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Original article

Novel pyrrolobenzoxaboroles: Design, synthesis, and biological evaluation against *Trypanosoma brucei*

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ABSTRACT

Human African trypanosomiasis is a fatal parasitic infection caused by the protozoan *Trypanosoma brucei*. The development of novel antitrypanosomal agents is urgently needed. Here we report the synthesis and structure–activity relationship of a new class of benzoxaboroles as antitrypanosomal agents. These compounds showed antiparasitic IC_{50} values ranging from 4.02 to 0.03 μg/mL and satisfactory cytotoxicity profile. Three of the lead compounds were demonstrated to cure the parasitic infection in a murine acute infection model. The structure–activity relationship of the pyrrolobenzoxaboroles are also discussed.

1. Introduction

Human African trypanosomiasis (HAT or sleeping sickness), a fatal parasitic disease caused by the protozoan *Trypanosoma brucei*, is transmitted to human hosts by the bite of tsetse flies. The disease threatens thirty-seven sub-Saharan countries which corresponds approximately to one-third of Africa's total land area and a population of about 60 million. HAT has become the second greatest cause of death, ahead of HIV/AIDS, in those areas [1,2]. Currently, there are five drugs available for the treatment, namely, pentamidine, suramin, melarsoprol, eflornithine, and nifurtimox. Although having been used for decades to a century, the exact intracellular targets of these drugs remain elusive with the exception of eflornithine which irreversibly inhibits ornithine decarboxylase. Pentamidine, suramin, melarsoprol, and nifurtimox have been found to disrupt mitochondrial processes, glycolysis, redox metabolism, and induce oxidative attack, respectively [3]. These drugs suffer from serious drawbacks: low efficacy, severe toxic side effects, and increasing drug resistance [4,5]. Recently, various combinations of eflornithine, melarsoprol, and nifurtimox have shown improved efficacy compared with monotherapy [6]. But combinations containing melarsoprol resulted in very high rates of severe adverse effects such as loss of consciousness and even death. At the same time, the development of new medicines against HAT underwent a serious setback when the development of pafuramidine maleate (DB289) failed due to nephrotoxicity [7]. Of the 336 new chemical entities proved during 2000–2011, only 1% contributed to neglected diseases while none of them was for the treatment of HAT [8]. Therefore, discovery and development of novel antitrypanosomal drugs are still in great need and present challenges for medicinal chemists.

Benzoxaboroles, which were reported as early as 1957 by Torssell [9], are cyclic hemiesters of phenylboronic acids. Since AN2690 (5-fluorobenzoxaborole) succeeded in clinical trials for the treatment of fungal infection [10,11], much attention has been paid to the application of this unique scaffold in medicinal chemistry. It has been utilized in the development of compounds for the treatment of periodontal disease [12], psoriasis, and atopic dermatitis [13].

We have previously reported C(6)-substituted benzoxaboroles as antitrypanosomal agents [14–18]. In this work, we report the development of a new series of 6-pyrrolobenzoxaboroles (Fig. 1) derived from the initial 6-indolylbenzoxaboroles. First, exploration of indolyl derivatives (**I**) gave only one active compound.

Abbreviations: HAT, human African trypanosomiasis; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; *T. brucei*, *Trypanosoma brucei*; b.i.d., twice a day; i.p., intraperitoneal.

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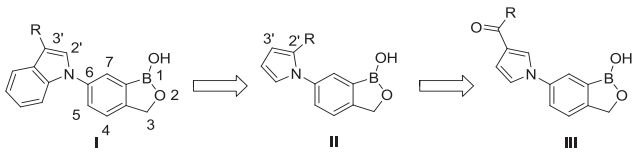


Fig. 1. Discovery of a new 6-pyrrolobenzoxaborole scaffold.

Subsequent replacement of the indolyl group with a pyrrolyl group (**II**) significantly improved the overall antitrypanosomal activity. Further structure–activity relationship studies revealed that moving the substituents from the pyrrolyl C(2′) to the C(3′) (**III**) gave significantly more potent antitrypanosomal 6-pyrrolobenzoxaboroles with IC_{50} values as low as 0.03 μg/mL and satisfactory cytotoxicity profile. Three of the lead compounds, **50**, **68**, and **78**, were demonstrated to effectively clear the parasitic infection in a murine acute infection model.

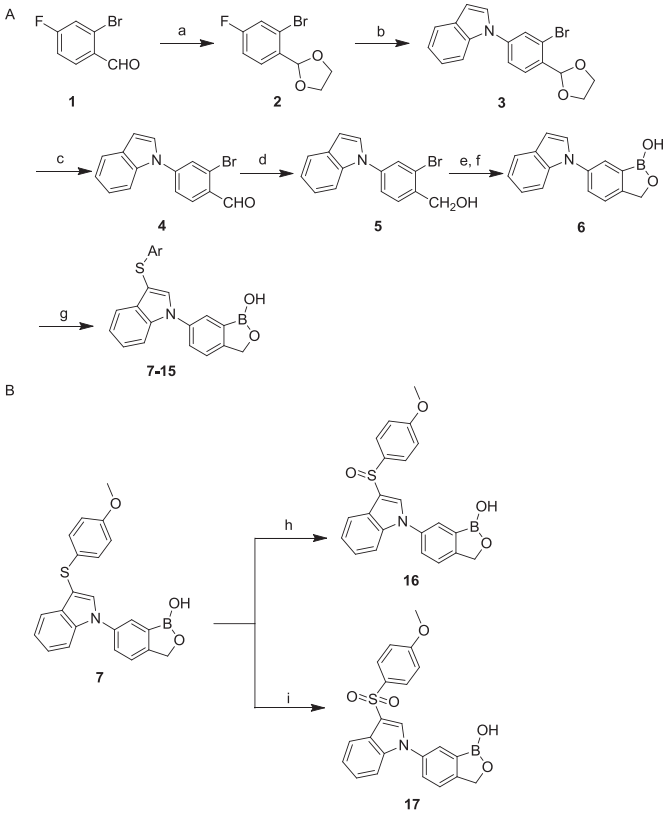
2. Chemistry

The 6-indolobenzoxaboroles **6**–**17** were prepared from 2-bromo-4-fluoro-benzaldehyde (**1**) (Scheme 1). After protection of the aldehyde in the form of acetal **2**, a nucleophilic replacement reaction by indole gave the indolyl intermediate **3**. After deprotection and reduction, compound **5** was converted to the 6-indolobenzoxaborole **6** by a one-pot treatment: first with *n*-BuLi and triisopropyl borate to install boron; and subsequently with hydrochloric acid to induce the spontaneous cyclization. Compound **6** was further reacted with various arylthiols in the presence of iodine to give 3′-thioethers **7**–**15** [19]. Thioether **7** was oxidized to sulfoxide **16** or sulfone **17** by addition of H_2O_2 at ambient or elevated temperature, respectively.

The 6-pyrrolobenzoxaborole scaffold **24** was prepared from 2-bromo-4-nitrotoluene (**18**) in six steps (Scheme 2). The aniline intermediate **21** was condensed with 2,5-dimethoxytetrahydrofuran to give the pyrrolyl intermediate **22** which was reduced and subjected to the one-pot boronylation to yield the parent 6-pyrrolobenzoxaborole **24** that would serve as the common intermediate for the synthesis of various derivatives as described below.

First, the parent 6-pyrrolobenzoxaborole **24** was readily converted to 2′-thioethers **31**–**33** after the treatment with various phenylthiophthalimides [20] (**28**–**30**) in the presence of $MgBr_2(Et_2O)_2$ (Scheme 3A) [21]. Second, formylation of the 6-pyrrolobenzoxaborole **24** with DMF/$POCl_3$ gave 2′-formyl compound **34** which was subsequently oxidized to carboxylic acid **35** (Scheme 3B). The carboxylic acid **35** would serve as a common intermediate in the synthesis of amides **36**–**40** under standard EDC/HOBt-assisted coupling condition. However, the methyl- and ethyl- amides (**42** and **43**) eluded this approach and were prepared by nucleophilic reaction with trichloroacetyl derivative **41** (Scheme 3C) [22].

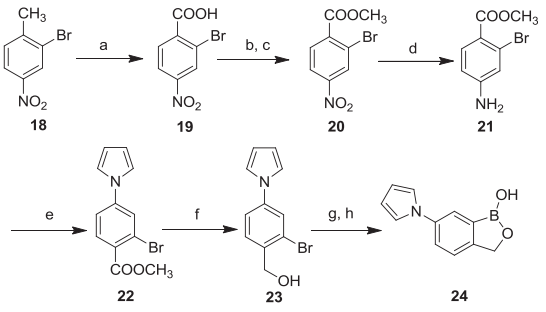
Friedel–Crafts reactions catalyzed by anhydrous stannic chloride was used to introduce arylacyl or alkylacyl substituents mainly on the pyrrolyl C(3′) position (**48**–**64**, **69**–**75**, **77**–**79**), while the C(2′)-acylated regio-isomers (**44**–**47**) were obtained at the same time in separable yields (Scheme 4A) [23]. In these cases, the 2′-acyl to 3′-acyl ratio ranges from 1:5 to 1:2. Removal of acetyl from compound **62** gave compound **65**. Treatment of the methyl ether **59** with boron tribromide afforded its demethylated analog **66**. Removal of Fmoc group from compounds **63** and **64** gave compounds **67** and **68**, respectively. Removal of the phthalimide protection of compound **75** by basic and subsequent acidic hydrolysis produced compound **76**. As the acylation reaction with acetyl



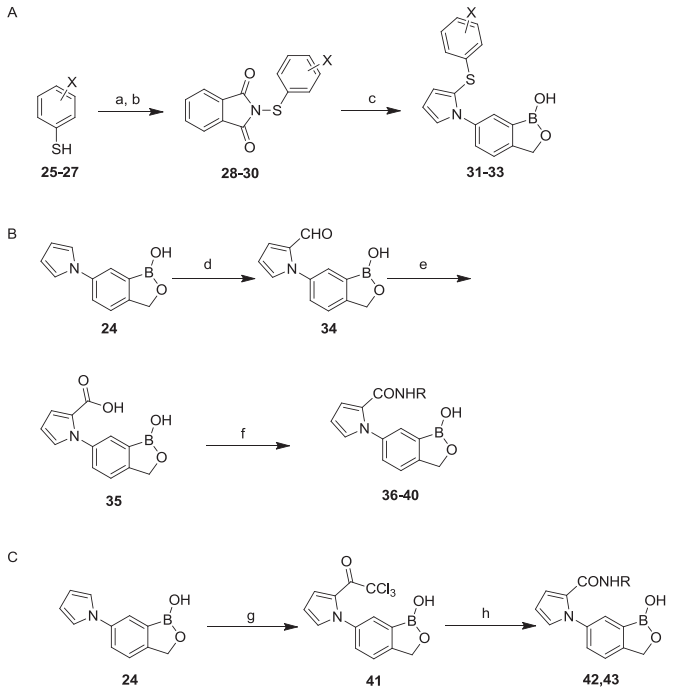
Scheme 1. Synthesis of 6-indolobenzoxaboroles. Reagents and conditions: (a) ethylene glycol, *p*-TsOH, toluene; (b) indole, Cs_2CO_3, DMF; (c) 1 M HCl, THF; (d) $NaBH_4$, MeOH; (e) B(*i*-PrO)$_3$, *n*-BuLi, THF, −78 °C to RT; (f) aq. HCl; (g) ArSH, I_2, EtOH, H_2O; (h) H_2O_2, AcOH, RT; (i) H_2O_2, AcOH, 75 °C.

chloride gave solely 3′-acetyl compound **48**, Vilsmeier–Haack reaction was employed to obtain its 2′-analog **80** (Scheme 4B) [24].

To demonstrate the essentiality of the 3′-carbonyl and the oxaborole moiety for good antitrypanosomal potency, compound **81** wherein the carbonyl was removed and compounds **84** and **92** wherein the oxaborole ring was either removed or replaced were synthesized as described in Scheme 5. Compound **81** was obtained by reduction of the compound **50** with sodium borohydride and boron trifluoride diethyl etherate (Scheme 5A). Compound **84** was prepared via Friedel–Crafts reaction of benzoyl chloride and compound **83** which was synthesized from phenylamine and 2,5-dimethoxytetrahydrofuran (Scheme 5B). Compound **92** was synthesized from alcohol **23** in eight steps (Scheme 5C). The 3′-



Scheme 2. Synthesis of the 6-pyrrolobenzoxaborole core structure. Reagents and conditions: (a) $KMnO_4$, pyridine, H_2O; (b) $SOCl_2$, reflux; (c) MeOH, Et_3N; (d) $SnCl_2 \cdot 2H_2O$, ethyl acetate, reflux; (e) 2,5-dimethoxytetrahydrofuran, AcOH, reflux; (f) $LiBH_4$, THF, 0 °C; (g) B(*i*-PrO)$_3$, *n*-BuLi, −78 °C to RT; (h) 2 M HCl.



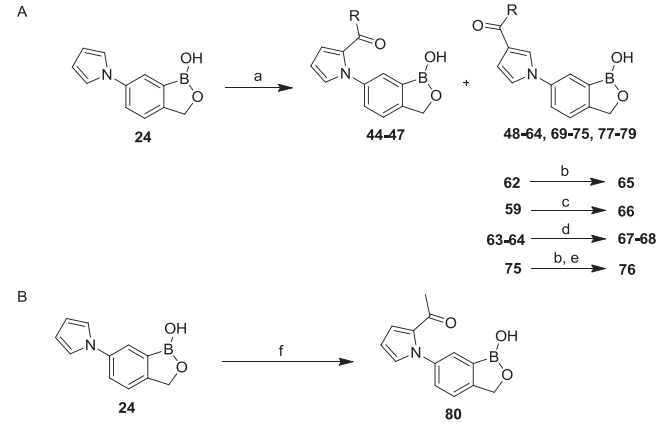
Scheme 3. Synthesis of 6-pyrrolobenzoxaboroles bearing arylsulfenyl or amide substituents. Reagents and conditions: (a) chlorine, *n*-pentane, 0 °C; (b) phthalimide, Et_3N, DMF; (c) compound **24**, $MgBr_2(Et_2O)_2$, *N*,*N*-dimethylacetamide; (d) DMF, $POCl_3$, DCM, 0 °C to RT; (e) $AgNO_3$, 6 M NaOH, H_2O, 0 °C; (f) the corresponding amine, EDC, HOBt, DCM, RT; (g) trichloroacetyl chloride, 75 °C; (h) the corresponding amine, DCM, 0 °C to RT.

phenylacylpyrrolyl intermediate **89** was obtained from **23** after sequential methylation, formylation, reduction, acetylation, and Friedel–Crafts reaction. Deacetylation of compound **89** followed by oxidation gave aldehyde **91** which was subsequently demethylated to yield the desired hemiacetal **92**.

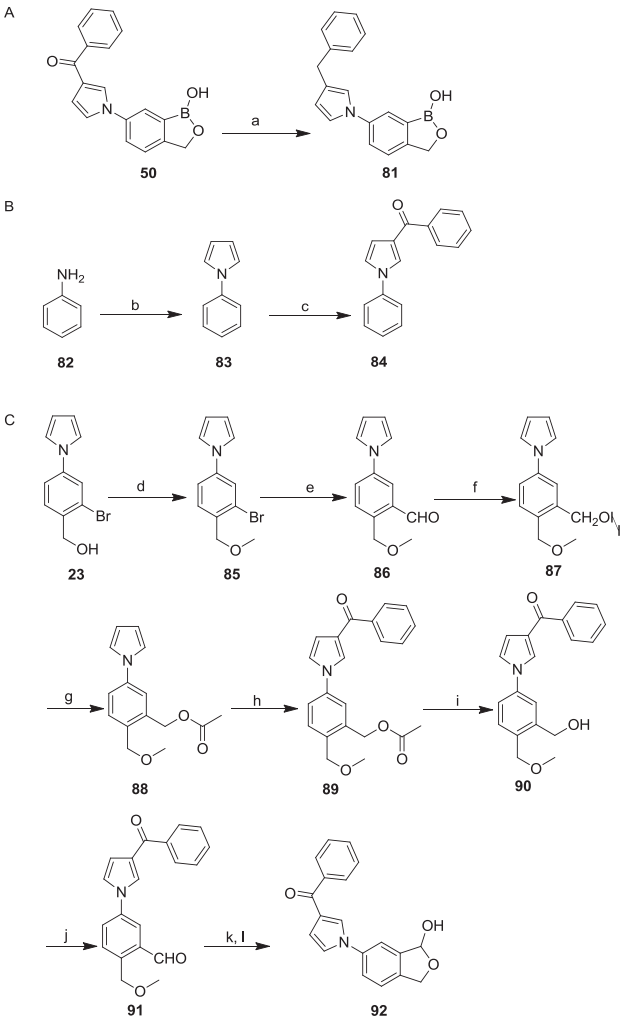
3. Results and discussion

3.1. Inhibition of T. brucei parasite growth

Indole is a privileged scaffold that is widely found in clinically used drugs and natural products [25,26]. We initiated our exploration of new antitrypanosomal benzoxaboroles by incorporating



Scheme 4. Synthesis of 2′- and 3′-acylpyrrolylbenzoxaboroles. Reagents and conditions: (a) the corresponding acyl chloride, $SnCl_4$, DCM, RT; (b) 1 M NaOH, RT, then 1 M HCl; (c) BBr_3, DCM, −80 °C to RT; (d) piperidine, acetone or trichloromethane, 0 °C to RT; (e) 6 M HCl, MeOH, reflux; (f) *N*,*N*-dimethylacetamide, $POCl_3$, DCM, 0 °C to RT.



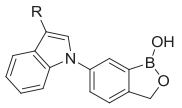
Scheme 5. Synthesis of compounds without 3′-carbonyl or oxaborole functionalities. Reagents and conditions: (a) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF; (b) 2,5-dimethoxytetrahydrofuran, AcOH, reflux; (c) benzoyl chloride, $SnCl_4$, DCM, RT; (d) CH_3I, NaH, THF; (e) *n*-BuLi, DMF, THF, −78 °C; (f) $NaBH_4$, MeOH, RT; (g) Ac_2O, Et_3N, DCM; (h) benzoyl chloride, $SnCl_4$, DCM, −40 °C; (i) 1 M NaOH, 1 M HCl, RT; (j) PCC, celite, DCM, RT; (k) BBr_3, DCM, −78 °C–0 °C; (l) MeOH, RT.

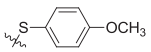
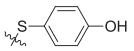
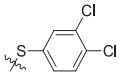
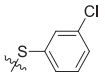
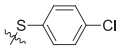
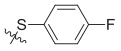
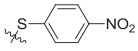
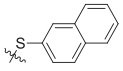
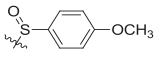
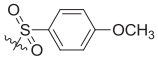
this privileged structure. A whole cell-based screening approach was taken with the aim to identify new compounds that can effectively inhibit the growth of *T. brucei* parasites.

However, the indolobenzoxaborole **6** and its thioether derivatives showed disappointing activity with only one active compound, namely the sulfoxide **16** (Table 1). Assuming that the rigidity of the indolobenzoxaborole structure may have led to the low activity via reduced solubility and permeability, we decided to reduce the indolyl ring size by replacing it with a pyrrolyl group. Indeed, the parent 6-pyrrolobenzoxaborole **24** showed an inhibitory IC_{50} of 1.98 μg/mL (Table 2). The 2′-thioether derivatives **31**–**33** were synthesized to compare with the indolylthioethers. The monochloro- compounds **31** and **32** showed activity similar to compound **16** while the dichloro- compound **33** was inactive.

In order to explore the C(2′) position in a more efficient manner, we decided to introduce a carboxylate group which can be easily converted to amides for rapid divergent derivatization. The carboxylic acid **35** (Table 2) showed a 15-fold increase in potency (IC_{50} = 0.13 μg/mL) as compared to the parent pyrrolobenzoxaborole **24**, which suggests the importance of introducing a hydrogen bond acceptor and donor on the pyrrole ring. Carboxylic

Table 1
Effect of substituted 6-indolobenzoxaboroles on *T. brucei* growth inhibition and cytotoxicity.[a]



Compd	R	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
6		>5	>10
7		>5	>10
8		>5	>10
9		>5	>10
10		>5	>10
11		>5	>10
12		>5	>10
13		>5	>10
14		>5	>10
15		>5	>10
16		1.56	>10
17		>5	>10

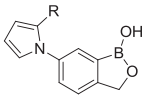
[a] IC_{50}: growth inhibition of *T. b. brucei* 427 strain (μg/mL). L929: IC_{50} against L929 cells (μg/mL). References: pentamidine (IC_{50}: 0.009 μg/mL) and suramin (IC_{50}: 0.007 μg/mL).

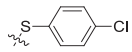
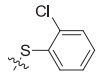
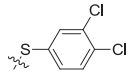
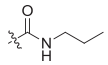
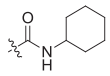
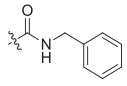
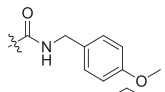
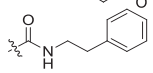
acid **35** was subsequently modified to give amides **36**–**40**, while amides **42** and **43** were obtained via an alternative trichloromethylketone intermediate. The bulky or small alkyl groups were explored as in compounds **36**–**37** and **42**–**43**, which showed much reduced activity as compared to the carboxylic acid **35**. The phenyl-containing derivatives **38**–**40** gave relatively better activity than the alkyl amides with IC_{50} values below 1 μg/mL. All compounds showed satisfactory cytotoxicity profile with IC_{50} values above 10 μg/mL against mouse lung fibroblast L929 cells.

Encouraged by the above preliminary result, we decided to explore the effect of introducing a carbonyl group as a hydrogen bond acceptor to either the C(2′) or the C(3′) of the pyrrole ring. Friedel–Crafts reaction gave 3′-acyl products as the major products with separable yields of 2′-acyl products, thus providing us the opportunity to directly compare the antitrypanosomal effect of the two regio-isomers as shown in Table 3. Although the acetyl compounds **80**/**48** and dichloro-compounds **44**/**49** showed comparable activity for the regio–isomer pairs, the 3′-acyl compounds generally showed apparently favorable antitrypanosomal activity as demonstrated by compounds **50**–**52** which showed significantly improved activity as compared to their 2′-acyl analogs **45**–**47**. This observation thus prompted us to focus our following exploration on the 3′-acyl derivatives.

As shown in Tables 3–4, a series of 3′-acylpyrrolobenzoxaboroles were explored. The chlorophenyl compounds **51**, **53**, and **54** gave reduced activity as compared to the parent phenyl compound **50**. The methylphenyl and ethylphenyl compounds **55**–**58**, with the exception of analog **57** (IC_{50} = 0.56 μg/mL) that has the methyl at the *ortho*- position, gave comparable inhibitory activity (IC_{50} = 0.08 and 0.09 μg/mL) to the parent phenyl compound **50**. The methoxyphenyl compounds **59**–**61** all showed good inhibitory activity, but the trimethoxyphenyl compound **61** exhibited the highest cytotoxicity (L929 IC_{50} = 1.15 μg/mL) among all compounds discussed in this work. Polar groups such as acetoxyl, hydroxyl and amino groups, were subsequently introduced onto the phenyl ring as represented by compounds **62** and **65**–**68** which showed excellent inhibitory activity. Among them, compounds **62**, **65**, and **68**

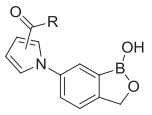
Table 2
Effect of 2′-substituted 6-pyrrolobenzoxaboroles on *T. brucei* growth inhibition and cytotoxicity.[a]

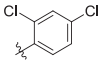
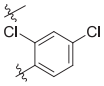


Compd	R	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
24		1.98	>10
31		1.16	>10
32		2.89	>10
33		>5	>10
35		0.13	>10
36		3.21	>10
37		2.85	>10
42		0.86	>10
43		1.85	>10
38		0.80	>10
39		0.70	>10
40		0.68	>10

[a] IC_{50}: growth inhibition of *T. b. brucei* 427 strain (μg/mL). L929: IC_{50} against L929 cells (μg/mL). References: pentamidine (IC_{50}: 0.009 μg/mL) and suramin (IC_{50}: 0.007 μg/mL).

Table 3
Effect of 2′-acyl versus 3′-acyl substitutions on *T. brucei* growth inhibition and cytotoxicity.[a]



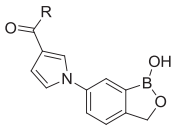
Compd	R	Position	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
80		2′	0.69	>10
44		2′	1.43	>10
45		2′	0.34	>10
46		2′	0.70	>10
47		2′	0.40	>10
48		3′	0.56	>10
49		3′	1.12	>10
50		3′	0.09	>10
51		3′	0.28	>10
52		3′	0.16	>10

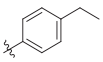
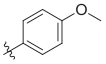
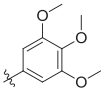
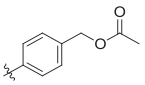
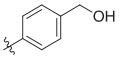
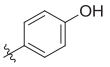
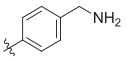
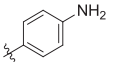
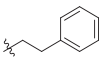
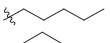
[a] IC_{50}: growth inhibition of *T. b. brucei* 427 strain (μg/mL). L929: IC_{50} against L929 cells (μg/mL). References: pentamidine (IC_{50}: 0.009 μg/mL) and suramin (IC_{50}: 0.007 μg/mL).

exhibited the highest inhibitory activity (IC_{50} = 0.03–0.04 μg/mL) among all compounds discussed in this work. Expansion of the size of the phenyl group or extension of the linker to the phenyl group (compounds **69**–**71**) did not enhance the activity as compared to the phenyl parent compound **50**. Next, alkyl ketones **72**–**76** were investigated. When compared to their methyl analog **48**, the larger propyl, pentyl, and cyclohexyl analogs **72**–**74** gave increased activity (IC_{50} = 0.09–0.13 μg/mL) which is comparable to the phenyl derivative **50**. However, addition of a terminal amino group to the alkyl chain significantly reduced the activity of compound **76**. Finally, thiophenyl ketones **77**–**79** were shown to have inhibitory activity similar to their phenyl analogs. With the exception of compounds **61** and **69**, the 3′-acyl compounds all showed satisfactory cytotoxicity profile. Although compounds **62**, **65**, and **68** have low L929 IC_{50} values, their selectivity indices are still well above 100.

In order to demonstrate the importance of the 3′-carbonyl oxygen and the oxaborole moiety in maintaining the antitrypanosomal activity of the 3′-acylpyrrolylbenzoxaboroles, we obtained the deoxy analog **81**, oxaborole-deleted analog **84**, and compound **92** whose boron atom was replaced by a carbon atom. They all showed significantly diminished activity as described in Table 5, thus demonstrating that the carbonyl oxygen and the oxaborole ring are indispensable for the antiparasitic activity.

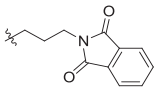
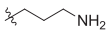
Table 4
Effect of different 3′-acyl substitutions on *T. brucei* growth inhibition and cytotoxicity.[a]



Compd	R	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
53		0.21	>10
54		0.35	>10
55		0.08	>10
56		0.09	>10
57		0.56	>10
58		0.07	>10
59		0.11	>10
60		0.17	>10
61		0.16	1.15
62		0.03	10
65		0.04	9.31
66		0.06	>10
67		0.18	>10
68		0.03	3.9
69		0.40	5.59
70		0.29	>10
71		0.19	>10
72		0.11	>10
73		0.09	>10
74		0.13	>10

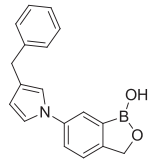
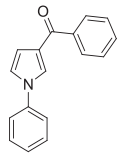
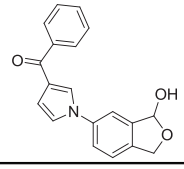
(*continued on next page*)

Table 4 (*continued*)

Compd	R	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
75		0.72	>10
76		4.02	>10
77		0.08	>10
78		0.07	>10
79		0.11	>10

[a] IC_{50}: growth inhibition of *T. b. brucei* 427 strain (μg/mL). L929: IC_{50} against L929 cells (μg/mL). References: pentamidine (IC_{50}: 0.009 μg/mL) and suramin (IC_{50}: 0.007 μg/mL).

Table 5
The effect of deletion of 3′-carbonyl or the oxaborole functionalities on *T. brucei* growth inhibition and cytotoxicity.[a]

Compd	Structure	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
81		2.17	>10
84		>5	>10
92		>5	8.18

[a] IC_{50}: growth inhibition of *T. b. brucei* 427 strain (μg/mL). L929: IC_{50} against L929 cells (μg/mL). References: pentamidine (IC_{50}: 0.009 μg/mL) and suramin (IC_{50}: 0.007 μg/mL).

3.2. Antitrypanosomal efficacy in a murine model

In order to evaluate the *in vivo* efficacy of the pyrrolobenzoxaboroles discussed above, five of the lead compounds, namely compounds **50**, **58**, **66**, **68**, and **78**, were tested in a murine model of acute blood stage *T. brucei* infection (Fig. 2). Treatment with each compound (50 mg/kg b.i.d., i.p.) was initiated 24 h post-infection, and was continued for 5 days. The ethylphenyl and hydroxyphenyl compounds **58** and **66** showed moderate extension of the survival time of the infected mice but failed to eradicate the infection. The phenyl, aminophenyl, and methylthiophenyl compounds **50**, **68**, and **78** gave 100% survival rate and clearance of blood parasites on day 30.

4. Conclusion

We have discovered 6-pyrrolobenzoxaboroles as a new class of potent antitrypanosomal agents. Three of the lead compounds were demonstrated to cure the parasitic infection in a murine acute infection model with complete clearance of the parasites in the blood. However, the mechanism of action of these 6-pyrrolobenzoxaboroles is unclear and we are currently undertaking the task to elucidate it. Whole-cell phenotypic screening has been a very useful approach in antiparasitic drug discovery and the subsequent identification of the cellular targets would further provide much needed novel therapeutic targets [27]. We believe these novel 6-pyrrolobenzoxaboroles will serve both as potential therapeutic agents and as molecular tools to explore new antiparasitic targets.

5. Experimental section

5.1. Chemistry

5.1.1. General

NMR spectra were recorded on a MercuryPlus 400 (Varian) or Mercury 300 (Varian). Chemical shifts (δ) are expressed in parts per million (ppm) 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 method A (a flow rate of 1 mL/min and a gradient of 10% MeCN/90% H_2O containing 0.1% TFA to 100% MeCN in 10 min) or method B (a flow rate of 1 mL/min and a gradient of 10% MeOH/90% H_2O containing 0.1% TFA to 100% MeOH in 20 min) using a VWD detector. A Waters Symmetry C18 column (4.6 × 150 mm, 5 μm) was used. Purity was based on the integrated UV chromatogram (254 nm). Column chromatography was performed using Huanghai silica gel (38–54 μm). Melting points were measured on a SGWX-4 melting point apparatus.

5.1.2. 2-(2-Bromo-4-fluorophenyl)-1,3-dioxolane (**2**)

To a solution of 2-bromo-4-fluoro-benzaldehyde (2.43 g, 12 mmol) in toluene (50 mL) were added ethylene glycol (7.44 g, 120 mmol) and *p*-toluenesulfonic acid monohydrate (0.23 g, 1.2 mmol). After heated to reflux and stirred overnight, the mixture was 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 compound **2** as an oil (2.07 g, 70.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, J = 8.6, 6.1 Hz, 1H), 7.30 (dd, J = 8.2, 2.5 Hz, 1H), 7.04 (ddd, J = 8.6, 8.2, 2.5 Hz, 1H), 6.03 (s, 1H), 4.16–4.09 (m, 2H) and 4.08–4.00 (m, 2H) ppm.

5.1.3. 2-(2-Bromo-4-(indol-1-yl)-phenyl)-1,3-dioxolane (**3**)

To a solution of compound **2** (200 mg, 0.81 mmol) in DMF (5 mL) were added Cs_2CO_3 (395 mg, 1.21 mmol) and indole (98.4 mg, 0.81 mmol). The mixture was heated to reflux and stirred for 2 h. The mixture was poured into water (20 mL), extracted with ether, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **3** as an oil (120 mg, 43.3% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.68 (dd, J = 7.9, 1.2 Hz, 1H), 7.56 (ddd, J = 8.2, 1.0, 0.8 Hz, 1H), 7.50 (dd, J = 8.3, 2.1 Hz, 1H), 7.30 (d, J = 3.3 Hz, 1H), 7.25 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.2 (ddd, J = 7.9, 7.1, 1.0 Hz, 1H), 6.7 (dd, J = 3.3, 0.8 Hz, 1H), 6.14 (s, 1H), 4.23–4.17 (m, 2H) and 4.16–4.10 (m, 2H) ppm.

5.1.4. (2-Bromo-4-(indol-1-yl))-benzyl alcohol (**5**)

To a solution of compound **3** (2.47 g, 7.2 mmol) in THF (20 mL) was added 1 M HCl (10 mL) dropwise and stirred for 3 h. After it was

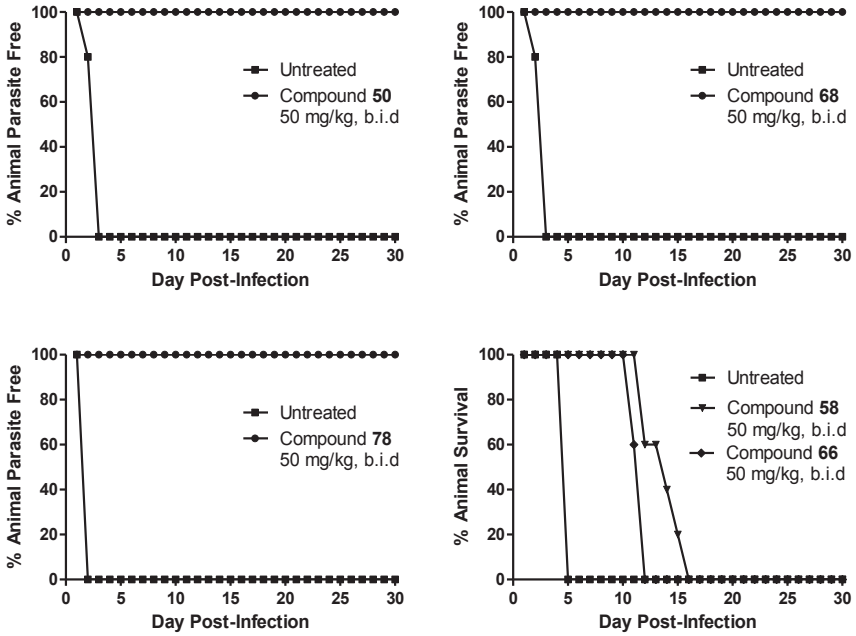


Fig. 2. Female BALB/c mice were inoculated with 600 *T. b. brucei* 221 parasites. Compounds **50**, **68** and **78** gave complete eradication of *T. b. brucei* parasites. Treatment with compounds **58** and **66** extended survival time of the infected mice but failed to cure them. Compounds were administered at a dosage of 50 mg/kg, b. i. d. Suramin was the reference compound.

neutralized with saturated $NaHCO_3$, the mixture was extracted with EtOAc, and dried over anhydrous Na_2SO_4. After evaporation the residue was redissolved in CH_3OH (30 mL). To this solution $NaBH_4$ (0.4 g, 10.8 mmol) was added and stirred for 1 h. The mixture was quenched with water (10 mL), evaporated, extracted with EtOAc, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **5** as an oil (2.01 g, 92.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.49 (dd, J = 8.2, 2.1 Hz, 1H), 7.30 (d, J = 3.3 Hz, 1H), 7.25 (dd, J = 8.2, 7.1 Hz, 1H), 7.21 (dd, J = 7.8, 7.1 Hz, 1H), 6.70 (d, J = 3.3 Hz, 1H) and 4.8 (s, 2H) ppm.

5.1.5. 1,3-Dihydro-1-hydroxy-6-(indol-1-yl)-2,1-benzoxaborole (**6**)

To a solution of compound **5** (400 mg, 1.32 mmol) in anhydrous THF (80 mL) at −78 °C under nitrogen atmosphere was added 1.6 M *n*-BuLi dropwise in THF (1.82 mL, 2.90 mmol). After 15 min, B(*i*-PrO)$_3$ (0.76 mL, 2.90 mmol) was added dropwise at −78 °C. The mixture was allowed to warm to r.t. gradually and stirred for overnight. After addition of 2 M HCl (10 mL), the mixture was stirred for 2 h and evaporated. The residue was dissolved in EtOAc, washed with water, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **6** as a solid (249 mg, 75.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 1H), 7.90 (d, J = 2.1 Hz, 1H), 7.69–7.65 (m, 3H), 7.60 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.20 (dd, J = 8.2, 7.1 Hz, 1H), 7.12 (dd, J = 7.8, 7.1 Hz, 1H), 6.69 (d, J = 3.3 Hz, 1H) and 5.06 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.8, 138.0, 135.2, 128.9, 128.6, 126.6, 125.4, 122.8, 122.2, 120.9, 120.1, 110.1, 103.3, 69.8 ppm; HRMS (ESI): $[M + Na]^+$ $C_{15}H_{12}BNO_2Na$ calcd 272.0859, found 272.0799; mp: 145–147 °C; HPLC: purity 95.6%, retention time 19.1 min with method A.

5.1.6. 6-(3-(4-Methoxyphenylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**7**)

To a mixture of compound **6** (50 mg, 0.20 mmol) and 4-methoxyphenylthiol (0.22 mmol) in EtOH (4 mL) and water (0.5 mL) was added dropwise a solution of I_2 (56 mg, 0.22 mmol) in EtOH (0.5 mL). After it was refluxed for 2 h, the mixture was poured into ice water, extracted with EtOAc, washed with water, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **7** as a solid (60 mg, 76.2% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (s, 1H), 8.08 (s, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.75 (dd, J = 8.1, 2.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.27 (dd, J = 8.3, 7.1 Hz, 1H), 7.22 (dd, J = 8.9, 2.2 Hz, 2H), 7.20 (dd, J = 7.8, 7.1 Hz, 1H), 6.86 (dd, J = 8.9, 2.2 Hz, 2H), 5.10 (s, 2H) and 3.69 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.8, 152.5, 137.2, 136.1, 134.0, 129.5, 129.1, 128.0, 127.0, 125.8, 123.3, 123.0, 121.2, 119.2, 114.7, 110.9, 104.6, 69.9, 55.1 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{19}BNO_3S$ calcd 388.1179, found 388.1167; mp: 99–100 °C; HPLC: purity 98.3%, retention time 16.1 min with method A.

5.1.7. 6-(3-(4-Hydroxyphenylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**8**)

Compound **8** (235 mg, 68.4% yield) as a solid was prepared following a similar procedure to compound **7**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.44 (s, 1H), 9.36 (s, 1H), 8.03 (s, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.74 (dd, J = 7.7, 2.1 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.57–7.54 (m, 2H), 7.28–7.19 (m, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 8.2 Hz, 2H) and 5.10 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.9, 152.2, 137.0, 135.9, 133.5, 129.7, 129.3, 126.7, 125.6, 125.4, 123.0, 122.8, 120.9, 119.0, 115.8, 110.7, 105.2, 69.7 ppm; HRMS (ESI): $[M + H]^+$ $C_{21}H_{17}BNO_3S$ calcd 374.1022, found 374.1001; mp: 221–224 °C; HPLC: purity 98.9%, retention time 14.8 min with method A.

5.1.8. 6-(3-(3,4-Dichlorophenylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**9**)

Compound **9** (283 mg, 82.7% yield) as a solid was prepared following a similar procedure to compound **7**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (s, 1H), 8.21 (s, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.78 (dd, J = 8.1, 2.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.51 (m, 2H), 7.38 (d, J = 2.2 Hz, 1H), 7.32 (ddd, J = 8.3, 7.1,

1.2 Hz, 1H), 7.25 (ddd, J = 7.9, 7.1, 1.0 Hz, 1H), 7.07 (dd, J = 8.4, 2.2 Hz, 1H) and 5.11 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 139.6, 138.3, 137.2, 134.4, 133.0, 130.6, 129.9, 129.0, 127.8, 127.6, 126.6, 125.5, 123.9, 122.7, 121.9, 119.9, 111.2, 102.8, 71.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{21}H_{15}BCl_2NO_2S$ calcd 426.0294, found 426.0272; mp: 104–105 °C; HPLC: purity 99.3%, retention time 17.8 min with method A.

5.1.9. 6-(3-(3-Chlorophenylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**10**)

Compound **10** (86 mg, 59.2% yield) as a solid was prepared following a similar procedure to compound **7**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (s, 1H), 8.19 (s, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.1, 2.0 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.32–7.09 (m, 6H) and 5.11 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 141.4, 138.4, 137.2, 134.9, 134.4, 130.1, 129.9, 127.8, 126.5, 125.9, 125.3, 124.3, 123.8, 122.7, 121.8, 120.0, 111.1, 103.2, 71.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{21}H_{16}BClNO_2S$ calcd 392.0683, found 392.0658; mp: 104–105 °C; HPLC: purity 99.2%, retention time 18.3 min with method A.

5.1.10. 6-(3-(4-Chlorophenylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**11**)

Compound **11** (162 mg, 51.6% yield) as a solid was prepared following a similar procedure to compound **7**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.34 (s, 1H), 8.17 (s, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.76 (dd, J = 8.1, 2.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.32 (dd, J = 8.2, 7.1 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.22 (dd, J = 7.9, 7.1 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H) and 5.09 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 138.1, 137.5, 137.0, 134.0, 130.8, 129.9, 128.8, 127.6, 127.4, 126.3, 123.5, 122.5, 121.5, 119.9, 111.0, 103.5, 71.2 ppm; HRMS (ESI): $[M]^+$ $C_{21}H_{15}BClNO_2S$ calcd 391.0605, found 391.0602; mp: 100–102 °C; HPLC: purity 99.0%, retention time 18.3 min with method A.

5.1.11. 6-(3-(2-Hydroxyphenylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**12**)

Compound **12** (160 mg, 53.4% yield) as a solid was prepared following a similar procedure to compound **7**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.97 (s, 1H), 9.36 (s, 1H), 8.05 (s, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 8.1, 2.0 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.30 (dd, J = 8.2, 7.2 Hz, 1H), 7.19 (dd, J = 7.6, 7.2 Hz, 1H), 6.95–6.89 (m, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 7.9 Hz, 2H) and 5.10 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.3, 152.5, 137.2, 136.3, 134.8, 129.9, 127.0, 126.2, 125.9, 125.7, 124.4, 123.3, 123.0, 121.2, 119.5, 119.3, 114.6, 111.0, 102.4, 69.9 ppm; HRMS (ESI): $[M + H]^+$ $C_{21}H_{17}BNO_3S$ calcd 374.1022, found 374.1021; mp: 133–136 °C; HPLC: purity 98.4%, retention time 14.4 min with method A.

5.1.12. 6-(3-(4-Fluorophenylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**13**)

Compound **13** (80 mg, 26.5% yield) as a solid was prepared following a similar procedure to compound **7**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.37 (s, 1H), 8.15 (s, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.77 (dd, J = 8.1, 2.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.51 (dd, J = 7.8, 1.1 Hz, 1H), 7.30 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 7.22 (dd, J = 8.9, 5.1 Hz, 2H), 7.20 (dd, J = 7.8, 7.1 Hz, 1H), 7.12 (t, J = 8.9 Hz, 2H) and 5.11 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.8 (d, J = 240.0 Hz), 152.6, 137.1, 136.3, 134.8, 133.5, 129.3, 128.3, 128.2, 127.1, 126.0, 123.4, 123.0, 121.4, 119.0, 116.1, 115.9, 111.1, 102.8, 69.8 ppm; HRMS (ESI): $[M + H]^+$ $C_{21}H_{16}BFNO_2S$ calcd 376.0979, found 376.0965; mp: 91–95 °C; HPLC: purity 98.7%, retention time 19.5 min with method A.

5.1.13. 6-(3-(4-Nitrophenylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**14**)

Compound **14** (75 mg, 23.3% yield) as a solid was prepared following a similar procedure to compound **7**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.38 (s, 1H), 8.26 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 1.9 Hz, 1H), 7.80 (dd, J = 8.1, 1.9 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.36 (dd, J = 8.2, 7.1 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.24 (dd, J = 7.8, 7.1 Hz, 1H) and 5.12 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.9, 148.7, 144.7, 137.0, 136.5, 135.7, 129.0, 127.2, 126.1, 125.4, 124.1, 123.7, 123.1, 121.8, 118.8, 111.4, 99.6, 69.9 ppm; HRMS (ESI): $[M + H]^+$ $C_{21}H_{16}BN_2O_4S$ calcd 403.0924, found 403.0907; mp: 115–118 °C; HPLC: purity 99.1%, retention time 20.1 min with method A.

5.1.14. 6-(3-(Naphthalen-2-ylsulfenyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**15**)

Compound **15** (77 mg, 25.6% yield) as a solid was prepared following a similar procedure to compound **7**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 1H), 8.21 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.84–7.80 (m, 3H), 7.74–7.66 (m, 3H), 7.59 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.47–7.40 (m, 2H), 7.35–7.33 (m, 1H), 7.30 (dd, J = 8.3, 7.1 Hz, 1H), 7.20 (dd, J = 7.8, 7.1 Hz, 1H), and 5.10 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.6, 137.2, 136.3, 135.6, 134.9, 133.2, 131.0, 129.5, 128.5, 127.6, 127.1, 126.8, 126.7, 126.0, 125.4, 124.8, 123.7, 123.4, 123.0, 121.4, 119.1, 111.1, 102.3, 69.9 ppm; HRMS (ESI): $[M + H]^+$ $C_{25}H_{19}BNO_2S$ calcd 408.123, found 408.1207; mp: 139–142 °C; HPLC: purity 96.7%, retention time 21.2 min with method A.

5.1.15. 6-(3-(4-Methoxyphenylsulfinyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**16**)

To a solution of compound **7** (100 mg, 0.26 mmol) in AcOH (10 mL) at 10 °C was added 4 M H_2O_2 in AcOH (0.13 mL) dropwise. The mixture was stirred for 2 h at r.t. After evaporation the mixture was dissolved in EtOAc, 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 compound **16** as a solid (65 mg, 62.4% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.39 (s, 1H), 8.38 (s, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.75 (dd, J = 7.9, 2.1 Hz, 1H), 7.67 (d, J = 7.9 Hz, 3H), 7.51 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.28 (dd, J = 8.3, 7.1 Hz, 1H), 7.13 (dd, J = 7.6, 7.1 Hz, 1H), 7.12 (d, J = 7.9 Hz, 2H), 5.11 (s, 2H) and 3.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.8, 153.1, 136.7, 136.6, 135.5, 132.3, 127.3, 126.2, 124.0, 123.8, 123.1, 121.8, 119.7, 118.8, 114.6, 111.4, 69.9, 55.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{19}BNO_4S$ calcd 404.1128, found 404.1125; mp: 119–120 °C; HPLC: purity 99.7%, retention time 15.1 min with method A.

5.1.16. 6-(3-(4-Methoxyphenylsulfonyl)-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**17**)

To a solution of compound **7** (80 mg, 0.13 mmol) in AcOH (5 mL) at 10 °C was added 4 M H_2O_2 in AcOH (0.2 mL) dropwise. The mixture was stirred for 2 h at 75 °C. After evaporation, the mixture was dissolved in EtOAc, 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 compound **17** as a solid (61 mg, 56.3% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.31 (s, 1H), 8.38 (s, 1H), 7.99 (d, J = 9.0 Hz, 2H), 7.89–7.86 (m, 1H), 7.58 (m, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.37–7.29 (m, 2H), 7.11 (d, J = 9.0 Hz, 2H), 7.11–7.06 (m, 2H), 5.10 (s, 2H) and 3.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 162.6, 156.4, 137.8, 135.9, 134.4, 132.8, 131.0, 128.8, 124.2, 123.6, 122.8, 122.4, 119.3, 117.5, 115.0, 114.6, 111.8, 111.3, 60.7, 55.7 ppm; HRMS (ESI): $[M + H + CH_3OH]^+$ $C_{23}H_{13}NO_6S$ calcd 452.1339, found

452.1150; mp: 177–179 °C; HPLC: purity 98.3%, retention time 17.3 min with method A.

*5.1.17. 2-Bromo-4-nitrobenzoic acid (**19**)*

To a mixture of 2-bromo-4-nitrotoluene (25 g, 116 mmol), pyridine (100 mL) and water (200 mL) was added $KMnO_4$ (102 g, 642 mmol) in portions. After the mixture was refluxed for 5 h, an additional amount of $KMnO_4$ (27.5 g, 174 mmol) was added. The mixture was refluxed and stirred for overnight, then filtered over celite. The filtrate was acidified with concentrated HCl (110 mL), extracted with EtOAc (600 mL), dried over anhydrous Na_2SO_4, and evaporated under vacuum to give compound **19** as a solid (19.4 g, 68.1% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 8.43 (d, J = 2.1 Hz, 1H), 8.18 (dd, J = 8.5, 2.1 Hz, 1H) and 7.86 (d, J = 8.5 Hz, 1H) ppm; mp: 153–155 °C.

*5.1.18. 2-Bromo-4-nitrobenzoic acid methyl ester (**20**)*

Compound **19** (5.7 g, 23.0 mmol) was dissolved in $SOCl_2$ (50 mL). This mixture was heated to reflux and stirred for 4 h. After evaporation, to the residue was added CH_3OH (50 mL) and TEA (4.8 mL) dropwise at 0 °C. The mixture was stirred for 1 h at r.t. After evaporation the residue was dissolved in EtOAc, washed with water, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **20** as a solid (5.66 g, 94.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 2.1 Hz, 1H), 8.24 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H) and 4.02 (s, 3H) ppm; mp: 83–86 °C.

*5.1.19. 2-Bromo-4-aminobenzoic acid methyl ester (**21**)*

To a solution of compound **20** (4.5 g, 17.0 mmol) in EtOAc (100 mL) was added $SnCl_2 \cdot 2H_2O$ (38.3 g, 0.17 mol). The mixture was heated to reflux and stirred for 4 h. The mixture was poured into saturated $NaHCO_3$ (500 mL) and EtOAc (370 mL). The organic layer was washed with brine (300 mL), and dried over anhydrous $MgSO_4$. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **21** as a solid (3.68 g, 94.2% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 2.2 Hz, 1H), 6.57 (dd, J = 8.5, 2.2 Hz, 1H), 4.04 (brs, 2H) and 3.86 (s, 3H) ppm; mp: 96–98 °C.

*5.1.20. 2-Bromo-4-(pyrrol-1-yl)-benzoic acid methyl ester (**22**)*

To a solution of compound **21** (3 g, 13.0 mmol) in AcOH (50 mL) was added 2,5-dimethoxytetrahydrofuran (2.15 g, 16.3 mmol). The mixture was heated to reflux and stirred for 4 h. After evaporation, the mixture was dissolved in EtOAc, washed with saturated $NaHCO_3$, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **22** as a solid (3.06 g, 84.3% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.5, 2.3 Hz, 1H), 7.10 (t, J = 2.2 Hz, 2H), 6.38 (t, J = 2.2 Hz, 2H) and 3.93 (s, 3H) ppm; mp: 50–53 °C.

*5.1.21. 2-Bromo-4-(pyrrol-1-yl)-benzyl alcohol (**23**)*

To a solution of compound **22** (1.1 g, 3.92 mmol) in anhydrous THF (20 mL) was added dropwise 2 M $LiBH_4$ in THF (2.95 mL, 5.89 mmol) at 0 °C under nitrogen. The mixture was stirred for overnight at r.t. then quenched with water. After evaporation, the mixture was extracted with EtOAc, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **23** as a solid (0.92 g, 93.8% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 2.2 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.36 (dd, J = 8.3, 2.2 Hz, 1H), 7.06 (t, J = 2.1 Hz, 2H), 6.36 (t, J = 2.1 Hz, 2H) and 4.76 (s, 2H) ppm; mp: 92–94 °C.

*5.1.22. 1,3-Dihydro-1-hydroxy-6-(pyrrol-1-yl)-2,1-benzoxaborole (**24**)*

To a solution of compound **23** (500 mg, 1.98 mmol) in anhydrous THF (80 mL) was added dropwise 1.6 M *n*-BuLi in THF (2.72 mL, 4.36 mmol) at −78 °C under nitrogen. After stirred for 15 min at −78 °C, B(*i*-PrO)$_3$ (1 mL, 4.36 mmol) was added dropwise. The reaction mixture was allowed to warm to r.t. gradually, and stirred for overnight at r.t. After addition of 2 M HCl (10 mL), the mixture was evaporated, extracted with EtOAc, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **24** as a solid (224 mg, 57% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (s, 1H), 7.79 (d, J = 2.2 Hz, 1H), 7.65 (dd, J = 8.2, 2.2 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 2.1 Hz, 2H), 6.25 (t, J = 2.1 Hz, 2H) and 5.03 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 140.4, 124.4, 124.1, 122.2, 120.4, 111.9, 70.9 ppm; HRMS (ESI): $[M + H]^+$ $C_{11}H_{11}BNO_2$ calcd 200.0883, found 200.0884; mp: 120–122 °C; HPLC: purity 98.5%, retention time 14.9 min with method A.

*5.1.23. N-(4-chlorophenylthio)-phthalimide (**28**)*

To a stirred solution of 4-chlorobenzenethiol (6.9 mmol) in *n*-pentane (15 mL), chlorine gas was added at 0 °C until the solution turned red orange to obtain the sulfenyl chloride. The sulfenyl chloride solution was added dropwise to a stirred solution of phthalimide (6.9 mmol) and TEA (9.0 mmol) in DMF (15 mL). The mixture was stirred for 30 min, transferred to a large beaker, and then cold water was added. The suspension was filtered to give compound **28** as a solid (967 mg, 48.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, J = 8.6, 2.4 Hz, 2H), 7.79 (dd, J = 8.6, 2.4 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H) and 7.29 (d, J = 8.5 Hz, 2H) ppm; mp: 179–182 °C.

*5.1.24. N-(2-chlorophenylthio)-phthalimide (**29**)*

Compound **29** (972 mg, 48.7% yield) as a solid was prepared following a similar procedure to compound **28**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (dd, J = 8.6, 2.4 Hz, 2H), 7.85 (dd, J = 8.6, 2.4 Hz, 2H), 7.37–7.34 (m, 1H), 7.16–7.14 (m, 2H) and 6.92–6.90 (m, 1H) ppm; mp: 217–219 °C.

*5.1.25. N-(3,4-dichlorophenylthio)-phthalimide (**30**)*

Compound **30** (670 mg, 37.0% yield) as a solid was prepared following a similar procedure to compound **28**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, J = 8.6, 2.4 Hz, 2H), 7.81 (dd, J = 8.6, 2.4 Hz, 2H), 7.68 (d, J = 2.0 Hz, 1H), 7.43 (dd, J = 8.4, 2.0 Hz, 1H) and 7.39 (d, J = 8.4 Hz, 1H) ppm; mp: 171–173 °C.

*5.1.26. 6-(2-(4-Chlorophenylsulfenyl)-pyrrol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**31**)*

A solution of compound **24** (200 mg, 1.0 mmol), $MgBr_2(Et_2O)_2$ (16.6 mg, 0.05 mmol) and compound **28** (1.1 mmol) in DMF (10 mL) was heated to reflux and stirred for overnight. The mixture was poured into ice water (20 mL), extracted with EtOAc, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compounds **31** as a solid (20 mg, 5.8% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.44 (s, 1H), 7.36–7.29 (m, 2H), 7.16 (dd, J = 3.0, 1.8 Hz, 1H), 7.12 (dd, J = 8.7 Hz, 2H), 6.79 (dd, J = 8.7 Hz, 2H), 6.69 (dd, J = 3.6, 1.8 Hz, 1H), 6.38 (dd, J = 3.6, 3.0 Hz, 1H) and 5.05 (s, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 154.5, 139.9, 139.5, 132.2, 130.3, 129.8, 129.1, 128.4, 122.6, 122.5, 119.0, 110.7, 72.0 ppm; $[M + H]^+$ $C_{17}H_{14}BClNO_2S$ calcd 342.0527, found 342.0524; mp: 105–107 °C; HPLC: purity 98.1%, retention time 25.4 min with method A.

*5.1.27. 6-(2-(2-Chlorophenylsulfenyl)-pyrrol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**32**)*

Compound **32** (40 mg, 11.7% yield) as a solid was prepared following a similar procedure to compound **31**. ^{1}H NMR (400 MHz, CD_3OD): δ 7.48 (s, 1H), 7.34–7.33 (m, 2H), 7.23 (dd, J = 3.0, 1.8 Hz, 1H), 7.20 (dd, J = 7.8, 1.4 Hz, 1H), 7.07 (ddd, J = 7.8, 7.5, 1.4 Hz, 1H), 7.00 (ddd, J = 7.8, 7.5, 1.7 Hz, 1H), 6.72 (dd, J = 3.7, 1.8 Hz, 1H), 6.54 (dd, J = 7.8, 1.7 Hz, 1H), 6.43 (dd, J = 3.7, 3.0 Hz, 1H) and 5.05 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 139.1, 138.6, 130.0, 129.4, 129.3, 127.9, 127.4, 127.2, 126.8, 126.1, 122.3, 121.6, 117.0, 110.3, 71.2 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{14}BClNO_2S$ calcd 342.0527, found 342.0526; mp: 106–109 °C; HPLC: purity 97.7%, retention time 20.6 min with method B.

*5.1.28. 6-(2-(3,4-Dichlorophenylsulfenyl)-pyrrol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**33**)*

Compound **33** (50 mg, 13.3% yield) as a solid was prepared following a similar procedure to compound **31**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.31–7.30 (m, 2H), 7.18 (d, J = 8.4 Hz, 1H), 7.12 (dd, J = 3.0, 1.7 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.75 (dd, J = 3.6, 1.7 Hz, 1H), 6.70 (dd, J = 8.4, 2.2 Hz, 1H), 6.39 (dd, J = 3.6, 3.0 Hz, 1H) and 5.04 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 139.7, 138.6, 133.0, 130.6, 129.5, 129.4, 128.3, 127.6, 127.4, 125.4, 122.0, 121.6, 117.3, 110.2, 71.2 ppm; HRMS $[M + H]^+$ $C_{17}H_{13}BCl_2NO_2S$ calcd 376.0137, found 376.0133; mp: 92–94 °C; HPLC: purity 98.3%, retention time 21.3 min with method A.

*5.1.29. 1,3-Dihydro-6-(2-formyl-pyrrol-1-yl)-1-hydroxy-2,1-benzoxaborole (**34**)*

To DMF (0.92 mL, 12.0 mmol) at 0 °C under nitrogen was added $POCl_3$ (1.1 mL, 12.0 mmol) dropwise. The mixture was stirred for 15 min at r.t. then cooled to 0 °C. A solution of compound **24** (2.1 g, 11.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The mixture was stirred for 1 h at r.t., and refluxed for 15 min. After the mixture was cooled to r.t., aq. NaOAc (5.3 g, 66.0 mmol) was added. The mixture was extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel, and recrystallization with acetone/petroleum ether to give compound **34** as a solid (1.1 g, 43.6% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.49 (s, 1H), 9.29 (s, 1H), 7.67 (t, J = 1.4 Hz, 1H), 7.51 (d, J = 1.4 Hz, 2H), 7.43 (dd, J = 2.6, 1.7 Hz, 1H), 7.20 (dd, J = 4.0, 1.7 Hz, 1H), 6.44 (dd, J = 4.0, 2.6 Hz, 1H) and 5.05 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.7, 153.3, 137.5, 132.1, 132.0, 128.5, 127.4, 122.7, 122.1, 110.8, 69.8 ppm; HRMS (ESI): $[M + Na]^+$ $C_{12}H_{10}BNO_3Na$ calcd 250.0651, found 250.0646; mp: 140–142 °C; HPLC: purity 97.1%, retention time 13.2 min with method B.

*5.1.30. 1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrole-2-carboxylic acid (**35**)*

To 6 M NaOH (10 mL) at 0 °C under nitrogen was added a solution of $AgNO_3$ (1.5 g, 8.8 mmol) in water (2 mL) dropwise. The mixture was stirred for 15 min at 0 °C, then compound **34** (500 mg, 2.2 mmol) was added in small portions. After warming to r.t. gradually the mixture was stirred for overnight. After filtration, the filtrate was acidified with concentrated HCl (10 mL), extracted with EtOAc (600 mL), and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **35** as a solid (150 mg, 26.6% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 1H), 9.25 (s, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 8.1, 2.1 Hz, 1H), 7.16 (dd, J = 2.6, 1.8 Hz, 1H), 6.99 (dd, J = 3.8, 1.8 Hz, 1H), 6.29 (dd, J = 3.8, 2.6 Hz, 1H) and 5.05 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.5, 153.3, 139.7, 130.6, 129.1, 128.1, 124.2, 122.0, 119.1, 109.5, 70.3 ppm; HRMS (ESI): $[M + Na]^+$ $C_{12}H_{10}BNO_4Na$ calcd 266.0601, found 266.0595; mp: 204–205 °C; HPLC: purity 96.2%, retention time 11.8 min with method A.

*5.1.31. 1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrole-2-carboxylic acid propylamide (**36**)*

To a solution of compound **35** (20 mg, 0.083 mmol) in CH_2Cl_2 (3 mL) was added EDC (18.8 mg, 0.098 mmol) and HOBt (13.3 mg, 0.098 mmol) at 0 °C. After the mixture was stirred at r.t. for 30 min, *n*-propylamine (5.8 mg, 0.098 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise. The mixture was stirred for overnight, washed with water, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **36** as a solid (10 mg, 42.9% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.40 (s, 2H), 6.88 (dd, J = 2.7, 1.6 Hz, 1H), 6.74 (dd, J = 3.6, 1.6 Hz, 1H), 6.29 (dd, J = 3.6, 2.7 Hz, 1H), 5.08 (s, 2H), 3.24 (q, J = 6.6 Hz, 2H), 1.53–1.43 (m, 2H) and 0.87 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 152.7, 140.1, 128.6, 128.1, 127.7, 127.4, 121.9, 113.8, 108.7, 70.3, 40.8, 23.0, 11.9 ppm; HRMS (ESI): $[M + Na]^+$ $C_{15}H_{17}BN_2O_3Na$ calcd 307.123, found 307.1222; mp: 148–149 °C; HPLC: purity 99.4%, retention time 12.9 min with method A.

*5.1.32. 1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrole-2-carboxylic acid cyclohexylamide (**37**)*

Compound **37** (67 mg, 50.4% yield) as a solid was prepared following a similar procedure to compound **36**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.25 (s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.31 (dd, J = 8.1, 2.1 Hz, 1H), 7.01 (dd, J = 2.7, 1.7 Hz, 1H), 6.83 (dd, J = 3.7, 1.7 Hz, 1H), 6.21 (dd, J = 3.7, 2.7 Hz, 1H), 5.03 (s, 2H), 3.54–3.51 (m, 1H), 1.72–1.54 (m, 4H) and 1.30–1.07 (m, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.2, 152.7, 140.1, 128.5, 128.2, 127.6, 127.3, 121.9, 113.8, 108.6, 70.3, 48.1, 32.9, 25.7, 25.3 ppm; HRMS (ESI): $[M + Na]^+$ $C_{18}H_{21}BN_2O_3Na$ calcd 347.1543, found 347.1531; mp: 158–160.5 °C; HPLC: purity 95.0%, retention time 16.1 min with method A.

*5.1.33. 1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrole-2-carboxylic acid benzylamide (**38**)*

Compound **38** (50 mg, 36.6% yield) as a solid was prepared following a similar procedure to compound **36**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 1H), 8.66 (t, J = 5.9 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.34 (dd, J = 8.1, 2.0 Hz, 1H), 7.32–7.21 (m, 5H), 7.06 (dd, J = 2.6, 1.7 Hz, 1H), 6.93 (dd, J = 3.7, 1.7 Hz, 1H), 6.25 (dd, J = 3.7, 2.6 Hz, 1H), 5.03 (s, 2H) and 4.32 (d, J = 5.9 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 152.3, 139.9, 139.6, 128.2, 128.1, 127.7, 127.2, 127.0, 126.9, 126.6, 121.4, 113.7, 108.3, 69.8, 41.9 ppm; HRMS (ESI): $[M + Na]^+$ $C_{19}H_{17}BN_2O_3Na$ calcd 355.1230, found 355.1218; mp: 178–180 °C; HPLC: purity 98.1%, retention time 15.1 min with method A.

*5.1.34. 1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrole-2-carboxylic acid 4-methoxy-benzylamide (**39**)*

Compound **39** (66 mg, 44.4% yield) as a solid was prepared following a similar procedure to compound **36**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.59 (t, J = 6.0 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.33 (dd, J = 8.1, 2.1 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.05 (dd, J = 2.7, 1.7 Hz, 1H), 6.89 (dd, J = 3.8, 1.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.23 (dd, J = 3.8, 2.7 Hz, 1H), 5.03 (s, 2H), 4.23 (d, J = 6.0 Hz, 2H) and 3.71 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 158.1, 152.3, 139.6, 131.8, 128.3, 128.2, 127.6, 127.3, 127.0, 121.4, 113.6, 108.3, 69.8, 55.0, 41.3 ppm; HRMS (ESI): $[M + Na]^+$ $C_{20}H_{19}BN_2O_4Na$ calcd 385.1336, found 385.1318; mp: 138–140 °C; HPLC: purity 97.4%, retention time 15.1 min with method A.

*5.1.35. 1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrole-2-carboxylic acid 2-phenyl-ethylamide (**40**)*

Compound **40** (72 mg, 50.7% yield) as a solid was prepared following a similar procedure to compound **36**. ^{1}H NMR (300 MHz, Acetone-d_6): δ 8.18 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.37 (dd, J = 8.1, 2.0 Hz, 1H), 7.32–7.18 (m, 5H), 7.01 (dd, J = 2.7, 1.7 Hz, 1H), 6.78 (dd, J = 3.8, 1.7 Hz, 1H), 6.24 (dd, J = 3.8, 2.7 Hz, 1H), 5.11 (s, 2H), 3.52–3.45 (m, 2H) and 2.85 (t, J = 7.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 152.2, 139.5, 139.4, 128.6, 128.3, 128.1, 127.4, 127.3, 126.8, 126.0, 121.4, 113.4, 108.2, 69.8, 35.2 ppm; HRMS (ESI): $[M + Na]^+$ $C_{20}H_{19}BN_2O_3Na$ calcd 369.1387, found 369.1378; mp: 173.5–175 °C; HPLC: purity 99.0%, retention time 15.7 min with method A.

*5.1.36. Trichloromethyl-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-2-yl)-methanone (**41**)*

Compound **24** (50 mg, 0.25 mmol) was dissolved in trichloroacetyl chloride (3 mL). The mixture was heated at 75 °C for 0.5 h. The reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **41** as a solid (20 mg, 23.0% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.67 (dd, J = 4.3, 1.6 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.34 (dd, J = 8.1, 2.0 Hz, 1H), 7.28 (dd, J = 2.6, 1.6 Hz, 1H), 6.45 (dd, J = 4.3, 2.6 Hz, 1H) and 5.13 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8, 154.1, 139.4, 135.9, 128.9, 128.0, 125.0, 122.6, 122.1, 111.1, 96.2, 70.4 ppm; HRMS (ESI): $[M + Na]^+$ $C_{13}H_9BCl_3NO_3Na$ calcd 365.9639, found 365.9642; mp: 132–134 °C; HPLC: purity 99.1%, retention time 10.7 min with method A.

*5.1.37. 1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrole-2-carboxylic acid methylamide (**42**)*

To a solution of compound **41** (180 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) was added dropwise 30% methylamine in EtOH (0.15 mL, 1.04 mmol) at 0 °C. This mixture was stirred for 2 d at r.t. The mixture was quenched with 2 M HCl, extracted with EtOAc, 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 **42** as a solid (56 mg, 42.0% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.51 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.37 (dd, J = 8.1, 2.0 Hz, 1H), 6.97 (dd, J = 2.7, 1.7 Hz, 1H), 6.80 (dd, J = 3.8, 1.7 Hz, 1H), 6.25 (dd, J = 3.8, 2.7 Hz, 1H), 5.00 (s, 2H) and 2.76 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.5, 152.7, 140.1, 128.6, 127.9, 127.8, 127.5, 121.9, 113.8, 108.7, 70.3, 26.0 ppm; HRMS (ESI): $[M + Na]^+$ $C_{13}H_{13}BN_2O_3Na$ calcd 279.0917, found 279.0911; mp: 195–197 °C; HPLC: purity 97.3%, retention time 12.0 min with method B.

*5.1.38. 1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrole-2-carboxylic acid ethylamide (**43**)*

To a solution of compound **41** (180 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) was added dropwise 70% ethylamine in water (0.25 mL, 3.13 mmol) at 0 °C. This mixture was stirred for overnight at r.t. The mixture was quenched with 2 M HCl, extracted with EtOAc, 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 **43** as a solid (60 mg, 42.5% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.52 (s, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.38 (dd, J = 8.1, 2.0 Hz, 1H), 6.98 (dd, J = 2.7, 1.7 Hz, 1H), 6.81 (dd, J = 3.9, 1.7 Hz, 1H), 6.25 (dd, J = 3.9, 2.7 Hz, 1H), 5.00 (s, 2H), 3.24 (q, J = 7.2 Hz, 2H) and 1.12 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.3, 152.2, 139.6, 128.1, 127.5, 127.2, 126.9, 121.4, 113.2, 108.2, 69.8, 33.3, 14.8 ppm; HRMS (ESI): $[M + Na]^+$ $C_{14}H_{15}BN_2O_3Na$ calcd 293.1073, found 293.1086; mp: 174–175 °C; HPLC: purity 95.6%, retention time 12.8 min with method B.

*5.1.39. (2,4-Dichlorophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-2-yl)-methanone (**44**)*

To a solution of 2,4-dichlorobenzoyl chloride (3.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise anhydrous $SnCl_4$ (0.36 mL, 3.0 mmol) at r.t. This mixture was stirred for 15 min at r.t. before a solution of compound **24** (300 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added slowly. After stirred for 1 d, the mixture was quenched with saturated $NaHCO_3$, 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 **44** as a solid (30 mg, 5.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 1.8 Hz, 1H), 7.49 (dd, J = 8.1, 1.8 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.38 (J = 8.2 Hz, 1H), 7.29 (dd, J = 8.2, 1.7 Hz, 1H), 7.11 (dd, J = 2.6, 1.5 Hz, 1H), 6.67 (dd, J = 3.9, 1.5 Hz, 1H), 6.32 (dd, J = 3.9, 2.6 Hz, 1H), 5.15 (s, 2H) and 4.97 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.3, 153.5, 139.5, 137.8, 136.3, 133.0, 132.8, 131.2, 130.4, 130.1, 129.1, 127.7, 126.9, 124.8, 121.7, 110.3, 71.1 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{14}BCl_2NO_3$ calcd 372.0366, found 372.0363; mp: 146–149 °C; HPLC: purity 98.7%, retention time 19.14 min with method B.

*5.1.40. Phenyl-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-2-yl)-methanone (**45**)*

Compound **45** (55 mg, 12.1% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 7.4 Hz, 2H), 7.58 (s, 1H), 7.57–7.53 (t, J = 7.4 Hz, 1H), 7.46–7.37 (m, 4H), 7.08 (dd, J = 2.8, 1.4 Hz, 1H), 6.90 (dd, J = 3.8, 1.4 Hz, 1H), 6.33 (dd, J = 3.8, 2.8 Hz, 1H), 5.77 (s, 1H) and 5.03 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.1, 153.1, 140.0, 139.1, 132.2, 131.6, 131.3, 129.7, 128.8, 128.3, 127.4, 123.8, 121.8, 109.7, 71.2 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{15}BNO_3$ calcd 304.1145, found 304.1152; mp: 120–124 °C; HPLC: purity 97.0%, retention time 17.8 min with method B.

*5.1.41. (2-Chlorophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-2-yl)-methanone (**46**)*

Compound **46** (60 mg, 8.9% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 1.9 Hz, 1H), 7.50 (dd, J = 8.1, 1.9 Hz, 1H), 7.44–7.28 (m, 5H), 7.10 (dd, J = 2.7, 1.4 Hz, 1H), 6.66 (dd, J = 3.9, 1.4 Hz, 1H), 6.35 (dd, J = 3.9, 2.7 Hz, 1H), 5.45 (brs, 1H) and 5.14 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.1, 153.0, 138.9, 138.8, 133.3, 131.1, 130.6, 130.0, 129.6, 129.0, 128.4, 127.2, 126.8, 124.1, 121.7, 110.1, 69.8 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{14}BClNO_3$ calcd 338.0755, found 338.0757; mp: 131–135 °C; HPLC: purity 98.1%, retention time 18.9 min with method A.

*5.1.42. (4-Fluorophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-2-yl)-methanone (**47**)*

Compound **47** (30 mg, 4.7% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, J = 8.6, 5.5 Hz, 2H), 7.62 (s, 1H), 7.42 (dd, J = 8.1, 1.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.13 (t, J = 8.6 Hz, 2H), 7.10 (dd, J = 2.9, 1.2 Hz, 1H), 6.87 (dd, J = 3.8, 1.2 Hz, 1H), 6.35 (dd, J = 3.8, 2.9 Hz, 1H), 5.14 (brs, 1H) and 5.16 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.6, 165.3 (d, J = 250.0 Hz), 153.2, 140.0, 135.3 (d, J = 3.0 Hz), 132.1 (d, J = 9.0 Hz), 131.6, 131.1, 128.8, 127.3, 123.5, 121.9, 115.4 (d, J = 22.0 Hz), 109.7, 71.2 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{14}BFNO_3$ calcd 322.1051, found 322.1051; mp: 114–117 °C; HPLC: purity 95.2%, retention time 13.5 min with method A.

*5.1.43. Methyl-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**48**)*

Compound **48** (40 mg, 16.6% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, CD_3OD): δ 8.00 (dd, J = 2.1, 1.7 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.67 (dd, J = 8.2, 2.1 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.26 (dd, J = 3.0, 2.1 Hz, 1H), 6.75 (dd, J = 3.0, 1.7 Hz, 1H), 5.14 (s, 2H) and 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.3, 152.1, 138.2, 127.2, 125.1, 123.3, 122.7, 121.9, 121.5, 109.8, 69.7, 27.0 ppm; HRMS (ESI): $[M + H]^+$ $C_{13}H_{13}BNO_3$ calcd 242.0988, found 242.0990; mp: 189–191 °C; HPLC: purity 97.6%, retention time 14.0 min with method B.

*5.1.44. (2,4-Dichlorophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**49**)*

Compound **49** (95 mg, 17.0% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 1.9 Hz, 1H), 7.51 (dd, J = 8.2, 1.9 Hz, 1H), 7.49 (dd, J = 2.4, 1.6 Hz, 1H), 7.44–7.40 (m, 3H), 7.32 (dd, J = 8.2, 1.8 Hz, 1H), 7.10 (dd, J = 2.8, 2.4 Hz, 1H), 6.80 (dd, J = 2.8, 1.6 Hz, 1H), 5.13 (s, 2H) and 5.03 (brs, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.6, 153.0, 138.9, 138.4, 135.2, 131.4, 130.5, 130.0, 127.9, 127.8, 126.4, 124.1, 123.24, 123.21, 122.7, 111.2, 70.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{13}BCl_2NO_3$ calcd 372.0366, found 372.0367; mp: 168–170 °C; HPLC: purity 95.4%, retention time 19.3 min with method B.

*5.1.45. Phenyl-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**50**)*

Compound **50** (105 mg, 23.1% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 7.1 Hz, 2H), 7.80 (d, J = 1.6 Hz, 1H), 7.63 (dd, J = 2.4, 1.6 Hz, 1H), 7.58–7.44 (m, 5H), 7.11 (dd, J = 2.7, 2.4 Hz, 1H), 6.88 (dd, J = 2.7, 1.6 Hz, 1H), 5.53 (s, 1H) and 5.15 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 152.7, 139.8, 139.3, 131.8, 129.1, 128.5, 126.6, 126.4, 124.4, 123.2, 122.6, 121.6, 112.7, 71.1 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{15}BNO_3$ calcd 304.1145, found 304.1143; mp: 148–151 °C; HPLC: purity 99.4%, retention time 17.4 min with method B.

*5.1.46. (2-Chlorophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**51**)*

Compound **51** (120 mg, 17.8% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 1.8 Hz, 1H), 7.51 (dd, J = 8.2, 1.8 Hz, 1H), 7.48–7.33 (m, 6H), 7.11 (dd, J = 2.8, 2.3 Hz, 1H), 6.83 (dd, J = 2.8, 1.5 Hz, 1H), 5.44 (brs, 1H) and 5.14 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.1, 152.5, 139.5, 137.9, 131.0, 129.9, 129.6, 128.7, 127.1, 126.9, 126.2, 123.7, 122.8, 122.6, 122.2, 110.8, 69.8 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{14}BClNO_3$ calcd 338.0755, found 338.0757; mp: 165–168 °C; HPLC: purity 97.3%, retention time 17.6 min with method B.

*5.1.47. (4-Fluorophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**52**)*

Compound **52** (140 mg, 21.8% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, J = 8.4, 5.5 Hz, 2H), 7.81 (d, J = 1.9 Hz, 1H), 7.64 (dd, J = 2.2, 1.7 Hz, 1H), 7.54 (dd, J = 8.2, 1.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.16 (t, J = 8.4 Hz, 2H), 7.11 (dd, J = 3.0, 2.2 Hz, 1H), 6.87 (dd, J = 3.0, 1.7 Hz, 1H), 5.70 (brs, 1H) and 5.16 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.6, 164.0 (d, J = 250.0 Hz), 152.3, 138.1, 135.7 (d, J = 3.0 Hz), 131.3 (d, J = 9.0 Hz), 126.1, 125.0, 123.6, 122.7, 122.1, 121.8, 115.3 (d, J = 22.0 Hz), 111.6, 69.7 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{14}BFNO_3$ calcd 322.1051, found 322.1059; mp: 160–162 °C; HPLC: purity 95.8%, retention time 17.7 min with method B.

*5.1.48. (4-Chlorophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**53**)*

Compound **53** (40 mg, 11.8% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.29 (s, 1H), 7.94–7.92 (m, 3H), 7.88–7.87 (m, 1H), 7.79 (dd, J = 8.4, 2.0 Hz, 1H), 7.60–7.55 (m, 3H), 7.44–7.42 (m, 1H), 6.85–6.84 (m, 1H) and 5.09 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.9, 152.3, 138.1, 137.8, 136.5, 130.5, 128.6, 126.4, 125.0, 123.6, 122.8, 122.2, 122.0, 111.6, 69.8 ppm; HRMS (ESI): $[M + Na]^+$ $C_{18}H_{13}BClNO_3Na$ calcd 360.0575, found 360.0503; mp: 149–151 °C; HPLC: purity 96.3%, retention time 18.8 min with method B.

*5.1.49. (3-Chlorophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**54**)*

Compound **54** (40 mg, 7.9% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, J = 2.2, 1.7 Hz, 1H), 7.78 (d, J = 2.1 Hz, 1H), 7.74 (ddd, J = 8.2, 1.6, 1.2 Hz, 1H), 7.60 (dd, J = 2.1, 1.6 Hz, 1H), 7.53 (dd, J = 8.2, 2.1 Hz, 1H), 7.50 (dd, J = 7.9, 2.1 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.41 (dd, J = 8.2, 7.9 Hz, 1H), 7.11 (dd, J = 3.1, 2.2 Hz, 1H), 6.85 (dd, J = 3.1, 1.7 Hz, 1H), 5.30 (brs, 1H) and 5.13 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.7, 152.4, 141.2, 138.1, 133.4, 131.4, 130.5, 128.0, 126.5, 124.8, 123.7, 122.8, 122.3, 122.2, 111.6, 69.8 ppm; HRMS (ESI): $[M + Na]^+$ $C_{18}H_{13}BClNO_3Na$ calcd 360.0575, found 360.0577; mp: 161–163 °C; HPLC: purity 97.2%, retention time 19.1 min with method B.

*5.1.50. (4-Methylphenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**55**)*

Compound **55** (40 mg, 12.8% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, CD_3OD): δ 7.76 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 2.1 Hz, 1H), 7.70 (dd, J = 2.2, 1.7 Hz, 1H), 7.63 (dd, J = 8.2, 2.1 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.28 (dd, J = 3.1, 2.2 Hz, 1H), 6.79 (dd, J = 3.1, 1.7 Hz, 1H), 5.09 (s, 2H) and 2.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 152.7, 142.3, 139.4, 137.2, 129.3, 129.1, 126.6, 126.3, 124.5, 123.1, 122.6, 121.5, 112.7, 71.1, 21.7 ppm; HRMS (ESI): $[M + H]^+$ $C_{19}H_{17}BNO_3$ calcd 318.1301, found 318.1305; mp: 161–163 °C; HPLC: purity 96.1%, retention time 18.3 min with method B.

*5.1.51. (3-Methylphenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**56**)*

Compound **56** (50 mg, 12.6% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 1.8 Hz, 1H), 7.68–7.62 (m, 3H), 7.53 (dd, J = 8.2, 1.8 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.36–7.34 (m, 2H), 7.10–7.09 (m, 1H), 6.87–6.86 (m, 1H), 6.08 (brs, 1H), 5.14 (s, 2H) and 2.42 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.2, 152.2, 139.3, 138.2, 137.8, 132.2, 128.9, 128.3, 125.9, 125.7, 125.3, 123.6, 122.7, 122.1, 121.7, 111.6, 69.7, 20.9 ppm; HRMS (ESI): $[M + H]^+$ $C_{19}H_{17}BNO_3$ calcd 318.1301, found 318.1308; mp: 180–182 °C; HPLC: purity 99.5%, retention time 18.7 min with method A.

*5.1.52. (2-Methylphenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**57**)*

Compound **57** (140 mg, 29.4% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 2.0 Hz, 1H), 7.50 (dd, J = 8.2, 2.0 Hz, 1H), 7.46–7.41 (m, 3H), 7.37–7.34 (m, 1H), 7.28–7.22 (m, 2H), 7.09 (dd, J = 3.0, 2.2 Hz, 1H), 6.82 (dd, J = 3.0, 1.7 Hz, 1H), 5.53 (brs, 1H), 5.13 (s, 2H) and 2.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.6, 152.3, 140.0, 138.1, 135.2, 130.7, 129.6, 127.4, 126.9, 126.3, 125.3, 123.6, 122.9, 122.3, 122.1, 111.1, 69.8, 19.3 ppm; HRMS (ESI): $[M + Na]^+$

$C_{19}H_{16}BNO_3Na$ calcd 340.1121, found 340.1052; mp: 134–135 °C; HPLC: purity 99.4%, retention time 18.1 min with method B.

*5.1.53. (4-Ethylphenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**58**)*

Compound **58** (160 mg, 32.1% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, CD_3OD): δ 7.81 (d, J = 8.0 Hz, 2H), 7.77 s (s, 1H), 7.75 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.31–7.30 (m, 1H), 6.82–6.81 (m, 1H), 5.12 (s, 2H), 2.72 (q, J = 7.6 Hz, 2H) and 1.28 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.7, 152.2, 147.8, 138.1, 136.7, 128.8, 127.8, 125.7, 125.3, 123.5, 122.7, 122.0, 121.6, 111.6, 69.7, 28.0, 15.1 ppm; HRMS (ESI): $[M + H]^+$ $C_{20}H_{19}BNO_3$ calcd 332.1458, found 332.1457; mp: 161–163 °C; HPLC: purity 98.6%, retention time 14.4 min with method A.

*5.1.54. (4-Methoxyphenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**59**)*

Compound **59** (50 mg, 15.0% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (d, J = 8.9 Hz, 2H), 7.79 (d, J = 2.1 Hz, 1H), 7.76 (dd, J = 2.2, 1.7 Hz, 1H), 7.67 (dd, J = 8.2, 2.1 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.32 (dd, J = 3.1, 2.2 Hz, 1H), 7.06 (d, J = 8.9 Hz, 2H), 6.81 (dd, J = 3.1, 1.7 Hz, 1H), 5.12 (s, 2H) and 3.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.7, 162.1, 152.1, 138.2, 131.6, 130.8, 125.4, 125.3, 123.5, 122.7, 122.0, 121.4, 113.7, 111.7, 69.7, 55.3 ppm; HRMS (ESI): $[M + Na]^+$ $C_{19}H_{16}BNO_4Na$ calcd 356.1070, found 356.0992; mp: 155–159 °C; HPLC: purity 95.1%, retention time 18.0 min with method B.

*5.1.55. (2-Methoxyphenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**60**)*

Compound **60** (130 mg, 25.9% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.2, 2.1 Hz, 1H), 7.46 (dd, J = 2.2, 1.7 Hz, 1H), 7.44–7.39 (m, 3H), 7.05 (dd, J = 3.1, 2.2 Hz, 1H), 7.02–6.98 (m, 2H), 6.80 (dd, J = 3.1, 1.7 Hz, 1H), 5.44 (brs, 1H), 5.13 (s, 2H) and 3.81 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.7, 156.7, 152.7, 138.6, 131.5, 130.7, 128.6, 127.7, 126.4, 123.9, 123.3, 122.4, 122.3, 120.6, 112.4, 111.4, 70.3, 55.9 ppm; HRMS (ESI): $[M + Na]^+$ $C_{19}H_{16}BNO_4Na$ calcd 356.1070, found 356.0991; mp: 177–179 °C; HPLC: purity 96.5%, retention time 16.5 min with method B.

*5.1.56. (3,4,5-Trimethoxyphenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**61**)*

Compound **61** (54 mg, 9.1% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, CD_3OD): δ 7.83 (dd, J = 2.2, 1.7 Hz, 1H), 7.78 (d, J = 2.1 Hz, 1H), 7.67 (dd, J = 8.1, 2.1 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.34 (dd, J = 3.0, 2.2 Hz, 1H), 7.20 (s, 2H), 6.84 (dd, J = 3.0, 1.7 Hz, 1H), 5.13 (s, 2H), 3.90 (s, 6H) and 3.86 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.7, 153.1, 152.7, 141.1, 138.7, 134.9, 126.4, 126.3, 125.7, 124.1, 123.3, 122.6, 122.5, 112.3, 106.8, 106.7, 106.6, 70.3, 60.5, 56.6, 56.5 ppm; HRMS (ESI): $[M + Na]^+$ $C_{21}H_{20}BNO_6Na$ calcd 416.1281, found 416.1297; mp: 147–149 °C; HPLC: purity 95.8%, retention time 17.0 min with method B.

*5.1.57. (4-Benzyl acetate)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol -6-yl)- pyrrol-3-yl)-methanone (**62**)*

Compound **62** (88 mg, 11.7% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3 + D_2O$): δ 7.87 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 1.7 Hz, 1H), 7.62–7.61 (m, 1H), 7.53 (dd, J = 8.2, 1.7 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.12–7.11 (m, 1H), 6.88–6.87 (m, 1H), 5.18 (s, 2H), 5.14 (s, 2H) and 2.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4, 171.0, 152.7, 139.7, 139.3, 129.4, 128.0, 126.5, 126.4, 124.5, 123.0, 122.7, 121.7, 112.6, 71.2, 65.9, 21.1 ppm; HRMS (ESI): $[M + H]^+$ $C_{21}H_{19}BNO_5$ calcd 376.1356, found 376.1359; mp: 160–162 °C; HPLC: purity 95.3%, retention time 16.5 min with method B.

*5.1.58. (4-((((9H-fluoren-9-yl)-methoxycarbonyl)-amino)-methyl)-phenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**63**)*

Compound **63** (160 mg, 4.8% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.1 Hz, 2H), 7.78–7.75 (m, 3H), 7.62–7.59 (m, 2H), 7.53 (d, J = 8.2 Hz, 1H), 7.44–7.28 (m, 8H), 7.13–7.12 (m, 1H), 6.88–6.87 (m, 1H), 5.78 (brs, 1H), 5.26–5.22 (m, 1H), 5.13 (s, 2H), 4.50 (d, J = 6.5 Hz, 2H), 4.45–4.43 (m, 2H) and 4.23 (t, J = 6.5 Hz, 1H) ppm; mp: 120–124 °C.

*5.1.59. (4-(((9H-fluoren-9-yl)-methoxycarbonyl)-amino)-phenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**64**)*

Compound **64** (50 mg, 3.7% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (300 MHz, CD_3OD): δ 7.84–7.79 (m, 3H), 7.75 (s, 1H), 7.73 (s, 1H), 7.71–7.69 (m, 2H), 7.63 (dd, J = 8.4, 1.5 Hz, 1H), 7.56–7.48 (m, 3H), 7.41–7.29 (m, 6H), 6.80–6.81 (m, 1H), 5.09 (s, 2H), 4.53 (d, J = 6.2 Hz, 2H) and 4.27 (t, J = 6.2 Hz, 1H) ppm; mp: 142–147 °C.

*5.1.60. (4-Hydroxymethyl-phenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**65**)*

A solution of compound **62** (45 mg, 0.12 mmol) in 1 M aq. NaOH (10 mL) was stirred at r.t. for 3 h. The mixture was acidified with 1 M aq. HCl (15 mL) to afford crude product. The crude product was washed with EtOAc to give compound **65** as a solid (29 mg, 72.5% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.87 (d, J = 8.0 Hz, 2H), 7.79–7.77 (m, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 3H), 7.34–7.33 (m, 1H), 6.84–6.83 (m, 1H), 5.13 (s, 2H) and 4.72 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.7, 152.8, 146.9, 138.6, 138.0, 129.1, 126.7, 126.4, 125.8, 124.1, 123.4, 122.6, 122.3, 112.2, 70.2, 63.0 ppm; HRMS (ESI): $[M + H]^+$ $C_{19}H_{17}BNO_4$ calcd 334.1251, found 334.1253; mp: 227–230 °C; HPLC: purity 95.1%, retention time 16.5 min with method B.

*5.1.61. (4-Hydroxyphenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**66**)*

To a solution of compound **59** (300 mg, 0.9 mmol) in CH_2Cl_2 (30 mL) was added BBr_3 (0.36 mL) at −80 °C under nitrogen atmosphere. After stirred for overnight at r.t. the mixture was quenched with water, extracted with EtOAc, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **66** as a solid (40 mg, 13.9% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 9.32 (s, 1H), 7.92 (d, J = 1.5 Hz, 1H), 7.84–7.82 (m, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.2 Hz, 1H), 7.47 (dd, J = 2.9, 2.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.74 (dd, J = 2.9, 1.6 Hz, 1H) and 5.04 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.7, 161.0, 152.1, 138.3, 131.2, 130.2, 125.5, 125.1, 123.5, 122.8, 122.0, 121.3, 115.1, 111.8, 69.8 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{15}BNO_4$ calcd 320.1094, found 320.1097; mp: 192–194 °C; HPLC: purity 96.4%, retention time 16.7 min with method A.

*5.1.62. (4-(Aminomethyl)phenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**67**)*

A solution of compound **63** (187 mg, 0.34 mmol) and piperidine (2 mL) in $CHCl_3$ (20 mL) was stirred at 20 °C for overnight. The residue after rotary evaporation was purified by recrystallization

with EtOAc and CH_3OH to give compound **67** as a solid (50 mg, 44.3% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.87 (d, J = 8.0 Hz, 2H), 7.61–7.60 (m, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.47–7.46 (m, 1H), 7.28–7.25 (m, 2H), 7.19 (d, J = 7.9 Hz, 1H), 6.79–6.78 (m, 1H), 4.89 (s, 2H) and 4.15 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.8, 152.1, 147.0, 138.1, 137.4, 128.6, 127.1, 125.7, 125.4, 123.5, 122.7, 122.1, 121.7, 111.6, 69.7, 45.0 ppm; HRMS (ESI): [M-H + Na]$^+$ $C_{19}H_{16}BN_2O_3Na$ calcd 354.1152, found 354.1307; mp: 300 °C decomposed; HPLC: purity 95.2%, retention time 12.7 min with method B.

5.1.63. (4-Aminophenyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**68**)

A solution of compound **64** (200 mg, 0.37 mmol) and piperidine (2 mL) in acetone (20 mL) was stirred at 20 °C for overnight. The residue after rotary evaporation was washed with 1% citric acid, extracted with EtOAc, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel and washed with ether to give compound **68** as a solid (30 mg, 25.5% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.3 (s, 1H), 7.92 (s, 1H), 7.81 (dd, J = 8.3 Hz, 1H), 7.79 (dd, J = 2.3, 1.7 Hz, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.3 Hz, 1H), 7.43 (dd, J = 3.0, 2.3 Hz, 1H), 6.69 (dd, J = 3.0, 1.7 Hz, 1H), 6.61 (d, J = 8.6 Hz, 2H), 5.93 (brs, 2H) and 5.04 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.1, 152.0, 138.4, 131.2, 126.8, 125.9, 124.3, 123.4, 122.8, 121.9, 120.9, 113.2, 111.9, 69.8 ppm; HRMS (ESI): [M + H]$^+$ $C_{18}H_{16}BN_2O_3$ calcd 319.1254, found 319.1252; mp: 167–169 °C; HPLC: purity 97.0%, retention time 16.1 min with method A.

5.1.64. Naphthalene-1-yl-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**69**)

Compound **69** (25 mg, 7.0% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 1H), 8.10 (d, J = 8.3 Hz, 1H), 8.06–8.02 (m, 2H), 7.84 (d, J = 2.1 Hz, 1H), 7.77 (dd, J = 7.2, 1.2 Hz, 1H), 7.76 (dd, J = 8.3, 2.3 Hz, 1H) 7.69 (dd, J = 2.0, 1.7 Hz, 1H), 7.63–7.50 (m, 5H), 6.79 (dd, J = 3.1, 1.7 Hz, 1H) and 5.02 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 190.7, 152.3, 138.0, 137.5, 133.3, 130.2, 129.9, 128.3, 127.3, 126.8, 126.6, 126.2, 126.1, 125.1, 124.8, 123.5, 122.7, 122.2, 122.0, 111.2, 69.7, ppm; HRMS (ESI): [M + H]$^+$ $C_{22}H_{17}BNO_3$ calcd 354.1301, found 354.1300; mp: 166–168 °C; HPLC: purity 96.2%, retention time 18.7 min with method B.

5.1.65. Benzyl-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**70**)

Compound **70** (40 mg, 12.6% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 2.1, 1.8 Hz, 1H), 7.50 (dd, J = 8.1, 2.0 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.33–7.29 (m, 4H), 7.24–7.21 (m, 1H), 7.02 (dd, J = 2.9, 2.1 Hz, 1H), 6.80 (dd, J = 2.9, 1.8 Hz, 1H), 5.56 (brs, 1H), 5.14 (s, 2H) and 4.09 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.8, 152.7, 138.7, 136.4, 130.0, 128.7, 127.0, 126.8, 126.0, 123.9, 123.3, 122.4, 122.3, 110.8, 70.3, 46.0 ppm; HRMS (ESI): [M + H]$^+$ $C_{19}H_{17}BNO_3$ calcd 318.1301, found 318.1303; mp: 159–161 °C; HPLC: purity 97.6%, retention time 17.4 min with method B.

5.1.66. (2-Phenylethyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**71**)

Compound **71** (100 mg, 30.2% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 1.8 Hz, 1H), 7.67 (dd, J = 2.2, 1.7 Hz, 1H), 7.50 (dd, J = 8.2, 1.8 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.29 (dd, J = 7.8, 6.9 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 7.19 (t, J = 6.9 Hz, 1H), 7.03 (dd, J = 2.5, 2.2 Hz, 1H), 6.77 (dd, J = 2.5, 1.7 Hz, 1H), 5.75 (brs, 1H), 5.14 (s, 2H) and 3.14–3.03 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 193.9, 152.0, 141.5, 138.2, 128.3, 128.1, 126.7, 125.7, 124.8, 123.2, 122.7, 121.8, 121.4, 109.8, 69.7, 40.1, 29.8 ppm; HRMS (ESI): [M + H]$^+$ $C_{20}H_{19}BNO_3$ calcd 332.1458, found 332.1442; mp: 122–124 °C; HPLC: purity 96.1%, retention time 18.7 min with method B.

5.1.67. (n-Propyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**72**)

Compound **72** (104 mg, 38.6% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (s, 1H), 8.16 (dd, J = 2.2, 1.7 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.78 (dd, J = 8.2, 2.1 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.40 (dd, J = 3.0, 2.2 Hz, 1H), 6.66 (dd, J = 3.0, 1.7 Hz, 1H), 5.05 (s, 2H), 2.78 (t, J = 7.3 Hz, 2H), 1.63 (h, J = 7.3 Hz, 2H) and 0.93 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.3, 152.1, 138.2, 127.2, 125.1, 123.3, 122.7, 121.9, 121.5, 109.8, 69.7, 27.0 ppm; HRMS (ESI): [M + H]$^+$ $C_{15}H_{17}BNO_3$ calcd 270.1301, found 270.1303; mp: 122–124 °C; HPLC: purity 95.6%, retention time 16.8 min with method B.

5.1.68. (n-Pentyl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**73**)

Compound **73** (80 mg, 18.8% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 2.0 Hz, 1H), 7.70 (dd, J = 2.2, 1.6 Hz, 1H), 7.53 (dd, J = 8.2, 2.0 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.04 (dd, J = 2.9, 2.2 Hz, 1H), 6.77 (dd, J = 2.9, 1.6 Hz, 1H), 5.15 (s, 2H), 2.78 (t, J = 7.4 Hz, 2H), 1.71–1.78 (m, 2H), 1.65–1.63 (m, 2H), 1.36–1.34 (m, 2H) and 0.90 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.0, 152.0, 138.3, 126.9, 124.6, 123.3, 122.7, 121.8, 121.4, 109.8, 69.7, 38.5, 31.0, 24.1, 21.9, 13.8 ppm; HRMS (ESI): [M + Na]$^+$ $C_{17}H_{20}BNO_3Na$ calcd 320.1434, found 320.1368; mp: 124–126 °C; HPLC: purity 95.4%, retention time 19.2 min with method B.

5.1.69. Cyclohexyl-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (**74**)

Compound **74** (90 mg, 23.1% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 1H), 8.20–8.19 (m, 1H), 7.92 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.41–7.40 (m, 1H), 6.65–6.64 (m, 1H), 5.03 (s, 2H), 3.13–3.14 (m, 1H), 1.77–1.65 (m, 5H), 1.40–1.33 (m, 4H) and 1.19–1.18 (m, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 198.2, 152.0, 138.3, 125.8, 124.5, 123.3, 122.7, 121.9, 121.5, 110.1, 69.7, 45.9, 29.3, 25.6, 25.2 ppm; HRMS (ESI): [M + Na]$^+$ $C_{18}H_{20}BNO_3Na$ calcd 332.1434, found 332.1357; mp: 161–163 °C; HPLC: purity 98.9%, retention time 19.1 min with method A.

5.1.70. 2-(4-(1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-4-oxo-butyl)-isoindole-1,3-dione (**75**)

Compound **75** (40 mg, 19.3% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, J = 8.5, 2.3 Hz, 2H), 7.78 (d, J = 2.0 Hz, 1H), 7.68 (dd, J = 8.5, 2.3 Hz, 2H), 7.66–7.65 (dd, J = 2.3, 1.7 Hz, 1H), 7.52 (dd, J = 8.2, 2.0 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.02 (dd, J = 3.0, 2.3 Hz, 1H), 6.73 (dd, J = 3.0, 1.7 Hz, 1H), 5.38 (brs, 1H), 5.14 (s, 2H), 3.81 (t, J = 6.9 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H) and 2.14 (dd, J = 7.3, 6.9 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.1, 168.1, 152.2, 138.4, 134.4, 131.8, 126.8, 124.9, 123.4, 123.0, 122.9, 122.0, 121.6, 110.0, 69.9, 37.3, 35.9, 23.1 ppm; HRMS (ESI): [M + Na]$^+$ $C_{23}H_{19}BN_2O_5Na$ calcd 437.1285, found 437.1195; mp: 158–160.5 °C; HPLC: purity 97.4%, retention time 18.0 min with method A.

5.1.71. 4-Amino-1-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-butan-1-one (**76**)

A solution of compound **75** (100 mg, 0.24 mmol) in 1 M aq. NaOH (5 mL) was stirred at r.t. for 30 min before 1 M aq. HCl (8 mL)

was added and the mixture was extracted with EtOAc. After evaporation the residue was dissolved in CH_3OH and 6 M aq. HCl (5 mL), and was refluxed for 2 d. After evaporation of organic phase, the residue was filtered and recrystallized with EtOAC and CH_3OH to give compound **76** as a solid (33 mg, 48.4% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 8.38 (dd, J = 2.2, 1.8 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.2, 2.0 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.54 (dd, J = 3.1, 2.2 Hz, 1H), 6.99 (dd, J = 3.1, 1.8 Hz, 1H), 5.16 (s, 2H), 4.09 (t, J = 7.5 Hz, 2H), 3.52 (t, J = 8.0 Hz, 2H) and 2.36–2.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.3, 153.6, 138.1, 130.4, 124.8, 123.9, 122.7, 122.3, 113.9, 110.0, 70.9, 51.7, 33.8, 20.2 ppm; HRMS (ESI): $[M - OH]^+$ $C_{15}H_{16}BN_2O_2$ calcd 267.1299, found 267.1275; mp: 250 °C decomp.; HPLC: purity 96.5%, retention time 14.8 min with method A.

5.1.72. (Thiophen-2-yl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (77)

Compound **77** (24 mg, 7.7% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 3.8 Hz, 1H), 7.83 (dd, J = 2.1 Hz, 1H), 7.81 (dd, J = 2.4, 1.6 Hz, 1H), 7.63 (d, J = 4.9 Hz, 1H), 7.55 (dd, J = 8.1, 2.1 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.16 (dd, J = 4.9, 3.8 Hz, 1H), 7.10 (dd, J = 2.7, 2.4 Hz, 1H), 6.94 (dd, J = 2.7, 1.6 Hz, 1H), 5.76 (brs, 1H) and 5.15 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.1, 152.3, 144.3, 138.2, 133.4, 132.5, 128.5, 125.0, 124.9, 123.7, 122.8, 122.2, 121.8, 111.4, 69.8 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{13}BNO_3S$ calcd 310.0709, found 310.0711; mp: 145–150 °C; HPLC: purity 97.3%, retention time 16.8 min with method B.

5.1.73. (5-Methylthiophen-2-yl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (78)

Compound **78** (40 mg, 12.4% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 2.1 Hz, 1H), 7.78 (dd, J = 2.4, 1.7 Hz, 1H), 7.68 (d, J = 3.7 Hz, 1H), 7.54 (dd, J = 8.1, 2.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.09 (dd, J = 3.0, 2.4 Hz, 1H), 6.91 (dd, J = 3.0, 1.7 Hz, 1H), 6.83 (dd, J = 3.7, 0.9 Hz, 1H), 5.70 (brs, 1H), 5.15 (s, 2H) and 2.56 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.7, 152.2, 147.8, 142.1, 138.2, 133.0, 127.2, 124.9, 124.5, 123.6, 122.7, 122.1, 121.5, 111.3, 69.7, 15.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{15}BNO_3S$ calcd 324.0866, found 324.0870; mp: 148–150 °C; HPLC: purity 95.3%, retention time 18.0 min with method B.

5.1.74. (3-Methylthiophen-2-yl)-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-3-yl)-methanone (79)

Compound **79** (60 mg, 18.6% yield) as a solid was prepared following a similar procedure to compound **44**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.79 (m, 2H), 7.55 (dd, J = 8.2, 1.8 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 4.9 Hz, 1H), 7.08–7.07 (m, 1H), 7.00 (d, J = 4.9 Hz, 1H), 6.95–6.94 (m, 1H), 5.58 (brs, 1H), 5.15 (s, 2H) and 2.58 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.6, 152.2, 143.3, 138.1, 134.5, 131.9, 129.6, 127.1, 124.9, 123.4, 122.8, 122.0, 121.6, 111.4, 69.7, 15.9 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{15}BNO_3S$ calcd 324.0866, found 324.0867; mp: 150–152 °C; HPLC: purity 97.7%, retention time 18.1 min with method B.

5.1.75. Methyl-(1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-pyrrol-2-yl)-methanone (80)

To DMF (0.17 mL, 2.4 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under nitrogen was added $POCl_3$ (0.22 mL, 2.4 mmol) dropwise. The mixture was stirred for 1 h at r.t. then cooled to 0 °C. After a solution of compound **24** (0.4 g, 2 mmol) in CH_2Cl_2 (5 mL) was added dropwise, the mixture was stirred for 1 d at r.t., and refluxed for 15 min. After cooled to r.t., aq. NaOAc (0.88 g, 11 mmol) was added before it was extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **80** as a solid (50 mg, 10.0% yield). ^{1}H NMR (300 MHz, CD_3OD): δ 7.50 (s, 1H), 7.47–7.44 (m, 1H), 7.39–7.35 (m, 1H), 7.30–7.28 (m, 1H), 7.12–7.11 (m, 1H), 6.38–6.35 (m, 1H), 5.15 (s, 2H) and 2.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8, 154.1, 139.4, 135.9, 128.9, 128.0, 125.0, 122.6, 122.1, 111.1, 96.2, 70.4 ppm; HRMS (ESI): $[M + Na]^+$ $C_{13}H_{12}BNO_3Na$ calcd 264.0808, found 264.0803; mp: 100–104 °C; HPLC: purity 99.0%, retention time 16.4 min with method A.

5.1.76. 6-(3-Benzyl-pyrrol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (81)

To a solution of compound **50** (150 mg, 0.48 mmol) in THF (5 mL) was added $NaBH_4$ (181.4 mg, 4.8 mmol) portionwise slowly. After 10 min $BF_3(Et_2O)$ (1.08 mL) was added dropwise slowly. The mixture was stirred for 2 h, and quenched with saturated $NaHCO_3$. After evaporation the residue was extracted with EtOAc, 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 **81** as a solid (40 mg, 28.8% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 2.1 Hz, 1H), 7.48 (dd, J = 8.2, 2.1 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.34–7.30 (m, 4H), 7.22–7.21 (m, 1H), 7.05 (dd, J = 2.6, 2.5 Hz, 1H), 6.87–6.86 (m, 1H), 6.21 (dd, J = 2.6, 1.9 Hz, 1H), 5.13 (s, 2H), 5.12 (brs, 1H) and 3.90 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 141.9, 140.3, 128.9, 128.5, 126.0, 125.9, 123.6, 122.3, 121.7, 119.6, 117.6, 111.5, 71.2, 33.7 ppm; HRMS (ESI): $[M + Na]^+$ $C_{18}H_{16}BNO_2Na$ calcd 312.1172, found 312.1163; mp: 112–114 °C; HPLC: purity 98.2%, retention time 19.9 min with method A.

5.1.77. 1-Phenyl-pyrrole (83)

To a solution of phenylamine (1.5 g, 15.6 mmol) in AcOH (20 mL) was added 2,5-dimethoxytetrahydrofuran (2.56 g, 19.2 mmol). After refluxed for 4 h, it was evaporated, re-dissolved in EtOAc, washed with saturated $NaHCO_3$, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound **83** as an oil (1.3 g, 58.2% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.39 (m, 4H), 7.27–7.23 (m, 1H), 7.10 (t, J = 2.1 Hz, 2H) and 6.36 (t, J = 2.1 Hz, 2H) ppm.

5.1.78. Phenyl-(1-phenyl-pyrrol-3-yl)-methanone (84)

To a solution of compound **83** (300 mg, 2.1 mmol) and benzoyl chloride (353.4 mg, 2.52 mmol) in CH_2Cl_2 (10 mL) was added anhydrous $SnCl_4$ (0.36 mL, 3.15 mmol) dropwise slowly. After stirred for 2 h, the mixture was quenched with saturated $NaHCO_3$, 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 **84** as an oil (230 mg, 44.2% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.89 (m, 2H), 7.61 (dd, J = 2.4, 1.7 Hz, 1H), 7.55–7.50 (m, 1H), 7.48–7.31 (m, 6H), 7.30–7.34 (m, 1H), 7.10 (dd, J = 2.9, 2.4 Hz, 1H) and 6.89 (dd, J = 2.9, 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 139.8, 131.5, 129.8, 128.9, 128.2, 127.1, 126.2, 126.1, 121.2, 121.1, 112.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{14}NO$ calcd 248.1057, found 248.1073; HPLC: purity 95.3%, retention time 19.9 min with method A.

5.1.79. 1-(3-Bromo-4-(methoxymethyl)-phenyl)-pyrrole (85)

To a solution of compound **23** (3 g, 12.0 mmol) in anhydrous THF (50 mL) was added NaH (60% in mineral oil 0.72 g, 0.018 mol). The mixture was stirred for 10 min at r.t. before CH_3I (0.7 mL, 14.0 mmol) was added dropwise slowly. After stirred for 6 h, the mixture was quenched with water and 2 M aq. HCl. After evaporation the residue was extracted with EtOAc, 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 **85** as a solid (3 g, 93.9% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 2.2 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.36 (dd, J = 8.3, 2.2 Hz, 1H), 7.06 (t, J = 2.2 Hz, 2H), 6.36 (t, J = 2.2 Hz, 2H), 4.54 (s, 2H) and 3.49 (s, 3H) ppm; mp: 59–62 °C.

*5.1.80. 2-(Methoxymethyl)-5-(pyrrol-1-yl)-benzaldehyde (**86**)*

To a solution of compound **85** (200 mg, 0.75 mmol) in anhydrous THF (10 mL) was added dropwise 1.6 M *n*-BuLi in THF (2.72 mL, 4.36 mmol) at −78 °C under nitrogen. After stirred for 5 min at −78 °C, DMF (0.34 mL, 4.5 mmol) was added dropwise. The reaction was quenched with 0.5 M HCl immediately. After evaporation, the residue was extracted with EtOAc, 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 **86** as a solid (122 mg, 75.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.62 (dd, J = 8.3, 2.3 Hz, 1H), 7.15 (t, J = 2.2 Hz, 2H), 6.39 (t, J = 2.2 Hz, 2H), 4.86 (s, 2H) and 3.50 (s, 3H) ppm; mp: 49–53 °C.

*5.1.81. 2-(Methoxymethyl)-5-(pyrrol-1-yl)-benzyl alcohol (**87**)*

To a solution of compound **86** (1.2 g, 5.6 mmol) in CH_3OH (20 mL) was added $NaBH_4$ (0.21 g, 5.6 mmol) portionwise slowly. After stirred for 30 min at r.t., the mixture was quenched with water. After evaporation, the residue was extracted with EtOAc, washed with water, and brine, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation gave crude compound **87** which was used without further purification.

*5.1.82. 2-(Methoxymethyl)-5-(pyrrol-1-yl)-benzyl acetate (**88**)*

To a solution of compound **87** (1.0 g, 4.6 mmol) in CH_2Cl_2 (20 mL), TEA (2.05 mL, 13.8 mmol) and Ac_2O (0.65 mL, 7 mmol) were added successively. After stirred for overnight at r.t., the mixture was quenched with 1 M aq. HCl. After evaporation, the residue was extracted with EtOAc, and dried over anhydrous Na_2SO_4, evaporated, and purified by column chromatography over silica gel to give compound **88** as an oil (1.13 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 2.2 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.34 (dd, J = 8.2, 2.2 Hz, 1H), 7.12 (t, J = 2.1 Hz, 2H), 6.37 (t, J = 2.1 Hz, 2H), 5.25 (s, 2H), 4.54 (s, 2H), 3.43 (s, 3H) and 2.14 (s, 3H) ppm.

*5.1.83. 2-(Methoxymethyl)-5-(3-benzoyl-pyrrol-1-yl)-benzyl acetate (**89**)*

To a solution of compound **88** (760 mg, 2.93 mmol) and benzoyl chloride (453.2 mg, 3.22 mmol) in CH_2Cl_2 (40 mL) was added anhydrous $SnCl_4$ (0.41 mL, 3.5 mmol) dropwise slowly at −40 °C. The reaction mixture was allowed to warm to 0 °C gradually before it was quenched with saturated $NaHCO_3$, 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 **89** as an oil (160 mg, 15.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 7.7 Hz, 2H), 7.62 (dd, J = 2.4, 1.6 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.50–7.46 (m, 4H), 7.36 (dd, J = 8.1, 2.4 Hz, 1H), 7.10 (dd, J = 2.9, 2.4 Hz, 1H), 6.87 (dd, J = 2.9, 1.6 Hz, 2H), 5.23 (s, 2H), 4.53(s, 2H), 3.42 (s, 3H) and 2.13 (s, 3H) ppm.

*5.1.84. 2-(Methoxymethyl)-5-(3-benzoyl-pyrrol-1-yl)-benzyl alcohol (**90**)*

A solution of compound **89** (100 mg, 0.27 mmol) in 1 M aq. NaOH (1 mL) and CH_3OH (30 mL) was stirred at r.t. for 15 min. The mixture was quenched with 1 M aq. HCl. After evaporation, the residue was extracted with EtOAc, washed with water, and brine, and dried over anhydrous Na_2SO_4. The residue after rotary evaporation gave crude compound **90** which was used without further purification.

*5.1.85. 2-(Methoxymethyl)-5-(3-benzoyl-pyrrol-1-yl)-benzaldehyde (**91**)*

To a solution of compound **90** (88 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) were added PCC (88.3 mg, 0.41 mmol) and Celite (132 mg). After stirred for 2 h at r.t., the mixture was purified by column chromatography over silica gel to give compound **91** as a solid (78 mg, 90.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 7.93 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.72 (d, J = 8.3 Hz, 1H), 7.67 (dd, J = 2.4, 1.7 Hz, 1H), 7.63 (dd, J = 8.3, 2.4 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.6, 7.2 Hz, 2H), 7.17 (dd, J = 2.9, 2.4 Hz, 1H), 6.91 (dd, J = 2.9, 1.7 Hz, 1H), 4.87 (s, 2H) and 3.50 (s, 3H) ppm; mp: 79–81 °C.

*5.1.86. 5-(3-Benzoyl-pyrrol-1-yl)-2-(hydroxymethyl)benzaldehyde and its hemiacetal isomer (**92**)*

To a solution of compound **91** (75 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (10 mL) was added BBr_3 (0.07 mL, 0.7 mmol) dropwise slowly at −78 °C. The reaction mixture was allowed to warm to 0 °C gradually before quenched with water, extracted with CH_2Cl_2, 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 **92** as a solid (60 mg, 83.6% yield). The compound exists as two tautomers in solution: aldehyde:hemiacetal = 4:5. ^{1}H NMR (400 MHz, CD_3OD): aldehyde: δ 10.31 (s, 1H), 8.12 (s, 1H), 7.89–7.85 (m, 3H), 7.67 (d, J = 8.2 Hz, 1H), 7.62–7.52 (m, 4H), 7.46–7.45 (m, 1H), 6.87–6.86 (m, 1H) and 5.06 (s, 2H) ppm; hemiacetal: δ 7.89–7.85 (m, 3H), 7.79–7.77 (m, 2H), 7.62–7.52 (m, 4H), 7.35–7.34 (m, 1H), 6.84–6.83 (m, 1H), 5.90 (s, 1H), 4.78 (d, J = 10.5 Hz, 1H) and 4.74 (d, J = 10.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 193.1, 192.8, 142.9, 141.5, 140.8, 140.7, 139.8, 136.5, 134.6, 134.0, 133.6, 133.2, 133.1, 130.0, 129.6, 127.7, 127.3, 126.6, 125.4, 122.8, 122.7, 122.2, 121.7, 120.7, 119.6, 113.7, 113.4, 101.8, 75.9 and 71.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{19}H_{16}NO_3$ calcd 306.1130, found 306.1104; HPLC: purity 98.2%, retention time 19.9 min with method A.

5.2. Biology

5.2.1. In vitro T. brucei assay

All *in vitro* antiparasitic assays were conducted with the bloodstream-form *T. 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 medium was complete HMI-9 medium (Hirumi, H.; Hirumi, K. Continuous cultivation of *T. brucei* bloodstream forms in a medium containing a low concentration of serum protein without feeder cell layers. *J. Parasitol.* **1989**, 75, 985–989) containing 10% FBS, 10% Serum Plus medium, and penicillin/streptomycin. To ensure log growth phase, trypanosomes were subcultured at appropriate dilutions every 2–3 days. The 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 2×10^5/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 was 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 1.0×10^5/mL parasites in 0.4% for DMSO. Trypanosomes were incubated with compounds for 72 h 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 h. 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 to determine IC_{50} values using XLfit curve fitting software from

IDBS (Guildford, U.K.). IC_{50} values were measured in triplicate with an error range of ±0.2 μM. Suramin and pentamidine are used as positive control, and typical average IC_{50} values are 0.007 μg/mL (0.005 μM) and 0.009 μg/mL (0.026 μM), respectively.

5.2.2. 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 DMEM 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 1×10^4/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 DMEM 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 h 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 h. 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).

5.2.3. In vivo biological assay

An acute murine model was used to evaluate the efficacy of compounds against acute parasite infection. Five female BALB/c mice per group were administered with 200 μL complete HIM-11 medium containing 600 *T. b. brucei* parasites by intraperitoneal injection. Compounds were dissolved in 5% ethanol, 45% sterilizing deionized water, and 50% PEG400. At 24 h after infection, mice were treated with compounds at a dosage of 50 mg/kg i.p., twice daily for 5 days. The infection status was monitored every other day for ten days, and then on a weekly basis, using trypan-blue-stained blood smear from tail vein. Mice parasite-free for 30 days were considered cured. Suramin was used as a reference compound at 20 mg/kg once daily for five days, which gave 100% survival rate and complete eradication of *T. b. brucei* parasites thirty days post-infection.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.04.079.

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