A series of oxazole and their imidazole derivatives were prepared from 6-bromo-2-chloro-3-formylquinoline. The structures of all the synthesized compounds were elucidated by elemental, IR, $^1$H NMR, $^{13}$C NMR spectra. They were assayed in vitro for their antimicrobial activity. It was revealed that some synthesized derivatives show remarkable biological activity against both gram-negative and gram-positive bacterial species and fungal microorganisms.

Key Words: Quinoline, Imidazole, Antibacterial activity.

INTRODUCTION

A wide variety of heterocyclic compounds of nitrogen containing five membered ring systems have been described for their chemotherapeutic importance and biological activity against various bacterial and fungal microorganisms. Besides this, the chemistry of quinoline and imidazoles have also been reviewed in a considerable number of publications and patents. A number of derivatives of quinoline serve as valuable therapeutic agents due to their versatile therapeutic activities like analgesic, antiulcer, antiviral, herbicidal, antitumor, antiallergic, etc. Considerable interest has been developed in the chemistry of quinoline derivatives due to their versatile therapeutic activities like bactericidal, antihistaminic, antimalarial, antidepressant, analgesic, antiulcer, antiviral, herbicidal, antitumor, antiallergic, anticonvulsant, antiinflammatory, etc. Some of the therapeutically active compounds derived from 2-chloro-3-formylquinoline derivatives are reviewed. Almost every class of imidazole derivatives has been used for different reactions to produce enormous number of heterocycles. Later, in last three decades many scientists have synthesized various imidazole heterocyclic precursors containing active hydrogen atom on nitrogen and evaluated in terms of their pharmacological activity. The emergence of powerful and elegant imidazole has stimulated major advances in chemotherapeutic agents of remarkable significance in medicine, biology and pharmacy. Besides this, it is also reported that imidazole compounds are one of the effective antifungal agents. They have a very broad spectrum, high activity and mild side effects. Looking to the above importance of both moieties, quinoline and imidazole, it is planned to synthesize quinoline based imidazole derivatives. The whole synthesis route is shown in Scheme-I.

where, IBM = (5Z)-3-(3-aminophenyl)-5-{[(6-bromo-2-chloro-3-quinolinyl)methylen]-2-phenyl-3,5-dihydro-4H-imidazol-4-one; IBP = (5Z)-3-(4-aminophenyl)-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one; IBBD = (5Z)-3-[4-(4-amino[1,1'-biphenyl]-4-yl]-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one; IBDS = (5Z)-3-{4-[(4-minophenyl)sulfonyl]phenyl}-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one; IBDD = (5Z)-3-[4-(4-minophenyl)sulfonyl]phenyl]-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one; IBT = (5Z)-3-[4-(4-minophenyl)sulfonyl]phenyl]-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one; IBTM = (5Z)-3-[4-(4-minophenyl)sulfonyl]phenyl]-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one; IBTD = (5Z)-3-{4-(4-minophenyl)sulfonyl]phenyl]-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one; IBDA = N-(4-minophenyl)-4-[(4Z)-4-[(6-bromo-2-chloro-3-quinolinyl)methylene]-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide; IBDT = (5Z)-3-[5-aminomethylphenyl]-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one

Scheme-I: (5Z)-3-(3-Aminophenyl)-5-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-3,5-dihydro-4H-imidazol-4-one
EXPERIMENTAL

Acetanilide and their derivatives were purified by crystallization in r-spirit. Dimethyl formamide and phosphorous oxychloride used were of analytical reagent grade. All of the organic solvents and hippuric acid, acetic anhydride, sodium acetate used were of analytical reagent grade. Eight diamines were used after recrystallization. The 2-chloro-3-formyl quinoline was synthesized by Vilsmeier-Haack reaction as reported in the literature.16,17 Melting points were measured in an open capillary tube and are uncorrected. Elemental analysis was obtained using Perkin-Elmer (USA) 2400, series II CHN-analyzer. In addition to this, the nitrogen content in all the imidazoles was estimated by Kjeldhal’s method19. IR spectra were recorded on a NICOLET-400 D spectrophotometer. 1H NMR spectra in CDCl3/DMSO-d6 at 400 MHz on a FT-NMR, R-1500 spectrometer (chemical shift in δ ppm) relative to TMS as an internal standard. Reactions were monitored by TLC, using silica gel as an adsorbent and ethyl acetate-hexane in different ratios as eluent.

Synthesis of 6-bromo-2-chloro-3-formylquinoline: The 6-bromo-2-chloro-3-formylquinoline was synthesized by Vilsmeier-Haack reaction by the procedure reported in the literature.20-22 For the preparation, cold dimethyl formamide (9.6 mL, 0.125 M) at 0 °C was taken in a three necked flask equipped with a drying tube. The phosphoryl oxycarbonyl was added (32.2 mL, 0.35 M) drop wise with continuous stirring. To this solution, 4-bromo acetanilide (0.05 M) was slowly added with continuous stirring. After 5 min, the solution was heated under reflux for 1 h at 80-90 °C. The reaction mixture was poured into ice water (300 mL) and stirred for 0.5 h at 0-10 °C. The product so formed was filtered and washed with water. It was crystallized by using r-spirit. The yield was 85 % and melting point was 148 °C.

((5Z)-4-[(6-Bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-1,3-oxazol-5(4H)-one: It was prepared by refluxing with benzoyl glycine (hippuric acid) (0.25 mol) and 6-bromo-2-chloro-3-formyl quinoline (0.25 mol) in acetic anhydride (0.75 mol) with freshly prepared sodium acetate (0.25 mol) for 2 h (Erlenmeyer oxazole condensation). After cooling, ethanol (10 mL) was added and kept overnight at 5 °C, the solid obtained was filtered, washed with alcohol, dried in vacuum and recrystallized by using benzene. Thus, as a result ((5Z)-4-[(6-bromo-2-chloro-3-quinolinyl)methylene]-2-phenyl-1,3-oxazol-5(4H)-one was separated out.

TABLE-1

<table>
<thead>
<tr>
<th>Imidazole</th>
<th>Elemental analysis of imidazoles based on 6-bromo-2-chloro-3-formylquinoline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elemental analysis (%)</td>
</tr>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Calcd.</td>
</tr>
<tr>
<td>IBMD</td>
<td>C8H8N3O2BrCl</td>
</tr>
<tr>
<td>IBPD</td>
<td>C8H8N3O2BrCl</td>
</tr>
<tr>
<td>IBBD</td>
<td>C9H9N3O2BrCl</td>
</tr>
<tr>
<td>IBOTD</td>
<td>C9H9N3O2BrCl</td>
</tr>
<tr>
<td>IBDS</td>
<td>C9H9N3O2SBrCl</td>
</tr>
<tr>
<td>IBDM</td>
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<tr>
<td>IBDA</td>
<td>C9H9N3O2SBrCl</td>
</tr>
<tr>
<td>IBDT</td>
<td>C9H9N3O2BrCl</td>
</tr>
</tbody>
</table>

*Estimated by the Kjeldhal’s method.
RESULTS AND DISCUSSION

In all the imidazole derivatives vinylic proton is seen around 6 ppm (δ). The aromatic protons are assigned to resonances in the range (δ) 7.00 to 8.2 ppm. The resonance due to -NH2 moiety is attributed to the peak in the range of 6.5 to 6.8 ppm. The resonance due to -CH3 is observed at 2.0-2.2 ppm. The compounds containing 4,4'-diamino diphenyl methane has a >CH3 signal of >CH3.

In all the compounds the peak at 158 ppm is assigned to Cl-C=N moiety. The peak around 165 ppm is attributed to C of >C=O (Table-2). In all the compounds the peak at 158 ppm is assigned to Cl-C=N moiety. The peak at 148 ppm is likely due to >C=N moiety. The peaks in the region 110-130 ppm are attributed to aromatic ring. The compounds containing 4,4'-diamino diphenyl methane shows a peak at 40 ppm which is due to =CH2.

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Imidazole} & \text{Peaks observed} & \text{Assignment} & \text{Peaks observed} & \text{Assignment} \\
\hline
\text{δ (ppm)} & \text{^1H NMR} & \text{δ (ppm)} & \text{^13C NMR} \\
\hline
\text{IBMD} & 6.03 & >CH vinylic & 165 & C=O \\
 & 6.80 & -NH2 & 147 & C=Cl \\
 & 7.8-3.86 & Aromatic protons & 158 & Cl-C=N \\
 & & & 110-130 & C in aromatic ring \\
\hline
\text{IBPD} & 5.90 & >CH vinylic & 165 & C=O \\
 & 6.80 & -NH2 & 147 & C=Cl \\
 & 7.0-3.86 & Aromatic protons & 158 & Cl-C=N \\
 & & & 115-135 & C in aromatic ring \\
\hline
\text{IBBD} & 5.9 & >CH vinylic & 165 & C=O \\
 & 6.8 & -NH2 & 147 & C=Cl \\
 & 7.3-3.86 & Aromatic protons & 157 & Cl-C=N \\
 & & & 115-135 & C in aromatic ring \\
\hline
\text{IBOTD} & 2.14 & CH3 & 163 & C=O \\
 & 2.24 & CH3 & 148 & C=Cl \\
 & 6.3 & >CH vinylic & 158 & Cl-C=N \\
 & 6.6 & >CH vinylic & 110-130 & C in aromatic ring \\
 & 7.0-3.86 & Aromatic protons & 18 & CH3 \\
 & & & 19 & CH3 \\
\hline
\text{IBDS} & 6.04 & >CH vinylic & 165 & C=O \\
 & 6.43 & -NH2 & 147 & C=Cl \\
 & 7.0-3.86 & Aromatic protons & 158 & Cl-C=N \\
 & & & 110-135 & C in aromatic ring \\
\hline
\text{IBDM} & 3.69 & CH3 & 165 & C=O \\
 & 6.2 & >CH vinylic & 148 & C=Cl \\
 & 6.43 & -NH2 & 158 & Cl-C=N \\
 & 7.1-3.87 & Aromatic protons & 112-135 & C in aromatic ring \\
 & & & 40 & CH3 \\
\hline
\text{IBDA} & 6.0 & >CH vinylic & 165 & C=O \\
 & 6.64 & -NH2 & 147 & C=Cl \\
 & 7.2-3.85 & Aromatic protons & 158 & Cl-C=N \\
 & 8.6 & N-H & 110-130 & C in aromatic ring \\
\hline
\text{IBDT} & 2.18 & CH3 & 162 & C=O \\
 & 6.0 & >CH vinylic & 147 & C=Cl \\
 & 6.82 & -NH2 & 149 & Cl-C=N \\
 & 7.2-8.00 & Aromatic protons & 110-130 & C in aromatic ring \\
 & & & 18 & CH3 \\
\hline
\end{array}
\]

In all the imidazole derivatives vinylic proton is seen around 6 ppm (δ). The aromatic protons are assigned to resonances in the range (δ) 7.00 to 8.2 ppm. The resonance due to -NH2 moiety is attributed to the peak in the range of 6.5 to 6.8 ppm. The resonance due to -CH3 is observed at 2.0-2.2 ppm. The compounds containing 4,4'-diamino diphenyl methane has a >CH3 signal of >CH3.

In all the compounds the peak at 158 ppm is assigned to Cl-C=N moiety. The peak around 165 ppm is attributed to C of >C=O (Table-2). In all the compounds the peak at 158 ppm is assigned to Cl-C=N moiety. The peak at 148 ppm is likely due to >C=N moiety. The peaks in the region 110-130 ppm are attributed to aromatic ring. The compounds containing 4,4'-diamino diphenyl methane shows a peak at 40 ppm which is due to =CH2.

Practically in all the compounds -NH2 asymmetric stretching vibration is assigned to a peak around 3400 cm⁻¹, while a peak around 3250 cm⁻¹ is attributed to -NH2 symmetric stretching vibration. The =CH stretching vibration in the vinyl moiety is attributed to the absorption at ca. 3040 cm⁻¹. The aromatic C-H stretching frequency, as expected is observed at around ca. 3010 cm⁻¹. The strong absorption at ca. 1700 cm⁻¹ is found to be present in majority of the compounds. The absorption will have contributions from stretching of >C=O and >C=N. The strong absorption at 1650 cm⁻¹ have contributions from v(C=N), v(C=C) and bending of -NH2. In most of the compounds the C-C stretching of the aromatic ring is around 1540 cm⁻¹.

A fairly strong absorption at ca.1300 cm⁻¹ is assigned to C-N stretching. The strong absorption in the region 810-840 cm⁻¹ is due to C-H out of plane bending in aromatic ring. The C-Cl stretching is attributed to the strong absorption in the region 740-720 cm⁻¹. Compounds containing O=S=O moiety show strong absorption in the region of 1050-1200 cm⁻¹ is due to O=S=O stretching. The C-H bending in the vinyl moiety is seen as a strong band around 800 cm⁻¹ in all the compounds. The compounds containing -CH3 group shows peaks due to asymmetric and symmetric bending of -CH3 group at 1475 and 1375 cm⁻¹, respectively and absorption at ca. 550 cm⁻¹ in the bromo compounds is assigned to C-Br stretching.

The synthesized compounds were screened in vitro for antimicrobial activity. From the data presented in Table-3, it is clear that out of eight imidazole compounds IBMD, IBBD, IBDM exhibited moderate inhibition against gram negative bacterial species and especially against Escherichia coli while IBBD, IBDM and IBOTD showed maximum activity against most gram negative organisms. Against gram positive organisms almost all compound of the series exhibited maximum inhibition, especially IBPD and IBBD showed highest inhibition against B. megaterium, while IBMD and IBDT showed good inhibition against fungal organism especially C. albicans. The other compounds exhibited moderate to less inhibition against fungal species, but IBMD showed good inhibition.

<table>
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<tr>
<th>Compounds</th>
<th>Escherichia coli</th>
<th>Pseudomonas aeruginosa</th>
<th>Bacillus subtilis</th>
<th>Bacillus megaterium</th>
<th>Aspergillus niger</th>
<th>Candida albicans</th>
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Antimicrobial activity of compounds at 10 mg% in DMSO.
REFERENCES