Research Article

Computer Aided Molecular Docking Studies on a Series of Benzothiazepines as Potential Anti Convalescent Agents

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ABSTRACT

Molecular docking study was performed on a series of 20 new benzothiazepines BTP1-BTP-20 as anti convalescent agents. The docking technique was applied to dock a set of representative compounds within the active site region of 1EOU using PyRx virtual screening tool and evaluation of these molecules is done by using the pymol and chimera software. For these compounds, the binding affinity (kcal/mol) was determined. The docking score of BTP-10 IS -6.6 kcal/mol and is compared with the standard drug as phenytoin and its docking score is -6.5 kcal/mol. Based on the validations and hydrogen bond interactions made by R substituents were considered for evaluation. The results avail to understand the type of interactions that occur between designed ligands with 1EOU binding site region and explain the importance of R substitution on benzothiazepine basic nucleus.

Keywords: Docking, benzothiazepines, PyRx virtual screening tool, Pymol, chimera.

INTRODUCTION

Drug discovery and development is an interdisciplinary, expensive and time-consuming process. Scientific technology advancements during the past two decades have changed the approach of the pharmaceutical research to generate novel bioactive molecules. Advances in computational techniques and in parallel hardware support made easy evaluation of molecules, and in structure-based drug design method, to speed up new target selection through the identification of hits to the optimization of lead compounds in the drug discovery process. Genomics, proteomics, bioinformatics and chemo informatics have gained immense popularity and have become an integral part of the industrial and academic research, directing drug design and discovery. Virtual screening emerged as an important tool in our quest to access novel drug like compounds 1-3. Rational drug design can be done in two ways: ligand-based or structure-based. With the availability of the 3D structure of a biological target, it is feasible to use a structure-based approach to evaluate and predict the binding mode of a ligand within the active site of the receptor with docking methods 4-8. Now it is a popular technique used for increasing the speed of drug designing process. This was made possible by the availability of many protein structures which helped in developing tools to understand the structure function relationships, automated docking and virtual screening. Furthermore, when no 3D structural information about target proteins with their receptor site is available ligand-based design is applied 9-12. The ligand-based approach starts with a group of ligands binding to the same receptor with the same mechanism. Today four different strategies based on the prior knowledge of the targets 3D structure and the ligands binding to it are predominant.

MATERIALS AND METHODS

Software methodology

In the present molecular docking study, software PyRx virtual screening tool along with Graphical User Interface (GUI), PyRx tools was utilized to generate grid, calculate dock score and evaluate conformers. PyRx is Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx enables Medicinal Chemists to run Virtual Screening from any platform and helps users in every step of this process - from data preparation to job submission and analysis of the results. While it is true that there is no magic button in the drug discovery process, PyRx includes docking wizard with easy-to-use user interface which makes it a valuable tool for Computer-Aided Drug Design. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engine that are essential for Rational Drug Design. Please visits http://pyrx.sourceforge.net to learn more about PyRx.

Molecular modeling

A set of 20 new benzothiazepines BTP-1-BTP-20 listed in table 1, were designed and modeled based on the compounds synthesized and reported earlier. In the present study, all isomers have been constructed and subjected for molecular docking experiments. However, certain chemical rules are utilized to prevent unreasonable structures during molecular design. For instance, structures that include heteroatoms bonded to each other (e.g. O-O, N-N and N-O etc.) and eliminating too many heteroatoms bonded to the same carbon atom. Also, certain fragments attached to an aromatic ring possess toxicity.

Ligand Preparation

The structures of benzothiazepines BTP1-BTP20 were drawn using MOL-EDITOR website and that files are saved in the form of sdf file format. finally subjected to energy minimization using virtual screening tool. The minimization was executed until the root mean square gradient value reached a value smaller than 0.001kcal/mol. Such energy minimized structures are considered for docking in the PyRx virtual screening tool.

Protein Selection

The selection of protein for docking studies is based upon several factors i.e. structure should be determined by X-ray diffraction, and resolution should be between 2.0-2.5Ao, it should contain a co-crystallized ligand; the selected protein should not have any protein breaks in their 3D structure. However, we considered Ramachandran plot statistics as the important filter for protein selection that none of the residues present in disallowed regions.

The protein that should be selected should meet requirements of docking studies and it should be downloaded in the form of pdb format.

Protein Preparation

1EOU X-ray crystal structure was obtained from the Brookhaven protein Data Bank (www.rcsb.org/pdb). Subsequent to screening for the above specific standards the resultant protein target (PDB Code: 1EOU) was selected and prepared for molecular docking simulation in such a way that all heteroatoms (i.e., nonreceptor atoms such as water, ions, etc.) were removed.

Software Method Validation

Software method validation was performed in PYRX VIRTUAL SCREENING TOOL using Protein Data Bank (PDB) protein 1EOU. The x-ray crystal structure of 1eou complex with co-crystallized ligand was recovered from PDB. The bio active co-crystallized bound ligand was docked with in the active site region of 1EOU. The resolution of 1EOU is 2.1A0 and R value free is 0.229 and R value work is 0.176 indicating that the parameters for docking simulation are good in reproducing X-ray crystal structure.

Molecular Docking

In the present investigation, we make use of a docking algorithm called molecular docking. Molecular docking is based on a new hybrid search algorithm, called guided differential evolution. The guided differential evolution algorithm combines the differential evolution optimization technique with a cavity prediction algorithm. We used PyRx virtual screening tool because it showed higher docking accuracy than other stages of the docking products (MVD: 87%, Glide: 82%, Surflex: 75%, FlexX: 58%) in the market 20, 21. coordinates in either sdf or PDB format. Non- polar hydrogen atoms were removed from the receptor file and their partial charges were added to the corresponding carbon atoms. Molecular docking was performed using Molecular docking engine of PyRx software. The binding site was defined as a spherical region which encompasses all protein atoms within 15.0 Ao of bound crystallographic ligand atom. Default settings were used for all the calculations. Docking was performed using a grid resolution. In results and discussions, the table-1 gives the information about ligands, structural information, binding affinity score and number of H-bonds/H-bond interacting residues and table-2 gives the information about docking result of the ligand BTP-8.

RESULTS AND DISCUSSIONS

General structure of benzothiazepine

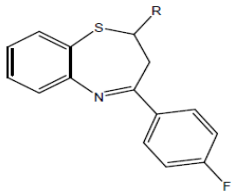


Table 1:

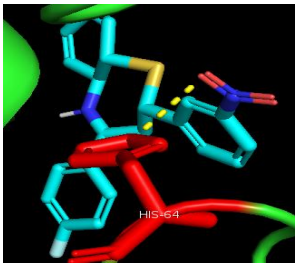
Ligand Code	R Group substituent	Binding Affinity (KCAL/MOLE)	No of H-bonds/H-bond interacting residues
BTP1	4-MeC6H5	-6.2	-
BTP2	4-FC6H5	-6.0	2/Interacted with sulfamate sugar moiety and one nonbonded atom in protein
BTP3	4-ClC6H5	-6.2	-
BTP4	2-clC6H5	-6.2	-
BTP5	2,4-FC6H4	-6.5	-
BTP6	2,4-ClC6H4	-6.3	-
BTP7	2-Cl-4-NO2C6H4	-6.4	-
BTP8	3-NO2C6H5	-6.5	1/HIS-64
BTP9	4-NO2C6H5	-6.1	-
BTP10	3-OHC6H5	-6.6	1/THR-199
BTP11	3-NO2-4-MeC6H4	-6.5	1/HIS-64
BTP12	3,4,5-Tri-OMeC6H4	-6.1	3/his-64(2)/interaceted with one nonbonded atom (1)
BTP13	4-diMe-amino-C6H4	-6.7	3/HIS-64(1)/interacted with nonbonded atoms (2)
BTP14	2-bromo furyl-C4H4	-6.1	2/interacted with two nonbonded atoms
BTP15	4-	-6.2	-

	dimethylamino-C6H4		
BTP16	3-OMe-4-OH-C6H4	-6.5	2/TRP-5(1), HIS-64
BTP17	-1-PYRIDINYL	-6.1	1/interacted with nonbonded atom
BTP18	-2-PYRIDINYL	-6.1	1/interacted with nonbonded atom
BTP19	-3-PYRIDINYL	-6.6	-
BTP20	-1-THIOPHENYL	-6.2	-

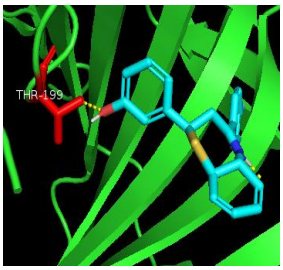
The ligands BTP-8, 10, 11, 16 should be considered as good ligands because they are not interacted with the non-bonded atoms in the protein (interaction with non-bonded atom with aromatic ring of the ligand should possess toxicity)

Table- 2:

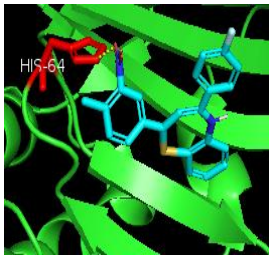
Ligand	Binding Affinity	rmsd/ub	rmsd/lb
1eou__uff_E=320.01	-6.5	0	0
1eou__uff_E=320.01	-6.4	5.291	2.541
1eou__uff_E=320.01	-6.3	7.387	4.193
1eou__uff_E=320.01	-6.3	2.115	1.756
1eou__uff_E=320.01	-6.2	4.993	2.395
1eou__uff_E=320.01	-6	6.862	3.441
1eou__uff_E=320.01	-5.8	5.849	3.327
1eou__uff_E=320.01	-5.8	8.066	4.608
1eou__uff_E=320.01	-5.8	5.812	2.843



(a)

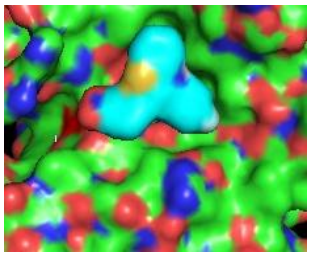


(b)

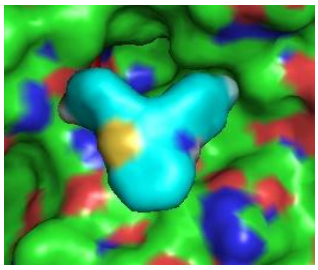


(c)

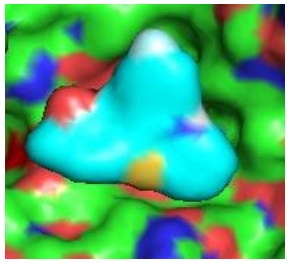
The Figure (a), (b), (c) shows the ribbon type of protein ligand interaction of BTP-8, 10 and 11 ligands respectively.



(a)



(b)



(c)

The Figure (a), (b), (c) shows the surface type of protein ligand interaction of BTP-8, 10 and 11 ligands respectively.

CONCLUSION

In this study the ligand-protein molecular docking simulation was used to preliminarily investigate and to confirm the potential molecular target for the designed ligands BTP1-BTP20. The analysis of the best docked ligands against selected target revealed the binding mode of compounds involved in this study and confirm the role as anti convalescent agents. Binding energies of the drug–enzyme (receptor) interactions are important to describe how fit the drug binds to the target macromolecule. The residues participated in the hydrogen bond formation within the active binding site region revealed the importance of these residues towards the observed binding energy with respect to the hit identified against 1EOU target protein. The obtained hypothesis could be the remarkable starting point to develop some new leads as potential 1EOU inhibitors with enhance the affinity as well as intrinsic activity. The results of this work indicate efficient computational tools are capable of identify potential ligands such asBTP-8, BTP-10,BTP-11,BTP-16 even though their biological profile has not known. The utilization of computational tools in the drug discovery and development can be used to save time and reduce the bench work of a medicinal chemist.

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