CHAPTER 10

IMIDAZOLINONES
Among the Nitrogen heterocycles, imidazoles and imidazolinones have received considerable attention on account of their potential biological action many clinically useful drugs have emerged from this class of compounds e.g. imidazolinone as adrenergic agents [4].

Imidazolinone (I) is a five membered heterocycle having 2-nitrogen atoms in the 1 and 3 positions and a carbonyl group at 5-position. The discovery of the 2-substituted-5-imidazolones dates back to the year 1888 [2].

![Imidazolinone](image)

The outstanding property of imidazolinone its greater chemical stability because of aromatic character. Its stability is proved by its greater resistance towards action by acids, bases and as well by the oxidizing agents. Considerable efforts have been made in simplifying the chemistry of imidazolinone because of its tautomeric equilibrium involving a shift of the proton on nitrogen. The problem has been overcome by alkylation one of the ring nitrogens, which led to potent biologically active compounds.

**Synthesis of the Compounds**

The ring closure can be effected under a variety of conditions. Different methods have been documented for the synthesis of imidazolinones in literature [3-10]. Some of the important methods are discussed.

Amides of α-acylamino acrylic acids obtained from the condensation of azlactone and primary amine can be converted into imidazolinone derivative as shown in equations 1.
This method has a great attention nowadays because of their wide range of pharmaceutical applications and their biological activities\textsuperscript{[11]}.

**Biological activities**

The imidazolinones are reported to exhibit a wide variety of therapeutic activities\textsuperscript{[12]}. On the other hand, 9-aminobenzophenone associated with various biological activities\textsuperscript{[13-14]}.

Member of this ring has considerable attention as therapeutic drugs. Typical examples are metronidazole (II), furdazole (III), ronidazole (IV).
The biological effects of imidazolinones resemble those of biogenic amines which show marked effects on the vessels of the circulatory system particularly as local vasoconstrictors, which are clinically useful as nasal decongestants. These adrenergic blocking agents have found clinically application in the treatment of hypertension e.g. Naphazoline.

Another interesting chemotherapeutic agent is an effective antibiotic azepinomycin (V) used in Japan. Which has been isolated from the cultures of streptomycetes.[15]

In view of the broad spectrum of [16-19] biological activity displayed by Imidazolinones containing efforts are being made in search of potent molecules and the literature was cited in table.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 3-dihydro-4-hydroxy-1, 5-dimethyl-3-phenyl-2H-imidazol-2-one.</td>
<td>Anticonvulsant</td>
<td>C. Sergio et al. [20]</td>
</tr>
<tr>
<td>1, 3-dihydro-1-methyl-5-nitro-2H-imidazol-2-one.</td>
<td>Amebicidal</td>
<td>K. Nagarajan et al. [21]</td>
</tr>
<tr>
<td>5-(4-chlorophenyl) methylene]-3, 5-dihydro-3-(2-hydroxy phenyl]-2-methyl]4H-imidazol-4-one.</td>
<td>Antibacterial</td>
<td>A.K. Sangupta et al. [22]</td>
</tr>
<tr>
<td>2-Alkyl-5-cycloalkylidene-4(5A)-imidazoliones</td>
<td>Hypnotic &amp; Sedative</td>
<td>M.W. Goldberg et al. [23]</td>
</tr>
<tr>
<td>1-(5-cyclohexyl-1, 3, 4-thiodiazol-2-yl)-(1, 5-dihydro-3propyl]-2H-imidazol-2-one.</td>
<td>Herbicide</td>
<td>K. John [24]</td>
</tr>
<tr>
<td>1-(dimethyl amino)-1, 3-dihydro-monohydrochloride-2H-imidazole-2-one.</td>
<td>Tumor</td>
<td>M. Michiko et al. [25]</td>
</tr>
<tr>
<td>2-amino-1, 3-dihydro-1-methyl-4H-imidazol-4-one.</td>
<td>Antidiabetic</td>
<td>M. Maciejewska et al. [26]</td>
</tr>
<tr>
<td>2-(2-amino ethyl]-3-(1, 1-dimethyl ethyl]-3, 5-dihydro-5, 5-diphenoxy-[4H-imidazol-4-one.</td>
<td>Histamine receptor</td>
<td>V.L. Goldfar et al. [27]</td>
</tr>
<tr>
<td>2-(4-chlorophenyl]-3-[2-(diethyl amino) ethyl]-3, 5-dihydro-5-[phenylmethylen]-4H-imidazol-4-one.</td>
<td>Antiarrhythmnic</td>
<td>E. Bousquet et al. [28]</td>
</tr>
<tr>
<td>5-(4-chlorophenyl] methylene]-3, 5-dihydro-2-methyl-3-[5-methyl]-1, 3, 4-thiadiazol-2-4H-imidazol-5-one.</td>
<td>CNS stimulant</td>
<td>S.S. Tiwari et al. [29]</td>
</tr>
<tr>
<td>4-[4-bromo benzoyl]-1, 3-dihydro-5-methyl-2H-imidazol-2-one.</td>
<td>Cardiotonic</td>
<td>Y.H. Chen et al. [31]</td>
</tr>
<tr>
<td>3-(1H-benzimidazol-2-yl)-3, 5-dihydro-2-methyl-5-(Phenyl methylene)-4H-imidazol-4-one.</td>
<td>Antinflammatory</td>
<td>M. Verma et al. [32]</td>
</tr>
</tbody>
</table>
Synthesis of compounds

The compounds selected for synthesis in our research study may be represented by the general formula given as under

\[ R=C_6H_5,2-Cl, C_6H_4,4-Cl, C_6H_4,2,4-Cl_2, C_6H_3,3,4-(OCH_3)_2, C_6H_3,2-OH, C_6H_4,4-OH, C_6H_4,4-OH,3-OH, C_6H_3,2-OCH_3, C_6H_4,3-NO_2, 4-NO_2, C_6H_4. \]

Synthesis of this series of compounds in the following two steps.

1. Preparation of 4-Arylidene-2-phenyl-5-oxazolinones.

2. Preparation of 4-(4'-benzylidene-2'-phenyl-5'-oxo-imidazolin-1'yl)Benzophenone.

Reactions involved

The reaction sequence involved in the synthesis of compounds of series (II) can be summarised as follows


**Mechanism**

Cyclisation of N-acyl-α-amino acid with acetic anhydride yields an oxazolone derivative on azlactone (I).
The methylene group in compound (I) is reactive and condenses with aldehyde, readily affords the benzylidene derivative (II).

![Diagram](image)

Benzylidene derivative (II) in which the electron density around the oxygen atoms is in oxazoline ring and this can be easily very less replaced by nitrogen.

![Diagram](image)

On cyclisation of the intermediate (III) by the removal of water molecule to gave the final product.
Materials and Methods

Step 1 : Preparation of 4-Benzylidene-2-phenyl-5-oxazolinone.

Place a mixture 2g (1.92 ml, 0.01mol) of redistilled benzaldehyde, 1.8g (0.01 mol) of benzoylglycine, 5.7g (0.05mol) of acetic anhydride and 1.5g (0.01mol) of anhydrous sodium acetate in 500 ml conical flask and heat an electric hotplate with constant shaking. As soon as the mixture has liquefied completely, transfer the flask to a water bath and heat for 2 hours. Then add 200 ml of methanol slowly to the contents of the flask, allow mixture to stand overnight, filter the crystalline product with suction wash with two 40 ml portions of ice-cold alcohol and then wash with two 10 ml portion of boiling water. dry at 100°C yield 58%. m.p. 164-165°C. C_{16}H_{13}NO_2 (Found : C 76.38%, H 5.16%, N 5.62%. Cal : C76.49%, H 5.17%, N 5.57%).

Step 2 : Preparation of 4-(4'-Benzylidene-2'-phenyl-5'-oxo-imidazolin-1'-yl)-benzophenone.

A mixture of 4-amino benzophenone (1.979, 0.01m) and 4-benzylidene-2-phenyl-5-oxazolinone (2.49g, 0.01m) was refluxed in pyridine for 6 hrs. Resulting mass was poured onto crushed ice and neutralised with HCl, filtered and the product was recrystallised from ethanol yield 60.2%. m.p. 169°C. m.f.C_{20}H_{19}N_{3}O_{2} (Found C : 81.30%, H 4.65%, N 6.61%. Cal : 81.31%, H 4.67%, N 6.54%).

Similar other substituted imidazolinones were obtained when 4-amino benzophenone was condensed with different azlactone. The physical data are recorded in Table 1.
<table>
<thead>
<tr>
<th>S. No</th>
<th>Name of the compound</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
<th>MF</th>
<th>C&lt;sub&gt;F&lt;/sub&gt;</th>
<th>H&lt;sub&gt;F&lt;/sub&gt;</th>
<th>N&lt;sub&gt;F&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FOUND CAL</td>
<td>CAL</td>
<td>FOUND CAL</td>
</tr>
<tr>
<td>A</td>
<td>4-(4'-phenylidene)-phenyl-5'-oxo-imidazol-yl benzophenone</td>
<td>170</td>
<td>68</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>81.36</td>
<td>81.30</td>
<td>4.56</td>
</tr>
<tr>
<td>B</td>
<td>4-(4'-(2'-chlorophenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>189</td>
<td>57</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;BrN&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>75.20</td>
<td>75.24</td>
<td>4.07</td>
</tr>
<tr>
<td>C</td>
<td>4-(4'-(4'-chlorophenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>178</td>
<td>65</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;BrN&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>75.28</td>
<td>75.24</td>
<td>4.15</td>
</tr>
<tr>
<td>d</td>
<td>4-(4'-2',6'dichlorophenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>168</td>
<td>58</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;BrN&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>70.08</td>
<td>70.02</td>
<td>3.58</td>
</tr>
<tr>
<td>e</td>
<td>4-(4'-3',4'dichlorophenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>183</td>
<td>62</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;BrN&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>70.14</td>
<td>70.02</td>
<td>3.64</td>
</tr>
<tr>
<td>f</td>
<td>4-(4'-3',4'dimethoxyphenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>210</td>
<td>67</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>76.32</td>
<td>76.29</td>
<td>4.91</td>
</tr>
<tr>
<td>g</td>
<td>4-(4'-2'-hydroxyphenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>137</td>
<td>54</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>78.40</td>
<td>78.37</td>
<td>4.49</td>
</tr>
<tr>
<td>H</td>
<td>4-(4'-4'-hydroxyphenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>205</td>
<td>56</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>78.35</td>
<td>78.37</td>
<td>4.53</td>
</tr>
<tr>
<td>i</td>
<td>4-(4'-(4'-hydroxy,3'-methoxyphenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>188</td>
<td>55</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>75.94</td>
<td>75.94</td>
<td>4.67</td>
</tr>
<tr>
<td>J</td>
<td>4-(4'-(2'-methoxyphenylidene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>158</td>
<td>60</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>78.56</td>
<td>78.60</td>
<td>4.84</td>
</tr>
<tr>
<td>K</td>
<td>4-(4'-(3'-nitrophenyldiene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>152</td>
<td>54</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>73.54</td>
<td>73.57</td>
<td>4.01</td>
</tr>
<tr>
<td>l</td>
<td>4-(4'-nitrophenyldiene)-phenyl-5'-oxo-imidazol-yl) benzophenone</td>
<td>175</td>
<td>60</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>73.62</td>
<td>73.57</td>
<td>4.06</td>
</tr>
</tbody>
</table>
Fig 10.1: IR spectrum

4-[4'-phenylidene-2'-phenyl-5'-oxo-imidazolin-1'-yl]benzophenone
Fig 10.2: IR spectrum

4-(4'-(2''-chloro phenylidene)-2''-phenyl-5''-oxo-imidazolin-1''-yl)benzophenone
Fig 10.3: IR spectrum
4-{4'-(2''',6'''-dichloro phenyldene)-2''-phenyl-5''-oxo-imidazolin-1''-yl}benzophenone
Fig 10.4: IR spectrum

4-[4'-{(2''-hydroxyphenyl)idene}-2'-phenyl-5'-oxo-imidazolin-1'-yl]benzophenone
Fig 10.5: IR spectrum

4-m-(3''-nitro phenylidene)-2'-phenyl-5'-oxo-imidazolin-1'-yl/ benzophenone
Fig 10.6: IR spectrum

4-[(4'-((3''',4''')-dimethoxy phenylidene)-2'-phenyl-5'-oxo-imidazolin-1'-yl)benzophenone
Fig 10.7: $^1$H-NMR spectrum

$4'$-[4'-(3''$,'4''$-dimethoxy phenylidene)$-2'$-phenyl-$5'$-oxo-imidazolin-1''$-yl]benzophenone
Results and Discussion

All the compounds gave satisfactory C, H, N analysis results. All the compounds gave moderate yields. Out of which compounds substituted by dichloro groups gave very good yields. Structure of the compounds have been confirmed by characteristic values of IR and PMR spectra as follows.

**Compound a**: IR Vmax Cm⁻¹ Fig(10.1): 3108.0(C-H Str.Aromatic), 2921.8 (C-H Str), 1692.2 (C=O Str. imidazole), 1623.6(C=OStr.benzophenone), 1582.9(C=N Str), 1493.5 (C=C Str), 1356.4(C-Hdef(Sym)), 1281.8(C-O-CStr(sym)).

**Compound b**: IR Vmax Cm⁻¹ Fig(10.2): 3065.0(C-H Str.Aromatic), 2991.4(C-H Str), 1659.8(C=O Str. imidazole), 1618.4(C=OStr.benzophenone), 1583.1(C=N Str), 1499.3 (C=C Str), 1359.7(C-Hdef(Sym)), 1288.8(C-O-CStr(sym)), 1088.1 (C-Cl Str).

**Compound d**: IR Vmax Cm⁻¹ Fig(10.3): 3055.0(C-H Str.Aromatic), 1685.2(C=O Str. imidazole), 1611.7(C=OStr.benzophenone), 1563.6(C=N Str), 1497.1 (C=C Str), 1360.8(C-Hdef(Sym)), 1294.8(C-O-CStr(sym)), 1099.6 (C-Cl Str).

**Compound g**: IR Vmax Cm⁻¹ Fig(10.4): 3445.0(O-H Str), 3075.2(C-H Str. Aromatic), 2960.0(C-HStr(asym)), 1667.5(C=OStr. imidazole), 1628.6(C=Ostr .benzophenone), 1566.8(C=N Str), 1494.3 (C=C Str), 1399.7 (C-Hdef(Sym)), 1278.5(C-O-CStr(sym)).

**Compound k**: IR Vmax Cm⁻¹ Fig(10.5): 3110.0(C-H Str. Aromatic), 2880.2(C-HStr(asym)), 1665.8(C=OStr. imidazole), 1627.1(C=Ostr .benzophenone), 1556.8(C=N Str), 1465.5 (C=C Str), 1384.7 (C-Hdef(Sym)), 1262.1(C-O-CStr(sym)), 880.2(C-N Str for ArNO2).

**Compound f**: IR Vmax Cm⁻¹ Fig(10.6): 3048.0(C-H Str. Aromatic), 2965.9(C-HStr(asym)), 2890.2(C-H Str ), 1691.5(C=OStr. imidazole), 1625.7(C=Ostr .benzophenone), 1583.1(C=N Str), 1486.1 (C=C Str), 1373.5 (C-Hdef(Sym)), 1261.0(C-O-CStr(sym)).

**HNMR**: Fig (10.7): 3.72(6H,S,(OCH₃)₂), 0.77(1H.S.=CH-Ar), 7.2-8.0(18H,m,Ar-H).
References


27. V.L. Goldfar et al., Pharmacology, 15(6), 512, 97; 7.


