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SYNTHESIS AND CHARACTERIZATION OF SOME SULPHA CONTAINING METAL COMPLEX AND THEIR BIOLOGICAL IMPLICATION

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ABSTRACT

Here, we present the new SwissADME 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. Easy efficient input and interpretation are ensured thanks to a user-friendly interface through the login-free website http://www.swissadme.ch. Specialists, but also nonexpert in cheminformatics or computational chemistry can predict rapidly key parameters for a collection of molecules to support their drug discovery endeavours.

KEYWORDS: *SwissADME, ulpha containing metal complex, pharmacokinetics, cheminformatics.*

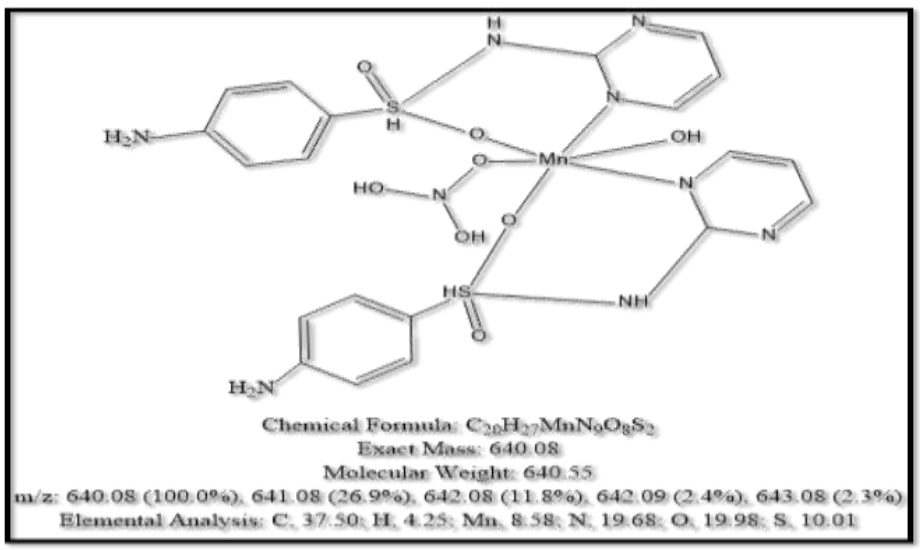
1. INTRODUCTION

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 SwissADME 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. 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. 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.

2. SYNTHESIS AND CHARECTERIZATION OF MN METAL WITH SULPHA DRUG COMPLEX

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 mixturewas stirred on a magnetic stirrer. The light brown crystalline product formed after 7-8 hrswere collected by filtration. The solid was washed several times with methanol (50 mL), then with diethyl ether (30 mL) and finallydried in a vacuum. Mol. Formula (Complex 1),

MnC20H20N10S2O11: Mol. Wt. 700.93, M.P. 2760C, Yield: 0.192g. Colour: Pale brown.



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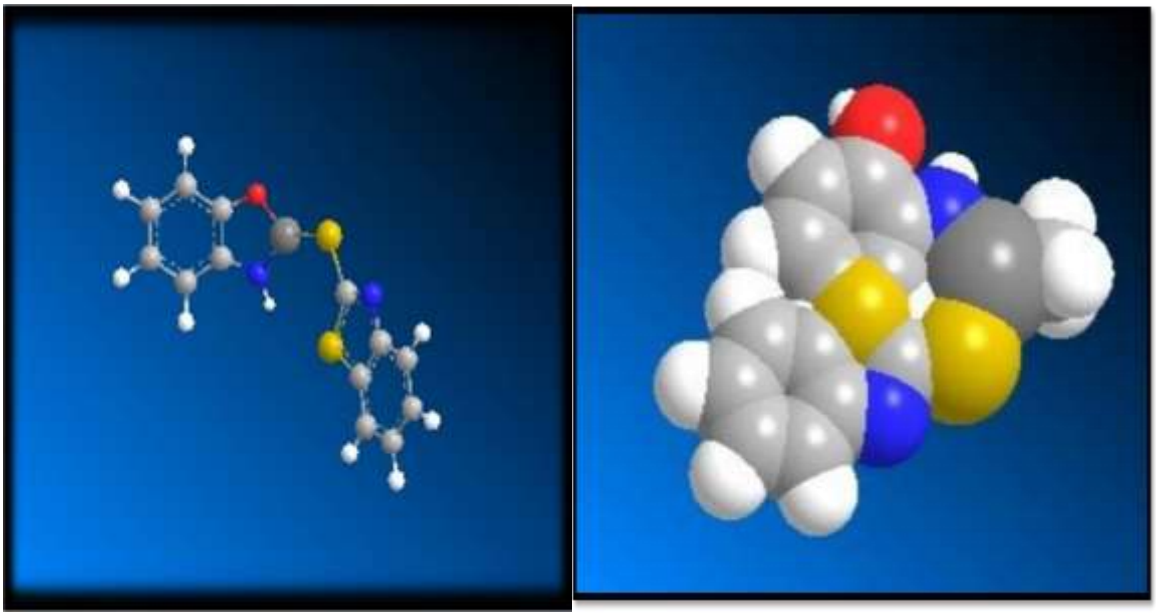
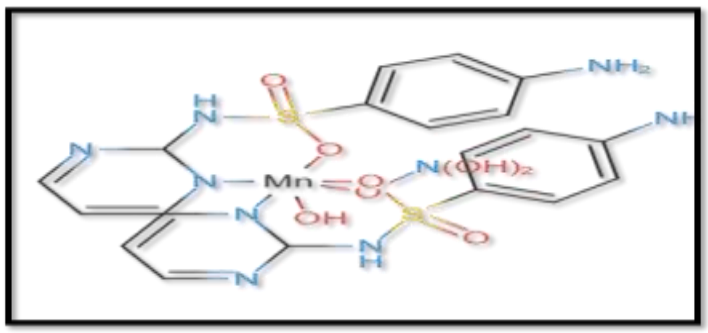


I. Predicted ADME properties of Mn containing(4-amino-N-(2- pyrimidinyl) benzenesulfonamide) through pkCSM

Molecule Depiction



Molecule Properties

Descriptor	Value
Molecular Weight	640.563
LogP	-0.711
#Rotatable Bonds	4
#Acceptors	15
#Donors	9
Surface Area	229.210

Property	Model Name	Predicted Value	Unit
	Water solubility	-2.854	Numeric (log mol/L)

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Absorption			
Absorption	Caco2 permeability	-0.017	Numeric (log Papp in 10-6 cm/s)
Absorption	Intestinal absorption (human)	8.034	Numeric (% Absorbed)
Absorption	Skin Permeability	-2.735	Numeric (log Kp)
Absorption	P-glycoprotein substrate	Yes	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	No	Categorical (Yes/No)
Distribution	VDss (human)	0.291	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.24	Numeric (Fu)
Distribution	BBB permeability	-2.204	Numeric (log BB)
Distribution	CNS permeability	-4.546	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)

3. SYNTHESIS AND CHARECTERIZATION OF ZN METAL WITH SULPHA DRUG COMPLEX

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 Zinc sulphate (0.245 g,1mmol). The reaction mixturewas stirred on a magnetic stirrer. The light brown crystalline product formed after 7-8 hrswere collected by filtration. The solid was washed several times with methanol (50 mL), then with diethyl ether (30 mL) and finallydried in a vacuum. Mol. Formula (Complex 1), ZnC20H20N10S2O11: Mol. Wt. 650.99, M.P. 2760C, Yield: 0.192g. Colour: White.

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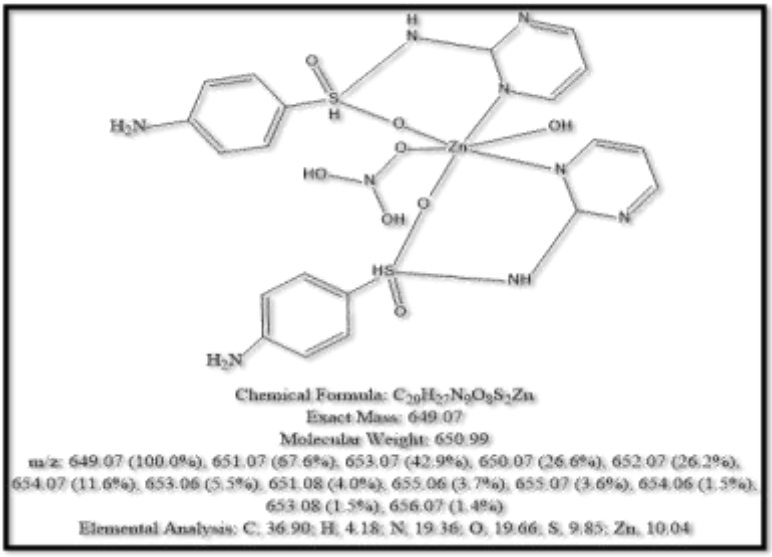

Descriptor	Value
Molecular Weight	651.015
LogP	-0.711
Rotatable Bonds	4
Acceptors	15
Donors	9
Surface Area	229.372

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-2.854	Numeric (log mol/L)
Absorption	Caco2 permeability	-0.017	Numeric (log Papp in 10-

Drug/Complexes Melting Point Conductivity

Table 3: Analytical data of Sulfadiazine and their Metal complexes

Drug/Complex	Melting Ponit	Conductivity
Sulfadiazine	253	0.88
MnC20H20N10S2O11	276	0.56
ZnC20H20N10S2O11	290	0.56
CoC20H20N10S2O11	281	0.39
CuC20H20N10S2O11	310	0.78
NiC20H20N10S2O11	347	0.32

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FT-IR Spectra

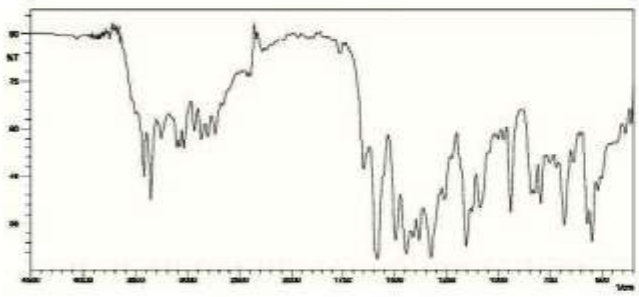
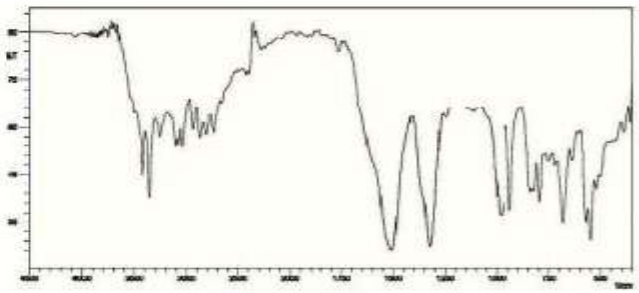
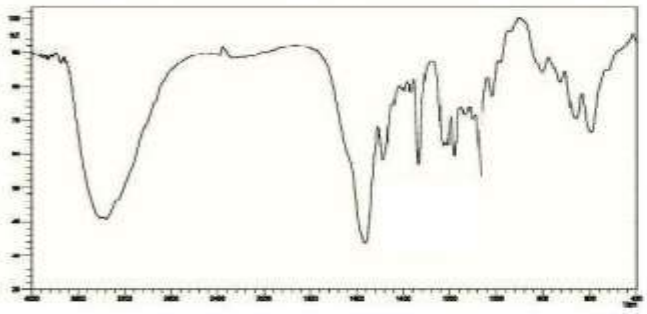


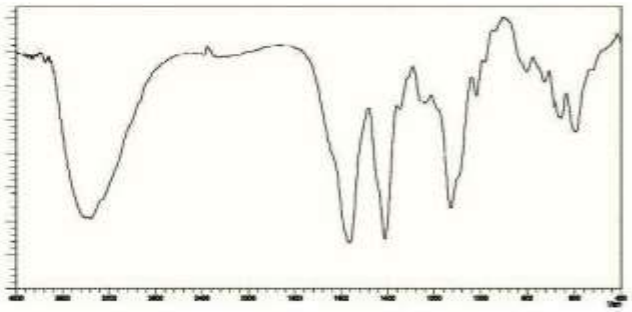
Fig 2 FT-IR Spectrum of Complex (1)



FT-IR Spectrum of Complex 2



FT-IR Spectrum of Complex 3



FT-IR Spectrum of Complex 4

Assignment	Sulphadiazine Cm-1	Complex - 1 Cm-1	Complex - 2 Cm-1	Complex - 3 Cm-1	Complex- 4 Cm-1	Complex- 5 Cm-1
N-Hof NH2	3425(vs)	3420	3410	3331	3419	3429
N-H(Sy)	3360	3355	3357	3355	3268	3362
SO2-N Moiety	1325	1342	1411	1370	1408	1350
SO2-N	1155	1126	1133	1120	1103	1128
S-N	945	973	1018	979	980	977
C=N	1652	1680	1610	1627	1611	1640

5. BIOLOGICAL EVALUATION

a. Antimicrobial studies

The invitro 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[54]..

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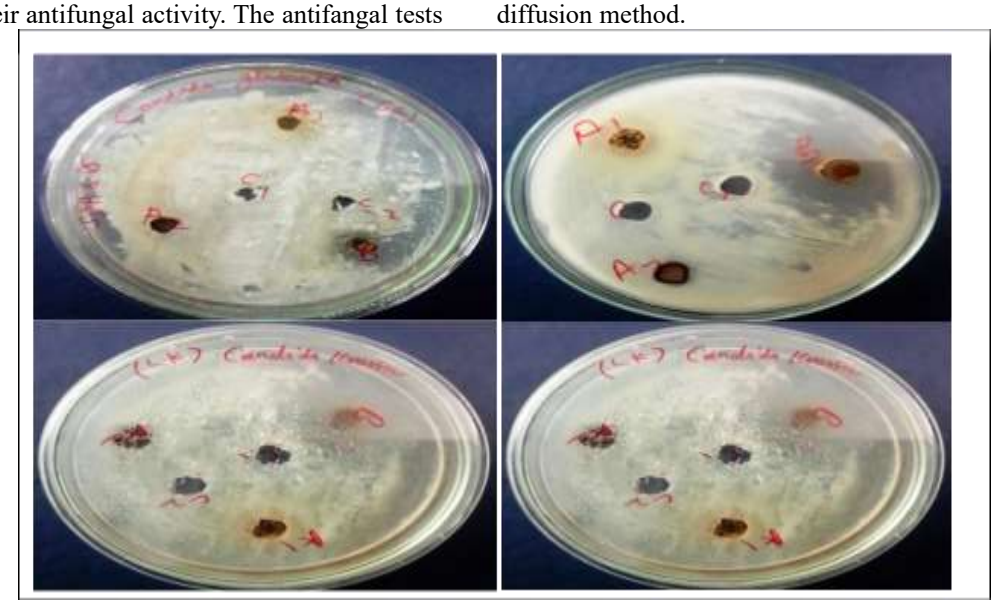
b. Antifungal Activity

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.



Systematic diagram representing the Antifungal activity in various complexes

6. SUMMARY &CONCLUSION

The present work focuses on the synthesis, characterization and biological studies of transition metal complexes (1-5) containing sulfadiazine drug as ligands. The structural information obtained from these complexes is inagreement 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(H2O) (NO3)].NO3. All the complexes have octahedral coordination in which the metal ions are coordinated tosulfadiazine molecule as bidentateligand, water molecule and nitrate ion as monodentateligands. The probablestructure of metal complexes were shown below in chart-1. Cyclic voltammetry studies of the metal complexes (1,3-5) and complex 2 revealed the irreversible and quasi-reversible one electron transfer redox processes respectively.Antimicrobial study reveals that metal complexes have more bioligical activity than the free ligand. Theantimicrobial activity of sulfadiazine drug enhanced upon complexation with metal ions particularly for Copper(II)and Zinc(II) ion.

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