Supplementary Information

Microwave Assisted Synthesis of Novel Six-Membered 4-C, 4-O and 4-S Lactams Derivatives: Characterization and *in vitro* Biological Evaluation of Cytotoxicity and Anticoagulant Activity

Nicolás E. Núñez-Navarro,[a] Gerardine F. Segovia,[a] Renato A. Burgos,[b] Carlos F. Lagos,[c,d] Nataly Fuentes-Ibacache,[c] Mario A. Faúndez[b] and Flavia C. Zacconi[a,e]*

[a]Departamento de Química Orgánica and [b]Departamento de Farmacia, Facultad de Química, Pontificia Universidad Católica de Chile, Avda. Vicuña Mackenna 4860, Macul, Santiago, Chile

[c]Departamento de Endocrinología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Lira 85, Piso 5, Santiago, Chile

[d]Facultad de Ciencia, Universidad San Sebastián, Campus Los Leones, Lota 2465, Providencia 7510157, Santiago, Chile

[e]Centro de Investigación en Nanotecnología y Materiales Avanzados, CIEN-UC, Pontificia Universidad Católica de Chile, Santiago, Chile

Experimental

Materials and methods

General synthetic remarks

All the reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were appropriately dried before use. Ullmann type reactions were placed on a microwave Synthesis Reactor Monowave 300, Anton Paar. All reactions were monitored by thin layer chromatography (TLC). Column chromatography purifications were performed using silica gel. The melting points of solid derivatives were measured using an Electrothermal IA9100 digital melting point apparatus (Staffordshire, UK). NMR spectra were recorded on Bruker Advance III HD 400 NMR spectrometer (400 MHz) with $CDCl_3$ as a solvent, except where indicated, the nuclear magnetic resonance (NMR) data are reported in δ (ppm) from tetramethylsilane (TMS). Elemental analyses were performed on a Fisons EA 1108 CHNS-O Element Analyzer. IR spectra were recorded in KBr pellet, on a BRUKER VECTOR 22 spectrophotometer. High resolution mass spectra (HRMS) were recorded on a Thermo Scientific Exactive Plus Orbitrap.

*e-mail: fzacconi@uc.cl

General synthesis compounds (**6**-**8**)

A mixture of CuI (0.21 mmol, 40 mg), *p*-iodoaniline or *p*-bromoaniline (4.2 mmol, 920 mg), δ-valerolactame (5.04 mmol, 500 mg), K_3PO_4 (8.40 mmol, 1.78 g), *N*,*N*'-dimethylethylenediamine (DMEN) (0.42 mmol, 37 mg, 45 µL) and dry toluene (10 mL) was placed in the microwave reactor (Synthesis Reactor Monowave 300, Anton Paar) and irradiated with power (4-6 bar, 850 watts) at 110 °C for 2 hours. The crude residue was purified by flash column chromatography on hand-packed columns of silica gel 60 (230-400 mesh) (Sigma-Aldrich, Missouri, USA) as stationary phase and ethyl acetate/methanol as the solvent mixture (mobile phase), to obtain the corresponding isolated arylamine.

1-(4-Aminophenyl)piperidin-2-one (**6**)

Brown solid; 60% yield; mp 182-184 °C; IR (KBr) ν / cm^{-1} 3440, 3325, 2951, 1642, 1518, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85-1.95 (m, 4H, $2CH_2$), 2.52 (t, 2H, *J* 5.7 Hz, CH_2), 3.56 (t, 2H, *J* 5.5 Hz, CH_2), 6.66 (d, 2H, *J* 8.5 Hz, 2Ar-H), 6.98 (d, 2H, *J* 8.5 Hz, 2Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 23.7, 32.8, 52.2, 115.6 (2C), 127.3 (2C), 134.3, 145.4, 170.3; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{11}H_{14}N_2O$ $[M + H]^+$: 191.1184, found: 191.1181; anal. calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73; found: C, 69.5; H, 7.45; N, 14.68.

4-(4-Aminophenyl)morpholin-3-one (**7**)

White solid; 75% yield; mp 171-175 °C; IR (KBr) ν / cm^{-1} 3437, 3320, 2948, 1640, 1516, 827; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.58 (t, 2H, *J* 3.6 Hz, CH_2), 3.91 (t, 2H, *J* 3.9 Hz, CH_2), 4.12 (s, 2H, CH_2), 5.11 (s, 2H, NH_2), 6.56 (d, 2H, *J* 6.6 Hz, 2Ar-H), 6.96 (d, 2H, *J* 6.9 Hz, 2Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.7, 63.6, 67.8, 113.7 (2C), 126.5 (2C), 130.5, 147.4, 165.9; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{10}H_{12}N_2O_2$ $[M + H]^+$: 193.0977, found: 193.0980; anal. calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57; found: C, 62.5; H, 6.27; N, 14.62.

4-(4-Aminophenyl)tiomorpholin-3-one (**8**)

Yellow solid; 70% yield; mp 150-152 °C; IR (KBr) ν / cm^{-1} 3337, 2921, 2851, 1619, 1515, 853, 642; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (t, 2H, *J* 5.6 Hz, CH_2), 3.24 (s, 2H, CH_2), 3.55 (t, 2H, *J* 5.6 Hz, CH_2), 6.61 (d, 2H, *J* 8.6 Hz, 2Ar-H), 6.95 (d, 2H, *J* 8.6 Hz, 2Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 29.4, 44.1, 115.5 (2C), 127.1 (2C), 133.6, 145.7, 168.3; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{10}H_{12}N_2OS$ $[M + H]^+$: 209.0749, found: 209.0740; anal. calcd. for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45; S, 15.40; found: C, 57.7; H, 5.85; N, 13.45; S, 15.44.

Peptide coupling reaction

A mixture of 1-hydroxybenzotriazole (HOBt) (2 equiv.), *N*-ethyl-*N*'-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC.HCl) (2 equiv.) and aryl amines (1 equiv.) were weighed and transferred into a dried reaction tube. The tube was evacuated and back filled with dry N_2. Fatty acids (1.2 equiv.), *N*,*N*-diisopropylethylamine (2.5 equiv.), pyridine (Py) (0.01 equiv.) and dry dichlorometane (DCM) (5 mL) were injected into the tube and stirred at room temperature for 6 h. The product was extracted with ethyl acetate (EtOAc), washed once with saturated $NaHCO_3$, and dried over anhydrous magnesium sulfate. The solvent was removed in vacuum and the remaining product was purified by flash column chromatography on hand-packed columns of silica gel 60 (230-400 mesh) (Sigma-Aldrich,

USA) as stationary phase and *n*-hexane/ethyl acetate as the solvent mixture (mobile phase). Moreover, informed yields correspond to isolated and purified compounds.

N-(4-(2-Oxopiperidin-1-yl)phenyl)hexanamide (**9a**)

Brown solid; 95% yield; mp 112-114 °C; IR (KBr) ν / cm^{-1} 3298, 3267, 2951, 2859, 1681, 1622, 1517, 847, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* 6.3 Hz, CH_3), 1.27-1.37 (m, 4H, $2CH_2$), 1.66-1.71 (m, 2H, CH_2), 1.90-1.96 (m, 4H, $2CH_2$), 2.24 (t, 2H, *J* 7.5 Hz, CH_2), 2.55 (s, 2H, CH_2), 3.57 (s, 2H, CH_2), 7.00 (d, 2H, *J* 8.3 Hz, 2Ar-H), 7.30 (d, 2H, *J* 8.4 Hz, 2Ar-H), 8.77 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.4, 22.5, 23.5, 25.4, 31.6, 32.8, 37.2, 52.1, 121.2 (2C), 126.4 (2C), 137.5, 138.3, 170.6, 172.2; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{17}H_{24}N_2O_2$ $[M + H]^+$: 289.1916, found: 289.1921; anal. calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71; found: C, 70.82; H, 8.34; N, 9.75.

N-(4-(2-Oxopiperidin-1-yl)phenyl)heptanamide (**9b**)

Brown solid; 98% yield; mp 202-204 °C; IR (KBr) ν / cm^{-1} 3307, 3275, 2924, 2854, 1684, 1626, 1541, 831, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* 6.5 Hz, CH_3), 1.27-1.39 (m, 6H, $3CH_2$), 1.62-1.71 (m, 2H, CH_2), 1.90-1.96 (m, 4H, $2CH_2$), 2.27 (t, 2H, *J* 7.6 Hz, CH_2), 2.56 (s, 2H, CH_2), 3.58 (s, 2H, CH_2), 7.03 (d, 2H, *J* 8.3 Hz, 2Ar-H), 7.32 (d, 2H, *J* 8.3 Hz, 2Ar-H), 8.42 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.5, 22.7, 23.6, 25.8, 29.2, 31.7, 32.9, 37.4, 52.1, 121.3 (2C), 126.5 (2C), 137.4, 138.5, 170.7, 172.1; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{18}H_{26}N_2O_2$ $[M + H]^+$: 303.2073, found: 303.2073; anal. calcd. for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26; found: C, 71.45; H, 8.68; N, 9.2.

N-(4-(2-Oxopiperidin-1-yl)phenyl)octanamide (**9c**)

Brown solid; 97% yield; mp 190-191 °C; IR (KBr) ν / cm^{-1} 3297, 3267, 2925, 2856, 1680, 1621, 1540, 850, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* 6.7 Hz, CH_3), 1.22-1.39 (m, 8H, $4CH_2$), 1.62-1.72 (m, 2H, CH_2), 1.94 (s, 4H, $2CH_2$), 2.26 (t, 2H, *J* 7.6 Hz, CH_2), 2.56 (s, 2H, CH_2), 3.58 (s, 2H, CH_2), 7.03 (d, 2H, *J* 8.4 Hz, 2Ar-H), 7.31 (d, 2H, *J* 8.4 Hz, 2Ar-H), 8.41 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.5, 22.8, 23.6, 25.8, 29.2, 29.5, 32.9, 37.4, 52.1, 121.3 (2C), 126.5 (2C), 137.4, 138.5, 170.7, 172.1; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{19}H_{28}N_2O_2$ $[M + H]^+$: 317.2229, found: 317.2233; anal. calcd. for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85; found: C, 72.1; H, 8.89; N, 8.87.

N-(4-(2-Oxopiperidin-1-yl)phenyl)nonanamide (**9d**)

Brown solid; 96% yield; mp 186-188 °C; IR (KBr) ν / cm^{-1} 3300, 3269, 2923, 2852, 1681, 1621, 1518, 849, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* 6.5 Hz, CH_3), 1.22-1.39 (m, 10H, $5CH_2$), 1.62-1.73 (m, 2H, CH_2), 1.91-1.97 (m, 4H, $2CH_2$), 2.26 (t, 2H, *J* 7.6 Hz, CH_2), 2.56 (s, 2H, CH_2), 3.58 (s, 2H), 7.03 (d, 2H, *J* 8.4 Hz, 2Ar-H), 7.32 (d, 2H, *J* 8.4 Hz, 2Ar-H), 8.35 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.5, 22.8, 23.6, 25.8, 29.3, 29.5, 32.0, 32.9, 37.5, 52.1, 121.3 (2C), 126.5 (2C), 137.3, 138.5, 170.6, 172.1; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{20}H_{30}N_2O_2$ $[M + H]^+$: 331.2386, found: 331.2391; anal. calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48; found: C, 72.75; H, 9.2; N, 8.43.

N-(4-(3-Oxomorpholine)phenyl)hexanamide (**10a**)

White solid; 95% yield; mp 192-193 °C; IR (KBr) ν / cm^{-1} 3312, 2929, 2858, 1681, 1638, 1540, 845, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* 6.7 Hz, CH_3), 1.30-1.38 (m, 4H, $2CH_2$), 1.63-1.75 (m, 2H, CH_2), 2.28 (t, 2H, *J* 7.6 Hz, CH_2), 3.71 (t, 2H, *J* 5.2 Hz, CH_2), 4.03 (t, 2H, *J* 5.3 Hz, CH_2), 4.33 (s, 2H, CH_2), 7.16 (d, 2H, *J* 8.6 Hz, 2Ar-H), 7.40 (d, 2H, *J* 8.6 Hz, 2Ar-H), 8.04 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 25.3, 31.5, 37.4, 50.0, 64.1, 68.5, 121.0 (2C), 126.0 (2C), 136.5, 137.4, 167.1, 171.9; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{16}H_{22}N_2O_3$ $[M + H]^+$: 291.1709, found: 291.1697; anal. calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65; found: C, 66.21; H, 7.66; N, 9.59.

N-(4-(3-Oxomorpholine)phenyl)heptanamide (**10b**)

White solid; 97% yield; mp 176-178 °C; IR (KBr) ν / cm^{-1} 3313, 2927, 2855, 1683, 1638, 1541, 845, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* 6.6 Hz, CH_3), 1.26-1.49 (m, 6H, $3CH_2$), 1.73-1.80 (m, 2H, CH_2), 2.38 (t, 2H, *J* 7.5 Hz, CH_2), 3.78 (t, 2H, *J* 5.2 Hz, CH_2), 4.09 (t, 2H, *J* 5.3 Hz, CH_2), 4.39 (s, 2H, CH_2), 7.32 (d, 2H, *J* 8.6 Hz, 2Ar-H), 7.53 (d, 2H, *J* 8.6 Hz, 2Ar-H), 7.62 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.6, 25.5, 29.0, 31.5, 37.6, 49.9, 64.3, 68.5, 121.2 (2C), 126.2 (2C), 136.8, 137.1, 166.8, 171.7; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{17}H_{24}N_2O_3$ $[M + H]^+$: 305.1865, found: 305.1873; anal. calcd. for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20; found: C, 67.10; H, 7.89; N, 9.18.

N-(4-(3-Oxomorpholin)phenyl)octanamide (**10c**)

White solid; 97% yield; mp 183-184 °C; IR (KBr) ν / cm^{-1} 3309, 2925, 2853, 1688, 1639, 1538, 849, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* 6.5 Hz, CH_3), 1.29 (d, 8H, *J* 6.6 Hz, $4CH_2$), 1.61-1.77 (m, 2H, CH_2), 2.29 (t, 2H, *J* 5.8 Hz, CH_2), 3.72 (t, 2H, *J* 5.2 Hz, CH_2), 4.03 (t, 2H, *J* 5.3 Hz, CH_2), 4.34 (s, 2H, CH_2), 7.16 (d, 2H, *J* 6.5 Hz, 2Ar-H), 7.41 (d, 2H, *J* 6.6 Hz, 2Ar-H), 7.99 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.6, 29.1, 29.3, 31.7, 37.5, 49.9, 64.1, 68.5, 121.0 (2C), 126.0 (2C), 136.5, 137.4, 167.0, 171.8, HRMS (FTMS + pESI) *m/z*, calcd. for $C_{18}H_{26}N_2O_3$ $[M + H]^+$: 319.2022, found: 319.2026; anal. calcd. for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80; found: C, 67.88; H, 8.24; N, 8.72.

N-(4-(3-Oxomorpholin)phenyl)nonanamide (**10d**)

White solid; 98% yield; mp 166-168 °C; IR (KBr) ν / cm^{-1} 3313, 2923, 2852, 1683, 1639, 1541, 845, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* 6.5 Hz, CH_3), 1.28 (d, 10H, *J* 3.0 Hz, $5CH_2$), 1.60-1.73 (m, 2H, CH_2), 2.28 (t, 2H, *J* 7.5 Hz, CH_2), 3.71 (t, 2H, *J* 5.0 Hz, CH_2), 4.02 (t, 2H, *J* 5.1 Hz, CH_2), 4.33 (s, 2H, CH_2), 7.16 (d, 2H, *J* 8.4 Hz, 2Ar-H), 7.41 (d, 2H, *J* 8.4 Hz, 2Ar-H), 7.96 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.4, 29.2, 29.3, 29.4, 31.8, 37.5, 50.0, 64.1, 68.5, 121.0 (2C), 126.0 (2C), 136.6, 137.4, 167.3, 171.8; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{19}H_{28}N_2O_3$ $[M + H]^+$: 333.2178, found: 333.2184; anal. calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43; found: C, 68.58; H, 8.5; N, 8.39.

N-(4-(3-Oxotiomorpholin)phenyl)hexanamide (**11a**)

Yellow solid; 95% yield; mp 190-192 °C; IR (KBr) ν / cm^{-1} 3314, 2927, 2857, 1681, 1642, 1517, 845, 726, 658; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, 3H, *J* 6.8 Hz, CH_3), 1.20-1.31 (m, 4H, $2CH_2$), 1.56-1.67 (m, 2H, CH_2), 2.21 (t, 4H, *J* 7.6 Hz, $2CH_2$), 2.95 (t, 2H, *J* 5.8 Hz, CH_2), 3.39 (s, 2H, CH_2), 3.85 (t, 2H, *J* 5.8 Hz, CH_2), 7.01 (d, 2H, *J* 8.6 Hz, 2Ar-H), 7.29 (d, 2H, *J* 8.6 Hz, 2Ar-H), 8.04 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.5, 25.4,

26.8, 30.7, 31.6, 37.4, 52.6, 121.2 (2C), 126.5 (2C), 137.5, 137.9, 167.4, 172.1; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{16}H_{22}N_2O_2S$ $[M + H]^+$: 307.1480, found: 307.1471; anal. calcd. for $C_{16}H_{22}N_2O_2S$: C, 62.71; H, 7.24; N, 9.14; S, 10.46; found: C, 62.7; H, 7.19; N, 9.2; S, 10.42.

N-(4-(3-Oxotiomorpholin)phenyl)heptanamide (**11b**)

Yellow solid; 95% yield; mp 202-204 °C; IR (KBr) ν / cm^{-1} 3318, 2928, 2851, 1685, 1654, 1535, 836, 723, 649; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* 5.6 Hz, CH_3), 1.16-1.43 (m, 6H, $2CH_2$), 1.59-1.75 (m, 2H, CH_2), 2.28 (t, 4H, *J* 7.5 Hz, $2CH_2$), 3.02 (t, 2H, *J* 5.6 Hz, CH_2), 3.46 (s, 2H, CH_2), 3.93 (t, 2H, *J* 5.8 Hz, CH_2), 7.07 (d, 2H, *J* 8.4 Hz, 2Ar-H), 7.35 (d, 2H, *J* 8.4 Hz, 2Ar-H), 8.19 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 23.0, 26.0, 27.1, 29.4, 31.1, 32.0, 37.8, 53.0, 121.5 (2C), 126.8 (2C), 137.8, 138.3, 167.8, 172.4; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{17}H_{24}N_2O_2S$ $[M + H]^+$: 321.1637, found: 321.1624; anal. calcd. for $C_{17}H_{24}N_2O_2S$: C, 63.72; H, 7.55; N, 8.74; S, 10.01; found: C, 63.76; H, 7.5; N, 8.79; S, 10.06.

N-(4-(3-Oxotiomorpholin)phenyl)octanamide (**11c**)

Yellow solid; 98% yield; mp 170-172 °C; IR (KBr) ν / cm^{-1} 3309, 2924, 2853, 1681, 1644, 1536, 847, 726; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* 5.6 Hz, CH_3), 1.21-1.41 (m, 8H, $4CH_2$), 1.58-1.75 (m, 2H, CH_2), 2.28 (t, 4H, *J* 7.3 Hz, $2CH_2$), 3.02 (t, 2H, *J* 5.2 Hz, CH_2), 3.45 (s, 2H, CH_2), 3.90 (t, 2H, *J* 5.2 Hz, CH_2), 7.05 (d, 2H, *J* 8.1 Hz, 2Ar-H), 7.35 (d, 2H, *J* 8.1 Hz, 2Ar-H), 8.41 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 167.5, 137.8, 137.6, 126.4 (2C),121.2 (2C), 52.6, 37.4, 31.8, 30.7, 29.4, 29.2, 26.8, 25.7, 22.7, 14.2; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{18}H_{26}N_2O_2S$ $[M + H]^+$: 335.1793, found: 335.1785; anal. calcd. for $C_{18}H_{26}N_2O_2S$: C, 64.64; H, 7.84; N, 8.38; S, 9.59; found: C, 64.69; H, 7.88; N, 8.4; S, 9.55.

N-(4-(3-Oxotiomorpholin)phenyl)nonanamide (**11d**)

Yellow solid; 95% yield; mp 166-168 °C; IR (KBr) ν / cm^{-1} 3317, 2952, 2849, 1685, 1630, 1540, 836, 720, 647; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* 5.6 Hz, CH_3), 1.19-1.40 (m, 10H, $5CH_2$), 1.58-1.75 (m, 2H, CH_2), 2.30 (t, 4H, *J* 7.3 Hz, $2CH_2$), 3.02 (t, 2H, *J* 5.2 Hz, CH_2), 3.46 (s, 2H, CH_2), 3.92 (s, 2H, CH_2), 7.10 (d, 2H, *J* 5.9 Hz, 2Ar-H), 7.38 (d, 2H, *J* 5.3 Hz, 2Ar-H), 8.01 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.7, 25.8, 26.8, 29.3, 29.5, 30.7, 31.9, 37.5, 52.7, 121.2 (2C), 126.5 (2C), 137.5, 137.9, 167.6, 172.2; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{19}H_{28}N_2O_2S$ $[M + H]^+$: 349.1950, found: 349.1939; anal. calcd. for $C_{19}H_{28}N_2O_2S$: C, 65.48; H, 8.10; N, 8.04; S, 9.20; found: C, 65.5; H, 8.12; N, 8.1; S, 9.25.

Spectroscopic data of new synthesized compounds

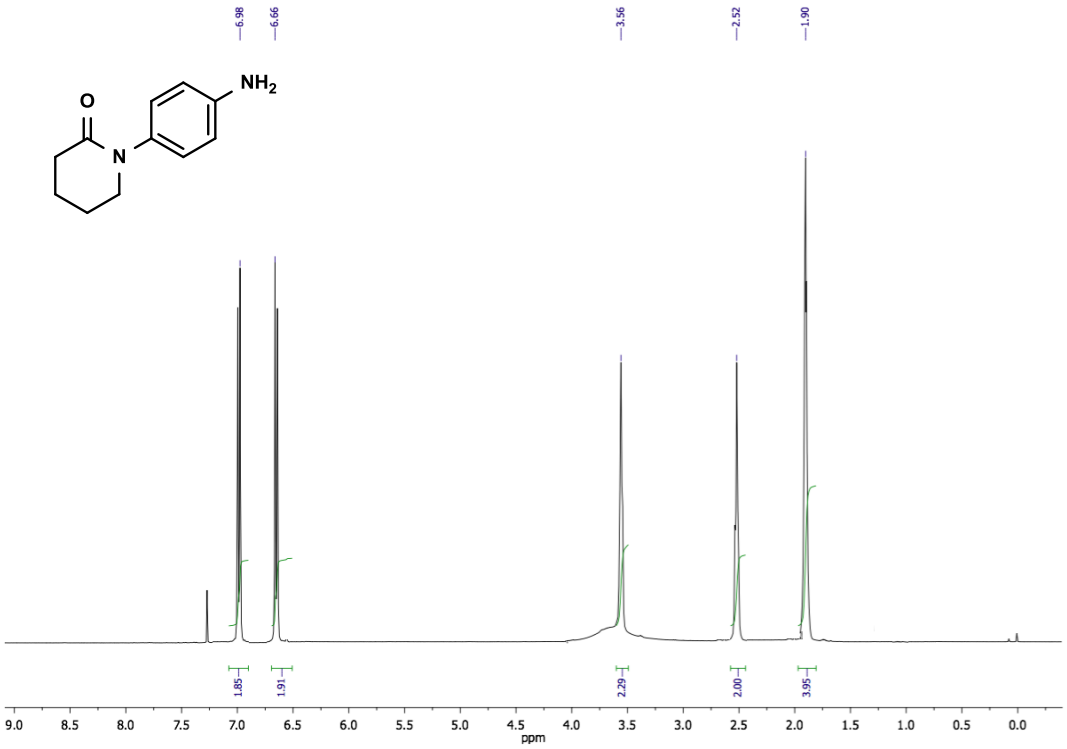


Figure S1. ^{1}H NMR (400 MHz, $CDCl_3$) of 1-(4-aminophenyl)piperidin-2-one (**6**).

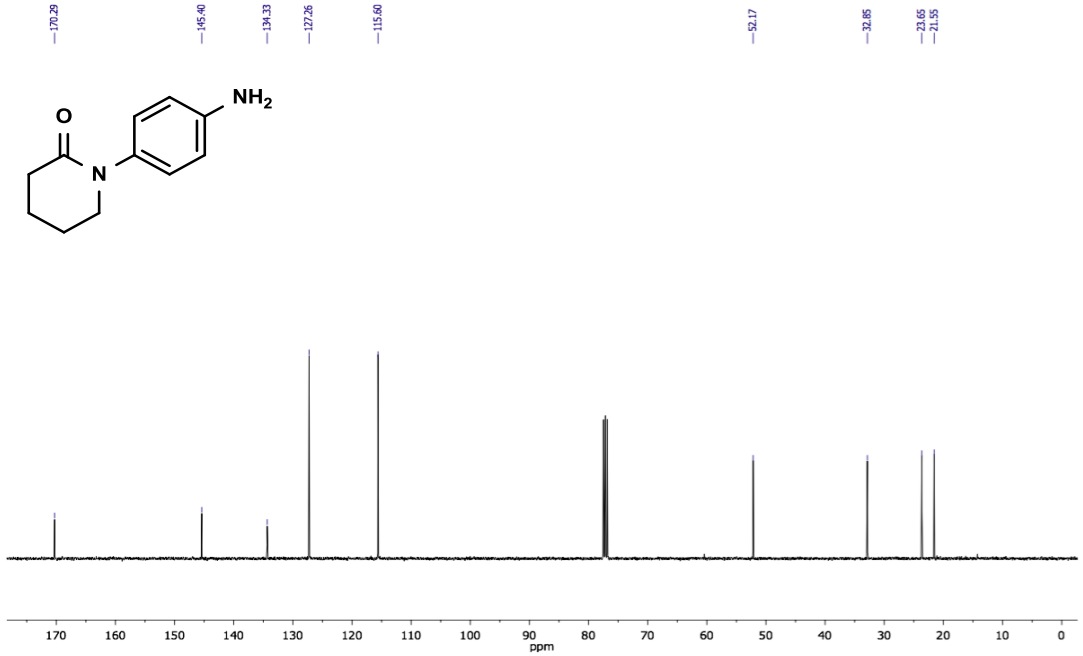


Figure S2. ^{13}C NMR (100 MHz, $CDCl_3$) of 1-(4-aminophenyl)piperidin-2-one (**6**).

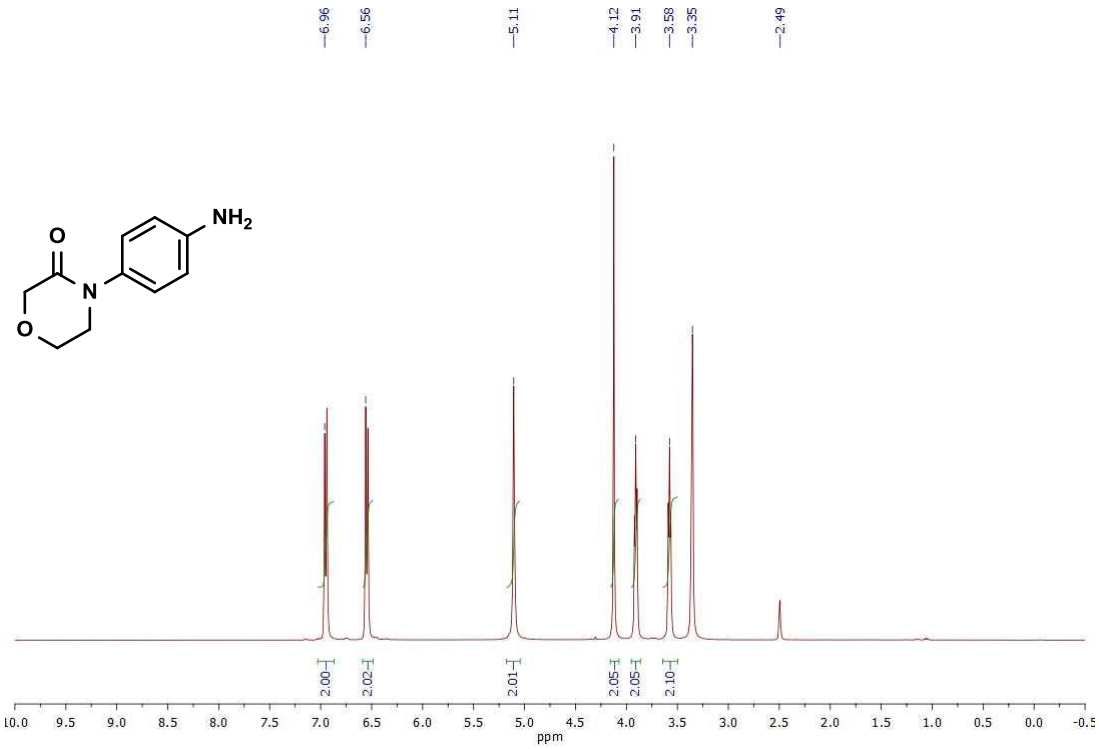


Figure S3. ^{1}H NMR (400 MHz, DMSO-d_6) of 4-(4-aminophenyl)morpholin-3-one (**7**).

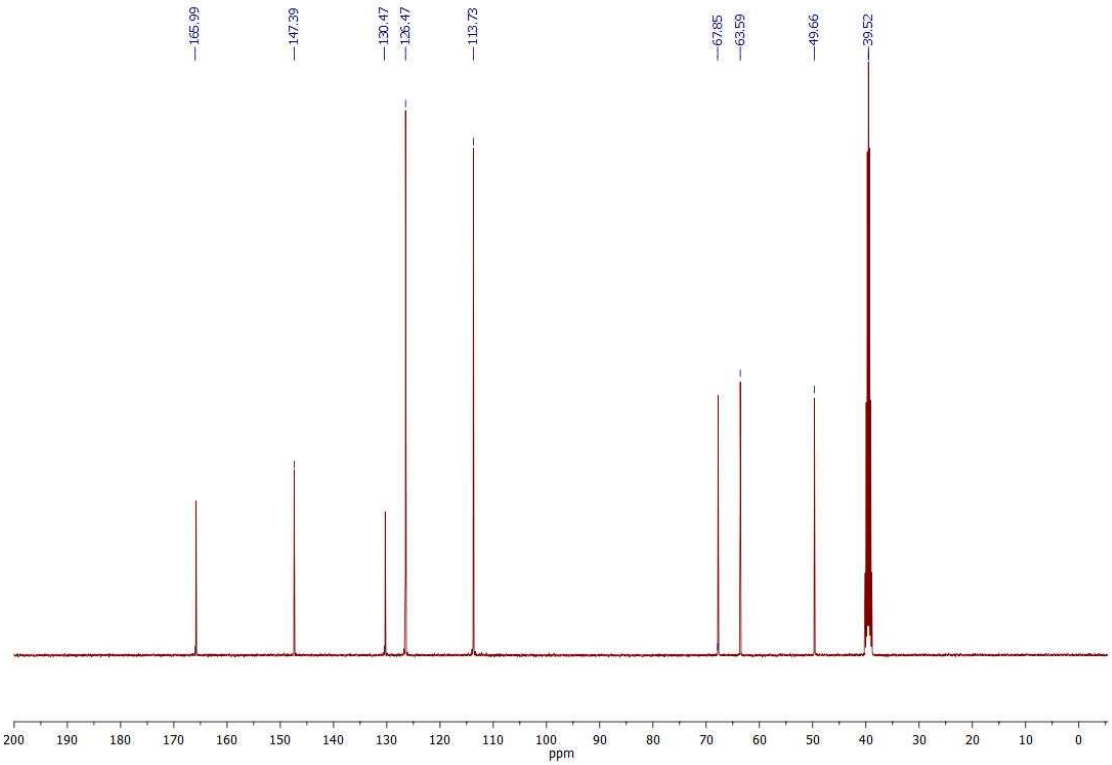


Figure S4. ^{13}C NMR (100 MHz, DMSO-d_6) of 4-(4-aminophenyl)morpholin-3-one (**7**).

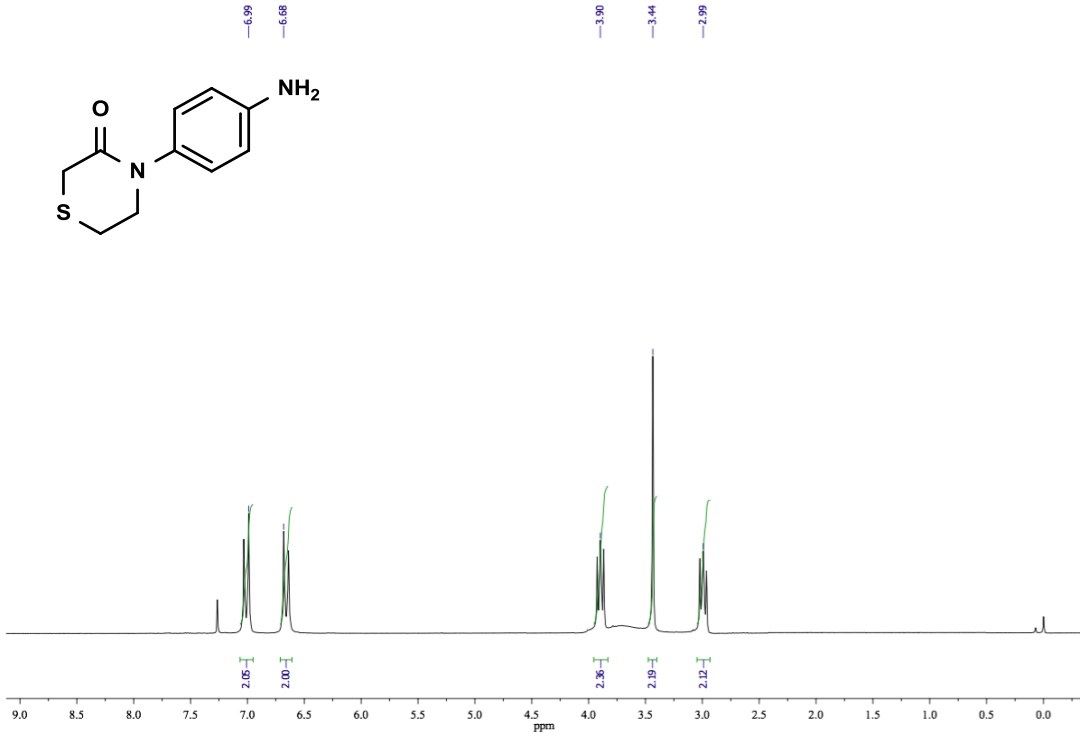


Figure S5. ^{1}H NMR (400 MHz, $CDCl_3$) of 4-(4-aminophenyl)tiomorpholin-3-one (**8**).

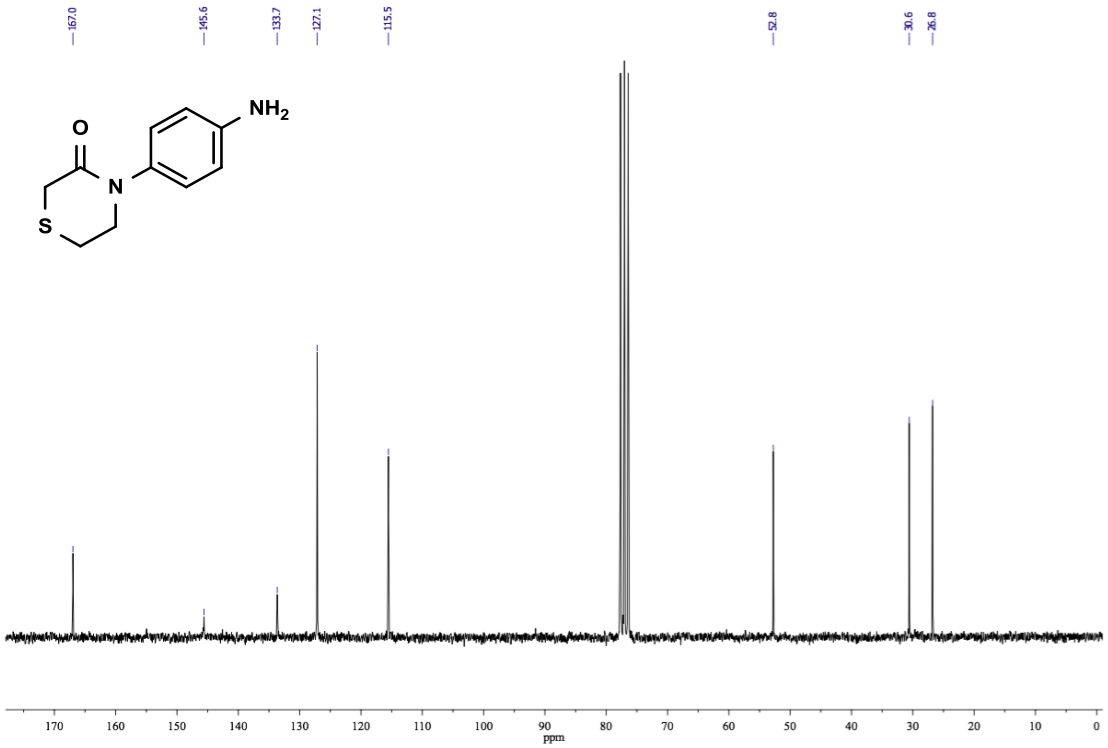


Figure S6. ^{13}C NMR (100 MHz, $CDCl_3$) of 4-(4-aminophenyl)tiomorpholin-3-one (**8**).

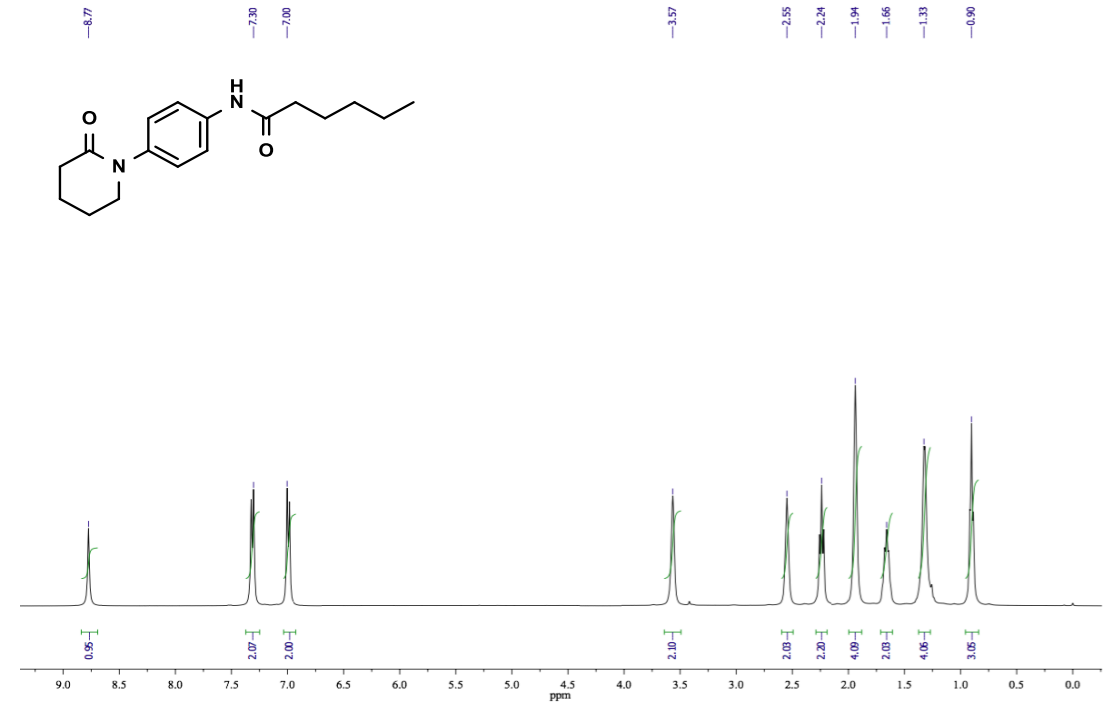


Figure S7. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(2-oxopiperidin-1-yl)phenyl)hexanamide (**9a**).

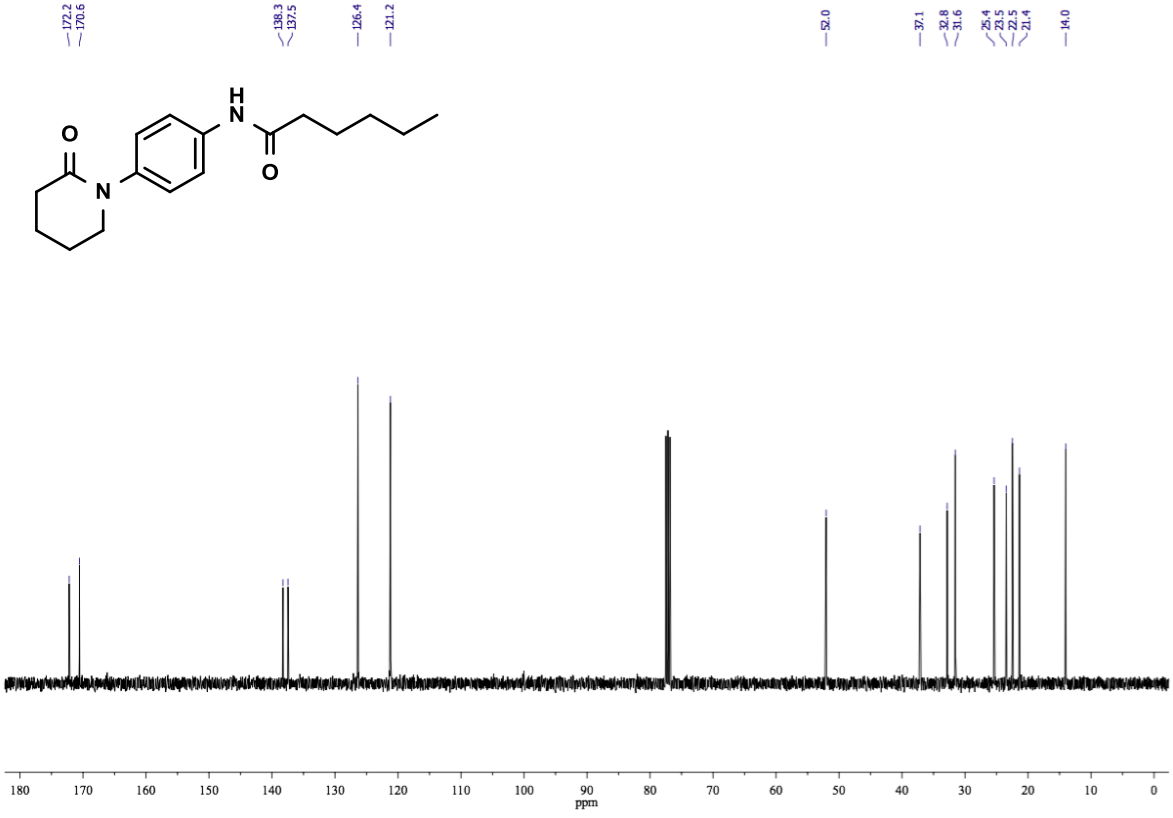


Figure S8. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(2-oxopiperidin-1-yl)phenyl)hexanamide (**9a**).

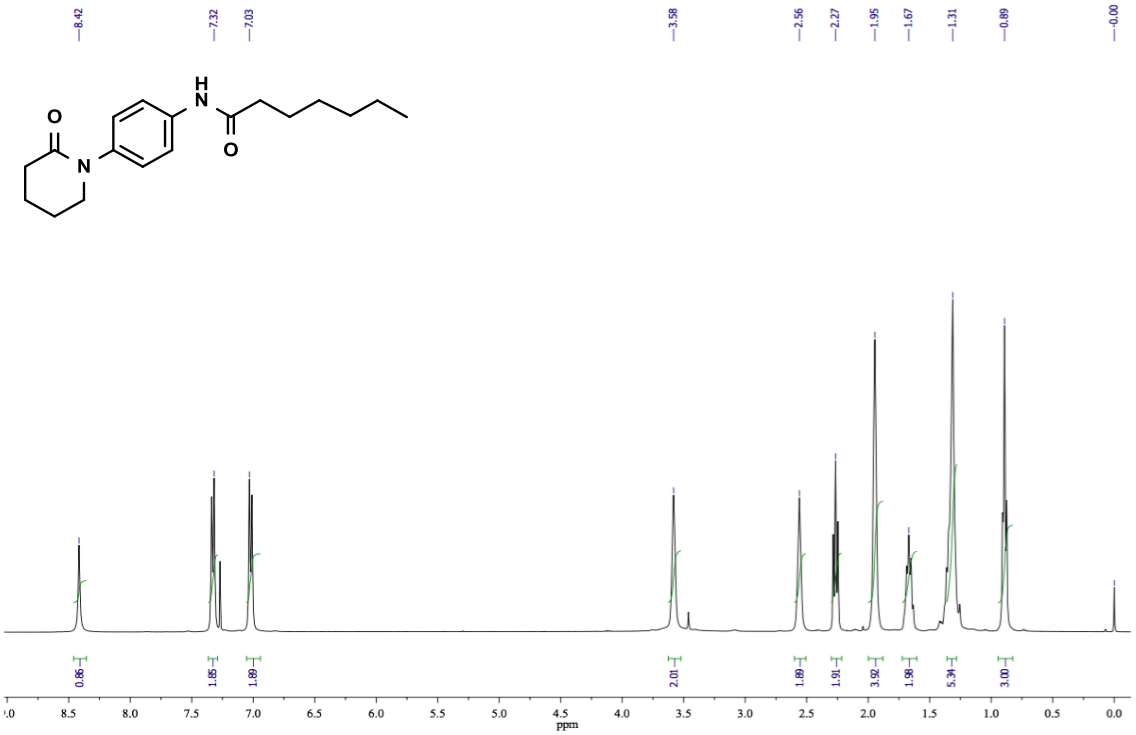


Figure S9. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(2-oxopiperidin-1-yl)phenyl)heptanamide (**9b**).

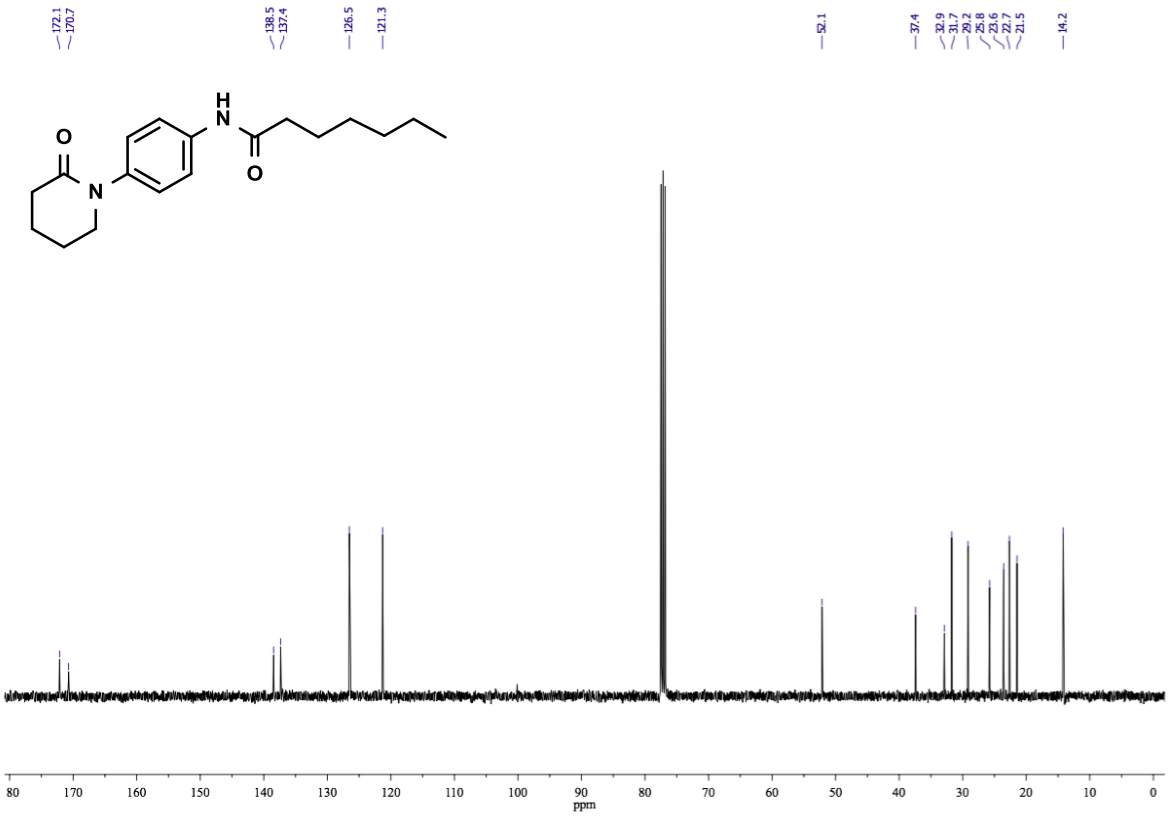


Figure S10. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(2-oxopiperidin-1-yl)phenyl)heptanamide (**9b**).

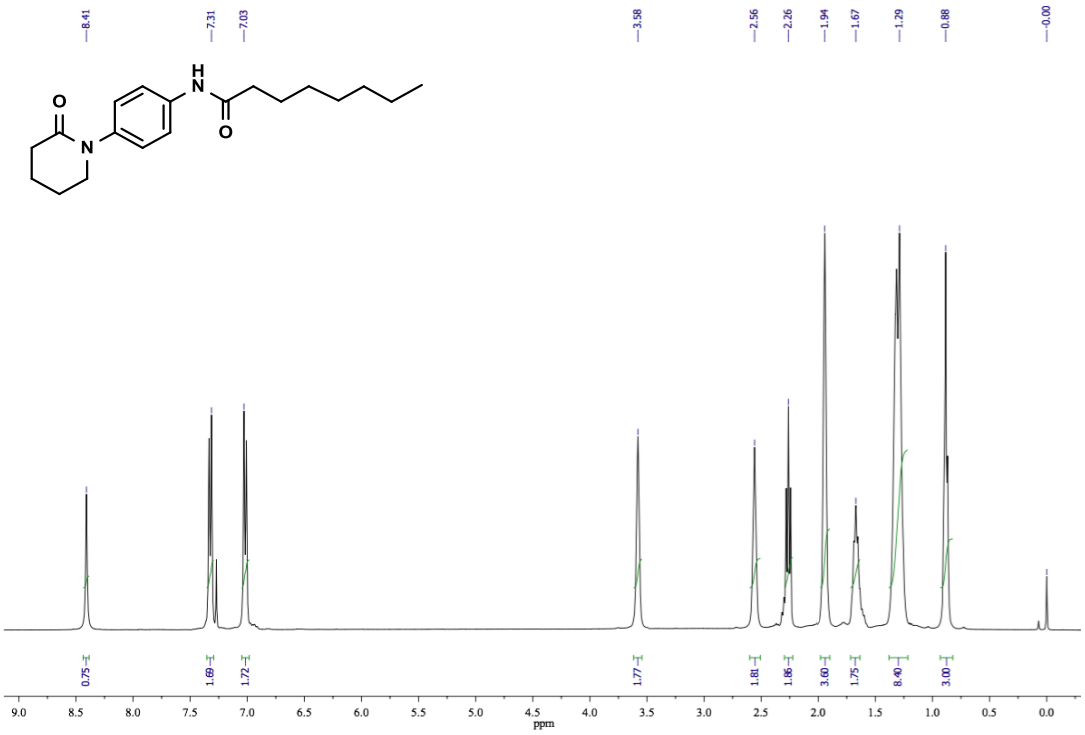


Figure S11. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(2-oxopiperidin-1-yl)phenyl)octanamide (**9c**).

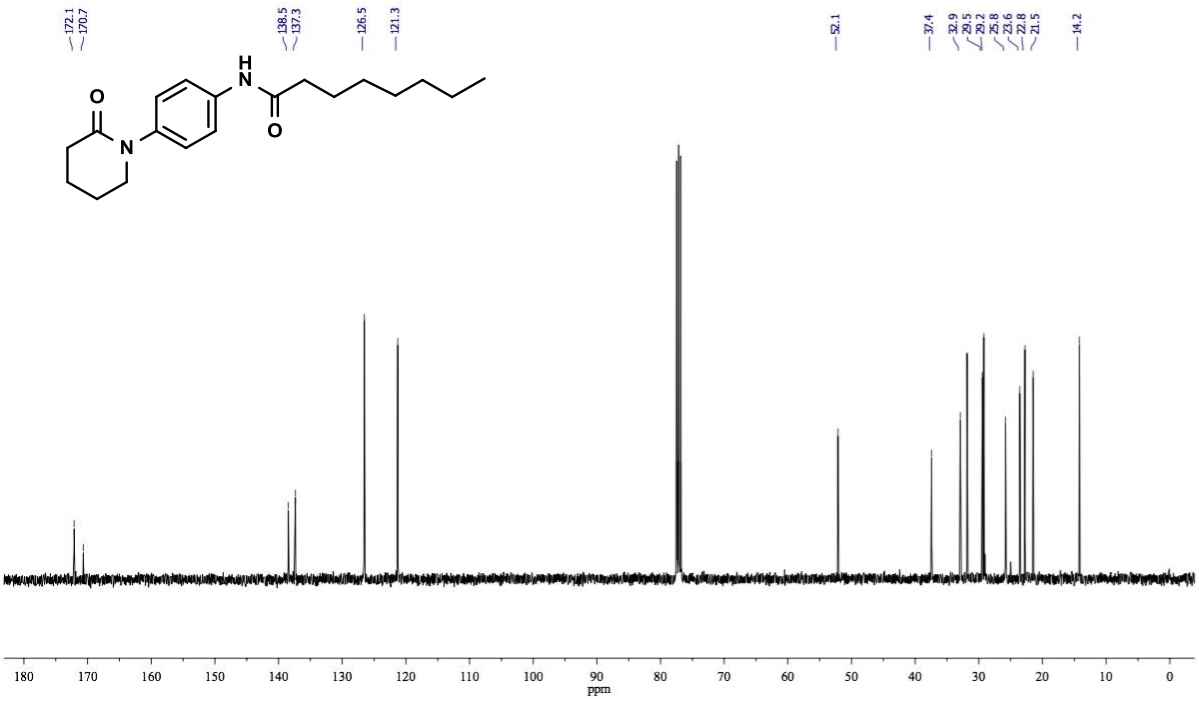


Figure S12. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(2-oxopiperidin-1-yl)phenyl)octanamide (**9c**).

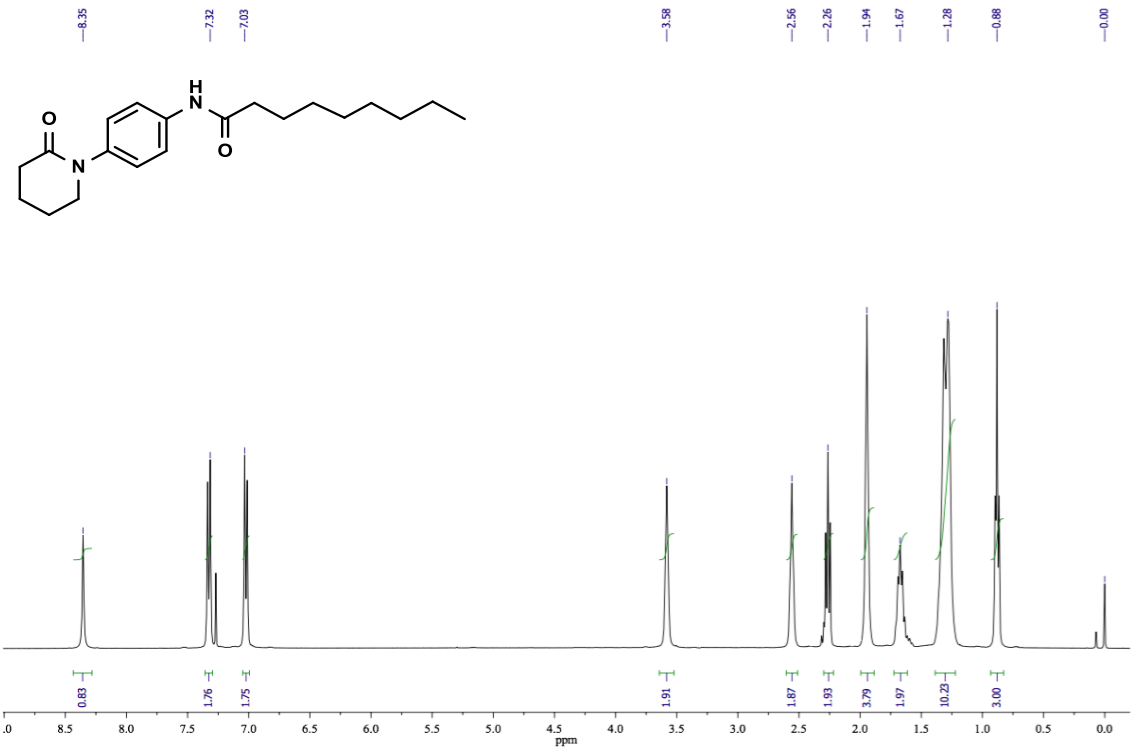


Figure S13. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(2-oxopiperidin-1-yl)phenyl)nonanamide (**9d**).

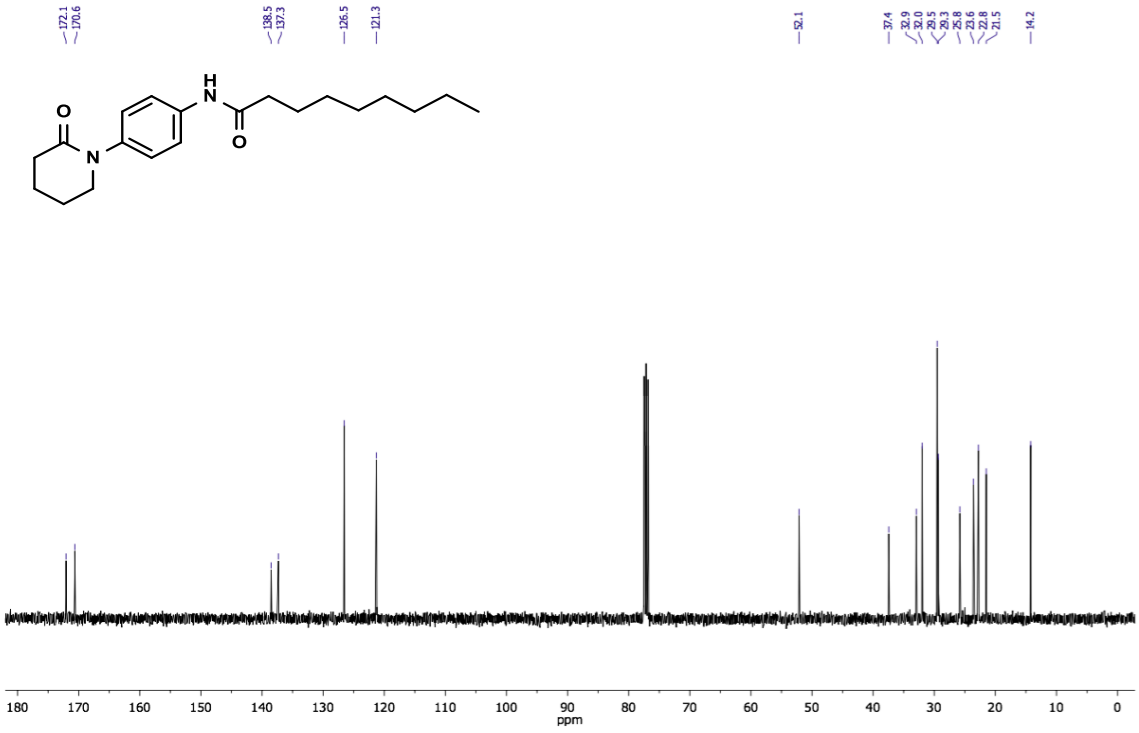


Figure S14. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(2-oxopiperidin-1-yl)phenyl)nonanamide (**9d**).

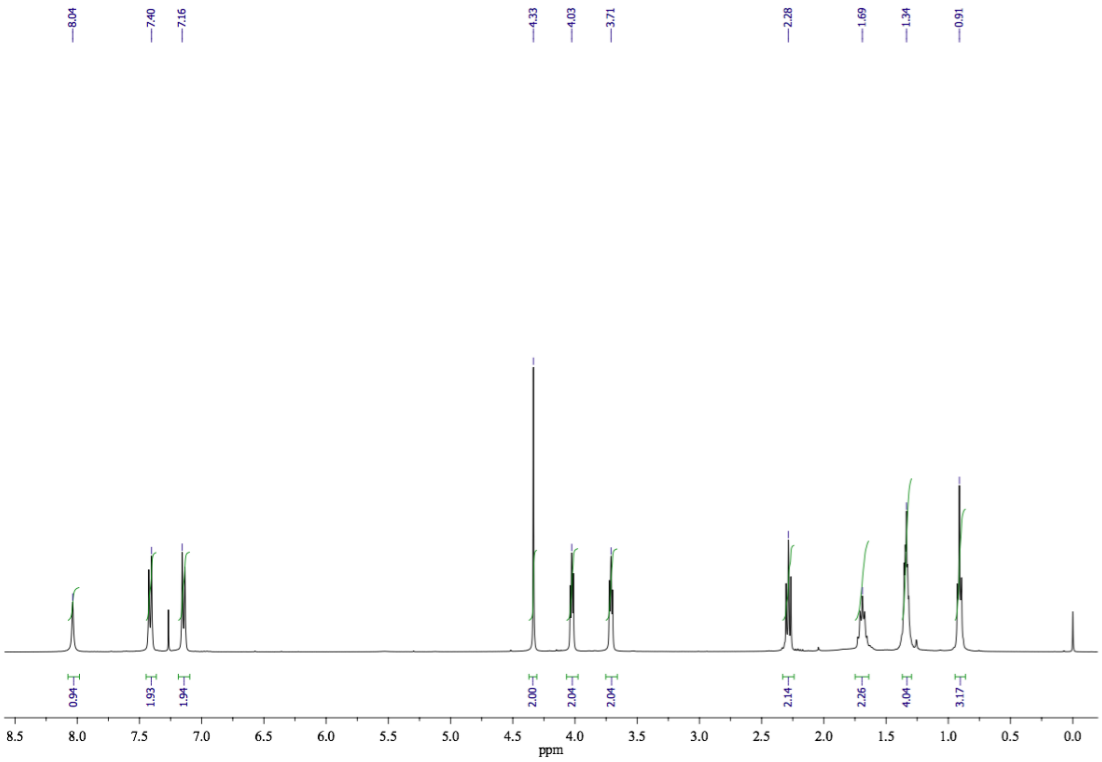


Figure S15. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxomorpholine)phenyl)hexanamide (**10a**).

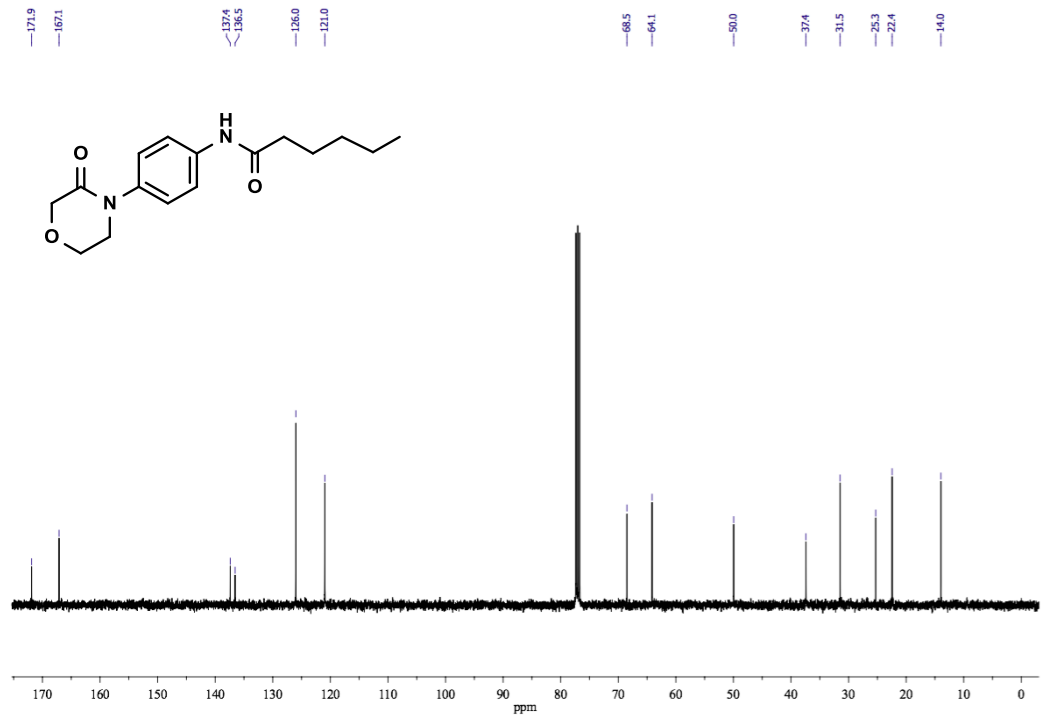


Figure S16. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(3-oxomorpholine)phenyl)hexanamide (**10a**).

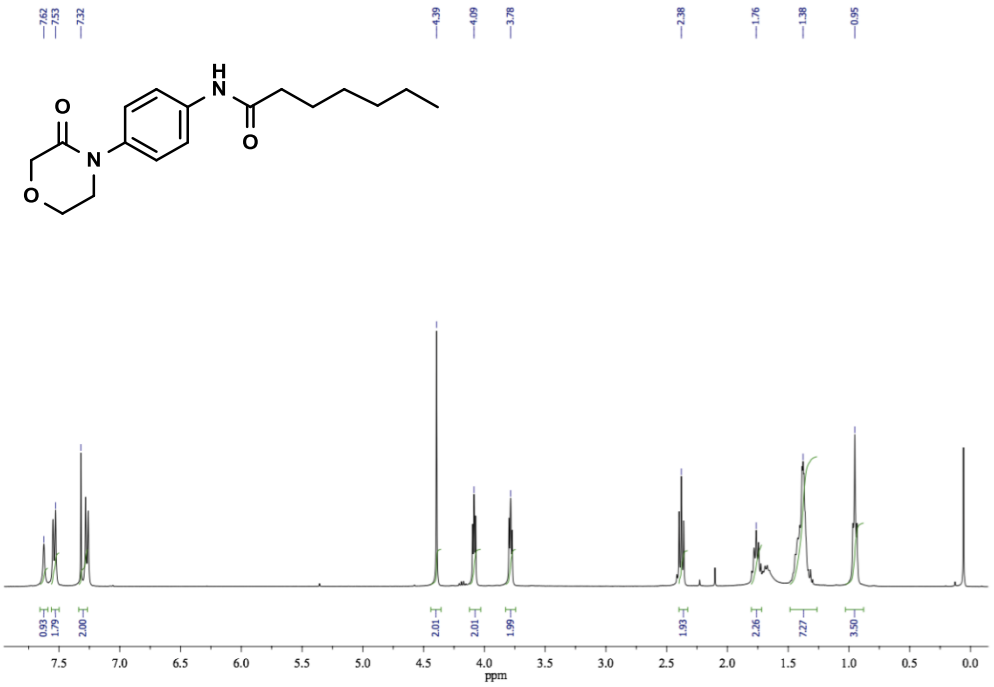


Figure S17. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxomorpholine)phenyl)heptanamide (**10b**).

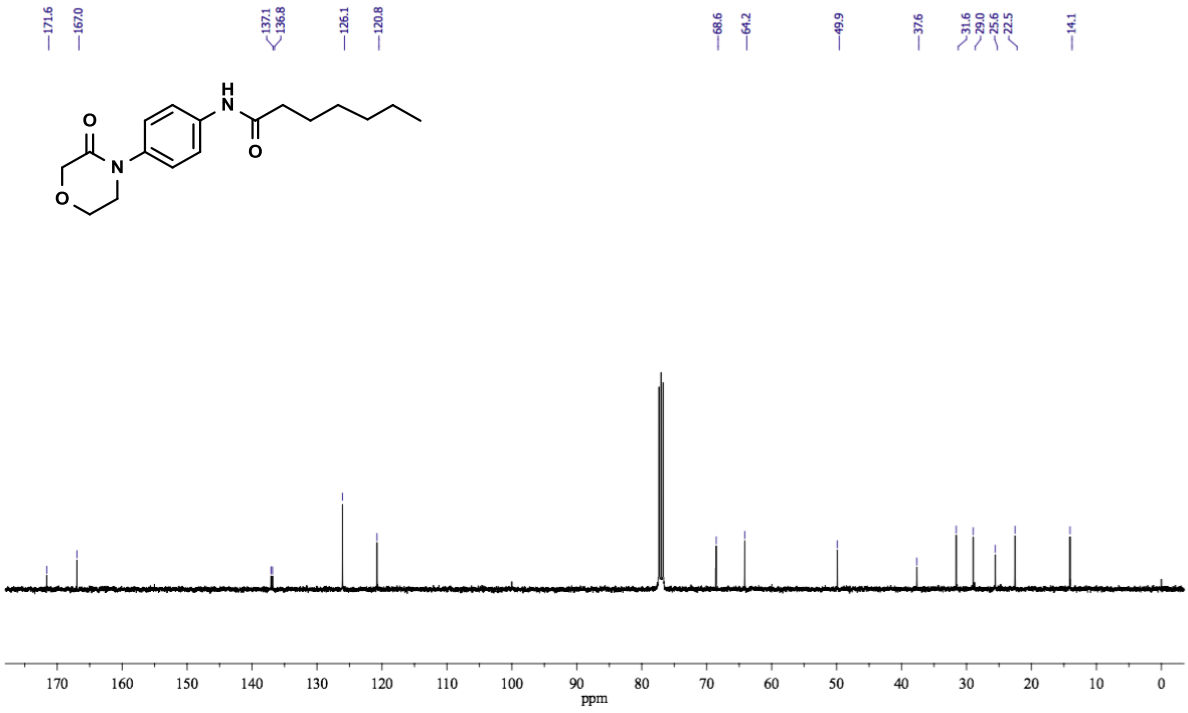


Figure S18. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(3-oxomorpholine)phenyl)heptanamide (**10b**).

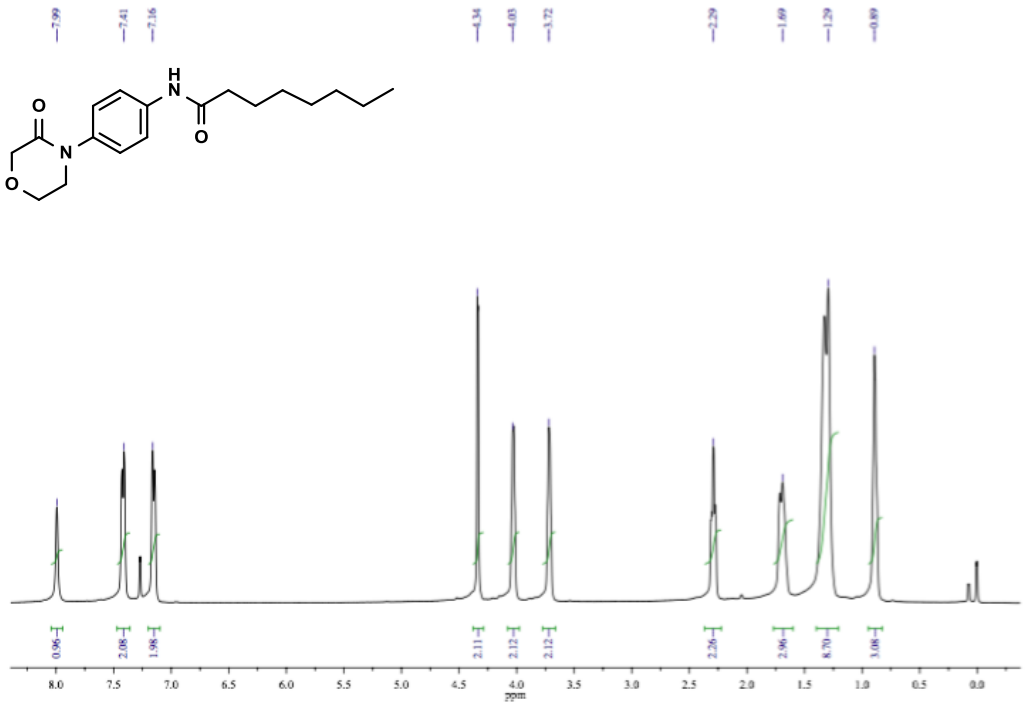


Figure S19. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxomorpholin)phenyl)octanamide (**10c**).

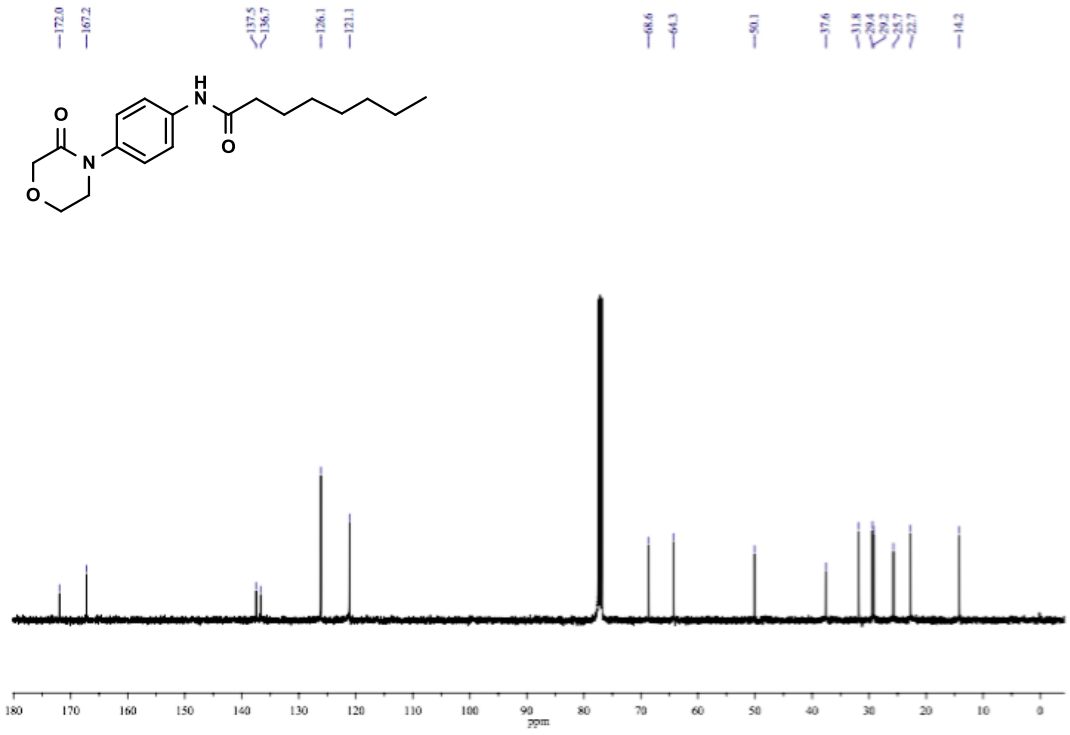


Figure S20. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(3-oxomorpholin)phenyl)octanamide (**10c**).

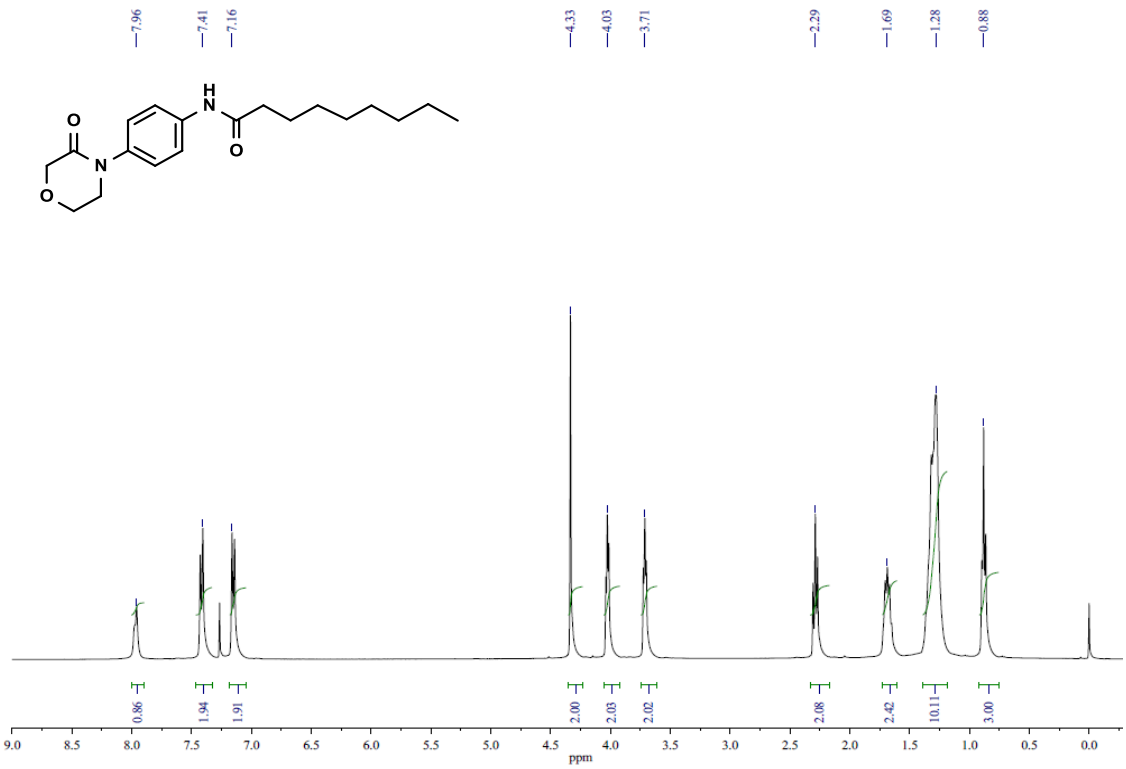


Figure S21. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxomorpholin)phenyl)nonanamide (**10d**).

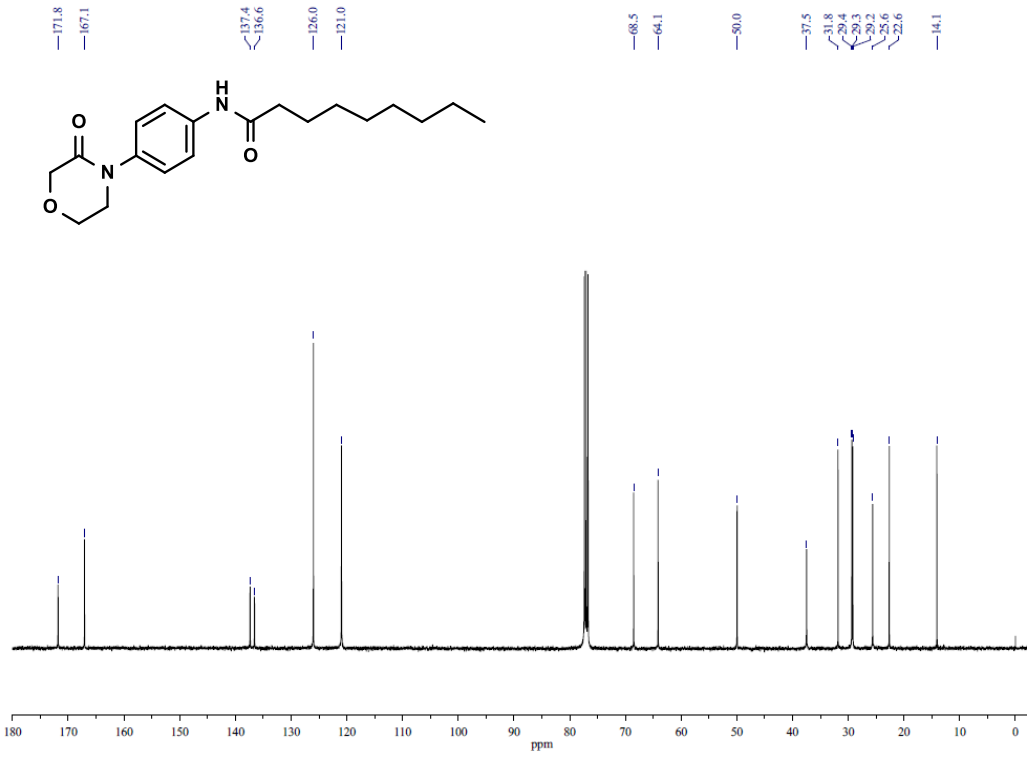


Figure S22. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(3-oxomorpholin)phenyl)nonanamide (**10d**).

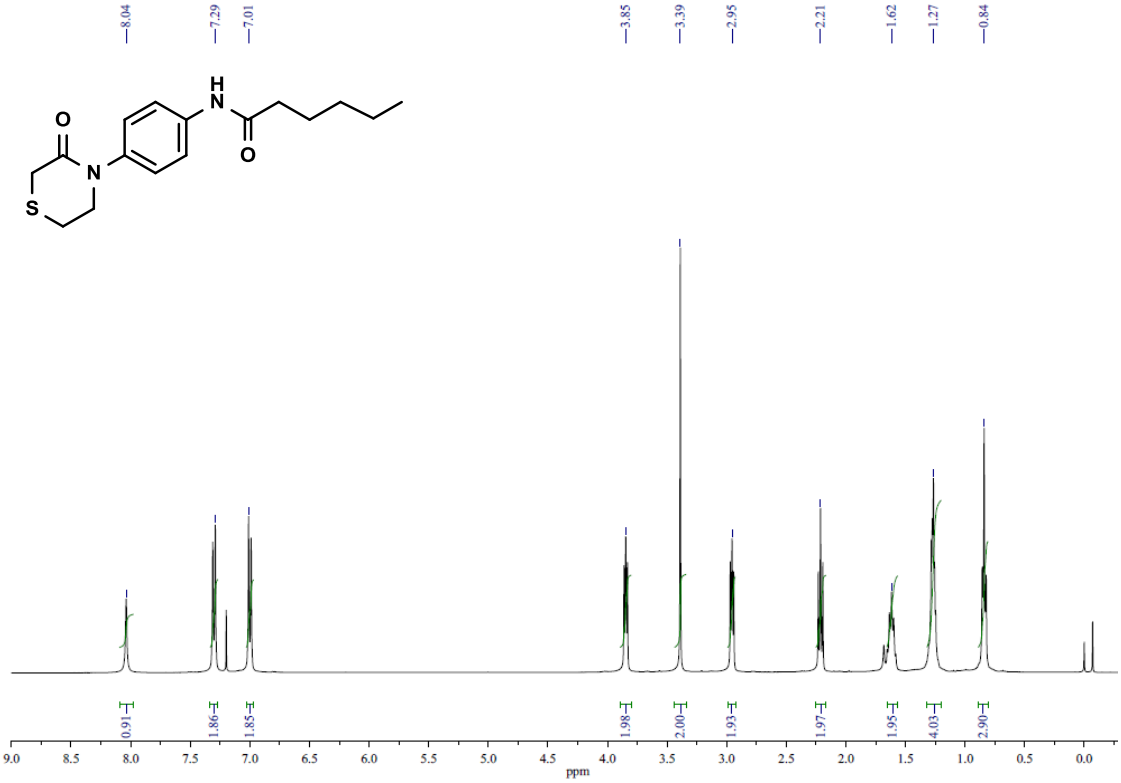


Figure S23. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxotiomorpholin)phenyl)hexanamide (**11a**).

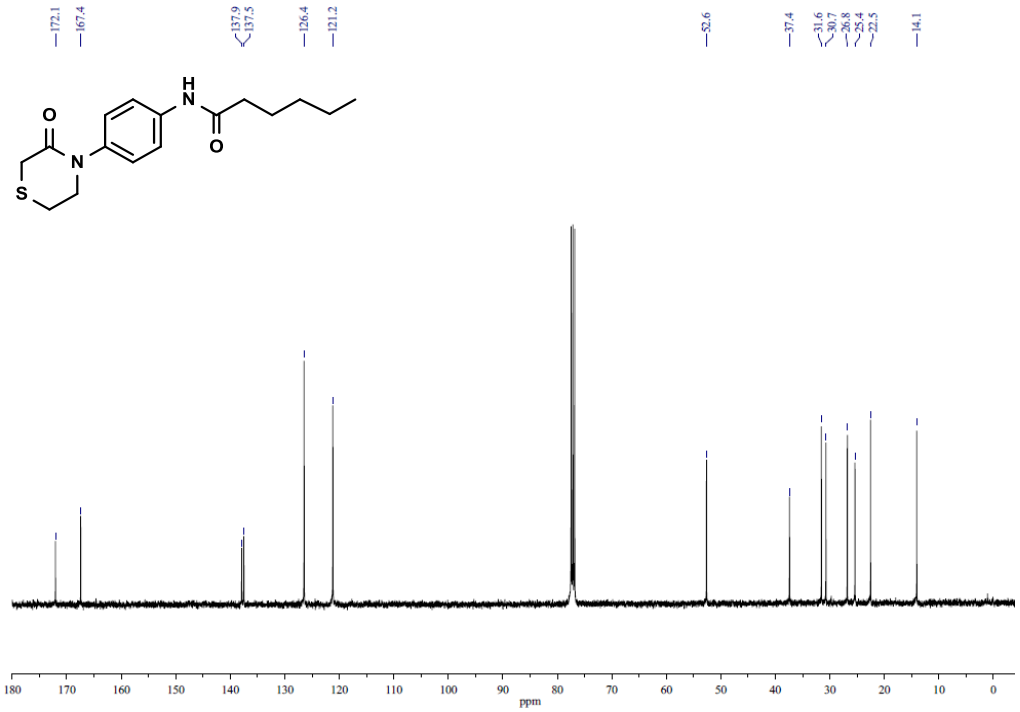


Figure S24. ^{13}C NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxotiomorpholin)phenyl)hexanamide (**11a**).

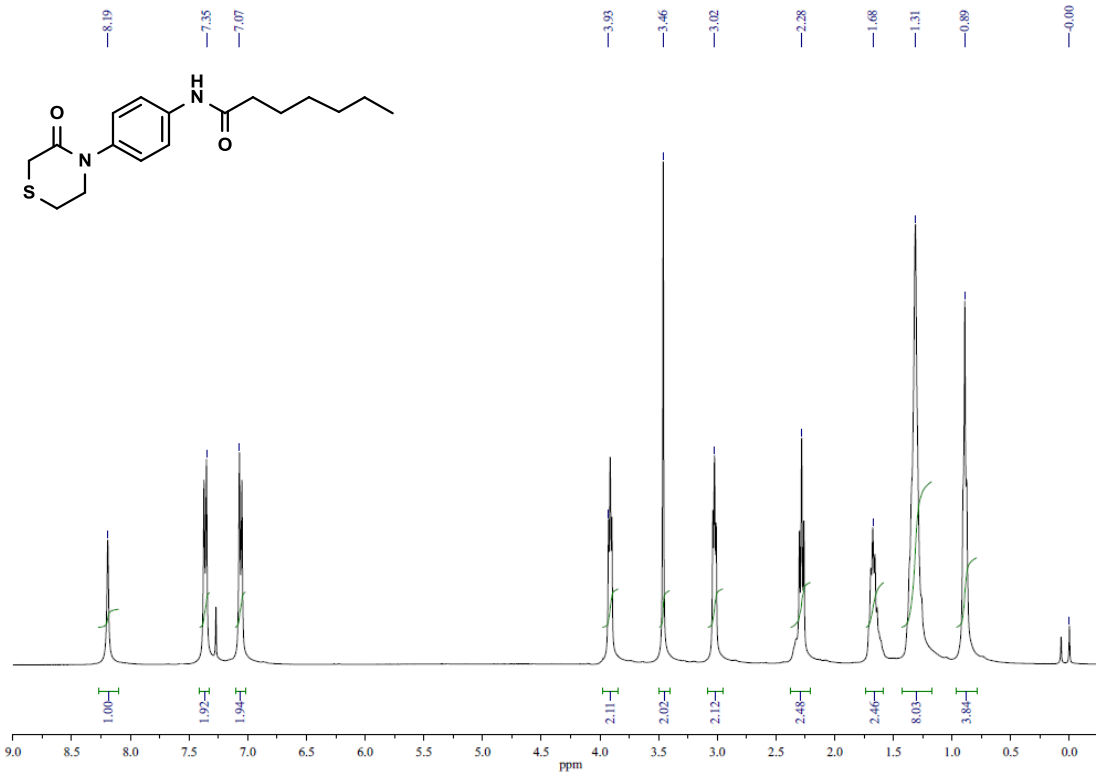


Figure S25. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxotiomorpholin)phenyl)heptanamide (**11b**).

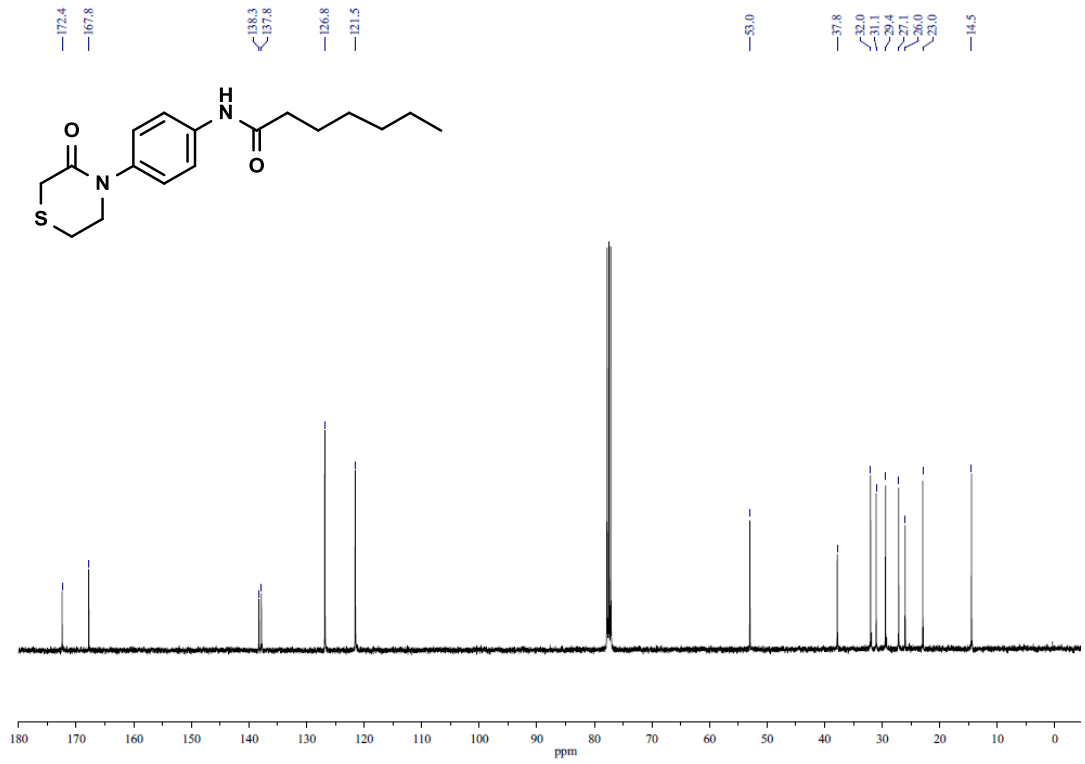


Figure S26. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(3-oxotiomorpholin)phenyl)heptanamide (**11b**).

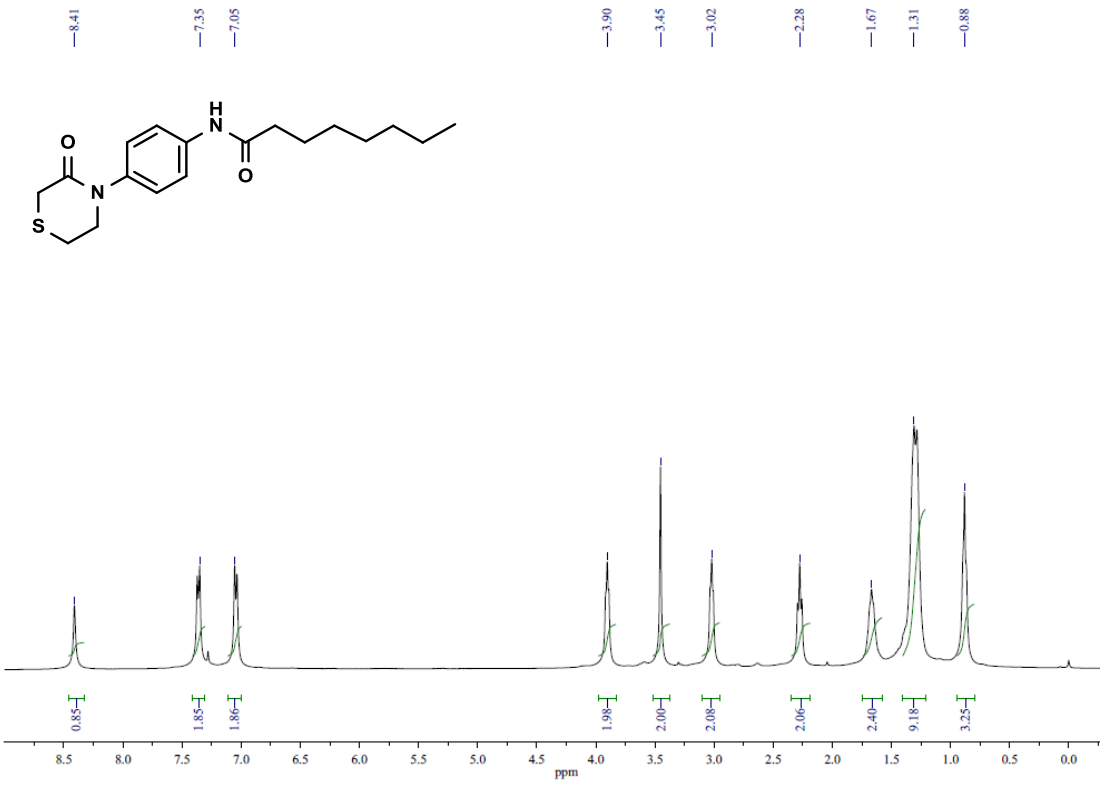


Figure S27. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxotiomorpholin)phenyl)octanamide (**11c**).

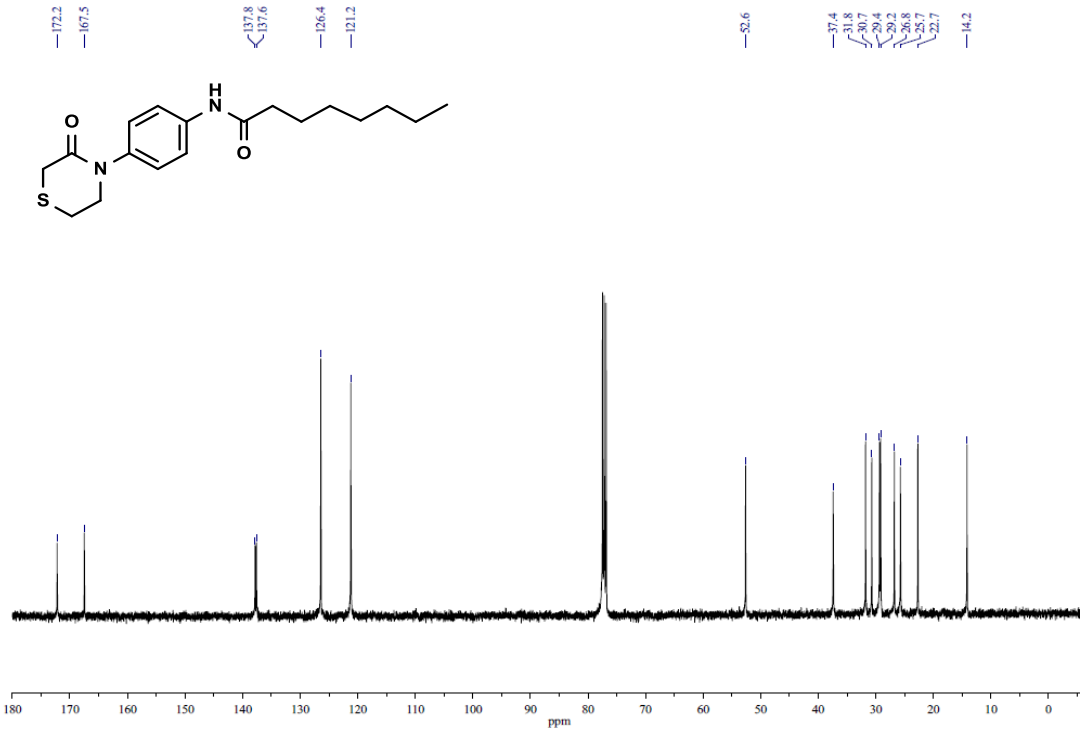


Figure S28. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(3-oxotiomorpholin)phenyl)octanamide (**11c**).

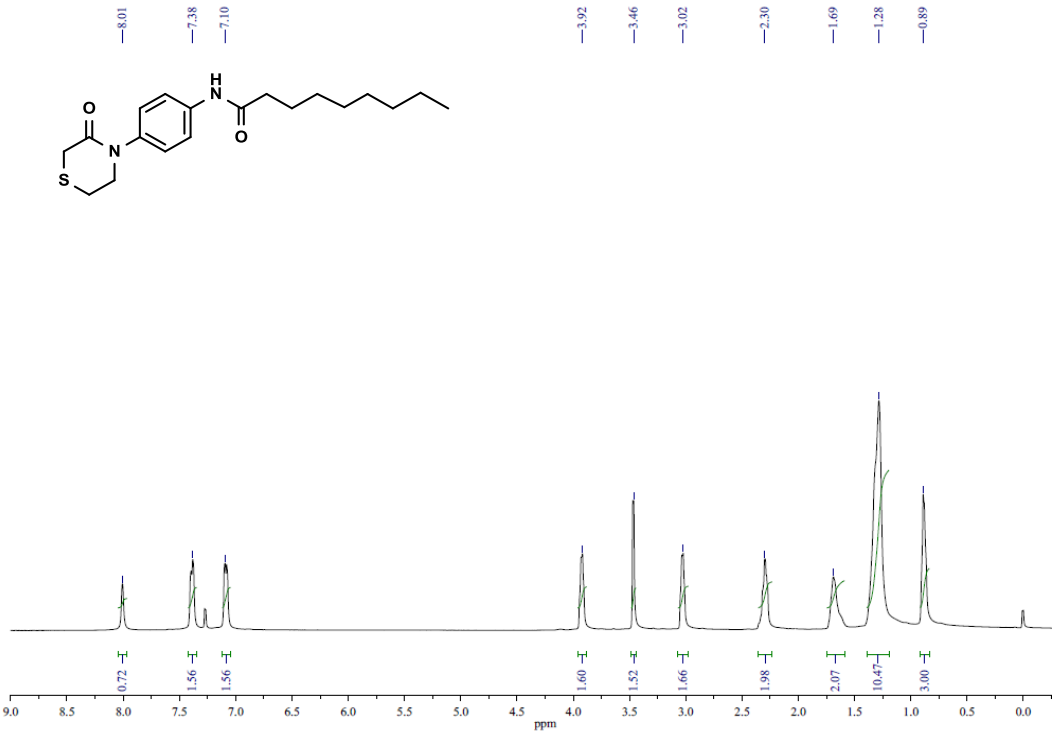


Figure S29. ^{1}H NMR (400 MHz, $CDCl_3$) of *N*-(4-(3-oxotiomorpholin)phenyl)nonanamide (**11d**).

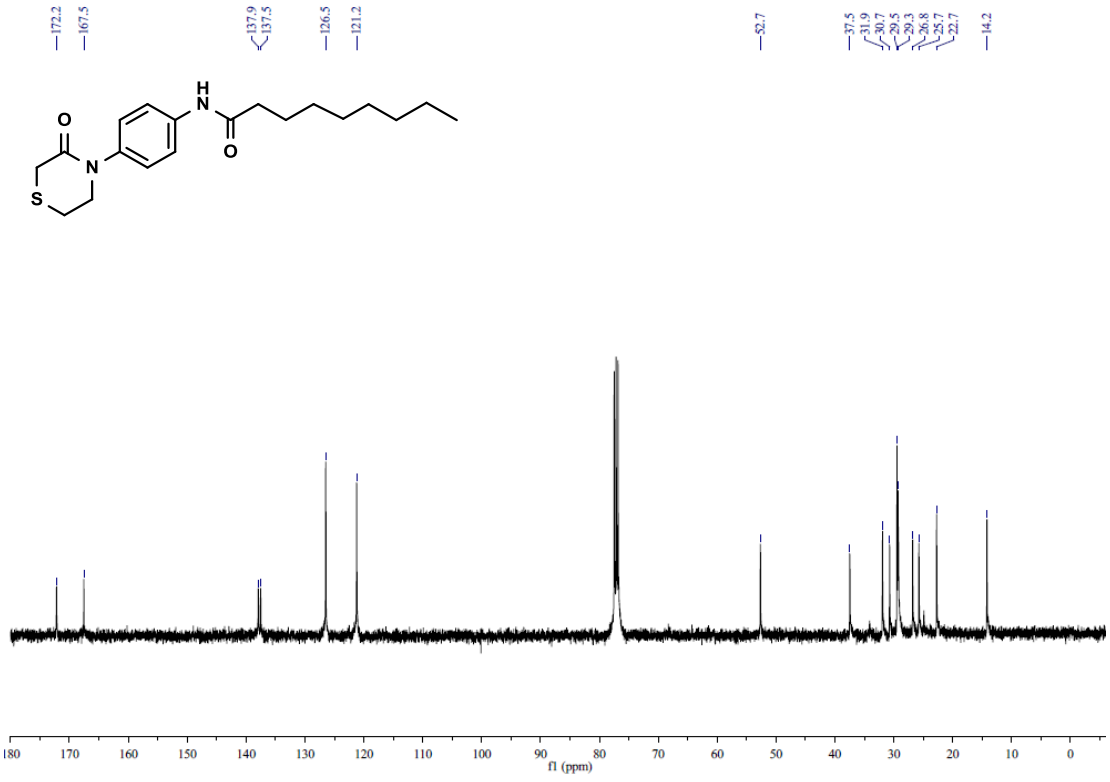


Figure S30. ^{13}C NMR (100 MHz, $CDCl_3$) of *N*-(4-(3-oxotiomorpholin)phenyl)nonanamide (**11d**).

Cell viability assay

HCT-116 (human colorectal carcinoma, ATCC number CCL-247), HeLa (human epithelial cervix carcinoma, ATCC number CCL-2) and HEK-293 (human embryonic kidney, ATCC number CRL-1573) cells were cultured in RPMI (revolutions *per* minute) 1640 medium, supplemented with 5% fetal bovine serum (FBS), in humidified air with 5% CO_2 at 37 °C. Cytotoxicity assays were performed using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium reduction assay. Ten thousand cells were seeded in 0.2 mL of culture medium using a flat-bottom 96-well plate. All synthesized compounds, Rivaroxaban (**1**) and Etoposide (positive control) were tested at least by triplicates at concentrations of 50 nM, 500 nM, 5 µM and 50 µM on HCT-116, HeLa and HEK-293 cell lines. MTT was added at a final concentration of 0.5 mg mL^{-1}, incubated for 4 h, and then solubilized with 10% sodium dodecyl sulfate 0.1 mM HCl and incubated overnight. Formazan production was measured at 570 nm in a multiwell reader.

Table S1. Cell viability assay data

Compound	HCT-116 IC_{50} / µM	r^2	HeLa IC_{50} / µM	r^2	HEK-293 IC_{50} / µM	r^2
1	> 50		> 50		> 50	
6	> 50		> 50		> 50	
7	> 50		> 50		> 50	
8	> 50		> 50		> 50	
9a	> 50		> 50		> 50	
9b	> 50		> 50		> 50	
9c	> 50		> 50		> 50	
9d	> 50		> 50		> 50	
10a	> 50		> 50		> 50	
10b	> 50		> 50		> 50	
10c	> 50		> 50		> 50	
10d	> 50		> 50		> 50	
11a	1.89 ± 0.30	0.83	> 50		> 50	
11b	> 50		> 50		> 50	
11c	> 50		> 50		> 50	
11d	> 50		> 50		> 50	
Etoposide	2.80 ± 0.40	0.93	5.40 ± 0.50	0.96	0.60 ± 0.09	0.97

FXa activity assay

The enzymatic kit was prepared according to manufacturer's instructions (ANASPEC, Sensolyte® 520 Factor Xa Assay Kit Fluorometric). 10 mL of buffer 2X was diluted in 10 mL of Milli-Q water obtaining buffer 1X. Then the factor Xa substrate was diluted 1:100 with the prepared buffer 1X. The factor Xa was diluted 1:200 with the prepared buffer 1X. Finally the inhibition control 1 mM was diluted 1:10 with the prepared buffer 1X obtaining the 0.1 mM

inhibition control. The 96-well plate for fluorescence was prepared with 40 µL of enzyme and 1 µL of each compound. To initiate the enzymatic reaction 50 µL of the factor Xa substrate was added to each well and then the plate was read with a fluorescence microplate reader FLx800 BioTek programmed to read continuously for 30 minutes at 37 °C, at a wavelength of Ex / Em 490 nm / 520 nm. All inhibition assays were performed at least by triplicates. The data obtained was analyzed with GraphPad Prism 6.0.

Table S2. FXa activity assay data

Compound	Concentration / (mol L^{-1})	FXa activity / %
1	1.00×10^{-7}	5
6	1.00×10^{-8}	75
7	1.00×10^{-9}	93
8	1.00×10^{-10}	80
9a	1.00×10^{-8}	80
9b	1.00×10^{-8}	80
9c	1.00×10^{-10}	84
9d	1.00×10^{-7}	77
10a	1.00×10^{-8}	96
10b	1.00×10^{-9}	96
10c	1.00×10^{-7}	89
10d	1.00×10^{-8}	94
11a	1.00×10^{-10}	84
11b	1.00×10^{-8}	84
11c	1.00×10^{-8}	85
11d	1.00×10^{-10}	87

log P of synthesized compounds

Table S3. Calculated log P of synthesized compounds

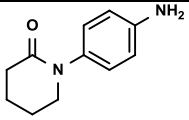
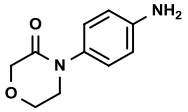
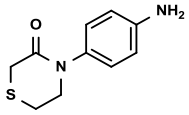
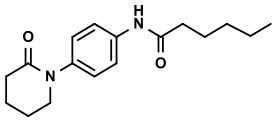
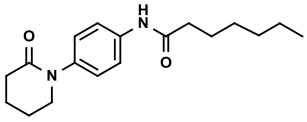
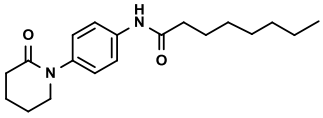
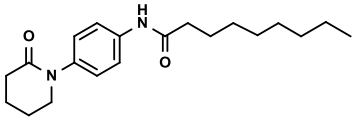
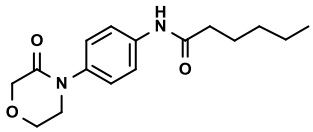
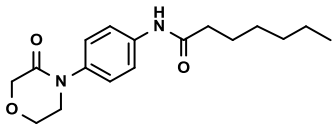
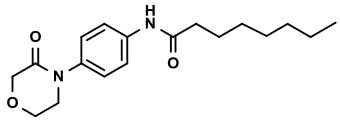
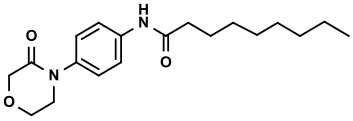
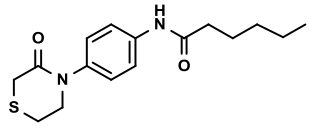
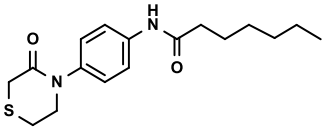
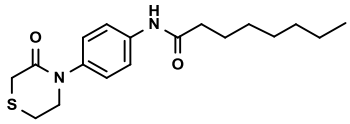
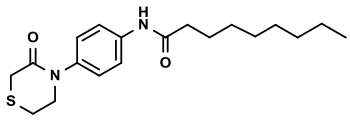
Compound	Chemical structure	log P[a]
6		0.92
7		–0.10
8		0.43

Table S3. Calculated log P of synthesized compounds (cont.)

Compound	Chemical structure	log P[a]
9a		3.02
9b		3.46
9c		3.91
9d		4.35
10a		2.00
10b		2.45
10c		2.89
10d		3.34
11a		2.53
11b		2.97
11c		3.42
11d		3.86

[a]log P of synthesized compounds were calculated using ChemAxon log P predictor.