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Antimicrobial Properties of Benzimidazole and Mannich Bases of Benzimidazole: A Review

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Abstract: ***The chemistry of heterocyclic compounds have shown enormous pharmacological properties and consequently many drugs, all used clinically, having main heterocyclic scaffold. Benzimidazole is one such nucleus. Benzimidazole based drugs are used as Antithelminitic, Analgesic, Vasodilator, Anticancer, Antihistaminic and Psychopharmacological agent. Studies reflect that the Benzimidazole based derivatives can act as antimicrobial agent. Moreover, Mannich base derivatives of Benzimidazole are reported as better antimicrobial drugs with lower cytotoxicity. This review highlights the importance of antimicrobial properties of Benzimidazole and its Mannich base derivatives.***

Keywords: Antimicrobial, Multi drug resistant, Heterocyclic, Benzimidazole, Mannich bases

1. Introduction

Humans, being living organisms are susceptible to diseases caused by pathogens (viruses, bacteria, fungi, protozoa). The fight against these pathogens dates back to Paul Ehrlich, ―the father of chemotherapy" who used chemicals against infection[1]. By 1910, Ehrlich had successfully developed salvarsar-a synthetic antimicrobial drug. In 1945 it was replaced by penicillin with which successful antimicrobial treatment was started.

Many antimicrobial drugs are now available and majority of the infectious diseases (tuberculosis, typhoid, syphilis, leprosy, diphtheria) have been brought under control. But even after this great achievement antimicrobial therapy has become a challenge for medicinal chemist as along with their success in developing new drugs, microbes are also keeping same pace in counteracting the effects of these drugs and posing the problem of Multi drug resistant(MDR) worldwide. So this threat like situation requires continuous screening for new effective compounds having different mechanism of action from existing drugs.

1.1 Heterocyclic compounds [2]

Research documented in literature on heterocyclic compounds proved the wide spectrum of pharmacological properties occurring naturally as well as synthetically. The heterocyclic compound is a carbocyclic compound in which at least one atom other than carbon atom forms a part of the ring system. Besides the most common atoms like N, O and S, the other heteroatoms are known widely. Furthermore there is rapid rise in number of heterocyclic compounds which may be aliphatic or aromatic in nature. Both these types of compounds differ in their properties due to the presence of ring strain.

The life essential heterocyclic compounds are vitamins, antibiotics, hormones, alkaloids, synthetic drugs and dyes. Therefore, heterocyclic chemistry knowledge is useful for biosynthesis, drug metabolism, heredity and evolution. A synthetic heterocyclic compound exists as valuable intermediates in synthesis with numerous important therapeutic applications. Benzimidazole moiety has attracted attention in recent times because of its presence in Vitamin B_{12} as 5, 6-dimethylbenzimidazole which represses the growth of bacterial cells [3]

2. Benzimidazole

The first azole, Benzimidazole was the landmark discovery by Wooley in 1944[4] as antifungal agent. The first benzimidazole based drug Thiabendazole [TBZ] marketed over few decades ago [3] It was used as fungicidal and in control of nematodes and lung worms. This was followed by subsequent discoveries of Ketoconazole and Fluconazole.

Since then, Benzimidazole derivatives were successfully used to develop as Anti-inflammatory [6a], Anthelmintic [6b], Antioxidant [6c], Antineoplastic [6d] and Antiviral [6e]. The available drugs for all the activities are [6g]

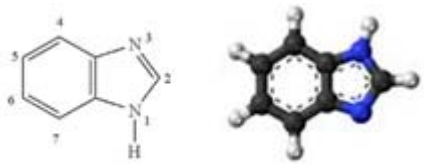
Antiulcer– Omeprazole, Rabeprazole, Lansoprazole, Pantoprazole, Esomeprazole**,** *Antithelminitic* – Thiabendazole, Mebendazole, Albendazole, Triclabendazole, Parbendazole, Cambendazole, Fenbendazole, Oxibendazole, Oxfendazole, Luxabendazole, *Antihistaminic* – clemizole, Astemizole, *Antiviral* – Enviroxime, *Uricosuric* – Irtemazole, *Anti-neoplastic* – Nocodazole, Imet 3393, *Analgesic* – Bezitramide, *Vasodilator* – Diabazole, *Psychopharmacological agent* – Benperidol, Droperidol

2.1 Antimicrobial Activity of Benzimidazole

The antimicrobial activity of Benzimidazole has been confirmed from various biological and pharmacological studies worldwide. The broad umbrella of antimicrobial activity comprises of Antibacterial, Antifungal, Antiviral and Antiparasitic agents. Benzimidazole derivatives are effective against various strains of microorganisms due to structural similarity to purine which explained its ability to compete with purines resulting in inhibition of the synthesis of bacterial nucleic acids and proteins. [7]

3. Chemistry of Benzimidazole [8]

3.1Structure of Benzimidazole



3D structure of Benzimidazole

Benzimidazole is a heterocyclic secondary amino Benzo derivative of imidazole.This compound contains imino nitrogen which is assigned position-1 and tertiary nitrogen atom is assigned position-3.The imino group (-NH) present in benzimidazole shows both acidic and basic characteristic i.e. it is strongly acidic and weakly basic therefore Benzimidazole is known to possesses both of these characteristics. Another characteristic feature is its ability to form salt either by protonation or substitution at nitrogen of imidazole ring. Unsubstituted –NH groups in benzimidazole exhibits prototropic tautomerism resulting in equilibrium mixtures of asymmetrically substituted compounds.

3.2 Chemical Reactions [9]

Benzimidazole modification by substitution: Substituted benzimidazole with fluorine, propylene, tetrahydroquinoline, cyclic compounds resulted in increased stability, bioavailability and significant biological activity. Metal complexes with heterocyclic benzimidazole and their derivatives proved to be more effective in coordination chemistry last few decades. Zinc (II) complexes with 1-benzylbenzimidazole derivatives resulted in increased antimicrobial activity. Oxadiazole substitution on benzimidazole showed antimicrobial activity(moderate antifungal activity).

$$C_6H_5COCH_3 + CH_2O + R_2NH.HCl \longrightarrow C_6H_5COCH_2CH_2NR_2.HCl + H_2O$$

4.2 Mannich Bases [11, 12]

Mannich bases are beta-amine ketones formed by nucleophilic addition in Mannich reaction. Literature studies reflect that these bases are very reactive and therefore can be converted into other compounds easily. The diverse pharmacological activities of Mannich bases and their derivatives in medicineare:

A change of amide group to anilide group on 2-phenyl benzimidazole was reported to produce antimicrobial activity. This way Benzimidazole moiety has proved to be a therapeutic agent. Although benzimidazole is a potent inhibitor of microbes but its drugs are not devoid of the side effects like toxicity, allergic reactions, less water solubility and nutritional loss. Moreover, the growing problem of resistance against microorganisms especially MDR has put pressure on medicinal chemist to screen new efficient compounds or to modify the existing drug molecules for better antimicrobial properties.

The modification of biological active compounds has been achieved by Mannich reaction and resulted into more potent products by showing better activity than its parent molecule.

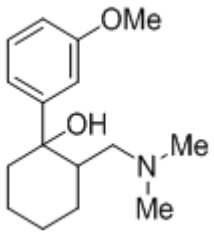
4. Mannich Reaction [10 a]

Mannich bases are the versatile synthetic intermediates formed by Mannich Reaction and find great use in medicinal chemistry. The significance of the Mannich reaction was first recognised by Carl Mannich and since then it developed into a vital reaction in the synthesis of various Pharmaceuticals and Natural products.

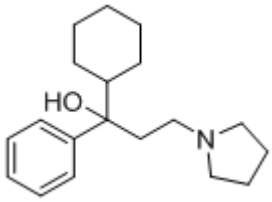
4.1 Chemistry of Mannich Reaction [10 b]

Mannich reaction is the C-C bond forming condensation reaction of ammonia, primary or secondary amine, formaldehyde and compound containing at least one hydrogen atom of pronounced reactivity.The characteristic feature of this reaction is aminomethylation (replacement of active hydrogen atom by aminomethyl or substituted aminomethyl groups).

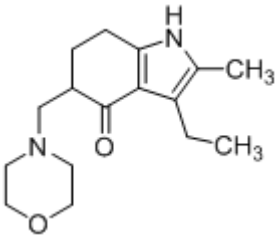
1. Analgesic- tramadol



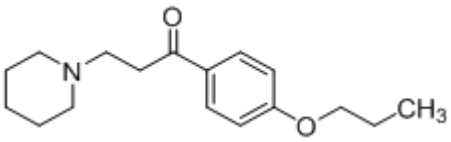
2. Antiparkinsonic -Osnervan



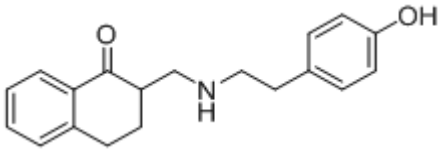
3. Neuroleptic -Moban



4. Anaesthetic- Falicain



5. Antihypertensive- Be-2254



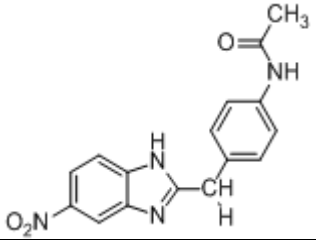
4.3 Antimicrobial Property of Mannich bases

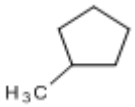
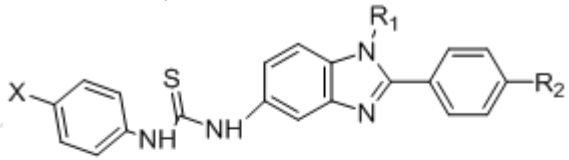
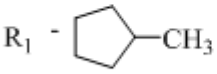
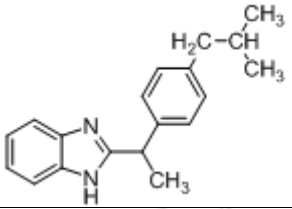
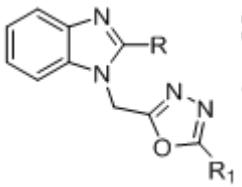
Apart from above mentioned applications chemist have found the antimicrobial properties of Mannich bases. Lorand et al. studied the antimicrobial properties of unsaturated Mannich ketones and he found that the presence of Mannich side chain increase the water solubility of unsaturated Mannich ketones[11-12].

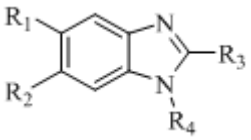
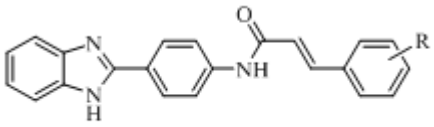
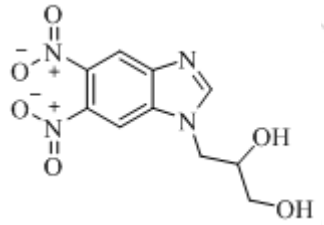
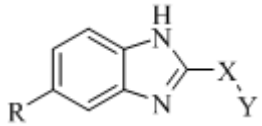
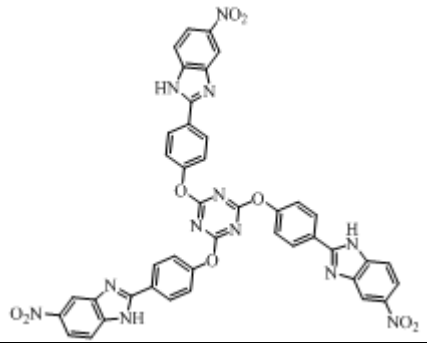
Hence, these Mannich derivatives are easily transported to the site of action and were found to be more potent than the parent molecule. He reported that the antibacterial Mannich products displayed much less cytotoxicity, which is a vital requirement for a molecule to be developed as drug.

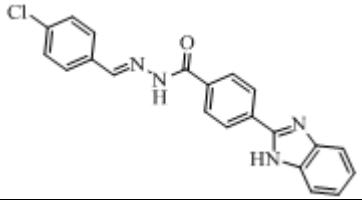
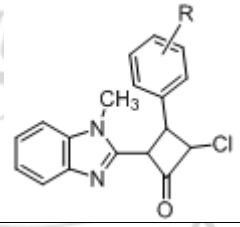
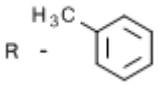
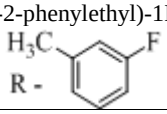
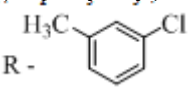
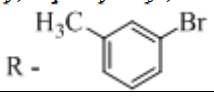
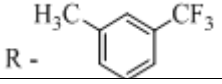
The following studies exhibits antimicrobial properties of benzimidazole and Mannich bases of benzimidazole as summarised in Table 1.

Table 1: Antimicrobial Activity of Benzimidazole and Mannich Bases of Benzimidazole [13-22]

Sr. No.	Study and year	Compounds	Reported Activity
		BENZIMIDAZOLE	
1. .	Ismail Yalcin et al(1998)	N-[4-(5-Nitro-1H-benzoimidazol-2-ylmethyl)-phenyl]-acetamide 	Antimicrobial activity
2.	GulgunAyhan-Kilcigil et.al (2006)	1-Phenyl-3-(2-phenyl-1-propyl-1H-benzimidazol-5-yl)-thiourea R1-C_3H_7, R2-H, X-H	
		1-(4-Chlorophenyl)-3-[2-(4-fluorophenyl)-3-[2-(4-fluorophenyl)-1-	

Sr. No.	Study and year	Compounds	Reported Activity
		BENZIMIDAZOLE	
		propyl-1H-benzimidazol-5-yl]- thiourea R1-C_3H_7, R2-F, X-Cl	
		1-[1-Cyclopenta-1, 3-dienyl-2-(4-fluorophenyl)-1H-benzimidazol-5-yl]-thiourea R1-  R2 F X H	
		1-(4-Chlorophenyl)-3-[1-cyclopenta-1, 3-dienyl-2-(4-fluorophenyl)-1H-benzoimidazol-5-yl]-thiourea   R_2 - F X - Cl	
3.	Anton Smith et.al(2008)	2, 3-dihydro-2-[1-(4-isobutyl-1-phenyl)ethyl]-1Hbenzo[d]Imidazole 	Antimicrobial activity
4.	K.F Ansari et al(2009)	Benzimidazole derivatives having Oxadiazole nucleus  R = H or CH_3 R1 = CH_3, -C_2H_5, - CH_2Cl, -CH_2CH_2Cl -C_6H_5, 2-ClC_6H_4	Antimicrobial activity
5.	Meral Tuncbilek(2009)	5-chloro-1-cyclopentyl-1H-benzimidazole R1-Cl, R2-H, R3-H, R4-Cyclopentyl	Potent activity against MRSA and Antifungal Activity
		5, 6-Dichloro-1-cyclopentyl-1H-benzimidazole R1-Cl, R2-Cl, R3-H, R4-Cyclopentyl	
		2, 5, 6-trichloro-1-cyclopentyl-1H-benzimidazole R_1-Cl, R_2-Cl, R_3-Cl, R_4-Cyclopentyl	
		5, 6-Dichloro-1-cyclopentyl-2-(isopropylamino)-1H-benzimidazole R_1-Cl, R_2-Cl, R_3- $NHCH(CH3)_2$, R_4-Cyclopentyl	
		2-Bromo-5, 6-dichloro-1-cyclopentyl-1H-benzimidazole R_1-Cl, R_2-Cl, R_3-Br, R_4-Cyclopentyl	
		2-Amino-5, 6-dichloro-1-cyclopentyl-1H-benzimidazole	

Sr. No.	Study and year	Compounds	Reported Activity
		BENZIMIDAZOLE	
		R1-Cl, R2-Cl, R3- NH_2, R4-Cyclopentyl	
		2-Amino-5-chloro-1-cyclopentyl-1H-benzimidazole R1-Cl, R2-H, R3- NH_2, R4-Cyclopentyl	
			
6.	Mishra et.al(2010)	Benimidazoyl chalcones: N1-[4-(1H-benzo[d]imidazole-2-yl)phenyl]-(E)-3-phenyl-2-propenamide  R - C_6H_5	Antimicrobial activity
7.	Mishra et.al(2010)	5, 6-Dinitro-1-(2, 3-dihydroxyprop-1-yl)benzimidazole 	Antimicrobial activity
8.	Mishra et.al(2010)	2-cyclopentyl benzimidazole R-H, Y- Cyclopentyl	Antimicrobial activity
		5-chloro-2-cyclopentylbenzimidazole R-Cl, Y-cyclopentyl	
		2-cyclopentylmethylbenzimidazole R-H, X-CH_2, Y-cyclopentyl	
		5-chloro-2-cyclopentylmethylbenzimidazole R-Cl, X-CH_2, Y-cyclopentyl	
		2-(2-cyclopentylethyl)benzimidazole R-H, X-C_2H_4, Y-cyclopentyl	
		5-chloro-2-(2-cyclopentylethyl)benzimidazole R-Cl, X-C2H4, Y-cyclopentyl	
			
9.	Ziya Erdem Koc et.al(2010)	Tripodal benzimidazoles 	Antimicrobial activity
10.	Yusuf Ozkay et al(2010)	4-(1H-Benzimidazol-2-yl)-benzoic acid(4-chloro-benzylidene)-hydrazide	Antimicrobial activity

Sr. No.	Study and year	Compounds	Reported Activity
		BENZIMIDAZOLE	
			
11.	Malleshappa Noolvi et.al(2011)	3-Chloro-4-(4-chlorophenyl)-1-(1-methyl-1H-benzimidazol-2-yl)azetidin-2-one R- 4-chloro	Antimicrobial activity
		3-chloro-1-(1-methyl-1H-benzimidazol-2-yl)-4-(4-nitrophenyl)azetidin-2-one R- 4-Nitro	
		3-Chloro-1-(1-methyl-1H-benzimidazol-2-yl)-4-(2-nitrophenyl)azetidin-2-one R- 2-Nitro	
		3-Chloro-1-(1-methyl-1H-benzimidazol-2-yl)-4-(3-nitrophenyl)azetidin-2-one R- 3- Nitro	
		3-Chloro-4-[4-(dimethylamino)phenyl]-1-(1-methyl-1H-benzimidazol-2-yl)-azetidin-2-one R - N, N-dimethyl amino	
		3-Chloro-4-(2, 5-dimethoxyphenyl)-1-(1-methyl-1H-benzimidazol-2-yl) azetidin 2-one R- 2, 5-dimethoxy	
		3-Chloro-4-(2-chlorophenyl)-1-(1-methyl-1H-benzimidazol-2-yl) azetidin-2-one R- 2-Chloro	
			
12.	Ozden Ozel Guuven et.al (2011)	1-(2-(Benzyloxy)-2-phenylethyl)-1H-benzimidazole 	Antimicrobial activity
		1-(2-(4-fluorobenzyloxy)-2-phenylethyl)-1H-benzimidazole 	
		1-(2-(4-Chlorobenzyloxy)-2-phenylethyl)-1H- benzimidazole 	
		1-(2-(4-Bromobenzyloxy)-2-phenylethyl)-1H-benzimidazole 	
		1-(2-(4-(Trifluoromrthyl)benzyloxy)-2-phenylethyl)-1H-benzimidazole 	

Sr. No.	Study and year	Compounds	Reported Activity
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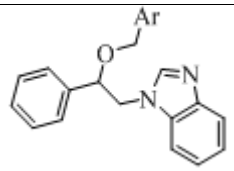
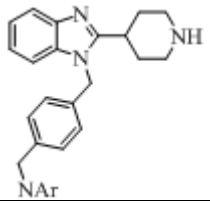
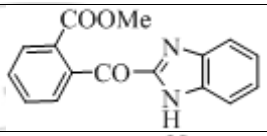
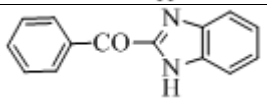
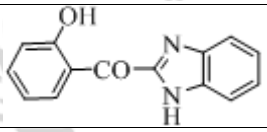
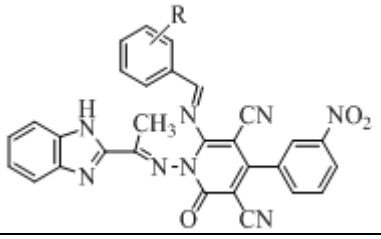
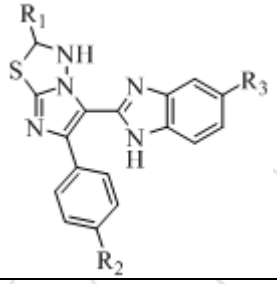
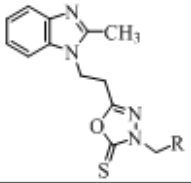
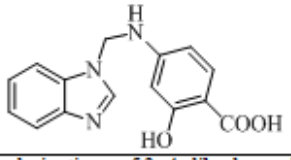
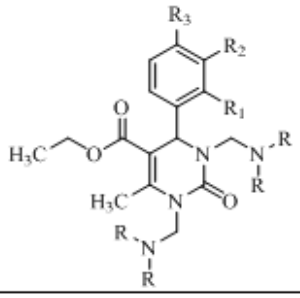
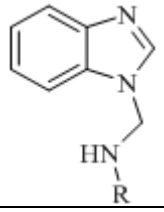
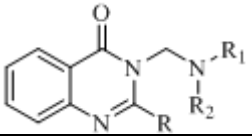
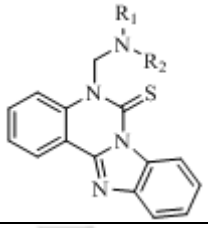
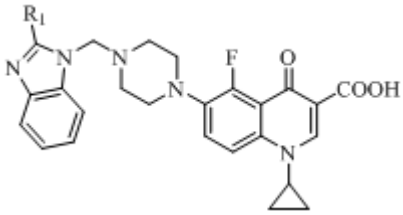
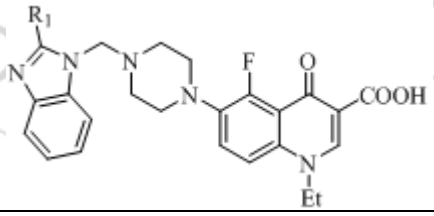
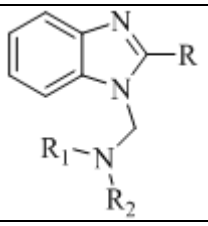
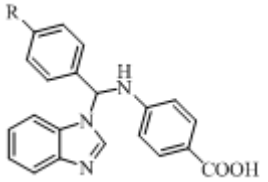
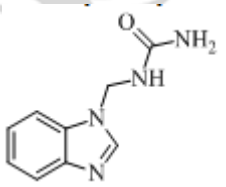
			
14.	S.L Khokhra et al. (2011)	Novel Benzimidazole derivatives	Antibacterial activity
			
15.	B.Sridivya et.al (2012)	Novel Benzimidazole derivatives by reaction with o-phenylenediamineand salicylic acid, acetyl salicylic acid, benzoic acid	Antimicrobial activity
			
			
			

Sr. No.	Study and Year	Compounds	Reported Activity
RECENT INVENTIONS ON BENZIMIDAZOLE			
1.	N.C.Desai et.al(2014)	Benzimidazole bearing 2-pyridone R = 3-F, 4-F, 3-Cl, 3-NO_2, 4-NO_2 	Antimicrobial activity
2.	Udayakumar Dalimba et.al (2015)	2-(imidazo [2, 1-b][1, 3, 4] thiadiazol-5-yl)-1H-benzimidazole derivatives 	Antimicrobial activity

Sr. No.	Study and Year	Compounds	Reported Activity
MANNICH BASE OF BENZIMIDAZOLE			
1.	A.H.El-masry et.al (2000)	Mannich base derivatives of Benzimidazole using secondary amines R = -N(C2H5)2, 4-methylmorpholine, 1, 4-dimethylpiperazine 	Antimicrobial activity
2.	Kamlesh and Arun(2009)	Benzimidazole-salicylic acid and complex of Mannich bases with transition metal. 	Antimicrobial activity
3.	T.B. Shah et al (2009)	N-Mannich base derivatives of 3, 4-dihydropyrimidine-2(1H)-one R_1=OHR_2, R_3 = HR=Benzimidazole, 2-methylbenzimidazole, 2-phenylbenzimidazole, Benzotriazole, Pthalimide, Morpholine, Tetrahydrocarbazole 	Antimicrobial activity

Sr. No.	Study and Year	Compounds	Reported Activity
		MANNICH BASE OF BENZIMIDAZOLE	
4.	P.Selvam et. al (2010)	N-substituted benzimidazole derivatives. R- sulphanilamide, Sulphadimide, Sulphamethoxazole, 2-aminopyrimidine, Pthalimide, Anthranilic acid, 2-mercaptobenzimidazole, Benzamide 	Anti-HIV, Anti-viral
5.	P.S. Misra et.al(2010)	Mannich Schiff base derivatives of 2-phenylbenzimidazole R=H, CH3, C6H5 R1, R2=CH3, C6H5 	Antimicrobial activity
6.	A.M. Saraswa et.al(2010)	Mannich base derivatives of Benzimidazo compounds R1, R2=CH3, C6H5, 4-methylmorpholine, 1-methylpiperidine 	Antimicrobial activity
7.	S.Jubie et.al(2010)	Microwave assisted benzimidazole derivatives R= H, CH2CH3, CH2CH2CH3  	Antimicrobial activity
8.	Sekar Vinoth Kumar et.al(2013)	N-mannich bases of 2-substituted Benzimidazole 3-{1-[(Dimethyl amino)methyl]-1H-benzimidazol-2-yl}-4-hydroxy benzene sulfonic acid R = C_6H_3(2-OH)(5-SO_2OH), R_1 = CH_3 R_2 = CH_3 3-{1-[(Diethyl amino)methyl]-1H-benzimidazol-2-yl}-4-hydroxy benzene sulfonic acid R = C_6H_3(2-OH)(5-SO_2OH) R_1 = C_2H_5 R_2 = C_2H_5 3-{1-[(Dimethyl amino)methyl]-1H-benzimidazol-2-yl}-4-hydroxy benzene sulfonic acid	Antimicrobial Activity

Sr. No.	Study and Year	Compounds	Reported Activity
		MANNICH BASE OF BENZIMIDAZOLE	
			
9.	Abhay Kumar Verma et.al(2014)	Novel Mannich bases of benzimidazole derivatives 4-[1H-Benzimidazole-yl(p-dimethylaminobenzal)methyl-amino]benzoic acid R=$(CH_3)N$ 4-[1H-Benzimidazole-yl(p-hydroxybenzal)methyl-amino]benzoic acid R = OH 4-[1H-Benzimidazole-yl(p-methoxybenzal)methyl-amino]benzoic acid R = OCH_3 	Antimicrobial Activity
10.	K. CHAKKARAVARTHI et.al(2014)	1-((1H-benzo[d]imidazole-1-yl)methyl)urea 	Antimicrobial activity

5. Conclusion

The antimicrobial properties of Benzimidazole based drugs provide a good opportunity to discover drugs with lower toxicity and better results. Its Mannich base derivatives could replace the existing problems associated with the drugs like resistance, toxicities and other adverse effects. Moreover, reported literature reveals the promising antimicrobial activity of such compounds. So, Mannich reaction is valuable reaction which provides Mannich bases as synthetic building blocks for the future pharmaceuticals and this review represents a small fraction of vast work associated with the Mannich reaction.

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