Mannich Bases of 2-Substituted Benzimidazoles - A Review

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Abstract: Mannich bases are the end products of mannich reaction and are known as beta amino ketone carrying compounds. Mannich reaction is a carbon carbon bond forming nucleophilic addition reaction which helps in synthesizing N-methyl derivatives and many other drug molecules. Mannich base derivatives of benzimidazoles possess many pharmacological properties such as anti-oxidant, anti-inflammatory, anticancer, antiviral, anthelmintic and play an important role in medical field. As these drugs are clinically useful in treatment of microbial infections and exhibit other therapeutic activities also, so this encouraged the development of more potent, novel and clinically significant compounds. In this review synthesis and various biological activities of new mannich bases of benzimidazole derivatives reported is discussed.

Keywords: Mannich Bases, Substituted Benzimidazoles, Pharmacological Activities.

1. INTRODUCTION

The fusion of benzene and imidazole forms a heterocyclic aromatic organic compound called Benzimidazole which is bicyclic in nature. It is an important pharmacophore and a privileged structure in medicinal chemistry. Heterocyclic compounds are more biologically active as compared to others (Padmavati...
Benzimidazole is one such compound which attract the attention of synthetic chemists for the designing more potent Benzimidazole derivatives having wide diverse of biological activity (Walia et al., 2011).

Literature reveals that benzimidazole-containing compounds show biological activities as anti-allergic agents (Nakano et al., 2000), PARP inhibitors- as anticancer agents (White et al., 2000) and as cytomegalovirus (HCMV) inhibitors (Zhu et al., 2000). They are also reported as anthelmintic agents and in diverse human therapeutic areas such as treatment of ulcers, anti inflammatory agents and as antihistaminics (Spasov et al., 1999). Benzimidazole derivatives are named as “privileged sub structures” for drug design because of their diverse uses (Evans et al., 1988; Mason et al., 1999).

Mannich reaction has been studied by several groups of workers in the field of medicinal chemistry, mainly because of the various pharmacological properties of the Mannich Bases so formed. A variety of Mannich Bases have been reported to possess analgesic (Malinka et al., 2005), anti-inflammatory (Kalluraya et al., 2005; Koksal et al., 2007), local anaesthetic, anticancer (Ivanova et al., 2007; Gul et al., 2000), anti convulsant (Vashishta et al., 2004), antipsychotic (Scott et al., 1992), antiviral (Edwards et al., 1983), anthelmintic (Bennet et al., 1996), antimalarial (Barlin et al., 1990), antibacterial (Ashok et al., 2007; Pandeya et al., 2000), antifungal (Pandeya et al., 2000; Singh et al., 2007) and several other activities. The earliest examples of the Mannich reactions were published in succession by Tollens and co-workers, Petrenko Kritschenko and by Mannich and Krosche. Mannich was the first to recognize reaction as the general one and a detailed investigation began in 1917 (Thompson et al., 1968).

1.2 MANNICH REACTION

\[
\begin{align*}
\text{H} \quad \text{C} - & \quad \text{H} \quad + \quad \text{NH}_4\text{Cl} \quad + \quad \text{CH}_3\text{C} - & \quad \text{R} \quad \xrightarrow{\text{H}^+ \text{ or } \text{OH}} \quad \text{H}_2\text{N} \quad \text{C} - & \quad \text{CH}_2\text{CH}_2\text{C} - & \quad \text{R} \\
\text{O} & & & & & & \text{O}
\end{align*}
\]

In Mannich reaction, formaldehyde or paraformaldehyde is condensed with ammonia in the form of its salt and a compound containing active hydrogen. This may formally be considered as an addition of ammonia to give $\text{H}_2\text{N}-\text{CH}_2\text{-OH}$, followed by a nucleophilic substitution. Instead of ammonia, the reaction may be carried out with salts of primary or secondary amines or with amides, in which cases the product is substituted on the nitrogen with $\text{R}$, $\text{R}_2$ and $\text{RCO}$ respectively (March, 1992).
Mechanism of formation of Mannich Bases (Cummings et al., 1960).

**The Acid Catalysed Reaction**

\[
\begin{align*}
\text{H--C--H} + (\text{R}_2\text{NH}) & \rightarrow \text{H--C--H} + \text{H}_2\text{C}==\text{C--R'} \\
\text{(A)} & \rightarrow \text{H} & \rightarrow \text{H} \\
\text{OH} & \rightarrow \text{OH} & \rightarrow \\
\text{N(R)₂} & \rightarrow \text{N(R)₂} & \rightarrow \\
\text{H--C--H} & \rightarrow \text{H--C--H} & \rightarrow \\
\text{C=O} & \rightarrow \text{C=O} & \rightarrow \\
\text{R'} & \rightarrow \text{R'} & \rightarrow \\
\end{align*}
\]

Mannich Bases possess several pharmacological properties which may be due to their reactive chemical nature, so they can be easily transformed into numerous other compounds. Studies on the chemistry of Mannich Bases are of interest in various areas of application. A large number of amino alkyl derivatives have been prepared in order to correlate their structure with pharmacological activities. The examples of clinically useful mannich bases having amino alkyl chain are cocaine, atropine, trihexiphenidyl, procyclidine, ranitidine, ethacrynic acid, fluoxetine, biperiden (Racane et al., 2001; Ashiyama et al., 1999; Bhusare et al., 2001).

2. MANNICH BASES OF BENZIMIDAZOLE DERIVATIVES

1) Some secondary amines (4-methyl morpholine, diethylamine, 1,4-dimethylpiperazine) and formaldehyde were used for the synthesis of Mannich base derivatives of benzimidazole (1). The synthesized compounds were then checked for their anti microbial activity against gram positive and gram negative bacterial strains, yeast and fungi. Some of the synthesized compounds were found active against bacterial strains but none of the compound was active against yeast and fungi (Araf et al., 2000).
Benzimidazole salicylic acid Mannich base (2) was synthesized by the reaction of benzimidazole, 4-amino salicylic acid and formaldehyde. Complexes of Mannich bases with transition metals were also prepared and studied (Kamlesh et al., 2009).

Derivatives of 1,2 disubstituted benzimidazole were synthesized by employing Mannich base reaction. Diamine and glycine in acidified ethanol were first heated and then substituted benzimidazole was dissolved in secondary amine and formaldehyde (Anil, 2009).
4) Novel series of N-mannich base derivatives of 3,4 dihydropyrimidine-2-H-one (4) with different heterocyclic amines and formaldehyde was also synthesized. All the compounds showed good biological activities against two bacterial and two fungal strains (Shah et al., 2009).

![Mannich Bases of 2-Substituted Benzimidazoles - A Review](image)

\[ R_1 = \text{OH, } R_2, R_3 = \text{H} \]

R=Benzimidazole, 2-methyl benzimidazole, 2-phenyl benzimidazole, benzotriazole, Pthalimide, Morpholine, Tetrahydrocarbazole

5) Various derivatives were synthesized. All the synthesized compounds were evaluated for anti-inflammatory and analgesic properties. All the compounds showed good corneal penetration but some of the compounds were found even more potent than paracetamol and diclofenac (Jasudason et al., 2009).

![Diagram](image)

\[ R_1 = \text{H,CH}_3,\text{CH} = \text{CHC}_6\text{H}_5 \]

\[ R_2 = \text{N(C}_3\text{H}_3)_2,\text{N(C}_2\text{H}_5)_2,1\text{-methylpiperiine, 4-methylmorpholine} \]
6) Mannich bases of 2-substituted benzimidazole derivatives (6) were synthesized by the reaction of amino phenyl acetic acid and ortho phenylene diamine, they were then reacted with formaldehyde and secondary amine (dimethyl amine) and evaluated for anti-inflammatory activity (Reddy, 2010).

7) Secondary amine, 2-substituted phenyl benzimidazoles and formaldehyde were employed for the synthesis of novel manich bases (Elrafi et al., 2010).

8) Some active hydrogen containing compounds such as sulphamethoxazole, sulphamidine, sulphadimidine, 2-amino pyrimidine, Pthalimide, benzamide, anthranilic acid were reacted with formaldehyde and benzimidazole to synthesize N-substituted benzimidazole derivatives (8) which were then evaluated for anti HIV and antiviral activities (Selvam et al., 2010).
9) New mannich Schiff bases of 2-phenyl benzimidazole were also synthesized (9) by refluxing anthranilic acid with alkyl amide and results in the formation of 2-alkyl-4-(3H)-quinzolinone which further underwent mannich reaction. All the compounds showed good potency towards antimicrobial agents (Misra et al., 2010).

10) Mannich base derivatives of benzimidazoles (10) were synthesized through cyclization reaction. All the compounds were evaluated for anti microbial activities. Some of the compounds emerged as moderate antibacterials whereas some possessed negligible antifungal activitiy (Saraswathi et al., 2010).
11) Novel mannich bases of 2-substituted benzimidazole (11) were synthesized by reacting orthophenylene diamine with carboxylic acid for 6-8 hrs at 100℃ and then mannich base was formed by reacting the above formed product with diethylamine and formaldehyde (Murugesan et al., 2011).

12) A series of 2-ethyl benzimidazole derivatives (12) have been synthesized by the condensation reaction of benzimidazole, primary and secondary amine and formaldehyde (Mariappan et al., 2011).
13) N-Mannich bases of benzimidazolyl substituted 1H-isoindole-1-(2H)-dione were synthesized (13). All the synthesized compounds were screened for anthelmintic activity. Piperazine hydrochloride was used as standard drug. All the synthesized compounds showed significant anthelmintic activity where as the derivatives substituted with piperazino, morpholine, diphenylamino, chloro, nitro and dinitro groups showed better activity than other derivatives (Rita and Shrivastava, 2012).

14) New derivatives of [1-(N,N-disubstituted)amino methyl-2-(2,4-dinitrophenyl) sulphonyl]-6-substituted-1 H-benzimidazoles (14) were synthesized by mannich reaction on 2-[(2,4 dinitrophenyl)sulphonyl]-5(6)-substituted-1 H-benzimidazoles with appropriate secondary amine and paraformaldehyde in presence of conc. hydrochloric acid in ethanol. The synthesized compounds were evaluated for analgesic and anti-inflammatory activity (Mohan Rao et al., 2013).

15) A series of mannich bases of 2-substituted benzimidazole derivatives were synthesized. The preliminary in vitro antibacterial and, antifungal
toxicological screening results of novel benzimidazole derivatives [5(A-G) a, b] reported good to moderate antimicrobial activity. The compound 5E (a) and (b) exhibited broad spectrum of antibacterial activity and antifungal activity (Kumar et al., 2013).

Two Mannich bases 1-(1H-benzimidazolyl) methyl urea (BIUF) and 1(3-Hydroxynaphthlen-2-yl) methyl thiourea (TNTUF) (16, 17) were synthesized and evaluated for antioxidant activity by employing hydrogen peroxide radical scavenging, DPPH radical scavenging and reducing power assays (Chakkaravarthi et al., 2013).
17) A series of mannich bases of benzimidazole derivatives were synthesized from o-phenylenediamine in two steps via benzimidazole intermediates. The anti fungal and anti bacterial activities of synthesized compounds 3a-c (18, 19, 20) were also checked and it was found that compounds 3a, 3b and 3c showed excellent antibacterial activity and compound 3a showed good antifungal activity than others (Aanadhi et al., 2013).
18) A series of novel manich bases of 2-substituted benzimiazoles were synthesized by the reaction of 2- substituted benzimidazoles with corresponding aldehyde and acetophenones and evaluated for analgesic and anti-inflammatory activity (Kumar et al., 2015)

CONCLUSION

As demonstrated by the frame of work reviewed in this paper, Mannich bases and their derivatives are found to have diverse activities. This review summarized various biological activities of manich base of 2- substituted benzimidazole derivatives. It can be concluded that synthesis of manich base derivatives provides a good opportunity to medicinal chemists for evolving better drugs with lower cytotoxicity.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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