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A Comprehensive Review on Therapeutic Potential of Benzimidazole: A Miracle Scaffold

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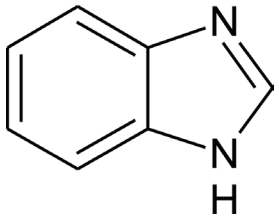
ABSTRACT

Background: Benzimidazole is a category of heterocyclic aromatic compounds formed from the fusion of six membered benzene with five membered imidazolering. The moiety possesses diverse biological and clinical applications. A number of studies have shown that a varied substituent around the benzimidazole nucleus results in pharmacologically active compounds of therapeutic interest.
Purpose: Owing to its number of pharmacological properties, this moiety is of choice of interest in designing and synthesis of new therapeutic compounds. The existence of the benzimidazole core in numerous groups of biological agents like antimicrobial, antiviral, antiparasitic, antihypertensive, anticancer, CNS stimulant as well as depressants has made important scaffold for development of many newer therapeutic agents. There is utmost need to understand the synthesis and associated role of benzimidazole derived compounds in different diseases. Therefore, in the present review, we attempt to discuss various derivatives of benzimidazole nucleus with different pharmacological activities.
Conclusion: Benzimidazoles have played a great role in discovery of drug and development. Huge attempt has been made towards benzimidazole heterocyclic-based organic compounds with great excellence that resulted in drugs with enormous biological activity. Therapeutic drugs containing benzimidazole nucleus are used in building drugs that serve to be an active area of research. This article becomes a source that will lead to discovery of new opportunities for all researchers interested in benzimidazole-based heterocyclic medicinal chemistry.

1. Introduction

Benzimidazole is an aromatic bicyclic heterocyclic ring system. It contains benzene and imidazole ring fused together at 4 and 5 position (Palit et al., 2016). They show both acidic and basic properties due to amphoteric nature of nitrogen atoms (Tahlan et al., 2019). It is a privileged macromolecule and entitled pharmacophore in medicinal chemistry. It is associated with various pharmacological and pharmacodynamic properties. Literature explored that within benzimidazole derivatives, 2-substitued compounds are identified to be pharmaceutically more effective and hence the pattern and chemistry of 2-substitued benzimidazoles become probable field of research (Chaudhari et al., 2018). This moiety **(1)** is of choice because of many pharmacological properties. Existence of benzimidazole scaffold in diverse group of biological agents such as antimicrobial, antiviral, antiparasitic, antihypertensive, anticancer, CNS stimulant as well as antidepressants has made it useful for the progression of many more therapeutic agents (Salahuddin et al., 2017). In 1960, Fort et al. described benzimidazole as proton pump inhibitors. Chemistry and evaluation of various substituted benzimidazole derivatives reported the invention of omeprazole, lansoprazole, rabeprazole, timoprazole and pantoprazole (Singh et al., 2012). Thiabendazole, mebendazole, albendazole, mebendazoleare widely used anthelmintic FDA approved drugs **(2)** which are currently available in market containing benzimidazole scaffold in their structure (Kohler et al., 2001).



Benzimidazole (1)

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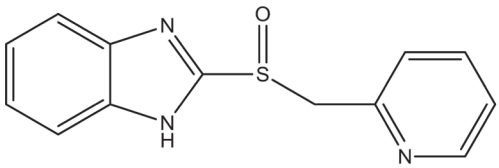
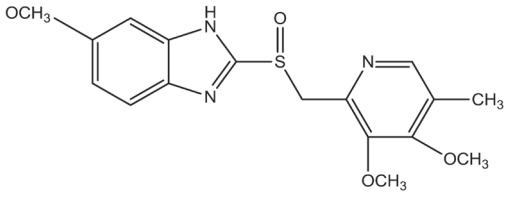
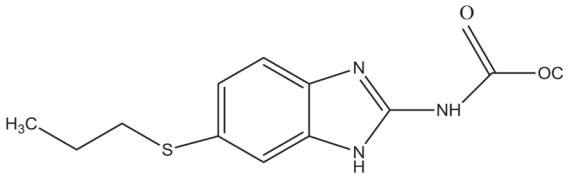


Timoprazole

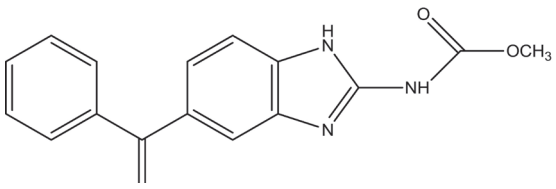
Timoprazole



OMEPRAZOLE



Albendazole

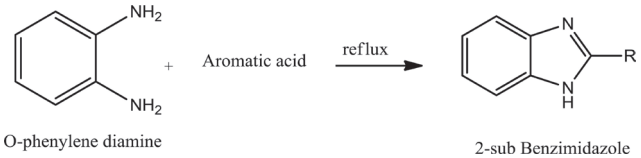


FDA Approved Drugs (2)

2. Chemistry

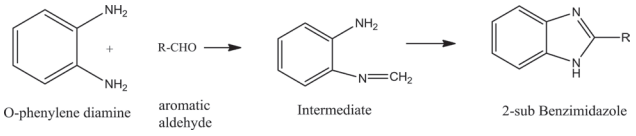
2.1. General Synthesis of benzimidazole

Benzimidazole is synthesized from o-phenylenediamine and different aromatic acids **(3)**. In this method, the diamine is initially refluxed with aromatic acid. The corresponding acid is converted into benzimidazole (Vineet and Amrita, 2017).



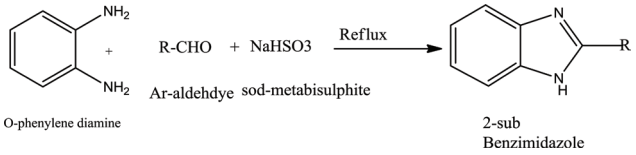
(3)

A wide range of benzimidazoles were synthesized by condensation of o-phenylene diamine with aldehydes to get 2 –substituted benzimidazoles **(4)** (Alaqeel, 2017).



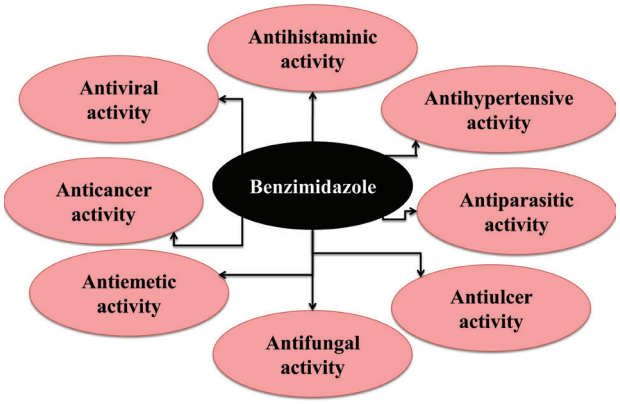
(4)

The formation of benzimidazole was done by reacting aryl aldehydes with aqueous solution of sodiumbisulphite **(5)**. The adduct of bisulphite was formed which was filtered and dried. O-phenylene diamine in DMF was added in adduct and heated for longer hours at high temperature, which was then cooled, filtered and recrystallized.



(5)

3. Pharmacological Activites of Benzimidazole



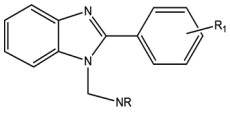
(6)

3.1. Anti-Bacterial Activity

Benzimidazole derivatives during literature survey found that, 2-substituted analogues are more dynamic and hence composition and synthesis of 2-substituted compounds are remarkable sector of research (Tahlan et al., 2019). Various 1-(substituted-methyl)-2(substituted-phenyl) benzimidazole derivatives were synthesized and reported for their antibacterial activity against bacterial strains of *S. aureus*, *B. pumillus* and *P. aeruginosa*, Compound **(7a)** revealed most potent antibacterial activity (Enumula et al., 2014).

Ghoneium et al. reported 2-(4-aminophenyl) sulphonyl derivatives of benzimidazole and screened for antimicrobial activity against *E. coli* bacterial strain by using disc diffusion method. All compounds showed antimicrobial activity **(7b).**

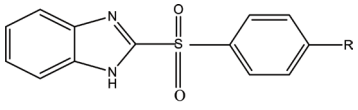
Various new benzamide benzimidazole compounds were manufactured using reaction through mannich procedure and assessed for their antimicrobial activity against *P. aeruginosa, B. subtilis, S. aureus and E. coli* Amongst all prepared derivatives, N-[2-(2-chloro-phenyl)- benzimidazol-1-ylmethyl]-benzamide,N-[2-(4-chloro-phenyl)-benzimidazol-1ylmethyl]-benzamide and N-[2-(2-bromo-phenyl)-benzimidazol-1-ylmethyl]-benzamide **(7c)** prevailed to be much productive antimicrobial compounds. Furthermore, *in simulated* studies were also done to define the interface of the suitable analogue with protein of microbe (Sethi et al., 2016).



R= piperazine, dimethylamine, diethylamine

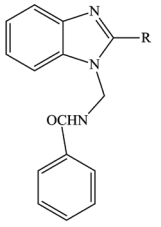
R = Cl

(7a)



R=4-NH_2 , 2,4-di-NH_2

(7b)



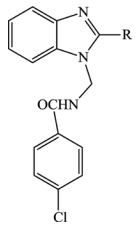
R= 2-Cl-C_6H4- ,4-Cl-C_6H_4-, 2-Br-C_6H_4-

(7c)

3.2. Anti-Fungal Activity

Fungal infections invade our tissues and spread to organs and affects the whole body that results in thoughtful attention towards new discovery and development of antifungal drugs. The invention of drug ketoconazole in 1981 by Janssen Pharmaceutical Ltd. to the search for new secured and competentagents (Keshav & Wakode, 2017).

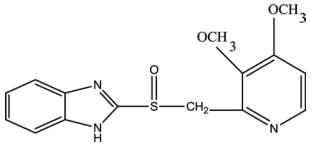
A series of novel N-(benzimidazol-1-ylmethyl)-4-chlorobenzamide derivatives were synthesized by mannich reaction and were confirmed by spectrometry and analytical techniques. Further these derivatives were also screened for their in vitro antimicrobial activity against some of the fungal strains, gram negative and gram-positive bacterial strains and also for anti-inflammatory potential. *In silico* studies were also done to show the linkage of the target compounds with protein of microbe. It was found that derivative **(8)** was found to be the most suitable antimicrobial compound among the manufactured derivatives (Sethi et al., 2018).



(8)

3.3. Anti-Ulcer Activity

Gastric acid plays an important role in gastrointestinal functions, including proper digestion, and defence against various infections. However, improper balance of acid release leads to various physiological actions that includes Acid reflux, indigestion and stomach ulcers (Olbe et al., 2003). Numerous2-[(difluro methoxy-2-pyridyl) methyl sulfinyl]-5-difluro methoxy benzimidazole substituents and were evaluated for antiulcer activity **(9)** and compounds were found to exhibit good antiulcer activity (Patil et al., 2010).

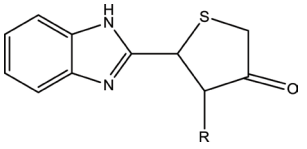


(9)

3.4. Anti-Inflammatory and Analgesic Activity

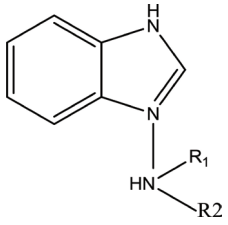
Some biological synthesized compounds having thiophene nucleus were decided to test for anti-inflammatory activity and compared with standard drug diclofenac sodium. The compounds **(10a**) showed significant effects when compared with standard drug (Suresh et al., 2011).

A series of [1-(N-substituted amino) methyl]-2 ethyl benzimidazole derivatives **(10b)** were found to have remarkable analgesic and anti-inflammatory action (Mariappan et al., 2011).



R= Cinnamaldehyde, m-nitrobenzaldehyde, m-methoxybenzaldehyde

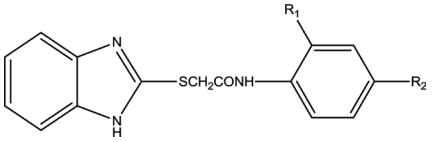
(10a)



NR_1R_2= Piperidino, 3,4-dichloroanilino, 4-floroanilino, 4-bromoanilino

(10b)

New substituted benzimidazole analogues were reported and evaluated for analgesic and anti-inflammatory activity by biological screening followed by antibacterial activity. These derivatives **(10c)** revealed prominent analgesic and anti-inflammatory activity (Gaud et al., 2011).



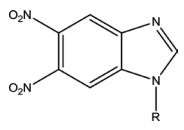
R_1= OH, NH_2R_2= CH_3,Cl

(10c)

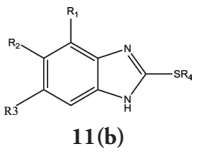
3.5. Anthelmintic Activity

Benzimidazole in parasitic infections was noticed after the invention of drug piperazine by Industry of Imperial Chemistry in the era of sixties (McFarland, 1972). The result of action of drug thiabendazole against various parasitic infections of both humans and various pet animals that gave a boost in new period of time to design new effective anthelmintic. Various benzimidazole-based wide range anthelmintic derivatives of azoles came as marketed drugs that respond by restraining the formation of micro-tubule like flubendazole, cyclobendazole, mebendazole, oxfendazole, nocodazole, albendazole (Salahuddin et al., 2012).

Some of 2-substituted benzimidazole compounds **(11a-11b**) that were screened for their anthelmintic activity were reported. All synthesized compounds showed significant anthelmintic activity. Amongst all prepared 2-substituted benzimidazole molecules, compound (**11b**) revealed greatest anthelmintic activity (Palit et al., 2016). The paralysis and death time were recorded and compared with standard drug piperazine citrate which is strong.



11(a)



11(b)

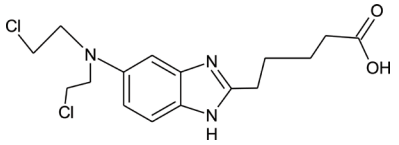
R=$CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(C_2H_5)$

R_1= R_2= R_3= H R_4= CH_2-CH_2-$N(CH_3)_2$

3.6. Anticancer Activity

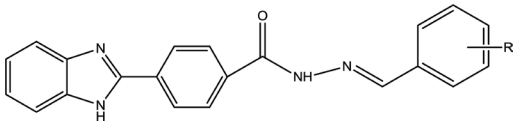
Cancer has turned out to be tougher to crack than everyone ever hoped. Major research has been concluded towards the discovery of various anti cancer therapies, including radiation therapy and chemotherapy. The mustard moiety of nitrogen molecule, a substituted benzimidazole ring, and an aromatic acid side chain containing alkane, were combined in a single molecule and synthesized which all might be liable for its chemotherapeutic action (Enumula et al., 2017). All 2-substituted compounds(**12a**) were characterized and subjected to anti-cancer activity against various cell lines of human hepato-cellular carcinogenic cell lines (HEPG2), Human Breast adenocarcinoma cell lines (MCF7) and colon carcinoma cell lines (HCT 116).

Some of the effective benzimidazole derivatives were screened for their antitumor activity and were also examined and checked by various spectrophotometric methods like IR, ^{13}CNMR, H^{1}NMR and analyzed for their antineoplastic activity against 60 different cancer cell lines. Among them 12b and 12c showed positive result against cell lines and 12 c compound was found to be more efficient because of their electron donating group substitution (Morcosset et al., 2020).



Nitrogen mustard alkylating agent

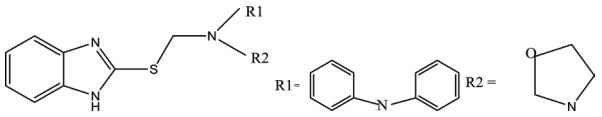
(12a)



R = 2,4 dichloro **(12b)** R = 3,4,5 trimethoxy **(12c)**

3.7. Anticonvulsant Activity

Gopal et al., synthesized series of 2-mercaptobenzimidazoles which were evaluated for their anti-convulsant action and most of these compounds **(13**) were found to be more efficient.

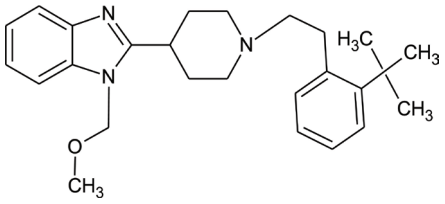


(13)

3.8. Antihistaminic Activity

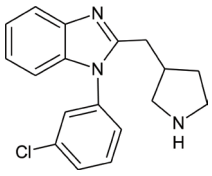
Histamine is a significant neurochemical that effects diverse physiological and patho physiological actions

in the body via activation of various receptors (Hough, 2001). Histamineis involved in inflammatory and various allergic reactions, gastric acid secretion, as well as in neuro-chemical release. The substituted benzimidazole **(14a-14b)** like bilastine, astemizole, mizolastine, emedastine, and clemizole, are performing an important role as good anti-histaminic antagonists. Some drugs were selected as good antagonist at receptor of histamine for the treatment of allergic conjunctivitis and urticaria (Walia et al., 2011). Histamine has a pathological role in maintaining the release of gastric juice in the stomach, it activates the parietal cells to release hydrochloric acid. In the 1970's, it was testified that H_2receptor antagonists blocked the action of histamine secretion in the body (Anand & Wakode, 2017). These drugs were active against the action of histamine on various cells (specifically H_2- receptors) in the stomach and limit the release of acid in the body.



BILASTINE

(14a)

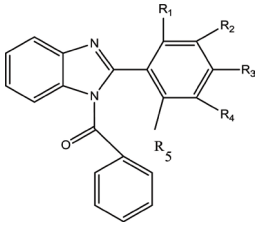


CLEMIZOLE

(14b)

3.9. Antiviral Activity

Viral infections threaten the human health including the immune system. Research has been done towards the invention of some related drugs of benzimidazole **(15)** against human herpes simplex virus, human immunodeficiency virus, and hepatitis B and C virus. An antiviral drug called Maribavir is a selective, ribosyl benzimidazole, which is used for the treatment of HCMV disease in blood stem cell. Thus, the benzimidazole nucleus can produce effective, secured and more novel drugs that fulfill the demanding urge of population with viral infections. Sharma et al. synthesized [2-(substitutedphenyl)-benzimidazol-1-yl]-pyridine-3-yl-methanones.These compounds showed great activity on viral strains (Sharma et al., 2012).

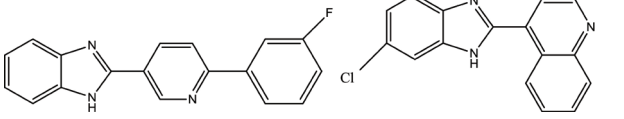


(15)

R_1	R_2	R_3	R_4	R_5
NO_2	H	H	H	H
COOH	H	H	H	H
OCH_3	H	H	H	H

3.10. Antioxidant Activity

New derivatives of benzimidazole were synthesized by the reaction of o-phenylenediamine with different aromatic aldehydes and benzoic acid. The novel analogues were characterized by FTIR and ^{1}HNMR techniques. The antioxidant assay was carried out using ABTS and DPPH method. Compound (**16a)** and (**16b)** showed good antioxidant activity when compared with Ascorbic acid (Singh & Parle, 2020).



(16a) **(16b)**

Conclusion

Benzimidazoles have played great role in discovery of drug and development. Huge attempt has been done towards benzimidazole heterocyclic-based organic compounds with great excellence that resulted in drugs with enormous biological activity. Therapeutic drugs containing benzimidazole nucleus are used in building of drugs that serve to be an active area of research. The novel experiments as well as advanced theory have been explored and used to discover various newly synthesized drugs in the future. We hopefully assume that this article will make a source that will lead to discovery of new opportunities for all researchers interested in benzimidazole-based heterocyclic medicinal chemistry.

Authorship Contribution

All the authors contributed enormously in the survey of literature review.

Conflict of Interest

The author declares no conflict of interest.

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