RESPONSE OF ORCHID CUT FLOWERS AS AFFECTED BY FLORAL PRESERVATIVES ON THE POSTHARVEST QUALITY

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ABSTRACT

Heterocyclic derivatives exhibit broad pharmacological properties and numerous drugs are used clinically having main heterocyclic frame. They are remarkable category of compounds for new drug development. The trio-component combination of mannich bases, by the reaction between benzimidazole and Schiff bases and their physiological evaluation declare them as most promising anti-bacterial, anthelmintic, anti-malarial, anti-inflammatory anti-cancer, anti-fungal, anti-oxidant and anti-viral agents. The Schiff base system also seems to reveal prominent catalytic activity in countless reactions and in the emergence of moisture. The coordination chemistry involving Schiff base system has also gain attention in current scenario because of its marvelous effect on analytical, biochemical industry. Mannich bases contain aminoalkyl chain hence they are also called as aminoalkylation reactions. The pharmacological action of mannich bases is designated to β unsaturated carbonyl group that can also be created by de-amination of hydrogen atom of the amine group. Synthetic utility of mannich base is known from recent times as they are used ligands for multiple receptors also in manufacture of leather and in industry of petroleum. The review on the whole narrates the literature survey that has revealed the mannichand schiff base as efficient biologically active molecules. New derivatives of schiff and mannich bases of benzimidazole accompanied by their patents have been studied in this review.

Keywords : Benzimidazole, schiff base, mannich base, antimicrobial activity, anti-cancer activity, published patents.

Introduction

Benzimidazole segment linked to a heterocyclic complexes a significant chemical class as a result of their marvelous biological actions (Tahlan et al., 2019). Benzimidazole scaffold is a biological macromolecule in recent drug development and its derivatives constitute major pharmacological profile with elite structures in heterocyclic chemistry (Chaudhari et al., 2014). Some analogues of benzimidazole such as albenzazole, mebendazole, omeprazole, bendamustine had gain attraction of many researchers and have been a drug of choice. Benzimidazole is a derivative of imidazole utilized in the progress of medicinal agents (Keshav and Wadoke, 2017). Its merged heterocyclic layout leads to the development of nucleic acid as they form the core of nitrogen bases (Ahmedi, 2016). The alluring pharmacological action of benzimidazole and its substituents are noticed in case of countless microbes and germs which include some viruses, fungi and bacteria.

Further more, Schiff bases are chief category of organic compounds. They were announced firstly by HugoSchiff in 1864 (Bala et al., 2013). They are nitrogen analogue of a ketonic or aldehydic group in which replacement of carbonyl compound is done by imines or azomethine substructure. They are designed by the condensation of aldehydes or ketones along with amino group. They are extensively used hetero compounds and have immense biological activities including anti-inflammatory, anti-bacterial, anti-viral, anti-fungal, anti-malarial, anti-oxidant etc. They are widely used as catalyst, complexing agents and in dyes and pigments (Ahmed et al., 2015). In addition to, they are a paramount class of compounds that manifest concern in manufacturing industries with numerous pharmacological and medicinal pertinence. They are acquired by a condensation reaction amongst carbonyl group with primary amines in alcoholic solution (Kalaraani et al., 2020). Search for new therapeutic aromatic schiff base hybrids have revealed more prospective in biological pertinence because of the delocalization of free electrons within the cyclic structure. Analogues of schiff bases comprehending benzimidazole nucleus have correspondingly been utilized in binding and cleavage of DNA segment as they are also characterized as inhibitors of topoisomerase with anticancer and antitumour applications (Fonkui et al., 2019).
Alternatively, mannich bases are the termination products of mannich reaction and are also recognized as beta-amino ketones formed by nucleophilic addition reaction where tri component condensation occurs amid a substrate with active hydrogen, an amine and an aldehyde (Kumar et al., 2013). These bases are reactive in nature and have multiple pharmacological activities such as anti-microbial, anti-cancer, anti-viral, anti-inflammatory, anti-convulsant, anti-oxidant (Marinescu et al., 2020). Moreover, mannich bases prepared from 2-substituted benzimidazoles would likely result in compounds having high biological activities towards many diseases. Mannich base which have amino alkyl side chain act as imperative bioactive molecule or pharmacophore which is further utilized for preparation of innumerable potential drugs of high medicinal value (Sethi et al., 2015). The instances of beneficial mannich bases utilized clinically encompassing amino-alkyl side chain are atropine, cocaine, ranitidine, procyclidine. Mannich bases are acknowledged to play a dynamic role in the progression of synthetic pharmaceutical chemistry.

**General Scheme for the synthesis of Schiff base**

Schiff base can be prepared from an aromatic or aliphatic amine and carbonyl group by nucleophilic addition reaction followed by production of an imine i.e., Schiff base. It is also called as a condensation reaction and is considered a sub class of imines which also embraces the involvement of various solvents like methanol, dichloroethane and tetrahydrofuran (Tadele et al., 2015).

![Fig. 1: General scheme for the synthesis of Schiff base derivatives](image)

**General scheme for the synthesis of Mannich base**

Mannich bases are beta amino ketone compounds formed from nucleophilic addition reaction, which comprises of condensation of substrate that carries an active hydrogen molecule, a formaldehyde and an amine. The terminal product formed is beta amino carbonyl derivative which have broad pharmacological activities (Singh et al., 2013).

![Fig. 2: General scheme for the synthesis of mannich base derivatives](image)

**Pharmacological activities of Schiff base analogues of 2-substituted benzimidazole**

**Antibacterial activity**

A novel sequence of schiff base analogues were prepared and have been pointed as promising antibacterial agents. The compounds have been analyzed against eight gram negative i.e., E. coli, E. cloacae, K. oxytoca, E. aerogenes, P. vulgaris, K. oxytoca, K. pneumonia, P. Mirabilis and six gram positive bacteria like S. epidermidis, S. aureus, B. cereus, M. smegmatis, B. subtilis, E. faecalis using broth dilution technique. The MIC of the compounds were compared with reference antibiotic agent such as streptomycin and nalidixic acid. Compounds (1a-c) displayed greater antibacterial activity (Fonkui et al., 2019).

![Schiff base analogues](image)

Several schiff base derivatives of 2-substituted benzimidazole derived from aminophenol, 5-chlorosalicylaldehyde and benzene-1,2-diamine including various methyl, chloro and nitro groups were prepared (Alterboni et al., 2020). Antimicrobial screening of the synthesized hybrids was done towards several bacteria i.e., K. pneumonia, E. coli, S. aureus, P. aeruginosa, P. mirabilis, S. epidermidis and some fungi like C. parapsilosis and C. albicans. Reports found that some of the benzimidazole Schiff base derivatives (2a-c) were found to have good antimicrobial activity.

![Compounds](image)

Furthermore, a new molecule (3) was synthesized and antimicrobial action of the compound was analyzed in vitro agar diffusion test counter to some strains like E. coli, P. aeruginosa with agar nutrient. In addition to, antifungal action was performed against C. albicans.Cu(II), Zn(II) and Co (II) complexes of schiff base ligand 2-(1H-Benzoz[d]imidazole-4yl imino) methyl phenol were prepared and tested for their antifungal and antimicrobial activity (Zoubi et al., 2013). The antimicrobial action of the complexes exhibited good efficiency against all bacterial and fungal strains.
Anti-Cancer Activity

Some novel schiff base metal complexes (4-5) containing 2-substituted benzimidazole moiety were prepared through the reaction of substituted aniline with distinct cyclic aldehydes. The in vitro antineoplastic activity of the various prepared hybrids was assessed towards diverse human carcinoma unit (HepG2, A549 MCF-7) using Sulforhoamine assay. They exhibited excellent cytotoxic properties especially with Zn II complex and Ni II complex in in vitro testing, after getting in vitro promising results, evaluation of their antineoplastic action in vivo in mice bearing Ehrlich Ascites Carcinoma model was done (Din et al., 2011).

Antioxidant Activity

Various new schiff bases derivatives including 2 -substituted benzimidazole scaffold were prepared by one step reaction method of 2-aminobenzimidazole with ketone under green chemistry. These compounds were evaluated as inhibitors of lipoxgenase enzyme. The compounds were further examined for antioxidant activity by in-vitro technique (Neochoritis et al., 2011). Seven new schiff base derivatives were prepared (6a-g) and many compounds gave significant results against lipoxgenase.

<table>
<thead>
<tr>
<th>Compd</th>
<th>R₁</th>
<th>R₂</th>
</tr>
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<tbody>
<tr>
<td>6a</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>6b</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>6c</td>
<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>6d</td>
<td>OMe</td>
<td>H</td>
</tr>
<tr>
<td>6e</td>
<td>H</td>
<td>OMe</td>
</tr>
<tr>
<td>6f</td>
<td>Cl</td>
<td>H</td>
</tr>
<tr>
<td>6g</td>
<td>-CH₃</td>
<td>-</td>
</tr>
</tbody>
</table>

Biological activities of Mannich base analogues of 2-substituted benzimidazole

Anti-inflammatory activity

Novel derivatives of 1-(N, N-disubstituted)-amino methyl-2-(2,4-dinitrophenyl)-sulphonyl]-6-substituted-1-H-benzimidazoles (7) were prepared by mannich reaction along with required amount of paraformaldehyde and secondary amine in the presence of concentrated strong acid in methanol (Mohan et al., 2013). These Compounds were screened for anti-inflammatory and analgesic activity.

\[
\text{(7)}
\]

Mannich bases containing 2-substituted benzimidazole moiety(8) were blended via the reaction of 2-substituted benzimidazoles with respective aldehydes and an active hydrogen compound and these compounds were assessed for anti-inflammatory as well as analgesic action (Kumar et al., 2013). Hybrids were found to be more potent for analgesic and anti-inflammatory activity.

Analgesic activity

Further exploration of variety of 1-(N-substituted amino)methyl]-2-substituted benzimidazole mannich base hybrids were designed and investigated for analgesic action. Several analogues (9a-c) displayed auspicious analgesic activity in comparison to the reference molecule diclofenac sodium (Datar et al., 2013).

<table>
<thead>
<tr>
<th>Compds</th>
<th>R₁</th>
<th>R₂</th>
</tr>
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<tbody>
<tr>
<td>9a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9c</td>
<td></td>
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</tbody>
</table>
Antimalarial activity

Few novel-pyrido-1[d]-benzimidazoles containing side chain of mannich base and their derivatives were prepared and investigated for in vitro anti-plasmodium action and in vivo antimalarial action in a mouse model. The following compounds showed potenti anti-plasmodium activity. Some compounds (10a-d) exhibit great antimalarial activity. Compound 10d showed greater potency and efficacy (Subramaniapillai et al., 2013).

<table>
<thead>
<tr>
<th>Comp</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a</td>
<td>4-CF₃</td>
<td>H</td>
<td>OH</td>
<td>CH₃N(CH₂CH₃)₂</td>
</tr>
<tr>
<td>10b</td>
<td>CF₃</td>
<td>H</td>
<td>CH₃N(CH₂CH₃)₂</td>
<td>OH</td>
</tr>
<tr>
<td>10c</td>
<td>CF₃</td>
<td>H</td>
<td>OH</td>
<td>CH₃N(CH₂CH₃)₂</td>
</tr>
<tr>
<td>10d</td>
<td>CF₃</td>
<td>H</td>
<td>F</td>
<td>CH₃N(CH₂CH₃)₂</td>
</tr>
</tbody>
</table>

Table 1: Published patents on Mannich and Schiff base analogues of benzimidazole scaffold

<table>
<thead>
<tr>
<th>Patent No.</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO2020047360</td>
<td>It reviews about the use of benzimidazole in the treatment of Alzheimer and Huntington incurable brain disease. It works by blocking QC inhibitors</td>
<td>(Chen et al., 2020)</td>
</tr>
<tr>
<td>US10202694B2</td>
<td>It summarises the use of 2-substituted benzimidazole as corrosion inhibitors. They protect metals against effect of corrosion in aqueous medium.</td>
<td>(Rane et al., 2019)</td>
</tr>
<tr>
<td>US8563856B2</td>
<td>It reviews about the importance of Schiff base as a complex for its use as a ligand in photoactive material.</td>
<td>(Herron et al., 2013)</td>
</tr>
<tr>
<td>EP3504303B1</td>
<td>The invention provides us information about the use of mannich base as medicinal agents and agrochemicals.</td>
<td>(Brian and Ananda, 2019)</td>
</tr>
<tr>
<td>US7935775B2</td>
<td>It reviews about the preparation of mannich base from phenolic compounds, formaldehyde and polyamines. It can be done by two stage process.</td>
<td>(Gerber et al., 2011)</td>
</tr>
<tr>
<td>US10106684B2</td>
<td>It provides information about the fluorescent Schiff base complex that are used in detecting Cu²⁺ ions. Xanthene dye is used as moiety.</td>
<td>(Helal et al., 2018)</td>
</tr>
</tbody>
</table>

Antiprotozoal activity

Nitrogen molecule pyridine in mannich base are clubbed with benzimidazole were prepared tested in-vitro for their antimycobacterial and antiprotozoal activity. Some of the compounds (IIa-IIb) were active against M. tuberculosis while others showed active potency (IIc-IId) against T. Cruzi and L. mexicana. Change in the position nitrogen atom on its pyridine ring modifies its biological activity (Patel et al., 2020).

Published patents on Mannich and Schiff base derivatives of benzimidazole scaffold

Mannich and Schiff bases of benzimidazole have been considered as privileged molecules due to their vast biological activities in various areas. Research scientists have been exploring this moiety to get a more potent drug and many patents have been published which are enlisted in Table1.

Conclusion

This review outlines the trio combination of benzimidazole substituted schiff and mannich bases which have been considered as integral class of heterocyclic compounds. These are designed and evaluated for potential treatment of multiple disorders and medical conditions. Immense growth has been made in the field of biological sector which explored them as promising anticancer and antimicrobial agents. Scientist also designed Schiff base for development in the field of biochemistry, inorganic and eco-friendly technology. Chemical modifications in structure activity relationship of mannich bases are done to improve their biological profile and medical health.

References


