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2-Aminobenzimidazoles as potent Aurora kinase inhibitors

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ABSTRACT

This Letter describes the discovery and key structure–activity relationship (SAR) of a series of 2-aminobenzimidazoles as potent Aurora kinase inhibitors. 2-Aminobenzimidazole serves as a bioisostere of the biaryl urea residue of SNS-314 (**1c**), which is a potent Aurora kinase inhibitor and entered clinical testing in patients with solid tumors. Compared to SNS-314, this series of compounds offers better aqueous solubility while retaining comparable in vitro potency in biochemical and cell-based assays; in particular, **6m** has also demonstrated a comparable mouse *iv* PK profile to SNS-314.

Aurora kinases[1–6] belong to the family of serine/threonine kinases and are composed of three isoforms in mammals: Aurora A, Aurora B, and Aurora C. They are expressed during G2/M phase of the cell cycle and are critical for the proper regulation of mitosis.[7–9] For example, Aurora A controls centrosome maturation and mitotic spindle formation; Aurora B ensures chromosome segregation and alignment as part of the chromosomal passenger protein complex; and Aurora C, though not well understood, is thought to function similarly to Aurora B. Over-expression of Aurora kinases is observed in various tumor cells.[10–14] It is believed that inhibition of Aurora kinases could lead to the G2 arrest of cancer cells and subsequently promote the death of cancer cells. Therefore, Aurora kinases have emerged as attractive oncology targets for small-molecule drug discovery.[6,15–17] As a result, many Aurora kinase inhibitors, including Aurora A selective, Aurora B selective, and *pan*-Aurora kinase inhibitors, have been discovered and advanced to human clinical trials.[18–26]

Recently, we reported the discovery of potent Aurora kinase inhibitor SNS-314 (**1c**) (Fig. 1), which exhibits a compelling preclinical profile and entered clinical trials in patients with solid tumors.[25,26] Structurally, **1c** is comprised of a thieno[3,2-*d*]pyrimidine as a purine mimetic and a biaryl urea residue as an essential binding element in the DFG pocket. **1c** displays low aqueous solubility which could be potentially attributed to the presence of a biaryl urea moiety. In order to address this issue, a number of strategies, such as introduction of polar functionalities,[25] application of urea bioisoteres, and preparation of prodrugs,[27] were considered in our search of backup compounds to **1c**. Herein, we report the preparation of 2-aminobenzimidazole (Fig. 2) as a

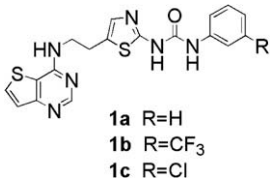

Figure 1. Potent Aurora kinase inhibitors bearing a biaryl urea residue.

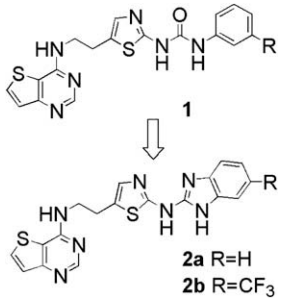

Figure 2. 2-Aminobenzimidazole as a bioisostere of biaryl urea.

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bioisostere of the biaryl urea residue of **1c**. This effort led to the discovery of a series of potent 2-aminobenzimidazole-based Aurora kinase inhibitors with improved intrinsic solubility.

As demonstrated by the crystal structure of **1b** (Fig. 1), which is a structurally close analog of **1c**, complexed with humanized mouse Aurora A, the urea residue, containing one hydrogen-bond acceptor and two hydrogen-bond donors, forms a strong hydrogen-bonding network with the protein through several water molecules in the DFG binding pocket.[25] It has been well documented that imidazole can serve as a bioisostere of urea.[28] Also, the presence of an imidazole residue in a molecule could potentially improve the intrinsic solubility. Preliminary computational modeling also suggested that **2a–b** overlapped well with the crystal structure of **1b**. Accordingly, several analogs were prepared to explore the viability of benzimidazole and other 1,3-azoles as urea bioisosteres for inhibition of Aurora kinases.

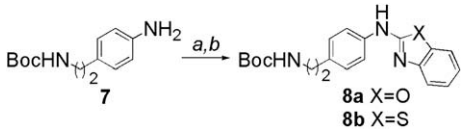
As shown in Scheme 1, treatment of readily available aminothiazole **3**[25,29] with 1,1′-thiocarbonyl-diimidazole, followed by addition of a substituted 1,2-diaminoarene gives a thiourea intermediate, which is cyclized in the presence of DCC to afford **4a–b**.[30] After removal of the Boc- groups from **4a–b**, the corresponding free amines react with 4-chlorothieno[3,2-*d*]pyrimidine to yield **2a–b**, respectively. The same approach was applied to the syntheses of **5a–b** and **6a–h** with commercially available 3- or 4-*N*-Boc-aminomethyl-aniline and 3- or 4-*N*-Boc-aminoethylaniline.

As described in Scheme 2, a copper-catalyzed cyclization of either a urea or a thiourea intermediate derived from **7** yields the corresponding benzoxazole **8a** or benzothiazole **8b**[31] for the preparation of **6f–g**.

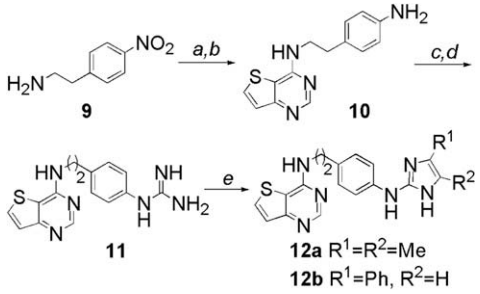
Compound **9** can be readily converted into guanidine-containing intermediate **11**, which is subsequently treated with either butan-2,3-dione or 2-bromo-1-phenylethanone to yield functionalized 2-aminoimidazole **12a** or **12b** (Scheme 3).

Benzimidazole analog **15** was synthesized as depicted in Scheme 4 to compare with **6h**. Boc-protection of readily available **13**,[32] followed by reduction of the NO_2 group, condensation with 3-trifluoromethylphenyl thioisocyanate, and cyclization in the presence of DCC gives key precursor **14** for the synthesis of **15**.

Since the biaryl urea series (SNS-314 series) has comparable activity against both Aurora A and B,[25] an Aurora B enzymatic assay and a BrdU cell proliferation assay were used to preliminarily test the initial set of benzimidazole analogs. Subsequently, selected compounds were further evaluated in an Aurora A enzymatic assay. As outlined in Table 1, benzimidazoles **2a–b** were found to be much less potent than the corresponding urea analogs **1a–b**, but the kinetic solubility[33] was improved as expected. Although earlier SAR of the biaryl urea series indicates that the introduction of a CF_3 group onto the phenyl residue of **1a** enhances the activity against both Aurora A and B (**1a** vs **1b**),[25] this effect was not observed on these benzimidazole derivatives (**2a** vs **2b**). One plausible explanation of this difference in potency lies in the different trajectory of the terminal phenyl ring in **2a** compared to **1a** due to the presence of a structurally constrained benzimidazole ring. This in turn leads to different binding affinities of the molecules



Scheme 2. Reagents and conditions: (a) 1,1′-carbonyldiimidazole (for **8a**, X = O) or 1,1′-thiocarbonyldiimidazole (for **8b**, X = S), THF, rt, 30 min; 2-iodoaniline (for **8a**) or 2-bromoaniline (for **8b**), rt, overnight; (b) CuI, 1,10-phenanthroline, acetonitrile, 80 °C; 55% (**8a**, X = O, two steps) or 70% (**8b**, X = S, two steps).

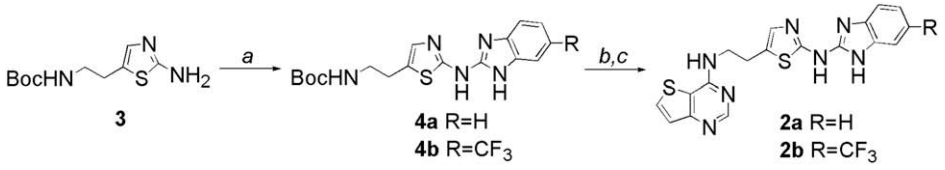


Scheme 3. Reagents and conditions: (a) 4-chlorothieno[3,2-*d*]pyrimidine, DIEA, DMF, 90 °C, 75%; (b) Zn, NH_4Cl, MeOH, 60 °C, 4 h, 90%; (c) *N*,*N*′-bis-Boc-*S*-methylisothiourea, THF, 60 °C, 4 h, 80%; (d) 4 M HCl/dioxane, quantitative; (e) butan-2,3-dione (for **12a**) or 2-bromo-1-phenylethanone (for **12b**), K_2CO_3, $MgCO_3$, THF, 60 °C, 4 h, 55% (for **12a**) or 60% (for **12b**).

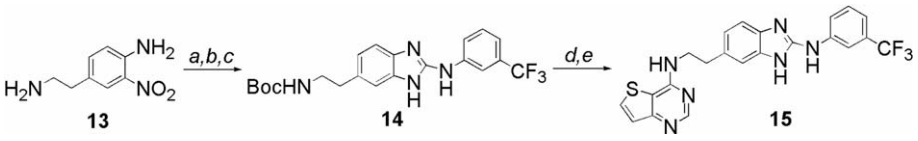
to the proteins. Subsequently, **5a–b** and **6a–b** were designed to explore the optimal distance and angle of the terminal phenyl ring of the benzimidazole series relative to the thieno[3,2-*d*]pyrimidine residue.

While **5a–b** exhibit comparable potency to **2a–b** and **6a** shows drastically reduced activity in Aurora B assay, **6b**[34] demonstrates good potency in Aurora A and B and BrdU assays, and improved aqueous solubility. Introduction of an additional nitrogen atom into the benzimidazole residue (**6c–d**) does not further improve the solubility relative to **6b** while the potency is significantly weaker. The 'NH' moiety in the benzimidazole residue is important to the activity, as *N*-methyl benzimidazole analog **6e**, benzoxazole analog **6f**, and benzothiazole analog **6g** display reduced potency in both Aurora B and BrdU assays. Replacement of the benzimidazole residue of **6b** with a substituted imidazole moiety (**12a–b**) significantly decreases the potency against Aurora B. As expected, the corresponding benzimidazole analogs of **1b–c** (**6h–i**) maintain comparable potency while having improved solubility. Furthermore, a differently constrained benzimidazole analog (**15**) showed much worse activity in the Aurora B enzymatic assay compared to **6h**.

The relatively more potent **6h–i** were evaluated with FACS analysis, a cell-based mechanistic assay used to measure Aurora kinase inhibition.[25] Compounds **6h–i** show weaker potency in FACS analysis relative to its urea analogs **1b–c**. It is worth mentioning that, as do other *pan*-Aurora or Aurora B-selective kinase inhibitors,[21,23,35] **6h–i** arrest HCT116 cells at G2 phase and cause poly-

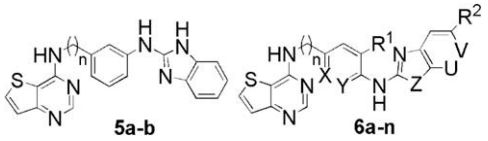


Scheme 1. Reagents and conditions: (a) 1,1′-thiocarbonyldiimidazole, THF, rt, 30 min; substituted 2-aminoaniline, rt, overnight; DCC, 60 °C, 1 h; 35–75% (three steps); (b) 4 M HCl/dioxane, quantitative; (c) 4-chlorothieno[3,2-*d*]pyrimidine, DIEA, DMF, 90 °C, 65–90%.



Scheme 4. Reagents and conditions: (a) Boc_2O, $NaHCO_3$, THF/H_2O, rt, 2 h, 90%; (b) 10% Pd/C, MeOH, H_2, 1 atm, rt, 2 h, quantitative; (c) 3-trifluoromethylphenyl thioisocyanate, THF, rt, 2 h; DCC, THF, 60 °C, 1 h; 55% (two steps); (d) 4 M HCl/dioxane, quantitative; (e) 4-chlorothieno[3,2-*d*]pyrimidine, DIEA, DMF, 90 °C, 65%.

Table 1
SAR of the 2-aminobenzimidazole analogs



Compound	*n*	X	Y	Z	U	V	R^1	R^2	Aurora A IC_{50}[a] (nM)	Aurora B IC_{50} (nM)	BrdU EC_{50}[b] (nM)	FACS EC_{50}[c] (nM)	Solubility[d] (μM)	Mouse *iv* PK[e]	
														$t_{1/2}$ (h)	CL (mL/min/Kg)
1a									52	120	45	16–63	100–200		
1b									22	14	13	<16	50–100		
1c									9	31	6	<16	50–100	1.4	48
2a									1400	420	NT[f]	NT	400–500		
2b									490	620	1900	NT	100–200		
5a	1								NT	580	8500	NT	NT		
5b	2								NT	1400	NT	NT	NT		
6a	1	CH	CH	NH	CH	CH	H	H	NT	>10,000	NT	NT	NT		
6b	2	CH	CH	NH	CH	CH	H	H	28	10	41	NT	>1000		
6c	2	CH	CH	NH	N	CH	H	H	NT	83	270	NT	>1000		
6d	2	CH	CH	NH	CH	N	H	H	NT	140	NT	NT	>1000		
6e	2	CH	CH	NMe	CH	CH	H	H	NT	280	NT	NT	>1000		
6f	2	CH	CH	O	CH	CH	H	H	NT	120	400	NT	200–300		
6g	2	CH	CH	S	CH	CH	H	H	NT	2500	NT	NT	100–200		
6h	2	CH	CH	NH	CH	CH	H	CF_3	40	6	5	16–63	750–1000	0.61	85
6i	2	CH	CH	NH	CH	CH	H	Cl	28	8	9	16–63	>1000	0.45	39
6j	2	CH	CH	NH	CH	CH	F	CF_3	64	21	80	63–250	750–1000		
6k	2	N	CH	NH	CH	CH	H	CF_3	NT	63	161	63–250	400–500		
6l	2	CH	N	NH	CH	CH	H	CF_3	NT	600	NT	NT	>1000		
6m	2	CH	CH	NH	N	CH	H	CF_3	17	5	<1	<16	100–200	1.5	32
6n	2	CH	CH	NH	N	CH	H	Cl	20	10	17	16–63	100–200		
12a									NT	5600	NT	NT	>1000		
12b									NT	>10,000	NT	NT	>1000		
15									NT	1400	NT	NT	NT		

[a] Typically average of at least two experiments. Variation generally is <100%. See Ref. 25 for assay protocols.
[b] Cellular proliferation as determined by BrdU incorporation using HCT116 cell line.
[c] Cell-cycle profile as determined by FACS analysis performed with 16 nM, 63 nM, 250 nM, and 1000 nM of a compound in HCT116 cell line, See Ref. 25 for assay protocol. EC_{50}s reported as a range when ⩾50% of the DNA content is 4 N or higher.
[d] Kinetic solubility reported as a range of low and high solubility at pH 4.0. For compounds having a low solubility of 1000 μM or higher, the value is reported as >1000 μM.
[e] PK experiments were carried out using a group of three mice administrated *iv* with a single dose of 5 mg/kg of a testing compound. Blood samples were taken at nine different time points (0.08, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h post dose) and the plasma concentrations were determined by LC/MS/MS.
[f] Not tested.

ploidy (formation of 8 N or higher cells). Compounds **6h–i** were also progressed into mouse *iv* PK studies; however, they have shorter $t_{1/2}$ compared to biaryl-urea analog **1c** (Table 1).

The much improved solubility encouraged us to structurally modify **6h–i** to search for compounds with strong in vitro potency, pharmaceutically acceptable physicochemical properties, and a good PK profile. As summarized in Table 1, although the introduction of a fluorine atom at the *ortho*-position of the central phenyl ring could potentially stabilize the molecule in vivo by reducing its electron density, significantly decreased activity in both BrdU and FACS analysis was observed (**6j** vs **6h**). Replacement of the central phenyl ring with a pyridyl moiety also causes a drop in the potency against Aurora B (**6k–l** vs **6h**). Interestingly, the installation of a nitrogen atom onto the benzimidazole residue either retains (**6n** vs **6i)** or improves (**6m** vs **6h**) the potency in all the in vitro assays, including Aurora A and B kinase assays, BrdU, and FACS analysis, that were used in the process of compound evaluation. These results are contradictory to the ones of the un-substituted benzimidazole analogs (**6c–d** vs **6b**). Balanced activities against both Aurora A and Aurora B kinases are observed for **6h–i** and **6m–n**, which suggest that these benzimidazole derivatives are similar to those biaryl ureas (**1a–c**), having low selectivity against these two proteins. Importantly, **6m** exhibits an improved mouse *iv* PK profile over its non-nitrogen substituted analog **6h**. This PK result is comparable to that of **1c**. It should be noted that **6m** has a much lower solubility than its non-nitrogen substituted derivative **6h**.

In summary, we have successfully discovered a series of potent 2-aminobenzimidazole-based Aurora kinase inhibitors derived from SNS-314 (**1c**). This series of compounds offers better aqueous solubility compared to their corresponding biaryl-urea analogs while maintaining good activity profile in various enzymatic and cell-based assays. In particular, **6m** demonstrates a comparable mouse *iv* PK profile to **1c**. The discovery of this series of potent benzimidazole-based Aurora kinase inhibitors represents another

successful example of using bioisostere strategy to improve physicochemical properties in the process of drug discovery.

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33. The solubility was measured using a UV direct method. No significant improvement of the solubility at pH 7.4 was observed, but the improvement becomes substantial at lower pH values.
34. A co-crystal structure of **6b** bound to humanized mouse Aurora A was obtained to provide insight of the binding of the compound to the protein. **6b** has a similar binding mode as that of **1b**:[25] thieno[3,2-*d*]pyrimidine binds in the hinge region while benzimidazole residue binds tightly in the DFG pocket. The pyrimidine residue forms hydrogen-bonding with the –NH of Ala213 (3.3 Å). Also, the aminoimidazole residue forms a bidentate H-bond interaction (3.5 Å and 2.8 Å) with the carboxylic acid residue of Glu194; however, there is no direct interaction (4.2 Å) with the catalytic lysine (Lys175) observed.
35. (a) Walsby, E.; Walsh, V.; Pepper, C.; Burnett, A.; Mills, K. *Haematology* **2008**, *193*, 662; (b) Chan, F.; Sun, C.; Perumal, M.; Nguyen, Q.-D.; Bavetsias, V.; McDonald, E.; Martins, V.; Wilsher, N. E.; Raynaud, F. I.; Valenti, M.; Eccles, S.; te Poele, R.; Workman, P.; Aboagye, E. O.; Linardopoulos, S. *Mol. Cancer Ther.* **2007**, *6*, 3147.