Open Access Contents
Int. J. Drug Dev. & Res.
| January - March 2014 | Vol. 6 | Issue 1 | ISSN 0975-9344 |
www.ijddr.in

Full Length Original Research Paper

Insilico biological evaluation of newly synthesized 1'-(4-Bromophenyl)-4'-{4-((2-oxo-1,2,3,4-tetrahydronaphthalen-2-ylidene) methyl) phenyl}-3'',4''-dihydroacenaphthylene-1-spiro-2'-pyrrolidine-3'-spiro-2''-naphthalene-2,1''(1H,2''H)-dione against fungal target

Saravanan B.*

Akhilesh Upgade

Manivannan V

Centre for Research & Development, PRIST University Thanjavur 613403, Tamilnadu, India

Corresponding Authors:
Email:
saran197209@gmail.com

Abstract:
Fungal infection is the commnest problem everywhere. Depending on the types of starin involves the strategy applies. Various spectral antibiotics have been incorporated as antifungals but fail to inhibit. This pilot study establishes the new synthesied compound 1'-(4-Bromophenyl)-4'-{4-((2-oxo-1,2,3,4-tetrahydronaphthalen-2-ylidene)methyl)phenyl}-3'',4''-dihydroacenaphthylene-1-spiro-2'-pyrrolidine-3'-spiro-2''-naphthalene-2,1''(1H,2''H)-dione tested against the fungal target. Selected target retrieved from database and selected using biosynthetic pathways by using the cellular mechanism. This can be act as a check point to interrupt the pathway. Newly introduced pyrolidine based compound were dock with the glucose 6 phosphate synthase insilico docking tools and analyzed by X ray crystallography. Docking by molegro virual docker (MVD) shows good docking score and poses. It shows -141kcal/mol in first pose which considers as a based score and structure based binding site. In conclusion, the synthesized compound can designate as drug.

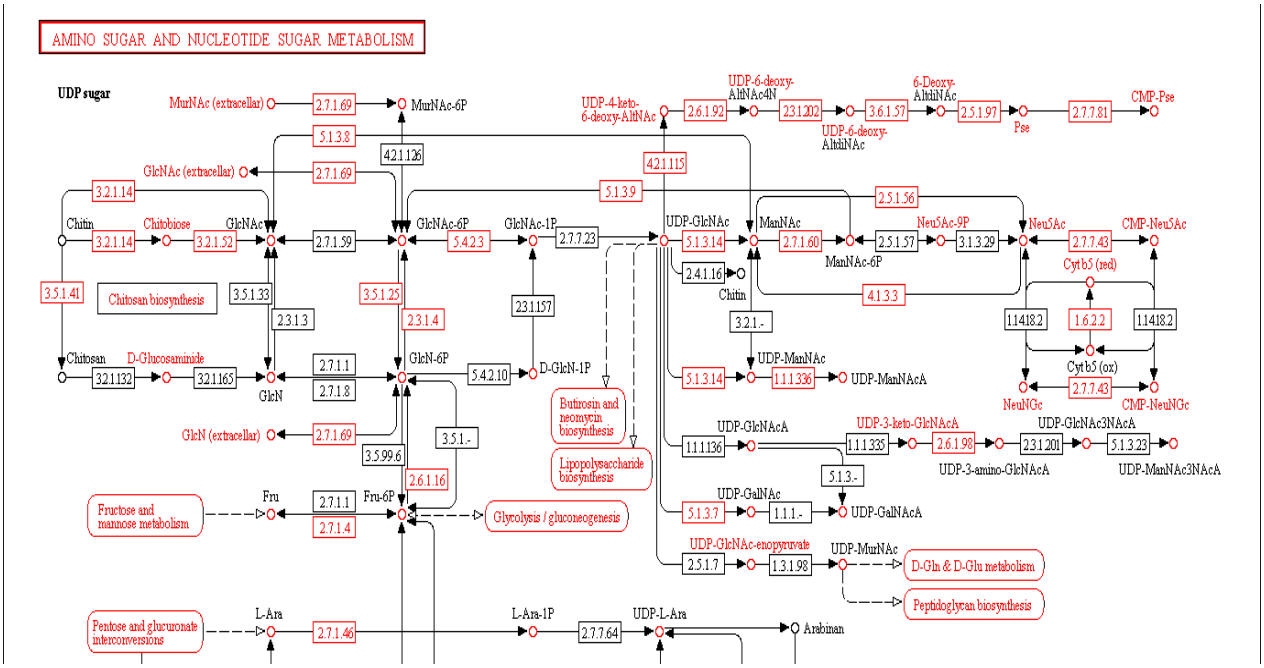
Keywords: Drug development, novel drug, antifungal drug.

Introduction:

Fungal Infection is the major cause of concern in this era, trichomonasis, candidiasis, like dual infection can be life thereating. All the antibiotics available in the market are either broad spectrum antibiotics or antifungal ones. All of the available antibiotics work at cellular inhibition. In this case, a hypothesis made to overcome the disease by synthesizing new compounds. Hence, there is an urgent need to develop newer and better antifungal drugs. The enzyme Glucosamine-6-phosphate (G-6-P) synthase well known target for ceasing the biosynthetic pathway useful for growth of cell membrane. Targeting such proteins can inhibit the growth of the fungus. The antifungals comprise Amphotericin B, Posaconazole and fluconazole and all azole compounds are nephrotoxic and hepatotoxic in nature. (1). Now a days various combinatorial therapies given, but in fungal cases popularity decreases due the acquisition of drug resistance among the species. In this pathways glucosamine 6 phosphate synthase acts as a accelerator for cellular growth of fungus hence it is targeted. Newly synthesised compound can have the synergetic effect on it. So that the pathways get affected and cell wall synthesis cease which automatic results into inhibition of chitin formation. Chitin called as bricks of the cell.(2,3) Syntheis of new pyrolidine based compound is due to its active biological actiovites previously observed by Amalraj et al. (4)

Covered in Scopus & Embase, Elsevier
Int. J. Drug Dev. & Res., January - March 2014, 6 (1): 120-124

Current study was planned to analyse synthesized compound and its biological activity against the fungal enzyme using insilico computational studies by various software's.



Materials and Methods:

Synthesis of the compounds:

To the solution of acenaphthequinone (3) (1.1 mmol), *N*-(*p*-bromo) phenyl glycine (2) (1.1 mmol) and 1,4-bis(3',4'-dihydro-1'- oxonaphthalen-2'-ylidene)benzene (1) (1.0 mmol) was refluxed in dry toluene. Completion of the reaction was evidenced by TLC analysis. The solvent was then removed in vacuum, diluted in dichloromethane, washed with water, and brine. The organic layer was separated and dried over Na_2SO_4.The organic solvent was removed and the residue was subjected to column chromatography using hexane/ethyl acetate (6:4) as eluent afforded the cycloadduct. (5)

X ray diffraction analysis:

Data was collected on a Bruker Kappa APEX II diffractometer using ω and φ scan mode with the range reflections $1.1 \leq \theta \leq 28.5^{\circ}$ using MoKa radiation. A total of 30711 reflections were collected, resulting in 6410 independent reflections of which 4539 had $I > 2\sigma(I)$(6). The intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SHELXS 97 program and final R-factor was 0.034. (7)

Computational molecular docking studies:

Crystallographic structures of protein were retrieved from the RCSB database with PDB ID 2VF4.Computational analysis was done to compute ligand protein binding affinity of the compound. Docking calculations were carried out using Molegro Virtual Docker (MVD). The MMFF94 force field was used for energy minimization of ligand using Docking Software. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged and rotatable bonds were defined. (8)

MVD is a flat platform for the ligand screening and protein interaction. It is based on the various algorithms. According to recent datum, 87%

Covered in Scopus & Embase, Elsevier Int. J. Drug Dev. & Res., January - March 2014, 6 (1): 120-124

accuracy was noted in case of MVD results keeping this in mind, the target were uploaded and allowed to dock for pose quenching. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. Pose organization was automatic adjusted and analysis table were generated.

Results:

X ray Diffraction analysis

CRYSTAL AND EXPERIMENTAL DATA

EMPIRICAL FORMULA	$C_{47}H_{34}BrNO_3$
TEMPERATURE	295 K
FORMULA WEIGHT	740.38
WAVELENGTH	0.71073 Å
CRYSTAL SYSTEM	Triclinic
SPACE GROUP	*P*$\bar{1}$
UNIT CELL DIMENSIONS (Å)	a= 8.4178 (2) A˚
	b = 13.2352 (3) A˚
	c = 15.9610 (3) A˚
	α= 98.143 (1)
	β= 92.744 (2) ◦
	γ=100.944(1)
VOLUME Å^3	1723.17 (7)Å^3
Z	2
CALCULATED DENSITY	1.427mg/m^3
ABSORPTION COEFFICIENT	1.24mm^{-1}
REFINEMENT METHOD	Full matrix
F(000)	764
CRYSTAL SIZE	0.20X0.19X0.18mm
Θ – RANGE FOR DATA COLLECTION	2.2 to 25.3◦
GOODNESS-OF-FIT ON F^2	1.03
REFLECTIONS COLLECTED/UNIQUE	26660/4328
R-FACTOR	0.034

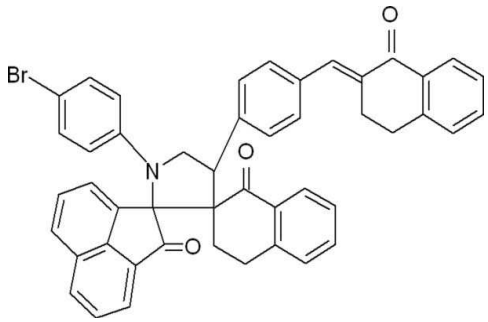


Fig 1: Ligand of 1'-(4-Bromophenyl)-4'-{4-((2-oxo-1,2,3,4-tetrahydronaphthalen-2-ylidene) methyl)phenyl}-3'',4''-dihydroacenaphthylene-1-spiro-2'-pyrrolidine-3'-spiro-2''-naphthalene-2,1''(1H,2''H)-dione compound)

Molecular docking Studies:

The structures of the ligand Diethyl 2-{(3-(2, 4, 6-trimethylbenzyl)-1phenylsulfonyl-1H-indol- 2yl) methylidene} propanedioate compound were drawn using tool Chembiodraw 11.0. (Fig.1)and converted into PDB format using molecular conversion tool VCC lab online server. The crystallographic structures of glucosamine 6 phosphate synthase were retrieved from the RCSB database with PDB ID 2VF4 was docked with ligand.

Lamarckian genetic algorithm is clearly depicted in the docking. The interaction shows efficient docked score -141 kcal/mol which is considered as a satisfactory score in ligand- protein interactions.table1.Hydrogen bonding in docking plays a significant role in interaction studies and graph plotted shown in Fig. 2, 3**.** The strong interaction between residues with a specific bond length, and hydrophobic interaction on surface of the protein shown in Fig 4, 5.

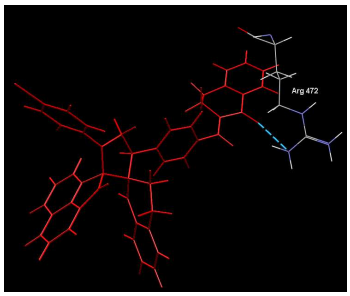


Figure 2: Lignad residue interaction

Covered in Scopus & Embase, Elsevier
Int. J. Drug Dev. & Res., January - March 2014, 6 (1): 120-124

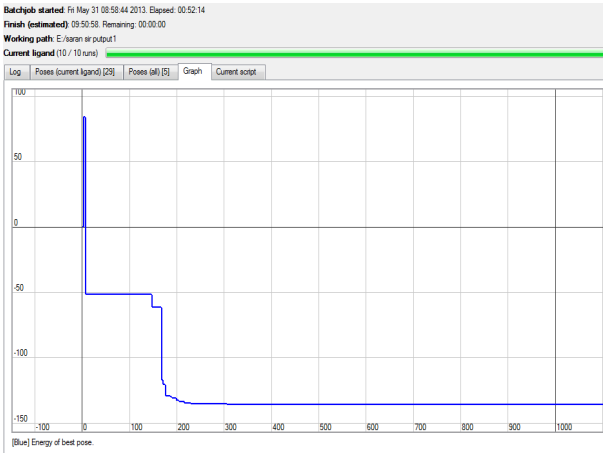


Figure 3 : docking analysis graph

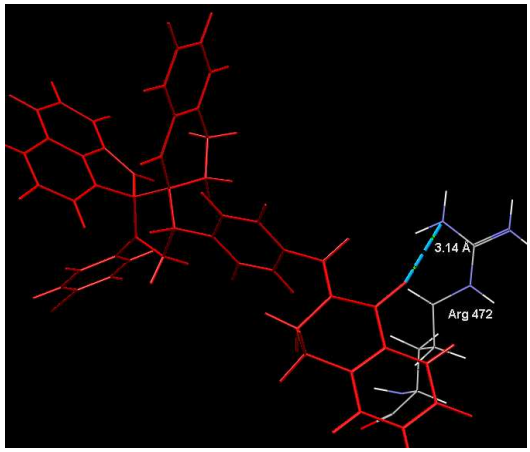


Figure 4: Docked image showing protein and ligand hydrogen bond interaction

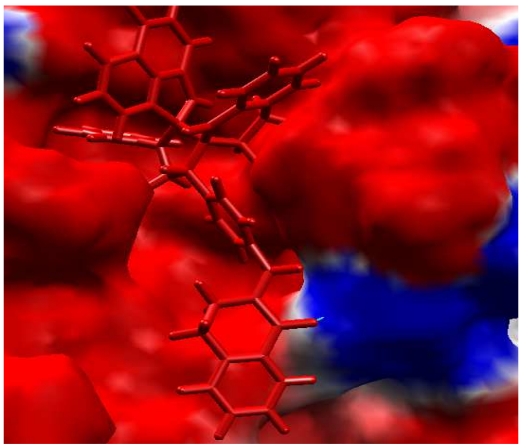


Fig 5: Surface interaction with ligand

Molecules	Mol dock score GRID	mol dock score	Pose rank score	RMSD	Torsions	H bond length
Protein ligand complex	-141.605	-141.605	-51.8307	36.6163	3	-1.32

Table 1: Energy values of docked 1'-(4-Bromophenyl)-4'-{4-((2-oxo-1,2,3,4-tetrahydronaphthalen-2-ylidene)methyl)phenyl}-3'',4''-dihydroacenaphthylene-1-spiro-2'-pyrrolidine-3'-spiro-2''-naphthalene-2,1''(1H,2''H)-dione compound ligand with rennin

Discussion:

Among the various fungal targets the chosen one is the key target. The sugar metabolism was elucidated and the check points were screened. In mechanistic approach among the fungi is there are multiple copies of same enzyme. So, that could be the reason that the antifungal are not working properly. In contrast, our first aim is to carryout this screening about the multienzymes. Amino sugar pathway has to check points which can be inhibited using glucose 6 phosphate synthase inhibitor which results in non synthesis of chitin and no cell wall. As the glucose level increases in the cell automatically the uptake is high and intercellular level of glucose 6 phosphate increases. This results into glycogen synthesis. (9) From biosynthetic pathway it is clear that if the glucose uptake more then, new "trihalose" a dimer of unusual glucose will form, that generally protect the cell wall from desiccation. According to this mechanism, new structure based inhibitor was synthesized. (10, 11, 12)

In this study a compound synthesized using standards and structure was resolved by universal method of X- ray crystallography to understand the molecular bonding. In the title compound, C47H34BrNO3, the central benzene ring makes a dihedral angle of 42.71 with the bromophenyl ring. The pyrrolidine ring adopts an envelope conformation. The molecular structure is stabilized by weak intramolecular C—H···O interactions and the crystal packing is stabilized by weak intermolecular C—H···π interactions.

According to the docking score, and other features revealed by the compound in this study such as poses were selected on the basis of score. The pyrolidine derivative known for the anti fungal activity may be due to the its benzene ring, the intermolecular forces are due to weak interaction with Arginine present in the pocket. RMSD value and 3 torsions predicts the stability. Negative value of hydrogen bond shows strong exothermic attachment with ligand.

From the other angle or perspectives this compound can be recommend as drug on the basis of structure activity relation and also opens way for further clinical research.

Conflict of interest:

Authors have read and approved the paper. The authors have no conflict of interests in regard to this self funded research work.

Acknowledgement:

Authors would like to thank Department of Physics, IIT madras, for XRD studies and Centre for research and development, PRIST University for support.

References:

1) Chayakulkeeree M *et al. Eur J Clin Microbiol Infect Dis.*2006 **25**: 215 (PMID: 16568297)
2) Pogell. B. M., R. M. Gryder R. M., J. Biol. Chem. 228 (1957) 701– 711
3) Saravanan, B., Rajesh. R., Raghunathan. R., Chakkaravarthi. G and Manivannan. V. (2010). Acta Cryst. E66, o2801
4) Amalraj A., Raghunathan R., Sridevi Kumari, M. R. & Raman N. (2003). Bioorg. Med. Chem. 11, 407–419
5) Aravindan, P. G., Selvanayagam, S., Velmurugan, D., Ravikumar, K., Sridhar, G. & Raghunathan, R. (2004). Acta Cryst. E60, o2149–o2151.
6) Bruker (2004). APEX2 and SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
7) Chakkaravarthi, G., Dhayalan, V., Mohanakrishnan, A. K. & Manivannan, V. (2007). Acta Cryst. E63, o3698
8) Friesner et al. (J. Med. Chem. 2004, 47, 1739-1749).
9) C Villar-Palasí.C and Guinovart J J june 1997The FASEB Journalvol. 11 no. 7 544-558
10) Djonović S, Urbach JM, Drenkard E, Bush J, Feinbaum R, et al. (2013) Trehalose Biosynthesis Promotes *Pseudomonas aeruginosa* Pathogenicity in Plants. PLoS Pathog 9(3): e1003217. doi:10.1371/journal.ppat.1003217
11) Takanobu Higashiyama,Novel functions and applications of trehalose, Pure Appl. Chem., Vol. 74, No. 7, pp. 1263–1269, 2002
12) Streeter, J. G. (1985). "Accumulation of a,a-trehalose by Rhizobium bacteria and bacteroids". *J. Bacteriol.* 164 (1): 78–84. PMC 214213. PMID 404453.

Article History: ----------
Date of Submission: 17-12-2013
Date of Acceptance: 09-01-2014
Conflict of Interest: NIL
Source of Support: NONE