IJBPAS, April, 2023, 12(4): 1645-1656

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF BENZOTHIAZOLE DERIVATIVES AS SIGNIFICANT ANTI-MICROBIAL AGENTS

SRIDARAN C[1], VIJAY BABU A[1], PRIYA D[1*] AND KATHIRAVAN MK[2]

1: Department of Pharmaceutical Chemistry, SRM College of Pharmacy, SRMIST, Kattankulathur, Chengalpattu District-603203, Tamil Nadu, India

2: Professor and Head, Department of Pharmaceutical Chemistry, SRMIST, Kattankulathur, Chengalpattu District-603203, Tamil Nadu, India

***Corresponding Author: Dr. D Priya: E Mail: priyarularasan@gmail.com**

Received 10th June 2022; Revised 17th July 2022; Accepted 3rd Sept. 2022; Available online 1st April 2023

https://doi.org/10.31032/IJBPAS/2023/12.4.7055

ABSTRACT

Most of the synthetic and natural compounds contain Benzothiazole nucleus that have various pharmacological activities like Anti-microbial Anti-parasitic, anti-bacterial, anti-fungal, antioxidant, anti-tubercular, antineoplastic, antiviral, anti-inflammatory, and so on. Microbial infections are the most widespread and dangerous infections in the world, caused by various viable pathogens. Hence, due to the rise of microbial infections, and widespread use of benzothiazole, the study is an attempt to identify a better anti-microbial agent through *in silico* studies. The binding energies of benzothiazole bearing chloro and nitro substitutions were to be -7.87 and -7.72 against the protein with PDB ID 2EG7. These two compounds were synthesised and evaluated for in vitro anti-microbial activity.

Keywords: - Benzothiazole, Anti-microbial activity, Docking, ADME, Toxicity

1. INTRODUCTION

Benzene fused with azoles is one of the most important groups of molecules that contain a heterocyclic skeleton in a variety of pharmacologically active and medicinally relevant compounds. These fused heterocyclic compounds are significant pharmacophores demonstrating an impressively broad spectrum of pharmacological activity **[1]**. Fused heterocycles like Benzothiazole are present in most of the synthetic and natural compounds and are associated with various

pharmacological activities like Anti-microbial **[2-6]**, Anti-parasitic **[7]**, Anti-bacterial **[8-9]**, Anti-fungal **[10]**, Antioxidant **[11]**, Anti-tubercular **[12]**, Antineoplastic **[13-14]**, Antiviral **[15]**, Anti-inflammatory **[16]**, Anthelmintic **[17]**, Analgesic **[18]**, Depressive, Hypnotic, Antipyretic, Anti-spasmolytic, and Insecticide effect [19]. The ability of substituted heterocycles like benzothiazole derivatives to interact with many cellular targets, including *Staphylococcus aureus*, DNA gyrase, *E.coli dihydrofolate synthase, Plasmodium dihydropteroate reductase,* and, more recently, *E.coli dihydroorotase*, was found to be responsible for their antimicrobial activity. Many of the drugs containing benzothiazole nucleus such as Riluzole, Ethoxzolamide, Pramipexole, Thioflavine T, etc. have been explored with different activities **[20]**. **Figure 1** gives the details of the drugs bearing benzothiazole nucleus having various pharmacological activities. These heterocyclic ring systems possess an interesting profile to treat microbial diseases and they play a vital role in the field of medicinal chemistry.

Microbial infections are the most widespread and dangerous infections in the world, caused by various viable pathogens. It has spread by various modes such as coughing, sneezing, contact with an infected person, from infected animals, consuming contaminated water or foods, and agricultural applications. As per World Health Organization, 1.4 million children died as a result of gut infections and dysentery caused by gram-negative pathogens such as *pseudomonas, shigellae*, and *salmonella*, as well as gram-positive pathogen such as *corynebacterium diphtheriae*. The microbial infection affects all the systems of the human body and the treatment becomes a major challenge even in developing countries. Antimicrobial drugs have a critical role in lowering the worldwide burden of infectious illnesses of both bacterial and fungal origin **[5]**. Many synthetic antimicrobial agents are widely prescribed in treating infectious diseases like cold, pneumonia, tuberculosis, hepatitis A, and B, influenza, SARS, malaria, AIDS, meningitis, etc. The rise of microbial infections has been ascribed to the widespread use of broad-spectrum antimicrobial drugs, due to acquired drug resistance. This led to the development of new medicines to combat microbial illnesses. The goal of this work is to evaluate the antimicrobial potential of newly designed and synthesized benzothiazole derivatives. To reach this goal, we used two strategies: an *in-silico* analysis in which computer-assisted docking was used to investigate the ability of the substituted benzothiazole derivatives to determine binding to the specified target protein. Secondly, an *in-vitro* approach in

which the inhibitory effect of synthesized compounds is tested on microbes. Benzothiazole heterocyclic nucleus was chosen for my studies due to its potency and significant pharmacological activity.

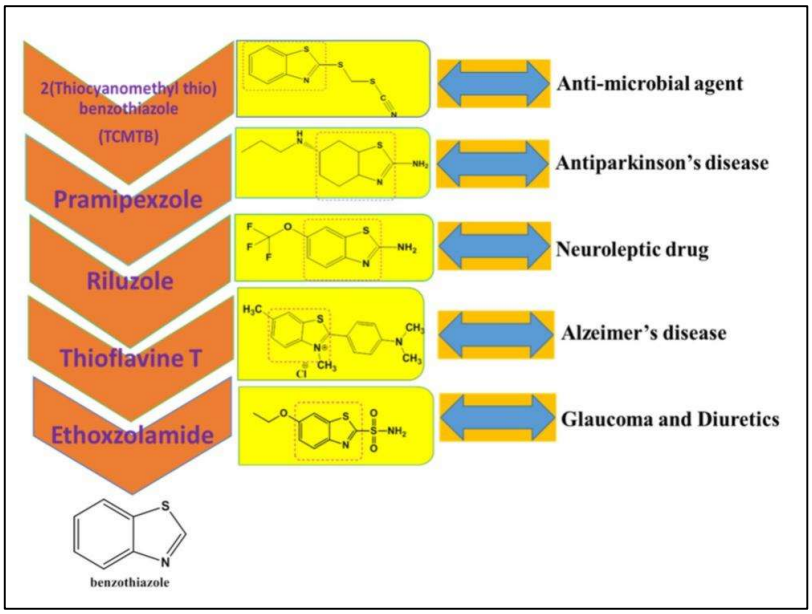

Figure 1: Drugs bearing benzothiazole nucleus having various pharmacological activities

2. EXPERIMENTAL

2.1. Materials and methods: For the synthesis, analytical grade chemicals and commercially available reagents were utilized. The melting points were estimated in an open capillary tube and are noted with help of digital melting point apparatus. Thin-layer chromatography (TLC) was used to verify the completeness of the reaction and the purity of the products by using a silica gel coated plate (Silica Gel 60 GF254) and visualized under a UV chamber with 254nm. IR spectra on the KBr disc were recorded from 4000 to 400 Cm^{-1} by using the Bruker FT-IR instrument. The Molecular weight of the synthesized compounds was identified by the SMADZO LC-MS instrument. The Anti-Microbial activity of synthesized compounds (5a&5b) was performed in Life Technology Research Center (Chennai) with tetracycline used as a control.

2.1.1. Software Requirements for *In-silico* studies: Software's and online tools like *ACD/ ChemSketch*, Open Babel (3.1.1) **[21]**, *Avogadro* (1.2.0) **[22]**, *Autodock* (4.2.6) **[23]**, *Osiris* **[24]**, *admetSAR*-(2.0), *Molinspiration* **[25]**, *Discovery studio visualizer* 3.0 (2019) **[26]** software was used for *in-silico* studies.

2.1.2. Experimental Procedure

Step 1: Synthesis of substituted benzanilide: 0.02mol of substituted aniline was mixed with 20ml of pyridine, followed with the addition of 0.02mol of benzoyl chloride drop wise. The mixture was then

refluxed for 2 hours, and poured into water. The precipitated product was recovered, washed with water, and finally recrystallized using methanol.

Step 2: Synthesis of substituted Thiobenzanilide from substituted Benzanilide

To make a transparent solution, a combination of the Lawesson's reagent (0.6molequiv) and substituted benzanilides (0.01mol) were refluxed with 5 to 10 ml of chlorobenzene for three hours. The product precipitated was cooled and separated on filtration. Recrystallized by using methanol.

Step 3: Synthesis of substituted Benzothiazole from substituted Thiobenzanilide

A little amount of ethanol (5.0mL) was used to moisten the substituted thiobenzanilides (0.01mol), and 8.0 mole equivalent of 30 percent sodium hydroxide solution was added. At 80–90°C, aliquots of this mixture (1 mL) were introduced at 1-minute intervals to a mixed solution of potassium ferricyanide (4.0molequiv) in water. The mixture was then heated for 30 minutes before being allowed to cool. The product was collected, purified, and recrystallized using methanol. **Figure 2** represents the scheme of the synthesis and **Table 1** provides the information of the substitution on Benzothiazole derivatives.

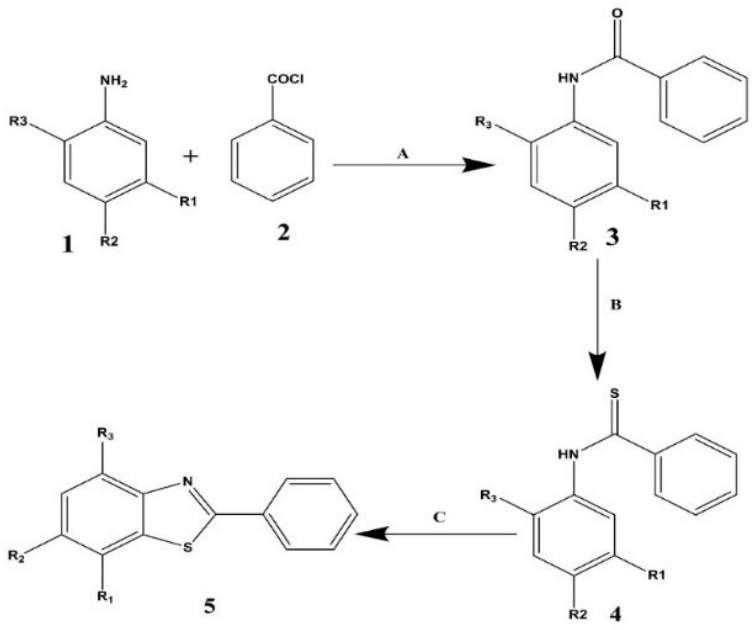

Figure 2: Experimental Scheme 1

Fig 2: A). Pyridine under reflux for 2 hours, B). Lawesson's reagent, chlorobenzene, reflux for 3 hours, C). K_3 [Fe (CN) $_6$], NaOH, Ethanol, 90^{0}C, and stir.

1. Substituted aniline, 2. Benzoyl chloride, 3. Substituted benzanilide, 4. Substituted thiobenzanilide, 5. Substituted 2-phenyl benzothiazole

Table 1: Information on the Benzothiazole derivatives

S. No	Compounds	R_1	R_2	R_3
1.	5a	H	H	NO_2
2.	5b	H	Cl	H
3.	5c	H	Cl	NO_2
4.	5d	H	H	OH
5.	5e	H	H	$COCH_3$
6.	5f	H	NO_2	NO_2
7.	5g	H	CH_3	H
8.	5h	H	$COCH_3$	H
9.	5i	H	COOH	H
10.	5j	H	Br	H
11.	5k	Br	$COCH_3$	H
12.	5l	H	NO_2	H

2.1.3. Molecular Docking:

Molecular docking acts as an important tool in the identification of new molecule by *in-silico* method. *In-silico* molecular docking of pharmacologically active synthetic compounds that attach to particular receptors gives information on the binding profile and affinity. Protein with PDB ID 2EG7 was obtained from the protein data bank (RCSB) based on Pharmacological activity and review of the literature. The interaction of substituted Benzothiazole derivatives with PDB ID **2EG7** was investigated in this work to assess their potent antimicrobial activity. Compounds (5a-5l) structures were drawn using ChemOffice (*ACD/ Chemsketch*) and they were energy minimized by using *Avogadro* (1.2.0) software. The energy minimized compounds (5a-5l) were docked into the active site of the protein 2EG7 using *AutoDock* (4.2.6) software. Before docking, the water molecule of protein was deleted and hydrogen atoms were added in the usual geometry. To render the complex receptor devoid of any ligand before docking, all heteroatoms were removed from the protein. Docking was performed following grid generation and finally the binding score was noted by the Lamarckian evolutionary method. Docked structures of all compounds were displayed in *Discovery Studio* 3.0 (2019). For each ligand, the lowest binding scores are regarded as the best-docked findings.

2.1.4. ADME Properties: The smiles code of the designed compounds was generated by using the *SwissADME* online tool to determine the ADME properties. To compute *in-silico* pharmacokinetic characteristics, we utilized the *admetSAR,* in which pharmacokinetic characteristics such as BBB, P-gpi, CYP inhibition, AMES mutagenesis, acute oral toxicity, and carcinogenicity were considered.

2.1.5. Toxicity Studies: *OSIRIS* properties were used to predict organ toxicity and toxicological endpoints for the designed compounds. Carcinogenicity, mutagenicity, reproductive effects, drug-likeness

properties, and irritants were evaluated and noted.

2.1.6. Lipinski Rule: Historically, medicines have been tiny compounds that adhere to *Lipinski's rule* of five [a molecule having a molecular mass below 500 Dalton, not greater than 5 Hydrogen bond donors, not more than 10 hydrogen bond acceptors, and partition coefficient (log P) less than 5, not greater than 3 rotatable bonds]. This rule is used to evaluate drug-likeness or to identify whether a chemical molecule with a specific pharmacological or biological activity has the physicochemical qualities which would make it a probable orally active drug in humans. These five rules of Lipinski if there are any changes in this; it suggests that there is poor absorption. The *Lipinski rule of five* (R05) of the designed compounds was noted with help of *Molinspiration*.

2.1.7. Anti-microbial activity

2.1.7.1. Inoculum Preparation: Stock cultures were kept at 4°C on the Nutrient agar Slant. Active cultures for testing were developed by shifting a loop of culture from the culture broth into a tube containing nutrient broth and incubating them for 24 hours around 37 ℃.

2.1.7.2. Assay Method [Agar disc diffusion: The antimicrobial activity of extracts was tested using the disc diffusion technique on the Muller Hinton agar (MHA) medium. The Petri plate is filled with MHA media and the colonies were distributed on the solid plates with a sterile swab wet with the bacterial suspension after the medium had hardened. The disc was put on MHA plates, and 20µl of the sample (concentration: 1000g, 750g, and 500 g) was added. The plates were incubated for 24 hours at 37 ℃ the diameter of the zone of inhibition was then measured to assess the antimicrobial activity.

3. RESULTS AND DISCUSSION

3.1. Molecular Docking results: Molecular Docking was performed for compounds 5a-5l **(Table 2)** which demonstrates the compounds binding affinity for **2EG7** target. The docking of the ligand molecules indicates that all inhibitor compounds in the active pockets are bonded to one or more amino acids and showed hydrogen bonding interaction with ARG 216. Binding scores are recorded and are tabulated in **Table 2**. The theoretical binding energies of all 12 compounds ranged from -7.87 kcal/mole to -6.31 kcal/mole. The Compounds 5a and 5b having higher binding energy when compared with others. **Figure 3 and 4** indicates binding conformation of the compound 5a and 5b.

3.2. ADME Properties

The ADME predictions like BBB, CYP450 inhibition, AMES toxicity, acute oral toxicity, and carcinogenicity properties of

all the 12 designed compounds when subjected to *admetSAR* were found to be within the range and the results are tabulated in **Table 3**.

3.3. Toxicity studies:

According to the *OSIRIS* software, it was found that all the designed compounds have good drug-likeness properties and are non-toxic. The results are tabulated in **Table 4**.

3.4. Lipinski rule of five

All Designed compounds have been following the *Lipinski rule of five* and it reveals that all compounds were within the acceptable range and are represented in **Table 5**.

3.5. Chemistry: Based on the toxicity profile, docking score, ADME, and physiochemical properties best two compounds bearing nitro and chloro substitutions in 2-phenyl Benzothiazole at the position of C-4 and C-6 (5a and 5b) were considered for the synthesis. Thus, substituted benzothiazole derivatives (compounds 5a and 5b) were synthesized by combining substituted aniline with benzoyl chloride to produce substituted benzanilides. Lawesson's reagent and Chloro-benzene were combined with the substituted benzanilide to produce substituted thiobenzanilide, which was then moistened with ethanol. Later, a sodium hydroxide solution was added and the mixture was maintained in an ice bath. To generate substituted benzothiazoles, potassium ferricyanide was added at a 1-minute time interval while stirring.

The 4-nitro-2-phenyl benzo[d]thiazole (5a) and 6-chloro-2-phenyl benzo[d]thiazole (5b) was synthesized in good yield. The compounds 5a and 5b were characterized by Infra-Red spectroscopy (FT-IR), Mass Spectra (MS), Thin-layer chromatography (TLC), and Melting point were performed to describe the synthesized substituted benzothiazole derivatives (5a & 5b).

4-nitro-2-phenyl benzo[d]thiazole **(5a)**

Yellow color Crystalline powder; yield: 69%; M.P: 478^{o}C; R_F: 0.42 (8:2 ratio of Acetone and n-hexane); M.W: 180.181 g/mole [M+H]; Solubility: Acetone and Chloroform. FT-IR (KBr): 3400 (ν N-H), 1650 (ν C=C), 1350 (C-N), 1000-670 (C-H), 850 (C-C). M.F: $C_7H_5N_3O_2S$.

6-chloro-2-phenyl benzo[d]thiazole **(5b)**

Crystalline brown color powder; yield: 66%; M.P: 399^{o}C; R_F: 0.57 (8:2 ratio of Acetone and n-hexane); ESI-MS: 184.641 g/mole [M+H], Solubility: Acetone and Chloroform. FT-IR (KBr): 3400 (ν N-H), 1700 (ν C=O), 1500 (C=C), 850 (C-C), 700 (C-Cl), 1000-667 (C-H), 770-730 (mono substitution). M.F: $C_7H_5N_2SCl$.

3.6. Anti-Microbial Activity

The best two compounds (5a and 5b) were synthesized in high yield and it's considered for antimicrobial activity *in-vitro* studies. The Anti-microbial activity was carried out on two microbes (*E. coli, S.*

aureus) using tetracycline as a standard. The zone of inhibition of the compounds 5a and 5b were determined. **Table 6** depicts the zone of inhibition of microbiological growth of the synthesized substituted benzothiazole derivatives. Compound 5a (*E. coli* 27mm and S. aureus 25mm) was found to have higher inhibition than that of compound 5b (*E. coli* 25mm, *S. aureus* 22mm) against the control of tetracycline **(Figure 7)**.

Table 2: Binding characteristics of designed compounds

S. No	Compounds	Binding Energy (Kcal/mole)
01.	5a	-7.87
02.	5b	-7.72
03.	5c	-7.42
04.	5d	-7.01
05.	5e	-7.32
06.	5f	-6.88
07.	5g	-7.27
08.	5h	-7.47
09.	5i	-6.31
10.	5j	-7.46
11.	5k	-7.11
12	5l	-7.15

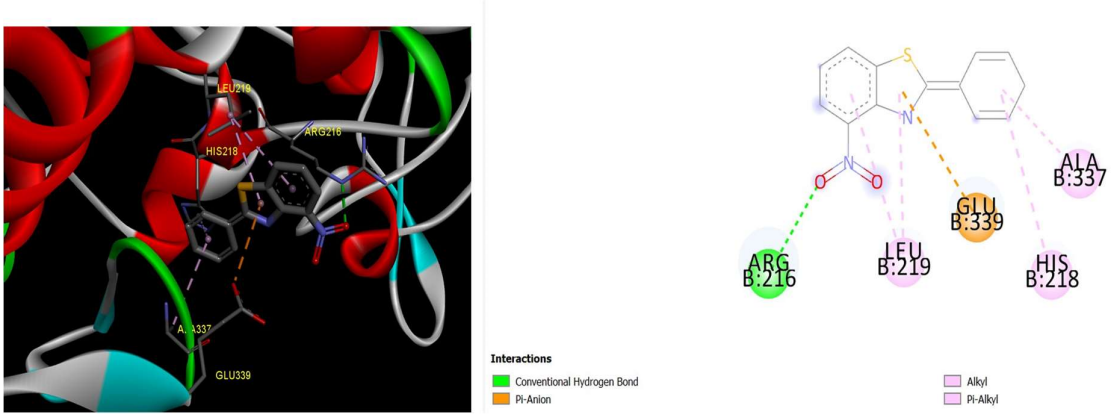

Figure 3: 3D and 2D image of Binding Conformation (5a)

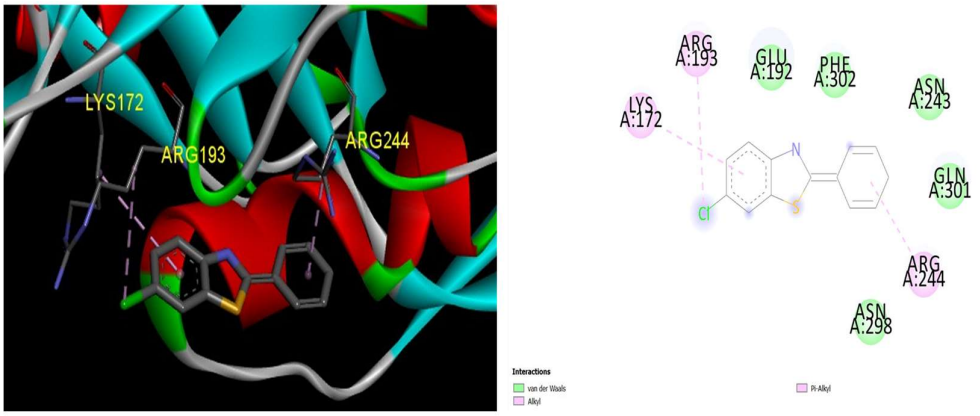

Figure 4: 3D and 2D image of Binding Conformation (5b)

Table 3: ADME properties of substituted Benzothiazole derivatives using *admetSAR*

S. No	Compounds	P-gpi	BBB	CYP Inhibition	AMES mutagenesis	Carcinogenicity	Acute oral toxicity
01.	5a	-	+	+	+	-	1.5334
02.	5b	-	+	+	-	-	2.2653
03.	5c	-	+	+	+	-	2.0637
04.	5d	-	+	+	-	-	1.5446
05.	5e	-	+	+	-	-	1.6351
06.	5f	-	+	+	+	-	1.8629
07.	5g	-	+	+	-	-	2.0172
08.	5h	-	+	+	-	-	1.3866
09.	5i	-	+	-	-	-	1.7198
10.	5j	-	+	+	-	-	2.3899
11.	5k	-	+	+	-	-	2.5915
12.	5l	-	+	+	+	-	1.8223
13.	Tetracycline	-	-	-	-	-	3.0108

Note: + indicates toxic, - Indicates non-toxic, P-gpi- P-Glycoprotein Inhibitor, BBB- Blood Brain Barrier.

Table 4: Toxicological properties of Benzothiazole derivatives using *OSIRIS* explorer Property

S. No	Compounds	Mutagenicity	Carcinogenicity	Irritant	Reproductive Effects	Drug- Likeness
01.	5a	Green	Green	Green	Green	-4.95
02.	5b	Green	Green	Green	Green	2.39
03.	5c	Green	Green	Green	Green	-3.37
04.	5d	Green	Green	Green	Green	2.26
05.	5e	Green	Green	Green	Green	2.14
06.	5f	Green	Green	Green	Green	-3.59
07.	5g	Green	Green	Green	Green	0.73
08.	5h	Green	Green	Green	Green	1.91
09.	5i	Green	Green	Green	Green	0.66
10.	5j	Green	Green	Green	Green	0.08
11.	5k	Green	Green	Green	Green	0.30
12.	5l	Green	Green	Green	Green	-4.80
13.	Tetracycline	Green	Green	Green	Red	5.59

Note: Green- Non-toxic, Red- Toxic

Table 5: *Lipinski's rule* for Substituted Benzothiazole derivatives

S. No	Comp	Log P	Molecular Weight	TPSA	No of Rotatable Bonds	No of Hydrogen Bond Donors	No of Hydrogen Bond Acceptor	Violation
01.	5a	4.20	256.29	58.72	2	0	4	0
02.	5b	4.94	245.73	12.89	1	0	1	0
03.	5c	4.83	290.73	58.72	2	0	4	0
04.	5d	4.02	227.29	33.12	1	1	2	0
05.	5e	4.14	253.33	29.96	2	0	2	0
06.	5f	4.11	301.28	104.54	3	0	7	0
07.	5g	4.71	225.32	12.89	1	0	1	0
08.	5h	4.16	253.33	29.96	2	0	2	0
09.	5i	4.18	255.30	50.19	2	1	3	0
10.	5j	5.08	290.19	12.89	1	0	1	1
11.	5k	5.06	320.21	22.13	2	0	2	1
12.	5l	4.22	256.29	58.72	2	0	4	0

Note: Log P- Partition co-efficient, TPSA-Total Polar surface Area

Table 6: Anti-microbial activity on sample

Organisms	Sample	Zone of inhibition Concentration			Antibiotic (1mg/ml)
		1000	750	500	
Staphylococcus aureus	5a	-	-	-	25
	5b	7	-	-	22
Escherichia coli	5a	14	6	6	27
	5b	9	7	7	25

4. CONCLUSION

The Benzothiazole derivatives were designed and, after performing *in-silico* studies, the best two compounds were synthesized and evaluated for anti-microbial activity against *E. coli and S. aureus.* The nitro and chloro substituted benzothiazole derivatives were found to possess better Anti-microbial activity against the standard tetracycline, and hence these two derivatives could be considered for future work.

ACKNOWLEDGEMENT

Authors are thankful to the Dean Dr. V. Chitra, Dr. M.K. Kathiravan, Professor, Department of Pharmaceutical Chemistry, and SRM College of Pharmacy for their support and suggestions.

REFERENCES

[1] Sharma P C, Sinhmar A, Sharma A, Rajak H, Pathak D P. (2013), Medicinal significance of benzothiazole scaffold: an insight view, Journal of enzyme inhibition and medicinal chemistry, 28(2), 2013, 240-66.

[2] Seenaiah D, Reddy P R, Reddy G M, Padmaja A, Padmavathi V. (2014), Synthesis, antimicrobial and cytotoxic activities of pyrimidinyl benzoxazole, benzothiazole and benzimidazole, European Journal of Medicinal Chemistry, 77, 2014, 1-7.

[3] Saeed S, Rashid N, Jones PG, Ali M, Hussain R. (2010), Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents, European journal of medicinal chemistry, 45(4), 2010 Apr 1, 1323-31.

[4] Singh MK, Tilak R, Nath G, Awasthi SK, Agarwal A. (2013), Design, synthesis and antimicrobial activity of novel benzothiazole analogs. European journal of medicinal chemistry. 2013 May 1; 63:635-44.

[5] Morsy M A, Ali E M, Kandeel M, Venugopala K N, Nair A B, Greish K, El-Daly M. (2020), Screening and molecular docking of novel benzothiazole derivatives as potential antimicrobial agents, Antibiotics, 9(5), 2020 May, 221.

[6] Klimešová V, Kočí J, Pour M, Stachel J, Waisser K, Kaustová J. (2002), Synthesis and preliminary evaluation of benzimidazole derivatives as antimicrobial agents, European journal of medicinal chemistry, 37(5), 2002 May 1, 409-18.

[7] Mahran M A, El-Nassry S M, Allam S R, El-Zawawy L A. (2003), Synthesis of some new benzothiazole derivatives as potential antimicrobial and antiparasitic agents, Die Pharmazie-An International Journal of Pharmaceutical Sciences, 58(8), 2003 Aug 1, 527-30.

[8] Stokes N R, Thomaides-Brears H B, Barker S, Bennett J M, Berry J, Collins I, Czaplewski L G, Gamble V, Lancett P, Logan A, Lunniss C J. (2013),

Biological evaluation of benzothiazole ethyl urea inhibitors of bacterial type II topoisomerases, antimicrobial agents and chemotherapy. 57(12), 2013, 5977-86.

[9] Haroun M, Tratrat C, Kositzi K, Tsolaki E, Petrou A, Aldhubiab B, Attimarad M, Harsha S, Geronikaki A, Venugopala K N, Elsewedy H S. (2018), New benzothiazole-based thiazolidinones as potent antimicrobial agents, Current topics in medicinal chemistry, 18(1), 2018, 75-87.

[10] Maddila S, Gorle S, Seshadri N, Lavanya P, Jonnalagadda S B. (2016), Synthesis, antibacterial and antifungal activity of novel benzothiazole pyrimidine derivatives, Arabian Journal of Chemistry, 9(5), 2016, 1681-7.

[11] Choudhary S, Kini SG, Mubeen M. (2013), Antioxidant activity of novel coumarin substituted benzothiazole derivatives, Der Pharma Chemica, 5(4), 2013, 213-2.

[12] Gill R K, Rawal R K, Bariwal J. (2015), Recent advances in the chemistry and biology of benzothiazoles, Archiv der Pharmazie, 348(3), 2015, 155-78.

[13] Pathak N, Rathi E, Kumar N, Kini S G, Rao C M. (2020), A review on anticancer potentials of benzothiazole derivatives, Mini reviews in medicinal chemistry, 20(1), 2020, 12-23.

[14] Caputo R, Calabrò M L, Micale N, Schimmer A D, Ali M, Zappalà M, Grasso S. (2012), Synthesis of benzothiazole derivatives and their biological evaluation as anticancer agents, medicinal chemistry research, 21(9), 2012, 2644-51.

[15] Asiri Y I, Alsayari A, Muhsinah A B, Mabkhot Y N, Hassan M Z. (2020), Benzothiazoles as potential antiviral agents, Journal of Pharmacy and Pharmacology, 72(11), 2020, 1459-80.

[16] Venkatesh P, Pandeya S N. Synthesis, characterisation and anti-inflammatory activity of some 2-amino benzothiazole derivatives.

[17] Munirajasekar D, Himaja M, Sunil M. (2011), Synthesis and anthemintic activity of 2-amino-6-subtituted benzothiazoles, international research journal of pharmacy, 2(1), 2011, 114-7.

[18] Siddiqui N, Rana A, Khan S A, Ahsan W, Alam M S, Ahmed S. (2008), Analgesic and antidepressant activities of benzothiazole-benzamides, Biomedical & Pharmacology Journal, 1(2), 2008, 297.

[19] Sever B, Altıntop M D, Özdemir A, Tabanca N, Estep A S, Becnel J J, Bloomquist J R. (2019), Biological evaluation of a series of benzothiazole derivatives as mosquitocidal agents, Open Chemistry, 17(1), 2019, 288-94.

[20] Keri R S, Patil M R, Patil S A, Budagumpi S. (2015), A

comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry, European Journal of Medicinal Chemistry, 89, 2015, 207-51.

[21] O'Boyle N M, Banck M, James C A, Morley C, Vandermeersch T, Hutchison G R. (2011), Open Babel: An open chemical toolbox, Journal of cheminformatics, 3(1), 2011, 1-4.

[22] Hanwell M D, Curtis D E, Lonie D C, Vandermeersch T, Zurek E, Hutchison G R. (2012), Avogadro: an advanced semantic chemical editor, visualization, and analysis platform, Journal of cheminformatics, 4(1), 2012, 1-7.

[23] Cabrera Perez L C, Padilla-Martínez II, Cruz A, Correa Basurto J, Miliar García Á, Hernández Zavala A A, Gomez Lopez M, Rosales Hernández M C. (2020), Design, synthesis, molecular docking and in vitro evaluation of benzothiazole derivatives as 11β-hydroxysteroid dehydrogenase type 1 inhibitors, Molecular diversity, 24(4), 2020, 1-4.

[24] Guerra L R, de Souza A M, Côrtes J A, Lione V D, Castro H C, Alves G G. (2017), Assessment of predictivity of volatile organic compounds carcinogenicity and mutagenicity by freeware in silico models, Regulatory Toxicology and Pharmacology, 91, 2017, 1-8.

[25] Molinspiration Cheminformatics [Internet sources]. Available from: https://www.molinspiration.com/, (2020).

[26] Morsy M A, Ali E M, Kandeel M, Venugopala K N, Nair A B, Greish K, El-Daly M. (2020), Screening and molecular docking of novel benzothiazole derivatives as potential antimicrobial agents, Antibiotics, 9(5), 2020, 221.