Bioorganic & Medicinal Chemistry Letters 22 (2012) 4528–4531

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Exploration of diverse hinge-binding scaffolds for selective Aurora kinase inhibitors

Zhiqin Ji *, Yujia Dai, Cele Abad-Zapatero, Daniel H. Albert, Jennifer J. Bouska, Keith B. Glaser, Patrick A. Marcotte, Nirupama B. Soni, Terry J. Magoc, Kent D. Stewart, Ru-Qi Wei, Steve K. Davidsen, Michael R. Michaelides

Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6100, USA

ARTICLE INFO

Article history:
Received 9 May 2012
Revised 30 May 2012
Accepted 31 May 2012
Available online 7 June 2012

Keywords:
Hinge-binding scaffold
Aurora kinase inhibitor
Anticancer drug

ABSTRACT

Four hinge-binding scaffolds have been explored for novel selective Aurora kinase inhibitors. The structure activity relationship, selectivity and pharmacokinetic profiles have been evaluated.

Aurora kinases consisting of Aurora A, Aurora B and Aurora C play critical roles during mitosis in chromosome segregation and cell division.[1–3] Aurora kinases are over-expressed in a variety of human tumors and the increased expression correlates with advanced clinical progression in several tumor types.[4–6] The inhibition of Aurora kinases is regarded as a promising approach for the development of anticancer drugs.[7–21] Several small molecule Aurora selective inhibitors, such as VX-680(MK-0457),[11] AZD-1152[12] and MLNM-8237[13] have demonstrated anti-tumor efficacy in tumor models and advanced to clinical development.

In our previous work, we discovered that thienopyrimidine, benzoisoxazole, benzoisothiazole, indazole and pyrrolotriazine were hinge binding moieties in a program targeting KDR kinase inhibitors.[23,24] As a part of Aurora kinase program at Abbott Laboratories, amide-based thienopyrimidine (**1**) was employed as a favorable hinge-binding scaffold resulting in a series of potent Aurora A and B inhibitors.[22] As a continuation of this effort, we explored the replacement of the thienopyrimidine core with other potential hinge binding moieties. We anticipated that amide-based heterocycles, namely benzoisoxazole (**2**), benzoisothiazole (**3**), indazole (**4**) and pyrrolotriazine (**5**), were suitable scaffolds for Aurora inhibitors (Fig. 1). The diverse hinge-binders provide us with more options to optimize the potency, efficacy and physical properties.

The general synthesis of the amide-based inhibitors containing benzoisoxazole (**2**), benzoisothiazole (**3**) and indazole (**4**) is outlined in Scheme 1. The key intermediate iodides **6**–**8** were prepared using literature reported procedures.[23,24] Palladium-catalyzed carbonylation of **6**–**8** with carbon monoxide in a methanol solution followed by saponification of generated esters **9**–**11** gave rise to carboxylic acids **12**–**14**. The anilines used for the last step were either from commercial resources or prepared as previously reported.[22]

Pyrrolotriazines (**5**) were synthesized via the route shown in Scheme 2. Compound **15** was prepared using the literature procedures[25] and then converted to nitrile **16** through a two-step reaction in one pot, via the corresponding oxime. N-amination of **16** followed by a cyclization reaction formed the intermediate

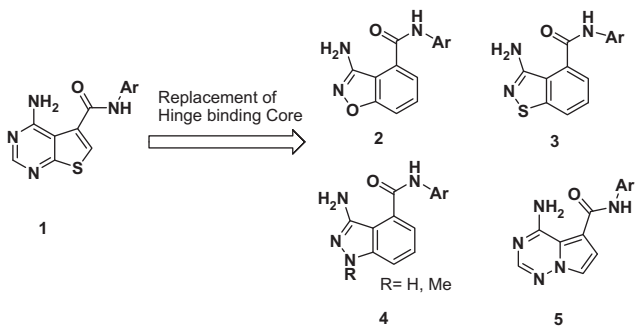
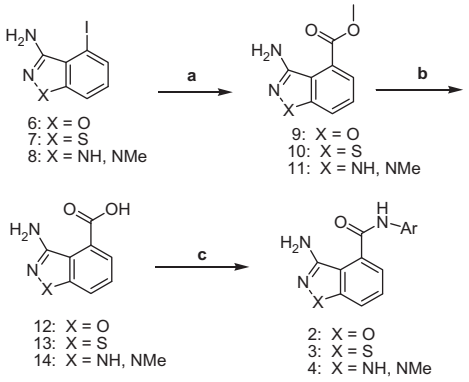


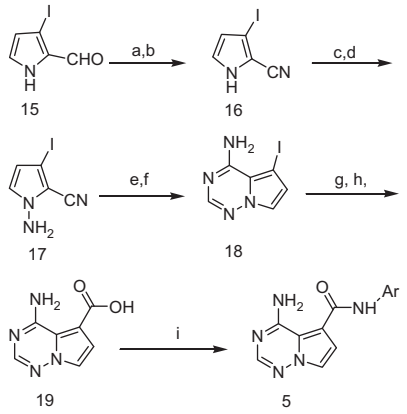
Figure 1. Rationale of inhibitor design.

* Corresponding author.
E-mail address: zhiqin.ji@abbott.com (Z. Ji).

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.05.125



Scheme 1. Reagents and conditions: (a) CO, MeOH, $PdCl_2(dppf)$, Et_3N; (b) LiOH, MeOH–THF; (c) $ArNH_2$, HATU, Et_3N, DMF.



Scheme 2. Reagents and conditions: (a) NH_2OH, pyridine; (b) Ac_2O, 90 °C, 6 h; (c) NaH, DMF RT; (d) $Ph_2PO(ONH_2)$, RT; (e) $HC(EtO)_3$, reflux 6 h ; (f) 7 M NH_3 in MeOH; (g) CO, MeOH, $PdCl_2(dppf)$, Et_3N; (h) LiOH, MeOH, (i) Ar-NH_2, HATU, Et_3N, DMF.

pyrrolotriazine **18**. Palladium-catalyzed carbonylation of **18** with carbon monoxide in a methanol solution followed by saponification of the generated ester gave rise to carboxylic acids **19**, which was then used in the last step for the synthesis of desired compound **5**.

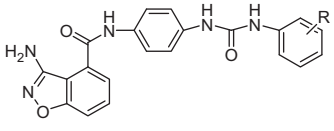
We first synthesized a series of benzoisoxazole amide analogs and evaluated their enzymatic activity against Aurora A and Aurora B in the presence of 1 mM ATP using a homogenous time-resolved fluroscence (HTRF) assay.[26] As shown in Table 1**,** substitution of benzoisoxazole for thienopyrimidine was generally well tolerated in terms of Aurora B kinase inhibition and a series of benzoisoxazole amide-based ureas were identified as potent Aurora B inhibitors. One carbon homologated *meta* ureas (**2e–2l**) are markedly more potent than the *para* diphenyl ureas (**2a–2d**) against Aurora B kinase inhibition. Among the four direct matched pairs included in Table 1, compounds **2e**, **2f**, **2g**, and **2h** are 7-, 11-, 20- and 46-fold more potent than **2a**, **2b**, **2c**, and **2d**, respectively. One notable feature of this series of compounds is their selectivity for Aurora B over Aurora A. All compounds listed in the Table 1 except for **2a** (Aurora A activity not available) are much more potent against Aurora B than against Aurora A, with the selectivity ranging from 26-fold for **2b** to over 1000-fold for **2k**.

Consistent with the results observed in the thienopyrimidine series, the urea link is important for potency.[22] Replacement of the urea link with either a sulfonamide (**2n**) or an amide (**2o**, **2p**) led to significant loss in Aurora B potency (Table 2).

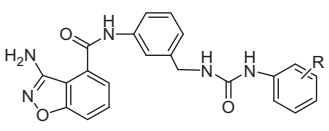
The compounds with potent Aurora B inhibitory activity were further evaluated for their ability to induce cellular nuclear polyploidy,[27] a phenotype associated with Aurora B kinase inhibition.[28] These results are expressed as EC_{15} values and also included in Table 1. In general, the cellular activity of these compounds reflected well their enzymatic potency against Aurora B; many of these compounds displayed single-digit or low double-digit nanomolar EC_{15} values in polyploidy induction.

After evaluating the benzoixozoles, we then looked briefly into benzoisothioazoles and indazoles. Similar to the benzoisoxazole, both benzoisothiazole and aminoindazole were as effective hinge-binding scaffolds. Some representative examples are listed in Table 3. For easy comparison, benzoisoxazoles **2j**, **2k** and **2l** are also included in Table 3. Benzoisothiazoles (**3a–c**) and indazoles (**4a–c**) exhibited very similar potency against Aurora B as their counterparts in the benzoisoxazole series (**2j–l**). The benzoisothiazole analogs are also very selective for Aurora B, having at least 250-fold lower activity against Aurora A. Similar to the benzoisoxazoles **2j–l**, benzoisothiazoles **3a–c** also exhibited potent activity in inducing cellular polyploidy. In general, the indazole analogs while equipotent in the enzymatic assay are less active in the cellular assay (**4a** and **4b** vs **2j** and **2l**). Additionally, methylation of indazole NH led to significant deterioration of Aurora B potency (**4c** and **4d**).

Table 1
Enzymatic and cellular activities of benzoisoxazole urea analogs



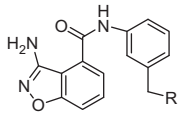
Structure A



Structure B

Compd	Structure	R	IC_{50}, nM		AurA/AurB	Polyploidy (EC_{15}, nM)
			AurB	AurA		
2a	A	H	127	Not tested		Not tested
2b	A	*p*-F	480	>12,500	>26	Not tested
2c	A	*p*-Me	82	>12,500	>152	Not tested
2d	A	*p*-Cl	140	>12,500	>89	Not tested
2e	B	H	18	3790	210	47
2f	B	*p*-F	41	12,200	298	30
2g	B	*p*-Me	4	586	146	1
2h	B	*p*-Cl	3	166	55	12
2i	B	*o*-F	55	>12,500	227	124
2j	B	*m*-F	59	3180	54	3
2k	B	*p*-CF_3	12	12,500	>1000	13
2l	B	3.4-*di*-F	7	4780	696	15

Table 2
Enzymatic activity of benzoisoxazole non-urea analogs



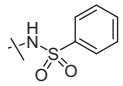
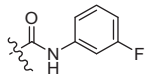
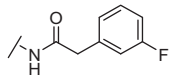
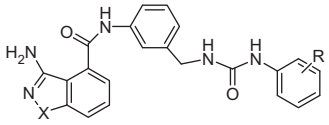
Compd	R	IC_{50}, nM	
		AurB	AurA
2m	NH_2	525	>12,500
2n		>12,500	>12,500
2o		450	>12,500
2p		>12,500	>12,500

Table 3
Enzymatic and cellular activities of compounds with different scaffolds

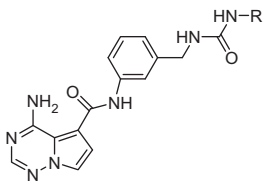


Compd	X	R	IC_{50}, nM		AurA/AurB	Polyploidy (EC_{15}, nM)
			AurB	AurA		
2j	O	*m*-F	59	3180	54	3
2k	O	*p*-CF_3	12	12,500	1041	13
2l	O	3,4-*di*-F	7	4870	696	15
3a	S	*m*-F	50	12,500	250	18
3b	S	*p*-CF_3	12	12,500	1042	18
3c	S	3,4-*di*-F	36	12,500	347	21
4a	NH	*m*-F	18	1279	71	111
4b	NH	3,4-*di*-F	28	1623	58	143
4c	NMe	*m*-F	938	12,500	13	Not tested
4d	NMe	*p*-CF_3	172	12,500	73	Not tested

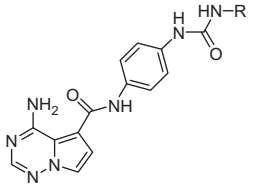
Based on the similarity between pyrrolotriazine and thienopyrimidine, the amide ureas of pyrrolotriazine were also expected to be active against Aurora kinases. Similar to thienopyrimidine amide ureas but unlike the bezoisoxazoles and benzoisothiazoles, these pyrrolotriazine analogs are potent inhibitors of both Aurora A and B kinases (Table 4). Consistent with their Aurora B enzymatic activity, many of these pyrrolotriazine amide ureas effectively induce cellular polyploidy at nanomolar concentrations.

Compounds **2j** and **5g** were selected for modeling analysis, and the proposed binding orientations are shown in Figure 2.[29] Both bind to the 'inactive' confirmation of Aurora B kinase, with the expected canonical hinge hydrogen bonds to Glu 155 and Ala 157. An intramolecular hydrogen bond between the amino group and the amide carbonyl that is present in both hinge heterocycles (benzoisoxazole and pyrrolotriazine, respectively) likely positions the diphenyl urea portion of the molecule into the back pocket. The conserved Lys residue, Lys 106, can donate a hydrogen bond to the inhibitor urea carbonyl. A hydrophobic pocket surrounds the terminal *meta*-fluoro-phenyl group of each inhibitor. Overlay of Aurora A and B structures indicates that one amino acid sequence difference is found in this hydrophobic pocket: Ile 113 in Aurora B/Leu 169 in Aurora A. The model indicates that differential occupation of this pocket and interaction with this varying residue

Table 4
Enzymatic and cellular activities of pyrrolotriazines



Structure A



Structure B

Compd	Structure	R	IC_{50}, nM		AurA/AurB	Polyploidy (EC_{15}, nM)
			AurB	AurA		
5a	A	*p*-Cl-Ph	0.9	46	51	1
5b	A	*p*-CF_3-Ph	24	786	33	6
5c	A	*p*-Me-Ph	1	46	46	1
5d	A	*m*-F-Ph	4	67	16	2
5e	A	*m*-Cl-Ph	10	186	19	2
5f	B	*m*-Me-Ph	38	171	4.5	9
5g	B	*m*-F-Ph	9	NA		3
5h	B	*p*-F-Ph	36	88	2.4	16
5i	B		33	37	1.1	15
5j	B		17	8	0.5	6

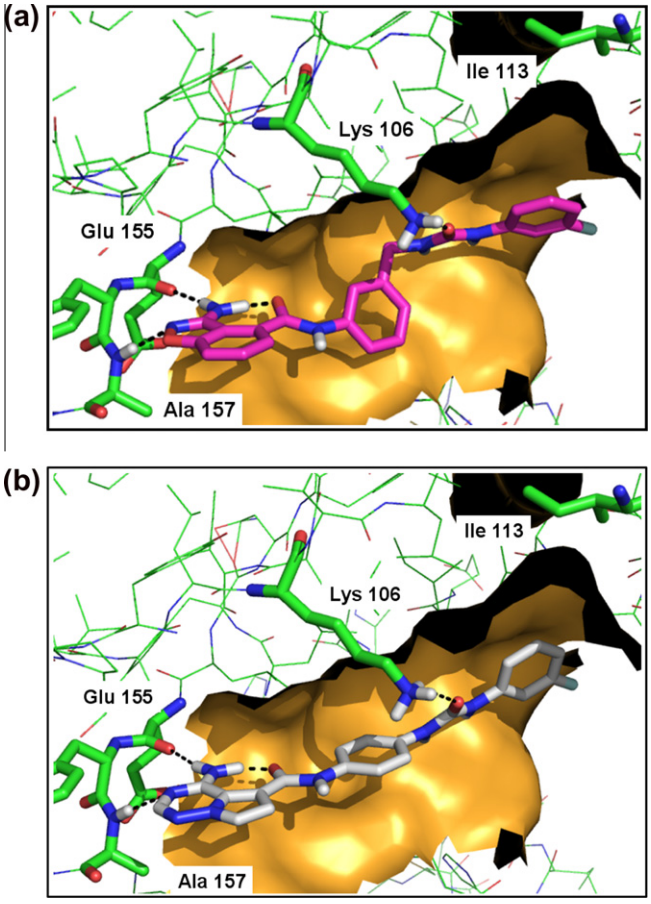


Figure 2. (a). Model of compound **2j** bound to Aurora B kinase (top picture). Hingehydrogen bonds to Glu 155 backbone C=O and Ala 157 N–H are shown with black dashed lines. An intramolecular H-bond between the amine and amide carbonyl exocyclic on the benzoisoxazole is shown. Lys 106 (the 'conserved' Lys) donates an H-bond to the urea carbonyl of the ligand. The fluorophenyl group projects into a hydrophobic pocket comprised of Leu 108, Ile 113, and Leu 122 in Aurora B kinase, corresponding to Leu 164, Leu 169, and Leu 178 in Aurora A kinase. Ile 113 is highlighted as it shows a point of sequence variation between the two kinases. (b) Model of compound **5g** with features highlighted as in (a) (bottom picture).

Table 5
Kinome selectivity profile of compound **5g**[a]

Kinase	IC_{50} (nM)	Kinase	IC_{50} (nM)
Aur A	<3	Jak2	>10,000
Aur B	<3	Jak3	8140
Alk1	>10,000	KDR	1180
Camk4	>10,000	Ick	566
Chk1	>10,000	Jnk1	>10,000
EGFR	2090	*c*-Met	>10,000
Erk2	296	Plk4	<3
Flt3	1100	P38	>10,000
Gsk3a	5340	Rock2	>10,000
IGF1R	>10,000	Src	>10,000
Irak4	340	TrkA	1870

[a] Assay was done in the presence of 10 μM ATP.

Table 6
Mouse pharmacokinetic profiles of selected compounds

Compd	iv (3 mg/kg)			po (10 mg/kg) AUC (μM h/mL)	*F* (%)
	V_d (L/kg)	Cl (L/h kg)	t_d (h)		
2j	0.54	0.53	0.7	5	28
2k	0.23	0.13	1.3	61	77
2l	0.96	0.39	1.7	8	31

might provide the basis for the selective binding observed for these compounds. A more detailed analysis at the atomic level will require crystallographic studies.

In general these compounds are highly selective for Aurora kinases. The selectivity is exemplified by the inhibition profile of compound **5g** against a selected panel of kinases as shown in Table 5.

A number of selected benzoisoxazole amide ureas were evaluated for their mouse pharmacokinetic profiles (Table 6). In general, these benzoisoxaole amide ureas possess a low plasma clearance after iv administration and good oral bioavailability, ranging from 28% for **2j** to 77% for **2k**. Pharmacokinetic evaluation of pyrrolotriazines was done employing an oral cassette dosing protocol. Compound **5a–c and 5e** were dosed in one cassette at 10 mpk, resulting in a good oral exposure AUC of 112, 185, 9.3 and 20.6 μM h/mL, respectively.

Additionally, compound **2l** was evaluated for its in vivo target modulation through inhibition of Histone 3 phosphorylation in leukemia engrafted mouse model. 87% inhibition of H3 phosphorylation was observed in 4 h after 50 mpk IP dosing.

Selected compounds were evaluated in vivo in tumor growth inhibition models. However, the overall safety and efficacy profile did not compare favorably with other series of inhibitors developed in our laboratories.[30]

In summary, we have prepared a series of potent Aurora inhibitors based on a heterocycle amide linked diaryl urea motif by successfully replacing the previously disclosed thienopyrimidine core with alternative hinge-binding moieties. The benzoisoxazole, benzoisothiazole and indazole series show potent Aurora B inhibition, while the pyrrotriazines potently inhibit both Aurora A and B. Additionally all series, with the exception of the indazoles are potent Aurora B cell inhibitors as measured by their ability to effectively induce polyploidy. Selected benzoisoxazoles display a favorable pharmacokinetic profile with good oral biobioavailability in mice.

References and notes

1. Li, J. J.; Li, S. A. *Pharmacol. Ther.* **2006**, *111*, 974.
2. Kimura, M.; Matsuda, Y.; Yoshioka, T.; Okano, Y. *J. Biol. Chem.* **1999**, *274*, 7334.
3. Andrews, P. D. *Oncogene* **2005**, *24*, 5005.
4. Cheung, C. H. A.; Coumar, M. S.; Hsieh, H.-P.; Chang, J.-Y. *Expert Opin. Investig. Drugs* **2009**, *18*, 379.
5. Zeng, W. F.; Navaratne, K.; Prayson, R. A.; Weil, R. J. *J. Clin. Pathol.* **2007**, *60*, 218.
6. Lee, E. C. Y.; Frolov, A.; Li, R.; Ayala, G.; Greenberg, N. M. *Cancer Res.* **2006**, *66*, 4996.
7. Gritsko, T. M.; Coppola, D.; Paciga, J. E.; Yang, L.; Sun, M.; Shelley, S. A.; Fiorica, J. V.; Nicosia, S. V.; Cheng, J. Q. *Clin. Cancer Res.* **2003**, *9*, 1420.
8. Carvajal, R. D.; Tse, A.; Schwartz, G. K. *Clin. Cancer Res.* **2006**, *12*, 6869.
9. Keen, N.; Taylor, S. *Nat. Rev. Cancer* **2004**, *4*, 927.
10. Fancelli, D.; Moll, J. *Expert Opin. Ther. Patents* **2005**, *15*, 1169.
11. Bebbington, D.; Binch, H.; Charrier, J.-D.; Everitt, S.; Fraysse, D.; Golec, J.; Kay, D.; Knegtel, R.; Mak, C.; Mazzei, F.; Miller, A.; Mortimore, M.; O'Donnell, M.; Patel, S.; Pierard, F.; Pinder, J.; Pollard, J.; Ramaya, S.; Robinson, D.; Rutherford, A.; Studley, J.; Westcott, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3586.
12. Mortlock, A. A.; Foote, K. M.; Heron, N. M.; Jung, F. H.; Pasquet, G.; Lohmann, J.-J. M.; Warin, N.; Renaud, F.; Savi, C. D.; Roberts, N. J.; Johnson, T.; Dousson, C. B.; Hill, G. B.; Perkins, D.; Hatter, G.; Wilkinson, R. W.; Wedge, S. R.; Heaton, S. P.; Odedra, R.; Keen, N. J.; Crafter, C.; Brown, E.; Thompson, K.; Brightwell, S.; Khatri, L.; Brady, M. C.; Kearney, S.; McKillop, D.; Rhead, S.; Parry, T.; Green, S. *J. Med. Chem.* **2007**, *50*, 2213.
13. Qi, W.; Cooke, L. S.; Liu, X.; Rimsza, L.; Roe, D. J.; Manziolli, A.; Persky, D. O.; Miller, T. P.; Mahadevan, D. *Biochem. Pharmacol.* **2011**, *81*, 881.
14. Pollard, J. R.; Mortimore, M. *J. Med. Chem.* **2009**, *52*, 2629.
15. Carpinelli, P.; Ceruti, R.; Giorgini, M. L.; Capprlla, P.; Gianellini, L.; Croci, V.; Degrassi, A.; Texido, G.; Rocchetti, M.; Vianello, P.; Rusconi, L.; Storici, P.; Zugnoni, P.; Arrigoni, C.; Soncini, C.; Alli, C.; Patton, V.; Marsiglio, A.; Ballinari, D.; Pesenti, E.; Fancelli, D.; Moll, J. *Mol. Cancer Ther.* **2007**, *6*, 3158.
16. Oslob, J. D.; Heumann, S. A.; Yu, C. H.; Allen, D. A.; Baskaran, S.; Bui, M.; Delarosa, E.; Fung, A. D.; Hashash, A.; Hau, J.; Ivy, S.; Jacobs, J. W.; Lew, W.; Maung, J.; McDowell, R. S.; Ritchie, S.; Romanowski, M. J.; Silverman, J. A.; Yang, W.; Zhong, M.; Fuchs-Knotts, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1409.
17. Prime, M. E.; Courtney, S. M.; Brookfield, F. A.; Marston, R. W.; Walker, V.; Warne, J.; Boyd, A. E.; Kairies, N. A.; Von der Saal, W.; Limberg, A.; Georges, G.; Engh, R. A.; Goller, B.; Rueger, P.; Rueth, M. *J. Med. Chem.* **2011**, *54*, 312.
18. Kerekes, A. D.; Esposite, S. J.; Doll, R. J.; Tagat, J. R.; Yu, T.; Xiao, Y.; Zhang, Y.; Prelusky, D. B.; Tevar, S.; Gray, K.; Terracina, G. A.; Lee, S.; Jones, J.; Liu, M.; Basso, A. D.; Smith, E. B. *J. Med. Chem.* **2011**, *54*, 201.
19. VanderPorten, E. C.; Taverna, P.; Hogan, J. N.; Ballinger, M. D.; Flanagan, W. M.; Fucini, R. V. *Mol. Cancer. Ther.* **2009**, *8*, 930.
20. Rawson, T. E.; Rüth, M.; Blackwood, E.; Burdick, D.; Corson, L.; Dotson, J.; Drummond, J.; Fields, C.; Georges, G. J.; Goller, B.; Halladay, J.; Hunsaker, T.; Kleinheinz, T.; Krell, H.-W.; Li, J.; Liang, J.; Limberg, A.; McNutt, A.; Moffat, J.; Phillips, G.; Ran, Y.; Safina, B.; Ultsch, M.; Walker, L.; Wiesmann, C.; Zhang, B.; Zhou, A.; Zhu, B.-Y.; Rüger, P.; Cochran, A. G. *J. Med. Chem.* **2008**, *51*, 4465.
21. Belanger, D. B.; Curran, P. J.; Hruza, A.; Voigt, J.; Meng, Z.; Mandal, A. K.; Siddiqui, M. A.; Basso, A. D.; Gray, K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5170.
22. McClellan, W. J.; Dai, Y.; Abad-Zapatero, C.; Albert, D. H.; Bouska, J. J.; Glaser, K. B.; Magoc, T. J.; Marcotte, P. A.; Osterling, D. J.; Stewart, K. D.; Davidsen, S. K.; Michaelides, M. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5620.
23. Ji, Z.; Ahmed, A. A.; Albert, D. H.; Bouska, J. J.; Bousquet, P. F.; Cunha, G. A.; Diaz, G.; Glaser, K. B.; Guo, J.; Harris, C. M.; Li, J.; Marcotte, P. A.; Moskey, M. D.; Oie, T.; Pease, L.; Soni, N. B.; Stewart, K. D.; Davidsen, S. K.; Michaelides, R. M. *J. Med. Chem.* **2008**, *51*, 1231.
24. Dai, Y.; Hartandi, K.; Ji, Z.; Ahmed, A. A.; Albert, D. H.; Bauch, J. L.; Bouska, J. J.; Bousquet, P. F.; Cunha, G. A.; Glaser, K. B.; Harris, C. M.; Hickman, D.; Guo, J.; Li, J.; Marcotte, P. A.; Marsh, K. C.; Moskey, M. D.; Martin, R. L.; Olson, A. M.; Osterling, D. J.; Pease, L. J.; Soni, N. B.; Stewart, K. D.; Stoll, V. S.; Tapang, P.; Reuter, D. R.; Davidsen, S. K.; Michaelides, M. R. *J. Med. Chem.* **2007**, *50*, 1584.
25. Ghosez, L.; Franc, C.; Denonne, F.; Cuisinier, C.; Touillaux, R. *Can. J. Chem.* **2001**, *79*, 1827.
26. To determine the activity of Aurora A and B kinases, a homogenous time-resolved fluorescence (HTRF) in vitro kinase assay was used: (a) Mathis, G. *HTRF(R) Technol. J. Biomol. Screen.* **1999**, *4*, 309; (b) Kolb, A. J.; Kaplita, P. V.; Hayes, D. J.; Park, Y-W; Pernell, C.; Major, J. S.; Mathis, G. *Drug Discovery Today* **1998**, *3*, 333.
27. To measure the induction of polyploidy: NCI-H1299 were seeded (4 K/well) into 96-well culture plates (tissue culture grade, black, flat-clear bottom) and incubated overnight to produce cell-to-plate adherence. Test drugs at varying concentrations were added into duplicate wells containing cells and culture media (RPMI 1640, 10% fetal calf serum) and incubated at 37 °C for 48 h. The plates were then washed with PBS and the adherent cells fixed by incubating with 3% formalin for 1 h. After washing four times with PBS, the cells were then stained with Hoechst and subjected to fluorescent (360i/460e) microscopic high content analysis to determine the effect of test drug on nuclear size. Polyploid cells (P4 N) were defined as those having nuclear area >750 l2. Test drug potency was expressed as the concentration of drug necessary to induce polyploidy in 15% of cells (EC15) and was calculated from least squares analysis of the log dose-response.
28. Hauf, S.; Cole, R. W.; LaTerra, S.; Zimmer, C.; Schnapp, G.; Walter, R.; Heckel. A., van Meel. J.; Rieder, C. L.; Peters, J.-M. *J. Cell Biol.* **2003**, *161*, 281.
29. Energy minimized structures of compounds **2j** and **5g** were dockedinto a homology model of human Aurora B. The model was built using PDB entry 3EFW as template: Cee, V. J. et al *Bioorg. Med. Chem. Lett* **2009**, *19*, 424.
30. Curtin, M. L.; Frey, R. R.; H. Heyman, H. R.; Soni, N. B.; Marcotte, P. A.; Pease, L. J.; Glaser, K. B.; Magoc, T. J.; Tapang, P.; Albert, D. H.; Osterling, D. J.; Olson, A. M.; Bouska, J. J.; Guan, Z.; Preusser, L. C.; Polakowski, J. S.; Stewart, K. D.; Tse, C.; Davidsen, S. K.; Michaelides, M. R. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3208.