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Synthesis and Evaluation of Mannich Bases of 2-(Benzimidazolylaminomethyl)thiazolidin-4-one as Antimicrobial Agents

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Mannich bases of 2-(benzimidazolylaminomethyl) thiazolidin-4-one are synthesized by amination at position 5 using formaldehyde and various secondary amines. The prepared compounds have been characterized by physico-chemical and spectral analysis and screened for their antibacterial activity.

Key Words: Benzimidazole, Mannich base, Condensation reaction.

INTRODUCTION

Compounds having benzimidazole nucleus are of great interest for a long time due to their unique chemical and biological properties mainly related to traditional anthelminitics. Albendazole, oxibendazole and benzimidazole derivatives have also been found to possess biological activities such as antiviral, antibacterial and anticancer[1]. Continual increase in bacterial resistance to existing drugs has been resulted due to wide spread use of antibacterial agents leading to research on new substances possessing antimicrobial activity[2]. Several benzimidazoles are commercially available as pharmaceuticals, veterinary products and fungicides. Standard methods of synthesis of these ring systems involve cyclization reactions for which 1,2-disubstituted benzenes of the appropriate type are the most common starting materials[3]. Benzene-1,2-diamine reacts with a wide range of carboxylic acid derivatives to give 2-substituted benzimidazoles[4]. This synthesis can usually be adapted to incorporate additional substituents in the benzenoid ring system, if required. Benzimidazole derivatives like enviroximf have shown high degree of antiviral activity against picorna viruses[2,5]. Other benzimidazole compounds like LY 122771-72 and LY 127123 have shown significant antiviral activity against picorna viruses. Benzimidazoles have been reported to show antibacterial activities beside other activities[6]. Various benzimidazole derivatives have also been found to be useful pharmacophores in building anti-convulsing agents. In some cases Mannich bases of bezimidazole are even found to have enhanced activity than starting compound[7]. 2-Aminoaryl thiazolidin-4-one derivatives have

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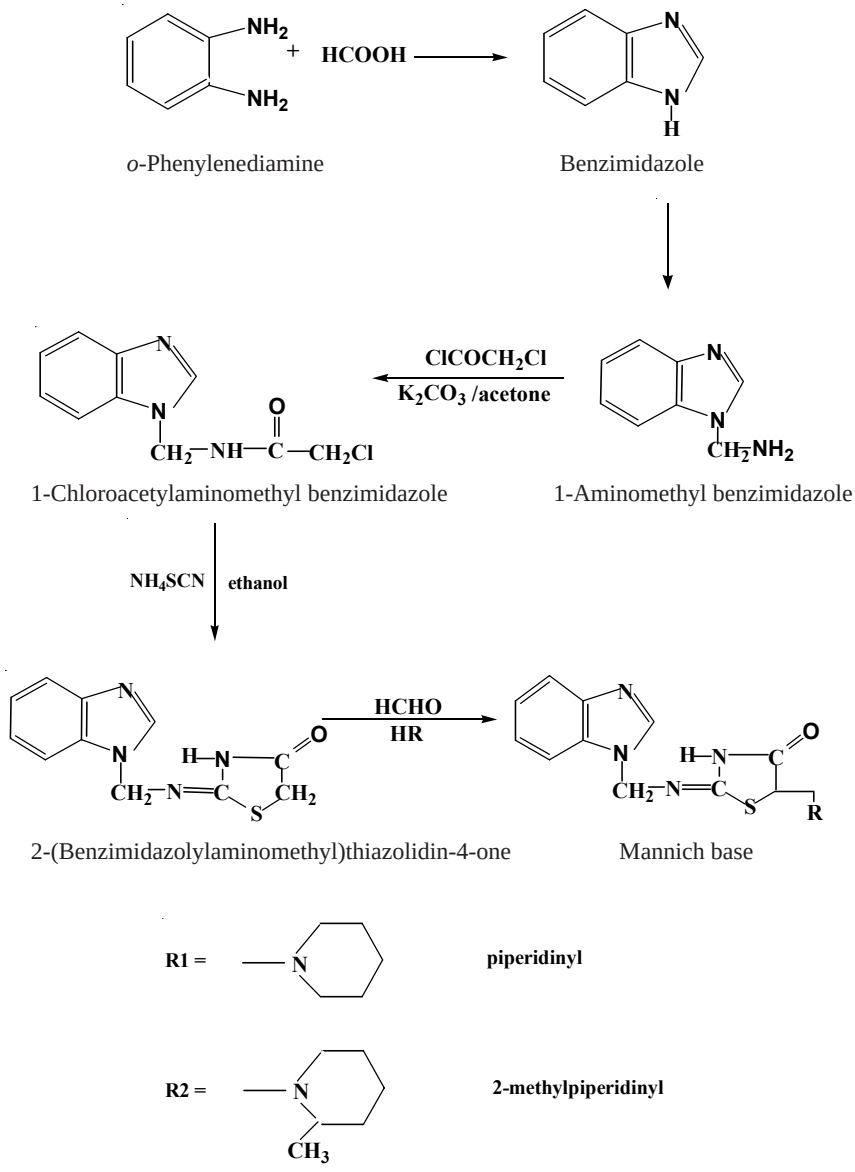
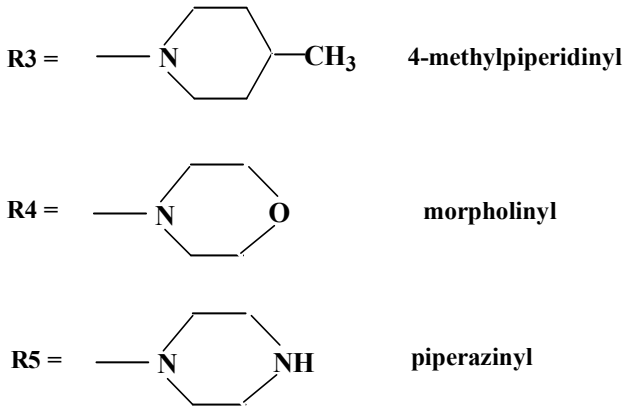
been reported to show various pharmacological activities such as antibacterial, antifungal[8], anticonvulsant[9], anticancer[10], antihistaminic[11], CHK inhibitor[12], anthelminitic[13], CNS depressant[14]. A molecule with thiazolidinone ring, a benzimidazole ring and substituted aminomethyl group may show antibacterial activity of higher degree[15]. It was, therefore, decided to synthesize and evaluate novel Mannich bases of benzimidazolylaminomethyl thiazolidin-4-one by condensing its derivatives with various secondary amines in presence of formaldehyde. The condensation reaction if run at room temperature binds the aminomethyl group at position 5 rather than position 3[15].





Synthesis Scheme

EXPERIMENTAL

Aminomethyl benzimidazole and thiazolidinone have been used as key intermediates for the synthesis. Aminomethyl benzimidazole was treated with chloroacetyl chloride in presence of K_2CO_3 in acetone. 1-Chloroacetylaminomethyl benzimidazole obtained was treated with ammonium thiocyanate in absolute ethanol to give 2-(benzimidazolylaminomethyl)thiazolidin-4-one. The product obtained was allowed to undergo the Mannich reaction in presence of formaldehyde with different secondary amines namely piperadine, 2-methylpiperadine, 4-methylpiperadine, morpholine and piperazine.

1-Chloroacetylaminomethyl benzimidazole: Aminomethyl benzimidazole (0.01 mol, 1.47 g) was dissolved in 25 mL of acetone in a round bottom flask. 2 g K_2CO_3 was added to the solution and then chloroacetyl chloride (0.01 mol, 1.12 mL) was added drop wise with constant stirring for *ca.* 2 h. The reaction mixture was filtered and the crude product was separated by evaporating acetone. The product was recrystellized using absolute alcohol.

2-(Benzimidazolylaminomethyl)thiazolidin-4-one: 1-Chloroacetylaminomethyl benzimidazole (0.05 mol, 12.3 g) was taken with ammonium thiocyanate (0.1 mol, 7.6 g) in 20 mL of absolute alcohol and was refluxed on a water bath for about 1 h. The reaction mixture was kept overnight and the crude product was filtered and finally recrystallized from ethanol.

5-Substituted 2-(benzimidazolylaminomethyl)thiazolidin-4-ones (Mannich bases): A solution of 0.5 mL of 37 % formaldehyde (0.0018 mol) and the secondary amine (0.002 mol) were added drop wise with vigorous stirring to a suspension of 2-(benzimidazolylaminomethyl)thiazolidin-4-one (0.002 mol, 0.5 g) in 5 mL of absolute ethanol. The mixture was refluxed for 4 h on water bath and cooled to room temperature. Then was precipitated, filtered, dried and recrystallized from ethanol.

RESULTS AND DISCUSSION

The synthesized compounds are subjected to physicochemical and spectral characterization (IR and Mass spectroscopy) (Table-1). IR spectra are recorded on a Shimadzu infrared spectrophotometer. Mass spectra are recorded on Jeol/SX-102/DA-600FABMS spectroscopy from CDRI, Lucknow. Melting points are subjected to Thiele's tube method. The purity of compounds is confirmed by thin layer chromatography using silica gel glass plates and a solvent system of benzene:ethanol (90:10). Iodine chamber is used for developments of spots.

In the IR spectra of the compounds, C1-C5 the N-H and C=O stretching bands of lactam groups were observed in the region 3450-3200 and near 1700 cm^{-1}, respectively. The existence of the N-H stretching bonds provide evidence that the C-C bond is formed at the 5-position of thiazolidinone rather than 3-position. Band or bands in the region 1650-1515 cm^{-1} caused primarily by NH_2 or N-H bending has also been the characteristics of few lactams[16]. Structure of the compounds synthesized are further supposed to be supported by mass spectroscopy (Table-1).

TABLE-1
PHYSICAL CHARACTERIZATION OF SYNTHESIZED COMPOUNDS AND SPECTRAL CHARACTERIZATION OF COMPOUNDS (C1-C5)

Compd.	Yield (%)	m.p. (ºC)	Spectral data
C1	40	190-191	IR (KBr, ν_{max}, cm^{-1}): 3433 (N-H), 1700 (C=O of thiazolidinone), 1043.42 (C-N), 1540 (N-H bending), 819.69; MS (m/z): 343.2 (M^+), 119.2 (base peak), 318.2, 134.2
C2	55	210-211	IR (KBr, ν_{max}, cm^{-1}): 3445 (N-H), 1694 (C=O of thiazolidinone), 2831 (C-H), 1031.85 (C-N), 1581.52 (N-H bending), 833.48; MS (m/z): 358 (M^+), 133 (base peak), 303.5, 134.2
C3	47	250-251	IR (KBr, ν_{max}, cm^{-1}): 3387 (N-H), 1699 (C=O of thiazolidinone), 2952 (C-H), 1031.85 (C-N), 1581.52 (N-H bending), 833.48; MS (m/z): 357 (M^+), 135.2 (base peak), 303.5, 134.2
C4	63	235-236	IR (KBr, ν_{max}, cm^{-1}): 3289 (N-H), 1701 (C=O of thiazolidinone), 1010 (C-N), 1550.66 (N-H bending), 1089 (C-O, cyclic ether), 867.91; MS (m/z): 348 (M^+), 119.2 (base peak), 345.2, 266.1, 134.2
C5	65	285-286	IR (KBr, ν_{max}, cm^{-1}): 3413 (N-H), 1730 (C=O of thiazolidinone), 2831 (C-H), 1000 (C-N), 1552.59 (N-H bending), 870; MS (m/z): 345.2 (M^+), 119.2 (base peak), 319.2, 256.1, 134.2

C1 = 5-(Piperidinylmethyl)-2-(benzimidazolylaminomethyl)thiazolidin-4-one.
C2 = 5-(2-Methylpiperidinylmethyl)-2-(benzimidazolylaminomethyl)thiazolidin-4-one.
C3 = 5-(4-Methylpiperidinylmethyl)-2-(benzimidazolylaminomethyl)thiazolidin-4-one.
C4 = 5-(1-Morpholinylmethyl)-2-(benzimidazolylaminomethyl)thiazolidin-4-one.
C5 = 5-(1-Piperazinylmethyl)-2-(benzimidazolylaminomethyl)thiazolidin-4-one.

Compounds C1-C5 were tested for their *in vitro* antibacterial activity against two gram positive bacteria, *S. aureus* and *B. subtilis*, two gram negative bacteria, *E. coli* and *P. aeruginosa* and antifungal activity against a pathogenic fungal strain *C. albicans*, by cup plate method[17] using a concentration of 10 and 4 mg/mL in distilled water.

Among these, two compounds (C2, C4) were found to be remarkably effective compounds with respect to their inhibitory activity against gram positive bacteria, *Bacillus subtilis* and gram negative bacteria, *Pseudomonas aerugenosa* and *E. coli*. while, other compounds did not shown any antibacterial activity. Compound C4 was found to be moderately active against *E. coli*, slightly active against *Bacillus subtilis* and *Pseudomonas aerugenosa* at lower concentration (4 mg/mL), but highly active against *Pseudomonas aerugenosa* at higher conc. (10 mg/mL) while, compound C2 was found to be moderately active against *Bacillus subtilis*, slightly active against *E. coli*, *Pseudomonas aerugenosa* at lower concentration but highly active against *Pseudomonas aerugenosa* at higher conc. (10 mg/mL). However, all the compounds were found to be inactive against *C. albicans* and *S. aureus* (Table-2).

TABLE-2
RESULTS OF ANTIMICROBIAL ACTIVITY OF THE TESTED COMPOUNDS

Compd.	Diameter of inhibition zones (mm)				
	B. subtilis	*E. coli*	*S. aureus*	*P. aureginosa*	*C. albicans*
C1	–	–	–	–	–
C2	++ (4 mg/mL) ++ (10 mg/mL)	+ (4 mg/mL) + (10 mg/mL)	–	+ (4 mg/mL) +++ (10 mg/mL)	–
C3	–	–	–	–	–
C4	+ (4 mg/mL) + (10 mg/mL)	++ (4 mg/mL) ++ (10 mg/mL)	–	+ (4 mg/mL) +++ (10 mg/mL)	–
C5	–	–	–	–	–

Highly active = +++ (inhibition zone >12 mm).
Moderately active = ++ (inhibition zone 9-12 mm).
Slightly active = + (inhibition zone 6-9 mm).
Inactive = - (inhibition zone < 6 mm).

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