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An insight into the medicinal perspectives of mannich bases of benzimidazole derivatives: A review

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Abstract

The heterocyclic aromatic compound benzimidazole is made up of benzene and an imidazole ring. In medicinal chemistry, it's a crucial pharmacophore and a privileged structure. It's a component of the vitamin cobalamin. Antimicrobial, antiviral, antidiabetic, anti-cancer, anti-helminthic, antioxidant, anti-fungal, anti-allergic, anti-parasitic, anti-proliferative, anti-HIV, anti-convulsant, anti-inflammatory, anti-hypertensive and proton pump inhibitors are only a few of the pharmacological functions of benzimidazole derivatives play a critical role throughout the medical sector. The Mannich reaction is one of the most versatile reaction in organic synthesis. This reaction can be used to make N-methyl derivatives and a variety of drug molecules. Mannich base benzimidazole derivatives play a significant role in medicine, with several medicinal applications including antibacterial, anthelmintic, antifungal, anti-inflammatory, antiviral, analgesic and anti-convulsant. Changes in their composition have provided a high degree of variety, which has been beneficial in the case of new therapeutic agents with increased efficacy and lower toxicity. This analysis emphasises the significance of synthesis and various biological activities of newly synthesized mannich bases of benzimidazole derivatives, as well as a few key synthesis methodologies.

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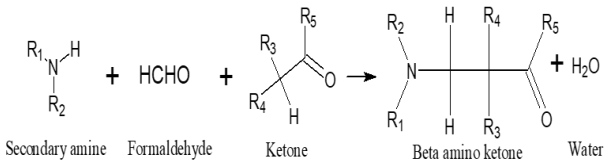
INTRODUCTION

Medicinal chemistry is the study of the discovery and synthesis of new medicinal chemicals, as well as their conversion into useful medicines. The most elegant method for discovering compounds with high specificity and biological activity is drug development. Heterocyclic ring structures are used in a wide variety of biochemical compounds and natural medicines. The existence of heterocyclic structures in such a wide range of compounds strongly suggest that these compounds have a

variety of pharmacological activities. In pharmaceutical chemistry, all heterocyclic compounds are of great interest. The benzfused heterocyclic compounds, such as benzimidazole and its derivatives, have a wide range of biological activities, including Antihypertensive (Kumar *et al.*, 2006), Antiviral (Tonelli *et al.*, 2008), Analgesic (Kaplancikli *et al.*, 2009), Anti-inflammatory (Babu *et al.*, 2010), Antiulcer (Thakare and Ansari, 2011), Anti-convulsant (Bhrigu *et al.*, 2012), Antioxidant (Chakkaravarthi *et al.*, 2014), Antiproliferative (Nowicka *et al.*, 2015), Anti-corrosion (Tiejun *et al.*, 2015), Anti-cancer (Manjula *et al.*, 2016; El-Meguid *et al.*, 2019), Antimicrobial activity (Negi *et al.*, 2017; Kamala *et al.*, 2018), Anti protozoal activity (Patel *et al.*, 2020), Anti-diarrheal (Saha *et al.*, 2020), Anti-malarial (Dziwornu *et al.*, 2021). The inclusion of benzimidazole nuclei is an essential part of drug discovery's synthetic strategy. Because of the high therapeutic properties of benzimidazole derivatives with mannich bases, scientists have been able to synthesize many therapeutic agents.



Scheme 1: Mannich base reaction

The Mannich reaction is an important organic reaction in which an acidic proton is put after a carbonyl functional group and is amino alkylated with formaldehyde, ammonia, and any primary or secondary amine. A β-amino carbonyl compound, also known as mannich base, may be the final product shown in Scheme 1. It's a condensation reaction. Antineoplastic, antimicrobial, anti-HIV, anticancer, tuberculosis, neurotoxicity, vasorelaxant, anti-inflammatory, anti-malarial, and analgesic are some of the biological activities of Mannich bases. In modern drug research, the benzimidazole ring (Figure 1) is a crucial pharmacophore. It was strongly drawn to the development of firmer benzimidazole derivatives with a wide range of biological activity (Obot and Edouk, 2017). This bicyclic compound contains the benzene and imidazole rings fused together. N-ribosyl-dimethyl benzimidazole is the most well-known benzimidazole compound in nature, serving as an axial ligand for cobalt in vitamin B_{12} (Datar and Limaye, 2015).

Mannich bases of benzimidazole derivatives

Jesudason *et al.* (2009) used the mannich reaction to synthesize the N-Mannich bases of benzimidazole (Scheme 2), which were then characterised using elemental analysis, spectrum analysis, ^{1}H NMR, and IR spectroscopy. Anti-inflammatory and analgesic properties were tested on all synthesized compounds.1-[(substituted-methyl)-2-steryl benzimidazole derivatives were more active than paracetamol and diclofenac, and most agents penetrated the cornea well.

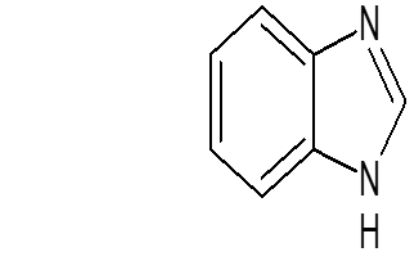
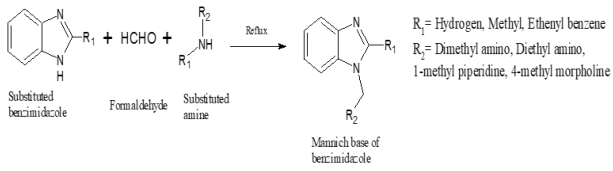
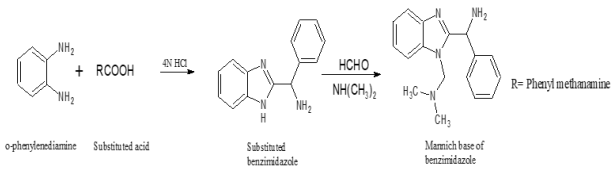


Figure 1: 1H-Benzimidazole



Scheme 2: Synthesis of N-mannich base of benzimidazole derivatives

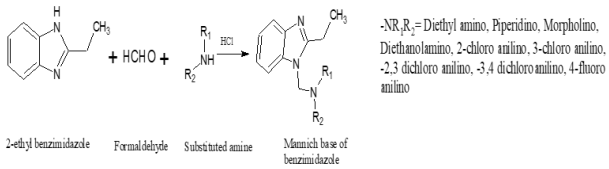
Reddy (2010) used mannich bases to make the 1, 2- disubstituted benzimidazole (Scheme 3). To produce 2-substituted benzimidazole, refluxed o-phenylene diamine(12 mmol) and phenyl glycine(36 mmol) in 4N HCl for four hours. Refluxing 2-(1-amino benzyl) benzimidazole (10 mmol) dissolved in dimethyl sulfoxide, corresponding secondary amine (10 mmol), and formaldehyde (15 mmol) for 5-8 hours yielded the mannich base of 1-dimethyl amino-2-(2-benzyl amine) benzimidazole. The chemical structure of the synthesized compounds were determined using IR, ^{1}H NMR, and mass spectral data, and their anti-inflammatory activity was tested in rats with carrageenan-induced hind paw edema.



Scheme 3: Synthesis of 1,2 disubstituted benzimidazole using mannich base

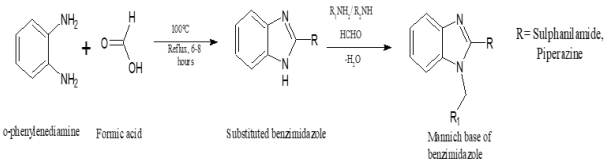
By condensing 2-ethyl benzimidazole with substituted primary and secondary amines and formalde-

hyde Mariappan *et al.* (2011) synthesized [1-(N-substituted amino) methyl]-2-ethyl benzimidazole derivatives shown in Scheme 4. Structures were determined using UV-visible, IR, ^{1}H NMR, and mass spectral data. At P<0.05 values, the experimental findings were found to be statistically significant.



Scheme 4: Synthesis of mannich bases of benzimidazole derivatives

Sugumaran and Rajasekhar (2012) synthesized a novel sequence of 2-substituted benzimidazole derivative N-mannich bases (Scheme 5). The N-mannich bases were made by reacting N-1 hydrogen of 2-substituted benzimidazole with primary (sulphanilamide) and/or secondary (piperazine) amines. UV, ^{1}H NMR, and mass spectral analysis were used to determine the structures of the synthesized compounds. Against the standard drugs ciprofloxacin (antibacterial) and ketoconazole (antifungal), many of the synthesized compounds showed excellent antibacterial and antifungal activity.



Scheme 5: Synthesis of novel N-mannich bases of benzimidazole derivatives

Kumar *et al.* (2013) stated that 2–substituted benzimidazole derivatives were synthesized using o-phenylene diamine and substituted acids. Secondary amines such as dimethylamine and diethylamine were used to make the mannich bases of 2-substituted benzimidazole derivatives (Scheme 6). The antimicrobial assay was performed using the microbroath dilution process, and the structures were elucidated. The cleavage of bacterial genomic DNA was determined using agarose gel electrophoresis. The compounds toxicity was investigated using a brine shrimp lethality assay.

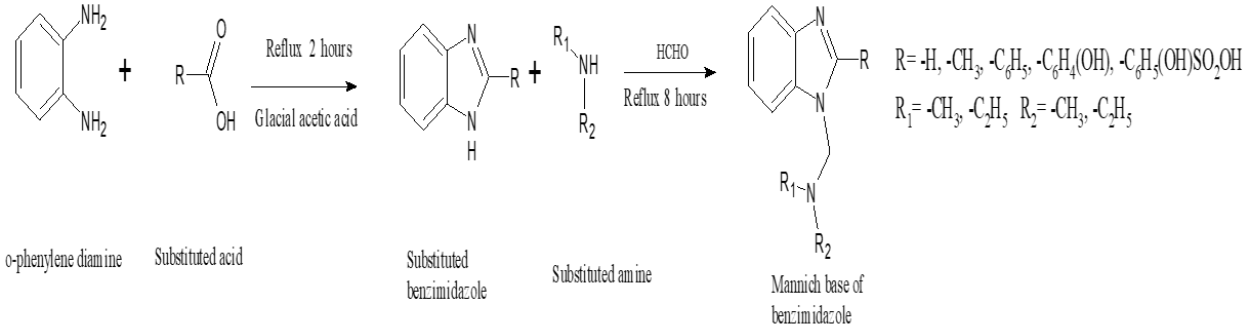
N-[(1H-benzimidazol-1yl) methyl)-4-(1-phenyl-5-substituted -4,5 dihydro-1H pyrazole-3yl] benzenamine (3) (Scheme 7) was synthesized by Krishnanjaneyulu *et al.* (2014). 1-(4-(1H-benzimidazol-1yl) methylamino) phenyl)-3-substituted prop-2-en-1-one(2) was synthesized by reacting 1-(4-[(1H-benzimidazol-1yl) methylamine) phenyl] ethenone (1) (0.01 mol) with various aromatic aldehydes (0.01 mol). All compounds were investigated for *in vitro* anti-microbial properties. FT-IR, ^{1}H NMR, Mass spectroscopy, and elemental analysis were used to identify most of the compounds.

Sethi *et al.* (2015) used the mannich reaction to create N-(2-substituted-benzimidazole-1-yl methyl) benzamide derivatives (Scheme 8). Two negative species, *Escherichia coli* and *Pseudomonas aeruginosa*, two positive organisms, *Bacillus subtilis* and *Staphylococcus aureus* and fungal strains, *Candida albicans* and *Aspergillus niger* were tested for *in vitro* antimicrobial activity and antioxidant activity was carried out by using 1,1 biphenyl-2-picryl-hydrazyl radical method. Antioxidant activity was observed in all the synthesized compounds.

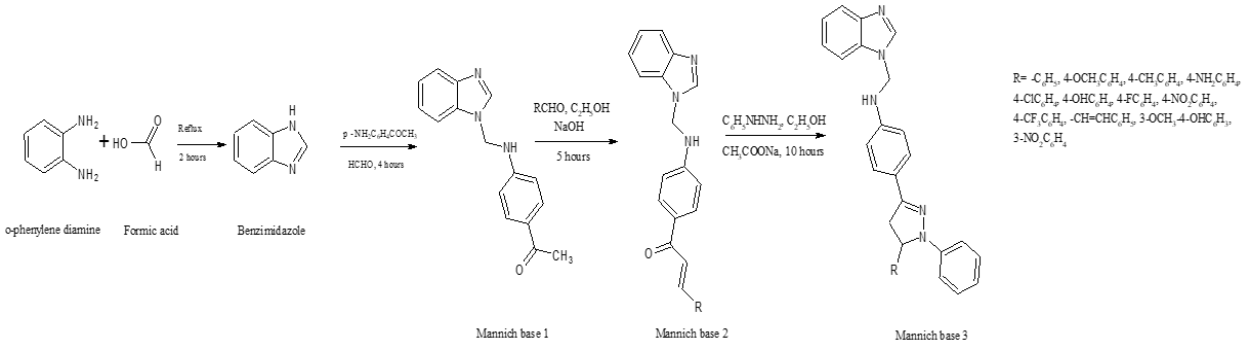
2-amino-6-{(2-substituted-1H-benzimidazole-1-yl) methyl} phenol derivatives (a) and 4-amino-2-{2-substituted-1H-benzimidazole-1-yl methyl} phenol derivatives (b) were synthesized by Kaur and Wakode (2016). Melting point, thin layer chromatography, infrared spectroscopy, and ^{1}H NMR spectrum were all investigated. The sulforhodamine B assay method was used to test anti-cancer activity. The cytotoxicity of the synthesized compounds against colon cancer produced significant result. Compound cytotoxicity was assessed in lung, prostate, and colon tissue (Scheme 9).

Durosinmi *et al.* (2017) used a condensation reaction of 1,2- diamino compounds and dicarboxylic acid to make bis (2-benzimidazolyl-methyl) amine (a), bis(2-benzimidazolyl-phenyl) amine (b), bis(2-benzimidazolyl-methyl-6-sulfonate) amine (c), and bis(2-benzimidazolyl-phenyl-6-sulfonate) amine (d).^{1}H, ^{13}C NMR, UV-visible, IR, metal analysis, conductivity, and magnetic susceptibility measurements were used to identify all the compounds. *In vitro* anti-bacterial and anti-fungal activities were determined by agar well diffusion process (Scheme 10).

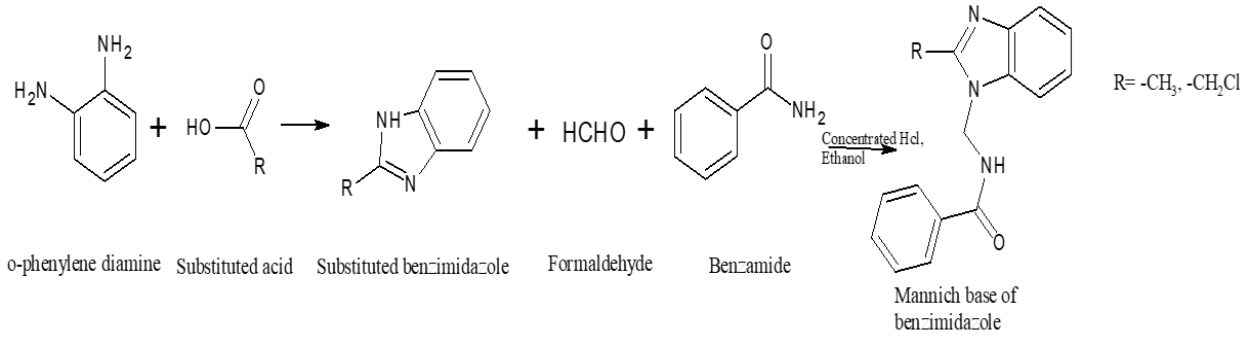
Vinothkumar *et al.* (2018) by refluxing a solution of o-phenylene diamine and an amino acid for two hours, 2-substituted benzimidazoles were formed. Refluxing a solution of 2-substituted benzimidazole (0.005 mol) in 10 ml ethanol, secondary amine like dimethylamine, diethylamine(0.005 mol), and formaldehyde (0.005 mol) for eight hours yielded the mannich bases of 2-substituted (phenyl, aminomethyl, Ethanamine, phenylethanamine, methyl butan-1-amine) benzimidazole derivatives were shown in Scheme 11. Physiochemically, IR, ^{1}H NMR spectral data, and *in silico* prediction were



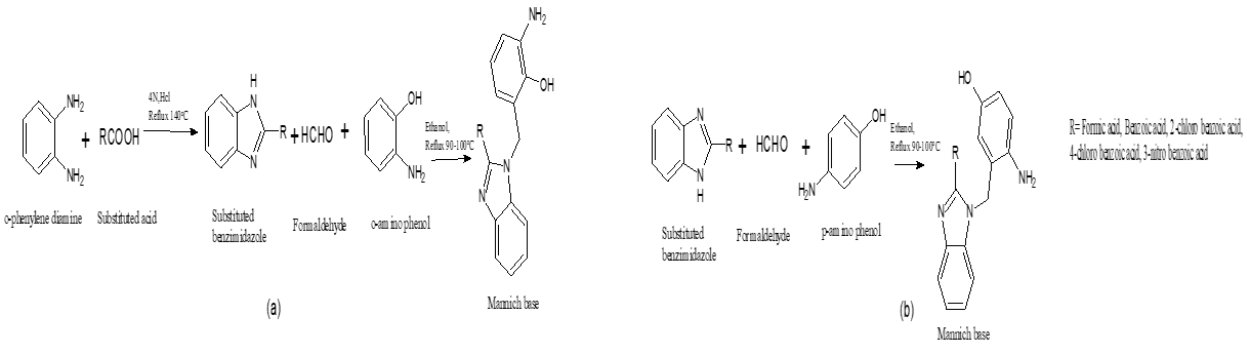
Scheme 6: Synthesis of mannich bases of 2-substituted benzimidazole derivatives



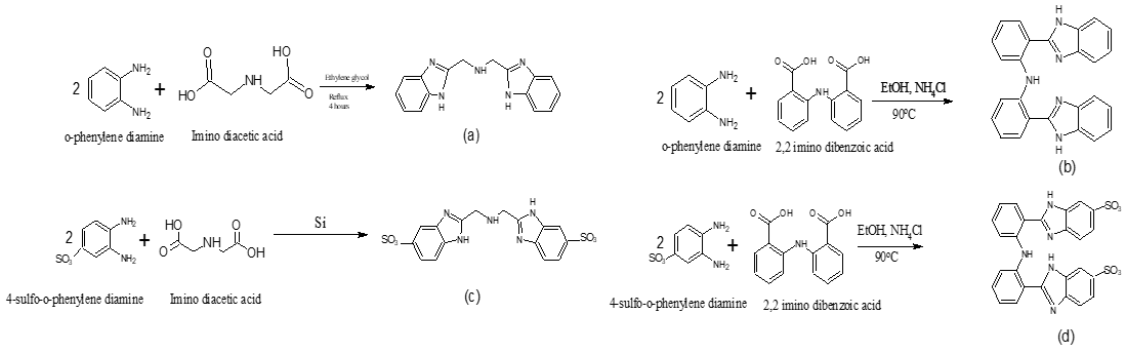
Scheme 7: Synthesis of novel benzimidazole derivatives using mannich base



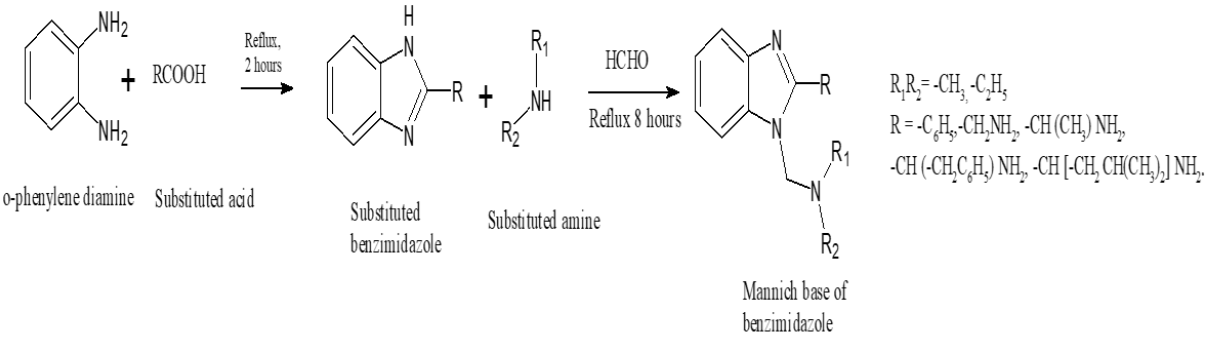
Scheme 8: Synthesis of mannich base of 2-substituted benzimidazole



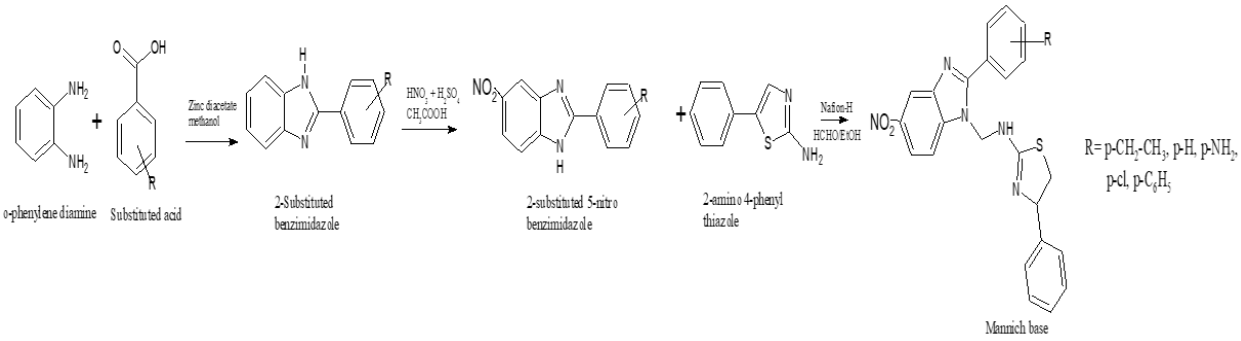
Scheme 9: Synthesis of mannich base of benzimidazole derivatives



Scheme 10: Synthesis of bis benzimidazole derivatives



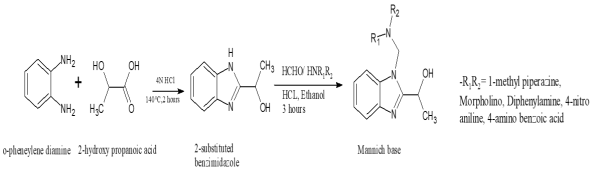
Scheme 11: Synthesis of 2-substituted benzimidazole derived mannich bases



Scheme 12: Synthesis of mannich base having benzimidazole moiety

used to characterize the synthesized compounds.

All the compounds were tested for antibacterial and antifungal activity, and the findings showed promising results.



Scheme 13: Synthesis of mannich bases of 2-substituted benzimidazole

Suryawanshi (2019) synthesized substituted benzimidazole from o-phenylene diamine and substituted acid in the presence of zinc diacetate, nafion-H on further treatment with 2-amino 4-phenyl 1,3 thiazole yields N-(5-nitro)-2-substituted 1H-benzo[d]imidazol-yl-substituted-4-phenyl thiazol-2-amine derivatives (Scheme 12).

Marinescu *et al.* (2020) reported that 1-(1-[(4-substituted-1-yl) methyl)-1H-benzo (d)imidazole-2-yl] ethanol (Scheme 13) was generated by heating o-phenylene diamine (50 mmol), 2-hydroxy propanoic acid (50 mmol), and 4N HCl at 140°C for two hours. The mannich bases were made by refluxing a solution of 1- [1H-benzo imidazol-2yl] ethanol (10 mmol), formaldehyde (10 mmol), and the corresponding amines (1-methyl piperazine, morpho-

line, diphenylamine, 4-nitroaniline, 4-amino benzoic acid) (10mmol)final products were investigated using ^{1}H NMR, ^{13}C NMR, FTIR spectra, and elemental analysis.

CONCLUSION

These results provide new possibilities for developing novel drug mannich bases of benzimidazole derivatives to combat the growing problem of drug resistance, as well as a prototype lead for further optimization and growth. For medical study, benzimidazole derivatives are a valuable resource. Mannich base benzimidazole derivatives provide a promising avenue for developing pharmacological activity while reducing toxicity. Mannich base derivatives may easily replace pathogenic resistant drugs currently in use. The biological profile of drug molecule is greatly enhanced when two or more heterocyclic moieties are fused or connected. Mannich bases of benzimidazole derivatives were found to have more potent and effective pharmacological activities.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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