Supporting Information

Novel Lipophilic Acetohydroxamic Acid Derivatives Based on Conformationally Constrained Spiro Carbocyclic 2,6-Diketopiperazine Scaffolds with Potent Trypanocidal Activity

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Experimental
Chemistry

General. Melting points were determined using a Büchi capillary apparatus and are uncorrected. The \(^1\)H and \(^{13}\)C NMR spectra were obtained on either a Bruker MSL 400 (400 MHz \(^1\)H; 100 MHz \(^{13}\)C) or Bruker 600 (600 MHz \(^1\)H) spectrometer, using CDCl\(_3\) or DMSO-\(d_6\) as solvent. Chemical shifts are reported in δ (ppm) with the tetramethylsilane or solvent (DMSO-\(d_6\)) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; dd, doublet of doublets; q, quartet; m, multiplet; br, broad; v br, very broad; sym, symmetrical. Coupling constants (\(J\)) are expressed in units of hertz (Hz). The spectra were recorded at 293 K (20 °C) unless otherwise specified. Carbon multiplicities were established by DEPT experiments. The 2D NMR experiments (HMBC and COSY) were performed for the elucidation of the structures of the newly synthesized compounds. Low resolution mass spectra (MS) were measured either in chemical ionization (CI) in positive mode using methane as CI reagent gas or in electron impact (EI) on a Thermo Electron Corporation DSQ mass spectrometer. High resolution mass spectra (HRMS) were performed on a hybrid LTQ-Orbitrap Discovery spectrometer under electrospray ionization (ESI) in positive mode. Optical rotations were measured on a Perkin Elmer 341 polarimeter at the sodium D line (589). Analytical thin-layer chromatography (TLC) was conducted on precoated Merck silica gel 60 F\(_{254}\) (layer thickness 0.2 mm) with the spots visualized by iodine vapors and/or UV light. Column chromatography purification was carried out on silica gel 60 (70-230 mesh), Elemental analyses (C, H, N) were performed by the Service Central de Microanalyse at CNRS (France), and were within ±0.4% of the theoretical values except where noted (compounds 10b.HCl and 38.HCl). Elemental analysis results for the tested compounds correspond to >95% purity. The commercial reagents were purchased from Alfa Aesar, Sigma-Aldrich, and Merck, and were used without further purification except for the benzyl bromoacetate. This reagent was purified by fractional distillation in vacuo prior to use. Organic solvents used were in the highest purity, and when necessary, were dried by the standard methods. Solvent abbreviations: THF, tetrahydrofuran; DMF, dimethylformamide; Et\(_2\)O, ethyl ether; MeOH, methanol; EtOH, ethanol; AcOEt, ethyl acetate; DMSO, dimethylsulfoxide.

N-Hydroxy-3,5-dioxospir[piperazine-2,2'-tricyclo[3.3.1.1\(^{3,7}\)]decane]-4-acetamide (7a)
Following the general hydroxylsolation procedure described in the main manuscript, O-benzyl hydroxamate 32 gave the title compound 7a as a white crystalline solid (96%): mp 193-195 °C (dec) (EtOH -Et\(_2\)O); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) δ 1.43 (d, 2H, \(J=12.0\) Hz, 4’e, 9’e-H), 1.55-1.68 (m, 4H, 6’e, 8’e, 10’e-H), 1.75 (s, 1H, 7’-H), 1.79 (s, 1H, 5’-H), 1.94 (s, 2H, 1’, 3’-H), 2.25 (t, 4H, \(J=10.6\) Hz, 4’a, 8’a, 9’a, 10’a-H), 3.13 (t, 1H, \(J=7.8\), 8.4Hz, 1-H), 3.56 (d, 2H, 1’=8.4Hz, 6-H), 6.17 (d, 2H, 5’-H)}.
4.14 (s, 1.5H, CH₂CONHOH, Z-isomer), 4.44 (s, 0.4H, CH₂CONHOH, E-isomer), 8.87 (s, 0.7H, CONHOH₂, Z-isomer), 9.28 (s, 0.2H, CONHOH₂, E-isomer), 10.15 (s, 0.2H, CONHOH, E-isomer), 10.55 (s, 0.7H, CONHOH, Z-isomer); ¹³C NMR (100 MHz , DMSO-d₆) δ 26.7 (5’-C), 26.9 (7’-C), 31.9 (1’ , 3’-C), 32.0 (4’ , 9’-C), 32.8 (8’ , 10’-C), 37.8 (6’-C), 39.2 (CH₂CONHOH, Z-isomer), 39.6 (CH₂CONHOH, E-isomer), 44.0 (6-C), 59.5 (2,2’-C), 164.2(CH₂CONHOH, Z-isomer), 169.6 (CONHOH, E-isomer), 172.3, 174.6 (3, 5-C). Anal. (C₁₅H₂₁N₃O₄) C, H, N. The hydrochloride salt (7a·HCl) was prepared by treating an ethanolic solution of 7a with ethereal HCl under ice cooling, and was fully precipitated by adding ether. The white solid was collected by filtration, triturated with ether, and dried in vacuo. Mp 219-222 °C (dec); Anal. (C₁₅H₂₂ClN₃O₄) C, H, N.

N-Hydroxy-1-methyl-3,5-dioxospiro[piperazine-2,2’-tricyclo[3.3.1.1³⁷]decane]-4-acetamide (7b)

Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 42 gave the title compound 7b as a white crystalline solid (80%): mp 190-192 °C (EtOH-Et₂O); ¹H NMR (400 MHz , DMSO-d₆) δ1.42 (d, 1H, J=10.4 Hz, 4’-e-H), 1.49 (d, 1H, J=10.6 Hz, 9’e-H), 1.55-1.74 (m, 5H, 6’, 8’, 10’e-H), 2.78 (s, 2H, 5’, 7’-H), 2.82-2.85 (m, 4H, 1’, 3’, 4’a, 9’a-H), 3.02 (t, 2H), 3.63 (s, 3H, CH₃). 2.68 (d, 1H, J=12.0 Hz, 10’a-H), 3.44-3.97 (q, 2H, AB, JAB=19.1 Hz, 6-H), 4.07-4.25 (q, 1.5H, AB, JAB=15.5Hz, CH₂CONHOH, Z-isomer), 4.39-4.53 (q, 0.5H, AB, JAB=16.9 Hz, CH₂CONHOH, E-isomer), 8.87 (s, 0.7H, CONHOH, Z-isomer), 9.30 (s, 0.2H, CONHOH₂, E-isomer), 10.17 (s, 0.2H, CONHOH₂, E-isomer), 10.63 (s, 0.7H, CONHOH, Z-isomer); ¹³C NMR (100 MHz , DMSO-d₆) δ25.9 (5’-C), 26.7 (7’-C), 30.0 (1’-C), 31.6 (3’-C), 31.7 (4’-C), 31.8 (9’-C), 32.7 (8’-C), 33.4 (10’-C), 36.7 (CH₃), 37.3 (6’-C), 38.9 (CH₂CONHOH, Z-isomer), 39.7 (CH₂CONHOH, E-isomer), 52.6 (6-C), 64.8 (2,2’-C), 164.1 (CONHOH, Z-isomer), 169.5 (CONHOH, E-isomer), 170.7, 173.8 (3, 5-C); Anal. (C₁₆H₂₃N₃O₄) C, H, N. The hydrochloride salt (7b·HCl) was prepared as described for 7a·HCl. Mp 215-218 °C (dec). Anal. (C₁₆H₂₃ClN₃O₄) C, H, N.

(S)-N-Hydroxy-6-methyl-3,5-dioxospiro[piperazine-2,2’-tricyclo[3.3.1.1³⁷]decane]-4-acetamide (7c)

Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 33 provided the title compound 7c as a white foamy solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent upon drying at 62-64 °C under vacuum (10⁻³ mmHg) in an Abderhalden apparatus gave 7c as a light yellow crystalline solid (91%): mp 88-91 °C; ¹H NMR (600 MHz , DMSO-d₆) δ1.25 (d, 3H, J=13.8 Hz, CH₃), 1.38 (d, 1H, J=12.1 Hz, 9’e-H), 1.47 (d, 1H, J=11.7 Hz, 4’e-H), 1.55-1.72 (m, 5H, 6’, 8’, 10’e-H), 1.76 (s, 1H, 7’-H), 1.79 (s, 1H, 5’-H), 1.85 (s, 1H, 3’-H), 2.08 (s, 1H, 1’-H), 2.16 (d, 1H, J=11.8Hz, 4’a-H), 2.44 (d, 1H, J=12.0Hz, 9’a-H), 2.84 (d, 2H, J=11.2 Hz, 1, 10’a-H), 3.55-3.66 (sym m, 1H, 6-H), 4.09-4.16 (q, 1.5H, AB, JAB=15.4 Hz, CH₂CONHOH, Z-isomer), 4.38-4.48 (q, 0.5H, AB, JAB=16.4 Hz, CH₂CONHOH, E-isomer), 8.82 (s, 0.6H, CONHOH₂, Z-isomer), 9.24 (s, 0.2H, CONHOH₂, E-isomer), 10.10 (s, 0.2H, CONHOH, E-isomer), 10.50 (s, 0.5H, CONHOH, Z-isomer); ¹³C NMR (100 MHz , DMSO-d₆) δ17.9, 18.0 (CH₃), 26.6 (5’-C), 26.8 (7’-C), 30.1, 30.3 (1’-C), 31.1 (4’-C), 32.1 (8’-C), 32.6 (9’-C), 33.4 (10’-C), 33.7, 33.8 (3’-C), 37.7 (6’-C), 39.4 (CH₂CONHOH, Z-isomer), 39.8 (CH₂CONHOH, E-isomer), 48.6 (6-C), 60.0 (2,2’-C), 164.1 (CONHOH, Z-isomer), 169.5 (CONHOH, E-isomer), 174.6 , 174.8 (3 , 5-C); [α]D289 -20 (c 0.2, CHCl₃); CD MS: m/z: 322.2 ([M+H]+, 7), 306.2 ([M-CH₃]+, 37), 278.2 (100); HRMS (ESI): [M+H]+ calec for C₁₅H₂₄N₃O₄, 322.1761, found 322.1739. The hydrochloride salt (7c·HCl) was prepared by treating an ether solution of 7c with ethereal HCl under ice cooling. The white precipitate was collected by
filtration, trititated with ether, and dried in vacuo. Mp 178-180 °C (dec). Anal. (C$_{16}$H$_{24}$Cl$_{3}$N$_{4}$O$_{4}$) C, H, N.

(S)-N-Hydroxy-3,5-dioxo-6-(phenylmethyl)spiro[piperazine-2,2′-tricyclo[3.3.1.1$^{3,7}$]decane]-4-acetamide (7d)

Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 34 provided the title compound 7d as a white foamy solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent as described for 7c gave 7d as a pale yellow crystalline solid (95%): mp 97 – 100 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $δ$1.29 (d, 2H, J=11.5 Hz, 4′, e, 9′-e-H), 1.41–1.73 (complex m, 7H, 4′-a, 6′, 7′, 8′, 10′-e-H), 1.76 (s, 1H, 5′-H), 1.82 (s, 1H, 3′-H), 2.05 (s, 1H, 1′-H), 2.17 (d, 1H, J=11.4 Hz, 9′-a-H), 2.66-2.90 (complex m, 3H, CH$_3$H$_2$Ph, 1, 10′a-H), 3.32 (dd, 1H, AMX, M region, $J_{CH}^X$=11.4 Hz, 9′H, 1, 10′H), 3.40-3.50 (m, 4H, CH$_2$Ph, 4), 4.42-4.52 (q, AB, 0,4 H, $J_{CH}^Y$=16.8 Hz, CH$_2$CONHOH, E- isomer), 7.16-7.23 (m, 1H, 4-aromatic H), 7.24-7.36 (m, 4H, 2, 3, 5, 6-aromatic H), 8.88 (s, 0.7H, CONHOH, Z- isomer), 9.30 (s, 0.2H, CONHOH, E-isomer), 10.16 (s, 0.2H, CONHOH, E- isomer), 10.56 (s, 0.7H, CONHOH, Z- isomer); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $δ$26.5 (5′-C), 29.7 (2, 3, 5-C), 29.9, 30.0 (1′-C), 30.8 (4′-C), 32.0 (9′-C), 32.7 (8′-C), 33.3 (10′-C), 34.0, 34.1 (3′-C), 37.3 (CH$_2$Ph), 37.7 (6′-C), 39.6 (CH$_2$CONHOH, Z-isomer), 39.9 (CH$_2$CONHOH, E-isomer), 54.26, 54.33 (6-C), 55.39, 55.93 (2,2′-C), 126.2 (4-aromatic C), 128.0, 129.0 (2, 3, 5, 6-aromatic C), 138.6 (1- aromatic C), 164.1 (CONHOH, Z-isomer), 169.5 (CONHOH, E-isomer), 173.7, 174.5 (3, 5-C); $[α]^{25}_{D590}$ -60 (c 0.2, CHCl$_3$); CI′ MS: m/z 398.2 ([M-H]$^+$), 398.2074, found 398.2059. The hydrochloride salt (7d.HCl) was prepared as described for 7c.HCl. Mp 143-146 °C (dec); Anal. (C$_{22}$H$_{28}$Cl$_{3}$N$_{4}$O$_{4}$) C, H, N.

(R)-N-Hydroxy-3,5-dioxo-6-(phenylmethyl)spiro[piperazine-2,2′-tricyclo[3.3.1.1$^{3,7}$]decane]-4-acetamide (7e)

Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 35 provided the title compound 7e as a light yellow crystalline solid (95%): mp 96–98 °C; NMR spectroscopic data of this compound are identical to that of 7d; $[α]^{25}_{D590}$ +59 (c 0.2, CHCl$_3$); EI MS: m/z 397.2 ([M$^+$], 7), 307.2 ([M+H-CH$_2$Ph]$^+$, 17), 306 ([M-CH$_2$Ph]$^+$, 100); HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{28}$N$_{4}$O$_{4}$, 398.2074, found 398.2064. The hydrochloride salt (7e.HCl) was prepared as described for 7c.HCl. Mp 142-145 °C (dec). Anal. (C$_{22}$H$_{28}$Cl$_{3}$N$_{4}$O$_{4}$) C, H, N.

(R,S)-N-Hydroxy-3,5-dioxo-6-(phenylmethyl)spiro[piperazine-2,2′-tricyclo[3.3.1.1$^{3,7}$]decane]-4-acetamide (8)

Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 36 provided the title compound 8 as a white foamy solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent as described for 7e gave 8 as a light yellow crystalline solid (96%): mp 90–92 °C. NMR spectroscopic data of this compound are identical to that of 7d; CI′ MS: m/z 398.3 ([M+H]$^+$, 100), 306.2 ([M-CH$_2$Ph]$^+$, 61); HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{28}$N$_{4}$O$_{4}$, 398.2074, found 398.2025. The hydrochloride salt (8.HCl) was prepared as described for 7c.HCl. Mp 135-138 °C (dec). Anal. (C$_{22}$H$_{28}$Cl$_{3}$N$_{4}$O$_{4}$) C, H, N.

N-Hydroxy-3,5-dioxo-1,4-diazaspiro[5.7]tridecane-4-acetamide (9a)

Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 60 provided the title compound 9a as a white foamy solid, which strongly binds the
eluting solvent (AcOEt, MeOH). Removal of the entrapped solvents as described for 7c gave 9a as a pale yellow solid (90%): mp 148–151 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$1.58-1.70 (m, 4H, 7, 9, 11, 13-H), 1.95-1.99 (q, 2H, J=6.7, 9.2 Hz, 7, 13-H), 2.98 (t, 1H, J=8.5 Hz, 1-H) 3.57 (d, 2H, J=7.9 Hz, 2-H), 4.13 (s, 1.5H, CH$_2$CONHOH, Z-isomer), 4.42 (s, 0.4H, CH$_2$CONHOH, E-isomer), 8.86 (s, 0.7H, CONHOH, Z-isomer), 9.27 (s, 0.2H, CONHOH, E-isomer), 10.15 (s, 0.2H, CONHOH, E-isomer), 10.52 (s, 0.7H, CONHOH, Z-isomer); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$20.9 (9, 11-C), 24.4 (10-C), 27.7 (8, 12-C), 30.2 (7, 13-C), 38.6 (CH$_2$CONHOH, Z-isomer), 38.8 (CH$_2$CONHOH, E-isomer), 44.7 (2-C), 58.9 (6-C), 163.9 (CONHOH, Z-isomer), 169.3 (CONHOH, E-isomer), 171.5, 176.3 (3, 5-C); CI$^+$ MS: m/z: 284.2 ([M+H]$^+$), 11), 268.2 (46), 240.2(100), 222.2 (72), 195 (70); HRMS (ESI): [M+H]$^+$ calcd for C$_{13}$H$_{22}$N$_3$O$_4$, 284.1605, found 284.1586. The hydrochloride salt (9a.HCl) was prepared as described for 7a.HCl. Mp 179-182 °C. Anal. (C$_{13}$H$_{22}$ClN$_3$O$_4$) C, H, N.

**N-Hydroxy-1-methyl-3,5-dioxo-1,4-diazaspiro[5.7]tridecane-4-acetamide (9b)**

Following the general hydrogenolysis procedure described in the main manuscript, 0-benzyl hydroxamate 72 provided the title compound 9b as a white foamy solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent as described for 7c gave 9b as a white crystalline solid (90%): mp 160–163 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$1.65-1.87 (m, 4H, 7, 9, 11, 13-H), 1.89-2.04 (m, 2H, 7, 13-H), 2.36 (s, 2.2H, CH$_2$, Z-isomer), 2.38 (s, 0.9H, CH$_3$, E-isomer), 3.73 (s, 2H, 2-H), 4.16 (s, 1.5H, CH$_2$CONHOH, Z-isomer), 4.46 (s, 0.5H, CH$_2$CONHOH, E-isomer), 8.88 (s, 0.8H, CONHOH, Z-isomer), 9.30 (br s, 0.3H, CONHOH, E-isomer), 10.18 (s, 0.3H, CONHOH, E-isomer), 10.63 (s, 0.7H, CONHOH, Z-isomer); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$20.4 (9, 11-C), 24.3 (10-C), 27.5 (8, 12-C), 29.3 (7, 13-C), 38.1 (CH$_2$CONHOH, Z-isomer), 38.5, 38.6 (CH$_3$). 38.9 (CH$_2$CONHOH, E-isomer), 53.7 (2-C), 63.7 (6-C), 164.0 (CONHOH, Z-isomer), 169.3 (CONHOH, E-isomer), 170.0, 175.5 (3, 5-C); CI$^+$ MS: m/z: 284.2 ([M+H]$^+$), 7), 282.2 ([M–CH$_2$]$^+$, 77), 281.2(26), 254.2(100), 236.2(89), 209.2(100); HRMS (ESI): [M+H]$^+$ calcd for C$_{13}$H$_{22}$N$_3$O$_4$, 298.1761, found 298.1738. The hydrochloride salt (9b.HCl) was prepared as described for 7a.HCl. Mp 163-165 °C (dec). Anal. (C$_{14}$H$_{24}$ClN$_4$O$_4$) C, H, N.

**(S)-N-Hydroxy-2-methyl-3,5-dioxo-1,4-diazaspiro[5.7]tridecane-4-acetamide (9c)**

Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 61 provided the title compound 9c as a white foamy solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent as described for 7c gave 9c as a white crystalline solid (90%): mp 82–85 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$0.28–0.4 (3H, 6, 10, 11-CH$_3$), 1.35-1.95 (complex m, 13H, 7, 8, 9, 10, 11, 12, 13-H), 2.07-2.13 (sym q, 1H, J=9.2 Hz, 13-H), 2.72 (br d, 1H, J=8.3 Hz, 1-H), 3.66 (~br t, 1H, J=6-7 Hz, 2-H), 4.07-4.16 (q, AB, 1.5H, J$_{AB}$=15.2 Hz, CH$_2$CONHOH, Z-isomer), 4.41 (s, 0.4H, CH$_2$CONHOH, E-isomer), 8.85 (s, 0.8H, CONHOH, Z-isomer), 9.26 (s, 0.2H, CONHOH, E-isomer), 10.13 (s, 0.2H, CONHOH, E-isomer), 10.51 (s, 0.8H, CONHOH, Z-isomer); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$17.0 (CH$_3$), 20.8 (9-C), 21.2 (11-C), 24.5 (10-C), 26.9 (8-C), 27.8 (7-C), 28.5 (12-C), 33.3 (13-C), 39.1 (CH$_2$CONHOH, Z-isomer), 39.2 (CH$_2$CONHOH, E-isomer), 48.8 (2-C), 59.8 (6-C), 163.9 (CONHOH, Z-isomer), 169.3 (CONHOH, E-isomer), 173.8, 176.6 (3, 5-C); [d$_{289}$]$^{12}$ +12 (c 0.1, CHCl$_3$); EI MS: m/z 297.2([M]$^+$, 11), 269.1([M–H$_2$O]$^+$, 61), 264.1(52), 209.2(53); HRMS (ESI): [M+H]$^+$ calcd for C$_{14}$H$_{24}$ClN$_3$O$_4$, 298.1767, found 298.1744. The hydrochloride salt (9c.HCl) was prepared as described for 7c.HCl. Mp 170-172 °C (dec). Anal. (C$_{14}$H$_{24}$Cl N$_3$O$_4$) C, H, N.
Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 62 provided the title compound 9d as a white foamy solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent upon drying at 50–55 °C under vacuum (10⁻³ mmHg) in an Abderhalden apparatus gave 9d as a white crystalline solid (98%): mp 65–68 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 1.18-1.67 (m, 11H, 7, 8, 9, 10, 11, 12-13-H), 1.69-1.82 (m, 2H, 7, 12-H), 2.0-2.12 (m, 1H, 13-H), 2.56-2.65 (m, 1H, 1-H), 2.68-2.82 (m, 1H, AMX, A region, CH₂H₃₂Ph), 3.32 (dd under DMSO water peak, 1H, AMX, X region, 2-Hx), 4.09-4.18 (q, AB, 1.6H, J₆₇=15.6 Hz, CH₂CONHOH, Z-isomer), 4.42 (s, 0.4H, CH₂CONHOH, E-isomer), 7.14-7.22 (m, 1H, 4-aromatic H), 7.23-7.33 (m, 4H, 2.3,5,6-aromatic H), 8.85(s, 0.7H, CONHOH, Z-isomer), 9.27 (s, 0.2H, CONHOH, E-isomer), 10.15(s, 0.2H, CONHOH, Z-isomer), 10.51 (s, 0.7H, CONHOH, Z-isomer); ¹³C NMR (100 MHz, DMSO-d₆) δ 205.1 (4, C), 217.5 (17, 21, C), 256.2 (86); HRMS (ESI): [M+H⁺]⁺ calcd for C₂₄H₂₆ClN₂O₂ 374.2069, found 374.2047. The hydrochloride salt (9d.HCl) was prepared as described for 7c.HCl. Mp 202-205 °C (dec). Anal. (C₂₄H₂₆ClN₂O₂) C, H, N.

N-Hydroxy-3,5-dioxo-1,4-diazaspiro[5.6]dodecane-4-acetamide (10a)

Following the general hydrogenolysis procedure described in the main manuscript, O-benzyl hydroxamate 63 provided the title compound 10a as a white foamy solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent as described for 7c gave 10a as a pale yellow crystalline solid (90%): mp 142–144 °C (dec); ¹H NMR (400 MHz, DMSO-d₆) δ 1.18-1.76 (m, 10H, 7, 8, 9, 10, 11, 12-H), 1.82-1.97 (m, 2H, 7, 12-H), 3.01 (br s 1H, 1-H), 3.56 (d, 2H, J₈₉=6.4 Hz, 2-H), 4.13 (s, 1.6H, CH₂CONHOH, Z-isomer), 4.42 (s, 0.4H, CH₂CONHOH, E-isomer), 8.87 (s, 0.7H, CONHOH, Z-isomer), 9.27 (s, 0.2H, CONHOH, E-isomer), 10.15 (s, 0.2H, CONHOH, Z-isomer), 10.53 (s, 0.7H, CONHOH, Z-isomer); ¹³C NMR (100 MHz, , DMSO-d₆) δ 217.8 (11, C), 29.4, 29.5 (9, 10-C), 35.1 (7, 12-C), 38.7(CH₂CONHOH, Z-isomer), 38.9 (CH₂CONHOH, E-isomer) 44.7 (2-C), 59.6, 59.7 (6-C), 163.9 (CONHOH, Z-isomer), 169.3 (CONHOH, E-isomer), 171.5, 176.9 (3, 5-C); CI⁺ MS: m/z 270.2([M+H⁺]⁺, 18), 252.1([M+H–H₂O+x]⁺, 24), 226.8(16), 209.1(100); HRMS (ESI): [M+H⁺]⁺ calcd for C₁₂H₁₅N₂O₄, 270.1448, found 270.1434. The hydrochloride salt (10a.HCl) was prepared as described for 7a.HCl. Mp 190-192 °C (dec). Anal. (C₁₂H₁₇ClN₂O₄) C, H, N.

N-Hydroxy-1-methyl-3,5-dioxo-1,4-diazaspiro[5.6]dodecane-4-acetamide (10b)

Following the general hydroxamate procedure described in the main manuscript, O-benzyl hydroxamate 73 provided the title compound 10b as a white crystalline solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent upon drying at 40 °C under vacuum (10⁻³ mmHg) in an Abderhalden apparatus gave 10b as a glass solid (93%): ¹H NMR (400 MHz, DMSO-d₆) δ 1.46-1.65 (br s, 8H, 8, 9, 10, 11-H), 1.78-2.0 (m, 4H, 7, 12-H), 2.37 (s, 2.2H, CH₃, Z-isomer), 2.39 (s, 0.8H, CH₃, E-isomer), 3.72 (s, 2H, 2-H), 4.16 (s, 1.4H, CH₂CONHOH, Z-isomer), 4.46 (s, 0.5H, CH₂CONHOH, E-isomer), 8.87 (s, 0.7H, CONHOH, Z-isomer), 9.29 (s, 0.2H, CONHOH, E-isomer), 10.17 (s, 0.2H, CONHOH, E-isomer), 10.62 (s, 0.7H, CONHOH, Z-isomer); ¹³C NMR (100 MHz, , DMSO-d₆) δ 216.8 (8, 11-C), 28.7 (9, 10-C), 33.4 (7, 12-C), 38.16, 38.21 (CH₃), 38.3 (CH₂CONHOH, Z-isomer), 39.0 (CH₂CONHOH, E-isomer), 53.7 (2-C), 64.6 (6-C), 163.9 (CONHOH, Z-isomer), 169.3 (CONHOH, E-isomer), 170.0, 175.4, 175.5 (3, 5-C); CI⁺ MS: m/z: 284.2 ([M+H⁺]⁺, 100), 283.2 ([M⁺]⁺, 21), 256.2(86); HRMS (ESI): [M+H⁺]⁺ calcd for C₁₃H₂₂N₃O₄, 284.1610, found 284.1573. The hydrochloride salt (10b.HCl) was prepared as described for 7c.HCl. Mp 132-136 °C (slightly hydroscopic). Anal. (C₁₃H₂₂ClN₃O₄) C, H, N.
3,5-Dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1\(^{7}\)]decane]-4-acetamide (43)

Using a procedure essentially similar to that described earlier for the preparation of compound 22, the amide ester precursor 17 (365 mg, 1.3 mmol) was treated with (CH\(_3\))\(_3\)SiNK (259 mg, 1.3 mmol), and the 2,6-DKP imidic potassium salt formed was subsequently reacted with bromoacetamide (190 mg, 1.37 mmol). The reaction mixture was then poured onto cold brine and quenched as in 22. The resulting residue was chromatographed on a silica gel column eluting first with AcOEt-Et\(_2\)O 1:1 and then AcOEt to give the title compound 43 as a white solid (191 mg, 50%): mp 168–169°C (EtOH – Et\(_2\)O); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\)1.43 (d, 2H, \(J=12.0\) Hz, 4′-H), 4.17 (s, 2H, C\(\_N\)), 8.89 (s, 0.5H, CON\(\_O\)), 4.84, 4.88 (s+s, 2H, CONHOC\(\_O\)), 7.37 (6-C’), 39.8, 39.9 (CH\(_2\)CONHCH\(_3\)), 44.2 (6-C), 60.3, 60.4 (2,2’-C), 78.1, 79.4 (CONHCH\(_3\)), 128.5, 128.8, 129.1, 129.3, 129.4 (2, 3, 4, 5, 6-aromatic C), 133.9, 134.9 (1-aromatic C), 165.4 (CONHCH\(_3\), Z-isomer), 170.5 (CONHCH\(_3\), E-isomer), 172.4, 172.5, 174.5, 174.6 (3, 5-C). Anal. (C\(_{15}\)H\(_{21}\)N\(_3\)O\(_3\)) C, H, N.

3,5-Dioxo-N-(phenylmethoxy)spiro[piperazine-2,2′-tricyclo[3.3.1.1\(^{7}\)]decane]-4-acetamide (32)

To a solution of the carboxylic acid 27\(^9\) (320 mg, 1.1 mmol) in dry THF (15mL) was added 1,1′-carbonyldiimidazole (214 mg, 1.32 mmol), and the mixture was stirred at 28°C for 1h under argon. Then, O-benzylhydroxylamine hydrochloride (210 mg, 1.32 mmol) and triethylamine (399 mg, 2.4 mmol) were added successively, and the stirring was continued at 28°C for 24h and then at 45°C for 1h under argon. After removal of the solvent in vacuo, water (20 mL) was added, and the mixture was extracted with ethyl acetate (3x20 mL). The combined extracts were washed with brine (2x20 mL) dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo. The viscous oily residue was purified by column chromatography on silica gel eluting first with Et\(_2\)O-n-hexane 2:1 and then AcOEt to give the corresponding O-benzyl hydroxamate 32 as a white solid (312 mg, 72%): mp 162-164°C (AcOEt); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.50 (d, 2H, \(J=12.5\) Hz, 4′-H), 1.62-1.75 (m, 4H, 6′-H), 1.79 (s, 1H, 7′-H), 1.86 (s, 1H, 5′-H), 1.94 (s, 1H, 1′-H), 1.99 (s, 1H, 3′-H), 1.90-2.08 (br s, 1H, 1-H), 2.23 (br s, 4H, 4′-a, 8′-a, 9′-a, 10′-a-H), 3.68, 3.72 (s+s, 2H, 6-H), 4.23 (s, 0.99H, CH\(_2\)CONHOCH\(_2\)Ph, E-isomer), 4.84, 4.88 (s+s, 2H, CONHOCH\(_2\)Ph, Z-isomer), 7.37 (br s, 5H, aromatic–H), 8.34 (s, 0.4H, CONHOCH\(_2\)Ph, E-isomer), 8.89 (s, 0.5H, CONHOCH\(_2\)Ph, Z-isomer); \(^1\)C NMR (100 MHz, CDCl\(_3\), 270K) \(\delta\) 26.8 (5-C), 27.0 (7′-C), 32.1 (4′, 9′-C), 32.3 (1′, 3′-C), 33.0 (8′, 10′-C), 37.7 (6-C), 39.8, 39.9 (CH\(_2\)CONHCH\(_2\)Ph), 44.2 (6-C), 60.3, 60.4 (2,2′-C), 78.1, 79.4 (CONHOCH\(_2\)Ph), 128.5, 128.8, 129.1, 129.3, 129.4 (2, 3, 4, 5, 6-aromatic C), 133.9, 134.9 (1-aromatic C), 165.4 (CONHOCH\(_2\)Ph, Z-isomer), 170.5 (CONHOCH\(_2\)Ph, E-isomer), 172.4, 172.5, 174.5, 174.6 (3, 5-C). Anal. (C\(_{22}\)H\(_{22}\)N\(_3\)O\(_4\)) C, H, N.

3,5-Dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1\(^{7}\)]decane]-4-acetoxydrazide (44)

Carboxylic acid 27\(^9\) (585 mg, 2.0 mmol) was treated with 1,1′-carbonyldiimidazole (390 mg, 2.4 mmol) in dry THF (26 mL) as described in 32. To the solution was then added benzylcarbazate (399 mg, 2.4 mmol), and the reaction mixture was stirred at 28°C for 25h under argon. After removal of the solvent in vacuo, the residue was dissolved in chloroform, and the resulting solution was dried with brine (2x30 mL), dried (Na\(_2\)SO\(_4\)) and evaporated. The residue was purified by column chromatography on silica gel eluting first with AcOEt-n-hexane 1:1 and then AcOEt to give a white foamy solid (700 mg): EI MS m/z 440.4 ([M]+, 7). This was then dissolved in EtOH (55 mL), and the solution was hydrogenated as described for the preparation of 7a-e, 8, 9a-d, 10a, and 10b to yield the acetoxydrazide 44 as a TLC and \(^1\)H NMR pure white solid (466 mg, 76% from 27), which was recrystalized from EtOH-Et\(_2\)O: mp 197 – 200°C (dec); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 1.43 (d, 2H, \(J=11.9\) Hz, 4′-H), 1.58-1.72 (m, 4H, 6′, 8′-E, 10′-E-H), 1.75 (s, 1H,
7°-H), 1.79 (s, 1H, 5'-H), 1.90-2.0 (s, 2H, 1', 3'-H), 2.26 (s, 4H, 4'a, 8'a, 9'a, 10'a-H), 3.13 (br s, 1H, 1-H), 3.56 (d, 2H, J = 7.0 Hz, 6-H), 3.92-4.75 (v br s, 2H, CONHNH₂), 4.18 (s, 1H, CH₂CONHNH₂, Z-isomer), 4.52 (s, 0.2H, CH₂CONHNH₂, E-isomer), 8.46 (s, 0.1H, CONHNH₂, E-isomer), 9.06 (s, 0.8H, CONHNH₂, Z-isomer); 13C NMR (100 MHz, DMSO-d₆) δ 26.6 (5'-C), 27.0 (5'-, 7-Ad C), 27.2 (7-Ad C), 29.6 (4-Ad C), 30.4 (9-Ad C), 33.4 (1'-Ad C), 34.1 (8'-Ad C), 34.7 (10'-Ad C), 36.5 (3'-Ad C), 37.4 (4'-Ad C), 32.7 (8'-, 10'-C), 37.7 (6'-C), 39.95, 40.02 (CH₂CONHNH₂), 44.0 (6-C), 59.4 (2', 2'-C), 166.5 (CONHNH₂), 172.2, 172.3, 174.5, 174.7 (3, 5-C). Anal. (C₁₃H₂₂N₄O₃) C, H, N.

N-Methoxy-3,5-dioxospiro[piperazine-2,2'-tricyclo[3.3.1.1³⁷]decane]-4-acetamide (45)

Prepared from carboxylic acid 27 in exactly the same procedure described in 32 except that O-methyl hydroxylamine hydrochloride was used. The resulting oily residue was chromatographed on silica gel column using AcOEt-EtOAc (82%); 1H NMR (400 MHz, CDCl₃) δ 1.51 (d, 2H, J = 12.3 Hz, 4'e, 9'e-H), 1.63-1.77 (m, 4H, 6', 8'e, 10'e-H), 1.82 (s, 1H, 7'-H), 1.86 (s, 1H, 5'-H), 1.92-2.10 (br s, 3H, 1', 1', 3'-H), 2.27 (d, 4H, J = 11.8 Hz, 4'a, 8'a, 9'a, 10'a-H), 3.60-3.88 (br s, 5H, CONHOC₂=O), 4.27 (br s, 1H, CH₂CONHOCH₃, Z-isomer), 4.63 (br s, 0.7H, CH₂CONHOCH₃, E-isomer), 8.97 (br s, 0.3H, CONHOCH₃, E-isomer), 9.67 (br s, 0.6H, CONHOCH₃, Z-isomer); 13C NMR (100 MHz, CDCl₃) δ 27.0 (5'-C), 27.2 (7'-C), 32.2 (4'-, 9'-C) 32.5 (1', 3'-C), 33.1 (8', 10'-C), 37.9 (6'-C), 39.8 (CH₂CONHOCH₃), 44.4 (6-C), 60.4 (2'-, 3'-C), 64.3, 65.1 (CONHOCH₃), 165.6 (CONHOCH₃, Z-isomer), 170.6 (CONHOCH₃, E-isomer), 172.6, 174.6 (3, 5-C), Cl⁺ MS: m/z 322.2 ([M+H]⁺, 24), 290.2 ([M-OCH₃]⁺, 15), 294.2 (64), 219.1 (79). The hydrochloride salt (45.HCl) was prepared by treating a solution of 45 in Et₂O-AcOEt 3:2 with ethereal HCl under ice cooling. The white solid was collected by filtration, triturated with Et₂O and dried at 62-64°C under vacuum (10⁻³ mmHg). Mp 193-195°C; Anal. (C₁₆H₂₄Cl₂N₄O₂.0.4Et₂O) C, H, N.

N-[2-Cyano(tricyclo[3.3.1.1³⁷]dec–2–yl)]–L–phenylalanine methyl ester (14)

Prepared by employing the Strecker reaction on the adamantanone 11 in exactly the same procedure described earlier for the preparation of compound 12, except that methyl L-phenylalanininate hydrochloride was used. The resulting off-white solid was purified by column chromatography on silica gel eluting first with Et₂O-n-hexane 1:2 and then 1:1 to afford the title compound 14 as a white crystalline solid (89%): mp 78-80°C (Et₂O-n-pentane); 1H NMR (400 MHz, CDCl₃) δ 1.15 (dd, 1H, J = 2.5, 12.4 Hz, 4e-Ad H), 1.40 (dd, 1H, J = 2.4, 12.7 Hz, 9e-Ad H), 1.48-1.62 (complex m, 4H, 4'a, 5, 6-Ad H), 1.64-1.88 (complex m, 6H, 1, 3, 7, 8e, 10e-Ad H, NH), 1.98 (d, 1H, J = 13.4 Hz, 8a-Ad H), 2.03-2.13 (m, 2H, 9a, 10a-Ad H), 2.76-2.81 (q, 1H, AMX, A region, J_{AM}=13.4 Hz, J_{AX}=8.0 Hz, NH-CH₂-CH₃H₃Ph), 2.92-2.97 (q, 1H, AMX, M region, J_{AM}=13.4 Hz, J_{MX}=5.6 Hz, NH-CH₂-CH₃H₃Ph), 3.58-3.62 (q, 1H, AMX, X region, J_{AX}=8.0 Hz, J_{MX}=5.6 Hz, NH-CH₂-CH₃H₃Ph), 3.64 (s, 3H, CH₃, Jₗ=7.07-7.24 (m, 5H, aromatic H); 13C NMR (100 MHz, CDCl₃) δ (ppm): 26.4 (5-Ad C), 26.6 (7-Ad C), 29.6 (4-Ad C), 30.4 (9-Ad C), 33.4 (1-Ad C), 34.1 (8-Ad C), 34.7 (10-Ad C), 36.5 (3-Ad C), 37.4 (3'-Ad C), 40.8 (CH₂Ph), 51.8 (CH₃), 57.7 (HN-CH), 60.7 (2-Ad C), 121.9 (CN), 126.7, 128.2, 129.5 (2, 3, 4, 5, 6-aromatic C), 137.1 (1-aromatic C), 174.8 (CO₂CH₃); [α]_{25}^{289} = -6 (c 0.2, AcOEt). Anal. (C₁₂H₂₀N₂O₂) C, H, N.

N-[2-Aminocarbonyl(tricyclo[3.3.1.1³⁷]dec–2–yl)]–L–phenylalanine methyl ester (19)

To a vigorous stirred solution of the aminonitrile 14 (1.93 g, 5.7 mmol) in CH₂Cl₂ (24 mL) was added dropwise H₂SO₄ 97% (9.5 mL), and the mixture was vigorously stirred at room temperature for 48 h. The reaction mixture was then poured onto ice (30 g) and neutralized with aqueous NH₃ 26% under ice cooling. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3x30 mL). The combined organic phase was washed with water (30
mL) and brine (30 mL), dried (Na$_2$SO$_4$), and evaporated. The resulted coloured residue was purified by column chromatography on silica gel using AcOEt-Et$_2$O 1:1 to afford the title compound 19 as a white crystalline solid (1.04 g, 51%): mp 141-143 °C (CH$_2$Cl$_2$-Et$_2$O); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$1.27 (~d, 1H, $J=11.7$ Hz, 9e-Ad H), 1.47-1.73 (complex m, 8H, 4a, 5, 6, 7, 8, 10e-Ad H), 1.74-1.92 (m, 3H, NH, 3, 10a-Ad H), 1.95 (s, 1H, 1-Ad H), 2.12 (d, 1H, $J$=12.6 Hz, 9a-Ad H), 2.67-2.72 (q, 1H, AMX, A region, $J_{AM}$=13.2 Hz, $J_{AX}$=7.8 Hz, NH-CH$_3$-CH$_2$HM), 2.80-2.85 (q, 1H, AMX, M region, $J_{AM}$=13.2 Hz, $J_{MX}$=5.7 Hz, NH-CH$_3$-CH$_2$HM), 3.53 (br s, 4H, CH$_3$, NH-CH$_3$-CH$_2$HM), 5.50 (br s, 2H, CONH$_2$), 7.05-7.22 (m, 5H, aromatic H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$26.7 (5-Ad C), 26.9 (7-Ad C), 31.4 (4-Ad C), 31.7 (1-Ad C), 32.1 (9-Ad C), 34.2 (3-Ad C), 34.4 (8-Ad C), 34.6 (10-Ad C), 37.6 (6-Ad C), 41.5 (CH$_2$Ph), 51.4 (CH$_3$), 56.3 (NHCH), 64.2 (2-Ad C), 126.5, 128.1, 129.6 (2, 3, 4, 5, 6-aromatic C), 137.5 (1-aromatic C), 175.4 (CO$_2$CH$_3$), 176.9 (CONH$_2$); [α]$_{D}^{25}$ = 12 (c 0.2, MeOH). Anal. (C$_{21}$H$_{28}$N$_3$O$_3$) C, H, N.

(S)-3,5-Dioxo-6-(phenylmethyl)spiro[piperazine-2,2’-tricyclo[3.3.1.1$^{3,7}$]decane]-4-acetic acid benzyl ester (24)

Prepared from the above amide-ester precursor 19 in exactly the same procedure described earlier for the preparation of compound 22. The resulted oily residue was purified by column chromatography on silica gel using Et$_2$O-n-hexane 1:1 to afford the title compound 24 as a colourless viscous oil (86%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$1.38 (d, 2H, $J$=12.9Hz, 4’e, 9’e-H), 1.29-1.48 (v br s, 1H, 1-H), 1.51-1.70 (complex m, 7H, 4’a, 6’, 7’, 8’, 10’e-H), 1.75 (br s, 2H, 3’, 5’-H ), 1.95 (d, 1H, $J$=12.8 Hz, 9’a-H), 2.02 (s, 1H, 1’, 1’-H), 2.82 (d, 1H, $J$=12.6 Hz, 10’a-H), 2.92-2.97 (q, 1H, AMX, A region, $J_{AM}$=13.8 Hz, $J_{AX}$=8.1 Hz, 6-CH$_2$HM), 3.30 (dd, 1H, AMX, M region, $J_{AM}$=13.8 Hz, $J_{MX}$=4.0 Hz, 6-CH$_2$HM), 3.77-3.87 (m, 1H, AMX, X region, 6-Hx), 4.33-4.53 (q, AB, 2H, $J$=16.8 Hz, CH$_2$CO$_2$CH$_3$Ph), 5.07 (s, 2H, CO$_2$CH$_3$Ph), 7.10-7.35 (m, 10H, aromatic H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$26.9 (5’-C), 27.0 (7’-C), 30.5 (1’-C), 31.3 (4’-C), 32.4 (9’-C), 33.2 (8’-C), 33.9 (10’-C), 34.8 (3’-C), 37.8 (CH$_3$Ph), 37.9 (6’-C), 40.9 (CH$_2$CO$_2$CH$_3$Ph), 54.1 (6-C), 60.8 (2,2’-C), 67.2 (CO$_2$CH$_3$Ph), 127.1, 128.3, 128.4, 128.6, 128.7, 129.2, 135.1, 136.6 (aromatic C), 168.0 (CO$_2$CH$_3$Ph) 173.5, 174.1 (3, 5-C); [α]$_{D}^{25}$ = 34 (c 0.2, CHCl$_3$); C$_7$H$_{17}$N$_2$O$_2$: m/z 473.3 ([M+H]$^+$, 50), 472.3 ([M]$^+$, 13), 382.2 ([M+CH$_2$CH$_2$]$^+$, 23), 381.2 ([M-CH$_2$]$^+$, 100); HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{23}$N$_3$O$_4$, 473.2440, found 473.2440.

(S)-3,5-Dioxo-6-(phenylmethyl)spiro[piperazine-2,2’-tricyclo[3.3.1.1$^{3,7}$]decane]-4-acetic acid (29)

Prepared from the above benzyl ester 24 by catalytic hydrogenolysis in EtOH-AcOEt 3:2 following the procedure described earlier for the preparation of carboxylic acid 27. White foamy solid which strongly binds the aforementioned solvents. Removal of the entrapped solvents upon drying at 62-64 °C under vacuum (10$^{-3}$ mmHg) in an Abderhalden apparatus gave the title compound 29 as a glass solid (almost quantitative yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$1.35-1.47 (m, 2H, 4’e, 9’e-H), 1.52-1.73 (m, 7H, 4’a, 6’, 7’, 8’, 10’e-H), 1.95 (d, 1H, $J$=12.5 Hz, 9’a-H), 2.05 (s, 1H, 1’, 1’-H), 2.84 (d, 1H, $J$=12.8 Hz, 10’a-H), 2.99-3.05 (q, 1H, AMX, A region, $J_{AM}$=13.8 Hz, $J_{AX}$=8.0 Hz, CH$_3$HM), 3.31 (dd, 1H, AMX, M region, $J_{AM}$=13.8 Hz, $J_{MX}$=4 Hz, CH$_2$HM), 3.82-3.85 (q, 1H, AMX, X region, $J_{AX}$=8.0 Hz, $J_{MX}$=4 Hz, 6-Hx), 4.35-4.51 (q, AB, 2H, $J_{AB}$=17.1 Hz, CH$_2$CO$_2$H), 4.20-6.80 (v br s, 2H, COO$_2$H, 1-H), 7.13-7.30 (m, 5H, aromatic H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$26.8 (5’-C), 26.9 (7’-C), 30.4 (1’-C), 31.3 (4’-C), 32.4 (9’-C), 33.2 (8’-C), 33.8 (10’-C), 34.7 (3’-C), 37.5 (CH$_3$Ph), 37.9 (6’-C), 40.7 (CH$_2$CO$_2$H), 54.0 (6-C), 61.1 (2,2’-C), 127.2, 128.8, 129.3 (2 3, 4, 5, 6-aromatic C), 136.3 (1-aromatic C), 173.0 (CO$_2$H), 173.5 (3, 5-C). The hydrochloride salt (29HCl) was prepared as described for 7cHCl. Mp 182-184 °C (dec); [α]$_{D}^{25}$ = 24 (c 0.2, MeOH). Anal. (C$_{22}$H$_{27}$Cl N$_2$O$_4$) C, H, N.
(S)-6-(Phenylmethyl)spiro[piperazine–2,2’–tricyclo[3.3.1.1\(^{3,7}\)]decane]–3,5–dione (37)

Prepared from the above amide-ester precursor 19 in exactly the same procedure described earlier for the preparation of the diketopiperazine 6a. White foamy solid which strongly binds the eluting solvents. Removal of the entrapped solvents upon drying at 62-64 °C under vacuum (10\(^{-3}\) mmHg) gave the title compound 37 as a glass solid (96%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.39 (d, 2H, J=12.4 Hz, 4’e, 9’e-H), 1.37-1.50 (v br s, 1H, 1-H), 1.53-1.70 (complex m, 7H, 4’a, 6’, 7’, 8’, 10’e-H), 1.74 (s, 1H, 3’-H), 1.80 (s, 1H, 5’-H), 1.92-2.05 (m, 2H, 1’, 9’a-H), 2.86 (d, 1H, J=12.9 Hz, 10’a-H), 2.97-3.02 (q, 1H, AMX, A region, J\(_{AM}\)=13.8 Hz, J\(_{AX}\)=7.6 Hz, CH\(_2\)HMPh), 3.28 (dd, 1H, AMX, X region, J\(_{AX}\)=13.8 Hz, J\(_{MX}\)=4.0 Hz, CH\(_2\)HMPh), 3.68-3.71 (q, 1H, AMX, X region, J\(_{AX}\)=7.6 Hz, J\(_{MX}\)=4.0 Hz, 6-Hx), 7.16-7.28 (m, 5H, aromatic H), 7.89 (s, 1H, 4-H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 26.3 (5’-C), 37.9 (6’-C), 33.2 (8’-C), 33.8 (10’-C), 34.6 (3’-C), 36.7 (CH\(_2\)Ph), 37.9 (6’-C), 53.6 (6-C), 61.1 (2’,2’-C), 127.1, 128.7, 129.3 (2, 3, 4, 5, 6-aromatic C), 136.6 (1’- aromatic C), 174.1, 174.8 (3, 5-C); CI\(^+\) MS: m/z 325.2 ([M+H]\(^+\)), 324.2 ([M+Na]\(^+\)). The hydrochloride salt (37.HCl) was prepared as described for 7c.HCl. Mp 185-187 °C (dec). [\(\alpha\)]\(^{25}\)_MeOH -38 (c 0.2, MeOH). Anal. (C\(_{20}\)H\(_{25}\)Cl N\(_2\)O\(_2\)) C, H, N.

1–Methylspiro[piperazine–2,2’–tricyclo[3.3.1.1\(^{3,7}\)]decane]–3,5–dione (6b)

A solution of diketopiperazine 6a (500 mg, 2.13 mmol) in THF-MeOH 1:1 (14 mL) was stirred for 3 h at room temperature, and NaCNBH\(_3\) (217 mg, 3.45 mmol) was then added in one portion. After stirring for 20 min the pH of the reaction mixture was adjusted to 6-7 by dropwise addition of acetic acid. Stirring was continued for 4 h at ambient temperature with the occasional addition of acetic acid to maintain the pH at 6-7. Solvents were evaporated in vacuo and the residue was treated with water (20 mL), and then NaOH 1N and solid Na\(_2\)CO\(_3\) until the pH was adjusted to 8. The off-white solid formed was isolated by vacuum filtration, washed with water (2 x 5 mL), and dried. Subsequent purification by column chromatography on silica gel using Et\(_2\)O-n-hexane 4:1 afforded the title compound 6b as a white crystalline solid (490 mg, 92%): mp 191-192 °C (CH\(_2\)Cl\(_2\)-n-pentane); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.47 (d, 1H, J=12.0 Hz, 4’e-H), 1.55 (d, 1H, J=12.3 Hz, 9’e-H), 1.61-1.91 (complex m, 7H, 3’, 5’, 6’, 7’, 8’, 10’e-H), 2.03-2.25 (complex m, 4H, 1’-H, 4a, 8a, 9a-H), 2.32 (s, 3H, CH\(_3\)), 2.76 (d, 1H, J=12.9 Hz, 10’a-H), 3.25-3.89 (q, 2H, AB, J\(_{AB}\)=19.0 Hz, 6-H), 7.87 (br, s, 1H, 4-H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 26.3 (5’-C), 27.1 (7’-C), 30.2 (1’-C), 31.8 (4’-C), 32.1 (3’, 9’-C), 33.2 (8’-C), 33.7 (10’-C), 37.4 (CH\(_3\)), 37.5 (6’-C), 53.0 (6-C), 65.7 (2, 2’-C), 172.0, 174.1 (3, 5-C). Anal. (C\(_{20}\)H\(_{20}\)N\(_2\)O\(_2\)) C, H, N.

1–Methyl-3,5–dioxospiro[piperazine–2,2’–tricyclo[3.3.1.1\(^{3,7}\)]decane]–4-acetic benzyl ester (40)

Sodium hydride (47 mg, 1.94 mmol) was added portionwise to a stirred solution of diketopiperazine 6b (400 mg, 1.61 mmol) in dry DMF (12 mL). After stirring at room temperature for 1 h under argon, benzyl bromoacetate (387 mg, 1.69 mmol), dissolved in dry DMF (4 mL) was added dropwise. Stirring was continued at rt for 48 h under argon, and the reaction mixture was then poured onto ice/water mixture (35 mL) and extracted with Et\(_2\)O (4x25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na\(_2\)SO\(_4\)), and evaporated in vacuo. The oily residue was purified by column chromatography on silica gel using Et\(_2\)O-n-hexane 1:1 to afford the title compound 40 as a colourless viscous oil (530 mg, 83%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.55 (dd, 1H, J=2.1, 12.2 Hz, 4’e-H), 1.85 (br s, 2H, 5’, 7’-H ), 2.06-2.28 (m, 4H, 1’, 3’, 4’a, 9’a-H), 2.36 (s, 3H, CH\(_3\)), 2.76 (d, 1H, J=13.0 Hz, 10’a-H), 3.36-4.03 (q, 2H, AB, J\(_{AB}\)=19.1 Hz, 6-H), 4.40-4.70 (q, 2H, AB, J\(_{AB}\)=16.8Hz, CH\(_2\)CO\(_2\)CH\(_2\)Ph), 5.15 (s, 2H, CO\(_2\)CH\(_2\)Ph), 7.28-7.40 (m, 5H, aromatic H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 26.3 (5’-C),
27.1 (7-H), 30.5 (1-H), 31.9 (4′-H) 32.1 (9′-H), 32.2 (3′-H), 33.1 (8′-H), 33.7 (10′-H), 37.3 (CH₃), 37.6 (6′-H), 40.4 (CH₂CO₂CH₂Ph), 53.3 (6-C), 65.5 (2′′-H), 67.3 (CO₂CH₂Ph), 128.3, 128.4, 128.5 (2, 3, 4, 5, 6-aromatic C), 135.1 (1-aromatic C), 168.0 (CO₂CH₂Ph), 171.2 , 174.0 (3, 5-C); CI⁺ MS: m/z 397.2 ([M+H]+), 23), 396.2 ([M]+, 18), 369.2 (100), 305.1 ([M-MeH]+, 12).

1-Methyl-3,5-dioxo[diketopiperazine-2,2′-tricyclo[3.3.1.1\(^3\)3\(^7\)]decane]-4-acetic acid (41)

Prepared from the above benzyl ester 40 in an almost quantitative yield by catalytic hydrogenolysis in exactly the same procedure described earlier for the preparation of carboxylic acid 27. White solid: mp 210-212 °C (EtOH-Et₂O); ¹H NMR (400 MHz , DMSO-d₆) δ1.42 (d, 2H, J=11.9 Hz, 4′-e-H), 1.52 (td, 2H, J=13.8, 16.8 Hz, 8′e, 9′-e-H), 1.59-1.75 (m, 4H, 6′, 8′a, 10′-e-H), 1.78 (s, 2H, 7′, 7′-H), 2.03-2.18 (m, 4H, 1′, 3′, 4′a, 9′a-H ), 2.33 (s, 3H, CH₃), 2.69 (d, 1H, J=12.2 Hz, 10′a-H), 3.0-3.85 (v br s, 1H, CO₂H), 3.47-3.99 (q, 2H, AB, J=19.2 Hz, 6-H), 4.19-4.39 (q, 2H, AB, J=16.9 Hz, CH₂CO₂H); ¹³C NMR (100 MHz , DMSO-d₆) δ 25.9 (5′-C), 26.7 (7′-C), 30.0 (1′-C), 31.5 (3′-C), 31.7 (4′-C), 31.8 (9′-C), 32.7 (8′-C), 33.4 (10′-C), 36.6 (CH₃), 37.3 (6′-C), 40.2 (CH₂CO₂H), 52.5 (6-C), 64.8 (2′′-C), 169.3 (CO₂H), 170.7 , 173.7 (3.5-C). Anal. (C₁₄H₂₂N₂O₄) C, H, N.

1-Methyl-1,4-diazaspiro[5,7]tridecane-3,5-dione (66)

Prepared by reductive methylation of diketopiperazine 64 (650 mg, 3.09 mmol) in MeOH-THF 1:3 (20 mL) as described above for the preparation of compound 6b. The resulting solid residue was purified by column chromatography on silica gel using AcOEt-Et₂O 1:1 to afford the title compound as a white crystalline solid 66 (600 mg, 87%): mp 134-136 °C (CHCl₃-n-pentane); ¹H NMR (400 MHz , CDCl₃) δ1.36-1.68 (complex m, 8H, 8, 9, 10, 11, 12-H) 1.70-1.87 (m, 4H, 7, 9, 11, 13-H), 2.02-2.08 (~q, 2H, J=8.0 , 9.9 Hz, 7, 13-H), 2.37 (s, 3H, CH₃), 3.61 (s, 2H, 2-H), 8.24 (br s, 1H, 4-H); ¹³C NMR (100 MHz , CDCl₃) δ 20.7 (9, 11-C), 24.5 (10-C), 27.9 (8, 12-C), 29.3 (7, 13-C), 39.3 (CH₃), 54.3 (2-C), 64.4 (6-C), 171.3, 176.4 (3, 5-C). Anal. (C₁₂H₂₀N₂O₂).

1-Methyl-3,5-dioxo-1,4-diazaspiro[5,7]tridecane-4-acetic acid benzyl ester (68)

Prepared from the diketopiperazine 66 in exactly the same procedure described above for the preparation of compound 40. The resulting oily residue was purified by column chromatography on silica gel eluting first with Et₂O-n-hexane 1:1 and then AcOEt-n-hexane 1:1 to afford the title compound 68 as a colourless viscous oil (92%): ¹H NMR (400 MHz, CDCl₃) δ1.38-1.67 (complex m, 8H, 8, 9, 10, 11, 12-H), 1.70-1.87 (m, 4H, 7, 9, 11, 13-H), 2.0-2.07 (~q, 2H, J=9.3 , 9.6 Hz, 7, 13-H), 2.39 (s, 3H, CH₃), 3.72 (s, 2H, 2-H), 4.54 (s, 2H, CH₂CO₂CH₂Ph), 5.12 (s, 2H, CO₂CH₂Ph), 7.28-7.43 (m, 5H, aromatic H); ¹³C NMR (100 MHz ,CDCl₃) δ 20.7 (9, 11-C), 24.5 (10-C), 27.9 (8, 12-C), 29.8 (7, 13-C), 39.2 (CH₃) 39.8 (CH₂CO₂CH₂Ph), 54.5 (2-C), 64.5 (6-C), 67.3 (CO₂CH₂Ph), 128.4, 128.5, 128.6 (2, 3, 4, 5, 6-aromatic C), 135.0 (1-aromatic C), 167.8 (CO₂CH₂Ph), 170.3, 175.9 (3, 5-C); CI⁺ MS: m/z 372.3 ([M]+, 34), 373.3 ([M+H]+, 100), 281.1 ([M-MeH]+, 41).

1-Methyl-3,5-dioxo-1,4-diazaspiro[5,7]tridecane-4-acetic acid (70)

Prepared from the above benzyl ester 68 in an almost quantitative yield by catalytic hydrogenolysis in exactly the same procedure described earlier for the preparation of carboxylic acid 27. White solid: mp 178-180 °C (EtOH-Et₂O); ¹H NMR (400 MHz , DMSO-d₆) δ1.20 – 1.57 (complex m, 8H, 8, 9, 10, 11, 12-H), 1.61-1.83 (complex m, 4H, J=11.9 Hz, 4′-e-H), 1.87-2.01 (m, 2H, 7, 13-H), 2.33 (s, 3H, CH₃), 3.72 (s, 2H, 2-H), 3.30-4.90 (v br s, 1H, CO₂H), 4.27 (s, 2H,
Table 2. Antitrypanosome action of acetamide 43, acetohydrazide 44, O-methyl hydroxamate 45, carboxylic acids 27-31, 41, 56, 59, and 71, 2,6-DKP scaffold molecules 6a, 6b, 37-39, and 64-67, and acetohydroxamic acid tested against cultured blood stream form *T. brucei* (pH=7.4).

| Compound | IC<sub>50</sub> (µM) | IC<sub>90</sub> (µM) | Compound | IC<sub>50</sub> (µM) | IC<sub>90</sub> (µM) |
|----------|-------------------|-------------------|----------|-------------------|-------------------|
| 43       | 200               | >300              | 71       |                   |                   |
| 44       | 118               | na<sup>b</sup>    | 6a       |                   |                   |
| 45       | 542               | na<sup>b</sup>    | 6b       | na                |                   |
| 27       | 469               |                   | 37       | 63.2              | 79.2              |
| 28       | 203               | 255               | 38       | 38.6              | 57.2              |
| 29       | 111               | 203               | 39       | 18.5              | 27.1              |
| 30       | 171               | 259               | 64       | na                |                   |
| 31       | 103               | 208               | 65       | >400              |                   |
| 41       | na                | na                | 66       | na                |                   |
| 56       | 760               |                   | 67       | >400              |                   |
| 59       | >400              |                   | Acetohydroxamic acid | 680     |                   |

<sup>a</sup>Compounds 45, 29-31, 37, and 38 were tested as hydrochloride salts.

<sup>b</sup>Data not available.

Experimental. Biological Assays.

Trypanocidal assays

Cultured bloodstream form *T. brucei* (strain 427) were maintained at 37 °C in modified Iscove’s medium (pH 7.4). Trypanocidal activity was assessed by growing parasites for 48 h in the presence of various drug concentrations to determine the levels which inhibited growth by 50% (IC<sub>50</sub>) and 90% (IC<sub>90</sub>). In the case of untreated cultures (volume 4 ml), cell densities increased from 0.5×10<sup>4</sup> to 1×10<sup>6</sup> cells ml<sup>−1</sup> over this period. Experiments were performed in triplicate. Cell densities at each drug concentration were determined using a hemocytometer (Weber Scientific International Ltd), and drug sensitivity was expressed as a percentage of growth of control cells. For *T. cruzi* epimastigotes (CL Brener clone), inhibition experiments were carried out in Nunclon 24 well plates in 2 ml of growth medium at an initial inoculum of 2 x 10<sup>5</sup> epimastigotes ml<sup>−1</sup>. After 5 days incubation at 28°C in RPMI medium (Kendall *et al*. 1990) in the absence of drug, cell density reached 2 x 10<sup>7</sup> parasites ml<sup>−1</sup>.
(25) Kendall, G.; Wilderspin, A. F.; Ashall, F.; Miles, M. A. and Kelly, J. M. *Trypanosoma cruzi* glycosomal glyceraldehyde-3-phosphate dehydrogenase does not conform to the "hotspot" topogenic signal model. *EMBO J.* 1990, 9, 2751-2758

**Cytotoxicity tests**

Cytotoxicity against mammalian cells was assessed using microtitre plates as described in Bot *et al.* (2010). Briefly, L6 cells (a rat skeletal muscle line) were seeded at $1 \times 10^4$ ml$^{-1}$ in 200 μl of growth medium containing different compound concentrations. The plates were incubated for 6 days at $37^\circ\text{C}$ and 20 μl Alamar Blue (Biosource UK Ltd.) was then added to each well. After further 8 h incubation, the fluorescence was determined using a Gemini fluorescent plate reader (Molecular Devices).

(26) Bot, C.; Hall, B. S.; Bashir, N.; Taylor, M. C.; Helsby, N. A.; Wilkinson, S. R. Trypanocidal activity of aziridinyl nitrobenzamide prodrugs. *Antimicrob. Agents Chemother.* 2010, 54, 4246-4252.

**Abbreviation used:** RPMI, Roswell Park Memorial Institute.

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**Table 3.** Elemental analysis data for the tested compounds synthesized in this study.

| Compounds | Molecular Formula | Calculated % | Found % |
|-----------|-------------------|--------------|---------|
|           |                   | C  | H  | N  | C  | H  | N  |
| 7a        | C$_{15}$H$_{21}$N$_3$O$_4$ | 58.62 | 6.89 | 13.67 | 58.62 | 6.98 | 13.71 |
| 7a.HCl    | C$_{15}$H$_{22}$ClN$_3$O$_4$ | 52.40 | 6.45 | 12.22 | 52.64 | 6.61 | 11.95 |
| 7b        | C$_{16}$H$_{23}$N$_3$O$_4$ | 59.79 | 7.21 | 13.08 | 59.52 | 7.30 | 13.37 |
| 7b.HCl    | C$_{16}$H$_{24}$ClN$_3$O$_4$ | 53.70 | 6.76 | 11.74 | 53.37 | 7.06 | 12.02 |
| 7c.HCl    | C$_{16}$H$_{24}$ClN$_3$O$_4$ | 53.70 | 6.76 | 11.74 | 53.58 | 7.16 | 11.61 |
| 7d.HCl    | C$_{22}$H$_{28}$ClN$_3$O$_4$ | 60.89 | 6.50 | 9.68 | 61.28 | 6.71 | 9.86 |
| 7e.HCl    | C$_{22}$H$_{28}$ClN$_3$O$_4$ | 60.89 | 6.50 | 9.68 | 60.52 | 6.77 | 10.02 |
| 8.HCl     | C$_{22}$H$_{28}$ClN$_3$O$_4$ | 60.89 | 6.50 | 9.68 | 61.26 | 6.83 | 9.91 |
| 9a.HCl    | C$_{13}$H$_{22}$ClN$_3$O$_4$ | 48.83 | 6.93 | 13.14 | 48.88 | 7.01 | 13.07 |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| 9b.HCl | C\textsubscript{14}H\textsubscript{24}ClN\textsubscript{3}O\textsubscript{4} | 50.37 | 7.25 | 12.59 | 50.75 | 7.60 | 12.28 |
| 9c.HCl | C\textsubscript{14}H\textsubscript{24}ClN\textsubscript{3}O\textsubscript{4} | 50.37 | 7.25 | 12.59 | 50.75 | 7.60 | 12.21 |
| 9d.HCl | C\textsubscript{20}H\textsubscript{28}ClN\textsubscript{3}O\textsubscript{4} | 58.60 | 6.89 | 10.25 | 58.63 | 6.99 | 10.20 |
| 10a.HCl | C\textsubscript{12}H\textsubscript{20}ClN\textsubscript{3}O\textsubscript{4} | 47.14 | 6.59 | 13.74 | 46.95 | 6.72 | 13.61 |
| 10b.HCl | C\textsubscript{11}H\textsubscript{22}ClN\textsubscript{3}O\textsubscript{4} | 48.83 | 6.93 | 13.14 | 48.40 | 7.28 | 12.72 |
| 43 | C\textsubscript{15}H\textsubscript{23}N\textsubscript{3}O\textsubscript{3} | 61.83 | 7.27 | 14.42 | 61.46 | 6.89 | 14.78 |
| 44 | C\textsubscript{15}H\textsubscript{22}N\textsubscript{4}O\textsubscript{3} | 58.80 | 7.24 | 18.29 | 58.55 | 7.13 | 17.91 |
| 45.HCl | C\textsubscript{16}H\textsubscript{24}ClN\textsubscript{3}O\textsubscript{4}.0.4 Et\textsubscript{2}O | 54.63 | 7.29 | 10.86 | 54.59 | 7.19 | 11.09 |
| 29.HCl | C\textsubscript{22}H\textsubscript{27}ClN\textsubscript{2}O\textsubscript{4} | 63.07 | 6.50 | 6.69 | 63.08 | 6.57 | 6.43 |
| 30.HCl | C\textsubscript{22}H\textsubscript{27}ClN\textsubscript{2}O\textsubscript{4} | 63.07 | 6.50 | 6.69 | 62.69 | 6.73 | 6.39 |
| 31.HCl | C\textsubscript{22}H\textsubscript{27}ClN\textsubscript{2}O\textsubscript{4} | 63.07 | 6.50 | 6.69 | 63.41 | 6.81 | 6.31 |
| 41 | C\textsubscript{16}H\textsubscript{22}N\textsubscript{2}O\textsubscript{4} | 62.73 | 7.24 | 9.15 | 62.61 | 7.14 | 9.23 |
| 59 | C\textsubscript{12}H\textsubscript{18}N\textsubscript{2}O\textsubscript{4} | 56.68 | 7.14 | 11.02 | 57.07 | 7.16 | 11.38 |
| 71 | C\textsubscript{13}H\textsubscript{20}N\textsubscript{2}O\textsubscript{4} | 58.19 | 7.51 | 10.44 | 58.44 | 7.90 | 10.18 |
| 6b | C\textsubscript{14}H\textsubscript{20}N\textsubscript{2}O\textsubscript{2} | 67.71 | 8.12 | 11.28 | 67.71 | 8.14 | 11.25 |
| 37.HCl | C\textsubscript{20}H\textsubscript{25}ClN\textsubscript{2}O\textsubscript{2} | 66.56 | 6.98 | 7.76 | 66.95 | 7.04 | 7.36 |
| 38.HCl | C\textsubscript{20}H\textsubscript{25}ClN\textsubscript{2}O\textsubscript{2} | 66.56 | 6.98 | 7.76 | 66.19 | 7.22 | 8.20 |
| 39 | C\textsubscript{20}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2} | 74.04 | 7.46 | 8.64 | 74.11 | 7.44 | 8.57 |
| 65 | C\textsubscript{10}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2} | 61.20 | 8.22 | 14.28 | 61.19 | 8.52 | 14.05 |
| 66 | C\textsubscript{12}H\textsubscript{20}N\textsubscript{2}O\textsubscript{2} | 64.25 | 8.99 | 12.49 | 64.10 | 8.99 | 12.65 |
| 67 | C\textsubscript{11}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2} | 62.83 | 8.63 | 13.32 | 63.01 | 9.02 | 12.97 |