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In-vitro bio-potential and pharmacological studies of newly synthesized Schiff base Cd(II) complex

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ABSTRACT

The post-transition '4d' Cd(II) metal complex were synthesized and characterized by the addition of neutral Schiff base (E)-N-(4-chlorobenzylidene)isonicotinohydrazide) as primary ligand and nitrite ion as mixed ligand. The Schiff base were synthesized with the addition of bio active Isoniazid and 4-chlorobenzaldehyde by eco-friendly technique (water as solvent). The synthesized complex where physically, chemically, spectroscopically and biologically characterized by various Physico-chemical, spectral and biological methods such as micro analytical data, namely elemental analysis & metal estimation, conductivity, Ultraviolet-visible, Infra-Red, Far-Infra Red, and Nuclear Magnetic Resonance (^{1}H &^{13}C) spectral studies. Based on the conductivity and spectral studies, the complex is neutral and non-electrolyte in nature. They have tetrahedral geometry around the Cd(II) metal ion. The *in-vitro* antibacterial and antifungal activities of Schiff base and Cd(II) complex were screened against *E. coli* and *A. Niger* by Agar disc diffusion method using Chloramphenicol and Fluconazole as standard control and DMSO as a solvent control. The results indicate that the complex have more potent than the Schiff base due to the chelation. The pharmacological studies of Schiff base and Cd(II) complex also predicted using a computational method by Swiss ADME software. The lipophilicity and medicinal chemistry importance of the Schiff base and Cd(II) complex were predicted and confirmed by the bio-potential activities.

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INTRODUCTION

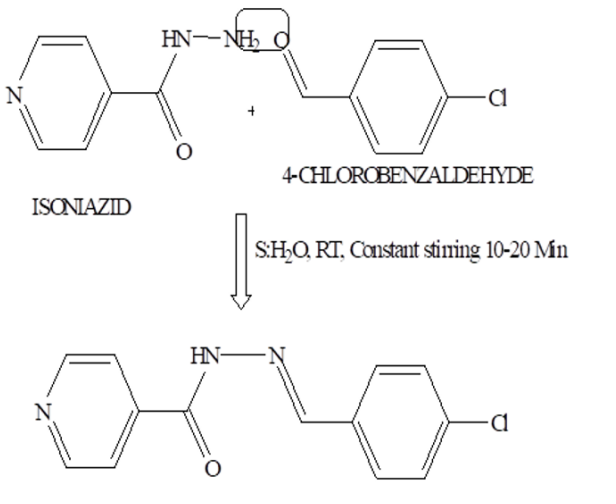
Coordination chemistry is a fast-growing important field in medicinal and bio-inorganic chemistry due to the availability of biologically active ligands such as Schiff base, Mannich base, etc., Isoniazid and its derivatives was used as the antibiotic (Pahlavani *et al.*, 2015) in the treatment of tuberculosis, antibacterial, antioxidant, anti-inflammatory and anticarcinogenic effect (Shingnapurkar *et al.*, 2012). The Schiff base and its transition and post-transition metal complexes have a variety of applications in the field of biological and pharmacological to develop the bio-important compounds (Orvig and Abrams, 1999). The pro drug Isoniazid has ther-

apeutic applications in pharmacological and biological fields. Schiff base ligands are very good coordinating molecule because of its different kinds of structure (Santos *et al.*, 2020). The Schiff bases are chelates ligand in coordination chemistry which are having antibacterial (Singh *et al.*, 2019), antifungal (Sharma *et al.*, 2010), herbicidal (Tajudeen and Kannappan, 2016), anti-inflammatory (Yong *et al.*, 2016), anticancer, anticonvulsant (Manimohan *et al.*, 2020) and anti-HIV agent (Hearn *et al.*, 2009). The largest applications of Schiff base in industrial and biological fields, the present studies aim to the synthesis of Schiff bases from Isoniazid and 4-chlorobenzaldehyde with water as a solvent. This method is a green synthetic route at room temperature. Synthesis and characterization of Cd(II) metal complex of Schiff base by green route method and characterized by various techniques such as physical, chemical, analytical, spectral, biological and pharmacological methods.

MATERIALS AND METHODS

Materials

The reagents and chemicals such as cadmium nitrate, Isoniazid (Alfa Aesar), 4-chlorobenzaldehyde (Alfa Aesar), DMSO, DMF, acetonitrile were of AnalaR grade at 99% pure and used as such without further purification. Alfa Aesar Company.

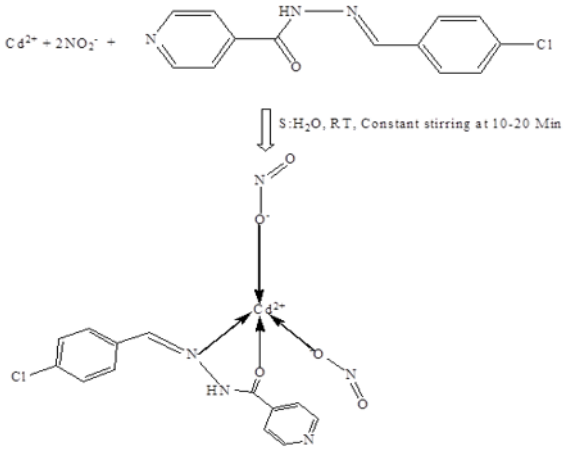


(*E*)-*N*'-(4-chlorobenzylidene)isonicotinohydrazide

Scheme 1: Synthesis of Schiff base

Methods

By using Vario make EL-III model instrument at 950-1200°C temperature, the elemental analysis was carried. The metal ions present in the complex were estimated by volumetric estimation after decomposing a known weight of complex in acids. The conductivity of the metal complex in acetonitrile solution at 10^{-3}M was measured using Conductivity Bridge. Using Varian make, CARY-5000 model, UV-VIS-NIR Spectrophotometer, the spectrum of the Ultraviolet region was measured. The IR spectra of ligand and its metal complex were recorded Using Schimadzu, FT-IR, 8400 S Model IR spectrometer. The Far IR spectra of the complex were recorded in a Bruker, Germany make, 3000 Hyperion Microscope with Vertex 80 FTIR system model instruments. Nuclear magnetic resonance spectra (^{1}H & ^{13}C) of Schiff base and diamagnetic complex at room temperature in DMSO-d6 were measured using the Bruker instrument.



Scheme 2: synthesis of Cd(II) complex

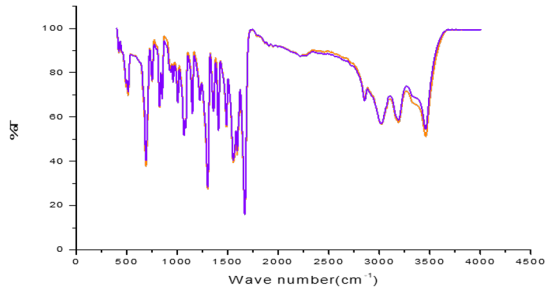


Figure 1: IR spectra of Schiff baseand Cd(II) complex

Synthesis of Schiff base

The Schiff base synthesized by mixing Isoniazid 0.528g in 10 ml water: methanol (1:1) and 0.541 g of 4-cholorobenzaldehyde in 5 ml of ethanol and add 15 ml water as a green solvent, and the mixture was stirred on 15-20 min at room temperature the precipitated white powder washed with water and dried in a desiccator. (Scheme 1)

Table 1: Analytical data

S.No.	Compound	MW (g/mol)	MP (°C)	Elemental analysis						Molar conductance (Ohm-1cm2mol-1
				%C	%H	%N	%O	%Cl	%M	
1	Schiff base	259.70	180-185	60.06 (48.01)	3.85 (3.90)	16.17 (16.10)	6.16 (6.10)	13.47 (13.19)	-	20.00
2	[Cd(SB)2(NO2)2	464.15	198	33.60 (33.90)	2.15 (2.40)	15.08 (15.90)	17.23 (17.90)	07.54 (07.87)	24.21 (24.50)	12.00

Table 2: IR stretching frequencies of Schiff base and metal complexes (cm^{-1})

S.No.	Compound	ν (C=O)	ν (H-C=N)	Sy (C=N)	Asy (C=N)	Sy (O-N=O)	Asy (O-N=O)	ν (N-O)
1	Schiff base	3456	1667	1552	1357	-	-	-
2	Cd(II)complex	3458	1668	1553	1368	1406	1300	1083

Table 3: Lipophilicity of Schiff base and Cd(II) complex

S.No.	Parameters	Schiff base	Cd(II) complex
1	Log $P_{o/w}$ (ilogP)	2.45	0.00
2	Log $P_{o/w}$ (XlogP3)	3.14	1.50
3	Log $P_{o/w}$ (WlogP)	3.66	3.00
4	Log $P_{o/w}$ (MlogP)	2.30	1.16
5	Log $P_{o/w}$ (SILICOS-IT)	3.65	3.04
6	Consensus log $P_{o/w}$	3.04	1.75

Table 4: Medicinal chemistry of Schiff base and Cd(II) complex

S.No.	Parameters	Schiff base	Cd(II) complex
1	GI absorption	High	Low
2	BBB permeant	Yes	No
3	P-gp substrate	No	No
4	CYP1A2 inhibitor	Yes	No
5	CYP2C19 inhibitor	Yes	No
6	CYP2C9 inhibitor	No	No
7	CYP2D6 inhibitor	No	No
8	CYP3A4 inhibitor	No	No
9	Log K_p (skin permeation)	-5.57 cm/s	-8.04 cm/s

Synthesis of Cd(II) complex

The Cd(II) complex were prepared by mixing Schiff base 0.842g 10 ml of methanol and sodium nitrite 0.447 g in 10 ml water to 1 g of cadmium nitrate in 15 ml of methanol and 10 ml of water added to the mixture used as a green solvent, and the mixture was stirred at 15-20 mins at room temperature, the precipitated colorless complex was filtered, washed with ethanol and dried in a desiccator and kept in an air-tight glass container. The complex is stable under ordinary conditions. (Scheme 2)

RESULTS AND DISCUSSION

Analytical Data

The elemental analysis, metal estimation of the synthesized complex were found in good agreement with the theoretical values (Table 1) confirmed by

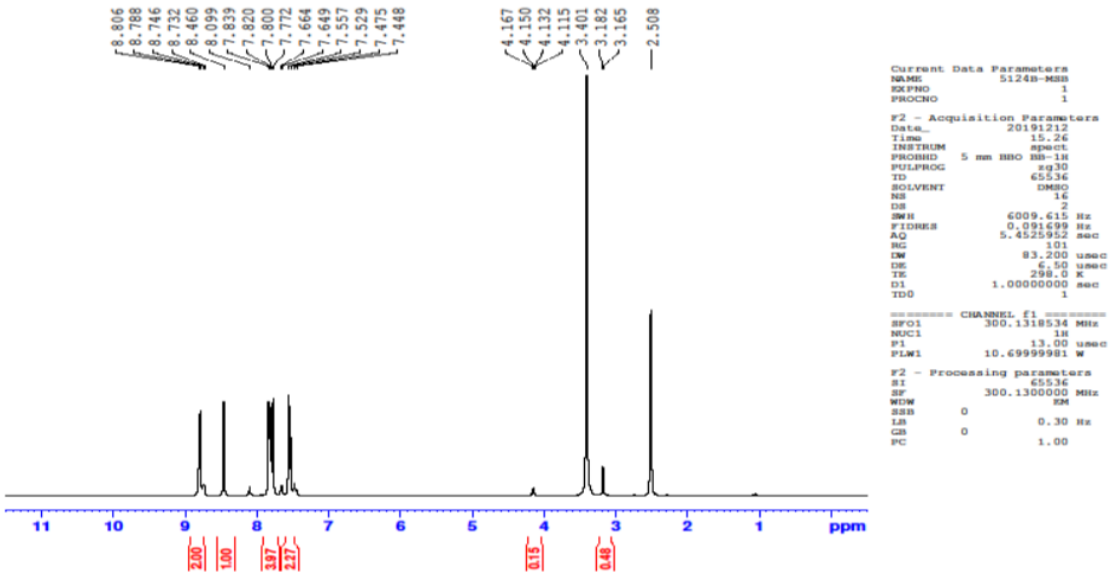


Figure 2: ^{1}H-NMR spectrum of (E)-N-(4-chlorobenzylidene) isonicotinohydrazide

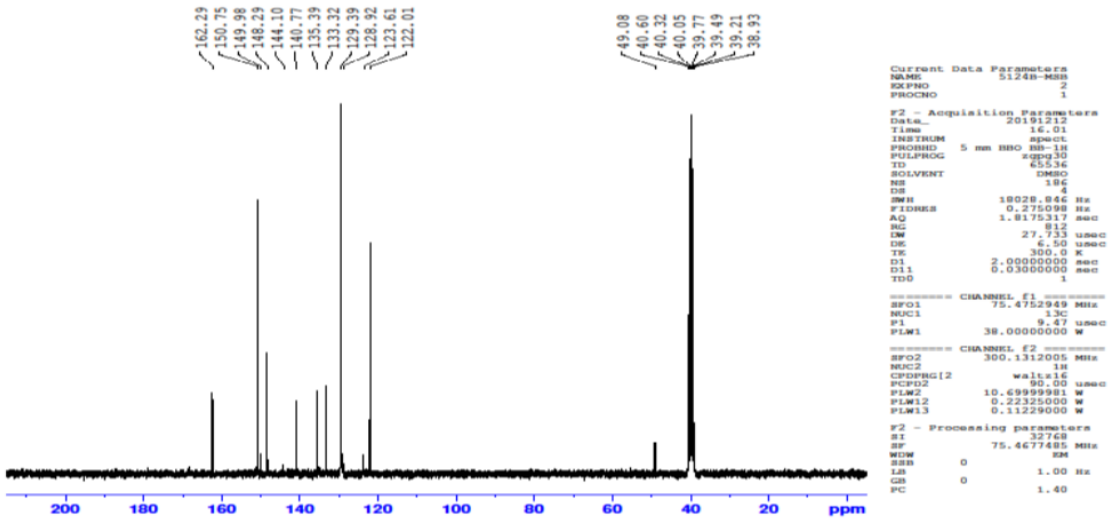


Figure 3: ^{13}C-NMR spectrum of (E)-N-(4-chlorobenzylidene) isonicotinohydrazide

the stoichiometry and molecular formula of the Cd(II) complex. The low molar conductance of the Cd(II) complex shows the non-electrolytic, neutral nature (1:0 type) of the complex, and the complex is perfectly neutral. There were no anionic and cationic species present outside the coordination sphere of the complex (Singh *et al.*, 2010).

UV Sspectrum

The free Schiff base exhibits a strong band at 32,258 cm^{-1}, 39,06 cm^{-1} which are reasonably accounted for the n→π* and π→π* transitions, respectively indicating the presence of imine C=N chromophoric and ketones C=O group present in the Schiff base. The Cd(II) complex shows the absorption value at 42016cm-1 in the UV region indicate no d-d transition is possible due to its completely filled 'd' sub shell. Only C-T (charge transfer transition) band is observed in the UV region, which confirms the tetrahedral geometry around the Cd(II) ion (Hussain *et al.*, 2004).

IR and Far-IR spectra

The IR spectrum of Schiff base shows a band at 3456 cm^{-1}, 1667 cm^{-1} and 1592 cm^{-1} correspond to ν(N-H), ν(N=CH) and ν(C=O) (Figure 1) respec-

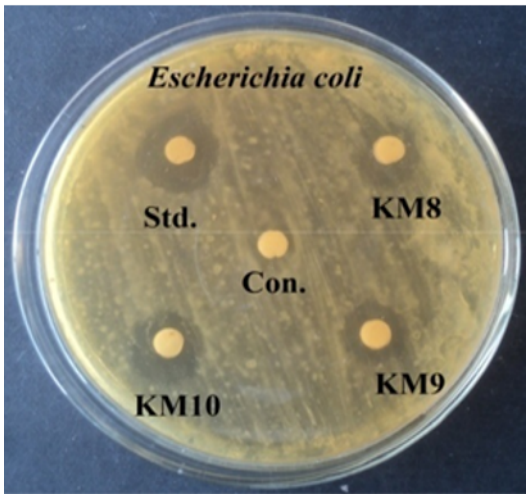


Figure 4: MIC of antibacterial disc

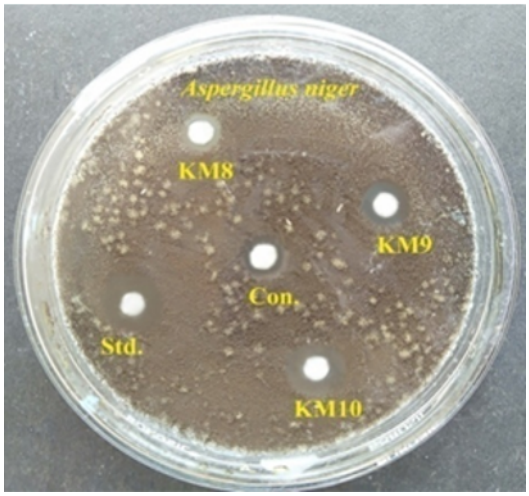


Figure 5: MIC of antifungal disc

tively, these are shifted to higher values because of the coordination of Schiff base through nitrogen atom of imine group and the oxygen atom of carbonyl group viz., bidentate mode (Spinu *et al.*, 2008). The anionic ligand nitrite ion shows the stretching frequencies at the lower region by skeletal mode at 1400 cm^{-1}, 1250-1320 cm^{-1} and 1050-1090 cm^{-1} corresponding to the symmetric O-N=O, asymmetric O-N=O and N-O, respectively (Table-2) in which the symmetric stretching frequency changed very little while asymmetric very large due to coordination of nitrite ion to the metal through oxygen atom (Singh *et al.*, 2006). The metal chelates atom ability was found from the Far-IR spectral data, the M-N and M-O coordination of Schiff base at 516 cm^{-1} and 490 cm^{-1} respectively confirm the coordination of metal ion through imine nitrogen and carbonyl oxygen atom of the secondary amine of Schiff base. The ambidentate nitrite ion coordinates through the oxygen atom is also confirmed by the lower frequency at the frequencies at 377 cm^{-1} (Ejidike and Ajibade, 2015).

NMR Spectra (^{1}H & ^{13}C)

The ^{1}H-NMR spectrum of the free Schiff base were recorded in DMSO-d6 at room temperature, and the relative peaks at 7.44 to 7.55 ppm, 7.64 to 7.66 ppm, 8.46 ppm, 8.09 ppm, 7.22-7.83 ppm, 8. 73- 8.80 shows the H_1, H_2, H_3, N-H_4, H_5 and H_6 respectively (Figure 2) confirm the formation, Schiff. (Weston and Brodasky, 1957) The 13C-NMR spec 135.39 ppm, 128.92 ppm, 129.39 ppm, 133.32 ppm, 144.10 ppm, 162.29 ppm, 140.77 ppm, 122.01 to 123.61 ppm, and 149-98 to 150.72 ppm, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, and C_9 (Figure 3) respectively also confirm the formation of Schiff base by dehydration of condensation by Isoniazid and 4-chlorobenzaldehyde in Cd(II) complex these chemical shift values are shifted to down or upfield due to the presence of resonance structure and conjugation of Schiff base and the also effective coordination of Schiff base through its nitrogen and oxygen atom of Schiff base and also confirmed the diamagnetic and tetrahedral geometry of the complex (Peterson *et al.*, 2009).

Bio-Potential activities

Antimicrobial activities were done by disc diffusion method using synthetic compounds. Petri plates were prepared by pouring 30 ml of nutrient agar (NA)/potatoes dextrose agar (PDA) medium. The test organism was inoculated on a solidified agar plate with the help of a micropipette and spread and allowed to dry for 10 minutes. The surfaces of media were inoculated with bacteria/fungi from a broth culture. A sterile cotton swab is dipped into a standardized microbe's test suspension and used to evenly inoculate the entire surface of the Nutrient agar /PDA plates. Briefly, inoculums containing of microbial strains were spread on Nutrient agar /PDA plates (Figure 4).

Using sterile forceps, the sterile filter papers (6 mm diameter) containing each 100μl of sample and 100μl Standard solution were laid down on the surface of an inoculated agar plate. The plates were incubated at 37 ºC for 24 h for the bacteria and 48 hr. for fungal strain. Each sample was tested in triplicates. The zones of inhibition of the tested microorganisms by the samples were measured using a millimeter scale.

The zone of inhibitory values of Schiff base and its complex shows good antibacterial activity against *E. coli* and moderate activity against *A. Niger* (Figure 5) due to the presence of azomethine (imine group) present in the Schiff base. The increased activity of metal chelates can also be explained on the basis of overtone cell permeability and Tweedy's chelation

theory (Firmino *et al.*, 2016). The permeability of lipid cell membrane accepts the lipid-soluble materials which reflect the lipophilicity, which is favor the antibacterial activities on chelation the polarity and π electron delocalization on the whole chelating ring increase the lipophilicity due to the partial sharing of positive charge with donor group. The other factors such as solubility conductivity, size and dipole moment are also favoring the microbial activities (Chandra *et al.*, 2009).

Pharmacokinetics study: General computational methodology

The SMILES for each structure were generated by the structure file generator, available at the free online tool SwissADME web page (Tables 3 and 4). Using the web tool, we calculated a number of simple molecular and physicochemical descriptors, such as the molecular weight (MW), molecular refractivity (MR), count of specific atom types and the topological polar surface area (TPSA), the latter proven as a useful descriptor in many models for estimation of membrane diffusion, ADME and pharmacokinetic behavior (Abou-Melha, 2008). The lipophilicity was assessed by means of five alternative predictive models, i.e. XLOGP; WLOGP; MLOGP; SILICOS-IT, iLOGP, together with a consensus logP estimation, based on the average value of the different computational parameters (Reingolas *et al.*, 2006).

CONCLUSION

The post-transition metal complex of Cd(II) with Schiff base and nitrite ion was synthesized by green route method using water as a green solvent. The molecular formula, monomeric and tetrahedral geometry of the complex confirmed by microanalysis, conductance and UV spectral data. Coordination of azomethine and the oxygen atom of carbonyl and nitrite ion was confirmed by IR and Far-IR spectral data. The diamagnetic nature and geometry of the complex were also confirmed by NMR spectral study. The complex shows higher biological activity against *E. coli* and moderately active against A. Niger. Biological activities were further confirmed by pharmacokinetics study.

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The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

Abou-Melha, K. S. 2008. Transition metal complexes of isonicotinic acid (2-hydroxybenzylidene) hydrazide. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 70(1):162–170.

Chandra, S., Jain, D., Sharma, A. K., Sharma, P. 2009. Coordination Modes of a Schiff Base Pentadentate Derivative of 4-Aminoantipyrine with Cobalt(II), Nickel(II) and Copper(II) Metal Ions: Synthesis, Spectroscopic and Antimicrobial Studies. *Molecules*, 14(1):174–190.

Ejidike, I. P., Ajibade, P. A. 2015. Synthesis, characterization, antioxidant, and antibacterial studies of some metal (II) complexes of tetradentate schiff base ligand:(4E)-4-[(2-(E)-[1-(2, 4-dihydroxyphenyl) ethylidene] aminoethyl) imino] pentan-2-one. *Bioinorganic Chemistry and Applications*, pages 1–9.

Firmino, G. S. S., de Souza, M. V. N., Pessoa, C., Lourenco, M. C. S., Resende, J. A. L. C., Lessa, J. A. 2016. Synthesis and evaluation of copper (II) complexes with isoniazid-derived hydrazones as anticancer and antitubercular agents. *BioMetals*, 29(6):953–963.

Hearn, M. J., Cynamon, M. H., Chen, M. F., Coppins, R., Davis, J., Kang, H. J.-O., Noble, A., Tu-Sekine, B., Terrot, M. S., Trombino, D. 2009. Preparation and antitubercular activities in vitro and in vivo of novel Schiff bases of isoniazid. *European Journal of Medicinal Chemistry*, 44(10):4169–4178.

Hussain, Z., Yousif, E., Ahmed, A., Altaie, A. 2004. Synthesis and characterization of Schiff's bases of sulfamethoxazole. *Organic and Medicinal Chemistry Letters*, 4(1).

Manimohan, M., Paulpandiyan, R., Pugalmani, S., Sithique, M. A. 2020. Biologically active Co (II), Cu (II), Zn (II) centered water soluble novel isoniazid grafted O-carboxymethyl chitosan Schiff base ligand and metal complexes: Synthesis, spectral characterisation and DNA nuclease activity. *International Journal of Biological Macromolecules*, 163:801–816.

Orvig, C., Abrams, M. J. 1999. Medicinal Inorganic Chemistry: Introduction. *Reviews in Inorganic*

Chemistry, 9.

Pahlavani, E., Kargar, H., Rad, N. S. 2015. A Study on Antitubercular and Antimicrobial Activity of Isoniazid Derivative. *Zahedan Journal of Research in Medical Sciences*, 17(7).

Peterson, Q. P., Hsu, D. C., Goode, D. R., Novotny, C. J., Totten, R. K., Hergenrother, P. J. 2009. Procaspase-3 activation as an anti-cancer strategy: Structure− activity relationship of procaspase-activating compound 1 (PAC-1) and Its cellular co-localization with caspase-3. *Journal of Medicinal Chemistry*, 52(18):5721–5731.

Reingolas, J. A., Son, C. A., Dullaghan, M., Oh, P. C., Frake, G. B., Carpenter, D. A., Sweigart 2006. π-Bonded quinonoid transition-metal complexes. *Dalton Transactions*, 20:2385–2398.

Santos, M. S. C., Matos, A. M., Reis, M., Martins, F. 2020. Lipophilicity assessment of some isoniazid derivatives active against Mycobacterium tuberculosis. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 599:124820.

Sharma, K. K., Singh, R., Fahmi, N., Singh, R. V. 2010. Synthesis, coordination behavior, and investigations of pharmacological effects of some transition metal complexes with isoniazid Schiff bases. *Journal of Coordination Chemistry*, 63(17):3071–3082.

Shingnapurkar, D., Dandawate, P., Anson, C. E., Powell, A. K., Afrasiabi, Z., Sinn, E., Pandit, S., Swamy, K. V., Franzblau, S., Padhye, S. 2012. Synthesis and characterization of pyruvate–isoniazid analogs and their copper complexes as potential ICL inhibitors. *Bioorganic and Medicinal Chemistry Letters*, 22(9):3172–3176.

Singh, A. K., Pandey, A. K., Banerjee, P., Saha, S. K., Chugh, B., Thakur, S., Pani, B., Chaubey, P., Singh, G. 2019. Eco-friendly disposal of expired antituberculosis drug isoniazid and its role in the protection of metal. *Journal of Environmental Chemical Engineering*, 7(2):102971.

Singh, B. K., Prakash, A., Rajour, H. K., Bhojak, N., Adhikari, D. 2010. Spectroscopic characterization and biological activity of Zn (II), Cd (II), Sn (II) and Pb (II) complexes with Schiff base derived from pyrrole-2-carboxaldehyde and 2-amino phenol. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 76(3-4):376–383.

Singh, K., Barwa, M. S., Tyagi, P. 2006. Synthesis, characterization and biological studies of Co (II), Ni (II), Cu (II) and Zn (II) complexes with bidentate Schiff bases derived by heterocyclic ketone. *European Journal of Medicinal Chemistry*, 41(1):147–153.

Spinu, C., Pleniceanu, M., Tigae, C. 2008. Biologically Active Transition Metal Chelates with a 2-Thiophenecarboxaldehyde-Derived Schiff Base: Synthesis, Characterization, and Antibacterial Properties. *Turkish Journal of Chemistry*, 32:487–493.

Tajudeen, S. S., Kannappan, G. 2016. Schiff Base-Copper (II) Complexes: Synthesis, Spectral Studies and Anti-tubercular and Antimicrobial Activity. *Indian Journal of Advances in Chemical Science*, 4(1):40–48.

Weston, R. E., Brodasky, T. F. 1957. Infrared Spectrum and Force Constants of the Nitrite Ion. *The Journal of Chemical Physics*, 27(3):683–689.

Yong, J., Mainsah, E., Ntum, S.-J., Ndifon, P. 2016. Synthesis, Characterization and Antibacterial Studies of Some Isoniazid-derived Schiff Bases. *International Research Journal of Pure and Applied Chemistry*, 12(1):1–8.