Microwave Assisted Synthesis, Molecular Docking Studies of New N-{[5-(Phenyl)-1,3,4-Thiadiazole-2-Yl]Carbamothioyl} Derivatives As Potent Antimicrobial Agents

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Abstract

Series of 1,3,4-thiadiazole derivatives were synthesized under microwave irradiation and evaluated for antimicrobial activity. Thiadiazole belong to the classes of nitrogen-sulfur heterocycles with extensive application as structural units of biologically active molecules and as useful intermediates in medicinal chemistry. The potency of the thiadiazole nucleus is demonstrated by the drugs currently used. 1,3,4-thiadiazoles and some of their derivatives are extensively studied because of their broad spectrum of pharmacological activities. Many of the reported 1,3,4-thiadiazole derivatives can be considered as lead compounds for drug synthesis, and several of them have demonstrated higher antimicrobial activity in comparison to standard drugs. Furthermore, taking into account the reactivity of the amine group in the derivatization process, All the compounds have been evaluated for their antimicrobial activities against several in-vitro strains of microbes and show significant activity. All the synthesized compounds were tested for in-vitro antibacterial (against Escherichia coli, Bacillus substilis, and Staphylococcus aureus) and antifungal activity (against Aspergillus Niger). Compound code 3d showed better inhibition as compared to the standard Ciprofloxacin and 3d showed good inhibition as compared to the standard Ketoconazole.

Keywords: *1,3,4-thiadiazole, Microwave method, Molecular docking, Antibacterial activity, Antifungal activity.*

1. INTRODUCTION

1,3,4-thiadiazole and its derivatives continue to be of great interest to a large number of researchers[1]. 1,3,4-thiadiazole is one of the most potent heterocyclic containing carbonic anhydrase and antibacterial inhibitor from the natural and synthetic origin. Till date many 1,3,4-thiadiazole nucleus containing drugs are available in the market such as acetazolamide, methazolamide, megazol[2]. 1,3,4-thiadiazole exhibit divers biological activities possibly due to the presence of =N–C–S moiety. Moreover, some bi-heterocyclic compounds incorporating 1,3,4-thiadiazole or 1,2,4triazole ring have been produced as antimicrobial agents. The cyclization of the compounds having thiosemicarbazide structure has shown to be an excellent strategy for the synthesis of 1,2,4-triazole, 1,3,4-thiadiazole, 1,3,4-oxadiazole and or 1,3,4-triazine derivatives[3]. Heterocycles bearing a symmetrical triazole or 1,3,4-thiadiazole moieties, represent an interesting class of compounds possessing a wide spectrum of biological activities such as anti-inflammatory, antiviral and antimicrobial properties. It has also been reported that derivatives of 1,2,4-triazole and 1,3,4-thiadiazole condensed nucleus systems exert diverse pharmacological activities such as anti-inflammatory, antitumor, antifungal and antibacterial[4]. A large no of thiadiazoles have been patented in the medicine field for the treatment of a wide variety of diseases and some of them have become commercial products compound in medicinal chemistry because of its therapeutic value .it is also known to have unique antibacterial and anti-inflammatory activities[5]. The thiazole moiety belongs to an important class of N and S- containing heterocycles and when attached to a thiourea functional group forms the building block for pharmaceutical agents. They exhibit a wide spectrum of pharmaceutical activity[6]. Thiadiazole is a very multifaceted moiety that shows a wide range of pharmacological activity. Thiadiazoles are bioisosteres of heterocycles such as oxadiazole, oxazole and benzene. Substitution of thiadiazoles with their bioisosteres increases activity[7-10]. Designing new compounds in order to deal with resistant bacteria has become one of the most significant and great areas of antibacterial research today[11-14]. Because the resistance of pathogenic bacteria toward common and available antimicrobial drugs is quickly becoming a major worldwide problem, so the discovery of new and potent antibacterial agent is more challenging and demanding for pharmacists and chemists nowadays. Synthesis of any chemical entities is major bottleneck in the drug discovery[15-16]. Conventional methods for different chemical synthesis is very well documented and practiced. The methods for synthesis of organic compounds had continuously modified from the last 10 years. The application of green chemistry principles and practices renders regulation, control, clean-up, and remediation of the environment. In year 1855 Robert Bunsen invented the burner acts as energy source for heating reaction vessel this was latter superseded by isomental, oil bath but the drawback of the heating though method remains the same[17-20]. Microwave Assisted Organic Synthesis had developed in now years which has been considered superior to traditional

heating. Microwave assisted organic synthesis has as a new “lead” in the organic synthesis. The 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. Important advantage of this technology includes highly accelerated rate of the reaction time with an improvement in yield and quality of product[21-24]. This technique is considered as important approach toward green chemistry because this technique is more environments friendly and this technology is used in the laboratory and has the potential to have a large impact on the fields of combinatorial chemistry, screening, medicinal chemistry and drug development. Conventional method of organic synthesis usually requires longer heating time, tedious apparatus setup which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution. Computational studies are the crucial steps in the drug designing. Docking study is the computational routine to determine probable binding manners of a ligand to the dynamic site of a receptor. It makes an image of the dynamic site with interaction points known as grid. Then it fits the ligand in the binding site either by grid search or energy search. Due to failure of ADME so it necessary to perform docking studies before pharmacological activity. An outbreak of coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) raises an unparalleled challenge in the discovery of appropriate drugs for prevention and treatment. Given the rapid pace of scientific research and clinical data produced by the large number of people quickly infected with SARS-CoV-2, clinicians need reliable proof of successful medical care for this infection as in intial stage with help of molecular docking software it is easy to do in-silico study[25-35]. The chemical modification of drug delivery system for protein and peptide drugs is important in improving both enzymatic stability and membrane permeations can help to have good biological activity from any heterocyclic compound modification. Someday soon, you might be making your own medicines at home. That’s because researchers have tailored a 3D printer to synthesize pharmaceuticals and other chemicals from simple, widely available starting compounds fed into a series[36-44].

2. MATERIALS AND METHODS

Chemistry

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

5-(3,5-dinitrophenyl)-1,3,4-thiadiazole-2-amine was prepared by dissolving 0.01 mol of 3,5-dinitro benzoic acid in 35 ml of methanol . Carboxylic acid group is esterified with methanol the reaction irradiated the mixture for 15 min by adding few drops of H_2SO_4 as catalyst. The final product was obtained as a no aqueous liquid which was continued for the next step for the preparation of N-{[5-(3,5dinitrophenyl)-1,3,4-thiadiazole -2-yl] carbamothioyl} derivatives).

General Procedure for the Synthesis of Synthesis of substituted benzoyl isothiocyanate (2)

The mixture of Substituted benzoyl chloride and ammonium thiocyanate was irradiated in microwave for 10 min in presence of acetone. The reaction mixture was then cooled and evaporated. The solid precipitate was obtained, dried and recrystallized from methanol.

General Procedure for the Synthesis of substituted N-{[5-(phenyl)-1,3,4-thiadiazole -2-yl] carbamothioyl} derivatives (3)

A solution of 0.01 mole of compound 1 and compound 2 was irradiated in microwave in the for 20 min. The precipitate was obtain and washed with water and cleaned with boiling ethanol and recrystallized from ethanol.

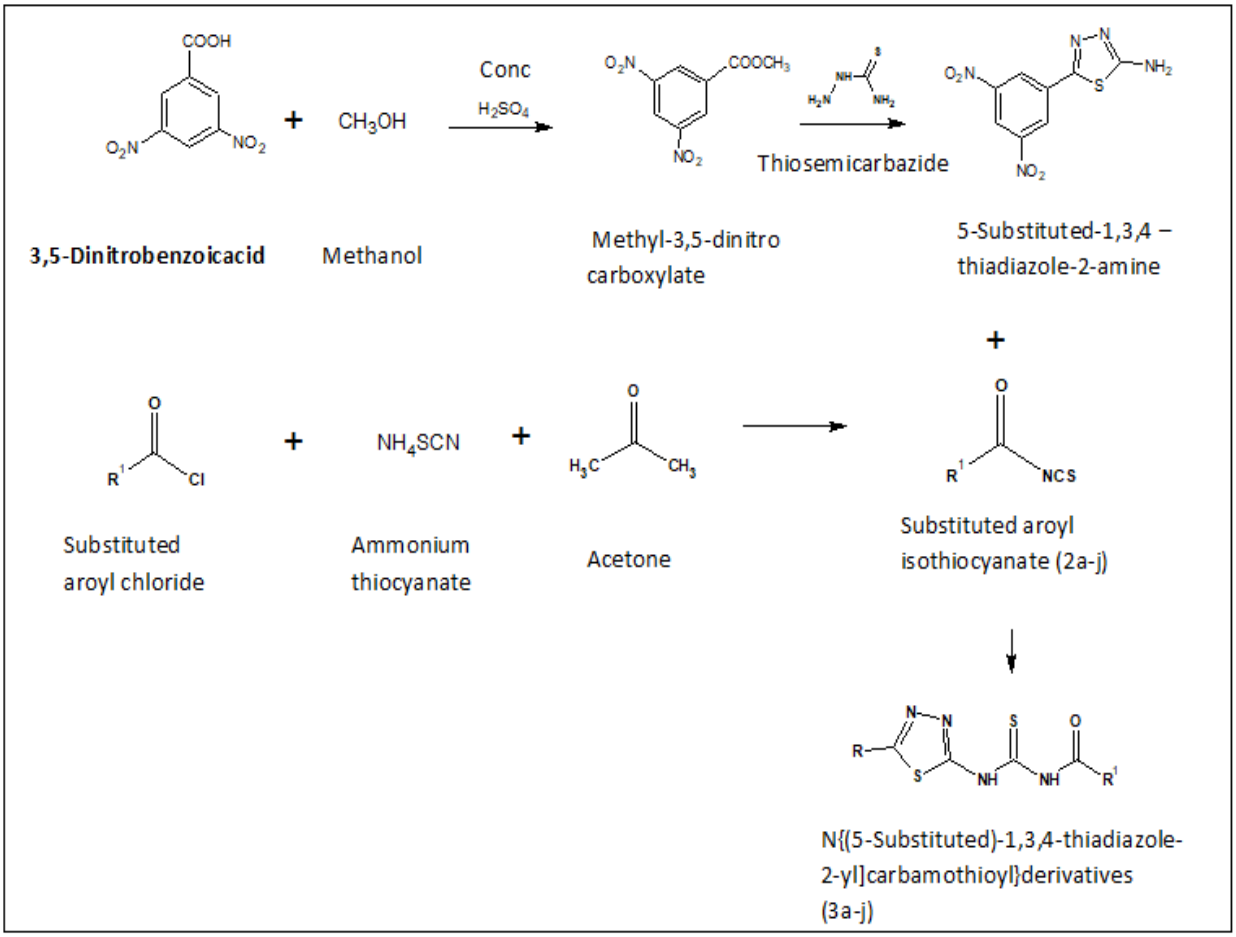


Fig 1. Scheme of work

Table 1. Physicochemical characteristic of substituted N-{[5-(phenyl)-1,3,4-thiadiazole -2-yl] carbamothioyl} derivatives (3a-j)

Compound code	R'	Melting Point (^{0}C)	Percentage yield (%)	R_f value
3a	Phenyl	102- 104	82%	0.94
3b	2-chlorophenyl	144-146	72%	0.84
3c	4-chlorophenyl	152- 154	76%	0.76
3d	2,4-chlorophenyl	124-126	79%	0.74
3e	Methoxyphenyl	128- 130	88%	0.78
3f	4-fluorophenyl	118- 120	73%	0.83
3g	4-nitro Phenyl	128-130	81%	0.92
3h	Thionyl	196-198	68%	0.82
3i	Pivolyl	144-146	78%	0.84
3j	Chloroacetyl chloride	132-134	82%	0.78

Molecular Docking Study

The docking study was performed using the VLife MDS 4.3. All the ten 5-(3,5-dinitrophenyl)-1,3,4-thiadiazole-2-amine derivatives. VLifeMDS provided both 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 knowledge-based protein modeling or homology modeling. The molecular docking tool has been developed to get a preferred geometry of interaction of ligand–receptor complexes having minimum interaction energy supported different scoring functions viz. only electrostatics, the sum of steric and electrostatic (parameters from the force field), and the dock score. This utility allowed us to screen a set of compounds for lead optimization. VLifeMDS uses the genetic algorithm, Piecewise Linear Pairwise

Potential (PLP) and Grid algorithms to minimize the interaction energy between the ligand and receptor protein.

Selection of receptor

The crystal structure of Rhodostomin ARLDDL mutant (3UCI; resolution: 1.35Å was extracted from the RCSB Protein Data Bank and water molecules in the crystal structure were deleted. The optimized receptor was then saved as mol file and used for docking simulation.

Ligand Preparation

The 2D structures of the compounds were built and then converted into the 3D. The 3D structures were then energetically minimized up to the rms gradient of 0.01 using MMFF.

Identification of Cavities

By using cavity determination option of software, cavities of enzyme were determined. The cavities in the receptor were mapped to assign an appropriate active site. The basic feature 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. Hence, all the cavities that are present in receptor are identifed and ranked based on their size and hydrophobic surface area. considering the dimensions and hydrophobic surface area, cavity with found to be the best void as an active site.

Scoring Function

Distinction of good or bad docked conformation is based on scoring or fitness function. MDS uses fitness functions on only electrostatic and both steric and electrostatic interactions between receptor ligand as well as dock score scoring function. The dock score compute binding affinity of a given protein-ligand complex with known 3D structure[45-49].

Antimicrobial Evaluation

Antibacterial activity

The synthesized compounds were screened for In vitro Antibacterial activity by cup plate method. This method is used for determining the selective effectiveness of the Antibacterial activity. The standard antibiotic selected for study of the Antibacterial activity is ciprofloxacin. In the present study Antibacterial activity of the synthesized compounds was determined in vitro by using cup plate method against S. aureus (ATCC 19433) and E. coli (ATCC 25922) at 100 µg/mL in the nutrient agar media.

Standard antibiotic ciprofloxacin was used as reference drug at 50 mg/mL concentration.This method is used for determining the selective effectiveness of the antibacterial activity. The standard antibiotic selected for study of the antibacterial activity is Ciprofloxacin.

Antifungal activity

The synthesized compounds were screened for In vitro Antifungal activity by cup plate method. This method is used for determining the selective effectiveness of the antifungal activity. The standard antibiotic selected for study of the antifungal activity is fluconazole. In the present study Aspergillus niger (ATCC 1015) were used. the antifungal activity of the synthesized compounds was determined in vitro by cup plate method against fungal strain C. albicans (ATCC 2091) at 100 µg/mL concentrations in sabouraud dextrose medium. Fluconazole was used as standard drug at 50 µg/mL concentrations. Solutions of required concentrations of test compounds were prepared by dissolving the compounds in DMF. The minimum inhibitory concentration (MIC) obtained for the test compounds and reference drugs are reported in Table. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of the compounds that inhibited visible growth of microorganisms on the plate[50-55].

3. RESULTS AND DISCUSSION

Chemistry

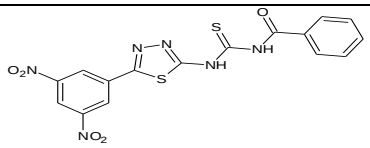
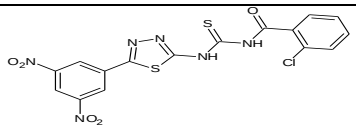
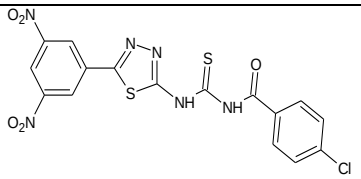
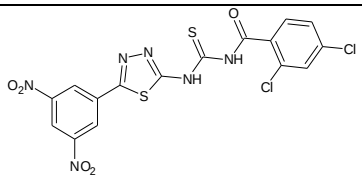
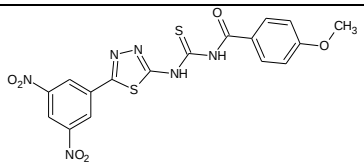
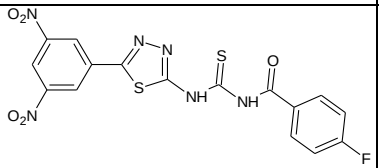
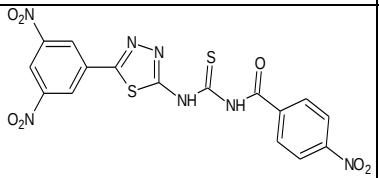
5-(3,5-dinitrophenyl)-1,3,4-thiadiazole-2-amine was prepared by dissolving 3,5-dinitro benzoic acid in methanol . Carboxylic acid group is esterified with methanol the reaction irradiated the mixture for 15 min by adding few drops of H_2SO_4 as catalyst. The final product was obtained as a no aqueous liquid which was continued for the next step for the preparation of N-{[5-(3,5-dinitrophenyl)-1,3,4-thiadiazole-2-yl] carbamothioyl} derivatives). Then mixture of Substituted benzoyl chloride and ammonium thiocyanate was irradiated in microwave for 10 min in presence of acetone. The reaction mixture was then cooled and evaporated. The solid precipitate was obtained, dried and recrystallized from methanol. In next step, a solution of compound 1 and compound 2 was irradiated in microwave. The precipitate was obtain and washed with water and cleaned with boiling ethanol and recrystallized from ethanol.

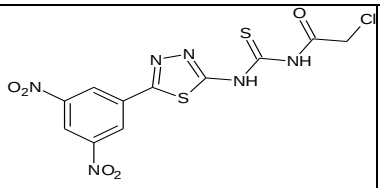
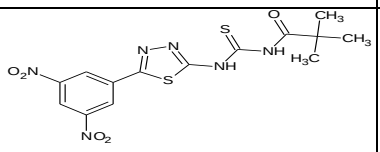
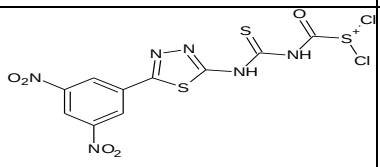
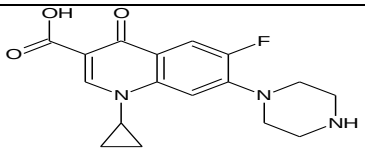
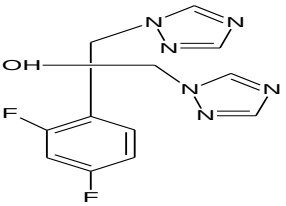
Molecular Docking Study

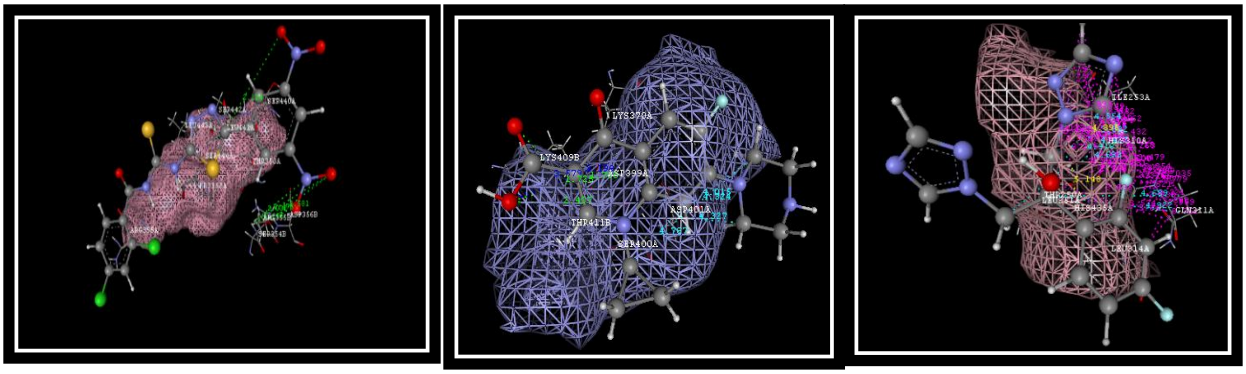
Docking is a method which used to predicts the preferred orientation of one ligand when bound in an active site to form a stable complex. Molecular docking is computational modeling of the structure of complexes formed by two or more interacting molecules. It is frequently used for prediction of the

binding orientation of the small molecule drug candidates to their protein targets in order to in turn prediction the affinity and activity of the small molecule. It used to study the biological interactions between two macromolecules (protein/protein or DNA /protein) or between ligand and the receptors of macromolecules. Docking methodologies employed by Vlife MDS. All designed compound adopt a very similar conformation at binding pocket, showing Hydrogen bond interaction with amino acid of SER442A, ARG355B, ASP356B Vander Waals binding with amino acid of THR350A, THR350A, PRO352A, ARG355A, SER440A, LEU441A. Which shown by 2D representation diagram. The dock score of standard drug ciprofloxacin was found be -46.37 and fluconazole was found -44.85.

Table 2. Antimicrobial activity result of molecular docking studies by using GRIP Batch docking

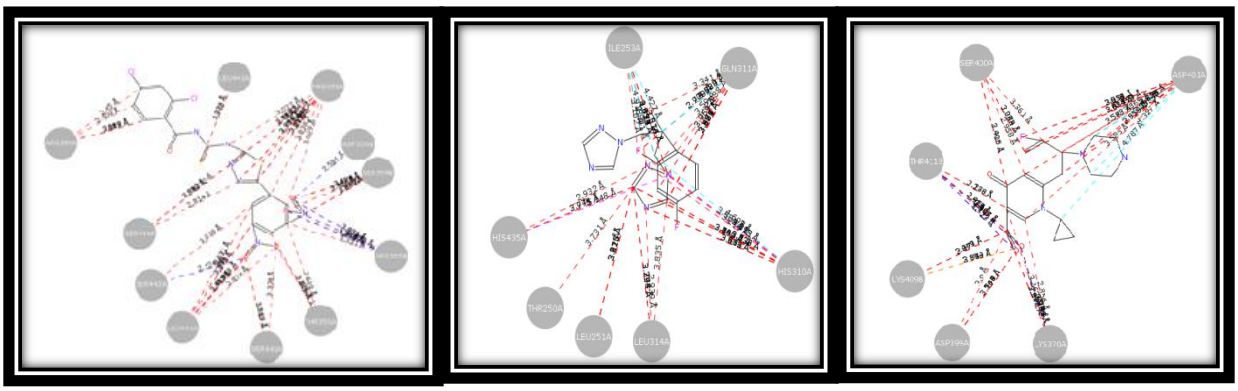
Sr. no	Compound code	Compound structure	Final energy	Final GRMS	Dock score
1	3a		81.8439	0.9965	-51.87
2	3b		79.7563	0.9426	-51.14
3	3c		82.4064	0.7295	-54.45
4	3d		77.9347	0.8905	-56.52
5	3e		91.3182	0.9718	-50.74
6	3f		81.2577	0.7305	-56.06
7	3g		100.9015	0.9408	-53.33

8	3h		65.1425	0.5545	-38.42
9	3i		67.7756	0.7084	-44.02
10	3j		69.4327	0.8093	-41.00
11	Standard ciprofloxacin		83.1066	0.6270	-46.37
12	Standard Fluconazole		42.1084	0.9661	-44.853



Compound code 3d Antibacterial Standard Antifungal Standard

Fig 2. Docking Poses of compound 3d and standard

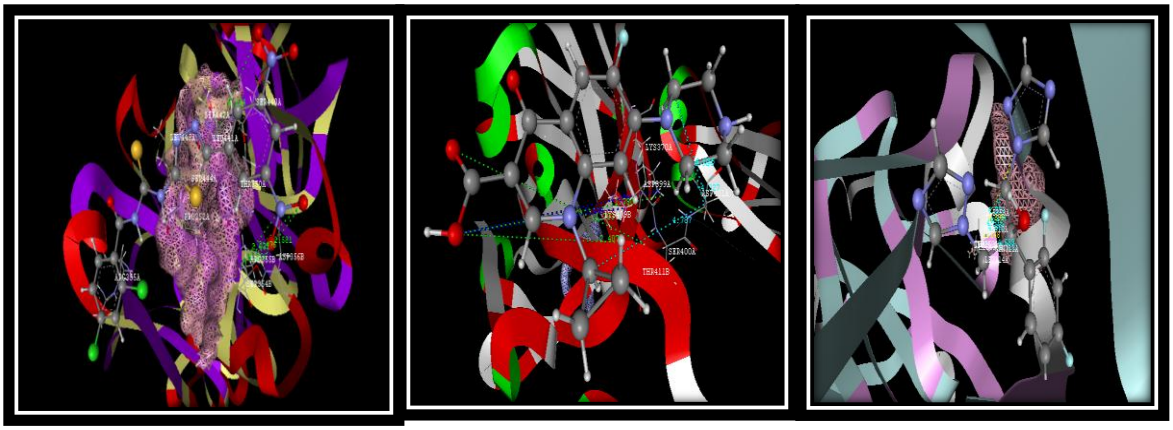


Compound code 3d Antibacterial Standard Antifungal Standard

Fig 3. 2D representation of docking poses of compound 3d

Table 3. Data for interaction of compound 3d with amino acid

Amino acid	Atom of ligand	Distance	Type of interaction
SER442A	29O	2.124	HYDROGENBOND INTERACTION
ARG355B	19N	2.032	HYDROGENBOND INTERACTION
ASP356B	31O	2.581	HYDROGENBOND INTERACTION
THR350A	4C	3.699	VDW INTERACTION
THR350A	6C	3.697	VDW INTERACTION
PRO352A	7C	3.774	VDW INTERACTION
ARG355A	22C	3.879	VDW INTERACTION
SER440A	29O	3.687	VDW INTERACTION
LEU441A	5C	3.878	VDW INTERACTION



Compound code 3d Antibacterial Standard Antifungal Standard

Fig 4. Superimpose image representation of docking poses of compound 3d and standard drug

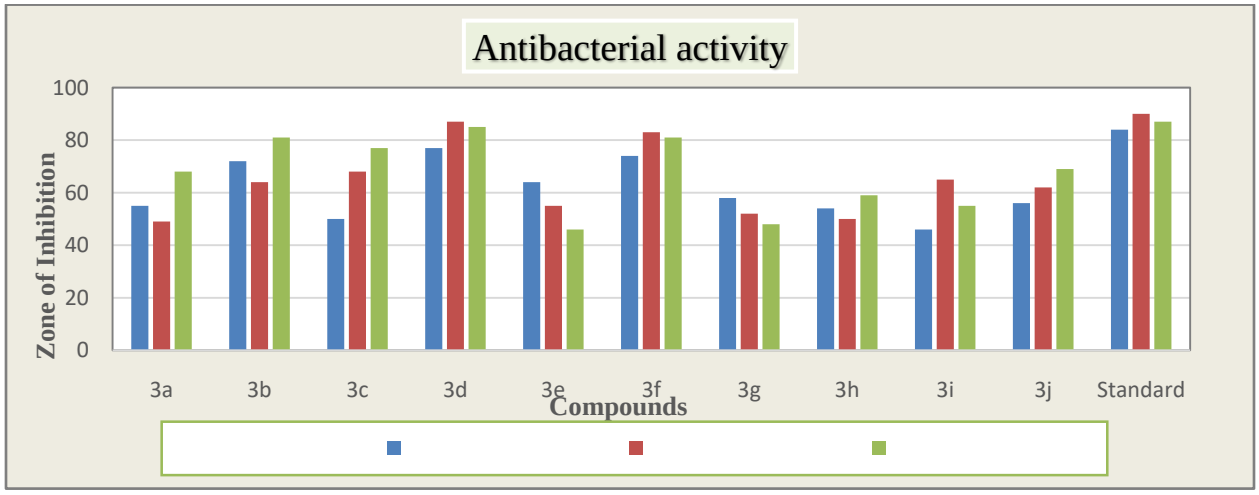
Antibacterial activity of the newly synthesized compounds (3a-f) was evaluated by the disc diffusion method against Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus strains of bacteria. Compound code 3d were found to be highly active against all the tested strains of bacteria showing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

Antimicrobial Evaluation

Present study was designed to synthesize and evaluate antibacterial activity and anti-fungal activity of several substituted 2,5-disubstituted 1,3,4-thiadiazole derivatives. Antibacterial and antifungal activities were measured by cup plate method. % inhibition for antibacterial activity revealed that some of the test compounds like 3d showed better inhibition as compared to the standard ciprofloxacin. against all the three bacterial strains Escherichia coli, Bacillus subtilis and Staphylococcus aureus. Antifungal screening revealed that the test compounds showed good to moderate activity against Aspergillus niger. % inhibition for antifungal activity revealed that some of the test compounds code 3d showed good inhibition as compared to the standard fluconazole.

Table 4. % Inhibition of compounds 3a-j against various bacteria

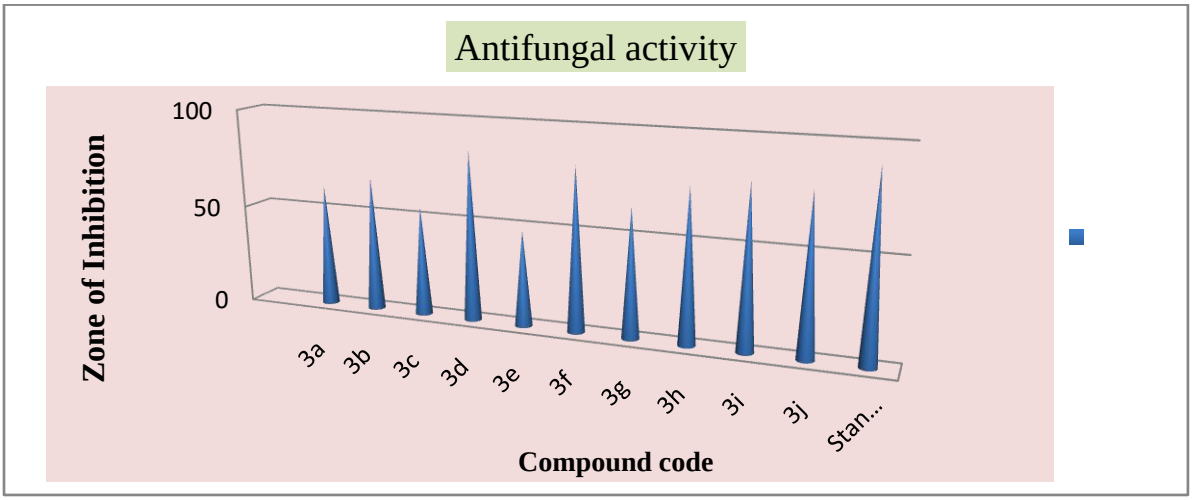
Compound code	Conc. µg/ml	% inhibition		
		E. coli	*B. subtilis*	*S. aureus*
3a	100	55	49	68
3b	100	72	64	81
3c	100	50	68	77
3d	100	77	87	85
3e	100	64	55	46
3f	100	74	83	81
3g	100	58	52	48
3h	100	54	50	59
3i	100	46	65	55
3j	100	56	62	69
Standard	50	84	90	87



Graph 1. Antibacterial Activity of synthesized compounds

Table 5. Inhibition of compounds 3a-j against A. niger

Compound code	Conc. µg/ml	% inhibition A. niger
3a	100	62
3b	100	68
3c	100	55
3d	100	85
3e	100	48
3f	100	82
3g	100	64
3h	100	76
3i	100	80
3j	100	78
Standard	50	91



Graph 2. Antifungal Activity of synthesized compounds

4. CONCLUSION

A series of ten thiadiazole derivatives were designed and synthesized using appropriate synthetic Scheme. The synthesized compounds were purified and well characterized by TLC. Compound code 3d showed better anti-bacterial and compound code 3d showed better anti-fungal activity, when compared with ciprofloxacin and fluconazole. Our present study makes it an interesting compound when compared to the present therapeutic agents and are considered the candidates to investigate further for the same purpose.

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