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Synthesis and antibacterial activity of some Schiff bases derived from 2-amino thiazole

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ABSTRACT

The following schiff bases have been synthesized: 2-(Thiazol-2yliminomethyl)-phenol(a), (2-Chloro-benzylidene)-thiazol-2-yl-amine(b), (2-Nitro-benzylidene)-thiazol-2-yl-amine(c),(3-Phenyl-allylidene) thiazol-2-yl-amine(d), (4-Hydroxy-3-methoxy-benzylidene)-thiazol-2-yl-amine(e), furan-2-yl methylene-thiazol-2-yl amine(f).They were screened as potential antibacterial agents against a number of medically important bacterial strains.

KEYWORDS

2-Amino thiazole;
Schiff bases;
Antibacterial activity;
N, N-dimethyl sulfoxide;
1,4-dioxane.

INTRODUCTION

The discovery and development of antibiotics are among the most powerful and successful achievements of modern science and technology for the control of infectious diseases. However, the increasing microbial resistance to antibiotics in use nowadays necessitates the search for new compounds with potential effects against pathogenic bacteria. The most spectacular advances in medicinal chemistry have been made when heterocyclic compounds played an important role in regulating biological activities. Extensive investigations in the field of schiff bases have been reported[1,2]. Their preparation, chemical and physical properties have been described by various workers[3,4]. Several workers have reported that schiff bases formed from aromatic aldehydes or aromatic ketones and their derivatives are quite stable[5]. Due to the great flexibility and diverse structural aspects of schiff bases, a wide range of these compounds have been synthesized and their complexation behavior were studied[6,7]. Nitro and halo derivatives of schiff bases are reported to have antimicrobial and antitumor activities[8]. Antimicrobial and antifungal activities of various schiff bases have also been reported[9,11]. Sahu et al[12]. reported fungi toxicity of some schiff bases. Gawad et al[13].synthesized some schiff bases and observed high microbial activities. Many schiff bases are known to be medicinally important and are used to design medicinal compounds[14-16]. In this work, the synthesis and characterization of some schiff bases for phar-

macological studies are reported.

EXPERIMENTAL

Reagents

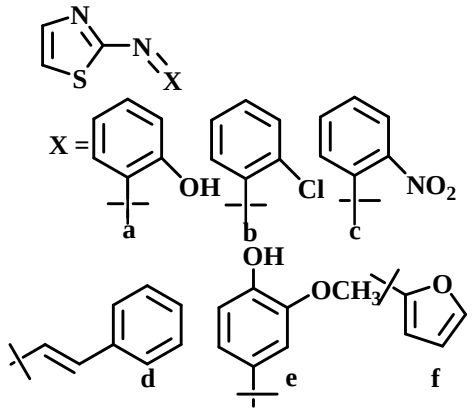
2-Aminothiazole (Merck, 99.9%), O-Chloroben zaldehyde(Ranchem ltd, 99.9%), Furfuraldehyde (Lancaster, 99%), Cinnamaldehyde(Lobachemie, India, 98%), Salicyladehyde(Lancaster (99%), Vanillin (Merck 99%), m-Nitrobenzaldehyde(SD Finechem, India, 98%). All the solvents used are from Rankem Ltd, Mumbai, India and are used without further purification.

Instruments

The IR spectra were obtained in KBr discs using a BIO-RAD FTS 135 spectrophotometer. The ^{1}H-NMR spectra(in DMSO-d_6) were recorded on a Varian Gemini 200 MHz spectrometer. Chemical shifts were reported as parts per million downfield from an internal Tetra methyl silane(TMS) standard (δ0.00 for ^{1}H-NMR while the C, H, N analysis were done at IICT, Hyderabad, India. Melting points were recorded on a POLMON T120 Melting point apparatus and are uncorrected.

Synthesis of schiff bases

The following six schiff bases were synthesized (Scheme) 2-(Thiazol-2yliminomethyl)-phenol**(a)**, (2-Chloro-]benzylidene)-thiazol-2-yl-amine**(b)**,(2-Nitrobenzylidene)-thiazol-2-yl-amine**(c)**, (3-Phenyl-allylidene) thiazol-2-yl-amine **(d)**, (4-Hydroxy-3-methoxy-benzylidene)-thiazol-2-yl-amine**(e)**, furan-2-yl methylene-thiazol-2-yl amine**(f)**.



SCHEME: Schiff bases

To 0.1mol of aldehyde dissolve in 20 volumes of methanol, 0.1mol of amine and few drops of glacial acetic acid were added and mixture was refluxed for 10-12 h at 70-75^{0}C. The resulting solution was cooled to room temperature, and poured over crushed ice with constant stirring. The precipitate was filtered and washed with sodium bisulphate solution to remove excess of aldehyde. The product was recrystallized from hot methanol and dried.

Test microorganisms

The bacterial strains studied were identified strains and were obtained from the national chemical laboratory (NCL), Pune, India and national institution of nutrition, Hyderabad, India: *A.faecalis* ATCC 8750, *E.aerogenes* ATCC 13048, *E.coli* ATCC 25922, *K.pneumoniae* NCIM 2719, *S.aureus* ATCC 25923, *P.vulgaris* NCIM 8313, *P.aeruginosa* ATCC 27853 and *S.typhimurium* ATCC 23564.

Preparation of the test compound

The compound were dissolved at a concentration of 10mg/ml in either of the two solvents (DMF/1,4-dioxane) in order to obtain a final concentration of 1mg/0.1ml. In all, 3 different concentrations of the drug were prepared(1mg/0.1, 0.1mg/0.1ml, 0.01mg/0.1ml) for the microbiological assays. The synthesized schiff bases are soluble only in DMF, 1,4-dioxane, DMSO and from these two solvents, i.e. DMF and 1,4-dioxane, were selected in the present work.

Preparation of the plates and microbiological assays

A loop full of the given test strain was inoculated in 25ml of the N-broth (Nutrient broth) and was incubated for 24h in an incubator at 37^{0}C in order to activate the bacterial strain. The plates were prepared by dissolving 38g of muller hinton agar No. 2 in 1000ml of distilled water. In order to proceed with agar ditch method[18], 28-30ml of the autoclaved Muller Hinton Agar No. 2 media was added into a 100mm diameter petri-plate. Inoculation of the test strain was done by the pour- plate technique. 0.2ml of the activated strain was inoculated into the media when it reached a temperature at 40-45^{0}C Proper homogenization of the strain was realized by gently shaking the sugar tube followed

by gently pouring into a petri-plate. Formation of air bubbles during this procedure of inoculation was strictly avoided. The complete procedure of the preparation of the plate was performed in Laminar airflow to maintain strict sterile and aseptic conditions. The media was allowed to solidify. After solidification of the media, a ditch/well was made in the plates with the help of a cup-borer(0.85cm) and then 0.1ml of the synthetic compound (dissolved in DMF/1,4-dioxane) was added into the well. The controls were maintained (for each bacterial strain and each solvent), where 0.1ml of the pure solvent was inoculated into the well. The antibacterial activities of the synthetic compounds were determined by the inhibition zone formed by these compounds against the particular test bacterial strain.

RESULTS AND DISCUSSION

In all, six compounds were synthesized and IR, EIS-MASS and NMR spectral data confirmed their molecular structure. The Melting points and percentage of yields of synthesized compounds are shown in TABLE 1. The IR, EIS-MASS, NMR, and C, H, N analysis data are given below.

2-(Thiazol-2yliminomethyl)-phenol (a)

IR (KBr, cm^{-1}): -OH (str): 3417, C-S (str): 684, C=N: 1606. ^{1}HNMR(DMSO-d_6, δppm): δ 6.79 (d, 1H, Ph-H), δ7.14 (t, 1H, Ph-H), δ7.21(d, 1H, Ph-H), δ7.23(t, 1H, Ph-H), δ8.26(d, 1H, -CH), δ8.51 (d, 1H, -CH), δ8.74(s, 1H, N=CH), 12.42(b, 1H, OH). EIS-Mass(70eV) m/z: 205.16 (M+H), 204.18(M+). Anal. (Calculated for $C_{10}H_8N_2OS$): C, 58.80, H, 3.39, N, 13.72, O, 7.83, S, 15.70; Found: C, 58.25, H, 3.37, N, 13.68, O, 7.85, S, 15.66.

(2-Chloro-benzylidene)-thiazol-2-yl-amine(b)

IR (KBr, cm^{-1}): C-S(str): 682, C=N: 1608, C-Cl(str.) 839. ^{1}HNMR(DMSO-d_6, dppm): δ7.34 (t, 1H, Ph-H), δ7.37(t, 1H, Ph-H), δ7.38(d, 1H,Ph-H), δ7.48(d, 1H, Ph-H), δ8.25(d, 1H, CH), d8.52(d, 1H, CH), δ9.26(s, 1H, N=CH). EIS-ass(70eV) m/z: 223.84(M+H), 222.70(M+). Anal.(Calculated for $C_{10}H_7ClN_2S$): C,53.93, H, 3.17, Cl, 15.92, N, 12.58, S, 14.40; Found: C, 53.90, H, 3.16, Cl, 15.88, N, 12.56, S, 14.38.

TABLE 1 : Compound code, molecular formula, molecular weight, melting point, percentage yields

Comp. code	Molecular formula	Molecular weight/g $mole^{-1}$	M.P(^{o}C)	Yield%
a	$C_{10}H_8N_2OS$	204.25	217	54
b	$C_{10}H_7ClN_2S$	222.69	185	67
c	$C_{10}H_7N_3O_2S$	233.25	252	66
d	$C_{12}H_{10}N_2S$	214.29	115	62
e	$C_{11}H_{10}N_2O_2S$	234.28	158	59
f	$C_8H_6N_2OS$	178.21	212	70

(2-Nitro-benzylidene)-thiazol-2-yl-amine (c)

IR (KBr, cm^{-1}): C-S (str): 684 , C=N: 1602, Ar-NO_2: 1571. ^{1}HNMR (DMSO-d_6, δppm): δ7.73 (d, 1H, Ph-H), δ7.75(t, 1H, Ph-H), δ7.77(d, 1H, Ph-H), δ7.80(d, 1H, Ph-H), δ8.25(d, 1H, CH), δ8.52 (d, 1H, CH), δ8.97(s, 1H, N=CH). EIS-Mass(70eV) m/z: 234.14(M+H), 233.25(M+). Anal.(Calculated for $C_{10}H_7N_3O_2S$): C, 51.49, H, 3.02, N, 18.02, O 13.72, S, 13.75; Found: C, 51.44, H, 3.02, N, 18.14, O, 13.69, S, 13.71.

(3-Phenyl-allylidene) thiazol-2-yl-amine (d)

IR (KBr, cm^{-1}): C-S(str): 680, C=N: 1600, C=C (str.): 1652.^{1}HNMR(DMSO-d_6, δppm): δ7.03 (t, 1H, CH), δ7.05 (d, 1H, CH), δ7.25(m, 2H, Ph-H), δ7.31 (m, 2H, Ph-H), 7.57 (t, 1H, Ph-H), δ8.36 (d, 1H, CH), δ8.53 (d, 1H, N=CH), δ8.63(d, 1H, CH). EIS-Mass (70eV) m/z: 215.24(M+H), 214.16 (M+). Anal.(Calculated for $C_{12}H_{10}N_2S$): C 67.26, H 4.70, N 13.07, S 14.96; Found: C 67.16, H 4.77, N 13.01, S 14.95.

(4-Hydroxy-3-methoxy-benzylidene)-thiazol-2-yl-amine(e)

IR(KBr, cm^{-1}): -OH(str.): 3367, C-H(asym. str.): 2922, C-S(str): 688, C=N: 1601, C-H(sym. str.): 1454, C-O-C(str): 1396, -OH(bend): 1315. ^{1}HNMR (DMSO-d_6, δppm): δ3.37(s, 3H, CH_3), δ4.90(b, 1H, OH), 6.86(d, 1H, Ph-H), δ7.12(s, 1H, Ph-H), δ7.37 (d, 1H, Ph-H), δ8.25(d, 1H, CH), δ8.52(d, 1H, CH), δ8.65(s, 1H, N=CH). EIS-Mass(70eV) m/z: 235.24 (M+H), 234.16 (M+). Anal.(Calculated for $C_{11}H_{10}N_2O_2S$): C, 56.39, H, 4.30, N, 11.96, O, 13.66, S, 13.69; Found: C, 56.44, H, 4.31, N, 11.93, O, 13.62, S, 13.70.

Furan-2-yl methylene-thiazol-2-yl amine(f)

IR (KBr, cm-1): C-S (str.): 683, C=N: 1600.8, C-O-C(str): 1388. ^{1}H-NMR (DMSO-d_6, δppm): δ6.50 (dd,

1H, CH), δ6.81(d, 1H, CH), δ7.57(d, 1H, CH), δ8.01(s, 1H, N=CH), δ8.25 (d, 1H, CH), δ8.52 (d, 1H, CH). EIS-Mass(70eV) m/z: 179.26.24(M+H), 178.25(M+). Anal.(Calculated for $C_8H_6N_2OS$): C, 53.92, H, 3.39, N, 15.72, O, 8.98, S, 17.99; Found: C, 53.88, H, 3.38, N, 15.68, O, 8.99, S, 17.95.

The six synthetic compounds and their respective controls produced different inhibition zones against the tested bacterial strains. The controls were deducted from the tested compounds; their effect was noticeably different depending on the type of solvent used. Of the three concentrations evaluated, the lowest concentration had little effect while the compounds were slightly effective at a concentration of 0.2mg/0.1ml (data is not shown). The third concentration (i.e., 1.0mg/0.1ml) was effective and only this data will be presented.

The in vitro antibacterial activity of the six-schiff bases in DMF and 1,4-dioxane against medicinally important Gram positive and Gram-negative bacteria are shown in TABLE 2.

In *A.faecalis* none of the compounds in DMF showed any antibacterial activity while in 1,4-dioxane, anti bacterial activity was observed to a certain extent, **(d)** and **(f)** showed comparatively more activity followed by **(c)** and **(e)**; **(a)** and **(b)** showed the least activity. An entirely different trend was observed when the same compounds were tested against *E.aerogenes* in DMF, **(d)** showed considerable inhibitory activity, followed by **(a)**, **(b)** and **(c)** were inactive while **(e)** and **(f)** showed intermediate activity. The schiff bases in 1,4-dioxane showed considerably less antibacterial activity than in DMF in *E.aerogenes*. **(b)**, **(c)** and **(e)** in 1,4-dioxane were not effective at all. Comparing the antibacterial activity of the six-schiff bases against *A.faecalis* and *E.aerogenes*, a differential effect of both of the solvents could be observed. All the compounds showed better antibacterial activity against *A.faecalis* when 1,4-dioxane was used as the solvent, while the same compounds showed no activity or less activity against *E.aerogenes*. Also, all the compounds showed no activity at all in *A.faecalis* when DMF was used, while in *E.aerogenes* these compounds showed antibacterial activity to a certain extent.

The different effect of the compounds against bacteria may be because of the structure of the compounds and also the solvent used. The diffusion capacity of the compounds varies with the employed solvent, which may be because of the polarity of the solvent. In all the six compounds, the central ligand is 2-amino thiazole with different side chains.

TABLE 2 : The *invitro* antibacterial activity of the synthesized schiff bases (10mg/ml)

	Inhibition zone (mm/100µl)											
	a		b		c		d		e		f	
Microorganisms	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
A.faecalis	0	0.7	0	0.2	0	1.6	0	2.1	0	1.5	0	2.2
E aerogenes	4.6	0.6	0.6	0	0.4	0	9.0	1.8	1.6	0	2.2	1.8
E.coli	0	0	0	0	0	0	7.1	1.2	1.3	0	2.2	1.5
K.pneumoniae	2.4	1.5	0	1.3	0	0	0	2.5	0	2	12.4	3
P.aeruginosa	0	0	0	0.3	0	0	0.2	0.1	0	0	0	0
P.vulgaris	2	0.2	0	0	0	0	0	0.4	0	0	1.1	0
S.typhimurium	0	1.5	0	0	0	0.9	0	0	1.2	0.2	0	0.2
S.aureus	0.1	0	0	0	4.0	3.4	0	0	0	0	16.2	21

Extraction solvent (100ml) A: Dimethyl formamide(DMF); B: 1,4-Dioxane

The antibacterial activity of the synthetic compounds against *E.coli* were similar to that shown in *A. faecalis*. None of the compounds in DMF showed any antibacterial activity, while in 1,4-dioxane **(a)**, **(b)**, and **(c)** showed no activity while other three compounds showed some antibacterial activity. This different response is because of the difference in their molecular structures. The compound **(f)** in DMF showed high inhibitory against *K.pneumoniae*, while **(a)** showed little and the other four compounds showed no inhibitory activity against these Gram-negative bacteria. The same compounds in 1,4-dioxane showed antibacterial activity against *K.pneumoniae*, except **(c)**. In *P.vulgaris*, only two compounds **(a** and **f)** showed inhibitory activity, while the compounds showed no antibacterial activity when 1,4-dioxane was the solvent used. None of the compounds in either of the solvents could inhibit *P.aeruginosa*; thus this bacterium appears to be most resistant bacterium. In *S.typhimurium*, the compounds extracted in DMF were inactive while the 1,4-dioxane extracted compounds showed low inhibitory activity. **(c)**and **(f)** were the only compounds, which showed antibacterial activity against Gram-positive bacteria *S.aureus*. These two compounds showed inhibitory zones in both solvents. **(c)** showed less activity while the maximum was shown by **(f)**.

It can be deduced from these results that the different response of the synthesized Schiff bases arise because of their structural differences and are also solvent dependent, i.e., the polarity of the solvent is also responsible for inhibition of the bacteria under investigation.

CONCULSION

From this study, it can be concluded that it cannot be assumed that one solvent is better than the other. It is dependent on the molecular structure and the particular bacterial strain considered. However, with the studied compounds, 1,4-dioxane appears to be a better solvent than DMF since it has a broad spectrum (though less) of inhibitory activity. In an earlier study[18], it was shown that cinnamaldehyde as a side chain and sulfonamide as central ligand exhibited considerable antibacterial activity. In the present study, the central ligand being 2-Amino thiazole, the same inhibition against these medicinally important bacteria could not be produced.

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