Supporting Information

Novel Cyclization of *Bis*-*Boc*-Guanidines: Expeditive Traceless Synthesis of 1,3,5-Oxadiazinones under Microwave Conditions

Gorakh S. Yellol, Chung Tsai Wen and Chung-Ming Sun*

Laboratory of Combinatorial Drug Discovery, Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan

*Corresponding author: cmsun@mail.nctu.edu.tw

Contents

General experimental methods S2

Microwave Irradiation and Conventional Experimental Methods S2

General synthetic scheme S3

Trapping of intermediate 5a S4

Mechanism of cyanation reaction S5

Library of *N*-cyano-Piperazinyl/Diazepanyl Oxadiazinones S6

General procedures for synthesis of guanidinylating reagent **3** S7

General procedures for synthesis of **7** and **8** S8

Experimental data of compounds **7a-7h** and **8a-8h** S11

^{1}H NMR and ^{13}C NMR spectrums of compounds **7a-7h** and **8a-8h** S19

^{1}H NMR spectrums of compounds **5a** S51

ORTAP diagram of compound **7b** S52

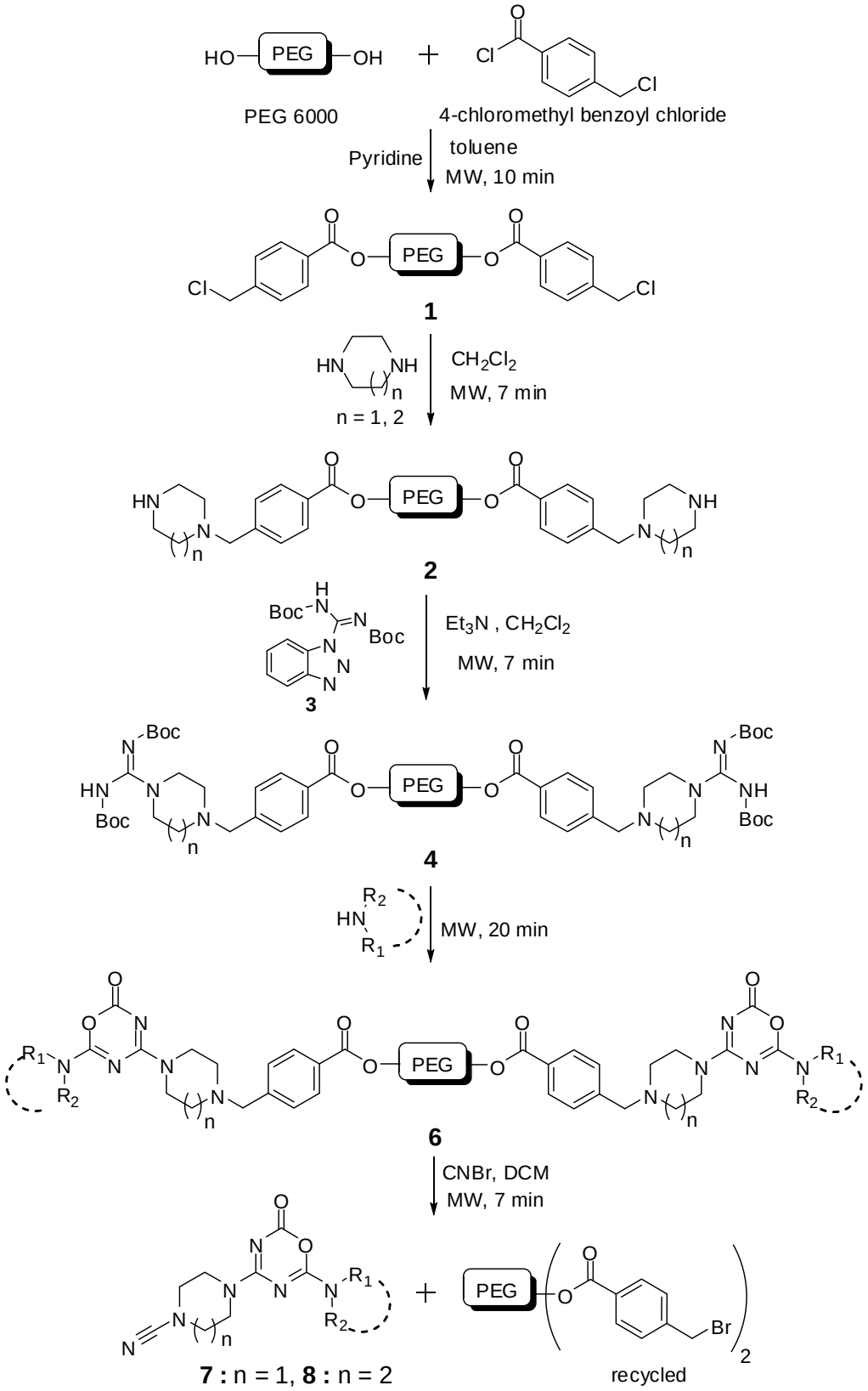
General experimental methods

Dichloromethane and methanol were distilled before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25mm silica gel coated Kiselgel 60 F_{254} plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230-400 mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. Normal phase HPLC was performed on a Shimadzu LC-10AT series machine with a Hypersil (250 x 4.6 mm) analytical column. PEG was purchased from SHOWA.

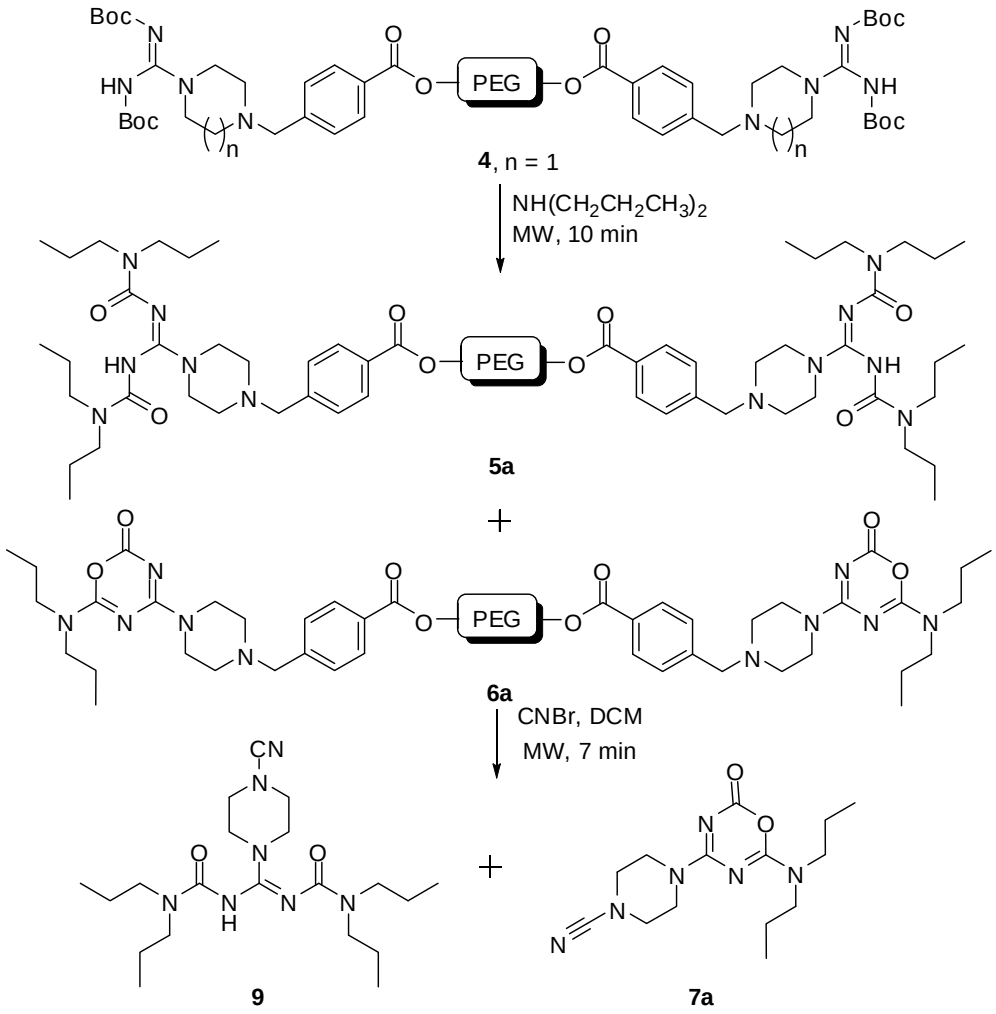
Microwave Irradiation and Conventional Experimental Methods.

A monomode CEM Discover™ microwave reactor with standard configuration operating at a maximum power of 300 W and equipped with an infrared pyrometer for the control of temperature and compressed air system for cooling was used. All the microwave experiments were performed under optimized reaction conditions of power and temperature in open vessel. To understand the significance of dielectric heating, few experiments were also carried out with the conventional method in round bottom flasks, using same reaction mixtures at room temperature or by classical heating in an oil bath. To monitor the progression of reaction on a polymer support, a small portion of the reaction mixture was pulled out, compound was precipitated and washed with cold ether, subsequently dried and proton NMR spectrum was recorded. The reaction progress and the stepwise transformations on a polymer support after each stage were cleanly observed in proton NMR spectra. The non polymer supported reactions were monitored by routine TLC analysis.

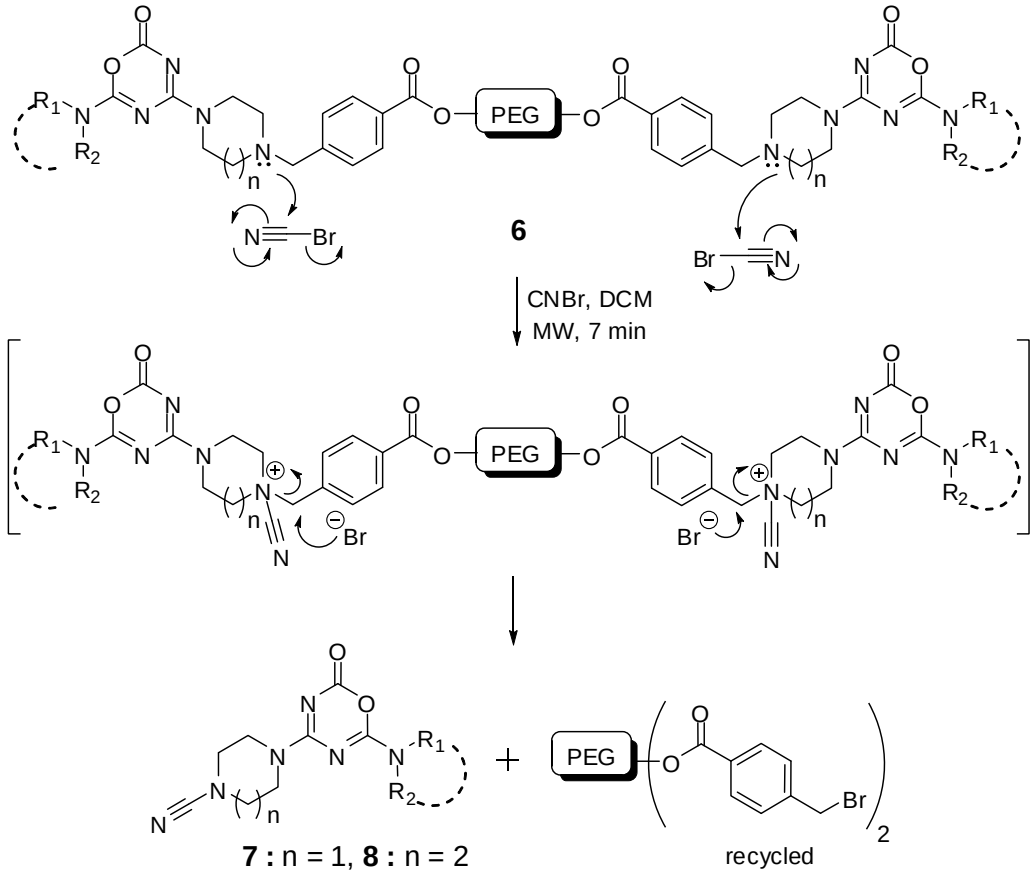
General Synthetic Scheme:



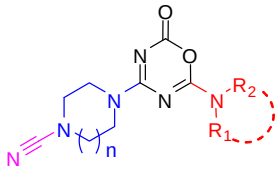
Trapping of Intermediate 5a:

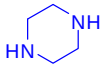
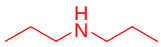
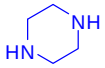
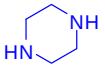
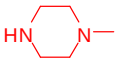
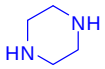
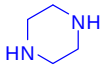
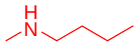
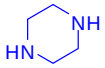
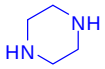
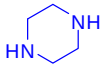
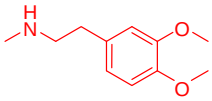
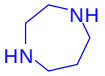
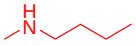
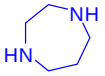
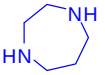
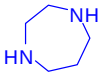
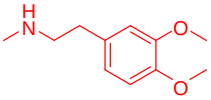
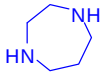
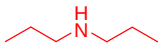
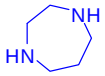
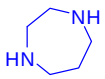
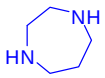


Mechanism of cyanation reaction:



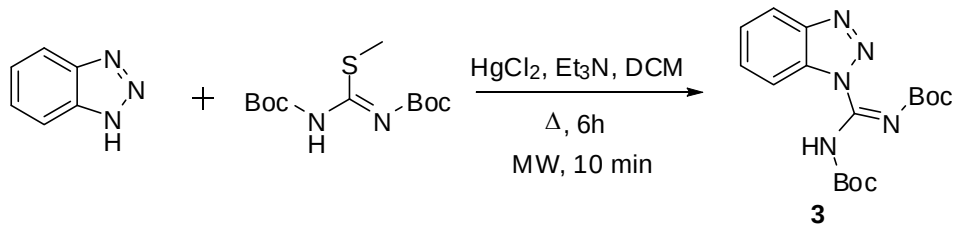
Library of *N*-cyano-Piperazinyl/Diazepanyl Oxadiazinones :



Comp.	Het.	NHR_1R_2	LRMS[a]	Yield[b]
7a	n = 1 : 		306	84%
7b	n = 1 : 		276	92%
7c	n = 1 : 		305	83%
7d	n = 1 : 		304	88%
7e	n = 1 : 		292	82%
7f	n = 1 : 		290	89%
7g	n = 1 : 		292	91%
7h	n = 1 : 		400	83%
8a	n = 2 : 		306	80%
8b	n = 2 : 		304	91%
8c	n = 2 : 		306	90%
8d	n = 2 : 		414	83%
8e	n = 2 : 		320	85%
8f	n = 2 : 		290	93%
8g	n = 2 : 		318	87%
8h	n = 2 : 		318	84%

[a]LCMS reported as *m/z*, [b]Yields were determined of purified samples.

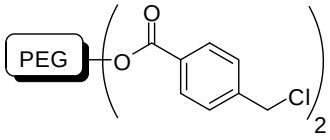
General experimental procedures for synthesis of *N,N'*-di-*tert*-butoxycarbonyl-1H-benzo[d][1,2,3]triazole-1-carboximidamide (Guanidine reagent 3):



1,3-*Bis*(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1g, 3.45 mmol) Benzotriazole (0.62g, 5.17 mmol) was added to the solution of and Mercury (II) chloride ($HgCl_2$) (1.86 g, 6.90 mmol) in dichloromethane under nitrogen. The triethylamine (1.41 ml, 10.35 mmol) was added dropwise in the reaction mixture and it was irradiated under microwave at 61W for 10 minutes. After completion, reaction mixture was filtered to remove insoluble material. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (Ethyl acetate: Hexane, 1:8) to obtain pure *N,N'*-di-*tert*-butoxycarbonyl-1H-benzo[d][1,2,3]triazole-1-carboximidamide (**3**) in 89% (1.1 g) yield.

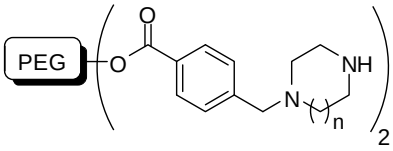
General experimental procedures for the synthesis of 7 and 8:

Preparation of PEG bound 4-(chloromethyl)benzoate (1).



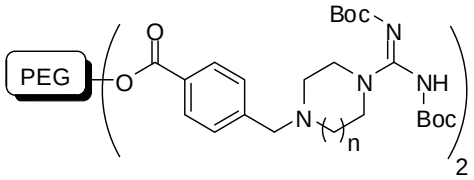
4-(Chloromethyl)benzoyl chloride (0.12 g, 0.6 mmol) was added in the solution of polyethylene glycol (5000) (1g, 0.2 mmol) in toluene (10 mL). Pyridine (0.077ml, 1.0 mmol) was added dropwise in the reaction mixture with stirring. Finally the reaction mixture was irradiated under microwave at 200W for 10 min. The reaction was monitored by TLC and ^{1}H NMR spectroscopy. After completion, the white solid (pyridine salt) was filtered out and then filtrate was concentrated under reduced pressure. It was then precipitated with cold ether. Precipitate was filtered, washed well and dried to afford white solid of PEG bound 4-(chloromethyl)benzoate (**1**) in 91% (3.3 g) yield.

Synthesis of PEG bound 4-(piperazin/1,4-diazepan-1-ylmethyl)benzoate (2).



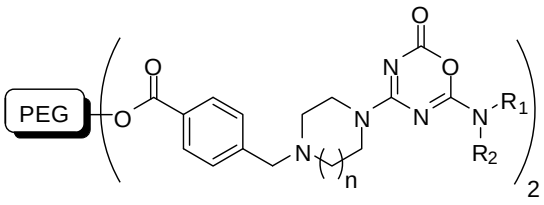
PEG bound 4-(chloromethyl)benzoate (**1**) (1g, 0.19 mmol) was added in the solution of piperazines or homopiperazines (0.95mmol) in dichloromethane (10 mL). The reaction mixture was stirred under microwave irradiation at 120W for 7 min. The reaction was monitored by TLC and ^{1}H NMR spectroscopy. After completion, reaction mixture was concentrated under reduced pressure. It was then precipitated with ice-cold ether. Precipitate was filtered, washed well and dried to afford white solid of PEG bound 4-(piperazin/homopiperazin-1-ylmethyl)benzoate (**2**) in 87% (0.88 g) yield.

General procedure for PEG bound 4-((4-(N,N'-bis(tert-butoxycarbonyl) carbamimidoyl)piperazin/1,4-diazepan-1-yl)methyl)benzoate (4).



PEG bound 4-(piperazin/homopiperazin-1-ylmethyl)benzoate (**2**) (1g, 0.19 mmol) was added in the solution of *N,N'*-di-*tert*-butoxycarbonyl-1H-benzo[d][1,2,3]triazole-1-carboximidamide (**3**) (0.10g, 0.28 mmol) in dichloromethane (10 mL). Then triethylamine (0.77 ml, 0.57 mmol) was added in the reaction mixture and it was treated under microwave irradiations at 150W for 7 minutes. The reaction was monitored by TLC and ^{1}H NMR spectroscopy. After completion, reaction mixture was concentrated under reduced pressure. It was then precipitated with ice-cold ether. Precipitate was filtered, washed well and dried to afford light yellow solid of PEG bound 4-((4-(*N,N'*-bis(*tert*-butoxycarbonyl)carbamimidoyl)piperazin/homopiperazin-1-yl)methyl) benzoate (**4**) in high yields (92-96%).

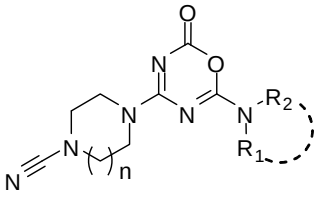
General procedure for PEG bound 4-((4-(6-(dialkylamino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazin /1,4-diazepan-1-yl)methyl)benzoate (6).



PEG bound 4-((4-(*N,N'*-bis(*tert*-butoxycarbonyl)carbamimidoyl)piperazin/diazepan-1-yl)methyl) benzoate (**4**) (1g, 0.18 mmol) was added in the solution secondary amines (0.9 mmol) [generally 3.0 equivalent secondary amine is sufficient, while to take the advantage of polymer supported

reaction, excess of amine (5 equivalent) can force the reaction to completing in short reaction time with enhance yields.] in tetrahydrofuran (10 mL). Then triethylamine (0.77 ml, 0.57 mmol) was added in the reaction mixture and it was treated under microwave irradiations at 200W for 7 minutes. The reaction was monitored by TLC and ^{1}H NMR spectroscopy. After completion, reaction mixture was concentrated under reduced pressure. It was then precipitated with ice-cold ether. Precipitate was filtered, washed well and dried to afford light yellow solid of PEG bound 4-((4-(6-(dialkylamino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazin/homopiperazin-1-yl)methyl)benzoate (**6**) in 80-93 % yield.

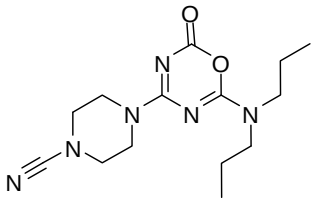
General procedure for *N*-cyanopiperazinyl and 1,4-diazepanyl oxadiazinones (7/8).



Cyanogen bromide (0.058g, 0.54 mmol) was added in the solution of PEG bound 4-((4-(6-(dialkylamino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazin/diazepan-1-yl)methyl)benzoate (**6**) (1g, 0.18 mmol) in tetrahydrofuran (10 mL). The reaction mixture was treated under microwave irradiations at 100W for 7 minutes. The reaction was monitored by TLC and ^{1}H NMR spectroscopy. After completion, reaction mixture was filtered to remove solid material and then filtrate was concentrated under reduced pressure. PEG bound 4-(bromomethyl)benzene was then precipitated with ice-cold ether. It was then removed by filtration. The filtrates were concentrated and subjected to HPLC purity. The crude HPLC purities were indicated in Table 1. It was further purified using column chromatography to furnish *N*-cyanopiperazinyl and homopiperazinyl oxadiazinones (**7**/**8**) in good to excellent (80-93%) yields.

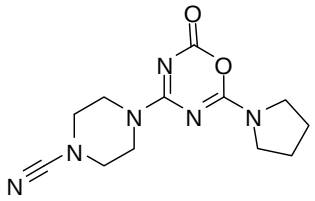
Experimental data for compounds 7a-7h and 8a-h:

4-(6-(dipropylamino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazine-1-carbonitrile (7a).



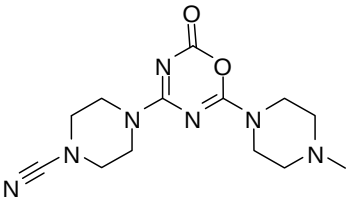
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (t, *J* = 5.1 Hz, 2H), 3.90 (t, *J* = 5.1 Hz, 2H), 3.45-3.37 (m, 4H), 3.27 (t, *J* = 5.1 Hz, 4H), 1.65 (sext, *J* = 7.5 Hz, 4H), 0.96-0.91 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 161.7, 151.4, 117.3, 49.9, 49.2, 49.2, 49.1, 43.3, 42.8, 21.7, 20.9, 11.7, 11.5; IR (cm^{-1}, neat): 2964, 2214, 1768, 1605, 1365; Mass spectrum (EI) *m/z* 306 (M+). Exact mass calcd for $C_{14}H_{22}N_6O_2$: *m/z* 306.1804. Found 306.1803.

4-(2-oxo-6-(pyrrolidin-1-yl)-2H-1,3,5-oxadiazin-4-yl)piperazine-1-carbonitrile (7b).



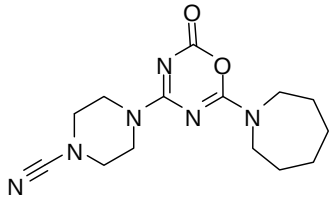
^{1}HNMR (300 MHz, $CDCl_3$) δ 3.98 (t, *J* = 5.1 Hz, 2H), 3.92 (t, *J* = 5.1 Hz, 2H), 3.59 (t, *J* = 6.8 Hz, 2H), 3.53 (t, *J* = 6.8 Hz, 2H), 3.25 (t, *J* = 5.1 Hz, 4H), 2.05-1.92 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 159.9, 151.4, 117.3, 49.2, 49.1, 47.3, 46.5, 43.2, 42.8, 25.5, 25.0; IR (cm^{-1}, neat): 2935, 2208, 1759, 1606, 1368; Mass spectrum (EI) *m/z* 276 (M+). Exact mass calcd for $C_{12}H_{16}N_6O_2$: *m/z* 276.1335. Found 276.1338.

4-(6-(4-methylpiperazin-1-yl)-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazine-1-carbonitrile (7c).



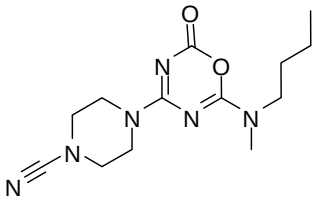
^{1}HNMR (300 MHz, $CDCl_3$) δ 3.82 (t, *J* = 4.8 Hz, 2H), 3.75 (s, 3H), 3.69 (t, *J* = 4.8 Hz, 2H), 3.63 (t, *J* = 4.5 Hz, 4H), 3.36 (t, *J* = 4.8 Hz, 4H) 3.24, (t, *J* = 4.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 161.1, 153.0, 117.2, 53.7, 50.0, 49.3, 48.9, 48.8, 46.7, 44.8, 39.2, 30.3; IR (cm^{-1}, neat): 2932, 2214, 1754, 1614, 1386; Mass spectrum (EI) *m/z* 305 (M+). Exact mass calcd for $C_{13}H_{19}N_7O_2$: *m/z* 305.1600. Found: *m/z* 305.1648.

4-(6-(azepan-1-yl)-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazine-1-carbonitrile (7d).



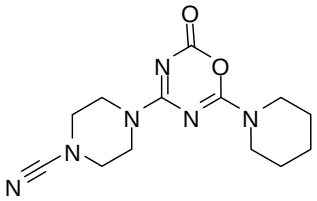
^{1}HNMR (300 MHz, $CDCl_3$) δ 4.00 (t, *J* = 5.1 Hz, 2H), 3.92 (t, *J* = 5.1 Hz, 2H), 3.67-3.62 (m, 4 H), δ 3.27 (t, *J* = 5.1 Hz, 4H), 1.82-1.68 (m, 4H), 1.65-1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 161.5, 151.5, 117.3, 49.2, 49.1, 47.9, 47.0, 43.3, 42.8, 28.2, 27.2, 27.1, 27.0; IR (cm^{-1}, neat): 2927, 2214, 1765, 1605, 1371; Mass spectrum (EI) *m/z* 400 (M+). Exact mass calcd for $C_{14}H_{20}N_6O_2$: *m/z* 304.3559. Found 304.3463.

4-(6-(butyl(methyl)amino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazine-1-carbonitrile (7e).



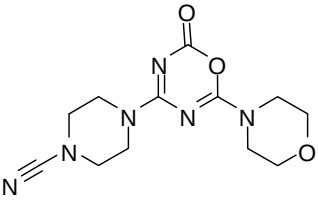
^{1}HNMR (300 MHz, $CDCl_3$) δ 4.01 (t, *J* = 5.1 Hz, 2H), 3.96-3.90 (m, 2H), 3.55-3.46 (m, 2H), 3.27 (t, *J* = 5.1 Hz, 4H), 3.11 (s, 3H), 1.61 (quint, *J* = 7.5 Hz, 2H), 1.35 (sext, *J* = 7.5 Hz, 2H), 0.99-0.94 (t, , *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 161.7, 151.2, 117.3, 49.2, 43.3, 42.9, 35.3, 34.4, 29.9, 29.1, 20.1, 14.1; IR (cm^{-1}, neat): 2956, 2214, 1747, 1614, 1376; Mass spectrum (EI) *m/z* 292 (M+). Exact mass calcd for $C_{13}H_{20}N_6O_2$: *m/z* 292.1648. Found 292.1653.

4-(2-oxo-6-(piperidin-1-yl)-2H-1,3,5-oxadiazin-4-yl)piperazine-1-carbonitrile (7f).



^{1}HNMR (300 MHz, $CDCl_3$) δ 4.01 (t, *J* = 5.1 Hz, 2H), 3.92 (t, *J* = 5.1 Hz, 2H), 3.73-3.62 (m, 4H), 3.27 (t, *J* = 5.1 Hz, 4H), 1.73-1.56 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 160.6, 151.4, 117.3, 49.2, 49.1, 45.5, 44.9, 43.3, 42.9, 26.0, 25.6, 24.3; IR (cm^{-1}, neat): 2926, 2214, 1756, 1606, 1367; Mass spectrum (EI) *m/z* 290 (M+). Exact mass calcd for $C_{13}H_{18}N_6O_2$: *m/z* 290.1491. Found 290.1482.

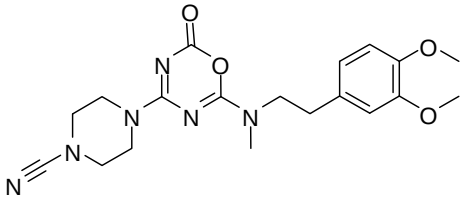
4-(6-morpholino-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazine-1-carbonitrile (7g).



^{1}HNMR (300 MHz, $CDCl_3$) δ 4.01 (t, *J* = 4.8 Hz, 2H), 3.91 (t, *J* = 4.8 Hz, 2H), 3.82-3.65 (m, 8H), 3.29-3.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 161.0, 150.6, 150.6, 66.5, 66.4,

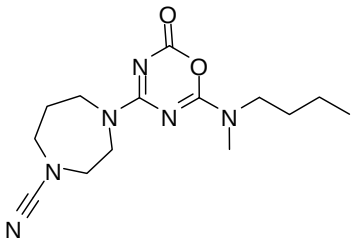
49.2, 49.1, 44.4, 44.1, 43.4, 42.9; IR (cm^{-1}, neat) : 2925, 2216, 1766, 1607, 1362; Mass spectrum (EI) *m/z* 292 (M+). Exact mass calcd for $C_{12}H_{16}N_6O_3$: *m/z* 292.1284. Found 292.1288.

4-(6-((3,4-dimethoxyphenethyl)(methyl)amino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)piperazine-1-carbonitrile (7h).



^{1}HNMR (300 MHz, $CDCl_3$) δ 6.82-6.66 (m, 3H), 4.01-3.94 (m, 2H), 3.91 (t, *J* = 5.1 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.62 (t, *J* = 5.1 Hz, 2H), 3.30-3.22 (m, 4H), 3.15 (d, *J* = 5.4 Hz, 3H), 2.90-2.83 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 161.8, 151.1, 149.5, 148.4, 130.6, 121.1, 117.2, 112.2, 111.8, 56.4, 56.3, 51.7, 50.7, 49.1, 43.3, 42.8, 35.8, 34.1; IR (cm^{-1}, neat) : 2850, 2210, 1747, 1668, 1372; Mass spectrum (EI) *m/z* 400 (M+). Exact mass calcd for $C_{19}H_{24}N_6O_4$: *m/z* 400.1859. Found 400.1853.

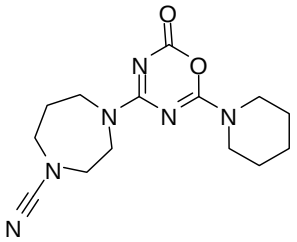
4-(6-(butyl(methyl)amino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)-1,4-diazepane-1-carbonitrile (8a).



^{1}HNMR (300 MHz, $CDCl_3$) δ 3.92-3.77 (m, 4H), 3.50-3.32 (m, 4H), 3.29-3.11 (m, 2H), 3.06 (s, 3H), 2.03-1.93 (m, 2H), 1.62-1.53 (m, 2H), 1.37-1.27 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 161.6, 151.2. 118.0, 52.0, 50.8, 48.4, 46.5, 34.3, 30.0, 29.2,

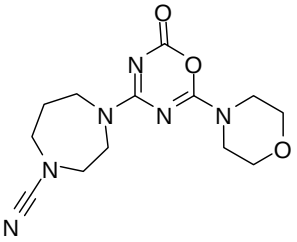
27.2, 20.2, 14.1; IR (cm-1, neat) : 2939, 2207, 1759, 1613, 1546, 1440, 1364; Mass spectrum (EI) m/z 306 (M+). Exact mass calcd for $C_{14}H_{22}N_6O_2$: m/z 306.1804. Found 306.1810.

4-(2-oxo-6-(piperidin-1-yl)-2H-1,3,5-oxadiazin-4-yl)-1,4-diazepane-1-carbonitrile (8b).



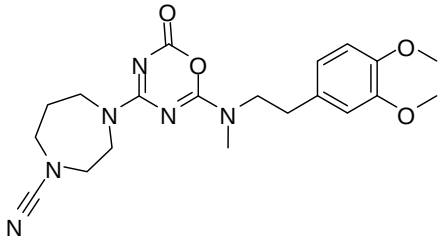
^{1}HNMR (300 MHz, $CDCl_3$) δ 3.93-3.80 (m, 4H), 3.69-3.62 (m, 4H), 3.42-3.36 (m, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 2.04 (quint, *J* = 6.8 Hz, 2H), 1.82-1.62 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 160.4, 151.3, 118.1, 50.8, 50.3, 47.2, 46.6, 45.4, 44.8, 27.3, 25.9, 25.6, 24.3; IR (cm^{-1}, neat): 2925, 2209, 1747, 1606, 1410; Mass spectrum (EI) *m/z* 304 (M+). Exact mass calcd for $C_{14}H_{20}N_6O_2$: *m/z* 304.1648. Found 304.1641.

4-(6-morpholino-2-oxo-2H-1,3,5-oxadiazin-4-yl)-1,4-diazepane-1-carbonitrile (8c).



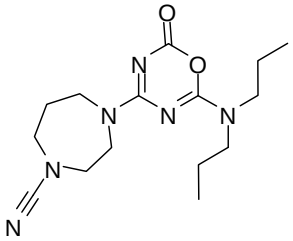
^{1}HNMR (300 MHz, $CDCl_3$) δ 3.75 (t, *J* = 5.1 Hz, 2H), 3.70-3.58 (m, 10H), 3.39 (t, *J* = 5.1 Hz, 2H), 3.29 (t, *J* = 6.1 Hz, 2H), 2.12-2.04 (quint, *J* = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 161.9, 150.5, 118.0, 66.5, 66.3, 50.2, 48.4, 47.3, 46.7, 44.3, 44.0, 27.2; IR (cm^{-1}, neat): 2921, 2207, 1732, 1614, 1362; Mass spectrum (EI) *m/z* 306 (M+). Exact mass calcd for $C_{13}H_{18}N_6O_3$: *m/z* 306.1440. Found 306.1446.

4-(6-((3,4-dimethoxyphenethyl)(methyl)amino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)-1,4-diazepane-1-carbonitrile (8d).



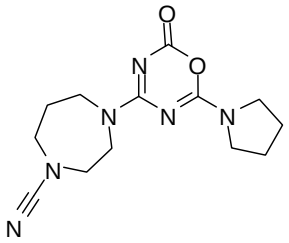
^{1}HNMR (300 MHz, $CDCl_3$) δ 6.79-6.64 (m, 3H), 3.94-3.78 (m, 2H), 3.88 (s, 3H), 3.85 (s, 6H), 3.71-3.64 (m, 2H), 3.42-3.30 (m, 2H), 3.25-3.19 (m, 2H), 3.22-2.96 (m, 2H), 2.87-2.80 (t, *J* = 6.0 Hz, 2H) , 1.98 (quint, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 161.6, 151.0, 149.5, 148.3, 130.5, 121.2, 117.9, 112.2, 111.8, 56.4, 56.3, 51.8, 50.8, 48.4, 47.3, 46.3, 35.8, 34.1, 27.1; IR (cm^{-1}, neat) : 2939, 2207, 1759, 1613, 1440; Mass spectrum (EI) *m/z* 414 (M+). Exact mass calcd for $C_{20}H_{26}N_6O_4$: *m/z* 414.2016. Found 414.2015.

4-(6-(dipropylamino)-2-oxo-2H-1,3,5-oxadiazin-4-yl)-1,4-diazepane-1-carbonitrile (8e).



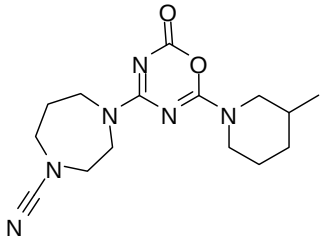
^{1}HNMR (300 MHz, $CDCl_3$) δ 3.72 (t, *J* = 4.8 Hz, 2H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.36 (t, *J* = 4.8 Hz, 2H), 3.33-3.19 (m, 6H), 2.05 (quint, *J* = 6.2 Hz, 2H), 1.52 (sext, *J* = 7.5 Hz, 4H), 0.93-0.82 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 158.6, 158.5, 118.1, 52.7, 50.5, 50.2, 48.9, 48.4, 45.8, 27.2, 22.0, 22.0, 11.9; IR (cm^{-1}, neat) : 2961, 2208, 1724, 1621, 1371; Mass spectrum (EI) *m/z* 320 (M+). Exact mass calcd for $C_{15}H_{24}N_6O_2$: *m/z* 320.1961. Found 320.1960.

4-(2-oxo-6-(pyrrolidin-1-yl)-2H-1,3,5-oxadiazin-4-yl)-1,4-diazepane-1-carbonitrile (8f).



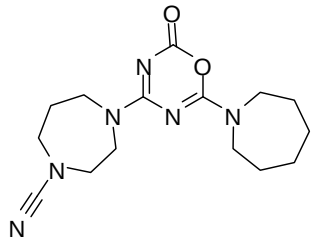
^{1}HNMR (300 MHz, $CDCl_3$) δ 3.96-3.79 (m, 4H), 3.63-3.50 (m, 4H), 3.43-3.37 (m, 2H), 3.28-3.23 (m, 2H), 2.09-1.99 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 159.9, 151.4, 117.3, 49.2, 49.1, 47.3, 46.5, 43.2, 42.8, 25.5, 25.0; IR (cm^{-1}, neat): 2943, 1702, 1650, 1337, 733; Mass spectrum (EI) *m/z* 290 (M+). Exact mass calcd for $C_{13}H_{18}N_6O_2$: *m/z* 290.1491. Found.

4-(6-(3-methylpiperidin-1-yl)-2-oxo-2H-1,3,5-oxadiazin-4-yl)-1,4-diazepane-1-carbonitrile (8g).

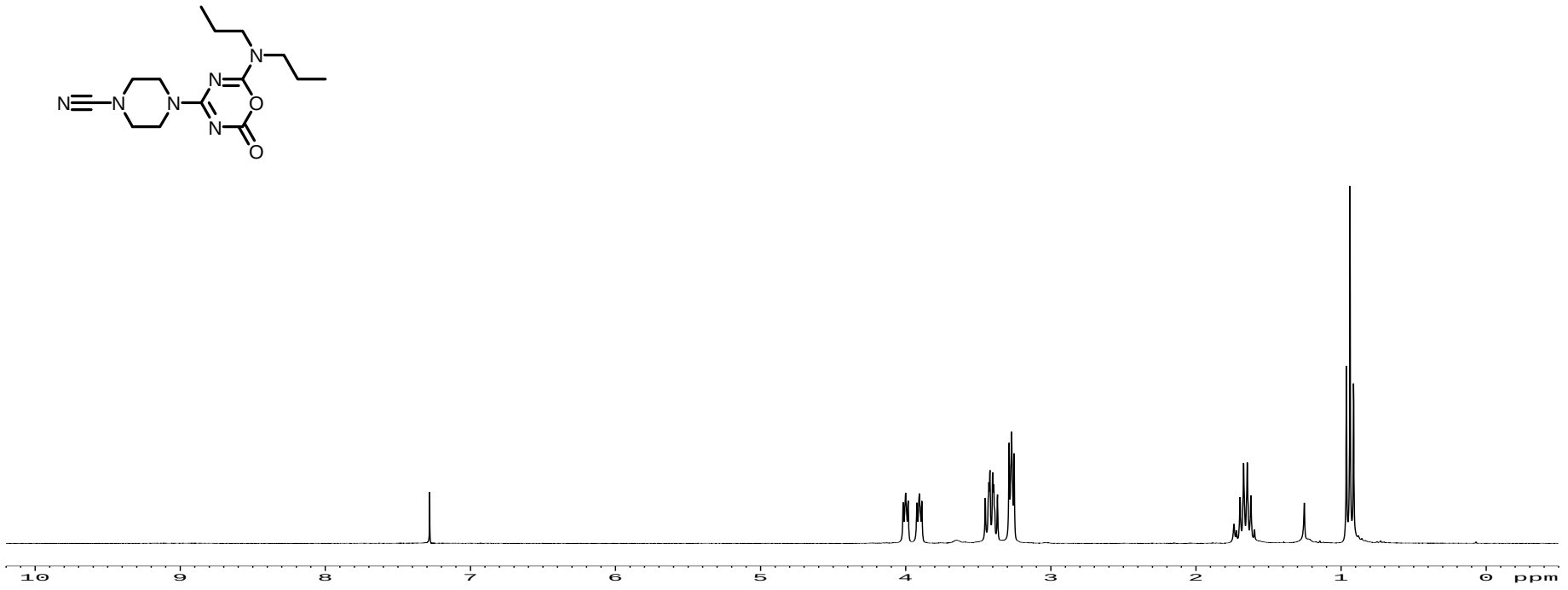


^{1}HNMR (300 MHz, $CDCl_3$) 4.33-4.18 (m, 2H), 3.92-3.77 (m, 4H), 3.40-3.35 (m, 2H), 3.26-3.22 (m, 2H), 3.92 (m, 1H), 2.61 (m, 1H), 2.02 (quint, *J* = 6.1 Hz, 2H), 1.92-1.48 (m, 4H), 1.20 (m, 1H), 0.93 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 160.4, 151.3, 118.1, 51.7, 51.5, 50.5, 48.7, 46.8, 44.6, 32.9, 31.3, 27.3, 24.9, 19.1; IR (cm^{-1}, neat): 2926, 2207, 1759, 1605, 1376; Mass spectrum (EI) *m/z* 318 (M+). Exact mass calcd for $C_{15}H_{22}N_6O_2$: *m/z* 318.1804. Found 318.1805.

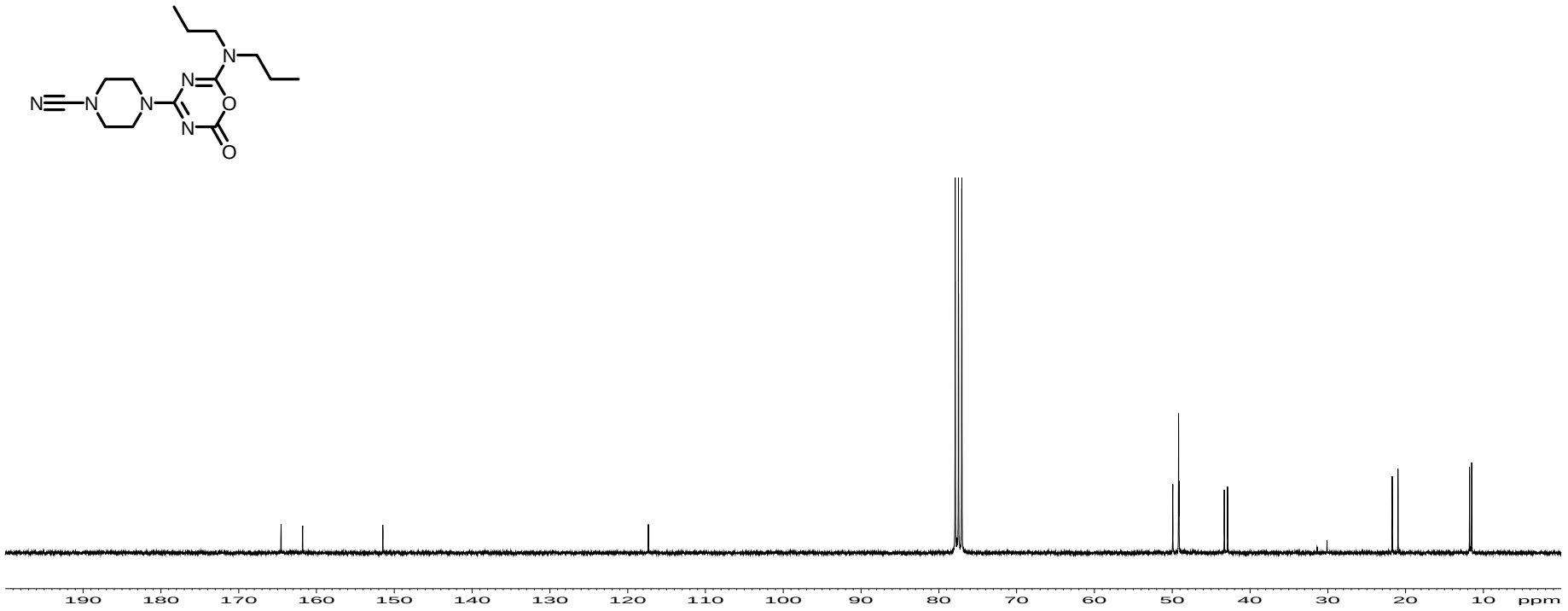
4-(6-(azepan-1-yl)-2-oxo-2H-1,3,5-oxadiazin-4-yl)-1,4-diazepane-1-carbonitrile (8h).



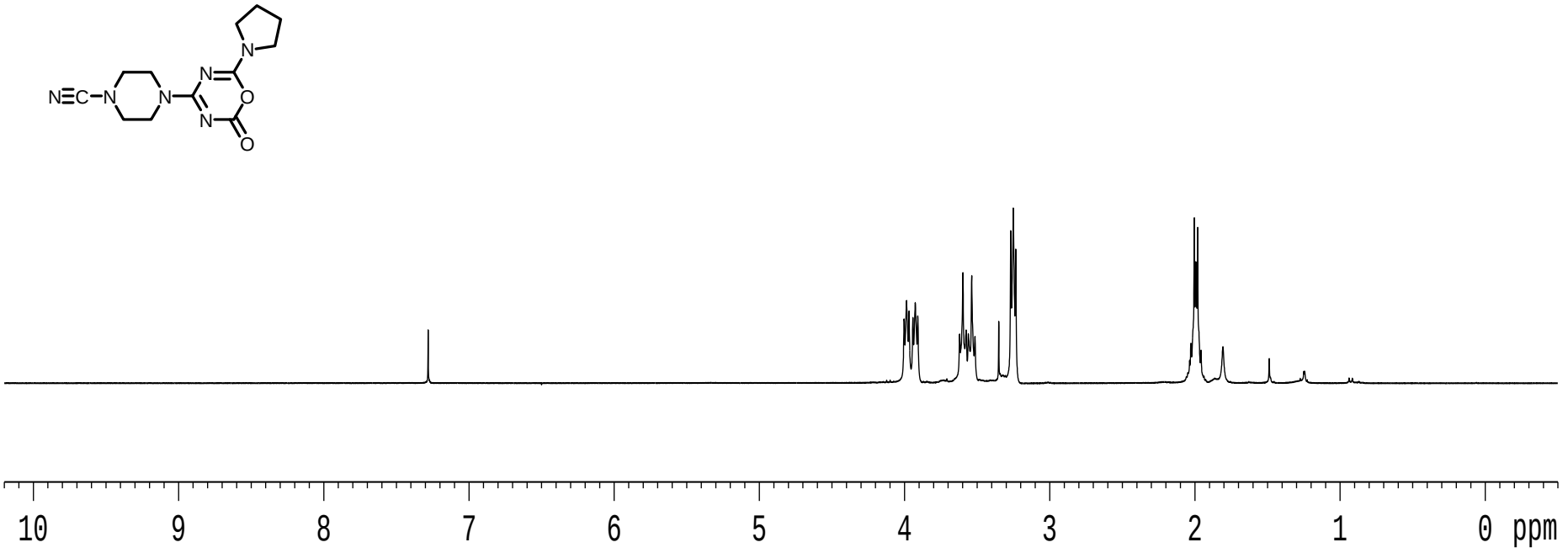
^{1}HNMR (300 MHz, $CDCl_3$) δ 3.96-3.81 (m, 4H), 3.67-3.60 (m, 4H), 3.43-3.36 (m, 2H), 3.29-3.24 (m, 2H), 2.07-2.00 (quint, *J* = 6.0 Hz, 2H), 1.88-1.72 (m, 4H), 1.62-1.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 161.3, 151.4, 118.0, 52.0, 50.8, 50.3, 48.5, 47.9, 47.2, 46.9, 28.2, 27.3, 27.2, 27.1; IR (cm^{-1}, neat) : 2930, 2207, 1760, 1605, 1372; Mass spectrum (EI) *m/z* 304 (M+). Exact mass calcd for $C_{15}H_{22}N_6O_2$: *m/z* 318.1804. Found.



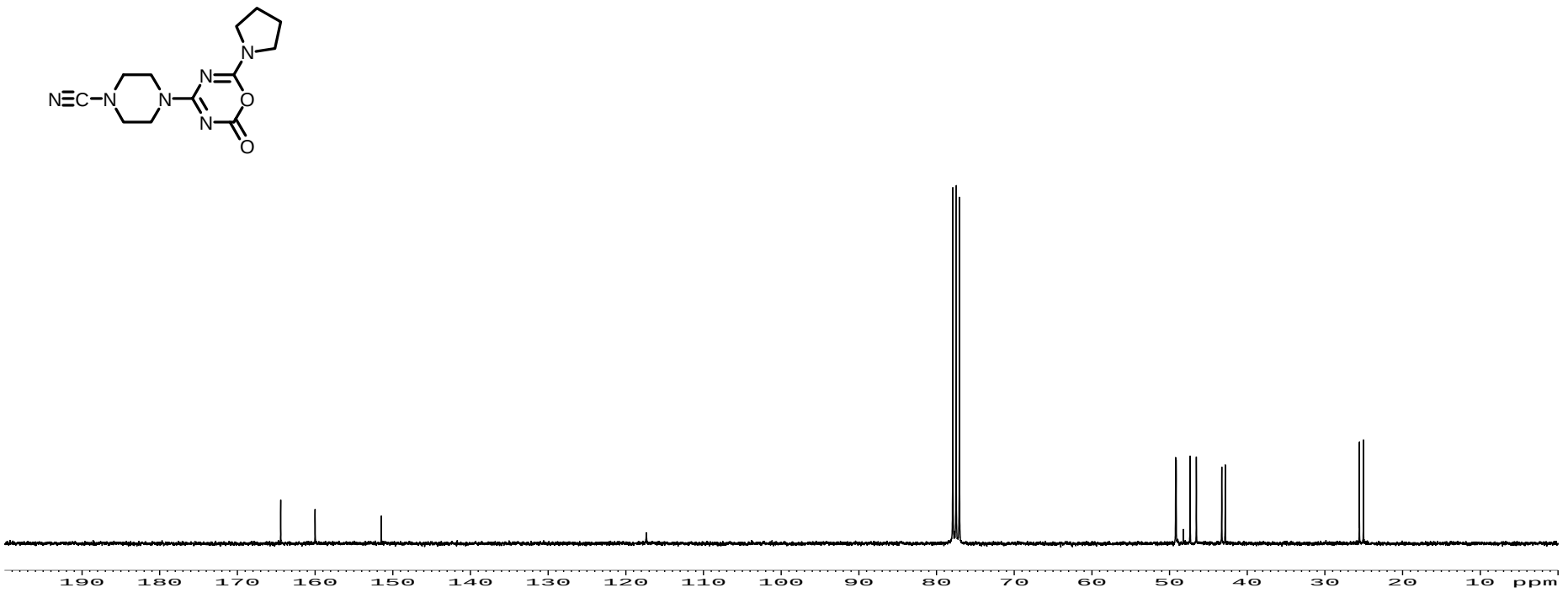
^{1}H NMR spectrum of Compound **7a**



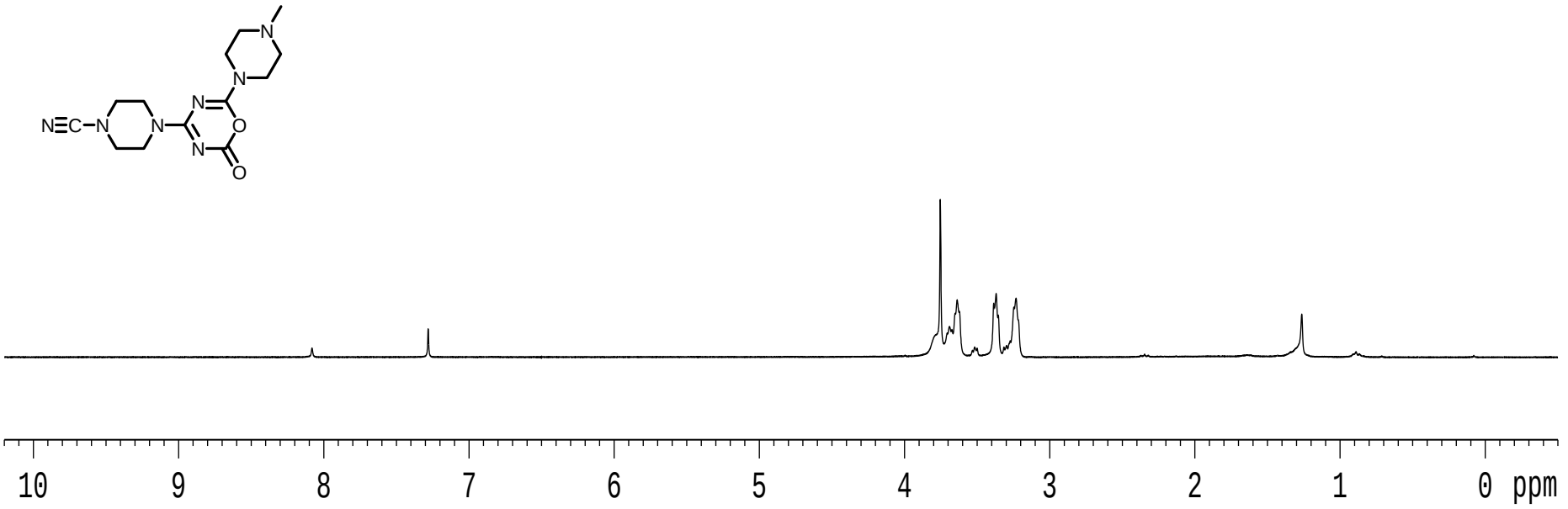
^{13}C NMR spectrum of Compound **7a**



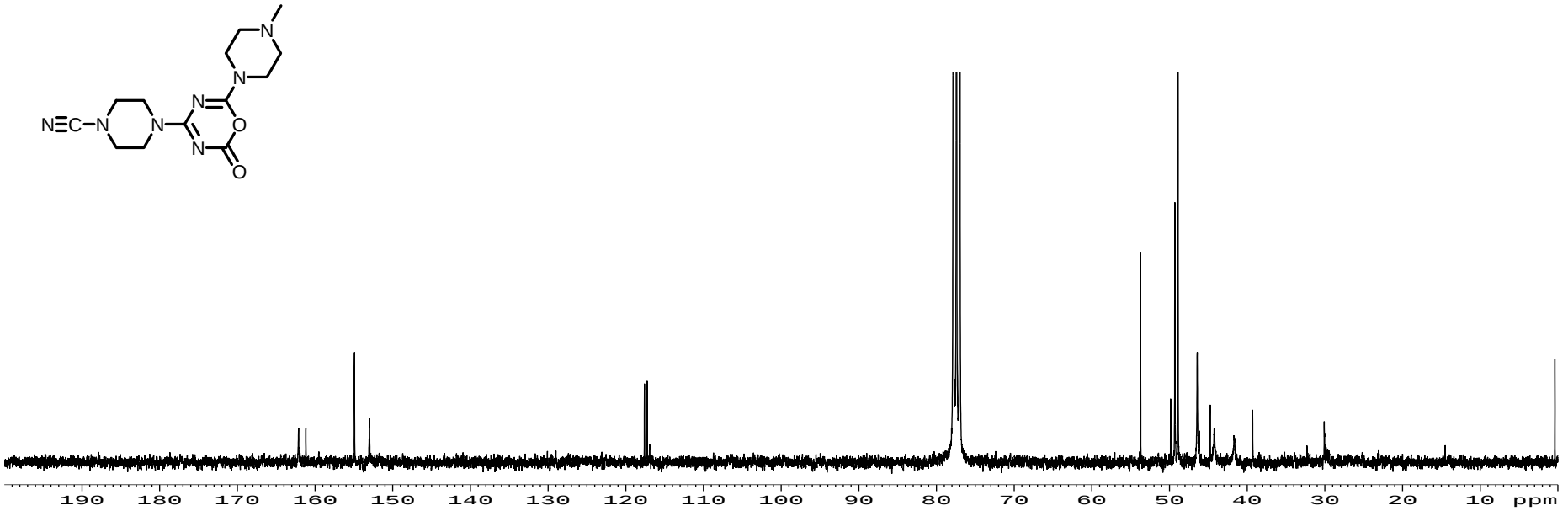
^{1}H NMR spectrum of Compound **7b**



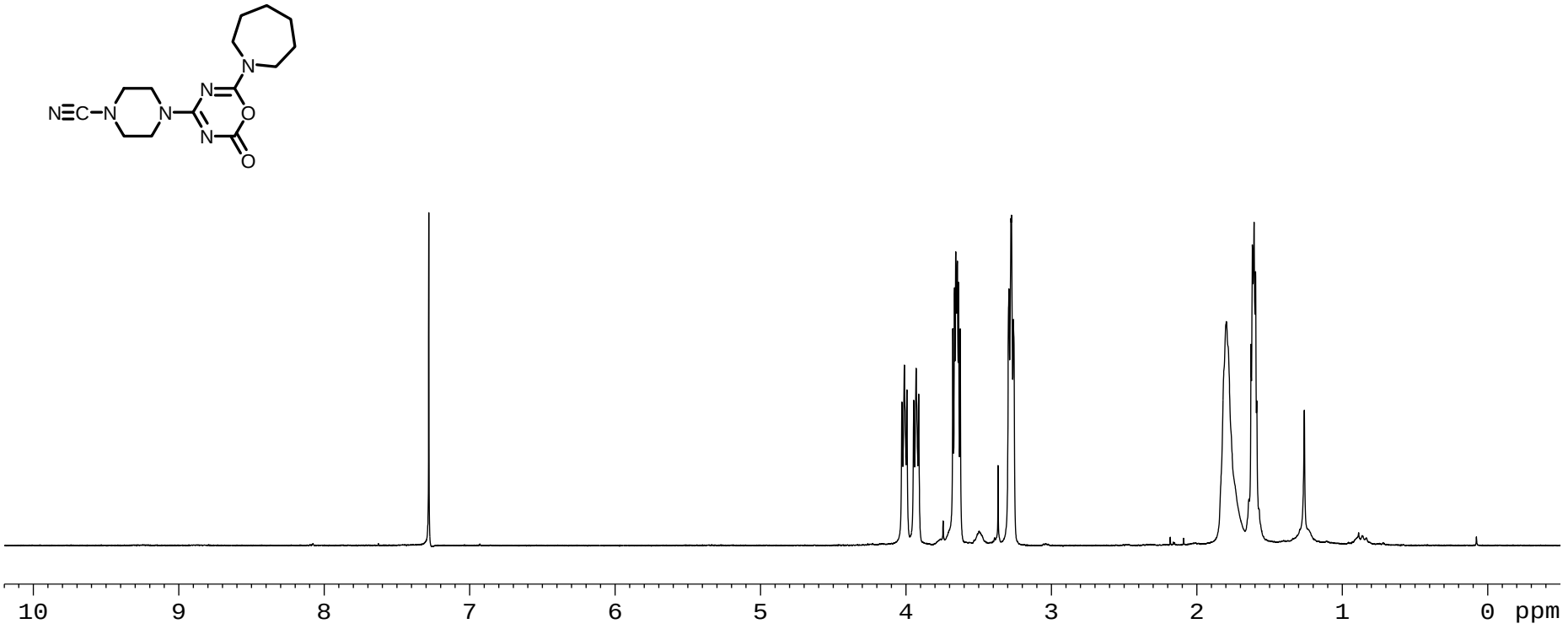
^{13}C NMR spectrum of Compound **7b**



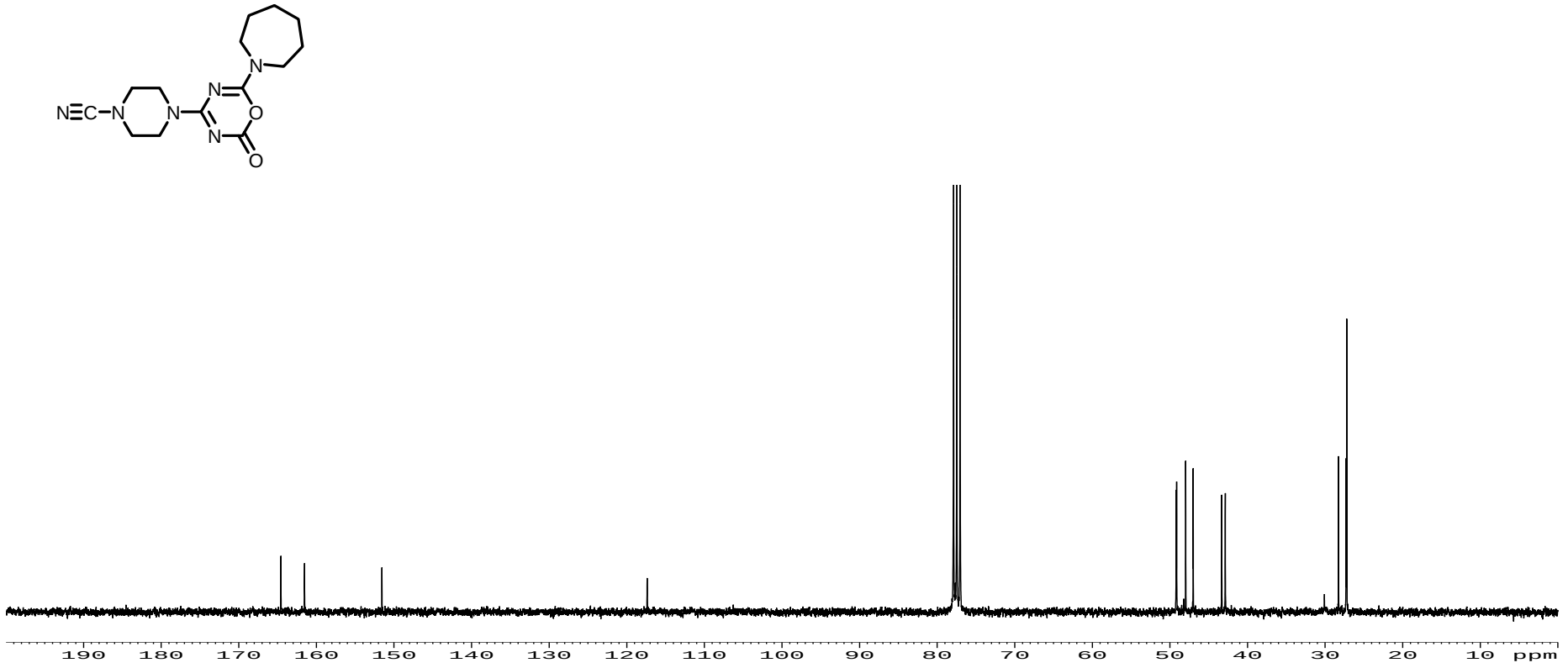
^{1}H NMR spectrum of Compound **7c**



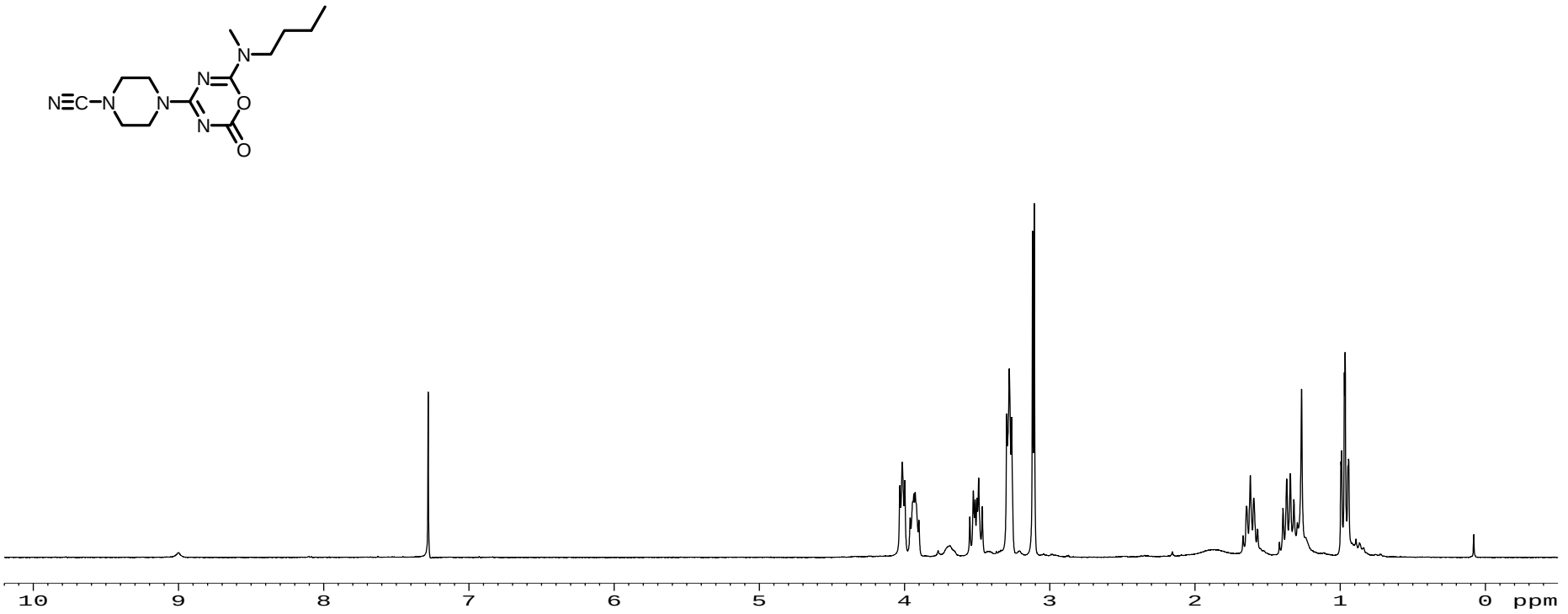
^{13}C NMR spectrum of Compound **7c**



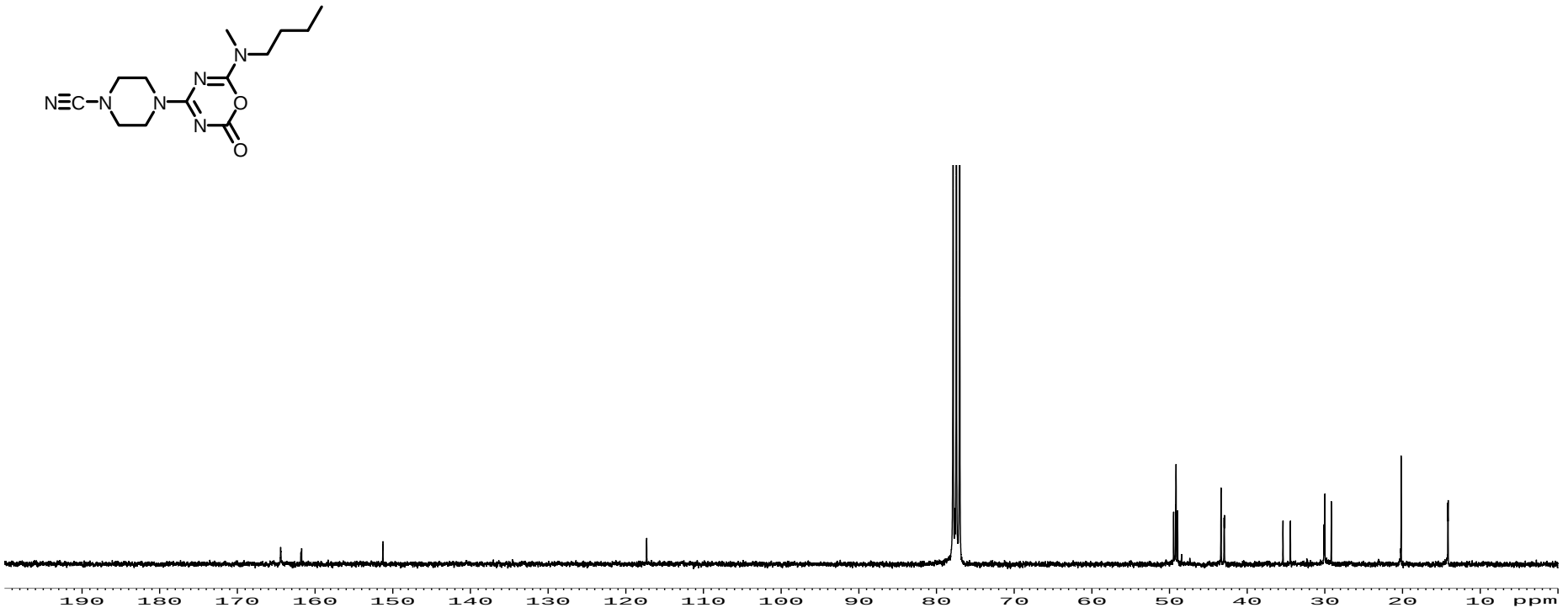
^{1}H NMR spectrum of Compound **7d**



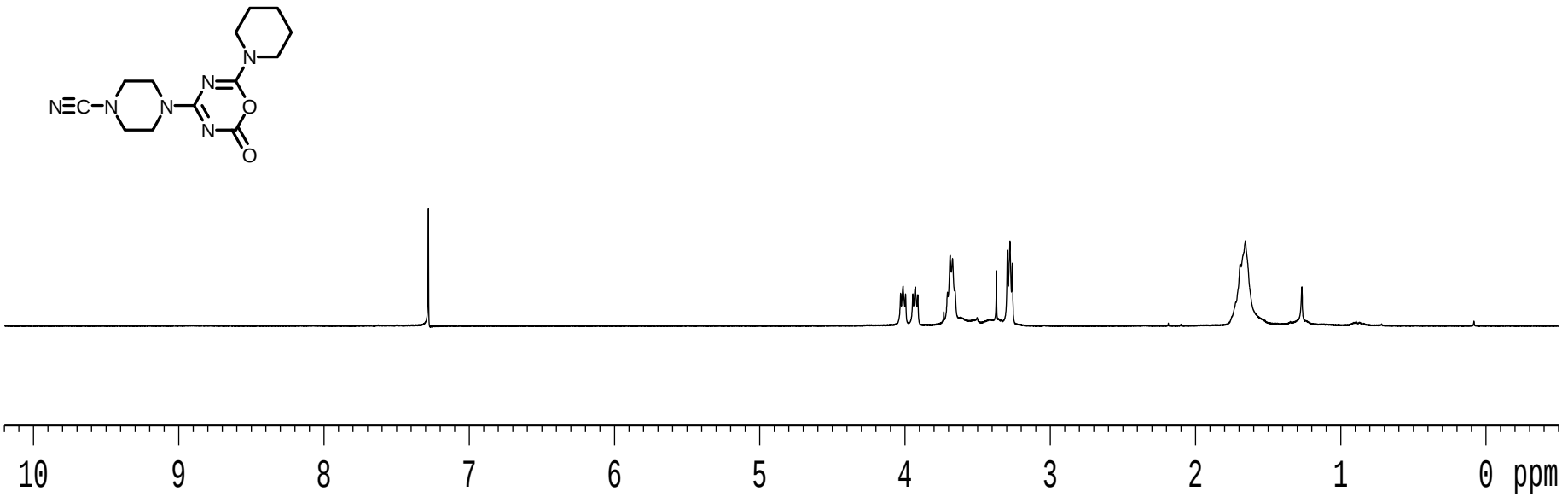
^{13}C NMR spectrum of Compound **7d**



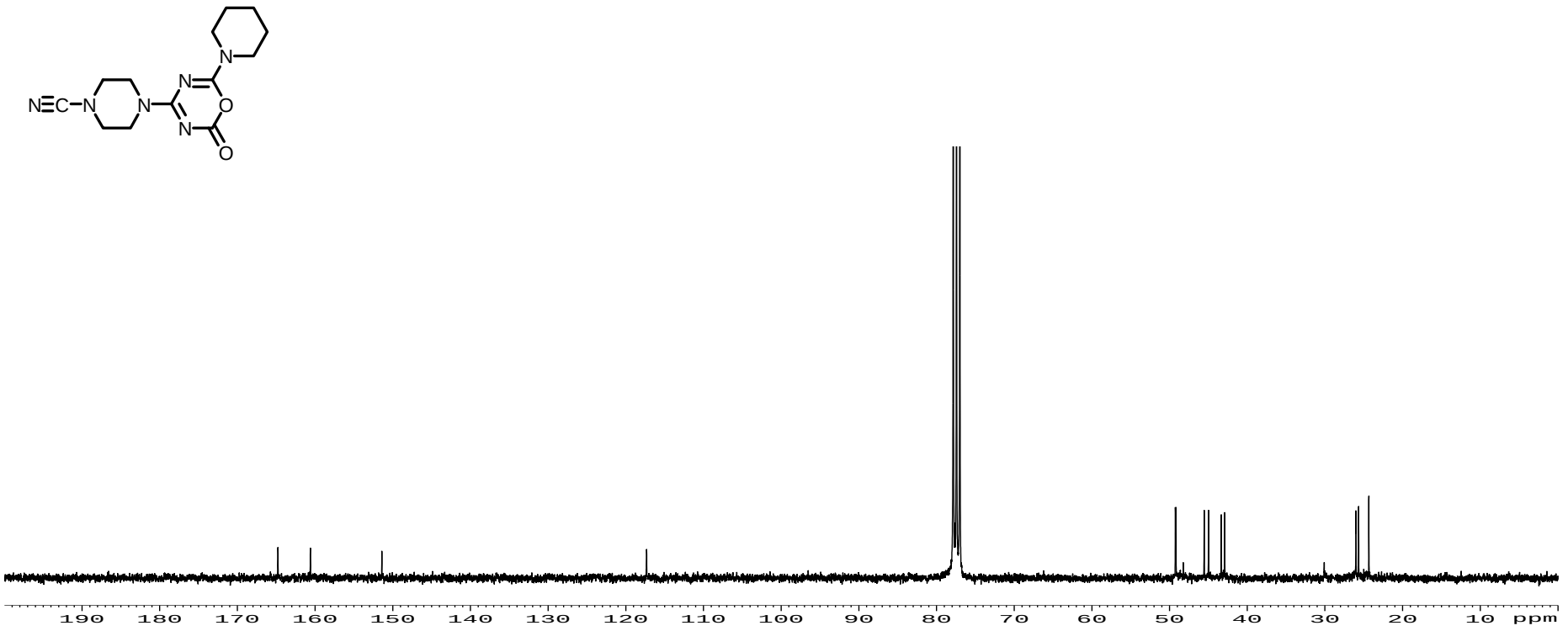
^{1}H NMR spectrum of Compound **7e**



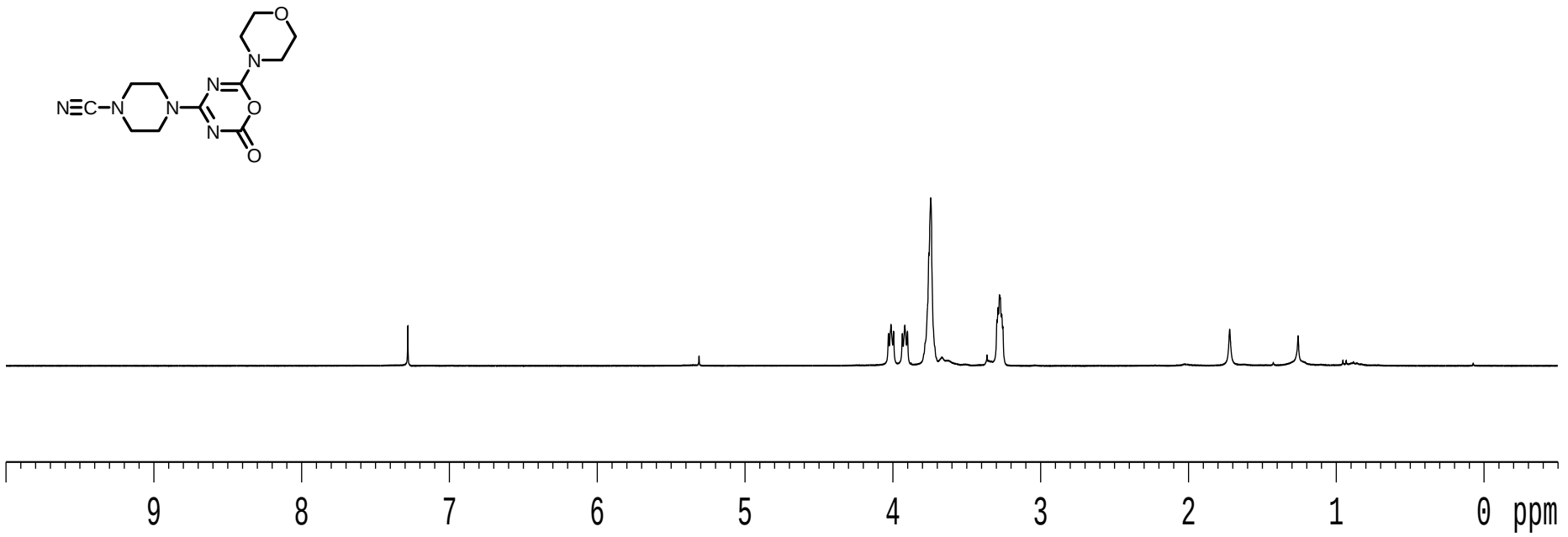
^{13}C NMR spectrum of Compound **7e**



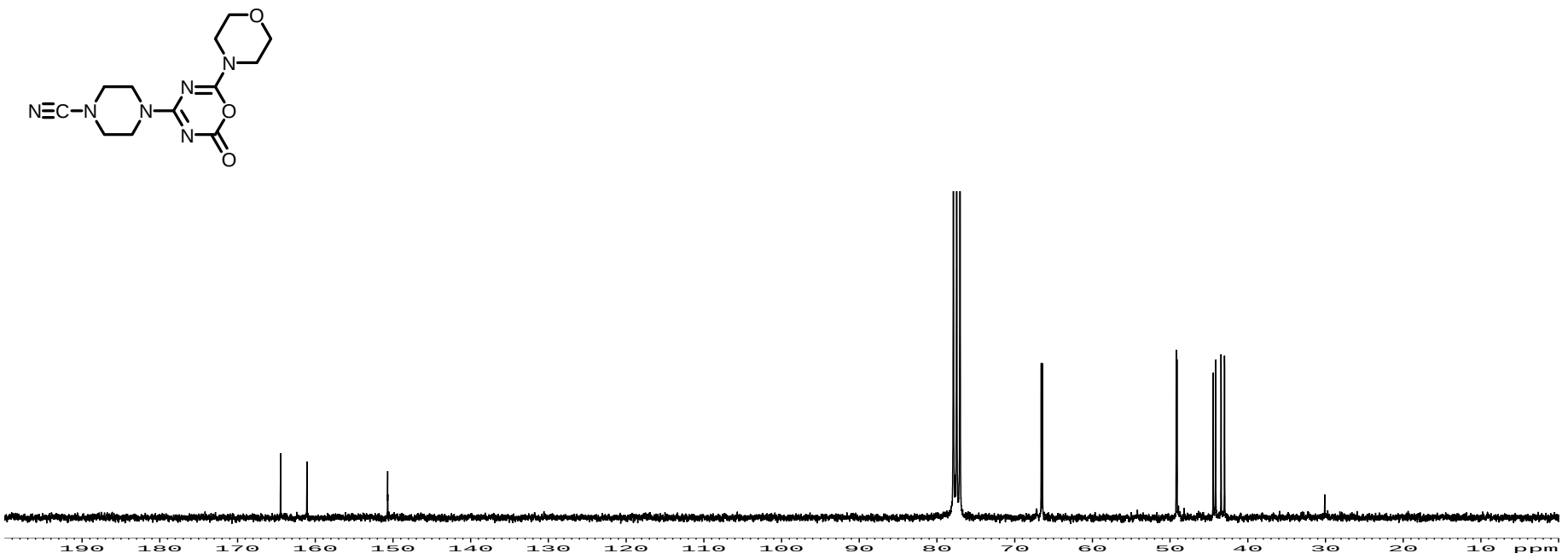
^{1}H NMR spectrum of Compound **7f**



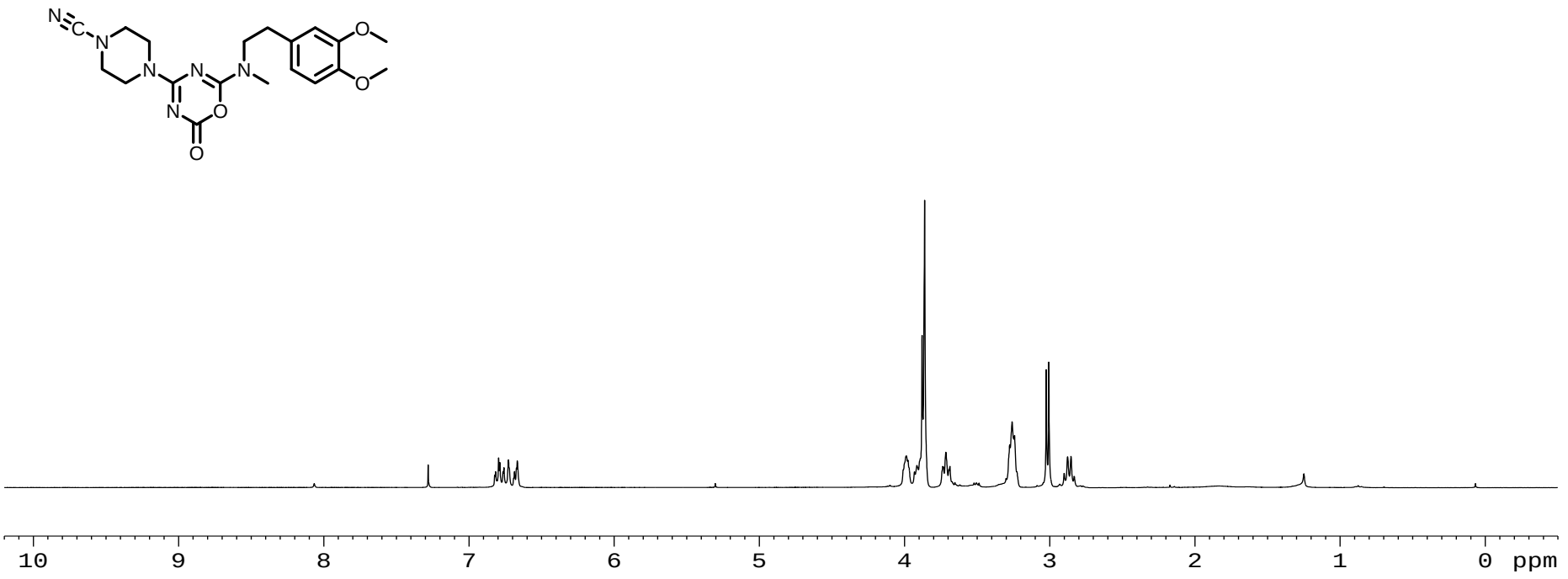
^{13}C NMR spectrum of Compound **7f**



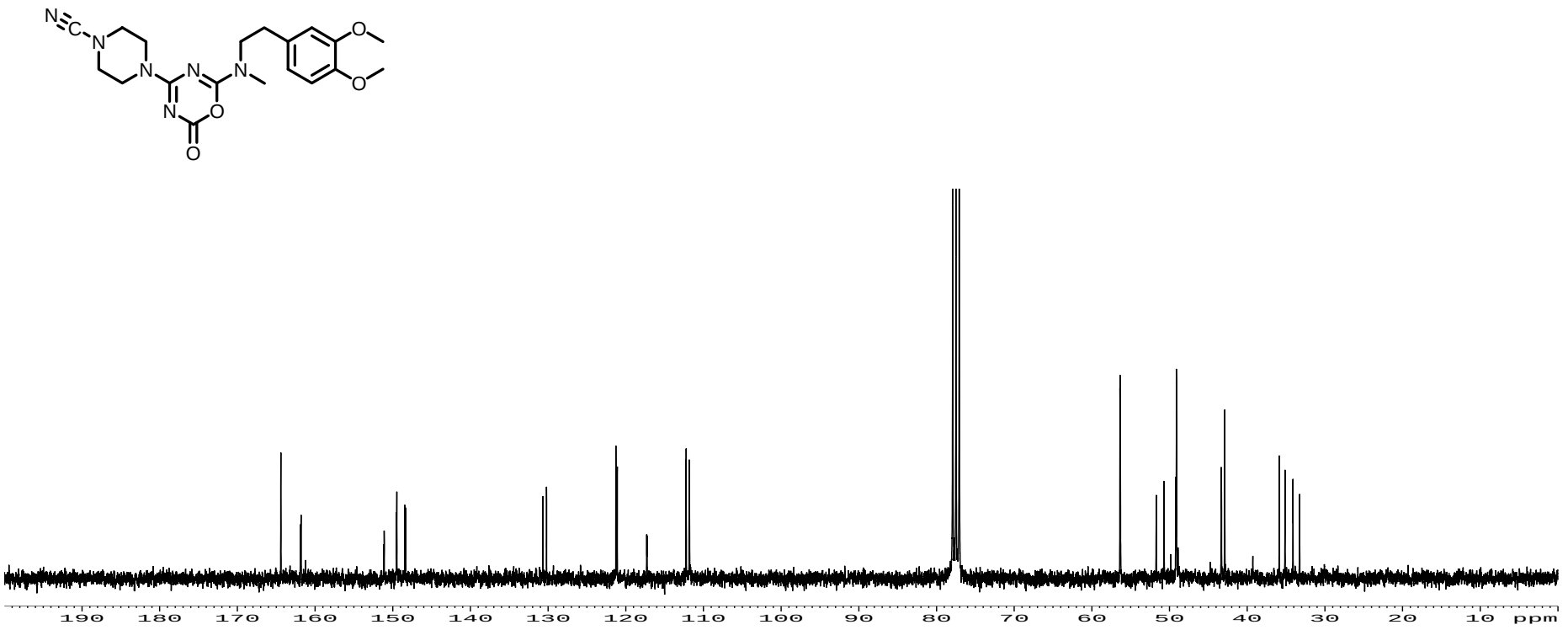
^{1}H NMR spectrum of Compound **7g**



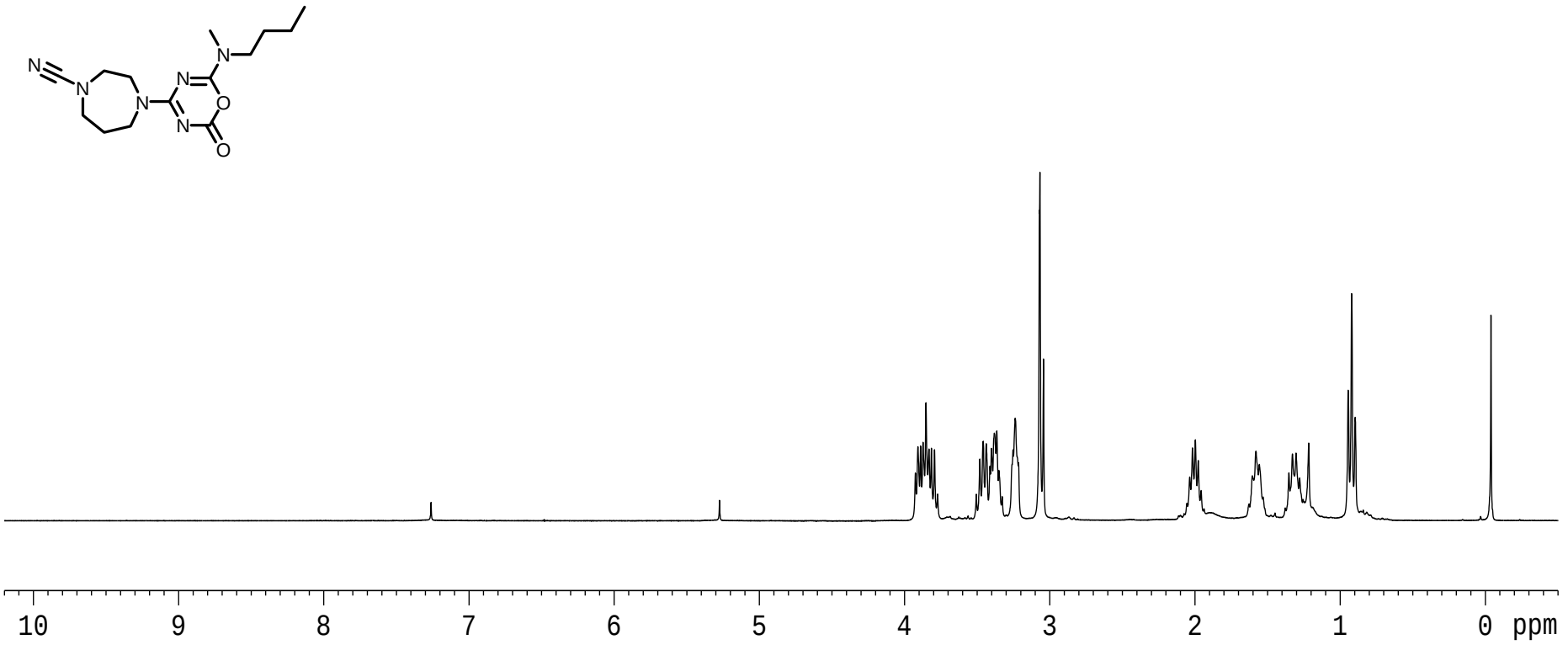
^{13}C NMR spectrum of Compound **7g**



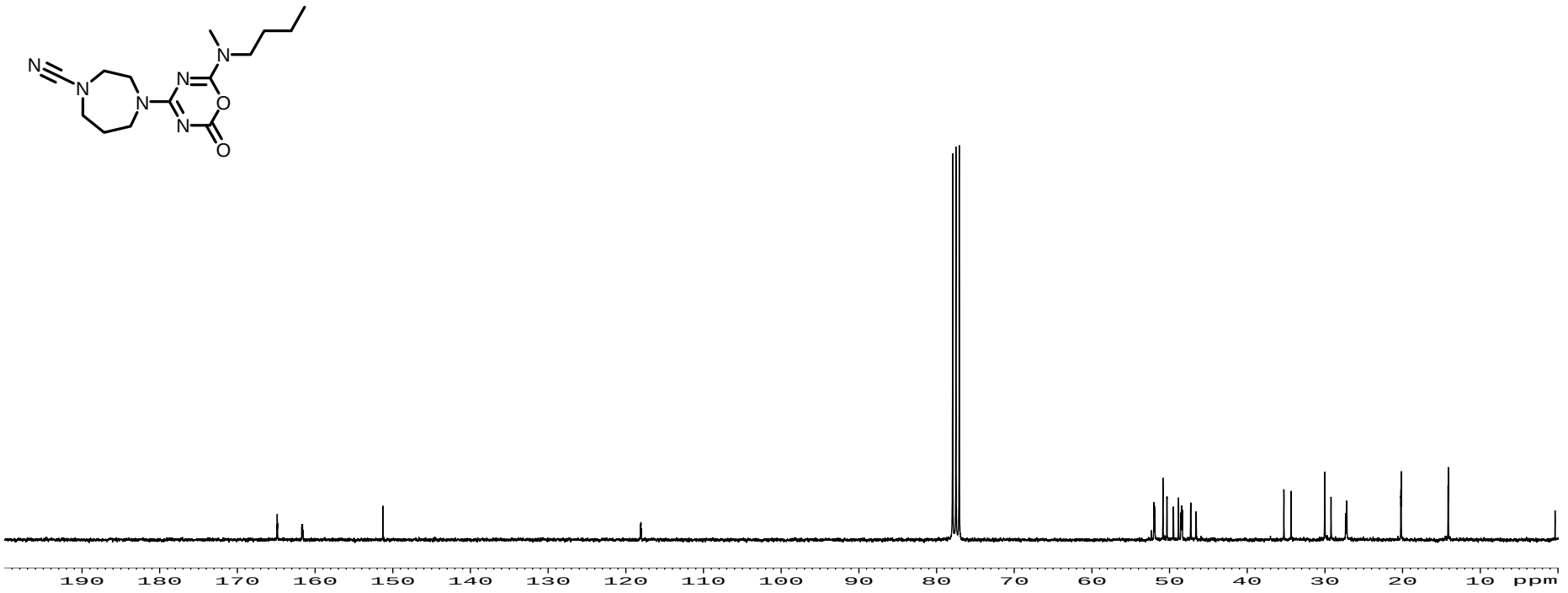
^{1}H NMR spectrum of Compound **7h**



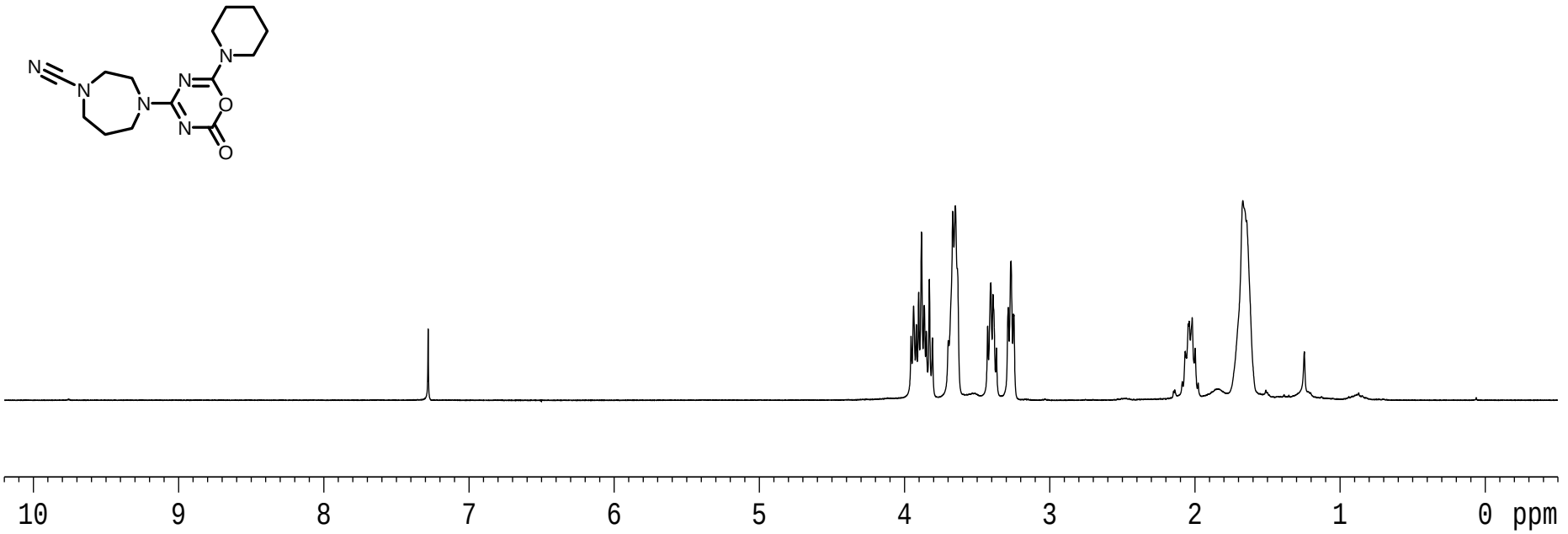
^{13}C NMR spectrum of Compound **7h**



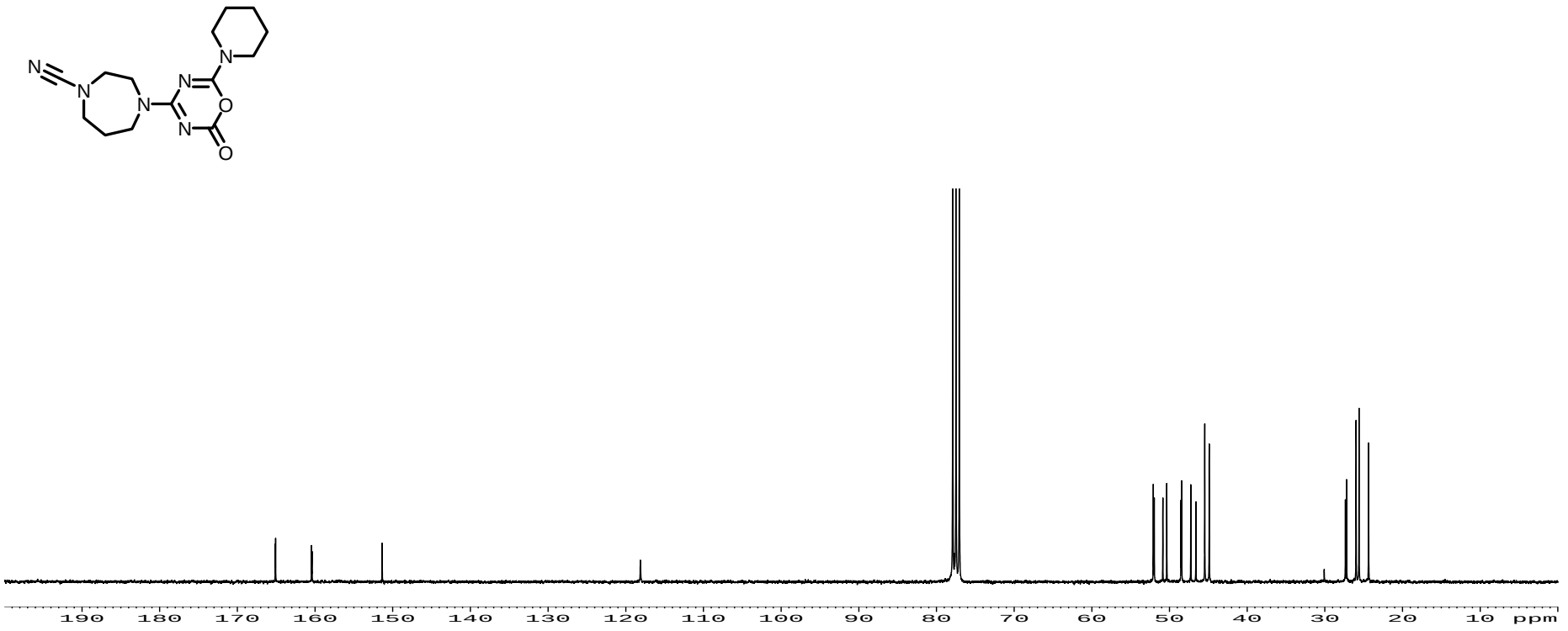
^{1}H NMR spectrum of Compound **8a**



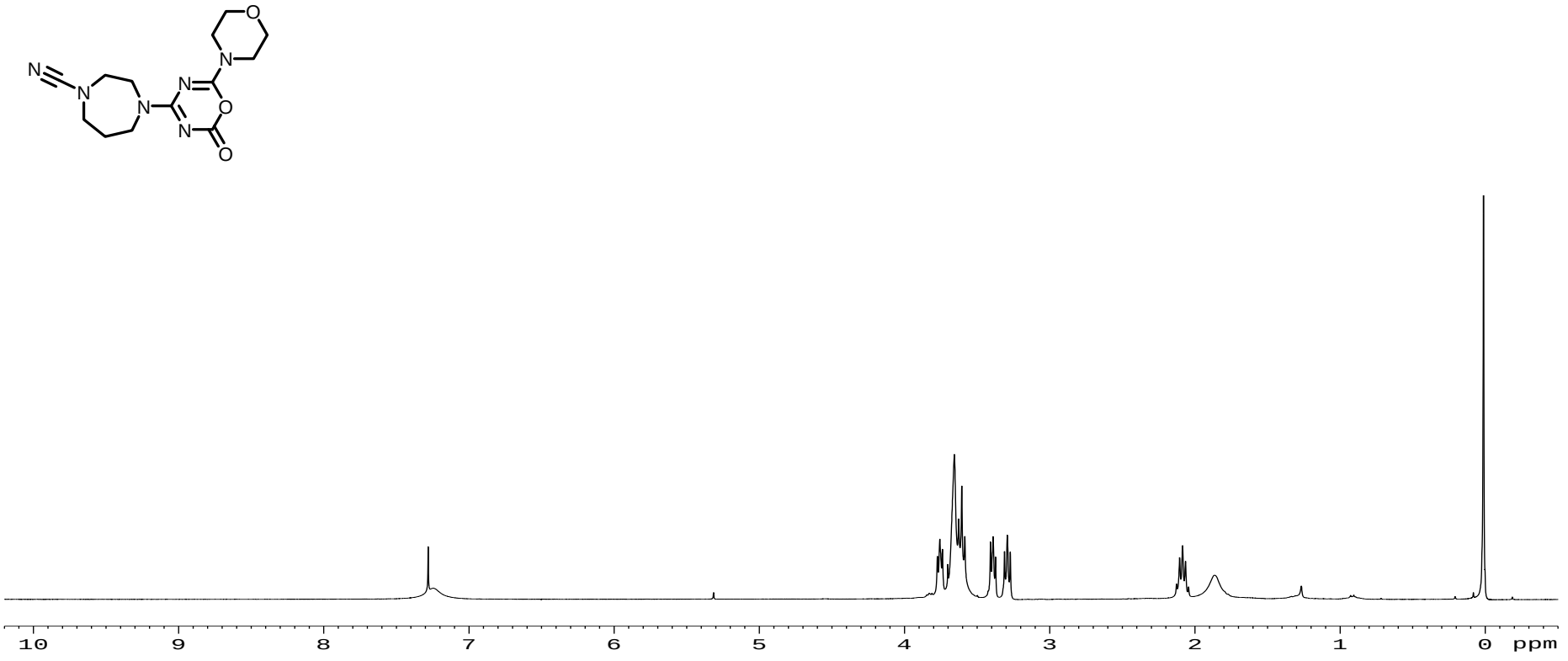
^{13}C NMR spectrum of Compound **8a**



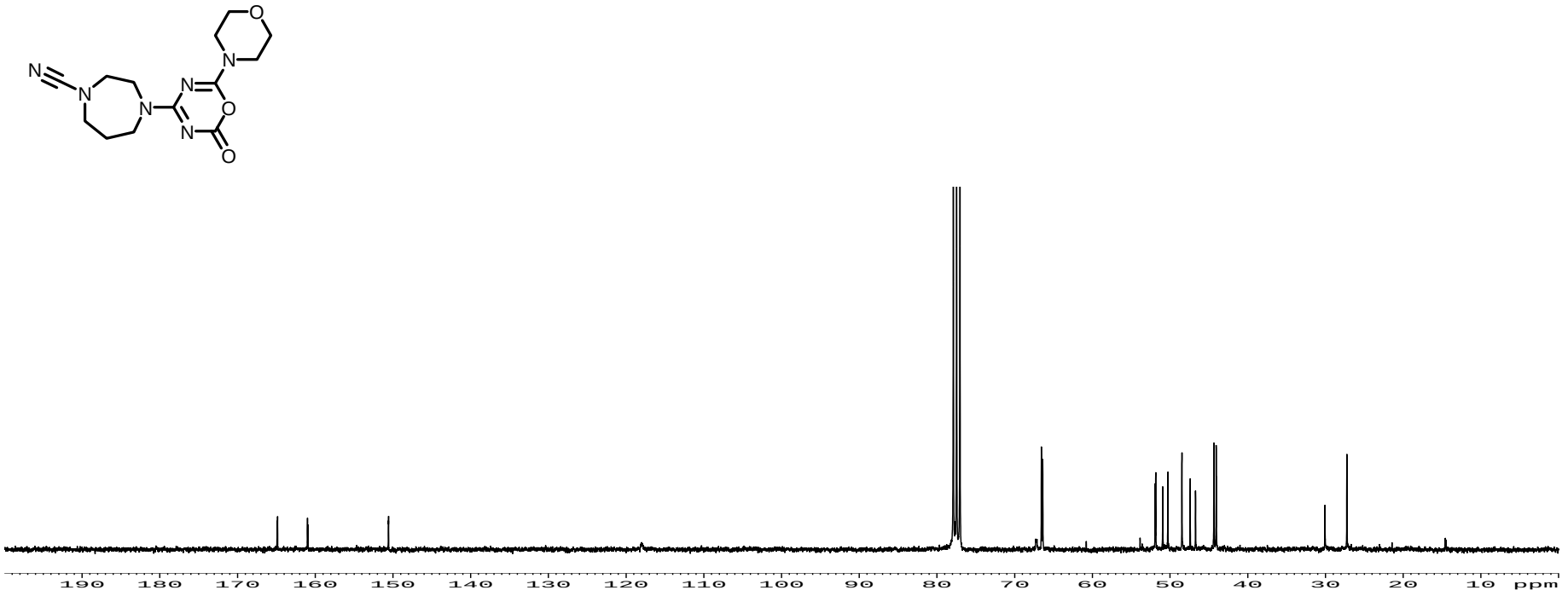
^{1}H NMR spectrum of Compound **8b**



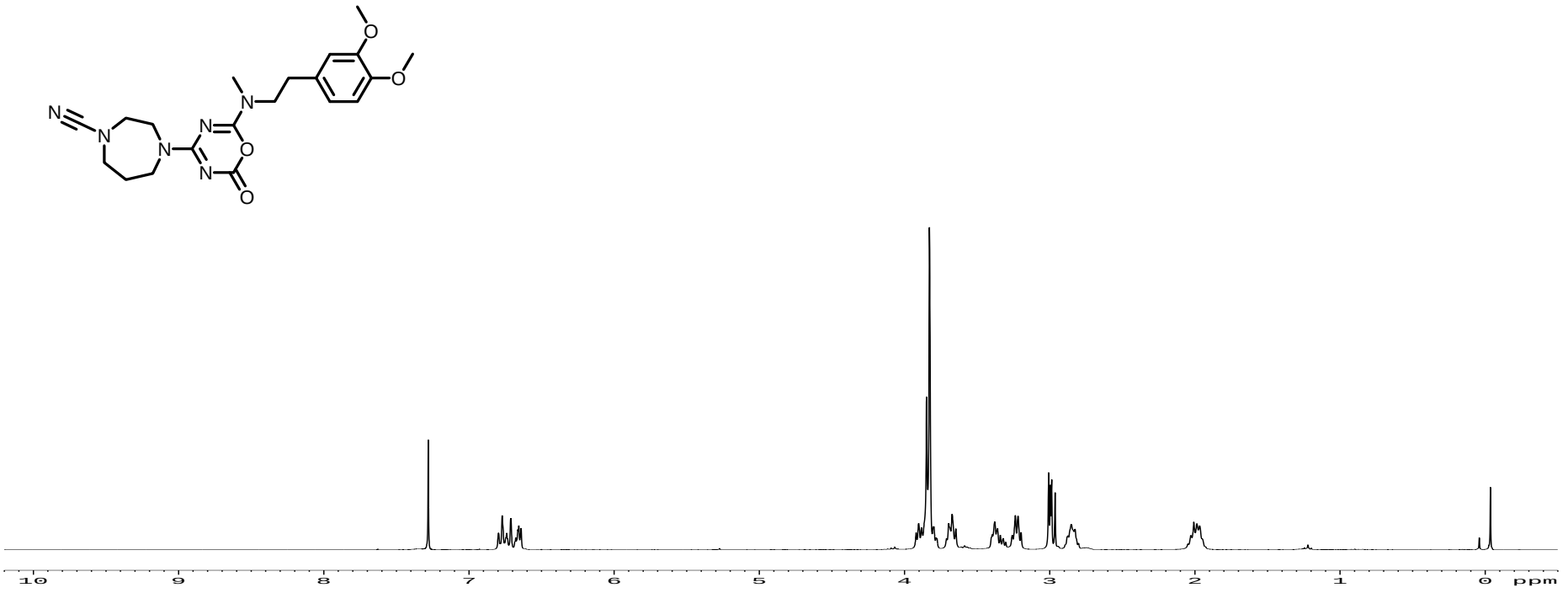
^{13}C NMR spectrum of Compound **8b**



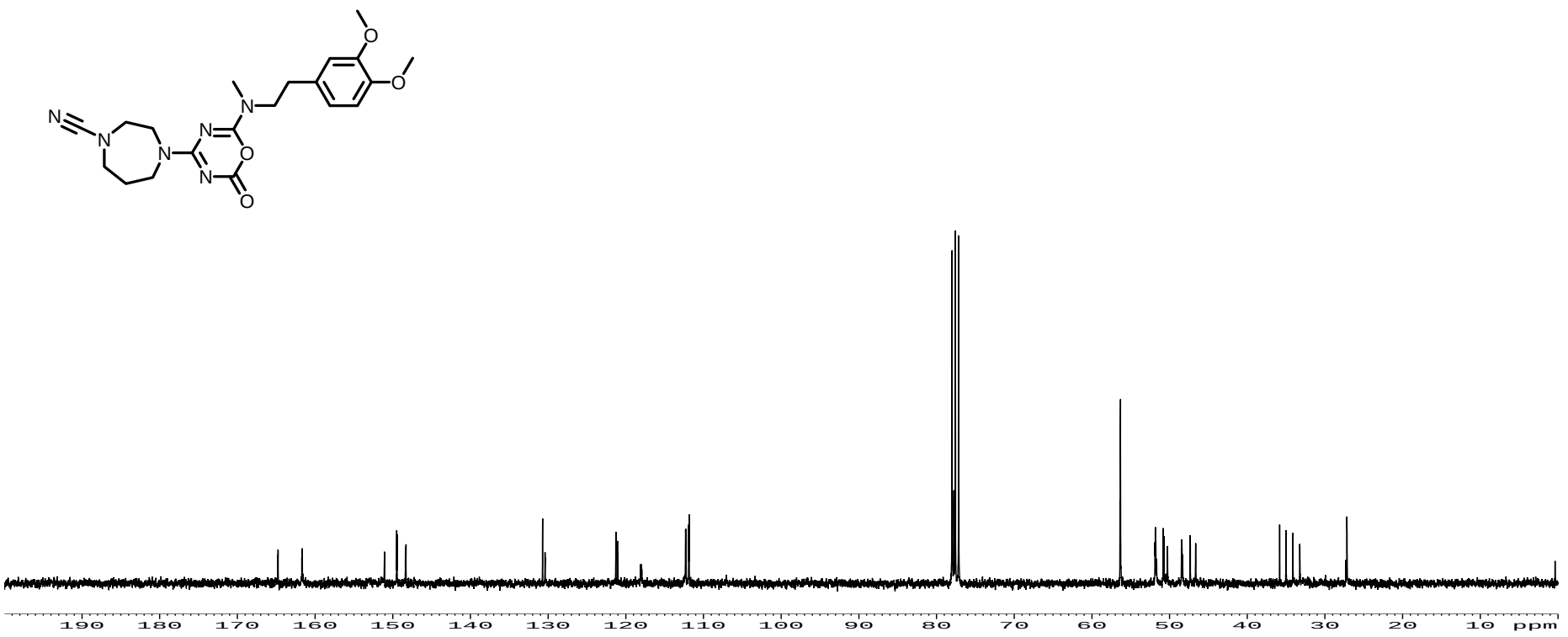
^{1}H NMR spectrum of Compound **8c**



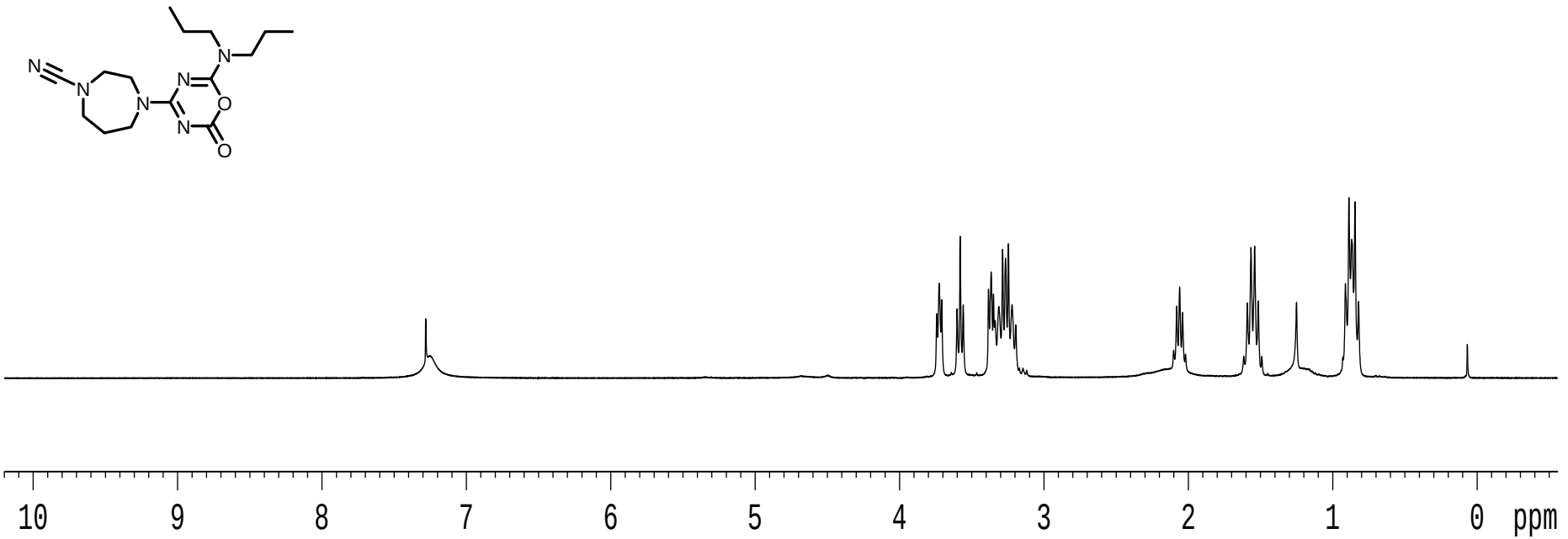
^{13}C NMR spectrum of Compound **8c**



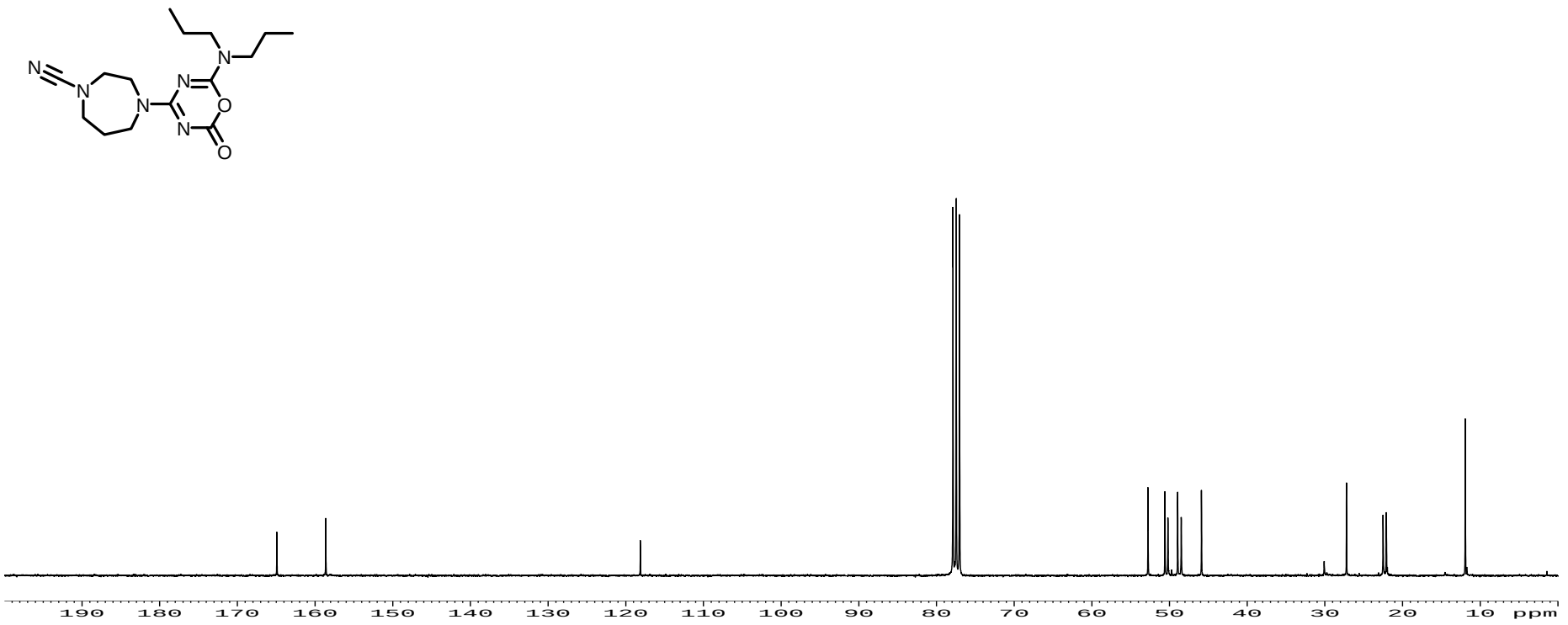
^{1}H NMR spectrum of Compound **8d**



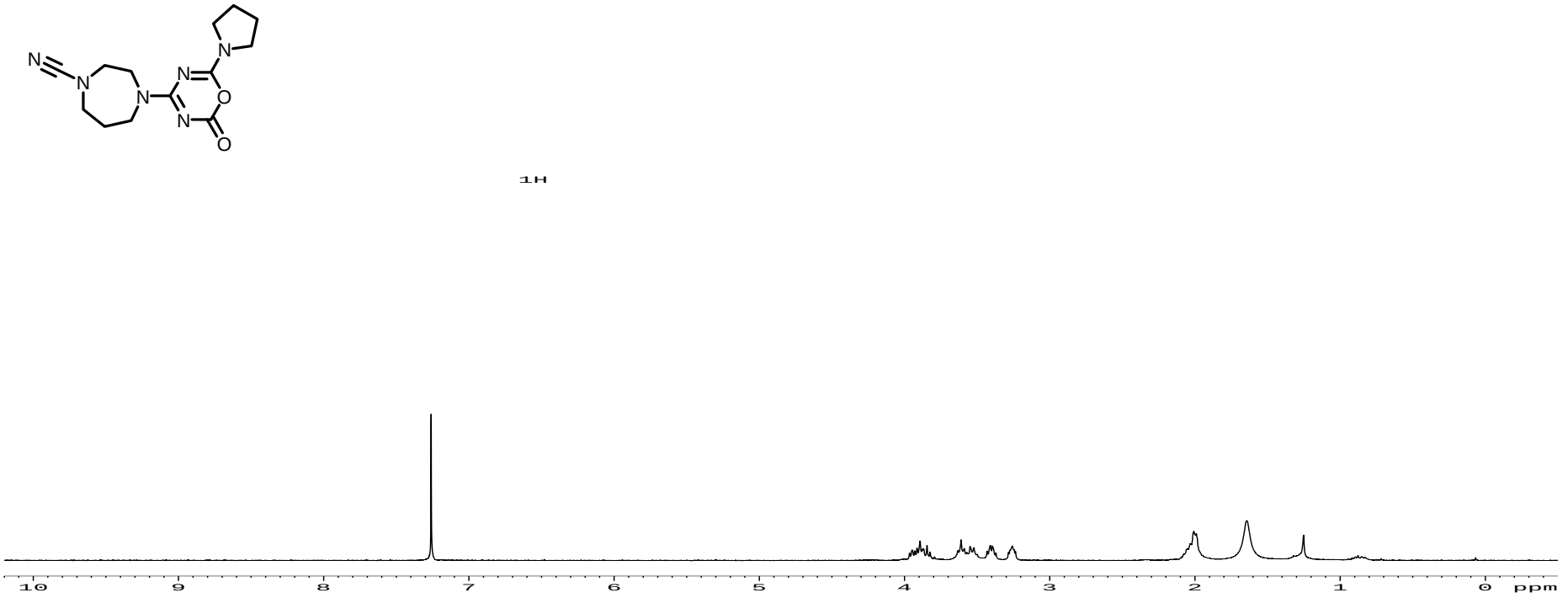
^{13}C NMR spectrum of Compound **8d**



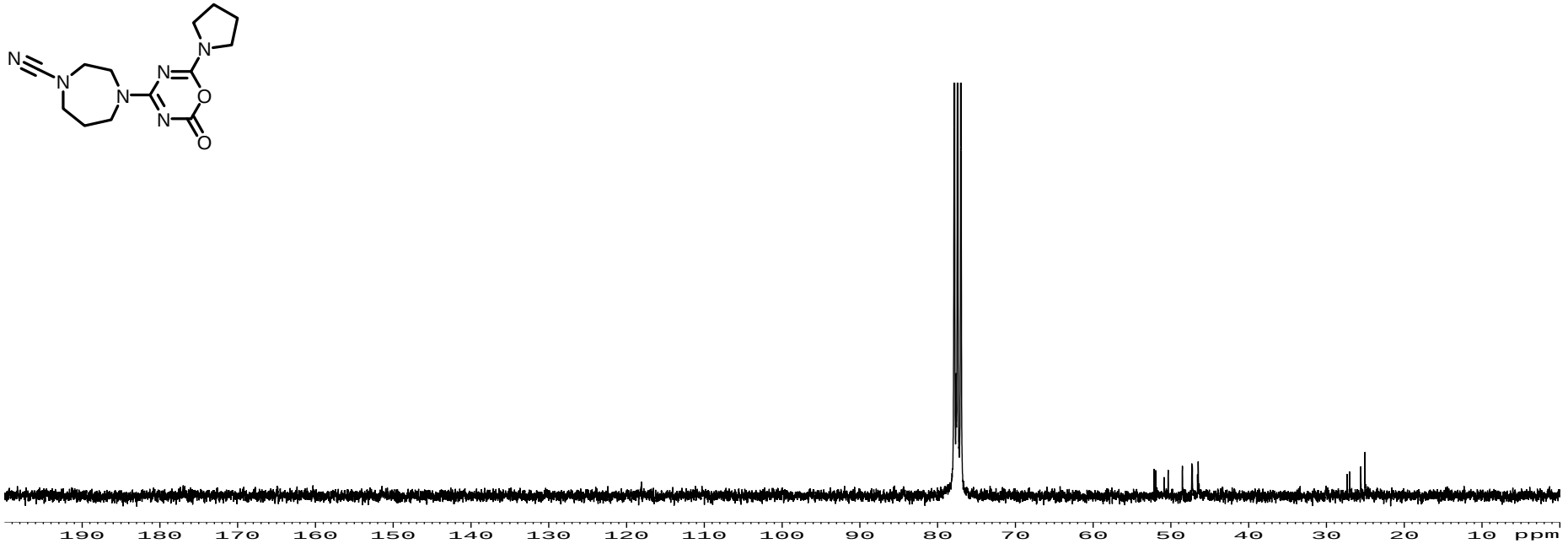
^{1}H NMR spectrum of Compound **8e**



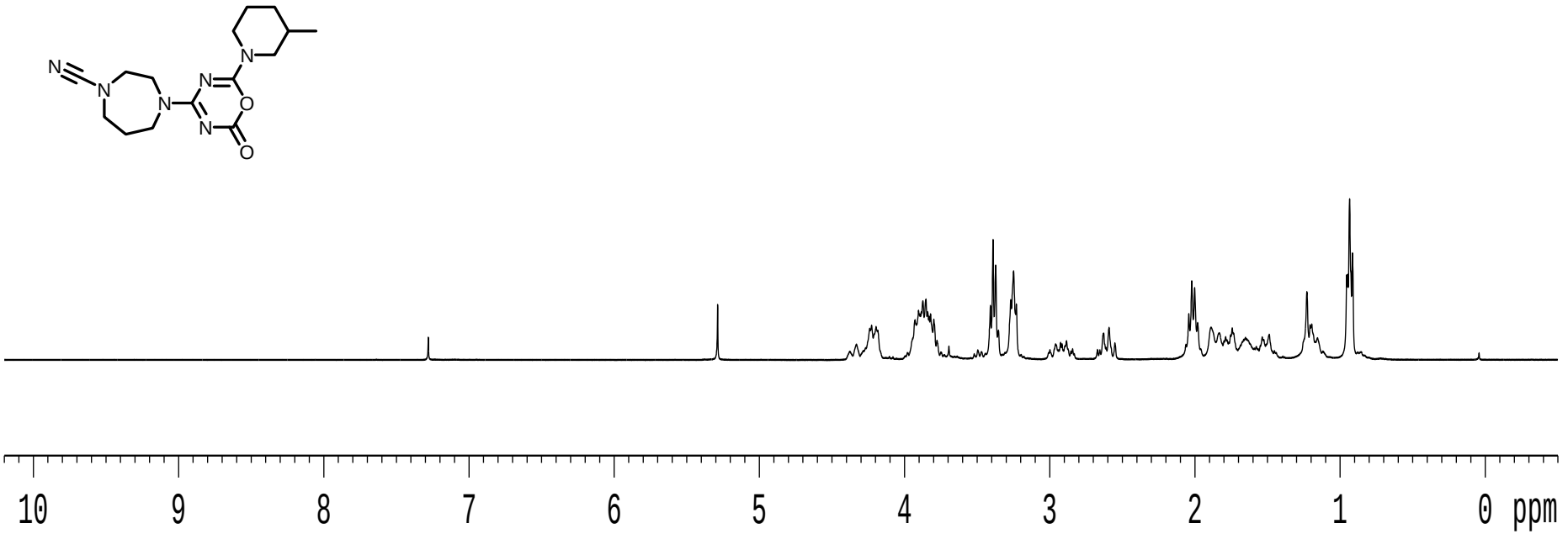
^{13}C NMR spectrum of Compound **8e**



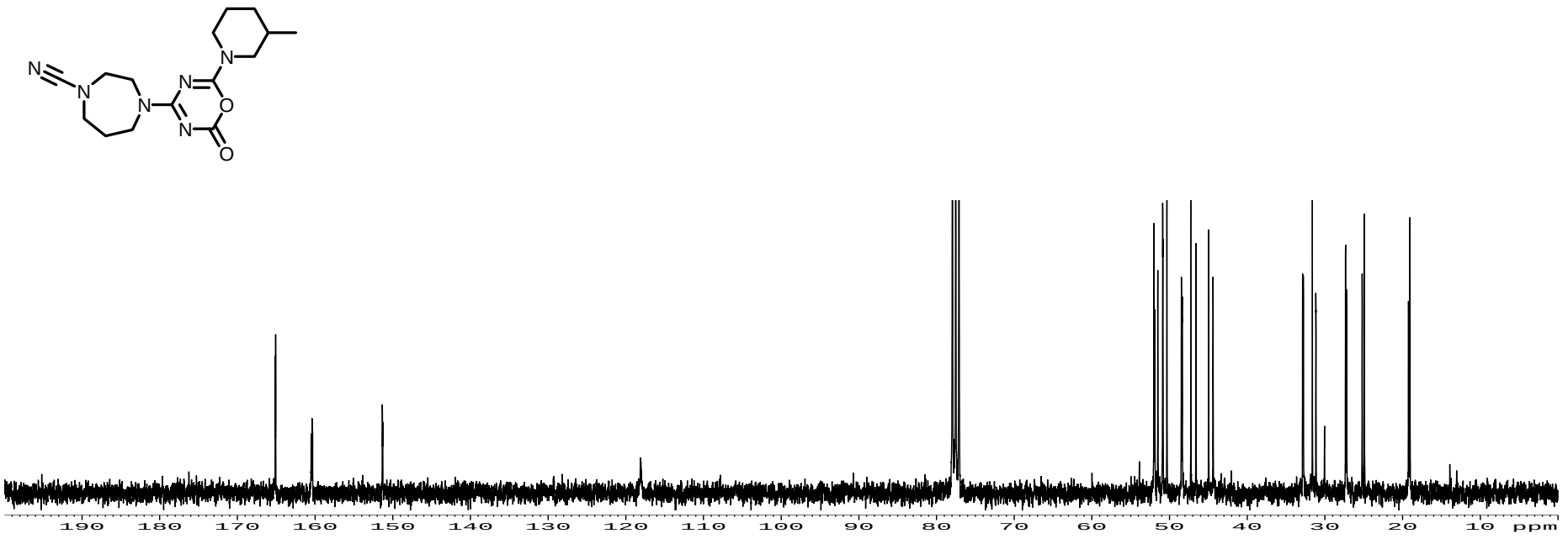
^{1}H NMR spectrum of Compound **8f**



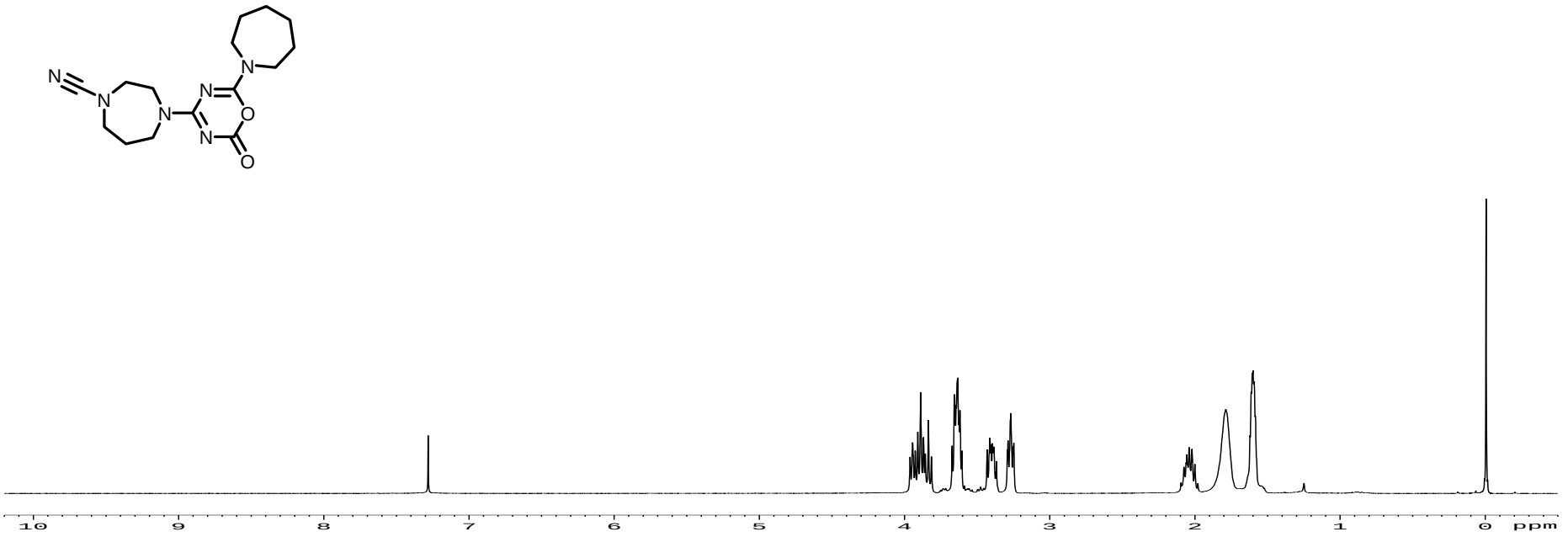
^{13}C NMR spectrum of Compound **8f**



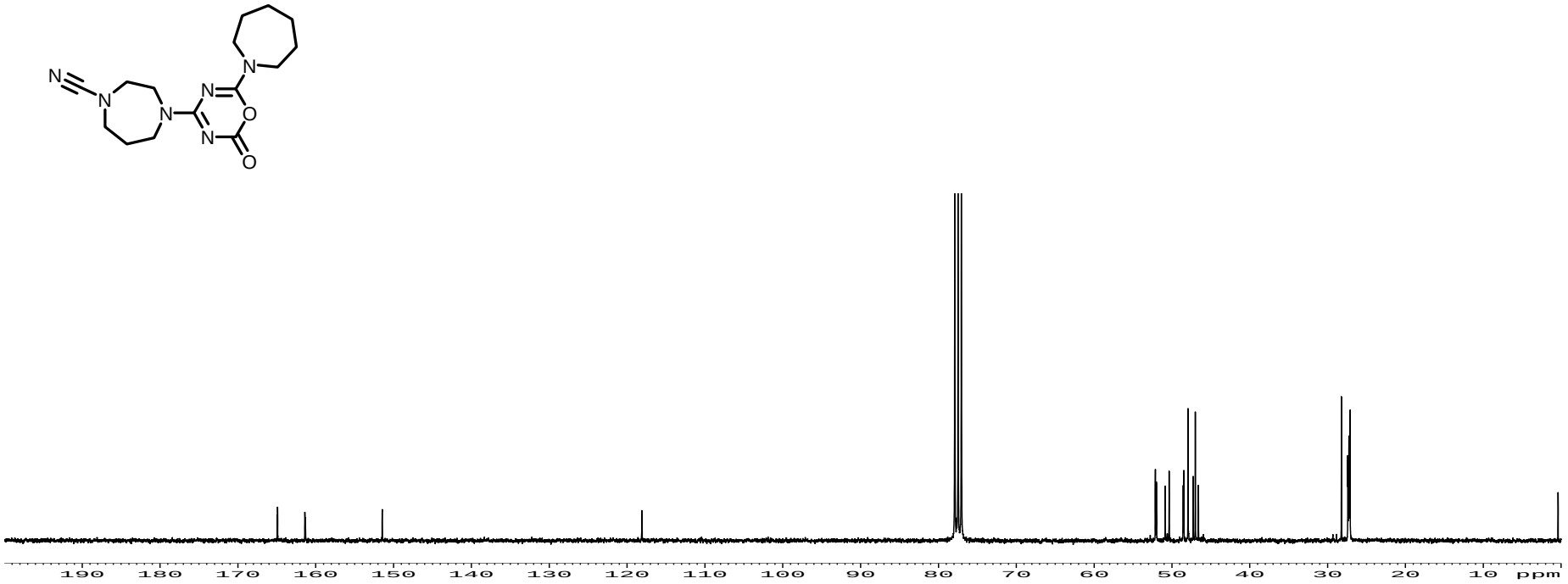
^{1}H NMR spectrum of Compound **8g**



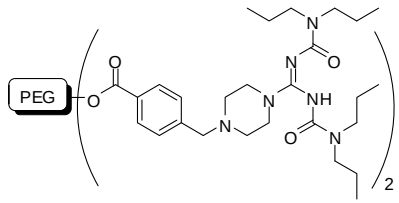
^{13}C NMR spectrum of Compound **8g**

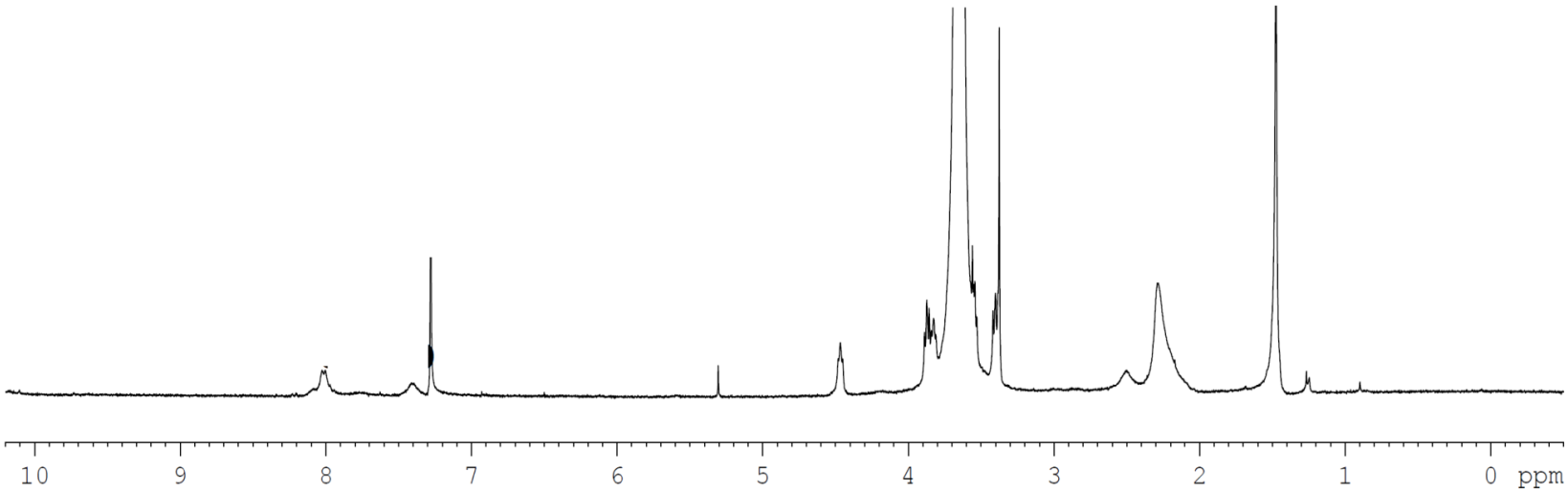


^{1}H NMR spectrum of Compound **8h**



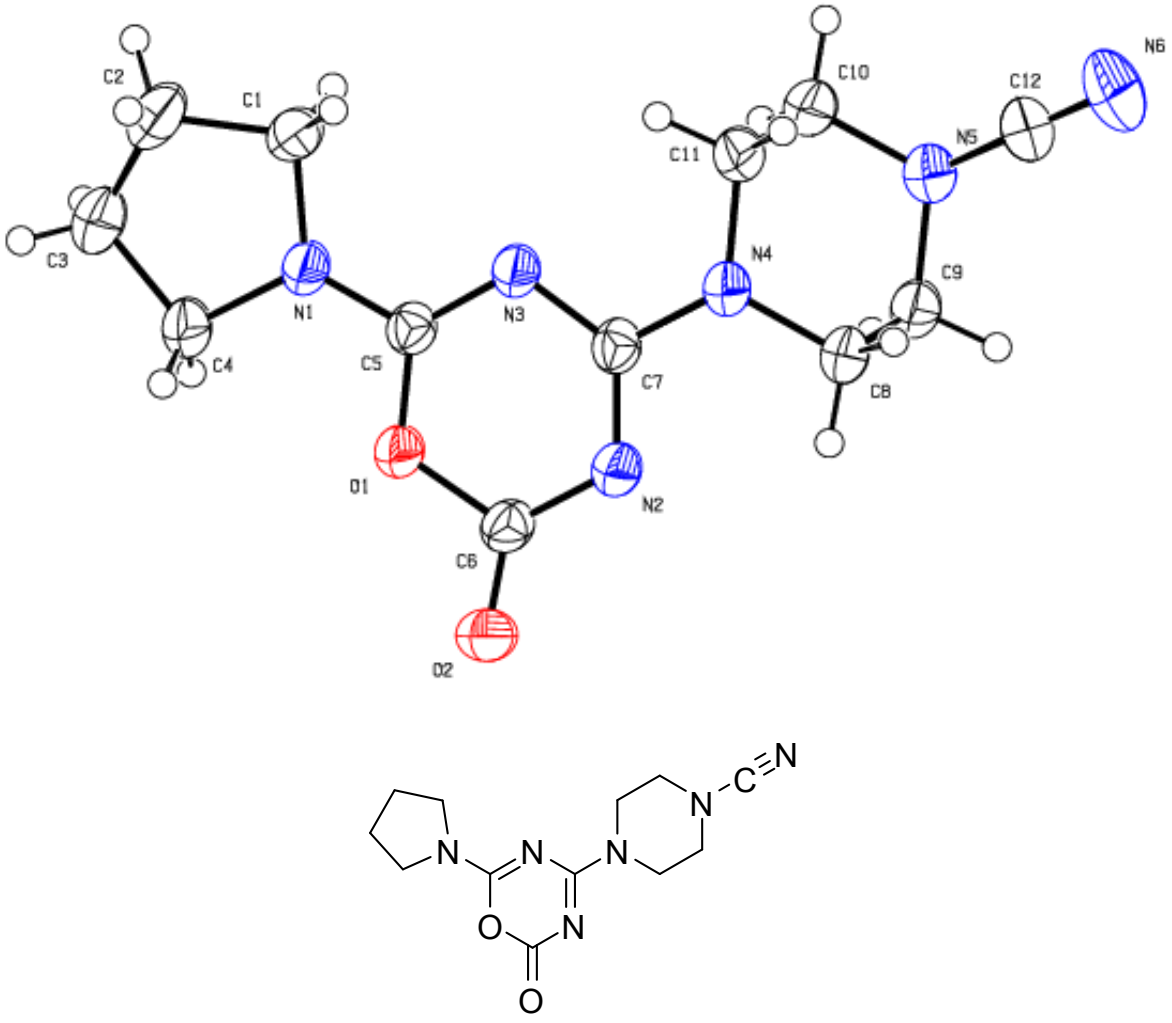
^{13}C NMR spectrum of Compound **8h**





^{1}H NMR Spectrum of compound **5a**

X- ray crystallographic data of compound 7b:



ORTEP diagram of compound **7b**