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A Novel *de novo* Drug Design: Application of Pseudo-Molecular Probe in Construction of Novel Compounds based on Target Structure.

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1. Introduction

The *de novo* drug design involves constructing novel molecules from the scratch. Since the compound space to be searched can become extremely huge, this approach is a particularly challenging task. Although quite a lot of molecules are commercially available and the database is usually a good source for virtual screening, we often encounter with difficulties in finding desired compounds from the database. Therefore, in spite of its difficulty, we feel a strong need of reliable *de novo* algorithms. After defining a binding site for drug molecules in a target, we must determine what atoms or functional groups should be placed at what loci at the binding site. This is one of the critical steps in the *de novo* design process and at the same time one of the difficult steps. We have developed a novel *de novo* drug design method employing a novel concept of pseudo-molecular probe.

2. Method

2.1. Placement of suitable functional groups in the binding site

We have introduced a novel concept of pseudo-molecular probe in order to search the appropriate functional groups to be placed at the specific loci of the binding site for drug candidates. The pseudo-molecular probe employed in this study consists of a common scaffold of 3-methylpropene with different functional groups attached to the methyl group as shown in Fig. 1. Functional groups suitable to drug molecules were extracted from the database of drugs clinically used in Japan (DCUJ)[1] now. Site Finder implemented in MOE (Molecular Operating Environment)[2] was used to generate alpha spheres at the binding site. A collection of the alpha spheres was used as a guide to determine the position and structure of the pseudo-molecular probes at the binding site by docking simulation. ASEDock[3] was used for this docking process.

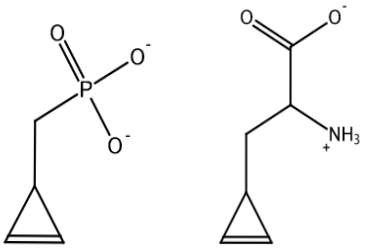

Fig. 1
Examples of Pseudo-Molecular Probes

2.2. Construction of virtual molecules

The pseudo-molecular probes should be appropriately connected by suitable linking chemical motifs. The methylene carbon can be used as an anchoring point. By linking multiple pseudo-molecular probes with linkers we can enumerate virtual molecules exhaustively. The linking chemical motifs were also obtained from DCUJ. Therefore the virtual molecules generated by this procedure consist only of chemical motifs contained in DCUJ. Actually, multiple possible conformations of each linker were generated. Accordingly,

multiple virtual molecules were generated for every combination of functional groups and linkers.

2.3. Selection of virtual molecules

The structure and orientation of the constructed virtual molecules at the binding site were optimized by docking simulation using ASEDock. Eligibility of the virtual molecules for drug candidates was judged by the interaction energy of $U_{dock} = U_{ele} + U_{vdw} + U_{strain}$. Here, U_{ele}, and U_{vdw} are electrostatic and van der Waals interactions between the small-molecule and the protein, respectively. U_{strain} is strain energy of the small-molecule caused by the interaction.

3. Results

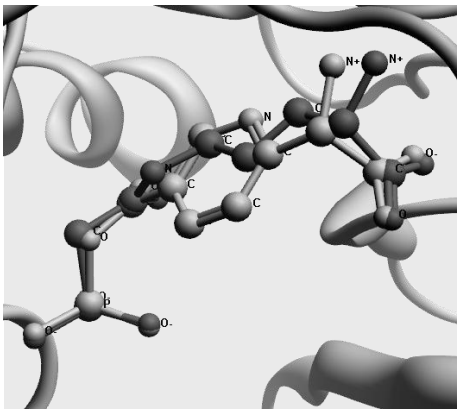

Fig. 2 Virtual molecules generated at the binding site of 1OTH

We have generated virtual molecules at the drug-binding sites of four proteins (1OTH, 1GKC, 1KE5, and 1T46 in the PDB[4] code) whose structures have been determined by X-ray analysis. Since these structures are the complexes between proteins and drugs, we can check whether the bound drugs can be regenerated by this method or not. The results obtained for these proteins are summarized in Table 1. In this abstract, the results for 1OTH are briefly described. Two functional groups as shown in Fig. 1 were used in this case. For linking moieties, 200 linker conformations based on 20 linkers from DCUJ were used. 989 structures for 254 virtual molecules were generated. These structures were docked to the binding site. The binding affinity was judged by U_{dock}. The structures with the first and second lowest U_{dock} are shown in dark and light grey, respectively, in Fig. 2. The former structure is almost identical with the X-ray structure. The root-mean-square deviation (RMSD) of non-hydrogen atoms between the X-ray structure and the predicted one was 1.13 Å. The U_{dock} values for these structures were -377.2 and -361.5 kcal/mol, respectively. Although better drug candidates were not unfortunately discovered through this validation process, the results clearly indicate that the present *de novo* method has significant potentialities in generating virtual drug candidates.

Table 1. Results of *de novo* drug design

PDB code	Number of linkers	Number of conformations	Lowest U_{dock} (kcal/mol)	Ligand in the entry U_{dock} (kcal/mol)	Rank of the X-ray structure	RMSD (Å)
1GKC	113	9113	-185.3	-157.8	65	1.08
1KE5	19	250	-89.38	-43.69	61	1.31
1OTH	20	989	-377.2	-377.2	1	1.13
1T46	137	11527	-107.6	-	-	-

References

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