REVIEW ARTICLE

Therapeutic Potential of Schiff and Mannich Bases of 2-Substituted Benzimidazole Analogues

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Received: 16th June, 2021; Revised: 07th October, 2022; Accepted: 16th June, 2023; Available Online: 25th June, 2023

ABSTRACT

Heterocyclic scaffolds reveal extensive biological profiles, and several drugs were employed therapeutically which possess heterocyclic framework. Likewise, 2-substituted benzimidazoles play a significant role in novel drug development. In addition, Mannich and schiff base derivatives of benzimidazole acknowledged them as favorable anti-inflammatory, antimicrobial, anticancer, anthelmintic, antiviral scaffolds. Schiff bases in innumerable organic reactions show affirmative catalytic activity. The current scenario also emphasizes the spectacular activity displayed by schiff bases in the biochemical, coordination and analytical industry. Similarly, aminoalkyl reactions are revealed by mannich bases as they enclose amino alkyl chain which is imperative for its therapeutic action. Mannich bases are the products of nucleophilic addition reaction with the elimination of hydrogen atom of the amine radical for its biological venture. From the latest era, the efficacy of mannich bases as ligands and in the petroleum and leather industry were perceptible. The entire review expounds the therapeutic profile of mannich and schiff bases of 2-substituted benzimidazoles as competent biologically dynamic hybrids. Neoteric analogues of mannich and schiff bases of 2-substituted benzimidazoles with their patents in diverse fields have also been summarized.

Keywords: Mannich base, Schiff base, Anticancer activity, Antimicrobial action, Patents.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.2.44

How to cite this article: Babbar R, Swikriti, Arora S, Singh TG. Therapeutic Potential of Schiff and Mannich Bases of 2-Substituted Benzimidazole Analogues. International Journal of Drug Delivery Technology. 2023;13(2):753-758.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Benzimidazole fragment associated to an organic heterocyclic compound has an efficacious spectacular therapeutic action.[1] Macromolecule benzimidazole and its derivatives possess chief biological profile with privileged analogs in heterocyclic chemistry.[2] Imidazole derivative, benzimidazole has been employed in the progression of a variety of medicinal agents.[3] Various hybrids of benzimidazole nucleus like omeprazole, bendamustine, mebendazole, albendazole have been a drug of choice for many researchers. The layout of benzimidazole analogues accomplishes analgesic and anti-inflammatory potential also.[4] Enthralling therapeutic action of benzimidazole, and its hybrids is observed in case of innumerable microorganisms which incorporate several fungal and bacterial strains.[5]

Moreover, Schiff bases are vital groups of organic molecules reported by Hugo Schiff in 1864.[6] These are analogues of nitrogen where replacement of carbonyl group is done by azomethine nucleus or imine group. The nucleophilic addition reaction of amino group with different ketonic and aldehydic molecules sketches the scaffolds. These bases are broadly unaccustomed hetero molecules with enormous pharmacological activities like antimicrobial, antioxidant, anti-inflammatory, antimalarial, autoimmune neurogenerative diseases[7] and are extensively used as complexing agents or in the formation of dyes and pigments. For manufacturing industries, they are considered as vital set of analogues with profuse biological and medicinal relevance.[8] Exploration for neoteric schiff base analogues acknowledged much more potential in pharmacological profile because of the resonance of the available electrons inside the heterocyclic configuration. Schiff base and its derivatives have been designated as inhibitors of topoisomerase employed in binding and cleavage of DNA fragments with antitumor and anticancer activities.[9]

On the other hand, mannich bases are designed by nucleophilic addition reaction of an active hydrogen compound, aldehydes, and an amine. The products created from mannich reaction are beta-amino ketones, also known as terminal products.[10,11] The reactive nature of mannich bases declare them promising biological agents with properties like

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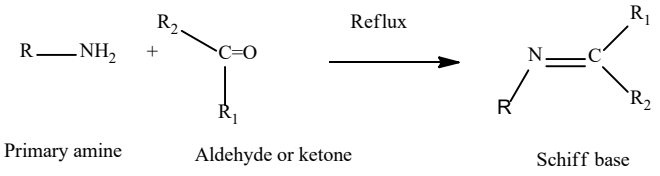


Figure 1: Methodology for schiff base hybrids

anticancer, antimicrobial, anti-inflammatory, and antioxidant.[12] Considering 2-substituted benzimidazole as a target to design mannich bases would probably result in derivatives with remarkable pharmacological activities for countless ailments. Amino alkyl side chain in mannich bases act as a vital bioactive scaffold for designing inestimable required drugs of potent therapeutic significance.[13] Ranitidine, Atropine, Cocaine are remarkable mannich bases incorporating amino alkyl side chains. In synthetic pharmaceutical chemistry, dynamic role has been accredited by mannich bases. This review aims in depth, regarding novel mannich and schiff base derivatives of benzimidazole with diverse applications in the field of modern medicinal chemistry.

General Synthesis of Schiff base and Mannich base Analogues

General method for the preparation of Schiff base

Schiff base also called as sub class of imines, are designed by nucleophilic addition reaction of aldehyde or ketone with aliphatic or aromatic amine (Figure 1). This condensation reaction also involves variety of solvents like tetrahydrofuran, dichloromethane, and methanol.[14]

Technique to produce Mannich base

Derivatives of beta amino ketones (Mannich bases) are formed by nucleophilic addition reaction which involves an active hydrogen substrate, an amine and formaldehyde (Figure 2). Product formed is β carbonyl amino derivative possessing wide range of biological properties.[15]

Biological Profile of 2-Substituted Benzimidazole Schiff Base Derivatives

Antimicrobial activity

New fangled Schiff base complexes were synthesized Figure 3 through condensation reaction between (1H-benzimidazole-2-yl)methenamine and 2-hydroxy naphthaldehyde and structures were revealed by spectral analysis. Neoteric prepared molecules against Bacillus subtilis displayed promising results, and *E. coli* followed by moderate action shown by *Aspergillus niger*.[16]

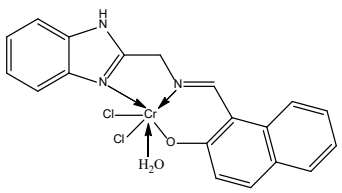


Figure 3: Compound (1)

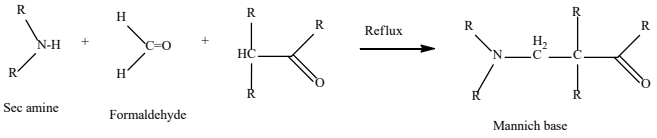


Figure 2: Technique for the synthesis of mannich base hybrids

In another study, designing and synthesis of various benzimidazole schiff base analogues was performed Figure 4 and evaluated for their antibacterial activity against various gram-positive and gram-negative bacterial strains. Scaffold N-hexyl-2-amino benzimidazole was found to be broadly active and potent amongst all.[17]

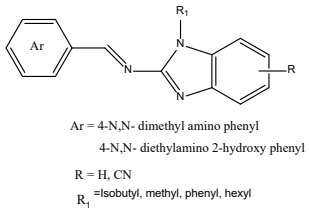
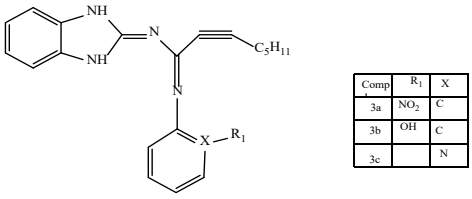


Figure 4: Compound (2)

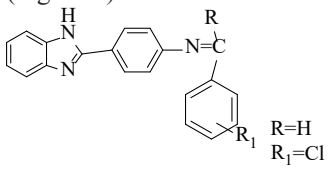
Furthermore, a series of schiff base scaffolds was designed and affirmed to be potent antibacterial agents. Analogues (3a-c) were scrutinized against diverse gram–ve bacteria like *P. vulgaris, E. coli, P. mirabilis* and some of the gram +ve microbes like *B. subtilis, E. faecalis, S. aureus* by means of microtitre dilution method. MIC values of all derivatives were analyzed and correlated with standard drugs nalidixic acid and streptomycin, respectively. Derivatives (3a-c) exhibited superior antibacterial action (Figure 5).[18]



Comp	R_1	X
3a	NO_2	C
3b	OH	C
3c		N

Figure 5: Compound (3a-c)

Similarly, preparation of 2-substituted benzimidazole schiff base analogues was done by the reaction between benzene-1,2-diamine, aminophenol and chloro salicylaldehyde incorporating a variety of methyl, chloro and nitro groups.[19] The derivatives were examined for various bacterial strains like *P. aeruginosa, S. aureus, S. epidermidis and E. coli*. and a few fungal strains *C. albicans* and *C. parapsilosis*. Analysis declared that various benzimidazole schiff base hybrids (4a-c) were established to possess superior action towards various microbes (Figure 6).



Comp	R_1	R_2
4a	CH_3	H
4b	CH_3	CH_3
4c	Cl	NO_2

Figure 6: Compound (4a-c)

Anticancer activity

Designing and synthesis of some novel benzimidazole imine ligands was done (5) and depicted for their anti-proliferative activity (Figure 7). The analogues were screened for their UV, IR, Mass, and elemental analysis. These scaffolds were examined for EAC cell lines, and few derivatives were found to display promising results.[20]

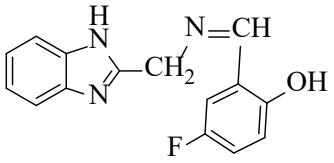


Figure 7: Compound (5)

Similarly, preparation of novel series of schiff benzimidazole hybrids was performed and these target scaffolds (6) were evaluated for their *in-vitro* cytotoxic activity against sixty cancer cell lines. Few of the derivatives were screened towards lung cancer A459, NCI-H460, out of this, few were more potent towards 4549 and NCI-H460 cell lines (Figure 8).[21]

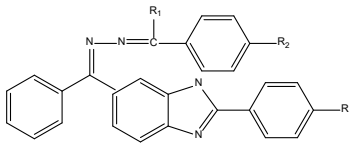


Figure 8: Compound (6)

Antioxidant activity

Under the reaction mechanism of green chemistry, various novel schiff base hybrids (7a-g) were integrated by combining ketones with 2-amino benzimidazole (Figure 9). Newfangled molecules were scrutinized by *in-vitro* technique as inhibitors of lipoxygenase enzyme.[22] Significant and remarkable results were noticed against lipoxygenase enzyme.

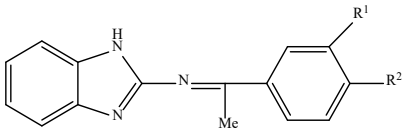


Figure 9: Compound (7a-g)

R^1= H, Me, OMe, Cl, CH_4
R^2= H, Me, OMe

Therapeutic Action of 2-Substituted Benzimidazole Mannich Base Scaffolds

Antimicrobial action

Sequence of neoteric sequence of pyrazolo-benzimidazole hybrid mannich bases (Figure 10) were scrutinized and characterized by IR, ^{13}C-NMR, ^{1}H-NMR and elemental analysis.[23] Series of compounds were analyzed against various gram +ve and gram-ve strains. Some of the molecules were potent antibacterial agents.

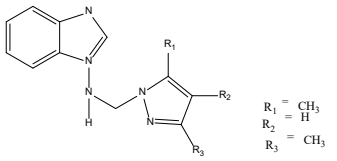


Figure 10: Compound (8)

In another research, designing and synthesis of sequence of neoteric benzimidazole mannich bases (9) was achieved via nucleophilic addition reaction between O-phenylenediamine with different aliphatic amino acids in the presence of conc. HCl.[24] Further, the cup-plate technique evaluated target derivatives for their *in-vitro* antimicrobial activity. Derivatives declared excellent action towards microbial strains (Figure 11).

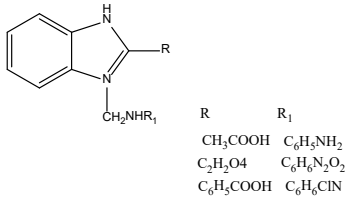


Figure 11: Compound (9)

In addition, N-Mannich derivatives of 2-phenyl imidazole (10) (Figure 12) with different amines were prepared, characterized, and screened for their anti-inflammatory action. The products were synthesized by a disconnection approach where disconnection reaction occured between a carbon and N-bond and few analogues displayed excellent results.[25]

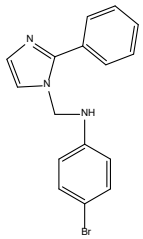
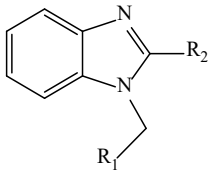


Figure 12: Compound (10)

Likewise, the analogues of benzimidazole mannich base hybrids (11a-c) (Figure 13) were prepared and were screened for analgesic action. Numerous molecules exhibited promising analgesic action in comparison to the standard diclofenac sodium.[26]



Compd	R_1	R_2
11a		
11b		
11c		-CH_3

Figure 13: Compound (11)

Table 1: Mannich and Schiff base hybrids depicting respective published patents

Patent Number	*Depiction*	*Reference*
US10106684B2	It has included the usage of xanthene dye as a moeity Several fluoresecent schiff base complexes were used to perceive Cu^{+2} ions.	[31]
US8563856B2	This patent abridged the utility of substituted benzimidazole as corrosion inhibitors. Protection in aqueous medium of metals was also emphasized.	[32]
US10202694B2	It narrated the usefulness of schiff base analogues as complex and ligand as photoactive material.	[33]
EP3504303B1	This innovation imparted us the particulars, regarding the utility of Mannich base as agrochemicals and medicinal agents.	[34]
US7935775B2	This patent highlighted the two-step procedure of preparation of mannich bases with various polyamines, formaldehyde, and phenolic groups.	[35]
US10584120B1	This patent provided us with the particulars regarding effectiveness of benzimidazole mannich bases in the management of Huntington and Alzheimer's brain ailment.	[36]

Antiprotozoal activity

A series of benzimidazole derivatives incorporating phenolic mannich side chain were designed, synthesized, and scrutinized for their antiprotozoal activity (12) (Figure 14). Results declared that *in-vivo* anti-protozoal studies against *Plasmodium berghei* displayed potent activity at stage-II and stage –III of gametocytes. Derivatives showed inhibitory effects on microtubules.[27]

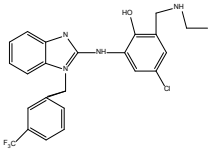
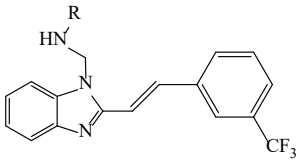


Figure 14: Compound (12)

Likewise, newfangled benzimidazole mannich bases (13) as strong anti-tubercular and anti-protozoal agents were examined (Figure 15). These novel benzimidazole scaffolds showed excellent potency against *T. cruzi* and *L. mexicana*. [28]



R= 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-methyl-2-pyridyl'

Figure 15: Compound (13)

Antioxidant activity

Novel hybrids of benzimidazole mannich bases were evaluated and screened for antioxidant potential. A small number of analogues (14) (Figure 16) were prepared by microwave and conventional methods and antioxidant action was calculated by DPPH assay and few compounds displayed significant scavenging action.[29]

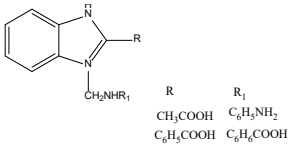
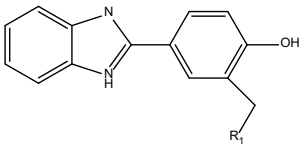


Figure 16: Compound (14)

Hybrids of benzimidazole mannich derivatives with phenolic group were assessed and examined for (15) antioxidant and anti-cholinesterase inhibitors (Figure 17). Oxidative stress was calculated by *in-vitro* technique from the brain of the rats against ferric chloride or ascorbic acid. Most of the derivatives were found to be effective radical scavengers.[30]



R_1 = Cl, Br

Figure 17: Compound (15)

Published Patents Exhibiting Analogues of Schiff and Mannich Bases of Benzimidazole Scaffold

The pharmacological profile of Schiff and mannich base of benzimidazoles have been appraised as affluent derivatives in assorted areas. Various research scientists completed a survey on this moiety to obtain more promising results and numerous patents have been published enrolled in Table 1.

CONCLUSION

This short review narrates the mixture of schiff and mannich base hybrids of benzimidazoles, regarded as the fundamental category of heterocyclic analogues. They were synthesized and assessed for prospective management of numerous disorders and medical circumstances. Immense research revealed them as favorable antimicrobial, anticancer, antiulcer, antioxidant and anti-inflammatory agents. In the growing area of inorganic, biochemical and eco-friendly domain, researchers designed novel schiff bases to attain maximum utility. Likewise, the biological profile of mannich base analogues of benzimidazole can be improved by modifying their structure-activity relationship.

ACKNOWLEDGMENTS

The authors would like to acknowledge Chitkara University for providing necessary facilities to finalize the review.

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