ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2024, Vol. 40, No.(5):
Pg. 1297-1305

Synthesis, Bioactivity Screening and Docking Analysis of Thiazole Derivatives Containing Quinoline Moieties

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http://dx.doi.org/10.13005/ojc/400511

(Received: July 13, 2024; Accepted: September 02, 2024)

ABSTRACT

A new series of quinoline-thiazole compounds **(1b-3b)** were synthesized by two step reaction where thiosemicarbazone derivatives **(1a-3a)** were obtained from quinolinecarbaldehyde and thiosemicarbazide. The final products **(1b-3b)** were synthesized from thiosemicarbazone and 3-chloroacetylacetone. Characterizations of all synthesized compounds **(1a-3a, 1b-3b)** were performed by IR, Proton and Carbon-13 NMR spectroscopic methods. *In vitro* antimicrobial studies of thiazole derivatives **(1b-3b)** were screened by agar disc diffusion method. Compounds **1b** and **3b** revealed significant antibacterial effects against *B. cereus, K. pneumonia, S. aureus* and **2b** revealed potential antibacterial effects against *S. aureus, K. pneumonia* with standard. Compounds **1b, 2b** and **3b** showed significant antifungal activities against the fungi *A. niger* with standard amphotericin B. *In silico* molecular docking studies performed by DFT method revealed that compound **1b** and **3b** showed good binding score against 2BTF protein taken from protein data bank.

Keywords: Thiazole Derivatives, Bioactivity, Molecular docking.

INTRODUCTION

Due to expansive and repeated uses of antibiotics, drug-resistant and multidrug resistant viral and bacterial infections are increasing in alarming rate that have brought out difficult to treat using previous antibiotic and take much time to cure[1]. Multidrug resistant grown up by accumulating multiple genes in bacteria and virus cell that code resistance to the drug or increasing the expression of genes coding for multidrug efflux[2]. This multidrug resistance caused by bacteria and virus accumulated genes drives the researchers to improve new and potential antibiotic agents to specific target. The synthesis of thiazole derivatives containing quinoline moieties is an attractive field in synthetic organic chemistry and therapeutic science. Thiazole moiety in natural products are found in vitamin B1 (thiamin), erythrazole B, firefly luciferin, marine natural products and other various compounds[3-5]. Thiazole and its derivatives exhibit wide range and important bioactivities i.e. antioxidant, antibacterial, anticancer, antifungal, anti-HIV, anti-inflammatory effects[6-8]. Having pharmacologically active properties most

uses drugs contain thiazole moiety, for examples Sulfathiazol as antimicrobial drug[9], Nitazoxanide as Antiparasitic Agent[10], Ravuconazole as Anti-fungal[11], Thiamethoxam as Insecticide[12], Ritonavir as Anti-HIV[13], Meloxicam as Antiinflammatory[14] etc.

Another novel compounds, quinoline alkaloids extracted from natural products show observable and distinctive biological activities and due to its simple structure and their significant properties, researchers have great interest to extract or synthesize quinoline and its derivatives[15]. Quinoline alkaloids are observed and derived from many organism i.e. animals and plants[16-17] those have numerous pharmacological and biological activities such as antibacterial effects against bacterial infections, antifungal effects against fungal infections, antitumor, anti-inflammatory, antioxidant, antiviral activities[18].

The combination of two or more bioactive molecules i.e. thiazole and quinoline moiety in a molecular scaffold shows good antimicrobial activity[19]. Moreover, in the research, has been found that thiazole and quinoline moieties have minimum cytotoxicity to hepatocyte cells[20].

Considering above biological significance as core structure of several drugs, a new series of thiazole derivatives containing quinoline moieties were synthesized and characterized. All synthesized quinoline thiazole derivatives were evaluated antibacterial and antifungal effects using agar disc diffusion method[21]. In these experiments, three *Gram-positive* bacteria called *B. cereus, S. aureus* and *B. magaterium*, three *Gram-negative* bacteria called *K. pneumonia, E. coli* and *P. aeruginosa*, two fungal strains called *T. harzianum* and *A. niger* were used.

MATERIALS AND METHODS

Chemicals (Reagents)

All required chemicals to prepare thiazole derivatives containing quinoline moieties were purchased from the Merck and Sigma aldrich and used without purification.

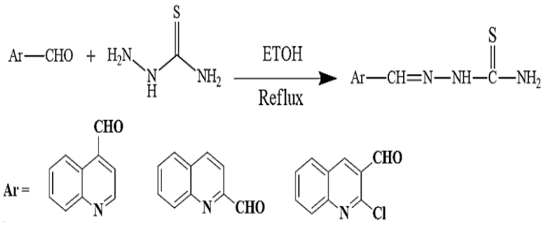
EXPERIMENTAL

Melting points of quinoline-thiazole derivatives were recorded in melting points apparatus of Fisher John (Model no. 1A 9000) and uncorrected. Infrared spectrum was measured in KBr disk on Shimadzu FTIR spectrophotometer (Model FTIR- IR Affinity-1) and printed in cm^{-1}. ^{1}H-NMR, ^{13}C-NMR, DEPT-135, COSY, HSQC and HMBC of the samples were performed by Bruker Advance-III HD spectrometer operated at 400 MHz and 100 MHz at Wazed Miah Scientific Research Centre, University of Jahangirnagar, Dhaka, Bangladesh. Chemical shifts (δ) were recorded in ppm relative to TMS and J in Hz unit. Spin multiplicities were expressed as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q) and multiplet (m).

Synthesis of Thiosemicarbazone

Synthesis of compounds (1a–3a)

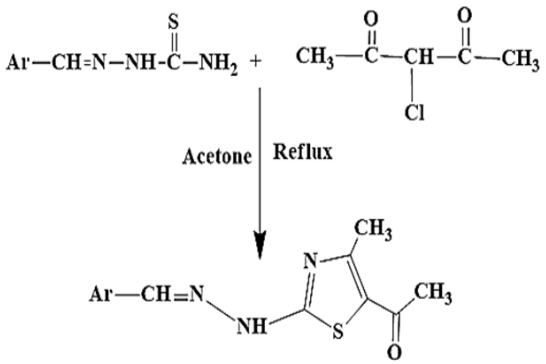
The thiosemicarbazide (3 mmol) and quinoline-carbaldehyde (3 mmol) were taken in a two neck flask with ethanol solvent and refluxed with stirring for eight hours at 78-80°C to obtain the thiosemicarbazone precipitate. Then it was kept in an ice-bath to cool down followed by filtration. The products were dried and weighed (Scheme 1).



Scheme 1. Procedure for thiosemicabazone synthesis

Synthesis of compounds (1b-3b)

3-chloroacetyleacetone (3 mmol) and thiosemicarbazone (3 mmol) were taken in a two neck flask with ethanol solvent and kept by stirring for 24 h followed by refluxing for three hours at 58-60°C. Then it was cooled down and precipitate was separated by filtration followed by dried and weighed (Scheme 2).



Scheme 2. Procedure for thiazole derivatives synthesis

RESULT AND DISCUSSION

Optimization of Reaction

Thiazole derivatives containing quinoline moieties were synthesized by two step reactions. In step-1 thiosemicarbazone derivatives were synthesized from quinoline-carbaldehyde and thiosemicarbazide in ethanol by refluxing for eight hours (Scheme 1). Then, the final products thiazole derivatives **(1b-3b)** were obtained from thiosemicarbazone derivatives and 3-chloroacetyleacetone by refluxing for three hours in acetone (Scheme 2). Characterizations of all synthesized compounds **(1a-3a, 1b-3b)** were performed by Infrared (IR), Proton (^{1}H) NMR, Carbon-13 (^{13}C) NMR, DEPT, COSY, HSQC and HMBC spectroscopic methods. Data obtained from the Scheme 1 and Scheme 2 reactions are given in the following Table 1.

Table 1: Compounds with yield(%) and time (hour)

Compounds	Colors	Texture	Time (h)	Yield(%)
1a	Yellow	Cotton like solid	6	76%
2a	Yellow	Powder	5	70%
3a	Yellow	Powder	6	69%
1b	Reddish orange	Crystal	4	68%
2b	Reddish orange	Crystal	5	71%
3b	Brown	Powder	7	69%

Characterizations of compounds

Compounds (1a–3a) showed sharp absorptions at λ_{max} cm^{-1}: 3439-3392 (N-H stretching) and 1610-1602 (N-H bending) in IR spectra. Absorption bands at λ_{max} 1278-1257, 1620-1615, 1610-1508 defined the presence of aromatic C=C, HC=N and C=S bonds respectively.

^{1}H NMR spectra revealed that aromatic protons are present at δppm 8.94-7.61. Olifinic protons (H-C=N) appeared at δ 8.88-8.24. NH_2 and NH protons appeared at δ 8.84-8.32 and 11.81-11.70 respectively. IR spectra of compounds (1b–3b) showed absorption bands at λ_{max} 1635-1616 for N-H bending and 3440-3385 for N-H stretching and bands at λ_{max} 1690-1685 for C=O carbonyl functions. In ^{1}H NMR, aromatic protons appeared at δ 9.04-7.20, olifinic protons (H-C=N) appeared at δ 8.92-8.35 and NH protons appeared at δ 12.16-11.85. Absorption peaks around at δ 2.55-2.50 due to $COCH_3$ and singlet around at δ2.46-2.42 for the methyl protons attached to carbon C4". The structures of all synthesized thiosemicarbazone and thiazole derivatives compounds were further confirmed by ^{13}C NMR and all the characteristic absorption values are shown in experimental data. Connectivity and correlations were confirmed by 2D COSY, HSQC and HMBC. The important correlations homo-nuclear (H-H) and hetero-nuclear (H-C) in HMBC are shown in Figure 1.

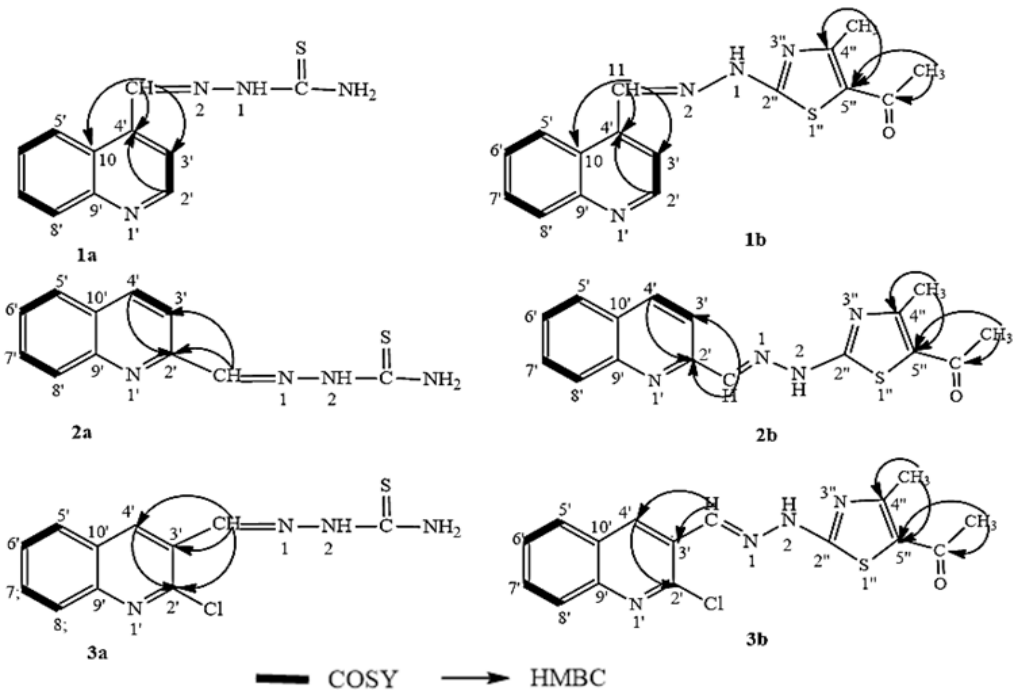
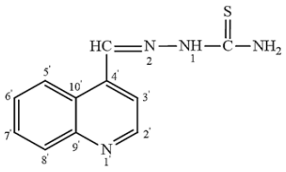


Fig. 1. COSY and HMBC of all synthesized compounds

Compound 1a

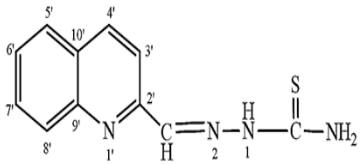
Mol. Formula: $C_{11}H_{10}N_4S_1$



Melting point :	260-263^{O}C
^{1}H NMR (DMSO) δ ppm:	8.94 (1H, d, H2'), 8.19 (1H, d, H3'), 8.09 (1H, d, H5'),7.72 (1H, t, H6'), 7.82 (1H, t, H7'), 8.31 (1H, d, H8'), 8.88 (1H, s, H11), 11.70 (1H, s, H-N) and 8.48 (2H, s, H_2-N)
^{13}C NMR (DMSO) δ ppm:	150.5(2'), 118.3(3'), 125.4(4'), 130.2(5'), 127.8(6'), 130.0(7'), 123.4(8'), 148.7(9'), 137.7(10'), 138.2 (CH=N), 178.9(C=S).
IR (KBr) λ_{max} cm^{-1}:	1610, 3439

Compound 2a

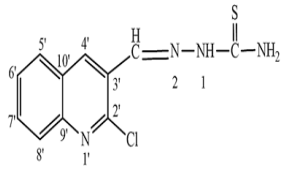
Mol. Formula : $C_{11}H_{10}N_4S_1$



Melting point :	217-220^{O}C
^{1}H NMR (DMSO) δppm:	8.44 (1H, d, H3'), 8.35 (1H, d, H4'), 8.00 (1H, d, H5'), 7.61 (1H, t, H6'), 7.77 (1H, t, H7'), 7.99 (1H, t, H8'), 8.24 (1H, s, CH=N), 11.79 (1H, s, H-N) and 8.32 (2H, s, H2-N)
^{13}C NMR (DMSO) δppm:	154.3(2'), 118.5(3'), 136.7(4'), 129.2(5'), 127.6(6'), 130.3(7'), 128.3(8'), 147.7(9'), 128.2(10'), 143.0(CH=N), 178.9(C=S).
IR (KBr) λ_{max} cm^{-1}:	1605, 3394

Compound 3a

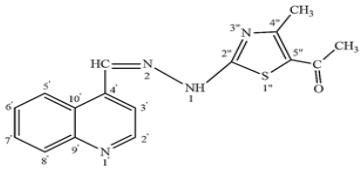
Mol. Formula : $C_{11}H_9Cl_1N_4S_1$



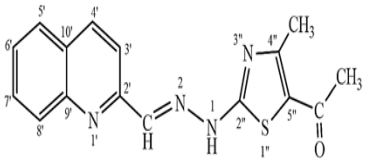
Melting point :	209-212^{O}C
^{1}H NMR (DMSO) δppm:	8.51 (1H, s, H4'), 7.94 (1H, d, H5'), 7.70 (1H, t, H6'), 7.84 (1H, t, H7'), 7.99 (1H, d, H8'), 8.27 (1H, s, CH=N), 11.81 (1H, s, H-N) and 8.47 (2H, s, H_2-N)
^{13}C NMR (DMSO) δppm:	148.8(2'), 126.6(3'), 137.2(4'), 128.3(5'), 128.2(6'), 132.0(7'), 128.9(8'), 147.3(9'), 127.4(10'), 136.5(CH=N), 178.8(C=S).
IR (KBr) λ_{max} cm^{-1}:	1602, 3392, 3261

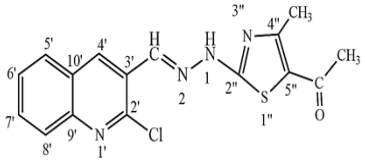
Compound 1b

Mol. Formula : $C_{16}H_{14}N_4O1S_1$



Melting point :	275-278^{o}C
^{1}H NMR (DMSO) δppm:	9.04 (1H, d, H2'), 8.42 (1H, d, H3'), 8.16 (1H, d, H5'), 7.85 (1H, t, H6'), 7.96 (1H, t, H7'), 8.36 (1H, d, H8'), 8.92 (1H, s, CH=N), 11.85 (1H, s, H-N), 2.55 (3H, s, CO-CH_3) and 2.46 (3H, s, CH_3)
^{13}C NMR (DMSO) δppm:	148.3(2'), 118.1(3'), 125.6(4'), 127.4(5'), 128.7(6'), 131.7(7'), 123.8(8'), 148.3(9'), 136.9(10'), 137.0(CH=N), 179.0(2''), 128.8(4''), 168.1(5''), 189.7(C=O), 29.9(CO-CH_3), 19.5(CH_3)
IR (KBr) λ_{max} cm^{-1}:	1627, 3430.

Compound 2b	
Mol. Formula : $C_{16}H_{14}N_4O_1S_1$	
Melting point :	222-225ºC
^{1}H NMR (DMSO) δppm:	8.14 (1H, d, H3'), 7.92 (1H, d, H4'), 8.18 (1H, d, H5'), 7.74 (1H, t, H6'), 7.92 (1H, t, H7'), 8.18 (1H, d, H8'), 8.86 (1H, s, CH=N), 12.16 (1H, s, H-N), 2.53 (3H, s, CO-CH_3) and 2.45 (3H, s, CH_3)
^{13}C NMR (DMSO) δppm:	152.0(2'), 118.0(3'), 132.5(4'), 128.9(5'), 128.6(6'), 132.3(7'), 128.9(8'), 140.5(9'), 128.3(10'), 141.7(CH=N), 169.8(2''), 128.2(4''), 168.3(5''), 189.7(C=O), 29.9(CO-CH_3), 18.1(CH_3)
IR (KBr) λ_{max} cm^{-1}:	1635, 3445, 3285.

Compound 3b	
Mol. Formula : $C_{16}H_{13}Cl_1N_4O_1S_1$	
Melting point :	232-235^{O}C
^{1}H NMR (DMSO) δppm:	8.50 (1H, s, H4'), 7.84 (1H, d, H5'), 7.20 (1H, t, H6'), 7.32 (1H, t, H7'), 7.52 (1H, d, H8'), 8.35 (1H, s, CH=N), 12.06 (1H, s, H-N), 2.50 (3H, s, CO-CH_3) and 2.42 (3H, s, CH_3)
^{13}C NMR (DMSO) δppm:	147.5(2'), 125.6(3'), 136.1(4'), 128.1(5'), 128.0(6'), 131.3(7'), 127.8(8'), 146.9(9'), 127.7(10'), 136.3(CH=N), 178.2(2''), 127.6(4''), 168.5(5''), 189.1(C=O), 29.3(CO-CH_3), 19.3(CH_3)
IR (KBr) λ_{max} cm^{-1}:	1616, 3439.

Biological activity

Preparation of Media

In vitro antimicrobial effects of all the synthesized thiazole derivatives were tested by Agar disc diffusion method[21]. Potato Dextrose and Mueller Hinton Agar (PDA & MHA) (HIMEDIA, India) media were taken as basal media for antimicrobial screening of experimental bacterial and fungal strains. In this method, the incubations of PDA and MHA were done for twenty four hours and then the contaminations were observed. After incubation, the bacterial and fungal strains were inoculated on media with sterile cotton bar. Then, the sample disc was put very carefully on agar medium that was pre-inoculated. The agar plates were aerobically incubated for twenty four hours at 37°C for antibacterial and for forty eight hours at 26°C for antifungal screening. The media were controlled by adding Dimethyl sulfoxide (DMSO). 25 µL of sample solution in DMSO were added each disc that contain 300 µg of thiazole derivatives. 25 µL of Ciprofloxacin and iconazole solution in DMSO was added on per disc as positive control of antibacterial and antifungal screening respectively. Finally, after 24 h incubation, the inhibition zone's diameter was measured by circling the disc.

Antibacterial activities assay

Antibacterial screening of these newly synthesized thiazole compounds were observed exhibiting different activities against the selected bacteria. All the compounds were observed remarkable antibacterial activities with *K. pneumonia, B. cereus, S. aureus* and *E. coli* bacterial strains. Moreover, **1b** revealed promising antibacterial effects against *B. Cereus, K. pneumonia E. coli* and *S. aureus*. **2b** revealed significant activities against *K. pneumonia* and *S. aureus* and **3b** revealed potential antibacterial effects against *S. aureus* and *E. coli* with standard Ampicillin In the antibacterial study, the DMSO as control and ampicillin as standard have been studied for the comparison. The inhibition zones by different compounds are shown in the Table 2. The results are also shown by graphical representation in Figure 2.

Table 2: Results of antibacterial studies of the compounds 1b, 2b and 3b

Test Samples	Zone of inhibitions in millimeter							
	Gram-positive bacteria			*Gram-negative* bacteria				
	Bacillus cereus	*Staphylococcus aureus*	*Bacillus magaterium*	*Klebsiella pneumonia*	*Pseudomonas aeruginosa*	*Escherichia coli*		
1b	20	21	8	22	9	20		
2b	16	24	0	24	7	22		
3b	18	23	7	21	0	24		
DMSO	0	0	0	0	0	0		
Ampicillin	32	29	32	34	29	28		

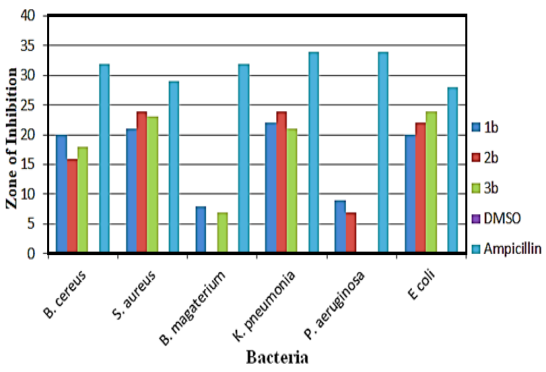


Fig. 2. Graphical representation of antibacterial activities of compounds 1b, 2b and 3b

Antifungal activities

The antifungal activities of newly prepared thiazole derivatives were observed inhibiting mycelial growth of experimental fungal strains. All the samples exhibited significant antifungal activities against the fungi *A. niger*. Moreover, compound **2b** also showed moderate antifungal activity against the fungi *T. harzianum*. Solvent DMSO and amphotericin B as standard have also been studies for the comparison. The inhibitions of mycelial growth by different test samples are shown in the Table 3 and also shown by a graphical representation in Figure 3.

Table 3: Antifungal activities of the compounds 1b, 2b and 3b

Test Samples	%Inhibition of mycelialgrowth	
	Aspergillus niger	*Trichoderma harzianum*
1b	20	0
2b	16	15
3b	18	0
DMSO	0	0
Amphotericin B	23	24

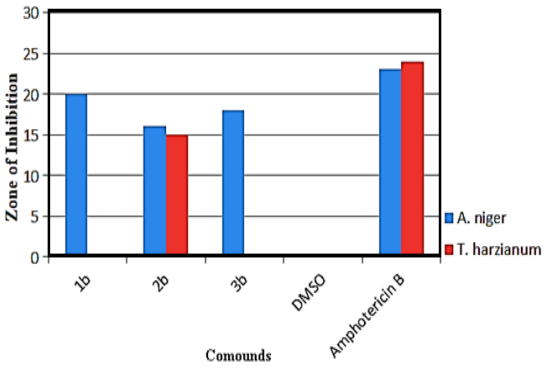


Fig. 3. Graphical representation of antifungal activities of compounds 1b, 2b and 3b

Molecular docking studies

In silico docking studies were conducted to support the design of synthesized compounds and invention of new drug molecule for the effective inhibition of target protein of disease development. Docking studies of thiazole analogs were carried out by software package i.e. Gaussian 09, PyRx 0.8, and Pymol. Using Gaussian 09 version, structure optimizations of the synthesized thiazole analogs were performed on the basis of B3LYP/6-31G (+, d, p) in the DFT method. Further, analyzing the docking results and calculating nonbonding interaction, Biovia Discovery Studio 4.1 was used. When docked against 2BTF, compound **1b** and **3b** showed binding score of -7.6 Kcal/mole and -7.9 Kcal/mole respectively. Interaction types and docking results are showed Figure 5 and Figure 6.

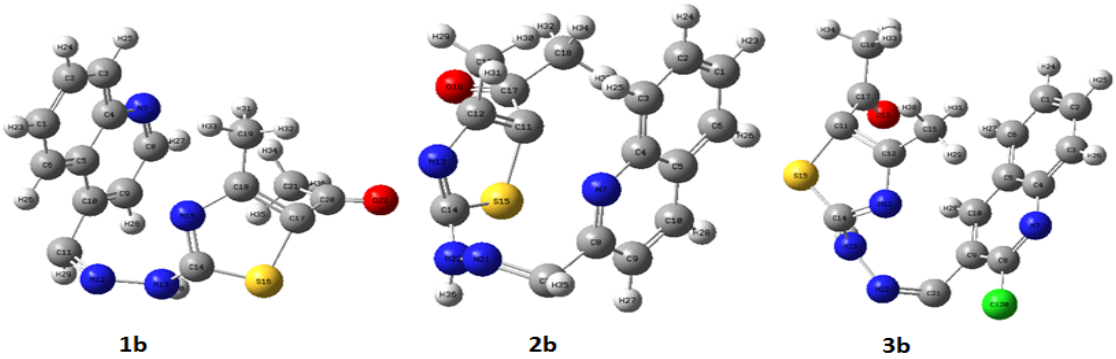


Fig. 4. Structures optimization of compounds 1b-3b

Table 4: Docking score and interaction type of compound 1b

Sample	Binding affinity (kcal/mol)	Residue in contact	Interaction types	Bond distance (Å)
1b	-7.6	ASP157	AC	5.27822
		GLU214	AC	4.83023
		ASP157	AC	4.40079
		GLU214	AC	4.44543
		GLY156	CHB	2.14822
		GLY302	CHB	2.78748
		MET305	Pi- A	4.71525

AC = Attractive charge, CHB = Conventional hydrogen bond, Pi-A = Pi- Alkyl

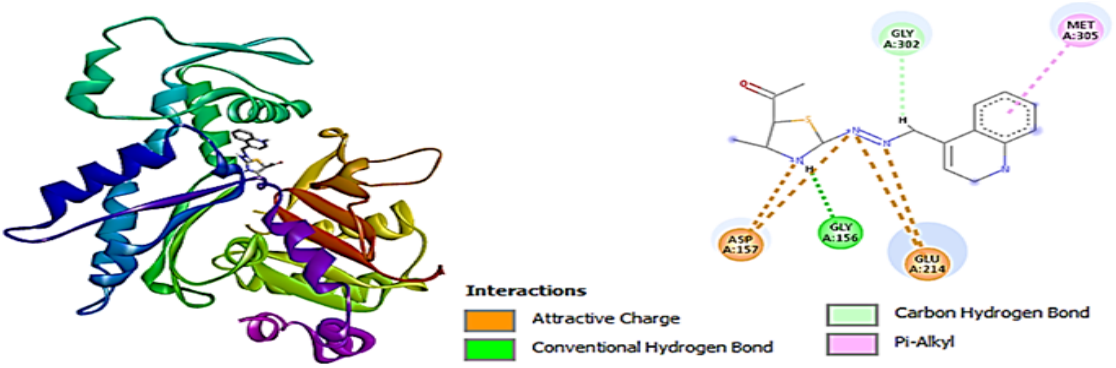


Fig. 5. Molecular docking studies of 1b against receptor 2BTF. (a) 3D docking predictions. (b) 2D interaction sketches

Table 5: Docking score and interaction type of compound 3b

Sample	Binding affinity (kcal/mol)	Residue in contact	Interaction types	Bond distance (Å)
3b	-7.9	PHE375	Salt Bridge AC	2.92903
		PHE375	AC	5.57027
		TYR133	CHB	2.16462
		LYS373	CHB	2.53984
		MET355	CH bond	2.59947
		LYS373	CH bond	2.88734
		ALA135	Pi-A	4.9566
		VAL139	Pi-A	4.70596
		LEU140	Pi-A	5.41948
		LEU346	Pi-A	4.14628

AC = Attractive charge, CH bond = Carbon Hydrogen bond, CHB = Conventional hydrogen bond, Pi-A = Pi- Alkyl

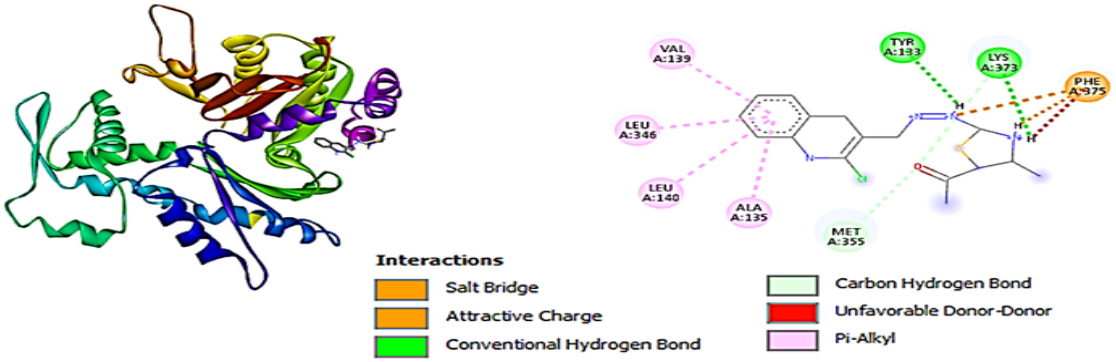


Fig. 6. Molecular docking studies of 3b against receptor 2BTF. (a) 3D docking predictions. (b) 2D interaction sketches

In silico ADMET Prediction

Pharmacokinetic properties of synthesized thiazole compounds were studied by *In silico* ADMET Prediction method. Absorption, distribution, metabolism and excretion are the four steps of pharmacokinetic properties. Toxicity studies are also performed as a part of pharmacokinetic properties where acronym stands ADMET prediction[22].

The ADMET predictions of synthesized thiazole compounds were determined by ADMET online tool (www.swissadme.ch). The determined molecular properties and pharmacokinetic properties are summarized in Table 6 and Table 7.

Table 6: Molecular properties of synthesized thiazole derivatives

Name	Molecular Weight	LogP	Rotatable H-Bonds	H-Bonds Acceptors	H-Bonds Donors	Surface Area
1b	310.382	3.64832	4	6	1	131.286
2b	310.382	3.64832	4	6	1	131.286
3b	344.827	4.30172	4	6	1	141.590
Ampicillin	349.412	0.3181	4	5	3	143.121

Table 7: Pharmacokinetic Properties: ADMET Prediction

Name	Water Solubility (log mol/L)	HIA (%Absorbed)	P-GI I inhibitor	BBB (log BB)	CNS (log PS)	hERG I inhibitor	hERG II inhibitor	ORAT (LD_{50}) (mol/kg)
1b	-4.038	93.099	No	0.168	-2.078	No	Yes	2.407
2b	-3.974	92.875	No	0.295	-2.112	No	Yes	2.417
3b	- 5.018	91.204	Yes	0.202	-1.949	No	Yes	2.358
Ampicillin	-2.396	43.034	No	-0.767	-3.166	No	No	1.637

HIA = Human intestinal absorption, BBB = Blood brain barrier, ORAT = oral Rat acute toxicity, CNS = Central nerve system, P-GI = P-glycoprotein inhibitor, hERG = human Ether-a-go-go Related Gene

CONCLUSION

Schiff base derivatives and their complexes are the most significant and valuable compounds which have many useful applications because of their chemical versatility. Most of the Schiff base thiazole compounds were used as active medicinal agents. As a consequence, the study focused on the synthesis and characterization of new thiosemicarbazones, thiazole derivatives containing quinolone moieties and screening their antibacterial and antifungal activities. First step syntheses compounds **1a**, **2a** and **3a**; thiosemicarbazone derivatives and second step syntheses **1b**, **2b** and **3b** thiazole derivatives compounds were characterized by Infrared, Proton-NMR, Carbon-13 NMR, DEPT, COSY, HSQC and HMBC spectroscopy. It was visualized that compounds **1b** and **3b** significantly exhibited antibacterial and antifungal activities. In the docking studies, compounds **1b** and **3**b showed binding score of -7.6 Kcal/mole and -7.9 Kcal/mole respectively.

ACKNOWLEDGEMENT

The authors are highly thanked to the

Ministry of Science and Technology, Peoples Republic of Bangladesh for providing financial assistance to accomplish this research work.

Conflict of interest

There is no conflict of interest among the authors.

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