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SYNTHESIS, CHARACTERIZATION, 3D STRUCTURE AND PREDICTED SWISS ADME STUDIES OF SOME NEW TRANSITION METALS AND THEIR ANTI MICROBIAL ACTIVITIES

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Abstract:

Sulpha containing the drug are chemotherapeutic agents whose molecules contain a 4- amino benzenesulfonamide moiety. Due to low cost, low toxicity, and excellent activity against bacterial diseases, Sulphadiazine is among the most widely used as antibacterial agents. Sulfadiazine is a sulphanilamide derivative that is used as an antibacterial as well as an antimalarial drug. The Sulphadiazine were the first effective chemotherapeutic agents to be employed systematically treatment of infectious diseases remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens..Some metals are essential for biological functions and are found in enzymes and cofactors required for various processes. For example, hemoglobin in red blood cells contains an iron porphyrin complex, which is employed for oxygen transport and storage within the body. Transition metal complexes have comprises of inorganic, Metallo-organic also as bio-inorganic elements because of their numerous applications in wide-ranging areas from material to biological sciences. the potent molecule must be the target within the body in sufficient concentration and stay there during a bioactive form for the expected biologic events to occur. The drug development process involves the moiety of drug during absorption, distribution, metabolism, and excretion (ADME) increasingly earlier within the preclinical studies, complex are numerous but access to the physical samples is limited. In that context, computer aided drug design constitute valid alternatives to experiments.

Key words: *Sulpha drugs,Charecterization, Swiss ADME, Antimicrobial Activities etc.*

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INTRODUCTION:

Sulpha drugs are chemotherapeutic agents whose molecular structures contain a 4- amino benzene sulfonamide moiety. Due to low cost, low toxicity, and excellent activity against bacterial diseases, Sulphadiazine are among the most widely used as antibacterial agents. Sulfadiazine is a sulphanilamide derivative that is used as an antibacterial as well as an antimalarial drug. However, it is mostly used now in combination therapy with pyrimethamine to treat chloroquine-resistant malaria parasite. Studies related to new developments in metal-based drugs are both promising and of great interest in the development of therapeutic agents. The Sulphadiazine were the first effective chemotherapeutic agents to be employed systematically treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents. The efficacy of the sulpha drugs can be enhanced upon coordination with a suitable metal ion. The metal complexes of sulfadiazine drug have gained considerable importance due to their pronounced biological activity. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity, possibly acting through mechanism of action, which is distinct from those of well-known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant. Therefore, new antimicrobial agents and nanotechnological materials have to be synthesized for the treatment of resistant bacterial diseases. Historically, medicinal inorganic chemistry is rich in metal- or metalloid-based drugs, including Paul Erlich's organo arsenic compound for the treatment of syphilis, antiarthritic gold preparations, and diagnostic agents for magnetic resonance imaging (Gd, Mn, Fe) among others. The field of bioinorganic chemistry, which deals with the study of role of metal complexes in biological systems, has opened a new horizon for scientific research in coordination compounds. Some metals are essential for biological functions and are found in enzymes and cofactors required for various processes. For example, haemoglobin in red blood cells contains an iron porphyrin complex, which is used for oxygen transport and storage in the body. Metals such as copper, zinc, iron and manganese are incorporated into catalytic proteins (the metalloenzymes), which facilitate a multitude of chemical reactions needed for life. Biological metal ions play key roles in the structural organization and activation of certain enzymes, which are involved in the transfer of genetic information from DNA, leading to the synthesis of specific proteins. Transition metal complexes have attracted attentions of inorganic, metallo-organic as well as bio-inorganic chemists because of their extensive applications in wide ranging areas from material to biological sciences. In this method 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. Specialists, but also non expert in chem. informatics or computational chemistry can predict rapidly key parameters for a collection of molecules to support their drug discovery endeavours.

1. Sulphadiazine contain metal moiety:

Sulphadiazine were the first effective chemotherapeutic agents employed systematically for the prevention and cure of bacterial infections in humans. Among the many and so different families of organic–inorganic chemicals being currently investigated today because of their applications, Sulphadiazine and their N-derivatives are one of the outstanding groups. Sulphadiazine represent an important class of medicinally important compounds which are extensively used as antibacterial agent. It interferes with PABA (p-aminobenzoic acid) in the biosynthesis of tetrahydrofolic acid, which is a basic growth factor essential for the metabolic process of bacteria. N-Substituted Sulphadiazine 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 Sulphadiazine while the pyrimidine, pyridine and pyridazine complexes had similar or less activity than the free ligands. In order to find an explanation for this behaviour lipophilicity and superoxide dismutase-like activity were tested, showing that the [Cu (sulfamethoxazol) 2 (H2O) 4] ·3H2O 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]·H2O and [Cu(L)2(H2O)4]·nH2O, 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, a new class of such compounds was reported by combining the chemistry of Sulphadiazine with indole-3-carbaldehyde and to explore their biological activities with theaim of obtaining more potent antibacterial and/or antifungal compounds. Structural inspections showed that the anti-bacterial entity of ligands remains non coordinated to metal ions in the complex high-lighting the factthat in each cluster, antiseptic activity of the metal has been associated to the anti-biotic activity of the ligand. The antibacterial activity of the complex is as important as the ligands one with the addition of antiseptic activity via the incorporation of copper ions.

2. Antibacterial activity in metal ions:

The antimicrobial function can be incorporated into textile either by chemical finishing of fabrics with biocidal agents or by physical incorporation of the agents into fibers. An area of polymer research that presents great current interest is that of the development of polymers with antimicrobial activities, generally known as polymeric biocides. In the area of health care and hygienic applications, biocidal polymers may be incorporated into fibres, or possibly extruded into fibres themselves, and used for contact disinfectants in many biomedical applications. One method of achieving antimicrobial polymers is to add an organic or inorganic biocide to the polymers during processing of the material. The antimicrobial study emphasise that Cu/oxidized polyvinyl pyridine (PVP) and Ag/oxidized PVP have retarded the growth of bacteria significantly, and Ag/oxidized PVP has a far better biocidal activity. A study was carried out using chitosan– metal complex aiming to impart the jute fabric antimicrobial properties. In this regard, Ag^{+}, Zn^{2+} and Zr^{2+} ions were allowed separately to form a complex with chitosan. It has been found that, jute fabrics treated with chitosan–metal complex show better antimicrobial properties than those fabrics treated with either chitosan or metal salt separately. Moreover, the jute fabrics treated with chitosan–Zn complex have higher antimicrobial properties compared with those samples treated with chitosan–Zr or chitosan–Ag complexes. The antimicrobial ceramics (AC) based on hydroxyapatite (HA) were made in a wet chemical process with additions of $AgNO_3$, $Cu(NO_3)_2{\cdot}3H_2O$ and $Zn(NO_3)_2{\cdot}6H_2O$.

3.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. The molecules must show high biological activity together with low toxicity. Equally important is the access to and concentration at the therapeutic target in the organism. The traditional way to consider pharmacokinetics (i.e. the fate of a therapeutic compound in the organism) is to break down the various effects that impact the access to the target into individual parameters. In turn, these ADME parameters (for Absorption, Distribution, Metabolism and Excretion) can be evaluated separately by dedicated methods. It has been demonstrated that early estimation of ADME in the discovery phase reduces drastically the fraction of pharmacokinetics-related failure in the clinical phases. Computer models have been fostered as a valid alternative to experimental procedures for prediction of ADME, especially at initial steps, when investigated chemical structures are numerous but the availability of compounds is scarce. During the time- and resource-consuming processes of drug discovery and development, a large number of molecular structures are evaluated according to very diverse parameters in order to steer the selection of which chemicals to synthetize, test and promote, with the final goal to identify those with the best chance to become an effective medicine for the patients. Finally, Swiss ADME is integrated in the Swiss Drug Design workspace. One-click interoperability gives access to various CADD tools developed by the Molecular Modelling Group of the SIB Swiss Institute of Bioinformatics, e.g.ligand-based virtual screening(SwissSimilarity),biotarget prediction (SwissTarget Prediction), molecular docking (SwissDock), bioisosteric design (SwissBioisostere), or molecular mechanics (SwissParam). The first section, including two-dimensional chemical structure and canonical SMILES, is located below the title. It shows on which chemical form the predictions were calculated. Moreover, our *Bioavailability Radar* is displayed for a rapid appraisal of drug-likeness. Six physicochemical properties are taken into account: lipophilicity, size, polarity, solubility, flexibility and saturation. A physicochemical range on each axis was defined by descriptors adapted and depicted as a pink area in which the radar plot of the molecule has to fall entirely to be considered drug-like. Leaving the mouse over the radar gives

further information about the descriptors. After all calculations completed, the "Show BOILED-Egg" red button appears below the sketcher to display the graphical output on the same page. The egg-shaped classification plot includes the yolk (i.e. the physicochemical space for highly probable BBB permeation) and the white (i.e. the physicochemical space for highly probable HIA absorption). Both compartments are not mutually exclusive and the outside grey region stands for molecules with properties implying predicted low absorption and limited brain penetration. In practice, the BOILED-Egg has proven straightforward interpretation and efficient translation to molecular design in a variety of drug discovery settings. Whereas the predictive power of the BOILED-Egg is broad in term of chemical space, it is restricted to passive penetration through gastro-intestinal wall and BBB.

4. EXPERIMENTAL SECTION

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.

(i) Formation of Mn complex with Sulphadiazine

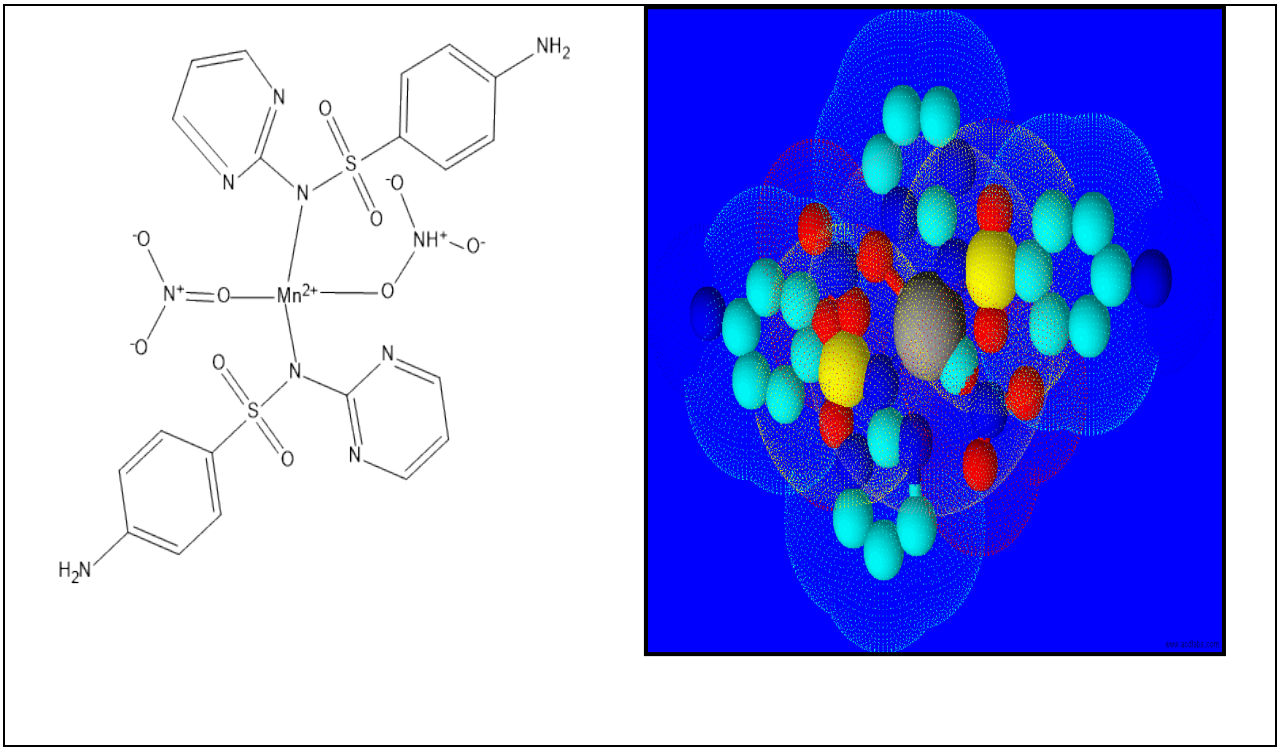
To a solution of Sulfadiazine (4-amino-N-(2-pyrimidinyl) benzenesulfonamide), (0.590 g, 2mmol) in 23 ml of methanol was treated with a methanolic solution of Manganese (II) nitrate (0.245 g,1mmol). The reaction mixture was stirred on a magnetic stirrer. The light brown crystalline product formed after 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.

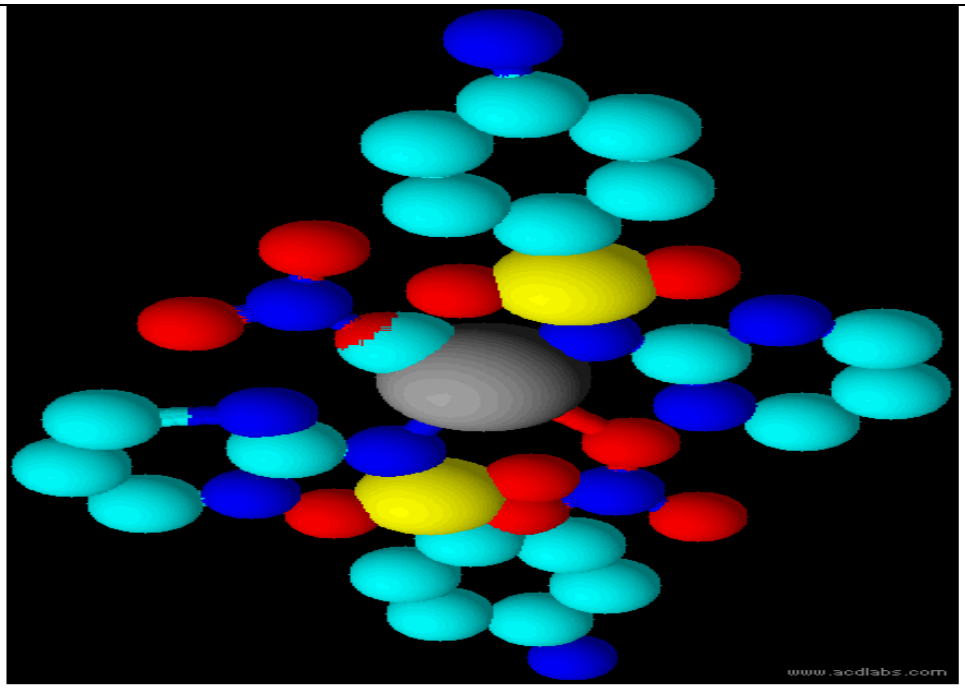
Mol. Formula $MnC_{20}H_{20}N_{10}S_2O_{11}$: Mol. Wt. 700.93, M.P. 276^{0}C, Yield: 0.192g. Colour: Pale brown.

(ii) Swiss ADME Studies of synthesized complex

Physicochemical Properties	
Formula	C25H34N9NiO7S2
Molecular weight	695.42 g/mol
Num. heavy atoms	44
Num. arom. heavy atoms	18
Fraction Csp3	0.24
Num. rotatable bonds	7
Num. H-bond acceptors	11
Num. H-bond donors	5
Molar Refractivity	176.27
TPSA	265.76 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	0.00
Log $P_{o/w}$ (XLOGP3)	2.25
Log $P_{o/w}$ (WLOGP)	1.63
Log $P_{o/w}$ (MLOGP)	0.39
Log $P_{o/w}$ (SILICOS-IT)	-1.73
Consensus Log $P_{o/w}$	0.51
Water Solubility	
Log *S* (ESOL)	-5.41
Solubility	2.71e-03 mg/ml ; 3.89e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.47
Solubility	2.37e-05 mg/ml ; 3.41e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-5.79
Solubility	1.13e-03 mg/ml ; 1.63e-06 mol/l

Class	Moderately soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.94 cm/s
Druglikeness	
Lipinski	No; 2 violations: MW>500, NorO>10
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 3 violations: MW>600, TPSA>150, H-acc>10
Bioavailability Score	0.17
Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: aniline, nitro_group, oxygen-nitrogen_single_bond
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	6.45





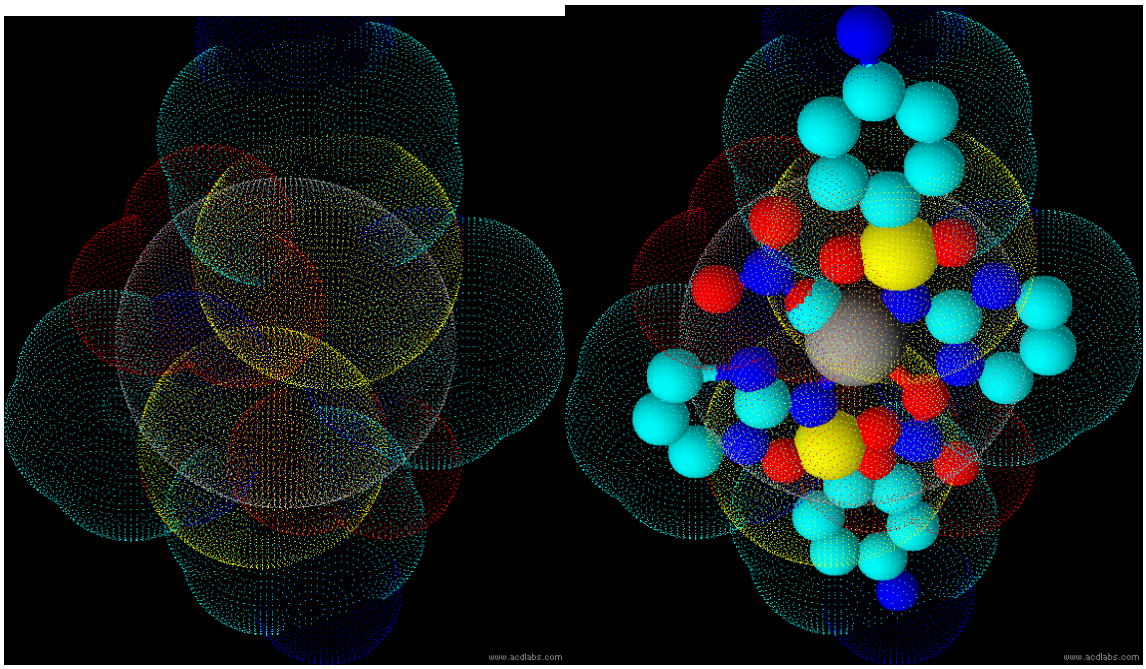


Fig.1 3D Molecular structure of Manganese II Metal complex

(iii) Melting point and conductance

The mononuclear complex was in powdery form. These complexes 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 complexe showed higher values (above 265^0C) 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.

(iv) 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 at320 nm is assigned 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.[30] High spin Mn (II) complexes are weakly coloured 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.

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-1andproposed 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 a 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.

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

Assignment	Sulphadiazine Cm^{-1}	Complex Cm^{-1}
N-Hof NH_2	3425(vs)	3420
N-H(Sy)	3360	3355
SO_2-N Moiety	1325	1342
SO_2-N	1155	1126
S-N	945	973
C=N	1652	1680
M-N	---	682
C-S	---	973

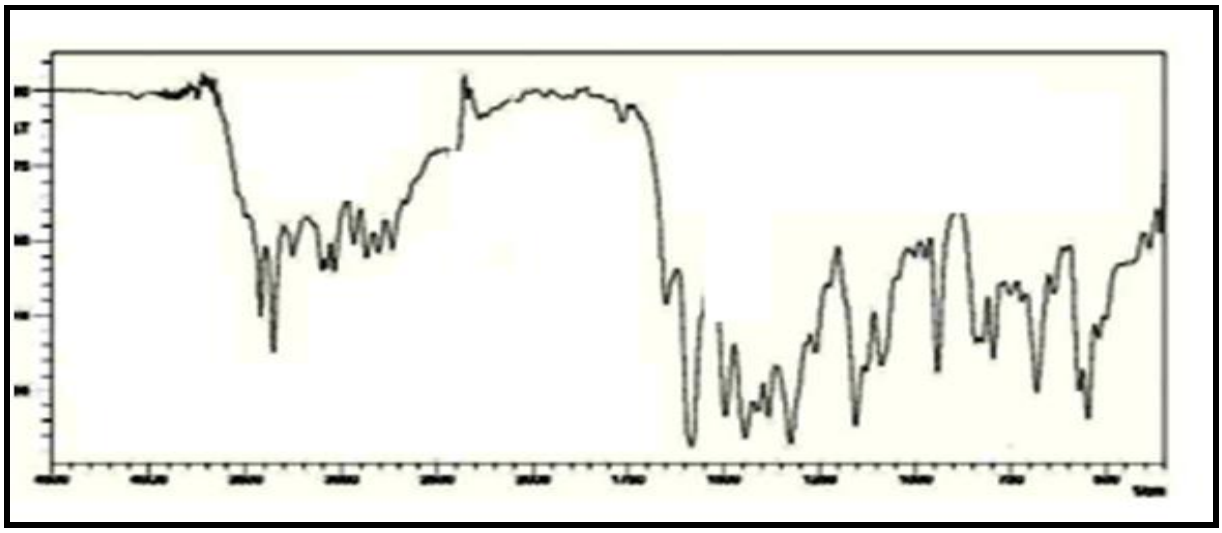


Fig.2 IR graph of the synthesized complex

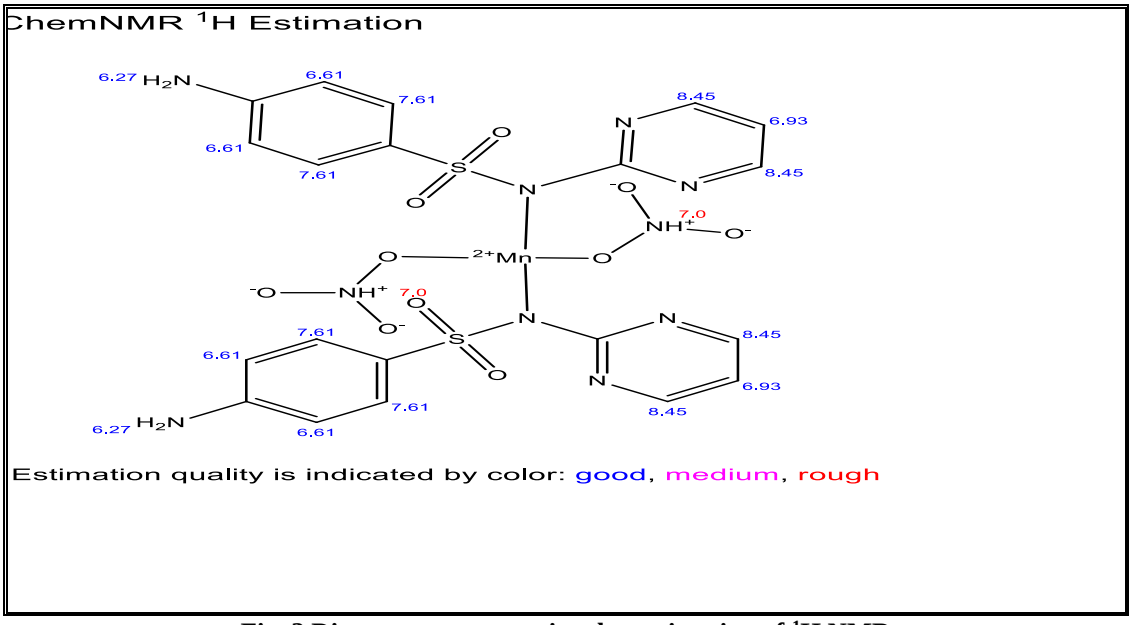


Fig. 3 Diagram representative the estimation of ^{1}H NMR

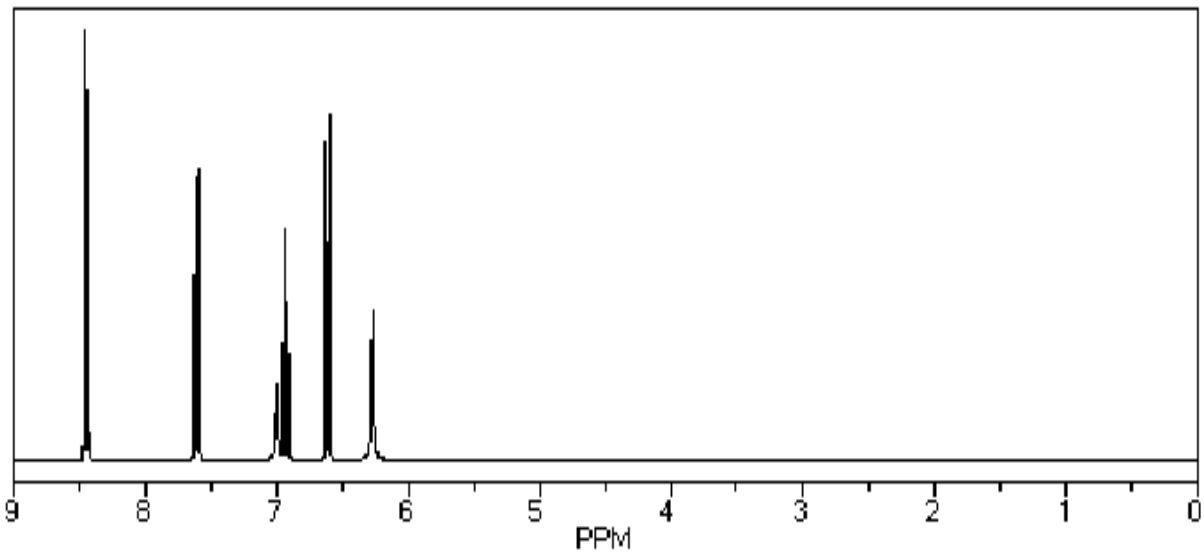


Fig.4 Predicted ^{1}H NMR Graph of Complex 1 by Chemdraw Software

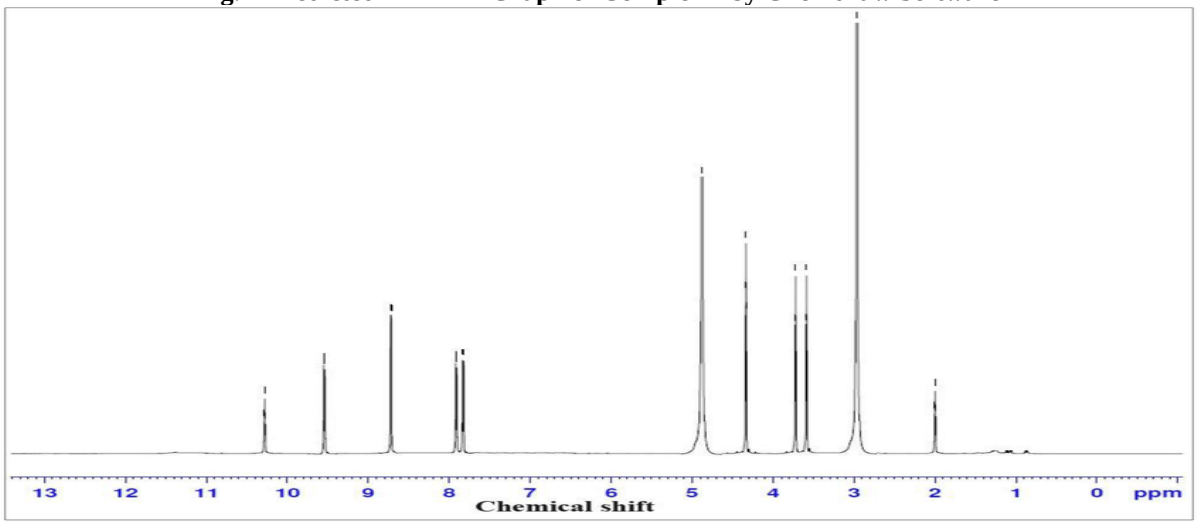


Fig.5 Practical graph of ^{1}H NMR Graph of Complex 1

It synthesizes 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 is assigned 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 Mn (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, C=N, M-N and C-S group of these compound.

5.BiologicalEvaluation

(i)Antimicrobial studies

The in vitro antimicrobial activity of sulfadiazine and its metal Complexes 1-5 was evaluated against gram positive, gram negative bacteria and fungi. The antimicrobial activities of all complexes were measured by measuring inhibition zone observed around the tested material. All metal complexes show increased zone of inhibition when compared with the ligand sulfadiazine against bacteria and fungi under study. Complexes 3, 4 and 5 were active against both gram positive (staphylococci) and gram negative (E.coli and pseudomonousauerginosa) bacteria, whereas Complexes1 and 2 show lesser activity (a)). Except Complex 3, Complexes 1, 2,4and 5exhibit lethal antifungal activity towards CandidaAlbicans, whereas Complexes 3,4and 5 were found to be active against aspergillus flavus. On comparing the antibacterial and antifungal activities of the metal complexes, it is observed that at the concentration level of 10ppm, Complexes 3and 4 gave promising results. It could be observed that the metal complexes have shown promising results compared to the ligand sulfadiazine drug. The increased inhibition activity of the metal complexes can be explained on the basis of Tweedy's Chelation theory.

(ii)Antifungal activity:

The compounds synthesized during the present investigation were screened for their antifungal activity. The anti-fungal 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.

MATERIALS USED:

- Sterilized Petri dishes
- Sterilized graduated pipettes
- Sterilized conical flasks, glass rod, beakers and watch glasses.
- Sterilized 6mm cork borer.
- Sterilized inoculation loop.
- 18-24 hours old growth culture on nutrient broth.
- Sterilized fine pointed forceps.
- Sterile tubercular syringes.
- Sterile cotton wool
- Sterile cotton swabs.

(iii) Preparation: Nutrient broth was prepared as follows:

Composition:

Peptone	: 20 g.
Beef extract	: 05 g.
Sodium Chloride	: 05 g.
Distilled water up to	: 1000 ml.

Nutrient broth is prepared by dissolving all these and steam for about 2 hour adjust the reaction mixture PH to about 7.2 and autoclave at 15 lbs/ in2 pressure for 20 minutes. One day prior to the testing, the organisms obtained from the laboratory stock were sub-cultured into sterile nutrient broth and incubated at 37oC for 24 hours. The culture growth thus obtained was used as inoculum for the anti-fungal testing.

(iv) Preparation of nutrient agar media:

The nutrient agar media was prepared by using the following ingredients.

Peptone	: 20 g.
Beef extract	: 05 g.
Sodium chloride	: 05 g.
Agar (Bacteriological)	: 20 g.
Distilled water up to	: 1000 ml.

Weighed quantities of peptone, beef extract was dissolved in distilled water by gentle warming, and then the specified amount of agar was dissolved by heating on boiling water bath. Then the PH of the above solution is adjusted by adding sodium chloride and the volume of final solution is made up to 1000 ml with distilled water. Then the above prepared nutrient agar media is sterilized by autoclave at 120 ºC for 20 minutes at 15 lbs/ in2 pressure.

(v) Preparation of test solution:

10mg of the test compound was dissolved in 10 ml of DMSO. From this 10 ml of solution was taken

and diluted to 100 ml with DMSO. Now the concentration of the test compound is 100 µg / ml. These sample solutions were made in suitably labelled sterilized test tubes.

(vi) Preparation of standard solution:
The standard drug used for the testing is Fluconazole. It is water soluble; the concentration of this drug is adjusted so as to contain 100 µg/ ml.

(vii) Method of testing:
The above prepared nutrient agar media is cooled to 45 ºC with gentle shaking to bring about uniform cooling. To this 0.5 – 0.6 ml of 18-24 hours old culture was injected aseptically and mixed well by gentle shaking. This was poured onto the Petri dishes (20-25ml in each Petri dishes of big size) and was allowed to set about for one hour. Thereafter the cups were made by punching into the set agar with a sterile cork borer and scooping out the punched part of the agar. The diameter of each cup was 48 6mm. To these cups 100µl of the test compound was put, which was prepared in DMSO. After adding the drug solution, it was allowed to diffuse for about 45 minutes, at room temperature. Then the plates were incubated at 37º C for 24 hours in an incubator. The extent of diameter of inhibition after 24 hours was measured as the zone of inhibition in millimetres.

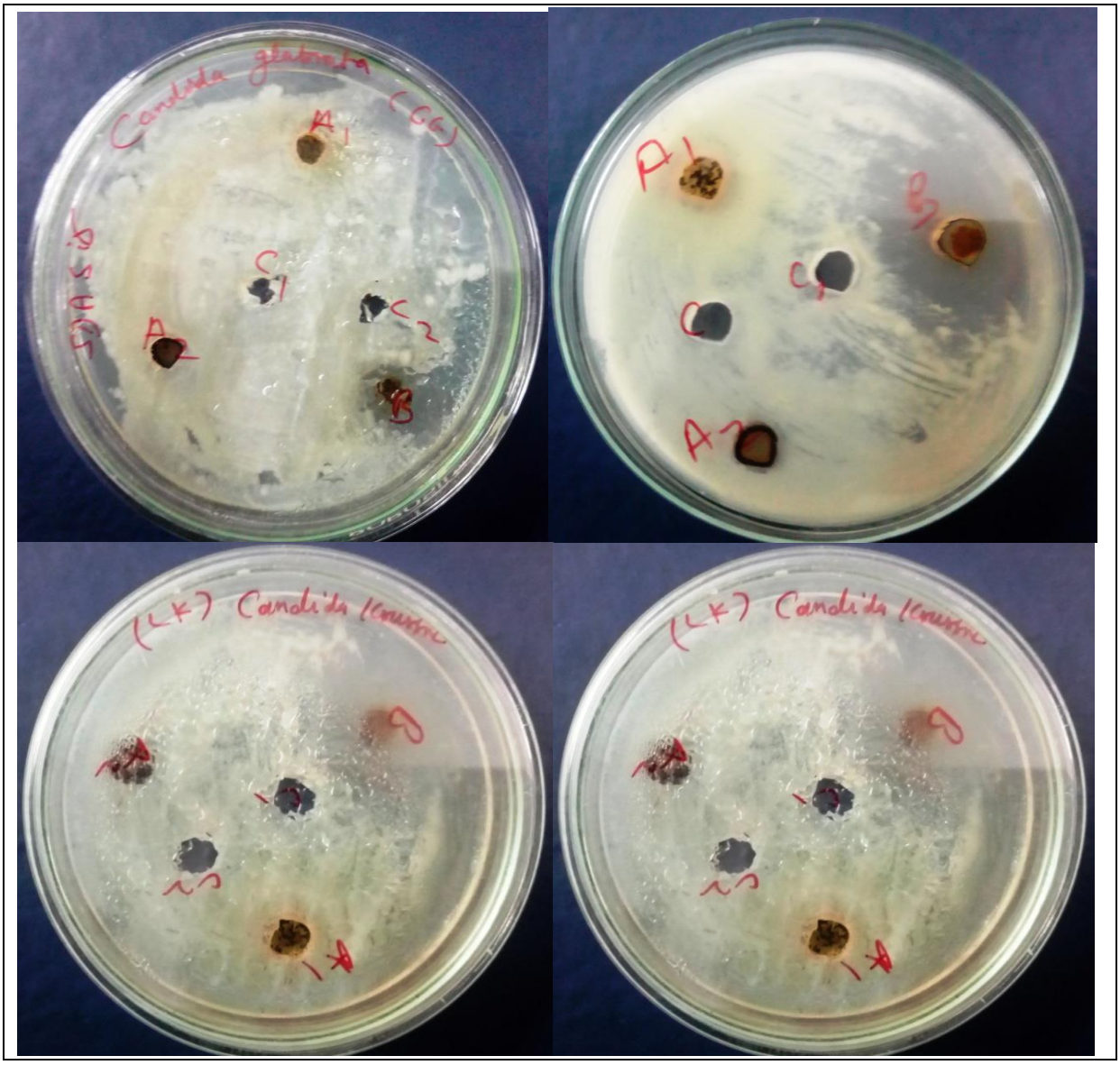


Fig.6 A,B,C and D Systematic diagram representing the Antifungal activity

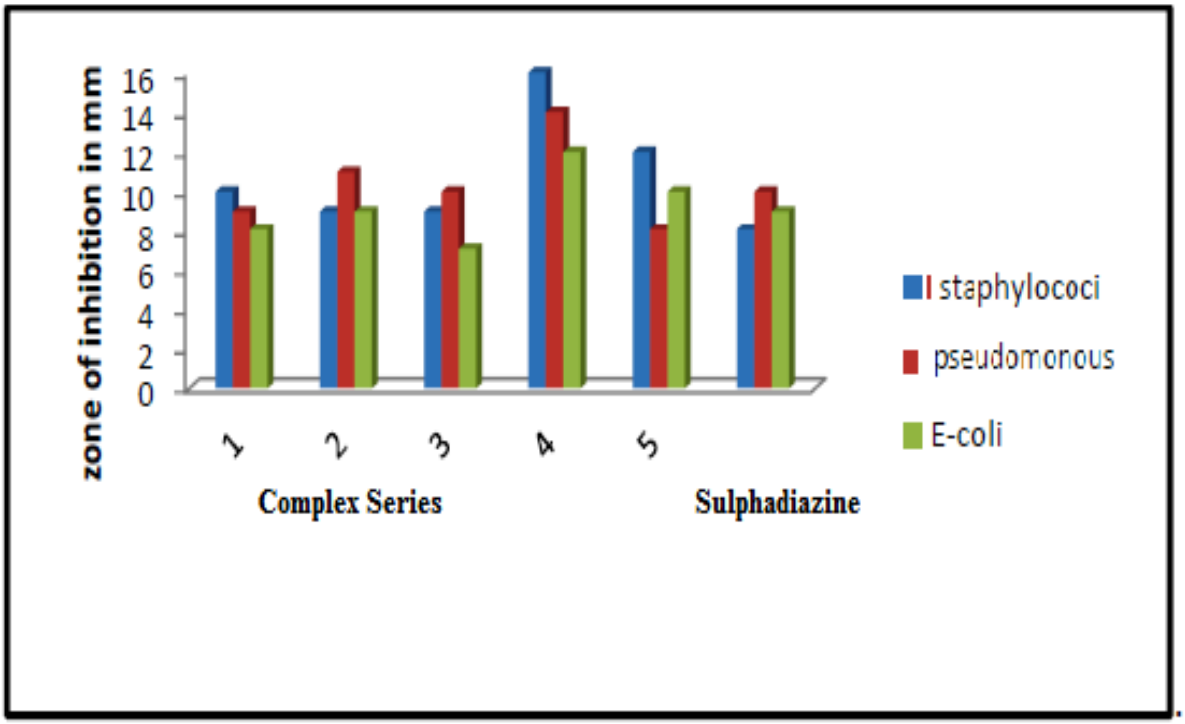


Fig.7 Bar graph showing the comparative studies of complex

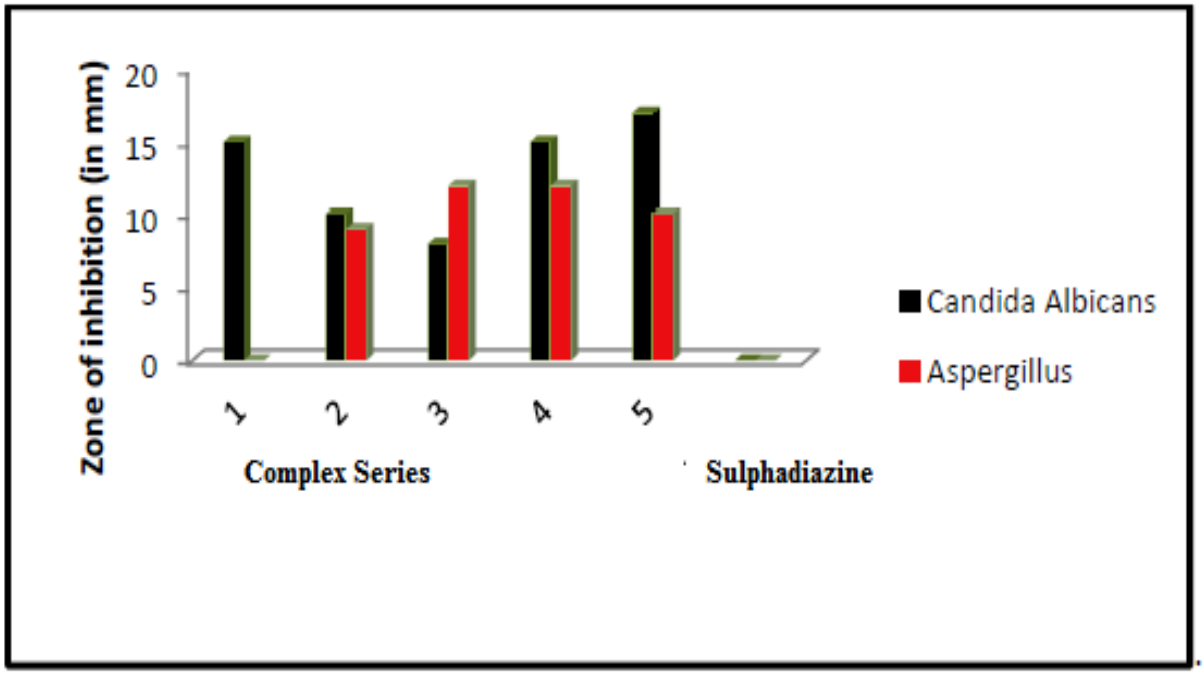


Fig.8 Bar graph showing the comparative studies of complex

SUMMARY & CONCLUSION:

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 IRand 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 bidentateligand, water molecule and nitrate ion as monodentate ligands. Theantimicrobial activity of sulfadiazine drug enhanced upon complexation with metal ions particularly for Copper (II)and Zinc(II) ion. The SwissADME 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 straightforward 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. The latter enables easy input and efficient analysis of the output through interactive capabilities, and does not require any prior knowledge in CADD. Moreover, interoperability allows for direct access to other SwissDrugDesign web tools, including SwissSimilarity (virtual screening), SwissBioisostere (ligand-based design), SwissTargetPrediction(prediction of biotargets), SwissDock(molecular docking), SwissSideChain(protein modelling) and SwissParam (molecular mechanics). As a result, SwissADME has been designed to support the entire community (specialists and nonexperts) in their drug discovery endeavours. It synthesizessulpha diazine complex perform various type of analytical data showing a stable complex. In this complex melting points of the showed higher values (above 265^0C) 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 is assigned 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 Mn (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, C=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 *Candidamaltosa*. 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 be easier for the complexes to diffuse inside the bacterial cell. In Gram negative bacteria the outer membrane is much thinner than by Gram positive ones and they possess the outer membrane. As other active compounds can one distinguish the para isomer, is nicotinic acid and its hydrazide, isoniazid which is a widely used anti-tuberculosis drug against *Plasmodium sp.* As well as isoniazid, also pyrazinamide is used along in treatment of tuberculosis. Although the results confirmed that the most active are Mn (II) carboxylates, their MIC values are quite high and thus cannot be classified as potent antimicrobial agents.

REFERENCES:

1. O.T Avery;C Macleod ;M McCarthy;*J. Exp. Med*. **1944**, 79, 137.
2. S.C Prescott; CG Duan; Industrial Microbiology, 3rd ed., McGraw HillKoyakesha, **1949**.
3. E Chargaff ;Experientia,**1950**, 6, 201.
4. J.D Watson;FHC Crick; *Nature***1953**, 171, 737-738.
5. A I A Vogel; Text Book of quantitative inorganic analysis (ELBS and Langmanns Green and Co, London) 3rdedition, **1962**.
6. K Nakamoto; Infraredspectra of Inorganic and coordination compounds, **1963** 2nd Ed Wiley-Inter science172,.
7. B.G Tweedy; Phytopathology,**1964**,55, 910.
8. J.A Vaichulish; U.S. Patent 3, 271, 251, *Chem. Abstr*.**1966**, 65, 199.

9. A B P Lever; Inorganic Electronic Spectroscopy, Elsevier Publishing Company, New York, **1968**.
10. D.F Lindow; CN Cortez;RG Harvey ; *J. Am. Chem. Soc*.**1972**, 94, 5406.
11. D.S Cook; MF Turner ;*J. Chem. Soc. Perkin. Trans*. **1975**,21021.
12. N.C Baenziger;AWStruss; *J. Inorg. Chem*.**1976**, 151,807.
13. J.C L Fox; SM Modak;JWStanford;PL Fox; *J. Plastic and Reconst. Sur*.**1979**,13, 89.
14. A H J Wang;GJQuigley; F J Kolpak; JL Crawford; JH Van Boom; G Van der Marel;ARich;*Nature*,**1979**,282, 680.
15. N Anand; ME Wolff; (Ed.),Burger's Medicinal Chemistry. Wiley Interscience, **1980,** New York 1-40.
16. R Wing; H Drew; T Takano; C Broka; S Tanaka;KItakura;RE Dickerson ;*Nature*,**1980**, 287, 755.
17. A Bult; *Int. J. Environ. Stud*.**1982**, 16, 261.
18. R Tribolet;H Sigel; *Eur. J. Biochem*.**1987**, 163, 353.
19. M Wisneiwski; A Opolski; J Wietrzyle ;*J. Inorg. Biochem*.**1987**,86, 480

A. EDerome,.Modern NMR Techniques for Chemistry Research, Pergamon Press,Oxford, **1987**.

20. J Pranata; SGWierschkaJorgenson,*J.Am. Chem. Soc*.**1991**,1132, 810
21. A Sharpia; PFBeales; M Halloran *Parasitology today*,**1993**,9, 168.
22. L .Menabue; M Saladini; .*J. Inorg. Biochem*.**1993**, 49,201.
23. J. B Chaires;*Biochemistry*, **1993**, 32(10), 2573.
24. W H Wernsdorfer; *ActaTropica*,**1994**,56, 143.
25. P.J Hore ; Nuclear Magnetic Resonance, Oxford University Press, NewYork, **1995**.
26. J Robert; J Xiao; B Schliesman; DJ Parsons; CF Shaw ; *J.Inorg.Chem*.**1996**,35, 424.
27. A Garcia-Raso; JJ Fiol; G Martorell; A Lopez-Zafra; M Quiros; *Polyhedron*,**1997**,1, 6613.
28. British Pharmacopoeia I I Biological assay and Tests, the Stationary Office Ltd., LondonA-205, **1998**.
29. MS Gunthkal; TR Goudal; SA Patil; *Ori. J. Chem*.**1998**,16151.
30. J.B Lambert; HF Shurvell; DA Lightner; RG Cooks; OrganicStructural Spectroscopy, Prentice-Hall, UpperSaddler River, New Jersey,**1998**.
31. E Balter; M Marshall;G Vogel; GTaubes; EPennis; M Enserink*M* .*Science*,**2000**,2904, 28.
32. A Garcia-Raso; JJ Fiol; A RigoSLopez-Lopez; E Molins; E Espinosa; A Borras;GBlzuet; J Orras; ACastineiras; *Polyhedron*, **2000**,19,991.
33. J.G Breman;.*Am. J. Trop. Med.Hyg*.**2001**, 6485, 95.
34. J.L Gallup; JD Sadd;*Am. J. Trop. Med. Hyg*.**2001**,63, 85.
35. M Navarro; EJ Cisnero-Fajardo; T Lehmann; RA Sanchez-Delgado; R Atencio, P Silvia; R Lira; JA Urbina;*J.Inorg. Chem*.**2001**,40, 6879.
36. A Rahman; MI Choudhary; W Thomson; J Bio assay techniques for drug developments. Harwood academicpublishers Netherlands, **2001**,16.
37. L Gutierrez; GAlzuet; J Borras; A Castineiras; A Rodriguez-Fortea; E Ruiz;*J.Inorg. Chem*. **2001**, 403,89.
38. L Delhaes; H Abessolo;CBiot ; L Berry; P Delcourt;LMaciejewski; L Brocard; J. Camus D Dive, D.Paras.Res. **2001**,87239.
39. Lipinski, C. A., Lombardo, F., Dominy, B. W. & Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug. Deliv. Rev*. **46**, 3–26 **2001**.
40. J Mukta; S Nehra ; Metal Based Drugs,**2002**, 9, 1.
41. NH Gokhale; SB Padhye; S L Croft; HD Kendrick; W Davies; CE Anson; AK Powell;*J*.Inorg.Biochem.**2003**,95, 249.
42. R.C Hahn; YT MoratoConciecao; NL Santos; JF FerreiraHamdan; Mycoses,**2003**, 46, 342.M Shakir ;P Chingsubam ;HTN Chishti; Y Azim, N Begum; *Ind. J. Chem*. **2004**,43A, 556.
43. M Navarr;etal.*J. Med. Chem*.**2004**,475, 204.
44. R Fernandez ;M Melchart;AHabtemariam; S Parsons; P Sadler; *J Chem. Eur*. **2004**, 10, 5173.
45. A Kreze;W Bal; *J. Inorg. Biochem*.**2004**, 98, 161.
46. R Robin; M Coombs; K Ringer; JM Blacquire; J C Smith; J Scott Neilsen;*J. Trans.Met.Chem*.**2005**, 30, 411.
47. S.A Lee; REyeson; ML Cheever; J Geng;V V Verkhusha;Burd;MOverduin;TGKutateladze; Proc. Natl. Acad.Sci.U. S. A.**2005**, 102, 13052.
48. K Ramakrishna Reddy;K Madhusudan Reddy; K Mahendra; *Ind.J.Chem*.**2006**,45A, 377.
49. T.L Hwang;AJShaka; J. Mag. Res. Series A,**1995**,112, 275.Origin, 7.5 Ed., OriginLab Corporation,Northampton, **2006**.
50. H Zahid; MM Naseer;*Appli. Organomet.Chem*.**2007**, 21, 728.
51. M.S Niasari;MBazarganipour; MR Ganjali; P Norouzi;*Trans. Met. Chem*.**2007**,32, 1.
52. Brenk, R. *et al*. Lessons learnt from assembling screening libraries for drug discovery for neglected diseases. *ChemMedChem* **3**, 435–444 **2008.**
53. Ertl, P. & Schuffenhauer, A. Estimation of synthetic accessibility score ofdrug-like molecules based on molecular complexity and fragment contributions. *J. Cheminform*. **1**, 8 **2009.**

54. Baell, J. B. & Holloway, G. A. New substructure filters for removal of pan assay interference compounds (PAINS) from screening libraries and for their exclusion in bioassays. *J. Med. Chem.* **53**, 2719–2740, **2010.**
55. Grosdidier, A., Zoete, V. & Michielin, O. SwissDock, a protein-small molecule docking web service based on EADock DSS. *Nucleic Acids Res*. **39**, W270–7 **2011.**
56. O'Boyle, N. M. *et al.* OpenBabel: An open chemical toolbox. *J. Cheminform*. **3**, 33:**2011.**
57. Bruns, R. F. & Watson, I. A. Rules for Identifying Potentially Reactive or Promiscuous Compounds. *J. Med. Chem.* **55**, 9763–9772,**2012.**
58. A Wajid; NZubair; RB Mohod;*J. Chem.Pharm. Resis*. 5 134 ,**2013.**
59. Cheng, F. *et al.* admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. *J. Chem. Inf. Model.* **52**, 3099–3105 **,2013**.
60. Hay, M., Thomas, D. W., Craighead, J. L., Economides, C. & Rosenthal, J. Clinical development success rates for investigational drugs. *Nature Biotechnol.* **32**, 40–51,**2014.**
61. Daina, A., Michielin, O. & Zoete, V. 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.* **54**, 3284–3301, **2014.**
62. Mitchell, J. B. O. Machine learning methods in chemoinformatics. *WIREs Comput. Mol. Sci.* **4**, 468–481, **2014.**
63. G.feller, D. *et al.* SwissTargetPrediction: a web server for target prediction of bioactivesmall molecules. *Nucleic Acids Res*. **42**, W32–W38 ,**2014.**
64. Dahlin, J. L., Inglese, J. & Walters, M. A. Mitigating risk in academic preclinical drug discovery. *Nature Rev. Drug Discov*. **14**, 279–294,**2015.**
65. Tian, S. *et al.* The application of in silico drug-likeness predictions in pharmaceutical research. *Adv Drug Deliv Rev* **86**, 2–10 ,**2015.**
66. Irwin, J. J. *et al.* An Aggregation Advisor for Ligand Discovery. *J. Med. Chem.* **58**, 7076–7087 ,**2015.**
67. Cereto-Massaguà, A. *et al.* Molecular fingerprint similarity search in virtual screening. *Methods* **71**, 58–63, **2015.**
68. Clark, A. M. *et al.* Open Source Bayesian Models. 1.Application to ADME/Tox and Drug Discovery Datasets. *J. Chem. Inf. Model.* **55**, 1231–1245,**2015.**
69. Pires, D. E. V., Blundell, T. L. & Ascher, D. B. pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. *J. Med. Chem.* **58**, 4066–4072,**2015.**
70. Daina, A. & Zoete, V. A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *ChemMedChem* **11**, 1117–1121,**2016.**
71. Zoete, V., Daina, A., Bovigny, C. & Michielin, O. SwissSimilarity: A Web Tool for Low to Ultra High Throughput Ligand-Based Virtual Screening. *J. Chem. Inf. Model.* **56**, 1399–1404,**2016.**
72. Narendra Kumar Chaudhary, and Parashuram Mishra, Metal Complexes of a Novel Schiff Base Based on Penicillin: Characterization, Molecular Modeling, and Antibacterial Activity Study, Bioinorganic Chemistry and Applications Volume 2017, Article ID 6927675, 13 pages,**2017**
73. Walaa H. Mahmoud, GehadGenidy Mohamedetal.**,M**etal complexes of novel Schiff base derived from the condensation of 2-quinoline carboxaldehyde and ambroxoldrug with some transition metal ions: Metal complexes of Ambroxol based Schiff base**,**Applied Organometallic Chemistry 32(7):e4392,**2018.**
74. Jie Yuetal., Investigating adsorption mechanism and surface complex formation modeling for aqueous sulfadiazine bonding on Fe/Mn binary oxides,Environmental Science and Pollution Research 26(1) June **2019.**
75. Angelo Frei, Metal Complexes, an Untapped Source of Antibiotic Potential, Antibiotics 2020, 9, 90; doi:10.3390/antibiotics9020090.**2020**