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A novel procedure for the synthesis of borylated quinolines and its application in the development of potential boron-based homeodomain interacting protein kinase 2 (HIPK2) inhibitors†

 Bhaskar C. Das, *^{ab} Pratik Yadav, ^a Sasmita Das^a and John Cijiang He^{bc}

Herein, we demonstrate a Pd catalyzed C-4 borylation of structurally complex chloroquinolines with bis(pinacolato)diboron under relatively simple and efficient conditions. Moreover, the borylated quinolines were converted into oxaborole, trifluoroborate salt and boronic acid and also rendered in the Suzuki reaction successfully. The method was also applied for the synthesis of potential boron-based homeodomain interacting protein kinase 2 (HIPK2) inhibitors. The strategy opens up new avenues for the functionalization of quinolines as potential probes and pharmacological agents for future biomedical research.

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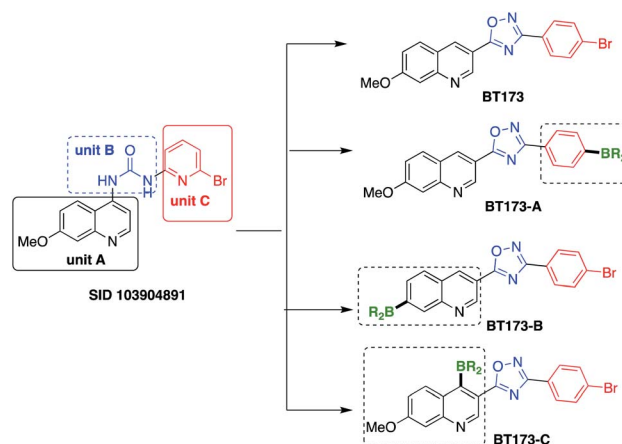
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Homeodomain interacting protein kinase 2 (HIPK2) plays a vital role in kidney fibrosis and has been identified as a key regulator for various profibrosis pathways.¹ In previous studies, it has been found that inhibition of HIPK2 might be a novel approach against fibrosis progression in kidney disease.^{2,3} However, HIPK2 inhibitors have not been well studied and are not available on a commercial scale. A recent report by Cozza *et al.*⁴ describes the discovery of a selective HIPK2 inhibitor, even though broad inhibition of HIPK2 function may not be beneficial in all cellular contexts.

For our ongoing project to develop novel anti-fibrotic drugs for kidney fibrosis, we focused on HIPK2 as potential target.^{5a} We performed a search for HIPK2 inhibitors and identified several potential compounds from a screening assay earlier studied by Abbott Labs.^{5b} We executed the SAR (Structure Activity Studies) study on one of these compounds (PubChem SID 103904891), which comprises three units (Scheme 1): unit A, unit B and unit C. To explore the possibility of synthesizing a new class of HIPK2 inhibitors, we focused on the design and modification of each unit with suitable subunits. In our initial efforts, we successfully synthesized **BT173** (Scheme 1),⁶ which was accomplished by the conversion of unit B into an oxadiazole subunit which serves as a bioisostere of guanidine structural motif. We found that the quinoline derived scaffold **BT173** showed specific pharmacologic inhibition of HIPK2 for

antifibrotic therapy.⁶ It strongly inhibited the ability of HIPK2 to potentiate the downstream transcriptional activity of Smad3 in kidney tubular cells.⁶ These data strongly support that **BT173** is a “proof-of-concept compound” as HIPK2 inhibitor for treatment of kidney fibrosis. However, **BT173** has low solubility and relatively low affinity. Therefore, we plan to use **BT173** as our starting point to develop better compounds for lead optimization.

SAR study of **BT173** revealed that by keeping quinoline and oxadiazole motifs intact in combination with boron at different positions of **BT173** could lead to the potential HIPK2 inhibitors. We, therefore, turned our attention towards the design and synthesis of new boron-based potential HIPK2 inhibitors **BT173-A**, **BT173-B** and **BT173-C** (Scheme 1).



Scheme 1 Structure of designed and targeted new class of HIPK2 inhibitors.

^aArnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, NY 11201, USA. E-mail: Bhaskar.Das@liu.edu

^bDivision of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

^cRenal Section, James J. Peters Veterans Affairs Medical Center, Bronx, NY 10468, USA

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Boron-based scaffolds have recently gained considerable attention as biologically significant nucleuses as well as in material science.⁷ Examples of some clinically approved boron-containing therapeutics have been shown in Fig. 1. Due to vacant p-orbitals of boron, the boron-containing compounds are prone to accept electrons from electron-donating atoms/groups and thereby exhibit strong interaction at the active sites of enzymes. Moreover, the boron-based compounds have a tendency to form H-bond networks governing several biological phenomena and play a vital role in drug-receptor interaction. These properties make them potential therapeutic agents for the development of new drug candidates.^{7,8}

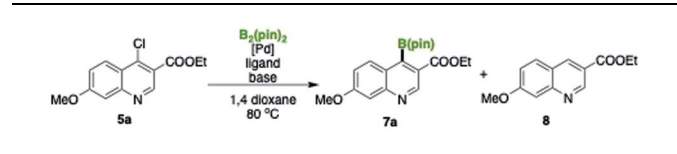
We anticipated that the designed scaffolds **BT173-A**, **BT173-B** and **BT173-C** (Scheme 1) could be efficiently synthesized by catalytic borylation of suitably functionalized halo-quinolines. We first started investigating borylation reaction for the synthesis of challenging target **BT173-C**. The strategized reaction was challenging due to the following reasons; (1) the presence of a nitrogen heterocycle and a hindered C-4 position of quinoline, (2) catalytic borylation of heteroaromatic organohalides with $B_2(\text{pin})_2$ are also very limited,⁹ (3) the probability of the formation of undesired N-B adduct, (4) rebellious nature of heteroaromatic organohalides coupling partners in metal-catalyzed cross coupling reactions.¹⁰

To our surprise, we could not find any previous report for the C-4 borylation of readily available chloroquinolines with bis(pinacolato)diboron ($B_2(\text{pin})_2$). Very recently, during the course of our study, Kwong group demonstrated only two successful examples for the borylation of chloroquinolines with bis(neopentyl glycolato)diborane.^{9a} However, in this study a tailor-made ligand has been used at higher temperature with a relatively low yield with ester group at C-3 position. To address these challenges, we developed an economically viable, environmentally sustainable methodology to synthesize C-4 substituted borylated quinoline scaffolds. As a part of our ongoing research program on the development of boron-based therapeutics,^{6-8,11} herein, we wish to report a simpler, efficient and economical method for the borylation of chloroquinolines. This methodology allows the construction of boron-based potential first-in-class HIPK2 inhibitors in higher yields. The

present strategy comprises a Pd-catalyzed borylation reaction¹² of differently substituted quinolines and $B_2(\text{pin})_2$ as a key step. To the best of our knowledge, this is the first report of Pd-catalyzed borylation of complex-chloroquinolines with readily available $B_2(\text{pin})_2$ at C-4 position. Furthermore, the synthesized borylated quinolines were successfully used as starting materials for the construction of potential biologically active pharmacophore groups *e.g.* oxaboroles, trifluoroborate salts, boronic acids and synthetically useful intermediates using the Suzuki reaction.

To achieve the synthesis of **BT173-C**, we started our optimization for the borylation reaction using ethyl 4-chloro-7-methoxyquinoline-3-carboxylate **5a** and $B_2(\text{pin})_2$ as a model substrate. We explored various reaction conditions and the results are summarized in Table 1. Our initial efforts with $Pd_2\text{dba}_3$ and $Pd(\text{dba})_2$ with XPhos using KOAc as a base did not yield the desired product ethyl 7-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-3-carboxylate **7a** (Table 1, entry 1 and 2). $Pd(\text{OAc})_2$ was found to be a better Pd source to yield 35% and 32% of the desired product **7a** with 2 mol% and 5 mol% catalyst loading respectively (Table 1, entry 3 and 4). In search of a superior catalytic system, we next tested the efficiency of $Pd(\text{PPh}_3)_2\text{Cl}_2$ with XPhos as a ligand. To our delight, the desired product was obtained in 65% yields (Table 1, entry 5). To gauge the influence of a ligand, we performed the reaction in the absence of XPhos which also resulted in the desired product with a slight increase in the yield (Table 1, entry 6). This result showed that the reaction can be performed without the use of an external ligand. We also tested the outcome of the reaction at low catalyst loading (2 mol%) and found that there was no substantial loss in yield and 75% yield of desired product was obtained. It was noteworthy that

Table 1 Screening of reaction conditions^a



Entry	Pd (mol%)	Ligand	Base	Yields ^d (%)	
				7a	8
1	$Pd_2(\text{dba})_3$	XPhos	KOAc	Traces	30
2	$Pd(\text{dba})_2$	XPhos	KOAc	Traces	20
3	$Pd(\text{OAc})_2$	XPhos	KOAc	35	10
4 ^b	$Pd(\text{OAc})_2$	XPhos	KOAc	32	15
5	$Pd(\text{PPh}_3)_2\text{Cl}_2$	XPhos	KOAc	65	20
6	$Pd(\text{PPh}_3)_2\text{Cl}_2$	—	KOAc	72	—
7 ^b	$Pd(\text{PPh}_3)_2\text{Cl}_2$	—	KOAc	75	—
8 ^b	$Pd(\text{PPh}_3)_2\text{Cl}_2$	—	$K_3\text{PO}_4$	55	—
9 ^b	$Pd(\text{PPh}_3)_2\text{Cl}_2$	—	Cs_2CO_3	40	—
10 ^c	$Pd(\text{PPh}_3)_2\text{Cl}_2$	—	KOAc	45	35

^a Reaction was performed using **5a** (0.5 mmol), $B_2\text{Pin}_2$ (0.75 mmol), base (1 mmol), Pd (5 mol%) and ligand (10 mol%) using 1,4 dioxane (2 mL). ^b Pd (2 mol%) and ligand (5 mol% if required). ^c Reaction was performed using **6** (0.5 mmol), $B_2\text{Pin}_2$ (0.75 mmol), base (1 mmol), Pd (2 mol%) and 1,4 dioxane (2 mL). ^d Isolated yield.

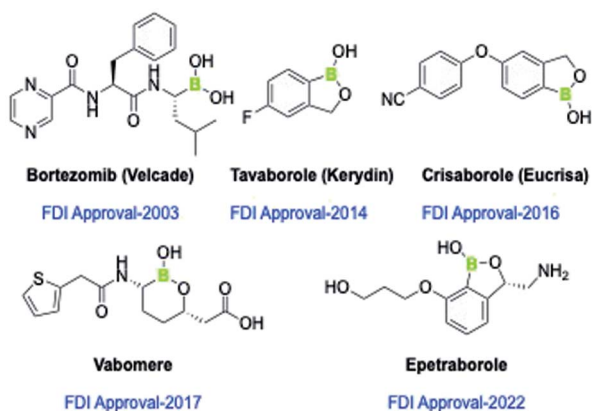


Fig. 1 Boron containing marketed drugs.

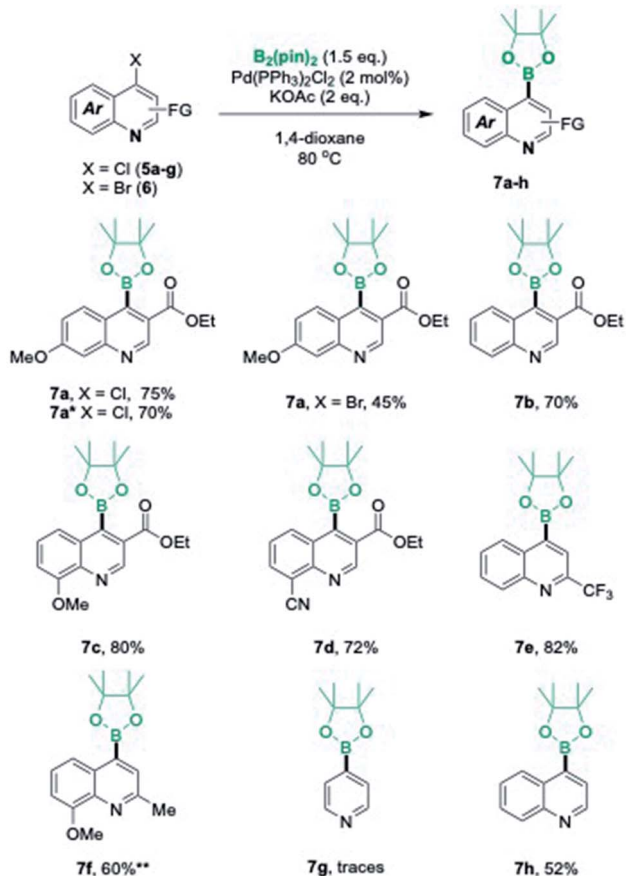


compound **8** was not formed with Pd(PPh₃)₂Cl₂ in the absence of ligand. Our attempt to convert ethyl 4-bromo-7-methoxyquinoline-3-carboxylate **6** into corresponding borylated product gave the desired product **7a** but in relatively low yield (45%) under similar catalytic system (Table 1, entry 10). A competitive reaction was also observed and it was interesting to find out that the bromoquinoline **6** resulted dehalogenation/hydrogenation compound ethyl 7-methoxyquinoline-3-carboxylate **8** (Table 1).

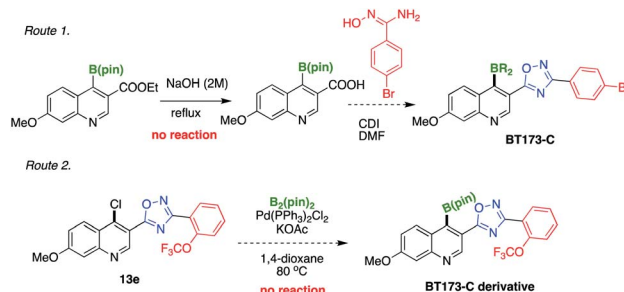
With the standardized reaction conditions in hand, we synthesized the required intermediate **7a** in good yield for the synthesis of BT173-C (Scheme 2). A gram scale synthesis of **7a** was also performed under the developed conditions for the broader utility of this valuable synthetic intermediate. To our delight, there was not much loss in the yields and the product was isolated in 70% yield. During the course of reaction, chloroquinolines were found better substrates under the developed reaction conditions for the C-4 borylation. To further check the effect of substituent and to expand the substrate scope, C-4 borylated-quinolines **7b–7d** were also synthesized. To our delight, the reaction conditions were found efficient for the substrates with electron neutral **7b**, electron donating **7c**, and

electron withdrawing **7d** groups in good yields (Scheme 2). To check the effect of ester group at C-3 position, we next tested the outcome of this reaction with 4-chloro-2-(trifluoromethyl)quinoline **5e** as a substrate. It was noteworthy that **5e** was also converted efficiently into **7e** in 82% yield. The efficacy of this catalytic system was further intended to explore with the electron-donating group on the pyridine ring instead of phenyl ring. To achieve this transformation 4-chloro-8-methoxy-2-methylquinoline **5f** was chosen as substrate. Our initial efforts with the current catalytic system did not work well and desired product **7f** was obtained in low yields (15%). However, addition of 2 mol% XPhos was found beneficial and product **7f** was obtained in 60% yield. 4-Chloropyridine did not work well under both the conditions and gave desired **7g** only in traces however 4-chloroquinoline **5h** was successfully converted into desired product 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline **7h** in moderate yield (52%) using the developed catalytic system (Scheme 2). Further development of this process with differently substituted functional groups is currently under investigation.

As anticipated, **7a** was a potential intermediate for the synthesis of BT173-C, we first attempted to convert compound **7a** into the corresponding acid which could be subsequently converted into oxadiazoles (Scheme 3, route 1) but we could not achieve hydrolysis of ester into acid.¹³ Subsequently, we planned to first synthesize oxadiazoles with chloro-group installed at C-4 position of quinoline and then converting these types of compounds into BT173-C derivatives (Scheme 3, route 2). To check our hypothesis compound 5-(4-chloro-7-methoxyquinolin-3-yl)-3-(2-(trifluoromethoxy)phenyl)-1,2,4-oxadiazole **13e** was synthesized (ESI, Scheme 3†). However our preliminary efforts to transform **13e** into BT173-C via our developed protocol did not give desired product (Scheme 3). Currently, we are investigating suitable conditions to synthesize our target compound BT173-C. Having a valuable synthon **7a** in hand, we decided to explore the synthetic utility of **7a** in various synthetic transformations. First, **7a** was subjected to reduction using NaBH₄ in ethanol followed by neutralization with 2 M HCl to convert it into corresponding alcohol. Interestingly, this reaction yielded *in situ* formation of 7-methoxy-[1,2]oxaborolo [4,3-*c*]quinolin-1(3*H*)-ol **9** in a tandem manner (Scheme 4a). Oxaboroles have shown broad range of biological activities previously.^{7,14} Compound **7a** was also anticipated as a suitable intermediate to develop the series of other boron-based

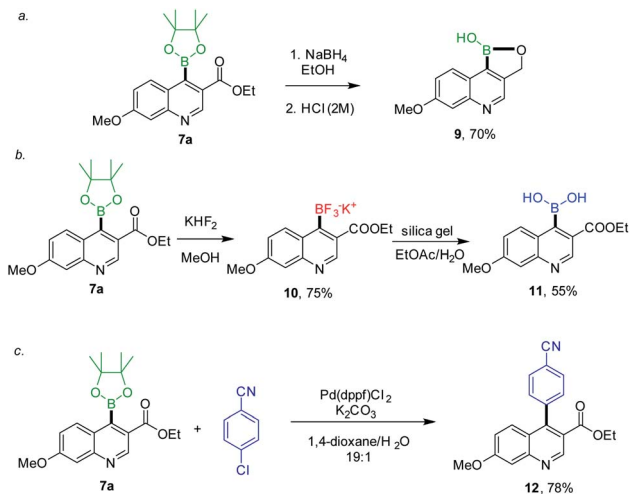


Scheme 2 Scope of borylation method and synthesis of **7a–h**. ^aReaction was performed using **5** (1 mmol), B₂(pin)₂ (1.5 mmol), base (2 mmol), Pd (2 mol%) using 1,4 dioxane (2 mL) as solvent, ^bisolated yields, * performed on 1 g scale, ** reaction was performed by adding XPhos (2 mol%).



Scheme 3 Planned routes to synthesize BT173-C.

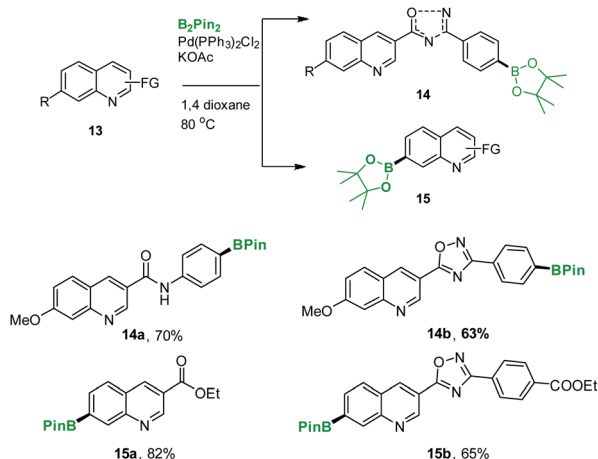




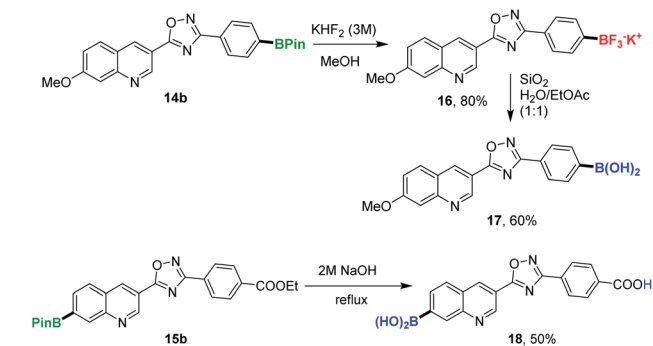
Scheme 4 (a–c) Synthetic utility of compound 7a.

biologically important scaffolds. Similar to oxaboroles, aryltrifluoroborate salts, and arylboronic acids are valuable from synthetic as well as from medicinal chemistry view point.¹⁵

Therefore, we next intended the synthesis of potassium (3-(ethoxycarbonyl)-7-methoxyquinolin-4-yl)trifluoroborate **10** and (3-(ethoxycarbonyl)-7-methoxyquinolin-4-yl)boronic acid **11** starting from **7a**. The synthesis of compound **10** was achieved by the treatment of compound **7a** with KHF_2 in MeOH in good yield (75%). Compound **10** was then converted into compound **11** in 55% yield with silica gel in ethyl acetate/water (Scheme 4b). Besides this, boron pinacol esters were also found suitable intermediate for the Suzuki reaction to construct biaryls *via in situ* generation from aryl halides^{16a} or separately.^{16b} This transformation has added benefits for exploring possibility of generating a library of C-4 functionalized quinolines. Therefore, we opted for intermediate **7a** for the Suzuki reaction (Scheme 4c). In our initial efforts, the reaction proceeded with 5 mol% of



Scheme 5 Synthesis of intermediates for the construction of BT173-A, B. ^aReaction was performed using **13** (0.5 mmol), $\text{B}_2(\text{pin})_2$ (0.75 mmol), base (1 mmol), Pd (2 mol%) using 1,4 dioxane (2 mL) as solvent, ^bisolated yields.

Scheme 6 Synthetic utility of **14b** and **15a** in other biologically interesting boron containing scaffolds.

$\text{Pd}(\text{dppf})\text{Cl}_2$ and K_2CO_3 in 1,4-dioxane/ H_2O (19 : 1) to provide desired product ethyl 4-(4-cyanophenyl)-7-methoxyquinoline-3-carboxylate **12** in 78% yield. The further development of this transformation is under progress.

After exploring the synthesis and utility of **7a**, we again turned our focus on the synthesis of BT173-A and BT173-B. The developed C-4 borylation of quinolones was found suitable for the borylation of differently functionalized complex heteroarenes **13a–d** (ESI, Scheme 2†). Using our newly established borylation-methodology, the synthesis of target compounds **14a–b** and **15a–b** was achieved efficiently and in good yields (Scheme 5). The reaction well-tolerated numerous medicinally important functional groups *e.g.* amide **14a**, oxadiazole **14b** and **15b**, ester **7a–d** and **15a** and nitrile **7d** (Schemes 2 and 5). These results clearly demonstrate the suitability of the current borylation protocol for the synthesis of various borylated heteroarenes even at gram scales making them viable synthons for synthetic as well as medicinal applications. This protocol also leads to the synthesis of target compounds BT173-A and BT173-B (**14b** and **15b**) and other related boron based HIPK2 inhibitors **16**, **17** and **18**.

For the synthesis of **16** and **17**, **14b** was first converted into corresponding trifluoroborate salt **16** using KHF_2 in 80% yield and **16** was subsequently converted into boronic acid **17** in 60% yield (Scheme 6). Our efforts to hydrolyse **15b** into carboxylic acids in the presence of 2 M NaOH gave compound **18** in 50% yield (Scheme 6).

In conclusion, we report here the design and synthesis of novel first-in-class boron-based scaffolds as a potential HIPK2 inhibitors and developed a new methodology to introduce boron atom at C-4 position of substituted quinolines. Borylation at C-4 position of hindered quinolines took place under relatively simple manner with $\text{B}_2(\text{pin})_2$. The protocol was found suitable for gram scale synthesis borylated quinolines as well. Additionally, the developed molecules were efficiently converted to other biologically as well as synthetically relevant scaffolds such as oxaborol, trifluoroborate salts and boronic acids. The C-4 borylated quinolines was successfully used for Suzuki–Miyaura coupling reaction. Therefore, this strategy also opens up new avenues for the functionalization of quinoline as well as for future drug discovery. The biological studies of these



pharmacophores are also being investigated in our laboratory currently.

Conflicts of interest

There are no conflicts to declare.

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