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Search For Potent And Selective Aurora A Inhibitors Based On General Ser/Thr Kinases Pharmacophore Model

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ASINEX inspired by Nature

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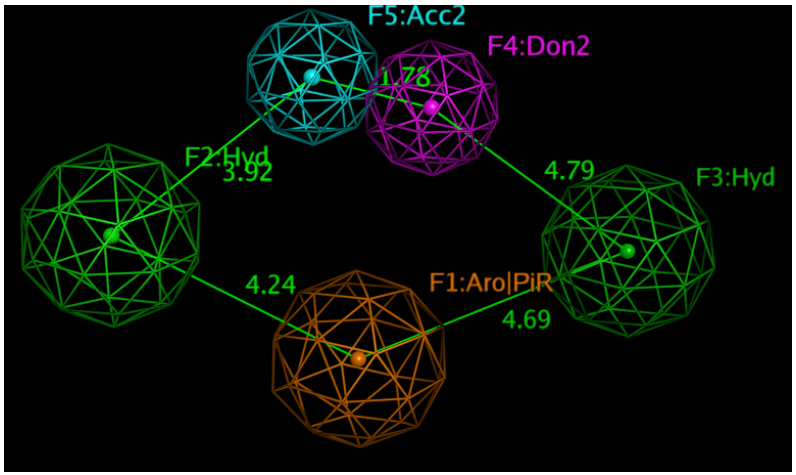
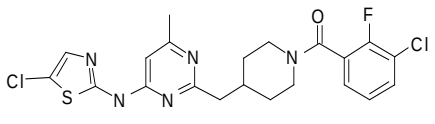
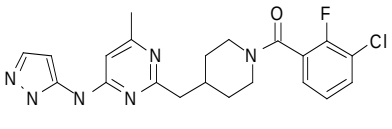


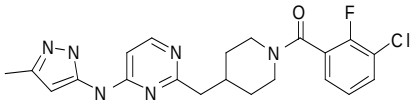
Aurora A, IC_{50}, nM



4.1±0.35



5.3±0.46



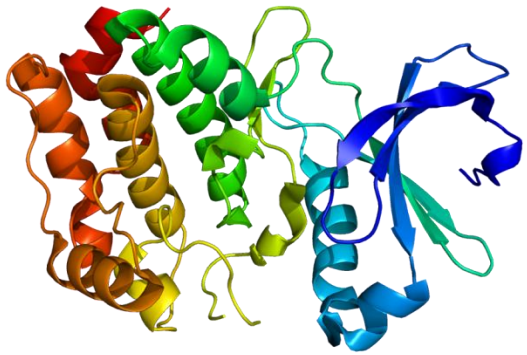
3.5±0.29

Abstract: Based on the data of compounds known from the literature to be active against various types of Ser/Thr kinases a general pharmachophore model for these types of kinases was developed. Search for the molecules fitting to this pharmacophore among ASINEX proprietary library revealed a number of compounds, which were tested and appeared to possess some activity against such Ser/Thr kinases as Aurora A, Aurora B and Haspin.
Our work on optimization of these molecules to Aurora A kinase allowed us to achieve several hits in 3-5 nM range of activity, with rather good selectivity and ADME properties.
Thus we showed the possibility of performing the fine-tuning of the general Ser/Thr pharmacophore designed to desired types of kinase to get active and selective compounds.

Keywords: general pharmachophore model, Ser/Thr kinases, Aurora A

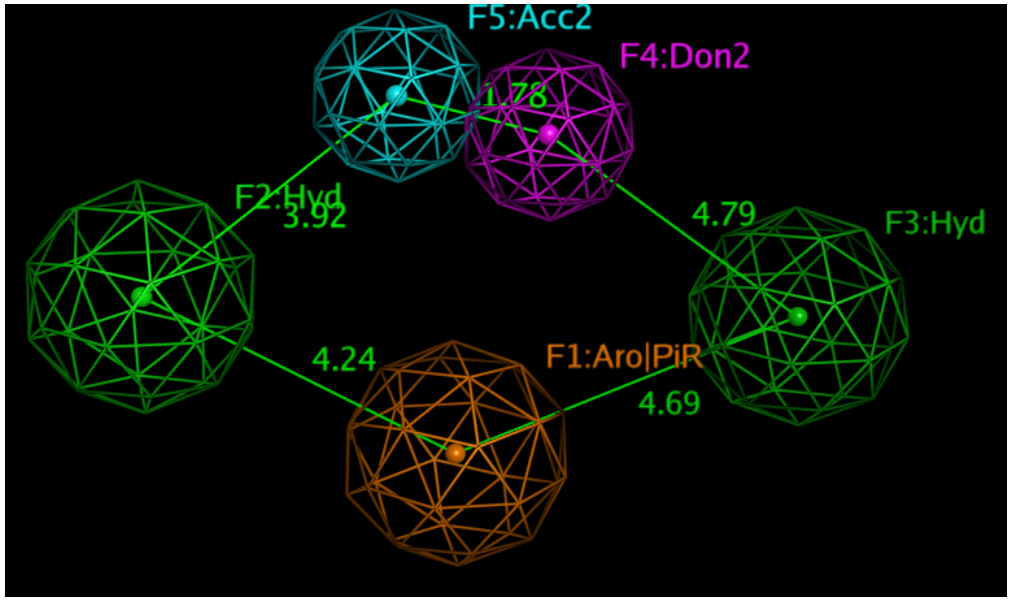
Introduction

- **Serine/threonine protein kinase** are kinase enzymes that phosphorylate the OH group of serine or threonine. At least 125 of the 500+ human protein kinases are serine/threonine kinases (STK).
- Inhibitors of Ser/Thr kinases can posses potential therapeutic uses—from treating cancer to immune disorders. Since they were found in a number mycobacterial organisms they can be also used for treatment of bacterial infections such as tuberculosis.
- A number of attempts have been done to construct a pharmacophore model for various Ser/Thr kinase inhibitors, such as STPK inhibitors of tuberculosis, mTor kinase inhibitors, Aurora A and B inhibitors, B-Raf inhibitors etc.
- We hypothesized that it is possible to find out some general features of all serine-threonine inhibitors and to construct a general pharmacophore model. Then this general model can be adjusted to specific kinds of serine-threonine kinase.



Results and discussion. General pharmacophore model construction

Known inhibitors of various serine-threonine kinases including both found in ASINEX proprietary collection and in literature were used to construct the general pharmacophore model. Pharmacophore elucidating functionality of MOE version 2010.10 was used.

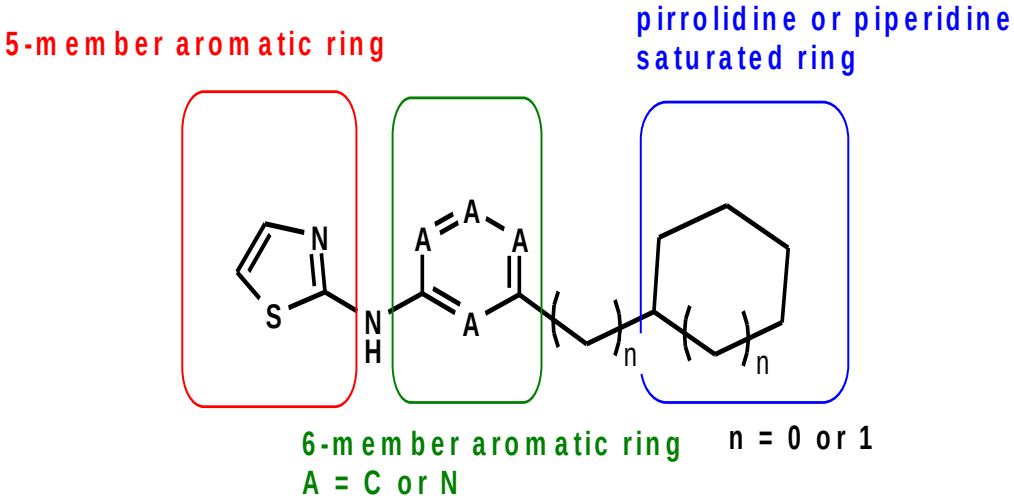


General pharmacophore of serine-threonine kinase inhibitors (MOE 2010.10)

The general pharmacophore found looks like a kind of rhomb with two opposite hydrophobic centers, one aromatic center and a couple of H-bond donor and acceptor projections in one corner. The length of a rhomb side is about 4 – 5 A

Results and discussion. Application of the general pharmacophore to ASINEX proprietary library

Application of the general pharmacophore to ASINEX proprietary library allowed to find a scaffold fitting to its requirements.



Results and discussion. Activity of compounds fitting to general pharmacophore model against selected Ser/Thr kinases

To confirm the activity against Ser/Thr kinases a set of compounds from ASINEX library belonging to the found scaffold was tested against Aurora A, Aurora B and Haspin kinases

The best compound against Aurora A kinase is 2 (100 nM)

Results and discussion. Activity of compounds fitting to general pharmacophore model against selected Ser/Thr kinases

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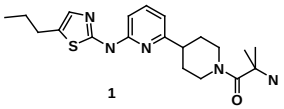
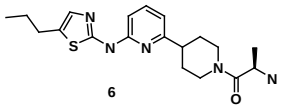
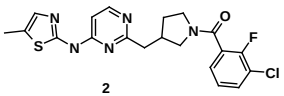
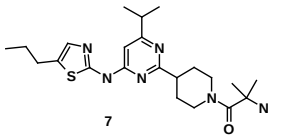
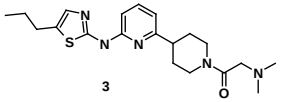
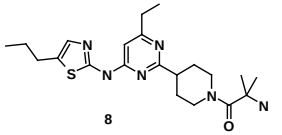
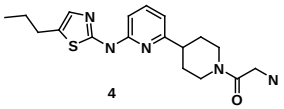
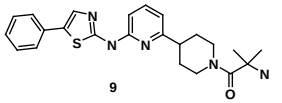
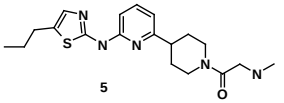
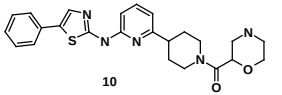
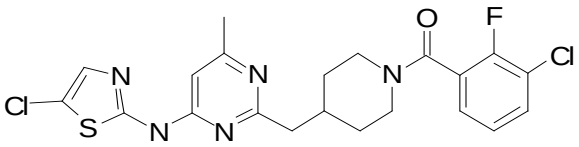
Structure	Aurora A	Aurora B	Haspin	Structure	Aurora A	Aurora B	Haspin
	IC_{50}, uM				IC_{50}, uM		
 1	2.06	1.45	1.49	 6	1.67	1.75	1.12
 2	0.10	3.46	105.2	 7	2.79	2.25	3.67
 3	1.95	1.76	7.06	 8	3.58	2.05	2.90
 4	2.08	1.72	0.08	 9	3.17	8.02	0.27
 5	1.44	0.91	0.43	 10	8.38	0.84	7.80

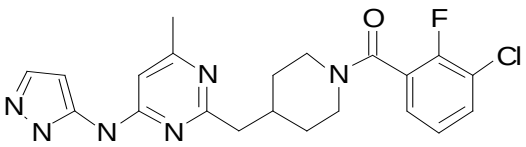
The best compound against Aurora A kinase is 2 (100 nM)

Results and discussion. Optimization of compound 2 for Aurora A activity

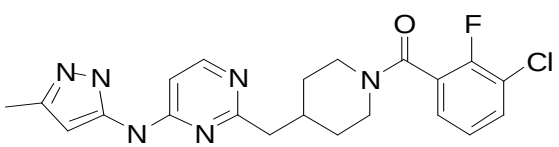
- To confirm the possibility of fine-tuning of the general pharmacophore for selected type of kinases we chose Aurora A kinase and tried to adjust the scaffold found to its specific requirements.
- With this goal a library of analogues of compound **2** was synthesized
- As a result of optimization compounds **29**, **30** and **32** were achieved



29, 4.1 nM



30, 5.3 nM



32, 3.5 nM

Results and discussion. Selectivity and ADME properties of compounds 29, 30 and 32

	29	**30**	**32**
	IC_{50}, nM	IC_{50}, nM	IC_{50}, nM
Aurora A	4.1	5.3	3.5
Aurora B	232.2	18300.0	4182.5
c-Kit	17000.00	21000	
EGFR			
CSK	9500.0		
EPHA2	9000.0		
GSK-3		109.0	292.8
Haspin			
JNK3	85.18	1634.0	572.5
LYN	3270.0		
PIM1			
PLK1			
RON	970.0		
CYP1A2			
CYP2C19		9597.0	965.7
CYP 2C9		3900.0	326.6
CYP3A4		15070.0	596.2
HERG			
Solubility (nephelometry)	< 10 ug/ml	>100 ug/ml	>100 ug/ml

Compound 30 has

- **Good selectivity,**
- **Low cytochrome inhibition,**
- **Low HERG channels inhibition and**
- **Good solubility**

Conclusions

- A general pharmacophore model applicable to various serine-threonine kinases was designed.
- A possibility of fine tuning of this pharmacophore to particular types of serine-threonine kinases was exemplified by design of potent And selective Aurora A inhibitors
- Several compounds with 3-5 nM potency, good selectivity and satisfactory ADME parameters were obtained

Acknowledgments

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