CHAPTER 5

2-Substituted-benzimidazoles,
tetrahydrobenzimidazoles
and imidazoles
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

5.1 Theoretical

The incorporation of the imidazole and benzimidazole nuclei is an important synthetic strategy in drug discovery. The high therapeutic properties of the related drugs have encouraged the medicinal chemists to synthesize the large number of novel chemotherapeutic agents. Imidazole and benzimidazole drugs have broaden scope in remedying various dispositions in clinical medicine. Optimization of benzimidazole based structures has resulted in marketed medicines such as Omeprazole and Pimobendan and lead compounds in a wide range of therapeutic areas (e.g. casein kinase, factor Xa, hepatitis C virus). Pharmaceutical properties including; antifungal and antimycotic, antiprotozoal and trichomonas infection, antineoplastic, antiulcer, antihistaminic, antiallergic, anesthetic, hypnotic, antihypertensive, anthelmintic, neuroleptic, antipsychotic and thromboxane synthetase inhibitor, all are unique characteristics known from imidazole and benzimidazole derivatives.

Benzimidazole is a versatile core contained in several substances possessing a broad spectrum of pharmacological activity such as anticancer, antimicrobial, pesticide, and anthelmintic properties. This class of molecules has also found commercial applications in several therapeutic areas such as antiulcerative, antiviral, and antihistaminic agents. Benzimidazoles exhibit significant activity against several viruses including HIV, herpes (HSV-1), RNA, influenza and human cytomegalovirus (HCMV). In recent years benzimidazoles have been reported to act as topoisomerase I inhibitors, selective neuropeptide YY1 receptor antagonists, angiotensin II (All) inhibitors, inhibition of HCMV replication, HT3 antagonists in isolated guinea pig ileum. Hence, the development of new synthetic methods for benzimidazoles, which are currently not easily attainable by existing methods, is considered important by organic chemists.

Several biologically active synthetic compounds possess five-membered nitrogen-containing heterocycles in their structures. The imidazole core is a
common moiety in a large number of natural products and pharmacologically active compounds. Recently, there has been considerable amount of progress in imidazole chemistry due to the recognition of the importance of the imidazole structure in biological processes and the increasing application of imidazole-containing compounds, such as etomidate, cimetidine, omeprazole and lansoprazole, in drug therapy. The imidazole ring system is a key structural fragment found in many natural products. It also serves as a good ligand for various metal ions. Metal binding properties of imidazole-based ligands have been explored in detail because of their presence at the active site of metallo-proteins or enzymes involved in several important metabolic processes.

N,N-Dimethylchlorosulfitemethaniminium chloride has been found to be an efficient reagent for the one-pot synthesis of benzimidazoles (iii) in excellent yield by condensation of carboxylic acids (i) with o-phenylenediamine (ii) (Scheme 5.1).

\[
\begin{align*}
\text{(i)} & : \quad R = \text{C}_6\text{H}_5, 3-\text{CH}_3-\text{C}_6\text{H}_4, 2-\text{Cl-}\text{C}_6\text{H}_4 \\
\text{(ii)} & : \quad \text{Me}_2\text{N}=\text{CH}-\text{O}-\text{SOCl} \cdot \text{Cl}^- \\
\text{(iii)} & : \quad \text{HCl} \cdot \text{DMF} \cdot \text{SO}_3 \cdot \text{H}_2\text{O}
\end{align*}
\]

Scheme 5.1

Vlaskina and Perevalov have synthesized substituted benzimidazoles (vi) by reduction of esters of 4-alkylamino-3,5-dinitrobenzoic acids (v) by tin chloride (Scheme 5.2).

\[
\begin{align*}
\text{(iv)} & : \quad R = \text{C}_6\text{H}_5, i-\text{Pr} \\
\text{(v)} & : \quad \text{Cl} \cdot \text{i-PrOH} , \text{HCl} \\
\text{(vi)} & : \quad \text{H} \cdot \text{N} \cdot \text{R}
\end{align*}
\]

Scheme 5.2
In an effort to find an orally bioavailable antiviral for the treatment of rhino/enteroviral infections, a series of vinylacetylene benzimidazoles \((\text{viii})\) were made by Tebbe \textit{et al.}\textsuperscript{35} (\textbf{Scheme 5.3}).

\begin{center}
\begin{align*}
\text{(vii)} & \quad \text{+} \quad \text{(vii)} \\
& \quad \text{(viii)}
\end{align*}
\end{center}

\textbf{Scheme 5.3}

Several 2'-aryl-5-substituted-2,5'-bi-1H-benzimidazole derivatives were synthesized\textsuperscript{36} and evaluated as topoisomerase I poisons and for their cytotoxicity toward the human lymphoblast cell line RPMI 8402 (\textbf{Scheme 5.4}).

\begin{center}
\begin{align*}
\text{(ix)} & \quad \text{+} \quad \text{(x)} \\
& \quad \text{(xi)}
\end{align*}
\end{center}

\textbf{Scheme 5.4}

The preparation and anthelmintic properties of methyl 5(6)-phenylsulfinyl-2-benzimidazolecarbamate \((\text{xii})\) were described by Averkin \textit{et al.}\textsuperscript{37}.

\begin{center}
\begin{align*}
\text{(xii)} \\
R= \text{PhS-O, PhS-, PhS-O}_2
\end{align*}
\end{center}

Walker \textit{et al.}\textsuperscript{38} have synthesized the 1-[4-(4-chlorophenyl)-2-(2,6-dichlorophenylthio)-n-butyl]-1-H-imidazole nitrate \((\text{xiii})\), as potent antifungal agent.
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

2-(N-Substituted)-aminobenzimidazoles are widely used structural motifs in medicinal chemistry as well as in drug discovery and can be found in a number of biologically active molecules. Several compounds from this class have been used as anticancer, antihistamine and antiviral agents. Some examples of pharmaceutical interest are given below.

Norastemizole: \( R = H \)  
Mebendazole (anticancer)

Astemizole: \( R = \) antiallergic, antihistamine

Das et al. have reported the highly efficient synthesis of 2-aminobenzimidazoles using various diamines and substituted dithiocarbamates. The reaction is promoted by dithiocarbamate and catalytic amount of CuO (Scheme 5.5).
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

**Scheme 5.5**

Antibacterial\(^{42-44}\), anti-inflammatory\(^{45}\), anti-ulcer\(^{46,47}\) and antiviral\(^{48,49}\) effects have been shown with various thiazolo-[3,2-a]-benzimidazole derivatives. Furthermore, certain thiazolo-[3,2-a]-benzimidazole derivatives, such as tilomisole (WY-18,251) \(\text{(xix)}\) was largely studied\(^50,51\) demonstrating their anti-inflammatory\(^52\) and immunomodulatory\(^53\) activities.

Also, some thiazolo-[3,2-a]-benzimidazole derivatives were used for treatment of cancer\(^54\), cerebral infarction\(^55\), neurogenic pain\(^56\), and bone diseases\(^57\).

A series of 2-(substituted phenyl)-1H-benzimidazole \(\text{(xxii)}\) derivatives with various substituents were synthesized via microwave irradiation using a short synthetic route and Na\(_2\)S\(_2\)O\(_5\) as oxidant\(^58\) (Scheme 5.6).

\[
\begin{align*}
\text{(xx)} & + \quad \text{(xxi)} & \quad \text{(xxii)} \\
\begin{array}{c}
\text{R}_1=\text{H, CH}_3; \quad \text{CF}_3, \quad \text{R}_2=\text{H, OCH}_3, \quad \text{NO}_2, \quad \text{OCH}_2\text{CH}_3; \quad \text{R}_3=\text{H, OCH}_3; \quad \text{R}_4=\text{H, OH, OCH}_3, \quad \text{N(CH}_3)_2; \quad \text{R}_5=\text{H, OCH}_3
\end{array}
\end{align*}
\]

**Scheme 5.6**
The interaction of 2-acetyl-(aroyl)-methyl-1\(H\)-benzimidazoles (xxiv) with phenylhydrazine on heating in trifluoroacetic acid proceeds by a type of Fischer reaction with the formation of 2-[2-methyl(aryl)-3-indolyl]-1\(H\)-benzimidazoles (xxv)\(^{59}\) (Scheme 5.7).

\[
\text{CH}_2\text{COR} \xrightarrow{\text{NH}_2\text{NPh, CF}_3\text{COOH, NH}_4\text{OH}} \text{N} - \text{N} \text{H} - \text{N}
\]

\[(xxiii) \quad (xxiv)\]

Scheme 5.7

Dzvinchuk et al.\(^{60}\) developed a convenient preparative method for synthesis of 2-(1,2,3-thiadiazol-5-yl)-1\(H\)-benzimidazoles (xxvi) based on reaction of benzoylhydrazones of 2-acylmethyl-1\(H\)-benzimidazoles (xxv) with thionyl chloride (Scheme 5.8).

\[
\text{R} = \text{C}_6\text{H}_5, \text{4-MeC}_6\text{H}_4, \text{4-MeOC}_6\text{H}_4, \text{3,4,5-(MeO)}_3\text{C}_6\text{H}_4, \text{2-thienyl, Me}
\]

Scheme 5.8

Some chloroaryloxyalkyl imidazole and benzimidazole derivatives were synthesized\(^{61}\). The relevant step in the synthetic sequence was the initial condensation of 4-chloro or 2,4-dichlorophenol with 1, n-dibromoalkanes (\(n = 2, 4, 5\)) (xxvii) to provide (xxviii) in sufficient yields. The subsequent condensation of (xxviii) with some imidazole derivatives and benzimidazole afforded products (xxix) and (xxx) in good yields (Scheme 5.9).
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

Scheme 5.9

A simple, high-yielding synthesis of 2,4,5-trisubstituted imidazoles (xxxiii) from 1,2-diketones (xxxi) and aldehydes (xxxii) in the presence of NH₄OAc under microwave irradiation in described

\[
\text{R₁} \quad \text{O} \quad \text{R₂} \quad \text{NH₄OAc (10 eqv)} \quad \text{H₂O Ac} \quad 180 \degree \text{C, microwave 5 minutes}
\]

\[(xxxi) \quad (xxxii) \quad (xxxiii)\]

Scheme 5.10

Frantz \textit{et al.}⁶³ has described synthesis of substituted imidazoles (xxxvii) via organocatalysis (Scheme 5.11).

\[(xxxiv) \quad (xxxv) \quad (xxxvi) \quad (xxxvii)\]

Scheme 5.11

Synthesis of 1,5-disubstituted and 1,4,5-trisubstituted imidazoles (xxxix) from aldimines and imidoyl chlorides was given by van Leusen \textit{et al.}⁶⁴ (Scheme 5.12).
Iizuka et al.\textsuperscript{65} have reported the synthesis of imidazole derivatives (xliv) as highly selective inhibitors of thromboxane synthetase (Scheme 5.13).

Synthesis of N-alkylated derivatives of imidazoles (xlvii) as antibacterial agents was reported by Khabnadideh et al.\textsuperscript{66} (Scheme 5.14).

Van Vliet et al.\textsuperscript{67} have reported the synthesis of 2-substituted-benzimidazoles (xlix) from nitroanilines using microwave conditions (Scheme 5.15).
Lin et al.\textsuperscript{68} reported the high-throughput synthesis of benzimidazoles (li) derivatives under microwave conditions (Scheme 5.16).
5.2 Convenient One-pot synthesis of Novel 2-Substituted-benzimidazoles, Tetrahydrobenzimidazoles and Imidazoles and Evaluation of their in vitro Antibacterial and Antifungal Activities*

The benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry, encompassing a diverse range of biological activities including antiarrhythmic, antiulcer, anthelmintical, inotropic, antihistamine, antifungal, antiviral, and cytotoxicity displaying diverse range of biological activities. Benzimidazoles exhibit significant activity as potential antitumor agents, smooth muscle cell proliferation inhibitors, a treatment for intestinal cystitis, and in diverse area of chemistry. The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds. Recently, there has been considerable amount of progress in imidazole chemistry due to the recognition of importance of the imidazole structure in biological processes and the increasing application of imidazole containing compounds, such asetomidate, cimetidine, omeprazole and lansoprazole, in drug therapy. Therefore the development of facile synthetic routes to achieve access to these molecules is of prime interest. In view of the above mentioned pharmacological applications of benzimidazoles and imidazoles and in continuation of the synthesis of biologically active molecules, the design and synthesis of hitherto unknown benzimidazoles and imidazoles bearing long alkenyl chain was carried out.

Further, the increasing number of multidrug resistant pathogens led to screen the newly synthesized derivatives against the representative panel of Gram positive and Gram negative bacteria and fungi.

5.3 Results and discussion

A typical one-pot procedure for the synthesis of 4a-l involves the addition of 1,2-phenylenediamine derivatives 2 to the acid chloride 1a-d (Scheme 5.17) at 0 °C in dry dioxane and stirring for 30 minutes at room temperature to furnish the corresponding N-acyl-1,2-phenylenediamine derivatives 3. To the prior, acid chloride 1a-d was synthesized from olefinic and hydroxy olefinic long-chain acids by in situ preparation.

Since acid chlorides 1a-d are not commercially available the present method has greatly solved the problem by facile and efficient in situ preparation. We have used BF3 OEt2 for cyclization of 3. BF3 OEt2 in dry dioxane was added to the 3 without isolating the product and reaction mixture refluxed for 1-2 hours at 130 °C.
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

Table 5.1 2-substituted-benzimidazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R₂</th>
<th>Starting from</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>1a</td>
<td>2a</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>1b</td>
<td>2a</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>1c</td>
<td>2a</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>1d</td>
<td>2a</td>
</tr>
<tr>
<td>5</td>
<td>NO₂</td>
<td></td>
<td>1a</td>
<td>2b</td>
</tr>
<tr>
<td>6</td>
<td>NO₂</td>
<td></td>
<td>1b</td>
<td>2b</td>
</tr>
<tr>
<td>7</td>
<td>NO₂</td>
<td></td>
<td>1c</td>
<td>2b</td>
</tr>
<tr>
<td>8</td>
<td>NO₂</td>
<td></td>
<td>1d</td>
<td>2b</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td></td>
<td>1a</td>
<td>2c</td>
</tr>
<tr>
<td>10</td>
<td>Cl</td>
<td></td>
<td>1b</td>
<td>2c</td>
</tr>
<tr>
<td>11</td>
<td>Cl</td>
<td></td>
<td>1c</td>
<td>2c</td>
</tr>
<tr>
<td>12</td>
<td>Cl</td>
<td></td>
<td>1d</td>
<td>2c</td>
</tr>
</tbody>
</table>

The yields of products 4a-l are excellent and independent of the substituents present in the precursor. The scope of the reaction using olefinic (internal and terminal) and hydroxy acids is found to be good. This strategy was also be used to increase the structural diversity of the member library through the synthesis of benzimidazole 4m-p (Scheme 5.18).

![Scheme 5.18 Synthesis of 2-substituted-imidazoles](image)

Similarly 4q-t (Scheme 5.19) have been prepared by the reaction of ethylenediamine 7 to the acid chloride 1a-d at 0 °C in dry dioxane and stirring for 30
minutes at room temperature to furnish the corresponding 8a-d which undergo cyclization in presence of BF$_3$OEt$_2$ to form the 4q-t.

![Scheme 5.19 Synthesis of 2-substituted-tetrahydrobenzimidazoles](image)

The yield of products was found to be appreciable. The preliminary study of 4a, 4b, 4r has been reported earlier. The newly synthesized compounds were analyzed for C, H and N content and structures were confirmed by IR, $^1$H NMR, $^{13}$C NMR and mass spectral data. IR absorptions at 1630 cm$^{-1}$ (C=N) was obtained for 2-(dec-9-enyl)-1H-benzimidazole 4a. The $^1$H NMR showed signal of methine proton of C-9 at $\delta$ 5.82. C-10 methylene designated as H$_E$ and H$_Z$ displayed two distinct $\delta$ values when coupled with adjacent C-9 methine protons. The spectrum showed two doublets of doublet at $\delta$ 5.02 and 4.90 for H$_Z$ and H$_E$ protons respectively. The structure of 4a was further supported by its mass spectral studies, which showed molecular ion peak at $m/z$ 256 consistent with its molecular formula C$_{17}$H$_{24}$N$_2$.

The antibacterial and antifungal screening revealed that all the tested compounds 4a-l, 4m-p, 4q-t showed moderate to good inhibition.
Table 5.1 *In vitro antibacterial activity of compounds 4a-t*

<table>
<thead>
<tr>
<th>Compound</th>
<th>E. coli</th>
<th>S. typhimurium</th>
<th>B. subtilis</th>
<th>S. aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>18(150)</td>
<td>16(75)</td>
<td>22(75)</td>
<td>20(150)</td>
</tr>
<tr>
<td>4b</td>
<td>16(150)</td>
<td>14(75)</td>
<td>21(75)</td>
<td>18(150)</td>
</tr>
<tr>
<td>4c</td>
<td>17(150)</td>
<td>12(75)</td>
<td>21(75)</td>
<td>19(150)</td>
</tr>
<tr>
<td>4d</td>
<td>17(150)</td>
<td>12(75)</td>
<td>19(75)</td>
<td>19(150)</td>
</tr>
<tr>
<td>4e</td>
<td>20(75)</td>
<td>12(37.5)</td>
<td>19(37.5)</td>
<td>22(150)</td>
</tr>
<tr>
<td>4f</td>
<td>20(75)</td>
<td>11(37.5)</td>
<td>20(37.5)</td>
<td>21(37.5)</td>
</tr>
<tr>
<td>4g</td>
<td>16(37.5)</td>
<td>12(37.5)</td>
<td>21(37.5)</td>
<td>19(37.5)</td>
</tr>
<tr>
<td>4h</td>
<td>18(37.5)</td>
<td>13(37.5)</td>
<td>22(37.5)</td>
<td>19(37.5)</td>
</tr>
<tr>
<td>4i</td>
<td>20(75)</td>
<td>14(37.5)</td>
<td>19(75)</td>
<td>22(37.5)</td>
</tr>
<tr>
<td>4j</td>
<td>18(75)</td>
<td>15(37.5)</td>
<td>18(75)</td>
<td>20(37.5)</td>
</tr>
<tr>
<td>4k</td>
<td>18(75)</td>
<td>17(37.5)</td>
<td>19(75)</td>
<td>21(37.5)</td>
</tr>
<tr>
<td>4l</td>
<td>19(37.5)</td>
<td>17(37.5)</td>
<td>20(75)</td>
<td>21(37.5)</td>
</tr>
<tr>
<td>4m</td>
<td>17(37.5)</td>
<td>11(75)</td>
<td>18(75)</td>
<td>18(75)</td>
</tr>
<tr>
<td>4n</td>
<td>17(150)</td>
<td>10(75)</td>
<td>19(75)</td>
<td>16(75)</td>
</tr>
<tr>
<td>4o</td>
<td>15(150)</td>
<td>12(75)</td>
<td>19(75)</td>
<td>17(75)</td>
</tr>
<tr>
<td>4p</td>
<td>16(150)</td>
<td>13(75)</td>
<td>23(75)</td>
<td>16(75)</td>
</tr>
<tr>
<td>4q</td>
<td>15(150)</td>
<td>14(74)</td>
<td>22(37.5)</td>
<td>16(150)</td>
</tr>
<tr>
<td>4r</td>
<td>11(150)</td>
<td>11(75)</td>
<td>19(37.5)</td>
<td>15(150)</td>
</tr>
<tr>
<td>4s</td>
<td>12(150)</td>
<td>12(75)</td>
<td>18(37.5)</td>
<td>15(150)</td>
</tr>
<tr>
<td>4t</td>
<td>12(150)</td>
<td>12(75)</td>
<td>19(37.5)</td>
<td>15(150)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>25(12.5)</td>
<td>20(6)</td>
<td>24(6)</td>
<td>26(12.5)</td>
</tr>
<tr>
<td>Control DMSO</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Values in brackets are MIC values (μg/ml)

The antibacterial screening indicated that among the tested bacterial strains, good inhibitory results were obtained against *Salmonella typhimurium* and *Escherichia coli*. The structural activity study showed that benzimidazoles and their substituted derivatives 4a-l have varying degrees of microbial inhibition. The antibacterial and antifungal activity seemed to be dependent on the heterocyclic moiety as well as on the nature of substituents. Although the benzimidazoles 4a-l itself are observed active but the activity was further enhanced by the presence of nitro and chloro substituent on the benzimidazoles moiety (Table 5.1).

The nitro substituted derivatives 4e, 4f have shown good activity against *E. coli* and *S. aureus*. The maximum inhibition was observed in 4h against *B. subtilis*. The chloro substituted derivatives 4i-l have shown maximum inhibition against *S. aureus*. The tetrahydrobenzimidazoles 4m-p are moderately active against *S. typhimurium* and 4m, 4p are best active against *E. coli* and *B. subtilis* whereas the imidazoles 4q-t showed moderate activity results against test bacterial strains.
In another set of experiments, the above mentioned compounds were also examined for antifungal activity (Table 5.2). Nystatin was used as standard drug for the comparison of antifungal results. The nitro and chloro substituted compounds 4e-1 showed same trend in case of fungal strains.

Table 5.2 In vitro antifungal activity of compounds 4a-t

<table>
<thead>
<tr>
<th>Compound</th>
<th>C. albicans</th>
<th>H. oryzae</th>
<th>A. niger</th>
<th>T. viridae</th>
<th>Penicillium sp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>19(75)</td>
<td>13(150)</td>
<td>14(150)</td>
<td>7(75)</td>
<td>18(75)</td>
</tr>
<tr>
<td>4b</td>
<td>19(75)</td>
<td>12(150)</td>
<td>16(150)</td>
<td>6(75)</td>
<td>18(75)</td>
</tr>
<tr>
<td>4c</td>
<td>19(75)</td>
<td>13(150)</td>
<td>16(150)</td>
<td>8(75)</td>
<td>19(75)</td>
</tr>
<tr>
<td>4d</td>
<td>18(75)</td>
<td>11(150)</td>
<td>14(150)</td>
<td>8(75)</td>
<td>17(75)</td>
</tr>
<tr>
<td>4e</td>
<td>18(37.5)</td>
<td>10(75)</td>
<td>15(37.5)</td>
<td>8(37.5)</td>
<td>18(37.5)</td>
</tr>
<tr>
<td>4f</td>
<td>19(37.5)</td>
<td>12(75)</td>
<td>15(37.5)</td>
<td>8(37.5)</td>
<td>18(37.5)</td>
</tr>
<tr>
<td>4g</td>
<td>19(37.5)</td>
<td>15(75)</td>
<td>16(37.5)</td>
<td>9(37.5)</td>
<td>19(37.5)</td>
</tr>
<tr>
<td>4h</td>
<td>19(37.5)</td>
<td>14(75)</td>
<td>14(37.5)</td>
<td>9(37.5)</td>
<td>19(37.5)</td>
</tr>
<tr>
<td>4i</td>
<td>18(37.5)</td>
<td>15(75)</td>
<td>15(37.5)</td>
<td>10(37.5)</td>
<td>19(37.5)</td>
</tr>
<tr>
<td>4j</td>
<td>18(37.5)</td>
<td>16(75)</td>
<td>15(37.5)</td>
<td>9(37.5)</td>
<td>19(37.5)</td>
</tr>
<tr>
<td>4k</td>
<td>18(37.5)</td>
<td>14(75)</td>
<td>14(37.5)</td>
<td>9(37.5)</td>
<td>19(37.5)</td>
</tr>
<tr>
<td>4l</td>
<td>18(37.5)</td>
<td>14(75)</td>
<td>14(37.5)</td>
<td>8(37.5)</td>
<td>19(37.5)</td>
</tr>
<tr>
<td>4m</td>
<td>18(75)</td>
<td>11(150)</td>
<td>12(37.5)</td>
<td>7(37.5)</td>
<td>18(75)</td>
</tr>
<tr>
<td>4n</td>
<td>18(75)</td>
<td>12(150)</td>
<td>13(37.5)</td>
<td>6(37.5)</td>
<td>17(75)</td>
</tr>
<tr>
<td>4o</td>
<td>17(75)</td>
<td>11(150)</td>
<td>12(37.5)</td>
<td>7(37.5)</td>
<td>16(75)</td>
</tr>
<tr>
<td>4p</td>
<td>19(75)</td>
<td>11(150)</td>
<td>12(37.5)</td>
<td>8(37.5)</td>
<td>17(75)</td>
</tr>
<tr>
<td>4q</td>
<td>19(75)</td>
<td>12(150)</td>
<td>11(150)</td>
<td>6(75)</td>
<td>16(150)</td>
</tr>
<tr>
<td>4r</td>
<td>18(75)</td>
<td>12(150)</td>
<td>12(150)</td>
<td>4(75)</td>
<td>17(150)</td>
</tr>
<tr>
<td>4s</td>
<td>18(75)</td>
<td>13(150)</td>
<td>13(150)</td>
<td>6(75)</td>
<td>18(150)</td>
</tr>
<tr>
<td>4t</td>
<td>18(75)</td>
<td>12(150)</td>
<td>14(150)</td>
<td>6(75)</td>
<td>19(150)</td>
</tr>
<tr>
<td>Nystatin</td>
<td>20 (6)</td>
<td>18(12.5)</td>
<td>18(12.5)</td>
<td>15(6)</td>
<td>20(6)</td>
</tr>
</tbody>
</table>

Control DMSO --- --- --- --- ---

Values in brackets are MIC values (µg/ml)

The excellent inhibition results were obtained against C. albicans and Penicillium sp. by 4e-h. The moderate activity was obtained in H. oryzae and A. niger. The inhibitory activity against the T. viridae was significantly lower than the other tested microorganisms. Hence we conclude that higher activity of compounds 4e-h and 4i-l may be attributed to the presence of nitro and chloro groups. The inhibition by 4a-d, 4m-p and 4q-t is due to the presence of benzimidazole, tetrahydrobenzimidazole and imidazole respectively. Thus the nature of substituents and basic skeleton of molecule have strong influence on the extent of antibacterial and
antifungal activities. Thus data revealed that all compounds have produced the marked enhancement in the potency of these analogues as antifungal and antifungal agents.
5.4 Experimental

The sources of all the fatty acids and instrumentation details are the same as given in Chapter 1 (page 38).

General procedure for the synthesis of 2-substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles (4a-t)

The acid chlorides 1a-d were prepared as reported earlier in Chapter 3 (page 67). Then, 1,2-phenylenediamine derivatives (0.01 mmol) 2a-c and 5 was added to the stirred solution of acid chloride at 0°C in dry dioxane and keep stirring for 30 minutes at room temperature to furnish the corresponding 3 and 6a-d respectively. Similarly 2-substituted imidazoles 4q-t was synthesized by utilizing cis cyclohexanediamine to furnish 8a-d. BF₃·OEt₂ (0.015 mol) in dry dioxane (10 ml) was added dropwise to the above stirred reaction mixture in 10 minutes and reaction mixture further refluxed for 1 to 2 hours at 130°C. The resulting solution was concentrated in vacuum, saturated NH₄Cl solution added at till the pH becomes 6, extracted with EtOAc, dried over anhydrous Na₂SO₄ and concentrated in vacuum to give the crude product 4a-t, which was further purified by column chromatography (Hexane:EtOAc, v:v) 4a, (99:1); 4b, (98:2); 4c, (97:3); 4d, (97:3); 4e, (99:1); 4f, (98:2); 4g, (97:3); 4h, (97:3); 4i, (99:1); 4j, (98:2); 4k, (97:3); 4l, (97:3); 4m, (99:1); 4n, (98:2); 4o, (97:3); 4p, (97:3); 4q, (99:1); 4r, (98:2); 4s (94:6); 4t, (94:6).

Antibacterial Activity

The antibacterial activity of test compounds and standard chloramphenicol was done by filter paper disc method⁷⁸ against Staphyloccous aureus MSSA 22, Escherichia coli K12, Bacillus subtilis ATCC 6501, Salmonella typhimurium MTCC 98 at a concentration of 100µg/ml. Media with DMSO was set up as control.
Antifungal activity

The standard agar disc diffusion method was performed to evaluate the antifungal property of the test compounds and standard nystatin. *Aspergillus niger* (lab isolate from ICAR, Jaipur), *Candida albicans* IOA-109, *Penicillium* sp (laboratory isolate), *Helminthosporum oryzae* (lab isolate from ICAR, Jaipur), *Trichoderma viridae* ATCC 5170 were used in this study. Solvent control DMSO was also run.

SPECTROSCOPIC DATA

2-(Dec-9-enyl)-1H-benzimidazole (4a)

Colorless oily liquid: yield: 89%

IR (KBr): 3350, 1630, 1585 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.01 (s, 1H, N-H), 6.73-6.71 (m, 4H, Ar-H), 5.82 (dd, 1H, \(J_{H-N}=6.6\) Hz, \(J_{H-H}=10.2\) Hz, \(J_{H-N}=17.1\) Hz, CH\(_2\)=CH-), 5.02 (dd, 1H, \(J_{H-N}=10.2\) Hz, \(J_{H-N}=17.1\) Hz, CH\(_2\)=CH-), 4.90 (dd, 1H, \(J_{H-N}=5.1\) Hz, CH\(_2\)=CH-), 2.34 (t, 2H, \(J=7.12\) Hz, \(J=2.34\) Hz, CH\(_2\)=CH-), 2.03 (m, 2H, CH\(_2\)=CH-), 1.63 (m, 2H, CH\(_2\)=CH-), 1.30 (br.s, 10H, chain CH\(_2\)).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): 143.44, 139.01, 133.56, 121.45, 118.17, 114.14, 34.25, 33.77, 29.20, 28.88, 24.73.

MS (m/z, %): (M+1)\(^+\) 257 (56), M\(^+\) 256 (45), 229 (34), 145 (40), 117 (100).

*Anal. Calcd.* for C\(_{17}\)H\(_{24}\)N\(_2\): C, 79.65; H, 9.43; N, 10.92. Found: C, 79.06; H, 9.49; N, 10.87%.

2-(Heptadec-8-enyl)-1H-benzimidazole (4b)

Pale yellow oily liquid; yield: 89%.

IR (KBr): 3360, 1640, 1590 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.12 (s, 1H, N-H), 6.73-6.70 (m, 4H, Ar-H), 5.38 (m, 2H, CH\(_2\)=CH-), 2.35 (t, 2H, \(J=7.22\) Hz, \(J=2.35\) Hz, CH\(_2\)=CH-), 2.02 (m, 4H, -
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

$\text{CH}_2\text{CH=CH-CH}_2\text{-}$, 1.61 (m, 2H, $\beta$ to benzimidazole ring), 1.30 (br.s, 18H, chain $\text{CH}_2$), 0.89 (3H, dist. t, $\text{CH}_3$).

$^{13}\text{C NMR}$ (100 MHz, CDCl$_3$): 143.22, 133.66, 122.77, 118.41, 34.20, 31.81, 29.65, 29.49, 29.09, 27.05, 24.72, 22.56, 22.45, 14.92.

$\text{MS}$ (m/z, %): (M+1)$^+$ 355 (40), M$^+$ 354 (34), 237 (25), 181 (25), 117 (100).

$\text{Anal. Calcd.}$ for C$_{24}$H$_{36}$N$_2$: C, 81.31; H, 10.79; N, 7.90. Found: C, 81.88; H, 10.73; N, 7.94%.

2-$\text{(8Z, 11R)-11-Hydroxyheptadec-8-enyl-1H-benzimidazole}$ (4c)

Yellow oily liquid; yield: 88%.

$\text{IR}$ (KBr): 3390, 1650, 1580 cm$^{-1}$.

$^1\text{H NMR}$ (400 MHz, CDCl$_3$): $\delta$ 9.25 (s, 1H, N-H), 6.72-6.70 (m, 4H, Ar-H), 5.42 (m, 2H, -CH=CH-), 3.66 (m, 1H, -CH-OH), 2.32 (t, 2H, $J = 7.19$ Hz, $\alpha$ to benzimidazole ring), 2.27 (m, 1H, -OH), 2.02 (m, 4H, -CH$_2$-CH=CH-CH$_2$-), 1.57 (m, 2H, $\beta$ to benzimidazole ring), 1.39 (br.s, 18H, chain CH$_2$), 0.88 (3H, dist. t, CH$_3$).

$^{13}\text{C NMR}$ (100 MHz, CDCl$_3$): 143.44, 134.09, 134.09, 123.22, 117.81, 34.02, 31.81, 29.56, 29.94, 29.92, 27.51, 24.27, 22.65, 22.54, 14.17.

$\text{MS}$ (m/z, %): (M+1)$^+$ 371 (38), M$^+$ 370 (34), 255 (20), 241 (100), 173 (15).

$\text{Anal. Calcd.}$ for C$_{24}$H$_{38}$N$_2$O: C, 77.79; H, 10.33; N, 7.56. Found: C, 77.16; H, 10.39; N, 7.51%.

2-$\text{(8R, 11Z)-8-Hydroxyheptadec-11-enyl-1H-benzimidazole}$ (4d)

Yellow oily liquid; yield: 88%.

$\text{IR}$ (KBr): 3355, 1626, 1596 cm$^{-1}$.

$^1\text{H NMR}$ (400 MHz, CDCl$_3$): $\delta$ 9.04 (s, 1H, N-H), 6.78-6.76 (m, 4H, Ar-H), 5.44 (m, 2H, -CH=CH-), 3.64 (m, 1H, -CH-OH), 2.31 (t, 2H, $J = 7.20$ Hz, $\alpha$ to benzimidazole ring), 2.11 (m, 1H, -OH), 2.04 (m, 4H, -CH$_2$-CH=CH-CH$_2$-), 1.61 (m, 2H, $\beta$ to benzimidazole ring), 1.40 (br.s, 18H, chain CH$_2$), 0.88 (3H, dist. t, CH$_3$).
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

$^{13}$C NMR (100 MHz, CDCl$_3$): 143.66, 133.17, 123.22, 118.12, 34.25, 31.41, 29.58, 29.39, 29.23, 27.26, 24.72, 24.22, 14.91.

MS (m/z, %): (M+1)$^+$ 371 (20), M$^+$ 370 (45), 299 (10), 245 (100), 131 (15).

Anal. Calcd. for C$_{24}$H$_{38}$N$_2$O: C, 77.79; H, 10.33; N, 7.56. Found: C, 77.21; H, 10.27; N, 7.53%.

2-(Dec-9-enyl)-5-nitro-1H-benzimidazole (4e)

Light yellow oily liquid; yield: 85%.

IR (KBr): 3375, 1660, 1575 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.22 (s, 1H, N-H), 7.12 (d, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 6.91 (m, 1H, Ar-H), 5.82 (tdd, 1H, $J_{H_{-}CH_2}$ = 6.6 Hz, $J_{H_{-}H_z}$ = 10.2 Hz, $J_{H_{-}H_6}$ = 17.1 Hz, CH$_2$-CH$\equiv$CH), 5.02 (dd, 1H, $J_{H_z-H_6}$ = 10.2 Hz, $J_{H_z-H_6}$ = 1.2 Hz, $H_2$C-CH), 4.90 (dd, 1H, $J_{H_{-}H_6}$ = 17.1 Hz, $J_{H_{-}H_6}$ = 1.2 Hz, H$_2$C=CH$\equiv$C), 2.28 (t, 2H, $J$ = 7.17 Hz, $\alpha$ to benzimidazole ring), 2.04 (m, 2H, -CH$_2$-CH=CH$_2$), 1.66 (m, 2H, $\beta$ to benzimidazole ring), 1.31 (br.s, 10H, chain CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): 143.12, 139.01, 136.22, 130.12, 131.65, 122.26, 117.31, 33.91, 31.61, 28.22, 27.19, 22.33.

MS (m/z, %): (M+1)$^+$ 302 (10), M$^+$ 301 (82), 274 (10), 176 (100), 162 (60).

Anal. Calcd. for C$_{17}$H$_{23}$N$_3$O$_2$: C, 67.76; H, 7.68; N, 13.94. Found: C, 67.30; H, 7.73; N, 13.99%.

2-(Heptadec-8-enyl)-5-nitro-1H-benzimidazole (4f)

Pale yellow oily liquid; yield: 84%.

IR (KBr): 3352, 1660, 1575 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.21 (s, 1H, N-H), 7.13 (d, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 6.90 (m, 1H, Ar-H), 5.38 (m, 2H, -CH=CH$\equiv$C), 2.34 (t, 2H, $J$ = 7.24 Hz, $\alpha$ to benzimidazole ring), 2.02 (m, 4H, -CH$_2$-CH=CH-CH$_2$), 1.63 (m, 2H, $\beta$ to benzimidazole ring), 1.30 (br.s, 18H, chain CH$_2$), 0.89 (3H, dist. t, CH$_3$).
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

$^{13}C\text{ NMR}$ (100 MHz, CDCl$_3$): 143.62, 136.06, 131.33, 129.71, 123.44, 118.13, 34.19, 31.41, 29.53, 28.99, 27.41, 22.32, 22.45, 14.15.

$MS$ (m/z, %): (M+1)$^+$ 400 (20), M$^+$ 399 (25), 286 (75), 190 (70), 162 (100).

$Anal. \ Calcd.$ for C$_{24}$H$_{37}$N$_3$O$_2$: C, 72.15; H, 9.33; N, 10.51. Found: C, 72.70; H, 9.28; N, 10.56%.

2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-S-nitro-1H-benzimidazole (4g)
Yellow oily liquid; yield: 82%.

$IR$ (KBr): 3355, 1640, 1580 cm$^{-1}$.

$^1H\text{ NMR}$ (400 MHz, CDCl$_3$): $\delta$ 9.25 (s, 1H, N-H), 7.13 (d, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 6.91 (m, 1H, Ar-H), 5.45 (m, 2H, -CH=CH-), 3.68 (m, 1H, -CH-OH), 2.33 (t, 2H, $J = 7.31$ Hz, a to benzimidazole ring), 2.23 (m, 1H, -OH), 2.04 (m, 4H, -CH$_2$-CH=CH-CH$_2$-), 1.61 (m, 2H, $\beta$ to benzimidazole ring), 1.36 (br.s, 18H, chain CH$_2$), 0.88 (3H, dist. t, CH$_3$).

$^{13}C\text{ NMR}$ (100 MHz, CDCl$_3$): 144.13, 135.44, 131.19, 129.31, 123.33, 117.71, 37.11, 34.26, 31.83, 29.61, 27.10, 25.81, 23.11, 22.15, 15.06.

$MS$ (m/z, %): (M+1)$^+$ 416 (35), M$^+$ 415 (70), 330 (100), 300 (70), 260 (20).

$Anal. \ Calcd.$ for C$_{24}$H$_{37}$N$_3$O$_3$: C, 69.37; H, 8.97; N, 10.11. Found: C, 69.79; H, 8.92; N, 10.16%.

2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-5-nitro-1H-benzimidazole (4h)
Yellow oily liquid; yield: 80%.

$IR$ (KBr): 3390, 1630, 1584 cm$^{-1}$.

$^1H\text{ NMR}$ (400 MHz, CDCl$_3$): $\delta$ 9.20 (s, 1H, N-H), 7.16 (d, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 6.93 (m, 1H, Ar-H), 5.43 (m, 2H, -CH=CH-), 3.67 (m, 1H, CH-OH), 2.36 (t, 2H, $J = 7.29$ Hz, a to benzimidazole ring), 2.21 (m, 1H, -OH), 2.04 (m, 4H, -CH$_2$-CH=CH-CH$_2$-), 1.64 (m, 2H, $\beta$ to benzimidazole ring), 1.42 (br.s, 18H, chain CH$_2$), 0.87 (3H, dist. t, CH$_3$).
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

$^{13}C\text{ NMR}$ (100 MHz, CDCl$_3$): 144.23, 135.64, 131.39, 129.41, 123.83, 117.71, 37.51, 34.66, 31.38, 29.51, 27.43, 25.44, 23.11, 22.15, 15.16.

$MS$ (m/z, %): (M+1)$^+$ 416 (10), M$^+$ 415 (70), 344 (100), 290 (25), 246 (20).

$Anal.\ Calcd.$ for C$_{24}$H$_{37}$N$_3$O$_3$: C, 69.37; H, 8.97; N, 10.11. Found: C, 69.84; H, 8.92; N, 10.13%.

2-(Dec-9-enyl)-5-chloro-1H-benzimidazole (4i)

Colorless oily liquid; yield: 88%.

$IR$ (KBr): 3368, 1640, 1578 cm$^{-1}$.

$^1H\text{ NMR}$ (400 MHz, CDCl$_3$): $\delta$ 9.01 (s, 1H, N-H), 7.43-7.31 (m, 3H, Ar-H), 5.82 (tdd, 1H, $J^H_{CH_2} = 6.6$ Hz, $J^H_{CH} = 10.2$ Hz, $J^H_{CH_2} = 17.1$ Hz, CH$_2$=CH), 5.02 (dd, 1H, $J^H_{CH_2} = 10.2$ Hz, $J^H_{CH} = 17.1$ Hz, $J^H_{CH_2} = 1.2$ Hz, H$_2$C=CH), 4.90 (dd, 1H, $J^H_{CH} = 1.2$ Hz, H$_2$C=CH), 2.31 (t, 2H, $J = 7.33$ Hz, $\alpha$ to benzimidazole ring), 2.04 (m, 2H, -CH$_2$-CH=CH$_2$), 1.63 (m, 2H, $\beta$ to benzimidazole ring), 1.33 (br.s, 10H, chain CH$_2$).

$^{13}C\text{ NMR}$ (100 MHz, CDCl$_3$): 142.81, 141.31, 132.91, 131.61, 129.71, 128.91, 124.71, 123.46, 29.71, 28.36, 27.91, 23.91, 22.45, 14.81.

$MS$ (m/z, %): (M+1)$^+$ 291 (10), M$^+$ 290 (85), 263 (100), 179 (25), 151 (40).

$Anal.\ Calcd.$ for C$_{17}$H$_{23}$ClN$_2$: C, 70.22; H, 7.96; N, 9.63. Found: 70.80; H, 7.92; N, 9.58%.

2-(Heptadec-8-enyl)-5-chloro-1H-benzimidazole (4j)

Light yellow oily liquid; yield: 87%.

$IR$ (KBr): 3370, 1655, 1589 cm$^{-1}$.

$^1H\text{ NMR}$ (400 MHz, CDCl$_3$): $\delta$ 9.12 (s, 1H, N-H), 7.55-7.20 (m, 3H, Ar-H), 5.44 (m, 2H, -CH=CH-), 2.24 (t, 2H, $J = 7.44$ Hz, $\alpha$ to benzimidazole ring), 2.04 (m, 4H, -CH$_2$-CH=CH-CH$_2$-), 1.56 (m, 2H, $\beta$ to benzimidazole ring), 1.29 (br.s, 18H, chain CH$_2$), 0.87 (3H, dist. t, CH$_3$).
2-Substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles

$^{13}C$ NMR (100 MHz, CDCl$_3$): 143.48, 133.85, 131.24, 129.57, 127.71, 121.61, 117.81, 37.41, 34.21, 33.92, 29.56, 29.13, 25.84, 23.13, 22.35, 14.12.

MS (m/z, %): (M+1)$^+$ 389 (30), M$^+$ 388 (75), 275 (15), 165 (100), 151 (80).

Anal. Calcd. for C$_{24}$H$_{37}$ClN$_2$: C, 74.11; H, 9.58; N, 7.20. Found: C, 74.68; H, 9.63; N, 7.16%.

2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-5-chloro-1H-benzimidazole (4k)

Yellow oily liquid; yield: 87%.

IR (KBr): 3412, 1648, 1572 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.25 (s, 1H, N-$H$), 7.43-7.31 (m, 3H, Ar-$H$), 5.46 (m, 2H, -CH=CH-$H$), 3.67 (m, 1H, -CHOH), 2.33 (t, 2H, $J$ = 7.12 Hz, $\alpha$ to benzimidazole ring), 2.27 (m, 1H, -OH), 2.02 (m, 4H, CH$_2$-CH=CH-CH$_2$), 1.57 (m, 2H, $\beta$ to benzimidazole ring), 1.39 (br.s, 18H, chain CH$_2$), 0.88 (3H, dist. t, C-$H$$_3$).

$^{13}C$ NMR (100 MHz, CDCl$_3$): 142.98, 133.76, 130.99, 129.76, 127.80, 121.53, 119.01, 37.03, 34.12, 33.57, 29.34, 28.37, 25.71, 23.91, 22.11, 15.17.

MS (m/z, %): (M+1)$^+$ 405 (15), M$^+$ 404 (70), 319 (100), 249 (85), 207 (90).

Anal. Calcd. for C$_{24}$H$_{37}$ClN$_2$: C, 71.18; H, 9.20; N, 6.91. Found: C, 71.66; H, 9.23; N, 6.87%.

2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-5-chloro-1H-benzimidazole (4l)

Yellow oily liquid; yield: 86%.

IR (KBr): 3349, 1629, 1590 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.29 (s, 1H, N-$H$), 7.46-7.33 (m, 3H, Ar-$H$), 5.45 (m, 2H, -CH=CH-$H$), 3.68 (m, 1H, -CHOH), 2.36(t, 2H, $J$ = 7.23 Hz, $\alpha$ to benzimidazole ring), 2.29 (m, 1H, -OH), 2.04 (m, 4H, -CH$_2$-CH=CH-CH$_2$), 1.62 (m, 2H, $\beta$ to benzimidazole ring), 1.28 (br.s, 18H, chain CH$_2$), 0.88 (3H, dist. t, CH$_3$).

$^{13}C$ NMR (100 MHz, CDCl$_3$): 142.68, 133.67, 130.89, 129.67, 127.82, 121.43, 119.01, 37.53, 34.41, 33.51, 29.43, 28.32, 25.17, 23.22, 22.13, 15.19.

MS (m/z, %): (M+1)$^+$ 405 (10), M$^+$ 404 (80), 333 (40), 279 (85), 179 (65).
2-Substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles

**Anal. Calcd.** for C\textsubscript{24}H\textsubscript{37}ClN\textsubscript{2}O: C, 71.18; H, 9.20; N, 6.91. Found: C, 71.71; H, 9.16; N, 6.94%.

2-(Dec-9-enyl)-4,5,6,7-tetrahydro-1H-benzimidazole (4m)
Pale yellow oily liquid; yield: 90%.

**IR** (KBr): 3338, 1632, 1580 cm\(^{-1}\).

\(^1\text{H} NMR\) (400 MHz, CDCl\textsubscript{3}): \(\delta\) 9.01 (s, 1H, N-H), 5.82 (tdd, 1H, \(J_{H-ZCH_2} = 6.6\) Hz, \(J_{H-H_z} = 10.2\) Hz, \(J_{H_z-H} = 17.1\) Hz, CH\(_2\)=CH-), 5.02 (dd, 1H, \(J_{H_z-H} = 10.2\) Hz, \(J_{H_z-H_z} = 3.6\) Hz, H\(_2\)C=CH), 4.90 (dd, 1H, \(J_{H_z-H} = 17.1\) Hz, \(J_{H_z-H_z} = 3.6\) Hz, H\(_2\)C=CH), 2.34 (t, 2H, \(J = 7.36\) Hz, \(\alpha\) to benzimidazole ring), 2.03 (m, 2H, -CH\(_2\)-CH=CH\(_2\)), 1.87 (m, 2H, -CH- ring), 1.69 (m, 2H, \(\beta\) to imidazole ring), 1.50 (m, 8H, -CH\(_2\)- ring), 1.30 (br.s, 10H, chain CH\(_2\)).

\(^{13}\text{C} NMR\) (100 MHz, CDCl\textsubscript{3}): 170.33, 139.81, 117.61, 64.01, 37.62, 31.91, 29.88, 28.35, 24.57, 22.50, 22.21.

**MS** (m/z, %): \((M+1)^+ 263 (30), M^+ 262 (70), 235 (100), 179 (70), 123 (60).**

**Anal. Calcd.** for C\textsubscript{17}H\textsubscript{30}N\textsubscript{2}: C, 77.82; H, 11.51; N, 10.67. Found: C, 77.30; H, 11.47; N, 10.70%.

2-(Heptadec-8-enyl)-4,5,6,7-tetrahydro-1H-benzimidazole (4n)
Light yellow oily liquid; yield: 89%.

**IR** (KBr): 3356, 1641, 1593 cm\(^{-1}\).

\(^1\text{H} NMR\) (400 MHz, CDCl\textsubscript{3}): \(\delta\) 9.12 (s, 1H, N-H), 5.38 (m, 2H, -CH=CH-), 2.34 (t, 2H, \(J = 7.30\) Hz, \(\alpha\) to benzimidazole ring), 2.02 (m, 4H, -CH\(_2\)-CH=CH-CH\(_2\)-), 1.86 (m, 2H, -CH- ring), 1.66 (m, 2H, \(\beta\) to imidazole ring), 1.50 (m, 8H, -CH\(_2\)- ring), 1.32 (br.s, 18H, chain CH\(_2\)), 0.88 (3H, dist. t, CH\(_3\)).

\(^{13}\text{C} NMR\) (100 MHz, CDCl\textsubscript{3}): 169.97, 63.91, 36.92, 31.88, 28.22, 27.36, 24.63, 22.49, 22.12, 21.90, 14.91.

**MS** (m/z, %): \((M+1)^+ 361 (40), M^+ 360 (85), 247 (45), 207 (50), 193 (67).**
2-Substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles

**Anal. Calcd.** for C_{24}H_{44}N_{2}: C, 79.95; H, 12.29; N, 7.76. Found: C, 79.40; H, 12.36; N, 7.72%.

2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-4,5,6,7-tetrahydro-1H-benzimidazole (4o)
Yellow oily liquid; yield: 88%.

**IR** (KBr): 3350, 1620, 1592 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.25 (s, 1H, N-H), 5.42 (m, 2H, -CH=CH-), 3.66 (m, 1H, -CH(OH)), 2.32 (t, 2H, \(J = 7.28\) Hz, a to benzimidazole ring), 2.27 (m, 1H, -OH), 2.02 (m, 4H, -CH\(_2\)-CH=CH\(_2\)-), 1.88 (m, 2H, -CH- ring), 1.67 (m, 2H, \(\beta\) to imidazole ring), 1.50 (m, 8H, -CH\(_2\)- ring), 1.39 (br.s, 18H, chain CH\(_2\)), 0.88 (3H, dist. t, CH\(_3\)).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): 169.99, 71.72, 63.89, 36.98, 34.22, 33.63, 31.66, 28.61, 27.63, 24.56, 22.91, 22.11, 21.81, 14.73.

**MS** (m/z %): (M+1)\(^+\) 377 (15), M\(^+\) 376 (70), 291 (10), 247 (85), 123 (100).

**Anal. Calcd.** for C_{24}H_{44}N_{2}O: C, 76.55; H, 11.77; N, 7.43. Found: C, 76.01; H, 11.82; N, 7.40%.

2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-4,5,6,7-tetrahydro-1H-benzimidazole (4p)
Yellow oily liquid; yield: 87%.

**IR** (KBr): 3358, 1658, 1577 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.72 (s, 1H, N-H), 5.44 (m, 2H, -CH=CH-), 3.68 (m, 1H, -CH(OH)), 2.28 (t, 2H, \(J = 7.39\) Hz, a to benzimidazole ring), 2.21 (m, 1H, -OH), 2.03 (m, 4H, -CH\(_2\)-CH=CH\(_2\)-), 1.87 (m, 2H, -CH- ring), 1.69 (m, 2H, \(\beta\) to imidazole ring), 1.52 (m, 2H, -CH\(_2\)- ring), 1.36 (br.s, 18H, chain CH\(_2\)), 0.88 (3H, dist. t, CH\(_3\)).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): 169.87, 71.73, 64.01, 36.89, 34.32, 33.36, 31.66, 28.64, 27.53, 24.65, 22.98, 22.11, 21.81, 14.69.

**MS** (m/z, %): (M+1)\(^+\) 377 (30), M\(^+\) 376 (50), 305 (10), 251 (75), 123 (100).
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

**Anal. calcd.** for C_{24}H_{44}N_{2}O: C, 76.55; H, 11.77; N, 7.43. Found: C, 76.98; H, 11.72; N, 7.47%.

2-(Dec-9-eyl)-1H-imidazole (4q)

Colorless oily liquid: yield: 89%.

**IR** (KBr): 3354, 1642, 1598 cm\(^{-1}\).

\(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.81 (s, 1H, N-H), 5.82 (tdd, 2H, \(J_{H-H_2} = 6.6\) Hz, \(J_{H-H_e} = 10.2\) Hz, \(J_{H-e-H_2} = 17.1\) Hz, CH\(_2\)=CH\(-\)), 5.02 (2H, dd, \(J_{H-e-H} = 10.2\) Hz, \(J_{H-e-H_2} = 3.6\) Hz, H\(_e\)=CH\(-\)), 4.90 (2H, dd, \(J_{H-e-H} = 17.1\) Hz, \(J_{H-e-H_2} = 3.6\) Hz, \(J_{H-e-H_2} = 3.6\) Hz, \(H_e\)=CH\(-\)), 2.31 (t, 2H, \(J = 7.16\) Hz, \(\alpha\) to imidazole ring), 2.04 (m, 2H, -CH\(_2\)-CH=CH\(_2\)), 1.66 (m, \(\beta\) to imidazole ring), 1.36 (br.s, 10H, chain CH\(_2\)).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): 152.31, 130.96, 125.93, 33.66, 32.81, 30.14, 23.26, 14.31.

**MS** (m/z, %): (M+1)^+ 207 (20), M^+ 208 (22), 176 (36), 109 (100), 81 (100).

**Anal. Calcd.** for C\(_{13}\)H\(_{22}\)N\(_2\): C, 75.69; H, 10.74; N, 13.57. C, 75.22; H, 10.70; N, 13.63%.


2-(Heptadec-8-enyl)-1H-imidazole (4r)

Pale yellow oily liquid: yield: 88%.

**IR** (KBr): 3367, 1644, 1590 cm\(^{-1}\).

\(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.77 (s, 1H, N-H), 5.62 (m, 2H, -CH=CH\(-\)), 2.33 (t, 2H, \(J = 7.35\) Hz, \(\alpha\) to imidazole ring), 2.05 (m, 4H, -CH\(_2\)=CH-CH=CH\(_2\)-), 1.62 (m, 2H, \(\beta\) to imidazole ring), 1.29 (br.s, 18H, chain CH\(_2\)), 0.87 (3H, dist. t, CH\(_3\)).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): 152.71, 131.76, 126.83, 33.38, 32.25, 30.44, 23.62, 14.38.

**MS** (m/z, %): (M+1)^+ 305 (40), M^+ 304 (22), 191 (31), 165 (31), 67 (100).

**Anal. Calcd.** for C\(_{20}\)H\(_{36}\)N\(_2\): C, 78.89; H, 11.91; N, 9.20. C, 78.35; H, 11.86; N, 9.15%.
2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-1H-imidazole (4s)

Yellow oily liquid: yield: 86%.

IR (KBr): 3378, 1655, 1597 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 9.81 (s, 1H, N-H), 5.66 (m, 2H, -CH=CH-), 3.59 (m, 1H, -CH-OH), 2.36 (t, 2H, J = 7.39 Hz, α to imidazole ring), 2.32 (m, 1H, -OH), 2.03 (m, 4H, -CH₂-CH=CH-CH₂-), 1.62 (m, 2H, β to imidazole ring), 1.29 (br.s, 18H, chain CH₂), 0.88 (3H, dist. t, CH₃).

¹³C NMR (100 MHz, CDCl₃): 152.91, 131.46, 126.57, 71.93, 36.97, 34.21, 33.62, 31.64, 28.51, 27.35, 24.62, 22.28, 22.11, 21.82, 14.36.

MS (m/z, %): (M+1)⁺ 321 (40), M⁺ 320 (22), 235 (100), 191 (31), 165 (100).

Anal. Calcd. for C₂₀H₃₆N₂O: C, 74.96; H, 11.31; N, 8.74. C, 74.61; H, 11.37; N, 8.70%.

2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-1H-imidazole (4t)

Yellow oily liquid: yield: 86%.

IR (KBr): 3354, 1628, 1578 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 9.81 (s, 1H, N-H), 5.59 (m, 2H, -CH=CH-), 3.61 (m, 1H, -CH-OH), 2.41 (t, 2H, J = 7.44 Hz, α to imidazole ring), 2.33 (m, 1H, -OH), 2.05 (m, 4H, -CH₂-CH=CH-CH₂-), 1.65 (m, 2H, β to imidazole ring), 1.30 (br.s, 18H, chain CH₂), 0.89 (3H, dist. t, CH₃).

¹³C NMR (100 MHz, CDCl₃): 152.81, 131.32, 126.33, 71.64, 36.87, 34.58, 33.36, 31.44, 28.45, 27.63, 24.52, 22.91, 22.27, 21.73, 14.34.

MS (m/z, %): (M+1)⁺ 321 (38), M⁺ 320 (46), 249 (100), 195 (18), 165 (73).

Anal. Calcd. for C₂₀H₃₆N₂O: C, 74.96; H, 11.31; N, 8.74. C, 74.48; H, 11.26; N, 8.69%.
2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles

5.5 References


2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles


2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles


2-Substituted-benzimidazoles, tetrahydrobenzimidazoles and imidazoles


