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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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. Spliting paterns are designated as s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet 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 ^{o}C) unless otherwise specified. Carbon multiplicities were established by DEPT experiments. The 2D NMR experiments (HMQC 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} plates (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_2O, ethyl ether; MeOH, methanol; EtOH, ethanol; AcOEt, ethyl acetate; DMSO, dimethylsulfoxide.

The ^{1}H and ^{13}C NMR spectra for all hydroxamate derivatives described in this report (compounds **7a-e**, **8**, **9a-d**, **10a**, **10b**, **32**-**36**, **42**, **60**-**63**, **72**, **73**, and **45**) and hydrazide **44**, are consistent with a Z/E conformational behavior of these molecules in solution. The detected double set of characteristic peaks in ^{1}H and ^{13}C NMR spectra confirm the occurrence of the two carbonyl conformers. The assignment of the Z or E conformers was based on literature data concerning Z/E conformational isomerism studies in simple hydroxamate and hydrazide structures,[24] and 2D NMR experiments.

(24) (a) Brown, D. A.; Glass, W. K.; Mageswaran, R.; Mohammed, S. A. ^{1}H and ^{13}C NMR studies of isomerism in hydroxamic acids. *Magn. Reson. Chem.* **1991**, *29*, 40-45, and references therein. (b) Bouchet, P.; Jacquier, R.; Pereillo, J. M.; Elguero, J. NMR study of configuration of hydrazides. *Bull. Soc. Chim. Fr.* **1972**, *6*, 2264-2271.

***N*-Hydroxy-3,5-dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-4-acetamide (7a)**
Following the general hydrogenolysis procedure described in the main manuscript, *O*-benzyl hydroxamate **32** gave the title compound **7a** as a white crystalline solid (96%): mp 193-195 ^{o}C (dec) (EtOH -Et_2O); ^{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′, 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, *J*=8.4Hz, 6-H),

4.14 (s, 1.5H, C*H*$_2$CONHOH, Z-isomer), 4.44 (s, 0.4H, C*H*$_2$CONHOH, E-isomer), 8.87 (s, 0.7H, CONHO*H*, Z- isomer), 9.28 (s, 0.2H, CONHO*H*, E- isomer), 10.15 (s, 0.2H, CON*H*OH, E-isomer), 10.55 (s, 0.7H, CON*H*OH, Z- isomer); ^{13}C NMR (100 MHz , DMSO-d_6) 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 (*C*H$_2$CONHOH, Z-isomer), 39.6 (*C*H$_2$CONHOH, E-isomer), 44.0 (6-C), 59.5 (2,2′-C), 164.2(*C*ONHOH, Z-isomer), 169.6 (*C*ONHOH, E-isomer), 172.3, 174.6 (3, 5-C). Anal. ($C_{15}H_{21}N_3O_4$) 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. ($C_{15}H_{22}ClN_3O_4$) C, H, N.

N-Hydroxy-1-methyl-3,5-dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]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-Et$_2$O); ^{1}H NMR (400 MHz , DMSO-d_6) 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), 1.78 (s, 2H, 5′, 7′-H), 2.02-2.20 (m, 4H, 1′, 3′, 4′a, 9′a-H), 2.31, 2.33 (s+s, 3H, C*H*$_3$), 2.68 (d, 1H, *J*=12.0 Hz, 10′a-H), 3.44-3.97 (q, 2H, AB, J_{AB}=19.1 Hz, 6-H), 4.07-4.25 (q, 1.5H, AB, J_{AB}=15.5Hz, C*H*$_2$CONHOH, Z-isomer), 4.39-4.53 (q, 0.5H, AB, J_{AB}=16.9 Hz, C*H*$_2$CONHOH, E-isomer), 8.87 (s, 0.7H, CONHO*H*, Z-isomer), 9.30 (s, 0.2H, CONHO*H*, E-isomer), 10.17 (s, 0.2H, CON*H*OH, E-isomer), 10.63 (s, 0.7H, CON*H*OH, Z-isomer); ^{13}C NMR (100 MHz , DMSO-d_6) 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 (*C*H$_3$), 37.3 (6′-C), 38.9 (*C*H$_2$CONHOH, Z-isomer), 39.7 (*C*H$_2$CONHOH, E- isomer), 52.6 (6-C), 64.8 (2,2′-C), 164.1 (*C*ONHOH, Z-isomer), 169.5 (*C*ONHOH, E-isomer), 170.7, 173.8 (3, 5-C); Anal. ($C_{16}H_{23}N_3O_4$) C, H, N. The hydrochloride salt (**7b.HCl**) was prepared as described for **7a.HCl**. Mp 215-218 °C (dec). Anal. ($C_{16}H_{24}ClN_3O_4$) C, H, N.

(*S*)-*N*-Hydroxy-6-methyl-3,5-dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]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; ^{1}H NMR (600 MHz , DMSO-d_6) δ1.25 (d, 3H, *J*=13.8 Hz, C*H*$_3$), 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, J_{AB}=15.4 Hz, C*H*$_2$CONHOH, Z-isomer), 4.38-4.48 (q, 0.5H, AB, J_{AB}=16.4 Hz, C*H*$_2$CONHOH, E-isomer), 8.82 (s, 0.6H, CONHO*H*, Z-isomer), 9.24 (s, 0.2H, CONHO*H*, E-isomer), 10.10 (s, 0.2H, CON*H*OH, E-isomer), 10.50 (s, 0.5H, CON*H*OH, Z-isomer); ^{13}C NMR (100 MHz , DMSO-d_6) δ17.9, 18.0 (*C*H$_3$), 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 (*C*H$_2$CONHOH, Z-isomer), 39.8 (*C*H$_2$CONHOH, E-isomer), 48.6 (6-C), 60.0 (2,2′-C), 164.1 (*C*ONHOH, Z-isomer), 169.5 (*C*ONHOH, E-isomer), 174.6 , 174.8 (3 , 5-C); $[\alpha]^{23}_{589}$ -20 (c 0.2, $CHCl_3$); CI$^+$ MS: m/z: 322.2 ($[M+H]^+$, 7), 306.2 ($[M-CH_3]^+$, 37), 278.2 (100); HRMS (ESI): $[M+H]^+$ calcd for $C_{16}H_{24}N_3O_4$, 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, triturated with ether, and dried in vacuo. Mp 178-180 °C (dec). Anal. ($C_{16}H_{24}ClN_3O_4$) 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) δ1.29 (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_AH$_M$Ph, 1, 10′a-H), 3.32 (dd, 1H, AMX, M region, J_{AM}=13.8 Hz, J_{MX}= 2.8 Hz, CH$_A$$H_M$Ph), 3.73 (td, 1H, *J*=3.3 Hz, 10.7 Hz, 6-Hx), 4.17 (s, 1.6H, CH_2CONHOH, Z-isomer), 4.42-4.52 (q, AB, 0,4 H, J_{AB}=16.8 Hz, CH_2CONHOH, E- isomer), 7.16-7.23 (m, 1H, 4-aromatic H), 7.24-7.36 (m, 4H, 2, 3, 5, 6-aromatic H), 8.88 (s, 0,7H, CONHO*H*, Z- isomer), 9.30 (s, 0,2H, CONHO*H*, E-isomer), 10.16 (s, 0,2H, CON*H*OH, E- isomer), 10.56 (s, 0,7H, CON*H*OH, Z- isomer); ^{13}C NMR (100 MHz, DMSO-d_6) δ26.5 (5′-C), 26.7 (7′-C), 29.9, 30.0 (1′-C), 30.8 (4′-C), 32.0 (9′-C), 32.7 (8′-C), 33.3 (10′-C), 34.0, 34.1 (3′-C), 37.3 (*C*H$_2$Ph), 37.7 (6′-C), 39.6 (*C*H$_2$CONHOH, *Z*-isomer), 39.9 (*C*H$_2$CONHOH, E-isomer), 54.26, 54.33 (6-C), 59.85, 59.93 (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 (*C*ONHOH, *Z*-isomer), 169.5 (*C*ONHOH, E-isomer), 173.7, 174.5 (3, 5-C); $[\alpha]^{25}_{589}$ -60 (c 0,2, $CHCl_3$); CI$^+$ MS: m/z 398.2 ([M+H]$^+$, 100), 306.1 ([M- CH$_2$Ph] $^+$, 57); HRMS (ESI): [M+H]$^+$ calcd. for $C_{22}H_{28}N_3O_4$, 398.2074, found 398.2059. The hydrochloride salt (**7d.HCl**) was prepared as described for **7c.HCl**. Mp 143-146 °C (dec); Anal. ($C_{22}H_{28}ClN_3O_4$) 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 white foamy solid, which strongly binds the eluting solvent (AcOEt). Removal of the entrapped solvent as described for **7c** gave **7e** as a light yellow crystalline solid (95%): mp 96–98 °C; NMR spectroscopic data of this compound are identical to that of **7d**; $[\alpha]^{25}_{589}$ +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 $C_{22}H_{28}N_3O_4$, 398.2074, found 398.2064. The hydrochloride salt (**7e.HCl**) was prepared as described for **7c.HCl**. Mp 142-145 °C (dec). Anal. ($C_{22}H_{28}ClN_3O_4$) 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 **7c** 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 $C_{22}H_{28}N_3O_4$, 398.2074, found 398.2025. The hydrochloride salt (**8.HCl**) was prepared as described for **7c.HCl**. Mp 135-138 °C (dec). Anal. ($C_{22}H_{28}ClN_3O_4$) 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) δ1.50 (br s, 8H, 8, 9, 10, 11, 12-H), 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, C*H*$_2$CONHOH, Z-isomer), 4.42 (s, 0.4H, C*H*$_2$CONHOH, E-isomer), 8.86 (s, 0.7H, CONHO*H*, Z-isomer), 9.27 (s, 0.2H, CONHO*H*, E-isomer), 10.15 (s, 0.2H, CON*H*OH, E-isomer), 10.52 (s, 0.7H, CON*H*OH, Z-isomer); ^{13}C NMR (100 MHz, DMSO-d_6) δ20.9 (9, 11-C), 24.4 (10-C), 27.7 (8, 12-C), 30.2 (7, 13-C), 38.6 (*C*H$_2$CONHOH, Z-isomer), 38.8 (*C*H$_2$CONHOH, E-isomer), 44.7 (2-C), 58.9 (6-C), 163.9 (*C*ONHOH, Z-isomer), 169.3 (*C*ONHOH, 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 $C_{13}H_{22}N_3O_4$, 284.1605, found 284.1586. The hydrochloride salt (**9a.HCl**) was prepared as described for **7a.HCl**. Mp 179-182 °C. Anal. ($C_{13}H_{22}ClN_3O_4$) 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, *O*-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) δ1.33-1.63 (m, 8H, 8, 9, 10, 11, 12-H), 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, C*H*$_3$, Z-isomer), 2.38 (s, 0.9H, C*H*$_3$, E-isomer), 3.73 (s, 2H, 2-H), 4.16 (s, 1.5H, C*H*$_2$CONHOH, Z-isomer), 4.46 (s, 0.5H, C*H*$_2$CONHOH, E-isomer), 8.88 (s, 0.8H, CONHO*H*, Z-isomer), 9.30 (br s, 0.3H, CONHO*H*, E-isomer), 10.18 (s, 0.3H, CON*H*OH, E-isomer), 10.63 (s, 0.7H, CON*H*OH, Z-isomer); ^{13}C NMR (100 MHz, DMSO-d_6) δ20.4 (9, 11-C), 24.3 (10-C), 27.5 (8, 12-C), 29.3 (7, 13-C), 38.1 (*C*H$_2$CONHOH, Z-isomer), 38.5, 38.6 (*C*H$_3$), 38.9 (*C*H$_2$CONHOH, E-isomer), 53.7 (2-C), 63.7 (6-C), 164.0 (*C*ONHOH, Z-isomer), 169.3 (*C*ONHOH, E-isomer), 170.0, 175.5 (3, 5-C); CI$^+$ MS: m/z: 298.2 ([M+H]$^+$, 7), 282,2 ([M–CH$_3$]$^+$, 77), 281.2(26), 254.2(100), 236.2(89), 209.2(100); HRMS (ESI): [M+H]$^+$ calcd for $C_{14}H_{24}N_3O_4$, 298.1761, found 298.1738. The hydrochloride salt (**9b.HCl**) was prepared as described for **7a.HCl**. Mp 163-165 °C (dec). Anal. ($C_{14}H_{24}ClN_3O_4$) 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) δ(ppm): 1.28 (d, 3H, *J*=6.8Hz, C*H*$_3$), 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, C*H*$_2$CONHOH, Z-isomer), 4.41 (s, 0.4H, C*H*$_2$CONHOH, E-isomer), 8.85 (s, 0.8H, CONHO*H*, Z-isomer), 9.26 (s, 0.2H, CONHO*H*, E-isomer), 10.13 (s, 0.2H, CON*H*OH, E-isomer), 10.51 (s, 0.8H, CON*H*OH, Z-isomer); ^{13}C NMR (100 MHz, DMSO-d_6) δ17.0 (*C*H$_3$), 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 (*C*H$_2$CONHOH, Z-isomer), 39.2 (*C*H$_2$CONHOH, E-isomer), 48.8 (2-C), 59.8 (6-C), 163.9 (*C*ONHOH, Z-isomer), 169.3 (*C*ONHOH, E-isomer), 173.8, 176.6 (3, 5-C); $[\alpha]^{26}_{589}$ +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 $C_{14}H_{24}N_3O_4$, 298.1767, found 298.1744. The hydrochloride salt (**9c.HCl**) was prepared as described for **7c.HCl**. Mp 170-172 °C (dec). Anal. ($C_{14}H_{24}Cl\ N_3O_4$) C, H, N.

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

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 ^{o}C under vacuum (10^{-3} mmHg) in an Abderhalden apparatus gave **9d** as a white crystalline solid (98%): mp 65–68 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.18-1.67 (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, CH_AH$_M$Ph), 3.32 (dd under DMSO water peak, 1H, AMX, M region, J_{MX}=3.6 Hz, CH$_A$$H_M$Ph), 3.75-3.86 (m, 1H, AMX, X region, 2-Hx), 4.09-4.18 (q, AB, 1.6H, J_{AB}=15.6 Hz, CH_2CONHOH, Z-isomer), 4.42 (s, 0.4H, CH_2CONHOH, E-isomer), 7.14-7.22 (m, 1H, 4-aromatic H), 7.23-7.33 (m, 4H, 2,3,5,6-aromatic H), 8.85(s, 0.7H, CONHO*H*, Z-isomer), 9.27 (s, 0.2H, CONHO*H*, E-isomer), 10.15(s, 0.2H, CON*H*OH, E-isomer), 10.51 (s, 0.7H, CON*H*OH, Z-isomer); ^{13}C NMR (100 MHz, DMSO-d_6) δ20.3 (9-C), 21.1 (11-C), 24.2 (10-C), 26.7 (8-C), 27.5 (7-C), 28.3 (12-C), 33.8 (13-C), 36.2 (*C*H$_2$Ph), 39.2 (*C*H$_2$CONHOH), 54.3 (2-C), 59.6 (6-C), 126.0 (4-aromatic C), 127.9, 129.0 (2, 3, 5, 6-aromatic C), 138.7 (1-aromatic C), 163.9 (*C*ONHOH, Z-isomer), 169.3 (*C*ONHOH, E-isomer), 172.9, 176.6 (3, 5-C); $[\alpha]^{21}_{589}$ -16 (C 0.2, CHCl$_3$) ; EI MS: m/z 373.1([M]$^+$, 4), 282,1([M–CH$_2$Ph]$^+$, 100); HRMS (ESI): [M+H]$^+$ calcd for $C_{20}H_{28}N_3O_4$, 374.2069, found 374.2047. The hydrochloride salt (**9d.HCl**) was prepared as described for **7c.HCl**. Mp 202-205 ^{o}C (dec). Anal. ($C_{20}H_{28}$Cl N_3O_4) 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 ^{o}C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ1.40-1.76 (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, *J*=6.4 Hz, 2-H), 4.13 (s, 1.6H, CH_2CONHOH, *Z*-isomer), 4.42 (s, 0.4H, CH_2CONHOH, E-isomer), 8.87 (s, 0.7H, CONHO*H* , Z-isomer), 9.27 (s, 0.2H, CONHO*H* , E-isomer), 10.15 (s, 0.2H, CON*H*OH, E-isomer), 10.53 (s, 0.7H, CON*H*OH, *Z*-isomer); ^{13}C NMR (100 MHz, , DMSO-d_6) δ21.7(8, 11-C), 29.4, 29.5 (9, 10-C), 35.1 (7, 12-C), 38.7(*C*H$_2$CONHOH, *Z*-isomer), 38.9 (*C*H$_2$CONHOH, E-isomer) 44.7 (2-C), 59.6, 59.7 (6-C), 163.9 (*C*ONHOH, *Z*-isomer), 169.3 (*C*ONHOH, E-isomer), 171.5, 176.9 (3, 5-C); CI$^+$ MS: m/z 270.2([M+H]$^+$, 18), 252,1([M+H–H$_2$O]$^+$, 24), 226.2(86), 209.1(96), 208.1(100); HRMS (ESI): [M+H]$^+$ calcd for $C_{12}H_{20}N_3O_4$, 270.1448, found 270.1434. The hydrochloride salt (**10a.HCl**) was prepared as described for **7a.HCl**. Mp 190-192 ^{o}C (dec). Anal. ($C_{12}H_{20}ClN_3O_4$) C, H, N.

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

Following the general hydrogenolysis 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 ^{o}C under vacuum (10^{-3} mmHg) in an Abderhalden apparatus gave **10b** as a glass solid (93%): ^{1}H NMR (400 MHz, DMSO-d_6) δ1.46-1.65 (br s, 8H, 8, 9, 10, 11-H), 1.78-2.0 (m, 4H, 7, 12-H), 2.37 (s, 2.2H, CH_3, Z-isomer), 2.39 (s, 0.8H, CH_3, E-isomer), 3.72 (s, 2H, 2-H), 4.16 (s, 1.4H, CH_2CONHOH, *Z*-isomer), 4.46 (s, 0.5H, CH_2CONHOH, E-isomer), 8.87 (s, 0.7H, CONHO*H* , Z-isomer), 9.29 (s, 0.2H, CONHO*H* , E-isomer), 10.17 (s, 0.2H, CON*H*OH, E-isomer), 10.62 (s, 0.7H, CON*H*OH, *Z*-isomer); ^{13}C NMR (100 MHz, , DMSO-d_6) δ21.6 (8, 11-C), 28.7 (9, 10-C), 33.4 (7, 12-C), 38.16, 38.21 (*C*H$_3$), 38.3 (*C*H$_2$CONHOH, *Z*-isomer), 39.0 (*C*H$_2$CONHOH, E-isomer), 53.7 (2-C), 64.6 (6-C), 163.9 (*C*ONHOH, *Z*-isomer), 169.3 (*C*ONHOH, 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 $C_{13}H_{22}N_3O_4$, 284.1610, found 284.1573. The hydrochloride salt (**10b.HCl**) was prepared as described for **7c.HCl**. Mp 132-136 ^{o}C (slightly hydroscopic). Anal. ($C_{13}H_{22}ClN_3O_4$) C, H, N.

3,5-Dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-4-acetamide (43)

Using a procedure essentially similar to that described earlier for the preparation of compound **22**,[9] the amide ester precursor **17** (365 mg, 1.3 mmol) was treated with $(CH_3)_3SiNK$ (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_2O 1:1 and then AcOEt to give the title compound **43** as a white solid (191 mg, 50%): mp 168–169^0 C (EtOH – Et_2O); ^{1}H NMR (600 MHz, DMSO-d_6) δ1.43 (d, 2H, *J*=12.0 Hz, 4′e, 9′e-H), 1.57-1.69 (m, 4H, 6′, 8′e, 10′e-H), 1.75 (s, 1H, 7′-H), 1.79 (s, 1H, 5′-H), 1.95 (s, 2H, 1′, 3′-H), 2.17-2.32 (m, 4H, 4′a, 8′a, 9′a, 10′a-H), 3.09 (br s, 1H, 1-H), 3.56 (d, 2H, *J*=6.5 Hz, 6-H), 4.17 (s, 2H, C*H*$_2$CONH$_2$), 6.99 (s, 1H, CON*H*H), 7.38 (s, 1H, CONH*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ26.6 (5′-C), 26.8 (7′-C), 31.8 (1′, 3′-C), 31.9 (4′, 9′-C), 32.7 (8′, 10′-C), 37.7 (6′-C), 41.4 (*C*H$_2$CONH$_2$), 43.9 (6-C), 59.3 (2, 2′-C), 168.5(*C*ONH$_2$), 172.1, 174.5 (3, 5-C). Anal. ($C_{15}H_{21}N_3O_3$) C, H, N.

3,5-Dioxo-*N*-(phenylmethoxy)spiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]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 ^{o}C for 1h under argon. Then, *O*-benzylhydroxylamine hydrochloride (210 mg, 1.32 mmol) and triethylamine (202 mg, 2 mmol) were added successively, and the stirring was continued at 28 ^{o}C for 24h and then at 45 ^{o}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_2SO_4) and evaporated in vacuo. The viscous oily residue was purified by column chromatography on silica gel eluting first with Et_2O-*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 ^{o}C (AcOEt); ^{1}H NMR (400 MHz , $CDCl_3$, 270K) δ 1.50 (d, 2H, *J*=12.5 Hz, 4′e, 9′e-H), 1.62-1.75 (m, 4H, 6′, 8′e, 10′e-H), 1.82 (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, C*H*$_2$CONHOCH$_2$Ph, *Z*-isomer), 4.59 (s, 0.94H, C*H*$_2$CONHOCH$_2$Ph, E-isomer), 4.84, 4.88 (s+s, 2H, CONHOC*H*$_2$Ph), 7.37 (br s, 5H, aromatic–H), 8.34 (s, 0.4H, CON*H*OCH$_2$Ph, E-isomer), 8.89 (s, 0.5H, CON*H*OCH$_2$Ph, *Z*-isomer); ^{13}C NMR (100 MHz , $CDCl_3$,270K) δ26.8 (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 (*C*H$_2$CONHOCH$_2$Ph), 44.2 (6-C), 60.3, 60.4(2,2′-C), 78.1, 79.4 (CONHO*C*H$_2$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 (*C*ONHOCH$_2$Ph, *Z*-isomer), 170.5 (*C*ONHOCH$_2$Ph, E-isomer), 172.4, 172.5, 174.5, 174.6 (3, 5-C). Anal ($C_{22}H_{27}N_3O_4$) C, H, N.

3,5-Dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-4-acetohydrazide (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 ^{o}C for 25h under argon. After removal of the solvent in vacuo, the residue was dissolved in chloroform, and the resulting solution washed with brine (2x30 mL), dried (Na_2SO_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 acetohydrazide **44** as a TLC and ^{1}H NMR pure white solid (466 mg, 76% from **27**), which was recrystalized from EtOH-Et_2O: mp 197 – 200^0 C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ1.43 (d, 2H, *J*=11.9 Hz, 4′e, 9′e-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 (~t, 4H, *J*=11.9, 12.8 Hz, 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, CONHNH_2), 4.18 (s, 1.7H, CH_2CONHNH_2, Z-isomer), 4.52 (s, 0.2H, CH_2CONHNH_2, E-isomer), 8.46 (s, 0.1H, CONHNH_2, E-isomer), 9.06 (s, 0.8H, CONHNH_2, Z-isomer); ^{13}C NMR (100 MHz, DMSO-d_6) δ26.6 (5′-C), 26.9 (7′-C), 31.8 (1′, 3′-C), 31.9 (4′, 9′-C), 32.7 (8′, 10′-C), 37.7 (6′-C), 39.95, 40.02 (*C*H_2CONHNH_2), 44.0 (6-C), 59.4 (2, 2′-C), 166.5 (*C*ONHNH_2), 172.2, 172.3, 174.5, 174.7 (3, 5-C). Anal. ($C_{15}H_{22}N_4O_3$) C, H, N.

_N_-Methoxy-3,5-dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane]-4-acetamide (45)

Prepared from carboxylic acid **27**[9] 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-Et_2O 1:1 to afford colourless viscous oil which strongly binds the aforementioned solvents. Removal of the entrapped solvents upon drying at 50 ^oC under vacuum (10^{-3} mmHg) in an Abderhalden apparatus gave the title compound **45** as a glass solid: (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ1.51 (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, CONHOCH_3, 6-H), 4.27 (br s, 1.1H, CH_2CONHOCH_3, Z-isomer), 4.63 (br s, 0.7H, CH_2CONHOCH_3, E-isomer), 8.97(br s, 0.3H, CONHOCH_3, E-isomer), 9.67 (br s, 0.6H, CONHOCH_3, Z-isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ27.0 (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 (*C*H_2CONHOCH_3), 44.4 (6-C), 60.4 (2,2′-C), 64.3, 65.1 (CONHO*C*H_3), 165.6 (*C*ONHOCH_3, Z-isomer), 170.6 (*C*ONHOCH_3, E-isomer), 172.6, 174.6 (3, 5-C); CI$^+$ MS: m/z 322.2 ([M+H]$^+$, 24), 290.2 ([M-OCH_3]$^+$, 15), 294.2 (64), 219.1 (79). The hydrochloride salt (**45.HCl)** was prepared by treating a solution of **45** in Et_2O-AcOEt 3:2 with ethereal HCl under ice cooling. The white solid was collected by filtration, triturated with Et_2O and dried at 62-64 ^oC under vacuum (10^{-3} mmHg). Mp 193-195 ^oC; Anal. ($C_{16}H_{24}ClN_3O_4$ 0.4Et_2O) C, H, N.

***N*–[2–Cyano(tricyclo[3.3.1.1^{3,7}]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**,[9] except that methyl *L*-phenylalaninate hydrochloride was used. The resulting off-white solid was purified by column chromatography on silica gel eluting first with Et_2O-*n*-hexane 1:2 and then 1:1 to afford the title compound **14** as a white crystalline solid (89%): mp 78-80 ^oC (Et_2O-*n*-pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ1.15 (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, 4a, 5, 6-Ad H), 1.64-1.88 (complex m, 6H, 1, 3, 7, 8e, 10e-Ad H, N*H*), 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-CH$_X$-CH_AH$_M$Ph), 2.92-2.97 (q, 1H, AMX, M region, J_{AM}=13.4 Hz, J$_{MX}$=5.6 Hz, NH-CH$_X$-CH$_A$$H_M$Ph), 3.58-3.62 (q, 1H, AMX, X region, J_{AX}=8.0 Hz, J_{MX}=5.6 Hz, NH-CH_X-CH$_A$H$_M$Ph), 3.64 (s, 3H, CH_3), 7.09-7.24 (m, 5H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (6-Ad C), 40.8 (*C*H_2Ph), 51.8 (*C*H3), 57.7 (HN-*C*H), 60.7 (2-Ad C), 121.9 (*C*N), 126.7, 128.2, 129.5 (2, 3, 4, 5, 6-aromatic C), 137.1 (1-aromatic C), 174.8 (*C*O_2CH_3); [α]$^{25}_{589}$= -6 (c 0.2, AcOEt). Anal. ($C_{21}H_{26}N_2O_2$) C, H, N.

***N*–[2–Aminocarbonyl(tricyclo[3.3.1.1^{3,7}]dec–2–yl)]–*L*–phenylalanine methyl ester (19)**

To a vigorous stirred solution of the aminonitrile **14** (1.93 g, 5.7 mmol) in CH_2Cl_2 (24 mL) was added dropwise H_2SO_4 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 NH_3 26 % under ice cooling. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic phase was washed with water (30

mL) and brine (30 mL), dried (Na_2SO_4), and evaporated. The resulted coloured residue was purified by column chromatography on silica gel using AcOEt-Et_2O 1:1 to afford the title compound **19** as a white crystalline solid (1.04 g, 51%): mp 141-143 ^{0}C (CH_2Cl_2-Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ1.27 (~d, 1H, *J*=11.7 Hz, 4e-Ad H), 1.39 (~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, N*H*, 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_X-C$H_A$$H_M$Ph), 2.80-2.85 (q, 1H, AMX, M region, J_{AM}=13.2 Hz, J_{MX}=5.7 Hz, NH-CH_X-$CH_A$$H_M$Ph), 3.53 (br s, 4H, C$H_3$, NH-C$H_X$-$CH_A$$H_M$Ph), 5.50 (br s, 2H, CON$H_2$), 7.05-7.22 (m, 5H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$) δ26.7 (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 (*C*H_2Ph), 51.4 (*C*H_3), 56.3 (NH*C*H), 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 (*C*O_2CH_3), 176.9 (*C*ONH_2); $[\alpha]^{25}_{589}$ +12 (c 0.2, MeOH). Anal. ($C_{21}H_{28}N_2O_3$) 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**.[9] The resulted oily residue was purified by column chromatography on silica gel using Et_2O-*n*-hexane 1:1 to afford the title compound **24** as a colourless viscous oil (86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.38 (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′-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-C$H_A$$H_M$Ph), 3.30 (dd, 1H, AMX, M region, J_{AM}=13.8 Hz, J_{MX}=4.0 Hz, 6-$CH_A$$H_M$Ph), 3.77-3.87 (m, 1H, AMX, X region, 6-Hx), 4.33-4.53 (q, AB, 2H, *J*=16.8 Hz, C$H_2CO_2CH_2$Ph), 5,07 (s, 2H, CO_2CH_2Ph), 7.10-7.35 (m, 10H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$) δ26.9 (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 (*C*H_2Ph), 37.9 (6′-C), 40.9 (*C*$H_2CO_2CH_2$Ph), 54.1 (6-C), 60.8 (2,2′-C), 67.2 (CO_2*C*H_2Ph), 127.1, 128.3, 128.4, 128.6, 128.7, 129.2, 135.1, 136.6 (aromatic C), 168.0 (*C*O_2CH_2Ph) 173.5, 174.1 (3, 5-C); $[\alpha]^{24}_{589}$ -34 (c 0.2, $CHCl_3$); CI$^+$ MS: m/z 473.3 ([M+H]$^+$, 50), 472.3 ([M]$^+$, 13), 382.2 ([M+H-CH_2Ph]$^+$, 23), 381.2 ([M- CH_2Ph]$^+$, 100); HRMS (ESI): [M+H]$^+$ calcd for $C_{29}H_{33}N_2O_4$, 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**.[9] White foamy solid which strongly binds the aforementioned solvents. Removal of the entrapped solvents upon drying at 62-64 ^{o}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, $CDCl_3$) δ1.35-1.47 (m, 2H, 4′e, 9′e-H), 1.52-1.73 (m, 7H, 4′a, 6′, 7′, 8′, 10′e-H), 1.79(s, 2H, 3′, 5′-H), 1.95 (d, 1H, *J*=12.5 Hz, 9′a-H), 2.05 (s, 1H, 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, C$H_A$$H_M$Ph), 3.31 (dd, 1H, AMX, M region, J_{AM}=13.8 Hz, J_{MX}=4.1 Hz, $CH_A$$H_M$Ph), 3.82-3.85 (q, 1H, AMX, X region, J_{AX}=8.0 Hz, J_{MX}=4.1 Hz, 6-Hx), 4.35-4.51 (q, AB, 2H, J_{AB}=17.1 Hz, CH_2CO_2H), 4.20-6.80 (v br s, 2H, COO*H*, 1-H), 7.13-7.30 (m, 5H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$) δ26.8 (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 (*C*H_2Ph), 37.9 (6′-C), 40.7 (*C*H_2CO_2H), 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 (*C*O_2H), 173.5 (3, 5-C). The hydrochloride salt (**29.HCl**) was prepared as described for **7c.HCl**. Mp 182-184 ^{o}C (dec); $[\alpha]^{25}_{589}$ -24 (c 0.2, MeOH). Anal. ($C_{22}H_{27}Cl\ N_2O_4$) 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**.[9] White foamy solid which strongly binds the eluting solvents. Removal of the entrapped solvents upon drying at 62-64 ^{o}C under vacuum (10^{-3} mmHg) gave the title compound **37** as a glass solid (96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.39 (d, 2H, *J*=12.4Hz, 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_AH$_M$Ph), 3.28 (dd, 1H, AMX, M region, J_{AM}=13.8 Hz, J_{MX}=4.0 Hz, CH$_A$$H_M$Ph), 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ26.9 (5′-C), 27.0 (7′-C), 30.3 (1′-C), 31.2 (4′-C), 32.5 (9′-C), 33.2 (8′-C), 33.8 (10′-C), 34.6 (3′-C), 36.7 (*C*H$_2$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]$^+$, 88), 324.2 ([M]$^+$, 21), 233.1 ([M-CH$_2$Ph]$^+$, 66). The hydrochloride salt (**37.HCl**) was prepared as described for **7c.HCl**. Mp 185-187 ^{o}C (dec). $[\alpha]^{25}_{589}$ -38 (c 0.2, MeOH). Anal. ($C_{20}H_{25}Cl\ N_2O_2$) 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**[9] (500 mg, 2.13 mmol) in THF-MeOH 1:1 (14 mL), aqueous formaldehyde 37 % (1 mL, 12.5 mmol) 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_2CO_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_2O-*n*-hexane 4:1 afforded the title compound **6b** as a white crystalline solid (490 mg, 92%): mp 191-192 ^{0}C (CH_2Cl_2-*n*-pentane); ^{1}H NMR (400 MHz , $CDCl_3$) δ1.47 (d, 1H, *J*=12.0 Hz, 4′e-H), 1.54 (d, 1H, *J*=12.3 Hz, 9′e-H), 1.61-1.91 (complex m, 7H, 3′, 5′, 6′, 7′, 8′e, 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); ^{13}C NMR (100 MHz , $CDCl_3$) δ26.3 (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 (*C*H$_3$), 37.5 (6′-C), 53.0 (6-C), 65.7 (2, 2′-C), 172.0, 174.1 (3, 5-C). Anal. ($C_{14}H_{20}N_2O_2$) 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_2O (4x25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and evaporated in vacuo. The oily residue was purified by column chromatography on silica gel using Et_2O-*n*-hexane 1:1 to afford the title compound **40** as a colourless viscous oil (530 mg, 83%): ^{1}H NMR (400 MHz , $CDCl_3$) δ1.49 (dd, 1H, *J*=2.1, 12.2 Hz, 4′e-H), 1.55 (dd, 1H, *J*=2.2, 12.1 Hz, 9′e-H), 1.58-1.77 (complex m, 5H, 6′, 8′, 10′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_2CO$_2$CH$_2$Ph), 5.15 (s, 2H, CO$_2$CH_2Ph), 7.28-7.40 (m, 5H, aromatic H); ^{13}C NMR (100 MHz , $CDCl_3$) δ 26.3 (5′-C),

27.1 (7′-C), 30.5 (1′-C), 31.9 (4′-C) 32.1 (9′-C), 32.2 (3′-C), 33.1 (8′-C), 33.7 (10′-C), 37.3 (*C*H_3), 37.6 (6′-C), 40.4 (*C*$H_2CO_2CH_2Ph$), 53.3 (6-C), 65.5 (2,2′-C), 67.3 (CO_2*C*H_2Ph), 128.3, 128.4, 128.5 (2, 3, 4, 5, 6-aromatic C), 135.1 (1-aromatic C), 168.0 (*C*O_2CH_2Ph), 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 ($[M-CH_2Ph]^+$, 12).

1–Methyl-3,5–dioxospiro[piperazine-2,2′-tricyclo[3.3.1.1^{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**.[9] White solid: mp 210-212 ^oC (EtOH-Et_2O); ^1H NMR (400 MHz , DMSO-d_6) 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, 5′, 7′-H), 2.03-2.18 (m, 4H, 1′, 3′, 4′a, 9′a-H), 2.31 (s, 3H, C*H*$_3$), 2.69 (d, 1H, *J*=12.2 Hz, 10′a-H), 3.0-3.85 (v br s, 1H, CO_2*H*), 3.47-3.99 (q, 2H, AB, J_{AB}=19.2 Hz, 6-H), 4.19-4.39 (q, 2H, AB, J_{AB}=16.9 Hz, C*H*$_2CO_2H$); ^{13}C NMR (100 MHz , DMSO-d_6) 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 (*C*H_3), 37.3 (6′-C), 40.2 (*C*H_2CO_2H), 52.5 (6-C), 64.8 (2,2′-C), 169.3 (*C*O_2H), 170.7 , 173.7 (3, 5-C). Anal. ($C_{16}H_{22}N_2O_4$) C, H, N.

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

Prepared by reductive methylation of diketopiperazine **64**[9] (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-Et_2O 1:1 to afford the title compound as a white crystalline solid **66** (600 mg, 87%): mp 134-136 ^oC (CH_2Cl_2–*n*-pentane); ^1H NMR (400 MHz , $CDCl_3$) 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, C*H*$_3$), 3.61 (s, 2H, 2-H), 8.24 (br s, 1H, 4-H); ^{13}C NMR (100 MHz , $CDCl_3$) δ20.7 (9, 11-C), 24.5 (10-C), 27.9 (8, 12-C), 29.3 (7, 13-C), 39.3 (*C*H_3), 54.3 (2-C), 64.4 (6-C), 171.3, 176.4 (3, 5-C). Anal. ($C_{12}H_{20}N_2O_2$).

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 Et_2O-*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, $CDCl_3$) 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, C*H*$_3$), 3.72 (s, 2H, 2-H), 4.54 (s, 2H, C*H*$_2CO_2CH_2Ph$), 5.12 (s, 2H, CO_2C*H*$_2$Ph), 7.28-7.43 (m, 5H, aromatic H); ^{13}C NMR (100 MHz ,$CDCl_3$) δ 20.7 (9, 11-C), 24.5 (10-C), 27.9 (8 , 12-C), 29.8 (7, 13-C), 39.2 (*C*H_3) 39.8 (*C*$H_2CO_2CH_2Ph$), 54.5 (2-C), 64.5 (6-C), 67.3 (CO_2*C*H_2Ph), 128.4, 128.5, 128.6 (2, 3, 4, 5, 6-aromatic C), 135.0 (1-aromatic C), 167.8 (*C*O_2CH_2Ph), 170.3, 175.9 (3, 5-C); CI^+ MS: m/z 372.3 ($[M]^+$, 34), 373,3 ($[M+H]^+$, 100), 281.1 ($[M-CH_2Ph]^+$, 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**.[9] White solid: mp 178-180 ^{o} C (EtOH-Et_2O); ^1H NMR (400 MHz , DMSO-d_6) δ1.20 – 1.57 (complex m, 8H, 8, 9, 10, 11, 12-H), 1.61-1.83 (complex m, 4H, 7, 9, 11, 13-H), 1.87-2.01 (m, 2H, 7, 13-H), 2.33 (s, 3H, C*H*$_3$), 3.72 (s, 2H, 2-H), 3.30-4.90 (v br s, 1H, CO_2*H*), 4.27 (s, 2H,

CH_2CO_2H); ^{13}C NMR (100 MHz , DMSO-d_6) δ 20.7 (9, 11-C), 24.6 (10-C), 27.8 (8 , 12-C), 29.5 (7 , 13-C), 38.8 (CH_3), 39.8 (CH_2CO_2H), 53.9 (2-C), 64.1 (6-C), 169.5 (CO_2H), 170.4 , 175.8 (3, 5-C). Anal. ($C_{14}H_{22}N_2O_4$) C, H, N.

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[(a)]	IC_{50} (μM)	IC_{90} (μM)	Compound	IC_{50} (μM)	IC_{90} (μM)
43	200		**71**	>300	
44	118		**6a**	na[b]	
45	542		**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		**66**	na	
56	760		**67**	>400	
59	>400		**Acetohydroxamic acid**	680	

[a]Compounds **45**, **29**-**31**, **37**, and **38** were tested as hydrochloride salts.
[b]Data not available.

Experimental. Biological Assays.

Trypanocidal assays

Cultured bloodstream form *T. brucei* (strain 427) were maintained at 37 ^oC 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_{50}) and 90% (IC_{90}). In the case of untreated cultures (volume 4 ml), cell densities increased from 0.5×10^4 to 1×10^6 cells ml^{-1} 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 innoculum of 2×10^5 epimastigotes ml^{-1}. After 5 days incubation at 28^oC in RPMI medium (Kendall *et al*. 1990) in the absence of drug, cell density reached 2×10^7 parasites ml^{-1}.

(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 x 10^4 ml^{-1} in 200 µl of growth medium containing different compound concentrations. The plates were incubated for 6 days at 37^{o}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.

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	$C_{15}H_{21}N_3O_4$	58.62	6.89	13.67	58.62	6.98	13.71
7a.HCl	$C_{15}H_{22}ClN_3O_4$	52.40	6.45	12.22	52.64	6.61	11.95
7b	$C_{16}H_{23}N_3O_4$	59.79	7.21	13.08	59.52	7.30	13.37
7b.HCl	$C_{16}H_{24}ClN_3O_4$	53.70	6.76	11.74	53.37	7.06	12.02
7c.HCl	$C_{16}H_{24}ClN_3O_4$	53.70	6.76	11.74	53.58	7.16	11.61
7d.HCl	$C_{22}H_{28}ClN_3O_4$	60.89	6.50	9.68	61.28	6.71	9.86
7e.HCl	$C_{22}H_{28}ClN_3O_4$	60.89	6.50	9.68	60.52	6.77	10.02
8.HCl	$C_{22}H_{28}ClN_3O_4$	60.89	6.50	9.68	61.26	6.83	9.91
9a.HCl	$C_{13}H_{22}ClN_3O_4$	48.83	6.93	13.14	48.88	7.01	13.07

9b.HCl	$C_{14}H_{24}ClN_3O_4$	50.37	7.25	12.59	50.75	7.60	12.28
9c.HCl	$C_{14}H_{24}ClN_3O_4$	50.37	7.25	12.59	50.37	7.60	12.21
9d.HCl	$C_{20}H_{28}ClN_3O_4$	58.60	6.89	10.25	58.63	6.99	10.20
10a.HCl	$C_{12}H_{20}ClN_3O_4$	47.14	6.59	13.74	46.95	6.72	13.61
10b.HCl	$C_{13}H_{22}ClN_3O_4$	48.83	6.93	13.14	48.40	7.28	12.72
43	$C_{15}H_{21}N_3O_3$	61.83	7.27	14.42	61.46	6.89	14.78
44	$C_{15}H_{22}N_4O_3$	58.80	7.24	18.29	58.55	7.13	17.91
45.HCl	$C_{16}H_{24}ClN_3O_4.0.4\ Et_2O$	54.63	7.29	10.86	54.59	7.19	11.09
29.HCl	$C_{22}H_{27}ClN_2O_4$	63.07	6.50	6.69	63.08	6.57	6.43
30.HCl	$C_{22}H_{27}ClN_2O_4$	63.07	6.50	6.69	62.69	6.73	6.39
31.HCl	$C_{22}H_{27}ClN_2O_4$	63.07	6.50	6.69	63.41	6.81	6.31
41	$C_{16}H_{22}N_2O_4$	62.73	7.24	9.15	62.61	7.14	9.23
59	$C_{12}H_{18}N_2O_4$	56.68	7.14	11.02	57.07	7.16	11.38
71	$C_{13}H_{20}N_2O_4$	58.19	7.51	10.44	58.44	7.90	10.18
6b	$C_{14}H_{20}N_2O_2$	67.71	8.12	11.28	67.71	8.14	11.25
37.HCl	$C_{20}H_{25}ClN_2O_2$	66.56	6.98	7.76	66.95	7.04	7.36
38.HCl	$C_{20}H_{25}ClN_2O_2$	66.56	6.98	7.76	66.19	7.22	8.20
39	$C_{20}H_{24}N_2O_2$	74.04	7.46	8.64	74.11	7.44	8.57
65	$C_{10}H_{16}N_2O_2$	61.20	8.22	14.28	61.19	8.52	14.05
66	$C_{12}H_{20}N_2O_2$	64.25	8.99	12.49	64.10	8.99	12.65
67	$C_{11}H_{18}N_2O_2$	62.83	8.63	13.32	63.01	9.02	12.97