Supporting information

Investigation around the oxadiazole core in the discovery of a new chemotype of potent and selective FXR antagonists

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EXPERIMENTAL SECTION

General Experimental Information. NMR spectra were performed on Varian Inova 400 and 500 NMR spectrometers (400 and 500 MHz for ^{1}H, 100 and 125 MHz for ^{13}C, respectively) equipped with a SUN hardware and recorded in CD_3OD (δ_H = 3.31 and δ_C = 49.0 ppm). Chemical shifts (δ) are reported in ppm and referred to CHD_2OD as internal standard; coupling constants *J* are in Hertz (Hz). Spin multiplicities are given as s (singlet), br s (broad singlet), d (doublet), t (triplet) or m (multiplet). High-resolution ESI-MS spectra were recorded with a Micromass Q-TOF mass spectrometer.

The reactions were monitored on TLC (Alugram® silica gel, G/UV254 plates, Macherey-Nagel Company). Flash chromatography was performed on silica gel (200-400 mesh, Macherey-Nagel Company). All chemicals (solvents and reagents) were purchased from Sigma- Aldrich, TCI and Fluorochem. All reactions were carried out using flame-dried glassware and under Ar atmosphere. HPLC analysis was performed using a Waters Model 510 pump equipped with Waters Rheodine injector and a differential refractometer, model 401. The purity of tested compounds (>95%) was determined by HPLC analysis using the solvent condition reported in the section corresponding to each individual compound.

General synthetic procedures for amidoxime 2a-f

To a solution of nitriles **1a-f** (1 eq.) in dry methanol, potassium carbonate (1.5 mol eq.) and hydroxylamine hydrochloride (2.5 mol eq.) were added, and the mixture was stirred at reflux for 2 h, under a nitrogen atmosphere. The resulting solution was then concentrated under vacuum, diluted with water and extracted with CH_2Cl_2. The organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give amidoximes **2a-f** (100-90% yield), that were subjected to next step without any purification.

General synthetic procedures for compounds 3a-f, 13 and 23

N,*N*-diisopropylethylamine (DIPEA) (1.8 mol eq.) was added to a solution of amidoximes **2a-f** (1 mol eq.) and *N*-Boc-isonipecotic acid (1.2 mol eq.) and then dissolved in DMF dry. HBTU (1.5 mol eq.), as coupling agent, was then added to the mixture at room temperature. The mixture was stirred vigorously at 80°C for 12 hours, then partitioned between water and EtOAc. The organic layer was collected and washed twice with a saturated LiBr solution, then with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulted residue was purified on silica column using CH_2Cl_2 100%, to give an intermediate that was subjected to a deprotection with CH_2Cl_2:TFA 1:1 (1 mL) for 2 h. Then was evaporated under vacuum to give oxadiazole derivatives **3a-f** (60-80% yield).

The same synthetic procedure was applied in preparing compounds **13** and **23**, starting from amidoxime **2e** and using *N*-Boc-L-pipecolic acid and *N*-Boc-L-proline, respectively.

3-phenyl-5-(piperidin-4-yl)-1,2,4-oxadiazole (**3a**). An analytic sample of **3a** was further purified by HPLC on a Luna Omega Polar C18 (5μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (55:45) as eluent (flow rate 1 mL/min, t_R = 13.8 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.06 (2H, d, *J* = 7.6 Hz), 7.54 (2H, ovl), 7.52 (1H, ovl), 3.53 (1H, ovl), 3.52 (2H, ovl), 3.23 (2H, m), 2.43 (2H, d, *J* = 14.6 Hz), 2.15 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.6, 169.6, 132.6, 130.0 (2C), 128.3 (2C), 127.3, 44.0 (2C), 32.9, 27.1 (2C); HR ESIMS *m/z* 230.1297$[M + H]^+$, $C_{13}H_{16}N_3O$ requires 230.1293.

5-(piperidin-4-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (**3b**). An analytic sample of **3b** was further purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (48:52) as eluent (flow rate 1 mL/min, t_R = 10.5 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.27 (2H, d, *J* = 8.1 Hz), 7.85 (2H, d, *J* = 8.1 Hz), 3.52 (3H, m), 3.23 (2H, m), 2.44 (2H, dd, *J* = 14.5, 2.7 Hz), 2.16 (2H, m); ^{13}C NMR (125 MHz, CD_3OD): δ_C 182.2, 168.5, 133.9, 132.1, 129.0 (2C), 127.1 (2C), 124.2, 43.9 (2C), 32.8, 27.1 (2C); HR ESIMS *m/z* 299.1171 $[M + H]^+$, $C_{14}H_{15}N_3OF_3$ requires 299.1167.

3-benzyl-5-(piperidin-4-yl)-1,2,4-oxadiazole (**3c**). An analytic sample of **3c** was further purified by HPLC on a Luna Omega Polar C18 (5μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (40:60) as eluent (flow rate 1 mL/min, t_R = 10.0 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.30 (5H, ovl), 4.07 (2H, s), 3.43 (3H, ovl), 3.16 (2H, m), 2.31 (2H, dd, *J* = 14.5, 3.0 Hz), 2.01 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.6, 170.8, 137.0, 130.0, 129.6 (2C), 128.0 (2C), 43.9 (2C), 32.8 (2C), 27.0 (2C); HR ESIMS *m/z* 244.1453 $[M + H]^+$, $C_{14}H_{18}N_3O$ requires 244.1450.

5-(piperidin-4-yl)-3-(4-(trifluoromethyl)benzyl)-1,2,4-oxadiazole (**3d**). An analytic sample of **3d** was further purified by HPLC on a Luna Omega Polar C18 (5 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (55:45) as eluent (flow rate 1 mL/min, t_R = 8.1 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.63 (2H, d, *J* = 8.1 Hz), 7.50 (2H, *J* = 8.1 Hz), 4.18 (2H,s), 3.40 (3H, m), 3.11 (2H, m), 2.30 (2H, m), 2.01 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.6, 170.1, 141.6, 130.7 (2C), 130.4, 126.3 (2C), 124.2, 44.0 (2C), 32.8, 32.6, 27.3 (2C); HR ESIMS *m/z* 312.1327 $[M + H]^+$, $C_{15}H_{17}N_3OF_3$ requires 312.1324.

3-(biphenyl-4-yl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (**3e**). An analytic sample of **3e** was further purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (55:45) as eluent (flow rate 1 mL/min, t_R = 8.8 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.14 (2H, d, *J* = 8.4 Hz); 7.79 (2H, d, *J* = 8.4 Hz); 7.69 (2H, d, *J* = 7.5 Hz); 7.49 (2H, t, *J* = 7.5 Hz); 7.39 (1H, t, *J* = 7.5 Hz); 3.54 (3H, m); 3.24 (2H, m); 2.44 (2H, m); 2.16 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.1, 168.5, 145.5, 141.3, 130.0 (2C), 129.1, 128.9 (2C), 128.6 (2C), 128.0 (2C), 126.7, 44.0 (2C), 32.9, 27.1 (2C); HR ESIMS *m/z* 306.1610 $[M + H]^+$, $C_{19}H_{20}N_3O$ requires 306.1606.

3-(naphthalen-2-yl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (**3f**). An analytic sample of **3f** was further purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (55:45) as eluent (flow rate 1 mL/min, t_R = 8.6 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.62 (1H, s), 8.11 (1H, d, *J* = 8.6 Hz), 8.00 (1H, d, *J* = 8.6 Hz), 7.99 (1H, ovl), 7.94 (1H, d, *J* = 7.2 Hz), 7.60 (1H, ovl), 7.59 (1H, ovl), 3.54 (3H, m), 3.26 (2H, m), 2.44 (2H, dd, *J* =14.5, 2.8 Hz), 2.19 (2H, m); ^{13}C NMR (100

MHz, CD_3OD): δ_C 181.7, 169.4, 136.1, 134.0, 129.9, 129.8, 128.9 (2C), 128.8 (2C), 128.1, 125.3,124.6, 44.0 (2C), 32.9, 27.1 (2C); HR ESIMS *m/z* 280.1453 $[M + H]^+$, $C_{17}H_{18}N_3O$ requires 280.1450.

(S)-3-(naphthalen-2-yl)-5-(piperidin-2-yl)-1,2,4-oxadiazole (**13**). An analytic sample of **13** was further purified by HPLC on a Luna Omega Polar C18 (5μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (50:50) as eluent (flow rate 1 mL/min, t_R = 14.0 min); ^1H NMR (400 MHz, CD_3OD): δ_H 8.67 (1H, s), 8.14 (1H, d, *J* = 8.5 Hz), 8.02 (1H, d, *J* = 8.7 Hz), 7.98 (1H, ovl), 7.95 (1H, d, *J* = 7.4 Hz), 7.62 (1H, ovl), 7.60 (1H, ovl), 4.90 (1H, ovl), 3.60 (1H, br d, *J* = 12.0 Hz), 3.25 (1H, m), 2.51 (1H, m), 2.03 (3H, m), 1.81 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 175.9, 169.2, 135.9, 134.1, 129.8, 129.6, 129.2, 128.8 (2C), 127.9, 124.3, 124.2, 52.9, 45.7, 28.1, 22.5, 22.0; HR ESIMS *m/z* 280.1455 $[M + H]^+$, $C_{17}H_{18}N_3O$ requires 280.1450.

(S)-3-(naphthalen-2-yl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole (**23**). An analytic sample of **23** was further purified by HPLC on a Luna Omega Polar C18 (5μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (50:50) as eluent (flow rate 1 mL/min, t_R = 11.0 min); ^1H NMR (400 MHz, CD_3OD): δ_H 8.65 (1H, s), 8.12 (1H, d, *J* = 8.5 Hz), 8.02 (1H, d, *J* = 8.6 Hz), 7.99 (1H, ovl), 7.95 (1H, d, *J* = 7.1 Hz), 7.61 (1H, ovl), 7.60 (1H, ovl), 5.19 (1H, t, *J* = 7.6 Hz), 3.59 (1H, m), 3.58 (1H, m), 2.69 (2H, m), 2.29 (2H, m); ^{13}C NMR (125 MHz, CD_3OD): δ_C 176.3, 168.8, 136.3, 134.3, 130.1, 129.8, 129.2, 129.0 (2C), 128.1, 124.4, 124.3, 55.6, 47.3, 30.3, 24.6; HR ESIMS *m/z* 266.1293$[M + H]^+$, $C_{16}H_{16}N_3O$ requires 266.1293.

General synthetic procedures for the alkylation of secondary amines 3f, 13 and 23

Secondary amines **3e**, **13** and **23** (1 mol eq.), N,N-diisopropylethylamine (3 mol eq.), methyl 3-bromopropanoate (1.5 mol eq.) in acetonitrile dry, were placed in a round bottom flask and stirred at 60°C over night. After completion of reaction (monitored by TLC) the resulting solution was then concentrated under vacuum, diluted with water and extracted with CH_2Cl_2. The organic fraction was dried over $NaSO_4$ and the solvent was removed under reduced pressure to yield the crude products **4**, **14** and **24**.

The same synthetic procedure was applied to prepare compounds **7, 17, 27, 10, 20, 30** starting from **3f**, **13** and **23** treated with methyl 4-bromobutanoate or methyl 5-bromopentanoate.

Methyl 3-(4-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)propanoate (**4**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (80:20) as eluent (flow rate 1 mL/min, t_R = 13.5 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.61 (1H, s), 8.10 (1H, d, *J* = 8.5 Hz), 7.99 (1H, ovl), 7.98 (1H, ovl), 7.93 (1H, d, *J* = 7.6 Hz), 7.59 (1H, ovl), 7.57 (1H, ovl), 3.70 (3H, s), 3.16 (1H, m), 3.02 (2H, d, *J* = 11.3 Hz), 2.76 (2H, t, *J* =7.4 Hz), 2.59 (2H, t, *J* = 7.2 Hz), 2.31 (2H, m), 2.20 (2H, m), 2.02 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 183.6, 174.4, 169.5, 136.1, 134.5, 129.9, 129.8, 128.9, 128.8 (2C), 128.0, 125.5, 124.6, 54.7, 53.5 (2C), 52.2, 35.4, 32.6, 30.3 (2C). HR ESIMS *m/z* 366.1812 $[M + H]^+$, $C_{21}H_{24}N_3O_3$ requires 366.1818.

Methyl 4-(4-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)butanoate (**7**). The mixture was purified by HPLC on a Luna Omega Polar C18 (5μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 21.0 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.61 (1H, s), 8.10 (1H, d, *J* = 8.5 Hz), 7.99 (1H, ovl), 7.98 (1H, ovl), 7.93 (1H, d, *J* = 7.6 Hz), 7.59 (1H, ovl), 7.58 (1H, ovl), 3.68 (3H, s), 3.14 (1H, m), 3.03 (2H, d, *J* = 11.3 Hz), 2.44 (2H, t, *J* = 7.4 Hz), 2.39 (2H, t, *J* = 7.2 Hz), 2.25 (2H, m), 2.22 (2H, m), 2.03 (2H, m), 1.86 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 184.5, 175.8, 168.7, 136.1, 134.0, 129.9, 129.8, 128.9, 128.8 (2C), 128.1, 125.1,124.6, 58.9, 53.7 (2C), 52.1, 35.4, 32.6, 30.1 (2C), 22.7. HR ESIMS *m/z* 380.1978 $[M + H]^+$, $C_{22}H_{26}N_3O_3$ requires 380.1974.

Methyl 5-(4-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pentanoate (**10**). The mixture was purified by HPLC on a Synergi Fusion RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (8:2) as eluent (flow rate 1 mL/min, t_R = 15.1 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.62 (1H, s), 8.10 (1H, d, *J* = 8.5 Hz), 8.00 (2H, ovl), 7.94 (1H, d, *J* = 7.6 Hz), 7.59 (1H, ovl), 7.58 (1H, ovl), 3.67 (3H, s), 3.15 (1H, m), 3.02 (2H, d, *J* = 10 Hz), 2.43 (2H, m), 2.38 (2H, t, *J* = 7.0 Hz), 2.22 (4H, m), 2.02 (2H, m), 1.64 (2H, m), 1.59 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 184.5, 175.8, 168.7,

136.1, 134.0, 129.9, 129.8, 128.9, 128.8 (2C), 128.1, 125.1, 124.6, 59.3, 53.6 (2C), 52.0, 35.3, 34.5, 30.1 (2C), 26.9, 24.0. HR ESIMS *m/z* 394.2136 $[M + H]^+$, $C_{23}H_{28}N_3O_3$ requires 394.2131.

(S)-Methyl 3-(2-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)propanoate (**14**). The mixture was purified by HPLC on a Synergi Hydro-RP 80A (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (80:20) as eluent (flow rate 1 mL/min, t_R = 17.5 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.12 (1H, d, *J* = 8.6 Hz), 8.01 (1H, d, *J* = 8.7 Hz), 7.99 (1H, ovl), 7.94 (1H, d, *J* = 7.4 Hz), 7.60 (1H, ovl), 7.59 (1H, ovl), 4.13 (1H, br t, *J* = 5.6 Hz), 3.63 (3H, s), 3.08 (1H, m), 2.82 (1H, m), 2.74 (1H, m), 2.53 (2H, ovl), 2.52 (1H, ovl), 2.00 (2H, m), 1.82 (1H, m), 1.74 (2H, m), 1.55 (1H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.7, 174.4, 169.3, 136.2, 134.5, 129.9, 129.8, 128.9, 128.8 (2C), 128.0, 125.3, 124.6, 59.2, 52.5, 52.2, 51.3, 33.0, 31.4, 26.4, 22.9; HR ESIMS *m/z* 366.1818 $[M + H]^+$, $C_{21}H_{24}N_3O_3$ requires 366.1816.

(S)-Methyl 4-(2-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)butanoate (**17**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 31.2 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.62 (1H, s), 8.11 (1H, d, *J* = 8.6 Hz), 8.00 (1H, ovl), 7.99 (1H, ovl), 7.93 (1H, d, *J* = 7.2 Hz), 7.59 (1H, ovl), 7.58 (1H, ovl), 4.04 (1H, m), 3.56 (3H, s),3.09 (2H, m), 2.40 (2H, m), 2.34 (2H, t, *J* = 7.1 Hz), 1.98 (2H, m), 1.81 (2H, m), 1.74 (2H, m), 1.55 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.3,175.5, 169.2, 136.2, 134.4, 129.9, 129.8, 128.9 (2C), 128.7, 128.0, 125.3, 124.6, 59.7, 56.1, 52.0, 51.7, 32.2, 31.6, 26.2, 22.9, 22.7; HR ESIMS *m/z* 380.1980 $[M + H]^+$, $C_{22}H_{26}N_3O_3$ requires 380.1974.

Methyl 5-(2-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pentanoate (**20**). The mixture was purified by HPLC on a Synergi Fusion RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 38.5 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.12 (1H, d, *J* = 8.5 Hz), 8.01 (1H, ovl), 8.00 (1H, ovl), 7.94 (1H, d, *J* = 7.6 Hz), 7.60 (1H, ovl), 7.58 (1H, ovl), 4.04 (1H, dd, *J* = 7.1, 4.8 Hz), 3.59 (3H, s), 3.11 (1H, m), 2.44 (2H, m), 2.37 (1H, m), 2.31

(2H, m), 1.99 (2H, m), 1.87 (1H, m), 1.74 (2H, m), 1.57 (5H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.7, 175.7, 169.4, 136.2, 134.5, 129.9, 129.8, 128.9 (2C), 128.8, 128.0, 125.3,124.6, 59.7, 56.7, 51.9, 51.8, 34.4, 31.7, 26.7, 26.3, 23.6, 23.2; HR ESIMS *m/z* 394.2138 $[M + H]^+$, $C_{23}H_{28}N_3O_3$ requires 394.2131.

(S)-Methyl 3-(2-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propanoate (**24**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (80:20) as eluent (flow rate 1 mL/min, t_R = 7.0 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.62 (1H, s), 8.10 (1H, d, *J* = 8.5 Hz), 8.00 (1H, dovl), 7.99 (1H, ovl), 7.96 (1H, d, *J* = 7.1 Hz), 7.61 (1H, ovl), 7.60 (1H, ovl), 4.12 (1H, dd, *J* = 8.3, 5.4 Hz), 3.61 (3H, s), 3.24 (1H, m), 3.08 (1H, m), 2.83 (1H, m), 2.62 (1H, m), 2.54 (2H,m), 2.38 (1H, m), 2.21 (1H, m), 2.08 (1H, m), 2.01 (1H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.4, 174.3, 169.5, 136.2, 134.5, 129.9, 129.8, 128.9, 128.8, 128.7, 128.0, 125.3, 124.6, 61.2, 54.5, 52.2, 50.9, 34.4, 31.5, 24.5; HR ESIMS *m/z* 352.1661 $[M + H]^+$, $C_{20}H_{22}N_3O_3$ requires 352.1659.

(S)-Methyl 4-(2-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)butanoate (**27**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 19.9 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.12 (1H, d, *J* = 8.5 Hz), 8.00 (1H, ovl), 7.99 (1H, ovl), 7.94 (1H, d, *J* = 6.9 Hz), 7.59 (1H, ovl), 7.58 (1H, ovl), 4.06 (1H, dd, *J* = 8.5, 5.8 Hz), 3.56 (3H, s), 3.26 (1H, m), 2.77 (2H, m), 2.57 (2H, m), 2.39 (2H, m), 2.20 (1H, m), 2.09 (1H, m), 2.00 (1H, m), 1.79 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.3,175.5, 169.5,136.2, 134.6, 130.0, 129.9, 129.0 (2C), 128.8, 128.1, 125.3,124.7, 61.6, 55.0, 54.7, 52.1, 32.3, 31.4, 24.7, 24.4; HR ESIMS *m/z* 366.1822 $[M + H]^+$, $C_{21}H_{24}N_3O_3$ requires 366.1818.

Methyl 5-(2-(3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)pentanoate (**30**). The mixture was purified by HPLC on a Synergi Fusion RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 24.6 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.63 (1H, s),

8.11 (1H, d, *J* = 8.5 Hz), 8.01 (1H, ovl), 7.99 (1H, ovl), 7.93 (1H, d, *J* = 7.6 Hz), 7.59 (1H, ovl), 7.58 (1H, ovl), 4.05 (1H, dd, J = 8.7, 5.8 Hz), 3.59 (3H, s), 3.24 (1H, m), 2.77 (1H, m), 2.56 (1H, m), 2.51 (1H, m), 2.38 (1H, m), 2.32 (2H, m), 2.20 (1H, m), 2.10 (1H, m), 2.00 (1H, m), 1.63 (2H, m), 1.55 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.6, 175.5, 169.4, 136.2, 134.5, 129.9, 129.8, 128.9 (2C), 128.7, 128.0, 125.4, 124.6, 61.4, 55.2, 54.4, 51.8, 34.5, 31.4, 28.8, 24.2, 23.7; HR ESIMS *m/z* 380.1981 $[M + H]^+$, $C_{22}H_{26}N_3O_3$ requires 380.1974.

General synthetic procedures for LiOH hydrolysis

Esters **4**, **7**, **10**, **14**, **17**, **20**, **24**, **27**, **30** (1.0 mol eq.) were dissolved in THF/H_2O (2:1) and treated with LiOH hydroxide (2 mol eq.) at 0 °C. The resulting mixture was stirred at room temperature for 24 h. The mixture was treated with 0.5 N HCl, until pH reached 7-8, then was partitioned three times with EtOAc and the combined organic extracts were dried over Na_2SO_4. The solution was concentrated in vacuum.

3-(4-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)propanoic acid (**5**). The mixture was purified by HPLC on a Luna C18 (10μm; 10 mm i.d. x 250 mm) with MeOH/H_2O (65:35) as eluent (flow rate 3 mL/min, t_R = 12.0 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.62 (1H, s), 8.10 (1H, d, *J* = 8.6 Hz), 8.00 (1H, *J* = 8.5 Hz), 7.99 (1H, d, *J* = 8.6 Hz), 7.94 (1H, d, *J* = 7.5 Hz), 7.60 (1H, ovl), 7.59 (1H, ovl), 3.36 (3H, m), 3.07 (2H, m), 2.81 (2H, m), 2.53 (2H, t, *J* = 6.9 Hz), 2.41 (2H, m), 2.17 (2H, m); ^{13}C NMR (125 MHz, CD_3OD): δ_C 181.7, 178.7, 169.5, 136.1, 134.5, 129.9, 129.8, 128.9 (2C), 128.8, 128.0, 125.3, 124.6, 57.7, 52.4 (2C), 33.9, 33.0, 29.0 (2C). HR ESIMS *m/z* 350.1516 $[M - H]^-$, $C_{20}H_{20}N_3O_3$ requires 350.1505.

4-(4-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)butanoic acid (**8**). The mixture was purified by HPLC on a Luna Omega Polar C18 (5μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (70:30) as eluent (flow rate 1 mL/min, t_R = 21.0 min);^{1}H NMR (500 MHz, CD_3OD): δ_H 8.61 (1H, s), 8.10 (1H, d, *J* = 8.6 Hz), 7.99 (2H, d, *J* = 8.6 Hz), 7.93 (1H, d, *J* = 7.5 Hz), 7.59 (1H, ovl), 7.58 (1H, ovl), 3.45 (3H, m), 2.98 (4H, m), 2.43 (4H, m), 2.25 (2H, m), 1.93 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.7, 178.0, 169.5, 136.1, 134.5, 129.9, 129.8, 128.9 (2C), 128.8, 128.0, 125.3,124.6,

59.6, 52.3 (2C), 37.4, 33.2, 28.3(2C), 21.7. HR ESIMS *m/z* 364.1672 $[M - H]^-$, $C_{21}H_{22}N_3O_3$ requires 364.1661.

5-(4-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pentanoic acid (**11**). The mixture was purified by HPLC on a Luna Omega Polar C18 (5µm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (7:3) as eluent (flow rate 1 mL/min, t_R = 6.7 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.62 (1H, s), 8.10 (1H, d, *J* = 8.5 Hz), 8.00 (1H, ovl), 7.98 (1H, ovl), 7.94 (1H, d, *J* = 7.6 Hz), 7.60 (1H, ovl), 7.57 (1H, ovl), 3.38 (3H, m), 2.86 (4H, m), 2.38 (2H, m), 2.28 (2H, m), 2.20 (2H, m), 1.74 (2H, m), 1.69 (2H, m); HR ESIMS *m/z* 378.1822 $[M - H]^-$, $C_{22}H_{24}N_3O_3$ requires 378.1818.

(S)-3-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)propanoic acid (**15**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4µm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (7:3) as eluent (flow rate 1 mL/min, t_R = 16.1 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.65 (1H, s), 8.12 (1H, d, *J* = 8.6 Hz), 8.01 (1H, ovl), 8.00 (1H, ovl), 7.94 (1H, d, *J* = 7.6 Hz), 7.61 (1H, ovl), 7.59 (1H, ovl), 4.15 (1H, t, *J* = 6.8 Hz), 3.13 (1H, m), 2.83 (1H, m), 2.73 (1H, m), 2.54 (2H, m), 2.45 (1H, m), 2.01 (2H, m), 1.85 (1H, m), 1.75 (2H, m), 1.57 (1H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.7, 178.0, 169.3, 136.2, 134.5, 129.9, 129.8, 128.9, 128.8 (2C), 128.0, 125.3, 124.6, 59.5, 52.4, 52.2, 33.8, 31.5, 26.3, 22.8;HR ESIMS *m/z* 350.1510 $[M - H]^-$, $C_{20}H_{20}N_3O_3$ requires 350.1505.

(S)-4-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)butanoic acid (**18**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4µm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (7:3) as eluent (flow rate 1 mL/min, t_R = 14.8 min);^{1}H NMR (500 MHz, CD_3OD): δ_H 8.65 (1H, s), 8.12 (1H, d, *J* = 8.6 Hz), 8.01 (1H, ovl), 8.00 (1H, ovl), 7.94 (1H, d, *J* = 7.6 Hz), 7.61 (1H, ovl), 7.59 (1H, ovl), 4.16 (1H, dd, *J* = 6.8, 4.5 Hz), 3.19 (1H, m), 2.55 (2H, m), 2.51 (1H, m), 2.32 (2H, m), 2.03 (2H, m), 1.82 (2H, m), 1.77 (2H, m), 1.58 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.2, 178.2, 169.4, 136.4, 134.6, 129.9 (2C), 129.0, 128.9, 128.8, 128.0, 125.0, 124.7, 59.7, 56.8, 51.7, 33.7, 31.4, 26.1, 23.0, 22.9; HR ESIMS *m/z* 364.1667 $[M - H]^-$, $C_{21}H_{22}N_3O_3$ requires 364.1661.

5-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pentanoic acid (**21**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 13.9 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.12 (1H, d, *J* = 8.4 Hz), 8.01 (1H, ovl), 7.99 (1H, ovl), 7.94 (1H, d, *J* = 7.6 Hz), 7.59 (1H, ovl), 7.57 (1H, ovl), 4.07 (1H, m), 3.12 (1H, m), 2.42 (1H, ovl), 2.40 (2H, ovl), 2.25 (2H, m), 2.00 (2H, m), 1.87 (1H, m), 1.75 (2H, m), 1.57 (5 H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.7, 177.8, 169.4, 136.2, 134.5, 129.9, 129.8, 128.9 (2C), 128.8, 128.0, 125.3,124.6, 59.7, 56.7, 51.9, 34.9, 31.7, 29.0, 26.3, 23.9, 23.2; HR ESIMS *m/z* 378.1820 $[M - H]^-$, $C_{22}H_{24}N_3O_3$ requires 378.1818.

(S)-2-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propanoic acid (**25**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (7:3) as eluent (flow rate 1 mL/min, t_R = 10.1 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.12 (1H, d, *J* = 8.5 Hz), 8.00 (1H, ovl), 7.99 (1H, ovl), 7.94 (1H, d, *J* = 7.6 Hz), 7.60 (1H, ovl), 7.59 (1H, ovl), 4.16 (1H, dd, *J* = 8.5, 5.9 Hz), 3.25 (1H, m), 3.10 (1H, m), 2.83 (1H, m), 2.67 (1H, m), 2.49 (2H, m), 2.38 (1H, m), 2.21 (1H, m), 2.10 (1H, m), 2.01 (1H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.2, 178.8, 169.5, 136.2, 134.5, 129.9, 129.8, 128.9 (2C), 128.7, 127.9, 125.4, 124.7, 61.2, 54.3, 51.8, 35.0, 31.3, 24.2; HR ESIMS *m/z* 336.1351 $[M - H]^-$, $C_{19}H_{18}N_3O_3$ requires 336.1348.

(S)-4-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)butanoic acid (**28**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (7:3) as eluent (flow rate 1 mL/min, t_R = 12 min);^{1}H NMR (500 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.11 (1H, d, *J* = 8.5 Hz), 8.01 (1H, ovl),7.99 (1H, ovl), 7.93 (1H, d, *J* = 7.6 Hz), 7.59 (1H, ovl), 7.58(1H, ovl), 4.12 (1H, dd, *J* = 8.4, 6.0 Hz), 3.28 (1H, ovl), 2.79 (1H, m), 2.61 (1H, ovl), 2.58 (1H, ovl), 2.37 (1H, ovl), 2.33 (2H, ovl), 2.19 (1H, m), 2.10 (1H, m), 2.02 (1H, m), 181 (2H, m);^{13}C NMR (100 MHz, CD_3OD): δ_C 182.3, 178.0, 169.5, 136.1, 134.5, 129.9, 129.8, 129.0, 128.9, 128.8, 128.0, 125.3, 124.6, 61.5, 55.2, 54.4, 33.2, 31.4, 24.9, 24.3; HR ESIMS *m/z* 350.1509 $[M - H]^-$, $C_{20}H_{20}N_3O_3$ requires 350.1505.

5-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)pentanoic acid (**31**). The mixture was purified by HPLC on a Luna Omega Polar C18 (5μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 12.5 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.11 (1H, d, *J* = 8.5 Hz), 8.01 (1H, ovl), 7.99 (1H, ovl), 7.94 (1H, d, *J* = 7.6 Hz), 7.60 (1H, ovl), 7.59 (1H, ovl), 4.07 (1H, dd, *J* = 8.1, 6.2 Hz), 3.24 (1H, ovl), 2.77 (1H, m), 2.57 (1H, m), 2.51 (1H, m), 2.38 (1H, m), 2.28 (2H, m), 2.20 (1H, m), 2.10 (1H, m), 2.00 (1H, m), 1.63 (2H, m), 1.58 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.6, 178.0, 169.4, 136.2, 134.5, 129.9, 129.8, 128.9 (2C), 128.8, 128.0, 125.3, 124.7, 61.6, 55.4, 54.4, 35.0, 31.4, 29.0, 24.2, 23.9; HR ESIMS *m/z* 364.1365 $[M - H]^-$, $C_{21}H_{22}N_3O_3$ requires 364.1361.

General synthetic procedures for DIBAL-H reduction

A solution of esters **4**, **7**, **10**, **14**, **17**, **20**, **24**, **27** and **30** (1 mol eq.) in tetrahydrofuran at 0°C was treated with a solution of diisobutylammonium hydride (1.0 M in toluene, 2 mol eq.), added dropwise. The reaction was allowed to warm slowly to ambient temperature and stirred at room temperature for 48 h total. The reaction was quenched by slow addition of methanol and then a solution of saturated sodium potassium tartrate was added and stirred for 1 h. The mixture was partitioned three times, and the combined organic extracts dried over Na_2SO_4.

3-(4-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)propan-1-ol (**6**). The mixture was purified by HPLC on a Luna Omega Polar C18 (5 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 13.3 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.61 (1H, s), 8.10 (1H, d, *J* = 8.5 Hz), 7.99 (1H, ovl), 7.98 (1H, ovl), 7.93 (1H, d, *J* = 7.6 Hz), 7.58 (2H, ovl), 3.64 (2H, t, *J* =6.3 Hz) 3.17 (1H, m), 3.07 (2H, d, *J* = 11.2 Hz), 2.56 (2H, t, *J* = 7.6 Hz), 2.29 (2H, t, *J* = 11.2 Hz), 2.20 (2H, d, *J* = 12.4 Hz), 2.03 (2H, m), 1.79 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 183.6, 169.4, 136.1, 134.5, 129.9 (2 C), 128.9, 128.7 (2C), 127.9, 125.5, 124.6, 61.8, 57.1, 53.7 (2C), 35.4, 30.2 (2C), 30.1; HR ESIMS *m/z* 338.1869 $[M + H]^+$, $C_{20}H_{24}N_3O_2$ requires 338.1865.

4-(4-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)butan-1-ol (**9**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 24.0 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.61 (1H, s), 8.09 (1H, d, *J* = 8.4 Hz), 7.99 (2H, d, *J* = 8.3 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.58 (1H, ovl), 7.57 (1H, ovl), 3.59 (2H, t, *J* = 5.9 Hz), 3.18 (1H, m), 3.07 (2H, d, *J* = 11.4 Hz), 2.47 (2H, t, *J* = 7.2 Hz), 2.30 (2H, m), 2.22 (2H, m), 2.02 (2H, m), 1.66 (2H, m), 1.60 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 184.5, 168.6, 136.1, 134.0, 129.9, 129.8, 128.9, 128.8 (2C), 128.1, 125.0,124.6, 62.8, 59.7, 53.7 (2C), 35.4, 32.0, 30.2 (2C), 24.5; HR ESIMS *m/z* 352.2029 $[M + H]^+$, $C_{21}H_{26}N_3O_2$ requires 352.2025.

5-(4-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pentan-1-ol (**12**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (4 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (8:2) as eluent (flow rate 1 mL/min, t_R = 13.1 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.61 (1H, s), 8.10 (1H, d, *J* = 8.5 Hz), 8.00 (1H, d, ovl), 7.99 (1H, ovl), 7.93 (1H, d, *J* = 7.1 Hz), 7.59 (1H, ovl), 7.57 (1H, ovl), 3.57 (2H, t, *J* = 6.5 Hz), 3.16 (1H, m), 3.05 (2H, m), 2.44 (2H, m), 2.27 (2H, m), 2.22 (2H, m), 2.05 (2H, m), 1.59 (4H, m), 1.40 (2H, m); ^{13}C NMR (125 MHz, CD_3OD): δ_C 183.6, 169.5, 136.1, 134.5, 129.9, 129.8, 128.9, 128.7, 128.0, 127.9, 125.5, 124.6, 62.3, 59.8, 53.7 (2C), 35.5, 33.5, 30.2 (2C), 27.3, 25.0; HR ESIMS *m/z* 366.2185 $[M + H]^+$, $C_{22}H_{28}N_3O_2$ requires 366.2182.

(S)-3-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)propan-1-ol (**16**). The mixture was purified by HPLC on a Luna Omega Polar C18 (5 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (78:22) as eluent (flow rate 1 mL/min, t_R = 11.0 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.12 (1H, d, *J* = 8.6 Hz), 8.01 (1H, ovl), 8.00 (1H, ovl), 7.94 (1H, d, *J* = 7.4 Hz), 7.60 (1H, ovl), 7.59 (1H, ovl), 4.06 (1H, dd, *J* =7.2, 4.3 Hz), 3.59 (2H, t, *J* = 6.1 Hz), 3.13 (1H, m), 2.57 (2H, m), 2.46 (1H, m), 1.99 (1H, m), 1.87 (2H, m), 1.73 (2H, m), 1.72 (2H, m), 1.56 (1H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.7, 169.4, 136.2, 134.5, 129.9, 129.8, 128.9 (2C), 128.8, 128.0, 125.1, 124.6, 61.6, 59.9, 54.6, 51.7, 31.8, 30.1, 26.3, 23.1; HR ESIMS *m/z* 338.1869 $[M + H]^+$, $C_{20}H_{24}N_3O_2$ requires 338.1865.

(S)-4-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)butan-1-ol (**19**). The mixture was purified by HPLC on a Nucleodur C18 (5 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 18.7 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.12 (1H, d, *J* = 8.6 Hz), 8.01 (1H, d, *J* = 8.7 Hz), 7.99 (1H, ovl), 7.94 (1H, d, *J* = 7.4 Hz), 7.60 (1H, ovl), 7.59 (1H, ovl), 4.08 (1H, br t, *J* =5.9 Hz), 3.52 (2H, t, *J* = 6.0 Hz), 3.14 (1H, m), 2.46 (2H, m), 2.43 (1H, m), 2.01 (2H, m), 1.89 (1H, m), 1.76 (2H, m), 1.61 (2H, m), 1.54 (1H, m), 1.50 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 181.7, 169.4, 136.2, 134.2, 129.9, 129.8, 129.0, 128.8 (2C), 128.1, 125.1, 124.6, 62.7, 59.6, 57.0, 51.6, 31.4, 31.3, 26.1, 23.8, 22.9; HR ESIMS *m/z* 352.2021 $[M + H]^+$, $C_{21}H_{26}N_3O_2$ requires 352.2025.

5-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pentan-1-ol (**22**). The mixture was purified by HPLC on a Luna Omega Polar C18 (5 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (8:2) as eluent (flow rate 1 mL/min, t_R = 18.4 min); ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.62 (1H, s), 8.11 (1H, dd, *J* = 8.6, 1.5 Hz), 8.00 (1H, d, ovl), 7.99 (1H, ovl), 7.93 (1H, d, *J* = 7.0 Hz), 7.59 (1H, ovl), 7.57 (1H, ovl), 4.04 (1H, dd, *J* = 7.3, 4.6 Hz), 3.50 (2H, t, *J* = 6.6 Hz), 3.11 (1H, m), 2.43 (2H, m), 2.36 (1H, m), 1.99 (2H, m), 1.88 (1H, m), 1.75 (2H, m), 1.53 (3H, ovl), 1.49 (2H, m), 1.31 (2H, m); ^{13}C NMR (125 MHz, CD_3OD): δ_C 181.7, 169.4, 136.2, 134.5, 129.9, 129.8, 128.9 (2C), 128.8, 128.0, 125.3, 124.6, 62.8, 59.7, 57.3, 51.9, 33.4, 31.6, 27.1, 26.2, 24.7, 23.2; HR ESIMS *m/z* 366.2186 $[M + H]^+$, $C_{22}H_{28}N_3O_2$ requires 366.2182.

(S)-3-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propan-1-ol (**26**). The mixture was purified by HPLC on a Synergi Fusion-RP 80 (5 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (68:32) as eluent (flow rate 1 mL/min, t_R = 27.0 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.11 (1H, d, *J* = 8.5 Hz), 8.01 (1H, d, ovl), 7.99 (1H, ovl), 7.95 (1H, d, *J* = 7.1 Hz), 7.61 (1H, ovl), 7.60 (1H, ovl), 4.08 (1H, dd, *J* = 8.5, 5.8 Hz), 3.63 (2H, t, *J* = 6.1 Hz), 3.28 (1H, ovl), 2.88 (1H, m), 2.62 (1H, m), 2.59 (1H, m), 2.40 (1H, m), 2.20 (1H, m), 2.11 (1H, m), 2.02 (1H, m), 1.76 (2H, ovl); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.3, 169.5, 136.4, 134.5, 129.9, 129.8, 129.0, 128.9, 128.8,

128.0, 125.4, 124.6, 61.6, 61.5, 59.2, 54.3, 32.2, 31.4, 24.3; HR ESIMS *m/z* 324.1712 $[M + H]^+$, $C_{19}H_{22}N_3O_2$ requires 324.1710.

(S)-4-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)butan-1-ol (**29**). The mixture was purified by HPLC on Synergi Fusion-RP 80 (4 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (75:25) as eluent (flow rate 1 mL/min, t_R = 10.0 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.63 (1H, s), 8.11 (1H, d, *J* = 8.5 Hz), 8.01 (1H, d, ovl), 7.99 (1H, ovl), 7.95 (1H, d, *J* = 7.1 Hz), 7.61 (1H, ovl), 7.60 (1H, ovl), 4.08 (1H, dd, *J* = 8.3, 6.1 Hz), 3.53 (2H, t, *J* = 5.9 Hz), 3.27 (1H, ovl), 2.78 (1H, m), 2.59 (1H, m), 2.54 (1H, m), 2.38 (1H, m), 2.21 (1H, m), 2.12 (1H, m), 2.02 (1H, m), 160 (2H, ovl), 1.57 (2H, ovl); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.3, 169.5, 136.1, 134.4, 130.0, 129.8, 129.1, 128.9, 128.7, 128.0, 125.4, 124.6, 62.7, 61.4, 55.8, 54.5, 31.5, 31.3, 26.1, 24.2; HR ESIMS *m/z* 338.1872 $[M + H]^+$, $C_{20}H_{24}N_3O_2$ requires 338.1869.

5-(2-(3-(Naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)pentan-1-ol (**32**). The mixture was purified by HPLC on a Luna Omega Polar C18 (5 μm; 4.6 mm i.d. x 250 mm) with MeOH/H_2O (85:15) as eluent (flow rate 1 mL/min, t_R = 11.4 min); ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.62 (1H, s), 8.11 (1H, d, *J* = 8.5 Hz), 8.00 (1H, d, ovl), 7.99 (1H, ovl), 7.94 (1H, d, *J* = 7.1 Hz), 7.59 (1H, ovl), 7.58 (1H, ovl), 4.06 (1H, dd, *J* = 8.6, 5.9 Hz), 3.51 (2H, t, *J* = 6.5 Hz), 3.25 (1H, ovl), 2.75 (1H, m), 2.58 (1H, m), 2.51 (1H, m), 2.39 (1H, m), 2.21 (1H, m), 2.11 (1H, m), 2.01 (1H, m), 1.53 (4H, m), 1.38 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ_C 182.5, 169.5, 136.2, 134.5, 129.9, 129.8, 128.9 (2C), 128.7, 128.0, 125.3, 124.6, 62.8, 61.4, 55.9, 54.7, 33.4, 31.4, 29.4, 24.7, 24.2; HR ESIMS *m/z* 352.2029 $[M + H]^+$, $C_{21}H_{26}N_3O_2$ requires 352.2025.

***In vitro* coactivator recruitment assay by Alpha Screening.** Activation of FXR has been measured by Alpha Screen Technology in a Coactivator Recruitment Assay. Anti-GST-coated acceptor beads were used to capture the GST-fusion FXR-LBD, whereas the biotinylated-SRC-1 peptide was captured by the streptavidin donor beads. Upon illumination at 680 nm, chemical energy is transferred from donor to acceptor beads across the complex streptavidin-donor/SRC-1-biotin/GSTFXR-LBD/anti-GST-acceptor and a signal is produced. The assay has been performed in white, low-

volume, 384-well Optiplates (PerkinElmer) using a final volume of 25 μL containing final concentrations of 10 nM of purified GST-tagged FXR-LBD protein, 30 nM biotinylated SRC-1 peptide, 20 mg/mL anti-GST acceptor beads, and 10 mg/mL of streptavidin donor bead (PerkinElmer). The assay buffer contained 50 mM Tris (pH 7.4), 50 mM KCl and 1 mM DTT. The stimulation times with 1 μL of tested compound (CDCA at 500 nM; compounds **3f** and **13** at 500 and 1000 nM) were fixed to 30 min at room temperature. The concentration of DMSO in each well was maintained at a final concentration of 2%. After the addition of the detection mix (acceptor and donor beads), the plates were incubated in the dark for 3 h at room temperature and then were read in an Envision microplate analyzer (PerkinElmer).

Cell culture. HepG2, an immortalized epatocarcinoma cell line, was cultured and maintained at 37 °C and 5% CO_2 in E-MEM additioned with 10% FBS, 1% glutamine and 1% penicillin/streptomycin.

Transactivation assay. To evaluate FXR mediated transactivation, HepG2 cells were transfected with 100 ng of human pSG5-FXR, 100 ng of human pSG5-RXR, 200 ng of the reporter vector p(hsp27)-TK-LUC containing the FXR response element IR1 cloned from the promoter of heat shock protein 27 (hsp27) and with 100 ng of pGL4.70 (Promega), a vector encoding the human Renilla gene. At 24 h post-transfection, cells were stimulated were stimulated with 10 μM of compounds and in another experimental setting with 50 μM of compounds in combination with 10 μM CDCA. After treatments, 10 μL of cellular lysates were read using Dual Luciferase Reporter Assay System (Promega Italia srl, Milan, Italy) according manufacturer specifications using the Glomax 20/20 luminometer (Promega Italia srl, Milan, Italy). Luciferase activities were assayed and normalized with Renilla activities.

To investigate the specificity of compounds **3f** and **13** versus PPARγ, HepG2 cells were transiently transfected with 200 ng reporter vector p(UAS)5XTKLuc, 100 ng pGL4.70 and with a vector containing the ligand binding domain of nuclear receptors PPARγ cloned upstream of the GAL4-DNA binding domain (pSG5-PPARγLBD-GAL4DBD). To evaluate PXR mediated transactivation ,HepG2 were transfected with 200 ng of the reporter vector pGL3HenancePXRE, 100 ng of human

pSG5-RXR, 100 ng pGL4.70 and with a vector containing the ligand binding domain of nuclear receptor PXR (pSG5hPXRT1). For LXRα and LXRβ mediated transactivation, HepG2 cells were transfected with 20 ng of the reporter vector p(UAS)5XTKLuc, 100 ng of a vector containing the ligand binding domain of LXRα or LXRβ cloned upstream of the GAL4-DNA binding domain (i.e. pSG5-LXRαLBD-GAL4DBD; pSG5-LXRβLBD-GAL4DBD) and 100 of pGL4.70 (Promega), a vector encoding the human Renilla gene. At 24 h post-transfection, cells were stimulated 18 h with GW3965 or 500 nM of rosiglitazone, and 10 μM of compounds **3f** and **13**. In another experimental setting at 24 h post-transfection, cells were stimulated with 5 μM of compounds in combination with 10 μM of different agonists. After treatments, 10 μL of cellular lysates were read using Dual Luciferase Reporter Assay System (Promega Italia srl, Milan, Italy) according manufacturer specifications using the Glomax 20/20 luminometer (Promega Italia srl, Milan, Italy). Luciferase activities were assayed and normalized with Renilla activities.

Dose-Response Curve on FXR. To calculate the IC_{50} of FXR, dose response curves were performed in HepG2 cells transfected as described above and then treated with increasing concentrations of compounds **3a-f**, **5**, **6**, **8**, **9**, **11-13**, **15**, **16**, **18**, **19**, **21-23**, **25**, **26**, **28**, **29**, **31** and **32** (from 0.1 to 100 μM) in combination with CDCA (10 μM). At 18 h post stimulations, cellular lysates were assayed for luciferase and Renilla activities using the Dual-Luciferase Reporter assay system (E1980, Promega). Luminescence was measured using Glomax 20/20 luminometer (Promega). Luciferase activities were normalized with Renilla activities.

RNA isolation and RT-PCR. HepG2 cells were plated at 2×10^6 cells/Flask in a T75 flask. After an overnight incubation, cells were starved and then stimulated for 18 h with 10 μM CDCA alone or in combination with increasing concentration of **3f** (0.1 and 1 μM). Total RNA was isolated from cells using the TRIzol reagent according to the manufacturer's specifications (Invitrogen). One microgram of purified RNA was treated with DNase-I and reverse transcribed with Superscript II (Invitrogen). For Real Time PCR, 10 ng template was dissolved in 25 μL containing 200 nmol/L of each primer and 12.5 μL of 2× SYBR FAST Universal ready mix (Invitrogen). All reactions were performed in

triplicate, and the thermal cycling conditions were as follows: 2 min at 95°C, followed by 40 cycles of 95°C for 20 s and 60°C for 30 s in StepOnePlus (Applied Biosystems). The relative mRNA expression was calculated accordingly to the Ct method. Primers were designed using the software PRIMER3, using published data obtained from the NCBI database. Forward and reverse primer sequences were the following: human *GAPDH*, gaaggtgaaggtcggagt and catgggtggaatcatattggaa; human *SHP*, tctcttcttccgccctatca and aagggcttgctggacagtta; human *OSTα*, tgttgggccctttccaatac and ggctcccatgttctgctcac; human *CYP7A1*, gacacacctcgtggtcctct and tttcattgcttctgggttcc; human *PEPCK*, cacactgaccctgctggag and ctactcgtgccacatccttg; human *GC6P*, tgggcattaaactcctttgg and ccaaaacccaccagtatgga; *CYP8B1*, gggtaccctcagctatgcag and gggtgcttcaggaggtacaa.

Physiochemical properties and pharmacokinetic characterization.

LC-MS/MS ADME Methods. Chromatography was performed using an Alliance pump system coupled to a Q-ToF Premiere (Waters Co.). The mixture was separated on a Phenomenex Luna C8(2) 5 µm, 100 Å, 150x2 mm. The mobile phase consisted of 0.2% formic acid (FA) in water as solvent A and 0.2% FA in acetonitrile as solvent B at a flow rate of 200 µL/min. The gradient was as follows: 0-2 min (75% A and 25% B), 2-20 min (5%A and 95%B), 20-30 min (75% A and 25% B). The detection of analytes was achieved by electrospray ionization (ESI) in the positive mode with the appropriate MS/MS transitions, if necessary.

Solubility Measurements. Ten microliters of a 10 mM solution in DMSO of the compound was diluted either in 490 µL of PBS pH 7.4 or in organic solvent MeOH (in triplicate). The tubes were gently shaken 24 h at room temperature, then centrifuged for 5 min at 4000 rpm. Ten microliters of sample was diluted in 490 µL of MeOH. The solubility is determined by the ratio of mass signal area PBS/organic solvent.

Microsomal Stability. Male mouse (CD-1) liver microsomes (Sigma-Aldrich) were used. All incubations were performed in duplicate in a shaking water bath at 37 °C. The incubation mixtures contained 1 µM compound with 1% DMSO used as a vehicle, mouse liver microsomes (0.3 mg of microsomal protein per mL), 5 mM $MgCl_2$, 1 mM NADP, 5 mM glucose 6-phosphate, 0.4 $U \cdot mL^{-1}$

glucose 6-phosphate dehydrogenase, and 50 mM potassium phosphate buffer (pH 7.4) in a final volume of 0.5 mL. Aliquots were removed at 0, 5, 10, 20, 30, and 40 min after microsome addition and the reaction was stopped by adding 200 μL of ice-cold acetonitrile. After two hours, the samples were centrifuged for 10 min at 10000 rpm, and the supernatants were transferred in matrix tubes for LC-MS/MS analysis. Propranolol, known as a high hepatic clearance drug in rodents, was used as a quality-control compound for the microsomal incubations. The slope of the linear regression of the curve obtained reporting the natural logarithm of compound area versus incubation time (-k) was used in the conversion to *in vitro* $t_{1/2}$ values by $t_{1/2}$=-ln(2)/k. *In vitro* intrinsic clearance (Cl_{int} expressed as μL/min/mg) was calculated according to the following formula: Cl_{int} = volume of reaction (μL)/ $t_{1/2}$(min)/protein of liver microsomes (mg). The percentage of unmodified compound has been calculated assuming the area of the compound peak at time 0 min as 100%.

PAMPA. Donor solution (250 μM) was prepared by diluting 5 mM DMSO compound stock solution using phosphate buffer (pH 7.4, 0.01 M). Filter membrane was coated with 5 μL of specific lipid solution prepared a 1% phosphatidylcholine solution in *n*-dodecane. Donor solution (150 μL) was added to each well of the filter plate. To each well of the acceptor plate 300 μL of solution (5% DMSO in phosphate buffer) were added. Each compound was tested in triplicate. The sandwich was incubated for 24 h at room temperature under gentle shaking. After the incubation time, the sandwich plates were separated and 250 μL of the acceptor plate and 100 μL of donor were transferred to a UV quartz microtiter plate and measured by UV spectroscopy, using a Multiskan GO microplate spectrophotometer (Thermo Scientific) at 250−500 nm at step of 5 nm. Reference solutions (250 μL) were prepared diluting the sample stock solutions to the same concentration as that with no membrane barrier. The permeability value Log Pe has been determined as previously reported[1]. The integrity of the membrane was checked using propanolol and furosemide as control molecules.

Molecular Docking. Docking simulations were performed with the Glide program as implemented in Maestro.[2] To perform such calculations, we selected the crystal structure of the FXR-LBD in complex with the selective antagonist *N*-benzyl-*N*-(3-(*tert*-butyl)-4-hydroxyphenyl)-2,6-dichloro-4-

(dimethylamino) benzamide (NDB) (PDB code 4OIV).[3] In fact, this is the only tridimensional structure of the FXR-LDB in complex with an antagonist available in the PDB. This structure was prepared through the Protein Preparation Wizard as implemented in Maestro.[4] In detail, bond orders were assigned and missing hydrogens added. A prediction of the receptor side chains ionization and tautomeric states was then performed using Epik[5]. Then, an optimization of the hydrogen-bonding network was carried out, and the positions of the hydrogen atoms were minimized. Finally, waters molecules beyond 3 Å from the co-crystallized ligand were removed, while the others were explicitly considered in the docking calculation. For the grid calculations, a virtual box of $25 \times 25 \times 25$ Å centered on the ligand binding cavity was created. The ligands' tridimensional structures were generated through the Maestro Build Panel and then refined using LigPrep as implemented in Maestro[6]. Protonation states at pH 7.4 were assigned using Epik. For docking, we selected the OPLS3 force field[7], otherwise default Glide parameters were applied. The standard precision (SP) mode of the GlideScore function[8] was used to score and rank the predicted binding poses.

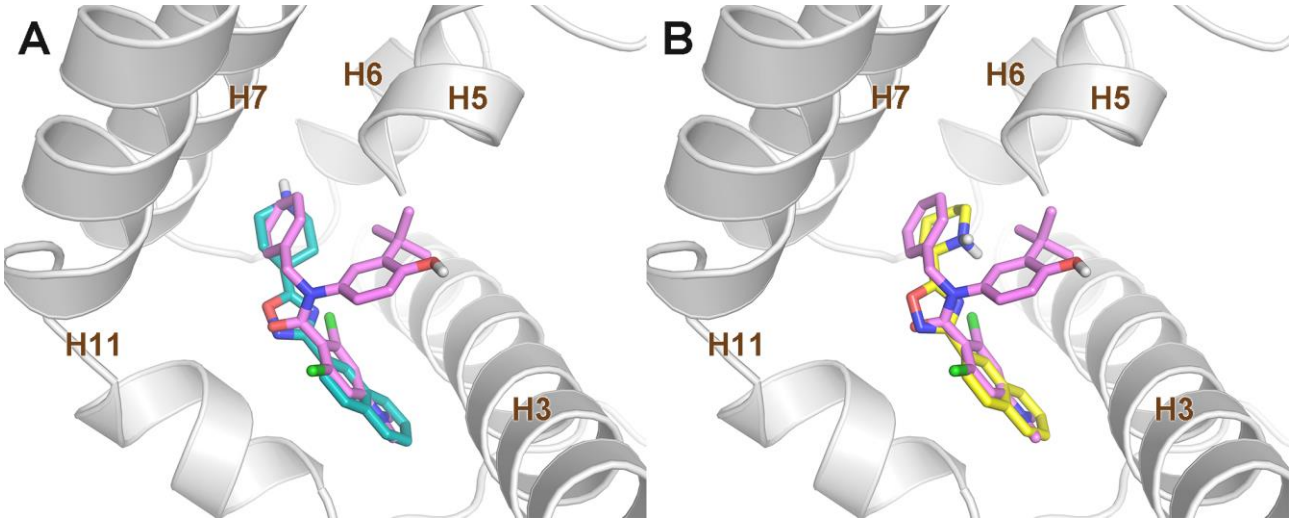


Figure S1. Superimposition between the docking pose of (A) **3f** (cyan sticks) and (B) **13** (yellow sticks) with the crystallographic pose of NBD (pink sticks) at the FXR-LBD (PDB code: 4OIV).[3] FXR is shown as grey cartoon, with amino acids important for ligand binding depicted as sticks. Non-polar hydrogens are omitted for clarity. Hydrogen bonds are shown as dashed black lines.

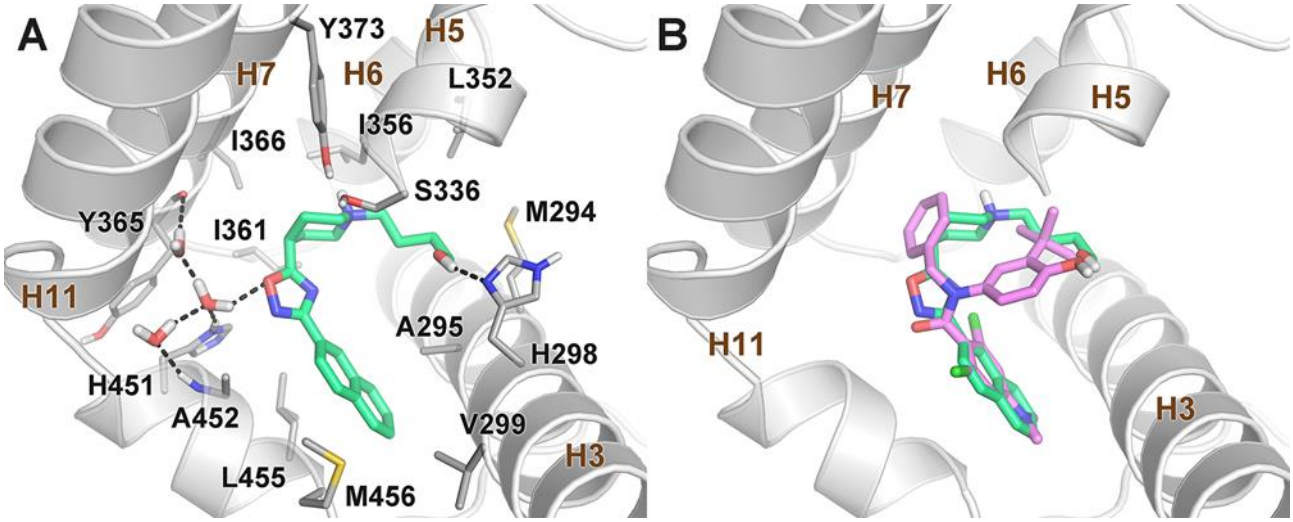


Figure S2. (A) Docking pose of **9** (green sticks) and (B) its superposition with the crystallographic pose of NBD (pink sticks) at the FXR-LBD (PDB code: 4OIV).[3] FXR is shown as grey cartoon, with amino acids important for ligand binding depicted as sticks. Non-polar hydrogens are omitted for clarity. Hydrogen bonds are shown as dashed black lines.

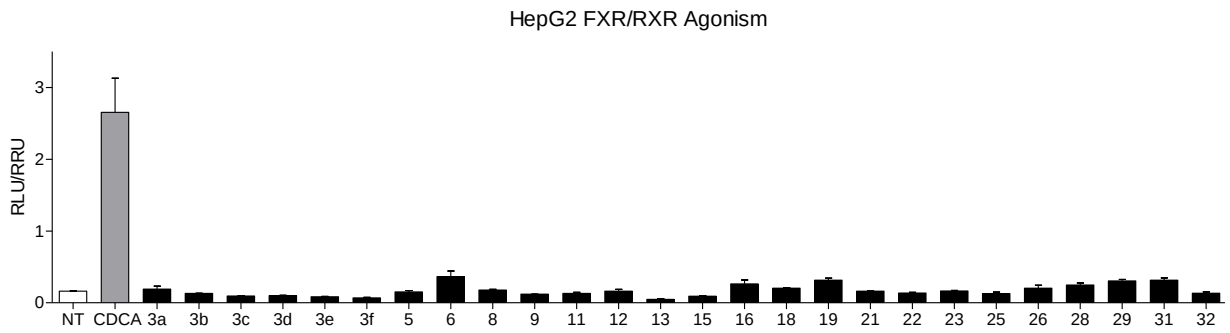


Figure S3. FXR transactivation on HepG2 cells. HepG2 cells were transfected with pSG5-FXR, pSG5-RXR, PGL4.70-Renilla, and reporter vector p(hsp27)-TK-LUC vectors. Cells were stimulated with 10 μM of compounds, CDCA (10 μM) was used as positive control.

Figure S4. ^{1}H NMR (400 MHz, CD_3OD) of compound **3a**

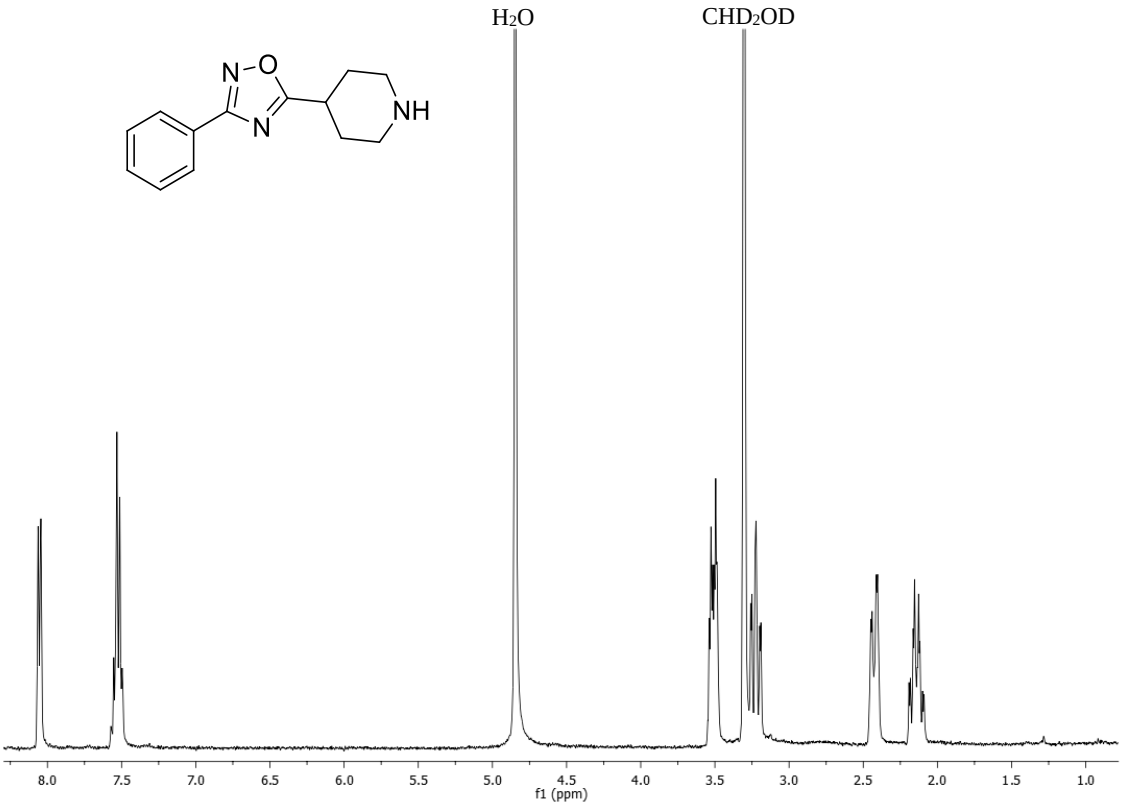


Figure S5. ^{1}H NMR (400 MHz, CD_3OD) of compound **3b**

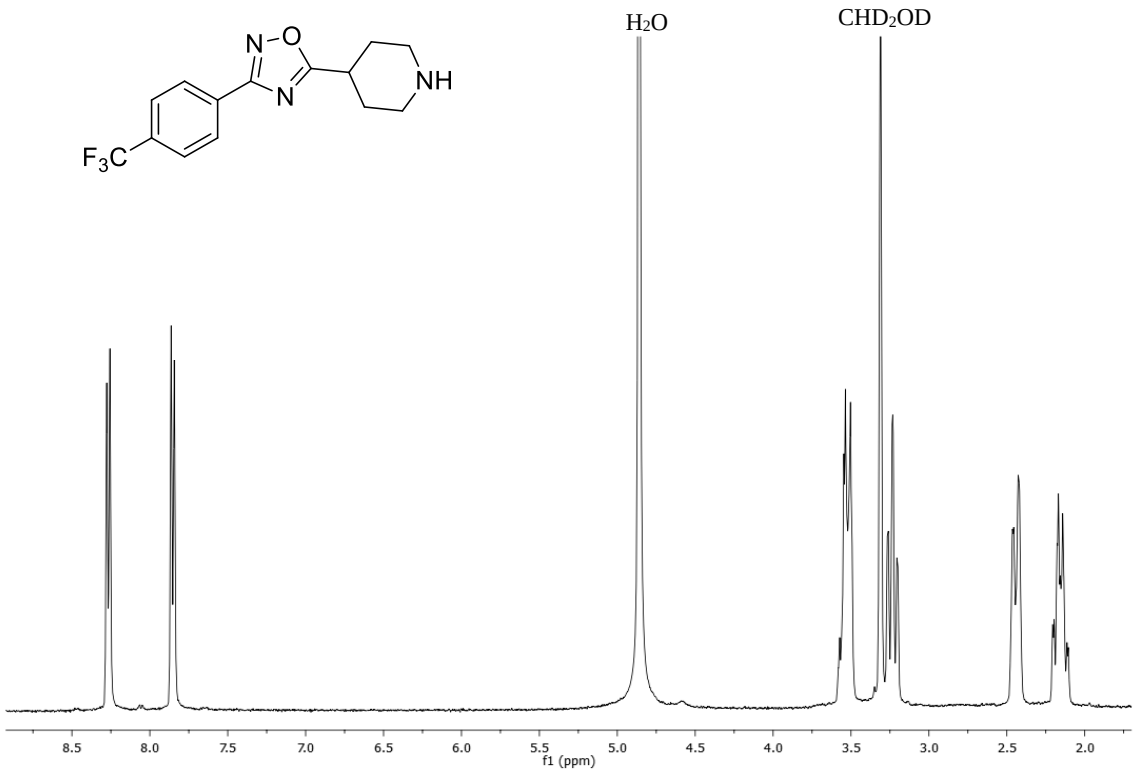


Figure S6. ^{1}H NMR (400 MHz, CD_3OD) of compound **3c**

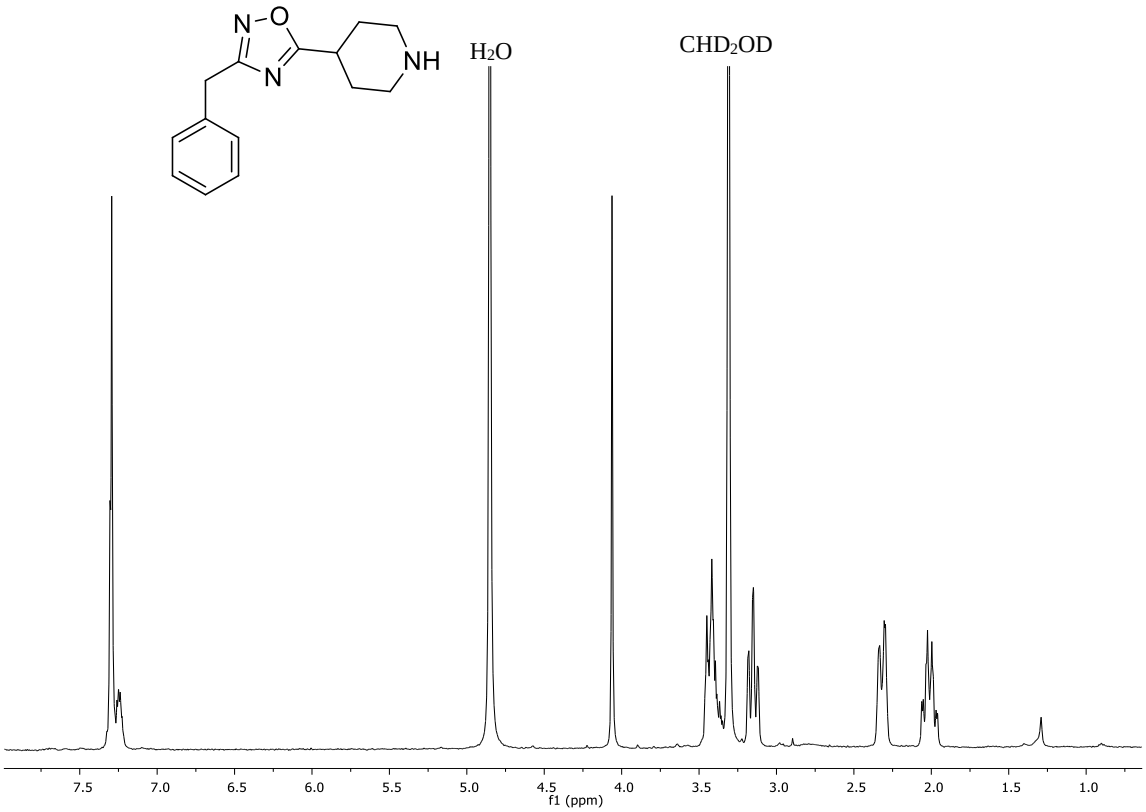


Figure S7. ^{1}H NMR (400 MHz, CD_3OD) of compound **3d**

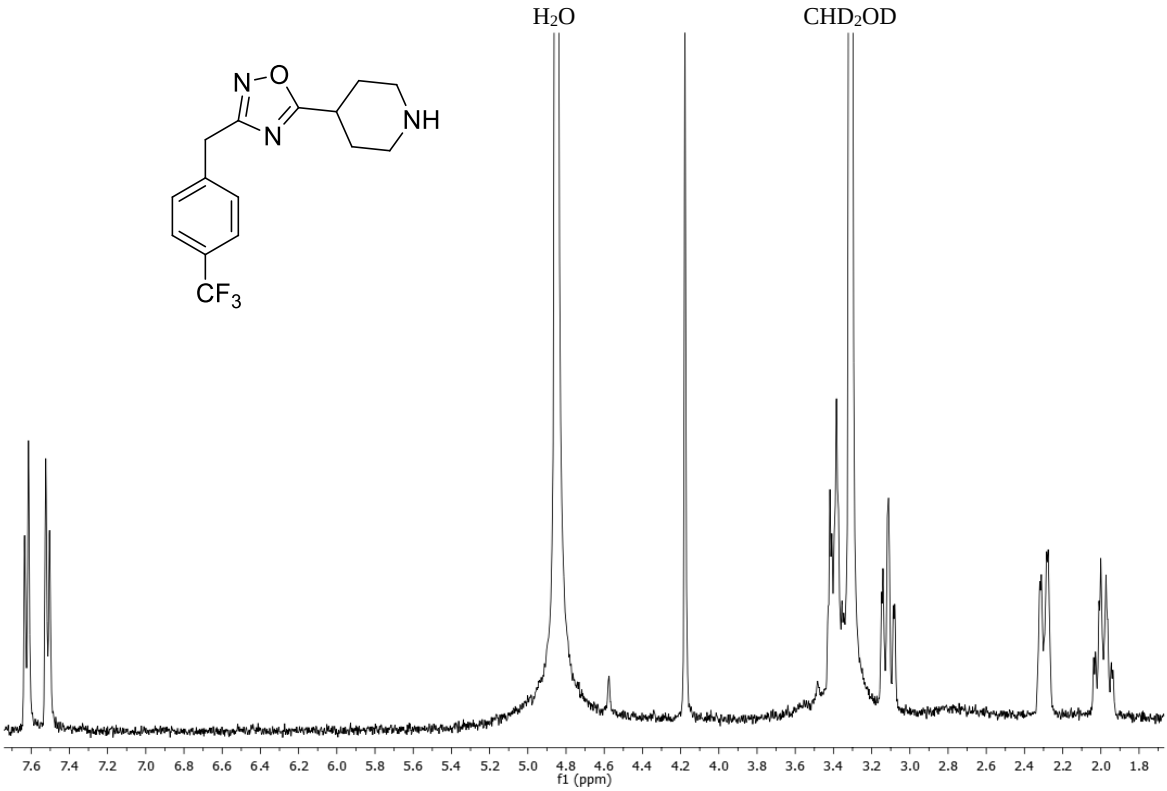


Figure S8. ^{1}H NMR (400 MHz, CD_3OD) of compound **3e**

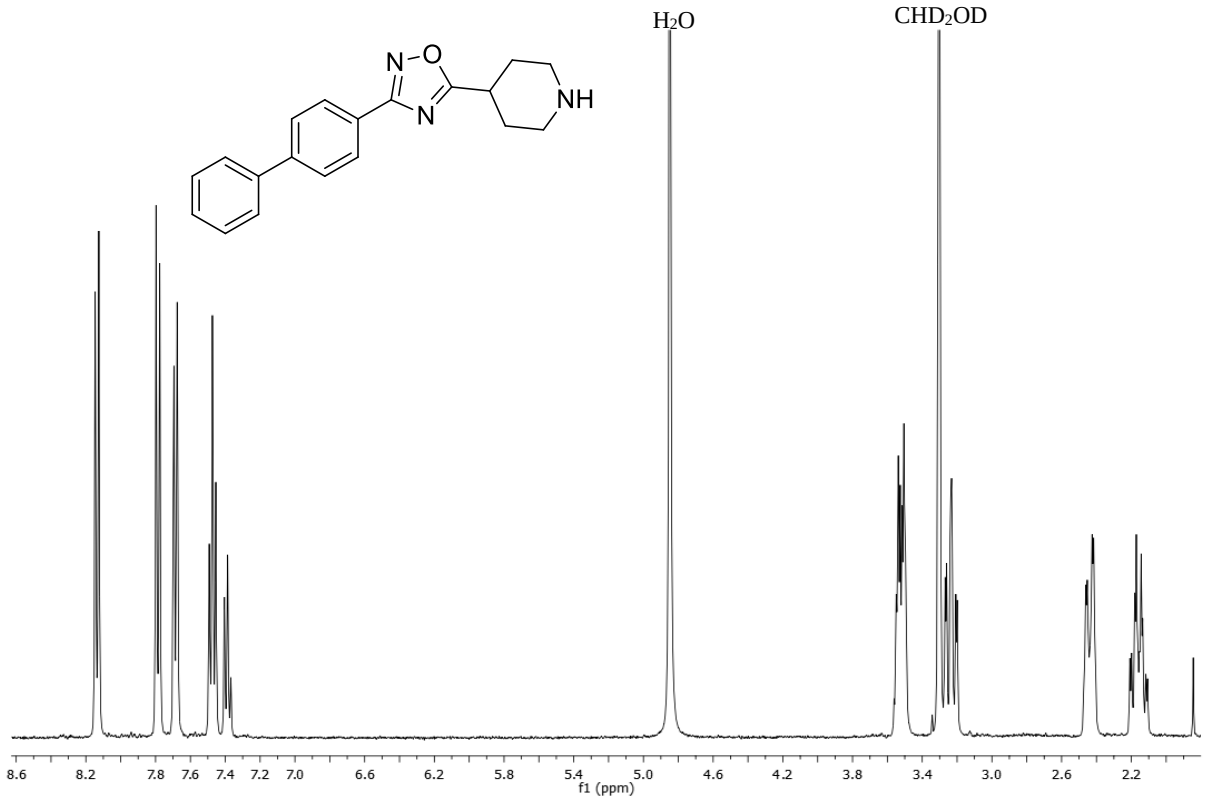


Figure S9. ^{1}H NMR (400 MHz, CD_3OD) of compound **3f**

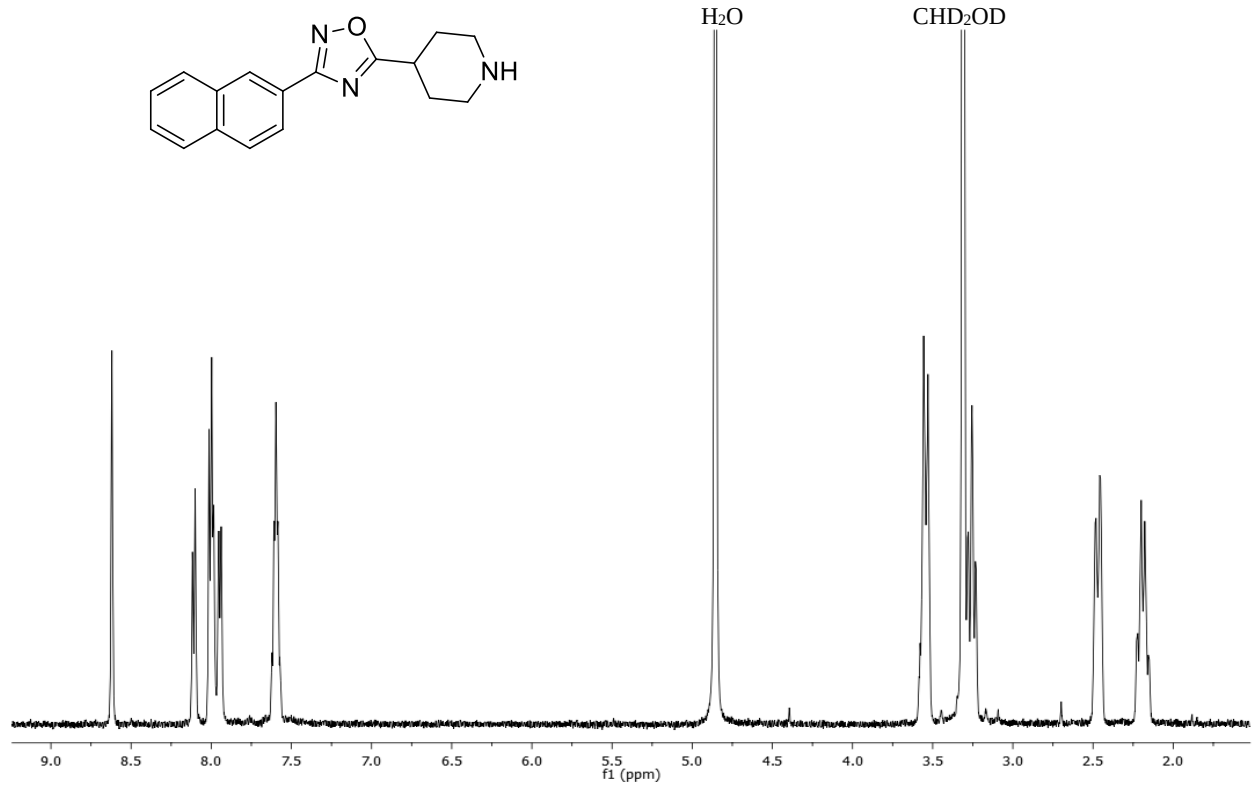


Figure S10. ^{1}H NMR (400 MHz, CD_3OD) of compound **4**

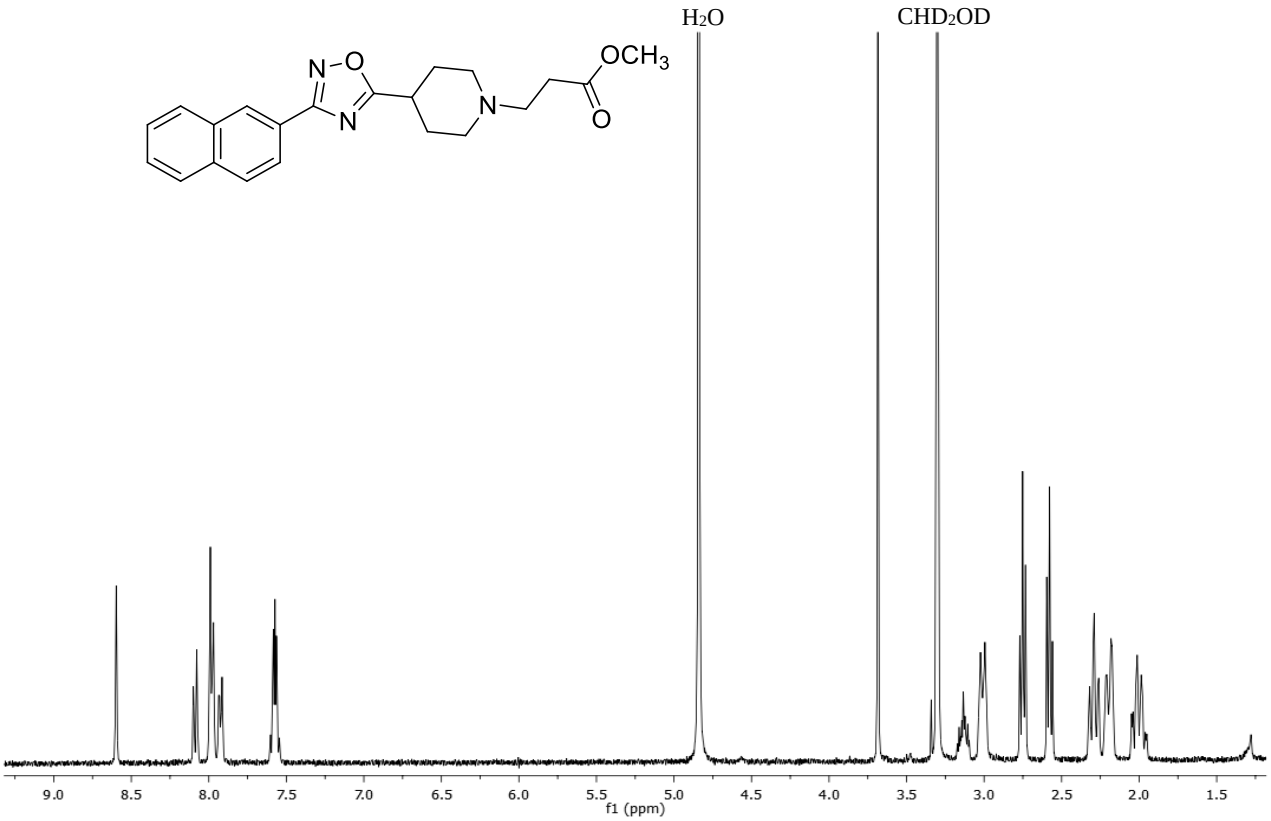


Figure S11. ^{1}H NMR (500 MHz, CD_3OD) of compound **5**

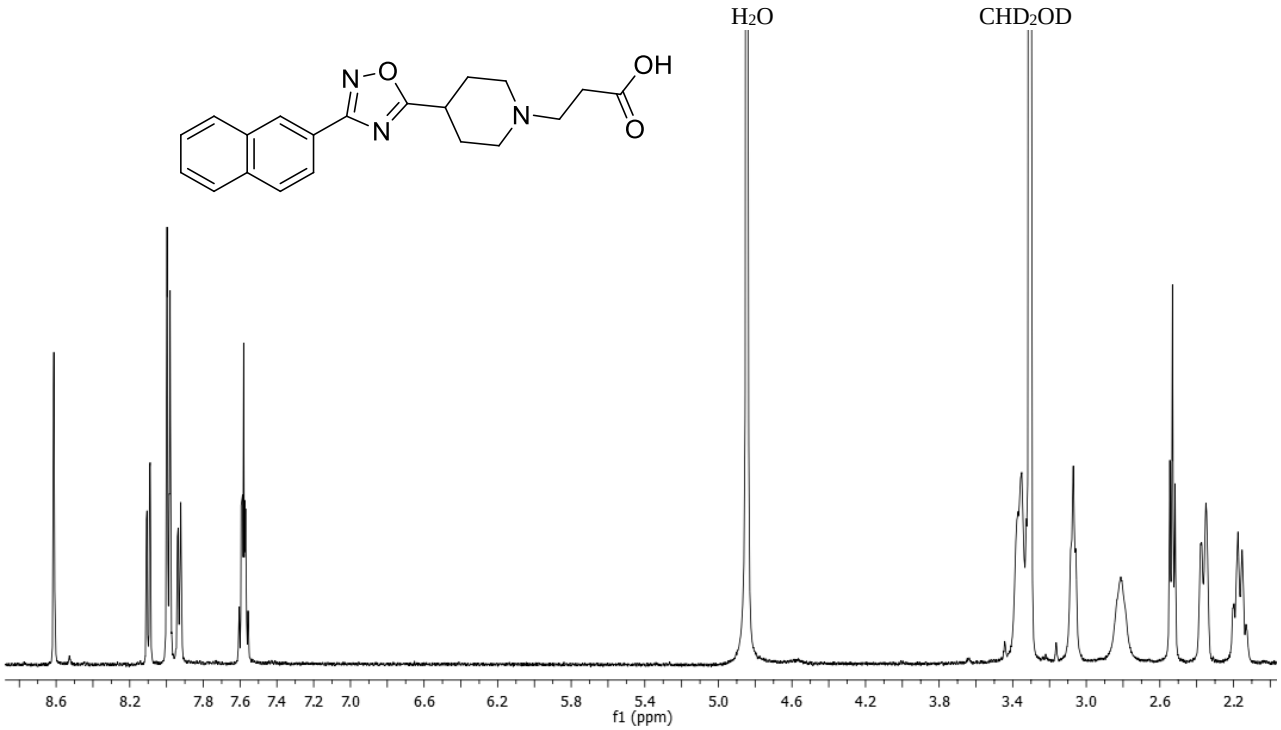


Figure S12. ^{1}H NMR (500 MHz, CD_3OD) of compound **6**

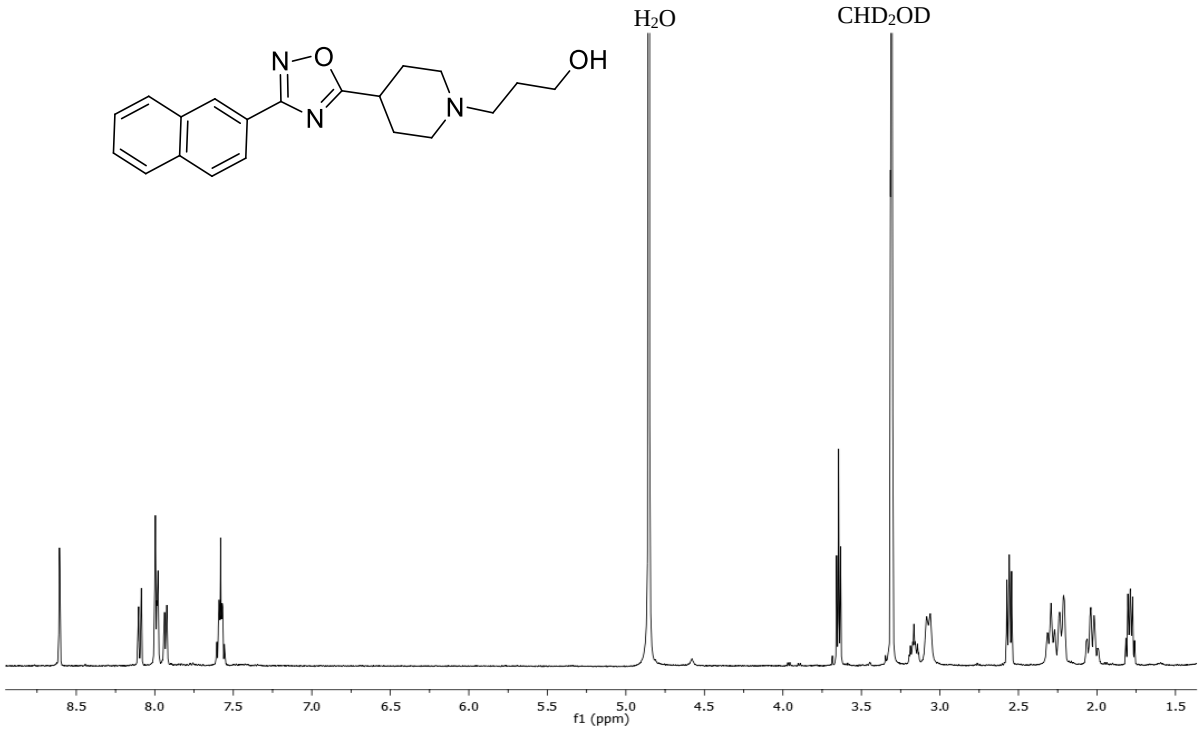


Figure S13. ^{1}H NMR (400 MHz, CD_3OD) of compound **7**

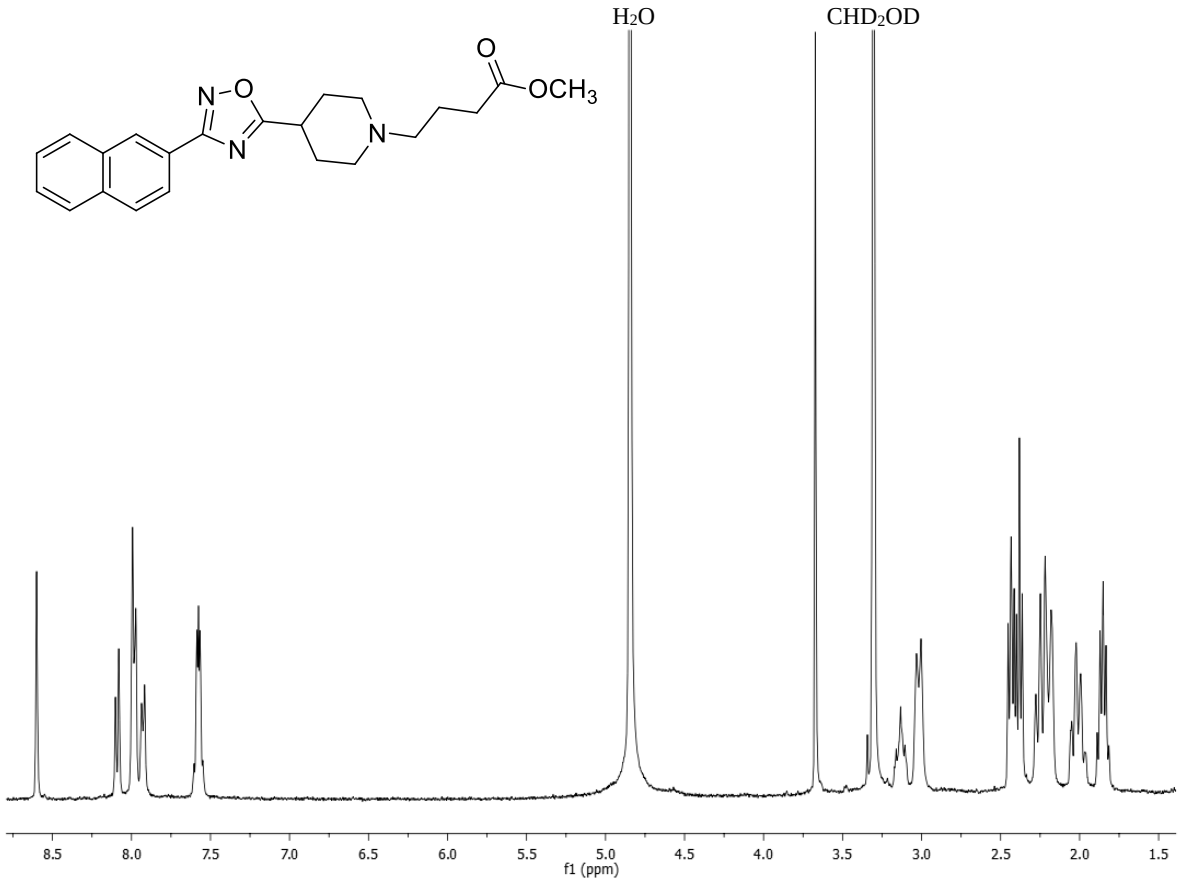


Figure S14. ^{1}H NMR (400 MHz, CD_3OD) of compound **8**

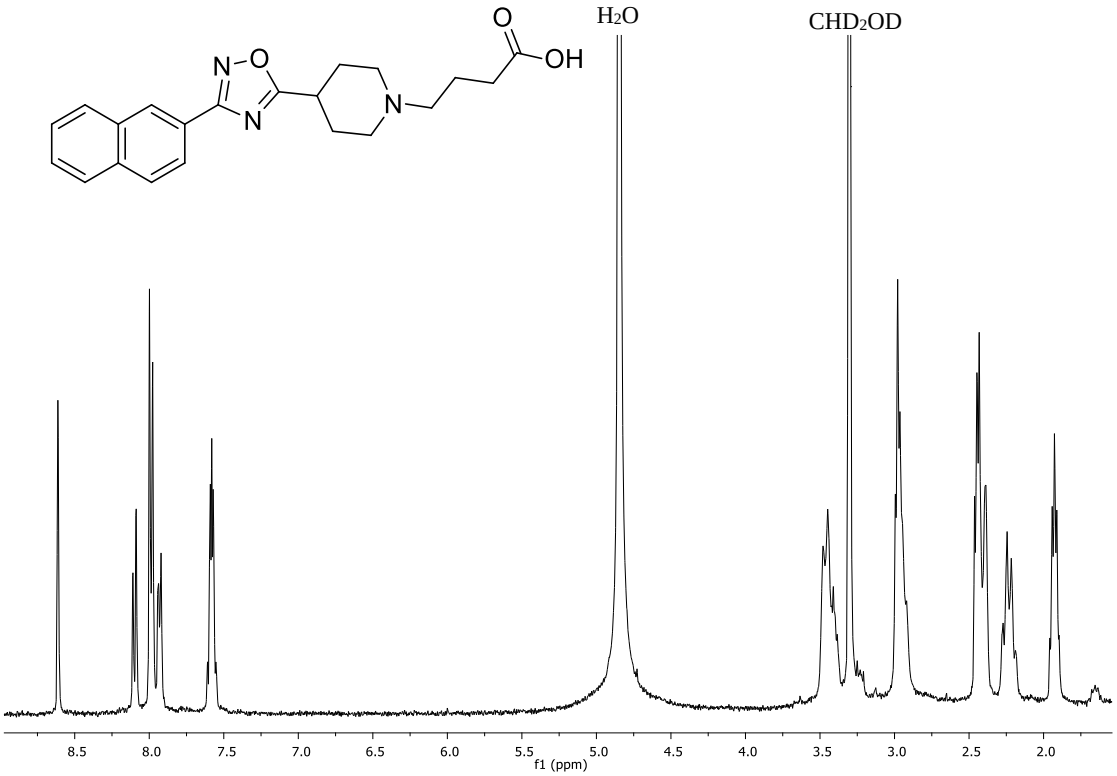


Figure S15. ^{1}H NMR (400 MHz, CD_3OD) of compound **9**

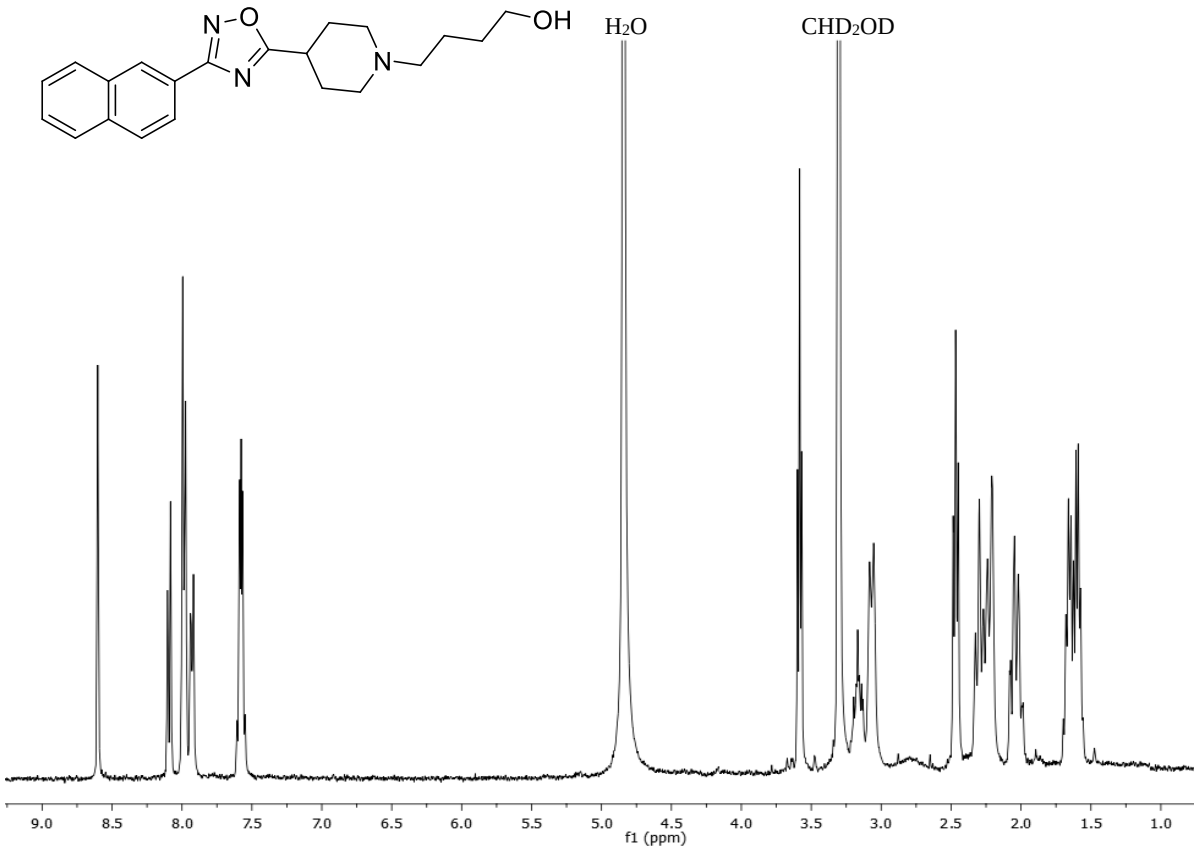


Figure S16. ^{1}H NMR (500 MHz, CD_3OD) of compound **10**

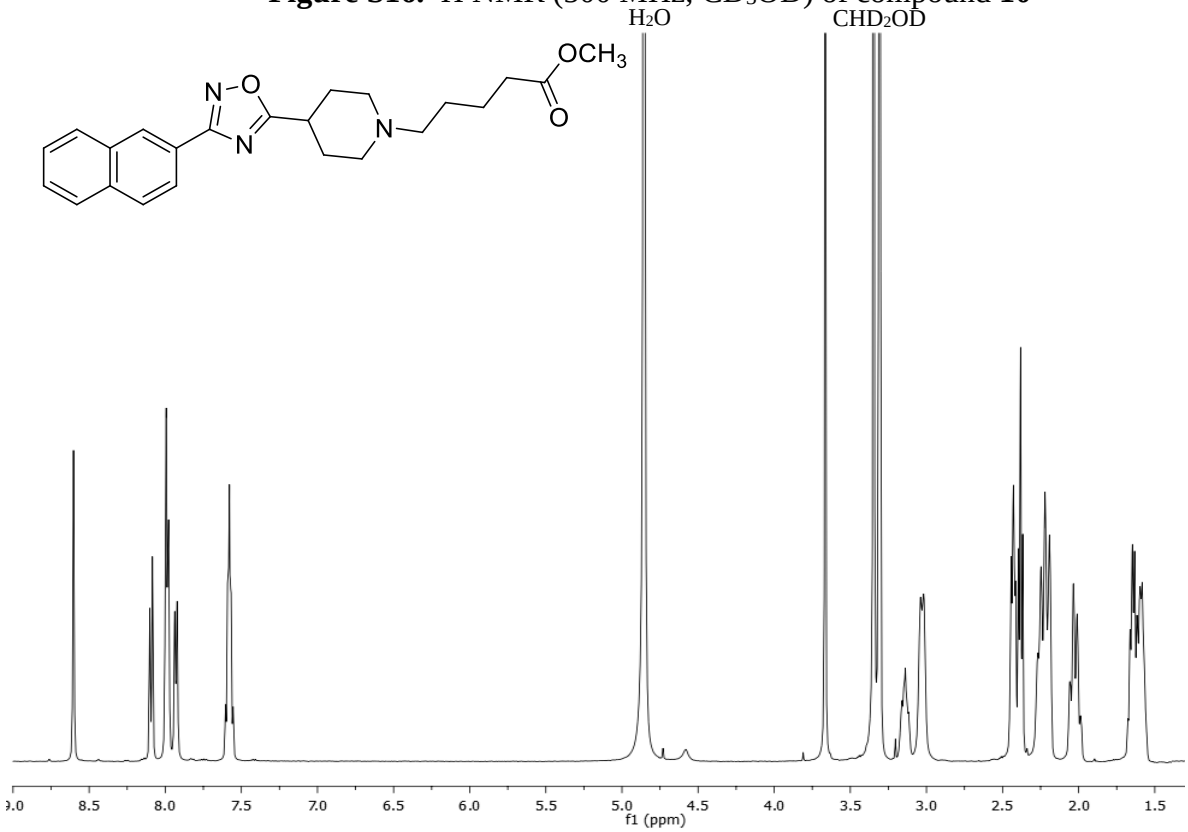


Figure S17. ^{1}H NMR (500 MHz, CD_3OD) of compound **11**

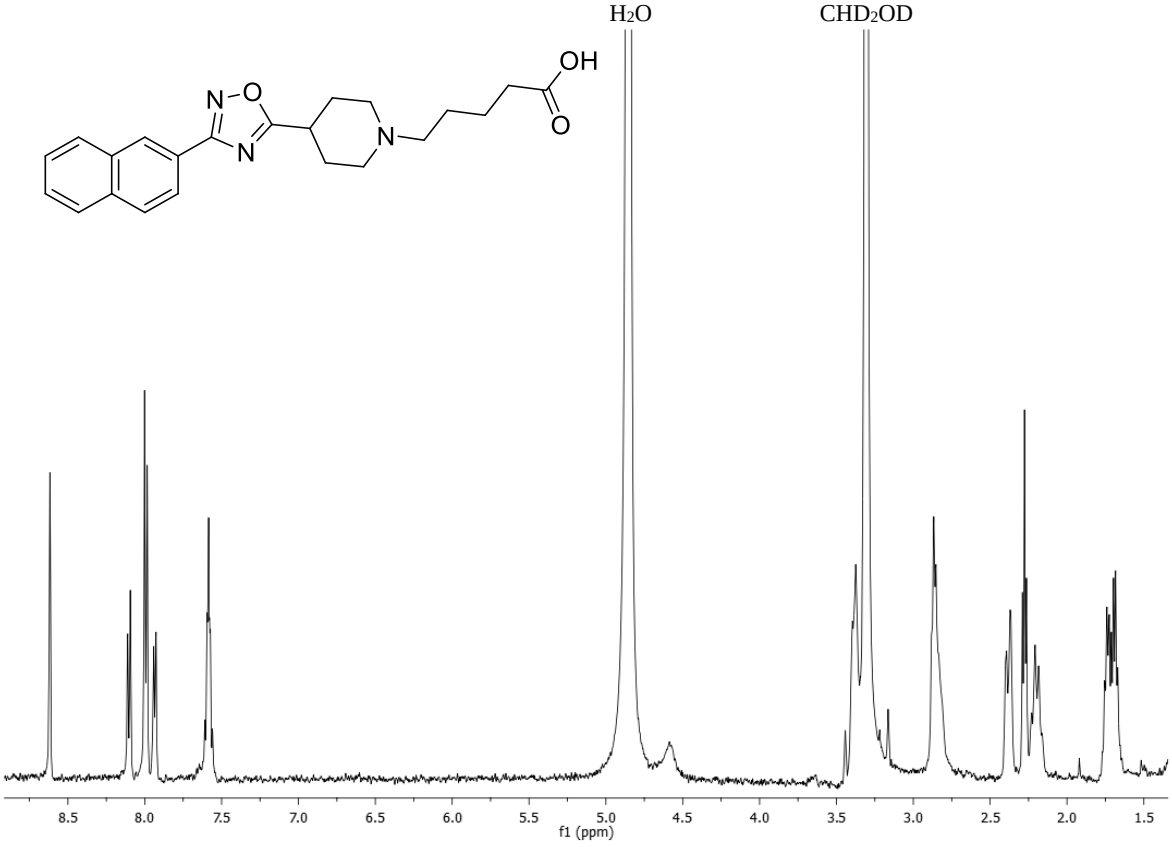


Figure S18. ^{1}H NMR (500 MHz, CD_3OD) of compound **12**

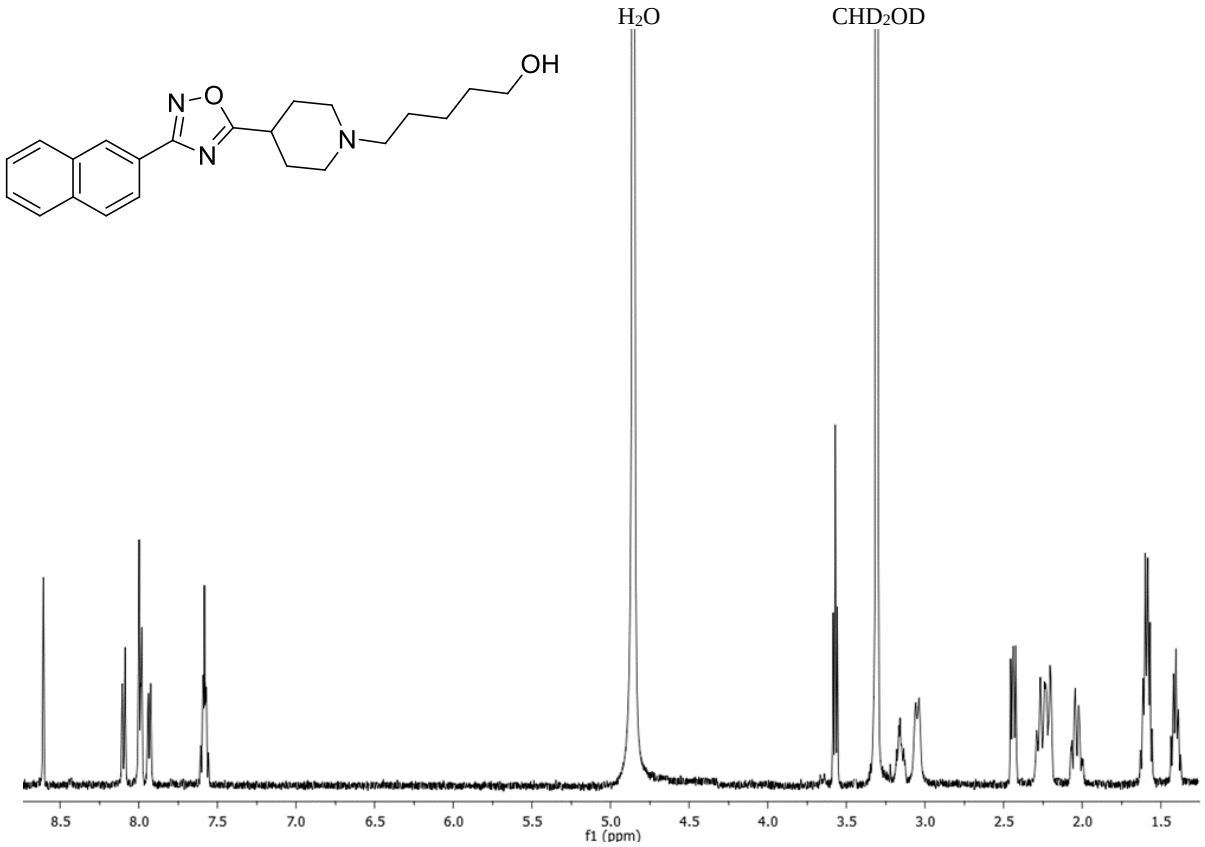


Figure S19. ^{1}H NMR (400 MHz, CD_3OD) of compound **13**

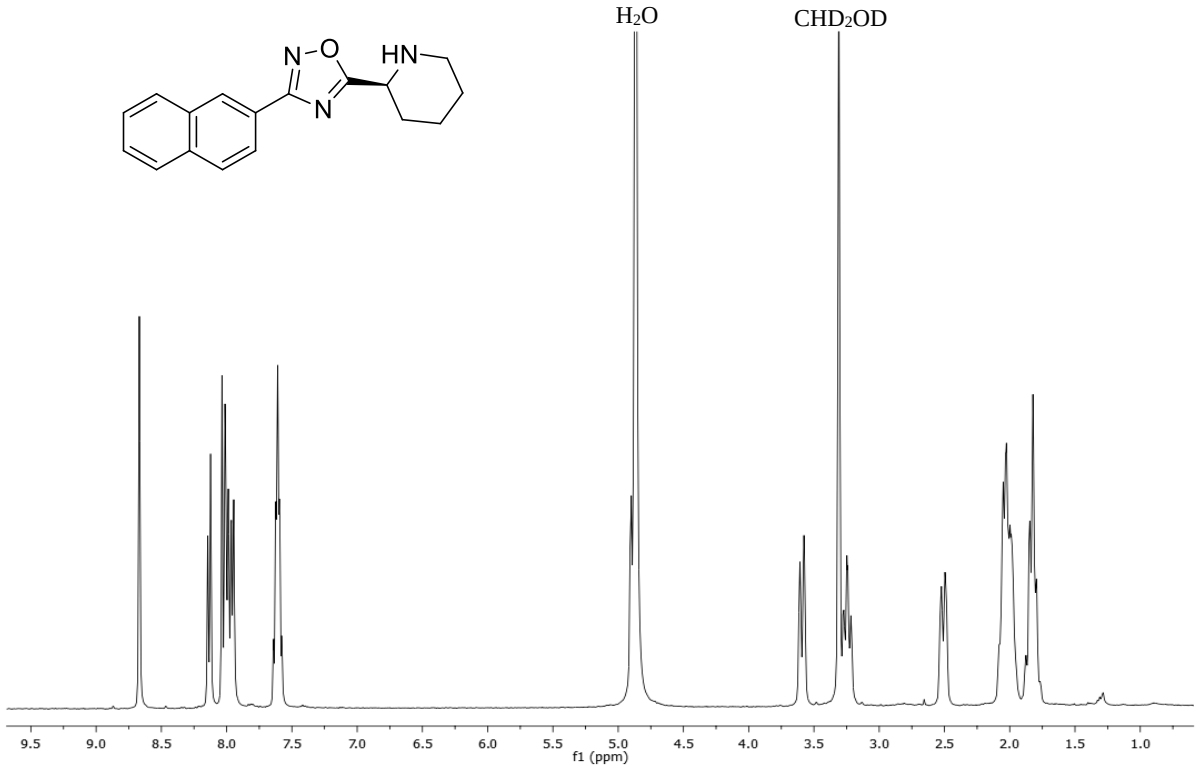


Figure S20. ^{1}H NMR (400 MHz, CD_3OD) of compound **14**

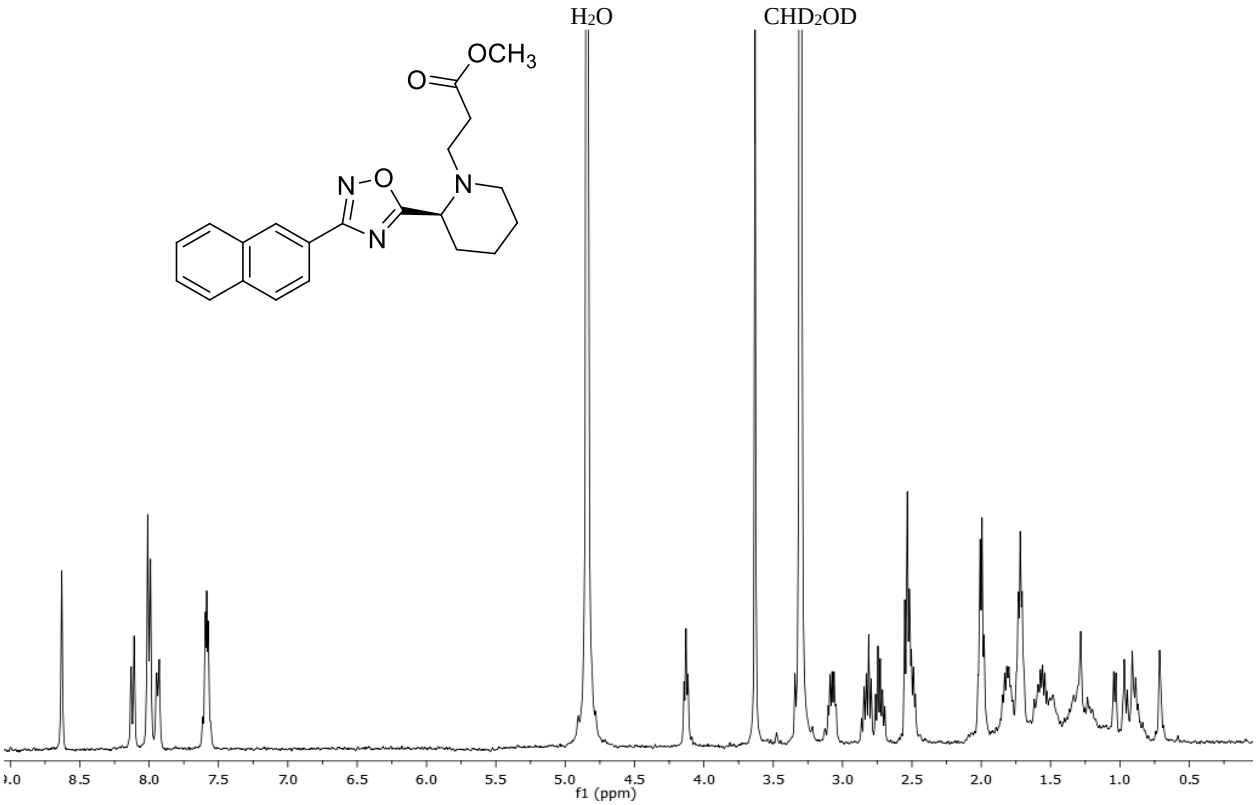


Figure S21. ^{1}H NMR (400 MHz, CD_3OD) of compound **15**

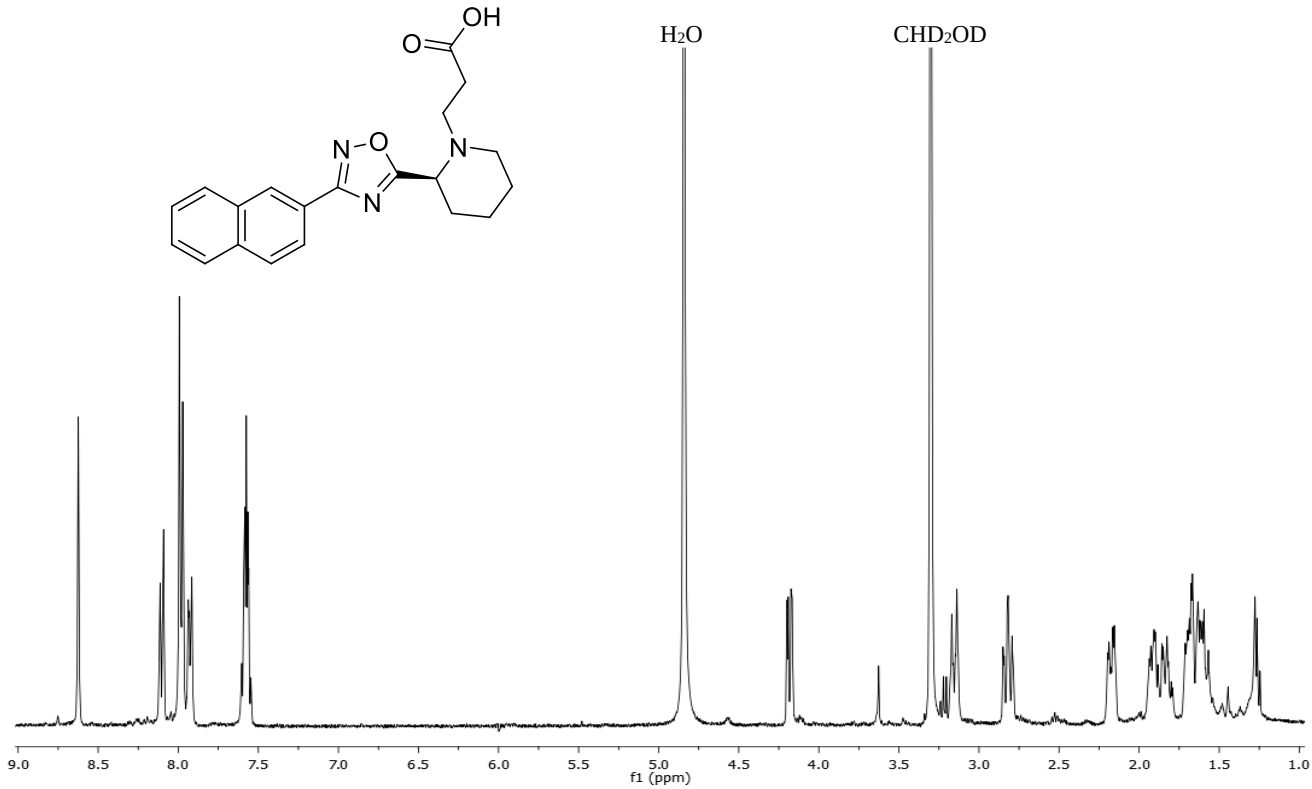


Figure S22. ^{1}H NMR (500 MHz, CD_3OD) of compound **16**

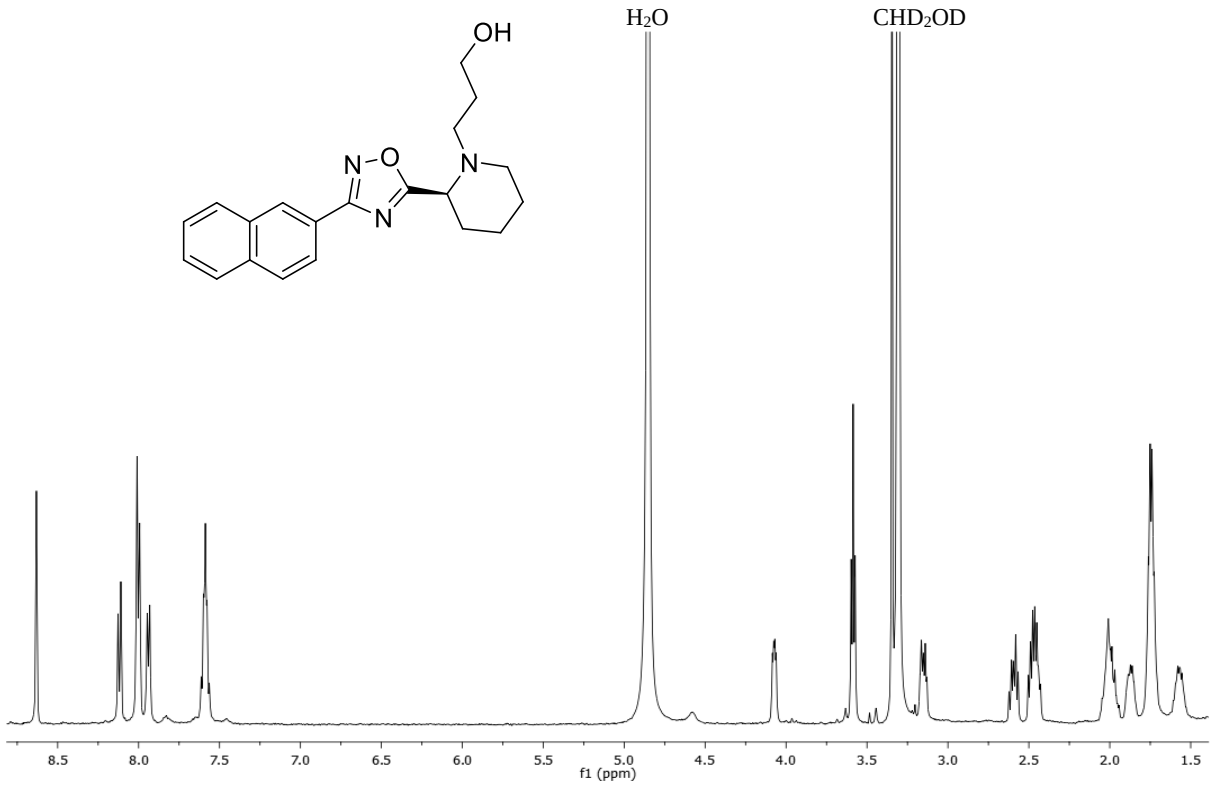


Figure S23. ^{1}H NMR (400 MHz, CD_3OD) of compound **17**

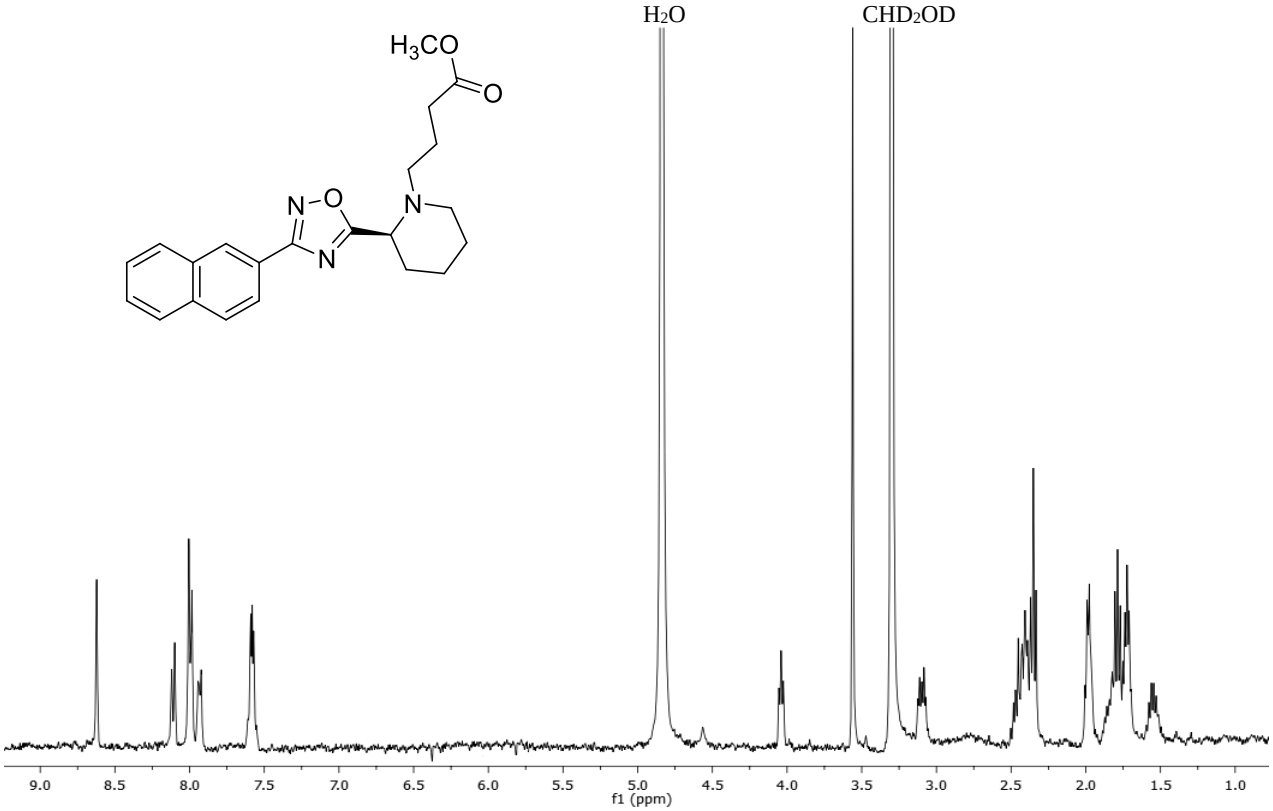


Figure S24. ^{1}H NMR (500 MHz, CD_3OD) of compound **18**

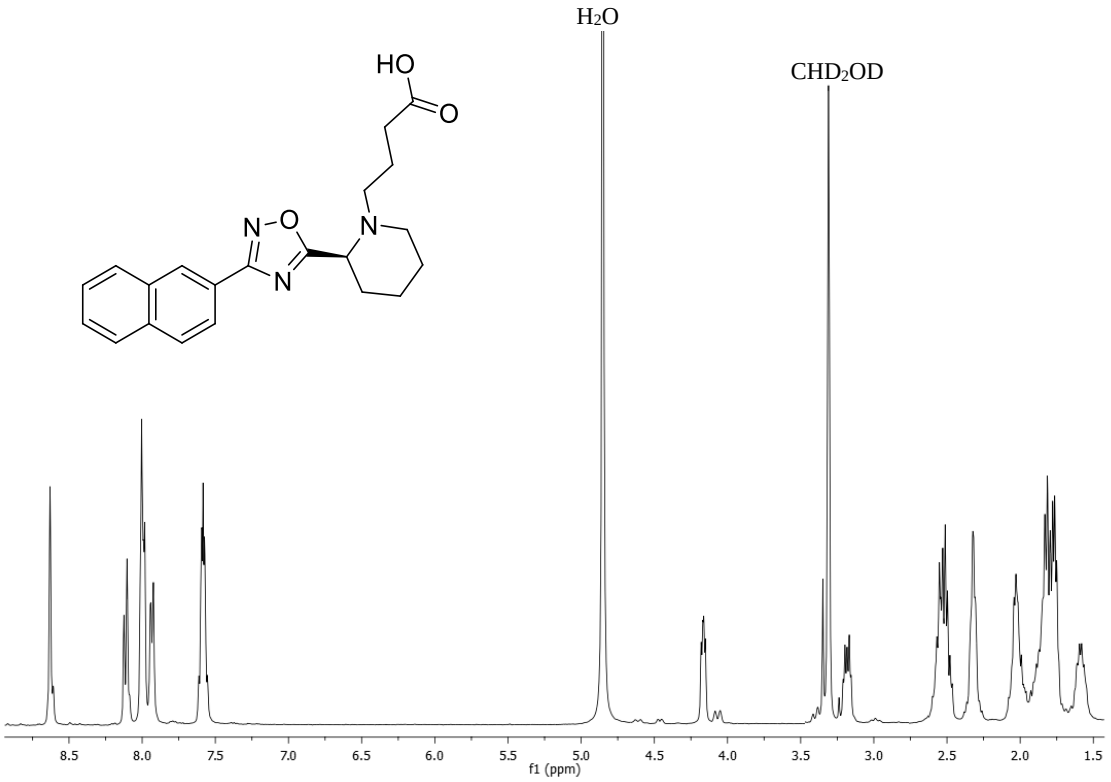


Figure S25. ^{1}H NMR (500 MHz, CD_3OD) of compound **19**

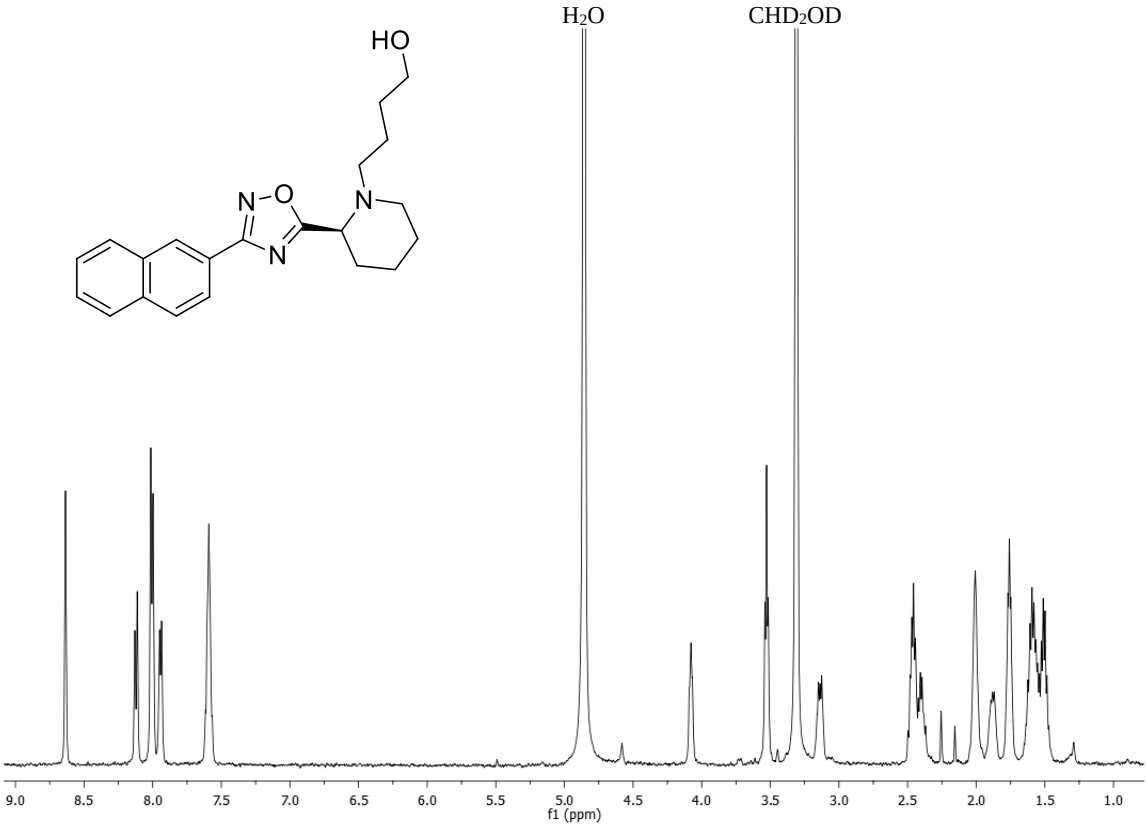


Figure S26. ^{1}H NMR (500 MHz, CD_3OD) of compound **20**

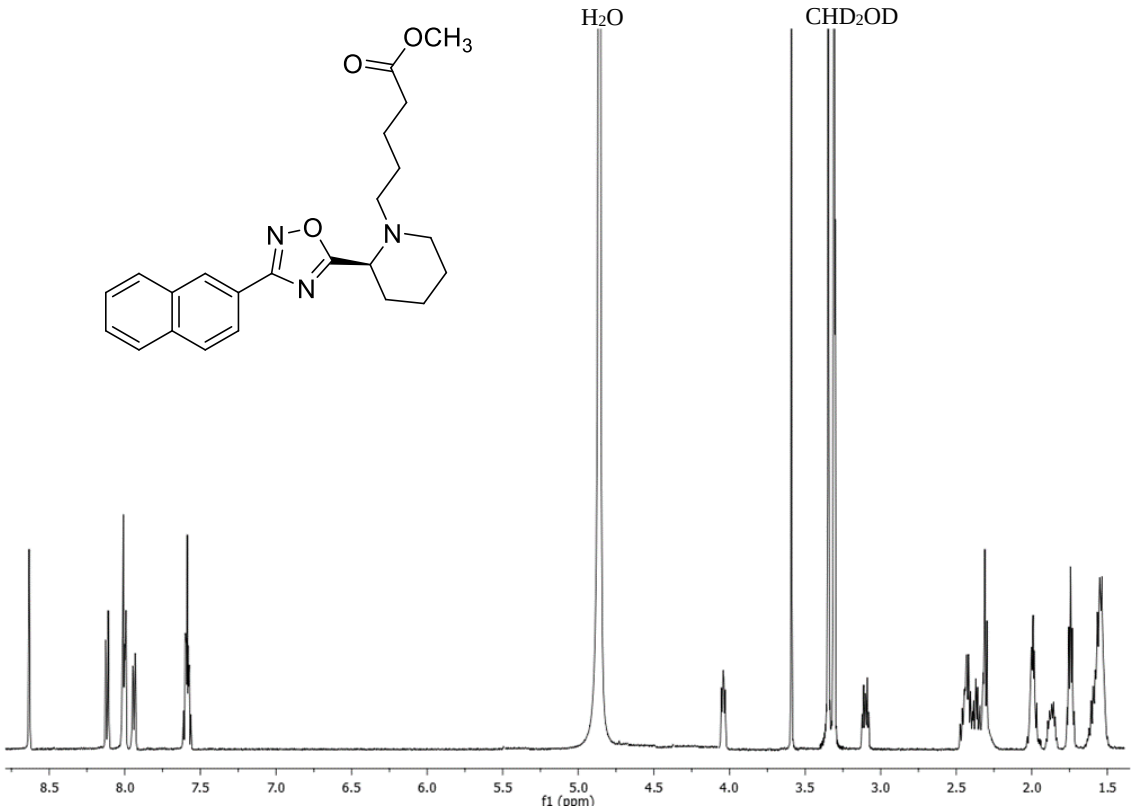


Figure S27. ^{1}H NMR (500 MHz, CD_3OD) of compound **21**

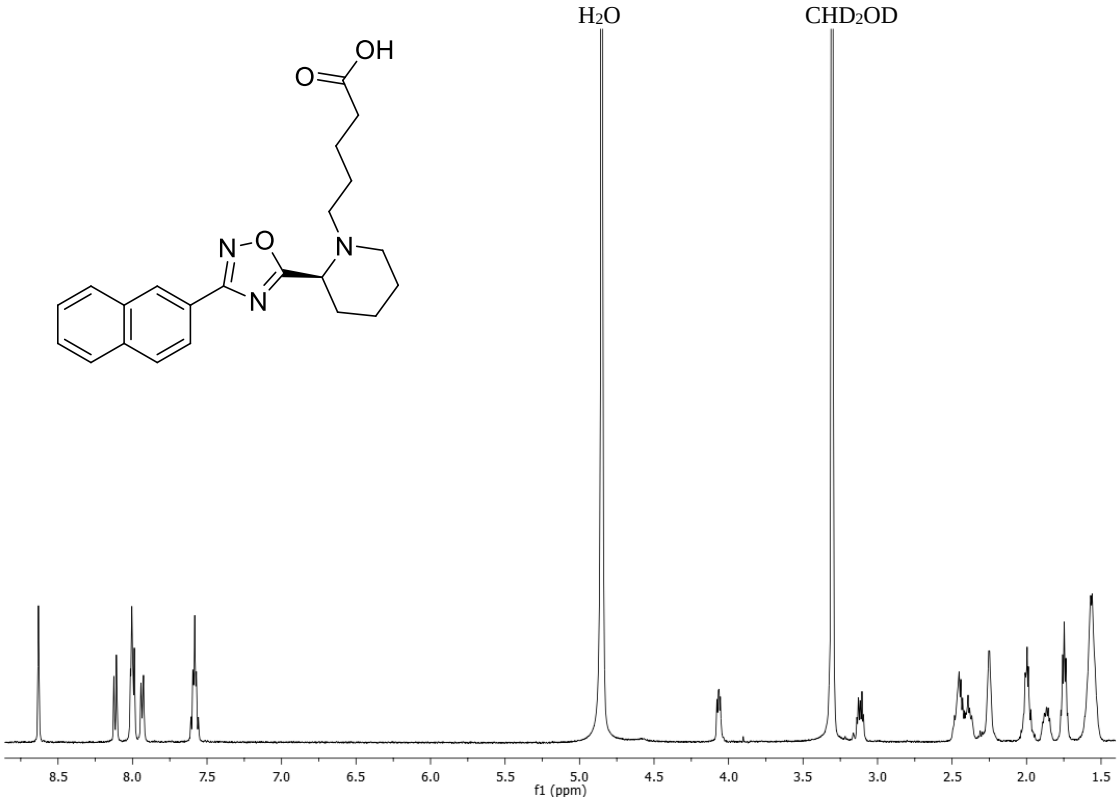


Figure S28. ^{1}H NMR (500 MHz, CD_3OD) of compound **22**

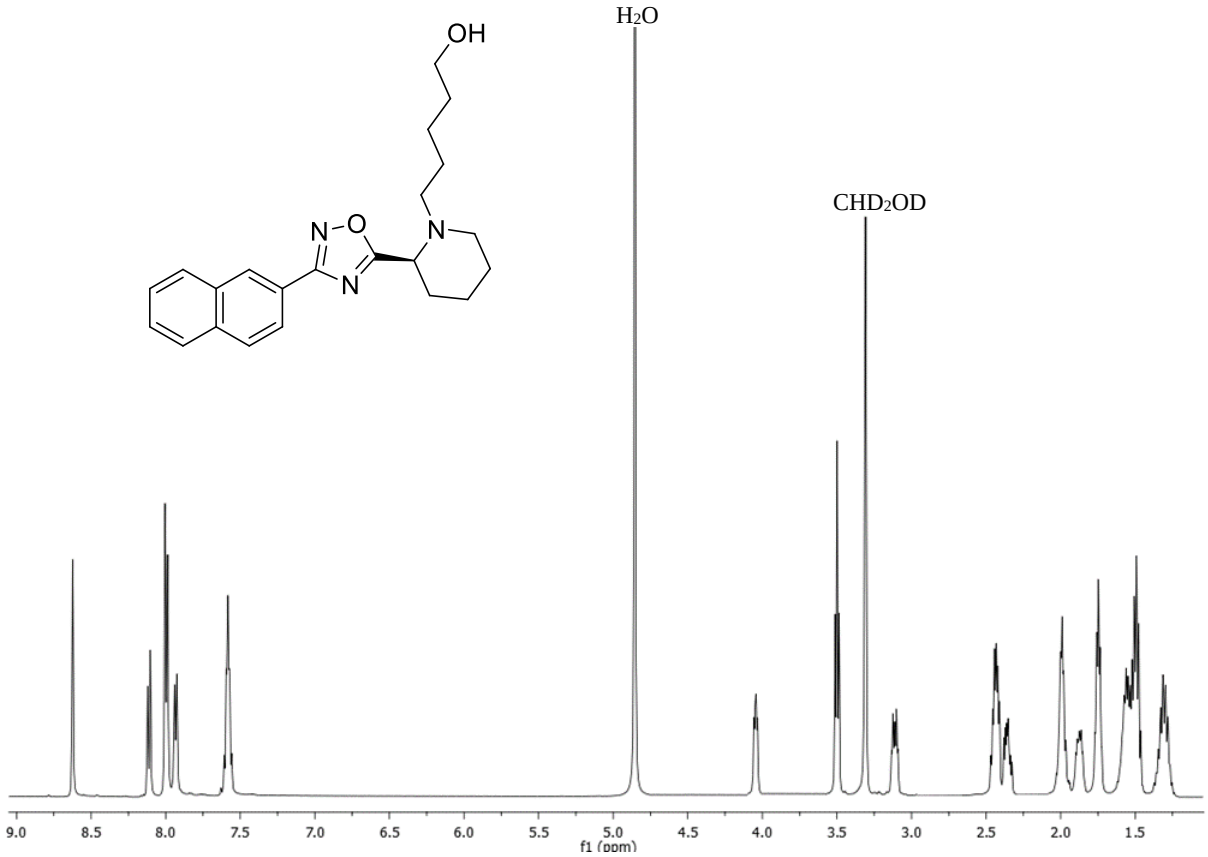


Figure S29. ^{1}H NMR (400 MHz, CD_3OD) of compound **23**

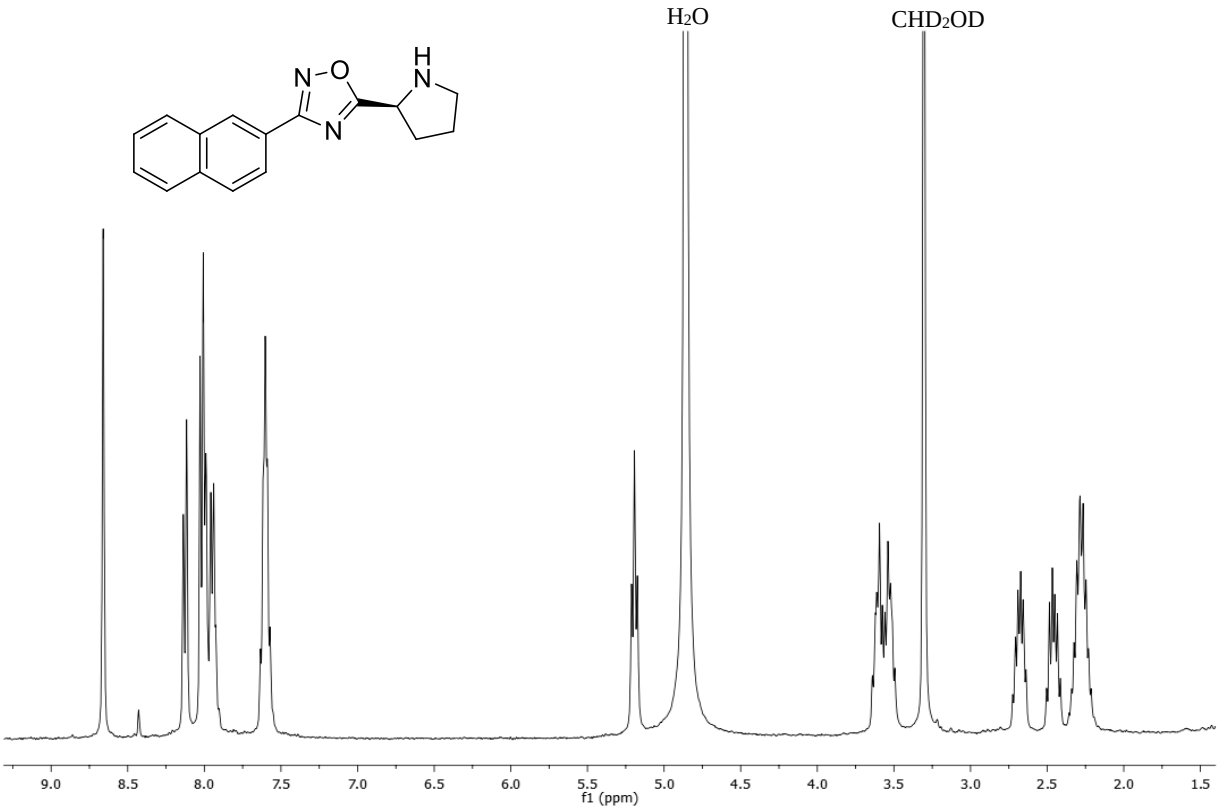


Figure S30. ^{1}H NMR (400 MHz, CD_3OD) of compound **24**

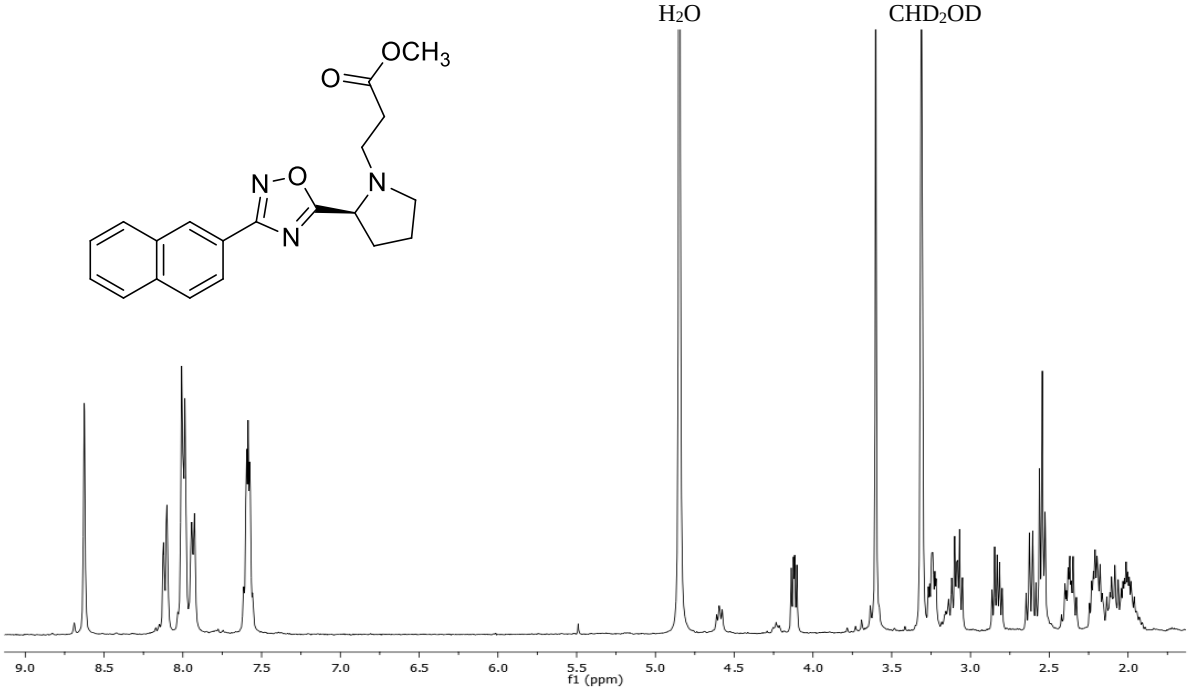


Figure S31. ^{1}H NMR (400 MHz, CD_3OD) of compound **25**

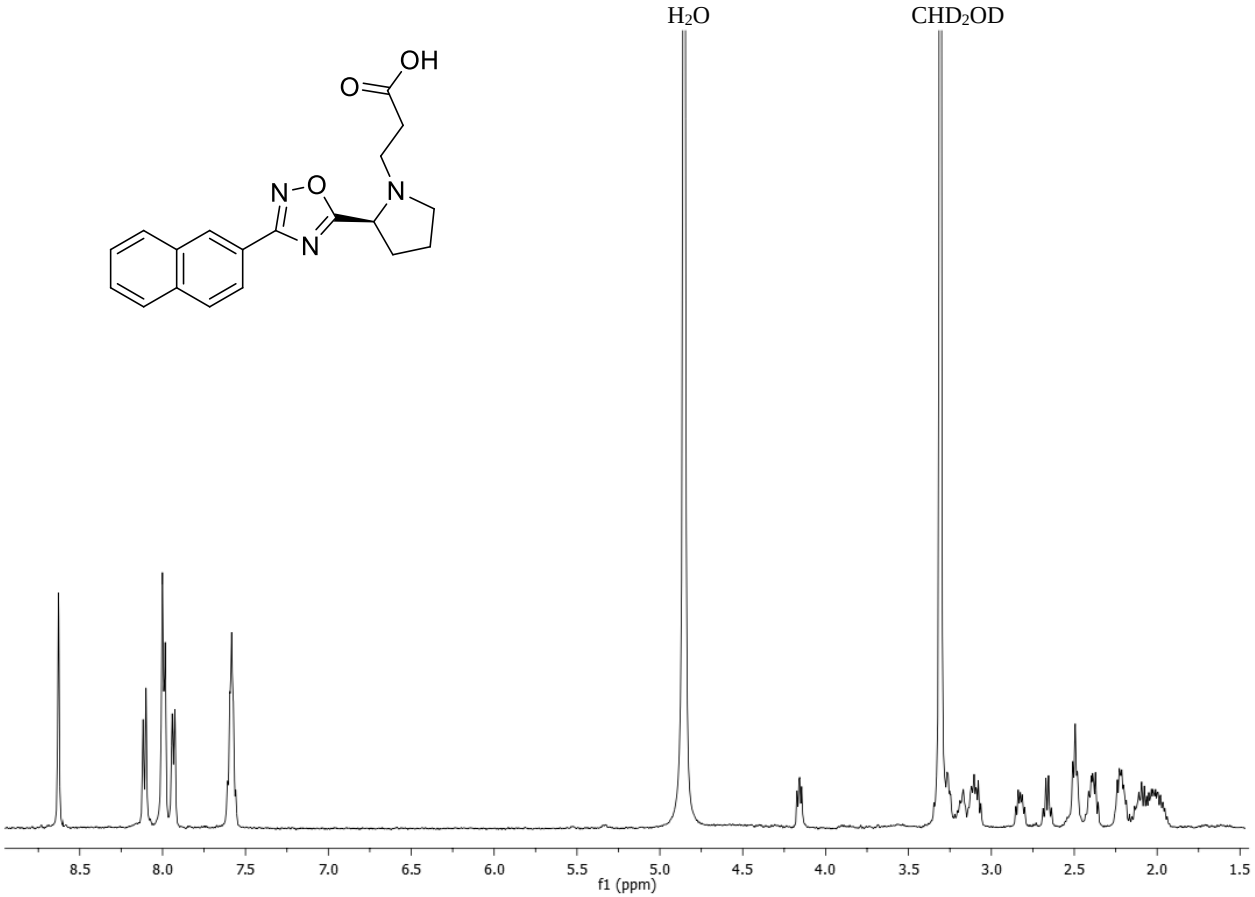


Figure S32. ^{1}H NMR (400 MHz, CD_3OD) of compound **26**

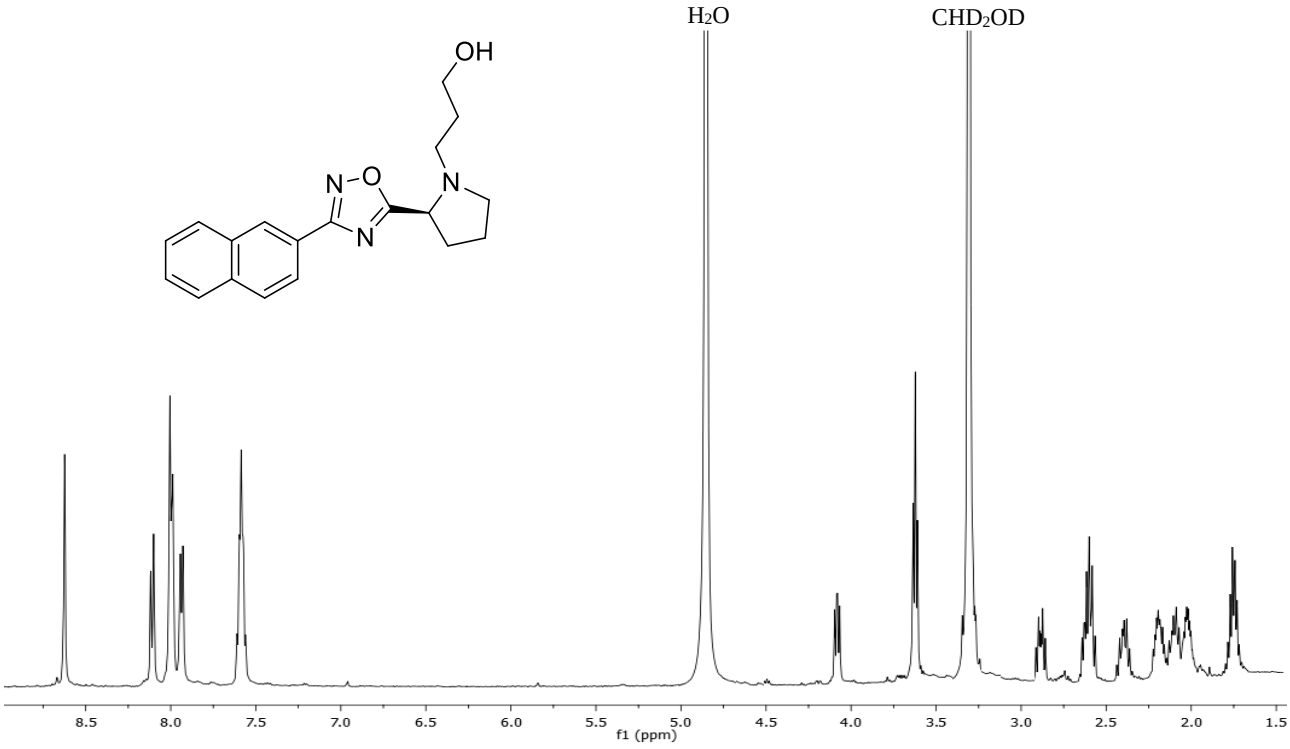


Figure S33. ^{1}H NMR (400 MHz, CD_3OD) of compound **27**

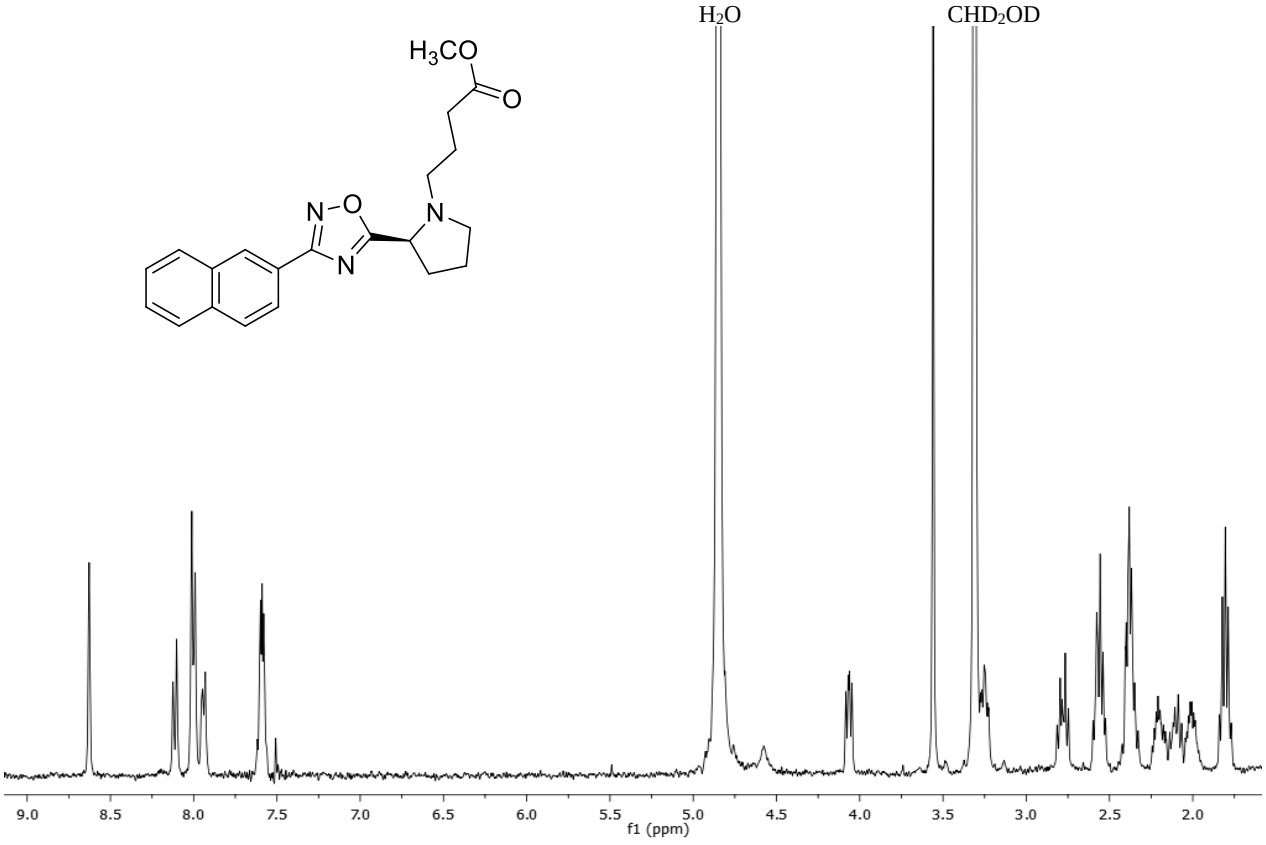


Figure S34. ^{1}H NMR (500 MHz, CD_3OD) of compound **28**

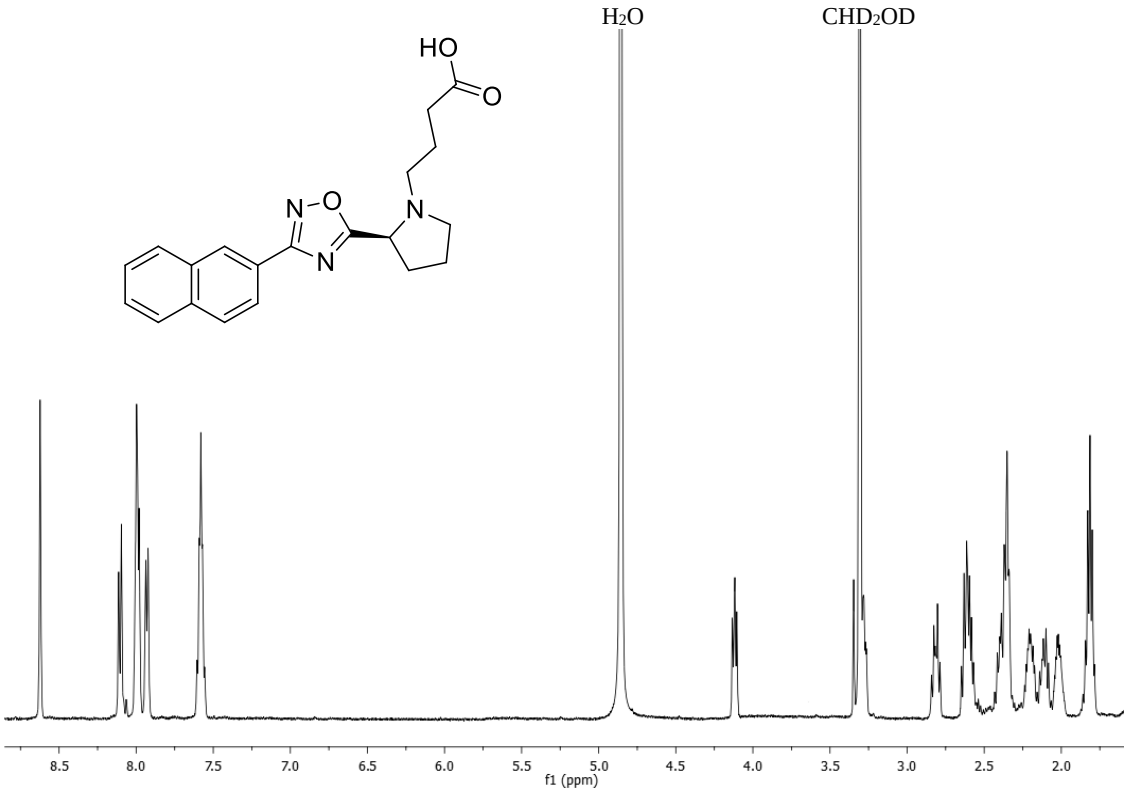


Figure S35. ^{1}H NMR (500 MHz, CD_3OD) of compound **29**

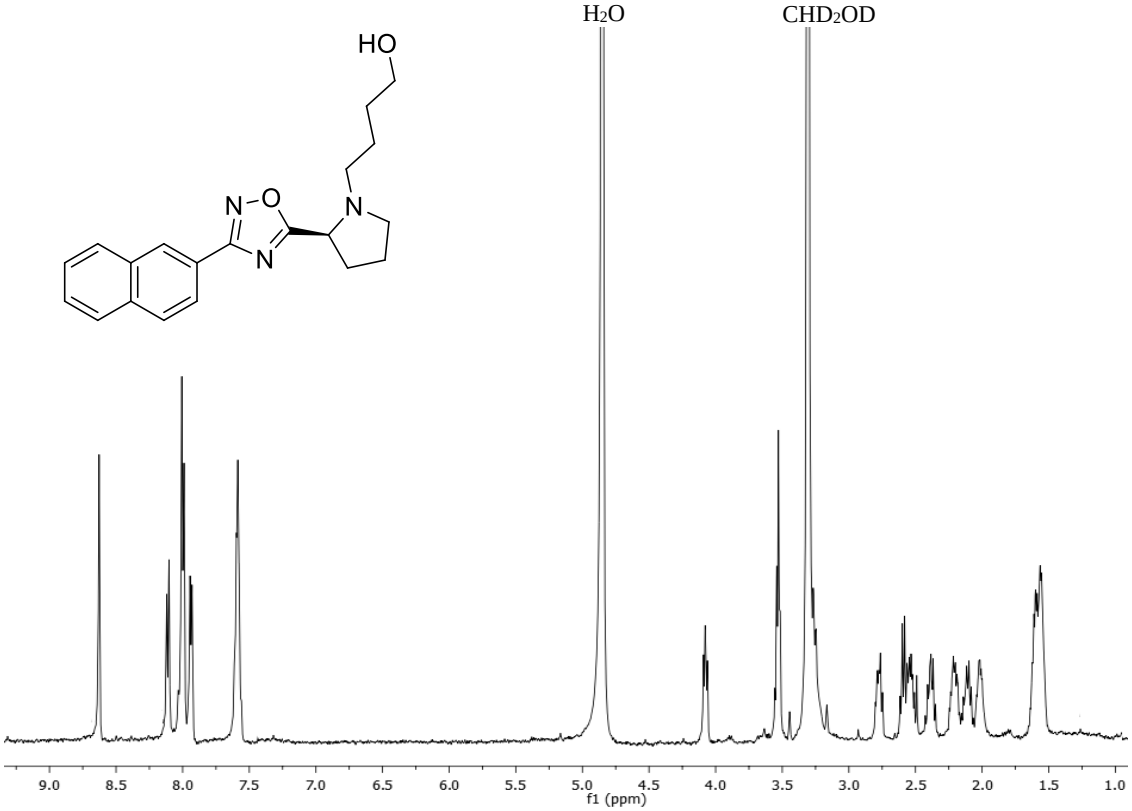


Figure S36. ^{1}H NMR (500 MHz, CD_3OD) of compound **30**

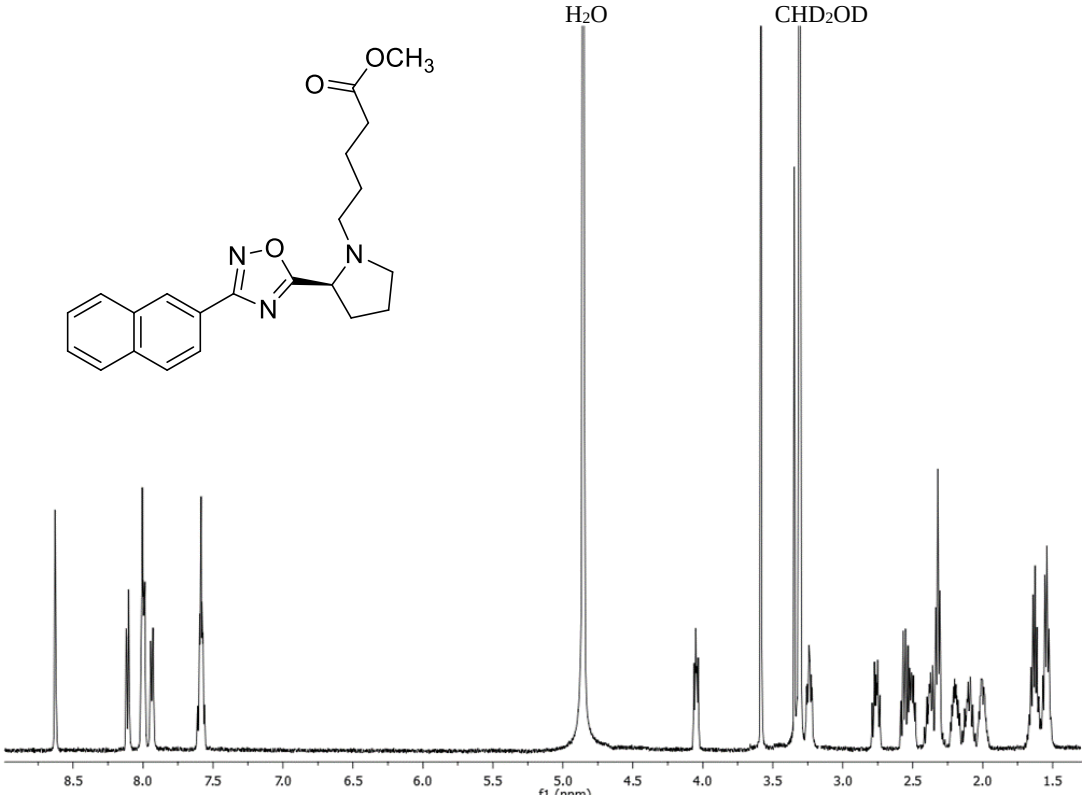


Figure S37. ^{1}H NMR (500 MHz, CD_3OD) of compound **31**

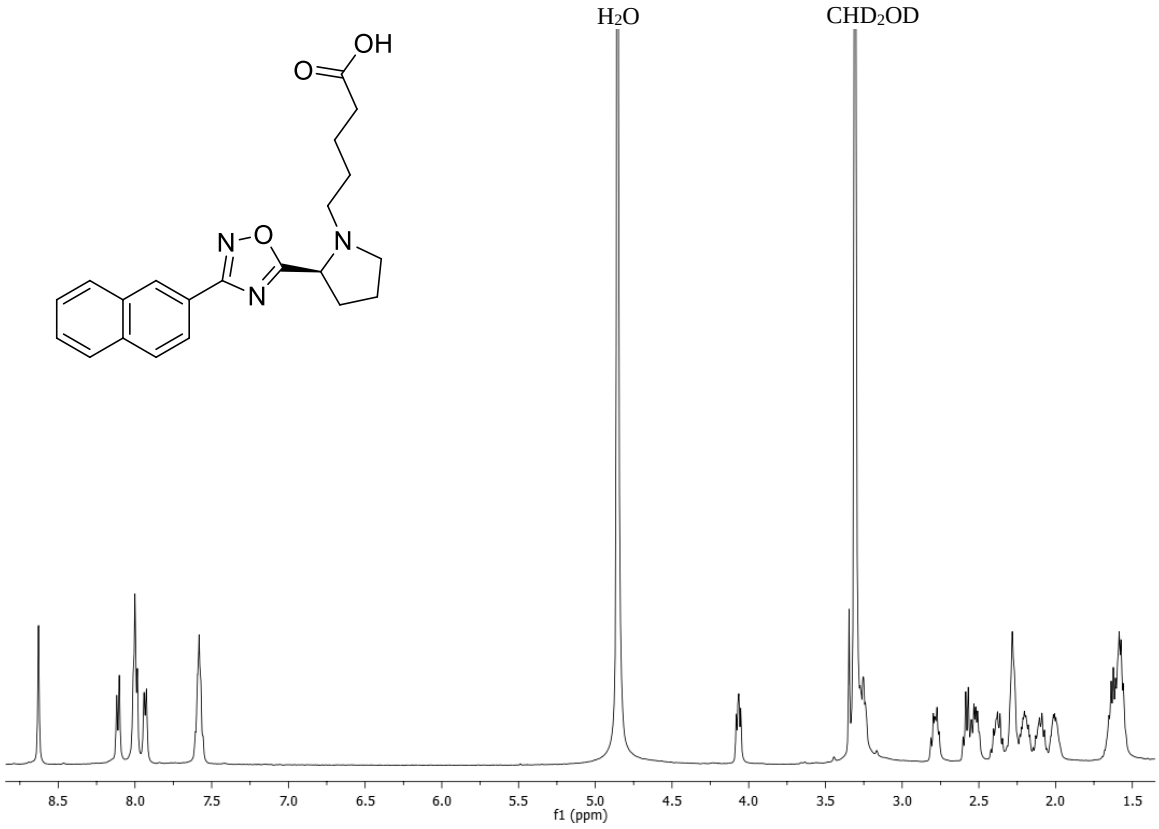
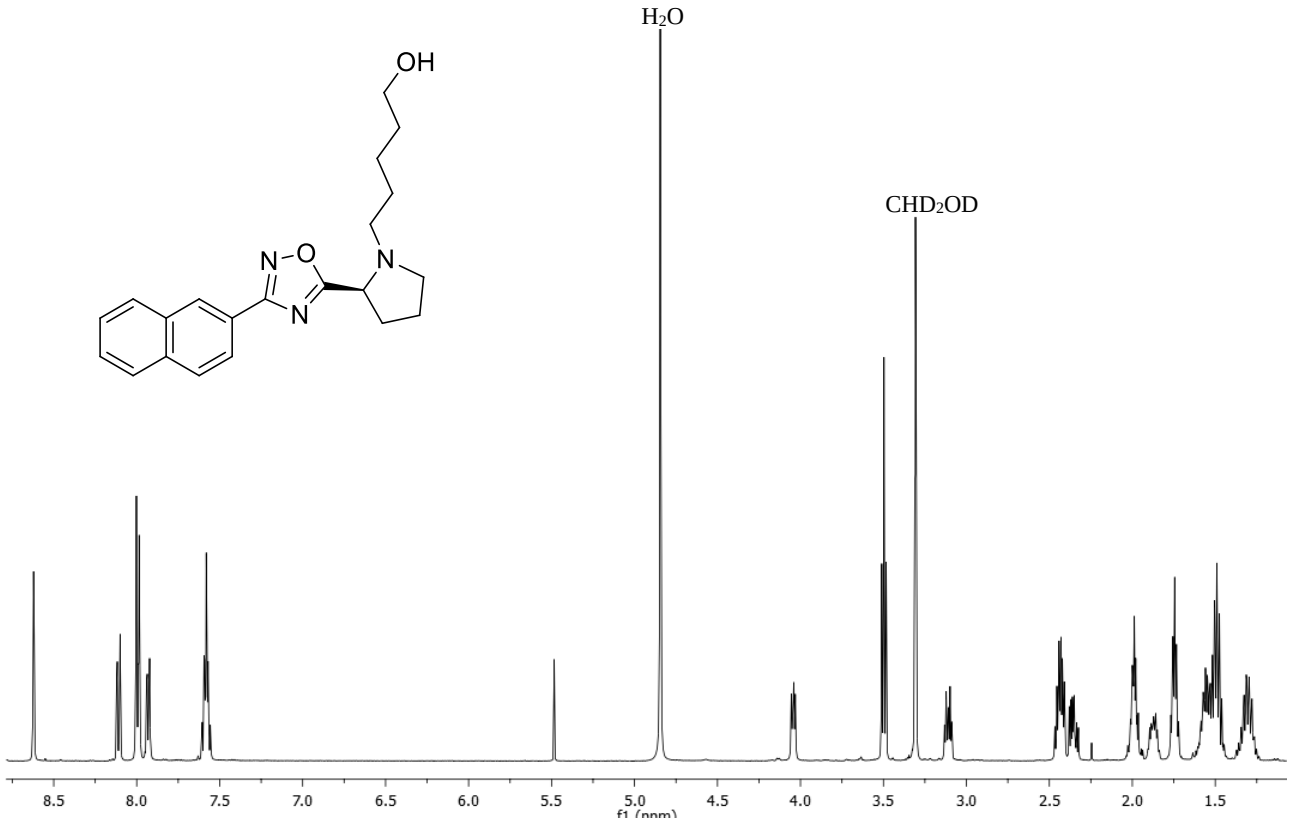


Figure S38. ^{1}H NMR (500 MHz, CD_3OD) of compound **32**



(1) Miele, E.; Valente, S.; Alfano, V.; Silvano, M.; Mellini, P.; Borovika, D.; Marrocco, B.; Po, A.; Besharat, Z.; Catanzaro, G.; Battaglia, G.; Abballe, L.; Zwergel, C.; Stazi, G.; Milite, C.; Castellano, S.; Tafani, M.; Trapencieris, P.; Mai, A.; Ferretti, E.; The histone methyltransferase EZH2 as a druggable target in SHH medulloblastoma cancer stem cells. *Oncotarget.* **2017**, *40*, 68557-68570.
(2) Glide, Schrödinger, LLC, New York, NY, **2018**.
(3) Xu, X.; Xu, X.; Liu, P.; Zhu, Z. Y.; Chen, J.; Fu, H. A.; Chen, L. L.; Hu, L. H.; Shen, X. Structural Basis for Small Molecule NDB (*N*-Benzyl-*N*-(3-(tert-butyl)-4-hydroxyphenyl)-2,6-dichloro-4-(dimethylamino) Benzamide) as a Selective Antagonist of Farnesoid X Receptor α (FXR α) in Stabilizing the Homodimerization of the Receptor *J. Biol. Chem.* **2015**, *290*, 19888-19899.
(4) Maestro, Schrödinger, LLC, New York, NY, **2018**.
(5) (a) Greenwood, J. R.; Calkins, D.; Sullivan, A. P.; Shelley, J. C. Towards the comprehensive, rapid, and accurate prediction of the favorable tautomeric states of drug-like molecules in aqueous solution. *J. Comput. Aided Mol. Des.* **2010**, *24*, 591-604; (b) Shelley, J.C.; Cholleti, A.; Frye, L; Greenwood, J.R.; Timlin, M.R.; Uchimaya, M. Epik: a software program for pKa prediction and protonation state generation for drug-like molecules. *J. Comp.-Aided Mol. Design* **2007**, *21*, 681-691.
(6) LigPrep, Schrödinger, LLC, New York, NY, **2018**.
(7) Harder, E.; Damm, W.; Maple, J.; Wu, C.; Reboul, M.; Xiang, J. Y.; Wang, L.; Lupyan, D.; Dahlgren, M. K.; Knight, J. L.; Kaus, J. W.; Cerutti, D. S.; Krilov, G.; Jorgensen, W. L.; Abel, R.; Friesner, R. A. OPLS3: a force field providing broad coverage of drug-like small molecules and proteins. *J. Chem. Theory Comput.* **2016**, *12*, 281-296.
(8) (a) Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *J. Med. Chem.* **2004**, *47*, 1739-1749; (b) Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 2. Enrichment Factors in Database Screening. *J. Med. Chem.* **2004**, *47*, 1750-1759.