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Design, Synthesis, and Antimicrobial Evaluation of Novel Benzothiazole-Based Thiazole Derivatives: Structure-Activity Relationship and Molecular Docking Insights

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Abstract: This research presents the synthesis and biological evaluation of novel benzothiazole-based thiazole derivatives bearing aryl azo moieties **4a-e** and **6a-e**. Utilizing a one-pot three-component reaction under solvent-free conditions, benzothiazole-2-aldehyde, thiosemicarbazide, and hydrazonyl chlorides were employed to synthesize various derivatives with yields ranging from 76% to 80%. The structures of the synthesized compounds were confirmed using spectral and analytical techniques, including IR, UV-vis, and ^{1}H-NMR spectroscopy. Notably, the antimicrobial potential of these compounds was assessed against Gram-positive bacteria (*Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli*), and fungal strains (*Botrytis fabae*). The derivatives demonstrated broad-spectrum antimicrobial activity, with specific compounds (e.g., **4a**, **4b**, **6a**, and **6b**) showing potency comparable to standard reference drugs like chloramphenicol and cephalothin. Structure-activity relationship analysis revealed that substitutions, such as chloro and phenyl groups, significantly influenced biological activity by enhancing lipophilicity and interaction with microbial membranes. Furthermore, molecular docking studies with PDB: 2EG7 confirmed strong binding affinities of the most active derivatives, highlighting their potential as antibacterial and antifungal agents. These findings provide valuable insights for the design of thiazole-based compounds with enhanced therapeutic properties.

keywords: Benzothiazole, Thiazole, Hydrazonyl chloride, Antimicrobial activity, Docking study

1. Introduction

Because of their many biological activities, including "antimicrobial [1], anticancer [2], anticonvulsant [3], antiviral [4], antitubercular [5], antimalarial [6], anthelmintic, analgesic [7], anti-inflammatory, antidiabetic [8], and fungicidal [9] properties", benzothiazole derivatives have garnered a lot of interest. The potential of these compounds as strong inhibitors of α-glucosidase, stearoyl-coenzyme A d-9 desaturase, selective fatty acid amide hydrolase, orexin receptor antagonist 2, LTD4 receptor antagonists, and histamine H2 antagonists has recently been investigated.

They also show promise as diagnostic agents for amyloid-binding in neurodegenerative disorders. Additionally, benzothiazole derivatives find applications as dye intermediates [10], β-amyloid plaque imaging agents [11], appetite suppressants [11], and photographic sensitizers. Their versatility extends to fields like polymer chemistry, dye production, and pharmaceuticals. Benzothiazole salts are reported as dyes [12, 13]. Several thiazole derivatives demonstrate notable antibacterial activity by inhibiting the MurB enzyme, essential for bacterial cell wall biosynthesis [14, 15]. Moreover, thiazoles exhibit analgesic and anti-inflammatory effects

[16], and their heterocyclic structures impart significant cytotoxic and anticancer potential [17]. The bioactivity of these derivatives, including their in-vitro antibacterial efficacy, has been further linked to the inclusion of a thioether moiety [18].

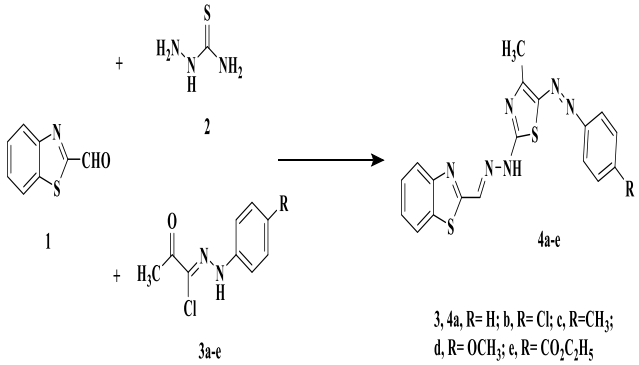
This study aimed to synthesize some new arylazothiazole and thiazolone derivatives as antimicrobial agents. The research was motivated by the remarkable bioactivities exhibited by thiazoles and the ongoing efforts to design and characterize sulfur-containing heterocyclic derivatives [19-21].

Azo compounds are reported to exhibit notable biological activities, including in vitro antibacterial properties [22]. Typically, azo drugs demonstrate limited effectiveness against both Gram-positive and Gram-negative bacteria [23]. This phenomenon is due to the similarity of its structure with azo compounds and stilbenes, which showed inhibiting ATP synthase binding at the α-γ subunit interface [24]. Efforts have been made to synthesize derivatives containing the azo moiety to enhance their antibacterial efficacy [25].

2. Results and Discussion

2.1. Chemistry

Benzothiazole-2-aldehyde **(1)** served as a key precursor for synthesizing novel thiazole derivatives containing an aryl azo moiety, known for their biological effect. This reaction involved compound **1**, thiosemicarbazide **(2)**, and hydrazonyl chloride **(3a-e)** [26-29] under solvent-free conditions (fusion in a pressure tube) without the use of a catalyst. The process yielded 2-(2-(4-methyl-5-(aryldiazenyl)thiazol-2-yl)hydrazineylidene)methyl)benzo[d]thiazole **(4a-e)** with a yield ranging from 76% to 80% **(Scheme 1)**. Compound **4a's** structure was verified using spectroscopic and analytical data. NH, C=N, and azo (N=N) functional groups were represented by distinctive absorption bands in the infrared spectra at *ν* 3220, 1625, and 1550 cm^{-1}, respectively. The presence of the azo form was confirmed by UV-vis analysis, which showed two λ_{max} at 290 nm and 333 nm due to n-π* and π-π* transitions [30]. Three separate singlet signals were detected in the ^{1}H-NMR spectrum of **4a** at δ 2.50, 7.94, and 12.00 ppm. These signals were ascribed to methyl protons, CH=N protons, and exchangeable NH protons, respectively. In addition to the typical signals seen for compound **4a**, the ^{1}H-NMR spectrum for compound **4d** showed a distinctive singlet at δ 3.80 ppm caused by the OCH_3 protons. Compound **4e's** infrared spectrum showed an absorption band for carbonyl ester at ν 1720 cm^{-1}. Furthermore, a triplet at δ 1.20 ppm and a quartet at δ 4.30 ppm, which correspond to CH_2-CH_3 protons, were detected in the ^{1}H-NMR of **4e**.

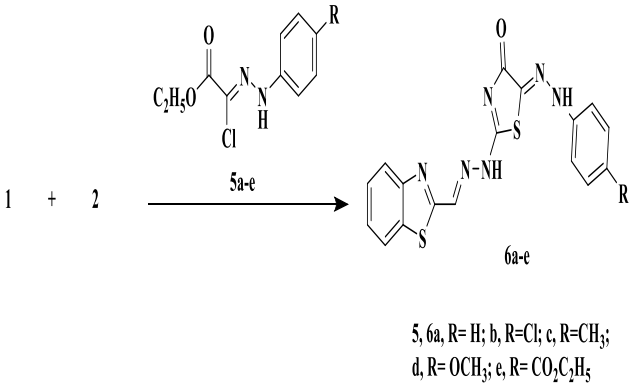


Scheme 1. Synthesis of benzothiazole-based arylazo thiazole **4a-e**Similarly, compound **1**, thiosemicarbazide **(2)**, and hydrazonyl chloride **(5a-e)** were reacted under solvent-free conditions without the use of a basic catalyst, yielding 2-(2-benzo[d]thiazol-2-ylmethylene)hydrazineyl)-5-(2-arylhydrazineylidene)thiazol-4(5H)-one **(6a-e) (Scheme 2)**.

The structure of compound **6a** was characterized using analytical and spectral data. The IR spectrum revealed absorption bands at *ν* 3250, 1685, and 1615 cm^{-1}, corresponding to NH, amidic carbonyl, and C=N functional groups, respectively. UV-vis analysis showed three λ_{max} values at 290 nm, 350 nm, and 410 nm due to σ-π*, n-π*, and π-π* transitions, confirming the presence of the hydrazo form [30]. The ^{1}H-NMR spectrum of **6a** displayed three singlet signals at δ 7.95, 9.90, and 11.71 ppm, attributed to the CH=N proton and two exchangeable NH protons, respectively.

In addition to the anticipated signals seen for compound **6a**, compound **6d's** ^{1}H-NMR spectrum also showed a noticeable singlet signal at δ 3.97 ppm caused by OCH_3 protons. Compound **6e's** infrared spectrum showed two distinct absorption bands at *ν* 1730 and 1681 cm-^{1}, which stand for amidic and ester carbonyl groups, respectively. A triplet signal at δ 1.24

ppm and a quartet signal at δ 4.38 ppm were also detected in the ^{1}H-NMR spectra of **6e**, and they were both ascribed to CH_2-CH_3 protons.



Scheme 2. Synthesis of benzothiazole-based arylazo thiazolone **6a-e**

This study also involved the reaction of benzothiazole derivative **(1)** with thiosemicarbazide **(2)** and various reagents, including chloroacetone, phenacyl bromide, *p*-chlorophenacyl bromide, 2-bromo-1-(naphthalen-2-yl)ethan-1-one, ethyl chloroacetate, or chloroacetyl chloride, under solvent-free conditions and without the use of a basic catalyst. These reactions produced the corresponding 4-substituted thiazole derivatives **(7–10)** and the thiazolone derivative **(11) (Scheme 3)**.

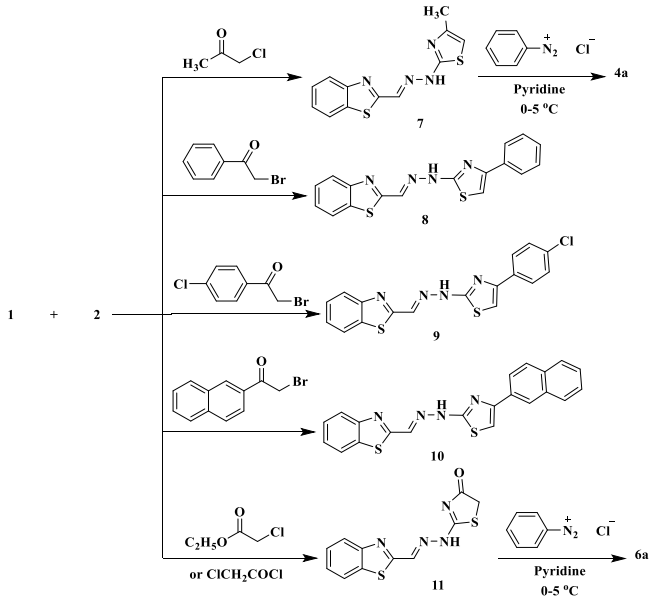
The IR spectra of compounds **7-10** generally showed characteristic absorption bands at *v* 3210 and 1615 cm^{-1}, corresponding to NH and C=N groups. In contrast, the IR spectrum of compound **11** exhibited absorption bands at *v* 3222, 1725, and 1617 cm^{-1}, attributed to NH, amidic carbonyl, and C=N functional groups, respectively. The ^{1}H-NMR spectra of compounds **7-10** typically displayed a distinct singlet signal at δ 6.18 ppm, corresponding to the thiazole-CH proton, while compound **11** exhibited a signal for thiazole-CH_2 protons at δ 4.15 ppm.

Notably, compounds **4a** and **6a** could also be synthesized by coupling the thiazole derivatives **7** and **11** with benzene diazonium chloride in pyridine, respectively **(Scheme 3)**.

2.2. Pharmacological Evaluation

2.2.1. Antimicrobial evaluation

The findings in **Table 1** show the inhibition zone diameters (mm) and Minimum Inhibitory Concentration (MIC) values of newly synthesized compounds against representative microorganisms, such as the Gram-positive *B. subtilis*, Gram-negative *E. coli*, and fungal species, *B. fabae* [31]. The following are the main findings and observations:



Scheme 3. Reaction of formyl benzothiazole, thiosemicarbazide, and α-haloketones

2.2.1.1. Comparison with Standard Drugs

Chloramphenicol and cephalothin, as standard antibacterial agents, exhibited potent activity against both *B. subtilis* (MIC = 3.125–6.25 µg/mL) and *E. coli* (MIC = 6.25 µg/mL), comparable to some synthesized compounds, particularly **4a**, **4b**, and **6a**.

Cycloheximide demonstrated exceptional antifungal activity (*B. fabae*, MIC = 3.125 µg/mL, inhibition zone = 42 mm), serving as the benchmark for antifungal comparisons.

2.2.1.2. Antibacterial Activity

Gram-positive Bacteria (*B. subtilis*)

Compounds **4a**, **4b**, **6a**, and **6b** showed excellent activity (MIC = 3.125 µg/mL) with large inhibition zones (44–45 mm), matching or exceeding the activity of chloramphenicol.

Activity decreased in other compounds, particularly **4e**, **6d**, and **6e**, which required much higher MICs (50 µg/mL) and exhibited smaller inhibition zones (18–20 mm).

Gram-negative Bacteria (*E. coli*)

Similar trends were observed, with **4a**, **4b**, **6a**, and **6b** displaying strong inhibition (MIC = 6.25 µg/mL), comparable to the standard drugs.

Compounds **4d**, **6c**, and **6e** showed reduced activity, requiring higher concentrations (MIC = 25–50 µg/mL).

2.2.1.3. Antifungal Activity

Compounds **4b** and **6b** emerged as the most effective antifungal agents, with MIC values of 12.5 µg/mL and inhibition zones of 30–32 mm against *B. fabae*. Their activity, while significant, was still lower than cycloheximide.

Most other compounds exhibited moderate to weak antifungal activity (MIC = 50–100 µg/mL, inhibition zones = 14–19 mm), underscoring the challenge of achieving broad-spectrum activity against fungi.

Table 1. The antimicrobial activity of all newly synthesized compounds

Compound No	MIC (µg/mL) and Inhibition Zone (ϕ mm)		
	Gram-positive bacteria	***Gram-negative bacteria***	***Fungi***
	B. subtilis	***E. coli***	***B. fabae***
4a	3.125 (44)	6.25 (38)	25 (26)
4b	3.125 (45)	6.25 (39)	12.5 (30)
4c	6.25 (38)	25 (25)	50 (18)
4d	12.5 (31)	50 (18)	100 (14)
4e	50 (20)	100 (14)	100 (15)
6a	3.125 (44)	6.25 (37)	50 (19)
6b	3.125 (43)	6.25 (38)	12.5 (32)
6c	6.25 (37)	25 (27)	100 (15)
6d	12.5 (30)	50 (20)	100 (14)
6e	50 (18)	100 (15)	50 (18)
7	25 (26)	100 (14)	100 (14)
8	25 (25)	100 (15)	100 (14)
9	6.25 (38)	25 (27)	25 (28)
10	50 (19)	100 (14)	100 (15)
11	25 (27)	50 (19)	100 (14)
Chloramphenicol	3.125 (44)	6.25 (38)	-
Cephalothin	6.25 (38)	6.25 (39)	-
Cycloheximide	-	-	3.125 (42)

2.2.2. Structure-Activity Relationship

The presence of the chloro group in compound **4b** as an electron-withdrawing group, enhances lipophilicity and improves interaction with bacterial cell membranes. This can increase antibacterial activity. Additionally, the thiazole and benzo[d]thiazole rings are known to enhance antibacterial properties. Moreover, compound **6b** contains both the **chloro group** and the benzo[d]thiazole core, both of which are favorable for activity. The presence of the hydrazineylidene moiety contributes to reactivity, making it a potent antibacterial agent. In compound **4a**, the **phenyl group** enhances lipophilicity and antibacterial activity. The lack of electron-donating or withdrawing groups, however, places this compound below the chloro-substituted analogs. Similar to **4a**, compound **6a** which has the thiazol-4(5H)-one scaffold, the phenyl group improves lipophilicity, although it is less potent than compounds with electron-withdrawing groups like chlorine. The ***p*-tolyl group (CH_3)** in compound **4c** is an electron-donating group, which may slightly reduce antibacterial activity compared to the phenyl or chloro-substituted compounds. However, the overall structure remains favorable for activity. Similar to **4c**, the ***p*-tolyl** group in compound **6c** slightly reduces potency due to its electron-donating nature. Compound **9** is similar to **4b**, but the **chlorophenyl** group is further away from the core structure, possibly reducing activity due to less effective interactions with bacterial enzymes. The **methoxy group (OCH_3)** in **4d** is an electron-donating group, which generally reduces activity compared to chloro or phenyl-substituted compounds. Similar to **4d**, compound **6d** showed the presence of the thiazol-4(5H)-one scaffold reduces potency compared to other compounds with phenyl or chloro substituents. The **phenyl group** in compound **8** lacks any electron-withdrawing or donating features that enhance activity, making it less potent than other derivatives with more favorable groups. Compound **11** has fewer favorable groups, with the structure lacking

additional substituents that might enhance lipophilicity or activity. The **methyl group (CH_3)** in compound **7** is not highly favorable for antibacterial activity, resulting in lower potency. In compound **10**, the **naphthyl group** is large and bulky, potentially introducing steric hindrance, reducing binding affinity, and lowering activity. The **ester group** in compound **6e** reduces activity by increasing steric hindrance and reducing interactions with bacterial membranes or proteins. Similar to **6e**, the **ethyl ester** group in compound **4e** reduces activity due to steric factors and reduced bacterial interaction.

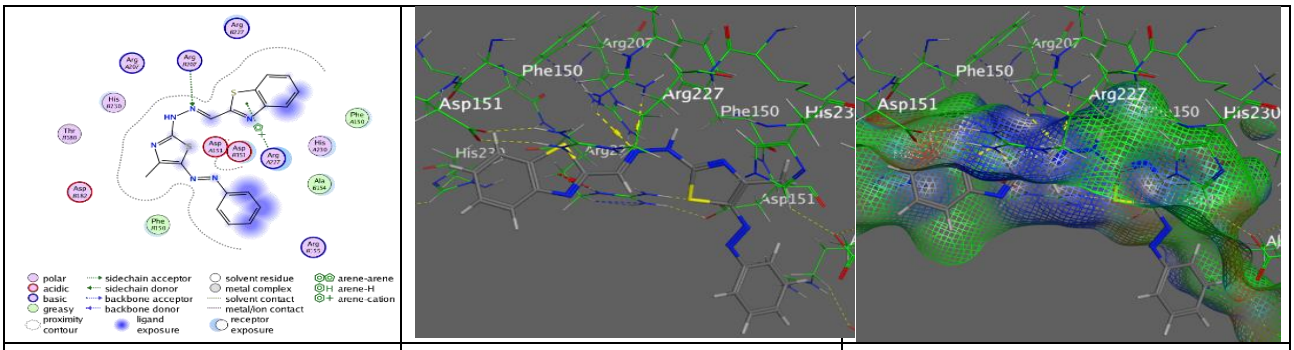
2.3. Molecular docking

The nominated derivatives (**4a**, **4b**, **6a,** and **6b**) with the remarkable antimicrobial activities were docked by appealing a selected PDBD: ID 2eg7 protein using the M.O.E. protocol, and their consequences were documented **(Table 2)**.

Table 2. Docking results of the synthesized derivatives with the higher score of MIC.

Der.	S (Kcal/mol)	RMSD	ligand bindings with the amino-acid residues	Types of Interactions	Distance (Å)
4a	-6.0491	1.9446	N 11 of hydrazide moiety with Arg 207 Thiazole-ring with Arg 227	H-acceptor pi-cation	3.24 4.08
4b	-6.3456	1.3479	S 14 of thiazole ring with Asp 151 N 11 of hydrazide moiety with Arg 207 N 17 of thiazole ring with Arg 227 Benzothiazole-ring with Arg 227 2nd Thiazole-ring with His 230	H-donor H-acceptor H-acceptor pi-cation Pi-H	3.10 3.11 3.31 4.60 4.32
6a	-6.6151	1.5471	Thiazole-ring with Arg 227	pi-cation	4.51
6b	-6.6810	1.6642	Thiazole-ring with Arg 227	pi-cation	4.53
Cephalothin	-6.5062	1.2930	O 10 of hydroxyl group of carboxylic acid with Asp 151 O 11 of carbonyl group of carboxylic acid with His 230 O 12 of lactam ring with Arg 227 O 16 of amide group with Arg 227	H-donor H-acceptor H-acceptor H-acceptor	2.78 3.26 3.16 3.00
Chloramphenicol	-6.0874	1.7994	Cl atom 8 with His 230 O 9 of alcoholic group with Arg 207 O 9 of alcoholic with Arg 227 O 20 of amide group with Arg 207 O 20 of amide group with Arg 227	H-acceptor H-acceptor H-acceptor H-acceptor H-acceptor	3.69 3.00 2.87 2.91 2.94

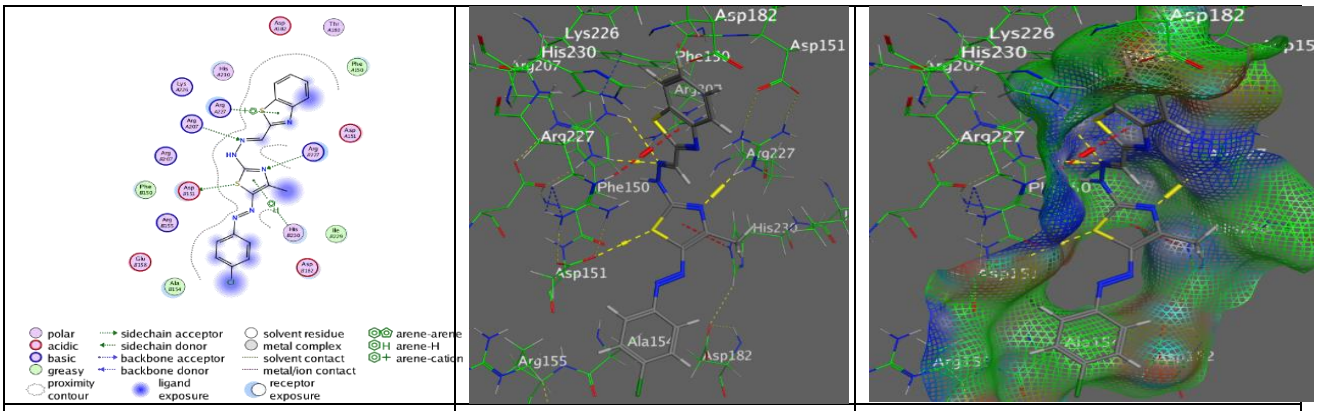
Derivative **4a** displayed a docking score = -6.0491 kcal/mol, RMSD = 1.9446 Å, through moderate interactions with key 2eg7 amino-acids, over binding among the N11 of the hydrazide moiety with Arg207, and the thiazole ring formed pi-cation interactions with Arg227, representative sensible binding affinity. However, the binding distances of 3.24 Å (H-acceptor) and 4.08 Å (pi-cation) suggest that optimization could enhance its interaction strength **(Figure 1)**.



2D	3D	Surface Map

Figure 1. Binding images between derivative 4a with PDB: 2EG7.

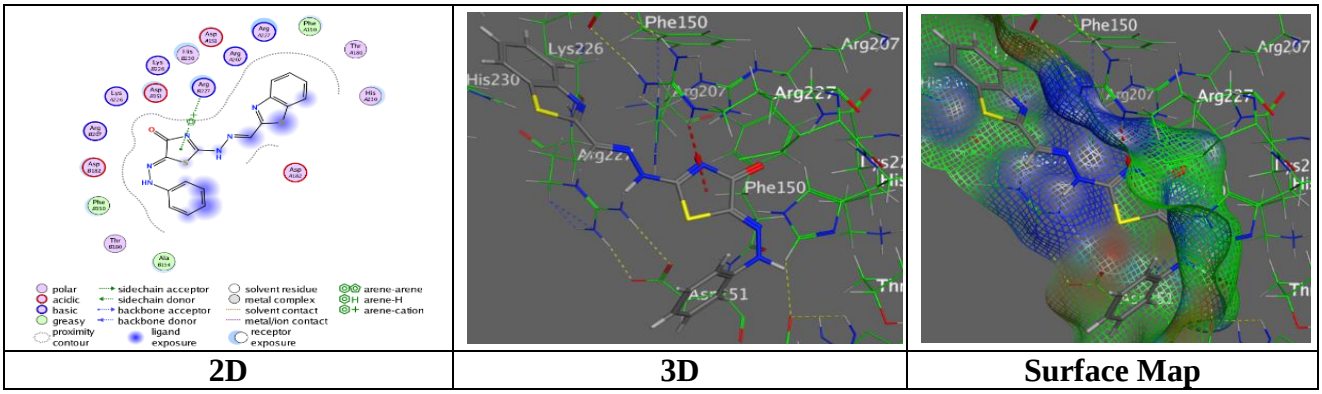
Meanwhile, derivative **4b** demonstrated docking Score = -6.3456 kcal/mol, through stronger bindings than derivative **4a**, with multiple points of interaction. Various interactions (H-donor, H-acceptor, pi-cation, and pi-H) were observed, including H-bonding between the S14 of the thiazole ring and Asp151, and pi-cation interactions among the benzothiazole ring and Arg 227. The lower RMSD = 1.3479 indicates a more stable binding conformation over distances 3.10–4.60 Å **(Figure 2)**.



2D	3D	Surface Map

Figure 2. Binding images between derivative 4b with PDB: 2EG7.

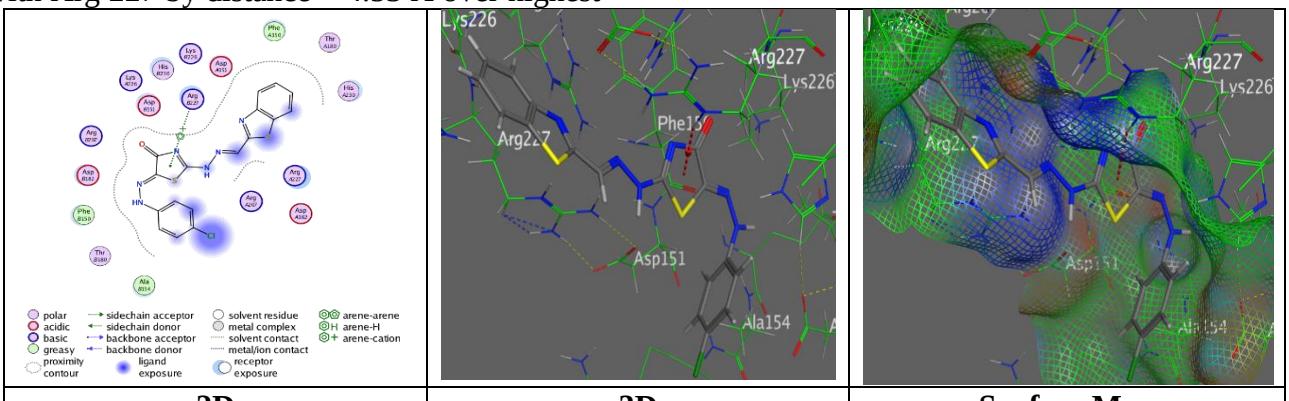
However, derivative **6a** showed docking Score = -6.6151 kcal/mol, RMSD = 1.5471 over Pi-cation interaction with a distance = 4.51 Å appeared from the thiazole ring which interacted with Arg 227 thru pi-cation binding **(Figure 3)**.



2D	3D	Surface Map

Figure 3. Binding images between derivative 6a with PDB: 2EG7.

Likewise, derivative **6b** exhibited only one Pi-cation interaction amongst the thiazole ring with Arg 227 by distance = 4.53 Å over highest docking Score = -6.6810 kcal/mol among the other derivatives **(Figure 4)**.



2D	3D	Surface Map

Figure 4. Binding images between derivative 6b with PDB: 2EG7.

Moreover, both Cephalothin and Chloramphenicol (references) presented docking Scores = -6.5062 kcal/mol, -6.0874 kcal/mol over RMSD = 1.2930 and 1.7994, respectively **(Figure 5)**. Cephalothin revealed strong hydrogen bonding with multiple 2eg7 amino acids, particularly Arg 227 and His 230, indicating good binding affinity. Its lower RMSD suggests a stable docking conformation. Nevertheless, chloramphenicol showed a reasonable binding score, with bindings involving five H-acceptor bonds over the chlorine atom and oxygen atoms from both the alcoholic and the amide groups with His230, Arg207, and Arg227.

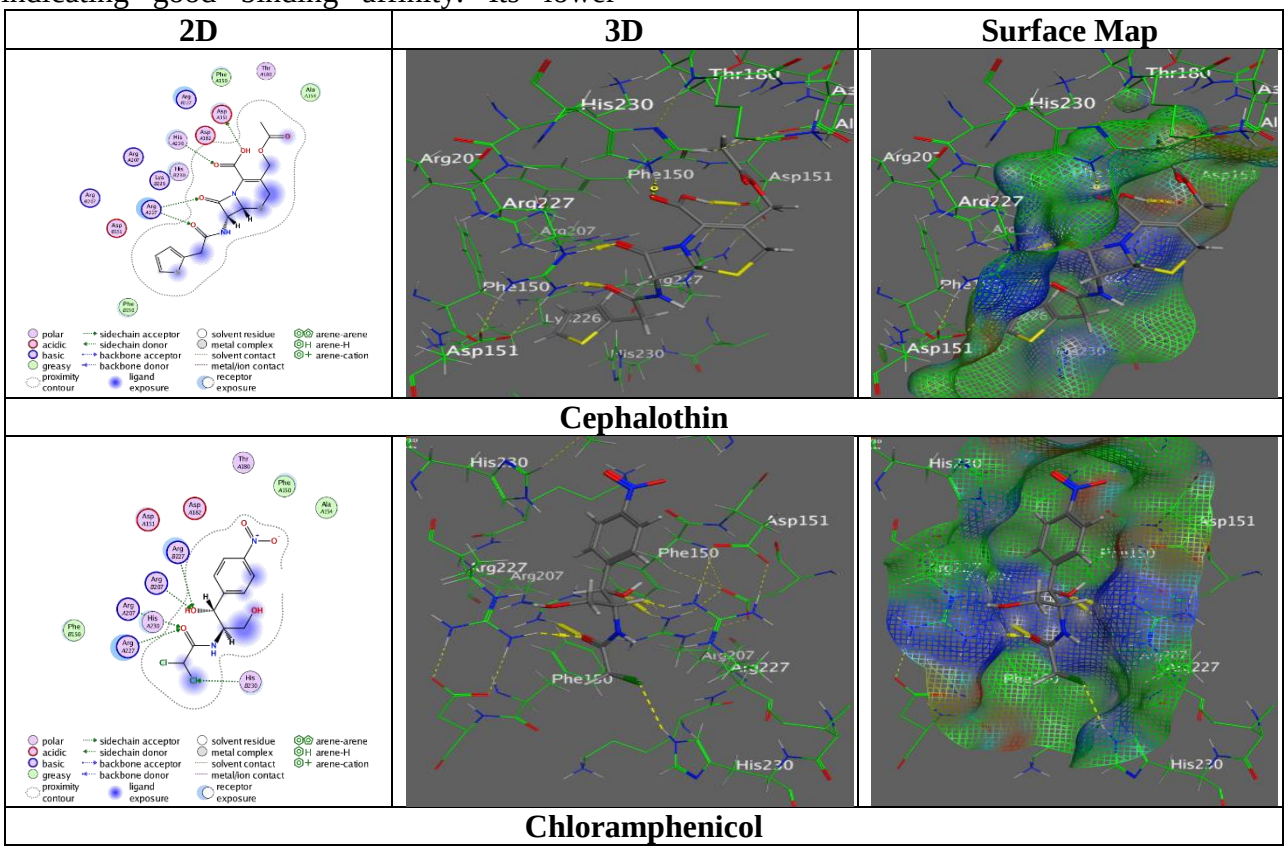


Figure 5. Binding images between Cephalothin and Chloramphenicol with PDB: 2EG7**.**

3. Experiment

3.1. Material and Methods

Synthesis of benzothiazol-2-aldehyde (1):

It was prepared according to previously reported work [32].

Synthesis of 2-oxo-*N*-arylpropanehydrazonoyl chloride (3a-e):

These compounds were prepared according to the reported procedures [26-29].

Synthesis of benzothiazoles 4, 6, and 7-11:

General procedure:

A solution containing thiosemicarbazide **(2)** (0.27 g, 3 mmol), benzothiazole-2-aldehyde **(1)** (0.49 g, 3 mmol), and either halogenated compounds (3 mmol) or hydrazonyl chloride (**3a-e** or **5a-e**) was heated in a silicon oil bath at 150 °C for two hours in a pressure tube. The reaction mixture was allowed to cool to room temperature before being poured into ice-cold water, and the precipitate that resulted was filtered off. The pure product was obtained by recrystallizing the precipitate from a 1:1 mixture of ethanol and DMF after it had been washed with cold ethanol.

3.2. Antimicrobial activity:

It occurred according to previously reported work [33].

3.3. Molecular docking study:

Benzothiazole hybrids were found to target the *E. coli* enzyme dihydrorotase. Molecular docking was used to determine the chemical basis of the interaction between *E. coli* dihydroorotase and benzothiazole derivatives [34]. The M.O.E. 2019 molecular docking program accurately simulates the bindings of the chosen synthetic analogues and the crystal structure of *E. coli* dihydroorotase, which was

obtained from the protein data bank (PDB ID 2eg7).

4. Conclusion

This study successfully synthesized and characterized novel benzothiazole-based thiazole derivatives through an efficient one-pot solvent-free reaction. The biological evaluation of these compounds revealed promising antimicrobial activity, with some derivatives demonstrating potency comparable to or exceeding standard reference drugs. The structure-activity relationship analysis emphasized the importance of substituents like chloro and phenyl groups in enhancing lipophilicity and biological effectiveness. Molecular docking studies further validated the strong binding affinities of the most active derivatives with microbial target proteins, supporting their potential mechanism of action. Collectively, these findings underscore the significant potential of these thiazole derivatives as candidates for the development of new antimicrobial agents. Future research could explore their optimization, toxicity profiling, and potential applications in pharmaceutical formulations.

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