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Computational Methods of Drug Designing and Docking studies of Synthesized Derivatives of 5-substiuted-1,3,4-Thidiazole-2-amine

Sushama Kadam*[1], G. M. Nazeruddin[2]
[1] Hon. Balasaheb Jadhav Arts,Comm. and Sci.College,Ale,Tal-Junnar, Pune (M.S.) India
[2]Department of Chemistry, Abeda Inamdar College, Pune (M.S.) India

ABSTRACT

A series of 2, 5-disubstitiuted 1,3,4-thidiazole derivatives were synthesized and screened their antimicrobial activities in silico as well as in vitro. In this research article main emphasis on the computational docking methods, with empirical scoring functions are used to predict binding affinities and ligand orientations inside the binding sites of proteins. Topoisomerase targets are widely used as antibacterial activity as per literature review study. In silico and in vitro studies of synthesized derivatives have comparative similar results which can be explained on molecular docking studies and structure activity relationship (SAR). Urea moiety enhances the pharmacological significance of derivatives. It has promoted research work to new direction considering all the factors such as binding sites, TPSA values, Log10P IC50 values and binding energies of the molecules.

Keywords: 2,5-Disubstitiuted 1,3,4-Thidiazole, Computational Docking Methods, SAR, Pharmacological Significance, In Silico, In Vitro

I. INTRODUCTION

James Black famously stated in 2000 that “the best way to discover a new drug is to start with an old one” [1]. Synthesis of novel molecules seems to be creativity of organic chemist. Now a day's researchers have been interested to synthesize analogues of known, proven drugs available in the market. For this Structure based drug discovery (SBDD) is a proven strategy for the rational development of small molecules of therapeutic interest without necessitating its synthesis at the preliminary stages. These are effective beta-lactamase inhibitors and potent ampicillin and cefazolin potentiators against both Gram-positive and Gram-negative beta-lactamase producing bacteria [2]. In this research article synthesized derivatives of 1,3,4-thidiazole in which disubstituted urea moiety acts as bridge between pharmacophore 1,3,4-thidiazole and another selected biologically active molecule. Synthetically and pharmacologically 1,3,4-thidiazole series of compounds have been recognized as a unique class of small compounds with a wide range of applications. 1,3,4-thidiazole derivative which has connecting urea moiety have been shown to be highly effective against various therapeutic activities, such as potent inhibitors of interleukin-8, anthelmintics, antimalarial, anti-HIV, diuretic, analgesic, antibacterial, antifungal, antimicrobial, algaecidal or antiperiphytic agents[3–6]. Literature survey reveals that N,N′-Disubstituted ureas, amides and carbamates are reported as new powerful and stable inhibitors of soluble epoxide hydrolase (SEHs), both in vivo and in vitro[7]. They were determined to be useful for the treatment of hypertension, Raynaud syndrome, respiratory distress syndrome, inflammation, diabetic complications, arthritis and renal type of diseases [8]. A urease is an enzyme that decomposes urea to ammonia and carbonic acid and provides nitrogen to an organism [9-10]. On the other hand, bacterial ureases cause different pharmacological problems, ranging from the development of infectious stones, pathogenesis of encephalopathy, pyelonephritis, urinary catheter encrustation and hepatic coma to peptic ulceration[11–14].

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

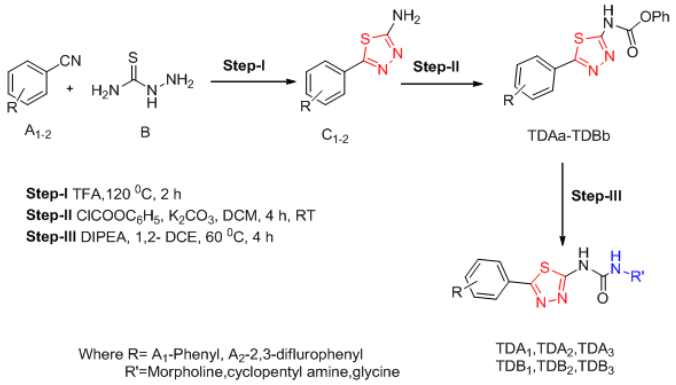
carried out in pursuit of designing some potential novel antimicrobial compounds carrying 1,3,4-Thiadiazoles ring as core nucleus.

II. EXPERIMENTAL

Methodology: Computational methods:
Software and program Schrodinger's maestro visualization program v9.6 [15] is utilized to visualize the receptors, ligand structures, hydrogen bonding network, to calculate length of the bonds and to render images. Chemsktech was used to draw the ligand compounds. Autodock 4.0 [16] is the primary docking program used in this work for the semi-flexible docking studies. Preparation of the ligands and protein receptors in pdbqt file and determination of the grid box size were carried out using Auto-Dock Tools version 1.5.6. Molinspiration, Orissis property explorer program was used to study the ADMET properties of the compounds. The crystal structure of the Topoisomerase IV (PDB ID: 3FV5) was obtained from the Protein Data Bank (PDB) [17]. The crystal structure contained many missing atoms which were supplemented by the repair commands module of AutoDock. Before docking, the protein crystal structure was cleaned by removing the water molecules. H-atoms were added to these target proteins for correct ionization and tautomeric states of amino acid residues. The modified structure so obtained was used for the semi-flexible dockings. The ligand molecules were drawn using chemsketch software. The energy of the ligand molecule and receptors were minimized in Steepest Descent and Conjugate Gradient methods using Accelrys Discovery Studio (Version 4.0, Accelrys Software Inc.) [18]. The minimization methods were carried out with CHARMM force field [19]. Semi-flexible docking Autodock Version 4.0 is used to predict binding pose with associated energy along with the IC_{50} value prediction of the compounds with drug target Topoisomerase IV (PDB ID: 3FV5) for anti-bacterial activity . Protocol followed for carrying out the docking studies using Autodock.

Chemistry:

General Scheme:



III. RESULTS AND DISCUSSION

Docking Studies of Synthesized Derivatives:
The binding energy of synthesized derivatives -4.40 to -6.84 Kcal/mol with critical interactions with residues hydrophobic interactions ALA A:86, GLU A:82, LEU A:89, HIS A:79, LEU A:94, ARG A:93, ILE A:90, SER A:117, VAL A:118, LEU A:91 with a half maximal inhibitory concentration (IC_{50}) value in between 1.97 to 50.0 micro molar. As per the docking study the best compound of docking interactions with Topoisomerase IV (PDB ID: 3FV5) for anti-bacterial activity is depicted below:

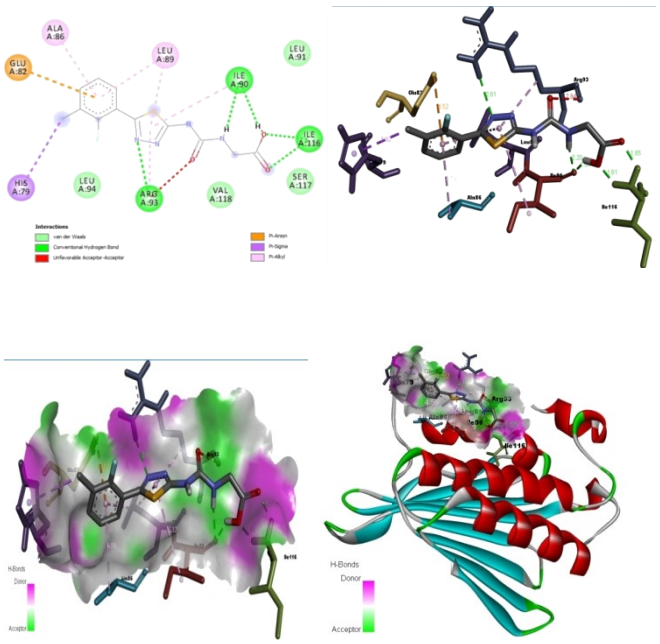


Figure 1. a) represents 2D interactions b) represents 3D interactions c,d) represents surface area interactions with Topoisomerase IV.

All the derivatives of 2, 5-disubstitiuted 1, 3,4-thidiazole were studied in this research work. They have shown to be successfully docking inside the active site of Topoisomerase IV (PDB ID: 3FV5) domain for anti-bacterial activity with a binding energy in a range of -4.40 to -6.84 Kcal/mol. The docking results with some of the FDA approved drug (Cefazoline) was identified and compared with docking studied synthesized derivatives. They are showing better binding energies than these controls.

IV. CONCLUSION

The present investigated derivatives of 2, 5-disubstitiuted 1, 3,4-thidiazole offers the possibility of appropriate additional modifications that could give rise to lead structures with enhanced inhibitory activity and selectivity towards the drug receptor target like Topoisomerase IV. The knowledge gained through this present study could be of high value for computational screening understanding the molecular interaction basis between ligand and receptor.

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