

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



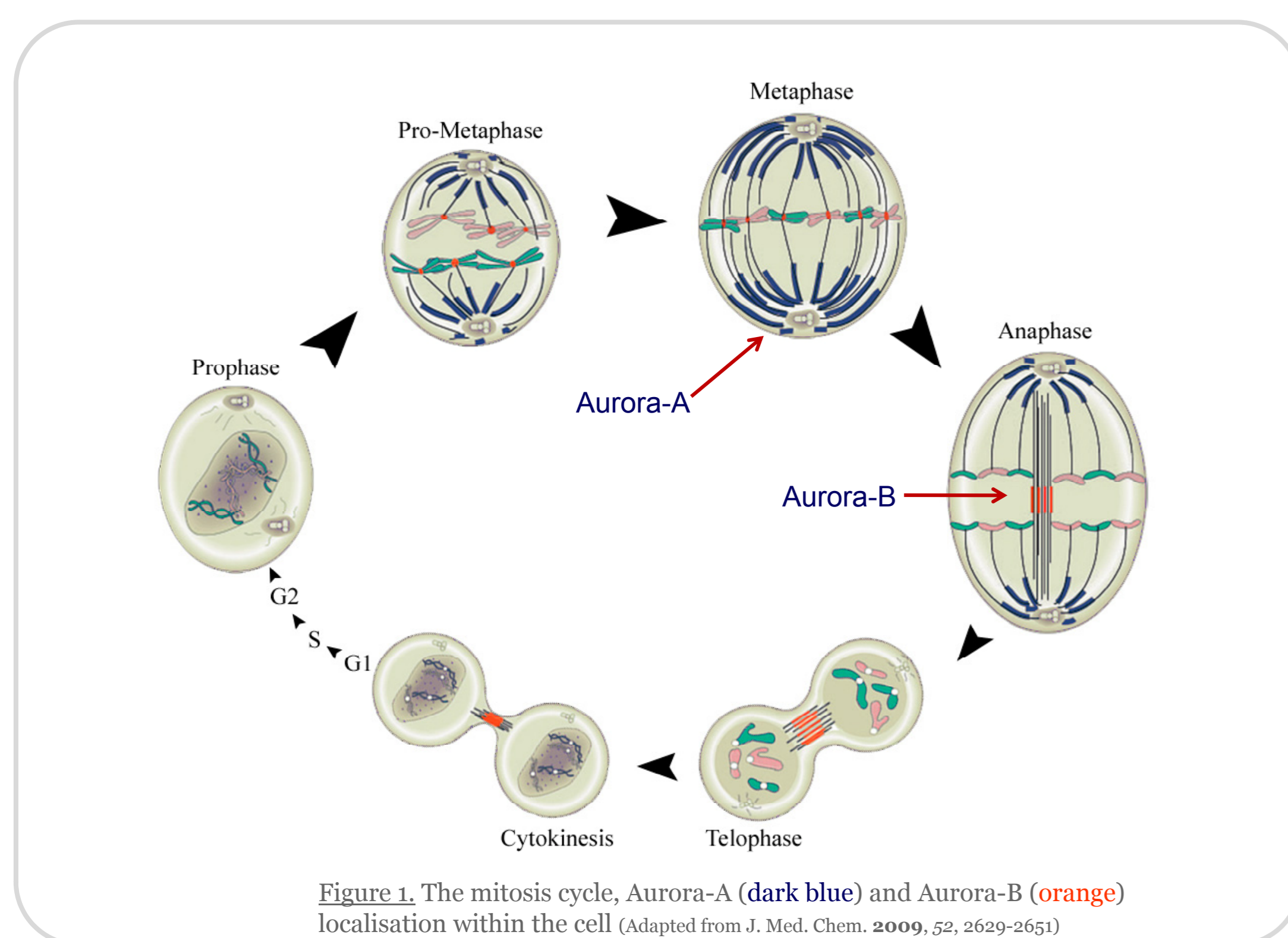
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## Introduction

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.

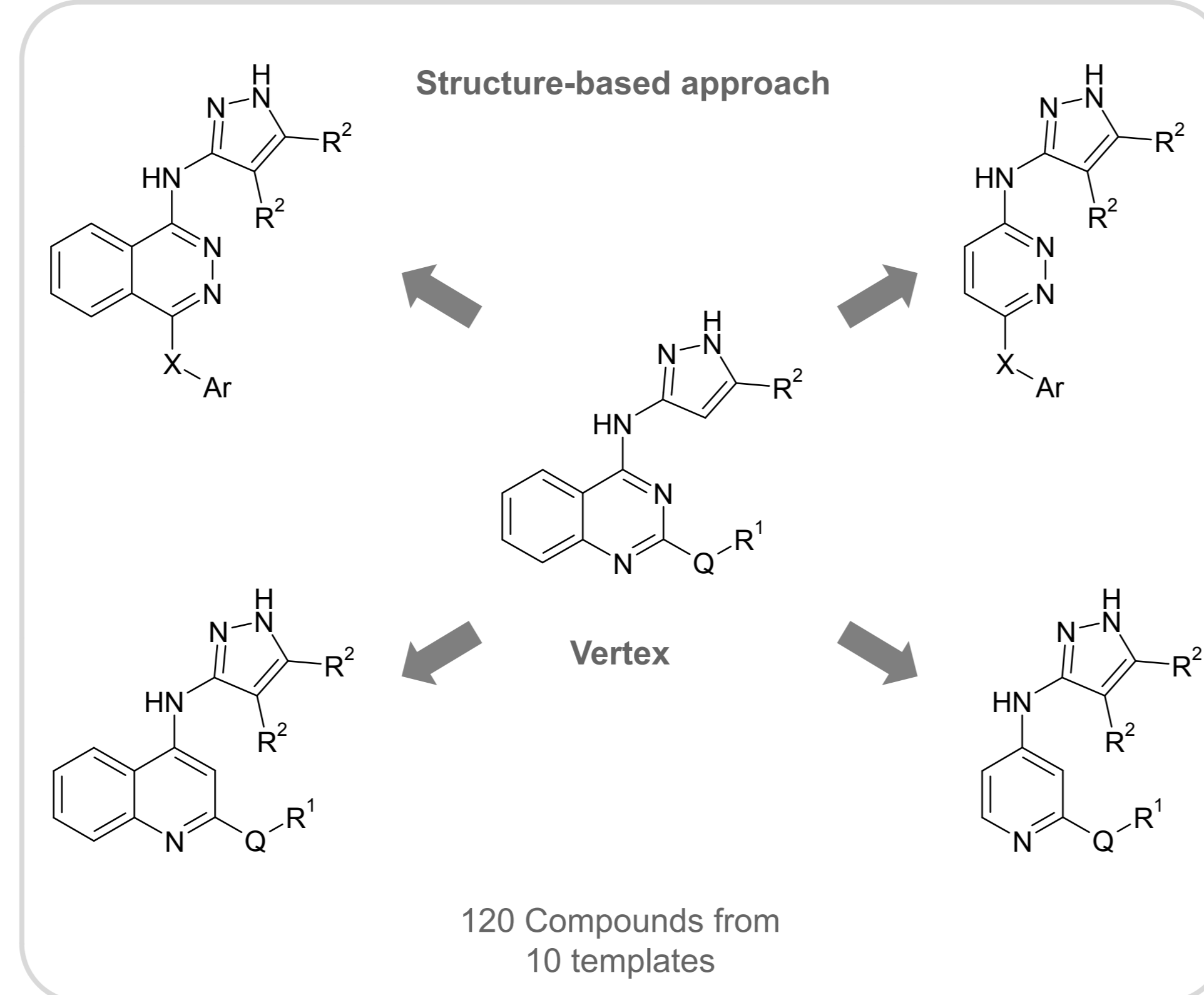
Aurora-A localises predominantly to the centrosome and is important for correct centrosome maturation and separation (loss or inhibition of Aurora-A arrests replicating cells in early mitosis). Aurora-A is highly expressed in many tumor types.



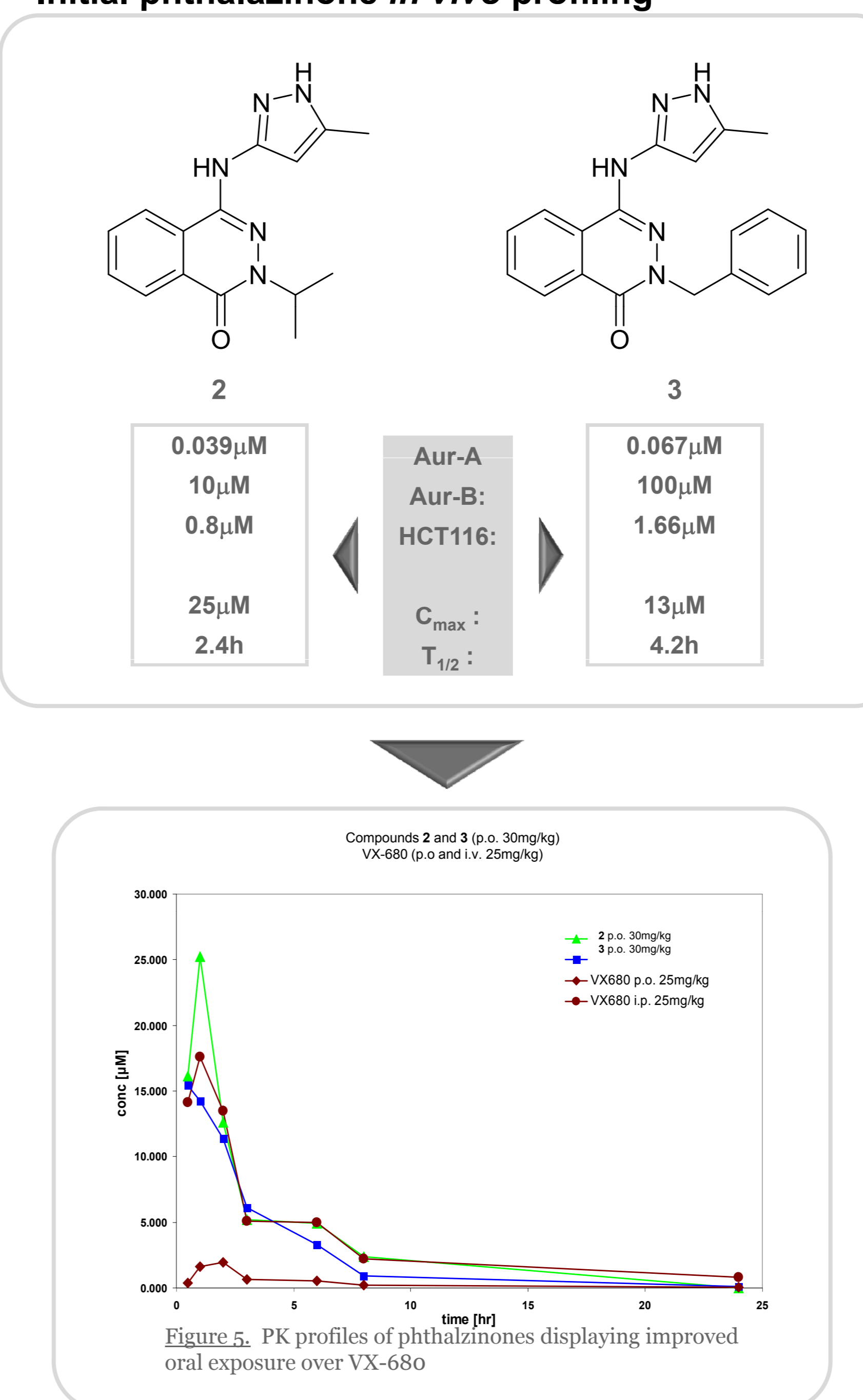
The aim of our efforts was to obtain a truly selective Aurora-A inhibiting small molecule which displayed suitable PK properties for oral dosing in Xenograft studies.

To this end a number of templates were prepared

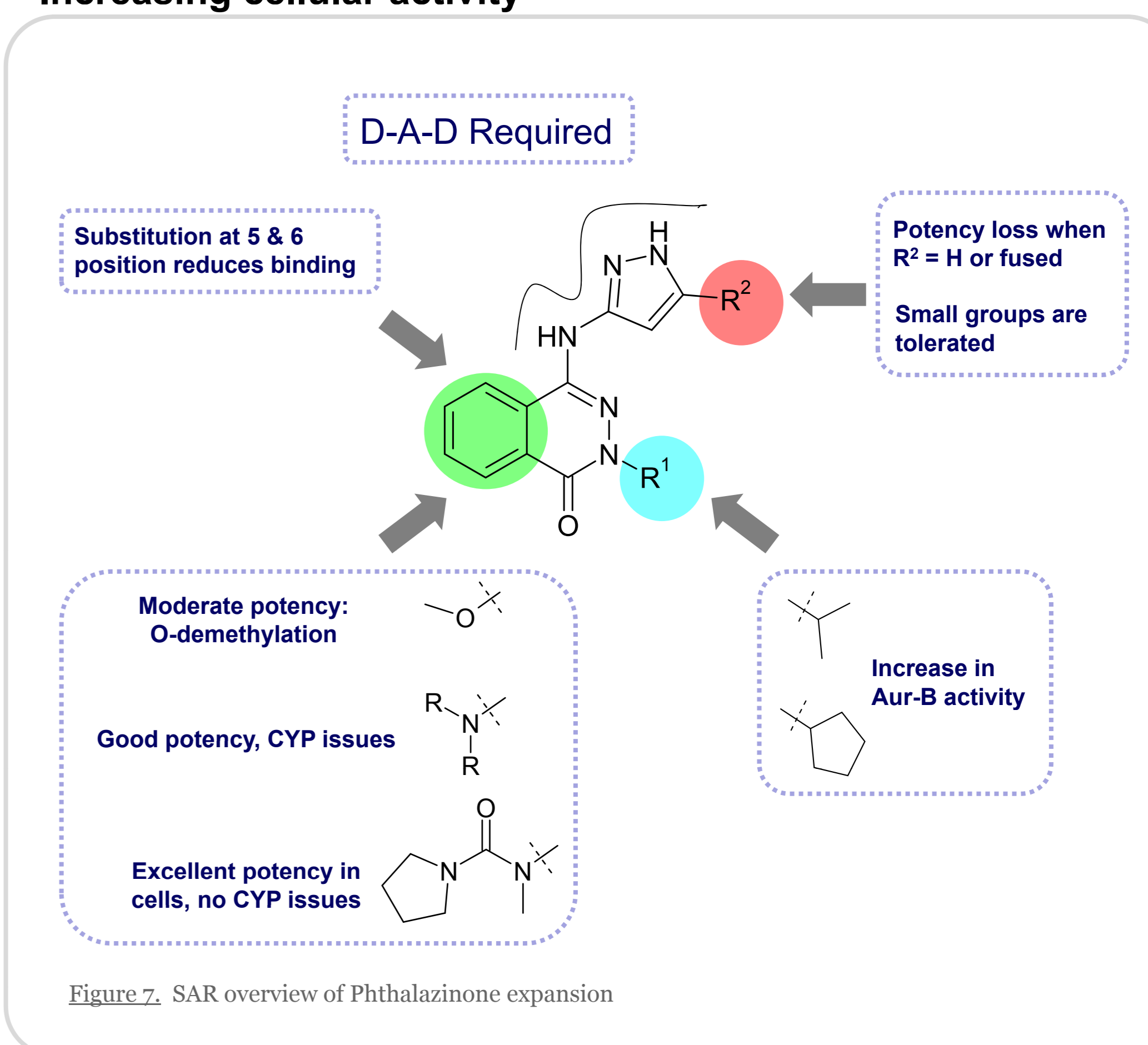
## Phthalazinone development



## Initial phthalazinone *in vivo* profiling

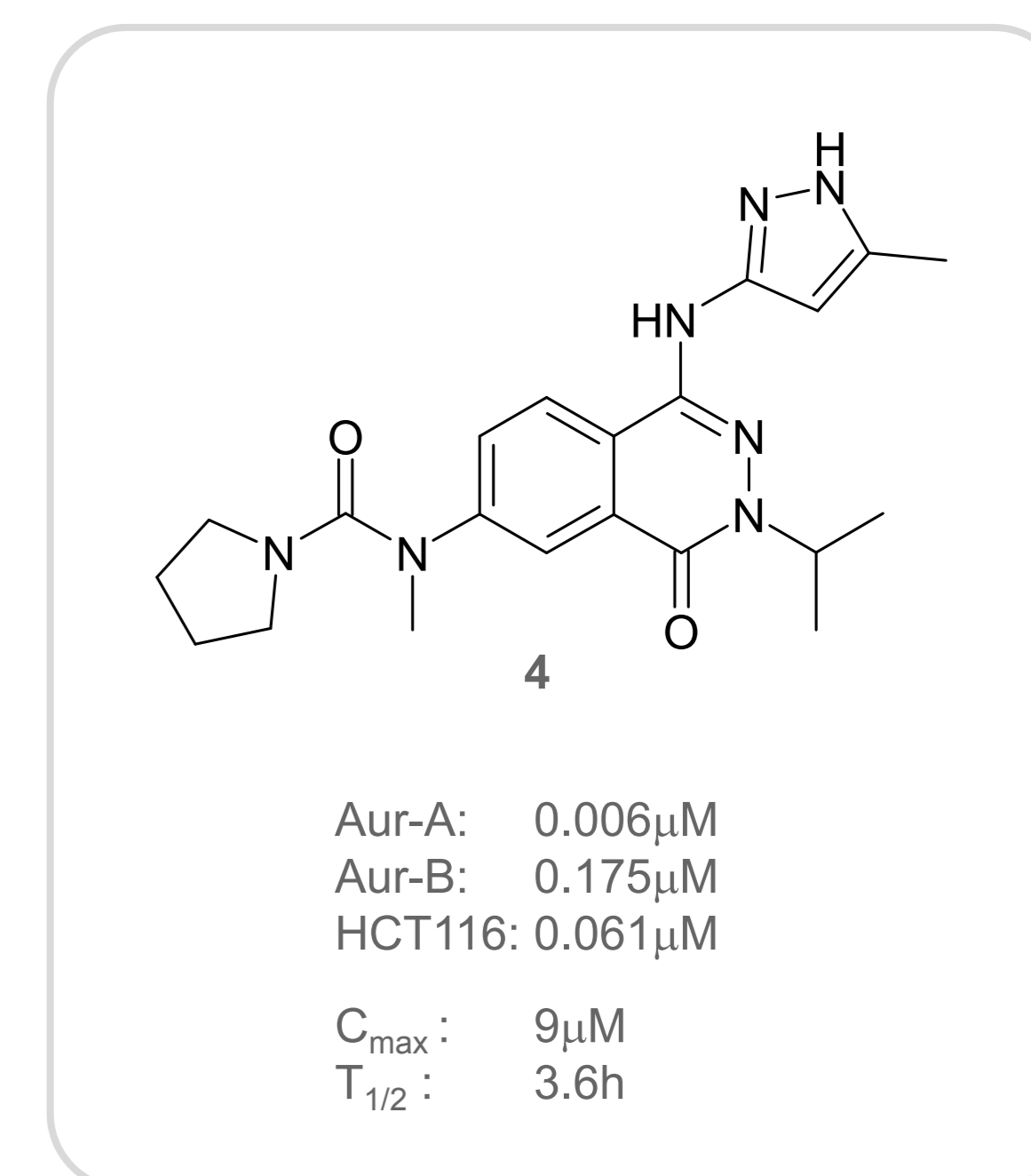


## Increasing cellular activity



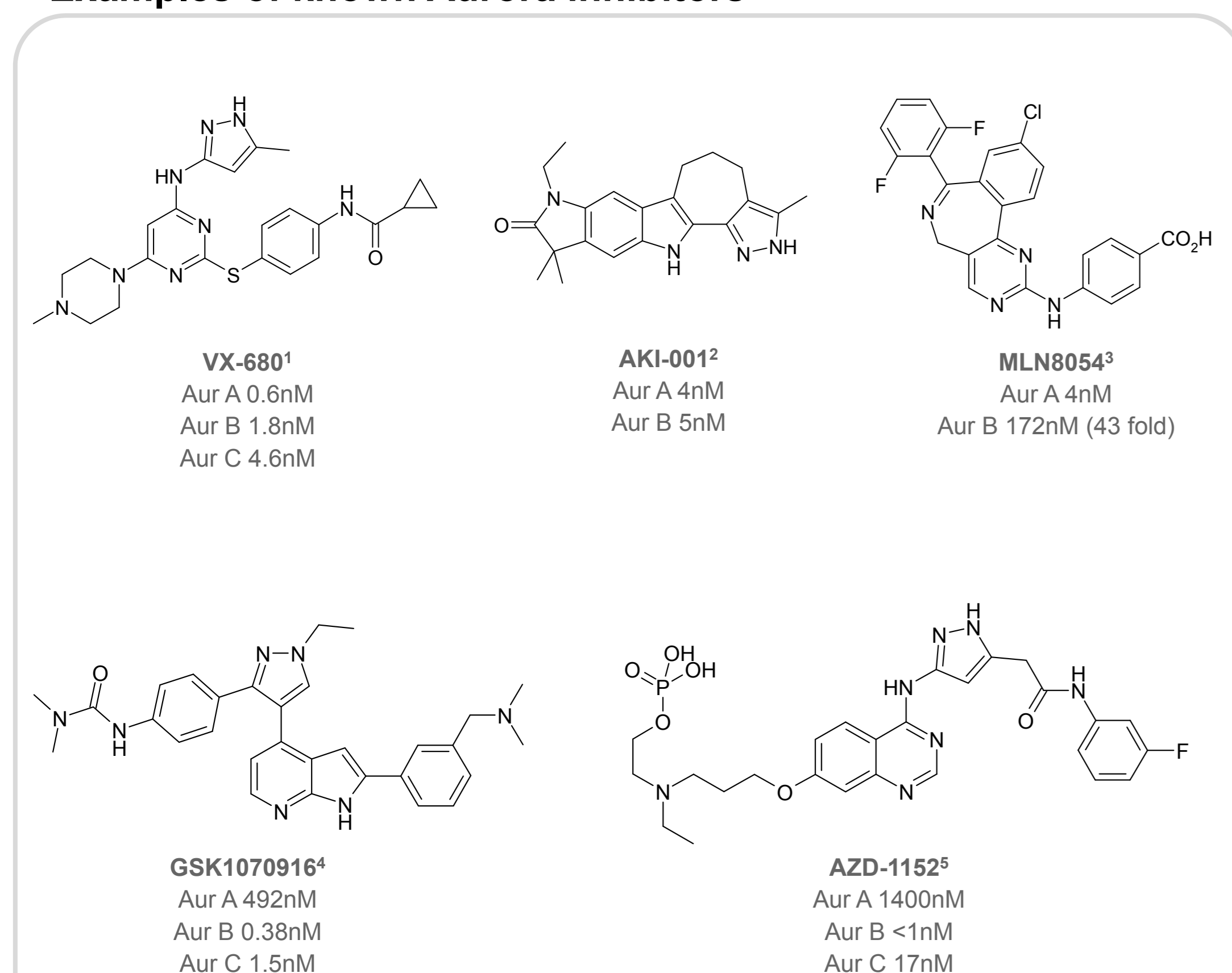
## Second generation profiling

Significant SAR expansion was carried out on the phthalazinone scaffold which led to the identification of compound 4 which displayed excellent potency against Aur-A and significantly improved activity in the HCT116 cell line.



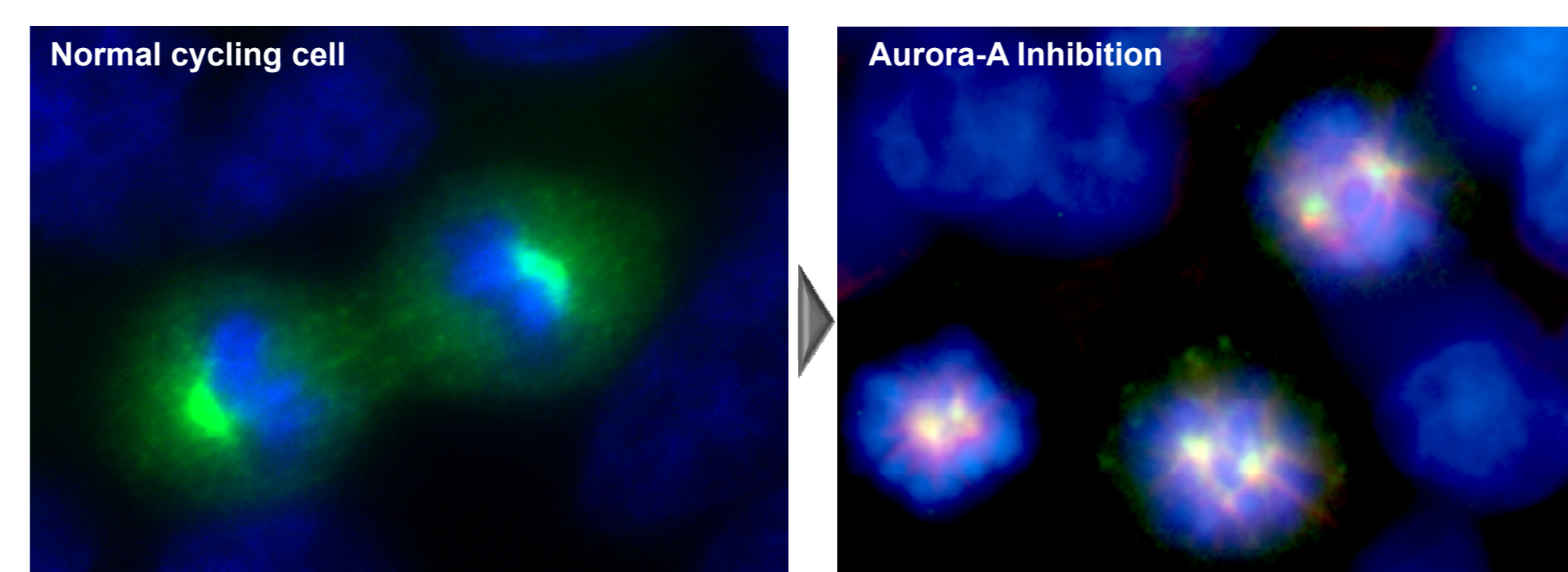
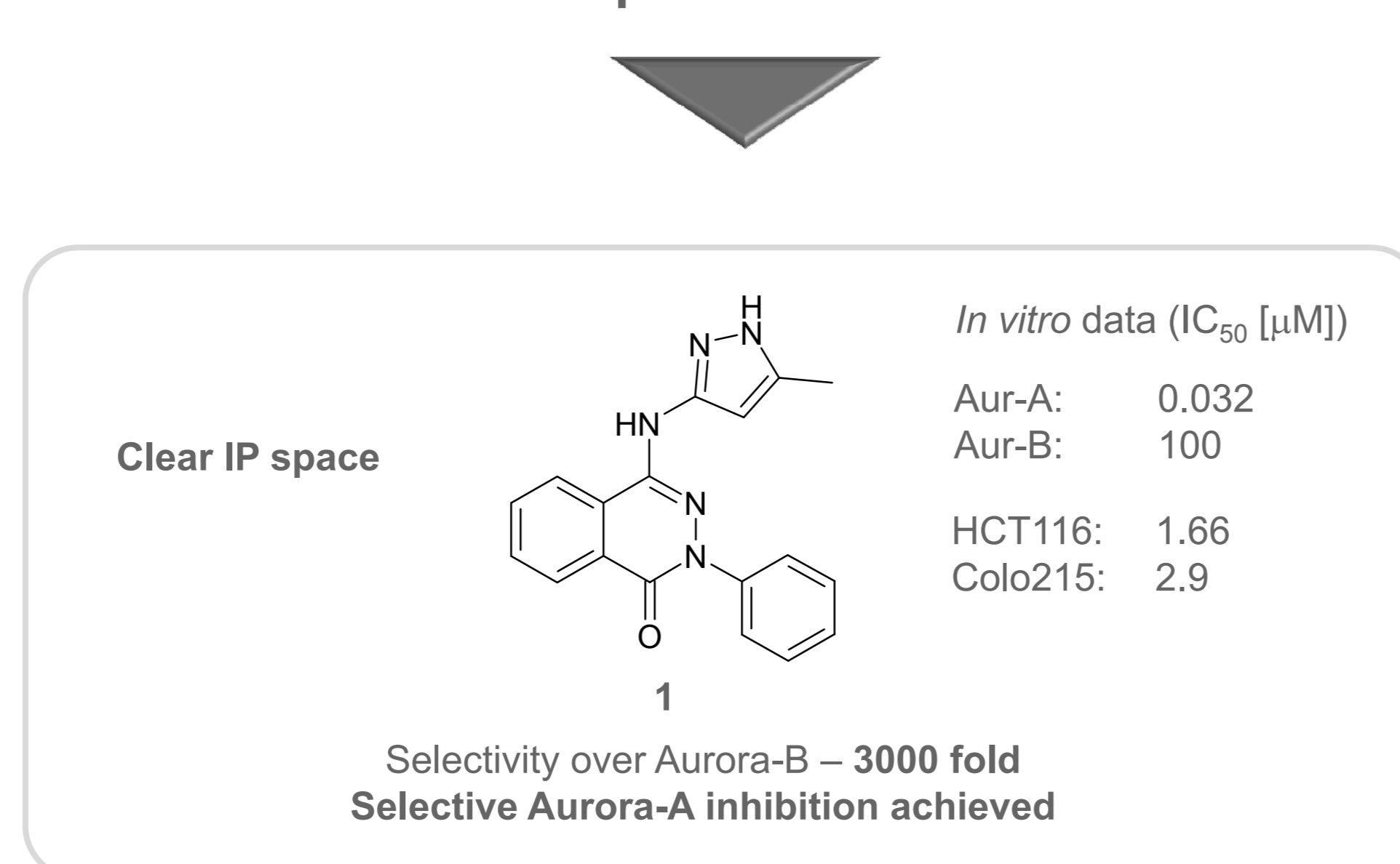
Human tumor cell lines depleted of Aurora-A transcripts arrest in mitosis. Accordingly, the specific inhibition of Aurora Kinase-A by selective inhibitors has been demonstrated to stop uncontrolled proliferation, re-establish mitotic checkpoint control and lead to apoptosis of tumor cells.

## Examples of known Aurora inhibitors



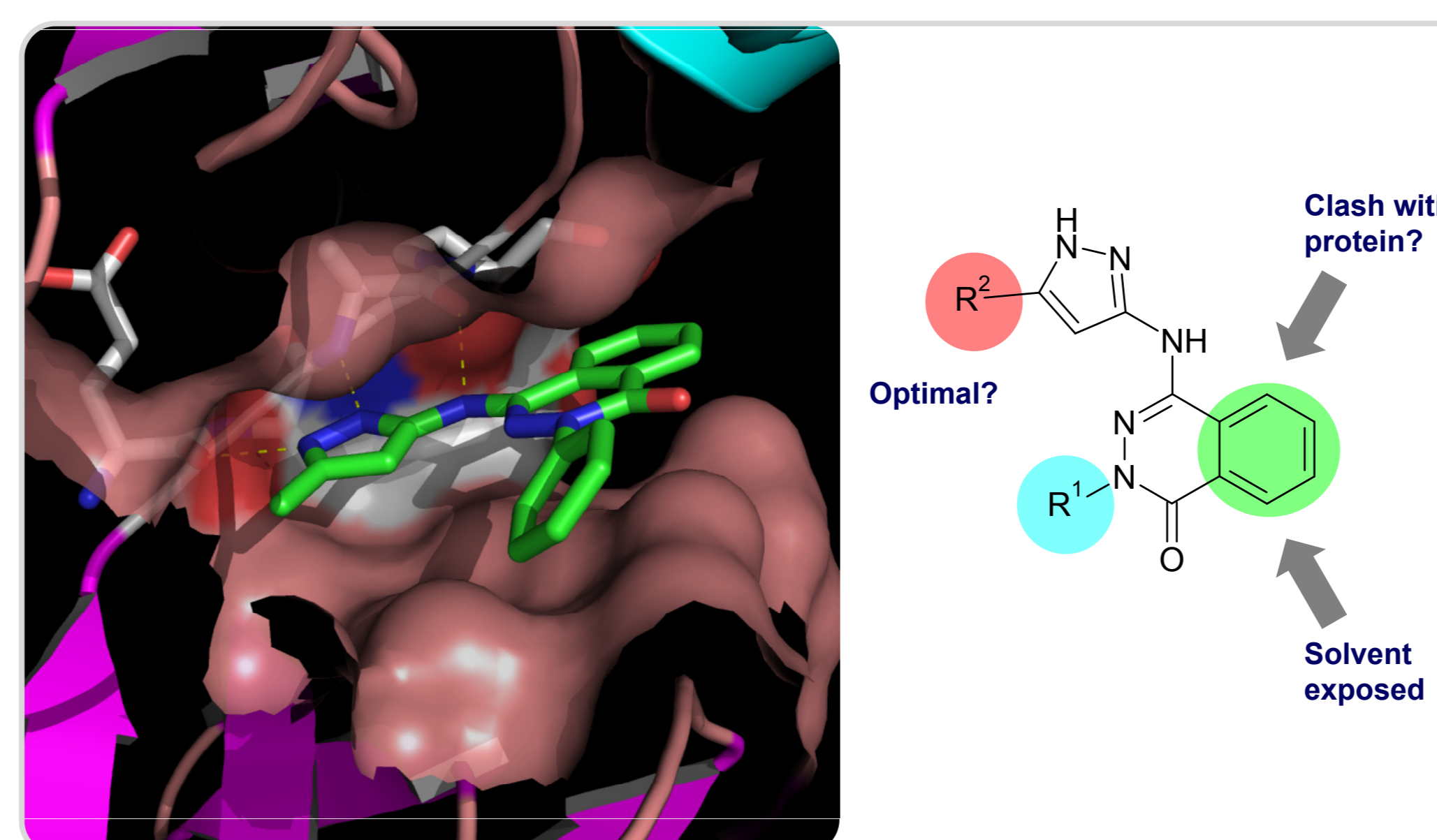
**Figure 2.** Literature Aurora Inhibitors 1-5

## Phthalazinone series selected for optimisation



Phthalazinones 2 and 3 both displayed significantly improved oral exposure compared to VX-680 (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-680. Second generation phthalazinones with increased cellular activity have been prepared and further molecules with improved Aurora-B activity are under investigation.

## References

- Harrington et al. Nat. Med. 2004, 10, 262-267.
- Rawson et al. J. Med. Chem. 2008, 51, 4465-4475.
- Manfredi et al. Proc. Natl. Acad. Sci. U.S.A. 2007, 104, 4106-4111.
- Adams et al. J. Med. Chem. 2010, 53, 3973-4001.
- Mortlock et al. J. Med. Chem. 2007, 50, 2213-2224.