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Research Article

Novel Benzothiazole Derivatives Synthesis and its Analysis as Diuretic Agents

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Benzothiazoles, an anticonvulsant, antiviral, antihypertensive, and cancer-fighting medication of the heterocyclic scaffold family, also acts as antibacterial and antiviral agents. There is much interest in this chemical's production because of the strong and vital biological action it possesses. Substituted aromatic aldehydes were combined with 2-amino-benzothiazole-6-sulfonic acid amides, or Schiff base derivatives, to create Schiff base derivatives. Recrystallized, characterized, and tested for diuretic efficacy in vivo using online tools, m.p. (melting point), Rf, FTIR (Fourier transform infrared), 1H-NMR (proton nuclear magnetic resonance) data The molecular characteristics of all the substances created were estimated using Lipinski's rule of 5, OSIRIS (software) molecular property explorer, Molsoft, and Autodock 4.0 docking software. Male Wistar rats were used to make all the compounds traditionally in order to test for diuretic activity. Neither the elemental nor the spectral information for the synthesized compounds disagreed. There were five different methods used to evaluate these compounds: Lipinski rule of five, Molsoft to determine molecular characteristics, PASS (prediction of activity spectra for substances) values to determine the diuretic effect, and OSIRIS software to determine toxicology. In order to investigate the diuretic effects of the selected drugs, docking analysis was used. Acetazolamide was shown to have a diuretic effect that was superior to that of compounds **IIIb** and **IIIe**, whereas 2-{(*E*)-[(3-hydroxyphenyl)methylidene]amino}-1,3-benzothiazole-6-sulfonamide (**IIIb**) was found to be the most promising potential.

1. Introduction

Patients with life-threatening diseases such as congestive heart failure, renal disease, hypertension, acute oedema of the lungs, and ascites may all improve from drug-induced diuresis. Because diuretics all cause potassium loss even if they work well at boosting sodium excretion, researchers have been searching for new diuretic medications that do not

cause potassium loss yet still work well at maintaining therapeutic efficacy [1, 2].

Derivatives of 2-aminobenzothiazoles are reported to have diverse biological activities like cytotoxicity, anti-inflammatory, analgesic, anthelmintic, antiviral, antidiabetic, antimicrobial, antileishmanial, anticonvulsant, Alzheimer's disease, and calcium channel blocking [3–6]. The present study was carried out on 6-sulfonamide containing 2-aminobenzothiazole Schiff bases derivatives as lead molecules of the study with the aid of docking for evaluating their diuretic activity, which is an adjutant therapy in treating hypertension [7–9].

It is a common practice in SBDD to use molecular docking because it can accurately anticipate the shape of small-molecule ligands in the target-binding site. In addition, it is one of the most reliable approaches. Molecular docking has been an essential method in drug discovery since the first algorithms were developed in the 1980s [10]. In order to find the most likely binding configurations, two processes must be completed: A wide range of probable binding modes is examined, and the interaction energy associated with each of these binding conformations is accurately predicted [11].

The software used to determine if a molecule is a drug or not follows the Lipinski rule of five [12]. It includes information on molecular weight, hydrogen bond donor, hydrogen bond acceptor, logP value, and molar refractivity. Molsoft L.L.C drug likeness and molecular property prediction provides a molecule's molecular formula, molecular weight, hydrogen bond acceptor, hydrogen bond donor, MolLogP, MolLogS, MolPSA, MolVol, pKa, BBB score, number of stereo centres, and drug likeness score [13–15]. OSIRIS property explorer offers information if a molecule [16], if produced, creates any toxicity impact by exhibiting in the window on the screen,; green colour indicates nontoxic while red colour harmful. Other data like solubility, TPSA, clogP, drug likeness, and drug score are also provided. The online freeware PASS (prediction of activity spectra for substances) determines whether a chemical is physiologically active as *Pa* or inert as *Pi*. Molinspiration and SWISS ADME [17] software's were used to determine drug activity ADME, physicochemical characteristics, GI absorption, drug likeness, GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor, and bioavailability score. Based on the premise, benzthiazoles (Figure 1) have diuretic action as such, the experiment was planned to synthesize derivatives if they exhibit diuretic activity.

2. Materials and Methods

There were three types of beakers used in this experiment: dry Borosil glass, round bottomed glass, and conical glass. MERCK precoated silica gel plates were utilized for TLC monitoring, and a JASCO UV chamber was employed to see spots in TLC.

Instruments for visual melting range measurements were purchased from Lab India. KBr (potassium bromide) disc on FTIR 8300, and KBr press Shimadzu were used to record the IR spectra of compound **IIIb**. The ^{1}H-NMR spectra of the synthesized chemical IIIb were acquired on a BRUKER-400 MHz spectrometer using DMSO as the solvent, and the results were analyzed. Digital flame photometer Cisco 381 was used for the estimation of ions.

2.1. Chemistry. The synthetic procedures that were followed in order to get the target compounds IIIa-i were represented in diagrams. The structures of synthesized substances were determined on the basis of elemental analysis and spectrum data collected throughout the process. The preceding starting ingredients for the synthesis of 2-amino-benzothiazole-6-sulfonic acid amide (**II**), which is a cyclisation process, were para-amino sulphanilamide and ammonium thiocyanate. Compounds IIIa-i were first made by reacting equimolar quantities of (**II**) with suitable aldehydes in 100% alcohol, which is an imine production reaction followed by a nucleophilic addition reaction. Compounds IIIb-i were then synthesized in the same manner [18].

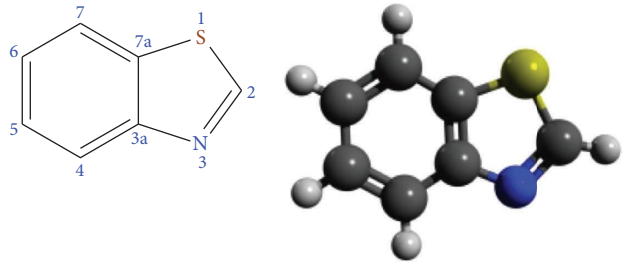
2.1.1. General Method for the Synthesis of 2-amino-benzothiazole-6-sulfonic acid amide (**II**). Everything was combined with glacial acetic acid, which had been precooled to 5°C, and 0.06 mol of sodium hydroxide and 0.06 mol of *p*-aminosulphanilamide. This mixture was kept in an ice bath and mechanically agitated while bromine (0.02 mol) was slowly introduced from an infusion funnel, maintaining a temperature rise of no more than 4–5°C during the process. The results were stunning. For an additional three hours, the mixture was continually churned in an ice bath at a temperature ranging from 0 to 10 °C. Acid was used to remove the hydrochloride salt from the filter and dry it before dissolving it in hot water. The water was used to wash the solution after it had been neutralized with aq. NH_3 solution (25 percent) and filtered. The needed pure chemical was obtained using benzene recrystallization (**II**) [18–20].

Yellowish brown; m.p. 230°C; Yield 80%.

*2.1.2. General Method for the Synthesis of Schiff's Bases of 2-amino benzothiazole Compounds (***IIIa-g**). In 20 mL of ethanol, 6-nitro-2-aminobenzothiazole **2a** (0.025 mol) was dissolved and 10 mL of ethanol was added in drops to the substituted aromatic aldehyde (0.030 mol). Twenty-four hours at room temperature were spent stirring the reaction mixture. A mixture of ethyl acetate:chloroform (1 : 2) was then evaporated, and the result was recrystallized from this combination to yield (**IIIa-g**) [21, 22].

2.2. In Silico Tools. Softwares of Lipinski rule of Five, Molsoft, PASS Online, OSIRIS Property Explorer, were used online [23–25].

AutoDock is a programme for simulating molecular models. Protein ligand docking is a particular strength of this method. Vina is an upgraded version of Auto Dock 4.0 and Auto Dock 4.2. Using Auto Dock 4.0, researchers follow four basic phases in the process, including synthesis of proteins, ligands, and grids [11].



(a) (b)

Figure 1: Benzothiazole. (a) Structure. (b) Model (ball and stick).

2.3. Molecular Docking Studies. Studies of enzyme-ligand interactions *in vivo* may be predicted by molecular docking studies. In order to do molecular docking experiments on the 3D structure of CA-II enzyme, we used 64-bit operating system under Windows 10 with an HP computer [Intel core i5 8th generation processor, 12 gigabytes of ram]. The 3D structure of the enzyme CA-II was downloaded from the RCSB-Protein Data Bank (PDB ID: 3BL1).

The enzyme's structure was improved and verified for any missing atoms, bonds, or connections. Remaining residues were carefully removed, omitting ligands and water molecules. Building the ligand molecules required the use of the builder molecule, which reduced their energy. It created an active site by using grid box tools, and an energy-efficient conformer was selected and its energy was minimized. For 3BL1 compounds, **IIIb**, **IIIe**, and standard, the optimum binding modes are shown as illustrated in Figures 2–4.

2.4. Effect on Electrolyte Concentration. Flame photometry was used to measure the concentration of Na^+ and K^+ ions. For flame photometric examination, the major standard solutions of sodium and potassium were produced at a weight concentration of 1000 ppm each.

This method was used to dilute these solutions to the correct concentrations before usage. Distilled water was used to dilute the urine (1–3 ml) to a final volume of 100 ml, and the resulting diluted solution was used to measure the ions Na^+ and K^+ in the urine.

2.5. Evaluation of Diuretic Activity. Methods of diuretic activity were carried out utilizing Lipschitz's approach. Institutional Animal Ethics Committee 4/IAEC/VCOP/2019 Central Animal House, Vaagdevi College of Pharmacy, Hanamkonda, Warangal approved the study's experimental procedure.

An acute investigation of diuretic action was conducted on five groups of male Wister rats ($n = 6$) whose weight was about 100–120 g that had been acclimatized for 10 days. Each group is housed in a metabolic cage with a wire mesh bottom and a urine collection funnel. The faeces are caught in stainless steel sieves in the funnel, which enable the urine to go through. A regular diet of Altromin pellets and water were given to the rats. The rats were fed and watered for fifteen hours before the experiment in order to measure diuretic activity. Gently compressing the pelvic region and tugging the tails of the animals helped empty their bladders. Individual cages for each animal were put 24 hours prior to the experiment's start date for environmental adaption. 0.9 percent NaCl solution was used to provide a dosage of 25 and 45 mg/kg of body weight, respectively. Only 0.9 percent NaCl solution is given to the control group. Both 25 and 45 mg/kg body weight of the test compounds were compared to the conventional diuretic acetazolamide in a 0.9 percent NaCl solution (Scheme 1).

A graduated cylinder was used to collect urine, and the volume was recorded every five hours and every 24 hours. Fluorescence photometric analysis was used to determine sodium and potassium concentrations, which were represented as mmol/L [26].

The amount of diuretic activity was determined by using the following formula:

$$\text{Urinary Excretion} = \frac{\text{Total urinary output (Vo)}}{\text{Total liquid administered (Vt)}} \times 100, \tag{1}$$

$$\text{Diuretic Action} = \frac{\text{Urinary Excretion in test group (UEt)}}{\text{Urinary Excretion in control group (UEc)}}, \tag{2}$$

$$\text{Diuretic Action} = \frac{\text{Diuretic action of the test group (DAt)}}{\text{Diuretic action of urea group (DAu)}}, \tag{3}$$

$$\text{Lipschitz value} = \frac{\text{Urinary Excretion of test group (UEt)}}{\text{Urinary Excretion of urea group (UEu)}}. \tag{4}$$

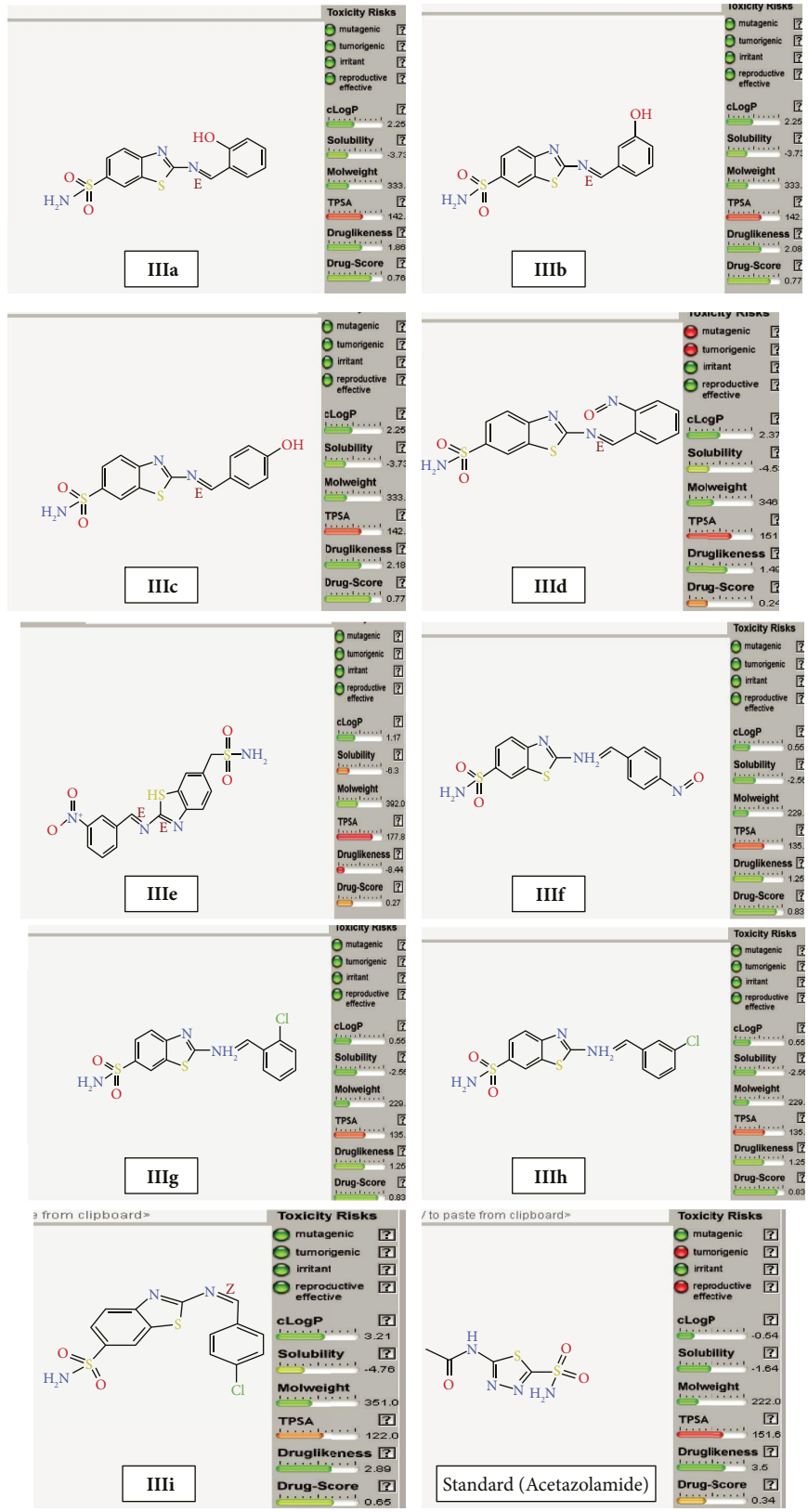


Figure 2: Molecular property explorers OSIRIS and standard for compounds **IIIa-IIIi**.

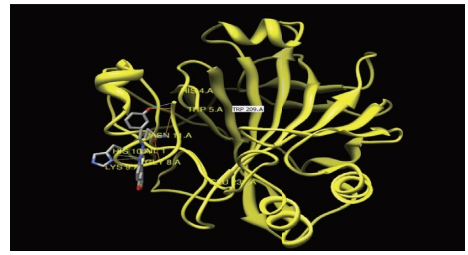


Figure 3: Protein-ligand complex of 3BL1 and **IIIb**.

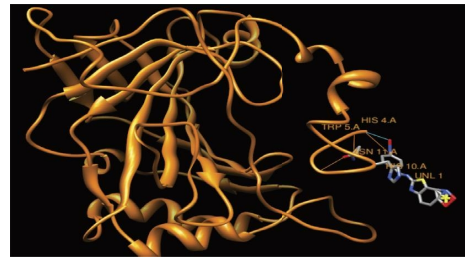


Figure 4: Protein-ligand complex of 3BL1 and **IIIe**.

Table 1: Lipinski filtering rule of five.

Compound	Molecular weight	Hydrogen bond donors	Hydrogen bond acceptors	Log p	Molar refractivity
IIIa	322	0	7	1.22	75.45
IIIb	322	0	7	1.15	76.10
IIIc	322	0	7	1.73	76.82
IIId	352	0	5	2.10	78.31
IIIe	352	0	5	1.78	78.10
IIIf	352	0	5	1.78	78.10
IIIg	341.50	0	6	2.14	74.35
IIIh	341.50	0	6	2.14	74.35
IIIi	341.50	0	6	2.14	74.35
Standard	216.00	0	7	0.30	40.97

Table 2: Exploration of Molsoft's properties.

Compound	Mol. formula	Mol. weight	HBA	HBD	Mlogp	Mlogs	Mol PSA	Mol volume
IIIa	$C_{14}H_{12}N_3O_3S_2$	334.03	7	4	3.10	−4.50	85.28	269.20
IIIb	$C_{14}H_{12}N_3O_3S_2$	334.03	7	4	3.22	−4.78	86.35	269.20
IIIc	$C_{14}H_{12}N_3O_3S_2$	334.03	7	4	3.22	−4.81	86.35	269.23
IIId	$C_{14}H_{11}N_4O_4S_2$	363.02	8	3	3.03	−5.16	101.81	283.12
IIIe	$C_{14}H_{11}N_4O_4S_2$	363.02	8	3	3.15	−5.73	102.11	283.74
IIIf	$C_{14}H_{11}N_4O_4S_2$	363.02	8	3	3.15	−5.81	101.11	283.67
IIIg	$C_{14}H_{11}ClN_3O_2S_2$	352.00	6	3	4.08	−5.73	68.73	273.35
IIIh	$C_{14}H_{11}ClN_3O_2S_2$	352.00	6	3	4.20	−5.84	68.73	275.95
IIIi	$C_{14}H_{11}ClN_3O_2S_2$	352.00	6	3	4.20	−5.91	68.73	275.87

Table 3: Pass results.

Compound	Carbonic anhydrase inhibition									
	I		II		IV		IX		XII	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
IIIa	0,012	0,003	—	—	—	—	0,026	0,006	0,048	0,006
IIIb	—	—	0,183	0,004	—	—	—	—	0,045	0,006
IIIc	0,015	0,012	0,015	0,003	—	—	—	—	0,051	0,005
IIId	—	—	0,199	0,002	—	—	—	—	0,057	0,005
IIIe	—	—	0,150	0,003	—	—	0,033	0,005	0,056	0,008
IIIf	0,019	0,008	0,188	0,002	—	—	—	—	0,064	0,004
IIIg	0,017	0,002	0,196	0,003	—	—	—	—	0,055	0,001
IIIh	—	—	0,070	0,004	—	—	0,032	0,005	0,057	0,005
IIIi	0,015	0,012	0,092	0,003	—	—	—	—	0,057	0,005
Standard	0,418	0,001	0,501	0,001	0,379	0,001	0,628	0,001	0,770	0,000

Here, *Pa*: probability to be active. *Pi*: probability to be inactive.

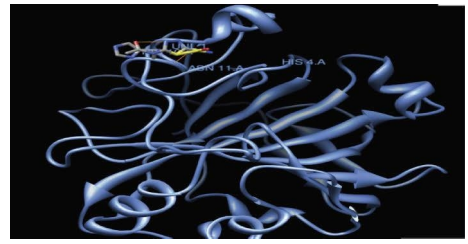


Figure 5: Protein-ligand complex of 3BL1 and standard (acetazolamide).

Table 4: The molecular docking interactions and the binding energy of 3BL1 compounds.

Ligand	Docking score (kcal/mol)	Number of hydrogen bonds	Key residues	Distance (Å)
IIIb	−5.63	5	HIS 4.A TRP10.A LYS 4.A HIS 10.A GLY 8.A	2.69 3.22 3.35 3.88
IIIc	−4.81	0	—	—
IIId	−3.95	1	ASN 11.A	3.53
IIIe	−5.08	3	HIS 10.A ASN 11.A HIS 4.A TRP 5.A	3.24 2.87 3.53
IIIf	−4.56	0	—	—
Acetazolamide	−3.38	2	HIS 10.A ASN 11.A	2.80 2.55

EtOH-Ethanol, GAA-Glacial acetic acid.

3. Results

3.1. In Silico Analysis. The results of Lipinski filtering rule of five, Molsoft's properties, PASS results are shown in Tables 1–3.

3.2. Docking Analysis. This approach, known as docking, is used to establish the exact binding conformation and orientation of ligand molecules into the active regions of proteins using computer simulation. Nine benzothiazole compounds were synthesized, and the standard (acetazolamide) was docked using AutoDock 4.2.6 against carbonic anhydrase II.

The finest conformers have been identified via the use of the Lamarckian genetic process. During each run of the evolutionary algorithm, the population size was set at 150 persons at random, and the maximum number of energy evaluations was restricted to 2,500,000 for each run. All active

Table 5: Physical data for synthesized compounds.

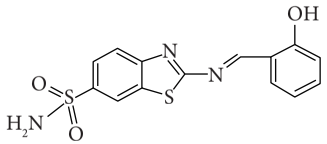
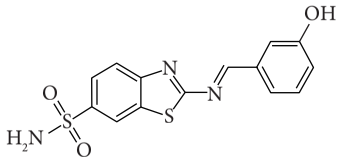
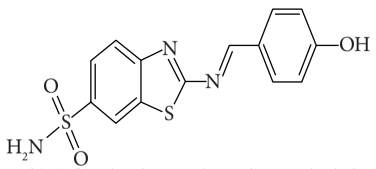
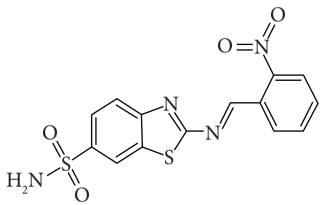
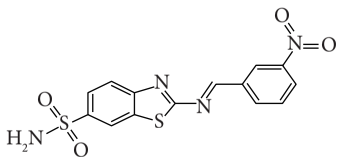
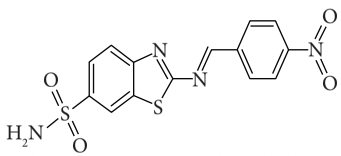
Code	Compounds	Mol Wt	Mol. Formula	Solubility	m.p (°C)	% Yield	R_f value
IIIa	 2-{(*E*)-[(2-hydroxy phenyl) methylidene]amino}-1,3-benzothiazole-6-sulfonamide	333.30	$C_{14}H_{11}N_3O_3S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	92–98	55	0.68
IIIb	 2-{(*E*)-[(3-hydroxyphenyl) methylidene]amino}-1,3-benzothiazole-6-sulfonamide	333.30	$C_{14}H_{11}N_3O_3S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	95–100	43	0.55
IIIc	 2-{(*E*)-[(4-hydroxyphenyl) methylidene]amino}-1,3-benzothiazole-6-sulfonamide	333.30	$C_{14}H_{11}N_3O_3S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	95–100	45	0.51
IIId	 2-{(*E*)-[(2-nitrophenyl) methylidene]amino}-1,3-benzothiazole-6-sulfonamide	294.37	$C_{14}H_{11}N_4O_4S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	105–109	39	0.59
IIIe	 2-{(*E*)-[(3-nitrophenyl) methylidene] amino}-1,3-benzothiazole-6-sulfonamide	294.37	$C_{14}H_{11}N_4O_4S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	101–105	45	0.82
IIIf	 2-{(*E*)-[(4-nitrophenyl)methylidene] amino}-1,3-benzothiazole-6-sulfonamide	294.37	$C_{14}H_{11}N_4O_4S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	95–100	48	0.64

Table 5: Continued.

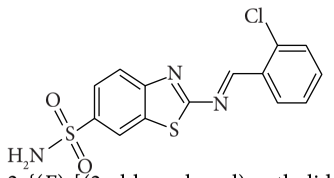
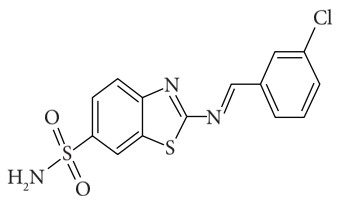
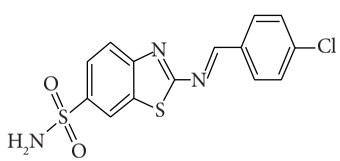
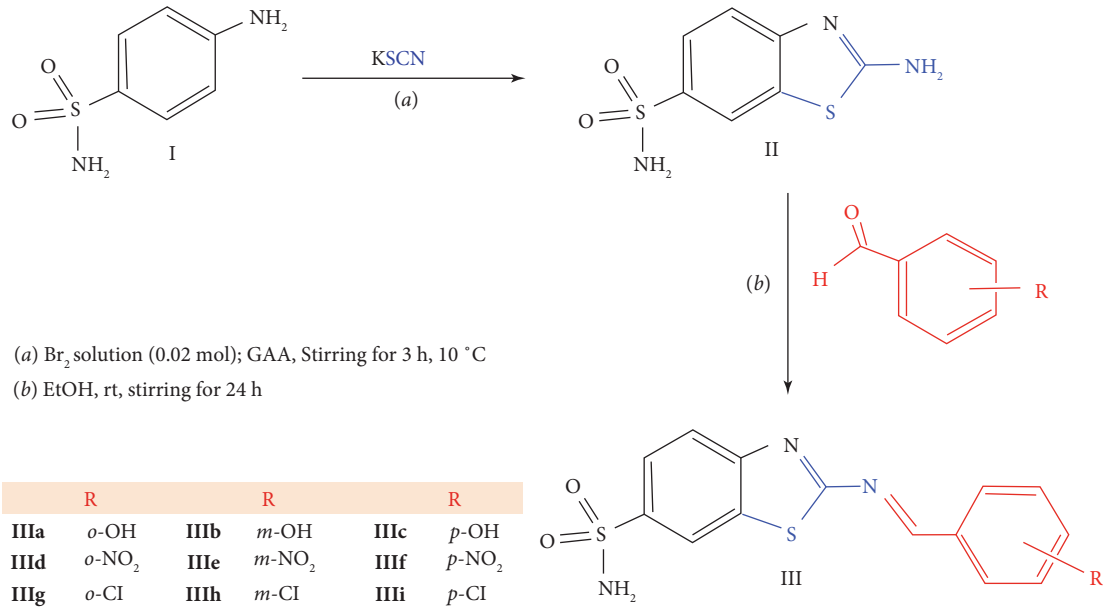
Code	Compounds	Mol Wt	Mol. Formula	Solubility	m.p (°C)	% Yield	R_f value
IIIg	 2-{(*E*)-[(2-chlorophenyl)methylidene]amino}-1,3-benzothiazole-6-sulfonamide	294.37	$C_{14}H_{11}ClN_3O_2S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	120–125	39	0.8
IIIh	 2-{(*E*)-[(3-chlorophenyl) methylidene] amino}-1,3-benzothiazole-6-sulfonamide	294.37	$C_{14}H_{11}ClN_3O_2S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	130–135	39	0.62
IIIi	 2-{(*E*)-[(4-chlorophenyl)methylidene] amino}-1,3-benzothiazole-6-sulfonamide	294.37	$C_{14}H_{11}ClN_3O_2S_2$	$CHCl_3$, CH_3OH, C_2H_5OH, DMSO	125–130	39	0.64

Table 6: Diuretic activity of IIIb and IIIe derivatives.

Treatment	Dose	Urinary volume (ml)	Urinary excretion (Vo/Vt) X 100	Diuretic action UEt/UEc	Diuretic activity DAt/DAu	Lipschitz value
Control	0.9% NaCl 25 ml/kg	2.2 ± 0.act25	68.75	—	—	—
Urea	1 gm/kg	4.1 ± 0.45***	128.12	1.86	—	1.67
Acetazolamide	25 mg/kg	3.56 ± 0.45***	114.83	1.67	0.89	0.89
	45 mg/kg	4.21 ± 0.45***	126.96	1.84	0.98	1.84
IIIb	25 mg/kg	3.7 ± 0.31***	112.12	1.63	0.87	0.87
	45 mg/kg	4.25 ± 0.21***	128.18	1.85	0.99	1.04
IIIe	25 mg/kg	3.81 ± 0.35***	119.06	1.73	0.93	0.92
	45 mg/kg	4.43 ± 0.26***	134.24	1.95	1.04	1.95

UEt = Urinary excretion in the test group; UEc = Urinary excretion in the control group; DAt = Diuretic action in the test group; DAu = Diuretic action of urea. *$P < 0.05$ (Dunnett's multiple comparison test) when using one way ANOVA. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$ (Dunnett's multiple comparison test) when using one way ANOVA.



	R		R		R
IIIa	*o*-OH	**IIIb**	*m*-OH	**IIIc**	*p*-OH
IIId	*o*-NO_2	**IIIe**	*m*-NO_2	**IIIf**	*p*-NO_2
IIIg	*o*-CI	**IIIh**	*m*-CI	**IIIi**	*p*-CI

Scheme 1: Synthesis of novel benzothiazole derivatives.

site residues in stiff macromolecules were included in the computations since the grid box size was increased to allow for all active site residues. To fit all of the active site residues, the grid box was centered at 9.323 Å × 1.691 Å x 15.842 Å and its X, Y, and Z co-ordinates were all changed to 90, 90, 90 to accommodate the active site residues.

Docking tests demonstrated that the top 5 ligands had the lowest affinity for the target protein carbonic anhydrase II, when compared to all other ligands evaluated in this study. The binding energy (Kcal/mol) and the number of hydrogen bonds formed with active site areas of the protein were measured and analyzed in the study of protein-ligand interactions. With the use of the Chimera 1.13.1 viewer, the docking contacts between the six ligands and carbonic anhydrase protein were seen and are shown in Figures 2–5. The final docked confirmation for the different ligands is shown in Tables 4–7 in accordance with the binding energy, the number of hydrogen bonds formed, the bond distance, and the interacting residues. Third, **IIIb** and acetazolamide had the lowest binding energy, with a docking score of −5.63 Kcal/mol (creating four hydrogen bonds with HIS) and −3.38 Kcal/mol (forming two hydrogen bonds with each of HIS and ASN), respectively.

3.3. Experimental. Compound **IIIb**: FTIR (cm^{-1}): 3376 (O-H str), 3154 (aromatic C-H str), 2923 (aliphatic C-H str), (C = N str), 1078 (C-N str), 1459 (C = C str), 1376 (SO_2NH_2 str), 721 (disubstituted benzene), 829 cm^{-1} (asymmetrically substituted benzene) (Figure 6).

^{1}H NMR (δ ppm, DMSO): 2.4 (s,1H, C-H); 6.9 (d, 1H,ArH); 7.0–7.4 (m, 3H, ArH); 7.8–8.0 (2d, 2H, ArH); 7.9 (d, 1H, ArH); 8.4 (s, 1H, ArH); 10.0 (s, 2H, NH_2) (Figure 7).

Table 7: Electrolyte excretion of IIIb and IIIe derivatives.

Treatment	Dose	Electrolyte Excretion Index	
		Na^+	K^+
Control	0.9% NaCl	125.83 ± 1.16	43.33 ± 1.86
Urea	1 gm/kg	144.83 ± 1.94***	54.55 ± 3.14**
Acetazolamide	25 mg/kg	193.83 ± 3.18***	76.33 ± 3.66**
	45 mg/kg	283.00 ± 2.75***	136.83 ± 3.24***
IIIb	25 mg/kg	215.33 ± 3.14***	84.5 ± 3.01**
	45 mg/kg	282.83 ± 2.41***	144.33 ± 1.63***
IIIe	25 mg/kg	188.83 ± 3.70***	69.33 ± 2.16**
	45 mg/kg	277.5 ± 2.48***	123.66 ± 1.75***

Results are presented as mean standard error of the mean ($n = 6$), with $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ (Dunnett's multiple comparison test) and one way ANOVA. Na^+ = sodium index, K^+ = potassium index.

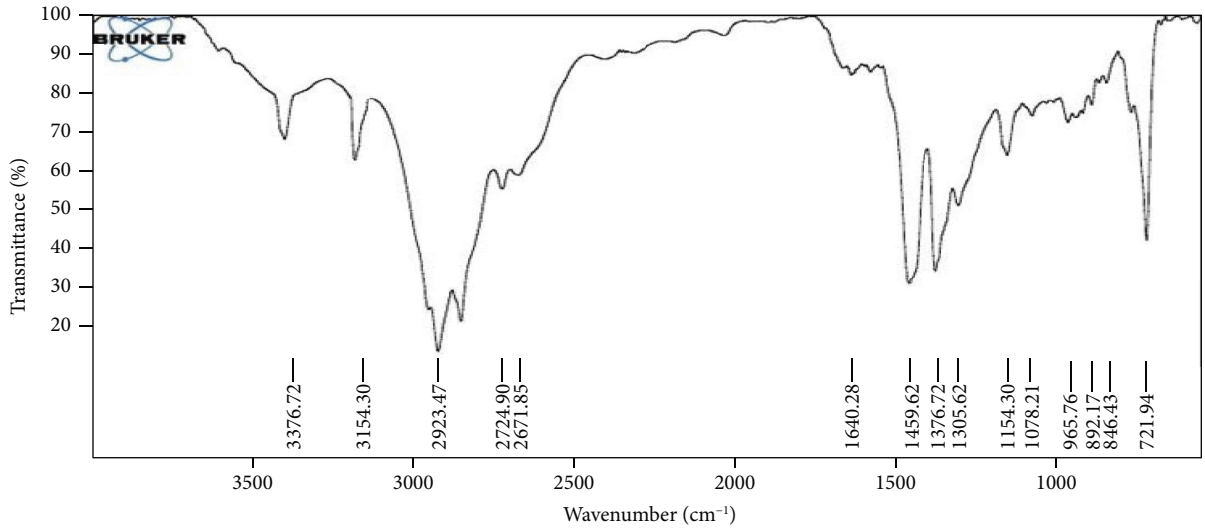


Figure 6: IR spectra of compound IIIb.

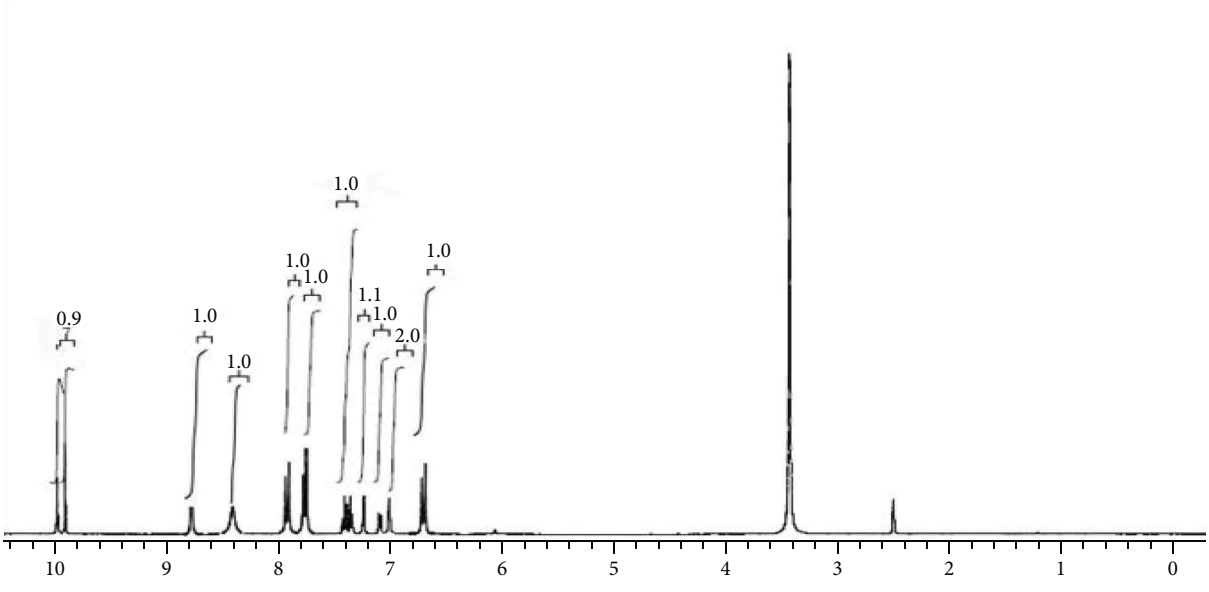


Figure 7: ^{1}H-NMR spectra of compound IIIb.

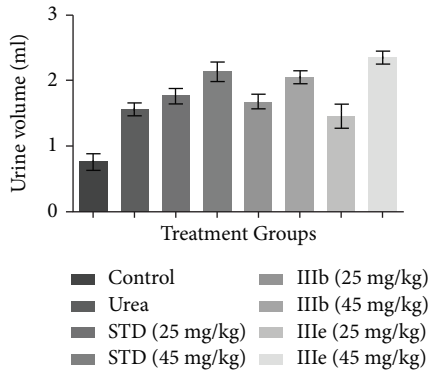


Figure 8: Diuretic activity in rats: a dose-response study.

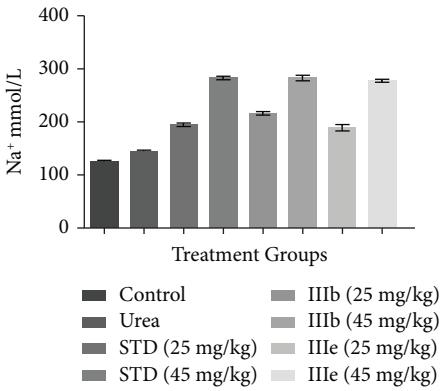


Figure 9: Electrolyte excretion (Na^+ mmol/L) in rats.

3.4. Diuretic Activity. The *in vivo* diuretic activity of the benzothiazole derivatives was determined using a conventional technique against male Wistar rats, and the results were compared to those of the reference compound (Tables 6–7 and Figures 8–10).

Both the synthesized compounds (**IIIb**) are found to be equipotent and (**IIIe**) is more potent than the standard drug (acetazolamide).

4. Discussion

Based on the results of Lipinski rule of five, the compounds synthesized were obeying Lipinski rule of 5. PASS values suggesting that all the synthesized compounds obey the PASS values. The standard (acetazolamide) has action nonselectivelyon all the sub classes of carbonic anhydrase enzyme. The molecules **IIIb, IIIc, IIId, IIIe, IIIf**, and **IIIg** have Pa > 0.1 primarily acting on carbonic anhydrase II, but the standard with Pa > 0.3 acting on all the subtypes of the enzyme. Toxicity (tumorigenic and reproductive effects) is present in the normal medicine, but not in the synthesized molecules except for **IIId** and **IIIf**, according to the OSIRIS molecular property explorer. The length of the hydrogen bonds produced with the interacting residues in the docking study findings reveals that the bonding was excellent for all of the ligands tested. The PDB sum predicted most of the

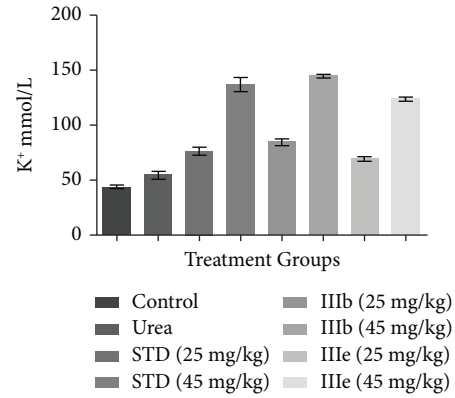


Figure 10: Electrolyte excretion (K^+ mmol/L) in rats.

important residues presented in Table 4 to be active site residues. All of the ligands have docking contacts with the protein carbonic anhydrase II, according to the docking score. This research used ligands having diuretic activity, which may have a distinct mechanism of action. Using molecular docking simulations, this research found that the **IIIb** and **IIIe**, block carbonic anhydrase II.

All of the more modern benzothiazole derivatives were created in the laboratory by mixing a number of different chemical reagents together. Hydroxyl derivatives were more productive in this case. TLC and melting points of the synthesized compounds differed significantly from those of the first stage product. One component, **IIIb**, was purified using column chromatography and characterized using spectroscopic methods including FTIR and ^{1}H NMR after it was produced and recrystallized from ethanol.

5. Conclusion

The results of the evaluation of diuretic activity indicated that the compound **IIIb** having urinary excretion, diuretic action, diuretic activity, and Lipschitz values higher than the standard drug which indicate that it is more potent than the standard. From Table 7 and Figures 8 and 9, it is evident that the sodium excretion is more and potassium excretion is moderate to that of the standard and urea-treated groups at 45 mg/kg dose.

Data Availability

All data used to establish the conclusions of this study are integrated into the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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