International Journal of
Analytical, Pharmaceutical and Biomedical Sciences

Volume: 3: Issue-2: April-June-2014 *Copyrights@2014* *ISSN: 2278-0246*
Received: 12th May-2014 *Revised: 27th May-2014* *Accepted: 28th May-2014*
Coden: IJAPBS *www.ijapbs.com* *Research article*

MOLECULAR DOCKING STUDIES OF 2-MERCAPTO-5-(3-METHOXYPHENYL) 1, 3, 4 OXADIAZOLE THIONES WITH FOCAL ADHESION KINASE

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ABSTRACT: The main objective of the present work is to perform molecular docking studies of the ligand 2-Mercapto-5-(3-Methoxy phenyl) 1,3,4 oxadiazole with protein focal adhesion kinase. A good correlation was observed in binding affinity of this complex. Using different inhibitors for this enzyme, it can be used as an anticancer therapy target.
Key words: 1,3,4 oxadiazole, docking, anticancer therapy target.

INTRODUCTION

Oxadiazole is a five membered heterocyclic aromatic compound [1]. Out of its four possible isomers 1,3,4-oxadiazole is widely exploited for various applications. These are azoles with oxygen and nitrogen.1,3,4-oxadiazole exhibit wide range of biological activities like, antibacterial, fungicidal, anti-inflammatory, analgesic, antipyretic, anti-tubercular, sedative and hypnotics, hypoglycemic agents, light screening agents, dyes and x-ray contrast materials[2,3]. The lead compound has been synthesized by incorporating substituents at 2nd and 5th position of the 1,3,4-oxadiazole heterocyclic ring system. It is clear from various literatures that these derivatives possess remarkable inhibitor for cancer activity [4,5]. The molecular docking studies of 2-Mercapto-5-(3-Methoxyphenyl) with protein focal adhesion kinase (FAK) was performed by using Argus lab.Docking studies have become nearly indispensable for study of macromolecular structures and interactions. Macromolecular modeling by docking studies provides most detailed possible view of drug receptor interaction and has created a new rational approach to drug design. Here the structure of drug is designed, based on its fit to three dimensional structures of receptor site, rather than by analogy to other active structures.

MATERIALS AND METHODS

Database and Software

Data collection and cell refinement- CAD-4 software, Data reduction- MOLEN, Structure solution and refinement - SHELXL97, Molecular graphics-ORTEP and PLATON, Manuscript preparation for publication -SHELX97, program used for docking Aurgus lab and Pymol, File Format conversion of the coordinates- openbabel.

Preparation of ligand structure

The crystals of the compound2-Mercapto-5-(3-methoxyphenyl) 1, 3, 4-oxadiazole **[**6,7**]** were grown by slow evaporation technique using ethanol as solvent. The x-ray intensity data of the crystals were collected on a Bruker smart CCD diffractometer on graphite monochromatic Mok**α** radiation. Crystal data are given in the Table 1 and chem3D structure of ligand is shown Figure 1.

Table 1: Crystal data of 2-Mercapto-5-(3-methoxyphenyl) 1, 3, 4-oxadiazole

Identification code	**GBD-1**
Empirical formula	C9 H8 N2 O2 S
Formula weight	208.23
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	Pn21a
Unit cell dimensions	a=9.4447(18) Å α=90^0 b=6.7023(13) Å β=90^0 c=15.260 (3) Å γ=90^0
Volume	966.0(3) A^3
Z	4
Calculated density	1.432Mg/m^3
Absorption coefficient	0.308mm^-1
F (000)	432
Crystal size	0.4x0.35x0.3mm
Theta range for data collection	2.54 to 27.96 deg
Limiting indices	-12<=h<=11,-8<=k<=8, -19<=1<=20
Reflections collected / unique	7720/2223 [R(int)=0.0212]
Completeness to theta	98.2%
Absorption correction	none
Refinement method	Full matrix least squares on F^2
Data / restraints / parameters	2223/1/148
Goodness-of-fit on F^2	1.102
Final R indices [I>2sigma(I)]	R1=0.0544, wR2=0.1335
R indices (all data)	R1=0.0692 wR2=0.1437
Absolute structure parameter	0.8(2)
Extinction coefficient	0.0018 (16)
Largest diff. peak and hole	0.446 and -0.202 e A^-3

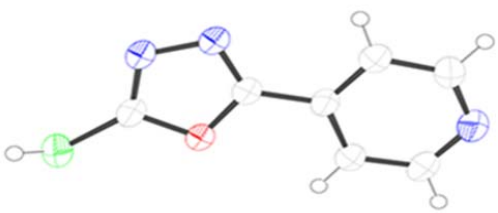

Figure 1: Structure of 2-Mercapto-5-(3-Methoxyphenyl) 1,3,4 oxadiazole

Preparation of protein structure

The 3D structure of FAK (PDB code: 2ETM) [8] was downloaded from protein data bank. The protein showed anticancer activity from the literature [9].The Pdb file was converted to ent file, all water molecules were removed and hydrogen atoms are added to the protein by using argus software.

Protein ligand interaction using Argus lab 4.0.1

Argus lab is an electronic structure program that is based on the quantum mechanics. It predicts the potential energies, molecular structures, geometry optimization of structure, and vibrational frequencies of coordinates of atoms, bond lengths, and bond angles. FAK was docked against the 2-Mercapto-5-(3-methoxyphenyl) 1, 3, 4-oxadiazole compound using argus lab 4.0.1 [10]. The interaction was carried out to find the favorable binding geometries of the ligand with the protein. Docking of the protein ligand complex was mainly targeted to the predicted active site. Docking was performed by selecting Argus dock as the docking engine. The selected residues of the receptor were defined to be part of the binding site. A spacing of 0.4 Å between the grid points was used and an exhaustive search was performed by enabling high precision option. Dock was chosen as the calculation type, flexible for the ligand and the score was used as the scoring function. A maximum of 150 posses were allowed to be analyzed, binding site box size was set to 39x39x39 Å so as to encompass the entire active site. The score function with the parameters read from the score. The entire compound in the data set was docked into the active site of FAK protein, using the same protocol. The docking poses saved for the compound were ranked according to their dock score function. The pose having the highest dock score was selected for further analysis. The ligand was docked with the target protein, and the best docking poses were identified.

RESULT AND DISCUSSION

The designed series of 1, 3, 4-oxadiazole were docked to the FAK protein with argus lab software. Docking result shows the best 9 binding sites (Table 2). Docked energy of 6.84913 Kcal/mol with two hydrogen bond shown in Figure 2. There was a change in the ligand structure after binding to the receptor shown in Figure 3. The molecular docking studies resulted in highlighting the ligands and their conformations which efficiently fit into the cavity of target protein. The higher the negative value of the energy of binding the better is affinity of the molecule to the receptor. Analysis of these ligands with the proteins brought in focus some important interactions operating at the molecular level.

Table 2: Best docking pose energy

Pose fitness	Affinity Kcal/mol
0	-6.84913
1	-6.77539
2	-6.77382
3	-6.77382
4	-6.77217
5	-6.76806
6	- 6.76806
7	-6.76734
8	-6.7654
9	-6.75904

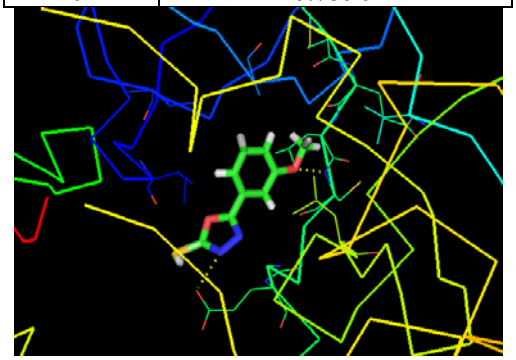

Figure 2: Binding pose of 1, 3,4oxadiazole in binding site

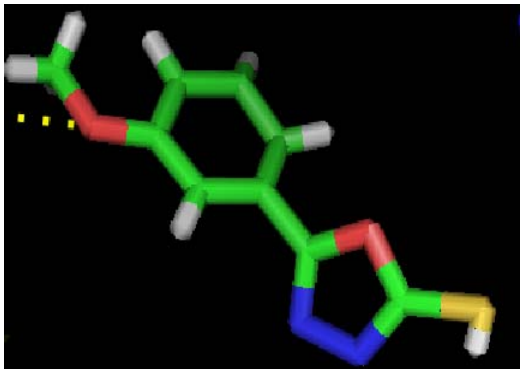

Figure 3: Changes in Ligand structure after Binding to receptor

CONCLUSION

The ligand synthesized for this study is considered as orally safe compound. The intermolecular interactions between the ligand and the protein were investigated. Synthesized chemical compound showed good fit with the protein**.**Thus the bioactive compound interacting with the target can be used as a potent inhibitor to block the action of FAK protein. The selected ligand can be verified at wet laboratory validations and made into an effective anticancer drug.

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