Supporting Information

Synthesis and Anticancer Activity of New Hydroxamic Acid Containing 1,4-Benzodiazepines

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General Experimental: Commercially available reagents and anhydrous solvents were used without further purification unless otherwise specified. Tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 (0.2 mm) precoated aluminum foil and visualized with an ethanolic solution of $KMnO_4$ and/or acidic solution of $FeCl_3$. Flash chromatography was performed with silica gel 60 (230–400 mesh) or iron-free silica gel where specified. ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature with the residual solvent peaks as internal standards. The line positions of multiplets are given in ppm (δ) and the coupling constants (*J*) are given as absolute values in Hertz. Infrared spectra were recorded by a FT-IR spectrometer and reported as cm^{-1}. All melting points were recorded uncorrected. High-resolution mass spectra (HRMS) data were obtained as specified.

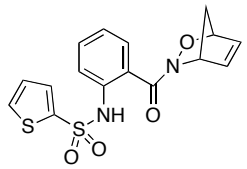
Preparation of Iron-Free Silica Gel:[1]

A slurry of silica gel (200 g) in 10% MeOH/CH_2Cl_2 (500 mL) was transferred to a 600 mL filter funnel with a coarse glass fritted disk. A hot MeOH solution (150 mL) of 3-hydroxy-2-methyl-4-pyrone (15 g) (maltol) was decanted (to remove insoluble solids) and the warm clear solution was added to the pad of silica. The silica gel was washed with 10% MeOH/CH_2Cl_2 (ca. 1.5 L) to elute the maltol-iron complex (orange band). When the filtrate eluted as a clear colorless solution, the silica gel was transferred to a 1L round bottom flask, concentrated to fine white solids, and then placed under vacuum for 18 h to afford iron-free silica gel.

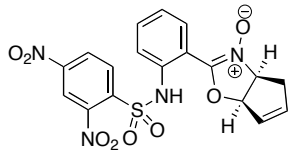
Description of Cellular Assays:

MCF-7 cells and PC-3 cells are both adherent cell lines for the assay. Cells were added to a 96 well microplate and incubated at 37 °C and 5% CO_2 for 24 h to allow the cells to adhere. They were then treated with a 20 μM concentration of each sample in 0.5% DMSO. After 72 h incubation with sample compound, the media was removed from the cells and the cells were fixed with a solution of glutaraldehyde. Cells were stained with crystal violet, washed and air dried. The stain was eluted with a solution of Triton-X-100. Optical density was measured at 595 nm. Compounds that had over 50% inhibition at 20 μM were then assayed at 8 different concentrations to estimate an IC_{50}. Trichostatin A was used as the positive control.

[1] Adapted from a procedure provided by Professor Seth M. Cohen (Department of Chemistry and Biochemistry, University of California, San Diego)



(±)-*N*-(2-((1*S,4*R**)-2-Oxa-3-azabicyclo[2.2.1]hept-5-enecarbonyl)phenyl)thiophene-2-sulfonamide (3b):** To a solution of (±)-2-aminophenyl)((1*S**,4*R**)-2-oxa-3-azabicyclo[2.2.1]hept-5-en-3-yl)methanone[2] (100 mg, 2.31 mmol), 2-thiophene sulfonyl chloride (101 mg, 0.555 mmol), and DMAP (5 mg) in anhydrous MeCN (1 mL) was added pyridine (0.044 mL, 0.555 mmol). After stirring for 16 h at rt, the mixture was diluted with 1M HCl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organics were washed with sat. NaCl, dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Flash chromatography (silica gel; eluted with 2:3 hexanes:ethyl acetate) provided 123 mg of **3b** (73%) as a pure white solid. mp = 128–130 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.85 (d, *J* = 9.0 Hz, 1H), 2.06 (d, *J*= 9.0 Hz, 1H), 5.28 (bs, 1H), 5.33 (s, 1H), 6.31 (s, 1H), 6.37 (bs, 1H), 6.98 (ddd, *J*= 0.9, 3.6, 4.5 Hz, 1H), 7.12 (dd, *J*= 7.5, 7.5 Hz, 1H), 7.44 (dd, *J*= 8.1, 8.1 Hz, 1H), 7.52 (dd, *J*= 3.9, 4.8 Hz, 2H), 7.67 (dd, *J*= 0.6, 7.5 Hz, 1H), 7.76 (d, *J*= 8.7 Hz, 1H), 9.69 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 48.5, 85.5, 121.3, 122.3, 123.8, 127.5, 130.6, 132.3, 132.7, 132.9, 133.6, 137.5, 140.6, 171.0; HRMS (FAB) calcd. for $C_{16}H_{15}O_4N_2S_2$ $(M+H)^+$: 363.0473, found 363.0487.

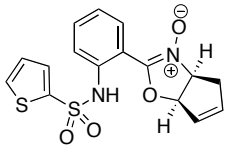


(±)-(3a*S,6a*R**)-2-(2-(2,4-Dinitrophenylsulfonamido)phenyl)-4,6a-dihydro-3a*H*-cyclopenta[*d*]oxazole 3-oxide (4):** To a solution of cycloadduct **3a** (175 mg, 0.392) in THF (6 mL) was added a solution of palladium acetate (5.0 mg, 0.020 mmol) and triphenylphosphine (15.4 mg, 0.0588 mmol) in THF (6 mL) and the solution was allowed to stir at 40 °C for 10 min. The reaction mixture was cooled, filtered through celite, washed with EtOAc, and concentrated to a brown oil. The brown oil was purified by flash chromatography (silica gel; eluted with 1:1 hexanes: EtOAc) to yield 120 mg (69%) of **4** as a pure light yellow powder. Recrystallization using vapor diffusion from CH_2Cl_2: hexanes gave yellow crystals suitable for X-ray structure determination. mp = 181–183 °C (dec.); ^{1}H NMR (300 MHz, DMSO–d_6) δ 2.85 (dd, *J*= 6.6, 18 Hz, 1H), 3.04 (d, *J*= 18 Hz, 1H), 5.07 (t, *J*= 7.5 Hz, 1H), 5.89 (dd, *J*= 2.1, 5.7 Hz, 1H), 6.01 (d, *J*= 8.1 Hz, 1H), 6.27 (d, *J*= 5.7 Hz, 1H), 7.33 (dd, *J*= 7.8, 7.8 Hz, 1H), 7.45 (d, *J*= 8.4 Hz, 1H), 7.58 (dd, *J*= 1.2, 7.8 Hz, 1H), 7.70 (ddd, *J*= 1.2, 8.4, 8.4 Hz, 1H), 8.06 (d, *J*= 8.4 Hz, 1H), 8.54 (dd, *J*= 2.4, 9 Hz, 1H), 8.86 (d, *J*= 2.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO–d_6) δ 35.9, 67.7, 89.2, 115.8, 120.2, 123.6, 125.2, 126.7, 127.1, 130.1, 131.2, 134.8, 137.1, 137.3, 138.4, 147.2, 149.9, 151.9.; IR (thin film)

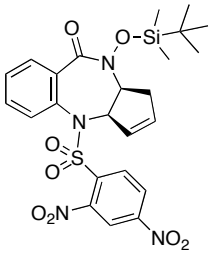
[2] For experimental of this compound as well as **1**, **2**, & **3a**, and spectral data for **5**, see Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 139.

3101, 3030, 2358, 1602, 1552, 1537, 1495, 1448, 1403 cm^{-1}; HRMS (FAB) calcd. for $C_{18}H_{15}O_8N_4S$ $(M+H)^+$: 447.0611, found 447.0623.

Optimized procedure for synthesis of (±)-(3a*R,10a*S**)-4-(2,4-Dinitrophenylsulfonyl)-10-hydroxy-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (5) using polymer bound Pd(0):** To a solution of cycloadduct **3a** (1.40 g, 3.14 mmol) in THF (20 mL) was added 997 mg of PS-PPh_3-Pd (Biotage, 0.11 mmol/g) and the solution was allowed to stir at 75 °C for 2 h. The reaction mixture was cooled and filtered to remove the resin. The filtrate was concentrated to a yellow solid. Trituration with 20 mL CH_2Cl_2 afforded 1.05 g of **5** as a pure off white powder (75%).

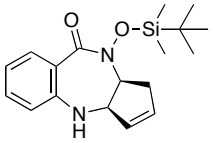


(±)-(3a*S,6a*R**)-2-(2-(Thiophene-2-sulfonamido)phenyl)-4,6a-dihydro-3a*H*-cyclopenta[*d*]oxazole 3-oxide (8):** To a solution of cycloadduct **3b** (60 mg, 0.166 mmol) in THF (2 mL) was added a solution of palladium acetate (2 mg, 0.008 mmol) and triphenylphosphine (6.5 mg, 0.025 mmol) in THF (1 mL) and the solution was allowed to stir at 40 °C for 10 min. The reaction mixture was cooled, filtered over celite, washed with EtOAc, and concentrated to a brown oil. The brown oil was purified by flash chromatography (silica gel; eluted with 1:4 hexanes: EtOAc) to yield 50 mg (83%) of **8** as a pure tan powder. mp = 151–153 °C; ^{1}H NMR (600 MHz, DMSO–d_6) δ 2.79–2.85 (m, 1H), 2.94–2.99 (m, 1H), 4.94 (ddd, *J*= 1.2, 7.2, 7.8 Hz, 1H), 5.86–5.89 (m, 2H), 6.29–6.31 (m, 1H), 7.08 (dd, *J*= 4.2, 4.8 Hz, 1H), 7.28 (dd, *J*= 1.8, 4.2 Hz, 1H), 7.35 (ddd, *J*= 1.2, 7.2, 7.8 Hz, 1H), 7.50 (dd, *J*= 1.2, 7.8 Hz, 1H), 7.53 (dd, *J*= 1.2, 8.4 Hz, 1H), 7.71 (ddd, *J*= 1.2, 7.2, 8.4 Hz, 1H), 7.85 (dd, *J*= 1.2, 4.8 Hz, 1H), 12.83 (s, 1H); ^{13}C NMR (150 MHz, DMSO–d_6) δ 36.0, 68.1, 88.1, 117.4, 125.8, 126.0, 126.9, 127.8, 129.7, 131.4, 133.2, 134.0, 137.1, 137.9, 140.1, 150.1; HRMS (FAB) calcd. for $C_{16}H_{15}O_4N_2S_2$ $(M+H)^+$: 363.0473, found 363.0467.

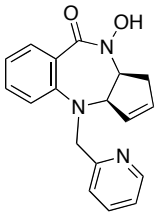


(±)-(3a*R,10a*S**)-10-(*tert*-Butyldimethylsilyloxy)-4-(2,4-dinitrophenylsulfonyl)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (10)**: A solution of benzodiazepine **5** (500 mg, 1.12 mmol) and TBDMSCl (506 mg, 3.36 mmol) in 8 mL anhydrous pyridine was stirred at rt for 16 h. The reaction mixture was concentrated under high vacuum to a tan solid. To the residue was added 10% aqueous citric acid (5 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and washed with 10% citric acid (3 × 10 mL). The organic layer was separated, then washed with sat. NaCl, dried with anhydrous

sodium sulfate, filtered, and concentrated to yield 495 mg of **10** as a pure white powder (79%). mp= 185–187 °C; ^{1}H NMR (600 MHz, DMSO–d_6) δ 0.13 (s, 3H), 0.18, (s, 3H), 0.93 (s, 9H), 1.69 (ddddd, *J*= 2.0, 2.0, 2.0, 5.5, 14.5 Hz, 1H), 2.64 (dddd, *J*= 2.4, 2.4, 10.2, 17.4 Hz, 1H), 4.71 (ddd, *J*= 7.2, 9.0, 9.0 Hz, 1H), 5.70 (dddd, *J*= 2.4, 2.4, 2.4, 6.0 Hz, 1H), 5.75–5.77 (m, 1H), 5.80 (dddd, *J*= 1.8, 3.0, 3.0, 9.0 Hz, 1H), 6.94, (dd, *J*= 1.2, 7.8 Hz, 1H), 7.51 (ddd, *J*= 1.8, 7.8, 7.8 Hz, 1H), 7.56 (ddd, *J*= 1.2, 7.2, 7.8 Hz, 1H), 7.66 (ddd, *J*= 0.61, 1.8, 7.5 Hz, 1H), 8.01 (dd, *J*= 0.6, 9.0 Hz, 1H), 8.54 (dd, *J*= 1.8, 8.4 Hz, 1H), 8.98 (d, *J*= 2.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO–d_6) δ –5.4, –4.9, 17.8, 25.7, 37.8, 62.7, 70.5, 120.3, 127.0, 127.4, 130.2, 130.7, 131.9, 132.1, 132.7, 132.9, 134.2, 135.1, 136.2, 147.1, 150.1, 164.1; IR (thin film) 3104, 2930, 2856, 1654, 1603, 1555, 1538, 1458 cm^{-1}; HRMS (FAB) calcd. for $C_{24}H_{29}O_8N_4SSi$ $(M+H)^+$: 561.1475, found 561.4462.

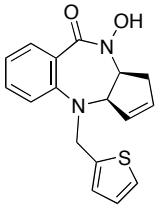


(±)-(3a*R,10a*S**)-10-(*tert*-Butyldimethylsilyloxy)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (11):** To a solution of benzodiazepine **10** (420 mg, 0.749 mmol) in anhydrous CH_2Cl_2 (6 mL) was added *n*-propylamine (0.615 mL, 7.49 mmol). The solution was allowed to stir for 2 h at rt. The solution was concentrated to a yellow solid. The crude material was purified by flash chromatography (silica gel; eluted with 2.5% MeOH/CH_2Cl_2) to give the secondary amine **11** as a pure white powder (84%). mp = 155–156 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 0.09 (s, 3H), 0.16 (s, 3H), 0.94 (s, 9H), 2.34 (dddd, *J*= 2.5, 4.5, 4.5, 17 Hz, 1H), 2.53–2.59 (m, 1H), 4.49 (ddd, *J*= 5.0, 8.0, 9.0 Hz, 1H), 4.53–4.58 (m, 1H), 5.45 (dddd, *J*= 2.0, 2.0, 2.0, 6.0 Hz, 1H), 5.75 (dddd, *J*= 1.5, 2.0, 2.5, 6.0 Hz, 1H), 6.06 (d, *J*= 3.5 Hz, 1H), 6.84 (ddd, *J*= 1.5, 6.75, 6.75 Hz, 1H), 6.89 (dd, *J*= 0.5, 8.0 Hz, 1H), 7.25 (ddd, *J*= 2.0, 6.75, 6.75 Hz, 1H), 7.74 (dd, *J*= 1.5, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO–d_6) δ –5.1, –4.9, 17.9, 25.9, 37.4, 64.8, 68.3, 119.7, 120.8, 131.0, 131.4, 131.7, 131.9, 148.4, 168.9; IR (thin film) 3285, 3059, 2929, 2857, 1640, 1604, 1479, 1443 cm^{-1}; HRMS (FAB) calcd. for $C_{18}H_{27}O_2N_2Si$ $(M+H)^+$: 331.1842, found 331.1847.



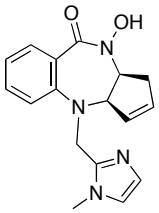
(±)-(3a*R,10a*S**)-10-Hydroxy-4-(pyridin-2-ylmethyl)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (13a):** To a solution of protected benzodiazepine **11** (40 mg, 0.121 mmol), 2-pyridinecarboxaldehyde (38 mg, 0.363 mmol) and 4Å molecular sieves in anhydrous CH_2Cl_2 (2 mL) was added glacial acetic acid (0.07 mL, 1.21 mmol). The reaction was stirred at 40 °C for 1 h. The reaction was cooled to rt and sodium triacetoxyborohydride (77.0 mg, 0.363 mmol) was added. The

reaction mixture was allowed to stir at rt for 16 h. Additional 2-pyridine carboxaldehyde (38 mg, 0.363 mmol) and sodium triacetoxyborohydride (77 mg, 0.363 mmol) were added and the reaction was stirred at rt for 3 h. To the reaction was added 10 mL CH_2Cl_2 and the organic layer was washed with sat. $NaHCO_3$ (3 × 5 mL). The organic layer was separated, then washed with sat. NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to a brown oil. Purification by flash chromatography (iron free silica gel; 1.5% IPA/CH_2Cl_2) yielded 20.3 mg of **12a** as a brown solid. A solution of **12a** (20.3 mg, 0.0473 mmol) and CsF (8 mg, 0.0522 mmol) in MeOH (1 mL) was allowed to stir at rt for 3 h. The reaction mixture was concentrated to an oil and purified by flash chromatography (iron free silica gel; 2% MeOH/CH_2Cl_2) to give 14 mg of a tan solid. Trituration with hexanes gave 12.5 mg of **13a** as a pure white powder (34% over two steps). mp = 139–141 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 1.88–1.98 (m, 1H), 2.50–2.56 (m, 1H), 4.49 (d, *J*= 15.5 Hz, 1H), 4.58–4.62 (m, 2H), 4.63 (d, *J*= 15.5 Hz, 1H), 5.68–5.71 (m, 1H), 5.85 (dddd, *J*= 1.4, 2.2, 2.4, 6.2 Hz, 1H), 6.96-7.04 (m, 2H), 7.22 (ddd, *J*= 1.0, 4.8, 7.6 Hz, 1H), 7.27 (ddd, *J*= 1.5, 6.5, 7.5 Hz, 1H), 7.38 (d, *J*= 8.0 Hz, 1H), 7.52 (dd, *J*= 2.0, 7.5 Hz, 1H), 7.70 (ddd, *J*= 2.0, 7.5 Hz, 1H), 7.70 (ddd, *J*= 1.5, 7.5, 7.5 Hz, 1H), 8.49 (dd, *J*= 1.0, 5.0 Hz, 1H), 10.10 (s, 1H); ^{13}C NMR (150 MHz, DMSO–d_6) δ 38.1, 56.5, 63.1, 73.3, 121.7, 121.9, 121.2, 121.6, 128.0, 129.8, 129.8, 131.0, 132.4, 136.7, 146.4, 148.8, 158.6, 165.0; IR (thin film) 3062, 2921, 1627, 1594, 1570, 1487, 1433 cm^{-1}; HRMS (FAB) calcd. for $C_{18}H_{18}O_2N_3$ $(M+H)^+$: 308.1399, found 308.1398.

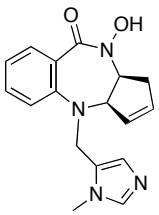


(±)-(3a*R,10a*S**)-10-Hydroxy-4-(thiophen-2-ylmethyl)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (13b):** To a solution of protected benzodiazepine **11** (100 mg, 0.303 mmol), 2-thiophenecarboxaldehyde (0.091 mL, 0.908 mmol) and 4Å molecular sieves in CH_2Cl_2 (3 mL) was added glacial acetic acid (0.175 mL, 3.02 mmol). The reaction was stirred at 40 °C for 1 h. The reaction was cooled to rt and sodium triacetoxyborohydride (192 mg, 0.908 mmol) was added. The reaction mixture was allowed to stir at rt for 16 h. To the reaction was added 10 mL CH_2Cl_2 and the organic layer was washed with sat. $NaHCO_3$ (3 × 5 mL) and sat. sodium bisulfite (1 × 5 mL). The organic layer was separated, then washed with sat. NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to a brown oil. Purification by flash chromatography (silica gel; 1.5% MeOH/CH_2Cl_2) yielded 70 mg of **12b** as a brown oil. A solution of the brown oil (70 mg, 0.164 mmol) and CsF (27 mg, 0.0522 mmol) in MeOH (1 mL) was allowed to stir at rt for 3 h. The reaction mixture was concentrated to an oil and purified by flash chromatography (iron free silica gel; 0.1% MeOH/CH_2Cl_2) to give 34 mg of **13b** as a pure white powder (38% over two steps). mp= 138–141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.54 (ddddd, *J*= 1.8, 2.4, 2.4, 4.5, 17.4 Hz, 1H), 2.54 (ddddd, *J*= 1.2, 1.2, 1.2, 7.8, 17.4 Hz, 1H), 4.60 (dd, *J*= 0.6, 13.8 Hz, 1H), 4.67–4.73, (m, 2H), 4.75 (dddd, *J*= 1.8, 1.8, 3.6, 9.0 Hz, 1H), 5.48 (dddd, *J*=

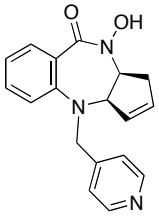
1.8, 1.8, 2.4, 6.3 Hz, 1H), 5.70 (dddd, *J*= 1.8, 2.4, 2.4, 6.3 Hz, 1H), 6.97 (dd, *J*= 3.6, 5.4 Hz, 1H), 7.02–7.04 (m, 1H), 7.05 (dddd, *J*= 1.2, 1.2, 1.2. 3.3 Hz, 1H), 7.09 (ddd, *J*= 2.4, 7.8, 7.8 Hz, 1H), 7.26–7.28 (m, 1H), 7.40 (ddd, *J*= 1.8, 6.6, 8.1 Hz, 1H), 7.93 (dddd, *J*= 0.6, 1.8, 1.8, 7.8 Hz, 1H), 8.97 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 38.3, 51.9, 63.2, 70.9, 120.8, 123.0, 125.8, 125.9, 126.1, 126.9, 128.3, 131.2, 132.3, 132.4, 142.6, 147.9, 165.5; IR (thin film) 3099, 3068, 2917, 2851, 1627, 1605, 1570, 1444 cm^{-1}; HRMS (FAB) calcd. for $C_{17}H_{17}O_2N_2S$ $(M+H)^+$: 313.1011, found 313.1019.



(±)-(3a*R,10a*S**)-10-Hydroxy-4-((1-methyl-1*H*-imidazol-2-yl)methyl)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (13c):** To a solution of protected benzodiazepine **11** (120 mg, 0.363 mmol), 1-methyl-1H-imidazole-2-carbaldehyde (120 mg, 1.09 mmol) and 4Å molecular sieves in CH_2Cl_2 (4 mL) was added glacial acetic acid (0.209 mL, 3.63 mmol). The reaction was stirred at 40 °C for 1 h. The reaction was cooled to rt and the sodium triacetoxyborohydride (230 mg, 1.09 mmol) was added. The reaction mixture was allowed to stir at rt for 16 h. To the reaction was added 10 mL CH_2Cl_2 and the organic layer was washed with sat. $NaHCO_3$ (3 × 5 mL). The organic layer was washed with sat. NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to a brown oil. Purification by flash chromatography (silica gel; 3% MeOH/ CH_2Cl_2) yielded 52 mg of **12c** as an oil. A solution of benzodiazepine **12c** (52 mg, 0.122 mmol) and CsF (20 mg, 0.134 mmol) in anhydrous MeOH (2 mL) was allowed to stir at rt for 3 h. The reaction mixture was concentrated and 2 mL CH_2Cl_2 was added and the mixture was filtered. The filtrate was purified by flash chromatography (iron free silica gel; 5% IPA/CH_2Cl_2) to give 36 mg of **13c** as a pure white powder (32% over two steps). mp = 110–114 °C (dec.); ^{1}H NMR (600 MHz, CD_3OD) δ 1.96 (ddddd, *J*= 1.8, 2.4, 3.0, 7.2, 16.8 Hz, 1H), 2.58 (dddd, *J*= 1.8, 2.7, 9.6, 17.1 Hz, 1H), 3.68 (s, 3H), 4.42–4.52 (m, 3H), 4.63 (ddd, *J*= 7.8, 9.0, 9.6 Hz, 1H) , 5.70–5.73 (m, 1H), 5.95 (dddd, *J*= 1.8, 1.8, 2.4, 6.3 Hz, 1H), 6.84 (d, *J*= 1.2 Hz, 1H), 7.02, (d, *J*=1.2 Hz, 1H), 7.13 (ddd, *J*= 0.6, 7.2, 7.2 Hz, 1H), 7.16 (dd, *J*= 1.2, 7.8 Hz, 1H), 7.40 (dd, *J*= 1.2, 7.8 Hz, 1H), 7.53 (ddd, *J*= 0.6, 1.8, 7.8 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 33.8, 39.2, 49.7, 64.9, 74.2, 124.1, 124.2, 125.2, 127.0, 127.7, 130.7, 131.6, 132.8, 134.3, 145.7, 147.4, 167.8; IR (thin film) 3110, 3058, 2926, 2855, 1735, 1638, 1593, 1501, 1459, 1412 cm^{-1}; HRMS (FAB) calcd. for $C_{17}H_{19}O_2N_4$ $(M+H)^+$: 311.1508, found 311.1524.



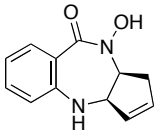
(±)-(3a*R,10a**S*)-10-Hydroxy-4-((1-methyl-1*H*-imidazol-5-yl)methyl)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (13d):** To a solution of protected benzodiazepine **11** (120 mg, 0.363 mmol), 1-methyl-1H-imidazole-5-carbaldehyde (100 mg, 0.908 mmol) and 4Å molecular sieves in anhydrous CH_2Cl_2 (4 mL) was added glacial acetic acid (0.209 mL, 3.63 mmol). The reaction was stirred at 40 °C for 1 h. The reaction was cooled to rt and the sodium triacetoxyborohydride (192 mg, 0.908 mmol) was added. The reaction mixture was allowed to stir at rt for 16 h. To the reaction was added 10 mL CH_2Cl_2 and washed with sat. $NaHCO_3$ (3 × 5 mL). The organic layer was washed with sat. NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to a brown oil (90 mg). A solution of the brown oil (**12d**, 90 mg) and CsF (30 mg) in anhydrous MeOH (2 mL) was allowed to stir at rt for 3 h. The reaction mixture was concentrated to an oil and purified by flash chromatography (iron free silica gel; 5% MeOH/ CH_2Cl_2) to give 37 mg of **13d** as a pure white powder (33%). mp = 189–191 °C (dec.); ^{1}H NMR (600 MHz, CD_3OD) δ 1.94–2.00 (m, 1H), 2.55–2.61 (m, 1H), 3.67 (s, 3H), 4.37 (d, *J*= 14.4 Hz, 1H), 4.43 (d, *J*= 14.4 Hz, 1H), 4.59–4.66 (m, 2H), 5.69–5.71 (m, 1H), 5.91 (ddd, *J*= 1.9, 4.0, 6.3 Hz, 1H), 6.95 (bs, 1H), 7.12 (ddd, *J*= 1.0, 7.3, 7.3 Hz, 1H), 7.16 (ddd, *J*= 0.5, 1.0, 8.2 Hz, 1H), 7.41 (ddd, *J*= 1.8, 7.5, 8.1 Hz, 1H), 7.53 (dd, *J*= 1.8, 7.8 Hz, 1H), 7.56 (bs, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 32.4, 39.2, 45.6, 64.9, 73.7, 124.3, 125.0, 127.9, 129.7, 129.7, 130.7, 131.7, 132.8, 134.0, 140.5, 147.8, 167.9; IR (thin film) 3056, 2923, 2855, 1721, 1634, 1513, 1487, 1455, 1419 cm^{-1}; HRMS (FAB) calcd. for $C_{17}H_{19}O_2N_4$ $(M+H)^+$: 311.1508, found 311.1510.



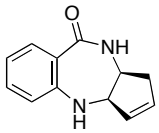
(±)-(3a*R,10a*S**)-10-Hydroxy-4-(pyridin-4-ylmethyl)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (13e):**

To a solution of benzodiazepine **11** (130 mg, 0.393 mmol), 4-pyridinecarboxaldehyde (0.055 mL, 0.590 mmol) and 4Å molecular sieves in anhydrous CH_2Cl_2 (4 mL) was added glacial acetic acid (0.113 mL) and stirred at 40 °C for 1 h. The solution was cooled to rt and the sodium triacetoxyborohydride (125 mg, 0.590 mmol) was added. The solution was stirred at rt overnight. To the solution was added 5 mL CH_2Cl_2 and the organic layer was washed with sat. $NaHCO_3$ (3 × 10 mL). The organic layer was washed with sat. NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to a brown oil. A solution of the oil (**12e**, 165 mg) and CsF (59 mg, 0.393 mmol) in anhydrous MeOH (4 mL) was allowed to stir at rt for 3 h. The reaction mixture was concentrated and 10 mL CH_2Cl_2 was added and the mixture was filtered. The filtrate was purified by flash chromatography (iron free silica gel; 2% MeOH/CH_2Cl_2) to afford 58 mg of **13e** as a pure white powder (48%). mp = 177–179 °C (dec.); ^{1}H NMR (600 MHz, CD_3OD) δ 2.03 (ddddd, *J*= 2.4, 2.4, 2.3, 7.0, 17.0 Hz, 1H), 2.62 (dddd, *J*= 2.4, 2.4, 9.4, 17.0 Hz, 1H), 4.44 (d, *J*= 15.9, 1H), 4.62–4.66 (m, 2H), 4.71 (dt, *J*= 7.1, 9.1, 9.4 Hz, 1H), 5.71–5.73 (m, 1H), 5.91 (dddd, *J*= 2.1, 2.1, 2.1, 6.3 Hz, 1H), 7.03

(dd, *J*= 0.9, 8.2 Hz, 1H), 7.09 (ddd, *J*= 1.2, 6.8, 7.5 Hz, 1H), 7.32 (ddd, *J*= 1.5, 6.9, 8.1 Hz, 1H), 7.48 (dd, *J*= 1.8, 4.4 Hz, 2H), 7.56 (dd, *J*= 1.8, 7.6, 1H), 8.41 (dd, *J*= 1.8, 4.7 Hz, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 39.3, 55.0, 65.2, 75.7, 124.0, 124.9, 125.0, 128.3, 131.0, 131.7, 132.8, 134.1, 147.7, 150.2, 151.1, 168.0; IR (thin film) 1417, 1451, 1485, 1562, 1606, 1631, 2851, 2918, 3059 cm^{-1}; HRMS (FAB) calcd. for $C_{18}H_{18}O_2N_3$ $(M+H)^+$: 308.1399, found 308.1392.

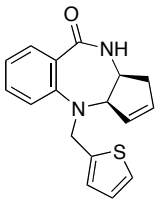


(±)-(3a*R,10a*S**)-10-Hydroxy-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (14):** To a solution of benzodiazepine **5** (180 mg, 0.403 mmol) in anhydrous CH_2Cl_2 (4 mL) was added *n*-propylamine (0.331 mL, 4.03 mmol). The solution was allowed to stir for 2 h at rt. To the solution was added 5 mL 10% citric acid and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to a solid. The crude material was adsorbed on iron free silica gel and purified by flash chromatography (iron free silica gel; 2% MeOH/CH_2Cl_2) to yield 61 mg of **14** as a pure white powder (70%). mp= 149–152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.79 (overlapping ddddd, *J*= 1.8, 2.4, 2.4, 4.5, 16.8 Hz, 1H), 2.83 (overlapping ddddd, *J*= 0.6, 1.8, 2.4, 7.2, 16.8 Hz, 1H), 4.02 (bs, 1H), 4.33 (d, *J*= 7.2 Hz, 1H), 4.48 (dd, *J*=6.6, 12.6 Hz, 1H), 5.70 (ddddd, *J*= 0.6, 1.8, 1.8, 3.3, 6.0 Hz, 1H), 6.04 (dddd, *J*= 1.2, 2.4, 2.7, 5.4 Hz, 1H), 6.78 (ddd, *J*= 0.6, 1.2, 7.8 Hz, 1H), 7.04 (ddd, *J*= 1.2, 7.2, 8.1 Hz, 1H), 7.32 (ddd, *J*= 1.2, 7.2, 8.1 Hz, 1H), 8.17 (dd, *J*= 1.8, 7.8, Hz, 1H), 9.39 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 38.0, 64.4, 66.5, 119.7, 120.1, 121.7, 129.6, 132.5, 132.9, 134.8, 147.8, 165.4; IR (thin film) 3218, 1625, 1468 cm^{-1}; HRMS (FAB) calcd. for $C_{12}H_{13}O_2N_2$ $(M+H)^+$: 217.0977, found 217.0987.

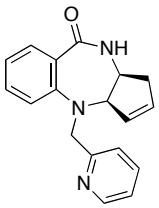


(±)-(3a*R,10a*S**)-3a,4,10,10a-Tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (15):** A solution of Cp_2TiCl_2 (2.24 g, 9.02 mmol) and zinc (1.18 g, 18.0 mmol) in THF (45 mL) was stirred at rt under Ar for 45 min. The mixture was cooled to −25° C (acetone/dry ice) and a solution of benzodiazepine **14** (780 mg, 0.138 mmol) in anhydrous MeOH (18 mL) was added dropwise over 20 min. After 45 min, 100 mL of sat. K_2CO_3 and 50 mL of EtOAc were added to the reaction mixture. The EtOAc layer was separated and filtered through a Whatman Glass Microfiber Filter (Type GF/F). This process was repeated 3 times. The combined organics (200 mL) were dried over anhydrous sodium sulfate, filtered and concentrated to a yellow solid. The crude material was adsorbed on silica gel and purified by flash chromatography (silica gel; eluted with 2–10% IPA/CH_2Cl_2), which provided 426 mg of **15** as a pure white powder (60%). mp = 209–211 °C (dec.); ^{1}H NMR (600 MHz, CD_3OD) δ 2.30 (ddddd, *J*= 1.8, 1.9, 2.5, 4.2,

17.0 Hz, 1H), 2.60 (ddddd, *J*= 1.2, 2.4, 3.4, 7.8, 17.0 Hz, 1H), 4.06 (ddd, *J*= 3.0, 3.5, 6.0 Hz, 1H), 4.48 (dddd, *J*= 1.2, 1.8, 3.5, 7.2 Hz, 1H), 5.72 (dddd, *J*= 1.8, 1.9, 2.4, 6.0 Hz, 1H), 5.79 (dddd, *J*= 1.6, 2.4, 2.4, 6.0 Hz, 1H), 6.97 (ddd, *J*= 0.4, 1.0, 8.0 Hz, 1H), 7.06 (ddd, *J*= 1.2, 7.0, 7.8 Hz, 1H), 7.34 (ddd, *J*= 1.8, 6.8, 8.0 Hz, 1H), 7.58 (ddd, *J*= 0.4, 1.8, 7.8 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 40.1, 54.7, 72.5, 123.7, 123.9, 129.5, 131.4, 131.8, 132.9, 133.6, 148.8, 174.5; IR (thin film) 1461, 1505, 1616, 1631, 3297 cm^{-1}; HRMS (FAB) calcd. for $C_{12}H_{13}ON_2$ $(M+H)^+$: 201.1028, found 201.1003.

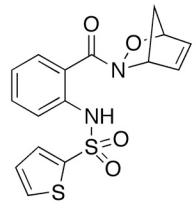


(±)-(3a*R,10a*S**)-4-(Thiophen-2-ylmethyl)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (16a):** To a solution of benzodiazepine **15** (75 mg, 0.375 mmol), 2-thiophenecarboxaldehyde (0.035 mL, 0.375 mmol), and 4Å molecular sieves in anhydrous CH_2Cl_2 (6 mL) was added glacial acetic acid (0.214 mL, 3.75 mmol). The reaction was stirred at 40 °C for 1 h. The reaction was cooled to rt and sodium triacetoxyborohydride (80 mg, 0.375 mmol) was added. The reaction mixture was allowed to stir at rt for 16 h. Additional 2-thiophenecarboxaldehyde (0.017 mL, 0.187 mmol) and sodium triacetoxyborohydride (40 mg, 0.187 mmol) were added and the reaction was stirred at rt for 3 h. To the reaction was added 10 mL CH_2Cl_2 and the organic layer was washed with sat. $NaHCO_3$ (3 × 8 mL). The organic layer was washed with sat. NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to a brown oil. Purification by flash chromatography (silica gel; 2% MeOH/CH_2Cl_2) yielded 78 mg of **16a** as a white powder (67%). mp = 147–149 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 1.97 (ddddd, *J*= 2.4, 2.4, 2.4, 7.6, 17.3 Hz, 1H), 2.40 (dddd, *J*= 2.1, 2.4, 9.1, 17.0 Hz, 1H), 4.07 (dt, *J*= 7.6, 8.8, 9.1 Hz, 1H), 4.43 (dddd, *J*= 1.2, 2.4, 2.4, 8.8 Hz, 1H), 4.53 (dd, *J*= 0.9, 14.4 Hz, 1H), 4.59 (dd, *J*= 1.2, 14.7 Hz, 1H), 5.70–5.72 (m, 1H), 5.97 (dddd, *J*= 2.1, 2.1, 2.3, 6.5 Hz, 1H), 6.88 (dd, *J*= 3.6, 5.4 Hz, 1H), 7.01 (dddd, *J*= 1.2, 1.2, 1.2, 3.5 Hz, 1H), 7.06–7.09 (m, 2H), 7.23 (dd, *J*= 1.2, 5.0 Hz, 1H), 7.33 (ddd, *J*= 1.5, 6.9, 8.1 Hz, 1H), 7.44 (dd, *J*= 1.8, 7.9 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 40.2, 51.3, 53.6, 74.8, 124.2, 124.8, 126.2, 126.8, 127.4, 128.6, 130.3, 132.5, 133.8, 134.4, 144.5, 148.7, 174.7; IR (thin film) 1441, 1464, 1598, 1652, 2360, 2854, 2924, 3051, 3212 cm^{-1}; HRMS (FAB) calcd. for $C_{17}H_{17}N_2OS$ $(M+H)^+$: 297.1062, found 297.1066.



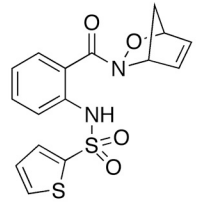
(±)-(3a*R,10a*S**)-4-(Pyridin-2-ylmethyl)-3a,4,10,10a-tetrahydrobenzo[*e*]cyclopenta[*b*][1,4]diazepin-9(1*H*)-one (16b):** To a solution of benzodiazepine **15** (50 mg, 0.250 mmol), 2-pyridinecarboxaldehyde (0.023 mL, 0.249 mmol) and 4Å molecular sieves in anhydrous CH_2Cl_2 (4 mL) was added glacial acetic acid (0.142 mL, 2.5 mmol). The reaction was stirred at 40 °C for 1 h. The reaction was cooled to rt and

sodium triacetoxyborohydride (53 mg, 0.250 mmol) was added. The reaction mixture was allowed to stir at rt for 16 h. Additional 2-pyridinecarboxaldehyde (0.012 mL, 0.125 mmol) and sodium triacetoxyborohydride (26 mg, 0.125 mmol) were added and the reaction was stirred at rt for 3 h. To the reaction was added 10 mL CH_2Cl_2 and the organic layer was washed with sat. $NaHCO_3$ (3 × 8 mL). The organic layer was washed with sat. NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to a brown oil. Purification by flash chromatography (silica gel; 3% MeOH/CH_2Cl_2) yielded 46 mg of **16b** as a pure white powder (60%). mp = 103–105 °C (dec.); ^{1}H NMR (600 MHz, CD_3OD) δ 2.02 (ddddd, *J*= 2.4, 2.4, 2.4, 7.3, 16.7 Hz, 1H), 2.45 (dddd, *J*= 2.4, 2.4, 8.8, 17.0 Hz, 1H), 4.11 (dt, *J*= 7.3, 8.8, 9.8 Hz, 1H), 4.39 (dddd, *J*= 1.2, 2.1, 2.4, 8.5 Hz, 1H), 4.48 (d, *J*= 15.3 Hz, 1H), 4.63 (d, *J*= 15.3 Hz, 1H), 5.77 (ddd, *J*= 2.6, 3.2, 6.5 Hz, 1H), 6.03 (dddd, *J*= 2.1, 2.1, 1.4, 6.3 Hz, 1H), 7.03 (d, *J*= 8.2 Hz, 1H), 7.07 (ddd, *J*= 0.9, 7.3, 7.5 Hz, 1H), 7.22–7.25 (m, 1H), 7.30 (ddd, *J*= 1.8, 6.8, 7.9 Hz, 1H), 7.46 (dd, *J*= 1.8, 7.6 Hz, 1H), 7.54 (d, *J*= 7.9 Hz, 1H), 7.70 (dd, *J*= 2.1, 6.9, 7.6 Hz, 1H), 8.42–8.43 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 40.0, 53.9, 57.3, 76.4, 123.9, 124.0, 124.4, 125.0, 128.8, 130.4, 132.6, 133.9, 134.5, 139.0, 148.3, 149.4, 160.2, 174.7; IR (thin film) 1434, 1474, 1593, 1655, 2360, 2915, 3057, 3216 cm^{-1}; HRMS (FAB) calcd. for $C_{18}H_{18}N_3O$ $(M+H)^+$: 292.1450, found 292.1461.



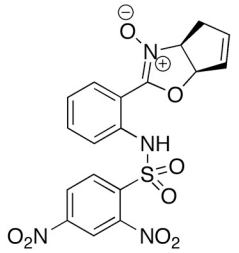
3b

^{13}C NMR (150 MHz, $CDCl_3$)



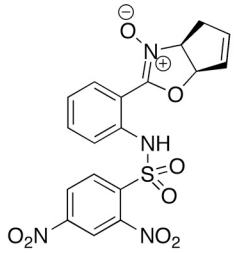
3b

^{1}H NMR (600 MHz, $CDCl_3$)



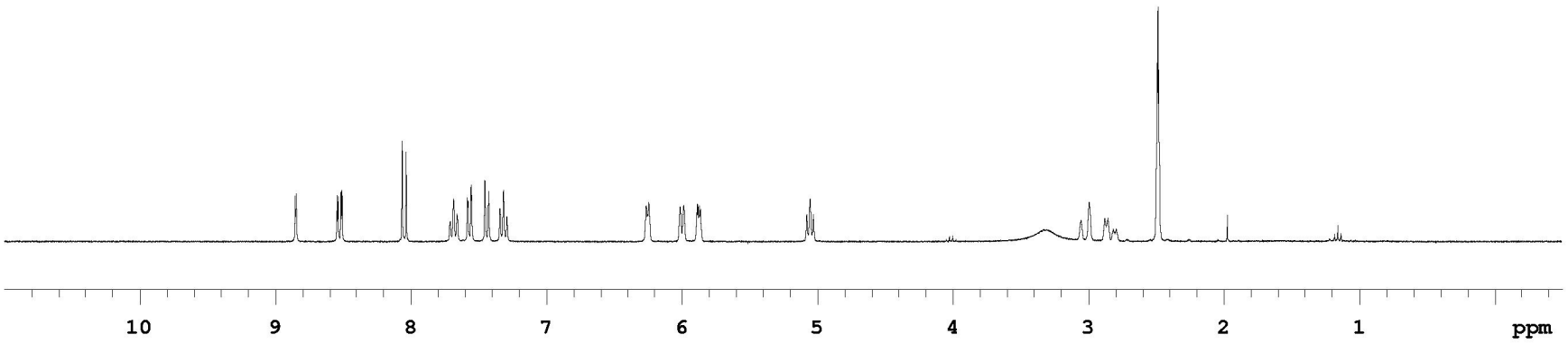
4

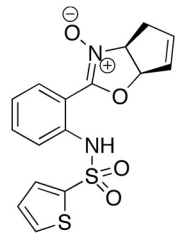
^{13}C NMR (125 MHz, DMSO-d_6)



4

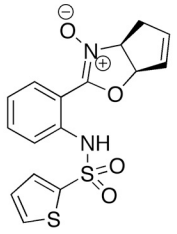
^{1}H NMR (300 MHz, DMSO-d_6)





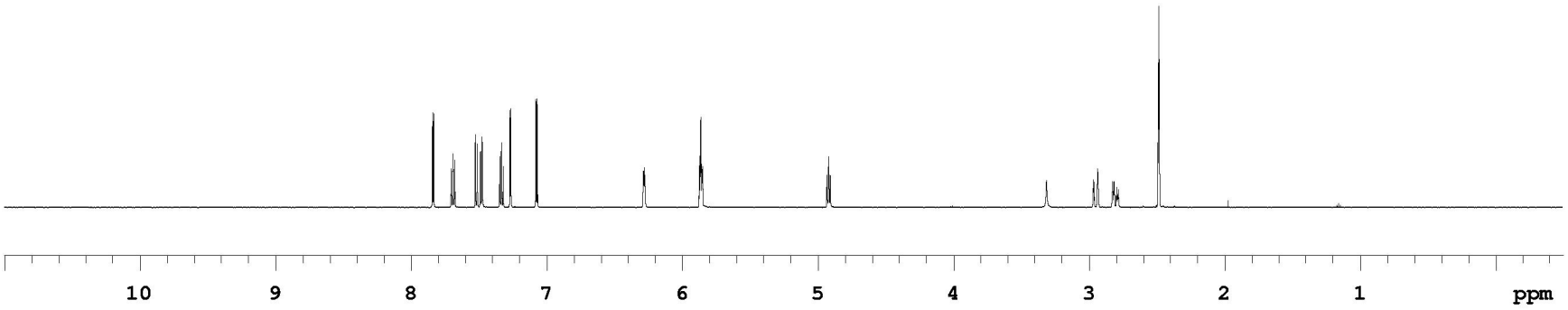
8

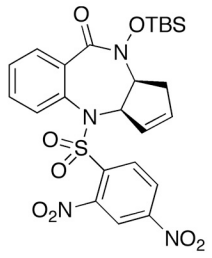
^{13}C NMR (150 MHz, DMSO-d_6)



8

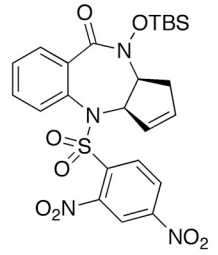
^{1}H NMR (600 MHz, DMSO-d_6)





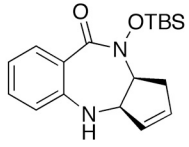
10

^{13}C NMR (150 MHz, DMSO-d_6)



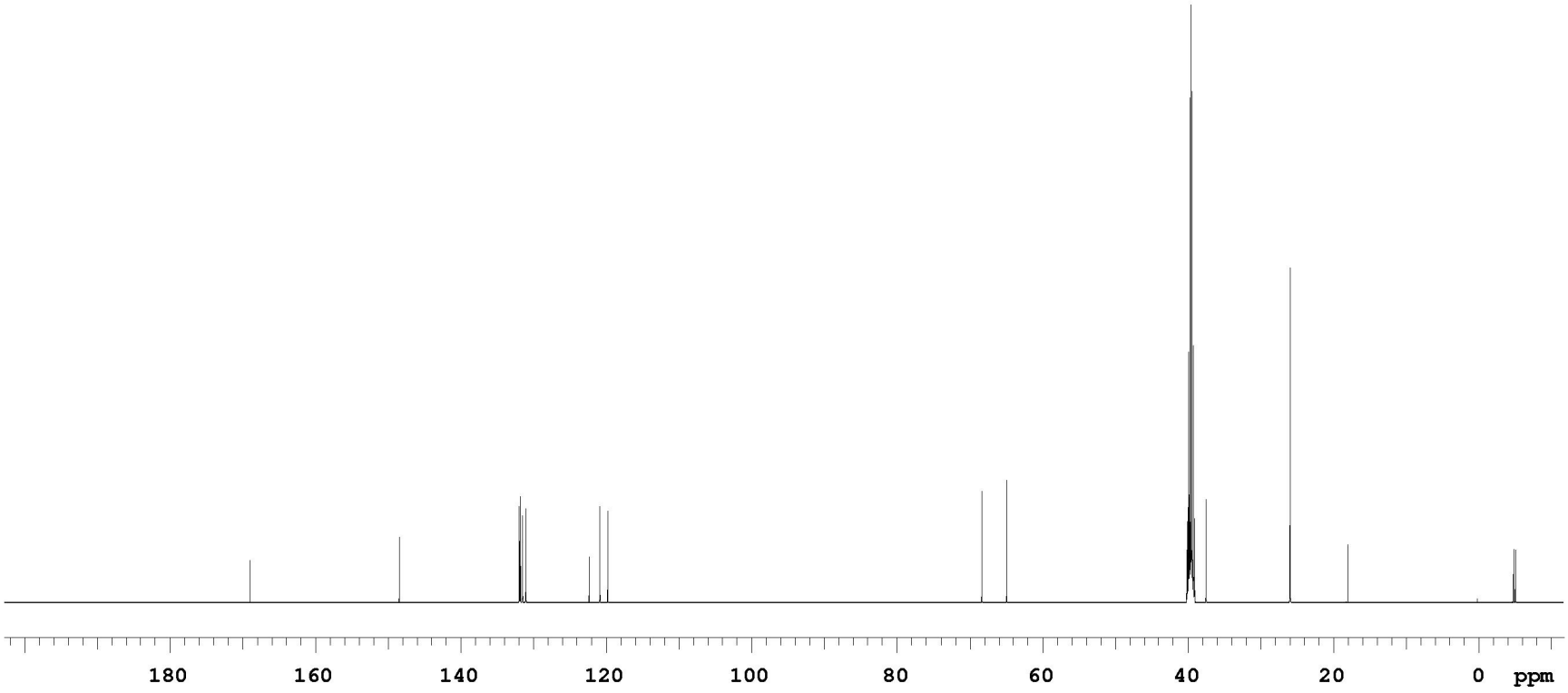
10

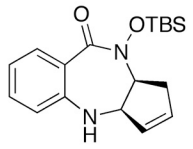
^{1}H NMR (600 MHz, DMSO-d_6)



11

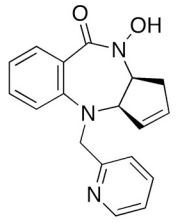
^{13}C NMR (125 MHz, DMSO-d_6)





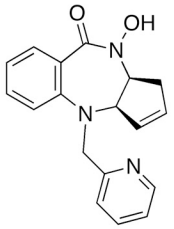
11

^{1}H NMR (500 MHz, DMSO-d_6)



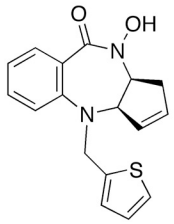
13a

^{13}C NMR (150 MHz, DMSO-d_6)



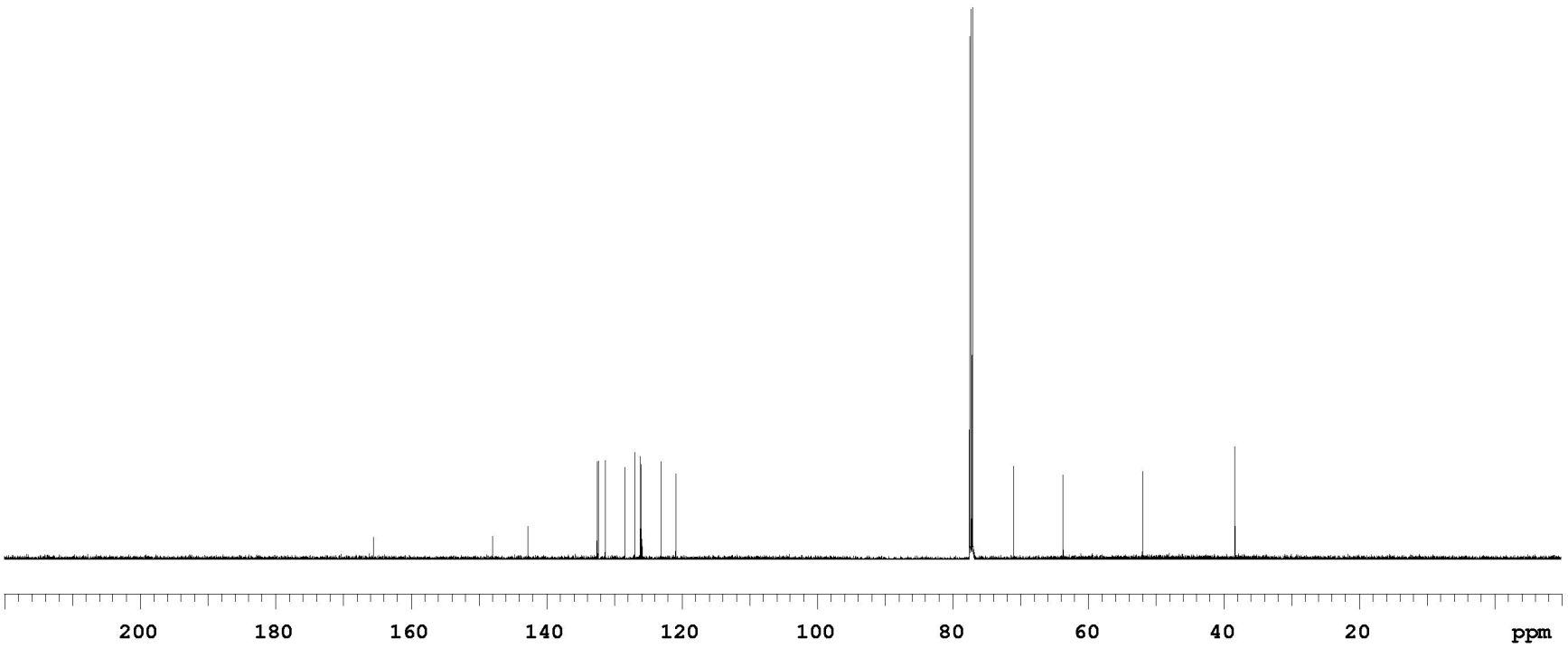
13a

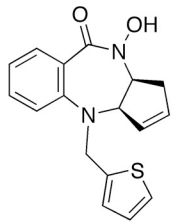
^{1}H NMR (500 MHz, DMSO-d_6)



13b

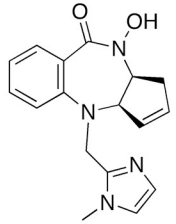
^{13}C NMR (150 MHz, $CDCl_3$)





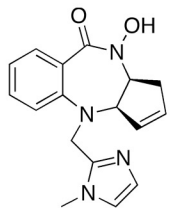
13b

^{1}H NMR (600 MHz, $CDCl_3$)



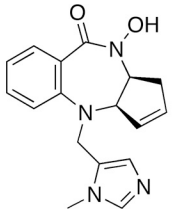
13c

^{13}C NMR (150 MHz, CD_3OD)



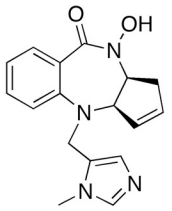
13c

^{1}H NMR (600 MHz, CD_3OD)



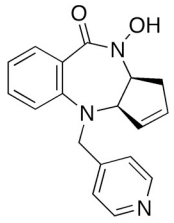
13d

^{13}C NMR (150 MHz, CD_3OD)



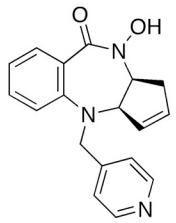
13d

^{1}H NMR (600 MHz, CD_3OD)



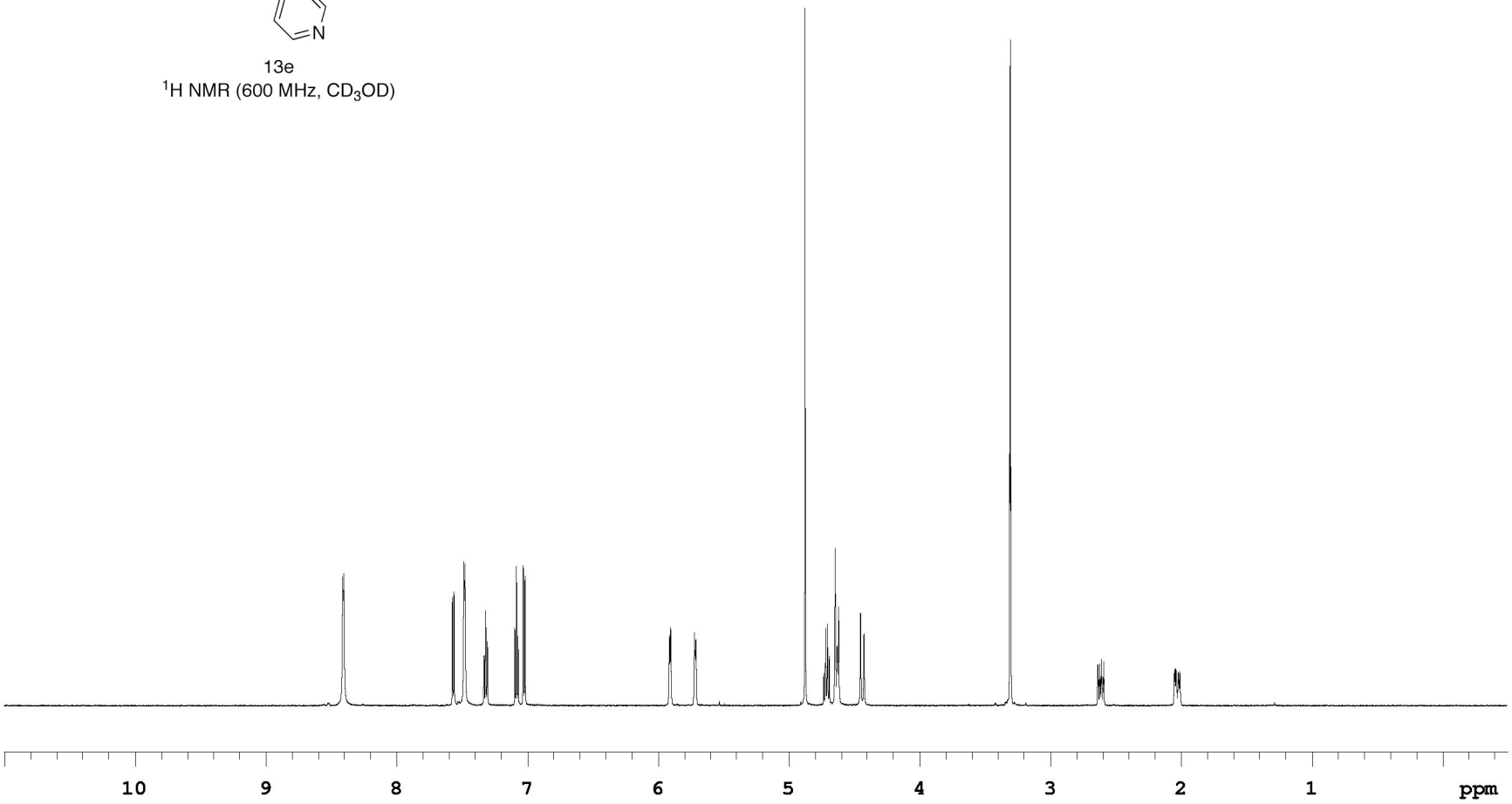
13e

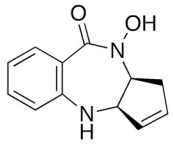
^{13}C NMR (150 MHz, CD_3OD)



13e

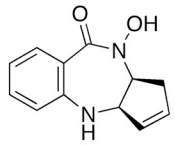
^{1}H NMR (600 MHz, CD_3OD)





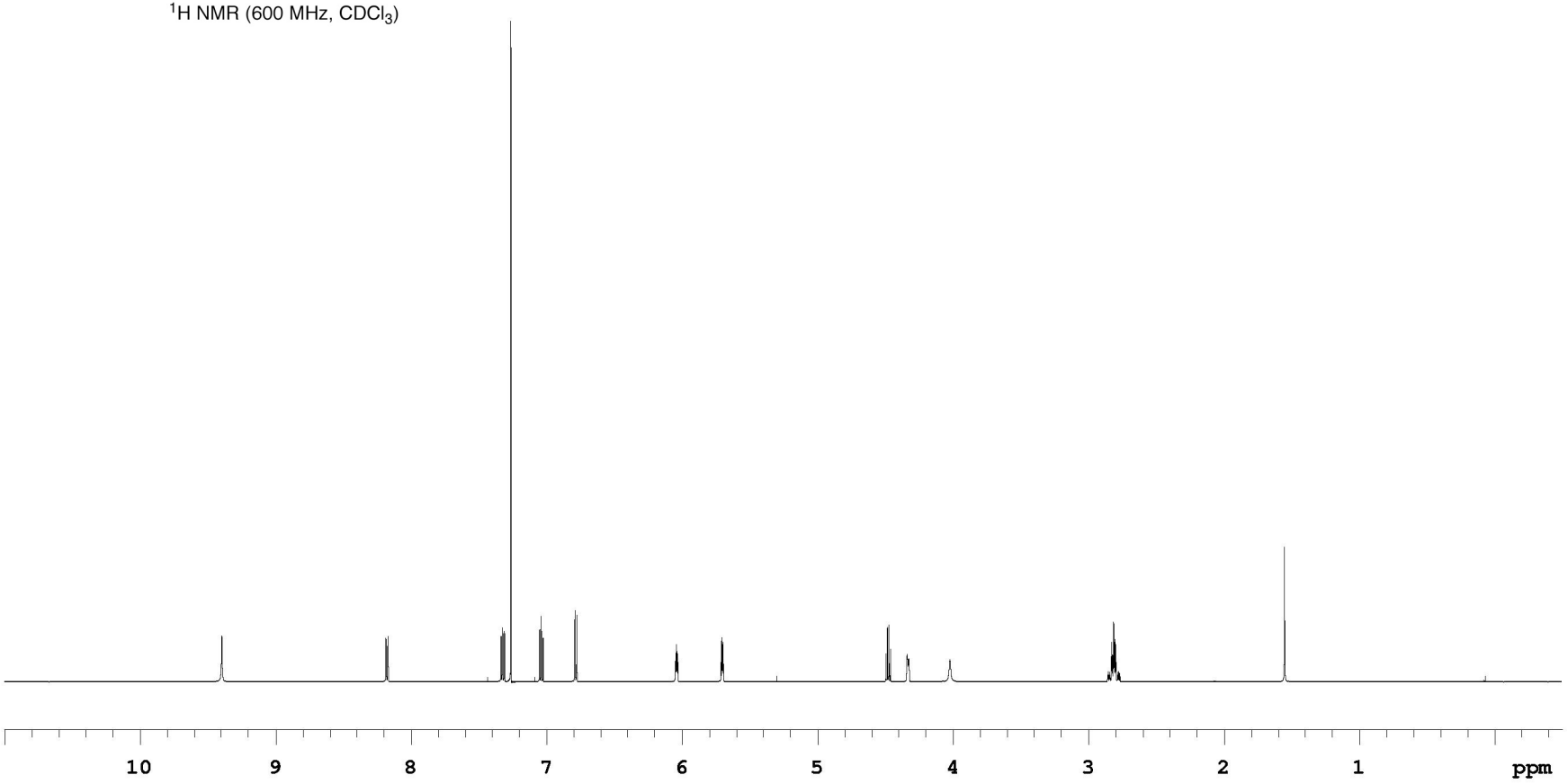
14

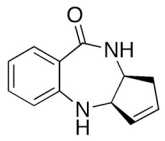
^{13}C NMR (150 MHz, $CDCl_3$)



14

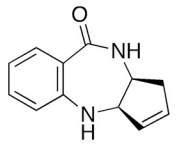
^{1}H NMR (600 MHz, $CDCl_3$)





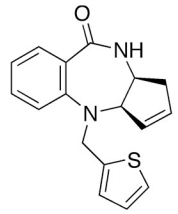
15

^{13}C NMR (150 MHz, CD_3OD)



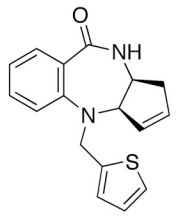
15

^{1}H NMR (600 MHz, CD_3OD)



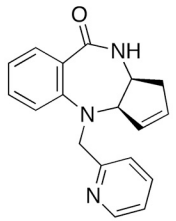
16a

^{13}C NMR (150 MHz, CD_3OD)



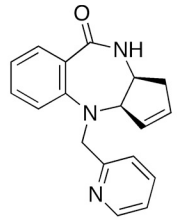
16a

^{1}H NMR (600 MHz, CD_3OD)



16b

^{13}C NMR (150 MHz, CD_3OD)



16b

^{1}H NMR (600 MHz, CD_3OD)