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RESEARCH ARTICLE

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SYNTHESI , CHARACTERISATION AND ANTIBACTERIAL, ANTIFUNGAL ACTIVITIES OF SCHIFF BASES OF 4 – (2- AMINPHENYL) MORPHOLINES.

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ABSTRACT

A Series of Schiff's bases of 4(2-amino phenyl) morpholines (1-V) were synthesized compounds were confirmed by IR, ^{1}HNMR and MASS spectrum. All the newly synthesized compounds have been screened for their in vitro antibacterial activities against S.aureus , S. epidermis, B. cereus, B. subtilis, Ps. aureus, Kl. pneumonia and E. coli and antifungal activities against A. niger and C. albicans. Their minimal inhibitory concentration (MIC) values ranged between 1-10 µg/ml. The screening data indicates that the compounds I to V have promising anti-bacterial activity and antifungal activity by disc diffusion method by measuring the zone of inhibition and the results were compared to standard drugs ciprofloxacin and ketoconazole respectively.

KEYWORDS

Synthesis, morpholines derivatives, Schiff base, Anti-bacterial activity

INTRODUCTION

Morpholine derivative plays an important role in the treatment of several diseases. Heterocyclic ring systems having morpholine nucleus have aroused great interest in recent years due to their variety of biological activities[1]. Morpholine derivatives were reported to possess anti-inflammatory[2], analgesic[2], Local anaesthetic [3], anti HIV[4], anticancer[6], appetite suppressant [7], antidepressant [8], anti microbial activity [9] etc. George Brown et al synthesised and resolution of 3-substituted morpholines and chiral synthesis via o-Arylhomoseries[7] .Franchis et al reported the Enamines in the synthesis & characterisation of 2-substituted amino-3-dialkyl chromanones [10]. Adrienne et al synthesised crystal structure of 9-amino-N-2-(4-morpholinyl) ethyl)-4-acridine carboxamide [11]. Afaf et al synthesised some new benzimidazole derivatives with substituted morpholines [12].Roy Beddoes et al synthesised X-ray crystal structure of N^1,N^1-Dimethyl-N^2-methylthio benzamidine with morpholines[13]. Hideo Sawada et al Synthesised Surfacant properties of novel fluoroalkylated amphiphilic oligomers[14]. Agarwal et al synthesised 2-aryl-1-(4-morpholino phenyl)-4-(3,4-disubstituted-benzylidine) imidazolin-5-one [15] .Verma et al synthesised the anti inflammatory activity of amino acyl benzoates [16].Zenitz et al synthesised benzoylphenyl lower alkanoyl piperidines[17].Varma et al reported the synthesis of 5-phenoxy-1,3-disubstituuted benzimidazolin- 2- thione [18]. Balsamo et al synthesised 2-(p-nitrophenyl)-substituted morpholines [19].

In view of these finding, we have planned to synthesize Schiff's base of 4-(2-aminophenyl) morpholinesfromorthonitrochlorobenzene, morpholine, reducing agents and various primary aromatic aldehyde using conventional method. All the synthesised compound screened for anti bacterial & anti fungal activity by standard protocols. The physico chemical properties and solubility data of the synthesized compounds are given in Table 1, Table 2

Table 1
Physico-chemical parameters of the synthesized compounds

Sl. No	compound	R	Mol. Formula	Mol. Weight	% value	Melting Point °C	Rf value	Log P Value
1	I	C_6H_5-CHO	$C_{17}H_{18}N_2O$	266.29	86	122	0.54	
2	II	C_4H_4O-CHO	$C_{15}H_{16}N_2O_2$	256.36	59	140	0.64	4.44
3	III	NO_2- C_6H_5-CHO	$C_{17}H_{17}N_3O_3$	311.26	87	110	0.61	5.21
4	IV	Cl -C_6H_5CHO	$C_{17}H_{17}N_2O$ Cl	300.08	65	158	0.64	4
5	V	C_6H_5CH=CH-CHO	$C_{19}H_{20}N_2O$	292.08	83	142	0.53	5.94

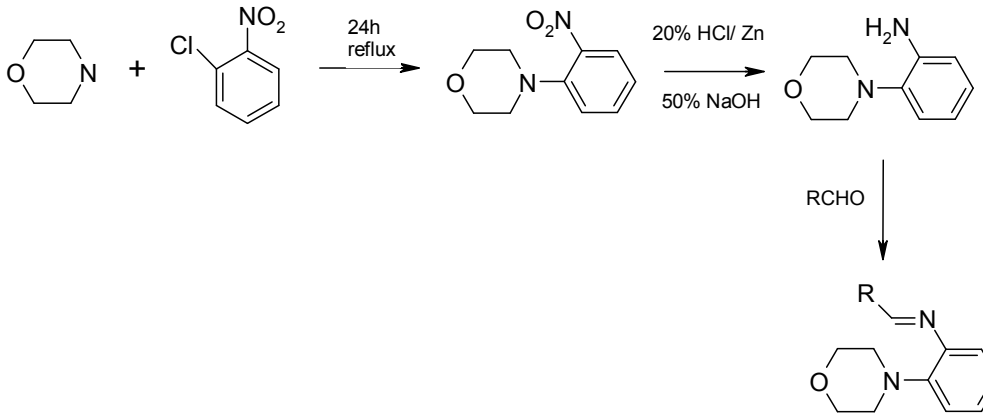
Table 2
Solubility data of the synthesized compound

S.No.	Solvent system								
	H_2O	Acetone	Benzene	$CHCl_3$	C_2H_5OH	MeOH	EA	G.AA	DMF
1.	-	++	++	++	+	++	++	++	++
2.	-	++	++	++	+	++	++	++	++
3.	-	++	++	++	+	++	++	++	++
4.	-	++	++	++	+	++	++	++	++
5.	-	++	++	++	+	++	++	++	++

++ = Freely soluble, + = slightly soluble, - = Insoluble

MATERIALS AND METHOD

Melting points were determined using an open ended capillary tube method and are uncorrected. The purity or compound was confirmed by TLC using silica gel pre coated plates or 0.25 mm thickness with ethyl acetate & hexane (1:4) as eluents and the spot is visualized by UV-Chamber. The structures were characterized by the spectral data. IR spectra were recorded on ABB Bomen MB spectro meter using KBr disc. ^{1}HNMR spectra at 200 MHZ on Brucker DPX spectrometer using DMSO as solvent & TMS as an internal standard.**Scheme**



R=C_6H_5-CHO , C_4H_4O-CHO, NO_2- C_6H_5-CH , Cl -C_6H_5CHO ,C_6H_5CH=CH-CHO

Synthesis of 4-(2- nitro phenyl) morpholines [10]

A mixture of 15.75 gm (0.1 mol) of 2-nitro chloro benzene and 150 ml of (1.70 mol) morpholine was refluxed for 24 hrs. The residue crystallized as orange prisms then cooled, collected on a filter paper and purified by recrystalliastion from absolute methanol, melting point 149-150^{o}c, yield 97%

Synthesis of 4-(2- amino phenyl) morpholines [10]

A solution of 3.0gm (0.0246 mol) of 2-nitro phenyl morpholine in 90ml of 20% hydrochloric acid solution was treated with small portion of zinc dust with stirring and gentle warming until all the yellow colour nitro compound had disappeared. The mixture was filtered to remove the excess zinc and the filterate make strongly basic with 50% aqueous sodium hydroxide. The tan coloured
Product was obtained. It was re-crystallised from methanol, melting point 129- 130^{o}c , yield 88%.

Synthesis of Schiff bases of 4-(2- imino phenyl) morpholines [11]

An equimolar mixture of 1.78gm (0.01 mole) of 2-amino phenyl morpholine and substituted aldehyde (0.01m) in absolute ethanol (100ml) was refluxed using Dean stark apparatus for 2hrs. The reaction mixture was allowed for filteration and recrystallised from methanol.

General synthetic method for the preparation of title compounds:

Synthesis of 4(2-(Benzylidene imino) phenyl) morpholines (I) :

An Equimolar mixture of (0.01mol) of 2-aminophenylmorpholine and benzaldehydes (0.01mol) in absolute ethanol (100ml) was refluxed using Dean stark apparatus for 2hrs. the reaction mixture as cooled for a while and solid separated was filtered and recrystallised using absolute ethanol.Brown crystals ,^{1}H NMR ($CDCl_3$, 200MHz, ppm): δ 3.19 (t, *J* = 4.7 Hz, 4H), 3.88 (t, *J* = 4.7 Hz, 4H), 6.95(d, *J* = 8.8 Hz, 2H), 7.26 (t, *J* = 9.1 Hz, 2H), 7.47-7.49 (t, *J* = 9.1Hz, 2H), 7.47-7.49 (m, 2H), .52 (s,1H) H, 1H). IR (KBr): 2950, 1630, 1503, 1316 cm^{-1}. MS (m/z) : 266(M^{+}+1).

***Synthesis of 4*(2-(2- Furfury imino) phenyl) morpholines (II):**

An Equimolar mixture of (0.01mol) of 2-aminophenylmorpholine and furfuraldehyde (0.01mol) in absolute ethanol (100ml) was refluxed using Deanstark apparatus for 2hrs. the reaction mixture was cooled for a while and solid separated was filtered and recrystallised using absolute ethanol. light yellow crystals ,^{1}H NMR ($CDCl_3$, 200MHz, ppm): δ 3.16 (t, *J* = 4.8 Hz, 4H), 3.88 (t, *J* = 4.7 Hz, 4H), 6.54-655(m,1H),7.26(d,j =8.8 Hz,2H) 7.59 (s, 1H), 8.32 (s,1H) . IR (KBr): 3083, 1675, 1474, 1333 cm^{-1}. MS (m/z) : 311(M^{+}+1).

***Synthesis of 4*(2-(3-nitrobenzylidine imino phenyl) morpholines (III):**

An Equimolar mixture of (0.01mol) of 2-aminophenylmorpholine and m-nitrobenzaldehyde (0.01mol) in absolute ethanol (100ml) was refluxed using Deanstark apparatus for 2hrs. the reaction mixture was cooled for a while and solid separated was filtered and recrystallised using absolute ethanol.Yellow crystals ^{1}H NMR ($CDCl_3$, 200MHz, ppm): δ 3.20 (t, *J* 4.9Hz, 4H), 3.88 (t, *J* = 4.7 Hz, 4H), 694(d,j=8.9 Hz,2H),7.61(t,J =7.9 Hz,1H) 8.21 (m, 2H), 8.72 (s,1H) . IR (KBr): 3083, 1645, 1488, 1300cm^{-1}. MS (m/z) : 256(M^{+}+1).

***Synthesis of 4*(2-(2-chloro Benzylidene imino) phenyl) morpholines (IV):**

An Equimolar mixture of (0.01mol) of 2-aminophenylmorpholine and p-chlorobenzaldehyde (0.01mol) in absolute ethanol (100ml) was refluxed using Deanstark apparatus for 2hrs. the reaction mixture was cooled for a while and solid separated was filtered and recrystallised using absolute ethanol.Yellow crystals ^{1}H NMR ($CDCl_3$, 200MHz, ppm): δ 3.18 (t, *J* = 4.9 Hz, 4H), 3.86(t, *J* = 4.9 Hz, 4H), 6.94 (d J=8.9 Hz,2H),7.26-7.43(m,5H) 8.21 (t,J =6.4 Hz,1H),8.95(s,1H). IR (KBr): 3061, 1647, 1463, 1291 cm^{-1}. MS (m/z) : 300(M^{+}+1).

***Synthesis of* 4(2-(phenyl propylidene imino) phenyl) morpholines (V):**An Equimolar mixture of (0.01mol) of 2-aminophenylmorpholine and cinnamaldehyde (0.01mol) in absolute ethanol (100ml) was refluxed using Deanstark apparatus for 2hrs. the reaction mixture was cooled for a while and solid separated was filtered and recrystallised using absolute ethanol. Brown crystals ^{1}H

NMR ($CDCl_3$, 200MHz, ppm): δ 3.18 (t, *J* = 4.7Hz, 4H), 3.87 (t, *J* = 4.7 Hz, 4H), 6.93(d J=9.2 Hz,2H),7.26-7.43(m,5H) ,8.21 (t,J= 6.4 Hz,2H)7.43(m, 3H), 8.32 (m,1H) . IR (KBr): 3026, 1625, 1490, 1332 cm^{-1}. MS (m/z) : 292 (M^++1).

Biological evaluation[11]

In vitro antibacterial activity [12]

Compounds were evaluated for their *in vitro* antibacterial activity against seven pathogenic bacteria from the Department of Microbiology, Institute of C. L. Baid Metha College of Pharmacy, Chennai . The paper disc diffusion method was performed by using nutrient agar medium (Hi media).[6] Suspension of each microorganism were prepared to contain approximately 10^5 cfu/ml and applied to plates with serially diluted compounds to be tested and incubated at 37 ° C overnight. The minimum inhibitory concentration (MIC) was defined as the lowest concentration that completely inhibited growth on agar plates, disregarding a single colony or a faint haze caused by the inoculum (**Table3**)

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Table 3

Antibacterial activity data of compounds 1-V

Test compound	Zone of inhibition (cm) / concentration of compound (10 µg/ml)						
	S.aureus	*S.epidermis*	*B.aureus*	*B.subtilis*	*P.aureus*	*K.pneumonia*	*E.coli*
1	22	14	21	19	20	19	18
II	18	17	14	17	16	18	19
III	20	20	20	20	21	21	18
IV	19	16	15	16	15	18	20
V	15	13	19	14	17	21	22
Std (10 µg/ml) ciproflaxcin	29	22	29	28	28	27	28

In vitro antifungal activity [12]

Compounds were evaluated for their *in vitro* antifungal activity against *Aspergillus Niger* and *Candida albicans* using the agar dilution method with Saburoud's dextrose agar (Hi-media). Suspension of each microorganism were prepared to contain approximately 10^5 cfu/ml and applied to plates with serially diluted compounds to be tested and incubated at 26º C for 48-72 hrs and the minimum inhibitory concentrations (MIC) were determined (**Table 4**

Table 4

Antifungal activity data of compounds 1-V

Test compound	Zone of inhibition (cm) / concentration of compound (10 µg/ml)	
	A.niger	C. albicans
I	19	23
II	28	21
III	21	22
IV	19	20
V	27	20
Std (10 µg/ml) ketoconazole	27	28

Summary :

Synthesis of Schiff bases of 4 – (2-aminphenyl)morpholines from morpholine, ortho nitro chloro benzene , reducing agents and various primary aromatic aldehyde using conventional method. All the synthesized compounds were tested for *in vitro* antibacterial activity by the agar dilution method. The MICs of the compounds against seven pathogenic bacteria are presented in Table 2 along with the activity of reference compound (ciprofloxacin). It has been observed that all the compounds tested showed mild to moderate activity against tested bacteria. 4 compounds have shown potential antibacterial activity. The antifungal activities of the compounds were studied with two pathogenic fungi. The results are summarized in Table 3. Ketoconazole has been used as the reference for inhibitory activity against fungi. All the compounds showed significant antifungal activity. The screening data indicates that the compounds **I, III** and **IV** have promising more anti-bacterial activity than other compounds and I-V have promising antifungal activity.

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