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

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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 benz fused 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), Antulcer (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), 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.

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 characterized 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.

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.
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 4](image)

**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 microbroth 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 Krishnananjeyulu et al. (2014). 1-{[(1H-benzimidazol-1yl) methylamino] phenyl}-3-substituted prop-2-en-1-one(2) was synthesized by reacting 1-{[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) 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 diphenyl-2-picryl-hydrazyl radical method. Antioxidant activity was observed in all the synthesized compounds.

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

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-y)]methyl)-1H-benzo (d)imidazol-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

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