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Synthesis, Characterization, Swiss ADME and Antimicrobial Activity of Copper (II) Complex with 2-Sulfanilamidopyrimidine: Through DFT Spectroscopic with Profound Biological Implications

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Sulphadiazine and their copper metal complexes are dexterous ligands, which are condensation products of primary amines with carbonyl compounds gaining importance day by day in the present scenario. Spectral characterization and examination of the potential antimicrobial and antioxidant activity of the synthesized complex were performed. The imine Cu(II) complex is characterized by FTIR and UV/Vis spectroscopy. The Stoichiometric M:L ratio was determined by Joe and Jones method. These compounds and their copper metal complex are very important in various biological systems and their medicinal and pharmaceutical fields. Schiff foundations show beneficial natural functions such as anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic, and antiglycation. The present review summarizes information on the diverse biological activities and also highlights the recently synthesized numerous Schiff bases and their metal complex as potential bioactive core.

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Keywords: Biological activity; swiss ADME; sulphadiazine; Cu^{2+} metal complexes; bioactive core.

1. INTRODUCTION

Metal structures play an important role in agriculture, pharmacy and industry. Ligand, a metal surrounded by a set of ions or molecules, is used to prepare complex substances called Schiff bases which are products of the dissolution of essential amines and aldehydes or ketones (RCH = NRC, also representing alkyl and / or aryl substituent's.Schiff properties such as stimulants, in various biological systems, polymers and dyes, among other uses such as contraceptives and enzymatic agents. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory [1-4], analgesic [2–5], antimicrobial [6,7], anticonvulsant [8], antitubercular [9], anticancer [10,11], antioxidant [12], anthelmintic [13], and so forth. The nitrogen atom of azomethine may be involved in the formation of a hydrogen bond with the active centers of cell constituents and interferes in normal cell processes [14,15]. Apart from biological activities, Schiff bases are also used as catalysts, intermediates in organic synthesis, dyes, pigments, polymer stabilizers [16], and corrosion inhibitors [17]. Studies enlightened that metal complexes show greater biological activity than free organic compounds [18].Augmentation of biological activity was reported by implementation of transition metals into Schiff bases [19]. Schiff bases played an influencing role in development of coordination chemistry and were involved as key point in the development of inorganic biochemistry and optical materials [20]. Schiff bases have been utilized as synthons in the preparation of a number of industrial and biologically active compounds like formazans,4-thiazolidinines, benzoxazines, and so forth, via ring closure, cycloaddition, and replacement reactions [21]. Schiff base derivatives in various processes promoted the researchers for designing of novel heterocyclic/aryl Schiff bases for development of new environmental-friendly technology [22]. Due to the excellent stability of Schiff bases for specific metal ions such as Al(II), Co(III), Ag(II), Gd(II), Cu(III), Hg(II), Ni(II), Pb(II), Y(III) and Zn(II), a large number of different Schiff base ligands have been used as carriers in potentiometric sensors, due to catalytic properties of Schiff bases exhibit the catalytic activity in the hydrogenation of olefins.One of the most interesting uses of these compounds is that they may be used as effective corrosion inhibitors. These are characterized by the presence of azomethine grouping (>C=N-) which offers one of the possible coordination sites through the donor nitrogen atom. Other functional groups such as –OH, -SH, -NH or –COOH etc. present in the molecule at suitable sites help in the formation of stable chelate rings. Depending upon the number of possible donor sites available in the molecule, Schiff bases are referred to as bi, tri, tetra, penta, hexa or polydentate ligands. It is desirable to investigate the reaction of tri and tetra-dentate ligands with transition metal ions to gain information concerning the coordination chemistry of these molecules in an unsymmetrical environment. Several studies have shown that the in vitro biological evaluation of free compounds against various pathogenic bacterial strains are less powerful than their complexes with metals, such as copper, nickel, zinc, and cobalt. [23]. The ligand and complexes were screened for antibacterial activity against Escherichia coli and Staphylococcus aureus, and antifungal activity against Aspergillums Niger and Candida albican, using discs diffusion method. It has been found that the ligand and the complexes showed different activities against microorganisms. The complexes show higher activity than the free Schiff base ligand [24].

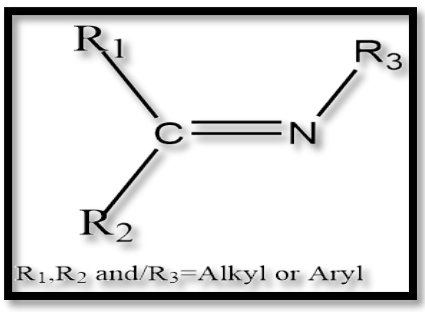


Fig. 1. General Structure of Schiff base

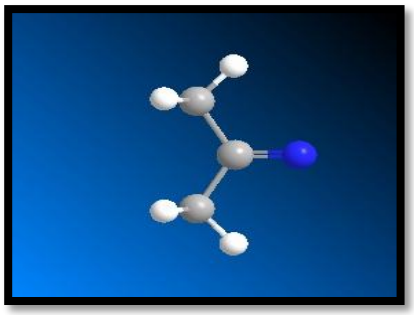


Fig. 2. 3D Structure of Schiff base

1.1 Metal Complex with Sulphadiazine Drug Moiety

The sulfonamides and their structurally related derivatives, such as the sulfamates and sulfamides, possess the general formula A-SO_2NHR, in which the functional group is either directly bound to an aromatic, heterocyclic, aliphatic, or sugar scaffold (of type A), or appended to such a scaffold via a heteroatom, most frequently oxygen or nitrogen (leading thus to sulfamates and sulfamides, respectively) [25,26,27,28]. It interferes with PABA (p-aminobenzoic acid) in the biosynthesis of tetrahydrofolic acid, which is a basic growth factor essential for themetabolic process of bacteria. N-Substituted sulfonamides are still among the most widely used antibacterial agents in the world, mainly because of their low cost, low toxicity, and excellent activity against bacterial diseases. Many activities apart from carbonic anhydrase have been recently reviewed that include endotel in antagonism, anti-inflammatory, tubular transport inhibition, insulin release and saluretic activity. The results showed that the complexes with five-membered heterocyclic rings were more active than the free sulfonamides while the pyrimidine, pyridine and pyridazine complexes had similar or less activity than the free ligands. In order to find an explanation for this behavior lipophilicity and superoxide dismutase-like activity were tested, showing that the [Cu(sulfamethoxazol)2(H_2O)$_4$]·3H_2O presented the highest antimicrobial potency and a superoxide dismutase-like activity comparable with pharmacological active compounds. Two kinds of complexes were obtained with the stoichiometries [Cu(L)2]· H_2O and [Cu(L)2(H_2O)$_4$]H_2O, which were characterized by infrared and electronic spectroscopies. The antimicrobial activity was evaluated for all the synthesized complexes and ligands using the agar dilution test. In spite of the fact that the different species were added in the agar as a suspension, due to their low solubility, all the compounds were active against S. aureus and E. coli. As thus, this class of compounds may lead to a huge range of derivatives, which are generally easily available through classical synthetic methodologies [29-31], and in addition, possess drug-like properties, well-known for decades [32-39].

1.2 Swiss ADME Studies

To be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous but access to the physical samples is limited. In that context, computer models constitute valid alternatives to experiments. Here, we present the new Swiss ADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILED-Egg, iLOGP and Bioavailability Radar.[40]

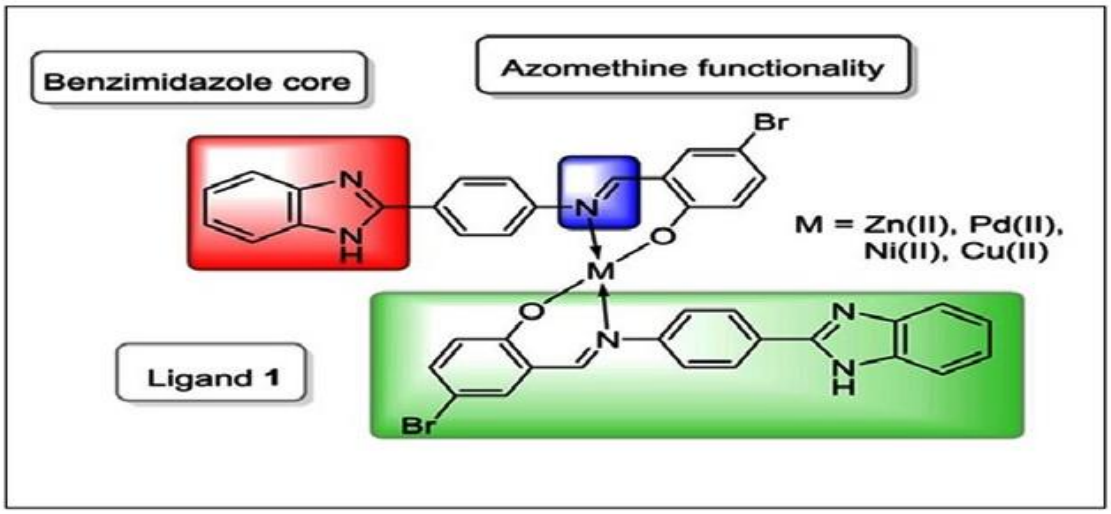


Fig. 3. Diagram represents the binding and antifungal activity

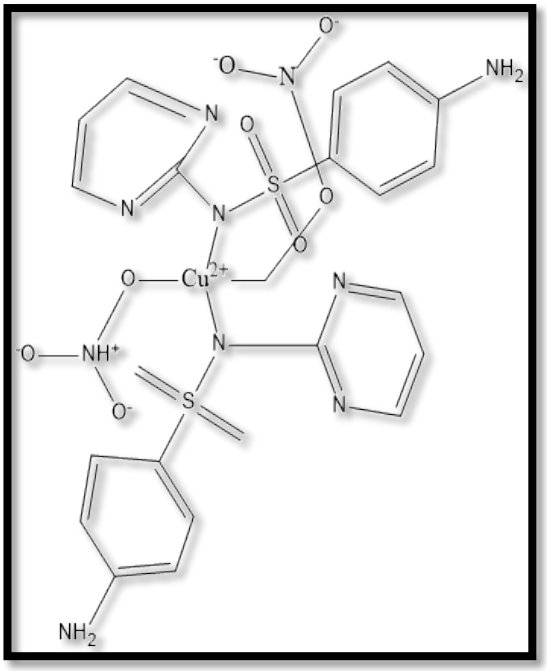
2. EXPERIMENTAL SECTION

The Schiff base ligand (0.121g, 0.5mmol) was dissolved in 15.00 ml hot ethanol. The hot ethanolic solution of the ligand was slowly added to a hot 1:1 (metal: ligand) aqueous ethanolic solution of the metal salts (nitrate salts). The resulting solution was refluxed for 6 h. The solution was reduced to one third by evaporating the solvent. The solution was cooled .The (Cu2+ -green) colored precipitate was separated by filtration. The solid was washed several times with ethanol. The complex was soluble in DCM, DMF and DMSO. The drugs (Sulfadiazine [4-amino-N-pyrimidin- 2-yl-benzenesulfonamide]), chemical and solvents (Methanol, Dimethylsulfoxide (DMSO), 10% Potassium hydroxide (KOH) solution and Diethyl ether) used in this study were of analytical grade and used as obtained from Aldrich without further purification. The antibacterial activities of the drug/complexes were assessed by using nutrient agar medium and antifungal activity by using potato dextrose agar medium.

2.1 Formation of Cu^{2+} complex with Sulphadiazine

To a solution of Sulfadiazine (4-amino-N-(2-pyrimidinyl) benzenesulfonamide), (0.590 g, 2mmol) in 23 ml of methanol was treated with a methanolic solution of Copper (II) sulphate (0.245 g,1mmol). The reaction mixture was stirred on a magnetic stirrer. The blue green violet crystalline product formed after 7-8 hrs were collected by filtration. The solid was washed several times with methanol (50 mL), then with diethyl ether (30 mL) and finally dried in a vacuum.

Mol.Formula:
$C_{23}H_{25}CuN_{10}O_8S_2$Mol.Wt.:697.18,M.P.276^{0}C, Yield: 0.192g.Colour: Blue green.



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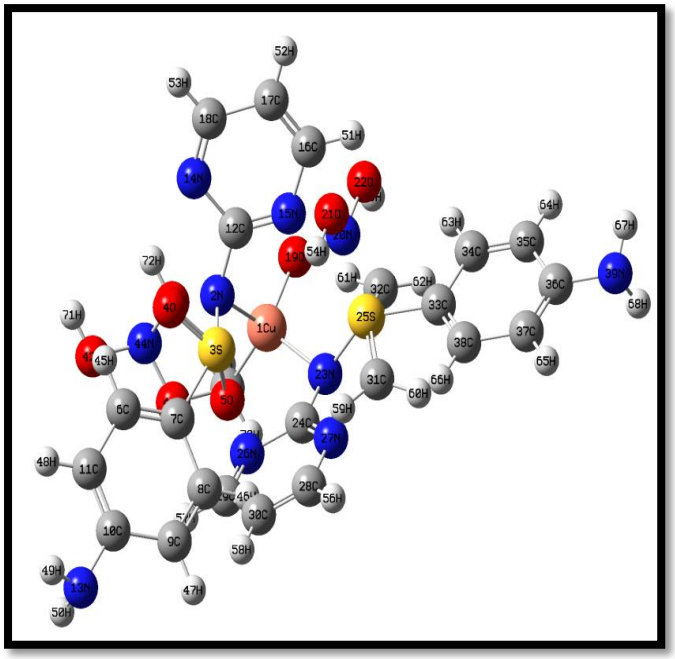

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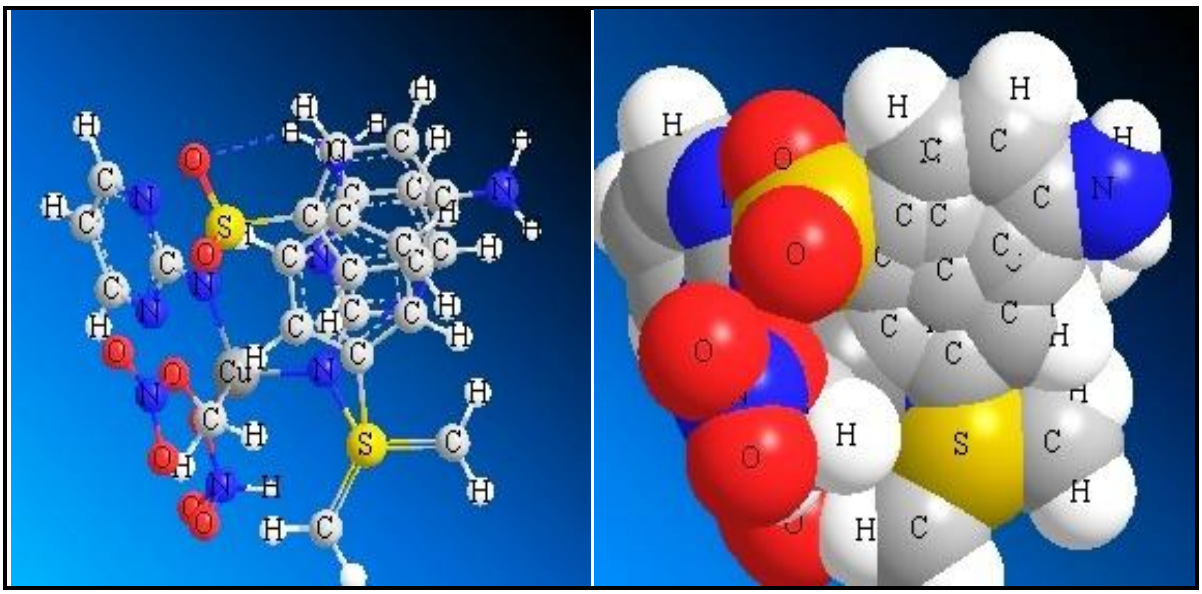

(III) (IV)

Fig. 4. 3D molecular structure of copper metal complex (I), (II), (III), (IV) & (V)

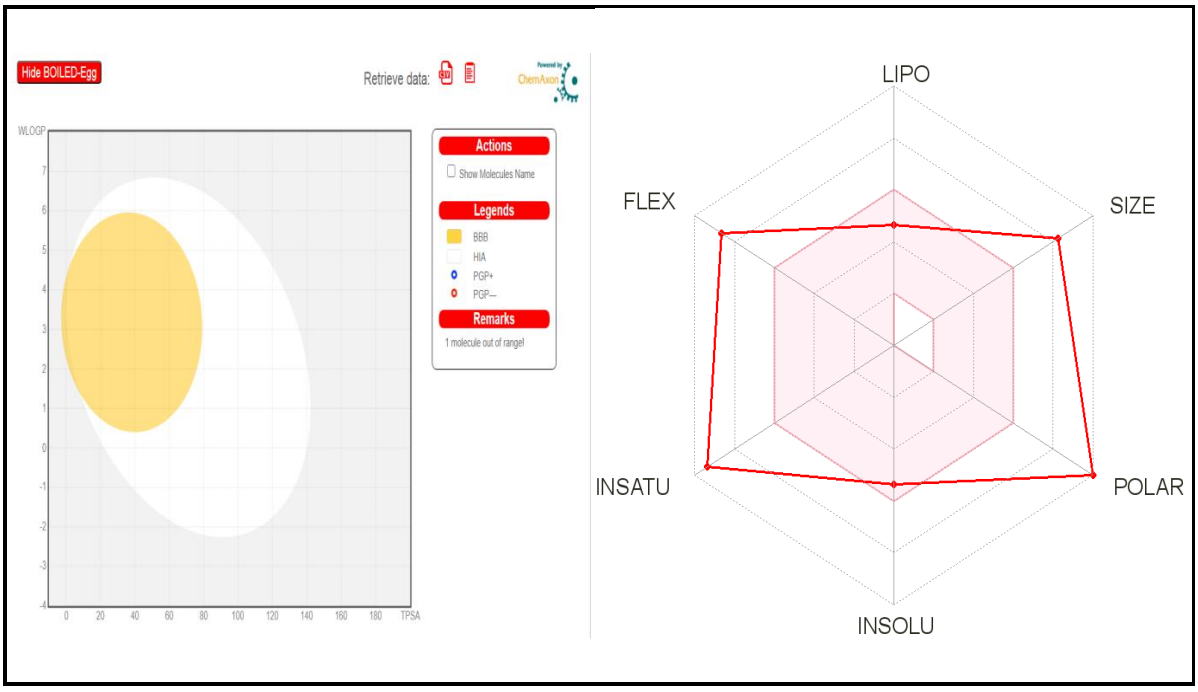

Image 1. Swiss ADME studies of copper complex

2.2 Swiss ADME Studies of Copper Complex

2.3 Melting Point and Conductance

The mononuclear complex were in powdery form. These complex obtained from nitrates were soluble in organic solvents such as DMSO and DMF. The analytical data (melting point and conductance) obtained. The analytical data of these complex showed that the solids are stable and can be stored for months without any significant change in their formulae. The melting points of the synthesized complexes showed higher values (above 265^{0}C) than the parent ligand (SD). This probably indicates the formation of complex. The molar conductivity values showed that the complex are non electrolytes in the solvent DMSO and establishes the stability of the complex.

Table 1. Tabular presentation of biophysical parameter of copper metal complex

Physicochemical Properties	Results
Formula	C23H25CuN10O8S2
Molecular weight	697.18 g/mol
Num. heavy atoms	44
Num. arom. heavy atoms	24
Fraction Csp3	0.04
Num. rotatable bonds	13
Num. H-bond acceptors	13
Num. H-bond donors	3
Molar Refractivity	163.13
TPSA	292.78 Å²
Lipophilicity	
Log Po/w (iLOGP)	0.00
Log Po/w (XLOGP3)	2.64
Log Po/w (WLOGP)	1.77
Log Po/w (MLOGP)	-3.05
Log Po/w (SILICOSIT)	-7.62
Consensus Log Po/w	-1.25
Water Solubility	
Log S (ESOL)	-5.37
Solubility	2.96e-03 mg/ml ; 4.25e-06 mol/l
Class	Moderately soluble
Log S (Ali)	-8.44
Solubility	2.54e-06 mg/ml ; 3.64e-09 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-4.02
Solubility	6.69e-02 mg/ml ; 9.59e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log Kp (skinpermeation)	-8.68 cm/s
Druglikeness	
Lipinski	No; 2 violations: MW>500, NorO>10
Ghose	No; 2 violations: MW>480, MR>130
Veber	No; 2 violations: Rotors>10, TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 3 violations: MW>600, TPSA>150, H-acc>10
Bioavailability Score	0.11
Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: aniline, oxygen nitrogen_single_bond, thiocarbonyl_ group
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	5.45

2.4 Electronic Absorption

The absorption of electromagnetic radiation in the visible and ultraviolet regions of the spectrum results in changes in the electronic structure of ions and molecules. When a molecule is irradiated with visible or ultraviolet light, it may undergo an electronic transmission during which

the molecule absorbs a quantum of energy and an electron is excited from the ground state to a higher energy state. The amount of energy involved in the excitation is proportional to the wavelength of light to cause the transition. The electronic spectra of simple ligand and the complexes were recorded in10-3 M DMSO solution in the range 200–800 nm. The ligand exhibits a band at around 275 nm which is due to the intra ligand π -π*transition. The peak at 320 nm isassigned to n-π* transition of imine group and the transitions occurring in the range of 275–300 nm are due to n -π* transitions of carbonyl group [30]. High spin Cu (II) complexes are weakly colored due to spin forbidden d-d transition. The d-d bands of Complex are not well defined and submerged in the tail of the strong inter ligand transitions or charge transfer bands.

2.5 FT-IR Spectra

Infrared spectroscopy is used for identifying functional groups in pure organic and inorganic compounds. The absorption of infrared light brings about the vibration of the molecules. An infrared spectrum originates from the different modes of vibration and rotation of a molecule. The infrared spectrum of a compound tells about the functional groups that are present in compounds/complexes. When the ligand forms a complex with a metal ion, there is a shift in the frequency of the region or disappearance of the region indicated that the ligand is involved in the complexation. The infrared spectroscopy has been used to study the mode of coordination of Drugs/Ligands and their metal complex. The IR spectra of the free ligand and its metal complex were measured in the region of 4000-400 cm-1 and proposed assignments for the spectral bands. Tentative band assignments (cm-1)of some characteristic bands of sulfadiazine and their related systems were reported. The IR spectra of an complex show abroad band at around 3440 cm-1 and a strong band between1610-1655 cm-1.These may be assigned to asymmetric O-H stretching, which indicates the presence of water molecule in the complexes.

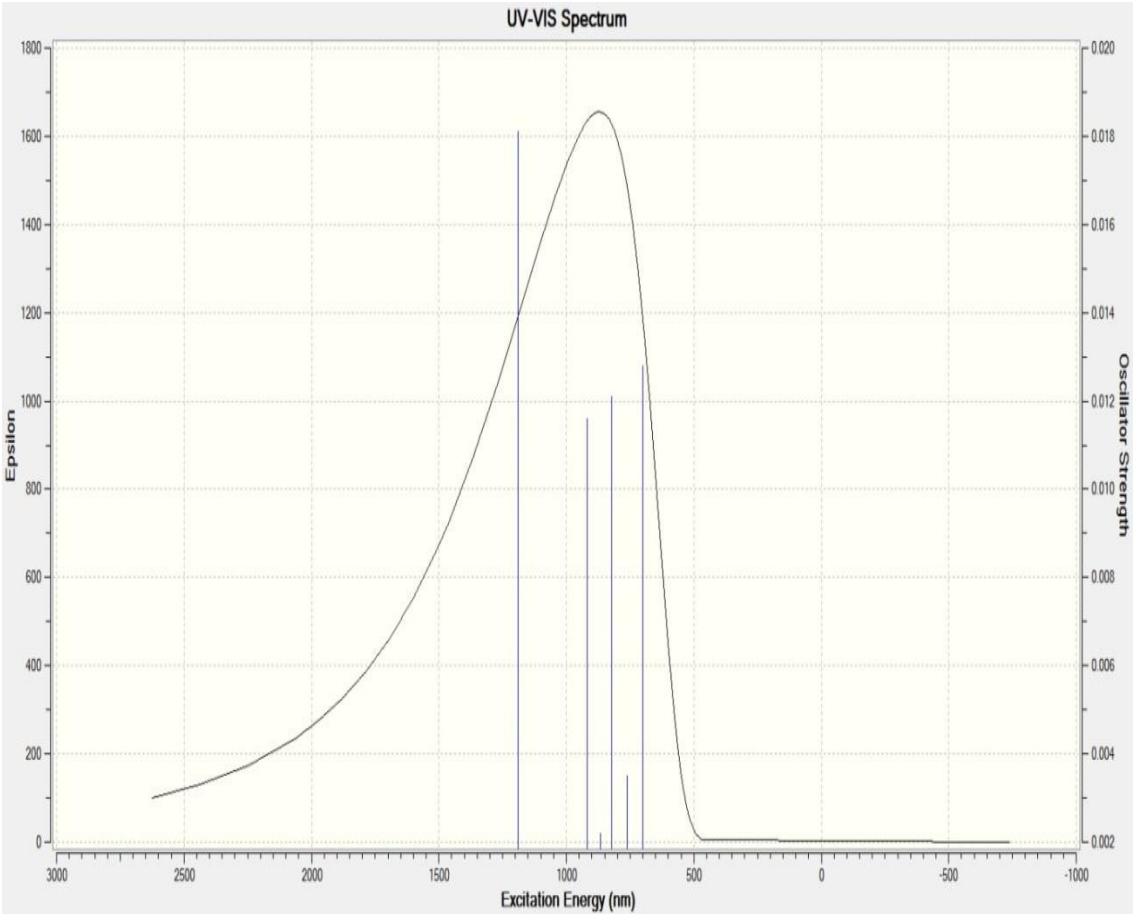

Fig. 5. Theoretical graph of copper metal complex

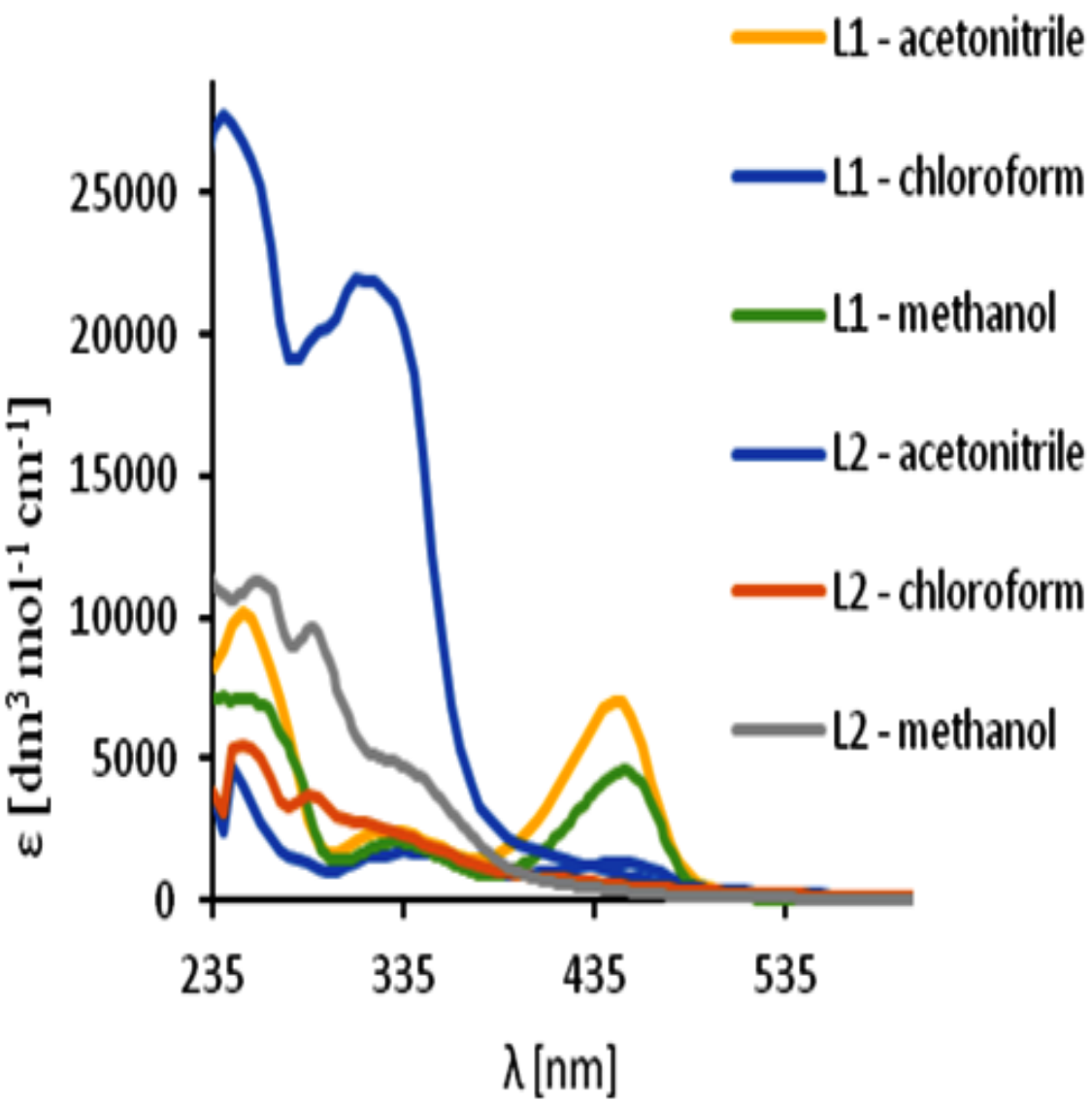

Fig. 6. Experimental graph of copper metal complex

Table 2. Important infrared frequencies (cm−1) of pure drug and their metal complex

Assignment	Sulphadiazine Cm^{-1}	Complex Cm^{-1}
Cu-C Moiety	3500	3460
N-Hof NH_2	3425(vs)	3410
N-H(Sy)	3360	3350
SO_2-N Moiety	1325	1340
SO_2-N	1155	1125
S-N	945	970
C=N	1652	1680
M-N	---	680
C-S	---	970

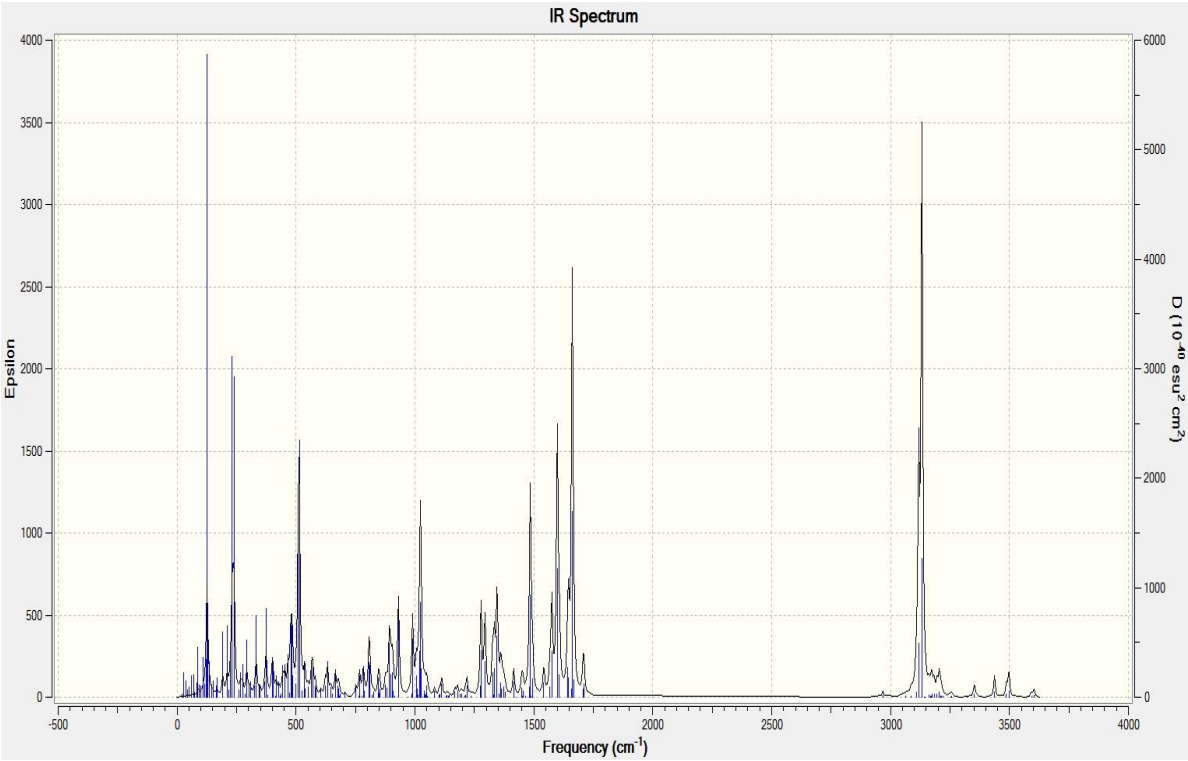

Fig. 7. Theoretical graph of copper metal complex

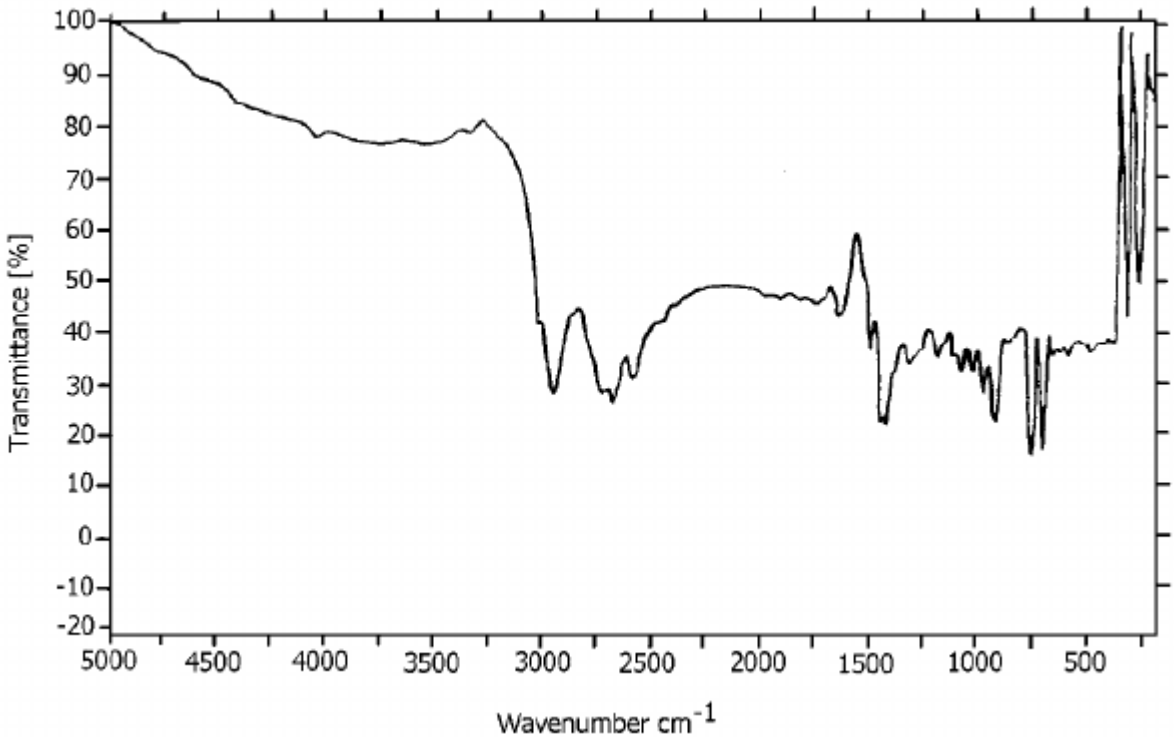

Fig. 8. Experimental graph of copper metal complex

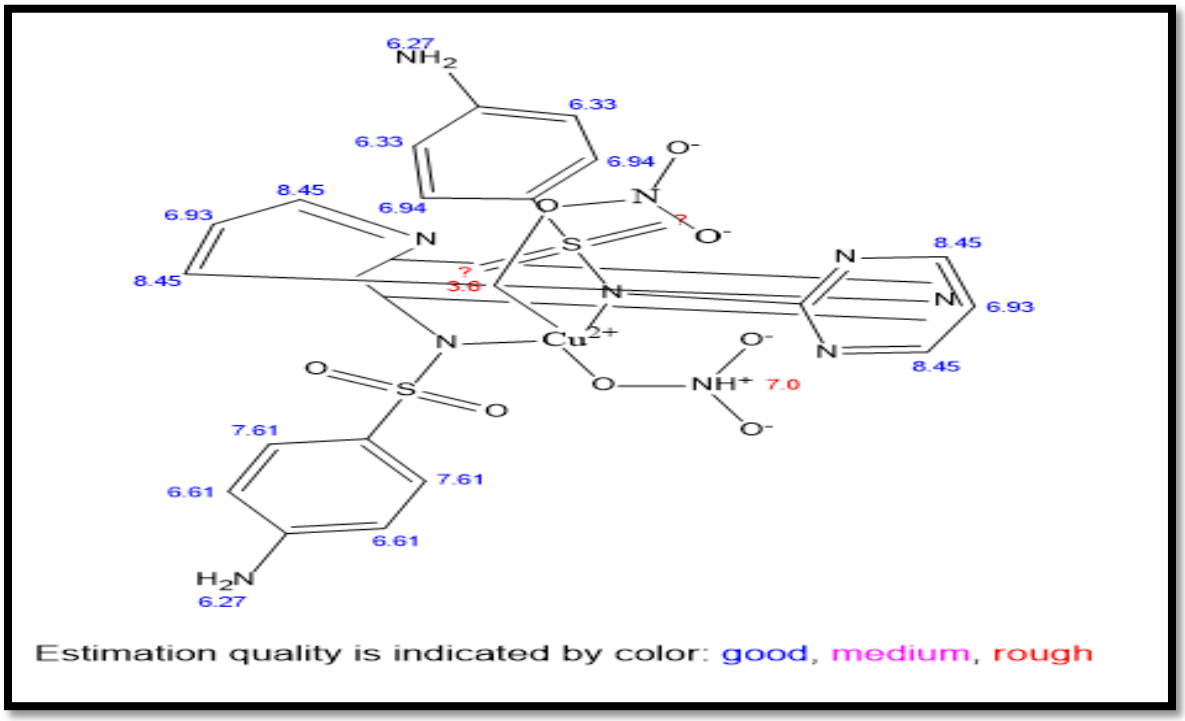

Fig. 9. Diagram representative the estimation of ^{1}H NMR

2.6 Estimation of ^{1}H NMR Spectra

The method is based on the analysis of NMR proton spin-lattice relaxation rates of a specific ligand in both the diamagnetic and paramagnetic conditions. The proposed procedure is also useful to calculate the ligand proton spin-lattice relaxation rate in the paramagnetic bound conditions, which is typically very difficult to determine experimentally. Miri was used to compare the ligand proton involvement toward different paramagnetic species, in particular the Copper(II)-Sulphadiazine system. Copper(II)-Sulphadiazine complex is one of the most active anti-bacterial and anti-fungal species. Miri provides an opportunity to improve our knowledge of metal-ligand complexes that play a fundamental role in bioinorganic interactions.

It synthesize sulphadiazine complex perform various type of analytical data showing a stable complex. In this complex melting points of the showed higher values (above 265^{0}C) than the parent ligand (SD) indicate the stability and formation of complex.In UV-Spectra showing exhibits a band at around 275 nm which is due to the intra ligand π -π*transition. The peak at320 nm isassigned ton-π*transition of imine group and the transitions occurring in the range of 275–300nm are due to n -π*transitions of carbonyl group. High spin Cu (II) complexes are weakly coloured due to spin forbidden d-d transition. The IR spectra of the free ligand and its metal complex were measured in the region of 4000-400 cm-1 and proposed assignments for the spectral bands. Tentative band assignments (cm-1)of some characteristic bands of sulfadiazine and their related systems were reported.Table.1 showing the various infrared frequencies (cm−1) of pure drug and their metal complex. Lastly complex analyze with 1 H NMR practically and predicted graph showing a well define peaks of NH_2, SO_2-N, S-N, Cu-N, M-N and C-S group of these compound.

3. BIOLOGICAL EVALUTION

3.1 Antifungal Activity

The infection of microorganism has caused massive economic losses and threats to the human population. One of the causes is the inappropriate uses of antibiotics notably mishandling that have caused a wide range of bacteria to develop antibiotic resistance. Interest in searching for novel active compounds derived from natural products that have effective antimicrobial activities have significantly increased over the years as the antimicrobial properties of natural products often cover a

wider range of bacteria with minimum side effects [41].The emergence of antibiotic resistance among microbial pathogens is a serious public health problem, resulting in a constant need of discovering new antibiotics. For this purpose, we synthetized and determined the antimicrobial activity of copper (Cu), cobalt (Co), and tin (Sn) complexes [42]. The compounds synthesized during the present investigation were screened for their antifungal activity. The antifangal tests were conducted on four common microorganisms such as, *C.albicans, M.audouinii, A.niger,* and *T.mentagrophytes*. The antifungal activity of the compounds was assessed by disc-diffusion method [43]. The preclinical data that resulted in the identification of SLC-0111, a sulfonamide in Phase Ib/II clinical trials for the treatment of hypoxic, advanced solid tumors, are detailed [44]. These drugs are widely used clinically and were recently shown to weakly inhibit isoforms CA I and II, but to possess stronger activity against isoforms involved in other important pathologies, for example, obesity, cancer, epilepsy and hypertension [45].The physical basis of our original GB/SA approach together with its predictive capacity, computational efficiency (1 to 2s per molecule), and tridimensional molecular graphics capability lay the foundations for a promising predictor, the implicit log P method (iLOGP), to complement the portfolio of drug design tools developed and provided by the SIB Swiss Institute of Bioinformatics [46]. Apart from efficacy and toxicity, many drug development failures are imputable to poor pharmacokinetics and bioavailability. Gastrointestinal absorption and brain access are two pharmacokinetic behaviors crucial to estimate at various stages of the drug discovery processes [47].

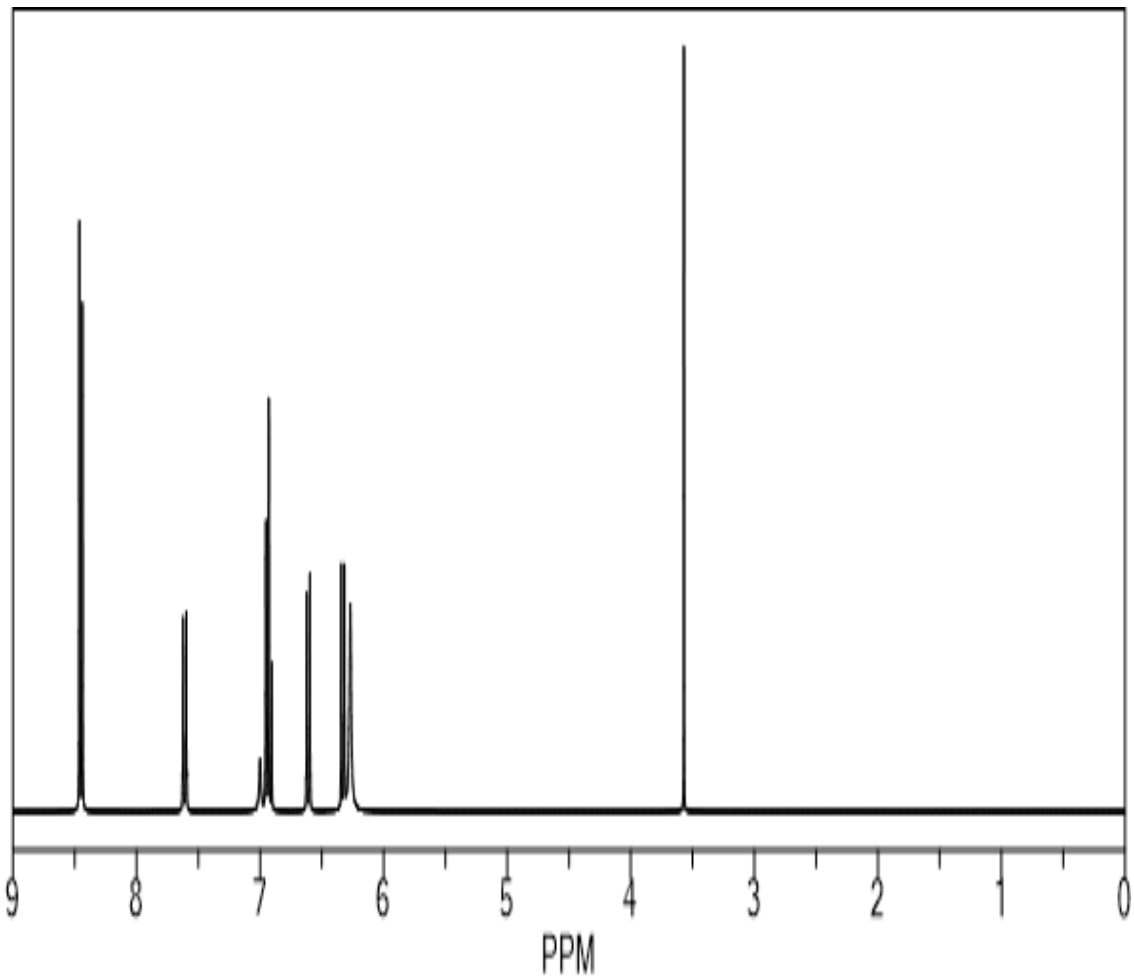

Fig. 10. Theoratical ^{1}H NMR spectra of copper metal complex

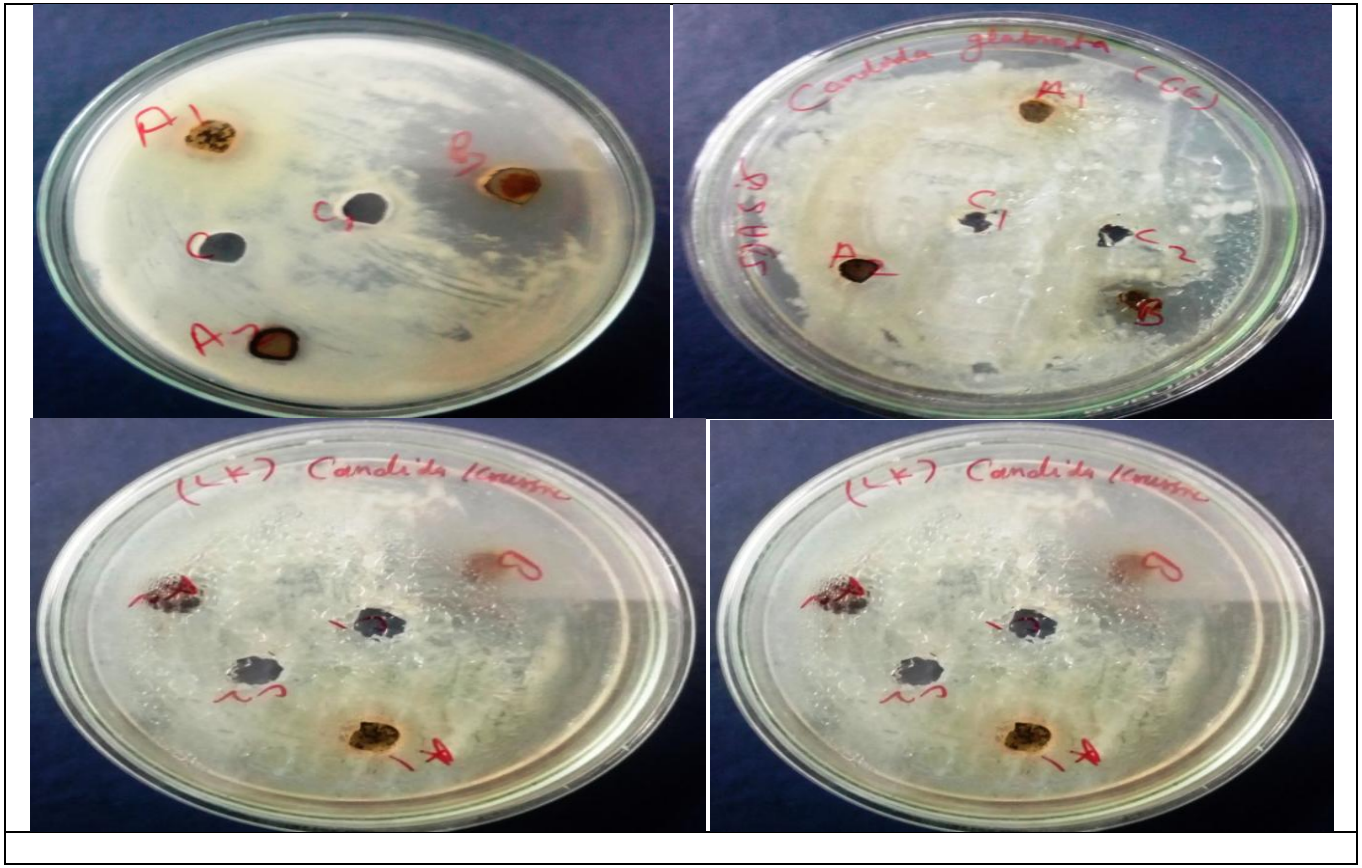

Fig. 12. A,B,C and D Systematic diagram representing the Antifungal activity

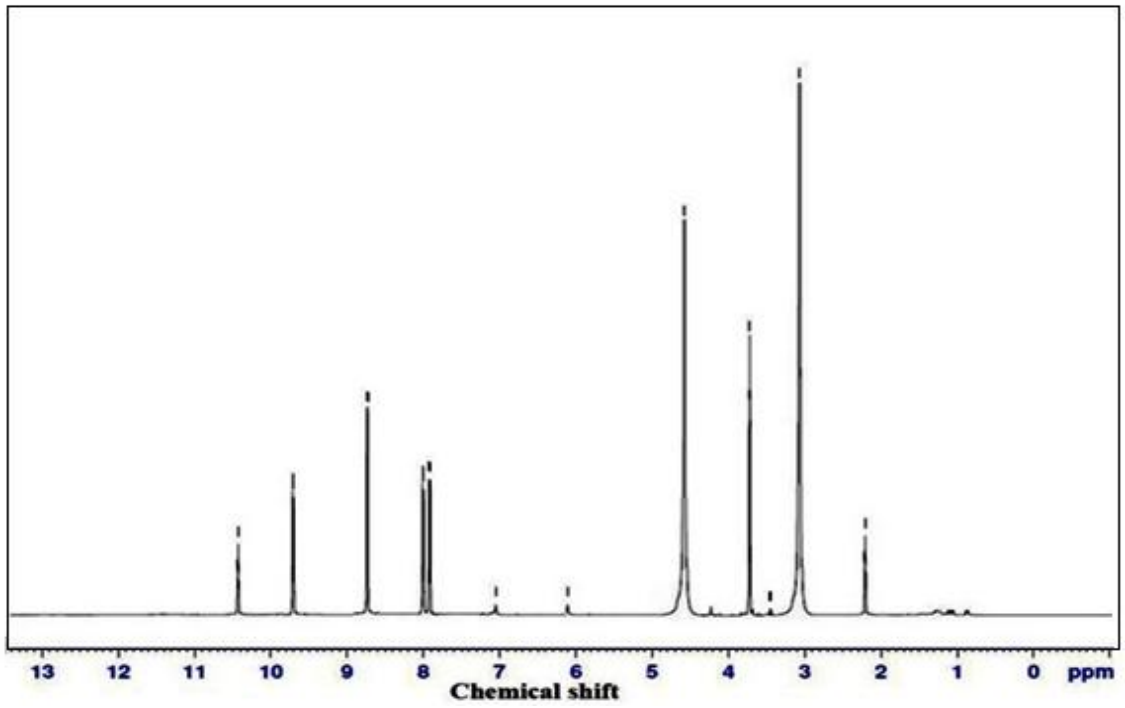

Fig. 11. Experimental ^{1}H NMR spectra of copper complex

4. RESULT AND DISCUSSION

The present work focuses on the synthesis, characterization and biological studies of transition metal complexes containing sulfadiazine drug as ligands. The structural information obtained from these complexes is in agreement with the data reported in this paper based on the elemental and thermal analyses, The IR and thermal studies confirmed the presence of water molecule and nitrate ion in the coordination sphere of [M $(SD)_2(H_2O)(NO_3)].NO_3$. All the complexes have octahedral coordination in which the metal ions are coordinated to sulfadiazine molecule as bidentate ligand, water molecule and nitrate ion as monodentate ligands. The antimicrobial activity of sulfadiazine drug enhanced upon complexation with metal ions particularly for Copper(II). The Swiss ADME Web tool enables the computation of key physicochemical, pharmacokinetic, drug-like and related parameters for one or multiple molecules. In one hand, efforts were put in the backend to embed free open-access and fast predictive models showing statistical significance, predictive power, intuitive interpretation, and straight forward translation to molecular design. These models are adapted from published renowned approaches or in-house original methods, specially developed and thoroughly benchmarked. On the other hand, we focused on an ergonomic and user-friendly graphical interface for the cost- and login-free Web site http://www.swissadme.ch. As a result, Swiss ADME has been designed to support the entire community (specialists and nonexperts) in their drug discovery endeavours. It synthesize copper sulphadiazine complex perform various type of analytical data showing a stable complex. In this complex melting points of the showed higher values (276^0C) indicate the stability and formation of complex. In UV-Spectra showing exhibits a band at around 275 nm which is due to the intra ligand π -π*transition. The peak at320 nm isassigned ton-π*transition of imine group and the transitions occurring in the range of 275–300nm are due to n -π*transitions of carbonyl group. High spin Cu2+ (II) complexes are weakly coloured due to spin forbidden d-d transition. The IR spectra of the free ligend and its metal complex were measured in the region of 4000-400 cm-1 and proposed assignments for the spectral bands. Tentative band assignments (cm-1)of some characteristic bands of sulfadiazine and their related systems were reported. Table 1 showing the various infrared frequencies (cm−1) of pure drug and their metal complex. Lastly complex analyze with 1 H NMR practically and predicted graph showing a well define peaks of NH_2, SO_2-N, S-N, Cu-N, M-N and C-S group of these compound. The series of complexes bearing heterocyclic ligands were tested for their in vitro antimicrobial activity against a number of standard microorganisms, ranging from Gram positive and Gram negative bacteria to yeast. The standard ligands and metal salts were also included for a comparison. In the modified agar diffusion assay the majority of the complexes showed some activity in the screen. Generally,The most pronounced activity with the inhibition zones of more than 14 mm was seen with the manganese complexes **1c**, **2b**, **4a** and **5c**. Interestingly, among the manganese active complex appeared to have very strong activity, with an inhibition zone above 20 mm in comparison to the results of the controls with known antibiotics. Only this complex possessed antifungal activity against *Candida maltosa*. Most of the tested compounds are devoid of antibacterial and antifungal properties up to the concentration of 125 μM. In this regard, platinum salt, picolinic acid and complexes inhibit the growth of *Bacillus subtilis* and a similar behavior is seen by the same compounds but complex against *Staphylococcus aureus*. Although the low degree of antibacterial activity prevents establishing extensive structure activity relationships,.While the walls of Gram positive bacterial cell lack the outer membrane, it might beeasier for the complexes to diffuse inside the bacterial cell.

5. CONCLUSION

In Gram negative bacteria theouter membrane is much thiner than by Gram positive ones and they possess the outermembrane. As otheractive compounds can one distinguish the para isomer, isonicotinic acid and its hydrazide, isoniazide which is a widely used anti-tuberculosis drug against *Plasmodium sp.* As well asisoniazid, also pyrazidamide is used along in treatment of tuberculosis.Although the results confirmed that the most active are Cu2+(II) carboxylates, their MIC values are quite high and thus cannot be classified as potent antimicrobial agents.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and

producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Schiff H. Mittheilungen aus dem Universita¨tslaboratorium in Pisa: eine neue reihe organischer Basen, Justus Liebigs Annalen der Chemie. 1984;131(1):118–119.
2. Dhar DN, Taploo CL. “Schiff bases and their applications,” Journal of Scientific and Industrial Research. 1982;41(8):501–506.
3. Sathe BS, Jaychandran E, Jagtap VA, Sreenivasa GM. “Synthesis characterization and anti- inflammatory evaluation of new fluorobenzothiazole schiff ’s bases,” International Journal of Pharmaceutical Research and Development. 2011;3(3):164–169.
4. Sondhi SM, Singh N, Kumar A, Lozach O, Meijer L. “Synthesis, anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/benzoxazole derivatives and some Schiff ’s bases,” Bioorganic and Medicinal Chemistry. 2006;14(11):3758–3765.
5. Pandey A, Dewangan D, Verma S, Mishra A, Dubey RD. “Synthesis of schiff bases of 2-amino-5-aryl-1,3,4-thiadiazole and its analgesic, anti-inflammatory, anti-bacterial and antitubercular activity,” International Journal of Chem Tech Research. 2011; 3(1):178–184.
6. Chandramouli C, Shivanand MR, Nayanbhai TB, Bheemachari B, Udupi RH. “Synthesis and biological screening of certain new triazole schiff bases and their derivatives bearing substituted benzothiazole moiety,” Journal of Chemical and Pharmaceutical Research. 2012; 4(2):1151–1159.
7. Chinnasamy RP, Sundararajan R, Govindaraj S. “Synthesis, characterization, and analgesic activity of novel schiff base of isatin derivatives,” Journal of Advanced Pharmaceutical Technology and Research. 2010;1(3):342–347.
8. Mounika K, Anupama B, Pragathi J, Gyanakumari C. “Synthesis, characterization and biological activity of a Schiff base derived from 3-ethoxy salicylaldehyde and 2-amino benzoic acid and its transition metal complexes,” Journal of Scientific Research. 2010;2(3):513–524.
9. Chaubey AK, Pandeya SN. “Synthesis & anticonvulsant activity (Chemo Shock) of Schiff and Mannich bases of Isatin derivatives with 2-Amino pyridine (mechanism of action),” International Journal of PharmTech Research. 2012;4(4):590–598.
10. Aboul-Fadl T, Mohammed FA, Hassan EA. “Synthesis, antitubercular activity and pharmacokinetic studies of some Schiff bases derived from 1- alkylisatin and isonicotinic acid hydrazide (INH),” Archives of Pharmacal Research. 2003;26(10):778–784.
11. Miri R, Razzaghi-asl N, Mohammadi MK. “Q M study and conformational analysis of an isatin Schiff base as a potential cytotoxic agent,” Journal of Molecular Modeling, 2013;19(2):727–735.
12. Ali SMM, Abul Kalam Azad M, Jesmin M, et al., “In vivo anticancer activity of Vanillin semicarbazone,” Asian Pacific Journal of Tropical Biomedicine, 2012;2(6):438–442.
13. Wei D, Li N, Lu G, Yao K. “Synthesis, catalytic and biological activity of novel dinuclear copper complex with Schiff base,” Science in China B, 49 3 (2006) 225–229.
14. Avaji PG, Vinod Kumar CH, Patil SA, Shivananda KN, Nagaraju C. “Synthesis, spectral characterization, in-vitro microbiological evaluation and cytotoxic activities of novel macrocyclic bis hydrazone,” European Journal of Medicinal Chemistry, 2009;44(9):3552–3559.
15. Venugopala KN, Jayashree BS. “Synthesis of carboxamides of 2 -amino-4 -(6-bromo-3-coumarinyl) thiazole as analgesic

and antiinflammatory agents," Indian Journal of Heterocyclic Chemistry 2003;12(4):307–310.
16. Cimerman Z, Miljanic S, Galic N. Schiff bases derived from aminopyridines as spectrofluorimetric analytical rea- gents, Croatica Chemica Acta. 2000;73(1):81–95.
17. Vashi K, Naik HB. "Synthesis of novel Schiff base and azetidinone derivatives and their antibacterial activity," European Journal of Chemistry, 1 (2004) 272–276.
18. Li S, Chen S, Lei S, Ma H, Yu R, Liu D. "Investigation on some Schiff bases as HCl corrosion inhibitors for copper," Corrosion Science. 1999;41(7):1273–1287.
19. Chohan ZH, Praveen M, Ghaffar A. "Structural and biological behaviour of Co(II), Cu(II) and Ni(II) metal complexes of some amino acid derived Schiff-bases," Metal-Based Drugs 1999; 4(5):267–272.
20. Ershad S, Sagathforoush L, Karim-Nezhad G, Kangari S. "Electrochemical behavior of N2SO Schiff-base Co(II) complexes in non-aqueous media at the surface of solid electrodes," International Journal of Electrochemical Science. 2009;4(6):846–854.
21. Tisato F, Refosco F, Bandoli G. "Structural survey of technetium complexes," Coordination Chemistry Reviews. 1994;135:325–397.
22. Jarrahpour A, Khalili D, De Clercq E, Salmi C, Brunel JM. "Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives," Molecules. 2007;12(8):1720–1730.
23. Bhattacharya A, Purohit VC, Rinaldi F. "Environmentally friendly solvent-free processes: novel dual catalyst system in Henry reaction," Organic Process Research and Development. 2003; 7(3):254–258.
24. Hussaini SY, Ahmad A, Sani S, Bayero J. Pure and Applied Sci. 2017;10(2):245.
25. Supuran CT. Advances in structure-based drug discovery of carbonic anhydrase inhibitors. Expert Opin. Drug Discov. 2018;12:61–88.
26. Carta F, Supuran CT, Scozzafava A. Sulfonamides and their isosters as carbonic anhydrase inhibitors. Future Med. Chem.2014; 6:1149–1165.
27. Scozzafava A, Owa T, Mastrolorenzo A, Supuran CT. Anticancer and antiviral sulfonamides. Curr. Med. Chem. 2003;10:925–953.
28. Capasso C, Supuran CT. Sulfa and trimethoprim-like drugs-antimetabolites acting as carbonic anhydrase, dihydropteroate synthase and dihydrofolate reductase inhibitors. J. Enzym. Inhib. Med. Chem. 2014;29:379–387.
29. Carta F, Scozzafava A, Supuran CT. Sulfonamides: A patent review (2008–2012) Expert Opin. Ther. Pat. 22. 2012; 747–758.
30. Scozzafava A, Carta F, Supuran CT. Secondary and tertiary sulfonamides: A patent review (2008–2012) Expert Opin. Ther. Pat. 2013;23:203–213.
31. Winum JY, Scozzafava A, Montero JL, Supuran CT. The sulfamide motif in the design of enzyme inhibitors. Expert Opin. Ther. Pat. 2006;16:27–47.
32. Supuran CT. Carbonic anhydrases: Novel therapeutic applications for inhibitors and activators. Nat. Rev. Drug Discov. 2008; 7:168–181.
33. Neri D, Supuran CT. Interfering with pH regulation in tumours as a therapeutic strategy. Nat. Rev. Drug Discov. 2011; 10:767–777.
34. Masini E, Carta F, Scozzafava A, Supuran CT. Antiglaucoma carbonic anhydrase inhibitors: A patent review. Expert Opin. Ther. Pat. 2013;23:705–716.
35. Monti SM, Supuran CT, De Simone G. Anticancer carbonic anhydrase inhibitors: A patent review (2008–2013) Expert Opin. Ther. Pat. 2013;23:737–749.
36. Supuran CT. Structure-based drug discovery of carbonic anhydrase inhibitors. J. Enzym. Inhib. Med. Chem. 2012;27:759–772.
37. Zanoaga M, Tanasa F. Antimicrobial reagents as functional finishing for textiles intended for biomedical applications. I. Synthetic organic compounds. Chem. J. Mold. 2014;9:14–32.
38. Upadhyay A, Upadhyaya I, Kollanoor-Johny A, Venkitanarayanan K. Combating pathogenic microorganisms using plant-derived antimicrobials: A minireview of the mechanistic basis. BioMed Res. Int. 2014; 2014:761
39. Scozzafava A, Supuran CT, Carta F. Antiobesity carbonic anhydrase inhibitors: A literature and patent review. Expert Opin. Ther. Pat. 2013;23:725–735.

40. Swiss ADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci. Rep. 2017;7:42717.
41. Zong Chin Khor, May Lee Low, Irene Ling, Schiff Bases and their Copper(II) Complexes Derived from Cinnamaldehyde and Different Hydrazides: Synthesis and Antibacterial Properties, Journal of Transition Metal Complexes, 2020;3:1-9.
42. Lorena S, Ferreira Jéssica, Andrad T, William, Lima G. synthesis, characterization and antimicrobial activity of new cu (ii), co (ii) and sn (ii) complexes with the sodium hydrotris (2-mercaptothiazolyl)borate ligand, Quím. Nova. 2020;43(5):593-598.
43. Emir Horozić, Jasmin Suljagić , Mersiha Suljkanović, Synthesis, Characterization, Antioxidant and Antimicrobial Activity of Copper(II) Complex with Schiff Base Derived from 2,2-dihydroxyindane-1,3-dione and Tryptophan, American Journal of Organic Chemistry. 2019; 9(1):9-13.
44. Supuran CT. How many carbonic anhydrase inhibition mechanisms exist? J. Enzym. Inhib. Med. Chem. 206;31:345–360.
45. Carta F, Supuran CT. Diuretics with carbonic anhydrase inhibitory action: A patent and literature review (2005–2013) Expert Opin. Ther. Pat. 2013; 23:681–691.
46. ILOGP: A simple, robust, and efficient description of n-octanol/water partition coefficient for drug design using the gb/sa approach. J. Chem. Inf. Model. 2014;54(12):3284-3301.
47. A Boiled-Egg to predict gastrointestinal absorption and brain penetration of small molecules. ChemMedChem. 2016;11(11): 1117-1121.

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