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Research Article

SYNTHESIS, MOLECULAR DOCKING STUDIES AND BIOLOGICAL EVALUATION OF 1,3,4-THIADIAZOLE DERIVATIVES AS ANTIMICROBIAL AGENTS

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A B S T R A C T

A new series of 1,3,4-thiadiazole were synthesized under microwave irradiation. Confirmation of the chemical structure of synthesized compounds was substantiated by IR, NMR and Mass spectroscopy. The derivatives with potent antibacterial activity were subjected to molecular docking studies to investigate the interactions between the active derivatives and amino acid residues existing in the active site to assess their antibacterial potential which docked against receptor crystal structure of Rhodostomin ARLDDL mutant (PDB Code-3UCI). The docking results highlight that fact that the compounds code 3b exhibited good docking score. All the synthesized compounds were screened for antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa, Bacillus cereus and Staphylococcus aureus* by disc diffusion method. Some of the compounds exhibited good antibacterial activity as compared to standard drug. This study provides valuable directions to our ongoing endeavor of rationally designing more potent antimicrobial agents.

INTRODUCTION

Now a days in synthetic chemistry focused on designing new molecule by the lead hybridization with high efficacy and lesser toxicity. The unique chemical properties and biological activity of 1,3,4-thiadiazoles make them as attractive targets for the medicinal chemists. 1,3,4-thiadiazoles nucleus represent an excellent pharmacophore with diverse activities such as antimicrobial, anti-tubercular, anticancer, CNS depressant, antioxidant, antiviral, antidiabetic and hypertensive etc[1]. Heterocyclic are the largest classical divisions of organic chemistry and are of immense importance in biologically and industrially. The chemistry of heterocyclic compounds has been an interesting field of study for a long time. The synthesis of novel thiadiazoles derivatives and investigation of their chemical and biological behaviour have gained more importance in recent decades for biological, medical and agriculture reasons[2]. Now due to the drug resistance and limitations of current uses of antimicrobial drugs, there is need to rapid development and discovery of novel antibacterial agents. Preferably with novel mechanisms of action. Consequently, in recent years, many small synthetic organic molecules with broad spectrum of antimicrobial activity have been reported, among which thiadiazole derivatives proved to have a very interesting inhibitory activity against microorganisms[3-4].

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Microwave-assisted methods have facilitated revolution in organic compound synthesis by which small molecules are built up into large polymers in a fraction of time compared to thermal methods ensuring the acceptance of microwave-assisted irradiation reactions as a powerful tool for accelerating the production of a wide variety of organic molecules. The advent of microwave assisted organic chemistry technology dates back to the mid-1980s and since the 1990s there has been a significant increase in the number of Microwave Assisted Organic Reactions (MAOS) due to the increased benefits associated with the process[5-8]. Promoting microwave-assisted reactions in organic chemistry has increased efficiency, reduced costs, reduced energy consumed making it a sustainable method and is commonly regarded as 'green chemistry' initiatives whose applications are being promoted today to minimize the use of non-renewable resources and polluting solvents, to reduce the production of often toxic secondary products and to regenerate them[9-14]. Microwave irradiation provides an alternative to the conventional methods, for heating or introducing energy into the system. Microwave heating is the best process due to the microwave couple directly with the molecule that are present in the mixture, leading to fast rise in temperature, faster reaction and cleaner chemistry[15-21]. Practical use of molecular docking includes databases for the target search with proper PDB format and the preparation methodology. Ligand as file with PDB. There are different software's to do this (Discovery Studio, etc.,) available from where to make a ligand in PDB Report type. The ability to interact with the target proteins/DNA provided. Docking molecules includes predefined sampling of possible

small molecules to a target ligand conformation in a particular target groove in an order. To determine the optimized structural conformation. This can be done using software scoring function. Hence homology modeling allows for the determination of the tentative structure of unknown structure proteins with strong sequence homology to known structure. This provides a substitute approach to the establishment of the target structure, which is the starting point for the discovery of silico drugs. Molecular docking helps in studying drug/ligand or receptor/protein interactions by identifying the suitable active sites in protein, obtaining the best geometry of ligand receptor complex and calculating the energy of interactions for different ligands to design more effective ligands[22-23].

MATERIALS AND METHODS

Chemistry

All chemicals and solvents were procured from commercial sources, purified and dried using standard procedures from literature whenever required the reagents were purchased from Research laboratory and Merck laboratory Mumbai. The melting points of synthesized compound were determined in open capillary tube method and are uncorrected. Thin layer chromatography was used confirmation of reaction and the purity of the intermediate and the final compounds by applying a single spot on TLC plate (silica gel G) using various solvents such as toluene, acetone, ethanol system. TLC plates were visualized under iodine chamber. IR spectra were recorded on FTIR. Chemical shift are reported in δ unit with respect to TMS as internal standard at Diya lab, Airoli, Mumbai. Mass spectra were recorded on Pe sciex (model no. API 2000) software analyst 1.4.2 mode: Q1MS Q1/AUTO INJECTION from Diya lab, Airoli, Mumbai. The test compounds were synthesized by following procedure.

General Procedure for the Synthesis of Methyl benzoate (1a)

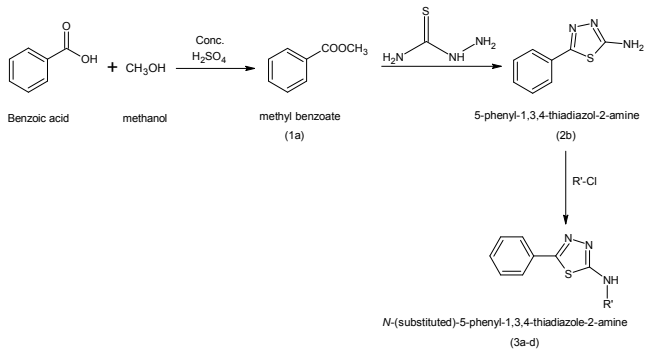
Methyl benzoate was synthesized by adding 0.1 mol of benzoic acid in 20 ml of methanol. and reaction mixture was irradiated in microwave for 15 min at 340 watt. By adding few drops of H_2SO_4 as catalyst. After completion of reaction solid mass was formed and TLC was checked.

General Procedure for Synthesis of 5-phenyl-1,3,4 thiadiazole-2-amine (2b)

In the mixture of above methyl benzoate, thiosemicarbazide (0.1mol) was added. The reaction mixture was irradiated in microwave for 20-30 min at 340 watt.

General Procedure for Synthesis of N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine (3a-d)

In 5-phenyl-1,3,4 thiadiazole-2-amine, add (0.1mol) of substituted nitrobenzene and irradiate this mixture in microwave for 30min at 340 watt. After the completion of the reaction solid mass was formed and TLC was checked, and the product was recrystallized with methanol.



Scheme 1 Synthetic route for the preparation of the title compound (3a-d)

Analytical Data of the N-(substituted)-5-phenyl-1,3,4-thiadiazol-2-amine

3a. N-(2-nitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine

Yield: 82%; m.p. 122-124^{0}C; IR (KBr, cm-1): 1456.91(C=N), 1565.56 (NO_2), 3156.21 (N-N str), 3412.65 (C-NH str), 1H NMR (DMSO-d6, 400MHz) δ: 3.38-3.42 (3H, t, Ar-H), 4.52 (s, 1H, NH), 7.34-7.41 (m, 5H, Ar-H); mass m/z (M+) 298.5.

3b. N-(2,4-dinitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine

Yield: 88%, m.p 131-133^{0}C, IR (KBr, cm-1): 1428.99 (C=N), 3224.14 (N-N Str), 1558.82 (NO_2), 1H NMR (DMSO-d6, 400MHz) δ: 3.24-3.99 (2H, d, Ar-H), 4.35 (s, 1H, NH), 7.29-7.83 (m, 5H, Ar-H); mass m/z (M+) 343.4.

3c. N-(3-nitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine

Yield: 74%, m.p 138-140^{0}C, IR (KBr, cm-1): 1429.42 (C=N), 1584.18 (NO_2), 3258.31 (N-N str), 3604.52 (C-NH str), 1H NMR (DMSO-d6, 400MHz) δ: 3.57-3.64 (3H, t, Ar-H), 4.21 (s, 1H, NH), 7.75-7.88 (m, 5H, Ar-H); mass m/z (M+) 298.4.

3d. N-(4-nitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine

Yield: 69%, m.p 147-149^{0}C, IR (KBr, cm-1): 1429.42 (C=N), 1549.23 (NO_2), 3243.12 (N-N str), 3615.35 (C-NH str), 1H NMR (DMSO-d6, 400MHz) δ: 3.49-3.52 (3H, t, Ar-H), 4.38 (s, 1H, NH), 7.51-7.62 (m, 5H, Ar-H); mass m/z (M+) 298.3.

Molecular Docking Studies

All Molecular docking were performed using the molecular modeling software (VLifeMDS) version 4.1. It provided a facility to dock different ligands in protein binding sites chosen by the user. VLifeMDS has provided rigid (no torsional flexibility for a protein as well as a ligand) and flexible (torsional flexibility to a ligand with a rigid protein) docking of the molecules. The target or receptor was either experimentally known or theoretically generated through homology modelling or knowledge-based protein modelling. The molecular docking tool has been developed to obtain a preferred geometry of interaction of ligand–receptor complexes having minimum interaction energy based on different scoring functions viz. only the dock score, electrostatics and the sum of steric and electrostatic (parameters from the force field). This utility allowed us to screen a set of compounds for the purpose of lead optimization. VLifeMDS uses the Piecewise Linear Pair Wise Potential (PLP), genetic algorithm and Grid algorithms to minimize the interaction energy between the ligand and receptor protein. BioPredicta produces least of inaccurate

poses and 85% of binding models from native co-crystallized structure. The docking studies were carried out using receptor of Crystal structure of Rhodostomin ARLDDL mutant (PDB Code-3UCI) for antibacterial activity. Ligand preparation 2D structure of 1,3,4-thiadiazole derivatives was drawn using chemsketch software. All structures were cleaned and 3D optimized. All the 3D structures were optimized using Merck molecular force field (MMFF) with distance dependent dielectric function and energy gradient of 0.01 kcal/mol A with 10000 numbers of cycles. The conformers for all structures were generated and the low energy conformer for each compound was selected and used for further study. The VLifeMDS 4.1 BioPredicta tool was used to evaluate the binding free energy of the inhibitors against the 3UCI receptor to gain insight into the binding modes of 1,3,4-thiadiazole.

Selection and preparation of ligands and target protein crystal structures

The ligands (1,3,4-thiadiazole) were studied for their binding activities. The 2D structures of were drawn using chemsketch software and converted to 3D conformations. The conformers thus obtained, were optimized (MMFF) till they reached a rms gradient energy of 0.001 kcal/mol. A The crystal structure of Rhodostomin ARLDDL mutant (3UCI; resolution: 1.35Å was extracted from the RCSB Protein Data Bank. All bound water molecules and ligands were removed from the proteins and polar hydrogens were added. The protein structure was energy minimized using Merck molecular force field (MMFF)] with distance dependent dielectric function and energy gradient of 0.01 kcal/mol A with 10000 numbers of cycles.

Identification of cavities

The cavities in the receptor were mapped to assign an appropriate active site. The basic features used to map the cavities were the surface mapping of the receptor and identifying the geometric voids as well as scaling the void for its hydrophobic characteristics using VLife MDS analyze tool. Hence all the cavities that are present in receptor are identified and ranked based on their size and hydrophobic surface area.

Run of docking study

The genetic algorithm (GA) docking of the conformers of each was done by positioning with the active site of cavity using V Life MDS 4.1 package following the standard operating procedures. The complexes were energy minimized using the MMFF method, till they reached an rms gradient of 0.1 kcal/mol. The binding energy in kcal/mol or the ligand–receptor interaction energy obtained after docking the ligands into the enzyme active site can be defined as:

E = InterEq + InterEvdW + IntraEq + IntravdW + IntraEtor
Where,

InterEq= Intermolecular electrostatic energy of complex;
InterEvdW= Intermolecular vdW energy of complex;
IntraEq= Intramolecular electrostatic energy of ligand;
IntraEvdW= Intramolecular vdW energy of ligand and
IntraEtor= Intramolecular torsion energy of ligand
The conformers for all structures were generated and the low energy conformer for each compound was selected and used for further study[24-29].

Antimicrobial Screening

Chemicals

All chemicals and solvent where procured from commercial sources, purified and sterilize using standard procedure from literature whenever required. MacConkey agar and nutrient agar medium used.

Dilution of compound

All the synthesized compound where dissolved in dimethyl sulphoxide [DMSO] so as to get concentration of 100µg/ml and 200µg/ml.

Sterilization of equipment and the chemicals

MacConkey agar, Nutrient agar medium [NO11], Normal saline solution where sterilized in autoclave. At 15 Ibs pressure [121^{0}C] for 150 min. Petri plates, Whatman filter paper, descant cotton swabs where sterilized in oven at 160^{0}C for 2 hours.

Preparation of MacConkey agar slant

MacConkey agar 206 mg was dissolved in 4ml of distilled water, boiled and poured test tube then plugged with cotton and sterilize in autoclave as 15 Ibs pressure 121°C for 15 min. After sterilization the tubes containing the MacConkeys agar were kept in inclined position from 30 min. Then on the surface of slants pure culture staphylococcus aureus where streaked in aseptic condition and incubated and 37°C for the 24 hours.

Preparation of nutrient agar medium slant

Nutrient agar medium 112 mg and agar powder 100 mg was dissolved in 4ml distilled water, boiled and then poured in test tube then plugged with cotton and sterilized in autoclave at 15 Ibs pressure (121°C) for 15 min. After the sterilization the tubes containing the nutrient agar medium were kept in inclined position for 30 min. Then on the surface of slants pure culture of *E.coli* were streaked in aseptic condition and incubated at 37°C for 24 hours.

Preparation of suspension of test bacteria

Using the 24 hours old growth of test bacteria from the slant, suspension of bacteria was made separately in sterile normal saline solution (0.85% NaCl in distilled water) in aseptic condition, to get moderate turbidity. The turbidity of each suspension was compared adjusted with the turbidity of the solution resulting by mixing 0.5 ml of 1.175% of barium chloride and 99.5 mi of 36 N of H_2SO_4.

Method: Disc Diffusion Method

Preparation of culture media for antibacterial sensitivity test

MacConkey agar (50ml) and nutrient agar (100ml) was prepared as per the procedure given for preparation of slants respectively. Then it was sterilized in autoclave at 15lbs pressure (121^{0}C) for 15 min. After sterilization the media was cooled up to 45^{0}C, poured 20-25 ml in sterile Petri plates in aseptic condition and allowed to solidify.

Inoculation of suspension of bacteria on culture media

Sterile, non toxic swab were dipped into the standardized inoculums and then the entire agar surface of the plate was streaked with the swab three times, turning the plate at 60 angles between streaking. Then the streaked inoculum was allowed to dry for 5-15 min with lid. Sterile whatman paper disc dipped separately into the solutions containing synthesized drug (100µg/ml and 200µg/ml) and standard drug ciprofloxacin (100µg/ml and 200µg/ml) in aseptic condition with the help of sterile forceps and placed on the surface of inoculated culture media after which the plates were kept in refrigeration for 30min. for the diffusion of the compound from the paper disc into the culture media. After 30min the plates were incubated at 37^0C for 24 hrs. All the synthesized compounds (3a-d) were observed for antibacterial activity. Observation was recorded in tables by measuring the zone of inhibition in millimeters[30-34].

RESULTS AND DISCUSSION

Chemistry

Methyl benzoate was synthesized by adding of benzoic acid in methanol and reaction mixture was irradiated in microwave for 15 min at 340 watts. By adding few drops of H_2SO_4 as catalyst. After completion of reaction solid mass was formed and TLC was checked. In next step mixture of methyl benzoate, thiosemicarbazide was added. The reaction mixture was irradiated in microwave for 20-30 min. at 340 watt. In 5-phenyl-1,3,4 thiadiazole-2-amine, add substituted nitrobenzene and irradiate this mixture in microwave for 30min at 340 watt. After the completion of the reaction solid mass was formed and further checked by TLC, and the product was recrystallized with methanol. The reaction sequence is shown in Scheme 1. Microwave assisted synthesis is faster, better and safer green chemistry approach for the traditional reactions. The time taken for the synthesis of 1,3,4-thiadiazole is drastically reduced by the microwave assisted synthesis. This technique offers clean, simple, efficient, fast and economic for the synthesis of a number of organic molecules such reaction has new tool in the organic synthesis and highly accelerated rate of the reaction time with an improvement in yield and quality of product. The IR, NMR and mass spectra are fully consistent with the structure.

Molecular docking study

The synthesized derivatives (3a-d) were evaluated for their anti-microbial activity. The dock score of compounds (3a-d) are shown in table and in that compound code 3b dock score is found to be -44.01 shown minimum dock score than other compounds. As we compared result of compound 3b to the literature this docking score indicated that designed compounds have good binding affinity for binding to receptor (PDB Code-3UCI). The best pose obtained by docking results is reported (fig 2) where main interaction between ligand and receptor can be observed. All designed compound adopt a very similar conformation at binding pocket, showing Hydrogenated bond interaction with amino acid of ARG56A, Hydrophobic interaction with amino acid of PRO65A, ARG56A, Vander Waals binding with amino acid of PRO65A, ARG56A, LEU53A, ASP52A Which shown by 2D representation diagram (fig 1). Superimpose image of 3b compound with receptor show in diagram (fig 3).

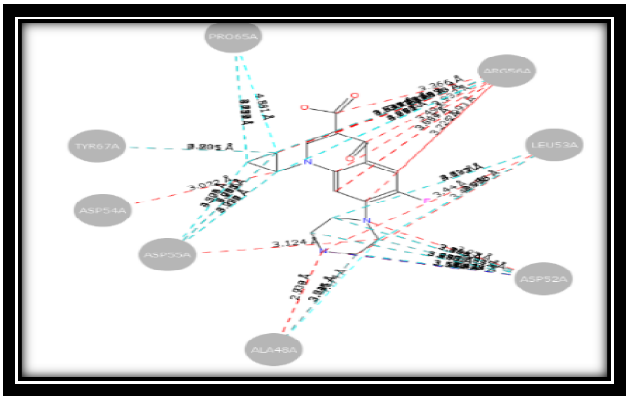


Figure 1 2D Representation of Docking Poses of Compound 3b

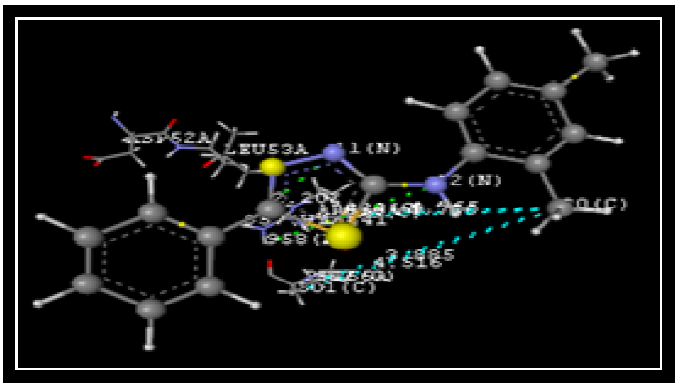


Figure 2 3D Representation of Docking Poses of Compound 3b

Figure 3 Superimpose Image Representation of Docking Poses of Compound 3b

Table 1 Antimicrobial activity result of molecular docking studies by using GRIP Batch docking

Sr. no	Compound code	Docking score (Kcal/mol)
1	3a	-34.62
2	3b	**-44.01**
3	3c	-32.54
4	3d	-39.03
5	ciprofloxacin	**-48.22**

Antimicrobial activity

Antibacterial activity of the newly synthesized compounds (3a-d) was evaluated by the disc diffusion method against Escherichia coli, Pseudomonas aeruginosa, Bacillus cereus and Staphylococcus aureus strains of bacteria. Compound code b were found to be highly active against all the tested strains of bacteria showing the broadest spectrum of antibacterial activity when compared with reference drugs ciprofloxacin.

Table 2: Antibacterial screening result of synthesized compounds measuring the zone of inhibition in millimeter

Sr. no	Compound code	Diameter of zone of inhibition (mm)							
		E. coli		P. aeruginosa		B. cereus		S. aureus	
		100 µg/ml	200 µg/ml	100 µg/ml	200 µg/ml	100 µg/ml	200 µg/ml	100 µg/ml	200 µg/ml
1	3a	9	11	12	15	9	14	10	15
2	3b	12	16	14	18	14	22	17	19
3	3c	7	12	9	12	8	13	9	11
4	3d	10	15	13	15	10	16	12	17
5	3e	9	13	11	14	6	11	10	15
6	3f	6	14	7	10	8	13	9	10
7	ciprofloxacin	13	18	15	21	12	19	11	22

CONCLUSION

All the synthesized derivatives were synthesized by microwave method as green chemistry approach. Synthesis of compounds by the microwave method gives more yield and requires less time to complete the reaction. So, the microwave synthesis better method. The molecular docking studies further help in understanding the various interactions between the ligands and enzyme active sites in detail and thereby help to design novel potent inhibitor. The docking experiments were carried out for all the synthesized compounds and compared the docking score with reference compound ciprofloxacin. The compounds code 3b showed higher binding score, which are further attributed to the anticancer activity of these compound. All the synthesized subjected for antimicrobial activity among all, the compound code 3b and 3d had good antimicrobial activity.

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