International Journal of All Research Education and Scientific Methods (IJARESM),
ISSN: 2455-6211, Volume 12, Issue 4, April-2024, Available online at: www.ijaresm.com

Synthesis, Spectroscopic Studies and Antibacterial Screening of Medicinally Important Mannich Bases Derived From (2s)-2- Amino-3-(3, 4-Dihydroxyphenyl) Propanoic Acid

Sourabh Muktibodh[1], Nishi Sharma[2]

[1,2]Mata Jijabai Government Girls PG College, Indore-452007, Madhya Pradesh, India

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ABSTRACT

In the present study, A new targeted series of Mannich base of (2S)-2-AMINO-3-(3, 4-DIHYDROXYPHENYL) PROPANOIC ACID have been synthesized for the first time with the help of sulphonamides and secondary amines via Mannich reaction. The aminomethylatio reaction of Levodopa carried out and then structure of newly synthesized compounds were established by on the basis of elemental analysis and spectral studies. The newly synthesized Mannich bases of Levodopa were evaluated against various gram positive and gram negative bacteria. The result has shown that some of newly synthesized compounds show prolongs activity their pathogens.

Keywords- (2S)-2-AMINO-3-(3, 4-DIHYDROXYPHENYL) PROPANOIC ACID, Sulphonamides, secondary amines, Mannich reaction, Mannich base,

INTRODUCTION

Since the first antibiotic, penicillin, was introduced into medicine in 1942, researchers have been engaged in a perpetual "race" to develop new medications that target harmful germs. Every day, thousands of potentially harmful compounds are created in labs all around the world as a result of this particular "arms race." For the synthesis and modification of physiologically active compounds, the chemistry of the amino alkylation of aromatic substrates by the Mannich reaction is quite interesting[1-5]. The Mannich reaction provides a prudent way to include a basic amino alkyl chain into a variety of medications and chemicals. A review of the literature in this area has turned up several findings on the antibacterial action of N-Mannich bases.

The final products of the Mannich reaction are compounds that contain beta-amino ketones, or Mannich bases. The Mannich reaction, a nucleophilic addition reaction, is the condensation of an amine (primary or secondary), formaldehyde (any aldehyde), and a molecule containing active hydrogen.

Mannich bases are also significant pharmacophores or bioactive leads that are employed in the synthesis of a variety of high-value pharmaceutical compounds with amino alkyl chains. The following are some examples of clinically relevant amino alkyl chain Mannich bases: cocaine, fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, procyclidine, ranitidine, biperiden, and so on. It is well known that mannich bases were essential to the advancement of synthetic medicinal chemistry[6-10].

Studies in the literature have shown that Mannich bases are highly reactive and readily changed into other substances, such as amino alcohols that are physiologically active when reduced. Strong properties such as anti-inflammatory, anticancer, antifilarial, antibacterial, antifungal, anticonvulsant, anthelmintic, antitubercular, analgesic, anti-HIV, antimalarial, antipsychotic, antiviral activities, and so on are known to be possessed by Mannich bases. Mannich bases are recognised for their use in surface active agents, resins, polymers, detergent additives, and other applications in addition to their biological activities.

To get around the restrictions, prodrugs of Mannich bases of different active compounds have been created[11-16]. Mannich bases (optically pure chiral) of 2-naphthol are used in metal-mediated and ligand-accelerated enantioselective carbon-carbon bond formation catalysis. The production of bioactive compounds uses Mannich bases and their derivatives as intermediates. The Mannich reaction is often employed in the synthesis of molecules containing nitrogen. Because of its use in antibacterial activities and other agrochemicals like plant growth regulators, mannich bases have become more significant[17-21].

The treatment result of Parkinson's disease has been revolutionised by the introduction of levodopa therapy about fifty years ago. Levodopa is still the gold standard today, despite the addition of a number of new medications to the treatment arsenal. When Cotzias et al. demonstrated in 1967 that oral levodopa had a significant and long-lasting impact on the symptoms of severely impaired Parkinsonian patients, the levodopa era officially began. The Swedish pharmacologist Arvid Carlsson, who shared the 2000 Nobel Prize in physiology and medicine, discovered dopamine, a neurotransmitter that could influence movement. This discovery served as the foundation for the fundamental research that resulted in the development of this miracle medication. The advent of carbidopa marked yet another significant turning point in the evolution of levodopa treatment[22-24]. We studied that the several Mannich bases that produced are less poisonous and more powerful than their parent sulphonamide. Given the distinct nature of (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid, sulphonamide was used as a component and the substrate was condensed using the Mannich process. This study presents the aminoalkylation of (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid. Furthermore described are the elemental analysis, spectral investigation, and antibacterial screening of the newly synthesised molecule.

Experimental:
All freshly synthesised compounds' melting points were measured in open capillary tubes and are uncorrected. A 90:10 combination of chloroform and methanol was utilised as the mobile phase in a thin layer chromatography procedure to verify the purity of freshly synthesised Mannich bases. The stationary phase was silica gel-G. A single clear spot was used in this procedure to determine the new compound's purity. UV-Vis with the assistance of Schimadzu UV-160 A. UV spectra were recorded within the spectrophotometer's range. Using potassium bromide pellets, the range of infrared spectra was acquired using a Schimadzu 820 IPC FTIR spectrophotometer. 1HNMR spectra were used to record chemical shifts as PPM versus TMS (Tetra methyl silane). The Cup plate technique was used to do the antibacterial screening. All of the chemicals and reagents utilised in this practical study were obtained from E. Merck and Aldrich, and substitutes for sulphonamides were gathered from reputable pharmaceutical establishments for this research work.

Synthesis:
General method for the synthesis of Mannich base of (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid is explain in following schemes and result of characterization are given below:
Synthesis of Mannich Bases of (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid from primary amine:
(2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid mannich bases were made by mixing the chemical in 20 millilitres of ethanol, 0.01 millilitres of sulphonamide, and 2.5 millilitres of formaldehyde solution while stirring continuously. To bring the pH of the reaction mixture down to 3.5, 0.5 ml of 1 mol L-1 hydrochloric acid was added gradually. The reaction mixture was placed on a water bath to facilitate reflux after being held for 30 minutes to ensure effective ice chilling. Reflux duration is dependent on sulphonamide. Following the reflux procedure, the reaction mixture was carefully stored at 0°C for four days. The final product was obtained in crystalline form, and it was subsequently recrystallized in a 1:1 ratio with the use of dry distilled ethanol and DMF.

Synthesis of Mannich Bases of (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid from secondary amine:
50 millilitres of the compound's ethanolic solution included 0.01 mol of secondary amine, which was added to create the Mannich bases of (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid. A 0.4 ml solution of formaldehyde was gradually added to two installments while being constantly stirred. For three to eight and a half hours, the reaction mixture was agitated using a magnetic stirrer. Dependent on the secondary amine is reaction time. The reaction mixture was carefully stored in the refrigerator for the whole night after the whole reaction completed. Excess solvent was distilled out of the reaction mixture under low pressure, and the mixture was then refrigerated to allow crystallisation. At last, a crystalline product was produced, and it was recrystallized using a 1:1 mixture of dry distilled ethanol and DMF.

RESULTS AND DISCUSSION

1.1 Physical, chemical and spectral characterization of synthesized Mannich Bases:
Compound 1a: (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid methyl sulphamethoxazole:
$C_{20}H_{22}N_4O_7S$, Yield – 68%, m.p.-210°C Anal. Calcd. C- 51.96, H-4.75, N- 12.11 Found C- 46.56, H-4.81, and N-10.57, UV (λ max) nm-207 (C=O), 193 (C=N), 229 (S=O), 282 (sulphonamide moiety).
IR (KBr) νmax in cm^{-1}: 3359 ν_s N-H, 3347 ν_{as} N-H in SO_2NH, 2958 C-H Aliphatic, 2943 ν_{as} C-H in CH_2,1673 ν_s C=O, 1345 ν_s S=O, 683 C-H in plane bending vibration of 1:4 disubstituted benzene. ^{1}H NMR 4.32 (S, 2H, CH_2), 4.0 (S, 1H, NH), 6.86 (m, ArH), 2.36 (S, 3H CH_3).

Compound 1b: (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid methyl silver sulfadiazine:
$C_{20}H_{20}N_5O_6SAg$, Yield – 90%, m.p.-120°C Anal. Calcd. C- 42.42, H- 3.53, N- 12.36 Found C- 45.90, H-4.81, and N-10.54, UV (λ max) nm-208 (C=O), 192 (C=N), 227 (S=O), 282 (sulphonamide moiety).

IR (KBr) νmax in cm^{-1}: 3370 ν_s N-H, 3336 ν_{as} N-H in SO_2NH, 2959 C-H Aliphatic, 2948 ν_{as} C-H in CH_2,1677 ν_s C=O, 1145 ν_s S=O, 670 C-H in plane bending vibration of 1:4 disubstituted benzene. ^{1}H NMR 4.32 (S, 2H, CH_2), 4.0 (S, 1H, NH), 6.86 (m, ArH).

Compound 1g: (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid methyl morpholine:
$C_{14}H_{20}N_2O_5$, Yield – 69%, m.p.-108°C Anal. Calcd. C- 63.17, H-7.51, N- 10.52 Found C- 50.63, H-8.31, and N-13.49, UV (λ max) nm-207 (C=O), 192 (C=N).
IR (KBr) νmax in cm^{-1}: 3421 ν_{as} N-H, 2926 C-H Aliphatic, 2857 ν_{as} C-H in CH_2,1626 ν_s C=O, 871 C-H in plane bending vibration of 1:4 disubstituted benzene. ^{1}H NMR 3.62 (M, 2H, CH_2), 2.0 (S, 1H, NH), 6.73 (m, ArH),

Compound 1i: (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid methyl diethylamine:
$C_{17}H_{22}N_2O_4$, Yield – 81%, m.p.-160°C Anal. Calcd. C- 64.17, H- 6.91, N- 8.80 Found C- 64.02, H-6.54, and N-8.49, UV (λ max) nm-208 (C=O), 192 (C=N).
IR (KBr) νmax in cm^{-1}: 3410 ν_s N-H, 3336 ν_{as} N-H in SO_2NH, 2982 C-H Aliphatic, 2925 ν_{as} C-H in CH_2,1616 ν_s C=O, 1383 ν_s S=O, 690 C-H in plane bending vibration of 1:4 disubstituted benzene. ^{1}H NMR 3.62 (S, 2H, CH_2), 2.0 (S, 1H, NH), 6.68 (m, ArH).

Antibacterial Screening Results of Mannich Bases:
Novel Mannich bases were subjected to antibacterial screening against E. coli and S. typhi in order to assess their biological importance. Utilising the cup plate technique, at various concentrations such as 80, 160, and 320 mg/ml. All of the identified drugs have exceptional effectiveness against these diseases. They also compared their activity with that of the parent sulphonamide. The antibacterial screening findings are all listed below.

Compound No.	***E.coli***				***S.typhi***			
	Concentration in µg/ml				Concentration in µg/ml			
	80.0	160.0	320.0	Avg	80.0	160.0	320.0	Avg
1a	8.9	11.4	10.8	13.03	-	6.7	7.2	5.8
1b	7.4	6.5	-	7.6	3.4	6.2	7.3	5.6
1g	13.7	15.2	17.4	16.3	-	-	7.6	7.9
1i	8.6	-	9.6	3.6	6.2	7.2	8.2	7.5

Table showed that in against *E. coli*, 1a and 1g mannich bases were found more potent than their other mannich bases and in against *S.typhi*, compound 1i was found more potency than their other compound.

CONCLUSION

We draw the conclusion that freshly synthesised Mannich bases of (2s)-2-amino-3-(3, 4-dihydroxyphenyl) propanoic acid exhibit pronounced and sustained action against antibacterial screening based on the data and discussion. Compared to their parent sulphonamide, several Mannich bases exhibit greater potency. This study explains how Mannich bases may be a useful medication to stop the growth of germs.

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