Structure-based Design of Novel Aurora Kinase A Inhibitors

Mohane Selvaraj Coumar, Paritosh Shukla, Ajay Kumar Dixit, Jiun-Shyang Leou John T.-A. Hsu, Su-Ying Wu and Hsing-Pang Hsieh*

Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes, 35, Ke-Yan Road, Zhunan Town, Miaoli, 35053, Taiwan. Tel: +886-37-246166 ext:35708; E-mail: hphsieh@nhri.org.tw

ABSTRACT

- Through virtual screening using the x-ray co-crystal structure of Aurora A protein (PDB Code: 1MQ4), we identified a novel pyrazole compound 1 to be an Aurora A inhibitor.
- X-ray co-crystal guided lead optimization of pyrazole hit 1b had led to the synthesis of 6h with a 400-fold improved Aurora A kinase inhibition potency.

INTODUCTION

- Aurora kinase, a member of serine/threonine kinase is involved in the regulation of cell division. Three isoforms of Aurora kinase, A, B and C are known.
- Aurora A and B are over expressed in many human cancers and are linked to chromosome instability, oncogenic transformation and tumor progression.
- Inhibitors of Aurora kinase have shown to promote cancer cell death by induction of apoptosis and mitotic catastrophe.

LEAD IDENTIFICATION STRATEGY

Gold 3.0 and Glide 4.5

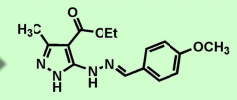
Aurora Kinase A (PDB code: 1MQ4)

Virtual Screening

(i) Over 60,000 compounds docked virtually in ATP binding pocket of Aurora kinase A

(ii) Top scoring 100 compounds purchased and assessed for Aurora kinase A activity

Aurora Inhibitor Lead 1b

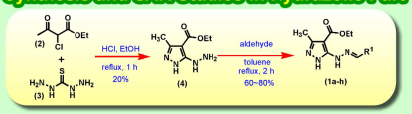


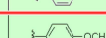
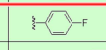
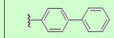
(1b)

Aurora A IC_{50} = 15.1 μM

LEAD OPTIMIZATION STRATEGY- A

Synthesis and SAR Studies in Hydrazone Part

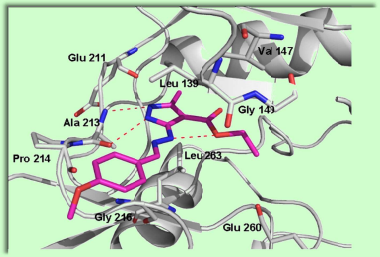


Compds	R^1	Aurora kinase A Inhibition	
		% Inhibition @ 10 μM	IC_{50} (μM)
1a		16	-
1b		35	15.1
1c		36	-
1d		28	-
1e		41	-
1f		4	-
1g		50	14.0

- SAR study in R1 (hydrazone) part shows that **1b** has optimal Aurora activity
- Further improvement in activity not possible by modification of R1

X-ray Co-crystal of 1b with Aurora A Protein

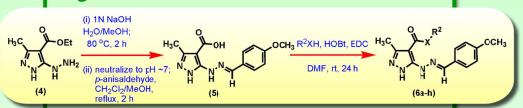
- Lead compound 1b was co-crystalized with Aurora A using hanging drop technique
- Co-crystal structure of Aurora A-inhibitor complex solved through x-ray diffraction studies



- Lead compound **1b** binds to the ATP binding pocket of Aurora A Two *H*-bonds observed between the pyrazole ring and Hinge Ala213 residue
- Intramolecular H-bond observed between the side chains of **1b**
- Hydrozone part is projecting towards solvent exposed part of Aurora A protein
- Ester function is projecting towards a hydrophobic region of Aurora A protein and introduction of hydrophobic group in the ester side chain can improve interaction with protein.

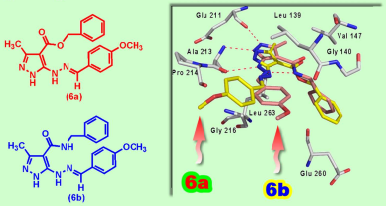
LEAD OPTIMIZATION STRATEGY - B

Synthesis and SAR Studies in Ester Part



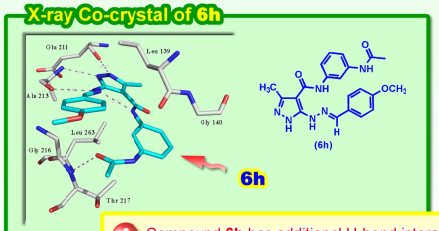
Compd	XR^2	Aurora kinase A Inhibition	
		% Inhibition @ 10 μM	IC_{50} (μM)
1b		35	15.100
6a		59	5.250
6b		86	1.590
6c		85	1.360
6d		93	0.800
6e		11.7	>50
6f		94	0.460
6g		95	0.450
6h		96	0.032

Superimposition of X-ray Co-crystal of 6a & 6b



- Compound **6a** has additional hydrophobic interaction through the Ph group with the protein
- Compound **6b**, three H-bonds observed between the pyrazole ring and Hinge residues Ala213 & Glu211. Intramolecular H-bonding pattern is different in case of 6b when compared to **1b/6a**.

X-ray Co-crystal of 6h



- Compound **6h** has additional H-bond interaction through 3-$NHCOCH_3$ carbonyl group with Thr217 residue of Aurora A

CONCLUSION

450-Fold improvement in Aurora A kinase activity through structure-guided lead optimization

ACKNOWLEDGEMENTS

The study was financially supported by National Health Research Institutes and National Science Council, Taiwan (NSC-95-2113-M-400-001-MY3)

Nature Precedings : doi:10.1038/npre.2009.2769.1 : Posted 10 Jan 2009