Supporting Information

Macrofilaricidal Benzimidazole-Benzoxaborole Hybrids as an Approach to the Treatment of River Blindness. Part 1. Amide Linked Analogs.

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2-(Methoxycarbonylamino)-1H-benzo[d]imidazole-5-carboxylic acid (6): A 25% aqueous solution of sodium hydroxide was added to an ice-cold stirred mixture of methyl carbamimidothioate sulfate (2.78g, 10mmol) and methyl carbonochloridate (1.89g, 20 mmol) in water (3.5 mL), until the pH of the reaction mixture reached 8.0. Care was taken to keep the temperature below 10-15°C. The pH of the reaction mixture was then adjusted to 5.0 with glacial acetic acid. To the above suspension was added 3,4-diaminobenzoic acid (1.87g, 10 mmol) followed by addition of water (40 mL). The resulting reaction mixture was stirred at 95 °C for 2h, then cooled to room temperature. A light grey solid precipitated from the reaction mixture which was collected by filtration, washed with water (50 mL), and air-dried. The solid was resuspended in methanol (100 mL), refluxed for 0.5 h, and then cooled to room temperature and collected by filtration. The solid was air-dried to give the title compound (1.8 g; yield: 64%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 3H), 8.02 (s, 1H), 7.73 (d, *J* = 8.0Hz, 1H), 7.44 (d, *J* = 8.0Hz, 1H), 3.77 (s, 3H) ppm.

Methyl (5-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (7a): To a solution of **6** (47 mg, 0.2mmol), 2-bromo-1-ethyl pyridinium tetrafluoroborate (77 mg, 0.28 mmol) and DIPEA (77 mg, 0.6mmol) in DMF (12 mL) was added compound 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol, prepared as described,[1] (30 mg, 0.2 mmol). The mixture was stirred at room temperature overnight. Ethyl acetate (30 mL) was added and the mixture was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give methyl 5-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-ylcarbamoyl)-1H-benzo[d]imidazol-2-ylcarbamate (24 mg; yield: 33%) as a white

solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.71-7.78 (m, 2H), 7.48 (d, *J* = 8.0Hz, 1H), 7.31 (d, *J* = 8.0Hz, 1H), 4.91 (s, 2H), 3.75 (s, 3H) ppm; HPLC purity: 100.0% at 220nm and 98.78% at 254nm; MS: m/z = 367.1 (M+1, ESI+).

Methyl (5-((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (7b): A mixture of **6** (132 mg, 0.56 mmol), 6-amino-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (100 mg, 0.56 mmol) prepared as described,[2] HATU (320 mg, 0.84 mmol) and DIPEA (216 mg, 1.68 mmol) in DMF (10 mL) was stirred at 60 °C for 16 h. The DMF was removed under reduced pressure and the residue purified by preparative HPLC to give the title compound (25 mg, 12%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (br s, 1H), 9.04 (br s, 1H), 8.06 (br s, 2H), 7.74 (br s, 2H), 7.47-7.36 (m, 2H), 3.75 (s, 3H), 1.43 (s, 6H).

Methyl (5-(((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (8a): A mixture of **6** (80 mg, 0.32 mmol), 6-(aminomethyl)-3,3-dimethylbenzo[c] -[1,2]oxaborol -1(3H)-ol (61 mg, 0.32 mmol), HATU (182 mg, 0.48 mmol) and DIPEA (124 mg, 0.96 mmol) in DMF (10 mL) was stirred at room temperature for 16 h under N2. The mixture was concentrated and the residue purified by preparative HPLC to give 8a (40 mg, 30%) as a white solid; 1H NMR (400 MHz, DMSO-d_6) δ 9.06 (t, J = 5.6 Hz, 1H), 8.00 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 7.6 Hz , 1H), 7.34 (d, J = 8.0 Hz , 1H), 4.49 (d, J = 4.8 Hz, 2H), 3.70 (s, 3H), 3.60 (s, 3H), 1.40 (s, 6H).

Methyl (6-(((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (8b): A

solution of **6** (236 mg, 1.0 mmol), 3-(aminomethyl)benzo[c][1,2]oxaborol-1(3H)-ol (200 mg, 1.0 mmol) prepared as described,[3] HATU (380 mg, 1.0 mmol), DIPEA (387 mg, 3.0 mmol) in DMF (10 mL) was heated at 50 °C . After 16 h the reaction mixture was cooled to room temperature and DMF was removed under reduced pressure. Water (25 mL) was added and the mixture was extracted with ethyl acetate (3×50 mL). The organic phase was dried to give the residue. The residue was recrystallized with MeOH to give methyl (6-(((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (15 mg, 4%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.60 (t, J = 5.6 Hz, 1H), 7.93 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.46-7.33 (m, 6H), 5.35-5.31 (m, 1H), 3.70-3.64 (m, 1H), 3.38-3.32 (m 1H).

Methyl (5-(((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (8c): A mixture of **6** (326 mg, 0.75 mmol), 6-(aminomethyl) benzo[c][1,2]oxaborol-1(3H)-ol hydrochloride (150 mg, 0.75 mmol) prepared as described,[4] HATU (428 mg, 1.12 mmol) and DIPEA (290 mg, 2.25 mmol) in DMF (10 mL) was stirred at 60 °C for 16 h. The DMF was removed under reduced pressure and the residue purified by preparative HPLC to give the title compound (70 mg, 24%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (br s, 1H), 9.16 (br s, 1H), 8.95 (s, 1H), 7.98 (s, 1H), 7.70-7.68 (m, 2H), 7.44-7.34 (m, 3H), 4.96 (s, 2H), 4.53 (br s, 2H), 3.76 (s, 2H).

Methyl (5-(((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)methyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (8d): A mixture of 5-(aminomethyl)-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride

(100 mg, 0.44 mmol), 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-((methoxycarbonyl)amino)-1H-benzo[d]imidazole-5-carboxylate (130 mg, 0.37 mmol, prepared from **6** and HATU) and DIPEA (142 mg, 1.1 mmol) in DMF (5 mL) was stirred at 35 °C for 5 h. The reaction was monitored by LCMS. The DMF was removed under reduced pressure and the residue purified by preparative HPLC to give the title compound (48 mg, 27%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (br s, 2H), 7.95 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 2H), 3.73 (s, 3H), 1.41 (s, 6H).

The activated benzimidazole-5-carboxylic acid was prepared as follows:

3H-[1,2,3]Triazolo[4,5-b]pyridin-3-yl 2-((methoxycarbonyl)amino)-1H-benzo[d]imidazole-5-carboxylate: To a solution of **6** (1 g, 4.25 mmol) in DMF (20 ml) was added HATU (2.4 g, 6.38 mmol) and DIPEA (1.65 g, 12.76 mmol). The mixture was stirred at room temperature for 3 h, filtered and dried. The crude was washed with MeOH (200 mL) and filtered to give the title compound (450 mg, 30%) as a yellow solid.

The 5-aminomethylbenzoxaborole derivative was prepared as follows:

5-(Aminomethyl)-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride: To a solution of 1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborole-5-carbaldehyde oxime (2.6 g, 12.6 mmol) in AcOH (30 ml) was added zinc powder (2.6 g, 40 mmol). The mixture was stirred at 45 °C for 3 h and the AcOH removed. 2 M HCl/ethyl acetate (20 ml) was added and the mixture concentrated to give the title compound (2.6 g,

89%) that was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.33 (bs, 3H), 7.67 (d, J = 7.6 Ha, 1H), 7.51 (s, 1H), 7.40 (d, J = 7.2 Hz, 1H).

1-Hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborole-5-carbaldehyde oxime: To a solution of Hydroxylamine hydrochloride (1.52 g, 22 mmol) in EtOH (30 ml) was added NaOAc (4.1 g, 50 mmol). After stirring for 10 min, 1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborole-5-carbaldehyde (3.1 g, 16.3 mmol) was added and allowed to stir at room temperature overnight. The mixture was diluted with ethyl acetate (100 ml), washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate, 3:1) to give the title compound (2.6 g, 78%) as a yellow solid.

1-Hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborole-5-carbaldehyde: To a solution of 3,3,5-trimethylbenzo[c][1,2]oxaborol-1(3H)-ol (2.7 g, 15.3 mmol) in CCl_4 (30 ml) was added NBS (5.4 g, 30.5 mmol) and AIBN (50 mg, 0.3 mmol). The mixture was stirred at reflux for 3 h. Then Na_2CO_3 (4.9 g, 46.2 mmol) in H_2O (30 mL) was added and the mixture stirred at 35 °C for 0.5 hour, diluted with DCM (100 ml), washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate, 5:1) to give the title compound (1.4 g, 48%) as a yellow solid.

3,3,5-Trimethylbenzo[c][1,2]oxaborol-1(3H)-ol: To a solution of 1-bromo-2-(2-(methoxymethoxy)propan-2-yl)-4-

methylbenzene (5 g, 18 mmol) and triisopropyl borate (5.16 g, 27 mmol) in THF (100 ml) was added dropwise n-butyllithium (15 ml, 2.5 M, 37.5 mmol) at -78 °C under N_2. The mixture was stirred at room temperature overnight. 5 N HCl was added dropwise to pH = 3. The mixture was stirred at 45 °C for 3 h. Then diluted with ethyl acetate (100 ml), washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate, 20:1 t o 3:1) to give the title compound (2.7 g, 84%) as a white solid.

1-Bromo-2-(2-(methoxymethoxy)propan-2-yl)-4-methylbenzene: To a solution of 2-(2-bromo-5-methylphenyl)propan-2-ol (20 g, 87 mmol) in DIPEA (60 ml) was added dropwise chloromethyl methyl ether (60 ml). The mixture was stirred at room temperature overnight, diluted with ethyl acetate (400 ml), washed with water (200 ml) and brine (200 ml), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate, 10:1 to 4:1) to give the title compound (18 g, 78%) as a colorless liquid.

2-(2-Bromo-5-methylphenyl)propan-2-ol: To a solution methyl 2-bromo-5-methylbenzoate

(20 g, 87 mmol) in THF (200 ml) was added dropwise methylmagnesium bromide (88 mL, 3 M, 264 mmol) at 0 °C under N_2. The mixture was stirred at room temperature overnight and then saturated NH_4Cl solution (70 ml) was added. The mixture was filtered and the organic layer was diluted with ethyl acetate (500 ml), washed with water (200 ml) and brine (200 ml), dried over Na_2SO_4, filtered and concentrated to provide the title compound as crude product (20 g, 100%)

that was used in the next step without further purification.

Methyl (5-(((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)carbamoyl)-1-methyl-1H-benzo[d]imidazol-2-yl)carbamate (8e): A mixture of 2-((methoxycarbonyl)amino)-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid (80 mg, 0.32 mmol), 6-(aminomethyl)-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (61 mg, 0.32 mmol), HATU (182 mg, 0.48 mmol) and DIPEA (124 mg, 0.96 mmol) in DMF (10 mL) was stirred at room temperature for 16 h under N2. The mixture was concentrated and the residue purified by preparative HPLC to give the title compound (40 mg, 30%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (t, J = 5.6 Hz, 1H), 8.00 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 7.6 Hz , 1H), 7.34 (d, J = 8.0 Hz , 1H), 4.49 (d, J = 4.8 Hz, 2H), 3.70 (s, 3H), 3.60 (s, 3H), 1.40 (s, 6H).

The starting N-methylbenzimidazole-5-carboxylic acid was prepared as follows:

2-((Methoxycarbonyl)amino)-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid: A mixture 3-amino-4-(methylamino)benzoic acid (750 mg, 4.51 mmol) and bis(methoxycarbonyl)-2-methylisothiourea (1.86 g, 9.00 mmol) in AcOH (10 mL) was stirred at 80 °C for 20 minutes, filtered and the filter cake washed with methanol (20 mL) and ethyl acetate (20 mL), dried in vacuo to give the title compound (850 mg, 76%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.80 (dd, J = 8.6, 1.4, 1H), 7.43 (d, J = 8.8 Hz, 1H), 3.62 (s, 3H), 3.50 (s, 3H).

3-Amino-4-(methylamino)benzoic acid: To a solution of 4-(methylamino)-3-nitrobenzoic acid (1.0 g, 5.10 mmol) in

methanol (30 mL) was added Pd/C (100 mg) and the mixture was stirred at 50 °C for 2 h under H2, filtered and the filtrate was concentrated to give the title compound (750 mg, 89%) as a white solid.

Methyl (6-(((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)carbamoyl)-1-methyl-1H-benzo[d]imidazol-2-yl)carbamate (8f): A mixture of 2-((methoxycarbonyl)amino)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid (100 mg, 0.4 mmol), 6-(aminomethyl)-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (76.6 mg, 0.4 mmol), HATU (229 mg, 0.6 mmol) and DIPEA (155 mg, 1.2 mmol) in DMF (3 mL) was stirred at room temperature for 16 h under N2. The mixture was concentrated and the residue purified by preparative HPLC to give the title compound (33 mg, 20%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (t, J = 5.6 Hz, 1H), 8.03 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.60 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.0 Hz , 1H), 7.35 (d, J = 7.6 Hz , 1H), 4.52 (d, J = 5.6 Hz, 2H), 3.70 (s, 3H), 3.60 (s, 1H), 1.40 (s, 6H).

The starting N-methyl-benzimidazole-6-carboxylic acid was prepared as follows:

2-((Methoxycarbonyl)amino)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid: A mixture of 4-amino-3-(methylamino)benzoic acid (400 mg, 2.41 mmol) and bis(methoxycarbonyl)-2-methylisothiourea (993 mg, 4.82mmol) in AcOH (8 mL) was stirred at 80 °C for 20 minutes. The mixture was filtered and the filter cake was washed with methanol (5 mL) and ethyl acetate (5 mL) and dried in vacuo to give the title compound (370 mg, 62%) as a white solid.

4-amino-3-(methylamino)benzoic acid: To a solution of 3-fluoro-4-nitrobenzoic acid (500 mg, 2.7 mmol) in ethanol (10 mL) was added methylamine (8 mL, 30% wt in ethanol) and the mixture was refluxed for 4 h, concentrated and 1N HCl (15 mL) added. The precipitate was collected by filtration and washed with water. The solid was dissolved in THF, dried over Na_2SO_4 and concentrated to give the title compound (500 mg, 94%) as a gray solid.

Methyl (6-(((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)(methyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (8g): A mixture of 3,3-dimethyl-6-((methylamino)methyl)benzo[c][1,2]oxaborol-1(3H)-ol (100 mg, 0.49 mmol), 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-((methoxycarbonyl)amino)-1H-benzo[d]imidazole-5-carboxylate (172 mg, 0.49 mmol) and DIPEA (126 mg, 0.98 mmol) in DMF (10 mL) was stirred at room temperature. After 6 h DMF was removed under reduced pressure and the residue purified by preparative TLC to give the title compound (150 mg, 72%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (br s, 1H), 7.71-7.20 (m, 6H), 4.72-4.50 (m, 2H), 3.79 (s, 3H), 2.86 (s, 3H), 1.42 (s, 6H).

The N-methyl benzoxaborole derivative was prepared as follows:

3,3-Dimethyl-6-((methylamino)methyl)benzo[c][1,2]oxaborol-1(3H)-ol: To a solution of tert-butyl ((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)carbamate (50 mg, 0.13 mmol) in THF (10 mL) was added $LiAlH_4$ (19 mg, 0.50 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. Water (2 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed to give the title compound (50 mg, 92%) that was used in the next step without further purification.

tert-Butyl ((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)carbamate: A mixture of 6-(aminomethyl)-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (300 mg, 1.57 mmol), Boc_2O (411 mg, 1.88 mmol) and DIPEA (405 mg, 3.14 mmol) in DCM (10 mL) was stirred at 50 °C for 1 h. The solvent was removed and the residue purified via flash chromatography on silica (eluent: petroleum ether/ethyl acetate, 50:1 to 5:1) to give the title compound (200 mg, 44%).

Methyl (6-((2-(dimethylamino)ethyl)((1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (8h): A mixture of 6-(((2-(dimethylamino)ethyl)amino)methyl)-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (120 mg, 0.46 mmol), 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-((methoxycarbonyl)amino)-1H-benzo[d]imidazole-5-carboxylate (130 mg, 0.37 mmol), and DIPEA (295 mg, 2.29 mmol) in DMF (6 mL) was stirred at 50 °C for 16 h. DMF was removed under reduced pressure and the residue purified by preparative HPLC to give the title compound (70 mg, 33%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (br s, 1H), 7.56 (s, 1H), 7.53 (br s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 4.63 (s, 2H), 3.76 (s, 3H), 3.61-3.58 (m, 2H), 3.38-3.35 (m, 2H), 2.84 (s, 6H), 1.41 (s, 6H).

The starting N-dimethylaminoethyl benzoxaborole was prepared as follows:

6-(((2-(Dimethylamino)ethyl)amino)methyl)-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol: A mixture of 1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborole-6-carbaldehyde (200 mg, 1.05 mmol), N^1,N^1-dimethylethane-1,2-diamine (102 mg, 1.16 mmol) and two drops of AcOH in MeOH

(15 mL) was stirred at 85 °C for 16 h. To this reaction mixture was added Pd/C (20 mg, 10% on charcoal). The mixture was stirred under H_2 at 40 °C for 16 h. The reaction was monitored by LCMS, filtered and the filtrate dried to provide the title compound (200 mg, 72%) as a brown oil that used in the next step without further purification.

Methyl (5-fluoro-6-(((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)methyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (8j): A mixture of 6-fluoro-2-((methoxycarbonyl)amino)-1H-benzo[d]imidazole-5-carboxylic acid (500 mg, 1.98 mmol, 1.0 eq), 6-(aminomethyl)benzo[c][1,2]oxaborol-1(3H)-ol hydrochloride (467 mg, 2.38 mmol, 1.2 eq), HATU (1.12 g, 2.97 mmol, 1.5 eq) and DIPEA (0.76 g, 5.94 mmol, 3.0 eq) in DMF (40 mL) was stirred at room temperature for 16 h. DMF was removed to give a residue which was triturated with methanol to afford the title compound (107 mg, 14%) as a light purple solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (br. s, 1H), 11.45 (br. s, 1H), 9.16 (s, 1H), 8.65 (s, 1H), 7.69 (s, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.35 (d, J =7.6 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 3.76 (s, 3H).

The starting 6-fluorobenzimidazole carboxylic acid was prepared as follows:

6-Fluoro-2-((methoxycarbonyl)amino)-1H-benzo[d]imidazole-5-carboxylic acid: To a mixture of 4,5-diamino-2-fluorobenzoic acid (2 g, 11.8 mmol, 1.0 eq) and bis(methoxycarbonyl)-2-methylisothiourea (4 g, 19.4 mmol, 1.64 eq) was added AcOH (20 mL). The mixture was stirred at 80° C. After 20 min, AcOH was removed to give a residue which was triturated with MeOH to afford 6-fluoro-2-((methoxycarbonyl)amino)-1H-benzo[d]imidazole-5-carboxylic acid (2.5 g, 84%) as a brown solid.

4,5-Diamino-2-fluorobenzoic acid: To a mixture of 4-amino-2-fluoro-5-nitrobenzoic acid (3.5 g, 17.5 mmol, 1.0 eq), Pd/C (0.2 g) in MeOH (50 mL) was stirred at 45 °C for 2 h under hydrogen atmosphere. After the reaction completed, the mixture was filtered and the filtrate was concentrated to give 4,5-diamino-2-fluorobenzoic acid (3 g, 100%) as a brown solid.

4-Amino-2-fluoro-5-nitrobenzoic acid: To a solution of 2,4-difluoro-5-nitrobenzoic acid (4.0 g, 19.7 mmol, 1.0 eq) and 15N ammonium hydroxide (20 mL) in THF (50 mL) was stirred at room temperature for 16 h. After the reaction completed, the mixture was filtered to give 4-amino-2-fluoro-5-nitrobenzoic acid (3.5 g, 89%) as a yellow solid.

Methyl (5-((2-(1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)ethyl)carbamoyl)-1H-benzo[d]imidazol-2-yl)carbamate (9a): A mixture of 6-(2-aminoethyl)-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride (120 mg, 0.50 mmol) prepared as described,[5] 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-((methoxycarbonyl)amino)-1H-benzo[d]imidazole-5-carboxylate (176 mg, 0.50 mmol) prepared as described above and DIPEA (322 mg, 2.50 mmol) in DMF (5 mL) was stirred at 50 °C for 8 h. The reaction was monitored by LCMS. The DMF was removed under reduced pressure and the residue purified by preparative HPLC to give the title compound (62 mg, 30%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, J = 6.8 Hz, 1H), 7.94 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.52 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.32 (s, 2H), 3.79 (s, 3H), 3.46-3.45 (m, 2H), 2.86 (t, J = 6.8 Hz, 2H), 1.41 (s, 6H).

Methyl (5-(1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxamido)-1H-benzo[d]imidazol-2-yl)carbamate (12a): A mixture of methyl (5-amino-1H-benzo[d]imidazol-2-yl)carbamate (150 mg, 0.73 mmol)

prepared as described,[6] and 1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxylic acid (130 mg, 0.73 mmol) prepared as described,[7] HATU (415 mg, 1.09 mmol) and DIPEA (281 mg, 2.18 mmol) in DMF (10 mL) was stirred at 35 °C for 16 hour. The reaction was monitored by LCMS. DMF was removed under reduced pressure and the residue purified by preparative HPLC to afford the title compound (22 mg, 8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 9.36 (s, 1H), 8.32 (s,1H), 8.05-8.04 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.37-7.35 (m, 1H), 3.75 (s, 3H), 1.44 (s, 6H).

Screening procedure for inhibition of molting of third stage larvae (L3s) of *Onchocerca volvulus:*

Third stage larvae (L3s) of *Onchocerca volvulus* previously collected and cryopreserved in Cameroon were rapidly thawed in a 37 °C water bath and washed in incomplete media comprised of a 1:1 ratio of Medium NCTC-109 and IMDM(1X) + Gluta Max containing 2X Antibiotic-Antimycotic (all from Gibco by Life Technologies, Grand Island, NY). The number of worms was adjusted to about 10 worms per 50 µL in complete medium (as above plus 20% heat inactivated Fetal Bovine Serum). Worms were distributed into the wells of a 96-well flat bottom plate containing 50 µL of 1.5 x 105 normal human PBMCs.

Test compounds were dissolved in DMSO at a concentration of 10 mM. Serial dilution of this stock solution to provide working solution concentrations of 10, 2, 0.6, 0.2, 0.06, 0.02, 0.006, and 0.002 µM was done in complete medium. 100 µl of this test compound solution was added to an assay well, in triplicate, to provide final test concentrations for 1, 0.3, 0.1, 0.03, 0.01, 0.003, and 0.001uM. Controls included 0.05% DMSO in complete medium and complete medium only.

Plates were incubated at 37 °C in a 5% CO2 incubator for 6 days, then molting was assessed visually using an inverted microscope. Molting was determined in each well by counting the presence of fourth stage larvae (L4s) and empty casts of L3s. The percent inhibition of molting was calculated based on the number of treated larvae that were able to molt in comparison to the number of control larvae that had successfully molted. IC_{50} values were calculated using GraphPad Prism v6.0 (http://www.graphpad.com). See Bullman et al., PLoS Negl. Trop. Dis., 2015, 9, e3534 for further details.

Adult *Brugia malayi* transplantation *in vivo* model procedure.

Gerbils (*Meriones unguiculatus*) were infected by transplantation of 10 male and 10 female adult *Brugia malayi* into the peritoneal cavity. Gerbils were acclimated for 7 days prior to treatment. Animals were dosed based on their body weight prior to each dosing. Animals were administered their doses at the same time each day and receive standard rodent laboratory diet and water ad libitum. Gerbils were humanely euthanized at the conclusion of each study. Peritoneal counts of male and female adult *B. malayi* and visual condition of the peritoneum were recorded.

***Brugia pahangi* L3 injection *in vivo* model procedure[8].**

Male gerbils (*Meriones unguiculatus*) approximately 6 weeks of age (50-60 g) were purchased from Charles Rivers (USA, Kingston K62 Gerbils) and infected by intraperitoneal injection with 200 *Brugia pahangi* third-stage larvae (L3) per animal (Filariatech, Inc., Athens, GA). Gerbils were housed with no more than 5 animals per cage and maintained 9 months prior to treatment. All gerbils were dosed in accordance with their body weight determined prior to each dosing. Animals were

administered their doses at the same time each day and are allowed to feed and drink ad libitum. Gerbils were euthanized following approved institutional protocols. Euthanized animals were weighed and examined for external and visceral pathologies. The adult *Brugia* worms were recovered by opening the body cavity and washing the peritoneal cavity with 100 mL of phosphate buffered saline. Male and female worms were counted using a dissecting microscope.

***Litomosoides sigmodontis* natural infection *in vivo* model procedure**[9].

All animal experiments with *L. sigmodontis* were conducted at the Institute for Medical Microbiology, Immunology and Parasitology (IMMIP), University Hospital of Bonn, in accordance to the European Union animal welfare guidelines. All protocols were approved by the local authorities (Landesamt für Natur, Umwelt und Verbraucherschutz, Cologne, Germany (AZ 84-02.04.2015.A507; 84-02.04.2012.A140). Female BALB/c wild type mice were obtained from Janvier (Saint-Berthevin, France) and were housed at the animal facility of the IMMIP in individually ventilated cages on a 12h light/dark cycle with food and water ad libidum. Mice were infected at 6-8 weeks of age via exposure to the natural mite vector *Ornithonyssus bacoti* containing infectious *L. sigmodontis* L3 larvae. To compare the infection, the same batch of mite-containing bedding was used to infect all animals of one experiment. 35 days post infection, a time point adult worms have developed within the thoracic cavity, mice were treated per oral gavage with the test compounds at concentrations indicated in the result section. As a vehicle, 1% CMC + 0.1% Tween80 was used. Negative controls were treated with vehicle and as positive control, mice were treated orally with doxycycline (Sigma) in 10% DMSO/1xPBS. Necropsies were performed at 64-77

days post infection using an overdose of isoflurane (Baxter, Germany) and adult worms were isolated from the thoracic cavity and peritoneum and enumerated.

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