INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

www.ijabpt.com ISSN : 0976-4550

Volume-6, Issue-2, April-June-2015 Coden IJABFP-CAS-USA

Received: 12th Mar-2015 *Revised: 13th April -2015* *Accepted: 13th April-2015*

Research article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITIES OF SOME NOVEL HETEROCYCLIC SCHIFF BASES

V.G. Deshpande, Seema I Habib, Naheed Azam and P.A. Kulkarni

P.G. Department of Chemistry and Organic Research Laboratory, Yeshwant Mahavidyalaya, Nanded-431602

Department of Chemistry, G. M. Momin College, Bhiwandi-421302. (MS) India.

Author E-mail: seemahabib12@gmail.com

ABSTRACT: A series of heterocyclic schiff bases have been synthesised by the condensation of 2-amino-4,6-dimethyl benzothiazole and selected heterocyclic α- hydroxy aldehyde and α-hydroxy ketones. The structures of the products were confirmed by spectral analysis (IR, ^{1}H NMR, ^{13}C NMR and Mass). All the newly synthesized compounds were screened for their antibacterial and antifungal activity against different fungal and bacterial strains.

Keywords: Schiff bases, spectral study, antimicrobial study

INTRODUCTION

The synthesis of a newer class of anti-bacterial and anti-fungal agents is in need of time, especially against drug-resistant bacteria and fungi, such as gram-positive and gram-negative strains, which are responsible for a number of serious infections in the acute and chronic care units in hospitals. Over the past few decades various classes of Schiff bases ligands have been extensively studied which can be prepared by condensation of different types of amines and carbonyl compounds. Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds via ring closure, cyclo addition and replacement reactions (Karia et.al., 1999). Moreover, Schiff bases derived from various heterocycles have been reported to possess cytotoxic (Tarafder et. al., 2002), anticonvulsant (Küçükgüzel et. al., 2004), antiproliferative (Vicini et. al., 2003), antimicrobial (Kahveci et. al., 2005), and anticancer activities (Bekircan et. al., 2006). In generally Schiff bases are reported to possess antimicrobial activities. Heterocycles bearing nitrogen, sulphur and thiazole moieties constitute the core structure of a number of biologically interesting compounds (Sharma and Sharma, 2009)[7].Schiff base complexes derived from heterocyclic compounds have found increased interest in the context of bioinorganic chemistry (Chaviara, *et al*., 2004; Ciller, *et al*., 2009; Agarwal, *et al*., 1990). Benzothiazole and its derivatives have been recognized as a class of medicinal importance (Pandeya, *et al*., 1999, Munirajasekar, *et al.,* 2011, Pramila, *et al*., 2008, Mathews, *et al.,* 2007, Srivastava, *et al*., 1982).

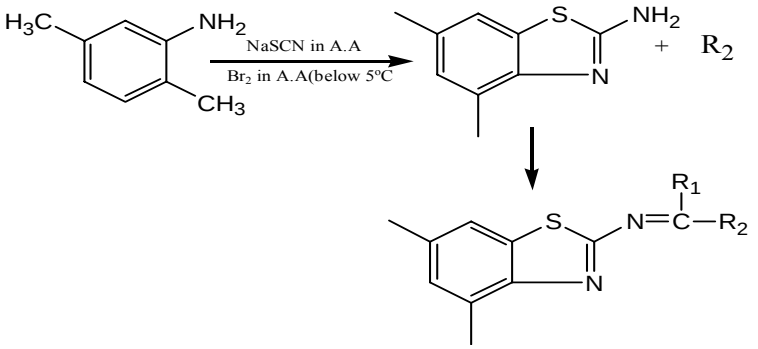
Keeping in view, in this paper we report the synthesis of Schiff base ligands by the conventional condensation reaction of biological and clinical importance 2-amino-4,6-dimethyl benzothiazole and selected heterocyclic α-hydroxy aldehyde and α-hydroxy ketones and their structural characterization by IR, ^{1}H NMR, ^{13}C NMR and Mass.

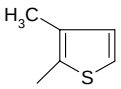
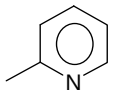
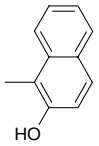
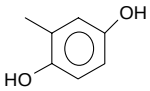
RESULTS AND DISCUSSIONS

In this present paper, a series of various substituted schiff bases were synthesised by the condensation of 2-amino-4, 6-dimethyl benzothiazole and selected heterocyclic α- hydroxy aldehyde and α-hydroxy ketones.

The products were confirmed by their spectral analysis. Appearance of IR bands at 3340-3448 (-OH) and 1555-1612 cm^{-1} (>C=N-) supported the structure. ^{1}H NMR spectra, the multiplet around the δ 7.2-8.4 ppm assigned to the aromatic protons. The aromatic -OH proton appeared as singlet at δ13.9-14.4 ppm, while other aliphatic protons are appeared at expected regions. The mass spectra of the compounds were showed corresponding molecular ion peak which was correlated with their molecular weight of that respected compounds. The results of antimicrobial data are given in Table-2. The data revealed that all the compounds were found to be active against almost all the tested fungi and bacteria.

Scheme-I



S.No.	Compound	Substituents	
		R_1	R_2
1	L_1	H	
2	L_2	H	
3	L_3	H	
4	L_4	H	
5	L_5	CH_3	

All chemicals used in the present study were of AR grade and those were procured from Sigma, Aldrich, Lancaster and Spectrochem and were used as such. Solvents used in the present study were procured locally and used as such. Completion of the reaction was monitored by thin layer chromatography (TLC) on pre coated sheets of silica gel-G

The present work involves synthesis of Schiff bases as ligands such as L_1 to L_5

Names of respective Schiff base (1—5) are as follows –

1. (4,6-Dimethyl-benzothiazol-2-yl)-(1H-pyrrol-2-ylmethylene)-amine
2. (4,6-Dimethyl-benzothiazol-2-yl)-(3-methyl-thiophen-2-ylmethylene)-amine
3. 4,6-Dimethyl-benzothiazol-2-yl)-pyridin-2-ylmethylene-amine
4. 1-[(4,6-Dimethyl-benzothiazol-2-ylimino)-methyl]-naphthalen-2-ol
5. 2-[1-(4,7-Dimethyl-benzothiazol-2-ylimino)-ethyl]-benzene-1,4-diol

a) Synthesis of 2-Amino-4,6 Dimethyl benzothiazole:

Synthesis of 2-amino-4,6-Dimethyl Benzothiazole was carried out by the standard method.(0.1M) 2,4-Xylidine (2,4-dimethylaniline) and sodium thiocyanate (0.2M) in 100ml glacial acetic acid were mixed together and reaction mixture was cooled to 0^{o}C temperature.

(0.2M) bromine in acetic acid (25ml) was added to the above solution drop wise and the mixture was stirred till the complete addition of bromine maintaining temperature below 5^{o}C throughout addition. Stirring was kept continued maintaining temperature below 5^{o}C for half an hour after addition of Bromine is made. The solid thus obtained after complete addition of bromine was filtered on vacuum and then dissolved in hot water. The solution was then treated with very dilute alkali like NaOH for the separation of free amine. The free amine thus obtained was filtered, washed and dried and was recrystallized from ethanol, M.P observed 140^{o}C, yield 80%. It was tested for free NH_2 group.

b) Synthesis of Schiff bases:

Schiff bases were synthesized by using equimolar ethanolic solutions of heterocyclic amine and hydroxyl aldehyde / ketone and refluxing mixture for 4-5 hours. Then the reaction was monitored by TLC method. Upon observing single spot the heating was stopped and reaction mixture was poured in ice cold water / on crushed ice the separated solid was collected by filtration, after washing and drying, it was recrystallized from ethanol. The melting points were recorded.

i) Synthesis of L_1, L_2, L_3 and L_4

Equimolar ethanolic solution of the L_1 (pyrrole-2-aldehyde), L_2 (3-Methyl Thiophene 2-aldehyde), L_3(pyridine-2-aldehyde), L_4 (2-hydroxy napthylaldehyde) and 2-amino-4,6-dimethyl benzothiazole were refluxed for 4-5 hours on water-bath and the reaction mixture was poured on ice cold water and the separated solid was collected by filtration, washing and drying, recrystallized from ethanol. M.P recorded.

ii) Synthesis of L_5:

Equimolar ethanolic solution of L_5 (2,5-dihydroxy acetophenone) and 2-amino-4,6-dimethyl benzothiazole were refluxed for 4-5 hours on water bath and the reaction mixture was poured on ice cold water and the separated solid was collected by filtration, washing and drying, recrystallized from ethanol. M.P recorded.

The synthesized Schiff bases are found to be stable in air and moisture, soluble in ethanol, chloroform, DMF and DMSO and insoluble in water. Conductance studies were performed on EQ-606 Equiptronics conductometer using cell internally calibrated and constant value 1.0. The structural features of the Schiff bases are elucidated with the help of elemental and spectral analysis.

Table 1: Physical and Analytical Data of Systhesized Schiff Base Ligands

S.No	Comp.	Mol. Formula	Mol .Wt	% Yield	Colour	M.P. ^{o}C	Elemental Analysis (%)		
							C% (Cal/found)	H% (Cal/found)	N% (Cal/found)
1.	L_1	$C_{14}H_{13}N_3S$	255	86	Faint Yellow	115	65.88/64.14	5.09/4.89	16.47/16.04
2.	L_2	$C_{15}H_{14}N_2S_2$	286	82	Orange	128	62.93/61.53	4.89/3.98	9.79/8.76
3.	L_3	$C_{15}H_{13}N_3S$	267	78	Brown	110	67.41/67.05	4.86/3.96	15.73/14.84
4.	L_4	$C_{20}H_{16}N_2SO$	332	90	Yellow	218	72.28/71.86	4.81/3.46	8.43/7.73
5.	L_5	$C_{17}H_{16}N_2SO_2$	312	88	Faint Brown	212	65.40/63.81	5.02/4.86	8.98/7.74

Spectroscopic data of selected compounds:

i) Compound L_1

IR (KBr) υ in cm^{-1}: 3186 (N-H), 2916 (C-H), 1612(C=N), 1550, 1496 (C=C),
^{1}H-NMR δ ppm: δ 2.3 (S, 3H Ar-CH_3), δ 2.5 (S, 3H Ar-CH3), δ 6.3 (S, 1H N-H), δ 7.0- 7.7 (M, 5H Ar-H), δ 8.8 (S,1H CH=N)
^{13}C NMR: δ 18, 22, 112, 119, 122, 127, 128, 130, 132, 134, 135, 149, 154, 170 ppm
Mass (M/z) % rel. intensity: 255(M^+)

ii) Compound L_2

IR (KBr) υ in cm^{-1}: 3086(C=CH), 1581(C=N), 1489, 1411((C=C), 825(C-S)
^{1}H-NMR δ ppm: δ 2.4(S, 3H Ar-CH3), δ 2.5(S, 3H Ar-CH3), δ 7.2-8.0(M,4H Ar-H), δ 9.2(S,1H CH=N)
^{13}C NMR: δ 14, 18, 22, 120, 128, 132, 134, 135, 136, 137, 146, 148, 152, 158, 170 ppm
Mass (M/z) % rel. intensity: 286(M^+)

iii) Compound L_3

IR (KBr) υ in cm^{-1}: 3340, 2913, 1585, 1457, 1263, 834, 741
^{1}H-NMR δ ppm: 2.0-2.5(S,6H), 6.8(S,1H,), 7.0-9.0(m,6H)
Mass (M/z) % rel. intensity: 267(M^+)

iv) Compound L_4

IR (KBr) υ in cm^{-1}: 3448 (-OH), 3009 (C=CH), 2901 (-CH_3), 1597 (C=N), 1550, 1465, 1442 (C=C)
^{1}H-NMR δ ppm: δ 2.4 (S, 3H Ar-H), δ 2.8 (S,3H,Ar-H), δ 7.1-8.4 (M,8H,Ar-H) δ 10.1 (S, 1H, CH=N), δ 14.4 (S,1H Ar-OH)
^{13}C NMR: δ 18, 22, 110, 118, 120, 121, 124, 126, 127, 128, 129, 130, 132, 133, 134, 135, 136, 138, 161, 166 ppm
Mass (M/z) % rel. intensity: 332 (M^+)

v) Compound L_5

IR (KBr) υ in cm^{-1}: 3444, 3217, 1621, 1555, 1460, 1251, 743
Mass (M/z) % rel. intensity: 314 (M^{+2})

Antimicrobial Activity

The antibacterial activity was measured by agar cup method[16] (Cruickshank, et.al., 1998). Nutrient agar (Himedia) was prepared and sterilized at 15 Psi for 15 minutes in the autoclave. It was allowed to cool below 45^0C and seeded with turbid suspension of test bacteria separately, prepared from 24 hours old slant cultures. 3% inocula were used every time. The bacterial cultures selected were, two gram negative cultures viz. *Escherichia coli, Salmonella typhi* and two Gram positive cultures viz. *Staphylococcus aureus, Bacillus subtilis*. This seeded preparation was then poured in sterile Petri plate under aseptic condition and allowed it to solidify.

Cups of 10 mm diameter were borered in the agar plate with sterile cork borer. 100 µl of compound solution prepared in Dimethylsulphoxide (1%) was added in the cup under aseptic condition with the help of micropipette. 100 µl of DMSO was also placed in one of the cup as blank (negative control). A standard antibiotic disk impregnated with 10 units of Penicillin was also placed on the seeded nutrient agar surface as standard reference antibiotic (positive control). The plates were kept in refrigerator for 15 minutes to allow diffusion of the compound from agar cup into the medium. Then the plates were shifted to incubator at 37^0C and incubated for 24 hours. After incubation plates were observed for the zone of inhibition of bacterial growth around the agar cup. Results were recorded by measuring the zone of inhibition in millimeter (mm) using zone reader in Tables 1 and 2.

Similarly the same compounds were screened for the antifungal activity against different organisms like *P.chrysogenum, A. niger, F. moniliformae*, and *A.Flavus* by using poison plate method. The medium used was Potato Dextrose Agar (Himedia). The medium was prepared and sterilized at 10 Psi in autoclave for 15 minutes. Then the compound to be tested is added to the sterile medium in aseptic condition so as to get final concentration as 1%. A plate with DMSO was prepared as blank (negative control) similarly a plate with 1% Grysofulvin was prepared as standard reference plate (positive control). *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme*, Aspergillus flavus were selected as test fungal cultures. They were selected as test fungal cultures. They were allowed to grow on slant for 48 hours so as to get profuse sporulation. 5 ml of 1:100 aqueous solution of Tween 80 was added to the slant and spores were scraped with the help of nicrome wire loop to form suspension. The fungal suspension was spot inoculated on the plate's prepared using compound with the help of nicrome wire loop. The plates were incubated at room temperature for 48 hours. After incubation plates were observed for the growth of inoculated fungi. Results were recorded as growth of fungi (no antifungal activity), reduced growth of fungi (moderate antifungal activity), and no growth of inoculated fungi (antifungal activity) in Table 2.

Table 2-Antimicrobial data

		Bacterial Strain				Fungal Strain			
Sr.No	**Comp.**	**Ec**	**St**	**Sa**	**Bs**	**An**	**Pc**	**Fm**	**Af**
1	L1	-ve	-ve	-ve	-ve	+ve	+ve	+ve	+ve
2	L2	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
3	L3	-ve	19mm	22mm	22mm	-ve	-ve	-ve	-ve
4	L4	11mm	-ve	-ve	13mm	+ve	+ve	-ve	+ve
5	L5	-ve	11mm	-ve	16mm	-ve	-ve	-ve	-ve
6	DMSO	-ve	-ve	-ve	-ve	NA	NA	NA	NA
7	Penicillin	13 mm	18mm	36mm	18mm	NA	NA	NA	NA
8	+ve control (blank)	NA	NA	NA	NA	+ve	+ve	+ve	+ve
9	(Grysofulvin)	NA	NA	NA	NA	-ve	-ve	-ve	-ve

Ec-E.coli, St-S.typhi, Sa- S.aureus, Bs-B.subtilis; An-A.niger, Pc-P.chrysogenum, Fm-F.moneliformae, Af-Aspergillus flavus; *-ve: No growth of fungi,+ve; Growth of fungi, RG-Reduced growth*, *NA-Not Applicable*, *Zone of inhibition was measured in mm*.

CONCLUSIONS

In summary, we have synthesized some novel Schiff bases. All the synthesized compounds gave satisfactory spectral and analytical data. The screening of antimicrobial data revealed that all the compounds show good antimicrobial activity.

ACKNOWLEDGMENTS

The authors are thankful to Principal, Yeshwant Mahavidyalaya, Nanded for providing laboratory facilities and also to the Director, IICT, Hyderabad for providing the instrumentation facilities.

REFERENCES

F. D. Karia, P. H. Parsania, (1999). Synthesis, biological and thermal properties of schiff bases of bisphenol-C., Asian J. Chem., 11, 991-995.

M.T. Tarafder, A. Kasbollah, N. Saravan, K. A. Crouse, A. M. Ali, O. K. Tin, (2002). S-methyldithiocarbazate and its schiff bases: Evaluation of bondings and biological properties, J. Biochem. Mol. Biol. Biophs., 6, 85-91.

I. Küçükgüzel, S. G. Küçükgüzel, S. Rollas, G. Ötük-Sani, O. Özdemir, T. Bayrak, I. Altug, J. P. T. Stables, (2004). 3-(Arylalkylthio)-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazole derivatives and their anticonvulsant activity. Farmaco, 59, 893-901.

P. Vicini, A. Geronikaki, M. Incerti, B. Busonera, G. Poni, C. A. Kabras, P. L. Colla, (2003). Synthesis and biological evaluation of benzo[d]isothiazole, benzothiazole and t hiazole Schiff bases, Bioorg. Med.Chem, 11, 4785-4789.

B. Kahveci, O. Bekircan, S. A. Karaoglu, (2005). Synthesis and antimicrobial activity of some 3-alkyl-4(arylmethyleneamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones., Indian J. Chem., 44B, 26142617.

O. Bekircan, B. Kahveci, M. Kucuk, (2006). Synthesis and anticancer evaluation of some new unsymmetrical 3,5-diaryl-4H-1,2,4-triazole derivatives., Tur. J. Chem., 30, 29-40.

B. V. Agarwal, & S. Hingorani, (1990). Characteristics IR and electronic spectral studies on novel mixed ligand complexes of copper (II) with thiosemicarbazones and heterocyclic bases, Synth. React. Inorg. Met-Org.Chem., 20:123-132

A. T. Chaviara, P. J. Cox, K. H. Repana, R. M. Papi, K. T. Papazisis, D. Zambouli, A. H. Kortsaris, D. A. Kyriakidis, & C. A. Bolos, (2004). Copper (II) Schiff base coordination compounds of dien with heterocyclic aldehydes and 2-amino-5-methyl-thiazole: synthesis, characterization, antiproliferative and antibacterial studies. Crystal structure of CudienOOCl2, J. Inorg. Biochem, 98(8): 1271-1283.

J. A. Ciller, C. Seoane, J. L. Soto, & B. Yruretagoyena, (2009). Synthesis of heterocyclic compounds Schiff bases of ethyl 2-amine of urancar oxylates, J.Heterocyclic. Chem. 23(5), 1583-1586

M. E. Mathews, S. J. Garden, & P. D. Fermades, (2007). Isatin inhibit cyclooxygenase-2 and inducible nitric oxide synthase in a mouse macrophase celliness. European Journal of Pharmacolology, 356, 206.

D. Munirajasekar, M. Himaja, & M. Sunil, (2011). Synthesis and anthemintic activity of 2-amino-6-subtituted benzothiazoles, International Research Journal of Pharmacy, 2(1); 114-117.

S. N. Pandeya, D. Sriram, G. Nath, & D. E. Clercq, (1999). Synthesis antibacterial antifungal and anti HIV evaluation of Schiff and Mannich bases of isatin with N-[6-chlorobenzothiazo-2-yl] thio semicarbazide, Indian Journal of Pharmaceutical Sciences, 61(6): 358

T. Pramila Bheemachari, V. Rajesh & R. H. Udupi, (2008). Condensed bridge head nitrogen heterocyclic systems synthesis and biological evaluation of substituted-s-triazole-thiazzolethiones and s-triazolo-thiadiazinones., Indian J Het Chem, 17, 229.

V. Sharma, & K.V. Sharma, (2009). Synthesis and Biological Activity of Some 3, 5-Diaryl-1-benzothiazolopyrazoline Derivatives: Reaction of Chalcones with 2-Hyrazinobenzothiazoles., E-Journal of Chemistry, 6(2), 348-356.

N. Srivastava, A. A. Gupta, & K. Anil, (1982). Synthesis and CNS activity of some 1-substituted amino methyl-3-[P-(N, N-diethyl carbamoyl) phenylimo]-substituted indolin-2-ones., Indian Journal of Chemistry; 21(B); 787

R.J. Cruickshan, P.Duguid, R.R. Swain, (1998). Medical Microbiology, Vol. 1, Publisher Churchill, Livingstone (1998).

ISSN : 0976-4550

INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

Email : ijabpt@gmail.com

Website: www.ijabpt.com