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Research Article

Spectral Characterization and Antimicrobial screening of a few Mannich bases

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Abstract

Some new Mannich bases **(1a-5a)** were synthesized by reacting morpholine with various aldehydes and the compounds containing active hydrogen atoms (acetophenone, thiourea and pheny urea). Structures of the compounds were confirmed by IR, ^{1}H-NMR, ^{13} C-NMR and mass spectra. Antimicrobial Studies were carried out for the synthesized compounds against various bacterial and fungal strains employing Ofloxacin as standard drug for antibacterial and amphotericin B as standard drug for anti fungal screening. The compounds **1a-3a** and **5a** have been possessed high antibacterial activity and the compounds **3a** and **5a** showed higher zone of inhibition against fungal strains. Particularly the compound **3a** exhibit higher zone of inhibition against *A.niger* and the compound **5a** showed higher activity against *A.niger* and *Trichophyton.*

Keywords: Mannich condensation; Antibacterial activity; Antifungal activity

1. Introduction

In recent years serious attention has been directed towards the discovery and development of new antimicrobial drugs. The main problem in the treatment of fungal infection is the increasing drug resistance subjected to antimycotic therapy such as persons infected with HIV [1]. Nosocomial infections during the past decade have invaded hospitals worldwide by multi drug resistant Gram-positive and Gram-negative pathogens. Searching for novel antimicrobial agents and new microbial targets is in demand to intervene to avert the danger caused by these life-threatening infections. Since the resistance towards the available antibiotics among pathogenic bacteria has grown rapidly, there is a clear need for the development of new and effective antimicrobial agents. Therefore, the success in designing antimicrobial agents which are distinct from those of the classical antibiotics is the key for treating such infectious diseases known for their chronicity and failure to treat with conventional antibiotics which will eventually lead to death [2,3].

Mannich bases have gained importance due to their applications in pharmaceutical industry and other applications including as agro chemicals and plant growth regulators. The presence of heterocyclic moieties in organic compounds is of interest in biology, pharmacology, optics, material science and so on [4-7]. The chemistry of the amino alkylation of aromatic substrates by the Mannich reaction is of great interest for the synthesis and modification of biologically active compound having physical and chemical importance as well as physiological properties because the amino group can be easily converted into a variety of other functionalities[8]. Mannich reaction offers a judicious method for introduction of basic aminoalkyl chain in various drugs/compounds. Further a considerable amount of work has been reported on synthesis and pharmacological activities as well as intermediates in drug synthesis [9]. Morpholine derivatives were reported to possess antimicrobial, anti-inflammatory and central nervous system activities [10-12].

Some of the Mannich bases containing heterocyclic ring and their names are given below. Therefore, bearing in mind the above observation, we were led to synthesize new series of Mannich base derivatives.

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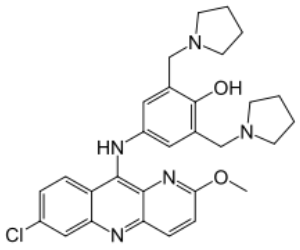
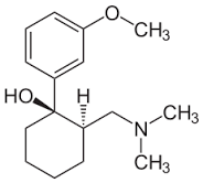


Pyronaridine



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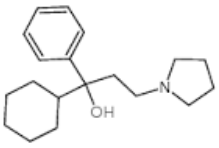
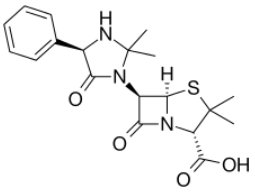
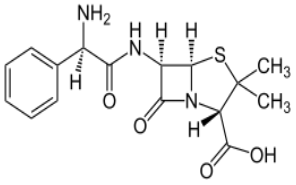


Osnervan



Hetacillin



Ampicillin

2. Materials and methods

All the reagents and solvents for synthesis were purchased from Alfa Aesar and sigma Aldrich Chemicals. Silica gel-GF coated glass plates were used for monitoring the reactions by iodine vapors as visualizing agents and methanol and acetone solvent system were used as TLC mobile phase. Melting points of compounds were determined using digital melting point apparatus and were uncorrected. The IR spectra were obtained on SHIMADZU FTIR spectrophotometer (KBr pellets, λ-max in cm-1) and ^{1}H-NMR spectra of compounds were recorded on Brucker Model-300 using DMSO-*d*6 as solvent. Mass spectra of the synthesized compounds were recorded on Jeol SX- 102/DA-6000 spectrometer.

2.1. General procedure for the synthesis of the compounds (1a-5a)

To a ethanolic solution of thiourea (0.76 g, 0.01 M),3 pellets of sodium hydroxide and morpholine (0.8 mL, 0.01M) were added followed by anisaldehyde (1.2 mL, 0.01M). The reaction mixture was taken in a RB flask and kept over a magnetic stirrer. The mixture was stirred under ice cold condition for 8 h. The precipitate formed was filtered, washed with water, dried and recrystallized from ethanol.

The reaction scheme is shown in figure 1.

2.2. Scheme

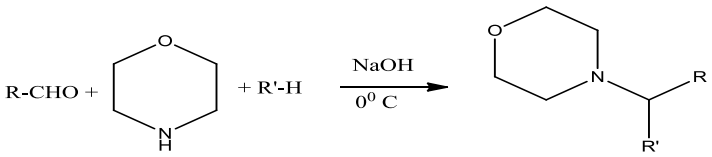
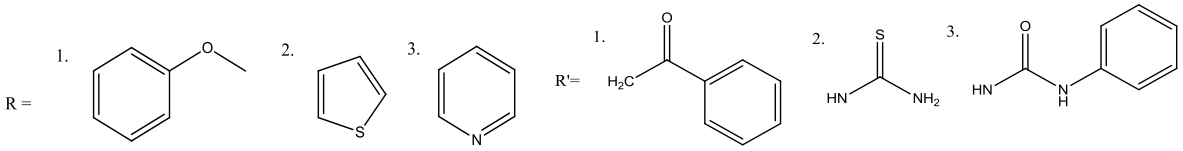


Figure 1 - Scheme of the reaction



3. Results and Discussion

1-((4-methoxyphenyl)(morpholino)methyl)thiourea (1a).

IR (cm^{-1}) KBr disc:3343.24 –NH str ; 2960 –CH str; 1605 –NH bend **^{1}H-NMR(ppm):** 9.8 1H of NH; 7.8 2H of –NH_2; 7.3-6.9 4H of Aromatic-H; 5.6 1H of –CH; 3.8-3.4 8H of morpholine **^{13}C-NMR(ppm):** 191 1C of C=S;164-113 6C of aromatic-C;66 1C of –CH;61-55 4C of morpholine **m/e:** 281.

1-(morpholino(thiophen-2-yl)methyl)-3-phenylurea (2a).

IR (cm^{-1}) KBr disc:3295 –NH str; 2960 –CH str;1637.90 C=O str; 1560 –NH bend **^{1}H-NMR(ppm):**8.5 1H of NH;7.5-7.0 8H of of Aromatic-H;6.9 1H of NH;5.8 1H of CH;3.3-3.2 8H of Morpholine**^{13}C-NMR(ppm):** 154 C=O, 144, 139, 128, 126, 124, 121, 117 aromatic-C, 68, 66(Morpholine), 47(CH) **m/e:** 317.

3-morpholino-1-phenyl-3-(thiophen-2-yl) propan-1-one (3a).

IR (cm^{-1}) KBr disc: 3459 –NH str; 3064 –CH str;1653 C=O str; 1591 –NH bend **^{1}H-NMR (ppm):** 8.0-6.9 8H of Aromatic H; 4.8 1H of CH; 2.9 2H of CH_2; 3.5-2.5 8H of Morpholine **^{13}C-NMR(ppm):** 205 C=O, 145, 143, 139, 131, 128, 127, 126, 125, 124, 123 aromatic-C, 74(CH2), 51(CH), 38, 36(Morpholine)**m/e:** 301.

1-(morpholino(pyridin-2-yl)methyl)-3-phenylurea (4a).

IR (cm^{-1}) KBr disc: 3425 –NH str; 3035 –CH str; 1655 CH str; 1594 –NH bend **^{1}H-NMR (ppm):** 9.2 1H of NH; 8.5 1H of Aromatic H; 6.4 1H of NH; 5.8 1H of CH; 3.3-2.5 8H of morpholine **^{13}C-NMR (ppm):** 157 1C of CO; 154-117 11C of aromatic C; 80 1C of CH; 62-59 4C of morpholine **m/e:** 312.

3-morpholino-1-phenyl-3-(pyridin-2-yl) propan-1-one (5a).

IR (cm^{-1}) KBr disc: 3412 –NH str; 2938 –CH str; 1678 C=O str; 1587 –NH bend **^{1}H-NMR (ppm):** 8.4 1H of Aromatic H; 7.9-7.4 8H of aromatic H; 7.2 1H of CH; 4.4-3.91 2H of CH_2; 3.5-2.3 8H of morpholine **m/e:** 297.

The compound **1a** was synthesized using anisaldehyde, Morpholine and acetophenone. Compounds **2a** and **3a** were prepared by reacting thiophene-2-carboldehyde, morpholine and active hydrogen compounds such as phenyl urea/acetophenone. Compound **4a** and **5a** were synthesized by adding Morpholine, pyridine-2-carboldehyde and active hydrogen compounds such as phenyl urea/acetophenone.

The molecular formula, colour, yield and melting point of the compounds are given in the Table 1. Melting points of the synthesized compounds were sharp indicating that the compounds are pure. The yield of the compounds is also suggested that the chemical methods were reliable for the synthesis of the compound. All spectral data were found to be match with the proposed structures.

Table.1: Analytical data of the synthesized compounds

S. No.	Molecular Formula	Molecular Weight	Melting Point (^{0}C)	Colour	Yield %
1a	$C_{13}H_{19}N_3O_2S$	281	135	Yellow solid	90
2a	$C_{16}H_{19}NO_2S$	317	144	White solid	95
3a	$C_{17}H_{19}NO_2S$	301	175	White Solid	90
4a	$C_{17}H_{20}N_4O_2$	312	134	Brown Solid	92
5a	$C_{18}H_{20}N_2O_2$	296	90	Brown Solid	98

3.2 Antimicrobial activity

The synthesized compounds were subjected for antimicrobial activity and the results were shown in the table 2. Three bacterial strains, two gram positive and one gram negative namely *B.subtilis*, *Enterobacter* and *Moraxella* were taken for antibacterial screening and two fungal pathogens, *A. neiger* and *Trichophyton* were tested for antifungal studies against the synthesized compounds using Ofloxacin and amphotericin B as standard drug. All the compounds, except **4a** are highly active against *B.subtilis*. The compound **5a** exhibits good activity against *Enterobacter* whereas the rest of the compounds show only lesser activity. The increased bacterial activity against *Moraxella* was exhibited by the compounds **5a** and **1a**. The activity of other compounds against *Moraxella* is found to be very less. All the compounds are active against the fungi, A.niger. The compounds **3a** and **5a** possessed higher activity and others showed lesser activity. The compound **5a** exhibit higher zone of inhibition against *Trichophyton* whereas the other compounds showed lower activity and the compound **4a** showed no activity. The structural features of the compounds like presence of phenyl ring, the heterocyclic compounds containing nitrogen and electron donating group like -OCH_3 group were the cause for increased biological activity. While other compounds which possess electron withdrawing substituent responsible for lesser activity. The enhanced antibacterial activity of the compound **1a** is due to the presence of thiocarbonyl sulfur (C=S) [13]. In case of antifungal activity, there are several reports are available that the derivatives with a N-containing hetero cycles [14] and the compounds which contains acetophenone shows significant activity [15-17].

Table.2: Antimicrobial activities of the synthesized compounds

Ligand	*B. subtilis*			*Enterobacter*			*Moraxella*			*A.niger*			*Trichophyton*		
	50 µl	**100** µl	**Control**	**50** µl	**100** µl	**Control**	**50** µl	**100** µl	**Control**	**50** µl	**100** µl	**Control**	**50** µl	**100** µl	**Control**
1a	21	**26**	30	--	10	32	14	16	30	10	12	30	10	**15**	18
2a	12	**18**	32	12	13	32	09	11	30	13	15	28	10	13	20
3a	15	**20**	32	10	11	32	--	09	30	15	**20**	28	10	12	20
4a	09	11	30	09	10	32	--	10	30	10	12	30	--	--	20
5a	**20**	**21**	30	15	**17**	32	**24**	**24**	30	**22**	**25**	30	**16**	**21**	20

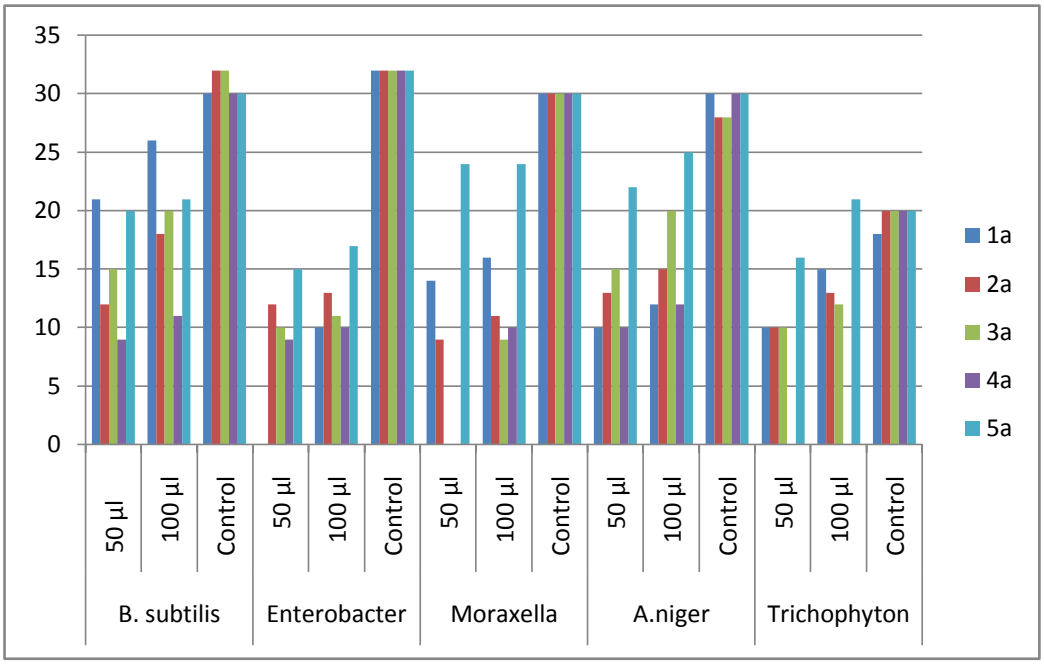


Figure 2: Antimicrobial screening of the synthesized compounds

4. Conclusion

Five new Mannich bases were synthesized incorporating different aldehydes with various active hydrogen compounds and morpholine. Synthesized compounds were characterized by FTIR, ^{1}H & ^{13}C-NMR and mass spectral studies. These derivatives were evaluated for their antimicrobial activity against three bacterial strains including two gram positive and one gram negative bacteria and two fungal strains. Almost all the compounds possessed good activity against bacteria and fungi strains. Compound **1a** showed higher zone of inhibition against B. subtilis due to the presence of C=S group. The compound **5a** showed higher antifungal activity compared to the standard drug. Pyridine ring is responsible for the stronger antifungal activity.

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