

# Indazoles as Potent and Selective Aurora Kinase Inhibitors

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## Introduction

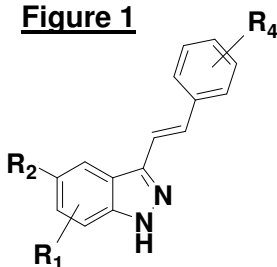
The Aurora kinases (A, B and C) are a small family of mitotic serine-threonine kinases. These enzymes have long been implicated in tumorigenesis due to their involvement in several aspects of mitosis and as a result have attracted attention as potential targets in oncology. Aurora A and B have attracted particular attention since they have been found to be over-expressed in a range of solid tumours, including among others breast, ovarian, prostate, pancreas and colorectal.<sup>1</sup>

Experiments using small molecule inhibitors of the Aurora kinases have confirmed the importance of both the A and B isozymes in mitosis. However, the phenotype observed using inhibitors with varied selectivities seems to correlate well with inhibition of Aurora B in particular.<sup>2</sup> It has been suggested that Aurora B may be the more relevant drug target since inhibition will result in rapid cell death due to abnormal mitosis.<sup>3</sup>

Furthermore, an inhibitor which exhibits high selectivity for the B isozyme might achieve the goal of cancer cell death while limiting toxicity.

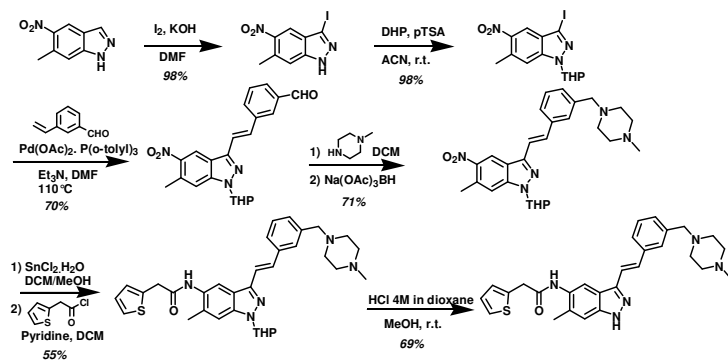
We screened our in house compound collection for inhibitors of Aurora A as part of our program towards the development of anticancer kinase inhibitors. The hit to lead process was heavily influenced by *prior art* in the area of kinase inhibitors and led to the design of new molecules based on the indazole moiety (Figure 1).

Figure 1



## Synthesis

A series of substituted indazoles was easily accessible using a high yielding procedure outlined here for a representative analogue.



## SAR of Alkenyl Indazoles

Substitution at 4 position renders selectivity towards Aurora-B.

1) Introduction of hydrogen bond donors improves IC<sub>50</sub>  
2) Introduction of hydrophilic groups improves solubility

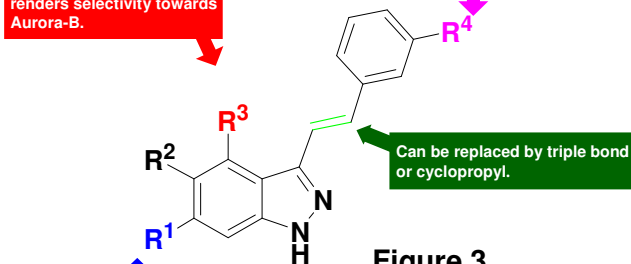


Figure 3

Cyclic amines seem to improve selectivity and solubility

## Biological data, Table 1

Entry	R <sup>2</sup>	R <sup>1</sup>	R <sup>3</sup>	R <sup>4</sup>	Aurora A (IC <sub>50</sub> )	Aurora B (IC <sub>50</sub> )
1			H	H	0.16	0.049
2			H	H	>10	0.67
3			H	H	0.61	0.13
4	NO <sub>2</sub>		H		0.35	0.10
5			H		0.13	0.062
6			H	H	0.092	0.10
7		Me	H	H	0.018	0.077
8		Me	H		0.008	0.031
9		H	H		0.036	0.023
10		H	Me		1.90	0.078

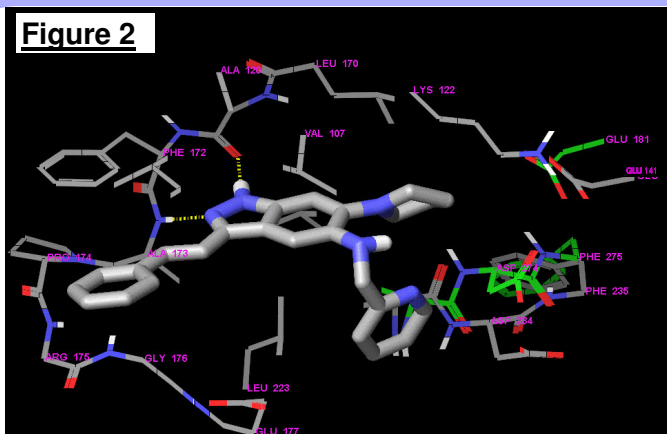
Aurora inhibition data for a selection of analogues are shown in Table 1. It was found that variation of R<sup>1</sup>, R<sup>3</sup> and R<sup>4</sup> led to altered selectivities towards the two Aurora kinases. Docking of the tested analogues into the two enzyme structures allowed these selectivity differences to be rationalised. The ATP binding sites of Aurora A and B are highly conserved. However, there is some divergence, primarily on the right hand side of the docking pose shown in Fig 2 (Glu141, Phe235 and Asp234 in Aurora B). Indeed it is when substituents docking in this region are altered that significant changes in isoform selectivity are observed. So, for example, when the pyrrolidine group of **3** is replaced with a bulkier *N*-methylpiperazine (**2**) the result is greater selectivity towards Aurora B.<sup>†</sup>

Also of note, is that introduction of a methyl group as R<sup>3</sup> also results in dramatically improved selectivity towards Aurora B (cf. **9** and **10**).

Unfortunately, in most cases improved selectivity towards Aurora B was accompanied by some loss in potency.

<sup>†</sup>When screened against a panel of 30 kinases, **2** showed no inhibition at 1 μM

Figure 2



- **3** (Table 1) docking into Aurora B (in grey)
- Shows areas where there is significant divergence in amino acid residue position between Aurora A (green) and B (grey).
- Indazole nitrogens form two H-bonds to enzyme's 'hinge' region.

## Conclusions

The alkenyl indazoles have been shown to be potent *in vitro* inhibitors of the Aurora kinases. Furthermore, it has been shown that the modest differences in active site architecture may be exploited so as to achieve some degree of isozyme selectivity. However, the secondary goal of achieving both high selectivity and potency towards Aurora B has proved challenging.

Further work is needed if these compounds are to be optimised in terms of potency, selectivity and ADME properties.

## References

1. J.R. Bischoff *et al.*, *EMBO J.* **1998**, *17*, 3052-3065.
2. S. Hauf *et al.*, *J. Cell Biol.*, **2003**, *161*, 281-294; C. Ditchfield *et al.*, *J. Cell Biol.*, **2003**, *161*, 267-280.
3. N.Keen, S.Taylor, *Nature Review* **2004**, Vol.4, 927

