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Research Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL HETEROCYCLIC MANNICH BASES

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ABSTRACT

Various novel heterocyclic mannich bases were prepared by using Mannich reaction. Acetanilide was treated with substituted benzaldehyde and morpholine / methyl amine to give corresponding titled compounds in good yields. The synthesized compounds were characterized by physical properties and spectral studies (IR, 1H-NMR) and tested for antimicrobial activity against Escherichia coli, Bacillus subtilis by using cup plate method with reference to the standard Streptomycin. All the titled compounds show good antimicrobial activity.

INTRODUCTION

The literature studies enlighten the fact that Mannich bases are very reactive and recognized to possess potent diverse activities[1] like anti-inflammatory, anticancer, antifilarial, anti-bacterial[2], antifungal[3], anticonvulsant[4], anthelmintic, antitubercular, analgesic, anti-HIV[5], antimalarial, antipsychotic, antiviral activities and so forth. In addition, several minor biological activities of Mannich bases, such as their ability to regulate blood pressure or inhibit platelet aggregation, their antiparasitic and anti-ulcer effects, as well as their use as agents for the treatment of mental disorders

Therefore, it seems promising to synthesize some novel heterocyclic mannich bases using compounds like acetanilide, substituted benzaldehyde and morpholine / methyl amine. Novel heterocyclic mannich bases possess numerous activities. As part of ongoing studies in developing new anti–microbials, we are reporting the synthesis of a novel novel heterocyclic mannich bases with interesting anti-microbial activity.

MATERIALS AND METHODS

Materials and reagents were purchased from commercial suppliers (Merck grade) and they were used without purification. Melting points were determined by using electrical melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC using Silica Gel G (Merck). IR spectra were recorded in KBr discs on a Bruker analyzer. ^{1}H-NMR spectra were recorded on a Bruker (400 MHz) spectrometer (chemical shifts in ppm) in DMSO using TMS as internal standard.

Experimental work: Scheme shown in Fig. 1.

General procedure for synthesis of novel heterocyclic mannich bases [6,7]:

A mixture of acetanilide (1.35 g), benzaldehyde (1.06 g) and morpholine (0.87 g) were taken in RBF and refluxed for 1 hour at a temperature of 60-70^{o}C. The progress of the reaction was checked by TLC. After completion of reaction, cool the solution and add cold water. The obtained precipitate was filtered and dried.

Various novel heterocyclic mannich bases synthesized from the above procedure are:

- ✓ 3-Morpholino-N-3-diphenyl propanamide (1a)
- ✓ 3-(4-hydroxy phenyl)-3-morpholino-N-phenyl propanamide (1b)
- ✓ 3-(4-chloro phenyl)-3-morpholino-N-phenyl propanamide (1c)
- ✓ 3-(4-flouro phenyl)-3-(methyl amino)-N-phenyl propanamide (1d)
- ✓ 3-(3,4,5-trimethoxy phenyl)-3-(methyl amino)-N-phenyl propanamide (1e)

Physical characterization of the synthesized Compounds:

Melting points were determined by open ended capillary tube and are uncorrected. Purity of the compounds was checked by the TLC. Physical results shown in Table 1.

IR Spectral Data of synthesized compounds:

3-Morpholino-N-3-diphenyl propanamide (1a)

IR [Cm^{-1}, KBr]: 3275 (NH), 1562 (C = O of amide group), 745 (C_6H_6)

^1H NMR (400 MHz, DMSO-d_6) δ: 7.23 (s,1H,NH), 2.67 (d,2H), 3.59 (d,2H), 7.19-7.61 (m,5H,Ar-H), 7.27-7.40 (m,5H,Ar-H), 4.13 (s,1H).

3-(4-hydroxy phenyl)-3-morpholino-N-phenyl propanamide (1b)

IR [Cm^{-1}, KBr]: 3289 (NH), 1591 (C = O of amide group), 749 (C_6H_6), 3742 (OH)

^1H NMR (400 MHz, DMSO-d_6) δ: 7.23 (s,1H,NH), 2.67 (d,2H), 3.59 (d,2H), 7.19-7.61 (m,5H,Ar-H), 6.70-7.12 (m,4H,Ar-OH), 4.13 (s,1H).

3-(4-chloro phenyl)-3-morpholino-N-phenyl propanamide (1c)

IR [Cm^{-1}, KBr]: 3275 (NH), 1562 (C = O of amide group), 745 (C_6H_6), 1675 (C-N)

3-(4-flouro phenyl)-3-(methyl amino)-N-phenyl propanamide (1d)

IR [Cm^{-1}, KBr]: 3292 (NH), 1661 (C = O of amide group), 751 (C_6H_6), 1206 (C-O-C)

^1H NMR (400 MHz, DMSO-d_6) δ: 7.23 (s,1H,NH), 2.52-2.77 (d,2H), 3.26 (s,3H), 7.19-7.27 (m,4H,Ar-F), 7.19-7.61 (m,5H,Ar-H), 4.13 (s,1H).

IR [Cm^{-1}, KBr]: 3275 (NH), 1562 (C = O of amide group), 745 (C_6H_6)

3-(3,4,5-trimethoxy phenyl)-3-(methyl amino)-N-phenyl propanamide (1e)

IR [Cm^{-1}, KBr]: 3252 (NH), 1652 (C = O of amide group), 742 (C_6H_6), 1301 (C-O-C)

Antimicrobial activity of synthesised compounds[8-10]

In the present work the antimicrobial activity was tested by cup plate method. The antimicrobial activity of novel heterocyclic mannich bases was tested and compared with the standard Streptomycin. The concentration of different test solutions is 100 µg/ml compared with standard solution at a concentration of 100 µg/ml. Acetone, chloroform were used as a solvents.

Test organisms: *Escherichia coli*, *Bacillus subtilis.*

Procedure for Antimicrobial activity:

Agar medium was inoculated at 1% level with 18 hrs old cultures of the above mentioned test organisms and were transferred into sterile petri dishes. The medium in the plates was allowed to set at room temperature for about 10 min and they were set to solidify in a refrigerator for 30 min. After that cylinders were made in the medium. The test solutions which were prepared in acetone and chloroform along with the standard solution of Streptomycin were placed in their respective cylinders. The plates thus prepared were left to stand in a refrigerator for about 1 hr to allow the test solution for diffusion. Then incubation of the above plates was done for 24 hrs at 37^0C. Then zone of inhibition was examined and the inhibition zone diameters were measured.

RESULTS AND DISCUSSION:

The present study aimed to synthesize novel heterocyclic mannich bases using the appropriate synthetic procedure i.e. reaction of acetanilide, substituted benzaldehyde with morpholine / methyl amine.

Novel heterocyclic mannich bases were tested for antimicrobial activity against *Escherichia coli*, *Bacillus subtilis* by using cup plate method with reference to the standard Streptomycin. After 24 hrs of incubation, zone of inhibition was measured (Table 2) and compare the antimicrobial activity of synthesized compounds (1a-1e) with standard (Fig. 2).

CONCLUSION

Novel heterocyclic mannich bases were synthesized by treating acetanilide, substituted benzaldehyde with morpholine / methyl amine to give corresponding titled compounds (1a-1e) in good yields. Synthesized compounds were characterized by physical data (Molecular formula, Molecular weight, Melting point and R_f value) and spectral data (IR spectra & H^1 NMR). Further titled compounds (1a-1e) tested for antimicrobial activity. All the titled compounds show good antimicrobial activity against *Escherichia coli*, *Bacillus subtilis* with respect to standard. Specifically 1a & 1b compounds possess very good antimicrobial activity against *Escherichia coli*, *Bacillus subtilis.*

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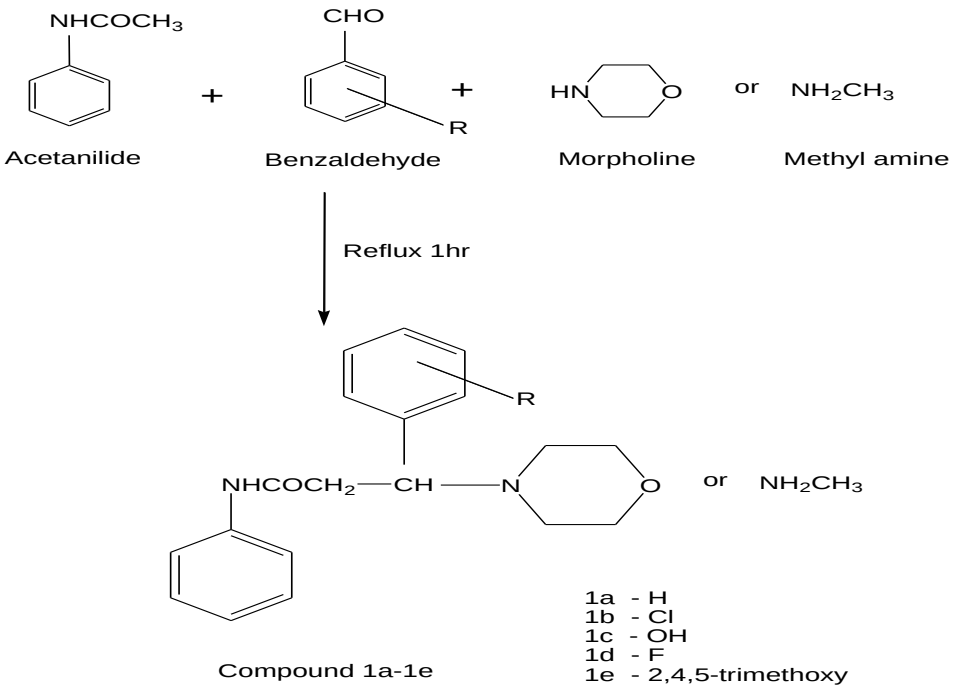

Fig. 1: Schematic representation

Table 1: Physical data of the synthesized compounds

Compound	Molecular formula	Molecular weight (gm)	Melting point (°C)	% yield	R_f value
1a	$C_{18}H_{21}N_2O_2$	326.39	82	40.32	0.53
1b	$C_{19}H_{22}N_2O_3$	344.39	80	33.74	0.63
1c	$C_{19}H_{21}N_2ClO_2$	344	62	97	0.65
1d	$C_{16}H_{17}NFO$	277	101	31.4	0.41
1e	$C_{19}H_{24}N_2O_3$	328	60	47.86	0.51

Table 2: Anti-microbial activity results

S. No.	Name of the organism	Average zone of inhibition (mm)					
		Standard (100 µg/ml)	1a (100 µg/ml)	1b (100 µg/ml)	1c (100 µg/ml)	1d (100 µg/ml)	1e (100 µg/ml)
1	*E. coli*	8.4	11.4	12.2	10.5	6.4	4.4
2	*B. subtilis*	7.3	13.2	13.4	9.6	4.3	5.3

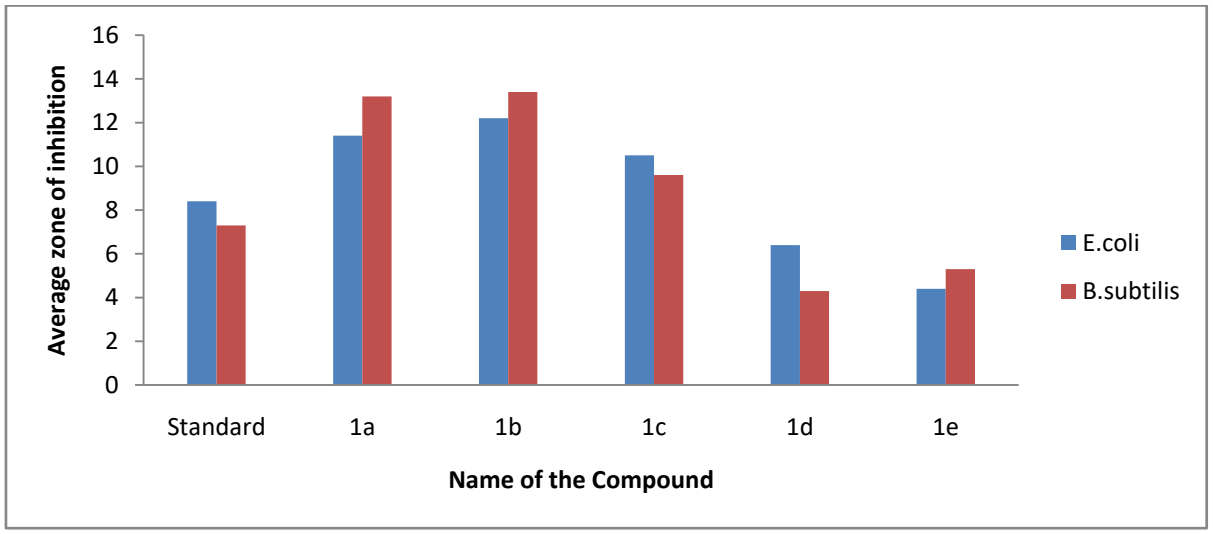

Fig. 2: Comparative antimicrobial activity of synthesized compounds (1a, 1b, 1c, 1d, 1e)