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Synthesis and SAR studies of imidazo-[1,2-*a*]-pyrazine Aurora kinase inhibitors with improved off-target kinase selectivity

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ABSTRACT

The structure–activity relationships of new Aurora A/B kinase inhibitors derived from the previously identified kinase inhibitor **12** are described. Introduction of acetic acid amides onto the pyrazole of compound **12** was postulated to influence Aurora A/B selectivity and improve the profile against off-target kinases. The SAR of the acetic acid amides was explored and the effect of substitution on enzyme inhibition as well as mechanism-based cell activity was studied. Additionally, several of the more potent inhibitors were screened for their off-target kinase selectivity.

The Aurora kinases are a member of the Ser/Thr family of kinases and play a vital role in the cell cycle during mitosis.[1] Currently three isoforms have been identified, Auroras A, B, and C. Aurora A and B both have been demonstrated to have essential roles in the cell cycle and Aurora C is believed to have a function related to Aurora B but with limited expression. While both Aurora A and B operate during mitosis, they affect different components of the cell cycle progression. Aurora A has been associated with cell cycle events including mitotic entry and exit, bipolar spindle assembly, and centromere maturation. Aurora B has been shown to phosphorylate histone H3, regulate chromosomal remodeling, kinetochore-spindle attachment, and cytokinesis. Inhibition of Aurora A results in G2/M delay, followed by apoptotic cell death, while inhibition of Aurora B gives rise to aberrant cell division followed by apoptosis. Dual inhibitors of Aurora A and B display the Aurora B phenotype.[2] These kinases have been found to be over expressed in a number of tumors which has instigated exploration of this family of kinases as a possible target for cancer therapy.[3] A number of Aurora kinase inhibitors are currently being examined in clinical trials in addition to several preclinical programs.[2b,4]

We have previously described our efforts towards the development of dual Aurora A/B inhibitors.[5] This work led to the discovery of several potent inhibitors, including compound **12** which had excellent inhibition of Aurora A and B and was potent in our mechanism based cell assay. While **12** satisfied or met desired criteria for activity the molecule had low solubility and <60 nM inhibition against off-target kinases VEGFR2, LCK, Chk1 IRAK4 and moderate potency (360 nM) against RSK2 (Table 4).[6] Based upon X-ray studies of the initial lead series,[5a] modeling studies of the expected key interactions of **12** with Aurora A are presented in Figure 1. The molecule binds in the adenosine triphosphate (ATP) binding pocket with the catalytically active 'DFG-in' conformation. The core N1 and 8-NH side chain form a hydrogen bonding network with Ala 213 in the hinge binding region and the 3-pyrazole NH forms a hydrogen bond with Asp 274. The piperidine isothiazole is located on a hydrophobic region at the front of the ATP binding pocket and extends toward the solvent accessible front. The bioactive conformation of this portion of the molecule is stabilized by a polar interaction between the isothiazole sulfur and N7 of the imidazo[1,2-*a*]pyrazine core. Previous published examples of dual Aurora A/B inhibitors suggested that by extending the molecule deeper into a hydrophilic binding pocket at the back of the ATP binding site improved selectivity for Aurora A/B over other off-target kinases.[4e] During the development of SAR around compound **12**, we became interested in exploring compounds that were substituted on the pyrazole nitrogen. We postulated that a side chain at this position could reach into the hydrophobic pocket improving selectivity. This binding mode also could potentially influence Aurora A verse Aurora B selectivity leading to selective inhibitors.[7] In particular, we were interested in examining substituted acetic acid amides at this position.[8]

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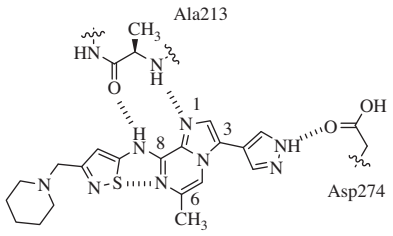
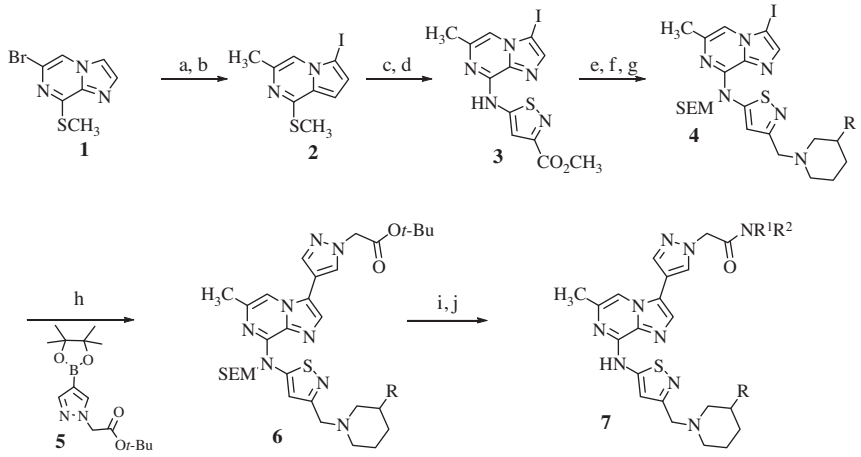


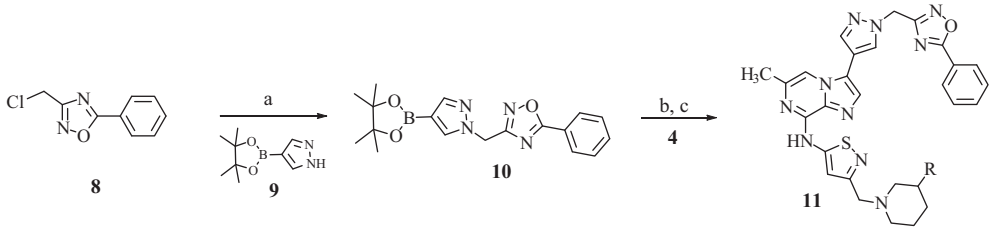
Figure 1. Summary of key interactions between **12** and Aurora A.

The synthesis of the desired compounds was carried out in a straightforward manner depicted in Scheme 1. The starting material for our sequence was 6-bromo-8-thiomethylimidazopyrazine **1** which was readily available on a multigram scale.[5d] Palladium-mediated methylation was followed by selective iodination with NIS to give compound **2**. The thiomethyl was activated for displacement by oxidation to the sulfone with *m*-CPBA and displaced with methyl 5-aminoisothiazole-3-carboxylate in DMF to afford **3**. Selective DIBAL-H reduction of the methyl ester produced the intermediate aldehyde in excellent yield. Subsequent reductive amination under standard conditions and protection of the free biaryl NH with SEMCl provided our key iodide intermediate **4**.[9] A Suzuki–Miyaura coupling of the pyrazole boronate **5** with iodide **4** afforded compound **6** in good to moderate yield. Removal of the *t*-butyl group and concomitant SEM-deprotection with TFA afforded an intermediate carboxylic acid, which was readily converted to compound **7** in good to excellent yields. A similar, but more convergent end game is presented in Scheme 2. This sequence was particularly useful in preparing a series were the amide was replaced by isosteres and preparing amide analogs **7** on larger scale. In this example pyrazole borate ester **9** was alkylated with 3-(chloromethyl)-5-phenyl-1,2,4-oxadiazole **8** to produce aryl amide mimetic **10**. With this approach the entire side chain could be appended onto iodide **4** in one step and acid deprotection of the SEM group affords analogs **11**.

Initially a number of aliphatic or aromatic amides were prepared utilizing the chemistry described in Schemes 1 and 2. All compounds were studied for there inhibition of Aurora A and B. Potent molecules were then tested in a mechanistic cell-based assay where the ability to inhibit the Aurora B mediated phosphorylation of histone H3 was measured.[10] The ability of these analogs to inhibit Aurora A/B is summarized in Table 1. The parent carboxylic acids (**13** and **14**) were also tested for enzyme inhibition; however, these compounds displayed only weak inhibition of both Aurora A and B. Primary amide **15** displayed good inhibition of Aurora B (IC_{50} = 28 nM) with 50-fold selectivity over Aurora A, however **15** did not inhibit phosphorylation of histone-H3 in our mechanism-based cell assay. Secondary amides **16** and **17** maintain moderate selectivity for Aurora B (IC_{50} = 193 nM and 44 nM) but were less potent and **17** displayed no cell activity. When tertiary amides were prepared such as dimethyl amide analog **18** no inhibition of either Aurora A or B was found. Introduction of polar functionality in the amide side chain (compounds **19** and **20**) produced only weak or no enzyme activity against Aurora A or B consistent with the proposed hydrophobic nature of the binding site. Encouraging results were obtained when a benzyl amide analog **21** was tested. This compound displayed excellent enzyme potency for both Aurora A (IC_{50} = 21 nM) and Aurora B (IC_{50} = ⩽13 nM), and had good cell-based activity with an IC_{50} = 129 nM. Also encouraging were the results of anilide **22** showing good enzyme inhibition of

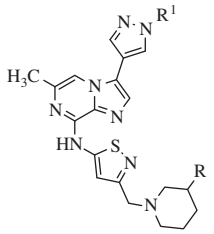


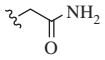
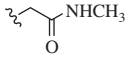
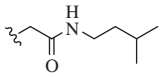
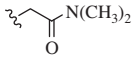
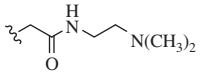
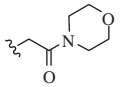
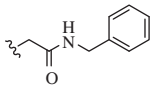
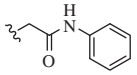
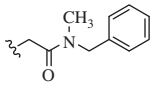
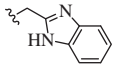
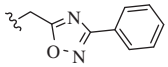
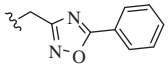
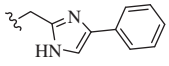
Scheme 1. Reagents and conditions: (a) Trimethylboroxine, $Pd(PPh_3)_4$, K_2CO_3, DMF, 100 °C, 63%; (b) NIS, DMF, 60 °C, 64%; (c) *m*-CPBA, DCM; (d) NaH, DMF, methyl 5-aminoisothiazole-3-carboxylate, 90% for two steps; (e) SEMCl, DMF, NaH, 40%; (f) DIBAL-H, −78 °C, THF, 95%; (g) amine, $NaB(OAc)_3H$, DCE, rt, 99%; (h) $PdCl_2dppf$, K_3PO_4, dioxane, H_2O, 90 °C, 79%; (i) TFA, CH_2Cl_2, 79%: (j) HNR^1R^2, HATU, DIPEA, DMF.



Scheme 2. Reagents and conditions: (a) K_2CO_3, DMA, 35%. (b) $PdCl_2dppf$, K_3PO_4, dioxane, H_2O, 90 °C, 51%. (c) HCl, 1,4-dioxane, sonication 42%.

Table 1
SAR of N-substituted pyrazoles **12–27**



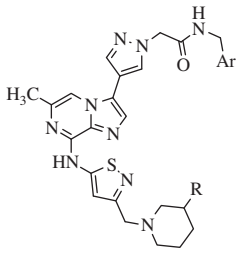
Compd	R	R^1	Aur A[a] IC_{50} (nM)	Aur B[a] IC_{50} (nM)	phos-HH3[a] EC_{50} (nM)
12	H	H	⩽4	⩽13	50
13	H		1,828	363	NT[b]
14	CH_3		836	146	NT
15	H		1567	28	>1000
16	H		>3000	193	NT
17	H		1803	44	>1000
18	H		>3000	>3000	NT
19	CH_3		>3000	761	NT
20	H		>3000	>3000	NT
21	CH_3		21	⩽13	129
22	CH_3		34	51	327
23	CH_3		1627	261	NT
24	CH_3		18	⩽13	534
25	H		⩽4	⩽13	>1000
26	H		⩽4	⩽13	>1000
27	H		583	21	887

[a] For assay conditions see footnote 10.
[b] Not tested.

both Aurora A (IC_{50} = 34 nM) and Aurora B (IC_{50} = 51 nM), as well as moderate cell-based potency (IC_{50} = 327 nM). Consistent with earlier observations, any attempt at modifying these compounds to tertiary amides (analog **23**) resulted in decreased inhibition. Finally a series of amide bond isosteres was synthesized with the assumption that replacement of the amide bond would produce compounds with improved ADMET properties. Phenyl oxadiazoles **25** and **26** proved to be excellent dual inhibitors of Aurora A and B and phenyl imidizole **27** was active in Aurora B however these analogs demonstrated only weak activity in the cell assay. Based on the results from Table 1, compounds **21** and **22** were selected as starting points for additional SAR development.

The SAR results from the benzyl acetamide analogs are provided in Table 2. We first prepared a series of mono- and di-fluorinated

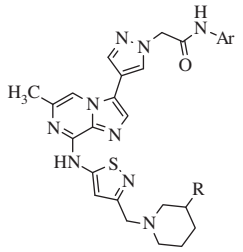
Table 2
SAR of aryl- and heteroaryl- aminomethylamides **27–42**



Compd	R	Ar	Aur A[a] IC_{50} (nM)	Aur B[a] IC_{50} (nM)	phos-HH3[a] IC_{50} (nM)
28	H	2-F-phenyl	44	⩽13	469
29	H	3-F-phenyl	30	⩽13	234
30	H	4-F-phenyl	40	⩽13	416
31	H	2,3-*di*-F-phenyl	45	⩽13	870
32	H	3,5-*di*-F-phenyl	22	⩽13	389
33	CH_3	3-Trifluoromethylphenyl	413	35	>1,000
34	CH_3	4-Trifluoromethylphenyl	>3,000	175	NT[b]
35	CH_3	3-Dimethylaminophenyl	859	155	NT
36	CH_3	3-Methoxyphenyl	57	41	442
37	CH_3	4-Methoxyphenyl	1,931	161	NT
38	CH_3	3-Pyridyl	434	439	NT
39	CH_3	4-Pyridyl	2,447	1,107	NT
40	CH_3	2-Oxazolyl	168	178	NT
41	CH_3	2-Furanyl	213	70	NT
42	CH_3	2-Thienyl	27	⩽13	193

[a] For assay conditions see footnote 10.
[b] Not tested.

Table 3
SAR of aryl- and heteroaryl-amides **43–58**



Compd	R	Ar	Aur A[a] IC_{50} (nM)	Aur B[a] IC_{50} (nM)	phos-HH3[a] IC_{50} (nM)
43	H	2-F-phenyl	198	35	388
44	H	3-F-phenyl	340	⩽13	892
45	H	4-F-phenyl	53	30	412
46	H	2,3-*di*-F-phenyl	122	⩽13	58
47	H	3,5-*di*-F-phenyl	1,223	94	2,378
48	CH_3	2-Thiazolyl	100	⩽13	>1,000
49	CH_3	2-Thiadiazolyl	30	18	>1,000
50	CH_3	2-Pyridazinyl	638	45	951
51	CH_3	2-Pyridyl	185	32	285
52	CH_3	3-Pyridyl	186	118	NT
53	CH_3	4-Pyridyl	12	⩽13	83
54	CH_3	4-Pyridyl-N-oxide	68	91	402
55	CH_3	4-(3-Hydroxy)-pyridyl	239	282	NT[b]
56	CH_3	4-(3-F)-pyridyl	<4	⩽13	62
57	CH_3	2-(6-F)-pyridyl	102	28	164
58	CH_3	3-(2-F)-pyridyl	753	81	110

[a] For assay conditions see foot note 10.
[b] Not tested.

benzyl amine analogs (**28–32**), and all showed excellent enzyme inhibition of both Aurora A (IC_{50} = 22–45 nM) and Aurora B (IC_{50} = ⩽13 nM). Unfortunately, these compounds exhibited only modest cell-based potency (IC_{50} = 234–870 nM). Substituting other halogens in the place of fluorine only produced less active analogs (data not shown). Other phenyl ring substitution such as trifluoromethyl, dimethylamino, or methoxy (**33–37**) also led to compounds with decreased potency compared to the fluoro analogs.

Table 4
Selectivity (IC_{50}, nM) of selected compounds against various kinases

Compd	Aur A	Aur B	VEGFR2	LCK	Chk1	IRAK4	RSK2
12	⩽4	⩽13	4	12	20	56	360
42	27	⩽13	234	579	300	873	7700
46	122	⩽13	481	>3,000	20	1,423	4,300
53	12	⩽13	108	731	100	1,142	1,100
56	⩽4	⩽13	253	271	300	1,219	6,800

In an effort to improve the solubility and absorption a series of pyridyl and five-membered ring heterocycles were also explored. The 3- and 4-pyridyl derivatives **38** and **39** lost significant potency in the enzyme assay while the 2-oxazolyl and 2-furanyl compounds **40** and **41** had modest potency in Aurora A and B. We found that the 2-thienyl analog **42** had excellent enzyme potency (Aurora A IC_{50} = 27 nM, Aurora B $IC_{50} \leqslant 13$ nM) and reasonable cell-based activity (IC_{50} = 193 nM), however taken as a series these analogs did not have desirable cell-based potency.

We next focused our attention on refining the SAR of aryl amide **22**, the results of which are presented in Table 3. As with the benzyl amine SAR, a series of mono- and di-fluoroaryl amides were prepared (**43**–**48**) and their ability to inhibit Aurora A/B was explored. As we had seen in the benzyl series these analogs generally showed good potency in Aurora A /B with moderate activity in the cell assay (phos-HH3). However there were two outliers, the 3,5-di-fluorophenyl analog **47** which was less active and of particular interest was 2,3-di-fluorophenyl analogs **46**, which displayed good inhibition of both Aurora A (IC_{50} = 122 nM) and B ($IC_{50} \leqslant 13$ nM), and had cell-based potency similar to **12** (phos-HH3, EC_{50} = 58 nM). Encouraged by these results phenyl ring isosteres were explored. Compounds derived from thiazoles, thiadiazoles, and pyridazinyl rings (**48**, **49**, **50**) displayed good enzyme inhibition, however lacked mechanism-based cell potency. Several aminopyridine analogs were also prepared and their activity was found to correlate to the regiochemistry of the aminopyridine. While the 2- and 3-aminopyridines **51** and **52** had moderate enzyme and cell potency the 4-aminopyridine containing analog **53** had excellent potency in both enzyme and cell assays (Aurora A IC_{50} = 12 nM, Aurora B $IC_{50} \leqslant 13$ nM, phos-HH3 EC_{50} = 83 nM). Addition of polar functional groups such as the pyridine N-oxide **55** and 3-hydroxyl pyridine **56** led to compounds with reduced activity. However, the potency of this series could be further optimized by combining fluorine with the aminopyridine. Once again, the regiochemistry of the aminopyridine proved critical, and it was found the 4-amino-3-fluoropyridine **56** provided optimal potency (Aurora A ⩽4 nM, Aurora B $IC_{50} \leqslant 13$ nM, phos-HH3 EC_{50} = 62 nM) over regioisomers **57** and **58**.

At this point with several potent cell active Aurora inhibitors in hand the off-target kinase selectivity was examined relative to our lead analog **12**. While compound **12** was a potent Aurora A/B inhibitor, it also displayed good potency (<60 nM) against several other kinases and Table 4 compares Aurora A/B potency with off-target kinases VEGFR2, LCK, Chk1, IRAK4, and RSK2. From the benzyl series the 2-aminomethyl thiophene amide **42** had 15- to 50-fold improvement in selectivity over the tested off-target kinases. The 2,3-difluorphenyl inhibitor **46** improved the selectivity by achieving ⩾400 nM potencies against the tested kinases except for Chk 1 where it was equipotent to **12**. The 4-pyridyl derivative **53** improved the Chk 1 selectivity fivefold, but suffered a minor loss in overall selectivity when compared to **46**. Finally the 3-fluoro pyridyl compound **56** demonstrated >10-fold selectivity against Chk 1 and 20- to 100-fold selectivity against the other tested kinases clearly showing that these analogs improve off-target selectivity compared to the unsubstituted pyrazole derivative **12**.

In reviewing the Aurora A/B inhibition data it was obvious while the selectivity over off-target kinases improved, the majority of the compounds demonstrated little or no preference for Aurora B over Aurora A and only a few simple amides such as **15** and **17** had reasonable Aurora B selectivity. This SAR seemed to be inconsistent with our postulated binding confirmation and we turned to X-ray crystallography to help us understand the binding mode of these inhibitors. Figure 2 has an overlay of X-ray structure of 3-fluoro-4-pyridyl acetamide **56** in Aurora A with an earlier published structure of **SCH 1473759**.[5c,11] The imidazo[1,2-*a*]pyrazine core, 6-aminoisothiazole, and 3-pyrazole overlap with the previous structure however, instead of binding to the protein in an extended conformation the acetamide side chain is almost orthogonal to pyrazole. The pyridine is oriented towards the glycine rich loop were the pyridyl nitrogen has a hydrogen bond to the NH of Phe 144. This interaction moves the glycine rich loop about 1.5 Å closer to the inhibitor when compared to the X-ray structure of **SCH 1473759** and while the acetamide NH of **56** maintains a hydrogen bond with Asp 274, the DFG loop is pushed out by approximately 1 Å to accommodate the increased bulk of the acetamide.

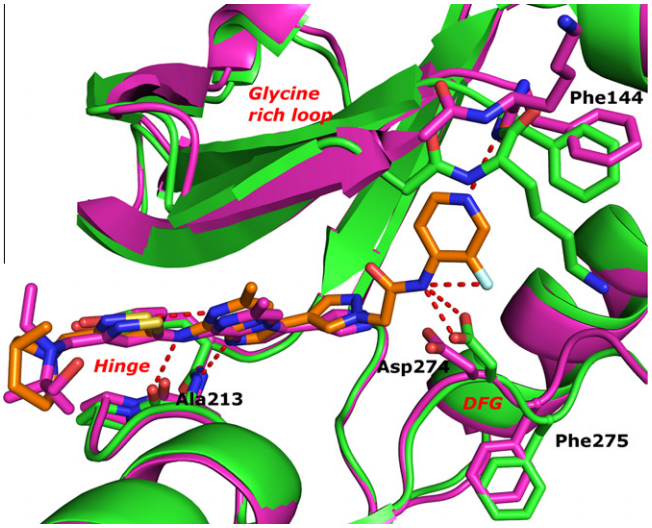


Figure 2. X-ray structure of compound **56** (green) overlaid with X-ray of **SCH 1473759** (magenta).[11,5e]

In summary, a new series of dual Aurora A/B kinase inhibitors has been developed based on compounds containing acetic acid amides. These inhibitors demonstrated excellent enzyme inhibition mechanism-based cell activity, and an improved profile against off-target kinases. X-ray crystallographic analysis gave an unexpected mode of binding allowing us to rationalize the desired improvement in off-target selectivity. The most potent compounds contained an aminopyridine amide motif and the activity of these amides was related to the regiochemistry of the aminopyridine. The 4-aminopyridine with fluorine substitution at the 3-position was found to be optimal substituent.

Acknowledgments

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References and notes

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6. Compound with good Aurora A/B enzyme potency and cell activity were screen against an in house panel of kinases including: Akt1, Camk4, Cdk2, Chk1, CSNK1d, EGFR, Ephb4, Erk2, IGRF, IKKb, IRAK4, Jak2, LCK, cMet, MST2, PKCa, PLK3, Rock2, RSK2, TSSK2, and VEGFR2.
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9. For this study piperidine and (±) 3-methylpiperdine were used interchangeably. Synthesis of the individual enantiomers in previous series demonstrated biochemical equivalence.
10. For a detailed description of the biochemical assays see footnote 15 in Ref. 5d.
11. The coordinates for compound **56** have been deposited in the RcSB Protein Data Bank under the Accession Code 3VAP.