

The Regioselective Nucleophilic Aromatic Substitution (S_NAr) Reaction of 2-Substituted-3,5-Dichloropyrazines

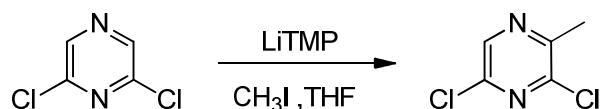
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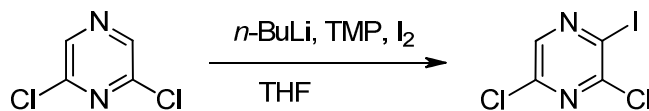
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A. Materials and Methods.

Unless stated otherwise, reactions were conducted in air-dried glassware under an atmosphere of nitrogen using commercial solvents without further drying or distilling. All commercially obtained reagents were used as received unless otherwise specified. Commercial reagents, including cesium fluoride (CsF), were obtained from Sigma-Aldrich unless otherwise specified. Reaction temperatures were controlled using an IKA Mag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, p-anisaldehyde, iodine, and potassium permanganate stains. Biotage and ISCO systems were used for flash column chromatography using compatible silica gel cartridges and eluting with ethyl acetate in heptanes unless otherwise noted. ¹H NMR spectra were recorded on Bruker spectrometers (at 300 MHz or 400 MHz) and are reported relative to deuterated solvent signals. ¹³C NMR spectra were recorded on Bruker spectrometers (at 75 MHz or 101 MHz) and are reported relative to deuterated solvent signals. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. High resolution mass spectra were obtained using an Agilent Jet Stream 6230 Accurate Mass TOF LC/MS.

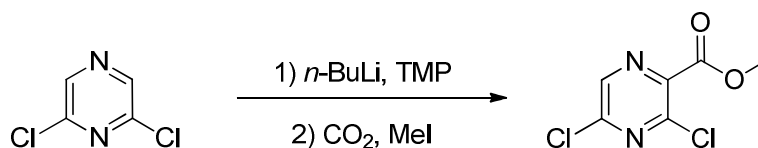
B. Preparation of 2-substituted-3,5-dichloropyrazines**(1): Preparation of 3,5-dichloro-2-methylpyrazine**

To a solution of *n*-BuLi (268 mL, 0.680 mol) in dry THF (2.5 L) was added tetramethylpiperidine (94.6 g, 0.680 mol) at -78 °C. After the addition, the mixture was warmed to 0 °C and stirred for 30 minutes at this temperature. The reaction mixture was cooled to -78 °C, then 2,6-dichloropyrazine (50.0 g, 0.340 mol, freshly re-crystallized from DCM) in THF (500 mL) was added into the reaction mixture dropwise. The mixture was stirred for another 30 minutes at -78 °C, CH₃I (240 g, 3.40 mol) was added, and the reaction mixture was slowly warmed to room temperature for 3 hours. The mixture was concentrated and diluted with H₂O (300 mL), extracted with DCM (100 mL X 4). The combined organic layers were washed with saturated NH₄Cl aqueous and water, dried over Na₂SO₄ then concentrated under vacuum. The residue was purified by chromatography (petroleum ether: ethyl acetate=30: 1) to give crude 3,5-dichloro-2-methylpyrazine (25 g, 46%), which was distilled under reduced pressure to give 3,5-dichloro-2-methylpyrazine (8.98 g, 16%) as yellow oil. ¹H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 2.58 (s, 0.88H), 2.63 (s, 3H), 8.43 (s, 1H).; ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 21.59 (s, 1 C) 142.31 (s, 1 C) 144.06 (s, 1 C) 146.40 (s, 1 C) 151.77 (s, 1 C); HRMS-(ESI+) for C₅H₃Cl₂N₂ [M+H]: calculated: 162.9824, found: 162.9828.

(2): Preparation of 3,5-dichloro-2-iodopyrazine

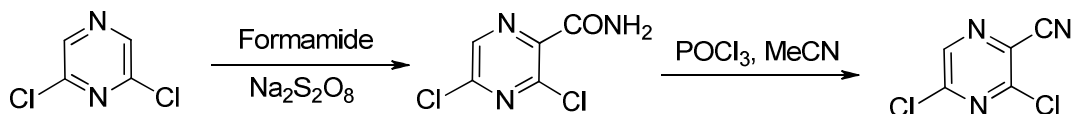
To a solution of tetramethylpiperidine (45.2 g, 0.320 mol) in dry THF (1 L) was added dropwise *n*-BuLi (2.5M solution in hexane, 128 mL, 0.32 mol) at -60 °C under N₂. The resulting mixture was stirred at 0 °C for 30 minutes. The mixture was cooled to -80 °C and a solution of 2,6-dichloropyrazine (40.0 g, 0.268 mol) in dry THF (800 mL) was added dropwise at -80 °C. After stirring at -80 °C for 30 minutes, a solution of I₂ (68.0 g, 0.280 mol) in dry THF (700 mL) was added to the mixture at -80 °C under N₂. The mixture was stirred at -80 °C for 10 minutes then quenched with ice water (100 mL). The mixture was diluted with EtOAc (2 L) and washed with Na₂S₂O₃ aq (200 mL) and brine (500 mL x 2). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with petroleum ether to afford 3,5-dichloro-2-iodopyrazine (30 g, 40.3%) as a white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 8.24 (s, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 118.77 (s, 1 C) 143.87 - 144.16 (m, 1 C) 146.17 (s, 1 C) 152.26 (s, 1 C).

(3): Preparation of methyl 3,5-dichloropyrazine-2-carboxylate



To a solution of tetramethylpiperidine (5.99 g, 40.2 mmol) in THF (200 mL) at -40 °C, was added *n*-BuLi (3.10 g, 48.0 mmol) and the reaction mixture was allowed to stir for 20 minutes. The reaction mixture was cooled to -78 °C and 2,6-dichloropyrazine (6.00 g, 40.2 mmol) was added as a solution in THF (50 mL). The reaction mixture was stirred for 5 minutes, then added to an Erlenmeyer flask containing crushed dry ice (240 g) as a solid powder. The solution was stirred rapidly and allowed to warm to room temperature overnight. Solvents were removed *in vacuo* and the residue dissolved in DMF (100 mL). To the solution was added sodium bicarbonate (2.8 g) and methyl iodide (10.4 mL) and the solution was allowed to stir for 3 hours. 10% citric acid was added and the aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with water (100 mL x 2) and brine (100 mL), then dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by column chromatography (DCM) and the clean fractions concentrated *in vacuo* to give methyl 3,5-dichloropyrazine-2-carboxylate (4.1 g, 49%) as a pale yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.95 (s, 3 H) 8.93 (s, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 53.78 (s, 1 C) 141.87 (s, 1 C) 143.23 (s, 1 C) 145.25 (s, 1 C) 148.76 (s, 1 C) 163.35 (s, 1 C). HRMS-(ESI+) for C₆H₅Cl₂N₂O₂ [M+H]: calculated: 206.9723, found: 206.9718.

(4): Preparation of 3,5-dichloropyrazine-2-carbonitrile



Step 1:

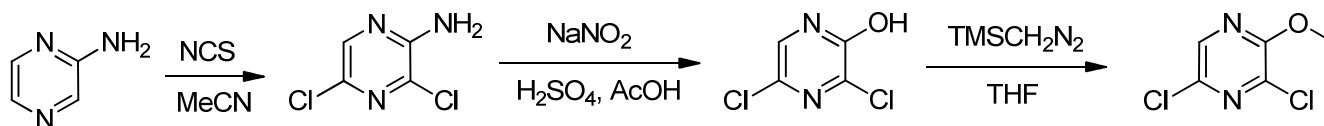
2,6-dichloropyrazine (5.5 g, 37.0 mmol) and formamide (33.2 g, 737 mmol) were combined and heated to 90 °C. Sodium persulfate (8.55 g, 36.0 mmol) was added to the reaction mixture at 90 °C. (Note, large exotherm on addition of the persulfate solid.) The reaction mixture was stirred at 90 °C for 2 hours, then allowed to stir at room temperature overnight. The reaction mixture was diluted with water (50 mL), and the aqueous layer extracted with IPA/chloroform (1/3, 3 x 75 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum to afford a viscous oil. The crude oil was purified by column chromatography (ethyl acetate/heptanes (0-100%)) to afford 3,5-dichloropyrazine-2-carboxamide (2.5 g, 36%) as an oil, which solidifies to a colorless solid on standing. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 8.87 (s, 1H), 8.18 (br. s., 1H), 8.01 (br. s., 1H).

Step 2:

To a solution of 3,5-dichloropyrazine-2-carboxamide (2.55 g, 13.3 mmol) in acetonitrile (50 mL) was added POCl₃ (5.80 g, 37.0 mmol). The reaction mixture was slowly heated to 80 °C and allowed to stir at that temperature for 4 hours. NaHCO₃ (sat., aq) was added and the aqueous layer was extracted with

ethyl acetate. The combined organic layers were dried over sodium sulfate then concentrated under vacuum. The crude residue was purified by column chromatography (0-30% ethyl acetate in heptanes) to give 3,5-dichloropyrazine-2-carbonitrile (1.53 g, 66%) as a colorless solid. ^1H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 8.64 (s, 1H) : ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 150.8, 150.43, 143.24, 128.06, 113.06.

(5): Preparation of 3,5-dichloro-2-methoxypyrazine



Step 1:

To a stirred solution of pyrazin-2-amine (50.0 g, 0.530 mol) in dry MeCN (1 L) was added NCS (140 g, 1.05 mol) portionwise at 10-20 °C under N_2 . The mixture was stirred at room temperature for 13 hours. The dark reaction mixture was concentrated under vacuum and the residue was purified quickly by column chromatography (EtOAc/hexane 1:20 to 1:9) to give 3,5-dichloropyrazin-2-amine (49.5 g, 29%) as a white solid.

Step 2:

To a stirred solution of 3,5-dichloropyrazin-2-amine (20.0 g, 122 mmol) in AcOH (200 mL) was added dropwise conc H_2SO_4 (36.6 mL) at 10-15 °C. The mixture was added dropwise to a solution of NaNO_2 (46.4 g, 671 mmol) in water (250 mL) at 10-15 °C during a period of 45 min. The resulting mixture was stirred at 10-15 °C for 1 hour. The mixture was poured into water (1 L) and extracted with EtOAc (500 mL x 3). The combined extracts were washed with NaHCO_3 (500 mL x 3), brine (400 mL), dried with Na_2SO_4 and concentrated under vacuum to give 3,5-dichloropyrazin-2-ol (29.5 g, 74%) as a yellow solid.

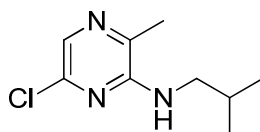
Step 3:

To a stirred solution of 3,5-dichloropyrazin-2-ol (11.1 g, 66.9 mmol) in THF (100 mL) was added dropwise TMSCH_2N_2 (50.2 mL, 100.5 mmol) at 0 °C during a period of 30 minutes under N_2 . The mixture was stirred at 0 °C for 40 minutes, then concentrated under vacuum. The residue was purified quickly by column chromatography (EtOAc/hexane, 1:100) to afford 3,5-dichloro-2-methoxypyrazine (5.95 g, 25%) as white solid. ^1H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 4.05 (s, 3H), 8.03 (s, 1H); ^{13}C NMR (101 MHz, DMSO-*d*₆) δ ppm 55.50 – 56.17 (m, 1 C) 135.09 (s, 1 C) 136.90 (s, 1 C) 139.23 – 139.50 (m, 1 C) 155.94 (s, 1 C); HRMS-(ESI+) for $\text{C}_5\text{H}_5\text{Cl}_2\text{N}_2\text{O}$ [M+H]: calculated: 178.9773, found: 178.9774.

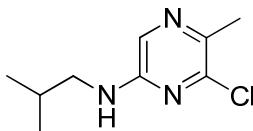
C. General procedure for the Nucleophilic Aromatic Substitution

To a solution of 2-substituted-3,5-dichloropyrazine (1 eq) in DMSO (0.3 M) was added CsF (3 eq) and amine (1 eq). The reaction was stirred at room temperature for 2 hours. If no product was formed, the reaction mixture was heated to 75 °C until all starting materials were consumed. Upon completion the crude reaction mixture was diluted with water and EtOAc. The layers were separated and the organic phase was washed with brine, dried over MgSO_4 , filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (heptanes/ethyl acetate). Clean fractions were combined and the solvent was removed under vacuum to give the desired product.

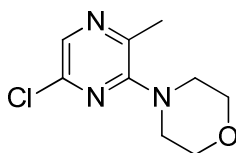
D. Characterization of products



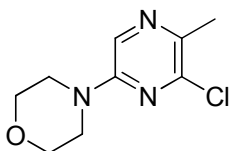
(6A): 6-chloro-3-methyl-N-(2-methylpropyl)pyrazin-2-amine: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.87 (d, $J=6.57$ Hz, 6 H) 1.86 - 1.95 (m, 1 H) 2.26 (s, 3 H) 3.10 (dd, $J=6.95, 5.68$ Hz, 2 H) 6.87 (t, $J=5.05$ Hz, 1 H) 7.53 (s, 1 H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ ppm 19.87 (s, 1 C) 20.40 (s, 2 C) 27.25 (s, 1 C) 48.35 (s, 1 C) 126.46 (s, 1 C) 138.89 (s, 1 C) 143.59 (s, 1 C) 153.00 (s, 1 C); HRMS-(ESI+) for $\text{C}_9\text{H}_{15}\text{ClN}_3$ [M+H]: calculated: 200.0949, found: 200.0956, Δ (3.36 ppm).



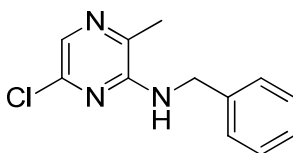
(6B): 6-chloro-5-methyl-N-(2-methylpropyl)pyrazin-2-amine: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.82 (s, 1H), 7.21 (br. s., 1H), 3.02 (t, $J=6.24$ Hz, 2H), 2.32 (s, 3H), 1.82 (quin, $J=6.65, 13.40$ Hz, 1H), 0.90 (d, $J=6.60$ Hz, 6H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 153.6, 144.4, 134.2, 130.1, 48.0, 27.4, 20.1, 19.9; HRMS-(ESI+) for $\text{C}_9\text{H}_{15}\text{ClN}_3$ [M+H]: calculated: 200.0949, found: 200.0959, Δ (4.08 ppm).



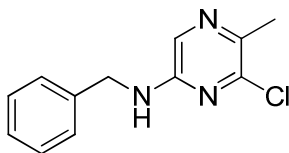
(7A): 4-(6-chloro-3-methylpyrazin-2-yl)morpholine: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 2.44 (s, 3 H) 3.14 - 3.24 (m, 4 H) 3.67 - 3.78 (m, 4 H) 8.12 (s, 1 H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ ppm 21.47 (s, 1 C) 48.70 (s, 1 C) 65.86 (s, 1 C) 133.81 (s, 1 C) 142.33 (s, 1 C) 144.06 (s, 1 C) 155.74 (s, 1 C); HRMS-(ESI+) for $\text{C}_9\text{H}_{13}\text{ClN}_3\text{O}$ [M+H]: calculated: 214.0742, found: 214.0734, Δ (-3.40 ppm).



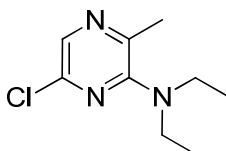
(7B): 4-(6-chloro-5-methylpyrazin-2-yl)morpholine: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 2.40 (s, 3 H) 3.42 - 3.51 (m, 4 H) 3.64 - 3.74 (m, 4H) 8.19 (s, 1 H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 20.20 (s, 1 C) 44.65 (s, 1 C) 65.70 (s, 1 C) 128.64 (s, 1 C) 137.33 (s, 1 C) 144.23 (s, 1 C) 153.18 (s, 1 C).



(8A): N-benzyl-6-chloro-3-methylpyrazin-2-amine: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 2.34 (s, 3 H) 4.54 (d, $J=5.84$ Hz, 2 H) 7.16 - 7.38 (m, 5 H) 7.51 (t, $J=5.84$ Hz, 1 H) 7.61 (s, 1 H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ ppm 19.73 (s, 1 C) 43.81 (s, 1 C) 126.65 (s, 1 C) 127.07 (s, 1 C) 127.20 (s, 2 C) 128.19 (s, 2 C) 138.85 (s, 1 C) 139.47 (s, 1 C) 143.31 (s, 1 C) 152.40 (s, 1 C); HRMS-(ESI+) for $\text{C}_{12}\text{H}_{13}\text{ClN}_3$ $[\text{M}+\text{H}]^+$: calculated: 234.0793, found: 234.0788, Δ (-1.73 ppm).

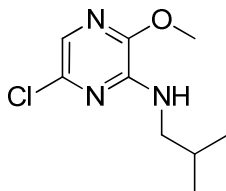


(8B): N-benzyl-6-chloro-5-methylpyrazin-2-amine: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.33 (s, 3 H) 4.43 (d, $J=5.75$ Hz, 2 H) 7.25 (d, $J=4.28$ Hz, 1 H) 7.33 (d, $J=4.28$ Hz, 4 H) 7.74 (br. s., 1 H) 7.85 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 20.46 (s) 44.41 (s) 127.36 (s) 127.86 (s) 128.82 (s) 130.65 (s) 135.58 (s) 139.65 (s) 144.93 (s) 153.65 (s); HRMS-(ESI+) for $\text{C}_{12}\text{H}_{13}\text{ClN}_3$ $[\text{M}+\text{H}]^+$: calculated: 234.0793, found: 234.0789, Δ (-3.04 ppm).

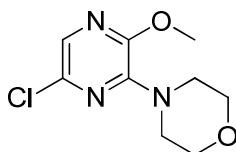


(9A): 6-chloro-N,N-diethyl-3-methylpyrazin-2-amine: ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ ppm 1.16 (t, $J=7.05$ Hz, 6 H) 2.48 (s, 3 H) 3.36 (q, $J=7.05$ Hz, 4 H) 7.90 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm

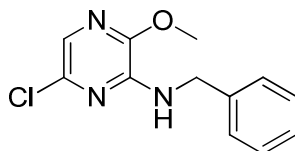
13.09 (s, 1 C) 22.44 (s, 1 C) 44.00 (s, 1 C) 48.90 (s, 1 C) 131.39 (s, 1 C) 142.48 (s, 1 C) 155.56 (s, 1 C); HRMS-(ESI+) for $C_9H_{15}ClN_3$ [M+H]: calculated: 200.0949, found: 200.0944, Δ (-2.48 ppm).



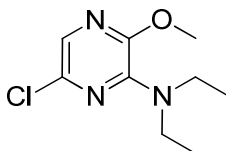
(10A): 6-chloro-3-methoxy-N-(2-methylpropyl)pyrazin-2-amine: 1H NMR (300 MHz, DMSO- d_6) δ ppm 0.86 (d, $J=6.59$ Hz, 6 H) 1.93 (dquin, $J=13.58$, 6.83, 6.83, 6.83, 6.83 Hz, 1 H) 3.09 (dd, $J=7.06$, 5.93 Hz, 2 H) 3.32 (s, 3 H) 7.15 (t, $J=5.75$ Hz, 1 H) 7.20 (s, 1 H); ^{13}C NMR (75 MHz, DMSO- d_6) δ ppm 20.11 (s, 2 C) 27.09 (s, 1 C) 47.66 (s, 1 C) 53.68 (s, 1 C) 121.27 (s, 1 C) 136.84 (s, 1 C) 144.94 (s, 1 C) 146.76 (s, 1 C); HRMS-(ESI+) for $C_9H_{15}ClN_3O$ [M+H]: calculated: 216.0898, found: 216.089, Δ (-3.88 ppm).



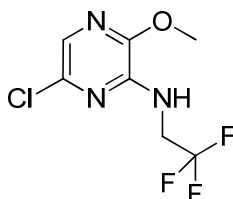
(11A): 4-(6-chloro-3-methoxypyrazin-2-yl)morpholine: 1H NMR (300 MHz, DMSO- d_6) δ ppm 3.48 - 3.52 (m, 4 H) 3.67 - 3.71 (m, 4 H) 3.90 (s, 3 H) 7.62 (s, 1 H); ^{13}C NMR (101 MHz, DMSO- d_6) δ ppm 47.15 (s, 2 C) 53.97 (s, 1 C) 65.78 (s, 2 C) 127.00 (s, 1 C) 135.89 (s, 1 C) 145.46 (s, 1 C) 149.27 (s, 1 C); HRMS-(ESI+) for $C_9H_{13}ClN_3O_2$ [M+H]: calculated: 230.0691, found: 230.0685, Δ (-2.69 ppm).



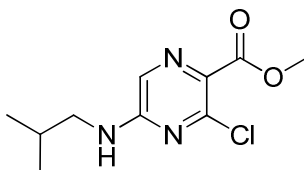
(12A): N-benzyl-6-chloro-3-methoxypyrazin-2-amine: 1H NMR (300 MHz, DMSO- d_6) δ ppm 3.91 (s, 3 H) 4.49 (d, $J=6.40$ Hz, 2 H) 7.17 - 7.26 (m, 2 H) 7.30 (d, $J=4.33$ Hz, 4 H) 7.75 (t, $J=6.12$ Hz, 1 H); ^{13}C NMR (75 MHz, DMSO- d_6) δ ppm 43.34 (s, 1 C) 53.82 (s, 1 C) 122.05 (s, 1 C) 126.69 (s, 1 C) 127.26 (s, 2 C) 128.18 (s, 2 C) 136.72 (s, 1 C) 139.31 (s, 1 C) 144.54 (s, 1 C) 146.97 (s, 1 C); HRMS-(ESI+) for $C_{12}H_{13}ClN_3O$ [M+H]: calculated: 250.0742, found: 250.0734, Δ (-2.99 ppm).



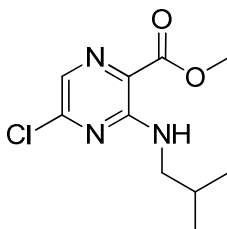
(13A): 6-chloro-*N,N*-diethyl-3-methoxypyrazin-2-amine: ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.12 - 1.24 (m, 6 H) 3.57 (q, $J=6.97$ Hz, 4 H) 3.92 (s, 3 H) 7.29 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-*d*₆) δ ppm 12.59 - 14.59 (m, 2 C) 44.23 (s, 2 C) 53.39 - 55.14 (m, 1 C) 122.69 - 124.82 (m, 1 C) 136.57 (s, 1 C) 145.15 (s, 1 C) 148.38 (s, 1 C); HRMS-(ESI+) for C₉H₁₅ClN₃O [M+H]⁺: calculated: 216.0898, found: 216.0902, Δ (1.58 ppm).



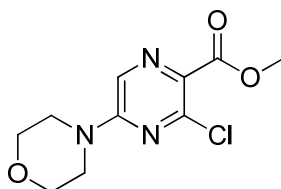
(14A): 6-chloro-3-methoxy-*N*-(2,2,2-trifluoroethyl)pyrazin-2-amine: ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.00 (s, 3 H) 4.17 (qd, $J=9.02$, 6.67 Hz, 2 H) 5.30 (br. s., 1 H) 7.40 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-*d*₆) δ ppm 40.41 - 41.85 (m, 1 C) 53.21 - 54.77 (m, 1 C) 122.73 - 125.19 (m, 1 C) 126.37 (s, 1 C) 136.20 (s, 1 C) 143.85 (s, 1 C) 147.16 (s, 1 C); HRMS-(ESI+) for C₇H₁₈ClF₃N₃O [M+H]⁺: calculated: 242.0303, found: 242.0293, Δ (-3.94 ppm).



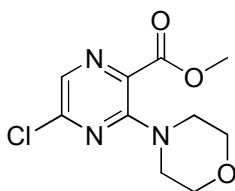
(15B): methyl 3-chloro-5-[(2-methylpropyl)amino]pyrazine-2-carboxylate: ^1H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.89 (s, 3 H) 0.91 (s, 3 H) 1.76 - 1.93 (m, 1 H) 3.12 (dd, $J=6.78$, 5.84 Hz, 2 H) 3.75 - 3.80 (m, 3 H) 7.92 (s, 1H) 8.25 (t, $J=5.56$ Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-*d*₆) δ ppm 20.05 (s, 1 C) 20.16 (s, 1 C) 27.45 (s, 1 C) 27.76 (s, 1 C) 27.91 (s, 1 C) 47.88 (s, 1 C) 51.76 (s, 1 C) 154.93 (s, 1 C) 163.71 (s, 1 C); HRMS-(ESI+) for C₁₀H₁₅ClN₃O₂ [M+H]⁺: calculated: 244.0847, found: 244.0848, Δ (0.29 ppm).



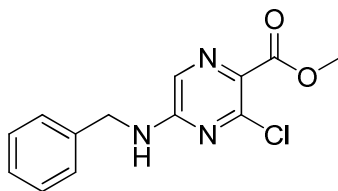
(15A): methyl 5-chloro-3-[(2-methylpropyl)amino]pyrazine-2-carboxylate: ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.92 (d, $J=6.72$ Hz, 6 H) 1.91 (dt, $J=13.48, 6.77$ Hz, 1 H) 3.19 - 3.33 (m, 3 H) 3.86 (s, 3 H) 7.87 (s, 1 H) 8.23 (t, $J=5.32$ Hz, 1 H); ^{13}C NMR (101 MHz, DMSO- d_6) δ ppm 20.44 (s, 1 C) 27.92 (s, 1 C) 48.10 (s, 1 C) 52.87 (s, 1 C) 122.93 (s, 1 C) 129.25 (s, 1 C) 150.42 (s, 1 C) 154.75 (s, 1 C) 166.64 (s, 1 C); HRMS-(ESI+) for $\text{C}_{10}\text{H}_{15}\text{ClN}_3\text{O}_2$ [M+H]: calculated: 244.0847, found: 244.0849, Δ (0.68 ppm).



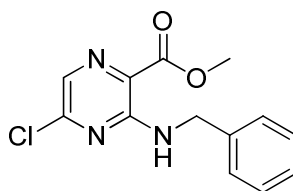
(16B): methyl 3-chloro-5-(morpholin-4-yl)pyrazine-2-carboxylate: ^1H NMR (300 MHz, DMSO- d_6) δ ppm 3.69 (s, 8 H) 3.81 (s, 3 H) 8.31 (s, 1 H); ^{13}C NMR (75 MHz, DMSO- d_6) δ ppm 41.96 - 47.15 (m, 2 C) 48.68 - 56.20 (m, 1 C) 63.25 - 68.54 (m, 2 C) 126.38 - 127.64 (m, 1 C) 129.78 (s, 1 C) 146.11 (s, 1 C) 153.59 (d, $J=10.43$ Hz, 1 C) 163.73 (d, $J=3.84$ Hz, 1 C); HRMS-(ESI+) for $\text{C}_{10}\text{H}_{13}\text{ClN}_3\text{O}_3$ [M+H]: calculated: 258.064, found: 258.0636, Δ (-1.44 ppm).



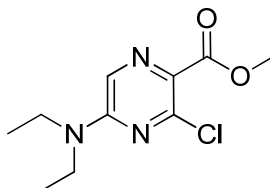
(16A): methyl 5-chloro-3-(morpholin-4-yl)pyrazine-2-carboxylate: ^1H NMR (300 MHz, DMSO- d_6) δ ppm 3.37 - 3.46 (m, 4 H) 3.62 - 3.71 (m, 4 H) 3.87 (s, 3 H) 8.03 (s, 1 H); ^{13}C NMR (101 MHz, DMSO- d_6) δ ppm 48.00 (s, 1 C) 53.17 (s, 1 C) 66.14 (s, 1 C) 129.31 (s, 1 C) 130.79 (s, 1 C) 146.68 (s, 1 C) 152.99 (s, 1 C) 165.93 (s, 1 C); HRMS-(ESI+) for $\text{C}_{10}\text{H}_{13}\text{ClN}_3\text{O}_3$ [M+H]: calculated: 258.064, found: 258.063, Δ (-4.01 ppm).



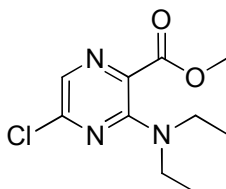
(17B): methyl 5-(benzylamino)-3-chloropyrazine-2-carboxylate: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 3.78 (s, 3 H) 4.53 (d, $J=5.84$ Hz, 2 H) 7.23 - 7.37 (m, 5 H) 7.96 (s, 1 H) 8.73 (t, $J=5.75$ Hz, 1 H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ ppm 43.94 (s, 1 C) 51.92 (s, 1 C) 127.21 (s, 1 C) 127.60 (s, 1 C) 128.47 (s, 1 C) 138.04 (s, 1 C) 154.56 (s, 1 C) 163.71 (s, 1 C) 188.60 (s, 1 C) 194.37 (s, 1 C); HRMS-(ESI+) for $\text{C}_{13}\text{H}_{13}\text{ClN}_3\text{O}_2$ [M+H]: calculated: 278.0691, found: 278.0684, Δ (-2.56 ppm).



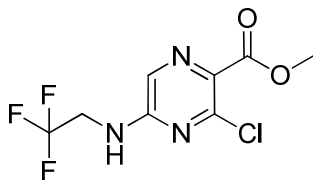
(17A): methyl 3-(benzylamino)-5-chloropyrazine-2-carboxylate: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.86 (s, 3H), 4.64 (d, $J=6.03$ Hz, 2H), 7.21-7.40 (m, 5H), 7.92 (s, 1H), 8.63 (t, $J=5.84$ Hz, 1H); HRMS-(ESI+) for $\text{C}_{13}\text{H}_{13}\text{ClN}_3\text{O}_2$ [M+H]: calculated: 278.0691, found: 278.0690, Δ (-0.15 ppm).



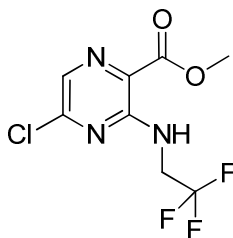
(18B): methyl 3-chloro-5-(diethylamino)pyrazine-2-carboxylate: ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ ppm 1.24 (t, $J=7.18$ Hz, 6 H) 3.59 (q, $J=7.05$ Hz, 4 H) 3.93 (s, 3 H) 7.87 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 12.88 (s, 2 C) 42.36 - 43.58 (m, 2 C) 51.35 - 53.40 (m, 1 C) 126.20 (s, 1 C) 128.15 (d, $J=4.39$ Hz, 1 C) 146.88 (s, 1 C) 152.96 (s, 1 C) 164.18 (s, 1 C); HRMS-(ESI+) for $\text{C}_{10}\text{H}_{15}\text{ClN}_3\text{O}_2$ [M+H]: calculated: 244.0847, found: 244.0859, Δ (4.97 ppm).



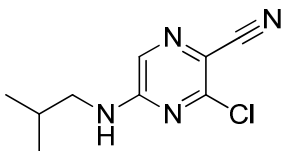
(18A): methyl 5-chloro-3-((diethylamino)pyrazine-2-carboxylate: ^1H NMR (400 MHz, CHCl_3 - d) δ ppm 1.22 (t, $J=7.05$ Hz, 6 H) 3.47 (q, $J=7.05$ Hz, 4 H) 3.96 (s, 3 H) 7.80 (s, 1 H).



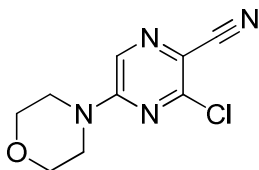
(19B): methyl 3-chloro-5-((2,2,2-trifluoroethyl)amino)pyrazine-2-carboxylate: ^1H NMR (400 MHz, $\text{Me}_2\text{SO}-d_6$) δ ppm 3.96 (s, 3 H) 4.31 (q, $J=9.06$ Hz, 2 H) 7.96 (s, 1 H); ^{13}C NMR (101 MHz, $\text{Me}_2\text{SO}-d_6$) δ ppm 52.04 (s, 1 C) 123.39 (s, 1 C) 126.17 (s, 1 C) 128.66 (s, 1 C) 146.21 (s, 1 C) 154.22 (s, 1 C) 154.31 (s, 1 C) 163.50 (s, 1 C); HRMS-(ESI+) for $\text{C}_8\text{H}_8\text{ClF}_3\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]$: calculated: 270.0252, found: 270.0247, Δ (-1.65 ppm).



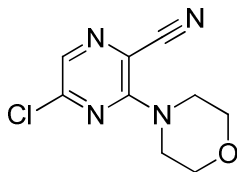
(19A): methyl 5-chloro-3-[(2,2,2-trifluoroethyl)amino]pyrazine-2-carboxylate: ^1H NMR (400 MHz, $\text{Me}_2\text{SO}-d_6$) δ ppm 3.99 (s, 3 H) 4.34 (q, $J=9.06$ Hz, 2 H) 7.99 (s, 1 H).



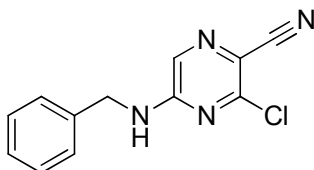
(20B): 3-chloro-5-[(2-methylpropyl)amino]pyrazine-2-carbonitrile: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.91 (d, $J=6.57$ Hz, 6 H) 1.78 - 1.93 (m, 1 H) 3.14 (t, $J=6.06$ Hz, 2 H) 7.94 (s, 1 H) 8.69 (br. s., 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 20.02 (s, 1 C) 27.30 (s, 1 C) 47.91 (s, 1 C) 110.92 (s, 1 C) 116.31 (s, 1 C) 133.63 (s, 1 C) 150.37 (s, 1 C) 155.05 (s, 1 C); HRMS-(ESI+) for $\text{C}_9\text{H}_{12}\text{ClN}_4$ $[\text{M}+\text{H}]$: calculated: 211.0745, found: 211.0736, Δ (-4.39 ppm).



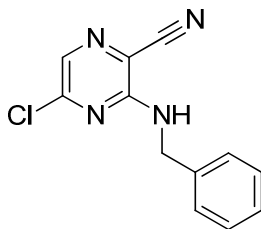
(21B): 3-chloro-5-morpholinopyrazine-2-carbonitrile: ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 3.68 - 3.76 (m, 8 H) 8.40 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ ppm 44.44 (br. s., 2 C) 65.50 (s, 2 C) 111.75 (s, 1 C) 116.08 (s, 1 C) 131.04 (s, 1 C) 149.09 (s, 1 C) 153.31 (s, 1 C); HRMS-(ESI+) for $\text{C}_9\text{H}_{10}\text{ClN}_4\text{O}$ [M+H]: calculated: 225.0538, found: 225.0533, Δ (-1.9 ppm).



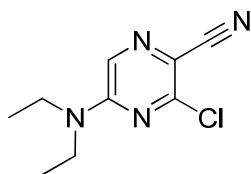
(21A): 5-chloro-3-(morpholin-4-yl)pyrazine-2-carbonitrile: ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 3.70 - 3.80 (m, 8 H) 8.16 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ ppm 46.74 (s, 2 C) 65.61 (s, 2 C) 111.61 (s, 1 C) 116.99 (s, 1 C) 132.96 (s, 1 C) 148.48 (s, 1 C) 154.92 (s, 1 C); HRMS-(ESI+) for $\text{C}_9\text{H}_{10}\text{ClN}_4\text{O}$ [M+H]: calculated: 225.0538, found: 225.053, Δ (-3.29 ppm).



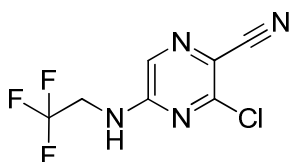
(22B): 5-(benzylamino)-3-chloropyrazine-2-carbonitrile: ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 4.55 (d, $J=5.65$ Hz, 2 H) 7.26 - 7.38 (m, 5 H) 8.00 (s, 1 H) 9.14 (t, $J=5.37$ Hz, 1 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 44.05 (s, 1 C) 116.24 (s, 1 C) 127.37 (s, 1 C) 127.75 (s, 2 C) 128.52 (s, 3 C) 133.70 (s, 1 C) 137.42 (s, 1 C) 154.69 (s, 1 C); HRMS-(ESI+) for $\text{C}_{12}\text{H}_{10}\text{ClN}_4$ [M+H]: calculated: 245.0589, found: 245.057, Δ (-5.92 ppm).



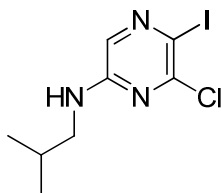
(22A): 3-(benzylamino)-5-chloropyrazine-2-carbonitrile: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 4.54 (d, $J=4.52$ Hz, 2 H) 7.19 - 7.40 (m, 5 H) 7.96 (s, 1 H) 8.65 (br. s., 1 H); HRMS-(ESI+) for $\text{C}_{12}\text{H}_{10}\text{ClN}_4$ $[\text{M}+\text{H}]$: calculated: 245.0589, found: 245.0589, Δ (0.14 ppm).



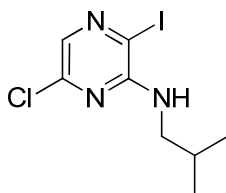
(23B): 3-chloro-5-(diethylamino)pyrazine-2-carbonitrile: ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ ppm 1.26 (t, $J=7.05$ Hz, 6 H) 3.60 (d, $J=6.80$ Hz, 4 H) 7.87 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 12.24 (br. s., 2 C) 42.71 (s, 2 C) 110.89 (s, 1 C) 116.20 (s, 1 C) 130.34 (s, 1 C) 149.31 (s, 1 C) 152.51 (s, 1 C); HRMS-(ESI+) for $\text{C}_9\text{H}_{12}\text{ClN}_4$ $[\text{M}+\text{H}]$: calculated: 211.0745, found: 211.0749, Δ (1.92 ppm).



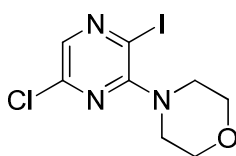
(24B): 3-chloro-5-[(2,2,2-trifluoroethyl)amino]pyrazine-2-carbonitrile: ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ ppm 4.20 (q, $J=9.32$ Hz, 2 H) 7.99 (s, 1 H); ^{13}C NMR (101 MHz, $\text{METHANOL}-d_4$) δ ppm 42.06 - 43.55 (m, 1 C) 116.41 (s, 1 C) 116.52 (s, 1 C) 121.39 - 130.72 (m, 1 C) 134.09 (br. s., 1 C) 151.92 (s, 1 C) 156.38 (s, 1 C).



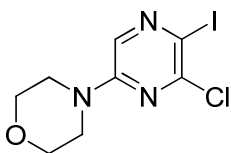
(25B): 6-chloro-5-iodo-N-isobutylpyrazin-2-amine: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 0.89 (d, $J=6.78$ Hz, 6 H) 1.81 (dquin, $J=13.45, 6.72, 6.72, 6.72, 6.72$ Hz, 1 H) 3.02 (dd, $J=6.78, 5.84$ Hz, 2H) 7.66 (t, $J=5.56$ Hz, 1 H) 7.75 (s, 1 H); HRMS-(ESI+) for $\text{C}_8\text{H}_{11}\text{ClIN}_3$ $[\text{M}]$: calculated: 310.9686, found: 310.969, Δ (1.21 ppm).



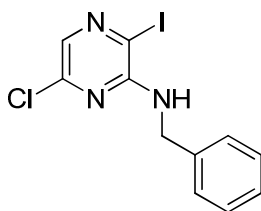
(25A): 6-chloro-3-iodo-N-isobutylpyrazin-2-amine: ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 0.80 - 0.91 (m, 6 H) 1.91 (dquin, $J=13.58$, 6.83, 6.83, 6.83 Hz, 1 H) 3.13 (dd, $J=7.06$, 5.93 Hz, 2 H) 6.83 (t, $J=5.75$ Hz, 1 H) 7.59 (s, 1 H); ^{13}C NMR (101 MHz, $\text{CHLOROFORM-}d$) δ 153.3, 146.9, 130.5, 103.0, 49.3, 27.9, 20.1; HRMS-(ESI+) for $\text{C}_8\text{H}_{12}\text{ClIN}_3$ [M+H]: calculated: 311.9759, found: 311.9754, Δ (-1.45 ppm).



(26A): 4-(6-chloro-3-iodopyrazin-2-yl)morpholine: ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 3.48 - 3.55 (m, 4 H) 3.65 - 3.71 (m, 4 H) 8.14 (s, 1 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 41.70 - 46.67 (m, 2 C) 97.90 (d, $J=12.08$ Hz, 1 C) 126.20 - 134.14 (m, 1 C) 149.47 (s, 1 C) 188.66 (s, 1 C); HRMS-(ESI+) for $\text{C}_8\text{H}_{10}\text{ClIN}_3\text{O}$ [M+H]: calculated: 325.9552, found: 325.9541, Δ (-3.19 ppm).

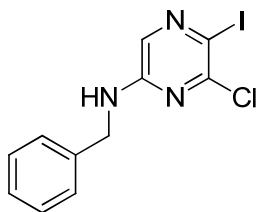


(26B): 4-(6-chloro-5-iodopyrazin-2-yl)morpholine: ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 3.30 - 3.35 (m, 4 H) 3.68 - 3.78 (m, 4 H) 8.10 (s, 1 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 47.14 - 52.69 (m, 2 C) 62.62 - 68.97 (m, 2 C) 108.89 (d, $J=10.43$ Hz, 1 C) 133.46 - 138.75 (m, 1 C) 144.54 (d, $J=8.23$ Hz, 1 C) 157.55 (s, 1 C); HRMS-(ESI+) for $\text{C}_8\text{H}_{10}\text{ClIN}_3\text{O}$ [M+H]: calculated: 325.9552, found: 325.9544, Δ (-2.31 ppm).

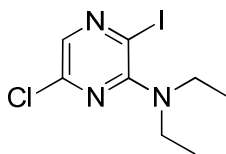


(27A): N-benzyl-6-chloro-3-iodopyrazin-2-amine: ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 4.52 (d, $J=6.22$ Hz, 2 H) 7.19 - 7.33 (m, 5 H) 7.55 (t, $J=6.12$ Hz, 1 H) 7.65 (s, 1 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm

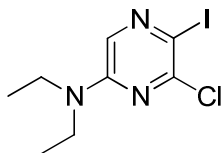
44.53 (s, 1 C) 103.64 (s, 1 C) 126.78 (s, 1 C) 127.16 (s, 2 C) 128.25 (s, 2 C) 129.96 (s, 1 C) 138.91 (s, 1 C) 145.53 (s, 1 C) 153.93 (s, 1 C); HRMS-(ESI+) for $C_{11}H_{10}ClIN_3$ [M+H]: calculated: 345.9602, found: 345.9593, Δ (-2.59 ppm).



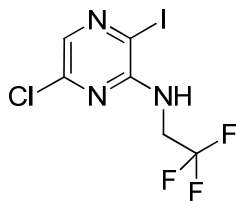
(27B): N-benzyl-6-chloro-5-iodopyrazin-2-amine: 1H NMR (400 MHz, DMSO- d_6) δ 8.14 (t, J =5.50 Hz, 1H), 7.80 (s, 1H), 7.30-7.39 (m, 4H), 7.21-7.30 (m, 1H), 4.43 (d, J =5.75 Hz, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 153.6, 150.0, 138.5, 132.2, 128.4, 127.5, 127.0, 95.9, 43.9; HRMS-(ESI+) for $C_{11}H_{10}ClIN_3$ [M+H]: calculated: 345.9602, found: 345.9599, Δ (-1.07 ppm).



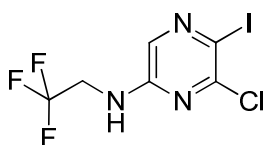
(28A): 6-chloro-N,N-diethyl-3-iodopyrazin-2-amine: 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.12 (t, J =6.95 Hz, 6 H) 3.44 (q, J =7.07 Hz, 4 H) 7.93 (s, 1 H); ^{13}C NMR (101 MHz, DMSO- d_6) δ ppm 13.20 (s, 1 C) 44.87 (s, 1 C) 105.09 (s, 1 C) 134.01 (s, 1 C) 144.31 (s, 1 C) 157.06 (s, 1 C); HRMS-(ESI+) for $C_8H_{12}ClIN_3$ [M+H]: calculated: 311.9759, found: 311.9747, Δ (-3.88 ppm).



(28B): 6-chloro-N,N-diethyl-5-iodopyrazin-2-amine: 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.03 - 1.16 (m, 6 H) 3.46 (q, J =7.07 Hz, 4 H) 7.93 (s, 1 H); ^{13}C NMR (101 MHz, DMSO- d_6) δ ppm 12.77 (s, 1 C) 42.64 (s, 1 C) 95.58 (s, 1 C) 130.11 (s, 1 C) 150.14 (s, 1 C) 152.18 (s, 1 C); HRMS-(ESI+) for $C_8H_{12}ClIN_3$ [M+H]: calculated: 311.9759, found: 311.9759, Δ (-0.02 ppm).



(29A): 6-chloro-3-iodo-*N*-(2,2,2-trifluoroethyl)pyrazin-2-amine: ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 4.17 (q, $J=9.06$ Hz, 2 H) 7.73 (s, 1 H); ^{13}C NMR (101 MHz, CHLOROFORM- d) δ 152.2, 146.6, 133.5, 124.1, 102.1, 42.8; HRMS-(ESI+) for $\text{C}_6\text{H}_5\text{ClF}_3\text{IN}_3$ [M+H]: calculated: 337.9163, found: 337.915, Δ (-3.89 ppm).



(29B): 6-chloro-5-iodo-*N*-(2,2,2-trifluoroethyl)pyrazin-2-amine: ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 3.93 - 4.00 (m, 2 H) 7.67 (s, 1 H); HRMS-(ESI+) for $\text{C}_6\text{H}_5\text{ClF}_3\text{IN}_3$ [M+H]: calculated: 337.9163, found: 337.948, Δ (-4.53 ppm)

E. X-ray Crystallography Data

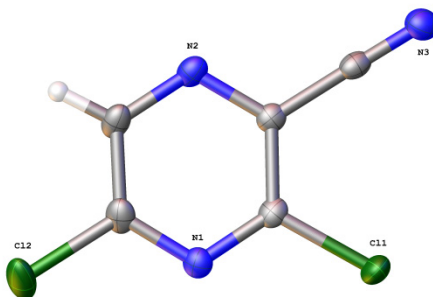


Figure S1. X-ray crystal structure of 3,5-dichloropyrazine-2-carbonitrile (4)

Table S1. Crystal data and structure refinement for 3,5-dichloropyrazine-2-carbonitrile

Identification code	PF-5249967
Empirical formula	$\text{C}_5\text{HCl}_2\text{N}_3$
Molecular formula	$\text{C}_5\text{HCl}_2\text{N}_3$
Formula weight	173.99

Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 10.9565(10) Å	$\alpha = 90^\circ$.
	b = 5.7167(6) Å	$\beta = 108.605(3)^\circ$.
	c = 16.5950(15) Å	$\gamma = 90^\circ$.
Volume	985.11(16) Å ³	
Z	6	
Density (calculated)	1.760 Mg/m ³	
Absorption coefficient	0.897 mm ⁻¹	
F(000)	516	
Crystal size	0.150 x 0.120 x 0.030 mm ³	
Crystal color, habit	Colorless Plate	
Theta range for data collection	2.590 to 26.350°.	
Index ranges	-13 ≤ h ≤ 13, -6 ≤ k ≤ 7, -20 ≤ l ≤ 20	
Reflections collected	6211	
Independent reflections	2007 [R(int) = 0.0394]	
Completeness to theta = 25.000°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7454 and 0.6398	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2007 / 0 / 181	
Goodness-of-fit on F ²	1.051	
Final R indices [I > 2σ(I)]	R1 = 0.0390, wR2 = 0.0801	
R indices (all data)	R1 = 0.0585, wR2 = 0.0875	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.341 and -0.590 e.Å ⁻³	

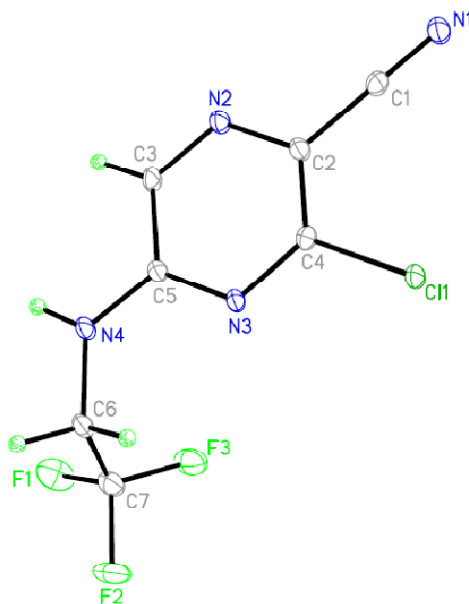


Figure S2. X-ray crystal structure of 3-chloro-5-[(2,2,2-trifluoroethyl)amino]pyrazine-2-carbonitrile (24B)

Table S2. Crystal data and structure refinement for 3-chloro-5-[(2,2,2-trifluoroethyl)amino]pyrazine-2-carbonitrile (24B)

Identification code	pflj228 (110636-1618-2)	
Empirical formula	C7 H4 Cl F3 N4	
Formula weight	236.59	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.531(2) Å	$\alpha = 90^\circ$
	b = 8.997(2) Å	$\beta = 109.605(10)^\circ$
	c = 11.626(3) Å	$\gamma = 90^\circ$
Volume	939.2(4) Å ³	
Z	4	
Density (calculated)	1.673 g/cm ³	
Absorption coefficient	0.423 mm ⁻¹	
F(000)	472	

Crystal size	0.33 x 0.28 x 0.08 mm ³
Theta range for data collection	4.07 to 25.07°
Index ranges	-11<=h<=11, -10<=k<=10, -11<=l<=13
Reflections collected	6677
Independent reflections	1644 [R(int) = 0.0399]
Completeness to theta = 25.00°	98.5 %
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	1644 / 0 / 136
Goodness-of-fit on F ²	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.1014
R indices (all data)	R1 = 0.0597, wR2 = 0.1138
Largest diff. peak and hole	0.414 and -0.305 e Å ⁻³

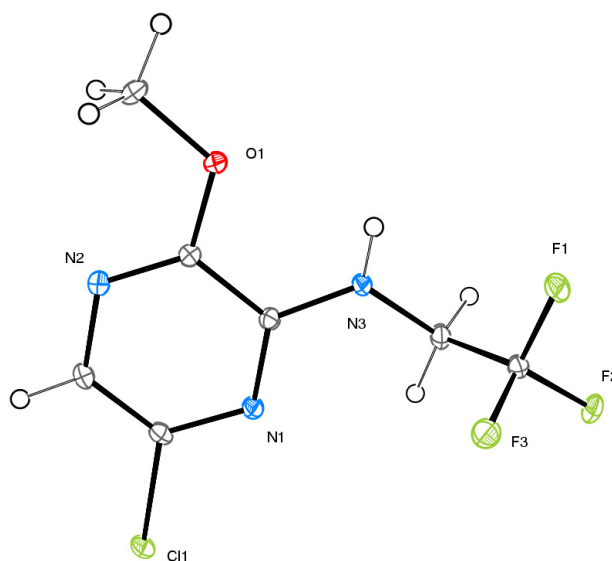


Figure S3. X-ray crystal structure of 6-chloro-3-methoxy-N-(2,2,2-trifluoroethyl)pyrazin-2-amine (14A)

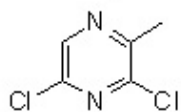
Table S3. Crystal data and structure refinement for 6-chloro-3-methoxy-N-(2,2,2-trifluoroethyl)pyrazin-2-amine (14A)

Identification code	110636-1428
Empirical formula	C7 H7 Cl F3 N3 O

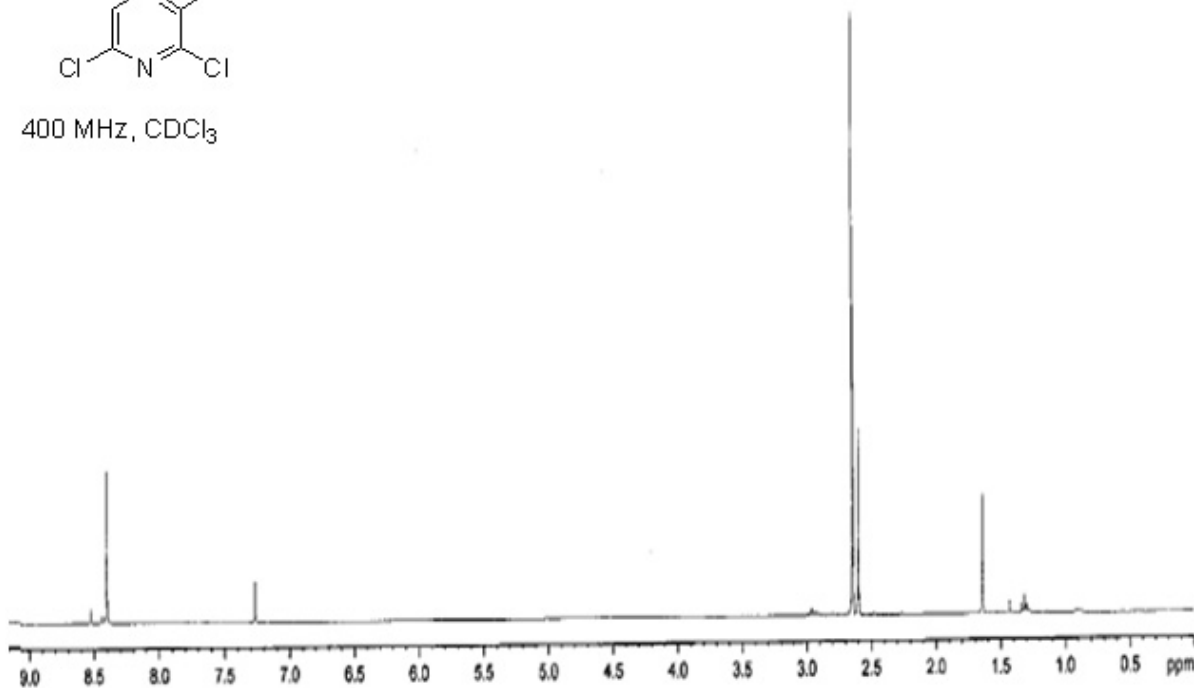
Formula weight	241.61	
Temperature	90(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 16.3661(6) Å	$\alpha = 90^\circ$.
	b = 6.7959(2) Å	$\beta = 90^\circ$.
	c = 33.9544(12) Å	$\gamma = 90^\circ$.
Volume	3776.5(2) Å ³	
Z	16	
Density (calculated)	1.700 Mg/m ³	
Absorption coefficient	3.894 mm ⁻¹	
F(000)	1952	
Crystal size	0.15 x 0.11 x 0.08 mm ³	
Crystal color, habit	Colorless Needle	
Theta range for data collection	3.75 to 68.33°.	
Index ranges	-15 ≤ h ≤ 19, -8 ≤ k ≤ 7, -40 ≤ l ≤ 40	
Reflections collected	16261	
Independent reflections	3394 [R(int) = 0.0405]	
Completeness to theta = 60.00°	98.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7458 and 0.5927	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3394 / 0 / 274	
Goodness-of-fit on F ²	1.028	
Final R indices [I > 2σ(I)]	R1 = 0.0300, wR2 = 0.0723	
R indices (all data)	R1 = 0.0368, wR2 = 0.0760	
Extinction coefficient	0.00019(3)	
Largest diff. peak and hole	0.260 and -0.314 e.Å ⁻³	

F. ¹H NMR & ¹³C NMR Spectral Data of starting materials:

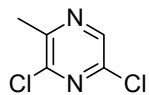
¹H NMR of 3,5-dichloro-2-methylpyrazine (**1**)



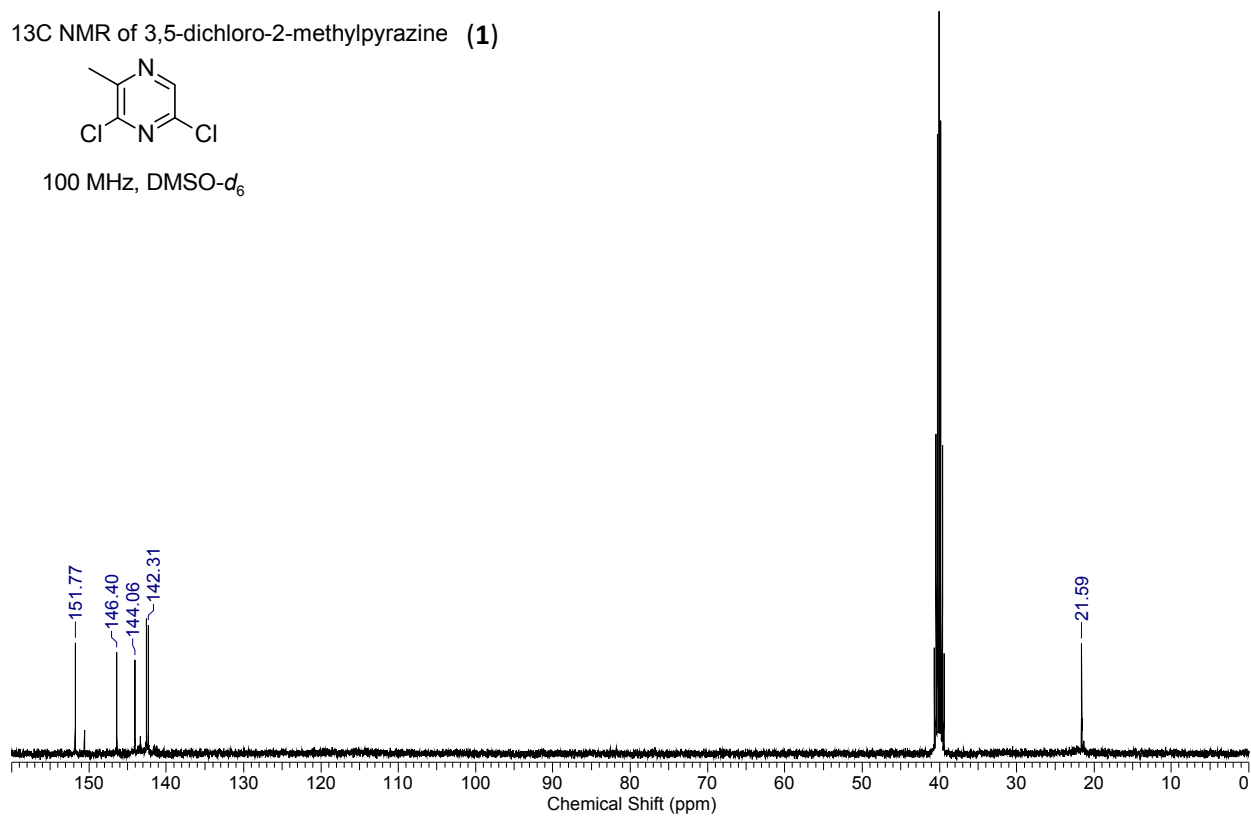
400 MHz, CDCl₃



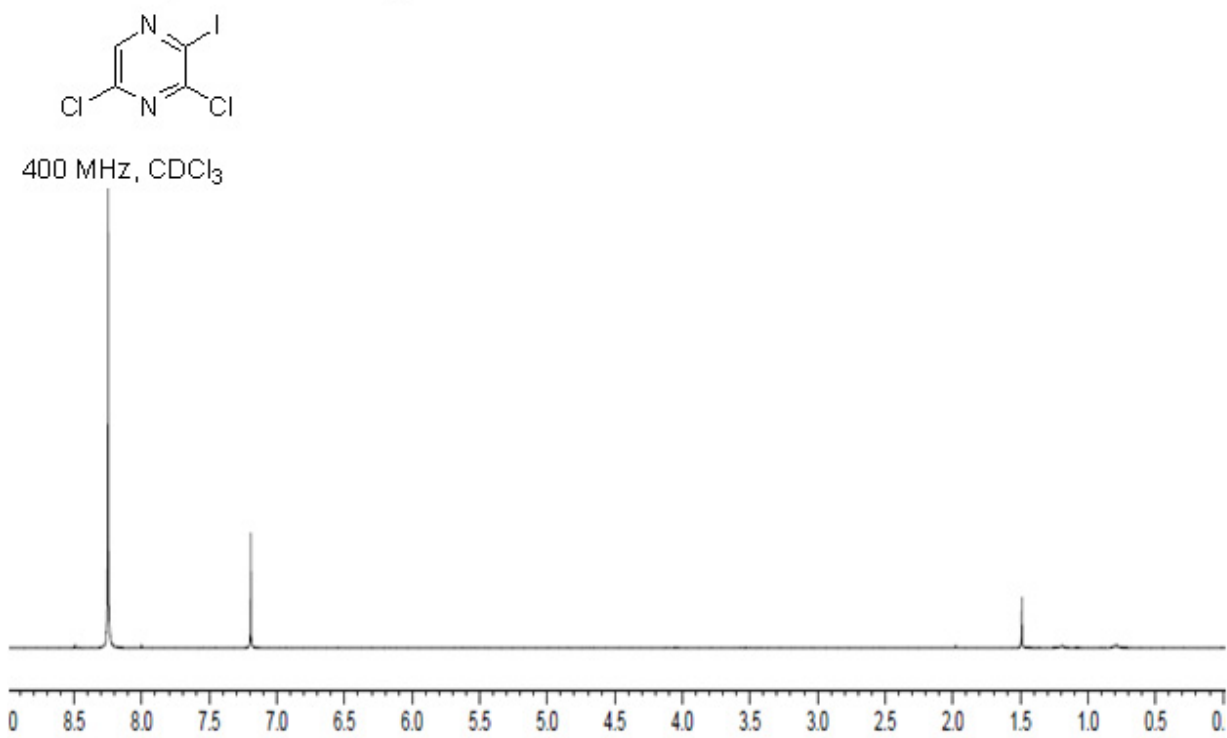
¹³C NMR of 3,5-dichloro-2-methylpyrazine (**1**)



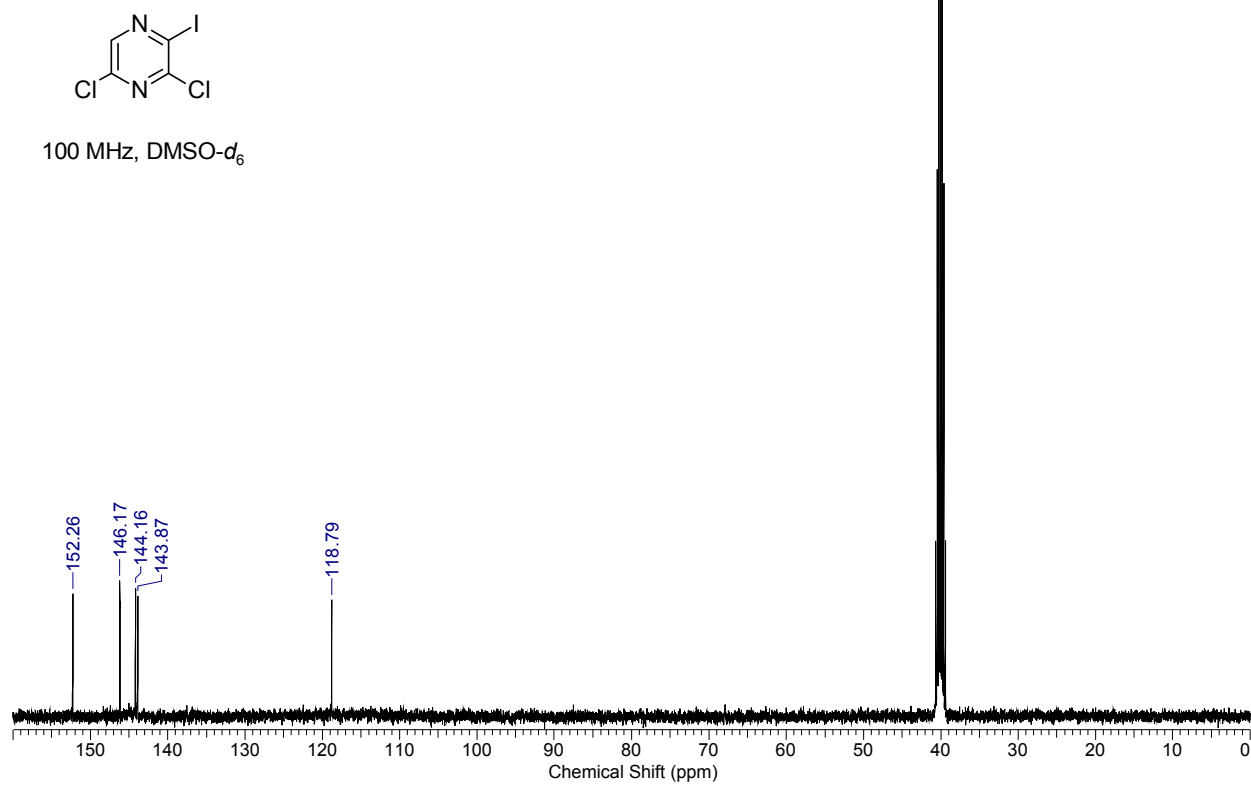
100 MHz, DMSO-*d*₆

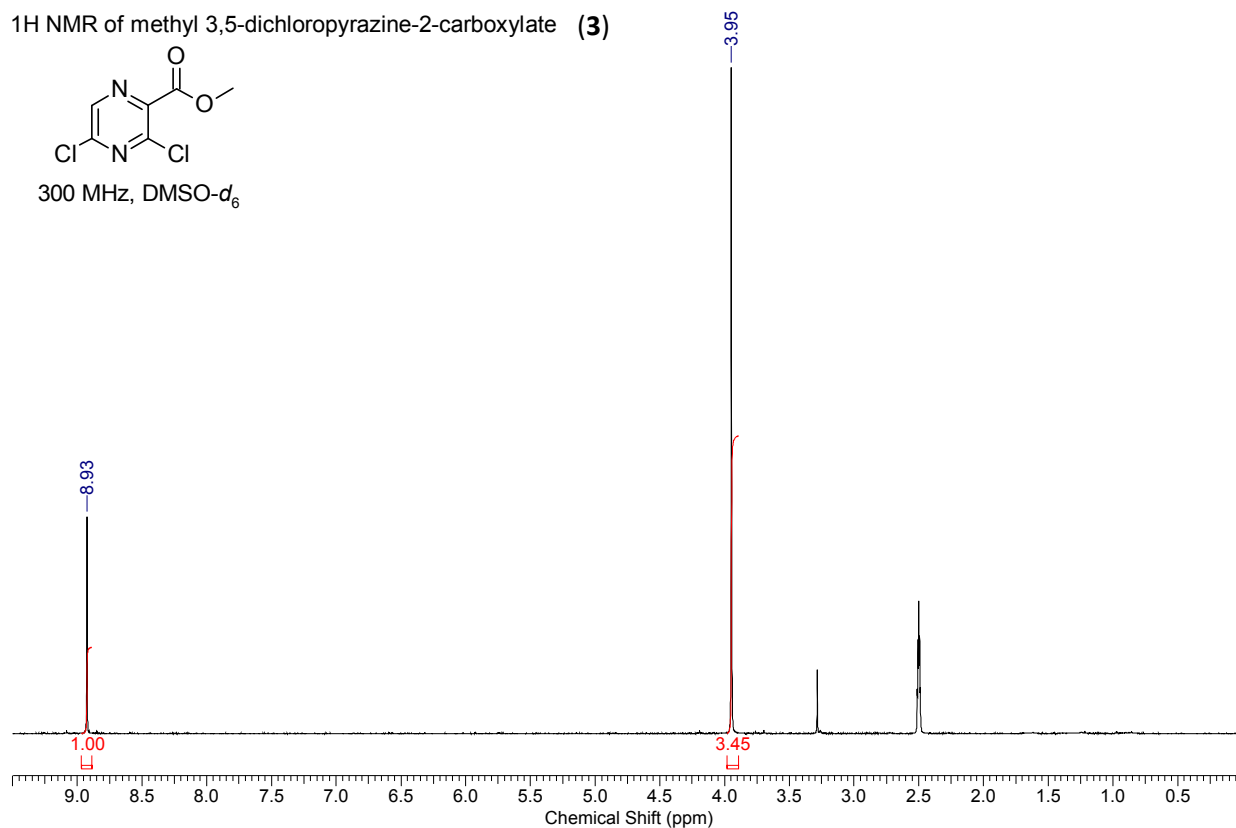
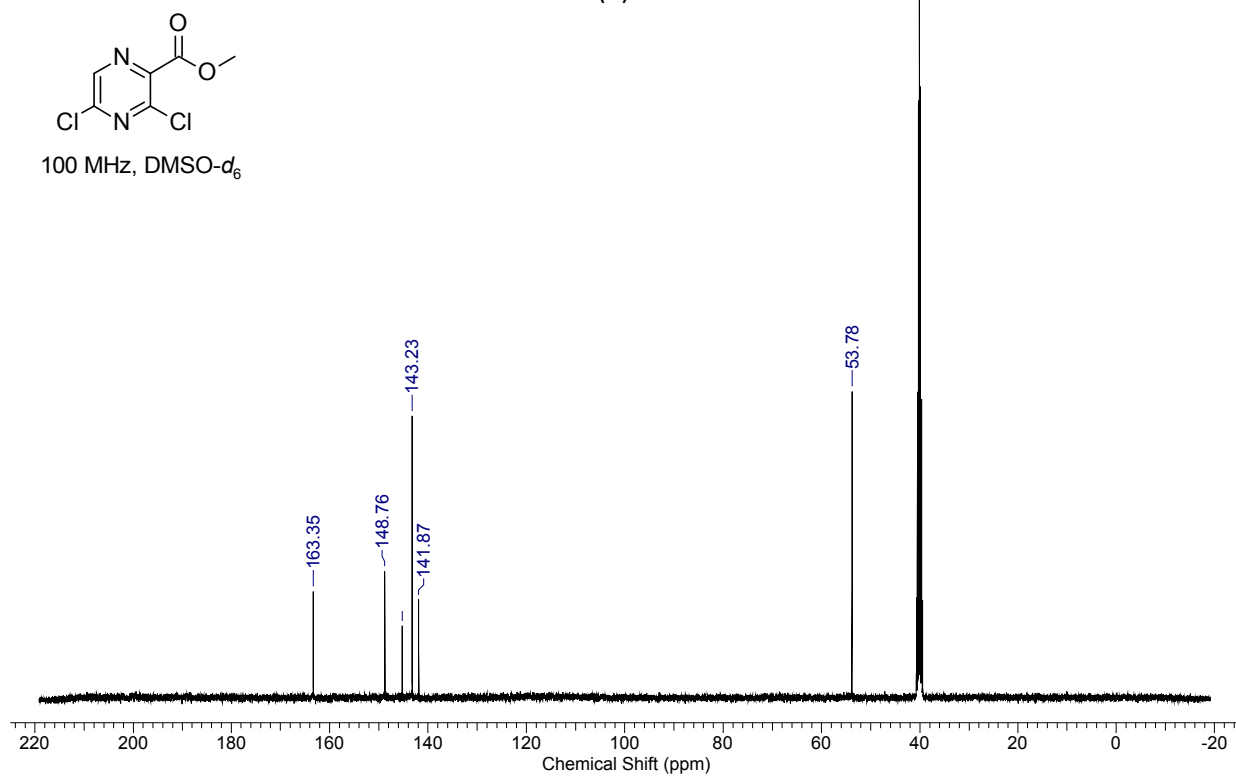


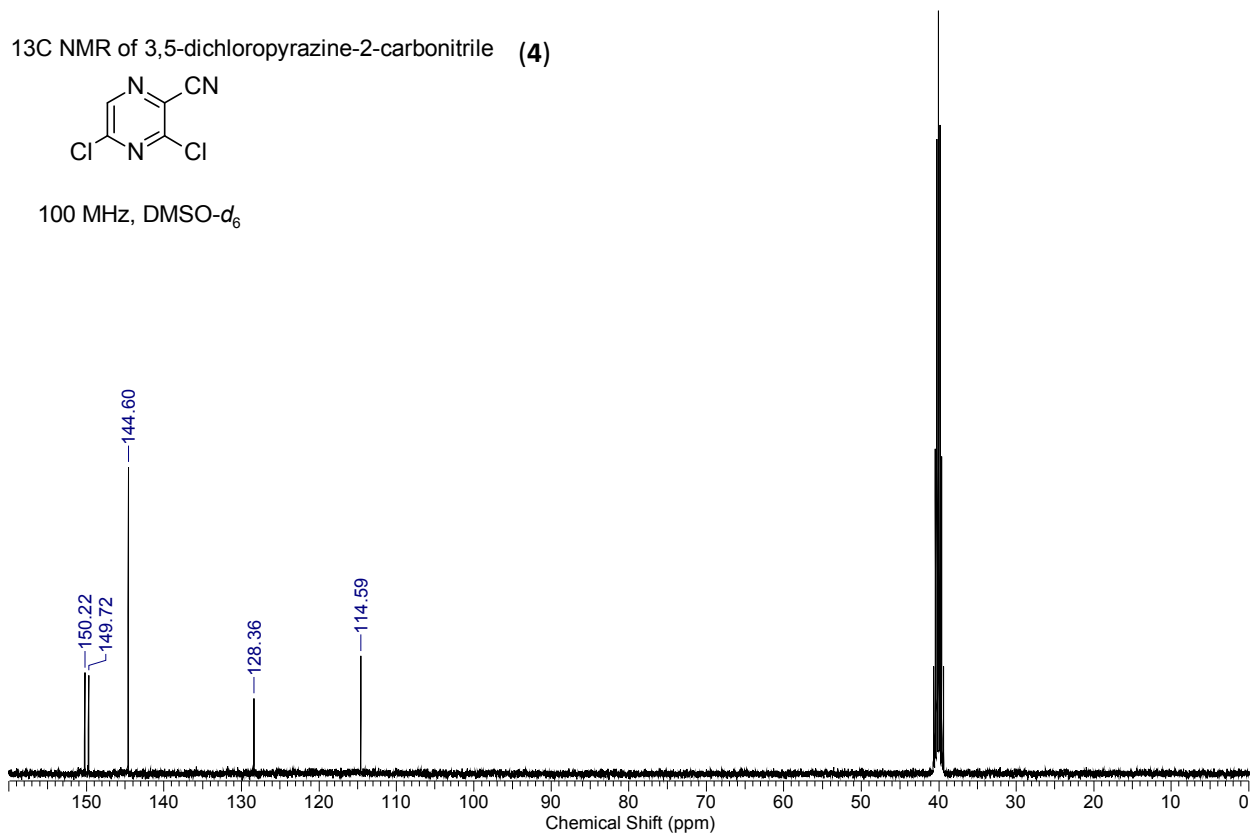
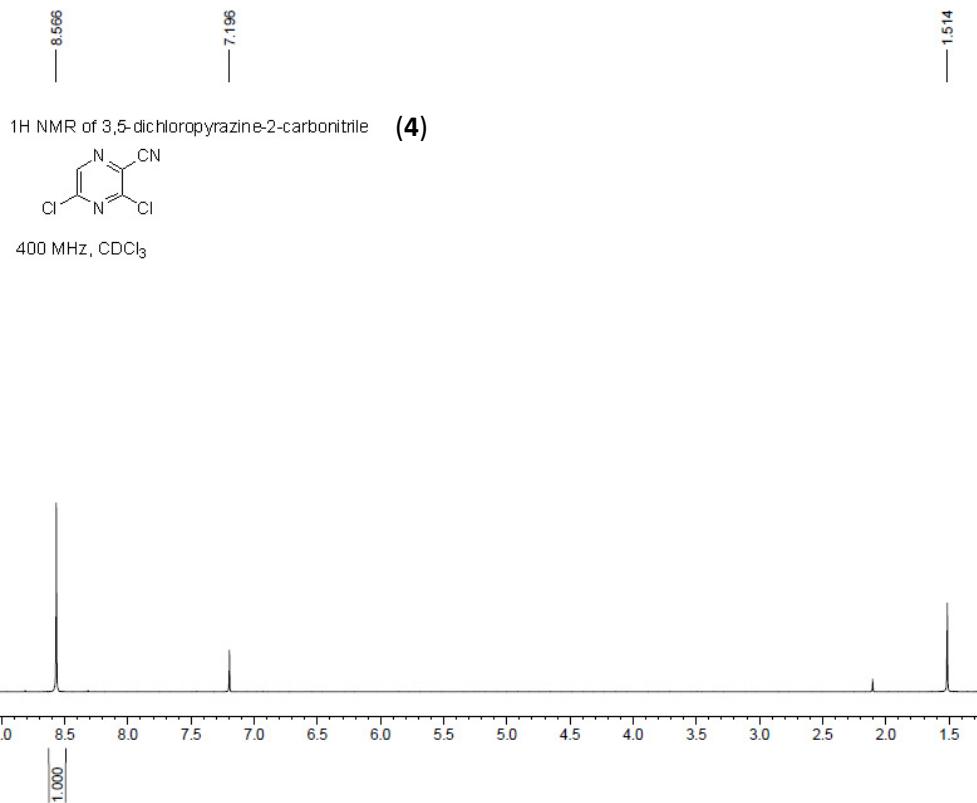
¹H NMR of 3,5-dichloro-2-iodopyrazine (2)



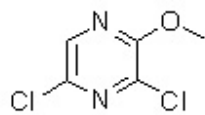
¹³C NMR of 3,5-dichloro-2-iodopyrazine (2)



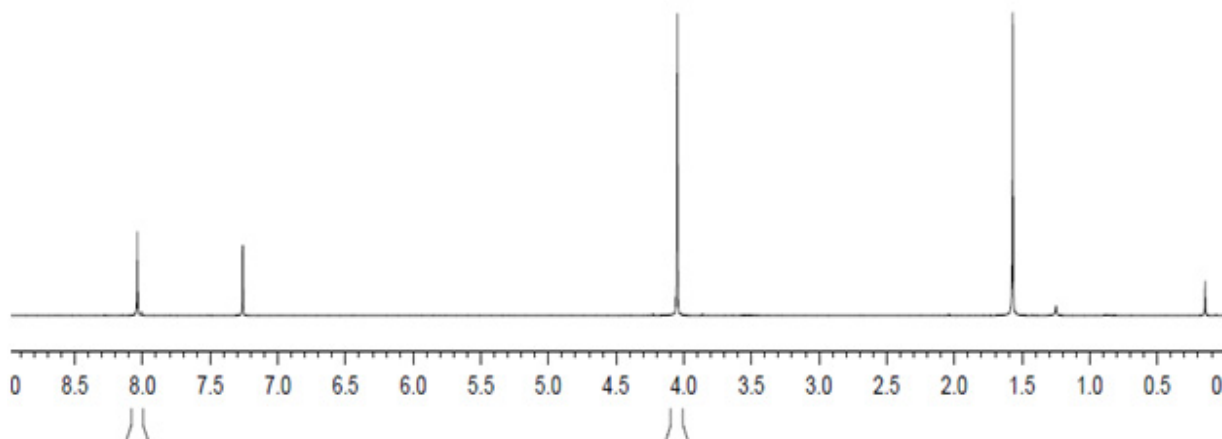
1H NMR of methyl 3,5-dichloropyrazine-2-carboxylate (**3**)13C NMR of methyl 3,5-dichloropyrazine-2-carboxylate (**3**)



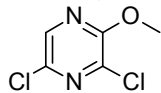
^1H NMR of 3,5-dichloro-2-methoxypyrazine (5)



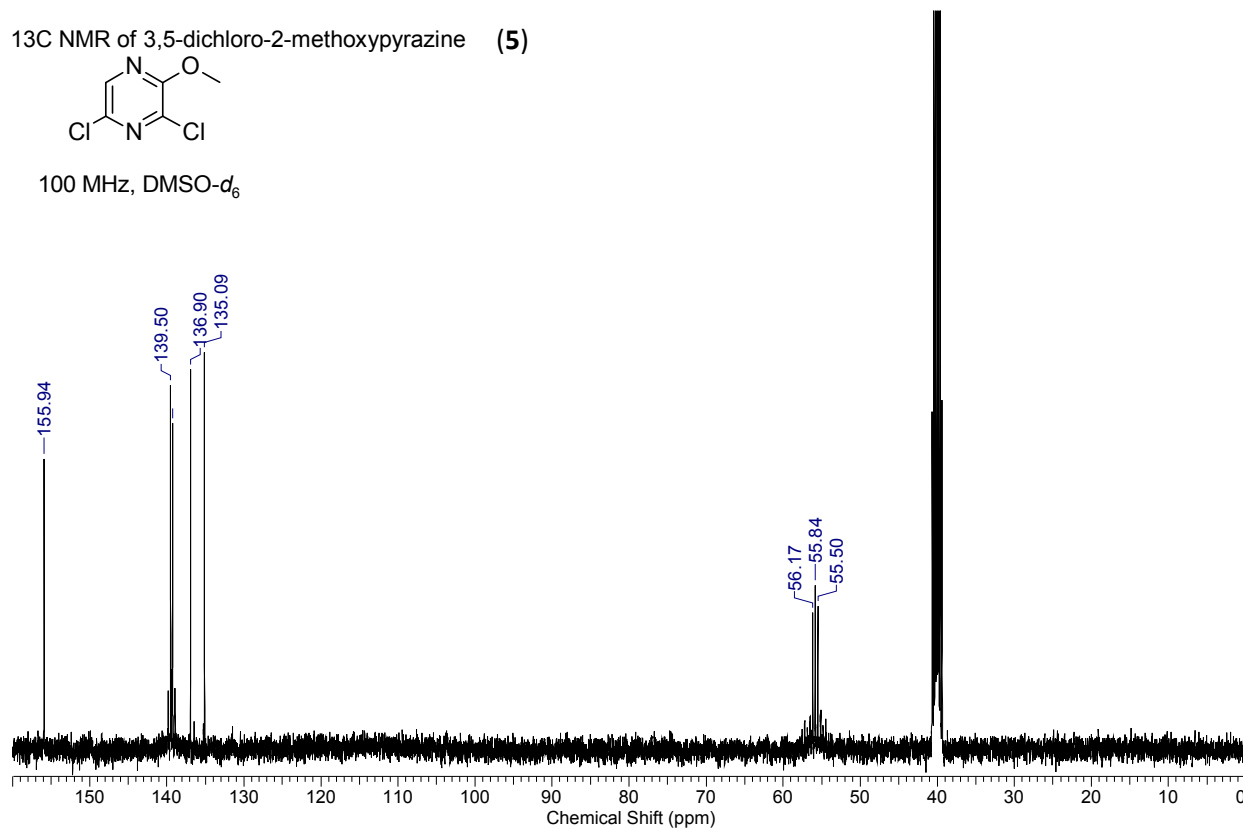
400 MHz, CDCl_3



^{13}C NMR of 3,5-dichloro-2-methoxypyrazine (5)

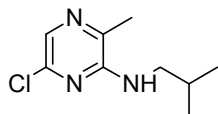


100 MHz, $\text{DMSO}-d_6$

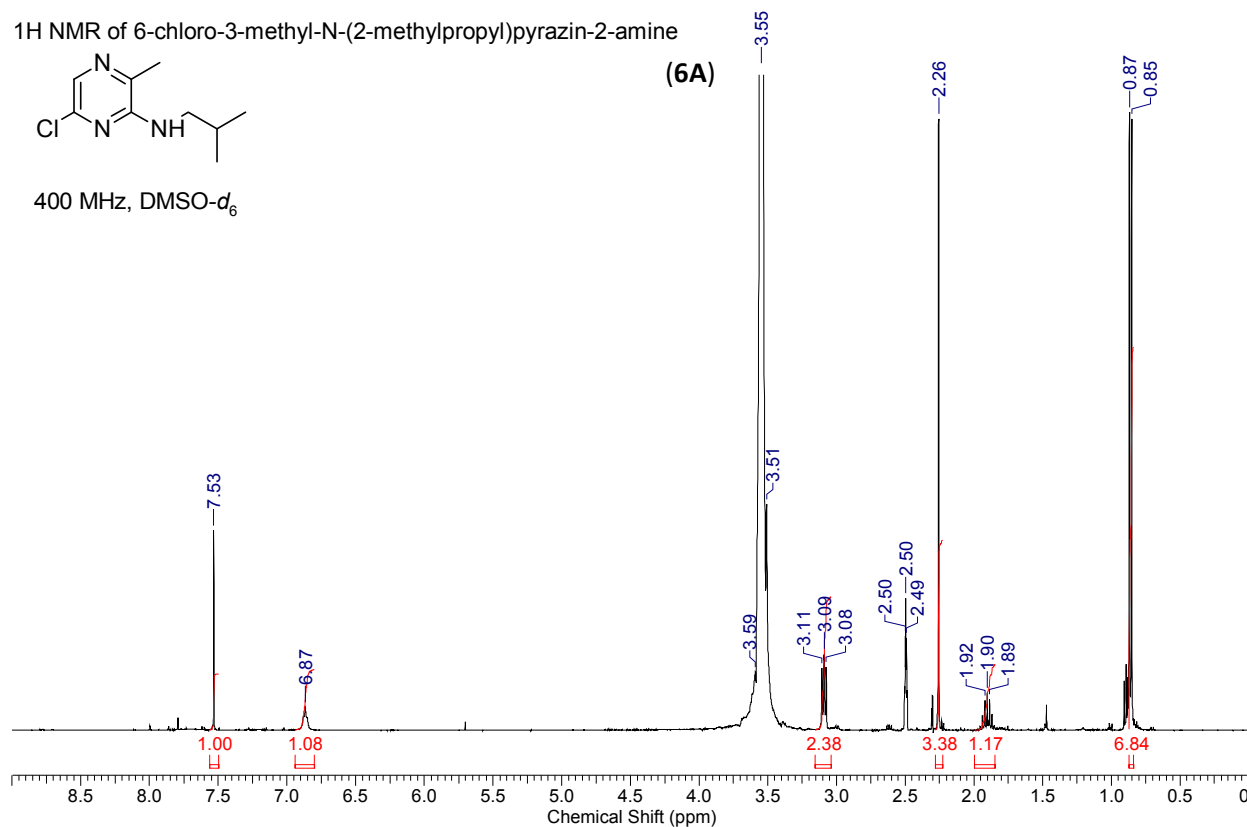


G. ^1H NMR, ^{13}C NMR, and NOE Spectral Data of products:

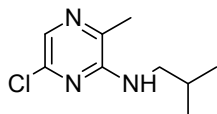
¹H NMR of 6-chloro-3-methyl-N-(2-methylpropyl)pyrazin-2-amine



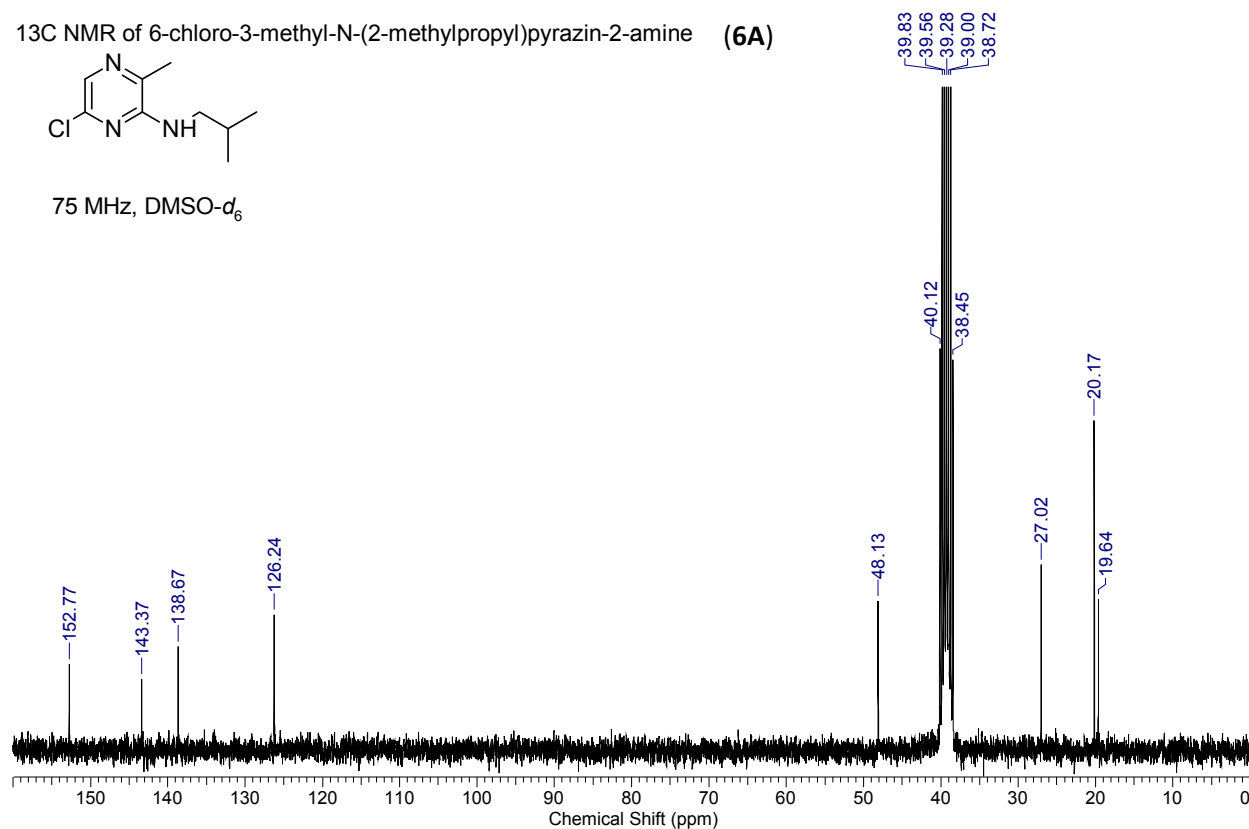
400 MHz, DMSO-*d*₆

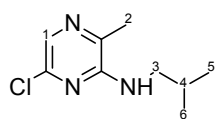


¹³C NMR of 6-chloro-3-methyl-N-(2-methylpropyl)pyrazin-2-amine (6A)

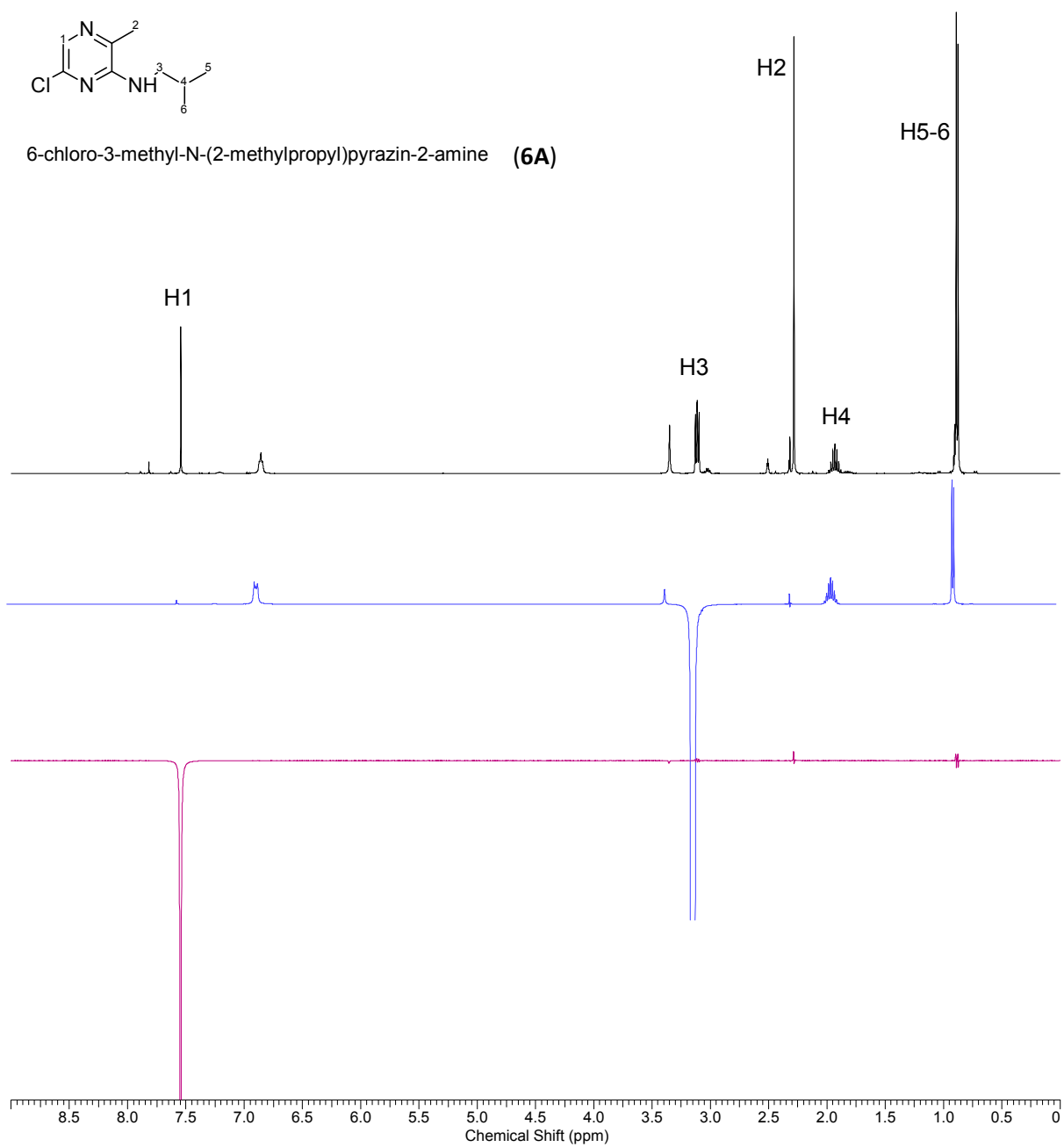


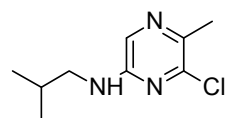
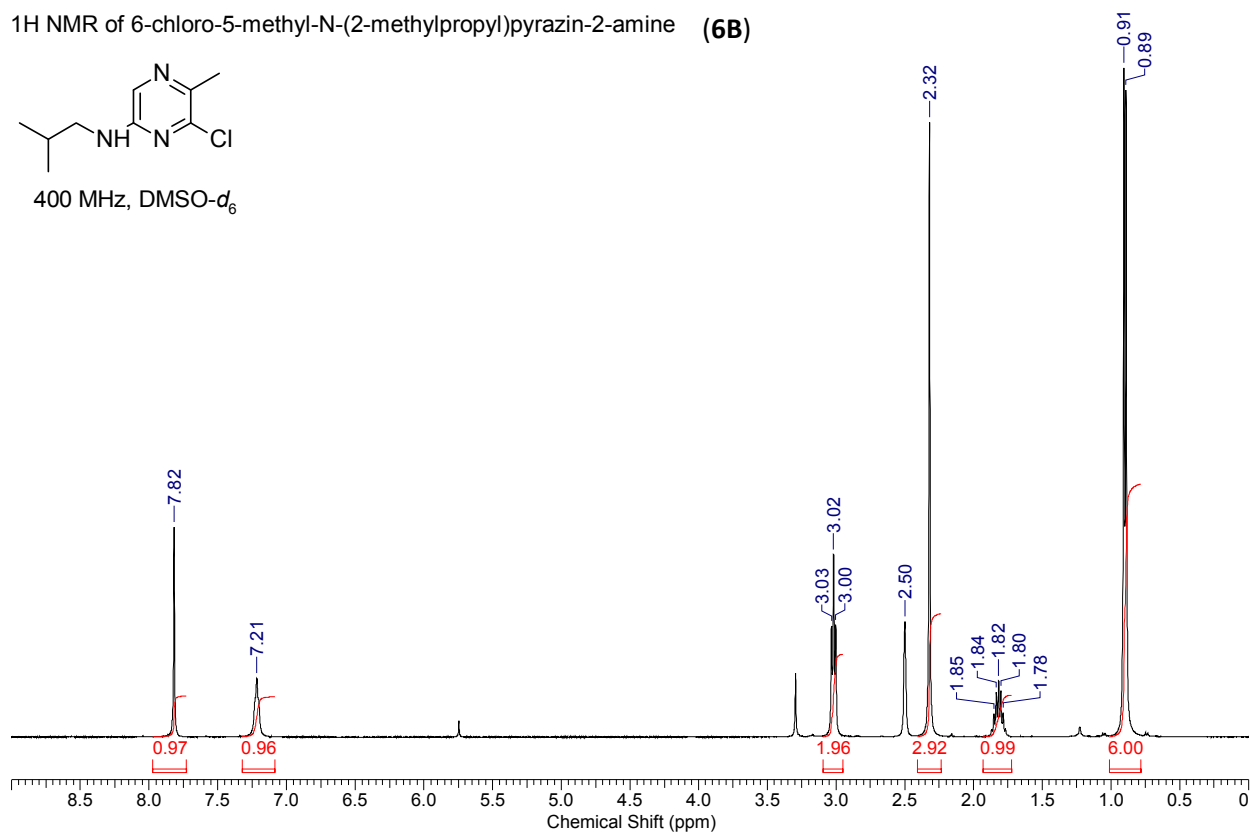
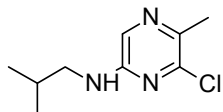
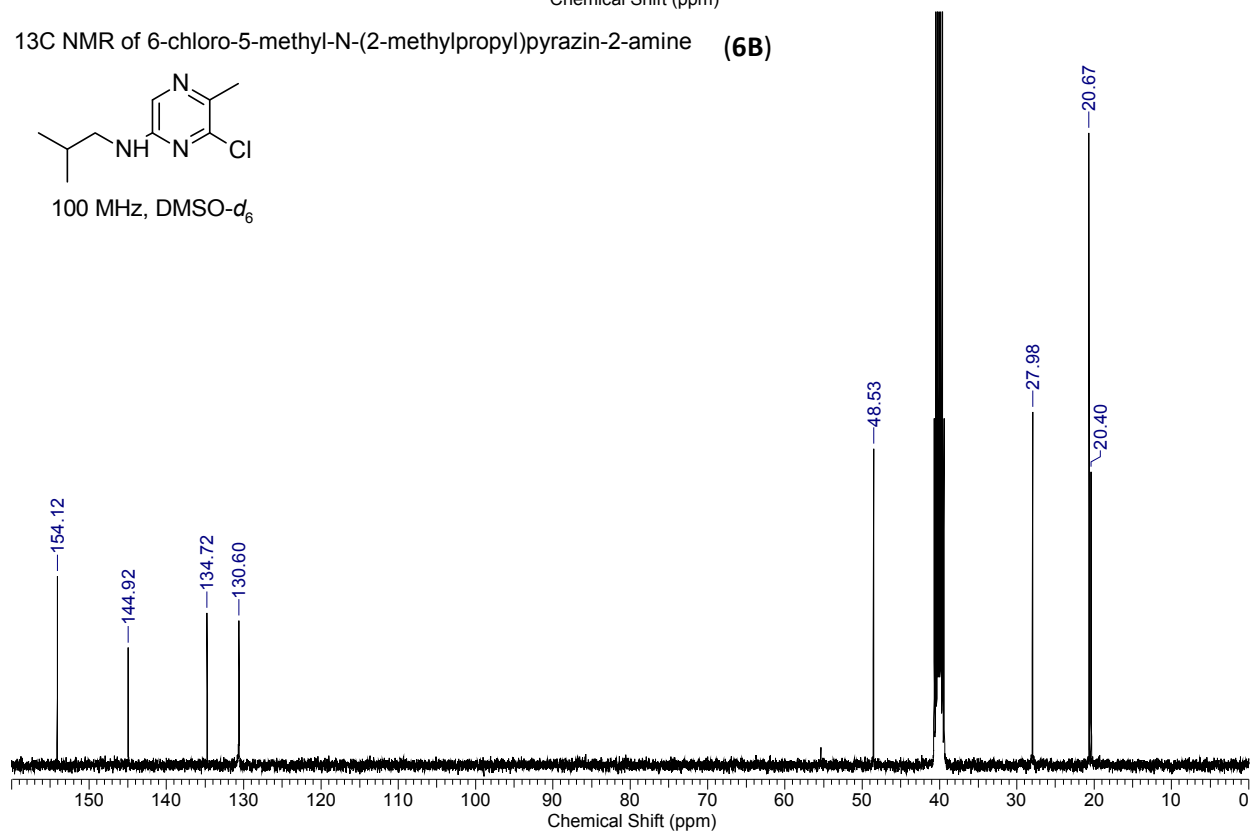
75 MHz, DMSO-*d*₆

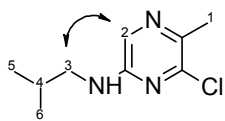




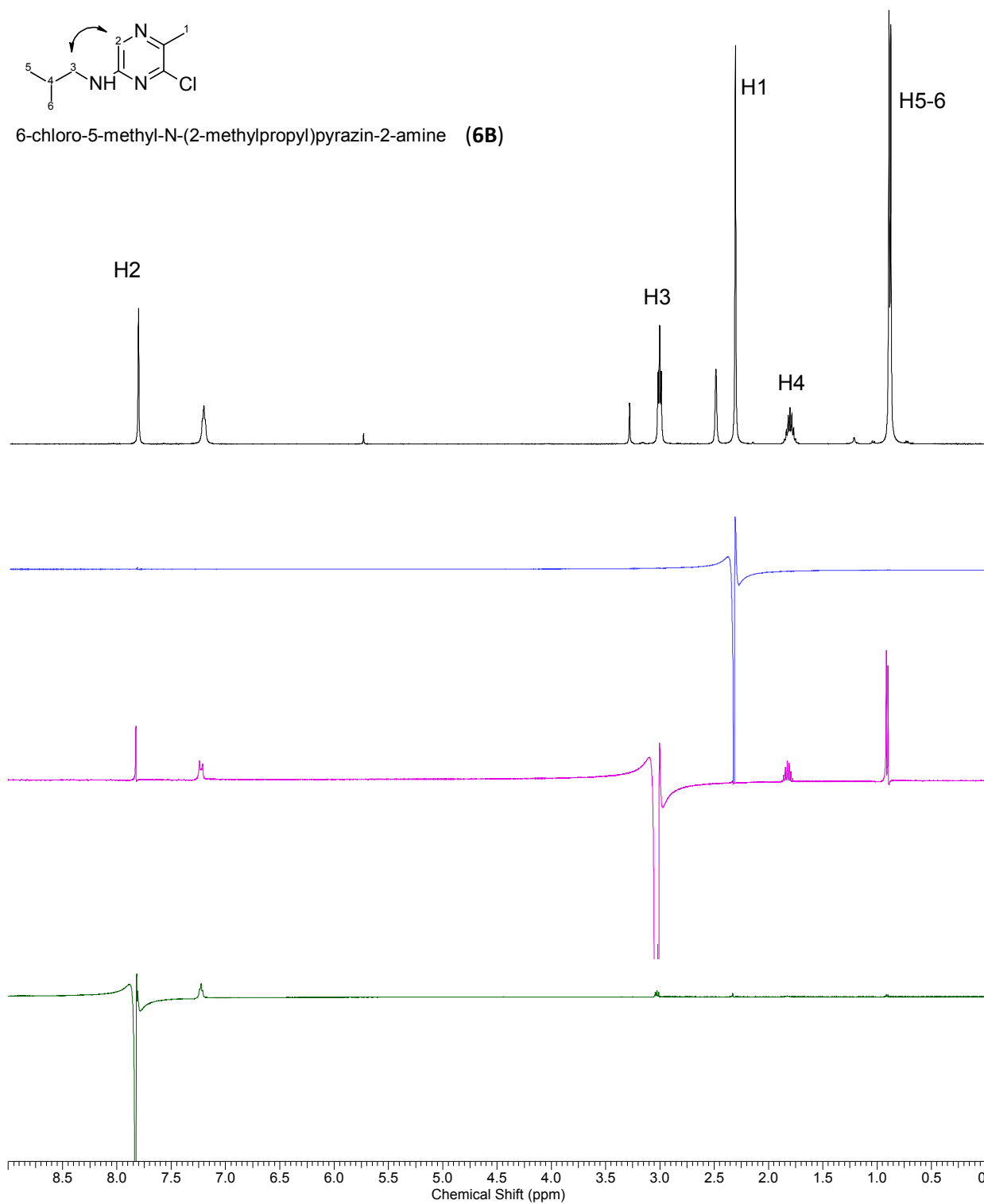
6-chloro-3-methyl-N-(2-methylpropyl)pyrazin-2-amine (**6A**)

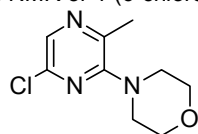
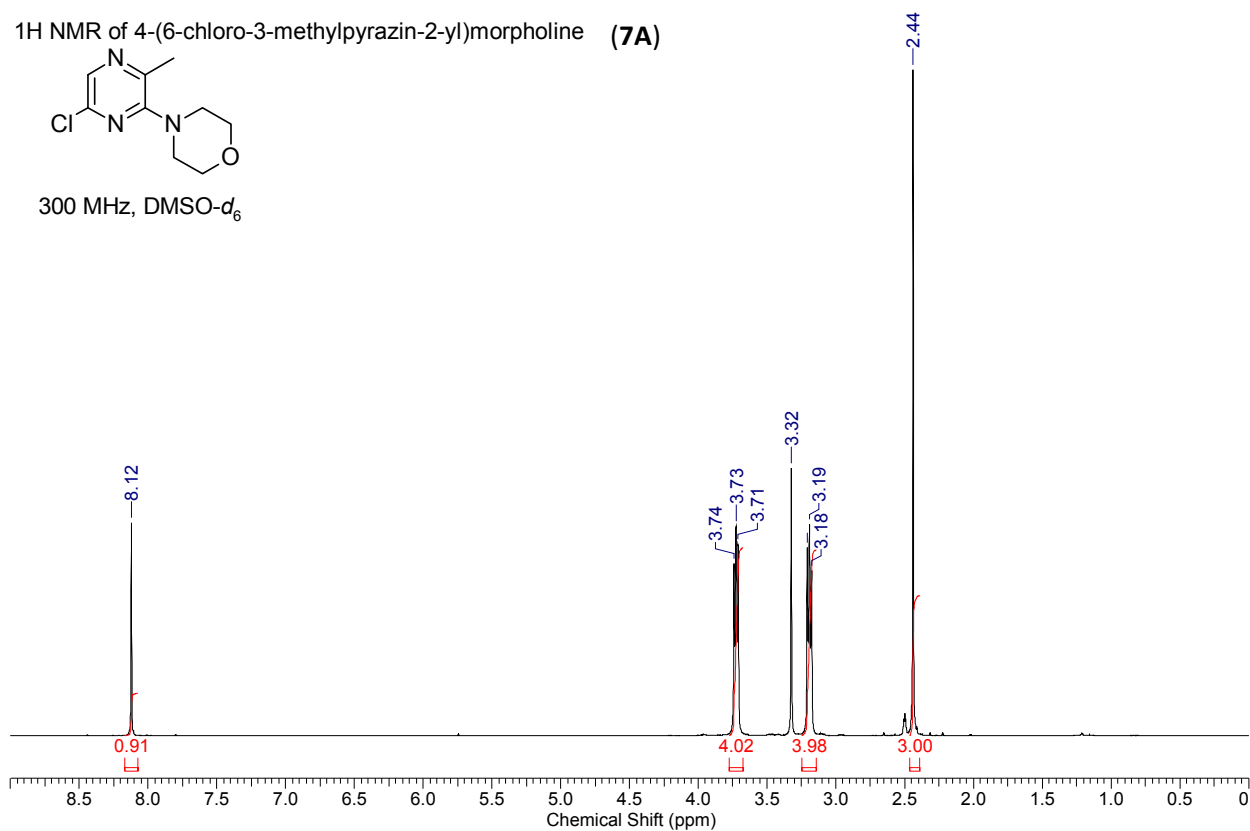
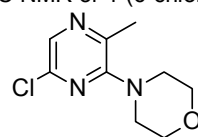
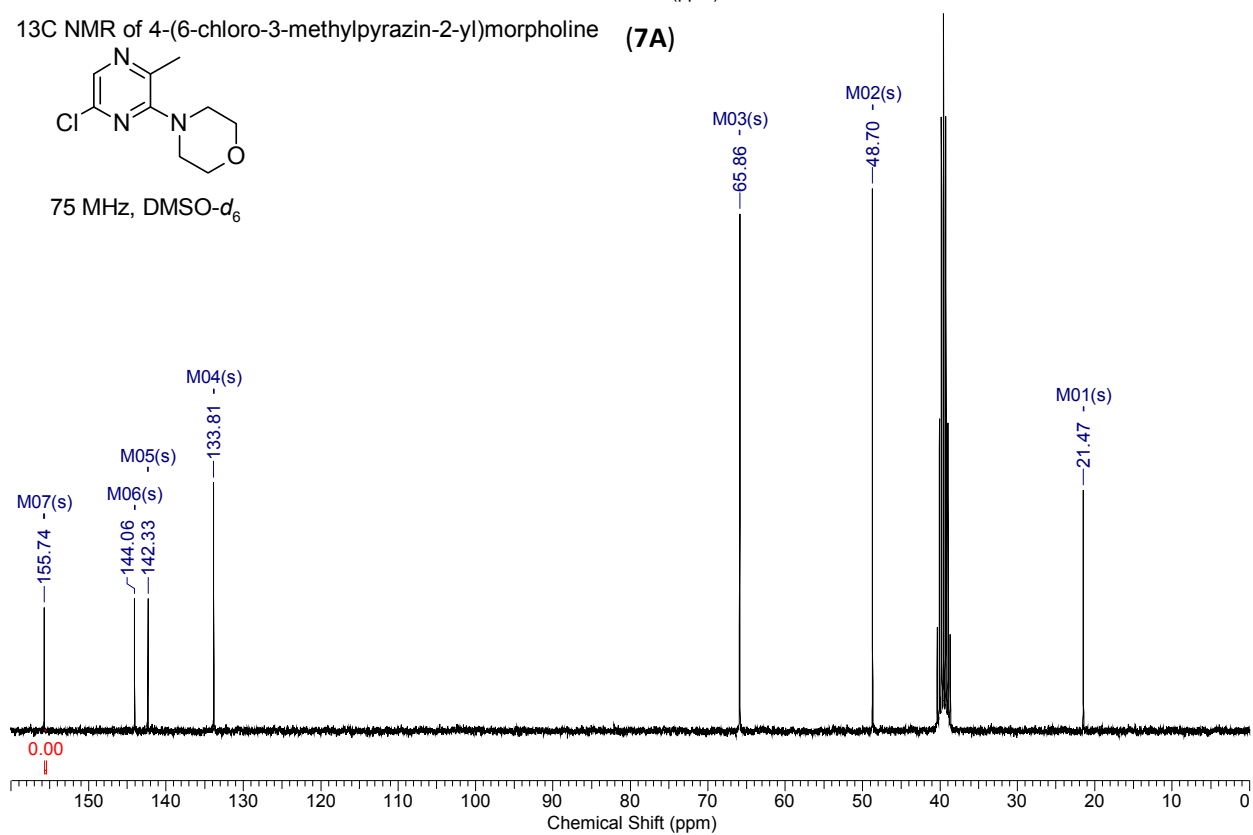


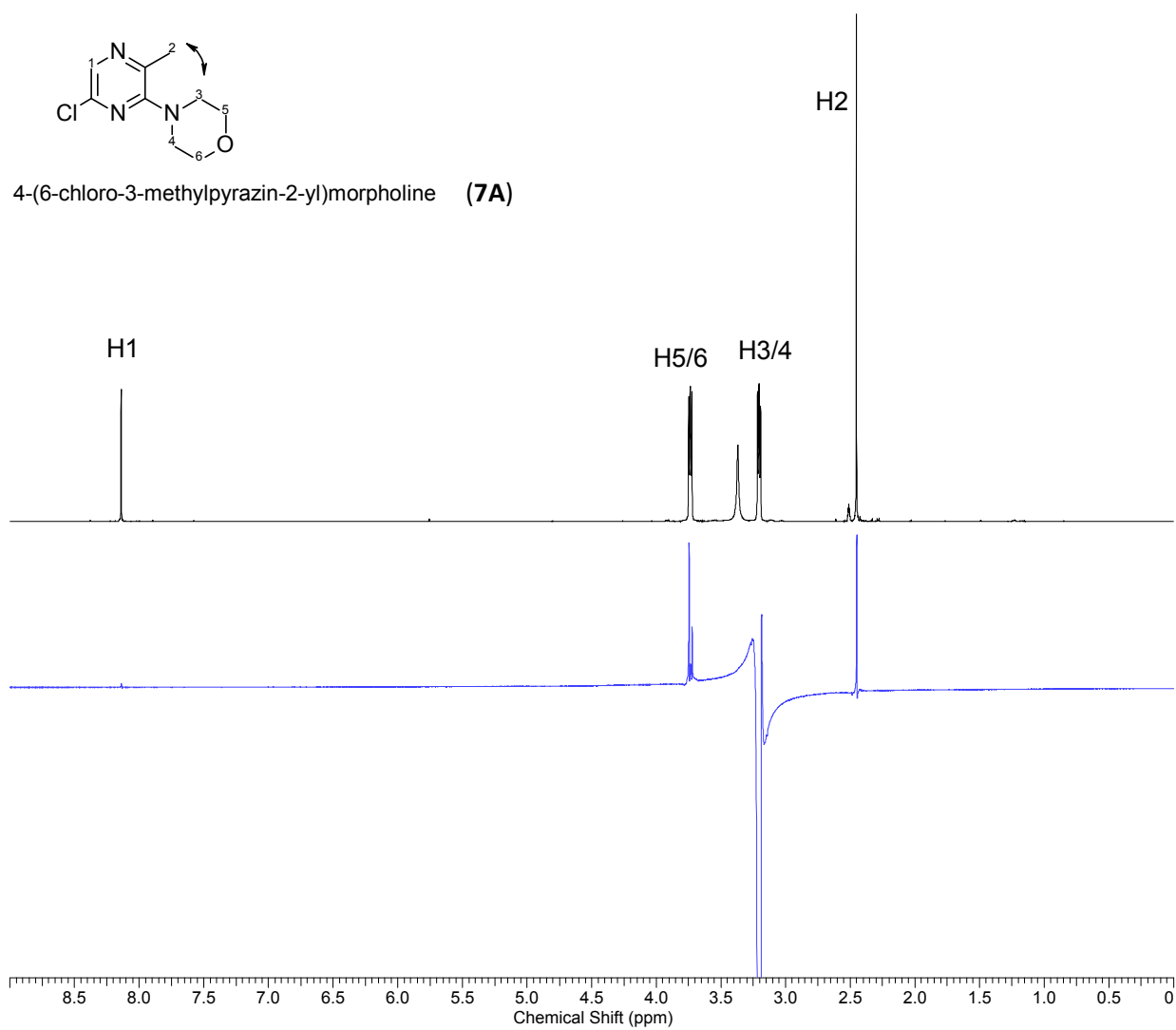
¹H NMR of 6-chloro-5-methyl-N-(2-methylpropyl)pyrazin-2-amine (**6B**)400 MHz, DMSO-*d*₆¹³C NMR of 6-chloro-5-methyl-N-(2-methylpropyl)pyrazin-2-amine (**6B**)100 MHz, DMSO-*d*₆

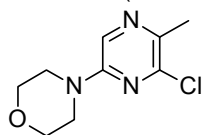
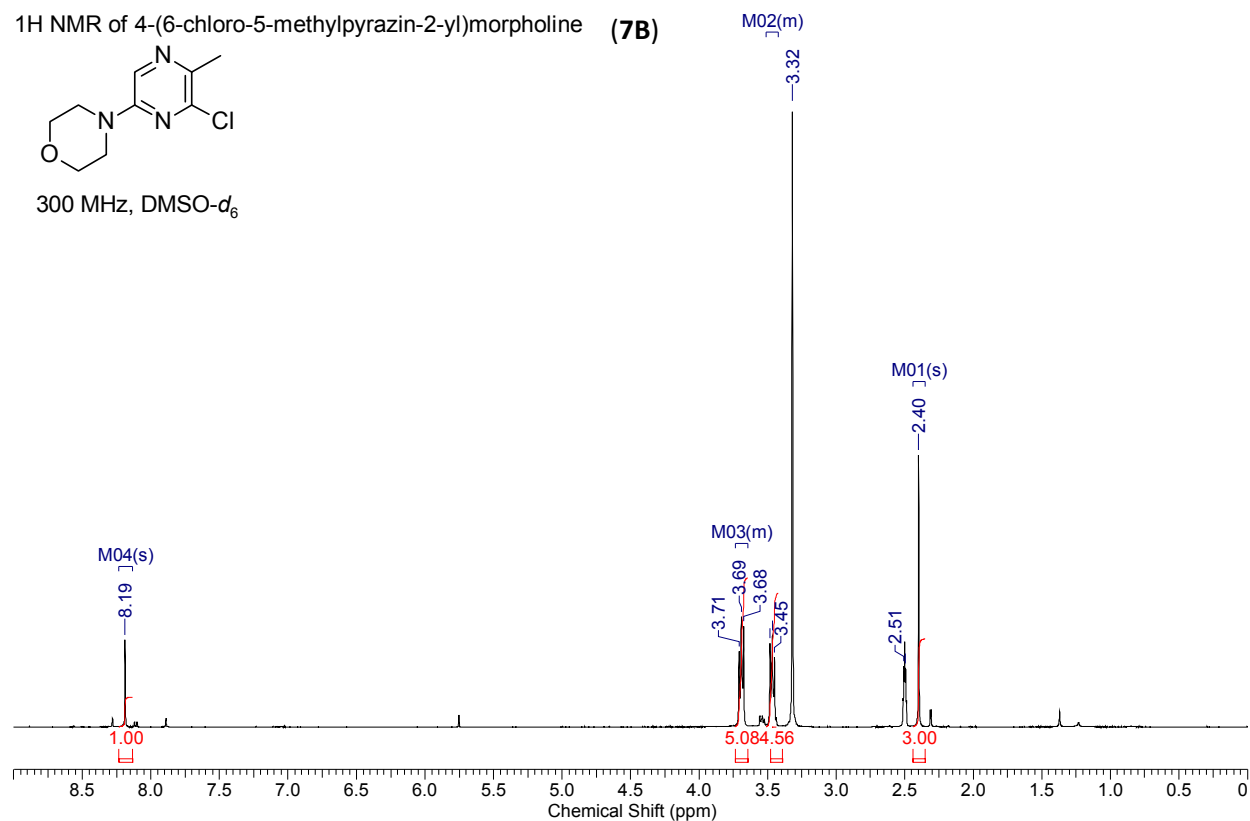
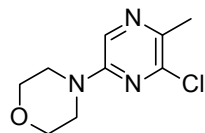
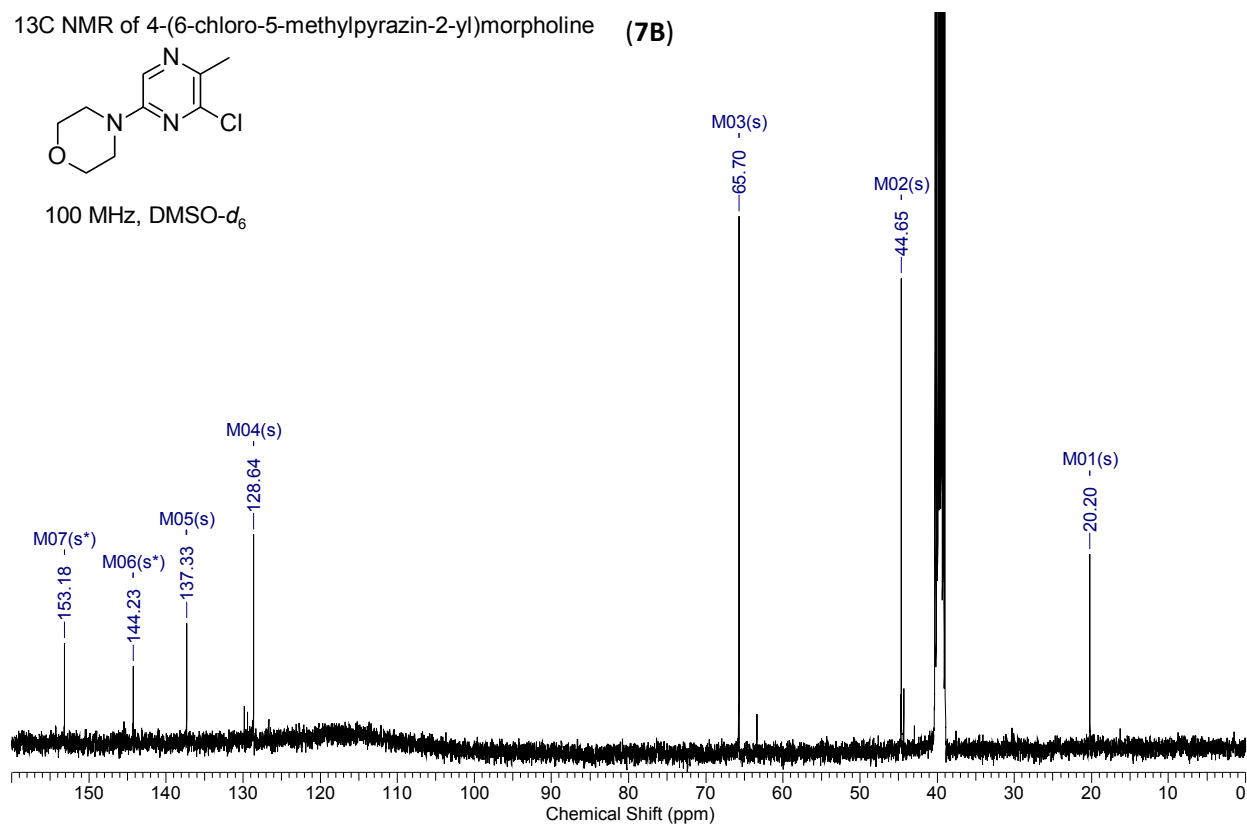


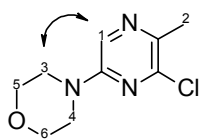
6-chloro-5-methyl-N-(2-methylpropyl)pyrazin-2-amine (**6B**)



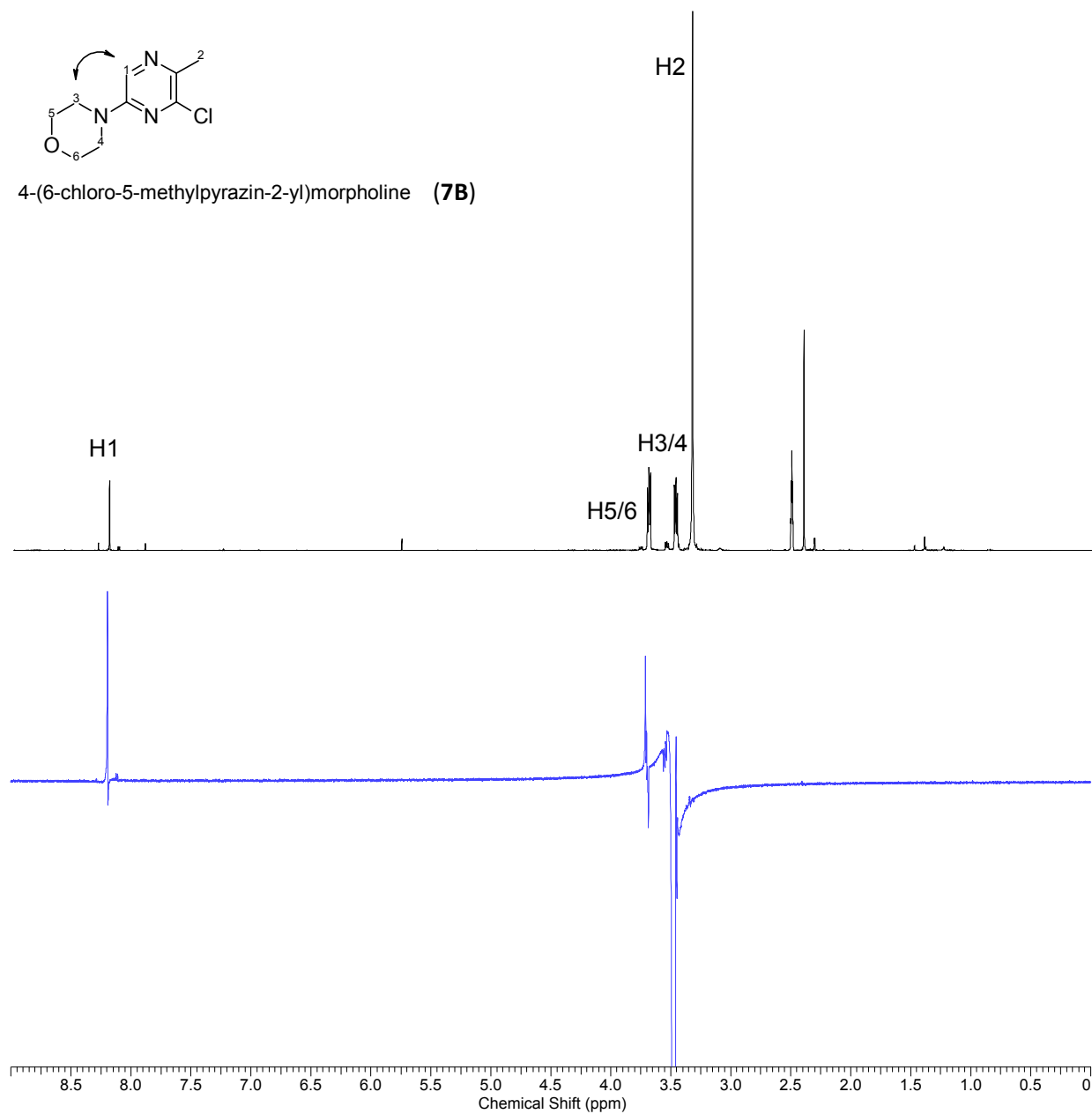
¹H NMR of 4-(6-chloro-3-methylpyrazin-2-yl)morpholine (**7A**)300 MHz, DMSO-*d*₆¹³C NMR of 4-(6-chloro-3-methylpyrazin-2-yl)morpholine (**7A**)75 MHz, DMSO-*d*₆

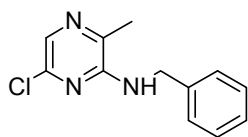
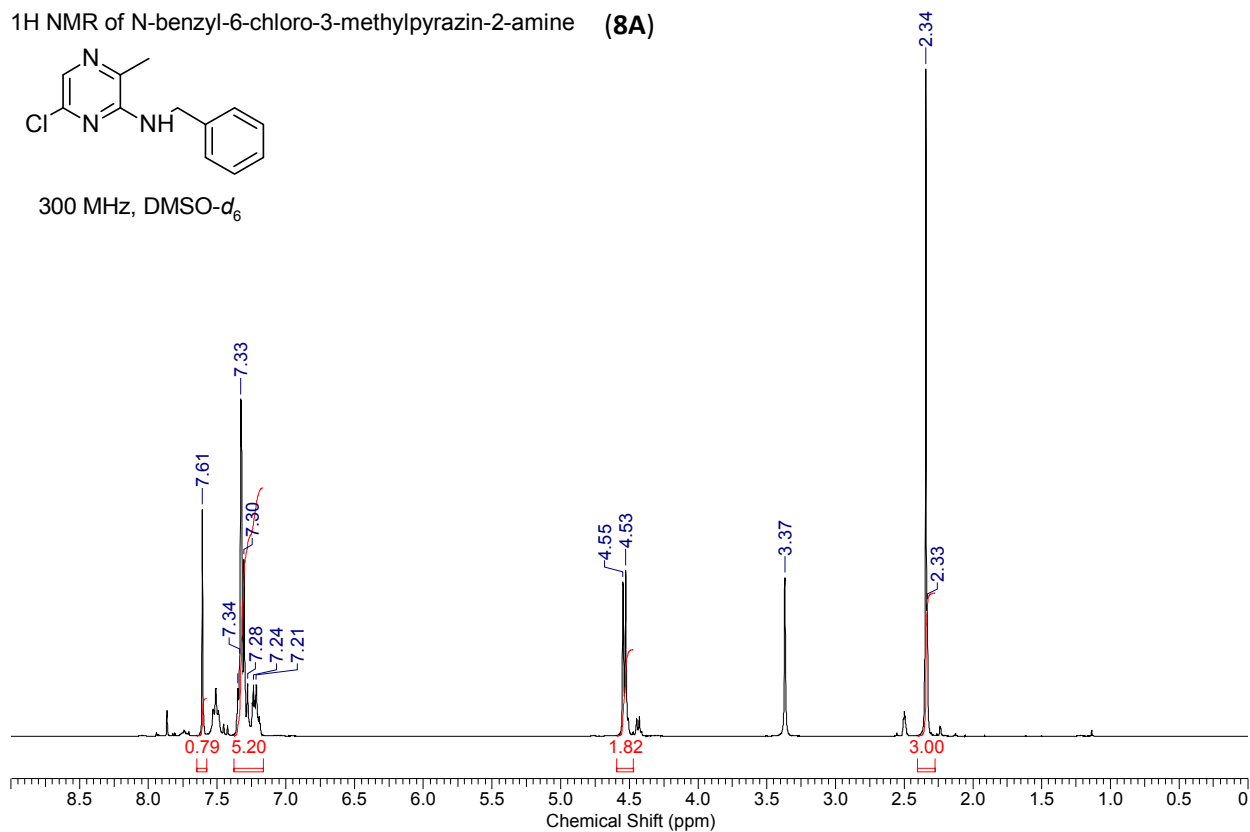


¹H NMR of 4-(6-chloro-5-methylpyrazin-2-yl)morpholine (**7B**)300 MHz, DMSO-*d*₆¹³C NMR of 4-(6-chloro-5-methylpyrazin-2-yl)morpholine (**7B**)100 MHz, DMSO-*d*₆

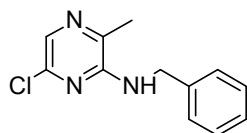
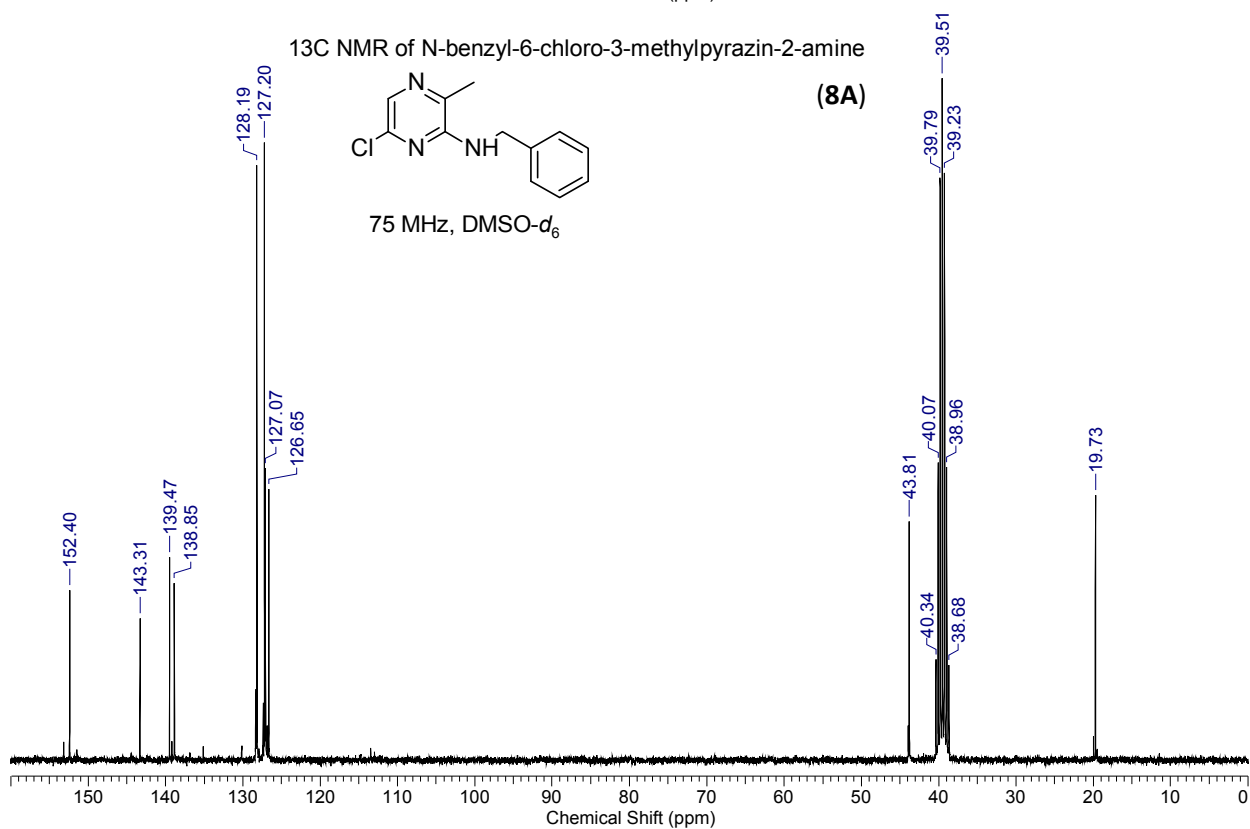


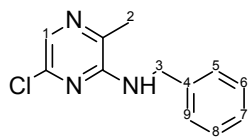
4-(6-chloro-5-methylpyrazin-2-yl)morpholine (**7B**)



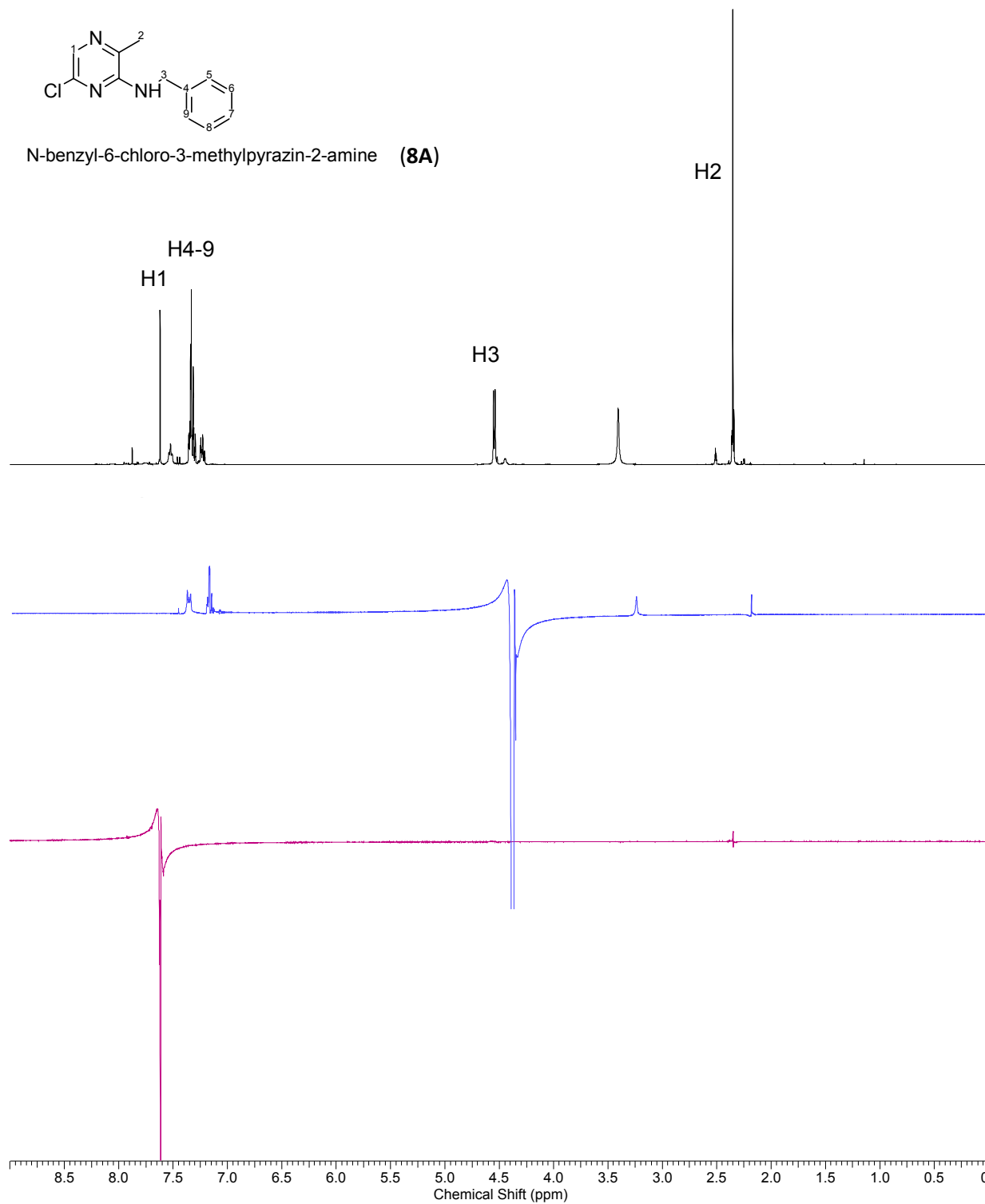
¹H NMR of N-benzyl-6-chloro-3-methylpyrazin-2-amine (8A)300 MHz, DMSO-*d*₆¹³C NMR of N-benzyl-6-chloro-3-methylpyrazin-2-amine

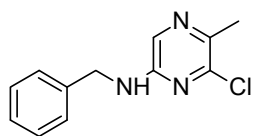
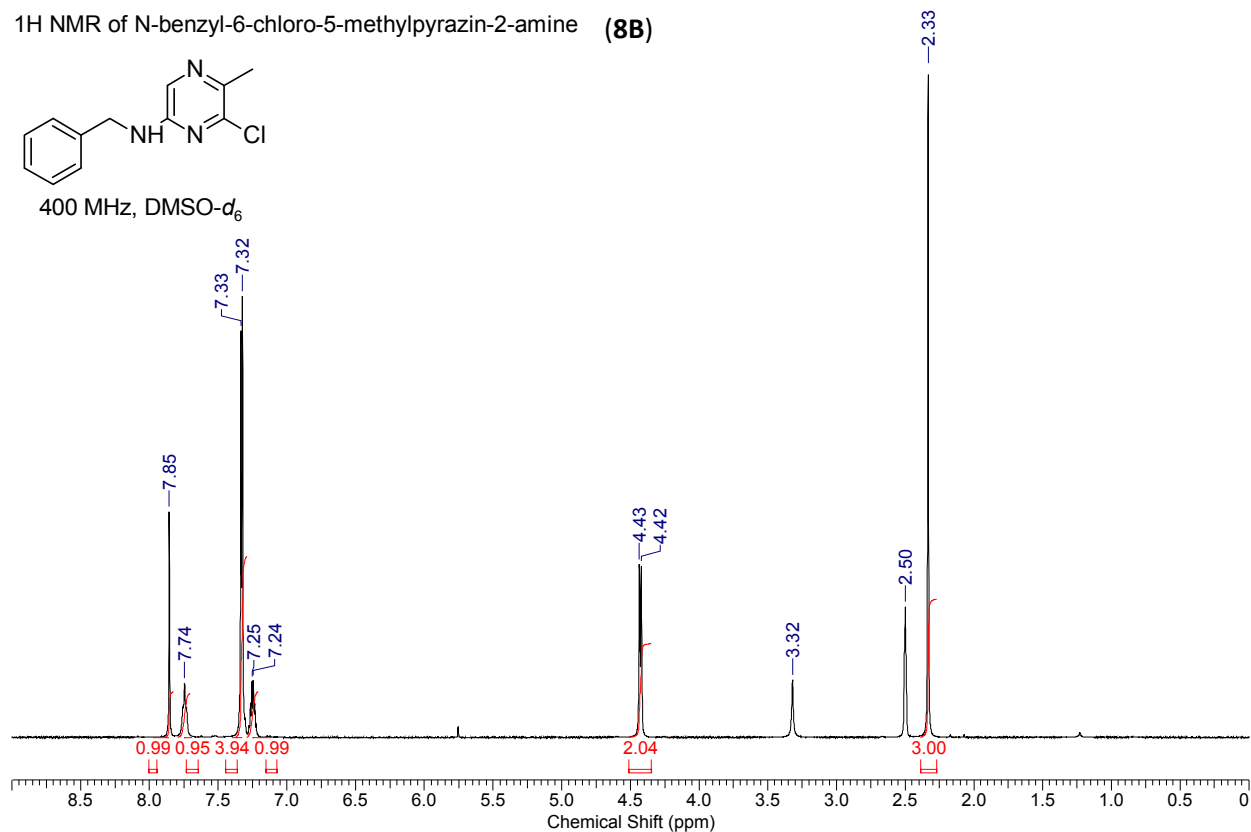
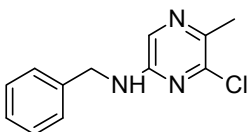
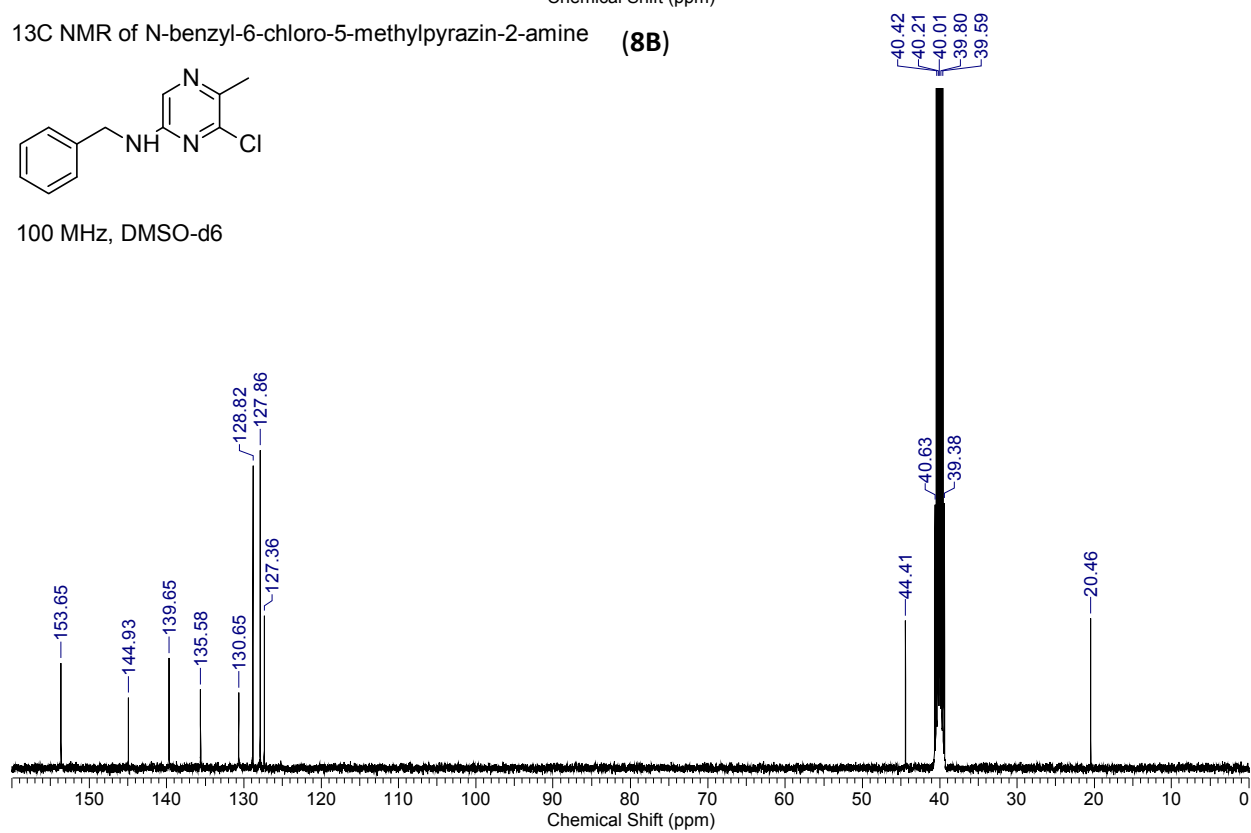
(8A)

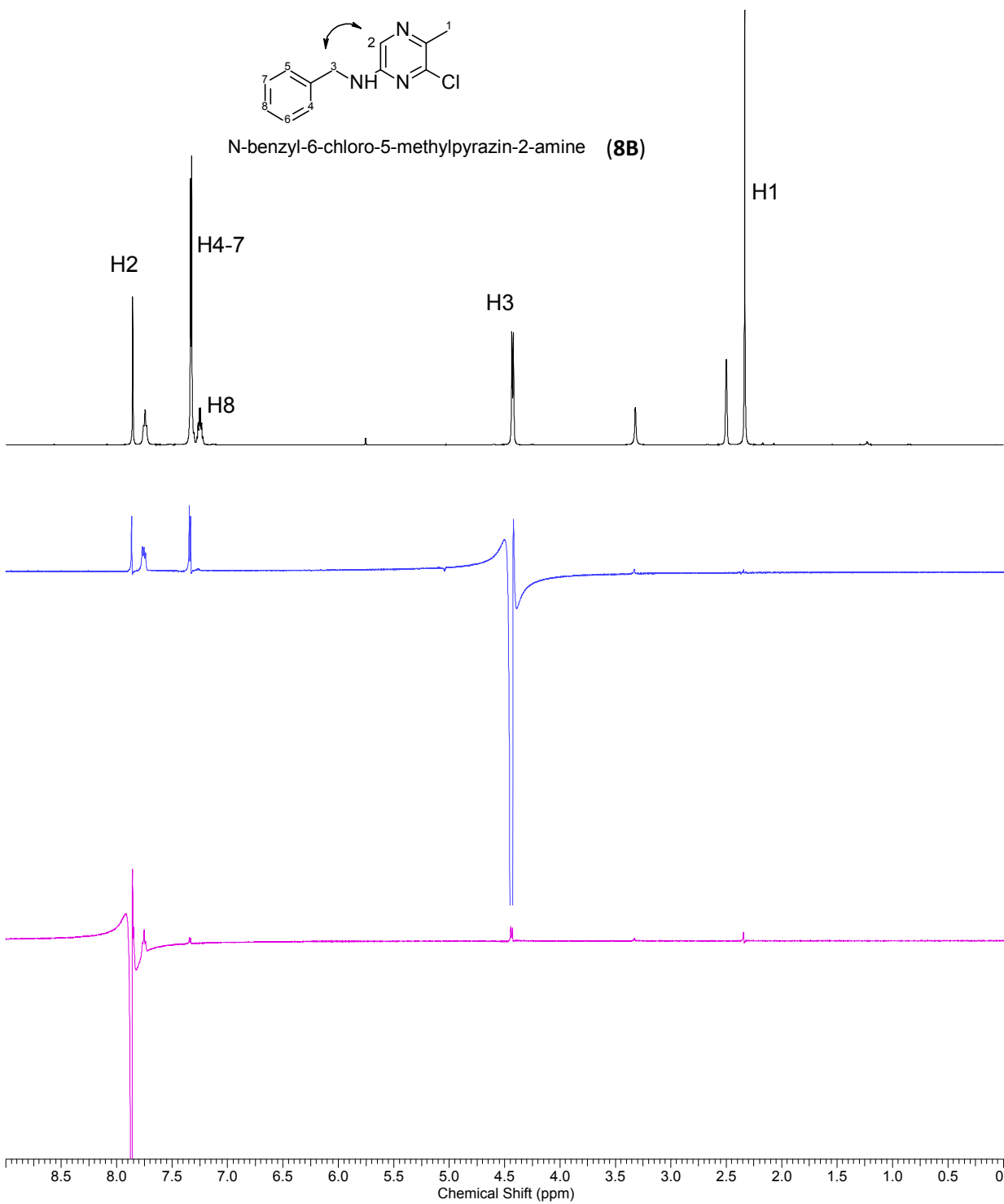
75 MHz, DMSO-*d*₆



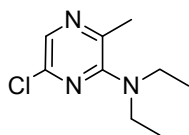
N-benzyl-6-chloro-3-methylpyrazin-2-amine (**8A**)



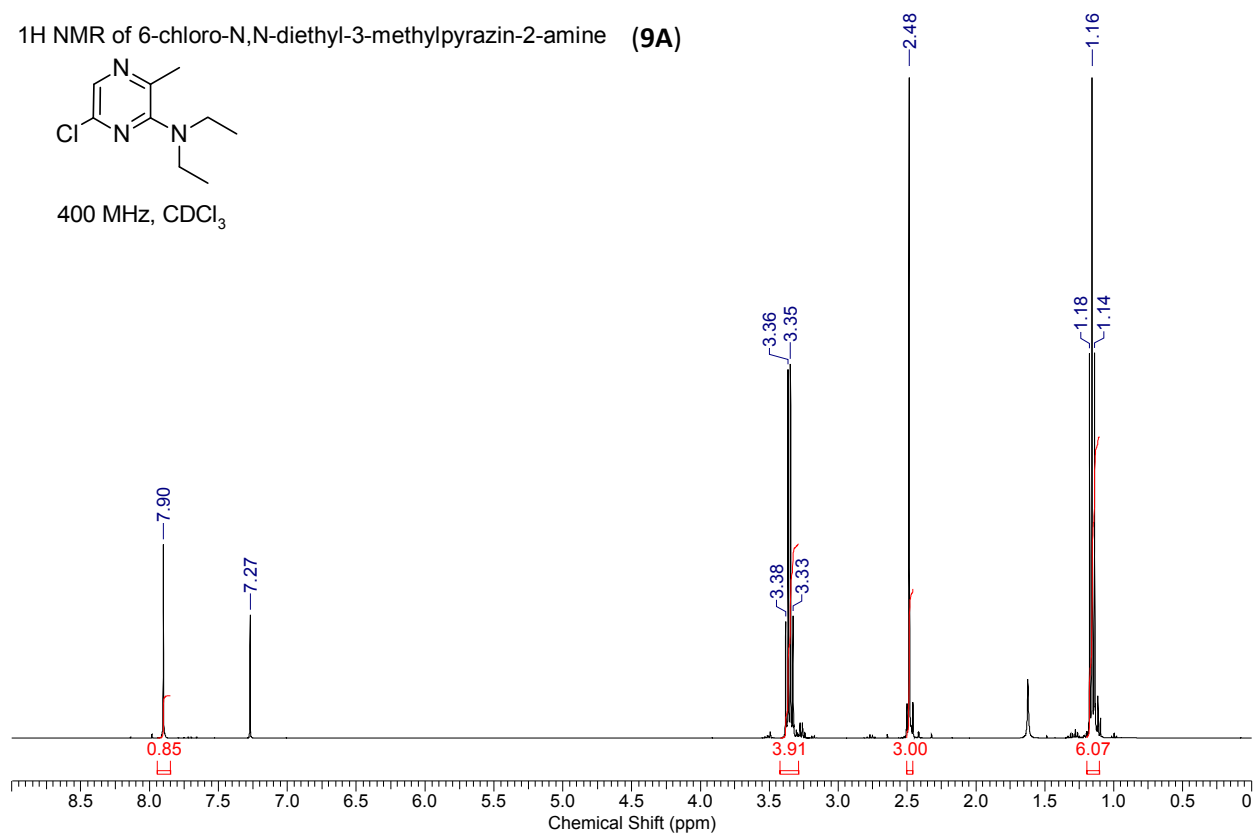
¹H NMR of N-benzyl-6-chloro-5-methylpyrazin-2-amine (**8B**)400 MHz, DMSO-*d*₆¹³C NMR of N-benzyl-6-chloro-5-methylpyrazin-2-amine (**8B**)100 MHz, DMSO-*d*₆



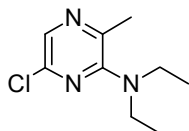
¹H NMR of 6-chloro-N,N-diethyl-3-methylpyrazin-2-amine (**9A**)



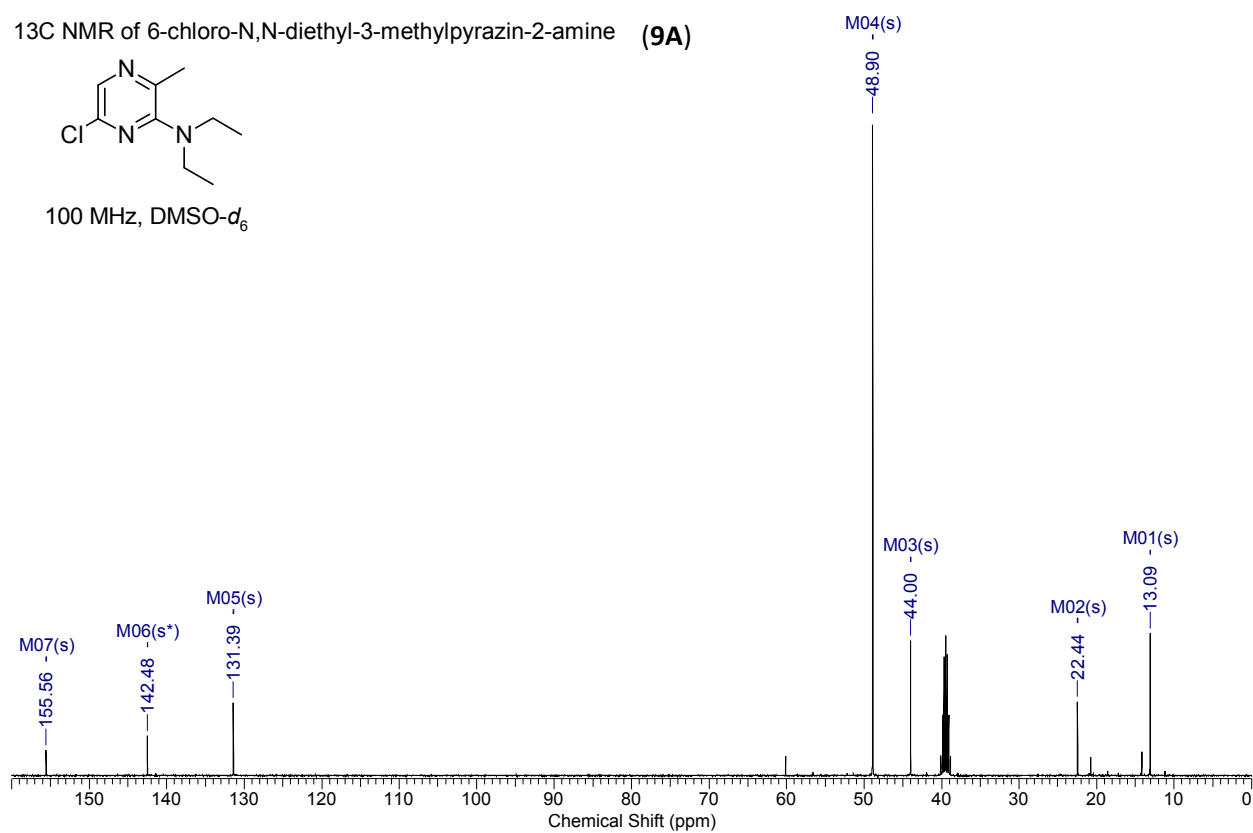
400 MHz, CDCl₃

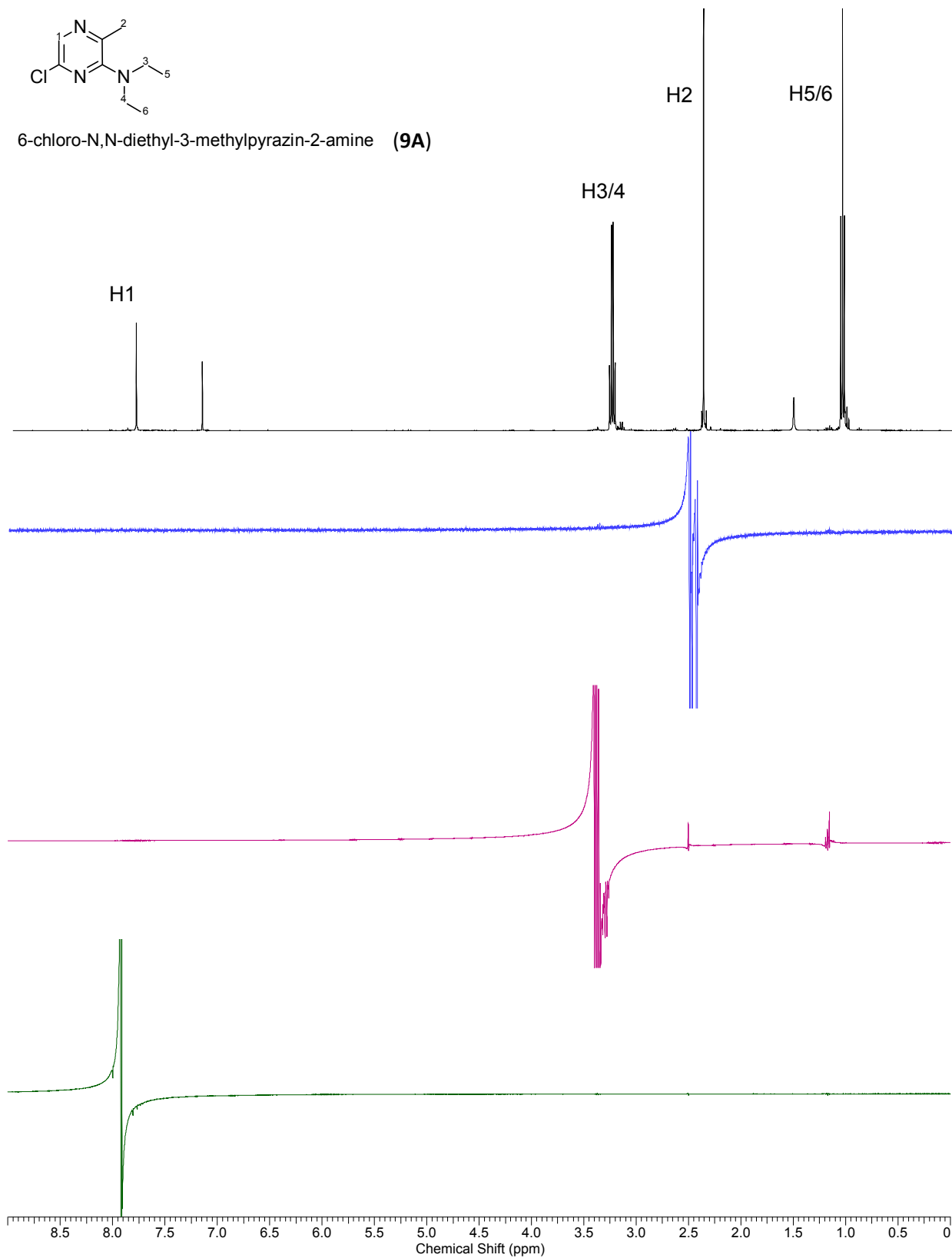


¹³C NMR of 6-chloro-N,N-diethyl-3-methylpyrazin-2-amine (**9A**)

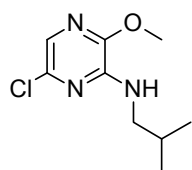


100 MHz, DMSO-*d*₆

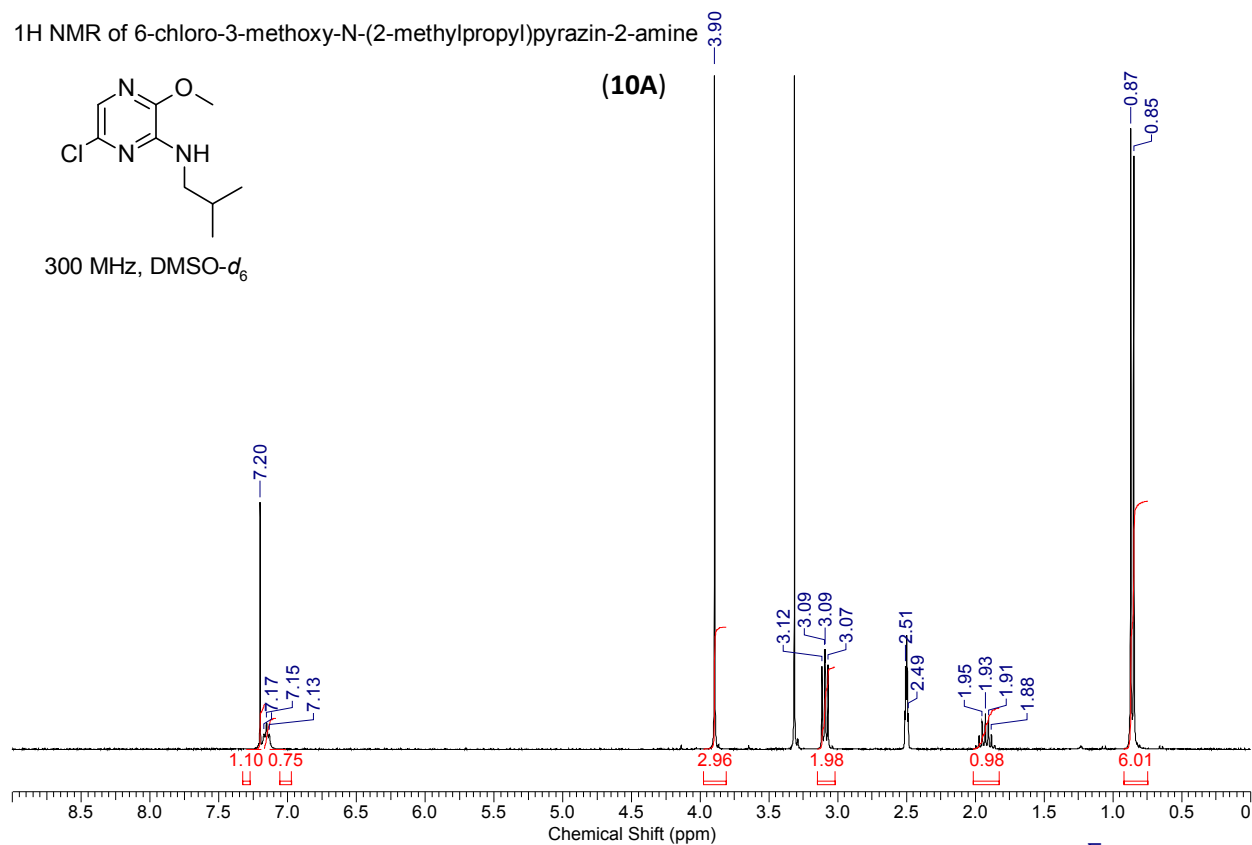




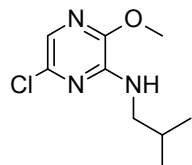
¹H NMR of 6-chloro-3-methoxy-N-(2-methylpropyl)pyrazin-2-amine (10A)



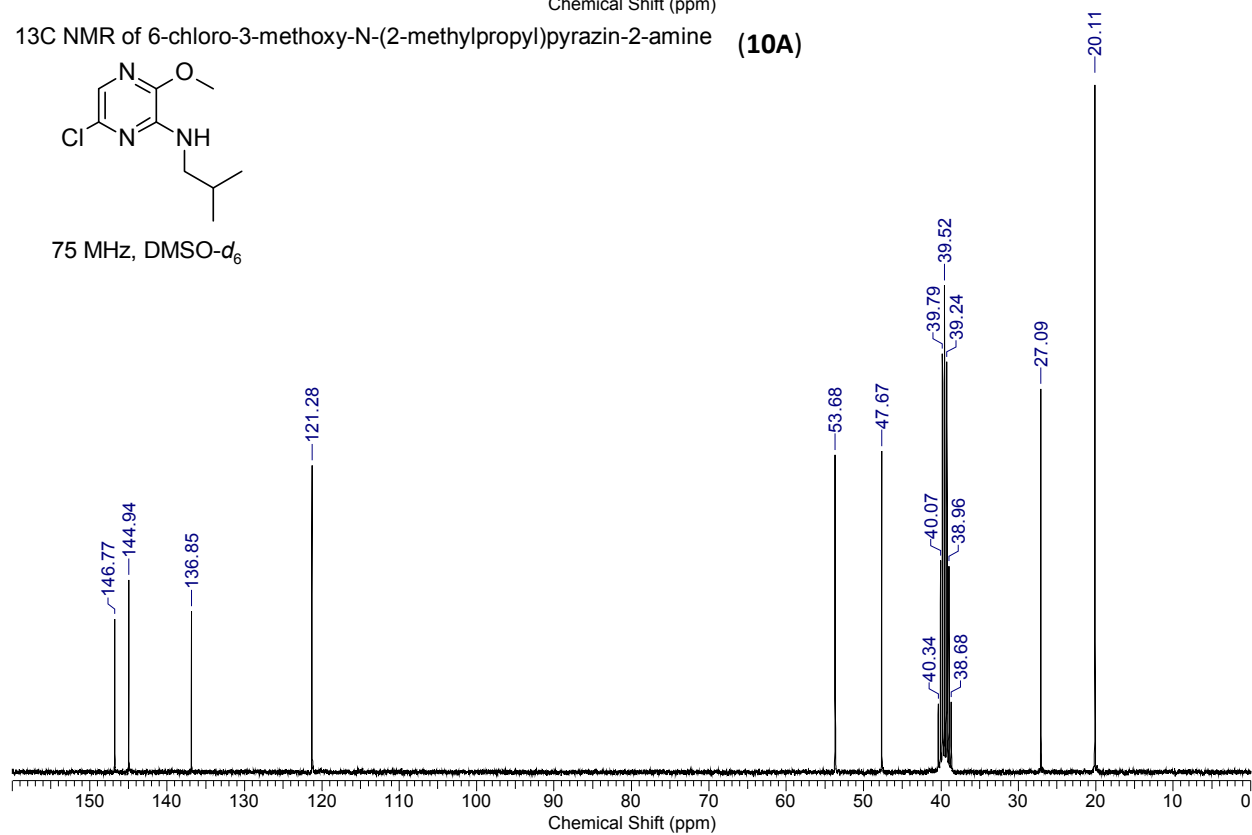
300 MHz, DMSO-*d*₆

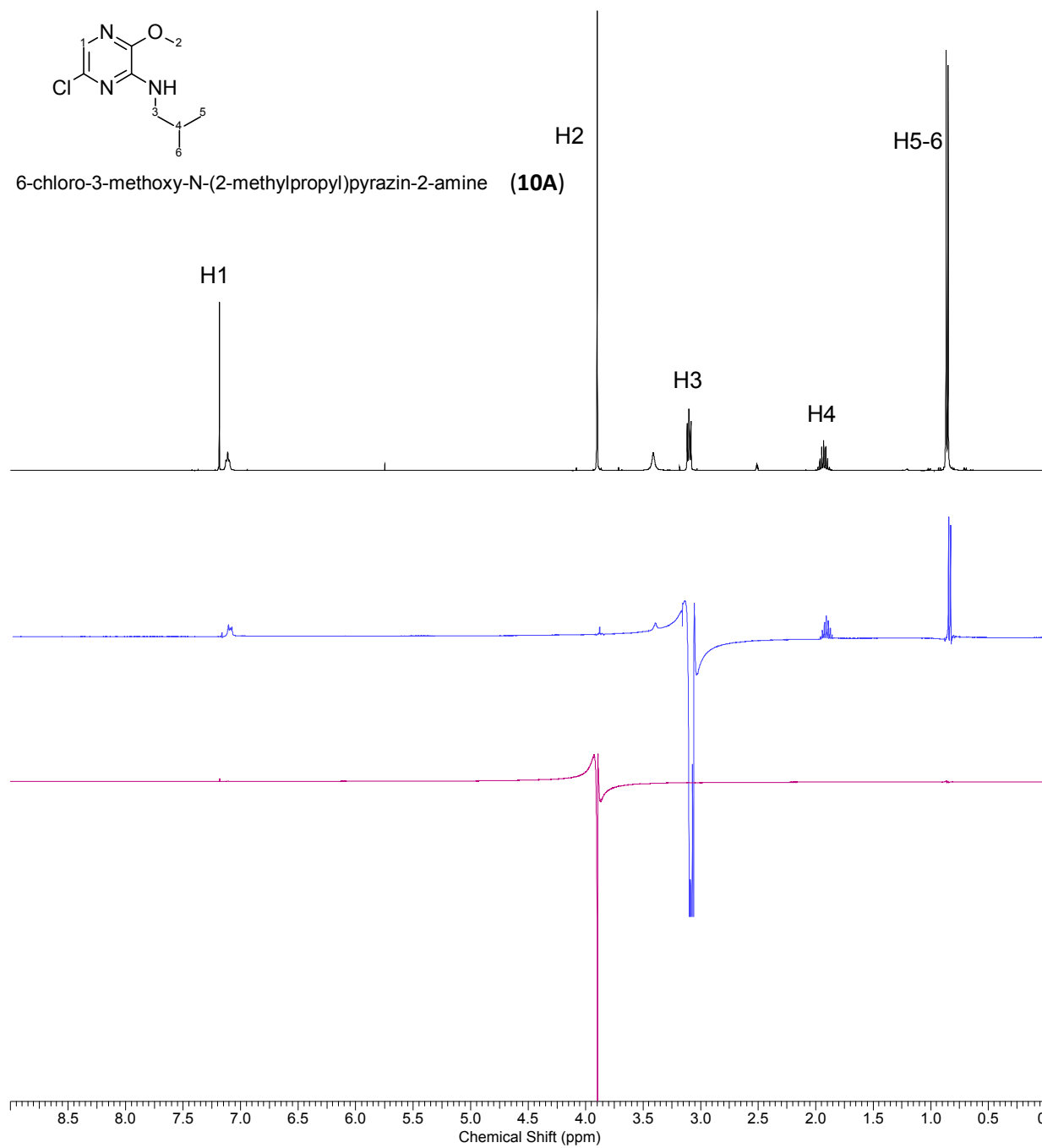


¹³C NMR of 6-chloro-3-methoxy-N-(2-methylpropyl)pyrazin-2-amine (10A)

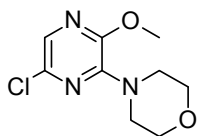


75 MHz, DMSO-*d*₆

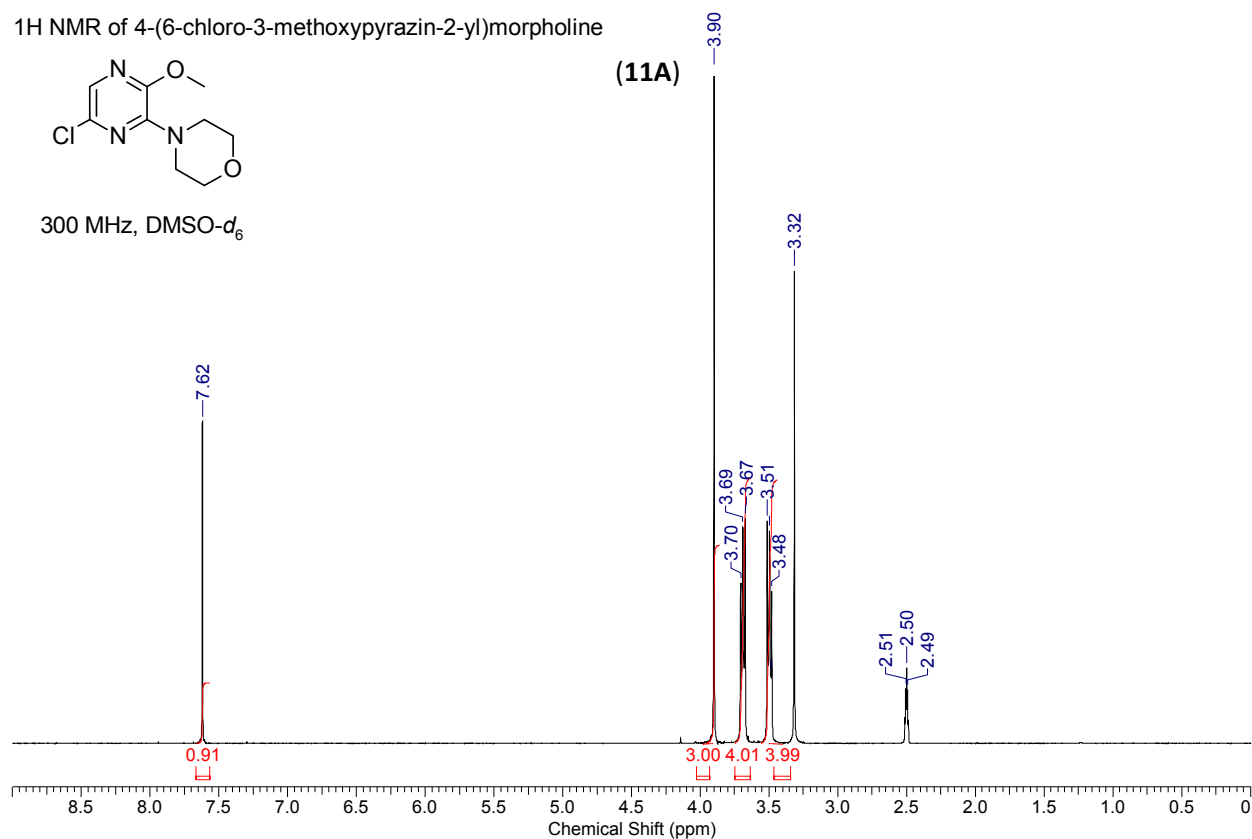




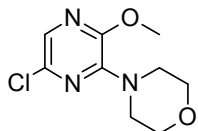
¹H NMR of 4-(6-chloro-3-methoxypyrazin-2-yl)morpholine



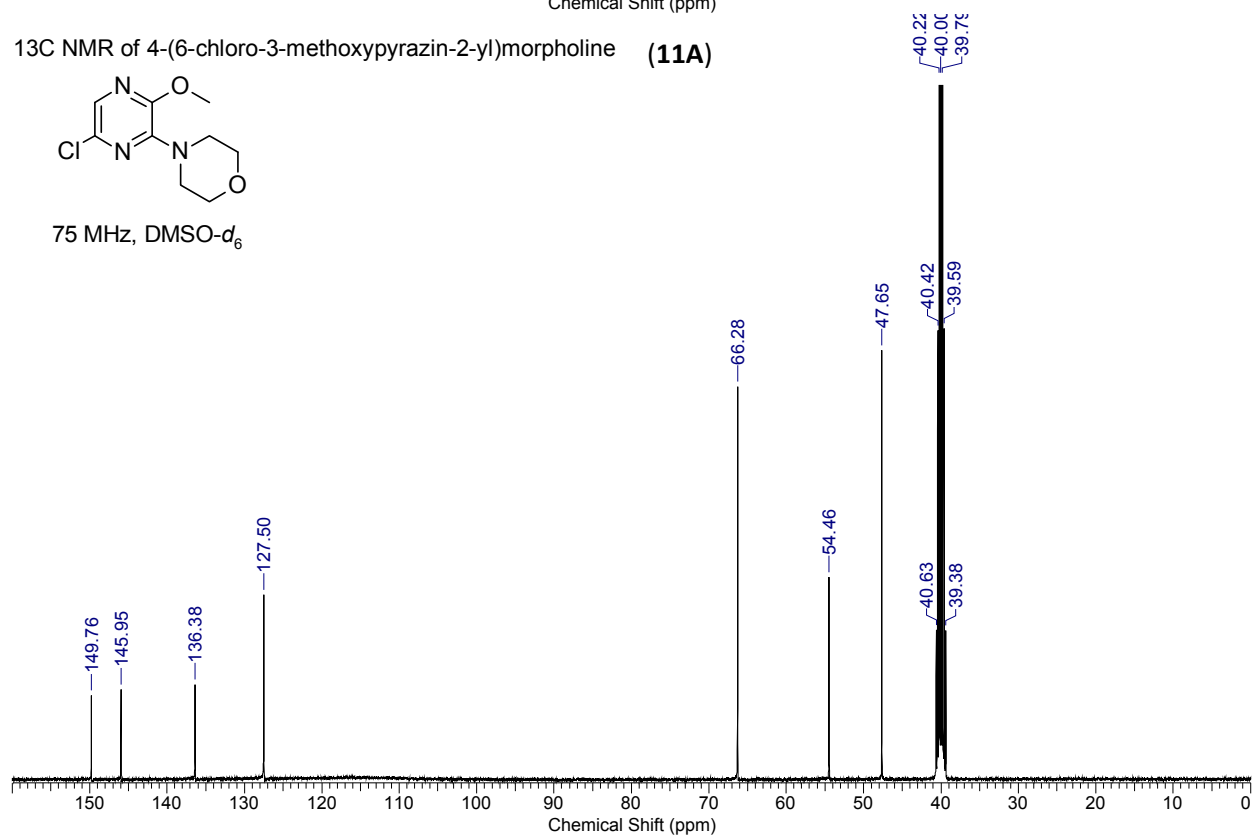
300 MHz, DMSO-*d*₆

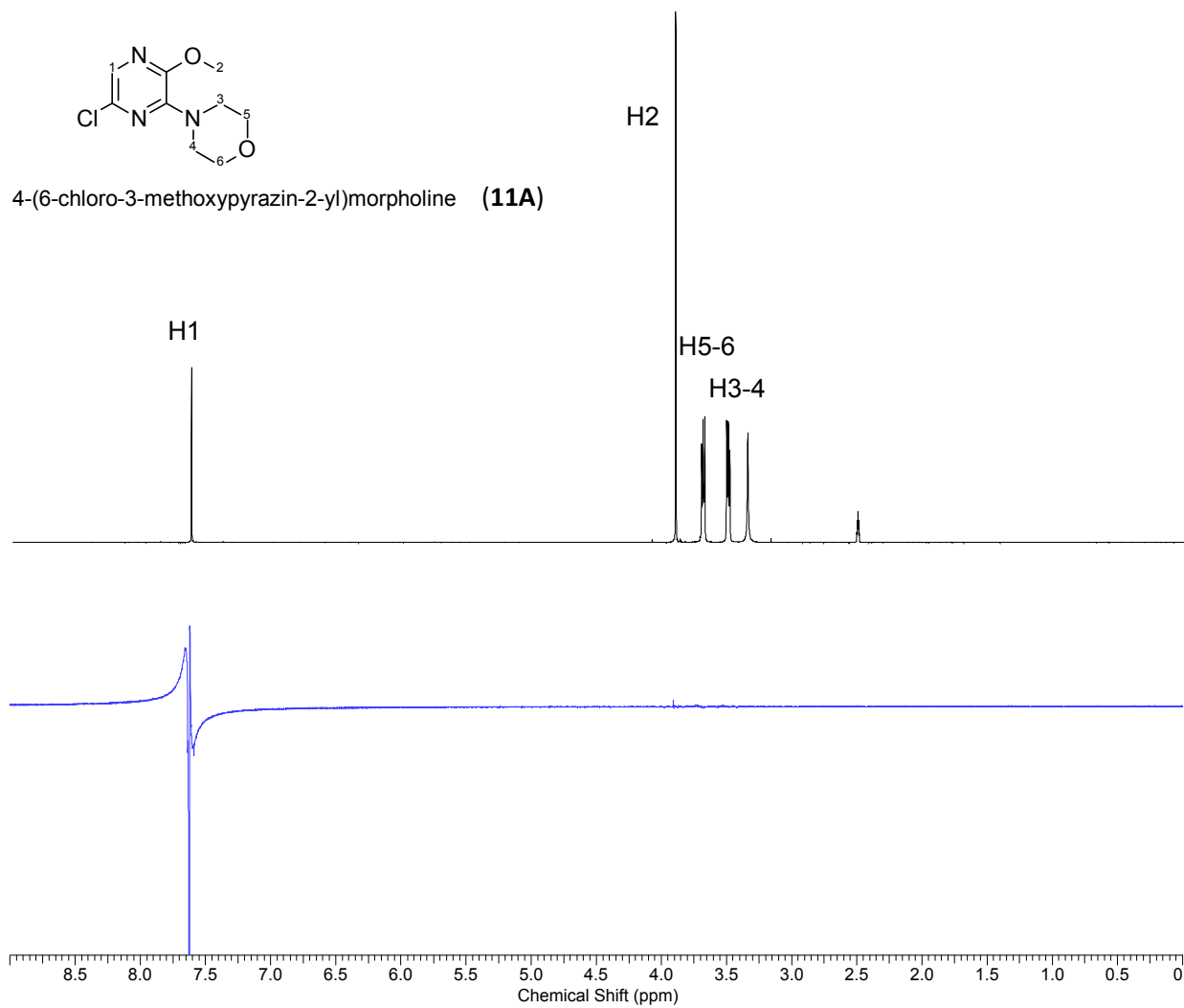


¹³C NMR of 4-(6-chloro-3-methoxypyrazin-2-yl)morpholine (11A)

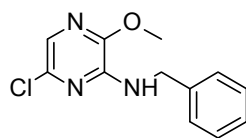


75 MHz, DMSO-*d*₆

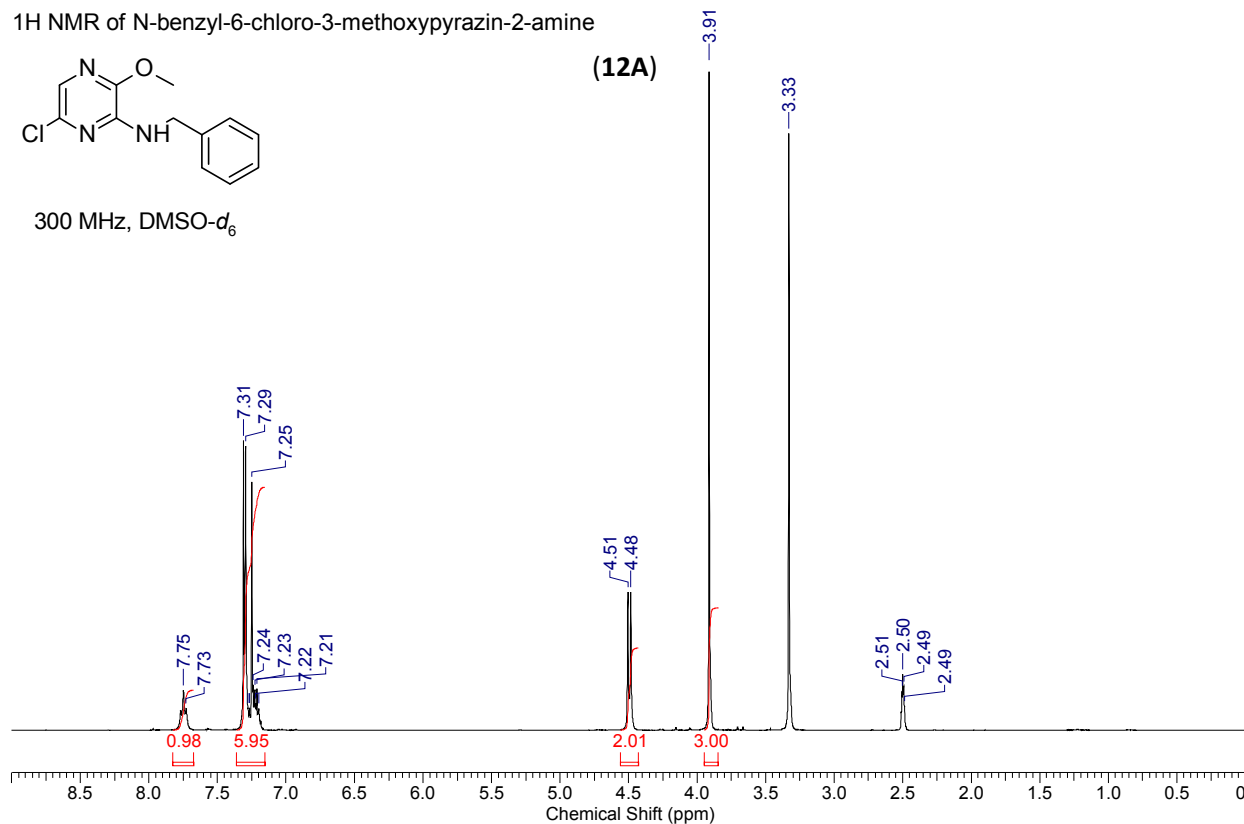




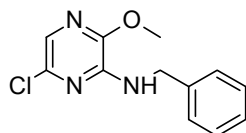
¹H NMR of N-benzyl-6-chloro-3-methoxypyrazin-2-amine



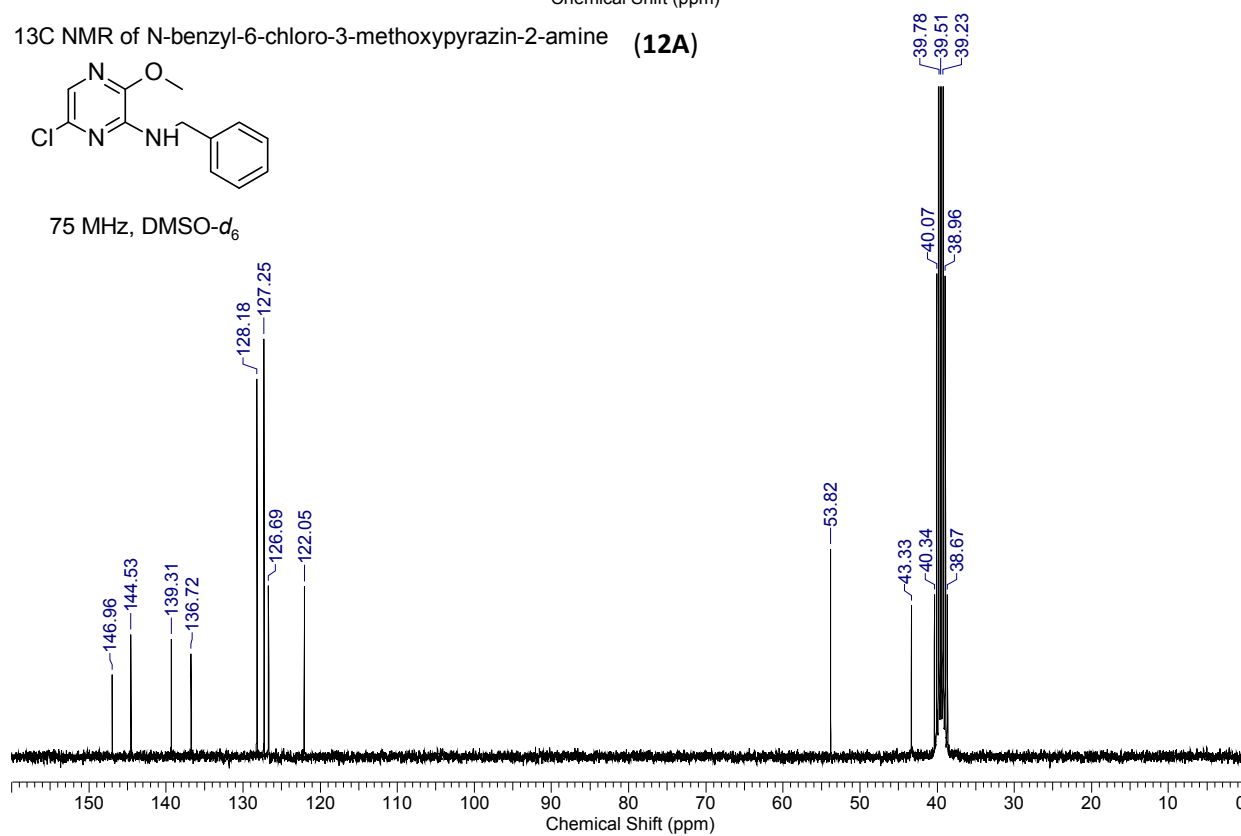
300 MHz, DMSO-*d*₆

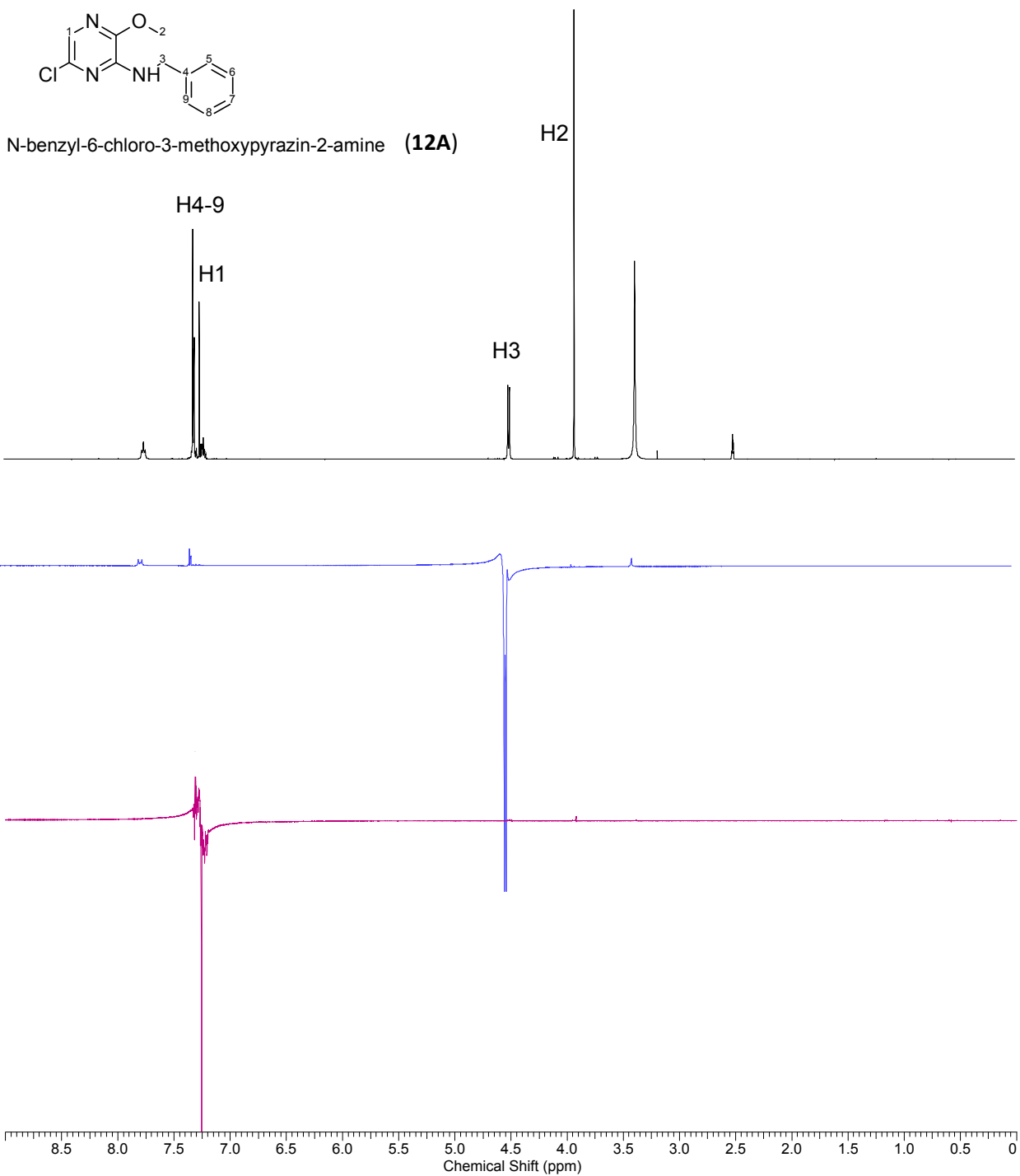


¹³C NMR of N-benzyl-6-chloro-3-methoxypyrazin-2-amine (12A)

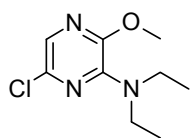


75 MHz, DMSO-*d*₆

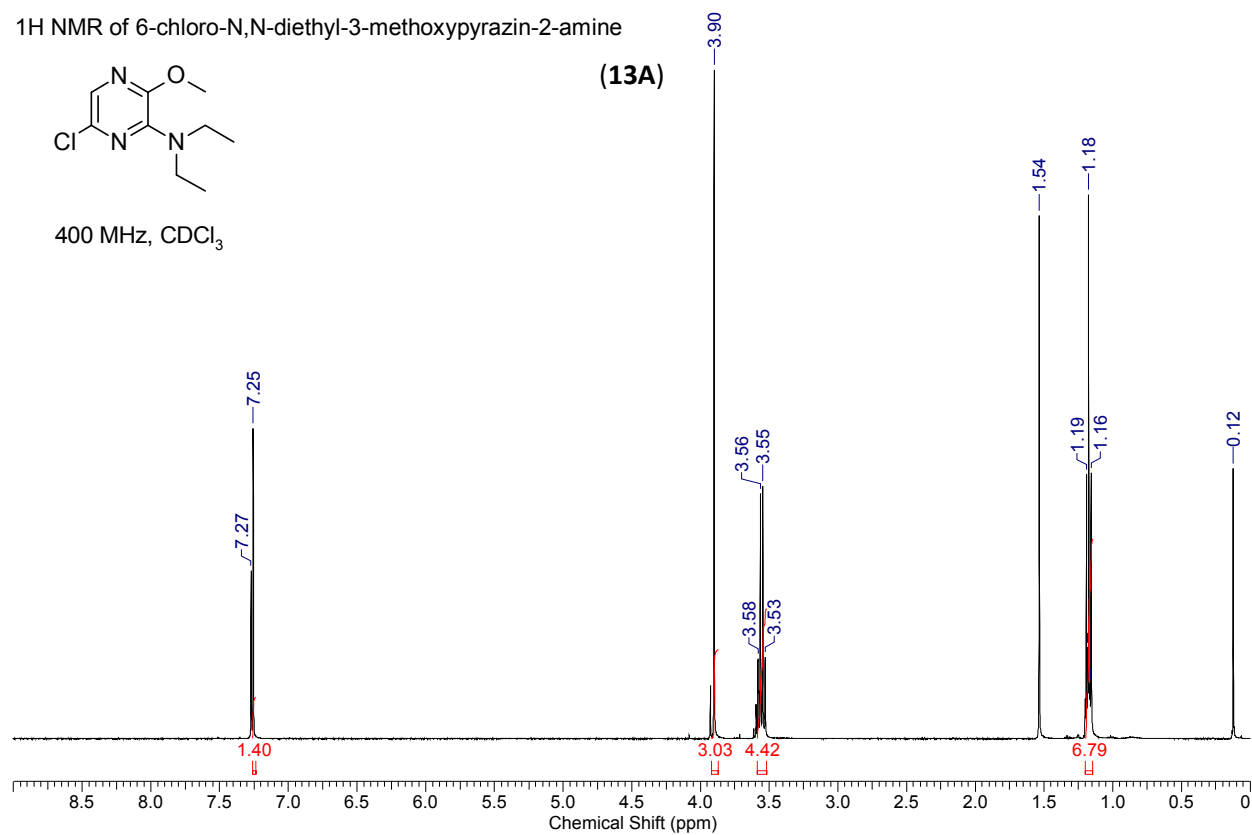




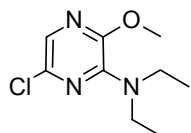
¹H NMR of 6-chloro-N,N-diethyl-3-methoxypyrazin-2-amine



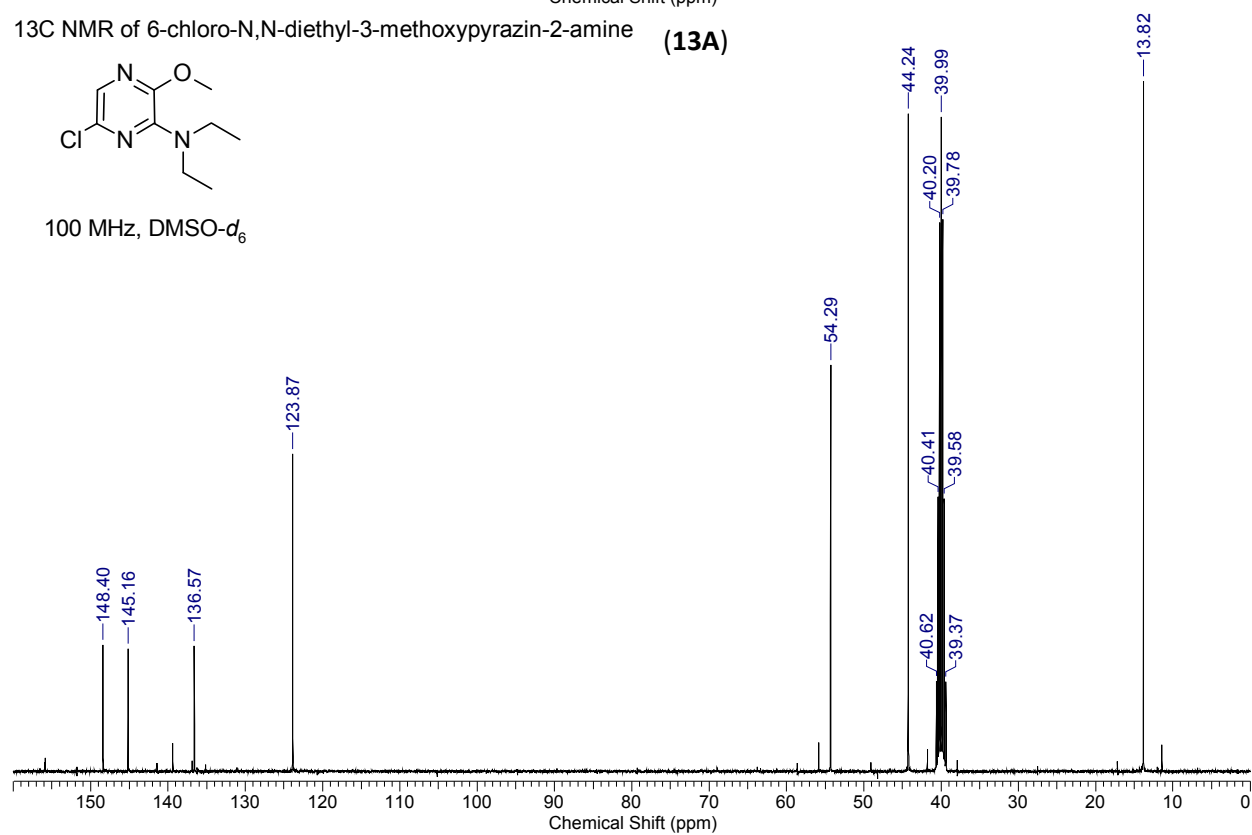
400 MHz, CDCl₃

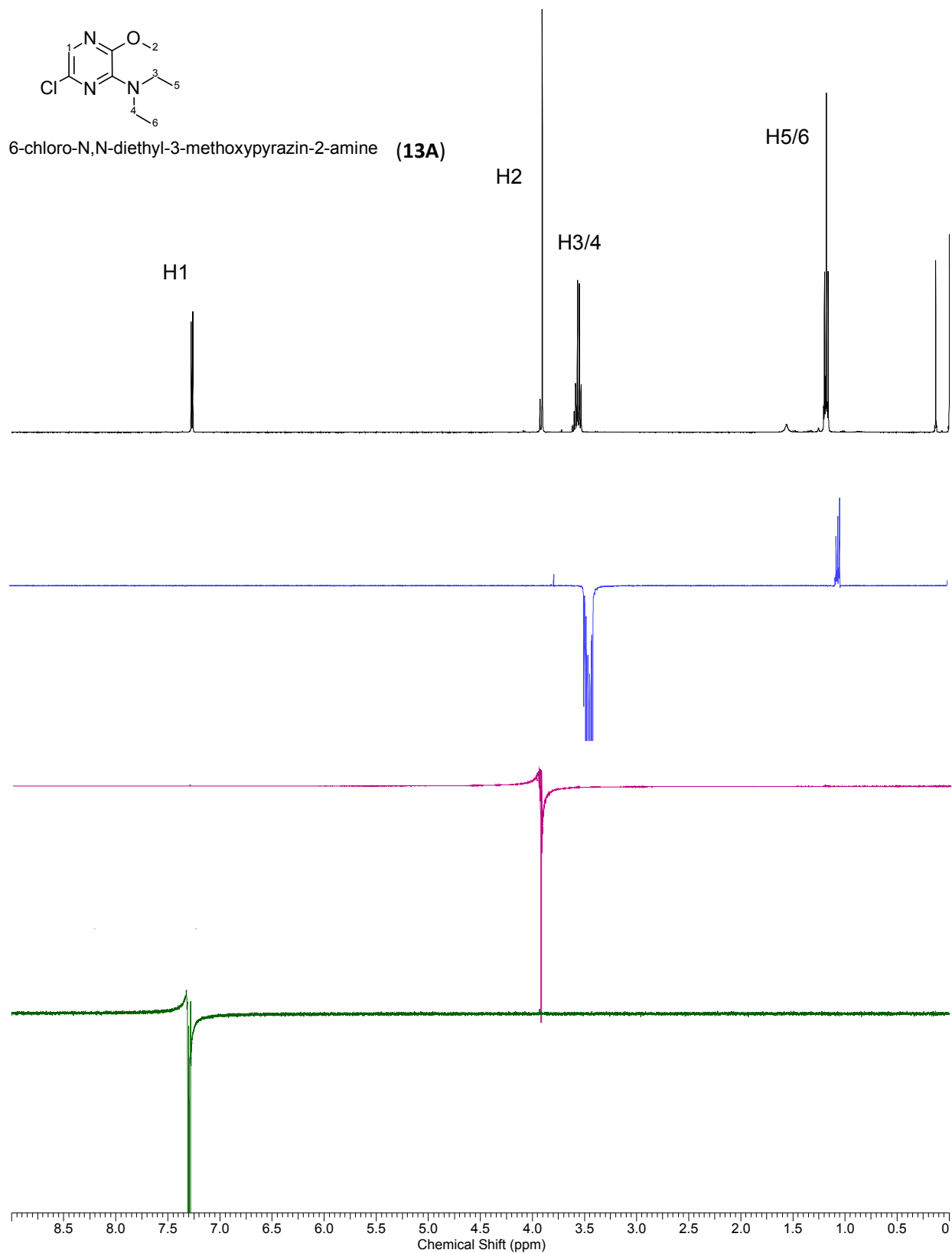


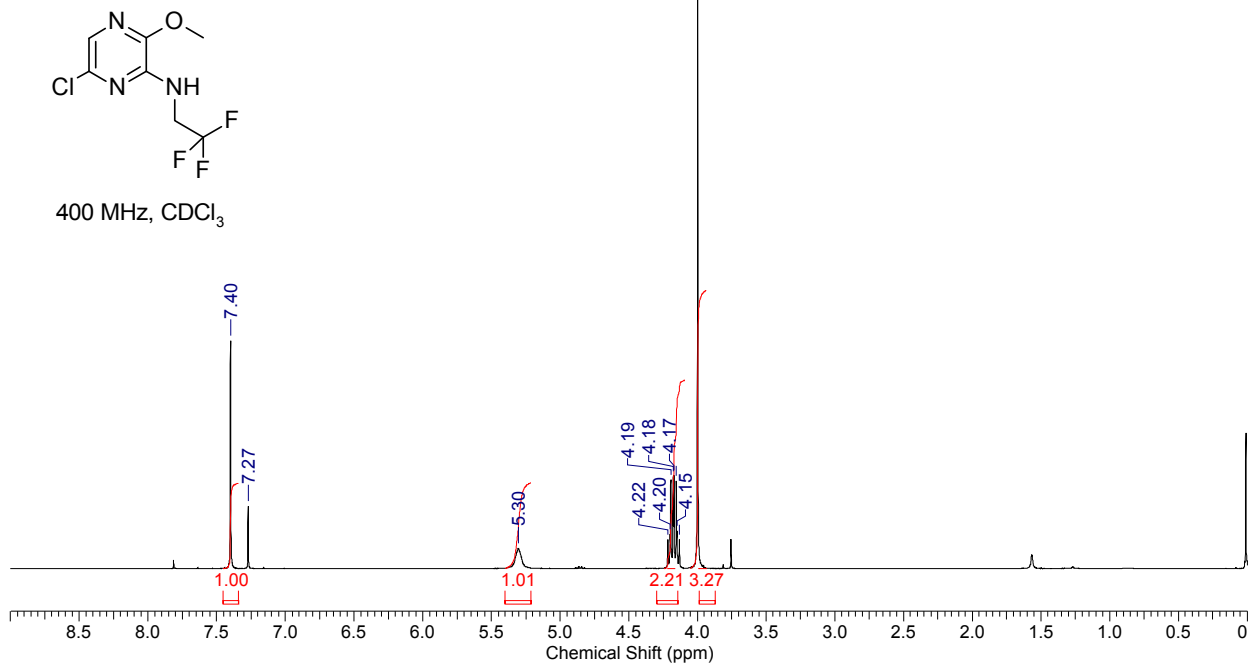
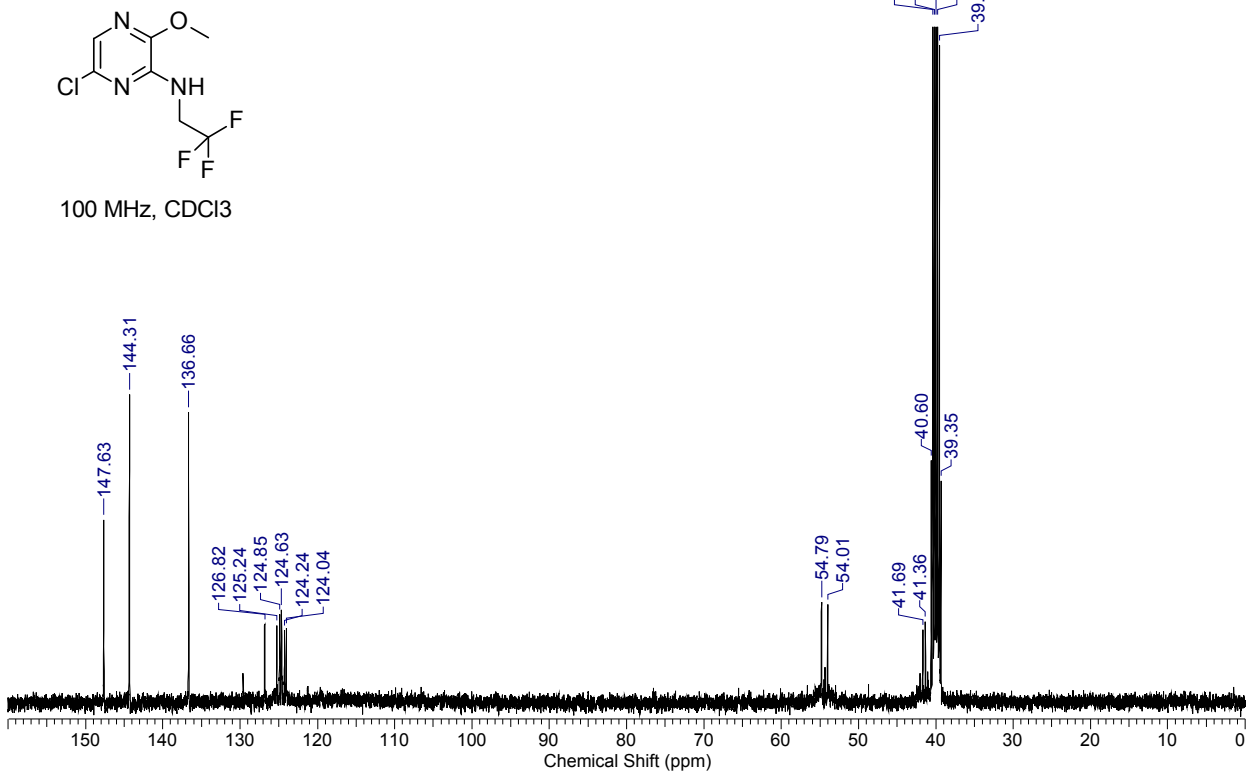
¹³C NMR of 6-chloro-N,N-diethyl-3-methoxypyrazin-2-amine (13A)

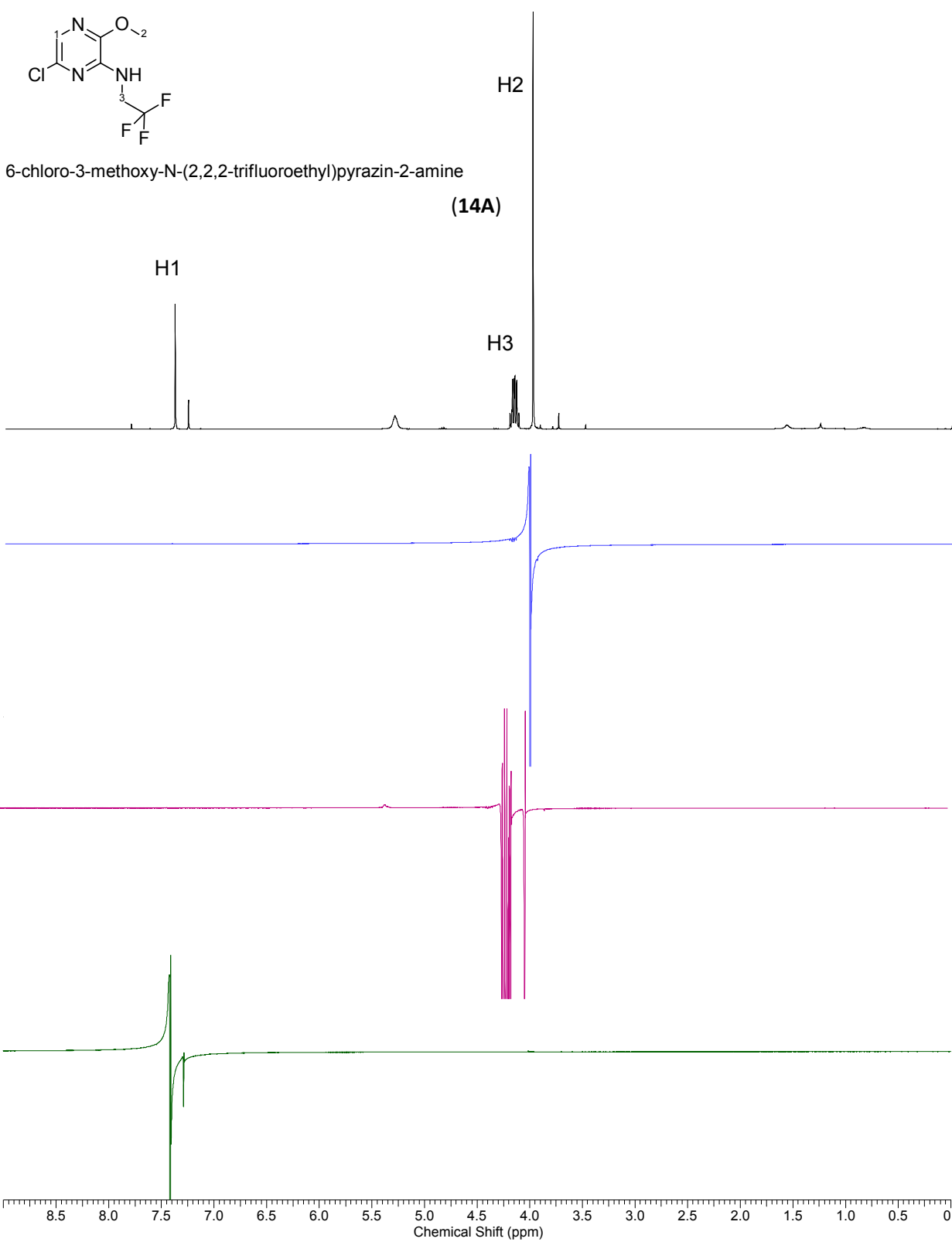


100 MHz, DMSO-*d*₆

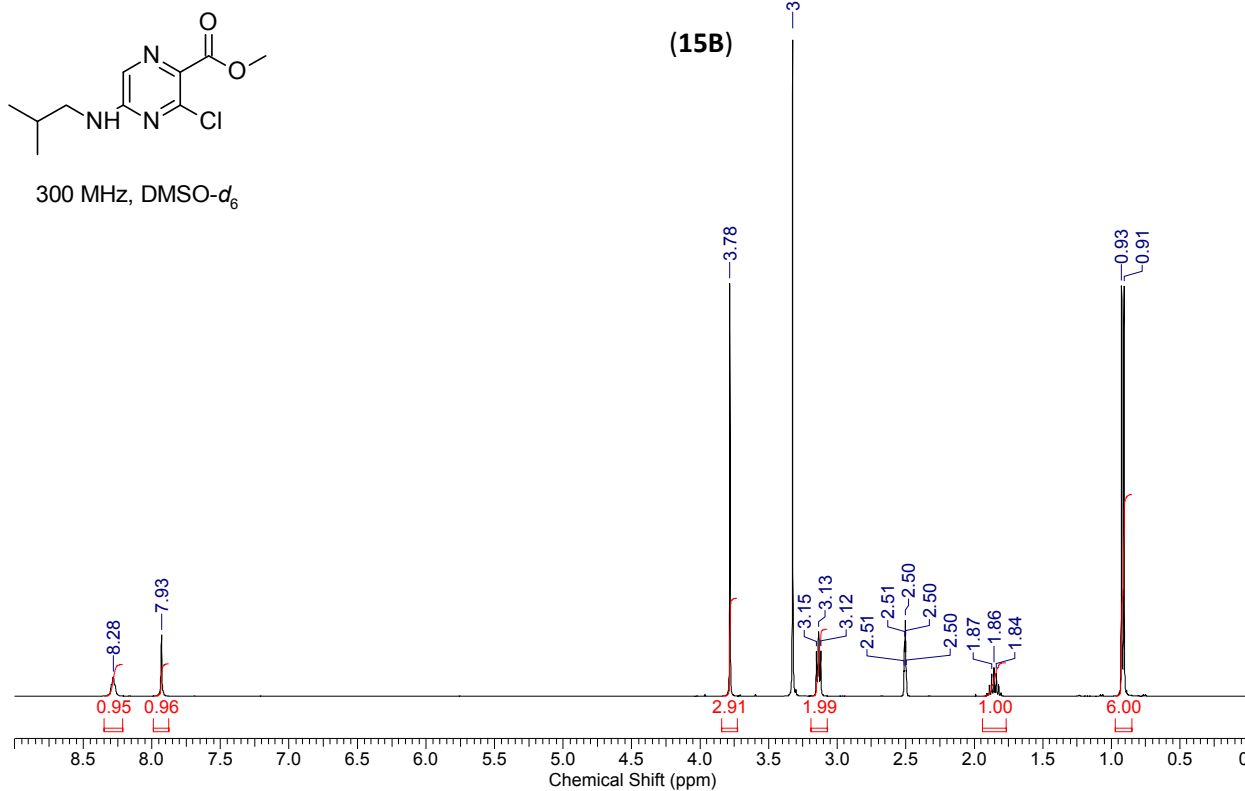




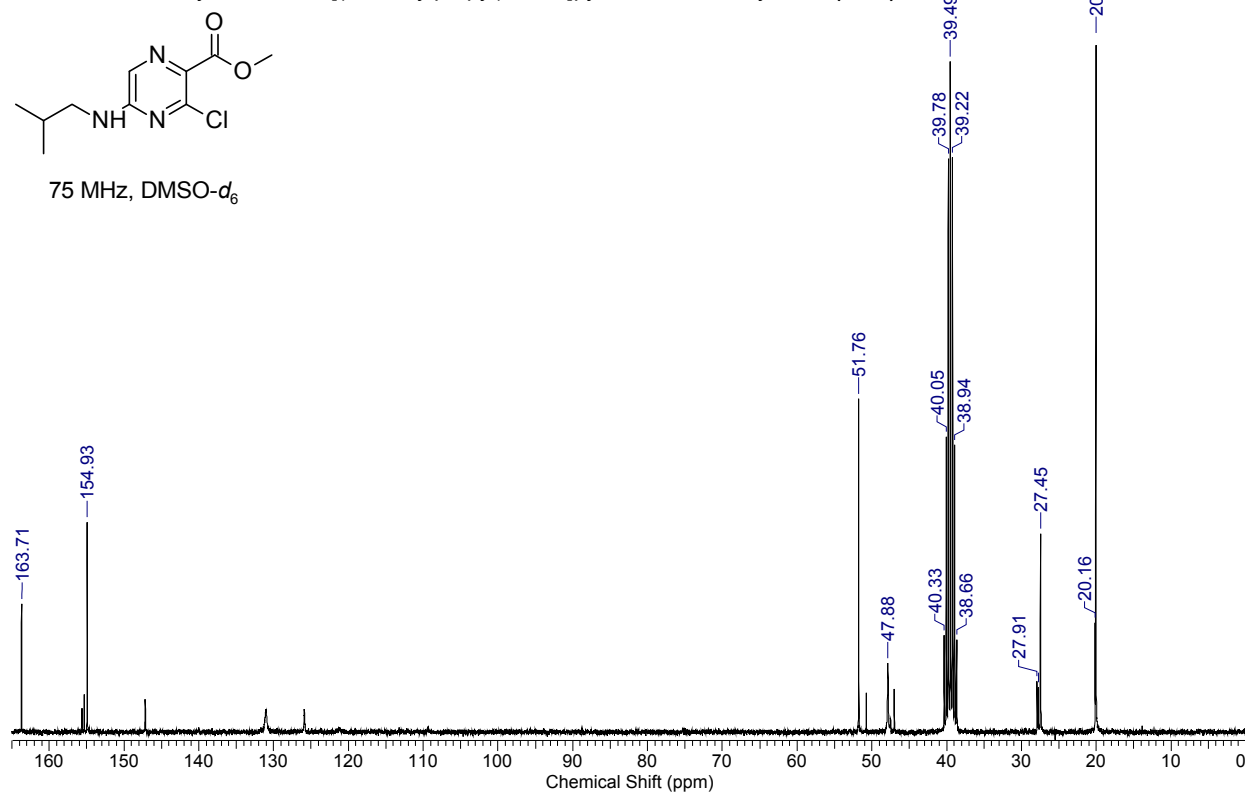
¹H NMR of 6-chloro-3-methoxy-N-(2,2,2-trifluoroethyl)pyrazin-2-amine (**14A**)¹³C NMR of 6-chloro-3-methoxy-N-(2,2,2-trifluoroethyl)pyrazin-2-amine (**14A**)

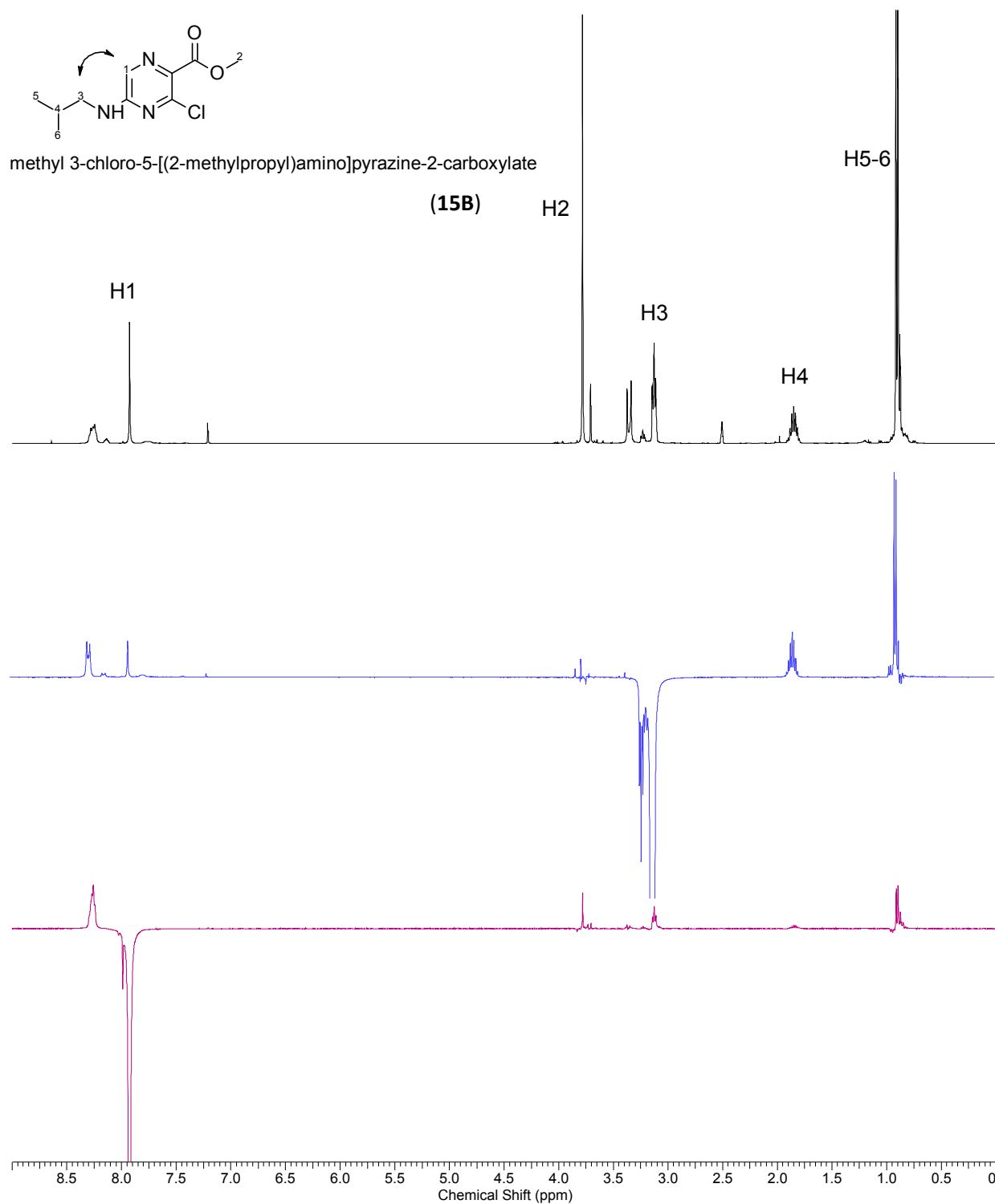


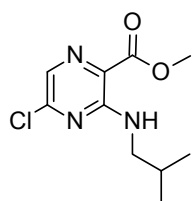
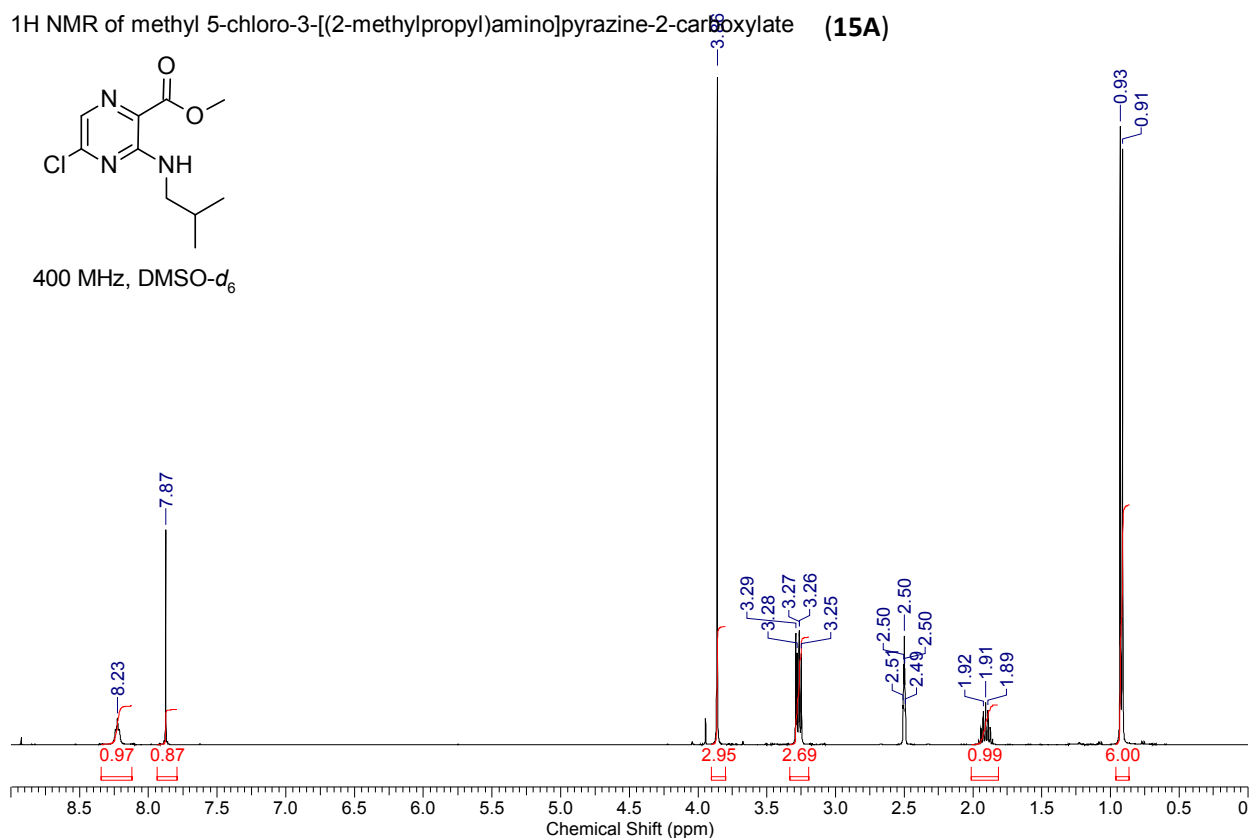
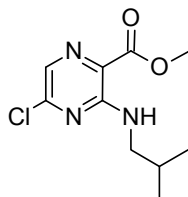
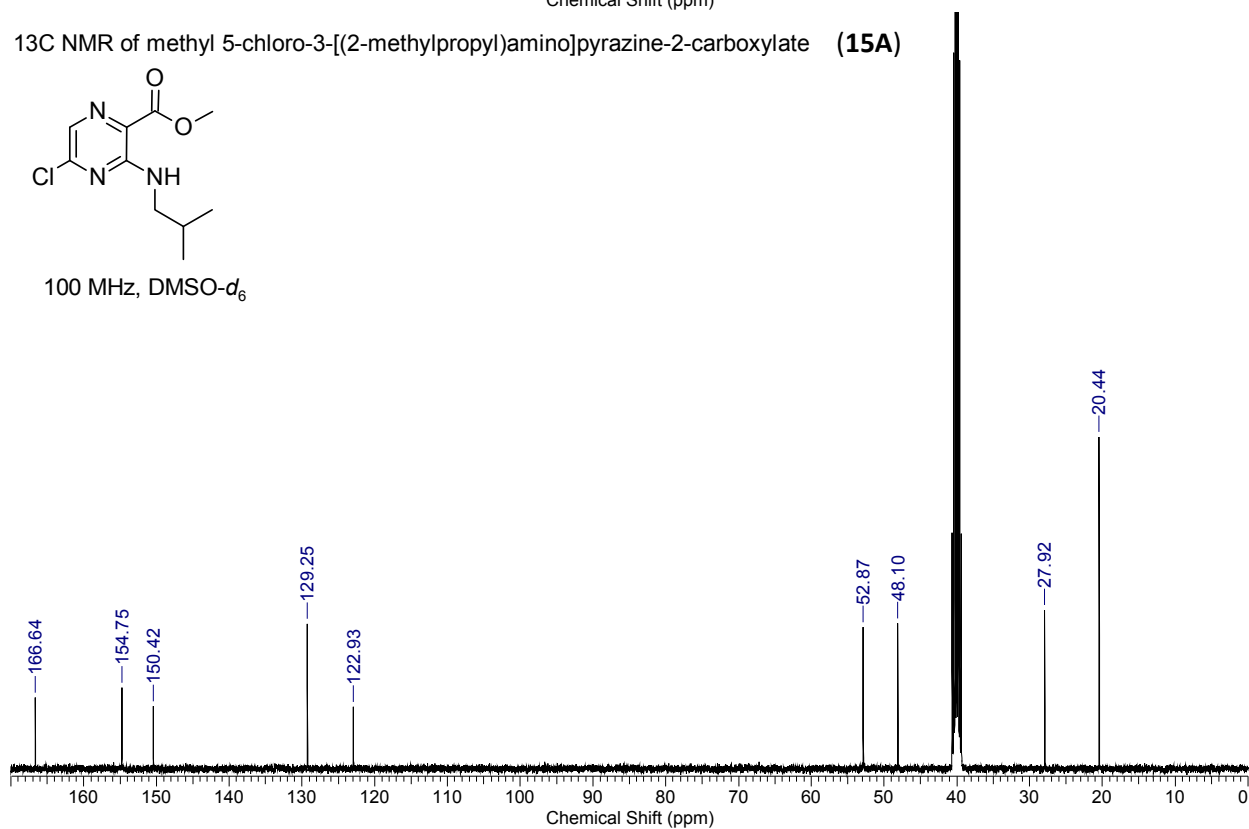
¹H NMR of methyl 3-chloro-5-[(2-methylpropyl)amino]pyrazine-2-carboxylate (15B)

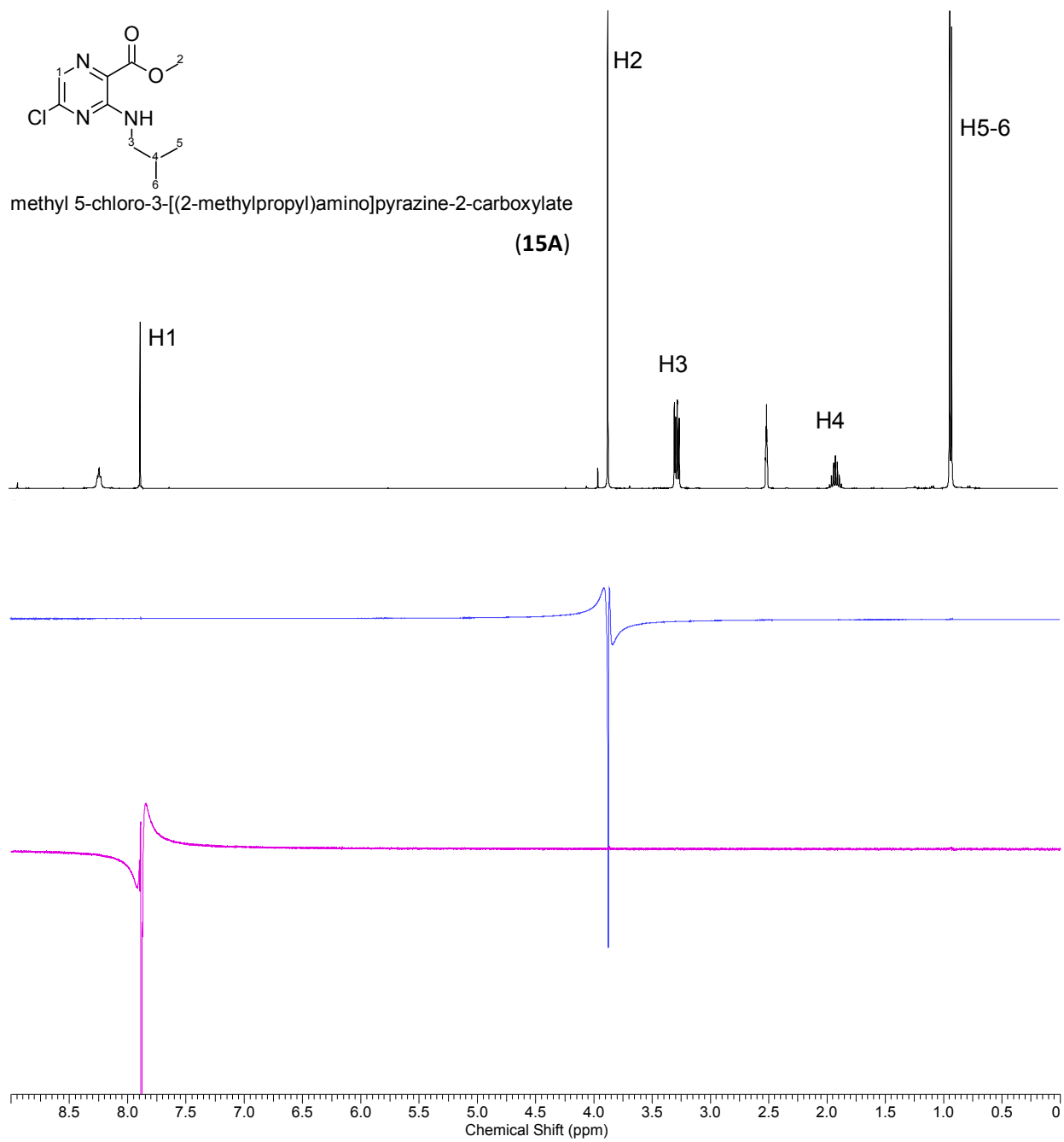


¹³C NMR of methyl 3-chloro-5-[(2-methylpropyl)amino]pyrazine-2-carboxylate (15B)

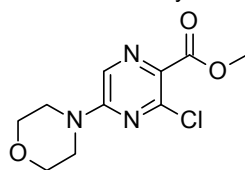




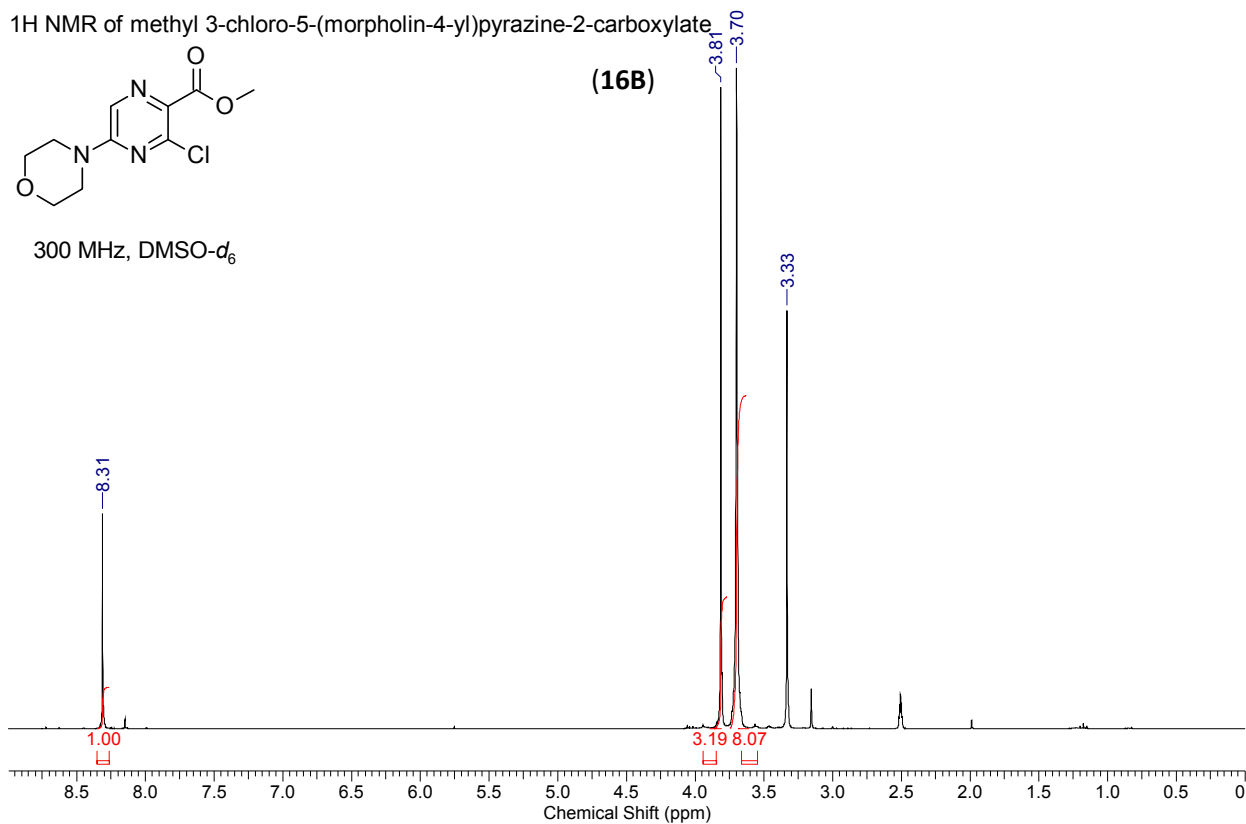
¹H NMR of methyl 5-chloro-3-[(2-methylpropyl)amino]pyrazine-2-carboxylate (**15A**)400 MHz, DMSO-*d*₆¹³C NMR of methyl 5-chloro-3-[(2-methylpropyl)amino]pyrazine-2-carboxylate (**15A**)100 MHz, DMSO-*d*₆



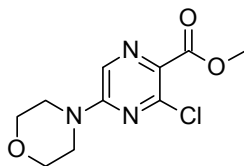
¹H NMR of methyl 3-chloro-5-(morpholin-4-yl)pyrazine-2-carboxylate



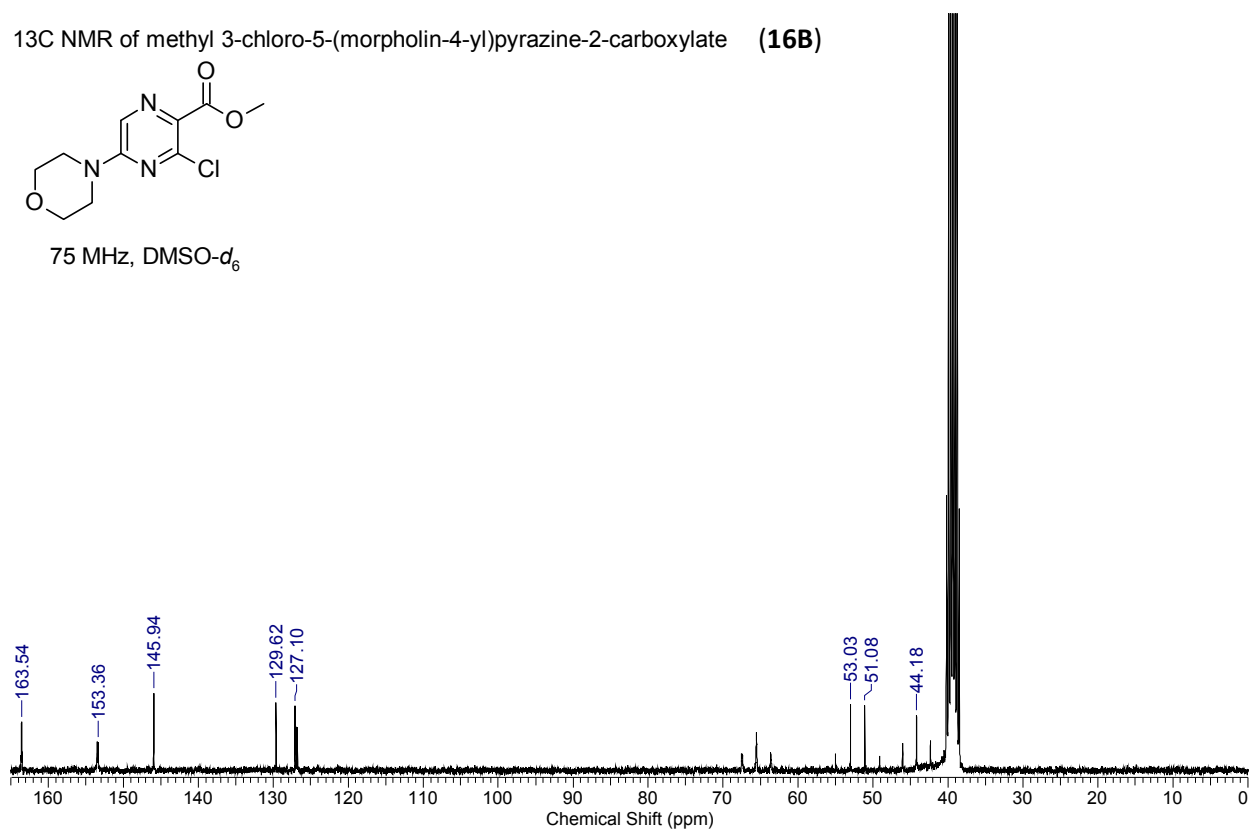
300 MHz, DMSO-*d*₆

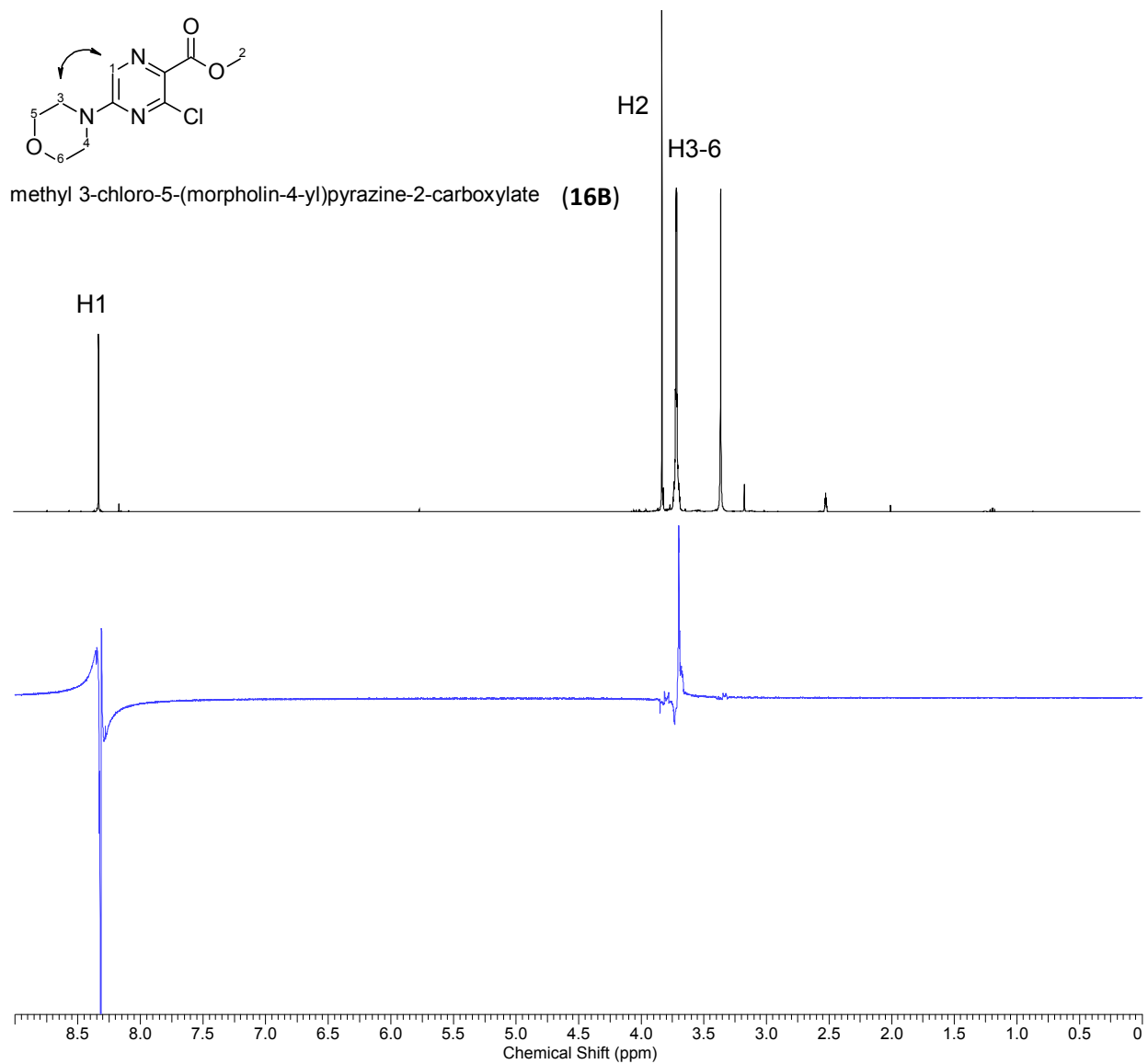


¹³C NMR of methyl 3-chloro-5-(morpholin-4-yl)pyrazine-2-carboxylate (16B)

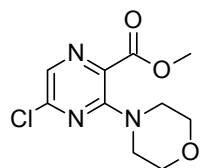


75 MHz, DMSO-*d*₆

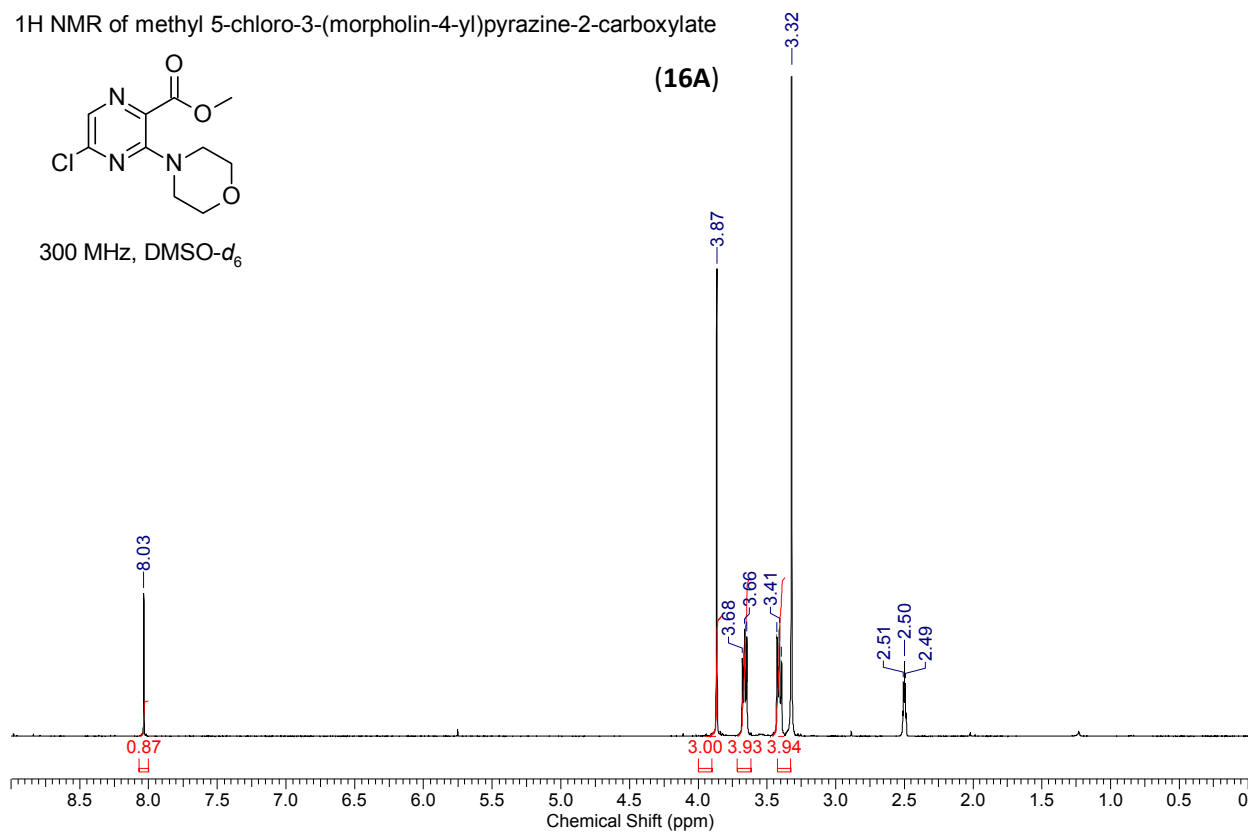




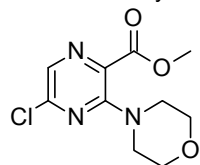
¹H NMR of methyl 5-chloro-3-(morpholin-4-yl)pyrazine-2-carboxylate



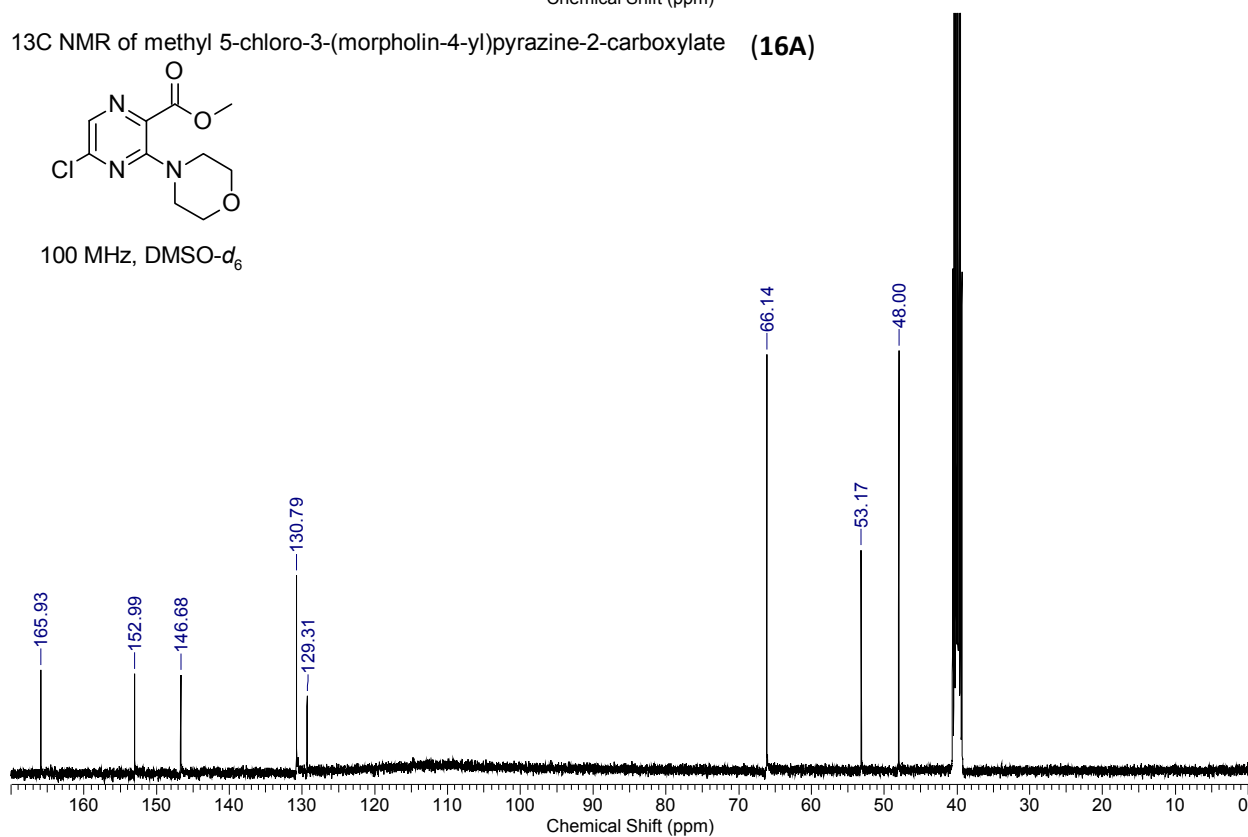
300 MHz, DMSO-*d*₆

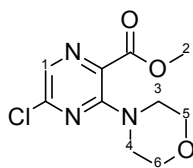


¹³C NMR of methyl 5-chloro-3-(morpholin-4-yl)pyrazine-2-carboxylate (16A)

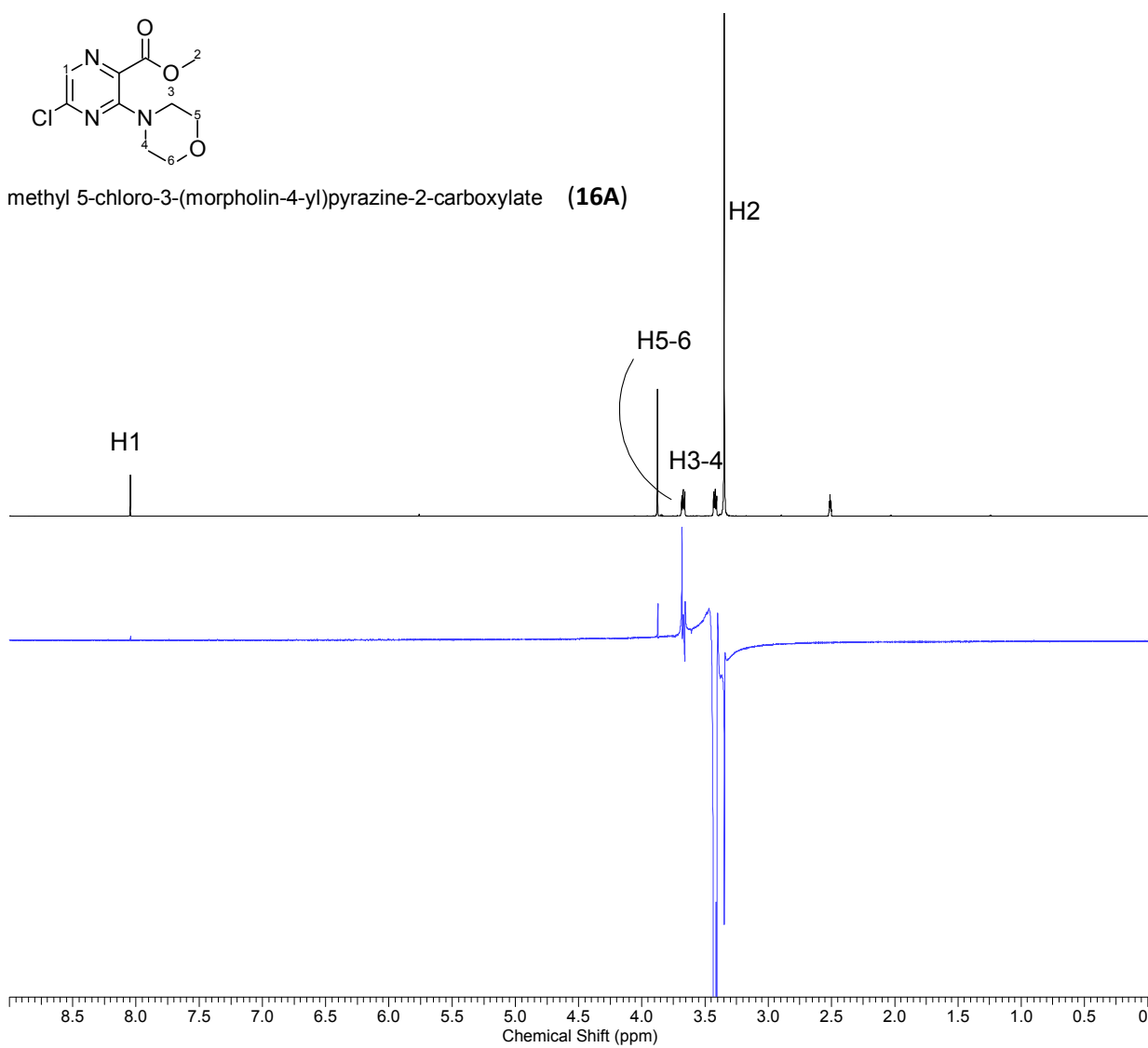


100 MHz, DMSO-*d*₆

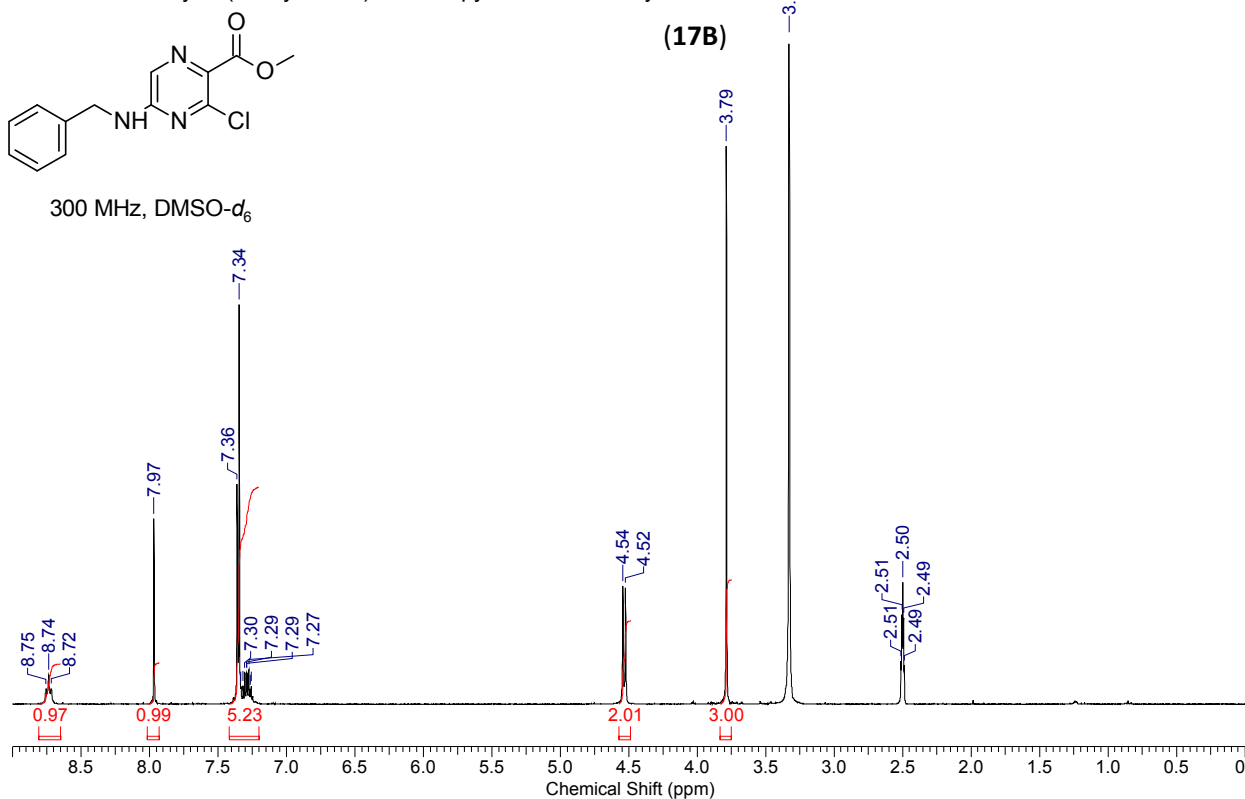




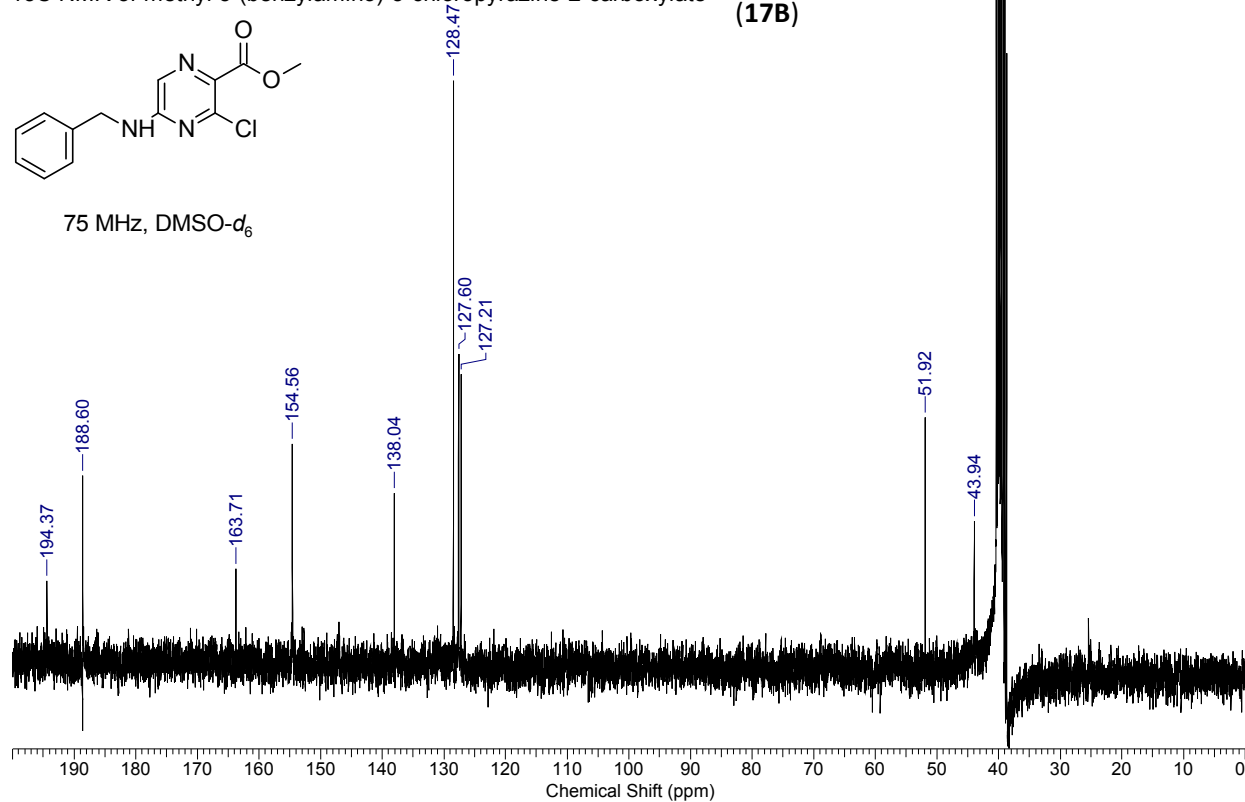
methyl 5-chloro-3-(morpholin-4-yl)pyrazine-2-carboxylate (**16A**)



¹H NMR of methyl 5-(benzylamino)-3-chloropyrazine-2-carboxylate

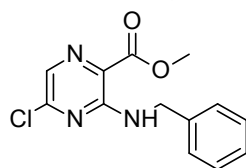


¹³C NMR of methyl 5-(benzylamino)-3-chloropyrazine-2-carboxylate

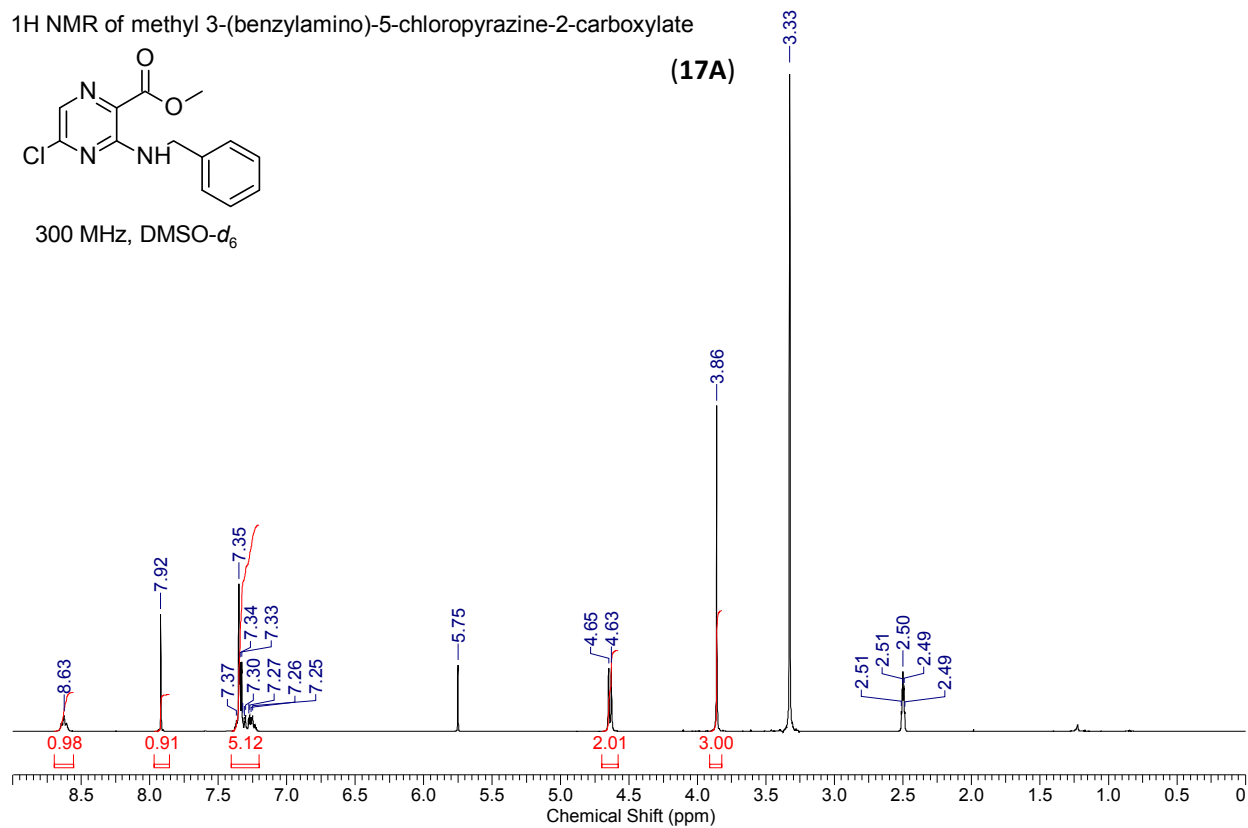




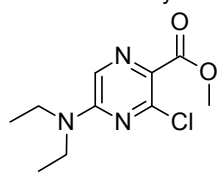
¹H NMR of methyl 3-(benzylamino)-5-chloropyrazine-2-carboxylate



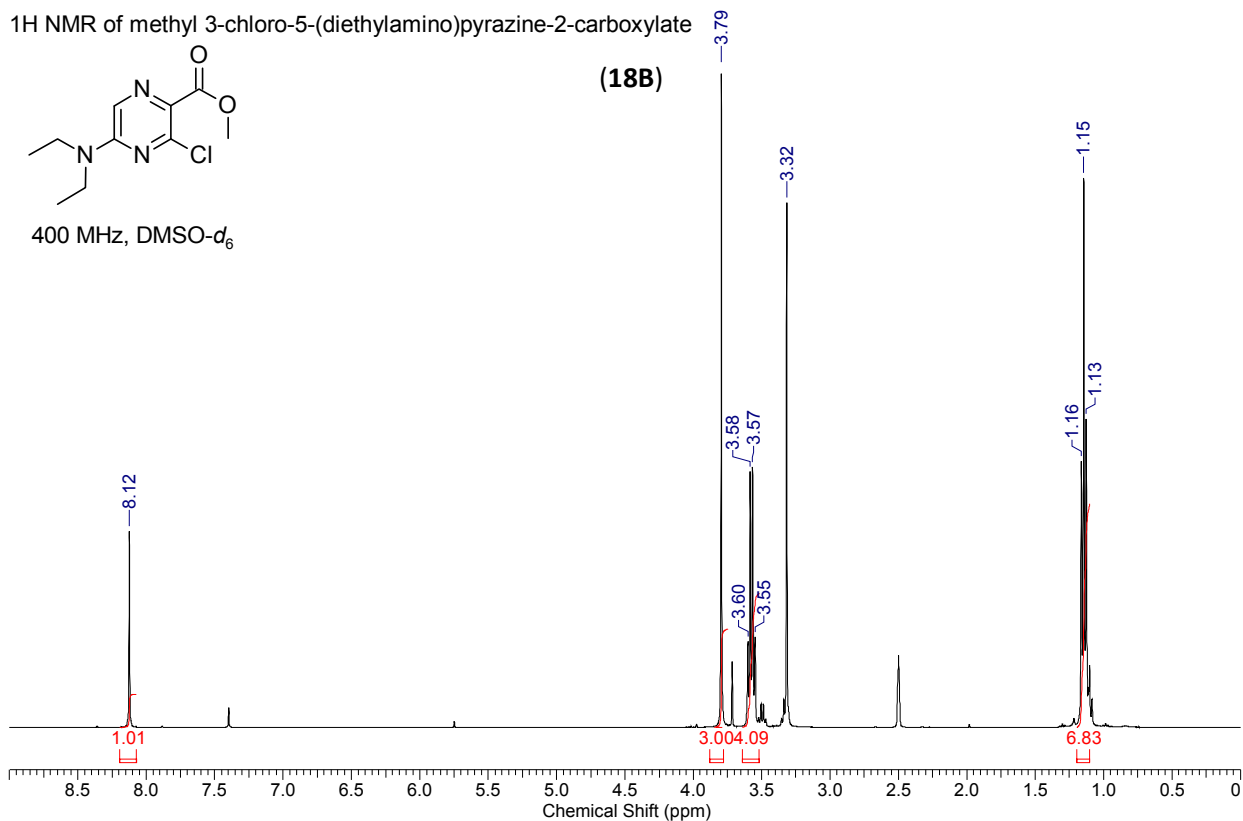
300 MHz, DMSO-*d*₆



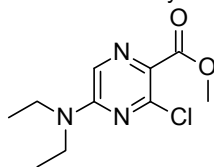
¹H NMR of methyl 3-chloro-5-(diethylamino)pyrazine-2-carboxylate



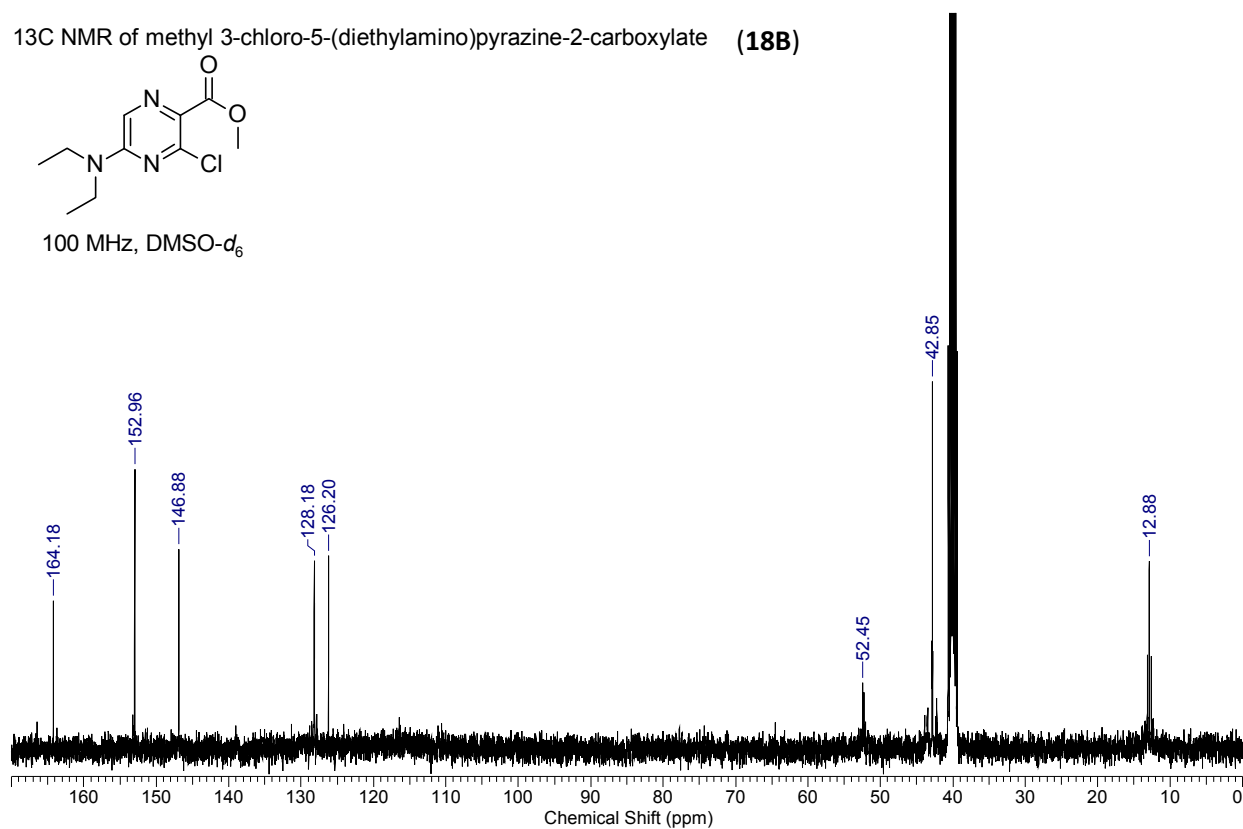
400 MHz, DMSO-*d*₆

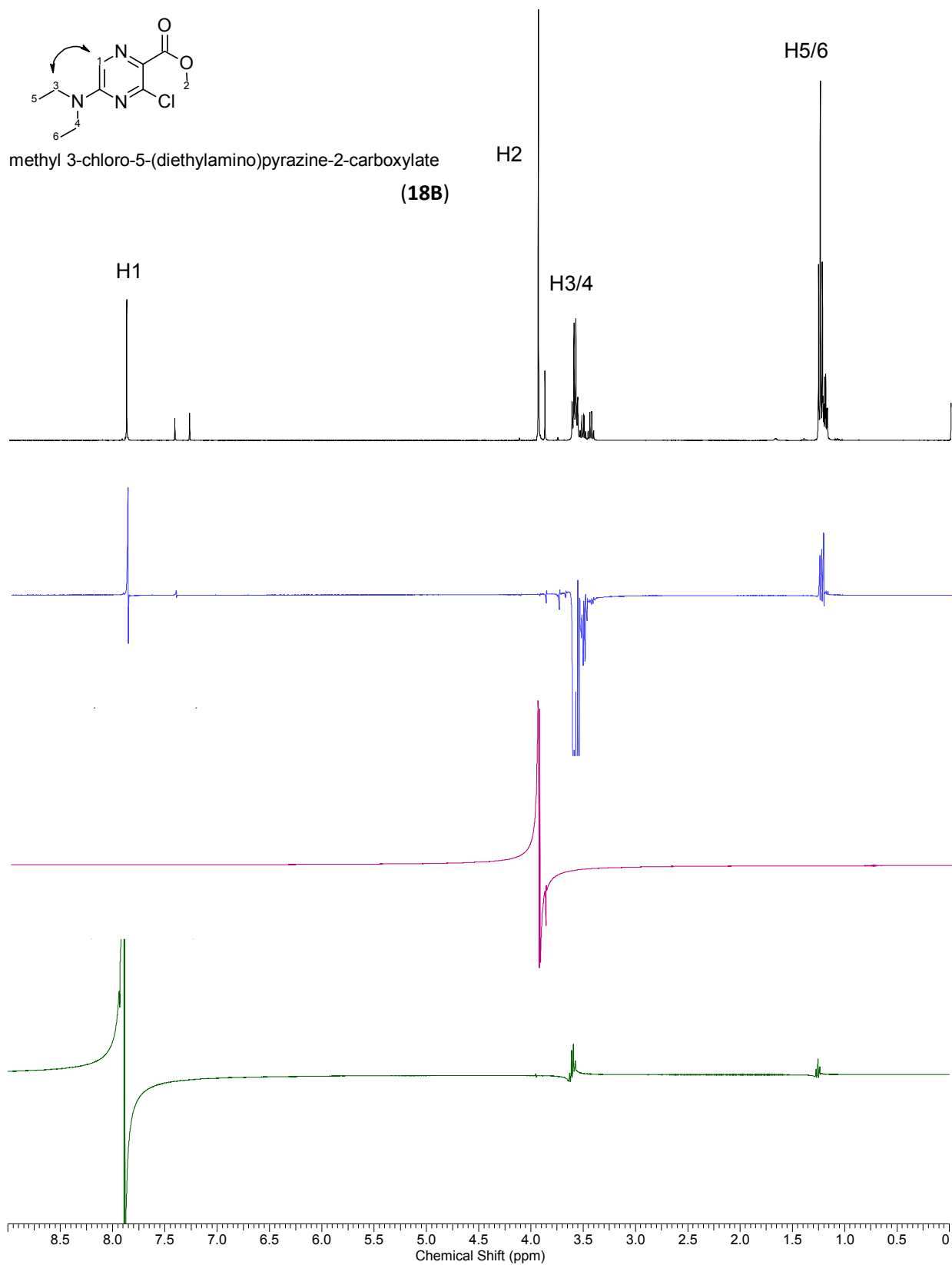


¹³C NMR of methyl 3-chloro-5-(diethylamino)pyrazine-2-carboxylate (18B)

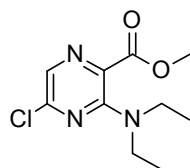


100 MHz, DMSO-*d*₆

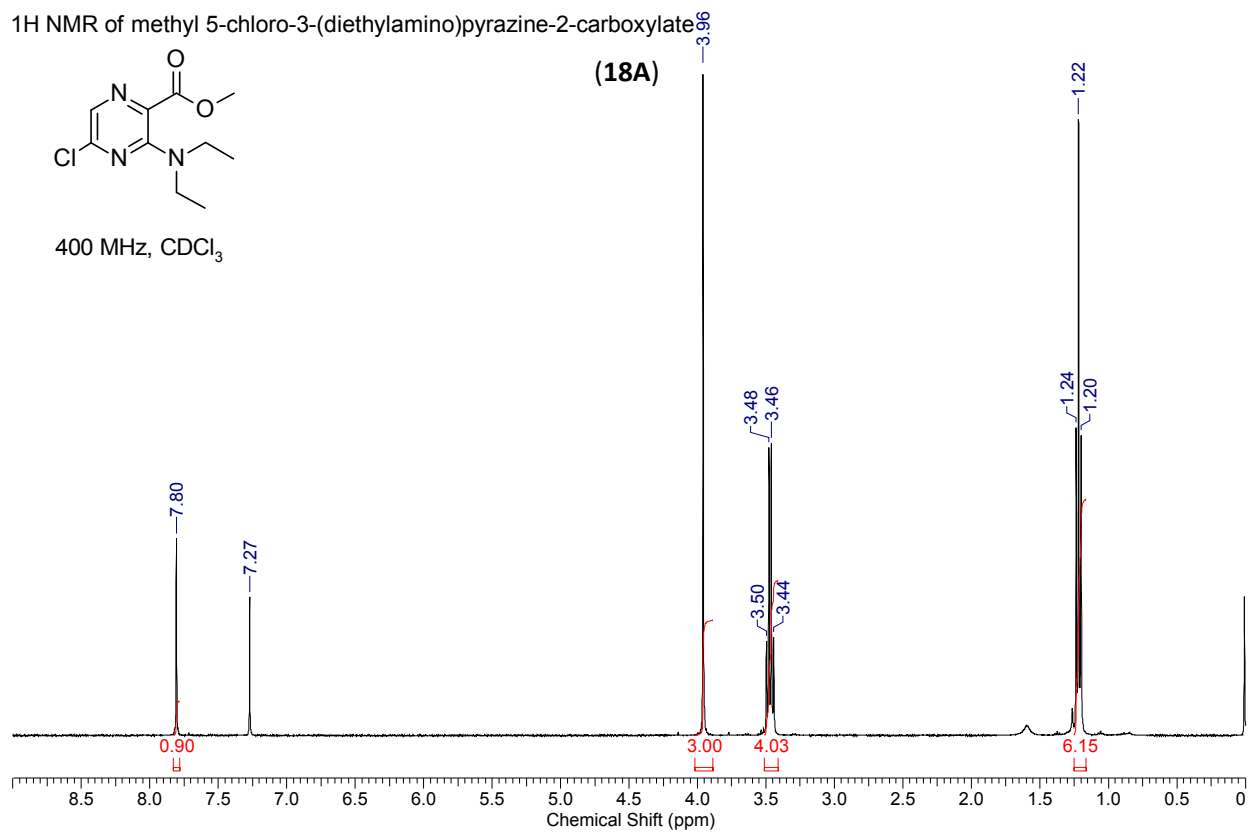


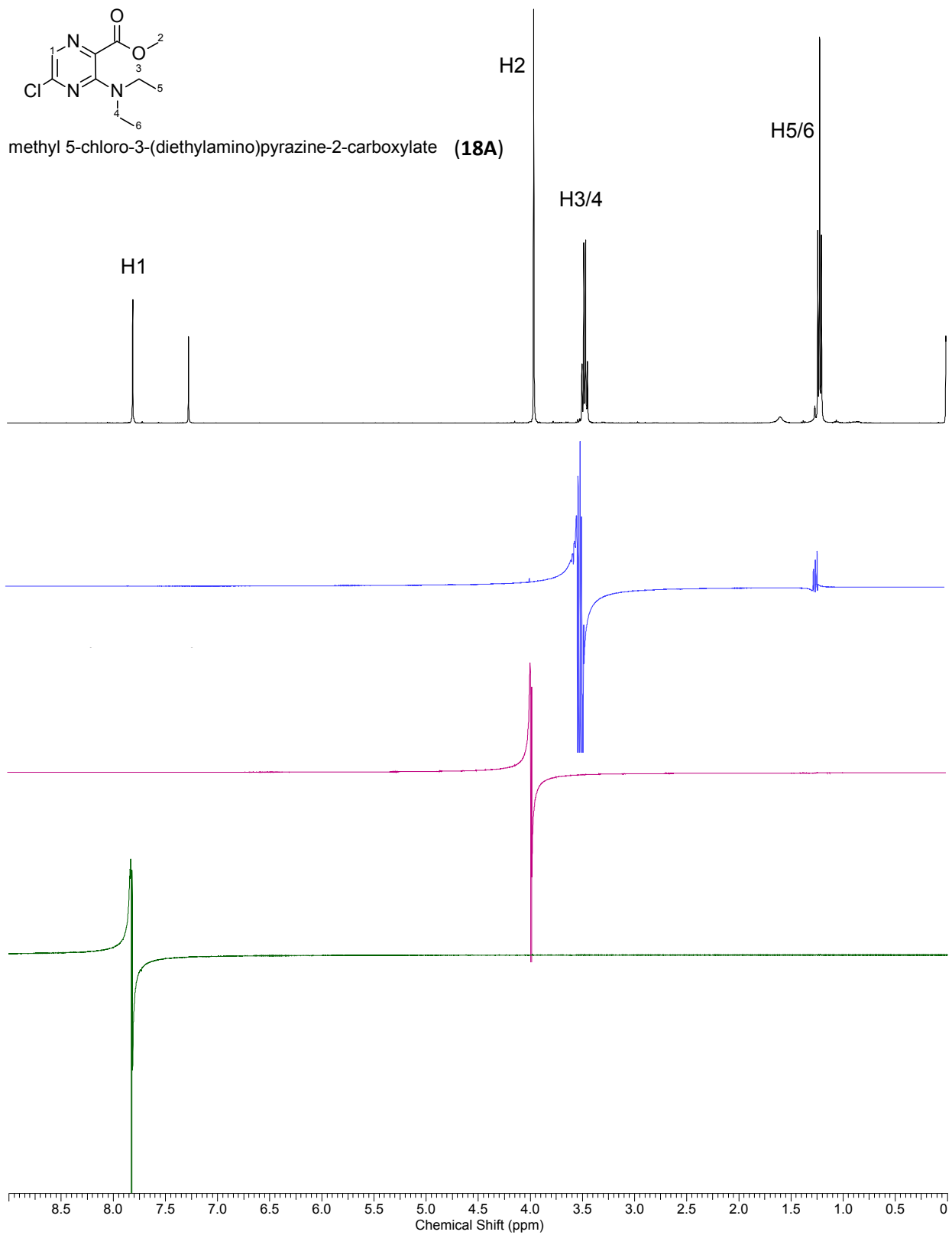


¹H NMR of methyl 5-chloro-3-(diethylamino)pyrazine-2-carboxylate

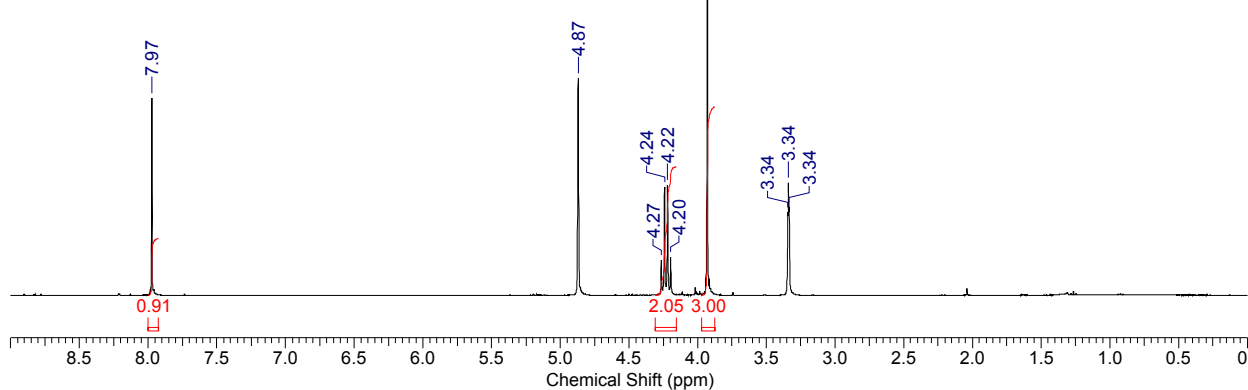
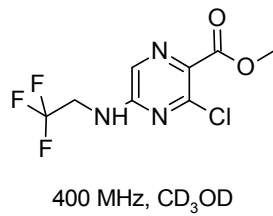


400 MHz, CDCl₃

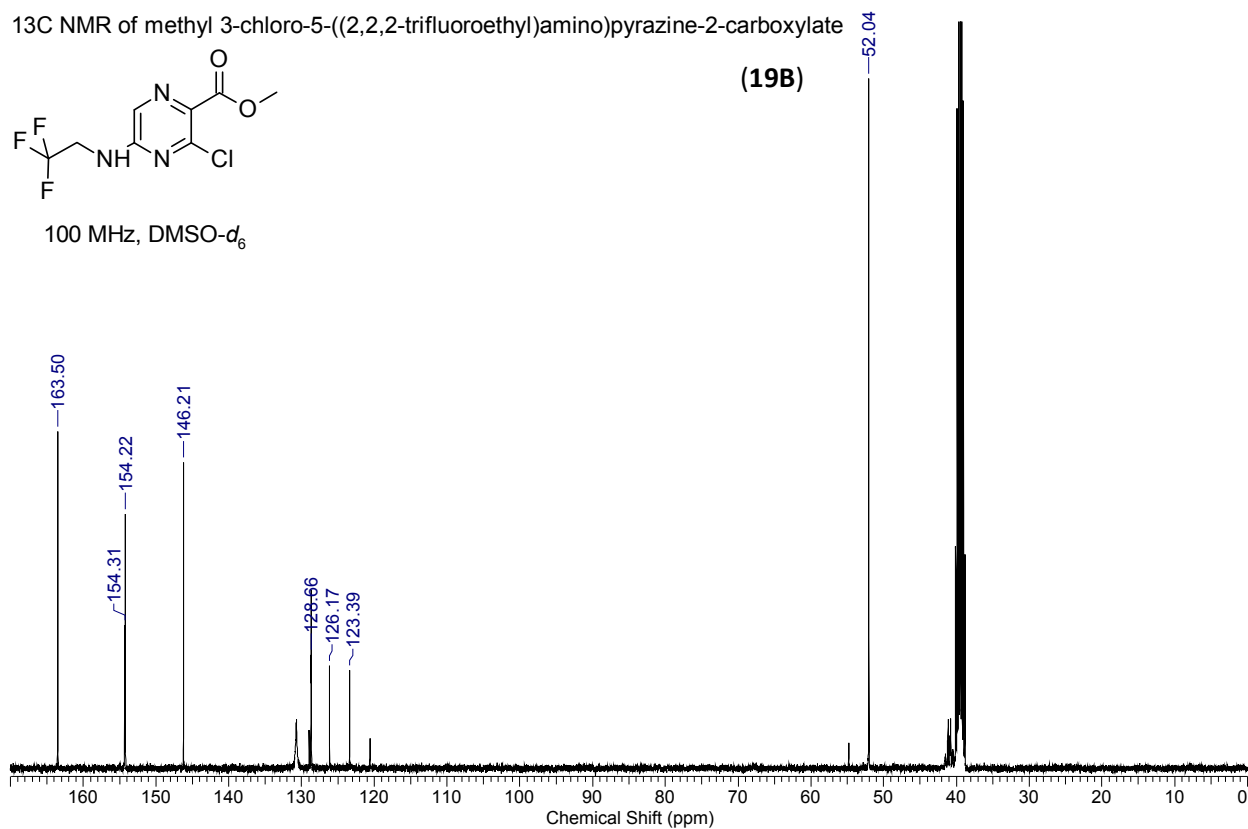
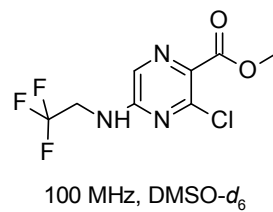


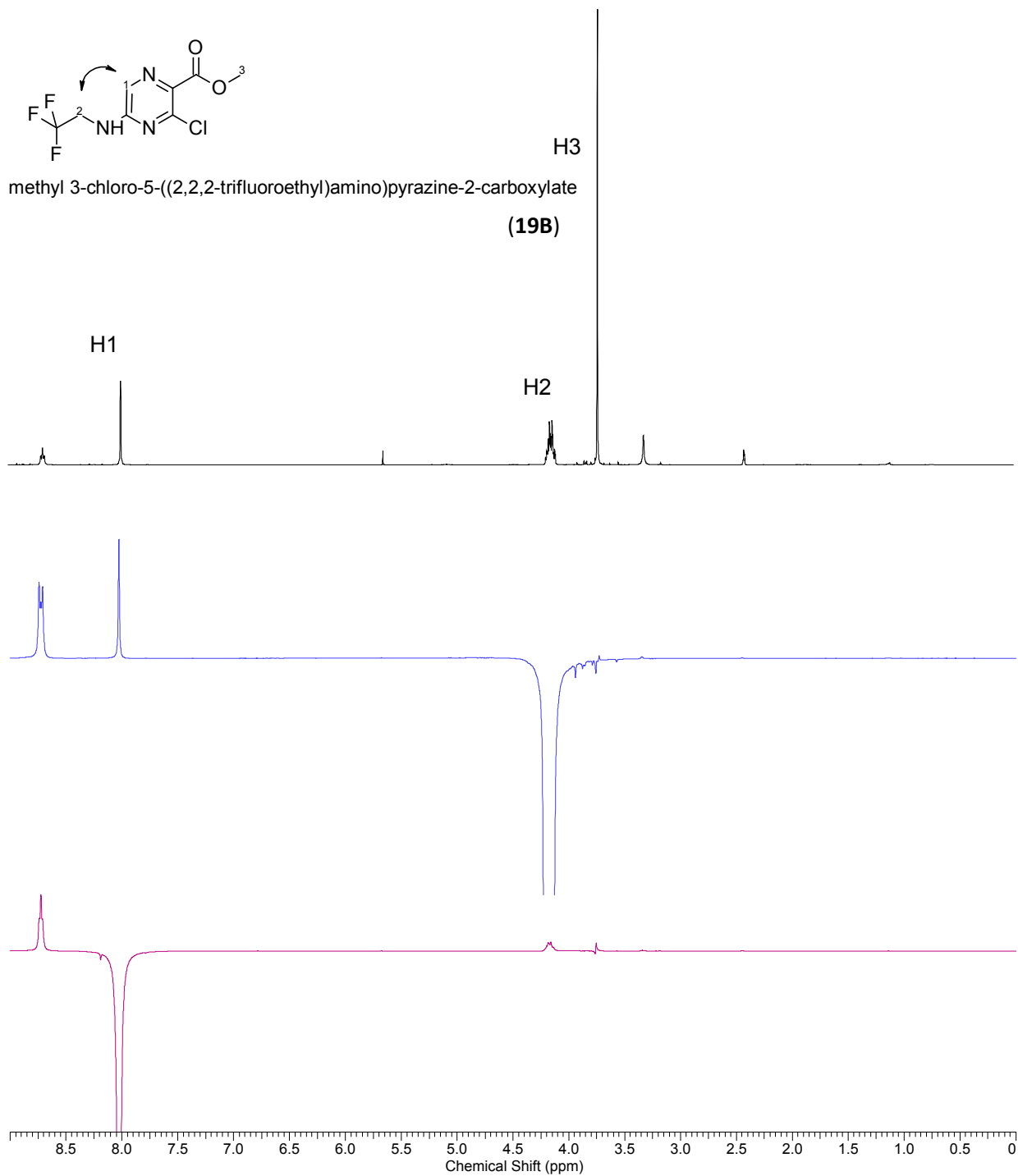


¹H NMR of methyl 3-chloro-5-((2,2,2-trifluoroethyl)amino)pyrazine-2-carboxylate (19B)

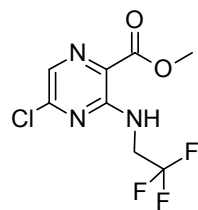


¹³C NMR of methyl 3-chloro-5-((2,2,2-trifluoroethyl)amino)pyrazine-2-carboxylate (19B)

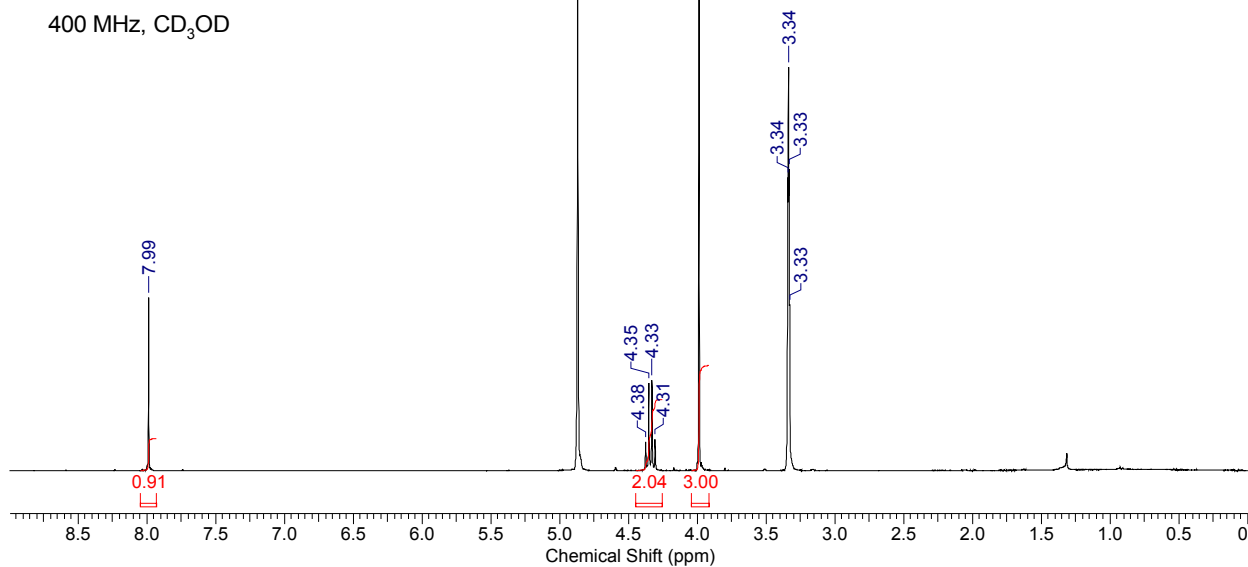




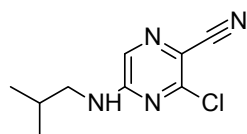
¹H NMR of methyl 5-chloro-3-[(2,2,2-trifluoroethyl)amino]pyrazine-2-carboxylate (**19A**)



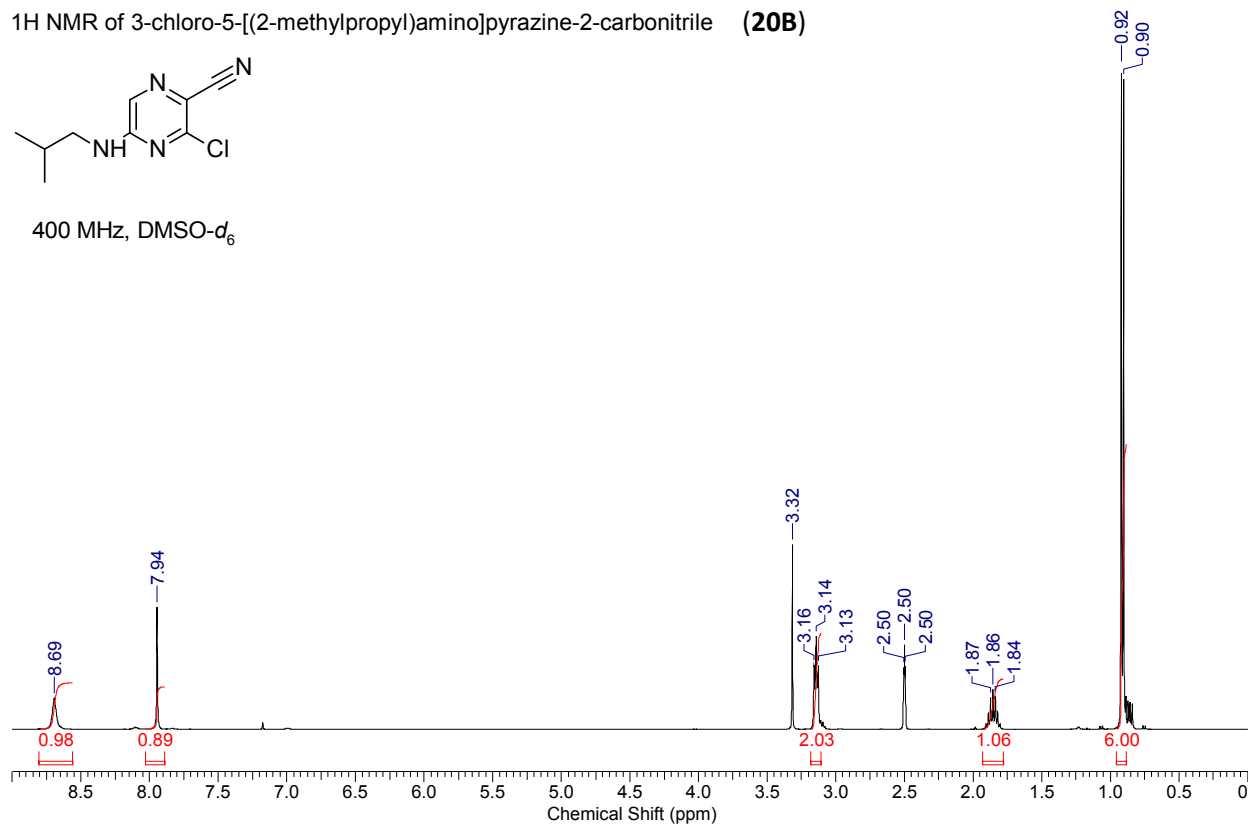
400 MHz, CD₃OD



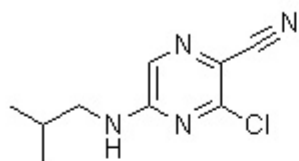
¹H NMR of 3-chloro-5-[(2-methylpropyl)amino]pyrazine-2-carbonitrile (**20B**)



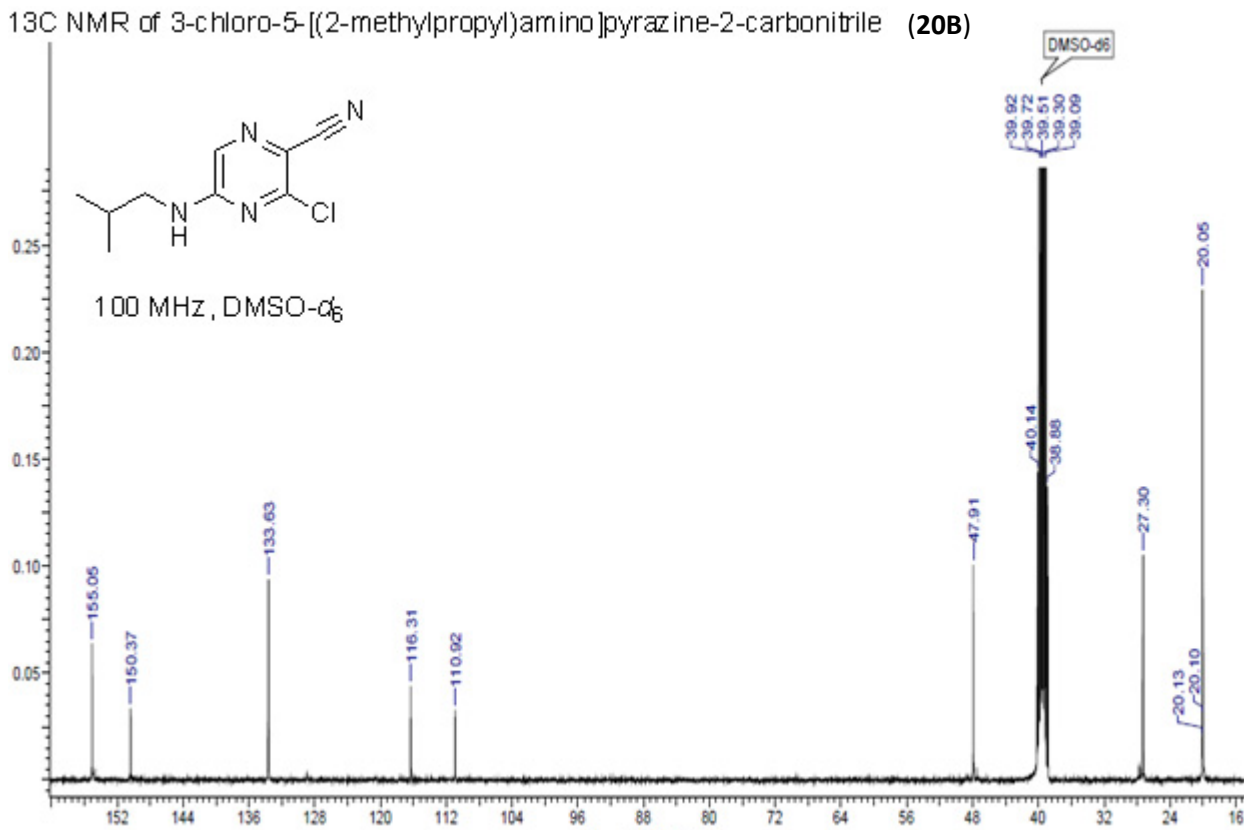
400 MHz, DMSO-*d*₆

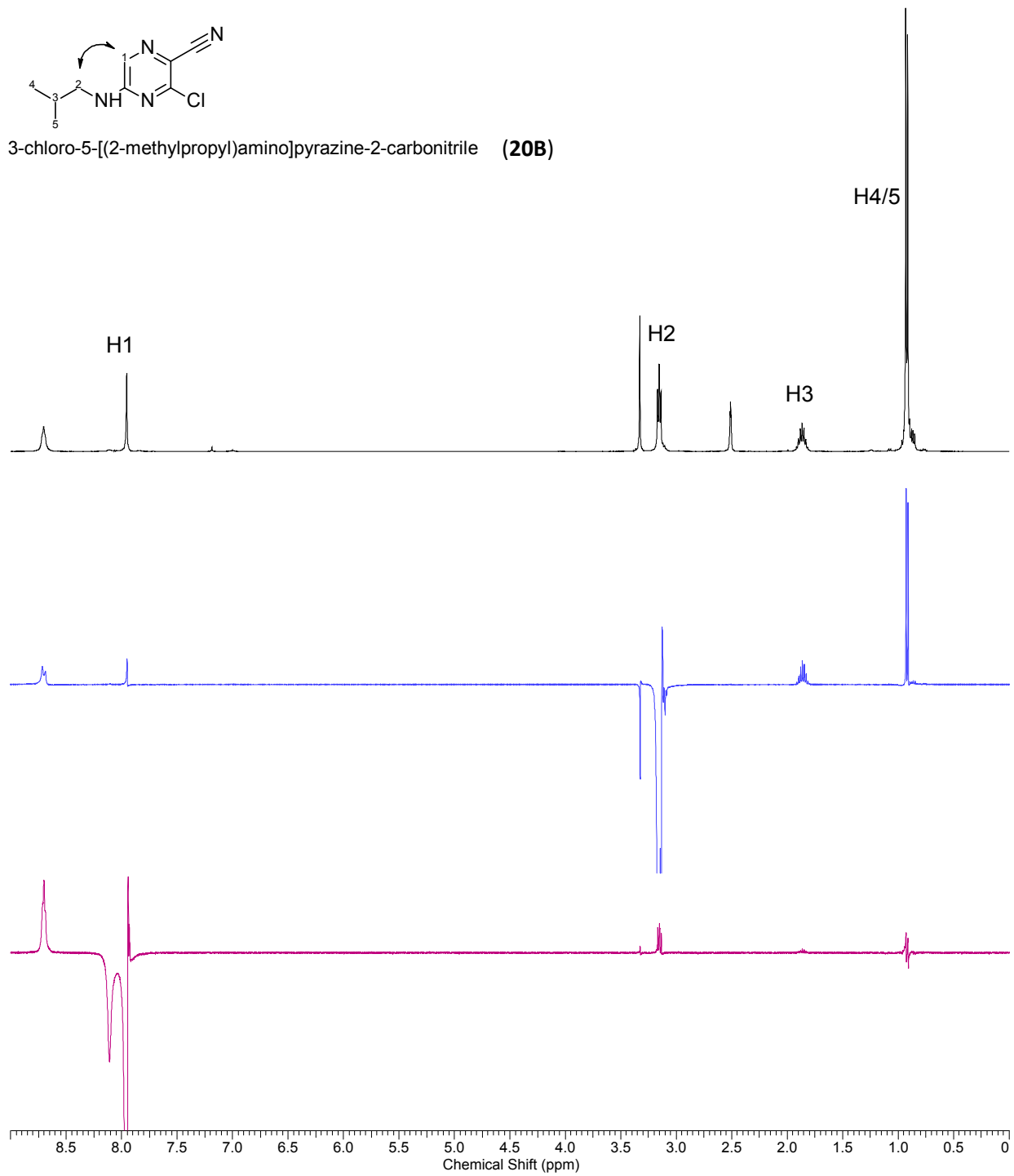


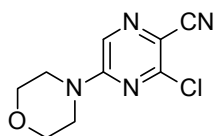
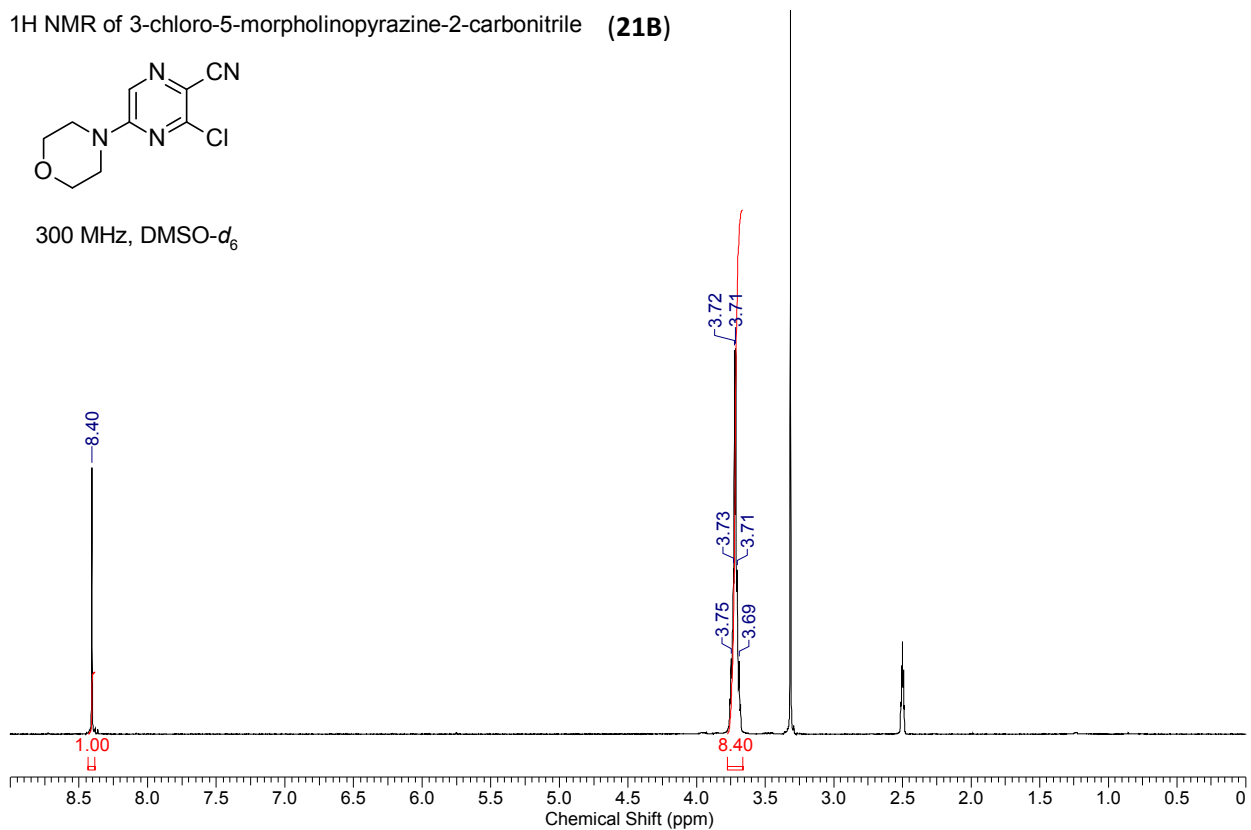
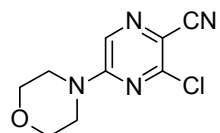
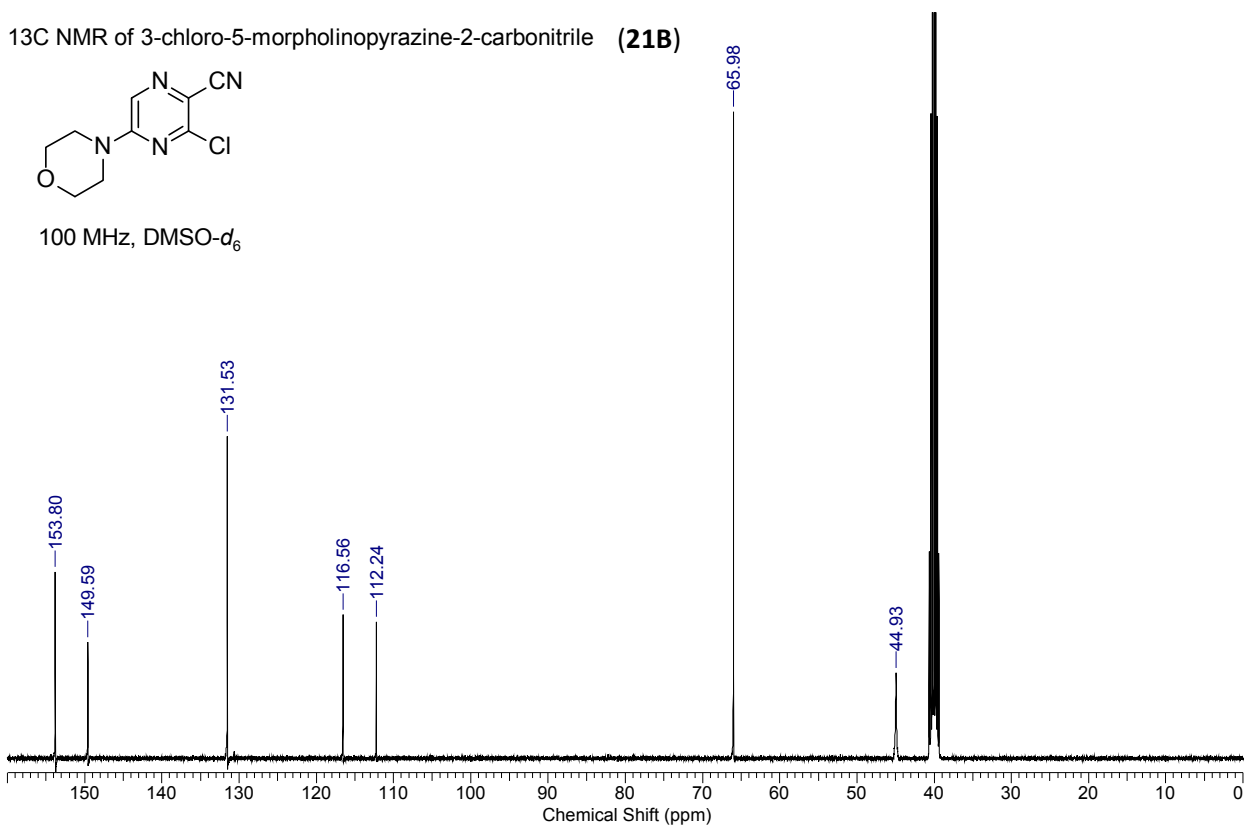
¹³C NMR of 3-chloro-5-[(2-methylpropyl)amino]pyrazine-2-carbonitrile (**20B**)

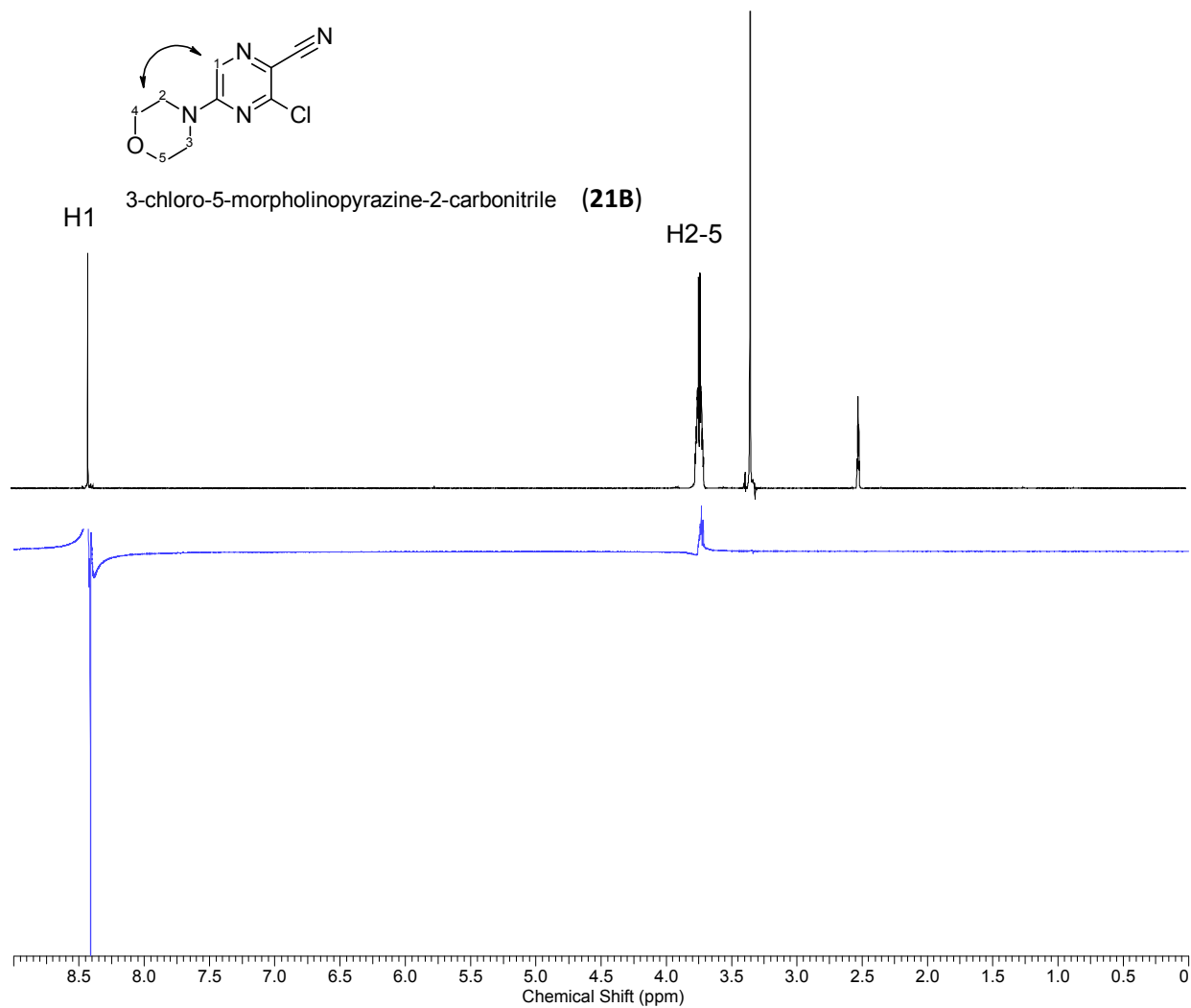


100 MHz, DMSO-*d*₆



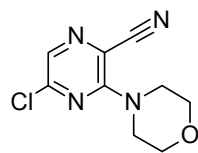


¹H NMR of 3-chloro-5-morpholinopyrazine-2-carbonitrile (**21B**)300 MHz, DMSO-*d*₆¹³C NMR of 3-chloro-5-morpholinopyrazine-2-carbonitrile (**21B**)100 MHz, DMSO-*d*₆

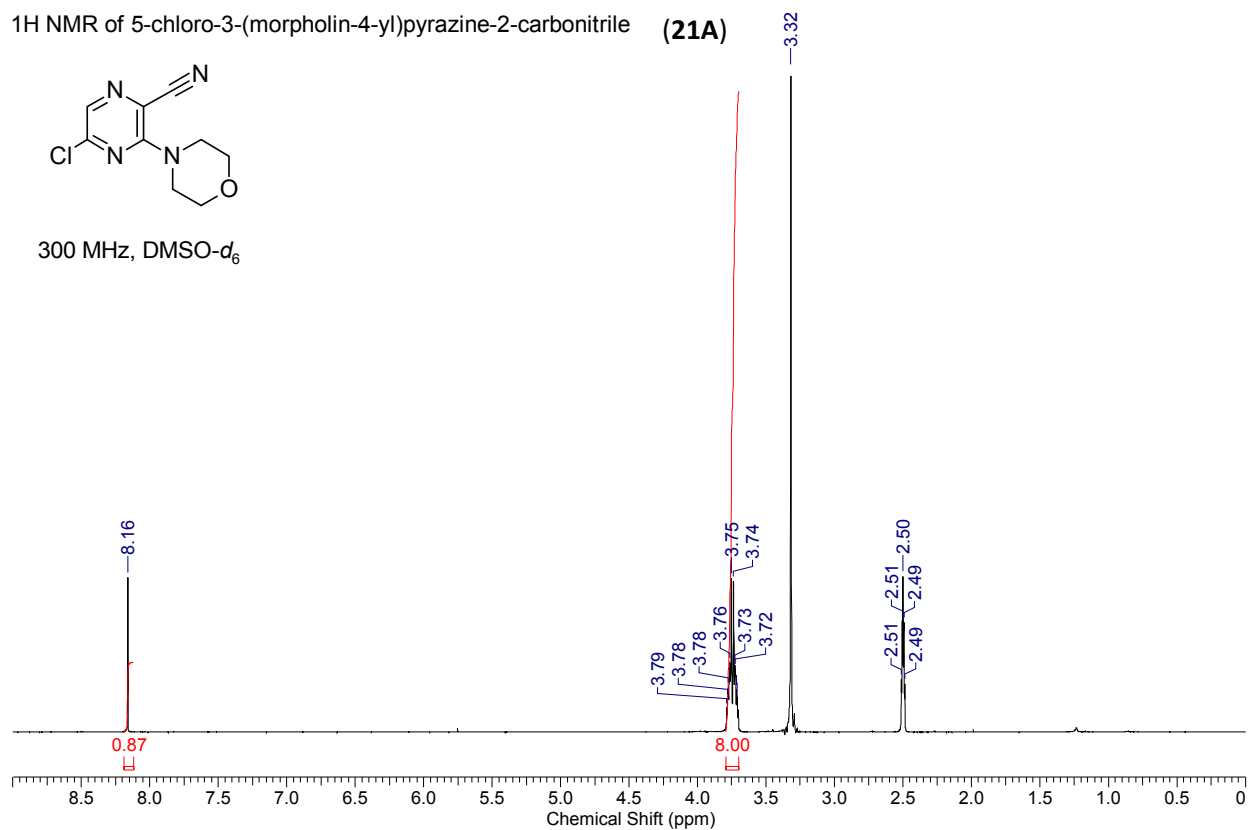


¹H NMR of 5-chloro-3-(morpholin-4-yl)pyrazine-2-carbonitrile

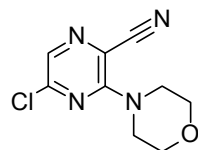
(21A)



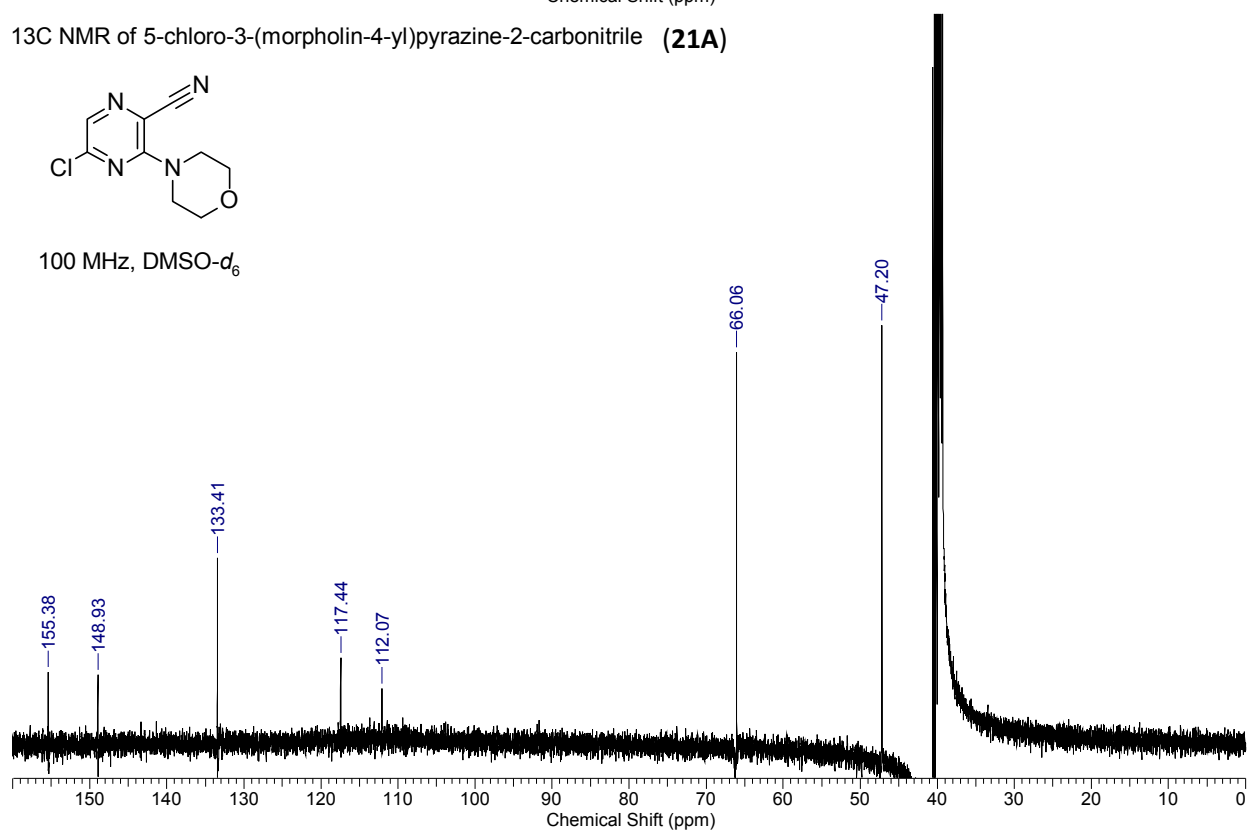
300 MHz, DMSO-*d*₆

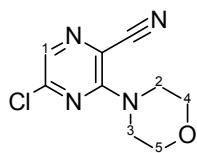


¹³C NMR of 5-chloro-3-(morpholin-4-yl)pyrazine-2-carbonitrile (21A)

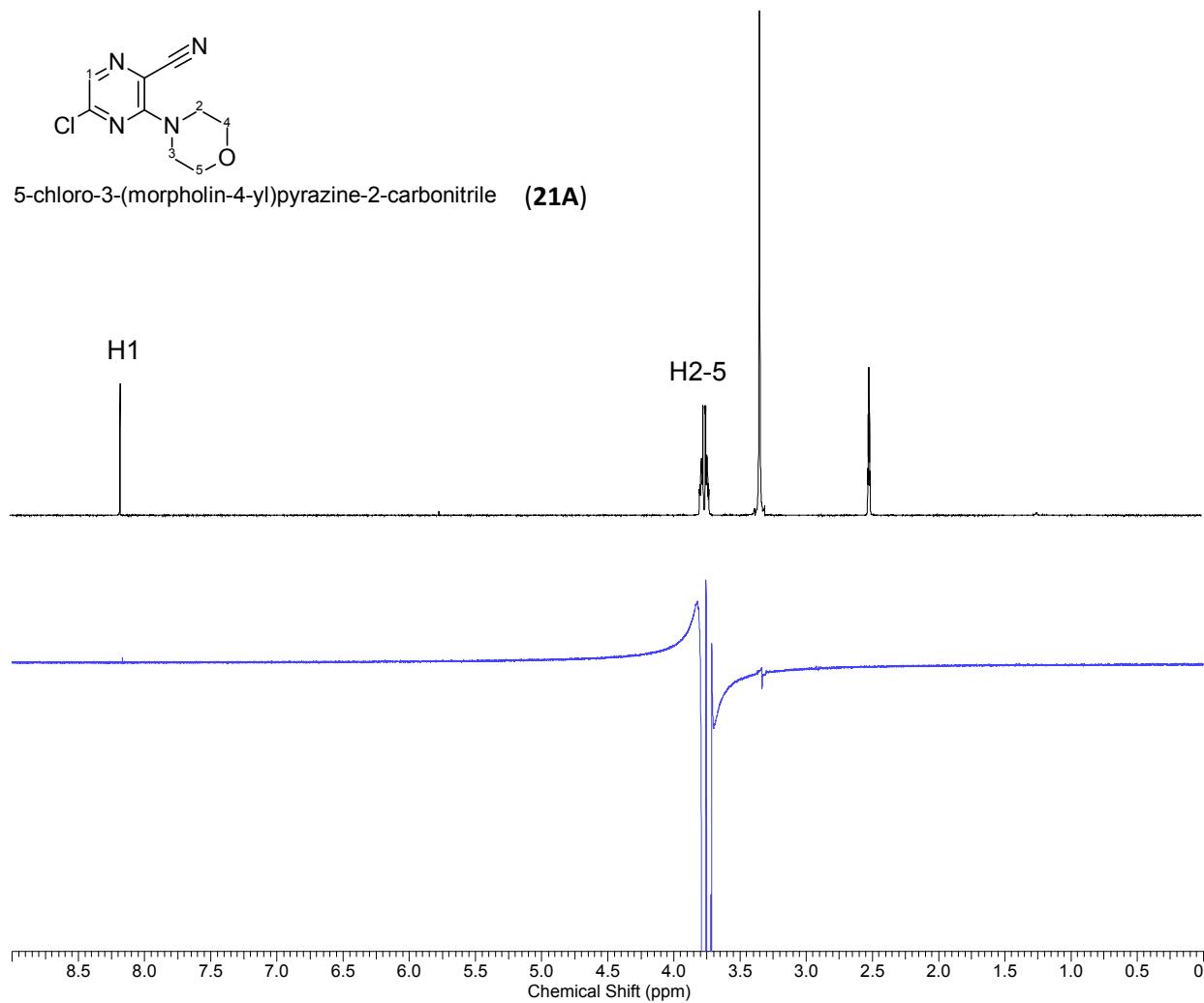


100 MHz, DMSO-*d*₆

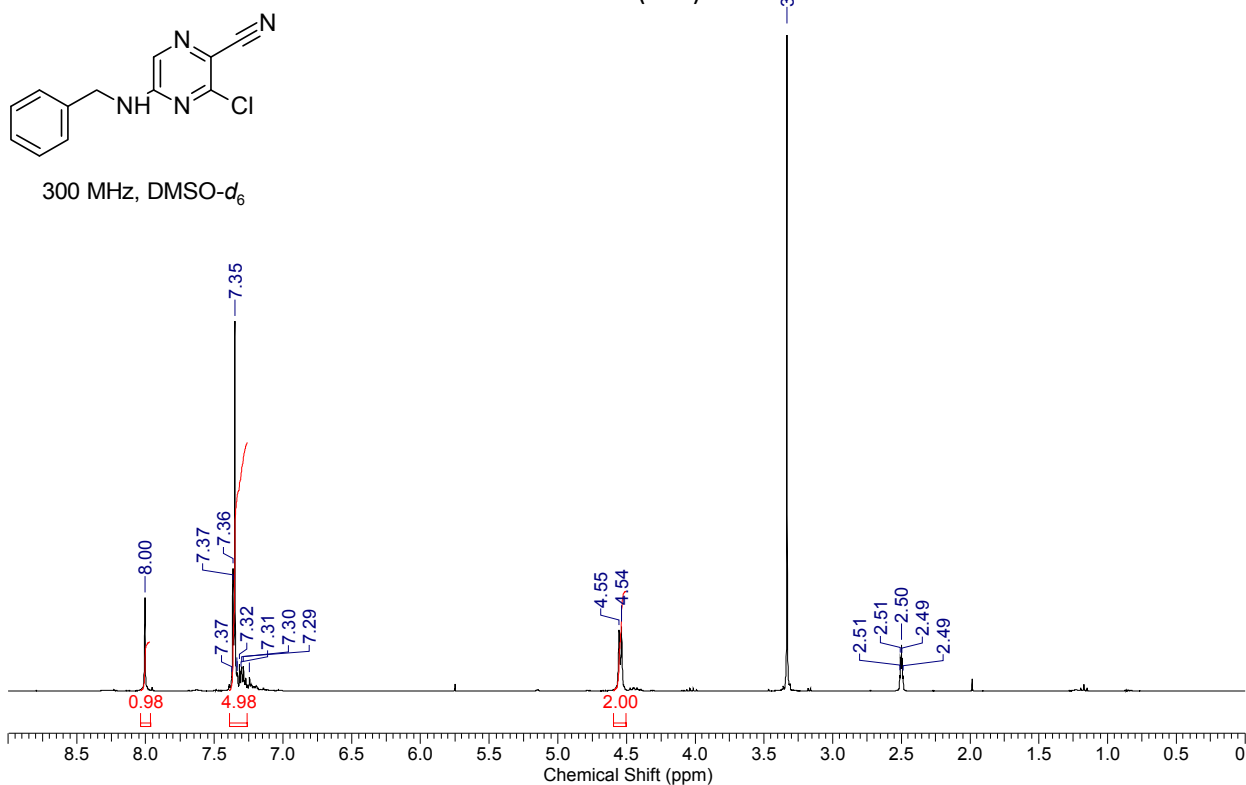




5-chloro-3-(morpholin-4-yl)pyrazine-2-carbonitrile (**21A**)

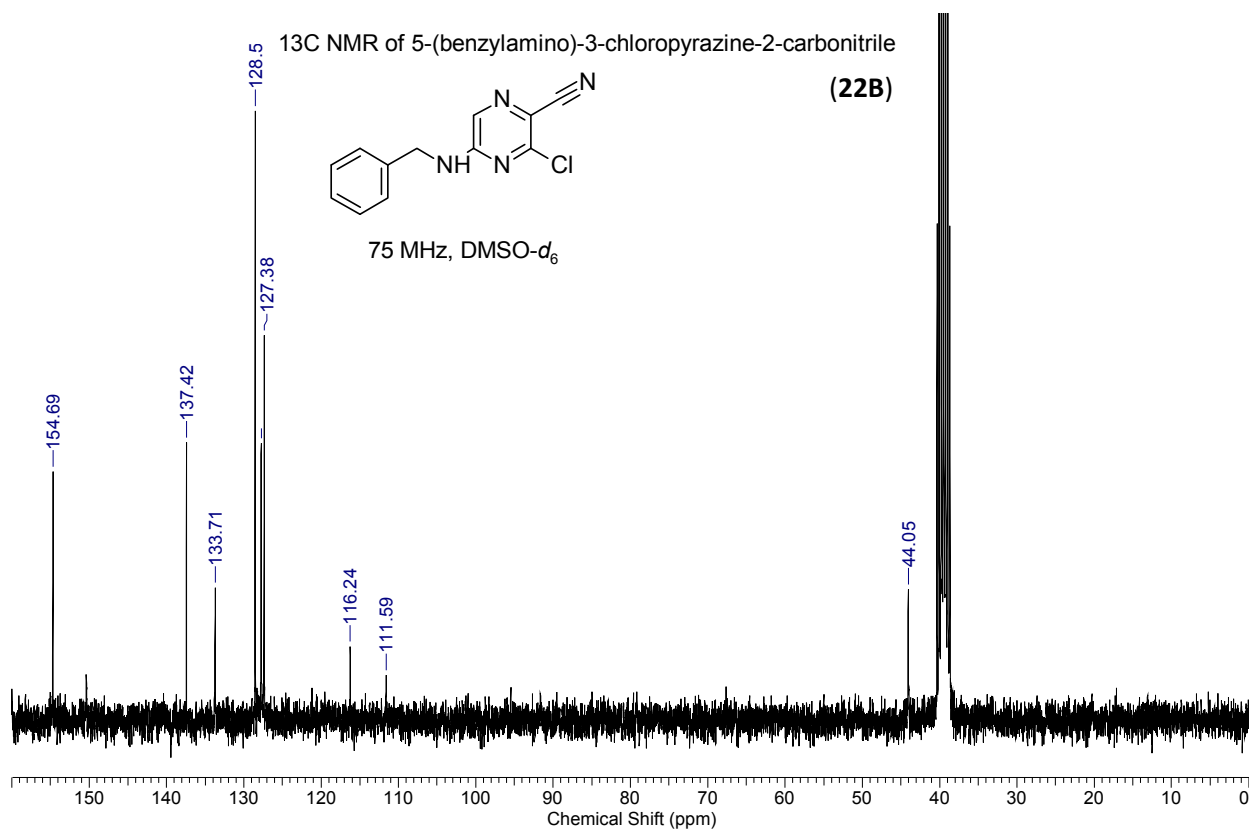


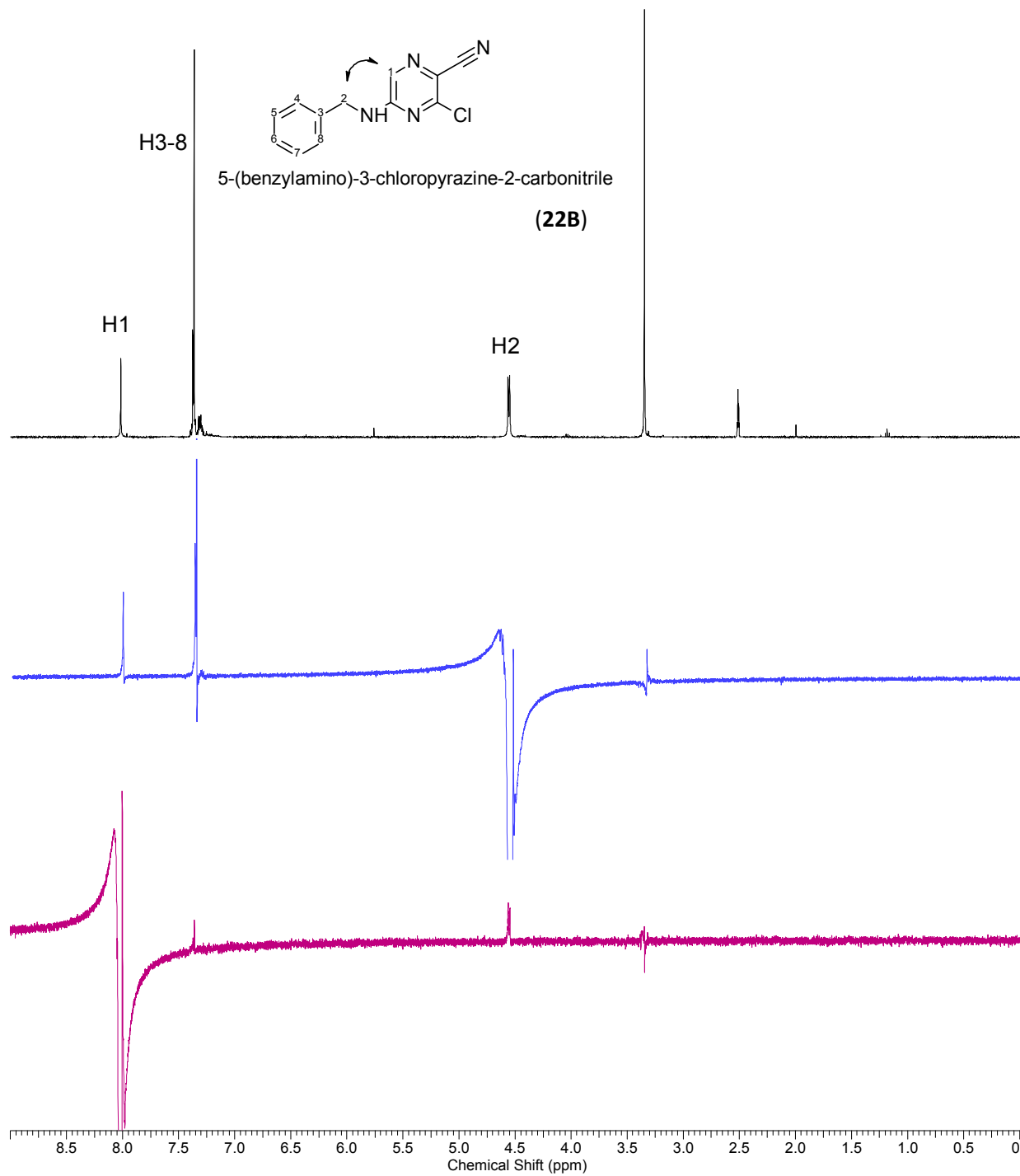
¹H NMR of 5-(benzylamino)-3-chloropyrazine-2-carbonitrile (**22B**)



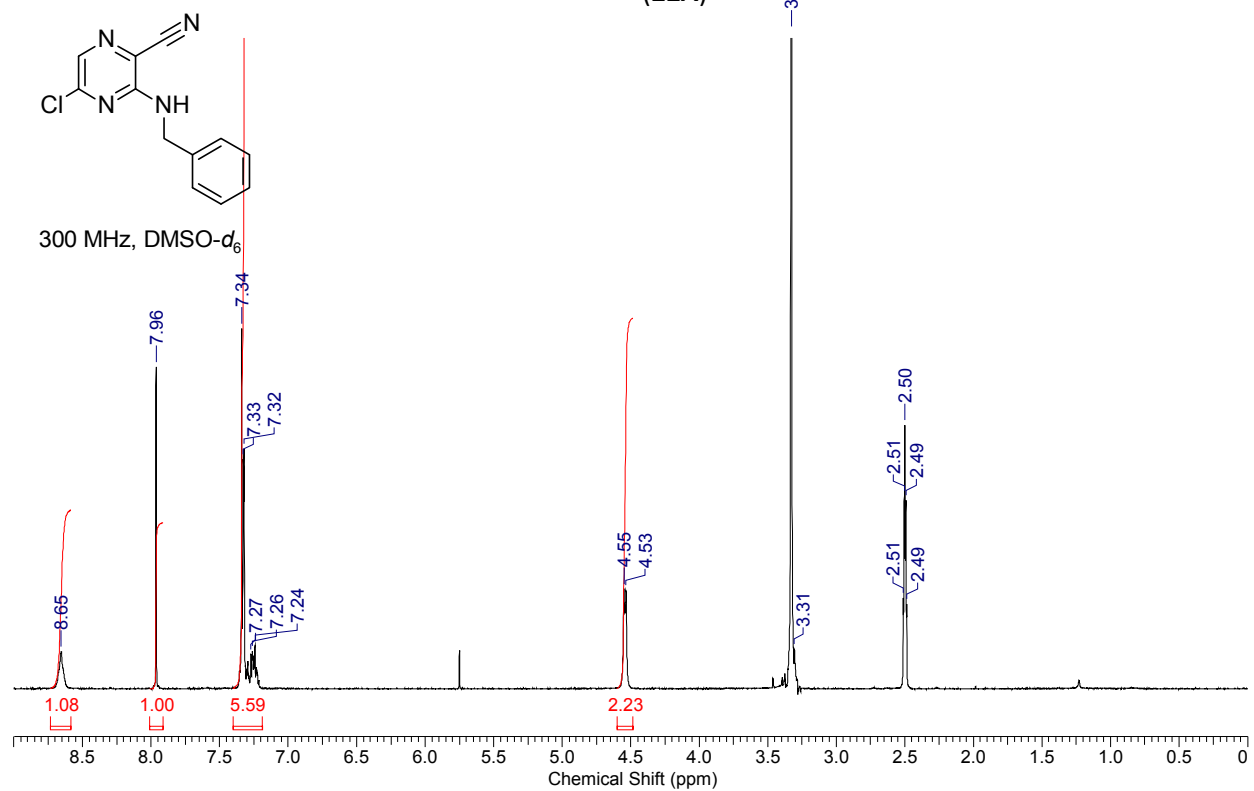
¹³C NMR of 5-(benzylamino)-3-chloropyrazine-2-carbonitrile

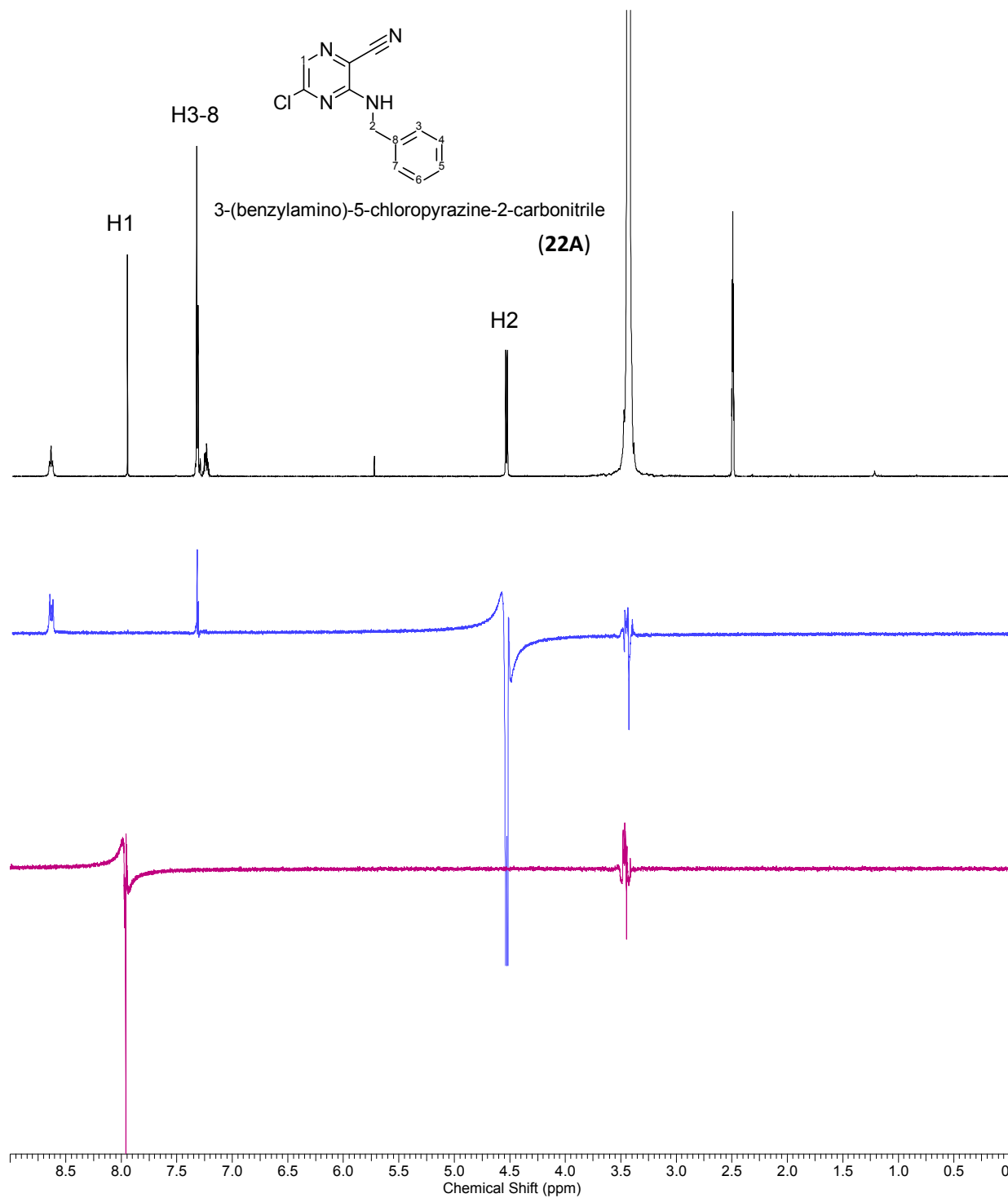
(**22B**)

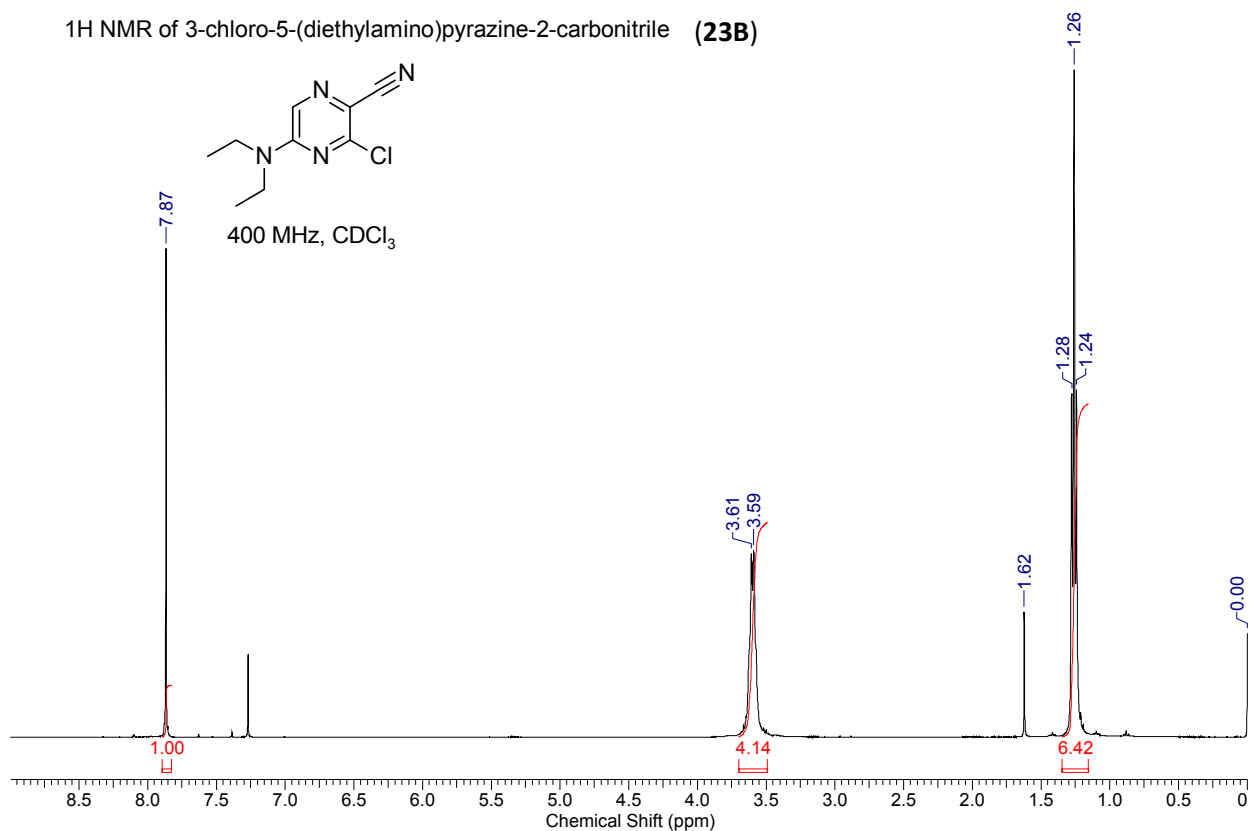
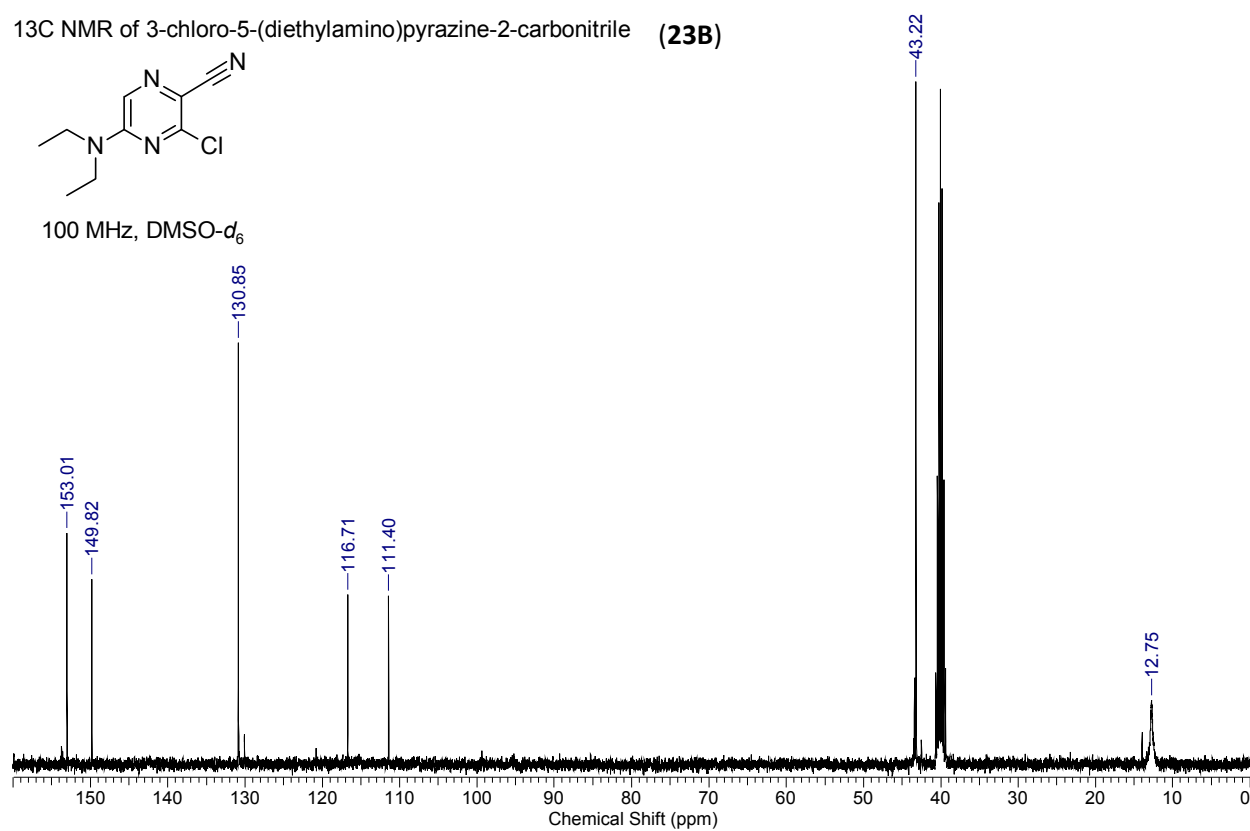


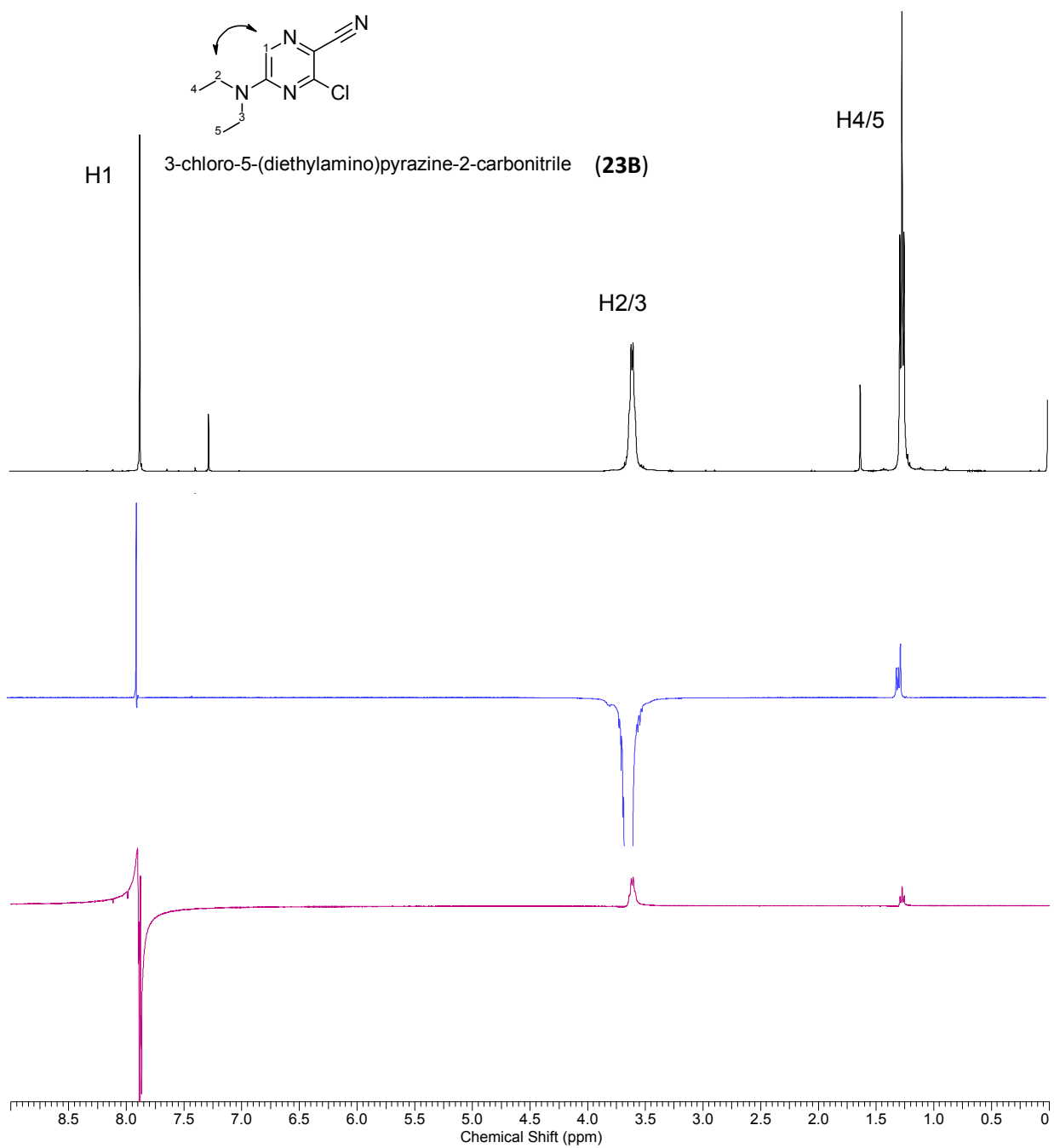


¹H NMR of 3-(benzylamino)-5-chloropyrazine-2-carbonitrile (**22A**)

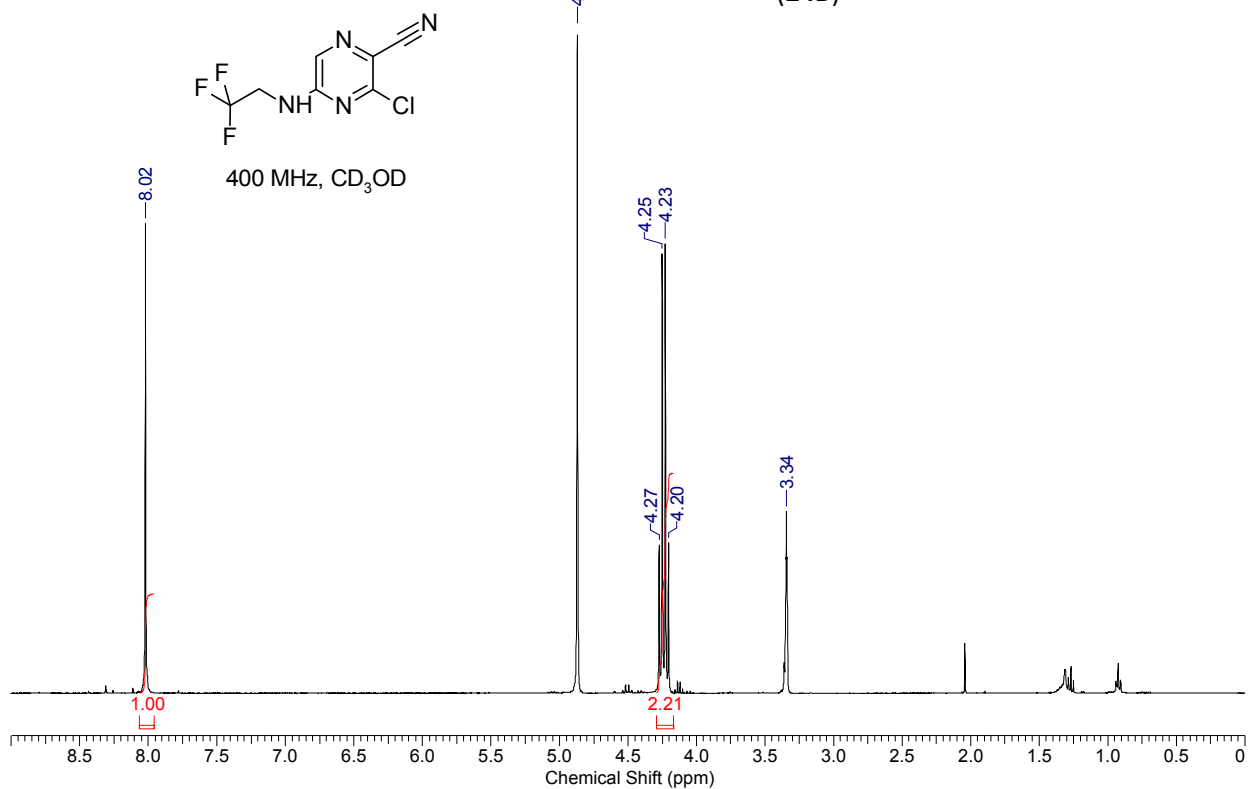




¹H NMR of 3-chloro-5-(diethylamino)pyrazine-2-carbonitrile (**23B**)¹³C NMR of 3-chloro-5-(diethylamino)pyrazine-2-carbonitrile (**23B**)

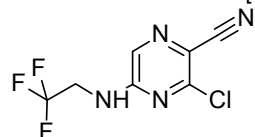


¹H NMR of 3-chloro-5-[(2,2,2-trifluoroethyl)amino]pyrazine-2-carbonitrile (**24B**)

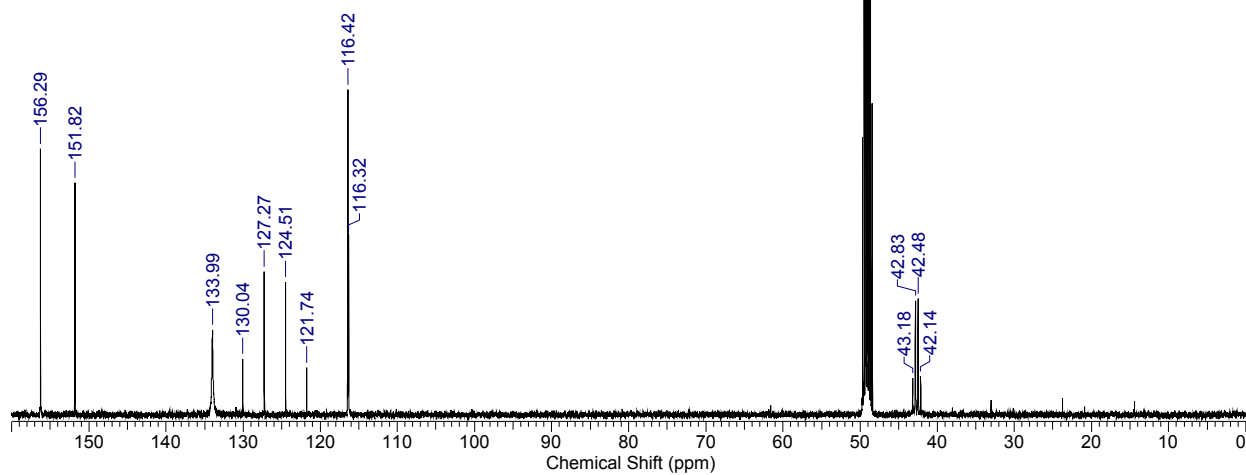


¹³C NMR of 3-chloro-5-[(2,2,2-trifluoroethyl)amino]pyrazine-2-carbonitrile

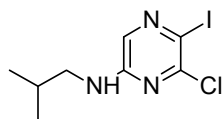
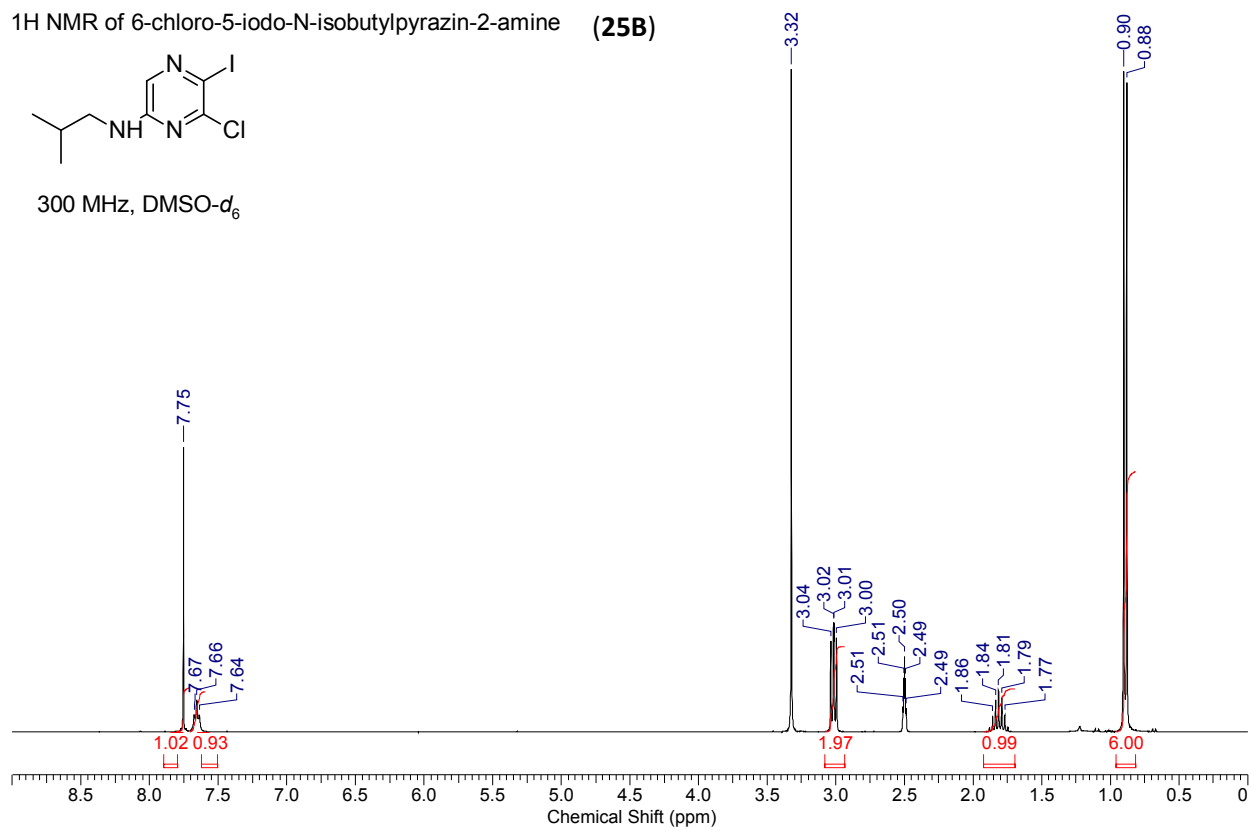
(**24B**)

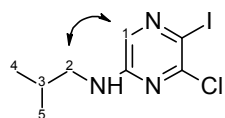


100 MHz, CD₃OD

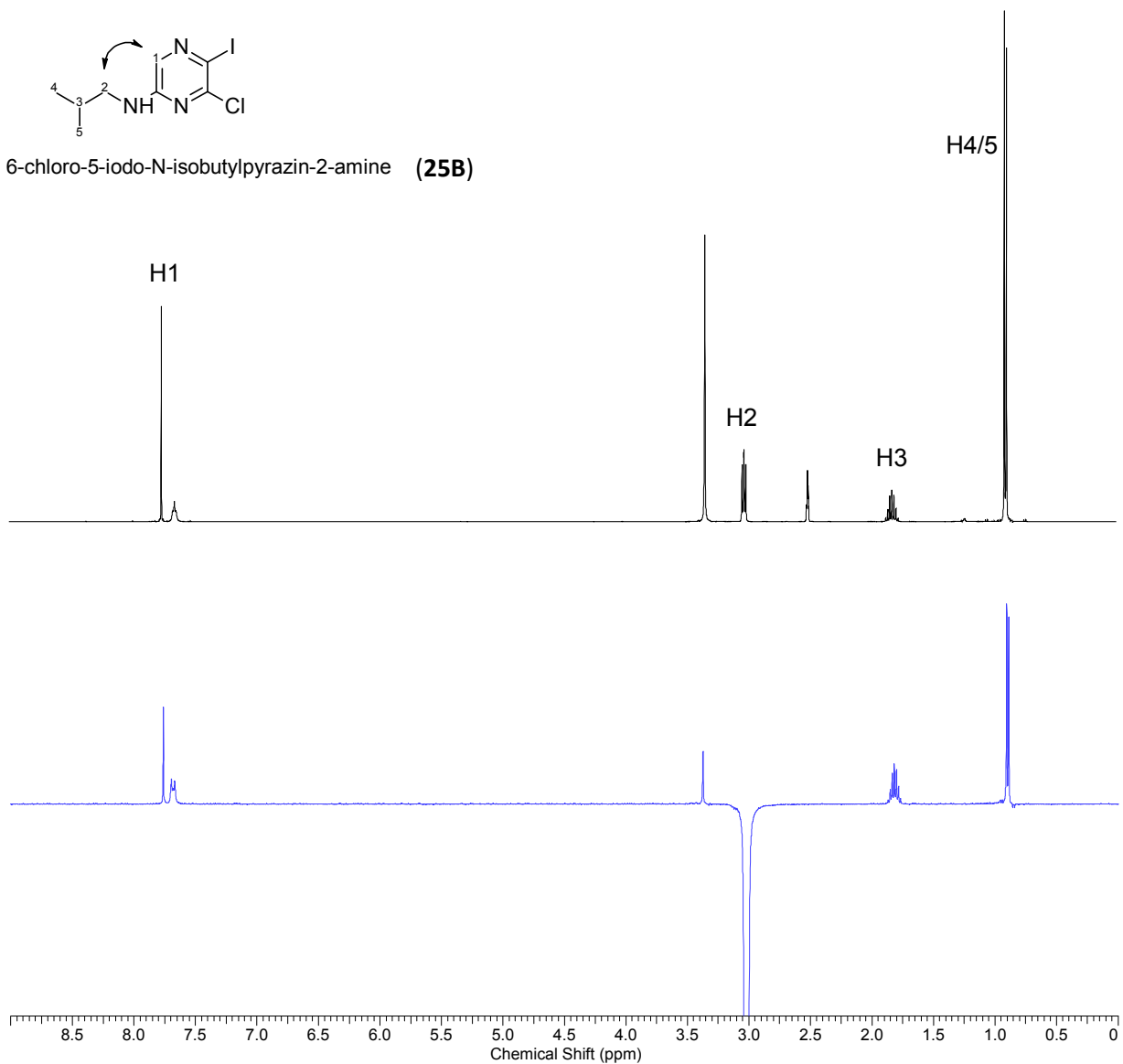


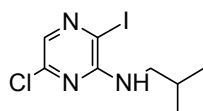
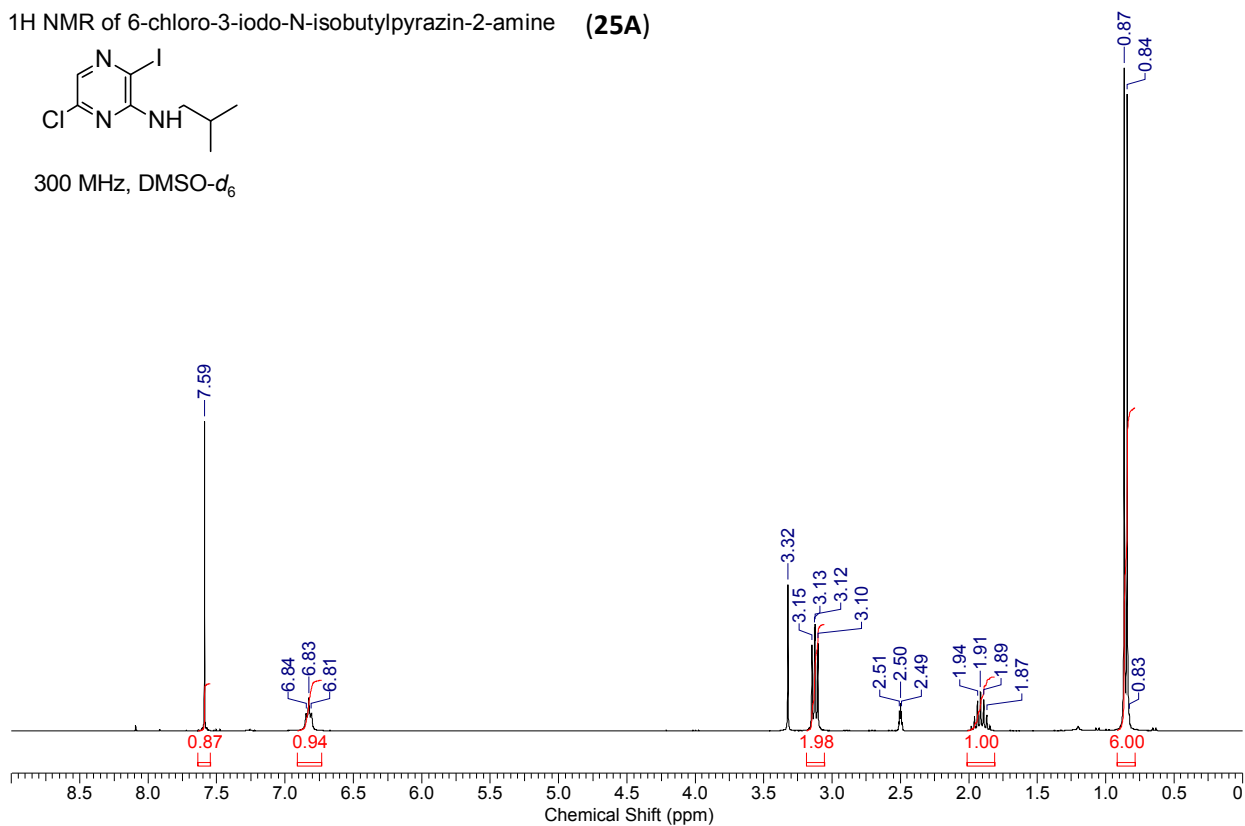
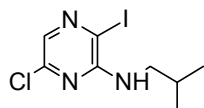
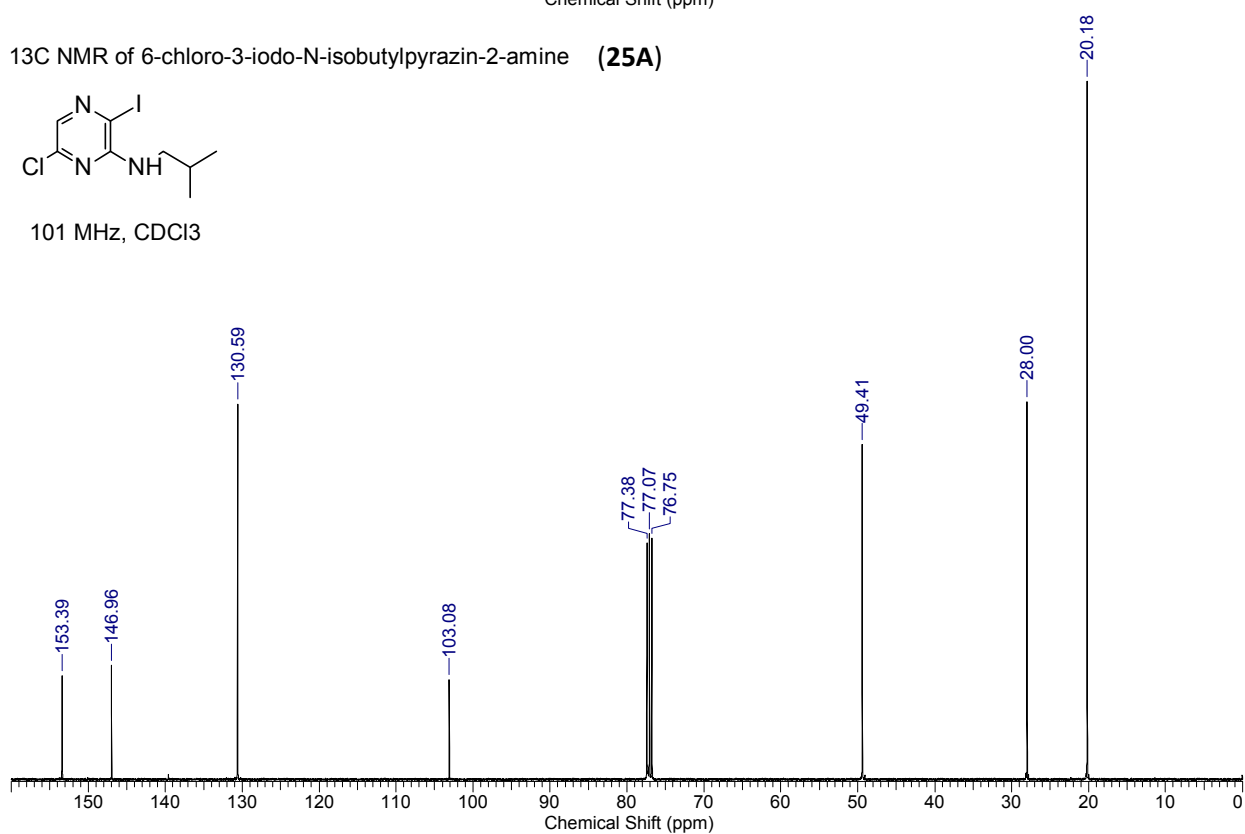
1H NMR of 6-chloro-5-iodo-N-isobutylpyrazin-2-amine (25B)

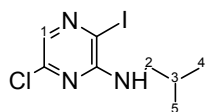
300 MHz, DMSO- d_6 



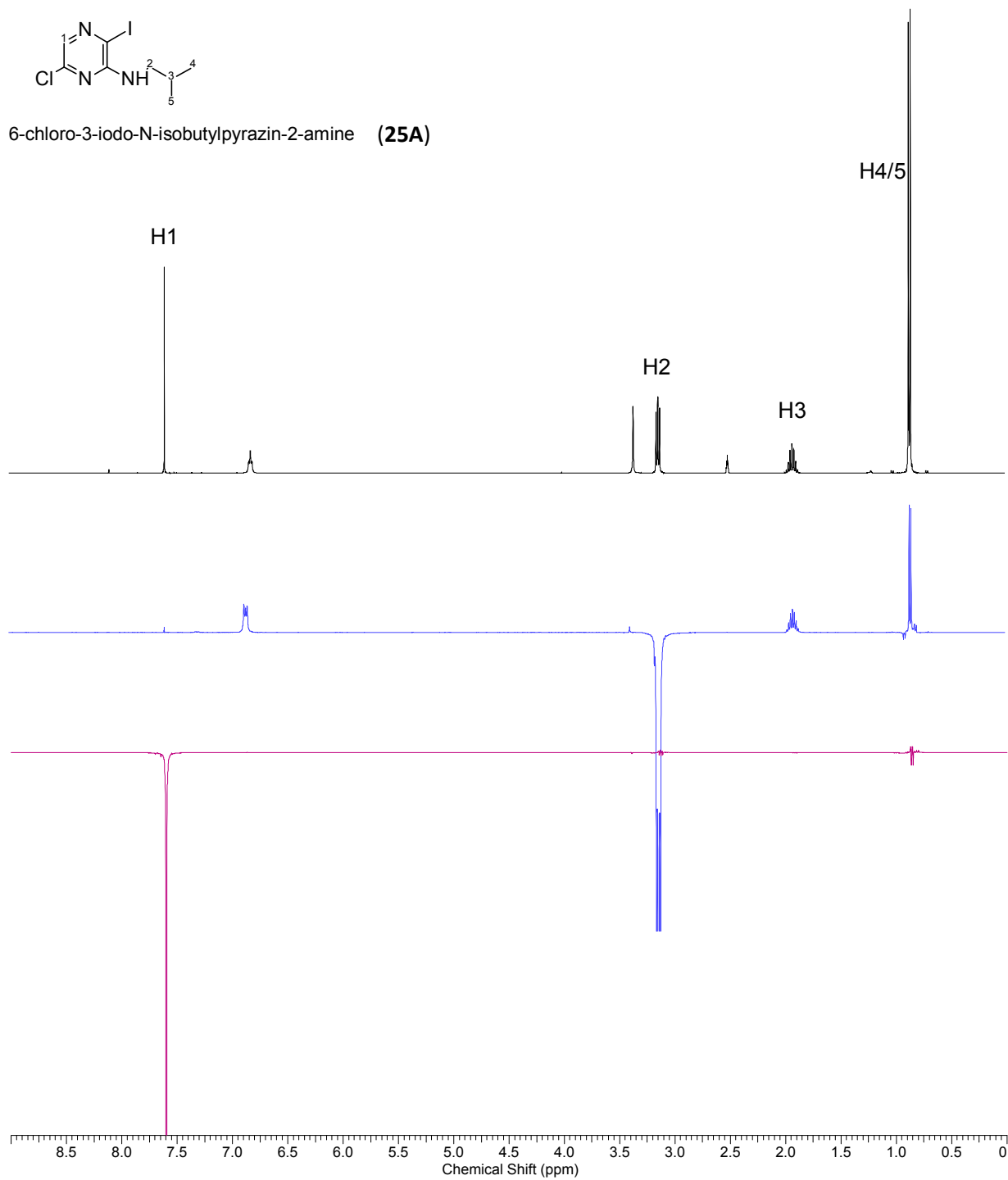
6-chloro-5-iodo-N-isobutylpyrazin-2-amine (**25B**)



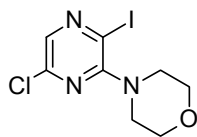
¹H NMR of 6-chloro-3-iodo-N-isobutylpyrazin-2-amine (**25A**)300 MHz, DMSO-*d*₆¹³C NMR of 6-chloro-3-iodo-N-isobutylpyrazin-2-amine (**25A**)101 MHz, CDCl₃



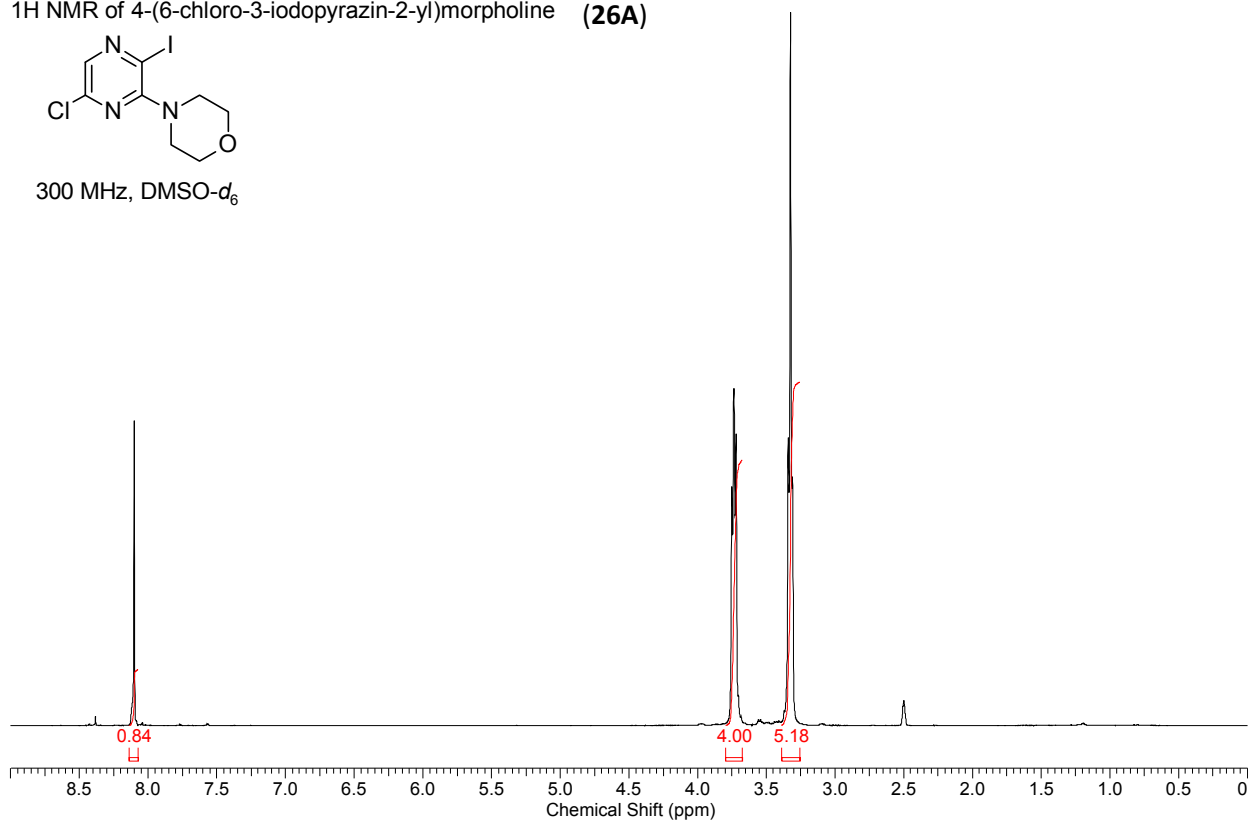
6-chloro-3-iodo-N-isobutylpyrazin-2-amine (**25A**)



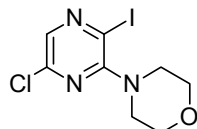
¹H NMR of 4-(6-chloro-3-iodopyrazin-2-yl)morpholine (**26A**)



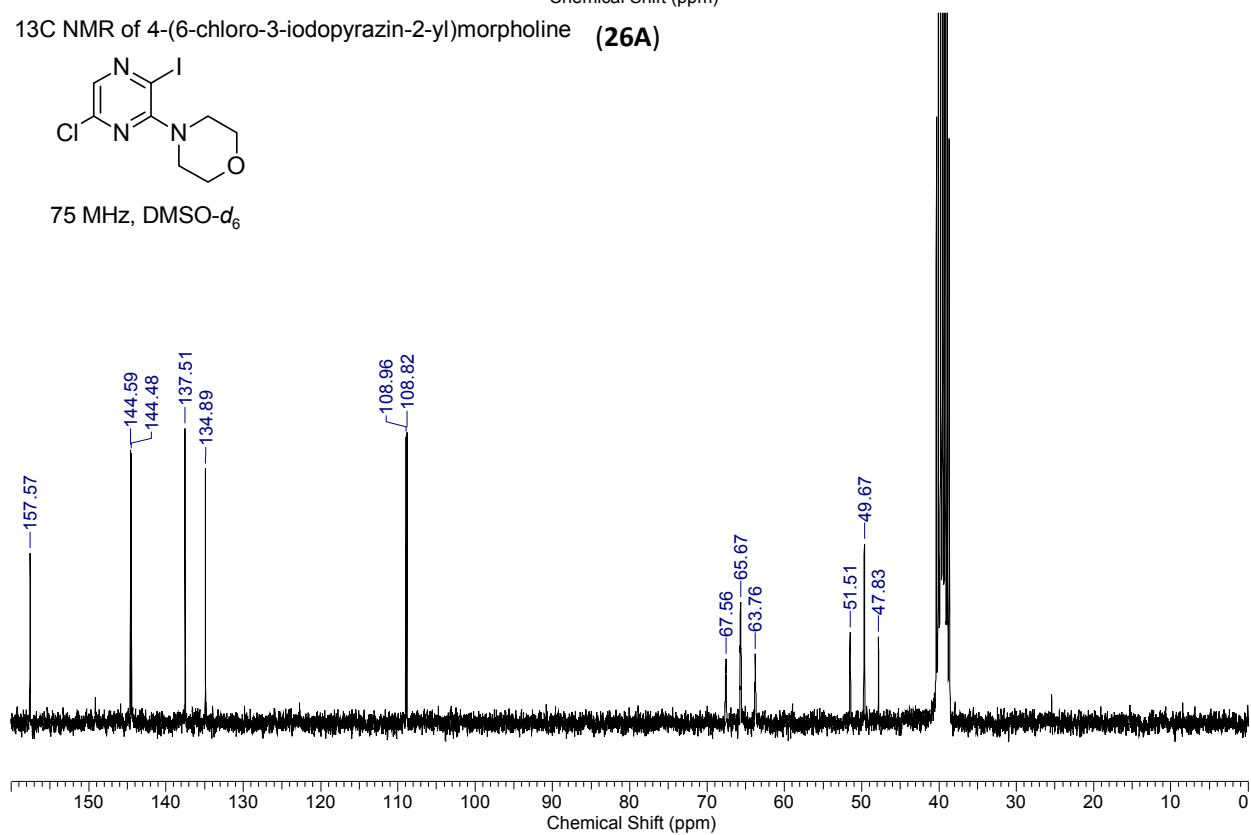
300 MHz, DMSO-*d*₆



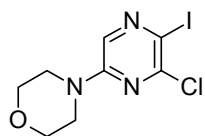
¹³C NMR of 4-(6-chloro-3-iodopyrazin-2-yl)morpholine (**26A**)



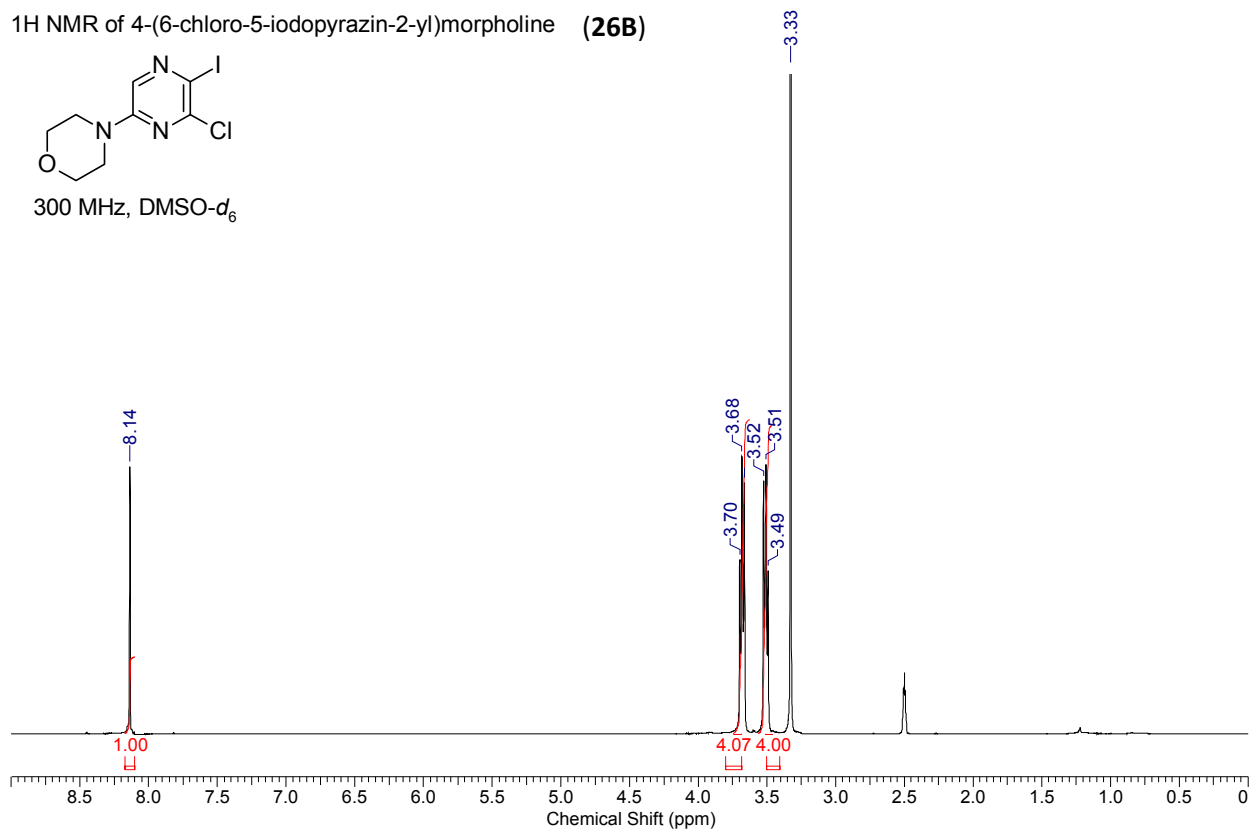
75 MHz, DMSO-*d*₆



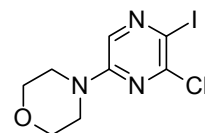
¹H NMR of 4-(6-chloro-5-iodopyrazin-2-yl)morpholine (**26B**)



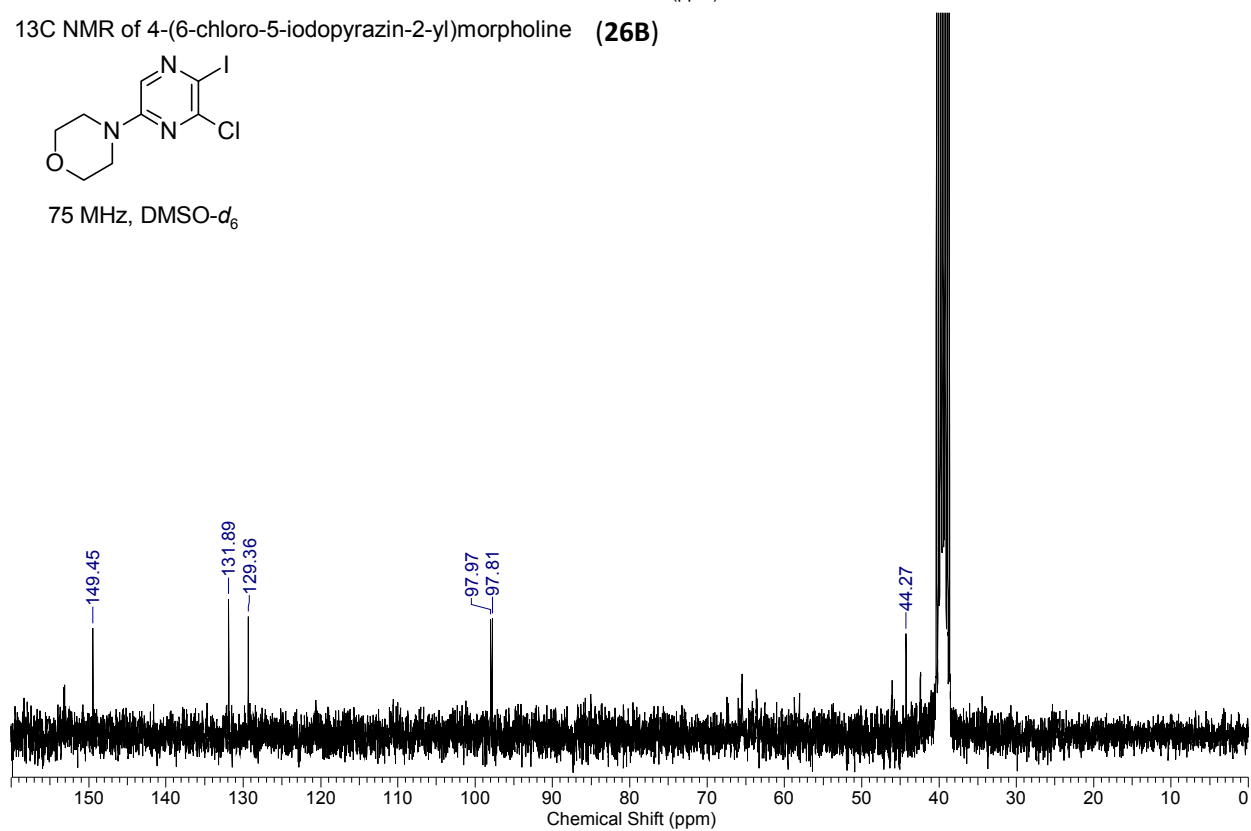
300 MHz, DMSO-*d*₆

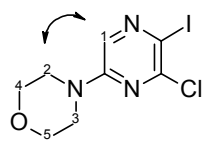


¹³C NMR of 4-(6-chloro-5-iodopyrazin-2-yl)morpholine (**26B**)

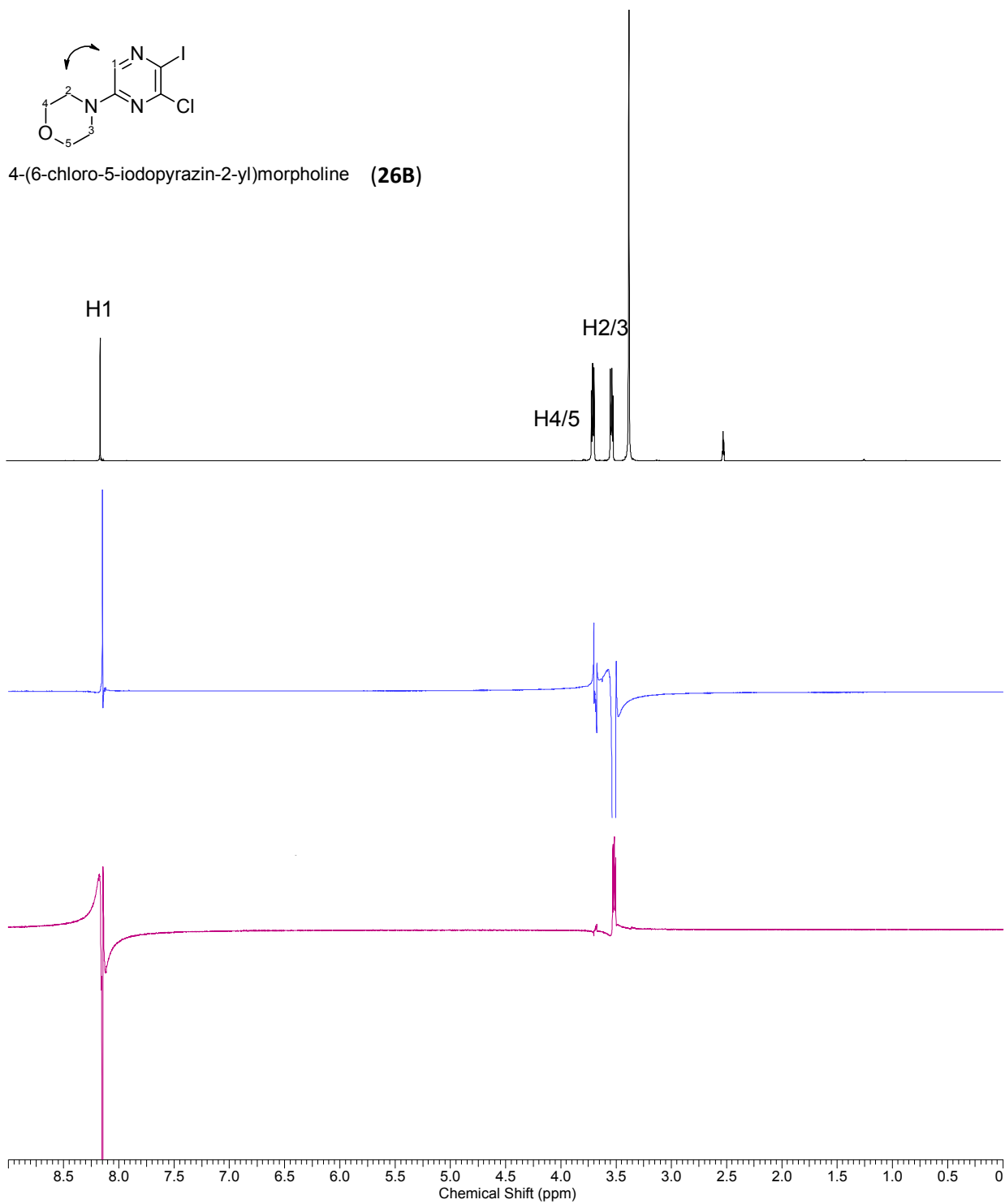


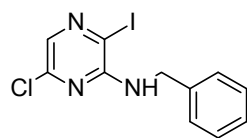
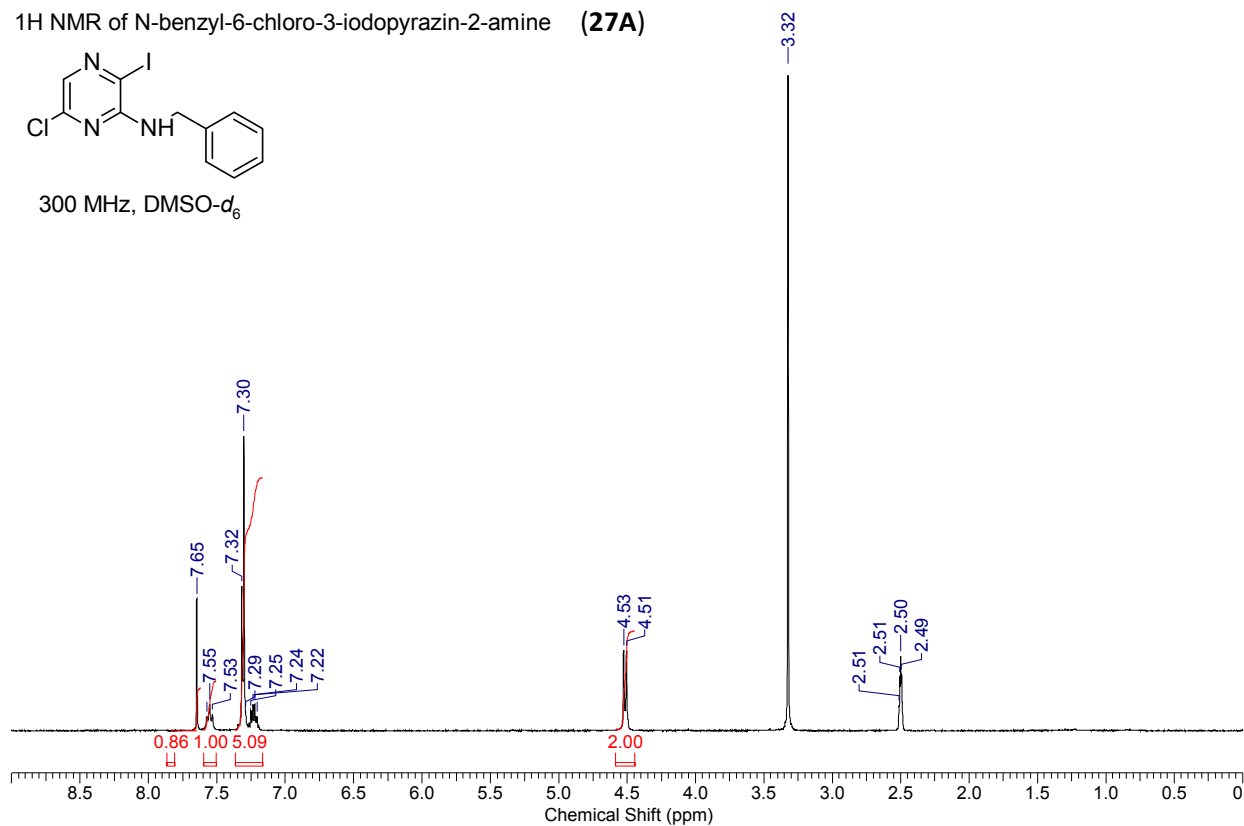
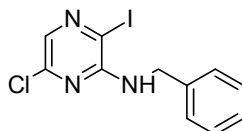
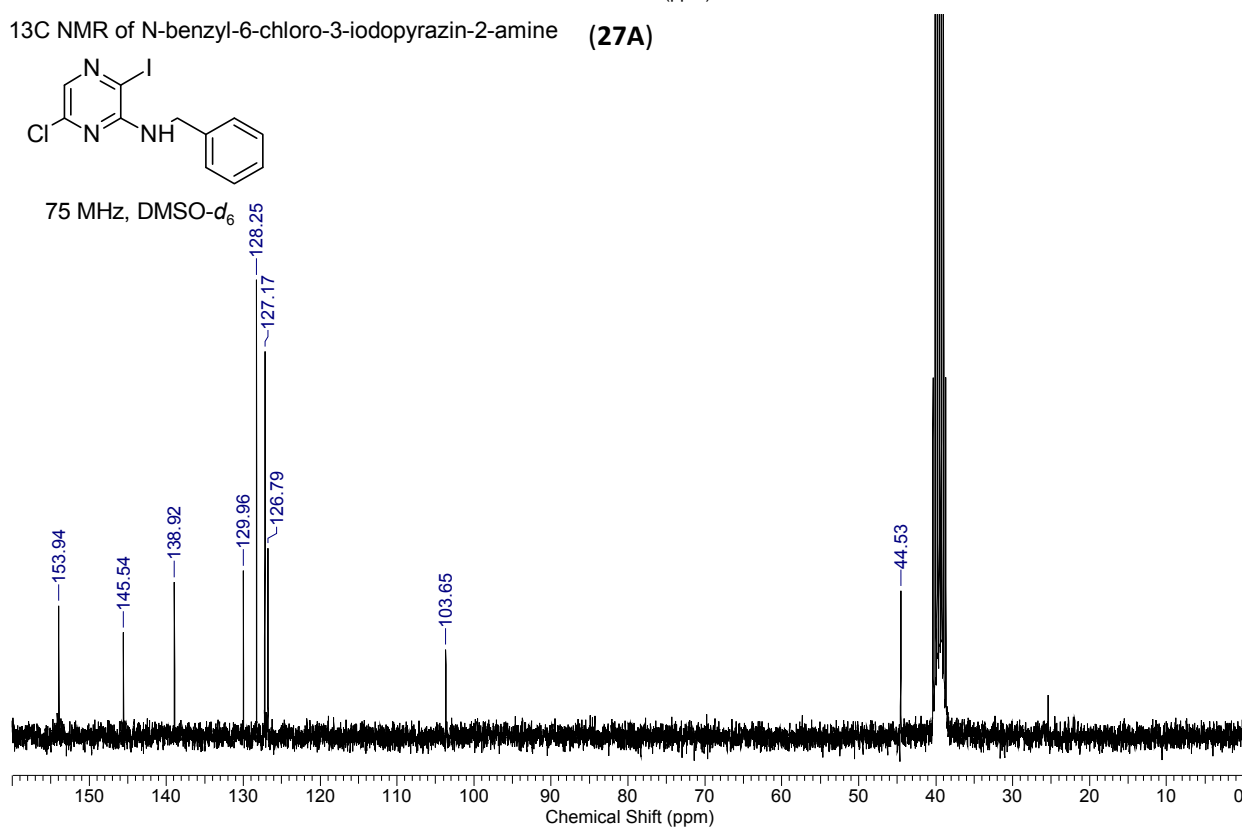
75 MHz, DMSO-*d*₆

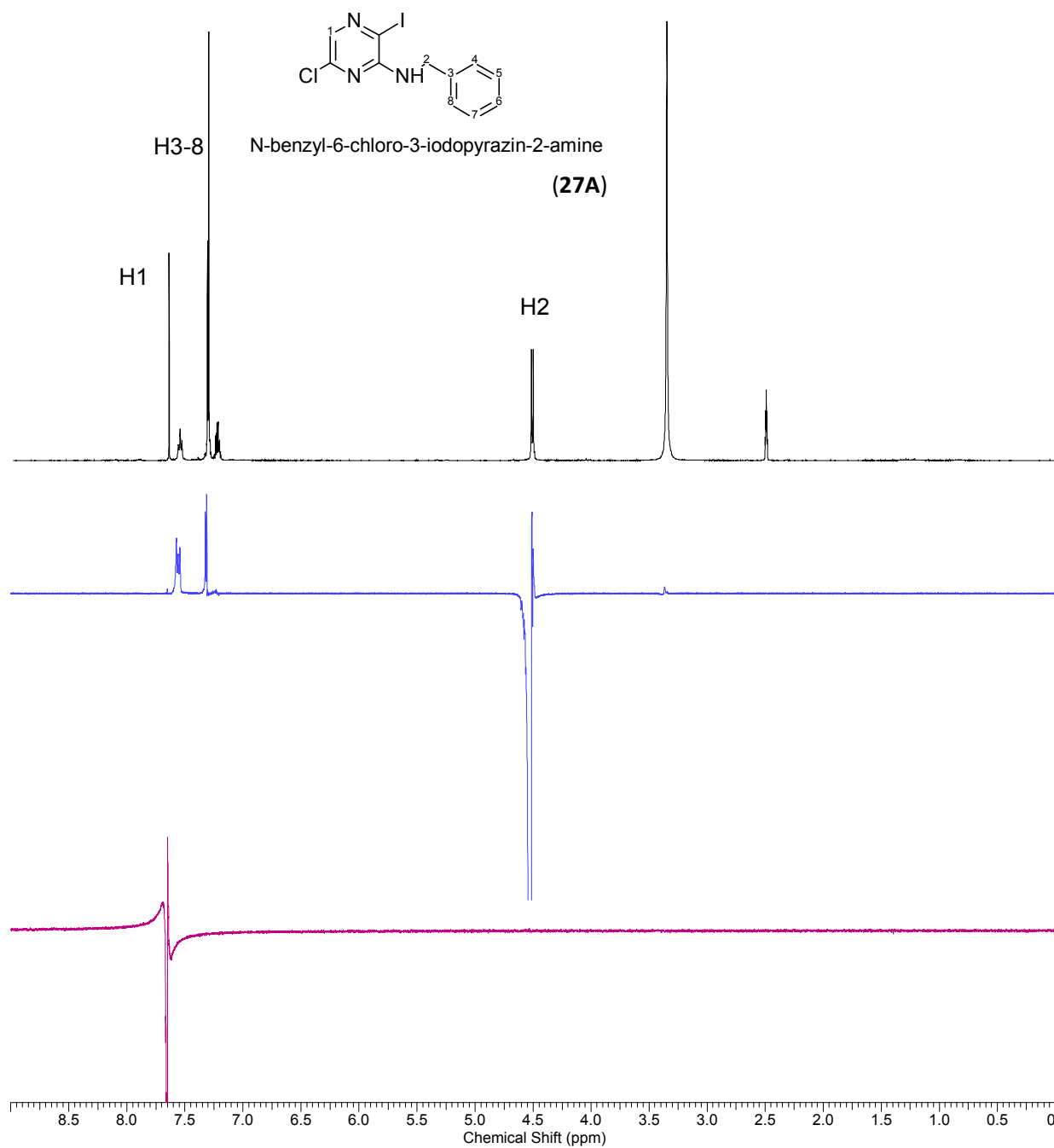


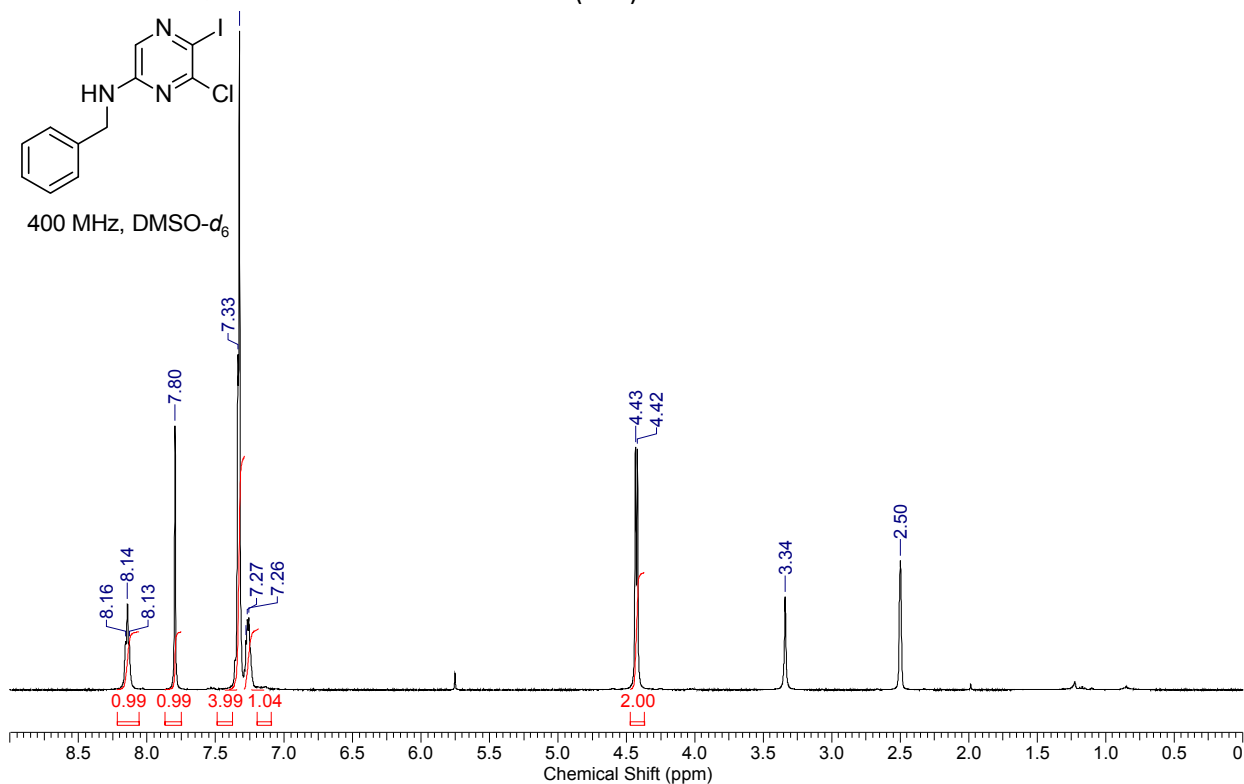
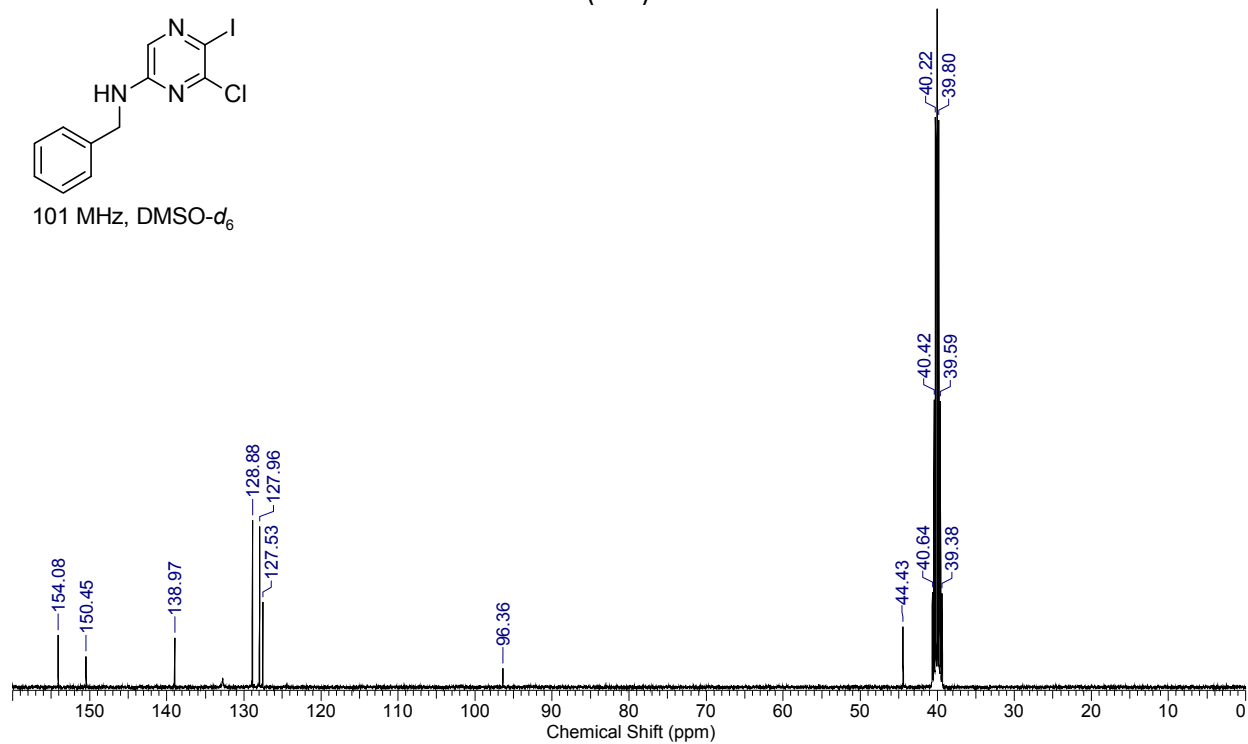


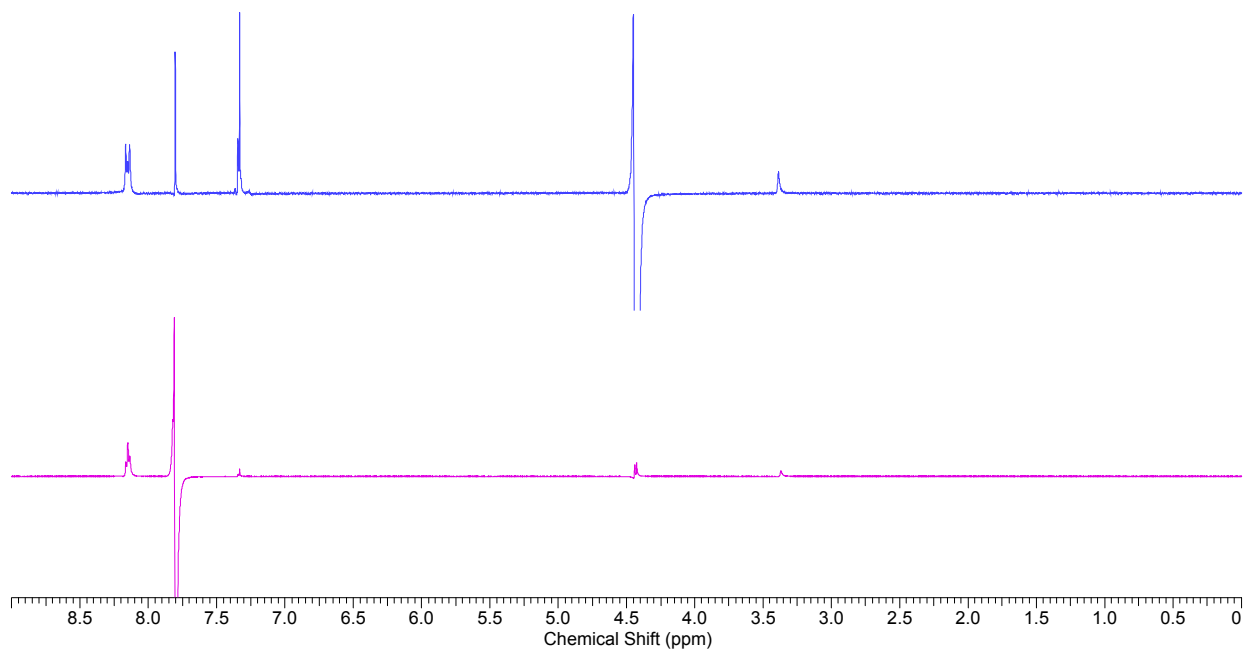
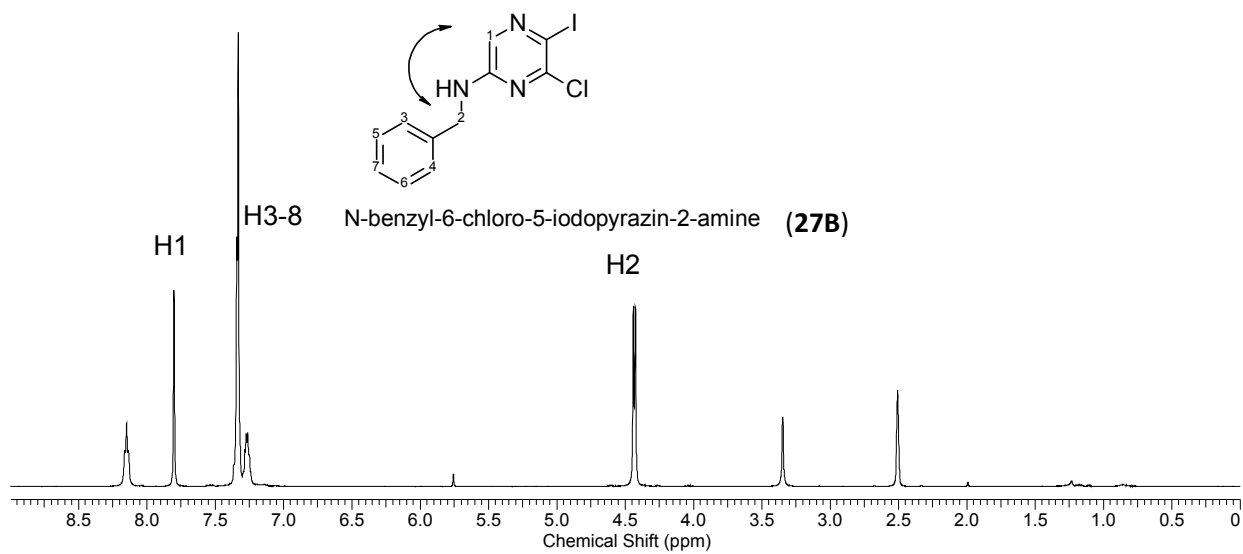
4-(6-chloro-5-iodopyrazin-2-yl)morpholine (**26B**)

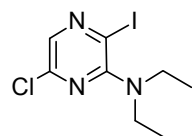
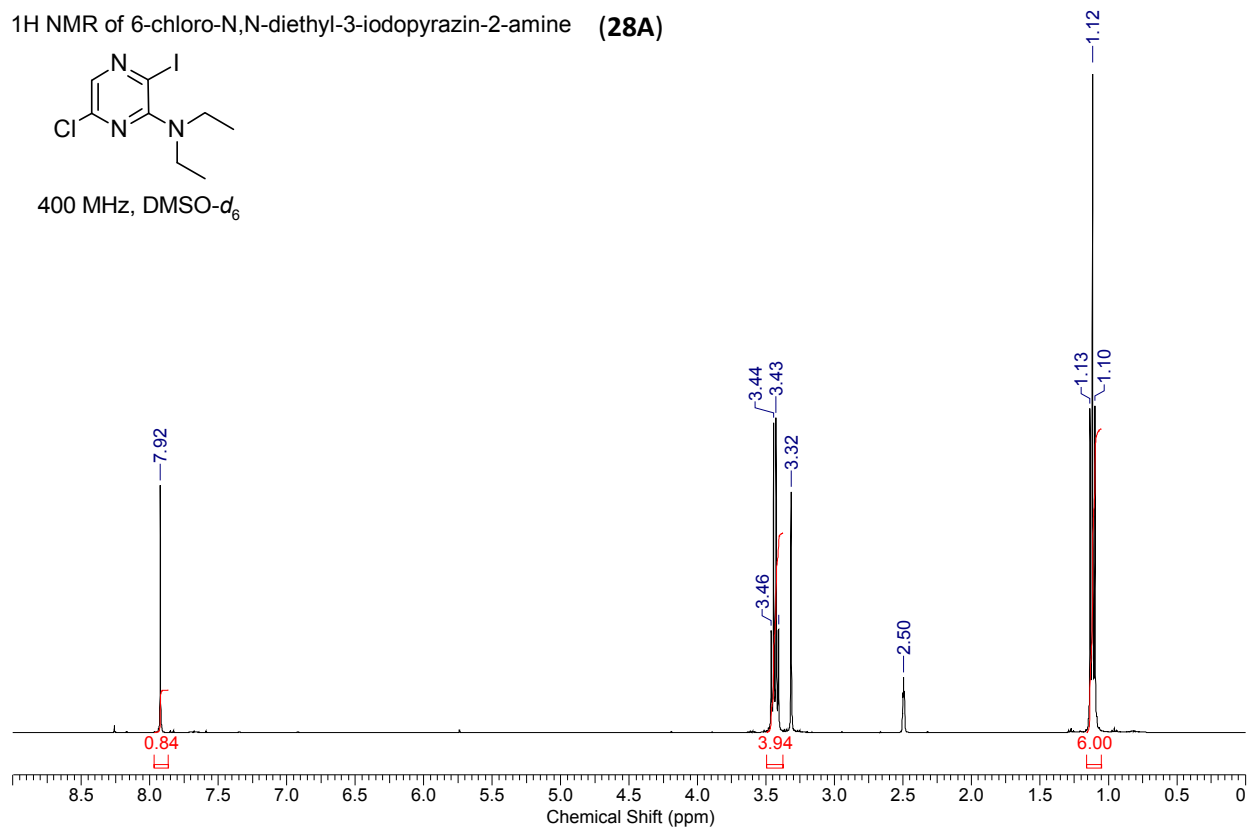
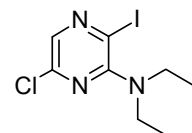
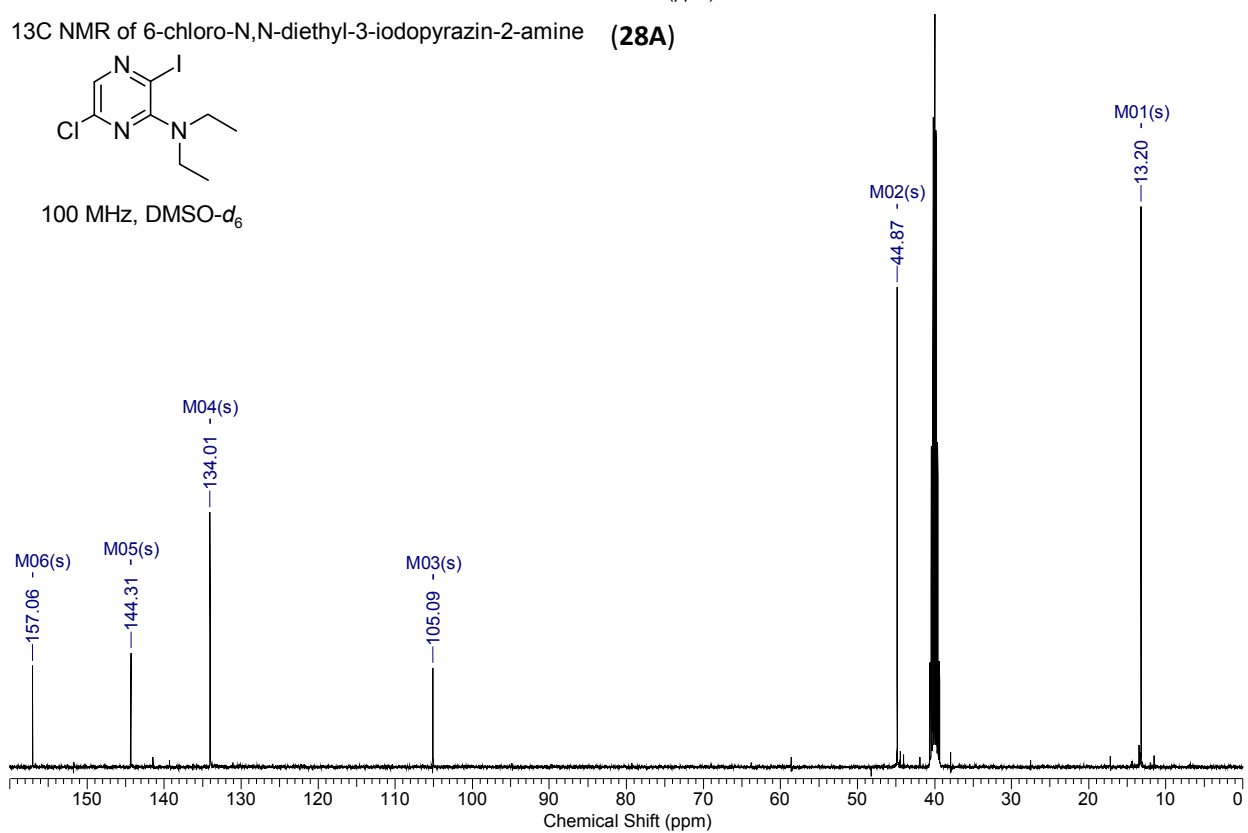


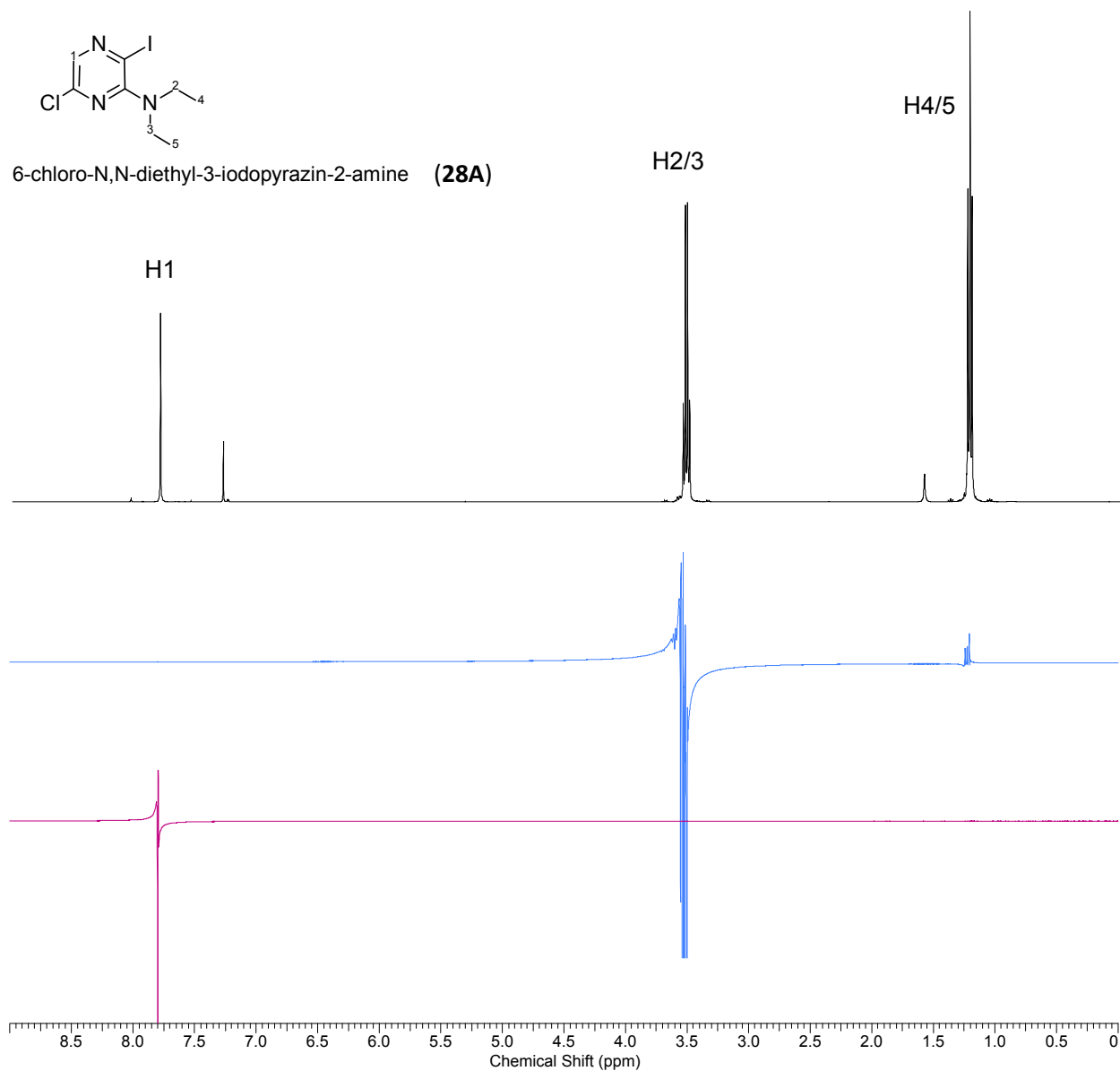
¹H NMR of N-benzyl-6-chloro-3-iodopyrazin-2-amine (**27A**)300 MHz, DMSO-*d*₆¹³C NMR of N-benzyl-6-chloro-3-iodopyrazin-2-amine (**27A**)75 MHz, DMSO-*d*₆



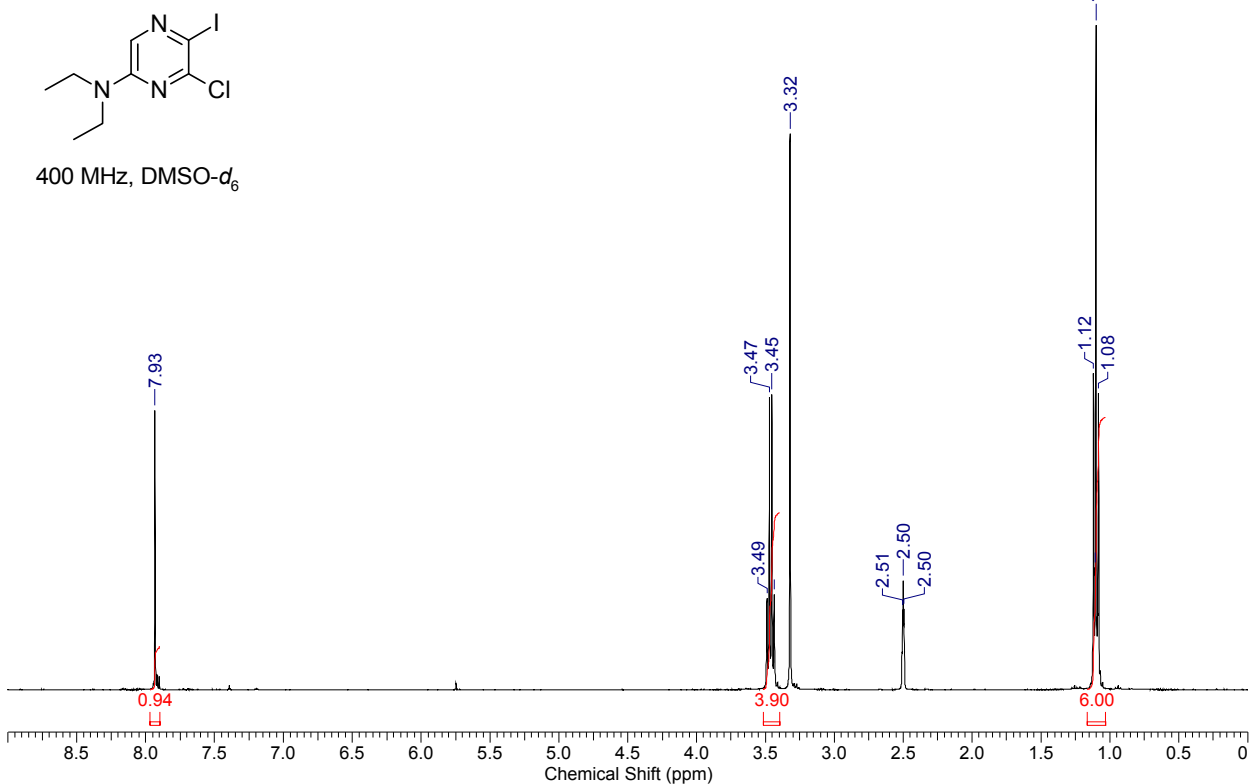
¹H NMR of N-benzyl-6-chloro-5-iodopyrazin-2-amine (**27B**)¹³C NMR of N-benzyl-6-chloro-5-iodopyrazin-2-amine (**27B**)



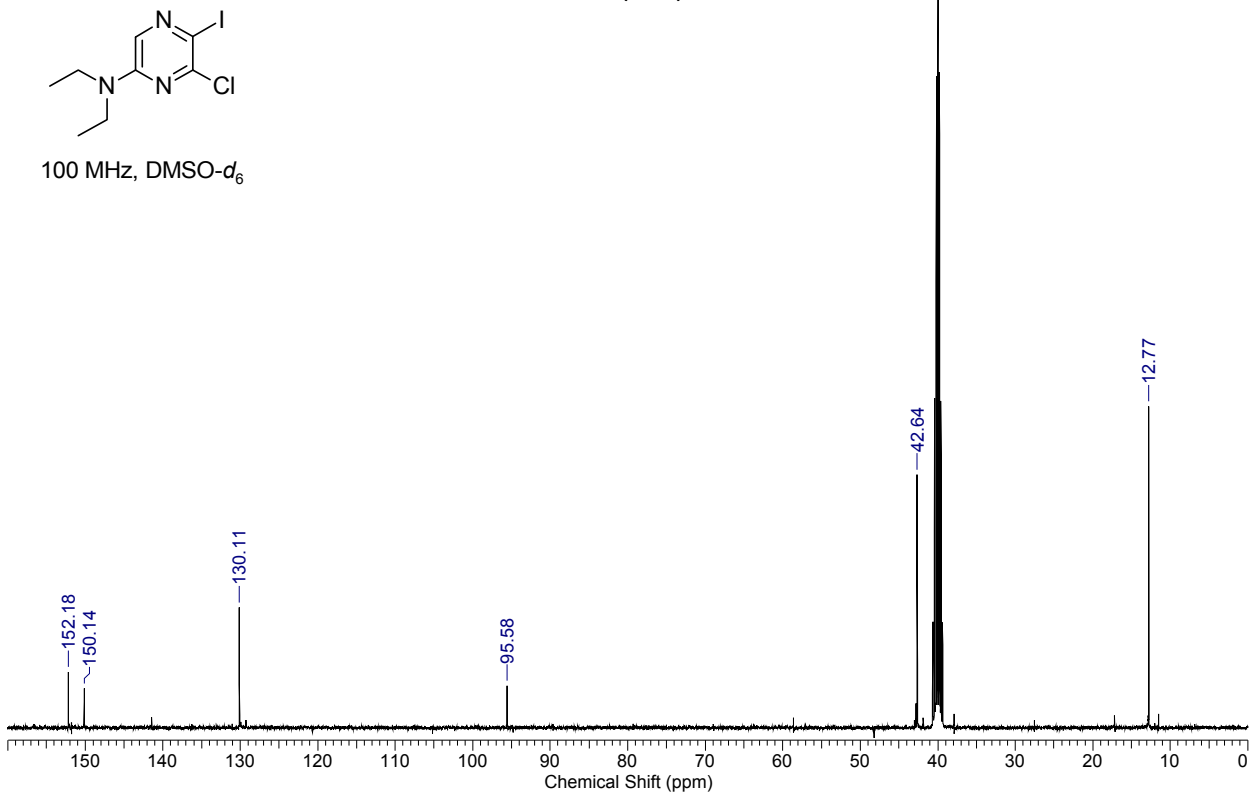
¹H NMR of 6-chloro-N,N-diethyl-3-iodopyrazin-2-amine (**28A**)400 MHz, DMSO-*d*₆¹³C NMR of 6-chloro-N,N-diethyl-3-iodopyrazin-2-amine (**28A**)100 MHz, DMSO-*d*₆

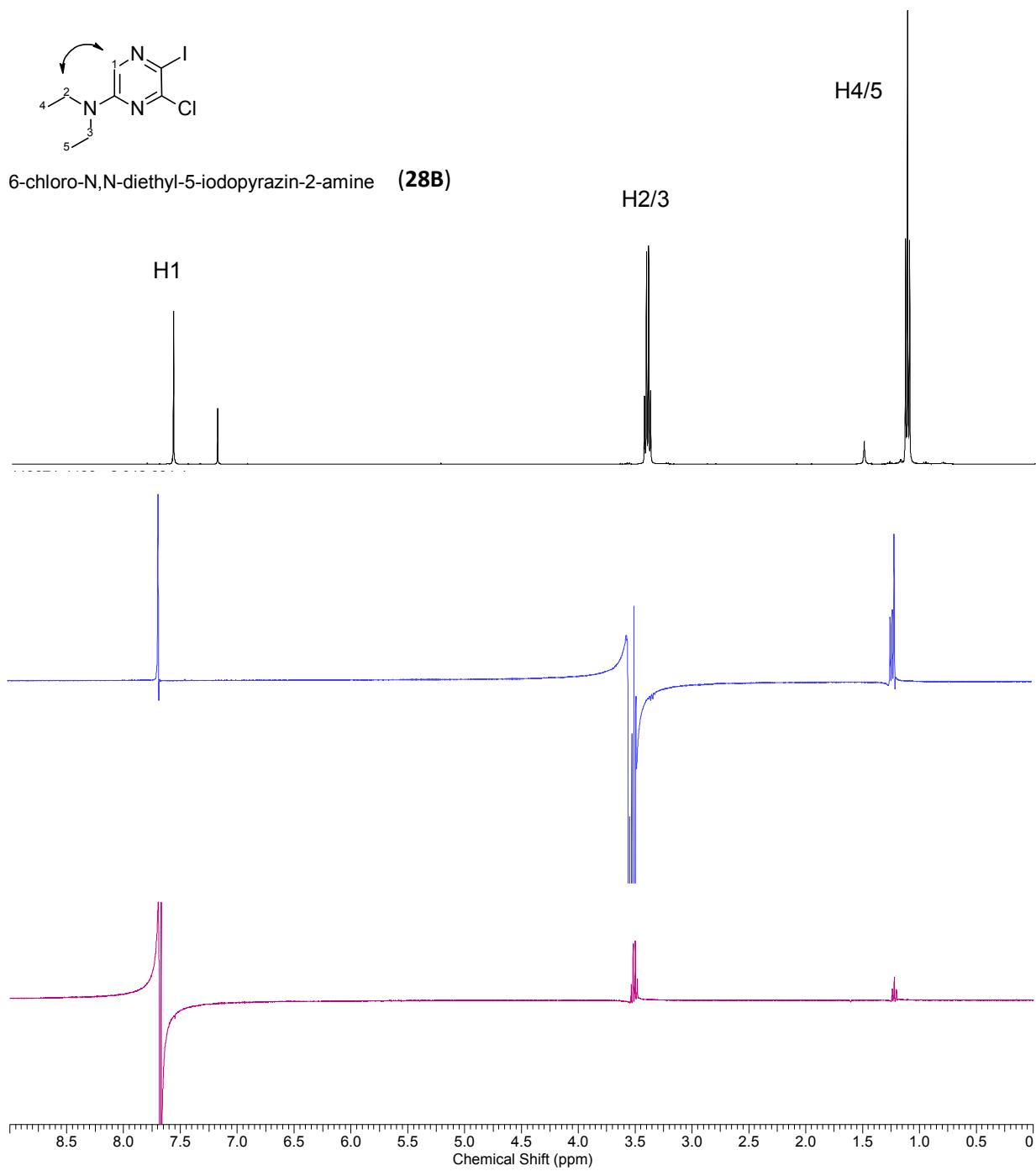


¹H NMR of 6-chloro-N,N-diethyl-5-iodopyrazin-2-amine (28B)

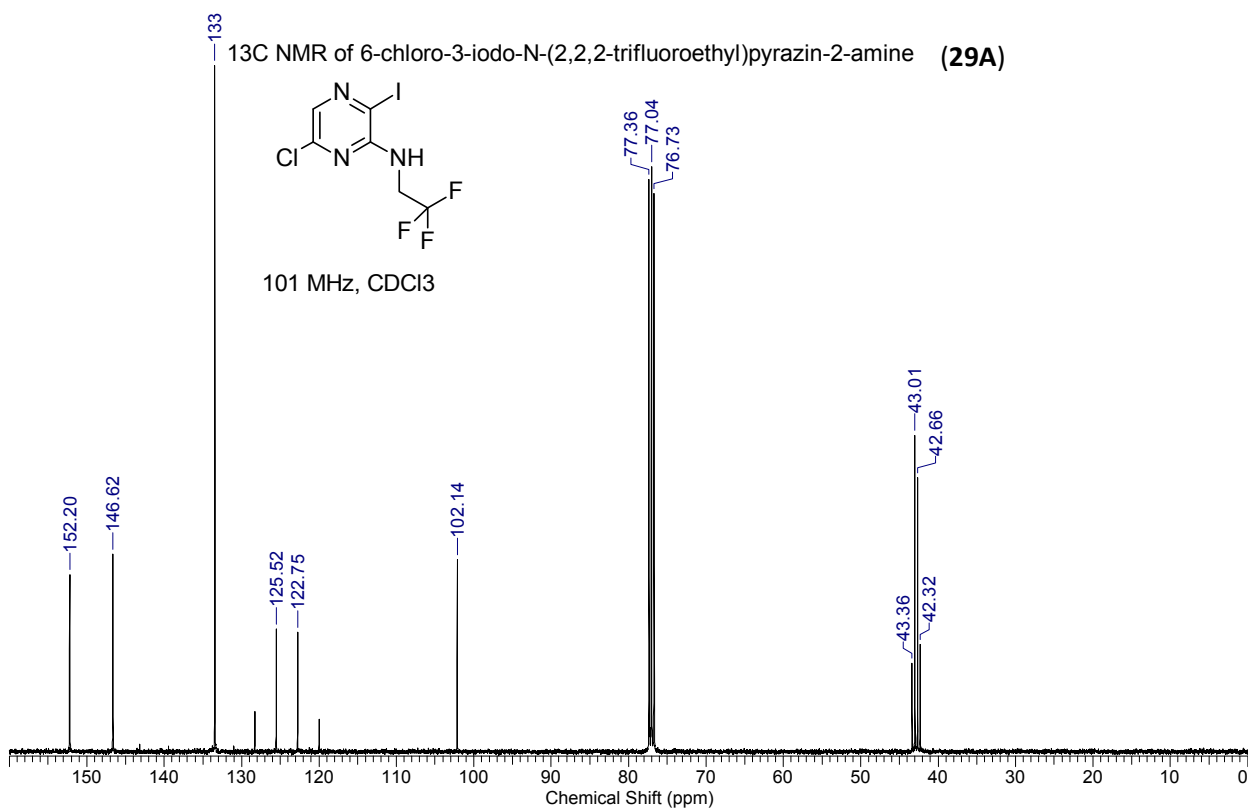
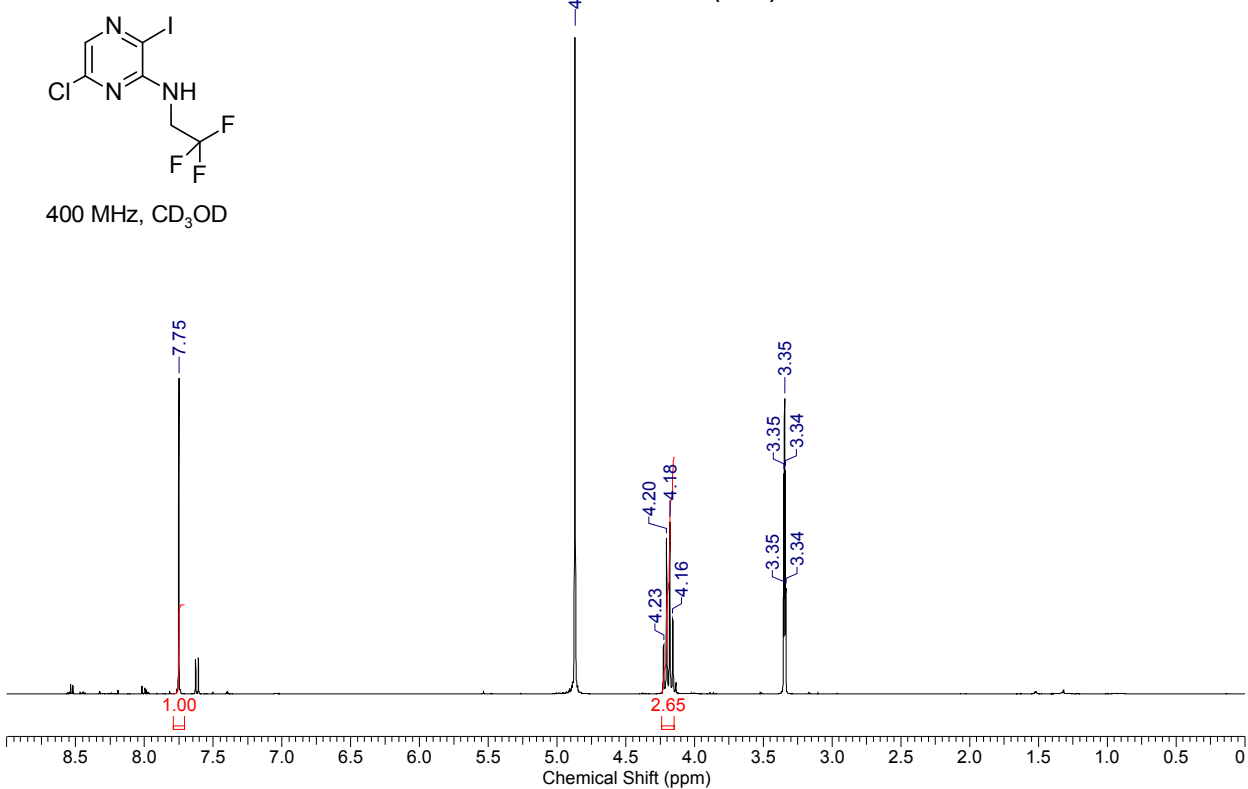


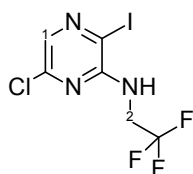
¹³C NMR of 6-chloro-N,N-diethyl-5-iodopyrazin-2-amine (28B)



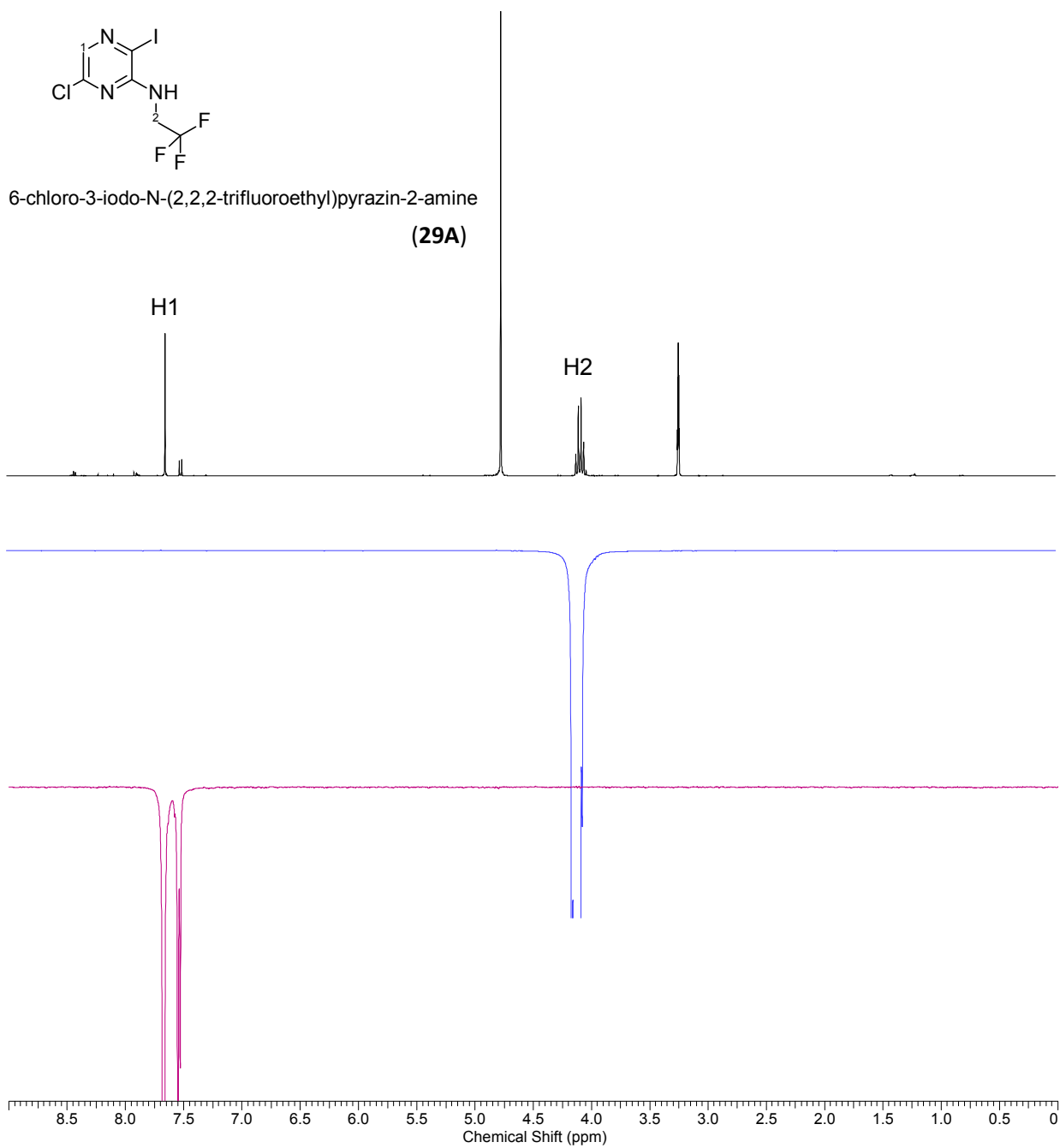


¹H NMR of 6-chloro-3-iodo-N-(2,2,2-trifluoroethyl)pyrazin-2-amine (**29A**)

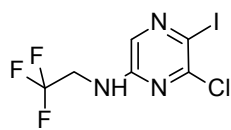




6-chloro-3-iodo-N-(2,2,2-trifluoroethyl)pyrazin-2-amine
(29A)



¹H NMR of 6-chloro-5-iodo-N-(2,2,2-trifluoroethyl)pyrazin-2-amine (**29B**)



400 MHz, CD₃OD

