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QSAR study of new potential Oxazolidinone molecules

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ABSTRACT
Taking into consideration the versatility of oxazolidinone nucleus, new oxazolidinone molecules were designed and docked with the active site using the 'Extra precision' Glide algorithm. Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active-site region of the receptor. Final scoring of docked ligand is carried out on the energy-minimized poses Glide Score scoring function. Docking Score of compounds 13, 16 and 17 was found to be comparable with G-score of standards Linezolid indicated that designed compounds may have good binding affinity.
Keywords: *QSAR, Docking, Oxazolidinones*

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INTRODUCTION

Oxazolidinones were found to be the essential compounds of all heterocyclic skeletal systems required for the development of new pharmaceutical drugs. Invention and detection of Oxazolidinones lead to the development of a wide range of medicinally active biological compounds[1]. The pharmacological activity of Oxazolidinones rings can be further explored for the development of potent and highly active drug molecules when fused with other ring structures. Heterocycles bearing nitrogen atoms constitute the core structure of a number of important physiologically active molecules and play a vital role in the metabolism of living cells. Synthesis of condensed nitrogen and oxygen heterocyclic systems containing oxazolidinone nucleus are the core centers for research and development of new drug molecules. Oxazolidinones are also important for drug development, especially in the area inhibitors of monoamine oxidase[2]. They also have potent pharmacological effects as cytokine modulators sigma receptors, psychotropic, anti-tubercular[3], anti-allergy agents, antibiotics and intermediates in the synthesis of renin inhibitors, β-lactam and macrolide antibiotics, immunosuppressant's and in various other applications like ability to inhibit protein synthesis by binding to the 50S subunit and preventing the 30S complex from forming the 70S complex, resulting in inhibition of translation. Linezolid[4] was re-classified as a Group A drug by the World Health Organization (WHO) for treatment of multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).

MOLECULAR DOCKING STUDIES

Molecular docking[5,6] is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand–protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks the candidate dockings. Docking can be used to perform virtual screening on large libraries of compounds, rank the results and propose structural hypothesis of how the ligands inhibit the target, which is invaluable in lead optimization.
The virtual molecules that are docked are models that may represent a small set suggested for synthesis or part of a large virtual database of commercially available molecules or combinatorial molecular structures constructed around scaffolds. In many applications, docking is expected to reduce the number of candidates to the most promising ones for subsequent biological screening.

MATERIAL AND METHODS

The Glide (Schrodinger 9.0) software was used to dock potential inhibitors (Ligand) in the binding pocket of the enzyme structure. Glide most commonly used and validated software designed to assist in high-throughput screening of potential ligands based on binding mode and affinity for a given receptor

molecule. One can compare ligand scores with those of other test ligands or compare ligand geometries with those of a reference ligand. There are four main stages to perform molecular docking studies using Glide (Schrodinger 9.0).

RECEPTOR PREPARATION AND SELECTION:

Docking studies were carried out using three PDB codes as 6E7J resolution of 1.30 Å, 6E9A resolution of 1.22 Å, and 5WEJ resolution of 1.95 Å was retrieved from the RCSB. The quality of the results obtained from Glide depends critically on the quality of the starting structures. These starting structures must include all hydrogen's, have correct charge states near the binding site and be reasonably free of major steric clashes. A typical PDB protein complex structure, as downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) web site (http://www.rcsb.org), has no hydrogen's and may have residues in unusual charge states. Therefore comprehensive protein preparation to ensure chemical correctness and optimization of protein structure was done in order to achieve best results. The typical structure file from the PDB is not suitable for immediate use in molecular modeling calculations as the PDB structure file consists only of heavy atoms and may include a co-crystallized ligand, water molecules, metal ions, and cofactors. Some structures are multimeric and may need to be reduced to a single unit. PDB structures may be missing the information on connectivity, which must be assigned along with bond orders and formal charges. Glide has therefore assembled a set of tools to prepare proteins in a form that is suitable for modeling calculations. All structures were prepared for docking using the 'protein preparation wizard' in Maestro wizard 8.5. In the refinement component, a restrained impact minimization of the co-crystallized complex was performed. This helps in reorientation of side chain hydroxyl group. It uses the OPLS.AA force field for this purpose.

RECEPTOR GRID GENERATION:

For receptors that adopt more than one conformation on binding, it is necessary to prepare grids for each conformation to ensure that possible actives are not missed. Grid files represent physical properties of a volume of the receptor (specifically the active site) that are searched when attempting to dock a ligand. Also the shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. Grids were generated by Receptor Grid Generation panel which define receptor structure by excluding any co-crystallized ligand that may be present, determine the position and size of the active site as it will be represented by receptor grids and set up Glide constraints. Grids were defined by centering them on the ligand in the crystal structure using the default box size.

LIGAND PREPARATION:

Ligand preparation was carried out using Ligprep panel in the software. The use of Ligprep produces a single low-energy 3D structure with correct chirality's for each successfully processed input structure. All the structures in .mol format were imported in the project file and subjected to ligand preparation using OPLS 2005 force field using default setting. Possible ionization states for each structure at the pH 7.0 ± 2.0 were generated using the ionizer option and only one low energy ring conformer per ligand was allowed to generate. Low energy stereo isomers 32 per ligand were allowed to generate to identify additional chiral atoms in the structures and generate additional structures with the same molecular formula but different chiral properties.

DOCKING AND SCORING FUNCTION:

The ligands were docked with the active site using the 'Extra precision' Glide algorithm. Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active-site region of the receptor. Final scoring of docked ligand is carried out on the energy-minimized poses Glide Score scoring function.

G Score = 0.065*vdW + 0.130*Coul + Lipo + Hbond + Metal + BuryP + RotB + Site

vdW: - Van der Waal energy; Coul: - Coulomb energy; Lipo: - Lipophilic contact term; HBond: - Hydrogen-bonding term; Metal: - Metal-binding term; BuryP: - Penalty for buried polar groups; RotB: - Penalty for freezing rotatable bonds; Site: - Polar interactions at the active site

RESULTS AND DISCUSSION

The docking results were evaluated mainly based on the Glide score (G Score), amino acids involved in the binding interactions, Hydrogen bonds (H-bond), Vander Wallis (VDW) interactions between ligands and receptor.

Sr. No.	Name of oxazolidinone derivative	6E7J	6E9A	5WEJ
1	Isobutyric acid	5.070	4.518	1.747
2	Isopentanoic acid	4.931	5.064	2.038
3	Isohexanoic acid	4.842	5.341	2.182
4	Hexanoic acid	4.882	5.213	1.846
5	Butanoic acid	5.007	4.753	2.928
6	Propanoic acid	5.518	5.134	2.071
7	Pentanoic acid	4.966	5.537	2.638
8	Chloroacetic acid	5.243	4.730	2.699
9	Bromoacetic acid	5.267	5.720	2.147
10	Nitroacetic acid	5.368	4.884	2.222
11	Iodoacetic acid	4.428	4.023	2.240
12	Dichloro acetic acid	5.121	4.876	2.537
13	Difluoroacetic acid	5.563	6.131	2.384
14	Phenoxyacetic acid	4.536	4.587	2.966
15	Phenyl acetic acid	4.975	5.037	2.050
16	Glycolic acid	5.421	5.749	2.519
17	Thioglycolic acid	5.569	6.020	3.230
18	Heptanoic acid	5.169	5.272	2.080

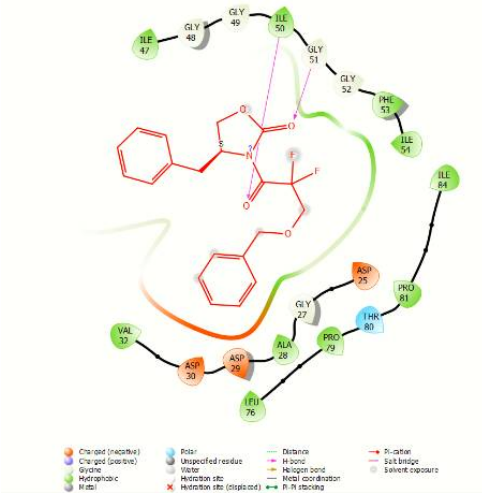

Figure 1 Receptor Interaction of Difluoroacetic acid derivative

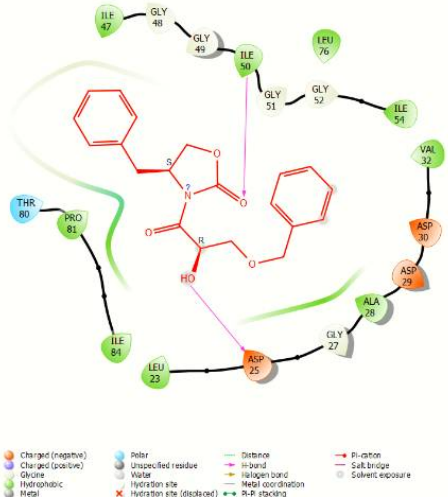

Figure 2 Receptor Interaction of Glycolic acid derivative

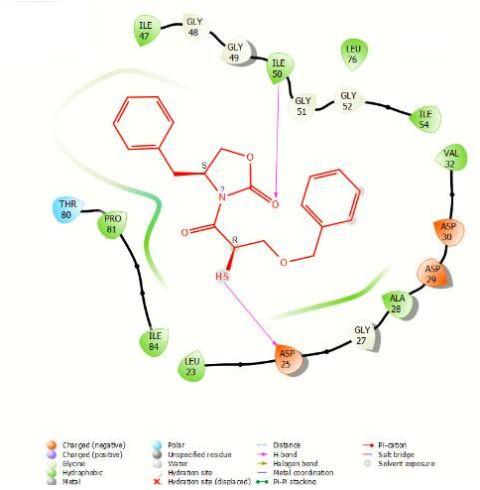

Figure 3 Receptor Interaction of Thioglycolic acid derivative

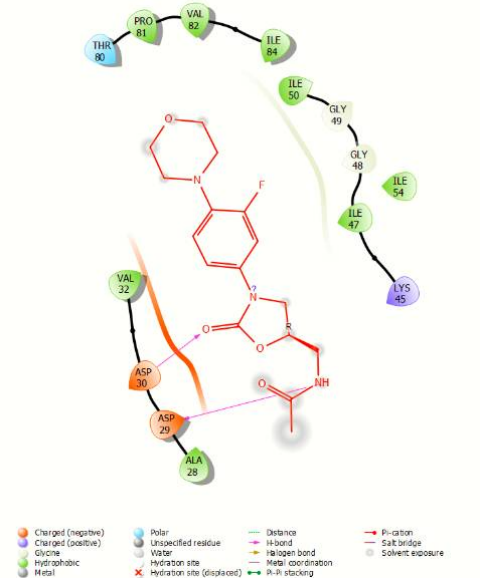

Figure.4 Receptor Interaction of Linezolid

Docking Score of compounds 13, 16 and 17 was found to be -6.131, -5.749, -6.020 respectively which was comparable with G-score of standards Linezolid (Score:-7.256) indicated that designed compounds may have good binding affinity for binding. The best poses obtained by docking results are reported in Figure 1, 2, 3, 4, where main interaction between ligands and receptors can be observed. Standards Linezolid show interaction with Asp 29 and Asp 30 amino acids by non-covalent hydrogen bond. All designed compounds adopt a very similar conformation at binding pocket, showing similar non-covalent hydrogen binding.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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