STRUCTURAL AND ENERGETIC INSIGHTS INTO AURORA A KINASE INHIBITION BY PYRAZOL BASED LIGANTS

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Abstract

General validity of the quantum mechanics-based scoring function developed recently in laboratory of Hobza has been successfully shown on complexes of human Aurora kinase A (AK) with a series of pyrazole based inhibitors with experimental values of IC_{50} of which were determined by Coumar and coworkers. Twentyfour distinct but similar ligands have been modeled in the AK active site based on the available crystal structure of one AK/inhibitor complex. Our approach extends the quantum mechanics-based scoring procedure, based on improved PM6 semi-empirical method which is augmented with empirical corrections for dispersion interaction, hydrogen- and halogen-bonding. Quantification of ligand-protein interaction includes interaction energy calculation, solvatation and deformation energy, determination and inclusion of entropy effects. The final model provided binding scores which showed a fair correlation of R^2=0.72 with the experimental IC_{50} values. This study shows the big impact of a correctly chosen variant of the molecular model on the calculated binding score and thus predictions of the affinity.

Key words: *Aurora A, scoring function, COSMO, GBM, SQM/MM*

Introduction

The aim of our work is research in the field of i*n silico* chemistry focused on development and application scoring function based on semiempirical quantum-chemistry (SQM) method PM6D3H4X [1]. The empirical corrections developed in our laboratory utilize the high-level SQM data of small-molecule complexes displaying various motifs of noncovalent interactions. Thus, the corrected SQM describe reliably standard hydrogen (H) and halogen (X) bonding as well as dispersion (D) interactions with comparable or even higher accuracy than much more computationally expensive QM methods. This approach was applied on series of two dozens pyrazol based ligands of enzyme Aurora A with experimental values of IC_{50} of which were determined by Coumar and coworkers [2]. Aurora kinases (AK) belong to a small family of eukaryotic serine/threonine protein kinases. A defect in AK-A function was shown to result in malignant transformation and thus have these enzymes become attractive anti-cancer targets. Complexes protein-ligand (PL) were calculated in water ambient characterized by two solvent models - Conductor-like screening model (COSMO) and generalized Born model (GBM). Experimental values of IC_{50} were correlate with dates obtained from our scoring function.

Material and methods

A starting X-ray structure of AK-A/inhibitor, PDB code 3FDN [2], was used to derive other inhibitor complexes. Subsequently, the geometries of the complexes were optimized at the SQM/MM level and scored according to the described procedure:

Briefly, the estimate of the binding free energy ΔG_w , the score, is expressed as a sum of a SQM-based particular terms: interaction energy ΔG_{int}^{w}, protein and ligand desolvation $\Delta\Delta G_{solv}(L)$ and ligand and protein deformation $\Delta G_{conf}^{w}(L)$, $\Delta G_{conf}^{w}(P)$ and binding entropy contributions $T\Delta S_{int}$ (eq.A). The scoring process is applied to the optimized complex structures, accroding to the following scheme:

$$\Delta G_w = \Delta G_{int}^{w} + \Delta\Delta G_{solv}(L) + \Delta G_{conf}^{w}(L) + \Delta G_{conf}^{w}(P) - T\Delta S_{int} \quad (A)$$

where,

$$\Delta G_{int}^{w} = \Delta E_{int+} + \Delta\Delta G_{int,solv} \quad (B)$$

The ΔE_{int} stands for the interaction energy in gas phase calculated on geometry optimized with an GBM implicit solvent model included in package AMBER [3], using SQM/MM method. The tern $\Delta\Delta G_{int,solv}$ corresponds to the desolvation interaction energy upon PL complex formation.

$$\Delta\Delta G_{solv}(L) = \Delta G_{solv}^{SMD} - \Delta G_{solv}^{GB} \quad (C)$$

Equation (C) specifies the solvation correction from the GBM solvation model to the implict universal solvation model (SMD).

$$\Delta G_{conf}^{w}(P) = \Delta E_{def}(P) + \Delta\Delta G_{conf,solv}(P) \quad (D)$$

The term $\Delta G_{conf}^{w}(P)$ in the equation (A) corresponds to the deformation free energy of protein.

$$\Delta G_{conf}^{w}(L) = \Delta E_{def}(L) + \Delta\Delta G_{conf,solv}(L) \quad (E)$$

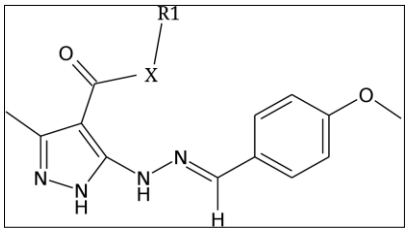
The term $\Delta E_{def}(L)$ denotes optimized energy of ligand using SQM method. The $\Delta\Delta G_{conf,solv}(L)$ term is the energy of free solvated ligand. Equation (E) shows the free deformation energy of ligand.
The last term in the eqution (A) - $T\Delta S_{int}$ represents the entropy change related to free rotatable bonds becoming hindered upon binding to the protein [4,5].

The calculated scores were correlated with the experimental IC_{50} on the base of aproximative approach, where the experimental binding free energies $\Delta G(exp.)$ were obtained as:

$$\Delta G(exp.) = RT\ln(IC_{50})$$

Special calculations were done for differ fragments of ligands X-R1 (pic.1.1), were evaluated by PM6-D3H4X method in the vaccum .

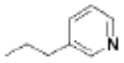
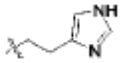
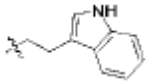
Pic. 1.1 Scelet of ligands 12b - 12w



Results and discussion

All PL complexes were calculated with PM6-D3H4X based scoring function. Ligands generated more izomers (containd o-, p-substituted fenyl) were scored in all affored positions. Interaction energy included in the final socre was recalculated by solvent model COSMO, so far from GBM model shown as less suitable for calculation protein-ligand interaction. The final correlation score (tab 1.1) with experiment was done without ligands 12f and 12g wich are out of the range of IC50. The final score was correlated by the method of least squares with R2= 0,72. Interaction energies of different fragments of ligands were evaluated with PM6-D3H4X method in vaccum. The results of IE (tab. 1.1) confirm the relevance of intramolecular hydrogen-bond and quantify the interactions of ligands ATP-binding of Aurora A. The strongest of IE expose the inhibitor 12w, this fragment binds via four H-bond interactions, three with hinge Ala213 and Glu211 residues, and one with nonconserved Thr217 residue.

Tab. 1.1 Serie of evaluated ligands

Ligand	X	R_1	IC_{50}[μM]	Score [kcal/mol]	IE X-R1 [kcal/mol]
12b	-NH-	$-CH_2Ph$	1.580	-22.4759	-15.229416
12c	-NH-	$-CH_2CH_2Ph$	1.350	-26.3978	-21.046348
12d	-NH-	$-CH_2CH_2CH_2Ph$	1.942	-22.9985	-23.22169
12e	-NH-	-Ph	0.804	-25.6819	-13.825762
12f	$-NCH_3-$	-Ph	>50	-17.0748	-18.388519
12g	$-NCH_3-$	$-CH_2Ph$	>50	-16.1010	-20.493176
12h	-NH-		1.484	-22.8416	-21.462332
12i	-NH-		1.937	-24.2069	-16.977547
12j	-NH-		1.071	-27.9078	-26.742175
12k	-NH-	$-CH_2(Ph\text{-}4\text{-}OCH_3)$	1.623	-24.4927	-25.418138
12l	-NH-	$-CH_2(Ph\text{-}3\text{-}OCH_3)$	0.838	-22.1485	-26.319874
12m	-NH-	$-CH_2(Ph\text{-}3\text{-}NHCOCH_3)$	1.746	-23.3131	-30.572372
12n	-NH-	$-CH_2CH_2(Ph\text{-}4\text{-}OCH_3)$	1.580	-25.2960	-27.773278
12o	-NH-	$-CH_2CH_2(Ph\text{-}3\text{-}OCH_3)$	2.895	-22.6516	-24.27315
12p	-NH-	$-Ph\text{-}4\text{-}OCH_3$	0.460	-21.9063	-21.438086
12q	-NH-	$-Ph\text{-}3\text{-}OCH_3$	0.449	-25.4417	-20.390261
12r	-NH-	$-Ph\text{-}2\text{-}OCH_3$	1.087	-23.8675	-15.608735
12s	-NH-	$-Ph\text{-}3,4\text{-}di\text{-}OCH_3$	0.960	-22.3956	-27.860132
12t	-NH-	$-Ph\text{-}4\text{-}N(CH_3)_2$	1.568	-22.9201	-21.187097
12u	-NH-	-Ph-4-F	1.447	-25.5695	-14.189024
12v	-NH-	$-Ph\text{-}4\text{-}NHCOCH_3$	0.719	-26.8839	-24.090921
12w	-NH-	$-Ph\text{-}3\text{-}NHCOCH_3$	0.033	-31.7374	-34.091526

Conclusion

Around two dozens complexes of Aurora A with potencial inhibitors were tested with PM6-D3H4X based scoring function. In the series of tested ligands nine of them were evaluaetd in two izomers positions. The structures were simulated in water enviroment calculated in two solvent models – COSMO and GBM. The results show COSMO solvent model as a more competent for PL interaction calculations. The final score was correlated by the method of least squares with R2= 0,72.

Interaction energies of different fragments of ligands were evaluated with PM6-D3H4X method in vaccum to understand quantitative structure–activity relationship (QSAR) and confirm the experiment.

References

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Abstrakt

Náš prístup vychádzal z novej skórovacej procedúry založenej na kvantovo-chemických výpočtových metódach vyvinutých v laboratóriu prof. Hobzu. Nosnou výpočtovou metódou je PM6 (Parametrized model 6) obsahujúcou empirickú korekciu na výpočet disperznej energie, vodíkovej a halogénovej väzby. Auróra kinázy (AK) sa zaraďujú medzi serín/treonínové proteínové kinázy. Zvýšená aktivita Auróra kináz bola preukázaná vo viacerych druhoch ľudských rakovinových nádorov a preto sa stali atraktívnym cieľom pre návrh liečiv potláčajúcich vznik tumorových ochorení. Vybrali sme sériu 22 ligandov na báze pyrazolového skeletu, ktorých experimentálne hodnoty IC50 boli získané výskumnou skupinou M. S. Coumara a podrobili sme ich in silico štúdii.