Journal of Exploratory Research in Pharmacology **2022** vol. 7(4) | 202–207
DOI: 10.14218/JERP.2022.00021

Original Article

Synthesis and Biological Study of Novel Schiff Base (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl) methylene) hydrazine) Ligand and Metal Complexes

Nirmal R. Joshi[1], Sandip G. Mule[1], Vishnu A. Gore[1], Ravindra D. Suryawanshi[2], Ganesh T. Pawar[2], Saroj R. Bembalkar[1*] and Rajendra P. Pawar[2*]

[1]*Department of Chemistry, Deogiri College, Aurangabad, Maharashtra, India;* [2]*Department of Chemistry, Shiv Chhatrapati College, Aurangabad, Maharashtra, India*

Received: February 24, 2022 | **Revised:** June 06, 2022 | **Accepted:** July 06, 2022 | **Published:** August 16, 2022

Abstract

Background and objectives: Hydrazone ligands along with their metal complexes exhibit important biological potential. Our objective was to synthesize new Schiff base ligands and their metal complexes which can act as vital drugs.

Methods: Metal complexes of Zn(II), Ni(II), Cu(II), Mn(II), Co(II), Hg(II), Cd(II), Sn(II), Zr(II), and Fe(II) were synthesized from a novel Schiff base (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)methylene) hydrazine) ligand using the condensation method. The ligand and metal complexes were characterized using analytical techniques. Their antimicrobial, antimalarial, and anti-tubercular activities were investigated.

Results: The synthesized ligand was found to be bidentate in nature. The stoichiometry of the metal ions to ligand was 1:2. Complexes of Co(II), Cu(II), Mn(II), and Cd(II) displayed excellent antimicrobial activity. The Mn(II) complex was active against M. TuberculosisThe Cu(II) and Cd(II) complexes displayed excellent activity against malaria, moderate to good antimicrobial and anti-tubercular activity while Zn(II), Co(II), Sn(II), Ni(II), Hg(II), and Fe(II) were active against malaria.

Conclusions: We report the synthesis and characterization of a new (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)methylene) hydrazine) Schiff base bidentate ligand and metal complexes. The antitubercular, antimicrobial, and antimalarial activity of the synthesized metal complexes revealed good antimicrobial potential of Cu(II), Co(II), Mn(II), and Cd(II) complexes. The Mn(II) was remarkably active against Mycobacterium Tuberculosis.

Keywords: Hydrazone; Ligand; Antimicrobial; Antitubercular; Antimalarial and metal complexes.

Abbreviations: DMSO, dimethyl sulfoxide; IR, infra-red; MIC, minimal inhibition concentration; NMR, nuclear magnetic resonance; TLC, thin layer chromatography; UV, ultraviolet.

[*]**Correspondence to:** Saroj R. Bembalkar, Department of Chemistry, Deogiri College, Aurangabad 431005, Maharashtra, India. ORCID: https://orcid.org/0000-0001-8249-6246. Tel: +91-240-2367335, Fax: +91-240-2367333, E-mail: s_bembalkar@yahoo.com; Rajendra P. Pawar, Department of Chemistry, Shiv Chhatrapati College, Aurangabad 431003, Maharashtra, India. ORCID: https://orcid.org/0000-0002-5861-2080. Tel: +91-240-2474872, Fax: +91-240-2480150, E-mail: rppawar@yahoo.com

How to cite this article: Joshi NR, Mule SG, Gore VA, Suryawanshi RD, Pawar GT, Bembalkar SR, *et al*. Synthesis and Biological Study of Novel Schiff Base (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl) methylene) hydrazine) Ligand and Metal Complexes. *J Explor Res Pharmacol* 2022;7(4):202–207. doi: 10.14218/JERP.2022.00021.

Introduction

Hydrazones are compounds that have an azomethine group, such as $CH{=}N{-}NH_2$ and are vital in applications of medicinal chemistry.[1] Hydrazones are the condensation products of amines and carbonyl compounds. Hydrazone ligand and metal complexes are commonly used as analytical reagents, as well as for treatment of various diseases.[2] In some chemical reactions, metal compounds of hydrazone are used as catalysts.[3] A Schiff base ligand forms a coordinated complex with metal ions. This metal complex exhibits a reversible association of ions or atoms by weak coordinate covalent bond formation. Schiff bases are important due to their

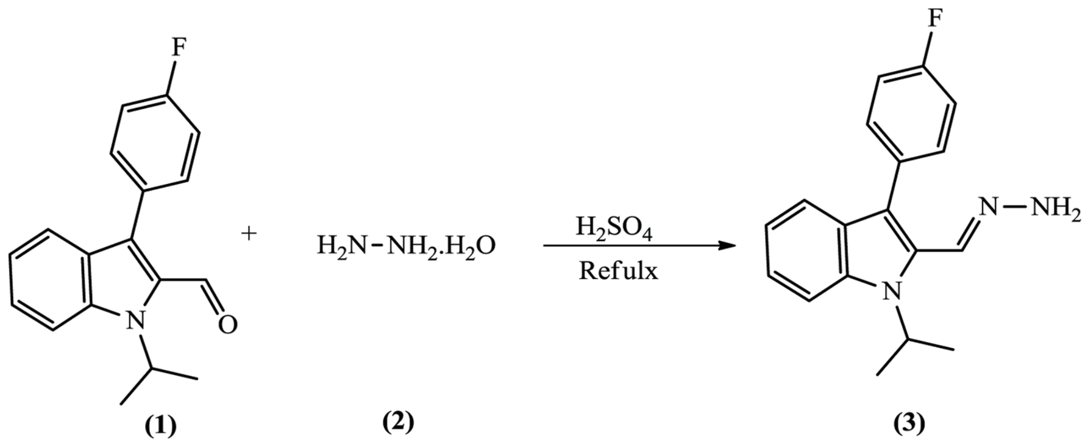

Fig. 1. Synthesis of [1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)methylene) hydrazine] ligand.

antimicrobial activity and are remarkable due to their stability and chelating properties.[4] Schiff bases can be used for the production of novel drugs. Schiff base complexes with metal ions have interested chemists due to applications of imines for their antituberculosis, antibacterial, antifungal, antimalarial, and antiviral activity.[5] Schiff bases and their metal complexes contain halogens that display antimicrobial activity.[6]

Herein, we report the synthesis and characterization of novel Schiff base hydrazone: (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)methylene) hydrazine) ligand. The ligand was prepared by condensing hydrazine hydrate and 3-(4-fluorophenyl)-1-isopropyl-1H-indole-2-carbaldehyde. The synthesized ligand and its metal complexes were screened for antimicrobial, anti-tubercular, and antimalarial activities.

Materials and methods

All metal salts, solvents, and chemicals purchased were analytical reagent grade and did not require further purification.

Synthesis of [1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl) methylene) hydrazine] ligand (L_2)

A mixture of 1 mmol of 3-(4-fluorophenyl)-1-isopropyl-1H-indole-2-carbaldehyde (1) and 8 mmol of hydrazine hydrate (2) was refluxed in ethanol in the presence of 1-2 drops of concentrated sulfuric acid for 5 h. The reaction progress was monitored using thin layer chromatography (TLC) in ethyl acetate:n-hexane (1:4). Upon completion of the reaction, the reaction mixture was cooled and poured onto crushed ice. The resulting product (3) was filtered off, dried, and purified by recrystallization from ethanol (Figure 1).

Synthesis of metal complexes

An ethanolic solution of metal salt (chlorides or nitrates) was mixed with an ethanolic ligand solution in a 2:1 (mmol) ratio. A slightly basic pH of the resulting reaction mixture was maintained with the addition of dilute ammonia, and the contents were refluxed for 6 h and the reaction was monitored using TLC in ethyl acetate: n-hexane as the mobile phase (1:4). After completion of the reaction, products were cooled, filtered off, dried (Figure 2), and confirmed using UV and IR spectra (Table 1).

Characterization

[1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl) methylene) hydrazine] L_2:^{1}HNMR (DMSO-d_6) δ ppm: 8.34 (s, 1H, CH, hydrazide) 6.95 (s, 2H, NH_2) δ 6.1 (m, 1H, CH, methine) 2.03 (s, 3H) 2.06 (s, 3H, CH_3) 1.57 (d, 3H) 1.62 (d, 3H CH_3) 7.51 (d, 2H, Ph), 7.67 (d, 2H, Ph) MS: m/z 295; FTIR: cm^{-1} 3,385 (NH), 1,600 (C=N), 3,053 (CH-Ar), 1,529 (C-C Ar), 2,972 (CH-Aliphatic)

IR Spectral analysis

IR spectral data ν cm^{-1} for C-H, M-N, C=N of ligand, and metal complexes are reported in Table 2. The IR frequency band due to the N-H bond in the free ligand was shifted to a lower value in the spectra of all synthesized complexes, showing the involvement of an N-H group in the complexes.

UV Spectral analysis of metal complexes

The λ_{max} values observed in the UV spectra of the synthesized metal complexes are summarized in Table 3. The UV spectra of the complexes were recorded in DMSO.

Biological activity

Antimicrobial study

The metal complexes were screened against four bacteria (*S. Pyogenus* MTCC 442, *E. Coli* MTCC 443, *P. Aeruginosa* MTCC 1688, and *S. Aureus* MTCC 96) and three fungal species (*C. Albicans* MTCC 227, *A. Niger* MTCC 282, and *A. Clavatus* MTCC 1323).

Antimicrobial activity was determined using the Broth dilution method.[7] Mueller–Hinton agar nutrient medium was used. The Hinton Broth Method was used to grow microbes and dilute the microbe compound suspension for the test.

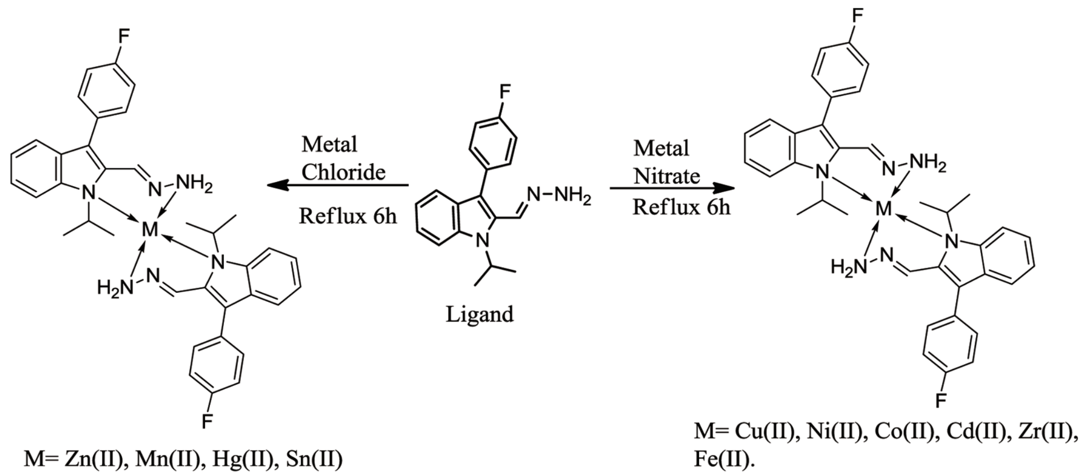

Fig. 2. Synthesis of metal complexes.

Table 1. Physical and analytical data of the synthesized ligand and complexes

Compound	Melting point (°C)	Color
Ligand (L_2)	119–120	Yellow
ZnL_2	258–260	Yellowish Brown
CuL_2	239–240	Yellowish Brown
NiL_2	>300	Yellow
CoL_2	268–270	Yellow
Mn L_2	>300	Yellow
Hg L_2	279–280	Yellow
CdL_2	263–265	Yellow
SnL_2	>300	Yellow
ZrL_2	279–280	Yellow
FeL_2	>300	Yellow

Table 2. IR spectral interpretation of ligand and metal complexes

Compound	ν cm^{-1} (C-H)	ν cm^{-1} (M-N)	ν cm^{-1} (C=N)	ν cm^{-1} (N-H)
Ligand	3,053	–	1,600	3,385
ZnL_2	3,064	420	1,531	2,966
CuL_2	3,062	426	1,531	2,970
NiL_2	3,059	426	1,527	2,873
CoL_2	3,064	420	1,531	2,906
Mn L_2	3,062	426	1,531	2,968
Hg L_2	3,062	429	1,529	2,968
CdL_2	2,980	424	1,527	2,665
SnL_2	2,974	422	1,527	2,974
ZrL_2	3,064	567	1,531	2,964
FeL_2	3,053	516	1,531	2,978

IR, infra-red.

Solutions of synthesized compounds were made in DMSO solvent (control). The sample tubes were also incubated at 37°C overnight. The minimal inhibition concentration (MIC) for the control test microbes was recorded to study the antimicrobial potential of the synthesized compounds. The MIC values for the synthesized metal complexes compared with ampicillin, chloramphenicol, nystatin, and greseofulvin are summarized in Table 4.

Antituberculosis activity

In vitro bacterial susceptibility tests were performed in bottles to determine antitubercular activity. *Mycobacterium Tuberculosis* (*$H_{37}Rv$ strain*) cultures were studied against the synthesized complexes.[8]

MIC values were determined for the antituberculosis activity. L.J inoculum nutrient medium (1 mg/mL) was used to grow the microorganisms. DMSO solvent was used to achieve the required concentration of test compounds. For primary and secondary screening, serial dilutions were prepared.

The MIC value was recorded as the highest dilution showing a minimum of 99% inhibition. MIC values of the synthesized compounds were recorded and compared with rifampicin and isoniazid as shown in Table 5.

Table 3. λ_{max} value of the synthesized metal complexes

Compound	Wavelength (λ_{max})
ZnL_2	256.50
CuL_2	205
NiL_2	206.50
CoL_2	205.50
Mn L_2	205.00
Hg L_2	204
CdL_2	203.4
SnL_2	229
ZrL_2	205
FeL_2	204.5

Table 4. Antimicrobial results of metal complexes

Compound	MIC						
	Antibacterial Activity				Antifungal Activity		
	S.PYOGENUS	*S.AUREUS*	*E.COLI*	*P.AERUGINOSA*	*A.NIGER*	*A.CLAVATUS*	*C.ALBICANS*
ZnL_2	500	500	250	500	>1,000	>1,000	500
CuL_2	100	250	100	100	1,000	1,000	1,000
NiL_2	500	50	50	250	>1,000	>1,000	500
CoL_2	100	250	125	62.5	500	500	500
Mn L_2	500	250	100	100	1,000	1,000	250
Hg L_2	500	500	250	250	>1,000	>1,000	500
CdL_2	250	200	100	250	500	1,000	250
SnL_2	500	250	500	500	1,000	1,000	500
ZrL_2	250	12.5	250	62.5	>1,000	>1,000	250
FeL_2	500	500	100	250	500	1,000	1,000
Ampicillin	100	250	100	–	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Nystatin	–	–	–	–	100	100	100
Greseofulvin	–	–	–	–	100	100	500

Antimalarial activity

The compounds were studied for antimalarial activity using the Rieckmann K.H. and co-worker's method.[9] An *in vitro* assay was used to evaluate antimalarial activity against *Plasmodium falciparum*; compound solutions were executed in 96 well microtiter plates.[10] Culture medium RPMI 1640 was used to grow the *P. Falciparum* strain. Test compounds were diluted using DMSO and further dilutions were made with culture medium. Results of the antimalarial activity of the metal complexes are summarized in Table 5.

The MIC values and the results of antimalarial activity were compared with chloroquine and quinine.[11]

Results and discussion

A ligand (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl) methylene) hydrazine) was synthesized from 3-(4-fluorophenyl)-1-isopropyl-1H-indole-2-carbaldehyde and hydrazine hydrate and used for the preparation of metal complexes which were characterized using spectroscopic methods and further studied for antimicrobial, antituberculosis, and antimalarial properties. The metal complexes of Zn(II), Cu(II), Ni(II), Co(II), Mn(II), Hg(II), Sn(II), Cd(II), Zr(II),

Table 5. Anti-tubercular and antimalarial activity of metal complexes

Compound	Anti-tubercular activity against $H_{37}R_v$ (MIC µg/mL)	Anti-malarial Activity (MEAN IC50 values)
ZnL_2	125	2.05 µg/mL
CuL_2	500	1.46 µg/mL
NiL_2	250	2.35 µg/mL
CoL_2	250	2.42 µg/mL
Mn L_2	62.5	3.10 µg/mL
Hg L_2	250	2.61 µg/mL
CdL_2	125	1.68 µg/mL
SnL_2	250	1.87 µg/mL
ZrL_2	250	3.82 µg/mL
FeL_2	500	2.25 µg/mL
Standard	Isoniazid 0.20 µg/mL, 99% inhibition	Chloroquine IC50–0.020 µg/mL
Standard	Rifampicin 40 µg/mL, 99% inhibition	Quinine IC50–0.268 µg/mL

and Fe(II) resulted in a ligand : metal ratio of 2:1.

The band at 1,600 cm^{-1} in the IR spectrum can be attributed to the stretching of the C=N group.[12] In cases of metal complexes, the spectral band that appeared at 420 cm^{-1} to 516 cm^{-1} is attributed to the presence of M-N bonds.[13] The IR band at 2,974 cm^{-1} to 3,064 cm^{-1} corresponds to the C-H stretching frequency. The ligand behaves as bidentate, coordinating with the metal ion through two nitrogen atoms present in the structure of the ligand. The λ_{max} values for metal complexes in the UV spectra were found in the range of 203 nm to 256 nm.[14] the Zn(II) complex showed a λ_{max} value at higher absorption.

The antimicrobial screening of metal complexes showed that Cu(II) and Co(II) were remarkably active against *S. Pyogenus* MTCC 442. The Cd(II) and Zr(II) complexes were active against *S. Aureus* MTCC 96. The Cu(II), Co(II), Mn(II), Cd(II), and Fe(II) complexes showed good activity against *E. Coli* MTCC 443, while Cu(II), Mn(II), and Zr(II) showed excellent activity against *P. Aeruginosa* MTCC 1688 compared to the standard drugs. Co(II) and Cd(II) were found to be active against *A. Niger* MTCC 282. Co(II) was found to be active against *A. Clavatus* MTCC 1323. Zn(II), Ni(II), Co(II), Mn(II), Hg(II), Cd(II), Sn(II), and Zr(II) showed good to excellent activity against the *C. Albicans* MTCC 227 fungus compared to standard drugs.

Mn(II) exhibited excellent antituberculosis activity against *MTB (H37Rv strain)*. Zn(II) and Cd(II) were active against *MTB* compared to the standard drugs (rifampicin and isoniazid).

Cu(II) and Cd(II) metal complexes exhibited promising antimalarial activity while Zn(II), Co(II), Sn(II), Ni(II), Hg(II), and Fe(II) were active against malaria.

Future directions

Coordination chemistry has remained a useful field in search of bioactive agents. In the present work, we reported the synthesis and characterization of metal complexes of bidentate (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)methylene) hydrazine) Schiff base ligands and demonstrated that these complexes had antitubercular, antimicrobial, and antimalarial properties. Future studies will focus on identifying new similar Schiff base ligands and their metal complexes as potential entities for searching bioactive metal complexes.

Conclusions

In conclusion, the present work reports the synthesis, characterization, and antimicrobial activity of a series of metal complexes of bidentate (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl) methylene) hydrazine) Schiff base ligands. The antitubercular, antimicrobial, and antimalarial activity of the synthesized metal complexes revealed good biological antimicrobial potential of Cu(II), Co(II), Mn(II), and Cd(II) complexes and the Mn(II) was remarkably active against *MTB*. The Cu(II) and Cd(II) displayed excellent activity against malaria compared to standard drugs, thus making the (1-((3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl) methylene) hydrazine) Schiff base ligands useful entities in coordination chemistry.

Acknowledgments

The authors thank Principal, Deogiri College, Aurangabad 431005 (MS), India for providing laboratory facilities.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Contributed to study concept and design (NRJ), acquisition of the data (SGM), assay performance and data analysis (VAG), drafting of the manuscript (RDS, GTP), critical revision of the manuscript (SRB), supervision (RPP).

Data sharing statement

No additional data are available.

References

[1] Karges J, Stokes RW, Cohen SM. Computational Prediction of the Binding Pose of Metal-Binding Pharmacophores. ACS Med Chem Lett 2022;13(3):428–435. doi:10.1021/acsmedchemlett.1c00584, PMID:35300086.

[2] Hameed A, Al-Rashida M, Uroos M, Abid Ali S, Khan KM. Schiff bases in medicinal chemistry: a patent review (2010-2015). Expert Opin Ther Pat 2017;27(1):63–79. doi:10.1080/13543776.2017.1252752, PMID:27774821.

[3] Manikandan R, Viswanathamurthi P, Muthukumar M. Ruthenium(II) hydrazone Schiff base complexes: synthesis, spectral study and catalytic applications. Spectrochim Acta A Mol Biomol Spectrosc 2011;83(1):297–303. doi:10.1016/j.saa.2011.08.033, PMID:21924947.

[4] Mary CPV, Shankar R, Vijayakumar S. Theoretical insights into the metal chelating and antimicrobial properties of the chalcone based Schiff bases. Molecular Simulation 2019;45(8):636–645. doi:10.1080/08927022.2019.1573370.

[5] Arulmurugan S, Kavitha HP, Venkatraman BR. Biological activities of Schiff base and its complexes: a review. Rasayan J Chem 2010;3(3):385–410.

[6] Wei L, Zhang J, Tan W, Wang G, Li Q, Dong F, *et al*. Antifungal activity of double Schiff bases of chitosan derivatives bearing active halogenobenzenes. Int J Biol Macromol 2021;179:292–298. doi:10.1016/j.ijbiomac.2021.02.184, PMID:33652045.

[7] Santos DA, Hamdan JS. Evaluation of broth microdilution antifungal susceptibility testing conditions for Trichophyton rubrum. J Clin Microbiol 2005;43(4):1917–1920. doi:10.1128/JCM.43.4.1917-1920.2005, PMID:15815018.

[8] Lall N, Das Sarma M, Hazra B, Meyer JJ. Antimycobacterial activity of diospyrin derivatives and a structural analogue of diospyrin against Mycobacterium tuberculosis in vitro. J Antimicrob Chemother 2003;51(2):435–438. doi:10.1093/jac/dkg068, PMID:12562718.

[9] Rieckmann KH, Davis DR, Hutton DC. Plasmodium vivax resistance to chloroquine? Lancet 1989;2(8673):1183–1184. doi:10.1016/s0140-6736(89)91792-3, PMID:2572903.

[10] Yeo AE, Rieckmann KH. Prolonged exposure of Plasmodium falciparum to ciprofloxacin increases anti-malarial activity. J Parasitol 1994;80(1):158–160. PMID:8308653.

[11] Chaulet JF, Robet Y, Prevosto JM, Soares O, Brazier JL. Simultaneous determination of chloroquine and quinine in human biological fluids by high-performance liquid chromatography. J Chromatogr

1993;613(2):303–310. doi:10.1016/0378-4347(93)80146-u, PMID:8491817.
[12] Clougherty L, Sousa J, Wyman G. C=N stretching frequency in infrared spectra of aromatic azomethines. J Org Chem 1957;22(4):462. doi:10.1021/jo01355a618.
[13] Percy GC, Thornton DA. N-aryl salicylaldimine complexes: Infrared and PMR spectra of the ligands and vibrational frequencies of their metal (II) chelates. J Inorg Nucl Chem 1972;34(11):3357–3367. doi:10.1016/0022-1902(72)80230-6.
[14] Al-Thib AT, Al-Salih MM. Spectral characterization and charge-transfer complexes of some schiff bases derived from aminopyridines and hydroxyacetophenones. Iraqi J of Sci 2010;55(3B):1127–1136.