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Fluorescence and molecular docking studies of some new Schiff bases of 6-chloro-2-hydroxyquinoline-3-carbaldehyde

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ABSTRACT

The synthesis of a novel series of Schiff bases of 2-hydroxy-6-chloro-3-formylquinoline (4a–e) and its Zn (II) and Cu (II) complexes are described in the present paper. The chemical structures of compounds have been elucidated by IR, ^{1}H NMR and Mass spectral data. Fluorescence properties of all the synthesized compounds have been tested. Molecular modeling tools were also used for a further analysis in order to estimate the druggability of the reported quinoline Schiff base derivatives.

Keywords: Vilsmeier–Haack reaction, Quinoline, Schiff base, fluorescence, docking.

INTRODUCTION

The Schiff bases have applications as dyes, catalysts, intermediates in organic synthesis as well as in polymer stabilizers [1]. Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties [2-3]. Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities [4–5].

The first preparation of imines was reported in the 19th century by Schiff (1864). Since then a variety of methods for the synthesis of imines have been described [6]. The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation [7]. Molecular sieves are then used to completely remove water formed in the system [8]. In the 1990s in-situ method for water elimination was developed, using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate [9-10]. In 2004, Chakraborti et al. [11] demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. They proposed as an alternative the use of substances that function as Bronsted-Lowry or Lewis acids to activate the carbonyl group of aldehydes, catalyze the nucleophilic attack by amines, and dehydrate the system, eliminating water as the final step [12]. Examples of Bronsted-Lowry or lewis acids used for the synthesis of Schiff bases include $ZnCl_2$, $TiCl_4$, $MgSO_4$-PPTS, $Ti(OR)_4$, Alumina, H_2SO_4, $NaHCO_3$, $MgSO_4$, $Mg(ClO_4)_2$, H_3CCOOH, $Er(OTf)_3$, P_2O_5/Al_2O_3, Acetic acid and HCl [13–23].
In synthetic medicinal chemistry the quinoline moiety is widely exploited revealing a broad spectrum of activity covering antimalarial [24], anticancer [25], antifungal, antibacterial, antiprotozoic antibiotic [26], and anti-HIV [27] effects. The Vilsmeier–Haack reaction on acetanilide provided a vital and efficient intermediate for synthesis of

several newer substituted heterocyclic compounds. The reaction was performed at 90^0C for 8–16 h, using typical Vilsmeier-Haack reagent derived from phosphorus oxychloride-N, N-dimethylformamide [28].

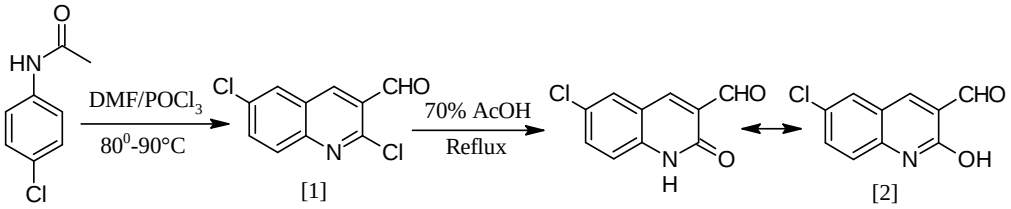
Metal coordination compounds are also called as metal complexes. The challenging topics nowadays in the chemistry of metal complexes are to design the unique chemical properties of transition metal complexes which have their usage in catalysis and optical and magnetic devices as well as in pharmaceutical field. The metal complexes find applications as dyes, pigments, drugs and contrast agents. Copper and Zinc are essential elements for life. Copper has been used since the middle ages for the treatment of arthritis. It has been observed that the copper complexes are more potent than free ligands and the copper salts. Zinc appears throughout the human body in a variety of tissues, such as skin, bone, brain, muscle as well as liver. Zinc (II) complexes of carboxylates appeared to have good antibacterial activity.

Molecular docking is commonly used in the field of drug design to predict the binding of small molecules to biological protein targets. This method gives the possibility to study an active site in detail and can be used for hit identification, virtual screening, binding mode determination, and lead optimization. Generally, the docking methodology is used to fit a compound into an artificial model or to a known three-dimensional binding site, which can be utilized to explore ligand conformation, orientation and feasible molecular interactions such as hydrogen bonding and hydrophobic interactions. Thus, molecular docking is a powerful tool for the design of ligands towards a specific protein target. Docking is a method which predicts the preferred orientations of one molecule to a second when bound to each other to form a stable complex.

EXPERIMENTAL SECTION

The chemicals for synthesis were purchased from Sigma Aldrich. All the used metal ions were prepared with chloride salts. All the materials and solvents were of analytical reagent grade quality and used without further purification. Melting points (M.P.) of the synthesized compounds were determined in open capillary tubes and are uncorrected; Infrared spectra were measured with KBr disk on a FTIR-7600 Lambda Scientific Pty. Ltd. in the 4000-400 cm^{-1}. 1H-NMR spectra were recorded on Varian-NMR-Mercury 300 MHz instruments using DMSO-d6 as a solvent and TMS as an internal standard; chemical shifts are expressed as d values (ppm). Mass spectra (MS) were taken in Mass spectra were recorded on BRUKER ESQUIRE HCT spectrometer. UV–Visible absorption spectra were obtained with UV spectrophotometer Shimadzu UV-1800 and recorded in quartz cells with 1 cm optical path length. Fluorescence spectra were acquired on a spectrofluorophotometer Shimadzu RF-5301pc and equipped with quartz cuvette of 1 cm path length. Analytical thin-layer chromatography (TLC) was performed on pre-coated TLC sheets of silica gel 60 F254 (Merck, Darmstadt, Germany), visualized by long- and short-wavelength UV lamps. Chromatographic purifications were performed on Merck silica gel (70–230 mesh). Molecular docking study was done with GLIDE92 V3.5 (Grid-based ligand docking with energetics) is docking software from Schrodinger.

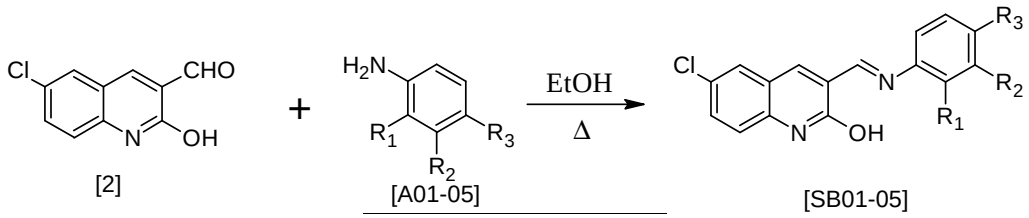
2.1 Synthesis of 6-chloro-2-hydroxyquinoline-3-carbaldehyde. [2]



2-oxo-quinoline-3-carbaldehyde was synthesized according to the literature [28-29]. 4-chloroacetanilide was prepared from reaction of 4-chloroaniline by treating with acetic anhydride in aqueous medium. 4-chloroacetanilide (5 mmol) was dissolved in dry DMF (15 mmol) and $POCl_3$ (60 mmol) was added drop wise at 0^0-5^0 C with constant stirring. The mixture stirred at 80^0-90^0 C for 8 hrs. The mixture was poured into crushed ice, stirred for 5 min. and the resulting solid filtered washed well with water and dried. The compound purified by recrystallization from Ethyl acetate. The suspension of substituted 2,6-dichloroquinoline-3-carbaldehyde[1] in 70% Acetic acid (10 ml) was heated under reflux for 6 hrs. The completion of the reaction was checked by TLC. Upon cooling the reaction mixture a yellow solid product precipitated out which was filtered. It was washed well with water, dried and purified by recrystallization from DMF.

Yield: 93%, **M.P.:** 303-304^{0}C; **Color:** Yellow; **^{1}H NMR (300 MHz, DMSO-d_6) δ ppm:** 7.25(m, 1H, H-7), 7.35(m, 1H, H-8), 7.66(m, 1H, H-6), 7.92(m, 1H, H-5), 8.50(d, 1H, H-4), 10.24(s, 1H, CHO), 12.23(s, 1H, OH); **FTIR(KBr cm^{-1})**: 3276, 3154, 3097, 3002, 2942, 2869, 1687, 1621, 1556, 1488, 1434, 1141, 1106, 898, 756. **MASS SPECTRA:** [M+] 174.05

2.2 Synthesis of schiff bases



Schiff Base	R_1	R_2	R_3
SB01	H	H	F
SB02	F	Cl	H
SB03	CF_3	H	H
SB04	H	CF_3	H
SB05	H	CF_3	CN

6-Chloro-2-hydroxyquinoline-3-carbaldehyde (0.01mol) and substituted aniline [A01-05] (0.01mol) taken in round bottom flax containing 10 cm^3 of ethanol. Reaction mixture was refluxed for 30 min. Completion of reaction is checked with TLC. Upon cooling the reaction mixture a solid product precipitated out which was filtered, dried and purified by recrystallization from Ethanol.

2.2.1 6-Chloro-3-{(*E*)-[(4-fluorophenyl)imino]methyl}quinolin-2-ol. [SB01]
Yield: 82%;M.P.: 293-294^{0}C; Color: Yellow; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.31–7.46 (m, 4H), 7.72–7.82 (m, 2H), 8.12 (d, 1H), 8.58 (d, 1H), 8.79 (s, 1H), 12.34 (s, 1H); FTIR (KBr) (cm^{-1}): 3147, 2989, 2917, 2840, 1673, 1502, 1234, 944, 831, 663,601. MASS SPECTRA: [M+1] 301.77

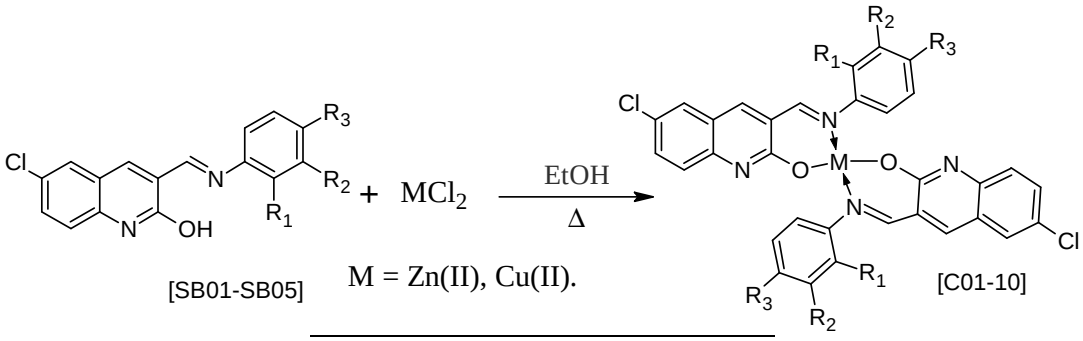
1.2.2 Synthesis of 6-chloro-3-{(*E*)-[(3-chloro-2-fluorophenyl)imino] methyl}quinolin-2-ol. [SB02]
Yield: 77% M.P.: Above 300^{0}C; Color: Bright yellow, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.35 (m, 2H), 7.65 (m, 2H), 8.05 (m, 1H), 8.46 (d, 1H), 8.60 (d, 1H), 8.68 (s, 1H), 12.30 (s, 1H); FTIR (KBr) (cm^{-1}): 3149, 2992, 2900, 2840, 1656, 1625, 1552, 1469, 1417, 1225, 1205, 1083, 950, 898, 819, 767, 603; MASS SPECTRA: [M+] 335.30

1.2.3 6-Chloro-3-[(*E*)-{[2-(trifluoromethyl)phenyl]imino}methyl] quinolin-2-ol. [SB03]
Yield: 72%; M.P.: Above 300^{0}C; Color: Yellow; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.26– 7.46 (m, 4H), 7.67 (m, 2H), 8.09 (d, 1H), 8.47 (d, 1H), 8.75 (s, 1H), 12.35 (s, 1H); FTIR (KBr) (cm^{-1}): 3139, 2985, 2900, 2850, 2730, 1679, 1617, 1552, 1479, 1417, 1207, 1108, 943, 815, 665, 613, 563; MASS SPECTRA: [M+1] 351.24

1.2.4 6-Chloro-3-[(*E*)-{[3-(trifluoromethyl)phenyl]imino}methyl] quinolin-2-ol. [SB04]
Yield: 68%; M.P.: Above 300^{0}C; Color: Yellow; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.30 (m, 2H), 7.55 – 7.60 (m, 4H), 8.03 (d, 1H), 8.54 (d, 1H), 8.77 (s, 1H), 12.35 (s, 1H); FTIR (KBr) (cm^{-1}): 3145, 3064, 2987, 2902, 2848, 2815, 2728, 1679, 1617, 1552, 1479, 1417, 1207, 1110, 943, 815, 665; Mass spectra: [M+1] 351.72

1.2.5 4-{[(*E*)-(6-Chloro-2-hydroxyquinolin-3-yl)methylidene]amino}-2-(trifluoro methyl) benzonitrile. [SB05]
Yield: 80%; M.P.: 290-291^{0}C; Color: Pale Yellow; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.23 – 7.37 (m, 4H), 7.62 (d, 1H), 8.04 (d, 1H), 8.65 (d, 1H), 8.70 (s, 1H), 12.25 (s, 1H); FTIR (KBr) (cm^{-1}): 3139, 2985, 2902, 2848, 2219, 1685, 1617, 1552, 1479, 1417, 1207, 943, 815, 665, 613; MASS SPECTRA: [M+1] 376.29

2.3 Synthesis of metal complexes.
Schiff base (0.050 mmol) was dissolved in 15 ml of absolute alcohol in round bottom flask fitted with reflux condenser and calcium chloride guard tube. Corresponding metal salt ($CuCl_2$, $ZnCl_2$) (0.025 mmol) was added and stirred the reaction mixture, finally Potassium hydroxide (0.050 mmol) was added and reaction mixture was refluxed for 3-5 hours in water bath. It was cooled and filtered the solid separated and dried in oven at 70-80°C.



Schiff Base	Zn(II) Complex	Cu(II) Complex
SB01	C01	C06
SB02	C02	C07
SB03	C03	C08
SB04	C04	C09
SB05	C05	C10

2.4 Molecular Docking Study:

The three dimensional structures of 3LAU protein was taken from the PDB database. The native autoinducer and all water molecules were removed from basic protein structures. Hydrogen were added using the templates for the protein residues. The three-dimensional structure of the ligand 6-ClQA (2) and SB01-05 were constructed. The active site of this protein was first identified and defined using an eraser size of 5.0 Å. The ligands were docked into the active site separately using the 'Flexible Fit' option. The ligand-receptor site complex was subjected to '*in situ*' ligand minimization which was performed using the in-built CHARMm force-field calculation. The non-bond cutoff and the distance dependence was set to 11 Å and (ε = 1R) respectively. The determination of the ligand binding affinity was calculated using the shape-based interaction energies of the ligand with the protein. Consensus scoring with the top tier of s=10% using docking score used to estimate the ligand-binding energies.

The binding sites for the docking are generated by using Glide software. The site of the protein having more site score is considered for the docking of ligand. The site which has maximum *site points*, located on the site in different colours as hydrophobic and hydrophilic maps. The hydrophilic maps are further divided into donor, acceptor, and metal-binding regions. Other properties characterize the binding site in terms of the size of the site, degrees of enclosure by the protein and exposure to solvent, tightness with which the site points interact with the receptor, hydrophobic and between them, and degree to which a ligand might donate or accept hydrogen bonds.

Table 01: Docking results of 6-ClQA and SB01-05 with 3LAU

Description	6-ClQA	SB01	SB02	SB03	SB04	SB05
Potential Energy OPLS 2005	31.725	74.178	80.725	89.64	79.476	82.589
RMS Derivative OPLS 2005	0.028	0.03	0.039	0.033	0.006	0.008
Glide lignum	06	05	09	07	01	03
Docking Score	**-7.301**	**-7.55**	**-6.599**	**-6.82**	**-6.55**	**-6.479**
Glide Ligand efficiency	-0.522	-0.36	-0.3	-0.284	-0.273	-0.249
Glide Ligand efficiency sa	-1.257	-0.992	-0.84	-0.82	-0.787	-0.738
Glide Ligand efficiency In	-2.006	-1.867	-1.613	-1.632	-1.568	-1.522
Glide gscore	-7.301	-7.55	-6.599	-6.82	-6.55	-6.479
Glide lipo	-1.985	-2.368	-2.535	-2.753	-2.265	-2.121
Glide H-bond	-0.321	-0.497	-0.277	-0.288	-0.261	-0.32
Glide metal	00	00	00	00	00	00
Glide reward	-3.058	-2.519	-1.624	-1.713	-1.932	-1.957
Glide evwd	-25.555	-31.374	-34.564	-35.822	-35.276	-35.509
Glide ecoul	-4.4	-6.225	-5.043	-3.798	-3.543	-3.039
Glide erotb	00	0.407	0.336	0.31	0.31	0.274
Glide esite	00	-0.071	-0.014	-0.016	-0.107	-0.124
Glide emodel	-42.845	-54.918	-55.038	-56.022	-53.702	-53.913
Glide energy	-29.954	-37.599	-39.607	-39.619	-38.819	-38.548
Glide einternal	0.013	0.32	0.401	0.071	1.657	0.889
Glide confnum	01	07	01	03	06	03
Glide posenum	206	195	299	322	251	321
H Bond	01	02	01	01	01	00
pi-pi interactions	00	02	00	01	02	00

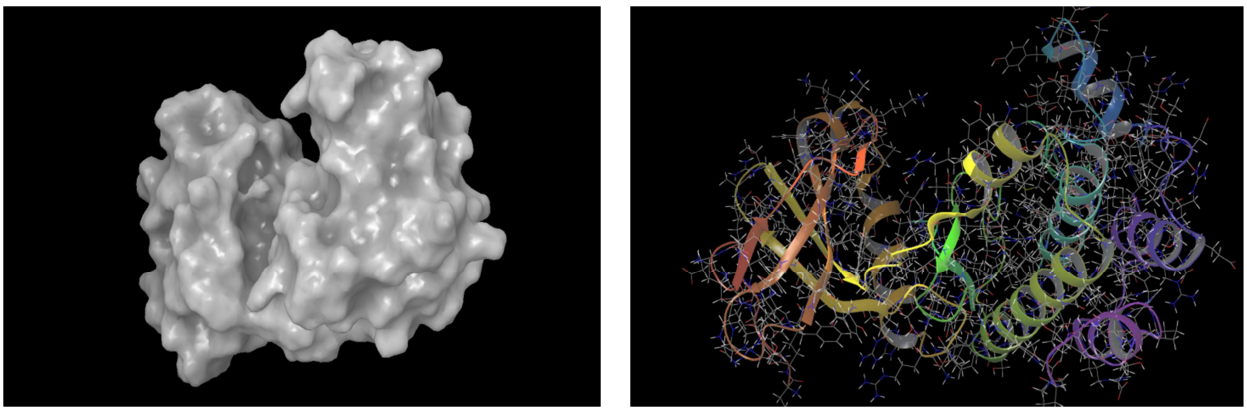


Figure 01: 3LAU

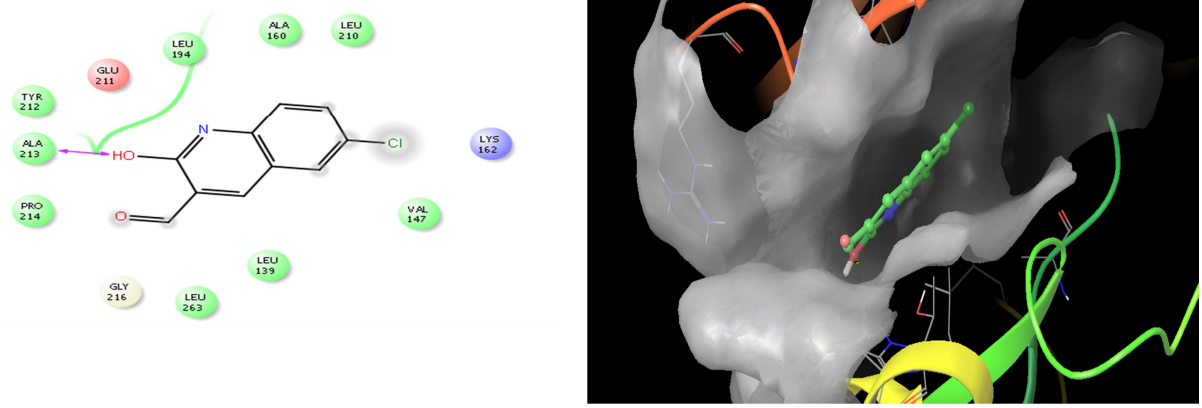


Figure 02: 2D AND 3D docking image of 6-Chloro-2-hydroxyquinoline-3-carbaldehyde

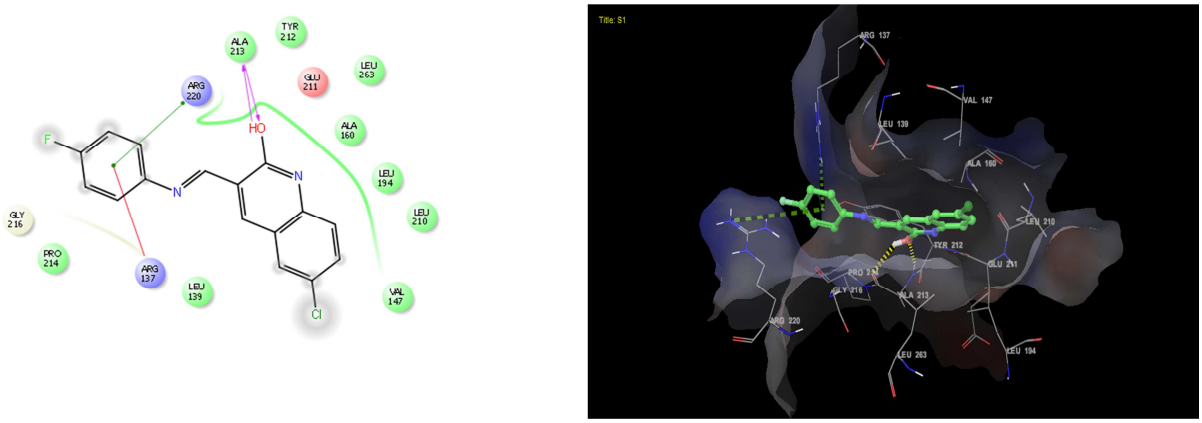


Figure 03: 2D and 3D docking image of SB01

The estimation of binding affinity of the ligand-receptor/protein complex is still a challenging task. Scoring functions (docking score) in docking programs take the ligand-receptor/protein poses as input and provides ranking or estimation of the binding affinity of the pose. These scoring functions require the availability of receptor/protein-ligand complexes with known binding affinity and use the sum of several energy terms such as van der Waals potential, electrostatic potential, hydrophobicity and hydrogen bonds in binding energy estimation. The second class consists of force field-based scoring functions, which use atomic force fields used to calculate free energies of

binding of ligand-receptor/protein complex. The docking score along with glide H-bond, glide erotb and glide ecoul of SB1 is higher than the other Schiff bases and ligand indicates SB1 is more preferably docked than others. The SB01 forms two hydrogen bonding with ALA273 and two pi-interactions with ARG220 and ARG137 amino acids of 3LAU while remaining forms only one hydrogen bonding with either ALA213 or GLU211 and SB05 does not forming any hydrogen bonding and pi-interaction.

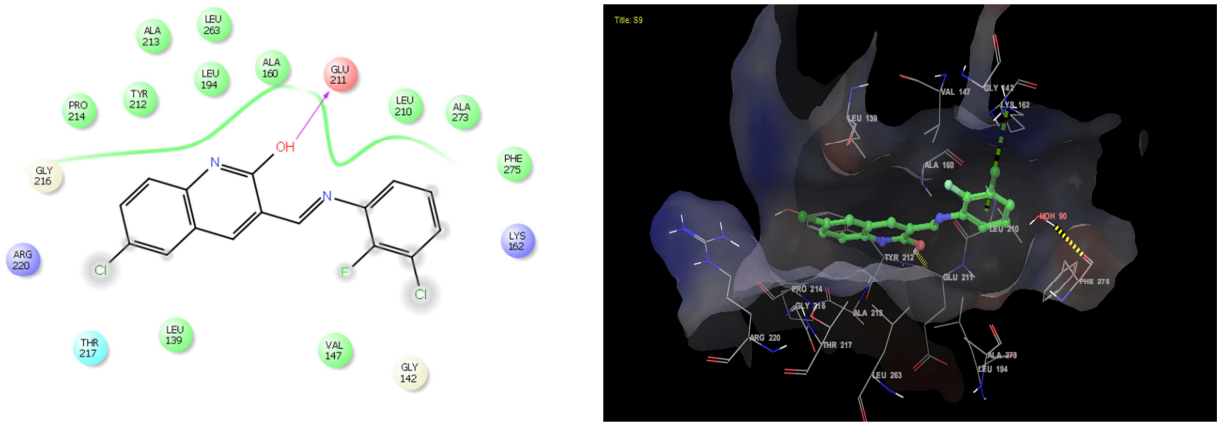


Figure 04: 2D and 3D docking image of SB02

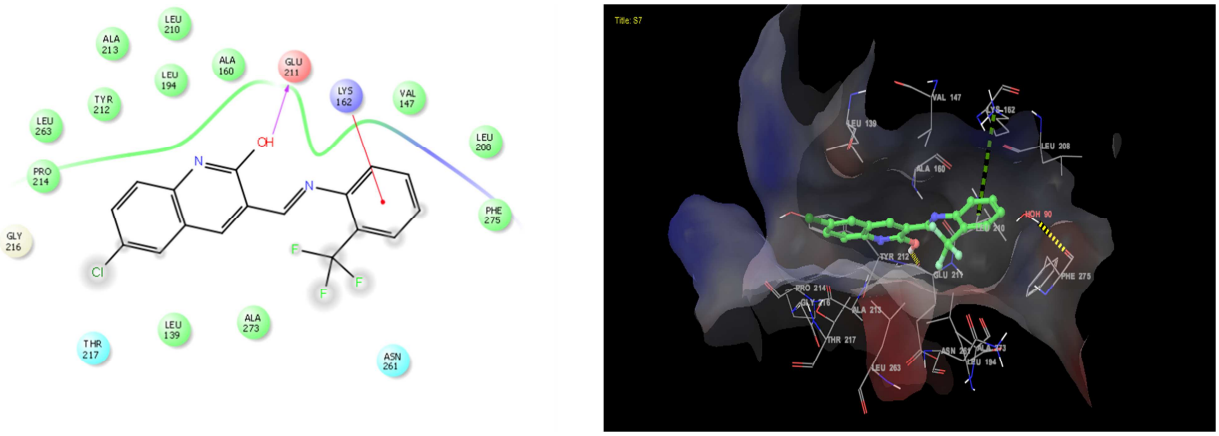


Figure 05: 2D and 3D docking image of SB03

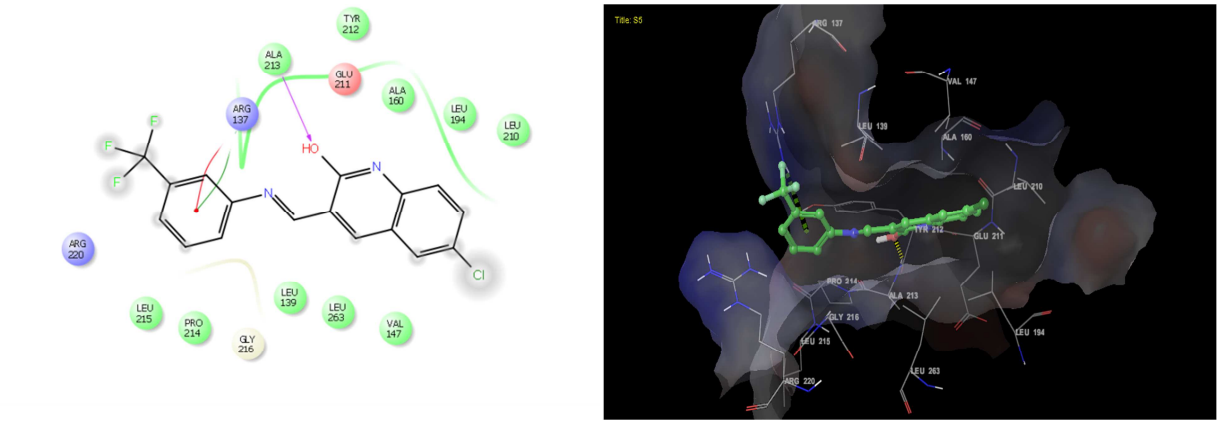


Figure 06: 2D and 3D docking image of SB04

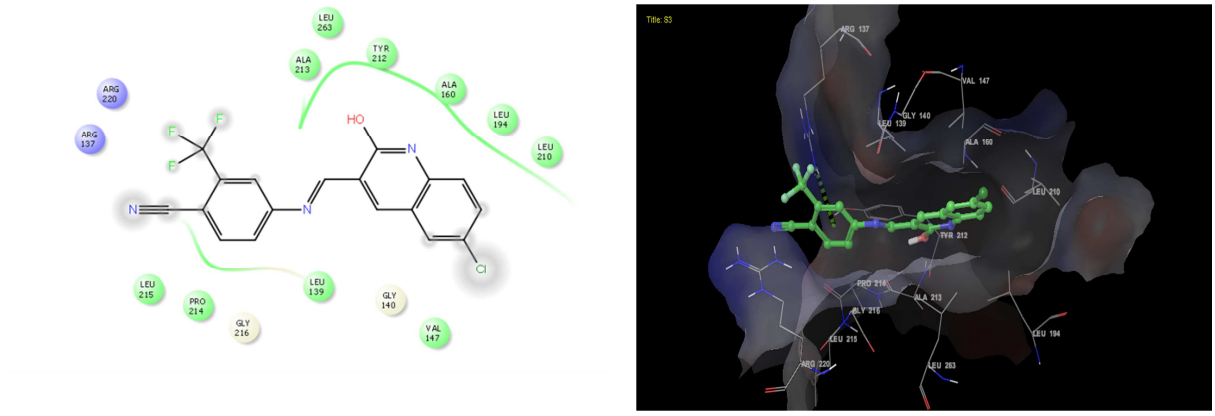


Figure 07: 2D and 3D docking image of SB05

2.5 FLUORESCENCE STUDY:

UV–Visible absorption spectra were recorded with UV spectrophotometer Shimadzu UV-1800 in quartz cells with 1 cm optical path length. Fluorescence spectra were measured on a Spectrofluorophotometer Shimadzu RF-5301pc and equipped with quartz cuvette of 1 cm path length using DMF as a solvent.

TABLE 02: The excitation and emission wavelength with intensity

Compound	Color of Compound	λ_{max} Absorption (intensity)	λ_{max} Emission (intensity)
SB01	Faint Yellow	309(1.16)	442(341.39)
SB02	Dark Yellow	308(3.00)	456(326.28)
SB03	Dark Yellow	304(2.78)	459(403.14)
SB04	Yellow	311(3.98)	451(530.31)
SB05	Faint Yellow	300(2.95)	456(213.67)
C01	Bright Yellow	396(2.11)	490(177.66)
C02	Dark Yellow	398(1.60)	455(168.16)
C03	Dark Yellow	395(1.34)	451(274.55)
C04	Shiny Yellow	394(1.18)	442(525.61)
C05	Dark Yellow	386(0.44)	375(905.38)
C06	Dark Green	396(1.60)	507(653.57)
C07	Green	398(0.79)	449(546.97)
C08	Green	396(0.69)	452(772.96)
C09	Green	395(2.11)	503(215.38)
C10	Yellowish Green	390(1.21)	377(184.02)

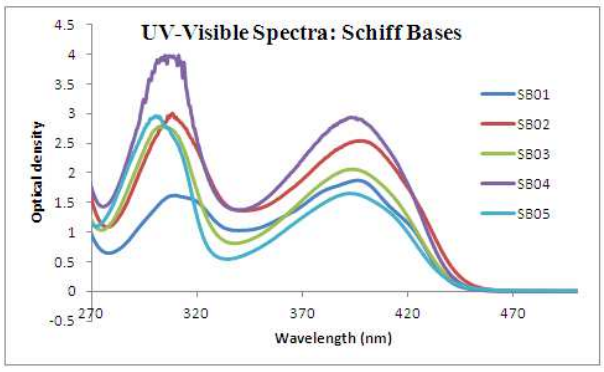


Fig. 08: UV-Visible absorption spectra of Schiff bases.

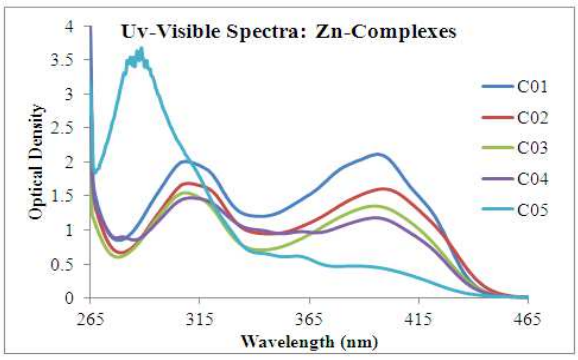


Fig. 09: UV-Visible Absorption Spectra of Zn(II) Complexes

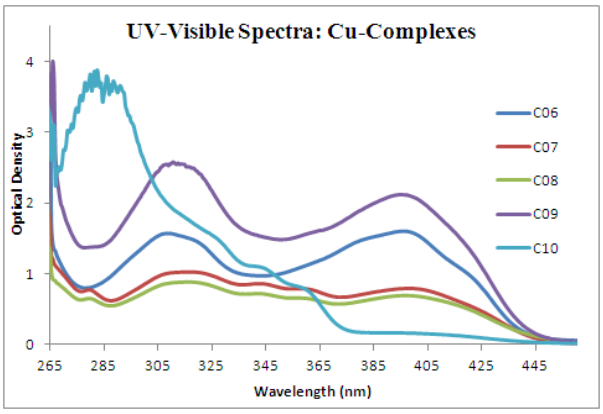


Fig. 11: UV-Visible Absorption Spectra of Cu(II) Complexes

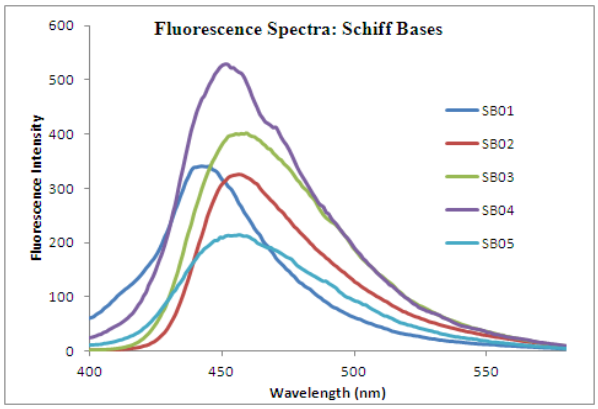


Fig. 12: Fluorescence Spectra of Schiff Bases

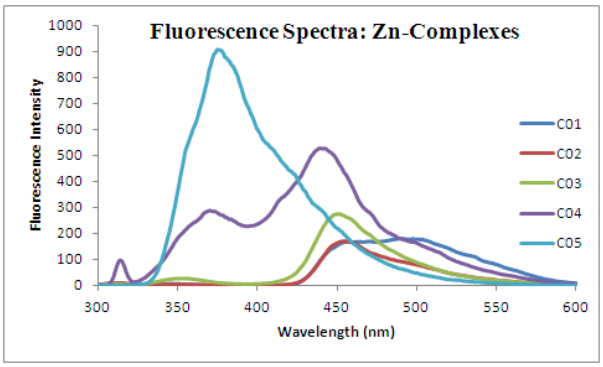


Fig. 13: Fluorescence Spectra of Zn(II) Complexes

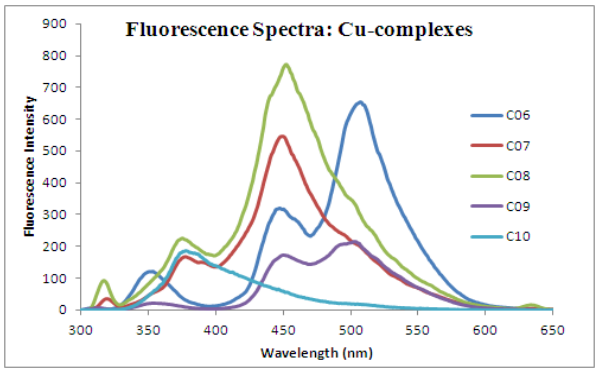


Fig. 14: Fluorescence Spectra of Zn(II) Complexes

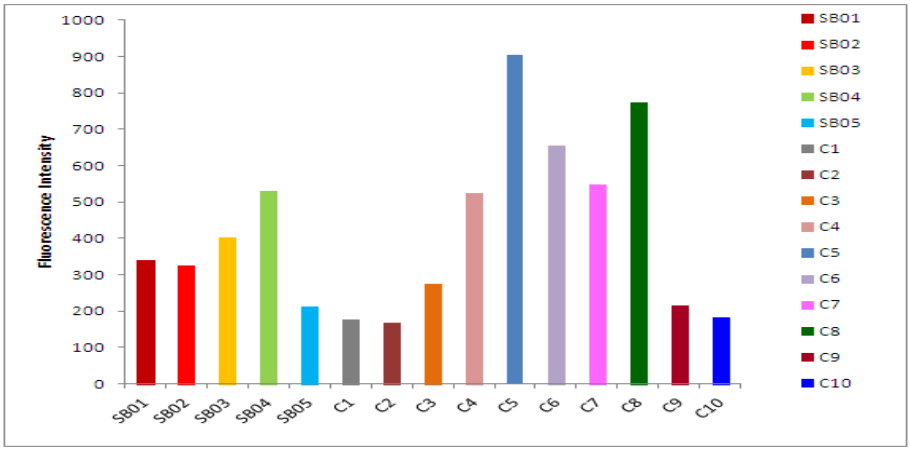


Fig. 15: Comparison of Intensity of Fluorescence

RESULTS AND DISCUSSION

Novel series of Schiff bases of quinoline were developed and characterized by H^1 NMR, FTIR and Mass Spectroscopy. The absorption spectra have shown broad peaks in a visible region assigned to metal-to-ligands charge transfer and UV region assigned to intraligand absorptions.

Copper complexes C06-C10 show red shift whereas Zinc complexes C01-C05 show blue shift as compared to their Schiff base ligand. It is observed that metal complexes [C01-C10] show hyperchromic shift when compared with

Schiff base ligands [SB01-SB05]. Emission intensity was improved when Schiff base ligands were complexed with Cu(II) and Zn(II) metal ions. The emission spectra of compounds SB01-SB05 showed emission band in the range of 442-459 nm and compounds C01-C10 showed emission band in the range of 375-507 nm.

All synthesized Schiff bases SB01-05 and 6-ClQA were docked with PDB 3LAU. SB01 show highest docking score. Among Schiff bases SB01 show minimum potential energy. Also SB01 Show two hydrogen bonding with ALA protein of 3LAU PDB. SB01, SB03 and SB04 show pi-pi interaction with different proteins of 3LAU. 6-ClQA show minimum glide energy.

CONCLUSION

We have designed and synthesized the Zn (II) and Cu (II) complexes of Schiff bases containing quinoline core. Zn (II) and Cu (II) complexes show improvement in fluorescence properties over Schiff base ligands. Schiff bases of quinoline show good docking score explains their biological applications in pharmaceutical area.

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