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ANTIMALARIAL ACTIVITY OF NEWLY SYNTHESIZED *N*-(8-HYDROXY QUINOLIN-5-YL)-2,4,6-TRIMETHYL BENZENESULFONAMIDE (8HQTBS) LIGAND AND THEIR METAL CHELATES

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ABSTRACT

The ligand namely *N*-(8-hydroxyquinolin-5-yl)-2,4,6-trimethylbenzene sulfonamide (8HQTBS) and its complexes with transition metals were synthesized using transition metal ions. Prepared ligand and their metal complexes were examined by the study of physicochemical properties, various spectral techniques, and magnetic susceptibility. Octahedral geometry of the transition metal complexes was proposed by spectral studies. The antimicrobial profile of prepared ligands and complexes (*In vitro*) showed better activity of ligands after metal complexation. Strong binding of transition metal complexes with CT-DNA was observed through the intercalation mechanism. A comparative molecular docking study between bacterial proteins and a DNA helix was performed, and the docking results obtained were in good agreement with the spectroscopic results. Some of the compounds showed good to moderate antimalarial activity.

Keywords: 8-Hydroxyquinoline, Sulfonamide, 8HQTBS, Molecular Docking Study, CT-DNA, Antimalarial Activity.

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INTRODUCTION

8-Hydroxyquinoline (8HQ) and its derivatives have been studied for wide-ranging biological applications like antibacterial, antifungal, anti-HIV, antileishmanial, antischistosomal agents as well as metal chelators for neuroprotection, metalloproteins, chelators, anticancer.[1] However, there are disadvantages to the uses of 8HQ and its derivatives as drug candidates like pharmacokinetics (ADMET) of 8HQs based drugs.[2] To reduce such limitations, 8-hydroxyquinoline (8-HQ) has been combined with other scaffolds to produce a biologically active molecule with superior efficacy and low toxicity.[3] Sulphonamides are proven therapeutics, against a wide bacterial spectrum and were taken as another biologically active scaffold earlier, such bacterial strains have developed resistance towards sulfonamides.[4,5] However, its use as a combination drug in the treatment of various diseases such as cancer, malaria, leprosy, and TB has been extended.[6] Hybrid compounds are more effective compared to multi-component drugs, because of drug-to-drug interactions.[7]

Therefore, the need for sulphonamides was increased in the treatment of diabetes, malaria psychosis, and tuberculosis.[8,9] Looking to the importance of the above two moieties, in continuation of our earlier work,[10-12] we were prompted towards carrying research on a new sulphonamide derivative namely 8HQTBS with a combination of 8-hydroxyquinoline and 2,4,6-trimethylbenzenesulfonylchloride.

EXPERIMENTAL

Chemicals and Reagents

All the chemicals and reagents used were of analytical grade and were obtained from Sigma-Aldrich.

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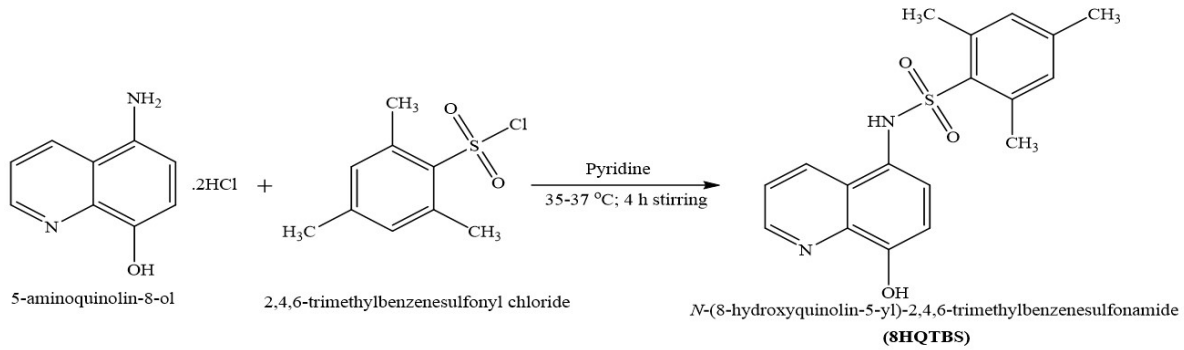
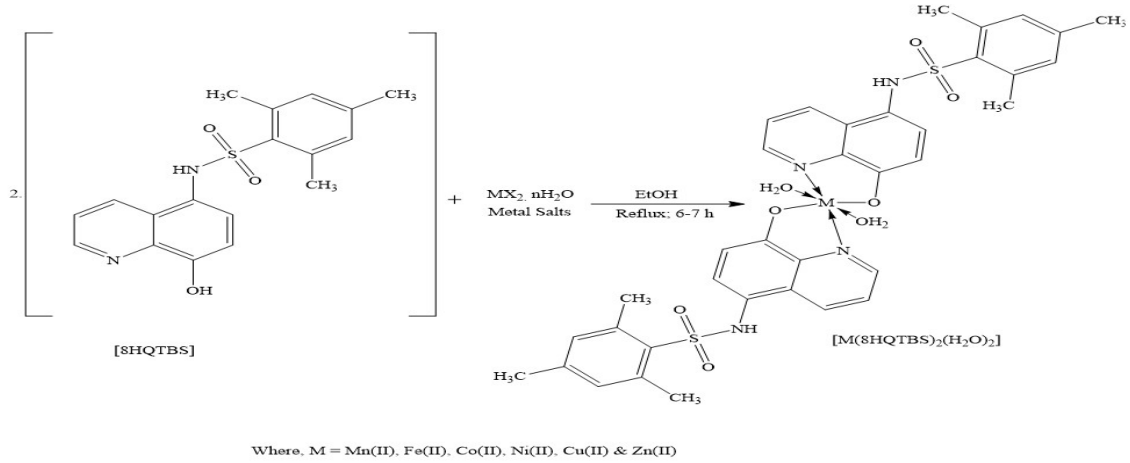
(i) Preparation of ligand N-(8-hydroxyquinolin-5-yl)-2,4,6-trimethylbenzenesulfonamide (8HQTBS)
0.75 mmol of 2,4,6-trimethylbenzenesulfonylchloride in pyridine was dissolved and the temperature of the reaction mixture was down to around 35 °C. 0.70 mmol of 5-amino-8-hydroxyquinoline di-hydrochloride in pyridine was added dropwise in the previous mixture and the mixture was stirred well for 6 h in the round bottom flask. The progress of the reaction was monitored by TLC. The obtained crude product was poured into an ice crust, and pH 6 is obtained by the addition of dilute hydrochloric acid. The light pink coloured precipitates so obtained were then filtered, properly rinsed out with water and organic solvents such as ethyl acetate, chloroform, and vacuum dried to achieve the target molecule.[13] The yield of the product was 89%. Reaction is given in Scheme 1.



Scheme-1: N, O-Donor Bidentate 8HQTBS Ligand Synthesis

(ii) Methodology of Metal (II) Complexes Synthesis of 8HQTBS Ligand
Transition metal complexes $(8HQTBS)_2M^{+2}$ was prepared with various divalent transition metal chlorides (Zn^{+2}, Cu^{+2}, Ni^{+2}, Co^{+2}, Fe^{+2}, and Mn^{+2}) and with previously formed ligand *N*-(8-hydroxyquinolin-5-yl)-2,4,6-trimethylbenzenesulfonamide (8HQTBS) in the stoichiometric ratio of 2:1 in the solvent ethanol at reflux conditions for 6-7 h. The pH was adjusted to ~ 8.5 using a very dilute alkali solution and the volume of the resultant mixture was reduced, followed by centrifugation. The product thus obtained was washed with distilled water followed by hot ethanol, after filtration, and was kept in vacuum desiccators to dry over calcium chloride.[14] The resultant yields of synthesized transition metal complexes were between 89-95%. Reaction Scheme-2 shows the synthetic procedure and the preliminary properties are represented in Table-1.



Scheme-2: Preparation Route of Metal Chelates Based on 8HQTBS Ligand

Biological Studies
Antibacterial and antifungal activity, DNA binding studies, Molecular Docking Studies, and antimalarial studies were performed using a standard protocol.[10-11]

RESULTS AND DISCUSSION

Physiochemical Properties

Analytical results and physiochemical properties of 8HQTBS ligand and its transition metals M(II) complexes supported the structure of synthesized compounds. Data shown in Table-1 of C, H, N, and M analysis, are in close conformity with the molecular formula of ligand and its metal (II) complexes as predicted.

Table-1: Preliminary Parameters of 8HQTBS and its Transition Metals Complexes

Ligand and Metal chelates (Chemical Formula)	Molecular Weight	Colour	Yield %	Melting Point (°C)	Elemental Analysis, % found (required)				
					C	H	N	S	Metal
8HQTBS ($C_{18}H_{18}N_2O_3S$)	342.41	Buff	89	245	62.16 (63.15)	5.40 (5.31)	8.15 (8.19)	9.08 (9.37)	--
$[Mn(8HQTBS)_2(H_2O)_2]$ ($C_{36}H_{38}MnN_4O_8S_2$)	773.78	Brown	92	257-259	53.14 (53.2)	3.59 (3.68)	10.88 (10.95)	8.26 (8.35)	7.11 (7.16)
$[Fe(8HQTBS)_2(H_2O)_2]$ ($C_{36}H_{38}FeN_4O_8S_2$)	774.69	Black	94	264 266	52.89 (52.94)	3.55 (3.66)	10.78 (10.89)	8.25 (8.31)	7.59 (7.61)
$[Co(8HQTBS)_2(H_2O)_2]$ ($C_{36}H_{38}CoN_4O_8S_2$)	777.77	Dark Yellow	93	268 270	52.91 (52.92)	3.68 (3.66)	10.78 (10.89)	8.28 (8.31)	7.58 (7.64)
$[Ni(8HQTBS)_2(H_2O)_2]$ ($C_{36}H_{38}N_4NiO_8S_2$)	777.53	Greenish Yellow	95	268 269	53.17 (53.13)	3.59 (3.67)	10.85 (10.93)	8.27 (8.34)	7.19 (7.29)
$[Cu(8HQTBS)_2(H_2O)_2]$ ($C_{36}H_{38}CuN_4O_8S_2$)	782.39	Yellowish Green	95	272 273	52.55 (52.61)	3.57 (3.64)	10.85 (10.83)	8.28 (8.26)	8.02 (8.19)
$[Zn(8HQTBS)_2(H_2O)_2]$ ($C_{36}H_{38}ZnN_4O_8S_2$)	784.22	Light Yellow	94	282 284	52.36 (52.48)	3.55 (3.63)	10.69 (10.8)	8.17 (8.24)	8.28 (8.4)

Mass Spectra of N-(8-hydroxyquinolin-5-yl)-2,4,6-trimethylbenzene sulphonamide (8HQTBS) Ligand

The mass spectrum of the 8HQTBS ligand shows a peak for the molecular ion at 341.41 m/z having relative abundance with the highest intensity belonging to the 8HQTBS ligand having a molecular weight of 342.41 gm/mole confirming that the target molecule is synthesized and is shown in Fig.-1.

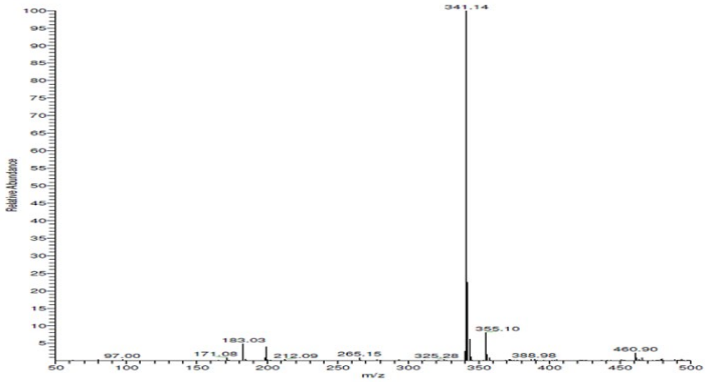


Fig.-1: Mass spectrum of 8HQTBS Ligand

In the mass spectrum of complex, $Cu(8HQTBS)_2(H_2O)_2$ at 781.98 m/z is the molecular ion peak of the complex, at 746.18 the small intense peak is the weight of complex after removal of water molecules present in the coordination with the structure of $Cu(8HQTBS)_2(H_2O)_2$, the peak at 342.04 m/z is of

remaining one 8HQTBS ligand present in the $Cu(8HQTBS)_2(H_2O)_2$. All these data suggest the formation of synthesized compounds.

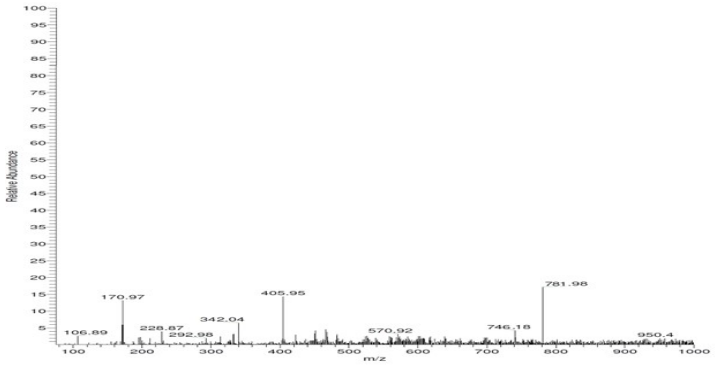


Fig.-2: Mass Spectrum of $[Cu(8HQTBS)_2(H_2O)_2]$ Complex

Infra-Red Interpretation of 8HQTBS Ligand and its Metal Complexes

IR spectra of synthesized 8HQTBS ligand are shown in Fig.-3 and its assignment is discussed herewith. Two bands at 3363 cm^{-1} and a sharp band at 1594 cm^{-1} correspond to stretching vibrations and bending vibrations of the O–H bond in the spectrum of the 8HQTBS ligand.[15] A sharp C–O stretching vibration band at 1071 cm^{-1} was attributed to the free 8HQTBS compound and its C–H stretching vibration of $–CH_2–$ showed at 2973 cm^{-1}.[16] 8HQTBS also showed some essential bands at 1635 cm^{-1} of C=C, at 1594 cm^{-1} of C=N and at 1446 cm^{-1} of C–C indicating the aromatic skeletal of the heterocyclic ring.[15] Further, a sharp band observed at 1332 cm^{-1} was assigned to S=O of the $–SO_2NH_2$ group, confirming the synthesis of the 8HQTBS ligand.[16] FT-IR spectra of 8HQTBS ligand showed some imperative characteristic differences upon coordination with metal salts. The broadband in the metal complexes spectrum at the region of 3410 cm^{-1} to 3425 cm^{-1}, confirms the participation of the free –OH group to form a coordination bond between the O - donor atom and the transition metal ions. Another difference was the shifting of the band at 1620 cm^{-1} to the lower frequencies due to C=N stretching vibration of 8-HQ moiety in 8HQTBS ligand, whereas the in-plane –OH deformation band at 1457 cm^{-1} shifted to lower frequencies in the case of metal complexes.[17,18] The above discussion confirms the formation of metal complexes with 8HQTBS ligand.

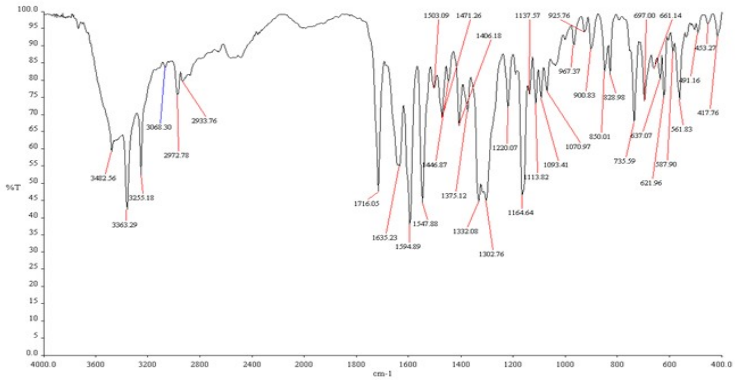


Fig.-3: Infra-Red Spectrum of 8HQTBS Ligand (cm^{-1})

Nuclear Magnetic Resonance Spectra of 8HQTBS

^{1}H-NMR Spectra

8HQTBS ligand is a buff-coloured compound and its ^{1}H-NMR spectrum was scanned at 400 MHz, DMSO-d_6, δ_H, ppm, 9.762 δ_H (1H of $–SO_2N\underline{H}–$), 8.830 δ_H (1H-Ar*H*, Py) 7.398 δ_H (2H Ar$\underline{H}$, C4 Py), 7.404 δ_H (1H py C3), 7.375 δ_H (Ar$\underline{H}$, 1H) 7.277 δ_H (Ar$\underline{H}$ benzene ring of Sulphonamide next to $–N\underline{H}–$), 9.986 δ_H (1H, of Aromatic –OH) 2.27 δ_H and 2.85 δ_H (9H, Ar–2,4,6-$C\underline{H}_3$) confirming the formation of 8HQTBS ligand and is shown in Fig.-4.

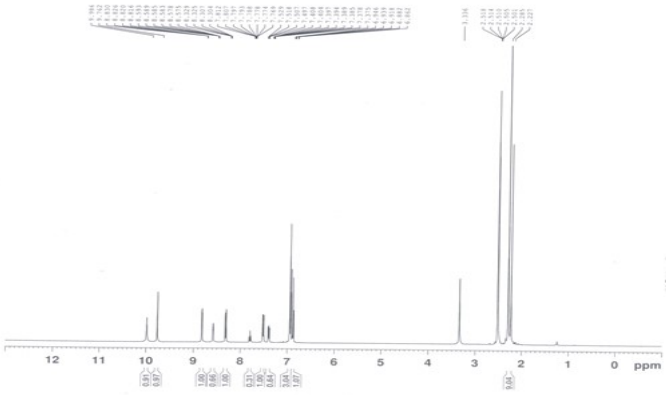


Fig.-4: ^{1}H-NMR Spectrum of 8HQTBS Ligand

^{13}C-NMR spectra of 8HQTBS

In the ^{13}C-NMR spectrum of 8HQTBS ligand, the peaks appeared between δ 110.28 - 152.81 ppm belonging to aromatic carbons and the peak appeared at δ 20.56 and 22.56 ppm of 2,4,6-trisubstituted - CH_3 group confirming the structure of 8HQTBS ligand and is shown in Fig.-5.

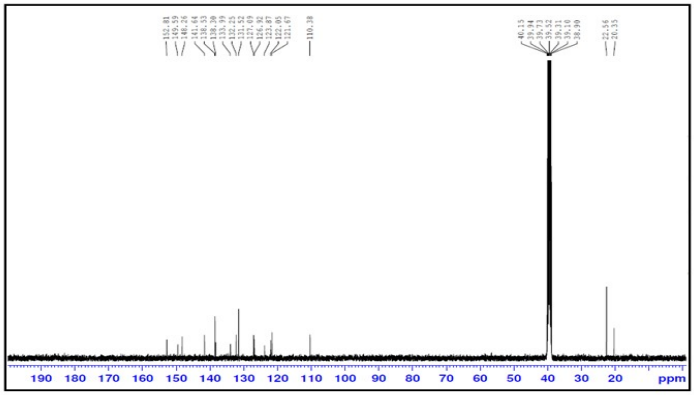


Fig.-5: ^{13}C-NMR Spectrum of 8HQTBS Ligand

Electronic Spectral Data

The electronic spectral results of 8HQTBS ligand and its metal complexes were measured in DMSO solvent in the range of 200 to 800 nm and the value of magnetic susceptibility of metal complexes was calculated using the Gouy method. The data obtained are listed in Table-2 and maximum absorption is shown between 300-700 nm as shown in Fig.-6. Studies support the formation of octahedral (Oh) and distorted octahedral geometry for all the metal complexes.[19, 20]

Table-2: Results of Electronic Spectra

Ligand and its Metal chelates	λ nm	Absorbance	Transition observed	Magnetic susceptibility values	Suggested structure
8HQTBS	320 390 485	0.88 0.35 0.19	π→ π* n→ π* n→ π*	--	--
$[Mn(8HQTBS)_2(H_2O)_2]$	265 355 600	0.90 0.34 0.19	π→ π* Ligand field[3] $^{6}A_{1g}(F)\rightarrow {}^{4}T_{2g}(D)$	5.77	Distorted Octahedral
$[Fe(8HQTBS)_2(H_2O)_2]$	268 390 615	0.85 0.31 0.15	π→ π* Ligand field[3] $^{5}T_{2}g\rightarrow {}^{5}Eg(D)$	5.12	Octahedral
$[Co(8HQTBS)_2(H_2O)_2]$	268 315 520 770	0.90 0.34 0.19 0.11	π→ π* Ligand field[3] $^{4}E_{2g}(F)\rightarrow {}^{2}T_{2g}$ $^{4}T_{1g}(F)\rightarrow {}^{4}T_{2g}(F)$	4.25	Octahedral

$[Ni(8HQTBS)_2(H_2O)_2]$	256 415 651	0.79 0.34 0.19	$\pi\rightarrow\pi^*$ $^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)$ $^3A_{2g}(F)\rightarrow{}^3T_{2g}(F)$	2.90	Octahedral
$[Cu(8HQTBS)_2(H_2O)_2]$	258 315 469	0.90 0.34 0.19	$\pi\rightarrow\pi^*$ Ligand field[3] $^2B_1g\rightarrow{}^2Eg$	1.75	Distorted Octahedral
$[Zn(8HQTBS)_2(H_2O)_2]$	261 315 469	0.89 0.34 0.19	$\pi\rightarrow\pi^*$ Ligand field[3] L→M	0	Distorted Octahedral

Magnetic susceptibility values indicate the paramagnetic nature of all the complexes except the Zn(II) complex showed diamagnetic nature.

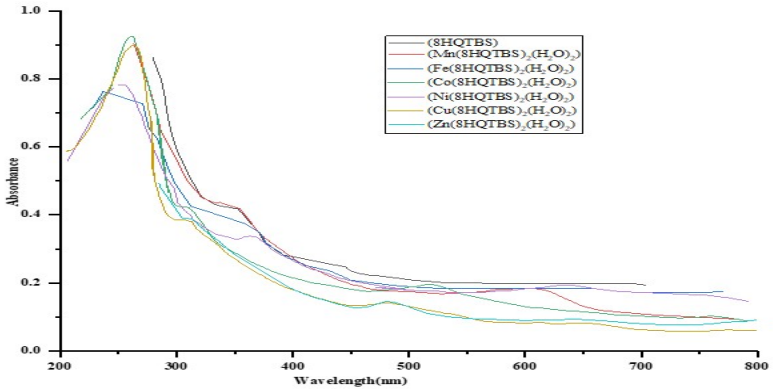


Fig.-6: UV absorption Spectra of 8HQTBS Ligand and its Metal Chelates

Biological Studies

***In vitro* Antimalarial and Antimicrobial Activity**

In vitro, antimalarial and antimicrobial studies of synthesized ligands 8HQTBS and their transition metal (II) chelates were carried out against strains of *Plasmodium falciparum* and two Gram^{+ve} (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram^{-ve} (*Pseudomonas aeruginosa* and *Escherichia coli*) bacterial strains. For antifungal activity, *Aspergillus niger* and *Aspergillus flavus* fungal strains were used. The study was carried out by Microcar Lab, Surat, Gujarat, India. Results are shown in Tables-3 and 4. The results of the study suggested the antimalarial potency of 8HQTBS ligand and its metal complexes is good to moderate. The antimalarial activity with IC_{50} 0.52 µg/m has been observed for, the 8HQTBS ligand, while its metal complexes have 0.32 to 1.56 µg/ml. Here, the obtained data from IC_{50} values are 0.32 and 0.45 µg/ml respectively, of Fe(II) and Zn(II) metal complexes, showing excellent activity on the malaria parasite. However, moderate activity was observed by other complexes as shown in Table-4. The antimalarial potency order for metal complexes is higher for Fe(II) and lower for Ni(II) complexes. Similarly, the antimicrobial activity of ligand 8HQTBS and their metal complexes was determined by the broth dilution method, and minimum inhibitory concentration was also determined. The results of MIC for gram^{+ve} and gram^{-ve} bacterial strains suggested the lowest concentration at which the growth was inhibited in the range of 50-125 µg/mL for ligand and metal complexes. The MIC values of the newly synthesized compounds were compared with standard drugs (ampicillin, chloramphenicol, nystatin, and griseofulvin) suggesting lower MIC values of ligands and their metal complexes compared to ampicillin standard and higher than chloramphenicol, nystatin, and griseofulvin).[20-22] The observed bactericidal activity was higher in Gram^{+ve} bacteria in contrast to the Gram^{-ve} bacteria because the 8HQTBS ligand has 8-HQ as a parent moiety, which forms complexes with the metal ion to form a lipophilic complex, which aids in the transportation of the compound inside the cell membrane of Gram^{+ve} bacteria. Whereas the effect on Gram^{-ve} bacteria was less, maybe due to the selective transport barrier of its cell wall, while antifungal activity was moderate. It showed that upon metal complexation formation, the antimicrobial potency of the 8HQTBS ligand increases. Perhaps the substitutions at the fifth position of 8-hydroxyquinoline increase the bioactivity of potent compounds and the increased lipophilic character of metal complexes.

Table-3: Antimalarial Activities of 8HQTBS and its Metal Complexes (IC_{50} values)

Ligand and Metal complexes	IC_{50}(µg/mL)
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)manganese	0.65
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)iron	0.32
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)cobalt	0.98
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)nickel	1.56
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)copper	0.75
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)zinc	0.45
Ligand (8HQTBS)	0.52
Chloroquine	0.020
Quinine	0.268

DNA Binding Studies

The interaction study of 8HQTBS and their metal complexes with DNA (Calf thymus DNA) were carried out to understand the binding affinity of synthesized 8HQTBS ligands and their metal complexes with DNA helix. For this purpose, absorption spectroscopy (Ultraviolet-Visible), viscosity measurements, and agarose gel electrophoresis methods were used.

Ultraviolet-Visible Absorption Spectroscopy Study

UV - absorbance spectra were recorded by absorption titration to determine the DNA binding affinity of the 8HQTBS ligand and its metal complex with CT-DNA and is shown in Fig.- 7. The intrinsic binding constant (K_b) values were calculated for 8HQTBS ligand and its metal (II) complexes, for that a graph plotted against [DNA]/($\varepsilon_a - \varepsilon_f$) *versus* [DNA] from its ratio of slope to Y–intercept and by monitoring the change in, the UV-Vis absorption spectroscopy study, a hypochromic shift was observed upon complexation of 8HQTBS with CT-DNA, suggesting intercalating binding mode. The K_b values of metal complexes were less than the value of EtBr but higher than the 8HQTBS ligand value.

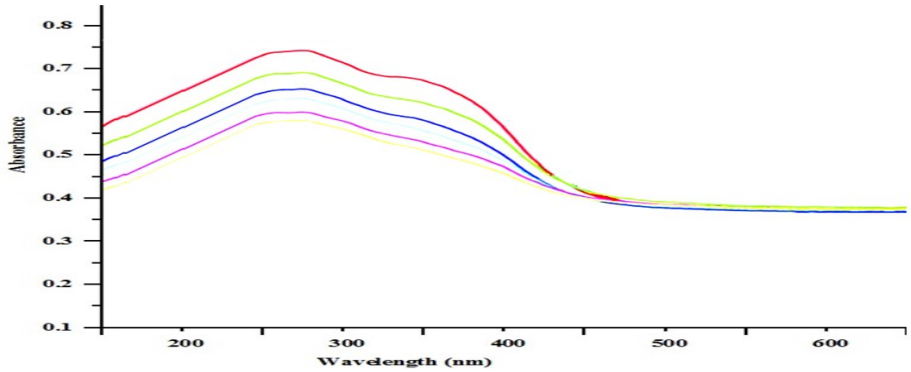


Fig.-7: UV - Visible Spectra after the Addition of CT-DNA to the Solution of $Ni(8HQTBS)_2(H_2O)_2$ Metal Chelate [Arrow Indicates the Change in Absorption with Increase in DNA Concentration]

Also, the binding constant (K_b) values of all the metal chelates of 8HQTBS, were found to be near to ethidium bromide (EtBr), a standard intercalating agent, K_b value 7×10^7 M^{-1}, which proves that the metal chelates of 8HQTBS are intercalating well to the DNA, while the K_b values of 8HQTBS ligand were very less than that of their metal chelates, which suggests their less binding affinity towards DNA helix. The study results conclude the higher binding affinity of 8HQTBS metal complexes towards DNA than ligands. The observed K_b values for all the metal complexes suggest that they bind to CT-DNA through intercalation binding mode and the values are comparable to that of EtBr binding constant value.

Table-4: K_b Values from Absorption Titration of 8HQTBS Ligand and Metal Complexes

Compounds name	$K_b \times 10^5\ M^{-1}$
8HQTBS *ligand*	0.9198
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)manganese	3.1288
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)iron	2.0427
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)cobalt	2.8137
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)nickel	3.9132
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)copper	2.7196
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)zinc	2.0514

Viscosity Measurement

DNA Binding Study by Viscosity Measurement

Viscometry was conducted using Ubbelohde viscometer to support the mode of binding between ligands, metal complexes, and DNA. As observed in the graph [Fig.-8] the increases in viscosity explain that the compounds are interacting with the DNA helix by intercalation mode.

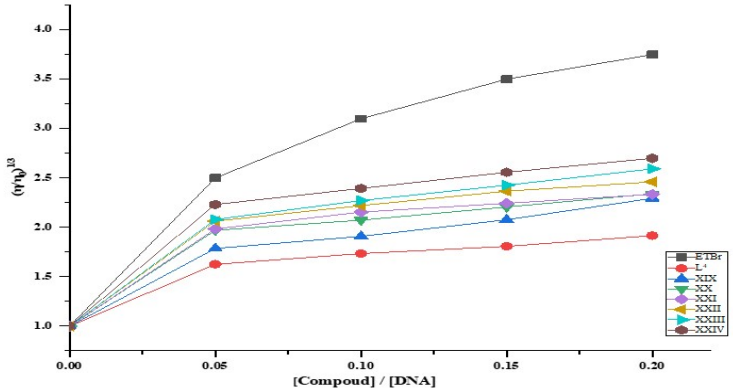


Fig.-8: Results of Viscosity Study of Ligand (8HQTBS) and its Metal(II) [$M(8HQTBS)_2(H_2O)_2$] Complexes

The viscosity of the solutions of all the synthesized compounds was found to be increasing on increasing the concentration of the compounds. This indicates that the synthesized compounds bind with CT-DNA through classical intercalative binding mode and it also supports the results of UV-Visible studies.[23,24] The compounds with their increasing viscosity orders are:

8HQTBS < $Mn(8HQTBS)_2(H_2O)_2$ < $Fe(8HQTBS)_2(H_2O)_2$ < $Co(8HQTBS)_2(H_2O)_2$ < $Ni(8HQTBS)_2(H_2O)_2$ < $Cu(8HQTBS)_2(H_2O)_2$ < $Zn(8HQTBS)_2(H_2O)_2$ < EtBr

Agarose Gel Electrophoresis

Gel electrophoresis is used to study the change in the electrophoretic migration of DNA in the absence and presence of 8HQTBS ligand and its metal complexes and its electro-phoretogram represented in Fig.-9. The electro-phoretogram showed that upon addition of 8HQTBS and metal complex to DNA solution (represented in a lane - 2 to lane - 8 respectively) migration of CT-DNA (Lane-1) had been slowed down, supporting the interaction of complex-DNA via intercalation.[25]

The viscosity measurement study data reveals that the viscosity of CT-DNA was found to be increased upon the addition of metal chelates of 8HQTBS, which proved the intercalation binding mode. Further, the agarose gel electrophoresis study showed a retardation motion in the run inside the gel matrix of the DNA complex with metal chelates of 8HQTBS in comparison to DNA. This holdup in the migration rate of DNA is due to the increase in the weight of DNA because of the intercalation of the 8HQTBS compound on it. This informs that the synthesized compound 8HQTBS binds well to the DNA helix by intercalation mode.

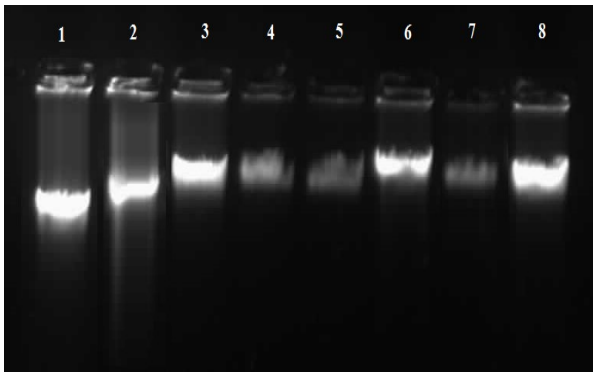


Fig.-9: Image of Agarose Gel Electrophoresis Study of Lane 1 CT-DNA, Lane 2 8HQTBS, and Lane-3 to Lane-8 are of Metal Chelates of Transition Metals (Mn, Fe, Co, Ni, Cu, Zn) Respectively

Computational Studies

In-silco ADMET and Pharmacokinetic Studies

Pharmacokinetic parameters of 8HQTBS ligand and its metal chelates were studied using OSIRIS Data Warrrior 4.7.2 program and pre-ADMET web server as a tool.[26] *In silico* ADMET properties prediction of the synthesized 8HQTBS ligand and its metal chelates were screened on the pre-ADMET tool, a web-based application. 8HQTBS ligand follows the Lipinski rule, where one rule violation is observed in the case of metal complexes as their molecular weight is higher (> 500). Tropical polar surface area (TPSA) values of 8HQTBS ligand and metal complexes are below 140 Å, which falls under the permeability index. The predicted values and related ADMET properties are shown in Table-5.

The above data shows that there is an association between BBB, % HIA, $Caco_2$, % PPB, and MDCK suggesting that 8HQTBS ligand and its metal chelates have low absorbance to CNS, middle permeability to $Caco_2$ and good human intestinal absorbance. No compound showed any kind of toxicity *in silico*. Therefore, the 8HQTBS ligand and its metal chelates can be a good drug candidate with high lipophilicity, good bioavailability, and less toxicity.

Table-5: Evaluation of Pharmacokinetic Parameters of 8HQTBS Ligand and its Metal Chelates

Name of Compounds	M.W.	Log P	Log S	H-Acceptor	H-Donor	TPSA
8HQTBS ligand	342	2.16	-4.69	5	2	87.7
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)manganese	773	4.51	-14.95	10	2	136.2
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)iron	774	4.51	-14.95			
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)cobalt	777	4.51	-14.95			
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)nickel	777	4.51	-14.95			
bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)copper	782	4.51	-14.95			

bis((5-((2,4,6-trimethylphenyl)sulfonamido)quinolin-8-yl)oxy)zinc	784.22	4.51	-14.95			

Molecular Docking

Molecular docking studies were carried out using AUTODOCK 4.2 package and the binding energy of prepared compounds was investigated based on its empirical scoring function.[27] The results were further visualized by using PyMol and BioDiscovery studio Visualizer software packages in 2D and 3D conformation.[28] The docking results thus obtained were compared with chloramphenicol standard reference drug by the reported method,[29] data are shown in Table 6 and are shown in Fig.-10 to 15.

Table-6: *In silico* Molecular Docking Studies of 8HQTBS Ligand and its Metal Chelates with Bacterial Proteins (represented with PDB: IDs) in Terms of Binding Affinity (kcal/mol)

Selected protein	Binding affinity for different proteins (kcal/mol)							
	8HQTBS	[Mn(8HQTBS)$_2$(H$_2$O)$_2$]	[Fe(8HQTBS)$_2$(H$_2$O)$_2$]	[Co(8HQTBS)$_2$(H$_2$O)$_2$]	[Ni(8HQTBS)$_2$(H$_2$O)$_2$]	[Cu(8HQTBS)$_2$(H$_2$O)$_2$]	[Zn(8HQTBS)$_2$(H$_2$O)$_2$]	Chloramphenicol
5H67	-7.6	-7.6	-7.6	-7.6	-7.6	-7.6	-7.6	-7.6
3TY7	-7.5	-7.5	-7.5	-7.5	-7.5	-7.5	-7.5	-7.5
3T88	-7.1	-7.1	-7.1	-7.1	-7.1	-7.1	-7.1	-7.1
3P3E	-7.4	-7.4	-7.4	-7.4	-7.4	-7.4	-7.4	-7.4

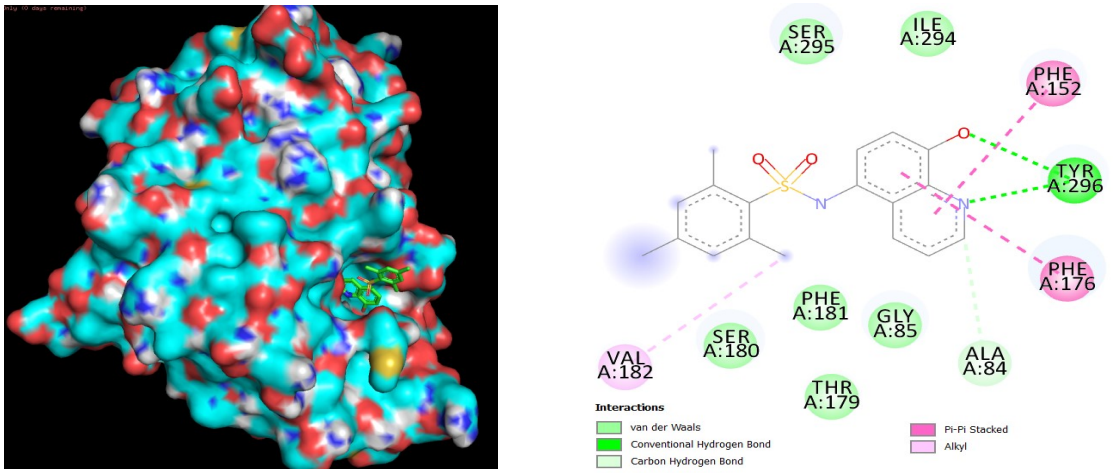


Fig.-10: Docked Image View of 8HQTBS Ligand Docked with Bacterial Protein (PDB ID: 3P3E) 3D (left) and 2D (right) View

A molecular docking study of 8HQTBS ligand and its metal chelates was made to dock compounds with DNA helix (PDB ID: 1BNA) to study the type of interaction involved.[29,30] It was observed that all the metal chelates were binding to the DNA helix by threading intercalation mode. The metal complexes were found to be intercalated into the G-C-rich region of the DNA employing π—π stacking interactions and hydrogen bonding, which is shown in Fig.- 16. The binding affinity was > -11 kcal M^{-1}, of all the metal chelates, which were found to be better than chloramphenicol drug, the value obtained suggests that the synthesized metal complexes bind tightly with DNA helix and showed good binding affinity in the receptor pocket compared to chloramphenicol. Overall, compared to its parent ligand 8HQTBS, the binding affinity of metal chelates was higher and these results are in resemblance concordance with *in*

vitro studies, wherein the metal complexes are binding more strongly than ligand 8HQTBS and chloramphenicol.

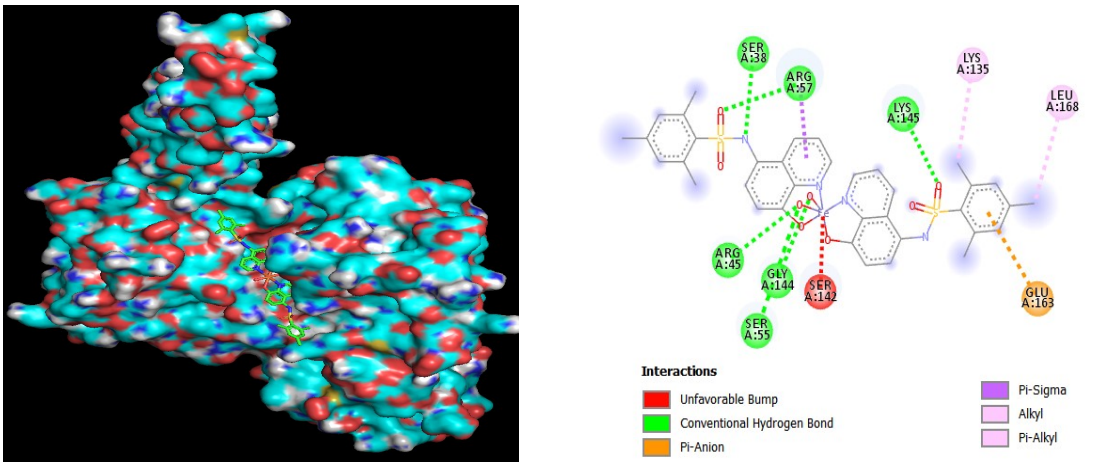


Fig.-11: Docked Image View of [Fe(8HQTBS)$_2$(H$_2$O)] Metal Chelate Docked with Bacterial Protein (PDB ID: 5H67) 3D (left) and 2D (right) View

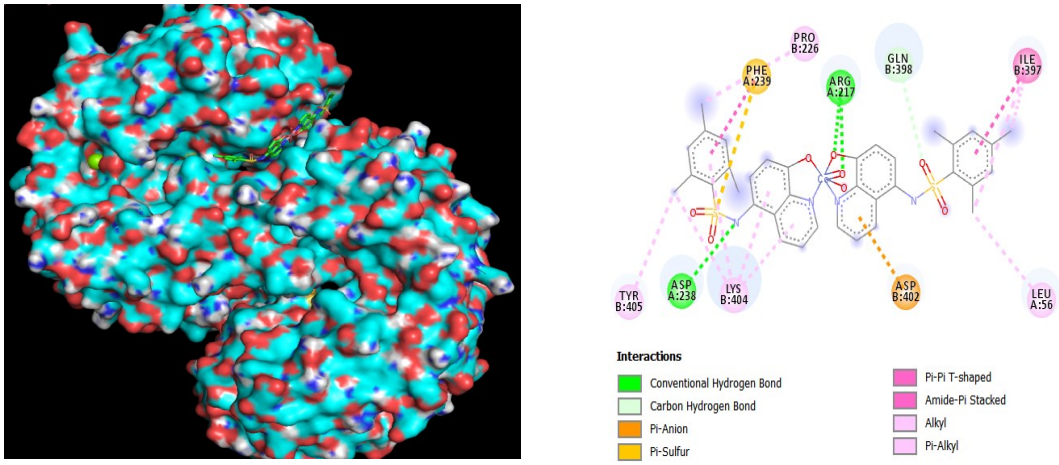


Fig.-12: Docked Image View of [Co(8HQTBS)$_2$(H$_2$O)] Metal Chelate Docked with Bacterial Protein (PDB ID: 3TY7) 3D (left) and 2D (right) View

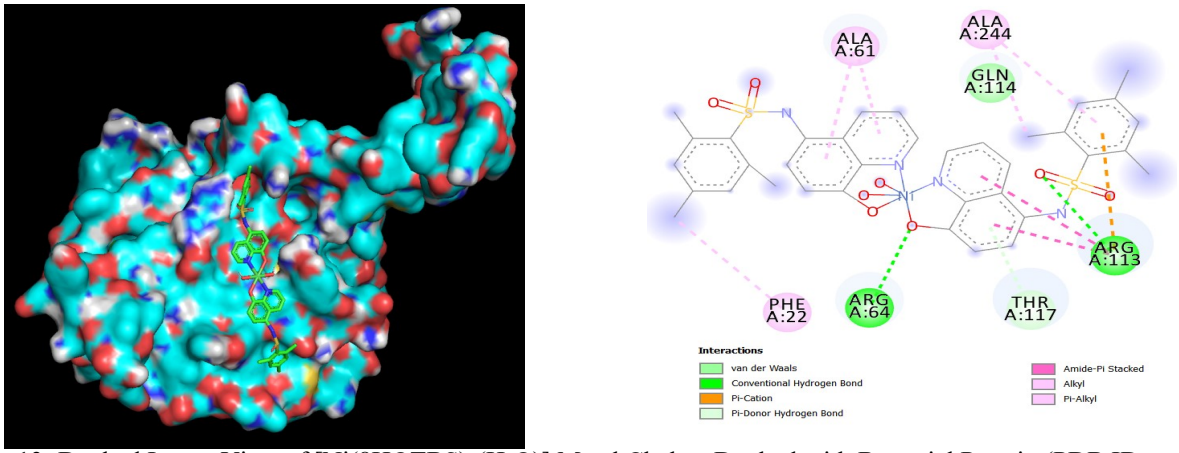


Fig.-13: Docked Image View of [Ni(8HQTBS)$_2$(H$_2$O)] Metal Chelate Docked with Bacterial Protein (PDB ID: 3T88) 3D (left) and 2D (right) View

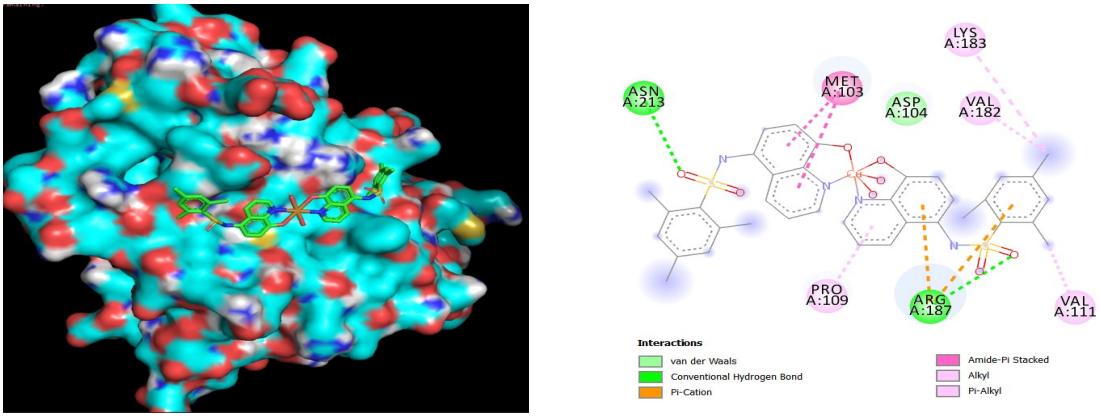


Fig.-14: Docked Image View of [Ni(8HQTBS)$_2$(H$_2$O)] Metal Chelate Docked with Bacterial Protein (PDB ID: 3P3E) Bi 3D (left) and 2D (right) View

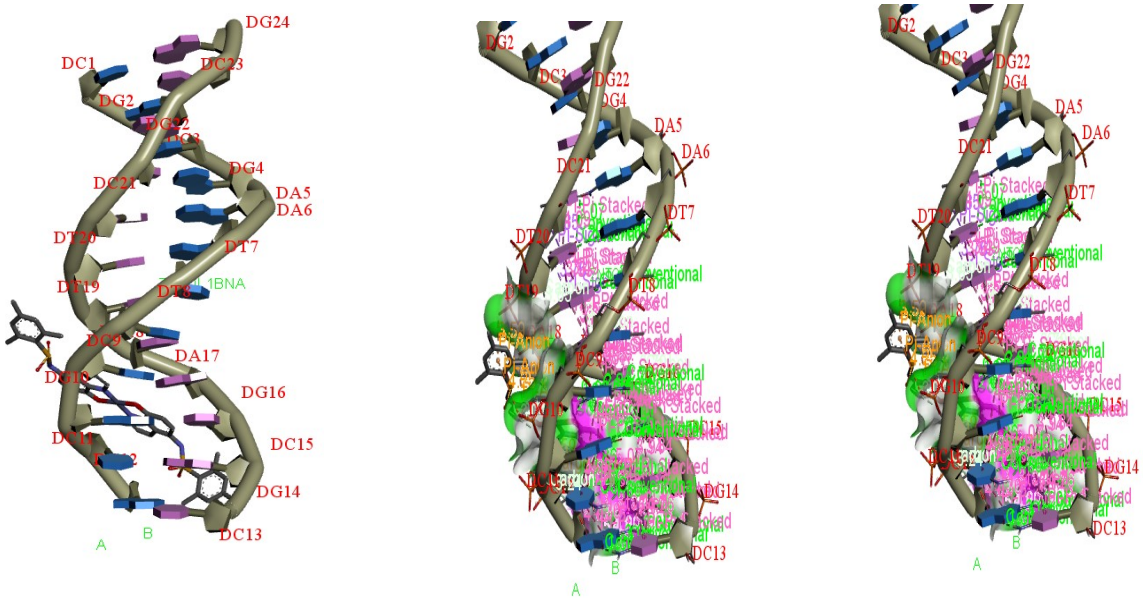


Fig.-15: Binding Via Intercalation of [(Cu-8HQTBS)$_2$(H$_2$O)$_2$] Metal Chelate (Stick Presentation) is shown with DNA (PDB ID: 1BNA)

CONCLUSION

A brief report from the present study reveals that a new N-(8-hydroxyquinolin-5-yl)-2,4,6-trimethylbenzenesulfonamide (8HQTBS) ligand and its transition metal complexes were synthesized and characterized well. Spectral and magnetic susceptibility analysis confirms the octahedral geometry of metal complexes. *In vitro*, biological screening results showed that the 8HQTBS ligand and its metal complexes have a good antimicrobial and antimalarial profile. Cu(II), Fe(II) and Ni(II) metal complexes showed better antibacterial and antifungal potential than Zn(II), Mn(II), and Co(II) complexes. DNA binding study showed the mode of intercalation type of binding. Besides this *In silico* study data, suggests that binding affinity with different bacterial proteins of ligand and metal complexes was supported by the experimental results. The binding affinities towards CT-DNA were better than chloramphenicol for the 8HQTBS ligand and its metal complexes. Moreover, *In-silico* pharmacokinetic parameters are in good agreement with a drug-like candidature of compounds. Anti-malaria potency of Fe (II) and Zn(II) metal complexes was observed most excellent with IC_{50} values of 0.32 and 0.45 µg/ml respectively.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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