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Staurosporine Analogs Via C−H Borylation

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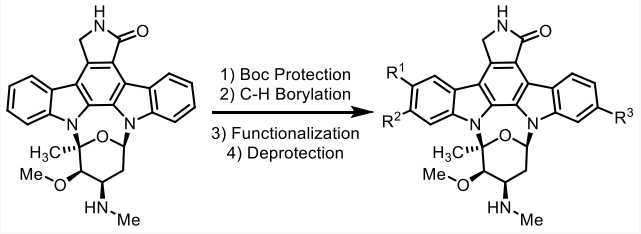
ABSTRACT: Staurosporine is among the most potent naturally occurring kinase inhibitors isolated to date and has served as a lead compound for numerous drug development efforts in several therapeutic areas. Herein we report that C−H borylation chemistry provides access to analogs of staurosporine that were previously inaccessible to medicinal chemists who, in the past four decades, have prepared over 1000 semisynthetic staurosporine analogs.



KEYWORDS: *Staurosporine, indolocarbazole, C−H activation, borylation*

Staurosporine (**1**), isolated by Ōmura and co-workers in 1977 from *Streptomyces staurosporeus*, exhibits potent inhibitory properties against a vast majority of the human kinome.[1,2] Since its isolation, numerous drug discovery efforts have attempted to capitalize on the potency of **1** and several other naturally occurring indolocarbazole-containing natural products (ICZs) through the preparation of semisynthetic analogs. The ICZ moiety of **1** (highlighted in red) has been demonstrated to play a key role in binding to the adenosine triphosphate (ATP) pocket of kinases, and thus, modifications to this core have been central to many structure−activity relationship (SAR) studies hoping to improve both selectivity and potency.[3−6] Although the homologous nature of the ATP binding sites in the human kinome has made the former quite challenging,[7−9] several compounds have moved into clinical trials (e.g., CEP-1347 (**3**)) and at least one (e.g., Midostaurin (**2**)) has been approved for use in cancer treatment (Figure 1).[10−12]

In previous SAR efforts (Scheme 1), the primary strategy taken in the semisynthetic preparation of ICZ-analogs has involved electrophilic aromatic substitution (EAS) chemistry,

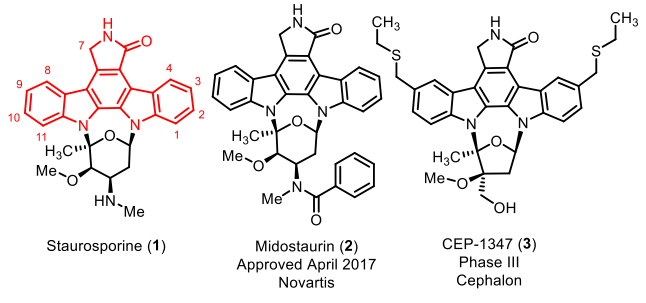
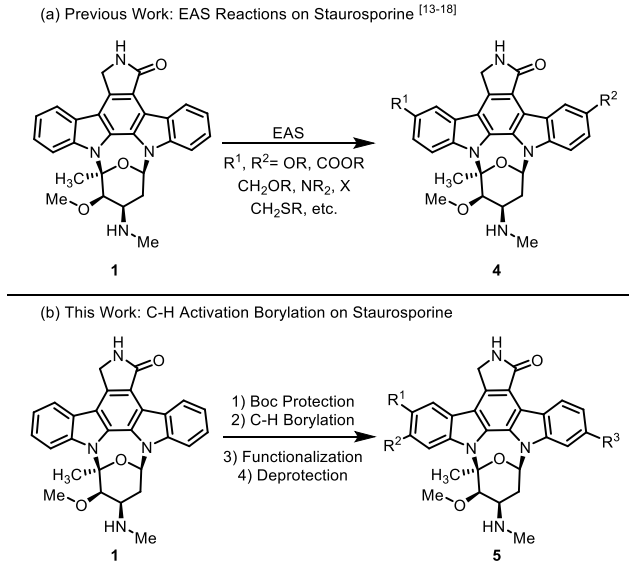


Figure 1. Staurosporine (**1**) and indolocarbazole containing active pharmaceuticals.[13]

Scheme 1. Functionalization on Staurosporine's ICZ Moiety



which has led to the development of over 1000 derivatives of **1** and related ICZs.[14−19]

However, without exception the regiochemical outcome of the EAS chemistry employed in these studies has been guided by electronic effects, which provide access to only two locations for substitution (Scheme 1a). As illustrated, this reactivity profile has limited functionalization to the upper half

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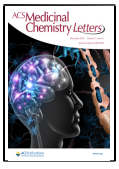

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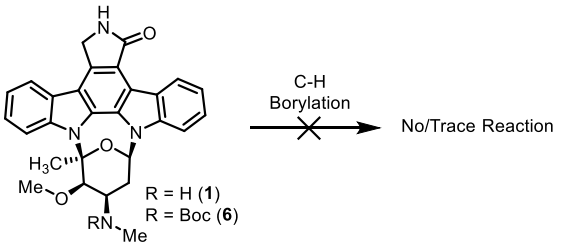
of the ICZ moiety; thus, there are no biological studies of synthetic analogs possessing functionality at C2 and C10. In fact, the natural product TAN-999, which possesses a methoxy substituent at C10, is the only compound falling into this latter category reported to date, and it has only been studied in the context of immunomodulatory properties.[20−22]

As part of an effort to fill the void in SAR studies of staurosporine's ICZ core, we began investigating C−H activation borylation as an orthogonal approach to EAS chemistry (Scheme 1b). In contrast to EAS, which provides regiochemical outcomes primarily dictated by the electronic effects of an aromatic ring, the regioselectivity of C−H activation borylation is primarily influenced by steric congestion around the C−H bond.[23−25,26−29] In addition to potentially providing access to regions of staurosporine that have yet to be investigated from an SAR standpoint (e.g., **5**, Scheme 1b), this chemistry also furnishes intermediate boronic esters which are exceedingly malleable with regard to subsequent transformations.

Our initial attempts to introduce a boronic ester employing **1** as substrate were unsuccessful, showing no signs of reaction despite high catalyst loadings, high temperatures, and reaction times spanning a few days (Scheme 2). Initially we attributed

Scheme 2. Attempted Borylation of 1 and 6[a,b]



Substrate	Catalyst Load (mol%)	Ligand	B_2Pin_2 Equiv.	T (°C)	Time	Result
1	5	DtBpy	1	80	24 h	No Rxn
1	5	DtBpy	1	80	40 h	No Rxn
1	5	Me_4Phen	1	80-100	21 h, 24 h	No Rxn
6	14	DtBpy	1.5	80	2.5 d	Trace[a]
6	61	Me_4Phen	4	80-100	31 h, 3.5 d	Trace[a]

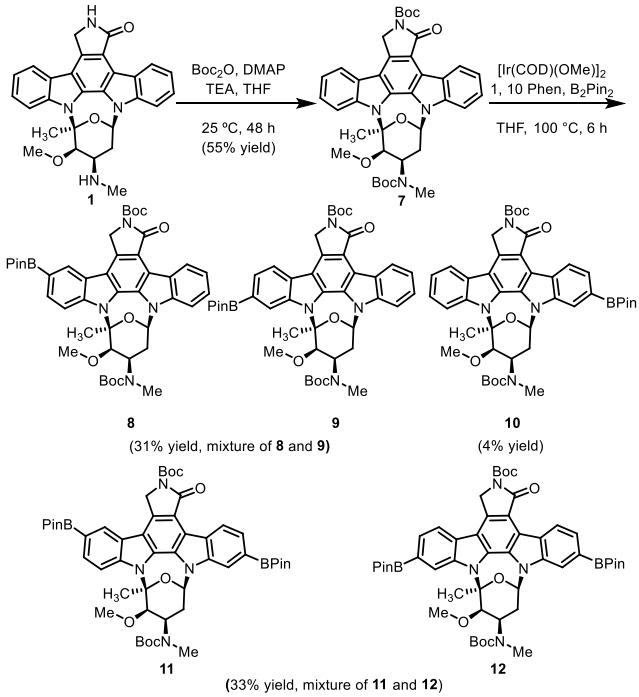
[a]Trace product observed by LC-MS. [b]Boc = *tert*-butyloxycarbonyl. All reactions were run in sealed reaction vessels using THF solvent and $[Ir(COD)OMe]_2$ precatalyst.

the lack of borylation to the poor solubility of **1** in solvents suitable for C−H activation borylation, such as THF or dioxane. To improve the solubility we prepared known *N*-Boc-carbamate **6** which was found to be readily soluble in THF.[30] Disappointingly, **6** required the use of superstoichiometric quantities of the active iridium complex, lengthy reaction times, and high temperatures, to produce trace quantities of borylation products as observed by LC-MS analysis.

Having ruled out issues with reaction heterogeneity, our next aim was to address the Lewis basicity of the amine and lactam. Coordination of strongly Lewis basic moieties to the iridium catalyst has been demonstrated to be problematic due to formation of an inactive 18e$^-$ iridium complex.[23,31−33] To circumvent this potential problem we protected both the amine and the lactam with a Boc group to furnish **7**. With **7** in hand we were delighted to find that borylation of this substrate proceeds to ca. 50% conversion (LC-MS monitoring) when using 4,4′-di-*tert*-butyl-2,2′-bipyridine ligand (DtBpy).

Based on this initial success, we performed a ligand screen that included Binap, TolBinap, DM-Segphos, 2,2′-bipyridine (Bpy), 4,4′-dimethoxy-2,2′-bipyridine (MeO_2Bpy), DtBpy, 2,2′-bipyridine (Bpy), neocuproine, 3,4,7,8-tetramethyl-1,10-Phen (Me4Phen), and 1,10-Phen. This effort revealed that employing the Phen ligand, THF as solvent, and heating to 100 °C in a sealed tube for 6 h gave the best conversion, producing three monoborylated products, **8**, **9**, and **10**, as well as two bis-boronic esters, **11** and **12** (Scheme 3). Notably, reaction times

Scheme 3. Borylation of Bis-Boc Staurosporine 7[a]



[a]DMAP = 4-dimethylaminopyridine, TEA = triethylamine, COD = 1,5-cyclooctadiene, Phen = 1,10-phenanthroline, B_2Pin_2 = bis-(pinacolato)diboron.

longer than 6 h led to decomposition of the products as observed by LC-MS monitoring. After purification of the crude reaction mixture, we were able to isolate mixtures of **8**/**9** and **11**/**12** in 31% and 33% yield, respectively, along with pure **10** in 4% yield. Attempts to make regiochemical assignments at this stage were hampered by significant overlap and broadening of the peaks in the ^{1}H NMR due to the rotameric nature of the protecting groups. Thus, we simply advanced the respective mixtures in hopes of finding a method for separating the derived analogs.

To the latter end, we turned toward functionalizing **8**−**12** by exploring reactivity under oxidation and chlorination conditions, two known transformations of boronic esters, which were chosen for their robustness (Scheme 4). Additionally, we initially speculated that the derived phenols and chlorides would allow a quick probe into the biological impact of their respective hydrogen bond donating and accepting properties. In the event, the boronic esters in **8**−**12** were transformed to the corresponding phenols by exposure to $NaBO_3$ (Table 1, entries 1−3).[34−36] Fortunately, after deprotecting the Boc groups under TFA conditions, we were able to separate the derived phenol regiomers **13**−**17**. Applying this same sequence to the mixtures of **8**/**9** and **11**/**12** but including a methylation

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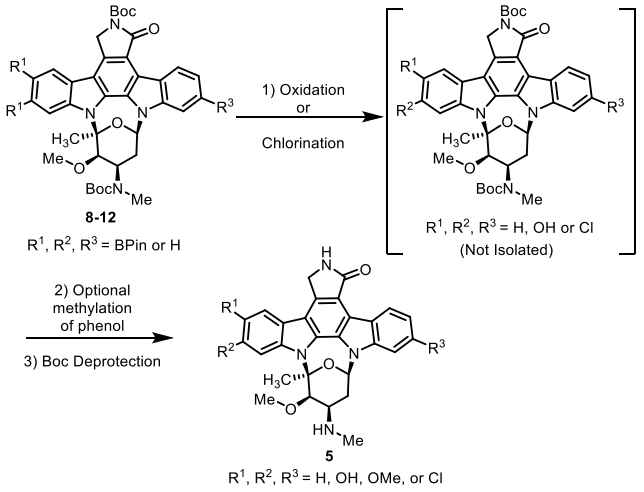
Scheme 4. Strategy for Analog Synthesis



step (MeI) prior to Boc deprotection furnished the corresponding methyl ethers **18**–**21** which, in contrast to their parent phenols, proved recalcitrant toward separation (Table 1, entries 4 and 5). Turning next to the chloride analogs, we opted to employ halogenation chemistry developed by Kabalka and Hartwig.[37,38] To this end, exposure of the Bpin analogs **8**/**9** and **11**/**12** to $CuCl_2$ furnished intermediate aryl chlorides which, upon Boc deprotection, provided separable mixtures of **22**/**23** and **24**/**25**, respectively (Table 1, entries 6 and 7).

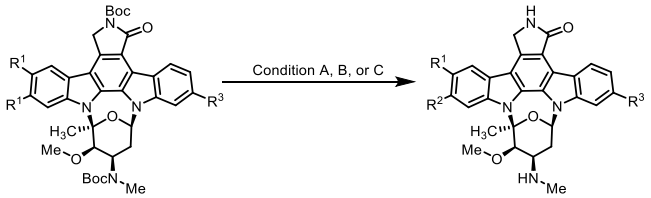
Having accessed several novel staurosporine analogs we turned to a brief investigation of biological activity. As indicated above, over 1000 semisynthetic analogs of ICZs have been assayed for activity since the original isolation of staurosporine by Ōmura, and among these, many have been produced via electrophilic aromatic substitution, which only provides access to functionality at C3 and C9.[16] To our knowledge the only known example of a staurosporine analog functionalized elsewhere on the aromatic indolocarbazole core is the natural product TAN-999 (**19**), which possesses a methoxy substituent at C10.[20] To date, detailed biological studies of **19** reported in the open literature have been focused on its immunomodulatory activity in macrophages and a brief notation that it inhibits protein kinase C.[20] In our studies, we evaluated the cytotoxicity of staurosporine (**1**) and novel phenol analogs **13** and **14** against breast cell lines including tumor-derived MDA-MB-231 cells and nontransformed, immortalized, HMLE cells (Table 2). The activities of **13** and **14** against the MDA-MB-231 cell line were found to be equipotent to staurosporine. Interestingly, these studies also revealed that inclusion of a phenol at either the C9 or C10 position selectively diminishes activity against HMLE with 9-OH- and 10-OH-staurosporine (**13** and **14**) being 5.6-fold and 12.0-fold less potent, respectively. Thus, activity toward the nontransformed mammary cell line, HMLE, was compromised indicating the possibility of an increased therapeutic index.

Table 2. Cytotoxic Activity of Staurosporine (1), 13, and 14[a]

	MDA-MB-231		HMLE	
compound	IC_{50} (nM)	SD	IC_{50} (nM)	SD
Staurosporine (**1**)	2.5	±0.2	4.9	±0.4
13	2.0	n.d.	27.5	±10.8
14	3.4	±1.3	58.7	±20.1

[a]MDA-MB-231 = human breast adenocarcinoma cell line, HMLE = immortalized human mammary epithelial cells, IC_{50} = half maximal inhibitory concentration, SD = standard deviation.

Table 1. Analogs of Staurosporine



Entry	SM	R^1	R^2	R^3	Condition	Product	R^1	R^2	R^3	Yield
1	**8**	Bpin	H	H	A[a]	**13**	OH	H	H	26%
	9	H	Bpin	H	A	**14**	H	OH	H	10%
2	**10**	H	H	Bpin	A	**15**	H	H	OH	21%
3	**11**	Bpin	H	Bpin	A	**16**	OH	H	OH	12%
	12	H	Bpin	Bpin	A	**17**	H	OH	OH	24%
4	**8**	Bpin	H	H	B[b]	**18**	OMe	H	H	52%[c]
	9	H	Bpin	H	B	**19**	H	OMe	H	[c]
5	**11**	Bpin	H	Bpin	B	**20**	OMe	H	OMe	23%[d]
	12	H	Bpin	Bpin	B	**21**	H	OMe	OMe	[d]
6	**8**	Bpin	H	H	C[e]	**22**	Cl	H	H	20%
	9	H	Bpin	H	C	**23**	H	Cl	H	51%
7	**11**	Bpin	H	Bpin	C	**24**	Cl	H	Cl	30%
	12	H	Bpin	Bpin	C	**25**	H	Cl	Cl	48%

[a]Condition A: (1) $NaBO_3$, H_2O:THF (1:1), 25 °C, (2) TFA:DCM (2:3), 25 °C. [b]Condition B: (1) $NaBO_3$, H_2O:THF (1:1), 25 °C, (2) MeI, K_2CO_3, THF, 40 °C, (3) TFA:DCM (1:4), 25 °C. [c]Combined yield of **18** and **19** in 1:2.3 ratio determined by ^1H NMR. [d]Combined yield of **20** and **21** in 1:1.4 ratio determined by ^1H NMR. [e]Condition C: (1) $CuCl_2$, H_2O:MeOH (1:1), 70 °C, (2) TFA:DCM (1:4), 25 °C; TFA = trifluoroacetic acid, DCM = dichloromethane, Bpin = pinacol boronic ester.

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Clearly these findings highlight the potential of applying C−H borylation/derivatization chemistry in preparing active analogs of other complex small molecules that are otherwise challenging to access.

In conclusion, we have developed a method for accessing novel analogs of staurosporine wherein functionality resides at C2 and C10 of the indolocarbazole aromatic region. This method will allow for the preparation of many new staurosporine analogs and potentially open the door to further improvements in the kinase specificity profile manifest by this class of molecules. In addition, we have established the viability of the method by preparing 13 analogs of **1** and, in a brief biological study, determined that introducing functionality in this previously inaccessible region does not abrogate kinase activity and indeed changes the cytotoxic selectivity profile. Characterization of the inhibitory selectivity profiles against kinase panels of selected new analogs is ongoing. The preparation of additional analogs and results of further biological evaluations will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.0c00420.

Experimental procedures for synthetic and biological studies, description of Scifinder searches, and NMR data (PDF)

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Author Contributions

KMG: Design and synthesis of analogs. Method development. Author of manuscript. KK: Design and synthesis of analogs. Method development. JLW: Project lead. KR: Design and execution of biological assays. JT: Project design, biological studies.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ICZ, indolocarbazole; ATP, adenosine triphosphate; SAR, structure activity relationship; EAS, electrophilic aromatic substitution; THF, tetrahydrofuran; LC-MS, liquid chromatography mass spectrometry; DtBpy, 4,4′-ditertbutyl-2,2′-bipyridine; Me_4Phen, 3,4,7,8-tetramethyl-1,10-phenanthroline; Boc, *tert*-butyloxycarbonyl; Binap, (2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl); TolBinap, 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl; DM-Segphos, 5,5′-bis-(diphenylphosphino)-4,4′-bi-1,3- benzodioxole; Bpy, 2,2′ bipyridine; 1,10-Phen, 1,10-phenanthroline; DMAP, 4-dimethylaminopyridine; TEA, triethylamine; B_2Pin_2, bis-(pinacolato)diboron; COD, 1,5-cyclooctadiene; TFA, trifluoroacetic acid; DCM, dichloromethane; Bpin, pinacol boronic ester; MDA-MB-231, human breast adenocarcinoma cell line; HMLE, immortalized human mammary epithelial cells; IC_{50}, half maximal inhibitory concentration; SD, standard deviation

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(12) For examples of CEP-1347 clinical trials see clinicaltrials.gov identifiers: NCT00040404, NCT00605163, and NCT00404170.
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