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Benzoxaborole antimalarial agents. Part 2: Discovery of fluoro-substituted 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaboroles

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ABSTRACT

A series of new boron-containing benzoxaborole compounds was designed and synthesized for a continuing structure–activity relationship (SAR) investigation to assess the antimalarial activity changes derived from side-chain structural variation, substituent modification on the benzene ring and removal of boron from five-membered oxaborole ring. This SAR study demonstrated that boron is required for the antimalarial activity, and discovered that three fluoro-substituted 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaboroles (**9**, **14** and **20**) have excellent potencies (IC_{50} 0.026–0.209 μM) against *Plasmodium falciparum*.

Malaria represents a continuing public health problem for close to half of the world's population. It 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 mortality of the disease. Current therapies to treat falciparum malaria are heavily reliant on artemisinin-based combinations (ACTs). However, emergence of resistance to the endoperoxide component of the combination has recently been identified, and resistance to older antimalarial drugs is already widespread. This fact has brought renewed urgency 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 that screening the Anacor boron-containing compound collection in a whole cell assay against the malaria parasite *P. falciparum* identified 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**1** in Fig. 1) with an IC_{50} of 44 nM.[2] In addition, we described a preliminary SAR investigation surrounding **1**, including modifications on side-chain and ring size and substitution of oxaborole ring.[2] In a continuing effort to optimize the potency of this series of antimalarial benzoxaboroles and to further explore the SAR, additional new compounds have been synthesized and evaluated against *P. falciparum*. Herein we report the synthesis and antimalarial activity of compounds **2**–**21**.

General methods for the preparation of a diverse number of substituted benzoxaboroles have recently been published.[3] The chemistry for the synthesis of compound **1** was described previously[2] and an improved method was also reported.[4] Scheme 1 illustrates the route for the synthesis of compound **2**. The ester group in compound **22**, prepared by the previous methods,[2] was reduced with excess $NaBH_4$ and followed by hydrolysis of the acetal group to provide **23**. The hydroxyl group was then protected with methoxymethyl chloride (MOMCl) to give **24**. Wittig reaction of aldehyde **24** was followed by catalytic hydrogenation to produce **26**. A hydroxyl group was introduced alpha to the ester function and this was then fluorinated using DAST to yield **28**. Boronylation of **28** was followed by successive acidic and then basic hydrolysis to produce **2**.

The methods for the syntheses of compounds **3–6** are shown in Scheme 2. The synthesis for **3** started with aldehyde **31**[2] which was reacted with tetraethyl methylenebis(phosphonate) to give the unsaturated phosphonate **32**. Compound **32** was then reduced to its saturated analog **33**, which gave the desired phosphonic acid **3** after removal of the ester groups. Compound **4** was synthesized

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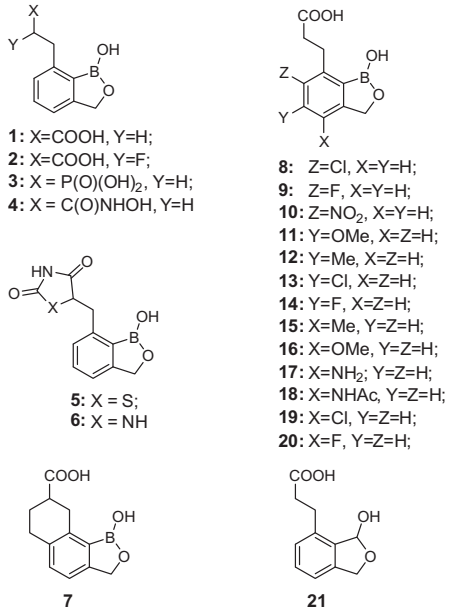


Figure 1. Chemical structures of the benzoxaborole compounds synthesized during a SAR investigation for the discovery of a new class of antimalarial agents by the side-chain variation (**2**–**7**), substituent change on the benzene ring (**8**–**20**) and removal of boron from five-membered oxaborole ring (**21**).

from **1** by an amidation reaction with *O*-benzylhydroxylamine followed by catalytic hydrogenation to remove benzyl group. Compounds **5** and **6** were prepared by condensation of aldehyde **31** with thiazolidine-2,4-dione or imidazolid-dine-2,4-dione, respectively, followed by catalytic hydrogenation of each compound.

The synthesis of compound **7** is illustrated in Scheme 3. Reaction of **37** with diethyl succinate introduced the bis-carboxylic acid side-chain of **38** that was reduced and then cyclized to provide intermediate **40**. Reduction of the ketone group in **40** gave **41** that was dehydroxylated and demethylated to generate compound **43**. The carboxylic acid of **43** was converted to its methyl ester (**44**) which was formylated to give **45**. The hydroxyl group of **45** was triflated and followed by the boronylation reaction to introduce the pinacolatoboron group giving **47**. Reduction of the aldehyde of **47** followed by acidification gave the benzoxaborole **48** which was hydrolyzed to the desired compound **7**.

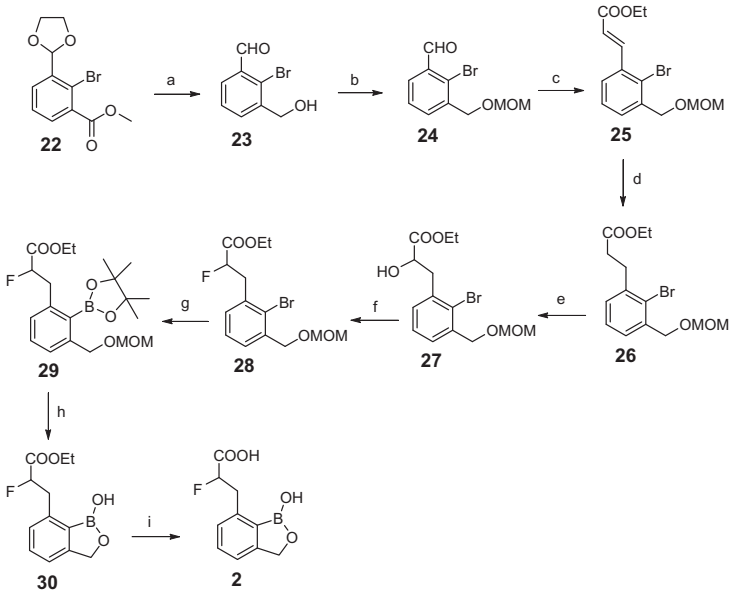
As shown in Scheme 4, compound **49** was chlorinated with sulfuryl dichloride to give a mixture of **50** and **51**, and this was followed by hydrolysis and separation to afford the final compounds **8** and **19**.

The chemistry for the synthesis of compound **9** is shown in Scheme 5. The aldehyde group was installed onto **52** to give **53**, which was converted to the α,β-unsaturated ester **54** by a Wittig reaction. The methyl group in **54** was then brominated to afford the dibromo derivative **55**, which was reacted with potassium acetate to yield **56**. Successive boronylation and hydrolysis produced benzoxaborole **58**, which led to **9** by catalytic hydrogenation.

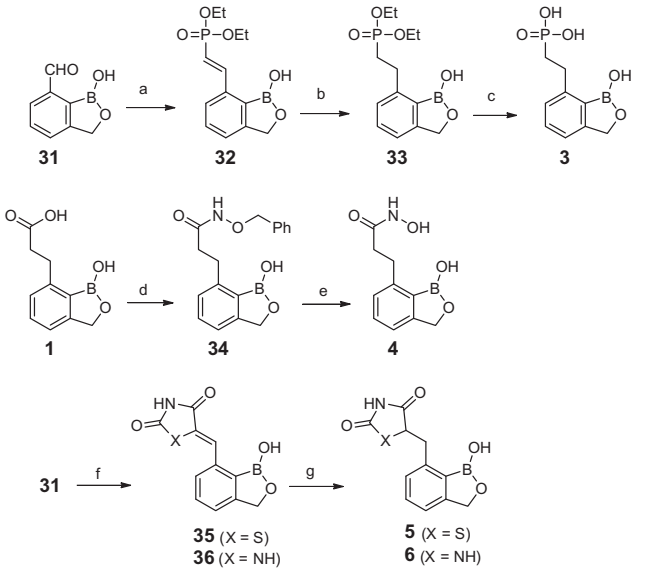
Scheme 6 illustrates the syntheses for compounds **10**, **17** and **18**. Nitration of the acid **1** gave a separable mixture of two nitro compounds **10** and **59**. Reduction of the 6-nitro compound **10** did not give the desired open-chain aniline compound, but resulted in the cyclized compound **60**. Reduction of **59** provided the amino compound **17** that was acetylated to afford **18**.

The synthetic route for the preparation of compounds **11**–**15** is shown in Scheme 7. Substituted salicylaldehydes **61**–**65** were reacted with a Wittig reagent to generate the ester extended side-chain of **66**–**70**, which were further formylated to install the adjacent aldehyde group in **71**–**75**, respectively. The phenol group was converted to the triflate of **76**–**80** in order to replace it with the pinancolatoboron moiety of **81**–**85**. By reduction with sodium borohydride, the aldehyde group was transformed into the hydroxymethyl group which spontaneously cyclized to form the oxaborole ring in **86**–**90** under acidic aqueous conditions. Subsequent reduction of the double bond in **86**–**90** and hydrolysis of the ester in **91**–**95** provided the final acids **11**–**15**.

The chemistry for the preparation of compound **16** is shown in Scheme 8. The aldehyde group in **53** was oxidized to the carboxylic acid **96**, which was then esterified to methyl ester **97**. The methyl group in **97** was di-brominated to give **98**, which was treated with NaOMe in methanol followed by treatment with aqueous acid to generate compound **99**. Protection of the aldehyde in **99** was



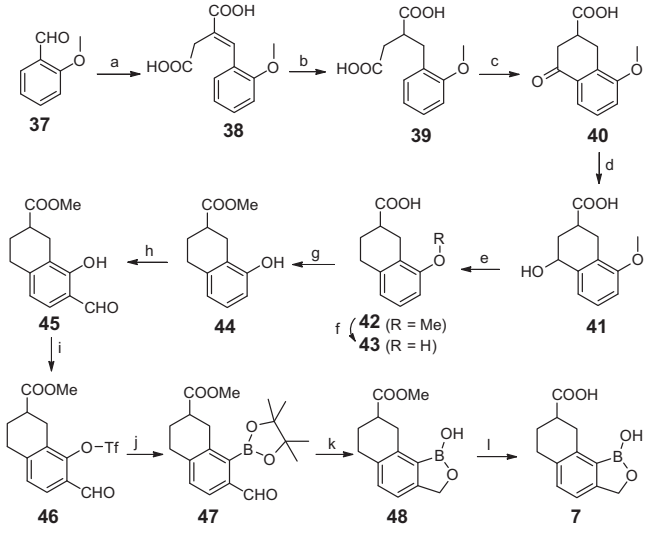
Scheme 1. Synthesis of compound **2**. Reagents and conditions: (a) excess $NaBH_4$, EtOH, rt, 48 h, then 1 N HCl; (b) MOMCl, DIPEA, DCM, 50 °C, 16 h; (c) Ph_3PCH_2COOEt bromide, *t*-BuOK, DMSO, rt, 16 h; (d) H_2, 10% Pd/C, EtOAc, rt, 1 h; (e) (1) KHMDS, THF, −78 °C, 30 min, (2) 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine, −78 °C to rt, 2 h; (f) DAST, DCM, 0 °C to rt, 16 h; (g) Pin_2B_2, $Pd(Ph_3P)_2Cl_2$, KOAc, 1,4-dioxane, N_2, 95 °C, 16 h; (h) 4 N HCl, THF, 50 °C, 4 h; (i) LiOH, THF/MeOH/H_2O (3:2:1, volume ratio), 40 °C, 1 h, then HCl acidification.



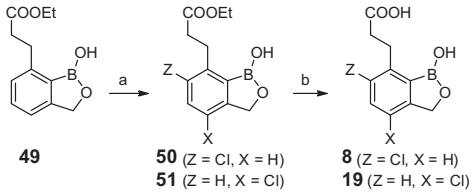
Scheme 2. Syntheses of compounds **3**-**6**. Reagents and conditions: (a) $CH_2[P(O)(OEt)_2]_2$, NaH, THF, 0 °C to rt, 10 h; (b) H_2, 10% Pd/C, rt, 1 h; (c) KI, Me_3SiCl, MeCN, rt, 10 h; (d) $BnONH_2$·HCl, EDC, HOAt, DIPEA, THF/DCM (1:1), rt, 4 h; (e) H_2, 10% Pd/C, MeOH, rt, 30 min; (f) (1) for **35**: thiazolidine-2,4-dione, NaOAc, 145 °C, 1 h, (2) for **36**: imidazolidine-2,4-dione, NaOAc, 145 °C, 1 h; (g) (1) for **5**: from **35**, pyridine, THF, $LiBH_4$, reflux, 2 h, (2) for **6**: from **36**, H_2, 10% Pd/C, 5% NaOH in water, rt, 16 h.

followed by boronylation to provide the bis-protected compound **101**. Reduction and hydrolysis then produced **102**, which reacted with 2,2-dimethyl-1,3-dioxane-4,6-dione to generate the final compound **16**.

For the synthesis of compound **20**, the chemistry is illustrated in Scheme 9. From a common intermediate **97**, compound **103** was obtained by mono-brominating the methyl group. The bromomethyl moiety was then converted to hydroxylmethyl **104**, which



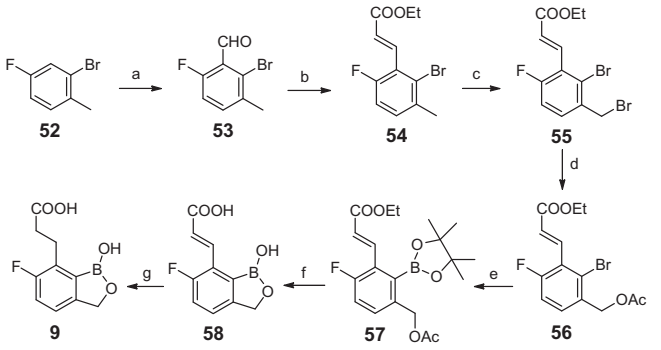
Scheme 3. Synthesis of compound **7**. Reagents and conditions: (a) diethyl succinate, *t*-BuOK, *t*-BuOH, 75 °C, 2 h; (b) H_2, 10% Pd/C, THF, HCl, rt, 5 h; (c) (1) $(COCl)_2$, DMF, DCM, 0 C, 1 h, (2) $AlCl_3$, DCM, 0 °C, 30 min; (d) $NaBH_4$, NaOH, H_2O, rt, 72 h, then 6 N HCl, H_2O; (e) Et_3SiH, TFA, rt, 16 h; (f) $AlCl_3$, toluene, N_2, reflux, 2 h, then 12 N HCl; (g) $SOCl_2$, MeOH, N_2, reflux, 16 h; (h) $(CH_2O)_n$, $MgCl_2$, TEA, THF, N_2, reflux, 16 h; (i) Tf_2O, pyridine, DCM, 0 °C to rt, 2 h; (j) Pin_2B_2, $Pd(Ph_3P)_2Cl_2$, KOAc, 1,4-dioxane, N_2, 80 °C, 16 h; (k) $NaBH_4$, MeOH, 0 °C to rt, 1.5 h, then 1 N HCl; (l) LiOH·H_2O, THF: H_2O (2:1), rt, 2 h, then 1 N HCl.



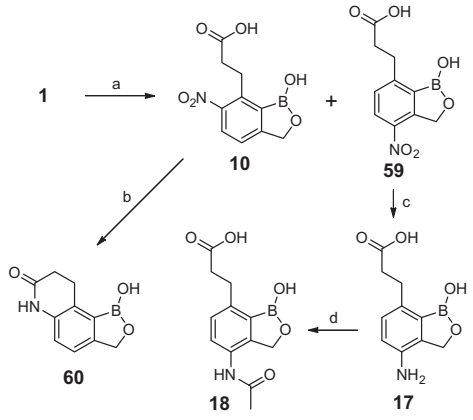
Scheme 4. Syntheses of compounds **8** and **19**. Reagents and conditions: (a) SO_2Cl_2, AcOH, 50 °C, 16 h; (b) NaOH, THF, H_2O, rt, 2 h, then 1 N HCl.

was oxidized to the aldehyde of **105** followed by protection to give **106**. Catalytic boronylation of **106** introduced pinancolatoboron into **107**, of which the ester group was reduced followed by hydrolysis to give **108**. Wittig reaction converted the aldehyde of **108** into an extending side-chain of **109**, which was hydrolyzed to the acid **110**. Compound **109** was also reduced to the saturated side-chain of **111**, which was hydrolyzed to give the final acid compound **20**.

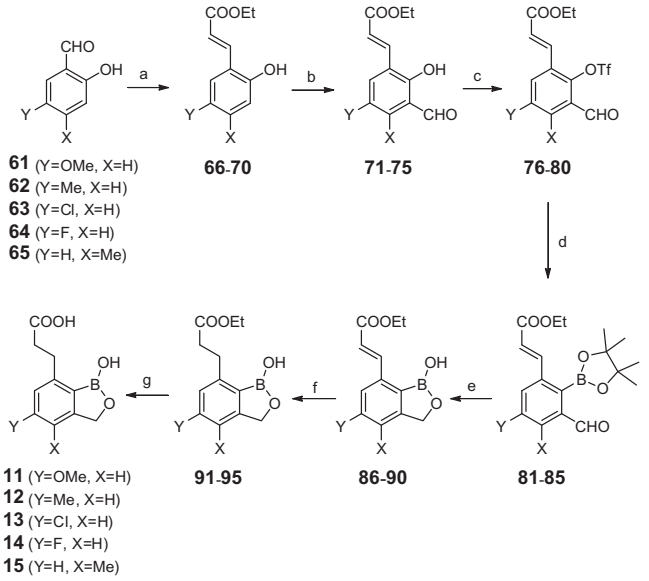
Synthesis of non-boron compound **21** is shown in Scheme 10. The carboxylic acid in **1** was transformed to its methyl ester **112**, which underwent Suzuki coupling to introduce the vinyl group in **113**. Protection of the hydroxyl group in **113** was followed by oxidation of the vinyl group in **114** to give **115**, which was hydrolyzed under the acidic condition to provide **116**. Under mild basic



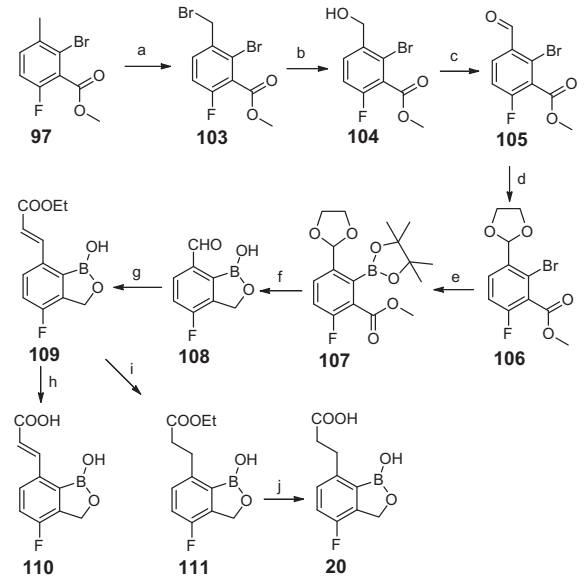
Scheme 5. Synthesis of compound **9**. Reagents and conditions: (a) (1) LDA, THF, −78 °C, 2 h, (2) DMF, −78 °C, 20 min; (b) Ph_3PCH_2COOEt bromide, *t*-BuOK, DMSO, 0 °C to rt, 3 h; (c) NBS, benzoyl peroxide, CCl_4, N_2, 85 °C, 2 h; (d) KOAc, DMF, 50 °C, 1 h; (e) Pin_2B_2, $Pd(Ph_3P)_2Cl_2$, KOAc, 1,4-dioxane, N_2, 85 °C, 16 h; (f) NaOH, EtOH, H_2O, 50 °C, 2 h, then 6 N HCl; (g) H_2, 10% Pd/C, EtOAc, rt, 1 h.



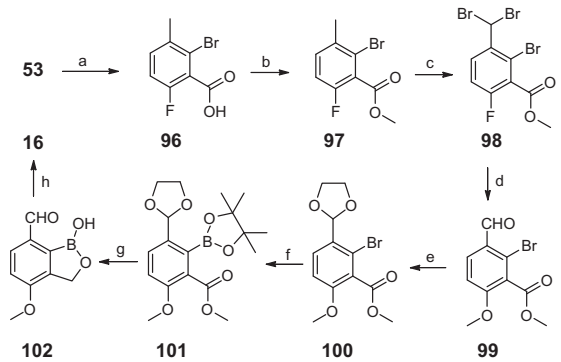
Scheme 6. Syntheses of compounds **10**, **17** and **18**. Reagents and conditions: (a) Fuming HNO_3, −30 °C, 30 min; (b) Fe, 12 N HCl, EtOH, rt. 1 h; (c) H_2, 10% Pd/C, EtOAc, rt, 1 h; (d) AcCl, TEA, DCM, THF, rt, 2 h.



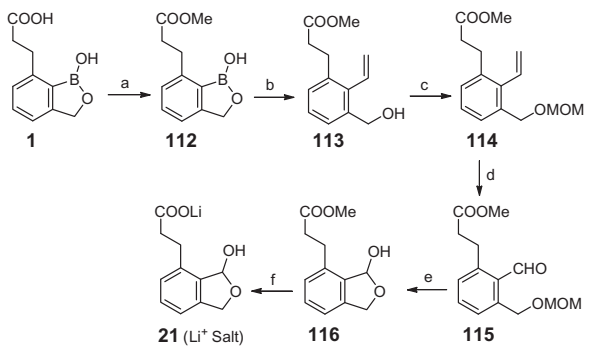
Scheme 7. Syntheses of compounds **11**–**15**. Reagents and conditions: (a) Ph_3PCH_2COOEt bromide, *t*-BuOK, DMSO, 0 °C to rt, 3 to 16 h; (b) $(CH_2O)_n$, $MgCl_2$, TEA, THF, N_2, reflux, 16 h; (c) Tf_2O, pyridine, DCM, 0 °C to rt, 2 h; (d) Pin_2B_2, $Pd(Ph_3P)_2Cl_2$, KOAc, 1,4-dioxane, N_2, 80–95 °C, 16 h; (e) $NaBH_4$, MeOH, 0 °C to rt, 1.5 h, then 1 N HCl; (f) H_2, 10% Pd/C, EtOAc, rt, 1 h; (g) LiOH·H_2O, THF:MeOH:H_2O (3:2:1), 40 °C, 1 h, then HCl acidification.



Scheme 9. Synthesis of compound **20**. Reagents and conditions: (a) 1 equiv NBS, benzoyl peroxide, CCl_4, N_2, reflux, 16 h; (b) $CaCO_3$, H_2O, 1,4-dioxane, 100 °C, 16 h; (c) PCC, DCM, rt, 4 h; (d) Pyridinium *p*-toluenesulfonate (PPTS), $(CH_2OH)_2$, toluene, reflux, 16 h; (e) Pin_2B_2, $Pd(Ph_3P)_2Cl_2$, KOAc, 1,4-dioxane, N_2, 95 °C, 16 h; (f) $NaBH_4$, EtOH, 0 °C to rt, 1.5 h, then 2 N HCl, rt, 30 min; (g) Ph_3PCH_2COOEt bromide, *t*-BuOK, DMSO, 0 °C to rt, 16 h; (h) and (j) LiOH·H_2O, THF/MeOH/H_2O (3:2:1), rt, 16 h, then HCl acidification; (i) H_2, 10% Pd/C, EtOAc, rt, 1 h.



Scheme 8. Synthesis of compound **16**. Reagents and conditions: (a) 2-Methyl-2-butene, $NaClO_2$, $NaH_2PO_4·3H_2O$, *t*-BuOH, H_2O, rt, 30 min, then 1 N HCl; (b) MeI, K_2CO_3, DMF, rt, 1 h; (c) 3 equiv NBS, benzoyl peroxide, CCl_4, N_2, reflux, 6 h; (d) NaOMe, MeOH, 65 °C, 4 h, then 2 N HCl; (e) Pyridinium *p*-toluenesulfonate, $(CH_2OH)_2$, toluene, reflux, 16 h; (f) Pin_2B_2, $Pd(Ph_3P)_2Cl_2$, KOAc, 1,4-dioxane, N_2, 95 °C, 16 h; (g) $NaBH_4$, MeOH, 0 °C to rt, 1.5 h, then 2 N HCl; (h) 2,2-dimethyl-1,3-dioxane-4,6-dione, HCOOH, TEA, rt, 1 h, then 114 °C, 16 h.



Scheme 10. Synthesis of compound **21**. Reagents and conditions: (a) MeI, K_2CO_3, DMF, N_2, rt, 3 h; (b) CH_2=CHBr, $Pd(PPh_3)_4$, Na_2CO_3, H_2O, toluene, THF, N_2, 90 °C, 16 h; (c) MOMCl, DIPEA, DCM, 0 °C to rt, 10 h; (d) $NaIO_4$, K_2OsO_4, H_2O, THF, rt, 10 h; (e) HCl, H_2O, THF, rt, 1 h; (f) LiOH·H_2O, CH_3CN, rt, 10 h.

conditions, the ester in **116** was hydrolyzed while the hemi-acetal was formed in parallel to generate the desired final compound **21** as a lithium salt.

The experimental procedures for the preparation of compounds **2**–**21** are described in the reference section.[5]

The in vitro inhibitory activities of compounds **1**–**21** and **110** against the malaria *P. falciparum* 3D7 strain were determined and their IC_{50} values are summarized in Table 1. Compounds **2**–**4** (see Fig. 1) were designed to examine the effect of the side-chain acidity on antimalarial activity. The fluoro atom substituted on the alpha-carbon of the carboxylic acid in **2** presumably increases the acidity in comparison to **1**. This structural change resulted in decrease of potency from IC_{50} value 0.044 μM of **1** to 0.83 μM of **2**. The replacement of the carboxylic acid group with a phosphonic acid gave an inactive compound **3** (IC_{50} > 5 μM). The hydroxamic acid group

Table 1
In vitro IC_{50} results of compounds **1**–**21** and **110** against the malaria parasite *Plasmodium falciparum* (3D7 strain)[a]

Compound	IC_{50} (μM) (*P. falciparum*)	Compound	IC_{50} (μM) (*P. falciparum*)
1	0.044	**12**	0.154
2	0.83	**13**	1.33
3	>5	**14**	0.061
4	1.55	**15**	1.45
5	0.46	**16**	0.62
6	>5	**17**	>5
7	1.82	**18**	>5
8	0.75	**19**	0.266
9	0.209	**20**	0.026
10	4.12	**21**	>5
11	3.48	**110**	>5

[a] Experimental procedure for the in vitro assay was described previously.[2] The activity of a reference compound, atovaquone, was 1 nM.

Table 2
In vitro cytotoxicity results of representative compounds[a]

Compound	HeLa cells% inhibition at 25 μM	Jurkat cells% inhibition at 25 μM
3	26.0	3.0
4	23.8	6.3
5	35.2	66.0
6	67.7	14.1
9	45.3	41.2
10	32.5	5.3
12	32.6	17.2
16	22.8	3.8
17	32.3	19.5
19	15.3	6.8
20	41.1	53.6
21	25.3	7.1
110	29.3	3.1

[a] Experimental procedure for the in vitro cytotoxicity assay was described previously.[2]

also decreased the activity of compound **4** giving an IC_{50} value of 1.55 μM. Compounds **5** and **6** were designed to use bioisosteres of the carboxylic group with the intention of improving the pharmacokinetic profile while maintaining potent activity. Compound **5** containing a thiazolidine-2,4-dione showed reasonable activity (IC_{50} = 0.46 μM) whereas compound **6** containing imidazolidine-2,4-dione, which is not acidic, lost activity (IC_{50} > 5 μM). Compound **7**, with a conformationally restricted side-chain carboxylic acid exhibited a 41-fold loss of potency (IC_{50} = 1.82 μM).

Compounds **8**–**20** were designed to investigate the antimalarial effect of various substituents at the 6-, 5- or 4-position of the benzene ring. At the 6-position, adjacent to the side-chain, albeit was possible to introduce a chloro- or fluoro-group, resulting in decreased potency (IC_{50} = 0.75 μM for **8** and 0.209 μM for **9**). The nitro analog **10** (IC_{50} = 4.12 μM) was made with the intention to prepare its amino and related derivatives. Interestingly, reduction of the nitro group in **10** generated a cyclic lactam compound **60** which was inactive against the parasite (IC_{50} > 5 μM). At the 5-position, which is para to the boron, four different substituents methoxy, methyl, chloro and fluoro (compounds **11**–**14**) were explored. The fluoro compound **14** and the methyl analog **12** had good potency (IC_{50} = 0.061 μM for **14** and 0.154 μM for **12**) while the chloro compound **13** and methoxy analogs **11** were much less potent (IC_{50} = 1.33 μM for **13** and 3.48 μM for **11**). At the 4-position, six variable substituents including methyl, methoxy, amino, acetamido, chloro and fluoro-group (compounds **15**–**20**) were investigated. The methyl compound **15** and the methoxy analog **16** showed moderate antimalarial activity (IC_{50} = 1.45 μM for **15** and 0.62 μM for **16**) whereas the amino compound **17** and the acetamido compound **18** lost activity (both IC_{50} > 5 μM). The chloro analog **19** exhibited reasonable activity (IC_{50} = 0.266 μM) while the fluoro compound **20** demonstrated excellent potency (IC_{50} = 0.026 μM).

Compound **21** was designed to replace the boron in **1** with carbon and to test whether boron is required for the antimalarial activity. This change resulted in a complete loss of biological activity (IC_{50} > 5 μM). As a close analog to **20**, compound **110** has a double bond in the side-chain and showed diminished activity (IC_{50} > 5 μM) indicating the importance of the flexible side-chain in **20**.

Representative compounds were selected for the in vitro cytotoxicity tests using human Jurkat (T cell) and human HeLa (cervical carcinoma) cell assays. The results are summarized in Table 2. These compounds were tested at the concentration of 25 μM and in general this class of compounds showed low cytotoxicities against the two human cell lines.

In summary, the SAR study described in this report demonstrated that in this chemical series, the boron is absolutely required for the antimalarial activity and that a carboxylic acid on the side-chain represents the best acidic function. In addition, four new ring-substituted compounds inhibited *P. falciparum* with $IC_{50} \leqslant 0.209$ μM. Three of the four compounds have a fluoro-substituent on the benzene ring, including 6-position (**9** with IC_{50} = 0.209 μM), 5-position (**14** with IC_{50} = 0.061 μM) or 4-position (**20** with IC_{50} = 0.026 μM). Further investigation on these active compounds is in progress and results will be disclosed in future publications.

References and notes

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5. *Synthesis of 2-fluoro-3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid* (**2**): To a solution of **22** (30 g, 104.5 mmol) in EtOH (500 mL) was added $NaBH_4$ (9.87 g, 261.25 mmol, 2.5 equiv) at 0 °C. The reaction was stirred at rt for 48 h, quenched with 1 N HCl and extracted with ethyl acetate (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 to give **23** (14 g, yield 64%). To a solution of **23** (7 g, 32.5 mmol) in dichloromethane (DCM, 160 mL) was added *N*,*N*-diisopropyl-*N*-ethylamine (DIPEA, 12.4 mL, 71.6 mmol, 2.2 equiv) and methoxymethyl chloride (MOMCl, 4 mL, 48.75 mmol, 1.5 equiv). The reaction was stirred at 50 °C overnight, quenched with saturated NH_4Cl and extracted with DCM. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography to give **24** (6.6 g, yield 78%). To a solution of Ph_3PCH_2COOEt bromide (45 g, 106 mmol, 2.5 equiv) in DMSO (350 mL) was added *t*-BuOK (10.3 g, 85 mmol, 2 equiv). The mixture was stirred at rt for 1 h, and then to the mixture was added a solution of **24** (11 g, 42.45 mmol, 1 equiv) in DMSO (74 mL). The reaction was stirred at rt overnight, quenched with saturated NH_4Cl and extracted with *t*-butyl methyl ether (TBME). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography to give **25** (13.9 g, yield 100%). To a solution of **25** (13.9 g, 42.45 mmol, 1 equiv) in EA (210 mL) was added 10% Pd/C (2.8 g). The reaction vessel was vacuumed and backfilled with H_2 for three times. After being stirred at rt for 1 h, the reaction was filtered and evaporated. The residue was purified by column chromatography to give **26** (6 g, yield 43%). To a solution of KHMDS (21.7 mL, 21.7 mmol, 1.2 equiv) in THF (30 mL) was added a solution of **26** (6 g, 18.1 mmol, 1 equiv) in THF (60 mL). The mixture was stirred at −78 °C for 30 min and then 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (6.613 g, 25.34 mmol, 1.4 equiv) was added at −78 °C. After being stirred at rt for 2 h, the reaction was quenched with saturated $NaHCO_3$ 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 to give **27** (4.3 g, yield 68%). ^1H NMR of **27** (500 MHz, DMSO-d_6): δ 7.36 (d, 1H), 7.26–7.32 (m, 2H), 5.61 (d, 1H), 4.71 (s, 2H), 4.58 (s, 2H), 4.28 (m, 1H), 4.06 (m, 2H), 3.32 (s, 3H), 3.17 (m, 1H), 2.97 (m, 1H) 1.13 (t, 3H) ppm. To a solution of **27** (2.8 g, 8.08 mmol) in DCM (16 mL) was added DAST (1.9 g, 12.1 mmol, 1.5 equiv) at 0 °C. The reaction was stirred at rt for 8 h, and then more DAST (1.9 g, 12.1 mmol, 1.5 equiv) was added at 0 °C. After being stirred at rt overnight, the reaction was quenched with saturated $NaHCO_3$ and extracted with DCM. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography to give

28 (730 mg, yield 26%). To a solution of **28** (400 mg, 1.145 mmol) in 1,4-dioxane (6 mL) was added KOAc (483 mg, 4.923 mmol, 4.3 equiv), Pin_2B_2 (349 mg, 1.37 mmol, 1.2 equiv) and $Pd(Ph_3P)_2Cl_2$ (80 mg, 0.114 mmol, 0.1 equiv). The reaction was vacuumed and backfilled with N_2 for three times. Then the reaction was stirred at 95 °C overnight. The residue after filtration and evaporation was purified by column chromatography to give **29** (148 mg, yield 32%). To a solution of **29** (140 mg, 0.363 mmol) in THF (0.9 mL) was added 4 N HCl (0.43 mL, 18.1 mmol, 5 equiv). The reaction was stirred at 50 °C for 4 h, added with EA and the organic phase was washed with brine, dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography to give **30** (20 mg, yield 22%). To a solution of **30** (20 mg, 0.079 mmol) in THF/MeOH/water = 3:2:1 (0.5 mL) was added $LiOH{\cdot}H_2O$ (13.3 mg, 0.317 mmol, 4 equiv). The reaction was stirred at 40 °C for 1 h, quenched 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 to give the final compound **2** (10 mg, yield 56%). ^{1}H NMR of **2** (300 MHz, DMSO-d_6): δ 13.10 (br s, 1H), 9.10 (br s, 1H), 7.40 (t, 1H), 7.27 (d, 1H), 7.20 (d, 1H), 5.33–5.13 (dm, 1H), 4.98 (s, 2H), 3.48–3.45 (m, 2H) ppm; HPLC purity: 94% at 220 nm; MS (ESI−): m/z = 223.0 (M−1).

Synthesis of (2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)ethyl)phosphonic acid (**3**): To a suspension of NaH (0.3 g, 7.40 mmol, 1.2 equiv) in THF (25 mL) was added a solution of tetraethyl methylenediphosphonate in THF (2.5 ml) at 0 °C and then a solution of **31** in THF (12 mL) was added. The reaction was stirred at rt for 10 h, water (20 mL) was added, and pH was adjusted to 5–7 with 1 N HCl. The mixture was extracted with DCM, and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography to give **32** (1.19 g, yield 65%). To a solution of **32** (1.13 g, 3.82 mmol) in EtOH (18 mL) under N_2 was added 10% Pd/C (0.6 g). 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 **33** (1.14 g, yield 100%). To a mixture of **33** (205 mg, 0.688 mmol) and KI (0.4 g, 3.1 mmol, 4.5 equiv) in MeCN (1.9 mL) was added chlorotrimethylsilane (0.395 mL, 3.1 mmol, 4.5 equiv). The reaction was stirred at rt for 10 h and LC–MS showed that all the starting material was converted to the desired product. The reaction was evaporated and the solid was washed with ether to give the desired product **3** as a white solid (151 mg, yield 90%). ^{1}H NMR of **3** (300 MHz, DMSO-d_6): δ 7.32 (t, 1H), 7.17 (d, 1H), 7,10 (d, 1H), 4.93 (s, 2H), 4.50 (br s, 2H), 3.10–2.90 (m, 2H), 1.89–1.93 (m, 2H) ppm; HPLC purity: 98.6% at 220 nm; MS (ESI+): m/z = 243.0 (M+1).

Synthesis of N-hydroxy-3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanamide (**4**): To a solution of **1** (0.5 g, 2.42 mmol) in a mixed solvent of THF (12 mL) and DCM (12 mL) were added DIPEA (3.4 mL, 19.36 mmol, 8 equiv), EDC HCl (975.5 mg, 5.08 mmol, 2.1 equiv), HOAt (395 mg, 2.9 mmol, 1.2 equiv) and $BnONH_2$ HCl (1.742 g, 10.89 mmol, 4.5 equiv). The reaction was stirred at rt for 4 h, evaporated and added with EA. The organic phase was washed with 1 N HCl, brine and dried over anhydrous Na_2SO_4. The residue was purified by column chromatography to give **34** (230 mg, yield 30%). ^{1}H NMR of **34** (300 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.95 (s, 1H), 7.72–7.38 (m, 6H), 7.21 (d, 1H), 7.09 (d, 1H), 4.95 (s, 2H), 4.57 (s, 2H), 3.01 (t, 2H), 2.29 (t, 2H) ppm; HPLC purity: 95.5% at 220 nm; MS (ESI−): m/z = 310 (M−1). To a solution of **34** (0.2 g, 0.643 mmol) in MeOH (3 mL) was added 10% Pd/C (80 mg), and the reaction vessel was vacuumed and backfilled with H_2 for three times. After being stirred at rt for 30 min, the reaction mixture was filtered and evaporated. The residue was purified by column chromatography to give the desired product **4** (55 mg, yield 41%). ^{1}H NMR of **4** (300 MHz, CD_3OD): δ 7.35 (t, 1H), 7.19 (d, 1H), 7.13 (d, 1H), 5.04 (s, 2H), 3.08 (t, 2H), 2.40 (t, 2H); HPLC purity: 96.4% at 220 nm; MS (ESI+): m/z = 222 (M+1).

Synthesis of 5-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl) methyl)thiazolidine -2,4-dione (**5**): A mixture of **31** (460 mg, 2.84 mmol), thiazolidine-2,4-dione (363 mg, 3.1 mmol, 1.1 equiv) and NaOAc (512 mg, 6.2 mmol, 2.2 equiv) was stirred at rt for 10 min and then at 145 °C for 1 h. The mixture was cooled to rt and diluted with water (2 mL), HCl (1 N, 2 mL) and EA (2 mL). After being stirred for 1 h, the solid was collected by filtration, washed with water (5 mL) and EA (10 mL), and dried under vacuum to give the desired product **35** as yellow solid (450 mg, yield 60%). ^{1}H NMR of **35** (300 MHz, DMSO-d_6): δ 12.58 (s, 1H), 9.35 (s, 1H), 8.30 (s, 1H), 7.64 (t, 1H), 7.49 (d, 1H), 7.44 (d, 1H), 5.04 (s, 2H) ppm; HPLC purity: 100% at 220 nm; MS (ESI−): m/z = 260 (M−1). To a solution of **35** (70 mg, 0.27 mmol) and pyridine (2 mL) in THF (5 mL) was added $LiBH_4$ (22 mg, 1 mmol, 3.7 equiv) in portions. The reaction mixture was refluxed for 2 h and then diluted with EA (10 mL) and HCl (1 N, 20 mL). The aqueous phase was extracted with EA (3 × 5 mL) and the combined organic phase was washed with brine, dried over $NaSO_4$ and evaporated. The residue was purified by column chromatography over silica gel eluted with DCM/MeOH/AcOH = 5:1:0.01 to give the desired product **5** as yellow solid (21 mg, yield 22%). ^{1}H NMR of **5** (300 MHz, DMSO-d_6): δ 11.97 (br s, 1H), 9.08 (s, 1H), 7.42 (t, 1H), 7.28 (d, 1H), 7.17 (d, 1H), 4.96 (s, 2H), 4.94 (t, 1H), 3.69–3.63 (m, 1H), 3.26–3.18 (m, 1H) ppm; HPLC purity: 94% at 220 nm; MS (ESI+): m/z = 264 (M+1).

Synthesis of 5-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl) methyl)imidazoli-dine-2,4-dione (**6**): Intermediate **36** was synthesized from imidazolidine-2,4-dione by a similar method described above for the synthesis of **35**. Yield 41%; ^{1}H NMR of **36** (500 MHz, DMSO-d_6): δ 11.20 (s, 1H), 10.50 (s, 1H), 9.16 (s, 1H), 7.71–7.66 (m, 1H), 7.49 (t, 1H), 7.34 (d, 1H), 6.99 (s, 1H), 5.00 (s, 2H). MS (ESI−): m/z = 243 (M−1). To a solution of **36** (100 mg, 0.4 mmol) in 5% NaOH aqueous solution (5 mL) was added 10% Pd/C (300 mg). The reaction was stirred at rt under H_2 overnight. It was filtrated and the aqueous phase was acidified by HCl (1 N, 5 mL), extracted with EA (3 × 5 mL). The combined organic phase was washed with brine, dried over $NaSO_4$ and evaporated. The solid residue was purified by column chromatography over silica gel eluted with DCM/MeOH/AcOH = 5:1:0.1 to give the desired product **6** as yellow solid (40 mg, yield 40%). ^{1}H NMR of **6** (300 MHz, DMSO-d_6): δ 10.50 (br s, 1H), 9.10 (br s, 1H), 7.64 (s, 1H), 7.38 (t, 1H), 7.24 (d, 1H), 7.15 (d, 1H), 4.96 (s, 2H), 4.38–4.36 (m, 1H), 3.28–3.17 (m, 1H), 3.03–2.96 (m, 1H) ppm; HPLC purity: 98.9% at 200 nm; MS (ESI+): m/z = 269 (M+23).

Synthesis of 1-hydroxy-1,3,6,7,8,9-hexahydronaphtho[1,2-c][1,2] oxaborole-8-carboxylic acid (**7**): To a solution of *t*-BuOK (35.08 g, 313 mmol, 1.4 equiv) in *t*-BuOH (150 mL) was added a solution of **37** (30.0 g, 220.6 mmol) and diethyl succinate (41.7 mL, 250 mmol, 1.13 equiv) in *t*-BuOH (23 mL). The mixture was stirred at 75 °C for 2 h, cooled to rt and evaporated to remove *t*-BuOH. Then water (333 mL) was added, followed by addition of a solution of KOH (28.6 g) in water (95 mL). After being refluxed overnight, the reaction mixture was cooled to rt, extracted with TBME (3 × 100 mL). The aqueous mixture was acidified with 6 N HCl to pH 1, cooled to 0 °C and filtered to collect the solid. The product was washed with water (2 × 30 mL), and then TBME (2 × 20 mL) to give **38** as a yellow solid (45.4 g, yield 74.0%). TLC analysis of **38** (silica gel plate, MeOH/DCM = 5:95): R_f = 0.2. To a solution of **38** (5.0 g, 21.18 mmol) in THF (70 mL) were added 10% Pd/C (1.25 g) and HCl (3 mL). The reaction vessel was vacuumed and backfilled with H_2. After being stirred at rt for 5 h, the mixture was filtered and evaporated to give a dark oil. The residue was recrystallized from toluene (15 mL) to give **39** as a white solid (2 g, yield 40%). TLC analysis of **39** (silica gel plate, MeOH/DCM = 5:95): R_f = 0.3. To a solution of **39** (5.0 g, 21 mmol) in DCM (50 mL) were added DMF (2 mL) and $(COCl)_2$ (5.87 g, 46.2 mmol) at 0 °C. The mixture was stirred for 1 h before $AlCl_3$ (8.4 g, 63 mmol, 3 equiv) in DCM (80 mL) was added. The mixture was stirred for 30 min and then poured into 200 mL ice-water followed by filtration. The filtrate was extracted with DCM (3 × 100 mL) and the organic layer was washed by brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography over silica gel eluted with PE/EA = 6:4 to give **40** (2.4 g, yield 53.0%). TLC analysis of **40** (silica gel plate EA/PE = 4:6): R_f = 0.3. To a solution of **40** (3.67 g, 183.5 mmol) in H_2O (50 mL) were added NaOH (0.74 g, 183.5 mmol, 1 equiv) and $NaBH_4$ (0.694 g, 183.5 mmol, 1 equiv). The reaction mixture was stirred at rt for 72 h. The mixture was acidified with 6 N HCl and filtered to give **41** as a solid (2.0 g, yield 55.0%). TLC analysis of **41** (silica gel plate EA/PE = 1:1): R_f = 0.3. To a solution of **41** (2.0 g, 8.99 mmol) in TFA (50 mL) was added Et_3SiH (1.73 ml, 1.2 equiv), and the reaction mixture was stirred at rt overnight. TFA was removed under vacuum and saturated $NaHCO_3$ was added to adjust pH 5. The mixture was extracted with EA (2 × 30 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography over silica gel eluted with PE/EA = 3:1 to give **42** as a white solid (1.3 g, yield 70%). TLC analysis of **42** (silica gel plate, EA/PE = 1:3): R_f = 0.3. To a solution of **42** (3 g, 14.4 mmol) in toluene (50 mL) was added $AlCl_3$ (4.85 g, 36 mmol, 2.5 equiv). The mixture was refluxed under N_2 for 2 h, cooled and poured into 100 mL ice water, followed by acidification to pH 1 with 12 N HCl. Then the mixture was extracted with EA (2 × 50 mL) and the organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography over silica gel eluted with PE/EA = 7:3 to give **43** (1.4 g, yield 52%). TLC analysis of **43** (silica gel plate, EA/PE = 3:7): R_f = 0.3. To a solution of **43** (1.4 g, 7.28 mmol) in MeOH (19 mL) was added $SOCl_2$ (2.6 g, 21.8 mmol, 3 equiv) under N_2. The mixture was refluxed overnight, cooled and evaporated to give **44** (1.2 g, yield 80%). TLC analysis of **44** (silica gel plate, EA/PE = 3:7): R_f = 0.3. To a mixture of $(CH_2O)_n$ (529 mg, 17.4 mmol, 3 equiv) in dry THF (19 mL) were added $MgCl_2$ (1.1 g, 11.63 mmol, 2 equiv), TEA (1.62 mL, 2 equiv) and a solution of **44** (1.2 g, 5.8 mmol) in dry THF (10 mL) at rt under N_2. The reaction mixture was refluxed overnight, cooled to rt and extracted with EA (40 mL). The organic layer was washed with 1 N HCl (2 × 20 mL), water (20 mL) and brine, and was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by column chromatography over silica gel eluted with PE/EA = 9:1 to give **45** (0.7 g, yield 51%). TLC analysis of **45** (silica gel plate, EA/PE = 1:3): R_f = 0.4. ^{1}H NMR of **45** (300 MHz, DMSO-d_6): δ 11.25 (s, 1H), 9.94 (s, 1H), 7.52 (d, 1H), 6.83 (d, 1H), 3.66 (s, 3H), 2.96–2.60 (m, 5H), 2.08–1.99 (m, 1H), 1.85–1.60 (m, 1H) ppm. To a solution of **45** (0.7 g, 2.98 mmol) in DCM (9.9 mL) were added pyridine (1.2 mL, 14.9 mmol, 5 equiv) and Tf_2O (1.1 mL, 6.56 mmol, 2.2 equiv) at 0 °C. The mixture was stirred at rt for 2 h and then washed with water (2 × 20 mL), 0.5 N HCl (2 × 20 mL), brine, dried and rotary evaporated. The residue was purified by column chromatography over silica gel eluted with PE/EA = 3:1 to give **46** (0.6 g, yield 55%). TLC analysis of **46** (silica gel plate, EA/PE = 1:4): R_f = 0.3. ^{1}H NMR of **46** (300 MHz, DMSO-d_6): δ 10.05 (s, 1H), 7.82 (d, 1H), 7.50 (d, 1H), 3.66 (s, 3H), 3.13–2.89 (m, 5H), 2.25–1.70 (m, 2H) ppm. To a solution of **46** (0.6 g, 1.66 mmol) in 1,4-dioxane (8.3 mL) were added KOAc (491 mg, 4.99 mmol, 3 equiv), Pin_2B_2 (635 mg, 2.5 mmol, 1.5 equiv). The solution was bubbled with N_2 for 15 min. $Pd(PPh_3)_2Cl_2$ (117.2 mg, 0.167 mmol, 0.1 equiv) was added and the reaction was stirred under N_2 at 80 °C overnight, cooled, filtrated, and evaporated. The residue was purified by column chromatography over silica gel eluted with PE/EA = 9:1 to give **47** (550 mg, yield 95.9%). TLC analysis of **47** (silica gel plate, EA/PE = 1:9): R_f = 0.3. To a solution of **47** (550 mg, 1.60 mmol) in MeOH (8 mL) was added $NaBH_4$ (66.5 mg, 1.75 mmol, 1.1 equiv) at 0 °C. The mixture was stirred for 1.5 h at rt and then 1 N HCl (4 mL) was added to adjust pH 1–2. After being stirred for 0.5 h, the mixture was extracted with EA (3 × 20 mL) and the combined organic

phase was washed with brine, dried and concentrated. The residue was purified by column chromatography over silica gel eluted with PE/EA = 4:1 to give **48** (11 mg, yield 2.8%). TLC analysis of **48** (silica gel plate, EA/PE = 1:4): R_f = 0.3. To a solution of **48** (11 mg, 0.0447 mmol) in THF/H_2O = 2:1 (0.5 mL) was added LiOH·H_2O (3.7 mg, 0.0894 mmol, 2 equiv). After being stirred at rt for 2 h, the mixture was acidified to pH 2 with 1 N HCl and followed by extraction with EA (3 × 10 mL). The combined organic layer was washed with brine, dried and evaporated. The residue was purified by column chromatography over silica gel eluted with PE/EA = 3:7 to give the final product **7** (3.2 mg, yield 31%). ^{1}H NMR of **7** (300 MHz, DMSO-d_6): δ 12.20 (br s, 1H), 8.85 (s, 1H), 7.17–7.08 (m, 2H), 4.90 (s, 2H), 4.14 (m, 1H), 3.21–2.64 (m, 4H), 2.10–1.70 (m, 2H) ppm; HPLC purity: 90% at 220 nm; MS (ESI+): m/z = 255 (M+23).

Syntheses of 3-(6-chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid (**8**) *and 3-(4-chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid* (**19**): To a solution of the ethyl ester of **1** (**49**, 1 g, 30 mmol) in AcOH (20 mL) was added SO_2Cl_2 (14.4 mL, 36 mmol, 1.2 equiv) and the mixture was stirred overnight at 50 °C. The mixture was concentrated and the residue was purified by prep-HPLC to afford a mixture containing both **50** and **51**. This mixture (0.5 g, 1.92 mmol) was mixed with 1 N NaOH (6 mL) in THF (30 mL) and stirred at rt for 2 h. The reaction mixture was acidified with 1 N HCl, extracted with EtOAc (100 mL) and concentrated to afford the residue (0.377 g, yield 95%). The residue was separated by SFC chiral chromatography over ChiralPak AD-5 μm to give **8** (150 mg) and **19** (120 mg). ^{1}H NMR of **8** (400 MHz, DMSO-d_6): δ 12.16 (s, 1H), 9.15 (s, 1H), 7.47 (d, 1H), 7.25 (d, 1H), 4.93 (s, 2H), 3.12 (t, 2H), 2.41 (t, 2H) ppm; HPLC purity: 95% at 220 nm; MS (ESI−): m/z = 239 (M−1). ^{1}H NMR of **19** (400 MHz, DMSO-d_6): δ 12.06 (s, 1H), 9.22 (s, 1H), 7.39 (d, 1H), 7.18 (d, 1H), 4.93 (s, 2H), 2.96 (t, 2H), 2.52 (t, 2H) ppm; HPLC purity: 97.5% at 220 nm; MS (ESI−): m/z = 239 (M−1).

Synthesis of 3-(6-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid (**9**): To a solution of diisopropylamine (20 mL, 1.1 equiv) in THF (250 mL) was added *n*-BuLi (2.5 M, 58 mL, 1.1 equiv) at −10 °C during 10 min. The mixture was stirred at −20 °C for 30 min and cooled to −78 °C. Then 2-bromo-4-fluoro-1-methylbenzene (**52**, 16.4 mL) was added to the solution for 10 min. After being stirred for 2 h, DMF (12 mL, 1.2 equiv) was added to the mixture during 10 min at −78 °C and stirred for additional 10 min. The mixture was quenched with water, extracted with EA (2 × 500 mL), dried over Na_2SO_4 and evaporated to give **53** (24 g, yield 84%). TLC analysis of **53** (silica gel plate, PE/EA = 10:1): R_f = 0.6. To a solution of Ph_3PCH_2COOEt bromide (73.7 g, 165.6 mol, 3.6 equiv) in DMSO (200 mL) was added *t*-BuOK (17.5 g, 156.4 mmol, 3.4 equiv) at 0 °C and the mixture was stirred for 1 h. A solution of **53** (10 g, 46 mmol) in DMSO (50 mL) was added at 0 °C and the mixture was stirred at rt for 3 h, quenched with water (200 mL), extracted with PE (3 × 200 mL), washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified on a silica gel column eluted from PE to PE/EA=20:1 to give **54** as an oil (10.5 g, yield 80%). TLC analysis of **54** (silica gel plate, PE/EA = 10:1): R_f = 0.6. To a solution of NBS (3.7 g, 20 mmol) and **54** (5 g, 17.4 mmol) in CCl_4 (174 mL) was added BPO (200 mg, 0.9 mmol) under N_2. The mixture was stirred at 85 °C for 2 h and cooled to rt. The organic phase was washed with water (100 mL) and brine, dried over Na_2SO_4, and evaporated. The crude residue was purified on a silica gel column eluted with PE/EA = 10:1 to give **55** (2.4 g, yield 38%). TLC analysis of **55** (silica gel plate, PE/EA = 10:1): R_f = 0.5. A mixture of **55** (1.28 g, 3.5 mmol) and KOAc in DMF (15 mL) was stirred at 50 °C for 1 h. The reaction was diluted with EA (20 mL) and water (50 mL). The aqueous phase was extracted with EA (2 × 20 mL). The combined organic phase was washed with water (100 mL) and brine, dried over Na_2SO_4 and evaporated. The oil residue was purified on a silica gel column eluted with PE/EA = 20:1 to give **56** (1.2 g, yield 100%). TLC analysis of **56** (silica gel plate, PE/EA = 10:1): R_f = 0.6. A solution of **56** (200 mg, 0.58 mmol), Pin_2B_2 (181 mg, 0.7 mmol), KOAc (195 mg, 1.74 mmol) and $Pd(PPh_3)_2Cl_2$ (17 mg, 0.04 equiv) in 1,4-dioxane (3 mL) was stirred at 80 °C under N_2 overnight. Then the reaction mixture was diluted with EA (2 mL) and water (5 mL). The aqueous phase was extracted with EA (2 × 2 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified on a silica gel column eluted with PE/EA = 10:1 to give **57** (115 mg, yield 51%). TLC analysis of **57** (silica gel plate, PE/EA = 10:1): R_f = 0.4. To a solution of **57** (500 mg, 1.3 mmol) in THF/MeOH/H_2O = 3:2:1 (20 mL) was added NaOH (160 mg, 4 mmol) at rt and the mixture was stirred for 2 h. It was acidified with HCl (6 N, 1 ~ 2 mL, pH 1 ~ 2) and stirred for additional 0.5 h. Then the mixture was diluted with water (20 mL) and EA (10 mL). The aqueous phase was extracted with EA (2 × 10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and evaporated to give a solid (420 mg). The solid was recrystallized from MeOH (15 mL) and dried under high vacuum to give **58** as a white solid (150 mg, yield 70%). ^{1}H NMR of **58** (300 MHz, DMSO-d_6): δ 12.48 (s, 1H), 9.45 (s, 1H), 7.97 (d, 1H), 7.37–7.50 (m, 2H), 6.77 (d, 1H), 4.99 (s, 2H) ppm. A solution of **58** (50 mg, 0.225 mmol) and 10% Pd/C (10 mg) in EA (10 mL) was stirred at rt under H_2 for 1 h. The mixture was filtered and evaporated to give the desired final compound **9** as a white solid (50 mg, 100% yield). ^{1}H NMR of **9** (500 MHz, DMSO-d_6): δ 12.07 (s, 1H), 9.10 (s, 1H), 7.27–7.21 (m, 2H), 4.94 (s, 2H), 3.01 (t, 2H), 2.49 (m, 2H) ppm; HPLC purity: 99.3% at 220 nm; MS (ESI+): m/z = 247 (M+23).

Syntheses of 3-(1-hydroxy-6-nitro-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid (**10**), *3-(4-amino-1-hydroxy-1,3-dihydrobenzo[c][1,2] oxaborol-7-yl)propanoic acid* (**17**), *3-(4-acetamido-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid* (**18**) *and 1-hydroxy-3,6,8,9-tetrahydro-[1,2]oxaborolo[3,4-f]quinolin-7(1H)-one* (**60**): To fuming HNO_3 (9.6 mL, 2 mL/mmol) was added **1** (2 g, 9.7 mmol) at −30 °C and the mixture was stirred for 0.5 h at −30 °C. The mixture was poured into ice-water, stirred for 20 min and extracted with EA. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after evaporation was purified on a silica gel column to give **10** (720 mg, yield 30%). ^{1}H NMR of **10** (500 MHz, DMSO-d_6): δ 12.15 (s, 1H), 9.38 (s, 1H), 7.99 (d, 1H), 7.47 (d, 1H), 5.06 (s, 2H), 3.21 (t, 2H), 2.55 (t, 2H) ppm. Also separated was compound **59** (720 mg, yield 30%). ^{1}H NMR of **59** (500 MHz, DMSO-d_6): δ 12.12 (s, 1H), 9.39 (s, 1H), 8.22 (d, 1H), 7.49 (d, 1H), 5.35 (s, 2H), 3.14 (t, 2H), 2.61 (t, 2H) ppm. To a solution of **59** (900 mg, 3.58 mmol) in EA (18 mL) was added 10% Pd/C (360 mg). The reaction vessel was vacuumed and backfilled with H_2 for three times. After being stirred at rt for 1 h, the mixture was filtered and evaporated. The residue was purified by column chromatography to give **17** (350 mg, yield 44%). ^{1}H NMR of **17** (500 MHz, DMSO-d_6): δ 11.89 (s, 1H), 8.71 (s, 1H), 6.83 (d, 1H), 6.55 (d, 1H), 4.80 (br s, 2H), 4.75 (s, 2H), 2.83 (t, 2H), 2.43 (t, 2H) ppm; HPLC purity: 99.4% at 220 nm; MS (ESI+): m/z = 222.3 (M+1). To a solution of **17** (100 mg, 0.45 mmol) in DCM/THF/MeOH (2 mL/4 mL/5 drop) was added TEA (94 μL, 0.675 mmol, 1.5 equiv) and AcCl (2 mL). The mixture was stirred at rt for 2 h and diluted with EA (50 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue was purified by column chromatography to give **18** (30 mg, yield 25%). ^{1}H NMR of **18** (300 MHz, DMSO-d_6): δ 12.02 (br s, 1H), 9.45 (s, 1H), 8.98 (br s, 1H), 7.48 (d, 1H), 7.11 (d, 1H), 5.00 (s, 2H), 2.97 (t, 2H), 2.51 (t, 2H), 2.04 (s, 3H) ppm; HPLC purity: 94% at 220 nm; MS (ESI+): m/z = 264 (M+1). To a solution of **10** (100 mg, 0.398 mmol) in EtOH (3.9 mL) was added Fe (220 mg, 3.98 mmol, 10 equiv) and 12 N HCl (0.66 mL, 7.96 mmol, 20 equiv). The mixture was stirred at rt for 1 h, filtered and evaporated. The residue was purified by column chromatography over silica gel to give **60** (30 mg, yield 34%). ^{1}H NMR of **60** (300 MHz, DMSO-d_6): δ 10.05 (s, 1H), 8.98 (s, 1H), 7.14 (d, 1H), 6.96 (d, 1H), 4.90 (s, 2H), 3.05 (t, 2H), 2.44 (t, 2H) ppm; HPLC purity: 100% at 220 nm; MS (ESI+): m/z = 204 (M+1).

Synthesis of 3-(1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid (**11**): To a solution of Ph_3PCH_2COOEt bromide (76.1 g, 177.56 mmol, 2 equiv) in DMSO (344 mL) was added *t*-BuOK (23.9 g, 195.3 mmol, 2.2 equiv) under N_2 and the mixture was stirred for 1 h at rt. A solution of 2-hydroxy-5-methoxybenzaldehyde (**61**, 13.5 g, 88.78 mmol) in DMSO (100 mL) was added and the mixture was stirred overnight at rt. It was quenched with water (800 mL) and stirred for 0.5 h. The mixture was extracted with EA (2 × 300 mL) and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography eluted with PE/EA = 4:1 to give **66** (12 g, yield 61%). TLC analysis of **66** (silica gel plate, EA/PE = 3:7): R_f = 0.3. To a mixture of $(CH_2O)_n$ (4.9 g, 162.1 mmol, 3 equiv) in dry THF (150 mL) were added $MgCl_2$ (10.2 g, 108 mmol, 2 equiv) and TEA (15 mL, 2 equiv) under N_2. Then a solution of **66** (12.0 g, 54.0 mmol, 1 equiv) in dry THF (120 mL) was added at rt. The mixture was refluxed overnight, cooled to rt and diluted with water and EA (400 mL). The organic layer was washed with 1 N HCl (2 × 200 mL), water (200 mL) and brine, dried over anhydrous sodium sulfate. The residue after evaporation was purified on a silica gel column eluted with PE/EA = 9:1 to give **71** (7.1 g, yield 53%). TLC analysis of **71** (silica gel plate, EA/PE = 1:9): R_f = 0.3. To a solution of **71** (6.0 g, 23.99 mmol) in DCM (160 mL) were added pyridine (9.7 ml, 119.95 mmol, 5 equiv) and Tf_2O (8.9 mL, 52.8 mmol, 2.2 equiv) at 0 °C. The mixture was stirred at rt for 2 h and then washed with water (2 × 60 mL), 0.5 N HCl (2 × 70 mL), brine, dried over anhydrous sodium sulfate. The residue after evaporation was purified on a silica gel column eluted with PE/EA=9:1 to give **76** (9.5 g, yield 89%). TLC analysis of **76** (silica gel plate, EA/PE = 1:9): R_f = 0.3. To a solution of **76** (3 g, 7.83 mmol) in 1,4-dioxane (40 mL) were added KOAc (1.92 g, 19.57 mmol, 2.5 equiv) and Pin_2B_2 (2.18 mg, 8.61 mmol, 1.1 equiv). The mixture was bubbled with N_2 for 15 min and then $Pd(PPh_3)_2Cl_2$ (550 mg, 0.783 mmol, 0.1 equiv) was added. The reaction mixture was stirred under N_2 at 95 °C overnight, cooled to rt and filtrated. The residue after evaporation was purified on a silica gel column eluted with PE/EA = 9:1 to give **81** (2.5 g, yield 89%). TLC analysis of **81** (silica gel plate, EA/PE = 1:9): R_f = 0.3. To a solution of **81** (2.5 g, 6.94 mmol) in MeOH (35 mL) was added $NaBH_4$ (289 mg, 7.63 mmol, 1.1 equiv) at 0 °C. The mixture was stirred for 1.5 h at rt and then 1 N HCl (5 mL) was added to adjust pH 1–2. After being stirred for 0.5 h, the mixture was extracted with EA (3 × 50 mL) and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluted with PE/EA = 4:1 to give **86** (300 mg, yield 17%). TLC analysis of **86** (silica gel plate, EA/PE = 3:7): R_f = 0.3. ^{1}H NMR of **86** (300 MHz, DMSO-d_6): δ 9.12 (s, 1H), 8.01 (d, 1H), 7.36 (s, 1H), 7.02 (s, 1H), 6.86 (d, 1H), 4.96 (s, 2H), 4.19 (q, 2H), 3.84 (s, 3H), 1.26 (t, 3H) ppm. Mass (ESI+): m/z = 263 (M+H). To a solution of **86** (430 mg, 1.6 mmol) in EA (8 mL) was added 10% Pd/C (126 mg). The reaction vessel was vacuumed and backfilled with H_2. After being stirred at rt for 2 h, the mixture was filtered and evaporated to give **91** (205 mg, yield 49%). TLC analysis of **91** (silica gel plate EA/PE = 3:7): R_f = 0.6. ^{1}H NMR of **91** (300 MHz, DMSO-d_6): 8.80 (s, 1H), 6.79 (s, 1H), 6.71 (s, 1H), 4.90 (s, 2H), 4.03 (q, 2H), 3.76 (s, 3H), 2.96 (t, 2H), 2.61 (t, 2H), 1.15 (t, 3H) ppm. HPLC purity: 95.1% at 220 nm; Mass (ESI+): m/z = 287 (M+23). To a solution of **91** (47.2 mg, 0.178 mmol) in MeOH/H_2O = 3:1 (1.2 mL) was added LiOH·H_2O (7.5 mg, 0.178 mmol). After being stirred at rt for 4 h, the mixture was acidified to pH 5 with AcOH and followed by extraction with EA (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified by silica gel column chromatography eluted with PE/EA = 7:3 to give the final compound **11** (13.4 mg, yield 32%). ^{1}H NMR of **11** (300 MHz, DMSO-d_6): 11.97 (br s, 1H), 8.76 (br s, 1H), 6.78 (s, 1H), 6.72 (s, 1H), 4.90 (s, 2H), 3.76 (s, 3H), 2.94 (t, 2H), 2.51 (t, 2H). HPLC purity: 100% at 220 nm; Mass (ESI+): m/z = 237 (M+1).

Synthesis of 3-(1-hydroxy-5-methyl-1,3-dihydrobenzo[c][1,2]oxaborol-7-

yl)propanoic acid (**12**): This compound was prepared by the similar method described above for the synthesis of **11**. ^{1}H NMR of **12** (500 MHz, DMSO-d_6): δ 11.98 (s, 1H), 8.83 (s, 1H), 7.01 s, 1H), 6.96 (s, 1H), 4.91 (s, 2H), 2.95 (t, 2H), 2.53 (t, 2H), 2.31 (s, 3H) ppm. HPLC purity: 98.2% at 220 nm; Mass (ESI+): m/z = 243 (M+23).

Synthesis of 3-(5-chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid (**13**): This compound was prepared by the similar method described above for the synthesis of **11**. ^{1}H NMR of **13** (500 MHz, DMSO-d_6): δ 12.06 (br s, 1H), 9.10 (s, 1H), 7.31 (s, 1H), 7.21 (s, 1H), 4.95 (s, 2H), 2.99 (t, 2H), 2.56 (t, 2H); HPLC purity: 96.8% at 220 nm; MS (ESI+): m/z = 241 (M+1).

Synthesis of 3-(5-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid (**14**): This compound was prepared by the similar method described above for the synthesis of **11**. ^{1}H NMR of **14** (500 MHz, DMSO-d_6): 12.05 (s, 1H), 9.00 (s, 1H), 7.05 (d, 1H), 6.99 (d, 1H), 4.94 (s, 2H), 3.00 (t, 2H), 2.56 (t, 2H) ppm; HPLC purity: 97.2% at 220 nm; Mass (ESI+): m/z = 225 (M+H).

Synthesis of 3-(1-hydroxy-4-methyl-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid (**15**): This compound was prepared by the similar method described above for the synthesis of **11**. ^{1}H NMR of **15** (500 MHz, DMSO-d_6): δ 11.97 (s, 1H), 8.88 (s, 1H), 7.13 (d, 1H), 7.05 (d, 1H), 4.92 (s, 2H), 2.96 (t, 2H), 2.51 (t, 2H), 2.17 (s, 3H) ppm; HPLC purity: 95.3% at 220 nm; Mass (ESI+): m/z = 243 (M+23).

Synthesis of 3-(1-hydroxy-4-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanoic acid (**16**): To a solution of **53** (1 g, 4.6 mmol) in *t*-BuOH (33 mL) were added 2-methyl-2-butene (3.4 mL, 32.2 mmol, 7 equiv), a solution of $NaClO_2$ (833 mg, 9.2 mmol, 2 equiv) and $NaH_2PO_4{\cdot}3H_2O$ (2.15 g, 13.8 mmol, 3 equiv) in water (14 mL). The mixture was stirred at rt for 30 min and then was quenched 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 evaporation was purified by silica gel column chromatography to give **96** (1.07 g, yield 100%). To a solution of **96** (1.53 g, 6.56 mmol) in DMF (30 mL) was added K_2CO_3 (2.26 g, 16.4 mmol, 2.5 equiv), and the mixture was stirred at rt for 10 min. MeI (0.815 mL, 13.1 mmol, 2 equiv) was added and then the reaction was stirred for 1 h, quenched with 1 N HCl and extracted with TBME. The organic phase was washed with saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by silica gel column chromatography to give **97** (1.5 g, 94%). A mixture of **97** (7.9 g, 32 mmol), NBS (17.1 g, 96 mmol, 3 equiv), BPO (0.78 g, 3.2 mmol, 0.1 equiv) in CCl_4 (133 mL, c = 0.24) was refluxed under N_2 for 6 h, cooled and filtered. The residue after rotary evaporation was purified by silica gel column chromatography to give **98** (11.4 g, yield 89%). To a solution of 1 N MeONa in MeOH (180 mL, 6 equiv) was added **98** (11.5 g, 28.3 mmol) at rt. The mixture was stirred at 65 °C for 4 h, quenched with 2 N HCl to adjust pH 2, and followed by addition of water 100 mL. The aqueous phase was extracted with EA (2 × 200 mL) and the combined organic phase was washed with brine and dried. The residue after evaporation was purified by silica gel column chromatography to give **99** (2.94 g, yield 38%). ^{1}H NMR of **99** (300 MHz, DMSO-d_6): δ 10.10 (s, 1H), 7.95 (d, 1H), 7.35 (d, 1H), 3.93 (s, 3H), 3.88 (s, 3H) ppm. To a solution of **99** (3.8 g, 13.97 mmol) in toluene (76 mL) were added PPTS (350 mg, 1.39 mmol, 0.1 equiv) and ethane-1,2-diol (1.73 g, 27.94 mmol, 2 equiv). The reaction was stirred at 130 °C overnight and evaporated to give yellow oil. The residue was purified by silica gel column chromatography eluted with PE/EA = 4:1 to give **100** (3.9 g, yield 89%). To a solution of **100** (0.5 g, 1.58 mmol) in 1,4-dioxane (8 mL) were added KOAc (388 mg, 3.95 mmol, 2.5 equiv), Pin_2B_2 (442 mg, 1.74 mmol, 1.1 equiv). The solution was bubbled with N_2 for 15 min and then $Pd(PPh_3)_2Cl_2$ (55.5 mg, 0.079 mmol, 0.05 equiv) was added. The mixture was stirred under N_2 at 95 °C overnight, cooled to rt and filtrated. The residue after evaporation was purified by silica gel column chromatography eluted with PE/EA = 9:1 to give **101** (230 mg, yield 40%). To a solution of **101** (450 mg, 1.23 mmol) in MeOH (6.2 mL) was added $NaBH_4$ (51.4 mg, 1.36 mmol, 1.1 equiv) at 0 °C. The reaction was stirred for 1.5 h at rt and 2 N HCl (5 mL) was added to adjust pH 1–2. The mixture was stirred for 0.5 h and extracted with EA (3 × 20 mL). The organic layer was washed by brine, dried over anhydrous sodium sulfate and concentrated. The residue after evaporation was purified by silica gel column chromatography eluted with PE/EA = 7:3 to give **102** (190 mg, yield 80%). ^{1}H NMR (300 MHz, DMSO-d_6): 10.19 (s, 1H), 9.10 (s, 1H), 7.97 (d, 1H), 7.27 (d, 1H), 5.03 (s, 2H), 3.94 (s, 3H) ppm; HPLC purity: 92.6% at 220 nm and 98.0% at 266 nm. Formic acid (0.32 mL, 8.85 mmol, 10 equiv) and TEA (0.49 mL, 3.54 mmol, 4 equiv) was mixed at 0 °C, and stirred at rt for 10 min. Then **102** (170 mg, 0.885 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (140 mg, 0.973 mmol, 1.1 equiv) were added. The mixture was stirred at rt for 1 h and at 114 °C overnight, cooled to rt and acidified with 1 N HCl at 0 °C. After being stirred for 10 min, it was extracted with EA (3 × 20 mL). The organic layer was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The residue after evaporation was purified by preparative TLC to give the final compound **16** (15.6 mg, yield 7.5%) as a white solid. ^{1}H NMR of **16** (300 MHz, DMSO-d_6): 11.95 (s, 1H), 8.95 (s, 1H), 7.11 (d, 1H), 6.94 (d, 1H), 4.89 (s, 2H), 3.78 (s, 3H), 2.93 (t, 2H), 2.50 (t, 2H) ppm; HPLC purity: 96.0% at 220 nm; Mass (ESI+): m/z = 237 (M+1).

Synthesis of 3-(4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-7-yl)propanoic acid (**20**): To a solution of **97** (4.6 g, 18.6 mmol) in CCl_4 (81 mL) was added NBS (3.31 g, 18.6 mmol, 1 equiv) and BPO (225 mg, 0.93 mmol, 0.05 equiv). The reaction was stirred under N_2 at 82 °C overnight, cooled to rt, filtered and evaporated. The residue was purified to give **103** (3.6 g, yield 60%). ^{1}H NMR of **103** (300 MHz, DMSO-d_6): δ 7.84 (m, 1H), 7.47 (m, 1H), 4.77 (s, 2H), 3.93 (s, 3H) ppm. To a mixture of **103** (3.6 g, 11 mmol) in 1,4-dioxane (22 mL) and water (9 mL) was added $CaCO_3$ (2.65 g, 26.5 mmol, 2.4 equiv). The reaction was stirred at 100 °C overnight, filtered 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 silica gel column chromatography to give **104** (2.4 g, yield 83%). ^{1}H NMR of **104** (500 MHz, DMSO-d_6): δ 7.67 (m, 1H), 7.43 (m, 1H), 5.55 (t, 1H), 4.51 (d, 2H), 3.91 (s, 3H) ppm. To a solution of **104** (2.4 g, 9.1 mmol) in DCM (46 mL) was added silica (2.4 g) and PCC (2.9 g, 13.6 mmol, 1.5 equiv). The mixture was stirred at rt for 4 h, filtered and evaporated. The residue was purified by silica gel column chromatography to give **105** (2 g, yield 84%). To a solution of **105** (2 g, 7.66 mmol) in toluene (33 mL) was added PPTS (192 mg) and ethane-1,2-diol (0.85 mL, 15.3 mmol, 2 equiv). The mixture was stirred at 138 °C overnight and then evaporated. The residue was purified by silica gel column chromatography to give **106** (2.23 g, yield 96%). ^{1}H NMR of **106** (300 MHz, DMSO-d_6): δ 7.72 (m, 1H), 7.47 (m, 1H), 5.96 (s, 1H), 3.91–4.11 (m, 7H) ppm. To a solution of **106** (3 g, 9.83 mmol) in 1,4-dioxane (49 mL) was added KOAc (4.142 g, 42.269 mmol, 4.3 equiv), Pin_2B_2 (3 g, 11.796 mmol, 1.2 equiv) and $Pd(Ph_3P)_2Cl_2$ (0.345 mL, 0.49 mmol, 0.05 equiv) under N_2. The reaction was stirred at 95 °C overnight under N_2, cooled and evaporated. The residue was purified by silica gel column chromatography to give **107** (3.46 g, crude yield 100%). To a solution of **107** (3.46 g, 9.83 mmol) in anhydrous EtOH (50 mL) was added $NaBH_4$ (929 mg, 24.5 mmol, 2.5 equiv) at 0 °C. The reaction was stirred at rt for 30 min and quenched with 2 N HCl. The mixture was stirred at rt for 30 min, followed by extraction with EA. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by silica gel column chromatography to give **108** (900 mg, yield 51%). ^{1}H NMR of **108** (300 MHz, DMSO-d_6): δ 10.34 (s, 1H), 9.49 (s, 1H), 7.96 (m, 1H), 7.51 (m, 1H), 5.02 (s, 2H) ppm; HPLC purity: 100% at 220 nm; MS (ESI+): m/z = 203 (M+23). To a solution of Ph_3PCH_2COOEt bromide (2.98 g, 6.9 mmol, 2.5 equiv) in DMSO (20 mL) was added *t*-BuOK (0.6783 g, 5.55 mmol, 2 equiv) under N_2. After being stirred at rt for 1 h, to the reaction mixture was added a solution of **108** (500 mg, 2.778 mmol) in DMSO (8 mL). The mixture was stirred at rt overnight, quenched with water 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 silica gel column chromatography to give **109** (560 mg, yield 80%). ^{1}H NMR of **109** (500 MHz, DMSO-d_6): δ 9.54 (s, 1H), 8.06 (d, 1H), 7.91 (m, 1H), 7.33 (m, 1H), 6.76 (d, 1H), 5.10 (s, 2H), 4.20 (q, 2H), 1.25 (t, 3H) ppm. To a solution of **109** (420 mg, 1.68 mmol) in EA (40 mL) was added 10% Pd/C (42 mg). The reaction vessel was vacuumed and backfilled by H_2 for three times. The mixture was stirred at rt for 1 h, filtered and evaporated. The residue was purified by silica gel column chromatography to give **111** (373 mg, yield 88%). ^{1}H NMR of **111** (500 MHz, DMSO-d_6): δ 9.20 (s, 1H), 7.14–7.21 (m, 2H), 5.04 (s, 2H), 4.02 (q, 2H), 3.01 (t, 2H), 2.60 (t, 2H), 1.14 (t, 3H) ppm; HPLC purity: 100% at 220 nm; MS (ESI+): m/z = 275 (M+23). To a solution of **111** (350 mg, 1.368 mmol) in THF/MeOH/water = 3:2:1 (7 mL) was added $LiOH{\cdot}H_2O$ (233 mg, 5.55 mmol, 4 equiv). The mixture was stirred at rt overnight, added with water 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 silica gel column chromatography to give the final compound **20** (250 mg, yield 81%). ^{1}H NMR of **20** (500 MHz, DMSO-d_6): δ 11.98 (s, 1H), 9.16 (s, 1H), 7.12–7.19 (m, 2H), 5.01 (s, 2H), 2.96 (t, 2H), 2.51 (t, 2H); HPLC purity: 98.9% at 220 nm; MS (ESI+): m/z = 225 (M+1).

Synthesis of 3-(3-hydroxy-1,3-dihydroisobenzofuran-4-yl)propanoic acid (**21**): Compound **112** was prepared from **1** as previously reported.[2] To a solution of **112** (2 g, 9.09 mmol) in toluene (57 mL) were added 20% Na_2CO_3/H_2O (5.5 mL) and $Pd(PPh_3)_4$ (1.05 g, 0.92 mmol, 0.1 equiv) under N_2. Then bromoethene in THF (19 mL, 2 equiv) was added and the reaction was stirred at 90 °C overnight. It was filtered and dried over anhydrous $MgSO_4$ followed by filtration and evaporation. The residue was purified by silica gel column chromatography to give **113** (0.91 g, yield 41%). To a solution of **113** (910 mg, 4.05 mmol) and DIPEA (1.53 mL, 8.91 mmol, 2.2 equiv) in DCM (20 mL) was added MOMCl (0.49 g, 6.08 mmol, 1.5 equiv) at 0 °C. The reaction was stirred at rt for 10 h, quenched with NH_4Cl-saturated aqueous solution and extracted with DCM (3 × 15 mL). The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The residue after rotary evaporation was purified by silica gel column chromatography to give **114** (0.67 g, yield 63%). To a mixture of **114** (600 mg, 2.27 mmol) and K_2OsO_4 (3 mg) in THF (10 mL) and water (0.8 mL) was added a solution of $NaIO_4$ (1.1 g) in water (3 mL) dropwise. The reaction mixture was stirred at rt for 10 h followed by filtration. The filtrate was extracted with DCM (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography to give **115** (390 mg, yield 64%). To a solution of **115** (300 mg, 1.13 mmol) in THF (2.8 mL) was added 4 N HCl (1.4 mL). The reaction mixture was stirred at rt for 1 h and quenched with saturated $NaHCO_3$ (30 mL). The aqueous phase was extracted with DCM (3 × 10 mL). The residue after evaporation was purified by silica gel column chromatography to give **116** (120 mg, yield 68%). ^{1}H NMR of **116** (500 MHz, DMSO-d_6): δ 7.28 (t, 1H), 7.16–7.12 (m, 2H), 6.63 (d, 1H), 6.42 (dd, 1H), 5.07 (d, 1H), 4.85 (d, 1H), 3.59 (s, 3H), 2.97-2.85 (m, 2H), 2.71–2.61 (m, 2H) ppm. To a solution of **116** (49.8 mg, 0.224 mmol) in MeCN (1.1 mL) was added $LiOH{\cdot}2H_2O$ (13.5 mg, 0.224 mmol, 1 equiv). The mixture was stirred at rt for 10 h, concentrated and dried under high vacuum to provide the final compound **21** as its lithium salt (51.5 mg, yield 100%). ^{1}H NMR of **21** lithium salt (500 MHz, DMSO-d_6): δ 7.38 (br s, 1H), 7.22 (t, 1H), 7.10 (d, 1H), 7.06 (d, 1H), 6.41 (s, 1H), 5.04 (d, 1H), 4.81 (d, 1H), 2.82–2.78 (m, 2H), 2.27–2.23 (m, 2H) ppm; HPLC purity: 92.5% at 220 nm. MS (ESI+): m/z = 191 (M−17).

Synthesis of 3-(4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-7-yl)acrylic acid (**110**): The mixture of **109** (80 mg, 0.3199 mmol) and $LiOH{\cdot}H_2O$ (53.9 mg,

1.28 mmol, 4 equiv) in THF/MeOH/water = 3:2:1 (2 mL) was stirred at rt overnight, added with water and extracted with EA. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The residue after evaporation was purified by silica gel column chromatography to give **110** (20 mg, yield 28%). ^{1}H NMR of **110** (500 MHz, DMSO-d_6): δ 12.25 (s, 1H), 9.50 (s, 1H), 8.02 (d, 1H), 7.86 (m, 1H), 7.32 (m, 1H), 6.64 (d, 1H), 5.09 (s, 2H) ppm; HPLC purity: 94.0% at 220 nm and 94.8% at 266 nm. MS (ESI+): m/z = 223 (M+1).