SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF IMINES AND THEIR METAL COMPLEXES

Ram U. Ambhure[a], Sunil R. Mirgane[b], Devidas U. Thombal[c],Suresh U. Shisodia[d], Sudam S. Pandule[d], László Kótai[e] and Rajendra P. Pawar[d]*

Keywords: Imines, metal complexes & microbial activity.

Two new schiff bases (*E*)-(4-chlorophenyl)-(4-chlorobenzylidene)acetohydrazide and *(E)*-(4-chlorophenyl)-(1-methoxynaphthalen-2-ylmethylene)acetohydrazide and their metal complexes were synthesized. All of the synthesized imines and their metal complexes were characterized and screened for antimicrobial activity.

* Corresponding Authors
E-Mail: rppawar@yahoo.com
Tel:+91-240-2334577
Fax: +91-240-2487284
[a] AAEFs College of Engineering, Pimple, Koregaon Bhima, Pune, Maharashtra, INDIA.
[b] Department of Chemistry, JES College, Jalna-431001, Maharashtra, INDIA.
[c] Department of Chemistry, LBS College, Partur-431501, Maharashtra, INDIA.
[d] Department of Chemistry, Deogiri College, Aurangabad-431005, Maharashtra, INDIA.
[e] Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, 1171, Magyar Tudósok krt. 2.

Introduction

Schiff bases, characterized by the azomethine group (–R-C=N–), form a significant class of compounds in medicinal and pharmaceutical chemistry and are known to have biological applications due to their antibacterial,[1-6] antifungal,[3-6] and antitumor[7,8] activity. Schiff base ligands are considered "privileged ligands" because they are easily prepared by the condensation between aldehydes and amines. The incorporation of transition metals into these compounds leads to the enhancement of their biological activities and decrease in the cytotoxicity of both metal ion and schiff base ligand.[9-11]

Schiff bases with donors (N, O, S, etc.) have structural similarities with neutral biological systems and due to presence of imine group are utilized in elucidating the mechanism of transformation of racemization reaction in biological system.[12-14]

Coordination chemistry, a study of metal complexes is an important research area in inorganic chemistry. Detail reviews regarding Schiff base metal complexes and their applications have been published by several scientist in recent years, Neelima Mishra et al.[15]and S. Arulmurugan et al.[16] on biological activities, Katarzyna Brodowska et al.[17] on using invarious fields of science, Ahmed M. Abu-Dief et al.[18] on versatile applications, and Kavita Rana et al.[19] on analgesic, anti-inflammatoryeffect.

Experimentals

Synthesis of Schiff base

In order to prepare Schiff base firstly esters of substituted phenylacetic acid were prepared, which were further reacted with hydrazine hydrate to obtain hydrazides from which Schiff base were prepared.

a) General procedure for the synthesis of esters

To a magnetically stirred ice cold solution of carboxylic acid (20 mmol) in methanol (20 mL), a catalytic amount of concentrated H_2SO_4 (2-3 drops) was added dropwise. The contents were gently warmed to room temperature and then refluxed for 2-3 h. After completion of the reaction as indicated by TLC (20% ethyl acetate: n-hexane); excess methanol was removed under reduced pressure on rotary evaporator. The reaction mixture was cooled to 0°C, basified with saturated aqueous $NaHCO_3$ and finally extracted with dichloromethane (3x15 mL). The combined organic layer was washed with water, separated, dried over sodium sulphate and concentrated on rotary evaporator to afford the corresponding esters as oily liquids.

b) General procedure for the synthesis of hydrazides

A mixture of carboxylic ester (20 mmol) and hydrazine hydrate (100 mmol) was refluxed at 100 °C for 1h. Progress of the reaction was monitored by TLC (50 % ethyl acetate: n-hexane).After completion of reaction; the excess amount of hydrazine hydrate was evaporated under reduced pressure. The crude product was triturated with petroleum ether under ice-cold condition, washed several times with water and dried by toluene azeotrope to get the corresponding hydrazide as the crystalline white solid.

c) General procedure for the synthesis of Schiff base

In equimolar mixture of aldehyde (2 mmol) and hydrazide (2 mmol) in ethanol (5 mL), 2-3 drops of glacial acetic acid were added at room temperature and the contents were refluxed till completion of reaction for appropriate time.

After completion of the reaction as monitored by TLC (3:7 ethyl acetate:n-hexane), excess of ethanol was evaporated on rotary evaporator and the contents of the flask poured over crushed ice. The solid obtained was filtered, washed with cold water, dried and finally recrystallized from chloroform: hexane (1:1).

Table 1. List of synthesized Schiff base ML_2 type metal complexes

	Schiff base aldehyde component, R=4-Cl	Metal	Time, h	Yield, %
A1	4-Cl-benzaldehyde	Zn	6.0	91
A2	4-Cl-benzaldehyde	Pd	6.5	87
A3	4-Cl-benzaldehyde	Co	7.5	81
A4	4-Cl-benzaldehyde	Cu	7.0	80
A5	4-Cl-benzaldehyde	Fe	6.0	84
A6	1-MeO-2-naphthaldehyde	Zn	6.5	89
A7	1-MeO-2-naphthaldehyde	Pd	6.0	82
A8	1-MeO-2-naphthaldehyde	Co	7.5	84
A9	1-MeO-2-naphthaldehyde	Cu	6.0	92
A10	1-MeO-2-naphthaldehyde	Fe	6.5	91

B) General procedure for preparation of Schiff bases metal-complexes

A mixture of Schiff bases (2 mmol) and nitrates of metal (1 mmol) in ethanol (5 ml) was refluxed for 6-8 hours. The pH of solution is adjusted to 7-8 by using alcoholic ammonia solution. The progress of reaction was monitored on thin layer chromatography (TLC) using petroleum ether: ethyl acetate (7:3 ml) eluent. The products were isolated after reduction of volume by evaporation. It was filtered, washed with ethanol, dried under vacuum and further recrystallized in ethanol. The reaction time and yield of complexes prepared are specified in Table 1.

Spectral analysis of Schiff bases

(4-Chlorophenyl)-(4-chlorobenzylidene)acetohydrazide

IR *v* max cm-1: 735, 812, 1012, 1087, 1140, 1296, 1393, 1491, 1612, 1668, 1896, 2862, 2966, 3083. ^{1}H NMR: δ 2.50 (s, 2H, Ar-CH_2-), δ 4.0 (b, 1H, -NH-N-), δ 7.30-7.80 (m, 8H, Ar-H), δ 8.0 (s, 1H, -N=CH). ^{13}C NMR: 40, 128.56, 128.86, 129.10, 129.35, 131.43, 131.79, 133.61, 134.64, 134.89, 135.03, 135.14, 145.81, 166.75, 172.47. EI-MS: 308.2 (M+, 65 %), 307.2 (80 %), 305.2 (100%).

(4-Chlorophenyl)-(1-methoxynaphthalen-2-ylmethylene)aceto-hydrazide

IR *v* max cm-1: 745, 806, 977, 1050, 1199, 1255, 1336, 1474, 1557, 1665, 2840, 3057, 3198. ^{1}H NMR: δ 2.52 (s, 3H, Ar-OCH_3), δ 3.90 (s, 2H, Ar-CH_2-), δ 4.2 (s, 1H, -NH-N-), δ 7.40-8.10 (m, 10H, Ar-H), δ 8.85 (s, 1H, -N=CH). ^{13}C NMR: 40, 57.13, 113.86, 124.40, 124.84, 125.49, 126.21, 127.59, 128.38, 129.211, 131.03, 132.54, 132.82, 133.12, 133.89, 135.04, 141.59, 158.05, 165.39, 170.95. EI-MS: 353 (M+, 45 %), 351.3 (100%).

Analysis of metal complexes

Characterization of all the prepared hydrazone-based Schiff base ligands complexes with metals Zn(II), Pd(II), Co(II), Cu(II), and Fe(II) were done. Their elemental analysis confirmed the ML_2 nature of complexes. The IR data of some complexes are given in the supplementary material.

Table 2. Anti-bacterial activity of ligand and complexes (in mm)

Compound	Inhibition zone, in mm		
	Escherichia coli	Bacillus subtilis	Pseudomonas aeruginosa
L1	14	20	17
L2	11	29	12
A1	21	25	20
A2	20	25	20
A3	18	20	17
A4	25	22	29
A5	19	26	18
A6	11	16	14
A7	19	22	18
A8	08	10	11
A9	24	31	27
A10	18	21	20
Penicillin	23	30	28

Antibacterial activity

Antibacterial activity of synthesized Schiff bases and their complexes has been screened against bacteria *Escherichia coli, Bacillus subtilis &Pseudomonasaeruginosa.* Results of the ligands and complexes prepared were showed moderate to excellent activity as compare to standard Penicillin Table 2.

Conclusion

In conclusion we synthesized novel Schiff bases and metal complexes.These ligands and metal complexes were screened for antibacterial activity. Ligand L2 showed good activity against *Bacillus subtilis.* Complex A1, A4 and A9 showed better activity against *Escherichia coli,* Bacillus *subtilis andPseudomonas aeruginosa*. All other compound were have variable but less than standard antibacterial activity.

Acknowledgment

The authors are thankful to the principal Dr. S. N. Thore, Deogiri College, Aurangabad for providing laboratory facilities and continue his encouragement during the said work.

References

[1]Abu-Hussen, A. A. A., *J. Coord. Chem.,***2006**, *59(2),* 157–176.

[2]Karthikeyan, M. S., Prasad, D. J., Poojary, B., Subrahmanya Bhat, K., Holla, B. S. and Kumari, N. S., *Bioorg. Med. Chem.,* **2006,** *14(22),* 7482–7489.

[3]Singh, K., Barwa, M. S. and Tyagi, P., *Eur. J. Med. Chem.,* **2006,** *41(1),* 147–153.

[4]Panneerselvam, P., Nair, R. R., Vijayalakshmi, G., Subramanian, E. H. and Sridhar, S. K., *Eur. J. Med. Chem.,***2005,** *40(2),* 225–229.

[5]Sridhar, S. K., Saravanan, M. and Ramesh, A., *Eur. J. Med. Chem.,,***2001,** *36(7-8),* 615–625.

[6]Pandeya, S. N., Sriram, D., Nath, G. and Declercq,E., *Eur. J.. Pharm. Sci.,* **1999,** *9(1),* 25–31.

[7]Mladenova, R., Ignatova, M., Manolova, N., Petrova, T. and Rashkov, I., *Eur. Polym. J.,* **2002,** *38(5),* 989–999.

[8]Walsh, O. M., Meegan, M. J., Prendergast, R. M. and Nakib, T. A., *Eur. J. Med. Chem.,* **1996,** *31(12),* 989–1000.

[9]Travnıcek, Z., Malon, M., Sindelar, Z., Dolezal, K., Rolcik, J., Krystof, V., Strnad, M., Marek, J., *J. Inorg. Biochem.,* **2001,** *84(1-2),* 23–32.

[10]El-Ayaan, U. and Abdel-Aziz, A. A. M., *Eur. J. Med. Chem.,* **2005,** *40(12),* 1214–1221.

[11]Sonmez, M., Berber, I. and Akbas, E., *Eur. J. Med. Chem.,* **2006,** *41(1),* 101–105.

[12]Keskioglu, E., Gunduzalp, A. B., Ete, S. C., Hamurcu, F. and Erk, B., *Spectrochimica Acta—Part A,* **2008,** *70(3),* 634–640.

[13]Wu, J. Z. and Yuan, L., *J. Inorg. Biochem.,* **2004,** *98(1),* 41–45.

[14]Balasubramanian, K. P., Parameswari, K., Chinnusamy, V., Prabhakaran, R. and Natarajan, K., *Spectrochim. Acta—Part A,* **2006,** *65(3-4),* 678–683.

[15]Mishra, N., Poonia, K., and Dinesh, K., *Int. J. Adv. Res. Technol.* (*IJOART*), **2013,** *2,* 52-66.

[16]Arulmurugan, S., Kavitha, H. P. and Venkatraman, B. R., *Rasayan J. Chem,* **2010,** *3,* 385-410.

[17]Brodowska , K., Łodyga-Chruścińska, E., *CHEMIK,* **2014,** *68*, 129-134.

[18]Ahmed, M., Ibrahim. A. D., Mohamed, M. A., *Beni-Suef Univ. J. Basic Appl. Sci.,* **2015,** *4,* 119-133.

[19]Rana, K., Pandurangan, A., Singh, N., Tiwari, A. K., *Int. J. Curr. Pharm. Res.,* **2012,** *4,* 5-11.

Received: 02.10.2016.
Accepted: 02.12.2016.