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Synthesis, Physicochemical Characterization and Biological Evaluation of Schiff Bases and their Ni (II) Complexes

Pratibha C. Dhale[1], Panchasheela A. Ubale[2*], Kundalkesha D. Gaikwad [3], Rekha M. Ovhal[4], Shashikant H. Gaikwad[5*]

[1, 3, 5] Chemistry Research Laboratory, Department of Chemistry, Shri Shivaji Mahavidyalaya, Barshi, Maharashtra, India.

[2] General Science Department, N.K.Orchid College of Engineering and Technology, Solapur, Maharashtra, India.

[3] Department of Chemistry, Sangmeshwar College, Solapur, Maharashtra, India.

[4] Department of Chemistry, Walchand College of Arts and Science, Solapur, Maharashtra, India.

Email: [2] panchsheela_ubale@rediffmail.com, [5] rasayanshg@gmail.com

Abstract

In this investigation, the chemical synthesis and physicochemical categorization of synthesized ligands (L_1–L_3) have been successfully designed and derived from substituted 4-amino-5-mercapto-1, 2, 4-triazole using various substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehyde and resultant Ni (II) complexes (C_1–C_3) have been described. The structures of synthesized ligand and the resultant complexes were inspected using UV-Vis spectroscopy, thermo gravimetric analysis, Fourier transform infrared spectroscopy and ^{1}H NMR. The consequential data revealed octahedral geometry for the resultant complexes. The novel nickel complexes have been ascertained as potential antimicrobial and antioxidant agents.

Keywords: Nickel complexes, Schiff base, biological Screening.

1. Introduction

Heterocyclic aromatic substituents are a decisive class of organic bilobates gained substantial attention to its biologic values in drug designing also in synthesis. N,O and S are the almost best-known hetero atoms [1]. In heterocyclic chemistry, triazole acquired unique position due to large number of biological activities. 1, 2, 4-Triazoles comprise five members in its ring with two carbon and three nitrogen atoms [2-3] whereas; pyrazoles are nitrogen comprising heterocyclic compounds having copious applications in pharmacological and agrochemical industries[4.] 1,2,4-Triazole have broad-ranging spectra of therapeutically fascinating drug like anticarcinogenic, analgetic, bactericidal, antimicrobic, antioxidant, antiurease, anti-inflammatory, diuretics, antiepileptic, hypoglycemic and anti-migraine agents [5-8].Ample of pyrazole derivatives are acknowledged because of their biotic activities such as antitubarcular[9], antidepressant and enzyme inhibitory activities.

The Hard N and S atoms in triazole based Schiff bases serve as plausible chelating agent.[10] These ligands can efficiently coordinate via N atom of imine linkage, S of thiol group or N atoms of triazole moiety to the transition metal ions. The biological activity of metal

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complexes were depends on the substituent connected to triazole moiety, configuration of complex, coordination sphere, magnetic behavior , redox behavior and the charge on central metal ion.[11, 12] The role of nickel in several biotic processes have conventional profound attention[13] Thus in this continuation with our earlier work we report herein the synthesis, physicochemical characterization of Schiff base ligands derived from 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol with 4-substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde and their Ni (II) metal complexes.

2. Experimenital

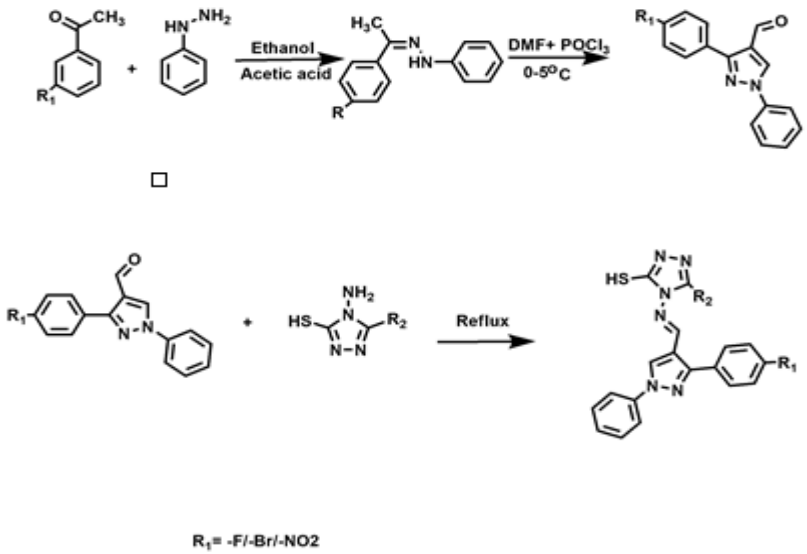
2.1 Materials and methods

The Schiff base ligands were synthesized by reported literature method, the condensation of 4-Amino-5-mercapto-1, 2, 4-triazole and 1, 3-diphenyl-1H-pyrazole-4-carboxaldehyde. In the frequency ranges between 4000-100 cm^{-1} by means of Perkin Elmer FT-IR spectrophotometer, Fourier transform infrared spectral measurements were done. The ^{1}H-NMR spectra have been registered using TMS as an internal standard and DMSO as a solvent for ligands on Bruker spectrometer. The electronic absorption spectra of ligands and its resultant complexes have been recorded in range 200-1000 nm. Thermo gravimetric analysis have been carried out with a heating rate of 10 °C min^{-1}; in an oxygen atmosphere in the temperature range 45-1000 °C using ceramic crucibles.

2.2 Chemical Synthesis

2.2.1 Synthesis of Schiff base ligands ($L_1 - L_3$):

The existing ligands have been prepared according to reported literature methods [14] as depicted in Scheme 1. Warm ethanolic solution of 0.293 g (1 mmol) of 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde, 0.327g (1mmol) of 3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde and 0.266 g (1 mmol) of 3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde with 0.144g (1mmol) 3-methyl-4-amino-5-mercapto-1,2,4-triazole on condensation by adding catalytic amount of glacial acetic acid as catalyst. The precipitate produced were filtered, washout with icy ethanol and recrystallized to acquire final pure products. The pureness of the products has been examined by TLC.



Scheme 1: General synthetic route of Schiff base ligands ($L_1 - L_3$).

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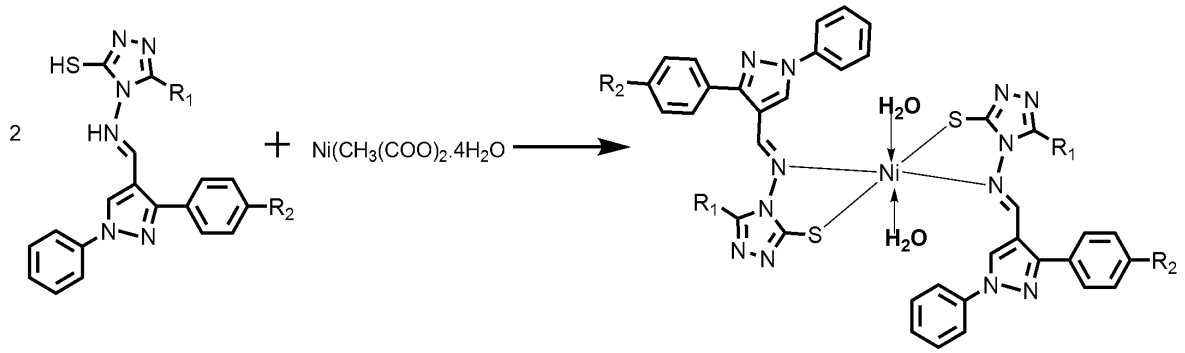
2.2.2 Synthesis of Nickel Metal Complexes ($C_1 – C_3$):

Nickel (II) acetate (0.15 g, 0.60 mmol) have been liquified in an aqueous ethanolic solution. A doubled ratio of the pertinent ligand (L_1- 0.486 g, L_2 -0.526 g L_3 - 0.453 g) (1.20 mmol) dissolved in ethanol (25 ml) were added together with continual stirring, results in changes in the colour, after refluxing the reaction mixture for 5-6 hours. The resultant solid compounds were filtered, get washed with lukewarm water, aqueous ethanolic solution then finally using ether and dried the compound in vacuum over $CaCl_2$. The plausible structure of complexes were shown in Scheme 2.

Ni ($C_{38}H_{32}N_{14}O_6S_2$) (C_1): FT-IR (cm^{-1}): 3315 (OH_2), 1598 (N=CH), 756 (C-S), 506 (Ni-N), 338 (Ni-S) ,Yield: 52%.

Ni ($C_{38}H_{32}Br_2N_{12}O_2S_2$) ($C_2$): FT-IR ($cm^{-1}$): 3350 ($OH_2$), 1594 (N=CH), 752 (C-S), 507 (Ni-N), 352 (Ni-S), Yield: 59%.

Ni ($C_{38}H_{32}F_2N_{12}O_2S_2$) ($C_3$): FT-IR ($cm^{-1}$): 3300 ($OH_2$), 1594 (N=CH), 756 (C-S), 502 (Ni-N), 359 (Ni-S), Yield: 55%.



R_1= -F/ -Br/-NO_2 **R_2= -CH_3**

Scheme 2: Probable structures of Nickel Complexes ($C_1 – C_3$).

2.3 Biological Assay

2.3.1 In vitro antimicrobial studies

The antimicrobic studies of synthesized ligands and its nickel (II) metal complexes have been carried out using *well plate diffusion method*[15, 16] against Gram-positive species *Staphylococcus aureus*, Gram-negative species *Escherichia* coli and fungi *Candida albicans.* From the bacterial cultures the inoculums of the microorganism were prepared. In clean sterilized Petri plates, 15ml of nutrient agar medium have been poured, allow cooling and solidifying. Pipette out 100 µl of broth of bacterial strain and spread with a spreading rod over the medium evenly till it gets dried properly. Using a sterile cork borer, wells of 6mm in diameter were bored. In water solutions of each compound were prepared. 100µl of drug sample solutions were added to the wells. At 37^0C for 24 h, the petri plates incubated. As positive control streptomycin and as negative control distilled water has been used. Antibacterial activities were assessed by measuring the zone of inhibitions (ZI). The diameter zone of the inhibition were measured in cm and the results were documented Table S2. Analogous procedures were continual for antifungal activities; using inoculation for fungal strain *Candida albicans* the agar plates were prepared. For 48 to 72 h, the agar plates have been incubated at 27 °C temperature. After incubation the plates were observed, around wells for zone of inhibition.

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2.3.2 Antitubercular activity:

The anti-tubercular activity of synthesized compounds were assessed against M. tuberculosis using micro plate Alamar Blue assay (MABA) [17]. The standard Strain and standard drugs used for evaluation are: Mycobacteria tuberculosis (Vaccine strain, H37 RV strain): ATCC No- 27294 and, Isoniazid, Ethambutol, Pyrazinamide, Rifampicin and Streptomycin respectively.

3. Results and Discussion

The chemical synthesis of Schiff base ligand and resultant Ni (II) complexes were accomplished by wide-ranging synthetic route in ethanolic solvent. The resultant complexes were quite stable at room temperature, in the solid state and are unsolvable in water and common organic solvents but are solvable in Dimethylformide and Dimethylsulfoxide. The yield and elemental investigation of each metal complex is bestowed in Table S1. The metal: ligand ratio in the Ni (II) complexes has been found to be 1:2 stoichiometries.

3.1 ^{1}H-NMR and Mass spectral analysis:

To elucidate the structure, the ^{1}H-NMR spectra of ligands were recorded using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as a solvent. The singlet appears between δ 8.947 ppm owing to pyrazole proton in the ligands. The spectrum of the ligand displays a wide singlet in the range of 13.56 ppm due to -SH proton (Figures S1-S2).The multiplets due to aromatic protons of Schiff bases were appeared at δ 7.32-7.47 ppm. Subsequently, nickel (II) complexes are paramagnetic; their ^{1}H-NMR spectra could not be obtained [18]. The characteristic ^{1}H-NMR spectra of L_2 is displayed in Figure 1. The mass spectra of ligands (L_1 - L_3) exhibit parental peak due to molecular ion (M+H) (Figures S7-S8). The molecular ion peak acquired at m/z 406.10, 439.06, and 379.11 respectively used for ligands.

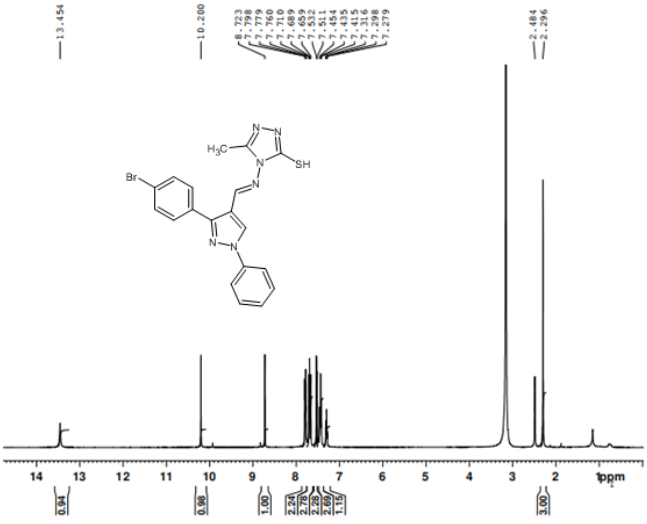

Figure1: ^{1}H-NMR spectrum of 4-[(Z)-{[3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl] methylidene} amino]-5-methyl-4H-1, 2, 4-triazole-3-thiol (L_2).

3.2 FT-IR spectral analysis:

The complexation of ligands with nickel ion through azomethine nitrogen and sulphur atoms is elucidated from FT- IR studies (Figures S3- S6). The FT-IR spectra of ligands (L_1-L_3) shows the probable typical azomethine stretching vibration band observed in the section

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1613-1615 cm^{-1} were lifted towards lesser frequency in the region 1592-1599 cm^{-1} after the complexation. In Ni (II) complexes [19], azomethine nitrogen is attuned to the metal ion. The Strong band at 2733-2758 attributed to υ (-SH). The υ (-SH) band will be disappear affirms the coordination of thiol group and deprotonation in the spectra of metal complexes [20]. The complexation were corroborate with appearance of additive feeble bands in the region 752 - 756 υ(C-S), cm^{-1}, 506-510 υ(M-N) cm^{-1} and 333-352 υ(M-S) cm^{-1} respectively (Figures 3-4).

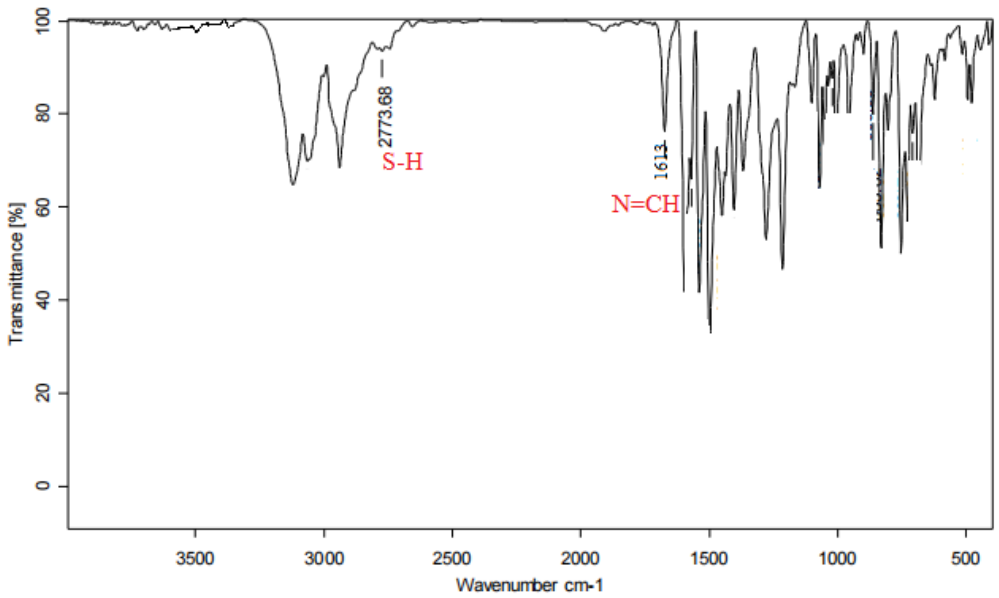

Figure3: FT- IR spectra of 4-[(Z)-{[3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl] methylidene} amino])-5-methyl-4H-1,2, 4-triazole-3-thiol (L_2).

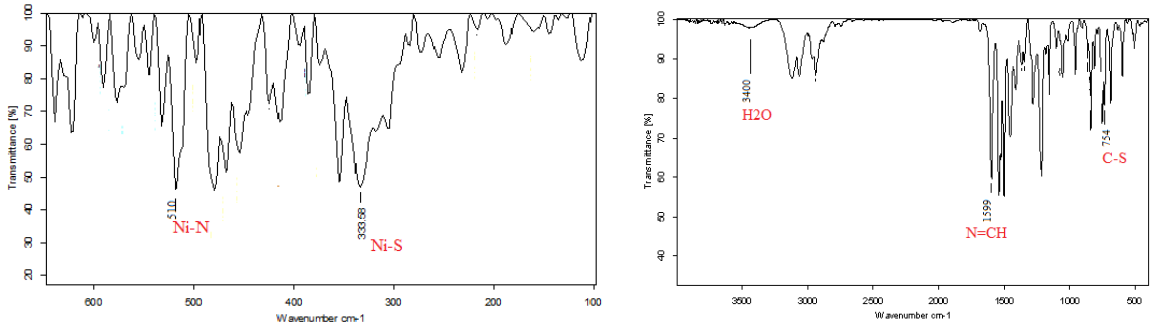

Figure3: FT- IR spectra of 4-[(Z)-{[3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl] methylidene} amino])-5-methyl-4H-1,2, 4-triazole-3-thiol (L_2).

3.3 UV-Visible Spectroscopy:

The photo physical properties of ligands and resultant Ni (II) complexes were carried out in UV-Visible spectroscopic analyses. The absorption spectra were documented, in DMSO solution. The spectra of L_1 –L_3 show two absorption bands as a result of the π - π* transitions within the aromatic moiety in between 274 to 303 nm (Fig. 5), while the bands observed in between 314- 337 nm (n - π*) changeovers due to azomethine group of L_1 – L_3, respectively. In the spectrum of metal complexes the absorption bands get lifted on account of coordination of metal ions with ligands [21].

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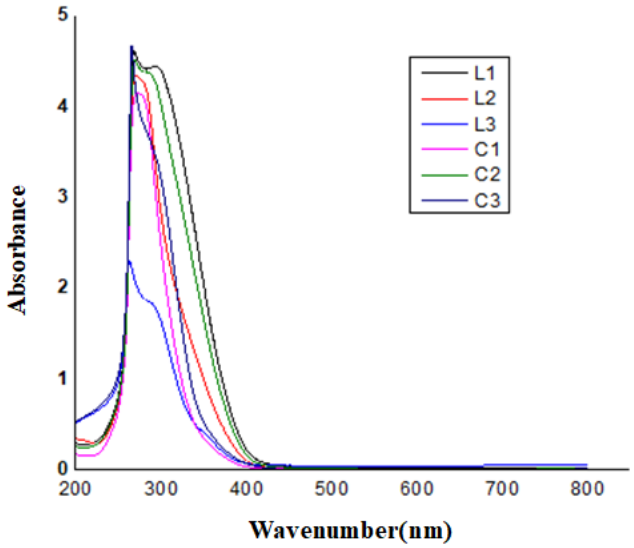

Figure 5: UV-Visible Spectra of Schiff bases (L_1-L_6) and their Ni complex (C_1-C_3)

3.4 Thermal Analysis:

By means of TGA studies, thermal decomposition processes of complexes were investigated Table 2 displays the recorded TGA curves of the complexes. The **C_1** complex endures three step disintegration routes (Figure 6). In the first step, the loss of two water molecules in the range of 40-180 °C has been done. In the range In the second step $_{at}$ 180-385 °C organic moiety decomposes and triazole moiety decomposes at 385-720 °C in the third step. In the similar manner, C_2 complexes also revealed three step degeneration processes. The preliminary weight demise occurs in low temperature range of 48-185 °C specifies loss of water molecules while the second step weight loss happens because of loss of organic moiety in temperature ranges of 185-390 °C and triazole moiety decomposes at 390-700 °C in the third step. The **C_3** complex displays three step disintegration stages analogous toward preceding two complexes. All the complexes (C_1-C_3) leave behind NiO as a residue [22].

Table 1: Stepwise thermal decomposition of metal complexes.

Compound	Thermogravimetry (TG)		Mass loss (%)		Decomposition product loss
	Stage	Temp (°C)	Found	Calculated	
C_1	I	40-180	4.14	3.98	-H_4O_2(water molecules)
	II	180-385	65.15	64.47	-$C_{32}H_{22}N_8O_4$(organic moiety)
	III	385-720	26.96	25.03	-$C_6H_6N_6S_2$(triazole moiety)
C_2	I	48-185	4.0	3.8	-H_4O_2(water molecules)
	II	185-390	60.32	62.53	-$C_{32}H_{22}N_6Br_2$(organic moiety)
	III	390-700	25.30	27.29	-$C_6H_6N_6S_2$(triazole moiety)
C_3	I	45-190	3.9	3.83	-H_4O_2(water molecules)
	II	190-380	70.32	69.23	-$C_{32}H_{22}N_6F_2$(organic moiety)
	III	380-710	25.22	24.08	-$C_6H_6N_6S_2$(triazole moiety)

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4. Biological Assay

4.1 In vitro antimicrobial and antifungal activities

In vitro antimicrobic prospective of Schiff base ligand and resultant Ni (II) complexes were assessed in Figure 7. The outcomes manifest the ligands display lesser activity whereas the complexes show average to outstanding activity in contrast to (*Staphylococcus aureus*) as Gram-positive bacteria and (*Escherichia coli*) as Gram-negative . Ligands and complexes indicate lesser antifungal activities against fungal strain (*Candida albicans*). C_3 complex is extremely active corresponding to the remaining complexes against *Staph.aureus* and *E. coli*. Whereas C_1 complex is discreetly active against *Candida albicans* .The examined tendency against *Staphylococcus aureus* and *Escherichia coli* has been summarized in Table S2 [23, 24]

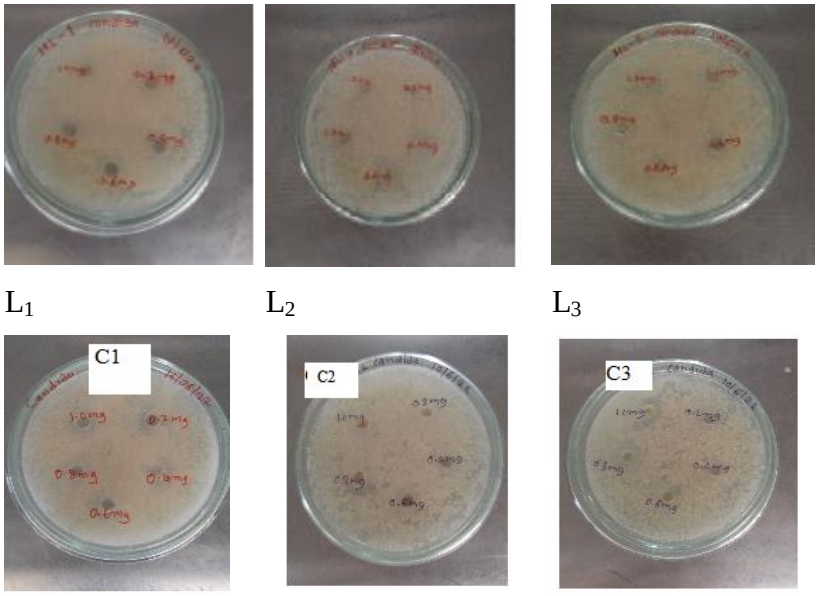
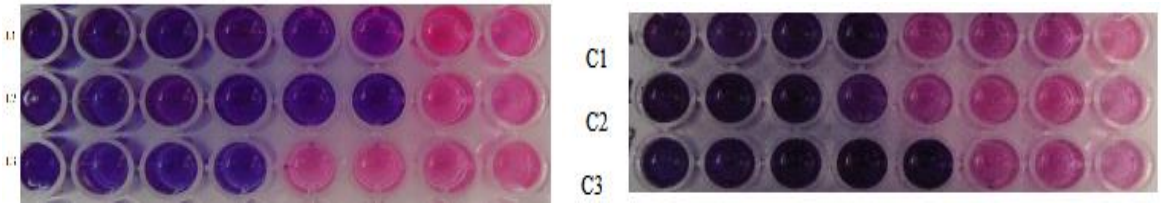


Figure 7: Plates showing antimicrobial activities of schiff bases (L_1- L_3) and Ni complexes(C_1-C_3 and) against *C. albicans*.

4.2Antitubercular activity:

The anti-mycobacterial activities of each of the synthesized compounds were assessed against M. tuberculosis using micro plate Alamar Blue assay (MABA).The standard Strain used: Mycobacteria tuberculosis ATCC No- 27294. It is worth to note that amongst all synthesized compounds, Schiff base ligands L_1, and L_2 are sensitive at 1.6 µg/ml concentration respectively while the C_1 and C_2 are sensitive at 6.25 µg/ml, concentrations; C_3 at 3.12 µg/ml, concentration. Further, ligands L_3 shows strong antitubercular activity as compare to L_1 and L_2 metal complexes while C_3 metal complex shows good activity as compared to L_3 Schiff base ligand (Figure 8) Table S1.



(a) (b)

Figure 8: a) Antitubercular activity of ligands (L1-L3); b) Antitubercular activity of Ni complexes (C1-C3).

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5. Conclusion

In summary, using Schiff base ligands, the of Ni (II) complexes series were efficaciously synthesized. The ligands react with Ni (II) metal ions to yield mononuclear complexes (C1-C3) and act as a bidentate ligand and the molecular structures of entire compounds were explicated by analytical and physical techniques. All the synthesized compounds shows good to excellent consequence in comparision with standardised drugs for biological screening

6. Acknowledgement

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References

[1] R. Haddad, E. Yousif, A. Ahmed, *Springer Plus*, **2**,510, (2013).

[2] Acheson, An *Introduction to chemistry of Heterocyclic Compound, New York, **3**: Willey*, 122, (1989).

[3] A. Siddeiqui, W. Ahsan, M. Alam, R. Ali, S. Jain, B. Azad, J. Akhtar, *Int.J.Pharm.Sci.Rev.and Res*., **8** (1), 161, (2011).

[4] D. Dheer, V. Singh, R. Shankar, BioorChem.71, 30-54, (2017), **DOI**:10.1016/j.bioorg.2017.01.010.

[5] P. R. Kate, S. H. Gaikwad, T. N. Lokhande, A. B. Shaikh, B. D. Sonawane, P. Choudhari, M.T.Bachute, *Rasayan J.Chem.*, 11(4), 1441-1450(2018). **DOI:**10.31788/RJC.2018.1143080

[6] J. R. Reid, N. D. Heindel, *J.Heterocycl.Chem*, **13**,925-926, (1976).

[7] S. Durairaja, S. Srinivasan, P. L. Perumalsamy, *Electran.J.Biol*., **5** (1), 5-10, (2009).

[8] S.Bala, R. P. Gupta, M. L Sachdeva, A. Singh, H. K Pujari, *Ind. J. Chem.*, **16**, 481-483, (1978).

[9] S. H. Gaikwad, T. N. Lokhande , M. A. Anuse, *Ind. J. Chem.*, **44A**, 1625, (2005).

[10] L.H. Abdel Rahman, A.M. Abu-Dief, R.M. El Khatib, S.M. Abdel Fatah.Bioorg Chem 69, 140-152 (2016). **doi: 10.1016/j.bioorg.2016.10.009.**

[11] J. Saranya, S. Kirubavathy, S. Chitra, A. Zarrouk,K. Kalpana, K. Lavanya, B. Ravikiran. Arab. J. Sci. Eng., 45, 4683–4695 (2020).

[12] A. Q, Ather, M.N.Khan, K.Mehmood, F.Chaudhary, Acta Cryst.E66, 3170, (2010). **DOI**: 10.1107/2FS1600536810045630

[13] Maria, C. S.; Lourenco, M. V.; Alessandra, C. P.; Marcelle, L. F.; Rasnisb, B. G.; Thais, C. M.; Monica, A. P. ARKIVOC 2007, XV, 181.

[14] Kavitha Vijayaraghavan, S.Mohamed Ali, international journal of innovative research in science Engineering and technology Vol 2 issue 2013, 12 7315-7321.

[15] J.Dundas, ; Z.Ouyang, ; J.Tseng, ; A.Binkowski, ; Y.Turpaz, ; J. Liang, CAST p: . *Nucleic Acids Res.* **2006**, *34*, W116–W118.

[16] R.A.Laskowski; M.B.Swindells, LigPlot+: Multiple ligand–protein interaction diagrams for drug discovery. *J. Chem. Inf. Model.* **2011**, *51*, 2778–2786.

[17] P A. Ashok, S.P. Kollur, N. Anil, B.P. Arun, S.N. Jadhav, *Molecules* **2020**, *25*(24), 5973; **DOI:**. 10.3390/molecules25245973.

[18] Sachin A Deodware, Umesh B Barache, Pratibha C Dhale, Panchsheela A Ubale, etal , *Molecules* **2022**, *27*(19), 6548; **doi.org/10.3390/molecules27196548.**

ISSN 2063-5346

[19] K. Singh, M.S. Barwa, P. Tyagi, Eur. J. Med. Chem. 41 (2006) 147e153.

[20] K. Singh, Y. Kumar, P. Puri, C. Sharma, K.R. Aneja, Med. Chem. Res. 2011. doi:10.1007/s00044-011-9683-4.

[21] UP Ashok, SP Kollur, N Anil, BP Arun, SN Jadhav, *Molecules* **2020**, *25*(24), 5973; **https://doi.org/10.3390/molecules25245973.**

[22] S. A. Deodware, S. H. Gaikwad, U. B. Chanshetti, D. J. Sathe, *Der Pharma Chemica*, **7** (7): 365-372, (2015).

[23] K. Vijayaraghavan, S. Mohamed Ali, *I.J. Inno. research in sci. Engi. and tech.*, **2**, 12, 7315-7321, (2013).

[24] Dr Prieto'S DPPH microplate Protocol 1-3, (2012). **DOI**: 10.1002/jsfa.5633.