Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Research Article

QSAR, Molecular Docking and Toxicology Profile of Synthesized Derivatives of 1, 3, 4-Thidiazole-2-Amine.

Kadam S. S.

Department of Chemistry, Hon. B. J. Arts, Comm. & Sci. College, Ale, Junnar, Pune, Maharashtra, India.

Received 10 December 2018; received in revised form 24 December 2018; accepted 24 December 2018
***Corresponding author E-mail address:** sushmakadam.24@gmail.com*

ABSTRACT

In the present research paper in silico evaluation of synthesized derivatives of 3, 4-disubstituted-1,3,4-thidiazole-2-amine based on their QSAR property, molecular docking and toxicology profile. The interaction of binding sites with bacterial protein receptor, the docking study was performed using DNA gyrase enzymes (PDB ID: 2XCT) by Schrodinger's Maestro program. Published previous research article reveals in vitro antibacterial activity of same compounds was studied and the MIC value was calculated by Kirbey Bauer method. Among all the synthesized compounds, some compounds showed potent antimicrobial activity. It concludes that most of the synthesized compounds were found more active against in virtual screening and all tested bacterial strains in comparison to the standard drug Ciprofloxacin.

KEYWORDS

QSAR, Molecular docking, Toxicology profile, DNA gyrase enzymes (PDB ID: 2XCT) ligand.

1. INTRODUCTION

The docking studies of synthesized derivatives of 3,4-disubstituted-1,3,4-thidiazole-2-amine based on the fact that there are attractive forces that helps in forming a protein-ligand complex; the overall goal of using the computational techniques is to visualize and understand the molecular level of interactions which are helping the intended protein-ligand complex formation in order to distinguish molecules which are not, thus helping us cut down the costs and time in the process of novel drug development[1]. Despite the wealth of structural information, the role of SBDD has been limited to suggest the analogues of existing leads and to post-rationalize the bioactivity data. Therefore, in this work, molecular docking is the primary computational method chosen for the identification of potential target specific ligands (lead generation), synthesis and biological evaluation were carried out in pursuit of designing some potential novel antimicrobial compounds carrying 1,3,4-Thiadiazoles rings as core nucleus. The presence of =N–C–S moiety and symmetrical structure of 1,3,4-thidiazole core has shown diverse range of biological properties.[2-6] In literature review on various synthetic aspects of synthesis approaches has related with thidiazole, carbondisulphide, hydrazine hydride, thiohydrazide, carbonothioic dihydrazide etc has seen to be more popular. The synthesis of selected route was use of substituted / unsubstituted nitriles and thiosemicarbazide as a starting material is rarely observed. This synthetic method based MCR's i.e. one pot synthesis, minimum time and ease to recovery of desired product in good yield.

1.1. General Scheme

For the synthesis of 3,4-Disubstituted-1,3,4-Thidiazole-2-Amine and Their Derivatives[7-11]:

2. MATERIALS AND METHODS

2.1 Software and program

Chemsketch was used to draw the ligand compounds. Accelry's Discovery studio v4.0 and Schrodinger's maestro visualization program v9.6 [12] were utilized to visualize the protein-ligand structures, H-bonds, measurement of bond lengths and to render images. Manual Pharmacophore hypothesis generation module of Schrodinger's maestro v9.6 was used for pharmacophore features mapping of the compounds along with location and calculation of distance between the pharmacophore features. MGL Tools version 1.5.6 was used for the preparation of the ligands and protein receptors in pdbqt format and to visualize and estimate the grid box size for docking calculations. Autodock 4.0 [13] is the software used for the docking calculation. Molinspiration and Orisis property explorer and programs were used to predict the ADMET properties of the compounds.

2.2 Preparation of protein receptor and Ligand

Protein Data Bank (PDB) [14] was used to retrieve the crystal structures DNA Gyrase (PDB ID: 2XCT); for anti-bacterial activity. Drug targets are prepared for docking studies via below steps using repair commands module of AutoDock:

1) All the co-crystallized water molecules were removed before docking.

2) Modifications of Bonds: The bonds in the protein are optimized to build by distance

3) Modifications of Atoms: Then the atoms are optimized for Auto Dock 4 parameters (AD4 type parameter) so that all the atoms in protein enable to process through Auto Dock.

4) Modifications of Hydrogen:

Missing hydrogen are added to the protein for correct tautomeric and ionization states of amino acid residues. Non polar centre in between hydrogen are merged. The protein file is fixed with pdb name errors if in case any by mistake. All the Histidine residues were listed to be protonated with (+1 charge)

5) Modifications of Charges: In order to optimize the protein and to fix its charges

kollman charges are added to protein. Gasteiger charges are added to protein. Finally kollman and Gasteriger charges adjusted for the protein to neutralize.

Totally missing atoms are repaired and finally the protein structures are optimized for *In Silico* docking studies and stored in .pdbqt format.

2.3 Preparation of Ligands

Designed ligands are drawn through the above ChemSketch and all the obtained ligands are stored in (.mol) structural format (2D structural format). The ligands in the (.mol) structural format are further processed for energy minimization by employing CHARMM force field [15] and developed in to 3D structural format by Accelry's Discovery studio visualiser 4.0. These energy minimized ligands are then stored in protein data bank (.pdb) format. Ligands stored in .pdb format are then imported into autodock software for docking calculations. Firstly, root of the ligand is auto detected. Then torsions of ligands are the molecules are set and no of torsions of the ligands are verified and adjusted. Then the output of ligand is stored in .pdbqt parameter.

2.4 Preparation for the Grid Parameter File

The macromolecule protein and ligand structures as rigid files are imported in the 3D space of the autodock software. Then, the energy scoring grid box was centered with 0.375 angstroms grid points spacing and size of the box was set to 126, 126 and 126 Å (x, y, and z) assigned with default atomic salvation parameters. The grid box was designed such that the whole macromolecule was surrounded by the three dimensional grid box centered. After the grid box fixation, all other required default parameters for grid are assigned and then the file output is saved as grid parameter file (.gpf)

2.5 Preparation for the Docking Parameter File

The macromolecule and ligand are exposed in the 3D viewer; macromolecule is set as a rigid file. Lamarckian Genetic Algorithm (LGA) [16] was selected as docking engine, which reports the best docking solution based on cluster analysis along with best IC50 values for each docked complex. Binding Gibbs free energy (ΔG) is calculated as a sum of six energy terms of electrostatic interactions, desolvation effects, hydrogen bonding, dispersion/repulsion, deviation from covalent geometry, and internal ligand torsional constraints. The lowest energy docking mode with respective IC50 prediction was selected from a total of 10 docking modes represented by LGA cluster analysis. Finally, a docking parameter file (.dpf) with all the input parameters was saved for to be used for execution of docking calculations.

3. RESULTS AND DISCUSSION:

Table 1. ADME parameters of the synthesized derivatives.

Sr. No.	synthesized derivative	Molecular Formula	Mol. wt.	Log P	H-bond donors	H-Bond acceptors	Rotatable bonds	TPSA

1	TDA	$C_8H_7N_3S$	177.2	1.6	1	3	1	80.0
2	TDA_1	$C_{14}H_{16}N_4OS$	288.3	2.9	2	5	3	95.1
3	TDA_2	$C_{13}H_{14}N_4O_2S$	290.3	1.9	1	6	2	95.5
4	TDA_3	$C_{11}H_{10}N_4O_3S$	278.2	0.8	3	7	4	132.4
5	TDB	$C_8H_5N_3F_2S$	213.2	1.8	1	3	1	80.0
6	TDB_1	$C_{14}H_{14}N_4OF_2S$	324.3	3.1	2	5	3	95.1
7	TDB_2	$C_{13}H_{12}N_4O_2F_2S$	326.3	2.1	1	6	2	95.5
8	TDB_3	$C_{12}H_{12}N_4O_3F_2$ S	310.3	1.3	3	7	4	132.4

3.1. QSAR study of the synthesized derivatives

Based on the descriptor values predicted by the Molinspiration and Osiris property explorer online servers [17] all the synthesized compounds successfully satisfied all the parameters of Lipinski's rule of five [18] (the mol. wt. must be less than 500 Da, the number of hydrogen donors and log P values should be less than five; the refractivity molar range shall be between 40 to 130 and the number of hydrogen bond acceptors should not exceed ten.) and all the present investigated synthesized compounds show that all the compounds have a promising oral bioavaibility and ADME. As per the Veber's rule, oral bioavailability of drugs could be measured by the total polar surface area (TPSA) of the compound along with molecular weight, number of H-bonds and the number of rotatable bonds. Good orally bioavailable small molecules is marked by small molecular weight (less than 500 Da); the number hydrogen donor/ acceptors combined shall be less than 12, TPSA values less than 140 and the number of rotatable bonds must be less than ten [19].

The toxicity predictions of the present studied synthesized derivatives using Osiris Property Explorer [20] were based on the functional group similarity for the query molecule with the *in vitro* and *in vivo* validated compounds in the database.

The result of toxicity analysis of all the analyzed compounds is described as follows "HIGH" means high tendency of toxicity; "MEDIUM" means the midcore and "NONE" means low toxic tendency. The result of Toxicology profile is depicted in Table 2.

Table 2. Toxicology profile of the present studied synthesized derivatives.

S. No	Compound Name	Mutagenic	Tumerogenic	Effect on Reproductive system	Eye Irritant
1	**TDA**	NONE	NONE	NONE	NONE
2	**TDA_1**	NONE	NONE	NONE	NONE
3	**TDA_2**	NONE	NONE	NONE	NONE
4	**TDA_3**	NONE	LOW	NONE	NONE
5	**TDB**	NONE	NONE	NONE	NONE
6	**TDB_1**	NONE	NONE	NONE	NONE
7	**TDB_2**	NONE	NONE	NONE	NONE
8	**TDB_3**	NONE	LOW	NONE	HIGH

Table 3. Docking results of Compounds targeting DNA Gyrase (PDB ID: 2XCT) for anti-bacterial activity.

Sr. No.	Compound Name	Binding Energy in Kcal/mol	Predicted IC50 value
1	**TDA**	-4.5	432.76 nM (nanomolar)
2	**TDA_1**	-6.8	124.57 nM (nanomolar)
3	**TDA_2**	-6.8	124.31 nM (nanomolar)
4	**TDA_3**	-5.6	283.18 nM (nanomolar)
5	**TDB**	-4.7	362.94 nM (nanomolar)
6	**TDB_1**	-6.7	129.71 nM (nanomolar)
7	**TDB_2**	-6.8	124.28 nM (nanomolar)
8	**TDB_3**	-5.9	213.68 nM (nanomolar)

IC_{50} value range of 432.76 nano molar to 124.28 nano molar levels with binding energy in a range of -4.50 to -6.8 Kcal/mol for DNA Gyrase drug target

3.2. TDB_2 (Best compound) docking interactions with DNA Gyrase (PDB ID: 2XCT) for anti-bacterial activity.

For DNA Gyrase drug target, compound TDB_2 has been identified as the best target specific binding compound based on the binding energies. From the visualization of the docked pose it was revealed that LYS1270, VAL11268, PHE1266, ALA1118, ASP1116, SER1098, MET1113, GLN1095, GLU1088 and GLY1115 residues were observed to be key role players towards stabilizing this protein-ligand complex shown in docked figures.

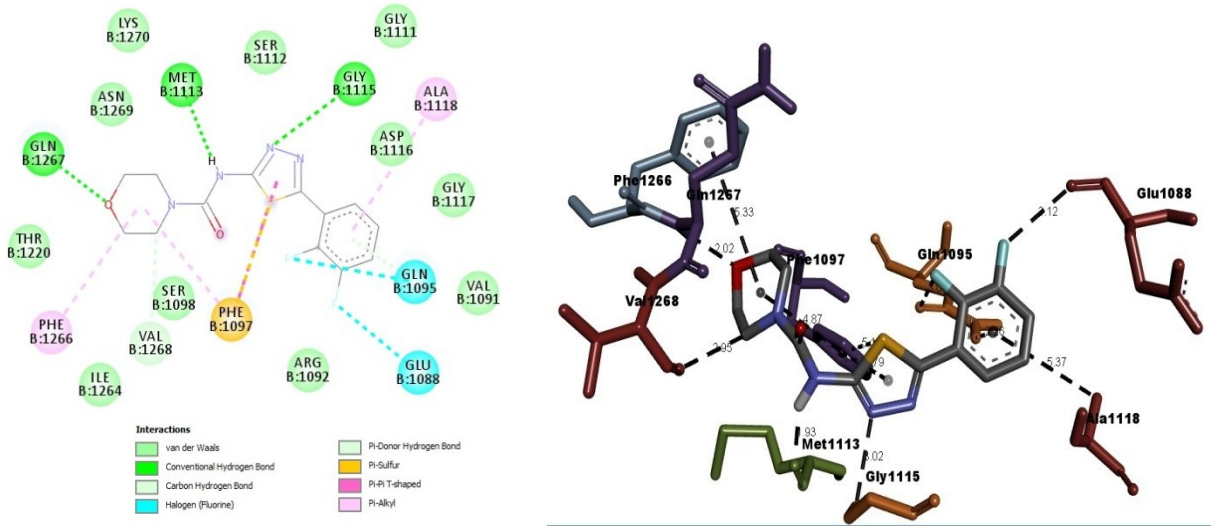
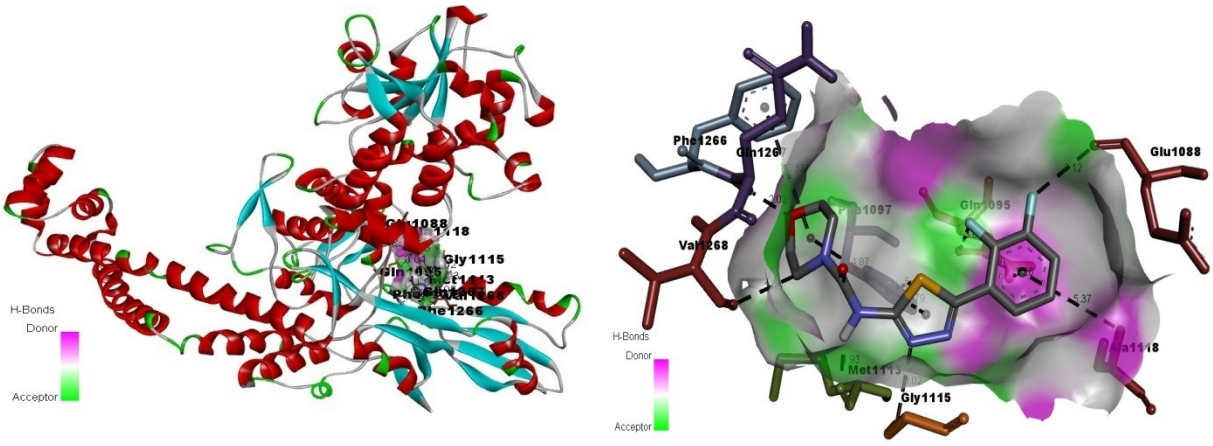


Figure 1. A) 2D interactions of TDB_2 **B)** 3D interactions formed by the TDB_2



C) & D) surface area interactions of TDB_2 with DNA Gyrase

4. CONCLUSION

It is observed that the studies provide high value for computational screening of targeting specific domain inhibitors by understanding the molecular interaction basis between ligand and receptor. Comparison of docking results with some approved drug of the FDA showing better IC_{50}.

5. ACKNOWLEDGEMENTS

My sincere thanks to my research guide Dr. G. M. Nazeruddin for their valuable guidance and Dr. Syed Hussain Basha Innovative Informatica Technologies, Hyderabad for assisting in producing the data require for this research work.

6. REFERENCES

[1] Gohlke, Holger, and Gerhard Klebe. (2001) *Current opinion in structural biology*. 11, 2, 231-235.

[2] Alegaon, S. G.; Alagawadi, K. R.; Sonkusare, P. V.; Chaudhary,S. M.; Dadwe, D. H.; Shah, A. S. (2012) *Bioorg. Med. Chem. Lett.* 22, 1917.

[3] Lincy Joseph, Mathew George, Prabha Mathews. (2015) *J. Pharm Chem Biol Sci.,* 3, 3, 29-345.

[4] Ashour, F. A.; Habib, N. S.; Taibbi, M.; Dine, S.; Dine, A. (1990) *Farmaco*. 45, 134-139.

[5] Rollas, S.; Karakus, S.; Durgun, B. B.; Kiraz, M.; Erdeniz, H. (1996) Farmaco. 51, 811-814.

[6] Foroumadi, A.; Soltani, F.; Moshafi, M. H.; Askari, A. O. (2003) *Farmaco*. 58, 1023-1028.

[7] Sushama S. Kadam, G. M. Nazeruddin. (2015) *Int. J. Curr. Res. Chem. Pharma. Sci.* 2, 12, 2348-5213.

[8] Sushama S. Kadam, G. M. Nazeruddin. (2016) *World Journal of Pharmaceutical Research*. 5, 2, 1456-1466.

[9] Sushama Kadam, Suryawanshi S.B. Nazeruddin G.M. (2016) *International Journal of Pharmacy and Pharmaceutical Research*. 8, 1, 40-54.

[10] Sushama S. Kadam, Dr. G. M. Nazeruddin. (2015) *International Journal of Pharmaceutical Research and Development* 6, 12, 57-65.

[11] Sushama S. Kadam, Dr. G. M. Nazeruddin, M. Rafique Sarkhwas, S. B. Suryawanshi. (2016) *World Journal of Pharmaceutical Research*. 5, 3, 1456-1466.

[12] Maestro (Version 9.6). 2013 New York, NY: Schrödinger, LLC.

[13] Goodsell, David S., Garrett M. Morris, and Arthur J. Olson. (1996) *Journal of Molecular Recognition*. 9, 1, 1-5.

[14] Bernstein, Frances C. (1978) *Archives of biochemistry and biophysics*. 185, 2, 584-591.

[15] Vanommeslaeghe, Kenno. (2010) "CHARMM general force field: A force field for drug- like molecules compatible with the CHARMM all- atom additive biological force fields." *Journal of computational chemistry*. 31, 4, 671-690.

[16] http://accelrys.com/products/discoverystudio/visualization-download.php.

[17] Morris, Garrett M. (1998) *Journal of computational chemistry*. 19, 14, 1639-1662.

[18] Lipinski, Christopher A. (2004) *Drug Discovery Today. Technologies.* 1, 4, 337-341.

[19] Veber, Daniel F. (2002) *Journal of medicinal chemistry.* 45, 12, 2615-2623.