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Brief Article

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Chalcone–Benzoxaborole Hybrid Molecules as Potent Antitrypanosomal Agents

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Supporting Information

ABSTRACT: We report the novel chalcone–benzoxaborole hybrids and their structure–activity relationship against *Trypanosoma brucei* parasites. The 4-NH_2 derivative **29** and 3-OMe derivative **43** were found to have excellent potency. The synergistic 4-NH_2-3-OMe compound **49** showed an IC_{50} of 0.010 μg/mL and resulted in 100% survival and zero parasitemia in a murine infection model, which represents one of the most potent compounds discovered to date from the benzoxaborole class that inhibit *T. brucei* growth.

INTRODUCTION

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a parasitic disease transmitted by the bite of tsetse flies. The disease mostly affects populations living in remote areas of Africa, especially sub-Saharan Africa. Untreated, this disease is usually fatal.[1] There are mainly four drugs registered to treat HAT, suramin and pentamidine for the early stage while melarsoprol and eflornithine are for the late-stage treatment.[2,3] All developed more than 30 years ago, the current therapeutic drugs face the challenge of high toxicity, potential development of resistance, and lack of efficacy. It is imperative to develop new drugs with low toxicity, improved efficacy, and affordable cost.[4,5]

During the past decade, advances have been made in the treatment of HAT,[6] for example, the nifurtimox–eflornithine combination (NECT) chemotherapy was developed to reduce resistance frequency.[7,8] There are also a number of new drug candidates that successfully entered clinical trials, including pafuramidine[9] and fexinidazole[10] (Figure 1), although pafuramidine

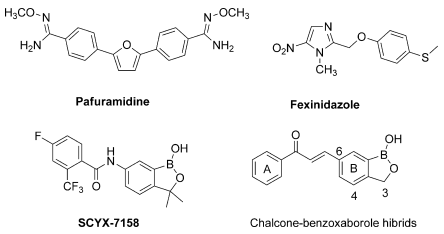

Figure 1. Structures of pafuramidine, fexinidazole, SCYX-7158, and chalcone–benzoxaborole hybrids.

was later halted due to toxicity emerged in phase III clinical trials. Benzoxaboroles, characterized by a unique five-membered oxaborole ring fused with a phenyl ring, were recently found to be effective antitrypanosomal agents.[11−13] In recent months, the preclinical study of a benzoxaborole lead compound 4-fluoro-*N*-(1-hydroxy-3,3-dimethyl-1,3-dihydro-benzo[*c*][1,2]oxaborol-6-yl-2-trifluoromethyl benzamide (SCYX-7158)[14] was completed successfully and a clinical trial is anticipated this year (Figure 1). Chalcones, possessing an aromatic α,β-unsaturated ketone, have attracted considerable scientific attention and continue to be a versatile scaffold in anticancer and antiprotozoal research.[15] Previously, chalcone-type compounds have been found to inhibit the growth of *Trypanosoma brucei* and *Trypanosoma cruzi* parasites.[16,17]

We were prompted by the above obsevations to investigate the potential synergistic effect of benzoxaborole and chalcone scaffolds. A series of chalcone–benzoxaborole hybrid molecules were synthesized, and their ability to inhibit bloodstream form of *T. brucei* was evaluated. From an exploration of the A ring substitutions, 4-NH_2 derivative **29** and 3-OMe derivative **43** were discovered as the lead compounds with IC_{50} value of 0.024 and 0.022 μg/mL, respectively. Combination of the structural features of compounds **29** and **43** gave 4-amino-3-methoxy compound **49**, which showed further improved IC_{50} of 0.010 μg/mL and represents one of the most potent compounds described to date from the benzoxaborole class that inhibit *T. brucei* growth. A significant decrease of potency was observed upon alteration or removal of either the benzoxaborole or the chalcone moiety, suggesting the potency of the hybrid molecules indeed attribute to both functionalities. Importantly, compounds **43** and **49** showed excellent in vivo efficacy in a murine model of *T. brucei* infection with 100% survival and no parasitemia 30 days postinfection.

CHEMISTRY

As shown in Scheme 1, the intermediate 6-formylbenzoxaborole **7** was prepared from the corresponding dimethylbromobenzene with 27.5% yield over six steps according to the previously reported method.[18,19] Dicarboxyl compound **2** was obtained from 2,6-dimethylbromobenzene **1** under the condition of $KMnO_4$ in *t*-BuOH/H_2O. Treatment of **2** with $SOCl_2$ followed

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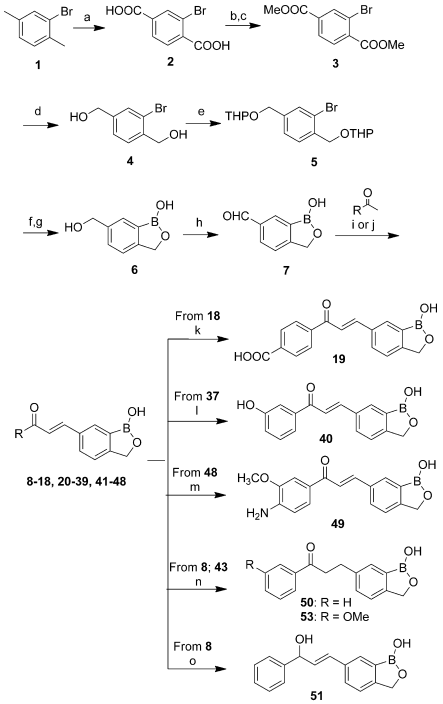
Scheme 1. Synthesis of Chalcone−Oxaborole Hybrids[a]



8: R = Ph
9: R = 4-Me-Ph
10: R = 4-Biphenyl
11: R = Naphth-1-yl
12: R = Pyridin-2-yl
13: R = Furan-2-yl
14: R = Thiophen-2-yl
15: R = 1-Methyl-pyrrol-2-yl
16: R = 4-NO_2-Ph
17: R = 4-CF_3-Ph
18: R = 4-COOEt-Ph
20: R = 4-F-Ph
21: R = 4-Cl-Ph
22: R = 4-Br-Ph
23: R = 4-I-Ph
24: R = 4-Et-Ph
25: R = 4-SMe-Ph
26: R = 4-OMe-Ph
27: R = 4-OBn-Ph
28: R = 4-OH-Ph
29: R = 4-NH_2-Ph
30: R = 4-AcNH-Ph
31: R = 2-F-Ph
32: R = 3-F-Ph
33: R = 3-Me-Ph
34: R = 3,4-DimethylPh
35: R = 3,4-DichloroPh
36: R = 2-MOM-Ph
37: R = 3-MOM-Ph
38: R = 3-NH_2-Ph
39: R = 2-OH-Ph
41: R = 3,4-DihydroxyPh
42: R = 2-OMe-Ph
43: R = 3-OMe-Ph
44: R = 3,4-DimethoxyPh
45: R = 2,4-DimethoxyPh
46: R = 3,4,5-TrimethoxyPh
47: R = 2,3-Dihydrobenzo[b][1,4]dioxin-6-yl
48: R = 3-OMe-4-NO_2-Ph
49: R = 3-OMe-4-NH_2-Ph

[a]Reagents and conditions: (a) $KMnO_4$, *t*-BuOH/H_2O, 70 °C; (b) $SOCl_2$, 100 °C; (c) MeOH, Et_3N; (d) $LiBH_4$, THF; (e) DHP, TsOH, DMF; (f) *n*-BuLi, $B(iPrO)_3$, THF; (g) 6 M HCl; (h) PCC, Celite, DCM; (i) NaOH, EtOH/H_2O; (j) CH_3COCl, EtOH; (k) NaOH/EtOH/H_2O; (l) concd HCl/EtOH; (m) $SnCl_2{\cdot}2H_2O$/EtOH; (n) Pd/C, H_2; (o) $NaBH_4$.

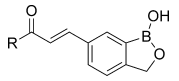
by CH_3OH/Et_3N gave ester **3**, which was subsequently reduced by $LiBH_4$ and protected with DHP to provide compound **5**. Benzoxaborole **6** was obtained by treatment of **5** with *n*-butyllithium and borate, followed by one-pot deprotection and cyclization in 6 M HCl with 65.4% yield over two steps. The critical aldehyde intermediate **7** was thus obtained by PCC oxidation of alcohol **6**. Chalcone−benzoxaborole hybrid molecules **8**−**18**, **20**−**39**, and **41**−**48** were prepared from aldehyde **7** by aldol condensation under alkalic or acidic condition. *E*-Isomers were obtained as the sole isomers as confirmed by the ^1H NMR coupling constant (J = 16 Hz) between the two vinyl protons. Ester **18** was converted to its carboxylic acid derivative **19** under alkalic condition. Deprotection of MOM protected compound **37** in the presence of concentrated HCl gave compound **40**. Nitro derivative **48** was converted to amine **49** by reduction with $SnCl_2{\cdot}2H_2O$. The C−C double bonds of compound **8** and **43** were reduced under hydrogen in the presence of Pd/C to give compound **50** and **53**, respectively. The carbonyl in compound **8** was reduced with $NaBH_4$ to provide alcohol **51**.

RESULTS AND DISCUSSION

Chalcone−benzoxaborole hybrid molecules with different A rings including phenyl, biphenyl, naphthyl, pyridyl, furanyl, thiophenyl, and pyrrolyl were synthesized (Scheme 1), and their ability to inhibit the in vitro growth of bloodstream form of *T. brucei* was tested (Table 1). The biphenyl and naphthyl groups gave inhibitory IC_{50} of 0.436 and 0.135 μg/mL, respectively, while the relatively compact aromatic rings including compounds **8** and **12**−**15** showed better potency with IC_{50} values below 0.1 μg/mL. Thiophenyl compound **14** showed the most favorable activity with IC_{50} of 0.045 μg/mL. Installation of a 4-methyl on the phenyl group (compound **9**) resulted in activity (IC_{50} = 0.046 μg/mL) as good as **14**. All compounds except naphthyl compound **11** showed satisfactory (IC_{50} >10 μg/mL) cytotoxicity profile against mouse lung fibroblast cells (L929).

Encouraged by the inhibitory activity of compound **9**, we focused on the exploration of the 4-substituted phenyl compounds as shown in Table 2. Compound **16**, with a strong

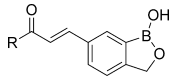
Table 1. The Effect of Different Aromatic A Rings on *T. brucei* Growth Inhibition[a]



compd	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
8	0.089	>10
9	0.046	>10
10	0.436	>10
11	0.135	3.67
12	0.099	>10
13	0.064	>10
14	0.045	>10
15	0.057	>10

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

Table 2. Exploration of the Effect of Different para-Substitutions on *T. brucei* Growth Inhibition[a]



compd	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
16	0.082	>10
17	0.133	>10
18	0.200	>10
19	4.450	>10
20	0.100	>10
21	0.060	>10
22	0.090	>10
23	0.171	>10
24	0.064	10
25	0.059	>10
26	0.071	>10
27	0.164	>10
28	0.043	>10
29	0.024	>10
30	0.040	>10

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

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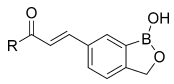
electron-withdrawing nitro group, showed inhibitory IC_{50} of 0.082 μg/mL, which is comparable to the unsubstituted phenyl compound **8**, suggesting the electron deficiency of the chalcone system does not affect activity. The CF_3- substituted compound **17** showed a decrease of activity (IC_{50} = 0.133 μg/mL) when compared to its methyl analogue **9**. Ester **18** showed a 22-fold increase of activity when compared to its carboxylic acid analogue **19**, which may be due to the enhanced membrane permeability of the ester group. Halogen substituted compounds **20**−**23** were synthesized, however, only the chloro compound **21** has improved potency than the unsubstituted compound **8**. Next, the 4-substituents with two heavy atoms were explored as shown by compounds **24**−**26**, which all showed improved activity than **8**. However, 4-benzyloxy substituent in compound **27** resulted in decreased activity (IC_{50} = 0.164 μg/mL). A number of substituents with potential hydrogen bonding ability were introduced into compounds **28**−**30**. Phenol **28** showed a moderate increase of potency, while aniline **29** exhibited a 4-fold increase of potency (IC_{50} = 0.024 μg/mL) when they are compared to compound **8**. When the amino group was capped by an acetyl group in compound **30**, the activity decreased. These observations in Table 1 and 2 suggest that compact substitution groups with hydrogen bonding capability on the phenyl group may be favored for antitrypanosomal activity.

Consequently, we continued to explore a variety of substitution patterns on the phenyl ring as shown in Table 3.

Table 3. The Effect of Different Phenyl Substitution Patterns on *T. brucei* Growth Inhibition[a]



compd	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
31	0.071	>10
32	0.046	>10
33	0.048	8.56
34	0.040	>10
35	0.090	>10
36	0.366	9.02
37	0.071	>10
38	0.056	10
39	0.172	>10
40	0.037	7.56
41	0.055	>10
42	0.058	6.35
43	0.022	>10
44	0.030	>10
45	0.037	7.87
46	0.113	>10
47	0.080	6.80
48	0.044	>10
49	0.010	1.45

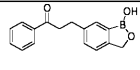
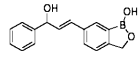
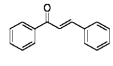
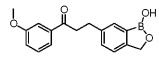
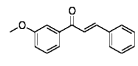
[a]IC_{50}: growth inhibition of *T. b. brucei* 427 strain (μg/mL). L929: IC_{50} against L929 cells (μg/mL). References: suramin and pentamidine.

First, 3-fluoro compound **32** showed improved activity (IC_{50} = 0.046 μg/mL) than its 4- and 2-analogues **20** and **31**. However, the substitution patterns of methyl groups (**33**, **34**, and **9**) had minimal effect on the inhibitory activity. Dichloro compound **35** gave almost comparable activity to the monochloro compound **21**. Considering the excellent potency of 4-amino compound **29**, a variety of substituents with hydrogen bonding capability was explored. The extended MOM chain structure was first installed, and the 2-MOM compound **36** gave a 4-fold decrease of activity compared to unsubstituted **8**, while the 3-MOM compound **37** gave improved activity. Aniline **38** with a 3-amino substitution showed a decreased activity (IC_{50} = 0.056 μg/mL) as compared to its 4-amino analogue **29**. Compound **40**, with a 3-OH group, showed improved inhibitory activity (IC_{50} = 0.037) as compared to its 4-OH, 2-OH, and 3,4-dihydroxy analogues **28**, **39**, and **41**. Although 4-methoxy compound **26** only showed a moderately improved activity, when the methoxy group was moved to C(3) position, compound **43** gave IC_{50} value as low as 0.022 μg/mL. Methoxy group at C(2) (compound **42**) gave decreased activity as compared to **26** and **43**. Disubstituted methoxy compounds **44** and **45** also gave good inhibitory activity (IC_{50} = 0.030; 0.037 μg/mL), however compound **45** showed significant L929 toxicity. Trisubstituted compound **46** and the cyclized disubstituted analogue **47** both showed decreased activity.

To capture the potential synergistic effect of the two lead compounds **29** and **43**, compound **49** with a combination of 3-methoxy and 4-amino functional groups was synthesized and proved to be the most potent in vitro antitrypanosomal compound in the benzoxaborole class reported to date (IC_{50} = 0.010 μg/mL). Although its L929 toxicity (IC_{50} = 1.45 μg/mL) is more significant than **29** or **43**, the "selectivity index" of compound **49** is still greater than 100.

To understand if the potent antitrypanosomal activity attributes the synergistic effect of both chalcone and benzoxaborole functional groups, compounds **50**−**52** were synthesized to evaluate the essentiality of chalcone or benzoxaborole moieties in parent structure **8**. Indeed, compounds **50** and **51**, with reduced chalcone structure, showed 4- and 3-fold decrease of inhibitory activity, and removal of the oxaborole moiety (compound **52**) also resulted in 5-fold decrease of activity. To further demonstrate the synergistic effect, the chalcone-reduced analogue and oxaborole-removed analogue of compound **43**, compounds **53** and **54**, were also synthesized and showed 31- and 18-fold decrease of antitrypanosomal activity. It is interesting to note that compounds **51**, **52**, and **54**, with altered chalcone or oxaborole structure, showed significant L929 toxicity (IC_{50} = 2.88; 6.92; 5.7 μg/mL), while their intact chalcone−benzoxaborole hybrid analogues **8** and **43** both showed satisfactory L929 toxicity above 10 μg/mL (Table 4).

Table 4. The Synergistic Effect of Chalcone−Benzoxaborole Hybrids[a]

Compd	Structure	*T. brucei* IC_{50} (μg/mL)	L929 IC_{50} (μg/mL)
50		0.331	>10
51		0.239	2.88
52		0.473	6.92
53		0.690	>10
54		0.395	5.70

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

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To evaluate the in vivo efficacy of the chalcone−benzoxaborole hybrid molecules, a total of 12 compounds were tested in a murine model of blood stage *T. brucei* infection. Mice were inoculated with 600 *T. b. brucei* 221 parasites, and treatment with compounds (50 mg/kg bid, ip) for 5 days was initiated 24 h postinfection. The unsubstituted phenyl compound **8** and its substituted analogues **20**, **21**, **22**, **26**, **30**, **33**, **37**, and **48** showed no therapeutic effect on the infected mice with zero survival rate. Thiophenyl compound **14** showed moderate in vivo efficacy with 20% survival rate. Methoxy compound **43** and the lead compound **49**, which are the most potent compounds in vitro, gave 100% survival rate and complete elimination of *T. b. brucei* parasites 30 days after infection (Figure 2A,B).

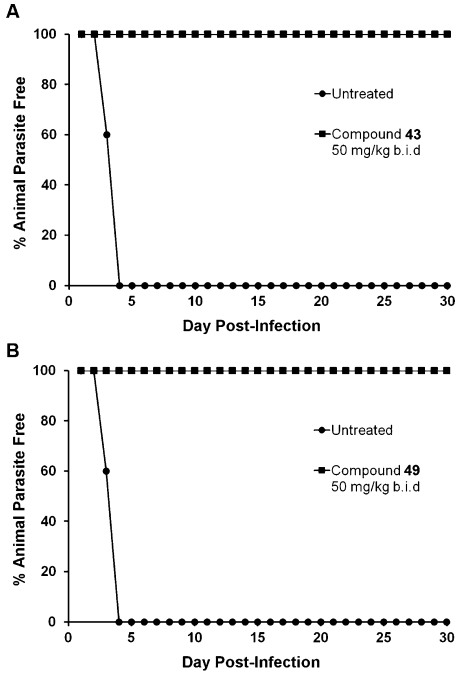

Figure 2. Female BALB/c mice were infected with 600 *T. b. brucei* 221 parasites. Treatment with compound **43** or **49** cured 100% of the mice (A and B). Dosage administered was 50 mg/kg, bid, and each testing group had five mice. Reference compound was suramin.

CONCLUSION

In conclusion, a novel class of chalcone−benzoxaborole hybrid molecules were synthesized and evaluated as antitrypanosomal agents. The most potent compound **49** with IC_{50} value of 0.010 μg/mL represents the most potent in vitro antitrypanosomal benzoxaborole compound reported to date. These compounds also possess satisfactory cytotoxicity profiles in general. Furthermore, compounds **43** and **49** demonstrated excellent in vivo efficacy in a murine infection model. However, the mechanism of action of these potent chalcone−benzoxaborole hybrids remain unknown and future efforts in the investigation of their cellular target(s) will help to eventually evaluate them as useful antitrypanosomal therapies.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Compounds 8−18, 20−39, and 41−48. Example A: (*E*)-[1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-3-phenyl]propenone (**8**). To a mixture of acetophenone (148 mg, 1.23 mmol), ethanol (8 mL), and water (1 mL) was added NaOH (197 mg, 4.92 mmol). After stirring for 5 min, compound **7** (200 mg, 1.23 mmol) was added and the reaction mixture was stirred at room temperature overnight before quenched with 1 M HCl to pH = 3−4. The resulting precipitate was collected by filtration and purified by recrystallization (hexane/ethyl acetate/THF) to obtain 105 mg of compound **8** (32.2%) as a yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09−8.03 (m, 3H), 7.91 (d, *J* = 15.9 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.63−7.49 (m, 4H), 7.42 (d, *J* = 8.4 Hz, 1H), 5.43 (s, 1H), 5.15 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 155.9, 144.9, 137.8, 133.7, 132.8, 131.1, 130.1, 128.5, 128.3, 121.6, 121.5, 71.2. HRMS-ESI: $[M + Na]^+$ $C_{16}H_{13}BO_3Na$ calcd, 287.0855; found, 287.0886; mp 146−148 °C; HPLC purity 97.6% (retention time 9.317 min). Example B: (*E*)-[3-(Biphenyl-4-yl)-1-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)]propenone (**10**). Compound **7** (80 mg, 0.49 mmol) and 4-biphenyl methyl ketone (97 mg, 0.49 mmol) were dissolved in anhydrous ethanol (15 mL) and cooled to 0 °C. To this solution under nitrogen was added 5 mL of acetyl chloride. The reaction mixture was stirred for 36 h at room temperature. Then the mixture was evaporated to its half volume (∼10 mL) and 5 mL of water was added. The resulting precipitate was collected by filtration and purified by recrystallization (hexane/ethyl acetate/THF) to obtain 31 mg of compound **10** (18.4%) as a yellow powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.31 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 2H), 8.16 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 15.6 Hz, 1H), 7.90−7.78 (m, 5H), 7.55−7.42 (m, 4H), 5.06 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.5, 156.4, 144.4, 144.1, 138.8, 136.3, 133.4, 131.3, 130.9, 129.2, 129.0, 128.3, 127.0, 126.9, 121.9, 121.6, 70.0. HRMS-ESI: $[M + Na]^+$ $C_{22}H_{17}BO_3Na$ calcd, 363.1168; found, 363.1176; mp 211−213 °C; HPLC purity 95.8% (retention time 12.754 min).

(*E*)-[1-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-3- (4-amino-3-methoxyphenyl)]propenone (49). A mixture of compound **48** (76 mg, 0.22 mmol), $SnCl_2{\cdot}_2H_2O$ (248 mg, 1.1 mmol), and ethanol (8 mL) was stirred at 60 °C for 3 h. After the mixture was cooled to room temperature, the solvent was removed by evaporation and the residue was purified by column chromatography over silica gel and further purified by preparative HPLC with a gradient of 50% H_2O/50% MeOH to 100% MeOH in 25 min to obtain 7 mg of compound **49** (10.1%) as a yellow powder. ^{1}H NMR (400 MHz, acetone-d_6): δ 8.17 (s, 1H), 8.09 (s, 1H), 7.93 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.88 (d, *J* = 15.6 Hz, 1H), 7.79−7.73 (m, 2H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.30 (s, 2H), 5.07 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.8, 155.7, 145.6, 143.8, 141.5, 133.8, 130.8, 130.5, 125.6, 124.6, 121.9, 121.8, 111.6, 109.6, 69.9, 55.3. HRMS-ESI: $[M + Na]^+$ $C_{17}H_{16}BNO_4Na$ calcd, 332.1070; found, 332.1063; mp 206−208 °C; HPLC purity 96.5% (retention time 7.536 min).

General Procedure for the Synthesis of Compounds 50 and 53. Example: 3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-1-phenylpropanone (**50**). To a solution of compound **8** (138 mg, 0.52 mmol) in methanol (6 mL) was added Pd/C (28 mg), and the reaction mixture was vacuumed and filled with hydrogen and stirred for 3 h at room temperature. The reaction mixture was filtered and evaporated. The residue was purified by preparative TLC to give 22 mg of compound **50** (15.8%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 1H), 7.99−7.97 (m, 2H), 7.65−7.61 (m, 2H), 7.54−7.50 (m, 2H), 7.40 (dd, *J* = 7.8 and 1.4 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 4.94 (s, 2H), 3.39 (t, *J* = 7.4 Hz, 2H), 2.99 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 152.0, 140.3, 136.8, 133.1, 131.7, 130.1, 128.6, 128.0, 121.2, 71.2, 40.5, 29.9. HRMS-ESI: $[M + Na]^+$ $C_{16}H_{15}BO_3Na$ calcd, 289.1012; found, 289.1016; mp 105−107 °C; HPLC purity 95.1% (retention time 9.533 min).

(*E*)-1,3-Dihydro-1-hydroxy-6-(3-hydroxy-3-phenylprop-1-enyl)-2,1-benzoxaborole (51). Compound **8** (117 mg, 0.44 mmol) was dissolved in ethanol (10 mL) and cooled to 0 °C. To this solution was added $NaBH_4$ (34 mg, 0.90 mmol). The reaction mixture was stirred for 40 min at 0 °C before being quenched with saturated NH_4Cl. After extraction with EtOAc, the organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography over silica gel and recrystallization (hexane/diethyl ether) to give 24 mg of

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compound **51** (20.4%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 1H), 7.74 (s, 1H), 7.54 (dd, J = 8.0 and 1.6 Hz, 1H), 7.42−7.29 (m, 5H), 7.26−7.22 (m, 1H), 6.68 (d, J = 15.6 Hz, 1H), 6.37 (dd, J = 16.0 and 6.4 Hz, 1H), 5.61 (d, J = 4.4 Hz, 1H), 5.27−5.25 (m, 1H), 4.96 (s, 2H). ^{13}C NMR (100 MHz, DMSO): δ 153.0, 144.4, 135.3, 133.3, 128.7, 128.1, 128.0, 126.8, 126.0, 121.5, 73.0, 69.7. HRMS-ESI: $[M + Na]^+$ $C_{16}H_{15}BO_3Na$ calcd, 289.1012; found, 289.1010; mp 178−180 °C; HPLC purity 95.2% (retention time 7.853 min).

■ ASSOCIATED CONTENT

Supporting Information

Compound characterization data and procedures for biological assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

HAT, human African trypanosomiasis; *T. brucei*, *Trypanosoma brucei*; *T. cruzi*, *Trypanosoma cruzi*; NECT, nifurtimox−eflornithine combination; bid, twice a day; ip, intraperitoneal

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