Phthalazinone pyrazoles as potent, selective and orally bio-available inhibitors of Aurora-A Kinase

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Introduction

The Aurora kinases (consisting of Aurora A, B and C) are a subfamily of serine/threonine kinases that carry out key protein phosphorylation events necessary for the successful completion of mitosis. Aurora-A localises predominantly to the centrosome and is important for correct centrosome maturation and separation (loss or inhibition of Aurora-A arrests replicating cells in early mitosis). Aurora-A is highly expressed in many tumor types.

Phthalazinone development

The aim of our efforts was to obtain a truly selective Aurora-A inhibiting small molecule which displayed suitable PK properties for oral dosing in Xenograft experiments. To this end a number of templates were prepared.

Phthalazinones 2 and 3 both displayed significantly improved oral exposure compared to VX-880 (Figure 5).

We then looked to develop a second generation series which displayed increased cellular activity. Inspection of the co-crystal of 1 with Aurora-A indicated significant scope for expansion (Figures 6 and 7) at the R1 position and also by aromatic substitution towards the solvent exposed region.

Conclusion

A novel series of selective Aurora-A inhibitors has been developed which display significantly improved oral exposure compared with VX-880. Second generation phthalazinones with increased cellular activity have been prepared and further molecules with improved Aurora-B activity are under investigation.

References

1) Hargrave et al., Nat. Med. 2004, 10, 265-270

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