ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

MOLECULAR DOCKING STUDIES OF THIAZOLOPYRIMIDINE DERIVATIVES AS ANTIMICROBIAL AGENTS

Shruti Aggarwal[1], Manish Devgun*[1], Rakesh Narang[1], Sukhbir Lal[1], Avtar Chand Rana[1], Rajat Goyal[2], Lalit Singh[3], Saurabh Sharma[4]

[1]*Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana, India*

[2]*MM School of Pharmacy, Maharishi Markandeshwar University, Sadopur, Ambala, Haryana, India*

[3]*Shri Ram Murti Smarak College of Engineering & Technology, Bareilly, Uttar Pradesh, India*

[4]*Vivek College of Technical Education, Bijnor, Uttar Pradesh, India*

**Corresponding author: manishdevgun@gmail.com*

ABSTRACT

Antimicrobial agents are essential drugs for the health of humans and animals as they cure infectious diseases produced by several contagious strains (bacteria, fungi, parasites, and viruses). Antibiotics efficacy is restricted by an increased number of antibiotic-resistant bacteria. Computational chemistry is crucial in the development of novel potential therapeutics. In this study, the objective was to integrate the two separately bioactive molecules, *i.e.,* thiazoles and pyrimidines into one molecule to produce compounds with better pharmacological activity. Various thiazolo-pyrimidine derivatives were planned through a suitable synthetic scheme and were docked on DNA gyrase subunit B and dihydrofolate reductase, which are established targets for microbial infection. The results were studied and the findings were compared to two known medications as well as potential inhibitors. The result recognizes few thiazolo-pyrimidine derivatives with increased binding efficiency leading to enhanced potency.

Keywords: Thiazolo-pyrimidine, Molecular docking, Antimicrobial, DNA gyrase, Dihydrofolate reductase.

1. INTRODUCTION

Over the last two decades, the world population has suffered tremendously from infectious illnesses caused by multi-drug resistance, which is frequently the result of over-expression and broad use of a multidrug efflux system. Microbial infections are the world's second-biggest cause of mortality after cardiac arrest, due to their fast spread, toxicity, and resistance to available antimicrobial agents [1]. Antimicrobial agents are essential drugs for the health of humans and animals as they cure infectious diseases produced by several contagious strains (bacteria, fungi, parasites, and viruses). Present clinical resistance and the emergence of infectious disease make treating infections a critical and complicated issue [2]. Bacterial drug resistance spreads quickly across the world. It is necessary to create new antimicrobial medicines with high potency to combat bacterial drug resistance [3]. The present class of antibiotics also faces problems with cross-resistance, making it essential that new agents can work against currently established targets through a novel mechanism or single binding [4]. Antibacterial resistance is growing enormously worldwide due to the misuse and overuse of antibiotics. The control of infectious disease is now severely threatened and is a major clinical and social problem [5]. In bacterial infection therapy and control, antibiotics are used. Antibiotics efficacy is restricted by an increased number of antibiotic-resistant bacteria. Bacterial resistance is considered a public health concern due to the high morbidity rates and mortality and increased treatment costs [6].

Infections due to fungi are on the rise, particularly in immunosuppressed patients, and are now a prominent source of morbidity and mortality [7]. The new development of antifungal drugs discovery has taken place since new antifungal drugs are crucially needed to combat invasive infections that are life-threatening [8]. However, intensive work in the development of more efficient and promising antifungal agents is still required.

Thiazole is the five-membered ring containing sulphur and nitrogen atom placed at 1, 3-positions in the heterocyclic ring depicted in (Fig. 1). Thiazoles are important structural units for medicinal chemistry and several biologically active molecules have been reported,

such as thiamine (vitamin B), as well as antibiotics such as penicillin [9, 10], and a variety of thiazole derivatives exhibit strong medicinal and pharmacological behaviours such as antibacterial and antifungal, anti-inflammatory.

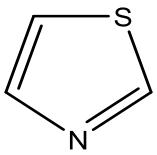


Fig. 1: General structure of thiazole

Pyrimidine is 1, 3-diazine, which is identical to benzene and pyridine and has nitrogen at the 1, 3-position depicted in (Fig. 2)**.** It has a broad variety of biological functions [11] such as calcium channel modulator, antimicrobial agents [12], anti-inflammatory, anti-HIV, anticancer [13]. The presence of heterocyclic nitrogenous bases cytosine and thymine are present in DNA, while uracil replaces thymine in RNA.

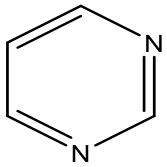


Fig. 2: General structure of pyrimidine

The majority of literature research has demonstrated that thiazoles and pyrimidines are very prominent components of medicinal chemistry and constitute a significant structural basis of numerous active organic and man-made compounds. In this study, the objective was to integrate the two separately bioactive molecules into one molecule to produce compounds (Fig. 3) with better biological activities, including antimicrobial [14], anticancer [15], anti-inflammatory [16], anti-Parkinson [17], antiviral [18] and antioxidant [19].

Rajitha et al (2020), [5] reported and investigated a new series of 3-substituted-5-phenylindeno-thiazolopyrimidinone derivatives and tested their antimicrobial potential. Compound with 4-methoxy phenyl group on the thiazole ring, exhibited potent antibacterial and antifungal activities.

Devineni et al (2019), [20] reported the preparation of thiazolo [3,2-a] pyrimidine analogues with 1,3-benzodioxole moiety and tested for antimicrobial activity. It was observed that the compounds containing 3,5-dimethoxy-4-hydroxyphenyl moiety were active against all fungi and the derivatives containing 1,3-benzo-dioxole and dimethylamino groups were found to be most potent towards bacterial strains.

Behalo (2018), [21] synthesized some novel thiazolo[3,2-a]pyrimidine derivatives and screened them for antibacterial activity towards *Streptococcus sp, B. subtilis, E.coli* and their anti-fungal activity towards two fungal strains including *Aspergillus Niger, Candida albicans* by using agar diffusion method.

Banoth et al (2017), [22] reported the synthesis of benzochromeno[2,3-d]thiazolopyrimidine derivatives**,** which were then assessed for antimicrobial activity. Compound with substitutions of 4-nitro, 4-bromo, and 4-methoxy exhibited good antibacterial activity and antifungal activity.

Molecular docking is a conceptual method for predicting the interaction of macromolecules to a small molecule. In this case, docking was used to evaluate the potential of compounds by binding with dihydrofolate reductase and DNA gyrase subunit B [23].

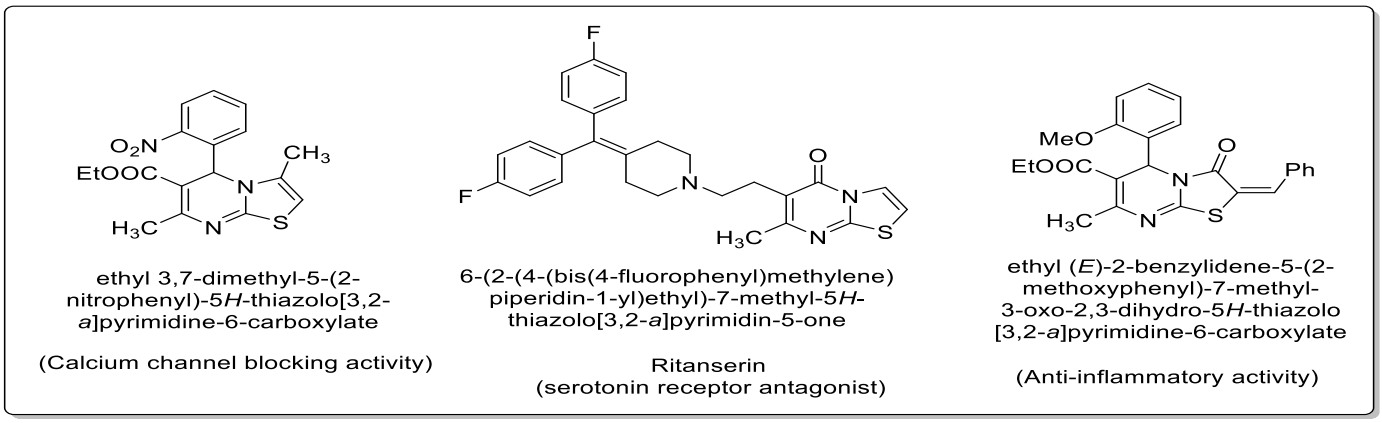


Fig. 3: Some of the biologically active thiazolopyrimidine derivatives.

2. MATERIAL AND METHODS

2.1. Chemistry

The scheme for synthesis of thiazolo-pyrimidine derivatives **6a-j** (Table 1) is outlined in (Fig. 4), here synthesis is proposed by one-pot three-component method via cyclocondensation of substituted 4-phenylthiazole-2-amine **3a-c**, acetylacetone, and various aldehydes along with p-toluene sulphonic acid under acetonitrile solvent medium. The starting material 4-phenylthiazole-2-amine was synthesized by reacting acetophenone **1** and thiourea **2** along with 10% bromine in acetic acid.

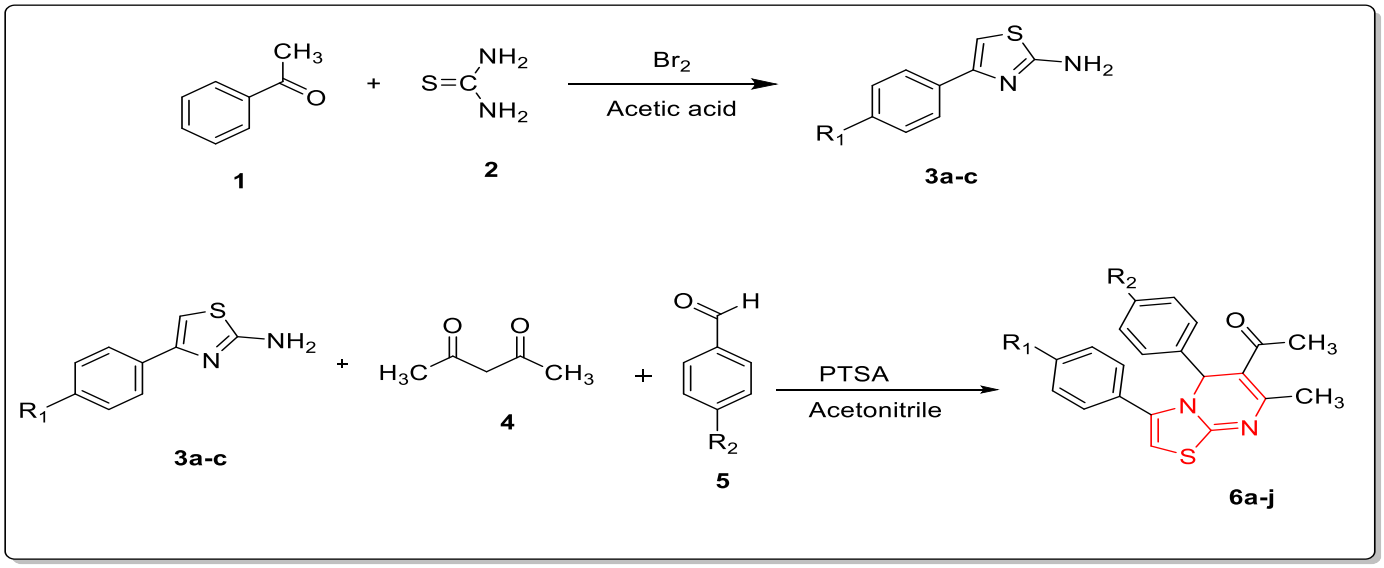


Fig. 4: Synthesis of thiazolo [3, 2-a] pyrimidine-yl derivatives

Table 1: Proposed synthesis of novel thiazolo-pyrimidine (6a-j)

Sr. No	Compounds	R_1	R_2
1	**6a**	H	OH
2	**6b**	H	3,4-OCH_3
3	**6c**	H	p-Br
4	**6d**	H	p-dimethyl
5	**6e**	p-OH	OH
6	**6f**	p-OH	3,4-OCH_3
7	**6g**	p-OH	p-dimethyl
8	**6h**	p-Br	3,4-OCH_3
9	**6i**	p-Br	p-Br
10	**6j**	p-Br	p-dimethyl

2.2. Molecular docking

The computational technique of docking was exploited to evaluate the binding of the compounds with dihydrofolate reductase (PDB id: 4HOE) and DNA gyrase subunit B (PDB id: 1kzn) which are keys targets for the production of antifungal and antibacterial medicines [24, 25]. These targets are selected because of their vital function in the creation of fungal cells and bacterial cells; hence targeting these proteins offers the apparent advantage of eliminating fungus and bacteria. The co-crystal ligand was re-docked using Autodock Vina to emphasize the location and direction of the compound identified in the crystal structure, ensuring the correctness of the docking parameters and procedure. The RMSD value was less than 2Å, confirming the correctness of the method used.

2.3. Ligand preparation

The ligand 2D structures were designed in ChemDraw Professional 15.0 and were converted to optimized 3D structures with the help of Chem 3D 15.0 for *in-silico* research. The AutoDock Vina (MGL tools-1.5.6) was utilized to obtain the neat structure of protein molecules by discarding molecules of water, hetero-atoms, and additional charges, and then the target protein file was visualized using the Discovery studio 4.0 tools.

2.4. Receptor preparation

The structure of DNA gyrase and dihydrofolate reductase was acquired from Research Collaboratory for Structural Bioinformatics PDB (https://www.rcsb.org/). The DNA gyrase complexed with clorobiocin (PDB id: 1kzn) attained X-Ray diffraction resolution of 2.30 Å and dihydrofolate reductase complexed with

NADPH and UCP11E (PDB id: 4HOE) with X-Ray diffraction resolution of 1.76 Å. The receptor file was transferred into the AutoDock Vina and the complex ligand clorobiocin was removed from the protein structure, also the water was removed, polar hydrogen and kollman charges were added.

3. RESULTS AND DISCUSSION

3.1. Docking process

The docking results were analyzed by Discovery studio 4.0 tools, which yielded crucial information regarding the attachment of potential compounds with their receptors. The findings (Table 2) of the docking indicate that the compound **6j** has a slightly better docking value against DNA gyrase subunit B (-6.6 kcal/mol) compared to standard ligand, tetracycline [25] (-6.2 kcal/mol). The standard ligand tetracycline binds at the target site of DNA gyrase subunit B with 6 conventional hydrogen bonds, and other interactions (GLU185, LYS212, TYR184, ARG209, GLU181, GLU183, and PHE182) as shown in (Fig. 5). Moreover, compound **6j** (Fig. 6) links strongly to the target site of 1kzn via one pi-donor hydrogen bond interaction (ASN46) and one pi-alkyl interaction (ILE90). Moreover, compounds **6d, 6g,** and **6a** show a similar docking score as that of tetracycline.

The docking results (Table 3) of antifungal agents indicate that the compound **6j** has a slightly better docking value (-8.3 kcal/mol) against dihydrofolate reductase, in contrast to standard ligand clotrimazole (-8.2 kcal/mol). The standard ligand binds at the target site dihydrofolate reductase with 5 interactions (PHE36, MET25, ILE62, ILE33, LEU69) as shown in (Fig. 7). However, **6j** binds strongly at the target site of 4HOE via one carbon-hydrogen bond and pi-alkyl interaction ILE112, PHE66 as shown in (Fig. 8).

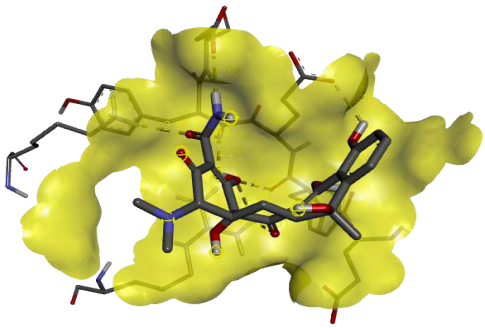
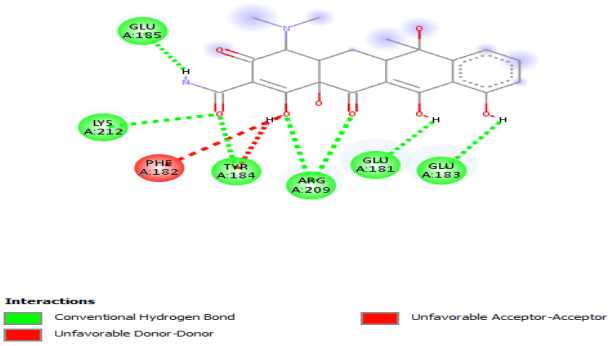


Fig. 5a



(a) Tetracycline with 1KZN at the binding sites; (b) 2D view of interaction

Fig. 5b

Fig. 5: Docked poses of tetracycline ligand with DNA gyrase subunit B (PDB ID: 1KZN)

Table 2: Autodock binding energies and residues involved in hydrogen bonds in the docking of ligands to DNA gyrase subunit B (PDB ID: 1KZN).

Product	Binding Energy	Residue involved in hydrogen bonding Interactions
Tetracycline	-6.2	GLU185,LYS212,PHE182,TYR184,ARG209, GLU181,GLU183
6a	-6.0	ASP49,GLU50,ILE78,ASN46,ILE90,PRO79
6b	-5.8	ASN46,GLU50,ILE78,ARG76,PRO76
6c	-5.9	GLU50,ARG76,PRO76,ILE78,ASN46
6d	-6.2	ASN76,ILE78,ARG,GLU50,ARG76,PRO79
6e	-6.1	ASP49,GLU50,ILE78,ILE90,ASN46
6f	-5.4	THR175,LYS21,ARG20,HTS147
6g	-6.2	ILE90,ASN46,ILE78,PRO79
6h	-6.2	ARG76,PRO79,ILE78,ASP49,ILE90,GLU50
6i	-5.9	ILE78,ARG76,GLU50,PRO79,ASN46
6j	-6.6	ILE90,ASN46,ILE78,PRO79

Table 3: Autodock binding energies and residues involved in hydrogen bonding interaction of ligands with dihydrofolate reductase (PDB ID: 4HOE)

Product	Binding energy	Residue involve in hydrogen bonding interaction
Clotrimazole	-8.2	PHE36,MET25,ILE62,ILE33,LEU69
6a	-7.5	ILE112,NDP201,PHE36,LEU69, MET25,ILE33
6b	-6.7	PRO70,ARG72,LEU69,ILE33,PHE36, MET25,NDP201
6c	-7.3	MET25,PHE66,ILE62,ILE33
6d	-6.9	ASN5,MET1,HIS129,ARG108
6e	-7.0	ASN5,MET1,GLY203,ARG108
6f	-7.6	NDP201,PHE36,ILE112,ILE62,LEU69,ARG28, MET25,ILE33
6g	-7.9	PHE36,ILE112,ILE62,LEU69,MET25, NDP201,ILE33
6h	-7.0	ARG108,ASN5,MET1,PHE167
6i	-6.6	ARG79,SER98,SER95
6j	-8.3	NDP201,PHE36,ILE112,ILE62,PHE66, LEU69,MET25,ILE33,NDP201

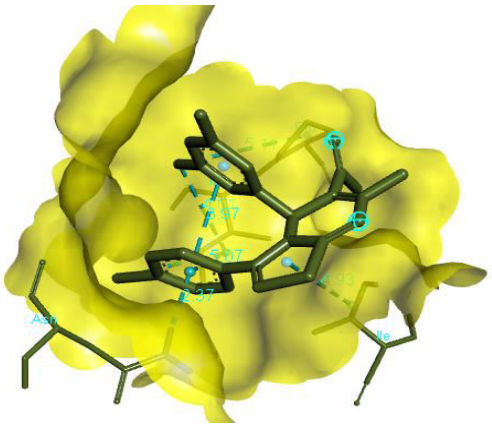
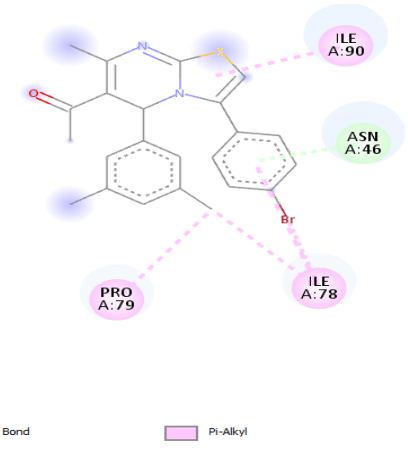


Fig. 6a



(a) Compound 6j with 1KZN at the binding site; (b) 2D view of interaction

Fig. 6b

Fig. 6: Docked poses of compound 6j with DNA gyrase subunit B (PDB ID: 1KZN)

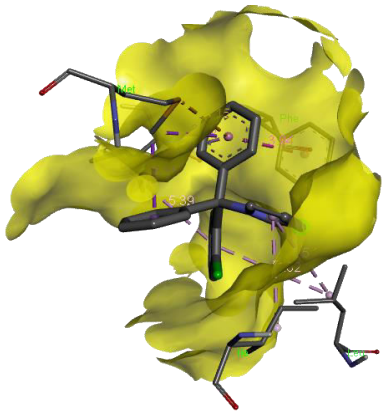
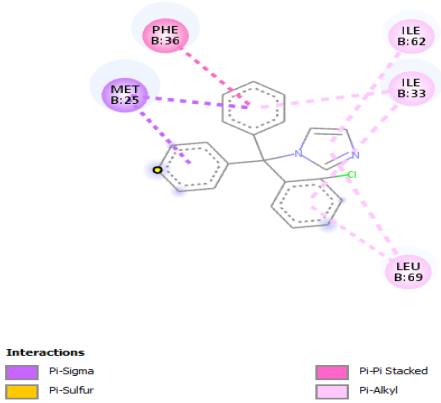


Fig. 7a



(a) Clotrimazole with 4HOE (Aromatic surface) at the binding site; (b) 2D view of interaction.

Fig. 7b

Fig. 7: Docked poses of clotrimazole with dihydrofolate reductase (PDB ID: 4HOE)

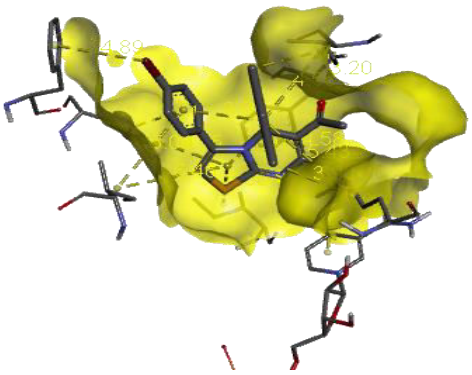
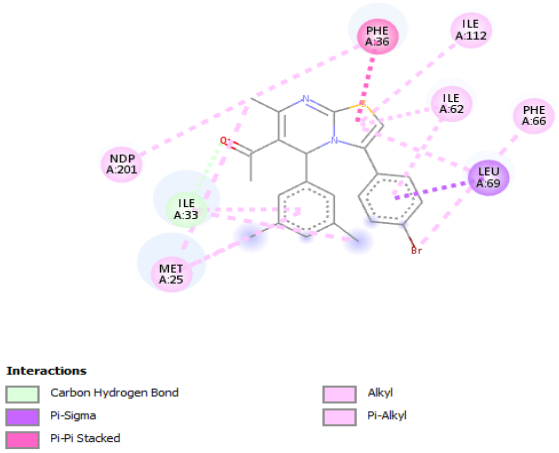


Fig. 8a



(a) compound 6j with 4HOE at the binding site; (b) 2d view of interaction.

Fig. 8b

Fig. 8: Docked poses of compound 6j with dihydrofolate reductase (PDB ID: 4HOE)

4. CONCLUSION

The exponential rise in creating DNA gyrase and dihydrofolate reductase inhibitors shows clearly the crucial role in the treatment of microbial infection, many of the molecules were identified to block the receptors by entirely binding the target receptors' active site. Most inhibitors were shown to be involved in both the hydrophobic interactions and hydrogen bonding with the receptors. The findings of molecular docking displayed in the figures confirm that the hydrophobic interactions and the hydrogen bonding with these targets had a key impact on the binding structures and binding free energy, whereas van-der-Waals and Pi-interactions helped to stabilize the binding structures. We expect that the current computational investigations will give important insight into the future rational structure-based design of innovative and powerful inhibitors by providing a full structural knowledge, binding mode and important parameters impacting binding free energy.

5. REFERENCES

1. Manuscript A, Society R, Manuscripts A, et al. RSC Advances.
2. Afradi M, Foroughifar N, Pasdar H, Moghanian H, Foroughifar N. *Appl Organomet Chem*, 2017; **31**:1-8.
3. Cai D, Zhang ZH, Chen Y, et al. *Molecules*, 2015; **20**:16419-16434.
4. Kumar Paul R, Azam MA, Jupudi S. *Fabad J Pharm Sci*., 2020; **45**:9-18.
5. Rajitha G, Arya CG, Janardhan B, Laxmi S V., Ramesh G, Kumari US. *Russ J Bioorganic Chem*. 2020; **46**:612-619.
6. Elhameed AAA, El-gohary NS, El-bendary ER, Shaaban MI, Said M. *Der Pharm. Lett*., 2018; **10**:55-72.
7. Chhabria M, Rathod I, Vala K, Patel P. *Med Chem Res*. 2011; **20**:1450-1454.
8. Gallagher JC, MacDougall C, Dodds Ashley ES, Perfect JR. *Expert Rev Anti Infect Ther*., 2004; **2**:253-268.
9. Abdu-rahem LR, Ahmad AK, Abachi FT. *Sys Rev Pharma*., 2021; **12**:290-295.
10. Prajapati AK, Modi VP. *J Chil Chem Soc*. 2010; **55**: 240-243.
11. Patel NB, Purohit AC, Rajani D. *Med Chem Res*., 2014; **23**:4789-4802.
12. Sawant RL, Bansode CA, Wadekar JB. *Med Chem Res*., 2013; **22**:1884-1892.
13. Rawal RK, Tripathi R, Katti SB, Pannecouque C, De Clercq E. *Bioorganic Med Chem*., 2007; **15**:3134-3142.
14. Balkan A, Urgun H, Özalp M. *Arzneimittel-Forschung Drug Res*., 2001; **51**:839-842.
15. Al-Omary FAM, Hassan GS, El-Messery SM, El-Subbagh HI. *Eur J Med Chem*., 2012; **47**:65-72.
16. Abu-Hashem AA, Gouda MA, Badria FA. *Eur J Med Chem*., 2010; **45**:1976-1981
17. Luthra PM, Mishra CB, Jha PK, Barodia SK. *Bioorganic Med Chem Lett*., 2010; **20**:1214-1218.
18. Umesha K, Sarojini BK, Darshan Raj CG, et al. *Med Chem Res*., 2014; **23**:168-180.
19. Maddila S, Damu GLV, Oseghe EO, Abafe OA,

Venakata Rao C, Lavanya P. *J Korean Chem Soc*., 2012; **56**:334-340.
20. Devineni SR, Madduri TR, Chamarthi NR, Liu CQ, Pavuluri CM. *Chem Heterocycl Compd*., 2019; **55**:266-274.
21. Behalo MS. *J Heterocycl Chem*., 2018; **55**:1391-1397.
22. Banoth S, Boda S, Perugu S, Balabadra S, Manga V. *Res Chem Intermed*., 2018; **44**:1833-1846.
23. Abdel-Motaal M, Almohawes K, Tantawy MA. *Bioorg Chem*., 2020; **101**:103972.
24. Jays J, Mohan S, Saravanan J. *Chem Methodol*., 2019; **3**:442-450.
25. Bhadraiah UK, Ningaiah S, Basavanna V, et al. *Biointerface Res Appl Chem*., 2021; **11**:9443-9455.