Chapter -5

Chemistry of Benzimidazoles
Imidazole (1) nucleus was first discovered by Debus in the year 1859 by reacting glyoxal and ammonia and to indicate its source he proposed the name glyoxaline. The term imidazole which is due to Hantzsch implies a five membered heterocyclic ring system containing imino group in addition to a tertiary nitrogen atom, that are located at the positions 1 and 3 respectively. Thus, the ring system in which benzene ring is fused to the 4,5-positions of imidazole ring is designated as benzimidazole (2). The various positions on the benzimidazole ring are numbered as shown below.

Benzimidazole possessing a free imino hydrogen and tertiary nitrogen are tautomeric systems (3) and (4). The two possible tautomeric forms of the benzimidazole are identical. Substitution of the imino hydrogen eliminates the possibility for tautomerism and a definite assignment of the structure becomes possible.

Benzimidazole derivatives are being explored in pharmaceutical industries and substituted benzimidazole derivatives have also been found in the diverse therapeutic applications such as in anti-ulcers, anti-
hypertensives, anti-virals, anti-fungals, anti-cancers and anti-histaminics. On the other hand, such benzimidazole derivatives are condensed with other heterocycles like pyrazole, thiadiazole, triazole, thiazole, coumarin and 2-azetidinone moieties which have shown diverse pharmacological activities.

The imidazole molecule is planar and exhibits aromaticity associated with six π-electrons one from each carbon atom, one from the pyridine nitrogen and two from the pyrrole nitrogen. Actually, a similar situation exists in case of benzimidazole, which can be envisaged as two overlapping sextets having 10 π-electrons. Benzimidazole is amphoteric compound, which is pseudo acidic in character. Its basic properties result from its ability of the pyridine nitrogen to accept a proton. Thus, benzimidazole (pKb 5.5) is a base considerably weaker than imidazole (pKb 6.95).

Ultraviolet (UV)

The ultraviolet spectra of benzimidazole and its derivatives have been studied in alkaline, neutral and acidic media. The bands observed in the case of benzimidazole are given below.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>λ_max (loge) m μ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>280 (3.89); 272 (3.91); 243 (3.80)</td>
</tr>
<tr>
<td>0.01 N HCl</td>
<td>274 (3.91); 268 (3.92), 235 (3.61)</td>
</tr>
<tr>
<td>0.01 N NaOH</td>
<td>277 (3.75); 271 (3.74), 240 (3.63)</td>
</tr>
</tbody>
</table>
The marked shifts in the position and intensity of the absorption spectra are because of the difference in electron distribution between the charged and uncharged ions.

**Infrared (IR)**

The infrared spectra of benzimidazole ring system has strong absorption band around 1400-1650 cm\(^{-1}\) for -C=N- stretching. It is very difficult to distinguish\(^{13,14}\) the C-H stretching vibrations occurring in the range of 3300-3100 cm\(^{-1}\) from the broad N-H stretching frequencies around 3300-2800 cm\(^{-1}\).

**Nuclear Magnetic Resonance (\(^1\)H NMR)**

The chemical shifts of benzimidazole have been manifested\(^{15,16}\) at lower field \(\delta\) 7.71 (C2-H), 7.67 (C4-H), 7.17 (C5-H), 7.24 (C6-H) and 7.32 ppm (C7-H) respectively. The overlapping signals ascribable to aromatic proton and proton to -NH have been observed at \(\delta\) 3.0-8.2 ppm, which are disappeared on D\(_2\)O addition. The chemical shift of C4-H and its deviation, because of various substituents is due to the magnetic anisotropy of the unsaturated nitrogen lone pair\(^{17}\), which is removed when protonation occurs.

**\(^{13}\)C NMR Spectroscopy**

The \(^{13}\)C NMR chemical shifts that have been reported by Pugmire and Grant\(^{18}\) for benzimidazole anion (V), benzimidazole (VI) and benzimidazole cation (VII) are tabulated as follows.
Chemistry of Benzimidazoles

<table>
<thead>
<tr>
<th>Compound</th>
<th>Position</th>
<th>δ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzimidazole anion</td>
<td>2</td>
<td>150.45</td>
</tr>
<tr>
<td></td>
<td>4,7</td>
<td>116.41</td>
</tr>
<tr>
<td></td>
<td>5,6</td>
<td>120.10</td>
</tr>
<tr>
<td></td>
<td>8,9</td>
<td>143.88</td>
</tr>
<tr>
<td>(5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzimidazole</td>
<td>2</td>
<td>141.46</td>
</tr>
<tr>
<td></td>
<td>4,7</td>
<td>115.41</td>
</tr>
<tr>
<td></td>
<td>5,6</td>
<td>122.87</td>
</tr>
<tr>
<td></td>
<td>8,9</td>
<td>137.92</td>
</tr>
<tr>
<td>(6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzimidazole cation</td>
<td>2</td>
<td>139.58</td>
</tr>
<tr>
<td></td>
<td>4,7</td>
<td>114.44</td>
</tr>
<tr>
<td></td>
<td>5,6</td>
<td>127.29</td>
</tr>
<tr>
<td></td>
<td>8,9</td>
<td>129.79</td>
</tr>
<tr>
<td>(7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mass spectroscopy (MS)

The mass spectrum of benzimidazoles exhibit molecular ion as a base peak.\(^9\) It also shows an odd electron ion (8) \(m/z\) 91 (C\(_4\)H\(_3\)N) by the loss of hydrogen cyanide, which further looses acetylene to lead to another odd electron ion, \(m/z\) 65 (C\(_4\)H\(_3\)N) and not the second molecule of hydrogen cyanide.\(^20\)

![Diagram](image)

\(\text{(8)}\)
Chemistry of Benzimidazoles

In the case of 2-methyl benzimidazole, molecular ion m/z 131 is formed by the loss of hydrogen radical from the methyl group, with a concomitant ring expansion to form the stable quinoxalinium cation.

Traditional benzimidazoles have been most commonly prepared from the reaction of 1,2-diaminobenzenes with carboxylic acids under harsh dehydrating reaction conditions, utilizing strong acids such as polyphosphoric acid, hydrochloric acid, boric acid or p-toluenesulfonic acid. However, the use of milder reagents, particularly Lewis acids, inorganic clays, or mineral acids, has improved both the yield and purity of this reaction.

On the other hand, the synthesis of benzimidazoles via the condensation of 1,2-diaminobenzenes with aldehydes requires an oxidative reagent to generate the benzimidazole nucleus. Various oxidative reagents, such as nitrobenzene, benzoquinone, sodium metabisulfite, mercuric oxide, lead tetraacetate, iodine, copper (II) acetate, indium perfluoroctane sulfonates, ytterbium perfluoroctane sulfonates and even air, have been employed for this purpose. Moreover, a variety of benzimidazoles can also
be produced via coupling of 1,2-diaminobenzenes with carboxylic acid derivatives such as nitriles, imidates, orthoesters, anhydrides or lactones.27

**Synthesis of 2-alkyl or aryl benzimidazoles**

$o$-Phenylenediamine (0.02 mol), the requisite acid (0.03 mol) and 20 mL of hydrochloric acid were boiled for 30-40 min under reflux.28 On neutralization of filtered solution with ammonia, the corresponding 2-alkyl or 2-aryl benzimidazole (9) is separated.

Where R = Formic, Acetic, Propionic, Glycolic, Lactic, Mandelic, Benzoic etc.

N-Arylamidine hydrochlorides were transformed to benzimidazoles (10) with sodium hypochlorite and base in excellent yields.29 The N-chloroamidine (11) was isolated as a discrete intermediate.
Amongst various derivatives of fatty acids described in literature\textsuperscript{30,31} for characterization of organic acids the 2-alkyl benzimidazoles of Seka and Muller\textsuperscript{32}, appeared most promising. These 2-alkyl benzimidazoles (12) were prepared by heating a mixture of acid and \textit{o}-phenylenediamine. The resulting compounds have comparatively high melting and the melting point range of the series was continuous and broad.

\[
\begin{align*}
\text{NH}_2 & + \text{R-COOH} & \xrightarrow{\Delta} & \text{N} \hspace{1cm} \text{H} \\
\text{NH}_2 & & & \text{R}
\end{align*}
\]

Where \(R\) = Fatty acid chain

The thermal decomposition of the amidrazonyletid gives 85\% yield of 2-phenyl benzimidazole (13).\textsuperscript{33}

\[
\begin{align*}
\text{Ph} & + \text{N-Ph} & \xrightarrow{172 \degree C} & \text{N} \hspace{1cm} \text{N} \hspace{1cm} \text{NMe}_3 \\
\text{N} & & & \text{N} \\
\text{H} & & & \text{H}
\end{align*}
\]

\textit{Synthesis of 2-benzimidazolylquinoxaline}

Mamedov \textit{et al.}, have developed highly efficient and versatile method for the synthesis of 2-benzimidazolylquinoxaline (14) on the basis of novel ring contraction of 3-aroyl- and 3-alkanoylquinoxalin-2-ones with 1,2-arylenediamines.\textsuperscript{34}

\[
\begin{align*}
\text{Ph} & + \text{Ph} \hspace{1cm} \text{NH}_2 & \xrightarrow{\text{AcOH}} & \text{Ph} \\
\text{NH}_2 & & & \text{N} \hspace{1cm} \text{N} \hspace{1cm} \text{N} \\
\text{N} & & & \text{H} \\
\text{H} & & & \text{H}
\end{align*}
\]
Synthesis of 1,2,4-triazino[4,5-a]benzimidazol-1-ones

Jakub Styskala et al., have prepared some of 1,2,4-triazino[4,5-a]benzimidazol-1-one derivatives (15 & 16) using coupling reactions of diazonium salts with 1,1-bis(1-ethoxycarbonyl-benzimidazol-2-yl)methane to obtain unstable hydrazones, which readily undergo cyclization.35

\[
\begin{align*}
\text{Ar} & \quad \text{CICOO}_{2} \quad \text{Ar} \\
\text{H} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{Ar} & \quad \text{N} \\
\text{Ar} & \quad \text{N} \\
\text{Ar} & \quad \text{N} \\
\text{N} & \quad \text{Ar} \\
\text{Ar} & \quad \text{N} \\
\end{align*}
\]

Synthesis of 2-aryl-3-(1H-benzimidazol-2-yl)-5,7-dimethoxyquinolines

Dzvinchuk et al., have developed three component cyclocondensation of p-(dimethylamino)benzaldehyde with 3,5-dimethoxyaniline and 2-phenacyl-1H-benzimidazoles which gave 2-aryl-3-(1H-benzimidazol-2-yl)-5,7-dimethoxyquinolines (17). The Hantzsch type reaction occurs in refluxing acetic acid and is accompanied by aromatization of 1,4-dihydroquinolines formed through loss of N,N-dimethylaniline.36
Takahashi and Kano have studied 1,3-dipolar additions with imidazole N-oxides. In this, phenyl isocyanate and phenyl isothiocyanate react with 1-methylbenzimidazole-3-oxide to yield the corresponding anilino-benzimidazoles (18) with the loss of carbon dioxide or carbonoxy sulphide.\(^{37}\)

\[
\begin{align*}
\text{Imidazole N-oxide} & \quad + \quad \text{Phenyl isocyanate (or isothiocyanate)} \\
& \rightarrow \text{Anilino-benzimidazole} (18)
\end{align*}
\]

\(X = O, S\)

**Synthesis of 6-hydroxy-(1,3,4)thiadiazolo(2,3-b)benzimidazoles**

Saxena and Soni have studied reactions of 2-aminothiadiazoles with carbonyl compounds. These authors reported the synthesis of 6-hydroxy-(1,3,4)thiadiazolo(2,3-b)benzimidazoles (19) by the condensation of \(p\)-benzoquinone with 2-aminothiadiazoles as follows.\(^{38}\)

\[
\begin{align*}
P-benzoquinone & \quad + \quad 2\text{-aminothiadiazole} \\
& \rightarrow \text{6-hydroxy-(1,3,4)thiadiazolo(2,3-b)benzimidazole} (19)
\end{align*}
\]

\(R = H, \text{alkyl, aryl}\)
Synthesis of 3-Alkyl-thiazolo [3,2-a] benzimidazole

Christian Roussel et al., showed that 3-Alkyl-thiazolo [3,2-a] benzimidazole derivatives (21) are obtained in high yields via the corresponding 4-alkyl-N-3-(2-aminophenyl)-thiazoline-2-thiones which are easily prepared from 1,2-diaminobenzene, CS₂ and halogenoketones.³⁹

\[
\begin{align*}
R^1 = & \text{CH}_3, \\
R^2 = & \text{H}
\end{align*}
\]

(21)

Synthesis of 2-(2-benzimidazolyl) chromones

Reddy et al., synthesized 2-(2-benzimidazolyl) chromones by refluxing o-hydroxyacetophenones with diethyl oxalate containing sodium methoxide gives methyl chromone-2-carboxylate as an intermediate. Then treating it with o-phenylenediamine in polyphosphoric acid gives the desired product (22).⁴

\[
R = \text{H}, \text{CH}_3, R^1 = \text{H}, \text{OCH}_3, \text{NHCOCH}_3, R^2 = \text{H, CH}_3
\]
Synthesis of oleobenzimidazoles

Recently, our research group has synthesized a series of 2-alkyl substituted oleobenzimidazoles using ethylene glycol as solvent. The reaction parameters such as temperature, density and yield have been studied to understand whether ethylene glycol is an efficient solvent and can have a positive effect on the synthesis of oleobenzimidazoles with good yields.\(^{40}\)

\[
\text{\begin{align*}
\text{+ HCOOR'} \\
\text{\text{Ethylene glycol}} \\
\text{H}_2\text{~N} \\
\text{\text{(20)}} \\
\text{\text{a}} \text{-H, b} \text{-Br, c} \text{-NO}_2 \\
\text{\text{R'}} \text{- (a') -} \\text{(CH}_2\text{)}_7\text{-CHOH-CHOH-(CH}_2\text{)}_5\text{-CH}_2\text{OH} \\
\text{b'} \text{-} \\text{(CH}_2\text{)}_7\text{-CH=CH-(CH}_2\text{)}_5\text{-CH}_2\text{OH} \\
\text{c'} \text{-} \\text{(CH}_2\text{)}_7\text{-CH=CH-(CH}_2\text{)}_7\text{-CH}_3 \\
\text{d'} \text{-} \\text{(CH}_2\text{)}_8\text{-CH=CH}_2
\end{align*}}
\]

Amongst the heterocycles, benzimidazole acquires a special place in view of its relation with vitamins and amino acids. Fischer\(^{41}\) in the year 1889 reported the bacteriostatic and fungicidal properties of the parent benzimidazole. Benzimidazole is known to exhibit a wide range of biological activities in the form of its innumerable derivatives.

**Anti-microbial agents**

The search for compounds with anti-bacterial activity has gained increasing importance in recent times, due to growing worldwide concern over the alarming increase in the rate of infection by antibiotic-resistant microorganisms.\(^{42}\) Owing to the current importance of developing novel
anti-microbials and the varied bioactivities exhibited by benzimidazoles, several researchers have investigated the anti-microbial activities of benzimidazole derivatives.

2-Mercapto benzimidazole derivatives are known to possess varied biological activities. Recently, an efficient and rapid synthesis of novel benzimidazole azetidin-2-ones (21) has been established and anti-bacterial screening revealed that all newly synthesized azetidin-2-ones (21) exhibited potent anti-bacterial activity against *Bacillus subtilis, Staphylococcus aureus* and *Escherichia coli*. In general, compounds (21a), (21i) and (21j) exhibited more pronounced anti-bacterial activity than compounds (21b-h), with better activity against both Gram-positive and Gram-negative bacteria. Among all the compounds investigated, (21i) and (21j) exhibited the greatest anti-bacterial activity against Gram-negative *E. coli* as compared to the anti-biotic streptomycin.

![Chemistry of Benzimidazoles](image)

(a) 4-NO₂, (b) 3,4,5 (OMe)₃, (c) 2-OH, (d) 3-OH, (e) 4-OH
(f) 2-OMe, (g) 4-OMe, (h) 2-Cl, (i) 3-Cl, (j) 4-Cl

Benzimidazole benzyl ethers (34) have exhibited good anti-bacterial activity against *S. aureus* and anti-fungal activity against *Candida albicans* and *Candida krusei*. In general the dichlorophenyl substituted benzimidazoles (34e), (34f) and (34h) showed the best anti-bacterial (MIC 3.12 µg/mL) and anti-fungal (MIC 12.5 µg/mL) activity.
Chemistry of Benzimidazoles

R = (a) 4-H, (b) 4-F, (c) 4-Cl, (d) 4-Br, (e) 2,4-di-Cl, (f) 2,6-di-Cl, (g) 2,3-di-Cl, (h) 3,4-di-Cl

In addition, 5-fluoro benzimidazole carboxamide derivatives \(^{46}\) (23) and benzimidazole isoxazolines \(^{47}\) (24) have been reported to show anti-bacterial and anti-fungal activities.

\[
\begin{align*}
R_j &= N -methylpiperazine, 3-methylpiperidine, 4-methylpiperidine, morpholine \\
R_2 &= H, n-propyl, cyclopropyl
\end{align*}
\]

Laixing Hu \textit{et al.}, have synthesized a series of bis-benzimidazole diamidine compounds containing different central linkers and evaluated for \textit{in-vitro} anti-bacterial activities, including drug-resistant bacterial strains. Seven compounds have shown potent anti-bacterial activities. The anti-MRSA and anti-VRE activities of compound (25h) were more potent than that of the lead compound (25a) and vancomycin.\(^{48}\)

\[
L = a) CH_2CH, b) CH=CH (trans), c) C === C, d) \begin{tikzpicture}
\draw (0,0) -- (0.5,0.5) -- (1,0) -- (0.5,-0.5) -- (0,0);
\end{tikzpicture}, e) CH_2O, f) SO_2NH, g) CH_2, h) O, i) S, j) NH, k) NMe, l) NPh, m) \begin{tikzpicture}
\draw (0,0) -- (0.5,0.5) -- (1,0) -- (0.5,-0.5) -- (0,0) node [below] {O};
\end{tikzpicture}
\]

(25)
Ansari and C. Lal have synthesized a series of 2-substituted-1-\{((5-substituted alkyl/aryl)-1,3,4-oxadiazol-2-yl)methyl\}-1H-benzimidazoles (26). All the synthesized compounds were screened for their anti-microbial activities. All the derivatives showed good activity towards Gram-positive bacteria and negligible activity towards Gram-negative bacteria. Some of the synthesized compounds showed moderate activity against tested fungi.49

The same author have synthesized a series of 3-chloro-1-\{5-[(2-methyl-1H-benzimidazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl\}-4-(substituted) phenylazetidin-2-one (27). The synthesized compounds were screened for their anti-bacterial activity against *Bacillus subtilis* (Gram-positive) and *Escherichia coli* (Gram-negative) and anti-fungal activity against *Candida albicans*, *Aspergillus flavus* and *Aspergillus niger* fungal strains. The compounds having o-chloro, o-methyl, p-methoxy, o-hydroxy and p-amino group in phenyl ring showed good anti-bacterial activity. Anti-fungal results indicated that some of the derivatives possessed a broad spectrum of activity against tested fungi, however, none of the derivatives showed a better spectrum of activity than the reference drug.50
Shweta Sharma et al. have synthesized a series of novel 2-substituted benzimidazoles (28) from long-chain alkenoic acids. The newly synthesized compounds were screened in vitro against an assortment of two Gram-positive bacteria Staphylococcus aureus, Bacillus subtilis and two Gram-negative bacteria Escherichia coli, Salmonella typhimurium and also screened for anti-fungal activity against Aspergillus niger, Candida albicans, Penicillium sp., Trichoderma viridae, Helminthosporum oryzae strains. The chloro substituted derivatives have shown maximum antibacterial and anti-fungal activities.

Rondla Rohini et al., have synthesized a series of mono, bis-2-o-arylideneaminophenylbenzimidazoles (29) and corresponding mono, bis-6-arylbenezimidazo[1,2-c]quinazolines (30). The target benzimidazo[1,2-c]quinazoline compounds were obtained by the condensation of 2-(o-aminophenyl)benzimidazole with mono and di carbonyl compounds, followed by oxidative cyclization of the resulting mono and bis-2-o-arylideneaminophenylbenzimidazoles. The anti-microbial activities
of all benzimidazoles against various bacteria and fungi were evaluated. Among the compounds tested, (30d-e) exhibited good anti-bacterial and anti-fungal activities while (29b-c) also showed notable anti-microbial activity with reference to standard drugs Ampicillin and Ketoconazole respectively.\footnote{52}

\begin{center}
\includegraphics[width=\textwidth]{30d-e.png}
\end{center}

\begin{center}
(30)
\end{center}

Ar = a) C₆H₅, b) 2-pyridyl, c) 2-thienyl, d) 2-furyl, e) 2-pyridyl

Recently, our research group has synthesized a new series of novel 5-(nitro/bromo)-styryl-2-benzimidazoles (31a) by simple and efficient synthetic protocol by attempted condensation of 5-(nitro/bromo)-o-phenylenediamine with trans-cinnamic acids in ethylene glycol. The synthesized compounds were screened for \textit{in vitro} anti-bacterial activity against \textit{Staphylococcus aureus}, \textit{Escherichia coli}, \textit{Enterococcus faecalis}, \textit{Klebsiella pneumoniae} bacterial strains and anti-fungal activity against \textit{Candida albicans} and \textit{Asperigillus fumigatus} fungal strains. Some of the compounds have shown excellent anti-bacterial and anti-fungal activities against the microbes.\footnote{53,54}

\begin{center}
\includegraphics[width=\textwidth]{31a-b.png}
\end{center}

\begin{center}
(31a)
\end{center}

R = -NO₂, -Br

R¹ = H, 3,4 (OCH₃), 4-CH₃, 3,4-(CH₂)O₂, 2,4-Cl, 3-OH
**Anthelmintic agents**

Anthelmintic resistance is almost cosmopolitan in distribution and it has been reported in almost all species of domestic animals and even in some parasites of human beings. All of the major groups of anthelmintics have encountered variable degrees of resistance from different species of gastrointestinal nematodes.\(^5^5\) Bearing in mind previous benzimidazole anthelmintics (e.g., albendazole, mebendazole), the search for new anthelmintic drugs is being actively pursued. Synthetic benzimidazole piperazine derivatives exhibited 50% anthelmintic activity in mice infected with *Syphacia obvelata*.\(^5^6\) Furthermore, piperazine derivatives of 5(6)-substituted-(1H-benzimidazol-2-ylthio)acetic acids (32-34)\(^5^7\) and benzimidazolyl crotonic acid anilide (35) have shown good anthelmintic activity.\(^5^8\)

\[\text{Chemistry of Benzimidazoles}\]

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Chassaing et al., have developed highly water-soluble prodrugs (36a-g) of anthelmintic benzimidazole carbamates (37a-g). These prodrugs combine high aqueous solubility and stability with high lability in the presence of alkaline phosphatases. The veterinary utility of (36a) was shown by a pharmacodynamic and pharmacokinetic study performed in swine. Comparable anthelmintic efficacy was observed with prodrug (36a) or the parent fenbendazole (37a). The pharmacokinetic results showed that (37a) is better absorbed when derived from (36a) than when applied as such.59

![Chemical structures](image)

R = a) PhS, b) PhSO, c) n-Prs, d) PhCO, e) 4F-PhCO, f) 4F-PhSO₃, g) n-Bu

**Anti-inflammatory, Analgesic and Anti-ulcer agents.**

Structure activity relationship (SAR) studies of the 5,6-dialkoxy-2-thiobenzimidazole derivatives (38) have revealed that compounds (38a-k) possess pronounced anti-inflammatory properties.60 Using the carrageenan model, the most significant anti-inflammatory effects were observed for compounds (38a), (38d), (38h), (38i), and (38j). While using the bentonite model, the maximum activities were observed for compounds (38e) and (38h). These results indicated that benzimidazoles are promising leads for the development of new anti-inflammatory agents.
Chemistry of Benzimidazoles

Pyrimidobenzimidazole (39)\textsuperscript{61} and dioxinobenzimidazothiazol-9-ones (40)\textsuperscript{62} exhibited anti-inflammatory and analgesic activity, as evaluated by carrageenan-induced rat paw edema and phenylquinone-induced writhing tests. In addition, N-benzoyl and N-tosyl benzimidazole compounds (41) showed significant anti-inflammatory activity, as indicated by ear swelling induced by xylene in mice, and their ulcer indices were all lower than those of aspirin.\textsuperscript{63} Furthermore, N-morpholinomethylbenzimidazole (42) and its derivatives have been recently reported to show significant anti-inflammatory activity.\textsuperscript{64}
Despite of the success of several commercial benzimidazole proton pump inhibitors for the treatment of ulcer disease, work is still in progress to discover new benzimidazole-derived anti-ulcer drugs. Cinitapride (43) related benzimidazole derivatives (44) have been prepared and studied for their anti-ulcerative activity.\(^6\) In addition, 1,3-disubstituted 3,4-dihydropyrimido[1,6-a]benzimidazoles (45) and 3-substituted 3,4-dihydropyrimido[1,6-a]benzimidazol-1(2\(^H\))-thiones (46) exhibited good gastric antisecretory activity (> 50% inhibition).\(^6\)

Philip Jesudason \textit{et al.}, synthesized a series of N-Mannich bases of benzimidazole derivatives and the compounds were screened for analgesic and anti-inflammatory activity. 1-(((Diethylamino)-methyl)-2-styryl benzimidazole (47) at 40 mg/kg was found to be equipotent to paracetamol. 1-(((Piperidin-1-yl) methyl)-2-styryl-benzimidazole at 40 mg/kg was found to be more potent than Diclofenac.\(^6\)
Cytotoxic and Anti-tumor agents

In cancer chemotherapy there is currently much interest in the design of small molecules that bind to DNA with sequence selectivity and non covalent interactions. A possible lead for this new class of compounds is Hoechst 33258 28, which recognizes A/T sequences in human DNA and is also an effective inhibitor of mammalian DNA topoisomerase.

Andrzejewska et al., have synthesized a series of several halogenated benzimidazoles substituted in position 2 with trifluoromethyl, pentafluoroethyl and 2-thioethylaminodimethyl group. Anti-protozoal and anti-cancer activity of a series of newly synthesized and previously obtained compounds was studied. All tested benzimidazoles showed remarkable anti-protozoal activity against Giardia intestinalis, Entamoeba histolytica and Trichomonas vaginalis. Of the studied collection of halogenated benzimidazoles the most anti-cancer was 5,6-dichloro-2-pentafluoroethyl compound (48), particularly against breast and prostate cancer cell lines.68

\[
\begin{align*}
\text{R}_1 &= \text{H, CH}_3, \text{CH} = \text{CH-C}_6\text{H}_5 \\
\text{R}_2 &= \text{N(CH}_3)_2, \text{N(C}_2\text{H}_5)_2, \text{N(C}_6\text{H}_5)_2, \begin{array}{c} \text{N} \\
\text{O} \end{array}
\end{align*}
\]
Thimmegowda et al., have synthesized a novel series of trisubstituted benzimidazole and its precursors and the compounds were evaluated for inhibition against MDA-MB-231 breast cancer cell proliferation. The results revealed that the compound N-(4-cyano-3-(trifluoromethyl) phenyl)-4-fluoro-3-nitrobenzamide (49) was the potent inhibitor.\(^{69}\)

![Chemical structure of 49](image)

Gellis et al., have synthesized a new benzimidazole-4,7-diones substituted at 2-position via a microwave-assisted reaction using 2-chloromethyl-1,5,6-trimethyl-1H-benzimidazole-4,7-dione as a key intermediate compound. Their cytotoxicity has been evaluated on colon, breast and lung cancer cell lines. The compound 2,2'-Bis(chloromethyl)-1,1''-dimethyl-5,5'-bi(1H-benzimidazole)-4,4',7,7'-tetraone (50) was shown to possess excellent cytotoxicity comparable to that of mitomycin C.\(^ {70}\)

![Chemical structure of 50](image)

Penning et al., have developed a series of cyclic amine-containing benzimidazole carboxamide PARP inhibitors with a methyl-substituted quaternary center at the point of attachment to the benzimidazole ring system. These compounds exhibit excellent PARP enzyme potency as well
as single-digit nanomolar cellular potency. These efforts led to the identification of 2-(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (51), currently in human phase I clinical trials. Compound (51) displayed excellent potency against both the PARP-1 and PARP-2 enzymes with a Ki of 5 nM and in C41 whole cell assay with an EC\textsubscript{50} of 2 nM. In addition, (51) is aqueous soluble, orally bioavailable across multiple species, and demonstrated good \textit{in vivo} efficacy in a B\textsubscript{16}F\textsubscript{10} subcutaneous murine melanoma model in combination with temozolomide (TMZ) and in an MX-1 breast cancer xenograft model in combination with either carboplatin or cyclophosphamide.\textsuperscript{71}

\[
\text{CONH}_2
\]

(51)

The benzimidazole-6,9-dione (52) has been found to be 300 times more cytotoxic towards the human skin fibroblast cell line in the MTT assay than the clinically used bioreductive drug, mitomycin C. Attaching methyl substituents onto the quinone moiety increased reductive potential and decreased cytotoxicity and selectivity towards hypoxia.\textsuperscript{72} In addition, the alkyl-linked bisbenzimidazole\textsuperscript{73} (53) and thiazolylnbenzimidazole-4,7-diones\textsuperscript{74} (54) exhibited cytotoxic activity against tumor cell lines.

\[\begin{align*}
(52) & \quad n = 1, 2, 3 \\
(53) & \\
(54) & R_1 = \text{NH}_2, \text{OMe}; \\
& R_2 = \text{NH}_2, \text{OBt, OH}
\end{align*}\]
Anti-tubercular agents

Tuberculosis (TB), a contagious infection caused by *Mycobacterium tuberculosis* (MTB), still remains the leading cause of the worldwide death among the infectious disease.\(^7\) The WHO has estimated that every year about eight million new cases of tuberculosis occur, and up to three million individuals die due to this disease (one person dies every 10 s).\(^6\) It is also estimated that between 2002 and 2020, approximately a billion people will be newly infected, more than 150 million people will get sick and 36 million will die of TB.

Jyoti Pandey *et al.*, have synthesized a series of imidazole based compounds by reacting simple imidazoles with alkylhalides or alkyl halocarboxylate in presence of tetrabutylammonium bromide (TBAB). The compounds bearing carbethoxy group undergo amidation with different amines in the presence of DBU to give respective carboxamides. The synthesized compounds were screened against *Mycobacterium tuberculosis* where compound (55) exhibited very good *in vitro* anti-tubercular activity and may serve as a lead for further optimization.\(^7\)

\[
\begin{array}{c}
\text{N} \\
\text{R}_1 \quad \text{R}_2 \\
\text{Aridoss *et al.*, have synthesized 3-tetrahydropyridin-4-ol based} \\
\text{benzimidazole and screened for anti-tubercular activity against} \\
\text{*Mycobacterium tuberculosis* H}_{37}\text{Rv. The compound (56) has shown good} \\
\text{activity compared to the standard Rifampicin drug.}^{78}
\end{array}
\]
Gill et al., have synthesized a series of 2- (3-fluoro-phenyl)-1-[1-(substituted-phenyl)-1H-[1,2,3]-triazol-4-yl-methyl]-1H-benzo[d]imidazoles (57). The synthesized compounds screened for anti-tubercular activity against Mycobacterium tuberculosis H37Rv. They conclude that the fluoro groups have enhanced anti-mycobacterial activity, more than 96% of inhibition at 6.25 mg concentration while other compounds exhibited less than 90% inhibition at the same concentration.79

Recently, our research group has synthesized a new series of novel 5-(nitro/bromo)-styryl-2-benzimidazoles (31) and screened for in vitro anti-tubercular activity against Mycobacterium tuberculosis H37 Rv, some of the synthesized compounds showed good activity.53
Anti-retroviral agents (Anti-HIV)

Human Immunodeficiency Virus (HIV) is the primary cause of acquired immunodeficiency syndrome (AIDS). The replication of HIV-1 in infected patients can be reduced considerably by HAART, a highly active combination of drugs with multiple viral targets. Officially approved drugs for anti-HIV treatment belong to the class of nucleoside/nucleotide and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs), to protease inhibitors (PIs) and more recently to viral entry (Enfuvirtide) and integrase inhibitors (Isentress). Despite the successes with such treatments, the permanent use of anti-AIDS drugs induces drug-resistant viral variants and the emergence of unwanted metabolic side effects.80

Monforte et al., synthesized several N1-substituted 1,3-dihydro-2H-benzimidazol-2-ones (58 & 59) and evaluated as anti-HIV agents. Some of them proved to be highly effective in inhibiting HIV-1 replication at nanomolar concentration as potent non-nucleoside HIV-1 RT inhibitors (NNRTIs) with low cytotoxicity. SAR studies highlighted that the nature of the substituents at N1 and on the benzene ring of benzimidazolone moiety significantly influenced the anti-HIV activity of this class of potent anti-retroviral agents.81
Barreca et al., have synthesized a series of $1H$, $3H$ thiazolo[3,4-a]benzimidazole derivatives (60) (TBZs). Some of the synthesized derivatives proved to be highly effective in inhibiting human immunodeficiency virus type-1 (HIV-1) replication at nanomolar concentrations with minimal toxicity, acting as reverse transcriptase (RT) inhibitors. Computational studies were used in order to probe the binding of our ligands to HIV-1-RT.  

![Chemistry of Benzimidazoles]

Xu et al., have synthesized 4-Oxo-4H-quinolizine-3-carboxylic acid derivatives bearing sulfamido, carboxylamido, benzimidazoles (61) and compounds were screened for possible HIV integrase inhibitory activity. They concluded that aryl diketoacid-containing compounds are the most promising HIV IN inhibitors.  

![Chemistry of Benzimidazoles]

Thiazolobenzimidazoles (62) proved to be highly potent inhibitors of HIV-1-induced cytopathic effects. Structure-activity relationship studies showed that the C-1 substituents in benzimidazole greatly influence the interaction of the active compound with the receptor. Substitution on the benzene-fused ring influences the inhibitory potency depending on the nature and position of the substituents, the presence of a methyl group at C-3 is favorable to the pharmacological profile.
Chemistry of Benzimidazoles

Enzyme and Receptor Agonists/Antagonists

Several benzimidazole derivatives have been reported to act on various enzymes and receptors. Some examples of benzimidazoles acting as agonists or antagonists of various receptors and enzymes are listed in Table - 1.

Table - 1 Benzimidazole derivatives that act on enzymes/receptors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Enzymes/Receptors</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Androgen receptor</td>
<td>Antagonist</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Cholecystokinin B receptor</td>
<td>Antagonist</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Cyclin-dependent kinase 1 (CDK1)</td>
<td>Inhibitory</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Enkephalinase B (DPP III)</td>
<td>Antagonist</td>
<td>88</td>
</tr>
<tr>
<td>Structure</td>
<td>Property</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>Tyrosine phosphatase Inhibitory</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Kinesin spindle protein (KSP) Inhibitory</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>Coxsackie virus B3 (CVB3) Inhibitory</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure" /></td>
<td>Opioid receptor-like 1 (ORL1) Antagonist</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure" /></td>
<td>Polo-like kinase (PLK) Inhibitor</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td><img src="image6.png" alt="Structure" /></td>
<td>Histone deacetylase inhibitors (HDAC) Inhibitor</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td><img src="image7.png" alt="Structure" /></td>
<td>Serotoninergic 5-HT\textsubscript{1A} or 5-HT\textsubscript{7} receptor Receptor</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>
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