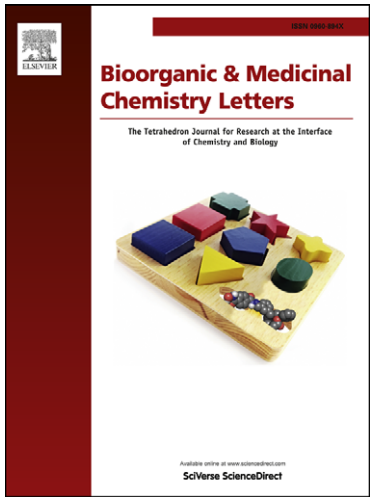

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Synthesis and antibacterial evaluation of a novel tricyclic oxaborole-fused fluoroquinolone

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Abstract—We have designed and synthesized a novel class of compounds based on fluoroquinolone antibacterial prototype. The design concept involved the replacement of 3-carboxylic acid in ciprofloxacin with an oxaborole-fused ring as an acid-mimicking group. The synthetic method employed in this work provides a good example of incorporating boron atom in complex molecules with multiple functional groups. The antibacterial activity of the newly synthesized compounds has been evaluated.

Fluoroquinolones represent an important class of synthetic antibiotics for the treatment of serious bacterial infections.[1] This class of compounds, exemplified by ciprofloxacin (Cipro™) (Figure 1), exhibit broad-spectrum activity for both Gram-negative and Gram-positive bacteria by inhibiting bacterial DNA replication.[2] However, the development of resistance to this class of drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious global health threat. Particularly, most clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) have become resistant to fluoroquinolone antibiotics within five years of their introduction.[3] Also, the proportion of clinical isolates of *Pseudomonas aeruginosa* that are resistant to fluoroquinolone antibiotics has increased by 30% over the past 20 years.[4] Furthermore, similar increases in resistance are now being observed with *Escherichia coli* on global FQ resistance,[5] which is a concern as *E. coli* causes more nosocomial blood stream infections than *S. aureus*.[6] Therefore, there is an urgent need to identify new fluoroquinolone derivatives with novel structural features.

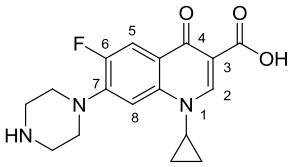


Figure 1. Ciprofloxacin and the numbering scheme of fluoroquinolone.

To date all of the marketed fluoroquinolone antibiotics contain the C-3 carboxylic acid group. The SAR investigations on fluoroquinolones revealed that the 3-carboxylic acid is important for their antibacterial activities.[7] Previous studies have produced no active quinolones with a modification of the 3-carboxylic acid group with the exception of the modified groups that could be converted to the carboxylic acid in vivo.[8] Figure 2 illustrates many examples of the "inactive or weakly active" replacements of the 3-carboxylic acid in fluoroquinolones, including sulfonic acid,[9] sulfonamide,[10] phosphonic acid,[10] hydroxamic acid,[11] and tetrazole.[12] Interestingly, bioisosteric replacement of the 3-carboxylic acid with a fused isothiazolone ring, originally discovered by Chu and co-workers, resulted in the active compound with enhanced acivity.[13] Recent investigations on new variations of this isothiazoloquinolone class led to the discovery of new antibacterial with excellent *in vitro* and *in vivo* profiles.[14] While the possible binding interactions of these tricyclic structures remain to be elucidated, these results prompt us to investigate other new ring-fused analogues by replacing the 3-carboxylic acid group in fluoroquinolone.

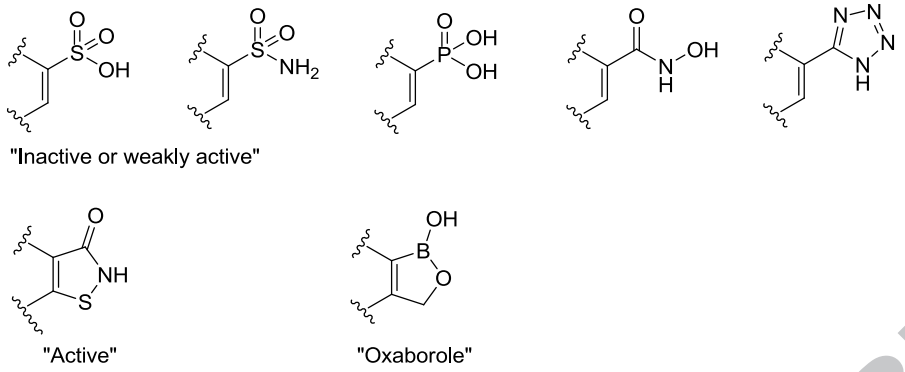


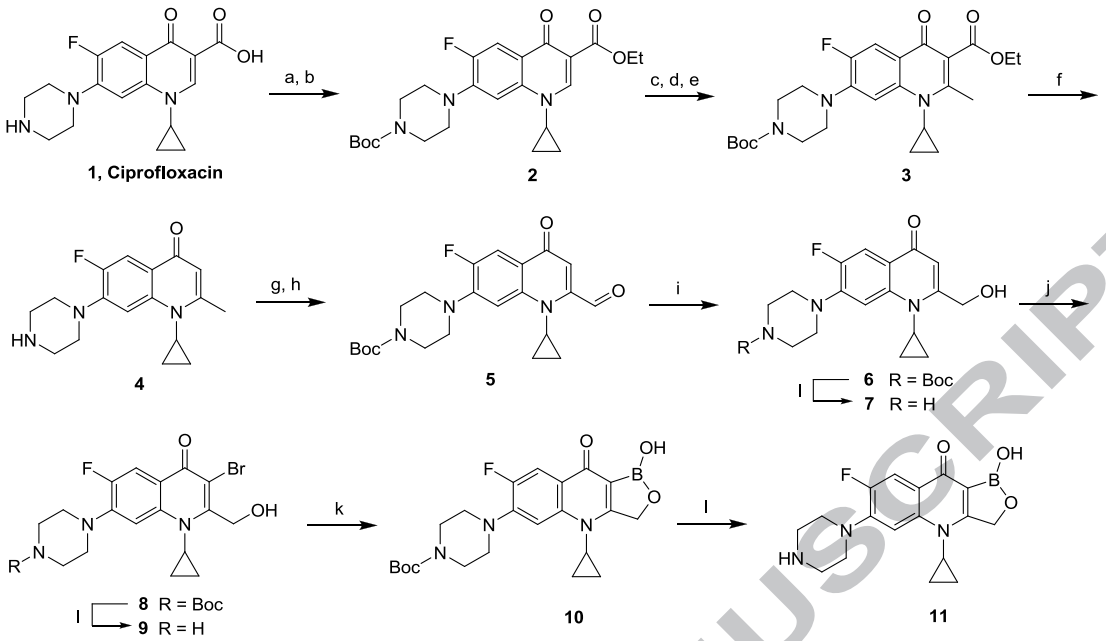
Figure 2. The 3-carboxylic acid replacements in fluoroquinolones reported in the literature and the proposed oxaborole replacement.

Boronic acids derivatives have been studied extensively as potential therapeutics.[15,16] Recently, we have discovered a diverse set of heterocyclic benzoxaboroles with broad applications to numerous disease indications.[17-20] Several benzoxaborole-based compounds have entered human clinical trials for antifungal, anti-inflammatory, antibacterial and antitrypanosomiasis indications, exemplified by AN2690,[17] AN2728,[18] AN3365 (GSK'052),[19] and AN5568 (SCYX-7158).[20] Importantly, benzoxaboroles are stronger acids than phenylboronic acids with lower pK_a values,[21] and they are metabolically stable with good drug-like properties. Therefore, we became intrigued by the idea of replacing the 3-carboxylic acid group in fluoroquinolone with a ring-fused oxaborole moiety (Figure 2). This paper describes the synthesis and antibacterial evaluation of the oxaborole-fused tricyclic ciprofloxacin (Scheme 1).

As shown in Scheme 1, we chose to start the synthesis from commercially available ciprofloxacin (**1**). Ciprofloxacin **1** was first converted to its ethyl ester and was then protected with the Boc group to give **2**. Compound **2** was converted to **3** by introducing methyl group at the C-2 position according to literature procedure.[22] Subsequently, reflux of compound **3** with 6N hydrochloric acid in ethanol afforded decarboxylated quinolone **4** in quantitative yield in a single step. In this step, the ester group of **3** was hydrolyzed to free carboxylic acid and decarboxylated, and the Boc-protecting group was also removed under the reaction conditions. 2-Methyl quinine **4** was protected with the Boc group and then was oxidized with selenium dioxide in dioxane to afford 2-formyl quinolone **5**. Reduction of **5** with sodium borohydride in methanol provided alcohol **6** in 58% yield for two steps. After selected bromination of **6** with pyridine tribromide in dichloromethane, 3-bromo quinolone **8** was obtained in 58% yield.

With the intermediate **8** prepared as a precursor for oxaborole formation, we turned our attention to the key step to introduce boron atom in the molecule. Since there is no literature precedent for introducing a boron atom into quinolones, compound **8**, which also contains a high density of multiple functional groups, poses a significant challenge as a starting point with potential poor yields or boronylation failure.[23] Initially, we investigated two standard boronylation procedures that we have extensively used in the past.[17-20] Treatment of bromide **8** with *n*-BuLi followed by reaction with triisopropyl borate gave the debrominated product **6** as a major product. Reaction of **8** with pinacol diboron in the presence of palladium catalyst gave a complex mixture containing debrominated product **6** and unidentified components. In either case, no trace amount of any desired boron-containing product (boronic acid, boronate or cyclized oxaborole) in the reaction mixture was identified after multiple attempts. The free hydroxyl group in **8** was also protected with MOM or acetyl group, and use of the resulting bromide under the same boronylation conditions failed to give any expected boron-containing product.

These results led to the consideration of investigating other reagents for boronylation with the hope that the desired boron product could be identified. Recently Knochel and co-workers have reported the use of turbo-Grignard reagents for selective lithiation, deprotonation and nucleophilic additions.[24] Towards that direction, we were gratified to find that treatment of bromide **8** with *i*-PrMgCl/LiCl, followed by reaction with trimethyl borate at room temperature afforded oxaborole **10** in 37% isolated yield. In a single step, bromide **8** was converted to lithium salt and reacted with trimethyl borate to give the intermediate boronate, which was simultaneously hydrolyzed and cyclized to the adjacent hydroxymethyl group to afford the five-membered oxaborole. HPLC analysis of the crude mixture suggested that 80% of oxaborole **10** was formed, along with 20% of debrominated product **6**. The low isolated yield of **10** (37%) was due to the loss of this polar compound during the column purification, and was not optimized. Finally, treatment of **10** with HCl in dioxane provided the oxaborole-containing ciprofloxacin **11** as a light yellow solid.[25]



Scheme 1. Reagents and conditions: (a) EtOH, conc. H_2SO_4, reflux, 15 h, 80%; (b) Boc_2O, TEA, DCM, rt, 24 h, 66%; (c) MeMgBr, CuI, THF, -78 °C, 2 h, 47%; (d) PhSeCl, NaH, THF, 0.5 h; (e) H_2O_2, DCM, 0 °C 1 h, 62% for two steps; (f) 6N HCl, EtOH, reflux, overnight, 100%; (g) Boc_2O, TEA, DCM, rt, 2 h, 64%; (h) SeO_2, dioxane, 80 °C, overnight; (i) $NaBH_4$, MeOH, 1 h, 58% for two steps; (j) pyridine tribromide, DCM, 2 h, 58%; (k) i-PrMgCl·LiCl, 1.3 M solution, THF, $B(OMe)_3$, -10 °C to rt, 2 h, 37%; (l) Conc. HCl, dioxane, rt, 0.5 h, 94-95%.

Compounds **7, 9, 10** and **11** were evaluated *in vitro* in the microbroth assay against some key Gram-negative and Gram-positive bacterial organisms.[26] The Gram-negative strains reported in Table 1 are *E. coli* (wild-type) and *tolC* (efflux pump deficient strain) and *gyrA* mutants. The Gram-positive strain reported in Table 1 is *Staphylococcus aureus*. As expected, decarboxylated analog **7** and 3-bromo analog **9** exhibited no antibacterial activity, suggesting that the 3-carboxylic acid is important for the antibacterial activity of fluoroquinolones. The lack of antibacterial activity of compound **7** is consistent with the recently reported results on the decarboxylated ciprofloxacin.[27] The Boc-protected compound **10** was found to be devoid of antibacterial activity. The final oxaborole-fused ciprofloxacin **11** showed weak activities against the *E. coli* and *S. aureus* strains. The loss of activity against the *E. coli gyrA* mutants demonstrated that this weak activity was on-target.

Table 1. Minimum inhibitory concentration (MIC) assay data

Compd	**MIC (μg/mL)**[a]				
	E. coli[b]	*E. coli tolC*[c]	*E. coli gyrA* S83L[d]	*E. coli gyrA* D87Y[e]	*S. aureus* 29213
7	>256	>256	>256	>256	>256
9	>256	128	256	>256	>256
10	>256	>256	>256	>256	>256
11	128	16	64	32	128
Ciprofloxacin	0.015	0.004	0.06	0.03	0.25

[a] MIC assay was performed at least in duplicate on separate days with the highest MIC being taken, as described in Ref. 26
[b] K12 Δ*lacU169*
[c] K12 Δ*lacU169 tolC::*Tn*10*
[d] K12 Δ*lacU169 tolC::*Tn*10 gyrA* S83L
[e] K12 Δ*lacU169 tolC::*Tn*10 gyrA* D87Y

It has been suggested that the planarity between the 3-carboxylic acid group and the 4-keto group may be important for binding to the DNA gyrase or topoisomerase.[7] Recently x-ray co-crystal structure of moxifloxacin with topoisomerase-DNA complexes revealed that the keto acid moiety coordinates the noncatalytic Mg^{2+} ion in the active site.[28] The "active" fused isothiazolone ring system possesses an aromatic character, and the nitrogen proton is very acidic and can be considered to mimic the 3-carboxylic acid.[7] For the oxaborole-fused ciprofloxacin **11,** our molecular modeling studies suggest that the oxaborole moiety maintains a flat coplanar structure with the quinolone ring system. One possible reason for the lack of activity is that the oxaborole moiety is not very acidic compared to a carboxylic

acid and does not effectively mimic the 3-carboxylic acid in fluoroquinolones. The next step in the exploration would be to design new boron-fused fluoroquinolone analogues with potentially improved acidity while maintaining the flat structure of the ring system.

In summary, we have synthesized and evaluated a novel class of compounds based on fluoroquinolone antibacterial prototype. The design concept involved the replacement of 3-carboxylic acid in ciprofloxacin with a fused oxaborole ring as an acid-mimicking group. To the best of our knowledge, this is the first example of oxaborole-fused quinolone (or oxaborole-fused pyridone) that has been reported. The synthetic method employed in this work provides a good example of incorporating boron atom in complex molecules with multiple functional groups. The oxaborole-fused ciprofloxacin displays weak antibacterial activity, presumably due to the weak acidity of the oxaborole moiety. Continuing studies are underway to identify more effective bioisosteric replacements of the 3-carboxylic acid group in fluoroquinolones and to uncover new compounds with improved antibacterial activity.

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25. Experimental procedure for synthesis of **11** from **8**: To a solution of compound **8** (500 mg, 1.0 mmol) in dry THF (2 mL) in a salt-ice bath was added *i*-PrMgCl·LiCl dropwise (Aldrich catalog# 656984, 1.3 M THF solution, 4.5 mL, 5.9 mmol) in 20 min. Subsequently, trimethyl borate (0.65 mL, 5.8 mmol) was added dropwise. The reaction mixture was stirred for additional 2 h with temperature rising to room temperature. HPLC analysis of the crude mixture suggested that 80% of **10** was formed, along with 20% of debrominated product **6**. After methanol (0.65 mL) was added to quench the reaction, and ethyl acetate and water were added for work-up. The mixture was extracted with ethyl acetate for three times. The organic phase was combined, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography eluted with 0-20% methanol in dichloromethane to give **10** as a yellow solid (140 mg, yield 37%). Mp: >220 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H, B-OH), 7.69 (d, 1H, $^{3}J_{F-H}$ = 13.6 Hz, ArH), 7.44 (d, 1H, $^{4}J_{F-H}$ = 7.2 Hz, ArH), 5.07 (s, 2H, CH_2-O-B), 3.50 (m, 4H, N-CH_2), 3.28 (m, 1H, CH), 3.13 (m, 4H, N-CH_2), 1.40 (s, 9H, CH_3), 1.23 (m, 2H, CH_2), 1.06 (m, 2H, CH_2). ^{13}C NMR (400 MHz, DMSO-d_6) 176.2 (C=O), 170.8 (C2), 154.1 (C=O), 152.2 (d, $^{1}J_{C-F}$ = 244.1 Hz, C6), 143.4 (d, $^{2}J_{C-F}$ = 10.4 Hz, C7), 140.2 (C9), 121.9 (d, $^{3}J_{C-F}$ = 6 Hz, C10), 111.5 (d, $^{2}J_{C-F}$ = 21.6 Hz, C5); 107.6 (C8), 79.5 (C), 67.1 (CH_2), 50.0 (CH_2), 44.0 (CH_2), 43.0 (CH_2), 29.5 (CH), 28.5 (CH_3), 9.3 (CH_2), C-3 adjacent to boron was not observed. HRMS calcd for $C_{22}H_{28}BFN_3O_5$ $(M+H)^+$, 444.2106; found, 444.2109. To compound **10** (37 mg, 0.08 mmol) in 5 mL of dioxane was added 2 mL of conc. HCl. The mixture was stirred at room temperature for 0.5 h. After LC/MS analysis indicated that **10** was completely consumed, the solvent was removed *via* rotary evaporation to give **11** as a light yellow solid (30 mg, yield 95%). Mp: >220 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (b, 2H), 7.73 (d, 1H, $^{2}J_{F-H}$=12.8 Hz, ArH), 7.46 (d, 1H, $^{3}J_{F-H}$=6.8 Hz, ArH), 5.10 (s, 2H, CH_2-O-B), 3.41 (m, 4H, N-CH_2), 3.32 (m, 1H, CH), 3.27 (m, 4H, N-CH_2), 1.23 (m, 2H, CH_2), 1.08 (m, 2H, CH_2). ^{13}C NMR (400 MHz, DMSO-d_6) 175.7 (C=O), 171.1 (C2), 152.1 (d, $^{1}J_{C-F}$ = 244.1 Hz, C6), 142.6 (d, $^{2}J_{C-F}$ = 10.4 Hz, C7), 140.2 (C9), 121.7 (d, $^{3}J_{C-F}$ = 6 Hz, C10), 111.6 (d, $^{2}J_{C-F}$ = 21.6 Hz, C5); 107.5 (C8), 67.2 (CH_2), 46.9 (CH_2), 42.9 (CH_2), 29.8 (CH), 9.4 (CH_2), C-3 adjacent to boron was not observed. HRMS calcd for $C_{17}H_{19}BFN_3O_3$ $(M+H)^+$, 344.1582; found, 344.1582.
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Synthesis and antibacterial evaluation of a novel tricyclic oxaborole-fused fluoroquinolone

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