6.1. **INTRODUCTION**

Benzoxazoles contain a phenyl ring fused to an oxazole ring, as indicated in the structure for benzoxazole $80a$. Benzoxazole and its isomers 1,2-benzisoxazole $80b$ and anthranil $80c$ offer a series of bicyclic molecules with different arrangements of two strongly electronegative heteroatoms.

![Chemical structures](image)

Benzoxazole is thermodynamically stable ($\Delta H_0^{\text{f}}$ 180.8 kJ mol$^{-1}$) than its isomers and has somewhat larger negative NICS associated with the hexagonal carbon cyclic ring. It has a single plane of symmetry and hence belongs to $C_s$ point group. Direct computation of the $\pi$-current density, that is, the ‘ring current’ of benzoxazole reveals different patterns of current flow, sustains strong benzene-like currents in the six-membered and bifurcated flow in the five-membered ring suggesting an aromaticity order $a \approx b > c$.\(^1\)

Benzoxazoles belong to biologically very active skeletons.\(^2\) They are the structural isosters of naturally occurring nucleotides such as adenine and guanine, which allows them to interact easily with the biopolymers of living systems.\(^3\) They undergo electrophilic substitution mainly at C-6 position and to a lesser extent at C-5 and nitration afford the 6-nitro-product. Besides halogenobenzoxazoles undergo a range of nucleophilic displacements. Benzoxazoles are stable towards a range of reductive conditions and are soluble in acids without ring cleavage. They react with two moles of diphenylketen in a $[2 + 2 + 2]$ cycloaddition involving the C=N double bond, affording an oxazoline-fused benzoxazoles.\(^4\)

6.2. **APPLICATIONS**

Benzoxazole moiety is an important pharmacophore due to the wide spectrum of biological activity displayed by 2-substituted benzoxazoles.\(^5\) These include melatonin receptor agonist,\(^6\) lysophosphatidic acid acyltransferase-β (LPAAT-β) inhibitor,\(^7\) anticancer,\(^8\) antimicrobial,\(^9\) antiparasitic,\(^10\) 5-HT\(_3\) antagonist, antimycobacterial\(^12\) elastase inhibitory,\(^13\) VLA-4 antagonist,\(^14\) potent protease inhibitory\(^15\) and cyclooxygenase inhibitor.\(^16\)
Benzoxazoles represents a rare category of heterocyclic natural compounds having a variety of pharmacological properties, including antitubercular activity. One very interesting subclass of this category is the marine benzoxazoles. The Caribbean sea whip *Pseudopterogorgia elisabethae* is a known source of the aforementioned subclass of benzoxazoles, and it contains several analogs that have been described as strongly antimycobacterial. Recently Rodriguez *et al* have isolated Ileabethoxazole, a new perhydroacenaphthelene-type diterpene alkaloid from the Caribbean sea whip *P. elisabethae* and screened for their antitubercular activity, which was found to have potent inhibitory activity (92%) against *Mycobacterium tuberculosis* (*H*37*Rv*) at the concentration range of 128-64 µg/mL within the range as that of the very active rifampin.

UK-1 **81a** is a structurally unique bis(benzoxazole) natural anticancer active product isolated from a strain of *Streptomyces sp.* 517-02.**18** UK-1 exhibits significant cytotoxic activity against B16, HeLa, and P338 cells but no activity against bacteria, yeast, of fungi. UK-1 binds to a variety of di- and tri-valent metal ions, particularly Mg$^{2+}$

![Chemical structures](https://example.com/structures.png)

- a. UK-1: $R^1 = \text{Me}, R^2 = \text{H}$
- b. MUK-1: $R^1 = \text{Me}, R^2 = \text{Me}$
- c. DMUK-1: $R^1 = \text{H}, R^2 = \text{H}$

81 ions, and form complexes with double-stranded DNA in the presence of Mg$^{2+}$ ions lead to biologically relevant complexes with a specific target in cancer cells. It displays a wide spectrum of potent anticancer activity against leukemia, lymphoma, and certain solid tumor cell lines with IC$_{50}$ values as low as 20 nM. The selective toxicity of UK-1 towards cancer cells indicates that it may have a unique mechanism of anticancer action$^{19}$ and also inhibits the activity of human topoisomerase II.$^{20}$ The 2-(2-hydroxyphenyl) benzoxazole moiety present in UK-1 also present in number of
synthetic metal chelators. Studies indicate that UK-1 is capable of binding a variety of biologically important metal ions, particularly Mg$^{2+}$ ions. Like the Mg$^{2+}$-binding aureolic acid group of antitumor antibiotics and synthetic antitumor quinobenzoxazines. UK-1 also form complexes of the type [ds + UK-1 + M$^{2+}$] with a variety of metal ions including Ni$^{2+}$, Co$^{2+}$, and Zn$^{2+}$.

Tsuji and co-workers isolated AJ19561 82 from *Streptomyces* sp. AJ956 which possess growth inhibitory activity against both Jurkat and murine cancer line P338 with IC$_{50}$ values of 0.88 and 1.6 µM, respectively. However the semi synthetic derivatives methyl UK-1 (MUK-1) 81b and demethyl derivative DMUK-1 81c both have activity against Gram-positive and Gram-negative bacteria. MUK-1 is also active against yeast and filamentous fungi.

Moreover, some polycyclic fused benzoxazole derivatives 83 have been reported as potent anticancer such as the tetracyclic 2,3-disubstituted-12H-benzoazolo[2,3-b]quinazolin-12-ones. This finding together with the fact that, majority of DNA intercalating antitumor agents comprises a planar tricyclic and tetracyclic chromophore. Rida *et al* designed a new series of substituted 3H-pyrido[2,1-b]benzoxazoles as another molecular variant of 83 showing potent antitumor activity. Some imidazopyrimido benzoxazoles were evaluated for affinity at BZR and found that imidazobenzoxazoles possess high affinity (IC$_{50}$ value of 77 nM) showing partial inverse agonist activity at BZR.

The benzoxazole derivative 84 3-(4,7-dichlorobenzoazol-2-ylmethylamino)-5-ethyl-6-methyl-pyridin-2-(1H)-one (L-697.661) was found to be an effective non-
nucleoside HIV-1 reverse transcriptase inhibitor. A combined therapy with zidovudine and L-697.661 achieved marked decrease of viremia in some primary HIV-infected patients. Calcimycin is an antibiotic that includes a 2-substituted benzoxazole ring in its molecular structure is very active against *Bacillus cereus*, *Bacillus megaterium*, and *Micrococcus lutes*.

The efficiency of various 2-substituted benxoxazole derivatives as antifungal, anti-inflammatory, antihelminitic, anti-HIV, analgesic, fungicidal, insecticidal, nematocidal, and herbicidal agents is well documented. Besides they also exhibit new non-nucleoside topoisomerase I poisons, eukaryotic topoisomerase II inhibitors and HIV-1 reverse transcriptase inhibitors. Further they are also used for vivo imaging of β-amyloid plaques with positron PET.

Recently Brown *et al* synthesized 2-ethoxy-benzoxazole derivative and screened against HRV which are associated with respiratory tract infection (colds), several upper and lower respiratory tract complications such as otitis media, chronic bronchitis and asthma. This derivative showed excellent anti-HRV activity and found to have superior HRV activity (median EC₅₀ 3.88 ng/mL) to known capsid-binders Pleconaril and Pirodavir.

Benzoxazoles also find applications in material sciences as photochromatic agents, laser dyes and also have a number of optical applications such as photoluminescents, fluorescent whitener. 2-substituted bis(benzoxazole) derivative having 2-aromatic substituent emits blue fluorescence and are applicable to thermo-induced fluorescence materials. Besides they are also interesting fluorescent probes which show high stokes shift and present thermal and photostability due to an excited state intramolecular proton transfer mechanism. Since they interfere with biosynthesis of colored carotenoids by inhibiting the enzyme phytoene desaturase, they are studied as
potential bleaching herbicides.\textsuperscript{53} Zoxazolamine \textbf{86} (2-amino-5-chlorobenzoxazole) is a muscle-relaxant and sedative drug.\textsuperscript{54}

These initial reports therefore stimulated us to convert carboxyl moiety of (2-arylaroxy) ethanoic acids \textbf{(58a-e)}, into benzoxazole ring as in (2-arylaroxy) methyl-benzoxazoles \textbf{(88a-e)}.

\section*{6.3. PLAN OF THE SYNTHESIS OF 2-(2-ARYLAROXY) METHYL-BENZOXAZOLES \textbf{(88a-e)}}

Condensation of (2-arylaroxy) ethanoic acids \textbf{(58a-e)} with 2-amino-phenol \textbf{87} in presence of PPA afforded (2-arylaroxy) methyl-benzoxazoles \textbf{(88a-e)}. Alternatively they were synthesized from \textbf{(58a-e)} in excellent yield, using 2-aminophenol \textbf{87} under MW irradiation (\textbf{scheme-8}).

\begin{center}
\textbf{58a-e} \hspace{1cm} \textbf{87} \hspace{1cm} \textbf{88a-e}
\end{center}

\begin{center}
\textbf{SCHEME - 8}
\end{center}

\subsection*{6.3.1. DISCUSSION ON THE EXPERIMENT LEADING TO THE SYNTHESIS OF 2-(2-ARYLAROXY) METHYL-BENZOXAZOLES \textbf{(88a-e)}}

Benzoxazoles were prepared in various ways using appropriate 2-aminophenols. Usually the simplest and most inexpensive process involves the reaction of an aminophenol with a carboxylic acid.\textsuperscript{1} Consequently, a number of synthetic approaches have been developed and most of these involve the reaction of an aminophenol with a carboxylic acid. The various strategies adopted for construction of benzoxazoles involves treatment of 2-aminophenol with a selenoester/amide (in ethanol at room temperature for 4 days or under reflux in pyridine for 14 h)\textsuperscript{55} or with an acid
fluoride/chloride. The other methodologies include the benzoazrole annulation by thermal/photochemical intramolecular aromatic nucleophilic substitution of 2-haloanilides in a basic medium, cyclodehydration with excess PPTS in xylene under reflux and intramolecular Mitsunoba reaction of 2-hydroxyanilide and acid catalyzed (with 2 equiv of p-TsoH in xylene under reflux for 2-72 h) deacylative condensation of the 2-acyloxyanilide. These methodologies suffer from limitations in the preparation of the starting materials (selenoester/amide, acid chlorides/fluorides, 2-hydroxy/acyloxy anilides), the requirement of excess reagents (PPTS, p-TsOH, SOCl₂/HF, PPh₃-DEAD, metal catalysts, ionic liquids, etc.), harsh reaction conditions, long reaction times, contamination of the product with trace amounts of metallic impurities is detrimental to the determination of biological activity and most methods are only applicable to the synthesis of 2-aryl substituted benzoazoles.

Hein et al. have synthesized 2-aryl substituted benzoazoles by heating 2-aminophenol and carboxylic acid in the presence of stoichiometric amount of PPA as an acidic activator. However, as the hydroxyl group is a poor leaving group it requires electrophilic activation of the carboxylic acid to form the intermediate anilide. The poor nucleophilicity of the phenolic hydroxyl group necessitates activation of the amide carbonyl for cyclodehydration which requires heating in the presence of an acidic activator such as PPA. By adopting this method 2-(2-aroyl-aroxy)methyl-benzoazoles (88a-e) were synthesized from 2-(2-aroylaroxy) ethanoic acids (58a-e). In a typical example, 88a was synthesized using equimolar mixture of 58a and 2-aminophenol in presence of PPA at 220°C.

Alternately by adopting one pot MW technique, reported by Kumar et al compound 88a-e were also synthesized in excellent yield. In a typical procedure a mixture of 58a (2 mmol) and 2-aminophenol (2 mmol) was subjected to MW irradiation operating at its 80% power for 15 min. The reaction was monitored on TLC using petroleum ether : chloroform (5:3 v/v) as the eluent and the compound 88a was extracted into dichloromethane. This method obviates the use of solvents and too many reagents required for lowering energy barrier. Also the consumption of time for completion of reaction in short and isolation of product was much easier. Beside this method afforded excellent yield of the product.

The product 88a-e obtained by the above two methods are identical and the time required for the progress of reactions and yield of compounds are as shown in table-3. The integrity of the products 88a-e was confirmed by the spectral data obtained. For
instance, in IR spectrum compound 88a showed the presence of absorption peaks in the expected region, 1620 and 1665 cm\(^{-1}\) due to C=N and C=O stretching frequencies, respectively. The \(^1\)H NMR absorption of 88a gave the signals due to two aromatic methyl and OCH\(_2\) protons which appeared as singlets at \(\delta\) 2.35, 2.41 and 5.0 respectively. The signals due to eleven aromatic protons appeared as two sets of doublets in A\(_2\) B\(_2\) pattern centered at \(\delta\) 7.24 (J = 8.3 Hz) and 7.66 (J = 8.5 Hz) and a multiplet in the range 6.98-7.58. Finally, the observance of M\(^+\) peak at m/z 357, with relative abundance of 78\% confirms the structure as 88a. Similarly compounds 88b and 88c-e showed M\(^+\) peak at m/z 378, 398, 361 and 382 with relative abundance of 71, 75, 77 and 73\% respectively.

The formation of the products is also supported by the mechanism delineated in scheme-9.
IR Spectrum of compound 88c
$^1$H NMR Spectrum of compound 88c
LC-Mass Spectrum of compound 88c
6.4. EXPERIMENTAL SECTION

6.4.1. GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-(2-AROYL-AROXY) METHYL-BENZOXAZOLES (88a-e)

A typical procedure is described for the synthesis of 2-[2-(4-methylbenzoyl)-4-methylphenoxy]methyl-benzoxazole (88a):

**Method A: Thermal:** To a mixture of 58a (0.56 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol) was added PPA (10 g). The mixture was mixed was stirred vigorously at 220 °C for 4 h, cooled and the reaction mixture poured into 10% sodium carbonate solution. The alkaline slurry was filtered and the precipitate washed with water (3x20 ml) and dried. The crude product obtained was purified by column chromatography, eluting with petroleum ether : chloroform (5:3 v/v) to afford pure solid 59a.

**Method B: MW irradiation:** A mixture of 58a (0.56 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol) was subjected to MW irradiation operating at its 80% power for 15 min. The reaction mixture was allowed to reach room temperature and was extracted with ether (2 x 15 ml). The combined ethereal extracts were washed with saturated sodium bi-carbonate (2 x 15 ml), brine (2 x 10 ml), water (2 x 15 ml) and dried over anhydrous sodium sulfate. After evaporation of ether under reduced pressure the crude solid was purified as described in the above method to afford pure solid 59a.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Thermal</th>
<th></th>
<th></th>
<th>MW</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time min</td>
<td>Yield% (g)</td>
<td>Time min</td>
<td>Yield% (g)</td>
<td></td>
</tr>
<tr>
<td>88a</td>
<td>240</td>
<td>61(0.42)</td>
<td>15</td>
<td>76(0.53)</td>
<td></td>
</tr>
<tr>
<td>88b</td>
<td>240</td>
<td>60(0.44)</td>
<td>17</td>
<td>73(0.54)</td>
<td></td>
</tr>
<tr>
<td>88c</td>
<td>270</td>
<td>59(0.46)</td>
<td>20</td>
<td>71(0.56)</td>
<td></td>
</tr>
<tr>
<td>88d</td>
<td>240</td>
<td>62(0.44)</td>
<td>17</td>
<td>73(0.51)</td>
<td></td>
</tr>
<tr>
<td>88e</td>
<td>270</td>
<td>58(0.43)</td>
<td>20</td>
<td>71(0.53)</td>
<td></td>
</tr>
</tbody>
</table>

The time required for the progress of reaction and yield of compounds 88a-e are shown in table-4.

M.p. 158-160°C; IR (Nujol): 1620 (C=N), 1660 cm⁻¹ (C=O); ¹H NMR (CDCl₃): δ 2.35 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 5.0 (s, 2H, OCH₂), 6.98-7.58 (m, 7H, Ar-H), 7.24 (d, J
= 8.3 Hz, 2H, Ar-H), 7.66 (d, J = 8.5 Hz, 2H, Ar-H); LC-MS: m/z 357 (M+, 78); Anal. Calcd. for C23H19NO3: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.21; H, 5.28; N, 3.85%.

2-[2-(4-Chlorobenzoyl)-4-methylphenoxy]methyl-benzoxazole (88b):

**Method A: Thermal:** Obtained from 58b (0.60 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol) and added PPA (10 g).

**Method B: MW irradiation:** Obtained 58b (0.6 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol).

M.p. 171-173°C; IR (Nujol): 1618 (C=N), 1651 cm⁻¹ (C=O); ¹H NMR (CDCl₃): δ 2.36 (s, 3H, CH₃), 4.58 (s, 2H, OCH₂), 7.0-7.7 (m, 11H, Ar-H); LC-MS: m/z 378 (M⁺, 71); Anal. Calcd. for C22H16ClNO₃: C, 69.94; H, 4.26; Cl, 9.38; N, 3.71. Found: C, 69.85; H, 4.21; Cl, 9.31; N, 3.65%.

2-[2-(4-Chlorobenzoyl)-4-chlorophenoxy]methyl-benzoxazole (88c):

**Method A: Thermal:** Obtained from 58c (0.65 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol) and added PPA (10 g).

**Method B: MW irradiation:** Obtained 58c (0.65 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol).

M.p. 183-185°C; IR (Nujol): 1618 (C=N), 1651 cm⁻¹ (C=O); ¹H NMR (CDCl₃): δ 4.80 (s, 2H, OCH₂), 7.17-7.72 (m, 11H, Ar-H); LC-MS: m/z 398 (M⁺, 75); Anal. Calcd. for C21H13Cl₂NO₃: C, 63.34; H, 3.29; Cl, 17.80; N, 3.51. Found: C, 63.25; H, 3.23; Cl, 17.73; N, 3.46%.

2-[2-(4-Methylbenzoyl)-4-fluorophenoxy]methyl-benzoxazole (88d):

**Method A: Thermal:** Obtained from 58d (0.57 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol) and added PPA (10 g).

**Method B: MW irradiation:** Obtained 58d (0.57 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol).

M.p. 141-143°C; IR (Nujol): 1615 (C=N), 1655 cm⁻¹ (C=O); ¹H NMR (CDCl₃): δ 2.43 (s, 3H, CH₃), 5.06 (s, 2H, OCH₂), 7.08-7.74 (m, 11H, Ar-H); LC-MS: m/z 361 (M⁺, 77); Anal. Calcd. for C22H16FNO₃: C, 73.12; H, 4.46; F, 5.26; N, 3.88. Found: C, 73.04; H, 4.37; F, 5.19; N, 3.80%.

2-[2-(4-Chlorobenzoyl)-4-fluorophenoxy]methyl-benzoxazole (88e):

**Method A: Thermal:** Obtained from 58e (0.61 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol) and added PPA (10 g).

**Method B: MW irradiation:** Obtained 58e (0.61 g, 2 mmol), 2-aminophenol 87 (0.21 g, 2 mmol).
M.p. 165-167°C; IR (Nujol): 1625 (C=O), 1651 cm\(^{-1}\) (C=O); \(^1\)H NMR (CDCl\(_3\)): δ 4.98 (s, 2H, OCH\(_2\)), 7.1-7.77 (m, 11H, Ar-H); LC-MS: m/z 382 (M\(^+\), 73); Anal. Calcd. for C\(_{21}\)H\(_{13}\)ClFNO\(_3\): C, 66.06; H, 3.43; Cl, 9.29; F, 4.98; N, 3.67. Found: C, 59.94; H, 3.37; Cl, 9.22; F, 4.89; N, 3.60%.

6.5. BIBLIOGRAPHY


