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Green Biocatalyst for Ultrasound-Assisted Thiazole Derivatives: Synthesis, Antibacterial Evaluation, and Docking Analysis

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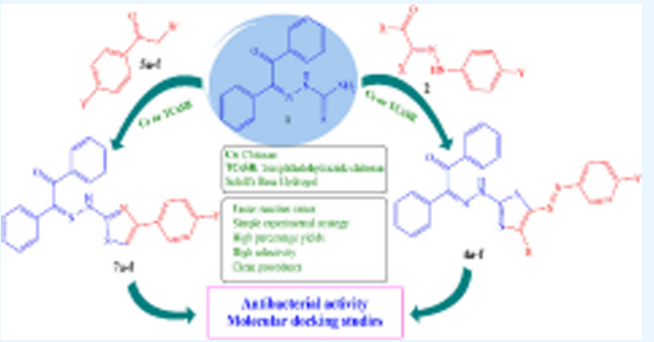
ABSTRACT: The catalytic activity of chitosan (Cs) and grafted Cs led to the preparation of terephthalohydrazide Cs Schiff's base hydrogel (TCsSB), which was then investigated as an eco-friendly biocatalyst for synthesizing novel thiazole derivatives. TCsSB exhibited greater surface area and higher thermal stability compared to Cs, making it a promising eco-friendly biocatalyst. We synthesized two novel series of thiazoles via the reaction of 2-(2-oxo-1,2-diphenylethylidene) hydrazine-1-carbothioamide with various hydrazonoyl chlorides and 2-bromo-1-arylethan-1-ones, employing ultrasonic irradiation and using TCsSB as a catalyst. A comparative study between Cs and TCsSB revealed higher yields than TCsSB. The methodology offered advantages such as mild reaction conditions, quick reaction times, and high yields. TCsSB could be reused multiple times without a significant loss of potency. The chemical structures of the newly synthesized compounds were verified through IR, ^{1}H NMR, ^{13}C NMR, and MS analyses. Six synthesized compounds were assessed for their in vitro antibacterial effectiveness by establishing the minimum inhibitory concentration against four distinct bacterial strains. The docking analyses revealed favorable binding scores against several amino acids within the selected protein (PDB Code-1MBT) for these compounds, with compound **4c** exhibiting particularly noteworthy binding properties. Additionally, the in silico ADME parameter estimation for all compounds indicated favorable pharmacological properties for these compounds.



1. INTRODUCTION

In recent years, there has been a significant focus on green chemistry driven by its potential to mitigate human risks, decrease environmental pollution, reduce chemical hazards, and minimize waste. The use of catalysts is crucial in organic synthesis to expedite reaction time and achieve high yields of the desired product.[1] The creation of heterogeneous catalytic systems for liquid-phase chemical and biological reactions is a significant field of study. Because catalysts are easily separated, recovered, and recycled, this research is crucial to the advancement of cleaner and more effective processes.[2,3]

In the fields of science and engineering, chitosan (Cs) a naturally occurring biopolymer made from polysaccharides has drawn a lot of interest.[4] Organic catalysis holds great potential for Cs-based catalysts because of its sustainable origin. Much research has focused on chemically modifying Cs to generate functional derivatives for particular purposes,[5] the benefits are various, enclosing cost-effectuality, eco-friendliness, hydrophilicity, modifying ability, thermal and chemical stability, nontoxicity, biodegradability, and metal chelating capabilities.[6−8] Its hydroxyl and amino groups, coupled with its insolubility in organic solvents, make it particularly attractive.[9,10] Macquarrie and Hardy conducted a survey on methodologies for Cs functionalization and how these functional Css are applied in catalysis.[2] Numerous documented studies have showcased the diverse applications of Cs-based catalysts in chemical synthesis,[2,3,11−13] with a specific emphasis on thiazole synthesis.[6,14−16]

Cs-based hydrogels have hydrophilic functional groups and numerous pores in their polymeric structure, allowing the hydrogel to absorb water and watery fluids, resulting in hydrogel expansion and occupation of greater volume. These factors indicate that using Cs hydrogel as a catalyst in organic synthesis is preferable to using Schiff-base complex-based catalysts. Although Schiff-base complexes of metal ions demonstrated good catalytic activity, improving the yield and selectivity in a variety of reactions,[17] Cs-based hydrogels are more potent in their catalytic capacity; in addition, they are environmentally green.[18,19]

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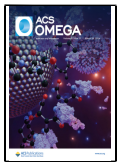


Many advantages come with using ultrasound-assisted reactions: quicker reaction times, an easy-to-implement experimental plan, high yields, enhanced selectivity, and clean processes.[20−22] One of the many advantages of ultrasonic irradiation is its ability to be a major player in chemistry, especially when conventional methods require high temperatures or extended reaction times.[23−25]

Bacterial infections pose a significant global health challenge, and there is a continuous rise in associated mortality rates, as documented in references.[26,27] Therefore, it is essential to discover new antibiotics. Pharmaceutical drug development increasingly relies on nitrogen-containing heterocyclic scaffolds.[14,28−30] Numerous researchers have given the thiazole scaffold a great deal of attention due to its high medicinal value, which has promoted the design and synthesis of many compounds that contain thiazoles exhibiting a wide range of pharmacological properties,[31−35] with a notable emphasis on antibacterial activity.[36−38] Many articles have documented the production of derivatives of 2-hydrazinylthiazole[39−41] due to their significant relevance in the field of medicinal chemistry,[42,43] particularly in terms of their antibacterial properties.[44−46] The structure−activity relationships (SARs) of thiazole derivatives reveal that the presence of suitable substituents with electron-donating properties significantly influences the microbial resistance characteristics of the resulting compounds.[47] Molecular docking is a crucial computational method employed to model the theoretical interactions between compounds and large molecular structures. It is important to emphasize that the incorporation of heteroatoms into molecules is not a random choice; instead, it should be based on their physicochemical characteristics and, more crucially, on optimizing the ADME (absorption, distribution, metabolism, and excretion) properties for the primary therapeutic compounds.

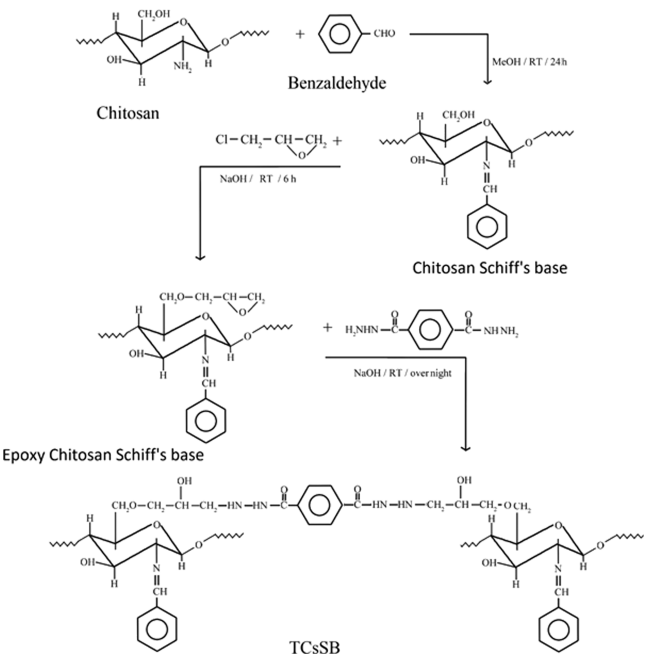
Continuing our commitment to green chemistry research[48−53] and recognizing the biological significance of thiazole derivatives,[51−58] this study aimed to harness the catalytic properties of TCsSB to efficiently synthesize novel thiazole derivatives using an eco-friendly and sustainable approach. The study not only successfully synthesized these compounds but also evaluated their potential as antibacterial agents and drug candidates, providing valuable insights into their pharmacological properties and binding interactions with a target protein.

2. RESULTS AND DISCUSSION

2.1. Synthesis of TCsSB. Cs as a cationic polymer has attracted significant interest as an eco-friendly catalyst because of its unique traits, which include mucoadhesive qualities, biodegradability, nontoxicity, biocompatibility, low allergenicity, cheap cost, and reusability.[59] Cs had some drawbacks, including low product yields in a number of the examined reactions and difficulty reusing due to its high hydrophilicity, which led to gel formation. Herein, to overcome the drawbacks of Cs and enhance its catalytic activity modification of Cs via cross-linking with a moiety containing terphthalohydrazide molecules was proceeded as mentioned in Scheme 1 to produce TCsSB as an efficient catalyst in the preparation of new thiazole derivatives.

2.1.1. FTIR Characterization. FTIR spectra of Cs and its derivatives are shown in Figure 1. Cs's spectrum showed characteristic bands at 1155, 1073, 1030, and 895 cm^{-1}, which affirms the saccharide structure. The two bands that appeared

Scheme 1. Preparation of TCsSB



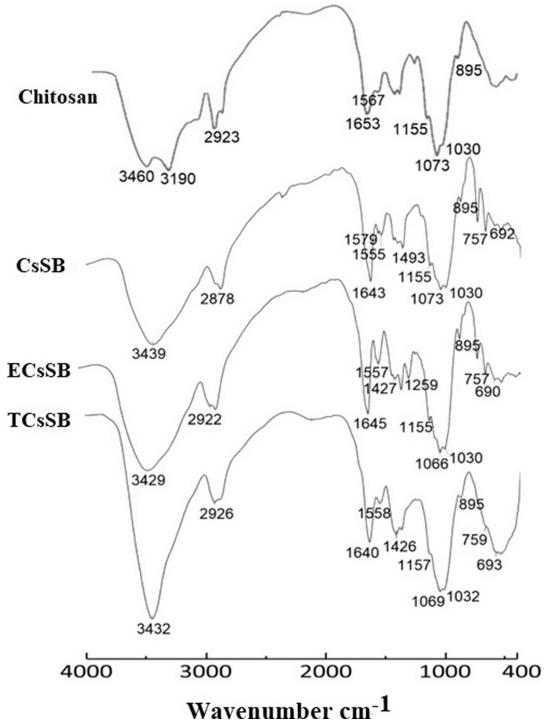


Figure 1. FTIR spectra of Cs, CsSB, ECsSB, and TCsSB hydrogel.

at 3460 and 3190 cm^{-1} were attributed to the absorption frequency of the hydrogen-bonded $-NH_2$ and $-OH$ groups. The band of C−H bonds in the pyranose ring is excited at 2923 cm^{-1}. Furthermore, two significantly weaker absorption bands appeared at 1653 and 1567 cm^{-1} related to amides I and II, respectively. This demonstrates that Cs has a significant deacetylation degree. A strong absorption band appeared at 1653 cm^{-1} representing the NH_2 bending vibration overlapped with amide I stretching vibration.[60] Spectrum of Cs Schiff's base (CsSB) displayed that the peaks attributed to the NH_2 groups of Cs at 3460 and 3190 cm^{-1} have completely vanished,

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and a single peak that has appeared around 3439 cm^{-1} is related to the hydrogen-bonded OH groups. This denotes the consumption of all the NH_2 groups via their reaction with the carbonyl groups of benzaldehyde molecules. Furthermore, there have been some novel peaks identified at 692 and 757 cm^{-1}, which are assigned to the out-of-plane monosubstituted benzene ring; additionally, at 1579, 1555, and 1493 cm^{-1}, which correspond to the C═N group and the benzene ring, respectively.[61] The FTIR spectra of Cs epoxy Schiff's base (ECsSB) displayed an extra distinct peak at 1259 cm^{-1}, which was related to the epoxy ring's −C−O−C− bond. The peak of the epoxy ring's C−O−C linkage at 1259 cm^{-1} vanished, confirming the full cross-linking of Cs and the opening of all epoxy rings as a result of their reaction with terephthaloyl dihydrazide, which validated the synthesis of TCsSB. Additionally, the absorption peaks of the terephthaloyl dihydrazide's − CO−, −NH−NH−, and aromatic rings overlapped with those of amide I at 1640 cm^{-1}, −OH at 3432 cm^{-1}, and the monosubstituted benzene ring at 693, 759, and 1558 cm^{-1}, respectively.

2.1.2. X-ray Diffraction. The X-ray diffraction (XRD) patterns of Cs, CsSB, ECsSB, and TCsSB are shown in Figure 2. The Cs pattern revealed two peaks, corresponding to its

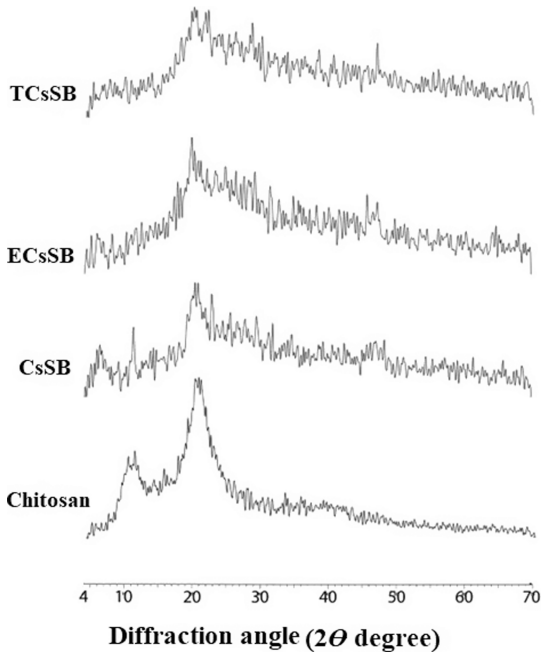

Figure 2. XRD patterns of Cs, CsSB, ECsSB, and TCsSB.

amorphous and crystalline portions, at $2\theta = 10°$ and $2\theta = 20°$, respectively.[62] This is explained by the fact that it contains a large number of hydroxyl groups in addition to NH_2 groups, which allow the creation of numerous intrachain and interchain H bonds. Its shape was significantly disrupted after the protection of the NH_2 groups and a chemical cross-linking at OH groups on C6 in Cs by adding benzaldehyde (CsSB), epichlorohydrin (ECsSB), and terephthaloyl dihydrazide (TCsSB).

This can be explained by the chains' dissociation from one another, a significant decrease in intra- and interchain hydrogen bonds, a significant reduction in the crystalline portion, and an increase in the amorphous portion. As seen by the XRD patterns of CsSB, ECsSB, and TCsSB, the peak at $2\theta = 10°$ has thus entirely vanished, while the peak at $2\theta = 20°$ has significantly diminished in strength.

2.1.3. SEM and Morphological Changes. The surface morphologies of Cs, CsSB, ECsSB, and TCsSB were examined using scanning electron microscopy (SEM); the SEM images of these samples are displayed in Figure 3. After benzaldehyde (CsSB) and epichlorohydrin (ECsSB) were added, the smooth surface of Cs changed to a rough surface, and after cross-linking with terephthaloyl dihydrazide moieties, it became very porous.

2.1.4. Thermal Stability of the TCsSB Hydrogel. The implementation of the natural biopolymer Cs as an eco-friendly green catalyst demands enhancement of its stability against thermal degradation. Chemical cross-linking of Cs is one of the most effective techniques to boost its thermal stability. Thus, it became of interest to perform a chemical modification of Cs by cross-linking process using terephthalohydrazido linkages to obtain a terephthalohydrazido Cs Schiff's base (TCsSB) hydrogel. Thermogravimetric analysis (TG) technique is used to evaluate the alteration in the thermal stability happens in after its modification by chemical cross-linking. The thermal stability and the degradation behavior of the inspected TCsSB hydrogel were studied using TG at temperatures ranging from 25 to 500 °C, at a heat rate of 10 °C min^{-1}, and under a stream of nitrogen of 30 mL min^{-1}. The weight losses in TCsSB hydrogel, relative to the virgin Cs, that were obtained via their TG analysis are shown in Figure 4 and Table 1.

TCsSB presented a special degradation style comparable to that of the parent Cs, involving two distinguishing events through which remarkable weight losses were observed.

The first weight loss event commenced at temperatures ranging from 25 to 150 °C, during which TCsSB lost 3.9% in comparison to 9% for the parent Cs as shown in Table 1. This loss in mass is attributable to the vaporization of the moisture adsorbed on the surface of both TCsSB and Cs. Above 100 °C, the weight loss may be resulted from breaking down the hydrogen bonds that bind water molecules with the highly polar functional groups on the investigated samples.

The second thermal degradation event was steep and initiated at 250 °C. The weight loss during the temperature range between 250 and 500 °C was 31.0% for TCsSB compared to 34.5% for Cs (based on the weight of the perfectly dried samples, by subtracting the weight loss occurred until 150 °C). The loss in mass of TCsSB was 36.4%, at 500 °C, as compared with 38.1% for Cs (based on the weight of the perfectly dried samples, by subtracting the weight loss occurring until 150 °C) (Table 1). This referred to decomposing of both TCsSB and virgin Cs that proceeded via a convoluted process, comprising the saccharide unit's dehydration, the splitting of the structural units randomly, and the releasing and evaporating of the resulting small degradation fragments. In addition, the loss in mass for TCsSB might be attributable to the water that was lost from the hydrazide groups of the terephthalohydrazide linkages, during thermal treatment, producing 1,3,4-oxadiazole units. This cyclodehydration reaction is not a real degradation reaction, however a thermo-chemical conversion reaction to the greatly thermally stable 1,3,4-oxadiazole rich-polymers.[63] The heat stability of TCsSB is slightly higher than that of the Cs; this is illustrated not only by its higher residual weight but also by its lower weight loss at all the examined temperatures. The better thermal stability of TCsSB than Cs may be ascribed to its

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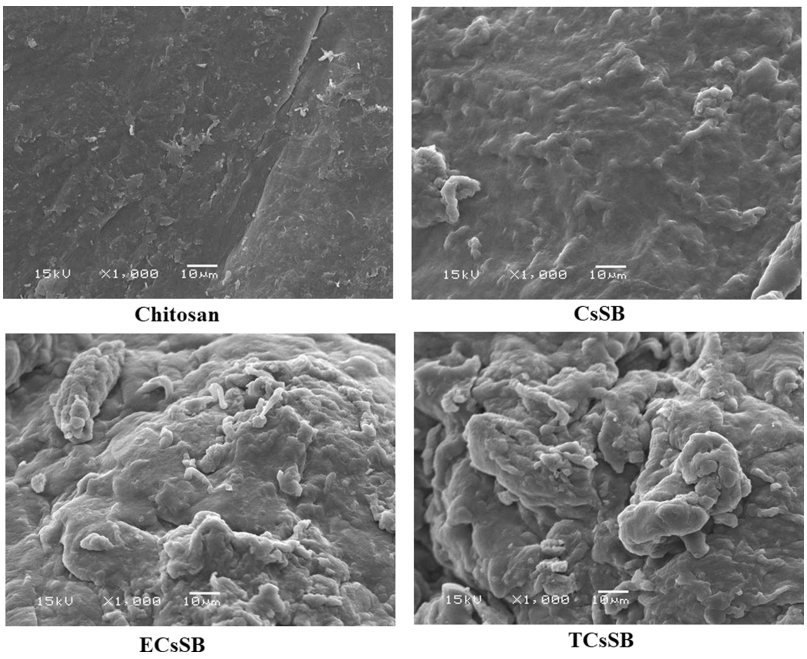

Figure 3. SEM images of Cs, CsSB, ECsSB, and TCsSB.

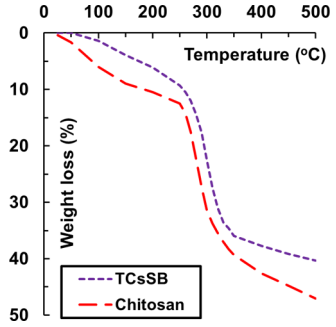

Figure 4. TG analysis of Cs and TCsSB hydrogel, recorded at 10 °C min^{-1} heating rate and under 30 mL min^{-1} nitrogen flow rate.

possession of both the terephthalohydrazido linkages and Schiff's base moieties that are characterized by their high heat stability and their resistance to the elevated temperatures.

2.2. Utilizing TCsSB as a Solid Basic Catalyst for the Synthesis of Thiazole Derivatives. In this article, we aim to present a straightforward and efficient approach for synthesizing novel thiazoles. The synthesis of the pivotal thiosemicarbazone derivative **1**[64] commenced with the condensation of benzil with thiosemicarbazide (in a 1:1 ratio) within an acidic ethanol solution, as illustrated in Scheme 2.

New thiazole derivatives **4a−f** were obtained by subjecting equimolar amounts of thiosemicarbazone derivative **1** to an equivalent quantity of hydrazonoyl halides **2a−f**[31,49,52,54,57] in the presence of Cs or TCsSB, as depicted in Scheme 2. Thin-layer chromatography (TLC) was used to monitor the progress of all of the reactions.

The chemical structure of all newly synthesized thiazoles **4a−f** was determined using spectral data, including IR, MS, ^{1}H NMR, ^{13}C NMR, and elemental analyses. The validation of their structure was confirmed by the ^{1}H NMR spectra of isolated derivatives **4a−f**, which exhibited the expected signals for the proposed structure. In the ^{1}H NMR of compound **4a**, for instance, we found the distinctive two singlet signals at 2.38 (thizole-CH_3), and 10.58 (D_2O-exchangable NH), in addition to 15 multiplet aromatic protons at 6.96−7.79 ppm. Additionally, its infrared spectra exhibited two distinct bands at wavenumbers of 3319 and 1694 cm^{-1}, which can be attributed to the NH and C═O groups, respectively.

Treating compound **1** with 2-bromo-1-arylethan-1-ones **5a−f**,[31,52,54,57] employing CS and TCsSB as basic catalysts under the identical reaction conditions outlined in Scheme 3, resulted in the formation of thiazoles **7a−f** as the ultimate products. Subsequently, we assessed the yield percentages of the resultant products **7a−f**, as presented in Table 2.

Table 1. TG Measurements Data of Cs and TCsSB at 10 °C min^{-1} Heating Rate and under 30 mL min^{-1} Nitrogen Flow Rate

	weight loss (%)	
temperature (°C)	Cs	TCsSB
25	0.4	0
50	1.7	0
100	6.0	1.4
150	9.0	3.9
200	10.5	6.1
250	12.5	9.3
260	14.3	10.5
270	17.5	12.0
280	22.2	14.4
290	27.3	17.6
300	31.4	22.5
310	33.8	27.4
320	35.5	31.0
330	37.1	33.7
340	38.3	34.6
350	39.4	36.0
400	42.6	37.7
450	44.8	39.2
500	47.1	40.3

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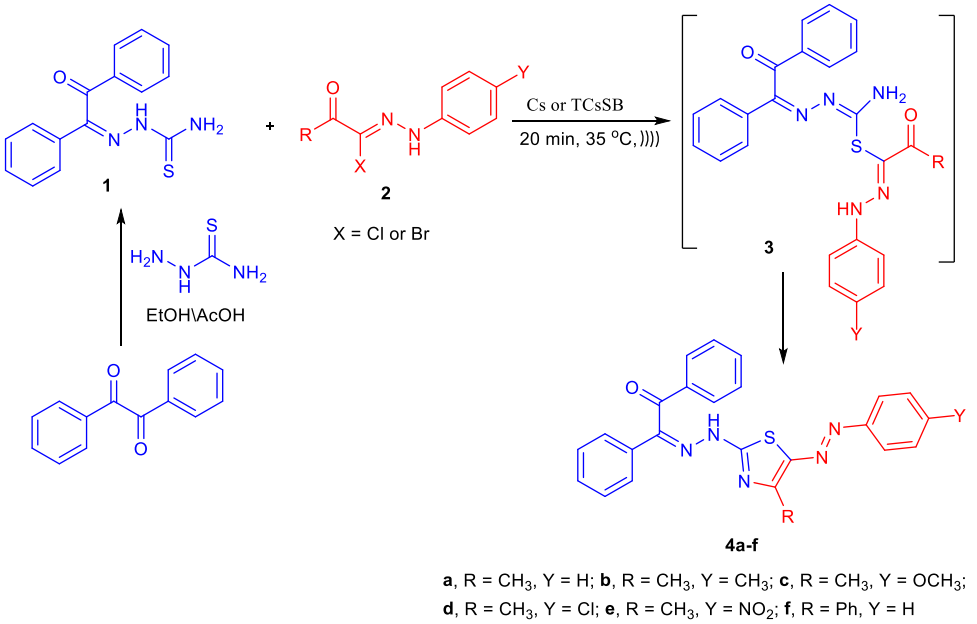
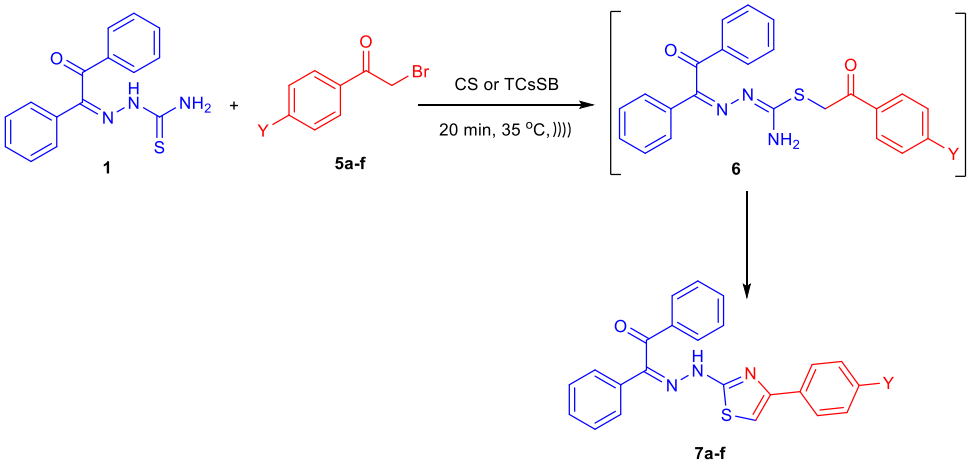
Scheme 2. Synthesis of Thiazoles 4a−f



The optimal catalytic conditions: TCsSB (15% wt.) in EtOH under USI at 35 °C for 20 minutes

Scheme 3. Synthesis of Thiazoles 7a−f



The optimal reaction conditions: TCsSB (15% wt.) in EtOH under USI at 35 °C for 20 minutes

Based on the experimentally demonstrated spectral and analytical data, the structures of products **7a−f** were clarified. For example, the IR spectra of the isolated products **7** showed the presence of the −NH and C═O group characteristic bands at normal wave numbers. The expected two singlet signals for the thiazole and NH hydrazone, as well as the anticipated aromatic protons, were observed in the ^{1}H NMR spectra of compounds **7a−f**.

The heightened catalytic activity of TCsSB is likely linked to the presence of a hydrazine group (−CO−NH−**NH**−CH_2−), which functions by abstracting a proton from the thiol form of thiosemicarbazone derivative **1**. This interaction results in the attachment of thiolate to the hydrazonoyl halide, forming the *S*-alkylated product. Subsequently, the *S*-alkylated product undergoes dehydrative cyclization, leading to the formation of the corresponding thiazole products **4a−f** (Scheme 4).

The investigation into the optimal primary catalyst commenced at the initial stages (Table 2).

As shown in Table 2, utilizing TCsSB as the basic catalyst under ultrasonic irradiation proved more effective compared to CS. Substituting CS with TCsSB resulted in enhanced yields of the desired products (**4a−f** and **7a−f**) and reduced reaction times while maintaining the same reaction conditions.

To establish the optimal experimental configuration and conditions (including solvent, temperature, reaction duration, and catalyst quantity) for the synthesis of thiazole derivative **4a** via the reaction of **1** + **2a** in the presence of a catalytic portion of TCsSB using ultrasonic irradiation (USI).

In the initial stage, we investigated the influence of varying catalyst quantities on the production of component **4a** (refer to Table 3, entries 1−3). Optimal results, with a yield of 87%, were observed when utilizing a catalyst concentration of 15 mol % (refer to Table 3, entry 3). Decreased yields were

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Table 2. Synthesis of Thiazoles 4a−f and 7a−f Utilizing Cs and TCsSB as Basic Catalysts

			Cs		TCsSB	
compound no.	R	Y	time (min)	(%) yield	time (min)	(%) yield
4a	Me	H	45	82	20	87
4b	Me	Me	40	79	19	83
4c	Me	MeO	42	78	22	82
4d	Me	Cl	37	83	18	89
4e	Me	NO_2	31	81	16	85
4f	Ph	H	38	85	20	87
7a		H	40	83	20	91
7b		Me	40	85	18	93
7c		MeO	45	80	21	90
7d		Cl	45	86	18	94
7e		Br	35	87	20	92
7f		NO_2	30	84	16	89

recorded when employing lower catalyst concentrations (see Table 3).

Subsequently, an investigation was conducted using USI to assess the efficiency of different solvents (refer to Table 3, entries 3−5). The results of the solvent screening revealed that the synthesis of product **4a** achieved the highest yield and the fastest reaction rate when employing EtOH (as indicated in Table 3, entry 3).

Morovere, in the USI evaluation of reaction time (as shown in Table 3, entries 3, 6, and 7), it was observed that a 20 min duration proved to be the optimal period for synthesizing product **4a** (as indicated in Table 3, entry 3).

Furthermore, an examination was conducted to assess the influence of the temperature on the reaction, and the results are presented in Table 3 (entries 3, 8−10). According to the data in Table 3, elevating the reaction temperature from 25 to 30 to 40 °C while utilizing USI led to a significant increase in product yields, with enhancements of 79, 85, and 87%, respectively. Ultimately, the optimal temperature was determined to be 35 °C (Table 3, entry 3).

Table 3. Optimizing the Reaction Parameters for the Synthesis of Thiazole 4a, Including Reaction Time, Temperature, Solvent, and Catalyst Loading

entry	catalyst (mol %)	solvent	time (min)	*T* (°C)	yield (%)
1	5	EtOH	20	35	72
2	10	EtOH	20	35	85
3[a]	15	EtOH	20	35	87
4	15	$CHCl_3$	20	35	84
5	15	dioxane	20	35	81
6	15	EtOH	15	35	85
7	15	EtOH	25	35	87
8	15	EtOH	20	25	79
9	15	EtOH	20	30	85
10	15	EtOH	20	40	87

[a]The optimal reaction conditions for compound **4a** synthesis: TCsSB (15% wt.) in EtOH under USI at 35 °C for 20 min.

Additionally, we examined the recyclability of TCsSB as a core catalyst. After each cycle, the catalyst was subjected to a cleaning process using distilled water and then dried at 50 °C for 30 min before reuse. The catalyst was employed three times under ideal conditions (15 wt % and 20 min), demonstrating no substantial reduction in catalytic efficiency (Table 4).

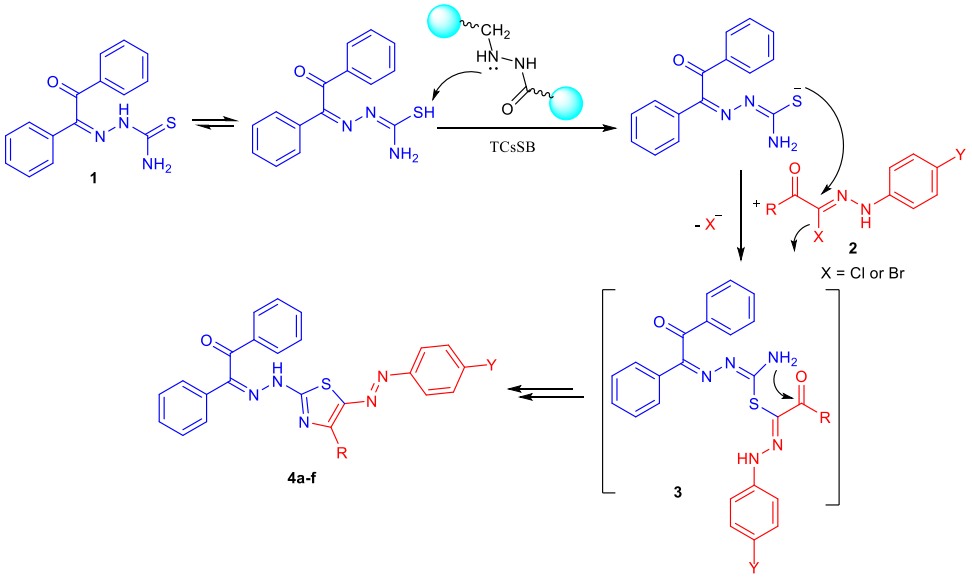
Table 4. Recyclability of TCsSB

		recycled catalyst			
state of catalyst	new catalyst	(1)	(2)	(3)	(4)
% yield of thiazole **4a**	87	83	81	57	42

The TCsSB's ability to be reused was put to the test four times, yielding 87−42% of the target product **4a** in roughly the same amount of time. Table 4 shows the results of the recycling experiments. The recovered catalyst can be used in future reactions at least two more times without a significant reduction in product yield.

The best reaction conditions for producing product **4a**, as indicated in Table 3, are a reaction of **1** + **2a** in EtOH\TCsSB (15 wt %) under USI at 35 °C for 20 min. Thus, under optimal

Scheme 4. Mechanism of Reaction of Thiosemicarbazone 1 with Hydrazonoyl Halides 2



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conditions, reactions of **1** + **2b−f** and **5a−f** resulted in the synthesis of thiazoles **4b−f** and **7a−f**, respectively (Schemes 2 and 3).

2.3. Antibacterial Activity of Compounds 4a−c and 7a−c. The synthesized compounds **4a−c** and **7a−c** were subjected to in vitro antibacterial assessment of four bacterial strains, including two Gram-negative strains, namely, *Escherichia coli* and *Pseudomonas aeruginosa*; two Gram-positive bacteria, *Staphylococcus aureus* and *Streptococcus pneumonia*, yielding promising results. All of the compounds exhibited minimum inhibitory concentration (MIC) values falling within a quantifiable concentration range, as detailed in Table 5.

Table 5. Antibacterial Activity Results of Compounds 4a−c and 7a−c[a]

	MIC (μg/mL)			
compound	*S. aureus*	*S. pneumonia*	*P. aeruginosa*	*E. coli*
ciprofloxacin	2.3 ± 0.4	6.5 ± 0.7	4.1 ± 0.4	1.5 ± 0.5
4a	8.0 ± 3.5	9.6 ± 4.1	8.5 ± 3.8	5.8 ± 2.9
4b	3.7 ± 2.8	7.9 ± 2.0	9.6 ± 3.0	6.7 ± 2.5
4c	2.1 ± 1.7	6.0 ± 1.8	4.9 ± 1.7	3.7 ± 1.5
7a	13.5 ± 4.2	15.2 ± 4.7	13.2 ± 4.0	8.3 ± 3.9
7b	11.2 ± 4.5	10.3 ± 2.7	12.0 ± 3.2	7.0 ± 1.8
7c	3.4 ± 1.5	5.3 ± 1.3	5.5 ± 1.6	1.9 ± 1.4

[a]Values are expressed using mean ± SEM, and the analysis was carried out using Microsoft Excel.

Notably, among these compounds, **4c** demonstrated efficacy comparable to that of the control drug (ciprofloxacin) against both Gram-positive and Gram-negative bacterial strains. Specifically, the MIC values for **4c** were 2.1 μg/mL for *S. aureus*, 6.0 μg/mL for *S. pneumonia*, 4.9 μg/mL for *P. aeruginosa*, and 3.7 μg/mL for *E. coli*. This indicates that **4c** exhibited superior potency compared to the positive control (ciprofloxacin), whose MIC values were 2.3 ± 0.4 μg/mL for *S. aureus* and 6.5 ± 0.7 μg/mL for *S. pneumonia*. Another noteworthy compound was **7c**, which displayed its highest efficacy against *E. coli* with an MIC value of 1.9 ± 1.4 μg/mL. Furthermore, it showed improved potency against *S. aureus* with an MIC of 3.4 ± 1.5 μg/mL when compared to the other compounds.

2.3.1. SAR Analysis for Synthesized Thiazole Derivatives. The SAR study of thiazoles explores how changes in the chemical structures of these compounds impact their biological activity. In this study, electron-donating groups (EDGs) such as methoxy and methyl groups exhibit notable antimicrobial activity, contrasting with the electron-withdrawing groups (EWGs) such as nitro, chloro, and bromo groups. EDGs are recognized for enhancing the effectiveness of certain compounds in antimicrobial activity. Both **4c** and **7c** share a common feature a thiazole ring with an electron-donating group (p-OCH_3). This characteristic may account for their substantial potency. In contrast, compounds **4b** and **7b**, which contain a p-CH_3 substitution, demonstrated superior antibacterial activity compared to the unsubstituted compounds **4a** and **7a**. Conversely, thiazole derivatives containing the EWG nitro, as seen in **4e** and **7f**, display weak antibacterial activity. Thiazole derivatives with an unsubstituted phenyl ring, as observed in **4a** and **7a**, demonstrate superior activity compared to those with EWGs. The absence of substitution on the phenyl ring corresponds to a notable decrease in activity within the series.

2.4. Molecular Docking Studies. In the context of molecular docking studies, we analyzed the interactions between the designed compounds and the target protein. We assessed the docked molecules by considering criteria such as binding affinity scores and the detection of noteworthy hydrogen bond and aromatic interactions (Table 5). The overall docking results were compared to ampicillin. It illustrated the interactions with protein residues (Figure 5). According to the results from molecular docking simulations, the test ligands exhibited higher binding energies in comparison to the standard inhibitor (−7.280 kcal/mol), as detailed in Table 6. Compound **4b**, for instance, formed a

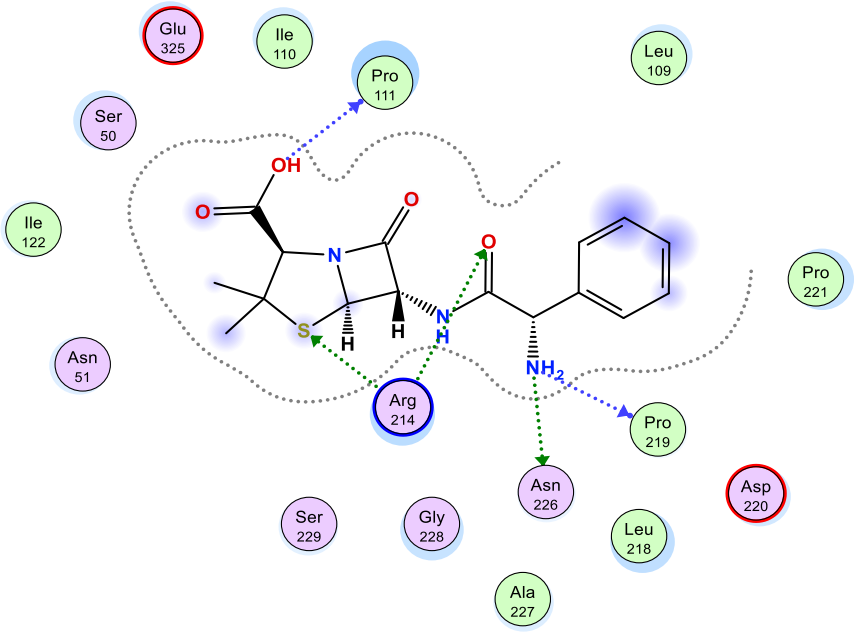

Figure 5. 2D binding of ampicillin (a reference ligand) with 1MBT.

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Table 6. Docking Score (kcal/mol), No. of Arene Interaction, and No. of HBonding Formed between Synthesized Compounds 4a−f and 7a−f with 1MBT Receptors When Compared to Ampicillin

entry	docking score (kcal/mol)	no. of arene interaction	no. of hydrogen bonding	acceptor atom	donor atom
4a	−8.266				
4b	−8.421		1 (Gly123)		*S*
4c	−8.559		1 (Gly47)	*N*	
4d	−8.015	1 (*π*−*H*) [Pro111]	1 (Ile45)		*Cl*
		1 (*π*−*H*) [Ser229]	1 (Arg214)	*O*	
4e	−8.396		1 (Pro111)		*S*
			1 (Gly47)	*O*	
4f	−8.383		1 (Glu325)		*S*
7a	−7.494		2 (Arg214)	*N*	
7b	−7.623		2 (Arg214)	*N*	
7c	−7.764		1 (Arg214)	*O*	
7d	−7.519	1 (*π*−*H*) [Asp220]	2 (Arg214)	*N*	
			1 (Ser229)	*O*	
7e	−7.586		1 (Arg214)	*N*	
7f	−7.661	1 (*π*−*H*) [Ser229]	2 (Lys262)	*O*	
			1 (Tyr158)		
			1 (Asn233)		
ampicillin	−7.280		2 (Arg214)	*S/O*	
			2 (Pro219)		*N/O*
			1 (Asn226)		*N*

hydrogen bond with Gly123, using its sulfur (S) atom as a hydrogen bond donor. In the case of compound **4c**, the 3D model revealed a hydrogen bond acceptor interaction between the nitrogen (N) atom of the thiazole ring and Gly47. In contrast, during the docking of **4d**, interactions included hydrogen bonding between the oxygen (O) atom in the carbonyl group and residue Arg214, as well as between the chlorine (Cl) atom and residue Ile45. Furthermore, thiazole **4d** exhibited *π*−H (pihydrogen) interactions with residues Pro111 and Ser229. On the contrary, the docking of **4e**, gave a Hbonding interaction between the *O* atom in the nitro group and the residue of Gly47 and between the *S* atom in the thiazole ring and the residue of Pro111. Compound **4f** formed a hydrogen bond between the sulfur atom in its thiazole ring and the side chain Glu325. Moreover, compounds **7a, b** have two hydrogen bond acceptors between their *N* atoms with Arg214. In the 3D model of compound **7c**, a single hydrogen bond acceptor was observed formed by the oxygen atom of its carbonyl group with Arg214. Conversely, when docking **7d**, we observed hydrogen bonding interactions between the oxygen atom in the carbonyl group and Ser229 residue, as well as between the nitrogen atom and Arg214 residue. Moreover, the thiazole **7d** forms an arene interaction (*π*−H) with the residue of Ser229. Moreover, compound **7e** has one hydrogen bond acceptor between its *N* atom with Arg214. Finally, compound **7f** formed four Hbonds acceptors between its oxygen of the nitro moiety with Lys262, Tyr158, and Asn233. In addition, arene interaction was present (Figures 6 and S1).

2.5. Design and Evaluation of Physicochemical Properties. Anticipated benefits such as enhanced renal excretion and reduced toxicity are linked to lower molecular weight and lipophilicity in molecules, which in turn lead to improved para-cellular and trans-cellular absorption characteristics.[65−67] Adhering to the 'rule of 5 (Ro5)' standards designates a compound as drug-like, requiring a molecular mass below 500, a log Po/w value under 5, and less than 5 hydrogen bond donors along with 10 acceptors.[68,69] As per the Veber rule, molecules with no more than 10 rotatable bonds, a polar surface area of 140 or less, and 12 or fewer hydrogen bond donors and acceptors demonstrate heightened oral bioavailability.[70] These criteria play a significant role in a molecule's absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile.[71] Hence, precise control over physicochemical properties has emerged as a pivotal determinant in assessing a compound's potential as a therapeutic candidate, impacting its performance across various stages of drug development.

2.6. ADME Study. The Swiss ADME web server[72] was utilized to assess various physiological parameters, including ADME, as well as drug similarity. To predict the physiological and pharmacokinetic characteristics of the synthesized thiazole compounds, the SMILE notation of each compound was input into the platform. The summarized outcomes can be found in Table S1. It is crucial that the compounds adhere to Lipinski's "rule of five," which establishes criteria for hydrogen bond acceptors (HBAs) and donors (HBDs) with a specified range of 10−5, respectively, within the studied structures. The computed values for HBAs and HBDs indicate that the synthesized compounds indeed meet this rule. Additionally, the topological polar surface area (TPSA), commonly used to assess the influence of polar groups on a structure's surface, should not exceed 140 Å^2. With the exception of compound **4e**, all of the other compounds satisfy this criterion. Regarding gastrointestinal (GI) absorption, all of the examined thiazole derivatives demonstrated high levels of absorption, except for **4a−f, 7f**, and ampicillin, based on their GI absorption data. Furthermore, it was observed that none of the thiazole compounds had permeability through the blood−brain barrier (BBB). In terms of in silico P-gp substrate inhibition, most thiazole derivatives did not exhibit inhibitory activity, except for compounds **4a** and **4e**. Among the investigated thiazoles, all but **4a** and **4e** acted as inhibitors of CYP2C19 and CYP2C9. Specifically, compounds **4b−d** exclusively inhibited CYP2C9, while compounds **7a−d** inhibited CYP3A4, CYP1A2, CYP2C19, and CYP2C9. On the other hand, compounds **7e** and **7f** inhibited CYP1A2, CYP2C19, and

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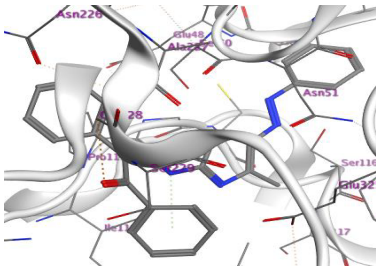
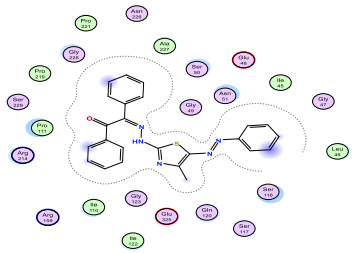
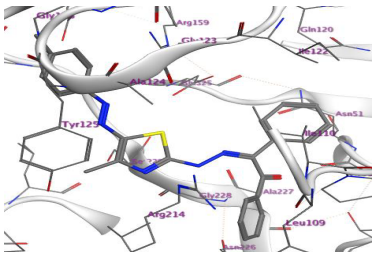
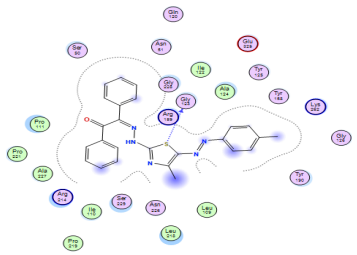
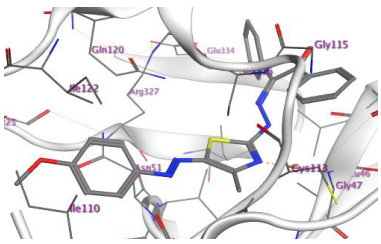
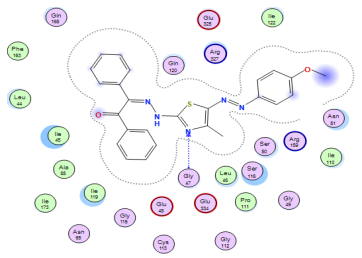
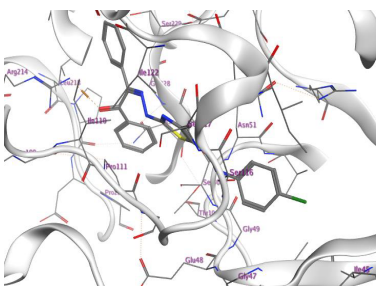
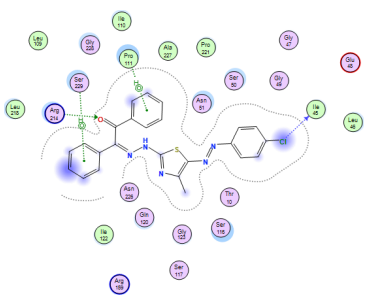
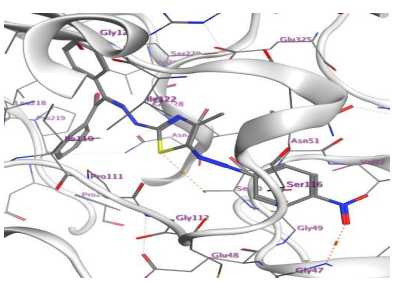
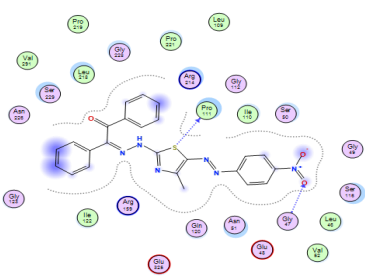
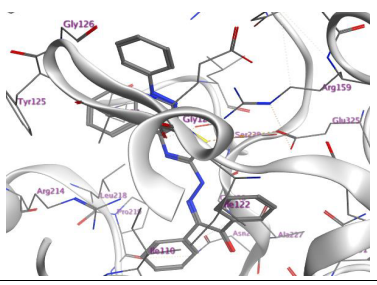
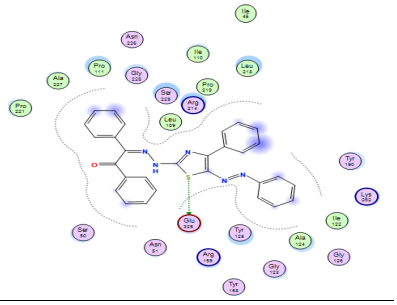
Compd.	3D Ligand interaction	2D Ligand interaction
4a		
4b		
4c		
4d		
4e		
4f		

Figure 6. Analyzing the interactions of compounds **4a−f** with the binding site of 1MBT (2D and 3D).

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CYP2C9. Notably, compound **4f** showed no inhibition against any of these enzymes, similar to ampicillin. According to the drug-likeness data, all of the evaluated thiazoles are considered drug-like compounds, with the majority meeting Lipinski and Veber criteria. Specifically, compounds **7a, 7c,** and **7f** satisfy Lipinski, Ghose, Veber, and Egan criteria for drug-likeness. Ampicillin also conforms to Veber, Muegge, Lipinski, and Ghose criteria for drug-likeness and significantly exhibits effective antibacterial activity against *E. coli*.

3. EXPERIMENTAL SECTION

3.1. Chemicals and Materials. All reagents and chemicals, sourced from Sigma-Aldrich (Germany), were employed in strict accordance with the provided instructions.

3.2. Methods. The apparatus and instrumentation details have been included in the Supporting Information file.

3.2.1. Preparation of the TCsSB Hydrogel. First, it is necessary to preserve the NH_2 groups through their interaction with benzaldehyde in order to direct the alteration of Cs toward the major −OH groups. Methanol (50 mL) and Cs (5 g) were mixed at 25 °C for 30 min, then 20 mL of benzaldehyde was added to the resultant suspension, and stirring was carried out continuously for 24 h. Filtration, regular washing with methanol, and drying at 60 °C for 6 h resulted in the formation of Cs Schiff's base. Second, to alkalize and swell Cs Schiff's base (4 g), it was agitated for 30 min at room temperature in 120 mL of an aqueous sodium hydroxide solution (1 mmol L^{-1}). Epichlorohydrin (10 mL) was then progressively added to this suspended solution, and stirring was maintained for a further 6 h. By filtration, rinsed with water and acetone, and drying for 6 h at 60 °C, the produced epoxy Cs Schiff's base was achieved. Third, 90 mL of an aqueous NaOH solution was used to suspend 3 g of epoxy Cs Schiff's base (1 mmol l^{-1}). This suspension was shaken overnight at 25 °C and a solution of terephthalohydrazide (2.813 g in 25 mL of DMF) gradually added. Filtered, then rinsed with water and methanol before being dried at 70 °C to a consistent weight, TCsSB was obtained.[73]

3.2.2. Synthesis of Thiazoles 4a−f and 7a−f. Method A: A mixture of 2-(2-oxo-1,2-diphenylethylidene) hydrazine-1-carbothioamide **1** (0.283 g, 1 mmol) and either hydrazonoyl halides **2**[31,49,52,54,57] or 2-bromo-1-arylethan-1-ones **5**[31,52,54,57] (1 mmol each) was prepared and then 15 mol % Cs was added. This mixture was exposed to ultrasonic waves at a frequency of 40 kHz and a power of 250 W for a duration between 15 and 50 min at a temperature of 35 °C. To extract the thiazole derivatives **4a−f** or **7a−f**, Cs was removed from the heated solution, and the resulting precipitate was filtered out.

Method B: Using TCsSB (15 mol %) in place of Cs, the same procedure as described in method A was followed.

The spectral data of the synthesized products **4a−f** and **7a−f** were listed below:

3.2.2.1. 2-(2-(4-Methyl-5-(phenyldiazenyl)thiazol-2-yl)-hydrazineylidene)-1,2-diphenylethan-1-one (4a). Red solid, mp. 216−218 °C; IR (KBr): ν 3319 (NH), 3050, 2936 (CH), 1694 (C═O), 1606 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 6.96−7.95 (m, 15H, Ar−H), 10.58 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 9.9 (CH_3), 104.1, 107.5, 116.7, 123.8, 126.2, 128.8, 128.9, 129.4, 129.5, 129.7, 130.0, 136.4, 140.8, 151.4, 155.7, 160.2 (Ar−H and C═N), 190.9 (C═O) ppm; MS m/z (%): 425 (M^+, 28). Anal. Calcd for $C_{24}H_{19}N_5OS$ (425.51): C, 67.75; H, 4.50; N, 16.46. Found: C, 67.62; H, 4.37; N, 16.35%.

3.2.2.2. 2-(2-(4-Methyl-5-(p-tolyldiazenyl)thiazol-2-yl)-hydrazineylidene)-1,2-diphenylethan-1-one (4b). Red solid, mp. 209−211 °C; IR (KBr): ν 3337 (NH), 3039, 2933 (CH), 1695 (C═O), 1603 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.84−7.91 (m, 14H, Ar−H), 10.57 (br s, 1H, NH) ppm; MS m/z (%): 439 (M^+, 100). Anal. Calcd for $C_{25}H_{21}N_5OS$ (439.54): C, 68.32; H, 4.82; N, 15.93. Found: C, 68.16; H, 4.69; N, 15.70%.

3.2.2.3. 2-(2-(5-((4-Methoxyphenyl)diazenyl)-4-methylthiazol-2-yl)hydrazineylidene)-1,2-diphenylethan-1-one (4c). Red solid, mp. 195−197 °C; IR (KBr): ν 3283 (NH), 3022, 2918 (CH), 1699 (C═O), 1601 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 6.88−7.80 (m, 14H, Ar−H), 10.86 (br s, 1H, NH) ppm; MS m/z (%): 455 (M^+, 57). Anal. Calcd for $C_{25}H_{21}N_5O_2S$ (455.54): C, 65.92; H, 4.65; N, 15.37. Found: C, 65.73; H, 4.68; N, 15.20%.

3.2.2.4. 2-(2-(5-((4-Chlorophenyl)diazenyl)-4-methylthiazol-2-yl)hydrazineylidene)-1,2-diphenylethan-1-one (4d). Red solid, mp. 213−215 °C; IR (KBr): ν 3330 (NH), 3037, 2917 (CH), 1707 (C═O), 1603 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H, CH_3), 7.08−7.82 (m, 14H, Ar−H), 10.46 (br s, 1H, NH) ppm; MS m/z (%): 461 (M^++2, 26), 459 (M^+, 83). Anal. Calcd for $C_{24}H_{18}ClN_5OS$ (459.95): C, 62.67; H, 3.94; N, 15.23. Found: C, 62.84; H, 3.75; N, 15.12%.

3.2.2.5. 2-(2-(4-Methyl-5-((4-nitrophenyl)diazenyl)thiazol-2-yl)hydrazineylidene)-1,2-diphenylethan-1-one (4e). Red solid, mp. 230−232 °C; IR (KBr): ν 3317 (NH), 3028, 2922 (CH), 1709 (C═O), 1613 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.40−8.14 (m, 14H, Ar−H), 10.87 (br s, 1H, NH) ppm; MS m/z (%): 470 (M^+, 66). Anal. Calcd for $C_{24}H_{18}N_6O_3S$ (470.51): C, 61.27; H, 3.86; N, 17.86. Found: C, 61.10; H, 3.74; N, 17.69%.

3.2.2.6. 1,2-Diphenyl-2-(2-(4-phenyl-5-(phenyldiazenyl)-thiazol-2-yl)hydrazineylidene)ethan-1-one (4f). Orange solid, mp. 239−241 °C; IR (KBr): ν 3306 (NH), 3026, 2942 (CH), 1690 (C═O), 1608 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.00−8.22 (m, 20H, Ar−H), 10.79 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 112.9, 119.2, 127.8, 128.6, 128.8, 129.0, 129.2, 129.3, 129.4, 129.5, 130.2, 131.7, 131.9, 133.7, 133.8, 135.6, 137.1, 150.0, 160.7, 166.8 (Ar−H and C═N), 191.8 (C═O) ppm; MS m/z (%): 487 (M^+, 100). Anal. Calcd for $C_{29}H_{21}N_5OS$ (487.58): C, 71.44; H, 4.34; N, 14.36. Found: C, 71.51; H, 4.24; N, 14.18%.

3.2.2.7. 1,2-Diphenyl-2-(2-(4-phenylthiazol-2-yl)-hydrazineylidene)ethan-1-one (7a). Yellow solid, mp 179−191 °C; IR (KBr): ν 3327 (NH), 3035, 2930 (CH), 1692 (C═O), 1602 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.21−8.13 (m, 13H, Ar−H and thiazole-H5), 11.66 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 21.4 (CH_3), 126.9, 127.9, 128.4, 128.9, 129.0, 129.3, 129.6, 129.8, 130.0, 130.4, 133.8, 135.2, 146.4, 152.3, 158.0 (Ar−H and C═N), 190.7 (C═O) ppm; MS m/z (%): 383 (M^+, 47). Anal. Calcd for $C_{23}H_{17}N_3OS$ (383.47): C, 72.04; H, 4.47; N, 10.96. Found: C, 72.01; H, 4.38; N, 10.85%.

3.2.2.8. 1,2-Diphenyl-2-(2-(4-(p-tolyl)thiazol-2-yl)-hydrazineylidene)ethan-1-one (7b). Yellow solid, mp 172−174 °C; IR (KBr): ν 3318 (NH), 3022, 2946 (CH), 1697 (C═O), 1606 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H, CH_3), 7.12 (s, 1H, thiazole-H5), 7.13−7.84 (m, 14H, Ar−H), 11.56 (br s, 1H, NH) ppm; MS m/z (%): 397 (M^+, 100). Anal. Calcd for $C_{24}H_{19}N_3OS$ (397.50): C, 72.52; H, 4.82; N, 10.57. Found: C, 72.71; H, 4.73; N, 10.46%.

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3.2.2.9. 2-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)-hydrazineylidene)-1,2-diphenylethan-1-one (7c). Yellow solid, mp. 190−192 °C; IR (KBr): ν 3339 (NH), 3037, 2928 (CH), 1691 (C═O), 1601 (C═N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.73 (s, 3H, OCH_3), 7.17−7.22 (s, 4H, Ar−H and thiazole-H5), 7.26−7.74 (m, 11H, Ar−H), 11.82 (br s, 1H, NH) ppm; MS m/z (%): 413 (M^+, 46). Anal. Calcd for $C_{24}H_{19}N_3O_2S$ (413.50): C, 69.71; H, 4.63; N, 10.16. Found: C, 69.53; H, 4.51; N, 10.05%.

3.2.2.10. 2-(2-(4-(4-Chlorophenyl)thiazol-2-yl)-hydrazineylidene)-1,2-diphenylethan-1-one (7d). Yellow solid, mp 200−202 °C; IR (KBr): ν 3323 (NH), 3046, 2927 (CH), 1704 (C═O), 1612 (C═N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.28 (s, 1H, thiazole-H5), 7.35−7.84 (m, 14H, Ar−H), 11.70 (br s, 1H, NH) ppm; MS m/z (%): 419 (M^++2, 12), 417 (M^+, 38). Anal. Calcd for $C_{23}H_{16}ClN_3OS$ (417.91): C, 66.10; H, 3.86; N, 10.06. Found: C, 66.03; H, 3.69; N, 10.00%.

3.2.2.11. 2-(2-(4-(4-Bromophenyl)thiazol-2-yl)-hydrazineylidene)-1,2-diphenylethan-1-one (7e). Yellow solid, mp 194−196 °C; IR (KBr): ν 3348 (NH), 3035, 2933 (CH), 1699 (C═O), 1608 (C═N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.33 (s, 1H, thiazole-H5), 7.34−7.58 (m, 14H, Ar−H), 11.80 (br s, 1H, NH) ppm; MS m/z (%): 464 (M^++2, 53), 462 (M^+, 55). Anal. Calcd for $C_{23}H_{16}BrN_3OS$ (462.37): C, 59.75; H, 3.49; N, 9.09. Found: C, 59.52; H, 3.37; N, 9.01%.

3.2.2.12. 2-(2-(4-(4-Nitrophenyl)thiazol-2-yl)-hydrazineylidene)-1,2-diphenylethan-1-one (7f). Brown solid, mp. 217−219 °C; IR (KBr): ν 3350 (NH), 3041, 2939 (CH), 1706 (C═O), 1615 (C═N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.35−7.41 (m, 8H, Ar−H), 7.58−7.59 (m, J = 7.6 Hz, 2H, Ar−H), 7.77 (s, 1H, thiazole-H5), 8.02−8.03 (d, J = 7.6 Hz, 2H, Ar−H), 8.19−8.20 (d, J = 8.5 Hz, 2H, Ar−H), 11.94 (br s, 1H, NH) ppm; MS m/z (%): 428 (M^+, 31). Anal. Calcd for $C_{23}H_{16}N_4O_3S$ (428.47): C, 64.47; H, 3.76; N, 13.08. Found: C, 64.60; H, 3.63; N, 13.02%.

3.3. Measurements. Details of apparatus and instrumentations were inserted in the Supporting Information file.

3.4. Antibacterial Assay. Details of antibacterial assay were inserted in the Supporting Information file.[74−78]

3.5. Docking Study. Details of molecular docking were inserted in the Supporting Information file.[79−81]

4. CONCLUSIONS

In this study, we synthesized and characterized TCsSB hydrogel using XRD, SEM, FTIR, and TG analysis. TCsSB proved to be an effective and environmentally friendly heterogeneous basic catalyst for the synthesis of valuable thiazole derivatives that are of significant industrial importance. The structures of the newly synthesized products were confirmed through spectroscopic data and elemental analysis. Furthermore, our findings indicated that TCsSB outperformed Cs as a heterogeneous basic catalyst in these reactions. Molecular docking plays a pivotal role in designing customized drug delivery systems. Within this context, our compounds exhibited varying degrees of antibacterial efficacy. Notably, compounds **4c**, **4b**, **7c**, and **7b** displayed the highest antibacterial activity, while compounds 4a and 4b demonstrated moderate to substantial antibacterial effects. Notably, compound **4c** exhibited the highest potency, as evidenced by its lower MIC value, particularly against Gram-positive strains when compared to Gram-negative strains. Moreover, we have outlined the significance of molecular docking studies in elucidating the binding interactions between thiazole derivatives and their target proteins. Finally, the utilization of ADME tools has demonstrated that the thiazole component exhibits favorable drug-like characteristics. We anticipate that this research will serve as a valuable resource for the scientific community dedicated to identifying effective drug candidates for combating bacterial infections.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c07785..

Additional supporting details, including molecular docking study, ADME study, methods and measurements, along with ^1H and ^{13}C NMR spectra for the synthesized compounds **4a−f** and **7a−f**, antibacterial assay, and molecular docking analysis (PDF)

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Notes

The authors declare no competing financial interest.

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