Supporting Information

Discovery of Novel Benzoxaborole-Based Potent Antitrypanosomal Agents

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General Procedures

NMR spectra were recorded on a MercuryPlus 400 (Varian) or Mercury 300 (Varian). Chemical shifts are expressed in parts per million (δ) relative to residual solvent as an internal reference. High resolution mass spectra were obtained on a Micromass GCT. High performance liquid chromatography analysis was performed on a Varian ProStar 230 with a flow rate of 1 mL/min and a gradient of 90% H_2O/10% MeCN to 100% MeCN using a VWD detector. A Waters Symmetry C18 column (4.6×150 mm, 5 μm) or Phenomenex Aqua 125-5 C18 column (4.6 x 50 mm) was used. Purity was based on the integrated UV chromatogram (220 or 254 nm). In general, compounds are of purity >95%. Column chromatography was performed using Huanghai silica gel (38-54 μm). Melting points were measured on a SGWX-4 melting point apparatus.

Preparation of Key Compounds

4-(3,4-Dichlorophenylsulfenyl)-2-bromobenzaldehyde (1, X = 3,4-Cl_2). 2-bromo-4-fluorobenzaldehyde (1 g, 4.92 mmol) was dissolved in DMF (25 mL) and cooled to 0 °C with ice bath. To this solution under nitrogen were added in sequence potassium carbonate (2.04 g, 9.85 mmol) and 3,4-dichlorobenzenethiol (882 mg, 4.92 mmol). The reaction mixture was stirred for 2.5 h then treated with iced water (25

mL). After extraction with ethyl acetate the organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **1** (**X = 3,4-Cl_2**) (1.38 g, 77.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.25 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 1.2 Hz, 1H), 7.33 (dd, J_1 = 8.4, J_2 = 2.0 Hz, 1H) and 7.15 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 146.5, 135.3, 134.1, 133.9, 133.0, 131.6, 131.2, 130.9, 130.1, 127.7, 126.7; HRMS-ESI$^+$: $C_{13}H_7BrCl_2OS$ calcd $[M+H]^+$ 360.8856, found 360.8899; mp: 125-126 ^{o}C.

(4-(3,4-Dichlorophenylsulfenyl)-2-bromophenyl)methanol (2, X = 3,4-Cl_2). Compound **1** (**X = 3,4-Cl_2**) (400 mg, 1.10 mmol) was dissolved in MeOH (20 mL) and cooled to 0 ^{o}C with ice bath. To this solution was added $NaBH_4$ (62.37 mg, 1.65 mmol). The reaction mixture was stirred for 0.5 h then treated with saturated $NaHCO_3$. After evaporation the residue was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous Na_2SO_4, then concentrated *in vacuo* to obtain compound **2** (**X = 3,4-Cl_2**) (400 mg, quantitative) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 4.65 (s, 2H) and 3.41 (br, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5, 135.4, 134.7, 134.6, 133.1, 131.6, 131.3, 130.8, 130.5, 129.5, 128.9, 122.6, 63.9; HRMS-ESI$^+$: $C_{13}H_9BrCl_2OS$ calcd $[M+Na]^+$ 384.8833, found 384.8842.

(3-Bromo-4-((methoxymethoxy)methyl)phenyl)(3,4-dichlorophenyl)sulfane (3, X = 3,4-Cl_2). Compound **2** (**X = 3,4-Cl_2**) (4.31 g, 11.84 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL). To this solution under nitrogen were added in sequence N,N-Diisopropylethylamine (7.32 mL, 41.45 mmol) and chloromethyl methyl ether (1.91 mL, 26.05 mmol). The reaction mixture was stirred overnight at room temperature then treated with water (15 mL). After extraction with dichloromethane, the organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After rotary evaporation the residue was purified by column chromatography over silica gel to give compound **3** (4.04 g, 83% yield) as a viscous oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66-7.58 (m, 3H), 7.53 (d, J = 8.4 Hz, 1H), 7.43 (dd, J = 8.4 & 2 Hz, 1H), 7.28-7.25 (m, 1H), 4.71 (s, 2H), 4.55 (s, 2H) and 3.31 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 135.6, 134.8, 134.7, 133.1, 131.6, 131.2, 130.7, 130.5, 129.6, 129.4, 123.1, 96.0, 68.2, 55.3; HRMS-ESI$^+$: $C_{15}H_{13}BrCl_2O_2S$ calcd $[M+Na]^+$ 428.9095, found 428.9160.

6-(3,4-Dichloro)phenylsulfenyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (8). Compound **3** (**X = 3,4-Cl_2**) (2.39 g, 5.86 mmol) was dissolved in anhydrous THF (25 mL) and cooled to -80 ^{o}C. To this solution under nitrogen was added dropwise 1.6 M n-BuLi (4.03 mL, 6.45 mmol) over 20 min. After stirred for 20 min at -80 ^{o}C, $B(iPrO)_3$ (1.48 mL, 6.45 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight at room temperature. After 6 M HCl (20 mL) was added and stirred for 3 h, the mixture was evaporated and extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The

residue after rotary evaporation was purified by column chromatography over silica gel to give compound **8** (607.5 mg, 33.3% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (s, 1H), 7.81 (s, 1H), 7.60-7.45 (m, 4H), 7.15 (dd, J = 8.4 & 2 Hz, 1H) and 5.03 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.77, 137.52, 135.17, 134.91, 132.95, 132.09, 130.60, 130.57, 130.38, 128.47, 122.31, 71.03; HRMS-EI: $C_{13}H_9BCl_2O_2S$ calcd 309.9793, found 309.9796; mp: 118-119 ^{o}C.

6-(3,4-Dichloro)phenylsulfinyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (13). Compound **8** (200 mg, 0.64 mmol) was dissolved in H_2O : MeOH = 10% (15 mL, v/v). To this solution was added sodium periodate (688 mg, 3.21 mmol). The reaction mixture was stirred for 1 h at 60 ^{o}C, then evaporated and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After rotary evaporation the residue was purified by re-crystallization (hexane/ethyl acetate) to give compound **13** (112.4 mg, 53.5% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.39 (s, 1H), 8.11 (s, 1H), 7.99 (d, J = 2 Hz, 1H), 7.88-7.81 (m, 2H), 7.69-7.60 (m, 2H) and 5.02 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.61, 144.94, 142.81, 135.87, 134.12, 131.49, 127.22, 127.10, 126.42, 123.73, 122.44, 70.75; HRMS-EI: $C_{13}H_9BCl_2O_3S$ calcd 325.9743, found 325.9740; mp: 141-143 ^{o}C.

6-(3,4-Dichloro)phenylsulfonyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (18). Compound **8** (260 mg, 0.83 mmol) was dissolved in H_2O : MeOH = 10% (15 mL, v/v). To this solution was added sodium periodate (894 mg, 4.17 mmol). The mixture was stirred overnight at 60 ^{o}C then evaporated and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4. After rotary evaporation, the residue was purified by re-crystallization (hexane/ethyl acetate) to give compound **18** (86 mg, 30% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.49 (s, 1H), 8.35 (s, 1H), 8.20 (s, 1H), 8.12 (dd, J = 8.4 & 2 Hz, 1H), 7.90 (d, J = 1.2 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H), and 5.06 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.64, 156.94, 137.94, 133.87, 130.29, 128.74, 128.65, 124.34, 121.25, 120.71, 120.61, 70.98; HRMS-EI: $C_{13}H_9BCl_2O_4S$ calcd 341.9692, found 341.9694; mp: 154-156 ^{o}C.

6-(4-Chlorophenyl)sulfenyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (7). It was synthesized in a similar manner to compound **8**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.42 (dd, J_1 = 7.8, J_2 = 1.6 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.22-7.11 (m, 4H) and 5.04 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.08, 135.04, 134.27, 133.81, 133.70, 132.73, 131.49, 129.20, 122.04, 71.01; HRMS-EI: $C_{13}H_{10}BClO_2S$ calcd 276.0183, found 276.0180; mp: 157-161 ^{o}C.

6-(4-Chloro)phenylsulfinyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (12). To a solution of compound **7** (1.5 g, 5.42 mmol) in DCM (100 mL) and THF (50 mL) at -20 ^{o}C was added a solution of *m*-chloroperbenzoic acid (77 % purity, 1.22 g, 5.42 mmol) in DCM (50 mL) in portions. After removing the cooling bath, the mixture was stirred for 45 min, evaporated to give the residue that was suspended in *i*-Pr_2O and sonicated to give the desired product as a white solid (0.9 g, yield 56.8 %). ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.41-7.33 (m, 3H) and 5.03 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.01, 143.81, 143.49, 137.38, 129.60, 127.03, 126.87, 125.94, 122.44, 70.91; HRMS-EI: $C_{13}H_{10}BClO_3S$ calcd 292.0132, found 292.0134; mp: 153-156 ^oC.

6-(4-Chloro)phenylsulfonyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (17). To a solution of compound **7** (1.1 g, 3.98 mmol) in THF (50 mL) and DCM (80 mL) at -60 ^oC with stirring was added a solution of *m*CPBA (1.78 g, 7.96 mmol, 2 eq.) in DCM (50 mL) in portions. After removal of the cooling bath, the mixture was stirred for 1 h from -60 ^oC to RT and 1 h at RT. It was washed with $NaHCO_3$ solution, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel with MeOH : EtOAc (1 : 2) to give the desired compound **17** (0.12 g, yield 9.8 %). ^{1}HNMR (300 MHz, DMSO-d_6): δ 9.48 (s, 1H), 8.31 (d, 1H), 8.04 (dd, 1H), 7.94 (d, 2H), 7.69 (d, 2H), 7.65 (d, 1H) and 5.04 (s, 2H) ppm. MS: m/z = 309 (M+1, ESI+) and 307 (M-1, ESI-); m.p: 157-163^oC.

Compounds **4**, **5**, **6**, **9**, **10**, **11**, **14**, **15** and **16** were synthesized in a similar manner to compound **7**, **8**, **12**, **13**, **17** and **18**.

6-Phenylsulfenyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.42 (dd, J_1 = 7.8, J_2 = 1.6 Hz, 1H), 7.30-7.10 (m, 6H) and 5.03 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.73, 136.18, 134.28, 134.09, 133.57, 130.43, 129.07, 126.77, 121.88, 71.01; HRMS-EI: $C_{13}H_{11}BO_2S$ calcd 242.0573, found 242.0574; mp: 121-124 ^oC.

6-(2-Chloro)phenylsulfenyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (5). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (s, 1H), 7.80 (d, J = 0.9 Hz, 1H), 7.50-7.59 (m, 3H), 7.25 (m, 2H), 6.91 (m, 1H) and 5.03 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.84, 136.64, 135.82, 135.60, 133.34, 132.90, 131.41, 129.79, 129.65, 127.11, 122.31, 71.09; HRMS-EI: $C_{13}H_{10}BClO_2S$ calcd 276.0183, found 276.0184; mp: 116-118 ^oC.

6-(3-Chloro)phenylsulfenyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (6). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (s, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.58 (dd, J_1 = 8, J_2 = 1.6 Hz, 1H), 7.5 (d, J = 8 Hz, 1H), 7.45-7.15 (m, 4H) and 5.02 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.54, 139.17, 135.17, 134.85, 134.71, 132.38, 129.95, 128.84, 127.31, 126.43, 122.18, 70.97; HRMS-EI: $C_{13}H_{10}BClO_2S$ calcd 276.0183, found 276.0176; mp: 125-126 ^oC.

6-Phenylsulfinyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (9). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.70 (s, 1H), 7.58 (m, 2H), 7.45-7.35 (m, 4H) and 5.04 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.71, 145.11, 144.37, 131.09, 129.32, 127.09, 126.97, 124.62, 122.26, 70.95; HRMS-EI: $C_{13}H_{11}BO_3S$ calcd 258.0522, found 258.0523; mp: 173-176 ^oC.

6-(2-Chloro)phenylsulfinyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (10). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.41 (s, 1H), 8.09 (d, J = 1.2 Hz, 1H), 8.01-7.97 (m, 1H), 7.83 (dd, J = 8.1, J_2 = 1.8 Hz, 1H), 7.71-7.65 (m, 1H), 7.61-7.51 (m, 3H) and 5.02 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.09, 142.84, 142.45, 132.10, 130.89, 129.92, 128.41, 128.27, 127.98, 125.41, 122.18, 70.90; HRMS-EI: $C_{13}H_{10}BClO_3S$ calcd 292.0132, found 292.0128; mp: 174-175 ^{o}C.

6-(3-Chloro)phenylsulfinyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (11). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.39 (s, 1H), 8.11 (s, 1H), 7.85 (dd, J_1 = 8.1, J_2 = 1.8 Hz, 1H), 7.78 (s, 1H), 7.69-7.63 (m, 1H), 7.59-7.56 (m, 3H) and 5.01 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.08, 147.21, 143.81, 135.50, 131.13, 130.52, 127.13, 126.92, 124.29, 122.55, 122.47, 70.95; HRMS-EI: $C_{13}H_{10}BClO_3S$ calcd 292.0132, found 292.0135; mp: 152-153 ^{o}C.

6-Phenylsulfonyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (14). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.55-7.35 (m, 4H) and 5.06 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.48, 141.38, 140.64, 133.17, 129.98, 129.71, 129.25, 127.45, 122.08, 70.98; HRMS-EI: $C_{13}H_{11}BO_4S$ calcd 274.0471, found 274.0473; mp: 152-155 ^{o}C.

6-(2-Chloro)phenylsulfonyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (15). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.50 (s, 1H), 8.35-8.30 (m, 2H), 8.00 (dd, J_1 = 8.1, J_2 = 1.8 Hz, 1H), 7.78-7.62 (m, 4H) and 5.08 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.74, 139.16, 138.18, 134.67, 132.70, 131.93, 130.84, 130.64, 127.29, 121.63, 71.03; HRMS-EI: $C_{13}H_{10}BClO_4S$ calcd 308.0081, found 308.0081; mp: 130-132 ^{o}C.

6-(3-Chloro)phenylsulfonyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (16). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.48 (s, 1H), 8.35-7.63 (m, 7H) and 5.06 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.87, 143.34, 140.07, 135.42, 133.27, 130.58, 130.17, 129.83, 127.50, 125.62, 122.24, 71.02; HRMS-EI: $C_{13}H_{10}BClO_4S$ calcd 308.0081, found 308.0082; mp: 142-143 ^{o}C.

2-Bromo-4-(4-nitrophenylsulfenyl)benzaldehyde (1, X = 4-NO_2). To a solution of 4-nitrobenzenethiol (3.1 g, 20 mmol), 2-bromo-4-fluorobenzaldehyde (4.1 g, 20 mmol) in DMF (40 mL) was added K_2CO_3 (5.5 g, 40 mmol). The mixture was heated under nitrogen at 100 ^{o}C overnight, then was cooled to room temperature, filtered through a short pack of diatomaceous earth to remove the solid residue. The filtrate was concentrated and poured into DCM (30 mL) and H_2O (30 mL). The aqueous phase was neutralized by addition of 3 M HCl, the layers were separated and the aqueous phase was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography, eluting with an EtOAc/heptanes gradient (0:100 to 100: 0) to give compound **1** (**X = 4-NO_2**) (4.3 g, 71%) as a fine yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): 10.35 (s, 1H), 8.43 (dd, J = 2.3, 0.6 Hz,

1H), 7.98 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.69-7.77 (m, 2H), 7.30 (dd, *J* = 8.6, 3.0 Hz, 1H), 7.12 (dd, *J* = 8.6, 0.8 Hz, 1H).

4-(4-Nitrophenylsulfenyl)-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (19, X = 4-NO_2). To a solution of 2-bromo-4-(4-nitrophenylsulfenyl)benzaldehyde (2.7 g, 8.0 mmol) in 1,4-dioxane (50 mL) was added bis-pinacoldiboron (2.23 g, 8.8 mmol), KOAc (2.35 g, 24.0 mmol) and $PdCl_2(dppf)_2$ (175 mg, 0.24 mmol). The mixture was degassed with N_2, heated at 80 ^oC overnight, then was cooled to room temperature and filtered though a short pack of diatomaceous earth. The filtrate was concentrated, and the residue was purified by flash chromatography eluting with an EtOAc/heptanes gradient (0:100 to 50: 50) to give compound **19** (**X = 4-NO_2**) (1.3 g, 42.5%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): 10.56 (s, 1H), 8.20-8.25 (m, 2H), 8.11-8.17 (m, 1H), 7.94-8.00 (m, 2H), 7.47-7.53 (m, 1H), 7.33-7.38 (m, 1H), 1.27 (s, 12H).

6-(4-Nitrophenylsulfenyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (20). To a suspension of **19** (**X = 4-NO_2**) (721 mg, 1.95 mmol) in EtOH (15 mL) at 0 ^oC was added $NaBH_4$ (73.8 mg, 1.95 mmol) in small portions. After complete addition, the mixture was stirred at 0 ^oC for 20 minutes and allowed to warm to room temperature in another 1 h. The mixture was then cooled to 0 ^oC, the clear solution was carefully quenched with H_2O (1 mL), followed by slow addition of HCl (5 mL, 3 N). The resulting yellow suspension was warmed to room temperature and stirred for 2 h. The mixture was neutralized to pH ~ 7 with saturated $NaHCO_3$, and the precipitate was collected by filtration. This crude product was purified by flash chromatography eluting with a MeOH/DCM gradient (0:100 to 10: 90) to afford compound **20** (510 mg, 96.4 %) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): 9.32 (s, 1H), 8.08-8.14 (m, 2H), 7.91 (d, *J* = 1.2 Hz, 1H), 7.67 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.57 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.22-7.28 (m, 2H), 5.05 (s, 2H). LCMS (m/z) 294 (M+23).

Using a procedure similar to that described for preparation of compound **20**, the following 6-S substituted benzoxaboroles **21**, **22**, **23** and **24** were prepared:

2-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-ylsulfenyl)-benzoic acid methyl ester (21). ^1H NMR (400 MHz, DMSO-d_6): 9.29 (s, 1H), 7.90 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.86 (d, *J* = 1.2 Hz, 1H), 7.58-7.64 (m, 1H), 7.50-7.57 (m, 1H), 7.38 (td, *J* = 7.7, 1.6 Hz, 1H), 7.22 (td, *J* = 7.6, 1.1 Hz, 1H), 6.73 (dd, *J* = 8.1, 0.8 Hz, 1H), 5.04 (s, 2H), 3.86 (s, 3H). LCMS (m/z) 323 (M+23).

6-(3-Methoxyphenylsulfenyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (22). ^1H NMR (400 MHz, DMSO-d_6): 9.24 (s, 1H), 7.74 (d, *J* = 1.2 Hz, 1H), 7.46-7.51 (m, 1H), 7.40-7.46 (m, 1H), 7.25 (t, *J* = 8.2 Hz, 1H), 6.82 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1H), 6.75-6.80 (m, 2H), 4.98 (s, 2H), 3.69 (s, 3H). LCMS (m/z) 273 (M+H).

6-(4-Aminophenylsulfenyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (24). To a 25 mL round-bottom flask fitted with magnetic stirring bar was added compound **20** (120 mg, 0.42 mmol), followed by addition of EtOH (4 mL) and THF (1 mL). The

flask was evacuated and recharged with nitrogen (2X). To the stirred solution was added 5% Pd/C (20 mg) and the flask was evacuated and recharged with hydrogen (3X). The reaction mixture was stirred under hydrogen at room temperature overnight, then was filtered through a short pack of diatomaceous earth and washed with MeOH (3 x 10 mL). The combined filtrate was concentrated under reduced pressure to give a white solid. The solid was dissolved in minimum amount of MeOH and treated with 12 M HCl. The precipitated salt was collected by filtration, washed with heptanes to give the hydrochloride salt of compound **24** (56.4 mg, 52.2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 7.72 (d, J = 3.9 Hz, 1H), 7.40-7.48 (m, 2H), 7.27-7.32 (m, 2H), 7.21 (t, J = 8.8 Hz, 2H), 4.97 (s, 2H). LCMS (m/z) 258 (M+H).

N-[4-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-ylsulfenyl)phenyl]-acetamide (23): To a 20 mL scintillation vial containing compound **24** (77 mg, 0.3 mmol) in DCM (4.0 mL) was added Et_3N (59 μL, 0.42 mmol), followed by acetyl chloride (26 μL, 0.36 mmol) and the mixture was stirred overnight. The resulting yellow suspension was quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The combined organic extract was dried over Na_2SO_4, filtered and evaporated to give the crude product, which was purified by flash chromatography eluting with a MeOH/DCM gradient (0:100 to 10:90) to give compound **23** (5.6 mg, 6.2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 10.05 (s, 1H), 7.55-7.59 (m, 3H), 7.28-7.38 (m, 4H), 4.94 (s, 2H), 2.02 (s, 3H). LCMS (m/z) 300 (M+H).

4-Phenoxy-2-bromobenzaldehyde (25). A mixture of phenol (6.95 g, 73.88 mmol), 2-bromo-4-fluorobenzaldehyde (15 g, 73.88 mmol) and potassium carbonate (18 g, 0.13 mol) in DMF (150 mL) was heated under nitrogen at 100 ^{o}C for 16 h. The mixture was filtered warm and the solid cake was washed with ethyl acetate. The solvents were removed by rotary evaporation under vacuum at 50 ^{o}C and the residue was suspended in n-pentane, sonicated, and filtered to provide compound **25** as a brown solid (18.9 g, yield 92.3%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.10 (s, 1H), 7.86 (d, 1H), 7.49 (t, 2H), 7.30 (d, 1H), 7.27 (d, 1H), 7.20-7.17 (m, 2H) and 7.06 (dd, 1H) ppm.

4-Phenoxy-2-bromobenzyl alcohol (26). To a solution of compound **25** (10.5 g, 37.89 mmol) in MeOH (300 mL) cooled in ice bath was added $NaBH_4$ (7.2 g, 5 eq) in portions. The solution was stirred at RT overnight and evaporated to remove MeOH. The residue was dissolved in water and extracted with CH_2Cl_2, dried, and evaporated to give the desired compound **26** as an oil (10.1 g, yield 95.5%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50 (d, 1H), 7.42-7.37 (m, 2H), 7.19-7.13 (m, 2H), 7.05-7.01 (m, 3H), 5.40 (t, 1H) and 4.47 (d, 2H) ppm.

5-Phenoxy-2-(methoxymethoxymethyl)phenyl bromide (27). To a mixture of compound **26** (10.1 g, 36.18 mmol) and DIPEA (11 mL, 1.75 eq) in CH_2Cl_2 (200 mL) was added dropwise methoxymethyl chloride (4.1 mL, 1.5 eq) at RT. The mixture was stirred under nitrogen at RT overnight. The mixture was washed with $NaHCO_3$ solution, dried, and evaporated to provide 12.17 g of compound **27** as a

yellow oil (quantitative yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.48 (d, 1H), 7.42 (t, 2H), 7.22-7.16 (m, 2H), 7.07-6.99 (m, 3H), 4.67 (s, 2H), 4.52 (s, 2H) and 3.30 (s, 3H) ppm.

[0001] 6-Phenoxy-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (28). A solution of compound **27** (11.7 g, 36.18 mmol) and (i-PrO)$_3$B (9.6 mL, 1.15 eq) in THF under N_2 was cooled to -78 ^{o}C and n-BuLi (1.6 M hexanes, 26 mL) was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 3 h. Hydrochloric acid (6 N, 20 mL) was added and the solution was concentrated. The residue was dissolved in methanol and 6 N HCl, and was refluxed for 1.5 h. Methanol was removed and the residue was extracted with ethyl acetate. The mixture after evaporation was purified by column chromatography with hexane : ethyl acetate (2 : 1, v/v) to afford 5.1 g of compound **28** as a white solid (yield 62.4%). **[0002]** ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.17 (s, 1H), 7.43-7.35 (m, 3H), 7.28 (s, 1H), 7.19-7.09 (m, 2H), 6.99 (d, 2H) and 4.96 (s, 2H) ppm; MS: m/z = 227 (M+1, ESI+) and m/z = 225 (M-1, ESI-); mp: 95-99 ^{o}C.

(2-Bromo-4-benzoyl)toluene (29). To a mixture of $AlCl_3$ (1.46 g, 11.0 mmol) in benzene (16 mL) was added a solution of 3-bromo-4-methylbenzoyl chloride (2.33 g, 10.0 mmol) in benzene (8 mL) dropwise at room temperature. This mixture was stirred for 2 h at 50 ^{o}C. The mixture was washed with 3 M HCl (20 mL) and saturated brine (20 mL), and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give 2.7 g of compound **23** (98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 6.9 Hz, 2H), 7.65 (dd, J_1 = 7.8, J_2 = 1.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H) and 2.49 (s, 3H) ppm.

(2-Bromo-4-benzoyl)benzyl alcohol (30). To a solution of compound **29** (2.7 g, 9.8 mmol) in CCl_4 (50 mL) was added NBS (1.75 g, 9.8 mmol) and Bz_2O_2 (0.12 g, 0.5 mmol). This mixture was heated to reflux and stirred overnight. The residue after rotary evaporation was purified by column chromatography over silica gel to give 1.71 g of (2-Bromomethyl-5-benzoyl)bromobenzene (49.3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 1.5 Hz, 1H), 7.79 (d, J = 7.8 Hz, 2H), 7.71 (dd, J_1 = 8.1, J_2 = 1.5 Hz, 1H) and 4.64 (s, 2H) ppm. To a solution of (2-Bromomethyl-5-benzoyl)bromobenzene (1.71 g, 4.83 mmol) in DMF (30 mL) was added sodium acetate (1.98 g, 24.15 mmol). This mixture was stirred at 60 ^{o}C overnight and poured into ice-water (50 g). The precipitate was filtered, washed with water, and dried under vacuum to give 1.63 g of compound (2-Bromo-4-benzoyl)benzyl acetate (100%). To a solution of (2-Bromo-4- benzoyl)benzyl acetate (1.63 g, 4.9 mmol) in methanol (25 mL) was added 15% aq. NaOH (5 mL). This mixture was refluxed for 1 h. After methanol was evaporated the mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by crystallization to give compound **30** (1.50 g, 100%).

(2-Bromo-4-benzoyl)benzaldehyde (31). To a solution of compound **30** (1.50 g, 5.15 mmol) in DCM (30 mL) was added PCC (2.22 g, 10.3 mmol) and Celite (2.5 g). This mixture was stirred overnight at room temperature and filtered. The residue after rotary evaporation was purified by crystallization to give 1.32 g of compound **31** (88.7%).

[2-(3-Bromo-4-(1,3-dioxolan-2-yl)phenyl)-2-phenyl]-1,3-dioxolane (32). To a solution of compound **31** (1.32 g, 4.57 mmol) in toluene (50 mL) was added ethylene glycol (2.83 g, 45.70 mmol) and p-toluenesulfonic acid monohydrate (69 mg, 0.36 mmol). This mixture was refluxed for 96 h. The mixture was washed with saturated $NaHCO_3$, water and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated to give compound **32** (1.51 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 1.5 Hz, 1H), 7.51 (m, 5H), 7.30 (m, 2H), 6.07 (s, 1H) and 4.07 (m, 8H) ppm.

(2-Formyl-5-benzoyl)phenylboronic acid (33). Compound **32** (0.50 g, 1.23 mmol) was dissolved in anhydrous THF (10 mL) and cooled to -80 ^{o}C. To this solution under nitrogen was added dropwise 1.6 M n-BuLi (0.88 mL, 1.41 mmol) over 15 min. After stirred for another 20 min at -80 ^{o}C, $B(iPrO)_3$ (0.33 mL, 1.41 mmol) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight at room temperature. After 6 M HCl (6 mL) was added and stirred for 2 h, the mixture was evaporated and extracted with ethyl acetate (25 mL × 5) and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **33** (0.31 g, 88%).

[6-(1-Phenyl-1-hydroxylmethyl)]-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (34). Compound **33** (0.75 g, 2.95 mmol) was dissolved in THF (8 mL) and water (0.5 mL). To this solution under stirring was added $NaBH_4$ (217 mg, 5.90 mmol) at room temperature. After stirred for 3 h, 3 M HCl (10 mL) was added to quench the reaction, and the mixture was evaporated, extracted with ethyl acetate (30 mL × 3), and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by crystallization to give compound **34** (0.35 g, 50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.1 (s, 1H), 7.71 (s, 1H), 7.46 (dd, J_1 = 8.1, J_2 = 1.8 Hz, 1H), 7.31 (m, 5H), 7.18 (d, J = 7.5 Hz, 1H), 5.89 (d, J = 3.9 Hz, 1H), 5.72 (d, J = 3.6 Hz, 1H) and 4.91 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.36, 153.24, 143.82, 142.98, 142.84, 142.33, 129.66, 129.47, 128.57, 128.42, 127.63, 127.46, 126.57, 126.46, 121.26, 121.16, 77.87, 76.26, 71.43, 71.10; HRMS-ESI$^-$: $C_{14}H_{13}BO_3$ calcd $[M-H]^-$ 239.0880, found 239.0886; mp: 116-118 ^{o}C.

6-Benzoyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (35). To a solution of compound **34** (0.2 g, 0.83 mmol) in DCM (15 mL) was added PCC (0.45 g, 2.08 mmol) and Celite (0.45 g). This mixture was stirred for 3 h at room temperature before filtration. The residue after rotary evaporation was purified by crystallization to give compound **35** (0.15 g, 76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (s, 1H), 8.12 (s, 1H), 7.87 (dd, J_1 = 8, J_2 = 1.6 Hz, 1H), 7.69 (m, 3H), 7.57 (m, 3H) and 5.08 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.37, 158.13, 137.52, 136.72, 132.94,

132.85, 132.58, 130.07, 128.38, 121.14, 71.14; HRMS-EI: $C_{14}H_{11}BO_3$ calcd 238.0801, found 238.0802; mp: 137-139 ^oC.

2-(2-Bromo-4-fluorophenyl)-1,3-dioxolane (36). To a solution of 2-bromo-4-fluorobenzaldehyde (50 g, 246 mmol) in toluene (500 mL) was added ethylene glycol (74.8 g, 1207 mmol) and p-toluenesulfonic acid monohydrate (2.48 g, 13 mmol). This mixture was refluxed for 2 h, washed with saturated $NaHCO_3$, water and brine, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give 53.35 g of compound **36** (87.8%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63-7.57 (m, 1H), 7.34-7.29 (m, 1H), 7.09-7.02 (m, 1H), 6.04 (s, 1H) and 4.18-4.04 (m, 4H) ppm.

2-(4-(Benzyloxy)-2-bromophenyl)-1,3-dioxolane (37). Compound **36** (52.7 g, 213 mmol) was dissolved in DMF (400 mL) and cooled to 0 ^oC with ice bath. To this solution under nitrogen were added in sequence sodium hydride (60% in mineral oil, 17 g, 426 mmol) and benzyl alcohol (25.30 g, 234.3 mmol). The reaction mixture was stirred for overnight at 65 ^oC and treated with cold water (600 mL). After extraction with ethyl acetate, the organic layer was washed with water and brine. The residue after rotary evaporation was purified by column chromatography over silica gel to give 42.4 g of compound **37** (60%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J = 8.7 Hz, 1H), 7.45-7.32 (m, 5H), 7.19 (d, J = 2.4 Hz, 1H), 6.94 (dd, J_1 = 2.4, J_2 = 8.4 Hz, 1H), 6.04 (s, 1H), 5.05 (s, 2H) and 4.19-4.01 (m, 4H) ppm.

5-(Benzyloxy)-2-formylphenylboronic acid (38). Compound **37** (20 g, 59.7 mmol) was dissolved in anhydrous THF (400 mL) and cooled to -80 ^oC. To this solution under nitrogen was added $B(iPrO)_3$ (15.8 mL, 68.6 mmol). After stirred for 20 min at -80 ^oC, 1.6 M n-BuLi (42.9 mL, 68.6 mmol) was added dropwise over 1 h. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight at room temperature. After 6 M HCl (100 mL) was added and stirred for 2 h, the mixture was evaporated, extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give 13.4 g of comound **38** (88%). ^1H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H), 8.25 (s, 2H), 7.85 (d, J = 8 Hz, 1H), 7.49-7.32 (m, 5H), 7.17-7.13 (m, 2H) and 5.25 (s, 2H) ppm.

6-Benzyloxy-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (39). Compound **38** (23 g, 89.84 mmol) was dissolved in THF (300 mL). To this solution under stirring was added $NaBH_4$ (4.34 g, 114.8 mmol) at 0 ^oC. After stirred for 1 h, 1 M HCl (180 mL) was added to quench the reaction. The mixture was evaporated, extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by crystallization to give 21.44 g of compound **39** (93%). ^1H NMR (300 MHz, DMSO-d_6): δ 9.15 (s, 1H), 7.47-7.27 (m, 7H), 7.11 (dd, J_1 = 7.2, J_2 = 3.2 Hz, 1H), 5.12 (s, 2H) and 4.90 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.50, 146.45, 137.24, 128.76, 128.13, 127.67, 122.24, 119.85, 114.56, 71.26, 70.48; HRMS-EI: $C_{14}H_{13}BO_3$ calcd 240.0958, found 240.0963; mp: 118-119 ^oC.

6-Hydroxyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (40). Compound **39** (3.12 g, 13 mmol) was dissolved in MeOH (300 mL). To this solution under nitrogen was added 10% Pd/C (200 mg). The reaction mixture was vacuumed and backfilled hydrogen for 3 times, then stirred overnight at room temperature. After filtration and rotary evaporation, the residue was purified by recrystallization to give 1.98 g of compound **40** (98%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.29 (s, 1H), 9.04 (s, 1H), 7.18 (d, J = 8.4 Hz, 2H), 6.87 (dd, J_1 = 8.1, J_2 = 2.4 Hz, 1H) and 4.86 (s, 2H) ppm; mp: 133-135 ^{o}C.

(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-N-phenylcarbamate (41). Compound **40** (100 mg, 0.667 mmol) was dissolved in DMF (10 mL) and cooled to 0 ^{o}C with ice bath. To this solution under nitrogen were added in sequence triethylamine (0.28 mL, 2 mmol) and isocyanatobenzene (0.852 mL, 6.67 mmol). The reaction mixture was stirred for 2 d at room temperature then treated with 1 M HCl (10 mL). After extraction with ethyl acetate, the organic layer was washed with water and brine. The residue after rotary evaporation was purified by column chromatography over silica gel to give 32 mg of compound **41** (18%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.23 (s, 1H), 9.25 (s, 1H), 7.53-7.02 (m, 8H) and 5.00 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.95, 150.13, 137.72, 129.29, 124.93, 123.98, 123.32, 122.25, 118.91, 71.27; HRMS-EI: $C_{14}H_{12}BNO_4$ calcd 269.0859, found 269.0866; mp: 178-180 ^{o}C.

***N*-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-benzamide (43)**. To a solution of compound **42** (*J. Am. Chem. Soc.* **1960**, *82*, 2172-2175.) (500 mg, 3.36 mmol) in acetonitrile (25 mL) was added sodium bicarbonate (845 mg, 10.1 mmol) and benzoyl chloride (859 μL, 7.38 mmol). The resulting mixture was stirred at RT for 2 h before the reaction was quenched with water and stirred for an additional 30 min. The reaction mixture was extracted with EtOAc and washed with saturated sodium bicarbonate, brine, then dried over Na_2SO_4. Concentration under vacuum precipitated the title compound which was collected by filtration and air dried to give 310 mg of compound **43**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.0-7.60 (m, 4H), 7.52-7.32 (m, 3H), 7.25 (dd, J = 7.8 Hz, 1H) and 5.00 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.60, 149.62, 137.07, 134.63, 131.66, 128.47, 127.11, 124.01, 122.17, 121.43, 71.00; HRMS-EI: $C_{14}H_{12}BNO_3$ calcd 253.0910, found 253.0915; mp: 186-193 ^{o}C.

6-Benzylamino-3-dihydro-1-hydroxy-2,1-benzoxaborole (44). To a solution of compound **42** (500 mg, 3.36 mmol) in DMF (15 mL) was added sodium bicarbonate (845 mg, 10.1 mmol) and benzyl bromide (398uL, 3.36 mmol). The resulting mixture was stirred at 100 ^{o}C for 1 h before the reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After purification by column chromatography on silica gel with EtOAc/Hexane = 1/4, 125 mg of compound **44** was obtained as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.19-7.32 (m, 5H), 7.03-7.06 (d, 1H),

6.84 (bs, 1H), 6.72-6.75 (d, 1H), 6.20-6.24 (t, 1H), 4.79 (s, 2H), 4.25-4.27 (d, 2H); mp: 126-133 ^{o}C.

***N*-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-benzenesulfonamide (45)**. To a solution of compound **42** (750 mg, 5.0 mmol) in acetonitrile (25 mL) was added potassium carbonate (1.74 g, 12.6 mmol) and benzenesulfonyl chloride (710 μL, 5.5 mmol). The resulting mixture was stirred at RT for 2 h before quenched with water and stirred for an additional 30 min. The reaction mixture was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. Concentration under vacuum precipitated the title compound which was collected by filtration and air dried to give 565 mg of compound **45** as a tan colored solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 6.9 Hz, 1H), 7.40-7.17 (m, 4H), 7.13 (d, *J* = 7.8 Hz, 1H) and 4.94 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.30, 139.05, 135.92, 132.67, 128.81, 126.95, 124.92, 123.26, 121.76, 70.88; HRMS-EI: $C_{13}H_{12}BNO_4S$ calcd 289.0580, found 289.0582; mp: 175-184 ^{o}C.

N-Methyl-4-benzylamino-2-bromobenzaldehyde (46): A solution of 2-bromo-4-fluorobenzaldehyde (6.09 g, 30 mmol), N-methylbenzylamine (3.58 g, 30 mmol) and K_2CO_3 (8.48 g, 60 mmol) in DMF (100 mL) was heated to 100 ^{o}C overnight, then was cooled to room temperature and filtered. The filtrate was evaporated and purified by flash chromatography eluting with an EtOAC/heptanes gradient (0:100 to 100:0) to afford compound **46** (8.10 g, 88.8%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 10.03-10.10 (m, 6H), 7.76 (dd, *J* = 8.9, 0.1 Hz, 6H), 7.23-7.35 (m, 23H), 7.15 (td, *J* = 1.2, 0.7 Hz, 7H), 7.05-7.14 (m, *J* = 1.4, 0.9, 0.6, 0.5, 0.5 Hz, 6H), 6.85 (d, *J* = 2.5 Hz, 7H), 6.67 (ddd, *J* = 8.9, 2.1, 0.5 Hz, 6H), 6.67 (d, *J* = 8.9 Hz, 3H), 4.61 (s, 15H), 3.11 (d, *J* = 0.1 Hz, 21H).

N-Methyl-4-benzylamino-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (47): To a solution of compound **46** (0.91 g, 3.0 mmol) in 1,4-dioxane (25 mL) was added bis-pinacoldiboron (0.84 g, 3.3 mmol), KOAc (0.88 g, 9.0 mmol) and $PdCl_2(dppf)_2$ (66 mg, 0.09 mmol). The mixture was degassed with N_2, heated at 90 ^{o}C overnight, then was cooled to room temperature and filtered though a short pack of diatomaceous earth. The filtrate was concentrated, and the residue was purified by flash chromatography eluting with an EtOAc/heptanes gradient (0:100 to 100:0) to give compound **47** (1.07 g, 99%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03-10.10 (m, 6H), 7.76 (dd, *J* = 8.9, 0.1 Hz, 6H), 7.23-7.35 (m, 23H), 7.15 (td, *J* = 1.2, 0.7 Hz, 7H), 7.05-7.14 (m, *J* = 1.4, 0.9, 0.6, 0.5, 0.5 Hz, 6H), 6.85 (d, *J* = 2.5 Hz, 7H), 6.67 (ddd, *J* = 8.9, 2.1, 0.5 Hz, 6H), 6.67 (d, *J* = 8.9 Hz, 3H), 4.61 (s, 15H), 3.11 (d, *J* = 0.1 Hz, 21H).

N-Methyl-6-(benzylamino)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (48). To a suspension of compound **47** (3.5 g, 10.0 mmol, 1.0 eq.) in EtOH (60 mL) at 0 ^{o}C was added $NaBH_4$ (378.3 mg, 10.0 mmol, 1.0 eq.) in small portions. The mixture was stirred at 0 ^{o}C for 20 minutes and allowed to warm to room temperature in another 1 h. After cooling to 0 ^{o}C, the clear solution was carefully treated with H_2O (1 mL), followed by slow addition of HCl (30 mL, 3N). The resulting yellow suspension was

allowed to warm to room temperature gradually and stirred for 2 h. The mixture was then treated with sat. $NaHCO_3$ drop wise until pH reaching 7. The precipitate was collected by filtration and washed with water to give compound **48** (1.70g, 67.2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.28-7.34 (m, 2H), 7.20 (q, *J* = 8.9 Hz, 4H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.86 (s, 2H), 4.58 (s, 2H), 3.01 (s, 3H).

6-Methylamino-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (49): To a solution of compound **48** (253.1 mg, 1.0 mmol, 1.0 eq.) in EtOH (15 mL) was added ammonium formate (630.6 mg, 10.0 mmol, 10.0 eq.) and 5% (w/w) Pd/C (40 mg). The mixture was heated in a preheated 65 ^{o}C oil bath under N_2. Upon complete consumption of the starting material (TLC), the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to give compound **49** as a light yellow solid (160 mg). The yellow solid was used to next step immediately. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.80 (s, 1H), 7.09-7.14 (m, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.73-6.78 (m, 1H), 4.87 (s, 2H), 3.79 (s, 1H), 2.77 (s, 3H).

N-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-N-methylbenzamide (50). To a 20 mL scintillation vial containing compound **49** (160 mg, 1.0 mmol) in DCM (10.0 mL) was added triethylamine (290 µL, 2.0 mmol, 2.0 eq.), followed by benzoyl chloride (160 µL, 1.4 mmol, 1.4 eq.). The resulting white suspension was stirred at room temperature for 8 hours, then was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a MeOH/DCM gradient (0:100 to 10: 90) to give compound **50** (123.0 mg, 46.1% over 2 steps) as a white solid. 1H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 7.41 (s, 1H), 7.16-7.27 (m, 7H), 4.87 (s, 2H), 3.33 (s, 3H); LCMS (m/z) 268 (M+H).

(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-carboxylic acid phenylamide (53). To a solution of NaOH (2.32 g, 58.0 mmol) in water (10 mL) was added silver nitrate (416 mg, 2.46 mmol) in water (3 mL). The mixture was stirred for 5 min at room temperature and cooled to 0 ^{o}C. To the mixture under stirring was added compound **51** (*Tetrahedron* **2009**, *65*, 8738-8744) (200 mg, 1.33 mmol) in portions. The reaction was sritted at 0 ^{o}C for 2 h before filtration. The filtrate was acidified with 1 M HCl to pH 3 and extracted with ethyl acetate. The extracts were dried over Na_2SO_4 and evaporated to give 175 mg of intermediate acid **52** (79.6%). To a mixture of compound **52** (175 mg, 0.98 mmol) and aniline (108 µL, 1.18 mmol) in DCM (8 mL) were added EDCI (377 mg, 1.97 mmol) and DMAP (5 mg, 0.04 mmol). The mixture was stirred at room temperature for 60 h before evaporation. The residue was dissolved in ethyl acetate, and washed with 1 M HCl and brine. The residue after evaporation was purified by column chromatography over silica gel to give 128 mg of compound **53** (51.6%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.29 (s, 1H), 9.34 (s, 1H), 8.30 (d, *J* = 0.8 Hz, 1H), 8.03 (dd, J_1 = 8, J_2 = 1.6 Hz, 1H), 7.77 (dd, J_1 = 8, J_2 = 0.8 Hz, 2H), 7.54 (d, *J* = 8 Hz, 1H), 7.34 (t, *J* = 8 Hz, 1H), 7.08 (t, *J* = 8 Hz, 1H) and 5.06 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.03, 141.43, 139.84, 138.18, 133.92, 131.35, 130.18, 129.79, 129.42, 126.58, 122.34, 71.03; HRMS-EI: $C_{14}H_{12}BNO_3$ calcd 253.0910, found 253.0912; mp: 282-285 ^{o}C.

(3-Bromo-4-methyl-phenyl)-phenyl-amine (54). To a mixture of iodobenzene (4.4 g, 21.56 mmol), 3-bromo-4-methylbenzamine (4.0 g, 21.56 mmol) and DMSO (50 mL) were added in sequence copper (I) iodide (0.82 g, 4.31 mmol), L-proline (0.99 g, 8.61 mmol) and NaOBu-t (4.14 g, 43.13 mmol) under N_2. The mixture was stirred at 50 ^oC for 48 h before poured onto ice (100 g) and extracted with EtOAc (100 mL × 3). The extracts were dried over Na_2SO_4 and the residue after rotary evaporation was purified by column chromatography to give 1.2 g of compound **54** (21.2%). ^{1}HNMR (300 MHz, DMSO): δ 8.19 (s, 1 H), 7.27-7.15 (m, 4 H), 7.05-7.01 (m, 2 H), 6.97 (dd, J_1 = 8.4, J_2 = 2.4 Hz, 1 H), 6.85 (m, 1 H) and 2.23 (s, 3 H) ppm.

(3-Bromo-4-methyl-phenyl)-phenyl-carbamic acid *t*-butyl ester (55). To a solution of compound **54** (3.26 g, 12.44 mmol) in THF (60 mL) was added dropwise LiHMDS (27.4 mL, 27.4 mmol) at -80 ^oC over 30 min. After stirring for another 30 min, Boc_2O (6.0 g, 27.4 mmol) was added dropwise over 10 min. The reaction was carried out for 14 h at room temperature. The mixture was evaporated to get the crude product which was purified by column chromatography to give 4.3 g of compound **55** (95%). ^{1}HNMR (300 MHz, DMSO): δ 7.44 (d, J = 2.1 Hz, 1 H), 7.39-7.30 (m, 3 H), 7.26-7.20 (m, 3 H), 7.11 (dd, J_1 = 8.4, J_2 = 2.4 Hz, 1 H), 2.31 (s, 3 H) and 1.37 (s, 9 H) ppm.

2-Bromo-4-(*t*-butoxycarbonyl-phenyl-amino)-benzyl alcohol (56). To a solution of compound **55** (4.3 g, 11.88 mmol) in tetrachloromethane (300 mL) was added NBS (2.54 g, 14.25 mmol) and Bz_2O_2 (0.28 g, 1.19 mmol). The reaction was refluxed for 20 h. The mixture was cooled to room temperature and filtered, and the filtrate was evaporated under vacuum to get the crude product which was purified by column chromatography to give 2.65 g of (3-Bromo-4-bromomethyl-phenyl)-phenyl-carbamic acid *t*-butyl ester (50.6%). ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 2.4 Hz, 1 H), 7.37-7.33 (m, 3 H), 7.19-7.17 (m, 3 H), 7.13 (dd, J_1 = 8.4, J_2 = 2.4 Hz, 1 H), 4.57 (s, 2 H) and 1.44 (s, 9 H) ppm. To a solution of (3-Bromo-4-bromomethyl-phenyl)-phenyl-carbamic acid *t*-butyl ester (2.65 g, 6.0 mmol) in DMF (50 mL) was added sodium acetate (2.46 g, 30 mmol). The mixture was stirred at 70 ^oC for 5 h. The mixture was poured onto ice (100 g) and extracted with EtOAc (100 mL × 3). The combined extracts were dried over Na_2SO_4 and evaporated to give 2.5 g of acetate intemediate (99%). To a solution of this acetate intermediate (2.5 g, 5.95 mmol) in MeOH (50 mL) was added NaOH (1.2 g, 29.76 mmol) in water (15 mL). The mixture was refluxed for 1 h. The residue after evaporation was extracted with EtOAc (40 mL × 3). The combined extracts were washed with water (40 mL × 2) and brine and dried over Na_2SO_4, and the solvent was evaporated to give 2.1 g of compound **56** (93.4%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.44 (d, J = 2.1 Hz, 1 H), 7.40-7.30 (m, 3 H), 7.23-7.14 (m, 4 H), 4.71 (s, 2 H) and 1.44 (s, 9 H) ppm.

[3-Bromo-4-(tetrahydro-pyran-2-yloxymethyl)-phenyl]-phenyl-carbamic acid t-butyl ester (57). To a solution of compound **56** (2.1 g, 5.55 mmol) in

dichloromethane (50 mL) were added in sequence 3, 4-dihydro-2H-pyran (0.93 g, 11.11 mmol), pyridine (28 mg, 0.35 mmol), and p-toluenesulfonic acid monohydrate (53 mg, 0.28 mmol). The reaction was carried out for 48 h at room temperature. The mixture was washed with water and brine, and dried over Na_2SO_4. The residue after evaporation was purified by column chromatography to give 2.2 g of compound **57** (85.7%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.44-7.42 (m, 2 H), 7.35-7.30 (m, 2 H), 7.23-7.13 (m, 4 H), 4.82-4.75 (m, 2 H), 4.54 (d, *J* = 13.2 Hz, 1 H), 3.94-3.87 (m, 1 H), 3.59-3.52 (m, 1 H), 1.94-1.50 (m, 6 H) and 1.45 (s, 9 H) ppm.

(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-phenyl-carbamic acid *t*-butyl ester (59). To a solution of compound **57** (2.56 g, 5.54 mmol) in anhydrous THF (50 mL) was added dropwise 1.6 M n-BuLi in hexane (3.98 mL, 6.37 mmol) at -80 ^{o}C under N_2 atmosphere over 20 min. After the mixture was stirred for another 20 min, $B(iPrO)_3$ (1.47 mL, 6.37 mmol) was added dropwise over 10 min. The mixture was allowed to warm to room temperature slowly and stirred overnight before 6 M HCl (10 mL) was added and stirred for another 1 h. After evaporation of THF the residue was extracted with EtOAc (40 mL × 5). The combined extracts were washed with water and brine, and dried over Na_2SO_4. The residue after evaporation was purified by column chromatography to give 0.64 g of compound **58** (27.0%). To a solution of compound **58** (0.64 g, 1.50 mmol) in EtOH (20 mL) was added pyridine (35 mg, 0.45 mmol) and p-toluenesulfonic acid monohydrate (85 mg, 0.45 mmol). The reaction was carried out at 50 ^{o}C for 4 h. The mixture was evaporated and the residue was dissolved in EtOAc (50 mL) and washed with water and brine, and dried over Na_2SO_4. After evaporation the residue was purified by column chromatography to give 0.44 g of compound **59** (90.3%). ^{1}HNMR (300 MHz, DMSO): δ 9.18 (s, 1 H), 7.53 (s, 1 H), 7.40-7.32 (m, 4 H), 7.21-7.18 (m, 3 H), 4.97 (s, 2 H) and 1.38 (s, 9 H) ppm.

6-Phenylamino-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (60). To a solution of compound **59** (150 mg, 0.46 mmol) in dichloromethane (10 mL) was added dropwise TFA (0.4 mL, 5.38 mmol) at 0 ^{o}C under N_2 atmosphere. The mixture was then slowly warmed to room temperature and stirred for 3 h before neutralization with saturated $NaHCO_3$. The organic phase was separated, washed with brine and dried over Na_2SO_4. The residue after evaporation was purified by column chromatography and recrystallization to 13.2 mg of compound **60** (12.7%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.07 (s, 1H), 8.12 (s, 1H), 7.50 (s, 1H), 7.22 (m, 4H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 7.2 Hz, 1H) and 4.91 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.38, 143.45, 142.33, 129.26, 121.74, 120.70, 119.03, 117.34, 71.10; HRMS-EI: $C_{13}H_{12}BNO_2$ calcd 225.0961, found 225.0955; mp: 108-110 ^{o}C.

4-Benzyl-2-methoxy-benzaldehyde (61). A mixture of benzylboronic acid (2.15 g, 10 mmol), 4-bromo-2-methoxy-benzaldehyde (2.44 g, 18 mmol), Pd(dppf)Cl_2 (1.46 g , 2 mmol), CsF (3.02 g, 20 mmol) and K_2CO_3 (4.14 g, 30 mmol) in dioxane (30 mL) was degassed for 10 min and heated at 80 ^{o}C for 16 h, cooled to RT, diluted with EtOAc, filtered through a pad of Celite and concentrated. The

residue was purified by chromatography to give compound **61** (2.24 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1 H), 7.77 (d, *J* = 8.2 Hz, 1 H), 7.30 – 7.10 (m, 5 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.77 (s, 1 H), 4.03 (s, 2 H), 3.85 (s, 3 H).

4-Benzyl-2-hydroxy-benzaldehyde (62). A mixture of compound **61** (1.14 g, 5 mmol), $CeCl_3$ (1.85 g, 7.5 mmol) and NaI (1.13 g, 7.5 mmol) in CH_3CN (20 mL) was refluxed for 18 h, diluted with EtOAc, washed with aqueous $Na_2S_2O_4$, dried and concentrated to give compound **62** (1.10 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1 H), 9.80 (s, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.30 – 7.10 (m, 5 H), 6.82 (m, 2 H), 3.98 (s, 2 H).

Trifluoro-methanesulfonic acid 5-benzyl-2-formyl-phenyl ester (63). To a cooled (-78 ^{o}C) solution of compound **62** (0.44 g, 2.08 mmol) in dichloromethane (10 mL) was added Et_3N (0.68 mL, 6.24 mmol) and then Tf_2O (0.40 mL, 3.12 mmol). The mixture was stirred at –78 ^{o}C for 30 min, quenched with H_2O (2 mL), diluted with dichloromethane (50 mL), washed with 1 N HCl (20 mL), dried and concentrated to give compound **63** (0.68 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1 H), 7.90 (d, *J* = 7.7 Hz, 1 H), 7.40 – 7.00 (m, 7 H), 4.00 (s, 2 H).

4-Benzyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzaldehyde (64). A mixture of compound **63** (0.68 g, 2.08 mmol), bis(pinocolato)diborane (0.80 g, 3.12 mmol), $Pd(dppf)Cl_2$ (0.31 g, 0.42 mmol) and KOAc (0.61 g, 6.24 mmol) in dioxane (15 mL) was heated at 80 ^{o}C for 16 h, cooled to RT, diluted with EtOAc, filtered through a pad of Celite and concentrated. The residue was purified by chromatography to give compound **64** (0.61 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.70 (s, 1 H), 7.40 – 7.10 (m, 6 H), 4.02 (s, 2 H), 1.40 (s, 12 H).

6-Benzyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (65). To a cooled (0 ^{o}C) solution of compound **64** (0.61 g, 1.89 mmol) in MeOH (10 mL) and THF (10 mL) was added $NaBH_4$ (0.16 g, 4.17 mmol) in portions. After the addition was over, the mixture was stirred at 0 ^{o}C for 30 min, quenched with 6 N HCl (0.5 mL) and diluted with H_2O (20 mL). The mixture was stirred at RT for 1 h. The solid formed was collected, washed with H_2O (10 mL) and dried under vacuum to give compound **65** (290 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.35-7.22 (m, 4H), 7.22-7.13 (m, 3H), 5.06 (s, 2H) and 4.01 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.56, 141.13, 140.04, 131.69, 130.57, 128.79, 128.44, 126.03, 121.03, 71.16, 41.78; HRMS-EI: $C_{14}H_{13}BO_2$ calcd 224.1009, found 224.1010; mp: 173-175 ^{o}C.

***In vitro* Biological Assay**

***In vitro Trypanosoma brucei* assay.** All *in vitro* anti-parasite assays were conducted with the bloodstream-form *Trypanosoma brucei brucei* 427 strain. Parasites were cultured in T-25 vented cap flasks and kept in humidified incubators at 37 °C and 5% CO_2. The parasite culture media was complete HMI-9 medium (Hirumi, H.; Hirumi, K. Continuous cultivation of *Trypanosoma brucei* blood stream

forms in a medium containing a low concentration of serum protein without feeder cell layers. *Journal of Parasitology* **1989**, *75*, 985-989.) containing 10% FBS, 10% Serum Plus medium and penicillin/streptomycin. To ensure log growth phase, trypanosomes were sub-cultured at appropriate dilutions every 2-3 days. Log phase cultures were diluted 1:10 in HMI-9 and 10 µL was counted using hemocytometer to determine parasite concentration. Parasites were diluted to 2 x 105/mL in HMI-9 to generate a 2-fold working concentration for assay. Compounds to be tested were serially diluted in DMSO and 0.5 µL added to 49.5 µL HMI-9 in triplicate 96-well plates using a Biomek NX liquid handler. Parasites from the diluted stock were added to each well (50 µL) using a Multidrop 384 dispenser to give a final concentration of 1.0 x 105/mL parasites in 0.4% for DMSO. Trypanosomes were incubated with compounds for 72 hrs at 37 °C with 5% CO_2. Resazurin (20 µL of 12.5 mg/mL stock) from Sigma-Aldrich was added to each well and plates were incubated for an additional 2-4 hrs. Assay plates were read using an EnVision plate reader at an excitation wavelength of 544 nm and emission of 590 nm. Triplicate data points were averaged to generate sigmoidal dose response curve and determine IC_{50} values using XLfit curve fitting software from IDBS (Guildford, UK). Suramin and pentamidine are used as positive control and typical average IC50 values are 0.007 µg/ml and 0.009 µg/ml respectively.

***In vitro* mammalian cell cytotoxicity assay.** For evaluation of compound effects on mammalian cells, L929 mouse fibroblast cells were used. Cells were maintained as adherent cultures in T-25 vented cap flasks in a humidified incubator at 37 °C in the presence of 5% CO_2. Culture media was D-MEM supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. L929 cells were maintained below confluent levels by sub-culturing at 1:10 dilution twice weekly using 0.05% trypsin for detachment. Sub-confluent L929 cells were trypsinized, resuspended in fresh media and 10 µL was counted using hemocytometer to determine cell concentration. Cells were diluted to 1 x 104/mL in DMEM, dispensed (100 µL) into 96-well plates using a Multidrop 384 dispenser and allowed to attach overnight. Spent media was replaced with 99.5 µL fresh D-MEM and compounds to be tested were serially diluted in DMSO and 0.5 µL added using a Biomek NX liquid handler. Plates were incubated with compounds for 72 hrs at 37 °C with 5% CO_2. Resazurin (20 µL of 12.5 mg/mL stock) from Sigma-Aldrich was added to each well and plates were incubated for an additional 3-4 hrs. Assay plates were read using an EnVision plate reader at an excitation wavelength of 544 nm and emission of 590 nm. Single data points were used to generate sigmoidal dose response curves and determine IC_{50} values using XLfit curve fitting software from IDBS (Guildford, UK).

***In vivo* Biological Assay**

Acute murine model using *T. b. brucei* EATRO 221 strain or *T. b. rhodesiense* IL1852 strain. In this model, 5 femal BALB/c mice per group were infected by intraperitoneal injection of 600 *T. b. brucei* strain EATRO 221 or 10,000 *T. b. rhodesiense* parasites, strain IL1852, on day 0. After 24 hours, the infected mice

were treated with Compound **12** by the i.p. route at a dose of 50 mg/kg, twice daily for 5 days. Mice were monitored for parasitemia on a weekly basis by visual examination of a trypan-blue-stained blood smear obtained from the tail vein. The studies were terminated on day 40 (*T. b. brucei*) or 60 (*T. b. rhdosiense*). Suramin was used as a reference compound. Treatment of mice infected with both *T. brucei* strains (EATRO 221 and IL1852) at 20 mg/kg, once a day x 5 days resulted in 100% survival and no parasitemia 40 days post infection.

Acute murine model using *T. b. brucei* EATRO 110 strain. Female Swiss Webster mice were inoculated with 250,000 parasites of the EATRO 110 strain of *T. b. brucei*. Twenty-four hours post-infection, treatment was initiated BID for 4 days with an aqueous solution of compound either intraperitoneally (IP) or orally (PO), using 3 mice per test group. Mice were monitored weekly for reappearance of parasites in the blood via tail vein sampling for 30 days. Animals which were free of parasites at the 30 day time point were considered cured. Pentamidine (single dose of 2 mg/kg, IP) was used as a positive control. For positive controls, infected mice were dosed with 2 mg/kg pentamidine in water once daily for 4 days. This treatment results in 3/3 or 100% cure rates of dosed animals, with no evidence of recrudescence for >30 days.