Asian Journal of Chemistry; Vol. 37, No. 9 (2025), 2202-2210
ASIAN JOURNAL OF CHEMISTRY
https://doi.org/10.14233/ajchem.2025.34249

Synthesis, Bioactivity Screening and *in silico* Studies of Phenyl Thiazole Derivatives Containing Arylidene Moieties

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Received: 14 June 2025 *Accepted*: 4 August 2025 *Published online*: 30 August 2025 AJC-22100

Thiazole, a heterocyclic compound containing Schiff bases being a compound's core can enhance the drug potency. This study contributes to the synthesis of three novel thiazole Schiff base derivatives **2a-c** by two-step synthesis method. The structures of the synthesized compounds were established by spectral analysis. Antimicrobial and antioxidant screening of synthesized compounds showed moderate to significant antimicrobial and antioxidant activities. Compounds **2c** showed excellent antimicrobial and antioxidant activities. The synthesized analogs showed good binding affinity and a variety of strong interactions with the effective binding sites of the target receptors. *In silico* studies support the antimicrobial results very well. It is expected that the synthesized analogs have a good drug score and contribute to the development of a more potent drug in the future.

Keywords: Synthesis, Thiazole, Bioactivity, *In silico* study, ADME prediction.

INTRODUCTION

Infectious diseases have always posed a serious threat to human existence and longevity [1]. The rise in outbreaks of new infectious diseases *i.e*. COVID-19 [2] has become a major global concern is called emerging infectious diseases (EID) [3]. This challenge is worsening with the global crisis of multi-drug resistance. Misuse and overuse of antimicrobial drugs are making pathogens resistant to multiple drug agents [4]. This medical emergency contributes to high morbidity and mortality rates, along with increasing healthcare expenses [5,6]. This situation emphasizes the pressing need for designing novel antimicrobial agents with different modes of action and no cross-resistance with the present drugs [7,8]. The heterocyclic compound with a thiazole ring at its core is the basic building block for many natural medicines [9] acts as a pharmacophore enhancing drug potency [10,11]. Numerous natural and synthetic compounds with a thiazole moiety in their structure exhibit immense pharmacological applications like antifungal, antioxidant, antibacterial, anti-inflammatory, anticancer and antiviral activities [12-18]. The ability of thiazole to target specific enzymes and receptors has shown promising results in drug discovery. This has led to the synthesis of novel drugs bearing a thiazole moiety as an interesting pursuit in medicinal chemistry [19].

Reactive oxygen species (ROS) is a key biological component [20]. Imbalanced ROS in cells causes oxidative stress, leading to non-communicable diseases (NCD) like diabetic, cancer, heart diseases and neurodegenerative disorders like (Alzheimer's and Perkinson's) [21-23]. Antioxidant therapy rebalances ROS production and protects cell wall integrity [24-26]. Thiazole derivatives having delocalized electrons can neutralize free radicals, scavenge ROS within an organism and stand out as promising antioxidants [27-29]. This research includes an in-depth study of synthesized compounds with *in vitro* antimicrobial activity testing utilizing agar disc diffusion method against selected Gram-positive, Gram-negative bacteria and fungal strains. Moreover, DPPH radical scavenging method was used for antioxidant investigation. *In silico m*olecular docking and ADME prediction of synthesized compounds were conducted to determine their interaction with target proteins and finally to evaluate pharmacokinetic properties.

EXPERIMENTAL

The analytical-grade chemicals and reagents used in this experiment were purchased from Sigma-Aldrich, USA. Melting points were recorded as uncorrected using electro-thermal melting point apparatus (model MPH-H290-264). Infrared spectra were measured in KBr disk on Shimadzu FTIR spectro-

photometer (Model FTIR-IR Affinity-1). The melting points were recorded in melting points apparatus of Fisher John (Model no. 1A 9000). ^{1}H NMR and ^{13}C NMR (DEPT-135, HSQC, HMBC, COSY) spectra of the samples were recorded from solutions in DMSO-d_6 and CD_3OD on a Bruker advance -III HD spectrometer operating at 400 and 100 MHz, respectively, using tetramethylsilane as an internal standard.

General procedure for the synthesis of benzaldehyde thiosemicarbazones (1a-c): A solution of thiosemicarbazide (5 mmol) and substituted benzaldehyde (**a-c**) (5 mmol) were mixed and allowed to reflux in the solution of ethanol (30 mL) at 80 ºC with continuous stirring until the reaction was completed (TLC). The reaction mixture was then cooled to room temperature and washed with *n*-hexene and filtered to collect the precipitate, which was then recrystallized from ethyl acetate with subsequent filtering to obtain pure crystals of substituted benzaldehyde thiosemicarbazones (**1a-c**), yield 68-70% (**Scheme-I**).

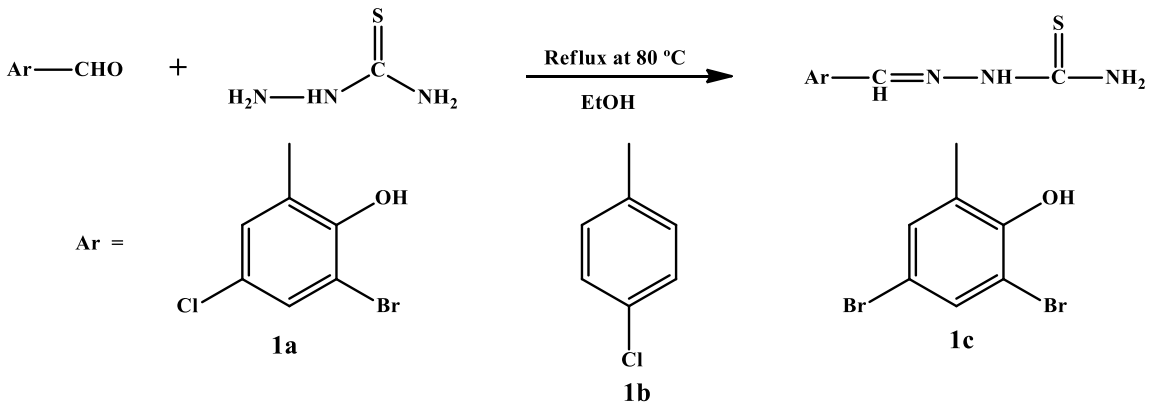
2-(3′-Bromo-5′-chloro-2′-hydroxyarylmethylidene)hydrazinecarbothiamide (1a): White solid, yield: 75%, m.p.: 244~246 ºC, IR (KBr, ν_{max} cm^{-1}): 3436 (N-H), 1598 (C=N), 1489 (C=S); ^{1}H NMR (DMSO-d_6, δ ppm): 7.65 (1H, d, J = 2.4 Hz, H-6′), 8.03 (1H, s, H-4′), 8.22 (1H, s, NH), 8.30 (1H, s, CH=N), 10.06 (1H, s, OH), δ 11.52 (2H, s, NH_2); ^{13}C NMR (DMSO-d_6, δ ppm): 113.1 (C1′), 151.9 (C2′), 125.1 (C3′), 126.5 (C4′), 142.5 (C5′), 133.1 (C6′), 138.9 (CH=N), 178.5 (C=S).

2-(4′-Chloro-arylmethylidene)hydrazinecarbothiamide (1b): White solid, yield: 80%, m.p.: 219~221 ºC, IR (KBr, ν_{max} cm^{-1}): 3436 (N-H), 1598 (C=N), 1489 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 7.45 (2H, dd, J = 8, 2.8 Hz, H-2′, H-6′), 7.83 (2H, dd, J = 8, 4.4 Hz, H-3′, H-5′), 8.03 (1H, s, CH=N), 8.20 (1H, s, NH), 11.44 (2H, s, NH_2); ^{13}C NMR (DMSO-d_6, δ ppm): 133.5 (C1′), 129.1 (C2′, C6′), 129.3 (C3′, C5′), 134.7 (C4′), 141.5 (CH=N), 178.5 (C=S).

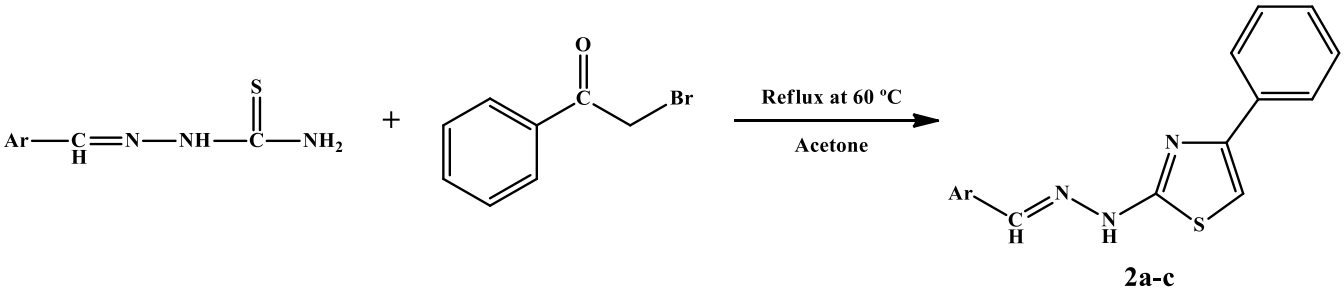
2-(3′,5′-Dibromo-2′-hydroxyarylmethylidene)hydrazinecarbothiamide (1c): White solid, yield: 91%, m.p.: 250 ~252 ºC, IR (KBr, ν_{max} cm^{-1}): 3430 (N-H), 1592 (C=N), 1485 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 7.75 (1H, d, J = 2.4, H-6′), 8.13 (1H, s, H-4′), 8.22 (1H, s, NH), 8.29 (1H, s, CH=N), 9.98 (1H, s, OH), 11.52 (2H, s, NH_2);+ ^{13}C NMR (DMSO-d_6, δ ppm): 112.5 (C1′), 152.3 (C2′), 112.2 (C3′), 130.3 (C4′), 112.8 (C5′), 135.6 (C6′), 138.8 (CH=N), 178.5 (C=S).

General procedure for the synthesis of arylidene thiazole derivatives (2a-c): A solution of 2-bromoacetophenone (3 mmol) was mixed with substituted benzaldehyde thiosemicarbazones (3 mmol) (**1a-c**) and allowed to reflux in the acetone solution (10 mL) at 60 ºC with continuous stirring until the reaction was completed (TLC). The mixture was left to cool and then filtered to collect the crude product. The crude product was recrystallized from ethyl acetate with excellent yield (72-75%) (**2a-c**) (**Scheme-II**).

2-(3′-Bromo-5′-chloro-2′-hydroxyarylmethylidene)-1-(4″-phenylthiazole-2″-yl)hydrazine (2a): Yellow amorphous solid, yield: 83%, m.p.: 267~269 ºC, IR (KBr, ν_{max} cm^{-1}): 3321 cm^{-1} (N-H), 1623 (C=N), 1491(C=S); ^{1}H NMR (DMSO -d_6, δ ppm): 7.32 (1H, t, J = 7.2 Hz, H-4‴), 7.36 (1H, s, H-5″), 7.43 (2H, t, J = 7.6 Hz, H-3‴, H-5‴), 7.64 (1H, s, H-4′), 7.66 (1H, d, J = 2.4 Hz, H-6′), 7.86 (2H, d, J = 7.6 Hz, H-2‴, H-6‴), 8.29 (1H, s, NH), δ 8.29 (1H, s, CH=N), δ 10.95 (1H, s, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 111.9 (C1′), 152.1 (C2′), 124.4 (C3′), 126.0 (C4′), 141.2 (C5′), 128.2 (C6′), 141.1 (CH=N), 166.5 (C2″), 167.7 (C4″), 104.0 (C5″), 124.4 (C1‴), 127.4 (C2‴), 129.1 (C3‴, C5‴), 128.8 (C4‴), 128.3 (C6‴).



Scheme-I: Synthesis of thiosemicarbazone analogs



Scheme-II: Synthesis of thiazole analogues

2-(4′-Chloro-arylmethylidene)-1-(4″-phenylthiazole-2″-yl)hydrazine (2b): Pale white amorphous solid, yield: 90.6%, m.p.: 224~226 ºC, IR (KBr, ν_{max} cm^{-1}): 3321 (N-H), 1623 (C=N), 1491 (C=S); ^{1}H NMR (DMSO-d_6, δ ppm): 7.32 (1H, t, *J* = 5.6, H-4‴), 7.34 (1H, s, H-5″), 7.41 (2H, t, *J* = 7.6 Hz, H-3‴, H-5‴), 7.49 (2H, d, *J* = 8.4 Hz, H-3′, H-5′), 7.68 Hz (2H, d, *J* = 8.4 Hz, H-2′, H-6′), 7.84 (2H, d, *J* =7.6 Hz, H-2‴, H-6‴), 8.04 (1H, s, NH), 8.07 (1H, s, CH=N); ^{13}C NMR (DMSO-d_6, δ ppm): 133.6 (C1′), 128.2 (C2′, C6′), 128.3 (C3′), 134.5 (C4′), 128.8 (C5′), 141.1 (CH=N), 168.6 (C2″), 150.1 (C4″), 104.4 (C5″), 134.2 (C1‴), 126.0 (C2‴, C6‴), 129.3 (C3‴, C5‴), 128.4 (C4‴).

2-(3′,5′-Dibromo-2′-hydroxyarylmethylidene)-1-(4″-phenylthiazole-2″-yl)hydrazine (2c): Yellow solid, yield: 82.7%, m.p.: 270~273 ºC, IR (KBr, ν_{max} cm^{-1}): 3323 (N-H), 1624 (C=N), 1495 (C=S); ^{1}H NMR (DMSO-d_6, δ ppm): 7.32 (1H, t, *J* = 7.2 Hz, H-4‴), 7.36 (1H, s, H-5″), 7.44 (2H, t, *J* = 7.6 Hz, H-3‴, H-5‴), 7.75 (1H, s, H-4′), 7.77 (1H, d, *J* = 2.4 Hz, H-6′), 7.86 (2H, d, *J* =7.6 Hz, H-2‴, H-6‴), 8.28 (1H, s, NH), 8.28 (1H, s, CH=N), 10.99 (1H, s, OH); ^{13}C NMR (DMSO-d_6, δ ppm): 111.9 (C1′), 152.5 (C2′), 112.8 (C3′), 129.1 (C4′), 112.2 (C5′), 135.6 (C6′), 141.1 (CH=N), 167.7 (C2″), 166.3 (C4″), 103.9 (C5″), 123.4 (C1‴), 128.3 (C2‴, C3‴,), 129.6 (C4‴), 126.0 (C5‴), 128.8 (C6‴).

Antimicrobial activity: The assessment of *in vitro* antibacterial efficacy of the synthesized compounds carried out using agar disc diffusion technique [30]. In brief, Mueller-Hinton Agar (MHA) from India and Potato Dextrose Agar (PDA) media obtained from Himedia, India, were utilized for testing bacterial and fungal species. In this method, the agar plates were aerobically incubated for 24h at 37 ºC for antibacterial and for 48 h at 26 ºC for antifungal screening. The media were controlled by adding DMSO. A 25 µL of sample solution in DMSO were added to each disc that contains 300 µg of thiazole derivatives, whereas 10 µL ceftriaxone and amphotericin B solution in DMSO were used to charge per disc, which contains 50 µg of standard ceftriaxone and amphotericin B. The study employed a pair of Gram-positive bacterial strains *Bacillus subtilis* along with *Staphylococcus aureus*, a pair of Gram-negative bacterial strains *Escherichia coli* as well as *Salmonella typhimurium* also a pair of fungal strains *Aspergillus niger* besides *Trichoderma harzianum*.

Antioxidant activity: Antioxidant studies of the synthesized compounds were performed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method [31-33]. The mixture was stirred for 24 h using an ethanolic solution of DPPH (6 µg/mL). Concentrations ranging from 500 µg/mL to 31.25 µg/mL were prepared by dissolving the synthetic analogs in ethanol. After transferring 4.0 mL DPPH radical solution to the different test solution, 100 µL of the prepared sample solution was added and the mixture was maintained in an ice-bath with darkness. To serve as a standard, the equivalent concentration of ascorbic acid solution in ethanol was made. After centrifuging every test sample for 10 sec, they were left in the dark for 15 min. For every solution, the absorbance at 517 nm was measured and compared to the blank. The following equation was used to compute the radical's inhibition (%):

$$\text{Inhibition } (\%) = \frac{A_{control} - A_{sample}}{A_{sample}} \times 100$$

where A_{sample} = absorbance of DPPH with sample and $A_{control}$ = absorbance of DPPH radicals.

Molecular docking studies: To strongly support the *in vitro* results of antimicrobial and antioxidant efficacy molecular docking study of the synthesized compounds (ligands) was done with three different target proteins in AutoDock Vina [34,35]. For docking purposes at first optimization of the synthesized compounds was performed (Fig. 1). All three compounds **2a-c** were docked against the co-crystals of *E. coli* (PDB ID: 1KZN) and co-crystals of *T. harzianum* (PDB ID: 5JBO) to investigate the antimicrobial activity. For studying the antioxidant activity compounds were docked against human antioxidant enzyme receptor (PDB ID: 3MNG).

Frontier molecular orbital analysis: Biological activity of a compound associated with the electronic transition between the HOMO and LUMO. Various molecular properties like chemical reactivity, optical polarizability, kinetic stability and so on can also be determined from the intermolecular charge transfer from HOMO to LUMO. This electronic transition is calculated as energy gap (ΔE). Important parameters such as hardness (η), softness (ζ), ionization potential (I), electron affinity (A), chemical potential (μ), electrophilicity (ψ) and electronegativity (χ) can also be calculated from the FMO analysis. All chemical reactivity parameters were calculated using the following equations:

$$\Delta E = E_{LUMO} - E_{HOMO}$$

$$\eta = \frac{(E_{LUMO} - E_{HOMO})}{2}$$

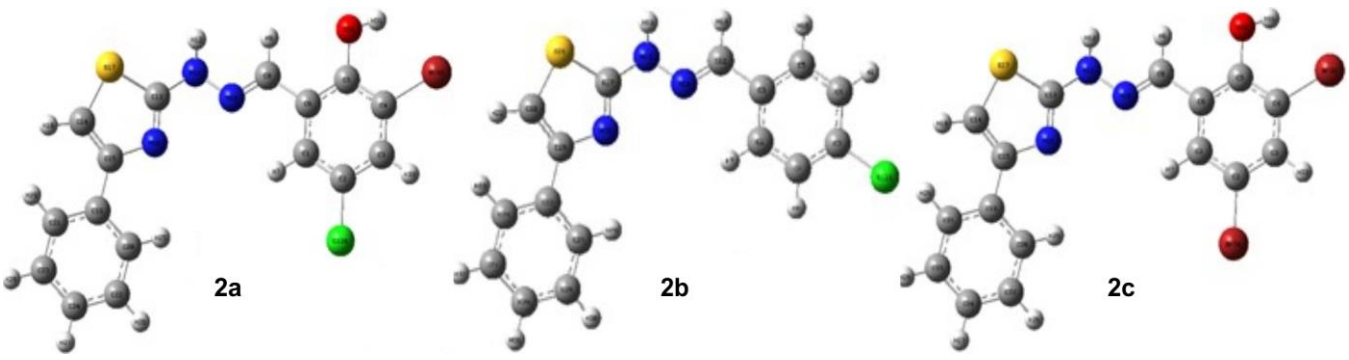


Fig. 1. Optimized structures of the synthesized derivatives **2a-c**

$$\zeta = \frac{1}{2\eta}$$

$$I = -E_{HOMO}$$

$$A = -E_{LOMO}$$

$$\mu = \frac{(E_{LUMO} + E_{HOMO})}{2}$$

$$\psi = \frac{\mu^2}{2\eta}$$

$$\chi = -\mu$$

***In silico* ADMET prediction:** *In silico* ADMET prediction is a computational method used to evaluate the essential properties of a drug molecule for its development as a drug [35]. Four phases of pharmacokinetics properties along with the toxicity can be predicted by *in silico* ADMET analysis using the QSAR method. It is a modern primary screening of a drug agent to minimize the time and money before the clinical phase. The absorption percent (% ABS) was calculated using the following formula:

$$ABS\ (\%) = 109 - (0.3459 \times TPSA)$$

RESULTS AND DISCUSSION

The synthesized phenyl-thiazole derivatives containing arylidene moieties, compounds **1a-c** and **2a-c** were characterized by spectroscopic method. Compounds **1a-c** showed sharp absorption bands at 3436-3430 cm^{-1} (N-H), 1598-1592 cm^{-1} (C=N) and 1489-1485 cm^{-1} (C=S) in IR spectra. ^1H NMR spectra revealed that aromatic protons appeared at δ ppm 8.03-7.65. Olefinic protons (H-C=N) appeared at δ 8.30-8.03. NH_2 and NH protons appeared at δ 11.52-11.44 and 8.22-8.20 respectively. IR spectra of compounds **2a-c** showed absorption bands at 3323-3321 cm^{-1} (N-H *str*.) 1624-1623 cm^{-1} for C=N and 1485-1489 cm^{-1} for C=S *str*. In ^1H NMR, aromatic protons appeared at δ 7.86-7.32, olefinic protons (H-C=N) appeared at δ 8.29-8.07 and NH protons appeared at δ 8.29-8.04. Absorption peaks around at δ 10.99-10.95 are due to phenolic O-H protons. The structures of all synthesized thiosemicarbazone and thiazole derivatives were further confirmed by ^{13}C NMR and all the characteristic absorption values are shown in compound data. Connectivity and correlations were confirmed by 2D COSY, HSQC and HMBC. The important hetero-nuclear (H^1-^{13}C) correlations in HMBC are shown in Fig. 2.

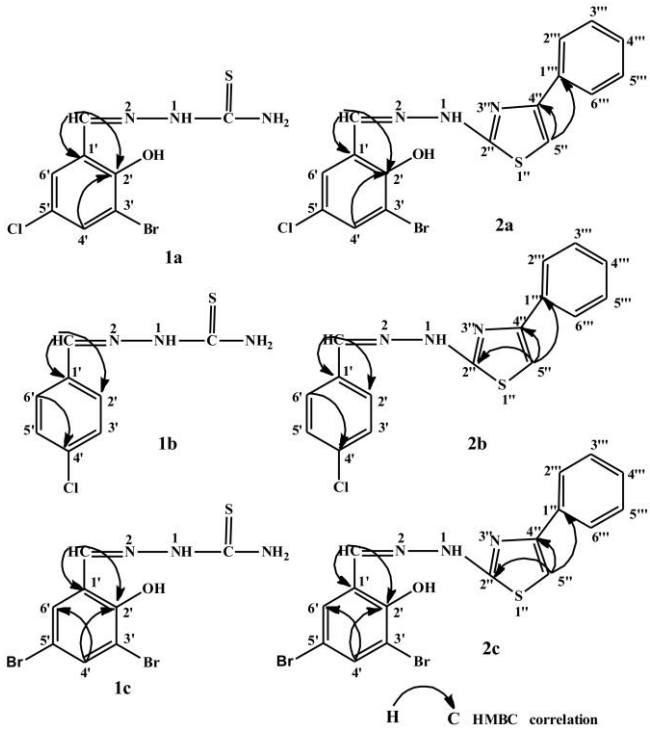


Fig. 2. Significant ^1H-^{13}C HMBC correlations of compounds (**1a-c**, **2a-c**)

Antimicrobial activity: *In vitro* antimicrobial screenings of the synthesized analogs **2a-c** were done against two Gram-positive, two Gram-negative bacterial cultures and two fungal strains with ceftriaxone and amphotericin B as standard, respectively. The agar disc diffusion method was used to analyze both screenings. The inhibition zone developed by the synthesized drugs is shown in Table-1. Compounds **2a** and **2c** showed moderate activities against bacterial strains (*E. coli*) on the other hand all three compounds **2a-c** showed excellent antifungal activities against fungal strains *T. harzianum* and *A. niger*. Out of all the analogs tested, compound **2c** exhibited the highest inhibition value of 23.0 ± 0.5 against *T. harzianum*, a fungal strain.

Antioxidant activity by DPPH method: Compounds with electron-donating groups (EDG) can easily and quickly donate electrons. So, compounds with EDGs are generally more promising antioxidants than the compounds containing electron-withdrawing groups (EWG) [35]. The IC_{50} value of the synthesized compounds was calculated by DPPH radical scavenging method and tabulated in Table-2, taking ascorbic acid as standard. A lower IC_{50} value indicates a higher potency

TABLE-1
DIAMETER OF INHIBITION ZONES (mm) OF THE SYNTHESIZED COMPOUNDS (**2a-c**)

Compound	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. aureus	*B. megnaterium*	*S. typhi*	*E. coli*	*T. harzianum*	*A. niger*
2a	–	–	–	15.0 ± 1.0	21.3 ± 1.5	17.3 ± 0.6
2b	11.0 ± 1.0	–	14.7 ± 0.6	–	–	17.0 ± 1.0
2c	–	–	–	15.0 ± 0.5	23.0 ± 0.5	–
Ceftriaxone	38.0 ± 1.0	34.0 ± 1.0	44.3 ± 0.6	40.0 ± 1.0		
Amphotericin B					17.7 ± 0.6	15.3 ± 0.6
DMSO	–	–	–	–	–	–

The individual data expressed as mean ± SD (Standard deviation) of three experiments. - Indicates no activity.

of the compounds as antioxidant drug agents. The presence of one hydroxyl group (EDG) in the *o*-position of compounds **2a** and **2c** increased their antioxidant activity. The antioxidant activity of compound **2c** was better than the standard due to the presence of the dibromo group and one hydroxyl group at the *m*-position and *o*-position of the molecule, respectively. The IC_{50} value of **2c** is 26.59 ± 3.29 µg/mL, which is a promising drug result (Table-2).

TABLE-2
ANTIOXIDANT ACTIVITY OF THE SYNTHESIZED ANALOGS **2a-c**

Compound	IC_{50} (µg/mL)
2a	33.43 ± 2.47
2b	88.24 ± 4.13
2c	26.59 ± 3.29
Ascorbic acid	27.34 ± 1.86

Molecular docking studies: All the synthesized compounds showed promising binding energy value with the three selected proteins (Table-3). When docked against 1KZN, compounds **2a-c** showed binding affinity of -7.3, -7.2 and -7.2 Kcal/mol, respectively. Against 5JBO they showed the highest binding value of -9.1, -8.4 and -9.2 Kcal/mol respectively, proving their potentiality as good antifungal same as the *in vitro* screening (Fig. 3). Lastly, compounds **2a-c** was docked against 3MNG as they have a potential IC_{50} value range closer to the standard, except **2b**. These compounds have shown good binding values of -6.7 and -6.9 Kcal/mol. Though the IC_{50} value of **2b** is not close enough to the standard value it showed a good binding value of -6.8 Kcal/mol against 3MNG protein.

Frontier molecular orbital analysis: In this experiment, compound **2c** has the lowest energy gap value and chemical hardness but the highest chemical softness. In comparison, compound **2b** containing an electron donating group (-Cl) exhibits the highest energy gap and hardness value but the lowest chemical softness. When the energy gap is low electrons can easily transit from HOMO to LUMO, which makes a compound more chemically reactive but less kinetically stable. Thus, the values signify that compound **2c** is more reactive but less stable while compound **2b** is least reactive (Table-4). Again, with FMO's analysis, potential reaction site of a compound can be identified as the HOMO and LUMO indicating the nucleophilic and electrophilic sites of a molecule, respectively.

***In silico* ADMET prediction:** Pharmacokinetics analysis of the synthesized compounds **2a-c** was observed with Lipinski's rule of five and Veber's rule. These two rules are majorly correlated with the oral bioavailability and ADME properties of a drug candidate. Lipinski's rule is all about the absorption of a drug. The ADME properties for compounds **2a-c** are summarized in Table-5. In this study, the synthesized compounds were compared with standard ceftriaxone, amphotericin B and ascorbic acid against some toxicity parameters (mutagenicity, tumorigenicity, irritancy and reproductive effects). Drug-likeness was also evaluated and compared, with the results summarized in Table-6, indicating low mutagenic and irritant effects but high tumorigenicity for all synthesized compounds

Conclusion

In this study, three new thiazole derivatives were synthesized compoun ds (**2a-c**) and characterized by IR, ^{1}H NMR,

TABLE-3
BINDING AFFINITY VALUE AND NON-BONDING INTERACTION INFORMATION OF COMPOUNDS **2a-c** AGAINST 1KZN, 5JBO AND 3MNG PROTEINS

Target protein	Compound	Binding affinity (Kcal/mol)	Residue in contact	Interaction type	Bond distance (Å)
1KZN	**2a**	-7.3	GLU50	Attractive charge	3.31
			GLU50	Attractive charge	3.04
			GLU50	Carbon hydrogen bond	2.91
			ASN46	Conventional hydrogen bond	2.92
			ASN46	Pi-Donor hydrogen bond	3.21
			ILE78	Pi-Alkyl	4.76
			ALA47	Pi-Alkyl	4.93
	2b	-7.2	GLU50	Salt bridge; Attractive charge	2.89
			ASN46	Conventional hydrogen bond	2.49
			ASN46	Conventional hydrogen bond	2.56
			ASN46, ALA47	Amide-Pi stacked	4.42
			GLU42	Pi-Anion	4.01
			ASP49	Pi-Anion	3.52
			ILE78	Pi-Sigma	3.91
			VAL43	Alkyl	5.16
			VAL120	Alkyl	4.83
			VAL167	Alkyl	4.51
	2c	-7.2	ASP49	Attractive charge	5.58
			THR165	Pi-Sigma	3.97
			ILE90	Alkyl	4.81
			ILE90	Pi-Alkyl	5.29
			ILE78	Pi-Alkyl	4.75
			ALA47	Pi-Alkyl	5.01

5JBO	**2a**	-9.1	GLU441	Salt bridge; Attractive charge	2.30
			GLU441	Attractive charge	3.71
			ASP444	Attractive charge	3.59
			ASP444	Attractive charge	4.29
			GLU172	Pi-Anion	4.02
			TRP357	Pi-Pi stacked	4.09
			TRP357	Pi-Pi stacked	4.33
			TRP357	Pi-Pi stacked	4.16
			TRP357	Pi-Pi stacked	4.83
			TRP126	Pi-Pi T-shaped	5.55
			TYR179	Pi-Pi T-shaped	5.64
			TYR316	Pi-Alkyl	5.24
			TRP434	Pi-Alkyl	3.58
			TRP434	Pi-Alkyl	4.10
	2b	-8.4	GLU172	Attractive charge	3.37
			GLU384	Attractive charge	5.58
			GLU441	Attractive charge	4.63
			GLU441	Carbon hydrogen bond	2.91
			ASN241	Pi-Donor hydrogen bond	2.99
			TRP357	Pi-Pi stacked	4.45
			TRP357	Pi-Pi stacked	4.26
			TRP357	Pi-Pi stacked	4.59
			TYR179	Pi-Alkyl	4.78
			ILE175	Pi-Alkyl	5.38
	2c	-9.2	GLU441	Salt bridge; Attractive charge	2.54
			GLU441	Attractive charge	3.92
			ASP444	Salt bridge; Attractive charge	3.12
			ASP444	Attractive charge	4.13
			GLU172	Pi-Anion	3.96
			TRP357	Pi-Pi stacked	4.14
			TRP357	Pi-Pi stacked	4.29
			TRP357	Pi-Pi stacked	4.07
			TRP357	Pi-Pi stacked	4.95
			TRP126	Pi-Pi T-shaped	5.39
			TYR179	Pi-Pi T-shaped	5.59
			TRP434	Pi-Alkyl	3.84
			TRP434	Pi-Alkyl	4.17
3MNG	**2a**	-6.7	ALA42	Conventional hydrogen bond	2.46
			ALA42	Conventional hydrogen bond	2.48
			ALA42	Conventional hydrogen bond	2.43
			THR44	Pi-Sigma	2.87
			PHE43	Pi-Pi stacked	3.76
			ILE119	Alkyl	3.67
			PRO45	Alkyl	4.70
			PHE120	Pi-Alkyl	4.99
			VAL80	Pi-Alkyl	4.19
			VAL80	Pi-Alkyl	5.25
	2b	-6.8	VAL94	Conventional hydrogen bond	1.94
			ARG86	Pi-Cation	4.54
			GLU16	Pi-Anion	4.06
			ARG95	Pi-Alkyl	4.89
			LEU96	Pi-Alkyl	5.17
	2c	-6.9	ALA90	Conventional hydrogen bond	2.53
			ALA90	Pi-Alkyl	5.02
			VAL94	Conventional hydrogen bond	1.87
			GLU16	Pi-Anion	4.35
			GLY92	Pi-Donor hydrogen bond	2.68
			GLU91	Pi-Sigma	3.92
			ARG95	Pi-Sigma	3.93
			ARG95	Pi-Alkyl	4.78
			VAL69	Alkyl	3.99
			ARG86	Pi-Alkyl	5.49
			LEU96	Pi-Alkyl	5.03

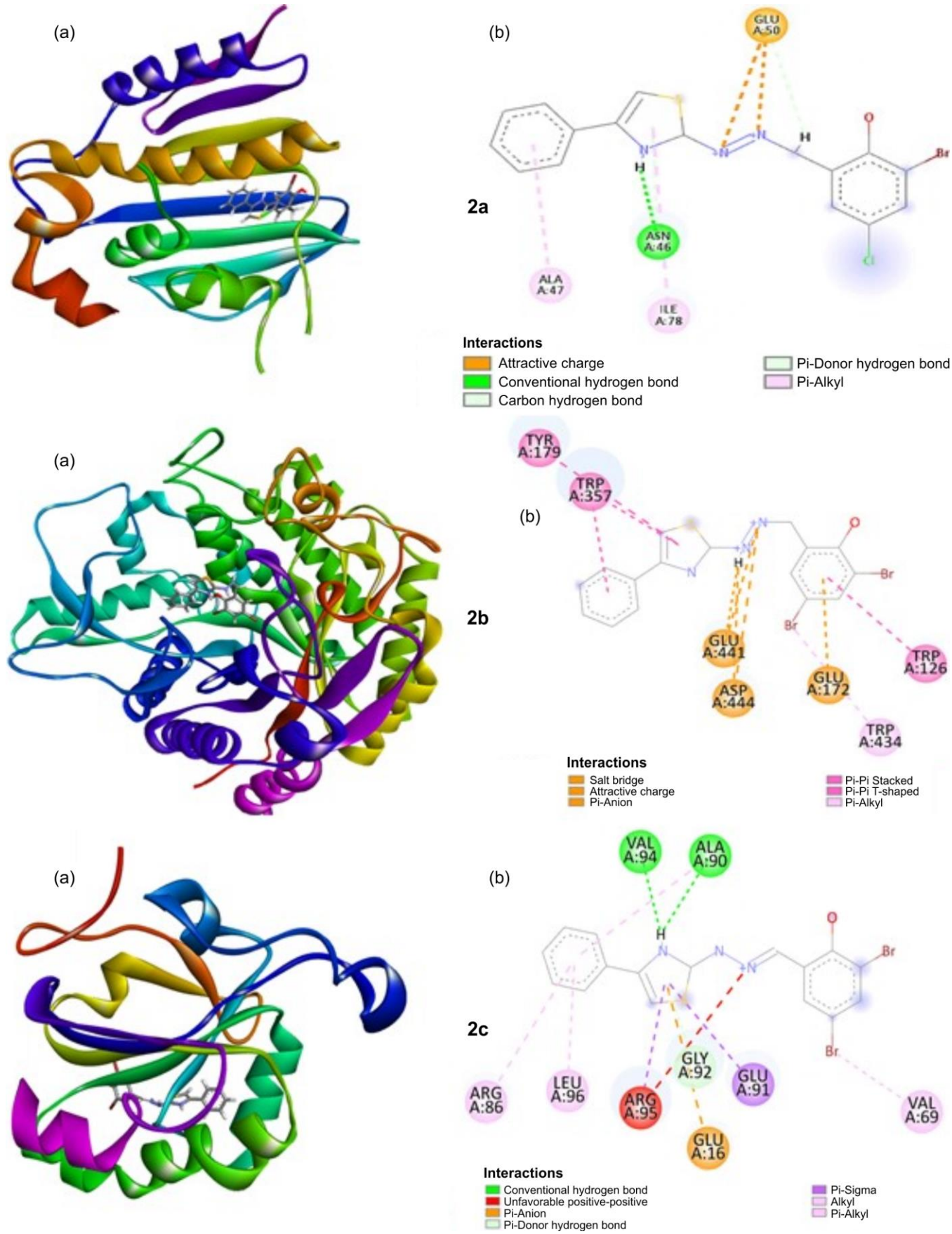


Fig. 3. Molecular docking studies of compound **2a** against (a) 1KZN and **2c** against (b) 5JBO and (c) 3MNG protein receptors, respectively. (a) 3D conformer and (b) 2D docking predictions

TABLE-4
HOMO-LUMO ENERGY GAP AND GLOBAL REACTIVITY DESCRIPTORS OF COMPOUNDS **2a-c**

Chemical reactivity indices (eV)	**2a**	**2b**	**2c**
E_{HOMO}	-5.68	-5.67	-5.61
E_{LUMO}	-2.09	-1.92	-2.08
Energy gap (ΔE)	3.59	3.75	3.53
Hardness (η)	1.79	1.88	1.77
Softness (ζ)	0.27	0.26	0.28
Ionization potential (I)	5.68	5.67	5.61
Electron affinity (A)	2.09	1.92	2.08
Chemical potential (μ)	-3.89	-3.79	-3.85
Electrophilicity (ψ)	4.23	3.82	4.19
Electronegativity (χ)	3.89	3.79	3.85

^{13}C NMR, COSY, HSQC and HMBC spectral analysis. All the compounds were also tested antibacterial, antifungal and antioxidant activities. In antimicrobial studies, compounds **2b** and **2c** showed moderate activities against *E. coli*, but **2b** showed potential antifungal activities against *T. harzianum* and *A. niger* with inhibition values of 21.3 ± 1.5 and 17.3 ± 0.6, respectively. Compound **2c** exhibited the highest inhibition value of 23.0 ± 0.5 against *T. Harzianum*. In antioxidant studies, the IC_{50} value of **2a** was observed 26.59 ± 3.29 μg/mL, which exceeded the standard. When the synthesized compounds **2a-c** were docked against 1KZN and 5JBO, all the compounds showed high binding energy -7.3, -7.2 and -7.2 Kcal/mol and -9.1, -8.4 and -9.2 Kcal/mol, respectively clearly outlined of their potentiality as good antifungal same as the *in vitro* screening. *In silico* Frontier molecular orbital (FMO) analysis also showed that compound **2c** is more reactive but less stable while compound **2b** is least reactive.

ACKNOWLEDGEMENTS

The authors are thankful to the Ministry of Science and Technology, Peoples Republic of Bangladesh for providing the financial assistance to accomplish this research work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-5
PREDICTED PHARMACOKINETIC PROPERTIES OF COMPOUNDS **2a-c**

Compound	Lipinski's violations (≤ 1)	Lipinski's rule				Veber's rule		logS[g]	%ABS[h]
		MW[a] (≤ 500)	HBA[b] (≤ 10)	HBD[c] (≤ 5)	clogP[d] (≤ 5)	NROTB[e] (≤ 10)	TPSA[f] (140 Å^2)		
2a	0	407.0	3	2	7.2	4	85.75	-5.93	79.34
2b	0	313.0	2	1	6.82	4	65.52	-5.4	86.34
2c	0	451.0	3	2	7.32	4	85.75	-6.03	79.34
Ceftriaxone	2	554.0	14	4	-2.95	8	287.3	-2.95	9.62
Amphotericin B	3	924.0	17	12	0.32	3	319.6	–5.08	-1.55
Ascorbic acid	0	176.12	6	4	-1.40	2	107.22	-0.55	72.00

[a]Molecular weight, [b]Number of hydrogen bond acceptors, [c]Number of hydrogen bond donor, [d]Lipophilicity, [e]Number of rotatable bonds, [f]Topological polar surface area, [g]Solubility parameter, [h]Percentage of absorption

TABLE-6
In silico TOXICITY EFFECTS AND DRUG-LIKENESS VALUES OF SYNTHESIZED ANALOGS **2a-c**

Compound	Toxicity effects				Drug-likeness	Drug score
	Mutagenic	Tumorigenic	Irritant	Reproductive		
2a	Low	High	Low	Low	2.10	0.18
2b	Low	High	Low	Low	4.93	0.23
2c	Low	High	Low	High	2.51	0.10
Ceftriaxone	Low	Low	Low	Low	16.69	0.63
Amphotericin B	Low	Low	Low	Low	-0.14	0.18
Ascorbic acid	High	High	Low	High	0.02	0.16

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