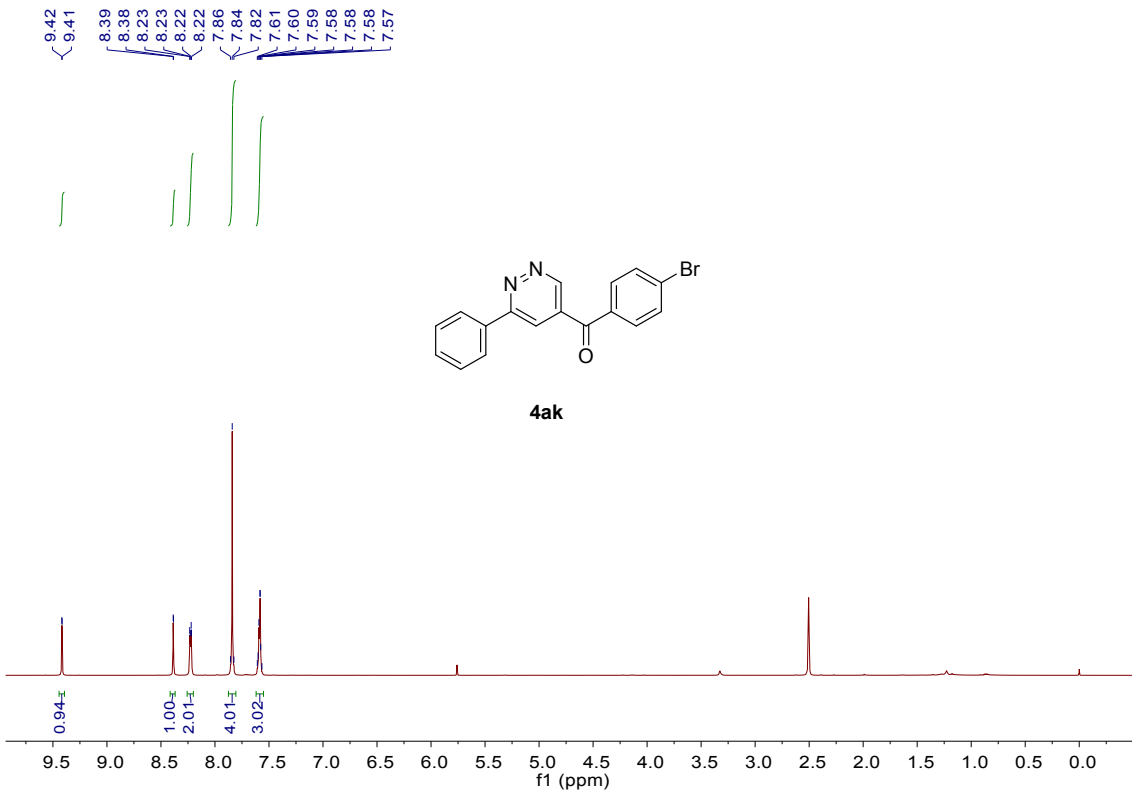
4ai


9.43
9.42
8.41
8.41
8.23
8.23
8.22
8.22
8.11
8.11
7.89
7.88
7.87
7.86
7.85
7.85
7.61
7.60
7.60
7.60
7.59
7.58
7.58
7.57
7.56
N
N
Cl
Cl
O
0.94
1.00
2.00
0.95
2.00
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

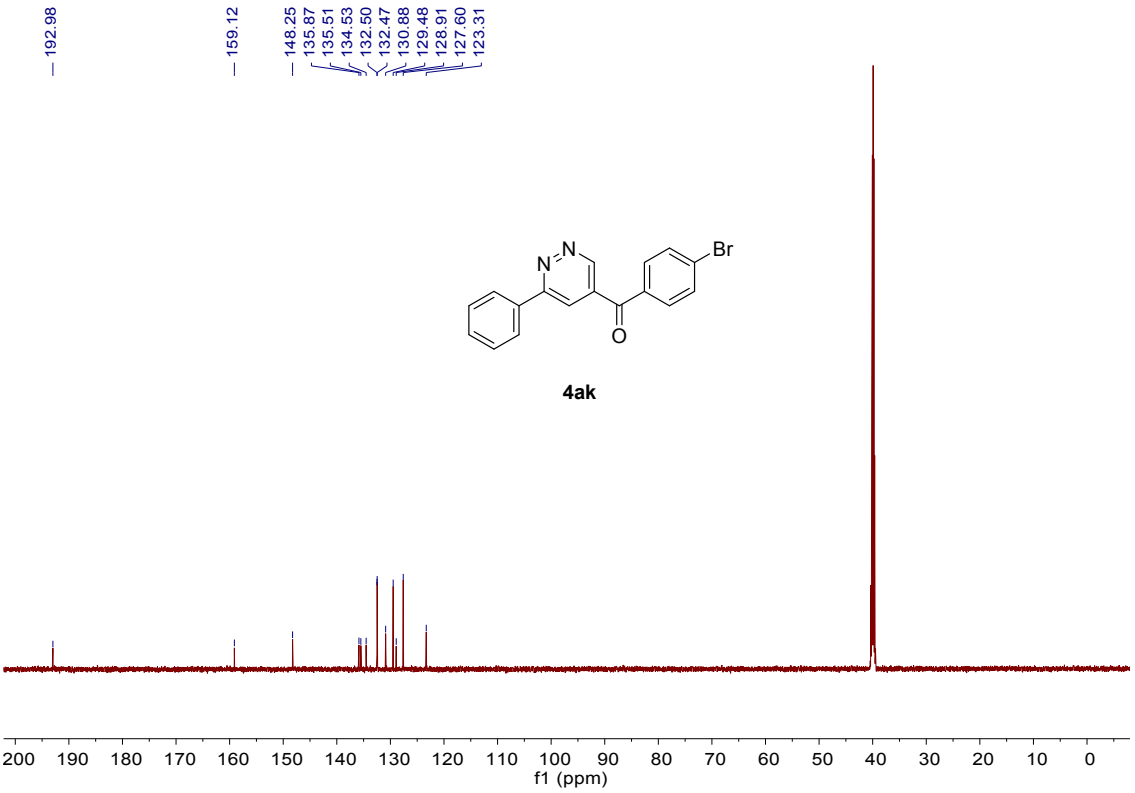
4aj


192.04
159.18
148.20
137.36
135.88
135.85
135.04
132.43
131.96
131.66
130.90
130.61
129.48
127.60
123.43
N
N
Cl
Cl
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

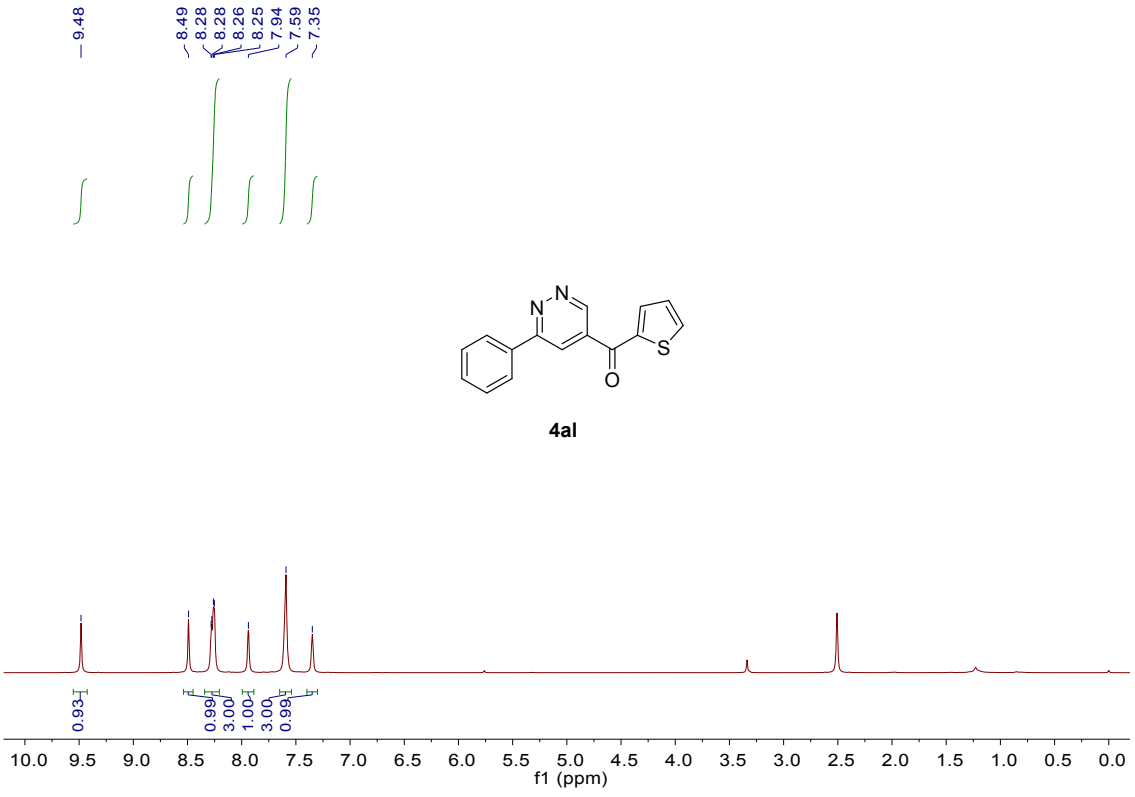
4aj


9.42
9.41
8.39
8.38
8.23
8.23
8.22
8.22
7.86
7.84
7.82
7.61
7.60
7.59
7.58
7.58
7.58
7.57
N
N
Br
O
0.94
1.00
2.01
4.01
3.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

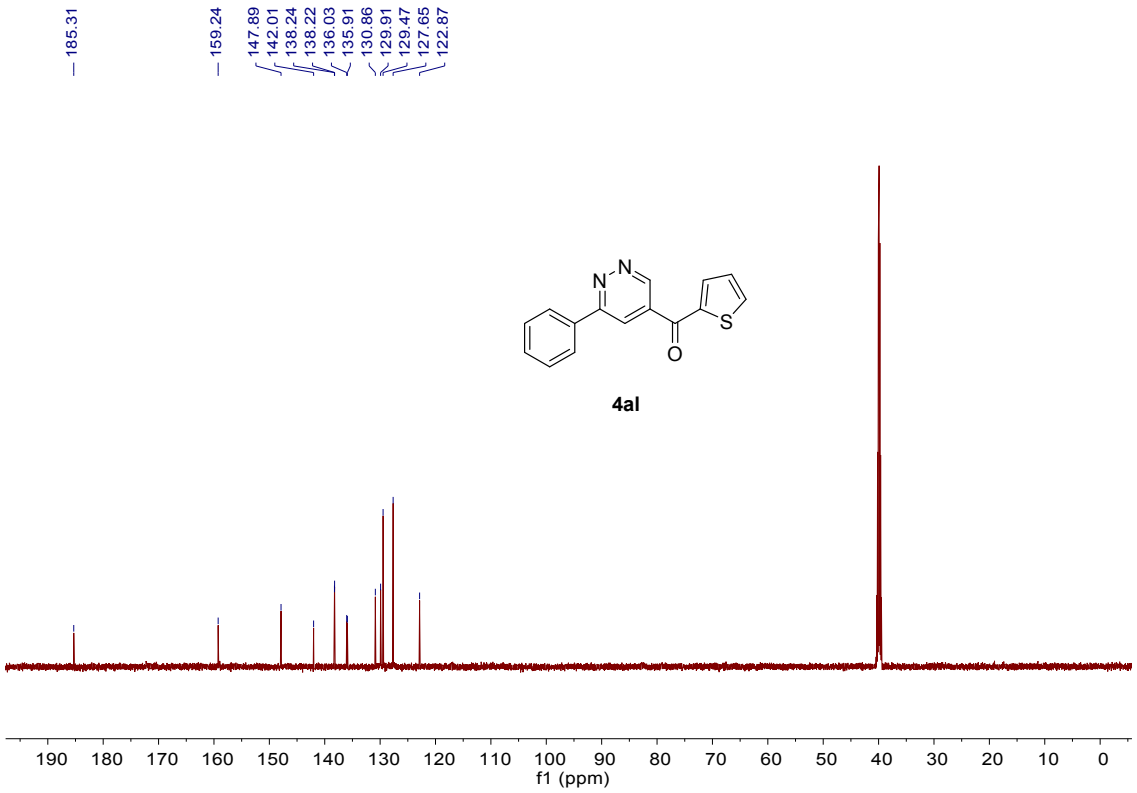
4ak


192.98
159.12
148.25
135.87
135.51
134.53
132.50
132.47
130.88
129.48
128.91
127.60
123.31
Br
N
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

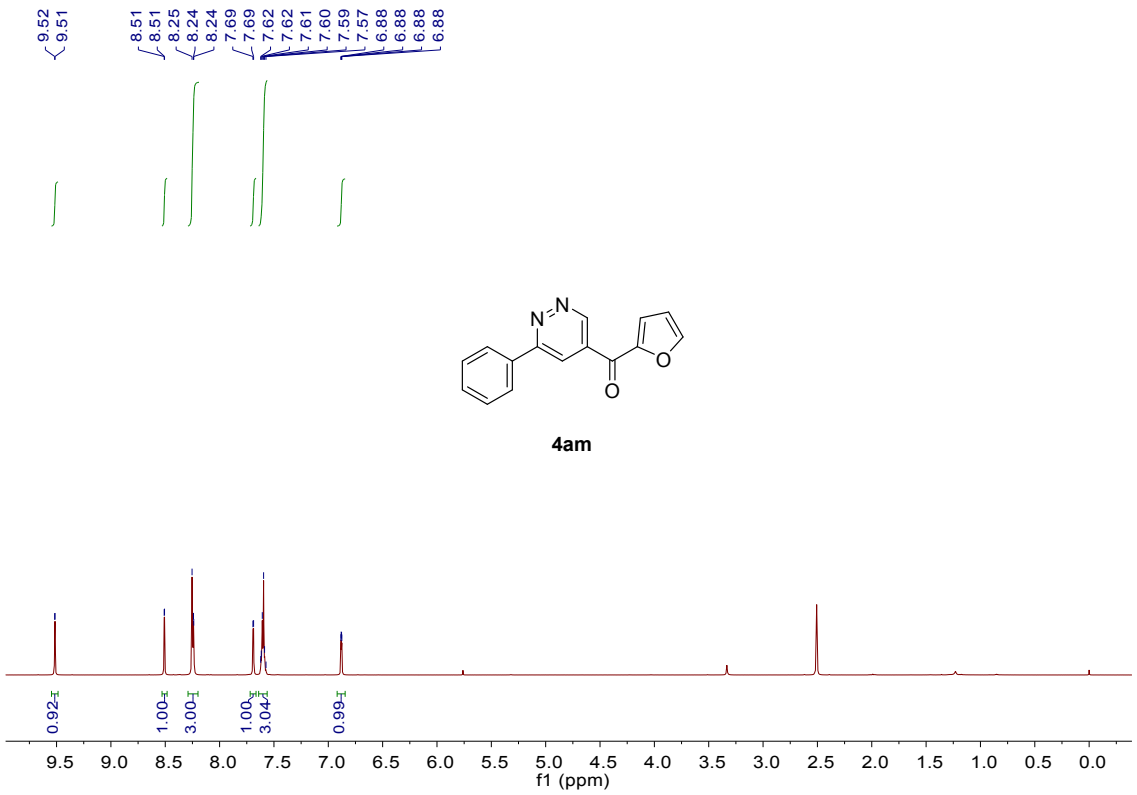
4ak


9.48
8.49
8.28
8.28
8.26
8.25
7.94
7.59
7.35
N
N
S
O
0.93
0.99
3.00
1.00
3.00
0.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

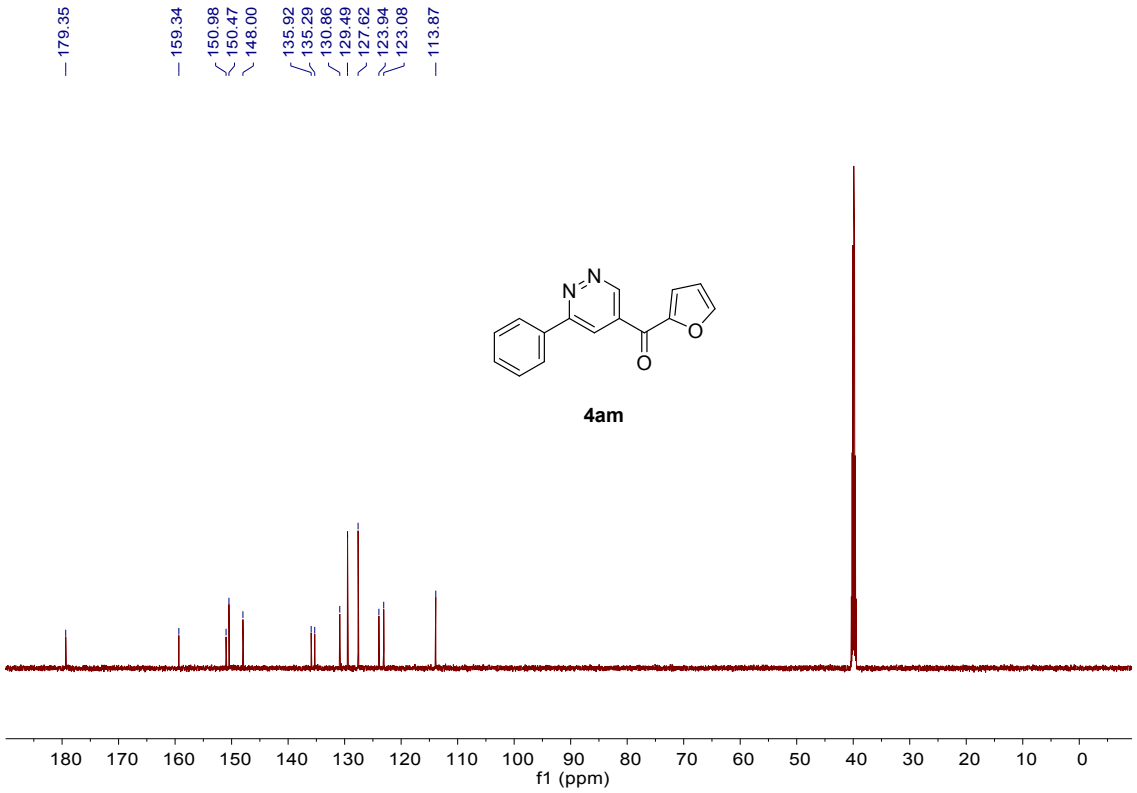
4al

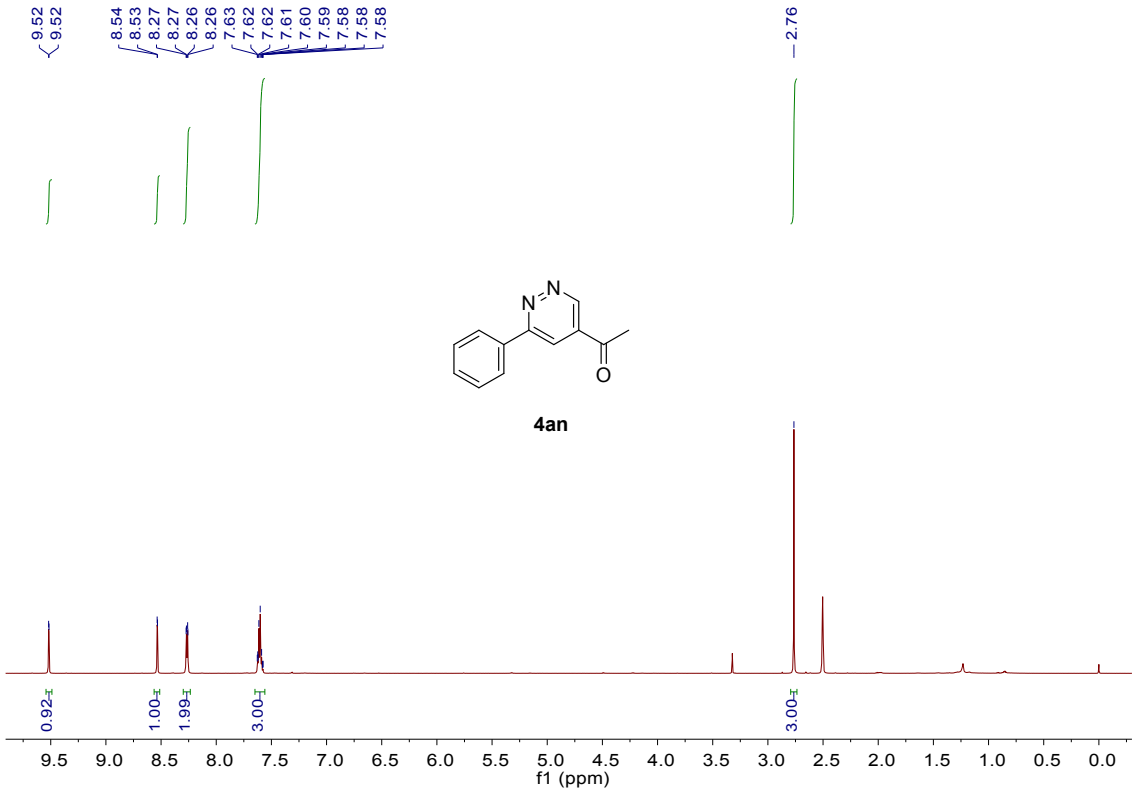

185.31
159.24
147.89
142.01
138.24
138.22
136.03
135.91
130.86
129.91
129.47
127.65
122.87
N
N
S
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

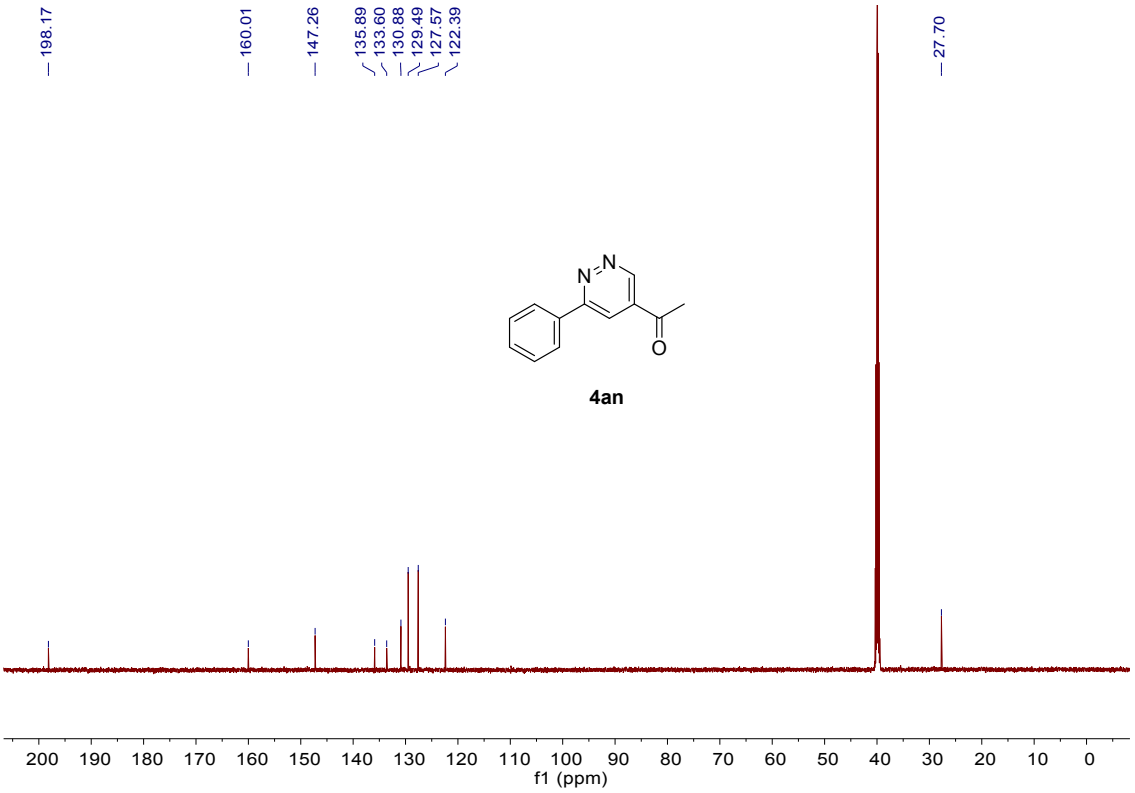
4al


9.52
9.51
8.51
8.51
8.25
8.24
8.24
7.69
7.69
7.62
7.62
7.61
7.60
7.59
7.57
6.88
6.88
6.88
N
N
O
O
0.92
1.00
3.00
1.00
3.04
0.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

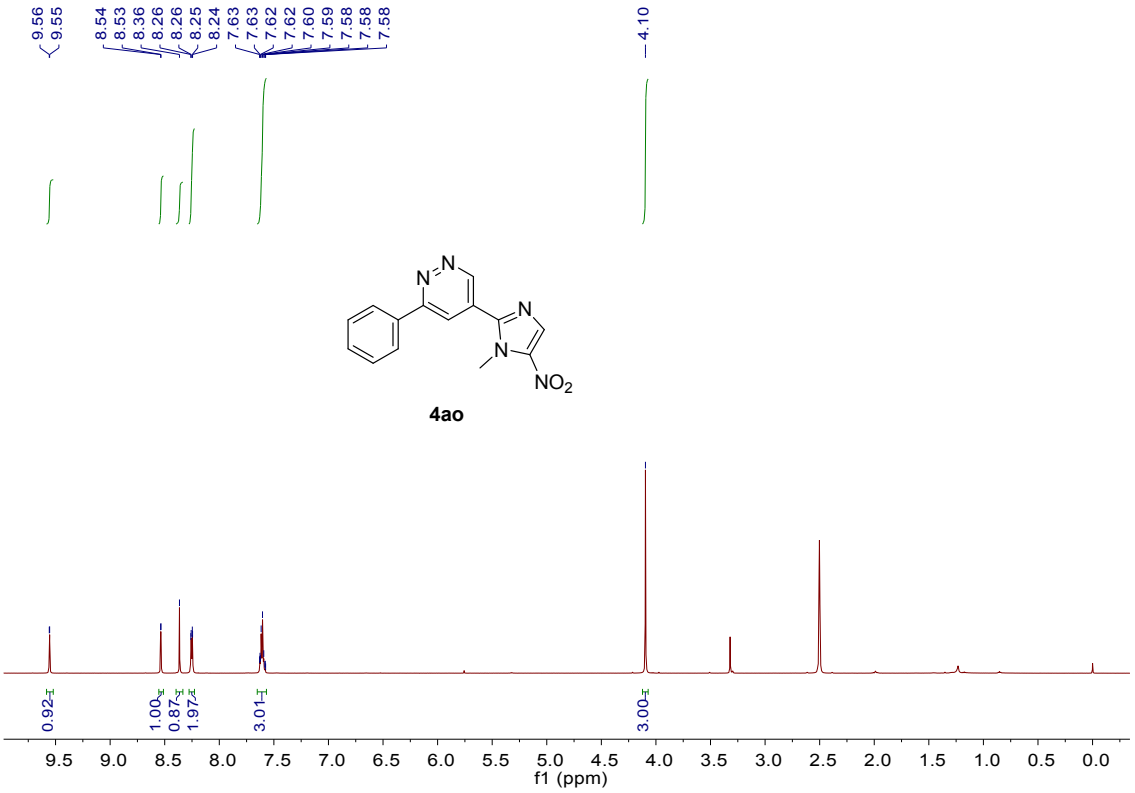
4am


179.35
159.34
150.98
150.47
148.00
135.92
135.29
130.86
129.49
127.62
123.94
123.08
113.87
N
N
O
O
4am
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

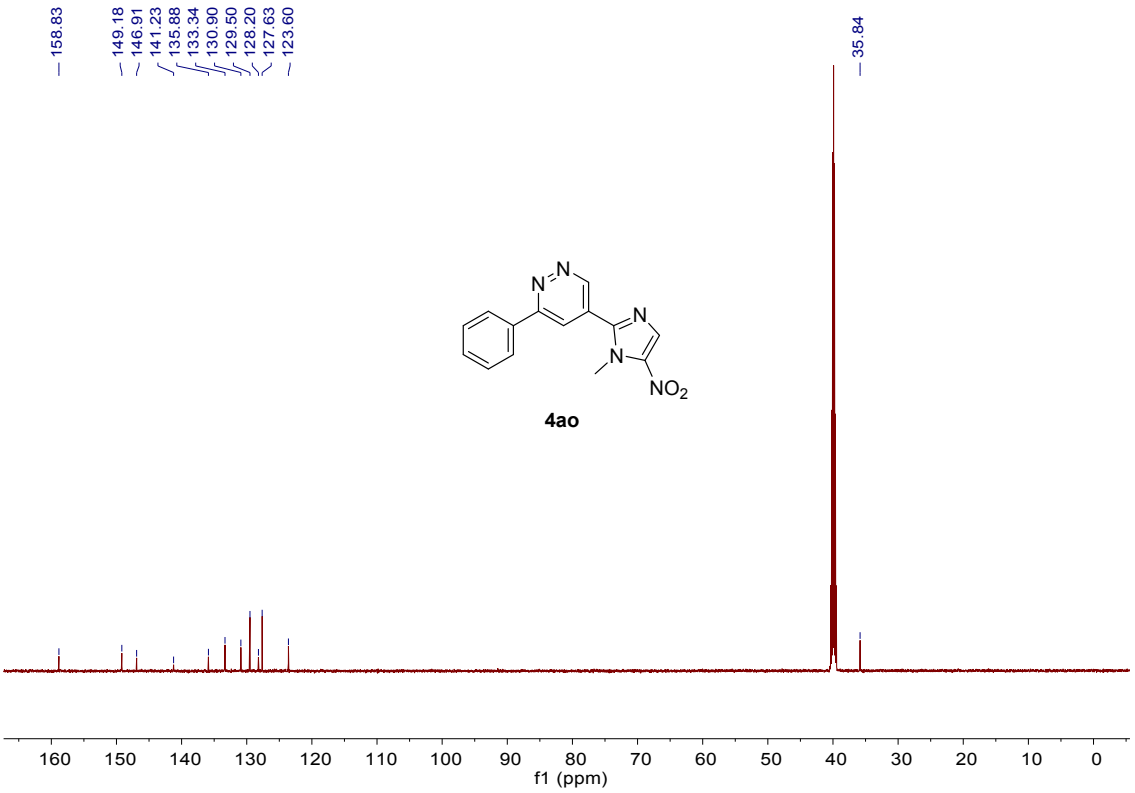

9.52
9.52
8.54
8.53
8.27
8.27
8.26
8.26
7.63
7.62
7.62
7.61
7.60
7.59
7.58
7.58
7.58
2.76
N
N
O
4an
0.92
1.00
1.99
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

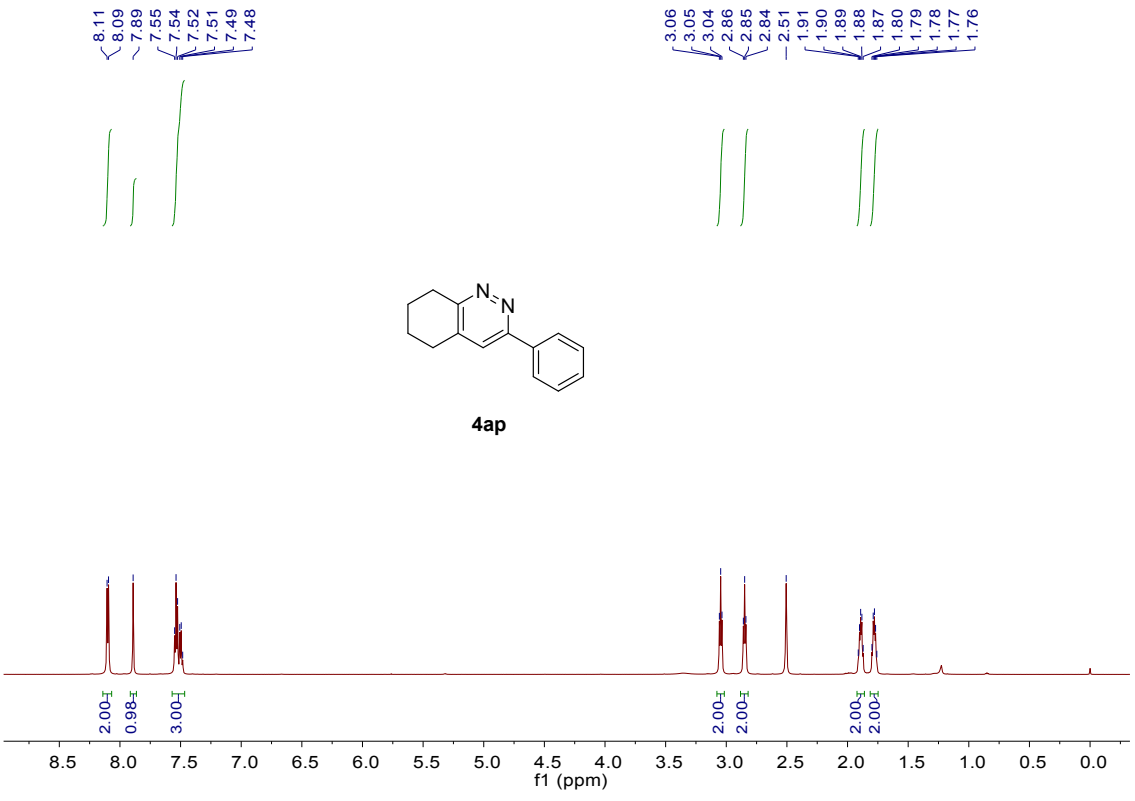

198.17
160.01
147.26
135.89
133.60
130.88
129.49
127.57
122.39
27.70
N
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

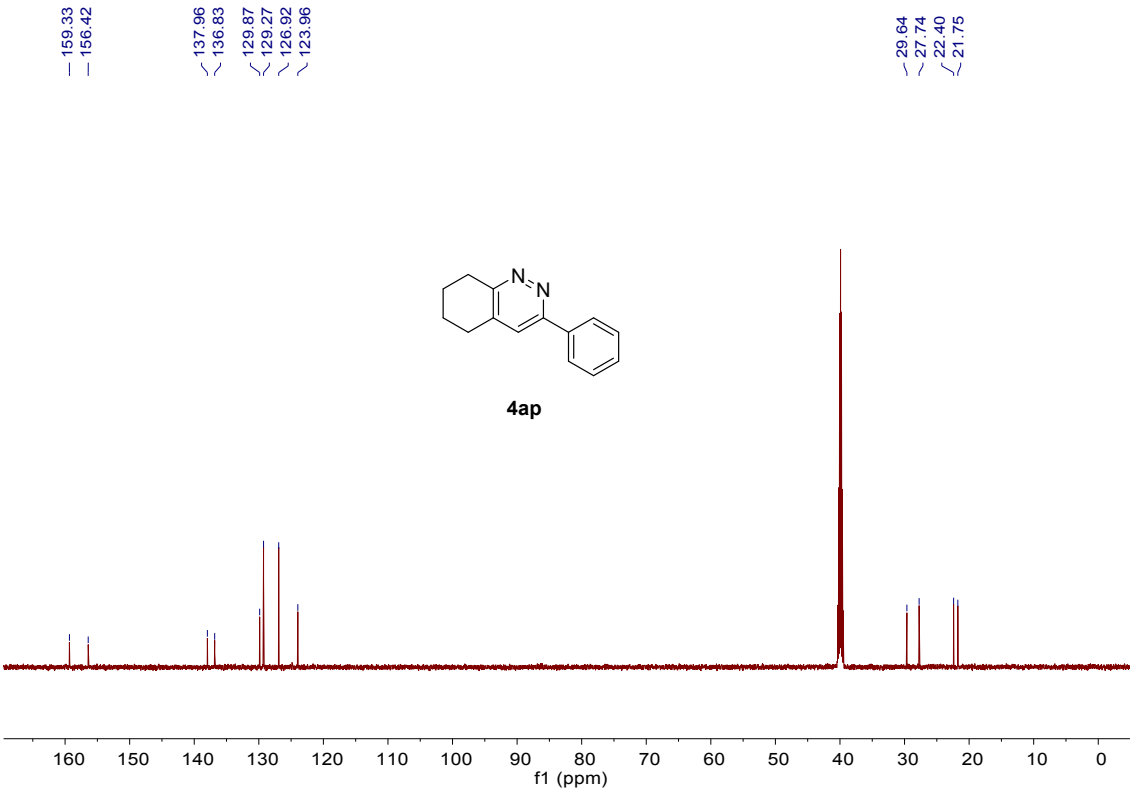
4an

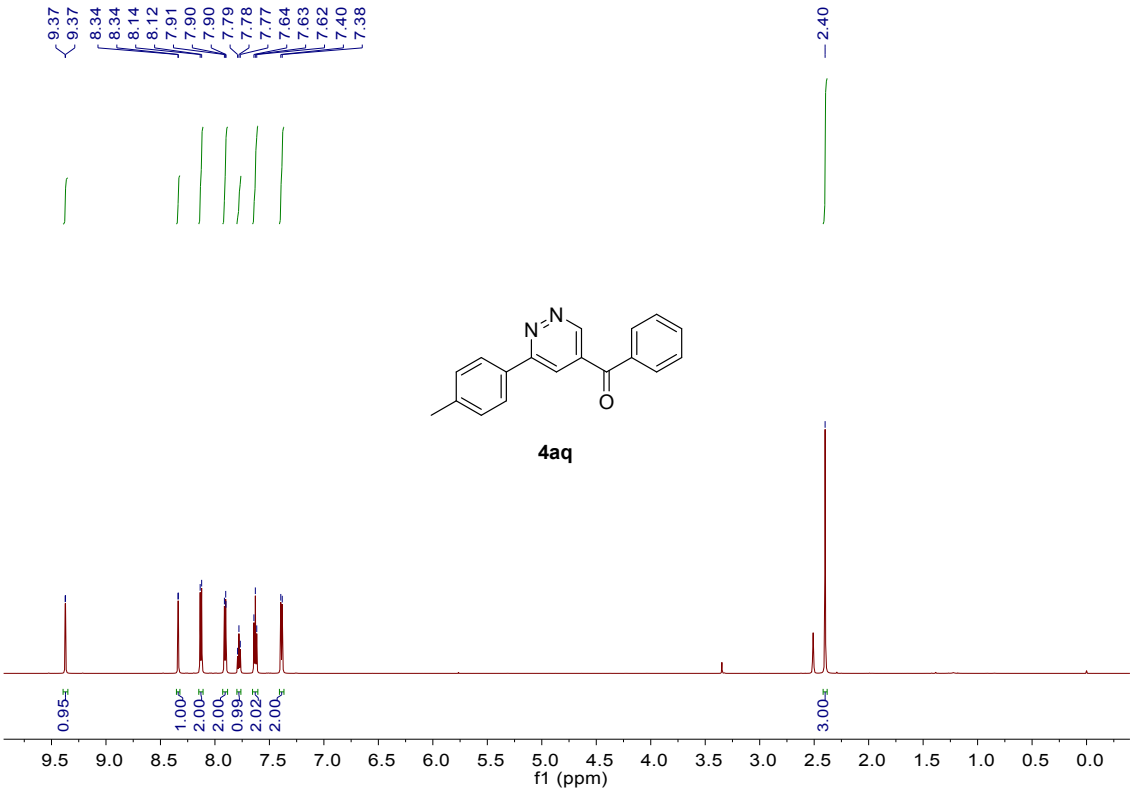

9.56
9.55
8.54
8.53
8.36
8.26
8.26
8.25
8.24
7.63
7.63
7.62
7.62
7.60
7.59
7.58
7.58
7.58
4.10
N
N
N
N
NO2
0.92
1.00
0.87
1.97
3.01
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

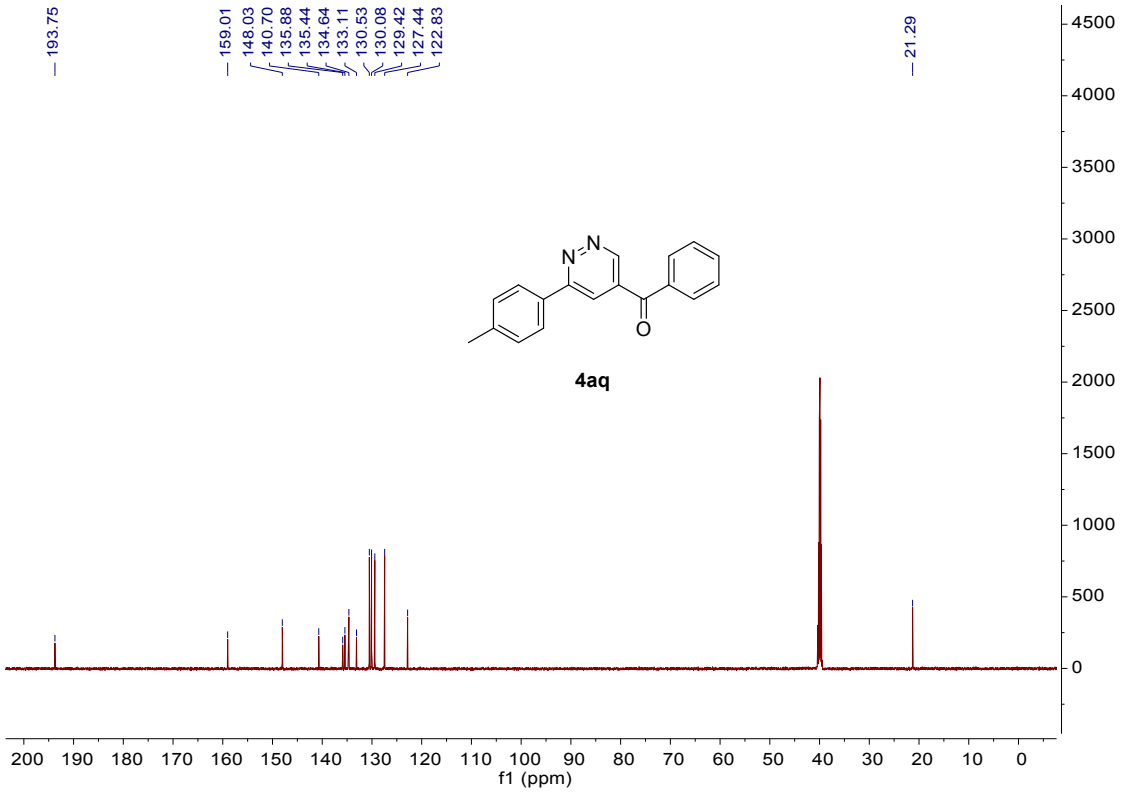
4ao


158.83
149.18
146.91
141.23
135.88
133.34
130.90
129.50
128.20
127.63
123.60
35.84
N
N
N
N
NO2
4ao
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

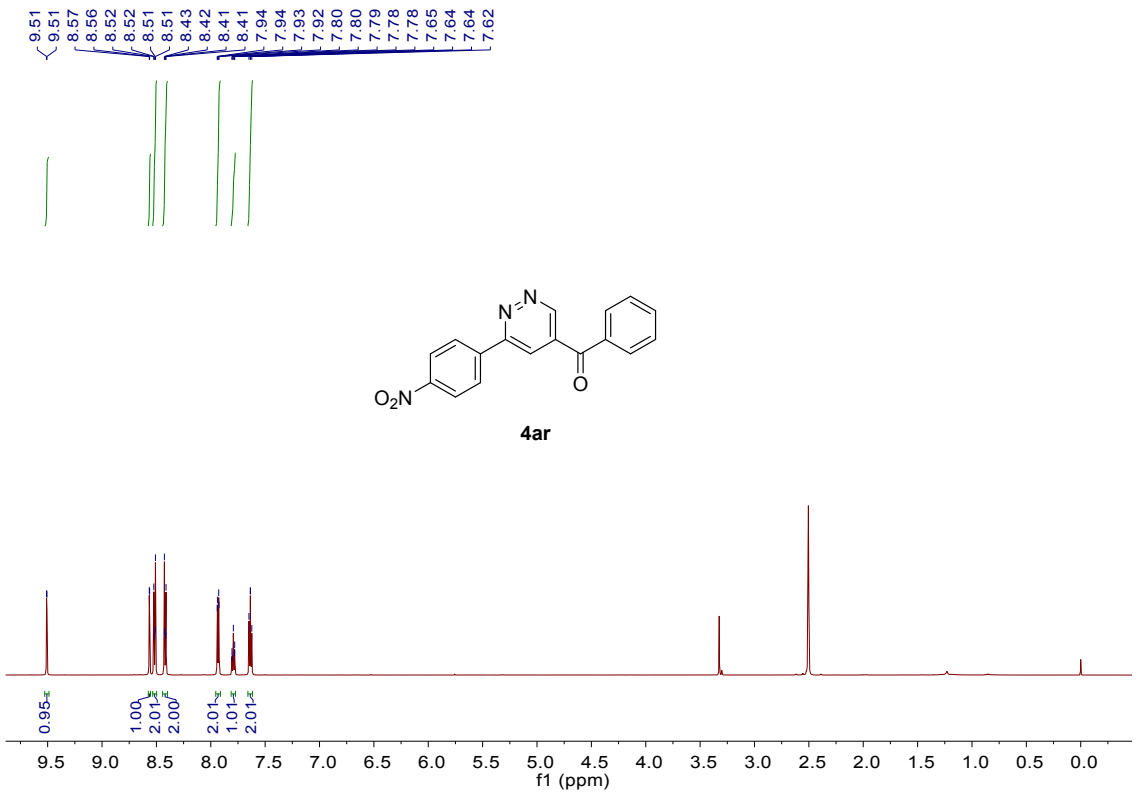

8.11
8.09
7.89
7.55
7.54
7.52
7.51
7.49
7.48
3.06
3.05
3.04
2.86
2.85
2.84
2.51
1.91
1.90
1.89
1.88
1.87
1.80
1.79
1.78
1.77
1.76
N
N
4ap
2.00
0.98
3.00
2.00
2.00
2.00
2.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


159.33
156.42
137.96
136.83
129.87
129.27
126.92
123.96
29.64
27.74
22.40
21.75
4ap
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

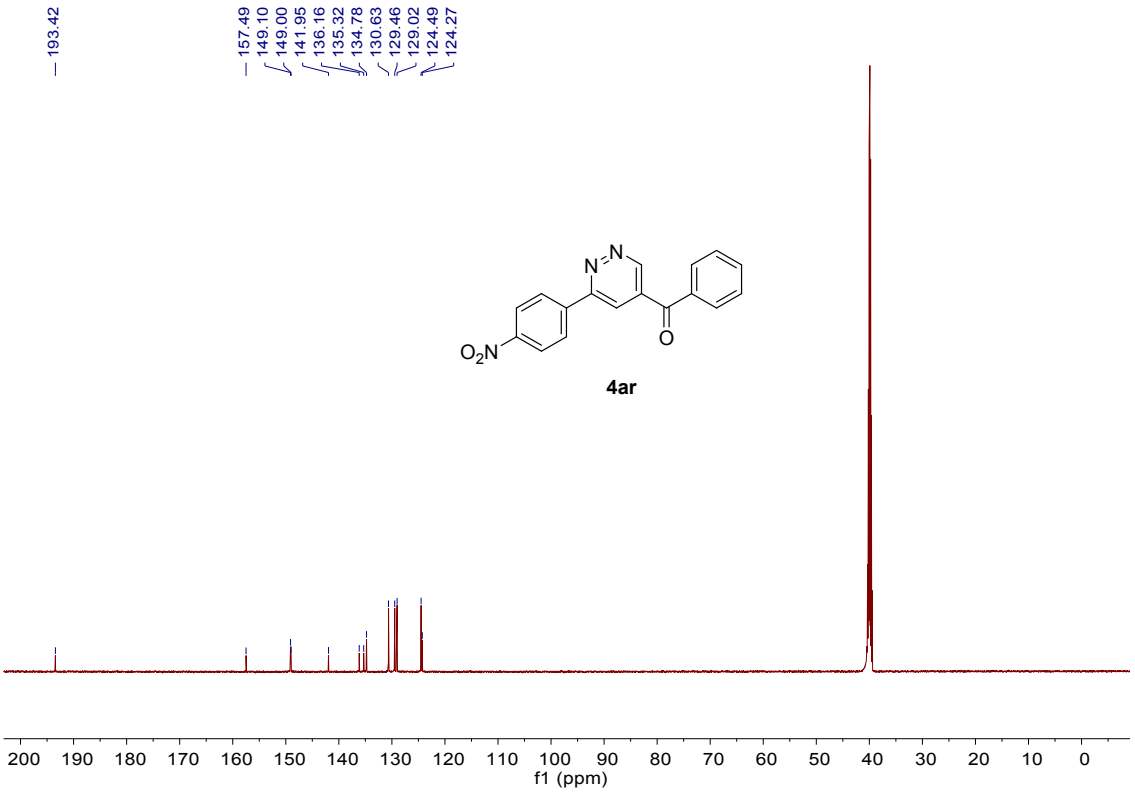

9.37
9.37
8.34
8.34
8.14
8.12
7.91
7.90
7.90
7.79
7.78
7.77
7.64
7.63
7.62
7.40
7.38
2.40
4aq
0.95
1.00
2.00
2.00
0.99
2.02
2.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


193.75
159.01
148.03
140.70
135.88
135.44
134.64
133.11
130.53
130.08
129.42
127.44
122.83
21.29
4500
4000
3500
3000
2500
2000
1500
1000
500
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

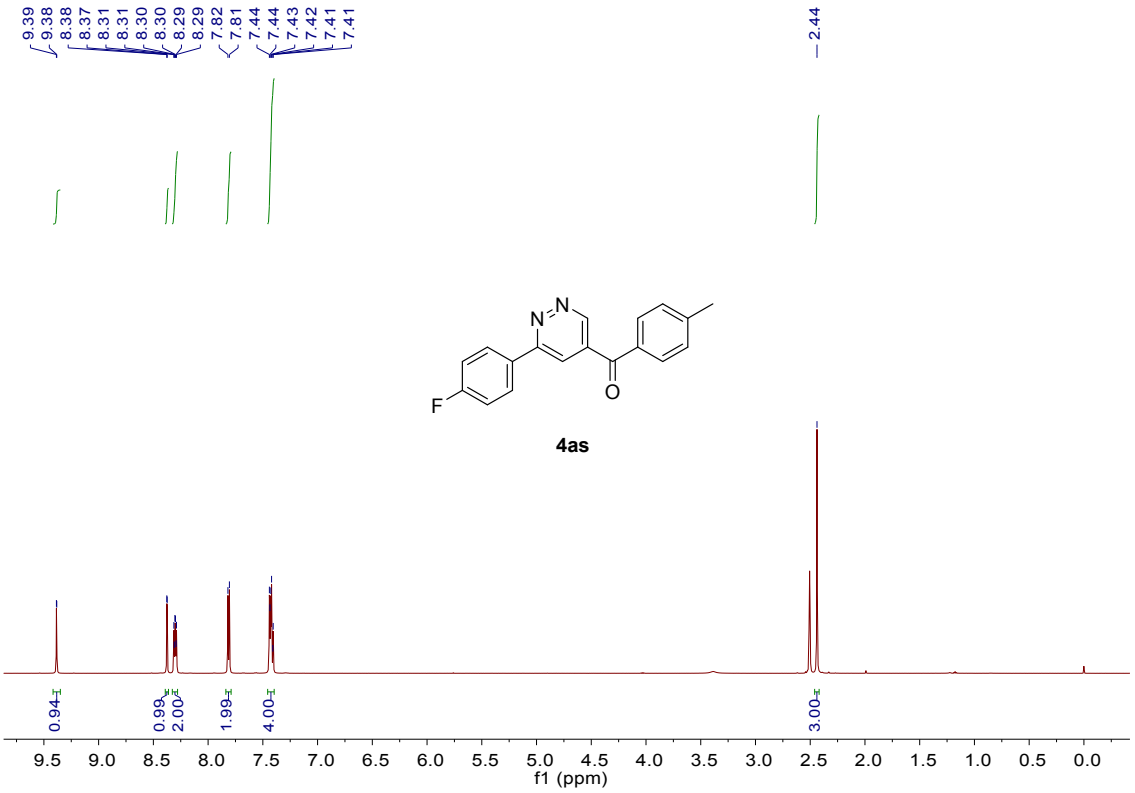
4aq


9.51
9.51
8.57
8.56
8.52
8.52
8.51
8.51
8.43
8.42
8.41
8.41
7.94
7.94
7.93
7.92
7.80
7.80
7.79
7.78
7.78
7.65
7.64
7.64
7.62
0.95
1.00
2.01
2.00
2.01
1.01
2.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

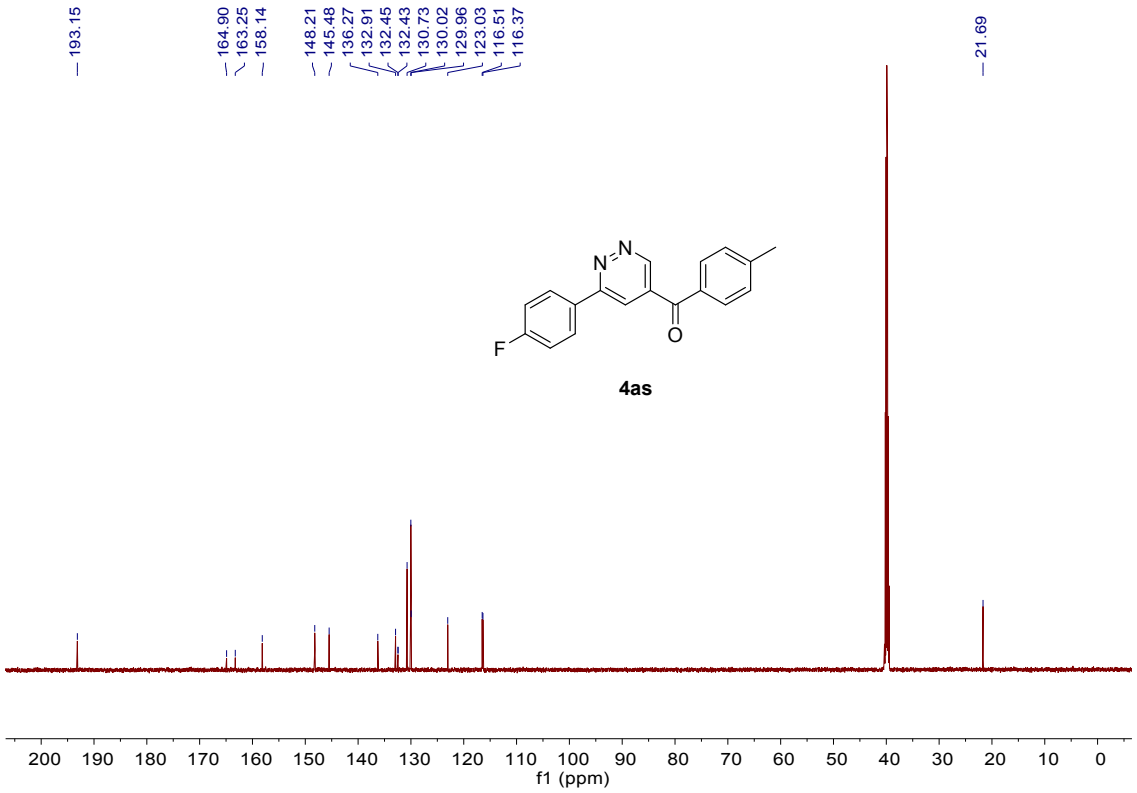
4ar


193.42
157.49
149.10
149.00
141.95
136.16
135.32
134.78
130.63
129.46
129.02
124.49
124.27
N
N
O
O2N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

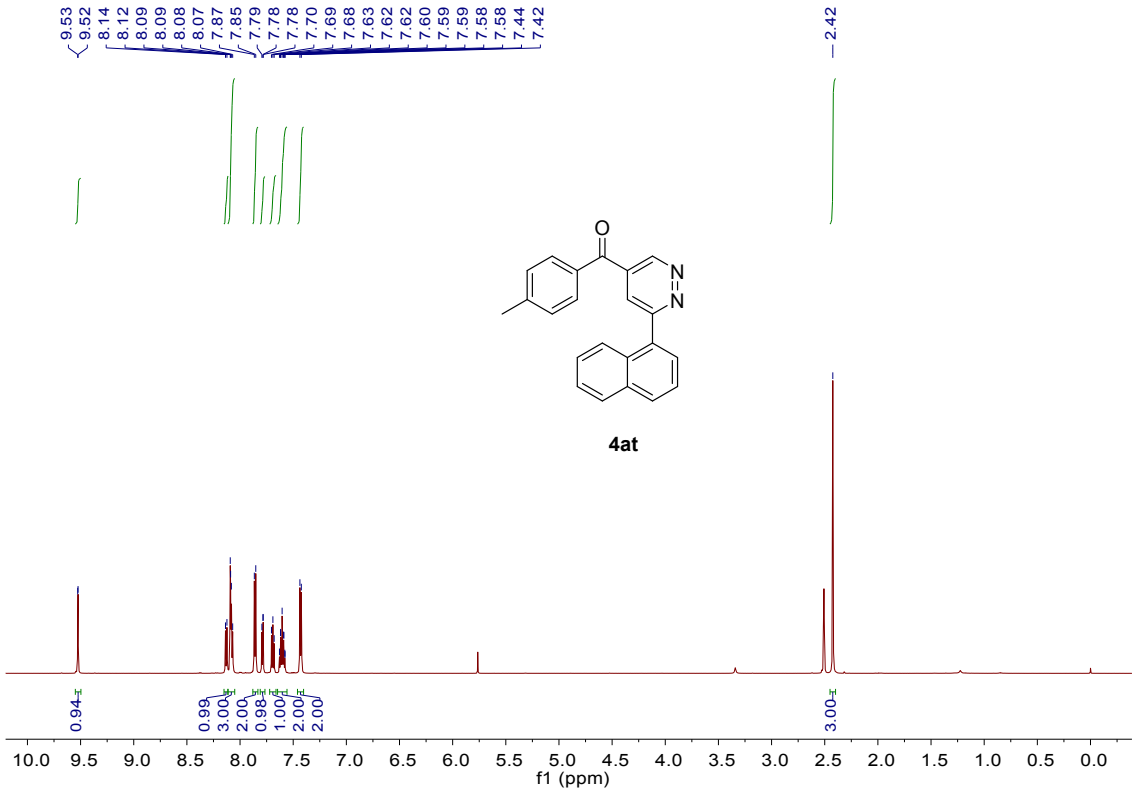
4ar


9.39
9.38
8.38
8.37
8.31
8.31
8.31
8.30
8.30
8.29
8.29
7.82
7.81
7.44
7.44
7.43
7.42
7.41
7.41
2.44
N
N
O
F
0.94
0.99
2.00
1.99
4.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

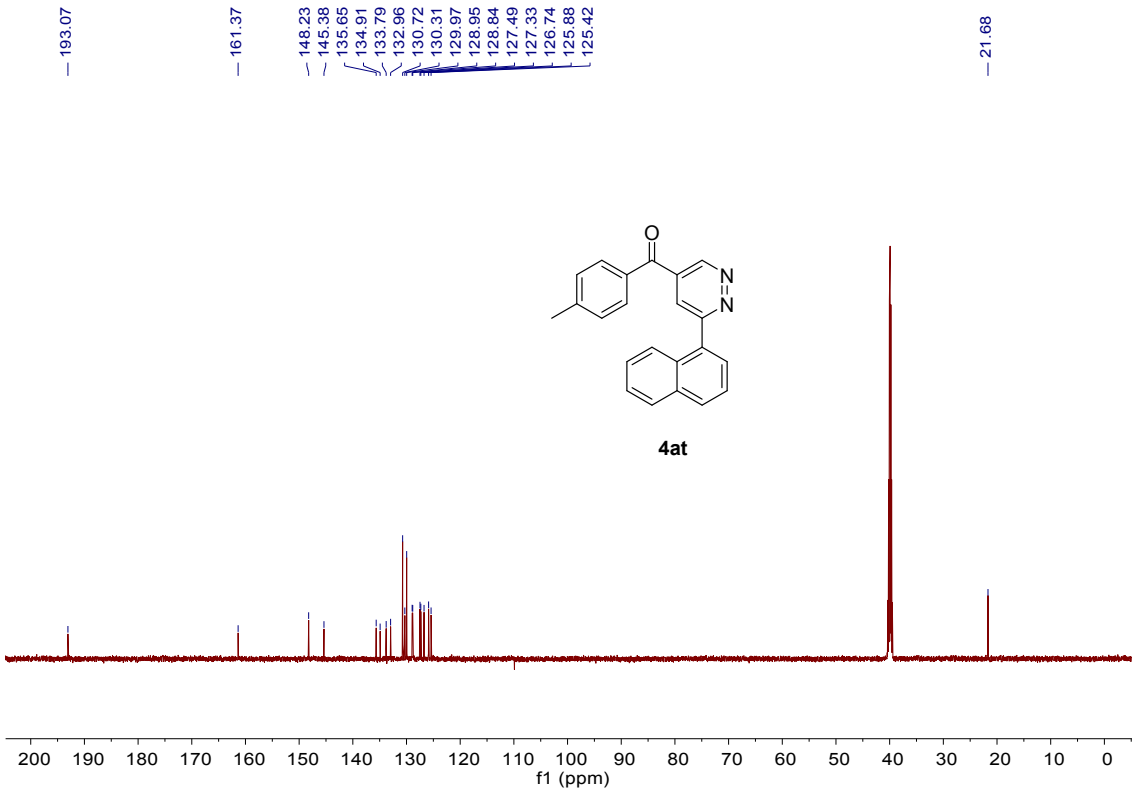
4as


193.15
164.90
163.25
158.14
148.21
145.48
136.27
132.91
132.45
132.43
130.73
130.02
129.96
123.03
116.51
116.37
21.69
F
O
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

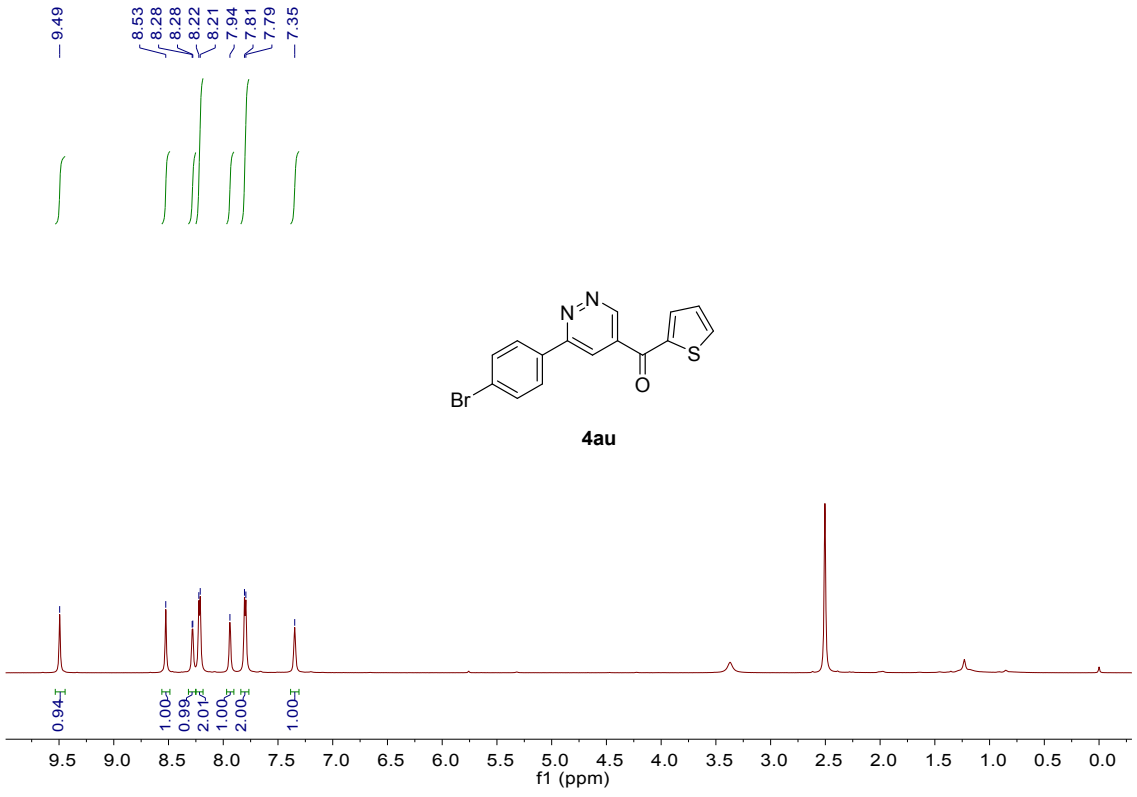
4as


9.53
9.52
8.14
8.12
8.09
8.09
8.08
8.08
8.07
7.87
7.85
7.79
7.78
7.78
7.70
7.69
7.68
7.63
7.62
7.62
7.60
7.59
7.59
7.58
7.58
7.44
7.42
2.42
O
N
N
0.94
0.99
3.00
2.00
0.98
1.00
2.00
2.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

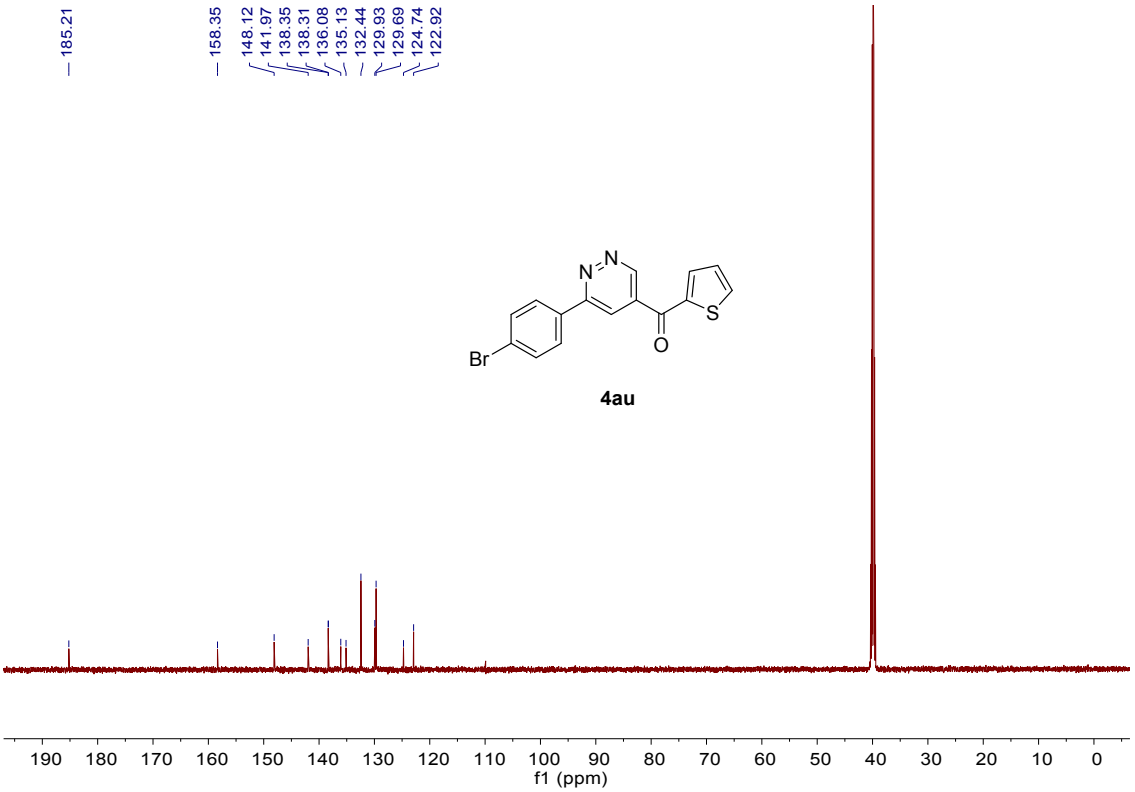
4at


193.07
161.37
148.23
145.38
135.65
134.91
133.79
132.96
130.72
130.31
129.97
128.95
128.84
127.49
127.33
126.74
125.88
125.42
21.68
O
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

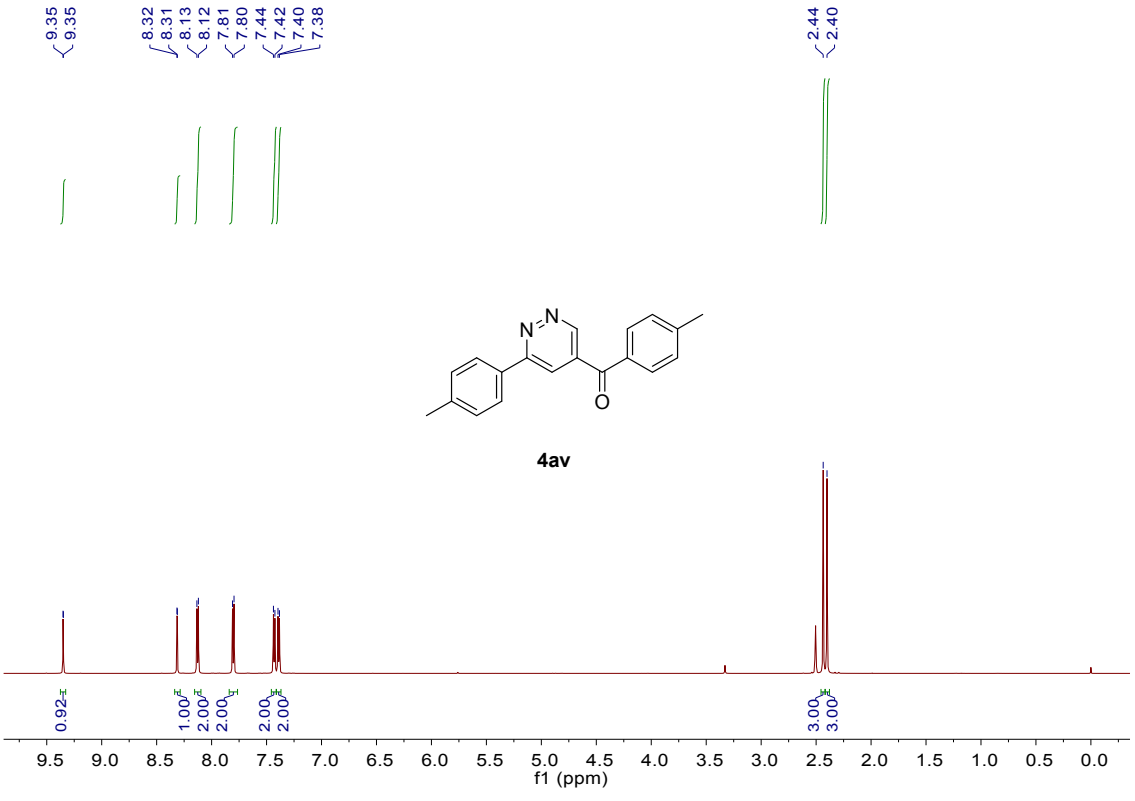
4at


9.49
8.53
8.28
8.28
8.22
8.21
7.94
7.81
7.79
7.35
N
N
S
O
Br
0.94
1.00
0.99
2.01
1.00
2.00
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

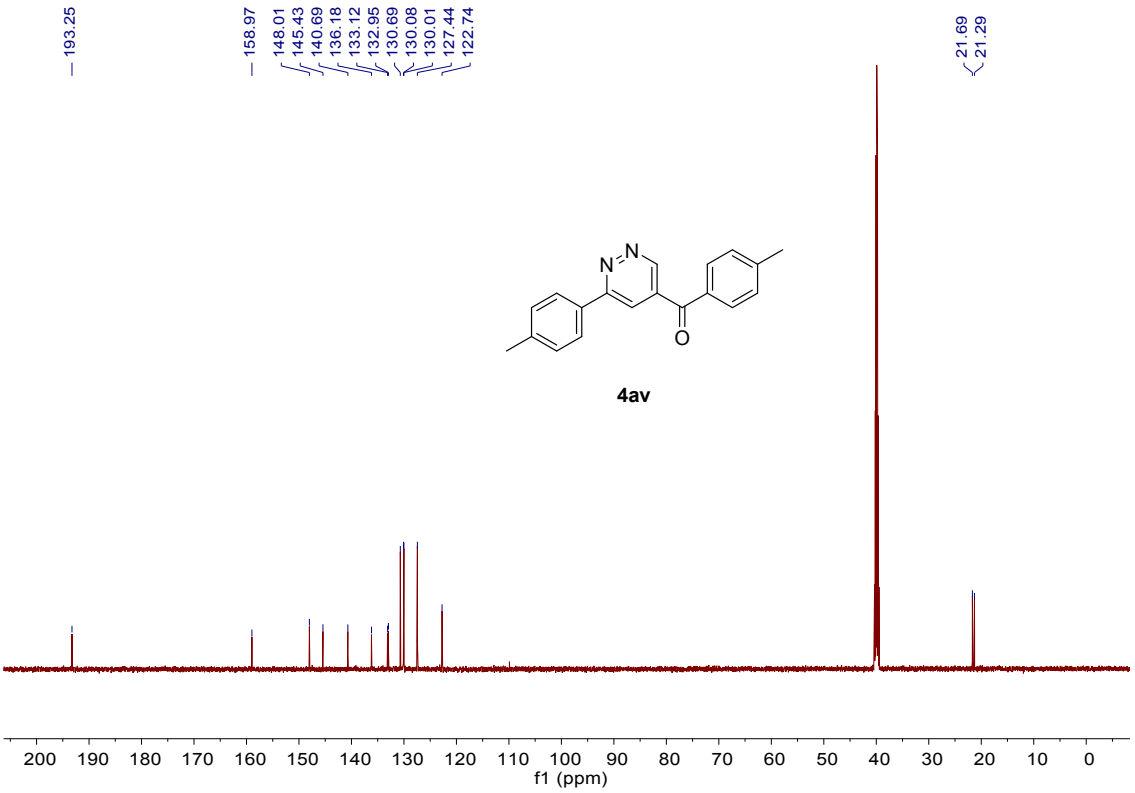
4au


185.21
158.35
148.12
141.97
138.35
138.31
136.08
135.13
132.44
129.93
129.69
124.74
122.92
N
N
S
O
Br
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

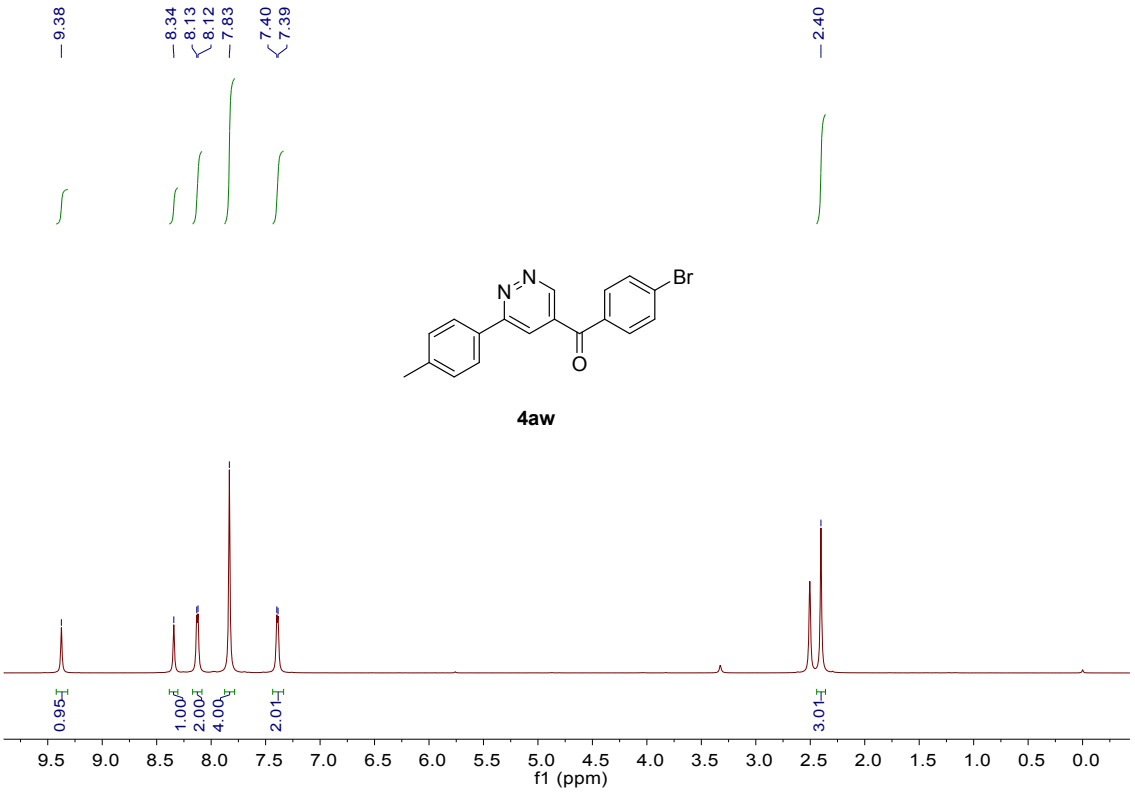
4au


9.35
9.35
8.32
8.31
8.13
8.12
7.81
7.80
7.44
7.42
7.40
7.38
2.44
2.40
N
N
O
0.92
1.00
2.00
2.00
2.00
2.00
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

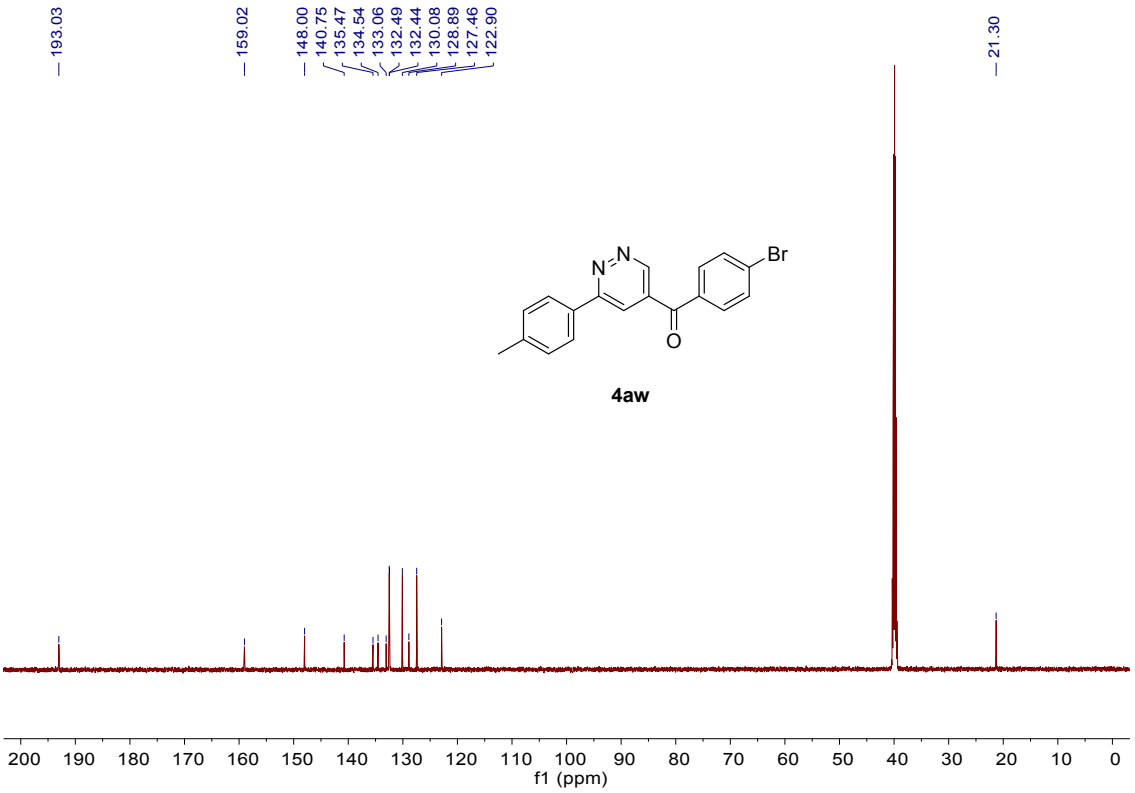
4av

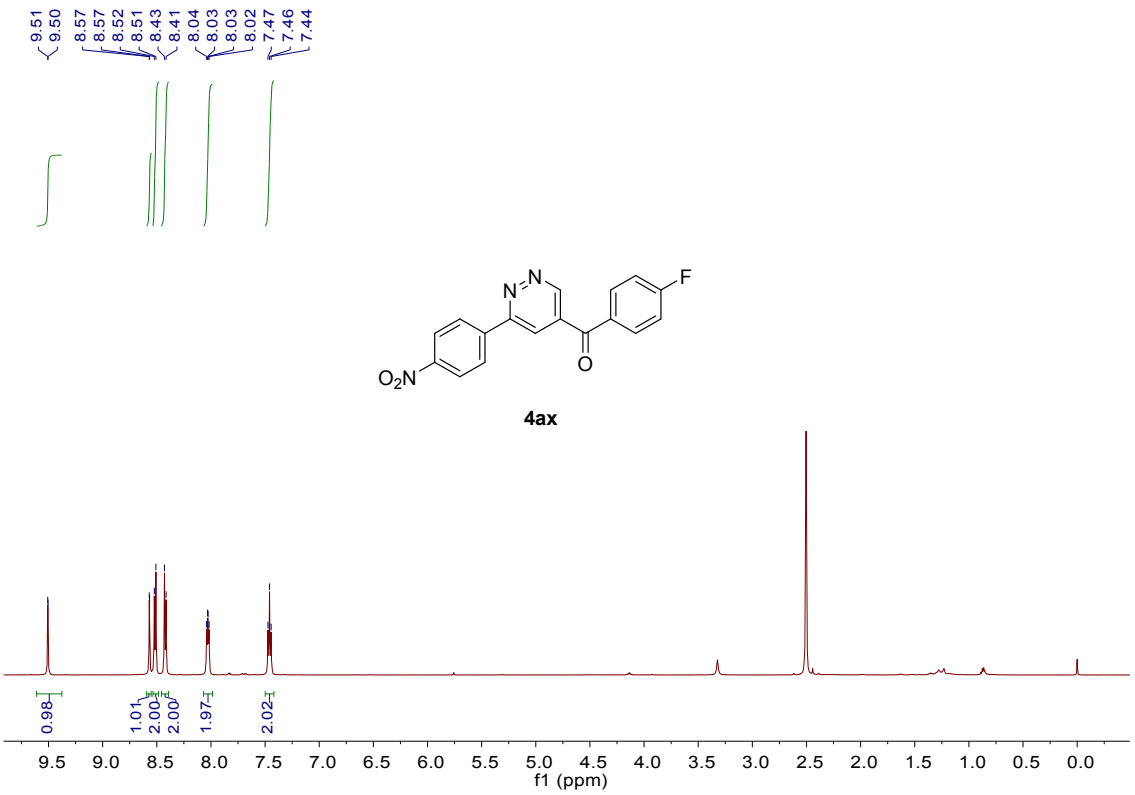

193.25
158.97
148.01
145.43
140.69
136.18
133.12
132.95
130.69
130.08
130.01
127.44
122.74
21.69
21.29
N
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

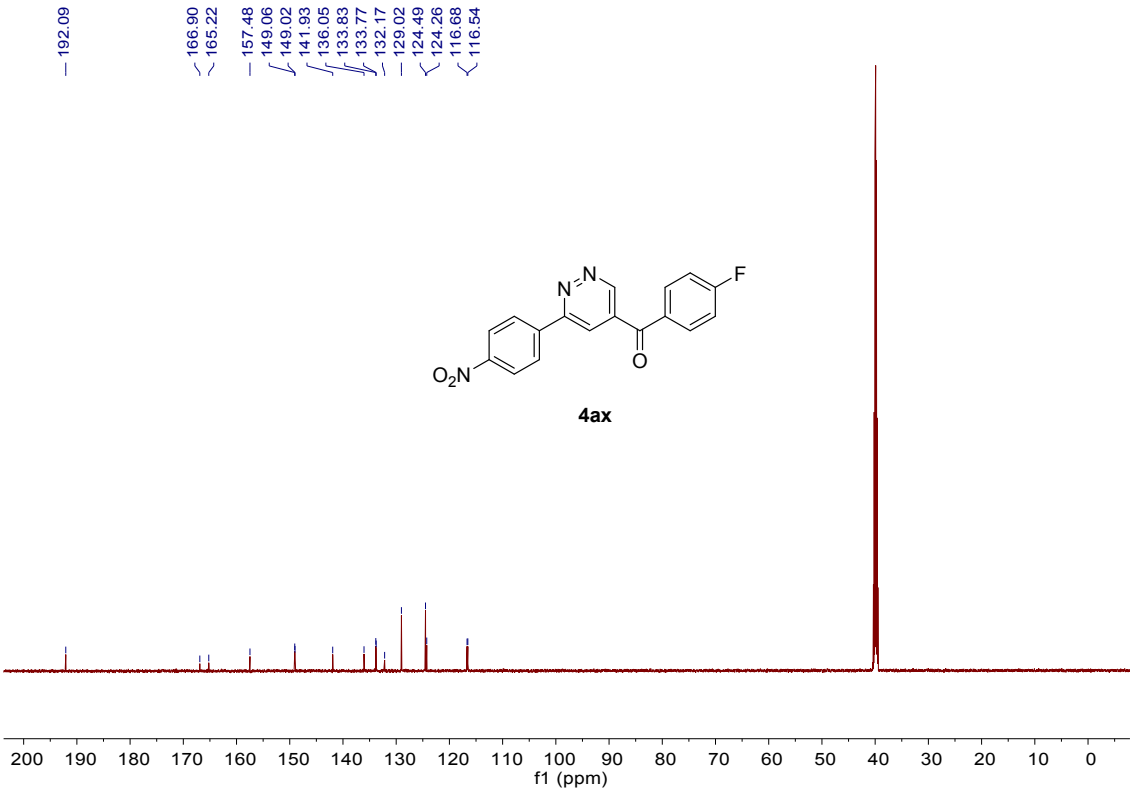
4av


9.38
8.34
8.13
8.12
7.83
7.40
7.39
2.40
N
N
Br
O
0.95
1.00
2.00
4.00
2.01
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

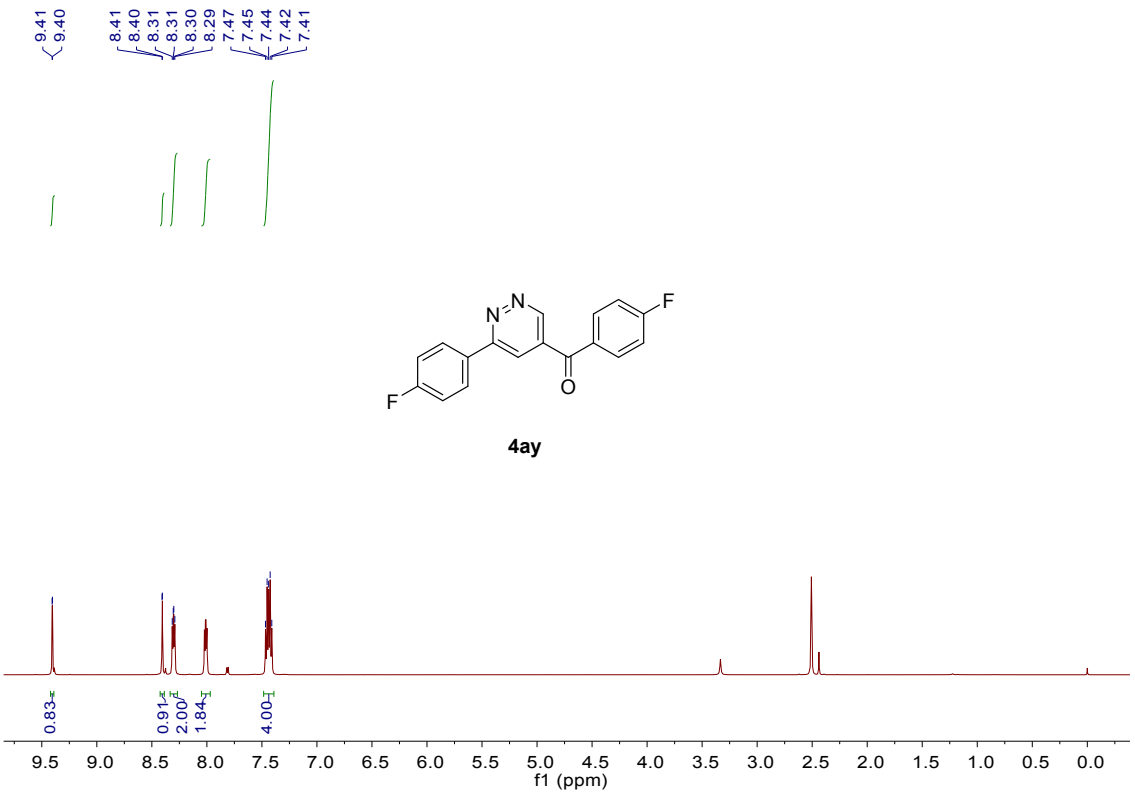
4aw


193.03
159.02
148.00
140.75
135.47
134.54
133.06
132.49
132.44
130.08
128.89
127.46
122.90
21.30
Br
O
4aw
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

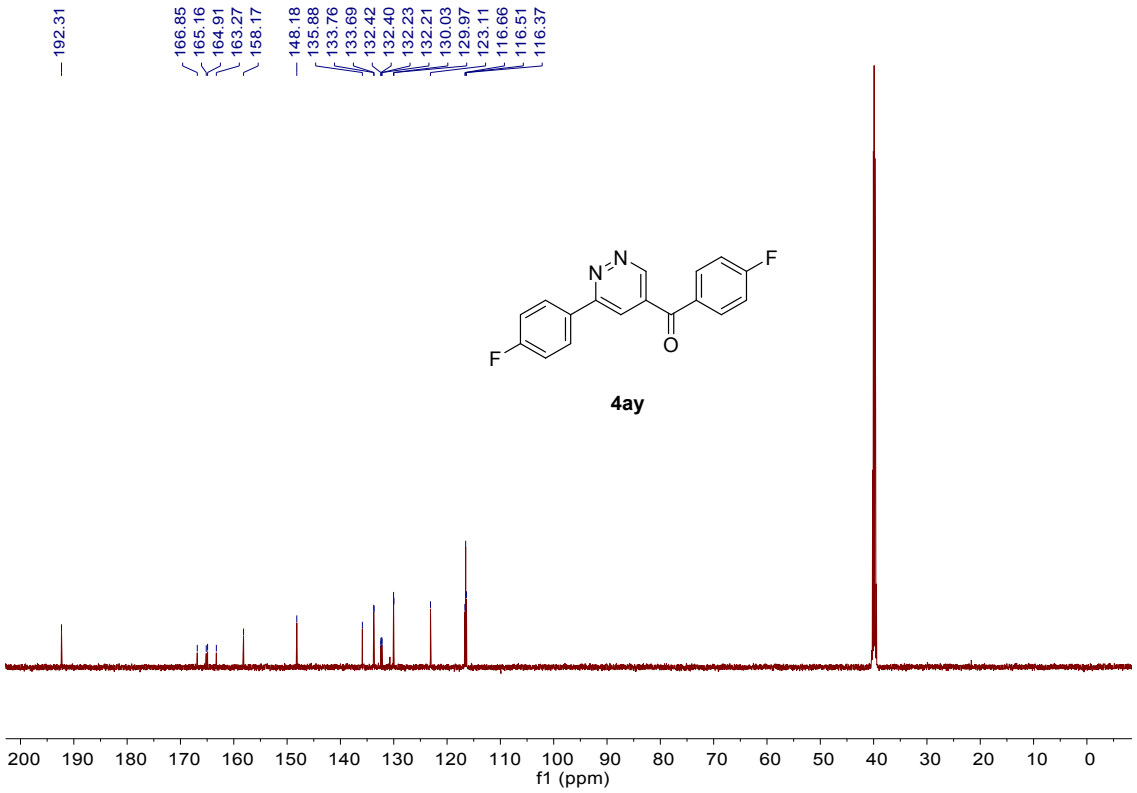

9.51
9.50
8.57
8.57
8.52
8.51
8.43
8.41
8.04
8.03
8.03
8.02
7.47
7.46
7.44
F
O
O2N
4ax
0.98
1.01
2.00
2.00
1.97
2.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


192.09
166.90
165.22
157.48
149.06
149.02
141.93
136.05
133.83
133.77
132.17
129.02
124.49
124.26
116.68
116.54
F
O
N
N
O2N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

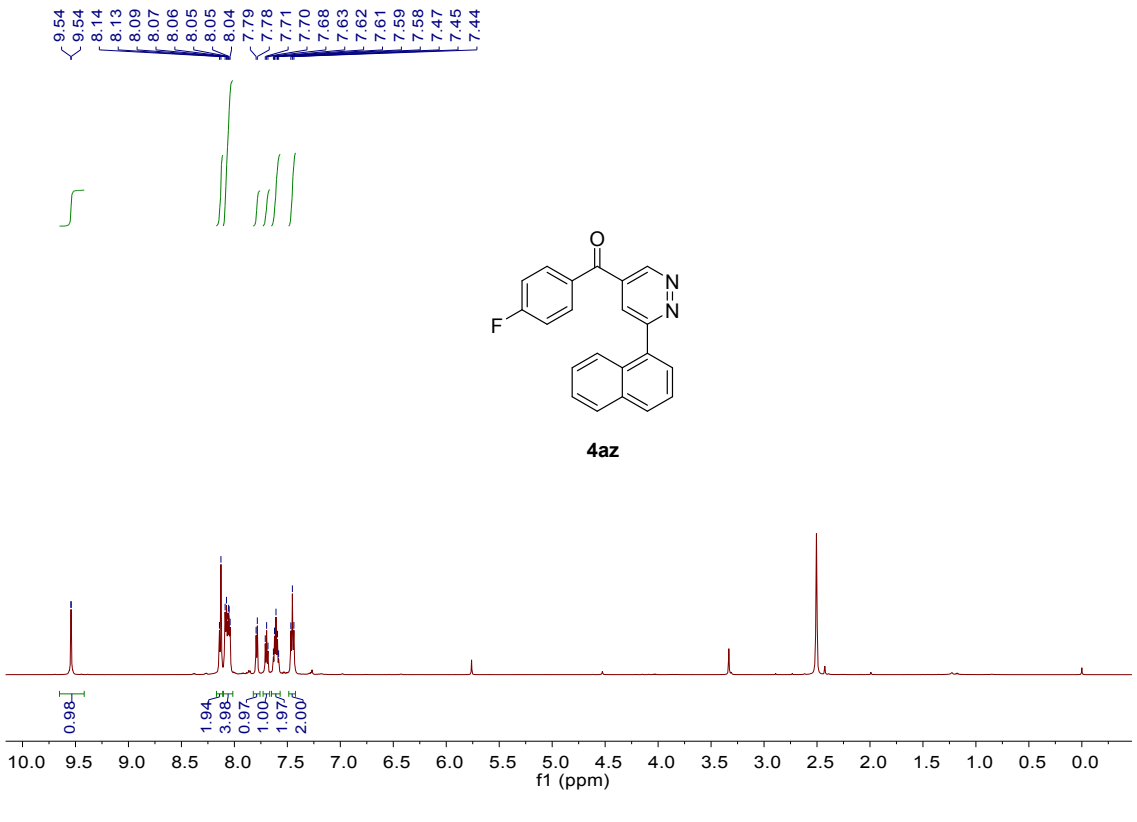
4ax


9.41
9.40
8.41
8.40
8.31
8.31
8.30
8.29
7.47
7.45
7.44
7.42
7.41
F
O
N
N
F
0.83
0.91
2.00
1.84
4.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

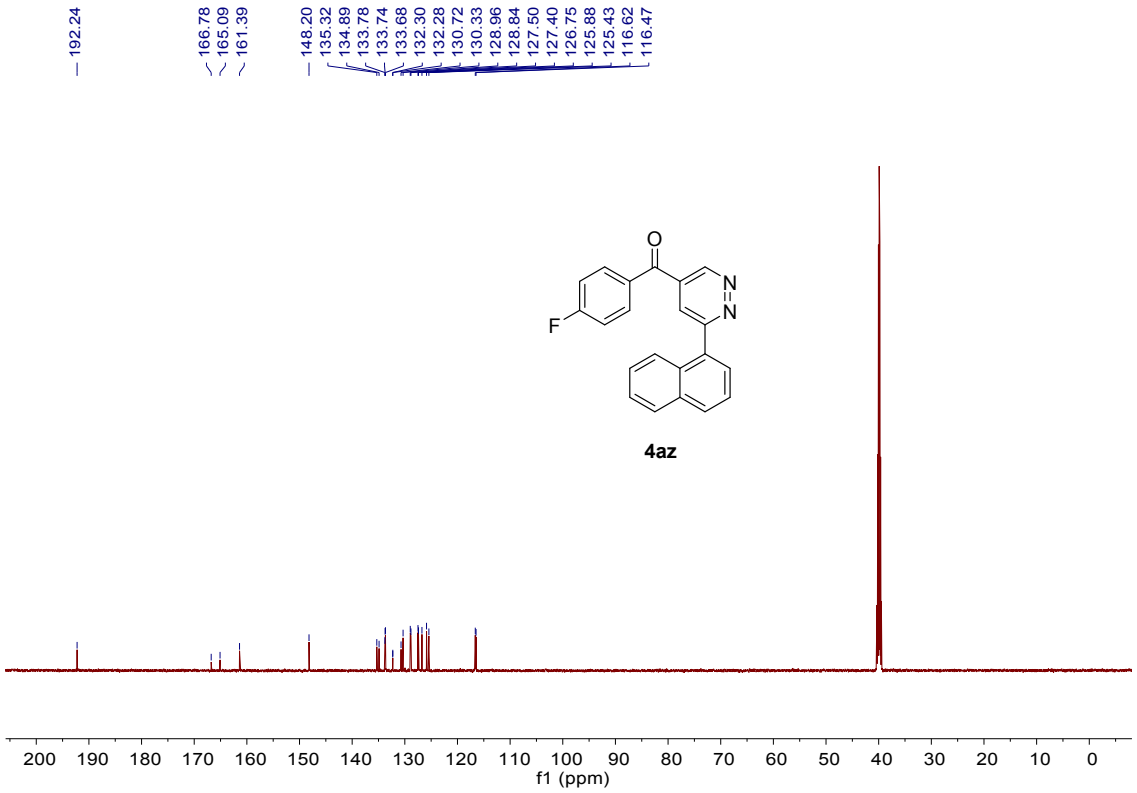
4ay


192.31
166.85
165.16
164.91
163.27
158.17
148.18
135.88
133.76
133.69
132.42
132.40
132.23
132.21
130.03
129.97
123.11
116.66
116.51
116.37
N
N
F
F
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

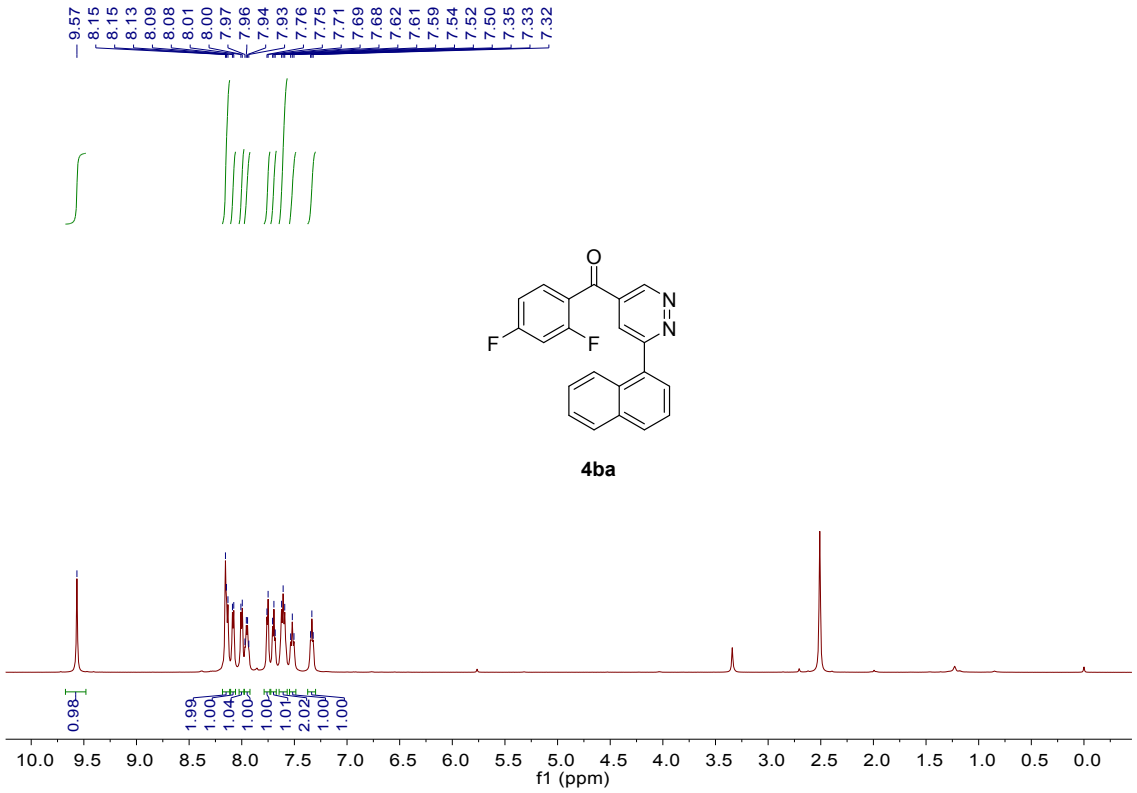
4ay


9.54
9.54
8.14
8.13
8.09
8.07
8.06
8.05
8.05
8.04
7.79
7.78
7.71
7.70
7.68
7.63
7.62
7.61
7.59
7.58
7.47
7.45
7.44
O
F
N
N
0.98
1.94
3.98
0.97
1.00
1.97
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

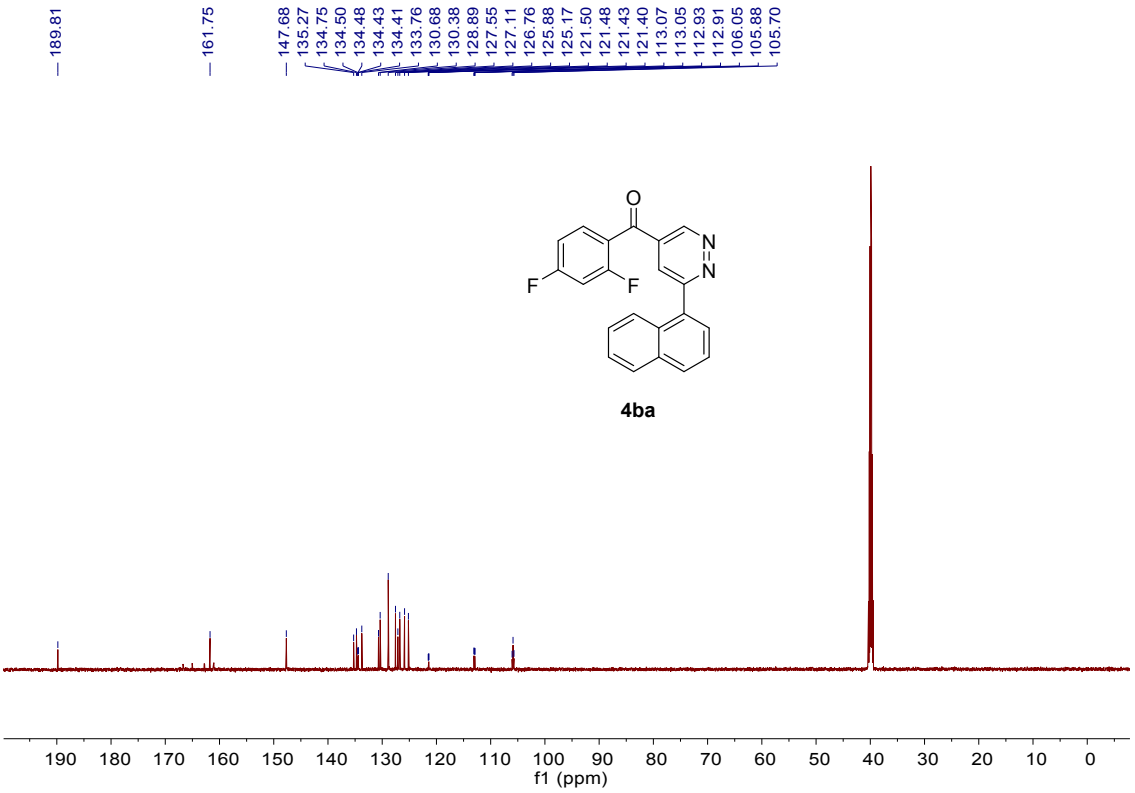
4az


192.24
166.78
165.09
161.39
148.20
135.32
134.89
133.78
133.74
133.68
132.30
132.28
130.72
130.33
128.96
128.84
127.50
127.40
126.75
125.88
125.43
116.62
116.47
O
F
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

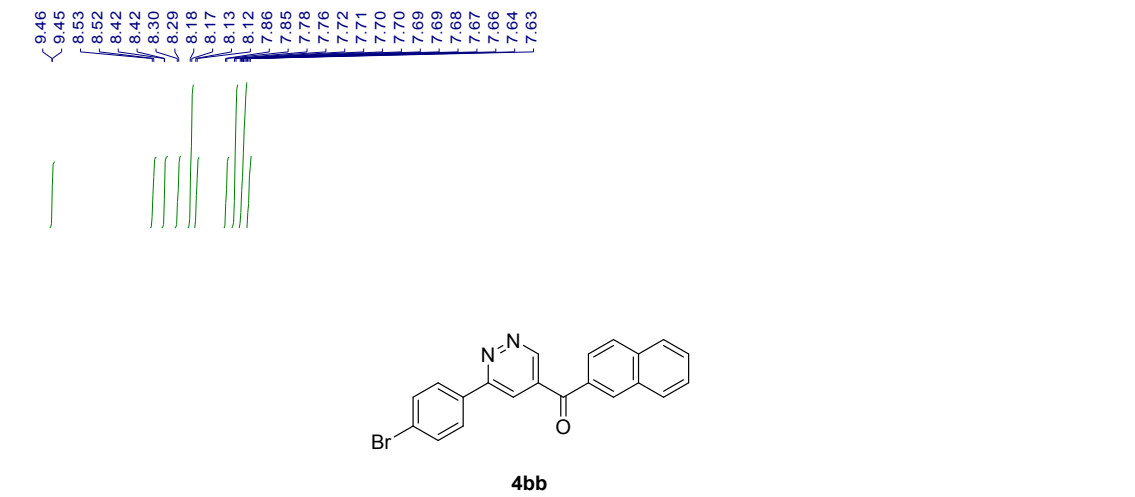
4az


9.57
8.15
8.15
8.13
8.09
8.08
8.01
8.00
7.97
7.96
7.94
7.93
7.76
7.75
7.71
7.69
7.68
7.62
7.61
7.59
7.54
7.52
7.50
7.35
7.33
7.32
O
F
F
N
N
0.98
1.99
1.00
1.04
1.00
1.00
1.01
2.02
1.00
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

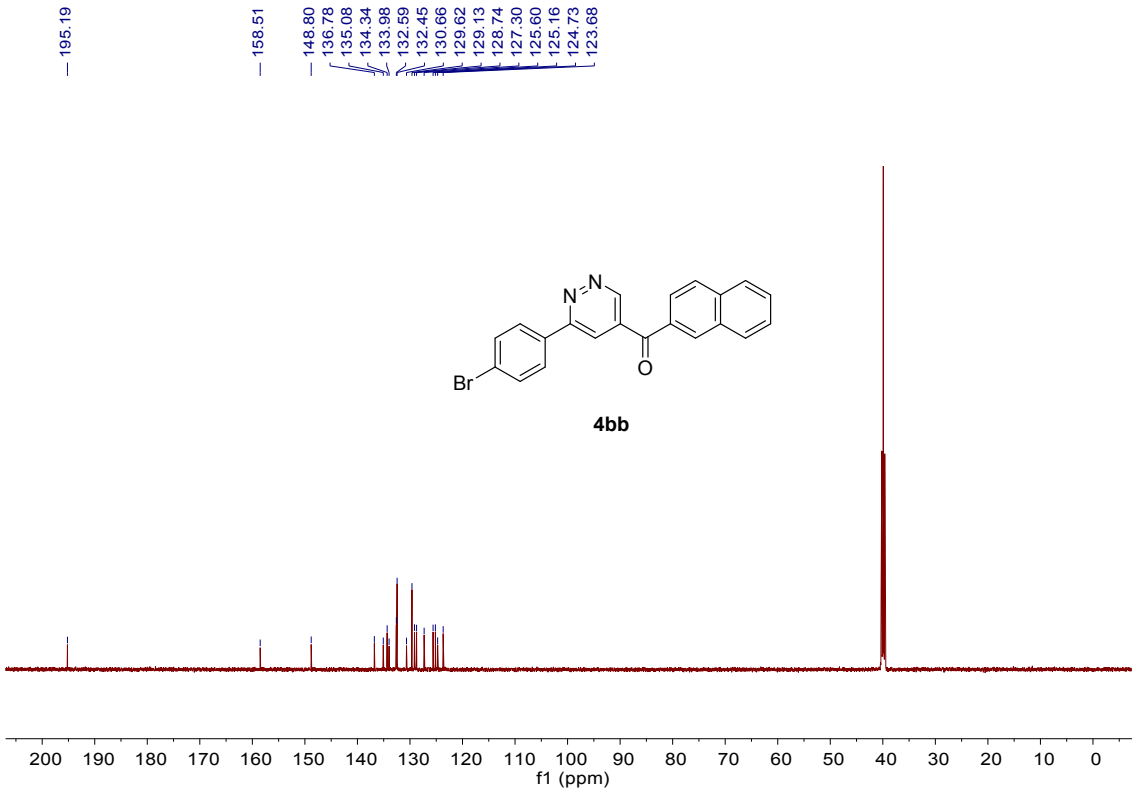
4ba


189.81
161.75
147.68
135.27
134.75
134.50
134.48
134.43
134.41
133.76
130.68
130.38
128.89
127.55
127.11
126.76
125.88
125.17
121.50
121.48
121.43
121.40
113.07
113.05
112.93
112.91
106.05
105.88
105.70
O
F
F
N
N
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

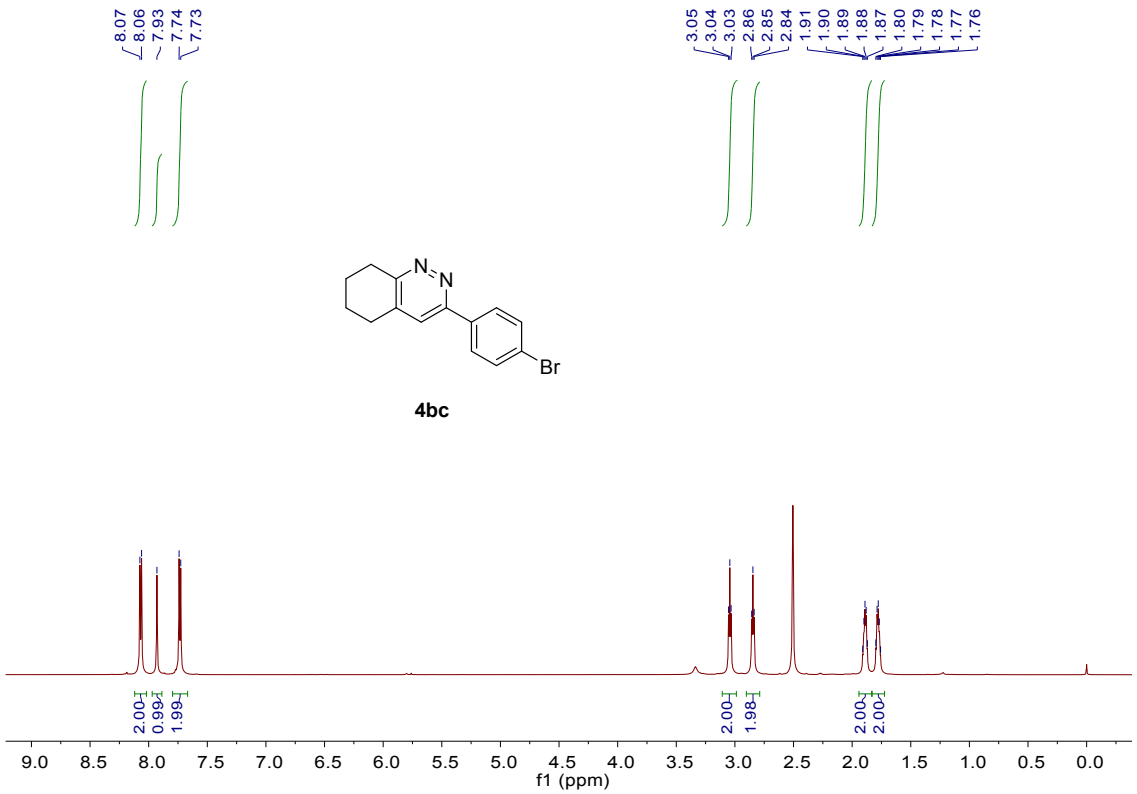
4ba


9.46
9.45
8.53
8.52
8.42
8.42
8.42
8.30
8.29
8.18
8.17
8.13
8.12
7.86
7.85
7.78
7.76
7.72
7.71
7.70
7.70
7.69
7.69
7.68
7.67
7.66
7.64
7.63
N
N
Br
O
0.93
0.99
1.00
1.01
2.00
0.99
0.99
2.00
2.03
1.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

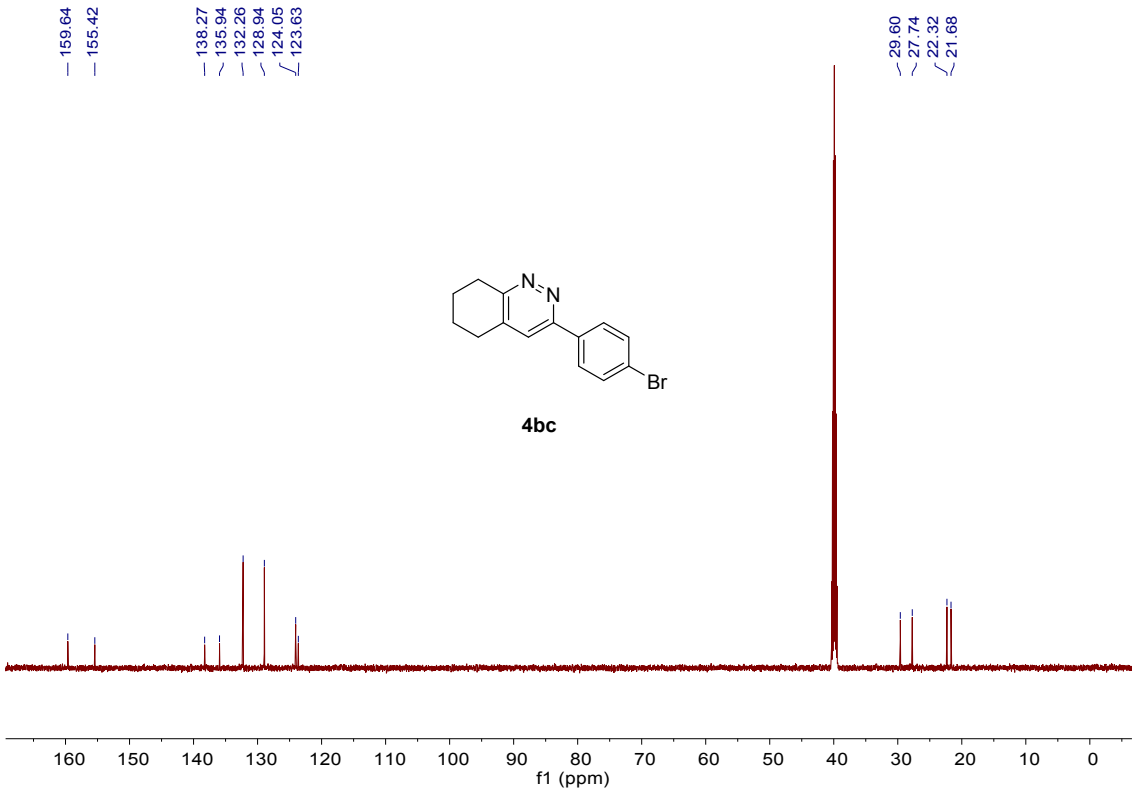
4bb


195.19
158.51
148.80
136.78
135.08
134.34
133.98
132.59
132.45
130.66
129.62
129.13
128.74
127.30
125.60
125.16
124.73
123.68
N
N
Br
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

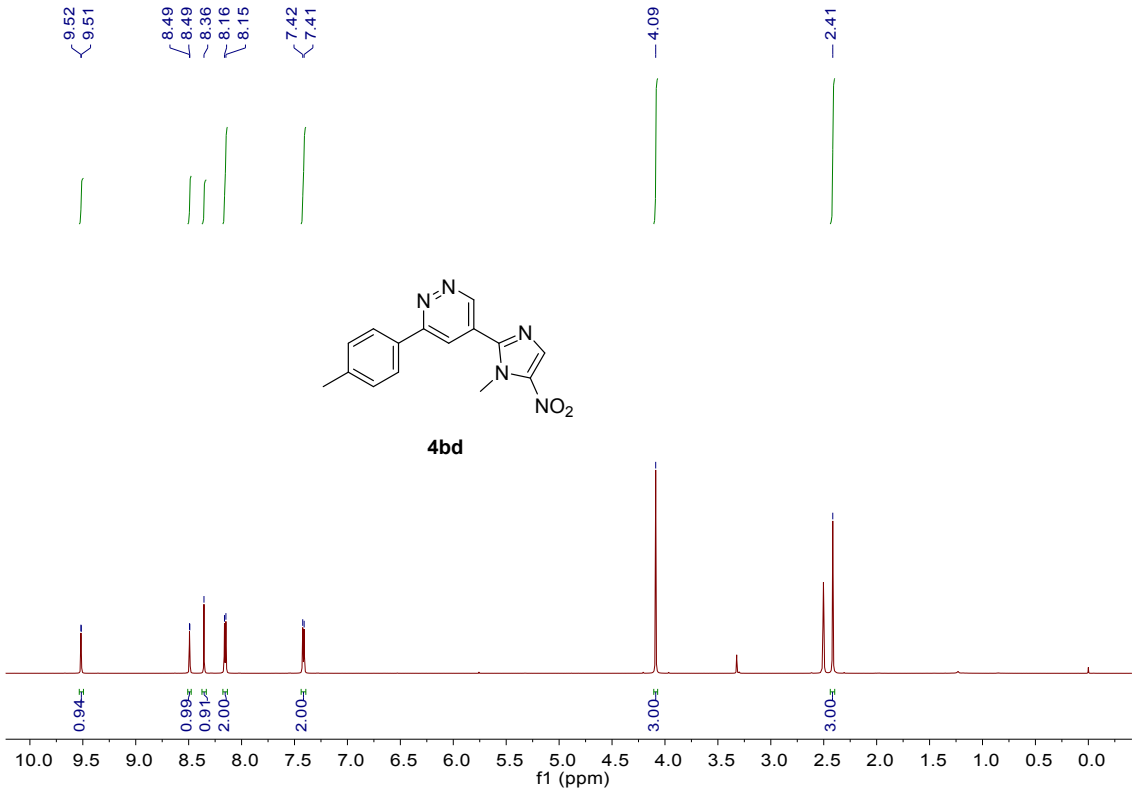
4bb


8.07
8.06
7.93
7.74
7.73
3.05
3.04
3.03
2.86
2.85
2.84
1.91
1.90
1.89
1.88
1.87
1.80
1.79
1.78
1.77
1.76
N
N
Br
2.00
0.99
1.99
2.00
1.98
2.00
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

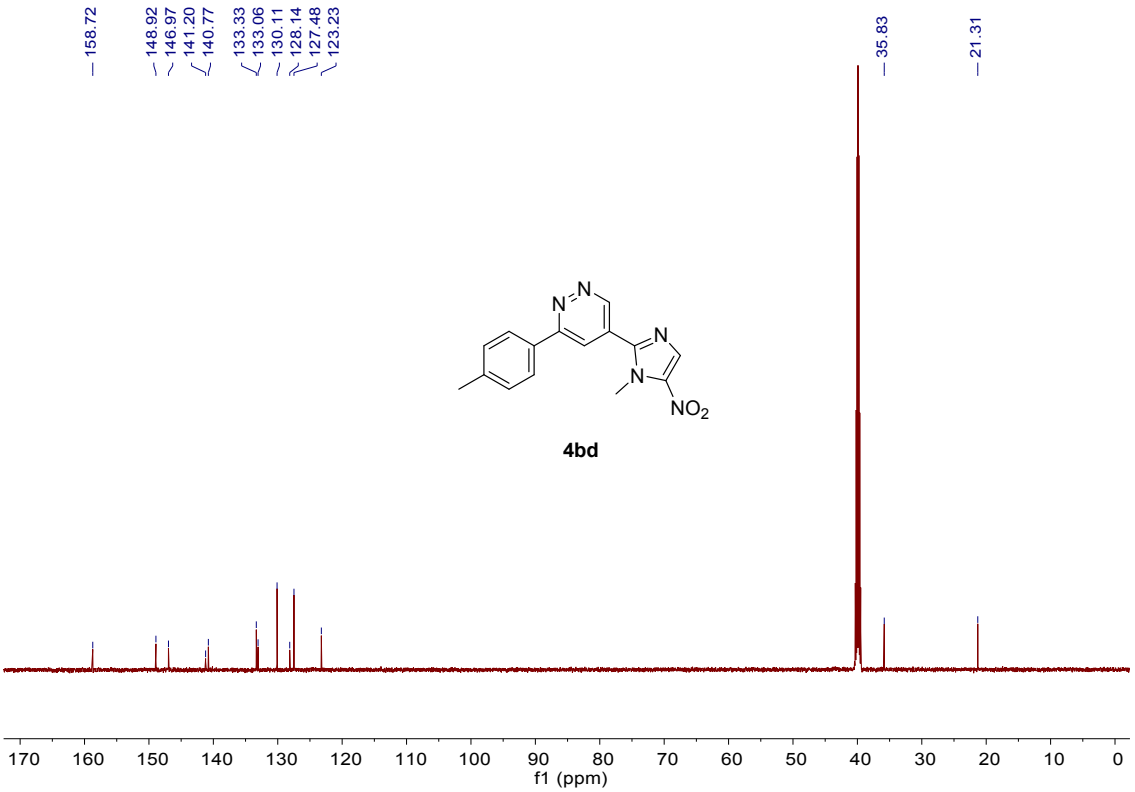
4bc


159.64
155.42
138.27
135.94
132.26
128.94
124.05
123.63
29.60
27.74
22.32
21.68
N
N
Br
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

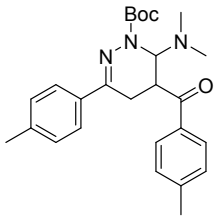
4bc


9.52
9.51
8.49
8.49
8.36
8.16
8.15
7.42
7.41
4.09
2.41
N
N
N
N
NO2
0.94
0.99
0.91
2.00
2.00
3.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

4bd


158.72
148.92
146.97
141.20
140.77
133.33
133.06
130.11
128.14
127.48
123.23
35.83
21.31
N
N
N
N
NO2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

4bd


Boc
N
N
N
O

3bg