ISSN- O: 2458 - 868X, ISSN –P: 2458 - 8687

International Journal of Medical Science and Innovative Research (IJMSIR)

IJMSIR : A Medical Publication Hub

Available Online at: www.ijmsir.com

Volume – 2, Issue –6, November – December - 2017, Page No. : 21-27

Molecular Docking Studies on a Series of Benzothiazepines as a New Class of Nucleoside Reverse transcriptase Inhibitors

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Conflicts of Interest: Nil.

Abstract

Molecular docking study was performed on a series of 20 new benzothiazepines BTP1-BTP-20 as nucleoside reverse transcriptase inhibitors. The docking technique was applied to dock a set of representative compounds within the active site region of 3DRP 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-8 IS -8.4 kcal/mol and is compared with the standard drug as Acyclovir and it's docking score is -5.8 kcal/mol. Based on the validations and hydrogen bond interactions made by R substituents were considered for evaluation. The results available to understand the type of interactions that occur between designed ligands with 3DRP binding site region and explain the importance of R substitution on benzothiazepine basic nucleus.

Keywords: Docking, benzothiazepine, Nucleoside reverse transcriptase protein, PyRx virtual screening tool, Pymol, chimera

Introduction

Molecular docking is a method to predict the preferred orientation of one molecule to second when bound to each other to form a stable complex. Computers and programs(software's) are used to predict or simulate the possible reaction (and interactions) between two molecules based on their 3-dimensional structures. Using software's, the interactions can be viewed and analyzed to understand and answers some biological important questions regarding a certain chemical or biological reaction. Analyzing the interactions basically comes with 3 D graphics which can be manipulated in several ways to clearly explore in detail (in atomic resolutions) the interaction involved between the atoms in the two interacting molecules.

This method can therefore be used not only to predict possible binders or inhibitors, but also to predict how strong the association between the molecules (called the binding affinity) can be. It is useful to know the binding strength (binding energy) when you are comparing(ranking) a group of compounds or derivatives to determine which derivative is the best binder or inhibitor (how strong a compound will bind to the target).

Prediction of the binding affinity will be useful when you are synthesizing compounds whereby you can predict the affinity of your desired compound towards a certain target.

This method is also useful when you want to screen (they call it "virtual screening") many compounds say from a natural product or plants/herbs to see whether your small molecules (from the medicinal plants/herbs) will have

certain pharmacological effects on a particular protein or enzyme (for example HIV protease etc.). Large pharmaceutical companies in Europe and US have been using this technique for some time in the discovery and development of new drugs.

There are two main types of docking (molecular docking) in practice: small molecule – protein (called "ligand – protein docking") and protein – protein docking. As mentioned earlier, there is also small molecule – DNA or RNA docking done by some researchers. I believe, this can be categorized as ligand – DNA/RNA docking.

Protein – protein docking involves two protein molecules simulated by the computer/computer program to bind/interact with one another. However, in this case, the interactions are basically rigid compared to the ligand – protein docking. You might be able to see that by simulating certain protein – protein interactions in a specific biological reaction, you can get some information or insights at the molecular level on how a certain mechanism took place.

Theory

The theory behind molecular docking lies behind the enzyme – substrate recognition process. The problem can be thought as a "lock – and – key" concept. In this problem, the orientation of the ligand (small molecule or substrate protein) will be "fitted" to the receptor of interest using either 2 approaches; matching technique, and simulation processes. Certain programs (software's) are able to rank the affinity of compounds towards the receptor studied.

The programs will "adjust" the conformation of the ligand and in some cases the conformation of the side chains of the receptors binding site (site of interaction) to see how they will fit each other. This is done by calculating the energy for each conformation of the complex and the molecules when they are in their uncomplex form (before binding).

Methods of Calculation

1st Method

The 1st methods use matching technique. This technique looks for complementary of the surfaces of each of the molecules (solvent-accessible surface area) to see whether it will match each other surface. This is called the shape complementary methods.

2nd Method

The second method uses simulation processes. This technique simulates the actual docking process by calculating the ligand-protein pairwise interaction energies (using empirical methods or molecular mechanics, take into account torsional energy between bonds, van der Waals energy, electrostatic energy, hydrogen bonding potential, atomic solvation energy, and so forth)

Procedure of Docking

Typically, you will need two types of file or input; one for the ligand/small molecule and another one for the target/receptor. The ligand or small molecule can be built from scratch using suitable software or taken from available databases. Some software comes with a 2-dimensional drawing which can be converted to 3dimensional type. There are software's with 3-dimensional drawing capabilities. The protein or receptor's structure can either be downloaded from several databases, for example protein databank (http://www.rcsb.org/) or you can build it based on a template using software's with amino acids/biopolymer construction features (called homology modelling).

The protein databank is a good resiporatory of large collections of x-ray crystallographic and NMR (nuclear magnetic resonance) 3D structures available for the public. You will need to check the structure built (the receptor) to validate the quality of your structure before

performing any docking. You can easily find programs to do this over the web. So now you have 2 inputs (in 3D) needed to perform your docking/simulation. One for the ligand, and the other one for your target/receptor.

Reliability of Docking Result

There are many docking programs available on the net, commercial or open source. However, the success of a program mainly depends on two components: the search algorithm and, the scoring function. Of course, it's only a computer, if you put "rubbish in", you get "rubbish out". You will need to carefully check all your inputs and parameters before accepting any results from the simulation. The resolution of the receptor used also play an important part in the accuracy of your simulation. The higher the resolution of your protein or receptor, the higher the accuracy of your result.

The Search Algorithm

The search algorithm is a process where all possible conformations and orientations of the complex (the paired ligand and protein) in a space (the binding site of interest) is being searched. If the ligand is flexible, then the program will calculate the energy for each rotation made of each and every rotatable bond it can find. The same goes for the protein/receptor. For each rotation of the side chain of the amino acids (in the binding site), the program will calculate the energy involved. Each energy value calculated will be presented as a "snapshot" of the pair.

In each of the snapshot, you will be able to see what kind of interactions are involved and which atoms are in contact or proximity making any kinds of bonding such as hydrogen bonds, hydrophobic interactions and many more. Each of the "snapshots" of the pair or the complex is called the binding "pose". A binding poses of the docked ligand.

The Scoring Function

The scoring function is a process where the program takes a binding pose and gives a number to indicate the likelihood whether the binding interaction is favorable. Molecular mechanics force field (physics based calculations) is used to estimate the energy of each pose. Each and every pose will come with an energy value and the scoring function of the program will rank the poses accordingly (normally in a descending manner). The lower the energy of the pose, the more stable the complex will be, and more likely the possibility of the binding will happen.

Application of Docking

As mentioned earlier, most application goes to the field of drug design. Most drugs, as we know are small organic molecules. Another application is in the prediction of the activation or inhibition of an enzyme or protein (or in some cases DNA) of interest. A ligand in the cavity/active site of a protein in the process of identifying potential drug candidates from large databases of drugs/small molecules, many efforts have been made to identify molecules with tendency to bind to a protein target of interest.

This process is sometimes called virtual screening or hits identification or in-silico drug screening where thousands of drug candidates are being screened rapidly using high speed or high-performance computing facilities. Docking can also be used in "lead optimization" process. This is a process where the lead or drug candidate which had earlier shown binding affinity towards the protein, is being structurally modified (in the computer) to enhance its binding potential. The potency and/or the selectivity of the drug candidate towards the protein, can therefore be improved. Researchers have been using this technique lately as part of an effort to help minimize the problems with late failure in drug development.

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 a 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.

Protein Preparation

All Nucleoside reverse transcriptase X-ray crystal structures were obtained from the Brookhaven protein Data Bank (http://www.rcsb.org/pdb). Subsequent to screening for the above specific standards the resultant protein target (PDB Code: 3DRP) 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.

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.

Software Method Validation

Software method validation was performed in PYRX VIRTUAL SCREENING TOOL using Protein Data Bank (PDB) protein 3drp. The x-ray crystal structure of 3drp 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 3DRP. The resolution of 3DRP is 2.6A0 and R value free is 0.251 and R value work is 0.187 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. 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.

Results & Discussions

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.

General structure of 1, 5-dihydro benzothiazepine

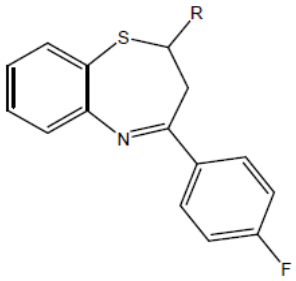


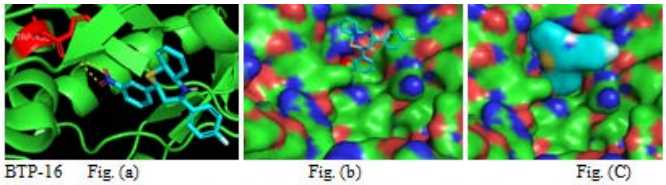
Table-1:

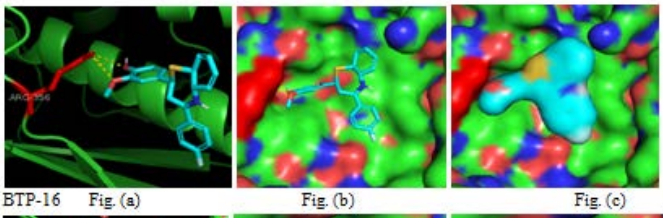
LIGAND CODE	R Group substituent	BINDING AFFINITY (KCAL/MOLE)	No of H-bonds/H-bond interacting residues
BTP7	2-Cl-4-NO2C6H4	-8.1	3/LYS-20(1), ARG-83(1), interacted with non-bonded atom (1)
BTP8	3-NO2C6H5	-8.4	2/TRP-402(2)
BTP9	4-NO2C6H5	-7.7	2/LYS-20(1), interacted with non-bonded atom (1)
BTP10	3-OHC6H5	-7.7	2/ARG-83(1), interacted with non-bonded atom (1)
BTP12	3,4,5-Tri-OMeC6H4	-7.4	4/LYS-22(1), ARG-82(1), interacted with non-bonded atom (2)
BTP16	3-OMe-4-OH-C6H4	-7.7	3/ARG-356
BTP17	-1-PYRIDINYL	-7.7	1/GLU-79
BTP18	-2-PYRIDINYL	-7.6	1/VAL-381

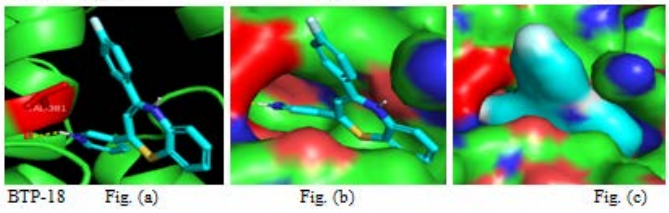
The ligands BTP-8,16,17,18 should be considered as good ligands because they are not interacted with the non-bonded atoms in the protein (interaction with non-bonded atom with aromatic ring of the ligand should possess toxicity)

Table-2 :(Docking Result of Btp-8)

Ligand	Binding Affinity (kcal/mol)	rmsd/ub	msd/lb
3drp__uff_E=320.01	-8.4	0	0
3drp__uff_E=320.01	-8.3	6.943	4.435
3drp__uff_E=320.01	-8.1	1.829	1.181
3drp__uff_E=320.01	-7.8	6.554	4.011
3drp__uff_E=320.01	-7.6	15.662	13.316
3drp__uff_E=320.01	-7.5	15.491	12.478
3drp__uff_E=320.01	-7.3	6.799	4.399
3drp__uff_E=320.01	-7.3	14.103	11.443
3drp__uff_E=320.01	-7.2	7.426	4.259







The figure (a) represents of protein-ligand interaction and (b) and (c) represents the molecular surface display type of protein ligand interactions of BTP-8,16,17 and 18 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 Nucleoside reverse transcriptase inhibitors. 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 3DRP target protein. The obtained hypothesis could be the remarkable starting point to develop some new leads as potential 3DRP 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-16,BTP-17,BTP-18 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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Journal of Pharmacy Research 2014,8(6),858-863