International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

Insilico Studies and Molecular Docking Of 1, 3, 4-Thiadiazole Derivatives as Antimicrobial Agents

Abhisha K., Babu G., and Shalima N.K., *
Department of Pharmaceutical Chemistry,Devaki Amma Memorial College of Pharmacy, Chelembra, Malappuram,Kerala,India-673634

Date of Submission: 01-11-2021 Date of Acceptance: 09-11-2021

ABSTRACT
With the goal of obtaining a novel bioactive compound with significant antimicrobial activity, a series of 1,3,4-thiadiazole derivatives (5 A1-5 C9) were designed and evaluated these compounds through Insilico studies. Molecular properties of designed compounds were studied by using Molinspiration. Theoretical absorption, distribution, metabolism, and excretion (ADME) predictions were calculated to seek their drug likeness of all compounds. ADME studies were performed by using QikProp software. Molecular docking studies were done by using Schrödinger maestro 2020-3 software to assess the binding mode and interactions of synthesized hits at binding site of receptors. Toxicity studies were done by using Lazar 1.4.2 software. Compounds 5 A4,5 A9, and 5 B3 shows excellent antibacterial activity on DHFR, DHPS and compound 5 C9 shows good antifungal activity on SAP2 receptor. Results of Insilico studies showed that most of the compounds have excellent drug likeness properties, pharmacokinetic profile and are preferable as an orally available drug.

KEY WORDS:1, 3, 4-thiadiazole, Anti-microbial activity, Insilico studies, Molecular docking

I. INTRODUCTION

Drug discovery can be described as the process of identifying chemical entities that have the potential to become therapeutic agents. A key goal of drug discovery campaigns is the recognition of new molecular entities that may be of value in the treatment of diseases that qualify as presenting unmet medical needs. Molecular modelling and computational chemistry are assuming an increasingly important role in understanding the basis of drug-receptor interactions and assisting the medicinal chemist in the design of new therapeutic agents.[1]

Microbial infections caused by various types of bacteria and fungi are one of the leading infections which are responsible for the deaths of the millions of patients worldwide [2]. Treatment of microbial infections including bacterial, fungal and tubercular is becoming difficult because of everlasting problem of microbial resistance towards antibiotics hence the need for new generations of anti-infective agents, and in particular new antimicrobial agents, is constant for effective treatment of microbial infections [3]. The need to design new compounds to deal with this resistance has become one of the most important areas of research today [4].

1,3,4-Thiadiazole is a privileged five-membered ring system that has gained prominence by exploring broad biological activity spectrum due to the presence of the N=C–S moiety.[5]There are several isomers of thiadiazole, that is 1,2,3 Thiadiazole, 1,2,5 Thiadiazole, 1,2,4 Thiadiazole and 1,3,4 Thiadiazole. 1,3,4 Thiadiazole is the isomer of thiadiazole series. A glance at the standard reference works shows that more studies have been carried out on the 1,3,4 Thiadiazole than all the other isomers combined. Members of this ring system have found their way in to such diverse applications as pharmaceuticals, oxidation inhibitors, cyanide dyes, metal complexing agents.[6]From the literature survey, it was noticed that 1,3,4-thiadiazole derivatives possess many pharmacological activities, such as antimicrobial, anti-hepatitis B viral, antitubercular, antileishmanial, analgesic, anti-inflammatory, anticancer, anticonvulsant, central nervous system (CNS) depressant, antioxidant, molluscicidal, antidiabetic, diuretic, and antihypertensive activities .[7-16]

Based on the above-mentioned points, present study aims to design potentially active novel 1, 3, 4-thiadiazole derivatives through in-silico drug design and to evaluate their antimicrobial activity via molecular docking studies.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

II. MATERIALS AND METHODS

In silicoStudies

Drug Likeness Study Using Molinspiration Molecular viewer

Molinspiration Cheminformatics offers broad range of tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomer's, molecule fragmentation, calculation of various molecular properties needed in quantitative structure activity relationship (QSAR) study, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. Drug-likeness is qualitative concept used for drug like property that described as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs. These molecular properties are mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features that influence the behaviour of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others.[17]

Smile notation of the selected derivatives were fed in the online Molinspiration software (http://www.molinspiration.com) to predict the drug likeness properties.

ACD/ChemSketch

ACD/ChemSketch is a molecular modelling program used to create and modify images of chemical structures. Also, there is a software that allows molecules and molecular models displayed in two and three dimensions, to understand the structure of chemical bonds and the nature of the functional groups.Chemical structures and SMILE notations of the compounds were obtained by using ACD labs ChemSketch version 12.0.[18]
(https://www.acdlabs.com/resources/freeware/chemsketch/)

Pharmacokinetics Properties

Lipinski's rule of five is used in drug design and development to predict oral bioavailability of potential lead or drug molecules.ADME refers to the absorption, distribution, metabolism, and excretion of a molecule in an organism. All these characteristics are very important for any drug. Having favourable ADME characteristics is one of the most daunting hurdles for drug development. Thus, early optimization is very essential in this process. A waste of time and money in the later stages of drug development can be prevented thanks to early optimization. The identification and elimination of unfavourable compounds makes the research process more cost-effective and efficient [19]. For this reason, the prediction of the pharmacokinetic properties of new drug candidates as early as possible in the drug development process is very important.[20]

QikProp software

QikProp is a program that efficiently evaluates pharmaceutically relevant properties for over half a million compounds per hour, making it a powerful lead generation and lead optimization tool. It provides the ability to detect problematic candidates early that can dramatically reduce the amount of wasted time and resources, and streamline the overall development process.[21]

Toxicity

It is essential, in order to minimise expensive drug failures due to toxicity being found in late development or even in clinical trials, to determine potential toxicity problems as early as possible. In view of the large libraries of compounds now being handled by combinatorial chemistry and high-throughput screening, identification of putative toxicity is advisable even before synthesis. Thus, the use of predictive toxicology is called for. A number of in-silico approaches to toxicity prediction are discussed.[22] In this study, the toxicity studies were performed by using Lazar 1.4.2 software.Lazar (Lazy Structure-Activity Relationships) takes a chemical structure as input and provides predictions for a variety of toxic properties. Lazar uses an automated and reproducible read across procedure to calculate predictions. Rationales for predictions, applicability domain estimations and validation results are presented in a clear graphical interface for the critical examination by toxicological experts. [23]

Molecular Docking

Molecular docking is a kind of computational modelling, which facilitates the prediction of preferred binding orientation of one molecule (e.g., ligand) to another (e.g., receptor), when both interact each other in order to form a stable complex. Information gained from the preferred orientation of bound molecules may be employed to predict the energy profiling (such as binding free energy), strength and stability (like

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

binding affinity and binding constant) of complexes. This can be done using scoring function of molecular docking.[24]In this study, molecular docking studies were performed by using Schrodinger Maestro interface running on windows 10 operating system. The structure of the ligand was built using the Schrödinger Maestro interface and was then submitted to the Protein Preparation Wizard protocol of the Schrödinger Suite 2016 Update 2. The ligands were prepared using LigPrep 3.8 to correctly assign the protonation states at pH 7.4±1.0, as well as the atom types.[20] The ligand preparation involves 2D or 3D structures and producing their low energy states in maestro format using OPLS 2005 force field, with the possibilities to extend each input structure by generating variation on ionization states. Bond orders were assigned and hydrogen atoms were added to the structures. PDB ID's of the three receptors (2ANO,1AJ0,1EAG) were download from protein data bank with suitable resolution. The protein chain was selected and residual water molecules was deleted which were beyond 5 Å, leaving behind water molecules near the ligand to yield energy minimized protein structures. This energy minimized protein structures were then used to generate grid. The grid generation was formed using the Glide 7.1 program. Finally docking was carried out using Glide software with Extra precision and write XP descriptor information. During this procedure, favourable ligand poses were then generated to determine their spatial fit into the active site of receptor and those who fitted best were then evaluated and minimized for generating glide scores. The Glide score, hydrogen bonds and pi-pi interactions formed with the surrounding amino acids were used to predict the binding affinities and proper alignment of these compounds at the active site of the receptors.

III. RESULT AND DISCUSSION

Structure of proposed ligand containing 1, 3, 4-thiadiazole is shown in Figure 1

Figure 1: Designed Ligand

Proposed compounds were designed and evaluated by various in-silico tools such as Chemsketch, Molinpiration, QikProp, Maestro Schrodinger, Lazar etc.Table-1 showing proposed derivatives of the designed ligand.

Table 1: proposed derivatives of designed ligand

Sl. No.	Compound Code	R1	R2
1	5 A1	Indole-3-acetic acid	p-Anisidine
2	5 A2	Indole-3-acetic acid	Aniline
3	5 A3	Indole-3-acetic acid	p-Nitroaniline
4	5 A4	Indole-3-acetic acid	p-Fluoro aniline
5	5 A5	Indole-3-acetic acid	Benzylamine
6	5 A6	Indole-3-acetic acid	Propylamine

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

7	5 A7	Indole-3-acetic acid	Isopropyl amine
8	5 A8	Indole-3-acetic acid	Amino phenol
9	5 A9	Indole-3-acetic acid	3-amino-1-propanol
10	5 B1	p-Nitro benzoic acid	p-Anisidine
11	5 B2	p-Nitro benzoic acid	Aniline
12	5 B3	p-Nitro benzoic acid	p-Nitroaniline
13	5 B4	p-Nitro benzoic acid	p-Fluoro aniline
14	5 B5	p-Nitro benzoic acid	Benzylamine
15	5 B6	p-Nitro benzoic acid	Propylamine
16	5 B7	p-Nitro benzoic acid	Isopropyl amine
17	5 B8	p-Nitro benzoic acid	Amino phenol
18	5 B9	p-Nitro benzoic acid	3-amino-1-propanol
19	5 C1	p-Amino benzoic acid	p-Anisidine
20	5 C2	p-Amino benzoic acid	Aniline
21	5 C3	p-Amino benzoic acid	p-Nitroaniline
22	5 C4	p-Amino benzoic acid	p-Fluoro aniline
23	5 C5	p-Amino benzoic acid	Benzylamine
24	5 C6	p-Amino benzoic acid	Propylamine
25	5 C7	p-Amino benzoic acid	Isopropyl amine
26	5 C8	p-Amino benzoic acid	Amino phenol
27	5 C9	p-Amino benzoic acid	3-amino-1-propanol

Determination of Drug Likeness Properties

We predicted the drug likeliness profile of the compounds through the analysis of pharmacokinetic properties of the compounds by using molinspiration online property toolkit. Based on the results obtained from molinspiration it was observed that all of the proposed compounds obeyed Lipinski rule of five. According to the Lipinski's rule of five new molecule designed for oral route should have a MW <500, log Po/w < 5, Not more than 5 hydrogen bond donors and not more than 10 hydrogen bond acceptors. The percentage of absorption (% ABS) was calculated from TPSA. The results are presented in Table 2

Table 2: Lipinski rule analysis of proposed derivatives

Sl No.	Cmpd Code	Molecular weight	log p	nON	nOHNH	Nrotb	No.of violations

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

1	5 A1	336.42	4.55	5	2	4	0
2	5 A2	306.39	4.49	4	2	4	0
3	5 A3	335.39	4.45	7	2	5	0
4	5 A4	324.38	4.65	4	2	4	0
5	5A5	320.42	3.75	4	2	5	0
6	5 A6	272..38	3.23	4	2	5	0
7	5 A7	272.38	3.03	4	3	4	0
8	5 A8	322.29	4.01	5	3	4	0
9	5 A9	288.38	3.99	5	3	6	0
10	5 B1	298.37	3.70	5	3	4	0
11	5 B2	268.35	3.64	4	3	3	0
12	5 B3	313.34	3.60	7	3	4	0
13	5 B4	286.33	3.80	4	3	3	0
14	5 B5	282.37	2.90	4	3	4	0
15	5 B6	234.33	2.38	4	4	4	0
16	5 B7	220.30	1.75	4	4	2	0
17	5 B8	284.34	3.16	5	5	4	0
18	5 B9	250.33	1.15	5	5	5	0
19	5 C1	328.35	4.58	7	7	5	0
20	5 C2	298.33	4.52	6	6	4	0
21	5 C3	264.31	3.01	6	6	5	0
22	5 C4	343.32	4.48	9	9	4	0
23	5 C5	312.35	3.40	6	6	4	0
24	5 C6	264.31	3.27	6	6	5	0
25	5 C7	316.32	4.69	6	6	4	0
26	5 C8	314.33	4.04	7	7	4	0
27	5 C9	280.31	4.03	7	7	6	0

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

Determination of ADME properties

Over the past decade, absorption, distribution, metabolism, and excretion (ADME) property evaluation has become one of the most important issues in the process of drug discovery and development. Since in vivo and in vitro evaluations are costly and laborious, in silico techniques had been widely used to estimate ADME properties of chemical compounds. Traditional prediction methods usually try to build a functional relationship between a set of molecular descriptors and a given ADME property.[25] ADME parameters of synthesized compounds (5 A1–5 C9) were calculated with the help of QikProp 4.8 software. Table 3 presents predicted ADME properties of all compounds, and this table contains the following parameters: absorption, percentage oral absorption, protein binding, Caco-2 permeability and metabolism. Consequently, according to predictions of the ADME properties, it can be suggested that the final compounds may have a good pharmacokinetic profile.

Table 3: ADME prediction by QikProp software

Cmpd code	Absorption (1 - 3)	Percentage oral absorption (0-100%)	Protein Binding (-1.5 - 1.5)	Caco-2 Permeability (>500)	Metabolism (1 - 8)
5 A1	3	89.98%	0.55	316.313	8
5 A2	3	100%	0.492	1771.299	8
5 A3	3	100%	0.486	1127.505	8
5 A4	3	100%	0.534	1619.783	7
5 A5	3	100%	0.648	1341.714	8
5 A6	3	100%	0.326	1548.761	7
5 A7	3	100%	0.352	1899.111	7
5 A8	3	100%	0.291	2127.95	8
5 A9	3	100%	0.66	1500.61	8
5 B1	3	89.83%	0.651	1986.846	8
5 B2	3	100%	0.634	2217.953	8
5 B3	3	100%	0.64	2029.724	8
5 B4	3	100%	0.587	984.721	7
5 B5	3	100%	0.598	3551.922	8
5 B6	3	100%	0.691	2785.355	7
5 B7	3	100%	0.631	2186.004	8
5 B8	3	100%	0.712	3454.216	8

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

5 B9	3	100%	0.586	4037.766	7
5 C1	3	100%	0.723	807.832	8
5 C2	3	100%	0.632	3695.538	8
5 C3	3	100%	0.245	2171.258	8
5 C4	3	93.56%	0.33	381.901	7
5 C5	3	100%	0.654	123.659	8
5 C6	3	100%	0.751	1126.545	8
5 C7	3	93.11%	0.133	1458.658	7
5 C8	3	89.34%	0.732	2163.954	8
5 C9	3	100%	0.352	1126.545	8

Molecular Docking studies

Molecular docking studies of 27 derivative of 1,3,4-thiadiazole compounds were done by using Schrodinger software.Docking studies were conducted on two anti-bacterial receptors DHFR and DHPS and one antifungal receptor is SAP2.Most of the designed compounds show potent antimicrobial activity.The docking scores of the derivatives are given in Table 4.

Table 4: **Docking scores of proposed derivatives**

Sl. No.	Compound code	2ANO	1AJ0	1EAG
1	5 A1	-8.5	-7.1	-7.1
2	5 A2	-8.4	-7.0	-7.3
3	5 A3	-8.0	-6.9	-7.5
4	5 A4	-8.8	-8.1	-8.1
5	5 A5	-8.4	-8.0	-7.6
6	5 A6	-7.0	-8.3	-7.1
7	5 A7	-7.2	-8.1	-7.8
8	5 A8	-7.4	-8.2	-7.5
9	5 A9	-8.9	-8.5	-8.3
10	5 B1	-8.2	-7.5	-7.9
11	5 B2	-8.4	-7.4	-8.0
12	5 B3	-8.7	-7.9	-8.4
13	5 B4	-8.1	-7.6	-8.1
14	5 B5	-8.3	-7.1	-8.0

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

15	5 B6	-8.0	-7.7	-8.2
16	5 B7	-7.7	-7.3	-8.3
17	5 B8	-7.5	-7.5	-8.1
18	5 B9	-7.8	-7.1	-8.0
19	5 C1	-7.3	-7.9	-8.1
20	5 C2	-7.1	-8.0	-7.9
21	5 C3	-7.4	-8.2	-8.0
22	5 C4	-7.9	-8.1	-7.6
23	5 C5	-7.7	-7.9	-7.7
24	5 C6	-7.6	-8.0	-7.5
25	5 C7	-7.7	-8.2	-7.2
26	5 C8	-7.4	-8.1	-6.9
27	5 C9	-7.2	-8.6	-6.5

All designed derivatives are docked with receptors DHFR,DHPS for antibacterial activity and SAP2 for antifungal activity. Docking interaction of compound 5A4 and 5A9 on DHFR (PDB ID:2ANO) shown in figure 2 and figure 3 respectively.

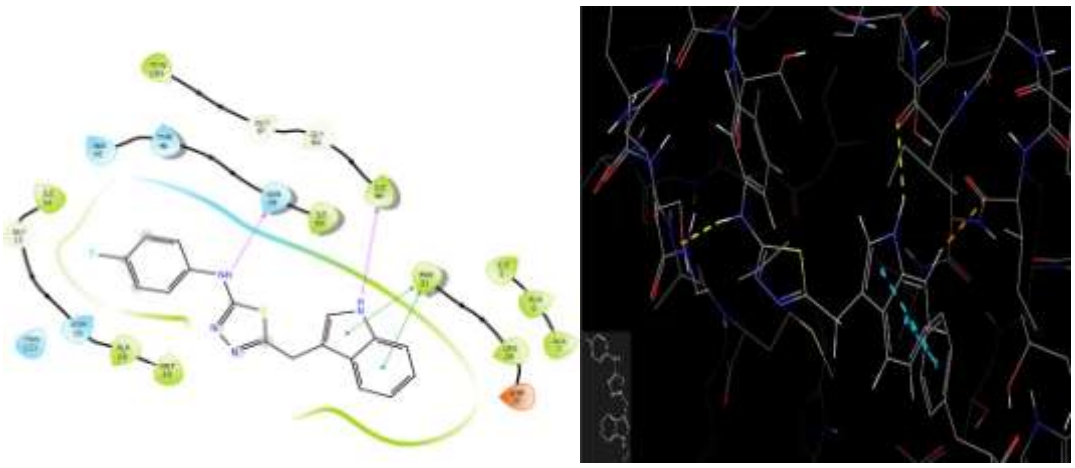

Figure 2: 2D and 3D binding interaction of compound 5 A4 in the active region of DHFR (PDB ID:2ANO)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

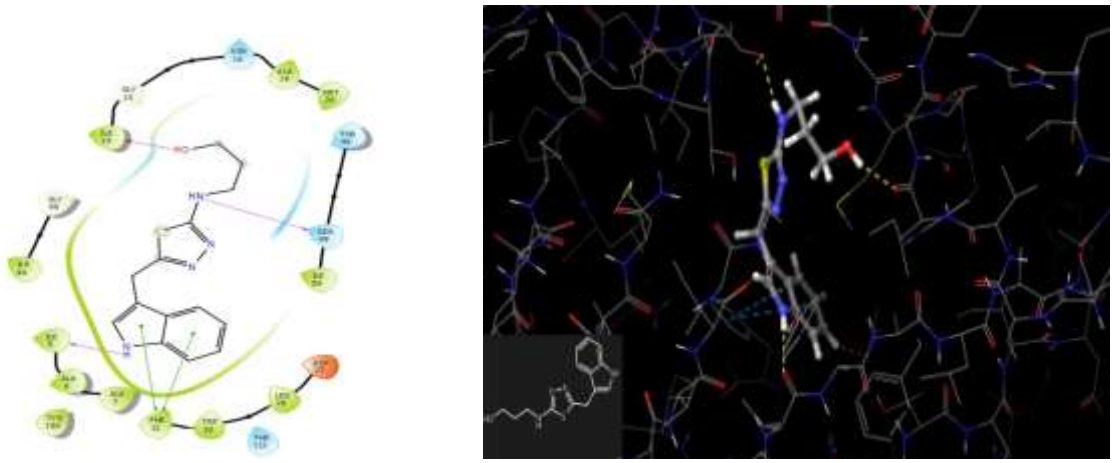

Figure 3: 2D and 3D binding interaction of compound 5 A9 in the active region of DHFR (PDB ID:2ANO)

Compounds 5 A1,5 A4,5 A9,5 B3 showed good docking score (-8.5, -8.8, -8.9.-8.7 respectively) in the active site of DHFR receptor. Docking interaction of designed compound on the receptor DHPS (PDB ID: 1AJ0)is shown in figure 4.

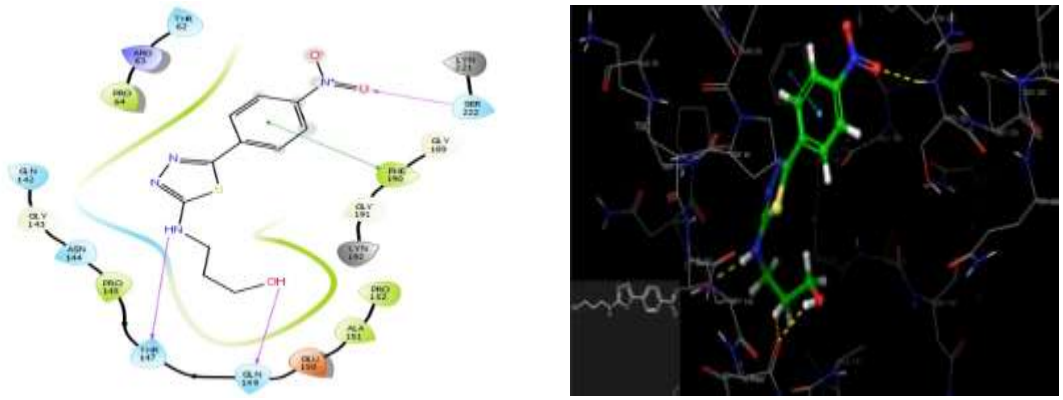

Figure 4: 2D and 3D binding interaction of 5C9 on the active site of DHPS (PDB ID:1AJ0)

Compounds 5A4,5A8,5 A9and 5C9 showed good docking score (-8.1, -8.2, -8.5, -8.6 respectively) in the active site of dihydropteroate synthase receptor (PDB ID :1AJ0). Docking interaction of compound 5B3 in the active site of secreted aspartic proteinase 2 receptor (PDB ID :1EAG) shown in figure 5.

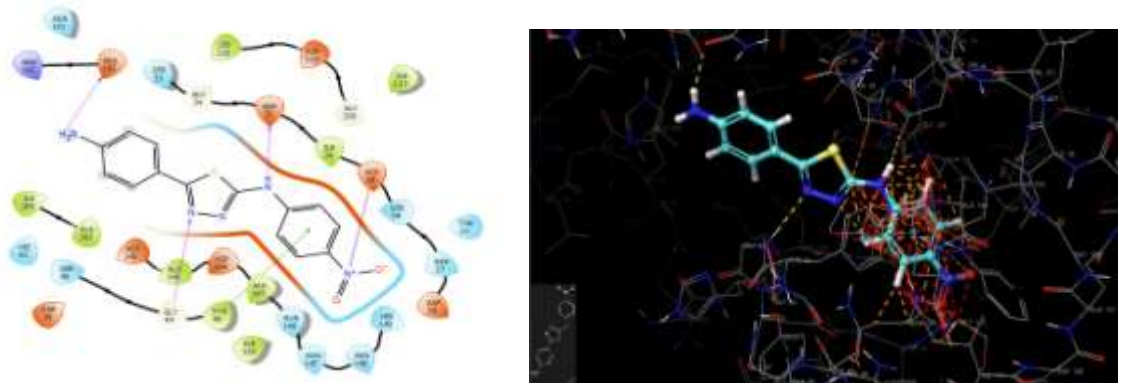

Figure5:2D and 3D interaction mode of compound 5B3 in the active site of SAP2 (PDB ID: 1EAG)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 05-15 www.ijprajournal.com ISSN: 2249-7781

Compounds 5 A4,5 A8,5 A9,5 B3 shows good docking score (-8.1,-8.2,-8.3,-8.4 respectively) in the active site of SAP2(PDB ID:1EAG).

Toxicity prediction

Toxicity prediction of compounds which is selected on the basis of molecular docking studies.4 compounds were evaluated by using Lazar 1.4.2 software and evaluated their carcinogenicity and mutagenicity characteristics of selected compounds. Selected 4 compounds shows non-carcinogenic and non-mutagenic in nature. The results of toxicity studies are given in Table 5.

Table 5: Toxicity prediction by Lazar 1.4.2 software

Sl. No	Compound code	Carcinogenicity	Mutagenicity
1	5 A4	Non-carcinogenic	Non-mutagenic
2	5 A9	Non-carcinogenic	Non-mutagenic
3	5 B3	Non-carcinogenic	Non-mutagenic
4	5 C9	Non-carcinogenic	Non-mutagenic

IV. CONCLUSION

In this study, we designed twenty-seven derivatives of 1, 3, 4-thiadiazole nucleus and evaluated their Molecular docking studies with the receptors DHFR and DHPS for the antibacterial activity and SAP2 for the antifungal activity through Insilco studies. All compounds in the series exhibited a good predicted pharmacokinetics profile. All compounds obeyed Lipinski rule of five which suggest that these compounds have excellent drug likeness properties and are preferable as an orally acting drug. Results of ADME prediction conclude that synthesized compounds may possess a good pharmacokinetic profile, increasing their pharmacological importance. All of the compounds which is selected for toxicity studies on the basis of molecular docking showsnon-toxic. Molecular docking study reveals that, compounds 5 A4,5 A9,5 B3,5 C9 excellent activity on DHFR,DHPS and SAP2 respectively. Consequently, based on the Insilco Drug likeness, ADME evaluation and molecular docking study, introduced new 1,3,4-thiadiazole derivatives as potent antimicrobial agents.

REFERENCES

[1]. Sausville, E. A.2012, Drug Discovery. Principles of Clinical Pharmacology; 507–515. doi:10.1016/b978-0-12-385471-1.00030-1

[2]. Kharb R., Kaur P., Sharma P. C., Yar M. S.,2011, Int. J. Res. Pharm. Bio. Sci; 2(4), 1520-1540.

[3]. Kharb R., Bansal K., Sharma A. K.,2012 Der Pharma Chemica.; 4(6), 2470-2488.

[4]. Bhuva H., Sahu D., Shah B. N., Modi D. C., Patel M. B., Pharmacologyonline, 2011; 1, 528-543.

[5]. Naggar E., Sallam M., Hanan A., Shaban, Safaa S., Wahab A., Salwa S., Amr E., Galil A. E., Mohammad E., Eman S., Al-Omar, Mohamed A.,2019,Design, Synthesis, and Molecular Docking Study of Novel Heterocycles Incorporating 1,3,4-Thiadiazole Moiety as Potential Antimicrobial and Anticancer Agents.,Molecules ,24(6).

[6]. Gupta J. K., Yadav R. K.,Dudhe R., Sharma P. K.,2010., Recent Advancements in the Synthesis and Pharmacological Evaluation of Substituted 1, 3, 4Thiadiazole Derivatives, International Journal of PharmTech Research,2(2), Vol.2, No.2, pp 1493-1507,

[7]. Jain, K.; Sharma, S.; Vaidya, A.; Ravichandran, V.; Agrawal, R.K. 2013,1,3,4-Thiadiazole and its derivatives: A review on recent progress in biological activities. Chem. Biol. Drug Des., 81, 557–576.

[8]. Kushwaha, N.; Kushwaha, S.K.S.; Rai, A.K.2012, Biological activities of thiadi¬azole derivatives: A review. Int. J. Chem. Res., 4, 517–531.

[9]. Gomha, S.M.; Salah, T.A.; Abdelhamid A.O. 2015,Synthesis, characterization, and pharmacological evaluation of some novel thiadiazoles and thiazoles incorporating pyrazole moiety as anticancer agents. Monatsh. Chem., 146, 149–158.

[10]. Gomha, S.M.; Abdel-aziz, H.M.2015, Synthesis and antitumor activity of 1,3,4-thiadiazole derivatives bearing coumarine ring. Heterocycles, 91, 583–592.

[11]. Siddiqui, N.; Ahuja, P.; Ahsan, W.; Pandeya, S.N.; Alam, M.S.2009, Thiadiazoles:

Progress report on biological activities. J. Chem. Pharm. Res., 1, 19–30.

[12]. Bhattacharya, P.; Leonard, J.T.; Roy, K.2005, Exploring QSAR of thiazole and thiadiazole derivatives as potent and selective human adenosine A3 receptor antagonists using FA and GFA techniques. Bioorg. Med. Chem., 15, 1159–1165.

[13]. Foroumadi, A.; Kargar, Z.; Sakhteman, A.; Sharifzadeh, Z.; Feyzmohammadi, R.; Kazemi, M.; Shafiee, A.2006, Synthesis and antimyco¬bacterial activity of some alkyl [5-(nitroaryl)-1,3,4-thiadiazol-2- ylthio] propionates. Bioorg. Med. Chem. Lett., 16, 1164–1167.

[14]. Kumar, D.; Kumar, N.M.; Chang, K.H.; Shah, K. 2010,Synthesis and anticancer activity of 5-(3-indolyl)-1,3,4-thiadiazoles. Eur. J. Med. Chem., 45, 4664–4668.

[15]. Sharma, B.; Verma, A.; Prajapati, S.; Sharma, U.K.,2013, Synthetic methods, chemistry, and the anticonvulsant activity of thiadiazoles. Int. J. Med. Chem. 348948.

[16]. Mathew, V.; Keshavayya, J.; Vaidya, V.P.; Giles, D.,2007 Studies on synthesis and pharmacological activities of 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and their dihydro analogues. Eur. J. Med. Chem., 42, 823–840.

[17]. Singh H. P., Sharma C. S., Mishra S. S., Pandiya H., Kumar N.,2017 Apr 17,In silico-ADME, Bioactivity and Toxicity Prediction of Some Selected Anti-Parkinson Agents. International Journal of Pharmaceutical and Phytopharmacological Research. ;6(3):64-7

[18]. Acdlabs chemsketch-(https://www.acdlabs.com/resources/freeware/chemsketch/)

[19]. Waterbeemd V. D., Gifford E.,2003,ADMET in silico modelling: Towards prediction paradise, Nat. Rev. Drug Discov, 192–204.

[20]. Karaburun A.C., Çevik U. A., Osmaniye D.,2018,1,2,Synthesis and Evaluation of New 1,3,4-Thiadiazole Derivatives as Potent Antifungal Agents,Molecules, 23,1-18

[21]. Kang N.F.,2013, An in-silico evaluation of the ADMET profile of the StreptomeDB database. Springerplus; 2:353. Published 2013 Jul 30. doi:10.1186/2193-1801-2-353

[22]. Dearden, J.C.,2003 In silico prediction of drug toxicity. J Comput Aided Mol Des **17,** 119–127. https://doi.org/10.1023/A:1025361621494

[23]. https://openrisknet.org/e-infrastructure/services/110/

[24]. Agarwal S., Mehrotra R., An overview of Molecular Docking. JSM Chem 4(2): 1024

[25]. Shen, J., Cheng, F., Xu, Y., Li, W., & Tang, Y.,2010,Estimation of ADME Properties with Substructure Pattern Recognition. Journal of Chemical Information and Modeling, 50(6), 1034–1041. doi:10.1021/ci100104j