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In-Silico Designing of 5-(3 Chloro-1-Benzothien-2yl)-4-Phenyl-4H-1,2,4 Triazole-3-Thiol derivatives and their Potential application on *Fusarium Solani*

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ABSTRACT

In silico methods can help in identifying drug targets via bioinformatics tools. The use of computers and computational methods permeates all aspects of drug discovery and forms the core of structure-based drug design. High-performance computing, data management software and internet are facilitating the access of huge amount of data generated and transforming the massive complex biological data into workable knowledge in modern day drug discovery process. In the present work insilico designing of 5-(3 Chloro-1-benzothien-2yl)-4-phenyl-4H-1,2,4 triazole-3-thiol derivatives has been performed in order to identify those structures that most likely to bind to a drug target, typically a protein receptor or enzyme. Studies have been performed for a series of substituted 5-(3 Chloro-1-benzothien-2yl)-4-phenyl-4H—1,2,4 triazole-3-thiol by correlating electronic, steric and lipophilic properties of the substituents against the biological activity of Fusarium solani. The work has been performed insilico using NCBI {Database}, Cactus server for protein format conversion {Database}, Swiss model {Server}, Molegro Virtual Docker {Software} to obtain antifungal properties. The results obtained demonstrate that derivative with dinitro substituents is effective antifungal agents against Fusarium solani. It shows that heterocycles containing Nitro group have potential pharmacological properties.

Key words: *Virtual screening, 5-(3 Chloro-1-benzothien-2 yl)-4-phenyl-4H-1,2,4 triazole-3-thiol, insilico.*

INTRODUCTION

Drug discovery and development is an intense, lengthy and an interdisciplinary endeavor. Today, the process of drug discovery has been revolutionized with the advent of genomics, proteomics, bioinformatics and efficient technologies like, combinatorial chemistry, high throughput screening (HTS), virtual screening, *de novo* design, *in vitro*, *in silico* ADMET screening and structure-based drug design. Virtual screening (VS) is a computational technique used in drug discovery research. The purpose of virtual screening to come up with hits of novel chemical structure that bind to the macromolecular target of interest. Several five membered heterocyclic compound for instance pyrroles, imidazole, oxazole, itraconazol act as antimicrobial agents [2]. Moreover, due to diverse applications as antibacterial, antimycobacterial, antimycotic, antifungal and antidepressant agents the triazoles have attracted widespread attention. Triazole is advantageous due to its broad range of application in the treatment of both superficial and systemic fungal infections and it also shows greater affinity for fungal rather than mammalian Cytochrome P-450 enzymes for ex. Fluconazole for treatment of Histoplasmosis [8].

The fungal infections still remain a significant cause of morbidity and mortality despite advances in medicine and the emergence of new antifungal agents. Immunocompromised patients are particularly at risk of developing these infections, with *Fusarium* sp. that are resistant to antifungal agents, making treatment options a concern [4]. Many reasons have been suggested for the resistance of *Fusarium* sp. The cell wall of pathogens contain mannoproteins, chitins, and α and β-glucans and plays an important role in protection, cell morphology, cell rigidity, metabolism, ion exchange and filtration, antigenic expression, primary interaction with the host and resistance to host cell-mediated immune function [3].

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Thus, novel targets have been explored in an attempt to overcome the problems derived from the exploitation of traditional targets. The antimicrobial identification using experimental techniques is invariably very expensive, requires extensive pains and labour. Therefore, *in silico* techniques, which have the power to cut down these unavoidable steps, would be valuable [6]. These *in silico* techniques are used in pharmaceutical companies in the process of drug discovery.

In the current study attempts have been made to do the *in silico* analysis of different derivatives of 5-(3-chloro-1-benzothien-2 yl)-4-phenyl-4H—1,2,4 triazole-3-thiol which is basic in nature [7] and to locate the novel drug target in *Fusarium solani.*

MATERIALS AND METHODS

Materials:

Following databases, softwares & online servers were used during the study:

- PDB {http://www.pdb.org}
- NCBI {Database: www.ncbi.nlm.nih.gov}
- Cactus server for protein format conversion {Database}
- Swiss model {Server :- http:/swissmodel.expasy.org}
- Molegro Virtual Docker {Software}

Methodology:

- Sequence retrieval

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- Homology modeling
- Generation of ligand library
- Virtual screening of the ligand library for minimum energy calculation

RESULTS AND DISCUSSION

Sequence Retrieval:

The sequence of amino acid of Taxane 13-α hydroxylase in *Fusarium solani* was retrieved in FASTA format which is as follows

Taxane 13-α hydroxylase [in Fusarium solani]:

EESIGIVRAALSRFLGPQALQNHFAKMSSGIQRHINEKWKGKDEVTVLPLVKD
LVFSVASRLFFGITEEHLQEQLHNLLEVILVGSFSVPLNIPGFSYHKAMQARAT
LADIMTSLIEKRRNELRAGTASENQDLLSVLLTFTDERGNSLADKEILDNFSM
LLHGSYDSTNSPLPMLIKVRASNPETI

Homology Modeling:

Prediction of structure of protein from its sequence with accuracy is achieved by homology modeling.

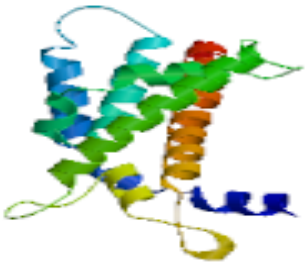


Fig. 1: Secondary structure of enzyme Taxane 13-α hydroxylase (Cytochrome P450) in *Fusarium solani*

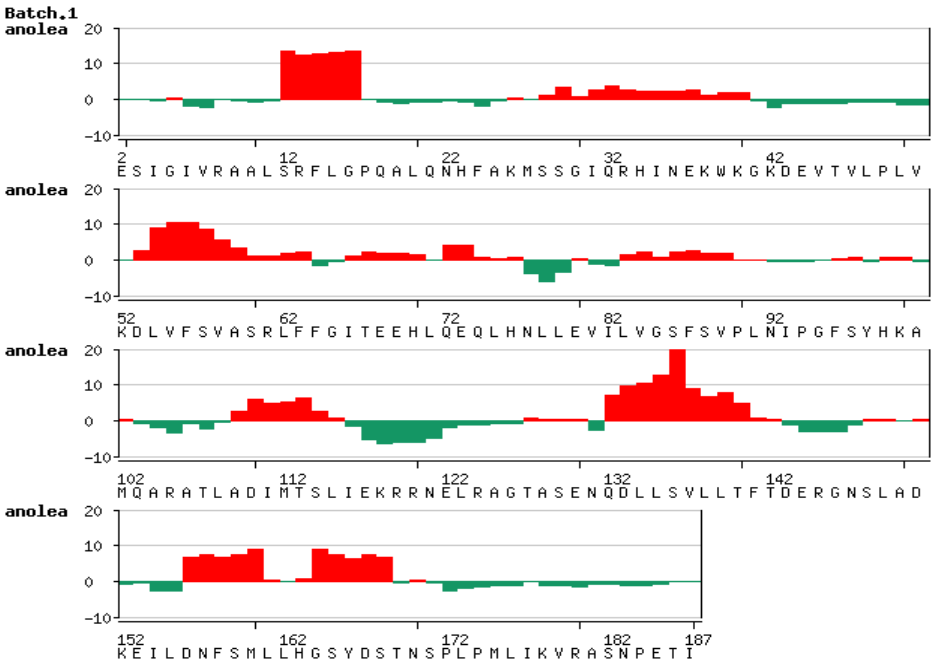
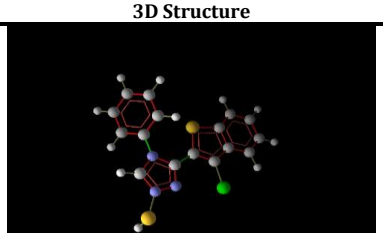
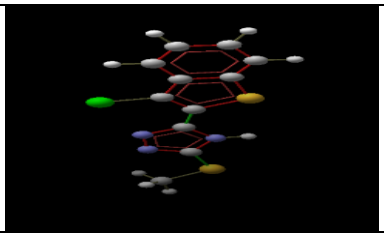


Fig. 2: Amino acid sequence *(*residue*)* in Taxane 13-α hydroxylase (Cyt P450) in *Fusarium.solani* Generation of Library Of Triazoles:

Ligand library is generated in mol 2 format. 3D structure and properties of the derivatives were tabulated as follows:

Nitrogen Carbon Sulphur Oxygen Chlorine

S.No	3D Structure	Properties
3.(a)		**Molecular Weight** : 344.862 **Molecular Formula**: $C_{16}H_{10}N_3S_2Cl$ **SMILES** CSc3nnc(c2sc1ccccc 1c2Cl)[nH]3 **IUPAC Name**: 5-(3-chloro-1-benzo thien-2-yl)-4-phenyl-4H-1,2,4-triazole -3 thiol **Heavy atoms**: 22 **Torsion** 2
3.(b)		**Molecular Weight** : 281.784 **Molecular Formula**: $C_{11}H_8N_3S_2Cl$ **Smile**: CSc3nnc(c2sc1ccccc 1c2Cl)[nH]3 **IUPAC Name**: 5-(3-chloro-1-benzo thien-2-yl)-4H-1,2,4-triazole-3- methyl thiol **Heavy atoms**: 17 **Torsion** 2

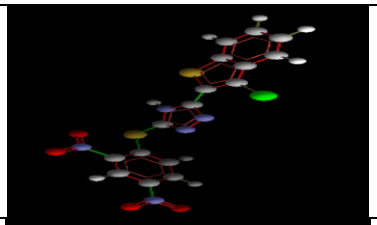
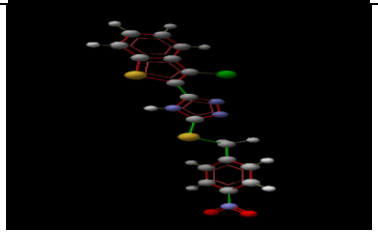
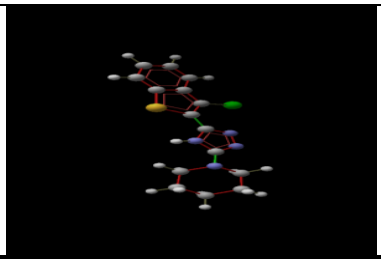
3(c)		**Molecular Weight** : 433.849 **Molecular Formula:** $C_{16}H_8N_5O_4S_2Cl$ **SMILES** O=N(=O)c4ccc(Sc3nnc(c2sc 1ccccc1c2Cl)[nH]3)c(N(=O)=O)c4 **IUPAC Name**: 5-(3-chloro-1-benzo thien-2-yl)-4H-1,2,4-triazole-3-(2,4-dinitrophenyl) thiol **Heavy atoms**: 28 **Torsion** 5
3.(d)		**Molecular Weight** : 402.878 **MolecularFormula**: $C_{17}H_{11}N_4O_2S_2Cl$ **SMILES** O=N(=O)c4ccc(CSc3nnc(c2sc1ccccc1c2Cl)[nH]3)cc 4 **IUPAC Name**: 5-(3-chloro-1-benzo thien-2-yl)-4H-1,2,4-triazole-3-(4-nitrophenyl) thiol **Heavy atoms**: 26 **Torsion** 5
3(e)		**Molecular Weight** : 318.824 **Molecular Formula**: $C_{15}H_{15}N_4SCl$ **SMILES** Clc3c(c2nnc(N1CCCCC1)[nH]2)sc4ccccc34 **IUPAC Name**: 5-(3-chloro-1-benzo thien-2-yl)-4H-1,2,4-triazole-3-N -piperidine **Heavy atoms**- 21 **Torsion**- 2

Fig. 3(a-e): Derivatives of *5-(3 Chloro-1-benzothien-2 yl)-4-phenyl-4H-1,2,4 triazole-3-thiol.*

Virtual screening of the Ligand Library of derivatives of 5-(3 Chloro-1-Benzothien-2-yl)-4-Phenyl-4H-1,2,4-Triazole-3-Thiol for Minimum energy calculation:

Docking score of different derivatives was calculated –

Table No. 1: Docking score of derivatives of "*5-(3 Chloro-1-benzothien-2yl) -4-phenyl-4H-1,2,4 triazole-3-thiol*" with *F.solani*

Molecular Formula	Mol Dock Score	Re-rank Score	H-Bond
$C_{16}H_{10}N_3S_2Cl$	-103.216	-42.7742	-2.47729
$C_{11}H_8N_3S_2Cl$	-93.1969	-74.0918	0
$C_{16}H_8N_5O_4S_2Cl$	-114.112	-75.6237	-0.00922391
$C_{17}H_{11}N_4O_2S_2Cl$	-120.676	-83.4269	-0.252175
$C_{15}H_{15}N_4SCl$	-83.3178	-13.3864	6.37927

5-(3-chloro-1-benzothien-2-yl)-4H-1,2,4-triazole-3-(4-nitrophenyl) thiol has minimum calculated energy (-120.676) and highest energy calculation is shown by 5-(3-chloro-1-benzothien-2-yl)-4H-1,2,4-triazole-3-N-piperidine (-83.3178).

Different poses of interaction between drug molecules and bio-molecules that is amino acids have been represented with the help of pictures capture by MVD.

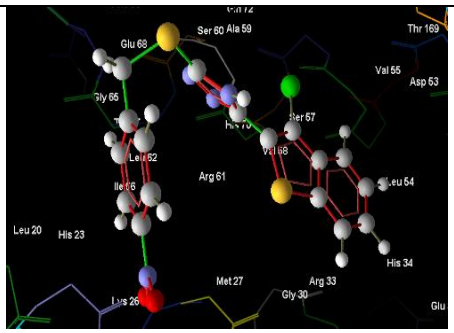


Fig. 4(a): Residue around the cavity with which receptor binds

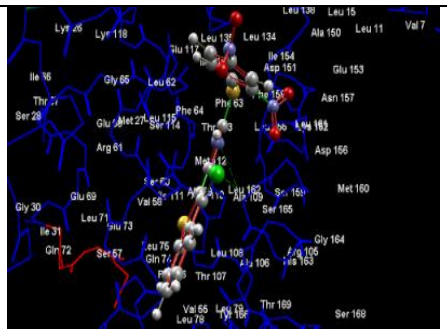


Fig. 4(b): Hydrogen bond interaction between lead compound and Leu 162

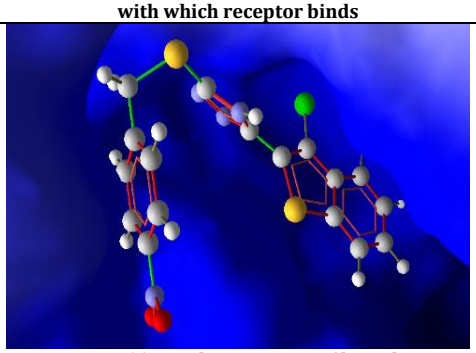


Fig. 4(c): Binding position of ligand at the surface of receptor

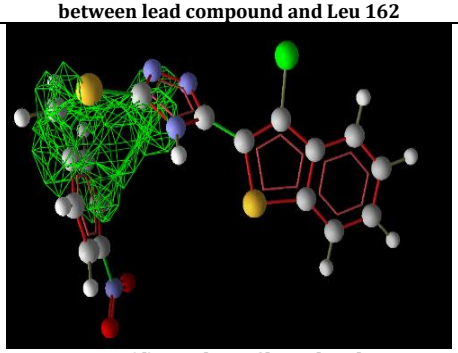


Fig. 4(d): Binding of ligand at the cavity of enzyme

Fig. 4(a-d): Interaction between top scorer derivative "5-(3-chloro-1-benzothien-2-yl)-4H-1,2,4-triazole-3-(2,4-dinitrophenyl) thiol" with *F.solani*

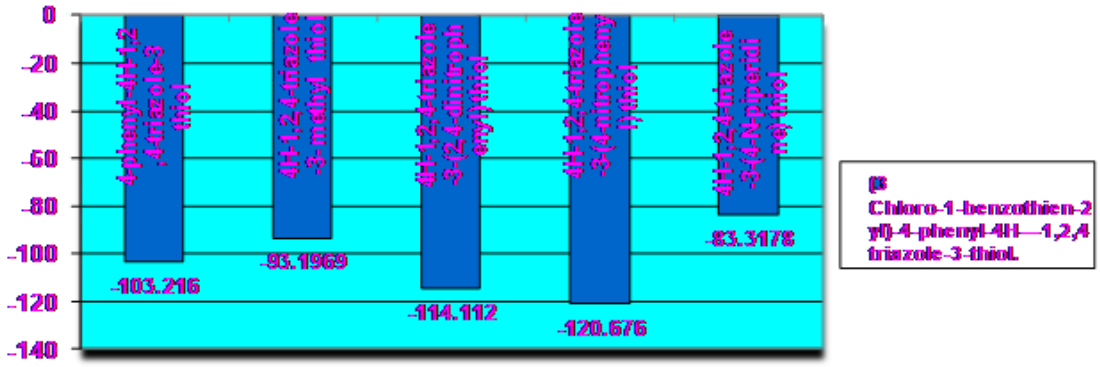


Fig. 5: Comparative inhibitory effect of derivatives of (3 Chloro-1-benzothien-2 yl)-4-phenyl-4H-1,2,4 triazole-3-thiol against *F.solani*

It has been observed that 5-(3-chloro-1-benzothien-2-yl)-4H-1,2,4-triazole-3-(2,4-dinitrophenyl) thiol shows the maximum inhibitory effect for *Fusarium solani* with minimum energy calculation.

The pharmacological properties of triazole containing Nitro group can be justified by the references [5, 9] according to which derivatives with Nitro groups behave as biologically active antifungal activity. Pharmacophore NO_2 easily binds with hydrophobic pocket and also decreases H_2O solubility of the resultant compound.

The results have been corroborated by the studies of QSAR studies are predominantly governed by **" Craig plot "** with regard to the various substituents in a new drug molecule. In our study the nitro group essentially enhances both electron withdrawing characteristics and hydrophobicity in the 'drug like molecule' by virtue of their σ +ve and π +ve effects**.**

The results are also in confirmation with the findings of reference [1] according to which electron withdrawing hetero aromatic nucleus appreciably acidified the remaining H-atom and increases drug potency, thus consistently improving antifungal activity.

CONCLUSION

The results obtained demonstrate that derivative with nitro substituent is effective antifungal agent against *Fusarium solani*. It shows that heterocycles containing Nitro group have potential pharmacological properties and are of a special interest because they constitute an important class of natural and non-natural products. Therefore, homology based rational drug designing can be a successful approach for designing of potent antifungal drug.

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