WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 10, 1058-1068. Research Article ISSN 2277–7105

MOLECULAR DOCKING STUDIES OF SOME PYRAZOLE AND ITS HETEROCYCLIC DERIVATIVES

Satish M. Bhalekar[1]*, Santosh V. Raskar[2] and Peter R. Rodrigues[3]

[*1]Department of Chemistry, S.I.W.S. College, Wadala, Mumbai - 400031, India.
[2]Department of Chemistry, Fr. Agnel Junior College, Bandra, Mumbai - 400050, India.
[3]Department of Chemistry, Sant Rawool Maharaj Mahavidyalay, Kudal, Sindhudurg – 416520. Maharashtra, India.

Article Received on
28 March 2025,
Revised on 17 April 2025,
Accepted on 07 May 2025
DOI: 10.20959/wjpr202510-36712

***Corresponding Author**
Satish M. Bhalekar
Department of Chemistry,
S.I.W.S. College, Wadala,
Mumbai - 400031, India.

ABSTRACT

Synthesis of 1-Thiocarboxamido-3-methyl -4-(4-arylhydrazono)-5-(5-bromopyridin-2-yl)imino-4,5-dihydropyrazole derivatives, 4-(4-Bromophenyl)-2-[4-(arylhydrazono-3-methyl-5-(5-bromopyridin-2-yl)imino-4,5-dihydropyrazol-1-yl]-1,3-thiazole derivatives and 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl)thiazol-2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine derivatives is reported. We are hereby reporting molecular docking studies of these molecules. Compounds 1 (a-h) have pyrazole and pyridine ring along with thiocarboxamide group. This thiocarboxamide group was cyclised to thiazole to obtain 2 (a-h). Compounds 3 (a-h) have pyrazole, thiazole and pyrimidine ring. Structures of these molecules were docked to the target protein molecules of disease producing pathogens using Auto Dock Vina, a docking tool. Swiss ADME studies were carried out to test the gastro- intestinal absorption and brain permeation.

KEYWORDS: Pyrazole, Thiazole, Pyridine, Pyrimidine, Molecular docking, Swiss ADME analysis.

INTRODUCTION

The analogues of nitrogen-based heterocycles occupy an exclusive position as a valuable source of therapeutic agents in medicinal chemistry. Pyrazole plays a vital role in many biological activities such as anti-bacterial and antifungal.[1,2] analgesic, anti-inflammatory and

anti –microbial.[3] Pyridine derivatives have been reported for variety of biological activities such as antibacterial.[4] antimicrobial.[4,5] and anti-inflammatory.[5]

Thiazole possess various biological activities such as antibacterial.[6,7,8] antifungal.[6] antitubercular.[7] and antioxidant activities.[8] Pyrimidine nucleus exhibited remarkable pharmacological activities. Condensed pyrimidine derivatives have been reported as analgesic, anti-viral, anti-inflammatory.[9] anti-HIV.[10] anti-tubercular.[11] agents.

Earlier we have reported Synthesis of 1-Thiocarboxamido-3-methyl -4-(4-arylhydrazono)-5-(5-bromopyridin-2-yl)imino-4,5-dihydropyrazole derivatives.[12] 4-(4-Bromophenyl)-2-[4-(arylhydrazono-3-methyl-5-(5-bromopyridin-2-yl)imino-4,5-dihydropyrazol-1-yl]-1,3-thiazole derivatives.[13] and 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl)thiazol-2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine derivatives.[14]

These compounds were assayed for their biological activity against a variety of microbes such as *E. coli, Staphylococcus aureus, Salmonella typhi and Bacillus subtilis*. Compound 2(b-d), 2f and 2g were found mildly active against *S. aureus*. Compound 2f was found to be moderately active against *E. coli* and *S. typhi*. Compound 3(a-d), 3f and 3h were found to be moderately active against *S. aureus*. All the other compounds were found to be inactive.[12,13,14]

The present paper describes the Computational study of these compounds which was carried out with the help of various computer applications available such as AutoDock Vina and Swiss ADME.

MATERIALS AND METHOD

In this study, Auto Dock Vina 1.5.7, a docking tool.[17,18] was used.

Swiss ADME online platform and the visualization is done with the help of biovia discovery software.

Ligand preparation

The synthesized compounds were used for the computational study against proteins of various disease producing pathogens such gram +ve bacteria (*Staphylococcus aureus, Bacillus subtilis*) and gram -ve bacteria (*Escherichia coli, Salmonella typhi).*[15] The molecular structure of these ligands were converted to PDB format using *Avogadro 2* app.[16]

Preparation of Target Protein

The proteins of gram +ve bacteria (*Staphylococcus aureus* (PDB ID: 2XCT), *Bacillus subtilis* (PDB ID: 1BAG)) and gram -ve bacteria (*Escherichia coli* (PDB ID:1KZN), *Salmonella typhi* (PDB ID: 1QFE) were referred and downloaded from rcsb.org site, which is repository of protein data, in PDB format. The protein receptor further prepared by removal of water molecule, adding polar hydrogen atoms, adding charges and atoms, then converted into PDBQT form using Auto Dock Tool -1.5.7.

Molecular Docking

All the synthesized drug molecule structures were docked to the target protein molecules of disease producing pathogens using AutoDock Vina 1.5.7, a docking tool.[17,18] For this process the Grid map optimization is done. The Grid Box co-ordinates can be saved so that synthesized molecules can be dock exactly at that position.

In this study blank docking processes[19] were used to find out positions as well as the highest binding energies.[20] Molecular docking is useful to determine binding affinities by following various steps such as preparing PDBQT files for proteins and ligands, Grid Box optimization, etc. The proteins in this study were kept rigid and ligands flexible.

Visualization and Molecular Interactions

The molecular interactions can be viewed using various visualization tools such as PyMOL, BIOVIA, Discovery Studio Visualizer etc. 2D and 3D interaction plots of ligand and protein were derived. The hydrogen bond interactions were studied, visualized. The binding affinity of the ligand-protein is the resultant of all such interactions and binding energy existing between them. The various conformations of ligands viewed using visualization tools and their positional pockets on the protein.[21]

SwissADME Analysis

Swiss ADME help to first find out possible drug candidates and their drug likeness.[22]

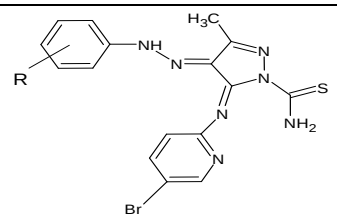
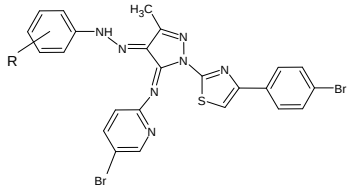
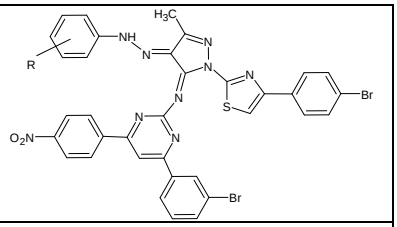
This is generally done during discovery phase to avoid loss of time, chemicals, manpower, expenditure etc. In this absorption, distribution, metabolism and excretion (ADME) properties are studied at the time of discovery. Pharmacokinetics allows one to study drug's ability to permeate blood brain barrier (BBB), absorption from Gastro-intestinal tract (GI) obtained from BOILED EGG model. BOILED-Egg method works by processing the polarity

and lipophilicity of synthesized molecules. It also helps to predict whether drug-candidate can act as inhibitor against several protein enzymes.

It analyzes the various points such as drugs likeness, permeation of Blood Brain, Total polar surface area[23], GI absorption analysis. The ADME analysis let know if a drug candidate is having pharmacological effect and provides specific targets for future research.

The structure of the molecules under investigation are depicted in the table no. 1.

Table 1: Structure of the compounds [1(a-h), 2(a-h), 3(a-h)].

		
1(a-h)	2(a-h)	3(a-h)
R = a) H, b) 2-OCH_3, c) 4-OCH_3, d) 4-Br, e) 4-Cl, f) 4-CH_3, g) 4-NO_2, h) 3-NO_2		

RESULT AND DISCUSSION

The docking results shows that all the docked ligands have a low crucial binding energy with proteins of *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Salmonella typhi*.

Table 2: Docking scores for antibacterial target selected for docking.

Binding Energy (kcal/mol)				
Compound	**Gram- positive**		**Gram-negative**	
	S.aureus	***B.subtilis***	***E.coli***	***S.typhi***
	2XCT	**1BAG**	**1KZN**	**1QFE**
Molecule 1a	-8.5	-6.3	-5.1	-5.4
Molecule 1b	-6.6	-5.6	-5.6	-5.4
Molecule 1c	-6.4	-5.5	**-6.0**	-5.3
Molecule 1d	**-9.1**	**-6.4**	-5.0	-5.7
Molecule 1e	-6.6	-6.1	-5.0	-5.8
Molecule 1f	-6.8	-5.9	-5.9	-5.8
Molecule 1g	-8.5	-6.0	-5.1	-6.1
Molecule 1h	-7.4	-5.9	-5.5	**-6.6**
Molecule 2a	-8.5	-6.6	**-8.0**	-7.3
Molecule 2b	-9.3	-7.2	-6.2	-6.7
Molecule 2c	-9.2	-7.3	-6.0	-6.2
Molecule 2d	-9.1	-7.5	-7.0	-7.1
Molecule 2e	-9.0	**-7.7**	-7.4	-7.4
Molecule 2f	**-9.9**	-7.5	-7.5	-7.3
Molecule 2g	-9.3	-7.6	-7.7	-6.7
Molecule 2h	-9.8	-7.3	-7.3	**-7.6**
Molecule 3a	**-12.3**	-9.5	-7.5	-8.2

Molecule 3b	-11.8	-9.4	-7.9	-8.1
Molecule 3c	-11.8	-9.4	-8.0	-8.0
Molecule 3d	-12.1	-9.6	-8.3	-8.2
Molecule 3e	-12.2	-9.4	-8.3	-8.3
Molecule 3f	-12.1	**-9.7**	-8.1	**-8.5**
Molecule 3g	-11.9	-9.1	-8.0	-8.1
Molecule 3h	-11.8	-9.0	**-8.6**	-8.2

The 2D and 3D interactions of some of the molecules with targeted proteins are illustrated in the following figures.

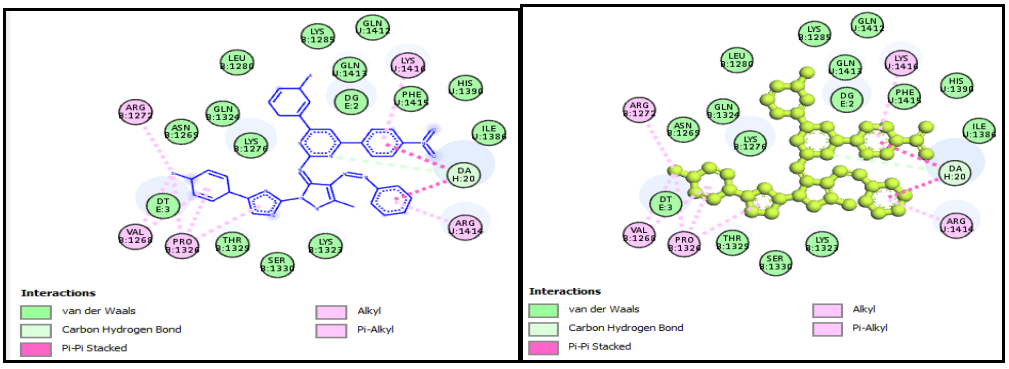


Fig. 1: 2D interaction of 3a with 2XCT.

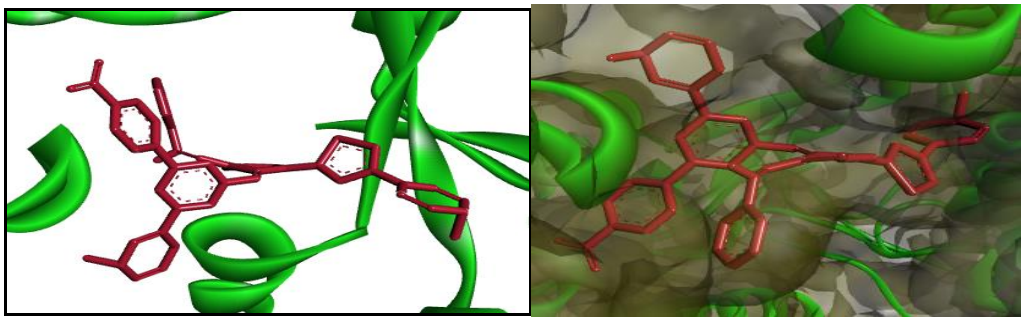


Fig. 2: 3D interaction of 3a with 2XCT.

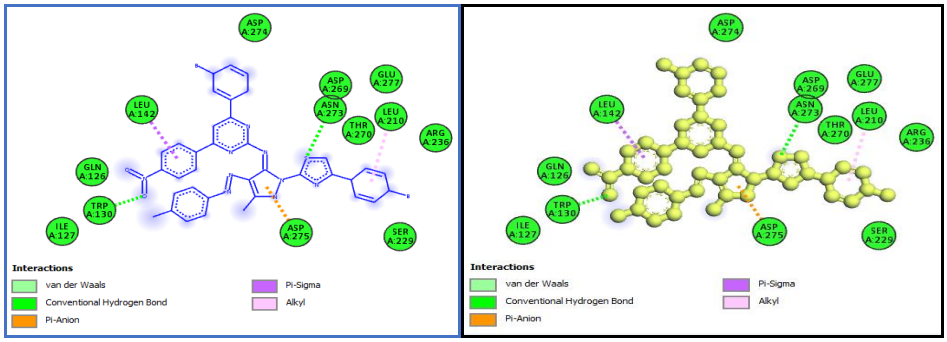


Fig. 3: 2D interaction of 3f with 1BAG.

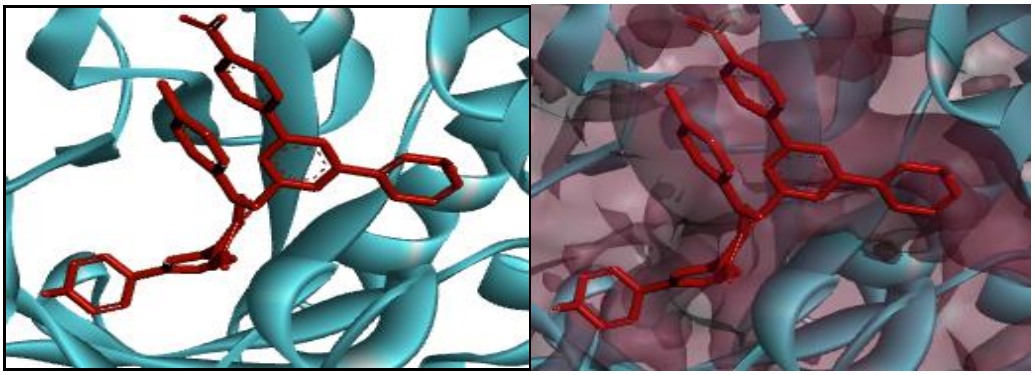


Fig. 4: 3D interaction of 3f with 1BAG.

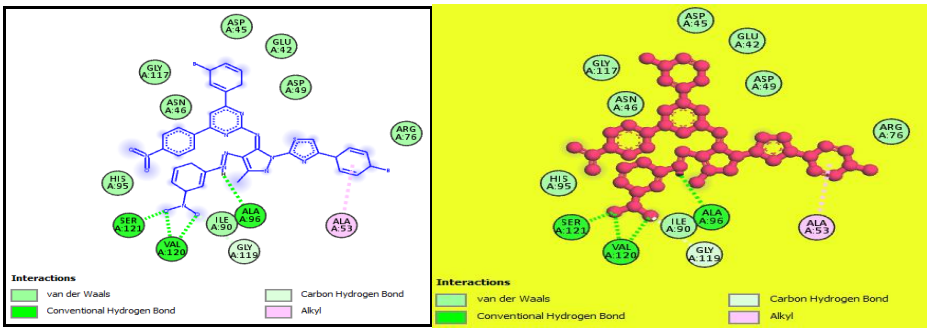


Fig. 5: 2D interaction of 3h with 1KZN.

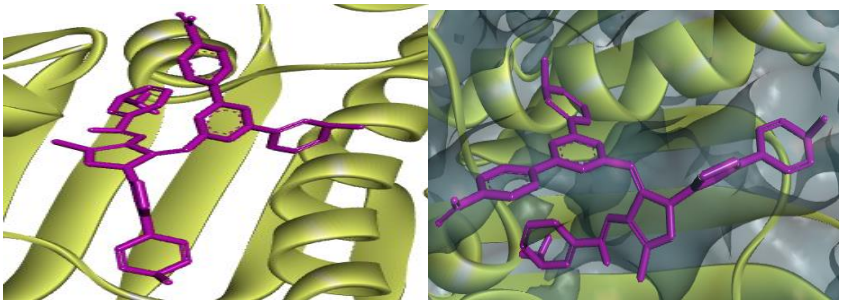


Fig. 6: 3D interaction of 3h with 1KZN.

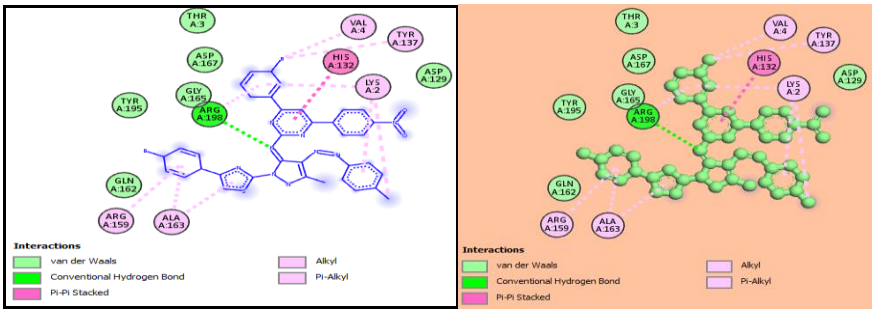


Fig. 7: 2D interaction of 3f with 1QFE.

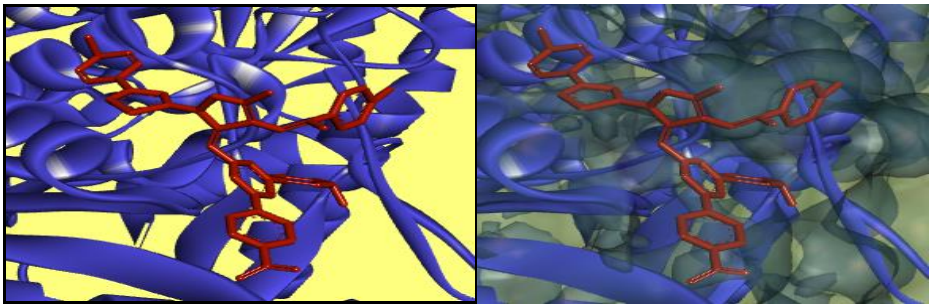


Fig. 8: 3D interaction of 3f with 1QFE.

Pharmacokinetic profile and boiled egg information could not be obtained for 1(a-h). Maybe they are not pharmacologically active molecules. All the remaining molecules [2(a-h and 3(a-h)] showed low GI absorption, no blood brain barrier permeation and only 3d, 3e and 3f were recognized by the P-glycoprotein (P-gp).

A bioavailability score of ≥ 0.55 suggest that the compound exhibits excellent absorption by the body.[24] Molecules [2(a-h and 3(a-h)] showed poor absorption by the body. According to the Lipinski rule, one of the most important chemical descriptors that correlate well with PK (Pharmacokinetic) properties is the topological polar surface area (TPSA), and the TPSA of a good drug should be less than 140 $Å^2$. In the present study, all the molecules except 1g,1h, 2g, 2h, 3(a-h) have TPSA less than 140 $Å^2$.

Table 3: Pharmacokinetic profile of the compounds.

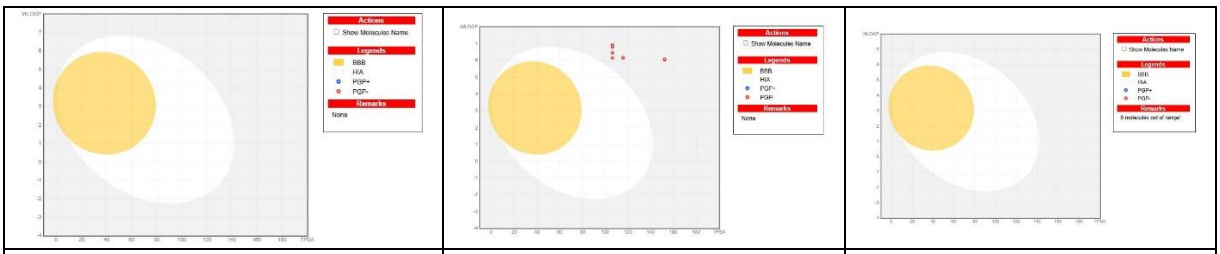
Molecule	GI absorption	BBB permeant	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	P-gp Substrate	Lipinski # violations
2a	Low	No	No	Yes	Yes	No	No	No	2
2b	Low	No	No	Yes	Yes	No	No	No	2
2c	Low	No	No	Yes	Yes	No	No	No	2
2d	Low	No	No	Yes	No	No	No	No	2
2e	Low	No	No	Yes	No	No	No	No	2
2f	Low	No	No	Yes	No	No	No	No	2
2g	Low	No	No	Yes	No	No	No	No	2
2h	Low	No	No	Yes	No	No	No	No	2
3a	Low	No	No	No	No	No	No	No	3
3b	Low	No	No	No	No	No	No	No	3
3c	Low	No	No	No	No	No	No	No	3
3d	Low	No	No	No	No	No	No	Yes	3
3e	Low	No	No	No	No	No	No	Yes	3
3f	Low	No	No	No	No	No	No	Yes	3
3g	Low	No	No	No	No	No	No	No	3
3h	Low	No	No	No	No	No	No	No	3

Table 4: Lipophilicity and Physiochemical property profile of the compounds.

Molecule	WLOGP	TPSA	Bioavailability Score
1a	2.32	123.35	---------
1b	2.33	132.58	--------
1c	2.33	132.58	----------
1d	3.09	123.35	----------
1e	2.98	123.35	----------
1f	2.63	123.35	----------
1g	2.23	169.17	----------
1h	2.23	169.17	----------
2a	6.17	106.37	0.17
2b	6.18	115.60	0.17
2c	6.18	115.60	0.17
2d	6.93	106.37	0.17
2e	6.83	106.37	0.17
2f	6.48	106.37	0.17
2g	6.08	152.19	0.17
2h	6.08	152.19	0.17
3a	8.81	165.08	0.17
3b	8.82	174.31	0.17
3c	8.82	174.31	0.17
3d	9.57	165.08	0.17
3e	9.46	165.08	0.17
3f	9.12	165.08	0.17
3g	8.72	210.90	0.17
3h	8.72	210.90	0.17

The BOILED-Egg model generally indicates the BBB and HIA evaluation where the Blue dots (PGP+) shows the molecules to be effluated. The Red dots (PGP-) addresses the molecules not to be effluated by the P-glycoprotein from central nervous system. The Yellow (yolk) region indicates high likelihood of brain penetration. The White region shows the region having passive gastrointestinal absorption.

In the BOILED-Egg model of Brain penetration (BBB), none of the molecule showed blood brain barrier permeation.



1(a-h)	2(a-h)	3(a-h)

Fig. 9: Brain permeation and passive gastrointestinal absorption.

(BOILED-Egg) of synthesized molecules.

CONCLUSION

The computational study analysis showed that all the synthesized molecules could bind with the receptor proteins. The antibacterial activity was suggested by the synthesized molecules in docking studies with good negative values of binding affinity for 3 (a-h) whereas 2 (a-h) showed moderate affinity and 1 (a-h) showed poor affinity. The molecular docking showed poor score of bioavailability for 2 (a-h) and 3 (a-h).

REFERENCES

1. Satheesha Rai N, Balakrishna K. A novel series of nitrofuran containing 1,3,4,5-tetra substituted pyrazole via 1,3 dipolar addition reaction. Indian J. of chem., 2007; 46B: 375-8.
2. Mari SK, Bantwal S, Holla, Nalilu S. Synthesis and antimicrobial studies on novel chloro-fluorine containing hydroxy pyrazolines. European Journal of Medicinal Chemistry, 2007; 42: 30-36.
3. Sahu SK, Banerjee M, Samantray A, Behera C, Azaml MA. Synthesis, Analgesic, Anti-inflammatory and Antimicrobial Activities of Some Novel Pyrazoline Derivatives. Tropical Journal of Pharmaceutical Research, 2008 June; 7(2): 961-8.
4. Furdui B, Parfene G, Ghinea IO, Dinica RM, Bahrim G, Demeunynck M. Synthesis and in Vitro Antimicrobial Evaluation of New N-Heterocyclic Diquaternary Pyridinium Compounds. Molecules, 2014; 19: 11572–11585.
5. Kamat V, Santosh R, Poojary B, Nayak SP, Kumar BK, Sankaranarayanan M, Faheem, Khanapure S, Barretto DA, Vootla SK. Pyridine- and Thiazole-Based Hydrazides with Promising Antiinflammatory and Antimicrobial Activities along with Their In Silico Studies. ACS Omega, 2020; 5: 25228–25239.
6. Balladka KS, Bettadapura GK, Chenna GD, Basavapattana RB, Hanumanthappa M. Synthesis, characterization, in vitro and molecular docking studies of new 2,5-dichloro thienyl substituted thiazole derivatives for antimicrobial properties. Eur. J Med Chem., 2010 Aug; 45(8): 3490-6.
7. Shiradkar MR, Murahari K, Hanimi Reddy Gangadasu, Tatikonda S, Chakravarthy AK, Panchal D, Kaur R, Burange P, Ghogare J, Mokale V, Raut M. Synthesis of new S-derivatives of clubbed triazolyl thiazole as anti-Mycobacterium tuberculosis agents. Bioorg. Med Chem., 2007 Jun 15; 15(12): 3997-4008.

8. Lemilemu F, Bitew M, Demissie TB, Eswaramoorthy R, Endale M. Synthesis, antibacterial and antioxidant activities of Thiazole-based Schiff base derivatives: a combined experimental and computational study. BMC Chem., 2021 Dec 23; 15(1): 67.
9. Amr AE, Nermien MS, Abdulla MM. Synthesis, Reactions and Anti-inflammatory activity of Heterocyclic systems Fused to a Thiophene Moiety Using Citrazinic acid as Synthon. Monatsh. Chem., 2007; 138: 699.
10. Fujiwara N, Nakajima T, Ueda Y, Fujita H, Kawakami H. Novel piperidinylpyrimidine derivatives as inhibitors of HIV-1 LTR activation. Bioorg. Med. Chem., 2008; 16: 9804-16.
11. Ballell L, Field RA, Chung GAC, Young RJ. New thiopyrazolo[3,4-d]pyrimidine derivatives as anti-mycobacterial agents. Bioorg. Med. Chem. Lett., 2007; 17: 1736-40.
12. Rodrigues PR, Bhalekar SM. Synthesis and Biological activity of 1-thiocarboxamido-3-methyl-4-(4-arylhydrazono)-5-(5-bromopyridin-2-yl) imino-4,5-dihydro pyrazole derivatives. International J of Chemical Sciences, 2016; 14(4): 2641-2644.
13. Rodrigues PR, Bhalekar SM. Synthesis and biological activity of 4-(4-bromophenyl)-2-[4-(arylhydrazono- 3- methyl-5-(5-bromopyridin-2-yl) imino- 4,5-dihydro pyrazol-1-yl] – 1,3-thiazole derivatives. International J. of Chemical Sciences, 2015; 13(4): 1844-1848.
14. Bhalekar SM, Rodrigues PR, Sapale SR. Synthesis and Biological activity of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl)thiazol- 2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine derivatives. Research Journal of Chemical Sciences, 2017 February; 7(2): 49-53.
15. Aazam ES, Zaki M. Synthesis and characterization of Ni (II)/Zn (II) metal complexes derived from Schiff base and ortho-phenylenediamine: in vitro DNA binding, molecular modeling and RBC hemolysis. Chemistry Select, 2020 Jan 16; 5(2): 610-8.
16. Allinger NL, Geise HJ, Pyckhout W, Paquette LA, Gallucci JC. Structures of norbornane and dodecahedrane by molecular mechanics calculations (MM3), X-ray crystallography, and electron diffraction. Journal of the American Chemical Society, 1989 Feb; 111(3): 1106-14.
17. Rawal K, Khurana T, Sharma H, Verma S, Gupta S, Kubba C, Strych U, Hotez PJ, Bottazzi ME. An extensive survey of molecular docking tools and their applications using text mining and deep curation strategies. Peer J Preprints, 2019 Feb 15; 7: 27538v1.
18. Vieira TF, Sousa SF. Comparing AutoDock and Vina in ligand/decoy discrimination for virtual screening. Applied Sciences, 2019 Oct 25; 9(21): 4538.
19. Ou-Yang SS, Lu JY, Kong XQ, Liang ZJ, Luo C, Jiang H. Computational drug discovery.

Acta Pharmacologica Sinica, 2012 Sep; 33(9): 1131-40.

20. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports, 2017 Mar 3; 7(1): 1-3.
21. Hassan AS, Askar AA, Naglah AM, Almehizia AA, Ragab A. Discovery of new Schiff bases tethered pyrazole moiety: design, synthesis, biological evaluation, and molecular docking study as dual targeting DHFR/DNA gyrase inhibitors with immunomodulatory activity. Molecules, 2020 Jan; 25(11): 2593.
22. Daina A, Zoete V. Application of the Swiss Drug Design online resources in virtual screening. International journal of molecular sciences, 2019 Sep 18; 20(18): 4612.
23. Wen H, Jung H, Li X. Drug delivery approaches in addressing clinical pharmacology-related issues: opportunities and challenges. The AAPS journal, 2015 Nov; 17(6): 1327-40.
24. Madanagopal P, Ramprabhu N, Jagadeesan R. In silico prediction and structure-based multitargeted molecular docking analysis of selected bioactive compounds against mucormycosis. Bulletin of the National Research Centre, 2022 Dec; 46(1): 1-21.