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Preparation, Structure Elucidation, HAS Interaction and Molecular Docking Investigations of Benzothiazole Derived Schiff Base Ligands

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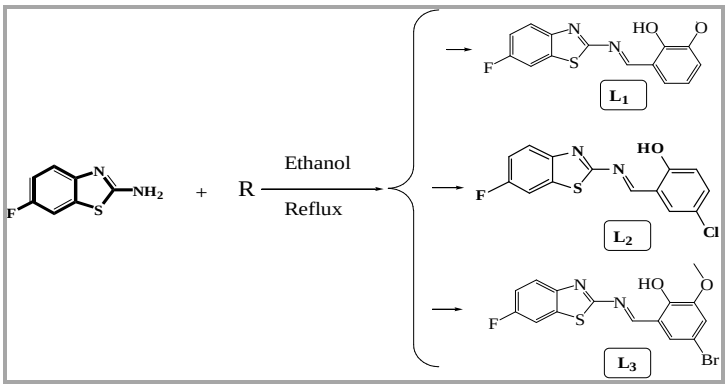
ABSTRACT

Herein we report the synthesis of benzothiazole derived Schiff base ligands such as 2-((E)-(6-fluorobenzo[d]thiazol-2-ylimino)methyl)-6-methoxyphenol (L_1), 4-chloro-2-{(E)-[(6-fluoro-1,3-benzo thiazol-2-yl)imino]methyl}phenol(L_2),(E)-1-(5-bromo-2-methoxyphenyl)-N-(6-fluoro1,3-benzothiazol-2-yl) methanimine (L_3). The prepared molecules were characterized using FT-IR, UV-Visible, NMR and mass spectroscopy. The analytical results revealed the structural information. Further, these molecules were investigated for Human serum albumin (HSA) binding, which showed that the probable mode of interaction strategy is found to be a static quenching process.

Graphical Abstract



Schematic representation for the synthesis of Schiff base ligands

Keywords: Schiff base, Spectroscopy, HAS interaction, Molecular docking.

INTRODUCTION

Imine bases are still evoking much current interest as precursors of many versatile organic processes for the production like skeletons for the building-up of scaffolds owing to their physicochemical, biological and pharmacological properties. Imine based compounds have referred to as imines, azomethines, anils or Schiff bases and these can be designated structurally as $RR_1C=NR_2$, where R, $R_1$and R_2=H, alkyl, aryl.

The study of imine based ligands is allied with many vital advances in chemistry. The synthesis and biological studies of benzothiazole analogs have long been as research interest in the field of medicine due to their potential activities. Various natural and its derivatives, also non-natural compounds containing imine group and such compounds are critical as therapeutic candidates.

2-Aminobenzothiazoles are considered as one of the most reactive synthon due to its amino group assisting the reaction with electrophiles constitutes with many fused heterocyclic molecules [**1, 2**]. With regards to present report, 6-fluoro benzothiazole derivatives, which are used in the current study are well-known to have a variety range of chemical reactivity and bioactivity owing to their basic functionalities. Different substituted benzothiazole derivatives with halogens, particularly, fluorine substituted molecules that have gained consideration for their potential biological efficacies [**3, 4**]. Aforementioned benzothiazole derivatives were intensively studied because of their unique and versatile scaffold, as they are one of the privileged structure in experimental drug design and is endowed with abundant bioactivities [5, **6**]. The approach towards the design and development of organic molecules as potential chemotherapeutic probes with immense biological properties like antimicrobial and anti-inflammatory activity plays a pivotal role in protecting the body from oxidative damage.

o-hydroxy imine bases have aroused as lead structures for the development of antimicrobial and antioxidant agents of vast applications due to their comprehensive spectrum of *in vitro and in vivo* chemotherapeutic values [**7, 8**]. In this regard, tremendous research efforts are under process for developing safer antibiotics. The antioxidant activity of natural and synthetic compounds (secondary metabolites) effective in preventing many diseases from free radical damage and are determined using various antioxidant methodologies, moreover anti-inflammatory and antioxidant are closely related in chronic bacterial infection/ inflammatory [**9**]. The emergence of more efficient multidrug-resistant strains of microbial pathogens for the development of a substantial chemotherapeutic agent for effective management of inflammation has undergone continual evolution. Imine base approach is one of the most promising amongst these.The literature survey allied to fluorinated benzothiazole derivatives revealed that compounds with these nuclei have vast medicinal importance in the field of pharmaceutical chemistry **[10-12]**.

With respect to above perception, the present work describes the synthesis of a series of three new Schiff base ligands of 6-fluorobenzothiazole substituted derivatives incorporated both from benzothiazole moiety and different aromatic aldehydes. These molecules were assessed for their binding potency with HSA.

MATERIALS AND METHODS

Analytical and physical measurements: Commercial reagent grade chemicals and solvents were used throughout the experiments without further purification. The melting point of all the compounds was determined on an ELICO-3210 apparatus in the open capillary tube using a precision digi melting point apparatus and was uncorrected. Elemental analysis (CHNO) was performed with a model 240 Perkin Elmer elemental analyzer. ESI (positive) mass spectra of synthesized compounds in DMSO were run in Synapt G2 HDMS spectrometer equipped with electrospray ion (ESI) source.IR spectra of newly synthesized molecules were recorded in 4000-400 cm^{-1}range using a Perkin–Elmer

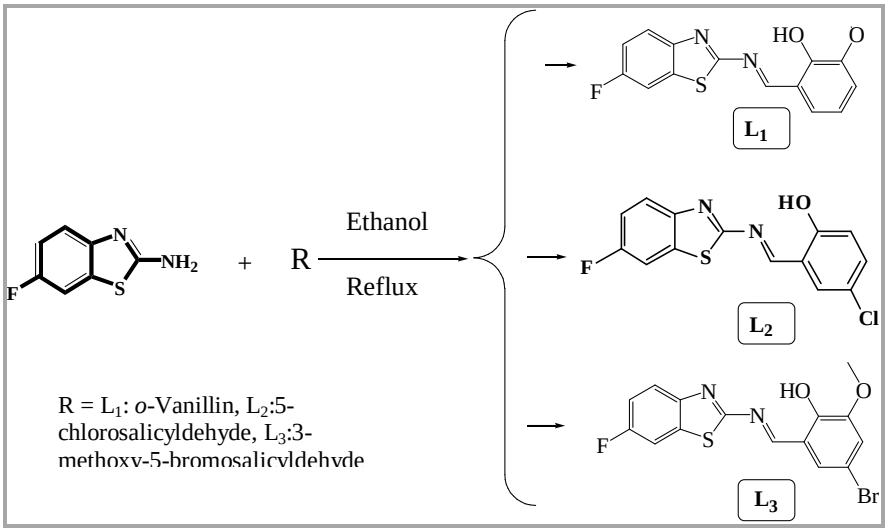
spectrophotometer version 10.03.09.*via*FT-ATR. UV-Vis spectrophotometer (DU 730 'Lifesciences' M/S Beckman coulter, USA) was used to record the absorption spectra of the prepared compounds lie in the range 200-800 nm.

For the structural identification, Agilent-NMR spectrophotometer (Model 400MR DD 22) was used to record ^{1}H and^{13}C spectra in d_6-DMSO solvent using TMS as an internal reference at ambient temperature.

Synthetic protocol for imine based ligands

Classical method: The preparation of series of Schiff base (L_1-L_3) is depicted in scheme 1 and each of these were prepared by the condensation of an equimolar ratio of substituted aldehydes [(*o*-vanillin (L_1), 5-chlorosalicyladehyde(L_2) and 5-bromo-3-methoxysalicyl- aldehyde (L_3)] and 6-fluoro-2-aminobenzothiazole dissolved in absolute hot ethanol. The resulting reaction mixture was stirred vigorously at ambient temperature(25°C), refluxed at 80°C for 6-7 h. The yellow solid precipitate of imine-based ligands was formed, which were then filtered, washed with cold ethanol and dried in a desiccator. TLC plates in n-hexane:ethyl acetate (8:2) was used intermittently to access the reaction and purity of synthesized compounds obtained from continuous recrystallization.

Microwave method: In this method, each ligand (L_1-L_3) was synthesized by an equimolar ratio of the mixture of 2-amino-6-fluoro benzothiazole and the corresponding aldehydes were thoroughly mixed in a grinder. The reaction flask sealed with Teflon was then irradiated in a microwave oven, connected to pressure gauge outside the oven and heated for 7 min at 140°C with a power level 7 (560 W) using dry methanol (10 mL) as a solvent. TLC was used to assess the completion of the reaction progress and to preliminary check on the purity of the product. The reaction mixture was allowed to attain room temperature (25±1°C). The colored solid was obtained after recrystallized from methanol.



Scheme 1. Schematic representation for the synthesis of Schiff base ligands.

Molecular Docking: The rigid molecular docking study is an interactive molecular graphics program to display feasible energetically favorable docking poses of compounds with proteins and enzymes. The structures of imine-based molecules (L_1-L_3) were drawn in 2D sketcher and geometry cleaning of the compounds was performed in Maestro 11.2 Schrödinger suite 2017-2 platform and their energy minimized by OPLS 2005 force field; the addition of hydrogen atoms, neutralization of charged groups and ionization state generation are noted. pH was set at 7.5 with Epik. Generation of tautomer and stereoisomers of 32 per ligand and low energy and low energy ring conformations were optimized by LigPrep.

Protein preparation for docking: *In silico* computational molecular docking studies were performed according to the protocol as reported **[13].** Concisely, the crystallographic structures of the PLA_2 (5G3N) and *E-coli* (1KE4) were imported from the protein data bank for the docking simulation. These structures were refined by multistep process in Maestro 11.2, includes energy minimization by OPLS-2005 force field, bond orders were assigned, hydrogen atoms were added and water molecules have been detached beyond 5Å form heteroatom were optimized. pH was fixed and tuned to 7.5 using PROPKA. Non-hydrogen atoms were minimized by restrained minimization to default RMSD to 0.3 Å. Docking grid was prepared by mapping using Site Map detection module wherein top-ranked potential receptor binding site was selected with at least 15 site points per reported site for protein molecules whose binding site is unknown. Using Extra-precision (XP) docking and scoring of each compound were docked into the receptor grid of respective radius for particular protein were chosen and the docking calculation was judged based on the XP G_{Score} and Glide energy and molecular visualization was done under Maestro workspace.

RESULTS AND DISCUSSION

Simple preparative accessibility protocols and optimized reaction conditions would pave for facile synthesis of imine-based ligands L_1-L_3 and microwave-assisted methods have been employed for the convenient and reproducible synthesis of imine base ligands were structurally elucidated by microanalyses and spectral data. The prepared compounds were stable at atmospheric conditions, non-hygroscopic and soluble in all common organic solvents. The progress and purity of the reaction and product respectively was monitored by TLC techniques and spots were visualized under UV light.

L_1:*2-{(E)-[(6-fluoro-1,3-benzothiazol-2-yl)imino]methyl}-6-methoxyphenol:*$C_{15}H_{11}FN_2O_2S$;Color: Turmeric yellow solid; Yield (%) and R_f value 74 (conv.), 88 (MW) and 0.55, M.p. (°C) 170-172;Elemental analysis Found (calc.) C 59.50 (59.02), H 3.68 (3.83), N 9.27 (9.03), O 10.58 (10.62); FT IR (υ_{max}./cm^{-1}) (υOH) 3200, (HC=N) azomethine 1650; ^{1}H NMR (295 K/ δ in ppm/ DMSO-d_6 400 MHz): $CH_3$3.81 (3H, s), HC=N 9.24 (1H, s); phenolic OH 6.87 (1H, s); Ar-H 7.26-7.42 (3H, 7.34 (dd, *J* = 10.4, 2.0 Hz), 7.38 (t, *J* = 8.1 Hz), 7.29 (dd, *J* = 8.1, 1.4 Hz)), 7.71 (1H, dd, *J* = 2.0, 0.4 Hz), 7.83 (1H, dd, *J* = 10.4, 0.4 Hz); ^{13}C NMR (295 K/ δ(ppm)/DMSO-$d_6$100 MHz): 161.226, 151.547, 145.371, 141.238, 134.803, 133.455, 129.612, 128.531, 127.562, 124.954, 123.283, 121.418, 118.286, 115.509, 112.619, 56.398; Mass (ESI MS) *m/z*302.05; UV-vis. ($\lambda_{max.}$, nm) 348-351.

L_2: *4-chloro-2-{(E)-[(6-fluoro-1,3-benzothiazol-2-yl)imino]methyl}phenol:* $C_{14}H_8ClFN_2OS$;Color: Yellow crystalline solid; Yield (%) and R_f value 78 (conv.), 89 (MW) and 0.62; M.p. (°C):170-172; Elemental analysis Found (calc.)C 54.80 (54.82), H 2.68 (2.63), N 9.11 (9.13), O 5.21 (5.22); FT IR (υ_{max}./cm^{-1}) (υOH) 3253, (HC=N) azomethine 1662; ^{1}H NMR (295 K/ δ in ppm/DMSO-d_6 400 MHz): HC=N 9.776 (1H, s); phenolic OH 11.45 (1H, s); Ar-H 7.0-7.9 (6H, m) [7.015-7.038 (dd, J=8.3, 1.4 Hz), 7.341 (dd, J=8.3, 0.5 Hz)), 7.13 (1H, dd, J=1.4, 0.5 Hz), 7.49 (1H, dd, J=8.0, 1.6 Hz), 7.99 (1H, dd, J=1.6, 0.4 Hz)]; ^{13}C NMR (295 K/δ(ppm)/ DMSO-$d_6$100 MHz):164.176, 161.261, 159.63, 158.848, 148.414, 135.710, 135.323, 129.215, 124.494, 123.880,119.463, 115.714, 109.423, 109.150; Mass (ESI MS) m/z 307.14 [M+1] 309.14 [M+3] **;** UV-vis. ($\lambda_{max.}$, nm) 321.

L_3: ***(****E)-1-(5-bromo-2-methoxyphenyl)-N-(6-fluoro-1,3-benzothiazol-2-yl)methanimine:*$C_{15}H_{10}BrFN_2O_2S$; Color: Yellow crystalline solid; Yield (%) and R_f value 76 (conv.), 89 (MW) and 0.48; M.p. (°C): 202-204; Elemental analysis Found (calc.)C 46.23 (47.26), H 2.60 (2.64), N 7.40 (7.35); O 5.21 (5.22); FT IR (υ_{max}./cm^{-1}) (υOH) 3189, (HC=N) azomethine 1617; ^{1}H NMR (295 K/δ in ppm/ DMSO-d_6 400 MHz): HC=N 9.30 (1H, s); phenolic OH 6.76 (1H, d, J=1.5 Hz); Ar-H 7.34-8.02 (4H, m) [7.34 (1H, dd, J=8.2, 2.0 Hz), 7.70 (1H, dd, J=2.0, 0.4 Hz), 7.82 (1H, dd, J=8.2, 0.4 Hz), 8.02 (1H, d, J=1.5 Hz)]; ^{13}C NMR (295 K/δ(ppm)/DMSO-$d_6$100 MHz):170.762, 170.732, 166.460, 161.231, 158.818, 151.040, 148.634, 148.444, 135.642, 135.528, 124.388, 124.297, 117.543, 115.661, 109.439, 56.485; Mass (ESI MS) m/z 380.14 [M+1] 381.14 [M+2]; UV-vis. ($\lambda_{max.}$, nm) 315.

NMR spectroscopy: ^{1}H-NMR of the ligands showed the presence of a high-resolution singlet peak at ~9.2–10.22 ppm corresponds to -CH=N, which confirmed the condensation between the amino group and the aldehyde group. The ^{1}H-NMR spectra of L_1, L_3 and L_3 shows higher field singlet at δ ~5-6.5 ppm (s, 1H, -OH) but the same phenolic H-bonded OH group was observed at δ 11.45 ppm for L_2. In compound L_5, an additional resonance was assigned to the $-CH_2$ (δ6.14 ppm, 2H), and 3 protons of the methoxy group in L_1 and L_3 falls at a lower field of 3 ppm were observed. The protonation constant of all the ligands was determined in the d_6-DMSO solvent, which is observed at ~2ppm.

FT-IR spectroscopy: The Fourier Transform Infrared Spectra (Figure 1**)** of the ligands exhibits a sharp band at 1662-1557 cm^{-1} due to azomethine group vibration. The compounds have typical characteristic bands at 1562 cm^{-1} for υC=N of thiazole ring and 748 cm^{-1} for υC-S-C [**14**]. The -OH group involved in intramolecular hydrogen bonding for L_1-L_3 indicated by a shallow/broadband extends within 3253-2700 cm^{-1} gives clue for the presence of enol form. The existence of the aromatic rings was demonstrated by the following bands: aromatic carbon-H stretching υC−H (3045−3040 cm^{-1}) and phenyl ring stretching υC−C (1575−1500 cm^{-1}) in synthesized compounds confirm the aromatic stretching vibrations and the appearance of a medium to strong absorption bands above 1600 cm^{-1}due to a stretching vibration of the imine (C=N) bond formation in synthesized compounds *via* condensation.

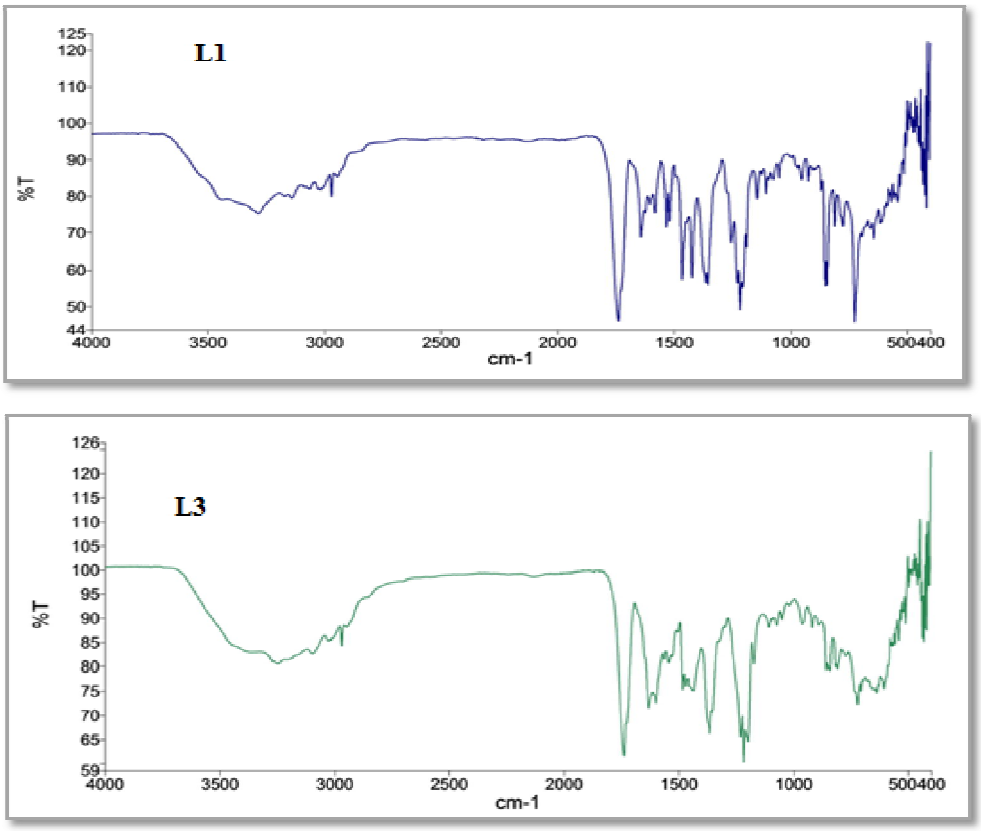


Figure 1. FT IR spectra of $L_1$and L_3.

Mass Spectroscopy: The mass spectra of the imine bases show the molecular ion peak [M^{+}] at their m/z values shows the molecular ion peak corresponding to their formulation. L_3shows the peaks at m/z 377.9 and 379.9 are representing [M+1]$^{+}$ and [M+2]$^{+}$, respectively (Figure 2). The observed first ion-peak at m/z 169 is due to the cleavage of 6-fluoro benzothiazole moiety. This fragment ion undergoes further fragmentation to give ion peak at m/z 79 (base peak) of phenyl ion radical.

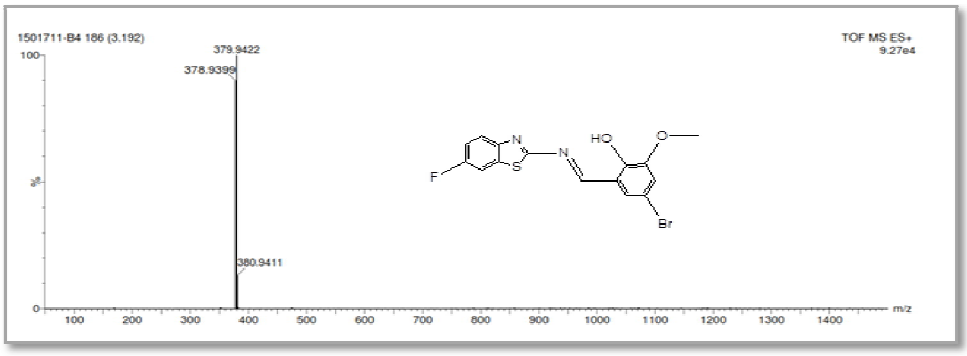


Figure 2. ESI-MS spectrum Schiff base ligand (L_3).

UV-Vis spectroscopy: The electronic absorption spectra of compounds display high energy bands in the UV region at ~266-270 nm corresponds to $\pi \rightarrow \pi^*$ transitions of the aromatic ring and within C=N group *i.e.*, electronic transitions between HOMO and LUMO. The absorption peak at the longer wavelength at ~340-374 nm is due to $n \rightarrow \pi^*$ intra-ligand charge transfer band with the involvement of imine group.

HSA interaction studies

UV-Vis spectral features: UV–Vis spectroscopy has been used to examine biomolecular interactions between ligands and HSA. As can be seen in the figure 3, compound L_1 show a trifling peak at ~238, 261 nm for n→ π^* transition existing in the peptide bond of protein helix. A near UV region shows a sharp absorption peak at 278-281 nm for $\pi \rightarrow \pi^*$ spin forbidden transition of the phenyl rings in aromatic amino acids Trp (tryptophan), Tyr (tyrosine), Phe (phenylalanine) residues and a peptide linkage. The spectral absorption of Tyr and Trp microenvironment can decide their polarity [**15**]. It was noticed in figure 3, a hyperchromic effect with slight blue shifts (~2-3 nm) and an isosbestic point exists. Majorly two absorption peaks at 284, 336 nm (L_1), 278, 348 nm (L_2) and 272, 315 nm (L_3) are appeared in the absorption spectra of HSA during the titration with ligands. On gradual addition of ligands, the enhanced absorption intensity of HSA on increments of compounds implied that the aromatic amino acid residues of the protein in a hydrophobic cavity were exposed to an aqueous environment upon complexation of compounds with HSA and could cause structural changes in the protein.

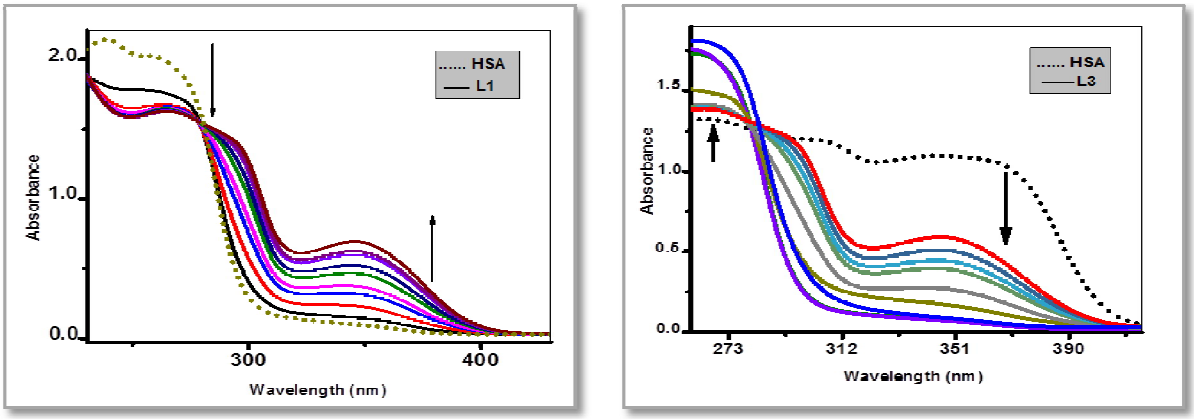


Figure 3. UV absorption spectra of HSA (2×10^{-6} mol L^{-1}) with varying concentrations of probes L_1 and L_3 ($0\text{-}6\times10^{-6}$ mol L^{-1}) at pH 7.4.

To confirm this view, simultaneous operation of both static and dynamic quenching was recommended. The process was assumed to be dynamic quenching and equation 2 gives the quenching formulation. The quenching rate constant (k_q =1 mol^{-1} s^{-1}) is obtained from the slope of SV

plot at the temperature of 27, 28 and 30°C. The rate constant of the protein quenching procedure was initiated by all the ligands (quenchers) found to be more than the k_q of the scatter process (Table 1). Hence, the phenomenon adequately demonstrated that ligands might initiate fluorescence quenching of HSA by specific long-range interaction of ligands–HSA complex formation, rather than a dynamic collision. It shows that the binding constant between the compounds and HSA is significant, and the effect of temperature is small. Thus, the compounds can be stored and removed by protein in the body.

Table 1. The quenching constants (k_{sv}), binding constants (K_b), number of binding sites (n) and corresponding thermodynamic binding parameters for HSA-ligand interaction system at different temperatures obtained from fluorescence spectrophotometry.

Probes	Temp. (K)	$k_{sv} \times 10^4$ (L mol^{-1})	$k_q \times 10^{12}$ (L mol^{-1}sec^{-1})	$K_b \times 10^5$ (L mol^{-1})	R^2	n	ΔG^o (KJ mol^{-1})	ΔH^o (KJ mol^{-1})	ΔS^o (J K^{-1}mol^{-1})
L_1	298	2.3851	2.3851	1.022	0.9768	0.81	-16.239	-78.314	-208.304
	303	1.8884	1.8884	1.004	0.9141	0.98	-15.197		
	310	1.8973	1.8973	0.783	0.9045	1.31	-13.739		
L_2	298	4.0251	4.0251	4.945	0.9895	1.51	-19.277	-98.741	-266.525
	303	4.3210	4.3210	2.105	0.9321	1.22	-18.235		
	310	3.1102	3.1102	1.012	0.8979	0.94	-16.118		
L_3	298	7.4145	7.4145	6.615	0.9314	0.97	-28.452	-101.342	-244.588
	303	6.6469	6.6469	6.102	0.9025	1.01	-27.229		
	310	6.2151	6.2151	5.457	0.9001	0.89	-25.519		

R^2 =Correlation coefficient for the K_b

Analysis of binding equilibria: Fluorescence quenching data analysis afforded quantitative evaluation of the non-covalent binding constant (K_b) and binding stoichiometry (n) for the HSA-compounds interaction process, and it was analyzed according to the modified Stern-Volmer Eq. (4)

$$\log\left[\frac{F_0-F}{F}\right] = \log K_b + n \log [Q] \qquad \ldots (4)$$

From table 3, it was observed that the binding constant (K_b) decreases as temperature rises which indicates the formation of unstable HSA-ligands complex. The observed values of n are close to unity indicating that there is one independent class of binding site on HSA for ligands.

Resonance energy transmission between HSA and ligands: The significance of the energy transfer in biochemistry is that the efficacy of transmission can be used to measure the distance between the compound and the tryptophan residues in the HSA. To find out the distance between compounds and Trp protein, it is possible to study Forster's non-radioactive process or fluorescence energy transfer (FRET) from a donor (HSA) to acceptor (ligands) as a spectroscopic ruler [**16**]. FRET occurs when the fluorescence spectrum of HSA (fluorophore) overlays on the UV absorption spectrum of compounds (acceptor) and is displayed for the representative L_1 and L_3 in figure 4.

Molecular docking: Protein-ligand docking favors the most promising targets for testing potency of compounds to exert its optimum regulatory or inhibitory activities on the target protein. In the present study, the author has elucidated the role of Schiff base molecules (L_1-L_3) against molecular targets associated with anti-inflammatory and antibacterial activities by using molecular docking protocol. $sPLA_2$ is an initiator of inflammation by cleavage of a phospholipid, especially arachidonic acid at *Sn-2*positions, which is further undergoes oxidative metabolism by downstream enzymes like COX-2 and LOX enzymes, resulting in the release of pro-inflammatory mediators like prostaglandins, thromboxanes and leukotrienes. The active site of $sPLA_2$is lined with His47; Asp48 and Phe5 residues connected helps in catalysis of phospholipid. Any structural perturbations in His47 results in inhibition of $sPLA_2$ [**17**]. In the present study, the observed interaction in L_1 attributes a π-π stacking with Phe5 and His47 along with a single hydrogen bonding with His47 added to this; a salt bridge

with calcium ion which resides at catalytic site (Figure 5) which marks its efficiency as an anti-inflammatory compound.

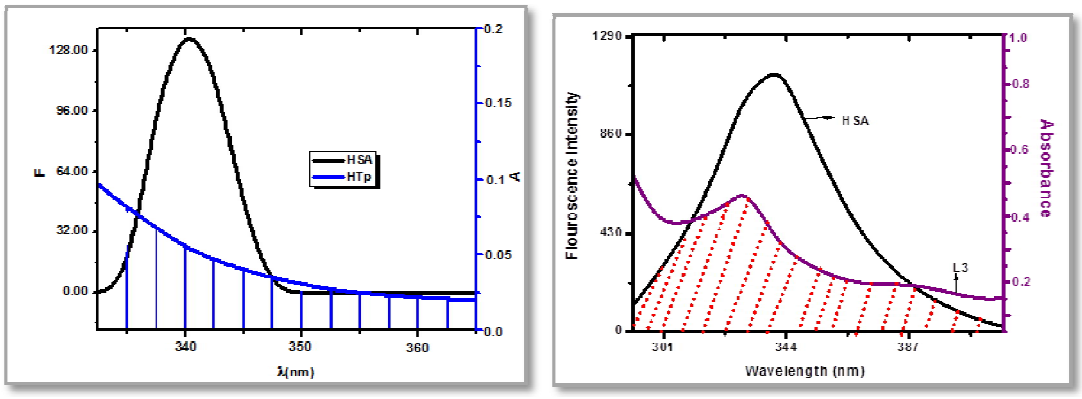


Figure 4. The overlap of the fluorescence spectrum of HSA and the absorption spectrum of L_1 (right) and L_2 (left) (λ_{ex}=280 nm, [HSA]/ [L]=1:1(5 mM)).

In order to check the pharmacological properties of other molecules (L_1-L_3), their antibacterial activity results (Table 1) are suggested that L_2 occupies the active site of AmpC β-lactamase, blocking its activity, because β-Lactamases are the most resistance to β-lactam antibiotics and are an increasing menace to public health. L_5 binds deeply into the active site of AmpC β-lactamase suggests a tight binding, which in turn inhibits the accessibility of the enzyme to act on the substrate [**18**].

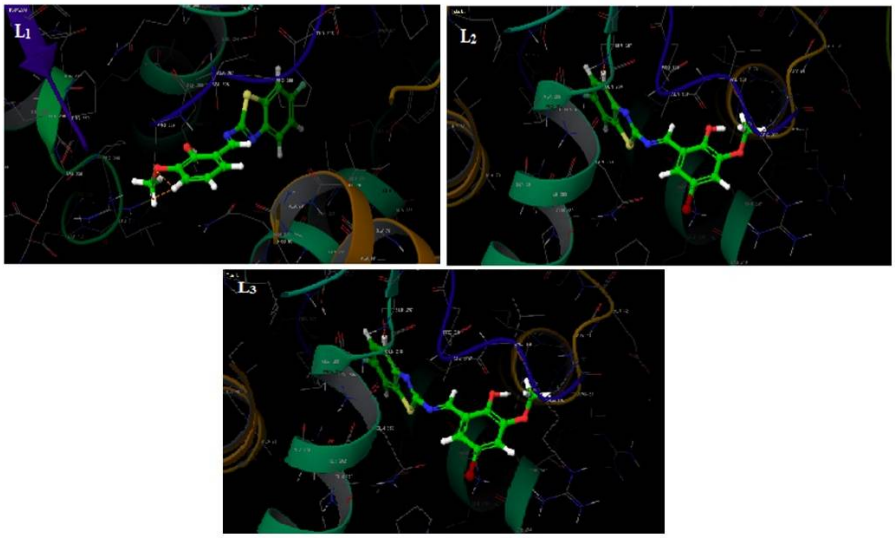


Figure 5. *In silico* analysis of sPLA$_2$(5G3N) and at the active site of the AmpC beta-lactamase from *E. coli* (PDB ID: 1KE4) with ligands showing molecular interactions.

APPLICATION

Present methos of synthesis will help the synthetic chemistry to design and develop the Schiff base ligand with potent medical applications.

CONCLUSION

A series of Schiff bases based on benzothiazole analogs (L_1-L_3) were synthesized in one-pot under green synthetic method. The synthesized compounds were characterized by physical methods

(melting point, TLC and elemental analysis), structurally elucidated by spectral studies. SAR has become a useful tool to study the molecular determinants leading to the bioactivity of synthesized analogs towards clinically important pathogens and was identified as viable leads for further studies. The binding constant between the compounds and HSA is significant, and the effect of temperature is small. Thus, the compounds can be stored and removed by protein in the body. Additionally, molecular docking studies conducted for the compounds with their antimicrobial and anti-inflammatory activities and ranking high inhibition constant and binding energy. The significant correlation was observed from the molecular docking simulations for the compounds with their corresponding experimental activities. Thus, the synthesis of imine bases and optimization of their bioactivity according to the identified structure-activity relationship is demonstrated and could be considered as possible hit as therapeutic agents.

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