Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

SUPPORTING INFORMATION

Modulating the reactivity of a-isocyano acetate: Multicomponent Synthesis of 5-Methoxyoxazole and Furopyrrolone

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Experimental Section

General information

Melting points were recorded using Reichert melting point apparatus.

Mass spectra were obtained either from an AEI MS-50 instrument using electron impact ionization (EI), from an AEI MS-9 using electron spray (ES), or from a MALDI-TOF type of instrument for the high resolution mass spectra (HRMS).

Proton NMR (^{1}H) spectra were recorded at 300 MHz or at 500 MHz. Carbon NMR (^{13}C) spectra were similarly recorded at 75 MHz on a Bruker AC-300 spectrometer, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence.

Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. NMR experiments were carried out in deuterochloroform ($CDCl_3$). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, brs: broad singlet for proton spectra. Coupling constants (*J*) are reported in Hertz (Hz).

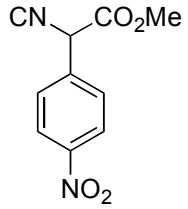
Infrared spectra were recorded on a Nicolet 205 FT-IR spectrometer.

Flash chromatography was performed using Kieselgel Si 60, 40-63 μm particle sized silica gel (200-400 mesh). Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with phosphomolybdic acid reagent or potassium permanganate ($KMnO_4$).

All reagents were obtained from commercial suppliers unless otherwise stated. Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under nitrogen. Other solvents were dried by distillation from the following: tetrahydrofuran (sodium/benzophenone); dichloromethane

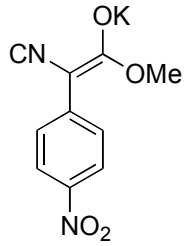
(calcium hydride); toluene (CaH_2). All reactions requiring anhydrous conditions were performed in flame-dried apparatus under a nitrogen atmosphere. Organic extracts were, in general, dried over anhydrous magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4).

Experimental data



6

To a solution of methyl α-isocyanoacetate (95 μL, 1 mmol, 1 equiv) in dry acetonitrile (10 mL) was added successively cesium hydroxide monohydrate (201 mg, 1.2 mmol, 1.2 equiv) and 4-fluoronitrobenzene (155 mg, 1.1 mmol, 1.1 equiv). The colour of the reaction mixture turned to purple. After 3 hours of reaction, ethyl acetate (30 mL) was added to the reaction mixture which was then washed once with HCl 0.1N. The reaction mixture turned back to yellow. The organic fraction was separated and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic fractions were combined, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. *Methyl 2-isocyano-2-(4-nitrophenyl)acetate* **6** was purified by column chromatography on silica gel (20 % ethyl acetate in heptane) to give pure title compound as a slightly yellow solid (91 mg, 41 %); IR: 2957, 2149, 1753, 1523, 1347 and 1212 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (3H, s, OMe), 5.53 (1H, s, CH), 7.72 (2H, d, J = 5.1 Hz, Ar-H) and 8.32 (2H, d, J = 5.1 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.4 (d), 54.3 (q), 124.4 (2d), 127.8 (2d), 137.9 (s), 148.7 (s), 163.6 (s) and 164.8 (s); *m/z* (ES+) 221 [$(M+H)^+$, 100 %], 275 (30) and 253 (85).



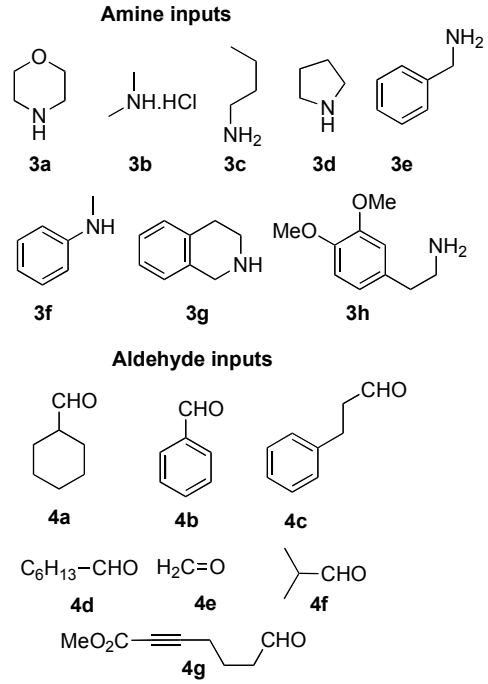
14

To a solution of the ester **6** (190 mg, 0.86 mmol, 1.0 equiv) in THF (2.5 mL) and water (0.5 mL) was added potassium hydroxide 50 mg, 0.86 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 5 h. The solvent was then removed *in vacuo* and the resulting salt **14** (220 mg, 100%) was used as such without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ 3.55 (3H, s, OCH_3), 8.00 (2H, d, J = 9.0 Hz), 8.11 (2H, d, J

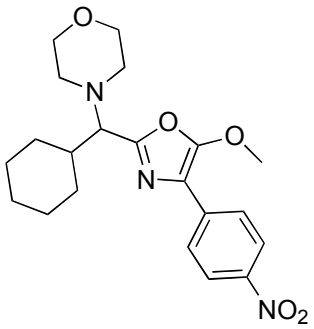
= 9.0 Hz).

Following amines and aldehydes were used for the preparation of 5-aminooxazole (Figure 1)

Figure 1



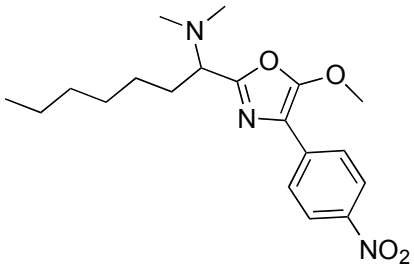
General procedure for the three-component synthesis of 5-methoxyoxazoles



7a

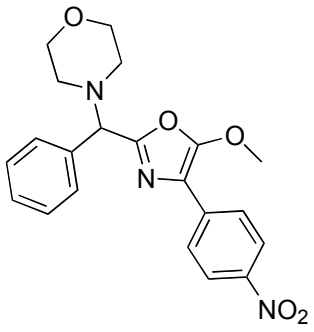
To a solution of morpholine **3a** (17 µL, 0.20 mmol, 1.3 equiv.) in toluene was added cyclohexanal **4a** (22 µL, 0.18 mmol, 1.2 equiv.) and the mixture was stirred for 10 min at room temperature. The isonitrile **6** (33 mg, 0.15 mmol, 1.0 equiv.) was then added to the reaction mixture and stirring was continued for 4 hours at room temperature. The solvent was removed *in vacuo*. Purification by flash column chromatography on silica gel (30 % ethyl acetate in heptane) gave *4-(Cyclohexyl(5-methoxy-4-(4-nitrophenyl)oxazol-2-yl)methyl) morpholine* **7a** as a yellow oil (55.3 mg, 92 %); IR: 2923, 2850, 1628, 1599, 1510, 1329, 1108, 1021 and 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78-1.38 (7H, m, Cy-H), 1.57-2.06 (4H, m, Cy-H), 2.37-2.56 (4H, m, 2 × CH_2N), 3.26 (1H, d, J = 10 Hz, CHN), 3.56-3.70 (4H, m, 2 × CH_2O), Ar-OCH_3), 4.08 (3H, s, OCH_3), 7.85 (2H, d, J = 9.0 Hz, Ar-H),

8.15 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9 (t), 26.0 (t), 26.6 (t), 30.3 (t), 30.5 (t), 36.6 (d), 50.0 (2t), 59.6 (q), 67.3 (2t), 68.5 (d), 111.6 (s), 124.0 (2d), 125.0 (2d), 138.3 (s), 145.5 (s), 153.4 (s) and 156.1 (s); [Found (ES+): $[M+H]^+$ 402.2028, $C_{21}H_{28}N_3O_5$ requires 402.2029].



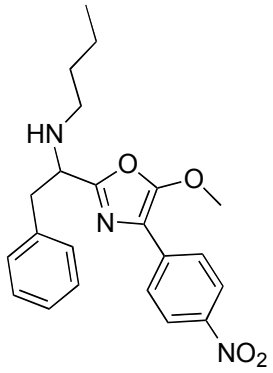
7b

1-(5-Methoxy-4-(4-nitrophenyl)oxazol-2-yl)-N,N-dimethylheptan-1-amine **7b** was purified by column chromatography on silica gel (40 % ethyl acetate in heptane) to give pure title compound as a yellow oil (52 mg, 96 %); IR: 2928, 1628, 1599, 1510, 1331, 1021 and 852 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 4.8 Hz, CH_3), 1.26-1.32 (8H, m, 4 × CH_2), 1.87 (2H, m, CH_2), 2.35 (6H, s, $(CH_3)_2N$), 3.59 (1H, dd, J = 6.3 Hz and J = 9.0 Hz, CH), 4.17 (3H, s, OCH_3), 7.95 (2H, d, J = 9.0 Hz, Ar-H), 8.23 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 26.4 (t), 29.1 (t), 30.3 (t), 31.6 (t), 41.8 (2q), 59.6 (q), 63.8 (d), 111.6 (s), 124.0 (2d), 124.9 (2d), 138.4 (s), 145.4 (s), 154.0 (s) and 156.1 (s); *m/z* (ES+) 362 [$(M+H)^+$, 35 %], 317 (30) and 201 (100).



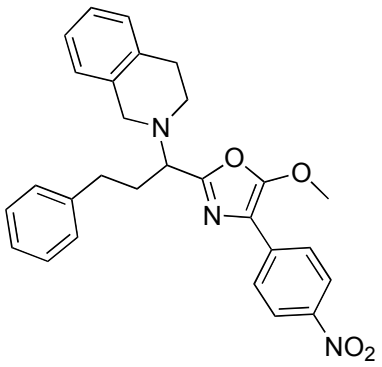
7c

4-((5-Methoxy-4-(4-nitrophenyl)oxazol-2-yl)(phenyl)methyl)morpholine **7c** was purified by column chromatography on silica gel (30 % ethyl acetate in heptane) to give pure title compound as a yellow oil (37.8 mg, 64 %); IR: 2955, 1628, 1599, 1509, 1333, 1110, 1022 and 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44-2.58 (4H, m, 2 × NCH_2), 3.74 (4H, m, 2 × OCH_2), 4.13 (3H, s, OCH_3), 4.55 (1H, s, CH), 7.32-7.40 (3H, m, Ar-H), 7.55 (2H, m, Ar-H), 7.91 (2H, d, J = 9.0 Hz, Ar-H), 8.21 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8 (2t), 59.7 (q), 66.9 (2t), 69.5 (d), 112.0 (s), 124.0 (2d), 125.0 (2d), 128.4 (d), 128.7 (4d), 136.5 (s), 138.0 (s), 145.6 (s), 152.8 (s) and 156.5 (s); [Found (ES+): $[M+Na]^+$ 418.1425, $C_{21}H_{21}N_3O_5Na$ requires 418.1379].



7d

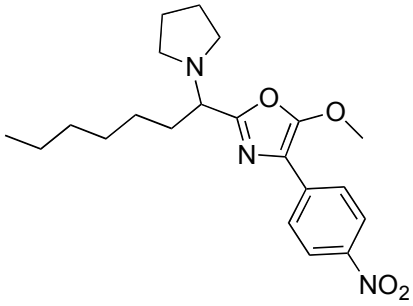
N-(1-(5-methoxy-4-(4-nitrophenyl)oxazol-2-yl)-2-phenylethyl)butan-1-amine **7d** was purified by column chromatography on silica gel (40 % ethyl acetate in heptane) to give pure title compound as a yellow oil (27.1 mg, 45 %); IR: 2955, 1631, 1601, 1511, 1334, 1021 and 854 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.5 Hz, CH_3), 1.27 (2H, sextet, J = 7.5 Hz, CH_2), 1.44 (2H, pentuplet, J = 7.5 Hz, CH_2), 1.72 (1H, brs, NH), 2.58 (2H, m, CH_2N), 3.15 (2H, d, J = 7.5 Hz, CH_2Ph), 4.04 (1H, t, J = 7.5 Hz, CH), 4.05 (3H, s, OCH_3), 7.16-7.28 (5H, m, Ar-H), 7.91 (2H, d, J = 9.0 Hz, Ar-H), 8.21 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 20.3 (t), 31.9 (t), 40.7 (t), 47.5 (t), 58.5 (q), 59.7 (d), 111.9 (s), 124.0 (2d), 124.9 (2d), 126.8 (d), 128.6 (2d), 129.2 (2d), 137.2 (s), 138.2 (s), 145.5 (s), 155.4 (s) and 156.0 (s); [Found (ES+): $[M+H]^+$ 396.1931, $C_{22}H_{26}N_3O_4$ requires 396.1923].



7e

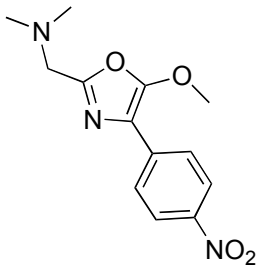
2-[1-(3,4-Dihydroisoquinolin-2(1H)-yl)-3-phenylpropyl]-5-methoxy-4-(4-nitrophenyl)oxazole **7e** was purified by column chromatography on silica gel (30 % ethyl acetate in heptane) to give pure title compound as a yellow oil (66.4 mg, 95 %); IR: 2923, 1628, 1599, 1509, 1330, 1022 and 854 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (2H, m, $PhCH_2\underline{CH_2}$),1.19-1.37 (8H, m, 4 × CH_2), 1.80 (4H, m, 2 × CH_2), 1.95 (2H, m, CH_2), 2.74-2.86 and 3.04-3.09 (4H, 2 × m, $\underline{CH_2CH_2}N$), 2.95 (2H, t, J = 5.5 Hz, $Ph\underline{CH_2}CH_2$), 3.79 and 3.93 (2H, 2 × d, J = 14.5 Hz, $Ph\underline{CH_2}N$), 3.89 (1H, t, J = 7.5 Hz, CH), 4.15 (3H, s, OCH_3), 7.13-7.31 (9H, m, Ar-H), 7.96 (2H, d, J = 9.0 Hz, Ar-H), 8.25 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9 (t), 31.7 (t), 32.4 (t), 47.2 (t), 52.0 (t), 59.6 (q),

61.3 (d), 111.7 (s), 124.0 (2d), 125.0 (2d), 125.7 (d), 126.0 (d), 126.2 (d), 126.6 (d), 128.4 (2d), 128.6 (2d), 128.8 (d), 134.3 (s), 134.8 (s), 138.3 (s), 141.4 (s), 145.5 (s), 153.7 (s) and 156.1 (s); *m/z* (ES+) 470 [$(M+H)^+$, 20 %], 492 (15), 468 (100), 280 (20), 189 (10) and 134 (50).



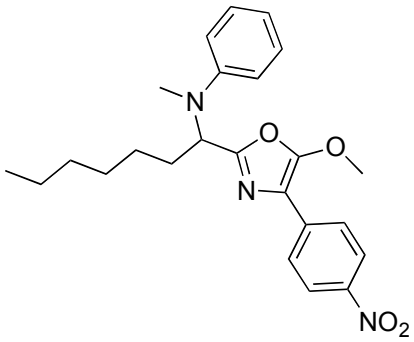
7f

5-Methoxy-4-(4-nitrophenyl)-2-(1-(pyrrolidin-1-yl)heptyl)oxazole **7f** was purified by column chromatography on silica gel (30 % ethyl acetate in heptane) to give pure title compound as a yellow oil (56.4 mg, 97 %); IR: 2928, 1630, 1600, 1512, 1333, 1023 and 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.0 Hz, CH_3), 1.19-1.37 (8H, m, 4 × CH_2), 1.80 (4H, m, 2 × CH_2), 1.95 (2H, m, CH_2), 2.55 and 2.74 (4H, 2 × m, 2 × CH_2N), 3.60 (1H, dd, J = 5.0 Hz and J = 9.5 Hz, CH), 4.17 (3H, s, OCH_3), 7.95 (2H, d, J = 9.0 Hz, Ar-H), 8.23 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 23.3 (2t), 26.1 (t), 29.1 (t), 31.6 (t), 32.4 (t), 51.1 (2t), 59.7 (q), 62.2 (d), 111.6 (s), 124.0 (2d), 125.0 (2d), 138.3 (s), 145.4 (s), 154.9 (s) and 156.1 (s); *m/z* (ES+) 388 [$(M+H)^+$, 100 %] and 317 (20).



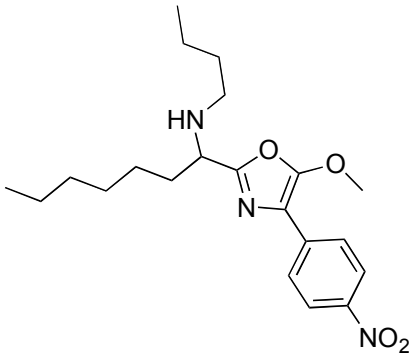
7g

1-(5-Methoxy-4-(4-nitrophenyl)oxazol-2-yl)-N,N-dimethylmethanamine **7g** was purified by column chromatography on silica gel (50 % ethyl acetate in acetone) to give pure title compound as a yellow oil (27 mg, 65 %); IR: 2945, 1628, 1599, 1509, 1331, 1020 and 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (6H, s, 2 × NCH_3), 3.58 (2H, s, NCH_2), 4.18 (3H, s, OCH_3), 7.94 (2H, d, J = 9.0 Hz, Ar-H), 8.23 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3 (2q), 56.0 (t), 59.7 (q), 112.0 (s), 124.0 (2d), 124.9 (2d), 138.1 (s), 145.5 (s), 152.0 (s) and 156.4 (s).



7h

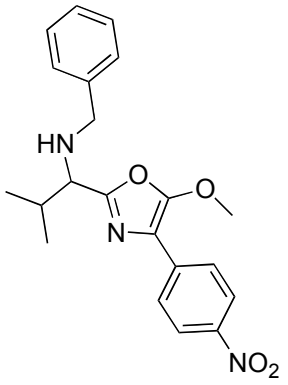
N-(1-(5-Methoxy-4-(4-nitrophenyl)oxazol-2-yl)heptyl)-N-methylaniline **7h** was purified by column chromatography on silica gel (30 % ethyl acetate in heptane) to give pure title compound as a yellow oil (14.7 mg, 23 %); IR: 2926, 1630, 1597, 1503, 1332, 1023 and 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.6 Hz, CH_3), 1.28-1.42 (8H, m, 4 × CH_2), 1.98-2.18 (2H, m, CH_2), 2.77 (3H, s, NCH_3), 3.97 (3H, s, OCH_3), 4.88 (1H, dd, J = 6.9 Hz and J = 8.4 Hz, CH), 6.80 (1H, t, J = 7.2 Hz, Ar-H), 6.92 (2H, d, J = 8.1 Hz, Ar-H), 7.23-7.31 (2H, m, Ar-H), 7.92 (2H, d, J = 9.0 Hz, Ar-H), 8.22 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 26.3 (t), 29.1 (t), 30.2 (t), 31.7 (t), 32.2 (q), 57.2 (q), 59.5 (d), 111.6 (s), 113.9 (2d), 117.9 (d), 124.0 (2d), 124.9 (2d), 129.2 (2d), 138.3 (s), 145.4 (s), 150.1 (s), 154.3 (s) and 156.0 (s); [Found (ES+): $[M+Na]^+$ 446.2087, $C_{24}H_{29}N_3O_4Na$ requires 446.2056].



7i

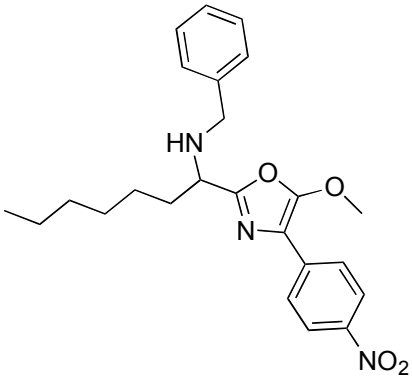
N-butyl-1-(5-methoxy-4-(4-nitrophenyl)oxazol-2-yl)heptan-1-amine **7i** was purified by column chromatography on silica gel (30 % ethyl acetate in heptane) to give pure title compound as a yellow oil (37.4 mg, 64 %); IR: 2928, 1633, 1601, 1513, 1334, 1023 and 854 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz, CH_3), 0.91 (3H, t, J = 7.5 Hz, CH_3), 1.27-1.43 (10H, m, 5 × CH_2), 1.45 (2H, m, CH_2), 1.83 (2H, m, CH_2), 2.59 (2H, t, J = 7.5 Hz, CH_2N), 3.76 (1H, t, J = 7.0 Hz, CH), 4.17 (3H, s, OCH_3), 7.94 (2H, d, J = 9.0 Hz, Ar-H), 8.24 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 14.1 (q), 20.4 (t), 22.6 (t), 25.9 (t), 29.1 (t), 31.6 (t), 32.2 (t), 34.4 (t), 47.5 (t), 57.2 (q), 59.7 (d), 111.8 (s), 124.0 (2d), 124.9 (2d), 138.3 (s), 145.4 (s), 156.0 (s) and 156.6 (s);

[Found (ES+): $[M+Na]^+$ 412.2241, $C_{21}H_{31}N_3O_4Na$ requires 412.2212].



7j

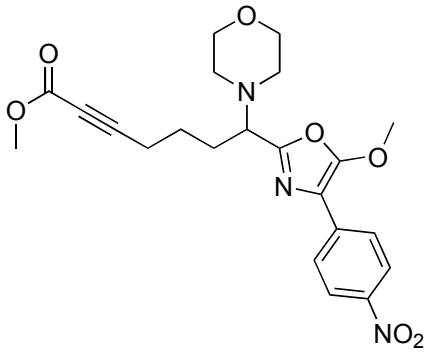
N-benzyl-1-(5-methoxy-4-(4-nitrophenyl)oxazol-2-yl)-2-methylpropan-1-amine **7j** was purified by column chromatography on silica gel (30 % ethyl acetate in heptane) to give pure title compound as a yellow oil (36.0 mg, 63 %); IR: 2958, 1630, 1600, 1509, 1332, 1022 and 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, d, J = 6.6 Hz, CH_3), 1.05 (3H, d, J = 6.6 Hz, CH_3), 1.86 (1H, brs, NH), 2.08 (1H, hept, J = 6.6 Hz, CH), 3.51 (1H, d, J = 6.9 Hz, CHN), 3.70 and 3.85 (2H, 2 × d, J = 13.2 Hz, CH_2N), 4.13 (3H, s, OCH_3), 7.28-7.35 (5H, m, Ar-H), 7.94 (2H, d, J = 9.0 Hz, Ar-H), 8.23 (2H, d, J = 9.0 Hz, Ar-H); [Found (ES+): $[M+Na]^+$ 404.1593, $C_{21}H_{23}N_3O_4Na$ requires 404.1586].



7k

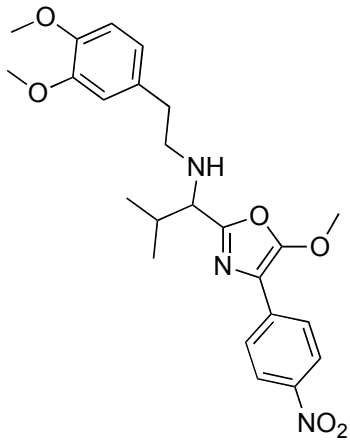
N-benzyl-1-(5-methoxy-4-(4-nitrophenyl)oxazol-2-yl)heptan-1-amine **7k** was purified by column chromatography on silica gel (30 % ethyl acetate in heptane) to give pure title compound as a yellow oil (39.3 mg, 62 %); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.0 Hz, CH_3), 1.24-1.35 (8H, m, 4 × CH_2), 1.43 (2H, m, CH_2), 1.64 (1H, brs, NH), 1.85 (2H, m, CH_2), 3.77 and 3.85 (2H, 2 × d, J = 13.0 Hz, CH_2Ph), 3.80 (1H, t, J = 7.0 Hz, CH), 4.15 (3H, s, OCH_3), 7.24-7.35 (5H, m, Ar-H), 7.95 (2H, d, J = 9.0 Hz, Ar-H), 8.25 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 25.9 (t), 29.0 (t), 31.6 (t), 34.4 (t), 51.7 (t), 56.3 (q), 59.6 (d), 108.4 (s), 124.0

(2d), 124.9 (2d), 127.1 (d), 128.2 (2d), 128.4 (2d), 138.3 (s), 145.5 (s), 153.3 (s) and 156.0 (s), one quaternary carbon was missing.



7l

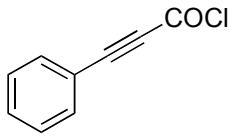
Methyl 7-(5-methoxy-4-(4-nitrophenyl)oxazol-2-yl)-7-morpholinohept-2-ynoate **7l** was purified by column chromatography on silica gel (50 % ethyl acetate in heptane) to give pure title compound as a yellow oil (52.7 mg, 79 %); IR: 2953, 1711, 1628, 1599, 1509, 1332, 1252, 1110, 1021 and 853 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.61-1.82 (2H, m, CH_2), 2.06 (2H, q, J = 7.5 Hz, $\underline{CH_2}CH$), 2.44 (2H, t, J = 7.5 Hz, $CH_2C\equiv$), 2.54 and 2.68 (4H, 2 × m, 2 × NCH_2), 3.66 (1H, t, J = 7.5 Hz, CH), 3.72 (4H, m, 2 × OCH_2), 3.77 (3H, s, CO_2CH_3), 4.18 (3H, s, OCH_3), 7.93 (2H, d, J = 9.0 Hz, Ar-H), 8.24 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 (t), 24.4 (t), 28.5 (t), 50.0 (2t), 52.6 (q), 59.7 (q), 62.3 (d), 67.2 (2t), 73.4 (s), 88.9 (s), 111.8 (s), 124.0 (2d), 125.0 (2d), 138.0 (s), 145.6 (s), 153.1 (s), 154.1 (s), 156.1 (s); [Found (ES+): $[M+Na]^+$ 466.1610, $C_{22}H_{25}N_3O_7Na$ requires 466.1590].



7m

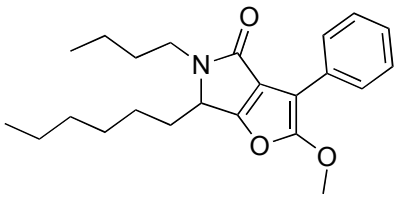
N-(3,4-Dimethoxyphenethyl)-1-(5-methoxy-4-(4-nitrophenyl)oxazol-2-yl)-2-methylpropan-1-amine **7m** was purified by column chromatography on silica gel (40 % to 50 % ethyl acetate in heptane) to give pure title compound as a yellow oil (92.4 mg, 68 %); IR: 2955, 1629, 1599, 1509, 1462, 1330, 1021 and 852 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 6.9 Hz, CH_3), 1.00 (3H, d, J = 6.9 Hz, CH_3), 1.59 (1H, brs, NH), 2.03 (1H, octet, J = 6.9 Hz, $Me_2\underline{CH}$), 2.77 (4H, m, $Ph\underline{CH_2CH_2}$), 3.48 (1H, d, J = 6.9 Hz, $\underline{CH}NH$), 3.82 (3H, s, $PhOCH_3$), 3.85 (3H, s, $PhOCH_3$), 4.08 (3H, s, OCH_3), 6.71-6.80 (3H, m, Ar-H), 7.90 (2H, d, J = 9.0 Hz, Ar-H), 8.21 (2H, d, J = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1 (q), 19.4 (q), 32.6 (d), 35.8 (t), 49.5 (t), 55.8 (q), 55.9 (q), 59.6 (q), 63.2 (d), 111.2 (d), 111.6 (s), 111.9 (d), 120.6 (d), 124.0 (2d), 124.9 (2d), 132.4 (s), 138.3 (s), 145.4 (s), 147.5 (s), 148.9 (s), 155.9 (s), 156.0 (s); *m/z* (ES+) 478 [$(M+Na)^+$, 100 %], 275 (90) and 258 (40).



9a

Oxalyl chloride (1.2 equiv) and dimethylformamide (0.02 equiv) were added to a solution of 3-phenylpropiolic acid (1.0 equiv) in CH_2Cl_2 and the mixture was stirred for 1 h at room temperature. After the excess reagent and solvent were distilled off, the residue was dry *in vacuo*. 3-Phenylpropioloyl chloride **9a** was used as such without further purification. IR 2202 and 1732 cm^{-1}; ^{13}C NMR (75 MHz, Acetone-d_6) δ 84.2 (s), 95.0 (s), 118.3 (d), 130.0 (2d), 133.5 (2d), 134.5 (s), 149.6 (s).



8a

From 5-methoxyoxazole and acid chloride

To a solution of *N-butyl-1-(5-methoxy-4-(4-nitrophenyl)oxazol-2-yl)heptan-1-amine* **7i** (14.5 mg, 36.5 µmol, 1.0 equiv.) in dry toluene (0.8 mL) at 0°C was added triethylamine (7.6 µL, 54.7 µmol, 1.5 equiv.) followed by a solution of 3-phenylpropioloyl chloride **9a** (6.6 mg, 40.1 µmol, 1.1 equiv.) in dry toluene (0.2 mL). The reaction was allowed to warm up to room temperature and it was then heated to reflux for 10 minutes.

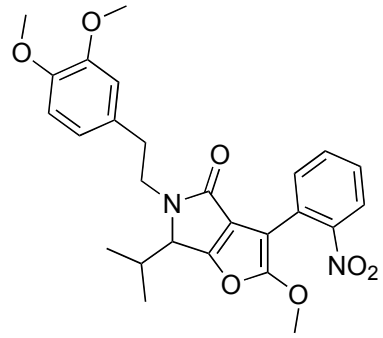
The solvent was then evaporated and *5-butyl-6-hexyl-2-methoxy-3-phenyl-5,6-dihydrofuro[2,3-c]pyrrol-4-one* **8a** was purified using preparative TLC on silica (30% ethyl acetate in heptane) to afford 11 mg of pure material as a colourless oil (81%)

One pot procedure : four-component synthesis of furopyrrolones

To a solution of *n*-butylamine (20 µL, 0.20 mmol, 1.3 equiv.) in toluene (1 mL) was added heptanal (25 µL, 0.18 mmol, 1.2 equiv.) and the mixture was stirred for 10 min at room temperature. The isonitrile **6** (33 mg, 0.15 mmol,

1.0 equiv.) was then added to the reaction and stirring was continued for 4 hours at room temperature. The reaction mixture was then cooled to 0°C and triethylamine (100 µL, 0.75 mmol, 5.0 equiv) followed by a toluene solution (0.7 mL) of 3-phenylpropioloyl chloride (49 mg, 0.30 mmol, 2.0 equiv) were introduced successively. The reaction was warmed up to room temperature and was then heated to reflux for 10 minutes. The solvent was removed *in vacuo*. *5-butyl-6-hexyl-2-methoxy-3-phenyl-5,6-dihydrofuro[2,3-c]pyrrol-4-one* **8a** was purified using preparative TLC on silica (30% ethyl acetate in heptane) to afford 28.5 mg of pure material as a colourless oil (51%).

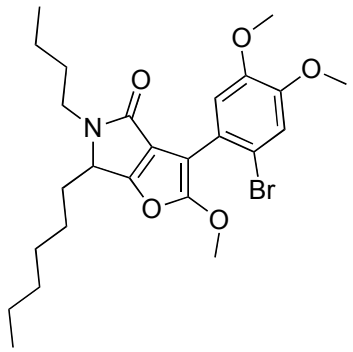
IR: 2928, 1686, 1591, 1456, 1407, 1354, 1321, 1148 and 945 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.6 Hz, CH_3), 0.91 (3H, t, J = 7.5 Hz, CH_3), 1.20-1.43 (10H, m, 5 × CH_2), 1.58 (2H, m, CH_2), 1.65 and 1.97 (2H, 2 × m, $\underline{CH_2}CHN$), 3.07 and 3.88 (2H, 2 × m, CH_2N), 4.08 (3H, s, OCH_3), 4.39 (1H, dd, J = 3.9 Hz and J = 7.5 Hz, CHN), 7.20 (1H, tt, J = 1.2 Hz, and J = 7.2 Hz, Ar-H), 7.38 (2H, t, J = 7.8 Hz, Ar-H), 8.15 (2H, dd, J = 1.2 Hz and J = 8.4 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 14.0 (q), 20.2 (t), 22.5 (t), 23.5 (t), 29.1 (t), 30.0 (t), 31.1 (t), 31.6 (t), 39.8 (t), 56.2 (q), 60.2 (d), 100.2 (s), 119.7 (s), 126.3 (d), 127.2 (2d), 128.5 (2d), 130.8 (s), 159.4 (s), 159.7 (s) and 165.4 (s); [Found (ES+): $[M+Na]^+$ 392.2187, $C_{23}H_{31}NO_3Na$ requires 392.2202].



8b

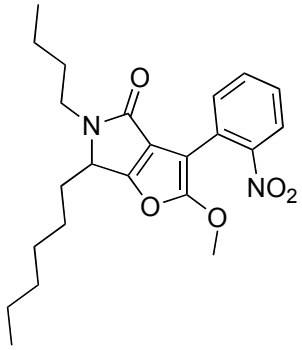
5-(3,4-Dimethoxyphenethyl)-6-isopropyl-2-methoxy-3-(2-nitrophenyl)-5,6-dihydrofuro[2,3-c]pyrrol-4-one **8b** was synthesized using the previous one-pot procedure. It was purified using preparative TLC on silica (30 % ethyl acetate in heptane) to afford pure material as a colourless oil (52 %); IR: 2958, 1686, 1598, 1514, 1260, 1235, 1141, 1025 and 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.61 (3H, d, J = 6.9 Hz, CH_3), 1.15 (3H, d, J = 6.9 Hz, CH_3), 2.21 (1H, m, $Me_2\underline{CH}$), 2.79-2.97 (2H, m, $\underline{CH_2}Ph$), 3.17 and 3.86 (2H, 2 × m, CH_2N), 3.83 (3H, s, $PhOCH_3$), 3.85 (3H, s, $PhOCH_3$), 3.97 (3H, s, OCH_3), 4.03 (1H, d, J = 3.6 Hz, CHN), 6.73-6.82 (3H, m, Ar-H), 7.37 (1H, dt, J = 1.5 Hz and J = 7.5 Hz, Ar-H), 7.59 (1H, dt, J = 1.5 Hz and J = 7.5 Hz, Ar-H), 7.82 (1H, dd, J = 1.5 Hz and J = 7.8 Hz, Ar-H), 7.88 (1H, dd, J = 1.5 Hz and J = 7.8 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0 (q), 18.8 (q), 28.1 (d), 34.7 (t), 42.2 (t), 55.9 (2q), 59.5 (q), 62.7 (d), 94.4 (s), 111.4 (d), 111.9 (d), 120.6 (d),

120.7 (s), 124.4 (s), 124.8 (d), 127.5 (d), 131?5 (s), 132.4 (d), 132.5 (d), 147.6 (s), 148.1 (s), 149.0 (s), 158.1 (s), 159.3 (s) and 165.1 (s); [Found (ES+): $[M+Na]^+$ 503.1815, $C_{26}H_{28}N_2O_7Na$ requires 503.1794].



8c

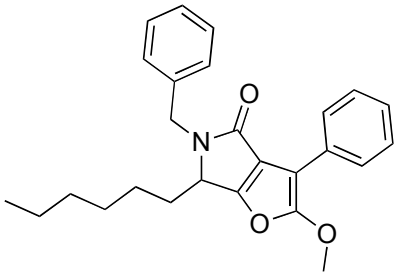
3-(2-Bromo-4,5-dimethoxyphenyl)-5-butyl-6-hexyl-2-methoxy-5,6-dihydrofuro[2,3-c]pyrrol-4-one **8c** was synthesized using the previous one-pot procedure and it was purified using preparative TLC on silica (30 % ethyl acetate in heptane) to afford pure material as a colourless oil (45 %); IR: 2928, 1687, 1593, 1508, 1247, 1209 and 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.6 Hz, CH_3), 0.92 (3H, t, J = 7.2 Hz, CH_3), 1.20-1.39 (10H, m, 5 × CH_2), 1.52 (2H, m, CH_2), 1.65 and 2.01 (2H, 2 × m, $\underline{CH_2}CHN$), 3.01 and 3.84 (2H, 2 × m, CH_2N), 3.87 (6H, s, 2 × $PhO\underline{CH_3}$), 3.96 (3H, s, OCH_3), 4.39 (1H, dd, J = 3.9 Hz and J = 7.8 Hz, CHN), 6.96 (1H, s, Ar-H), 7.08 (1H, s, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 14.0 (q), 20.1 (t), 22.6 (t), 23.8 (t), 29.1 (t), 30.1 (t), 31.1 (t), 31.7 (t), 39.5 (t), 56.2 (3q), 60.1 (d), 97.9 (s), 114.0 (s), 114.8 (d), 115.7 (d), 120.7 (s), 123.0 (s), 148.1 (s), 149.0 (s), 159.0 (s), 159.2 (s) and 164.8 (s); [Found (ES+): $[^{79}BrM+Na]^+$ 530.1492, $C_{25}H_{34}{}^{79}BrNO_5Na$ requires 530.1518 ; $[^{81}Br\ M+Na]^+$ 532.1489, $C_{25}H_{34}{}^{81}BrNO_5Na$ requires 532.1498].



8d

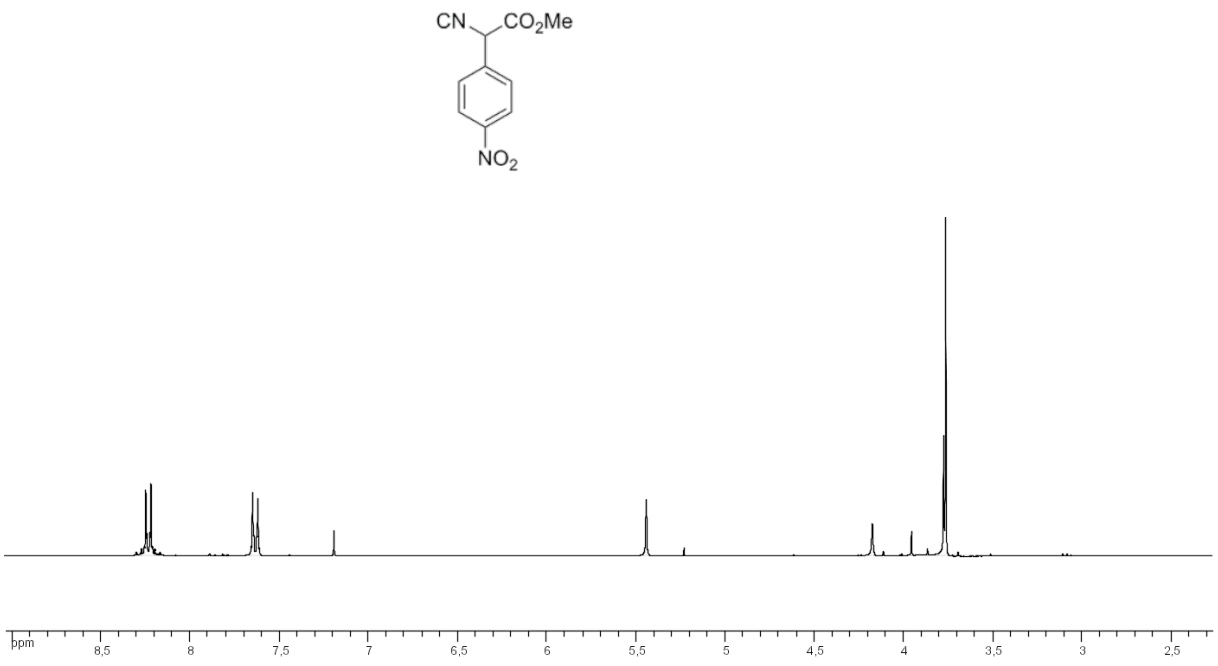
5-Butyl-6-hexyl-2-methoxy-3-(2-nitrophenyl)-5,6-dihydrofuro[2,3-c]pyrrol-4-one **8d** was synthesized using the previous one-pot procedure. It was purified using preparative TLC on silica (30 % ethyl acetate in heptane) to afford pure material as a colourless oil (40 %); IR: 2928, 1687, 1626, 1598, 1527, 1455, 1332, 1208 and 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.9 Hz, CH_3), 0.93 (3H, t, J = 7.2 Hz, CH_3), 1.20-1.41 (10H, m, 5

× CH_2), 1.55 (2H, m, CH_2), 1.57 and 1.98 (2H, 2 × m, $\underline{CH_2}$CHN), 3.03 and 3.84 (2H, 2 × m, CH_2N), 3.97 (3H, s, OCH_3), 4.40 (1H, dd, *J* = 3.9 Hz and *J* = 7.8 Hz, CHN), 7.35 (1H, dt, *J* = 1.5 Hz and *J* = 7.8 Hz, Ar-H), 7.57 (1H, dt, *J* = 1.5 Hz and *J* = 7.8 Hz, Ar-H), 7.84 (2H, dd, *J* = 1.5 Hz and *J* = 7.8 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 14.0 (q), 20.1 (t), 22.5 (t), 23.7 (t), 29.1 (t), 30.0 (t), 31.1 (t), 31.6 (t), 39.7 (t), 56.5 (q), 59.4 (d), 94.6 (s), 119.6 (s), 124.0 (d), 124.4 (s), 124.8 (d), 127.4 (d), 132.5 (d), 148.1 (s), 159.2 (s), 159.6 (s) and 164.7 (s); [Found (ES+): $[M+Na]^+$ 437.2021, $C_{23}H_{30}N_2O_5Na$ requires 437.2052].



8e

5-benzyl-6-hexyl-2-methoxy-3-phenyl-5,6-dihydrofuro[2,3-c]pyrrol-4-one **8e** was synthesized using the previous one-pot procedure. It was purified using preparative TLC on silica (30 % ethyl acetate in heptane) to afford pure material as a colourless oil (42 %); IR: 2928, 1687, 1591, 1455, 1405, 1350, 1331, 1075 and 949 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.0 Hz, CH_3), 1.08-1.38 (8H, m, 4 × CH_2), 1.69 and 1.96 (2H, 2 × m, $\underline{CH_2}$CHN), 4.08 (3H, s, OCH_3), 4.16 and 5.28 (2H, 2 × d, *J* = 15.5 Hz, CH_2Ph), 4.27 (1H, dd, *J* = 3.5 Hz and *J* = 7.5 Hz, CHN), 7.23-7.36 (6H, m, Ar-H), 7.43 (2H, t, *J* = 7.5 Hz, Ar-H), 8.20 (2H, dd, *J* = 1.5 Hz and *J* = 8.5 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (q), 22.5 (t), 23.4 (t), 29.0 (t), 29.7 (t), 31.6 (t), 43.9 (t), 55.9 (q), 60.2 (d), 100.2 (s), 119.3 (s), 126.4 (d), 127.2 (2d), 127.5 (d), 127.9 (2d), 128.6 (2d), 128.7 (2d), 130.7 (s), 137.9 (s), 159.5 (s), 160.1 (s) and 165.6 (s); [Found (ES+): $[M+Na]^+$ 426.2053, $C_{26}H_{29}NO_3Na$ requires 426.2045].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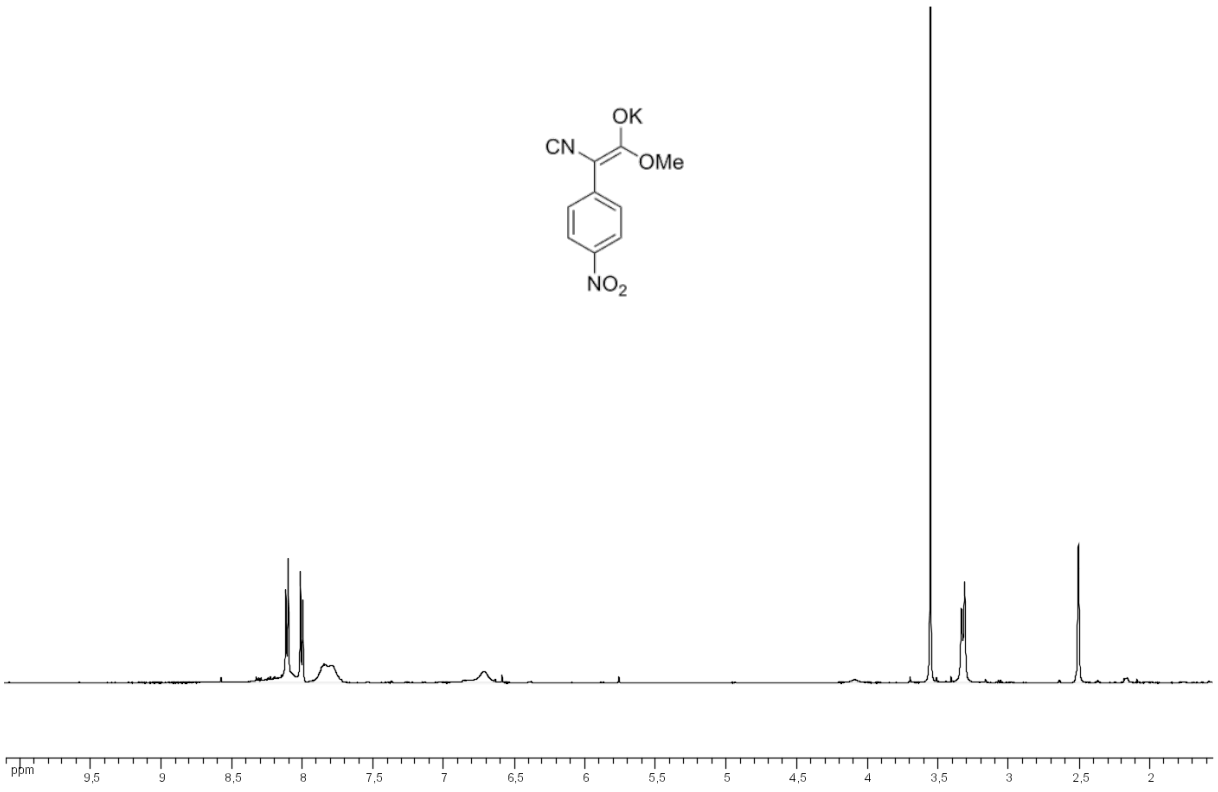
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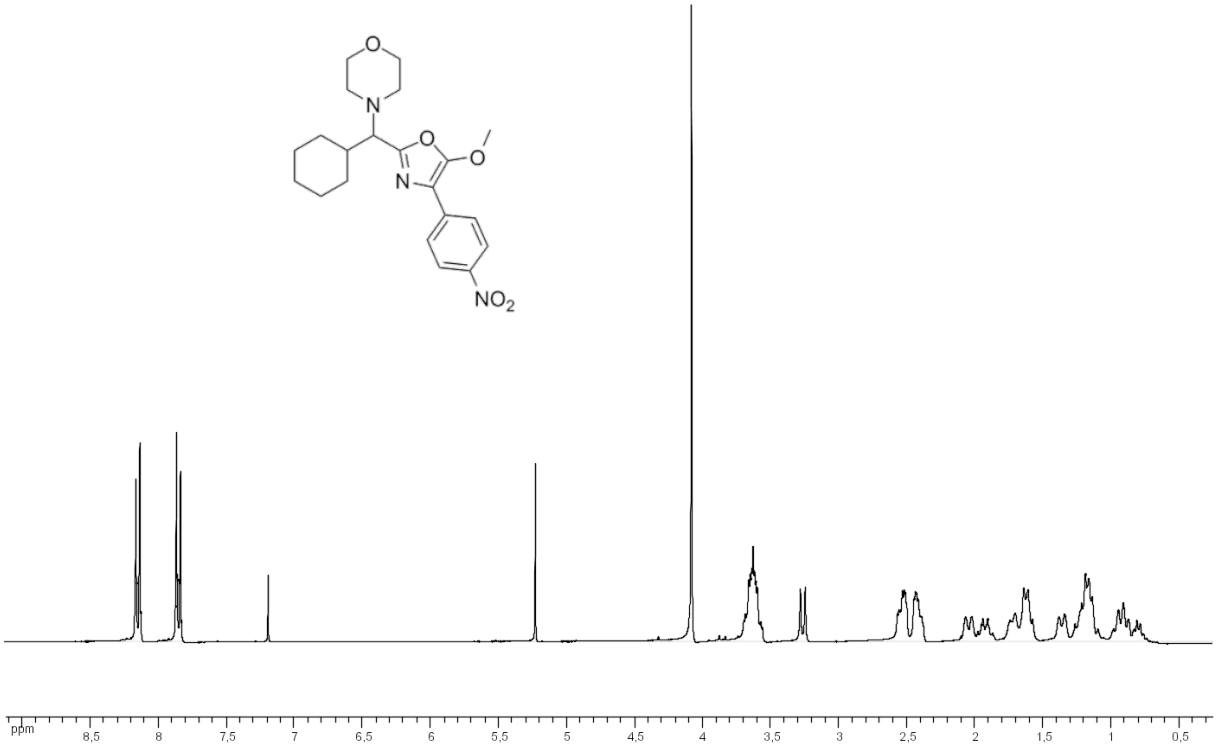
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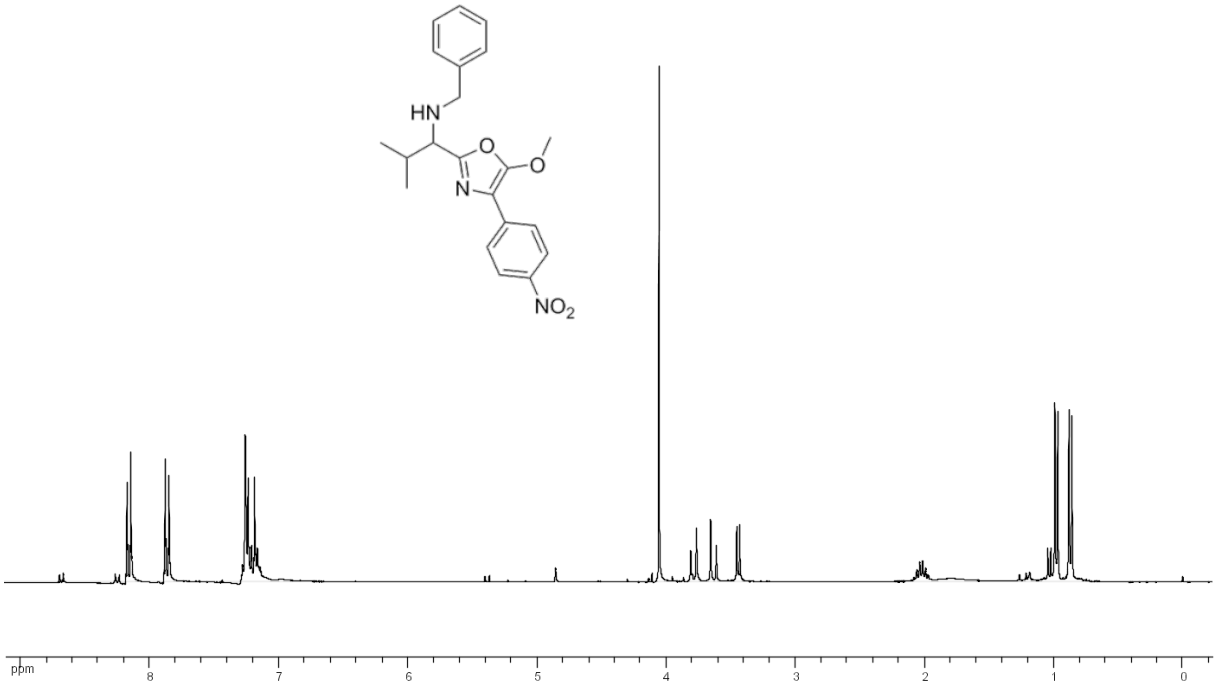
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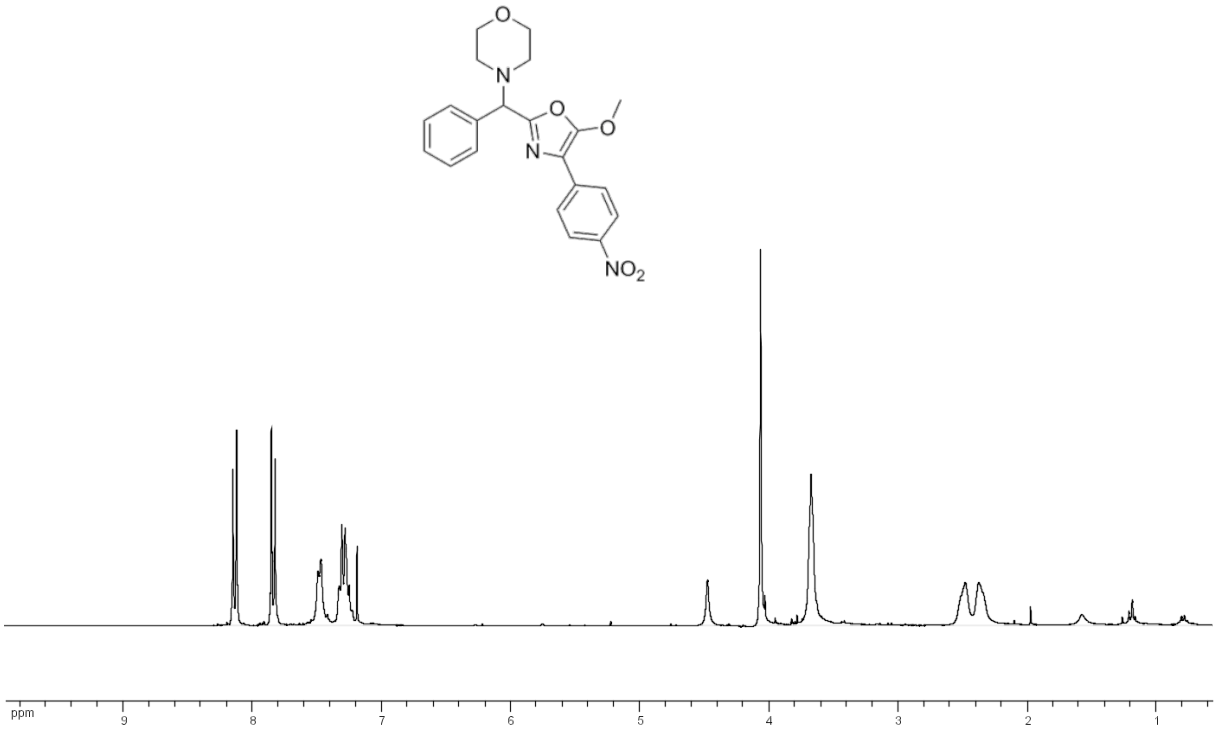
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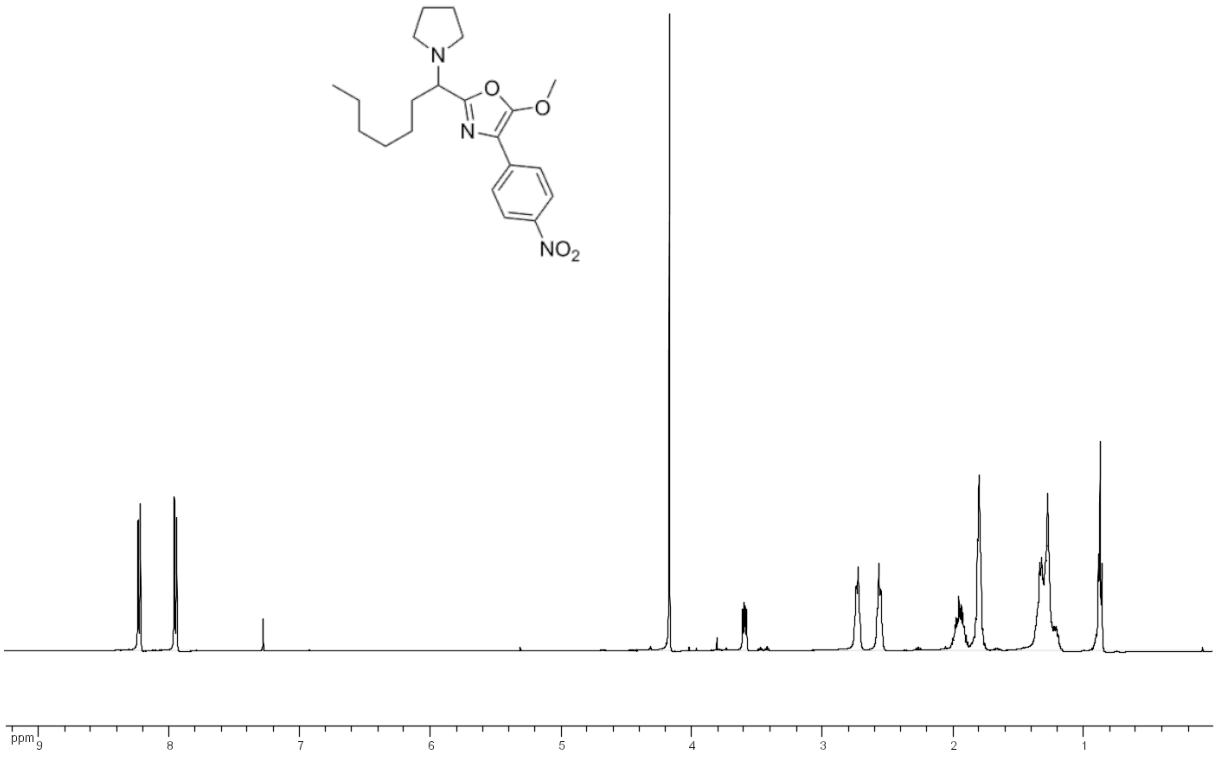
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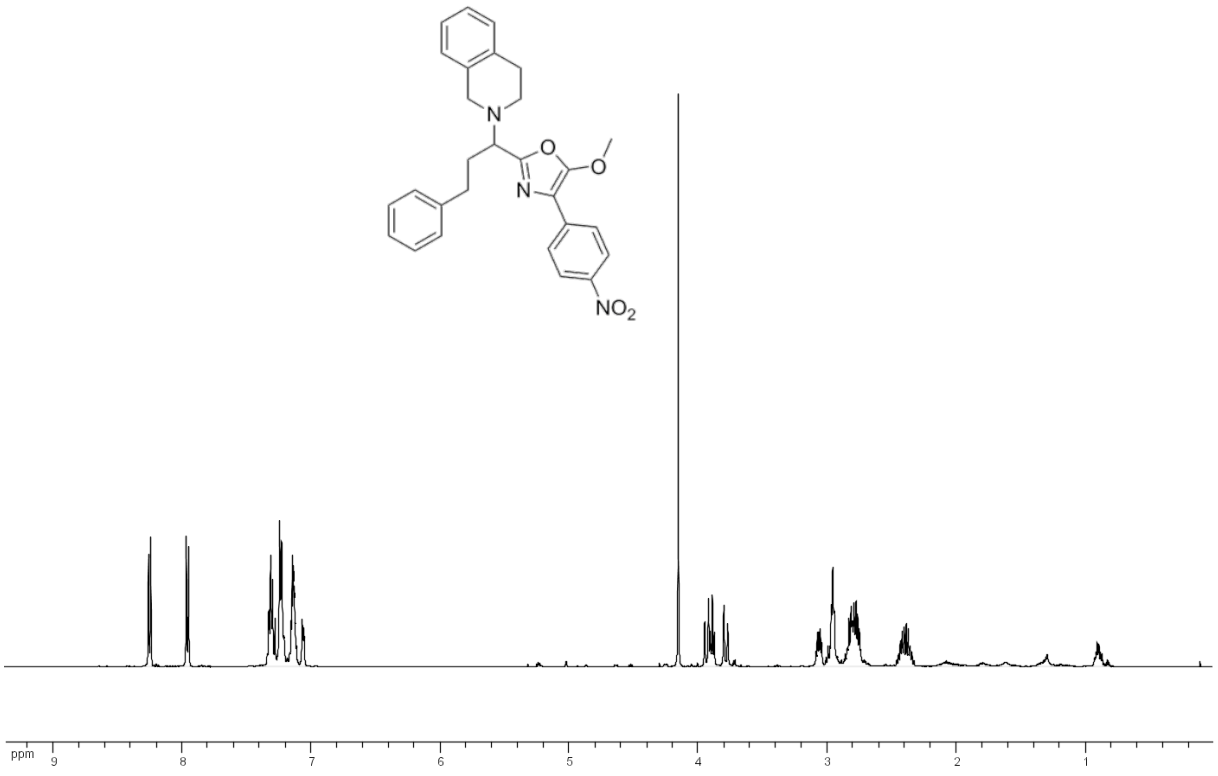
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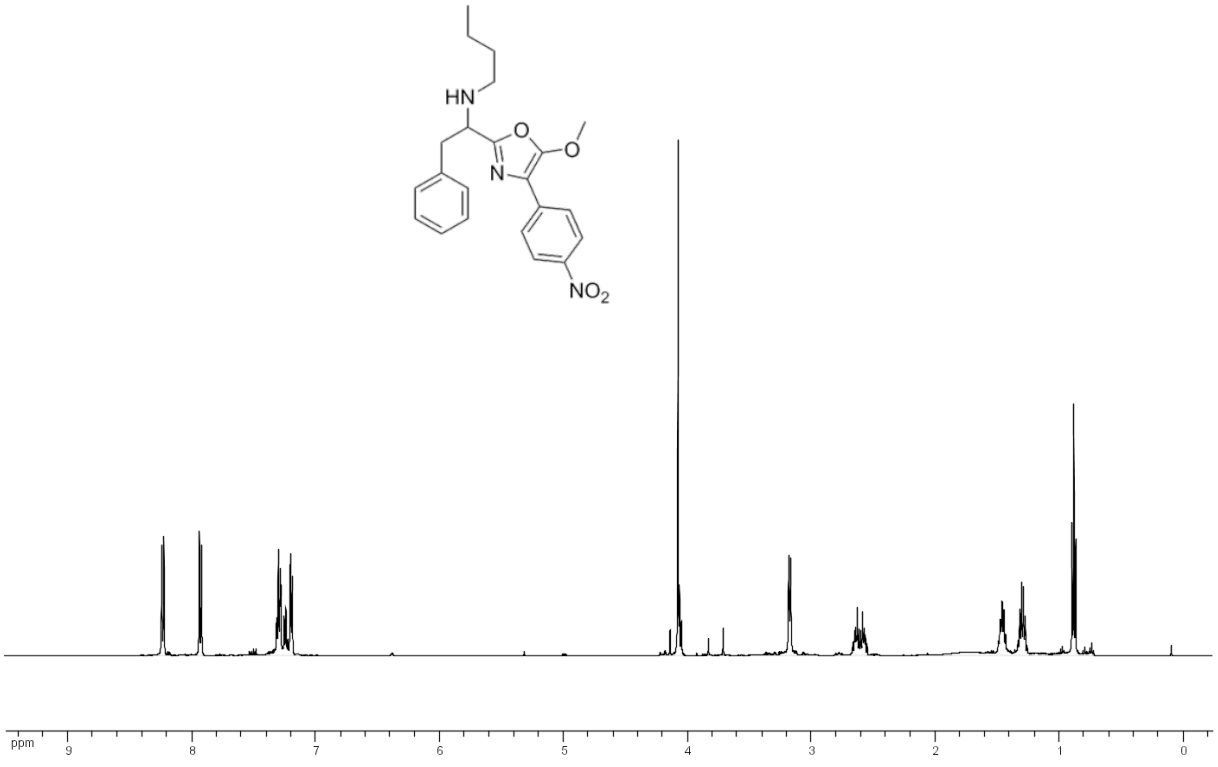
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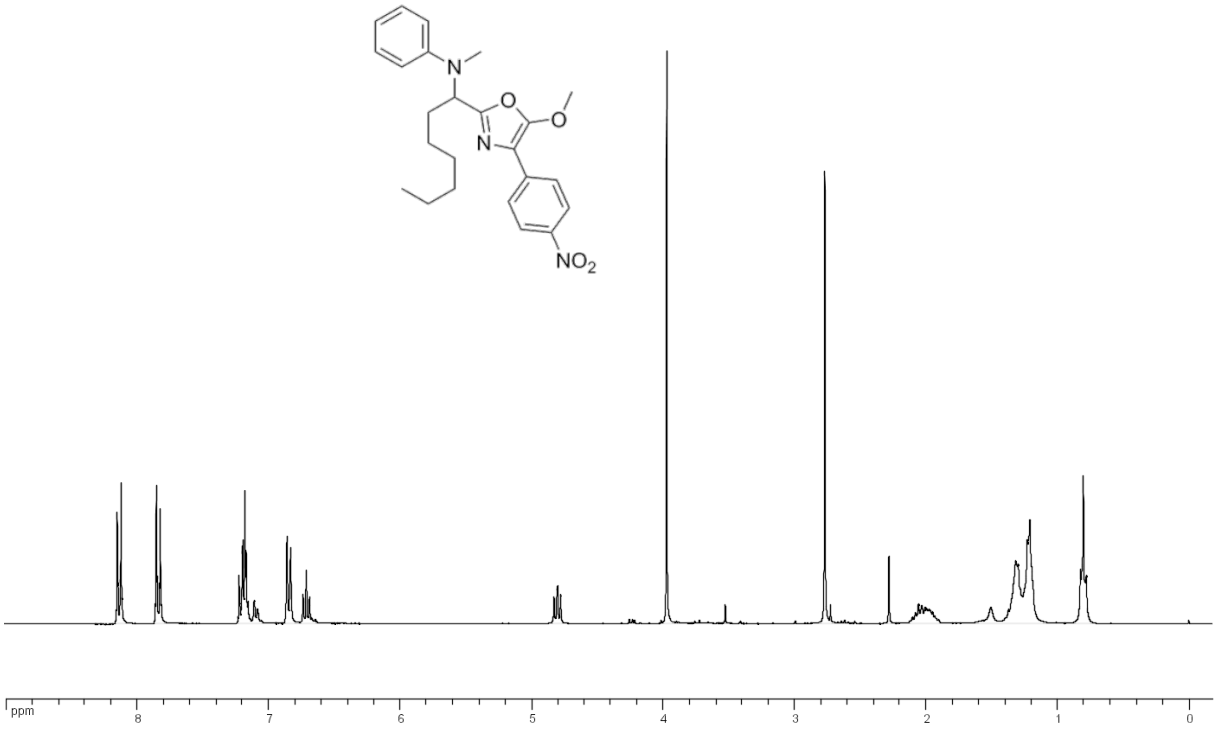
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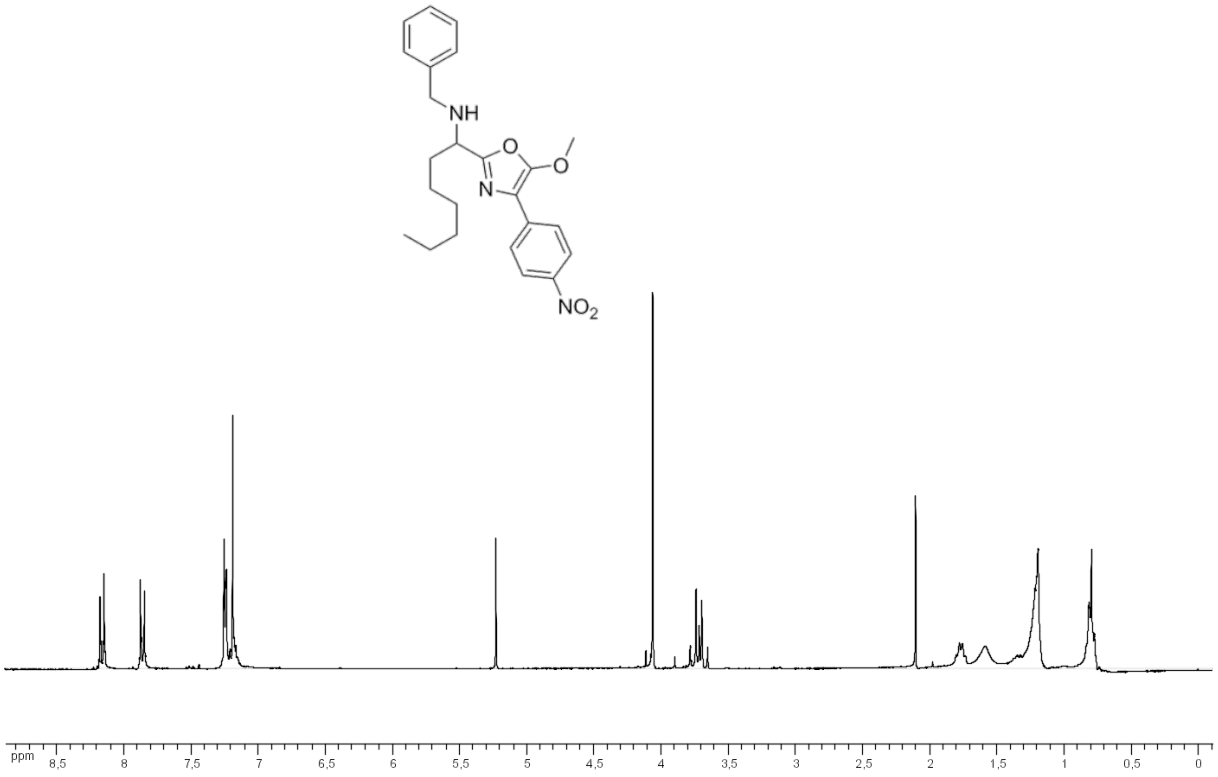
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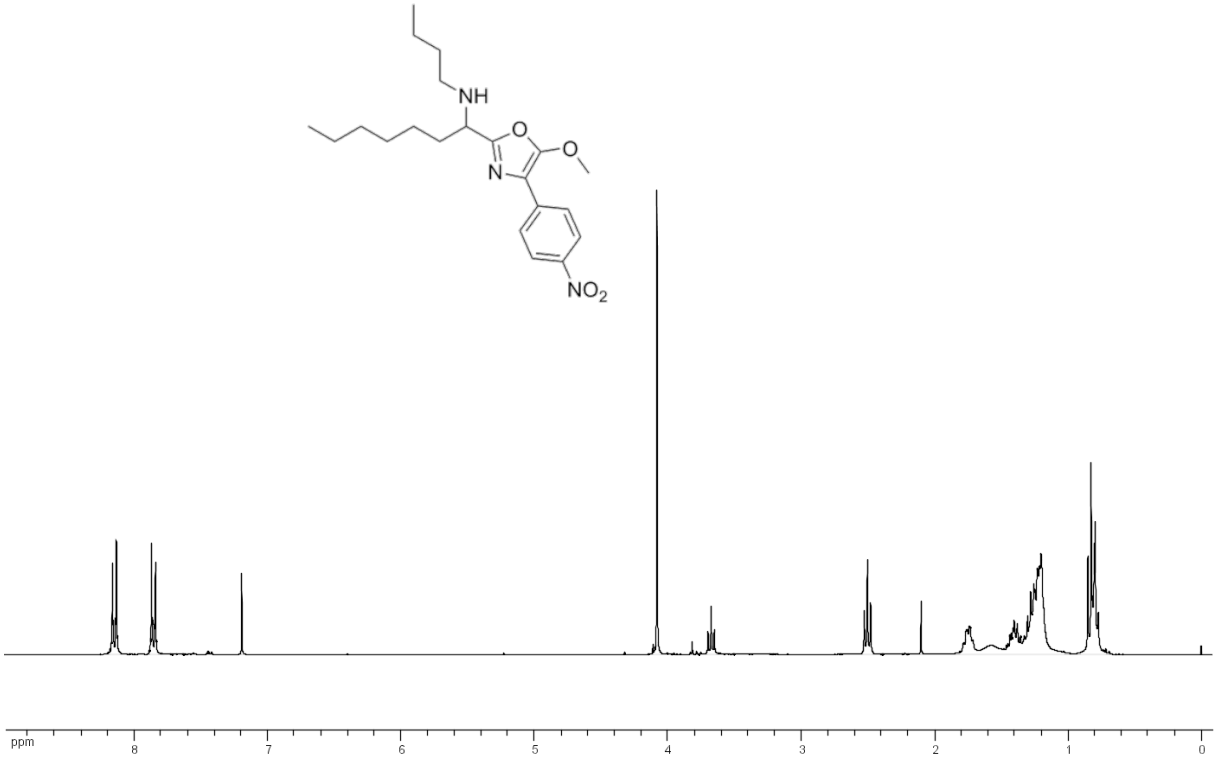
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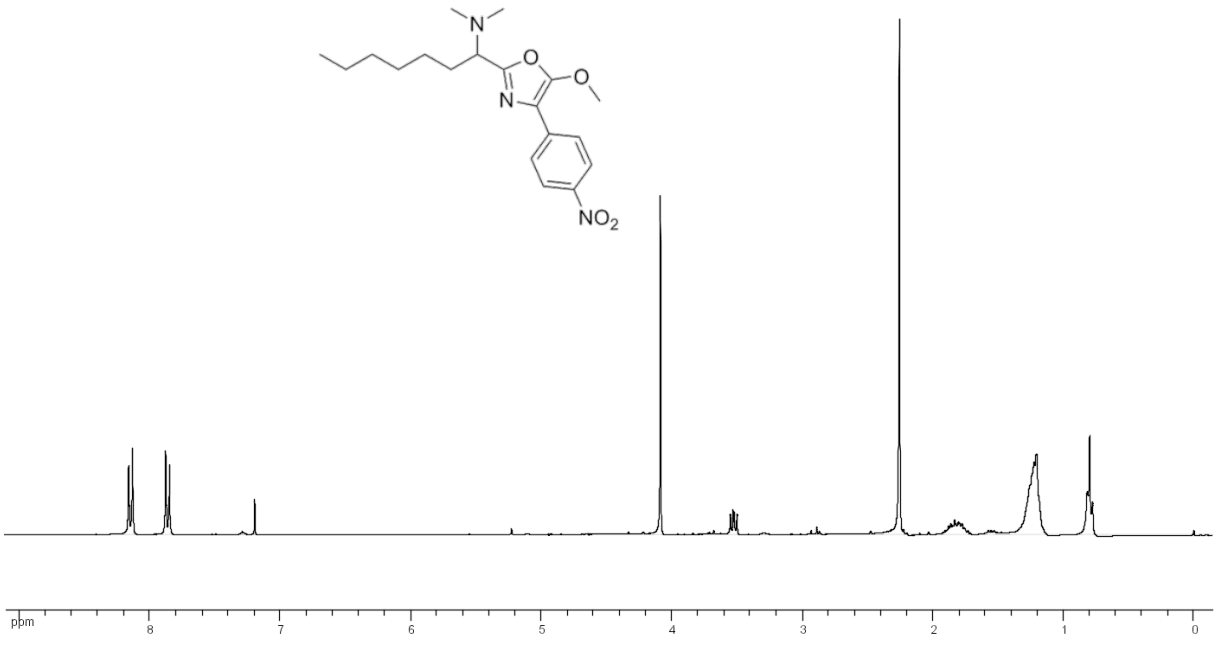
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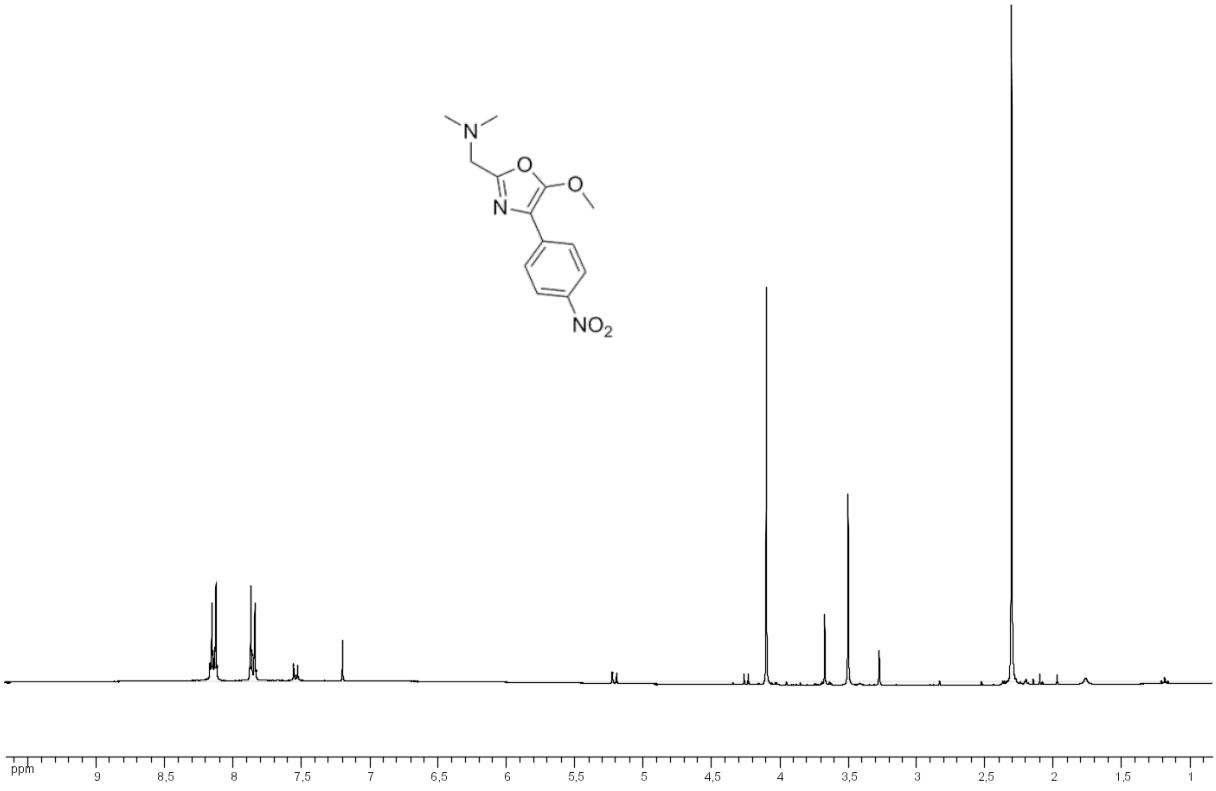
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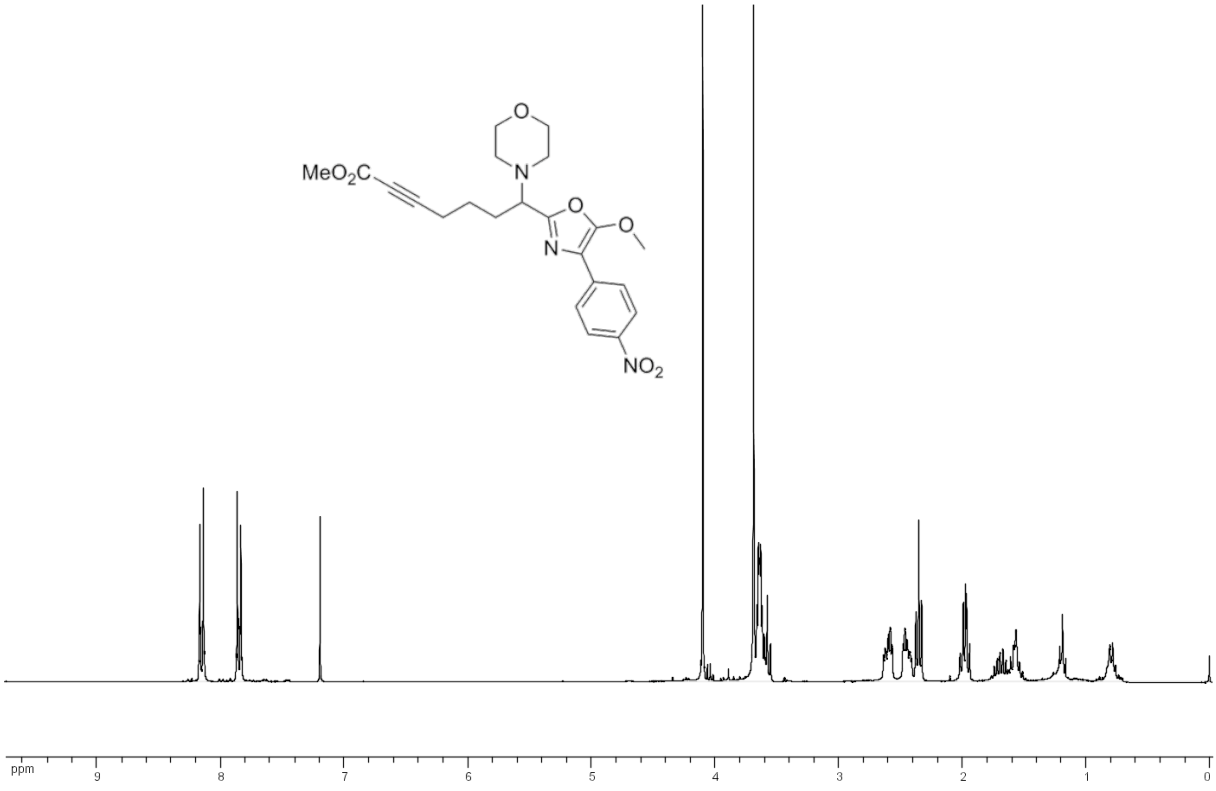
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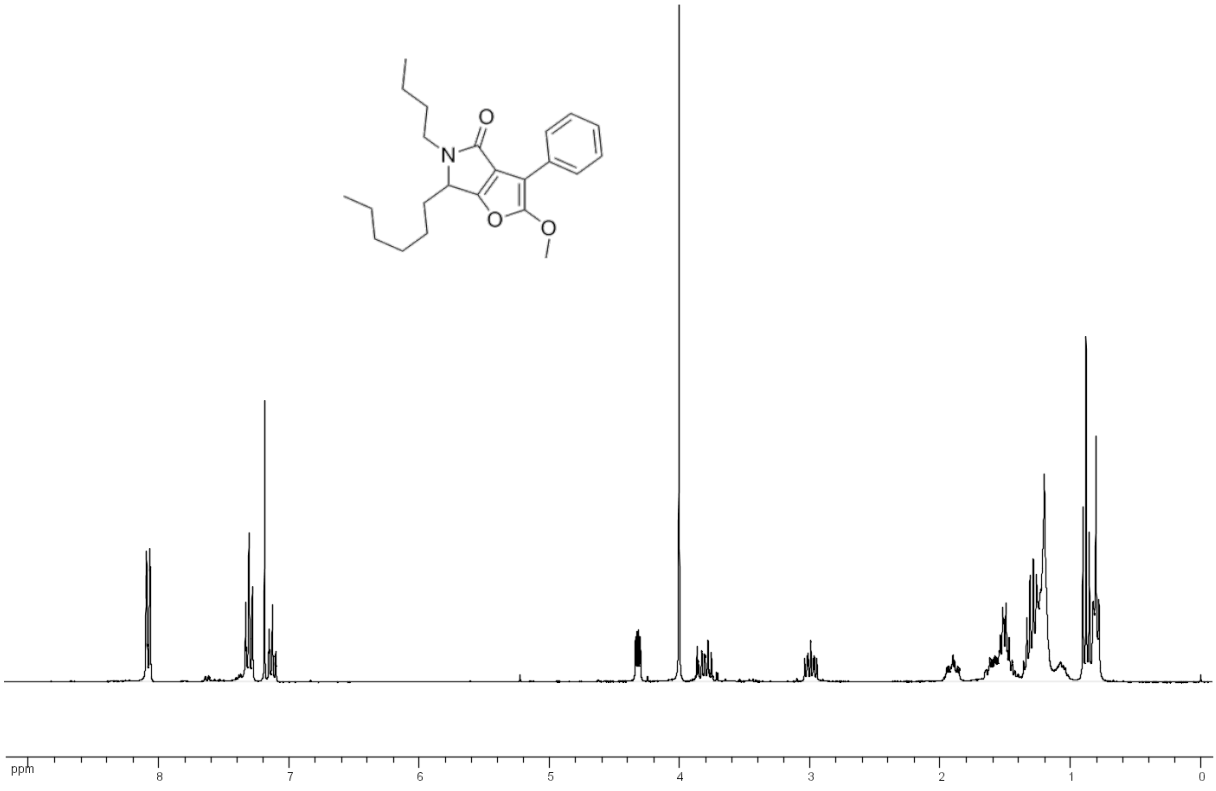
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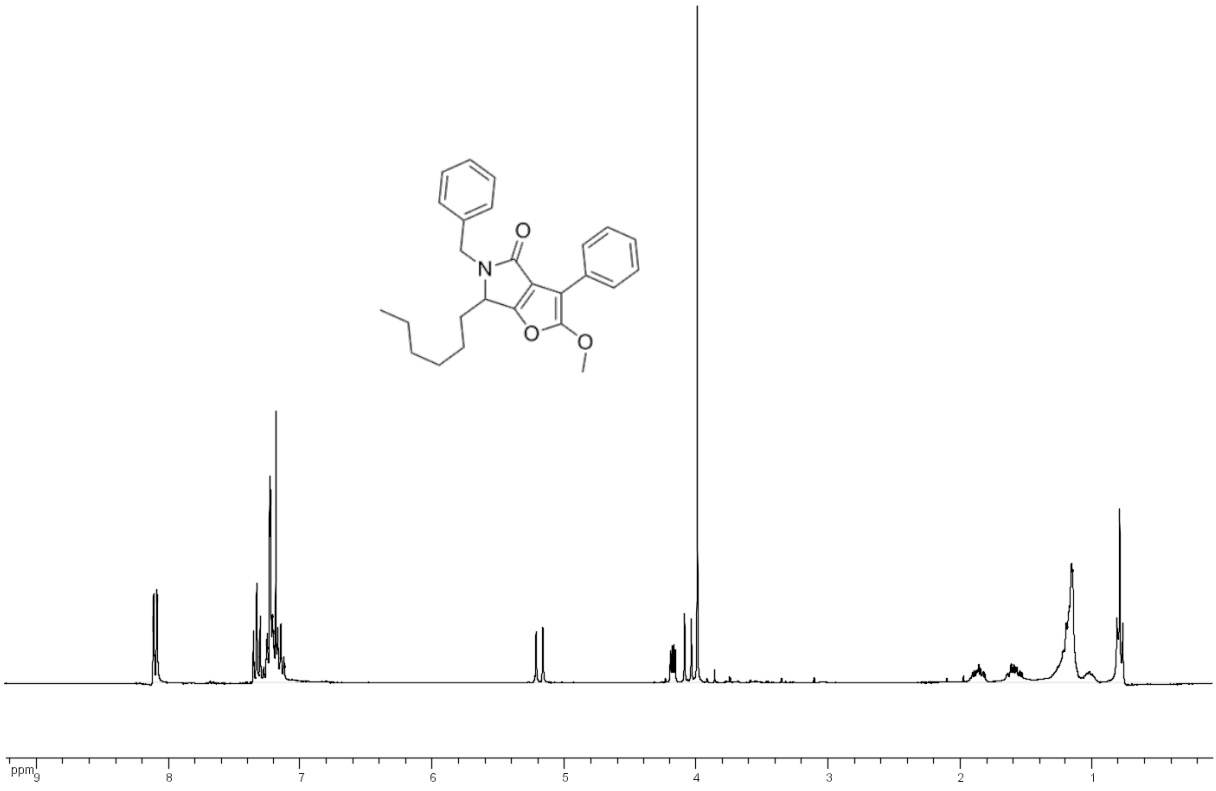
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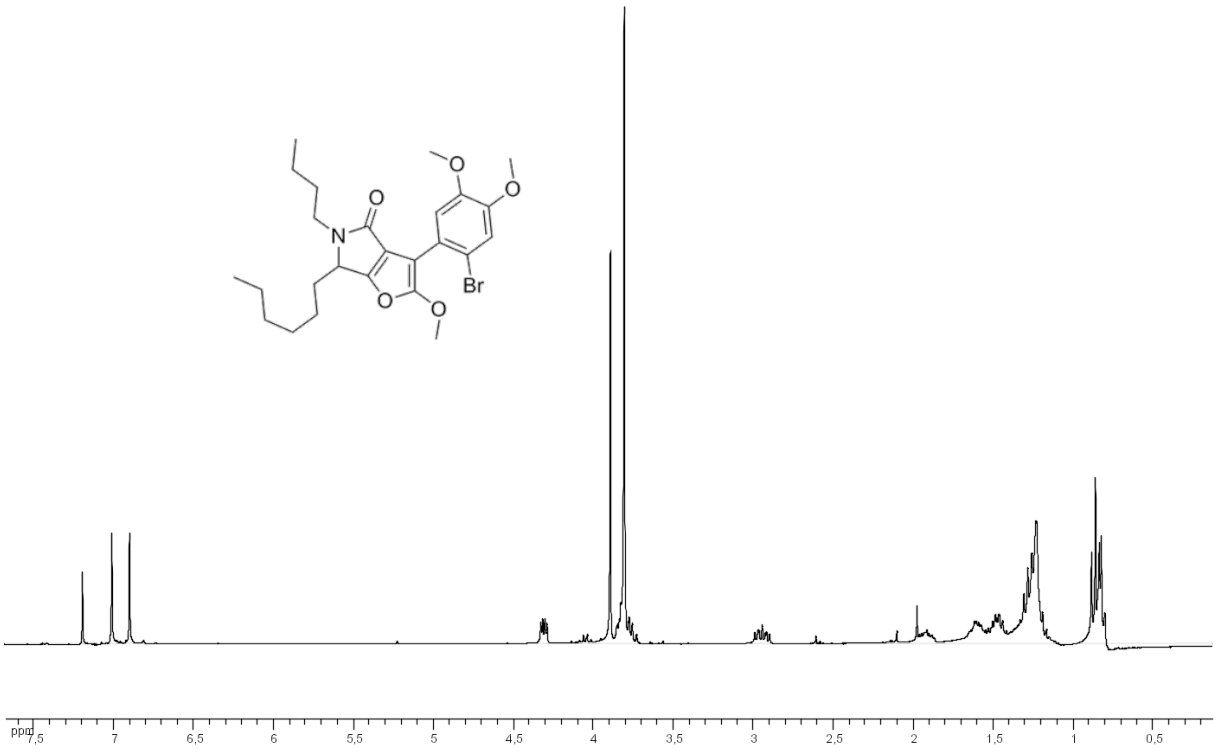
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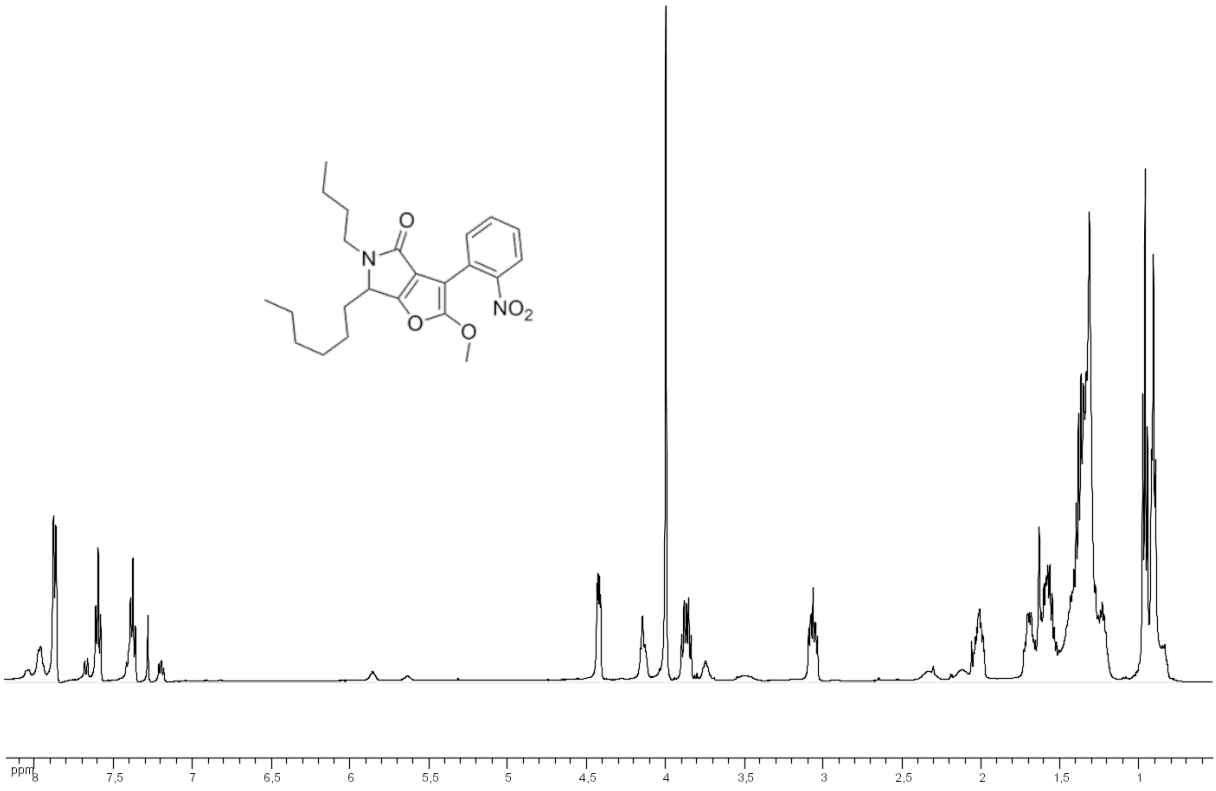
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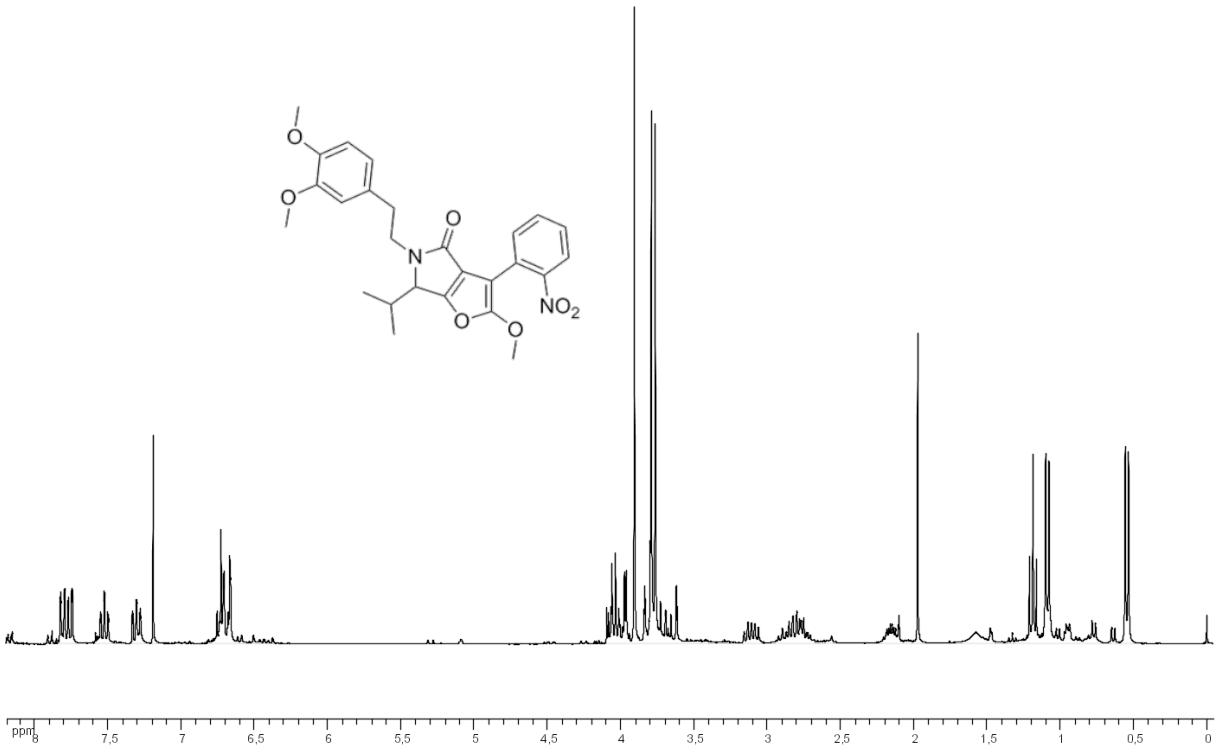
O
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2
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