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In silico binding free energy predictability with π–π interaction energy-augmented scoring function: Benzimidazole Raf inhibitors as a case study

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ABSTRACT

The ability to estimate binding affinities of ligands precisely is of paramount importance in designing drugs. Docking programs are used primarily to predict the binding mode of ligands to receptors. However, current scoring functions as used in docking programs are not reliable enough to predict binding affinities of ligands without any further calculations. In the present study, we investigate the usefulness of adding π–π interaction energies between ring groups of residues and ligands to the scoring function for docking. It is found that such addition helps ranking ligand activities more correctly. LMP2 calculation is used to measure π–π interaction energies between ring groups. The result of this simple addition shows possibility of π–π interaction generalization in scoring functions.

Virtual screening using molecular docking program has become one of the standard procedures for lead discovery in new drug development.[1,2] All docking programs consist of *a scoring function* that estimates binding affinity between protein and ligand at a specific binding pose and *a search algorithm* that finds binding poses of ligands.[3,4] There have been intensive attempts to improve scoring functions and search algorithms for better docking performance.[5,6] Indeed, the performance of docking programs has improved to such extent that it is generally believed that it could predict binding poses effectively enough to be used in lead discovery and optimization. However, docking programs usually exhibit poor performance in predicting binding affinity.[7] In fact, there are many cases in which docking programs select poor binding poses due to imperfect scoring functions, which leave room for further improvement. Scoring functions are summation of several separated energetic terms (electrostatic, van der Waals, etc.) reflecting specific non-covalent interactions between protein and ligand. Adding a new non-covalent interaction energy term is one way to refine scoring functions.[5,6]

The π–π interaction, which can be defined as a type of non-covalent interaction that involves π systems (e.g., two aromatic rings) has attracted our attention as one of many possible considerations.[8] In many experimental data (X-ray crystallography and NMR), the aromatic ring moieties of ligands are found to be close enough to have π–π interaction with aromatic ring moieties of protein residues (such as Phe, Tyr, Trp and His), and there are many cases where the difference of affinity cannot be explained without consideration of π–π interaction. However, there have been only few attempts to utilize π–π interaction for scoring functions.[9] One reason could be that the π–π interaction energy value is small compared to total protein–ligand interaction energy. But, if there are several aromatic ring moieties in the active site and ligand, the total summation of π–π interaction energies can be a critical factor in total interaction energy.

In the present study, we try to prove that the addition of π–π interaction energies between aromatic ring moieties of active site and ligand to energy function could significantly improve the prediction capability of ligands' activity and their ranking. We test the plausibility by applying the proposed scoring function to a protein kinase, B-Raf and its series of inhibitors, benzimidazoles derivatives (Table 1) in which there are 3–4 aromatic ring moieties in the active site and the ligand's scaffold (Fig. 1).[10,11] In order to compare a normal scoring function and a π–π interaction added scoring function, we analyzed correlation between the biological activities and the predicted activities from them. For matter of convenience, we performed rescoring after generation of plausible docking poses using an existing docking program, Glide.[12,13]

We cannot check the accuracy of the docking poses without crystal structures, but the plausibility can be confirmed using a

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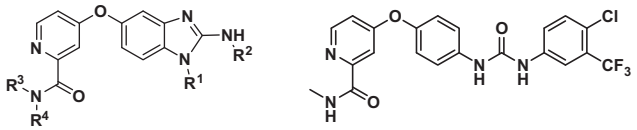
Table 1
The structures and observed B-Raf inhibitory activities



Scaffold Sorafenib

No.	R^1	R^2	R^3	R^4	IC_{50}	pIC_{50}
1[a]					0.011×10^{-6}	7.959
2	H	4-Cl-3-CF_3	H	Me	0.280×10^{-6}	6.553
3	H	Phenyl	H	Me	7.700×10^{-6}	5.114
4	H	2-Br	H	Me	2.400×10^{-6}	5.620
5	H	3-Br	H	Me	1.300×10^{-6}	5.886
6	H	4-Br	H	Me	0.039×10^{-6}	7.409
7	H	2-CF_3	H	Me	9.000×10^{-6}	5.046
8	H	3-CF_3	H	Me	0.300×10^{-6}	6.523
9	H	4-CF_3	H	Me	0.110×10^{-6}	6.959
10	H	3-*t*-Bu	H	Me	0.026×10^{-6}	7.585
11	H	4-*t*-Bu	H	Me	0.063×10^{-6}	7.201
12	Me	Phenyl	H	Me	0.130×10^{-6}	6.886
13	Me	4-Cl-3-CF_3	H	Me	0.028×10^{-6}	7.553
14	Me	2-Br	H	Me	0.039×10^{-6}	7.409
15	Me	3-Br	H	Me	0.025×10^{-6}	7.602
16	Me	4-Br	H	Me	0.002×10^{-6}	8.699
17	Me	2-CF_3	H	Me	1.900×10^{-6}	5.721
18	Me	3-CF_3	H	Me	0.008×10^{-6}	8.097
19	Me	4-CF_3	H	Me	0.088×10^{-6}	7.056
20	Me	3-*t*-Bu	H	Me	0.045×10^{-6}	7.347
21	Me	4-*t*-Bu	H	Me	0.140×10^{-6}	6.854
22	Me	Cyclohexyl	H	Me	4.400×10^{-6}	5.357
23	Me	Cyclohexylmethyl	H	Me	0.140×10^{-6}	6.854
24	Et	4-Br	H	Me	0.068×10^{-6}	7.167
25	Me	4-Bromobenzene	H	Et	0.013×10^{-6}	7.886
26	Me	5-Bromobenzene	H	2-Morpholinoehyl	0.031×10^{-6}	7.509
27	Me	6-Bromobenzene	H	2-Hydroxyethyl	0.011×10^{-6}	7.959
28	Me	7-Bromobenzene	Me	2-Propylpiperidine	0.007×10^{-6}	8.155

[a] Sorafenib.

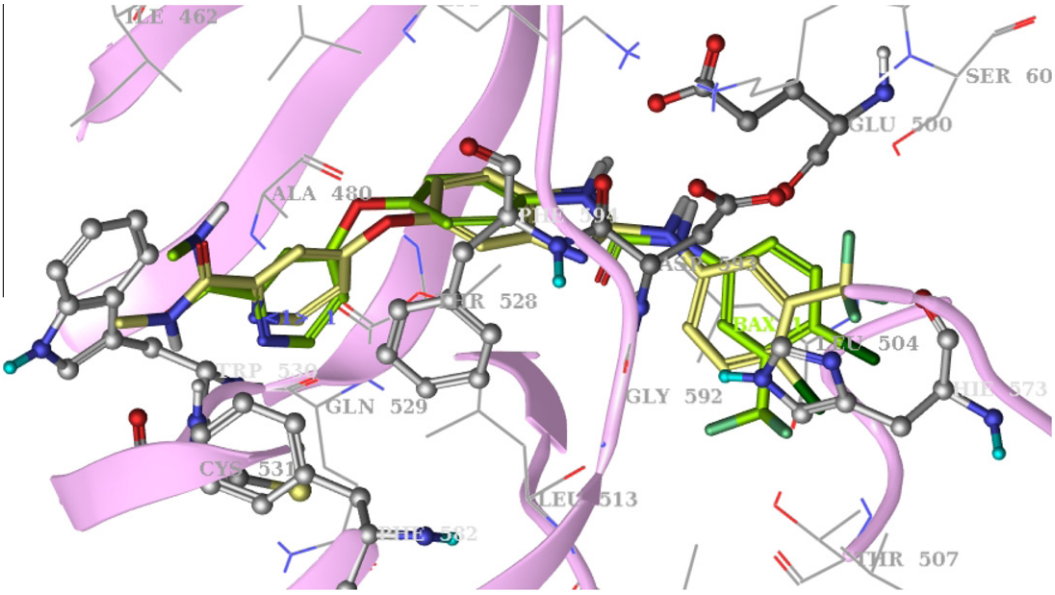


Figure 1. The binding poses of compounds **1** (green) and **2** (yellow) in the B-Raf active site.

three dimensional quantitative structure–activity relationship (3D-QSAR) method, Comparative Molecular Field Analysis (CoMFA).[14] 3D-QSAR was originally used to make a model for predicting biological activities of unknown compounds based on a model developed from known ligands and their biological activities.[15] In order to construct the model, the 3D-QSAR requires aligned conformations of input ligands and the reliability of this alignment is critical in the whole process. In other words, the high statistic value of