Supporting Information

Synthesis of Pyridazine-Based Scaffolds as α-Helix Mimetics

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S2-S13 General procedures for the synthesis of all the intermediates and final compounds, their characterizations and the molecular modeling.

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General Methods: Commercially available reagent-grade solvents were employed without purification. ^{1}H and ^{13}C NMR spectra were recorded on 300 or 600 MHz spectrometers. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C = 0.00).

Molecular modeling and compound superimpositions were carried out using the HyperChem™ 7.51 program. Structures were minimized using the MM+ forcefield and then the AM1 semi empirical method. The final rendering was obtained with WebLabViewerPro 4.0.

Materials: Key intermediate **6** was obtained according to the literature.[1] Benzyl and *iso*-butyl alkynyl alcohols **7a,b** were obtained by reacting the corresponding aldehydes with ethynylmagnesium bromide and their ^{1}H NMR and ^{13}C NMR spectral data were in agreement with those previously reported.[2] *N*-acyl hydrazides **17a,b** were obtained by reaction between hydrazine and the corresponding esters and their ^{1}H NMR and ^{13}C NMR spectral data were in agreement with those previously reported.[3]

Homolytic radical alkylation of 3-chloro-6-carboxypyridazine ethyl ester 6. To a suspension of 3-chloro-6-carboxypyridazine ethyl ester **6** (1.86 g, 10 mmol) in distilled water (30 mL) *iso*-butyl carboxylic acid (2.1 mL, 2.25 mmol), conc. H_2SO_4 (0.8 mL, 15 mmol) and $AgNO_3$ (169 mg, 1 mmol) were added at room temperature. The mixture was heated at 65-75 °C and a solution of $NH_4S_2O_8$ (3.4 g, 15 mmol) in distilled water (10 mL) was added dropwise in 10-15 minutes. The reaction was stirred for an additional 30 minutes at 70-75 °C, then poured over ice, then neutralized with a 30% aqueous solution of NH_4OH and immediately extracted twice with dichloromethane. The collected organic layers were anhydrified over magnesium sulfate, the solvent removed under reduced pressure and the crude purified by flash chromatography to give 1.13 g of regioisomer **3** and 564 mg of regioisomer **4**.

Ethyl-6-chloro-5-*iso*-butylpyridazine-3-carboxylate 3: R_f = 0.49 (Hexane/AcOEt = 70:30); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (s, 1H), 4.48 (q, *J* = 7.4 Hz, 2H), 2.64 (d, *J* = 7.0 Hz, 3H), 2.03 (m, 1H), 1.41 (t, *J* = 7.4 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 160.1, 150.5, 141.5, 129.6, 62.6, 41.2, 27.7, 22.1, 14.0; ESI (*m/z)* 265 [M^++Na, (50)], 243 [M^++1, (100)].

[1] Morishita, M., Kobayashi J.; Yamada, H.; Yajima, T. *Chem. Pharm. Bull.* **1994**, *42*, 371-372.
[2] (a) Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2006**, *71*, 4951-4955. (b) Fleming, S. A.; Liu, R.; Redd, J. T. *Tetrahedron Lett.* **2005**, *46*, 8095-8098.
[3] Khan, K. M.; Rasheed, M.; Ullah, Z.; Hayat, S.; Kaukab, F.; Choudhary, M. I.; Rahman, A.; Perveen, S. *Bioorg. Med. Chem.* **2003**, *11*, 1381-1387.

Ethyl-6-chloro-4-*iso*-butylpyridazine-3-carboxylate 4: R_f = 0.55 (Hexane/AcOEt = 70:30); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (s, 1H), 4.46 (q, *J* = 7.0 Hz, 2H), 2.71 (d, *J* = 7.0 Hz, 3H), 1.89 (m, 1H), 1.40 (t, *J* = 7.4 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 157.3, 152.5, 143.9, 129.5, 62.4, 40.4, 29.2, 22.1, 14.0; ESI (*m/z)* 265 [M^++Na, (62)], 243 [M^++1, (100)], 197 (83).

Sonogashira coupling on ethyl-6-chloro-5-*iso*-butylpyridazine-3-carboxylate 3. General procedure. To a stirred solution of ethyl-6-chloro-5-*iso*-butylpyridazine-3-carboxylate **3** (1 equiv.) in dry THF (0.5 M solution) ethynyl alcohol (1.25 equiv.), dry TEA (2.7 equiv.), CuI (0.03 equiv.) and $Pd(PPh_3)_2Cl_2$ (0.03 equiv.) were added at room temperature under nitrogen atmosphere. The reaction was heated at 70 °C and stirred for 2 hours. The suspension was cooled to room temperature, diluted with AcOEt, filtered, the solvent removed under reduced pressure and the crude purified by flash chromatography.

Ethyl-6-(3-hydroxy-5-methylhex-1-ynyl)-5-*iso*-butylpyridazine-3-carboxylate 8a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 4.78 (br s, 1H), 4.48 (q, *J* = 7.0 Hz, 2H), 4.11 (br s, 1H), 2.63 (m, 2H), 1.99 (m, 1H), 1.92 (m, 1H), 1.78 (m, 1H), 1.71 (m, 1H), 1.41 (t, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 5.7 Hz, 3H), 0.93 (d, *J* = 5.7 Hz, 3H), 0.88 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 150.1, 148.7, 143.8, 127.1, 101.6, 79.3, 62.5, 60.9, 46.1, 41.5, 28.6, 24.6, 22.4, 22.3, 22.1, 14.0; ESI (*m/z)* 341 [M^++Na, (32)], 319 [M^++1, (100)], 121 (89).

Ethyl-6-(3-hydroxy-4-phenylbut-1-ynyl)-5-*iso*-butylpyridazine-3-carboxylate 8b: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.33-7.20 (m, 5H), 4.99 (br s, 1H), 4.50 (q, *J* = 7.0 Hz, 2H), 4.28 (br s, 1H), 3.21 (dd, *J* = 13.6 and 6.5 Hz, 1H), 3.26 (dd, *J* = 13.6 and 7.0 Hz, 1H), 2.50 (d, *J* = 7.4 Hz, 2H), 1.89 (m, 1H), 1.44 (t, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 4.4 Hz, 3H), 0.81 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 149.9, 148.6, 143.9, 136.4, 129.5, 128.2, 126.9, 126.6, 100.6, 80.2, 63.4, 62.4, 43.4, 41.1, 28.3, 22.0, 21.9, 14.0; ESI (*m/z)* 375 [M^++Na, (32)], 353 [M^++1, (72)], 121 (100).

Oxidation of alkynyl alcohols 8a,b. General procedure. To a solution of alkynil alcohol (1 equiv.) in dichloromethane (0.07 M solution) Dess-Martin periodinane (1.1 equiv.) was added at room temperature. The mixture was stirred over-night, filtered, the solvent removed under reduced pressure and the crude purified by flash chromatography.

Ethyl-5-*iso*-butyl-6-(5-methyl-3-oxohex-1-ynyl)pyridazine-3-carboxylate 9a: R_f = 0.17 (Hexane/AcOEt = 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 4.50 (q, *J* = 7.2 Hz, 2H), 2.69 (d, *J* = 7.2 Hz, 2H), 2.59 (d, *J* = 7.2 Hz, 2H), 2.17 (m, 1H), 2.00 (m, 1H), 1.44 (t, *J* = 7.2 Hz, 3H), 0.96 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.5, 163.6, 149.5, 148.6, 145.3, 127.2, 93.7, 82.6, 62.8, 54.3, 41.4, 29.1, 25.0, 22.3, 22.2, 14.1; ESI (*m/z)* 339 [M^++Na, (25)], 317 [M^++1, (100)].

Ethyl-5-*iso*-butyl-6-(3-oxo-4-phenylbut-1-ynyl)pyridazine-3-carboxylate 9b: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.38-7.32 (m, 5H), 4.56 (q, *J* = 7.0 Hz, 2H), 4.04 (s, 2H), 2.59 (d, *J* = 7.0 Hz, 2H), 1.94 (m, 1H), 1.49 (t, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.8, 164.7, 149.6, 148.5, 145.3, 132.0, 129.8, 128.9, 127.7, 127.2, 93.4, 84.7, 62.9, 52.1, 41.3, 29.0, 22.2, 14.2; ESI (*m/z)* 373 [M^++Na, (6)], 351 [M^++1, (100)].

Synthesis of pyrazole derivatives 10a,b. General procedure. To a solution of propargyl ketone (1 equiv.) in MeOH (0.2 M solution) hydrazine hydrate (1 equiv.) was added at 0 °C. The solution was stirred at 0 °C for one hour, heated to room temperature, the solvent removed under reduced pressure and the crude purified by flash chromatography.

Ethyl-5-*iso*-butyl-6-(3-*iso*-butyl-1*H*-pyrazol-5-yl)pyridazine-3-carboxylate 10a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.81 (s, 1H), 4.55 (q, *J* = 7.7 Hz, 2H), 3.09 (d, *J* = 7.7 Hz, 2H), 2.63 (d, *J* = 7.7 Hz, 2H), 2.01 (m, 2H), 1.48 (t, *J* = 7.7 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 6H), 0.94 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 154.8, 149.1, 139.4, 129.5, 125.2, 106.7, 106.5, 62.4, 41.5, 35.7, 28.8, 27.9, 22.3, 22.2, 14.2; ESI (*m/z)* 353 [M^++Na, (12)], 331 [M^++1, (100)].

Ethyl-6-(3-benzyl-1*H*-pyrazol-5-yl)-5-*iso*-butylpyridazine-3-carboxylate 10b: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.31 (m, 5H), 6.75 (s, 1H), 4.56 (q, *J* = 7.7 Hz, 2H), 4.14 (s, 2H), 2.90 (d, *J* = 7.7 Hz, 2H), 2.00 (m, 1H), 1.49 (t, *J* = 7.7 Hz, 3H), 0,93 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 153.9, 149.3, 139.2, 138.4, 129.6, 128.8, 128.7, 126.7, 106.8, 62.4, 41.5, 33.5, 27.7, 22.3, 14.2; ESI (*m/z)* 387 [M^++Na, (16)], 365 [M^++1, (100)].

Synthesis of pyrimidine derivative 13. To a solution of sodium ethoxide (1.3 equiv.) in absolute ethanol (0.25 M solution), formamidine hydrochloride (1.3 equiv.) was added at room temperature under nitrogen atmosphere. The resulting suspension was stirred for 30 minutes. A solution of alkynyl ketone (1 equiv.) in a minimal amount of absolute ethanol was added and the suspension was refluxed over-night. The mixture was cooled to room temperature, filtered, the solvent removed under reduced pressure and the crude purified by flash chromatography.

Ethyl-5-*iso*-butyl-6-(6-*iso*-butylpymiridin-4-yl)pyridazine-3-carboxylate 13: R_f = 0.17 (Hexane/AcOEt = 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, *J* = 0.9 Hz, 1H), 8.05 (s, 1H), 7.95 (d, *J* = 0.9 Hz, 1H), 4.53 (q, *J* = 7.2 Hz, 2H), 3.02 (d, *J* = 7.2 Hz, 2H), 2.72 (d, *J* = 7.2 Hz, 2H), 2.18 (m, 1H), 1.82 (m, 1H), 1.47 (t, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 6H), 0.81 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 164.1, 162.5, 159.0, 157.6, 150.7, 142.5, 129.9, 121.2, 62.6, 47.2, 40.9, 29.2, 28.6, 22.4, 22.2, 14.2; ESI (*m/z)* 365 [M^++Na, (13)], 343 [M^++1, (100)].

Hydrolysis of the ethyl esters 10a,b and 13. General procedure. To a solution of ethyl ester (1 equiv.) in a 4:1 mixture of THF/H_2O (0.05 M solution) LiOH hydrate (1.2 equiv.) was added at 0

°C. After the hydrolysis is completed (TLC monitoring) the solution was acidified carefully with a 1N HCl aqueous solution, heated to room temperature and extracted with AcOEt. The collected organic layers were anhydrified over magnesium sulfate, filtrated and the solvent removed under reduced pressure leading to the free carboxylic acid that was used without any further purification.

Coupling leading to the scaffolds 12a-d and 21b,c. General procedure. To a solution of the free carboxylic acid (1 equiv.) in dry dichloromethane (0.05 M solution) (*S*)-*N*-1-Boc-2-benzylpiperazine (1.05 equiv.), EDCI (1.1 equiv.), HOBt (1.1 equiv.) and DIPEA (2 equiv.) were added at room temperature. The reaction was stirred over-night, the solvent evaporated under reduced pressure and the crude purified by flash chromatography.

(***S*)-*tert*-butyl-2-*iso*-butyl-4-(5-*iso*-butyl-6-(3-*iso*-butyl-1*H*-pyrazol-5-yl)pyridazine-3-carbonyl)piperazine-1-carboxylate 12a**: R_f = 0.46 (CH_2Cl_2/MeOH = 95:5);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 10.76 (br s, 1H), 7.70 (s, 1H), 6.79 (s, 0.6H), 6.77 (s, 0.4H), 4.70 (d, *J* = 12.6 Hz, 0.4H), 4.64 (d, *J* = 12.6 Hz, 0.6H), 4.38 (d, *J* = 11.4 Hz, 0.6H), 4.27 (d, *J* = 11.4 Hz, 0.4H), 4.19-3.98 (m, 2H), 3.54 (dd, *J* = 13.8 and 3.6 Hz, 0.4H), 3.29-2.87 (m, 4.6H), 2.63 (d, *J* = 7.2 Hz, 2H), 2.02 (m, 2H), 1.61 (m, 2H), 1.50 (m, 9H), 1.27 (m, 1H), 1.00-0.95 (m, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) mixture of conformers δ 166.1, 165.8, 154.5, 154.4, 154.1, 154.0, 140.2, 140.1, 129.7, 129.5, 128.9, 125.2, 120.3, 109.3, 106.1, 80.2, 80.1, 50.3, 47.6, 45.7, 42.7, 41.6, 38.0, 35.7, 28.8, 28.4, 27.9, 24.7, 22.8, 22.75, 22.71, 22.6, 22.4, 22.38, 22.32, 22.2; ESI-TOF high accuracy: expected mass 527.3709 (M^++1), found 527.3700.

(*S*)-*tert*-butyl-2-benzyl-4-[5-*iso*-butyl-6-(3-*iso*-butyl-1*H*-pyrazol-5-yl)pyridazine-3-carbonyl]piperazine-1-carboxylate 12b: R_f = 0.21 (CH_2Cl_2/MeOH = 98:2);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 7.83 (s, 0.4H), 7.79 (s, 0.6H), 7.32 (m, 3H), 7.23 (m, 1H), 7.01 (br s, 1H), 6.97 (m, 1H), 6.82 (s, 0.6H), 6.78 (s, 0.4H), 4.74 (d, *J* = 13.2 Hz, 0.4H), 4.67 (d, *J* = 13.2 Hz, 0.6H), 4.47 (m, 2H), 4.10 (m, 1H), 3.57 (dd, *J* = 14.3 and 4.4 Hz, 0.4H), 3.47 (m, 0.6H), 3.35 (m, 0.4H), 3.26 (m, 0.6H), 3.12 (m, 5H), 2.64 (d, *J* = 6.6 Hz, 2H), 2.02 (m, 2H), 1.39 (m, 9H), 1.01 (d, *J* = 6.6 Hz, 6H), 0.98 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 154.4, 154.3, 154.1, 153.8, 140.3, 138.0, 129.8, 129.6, 129.0, 128.5, 126.5, 106.2, 80.2, 47.5, 42.8, 41.6, 36.0, 35.7, 28.8, 28.3, 28.2, 27.9, 22.5, 22.4, 22.3; ESI-TOF high accuracy: expected mass 561.3547 (M^++1), found 561.3540.

(*S*)-*tert*-butyl-4-(6-(3-benzyl-1*H*-pyrazol-5-yl)-5-*iso*-butylpyridazine-3-carbonyl)-2-isobutylpiperazine-1-carboxylate 12c: R_f = 0.38 (CH_2Cl_2/MeOH = 95:5);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 7.72 (s, 1H), 7.35-7.27 (m, 5H), 6.75 (s, 0.6H), 6.74 (s, 0.4H), 4.68 (d, *J* = 12.6 Hz, 0.4H), 4.63 (d, *J* = 12.6 Hz, 0.6H), 4.36 (m, 1H), 4.25-3.97 (m, 4H), 3.53 (dd, *J* = 13.2 and 3.6 Hz, 0.4H), 3.27-2.80 (m, 4.6 H), 1.99 (m, 1H), 1.61 (m, 1H), 1.49 (m, 9H), 1.27 (m,

2H), 0.99-0.82 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 165.7, 154.5, 154.1, 154.0, 140.0, 139.8, 138.2, 129.8, 129.6, 128.7, 126.7, 106.4, 80.2, 80.1, 50.2, 47.5, 45.7, 42.7, 41.5, 37.9, 33.3, 28.4, 27.7, 24.7, 24.5, 22.8, 22.7, 22.5, 22.3, 22.2; ESI-TOF high accuracy: expected mass 561.3547 (M^++1), found 561.3542.

(*S*)-*tert*-butyl-2-benzyl-4-[6-(3-benzyl-1*H*-pyrazol-5-yl)-5-*iso*-butylpyridazine-3-carbonyl]piperazine-1-carboxylate 12d: R_f = 0.16 (CH_2Cl_2/MeOH = 98:2);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 7.72 (s, 0.4H), 7.68 (s, 0.6H), 7.19 (m, 8H), 6.99 (m, 1H), 6.87 (m, 1H), 6.61 (s, 0.6H), 6.64 (s, 0.4H), 4.60 (d, *J* = 12.4 Hz, 0.4H), 4.57 (d, *J* = 12.4 Hz, 0.6H), 4.05 (d, *J* = 4.7 Hz, 2H), 3.99 (m, 1H), 3.46 (dd, *J* = 14.3 and 3.8 Hz, 0.4H), 3.37 (m, 0.6H), 3.22 (m, 0.4H), 3.16 (m, 0.6H), 3.00-2.76 (m, 5H), 1.92 (m, 1H), 1.30 (m, 9H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 154.4, 154.3, 154.2, 153.9, 140.1, 138.2, 138.1, 129.9, 129.6, 129.0, 128.8, 128.5, 128.3, 126.8, 126.5, 106.5, 80.3, 47.5, 42.8, 41.6, 36.0, 33.3, 28.3, 28.2, 27.8, 22.5, 22.4; ESI-TOF high accuracy: expected mass 595.3391 (M^++1), found 595.3389.

(*S*)-*tert*-butyl-2-benzyl-4-[4-*iso*-butyl-6-(2-*iso*-propylphenyl)pyridazine-3-carbonyl]piperazine-1-carboxylate 21b: R_f = 0.33 (CH_2Cl_2/MeOH = 98:2);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 7.51-7.15 (m, 10H), 4.73 (d, *J* = 13.6 Hz, 1H), 4.98 (m, 0.7H), 4.40 (m, 0.3H), 4.05 (m, 1H), 3.66 (m, 0.7H), 3.55 (d, *J* = 3.9 Hz, 0.3H), 3.43-2.96 (m, 6H), 2.75 (m, 2H), 2.05 (m, 1H), 1.47 (s, 9H), 1.27-1.23 (m, 6H), 1.00-0.98 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 162.2, 155.4, 154.4, 147.2, 139.8, 135.9, 129.9, 129.8, 129.6, 129.3, 128.6, 128.4, 126.6, 126.2, 125.9, 80.4, 47.0, 41.8, 40.5, 36.0, 29.5, 29.0, 28.3, 28.2, 24.3, 24.2, 22.5, 22.4; ESI-TOF high accuracy: expected mass 557.3486 (M^++1), found 557.3482.

(*S*)-*tert*-butyl-4-(4-*iso*-butyl-6-(2-*iso*-propylphenyl)pyridazine-3-carbonyl)-2-*iso*-propylpiperazine-1-carboxylate 21c: R_f = 0.45 (CH_2Cl_2/MeOH = 95:5);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 7.49 (m, 3H), 7.42 (s, 1H), 7.34 (m, 2H), 4.96 (d, *J* = 13.1 Hz, 0.7H), 4.73 (d, *J* = 13.1 Hz, 0.3H), 4.02 (m, 2H), 3.62 (d, *J* = 13.1 Hz, 0.3H), 3.57 (br d, *J* = 11.0 Hz, 0.7H), 3.30 (dd, *J* = 13.6 and 3.9 Hz, 0.3H), 3.15 (m, 1.7H), 3.00 (m, 1H), 2.66 (m, 2H), 2.21 (m, 1H), 2.02 (m, 1H), 1.49 (m, 10H), 1.26-1.16 (m, 9H), 1.00-0.86 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 162.0, 155.4, 155.1, 154.7, 147.1, 139.6, 136.1, 136.0, 132.1, 131.9, 129.9, 129.8, 129.7, 129.2, 128.6, 128.5, 128.4, 128.1, 126.1, 125.8, 80.2, 47.3, 47.1, 43.0, 41.6, 40.5, 40.2, 29.6, 29.5, 28.9, 28.4, 28.3, 26.0, 25.7, 24.2, 24.1, 22.6, 22.4, 22.3, 20.4; ESI-TOF high accuracy: expected mass 509.3413 (M^++1), found 509.3480.

Suzuki coupling leading to esters 16a,b. General procedure. To a solution of **4** (1 equiv.) in dry DME (0.05 M solution), $Pd(PPh_3)_4$ (0.07 equiv.)was added and the mixture stirred for 15 min

under N_2 atmosphere. A solution of 2-(isopropyloxyphenyl)-boronic acid (1.1 equiv.) in a minimal amount of EtOH was added followed by a saturated aqueous $NaHCO_3$ solution (1/3 of the DME volume). The mixture was refluxed under nitrogen atmosphere for 2 h, cooled to room temperature, and extracted with DCM. The collected organic layers were anhydrified over magnesium sulfate, filtrated, the solvent removed under reduced pressure and the crude purified by flash chromatography.

Ethyl 4-*iso*-butyl-6-(2-phenoxyphenyl)pyridazine-3-carboxylate 16a: R_f = 0.42 (Hexane/AcOEt = 80:20);^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.5 and 1.5 Hz, 1H), 7.91 (s, 1H), 7.43 (m, 1H), 7.25 (m, 3H), 7.02 (m, 2H), 6.93 (m, 2H), 4.50 (q, *J* = 7.2 Hz, 2H), 2.71 (d, *J* = 7.2 Hz, 2H), 1.86 (m, 1H), 1.44 (t, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.3, 157.9, 156.7, 154.4, 151.2, 140.6, 131.7, 131.5, 129.9, 129.8, 128.2, 124.4, 123.3, 119.7, 118.0, 62.0, 40.9, 29.1, 22.2, 14.1; ESI (*m/z)* 377 [M^++1, (100)].

Ethyl 4-*iso*-butyl-6-(2-*iso*-propoxyphenyl)pyridazine-3-carboxylate 16b: R_f = 0.35 (Hexane/AcOEt = 70:30);^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.9 and 1.7 Hz, 1H), 8.00 (s, 1H), 7.43 (m, 1H), 7.11 (m, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 4.65 (septet, *J* = 6.1 Hz, 1H), 4.54 (q, *J* = 7.4 Hz, 2H), 2.81 (d, *J* = 7.0 Hz, 2H), 2.00 (m, 1H), 1.50 (t, *J* = 7.4 Hz, 3H), 1.31 (d, *J* = 6.1 Hz, 6H), 0.99 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 159.1, 155.6, 151.0, 140.0, 136.9, 132.6, 131.8, 131.3, 130.4, 126.2, 121.1, 120.9, 113.9, 112.3, 70.9, 62.0, 41.1, 29.4, 22.5, 22.1, 14.2; ESI (*m/z)* 365 [M^++Na, (6)], 343 [M^++1, (100)].

Suzuki coupling leading to carboxylic acid 20. A solution of **4** (172 mg, 0.71 mmol), 2-*iso*-propyl-phenylboronic acid (175 mg, 1.5 mmol), $Pd(PPh_3)_4$ (25 mg, 0.03 mmol), 2M aqueous Na_2CO_3 (0.750 mL, 2.1 mmol) in dry toluene (4.5 mL) was flushed with nitrogen for 5 minutes. The mixture was refluxed under nitrogen atmosphere over-night, cooled to room temperature, diluted with water and extracted with AcOEt. The collected organic layers were anhydrified over magnesium sulfate, filtrated, the solvent removed under reduced pressure and the crude purified by flash chromatography affording 116 mg of **20**.

4-*iso*-butyl-6-(2-*iso*-propylphenyl)pyridazine-3-carboxylic acid 20: ^{1}H NMR (300 MHz, CD_3OD) δ 7.64 (s, 1H), 7.45 (m, 2H), 7.29 (m, 1H), 7.22 (m, 1H), 3.07 (br s, 2H), 2.92 (m, 1H), 2.05 (m, 1H), 1.09 (d, *J* = 6.3 Hz, 6H), 0.92 (d, *J* = 6.3 HZ, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 148.2, 137.0, 135.9, 135.5, 133.2, 133.1, 130.9, 129.9, 129.8, 127.0, 126.9, 30.8, 30.6, 24.3, 22.8; ESI (*m/z)* 321 [M^++Na, (18)], 299 [M^++1, (100)].

Synthesis of bis-acylhydrazides 18a-d. General procedure. To a solution of ethyl ester (1 equiv.) in a 4:1 mixture of THF/H_2O (0.05 M solution) LiOH hydrate (1.2 equiv.) was added at 0 °C. After the hydrolysis is completed (TLC monitoring) the solution was acidified carefully with a

1N HCl aqueous solution, heated to room temperature and extracted with AcOEt. The collected organic layers were anhydrified over magnesium sulfate, filtrated and the solvent removed under reduced pressure leading to the free carboxylic acid that was used without any further purification. To a solution of the free carboxylic acid in dry dichloromethane (0.05 M solution) *N*-acylhydrazine (1.05 equiv.), EDCI (1.1 equiv.), HOBt (1.1 equiv.) and DIPEA (2 equiv.) were added at room temperature. The reaction was stirred over-night, the solvent evaporated under reduced pressure and the crude purified by flash chromatography.

4-*Iso*-butyl-*N*'-*iso*-butyryl-6-(2-phenoxyphenyl)pyridazine-3-carbohydrazide 18a: R_f = 0.47 (CH_2Cl_2/MeOH = 95:5);^{1}H NMR (600 MHz, $CDCl_3$) δ 10.33 (d, *J* = 4.9 Hz, 1H), 8.45 (d, *J* = 4.9 Hz, 1H), 8.14 (dd, *J* = 7.9 and 1.7 Hz, 1H), 7.95 (s, 1H), 7.48 (m, 1H), 7.32 (m, 3H), 7.07 (m, 2H), 6.95 (m, 2H), 2.98 (d, *J* = 7.0 Hz, 2H), 2.59 (m, 1H), 1.95 (m, 1H), 1.28 (d, *J* = 7.0 Hz, 6H), 0.88 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 161.0, 158.6, 156.7, 154.6, 148.5, 142.6, 131.8, 131.6, 131.2, 129.9, 128.0, 124.5, 123.5, 119.8, 118.2, 41.1, 33.8, 29.2, 22.3, 19.4; ESI (*m/z)* 455 [M^++Na, (3)], 433 [M^++1, (32)], 121 (100).

4-*Iso*-butyl-6-(2-phenoxyphenyl)-*N*'-(2-phenylacetyl)pyridazine-3-carbohydrazide 18b: R_f = 0.42 (CH_2Cl_2/MeOH = 95:5);^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.10 (dd, *J* = 7.9 and 1.7 Hz, 1H), 7.93 (s, 1H), 7.47 (m, 1H), 7.35 (m, 9H), 7.09 (m, 2H), 6.95 (m, 2H), 3.72 (s, 2H), 2.94 (d, *J* = 7.0 Hz, 2H), 1.91 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 161.4, 158.5, 156.7, 154.5, 148.6, 142.5, 133.8, 131.8, 131.5, 131.2, 129.9, 129.3, 128.9, 127.4, 127.3, 124.4, 123.5, 119.8, 118.1, 41.5, 40.9, 29.0, 22.3; ESI-TOF high accuracy: expected mass 481.2234 (M^++1), found 481.2227.

4-*Iso*-butyl-*N*'-*iso*-butyryl-6-(2-*iso*-propoxyphenyl)pyridazine-3-carbohydrazide 18c: R_f = 0.35 (CH_2Cl_2/MeOH = 95:5);^{1}H NMR (600 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.62 (s, 1H), 7.98 (dd, *J* = 7.4 and 1.3 Hz, 1H), 7.97 (s, 1H), 7.42 (m, 1H), 7.09 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 4.64 (septet, *J* = 6.1 Hz, 1H), 3.00 (d, *J* = 7.0 Hz, 2H), 2.58 (m, 1H), 2.05 (m, 1H), 1.30 (d, *J* = 6.1 Hz, 6H), 1.25 (d, *J* = 7.0 Hz, 6H), 0.97 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 161.5, 159.5, 155.7, 148.3, 141.9, 131.7, 131.6, 131.5, 125.8, 121.2, 113.9, 70.9, 41.3, 33.7, 29.4, 22.6, 22.1, 19.4; ESI-TOF high accuracy: expected mass 399.2391 (M^++1), found 399.2385.

4-*Iso*-butyl-6-(2-*iso*-propoxyphenyl)-N'-(2-phenylacetyl)pyridazine-3-carbohydrazide 18d: R_f = 0.35 (CH_2Cl_2/MeOH = 95:5);^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.96 (m, 1H), 7.30 (m, 8H), 7.09 (m, 2H), 4.64 (septet, *J* = 6.0 Hz, 1H), 3.71 (s, 2H), 2.97 (d, *J* = 6.9 Hz, 2H), 2.02 (m, 1H), 1.30 (d, *J* = 6.0 Hz, 6H), 0.95 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 168.3, 161.8, 155.6, 148.2, 141.9, 134.0, 131.7, 131.6, 129.4, 129.3, 128.9, 127.4, 127.3,

121.0, 113.8, 70.8, 41.8, 41.5, 41.2, 29.3, 22.6, 22.0; ESI-TOF high accuracy: expected mass 447.2391 (M^++1), found 447.2385.

Synthesis of scaffold 2a-d. General procedure: To a solution of bis-acylhydrazide (1 equiv.) in dry CH_3CN (0.1 M solution) $POCl_3$ (12 equiv.) was added drop-wise. The mixture was refluxed 12 h, cooled to room temperature, poured in ice, basified with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The collected organic layers were anhydrified over magnesium sulfate, filtrated, the solvent removed under reduced pressure and the crude purified by flash chromatography.

2-(4-*Iso*-butyl-6-(2-phenoxyphenyl)pyridazin-3-yl)-5-*iso*-propyl-1,3,4-oxadiazole 2a: R_f = 0.38 (Hexane/AcOEt = 70:30);^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 7.4 and 1.7 Hz, 1H), 8.03 (s, 1H), 7.67 (m, 1H), 7.30 (m, 3H), 7.06 (m, 2H), 6.96 (d, *J* = 7.4 Hz, 1H), 3.35 (septet, *J* = 7.0 Hz, 1H), 3.02 (d, *J* = 7.0 Hz, 2H), 1.96 (septet, *J* = 6.5 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 6H), 0.89 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 162.3, 157.4, 156.8, 154.7, 145.8, 141.3, 131.8, 131.7, 129.9, 128.1, 124.5, 123.5, 119.9, 118.2, 41.5, 28.5, 26.5, 22.2, 20.0; ESI-TOF high accuracy: expected mass 415.2128 (M^++1), found 415.2123.

2-Benzyl-5-(4-*iso*-butyl-6-(2-phenoxyphenyl)pyridazin-3-yl)-1,3,4-oxadiazole 2b: R_f = 0.65 (Hexane/AcOEt = 60:40);^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.4 Hz, 1H), 8.04 (s, 1H), 7.49 (m, 1H), 7.44-7.29 (m, 8H), 7.08 (m, 2H), 6.98 (m, 2H), 4.38 (m, 2H), 3.02 (d, *J* = 7.0 Hz, 2H), 1.96 (septet, *J* = 6.6 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 162.8, 157.5, 156.8, 154.7, 145.6, 141.4, 133.6, 131.8, 131.7, 129.9, 129.8, 129.0, 128.9, 128.8, 127.6, 124.5, 123.5, 119.9, 118.2, 41.1, 31.9, 31.8, 29.7, 28.4, 22.2; ESI-TOF high accuracy: expected mass 463.2128 (M^++1), found 463.2117.

2-(4-*Iso*-butyl-6-(2-*iso*-propoxyphenyl)pyridazin-3-yl)-5-*iso*-propyl-1,3,4-oxadiazole 2c: R_f = 0.33 (Hexane/AcOEt = 70:30);^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, *J* = 1.7 Hz, 1H), 8.13 (d, *J* = 1.7 Hz, 1H), 8.12 (s, 1H), 7.47 (m, 1H), 7.15 (m, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 4.70 (septet, *J* = 7.0 Hz, 1H), 3.38 (septet, *J* = 6.2 Hz, 1H), 3.10 (d, *J* = 7.0 Hz, 2H), 2.11 (m, 1H), 1.55 (d, *J* = 7.0 Hz, 6H), 1.36 (d, *J* = 6.2 Hz, 6H), 1.03 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 162.5, 158.4, 155.9, 145.4, 140.7, 131.8, 131.5, 130.4, 125.9, 121.2, 113.9, 70.9, 41.7, 28.7, 26.5, 22.5, 22.1, 20.1; ESI-TOF high accuracy: expected mass 381.2285 (M^++1), found 381.2280.

2-Benzyl-5-(4-*iso*-butyl-6-(2-*iso*-propoxyphenyl)pyridazin-3-yl)-1,3,4-oxadiazole 2d: R_f = 0.35 (Hexane/AcOEt = 70:30);^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.4 and 1.7 Hz, 1H), 8.08 (s, 1H), 7.43 (m, 3H), 7.36 (m, 2H), 7.29 (m, 1H), 7.11 (m, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 4.67 (septet, *J* = 5.7 Hz, 1H), 4.36 (s, 2H), 3.05 (d, *J* = 7.4 Hz, 2H), 2.06 (m, 1H), 1.32 (d, *J* = 5.7 Hz, 6H), 0.98 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 163.0, 158.5, 155.9, 145.3,

140.7, 133.6, 131.8, 131.6, 130.4, 129.1, 129.0, 127.6, 125.4, 121.2, 113.9, 70.9, 41.6, 31.9, 28.7, 22.5, 22.1; ESI-TOF high accuracy: expected mass 429.2276 (M^++1), found 429.2276.

Synthesis of acetylated scaffolds 1a-d, 14a-c, 22a,b. General procedure: A solution of *N*-Boc protected α-helix mimic compound (1 equiv.) in a 10% solution of TFA in dry DCM (0.05M solution) was stirred for 1 h at room temperature. The solution was basified with saturated aqueous $NaHCO_3$ and extracted with DCM. The collected organic layers were anhydrified over magnesium sulfate, filtrated and the solvent removed under reduced pressure. The so obtained free amine was dissolved in dry CH_3CN (0.01M solution) and dry TEA (1.5 equiv.) followed by AcCl (1 equiv.) were added at rt. After the reaction was completed (TLC monitoring) the solvent was removed under reduced pressure and the crude purified by flash chromatography.

(*S*)-1-(2-*iso*-butyl-4-(5-*iso*-butyl-6-(3-*iso*-butyl-1*H*-pyrazol-5-yl)pyridazine-3-carbonyl)piperazin-1-yl)ethanone 1a: R_f = 0.18 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 10.77 (br s, 1H), 7.77 (s, 1H), 7.73 (s, 0.4H), 6.81 (s, 0.6H), 6.80 (s, 0.4H), 5.00 (m, 0.2H), 4.70 (m, 1.4H), 4.49 (m, 1H), 4.33 (d, *J* = 13.9 Hz, 0.3H), 4.13 (m, 0.2H), 4.04 (m, 0.3H), 3.84 (m, 0.2H), 3.72-3.49 (m, 1.4H), 3.18 (m, 1H), 3.04-2.90 (m, 3H), 2.63 (d, *J* = 6.6 Hz, 2H), 2.20-2.14 (four s, 3H), 2.02 (m, 2H), 1.88-1.24 (m, 3H), 1.00-0.83 (m, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 169.0, 166.3, 165.9, 165.6, 153.9, 153.8, 153.7, 140.4, 140.3, 140.1, 130.0, 129.8, 129.7, 129.6, 106.2, 106.1, 60.0, 52.9, 50.4, 47.8, 47.5, 47.2, 47.0, 45.8, 45.4, 42.9, 42.3, 41.6, 41.1, 38.6, 37.8, 37.7, 37.0, 36.7, 28.9, 28.8, 28.0, 27.9, 25.0, 24.8, 24.7, 23.4, 22.9, 22.8, 22.7, 22.5, 22.4, 22.3, 22.2, 21.9, 21.8, 21.4; ESI-TOF high accuracy: expected mass 468.3213 (M^++1), found 468.3216.

(*S*)-1-(4-(6-(3-benzyl-1*H*-pyrazol-5-yl)-5-*iso*-butylpyridazine-3-carbonyl)-2-*iso*-butylpiperazin-1-yl)ethanone 1b: R_f = 0.12 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 7.77 (s, 0.5H), 7.72 (s, 0.5H), 7.38-7.28 (m, 5H), 6.77 (br s, 1H), 5.02 (m, 0.3H), 4.80-4.63 (m, 1.5H), 4.53 (m, 0.8H), 4.42 (m, 0.3H), 4.30 (m, 0.3H), 4.14 (s, 2H), 4.04 (m, 0.3H), 3.84 (m, 0.2H), 3.72 (m, 0.6H), 3.63 (m, 0.3H), 3.50 (m, 0.7H), 3.19 (m, 1H), 3.08-2.81 (m, 2.7H)), 2.20-2.14 (four s, 3H), 2.00 (m, 1H), 1.80-1.24 (m, 3H), 1.00-0.83 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 168.9, 165.7, 165.6, 165.5, 154.0, 153.9, 153.8, 140.1, 140.0, 138.1, 130.1, 129.9, 129.8, 129.7, 128.8, 126.8, 106.5, 52.9, 52.7, 50.4, 49.9, 47.8, 47.5, 47.2, 47.0, 45.9, 45.4, 42.9, 42.3, 41.6, 41.1, 38.6, 37.8, 36.9, 33.4, 33.3, 27.8, 24.9, 24.8, 24.7, 23.4, 22.9, 22.8, 22.7, 22.6, 22.45, 22.41, 22.3, 21.9, 21.8, 21.4; ESI-TOF high accuracy: expected mass 525.2948 (M^++Na), found 525.2947.

(*S*)-1-(2-benzyl-4-(5-*iso*-butyl-6-(3-*iso*-butyl-1*H*-pyrazol-5-yl)pyridazine-3-carbonyl)piperazin-1-yl)ethanone 1c: R_f = 0.15 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture of

conformers δ 10.78 (br s, 1H), 7.86-7.79 (three s, 1H), 7.34-7.19 (m, 4H), 7.05-6.99 (m, 1H), 6.83-6.78 (three s, 1H), 5.05 (m, 0.3H), 4.91 (m, 0.2H), 4.83 (m, 0.6H), 4.75 (m, 0.6H), 4.66 (m, 0.6H), 4.57 (m, 0.6H), 4.39 (m, 0.2H), 4.14 (m, 0.8H), 3.93 (m, 0.2H), 3.80 (m, 0.4H), 3.67 (m, 0.3H), 3.56 (m, 0.6H), 3.37 (m, 0.4H), 3.23-2.80 (m, 5.2H), 2.65 (d, J = 6.6 Hz, 2H), 2.19-2.06 (three s, 3H), 2.02 (m, 2H), 1.02-0.95 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.6, 169.4, 160.0, 165.8, 153.9, 153.8, 140.4, 140.3, 137.6, 137.4, 130.0, 129.8, 129.7, 129.3, 128.9, 128.8, 128.7, 128.4, 128.3, 127.0, 126.6, 126.5, 106.2, 56.9, 56.6, 51.05, 50.3, 50.01, 47.6, 47.55, 47.51, 45.5, 43.7, 42.9, 42.8, 41.6, 37.1, 36.4, 35.7, 35.6, 28.8, 28.0, 22.5, 22.4, 21.8, 20.9; ESI-TOF high accuracy: expected mass 468.3213 (M^++1), found 468.3216.

(*S*)-1-(2-benzyl-4-(6-(3-benzyl-1*H*-pyrazol-5-yl)-5-*iso*-butylpyridazine-3-carbonyl)piperazin-1-yl)ethanone 1d: R_f = 0.16 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 10.64 (br s, 1H), 7.84-7.77 (three s, 1H), 7.37-7.19 (m, 9H), 7.05-6.99 (m, 1H), 6.79-6.74 (three s, 1H), 5.05 (m, 0.2H), 4.91 (m, 0.1H), 4.83 (m, 0.5H), 4.77-4.64 (m, 1.2H), 4.58-4.46 (m, 0.7H), 4.35 (m, 0.1H), 4.15 (s, 2H), 3.99 (m, 0.2H), 3.80 (m, 0.4H), 3.69 (m, 0.2H), 3.57 (m, 0.5H), 3.36 (m, 0.3H), 3.25-2.78 (m, 6.6H), 2.11-2.07 (two s, 3H), 2.03 (m, 1H), 0.97-0.94 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 169.3, 165.9, 153.9, 137.4, 137.2, 130.1, 129.9, 129.7, 129.4, 129.0, 128.9, 128.8, 128.7, 128.5, 128.3, 127.0, 126.9, 126.6, 126.5, 106.5, 60.4, 56.9, 56.6, 51.0, 50.6, 48.2, 47.6, 47.5, 45.6, 43.7, 42.9, 42.8, 41.7, 41.6, 37.1, 36.4, 36.1, 35.9, 35.5, 34.8, 33.3, 29.7, 27.8, 22.5, 22.4, 22.3, 21.8, 21.7, 21.1, 20.9, 20.7, 14.2; ESI-TOF high accuracy: expected mass 537.2972 (M^++1), found 537.2980.

(*S*)-1-(2-*iso*-butyl-4-(5-*iso*-butyl-6-(6-*iso*-butylpyrimidin-4-yl)pyridazine-3-carbonyl)piperazin-1-yl)ethanone 14a: R_f = 0.21 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 9.21 (s, 1H), 7.98-7.93 (four s, 1H), 7.87-7.82 (three s, 1H), 5.03 (m, 0.3H), 4.83-4.66 (m, 1.4H), 4.56 (m, 0.3H), 4.44 (m, 0.4H), 4.37 (m, 0.3H), 4.24 (m, 0.3H), 4.06 (m, 0.3H), 3.87 (m, 0.2H), 3.74 (m, 0.5H), 3.62 (m, 0.3H), 3.50 (m, 0.7H), 3.23 (m, 1H), 3.04 (m, 3H), 2.79 (m, 2H), 2.27 (m, 1H), 2.21-2.14 (four s, 3H), 1.82 (m, 0.3H), 1.73 (m, 0.5H), 1.60 (m, 0.2H), 1.52 (m, 1H), 1.31 (m, 1H), 1.02-0.87 (m, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 169.1, 169.0, 168.9, 166.0, 165.6, 165.3, 162.6, 158.4, 158.3, 157.7, 155.6, 155.4, 143.1, 142.9, 130.4, 130.2, 130.0, 121.0, 120.9, 52.9, 52.8, 50.4, 50.3, 47.8, 47.5, 47.3, 47.2, 46.9, 45.9, 45.4, 42.9, 42.8, 42.2, 41.1, 41.0, 40.9, 38.6, 37.8, 37.7, 36.9, 29.7, 29.2, 28.8, 28.7, 25.0, 24.8, 24.7, 23.4, 22.9, 22.8, 22.7, 22.5, 22.4, 22.3, 22.2, 21.9, 21.8, 21.4; ESI-TOF high accuracy: expected mass 481.3285 (M^++1), found 481.3278.

(*S*)-1-(2-benzyl-4-(5-*iso*-butyl-6-(6-*iso*-butylpyrimidin-4-yl)pyridazine-3-carbonyl)piperazin-1-yl)ethanone 14b: R_f = 0.14 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture

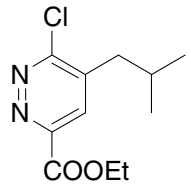
of conformers δ 9.28 (s, 1H), 7.93-7.88 (six s, 2H), 7.36-7.00 (m, 5H), 5.06 (m, 0.2H), 4.93 (m, 0.2H), 4.85 (m, 0.5H), 4.77 (m, 0.3H), 4.66 (m, 0.7H), 4.48 (m, 0.5H), 4.31 (m, 0.2H), 4.15 (m, 0.3H), 4.01 (m, 0.2H), 3.83 (m, 0.3H), 3.70 (m, 0.2H), 3.58 (m, 0.4H), 3.39-2.95 (m, 4.5H), 2.94-2.82 (m, 0.5H), 2.79 (d, *J* = 7.5 Hz, 2H), 2.28 (m, 1H), 2.13 (s, 0.4H), 2.12 (s, 0.6H), 1.92 (m, 1H), 1.82 (s, 1H), 1.64 (br s, 3H), 1.03 (d, *J* = 6.7 Hz, 6H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 165.7, 162.6, 158.5, 157.8, 143.1, 137.4, 130.5, 130.3, 129.7, 129.4, 129.0, 128.9, 128.8, 128.5, 128.3, 127.1, 126.6, 126.5, 121.0, 104.6, 57.3, 56.9, 51.4, 50.8, 50.7, 48.5, 47.95, 47.91, 47.7, 45.9, 44.1, 43.2, 43.1, 42.0, 41.4, 41.3, 37.4, 36.8, 36.4, 36.2, 35.9, 30.1, 29.6, 29.3, 29.2, 29.1, 26.6, 22.9, 22.87, 22.86, 22.81, 22.7, 22.68, 22.66, 22.3, 21.4, 21.1; ESI-TOF high accuracy: expected mass 515.3129 (M^++1), found 515.3125.

(*S*)-1-(4-(5-*iso*-butyl-6-(6-*iso*-butylpyrimidin-4-yl)pyridazine-3-carbonyl)-2-*iso*-propylpiperazin-1-yl)ethanone 14c: R_f = 0.20 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 9.26 (s, 1H), 7.98 (s, 0.7H), 7.94 (s, 0.3H), 7.86-7.81 (four s, 1H), 5.03 (d, *J* = 13.6 Hz, 0.4H), 4.96 (d, *J* = 13.6 Hz, 0.3H), 4.78 (m, 0.5H), 4.57 (m, 0.4H), 4.43 (m, 0.5H), 4.33 (m, 0.5H), 3.78 (m, 0.2H), 3.64 (m, 0.6H), 3.55 (m, 0.4H), 3.43 (m, 0.5H), 3.33 (m, 0.2H), 3.22 (m, 0.7H), 3.09-2.96 (m, 3.4H), 2.79 (m, 2H), 2.26 (m, 1H), 2.20-2.15 (three s, 3H), 1.89 (m, 1H), 1.28 (m, 1H), 1.19-0.70 (m, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 169.4, 169.1, 165.5, 165.2, 162.6, 158.3, 157.7, 155.5, 143.1, 143.0, 130.4, 130.2, 130.0, 121.0, 120.0, 61.7, 61.1, 55.4, 54.9, 48.8, 48.4, 48.2, 47.9, 47.6, 44.7, 44.4, 43.2, 43.0, 42.9, 42.0, 41.35, 41.31, 37.4, 36.6, 29.6, 29.58, 29.57, 29.2, 29.1, 26.6, 26.4, 26.0, 25.8, 22.9, 22.86, 22.84, 22.78, 22.70, 22.65, 22.63, 22.61, 22.2, 22.1, 22.0, 20.9, 20.6, 20.5, 20.1, 19.3, 18.9, 18.7; ESI-TOF high accuracy: expected mass 467.3129 (M^++1), found 467.3135.

(*S*)-1-(2-benzyl-4-(4-*iso*-butyl-6-(2-*iso*-propylphenyl)pyridazine-3-carbonyl)piperazin-1-yl)ethanone 22b: R_f = 0.27 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 7.52-7.27 (m, 10H), 5.08 (m, 0.4H), 4.95-4.72 (m, 1H), 4.60 (m, 0.4H), 4.16 (m, 0.4H), 4.00 (m, 0.2H), 3.74 (m, 1H), 3.64-3.49 (m, 0.6H), 3.36-3.09 (m, 4H), 2.98-2.55 (m, 3H), 2.06 (m, 2H), 1.87-1.60 (m, 6H), 1.00-0.98 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 169.5, 166.4, 166.2, 162.3, 155.1, 155.0, 147.1, 139.8, 139.7, 137.4, 137.3, 135.9, 132.1, 132.0, 129.9, 129.88, 129.81, 129.7, 129.5, 129.4, 129.39, 129.36, 129.1, 128.9, 128.5, 128.4, 127.1, 126.6, 126.1, 125.9, 56.8, 50.9, 47.2, 47.0, 44.4, 42.8, 42.5, 40.4, 36.8, 36.4, 35.7, 29.5, 29.1, 24.2, 24.1, 22.5, 22.4, 22.2, 21.0; ESI-TOF high accuracy: expected mass 499.3067 (M^++1), found 499.3076.

(*S*)-1-(4-(4-*iso*-butyl-6-(2-*iso*-propylphenyl)pyridazine-3-carbonyl)-2-*iso*-propylpiperazin-1-yl)ethanone 22c: R_f = 0.53 (AcOEt);^{1}H NMR (600 MHz, $CDCl_3$) mixture of conformers δ 7.50-7.34 (m, 5H), 5.08 (d, *J* = 13.6 Hz, 0.3H), 5.01 (d, *J* = 13.6 Hz, 0.3H), 4.80 (m,

0.3H), 4.58 (m, 0.6H), 4.32 (m, 0.1H), 3.79-3.54 (m, 2H), 3.32-3.10 (m, 2H), 2.98 8m, 1.3H), 2.66 (m, 1.4H), 2.54 (m, 0.2H), 2.37 (m, 0.5H), 2.22 (m, 2H), 2.00 (m, 1H), 1.62 (s, 3H), 1.26-1.20 8m, 6H), 0.99-0.76 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.5, 166.5, 166.2, 162.6, 155.6, 155.3, 147.5, 140.4, 140.0, 136.5, 136.4, 132.6, 132.5, 132.3, 130.3, 130.2, 130.1, 129.8, 129.7, 129.1, 128.9, 128.8, 128.7, 126.5, 126.3, 61.7, 61.5, 55.4, 55.2, 47.9, 47.4, 43.8, 43.5, 42.7, 40.8, 37.0, 29.9, 29.5, 29.4, 16.6, 16.0, 24.6, 24.5, 24.4, 22.8, 22.7, 22.2, 22.0, 20.8, 20.6, 19.4, 19.0; ESI-TOF high accuracy: expected mass 450.2995 (M^++1), found 450.2991.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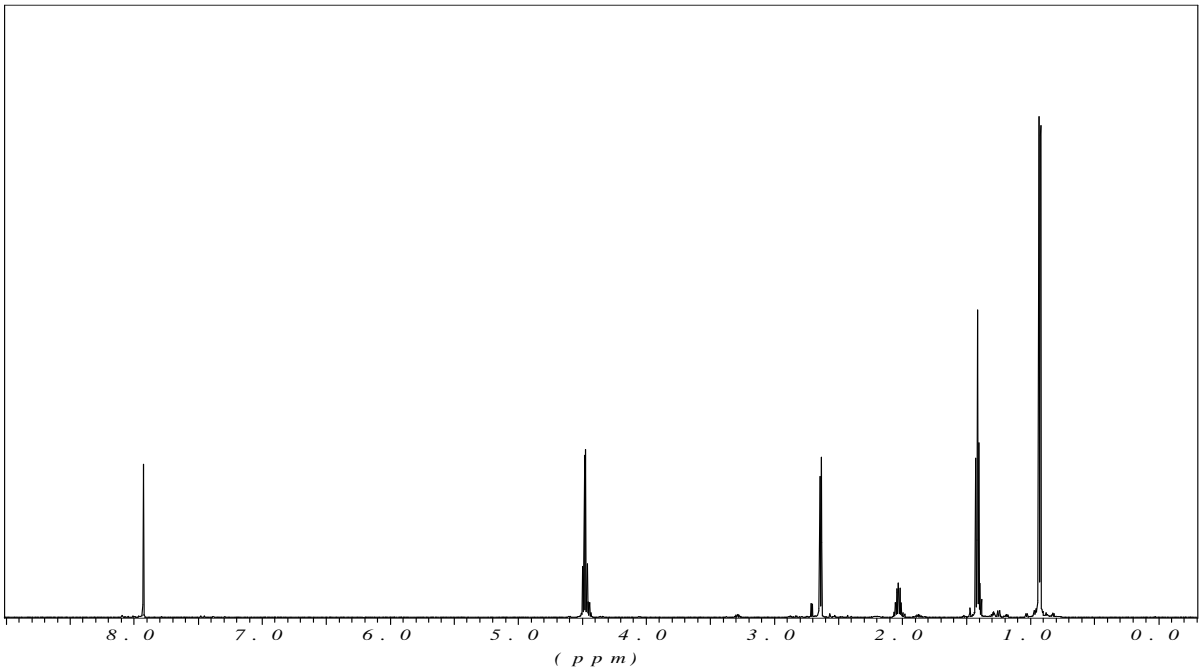
3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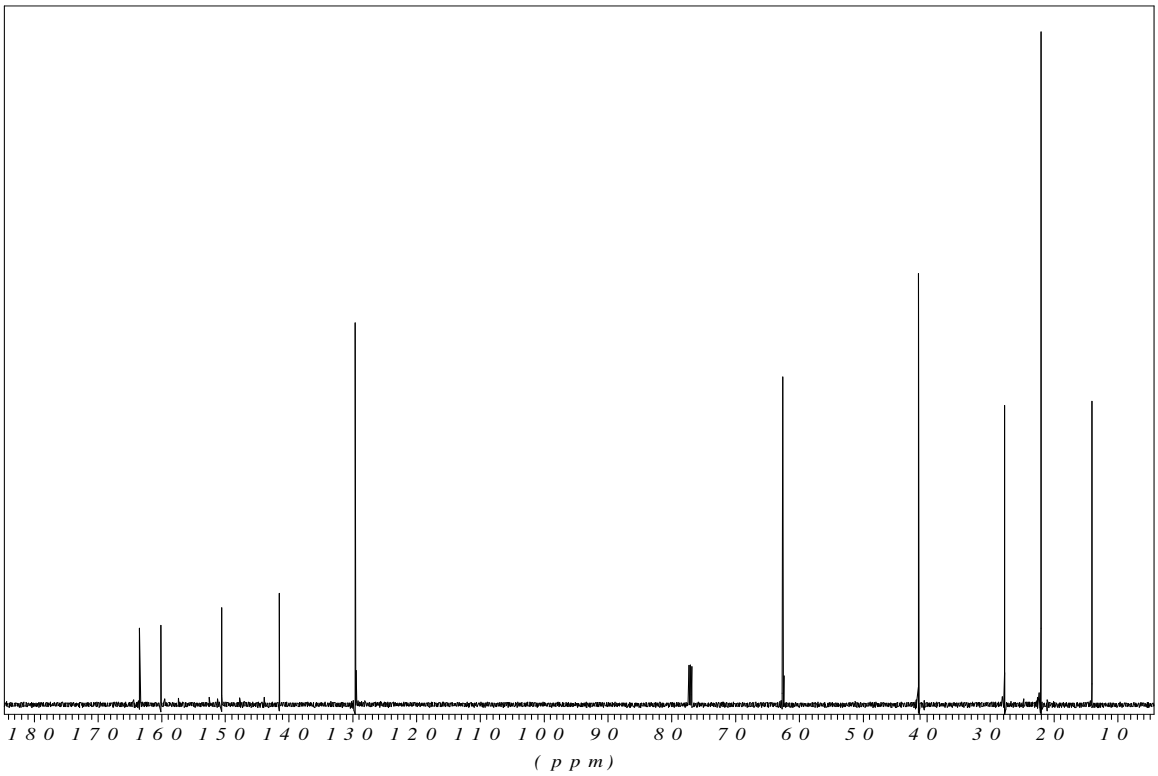
(ppm)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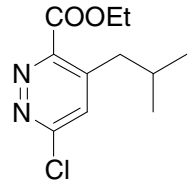
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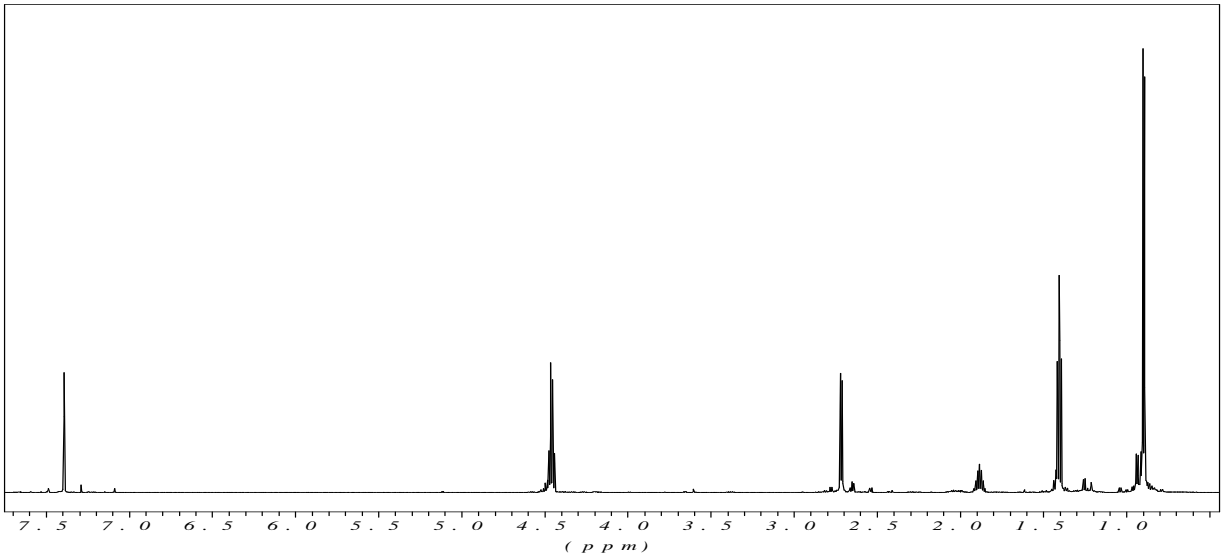
N
N
Cl

4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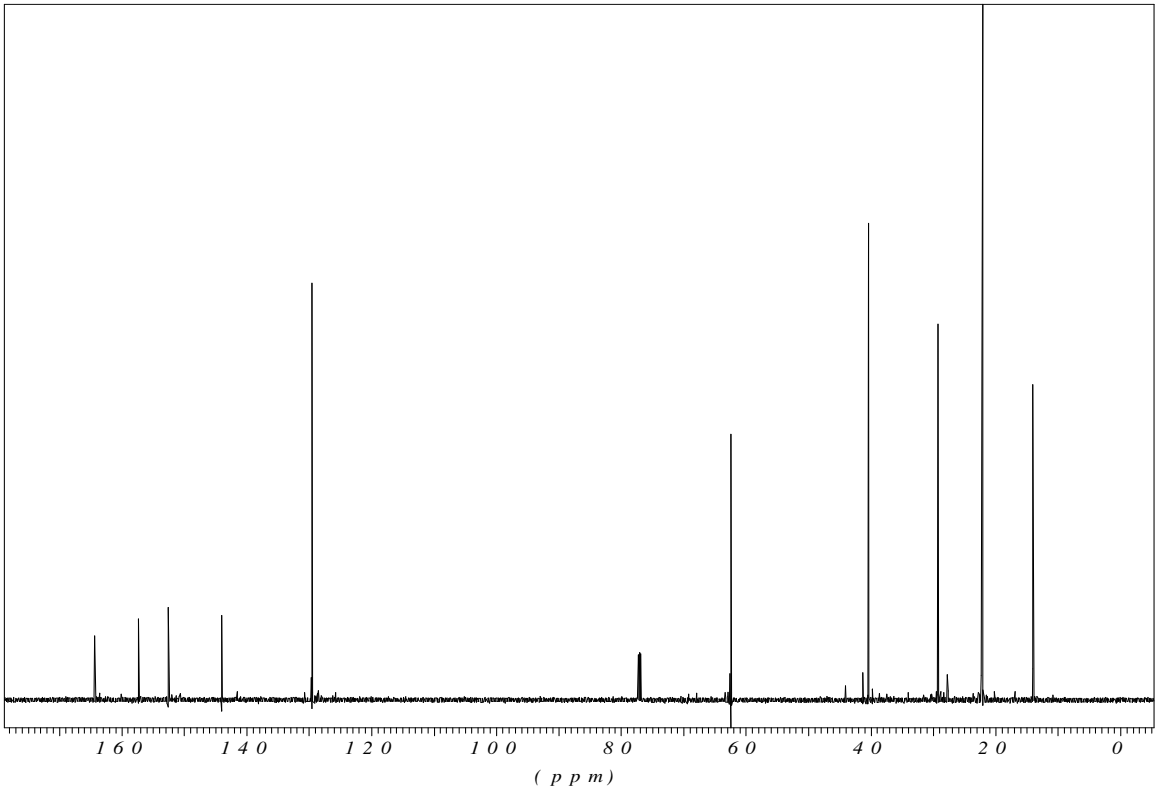
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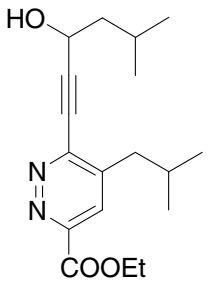
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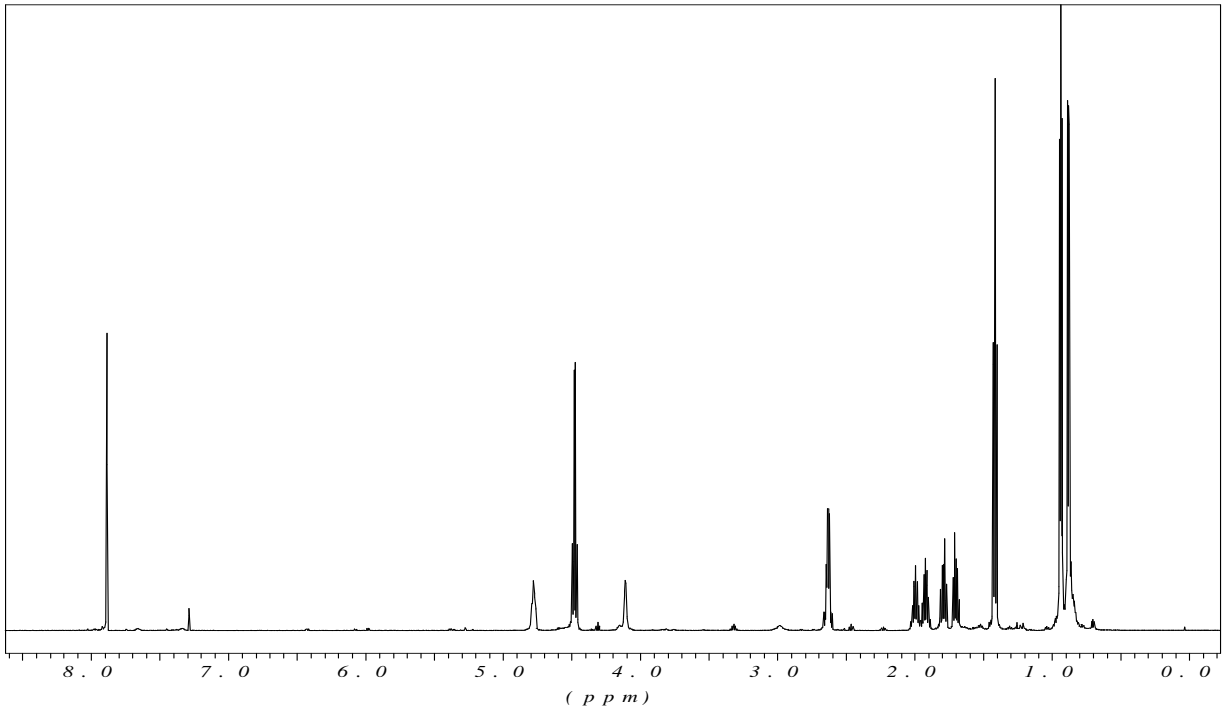
N
COOEt

8a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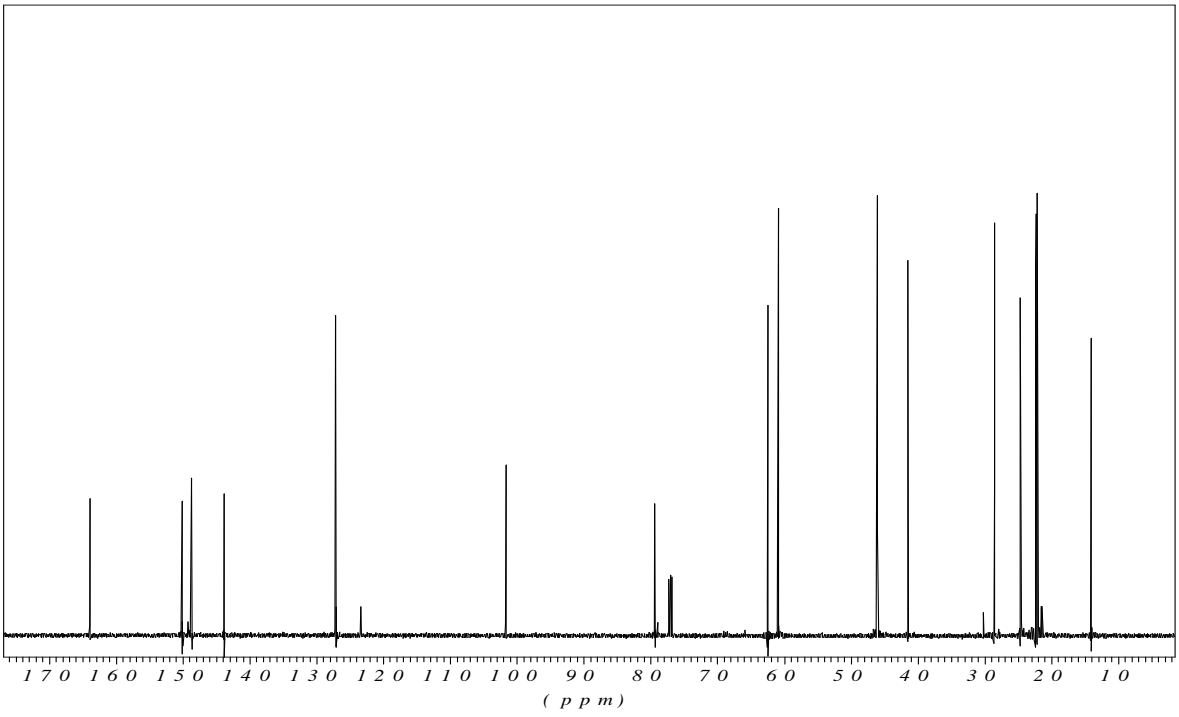
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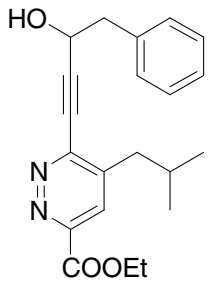
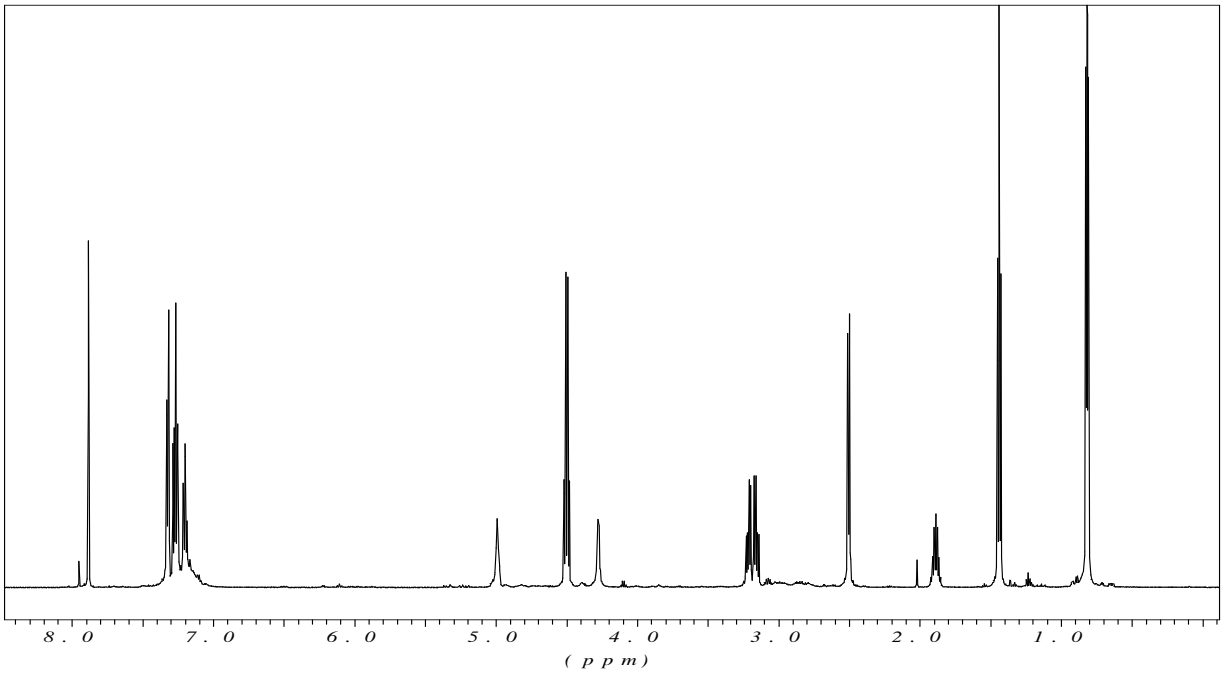

HO
N
N
COOEt

8b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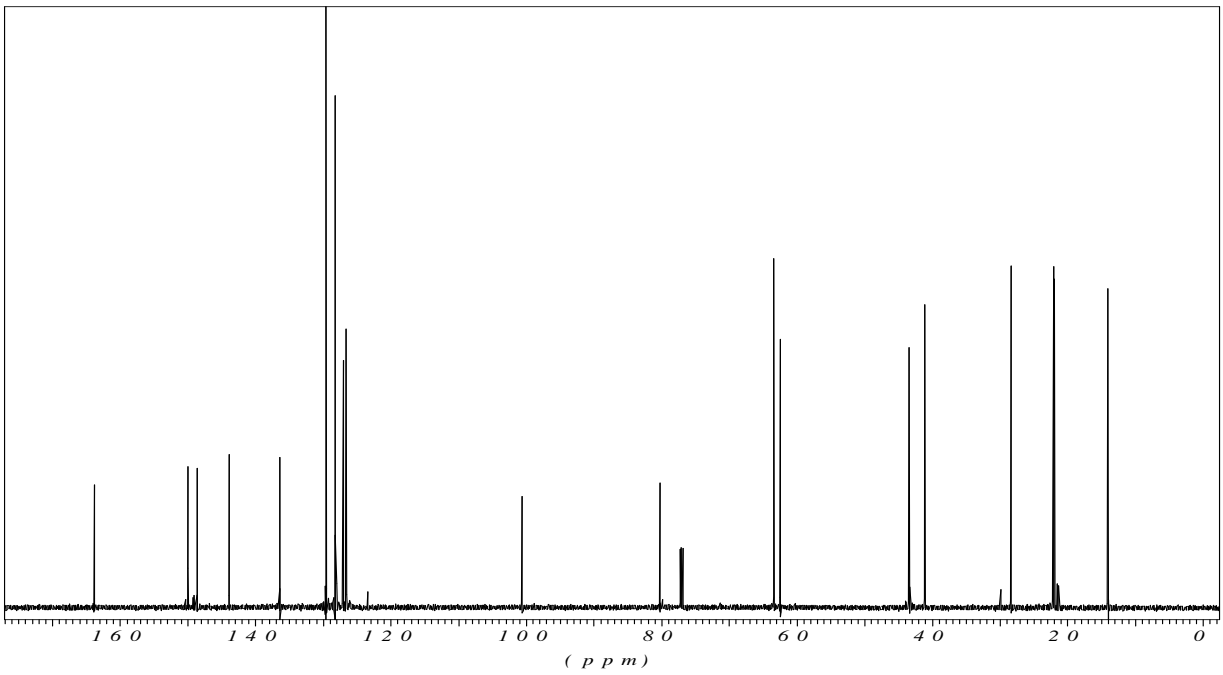
(ppm)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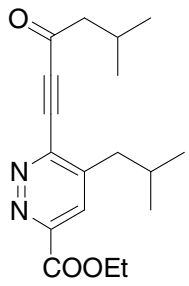
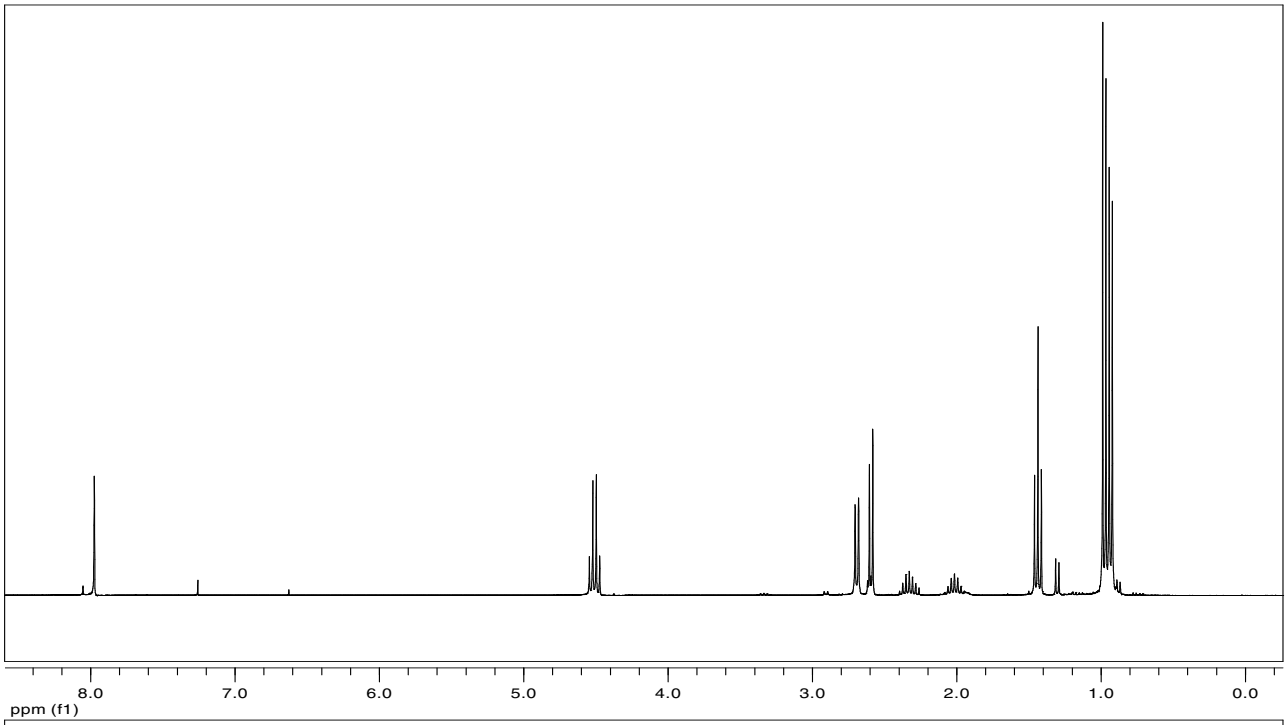
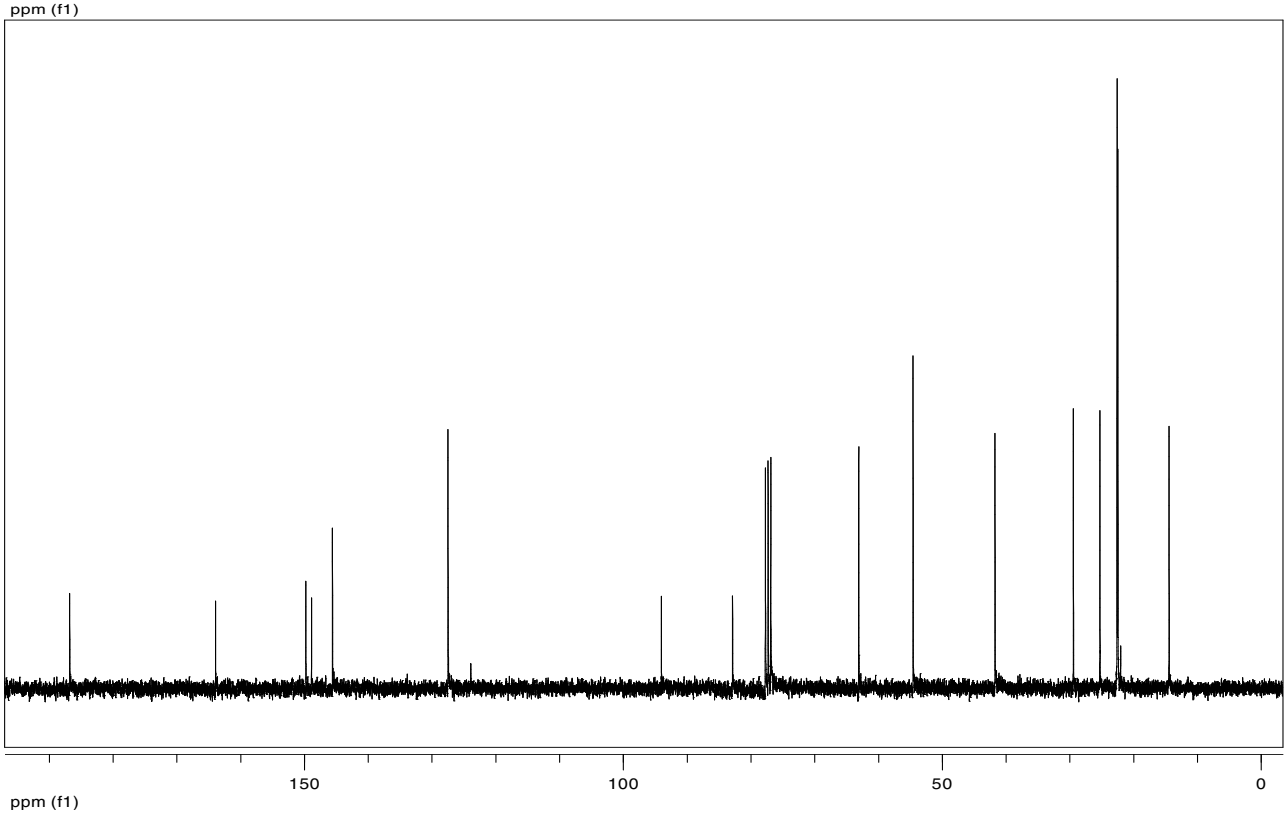
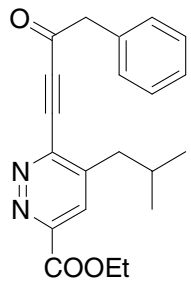


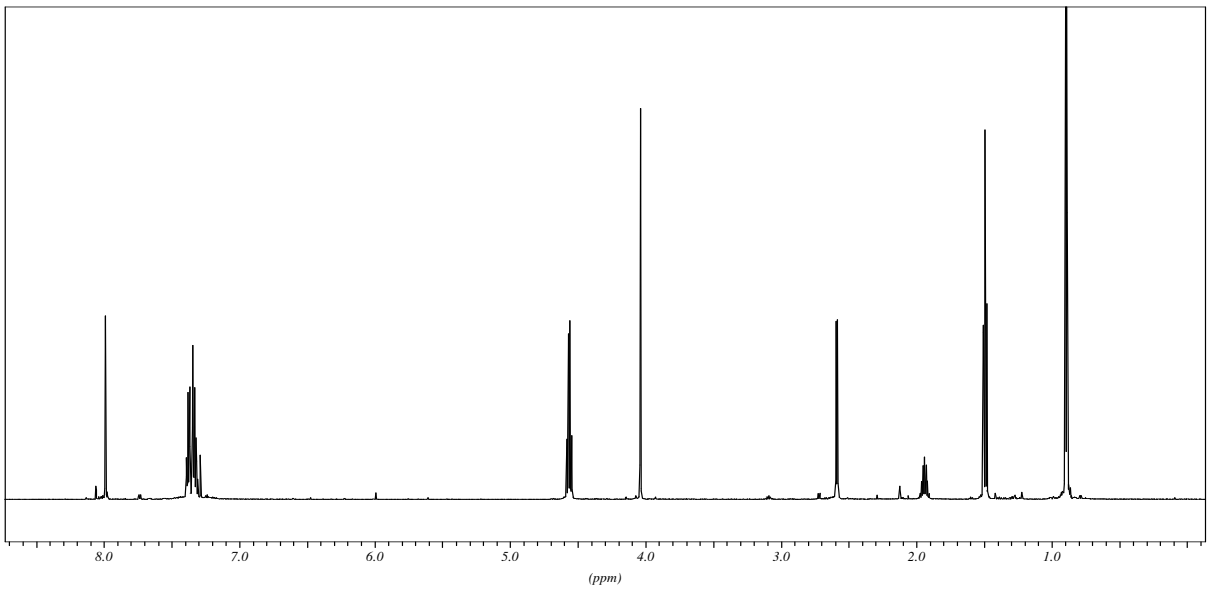
9a






O
N
N
COOEt

9b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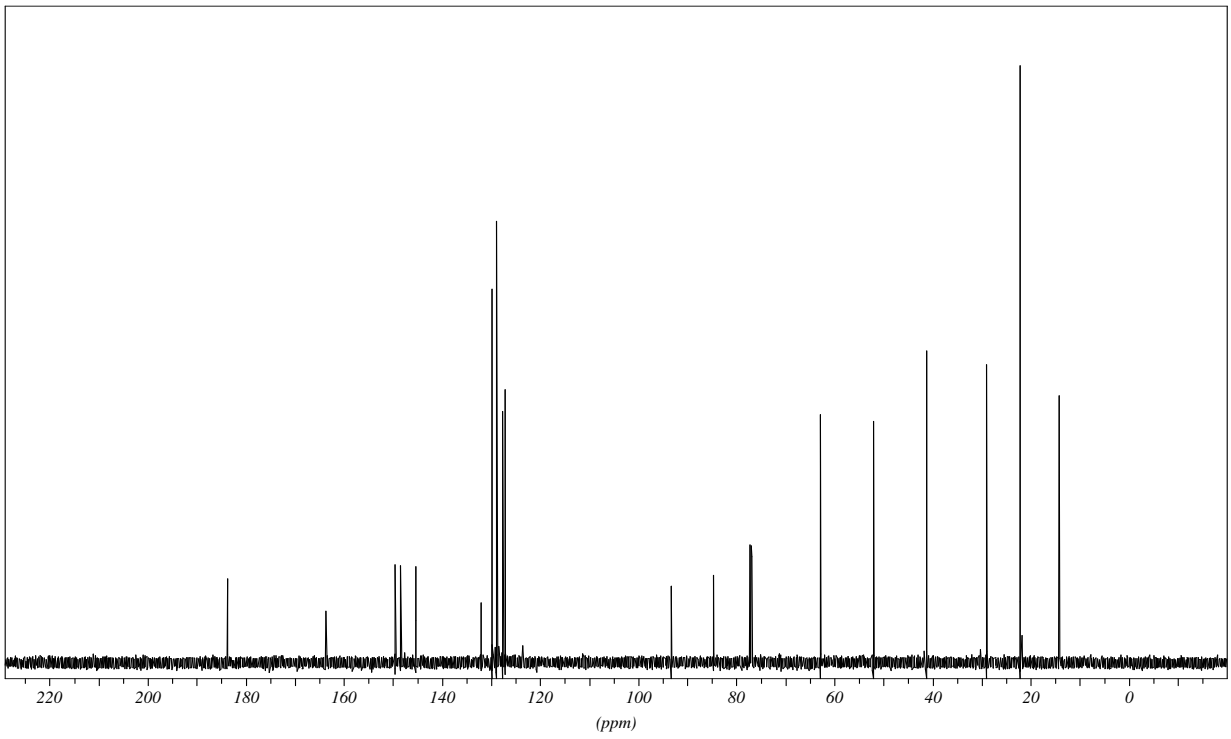
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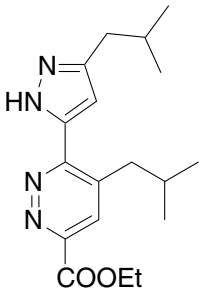
(ppm)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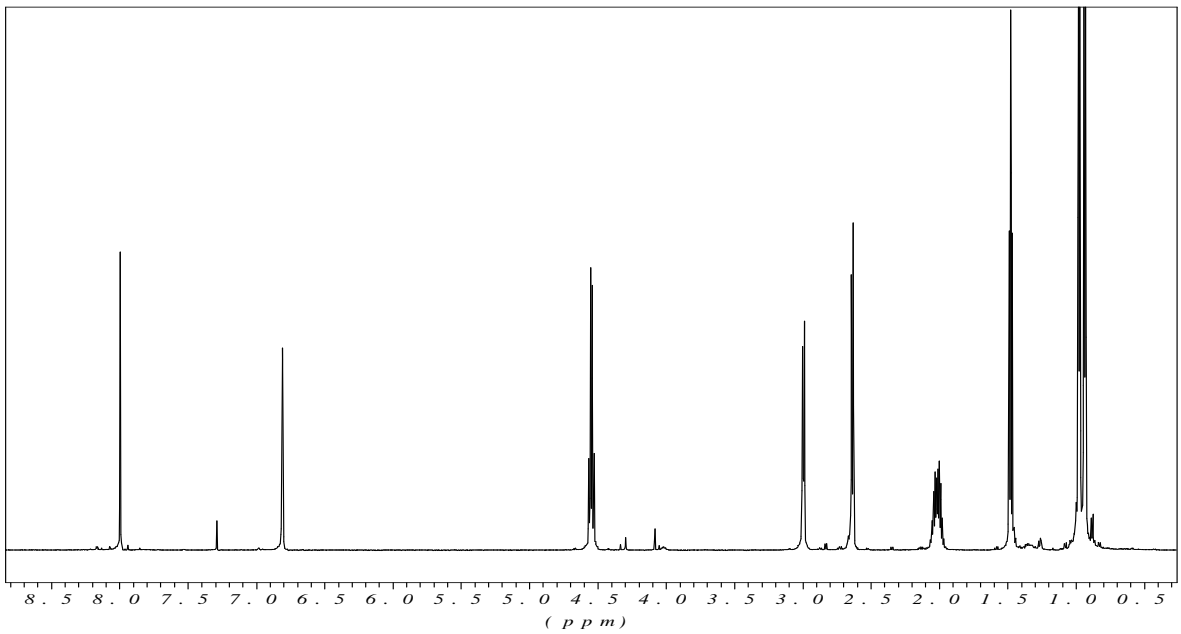
N
N
COOEt

10a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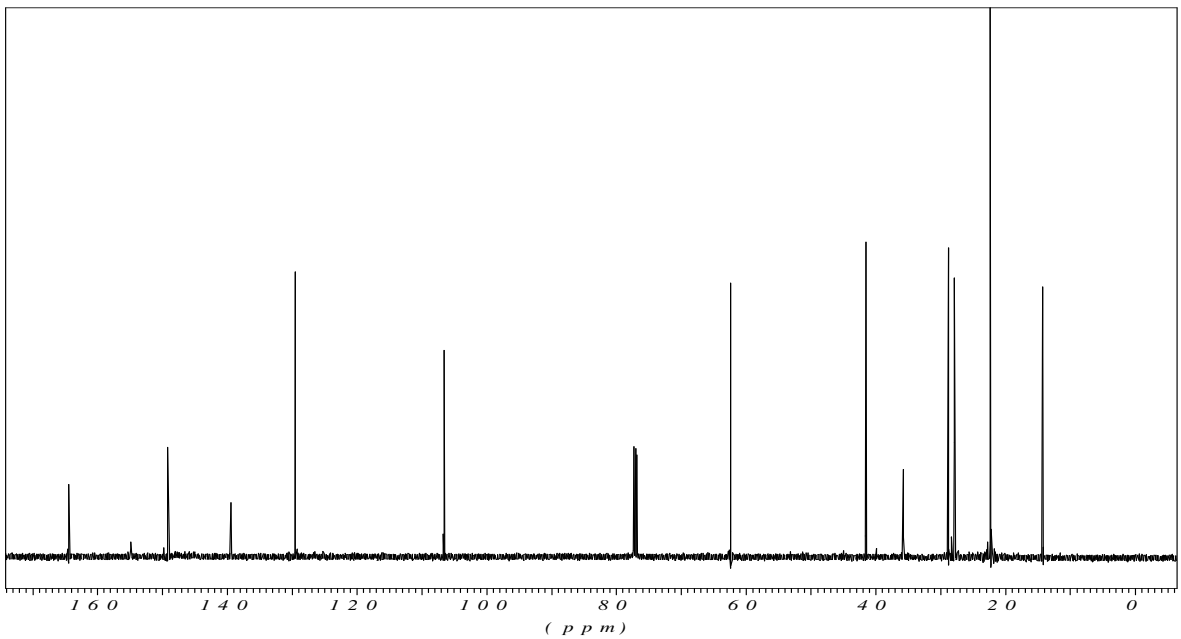
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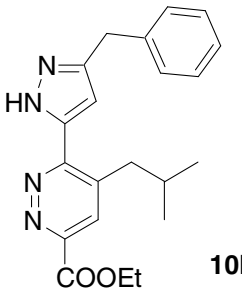
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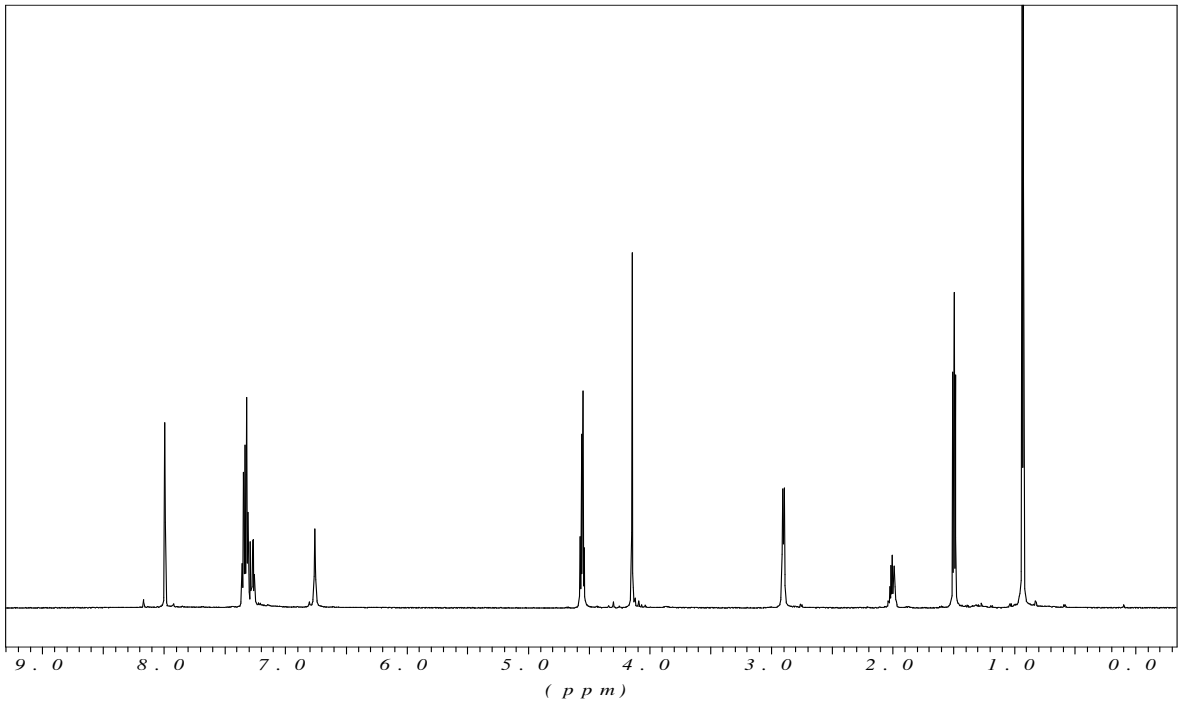
HN
N
N
COOEt

10b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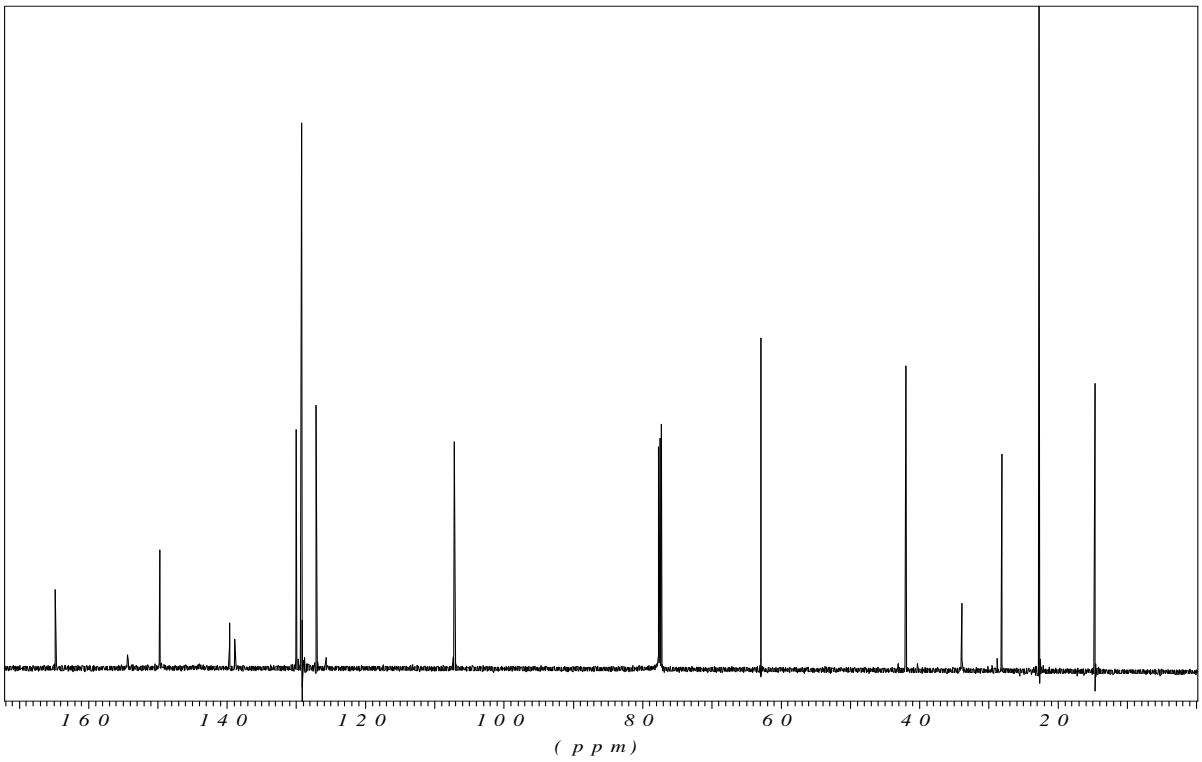
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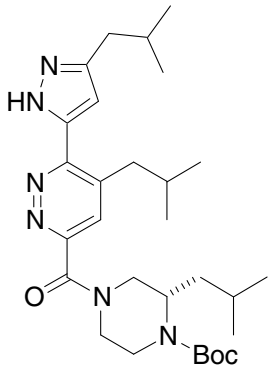
(ppm)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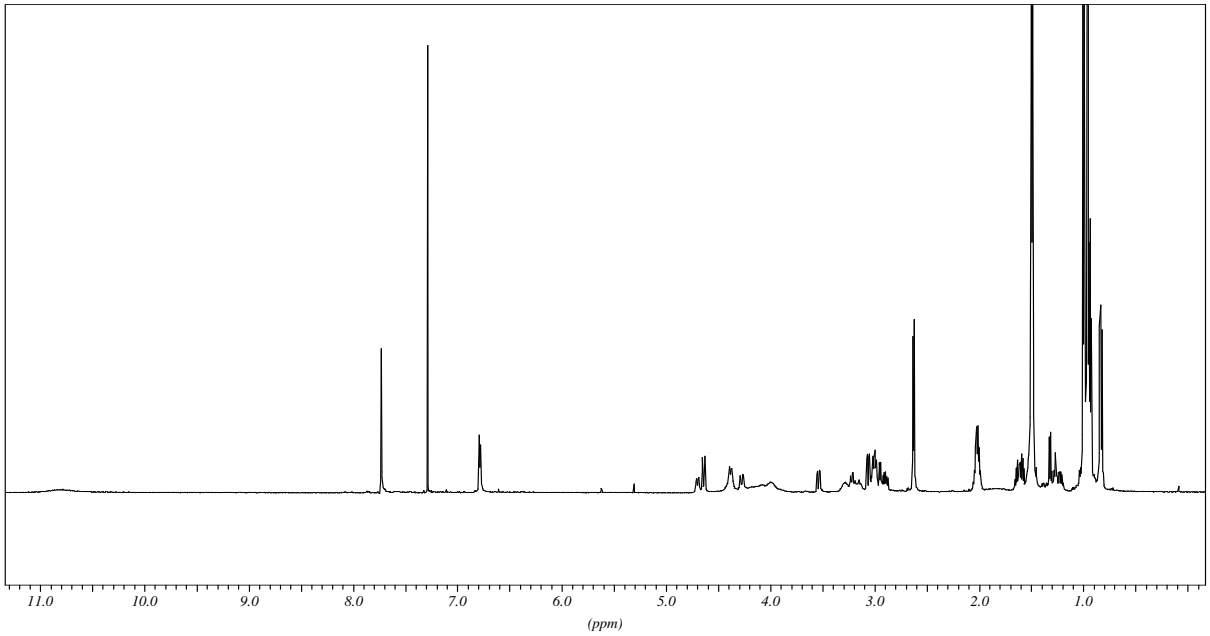
HN
N
N
O
N
N
Boc

12a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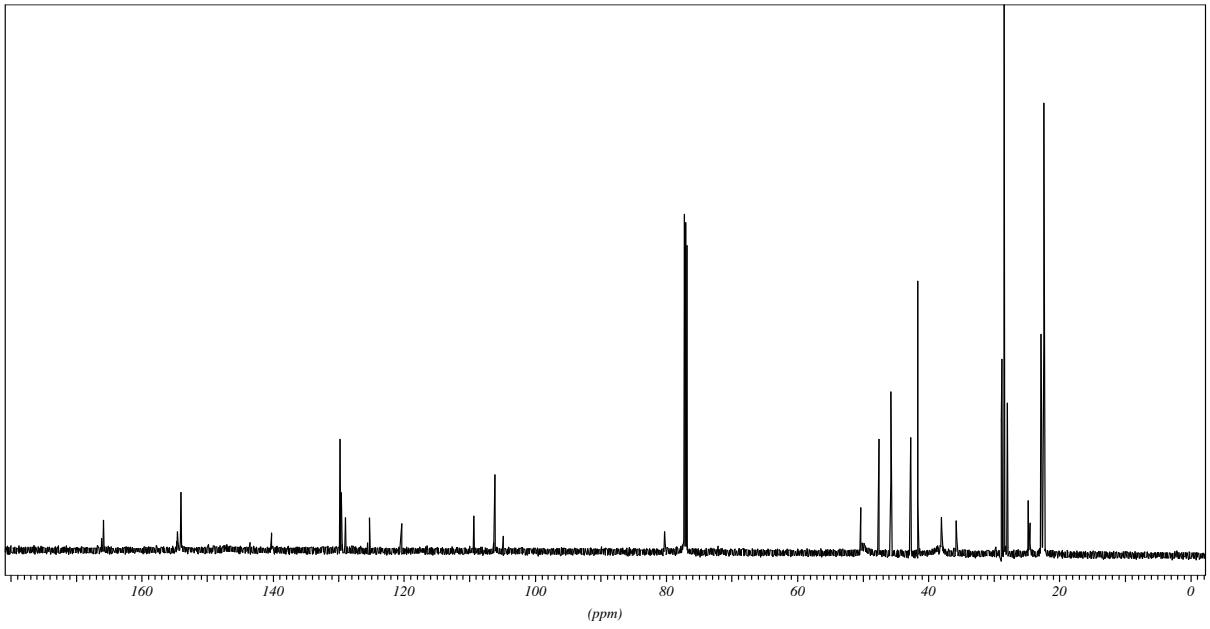
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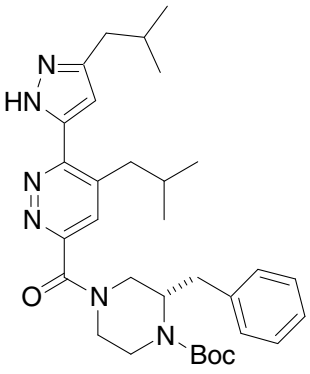
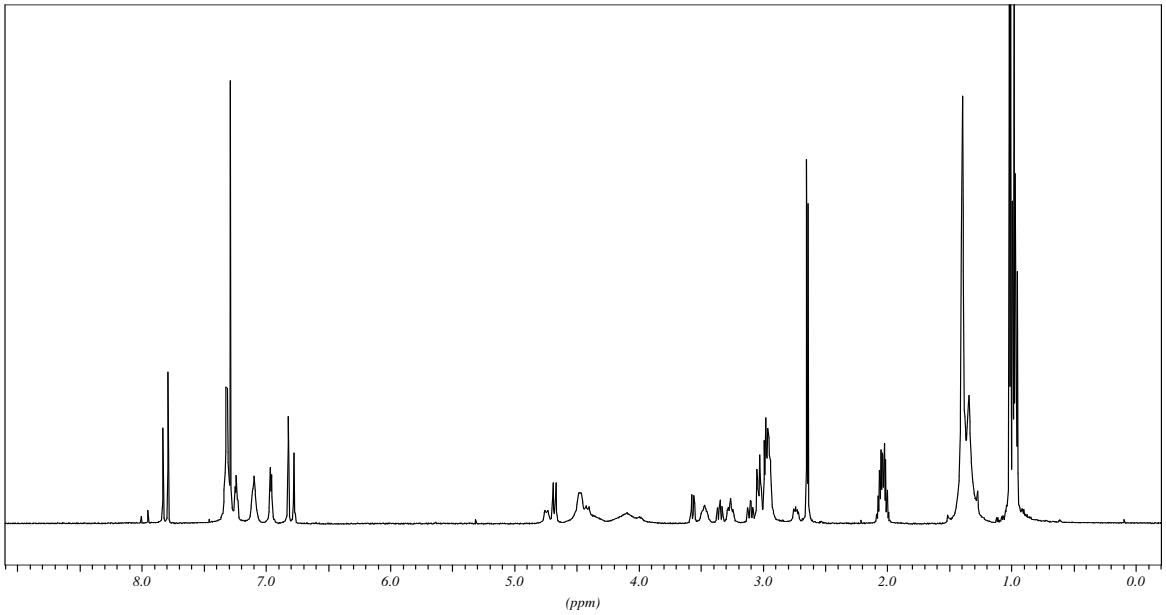

N
HN
N
N
O
N
N
Boc

12b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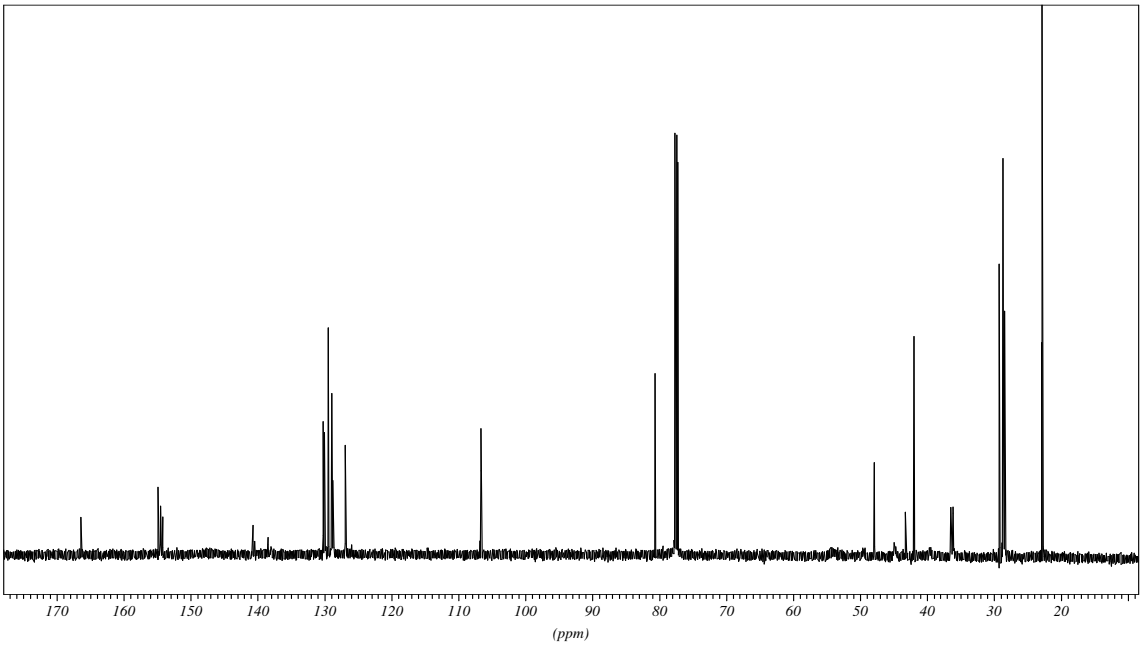
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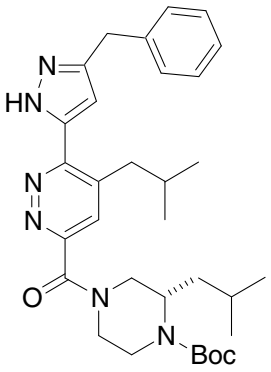
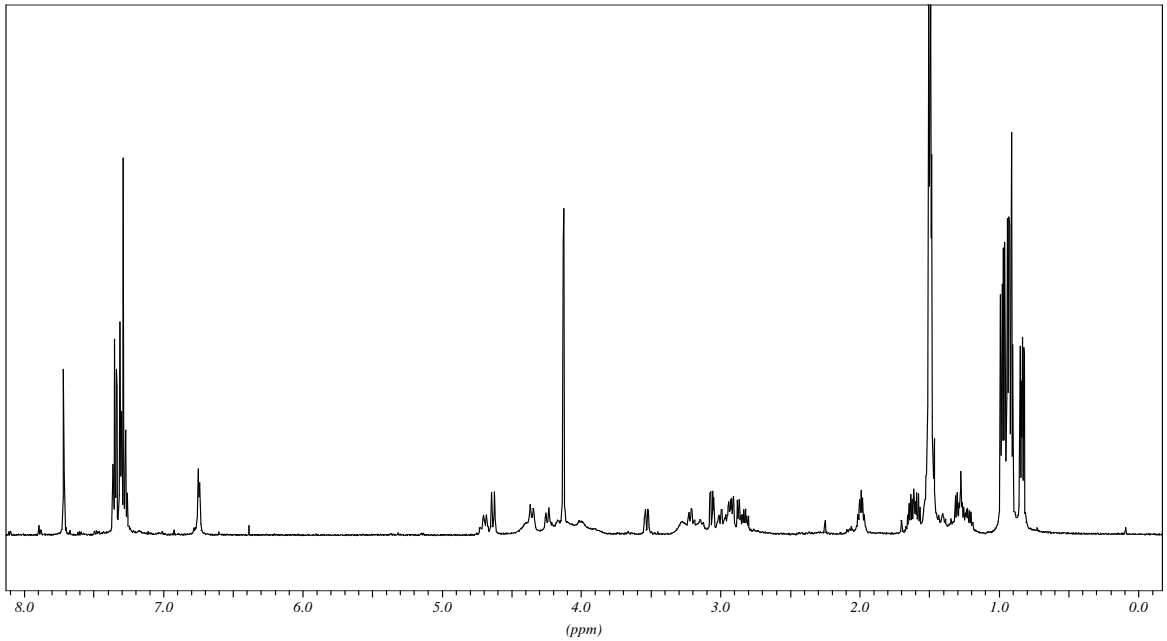
(ppm)


N
HN
N
N
O
N
N
Boc

12c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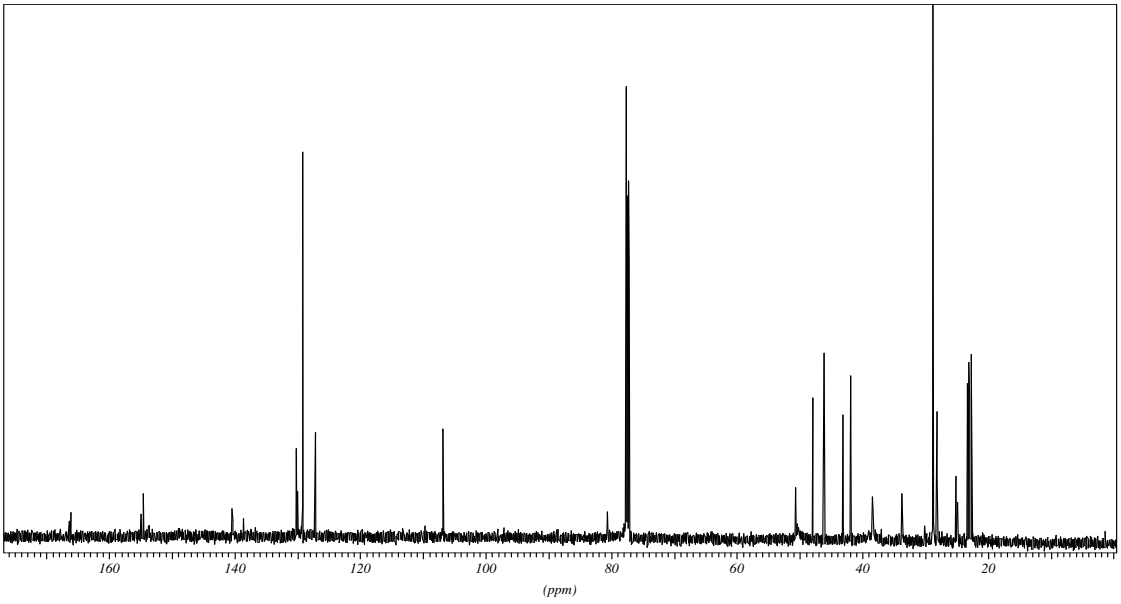
(ppm)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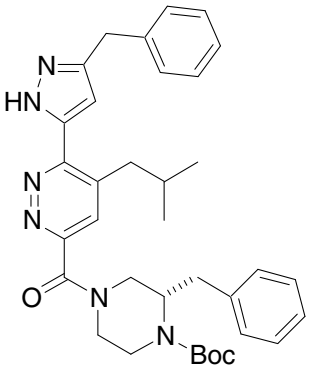
20
(ppm)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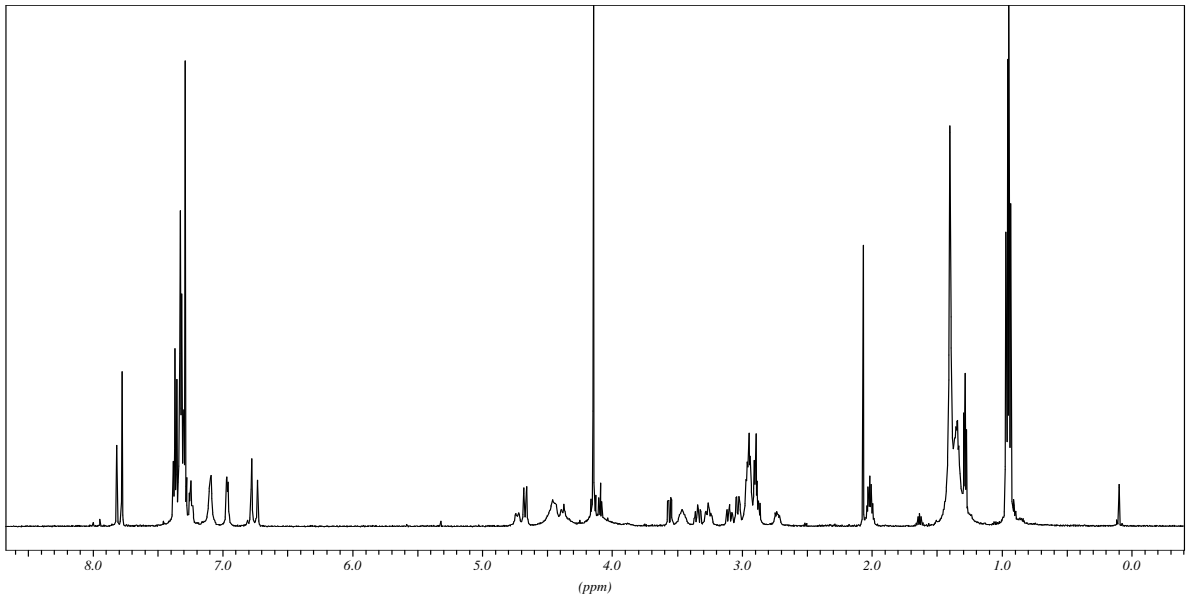
N
Boc

12d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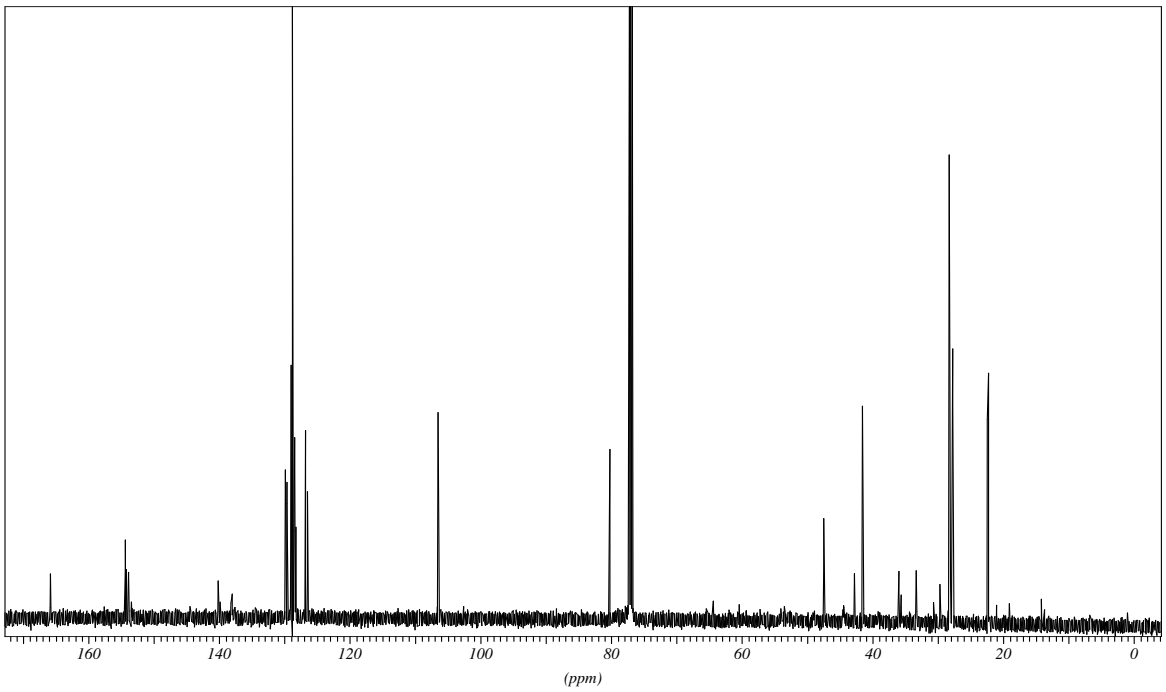
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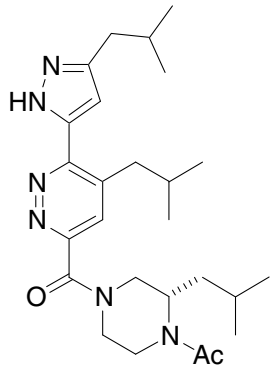
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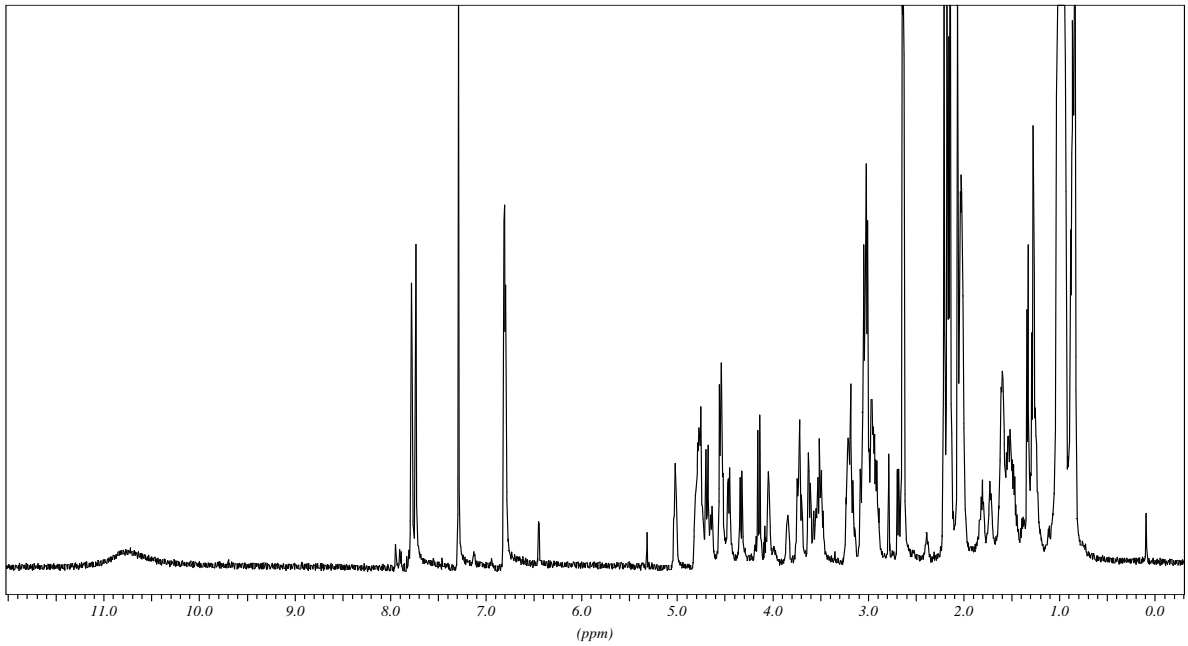
O
N
N
Ac

1a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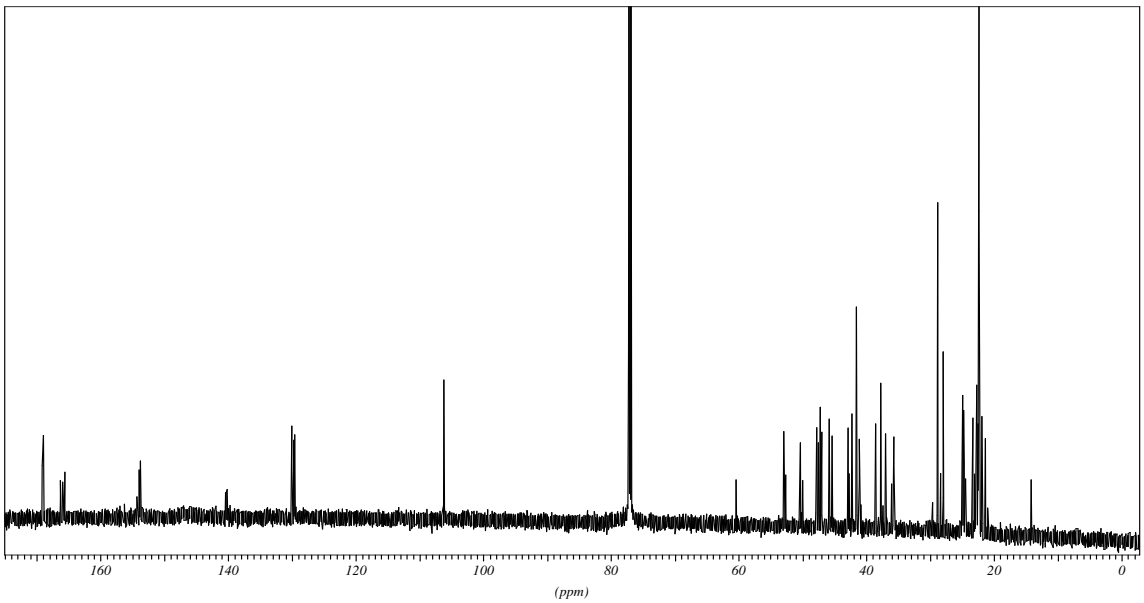
(ppm)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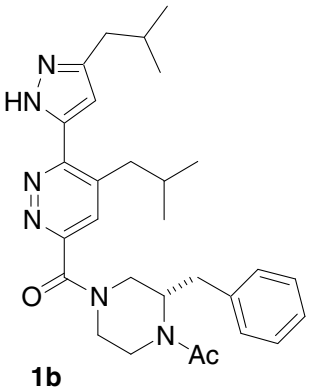
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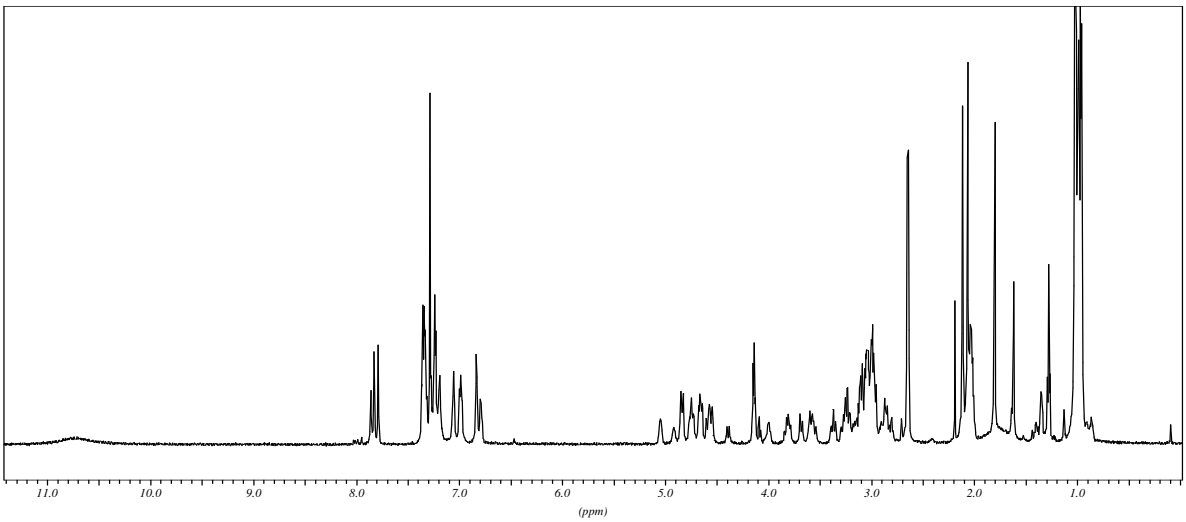
O
N
N
Ac

1b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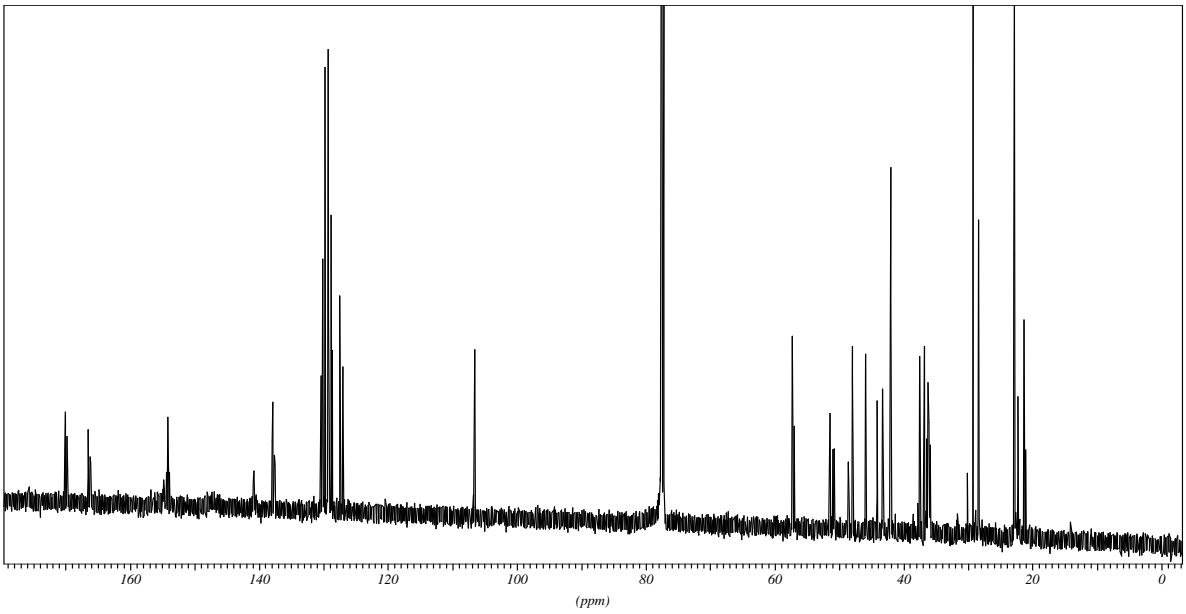
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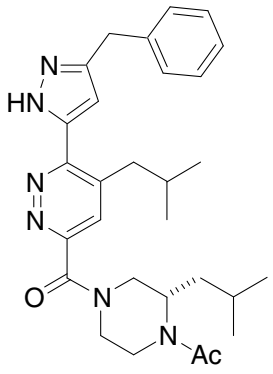
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N
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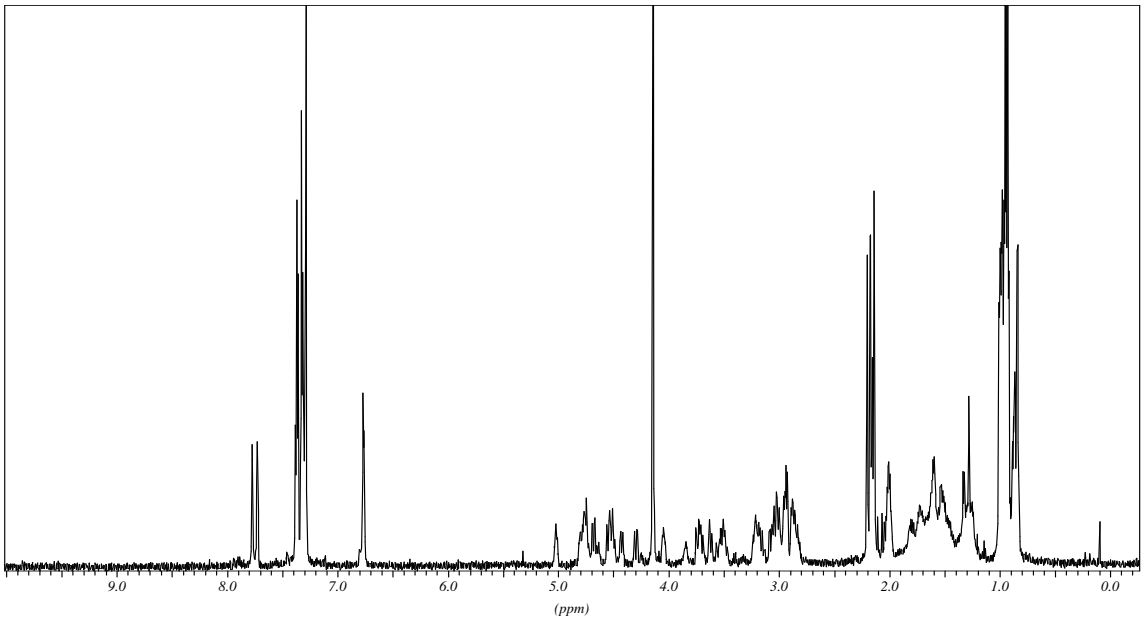
O
N
N
Ac

1c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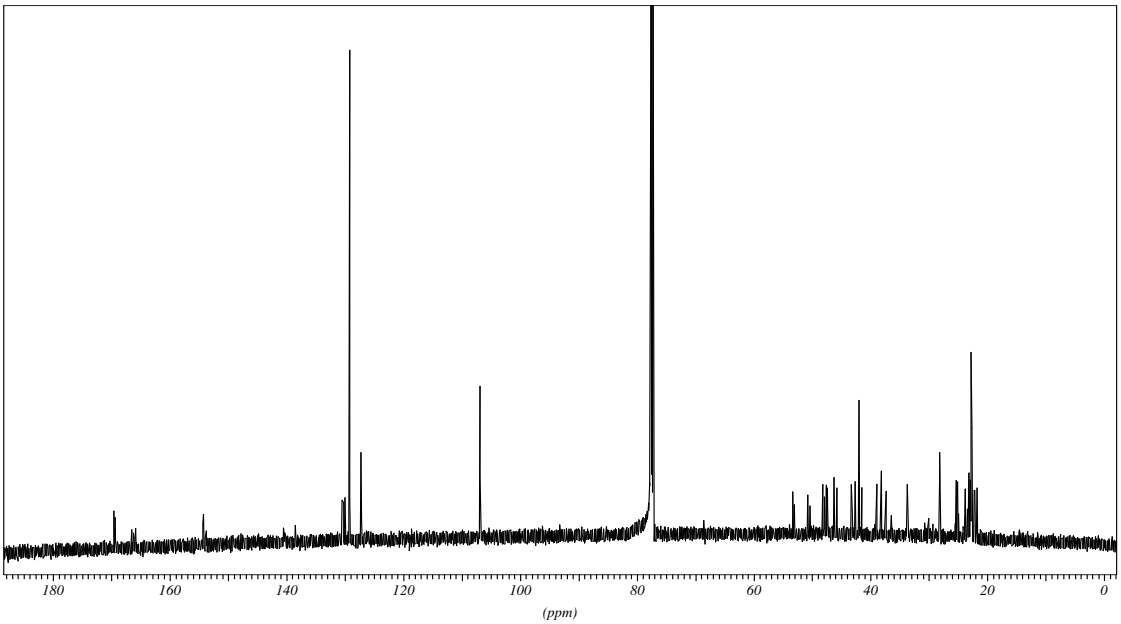
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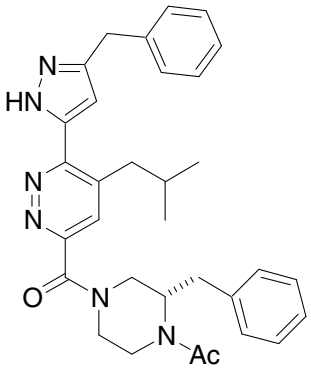
(ppm)


N
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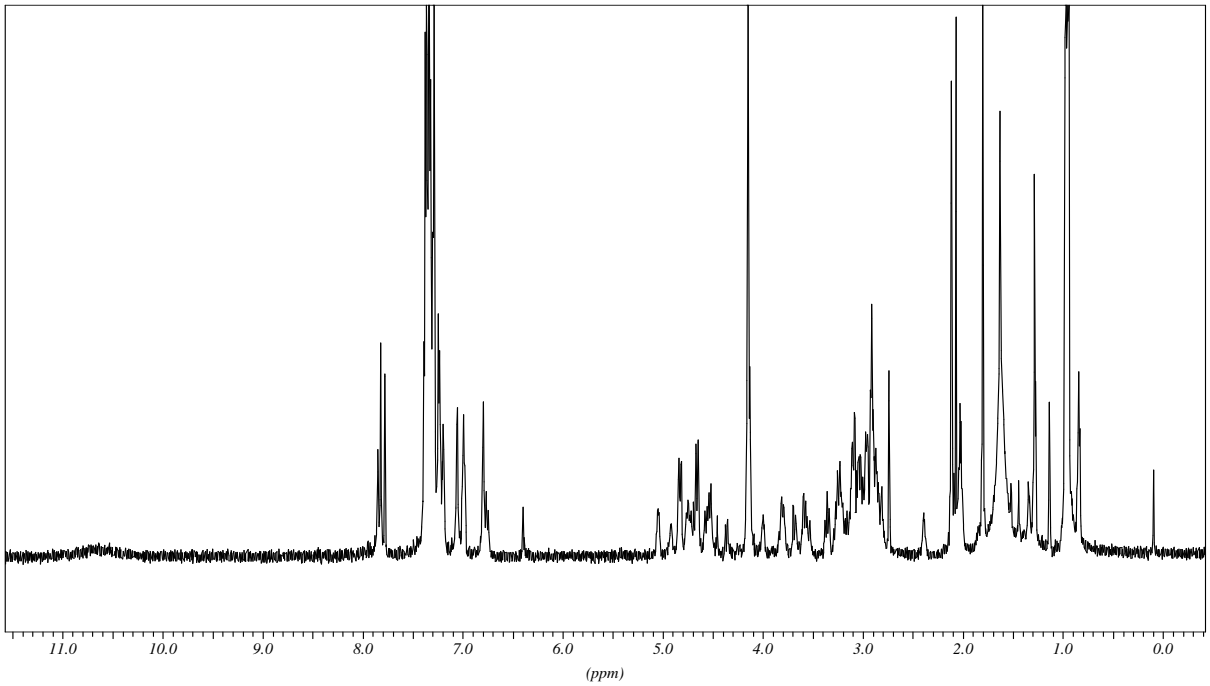
N
N
O
N
N
Ac

1d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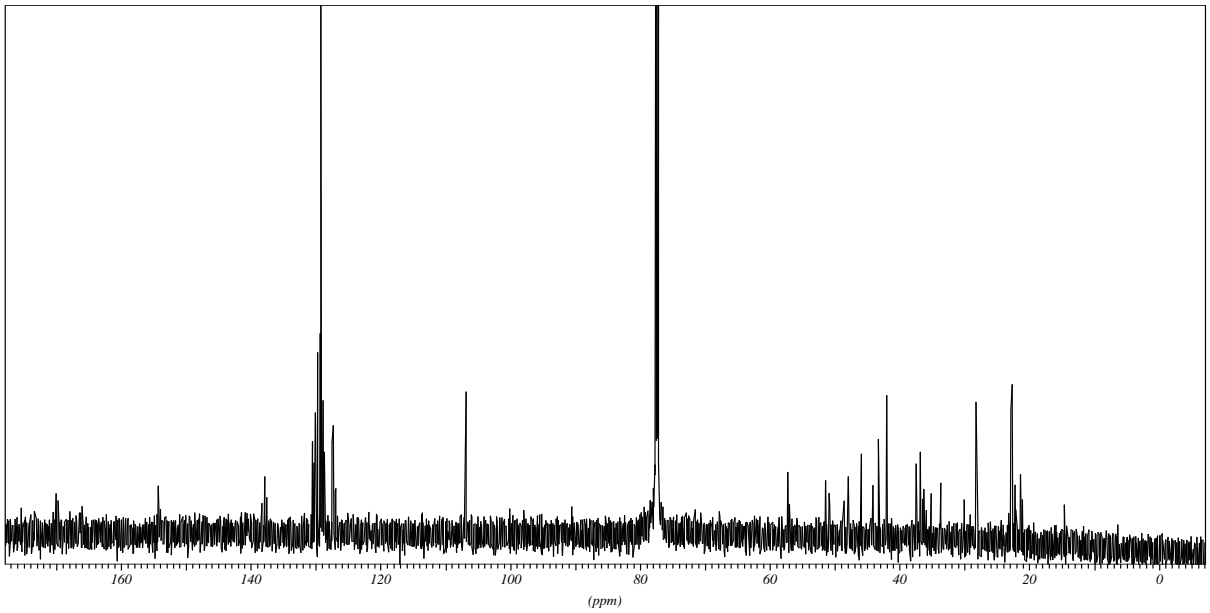
(ppm)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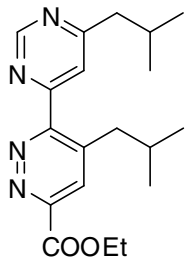
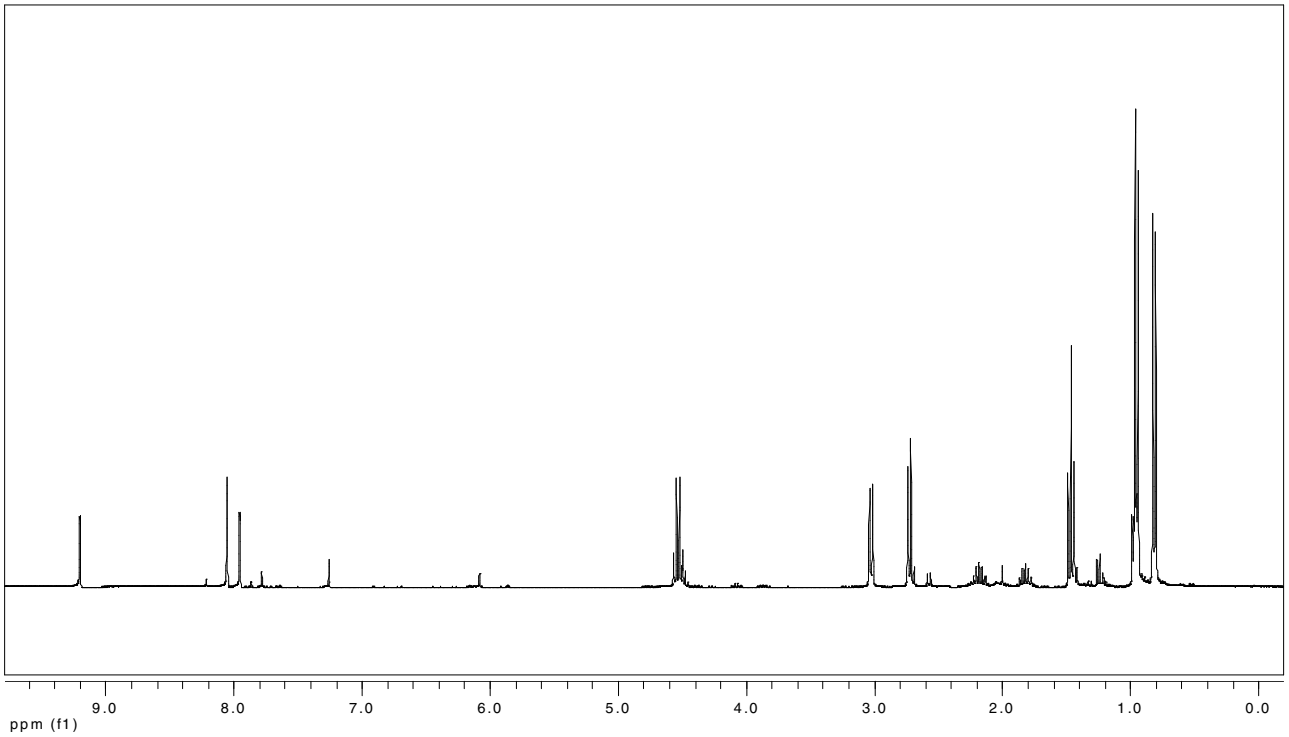
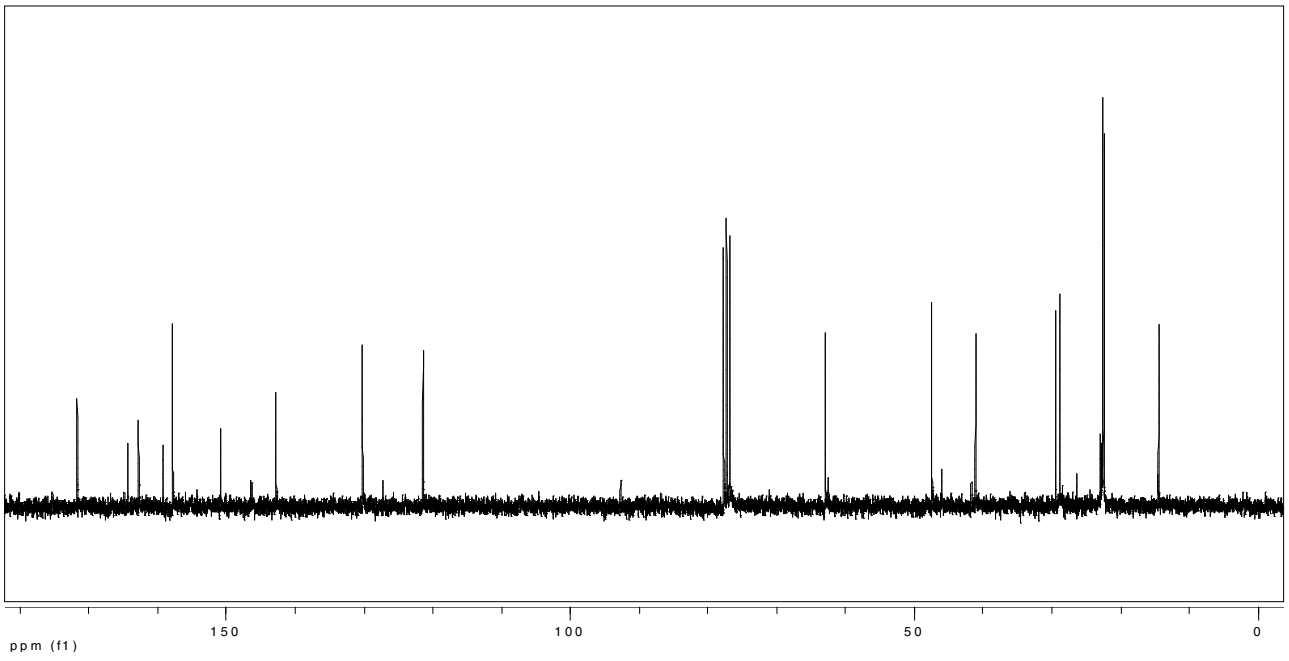
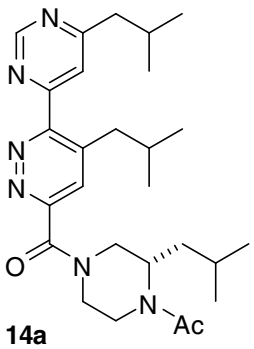
(ppm)



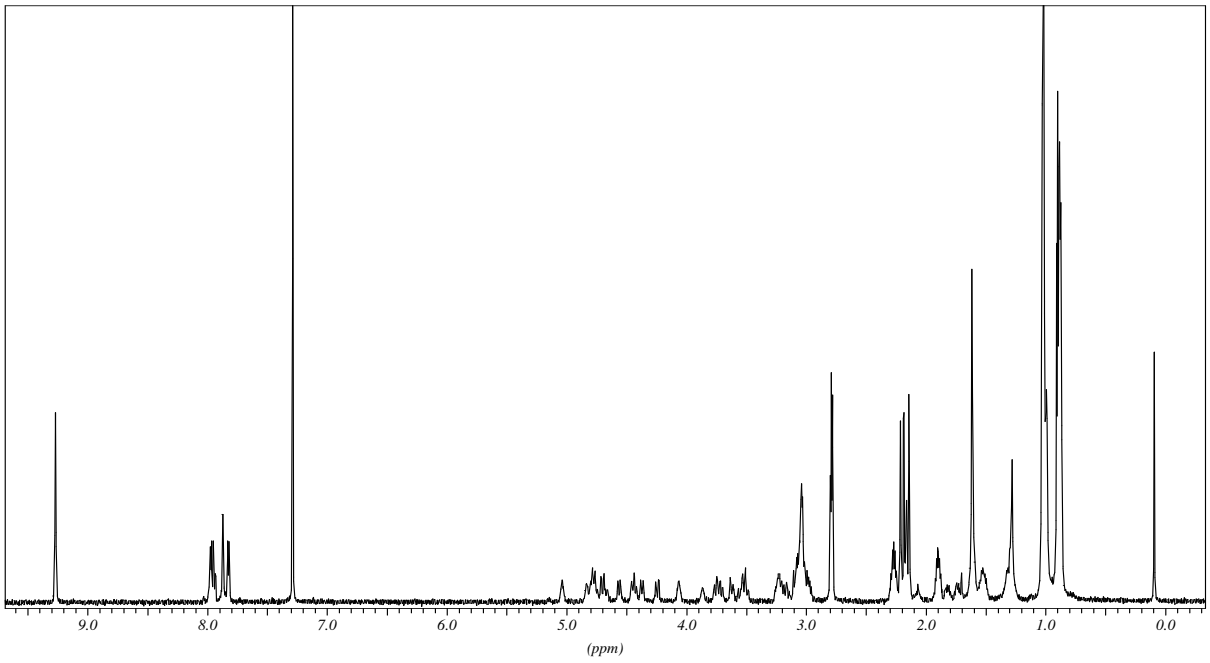
13






N
N
N
N
O
N
N
Ac

14a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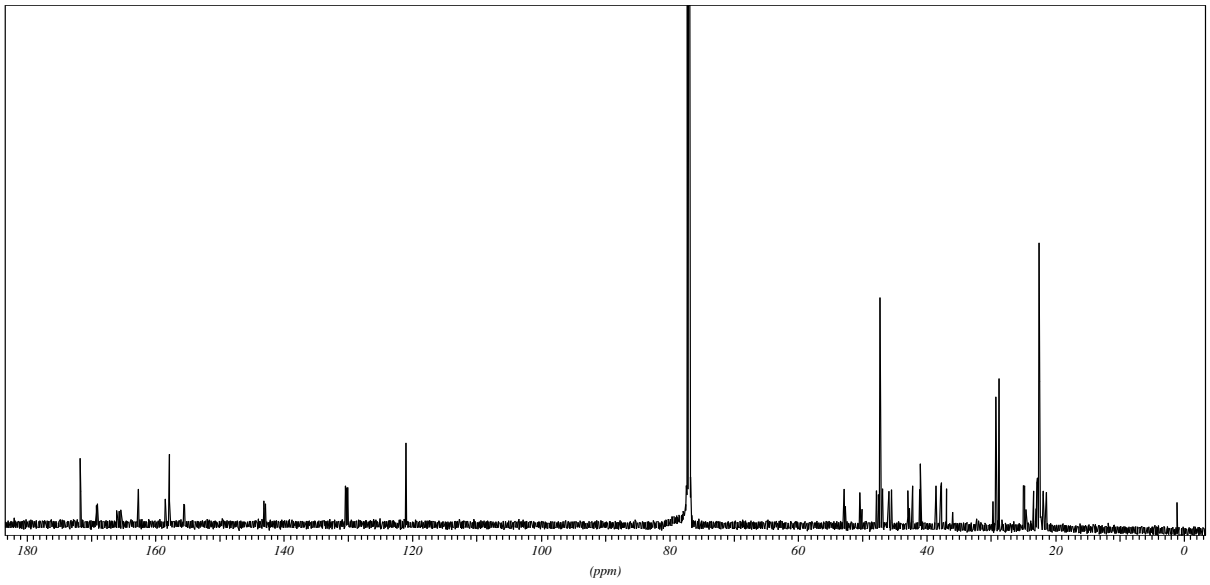
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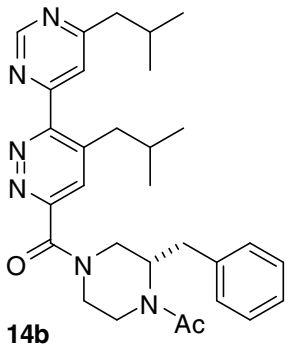
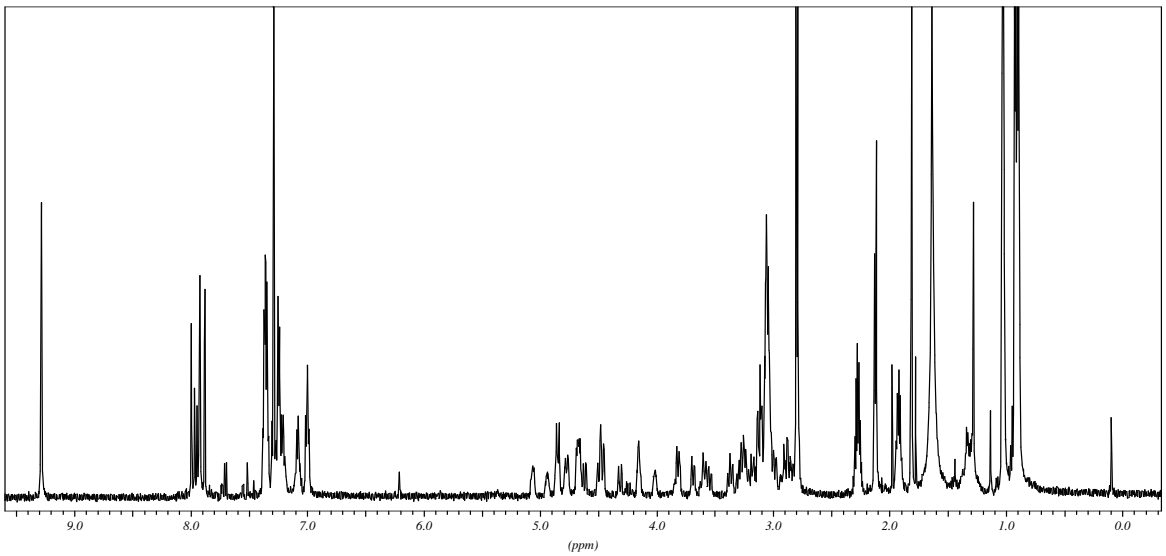
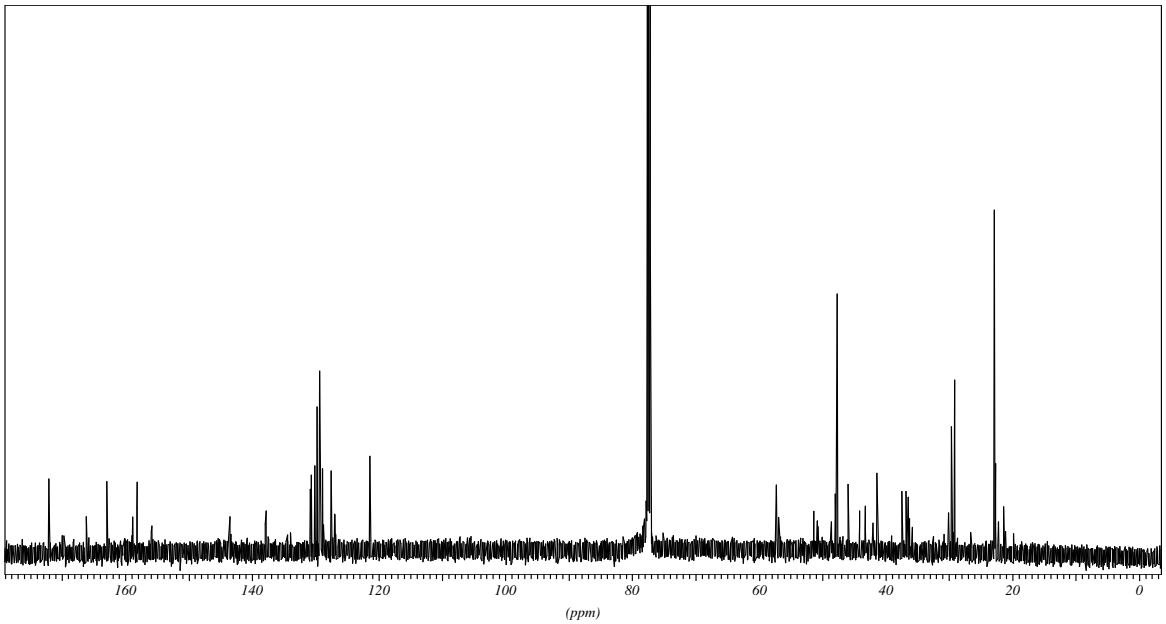
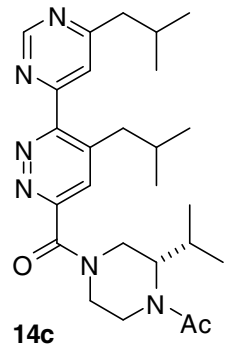
(ppm)



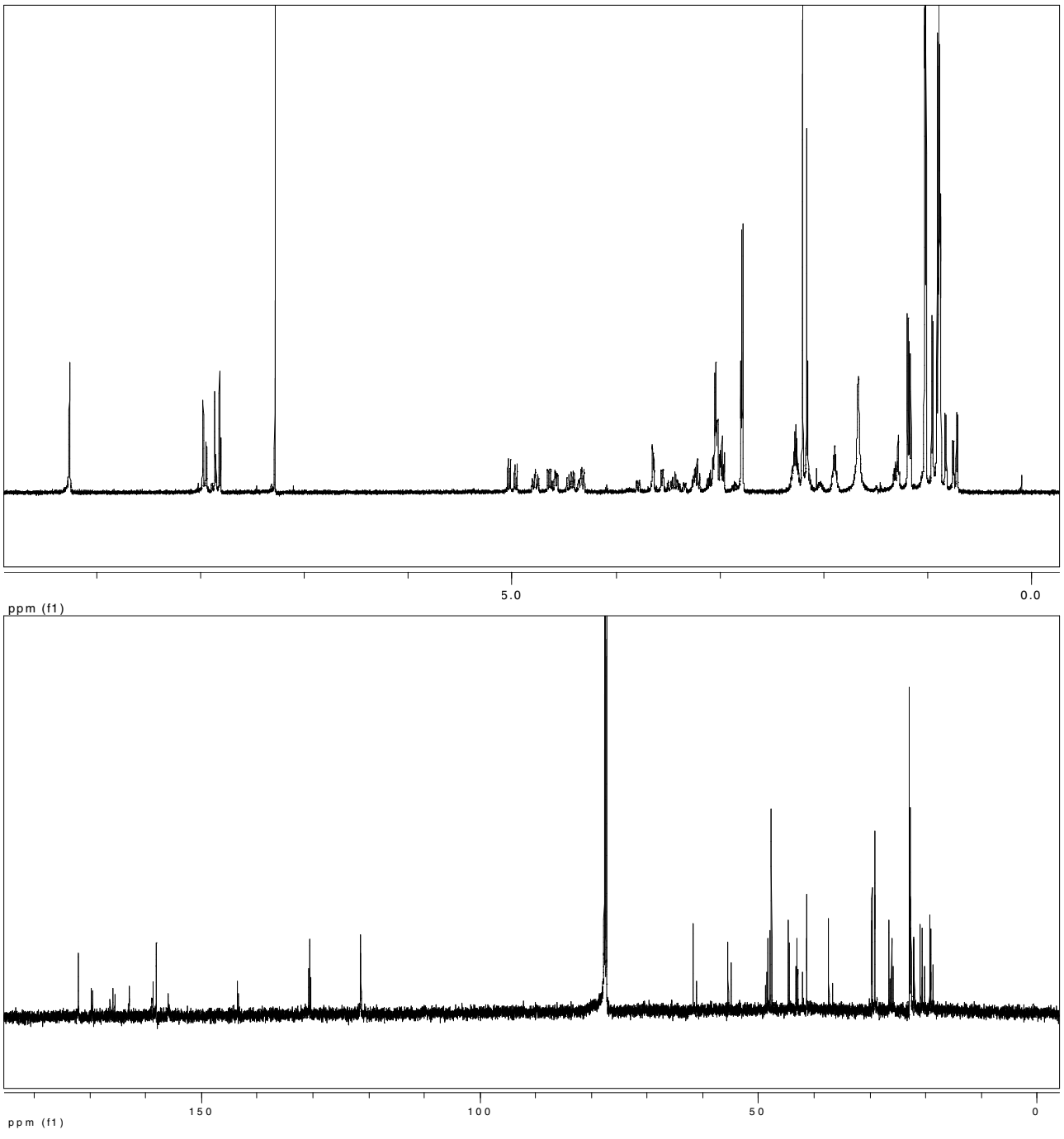
14b

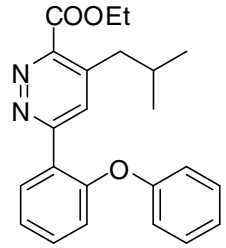




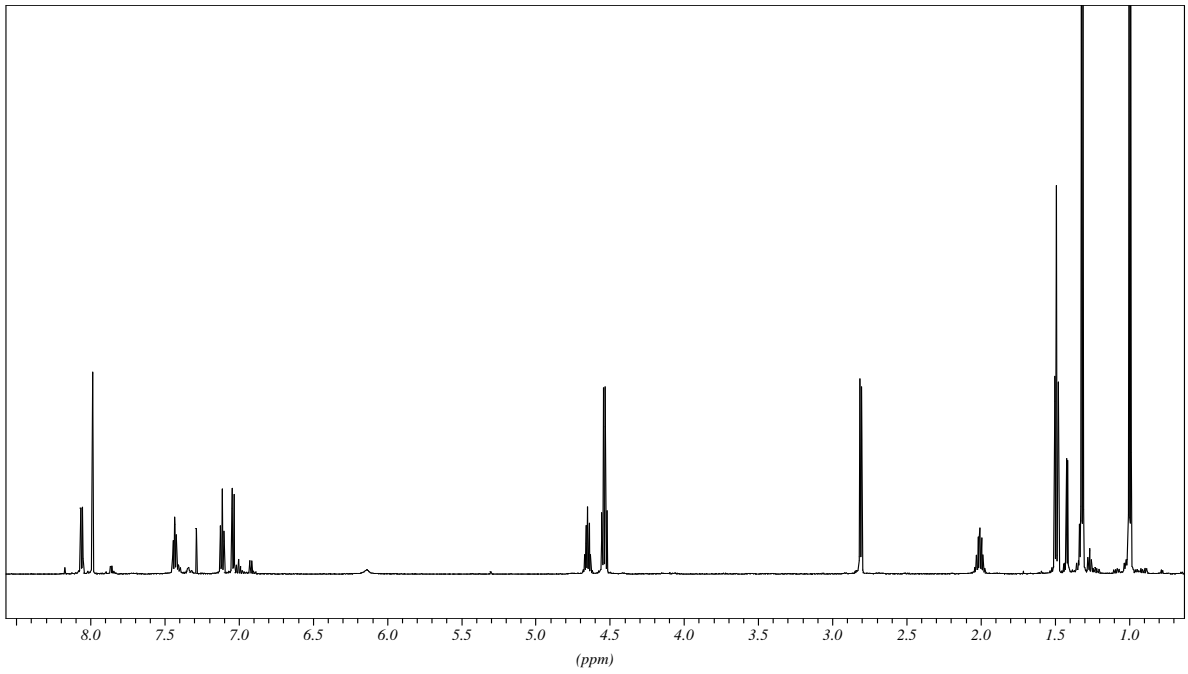


14c




COOEt
N
N
O

16a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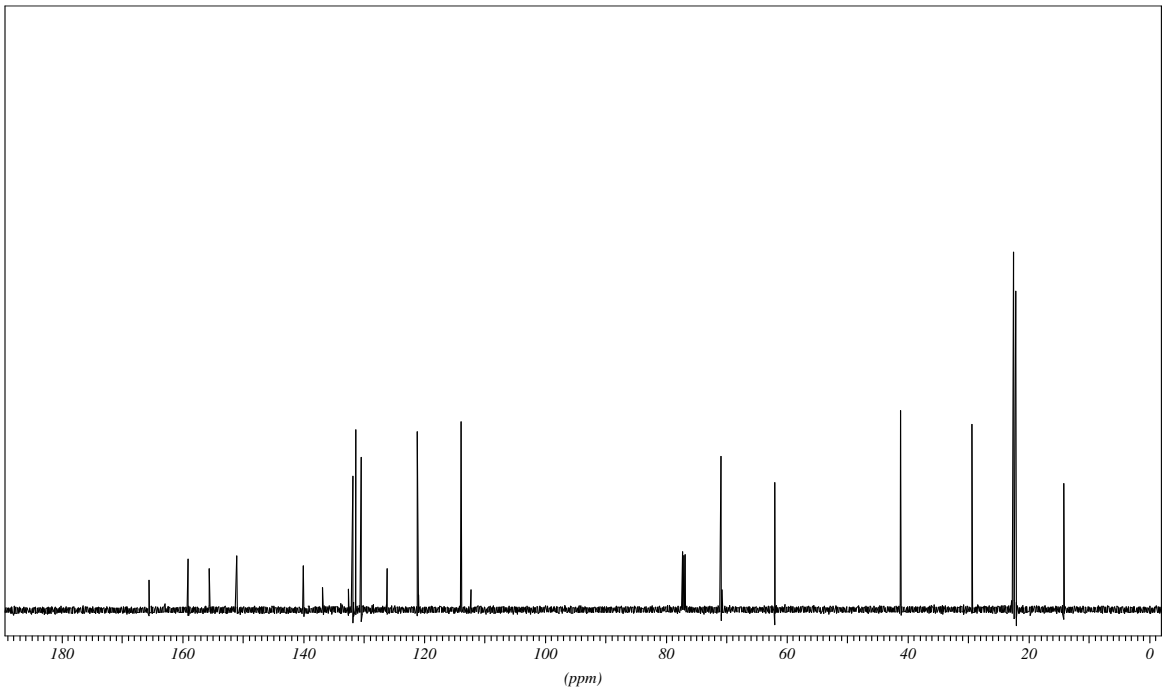
2.0
1.5
1.0
(ppm)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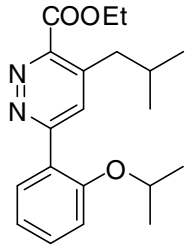
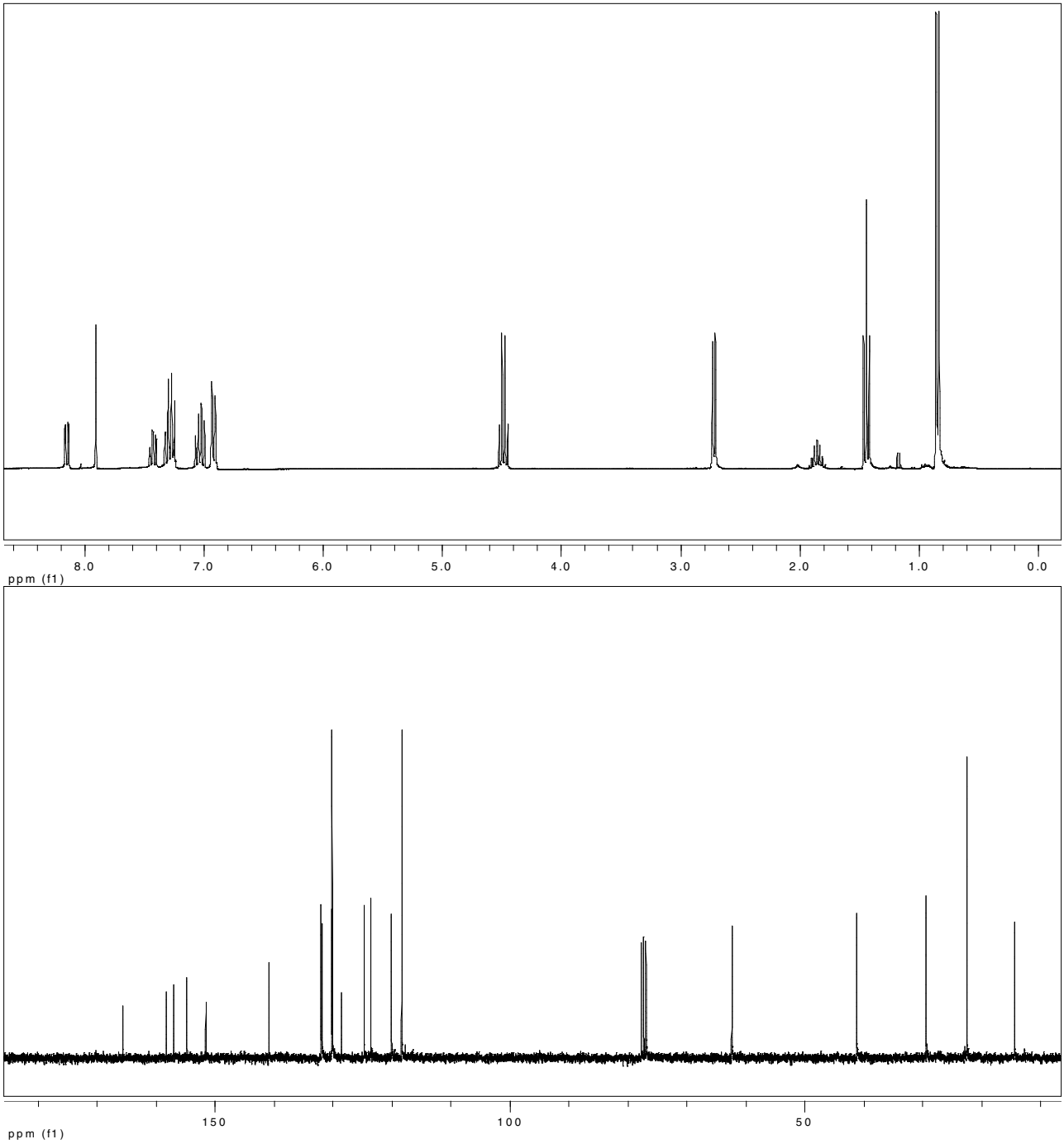
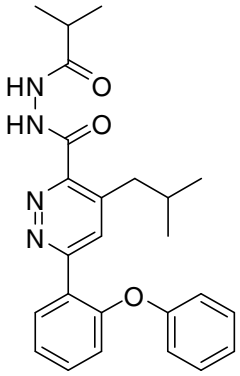
(ppm)



16b

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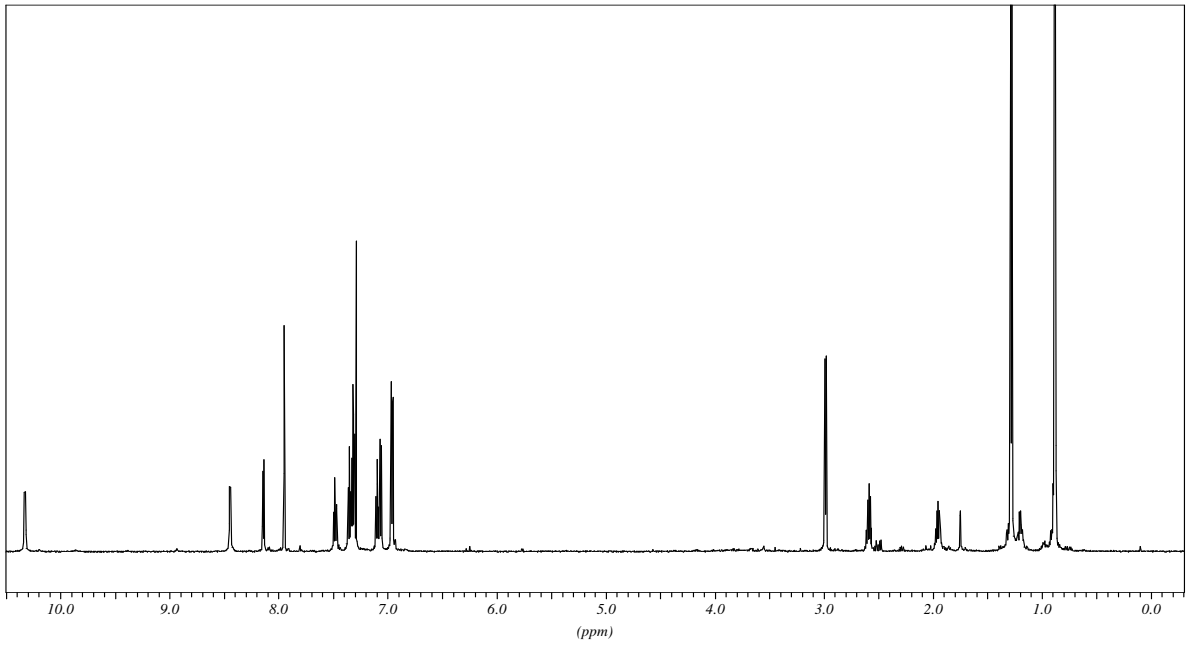
O
HN
O
N
N
O

18a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3.0
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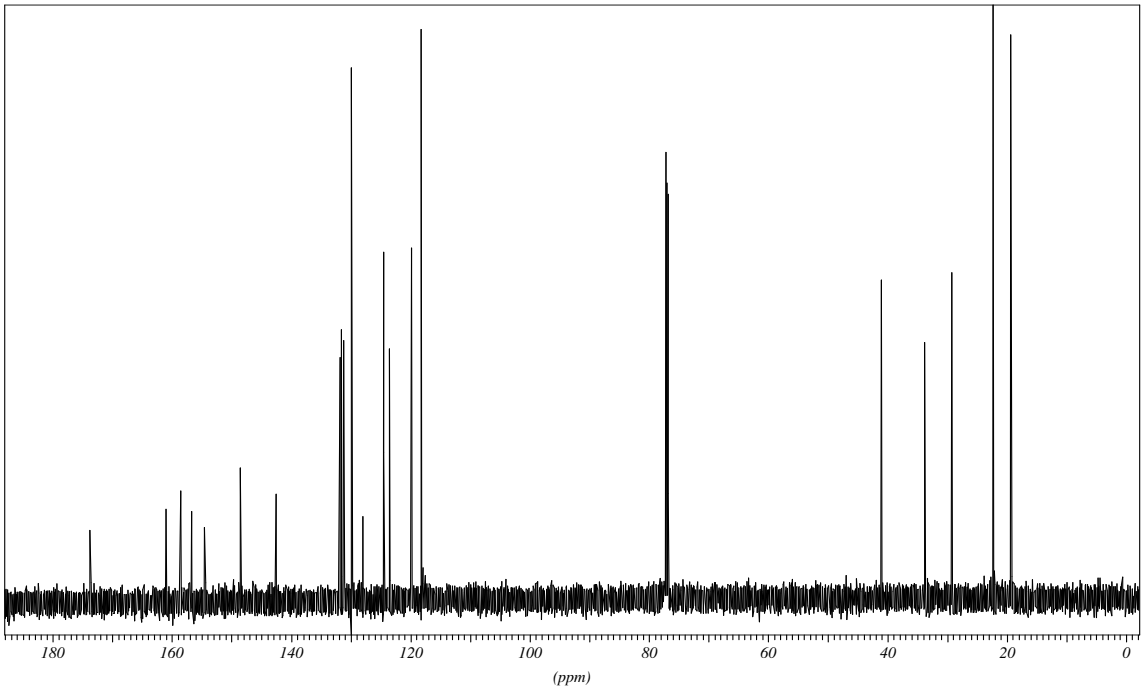
(ppm)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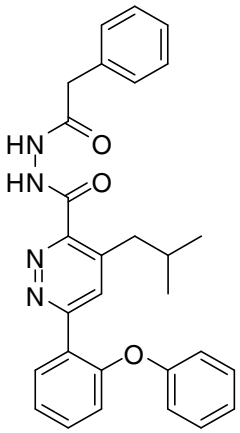
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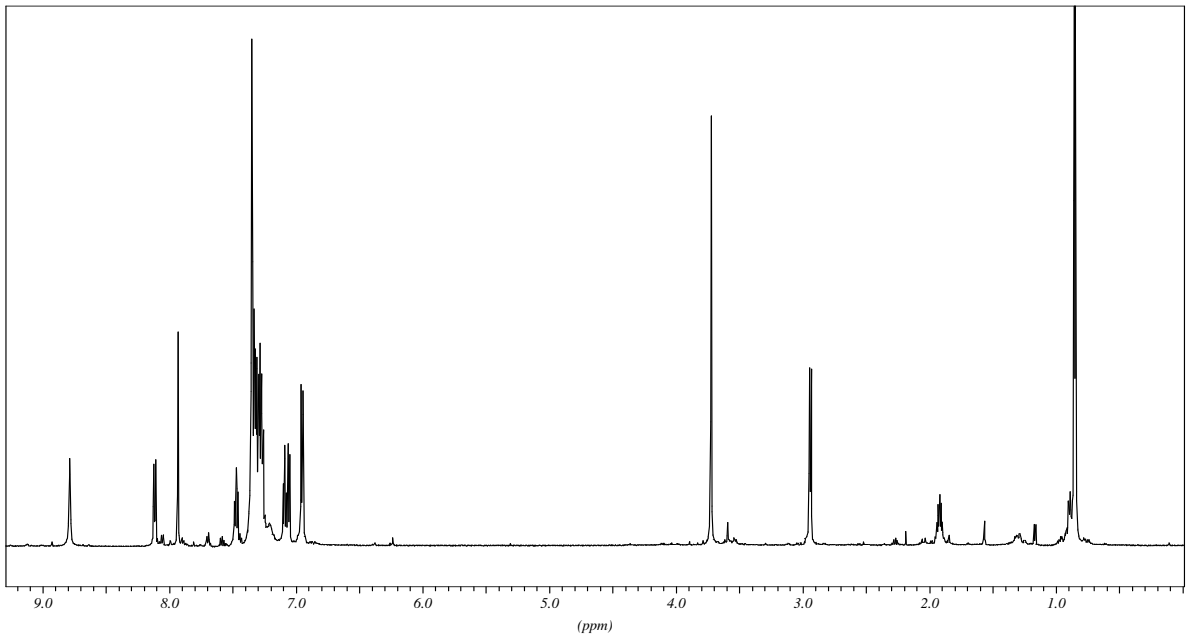
O
N
N
O

18b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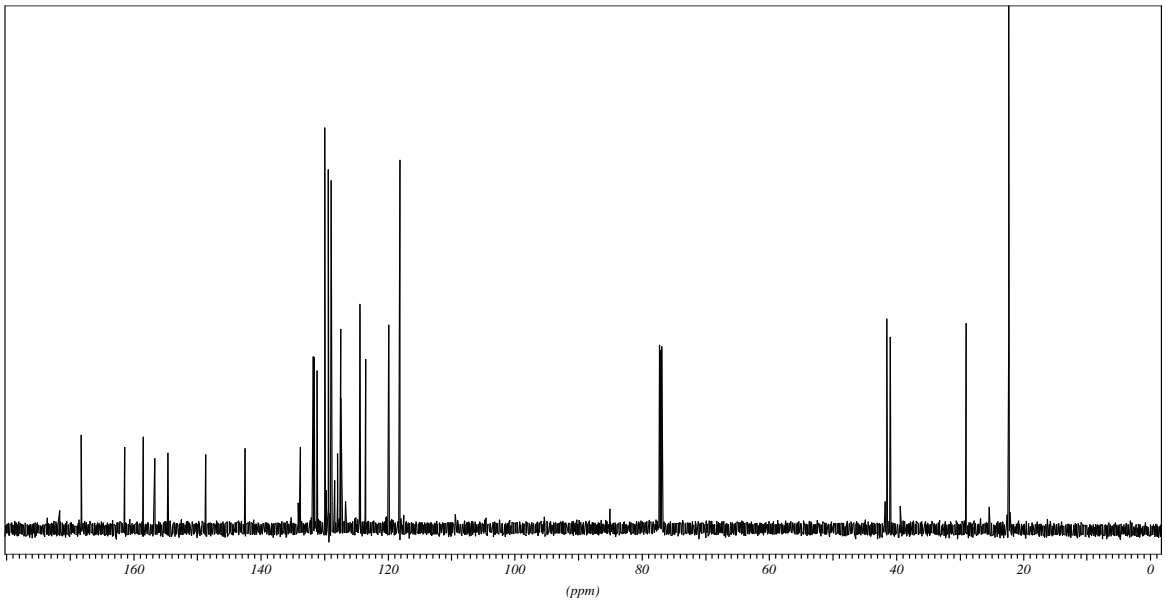
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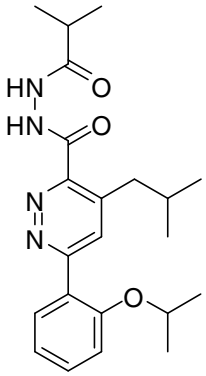
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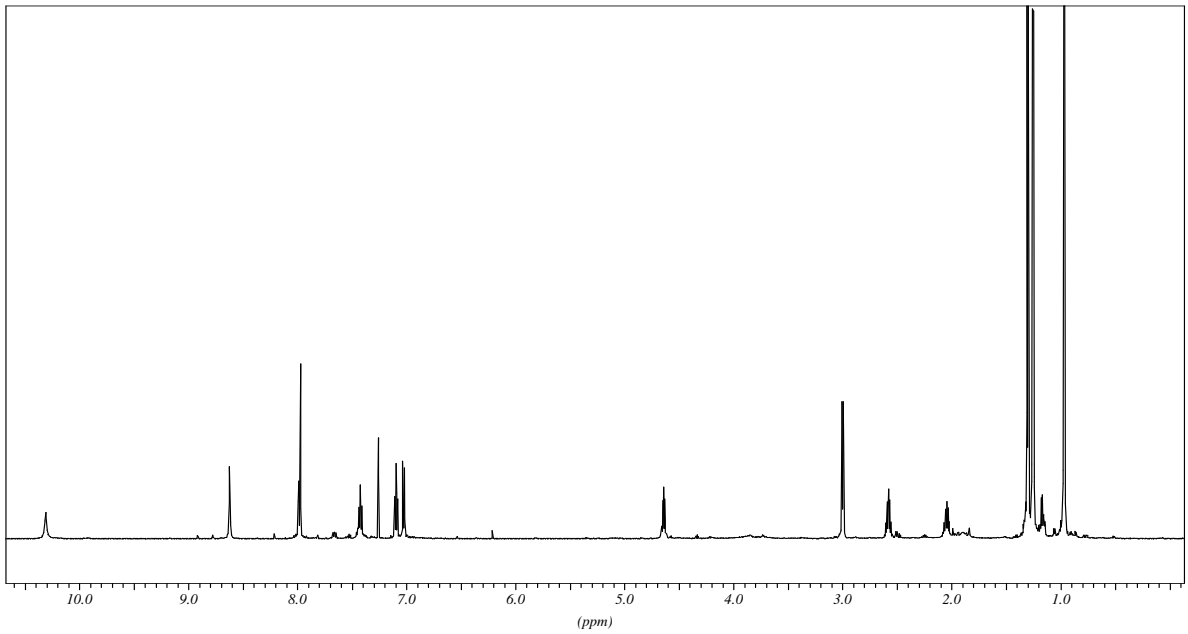
O
N
N
O

18c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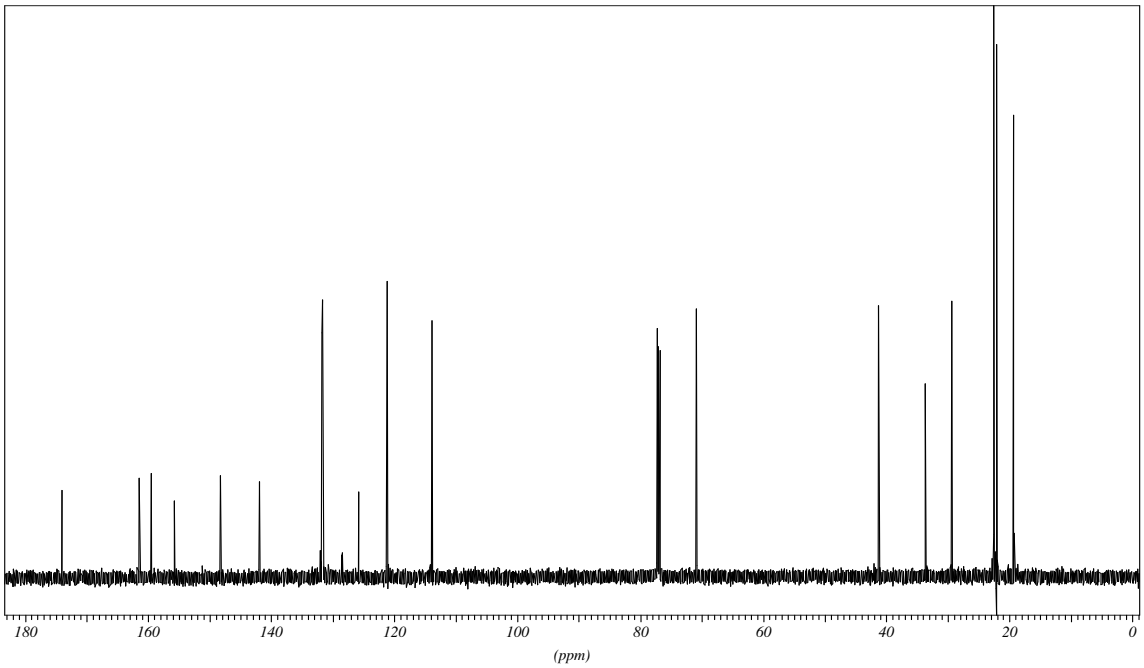
(ppm)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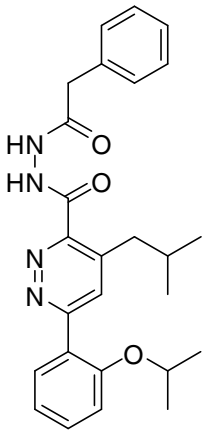
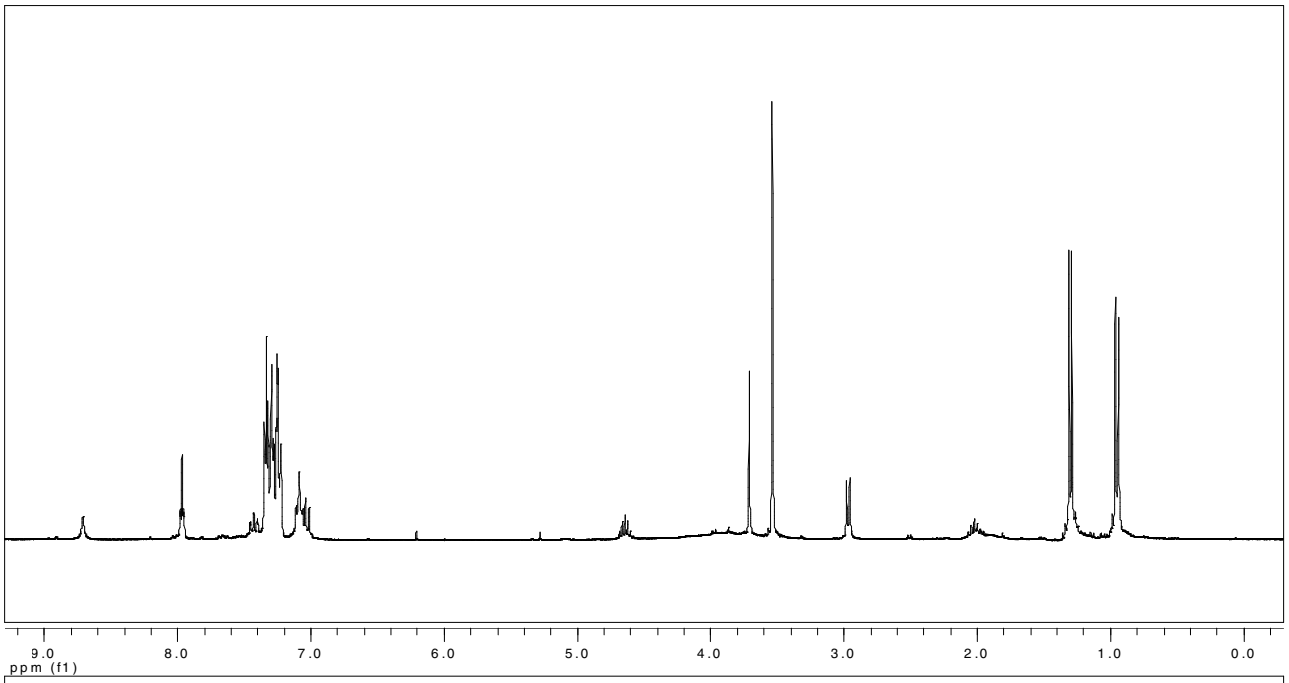
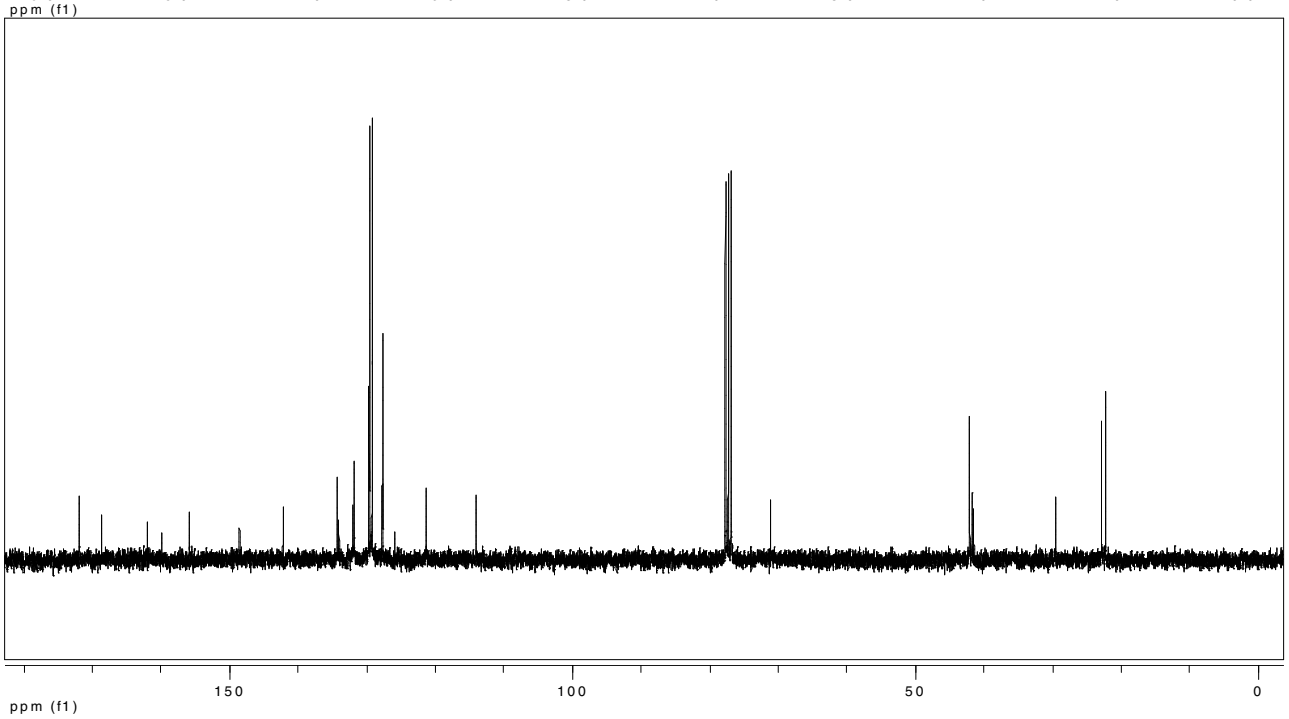
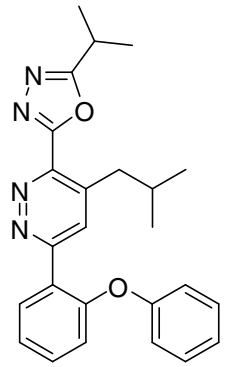
(ppm)



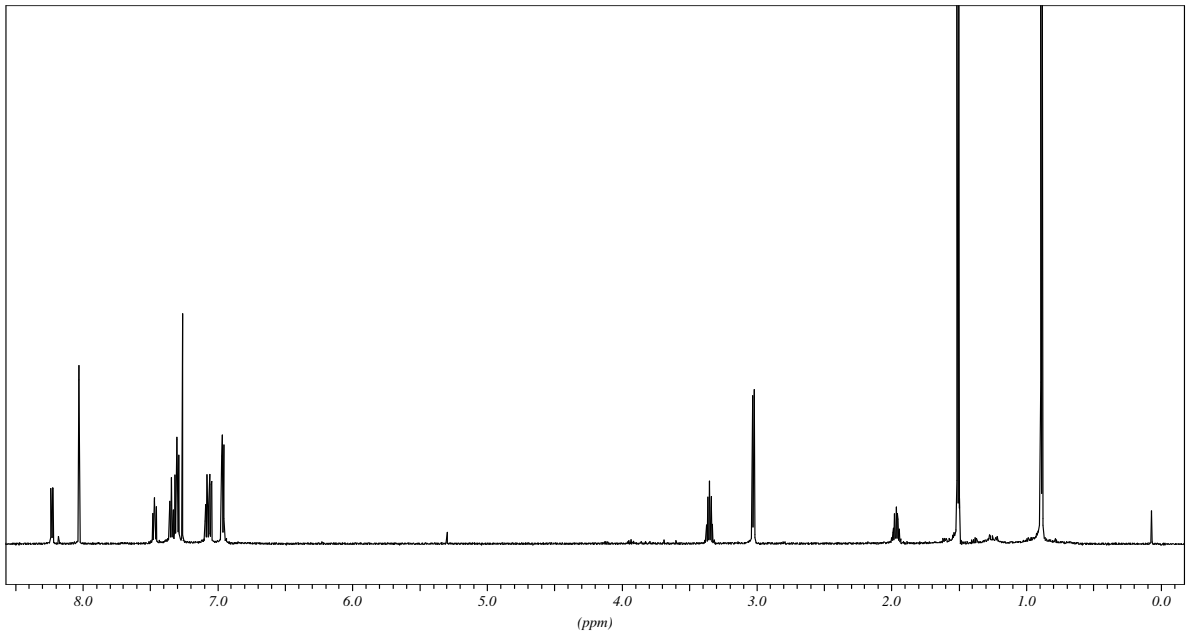
18d







2a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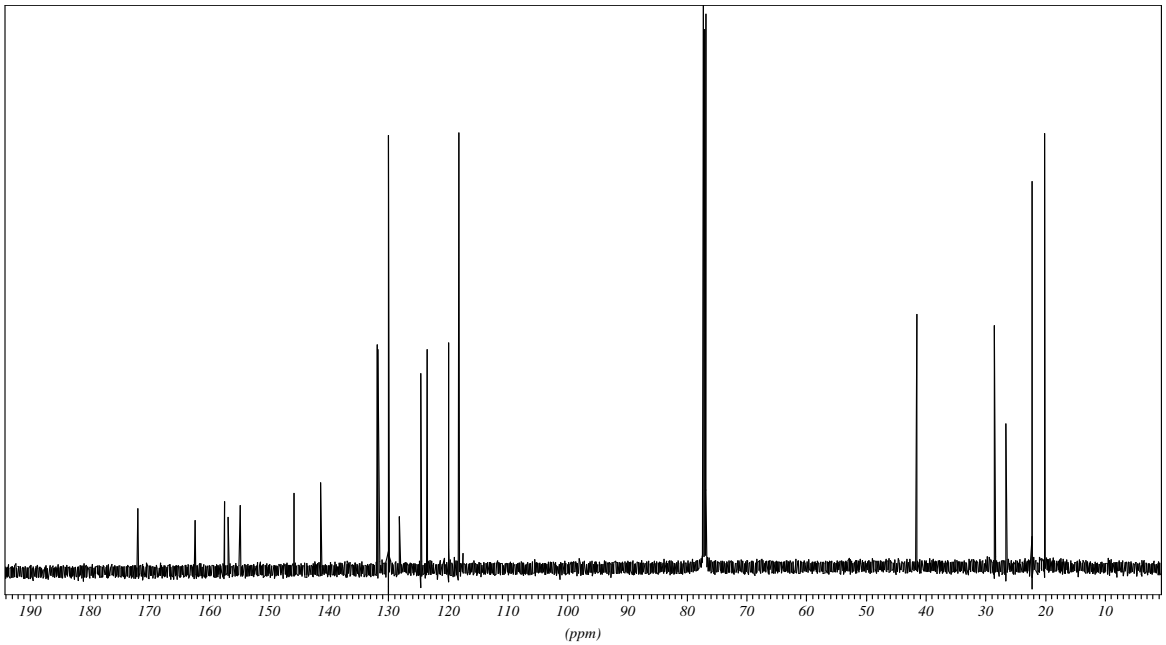
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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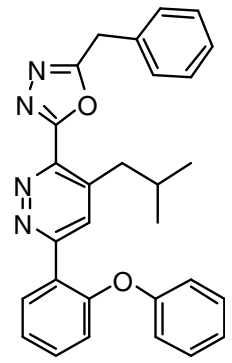
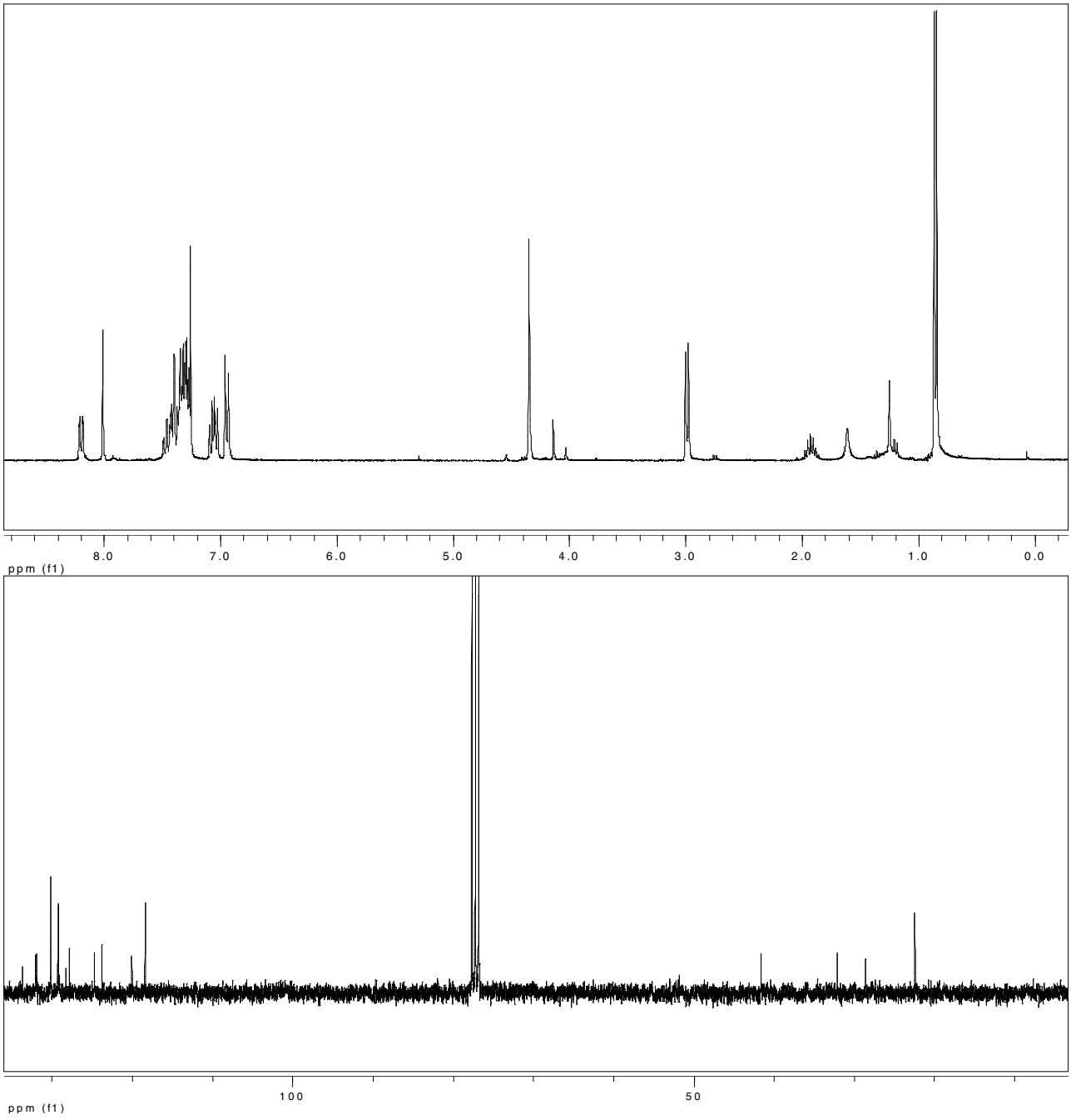
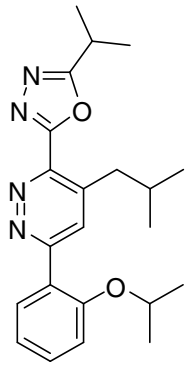
10
(ppm)

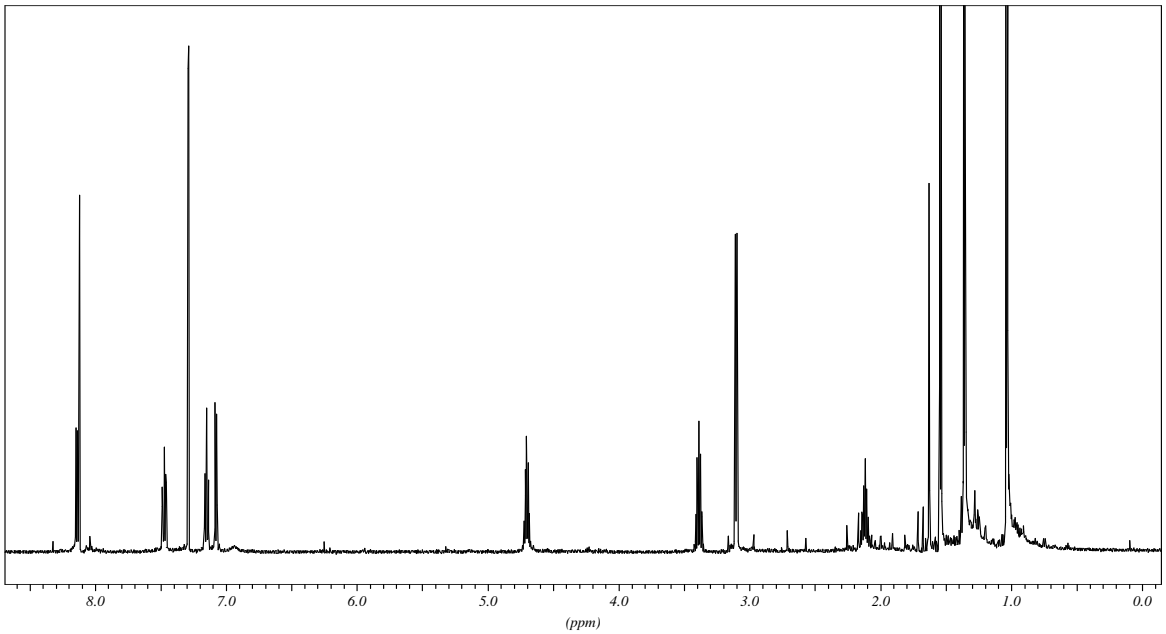


2b





2c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4.0
3.0
2.0
1.0
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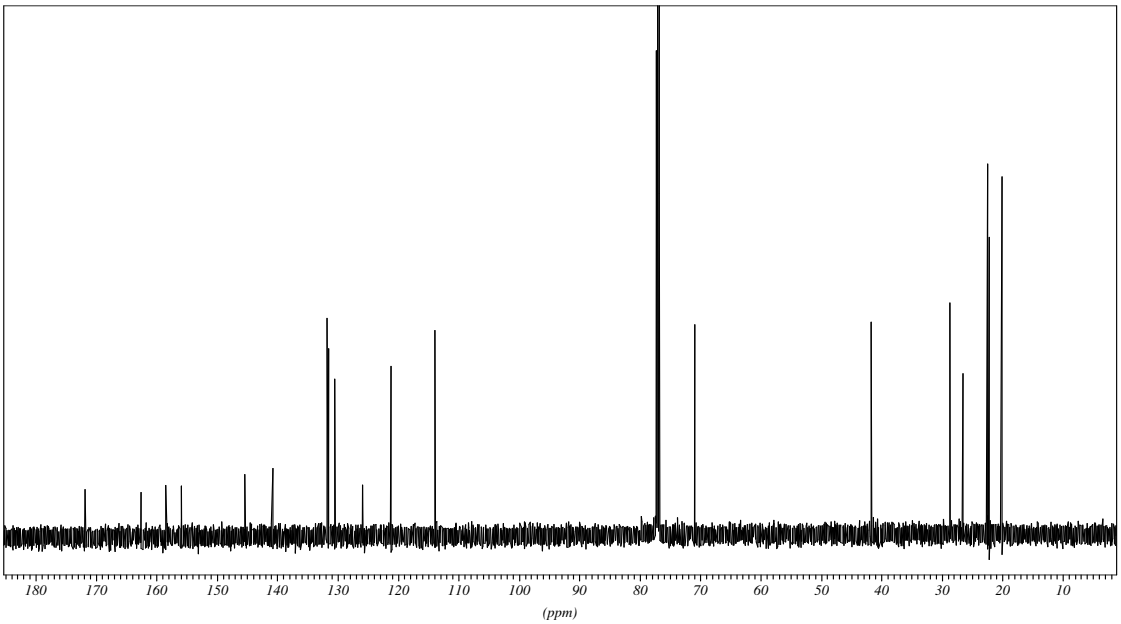
(ppm)


180
170
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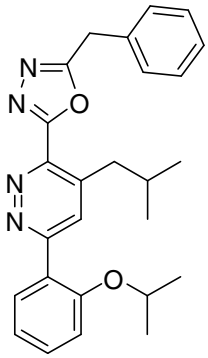
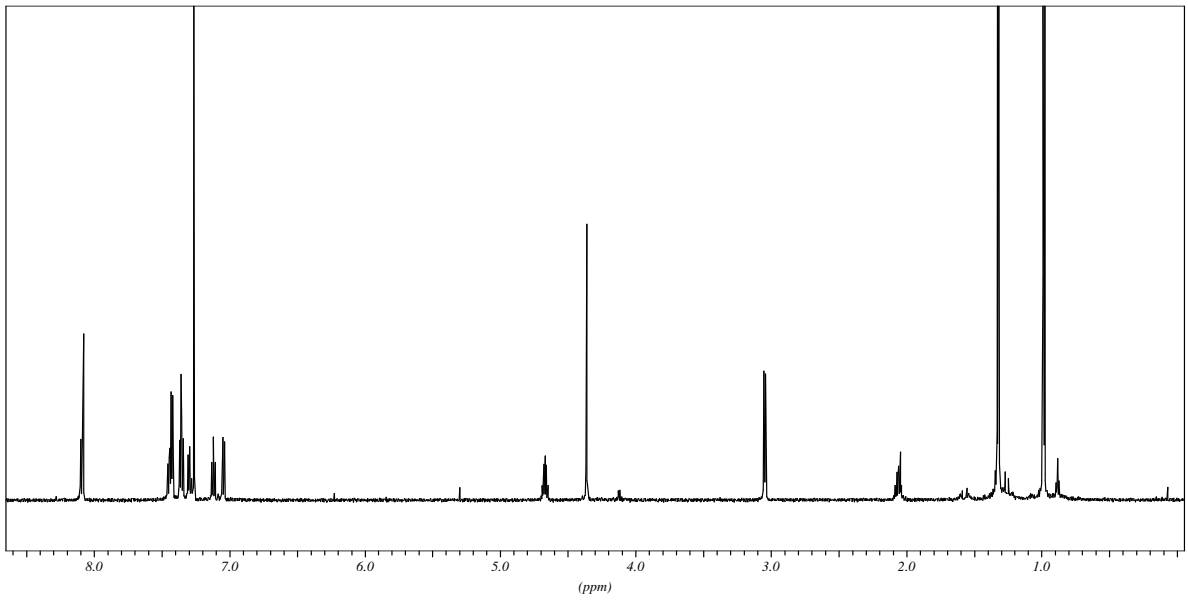
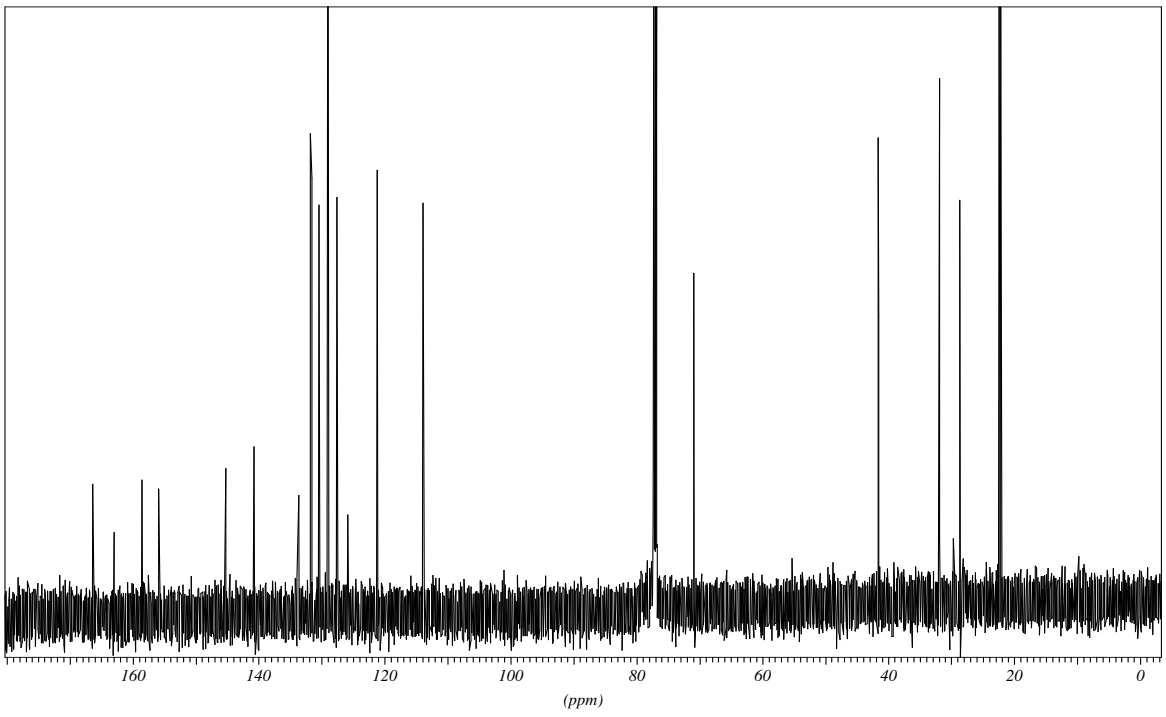
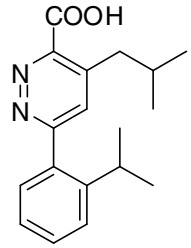
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)



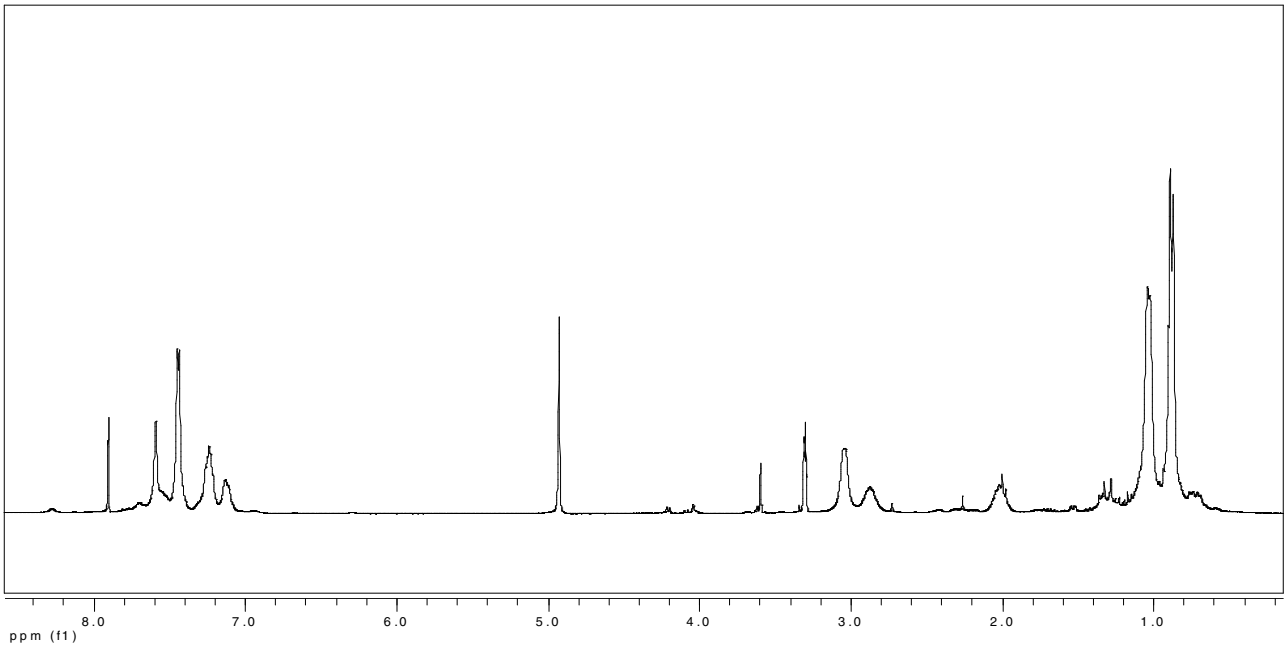
2d

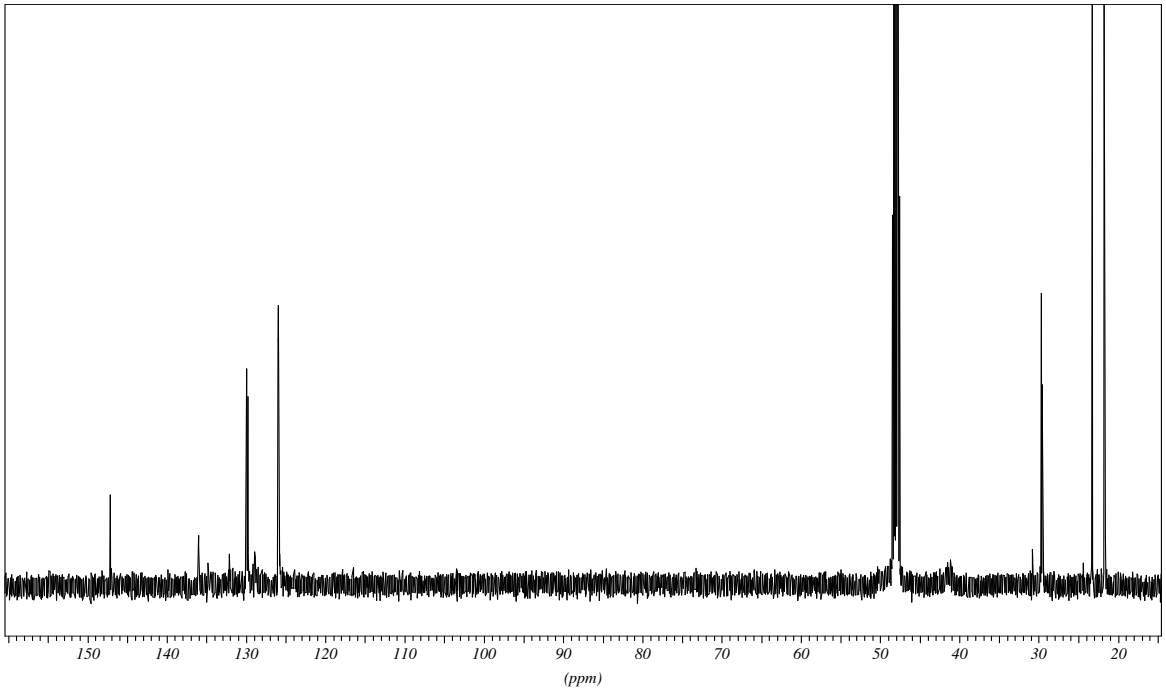





COOH
N
N

20


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)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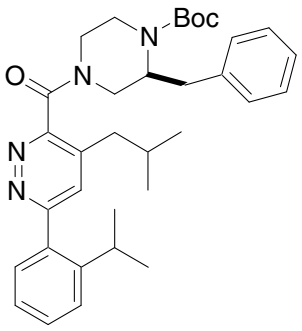
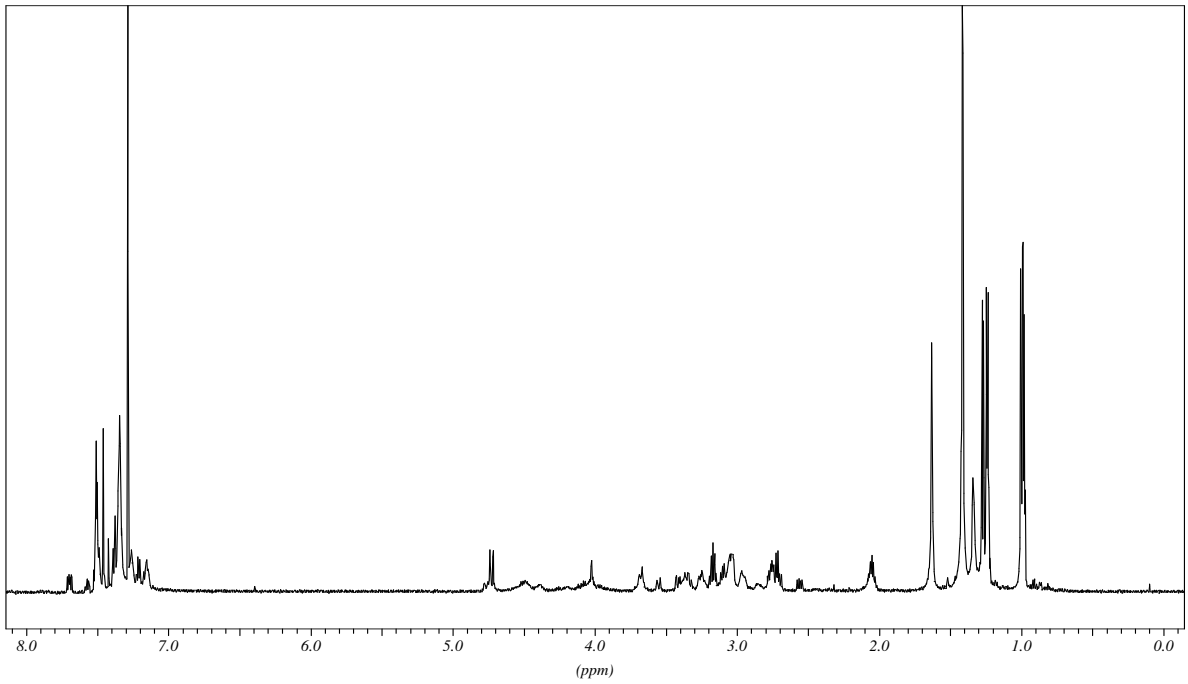
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


Boc
N
O
N
N
N

21b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4.0
3.0
2.0
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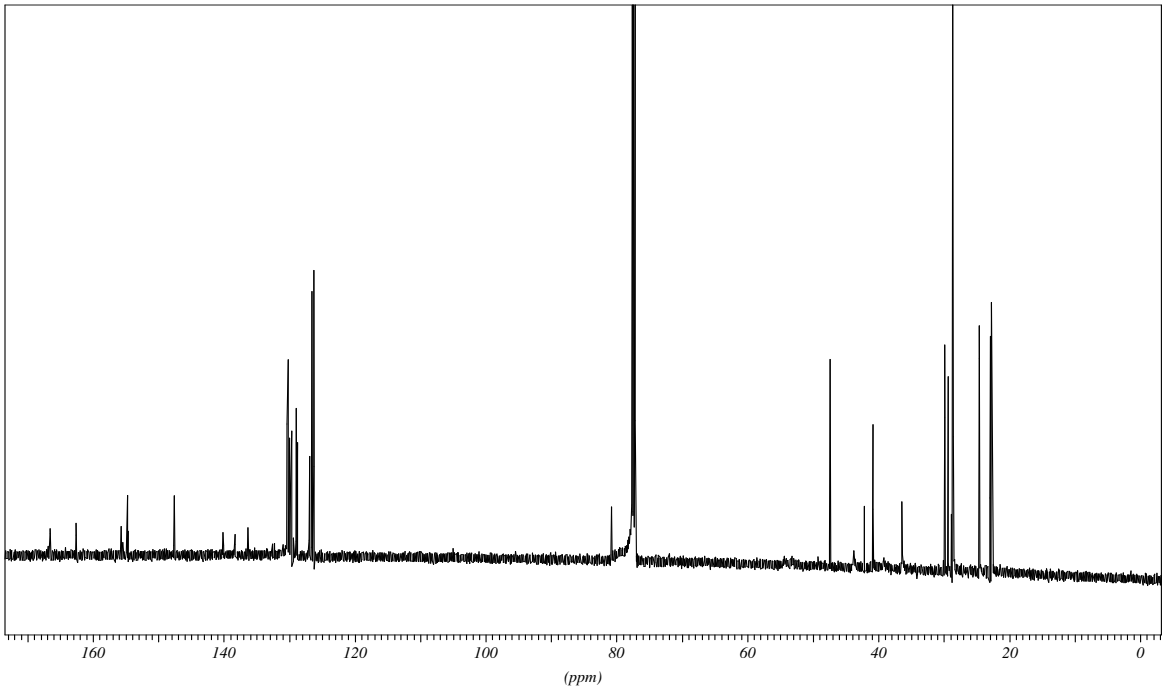
(ppm)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80
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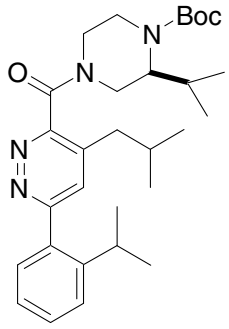
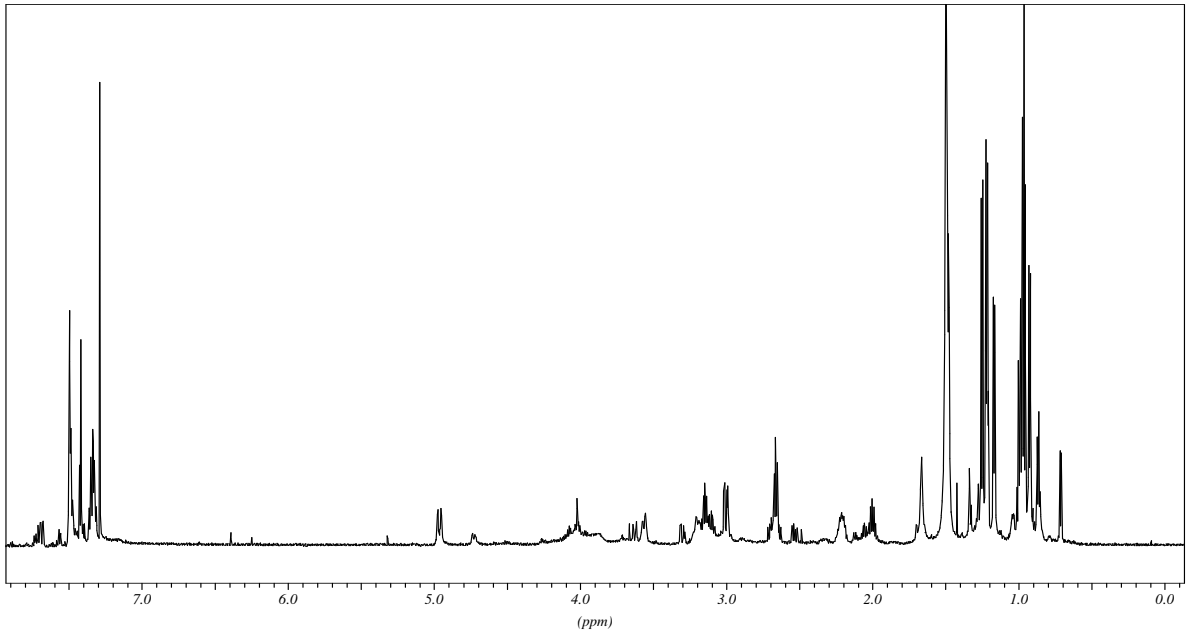
40
20
0
(ppm)


Boc
N
O
N
N
N

21c


7.0
6.0
5.0
4.0
3.0
2.0
1.0
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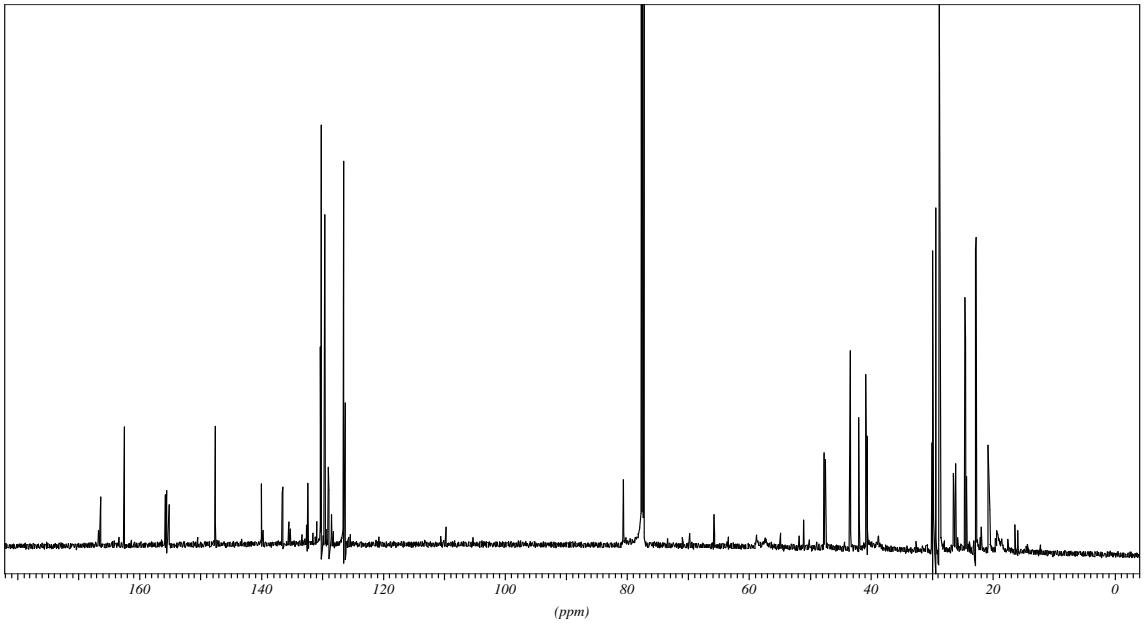
(ppm)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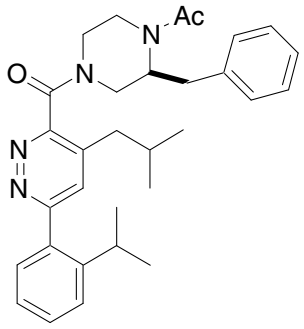
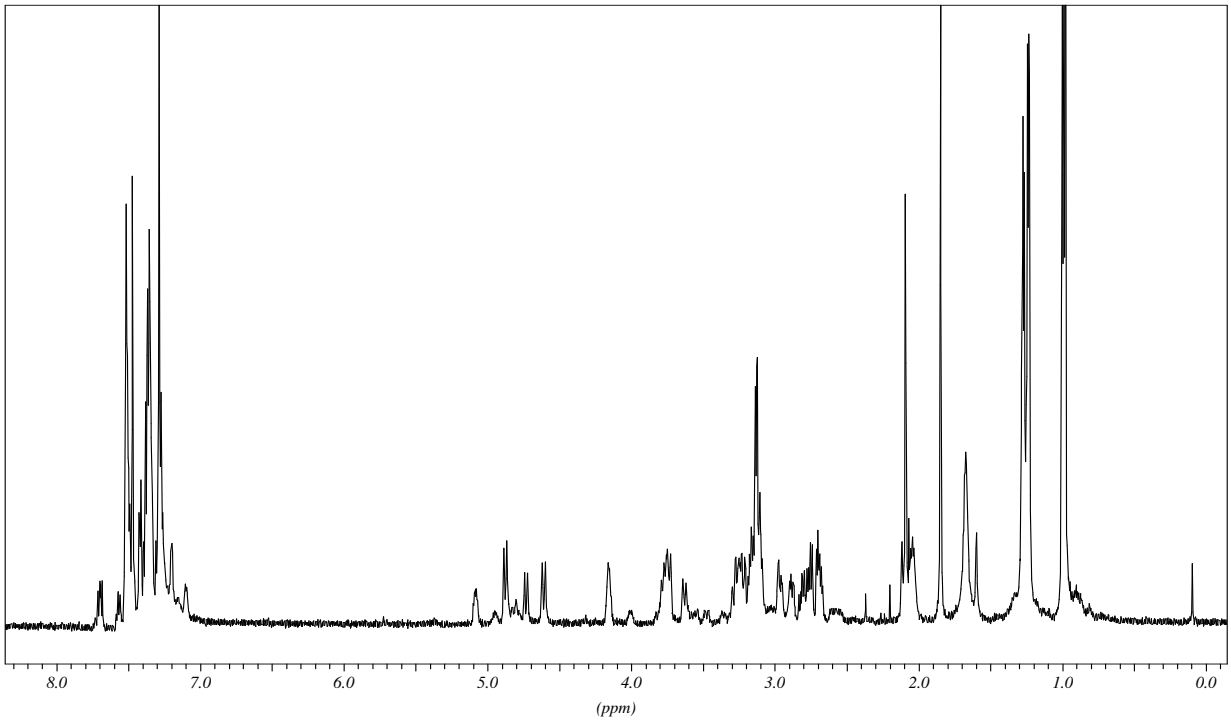
(ppm)


Ac
N
O
N
N
N

22b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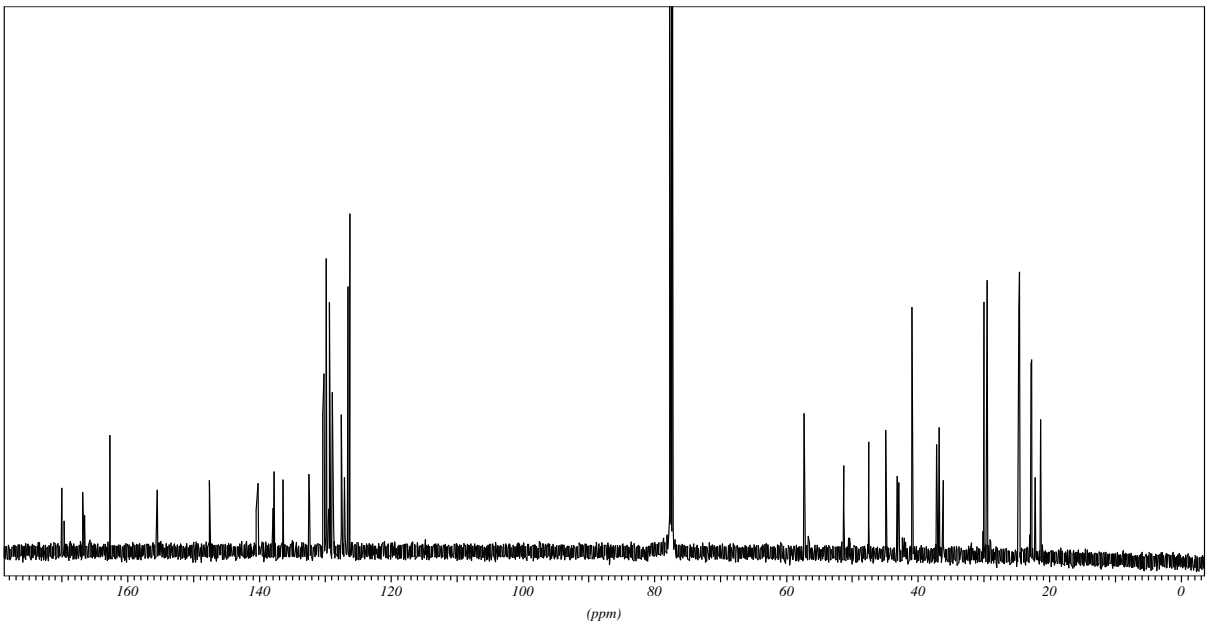
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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40
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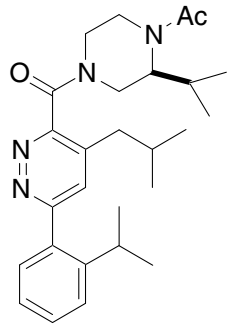
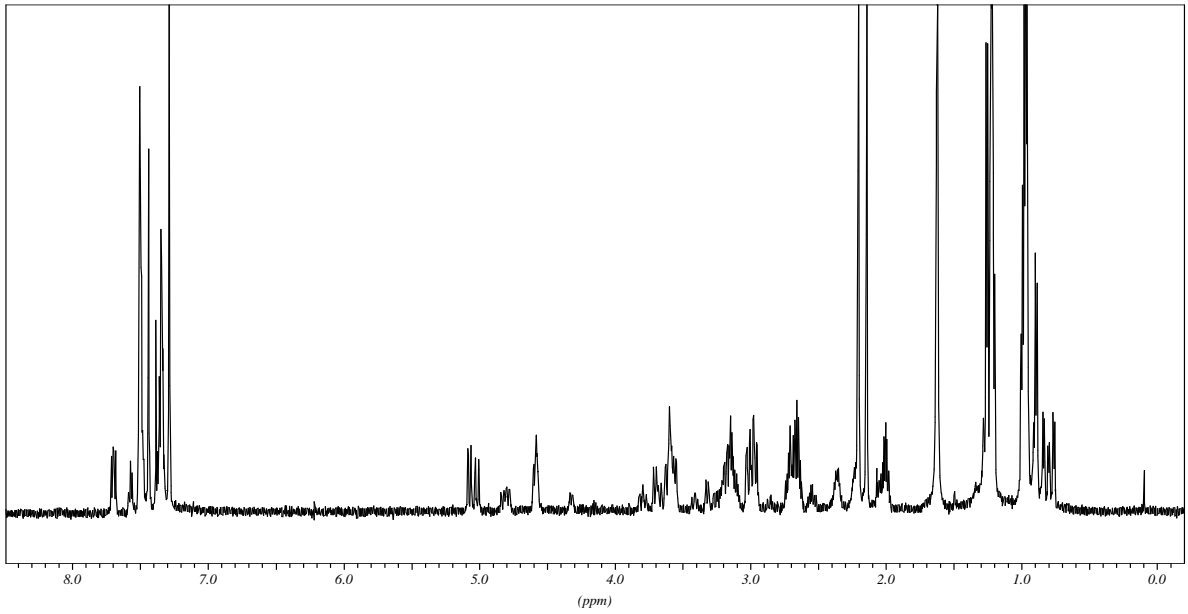
0
(ppm)


Ac
N
O
N
N
N

22c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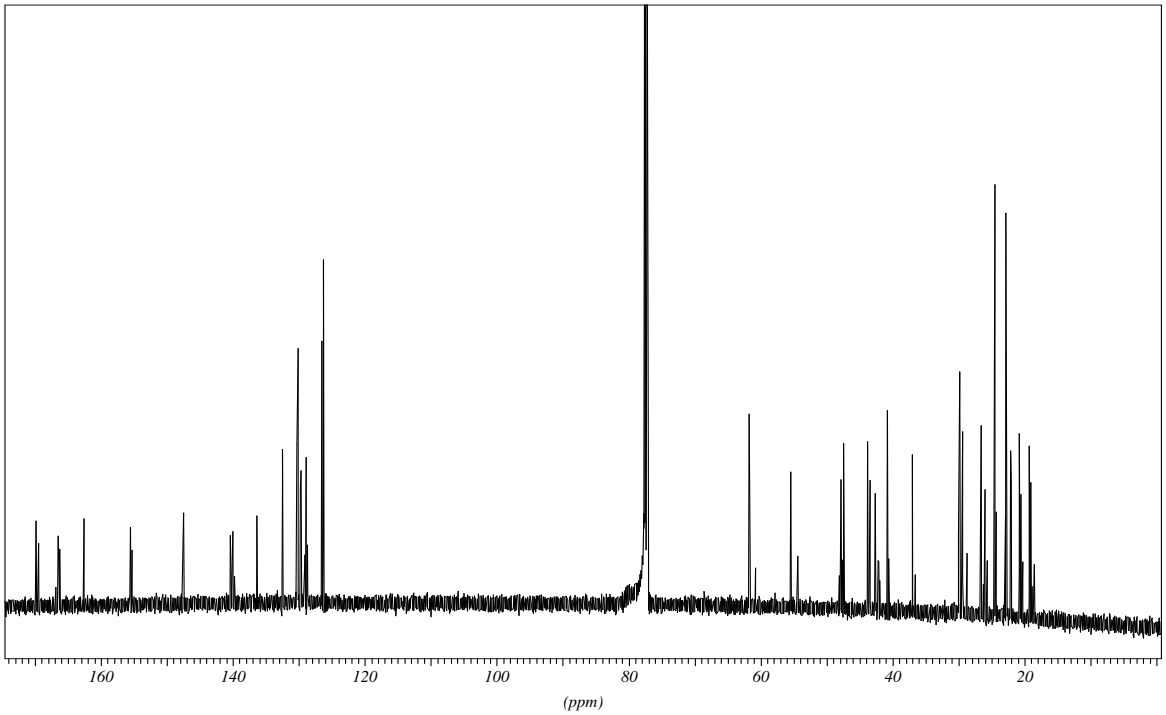
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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140
120
100
80
60
40
20
(ppm)