In silico and antibacterial studies of Thiadiazole and Triazole linked 1,8-Napthyridine derivatives

Bhargavi Lakshmi J.[1], Bhaskar Pittala[2], Laxminarayana Eppakayala[2*], Paramesh Donta[2] and Chittireddy Venkata Ramana Reddy[3,4]

1. Geethanjali College of Engineering and Technology, Keesara, Rangareddy-501301, INDIA
2. Sreenidhi Institute of Science and Technology (Autonomous) Yamnampet, Ghatkesar, Hyderabad-501301, INDIA
3. Jawaharlal Nehru Technological University, Hyderabad, Kukatpally, Hyderabad-500 085, INDIA
4. Vignana Bharathi Institute of Technology, Aushapur, Ghatkesar, Hyderabad, 501301, INDIA

*elxnkits@yahoo.co.in

Abstract

A series of thiadiazole and triazole linked 1,8-napthyridine derivatives were screened for antibacterial activity and docking studies were performed. Compared to the tetracycline, all these compounds have shown good to moderate antibacterial activity against Staphylococcus aureus, Bacillus cereus, Micrococcus luteus, Klebsiella pneumonia, Salmonella paratyphi A and Escherichia coli.

Keywords: Synthesis, Naphthyridine, Thiazolidine, Triazole, Antibacterial activity, Docking studies.

Introduction

Heterocyclic derivatives accounted for the majority of organic chemistry research and development during the last few decades. Given their significance for biology and industry, attempts have been made to improve these heterocycles quality of life in comparison to other substances. Approximately half of the 20 million chemical compounds that were found by the end of the second millennium, are heterocyclic and more than two thirds are completely or partly aromatic. The development of novel, effective medications that successfully enter the market and complete clinical trials is crucial. It is important to realize right away that the term 'drug discovery' in pharmaceutical research and development is not always clear. It can be defined for example, with a number of alternatives for each category, utilizing programmatic, organizational, or even both ways.

As a result, it is crucial to define the variability precisely and to grasp it first Naphthyridine derivatives are heterocyclic analogues of naphthalenes that contain nitrogen. The group of diazanaphtalenes that make up the pyrido pyridines, also known as benzodiazines or naphthyridines, has one nitrogen atom in each ring in the bridge head position. 1,8-naptharidines moiety assumed enormous significance as a pharmacophore with its presence in various active pharmaceutical ingredients. Several naphthyridine derivatives find applications as promising drugs in different therapeutic categories as analagecis[3,18], anti-biotics[14], anti-cytotoxic[7], anti-malarial[16], anti-bacterial[9,11] and anti-tumor[8,22] etc.1, 2, 4-triazole is a five-membered heterocyclic molecule comprising of two carbons and three nitrogens.

There are two tautomeric variants of it: 1H and 4H-1. 2, 4-triazole is regarded as a nucleus with significant pharmacological importance. Literature study reveals that 1, 2, 4-triazoles have a broad range of biological actions. Particularly, they are well known for their anti-tumor[10], anti-cancer[21], anti-fungal[12], anti-diabatic[20], cytotoxic[6] and anti-microbial activites[17]. One of the most significant and well-known heterocyclic nuclei, the 1,3,4-thiadiazole nucleus is a common and essential component of many natural products and pharmaceuticals. Thiadiazole nucleus is present as a core structural component in an array of drug categories such as anti-cancer[5,19], anti fungal[23], antimicrobial[2], anti-inflammatory[1], analgesic[1], antiviral agents[4].

The broad and potent activities of thiadiazole and their derivatives have established them as pharmacologically significant scaffolds. In this study, an attempt has been made with recent research findings on this nucleus, to review the structural modifications on different thiadiazole derivatives for various pharmacological activities.

According to antibacterial screening, all of the newly synthesized 1,8 naphthyridine derivatives of thiadiazole and triazole showed strong antibacterial activity against *Staphylococcus aureus*, *Bacillus cereus*, *Micrococcus luteus*, *Klebsiella pneumonia*, *Salmonella paratyphi A* and *Escherichia coli.* New naphthyridines, thiadiazole and triazole derivatives have recently been synthesized quickly and efficiently. Its antibacterial activity against Gram *E.coli* was superior to that of any other compound when measured against the antibiotic *streptomycin.* Derivatives of thiadiazol and triazole are important to industry because of their diverse biological activities. Researchers are always drawn to thiadiazol and triazole derivatives due to their effectiveness in a variety of pharmacological applications.

Material and Methods

1,8-naphthyridines derivatives have been extensively studied as biologically active compounds possessing a wide spectrum of activities. It was therefore considered worthwhile to evaluate the present 1,8-naphthyridine derivatives synthesized for their possible antibacterial activities.

The present study has aimed at antimicrobial activity of newly synthesized 1,8-naphthyridine containing carbaldehydes, methylene hydrazines, thiadiazol amines and triazole thiols. The antibacterial effect of compounds was

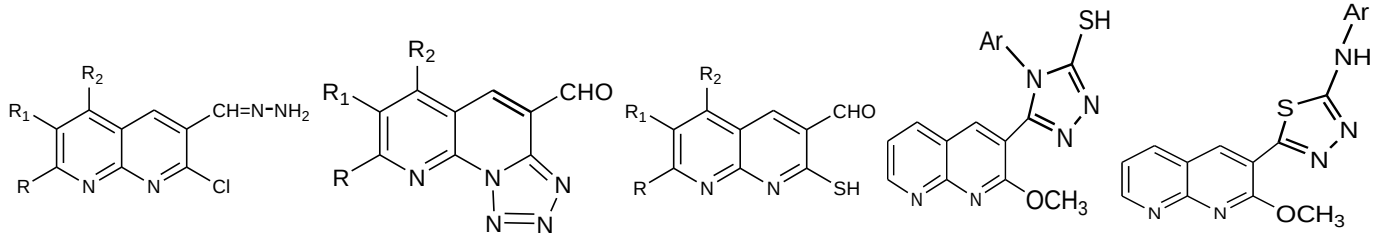
evaluated using well-diffusion method. Their possible antibacterial activities are given in table 1 and table 2.

Molecular Docking: Synthesized compound molecular docking was conducted for DNA gyrase B (ID: 4URO) using structures obtained from the protein data bank. Ligands and protein structures were prepared independently. Auto Dock v4.0 software was employed for molecular docking to the binding site, with a grid box generated around the co-crystallized ligand[15]. The best-scoring pose and complex were constructed and visualized in Discovery Studio software. 2D and 3D images were generated in Discovery Studio.

Results and Discussion

The focus of the current study is on the investigation and creation of highly effective heterocyclic compounds with potential applications in medicine. Our research involves the synthesis of naphthyridine derivatives using various substituents. According to findings, compounds 15, 17, 25, 26, 49 and 50 exhibit superior antibacterial action against the nearly equal to the standard drug.

However, a few molecules that share the same functional group also exhibited strong action. Gram negative strains have greater susceptibility to drugs that have been evaluated. The inhibitory zone was displayed in mm.



(1-9) **(10-18)** **(19-27)** **(28-40)** **(41-53)**

Fig. 1: Structure of compounds with various substituents

Table 1
Effect of the synthesized compounds with various substituents (1-27) on six types of bacteria.

Compound No.	R/ R_1/R_2	*S. aureus*	*B. cereus*	*M. luteus*	*K. pneumoniae*	*S. paratyphi A*	*E. coli*
1	H/H/H	4	3	7	2	1	2
2	NH_2/H/H	6	2	8	3	1	3
3	Cl/H/H	8	3	8	7	2	3
4	CH_3/H/H	6	4	1	1	1	2
5	H/CH_3/H	9	9	8	4	2	2
6	H/Cl/H	9	2	6	2	1	2
7	H/Br/H	11	9	6	4	2	3
8	H/H/CH_3	10	11	14	9	2	3
9	Br/H/H	6	4	5	6	1	2
10	H/H/H	8	7	7	6	1	1
11	NH_2/H/H	12	11	13	7	2	3
12	Cl/H/H	6	4	1	1	1	2
13	CH_3/H/H	17	7	5	1	6	13
14	H/CH_3/H	1	8	3	2	1	1
15	H/Cl/H	17	1	10	11	1	9
16	H/Br/H	2	4	8	6	8	6
17	H/H/CH_3	9	10	10	7	11	12
18	Br/H/H	9	8	5	8	8	10
19	H/H/H	5	6	4	1	1	2
20	NH_2/H/H	2	5	1	2	1	1
21	Cl/H/H	1	8	2	1	1	3
22	CH_3/H/H	2	10	2	1	2	3
23	H/CH_3/H	1	12	1	1	2	3
24	H/Cl/H	4	2	1	2	6	4
25	H/Br/H	1	11	12	11	12	5
26	H/H/CH_3	2	10	13	11	10	2
27	Br/H/H	5	6	2	4	5	12
Tetracycline		25	20	17	18	16	15

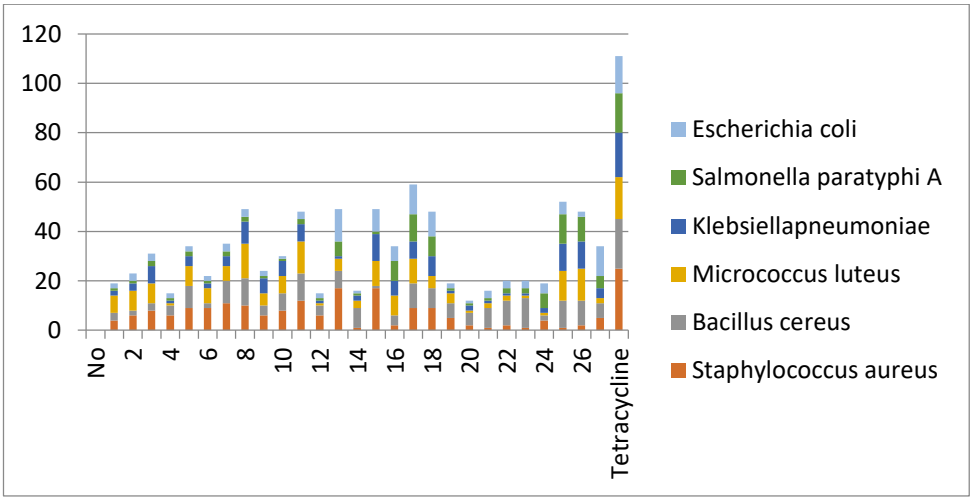


Figure 2: The graph showing the effect of the synthesized compounds with various substituents (1-27) on six types of bacteria

Table 2
Effect of the synthesized compounds with various substituents (28-53) on six types of bacteria

Compound No.	Ar	*Bacillus magatetium*	*Staphylococcus aereus*	*Escherichia coli*	*Proteus vulgaris*	*Bacillus subtilis*	*Enterobacter aerogeus*
28	-H	1	5	2	10	5	3
29	4--Cl	1	2	6	12	6	5
30	2-Cl	2	6	4	11	9	7
31	4--F	3	4	9	15	5	8
32	4-OMe	1	3	5	-	4	5
33	2-OMe	4	1	8	12	1	2
34	3-OMe	2	5	2	13	1	3
35	4-NO_2	6	2	4	11	2	3
36	3- NO_2	6	9	6	10	1	2
37	2- NO_2	5	4	8	16	2	2
38	2-OMe 4- NO_2	4	3	2	14	1	2
39	3-Me	1	9	4	11	2	3
40	2-Me	-	1	6	12	2	3
41	-H	-	4	6	13	1	2
42	4--Cl	2	6	6	15	1	1
43	2-Cl	1	5	3	11	2	3
44	4--F	3	4	1	12	1	2
45	4-OMe	1	5	5	10	6	13
46	2-OMe	1	6	8	9	1	1
47	3-OMe	1	1	2	8	1	9
48	4-NO_2	2	4	8	9	8	6
49	3- NO_2	-	1	2	11	11	12
50	2- NO_2	1	8	4	10	8	10
51	2-OMe 4- NO_2	2	6	4	5	1	2
52	3-Me	-	5	5	8	2	6
53	2-Me	-	2	2	7	3	5
Tetracycline		16	25	15	17	19	20

Molecular Docking: The study used DNA gyrase B (PDB ID: 4URO) to explore small molecule compounds as antimicrobial agents[13]. Docking scores from Auto dock were analyzed against the crystal structure (PDB: 4URO). Bacterial DNA gyrase, vital for antibacterial investigations, breaks double-stranded DNA, crucial for replication. The analysis included novobiocin's impact on the ATPase binding site, affecting key residues in the cell wall (Ser55, Ala64, Asn65, Asp89, Thr164, Thr173 and Val79). The inhibitory effects stem from structural differences in cell walls between Gram-negative (thin peptidoglycan with an outer membrane) and Gram-positive bacteria (thick peptidoglycan without an outer membrane).

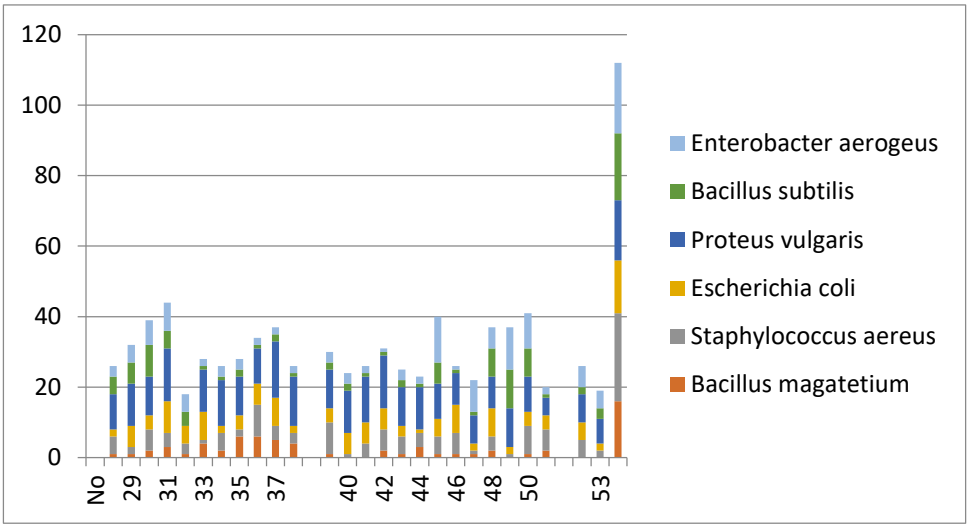
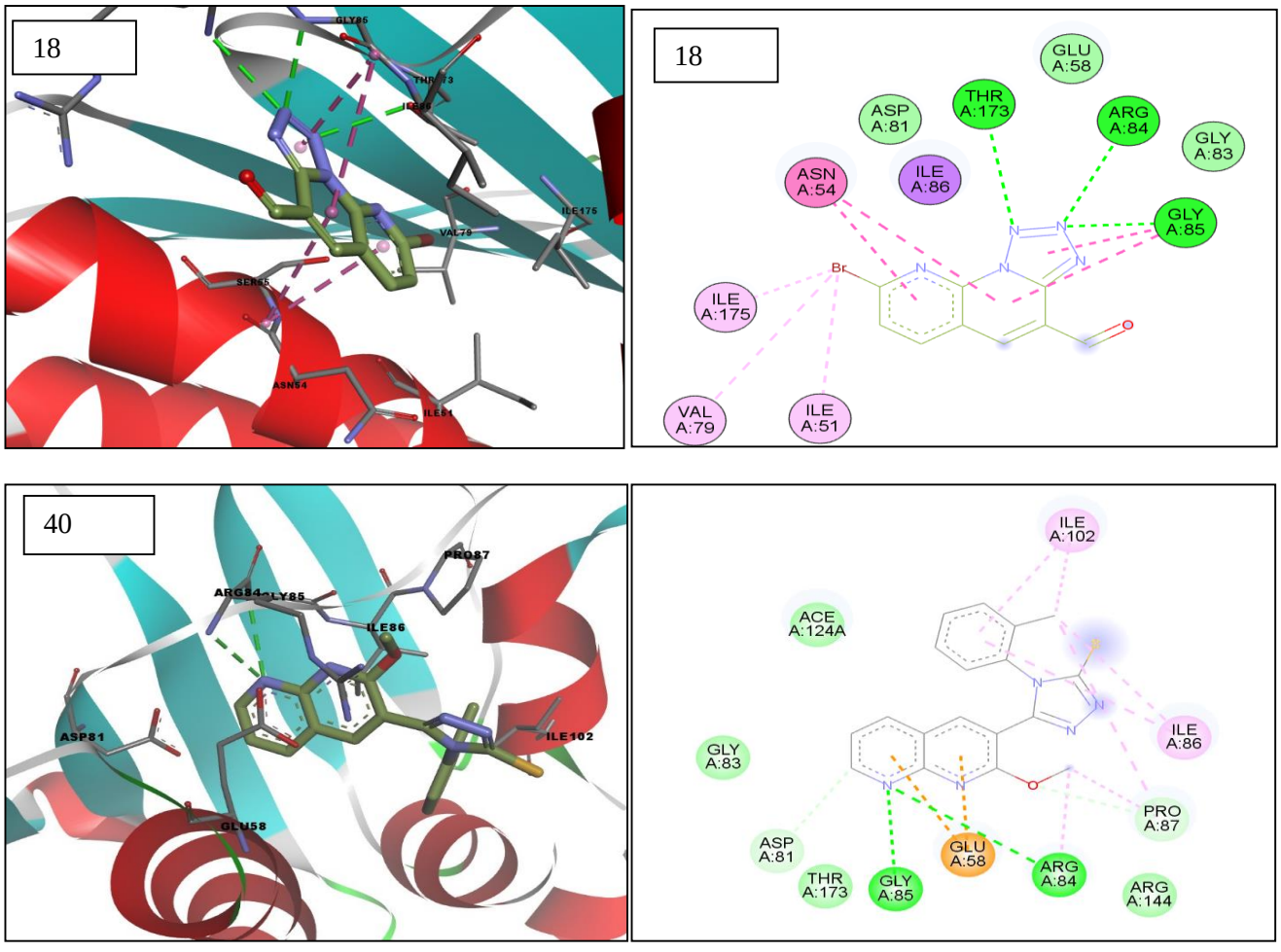


Figure 3: The graph showing the effect of the synthesized compounds with various substituents (29-53) on six types of bacteria



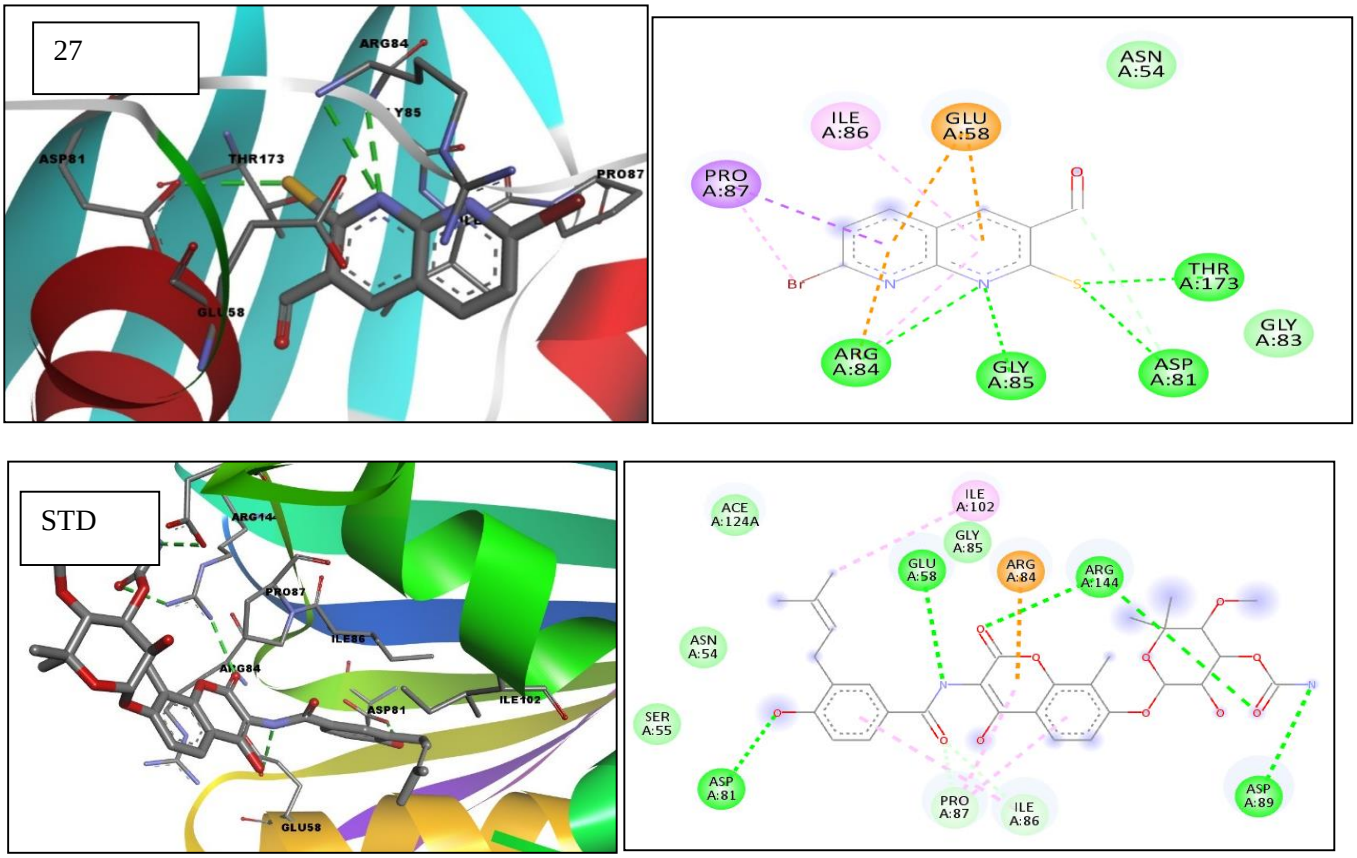


Figure 4: Docking pose of the compounds

Table 3
Docking score of the compounds

Compound No.	MW	Dock Score
18	278.1	-6.938
53	349.4	-6.685
40	349.4	-5.726
27	269.1	-7.749
9	285.5	-6.675
Std	612.6	-7.773

Peptidoglycan, a mesh-like polymer, shields microorganisms from antibacterial agents like antibiotics, toxins, chemicals and degradative enzymes. The compounds were redocked into the active site without a reference inhibitor, successfully forming complexes with the enzyme's active sites. Initially, poses with the lowest docking scores were chosen. These were then filtered based on the lowest binding affinity, determined by the smallest root mean square deviation (RMSD) against the reference drugs (Table 1). Compound 27 demonstrated the highest binding affinity to DNA gyrase (−7.74 kcal/mol) among the compounds, as detailed in table 1. Its superior antimicrobial activity may be attributed to robust interactions with the binding site, forming H-bonds with crucial amino acids (Arg84, Gly85, Asp89, Thr164 and Asp81) as shown in fig. 1-4 (Table 1).

Compound 18 exhibited a binding energy of −6.93 kcal/mol, interacting with the binding pocket through H-bonds with Arg84, Gly85 and Thr173 (Fig. 2). The diverse interaction modes of ligands with the gyrase binding site's hydrophilic amino acid backbone (Fig. 1) suggest the importance of hydrophilic fragments (Asp and Asn) in the synthesized compounds for binding to DNA gyrase.

Conclusion

In conclusion, it is proved that the compounds 15, 17, 25, 26, 49 and 50 showed good biological activity against six different strains of bacteria. The inhibitory efficiency against bacterial growth is attributed to attacking the naked peptide glycan in the cell wall, implying that these compounds possess significant biological functions.

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