Microwave-Enhanced Synthesis of 2,3,6-Trisubstituted Pyridazines: Application to Four-Step Synthesis of Gabazine (SR-95531)

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SUPPLEMENTARY INFORMATION

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EXPERIMENTAL

General details

All glass apparatus were oven dried prior to use. All chemicals used were purchased from Aldrich Chemical Co. Ltd. (St Louis, MO), Boron Molecular Inc. (NC, USA) and were of highest commercially available purity. All solvents were distilled by standard techniques prior to use. Where stated, reactions were performed under an inert atmosphere of nitrogen. Melting points were measured on a Stuart SMP10 (UK) melting point apparatus. ^{1}H NMR spectra were recorded at 400 MHz using a Varian (Palo Alto, CA) Gemini 400 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm), referenced externally to tetramethyl silane at 0 ppm. ^{13}C NMR spectra were recorded at 100 MHz using a Varian (USA) 400 MI spectrometer. Chemical shifts (δ) are quoted in ppm, referenced internally to $CDCl_3$ at 77.0 ppm. All coupling constants (*J*) are given in Hertz. IR spectra were recorded with a Shimadzu IR 440 spectrometer as KBr pellets. Low Resolution Mass Spectra (LRMS) was carried out using a Bruker (USA) Daltronics BioApexII with a 7T superconducting magnet and an analytical ESI source. High Resolution Mass Spectra (HRMS) were obtained by the Mass Spectrometry Unit at the School of Chemistry, The University of Sydney, on a Bruker 7T Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. GCMS was performed on a PolarisQ GC-MS-MS ion trap mass spectrometer coupled to a Trace GC and automated injections were performed on an AS2000 Autosampler. Thin layer chromatography was performed on Merck aluminium backed plates, precoated with silica (0.2 mm, $60F_{254}$), which were developed using one of the following techniques: UV fluorescence (254 nm), alkaline

potassium permanganate solution (0.5% w/v) or ninhydrin (0.2% w/v) and Iodine vapors. Flash chromatography was performed on silica gel (Merck silica gel 60H, particle size 5−40 μm). All microwave irradiation reactions were conducted by using CEM Discover S-Class microwave reactor (Single mode reactor, dynamic mode at power 300W).

Typical Procedure for Selective Mono-amination of 3,6-Dichloropyridazine under Microwave Irradiation: 3-Amino-6-chloropyridazine (4)

To a thick-wall borosilicate glass vial (20 mL) were added 3,6-dichloropyridazine **3** (1.5 gm) and NH_4OH solution (5 mL; NH_3 content: 28 to 30%). The vial was sealed with a lid and placed in the microwave reactor for 30 min at 120°C (power: 300W). After cooling down, the precipitate that deposited was filtered off, washed with ethyl acetate:hexane (3:7), dried to give as a light yellowish-white solid of 3-amino-6-chloropyridazine **4** (87% yield, require no further purification).

General Procedure for Suzuki Cross-coupling of 3-Amino-6-chloropyridazine with Substituted Boronic Acids under Microwave Irradiation:

To a thick-wall borosilicate glass vial (10 mL) were added 3-amino-6-chloropyridazine **4** (1 mmol), base (1.5 equiv.), aryl/heteroarylboronic acid (1.2 equiv), catalyst as described and solvent (2 mL). The mixture was degassed with nitrogen for 5 minute and then vial was sealed with a lid. The reaction mixture was pre-stirred for 1 minute to ensure sufficient mixing of the reagents. The reaction mixture was irradiated for 10 min at given temperature and 300W power. The reaction mixture is filtered and extracted with ethyl acetate (The product can also purified without extraction by flash chromatography: The reaction mixture is dried under reduced pressure and crude mixture is loaded on flash chromatography for purification). The collected organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography to give desired coupled products.

General Procedure for Selective N(2)-Alkylation under Microwave Irradiation

To a thick-wall borosilicate glass vial (10 mL) were added appropriate 3-amino-6-arylpyridazine (1 mmol), alkyl halide (1.2 equiv.). The reaction was carried out with or without any solvent as described. The vial was sealed with a lid and then reaction mixture was pre-stirred for 1 minute to ensure sufficient mixing of the reagents. . The reaction mixture was irradiated for 15 min at 80°C (power: 300W). The hot solution was either poured with stirring into ethyl acetate (30 mL), affording a crystalline compound or concentrated under reduced pressure and the residue triturated with a mixture of Et_2O-*i*-PrOH (1:1) to give appropriate N(2)-alkylated product. The N2-alkylated product, which is in the salt form, requires no further purification (compound **7f** and **7h** were triturated with hot isopropanol solution (~1 mL for further purification). The selective N(2)-alkylated products were confirmed by IR and NMR spectroscopy.

Four-Step Synthesis of Gabazine (SR-95531) 2

Step 1: Synthesis of 3-Amino-6-chloropyridazine 4 under Microwave Irradiation

3-amino-6-chloropyridazine was prepared by an above described mono-amination procedure.

Step 2: Synthesis of 3-Amino-6-(4-methoxyphenyl)pyridazine 6a under Microwave Irradiation

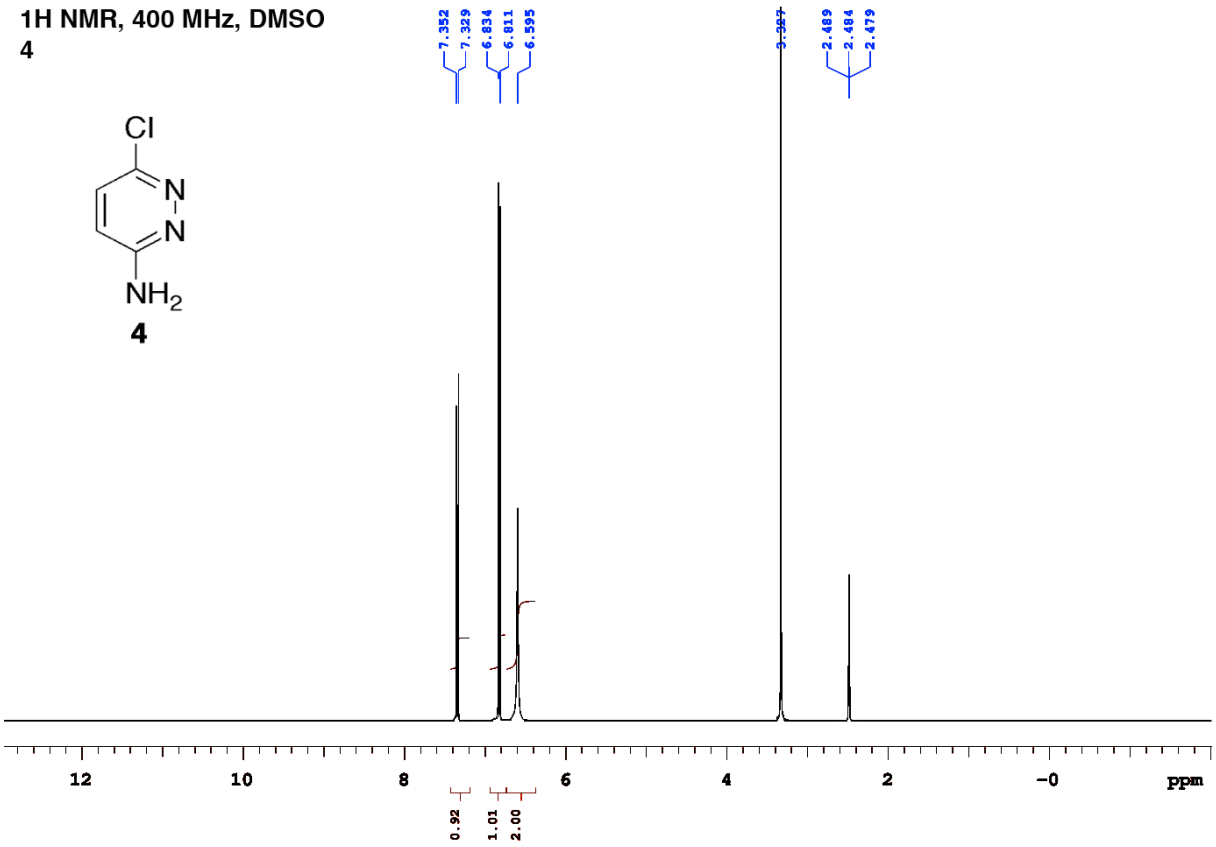
3-Amino-6-(4-methoxyphenyl)pyridazine was prepared by an above described Suzuki cross-coupling using appropriate starting materials and reaction condition.

Step 3 and 4: Synthesis of Gabazine (SR-95531) 2

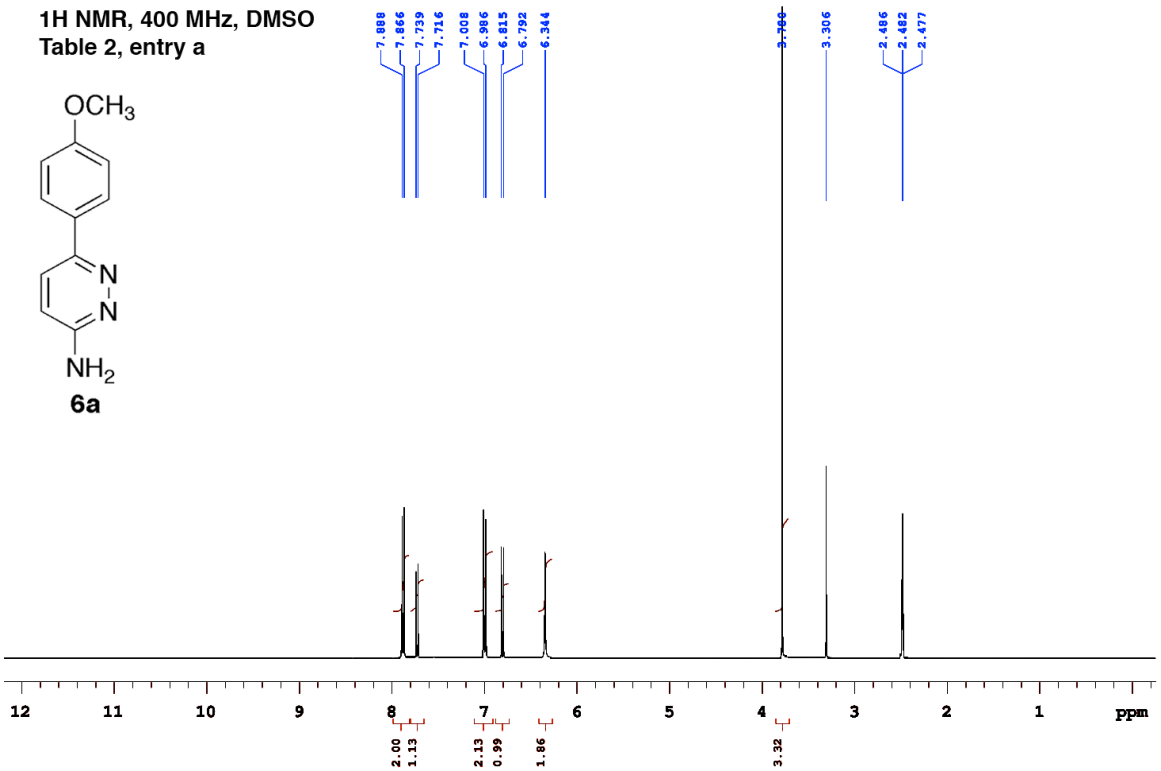
To a thick-wall borosilicate glass vial (10 mL) were added 3-amino-6-(4-methoxyphenyl)pyridazine **6a** (500 mg, 1 equiv.), ethyl 4-bromobutyrate (0.434 mL, 1.2 equiv.). The vial was sealed with a lid and then reaction mixture was pre-stirred for 1 minute to ensure sufficient mixing of the reagents. . The reaction mixture was irradiated for 15 min at 80°C (power: 300W). The hot solution was poured with stirring into ethyl acetate (30 mL), affording a crystalline compound to give ethyl-4-[6-imino-3-(4-methoxyphenyl)pyridazin-1-yl] butanoic acid hydrobromide **7b** (95% yield). To a solution of ethyl-4-[6-imino-3-(4-methoxyphenyl)pyridazin-1-yl] butanoic acid hydrobromide **7b** (500 mg) in water (1.5 mL) was added NaOH (208 mg) at room temperature. The resulting mixture was stirred for 2 h, maintaining 40-45°C using conventional heating. After cooling to 10°C, to the reaction mixture was added water (5 mL) and ethyl acetate (10 mL). The aqueous layer was separated, washed with ethyl acetate (2.5 mL) and treated with 17.5% hydrogen chloride in water to adjust the pH to 0.5-1.0 at 20-25°C. The resulting mixture was further stirred at 0-5°C for 1 h, and the precipitate was filtered off and washed with water (1 mL). Drying under reduced pressure afforded crude gabazine **2** (375 mg, 90% yield) of 95% purity as a light yellowish solid. The crude gabazine **2** (375 mg) was treated with carbon (15 mg) in a mixture of 2-propanol (2 mL) and water (1 mL) at 80°C. The filtrate was cooled to 0°C, and the precipitate was filtered off and washed with a mixture of 2-propanol (0.5 mL) and water (0.3 mL), and successively water (0.5 mL). Drying under reduced pressure afforded purified gabazine **2** (347 mg, 85% yield) of 100% purity as a white solid.

CHARACTERIZATION DATA

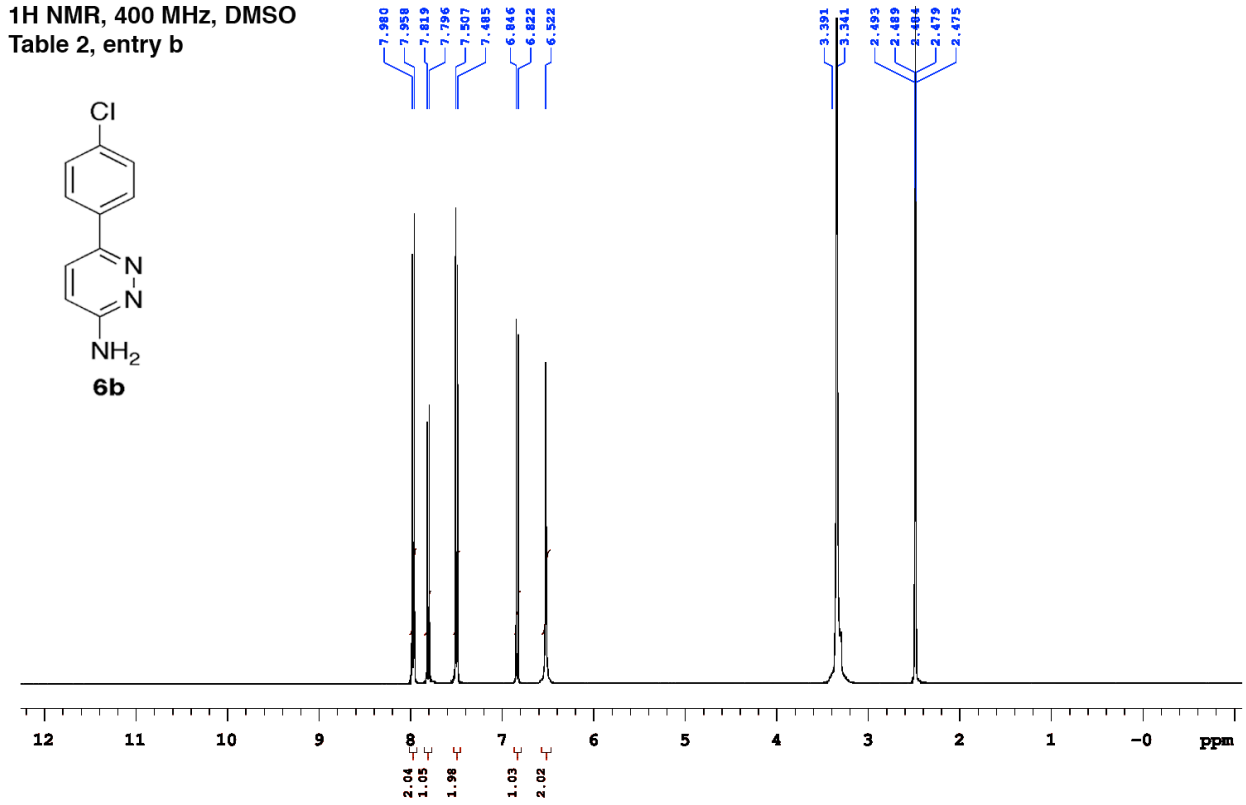
Compound 4[1]: light yellowish-white color solid; 87% yield; mp 229-232°C; MS (ESI) m/z =130.46 [M + 1]; HRMS (ESI) calcd for $C_4H_4N_3Cl$ [M^+] 129.5477, found 129.5662.



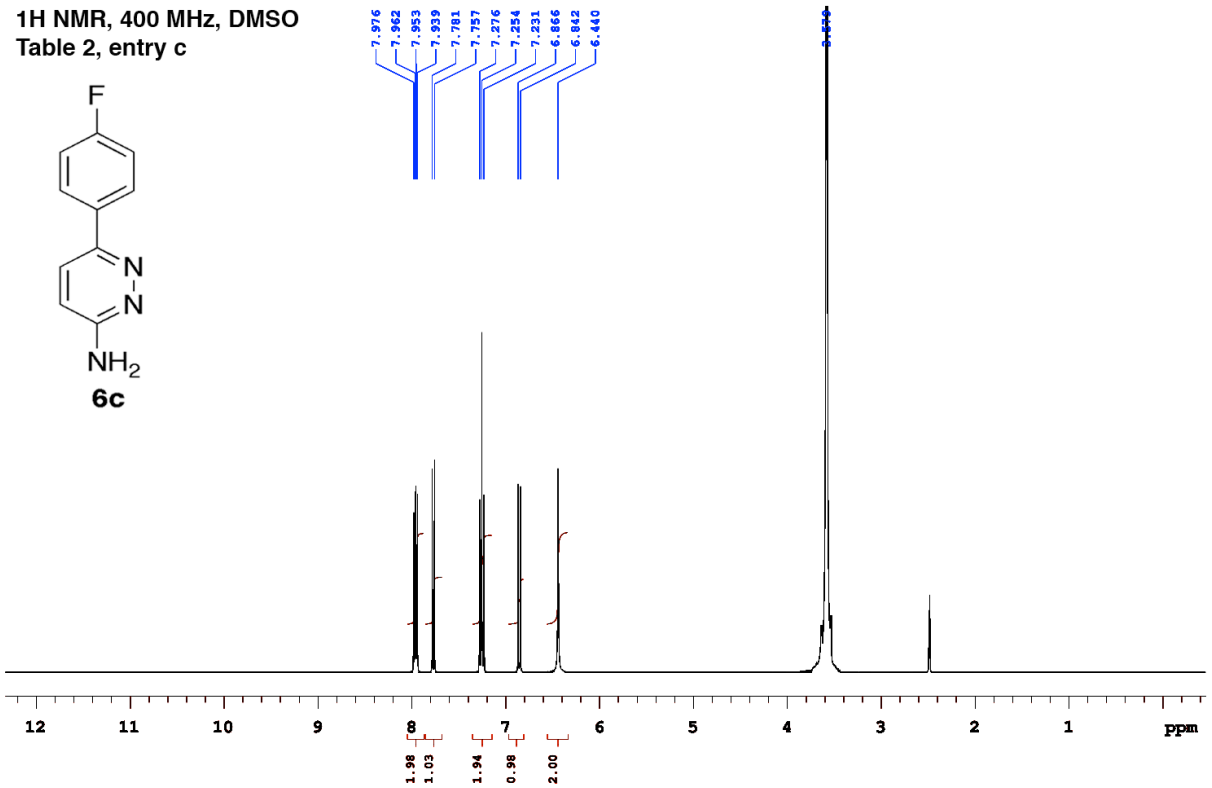
Compound 6a[2]: white color solid; 94% yield; mp 195-198°C; MS (ESI) m/z =202.33 [M + 1]; HRMS (ESI) calcd for $C_{11}H_{11}N_3O$ [M^+] 201.0902, found 201.0904.



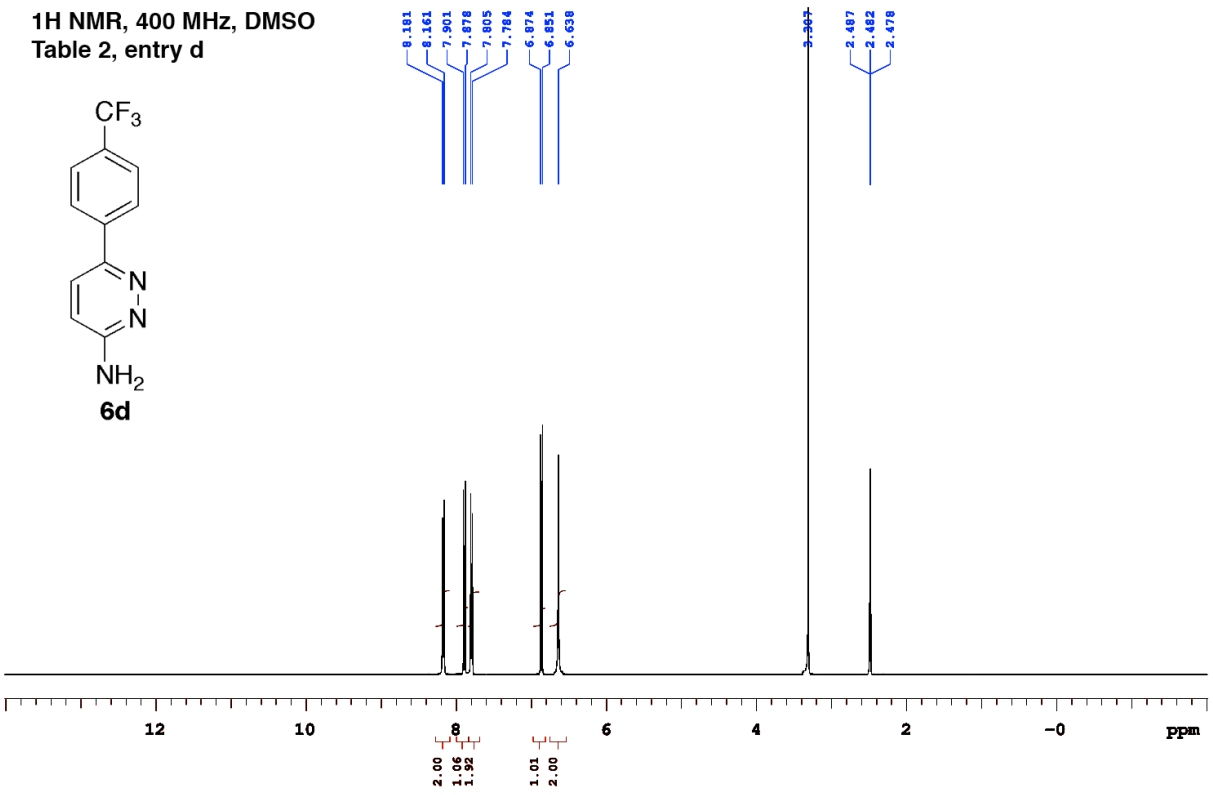
Compound 6b[2]: white color solid; 88% yield; mp 177-180^{0}C; MS (ESI) m/z =206.57 [M + 1].

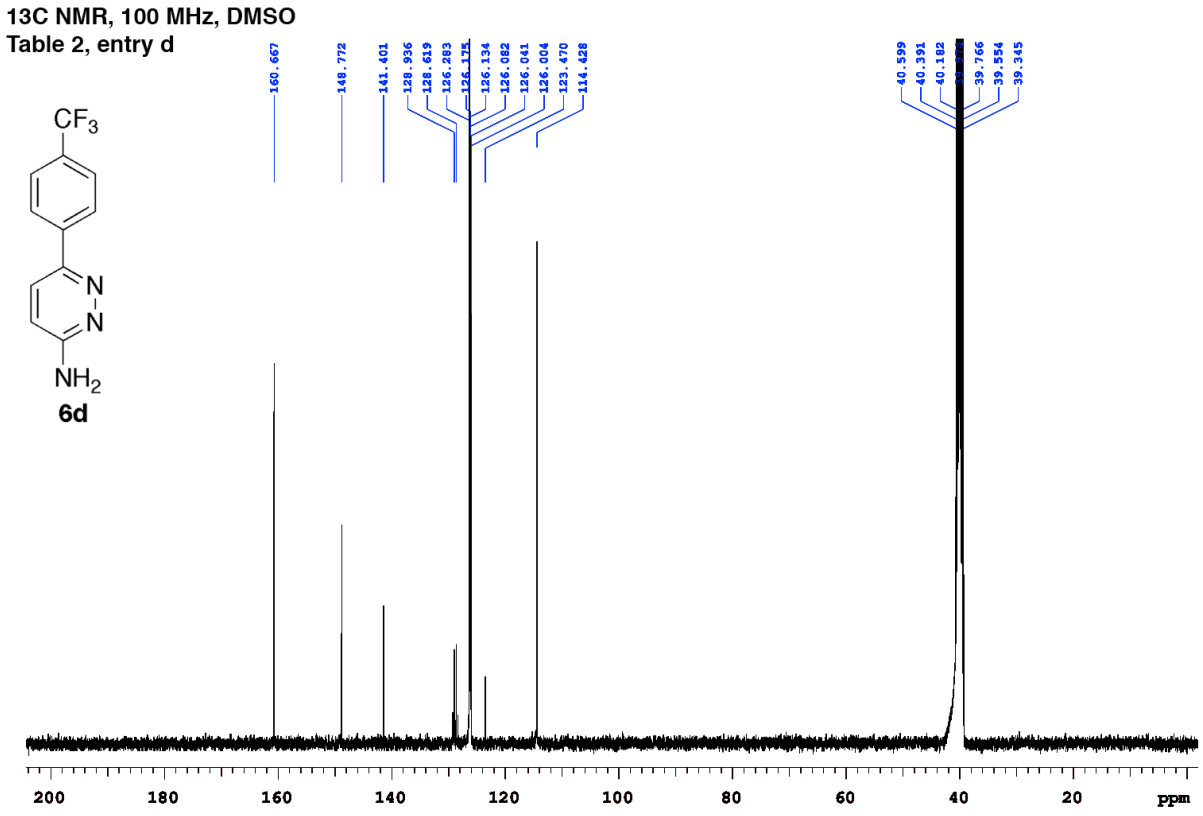


Compound 6c[3]: white color solid; 95% yield; mp 165-168°C; MS (ESI) m/z =190.15 [M + 1].

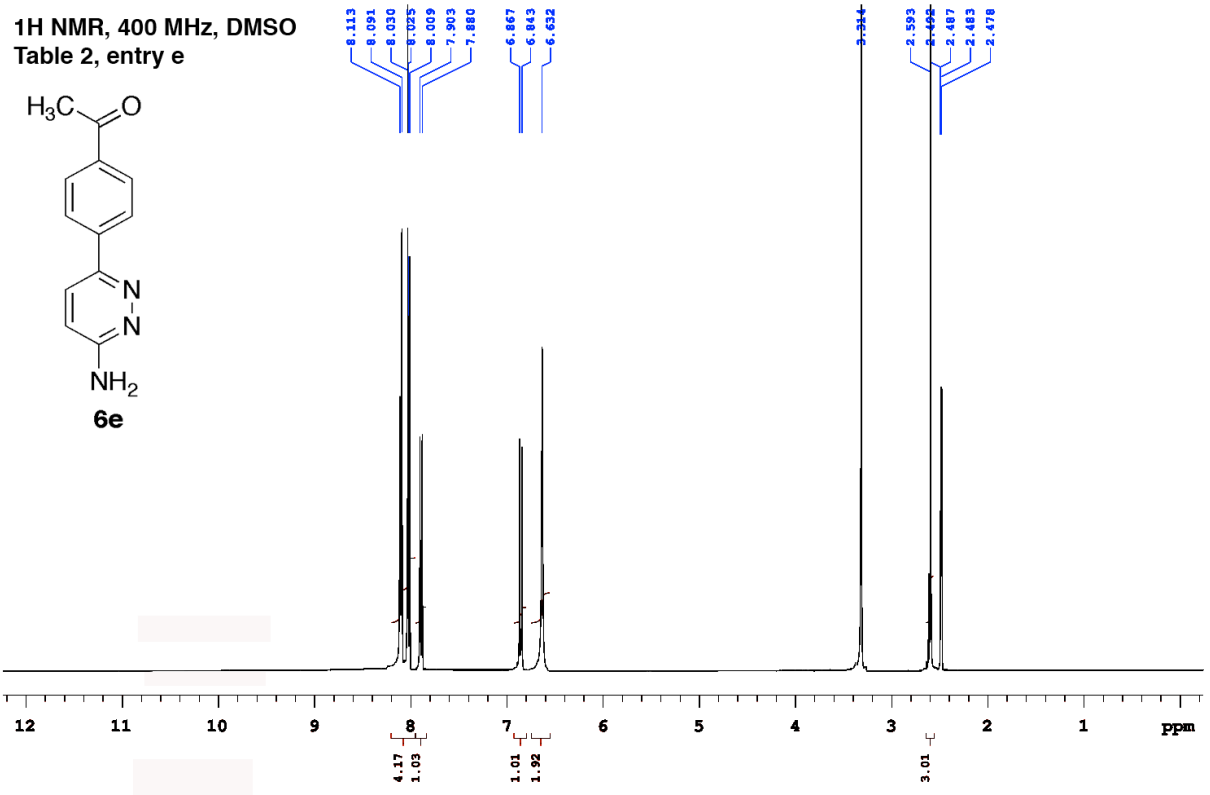


Compound 6d: off-white color solid; 86% yield; IR (KBr): 3355, 3308, 3124, 1645, 1605, 1071, 1050, 842 cm^{-1}; MS (ESI) m/z = 240.13 [M + 1]; HRMS (ESI) calcd for $C_{11}H_8F_3N_3$ [M^+] 239.0670, found 239.0766.



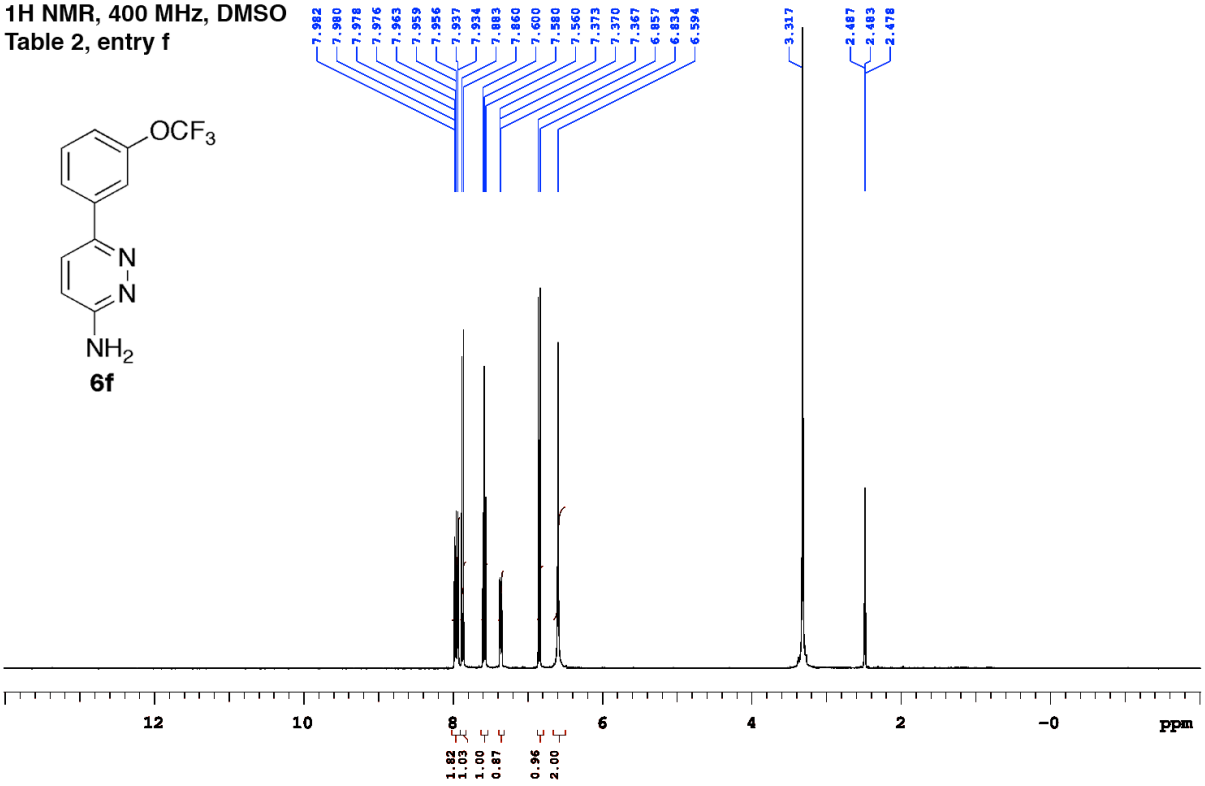


Compound 6e: off-white color solid; 90% yield; IR (KBr): 3413, 3285, 3124, 1615, 1598, 1098, 836 cm^{-1}; MS (ESI) m/z = 214.18 [M + 1]; HRMS (ESI) calcd for $C_{12}H_{11}N_3NaO$ [M^+ + Na] 236.0800, found 236.0797.

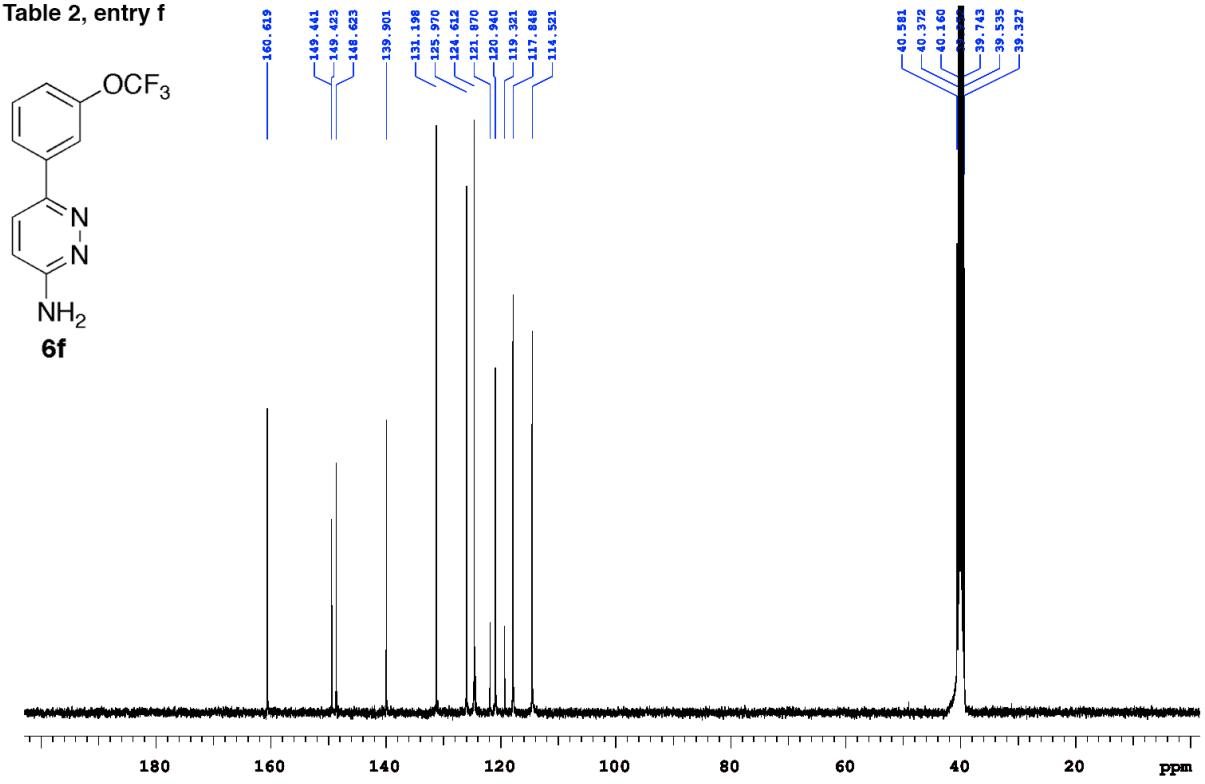


Compound 6f: off-white color solid; 92% yield; IR (KBr): 3415, 3292, 3108, 1649, 1606, 1096, 824 cm^{-1}; MS (ESI) m/z = 256.09 [M + 1]; HRMS (ESI) calcd for $C_{11}H_8F_3N_3O$ [M^+] 255.0619, found 255.0622.

1H NMR, 400 MHz, DMSO
Table 2, entry f

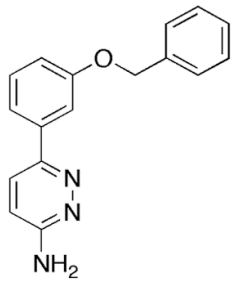


13C NMR, 100 MHz, DMSO
Table 2, entry f



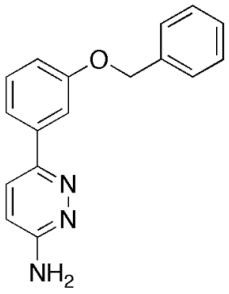
Compound 6g: white color solid; 88% yield; IR (KBr): 3452, 3345, 3417, 1632, 1512, 1132, 841 cm^{-1}; MS (ESI) m/z = 278.27 [M + 1]; HRMS (ESI) calcd for $C_{17}H_{16}N_3O$ [M^+ + H] 278.1293, found 278.1288.

1H NMR, 400 MHz, DMSO
Table 2, entry g



6g

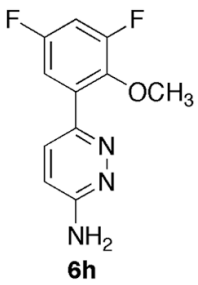
13C NMR, 100 MHz, DMSO
Table 2, entry g



6g

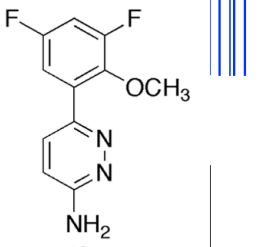
Compound 6h: white color solid; 92% yield; IR (KBr): 3415, 3294, 3120, 1648, 1606, 1136, 832 cm^{-1}; MS (ESI) m/z = 238.17 [M + 1]; HRMS (ESI) calcd for $C_{11}H_9F_2N_3NaO$ [M^+ + Na] 260.0611, found 260.0616.

1H NMR, 400 MHz, DMSO
Table 2, entry h



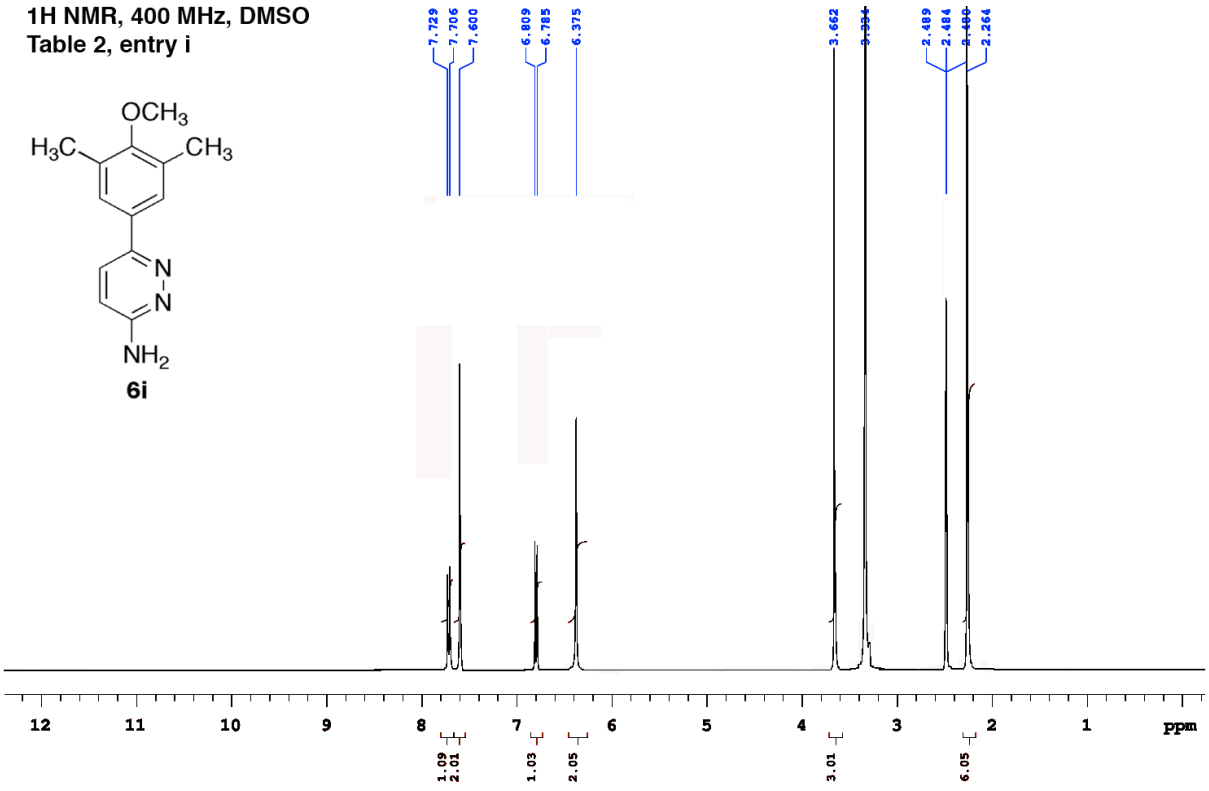
6h

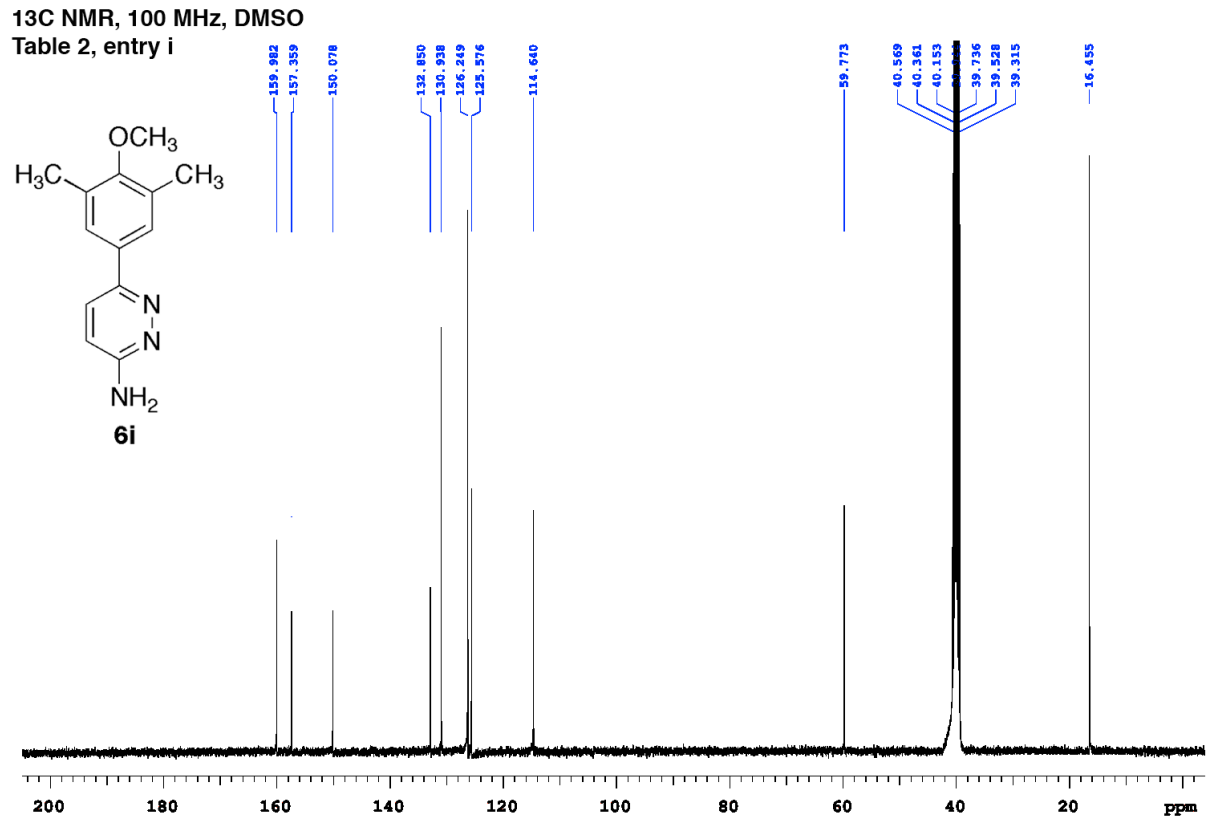
13C NMR, 100 MHz, DMSO
Table 2, entry h



6h

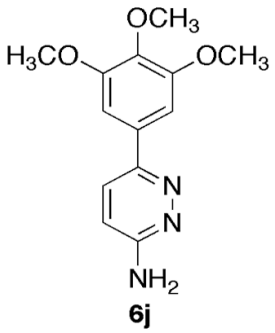
Compound 6i: white color solid; 84% yield; mp 147-150°C; MS (ESI) m/z = 230.24 [M + 1]; HRMS (ESI) calcd for $C_{13}H_{15}N_3O$ [M^+] 229.1215, found 229.1210.





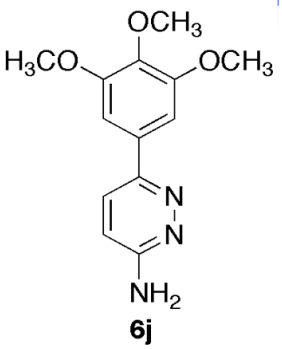
Compound 6j: white color solid; 82% yield; IR (KBr): 3415, 3294, 3112, 1646, 1612, 1028, 829 cm^{-1}; MS (ESI) m/z = 262.20 [M + 1]; HRMS (ESI) calcd for $C_{13}H_{16}N_3O_3$ [M^+ + H] 262.1192, found 262.1188.

1H NMR, 400 MHz, DMSO
Table 2, entry j



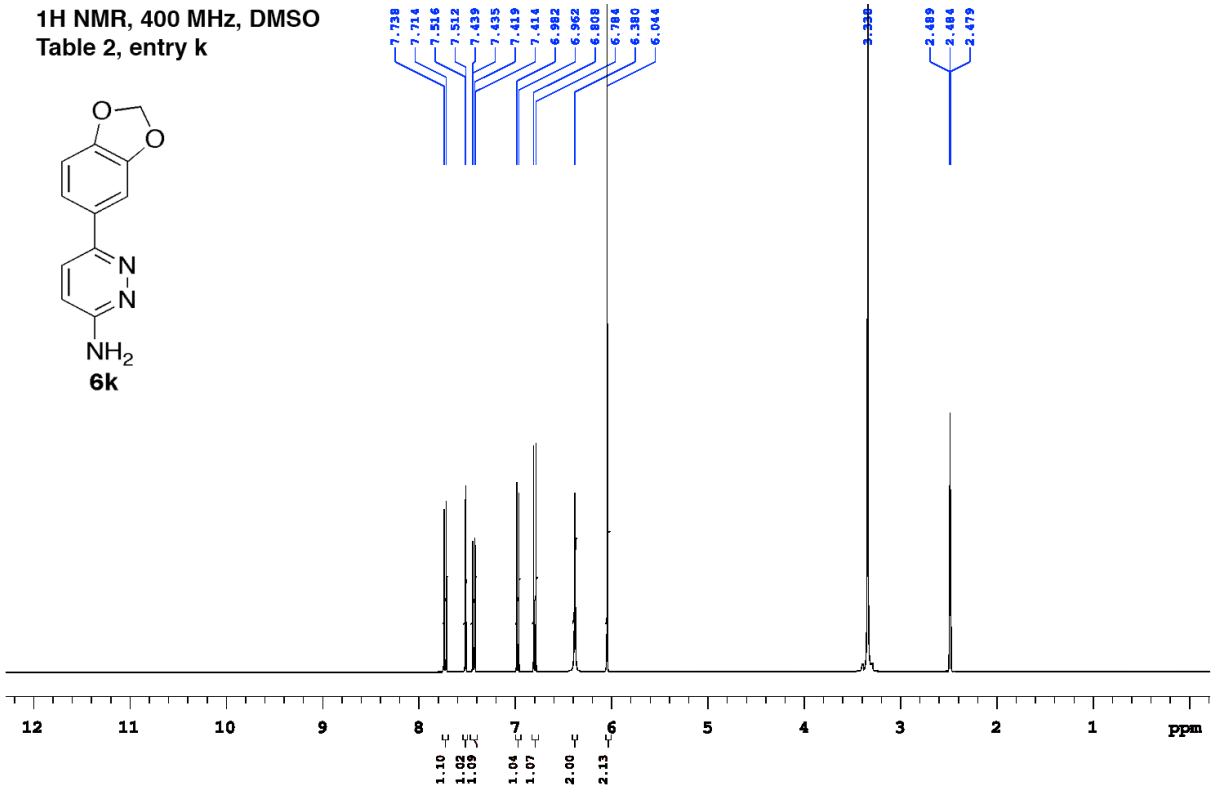
6j

13C NMR, 100 MHz, DMSO
Table 2, entry j

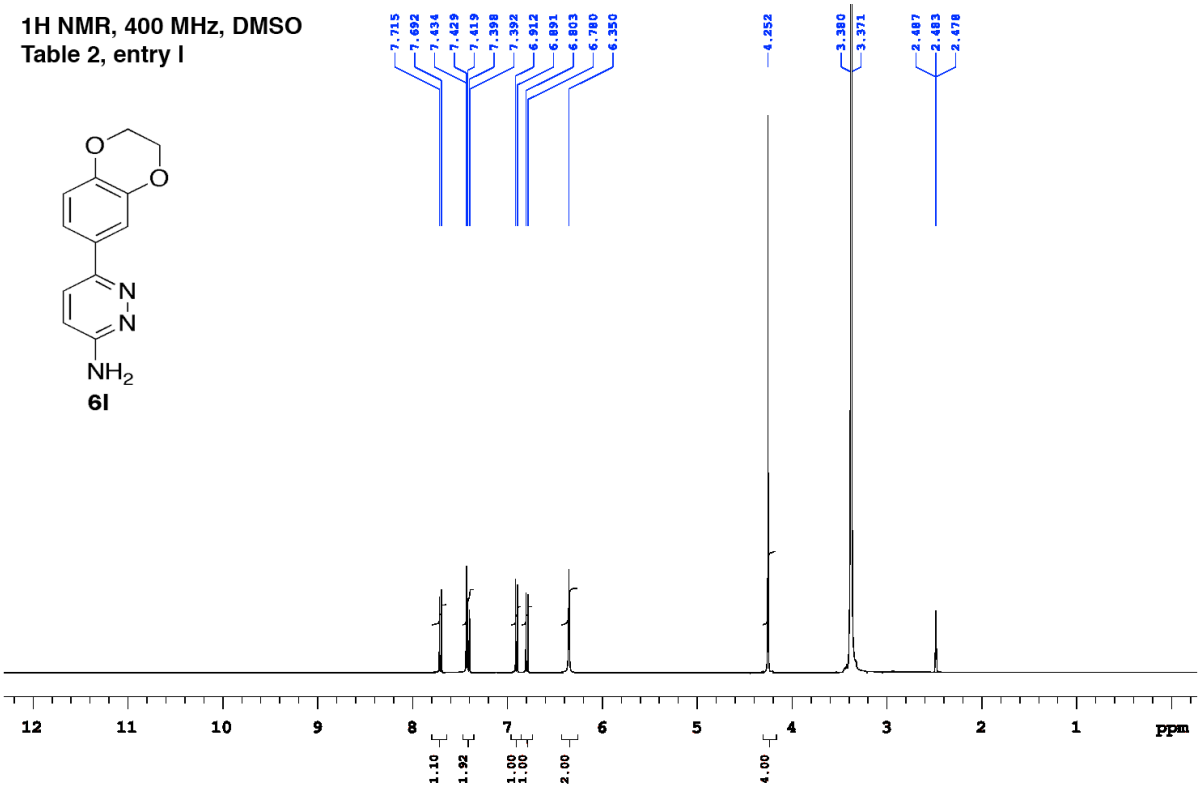


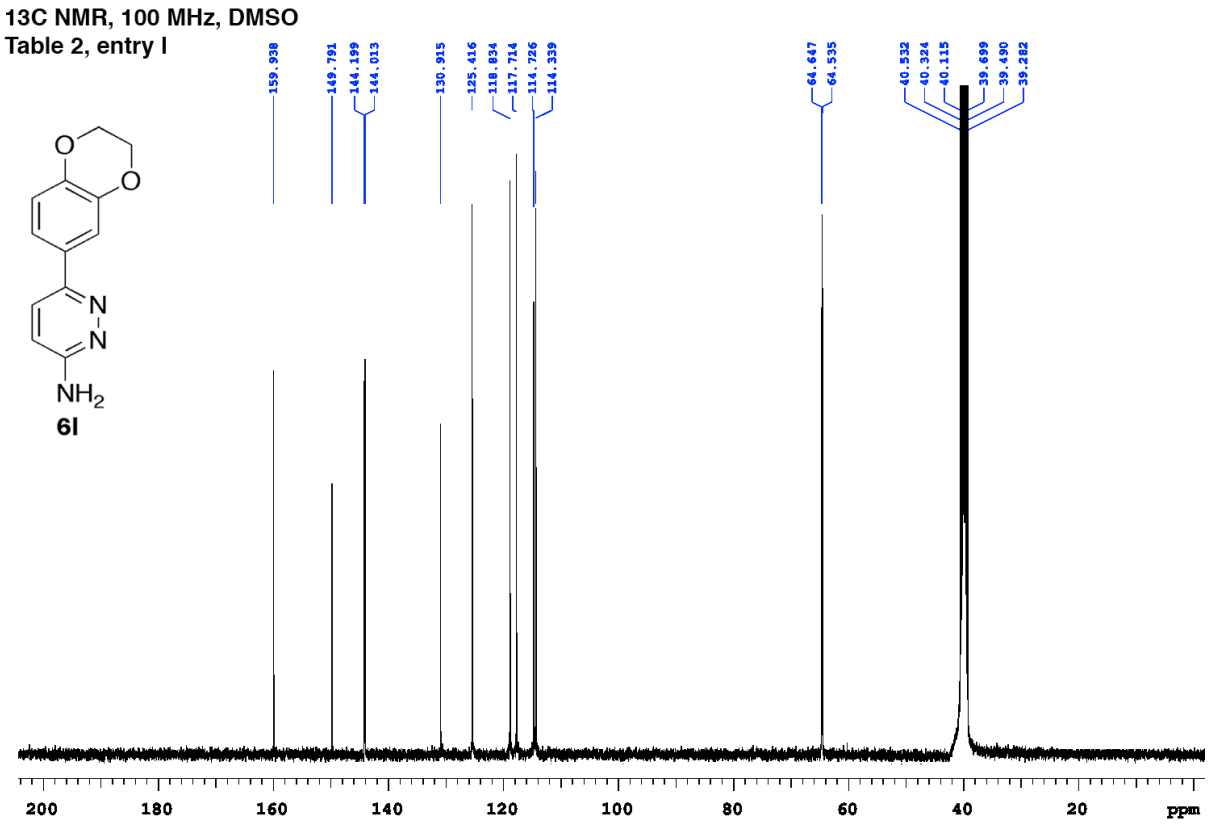
6j

Compound 6k[2]: white color solid; 92% yield; mp 191-193°C; MS (ESI) m/z = 216.12 [M + 1]; HRMS (ESI) calcd for $C_{11}H_9N_3NaO_2$ [M^+ + Na] 238.0592, found 238.0592.

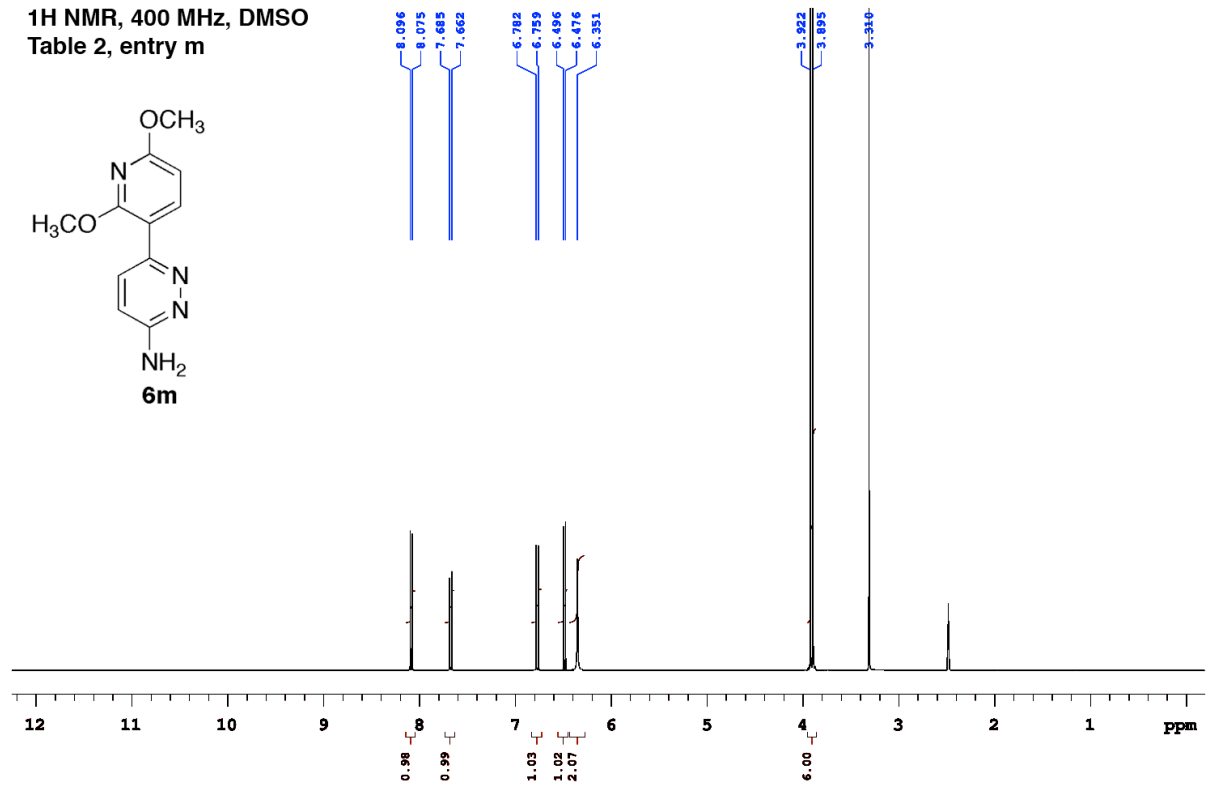


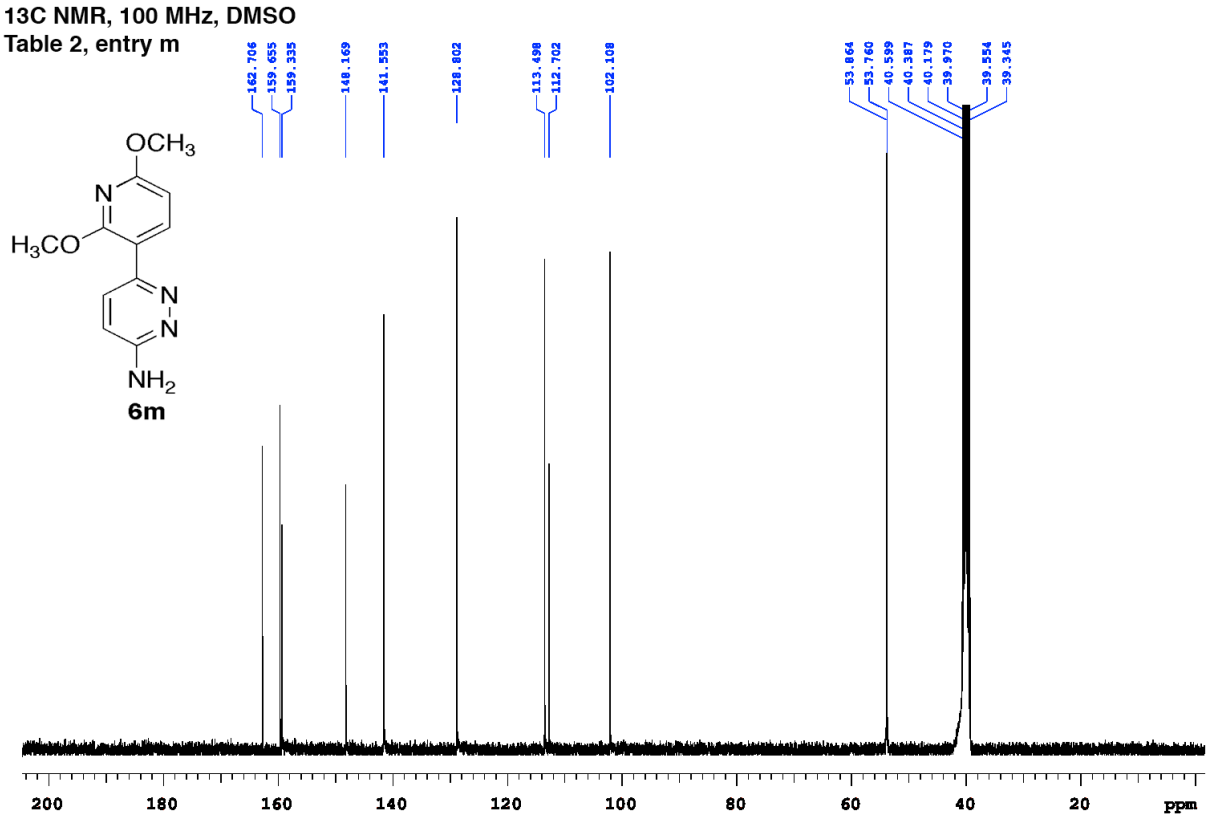
Compound 6l: white color solid; 90% yield; IR (KBr): 3417, 3288, 3111, 1654, 1612, 1062, 834 cm^{-1}; MS (ESI) m/z = 230.21 [M + 1]; HRMS (ESI) calcd for $C_{12}H_{11}N_3NaO_2$ [M^+ + Na] 252.0749, found 252.0745.



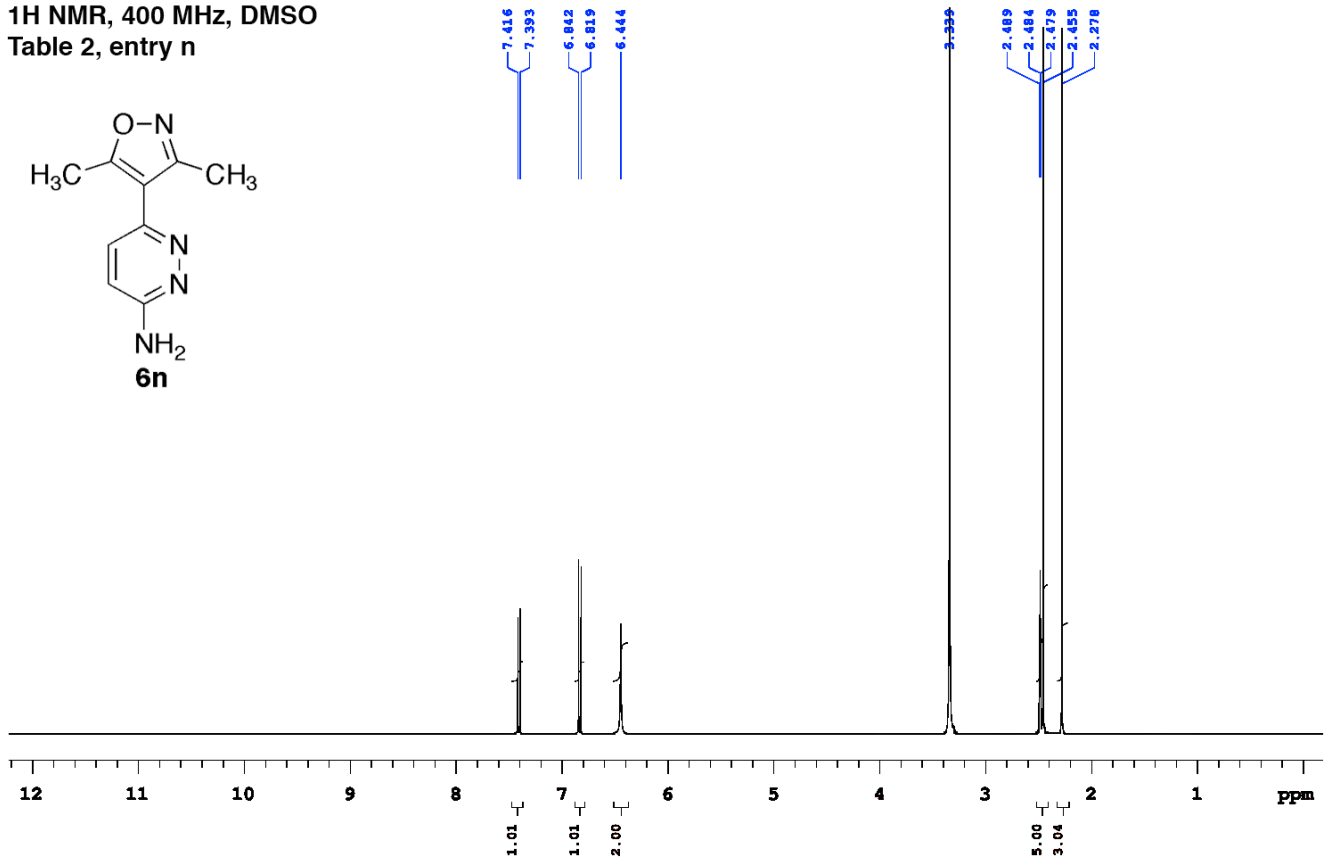


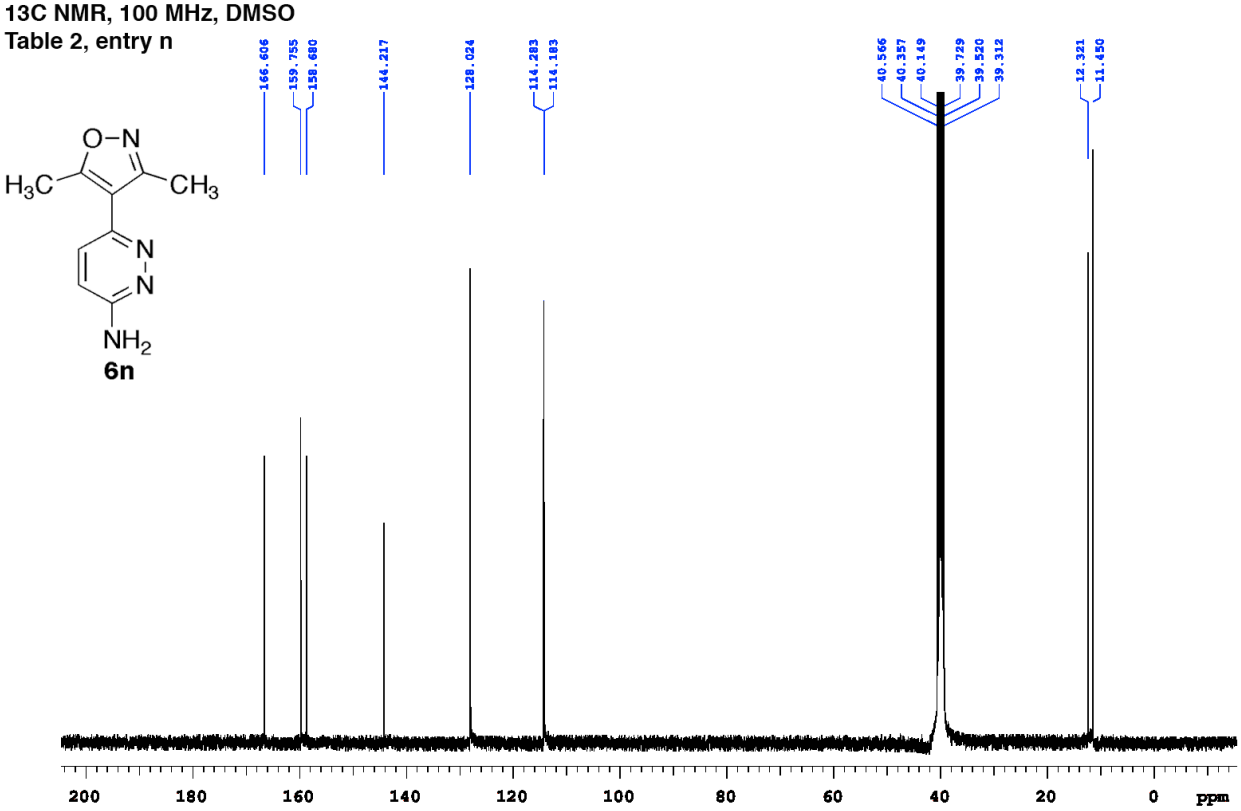
Compound 6m: white color solid; 86% yield; mp 197-200°C; MS (ESI) m/z = 233.18 [M + 1]; HRMS (ESI) calcd for $C_{11}H_{13}N_4O_2$ [M^+ + H] 233.1039, found 233.1040.



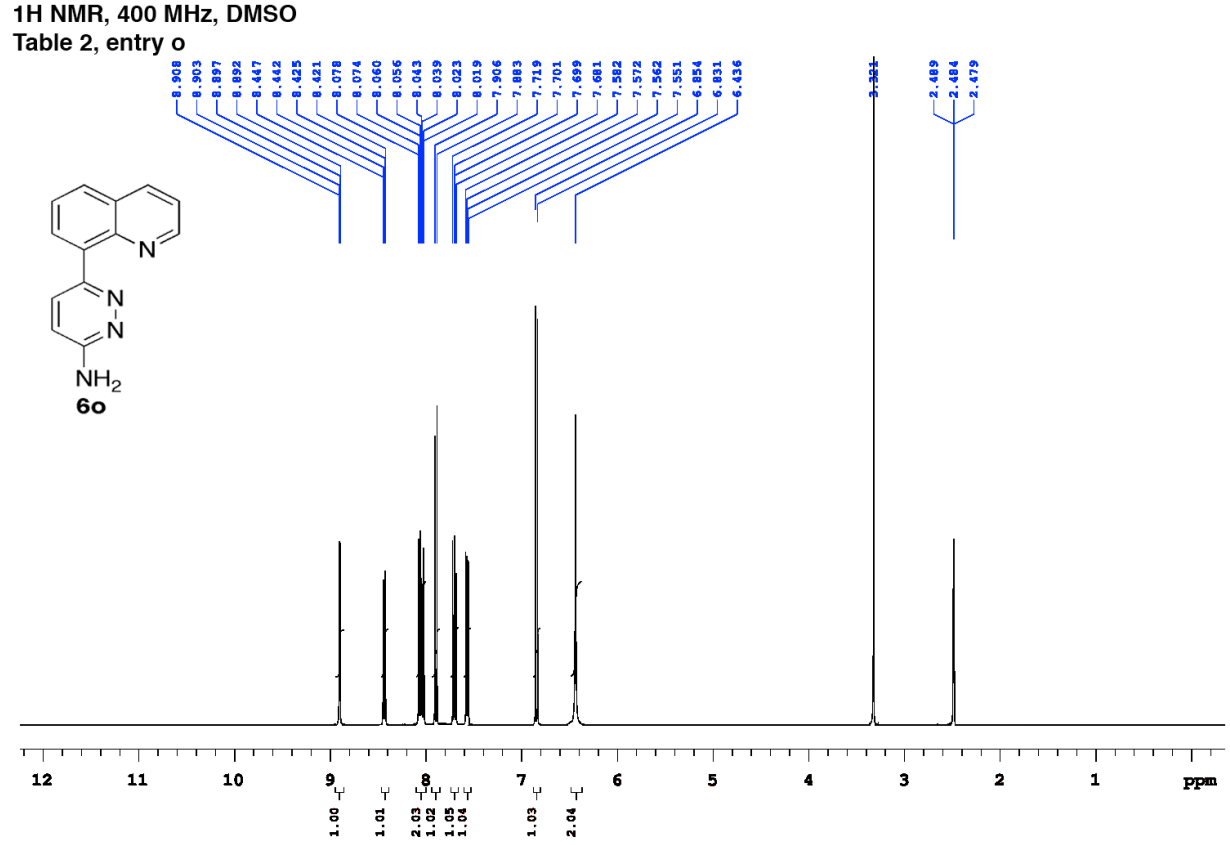


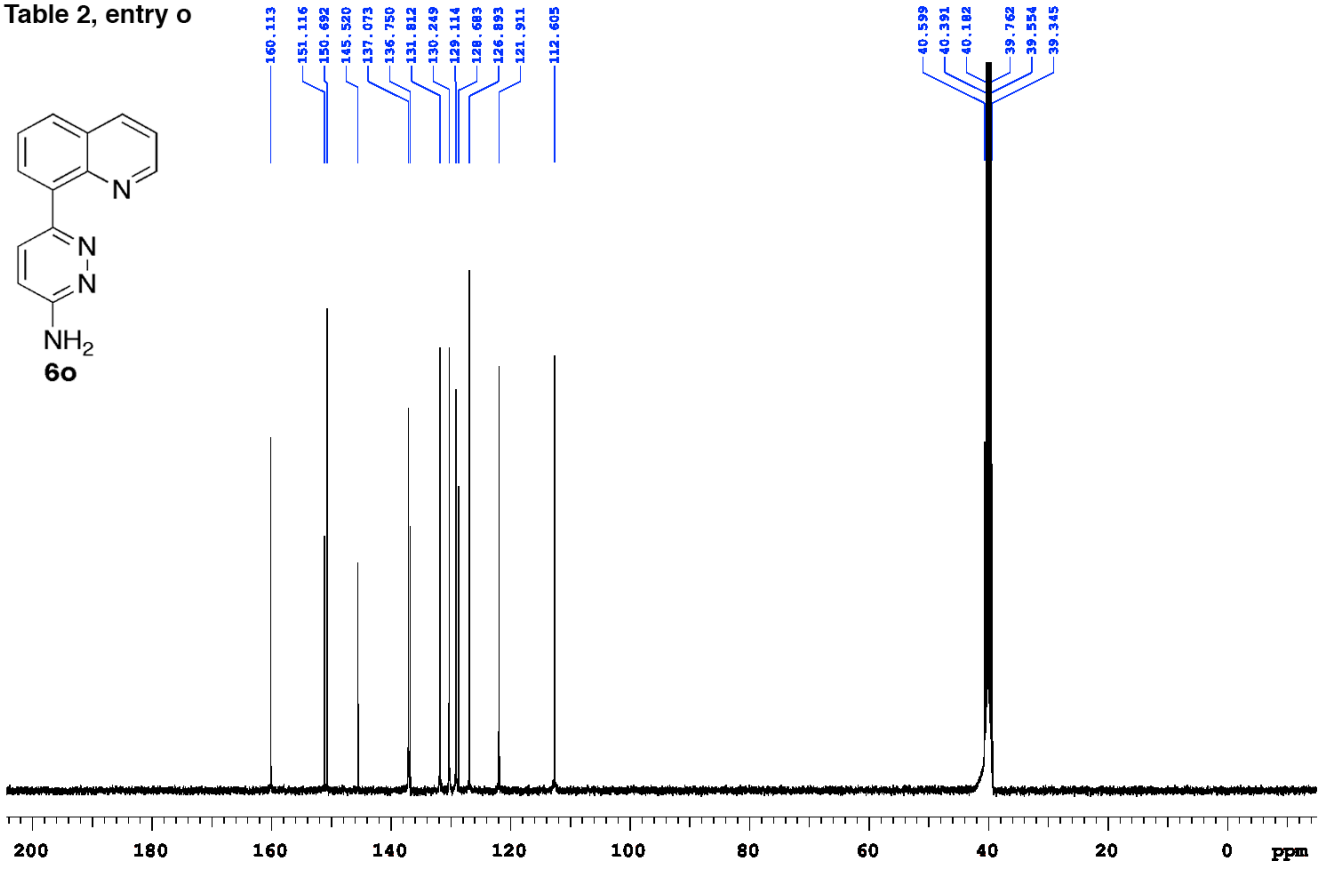
Compound 6n: white color solid; 91% yield; mp 187-190°C; MS (ESI) m/z = 191.17 [M + 1]; HRMS (ESI) calcd for $C_9H_{10}N_4O$ [M^+] 190.0855, found 190.0859.



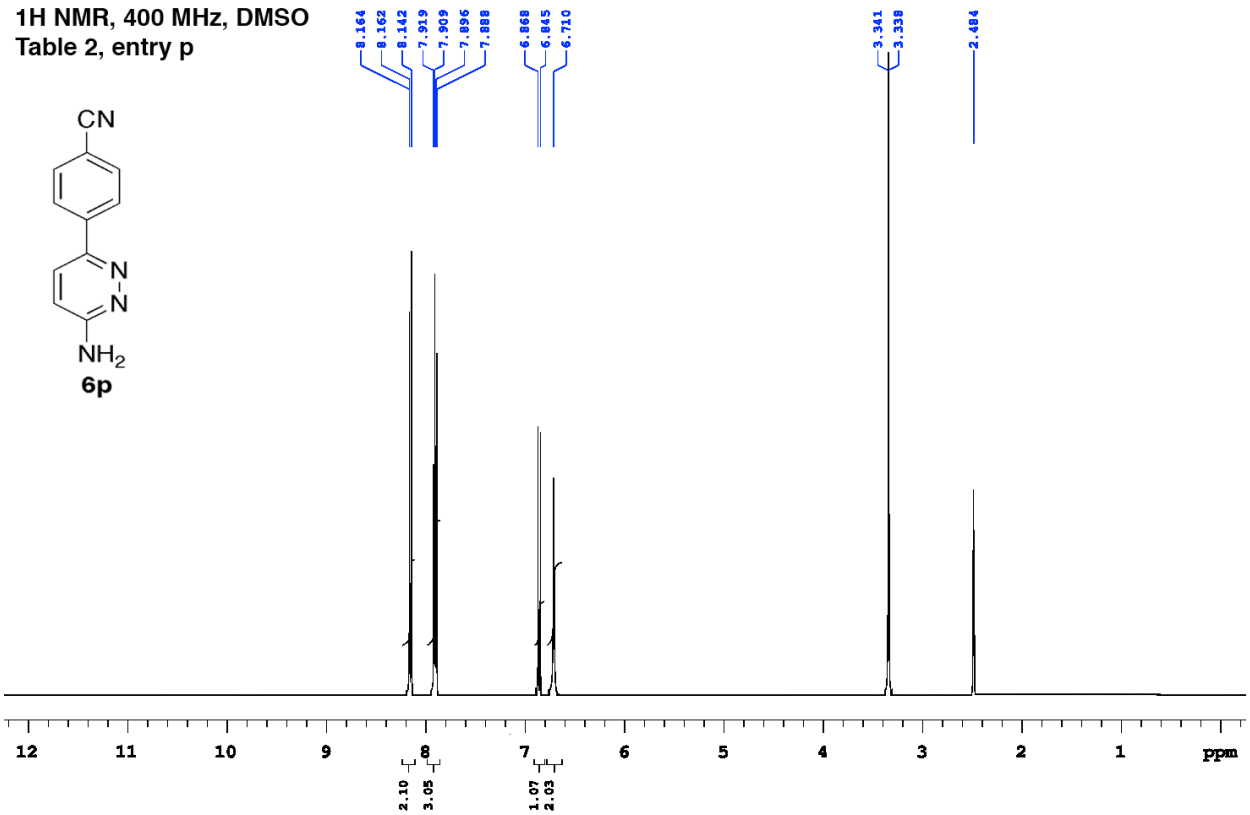


Compound 6o: white color solid; 87% yield; mp 163-166°C; MS (ESI) m/z = 223.22 [M + 1]; HRMS (ESI) calcd for $C_{13}H_{11}N_4$ [M^+ + H] 223.0984, found 223.0981.

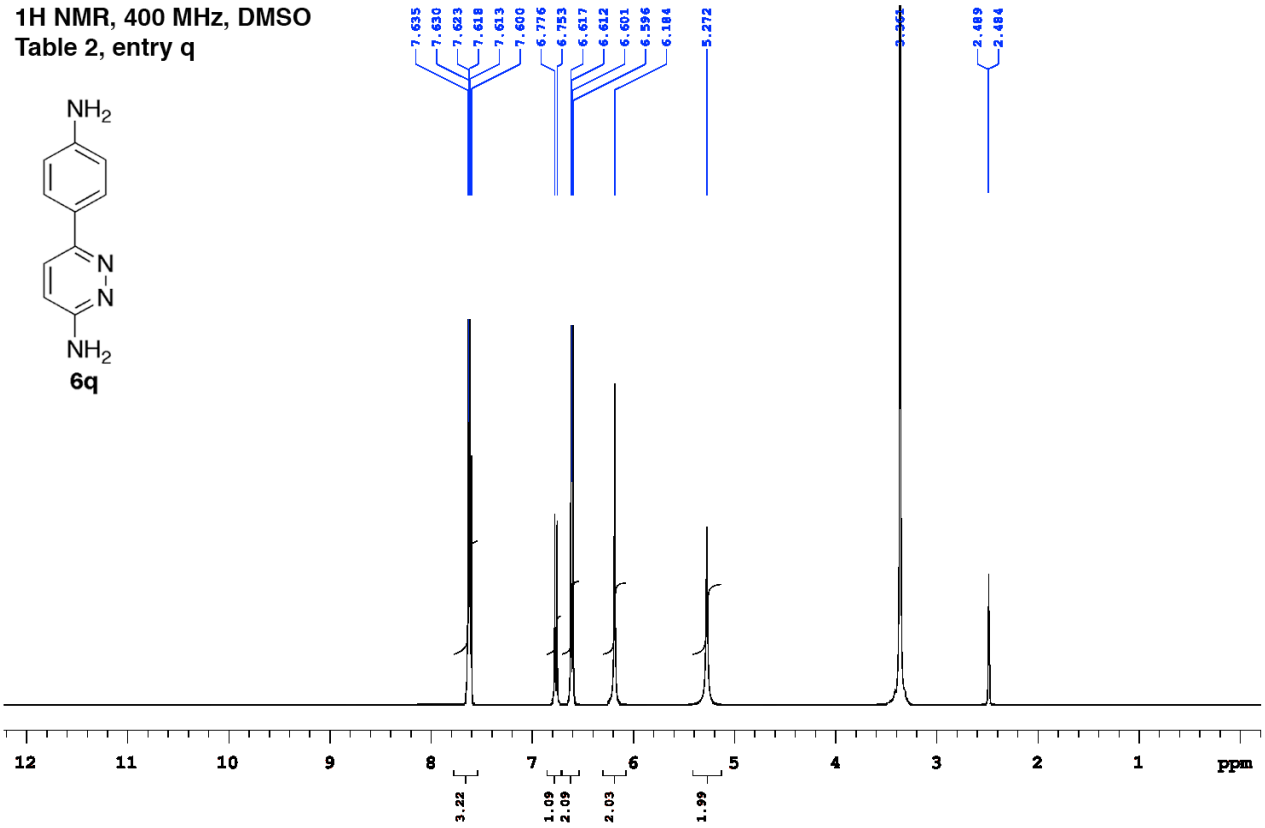


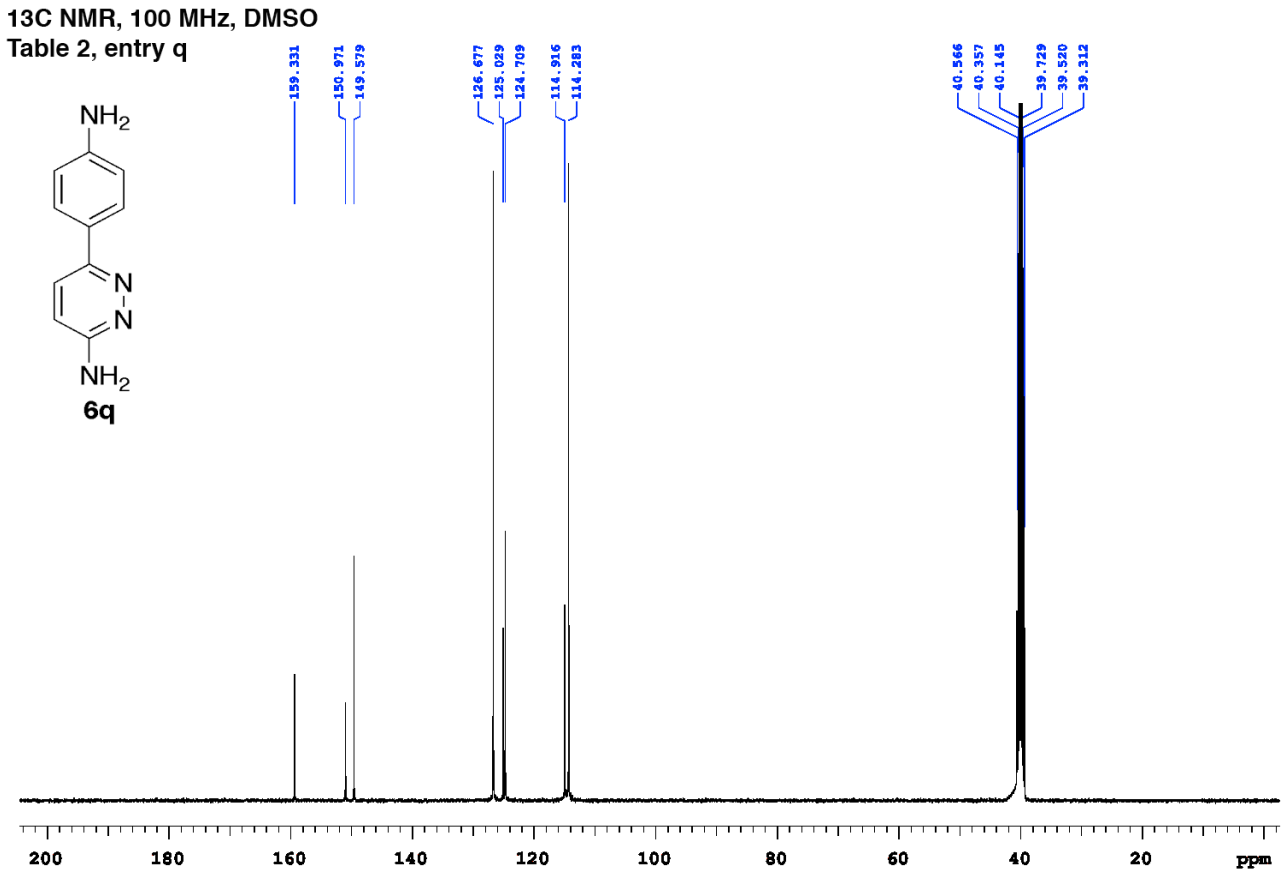


Compound 6p: off-white color solid; 79% yield; MS (ESI) m/z = 197.17 [M + 1]; HRMS (ESI) calcd for $C_{11}H_8N_4$ [M^+] 196.0749, found 196.0753.

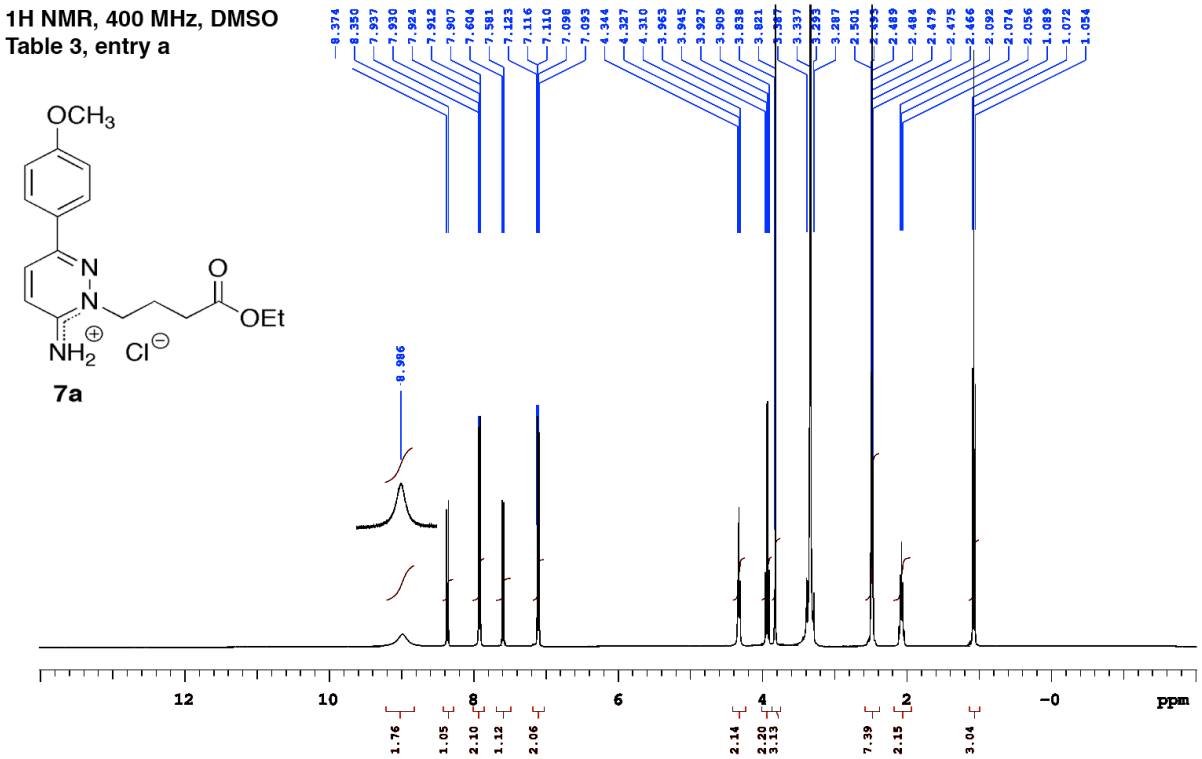


Compound 6q: yellowish-brown color solid; 75% yield; MS (ESI) m/z = 187.12 [M + 1]; HRMS (ESI) calcd for $C_{10}H_{11}N_4$ [M^+ + H] 187.0984, found 187.0979.

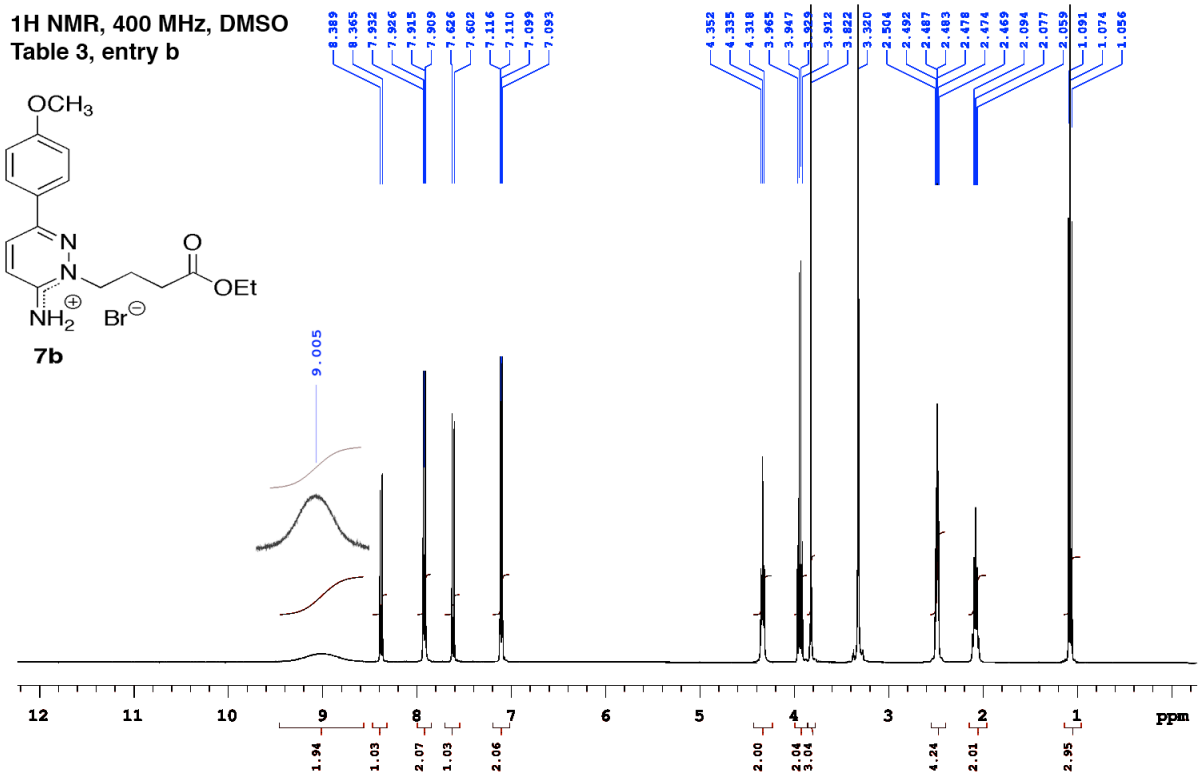




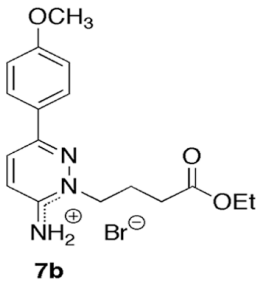
Compound 7a: off-white color solid; 84% yield.



Compound 7b: off-white color solid; 95% yield; mp 239-242°C; MS (ESI) m/z = 317.27 [M + 1]; HRMS (ESI) calcd for $C_{17}H_{22}N_3O_3$ [M^+ - Br] 316.1661, found 316.1655.



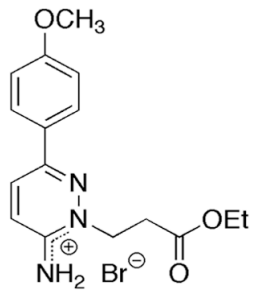
13C NMR, 100 MHz, DMSO
Table 3, entry b



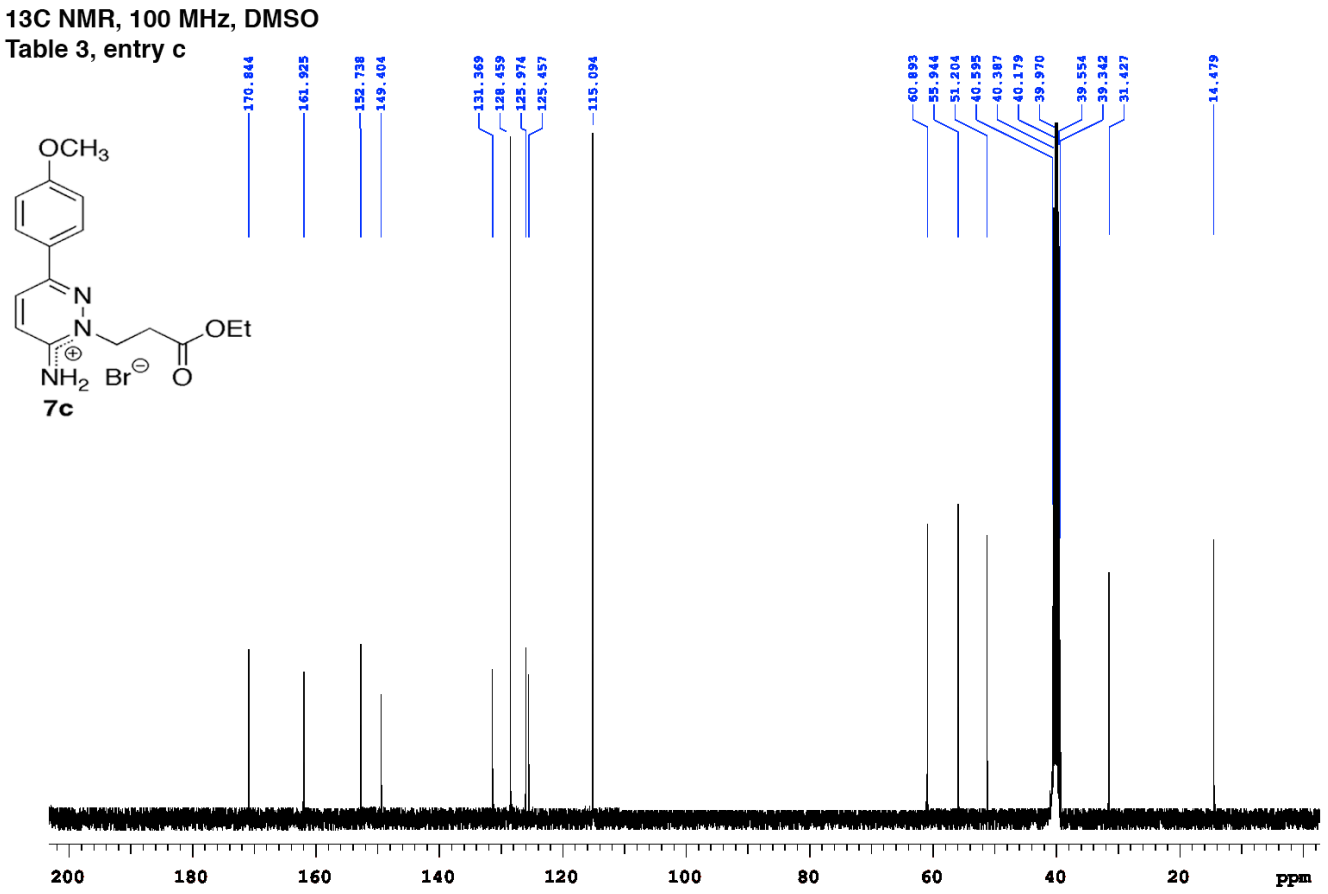
7b

Compound 7c: off-white color solid; 93% yield; MS (ESI) m/z = 303.25 [M + 1]; HRMS (ESI) calcd for $C_{16}H_{20}N_3O_3$ [M^+ - Br] 302.1505, found 302.1505.

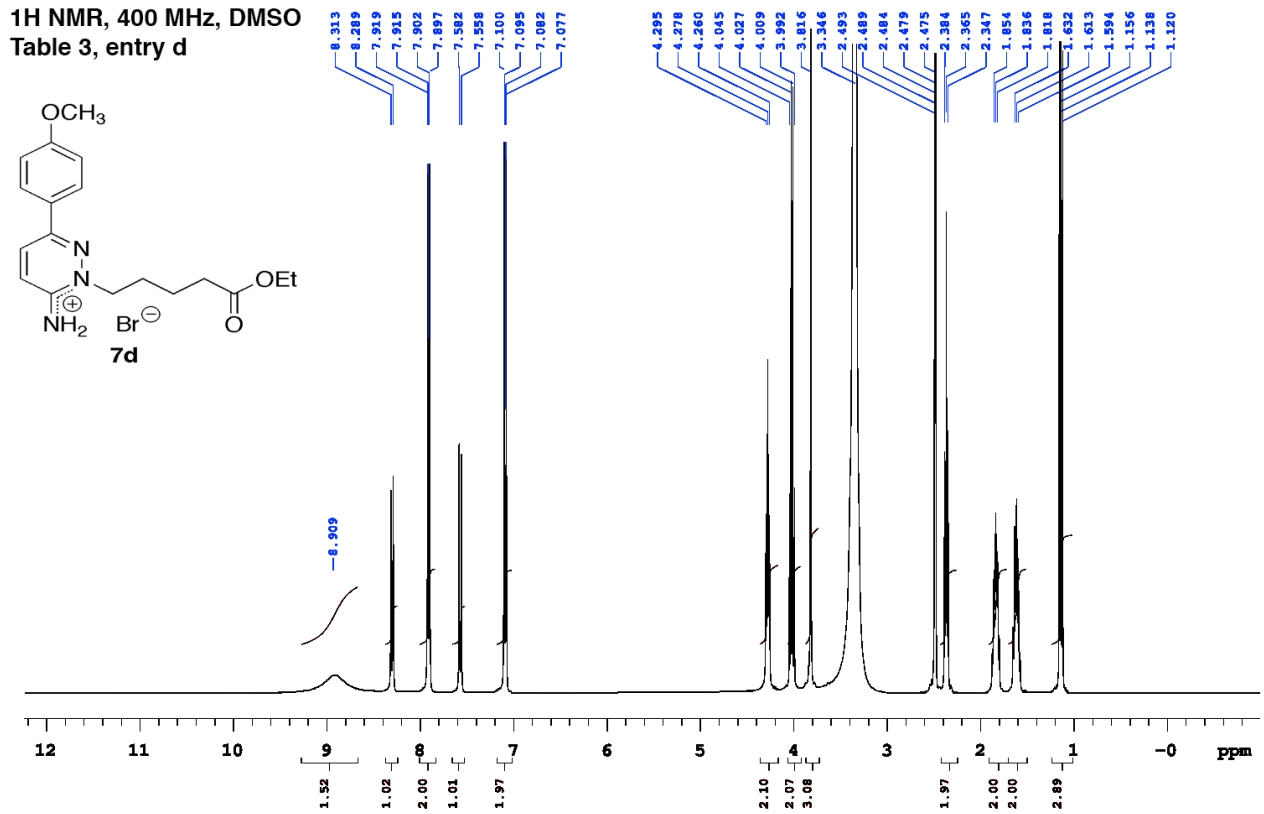
1H NMR, 400 MHz, DMSO
Table 3, entry c

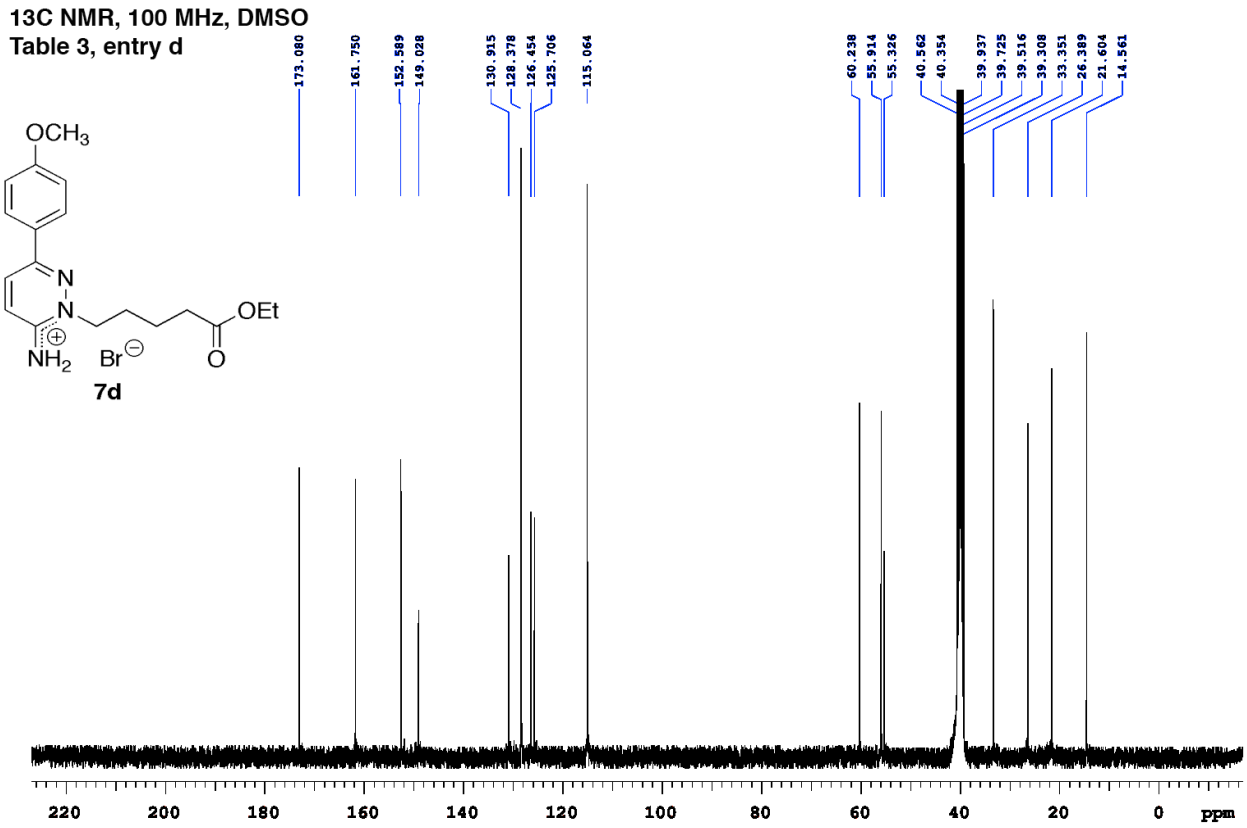


7c

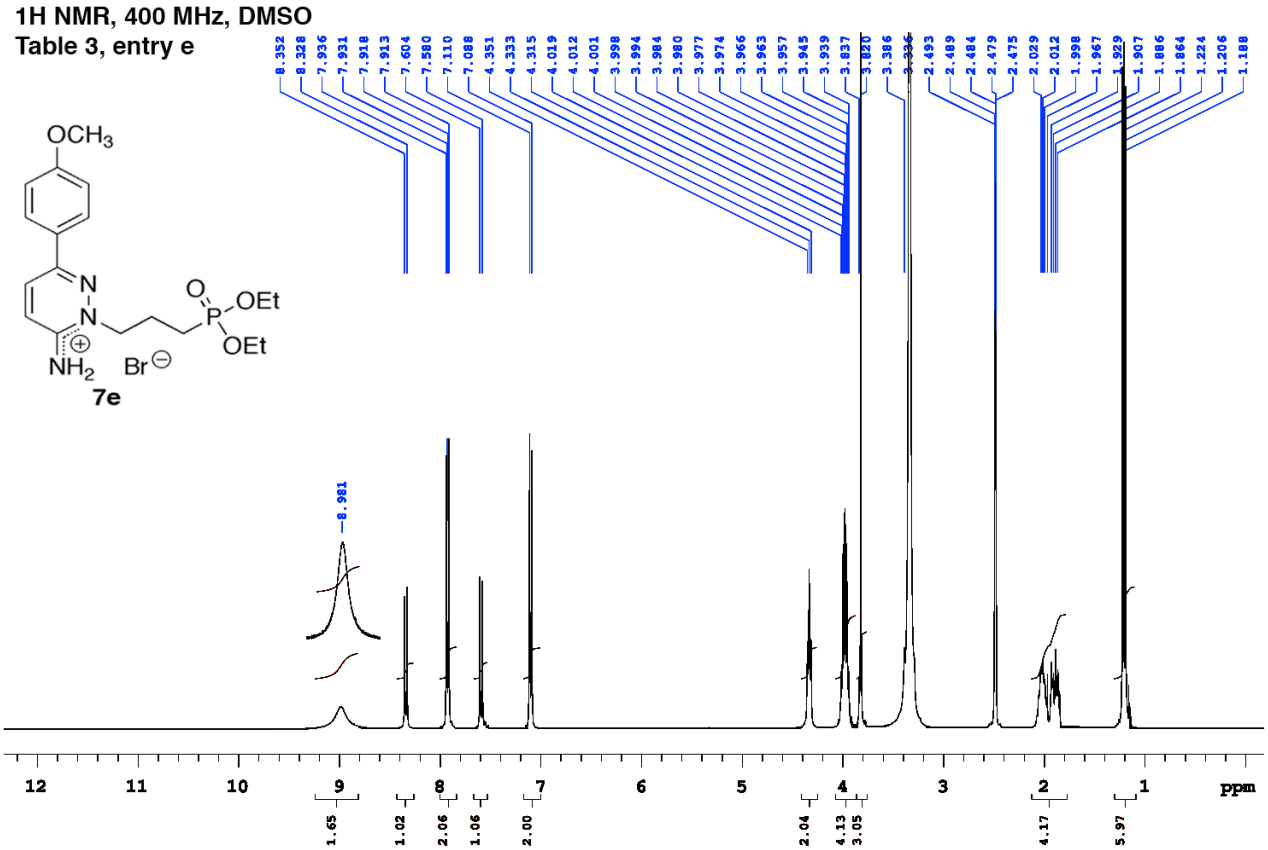


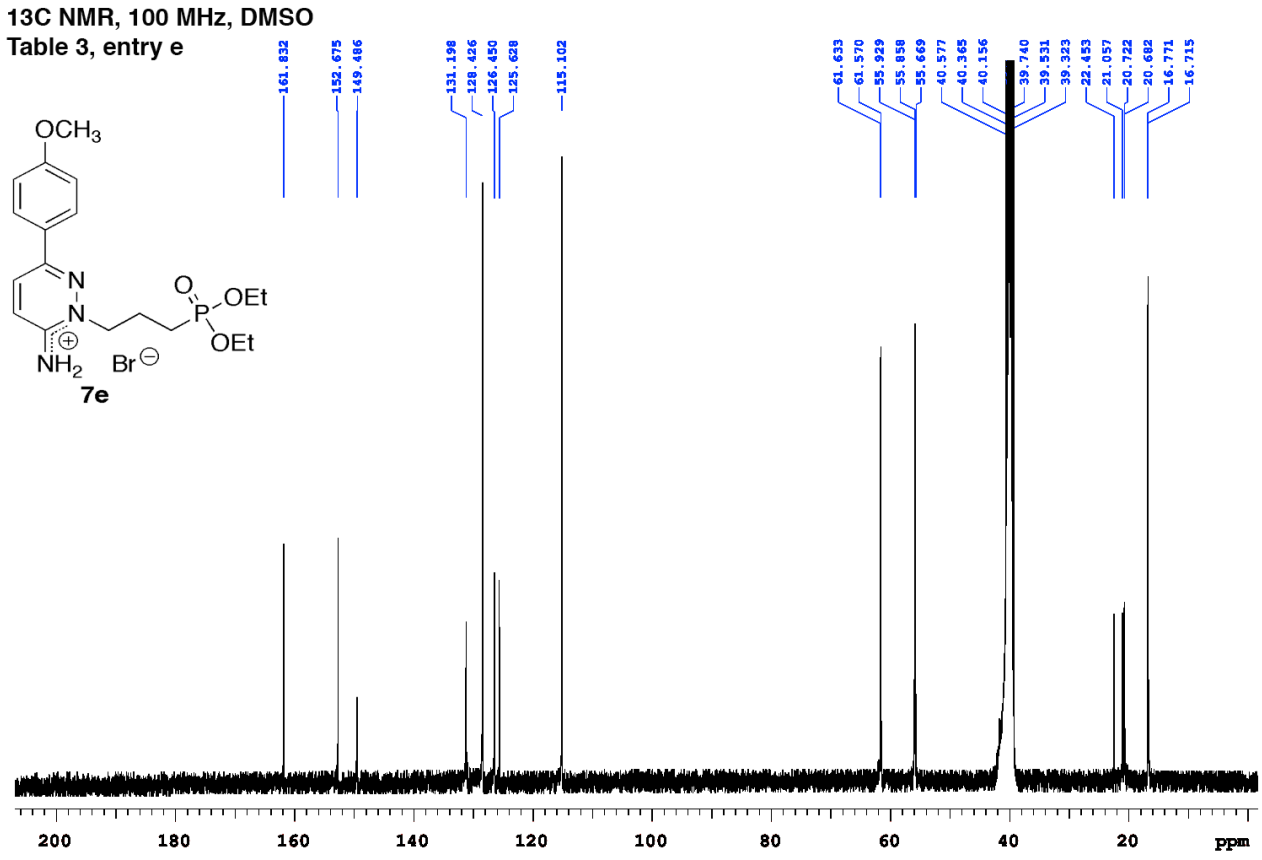
Compound 7d: off-white color solid; 96% yield; MS (ESI) m/z = 331.34 [M + 1]; HRMS (ESI) calcd for $C_{18}H_{24}N_3O_3$ [M^+ - Br] 330.1818, found 330.1815.



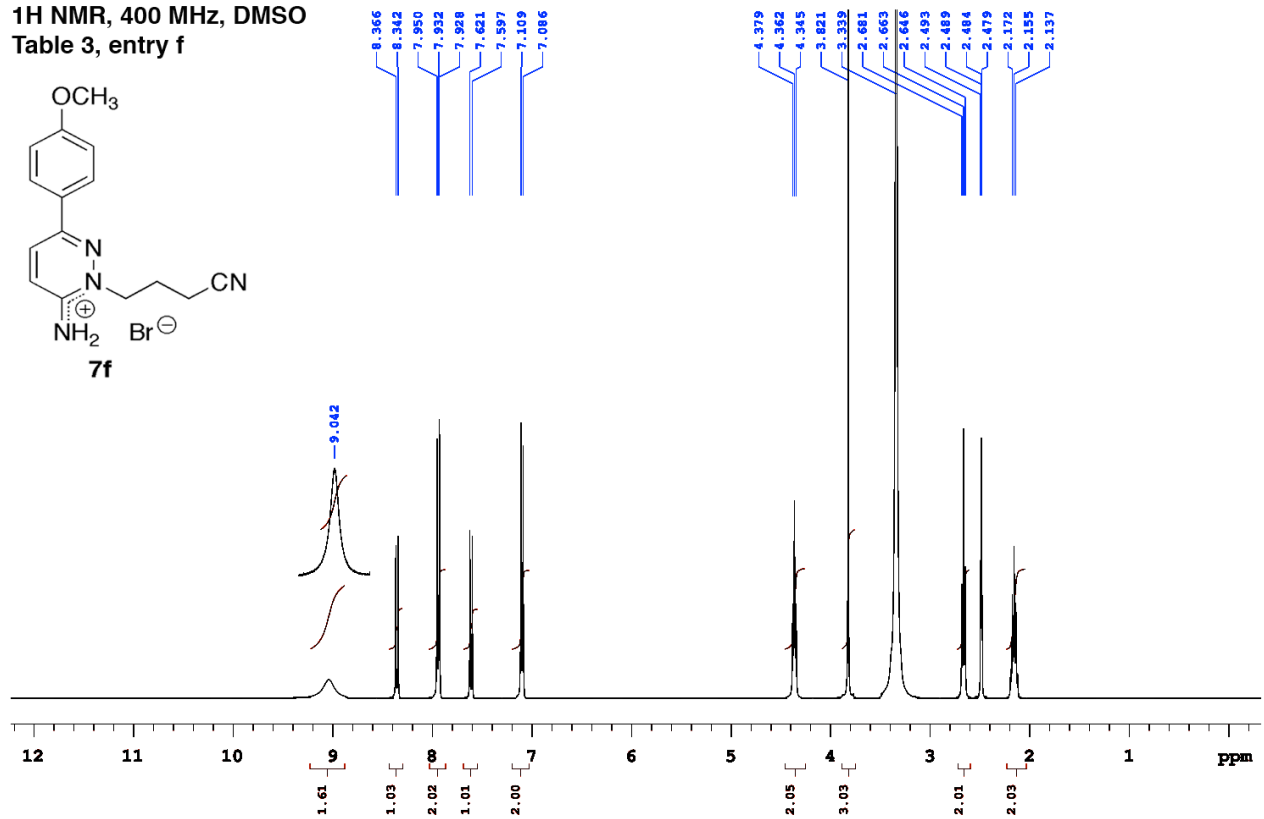


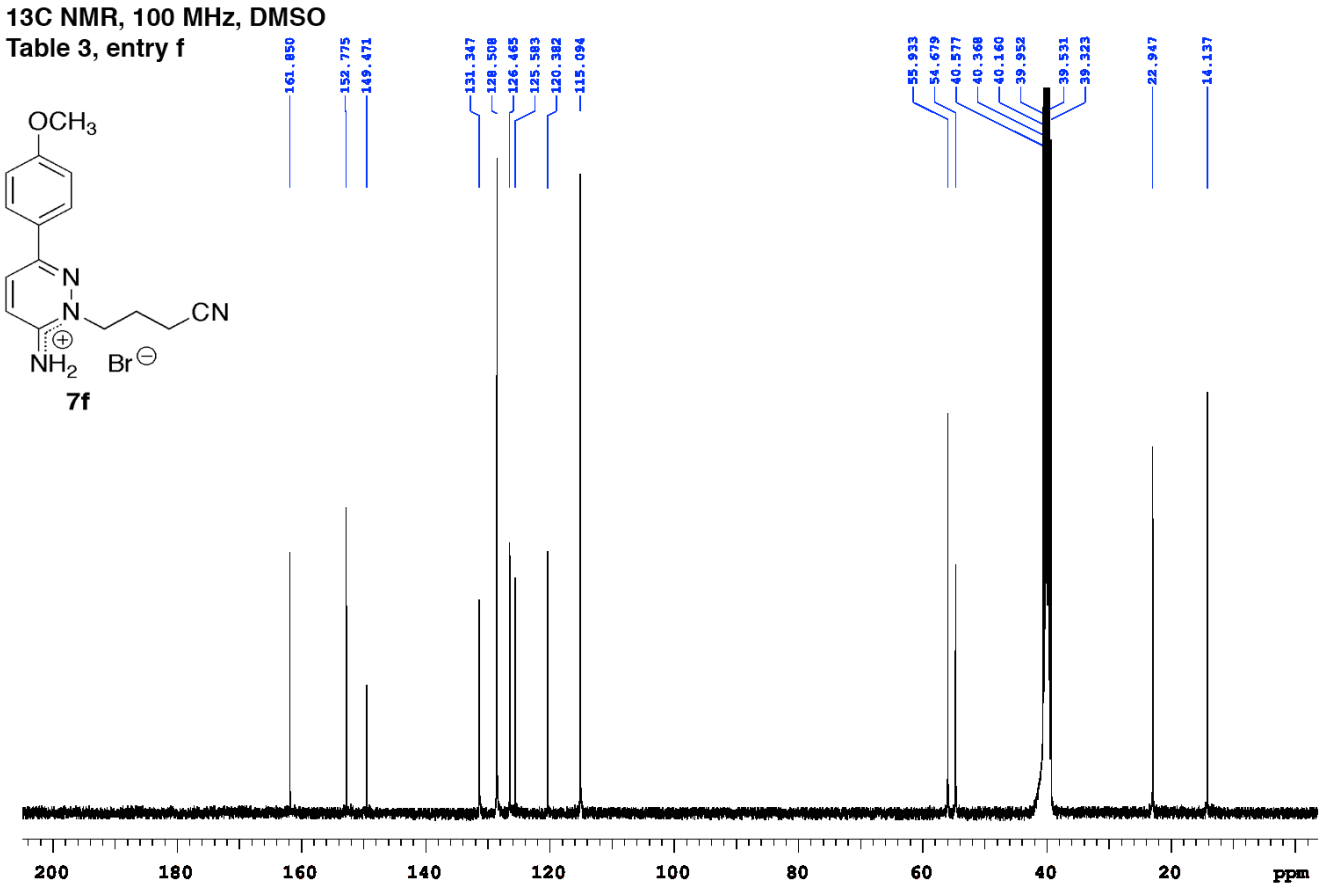
Compound 7e: off-white color solid; 90% yield; mp 173-176°C; MS (ESI) m/z = 381.24 [M + 1]; HRMS (ESI) calcd for $C_{18}H_{27}N_3O_4P$ [M^+ - Br] 380.1739, found 380.1737.



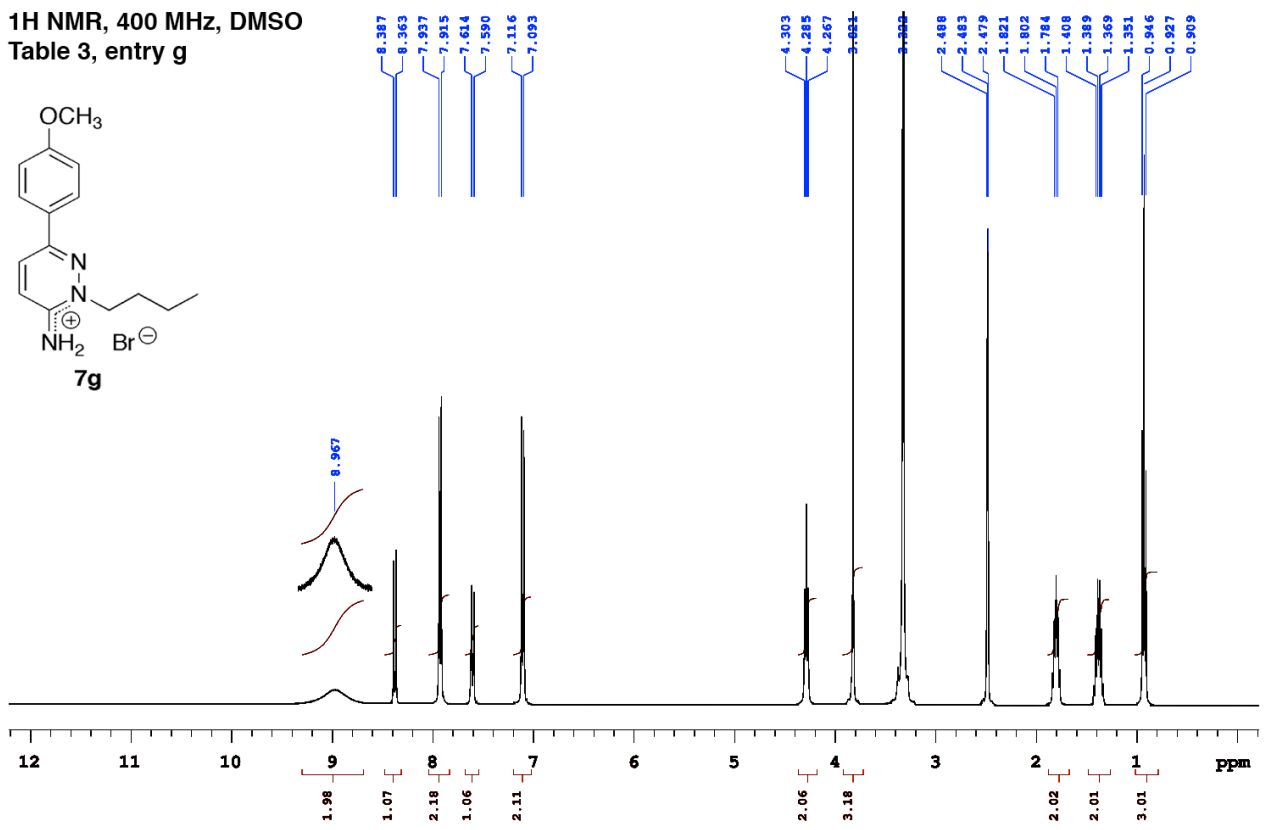


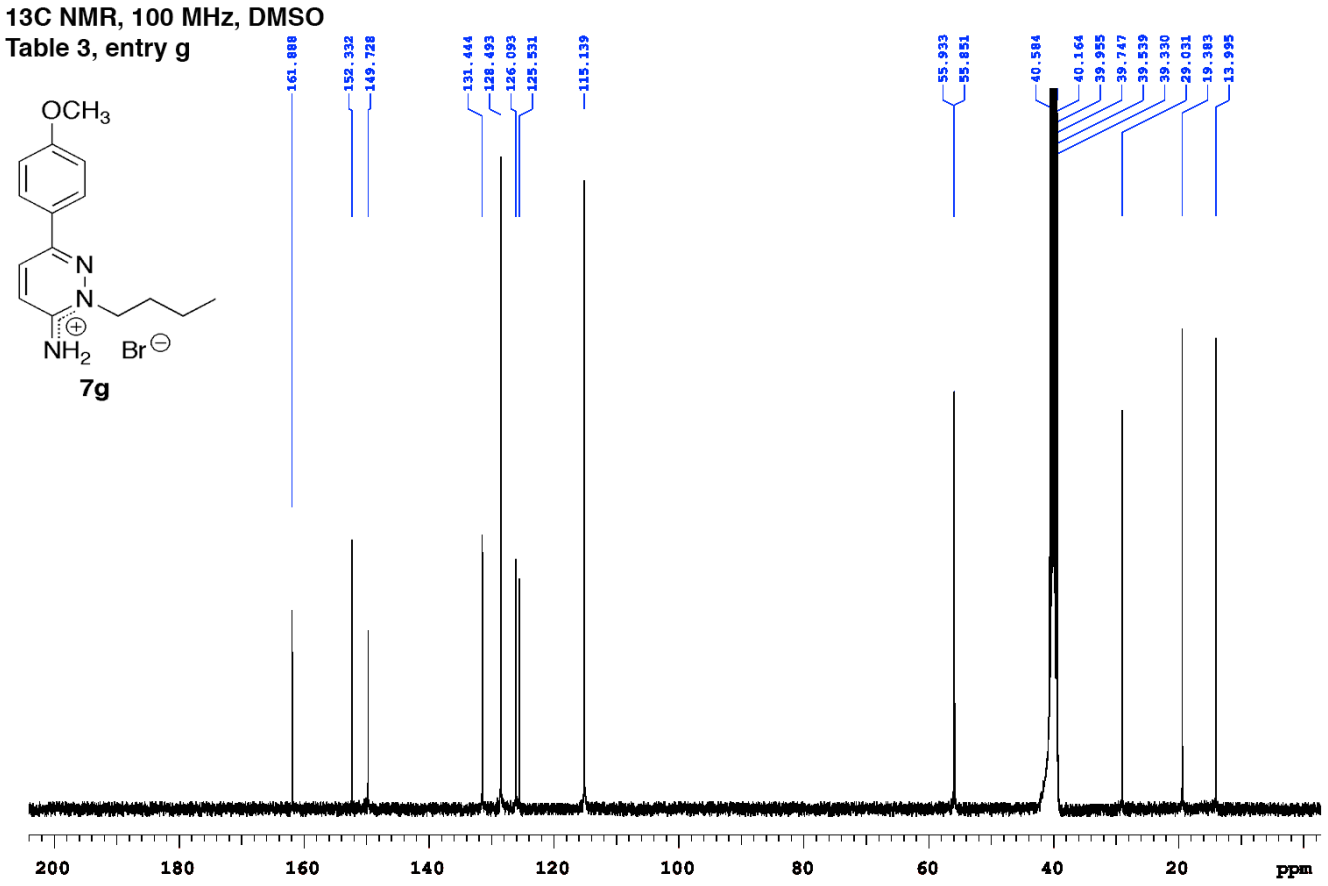
Compound 7f: off-white color solid; 92% yield; mp 263-266°C (decomposition); MS (ESI) m/z = 270.24 [M + 1]; HRMS (ESI) calcd for $C_{15}H_{17}N_4O$ [M^+ - Br] 269.1402, found 269.1399.



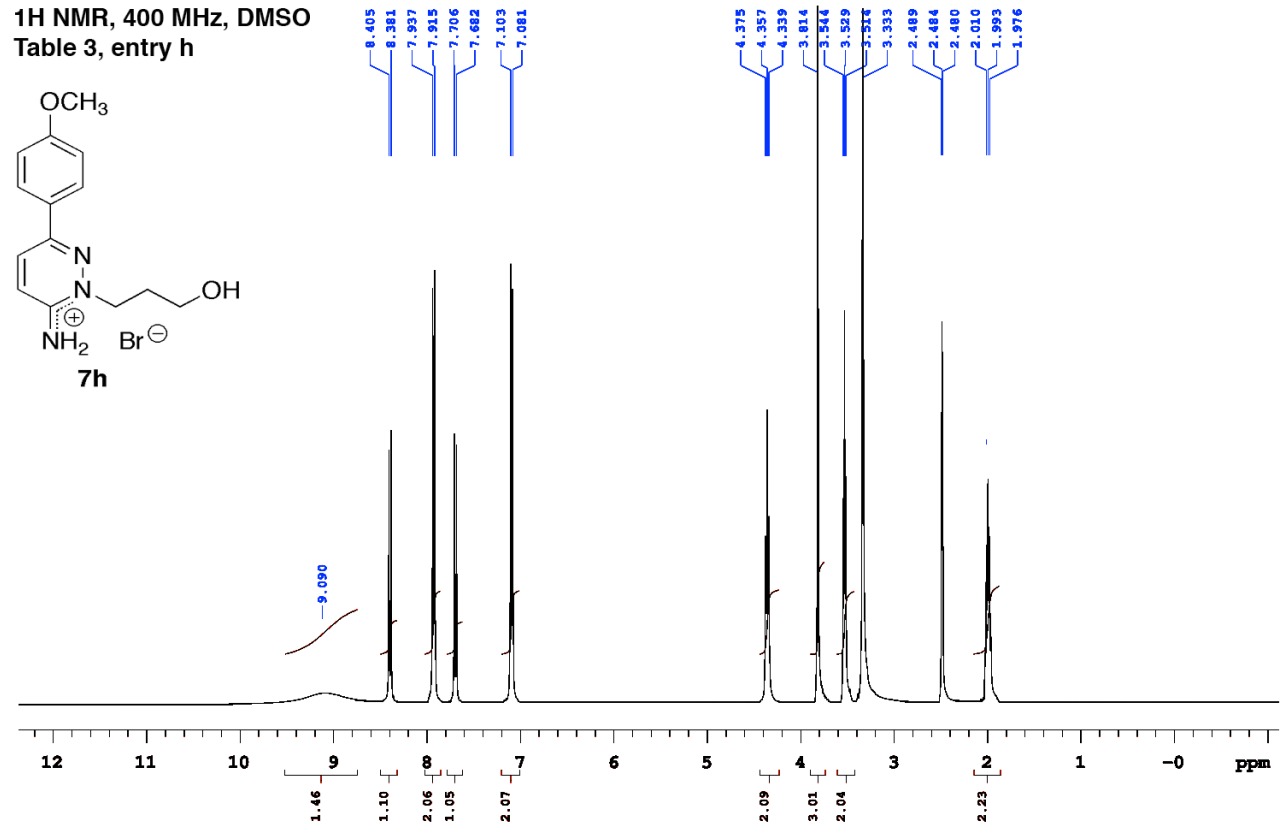


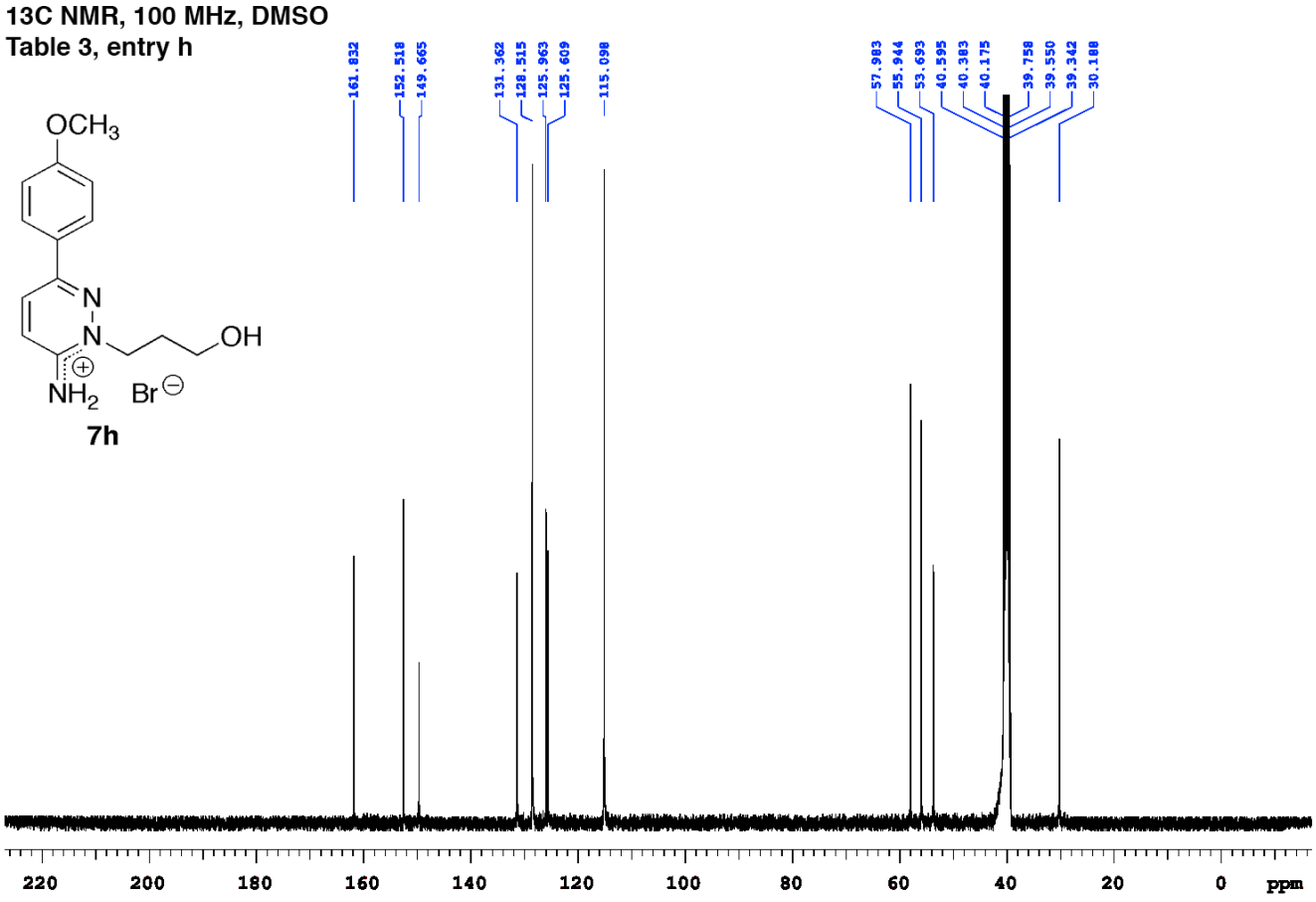
Compound 7g: off-white color solid; 93% yield; mp 275-278°C (decomposition); MS (ESI) m/z = 259.27 [M + 1]; HRMS (ESI) calcd for $C_{15}H_{20}N_3O$ [M^+ - Br] 258.1606, found 258.1600.



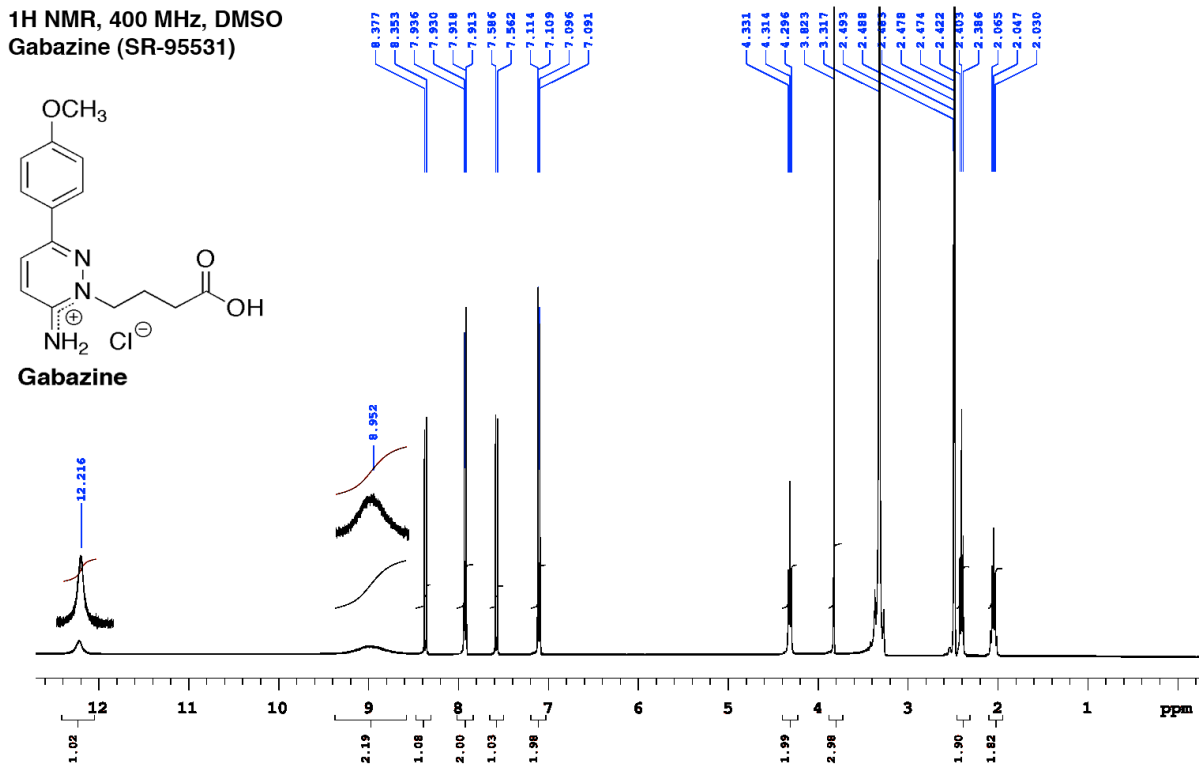


Compound 7h: off-white color solid; 52% yield; MS (ESI) m/z = 261.30 [M + 1]; HRMS (ESI) calcd for $C_{14}H_{18}N_3O_2$ [M^+ - Br] 260.1399, found 260.1403.

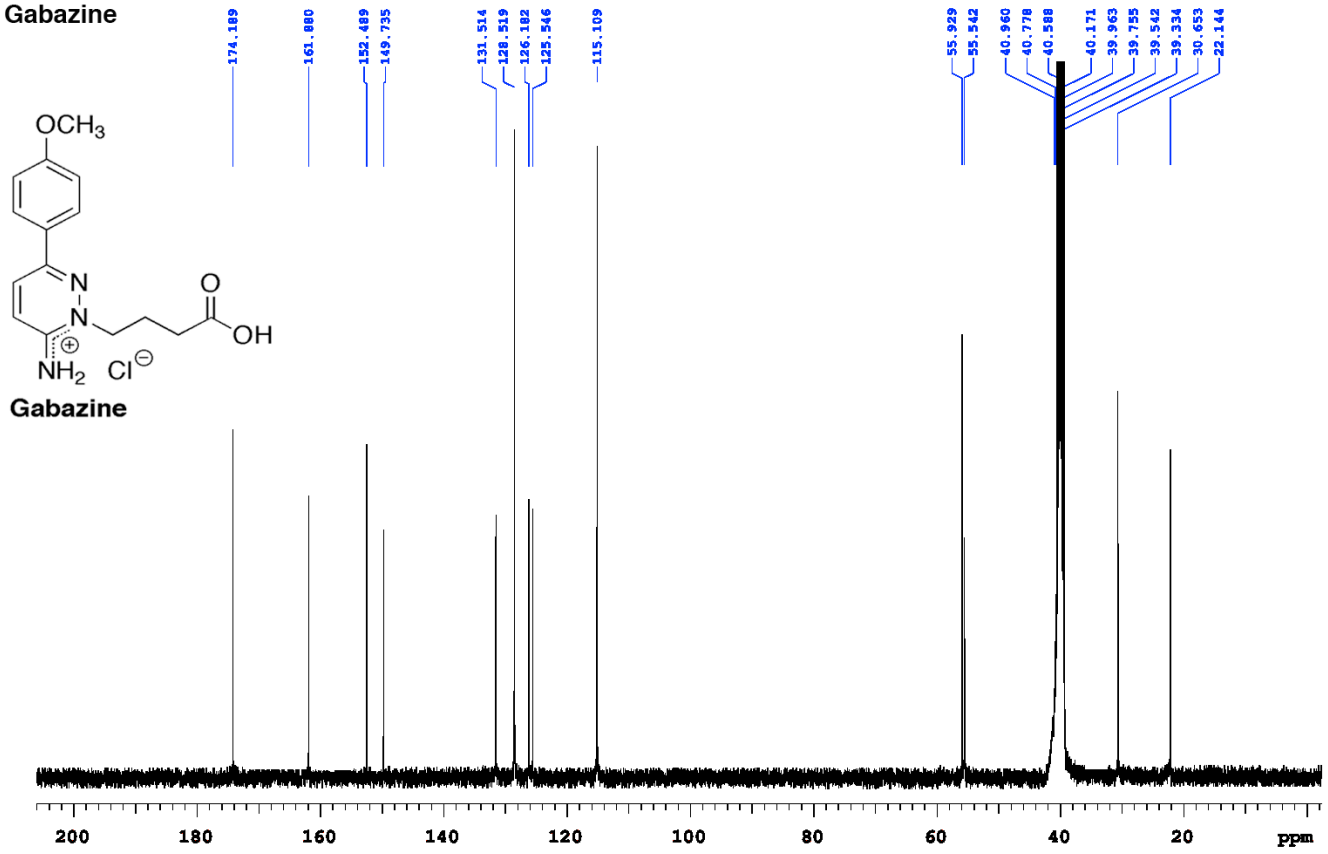




Gabazine (SR-95531): white color solid; 85% yield; mp 219-222°C; MS (ESI) m/z = 288.07 [M^+]; HRMS (ESI) calcd for $C_{15}H_{18}N_3O_3$ [M^+ - Cl] 288.1348, found 288.1337.



13C NMR, 100 MHz, DMSO
Gabazine



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1. R. Sun, Y. Zhang, F. Bi, and Q. Wang. *J. Agric. Food Chem.,* 2009, **57**, 6356-6361.
2. S. Guery, I. Parrott, Y. Rival and C. G. Wermuth, *Tetrahedron Lett.,* 2001, **42**, 2115-2117.
3. B. U. W. Maes, G. L. F. Lemière, R. Dommisse, K. Augustyns and A. Haemers, *Tetrahedron,* 2000, **56**, 1777-1781.