Synthesis and Biological Activity of Important Phenolic Mannich Bases

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(Received: 16 August 2011;

Accepted: 9 July 2012)

AJC-11820

A series of Mannich bases were synthesized by the condensation reaction of phenols and amines in the presence of formaldehyde. The newly synthesized Mannich bases were well characterized by FT-IR spectroscopy. All the synthesized compounds were tested for their antibacterial activity against *Pasturella multocida* and *Staphylococcus aureus*. The results have shown that most of the compounds are quite active against these pathogenic bacteria.

Key Words: Mannich bases, *Pasturella multocida*, *Staphylococcus aureus*.

INTRODUCTION

The Mannich base is an end product in the Mannich reaction, which mainly consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with aldehyde and amine. The final product is a β -amino-carbonyl compound also known as Mannich base¹.

The Mannich-reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics and alkaloids (e.g. tropinone). Other applications are in agro chemicals such as plant growth regulators². Various drugs obtained from Mannich reaction have proved to be more effective and less toxic than their parent compounds³. They have also been encountered with antibacterial, antimalarial anticancer, analgesic, antiinflammatory, anticonvulsant, antiviral and CNS depressant activities⁴⁻⁷.

Due to the vast applications of Mannich bases in pharmaceutical products and other fields of life, this reaserch work was conducted to synthesize some important phenolic Mannich bases and evaluated its antibacterial activities.

EXPERIMENTAL

The experimental protocol consists three steps: (i) Synthesis of Mannich bases with different reactants. (ii) Characterization of Mannich bases, (iii) Application of Mannich bases for antibacterial screening.

Synthesis of Mannich bases with different reactants:

Mannich bases were prepared according to the method given by Ibrahim and Sharif⁸ with some modifications. It includes the condensation reaction of aromatic amines (both substituted and unsubstituted) with phenols (both substituted and unsubstituted) and formaldehyde in the presence of acetic acid as catalyst using ethanol as solvent.

Procedure: One gram of each phenols were dissolved in ethanol (20 mL) separately. After it, 4-5 mL formaldehyde was added to the amine solution. Both the solutions were mixed and 3-4 mL acetic acid was added. The reaction mixture was stirred for 1 h. The stirring time could be varied depeneded upon reactants. Crude product obtained after filtration was recrystallized from DMSO and then characterized.

Antibacterial screening: In the third step, the antimicrobial e.g., antibacterial screening was performed using disc diffusion method against pathogenic strains *Staphylococcus aureus* and *Pasturella multocida* in comparison with standard commercial antimicrobial agents.

RESULTS AND DISCUSSION

The results revealed that both the partners having naphthyl moiety expressed exellent activity in Mannich reaction as among the phenols 2-naphthol and 1-naphthol and among the amines 1-naphthylamine was given all condensation products with all amines in high yields in the range 31.61-85.44 % and 59.34-76.07 %. Observations also indicated that electron withdrawing and electron donating groups attached to phenolic component did not expressed successful activity but presence of electron withdrawing groups on the amines i.e., *p*-nitroaniline

Same reaction was carried out for other Mannich bases but with different phenols,
A2: *o*-Cresol, A3: 2-Naphthol, A4: 1-Naphthol and A5: *p*-Nitrophenol

Scheme-I: Condensation reaction of phenols and *p*-toluidine

Same reaction was carried out for other Mannich bases but with different phenols,
B2: *o*-Cresol, B3: 2-Naphthol, B4: 1-Naphthol and B5: *p*-Nitrophenol

Scheme-II: Condensation reactions of phenols with 1-naphthylamine

Same reaction was carried out for other Mannich bases but with different phenols,
C2: *o*-Cresol, C3: 2-Naphthol, C4: 1-Naphthol and C5: *p*-Nitrophenol

Scheme-III: Condensation reaction of phenols with *p*-nitroaniline

Same reaction was carried out for other Mannich bases but with different phenols,
D2: *o*-Cresol, D3: 2-Naphthol, D4: 1-Naphthol and D5: *p*-Nitrophenol

Scheme-IV: Condensation reaction of phenols with aniline

Same reaction was carried out for other Mannich bases but with different phenols,
E2: *o*-Cresol, E3: 2-Naphthol, E4: 1-Naphthol and E5: *p*-Nitrophenol

Scheme-V: Condensation reaction of phenols and *p*-bromoaniline

Same reaction was carried out for other Mannich bases but with different phenols,
F2: *o*-Cresol, F3: 2-Naphthol, F4: 1-Naphthol and F5: *p*-Nitrophenol

Scheme-VI: Condensation reaction of phenols and 1-Naphthylamine-4-SO₃H

proved more active for Mannich reaction when compared¹¹ to *p*-toluidine and *p*-bromoaniline. From 30 experiments, sixteen products were obtained while thirteen were obtained in good yields. The reactions did not occur (A4, A5, C1, E1, E2, E5, D1-D4, F1, F2 and F5) which might be due to the reason that both of the reactants were not miscible in same solvent ethanol or may be reason behind is that the reaction conditions *i.e.* shaking time, temperature provided were not suitable for these reactions.

The IR spectra of Mannich bases were found to be fully consistent with the predicted structures. The IR spectrum of Mannich base A2 showed a sharp absorption peak at 3516 cm⁻¹ indicating the presence of -OH group in *ortho* substituted phenols or may be due to the -NH str vibrations of secondary aromatic amines. The sharp absorption band appears at 1616 cm⁻¹ due to bending vibrations of -NH functional group and absorption bands in the region of 1360-1250 cm⁻¹ arising due to the -C-N str vibrations confirmed the presence of -C-NH-C group in Mannich base A2.

Mannich base B1 showed absorption bands at *ca.* 1581 and 1398 cm⁻¹, which could be attributed to the -NH (due to bending vibrations) and -C-N- (due to stretching vibrations) functional groups, respectively. The sharp broad band *ca.* 3400-

3200 cm⁻¹ region arises due to intermolecular hydrogen bonding of -OH functional group in phenols.

In the IR spectrum of Mannich base C3, a strong absorption band at 1596 cm⁻¹ could be attributed to -NH functional group characteristic feature of Mannich base structure, while the absorption bands at 1316 and 1326 cm⁻¹ arising due to the -C-N- stretching vibrations. The absorption bands appear at 1326 and 1516 cm⁻¹ (due to stretching vibrations) and absorption bands at around 808 cm⁻¹ (due to -C-N- str. vibrations in nitro benzenes) confirmed the presence of -NO₂ group in Mannich base C3. The absorption bands near 1200 cm⁻¹ corresponded to the -C-O- functional group of phenolic compounds.

Biological activity: Antibacterial screening data expressed that all the tested compounds showed moderate to good inhibition. Mannich base F3 derived from 1-naphthylamine-4-SO₃H showed maximum inhibition zones 33 mm against *Pasturella multocida* and 38 mm against *Staphylococcus aureus* exact near to reference compound (39 mm), respectively (Fig. 1). Mannich bases B1, B5 and C3 showed good inhibition zones in the range 21-26.5 mm and Mannich bases B2, B3, C4, E4 showed moderate inhibition zones (Fig. 1). All compounds of B1-B5 (having 1-naphthylamine moiety) and F3 (derived from

Fig. 1. Antibacterial activity of different Mannich bases

1-naphthylamine-4-SO₃H) have showed maximum antibacterial activity than all other compounds which indicated that Mannich bases derived from 1-naphthylamine and its derivatives are the best compounds for the point of biological

activity. So these results revealed that newly synthesized Mannich bases have effective antibacterial potential and these can be proved important drug intermediates for the synthesis of antibacterial drugs.

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