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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL N-MANNICH BASES OF BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

The current interest in the development of new antimicrobial chemotherapy has been the mainstay of medicinal intervention against infectious diseases caused by various pathogens. A matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs. There is a real perceived need for the discovery of new compounds that are endowed with antimicrobial activities, possibly acting through mechanism of action, to which many clinically relevant pathogens are now resistant. In order to expand the group of benzimidazole derivatives, we synthesized several new benzimidazole ring containing N-mannich bases. It has been observed that the presence of two (or) more heterocyclic moieties fused or linked enhance the biological profile of drug molecules by many folds. We reported our results from a study of replacing the N-1 hydrogen of novel benzimidazole derivatives with different types of substitutions like sulphanilamide and piperazine to form N-methyl substituted benzimidazole derivatives by mannich reaction. The structure of the synthesized compounds were elucidated by physical and spectral (UV, IR, ^{1}H NMR and Mass) analysis.

KEYWORDS: Benzimidazole derivative, Mannich base, O-phenylene diamine, Propionic acid, Acetic acid, Butyric acid.

INTRODUCTION

Mannich bases form a promising group of chemicals which may be a good source of potential candidates for future drugs. Our knowledge about their activities at the cellular and tissue level is, however, still rather limited. α, β – unsaturated ketones released by mannich bases exert their biological activities such as cytotoxicity and anti- fungal activity by reacting with the vital thiol groups in the living organisms.

Mannich reaction is one of the most important C-C bond forming reactions in organic synthesis for the preparation of secondary and tertiary amine derivatives.[1] These amines are further used for the synthesis of many intermediates, biologically active and natural products such as alkaloids and polypeptides. The products of Mannich reaction are mainly amino carbonyl compounds and its derivatives that are used for the synthesis of amino alcohols, peptides and lactams and as precursors to optically active amino acids. The ring system in which a benzene ring is fused to the 4,5-positions of imidazole is designated as benzimidazole.[2] The various positions on the benzimidazole ring are numbered in the manner indicated with the imino function as number one. The benzimidazoles possessing free imino hydrogen are tautomeric systems. The two possible tautomeric forms of benzimidazole (and of those of its derivatives possessing a plane of symmetry) are identical and a definite assignment of structure is possible. The formations of the product were confirmed by the analytical and spectral data. Antiinflammatory activity of the synthesized compound was confirmed by significant effect over antimicrobial activity.[3-5]

MATERIALS AND METHODS

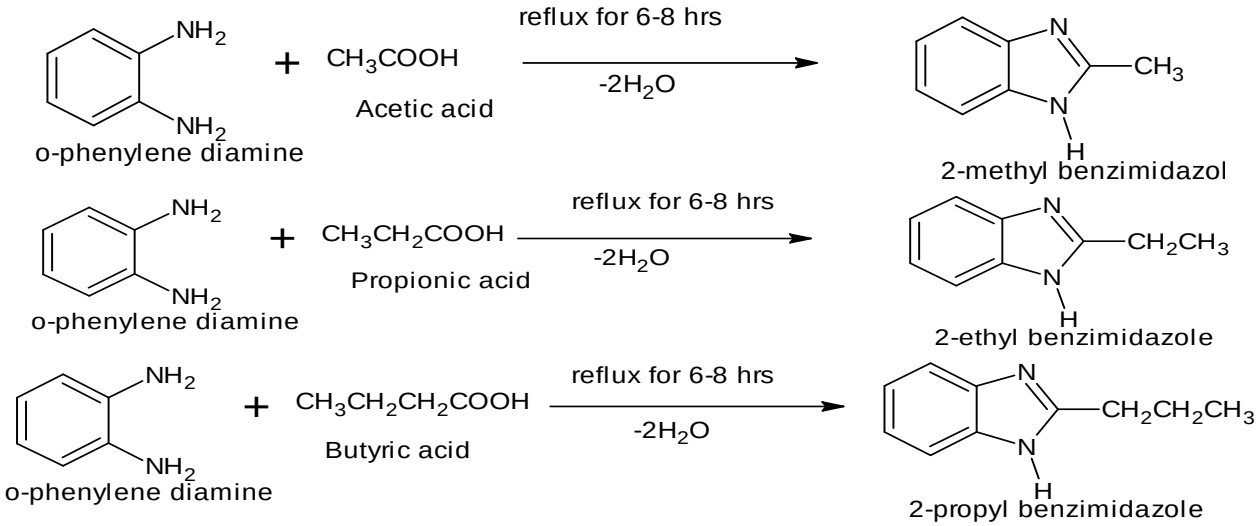
Established synthetic procedures were employed for synthesis of compounds SR_1 to SR_9 and the reactions were monitored by Thin Layer Chromatography (TLC) employing 6'' X 2'' plates coated with 0.25 mm thick layer of silica gel (pre-activation by heating at 110° C for one h). Solvent systems of varying polarity ranging from methanol to water mixtures (9.5:0.5, 9:1, 8.5:1.5, 8:2 and 7:3) were used to monitor the reactions. The plates were visualized in an iodine chamber.[6]

Synthesis of compounds

Synthesis of 2–methyl/ethyl/propyl-benzimidazole: (SR_1, SR_2, SR_3)

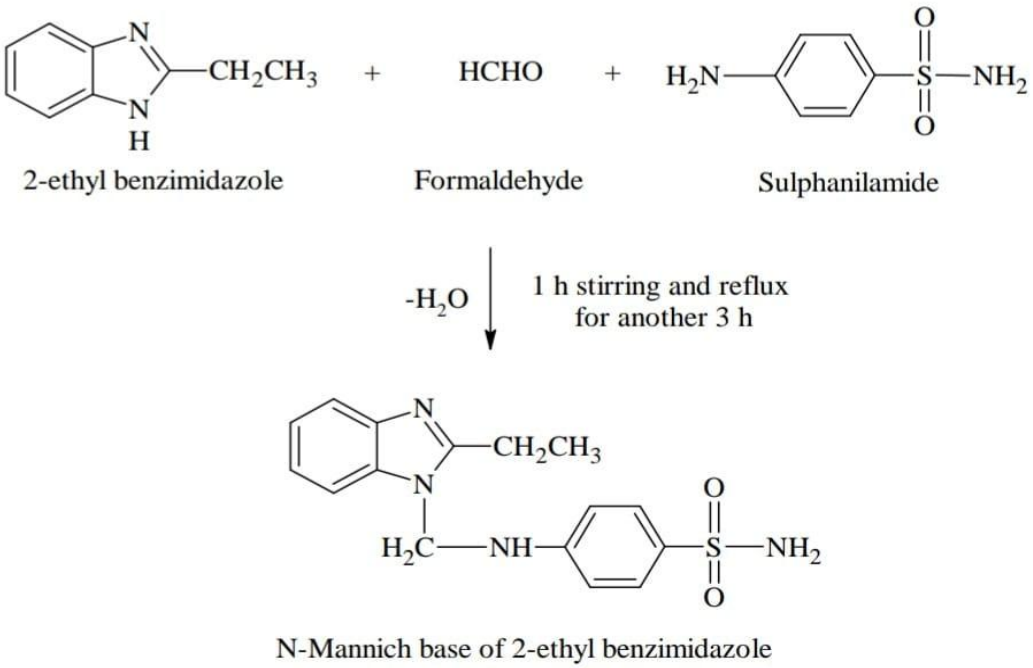
13.5 g (0.125mol) of O-phenylene diamine was placed in a 250 ml of round bottom flask and added 10.2 g (0.17 mol) of acetic acid/propionic acid/butyric acid. The mixture was heated on a water bath at 100° C for 6-8 h, cooled and added 10% sodium hydroxide solution slowly with constant rotation of the flask, until the mixture was

just alkaline to litmus. The crude benzimidazole derivative was filtered at the pump, and then washed with ice cold water, drained well and washed again with 25 ml of cold water. The crude product was dissolved in 200 ml of boiling water; 2 g of decolorizing carbon was added and digested for 15 min. The product was filtered rapidly at the pump through preheated buchner funnel and flask. The filtrate was cooled to about 10° C and the filtered product of 2-methyl-benzimidazole was again washed with 25 ml of cold water, dried at 100° C and weighed.[7-8]



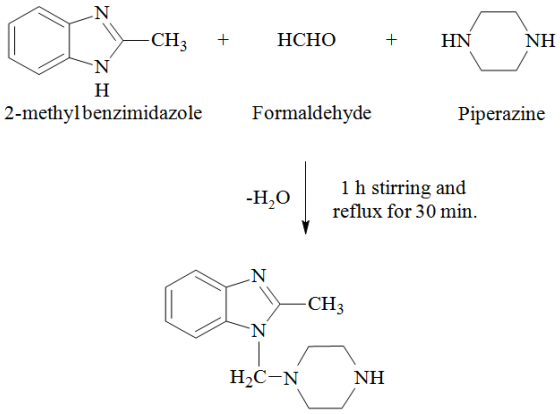
Synthesis of 1-((sulphanilamido) methyl)-2-methyl/ethyl/propyl-benzimidazole (SR_4, SR_5, SR_6)

To the 15 ml of methanolic solution, 0.66 g (0.005 mol) of 2-methyl/ethyl/propyl benzimidazole was added to 0.86 g (0.005 mol) of sulphanilamide slowly with constant stirring under rigorous ice cooling. The reaction mixture was cooled well and 0.138 ml (0.005 mol) of formaldehyde solution (37% v/v) was added slowly with constant stirring. The reaction mixture was then adjusted to the pH of 3.5 with hydrochloric acid. The reaction mixture was kept in efficient ice cooling for half an hour to avoid losses of formaldehyde and then refluxed on water bath up to 3 h. The reflux time was dependent upon the sulphonamide chosen. After refluxing, the refluxed mixture was cooled at 0° C for 4 days, when crystallized product was obtained, which was recrystallized with dry distilled ethanol and DMF. (Sheela Joshi *et al.*, 2005)[9]



Synthesis of 1-((pipearzino) methyl)-2-methyl-benzimidazole (SR_7)

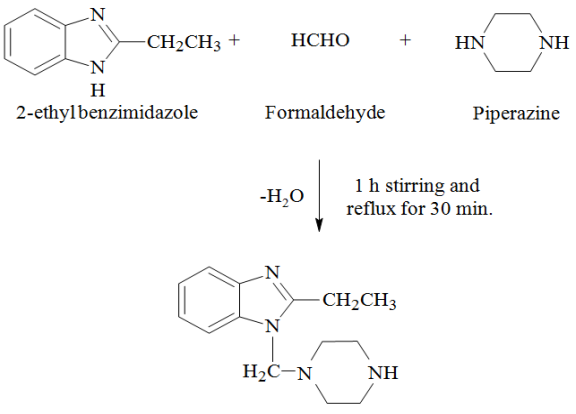
To a solution 1.32 g (0.01mol) of 2-methyl benzimidazole in 15 ml of ethanol, 0.86 g (0.01mol) of piperazine and 0.30 ml (0.01 mol) of formaldehyde solution (37% v/v) were added slowly with constant stirring under rigorous ice cold condition. The reaction mixture was kept in efficient ice cooling for half an hour to avoid losses of formaldehyde and then the reaction mixture was refluxed on water bath up to 30 min. The refluxed mixture was cooled at 0° C for 2-3 days in deep freeze. When crystallized product was obtained, filtered and dried. The product obtained was purified by recrystallized with dry distilled ethanol. (Rita Bamnela *et al.*, 2011).[10]



N-Mannich base of 2-methyl benzimidazole

Synthesis of 1-((pipearzino) methyl)-2-ethyl-benzimidazole (SR_8)

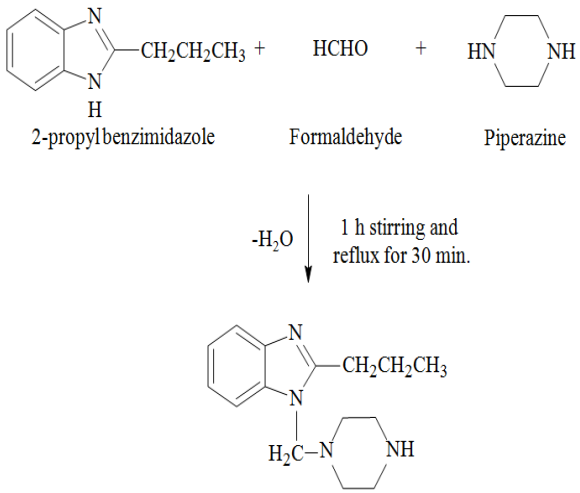
To a solution 1.46 g (0.01mol) of 2-ethyl benzimidazole in 15 ml of ethanol, 0.86 g (0.01 mol) of piperazine and 0.30 ml (0.01 mol) of formaldehyde solution (37% v/v) were added slowly with constant stirring under rigorous ice cold condition. The reaction mixture was kept in efficient ice cooling for half an hour to avoid losses of formaldehyde and then the reaction mixture was refluxed on water bath up to 30 min. The refluxed mixture was cooled at 0° C for 2-3 days in deep freeze. When crystallized product was obtained, filtered and dried. The product obtained was purified by recrystallized with dry distilled ethanol.[11-12]



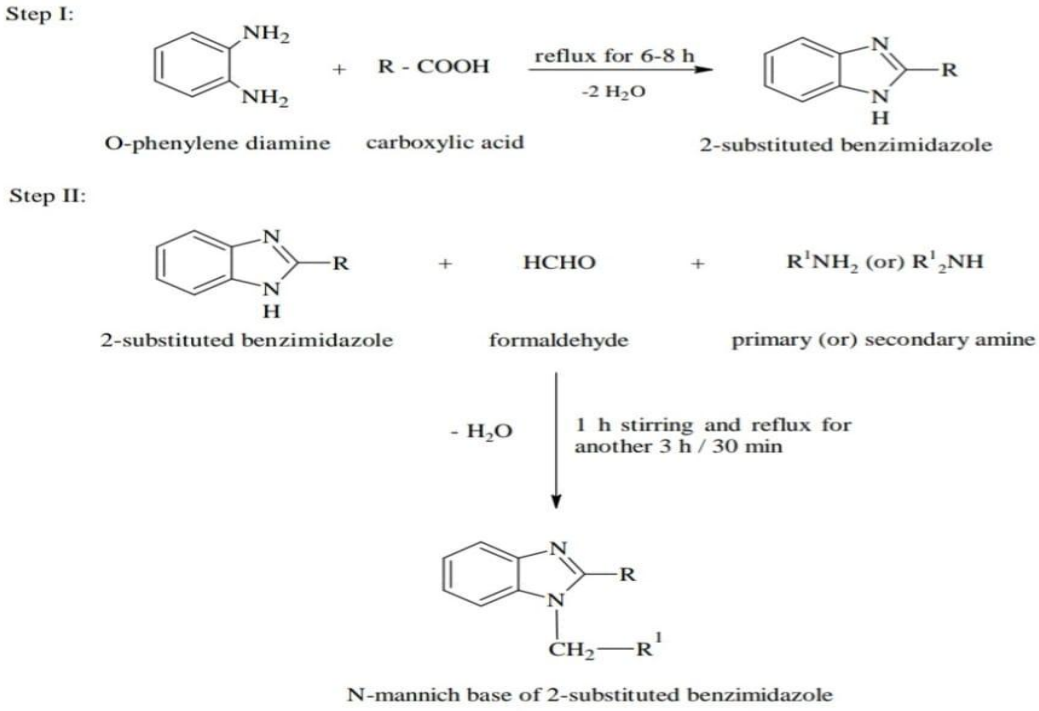
N-Mannich base of 2-ethyl benzimidazole

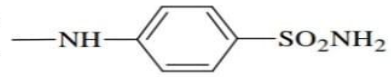
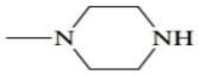
Synthesis of 1-((pipearzino) methyl)-2-propyl-benzimidazole (SR_9)

To a solution 1.60 g (0.01mol) of 2-propyl benzimidazole in 15 ml of ethanol, 0.86 g (0.01 mol) of piperazine and 0.30 ml (0.01 mol) of formaldehyde solution (37% v/v) were added slowly with constant stirring under rigorous ice cold condition. The reaction mixture was kept in efficient ice cooling for half an hour to avoid losses of formaldehyde and then the reaction mixture was refluxed on water bath up to 30 min. The refluxed mixture was cooled at 0° C for 2-3 days in deep freeze. When crystallized product was obtained, filtered and dried. The product obtained was purified by recrystallized with dry distilled ethanol.[13]



N-Mannich base of 2-propyl benzimidazole



Code. No	R	R^1
SR_1	$-CH_3$	-
SR_2	$-CH_2CH_3$	-
SR_3	$-CH_2CH_2CH_3$	-
SR_4	$-CH_3$	
SR_5	$-CH_2CH_3$	
SR_6	$-CH_2CH_2CH_3$	
SR_7	$-CH_3$	
SR_8	$-CH_2CH_3$	
SR_9	$-CH_2CH_2CH_3$	

Scheme 17: Synthetic route of title compounds

Table 1: Physical and Analytical data of the synthesized compounds.

Sl.No	Comd.Code	M.P˚C	%Yield	Mol. Formula	M.Wt.	Rf Value*	Calculated (%)		
							C	H	N
1	SR_1	176*(174-178)	60.73	$C_8H_8N_2$	132.16	0.80	62.49	3.39	8.57
2	SR_2	211*(213-215)	38.89	$C_9H_{10}N_2$	146.18	0.64	63.44	3.85	8.22
3	SR_3	183*(180-184)	85.86	$C_{10}H_{12}N_2$	160.21	0.95	63.44	3.85	8.22
4	SR_4	142	45.58	$C_{15}H_{16}N_4O_2S$	316.37	0.76	63.44	3.85	8.22
5	SR_5	123	31.61	$C_{16}H_{18}N_4O_2S$	330.40	0.74	66.23	3.92	9.09
6	SR_6	149	28.45	$C_{17}H_{20}N_4O_2S$	344.43	0.68	67.07	4.38	8.69
7	SR_7	148	71.17	$C_{13}H_{18}N_4$	230.30	0.71	67.07	4.38	8.69
8	SR_8	161	92.70	$C_{14}H_{20}N_4$	244.33	0.57	67.07	4.38	8.69
9	SR_9	174	69.10	$C_{15}H_{22}N_4$	258.36	0.83	62.95	3.73	8.64

Reported melting points. (Jubie S., *et al*., 2010; Kalirajan R., *et al*., 2009)

Screening of antibacterial activity

The synthesized compounds were evaluated *in vitro* anti bacterial activity against gram negative bacteria *Escherichia coli* MTCC 1302, *Pseudomonas aeruginosa* MTCC 741 and gram positive bacteria *Staphylococcus aureus* MTCC 740 and *Bacillus subtilis* MTCC 121. These are the agents commonly causes gastrointestinal tract infection and biliary tract infection. The gram negative organism *Escherichia coli* and *Pseudomonas aeruginosa* causes septicemia, gastroenteritis with mild to severe bloody diarrhea, hemorrhagic colitis and hemolytic-uremic syndrome. The gram positive

organism *Staphylococcus aureus* and *Bacillus subtilis* causes diarrhoea, pyogenic infection and septicemia.[14]

As per the data obtained, it was confirmed that all the tested compounds possess antibacterial activity against both gram positive and gram negative organisms.

The compound SR_4 showed the significant activity in the following order: *Staphylococcus aureus* > *Pseudomonas aeruginosa* > *Bacillus subtilis* > *Escherichia coli*. The compound SR_5 showed the significant activity in the following order: *Staphylococcus aureus* > *Pseudomonas aeruginosa* > *Escherichia coli* > *Bacillus subtilis*. The compound SR_6 showed the significant activity in the following order: *Bacillus subtilis* > *Pseudomonas aeruginosa* > *Escherichia coli* > *Staphylococcusaureus*.

The compound SR_7 showed the significant activity in the following order: *Escherichia coli* > *Pseudomonas aeruginosa* > *Bacillus subtilis* > *Staphylococcus aureus*. The compound SR_8 showed the significant activity in the following order: *Escherichia coli* > *Pseudomonas aeruginosa* > *Bacillus subtilis* > *Staphylococcus aureus*.

The compound SR_9 showed the significant activity in the following order: *Escherichia coli* ≥ *Pseudomonas aeruginosa* > *Bacillus subtilis* > *Staphylococcus aureus*. However the antibacterial activity of all the tested compounds against the tested organisms was found to be less than that of standard antibacterial drug ciprofloxacin at tested dose level.[15]

Table 2: *In vitro* antibacterial activity of synthesized compounds by disc diffusion method.

Microorganisms	Diameter of zone of inhibition (in mm)												
	SR_4 (µg/ disc)		SR_5 (µg/ disc)		SR_6 (µg/ disc)		SR_7 (µg/ disc)		SR_8 (µg/ disc)		SR_9 (µg/ disc)		Ciprofloxacin (µg/disc)
	25	100	25	100	25	100	25	100	25	100	25	100	100
Staphylococcusaureus	17	21	17	25	12	17.3	12	15	11	15.6	10	16	28
Bacillus subtilis	13	17	11	14	21	27	11	16.4	12.6	17.5	13	16	29
Escherichia coli	12	17	13	17	19	22.3	20	25	21	27	14	17	30
Pseudomonasaeruginosa	15	18	17	22	20	24	17	21.5	21	26	14	17	32

Screening of antifungal activity

The synthesized compounds were evaluated for *in vitro* antifungal activity againsttwo fungal organisms *Candida albicans* ATCC 24433 and *Trichophyton rubrum* ATCC 2327. These organisms cause serious dental infections. As per the data obtained, it was confirmed that all the tested compounds possessed anti-fungal activity. However, SR_9, 1-((piperazino) methyl)-2-propyl-benzimidazole exhibited more potent anti fungal activity against both fungal organisms among the test compounds.

The compound SR_4 showed the significant activity in the following order: *Candida albicans* > *Trichophyton rubrum*. The compound SR_5 showed the significant activity in the following order: *Candida albicans* > *Trichophyton rubrum*. The compound SR_6 showed the significant activity in the following order: *Trichophyton rubrum* > *Candida albicans*. The compound SR_7 showed the significant activity in the following order: *Trichophyton rubrum* > *Candida albicans*. The compound SR_8 showed the significant activity in the following order: *Candida albicans* > *Trichophyton rubrum*. The compound SR_9 showed the significant activity in the following order: *Trichophyton rubrum* > *Candida albicans*.

However, the anti-fungal activity of the compound SR_9 against the tested organism was found to be less than that of antifungal drug ketoconazole at tested dose level.[16]

Table 3: *In vitro* antifungal activity of synthesized compounds by disc diffusion method.

Microorganisms	Diameter of zone of inhibition (in mm)												
	SR_4 (µg/ disc)		SR_5 (µg/ disc)		SR_6 (µg/ disc)		SR_7 (µg/ disc)		SR_8 (µg/ disc)		SR_9 (µg/ disc)		Ketoconazole (µg/ disc)
	25	100	25	100	25	100	25	100	25	100	25	100	100
Candida albicans	16	21	17	21	14	17	11	14	20	22	23	26	31
Trichophyton rubrum	12	15	14	17.5	16	19.1	13	18	17	20	24	29	30

SUMMARY AND CONCLUSION

The current interest in the development of new antimicrobial chemotherapy has been the mainstay of medicinal intervention against infectious diseases caused by various pathogens. A matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs. There is a real perceived need for the discovery of new compounds that are endowed with antimicrobial activities, possibly acting through mechanism of action, to which many clinically relevant pathogens are now resistant (Uday Kalidhar., 2011).[41] In order to expand the group of benzimidazole derivatives, we synthesized several new benzimidazole ring containing N-mannich bases. It has been observed that the presence of two (or) more heterocyclic moieties fused or linked enhance the

biological profile of drug molecules by many folds.

The appropriate carboxylic acids were reacted with O-phenylene diamine to give the corresponding 2-substituted benzimidazole in good to excellent yields by Phillip's reaction. Then, a series of six novel mannich bases of 2-alkyl substituted benzimidazole derivatives were synthesized using mannich reaction by reaction with amines (primary and secondary) and formaldehyde. The purity of the synthesized compounds was checked by performing Thin Layer Chromatography (TLC) and determining melting points.[17]

We reported our results from a study of replacing the N-1 hydrogen of novel benzimidazole derivatives with different types of substitutions like sulphanilamide and piperazine to form N-methyl substituted benzimidazole derivatives by mannich reaction. The structure of the synthesized compounds were elucidated by physical and spectral (UV, IR, ^{1}H NMR and Mass) analysis. The NH band (3164-3385 cm^{-1}) and NH proton signal (δ 4.80 – 5.0 ppm) of 2-substituted benzimidazole in IR and ^{1}H NMR spectrum respectively in the synthesized compounds (SR_1–SR_3), confirmed the formation of benzimidazole nucleus. In SR_1, ^{1}H NMR spectrum showed a singlet for 3 protons at δ 2.42 confirmed the substitution of methyl group at C_2 of benzimidazole nucleus. In SR_2, gave quartet peak for 2 protons at δ 2.59 and a triplet peak for 3 protons at δ 1.27 indicated the presence of ethyl group at C_2 of benzimidazole. In SR_3, a two triplet peak for 5 protons at δ 2.55 and δ 0.96 and a multiplet peak for 2 protons at δ 1.66 indicated the presence of propyl group at C_2 of benzimidazole.[18]

The IR spectrum of each N-mannich bases of SR_4 to SR_6 showed the characteristic IR absorption bands in the region of 3376-3385 cm^{-1}, 3263-3289 cm^{-1} and 1312-1320 cm^{-1} due to the presence of primary amino, secondary amino and SO_2 stretching of sulphonamide moiety. The structural confirmation of each N-mannich bases of SR_4 to SR_6 was further made using ^{1}H NMR spectra. It showed signals atδ, ppm: 6.06 - 6.18 (2H, s, -CH_2 proton), 4.57 – 4.60 (2H, s, SO_2NH_2 proton) and 5.76– 5.83 (1H, s, NH of sulphonamide). Thus, confirmed the proposed structures for above N-mannich bases of corresponding 2-substituted benzimidazole derivatives.

The IR spectrum of each N-mannich bases of SR_7 to SR_9 showed the characteristic IR absorption bands in the region of 3385 - 3416 cm^{-1} due to the presence of 2° N-H (secondary amino) streching of piperazine ring. The structural confirmation of each N-mannich bases of SR_7 to SR_9 was further made using ^{1}H NMR spectra. It showed signals at δ, ppm: 2.37 – 2.93 (8H, m, -CH_2 of piperazine), 5.47 – 5.61 (2H, s, CH_2 proton) and 1.13 – 1.15 (1H, s, NH of piperazine). Thus, confirmed the proposed structures for above N-mannich bases of corresponding 2-substituted benzimidazole derivatives.[19]

The structural confirmation of synthesized compounds of SR_1 to SR_9 was further made using Mass spectra. The molecular ion (M^+) peaks such as 132.12, 146.21, 160.11, 316.37, 330.40, 344.43, 230.30, 244.33 and 258.36 for SR_1, SR_2, SR_3, SR_4, SR_5, SR_6, SR_7, SR_8 and SR_9 respectively corresponded with their molecular weights. The predicted chemical structure of title compounds was further supported by the fragmentation peaks.

The compounds were screened for their antibacterial and antifungal activities. The activities reported by means of zone of inhibition in millimeter. All the compounds showed very good antibacterial and antifungal activities at the tested dose level.[20]

The sulphanilamide group containing N-mannich bases were more superior for inhibiting the growth of *Staphylococcus aureus* and *Bacillus subtilis* than piperazine containing N-mannich bases. Among the compounds, SR_4 to SR_6, the compound SR_5 was more active than the other compounds against the growth of *Staphylococcus aureus*. Likewise, the compound SR_6 was more active than SR_4 and SR_5 to inhibit the growth of *Bacillus subtilis.*

The piperazine group containing N-mannich bases were more superior for inhibiting the growth of *Escherichia coli* and *Pseudomonas aeruginosa* than sulphanilamide group containing N-mannich bases. Among the compounds SR_7 to SR_9, the compound SR_8 was more active than the other compounds against the growth of *Escherichia coli* and *Pseudomonas aeruginosa*.

Among the tested compounds, piperazine derivatives were more superior to sulphanilamide derivatives against gram negative bacteria. But sulphanilamide derivatives were more active than piperazine derivatives against gram positive bacteria.

The anti-fungal evaluation of compounds (SR_4 to SR_9), the piperazine group containing N-mannich bases were more superior for inhibiting the growth of *Candida albicans* and *Trichophyton rubrum* than sulphanilamide group containing N-mannich bases. Among the compounds of SR_7 to SR_9, the compound SR_9 was more active than the other compounds against the growth of *Candida albicans* and *Trichophyton rubrum*.

Even though, the anti microbial activity of tested compounds was less than their standard compounds are ciprofloxacin (antibacterial) and ketoconazole (antifungal) in the present study. In future study, it could be increased (or) equalizedby altering the number of carbon atoms in side chain (or) introducing aromatic ring (or) substituted aromatic ring (or) heterocyclic ring (or) by introducing double bond in side chain in the 2nd position of benzimidazole nucleus. In other way, the

synthesis of 2-substituted benzimidazoles can be altering the complex with amines, like as pyrrolidine, imidazole, piperidine, morpholine and N-methyl piperazine etc. in the 1st position of benzimidazole nucleus.[21]

Since a fewer species have been used in this study, it was warranted to screen these compounds with varied species and resistant strains. Further experiments were needed to elucidate their exact mechanism of activity. These results suggest that the benzimidazole ring is an important pharmacophore in modern drug discovery and the tested derivatives of benzimidazoles have excellent scope for further development as commercial antimicrobial agents in the chemotherapeutic approach in human. Our findings will prove useful to those chemists, pharmacists, medicinal chemists who are interested in the synthesis of potential Mannich bases as drugs with minimum side effects and also have comparatively low cost.

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