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Synthesis and structure–activity relationships of novel benzoxaboroles as a new class of antimalarial agents

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ABSTRACT

A series of boron-containing benzoxaborole compounds was designed and synthesized for a structure–activity relationship investigation surrounding 7-($HOOCCH_2CH_2$)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**1**) with the goal of discovering a new antimalarial treatment. Compound **1** demonstrates the best potency (IC_{50} = 26 nM) against *Plasmodium falciparum* and has good drug-like properties, with low molecular weight (206.00), low ClogP (0.86) and high water solubility (750 μg/mL at pH 7).

Malaria is a parasitic infection that is responsible for an estimated 250 million clinical cases and nearly 1 million deaths worldwide each year, 85% of which occur in children under the age of five. The most important causative parasite *Plasmodium falciparum* is transmitted to humans by mosquitoes and is responsible for a majority of the serious morbidity and mortality of the disease. While there are a number of effective therapeutics available, resistance to even the newest medications is appearing and is a significant concern. There is an urgent need to discover new medications that counter resistance and that are safe and easy for use in the most vulnerable populations.[1]

Previously we have reported benzoxaboroles with selective activity against fungi,[2] bacteria,[3] inflammation[4] and parasites,[5] including the trypanosome, *Trypanosoma brucei* and the filarial worm, *Brugia malayi*. As an extension of this work, we have screened our boron-containing compound collection in a whole cell assay against the malaria parasite *P. falciparum*. This screening campaign identified a number of potent hits under 1 μM, including 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**1** in Fig. 1) with an IC_{50} of 26 nM. In order to explore the SAR for this new class of boron-containing anti-malarial compounds, we synthesized a series of analogs of **1** that were designed to asses the structural features required for potent antimalarial activity. We examined a number of changes to structure **1**, including length of the side-chain on the oxaborole nucleus, the attaching positions of the side-chain, the side-chain functional groups and modifications to the benzoxaborole scaffold. Herein we report the synthesis and the SAR for in vitro potency for compounds **1–20**.

The chemistry for the synthesis of compound **1** is shown in Scheme 1. The acid **21** was converted to cyano compound **22** by amide formation followed by dehydration reaction. Bromination on the methyl of **22** and further substitution with acetate anion gave compound **23** that was catalytically boronylated to replace the bromo atom providing **24**. Hydrolysis of the acetate group of **24** followed by acidification generated the cyano boron compound **25** that was treated with Raney nickel in aqueous formic acid to give the aldehyde **26**. Final acid compound **1** was obtained by reacting **26** with 2,2-dimethyl-1,3-dioxane-4,6-dione in the presence of HCOOH and triethylamine.

Compound **2** was synthesized by the methods in Scheme 2. Reduction of the cyano group of **23** gave the aldehyde **27** that was converted to **28** via the Wittig reaction. Hydrogenation of **28** followed by treatment with acid generated the alcohol **29** that was oxidized to the aldehyde **30**. Further oxidation of **30** gave the acid **31** that was alkylated to the ester **32**. The bromo atom

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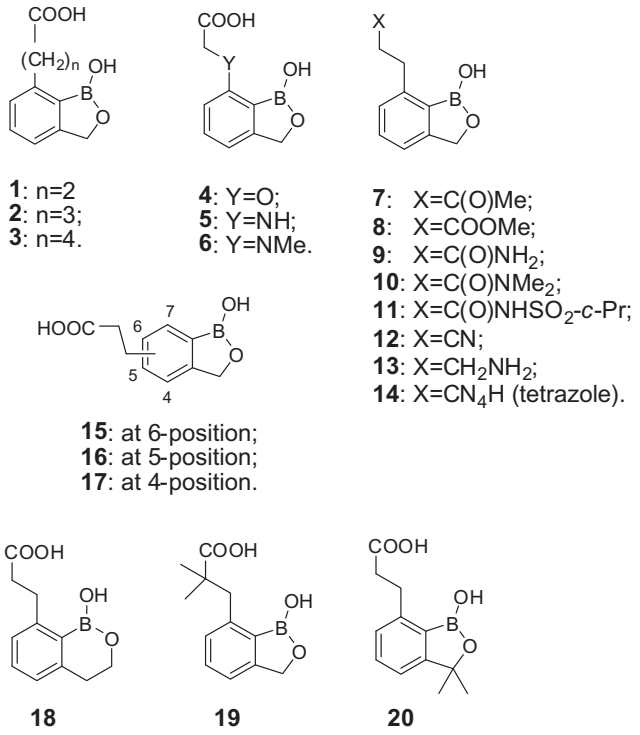
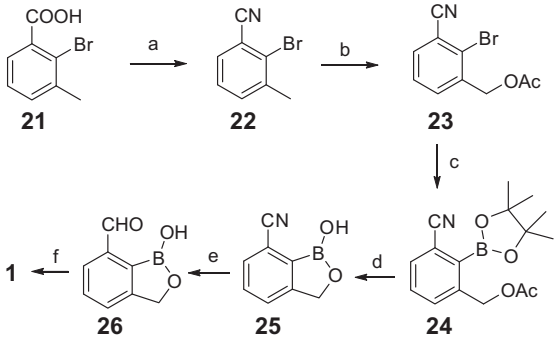


Figure 1. Chemical structures of the benzoxaborole compounds synthesized[6] during a structure–activity relationship investigation for the discovery of a new class of antimalarial agents by variations of the side-chain length (**1**–**3**), one of the side-chain CH_2 with hetero atoms such as O or N (**4**–**6**), the side chain functional group (**7**–**14**), the position of attachment of the side chain on the benzoxaborole scaffold (**15**–**17**), the oxaborole ring size (**18**) and additional substitution changes on the α-carbon next to the carboxylic group (**19**) and to oxaborole 3-position carbon (**20**).



Scheme 1. Synthesis of compound **1**. Reagents and conditions: (a) (1) *i*-PrOC(O)Cl, TEA, DCM, 0 °C, 10 min, (2) NH_4OH, 0 °C, 2 min, (3) $(CNCl)_3$, rt, 16 h; (b) (1) NBS, Bz_2O_2, CCl_4, reflux, 16 h, N_2, (2) KOAc, DMF, 80 °C, 1 h; (c) Pin_2B_2, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, reflux, 16 h, N_2; (d) (1) NaOH, MeOH, rt, 2 h, (2) HCl, H_2O, THF, rt, 50 min; (e) Raney Ni, HCOOH, H_2O, 100 °C, 1 h; (f) 2,2-dimethyl-1,3-dioxane-4,6-dione, HCOOH, TEA, reflux, 15 h.

in **32** was replaced with (pinacolato)boron group by a catalytical boronylation to give **33** which was hydrolyzed and then acidified to generate the final acid boron compound **2**.

Scheme 3 illustrates the synthesis of the long side-chain compound **3** starting from the aldehyde **26** by a Wittig reaction to provide **34** that was reduced by the hydrogenation reaction.

Synthesis of compound **4** is shown in Scheme 4. The phenol group of **35** was alkylated to introduce the side-chain of **36** that was catalytically boronylated to generate **37**. Aldehyde reduction of **37** followed by acidification provided the cyclic boron compound **38** that was hydrolyzed to give the final acid compound **4**.

Scheme 5 illustrates the chemistry for the synthesis of **5** and **6**. The amino group in **39** was converted to bromo in **40** of which the methyl group was bromonated to give **41**. This compound was transformed to the 7-amino boron compound **45** by substitution of the bromo with acetate, boronylation of **42**, hydrolysis and acidification of **43** and then reduction of **44**. Subsequent alkylation of the amino of **45** and then hydrolysis of the ester in **46** resulted in **5**. Methylation of **46** followed by hydrolysis of **47** provided the analog **6**.

The synthesis of the ketone boron compound **7** is shown in Scheme 6. Wittig reaction with **27**'s aldehyde group gave compound **48** that was reduced to provide **49**. Further boronylation of **49** followed by hydrolysis and acidification of **50** generated the final compound **7**.

Scheme 7 shows the chemistry for the synthesis of compounds **8**–**14**. Methylation of acid **1** gave ester **8** that was converted to amide **9** by treatment with NH_4OH. Also from acid **1**, compounds **10** and **11** were prepared by the corresponding amide formation reactions. Dehydration of **9** gave the cyano compound **12** which was transformed to amine **13** by reduction and to tetrazole **14** by reacting with sodium azide.

Acids **15**–**17**, the three regio-isomers of **1**, were synthesized by the methods same as that shown in Scheme 1 with the variation of the cyano substitution patterns of the starting materials.

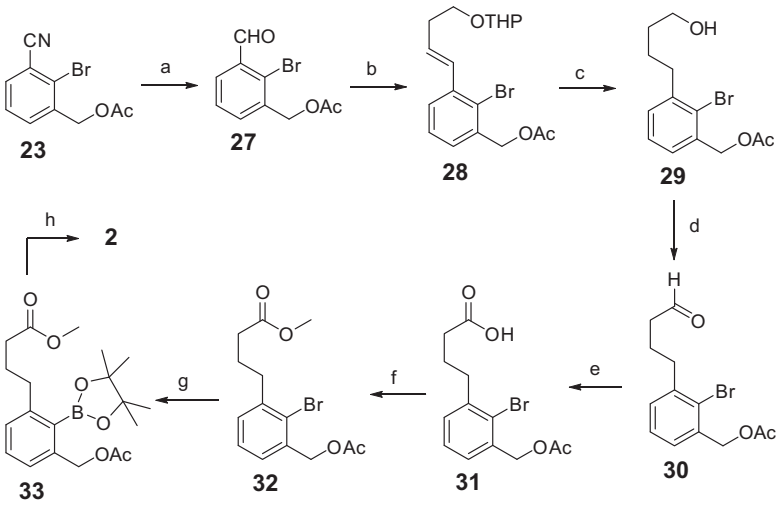
Synthesis of the six-membered ring compound **18** is illustrated in Scheme 8. Hydrolysis of the acetate group in **23** gave the alcohol **51** that was oxidized to the aldehyde **52**. Wittig reaction with **52** generated the methoxy vinyl compound **53** that was hydrolyzed to provide the one-carbon-extended aldehyde **54**. Further reduction of **54** followed by alcohol protection of **55**, catalytical boronylation of **56**, and hydrolysis and acidification of **57** provided the cyclic boron compound **58**. The cyano group in **58** was reduced to the aldehyde of **59** that went a Wittig reaction to give **60**. The final compound **18** was achieved by double bond reduction of **60** followed by ester hydrolysis and acidification of **61**.

The dimethyl-substituted compound **19** was synthesized by the method shown in Scheme 9. Substitution of the benzyl bromo in **62** by the anion generated from ethyl isobutyrate and $LiN(i\text{-}Pr)_2$ gave **63** that was reduced to the aldehyde **64**. Further boronylation of **64** gave **65** that was reduced and acidified to generate **66**. Hydrolysis and acidification of **66** finally yielded **19**.

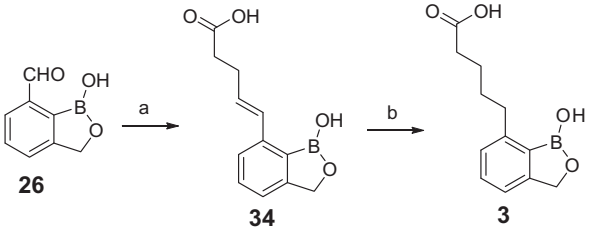
Scheme 10 illustrated the methodologies for the synthesis of compound **20**. Esterification and bromination converted **21** to **67** of which the bromo atom was replaced with hydroxyl group forming **68**. Further oxidation of the alcohol in **68**, aldehyde protection of **69**, dimethyl formation from **70** to **71**, boronylation and acidification of **71** generated compound **72** that was reacted with 2,2-dimethyl-1,3-dioxane-4,6-dione to give the final acid compound **20**.

The experimental procedures for the preparation of compounds **1**–**20** is described in the reference section.[6]

The in vitro inhibitory activity of compounds **1**–**20** against the malaria parasite *P. falciparum* was tested and their IC_{50} values are summarized in Table 1. Compounds **1**–**3** (see Fig. 1) were designed and synthesized for testing the effect of side-chain length. Compound **1** with two carbon space (C_2) between the carboxylic acid group and the benzene ring was 24-fold more potent than compound **2** with C_3 space. Additional 3-fold potency loss resulted when the space was increased to C_4 of compound **3**. The effect of side-chain atom variation is observed among compounds **1** and **4**–**6**. Replacement of the side-chain next-to-benzene CH_2 of **1** with O-atom of **4**, NH of **5** and NMe of **6** gives IC_{50} values of 0.46, 0.95 and >5 μM, respectively. The potency was sensitive to the side-chain electron change from CH_2 to O to NH, and the steric variation of the chain from NH to NMe.



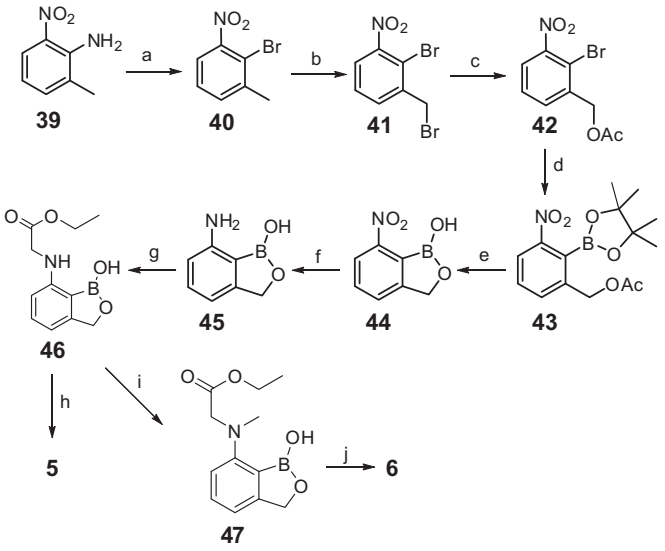
Scheme 2. Synthesis of compound **2**. Reagents and conditions: (a) Raney Ni, HCO_2H, H_2O, 100 °C, 1 h; (b) $Ph_3P{=}CHCH_2CH_2OTHP$, THF, −78 °C to rt, 20 h; (c) (1) H_2, Pd/C, EtOAc, rt, 1 h, (2) 2 N HCl, EA, MeOH, H_2O, 40 °C, 0.5 h; (d) $(COCl)_2$, DMSO, DCM, −78 °C, 15 min, then TEA, rt, 2 h; (e) 2-methylbut-2-ene, $NaClO_2$, NaH_2PO_4, *t*-BuOH, rt, 1.5 h; (f) MeI, K_2CO_3, DMF, rt, 1 h; (g) Pin_2B_2, KOAc, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, N_2, 85 °C, 16 h; (h) (1) NaOH, MeOH, rt, 2 h, (2) HCl, H_2O, THF, rt, 1 h.



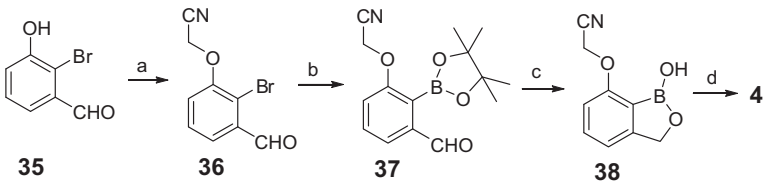
Scheme 3. Synthesis of compound **3**. Reagents and conditions: (a) $Ph_3PCH_2CH_2CH_2$ COOH bromide, NaH, DMSO, rt, 4 h; (b) H_2, Pd/C, EtOAc, rt, 1 h.

Compounds **7**–**14** were synthesized to examine the effect of side-chain terminal functional group variation. Ketone compound **7** showed weak activity with 2.72 μM IC_{50} and the methyl ester **8** had 0.32 μM IC_{50}. The primary amide **9** with 1.30 μM IC_{50} was 50-fold less potent than the acid **1** whereas addition of the dimethyl to the amide nitrogen resulted in an inactive compound **10** with IC_{50} >5 μM. Modification on the amide nitrogen with a cyclopropylsulfonyl group increased the potency by 3-fold from 1.30 μM of **9** to 0.46 μM of **11**, which has the acidic $C(O)NHSO_2$ group. Replacement of the carboxylic group in **1** by the cyano group in **12** resulted in an IC_{50} of 1.02 μM, a 39-fold potency decrease. Transformation of the cyano group to the aminomethyl of **13** and tetrazole of **14** improved the potency by 2- and 6-fold, respectively. The tetrazole compound **14** was the most potent among **7**–**14** from side chain terminal modification.

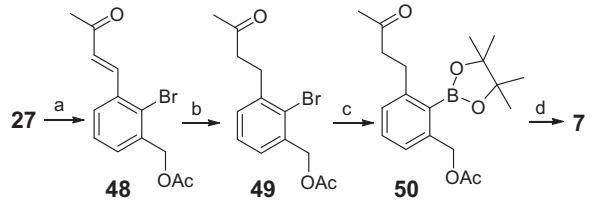
The effect of the side-chain substitution position change on antimalarial activity is clearly demonstrated among compounds **1** and **15**–**17** in a potency sequence of 7-position of **1** (26 nM) > 6-position of **15** (0.12 μM) > 5-position of **16** (2.89 μM) > 4-position of **17** (>5 μM). Expanding the ring size, that is, six-membered of **18**, decreased the activity to IC_{50} >5 μM. Dimethyl substitution on the side chain carbon next to COOH in **19** or on the 3-position of



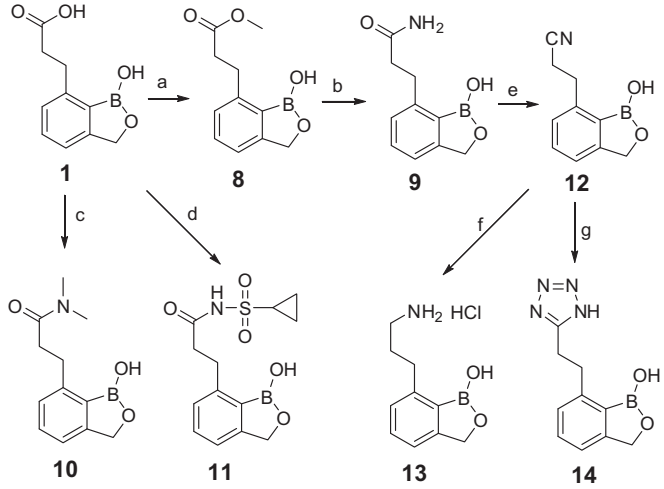
Scheme 5. Synthesis of compounds **5** and **6**. Reagents and conditions: (a) (1) $NaNO_2$, 40% aq HBr, 0 °C, 1 h, (2) CuBr, 100 °C, 1 h; (b) NBS, CCl_4, AIBN, reflux, 16 h; (c) NaOAc, DMF, 70 °C 16 h; (d) Pin_2B_2, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, 95 °C, 20 h; (e) NaOH, MeOH, rt, 24 h, then 5 N HCl, THF, 40 °C, 16 h; (f) H_2, Pd/C, rt, 2.5 h; (g) ethyl 2-bromoacetate, K_2CO_3, DMA, rt, 16 h; (h) LiOH, THF/MeOH/H_2O, rt, 2 h; (i) DMF,CH_3I, K_2CO_3, DMF, rt, 2 h; (j) LiOH, THF/MeOH/H_2O, rt, 2 h.



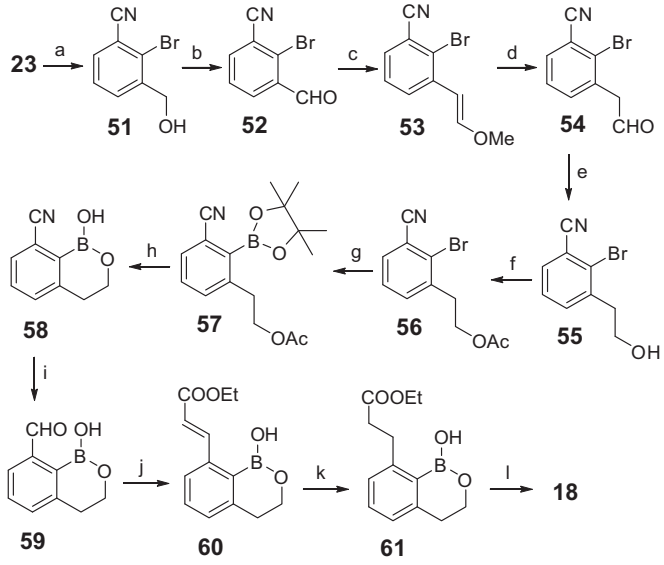
Scheme 4. Synthesis of compound **4**. Reagents and conditions: (a) $BrCH_2CN$, K_2CO_3, DMF, rt 20 h; (b) Pin_2B_2, $Pd(dppf)Cl_2$, KOAc, 1,2-DME, 90 °C 16 h; (c) $NaBH_4$, EtOH, rt, 1 h, then HCl; (d) HCl (g), MeOH, H_2O, rt, 1 h.



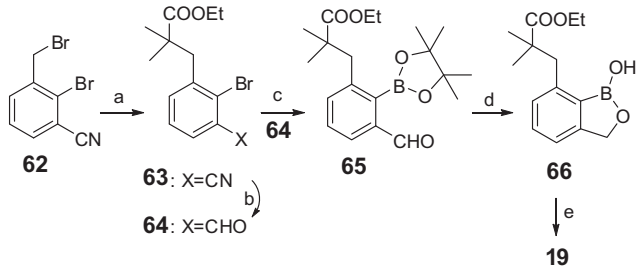
Scheme 6. Synthesis of compound **7**. Reagents and conditions: (a) $Ph_3P{=}CHCOCH_3$, PhMe, 90 °C, 1 h; (b) H_2, 10% Pd/C, EA, rt, 1 h; (c) Pin_2B_2, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, 103 °C, 16 h; (d) NaOH, MeOH, rt, 1 h, then HCl, THF.



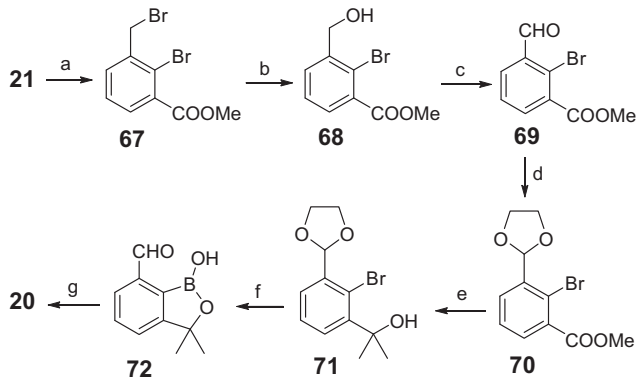
Scheme 7. Synthesis of compounds **8**–**14**. Reagents and conditions: (a) MeI, K_2CO_3, DMF, rt, 1 h; (b) NH_4OH, MeOH, 50 °C, 16 h; (c) Me_2NH HCl, EDC HCl, DIPEA, HOAt, THF, DCM, rt, 3 h; (d) (1) CDI, THF, reflux, 1 h, (2) cyclopropanesulfonamide, DBU, rt, 16 h; (e) $(CNCl)_3$, DMF, rt, 16 h; (f) H_2, Ni, NH_4OH, MeOH, rt, 1 h; (g) NaN_3, NH_4Cl, DMF, 95 °C, 3 days.



Scheme 8. Synthesis of compound **18**. Reagents and conditions: (a) LiOH, THF/MeOH/H_2O, rt 1 h; (b) PCC, DCM, rt, 2 h; (c) Ph_3PCH_2OMe chloride, *t*-BuOK, DMSO, 0 °C to rt, 16 h; (d) 6 N HCl, THF, reflux 1 h; (e) $NaBH_4$, MeOH, rt, 1 h; (f) CH_3COCl, Et_3N, DCM, 0 °C, 2 h; (g) Pin_2B_2, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, N_2, reflux, 2 h; (h) NaOH, MeOH, H_2O, then HCl, THF; (i) Raney Ni, HCO_2H, H_2O, 100 °C, 1 h; (j) $Ph_3PCH_2COOCH_2CH_3$ bromide, NaH, THF, 0 °C to rt, 16 h; (k) H_2, Pd/C, EtOAc, rt, 2 h; (l) NaOH, MeOH, H_2O, rt, 16 h, then HCl.



Scheme 9. Synthesis of compound **19**. Reagents and conditions: (a) LiN(*i*-Pr)$_2$, ethyl isobutyrate, −20 °C, 45 min; (b) Raney Ni, HCO_2H, H_2O, 100 °C, 1 h; (c) Pin_2B_2, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, N_2, 103 °C, 16 h; (d) $NaBH_4$, EtOH, 0 °C to rt, 1 h, then HCl; (e) LiOH, THF/MeOH/H_2O, rt, 16 h, then HCl.



Scheme 10. Synthesis of compound **20**. Reagents and conditions: (a) (1) $SOCl_2$, MeOH, reflux, 3 h, (2) NBS, Bz_2O_2, CCl_4, 80–85 °C, 5 h; (b) $CaCO_3$, H_2O, 1,4-dioxane, 100 °C, 5 h; (c) silica gel, PCC, DCM, 0–5 °C, 3 h; (d) $HOCH_2CH_2OH$, *p*-TsOH, toluene, reflux, 5 h; (e) MeMgBr, THF, −10 °C to rt, 16 h; (f) *n*-BuLi, THF, −78 °C, 0.5 h, then $B(OMe)_3$, −78 °C to rt, 16 h, and finally HCl, H_2O, rt, 1 h; (g) 2,2-dimethyl-1,3-dioxane-4,6-dione, HCOOH, Et_3N, 100 °C, 12 h.

Table 1
In vitro IC_{50} results of benzoxaborole compounds **1–20** against the malaria parasite *Plasmodium falciparum*[a]

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
1[b]	0.026	**11**	0.46
2	0.62	**12**	1.02
3	2.01	**13**	0.52
4	0.46	**14**	0.16
5	0.95	**15**	0.12
6	>5	**16**	2.89
7	2.72	**17**	>5
8	0.32	**18**	>5
9	1.30	**19**	>5
10	>5	**20**	>5

[a] Experimental procedure for the in vitro assay is described in the references and notes section.[7]

[b] Cytotoxicities of compound **1**: human Jurkat cell IC_{50} = 60.5 μM and human HeLa cell IC_{50} >100 μM.[8]

the oxaborole ring in **20** is expected to improve the pharmacokinetic profile of **1** by decreasing the possible glucuronidation of the carboxylic acid or by minimizing the oxidative metabolism of boron through steric hindrance of the dimethyl groups, but these substitutions resulted in loss of antimalarial activity (>5 μM).

In summary, this series of compounds is distinguished from our earlier benzoxaborole analogs[2–5] by the presence of a carboxy-substituted side chain, which appears to be associated with potent antimalarial activity. The structure–activity relationship

investigation yielded two additional compounds with $IC_{50} \leqslant 0.16$ μM against *P. falciparum*, compound **14** containing tetrazole at the terminal side-chain (0.16 μM) and compound **15** containing the side-chain at the 6-position (0.12 μM). Compound **1** demonstrated the best potency (26 nM) among this series of benzoxaborole scaffolds. It showed low cytotoxicities against human cells (Jurkat IC_{50} = 60.5 μM and HeLa IC_{50} >100 μM). This compound also has good drug-like properties with low molecular weight (206.00), low ClogP (0.86) and high water solubility (750 μg/mL at pH 7). Further study of this compound is in progress and results will be documented in future publications.

References and notes

1. (a) Enserink, M. *Science* **2010**, *328*, 844; (b) Kappe, S. H. I.; Vaughan, A. M.; Boddey, J. A.; Cowman, A. F. *Science* **2010**, *328*, 862; (c) Mackinnon, M. J.; Marsh, K. *Science* **2010**, *328*, 866; (d) Enserink, M. *Science* **2010**, *328*, 842; (e) Rottmann, M.; McNamara, C.; Yeung, B. K.; Lee, M. C.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; Gonzalez-Paez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H. P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175; (f) Medicines for Malaria Venture 2009 annual report, www.mmv.org.
2. Baker, S. J.; Zhang, Y.-K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R. K.; Sanders, V.; Plattner, J. J. *J. Med. Chem.* **2006**, *49*, 4447.
3. (a) Rock, F. L.; Mao, W.; Yaremchuk, A.; Tukalo, M.; Crépin, T.; Zhou, H.; Zhang, Y.-K.; Hernandez, V.; Akama, T.; Baker, S. J.; Plattner, J. J.; Shapiro, L.; Martinis, S. A.; Benkovic, S. J.; Cusack, S.; Alley, M. R. K. *Science* **2007**, *316*, 1759; (b) Baker, S. J.; Akama, T.; Zhang, Y.-K.; Sauro, V.; Pandit, C.; Singh, R.; Kully, M.; Khan, J.; Plattner, J. J.; Benkovic, S. J.; Lee, V.; Maples, K. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5963.
4. (a) Zhang, Y.-K.; Plattner, J. J.; Akama, T.; Baker, S. J.; Hernandez, V.; Sanders, V.; Freund, Y.; Kimura, R.; Bu, W.; Hold, K. M.; Lu, X. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2270; (b) Akama, T.; Baker, S. J.; Zhang, Y.-K.; Hernandez, V.; Zhou, H.; Sanders, V.; Freund, Y.; Kimura, R.; Maples, K. R.; Plattner, J. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2129.
5. Ding, D.; Zhao, Y.; Meng, Q.; Xie, D.; Nare, B.; Chen, D.; Bacchi, C. J.; Yarlett, N.; Zhang, Y.-K.; Hernandez, V.; Xia, Y.; Freund, Y.; Abdulla, M.; Ang, K. H.; Ratnam, J.; McKerrow, J. H.; Jacobs, R. T.; Zhou, H.; Plattner, J. J. *ACS Med. Chem. Lett.* **2010**, *1*, 165.
6. *Synthesis of 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid* (**1**): To 2-bromo-3-methylbenzoic acid (**21**, 159 g, 739 mmol) in dichloromethane (1000 mL) was added triethylamine (TEA, 119.7 mL, 813 mmol, 1.1 equiv) followed by *iso*-butyl chloroformate (101.5 mL, 813 mmol, 1.1 equiv) in dichloromethane (DCM, 200 mL) at 0 °C over 10 min. Concentrated ammonia water (323 mL) was then added at 0 °C over 2 min. The reaction mixture was poured into water (200 mL), cooled to rt and filtered. The solid was washed with water (2 × 300 mL), 0.5 N HCl (2 × 150 mL) and dried to give the amide as a solid (120 g, yield 76%). To the solution of the amide obtained (50 g, 233.6 mmol) in DMF (300 mL) was added 2,4,6-trichloro-1,3,5-triazine (64.6 g, 350.4 mmol, 1.5 equiv) dropwise at 0 °C and the reaction was stirred at rt overnight. To the reaction was added 600 mL of water and the reaction was stirred for 30 min. All insoluble was removed by filtration and the solid was triturated with ethyl acetate (EA, 3 × 100 mL) for 40 min and filtered. The filtrate was washed with saturated sodium carbonate (3 × 200 mL), saturated sodium chloride (200 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give **22** as a solid (42 g, yield 87.3%). To a solution of **22** (20 g, 102.2 mmol, 1 equiv) in CCl_4 (200 mL) was added NBS (18.2 g, 102.0 mmol, 1.0 equiv), Bz_2O_2 (0.15 g, 0.6 mmol, 0.006 equiv). The reaction was refluxed overnight under N_2, cooled and filtered. The filtrate was crystallized at 0 °C to provide the brominated intermediate (15 g, yield 53.6%). To a solution of the brominated intermediate (90 g, 327.3 mmol) in DMF (760 ml) was added KOAc (38.6 g, 393.1 mmol, 1.2 equiv). The reaction mixture was stirred at 80 °C for 1 h, cooled and water (1 L) was added. The mixture was extracted with EA (1 L). The organic layer was washed with 0.5 N HCl (3 × 200 mL), 2% $NaHCO_3$ (200 mL) and dried over anhydrous sodium sulfate. The solvent was removed to give **23** as a yellow solid (77.3 g, yield 92.9%). ^{1}H NMR of **23** (500 MHz, $CDCl_3$): δ 2.16 (s, 3H), 5.21 (s, 2H), 7.43–7.46 (t, 1H,), 7.63 (m, 2H) ppm. To a solution of **23** (20 g, 78.8 mmol) in 1,4-dioxane (400 mL) was added bis(pinacolato)diboron (30 g, 118.1 mmol, 1.5 equiv) and KOAc (33.2 g, 338.1 mmol, 4.3 equiv). After being de-gassed and backfilled with nitrogen, Pd(dppf)Cl_2 (3.2 g, 3.935 mmol, 0.05 equiv) was added. The reaction was refluxed overnight under nitrogen, cooled and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography eluted with petroleum ether (PE)/EA = 5:1 to give **24** as red oil (29 g, crude yield 100% with 80% purity). ^{1}H NMR of **24** (500 MHz, DMSO-d_6): δ 1.42 (s, 12H), 2.20 (s, 3H), 5.25 (s, 2H), 7.44–7.49 (t, 1H), 7.57–7.64 (m, 2H) ppm. To a solution of **24** (29 g) in MeOH (100 mL) was added a solution of NaOH in MeOH (7.0 g/130 mL, 175.8 mmol, 2.3 equiv) and the reaction was stirred for 2 h at rt. The reaction mixture was concentrated under vacuum and the residue was dissolved in THF (150 mL) and 2 N HCl (138 mL, 69 mmol, 0.9 equiv). The reaction was stirred at rt for 50 min, concentrated and filtered. The solid was washed with water (3 × 20 mL) and petroleum ether (3 × 20 mL) to provide **25** (7.6 g, yield 62%). ^{1}H NMR of **25** (500 MHz, DMSO-d_6): δ 5.05 (s, 2H), 7.63–7.68 (t, 1H), 7.73–7.81 (m, 2H) ppm. To Raney Ni (0.849 g, 14.5 mmol, 2.3 equiv) in formic acid (10 mL) and water (2 mL) was added **25** (1 g, 6.29 mmol) at rt. The reaction was stirred at 100 °C for 1 h, cooled and then filtered. The solvent was removed to give a solid that was purified by silica gel column chromatography eluted with CH_2Cl_2 to give **26** as a solid (0.714 g, yield 70%). ^{1}H NMR of **26** (500 MHz, $CDCl_3$): δ 10.03 (s, 1H), 8.08 (s, 1H), 7.86 (t, 1H), 7.63–7.71 (m, 2H), 5.20 (s, 2H) ppm. To a mixture of HCOOH (116.2 g, 10.0 equiv) and TEA (102.2 g, 4.0 equiv) were added **26** (40.9 g, 252.5 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (43.7 g, 1.2 equiv). The resulting mixture was refluxed for 15 h and cooled to rt. Hydrochloric acid (2 N, 320 mL) was added into the mixture that was then extracted with ethyl acetate twice (2 × 250 mL). The combined organic layer was washed with 2 N HCl (160 mL) and rotary evaporated to give the crude product that was recrystallized from DMF and 2 N HCl (34:204 mL) providing compound **1** as a white solid (15.6 g, yield 30%). An additional recrystallization from DMF and 2 N HCl (16:96 mL) was performed to give high purity product (12.9 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.02 (s, 1H), 8.95 (s, 1H), 7.37 (t, 1H), 7.13–7.22 (m, 2H), 4.96 (s, 2H), 3.00 (t, 2H), 2.54 (t, 2H) ppm. HPLC purity: 99.50% at 220 nm and 99.51% at 266 nm. MS: m/z = 205 (M−1, ESI−).

Synthesis of 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)butanoic acid (**2**): To a mixture of Raney nickel (0.533 g, 9 mmol, 2.3 equiv) in formic acid (10 mL) and water (2 mL) was added **23** (1 g, 3.9 mmol, 1.0 equiv) at rt. The reaction mixture was stirred at 100 °C for 1 h, cooled to rt and then filtered. The filtrate was concentrated in vacuum to give a solid residue that was purified by silica gel column chromatography eluted with EA/PE (1:4, v/v) to give **27** as a solid (600 mg, yield 60%). A mixture of $Ph_3PCH_2CH_2CH_2OTHP$ bromide (3.77 g, 7.78 mmol, 2.0 equiv) in THF (19.5 mL) was treated *n*-BuLi (2.644 mL, 6.61 mmol, 2.5 M in hexanes) at −78 °C, and then stirred for 1 h. Compound **27** (1 g, 3.89 mmol, 1.0 equiv) was then added, followed by removal of the cooling bath. After 20 h, the reaction mixture was diluted with ethyl acetate, and then washed with water, brine, dried over anhydrous sodium sulfate and evaporated. The crude residue was purified by column chromatography eluted with 5% EA/DCM to give **28** (1.25 g, yield 87%). To a solution of **28** (3.1 g, 8.09 mmol, 1 equiv) in EA (40 mL) was added Pd/C (310 mg, 10 wt %). The reaction flask was vacuumed and backfilled with hydrogen for three times. The reaction was stirred at rt for 1 h, filtered and evaporated. The residue was dissolved in a mixed solvents of EA, MeOH and 2 N HCl (8/15/8 mL), and then stirred at 40 °C for 0.5 h. The reaction was extracted with EA. The organic phase was washed with brine, dried over anhydrous sodium sulfate and evaporated to give a crude residue. The residue was purified by column chromatography eluted with EA/PE (30%) to give **29** (1.54 g, yield 63.4%). To a stirred solution of oxalyl chloride (480 μL, 5.6 mmol, 1.4 equiv) in DCM (28 mL) was added DMSO (513 μL, 7.2 mmol, 1.8 equiv) dropwise at −78 °C. After gas evolution was subsided, **29** (1.2 g, 4 mmol, 1.0 equiv) in DCM (5 mL) was added. After 15 min, the white suspension was treated dropwise with TEA (2.8 mL, 20 mmol, 5.0 equiv) and the cooling bath was removed and stirring was continued for 2 h. The reaction was diluted with DCM and then washed with water, brine, dried over anhydrous sodium sulfate, and evaporated to give a crude residue. The residue was purified by column chromatography eluted with EA/PE (20%) to give **30** (0.981 mg, yield 82%). To a solution of **30** (1.2 g, 4 mmol) in *tert*-butyl alcohol (28.5 mL) was added 2-methyl-2-butene (3 mL) and a solution of $NaClO_2$ (723.5 mg, 8 mmol, 2 equiv) and NaH_2PO_4 (1.872 g, 12 mmol, 3 equiv) in water (12 mL) at rt. The reaction was stirred at rt for 90 min, quenched with 1 N HCl and extracted with EA. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude was titrated with PE for 10 min and then filtered to give **31** (1.1 g, yield 87%). To a solution of **31** (1 g, 3.2 mmol, 1 equiv) in DMF (16 mL) was added potassium carbonate (0.877 g, 6.35 mmol, 2 equiv). The reaction was stirred at rt for 20 min. To the mixture was added iodomethane (987 μL, 16 mmol, 5 equiv), and the reaction was stirred at rt for 1 h. The reaction was quenched with water and extracted with EA. The organic phase was washed with 0.5 N HCl, saturated Na_2CO_3, and brine, dried over anhydrous Na_2SO_4 and filtered. The organic phase was evaporated to give a crude residue. The residue was purified by column chromatography eluted with EA/PE (20%) to give **32** (0.9 g, yield 89%). To a solution of **32** (300 mg, 0.91 mmol, 1 equiv) in 1,4-dioxane (4.55 mL) was added bis(pinacolato)diboron (277 mg, 1.09 mmol, 1.17 equiv), KOAc (384.24 mg, 4.08 mmol, 4.3 equiv). The flask was vacuumed and bubbled with nitrogen for 15 min. To the reaction mixture was added Pd(dppf)Cl_2 (74 mg, 0.09 mmol, 0.1 equiv), then vacuumed and backfilled with nitrogen. The reaction was stirred at 85 °C overnight, cooled, and filtered. The filtrate was evaporated to give a crude residue that was purified by column chromatography eluted with EA/PE (10%) to give **33** (350 mg, yield 100%). To a solution of **33** (342 mg, 0.9 mmol) in methanol was added NaOH (118 mg, 2.97 mmol, 3.3 equiv) at 0 °C, then stirred at rt for 2 h. The reaction mixture was concentrated under vacuum at 35 °C. The residue was dissolved in HCl/THF (2 N, 1.5 mL) and the reaction was stirred at rt for 1 h. The mixture was extracted with EA. The organic phase was washed with brine, dried over anhydrous sodium sulfate, and evaporated to give a crude residue that was purified by column chromatography eluted with EA/PE (30%) to give the desired final compound **2**. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.00 (br s, 1H), 8.89 (br s, 1H), 7.39–7.36 (m, 1H), 7.20 (d, 1H), 7.10 (d, 1H), 4.96 (s, 2H), 2.80–2.76 (m, 2H), 2.20–2.16 (m, 2H) and 1.84–1.77 (m, 2H) ppm; MS: m/z = 219 (M−1, ESI−).

Synthesis of 5-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)pentanoic acid (**3**): To a solution of $Ph_3PCH_2CH_2CH_2COOH$ bromide (5.3 g, 12.35 mmol,

4 equiv) in DMSO (16 mL) was added a suspension of NaH (1.18 g of 50% oil dispersion) in DMSO (19.7 mL). After being stirred for 20 min at rt, a solution of **26** (500 mg, 3.09 mmol) in DMSO (6.4 mL) was added in one portion. The reaction was stirred at rt for 4 h, quenched with saturated NH_4Cl, adjusted to pH 1–2 with 1 N HCl and extracted with EA. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography eluted with EA/PE (50%) to give **34** as a solid (120 mg, yield 16%). TLC analysis (silica gel plate, EA/PE = 1:1): R_f = 0.3. To a solution of **34** (120 mg, 0.517 mmol) in EA (2.6 mL) was added Pd/C (120 mg). The reaction was stirred under hydrogen at rt for 1 h. The reaction was filtered and the residue after rotary evaporation was purified by preparative TLC (EA/PE = 1:1) to give **3** (30 mg, yield 25%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.90 (s, 1H), 8.85 (s, 1H), 7.37 (t, 1H), 7.19 (d, 1H), 7.09 (d, 1H), 4.95 (s, 2H), 2.79 (t, 2H), 2.19 (t, 2H), 1.48–1.60 (m, 4H) ppm. Mass: m/z = 235 (M+1, ESI+).

Synthesis of 2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yloxy)acetic acid (**4**)*:* The mixture of **35** (20.3 g, 101 mmol), $BrCH_2CN$ (15.75 g, 131 mmol, 1.3 equiv) and K_2CO_3 (20.9 g, 151 mmol, 1.5 equiv) in DMF (50 mL) was stirred at rt for 20 h and water was added. The mixture was extracted with EA, dried over anhydrous Na_2SO_4, filtered and rotary evaporated to give a crude solid that was recrystallized from DCM/hexane providing **36** as light brown solid (13.2 g, yield 54%). Compound **36** (13.2 g, 55.0 mmol) was catalytically boronylated with pin_2B_2 (27.9 g, 110.0 mmol, 2 equiv), Pd(dppf)Cl_2 (2.9 g, 0.075 equiv) and KOAc (16.2 g, 165 mmol, 3 equiv) under N2 in 1,2-DME at 90 °C for 16 h. Normal work-up gave **37** as a yellow solid (10.92 g, yield 69%). Compound **37** (1.02 g, 4 mmol) in MeOH (10 mL) was reduced with $NaBH_4$ (0.18 g, 4.8 mmol, 1.2 equiv) at 0 °C for 1 h. Then DCM (5 mL) and HCl (2 N) were added to pH = 3 and the mixture was stirred at 0 °C for 1 h. Normal work-up provided crude **38** that was purified by silica gel column chromatography (2% MeOH/DCM) giving **38** as a white solid (0.26 g, yield 34%). Gas of HCl was bubbled through a solution of **38** (0.132 g, 0.67 mmol) in MeOH/H_2O (8:2, 25 mL) at 0 °C for 5 min and the mixture was stirred at 0 °C for 10 min and at rt for 1 h. Removal of MeOH and then the pH was adjusted to 6 resulting in white precipitates which was collected and washed with ether to give the final compound **4** (0.105 g, yield 76%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.38 (t, 1H), 6.98 (d, 1H), 6.77 (d, 1H), 4.90 (s, 2H), 4.13 (s, 2H) ppm. HPLC purity: 92.8% at 220 nm and 95.5% at 282 nm. MS: m/z = 207 (M−1, ESI−).

Synthesis of 2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-ylamino)acetic acid (**5**)*:* The suspension of **39** (30.4 g, 0.2 mol) in water (250 mL) and HBr (100 mL, 40% aq) was refluxed for 10 min and then was cooled to 0 °C. A solution of $NaNO_2$ (13.8 g, 0.2 mol) in water (80 ml) was added dropwise at <5 °C. The dizaonium solution was stirred for a further 30 min at 0–5 °C and then added slowly to a stirring mixture of CuBr (28.7 g, 0.2 mol) in HBr (80 mL) and water (150 mL) at rt. The mixture was stirred at rt for 30 min and then on a steam-bath for 1 h. The mixture was washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography with petroleum ether as eluent to give **40** as a pale yellow solid (25.9 g, yield 60%). The mixture of **40** (14.3 g, 0.066 mol), NBS (17.7 g, 0.099 mol) and AIBN (0.3 g, 1.8 mmol) in CCl_4 (250 ml) was refluxed overnight. The mixture was filtered and the filtrate was concentrated to give **41** as a red liquid (21 g). The mixture of **41** (21 g) and NaOAc (16.4 g, 0.2 mol) in DMF (300 mL) was stirred at 70 °C overnight, and then diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography with PE/EA (20:1, v/v) as eluent to give **42** as a white solid (7.7 g, 42% over two steps). To the solution of **42** (16.5 g, 0.06 mol) in 1,4-dioxane (250 mL) was bubbled with nitrogen for 20 min. Potassium acetate (20.6 g, 0.21 mol), Pd (dppf)Cl_2 (3.92 g, 4.8 mmol) and bis(pinacolato)diboron (22.9 g, 0.09 mol) were added and the reaction mixture was stirred under N_2 at 95 °C for 20 h. The reaction mixture was then cooled and evaporated. The residue was partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography with PE/EA (20:1, v/v) as eluent to give **43** as a yellow oil (9.9 g, 51%). MS: m/z = 322 (M+1, ESI+). To the solution of **43** (9.9 g, 0.03 mol) in methanol (300 mL) was added NaOH (5 N, 12 mL, 0.06 mol). The reaction mixture was stirred and refluxed under nitrogen for 24 h. It was then concentrated under vacuum and the residue was dissolved in THF (100 mL). HCl (5 N, 60 mL, 0.3 mol) was added and the reaction mixture was stirred and heated at 40 °C for 16 h. It was cooled, diluted with EtOAc and poured into brine. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was recrystallized from the mixed solvents of EA and PE to give **44** as a yellow solid (3.8 g, yield 71%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.99 (s, 1H), 8.01 (d, 1H), 7.81 (m, 2H), 5.05 (s, 2H) ppm. MS: m/z = 180 (M+1, ESI+). To the solution of **44** (0.92 g, 5.1 mmol) in MeOH (50 mL) was added Pd/C (0.5 g) and the hydrogenation was conducted at one atmosphere and rt for 2.5 h to provide the desired product **45** as a solid (0.68 g, yield 88%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.78 (s, 1H), 7.10 (t, 1H), 6.47 (d, 1H), 6.39 (d, 1H), 5.32(s, 2H), 4.82(s, 2H) ppm. MS: m/z = 150 (M+1, ESI+). To a mixture of **45** (800 mg, 5.37 mmol) and K_2CO_3 (2.23 g, 0.0161 mol) in *N*,*N*-dimethylacetamide (17.9 mL) was added ethyl bromoacetate (0.623 mg, 3.76 mmol). The reaction was stirred overnight at rt. It was diluted with water and extracted with EA. The organic layer was washed with 2 N HCl, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography eluted with EA/DCM (10%) to give the desired product **46** as a solid (380 mg, yield 30%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.20 (t, 1H), 6.60 (d, 1H), 6.25 (d, 1H), 5.63 (s, 1H), 4.86 (s, 2H), 4.14 (q, 2H), 3.80 (s, 2H), 1.20 (t, 3H) ppm. The mixture of **46** (30 mg, 0.127 mmol) and LiOH·H_2O (10.7 mg, 0.255 mmol) in THF/MeOH/H_2O = 3:2:1 (0.51 mL) was stirred for 2 h. The mixture was purified by preparative TLC (EA/PE = 1:1) to give the desired final compound **5** as a solid (11 mg, yield 42.3%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.99 (s, 1H), 7.19 (s, 1H), 6.53 (d, 1H), 6.23 (s, 1H), 5.72 (s, 1H), 4.83 (s, 2H), 3.75 (s, 2H) ppm. MS: m/z = 205.8 (M−1, ESI−).

Synthesis of 2-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl) (methyl)amino) acetic acid (**6**): To the mixture of **46** (100 mg, 0.435 mmol) and K_2CO_3 (176 mg, 1.27 mmol) in DMF (2.1 mL) was added CH_3I (302 mg, 2.12 mmol). The reaction was stirred for 2 h, diluted with water and extracted with EA. The organic layer was washed with 0.5 N HCl, brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (EA/PE = 1:1) to give **47** (39 mg, yield 37%) as a solid. ^{1}H NMR (500 Hz, DMSO-d_6): δ 9.03 (s, 1H), 7.28 (t, 1H), 6.70 (d, 1H), 6.57 (d, 1H), 4.87 (s, 2H), 4.46 (s, 2H), 4.05 (q, 2H), 2.95 (s, 3H), 1.15 (t, 3H) ppm. Mass: m/z = 250 (M−1, ESI−). The mixture of **47** (60 mg, 0.24 mmol) and LiOH·H_2O (20.2 mg, 0.255 mmol) in THF/MeOH/H_2O = 3:2:1 (0.936 mL) was stirred for 2 h. The mixture was purified by preparative TLC (EA/PE = 1:1) to give **6** (17 mg, yield 34.9%) as a solid. ^{1}H NMR (300 Hz, DMSO-d_6): δ 9.05 (s, 1H), 7.26 (t, 1H), 6.67 (d, 1H), 6.56 (d, 1H), 4.86 (s, 2H), 4.39 (s, 2H), 2.96 (s, 3H) ppm. Mass: m/z = 220 (M−1, ESI−).

Synthesis of 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)butan-2-one (**7**): To a solution of **27** (1 g, 3.9 mmol) in toluene (30 mL) was added the Wittig reagent $Ph_3P{=}CHC(O)CH_3$ (1.48 g, 5 mmol, 1.3 equiv). The reaction was stirred at 90 °C for 1 h. The residue after rotary evaporation was purified by column chromatography to give the desired product **48** (0.5 g, 43.5% yield). TLC analysis (silica gel plate, EA/PE = 1:9): R_f = 0.2. To a solution of **48** (2.1 g, 7.06 mmol) in EA (35 mL) under nitrogen was added Pd/C (600 mg). The reaction vessel was vacuumed and backfilled with H_2 for three times. The reaction was stirred at rt for 1 h, filtered and evaporated. The residue was purified by column chromatography to give **49** (1.1 g, 53% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.30 (m, 3H), 5.11 (s, 2H), 2.91 (t, 2H), 2.76 (t, 2H), 2.10 (s, 3H), 2.08 (s, 3H) ppm. To a solution of **49** (500 mg, 1.67 mmol) in 1,4-dioxane (8.4 mL) was added KOAc (709 mg, 7.22 mmol, 4.3 equiv), bis(pinacolato)diboron (640 mg, 2.52 mmol, 1.5 equiv) and Pd(dppf)Cl_2 (137 mg, 0.167 mmol, 0.1 equiv). The reaction vessel was vacuumed, backfilled by N_2 for three times and stirred at 103 °C overnight. The reaction was filtered and evaporated. The residue was purified by column chromatography to give **50** (600 mg, 100% yield). To a solution of **50** (580 mg, 1.67 mmol) in MeOH (5 mL) was added NaOH (154 mg, 3.86 mmol, 2.3 equiv). The reaction was stirred at rt for 1 h and then rotary evaporated. THF (2.5 mL) and 2 N HCl (2.4 mL) were added. The reaction was stirred at rt for 0.5 h and then extracted with EA. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography (EA/PE = 1:1) to give the final compound **7** as a slight yellow solid (50 mg, yield 15%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.36 (t, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 4.95 (s, 2H), 2.9 (t, 2H), 2.76 (t, 2H), 2.08 (s, 3H) ppm; HPLC purity: 99.6% at 220 nm and 100% at 254 nm; MS: m/z = 227.2 (M+23, ESI+).

Synthesis of methyl 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl) propanoate (**8**): To a solution of **1** (300 mg, 1.45 mmol) in DMF (7 mL) was added K_2CO_3 (501 mg, 3.625 mmol, 2.5 equiv). The reaction was stirred at rt for 10 min and then CH_3I (907 μL, 14.56 mmol, 10 equiv) was added. The reaction was stirred at rt for 1 h and quenched with 1 N HCl and extracted with *t*-butyl methyl ether (TBME). The organic phase was washed with saturated $NaHCO_3$, then brine, dried over anhydrous Na_2SO_4 and filtered. The residue after rotary evaporation was purified by column chromatography (EA/PE = 1:2) to give the desired product as white solid (220 mg, yield 69%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.40 (t, 1H), 7.21 (d, 1H), 7.15 (d, 1H), 4.96 (s, 2H), 3.81 (s, 3H), 3.00 (t, 2H), 2.65 (t, 2H) ppm. Mass: m/z = 221.1 (M+1, ESI+).

Synthesis of 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanamide (**9**): To a solution of **8** (1 g, 4.5 mmol, 1 equiv) in MeOH (22 mL) was added NH_4OH (20 mL, 337.5 mmol, 75 equiv). The reaction was stirred at 50 °C overnight and evaporated. EA (100 mL) was added and the organic phase was washed with 0.1 N HCl, then brine, dried over anhydrous Na_2SO_4 and filtered. The residue after rotary evaporation was stirred in Et_2O and filtered to give the amide compound **9** as white solid (700 mg, yield 82%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.38 (t, 1H), 7.24 (br s, 1H), 7.21 (d, 1H), 7.14 (d, 1H), 6.76 (br s, 1H), 4.95 (s, 2H), 2.98 (t, 2H), 2.37 (t, 2H) ppm. Mass: m/z = 206.5 (M+1, ESI+).

Synthesis of 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)-N,N-dimethyl-propanamide (**10**): To a mixture of **1** (100 mg, 0.485 mmol) in THF (2.4 mL) and DCM (2.4 mL) were added DIPEA (344.8 mg, 2.66 mmol, 5.5 equiv), EDC·HCl (200 mg, 1 mmol, 2 equiv), HOAt (79 mg, 0.58 mmol, 1.2 equiv) and dimethylamine hydrochloride (180 mg, 2.2 mmol, 4.5 equiv). The reaction mixture was stirred at room temperature for 3 h, evaporated, and then EA (20 mL) was added. The organic phase was washed with 1 N HCl, brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by preparative TLC (EA/PE = 1:1) to give **10** (56 mg, yield 50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.94 (s, 1H), 7.37 (t, 1H), 7.21 (m, 1H), 7.14 (d, 1H), 4.95 (s, 2H), 2.95 (t, 2H), 2.93 (s, 3H), 2.81 (s, 3H), 2.49 (t, 2H). Mass: m/z = 234 (M+1, ESI+).

Synthesis of N-(cyclopropylsulfonyl)-3-(1-hydroxy-1,3-dihydrobenzo[c] [1,2]oxaborol-7-yl) propanamide (**11**): The mixture of **1** (0.377 g, 1.83 mmol) and CDI (0.892 g, 5.5 mmol, 3 equiv) in THF (15 mL) was refluxed for 1 h. After being cooled down to rt, the solution was transferred with a syringe into a solution of cyclopropanesulfonamide (0.667 g, 5.5 mmol, 3 equiv) in THF (5 mL), followed by addition of DBU (0.56 g, 3.66 mmol, 2 equiv). The resulting mixture was stirred overnight, quenched with 1 N HCl and extracted with EtOAc (100 mL). The organic layer was concentrated and the residue was purified by preparative HPLC (column: Luna 300 × 50.0 mm, 10μ; liquid phase: [A—H_2O; B—CH_3CN + 0.1% TFA] B%: 18–48%, 25 min) and freeze-dried to afford the compound **11** (270 mg, yield 48.2%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.57 (s, 1H), 8.97 (s, 1H), 7.39–7.34 (m,

1H), 7.21 (d, 1H), 7.14–7.12 (d, 1H), 4.95 (s, 2H), 3.01 (t, 2H), 2.92–2.89 (m, 1H), 2.59 (t, 2H), 1.05–1.03 (m, 4H) ppm. HPLC purity: 99.58% at 220 nm and 100% at 254 nm.

Synthesis of 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanenitrile (**12**): To a solution of **9** (700 mg, 3.414 mmol) in DMF (17 mL) was added $(CNCl)_3$ (945 mg, 5.1 mmol, 1.5 equiv). The reaction was stirred at rt overnight, quenched with water and extracted with EA. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The residue after rotary evaporation was purified by column chromatography to give the cyano compound **12** as white solid (370 mg, yield 58%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.07 (s, 1H), 7.41 (t, 1H), 7.27 (d, 1H), 7.21 (d, 1H), 4.98 (s, 2H), 3.06 (t, 2H), 2.80 (t, 2H) ppm. MS: m/z = 186 (M−1, ESI−).

Synthesis of 7-(3-aminopropyl)benzo[c][1,2]oxaborol-1(3H)-ol HCl salt (**13**): To a solution of **12** (70 mg, 0.37 mmol) in MeOH (2 mL) was added Raney Ni (21 mg) and NH_4OH (140 μL). The reaction flask was vacuumed and backfilled with H_2 for three times. The reaction was stirred at rt for 1 h. The reaction was filtered and evaporated. The residue was purified by preparative TLC and treated with HCl to give **13** as HCl salt (19 mg, yield 27%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.86 (br s, 3H), 7.41 (t, 1H), 7.24 (d, 1H), 7.14 (d, 1H), 4.98 (s, 2H), 2.84–2.73 (m, 4H), 1.85 (t, 2H) ppm. Mass: m/z = 193 (M−1, ESI−).

Synthesis of 7-(2-(1H-tetrazol-5-yl)ethyl)benzo[c][1,2]oxaborol-1(3H)-ol (**14**): To a solution of **12** (130 mg, 0.695 mmol) in DMF (3.5 mL) were added NaN_3 (76.8 mg, 1.18 mmol, 1.7 equiv) and NH_4Cl (63.13 mg, 1.18 mmol, 1.7 equiv). The reaction was stirred at 95 °C for 3 days, quenched with 0.5 N HCl and extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by preparative TLC plate (EA/PE = 1:2) to give the tetrazole compound **14** (20 mg, yield 12.5%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 15.9 (br s, 1H), 8.96 (s, 1H), 7.36–7.24 (m, 1H), 7.20 (d, 1H), 7.04 (d, 1H), 4.97 (s, 2H), 3.40 (m, 4H) ppm. Mass: m/z = 231 (M+1, ESI+) and 229 (M−1, ESI−).

Synthesis of 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl) propanoic acid (**15**): This compound was synthesized starting with 3-bromo-4-methylbenzonitrile by the method similar to that used for the synthesis of **1**. Compound **15** was obtained as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.08 (s, 1H), 9.09 (s, 1H), 7.56 (s, 1H), 7.32 (m, 2H), 4.94 (s, 2H), 2.86 (t, 2H), 2.53 (t, 2H) ppm. MS: m/z = 205 (M−1, ESI−). HPLC purity: 95.64% at 220 nm and 95.78% at 254 nm.

Synthesis of 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl) propanoic acid (**16**): This compound was synthesized starting with 4-bromo-3-methylbenzonitrile by the method similar to that used for the synthesis of **1**. Compound **16** was obtained as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.13 (s, 1H), 9.10 (s, 1H), 7.64 (d, 1H), 7.22 (m, 2H), 4.97 (s, 2H), 2.87 (t, 2H), 2.58 (t, 2H) ppm. Mass: m/z = 205 (M−1, ESI−).

Synthesis of 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-4-yl) propanoic acid (**17**): This compound was prepared starting with 3-bromo-2-methylbenzonitrile by the method similar to that described for **1**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.10 (s, 1H), 9.08 (s, 1H), 7.57 (d, 1H), 7.29 (m, 2H), 5.03 (s, 2H), 2.76 (t, 2H), 2.53 (t, 2H) ppm. Mass: m/z = 205 (M−1, ESI−). Purity: 96.72% at 220 nm.

Synthesis of 3-(1-hydroxy-3,4-dihydro-1H-benzo[c][1,2]oxaborinin-8-yl) propanoic acid (**18**): To the solution of **23** (26.0 g, 0.103 mol) in THF/MeOH/H_2O (55:50:100 mL) was added LiOH·H_2O (17.3 g, 0.411 mol, 4 equiv). The mixture was stirred for 1 h and concentrated. DCM was added. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was washed with PE to give the product **51** (16.2 g, yield 80%). To the mixture of **51** (14.2 g, 67 mmol) and silica gel (14.2 g) in DCM (268 mL) was added PCC (21.6 g, 0.1005 mol, 1.5 equiv). The mixture was stirred for 2 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography to give the desired product **52** (11.8 g, 84.2%) as a solid. To the solution of **52** in DMSO (75 mL) were added Ph_3PCH_2OMe chloride (29.4 g, 3.6 equiv) in DMSO (75 ml) and *t*-BuOK (9 g, 3.4 equiv) in one portion. The mixture was stirred for 1 h at rt and **52** (5 g, 1 equiv) in DMSO (50 mL) was added in one portion at 0 °C, and then stirred overnight. The reaction solution was poured into water, extracted with EA, washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column to give **53** (4.1 g, yield 72%) as a yellow solid. TLC (silica gel plate, PE/EA = 10:1): R_f = 0.45. To the solution of **53** (2 g, 8.37 mmol) in THF (42 mL) was added HCl (6 N, 14 mL) at rt and the reaction was refluxed for 1 h. The reaction was cooled, poured into water, extracted with EA, washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated to give **54** (2.54 g) as crude oil. TLC (silica gel plate, PE/EA = 10:1): R_f = 0.2. To the solution of **54** (2.54 g) in methanol (20 mL) was added $NaBH_4$ (319 mg, 1 equiv) in portions for 10 min. The solution was stirred for 1 h and water (50 mL) was added for 10 min. The solution was extracted with EA, washed with water, dried over Na_2SO_4 and evaporated to give **55** (2.41 g) as crude oil. TLC (silica gel plate, PE/EA = 3:1): R_f = 0.3. To the solution of **55** (2.41 g) and Et_3N (1.2 g, 1.1 equiv) in DCM (35 mL) was added acetyl chloride (0.84 g, 1 equiv) dropwise at 0 °C. The reaction was stirred at 0 °C for 2 h and water (50 mL) was added to the reaction solution. The solution was extracted with EA and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by silica gel column (PE/EA = 10:1) to give the product **56** (2.2 g, 98% of three steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, 1H), 7.48 (d, 1H), 7.37 (t, 1H), 4.32 (t, 2H), 3.15 (t, 2H), 2.03 (s, 1H) ppm. To the mixture of **56** (1 g), pin_2B_2 (1.04 g, 1.1 equiv) and KOAc (0.73 g, 2 equiv) in 1,4-dioxane (20 mL) was added Pd(dppf)Cl_2 (100 mg, 5% equiv) under N_2. The reaction was refluxed for 2 h. The reaction solution was cooled to rt, poured into water (50 mL) and extracted with EA. The organic phase was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column (PE/EA = 10:1) to give **57** (0.9 g) as a colorless oil. TLC (silica gel plate, PE/EA = 3:1): R_f = 0.7. To the solution of **57** (1 g) in MeOH (20 mL) was added NaOH (0.254 g, 2 equiv) in one portion at 0 °C. The reaction solution was stirred at rt for 1 h. MeOH was rotary evaporated to give a residue that was mixed with HCl (6 N, 1.1 mL). The reaction was stirred overnight, quenched with NaOH (1 N, 10 mL), washed with EA. The aqueous phase was acidified with HCl (1 N) to pH 1–2 and extracted with EA. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give **58** (540 mg, yield 51%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.84 (s, 1H), 7.67 (d, 1H), 7.54 (m, 2H), 4.07 (t, 2H), 2.94 (t, 2H). MS: m/z = 174 (M+1, ESI+). To the solution of **58** (540 mg, 3.12 mmol) in HCOOH/water (5.4:0.54 mL) was added Raney Ni. The reaction was stirred at 100 °C for 1 h, cooled to rt, quenched with water and extracted with EA. The organic phase was washed with water, brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column (PE/EA = 3:1) to give **59** (460 mg, 85%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.69 (s, 1H), 9.01 (s, 1H), 7.74 (q, 1H), 7.54 (m, 2H), 4.09 (t, 2H), 2.96 (t, 1H) ppm. MS: m/z = 177 (M+1, ESI+). To the solution of $Ph_3PCH_2COOCH_2CH_3$ bromide in THF (6 mL) was added NaH (60%, 68 mg, 3 equiv). The reaction was stirred under N_2 for 1 h at rt. Compound **59** (100 mg, 1 equiv) in THF (2 mL) was added in one portion at 0 °C. The mixture was stirred overnight, quenched with water (10 mL) and HCl (1 N 10 mL), extracted with EA. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column (PE/EA = 10:1–3:1) to give **60** (140 mg, yield 98%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.73 (s, 1H), 8.70 (d, 1H), 7.70 (d, 1H), 7.42 (t, 1H), 7.26 (d, 1H), 6.45 (d, 1H) 4.30 (q, 2H), 4.03 (t, 2H), 2.89 (t, 2H), 1.20 (t, 3H) ppm. MS: m/z = 255 (M+23, ESI+). The mixture of **60** (60 mg, 0.24 mmol) and Pd/C (10% 10 mg) in MeOH (20 mL) was stirred under H_2 for 2 h. The reaction solution was filtered and concentrated to give **61** as oil (54 mg, yield 90%). TLC (PE/EA = 3:1): R_f = 0.5. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.40 (s, 1H), 7.26 (t, 1H), 7.04 (m, 2H), 4.00 (m, 4H), 3.15 (t, 2H), 2.83 (t, 2H) 2.56 (t, 2H), 1.15 (t, 3H). MS: m/z = 249 (M+1, ESI+). To the solution of **61** (50 mg) in MeOH/H_2O (10/1 mL) was added NaOH (50 mg, 6 equiv) in one portion. The mixture was stirred overnight at rt, quenched with NaOH (1 N, 5 mL) and washed with EA. The aqueous phase was acidified with 1 N HCl to pH 1–2, extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column to give the product **18** (17 mg, yield 38% over 2 steps) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.41 (s, 1H), 7.25 (t, 1H), 7.05 (m, 2H), 3.98 (t, 2H), 3.07 (t, 2H), 2.82 (t, 2H), 2.48 (t, 2H) ppm. MS: m/z = 243 (M+23, ESI+) and 463 (2 M+23).

Synthesis of 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)-2,2-dimethyl propanoic acid (**19**): To a solution of *i*-Pr_2NH (3.44 mL, 24.55 mmol, 2.25 equiv) in THF (15 mL) was added *n*-BuLi (7.84 mL, 19.6 mmol, 1.8 equiv) dropwise at −78 °C under N_2. The reaction was stirred at −20 °C for 20 min. To the reaction was added, a solution of ethyl isobutyrate (2.2 mL, 16.36 mmol, 1.5 equiv) in THF (2 mL) over 10 min. The reaction was stirred for 45 min, and then the solution of **62** (3 g, 10.9 mmol, 1 equiv) in THF (12 mL) was added. The reaction was stirred at −20 °C for 45 min, quenched with saturated NH_4Cl and extracted with EA. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography to give **63** (3.2 g, yield 97.5%). A mixture of Raney Ni (4 g), **63** (4 g, 12.9 mmol) in HCOOH and water (20/2 mL) was stirred at 100 °C for 1 h. The reaction was cooled and filtered. The residue after rotary evaporation was purified by column chromatography to give **64** as a solid (3.2 g, yield 80%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.32 (s, 1H), 7.71 (m, 1H), 7.75 (m, 2H), 4.09 (q, 2H), 3.16 (s, 2H), 1.01–1.23 (m, 9H). To a solution of **64** (2 g, 6.4 mmol) in 1,4-dioxane (32 mL) was added KOAc (2.7 g, 27.5 mmol, 4.3 equiv), pin_2B_2 (2.44 g, 9.6 mmol, 1.5 equiv) and Pd(dppf)Cl_2 (522 mg, 0.64 mmol, 0.1 equiv). The reaction was vacuumed and backfilled by N_2 for three times. The reaction was stirred at 103 °C overnight, filtered and evaporated. The residue was purified by column chromatography eluted with EA/PE (1:3) to give **65** (2.4 g, yield 100%). To a solution of **65** (2.3 g, 6.4 mmol) in EtOH (32 mL) was added $NaBH_4$ (0.241 g, 6.4 mmol, 1 equiv) at 0 °C. The reaction was stirred at rt for 1 h, quenched with 0.5 N HCl and extracted with EA. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography eluted with EA/PE (1:2) to give **66** (900 mg, yield 56%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.93 (s, 1H), 7.38 (t, 1H), 7.21 (d, 1H), 6.97 (d, 1H), 4.95 (s, 2H), 4.02 (m, 2H), 3.06 (s, 2H), 1.01–1.23 (m, 9H) ppm. MS: m/z = 264 (M+1, ESI+). To a mixture of **66** (350 mg, 1.335 mmol) in THF/MeOH/water = 3:2:1 (6.6 mL) was added LiOH (224 mg, 5.34 mmol, 4 equiv). The reaction was stirred at rt overnight and then evaporated. The residue was acidified with 0.5 N HCl and extracted with EA. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by preparative TLC to give the acid **19** (22 mg, yield 7%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.19 (s, 1H), 8.92 (s, 1H), 7.36 (t, 1H), 7.23 (d, 1H), 7.08 (d, 1H), 4.96 (s, 2H), 3.06 (s, 2H), 1.05 (s, 6H) ppm. MS: m/z = 233 (M−1, ESI−).

Synthesis of 3-(1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo[c][1,2] oxaborol-7-yl)propanoic acid (**20**): To a solution of **21** (150 g, 697.5 mmol) in MeOH (1350 mL) was added $SOCl_2$ (165.0 g, 2.0 equiv) dropwise at 5–10 °C. The mixture was refluxed for 3 h and then MeOH was removed. EA was added to extract the product and the EA layer was washed by water, Na_2CO_3/H_2O, separated and concentrated to give the methyl ester as orange oil (158.7 g, yield 99.5%). HPLC purity is 96%. To a 2 L 3-necked flask were added the methyl ester obtained (158.7 g), CCl_4 (1440 mL), NBS (128.7 g, 1.05 equiv) and BPO (8.4 g, 0.05 equiv). The mixture was heated to 80–85 °C, stirred for 5 h, cooled to rt and filtrated. After removal of solvent, EA was added into the residue, washed with 2 N $Na_2S_2O_3$, concentrated to give **67** as orange oil (229.5 g, yield 100%). $CaCO_3$ (166.3 g, 2.4 equiv) was added into the solution of **67** (229.5 g) in a mixed solvent of THF (1380 mL) and H_2O (1380 mL). The mixture was stirred at 100 °C for 5.0 h, cooled

to rt, filtered, extracted with EA, concentrated to give the crude **68** as orange oil (199.0 g) that was purified by a short silica gel column to give **68** with 100% HPLC purity as yellow solid (89.4 g, yield 52.6%). Silica gel (152.5 g) was added into the solution of **68** (152.5 g) in DCM (2280 mL). PCC (201.0 g, 1.5 equiv) was added in portions at 0–10 °C and the mixture was stirred for 3 h. The solvent was removed to give the crude **69** (163.0 g) that was purified by a short silica gel column to give **69** as black oil (142.7 g, yield 94.4%). Pyridinium *p*-toluenesulfonate (PPTS, 14.7 g, 0.1 equiv) was added into the solution of **69** (142.7 g) in toluene (2.8 L) and ethylene glycol (72.9 g, 2.0 equiv). The mixture was stirred at 130 °C for 5.0 h, cooled to 40 °C and concentrated. The residue was purified by a short silica gel column to give **70** as yellow oil (160.1 g, yield 95.0%). To a solution of **70** (5 g, 17.48 mmol) in dry THF (90 mL) was added CH_3MgI (25 mL, 4 mol/L) dropwise at −10 °C. The mixture was stirred overnight warming to rt, quenched by $NaHCO_3$ and extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EA = 4:1) to give **71** (4.2 g, yield 84%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 1H), 7.53 (d, 1H), 7.33 (t, 1H), 6.23 (s, 1H), 4.18–4.05 (m, 4H), 2.81 (s, 1H), 1.78 (s, 6H). MS: m/z = 287 and 289 (M+1, ESI+). To a solution of **71** (4.2 g, 14.634 mmol) in dry THF (70 mL) was added *n*-BuLi (12.3 mL, 2.5 M, 2.1 equiv) dropwise at −78 °C under N_2 and stirred for 30 min. Trimethyl borate (3.2 mL, 2 equiv) was added at −78 °C. The mixture was stirred overnight warming to rt, quenched with water and acidified with 1 N HCl to pH 2–3. The reaction mixture was stirred for 1 h and extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EA = 3:1) to give **72** (176 mg, yield 6.8%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.36 (s, 1H), 9.08 (s, 1H), 7.78–7.86 (m, 2H), 7.68 (t, 1H), 1.51 (s, 6H) ppm. MS: m/z = 191 (M+H). A mixture of **72** (176 mg, 0.9263 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (147 mg, 1.019 mmol, 1.1 equiv) in HCOOH/TEA (1.9 mL, v/v = 5:2) was heated to 110 °C for 12 h. The mixture was cooled to rt and powered into ice-water. The mixed solution was acidified with 1 N HCl to pH 1 and extracted with EA. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative TLC (PE/EA = 2:1) to give **20** (23.5 mg, yield 10.8%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.00 (s, 1H), 8.80 (s, 1H), 7.35 (t, 1H), 7.20 (d, 1H), 7.12(d, 1H), 2.98 (t, 2H), 2.54 (t, 2H), 1.44 (s, 6H) ppm. MS: m/z = 235 (M+1, ESI+) and 233 (M−1, ESI−). HPLC purity: 95.0% at 220 nm and 98.6% at 266 nm.

7. *Method for determining IC_{50} for growth inhibition of erythrocytic-stage P. falciparum by benzoxaboroles* **1**–**20**: Erythrocytic-stage W_2 strain *P. falciparum* parasites were cultured in human erythrocytes and RPMI-1640 culture media with either 10% human serum or 0.5% Albumax serum substitute. Parasites were synchronized to ring stage by treatments with 5% D-sorbitol. Benzoxaboroles with serial dilutions from 5 to 10 mM stock concentrations were used to determine IC_{50} values in 96 well microplate cultures in 200 μL of media/well, 2% hematocrit, 1% parasitemia, under atmosphere 3% O_2, 5% CO_2 balance N_2. At the completion of 48 h incubations, cultures were fixed with 2% formaldehyde, After 48 h of fixation, 5 μL aliquots were transferred to another 96 well plate containing 150 μL/well of staining solution: PBS, 100 mM NH_4Cl, 0.1% Triton X-100, and 1 nM YOYO-1. Parasites per erythrocyte were then determined by flow cytometry from plots of forward scatter against fluorescence (excitation 488 nm, emission 520 nm) using FacSort flow cytometer (Beckton Dickinson) equipped with AMS Loader (Cytek Development). All values were normalized to percent control activity, and IC_{50}'s were calculated using the Prism 3.0 program (GRAPHPAD Software). Goodness of fit was assessed by R^2 values, with the expectation that meaningful dose-response curves should yield R^2 values >0.95.
8. Cytotoxicity was determined against human Jurkat and HeLa cells. For each cell line, IC_{50}'s were measured using a 12-point concentration curve, in triplicate and viability was determined using 3-(4,5-dimethylthiazol-2-yl)-2,5diphenyl-tetrazolium bromide (MTT) after 72 h exposure to compounds.