RESEARCH

Vol.13, 2019

ISSN 2278–540X EISSN 2278–5396

DRUG DISCOVERY

Synthesis and biological evaluation of some "N" containing heterocyclic Schiff base metal complexes

Anupama B✉, Chenchu Lakshmi KNV, Reshma Chowdary B, Ch.Vennela

A new Schiff base has synthesized from 4-(1H-benzo[d]imidazol-2-yl) aniline and different aromatic carbonyl compounds. Metal complexes of the Schiff base have been synthesized from salts Fe (II), Ag (II) metal in the alcoholic medium. The newly prepared Schiff base ligand and metal complexes have been characterized by various physicochemical techniques such as Elemental analysis, IR, ^{1}H NMR spectral techniques. The metal complexes were evaluated for their antimicrobial studies and some of the compounds has shown significant activity when compared with the standard.

INTRODUCTION

Heterocyclic compounds are one of the important bioactive molecules found in nature. These heterocyclic compounds fulfill important physiological functions. Observations of these activities in nature led humans to the discovery many healing materials. Among these heterocyclic compounds N-Heterocyclic's were found to have good biological activity. Hence in the past few decades, the synthesis of these heterocyclic compounds has been a subject of great interest because of their wide applicability[1,2,13-15]. Nitrogen-containing heterocycles have been used as medicinal compounds for many decades, and form the basis for many common drugs such as Morphine (analgesic), Captopril (hypertension), and Vincristine, (cancer chemotherapy).

A Germen chemist Hugo Schiff in 1864 developed a new class of organic compounds. The group of compounds, imines are often referred to as Schiff bases[3] in his honor. The preparations of these compounds are simple and attractive. They are prepared by condensing a carbonyl compound with an amine, generally refluxing in alcohol. The active and well-designed Schiff base ligands are considered as "privileged ligands".

Ligands containing Sp^2 hybridized nitrogen atoms, particularly those in which the N-atom is a part of the aromatic system, show very extensive coordination chemistry. Because of the relative easiness of preparation, synthetic flexibility, and the special property of C=N group, Schiff bases are considered as excellent chelating agents especially when a functional group like -OH or -SH is present close to the azomethine group so as to form a five or six membered chelate ring with the metal ion. A reaction for preparation[4,5] of Schiff base begins with nucleophilic addition of primary amines of the type RNH2, ArNH2 to carbonyl compounds (ketones or aldehydes).

Department of Pharmaceutical Chemistry, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada- 520010, Andhra Pradesh, India
✉*Corresponding author:* Associate Professor& HOD, Department of Pharmaceutical Chemistry, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada- 520010, Andhra Pradesh, India; Email: anurochi8@gmail.com

Many Schiff bases are known to be medicinally important and are used to design medicinal compounds. Schiff bases appear to be important intermediates in a number of enzymatic reactions involving interaction of the amino group of an enzyme, with a carbonyl group of the substrate [6]. Schiff bases have been reported to have pharmacological effect which is considerably enhanced by the presence of metal ions [7].

MATERIALS & METHODS

Materials and instruments were obtained from LOBA Chemicals and were used without further purification. Progress of the reaction and purity of the compounds was checked on thin layer chromatography plates. Melting points were determined on Gallen Kamp melting point apparatus and were uncorrected. IR spectra were recorded in KBr discs on a Bruker analyzer. ^{1}H NMR and ^{13}CNMR spectra were recorded on a Bruker spectrometer in DMSO using TMS as internal standard.

General Procedure for the Synthesis of Compounds: Formation of Schiff Base -Metal Complexes (1-10).

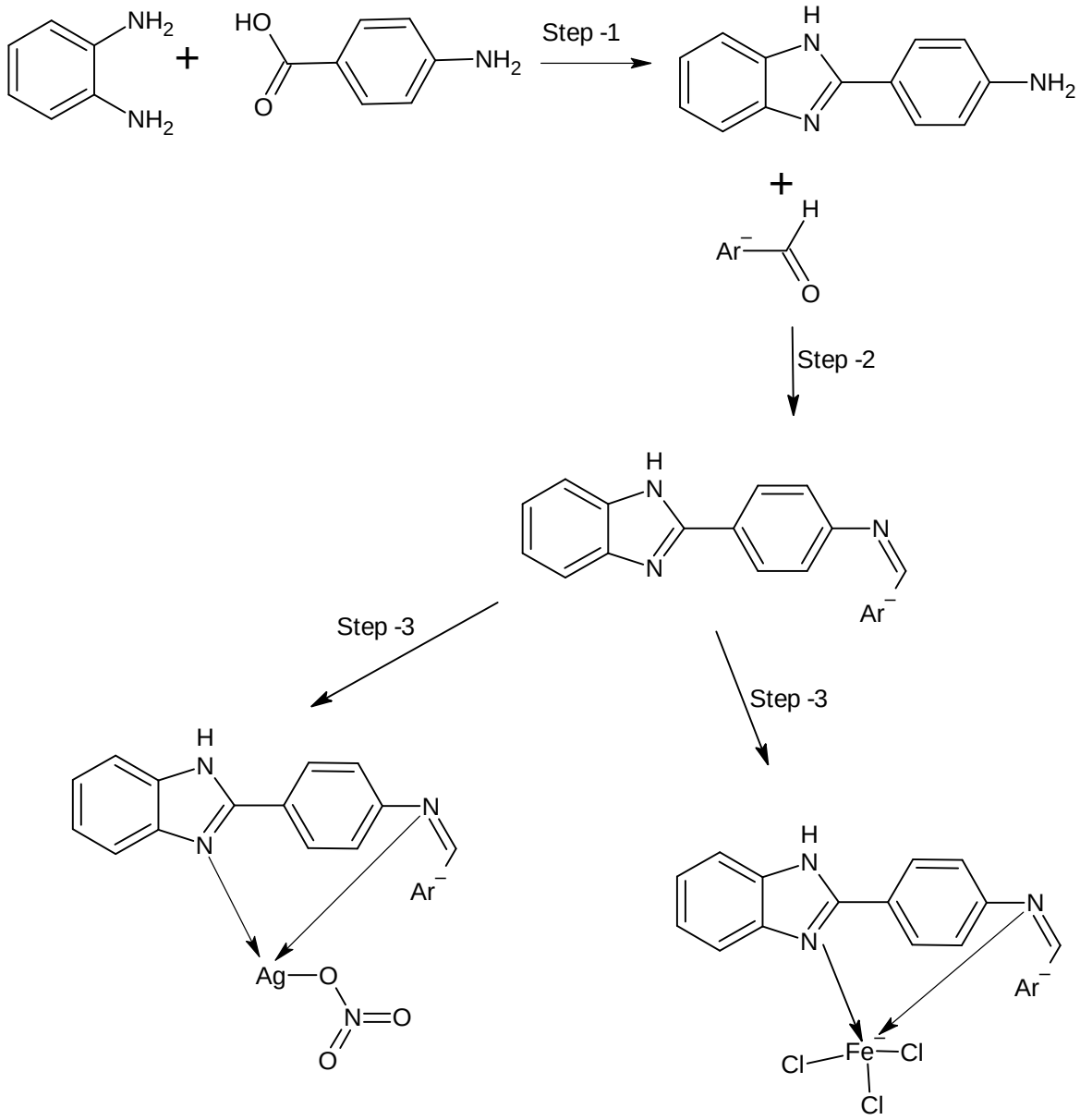
Step-1:-Synthesis of 4-(1H-benzo[d]imidazol-2-yl) aniline:

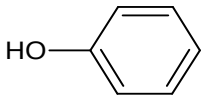
A mixture of p-amino benzoic acid (0.03 mmol) and O-phenylene diamine (0.03 mmol) were heated under reflux at 180° C for 2 h using sand bath(SiO_2).The reaction mixture was partially cooled, poured on to crushed ice and neutralized with10% NaOH solution. The precipitated product was collected by vacuum filtration, washed with excess 10% NaOH solution was dried and recrystallized.

Step-2:-Synthesis of Schiff base:

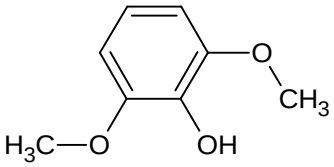
4-(1H-benzo[d]imidazol-2-yl) aniline (amino compound) and different aromatic carbonyl compound were taken and proceed for reaction using magnetic stirrer.

Scheme -I

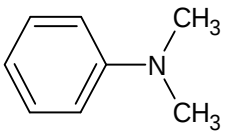




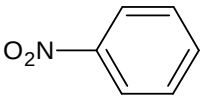
1, 5(Fe,Ag)



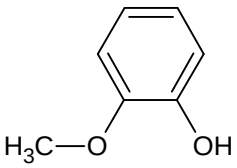
2



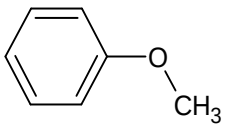
3



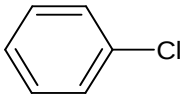
4



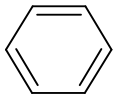
6



7, 8 (Fe,Ag)



9



10

Table 1 Antibacterial Activity of metal complexes

INHIBITION ZONES IN cm								
Compound	***E-coli***				***Staphylococcus aureus***			
	100 µ/ml	**150 µ/ml**	**200 µ/ml**	**250 µ/ml**	**100 µ/ml**	**150 µ/ml**	**200 µ/ml**	**250 µ/ml**
1	0.9	1.5	1.3	2	0.9	1.5	1.3	1.4
2	1.3	1.3	1.4	1.5	1.1	1.3	1.3	1.5
3	1.2	1.3	2	1.5	1.1	1.2	1.2	1.2
4	1	1.1	1.2	1.2	1.1	1.2	1.2	1.3
5	1	1.1	1.1	1.1	1.1	1.1	1.2	1.2
6	1.3	1.4	1.5	1.5	1.2	1.5	1.2	1.3
7	1.2	1.2	1.3	1.3	1.1	0.9	1.1	1.2
8	1.1	1.2	1.2	1.3	1	1.1	1.2	1.3
9	1.1	1.1	1.2	1.2	1.1	1.2	1.3	1.3
10	1.2	1.3	1.3	1.4	1.1	1.1	1.1	1.2
STANDARD	1.1	1.2	1.2	1.3	1.1	1.1	1.1	1.2

Table 2 Antifungal Activity of metal complexes

INHIBITION ZONES IN cm				
COMPOUND	***Aspergillus niger***			
	100 µ/ml	**150 µ/ml**	**200 µ/ml**	**250 µ/ml**
1	0.8	0.9	1	1.1
2	0.9	1.1	1.2	1.3
3	0.9	1	1.1	1.2
4	0.9	1	1.1	1.2
5	0.9	1	1.2	1.3
6	0.8	0.9	1	1.1
7	0.8	0.8	1	1.1
8	0.8	0.9	1.1	1.2
9	0.9	1	1.2	1.3
10	0.7	0.8	1	1.1
STANDARD	0.8	0.9	1	1.1

Step-3:- Synthesis of Schiff base metal complexes:

Methanol solution of the metal ions [$FeCl_3$ or $AgNO_3$] was added to ethanol solution of compounds obtained from step 2 in 1:2 (metal: ligand) molar ratio. Then, the mixture was heated under reflux for half an hour and coloured precipitates were obtained. Later, the precipitates were filtered out, washed with distilled water and finally recrystallized from ethanol. The compounds were identified by physical characterisation such as melting point, TLC. The chemical and spectral data are given. The synthetic procedure has shown in scheme-I

Compound 1:-

%yield: 0.212;**M.P**(ºC):190 ºC; **IR:** 3742 (-NH), 3188 (-OH), 1402 (C=N), C=C-H AROMATIC, 1614 -1523(C-H), 690 (-Cl), SHIFT OF IR VALUE FROM 790 TO 743 BECAUSE OF "N" COMPLEX WITH METAL ION

Compound 2:-

%yield: 1.617;**M.P**(ºC):200 ºC; **IR:** 3743 (-NH), 3335(-OH), 1394(C=N), 1614(C-H),710 (-Cl), SHIFT OF IR VALUE FROM 790 TO 740 BECAUSE OF "N" COMPLEX WITH METAL ION.

Compound 3:-

%yield: 1.491;**M.P**(ºC): **180** ºC; **IR:** 3857 (-NH), 2900 (C-H), 1386(C=N), 3333(-OH), 693(-Cl), SHIFT OF IR VALUE FROM 790 TO 748 BECAUSE OF "N" COMPLEX WITH METAL ION, 1600-1533(C-H STRETCHING).

Compound 4:-

%yield: 1.511;**M.P**(ºC): **195** ºC; **IR:** 3741(-NH), 333.27(-OH), 2906(CH STRETCHING),616(-Cl), 1614-1523(C-H), SHIFT OF IR VALUE FROM 739 TO 743 BECAUSE OF "N" COMPLEX WITH METAL ION.

Compound 5:-

%yield: 1.017;**M.P**(ºC): **205** ºC; **IR:** 3741(-NH), 3363(-OH), 2100 (-TRANSITION METALS), 616 (-Cl), SHIFT OF IR VALUE FROM 745 TO 780 BECAUSE OF "N" COMPLEX WITH METAL ION.

Compound 6:-

%yield: 1.625; **M.P**(ºC)**:**160; **I.R**:3858cm^{-1}(NH), 3357cm^{-1} (OH), 615 PRESENCE OF CHLORINE, SHIFT OF IR VALUE FROM 742 TO 780 BECAUSE OF "N" COMPLEX WITH METAL ION.

Compound 7:-

%yield: 0.2433; **M.P**(ºC)**:** 230; **I.R**: 3538 cm^{-1} (NH), 3742 cm^{-1} (OH); ^{1}H NMR: 2.036 (CH3), 7.26, 7.286, 7.502, 7.784 (AROMATIC PROTONS), 8.345(NH), 55.64(CH3), 113-148(AROMATIC CARBONS), 162.79(C-O).

Compound 8:-

%yield: 0.676; M.P (ºC)**:** 130; **IR:** 3053 cm^{-1} (CH), 3235 cm^{-1} (NH); **^{1}H NMR**: 2.505(CH_3), 55.54 (NH), 7.666,7.674, 7.601, 7.689, 7.724, 7.728, 7.733 (AROMATIC PROTONS), 111 TO 161(AROMATIC CARBONS).

Compound 9:-

%yield: 0.453; **M.P**(ºC)**:** 190**; IR:** 3055 cm^{-1} (CH), 5.623 cm^{-1} (OH), 616 PRESENCE OF CHLORINE, SHIFT OF IR VALUE FROM 744 TO 834 BECAUSE OF "N" COMPLEX WITH METAL ION.**^{1}H NMR:**2.508(CH_3), (7.045, 7.062, 7.385, 7.556, 7.645, 7.731 AROMATIC PROTONS), 111 TO 151 AROMATIC CARBONS)

Compound 10:-

%yield: 1.688; **M.P**(ºC): 230; **IR:** 3857 cm^{-1} (NH), 638 PRESENCE OF CHLORINE, SHIFT OF IR VALUE FROM 735 TO 765 BECAUSE OF "N" COMPLEX WITH METAL ION.

Antibacterial activity

All the synthesized compounds 1-10 were examined for *in-vitro* antibacterial activity[8,9] against an assortment of one gram-positive

bacteria *Staphylococcus aureus NCIM 2901* and one Gram-negative bacteria *Escherichia coli NCIM 2563* by diffusion method. The agar medium was purchased from HI- media laboratories limited. Nutrient agar was dissolved and distributed in 25ml quantities in an boiling tubes and were sterilized in an autoclave at 121^0C (15LBS/52.in) for 20 minuts.

The medium was inoculated at one percent level using 18 hours old cultures of the test organism mentioned above aseptically into sterile petri dishes and allowed to set at room temperature for above 30min. The test and standard solutions of different concentrations were added and in to cups, left for 90 minutes in a refrigerator for diffusion. After incubation for 24 hours at 37^0C the plates were examined for inhibition zones. The experiment was performed in duplicate and the average diameter of the zones of inhibition measured and recorded. The results were represented in Table 1.

Antifungal activity

The antifungal activity[10,11,12] of compounds were assayed against four one strain of *Aspergilus niger MTCC 282.*Potato dextrose agar (Hi-media) was dissolved and distributed in 25 ml quantities in 100ml conical flasks and were sterilized in an autoclave at 121^0C (15lbs/sq.in) for 20 minutes. The medium was inoculated at one percent level using 18hr old cultures of organisms mentioned above aseptically in to sterile petri dish and allowed to set at room temperature for about 30 minutes. The solutions of test and standard at concentrations (250µg/ml, 200µg/ml, 150µg/ml, 100µg/ml and 50µg/ml) were added to respective cup aseptically and labelled accordingly. DMF as control did not show any inhibition. The plates were left for 90 minutes in refrigerator for diffusion. After incubation for 24 hrs at $37^0 \pm 1^0$c. The plates were examined for incubation inhibition zones. The experiments were performed in duplicate and the average diameters of the zones of inhibition were summarized in Table 2.

RESULTS AND DISCUSSION

The compounds (1-10) were tested for antibacterial activity against an assortment of one gram positive, were used as standards. *Staphylococcus aureus* NCIM 2901 and one Gram-negative bacteria *Escherichia coli* NCIM 2563.Of all derivatives synthesized compounds these exhibit 3,6,10 anti-bacterial activity. The compounds (1-11) were tested for antifungal activity. The compounds 2, 11, 1, and 8 were found to exhibit the most potent *in vitro* anti-fungal activity against Algae.

CONCLUSION

The findings of the study inferred the design and that the functioning of synthesized compounds as antibacterial, antifungal activities rendering them as lead molecules for further development of newer agents with greater efficacy and safety. Of all derivatives synthesized compounds these exhibit 3,6,10 anti-bacterial activities. Compounds 2, 11, 1, and 8 were found to exhibit the most potent *in vitro* anti-fungal activity against Algae.

REFERENCES

1. B.N.B.Vaidehi and K.Gnana Deepika. Synthesis and Biological Evaluation of 2-Substituted Benzimidazoles. Int. J of Pharma and Bio Sci. 2012: 3: 26-31.
2. R.A. Khalil, A.H. Jalil and A.Y. Abd-Alrazzak. Application of A Schiff Base Derived From Sulfanilamide As An Acid-Base Indicator. Journal of the Iranian Chemical Society. June 2009: 345-52.
3. Arun Mishra, Jayntrathod, Diptinamera, Shaileshthakrar, Anamikshah. Synthesis and Antimicrobial Activity of Coumarinyl Schiff Base Derivatives; Int of Chemistry, Physics and Astronomy. 2014:30: 193-201.
4. Shrirambairagi, Ashokbhosale and Meenakshi N Deodhar. Design, Synthesis and Evaluation of Schiff's Bases Of 4-Chloro-3-Coumarin Aldehyde as Antimicrobial Agents; E-Journal of Chemistry 2009, 6,759-762.
5. Anita Sharma and Manish Shah. Synthesis and Characterization of some Transition metal complexes derived from Bidentate Schiff Base Ligand. IOSR Journal of Applied Chemistry.2013:3:62-66
6. Garcia-Valverde, M., Torroba, T. Sulfur-Nitrogen heterocycles. Molecules. 2005, 10, 318-320.
7. Andersen, K. E., Lundt, B. F., Jørgensen, A. S., Braestrup, C. Oxadiazoles as bioisosteric transformations of carboxylic functionalities. Eur. J. Med. Chem. 1996, 31, 417-425.
8. Naveen PV, Susmitha B, Jhansi G et al. Synthesis and Anti-bacterial studies of new sulfonyl benzocoumarin derivatives. Int J of Research in Pharma and Chem 2013:3:808-12.
9. B.Anupama, Subas Chandhra Dinda, Y.Rajendra Prasad, A.Vasudeva Rao. Synthesis and antimicrobial activity of some new 2,4,6 tri substituted pyrimidines. Int. J. of Research in Pharma and Chem 2012:2:231-36.
10. P.Pavan Kumar, S.Sridhar, K.Jagatheesh, E.Namasivayam. Synthesis and biological activity of imidazole derived chalcones and its pyrimidines.Int.J.Res. Ayurveda Pharma. 2013.
11. G.Jhansi, G.Chaitanya, B.Susmitha et al. Synthesis and Evaluation of Schiff Bases of 1,3,4-Thiadiazolidine Derivatives. Sch. Acad. J. Pharm 2014:3:228-236.
12. Chaitanya G, Jhansi G, Susmitha B et al. Synthesis and Evaluation of 2-Substituted Thiadiazole Schiff Bases Int J Pharm 2014: 4:123-131.
13. Dinkar Malik, Sandeep Kumar, Punam Yadav, Vijai Malik. Synthesis and fungicidal activities of transition metal complexes of the 2-Amino - 4- (P- Methoxy Phenyl) Thiazole. Science & Technology, 2015, 1(3), 106-108
14. Dayakar G, Jeyanthi A, Kalyani T. Synthesis of 2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-arylidenethiazolidin-4-ones, 1-(1H-imidazo[4,5-b]pyridin-2-yl)-5-methyl-3-aryl-1,3,5-triazinane-2-thiones and 3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-aryl-1,3,5-oxadiazinane-4-thiones. Discovery Science, 2013, 3(8), 13-15
15. Shaukath Ara Khanum, Noor Fatima Khanum. Evaluation of in-vitro antimicrobial activity of 2-aryloxy methyl oxazoline analogues. Discovery, 2014, 12(30), 41-46

Article Keywords

Schiff base, Metal complex, Spectral techniques

Acknowledgement

Authors are thankful to Siddhartha Academy of General and Technical Education for providing necessary facilities to carry out this research work.

Article History

Received: 06 October 2018
Accepted: 23 November 2018
Published: January 2019

Funding: This study has not received any external funding.

Conflict of Interest: The authors declare that there are no conflicts of interests.

Data and materials availability:

All data associated with this study are present in the paper.

Citation

Anupama B, Chenchu Lakshmi KNV, Reshma Chowdary B, Ch.Vennela. Synthesis and biological evaluation of some "N" containing heterocyclic Schiff base metal complexes. *Drug Discovery*, 2019, 13, 6-9