ABSTRACT
Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene and imidazole. Benzimidazoles are used as biochemical precursors for carbendazim (MBC) also being marketed as a fungicidal agent. After its introduction, a number of alternative benzimidazoles have found widespread use as fungicidal agents, including benomyl (BEN) and thiophanate-methyl (TM), which are precursors of carbendazim (MBC).

INTRODUCTION
All the heterocyclic compounds have a great interest in pharmaceutical chemistry. Out of these heterocyclic compounds the benzimidazole nucleus possess antiulcer, antimicrobial, anticancer, cycloxygenase inhibitor, and HIV-1 reverse transcriptase inhibitor activities.

Review Article

BENZIMIDAZOLE: A VERSATILE CHEMICAL ENTITY
P.C Santosh*, S.N. Pandeya, Ashish K. Pathak
Saroj Institute of Technology & Management, Lucknow, U.P, India

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*Corresponding author
Email: pcspharma@gmail.com

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INTRODUCTION
All the heterocyclic compounds have a great interest in pharmaceutical chemistry. Out of these heterocyclic compounds the benzimidazole nucleus possess antiulcer, antimicrobial, anticancer, cycloxygenase inhibitor, and HIV-1 reverse transcriptase inhibitor activities.

Keywords: Benzimidazole, Antiulcer Agents, Antihelmenthic, Anti-inflammatory.

COMPOUNDS HAVING BENZIMIDAZOLE NUCLEUS
As Antiulcer Agents

benzimidazole to be marketed over 40 years ago. It has been used widely for control of gastrointestinal nematodes, lungworms and as a fungicidal agent. After its introduction, a number of alternative benzimidazoles offering similar activity came to the market, such as parbendazole (PAR), cambendazole (CAM), mebendazole (MBZ) and oxibendazole (OXI). Benzimidazoles possessing sulphide and sulphoxide functional groups were subsequently introduced, offering a wider spectrum of activity and improved efficacy. Albendazole (ABZ), fenbendazole (FBZ) and oxfendazole (OFZ) were the first such benzimidazoles to be successfully used in the treatment of all growth stages of gastrointestinal nematodes. They may be used also in the treatment of lungworms, tapeworms and adult stages of liver fluke. The benzimidazole, triclabendazole (TCB) was later introduced as an antihelmenthic agent for treatment of all stages of liver fluke, but it is ineffective against nematodes. Luxabendazole (LUX) is another benzimidazole-sulphide used in the treatment of food-producing animals but is not licensed for use in the EU. The low solubility of benzimidazole sulphides and sulphoxides leads to their low absorption from the gut, resulting in low bioavailability. Nitobimin (NETO) and febantel (FEB), which are the pro-drugs of ABZ and FBZ, respectively, have greater water solubility resulting in improved absorption and increased bioavailability. Similar probenzimidazoles have found widespread use as fungicidal agents, including benomyl (BEN) and thiophanate-methyl (TM), which are precursors of carbendazim (MBC).
As Anthelmintic Drugs

2-Thiazol-4-yl-1H-benzimidazole
[Thiabendazole]

(5-Benzoyl-1H-benzoimidazol-2-yl)-carbamic acid methyl ester
[Mebendazole]

(5-Propylsulfanyl-1H-benzoimidazol-2-yl)-carbamic acid methyl ester
[Albendazole]

6-Chloro-5-(2,3-dichloro-phenoxy)-2-methylsulfanyl-1H-benzoimidazole
[Triclabendazole]

(6-But-3-enyl-1H-benzoimidazol-2-yl)-carbamic acid methyl ester
[Parbendazole]

{1-[2-(4,5-Dihydro-thiazol-4-yl)-3,5-dihydro-imidazol-4-ylidenemethyl][-vinyl]-carbamic acid isopropyl ester
[Cambendazole]
LITERATURE REVIEW

Chemical Review

A.K. Tiwari et al. (2005) reported the synthesis of N substituted 2- substituted benzimidazole. 4

\[
\text{NH}_2 + \text{HOOC-R} \xrightarrow{\text{Corboxylic acid}} \text{N} \quad \text{R} \\
\text{O- phenylenediamine} \quad \text{NaOH} \quad \text{R'-X} \\
\text{N-Substituted-2-substituted benzimidazole}
\]

R=CH₂CH₂COOH; R’=CH₂C₆H₅

Nagawade et al. (2006) reported the BF₃.OEt₂ catalyzed synthesis of benzimidazole. 5

\[
\text{NH}_2 + \text{R’-CHO} \xrightarrow{\text{BF₃.OEt₂(Cat)}} \text{N} \quad \text{R} \\
\text{O- phenylenediamine} \quad \text{R’}
\]

Wang Yulu et al. (2007) reported the p-TsOH Catalyzed synthesis of 2-arylsubstituted benzimidazoles. 6

\[
\text{NH}_2 + \text{RCHO} \xrightarrow{\text{p-TsOH,80°C}} \text{N} \quad \text{R} \\
\text{O- phenylenediamine}
\]
A. Anton Smith et al. (2008) reported the Synthesis of 2, 3-dihydro -2-[1-(4-isobutyl1 phenyl) ethyl]-IH benzo[d] Imidazole.\(^7\)

\[
\begin{align*}
\text{Ibuprofen} & \quad \text{o-Phenylediamine} \\
\text{+} & \quad \text{10\%KOH} \\
& \quad \text{Heat 2 Hr}
\end{align*}
\]

Jat Rakesh Kumar et al. (2006) reported the Synthesis of 2-substituted Benzimidazole.\(^8\)

\[
\begin{align*}
\text{o-Phenylediamine} & \quad \text{R=Alkyl/Aryl} \\
\text{+} & \quad \text{R'-OH, Acid} \\
& \quad \text{R''=H, Aldehyde}
\end{align*}
\]

Mukesh C. Sharma et al. (2010) reported the Synthesis of (1H-Benzimidazol-2-yl)-phenyl-methanol.\(^9\)

\[
\begin{align*}
\text{o-Phenylediamine} & \quad \text{Hydroxy-phenyl-acetic acid} \\
\text{+} & \quad \text{4NHCl}
\end{align*}
\]

Anoop Singh et al. (2010) reported the synthesis of benzimidazole-2-thione.\(^10\)

\[
\begin{align*}
\text{o-Phenylediamine} & \quad \text{Thiourea} \\
\text{+} & \quad \text{DMF}
\end{align*}
\]

**Biological Review**

**Antimicrobial Activity**

A. Anton Smith et al. (2008) reported the synthesis of 2, 3-dihydro-2-[1-(4-isobutyl1 phenyl) ethyl]-IHbenzo[d] Imidazole was evaluated for its antimicrobial activity against *S. aureus, E. coli, P. aeruginosa*.\(^7\)
K.F. Ansari et al. (2009) reported the synthesis of benzimidazole derivatives having oxadiazole nucleus which shows the antimicrobial activity.\(^\text{11}\)

\[
\text{N} = \text{H or CH}_3; \quad \text{R}_1 = -\text{CH}_3, -\text{C}_2\text{H}_5, -\text{CH}_2\text{CH}_3\text{Cl}, -\text{C}_6\text{H}_5, 2-\text{ClC}_6\text{H}_4
\]

Mishra et al. (2010) reported the synthesis of novel benzimidazolyl chalcones which shows the antimicrobial activity.\(^\text{12}\)

\[
\text{N} = \text{H or CH}_3; \quad \text{R}_1 = -\text{CH}_3, -\text{C}_2\text{H}_5, -\text{CH}_2\text{Cl}, -\text{CH}_2\text{CH}_2\text{Cl}, -\text{C}_6\text{H}_5, 2-\text{ClC}_6\text{H}_4
\]

Mishra et al. (2010) reported the synthesis of nitro and halogeno-substituted benzimidazole derivatives which shows the antimicrobial activity.\(^\text{12}\)

\[
\text{N} = \text{H or CH}_3; \quad \text{R}_1 = -\text{CH}_3, -\text{C}_2\text{H}_5, -\text{CH}_2\text{Cl}, -\text{CH}_2\text{CH}_2\text{Cl}, -\text{C}_6\text{H}_5, 2-\text{ClC}_6\text{H}_4
\]

Mishra et al. (2010) reported the synthesis of some novel 5-substituted benzimidazole derivatives which shows the antimicrobial activity.\(^\text{12}\)

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Y</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>cyclopentyl</td>
<td>2-Cyclopentyl benzimidazole</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>cyclopentyl</td>
<td>5-Chloro-2-cyclopentyl benzimidazole</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>CH2</td>
<td>cyclopentyl</td>
<td>2-Cyclopentylmethylbenzimidazole</td>
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<tr>
<td>Cl</td>
<td>CH2</td>
<td>cyclopentyl</td>
<td>5-Chloro-2-cyclopentylmethyl benzimidazole</td>
</tr>
<tr>
<td>H</td>
<td>C2H4</td>
<td>cyclopentyl</td>
<td>2-(2-Cyclopentylethyl) benzimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>C2H4</td>
<td>cyclopentyl</td>
<td>5-Chloro-2-(2-cyclopentylethyl) benzimidazole</td>
</tr>
<tr>
<td>H</td>
<td>C2H4</td>
<td>cyclohexyl</td>
<td>5-Chloro-2-(2-cyclohexylethyl) benzimidazole</td>
</tr>
</tbody>
</table>

Gulgun Ayhan-Kilecigil et al. (1999) reported the synthesis of 1-Benzyl-2-(4-benzylxy-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl ester which shows the antimicrobial activity.\(^\text{13}\)

Ismail Yalcin et al. (1998) reported the synthesis of N-[4-(5-Nitro-1H-benzoimidazol-2-ylmethyl)-phenyl]-acetamide which shows the antimicrobial activity.\(^\text{14}\)
Ziya Erdem Koc et al. (2010) reported the synthesis of tripodal-benzimidazoles which shows the antimicrobial activity.\(^{15}\)

\[
\begin{array}{c}
\text{NO}_2 \\
\text{HN} \\
\text{N} \\
\text{HN} \\
\text{O}_2 \text{N} \\
\end{array}
\]

Yusuf Ozkay et al. (2010) reported the synthesis of \(4-(1H\text{-Benzimidazol-2-yl})\text{-benzoic acid (4-chloro-benzylidene)}\)-hydrazide which shows the antimicrobial activity.\(^{16}\)

\[
\begin{array}{c}
\text{Cl} \\
\text{HN} \\
\text{N} \\
\text{HN} \\
\text{Cl} \\
\end{array}
\]

Meral Tunçbilek et al. (2009) reported the synthesis of some novel substituted benzimidazole derivatives having potent activity against MRSA and also showed antifungal activity.\(^{17}\)

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\end{array}
\]

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>Cyclopentyl</td>
<td>5-Chloro-1-cyclopentyl-1H-benzimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>Cyclopentyl</td>
<td>5,6-Dichloro-1-cyclopentyl-1H-benzimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>Cyclopentyl</td>
<td>2,5,6-Trichloro-1-cyclopentyl-1H-benzimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>NHCH(CH3)2</td>
<td>Cyclopentyl</td>
<td>5,6-Dichloro-1-cyclopentyl-2-(isopropylamino)-1Hbenzimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>Br</td>
<td>Cyclopentyl</td>
<td>2-Bromo-5,6-dichloro-1-cyclopentyl-1H-benzimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>NH2</td>
<td>Cyclopentyl</td>
<td>2-Amino-5, 6-dichloro-1-cyclopentyl-1H-benzimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>H</td>
<td>NH2</td>
<td>Cyclopentyl</td>
<td>2-Amino-5-chloro-1-cyclopentyl-1H-benzimidazole</td>
</tr>
</tbody>
</table>

Malleshappa Noolvi et al. (2011) reported the synthesis of antimicrobial and cytotoxic activity of novel azetidine-2-one derivatives of 1H-benzimidazole.\(^{18}\)
Ozden Ozel Guuven et al. (2011) reported the synthesis and antimicrobial activity of some novel phenyl and benzimidazole substituted benzyl ethers.¹⁹

Gulgun Ayhan-Kilecil et al. (2006) reported the synthesis of some benzimidazole derivatives and their in vitro antifungal activities were tested against Candida albicans, Candida glabrata and Candida krusei. Compounds possessed activity comparable to fluconazole against C. albicans with a minimum inhibitory concentration of 12.5 g/mL.¹³
R1 R2 X  IUPAC Name
C3H7 H H  1-Phenyl-3-(2-phenyl-1-propyl-1H-benzimidazol-5-yl)-thiourea
C3H7 F Cl  1-(4-Chloro-phenyl)-3-[2-(4-fluoro-phenyl)-1-propyl-1H-benzimidazol-5-yl]-thiourea
F H  1-[1-Cyclopenta-1,3-dienyl-2-(4-fluoro-phenyl)-1H-benzimidazol-5-yl]-3-phenyl-thiourea
F Cl  1-(4-Chloro-phenyl)-3-[1-cyclopenta-1,3-dienyl-2-(4-fluoro-phenyl)-1H-benzoimidazol-5-yl]-thiourea

Antiulcer activity
Brumagniez et al. (2008) reported the synthesis of 2-(thiopropyne) - 5- (imidazole -1-y1.) benzimidazole which exhibited moderate antiulcer activity against ulcer induced by anti inflammatory agents in rats orally.²⁰

Kovalev et al. (2008) reported the synthesis of 9-(diethyl amino ethylene) 2 – phenyl imidazo [1, 2-a] benzimidazole, which was found to be more potent than omeprazole. ²⁰

Keiji Kubo et al. (2008) reported the synthesis of 2-[(3-methyl , 4- trifluro ethoxy ) 2- pyridyl methyl , sulfinyl ] benzimidazole which showed antisecretory, antiulcer , cytoprotective activity. After examining the pharmacological and toxicological properties Lansoprazole was selected as a promising antiulcer agent.²⁰

Shimamura et al. (2008) reported the synthesis of 2-[(4-dimethyl amino, 5 carboxylate 2 pyrimidinyl) methyl sulfinyl] benzimidazole in which the pyridine nucleus of omeprazole is replaced by ethyl 4- dimethyl amino-5- pyrimidine carboxylate showed good antiulcer , gastroprotective and antisecretory activity.²⁰

Katano et al. (2008) reported the synthesis of 2 - [(2, 2, 6, 6 tetramethyl piperidine) ethyl thio] 5- methoxy benzimidazole which showed moderate activity.²⁰
Braendstroem et al. (2008) reported the synthesis of 2-[(3, 4 dimethoxy, 2-pyridyl) methyl, sulfinyl] 5- acetyl, 6-methyl benzimidazole which inhibited gastric acid secretion in dogs.  

\[
\text{H}_2\text{C}\text{O} - \text{S} - \text{N} - \text{H} - \text{N} - \text{S} - \text{H} - \text{2C} - \text{H}_3\text{C} - \text{O} - \text{N} - \text{O} - \text{C} - \text{H}_3\text{C} - \text{O} - \text{S} - \text{H}_3\text{C} - \text{O}\]

Sohda et al. (2008) reported the synthesis of 2-[(3-methyl, 4-difluromethoxy, 2-pyridyl) methyl, sulfinyl] benzimidazole inhibited ethanol induced ulcers in rats.  

\[
\text{H}_2\text{C} - \text{O} - \text{H}_2\text{C} - \text{O} - \text{N} - \text{S} - \text{H}_3\text{C} - \text{O} - \text{N} - \text{O} - \text{C} - \text{H}_3\text{C} - \text{O} - \text{S} - \text{H}_3\text{C} - \text{O}\]

Shin-ichi et al. (2008) reported the synthesis of 2-[(4-methoxy, 6,7,8,9- tetrahydro- 5H – cyclohepta pyridine –9-yl ) sulfinyl ] 1-H benzimidazole sodium salt which showed promising antiulcer activity and stability on isolated H/K -ATPase of rabbit gastric mucosa.  

\[
\text{H}_2\text{C} - \text{O} - \text{H}_2\text{C} - \text{O} - \text{N} - \text{S} - \text{H}_3\text{C} - \text{O} - \text{N} - \text{O} - \text{C} - \text{H}_3\text{C} - \text{O} - \text{S} - \text{H}_3\text{C} - \text{O}\]

Bernhard et al. (2008) reported the synthesis of 2-[(difluoro methoxy-2-pyridyl) methyl sulfinyl] 5- difluromethoxy benzimidazole was highly active against H/K -ATPase.  

\[
\text{F}_2\text{HCO} - \text{S} - \text{N} - \text{H} - \text{N} - \text{S} - \text{H}_3\text{C} - \text{O} - \text{N} - \text{O} - \text{C} - \text{H}_3\text{C} - \text{O}\]

Kim et al. (2008) reported the synthesis of 2-[(3-methyl, 4-methoxy, 2-pyridyl) methyl, sulfinyl 5- (1-pyrrolyl) benzimidazole which showed moderate activity against H/K ATPase with low toxicity.  

\[
\text{N} - \text{H}_2\text{C} - \text{S} - \text{N} - \text{H}_2\text{C} - \text{S} - \text{N} - \text{H}_2\text{C} - \text{S} - \text{N} - \text{H}_2\text{C} - \text{S} - \text{N}\]

Kohl et al. (2008) reported the synthesis of 2-[3-methyl, 4 (N-methyl, 1, 2, 4 triazole 3 yl, 1, 3 dithiane) 2 pyridyl ] methyl thio benzimidazole which showed high activity against Helicobacter Pylori.  

\[
\text{N} - \text{H}_2\text{C} - \text{S} - \text{N} - \text{H}_2\text{C} - \text{S} - \text{N} - \text{H}_2\text{C} - \text{S} - \text{N}\]
Braendstroem et al. (2008) reported the synthesis of Methyl 2-((3, 4-dimethoxypyridin-2-yl) methylsulfinyl)-6-methyl-1H-benzimidazole-5-carboxylate which showed high activity in dog & rat.  

Tsukahara et al. (2008) reported the synthesis of 2- (1H benzimidazole 2-sulfinyl methyl) phenyl isobutyl methyl amine which showed good antiulcer activity.  

Yum et al. (2008) reported the synthesis of 2- [[ 2,2 dimethyl 2-H pyrano (3,2-c) 2- pyridyl ] methyl, sulfinyl ] 4- methoxy benzimidazole which showed high activity against H⁺ / K⁺ ATPase.  

Shrinivasulu et al. (2008) reported the synthesis of 2- n propyl, 5 (N methyl 3, 4 cyclo hexane, 4 amino piperidine) keto, 6 ethoxy, benzimidazole which exhibited good antiulcer activity.  

Antiviral Activity  
Laila A. Abou-zeid et al. (2008) reported the synthesis of 4-Amino-6-(2-methyl-1H-benzimidazol-5-ylamino)-[1, 3, 5] triazine-2-carboxylic acid hydrazide which shows the antiviral activity.  

A.K.Tiwari et al. (2006) reported the synthesis of 3-(1-Benzyl-1H-benzimidazol-2-yl)-propionic acid which shows the antiviral activity.  

J.M. Gardiner et al. (2006) reported the synthesis of 2-Ethyl-4-methyl-1-propoxy-1H-benzimidazole which shows the antiviral activity.
Anti-inflammatory activity
Gummadi et al. (2010) synthesized a series of novel isatinylidene-hydrazinecarboxamide derivatives and evaluated for in vivo antiinflammatory activity. 24

Sawhney et al. (1990) synthesized certain 2-(5-aryl-4, 5-dihydropyrazol-3-yl)- and 2-(2-aminophenyl)benzimidazoles and screened them for antiinflammatory activity. 25

Antihypertensive activity
Jat Rakesh Kumar et al. (2006) reported the synthesis of 4’-(5-Amino-2-phenyl-benzimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid which shows the antihypertensive activity. 8

Mukesh C. Sharma et al. (2010) reported the synthesis of 4’-[5-Amino-2-(phenylmethyl)-benzimidazol-1-ylmethyl]-biphenyl-2-carboxylic acid which evaluated for nonpeptide angiotensin II receptor antagonists. 26

REFERENCES


