3.1. INTRODUCTION

The benzimidazoles contain a phenyl ring fused to an imidazole ring, as indicated in the structure for benzimidazole 50. Its close structural relationship to benzodiazepines suggested its inclusion in the general family of ‘privileged structures’. Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize. This tautomerism is analogous to that found in the imidazoles and amidines. The benzimidazoles, in fact, may be considered as cyclic analogues of the amidines. Because of this tautomerism in benzimidazoles certain derivatives which appear at first to be isomers are in reality tautomers. Benzimidazoles with the imide nitrogen are usually more soluble in polar solvents and less soluble in organic solvents. Benzimidazoles are weakly basic, being somewhat less basic than the imidazoles. Accordingly they are in general soluble in dilute acids. The pKa value is 5.30 and 12.3. Benzimidazoles are also sufficiently acidic to be generally soluble in aqueous alkali and form N-metallic compounds. The acidic properties of benzimidazoles, like those of imidazoles, seem to be due to stabilization of the ion by resonance.

The benzimidazole ring possesses a high degree of stability and is not affected by concentrated sulfuric acid when heated under pressure to 270°C, or by vigorous treatment with hot hydrochloric acid or with alkali. Oxidation cleaves the benzene ring of benzimidazole only under vigorous conditions. The benzimidazole ring is also quite resistant to reduction. Benzimidazole gives a negative test with sodium nitroprusside and alkali. Benzimidazoles form salts with acids readily and upon alkylation with alkyl halides, yield 1-alkylbenzimidazoles and, under vigorous conditions, 1,3-dialkylbenzimidazolium halides. The hydrogen in the 1-position of benzimidazoles is...
sufficiently acidic to be replaced by metals and give N-metal benzimidazoles. 2-aminobenzimidazole coordinates with metals such as copper to give a complex. Benzimidazoles are stable to oxidation. Because of the stability of the benzimidazole to oxidation it is possible to oxidize substituent groups without affecting the ring.

Benzimidazole nucleus does not appear to occur very widespread in nature. However the 5,6-dimethylbenzimidazole moiety has been shown to be part of the structure of vitamin B\textsubscript{12}.\textsuperscript{1}

### 3.2. APPLICATIONS

The literature on potential uses of various substituted benzimidazole analogues is quite voluminous. The benzimidazole nucleus is of significant importance to medicinal chemistry\textsuperscript{4} and their derivatives are of wide interest because of their diverse biological activity and clinical applications.\textsuperscript{5} Benzimidazoles have acquired much importance as these compounds have been investigated for their antitumor,\textsuperscript{6} antimycobacterial,\textsuperscript{7} antiparasitic,\textsuperscript{8} anti-inflammatory,\textsuperscript{9} antioxidant,\textsuperscript{10} herbicidal,\textsuperscript{11} analgesic,\textsuperscript{12} antiallery,\textsuperscript{13} antihistaminic,\textsuperscript{14} antifungal,\textsuperscript{15} antiviral,\textsuperscript{16} anthelmintic,\textsuperscript{17} anti-HIV,\textsuperscript{18} insecticidal,\textsuperscript{19} antiarrhythmic,\textsuperscript{20} antiulcer,\textsuperscript{21} antiproliferative,\textsuperscript{22} antibacterial,\textsuperscript{23} anticancer and antiprotozoal activities.\textsuperscript{24} They also display affinity towards a variety of enzymes and protein receptors, medicine chemists would certainly classify them as ‘privileged sub-structures’ for drug design.\textsuperscript{25} The benzimidazole compounds have been proved to be the most important group of fungicides with systemic activity and are well known for their pronounced ability to control a large number of fungal diseases Benzimidazole fungicides are also used to prevent post-harvest rots and as soil-drench treatments.\textsuperscript{26}

Benzimidazoles are considered as potent inhibitors of selective neuropeptide YYI receptor antagonists,\textsuperscript{27} DNA gyrase,\textsuperscript{28} polio virus multiplication,\textsuperscript{29} 5-lipoxygenase inhibitors,\textsuperscript{30} cyclooxygenase,\textsuperscript{31} factor Xa (FXa),\textsuperscript{32} poly (ADP-ribose) polymerase (PARP),\textsuperscript{33} HCMV inhibitors,\textsuperscript{34} inhibition of proton pumps,\textsuperscript{35} lysophosphatidic acid acyltransferase-\textbeta,\textsuperscript{36} HIV reverse transcriptase,\textsuperscript{37} and Casein kinases.\textsuperscript{38} Various benzimidazoles have been shown to inhibit phosphodiesterase IV in the lung for the treatment of asthma\textsuperscript{39} and protein tyrosine phosphatase activity and used for the treatment of several immune diseases.\textsuperscript{40}
The benzimidazole scaffold has received extensive attention in medicinal chemistry. Astemizole \textsuperscript{51} and Omperazole \textsuperscript{52} a well established commercial drugs containing benzimidazole scaffold have demonstrated pronounced antihistaminic and antiulcer activity respectively.

He \textit{et al}\textsuperscript{43} have synthesized compound \textbf{53} by replacement of a key chlorobenzothiophene group in a novel series of nanomolar factor Xa inhibitors with benzimidazole and its isosteres and found to be very selective potent factor Xa inhibitor with a $K_i$ of 3 nM. Conformation restriction via potential hydrogen bonding through N or NH of benzimidazoles with factor Xa might improve potency and they have very different chemical and physical properties from benzothiophenes and thus such derivatives will possess quite different PK/Pd profiles.

Substituted benzimidazoles have proven as drug leads, which have exhibited pharmacological interest.\textsuperscript{41} They are evaluated as potent antitumor, antifungal and
antiparasitic agents, whose mode of action is thought to result from their inhibition of microtubule formation.\textsuperscript{44} A series of 2-phenylbenzimidazole-4-carboxamides have shown in vitro and in vivo antitumour activity and DNA-binding affinity.\textsuperscript{45} Further, some 2,5-disubstituted benzimidazole \textsuperscript{54} are known to act as topoisomerase I poisons and also shown cytotoxic activity against human lymphoblastoma, and RPMI 8402 cells.\textsuperscript{46} Several groups have explored the possibility of utilizing the pharmacophore like benzimidazoles motif derived from the well established bis-benzimidazole dye Hoechst-33528.\textsuperscript{47, 48} This compound not only shows in vitro antitumour activity but also act as an inhibitor of DNA topoisomerase I. It has been revealed from the footprinting and related structural methods that Hoechst-33528 recognizes 3-4 consecutive A/T base pairs by hydrogen bonding to base edges in 1:1 complexes.\textsuperscript{49}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Structure of substituted benzimidazole analogues.}
\end{figure}

Kamal et al.\textsuperscript{50} synthesized substituted benzimidazole analogues \textsuperscript{55(a-c)} that have been linked through different alkyl chain spaces at C8-position of DC-81 which exhibits potential anticancer activity in a number of cancer cell lines and reveals the significance of combining a non-covalent DNA-binding component (substituted benzimidazoles) to the covalent binding PBD moiety.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Substituted benzimidazole analogues.}
\end{figure}

The first report on antibacterial activity of halogenated benzimidazoles was published in 1964.\textsuperscript{51} Amido benzimidazole \textsuperscript{56} has been identified as inhibitors of the bacterial Kin A/Spo0F two-component system (TCS). These inhibitors exhibit in vitro antibacterial activity against a variety of susceptible and resistant Gram-positive organisms. In addition they showed good activity against VRE, a significant nosocomial pathogen especially among immunocompromised patients.\textsuperscript{52} Recently a novel series of benzimidazoles were identified to bind the bacterial \textit{E. coli} 165 ribosomal RNA A-site.
using a mass spectrometry-based assay. Nucleosides of halogenosubstituted benzimidazoles exhibit various pharmacological activities. For instance, 5,6-dichlorobenzimidazole ribonucleoside (DRB) has been found to inhibit topoisomerases and casein kinases as well as viral and cellular RNA synthesis. L-ribonucleoside of 5,6-dichloro-2-isopropylaminobenzimidazole (1263W94) was found to exert practically no effect on normal human cells while being highly no effect against Epstein-Barr virus.

In addition to these medicinal uses benzimidazoles also possess industrial applications like sunburn preventatives, dye stuffs, UV absorbing and fluorescent materials. A large number of patents describe benzimidazole derivatives of use in the textile industry as wetting, emulsifying, foaming, or softening agents or as dispersants for use in dyeing and also in the treatment of fibers to improve whiteness of undyed material or as optical bleach. 2-mercaptobenzimidazoles have found use in the photography industry. These compounds reduce photographic ‘fog’ and increase contrast and speed and hence have found use in photographic developing and fixing solutions. Besides 2-mercaptobenzimidazoles has been found to be value, too, as an oxidant for rubber and as a specific reagent for the detection of various metals. Methylbenzimidazole is used as a camphor substitute, polymerization inhibitor and initiator in isoprene. A number of salts of benzimidazolesulfonic acid are said to be of value in preparation for the care of the mouth and teeth.

The derivatives of ethyl (2-aroylphenoxy)acetates (57a-e) as shown in scheme-3, also exhibit various biological activities. For instance, ethyl [4-(4-hydroxybenzoyl)-2,3-dichlorophenoxy]acetate showed diuretic activity in rats. Phenoxy acetates possess analgesic properties, which are comparable to that of morphine and at the same time are able to reverse dicyclomine-induced amnesia. In addition to this they exhibit nootropic activity. Phenoxy acetates also exhibit anti-inflammatory activity which is related to ibuprofen.

Methyl [4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetate has been identified as the most interesting member of a series of selective β₃-adrenergic agonists of brown adipose tissue and thermogenesis in rats. They are also considered as selective histamine H₂-receptor antagonist on mucin in rat gastric mucosa.

Literature survey revealed that no efforts were directed towards the study effect of deprotonated benzimidazole moiety integrated with benzophenone framework. Encouraged by these information it was considered valuable to synthesize 1-[(4-
chlorophenyl)methyl]-(2-arylaroxy)methyl-benzimidazoles (61a-e) as bacteriological agents, using thermal and MW technique as shown in Scheme-3.

3.3. PLAN OF SYNTHESIS OF 1-(4-CHLORO)BENZYL-2-(2-ARYLAROXY) METHYL-BENZIMIDAZOLES (61a-e)

Alkaline hydrolysis of ethyl (2-arylaroxy) acetates (57a-e), furnished (2-arylaroxy) ethanoic acids (58a-e). This on condensation with 1,2-phenylene-diamine (59) in presence of PPA afforded (2-arylaroxy) methyl-benzimidazole (60a-e). N-alkylation of (60a-e) with K$_2$CO$_3$ in acetone followed by reaction with 4-chlorobenzyl bromide afforded 1-[(4-chlorophenyl)methyl]-2-(2-arylaroxy)methyl-benzimidazoles (61a-e). Alternatively they were synthesized from (58a-e) in excellent yield, under MW irradiation (scheme-3).
3.3.1. DISCUSSION ON THE EXPERIMENT LEADING TO THE SYNTHESIS OF ETHYL (2-AROYLAROXY) ACETATES (57a-e)

Preparation of aroxy acetates is an important synthetic reaction for which a wide variety of procedures have been developed. Generally they were synthesized by the condensation of phenolic hydroxyl group with halo acetate in dry acetone along with anhydrous potassium carbonate. For instance, Hird et al have synthesized 1-benzyloxy-2,3,4-trifluoro-5-octyloxybenzene by refluxing equimolar mixture of 5-benzyloxy-2,3,4-trifluorophenol and 1-bromooctane with anhydrous potassium carbonate in dry acetone. In contrast, Wyatt et al have synthesized in particular, ethyl
(2-aroyl-phenoxy)acetates by treating (2-hydroxy-phenyl) aryl methanone with halo acetate and sodium hydride in the presence of dimethylformamide. But this method afforded low yield of product and work up procedure is too long. Thereby ethyl (2-aroylaroxy)acetates (57a-e) were prepared from (46a-e) by adopting Hird et al procedure. In a typical example, 57a was synthesized by refluxing 46a (0.02 mol) in dry acetone with ethyl chloroacetate (0.02 mol) and anhydrous potassium carbonate (0.04 mol) for 8 h. The compounds 57a-e obtained are confirmed by IR, $^1$H NMR and mass spectral data. For example, IR spectrum, IR spectrum of 57a showed absorption in the region 1660 and 1730 cm$^{-1}$ corresponding to aromatic carbonyl and ester carbonyl stretching frequencies, respectively. The $^1$H NMR spectrum of 57a showed a triplet centered at $\delta$ 1.2 with the coupling constant J at 7 Hz, corresponding to methyl protons of ethyl group and two singlets at $\delta$ 2.32 and 2.41 assigned to two aromatic methyl protons. It also showed a quartet centered at $\delta$ 4.2 with J value at 6 Hz and a singlet at $\delta$ 4.42 corresponding to CH$_2$ of ethyl and OCH$_2$ groups, respectively. In addition, it showed two doublets centered at $\delta$ 7.0 (J = 8.3 Hz) and 7.49 0 (J = 8.3 Hz) in A$_2$B$_2$ pattern and a multiplet in the range $\delta$ 6.8-7.41 corresponding to seven aromatic protons. The mass spectrum of compound 57a gave significant stable M$^+$ peak at m/z 312 with relative abundance of 61%. Correspondingly, compounds 57b and 57c-e gave significant stable M$^+$ peak at m/z 333, 353, 316 and 336 with relative abundance of 59, 62, 61 and 60% respectively.

3.3.2 DISCUSSION ON THE EXPERIMENT LEADING TO THE SYNTHESIS OF 2-(2-AROYLAROXY) ETHANOIC ACIDS (58a-e)

A convenient synthesis for the valuable building blocks, of (2-aroylaroxy) ethanoic acids was achieved by a simple laboratory procedure which derives from the reaction of (2-aroylaroxy) acetates in ethanol and sodium hydroxide solution. For the present work the desired (2-aroylaroxy) ethanoic acids (58a-e) were gratifyingly synthesized by the alkaline hydrolysis of (2-aroylaroxy) acetates (57a-e) in excellent yield. Compound 58a is taken as a representative of 58a-e series, to explain the IR, $^1$H NMR and mass spectral data. In IR spectrum three absorptions at 1660, 1738 and 3470-3575 cm$^{-1}$ assigned to aromatic carbonyl, acid carbonyl and acid OH stretching frequencies, respectively. $^1$H NMR spectrum of 58a showed three singlets at $\delta$ 2.36, 2.46 and 4.78 assigned to two aromatic methyl and OCH$_2$ protons. It showed two sets of doublets in A$_2$B$_2$ pattern centered at $\delta$ 7.31 (J = 8.3 Hz) and 7.78 (J = 8.5 Hz) and a
multiplet in the range $\delta$ 7.0-7.37 for seven aromatic protons. In addition, it showed a broad singlet at $\delta$ 9.1 (D$_2$O exchangeable) assigned to acid OH proton. Finally, the observance of M$^+$ peak at m/z 284, with relative abundance of 55% confirms the structure as 58a. Similarly compounds 58b and 58c-e showed M$^+$ peaks at m/z 305, 325, 288 and 308 with relative abundance of 60, 59 and 58% respectively.

3.3.3. DISCUSSION ON THE EXPERIMENT LEADING TO THE SYNTHESIS OF 2-(2-ARYLAROXY) METHYL-BENZIMIDAZOLES (60a-e)

Benzimidazoles are prepared in various ways using appropriate 1,2-phenylenediamines. Usually the simplest and most inexpensive process involves the reaction of an aminophenol with a carboxylic acid. Consequently, a variety of methods, currently available for the synthesis of benzimidazoles including cyclodehydration using polyphosphoric acid, the use of polymer-bound scavengers and reagents, triphenyl phosphate in pyridine, inorganic clays, mineral acids, PS-PPh$_3$ resin, and mercury (II) chloride catalysed liquid phase. Alternately, a two step procedure is used in which appropriate 1,2-phenylenediamine is treated with an acid chloride to give acylated derivative and then followed by cyclodehydration using aqueous acid or pyrolysis at high temperature. However many of these synthetic protocols reported suffer from disadvantages, such as, needing anhydrous condition, prolonged reaction time, use of organic solvents, harsh reaction conditions and use of expensive reagents. Recently Yildiz-Oren et al synthesized 2-substituted benzimidazoles using aqueous hydrochloric acid as the condensation reagent according to well known Philip’s method. On the basis of prior reports, 2-(2-arylaroxy) methyl-benzimidazoles (60a-e) were synthesized from (58a-e) in 58 to 63% yield. For example, compound 60a was obtained from 58a (1 mmol) and 1,2-phenylenediamine 59 (1 mmol) by heating under reflux by stirring in 6 N hydrochloric acid for 3 h.

Alternately by adopting one pot MW technique with polyphosphoric acid (PPA), reported by Yu et al, compounds 60a-e were also synthesized in excellent yield. In a typical procedure, a mixture of 58a (1 mmol), 2-phenylenediamine 59 (1 mmol) and PPA (20 ml) was subjected to MW irradiation operating at its 80% power for 7 min. The reaction was monitored on TLC using hexane: chloroform (6:3 v/v) as the eluent and the compound was extracted into ether. 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 is short and isolation of product was much easier. Beside this method afforded excellent yield of the product.

The product 60a obtained by the above two methods are identical and the time required for the progress of reaction and yield of compounds are shown in table-3. The integrity of the products 60a-e was confirmed by the spectral data obtained. For instance, in IR spectrum of compound 60a showed the presence of stretching frequencies in the expected region, 1618, 1662 and 3410 cm\(^{-1}\) due to C=N, C=O and NH groups, respectively. The \(^1\)H NMR spectrum of 60a gave the signals due to two aromatic methyl and OCH\(_2\) protons at \(\delta\) 2.31, 2.41 and 5.45 respectively as three singlets. It showed the presence of a broad singlet at \(\delta\) 12.28 attributed to NH (D\(_2\)O exchangeable) protons. Moreover, the 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) attributed to four protons and a multiplet in the range \(\delta\) 7.13-7.76 for seven aromatic protons. It gave significantly stable M\(^+\) peak at m/z 356 with relative intensity of 100%. Similarly the other analogues 60b-e were synthesized and confirmed by spectral data. The M\(^+\) peak for compounds 60b and 60c-e were cited at m/z 377, 397, 360 and 381 with relative intensities of 100% as base peaks.

The formation of the products is also supported by the mechanism delineated in scheme-4.
3.3.4. DISCUSSION ON THE EXPERIMENT LEADING TO THE SYNTHESIS OF 1-(4-CHLORO)BENZYL-2-(2-AROYLABOXY)METHYL-BENZIMIDAZOLES (61a-e)

N-alkylation of azoles is a useful reaction commonly employed in the preparation of value intermediates of pharmacologically interesting compounds. N-alkylation of azoles is a useful reaction commonly employed in the preparation of value intermediates of pharmacologically interesting compounds. Classical procedures have been reported for the synthesis of N-alkylated azoles, most of which suffer long reaction times and yielding complex mixture of products, which need further delicate separations. Moreover, they have shown low selectivity. Consequently a number of procedures have been reported for the N-alkylation of aromatic compounds involving nitrogen heterocycles with alkyl halides and most of these includes potassium carbonate or sodium hydride, the use of phase transfer catalytic conditions (PTC) such as potassium hydroxide, potassium tertiary–butoxide as a base in presence of crown ethers, polyethylene glycols (PEG) or their dialkyl ethers as PTC. On the basis of previous reports, 1-(4-chloro)benzyl-2-(2-aroylaroxy)methyl-benzimidazoles (61a-e) were synthesized in 74-79% yield from 2-(2-aroylaroxy)methyl-benzimidazoles (60a-e). In a typical example, 61a was synthesized by refluxing 60a (1 mmol) in dry acetone with 4-chlorobenzyl bromide (1 mmol) and anhydrous potassium carbonate (2 mmol) for 8 h. The compounds (61a-e) were characterized by IR, \(^1\)H NMR and mass spectral studies. For instance, in IR spectrum of compound 61a showed the presence of absorption peaks in the expected region, 1618, and 1662 cm\(^{-1}\) due to C=N and C=O stretching frequencies, respectively. The \(^1\)H NMR spectrum of 61a gave the signals due to two aromatic methyl, OCH\(_2\) and NCH\(_2\) protons at \(\delta\) 2.31, 2.41 5.45 and 5.65 respectively as four singlets. The aromatic protons appeared as a multiplet in the...
range $\delta$ 7.17-7.79 for fifteen aromatic protons. It gave significantly stable M$^+$ peak at m/z 481 with relative intensity of 50%. Similarly the other analogues 61b-e were synthesized and confirmed by spectral data. The M$^+$ peak for compounds 61b and 61c-e were cited at m/z 501, 522, 485 and 505 with relative intensities of 49, 51, 52 and 50%.

3.4. EXPERIMENTAL SECTION

3.4.1. GENERAL PROCEDURE FOR THE SYNTHESIS OF ETHYL (2-AROYL-AROXY) ACETATES (57a-e)

A typical procedure is described for the synthesis of ethyl [2-(4-methylbenzoyl)-4-methylphenoxy]acetate (57a): A mixture of 46a (6.32 g, 0.028 mol), ethyl chloroacetate (3.43 g, 0.028 mol) in dry acetone (70 ml) and anhydrous potassium carbonate (7.33 g, 0.056 mol) was refluxed for 8 h then cooled and the solvent removed under reduced pressure. The residual mass was triturated with ice water to remove potassium carbonate and extracted with ether (3x60 ml) and the ether layer was washed with 10% sodium hydroxide solution (3x40 ml) followed by distilled water (3x40 ml) and then dried over anhydrous sodium sulfate and evaporated to dryness to get crude solid, which on recrystallization with ethanol gave white flakes of 57a. Yield 6.27 g (72%). M.p. 57-59°C; IR (Nujol): 1660 (C=O), 1730 cm$^{-1}$ (ester, C=O); $^1$H NMR (CDCl$_3$): $\delta$ 1.2 (t, J = 7 Hz, 3H, CH$_3$ of ester), 2.32 (s, 3H, CH$_3$), 2.41 (s, 3H, CH$_3$), 4.2 (q, J = 6Hz, 2H, CH$_2$ of ester), 4.42 (s, 2H, OCH$_2$), 6.8-7.41 (m, 3H, Ar-H), 7.2 (d, J = 8.3 Hz, 2H, Ar-H), 7.62 (d, J = 8.5 Hz, 2H, Ar-H); LC-MS: m/z 312 (M$^+$, 61); Anal. Calcd. for C$_{19}$H$_{20}$O$_4$: C, 73.06; H, 6.45. Found: C, 69.97; H, 6.41%.

Ethyl [2-(4-chlorobenzoyl)-4-methylphenoxy]acetate (57b): Obtained from 46b (6.9 g, 0.028 mol), ethyl chloroacetate (3.43 g, 0.028 mol) and anhydrous potassium carbonate (7.33 g, 0.056 mol) in presence of dry acetone as white solid. Yield 7.53 g (81%). M.p. 89-91°C; IR (Nujol): 1670 (C=O), 1735 cm$^{-1}$ (ester, C=O); $^1$H NMR (CDCl$_3$): $\delta$ 1.2 (t, J = 7 Hz, 3H, CH$_3$ of ester), 2.32 (s, 3H, CH$_3$), 4.21 (s, 3H, CH$_3$), 4.45 (s, 2H, OCH$_2$), 6.85-7.6 (m, 7H, Ar-H); LC-MS: m/z 333 (M$^+$, 59); Anal. Calcd. for C$_{18}$H$_{17}$ClO$_4$: C, 64.96; H, 5.15; Cl, 10.65. Found: C, 64.87; H, 5.11; Cl, 10.61%.

Ethyl [2-(4-chlorobenzoyl)-4-chlorophenoxy]acetate (57c): Obtained from 46c (7.47 g, 0.028 mol), ethyl chloroacetate (3.43 g, 0.028 mol) and anhydrous potassium carbonate (7.33 g, 0.056 mol) in presence of dry acetone as white solid. Yield 7.01 g (71%). M.p. 112-114°C; IR (Nujol): 1672 (C=O), 1737 cm$^{-1}$ (ester, C=O); $^1$H NMR
(CDCl$_3$): $\delta$ 1.22 (t, $J = 7$ Hz, 3H, CH$_3$ of ester), 4.21 (q, $J = 6$Hz, 2H, CH$_2$ of ester), 4.53 (s, 2H, OCH$_2$), 6.8-7.82 (m, 7H, Ar-H); LC-MS: m/z 353 (M$^+$, 62); Anal. Calcd. for C$_{17}$H$_{14}$Cl$_2$O$_4$: C, 57.80; H, 3.99; Cl, 20.08. Found: C, 57.76; H, 4.01; Cl, 19.08%.

**Ethyl [2-(4-methylbenzoyl)-4-fluorophenoxy]acetate (57d):** Obtained from 46d (6.44 g, 0.028 mol), ethyl chloroacetate (3.43 g, 0.028 mol) and anhydrous potassium carbonate (7.33 g, 0.056 mol) in presence of dry acetone as white solid. Yield 6.98 g (79%). M.p. 51-53 $^\circ$C; IR (Nujol): 1664 (C=O), 1745 cm$^{-1}$ (ester, C=O); $^1$H NMR (CDCl$_3$): $\delta$ 1.22 (t, $J = 7$ Hz, 3H, CH$_3$ of ester), 2.4 (s, 3H, CH$_3$), 4.2 (q, $J = 6$Hz, 2H, CH$_2$ of ester), 4.52 (s, 2H, OCH$_2$), 6.83-7.65 (m, 7H, Ar-H); LC-MS: m/z 316 (M$^+$, 61); Anal. Calcd. for C$_{18}$H$_{17}$FO$_4$: C, 68.35; H, 5.41; F, 6.01. Found: C, 68.28; H, 5.36; F, 5.96%.

**Ethyl [2-(4-chlorobenzoyl)-4-fluorophenoxy]acetate (57e):** Obtained from 46e (7.01 g, 0.028 mol), ethyl chloroacetate (3.43 g, 0.028 mol) and anhydrous potassium carbonate (7.33 g, 0.056 mol) in presence of dry acetone as white solid. Yield 7.15 g (76%). M.p. 63-65 $^\circ$C; IR (Nujol): 1665 (C=O), 1760 cm$^{-1}$ (ester, C=O); $^1$H NMR (CDCl$_3$): $\delta$ 1.22 (t, $J = 7$ Hz, 3H, CH$_3$ of ester), 4.21 (q, $J = 6$Hz, 2H, CH$_2$ of ester), 4.51 (s, 2H, OCH$_2$), 6.84-7.83 (m, 7H, Ar-H); LC-MS: m/z 336 (M$^+$, 60); Anal. Calcd. for C$_{17}$H$_{14}$ClFO$_4$: C, 60.63; H, 4.19; Cl, 10.52; F, 5.63. Found: C, 60.57; H, 4.15; Cl, 10.48; F, 5.61%.

### 3.4.2. GENERAL PROCEDURE FOR THE SYNTHESIS OF (2-AROYL-AROXY)ETHANOIC ACIDS (58a-e)

A typical procedure is described for the synthesis of [2-(4-methylbenzoyl)-4-methylphenoxy]ethanoic acid (58a): 57a (3.5 g, 11.21 mmol) was dissolved in ethanol (10 ml) and treated with a solution of sodium hydroxide (0.65 g, 16.37 mmol) in water (10 ml). The mixture was heated under reflux for 4 h, cooled and acidified with 1 N hydrochloric acid. The oily residue was extracted with dichloromethane (3x20 ml) and the solution washed with distilled water (3x20 ml), dried and evaporated to give crude product which was recrystallized from hexane to afford 58a as white solid. Yield 2.26 g (70%). M.p. 85-87 $^\circ$C; IR (Nujol): 1600 (C=O), 1738 (acid C=O), 3470-3575 cm$^{-1}$ (acid OH); $^1$H NMR (CDCl$_3$): $\delta$ 2.36 (s, 3H, CH$_3$), 2.46 (s, 3H, CH$_3$), 4.78 (s, 2H, OCH$_2$), 7.0-7.37 (m, 3H, Ar-H), 7.31 (d, $J = 8.3$ Hz, 2H, Ar-H), 7.78 (d, $J = 8.5$ Hz, 2H, Ar-H), 9.1 (s, 1H, COOH, D$_2$O exchangeable); LC-MS: m/z 284 (M$^+$, 55); Anal. Calcd. for C$_{17}$H$_{16}$O$_4$: C, 71.82; H, 5.67. Found: C, 71.76; H, 5.61%.
[2-(4-Chlorobenzoyl)-4-methylphenoxy]ethanoic acid (58b): Obtained from 57b (3.5 g, 10.52 mmol) and sodium hydroxide (0.65 g, 16.37 mmol) as white solid. Yield 2.4 g (75%). M.p. 109-111 °C; IR (Nujol): 1670 (C=O), 1735 (acid C=O), 3400-3500 cm⁻¹ (acid OH); ¹H NMR (CDCl₃): δ 2.36 (s, 3H, CH₃), 4.78 (s, 2H, OCH₂), 7.02-7.81 (m, 7H, Ar-H), 9.1 (s, 1H, COOH, D₂O exchangeable); LC-MS: m/z 305 (M⁺, 60); Anal. Calcd. for C₁₆H₁₃ClO₄: C, 63.05; H, 4.30; Cl, 11.63. Found: C, 62.98; H, 4.26; Cl, 11.58%.

[2-(4-Chlorobenzoyl)-4-chlorophenoxy]ethanoic acid (58c): Obtained from 57c (3.5 g, 9.91 mmol) and sodium hydroxide (0.65 g, 16.37 mmol) as white solid. Yield 2.35 g (73%). M.p. 120-122 °C; IR (Nujol): 1675 (C=O), 1730 (acid C=O), 3410-3510 cm⁻¹ (acid OH); ¹H NMR (CDCl₃): δ 4.82 (s, 2H, OCH₂), 7.08-7.85 (m, 7H, Ar-H), 9.5 (s, 1H, COOH, D₂O exchangeable); LC-MS: m/z 325 (M⁺, 59); Anal. Calcd. for C₁₅H₁₀Cl₂O₄: C, 55.40; H, 3.10; Cl, 21.81. Found: C, 55.36; H, 3.06; Cl, 21.78%.

[2-(4-Methylbenzoyl)-4-fluorophenoxy]ethanoic acid (58d): Obtained from 57d (3.5 g, 11.07 mmol) and sodium hydroxide (0.65 g, 16.37 mmol) as white solid. Yield 2.35 g (74%). M.p. 79-81 °C; IR (Nujol): 1655 (C=O), 1733 (acid C=O), 3450-3540 cm⁻¹ (acid OH); ¹H NMR (CDCl₃): δ 2.46 (s, 3H, CH₃), 4.79 (s, 2H, OCH₂), 7.03-7.78 (m, 7H, Ar-H), 9.3 (s, 1H, COOH, D₂O exchangeable); LC-MS: m/z 288 (M⁺, 58); Anal. Calcd. for C₁₆H₁₃FO₄: C, 66.65; H, 4.55; F, 6.59. Found: C, 66.61; H, 4.52; F, 6.51%.

[2-(4-Chlorobenzoyl)-4-fluorophenoxy]ethanoic acid (58e): Obtained from 57e (3.5 g, 10.40 mmol) and sodium hydroxide (0.65 g, 16.37 mmol) as white solid. Yield 2.2 g (69%). M.p. 89-91 °C; IR (Nujol): 1665 (C=O), 1735 (acid C=O), 3410-3555 cm⁻¹ (acid OH); ¹H NMR (CDCl₃): δ 4.8 (s, 2H, OCH₂), 7.05-7.83 (m, 7H, Ar-H), 9.4 (s, 1H, COOH, D₂O exchangeable); LC-MS: m/z 308 (M⁺, 58); Anal. Calcd. for C₁₅H₁₆ClFO₄: C, 58.35; H, 3.27; Cl, 11.48; F, 6.15. Found: C, 58.31; H, 3.22; Cl, 11.42; F, 6.10%.
IR Spectrum of compound 60c
$^1$H NMR Spectrum of compound 60c
LC-Mass Spectrum of compound 60c
3.4.3. GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-(2-AROYL-AROXY)METHYL-BENZIMIDAZOLES (60a-e)

A typical procedure is described for the synthesis of 2-[2-(4-methylbenzoyl)-4-methylphenoxy]methyl-benzimidazole (60a):

**Method A: Thermal:** A mixture of 58a (0.56 g, 2 mmol) and 1,2-phenylene diamine 59 (0.21 g, 2 mmol) in 6 N hydrochloric acid (10 ml) was refluxed with stirring for 8 h in. At the end of the reaction period, the reaction mixture was poured into ice cold water and neutralized with excess of NaHCO₃ and the resulted precipitate was filtered. The collected precipitate washed with water (3x20 ml), dried and extracted with ethyl acetate to separate from impurities. The combined organic solution was dried with anhydrous sodium sulfate and filtered and the solvent was removed under reduced pressure. The crude product was obtained and purified by column chromatography, eluting with hexane and chloroform (6:3 v/v) and recrystallized with ethanol to afford 60a as white crystals.

**Method B: MW irradiation:** A mixture of 58a (0.56 g, 2 mmol), 2-phenylene diamine 59 (0.21 g, 2 mmol) and PPA (3 g) was mixed to give a stirrable paste and subjected to MW irradiation operating at its 80% power for 8 min. The completion of the reaction was monitored on TLC and the reaction mixture cooled and poured into 10% sodium carbonate solution. The alkaline slurry was filtered and the precipitate washed with water (3x20 ml) and dried. Finally the crude product was purified and recrystallized as described in the above method to afford 60a as white crystals.

<table>
<thead>
<tr>
<th>Table-3: Synthesis of 60a-e using MW irradiation</th>
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<tr>
<td><strong>Compounds</strong></td>
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<td>60e</td>
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The time required for the progress of reaction and yield of compounds 60a-e are as shown in table-3.

M.p. 157-159°C; IR (Nujol):, 1618 (C=N), 1662 (C=O), 3410 cm⁻¹ (NH); ¹H NMR (CDCl₃): δ 2.31 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 5.45 (s, 2H, OCH₂), 7.13-7.76 (m, 7H, Ar-H), 7.24 (d, J = 8.3 Hz, 2H, Ar-H), 7.66 (d, J = 8.5 Hz, 2H, Ar-H), 12.28 (bs, 1H, NH); LC-MS: m/z 356 (M⁺, 100); Anal. Calcd. for C₂₃H₂₀N₂O₂: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.45; H, 5.58; N, 7.79%.

2-[(2-(4-Chlorobenzoyl)-4-methylphenoxy)methyl]-benzimidazole (60b):

Method A: Obtained from 58b (0.6 g, 2 mmol) and 1,2-phenylenediamine 59 (0.21 g, 2 mmol) in presence of 6 N hydrochloric acid (10 ml) as white crystals.

Method B: Obtained from 58b (0.6 g, 2 mmol) and 1,2-phenylenediamine 59 (0.21 g, 2 mmol) and PPA (3 g) as white crystals.

M.p. 175-177°C; IR (Nujol): 1624 (C=N), 1665 (C=O), 3402 cm⁻¹ (NH); ¹H NMR (CDCl₃): δ 2.35 (s, 3H, CH₃), 5.42 (s, 2H, OCH₂), 7.17-7.72 (m, 11H, Ar-H), 12.3 (bs, 1H, NH); LC-MS: m/z 377 (M⁺, 100); Anal. Calcd. for C₂₂H₁₇ClN₂O₂: C, 70.12; H, 4.55; Cl, 9.41; N, 7.41. Found: C, 70.05; H, 4.51; Cl, 9.35; N, 7.35%.

2-[(2-(4-Chlorobenzoyl)-4-chlorophenoxy)methyl]-benzimidazole (60c):

Method A: Obtained from 58c (0.65 g, 2 mmol) and 1,2-phenylenediamine 59 (0.21 g, 2 mmol) in presence of 6 N hydrochloric acid (10 ml) as white crystals.

Method B: Obtained from 58c (0.65 g, 2 mmol) and 1,2-phenylenediamine 59 (0.21 g, 2 mmol) and PPA (3 g) as white crystals.

M.p. 168-170°C; IR (Nujol): 1624 (C=N), 1665 (C=O), 3416 cm⁻¹ (NH); ¹H NMR (CDCl₃): δ 5.28 (s, 2H, OCH₂), 7.16-7.7 (m, 11H, Ar-H), 12.37 (bs, 1H, NH); LC-MS: m/z 397 (M⁺, 100); Anal. Calcd. for C₂₁H₁₄Cl₂N₂O₂: C, 63.49; H, 3.54; Cl, 17.85; N, 7.04. Found: C, 63.45; H, 3.49; Cl, 17.76; N, 6.96%.

2-[(2-(4-Methylbenzoyl)-4-fluorophenoxy)methyl]-benzimidazole (60d):

Method A: Obtained from 58d (0.57 g, 2 mmol) and 1,2-phenylenediamine 59 (0.21 g, 2 mmol) in presence of 6 N hydrochloric acid (10 ml) as white crystals.

Method B: Obtained from 58d (0.57 g, 2 mmol) and 1,2-phenylenediamine 59 (0.21 g, 2 mmol) and PPA (3 g) as white crystals.

M.p. 161-163°C; IR (Nujol): 1615 (C=N), 1657 (C=O), 3400 cm⁻¹ (NH); ¹H NMR (CDCl₃): δ 2.49 (s, 3H, CH₃), 5.29 (s, 2H, OCH₂), 7.16-7.7 (m, 11H, Ar-H), 12.37 (bs, 1H, NH); LC-MS: m/z 360 (M⁺, 100); Anal. Calcd. for C₂₂H₁₇FN₂O₂: C, 73.31; H, 4.76; F, 5.27; N, 7.76. Found: C, 73.24; H, 4.68; F, 5.19; N, 7.70%.
2-[2-(4-Chlorobenzoyl)-4-fluorophenoxy]methyl-benzimidazole(60e):

**Method A:** Obtained from 58e (0.61 g, 2 mmol) and 1,2-phenylenediamine 59 (0.21 g, 2 mmol) in presence of 6 N hydrochloric acid (10 ml) as white crystals.

**Method B:** Obtained from 58e (0.61 g, 2 mmol) and 1,2-phenylenediamine 59 (0.21 g, 2 mmol) and PPA (3 g) as white crystals.

M.p. 142-144°C; IR (Nujol): 1612 (C=N), 1655 (C=O), 3412 cm\(^{-1}\) (NH); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 5.35 (s, 2H, OCH\(_2\)), 7.18-7.72 (m, 11H, Ar-H), 12.37 (bs, 1H, NH); LC-MS: m/z 381 (M\(^+\), 100); Anal. Calcd. for C\(_{21}\)H\(_{14}\)ClF\(_2\)N\(_2\)O\(_2\): C, 66.23; H, 3.71; Cl, 9.30; F, 4.98; N, 7.36. Found: C, 60.19; H, 3.67; Cl, 9.24; F, 4.91; N, 7.28%.
$^1$H NMR Spectrum of compound 61a
LC-Mass Spectrum of compound 61a
3.4.4. GENERAL PROCEDURE FOR THE SYNTHESIS OF 1-(4-CHLORO) BENZYL-2-(2-AROYLAROXY)METHYL-BENZIMIDAZOLES (61a-e)

A typical procedure is described for the synthesis of 1-(4-chloro)benzyl-2-[2-(4-methylbenzoyl)-4-methylphenoxy]methyl-benzimidazole (61a): A mixture of 60a (0.35 g, 1 mmol), 4-chlorobenzyl bromide (0.2 g, 1 mmol) in dry acetone (20 ml) and anhydrous potassium carbonate (7.33 g, 2 mmol) was refluxed for 8 h then cooled and the solvent removed under reduced pressure. The residual mass was triturated with ice water to remove potassium carbonate and extracted with dichloromethane (3x10 ml) and the dichloromethane layer was washed with 10% sodium hydroxide solution (3x15 ml) followed by distilled water (3x15 ml) and then dried over anhydrous sodium sulfate and evaporated to dryness to get crude solid, which on recrystallization with ethanol gave pure 61a. Yield 0.38 g (81%). M.p. 170-172°C; IR (Nujol): 1618 (C=N), 1662 (C=O); \( ^1 \)H NMR (CDCl\(_3\)): \( \delta \) 2.31 (s, 3H, CH\(_3\)), 2.41 (s, 3H, CH\(_3\)), 5.45 (s, 2H, OCH\(_2\)), 5.45 (s, 2H, NCH\(_2\)), 7.17-7.79 (m, 15H, Ar-H); LC-MS: m/z 481 (M\(^+\), 50); Anal. Calcd. for C\(_{30}\)H\(_{25}\)ClN\(_2\)O\(_2\): C, 74.90; H, 5.24; Cl, 7.36; N, 5.81. Found: C, 74.85; H, 5.18; Cl, 7.31; N, 5.76%.

1-(4-Chloro)benzyl-2-[2-(4-chlorobenzoyl)-4-methylphenoxy]methyl-benzimidazole (61b): Obtained from 60b (0.37 g, 1 mmol), 4-chlorobenzyl bromide (0.2 g, 1 mmol) and anhydrous potassium carbonate (7.33 g, 0.056 mol) in presence of dry acetone as white solid. Yield 0.38 g (78%). M.p. 185-187°C; IR (Nujol): 1624 (C=N), 1665 (C=O); \( ^1 \)H NMR (CDCl\(_3\)): \( \delta \) 2.35 (s, 3H, CH\(_3\)), 5.42 (s, 2H, OCH\(_2\)), 5.51 (s, 2H, NCH\(_2\)), 7.15-7.72 (m, 15H, Ar-H); LC-MS: m/z 501 (M\(^+\), 49); Anal. Calcd. for C\(_{29}\)H\(_{22}\)Cl\(_2\)N\(_2\)O\(_3\): C, 69.47; H, 4.42; Cl, 14.13; N, 5.59. Found: C, 69.42; H, 4.37; Cl, 14.09; N, 5.53%.

1-(4-Chloro)benzyl-2-[2-(4-chlorobenzoyl)-4-chlorophenoxy]methyl-benzimidazole (61c): Obtained from 60c (0.39 g, 1 mmol), 4-chlorobenzyl bromide (0.2 g, 1 mmol) and anhydrous potassium carbonate (7.33 g, 0.056 mol) in presence of dry acetone as white solid. Yield 0.37 g (73%). M.p. 196-198°C; IR (Nujol): 1621 (C=N), 1660 (C=O); \( ^1 \)H NMR (CDCl\(_3\)): \( \delta \) 5.28 (s, 2H, OCH\(_2\)), 5.49 (s, 2H, OCH\(_2\)), 5.51 (s, 2H, NCH\(_2\)), 7.14-7.71 (m, 15H, Ar-H); LC-MS: m/z 522 (M\(^+\), 51); Anal. Calcd. for C\(_{28}\)H\(_{19}\)Cl\(_3\)N\(_2\)O\(_3\): C, 64.45; H, 3.67; Cl, 20.38; N, 5.37. Found: C, 64.39; H, 3.62; Cl, 20.31; N, 5.32%.

1-(4-Chloro)benzyl-2-[2-(4-methylbenzoyl)-4-fluorophenoxy]methyl-benzimidazole (61d): Obtained from 60d (0.36 g, 1 mmol), 4-chlorobenzyl bromide
(0.2 g, 1 mmol) and anhydrous potassium carbonate (7.33 g, 0.056 mol) in presence of dry acetone as white solid. Yield 0.38 g (79%). M.p. 179-181°C; IR (Nujol): 1615 (C=N), 1657 (C=O); ¹H NMR (CDCl₃): δ 2.47 (s, 3H, CH₃), 5.29 (s, 2H, OCH₂), 5.57 (s, 2H, NCH₂), 7.14-7.72 (m, 15H, Ar-H); LC-MS: m/z 485 (M⁺, 52); Anal. Calcd. for C₂₉H₂₂ClFN₂O₂: C, 71.81; H, 4.56; Cl, 7.30; F, 3.92; N, 5.57. Found: C, 71.76; H, 4.52; Cl, 7.26; F, 3.88; N, 5.53%.

1-(4-Chloro)benzyl-2-[2-(4-chlorobenzoyl)-4-fluorophenoxy]methyl-benzimidazole (61e): Obtained from 60e (0.38 g, 1 mmol), 4-chlorobenzyl bromide (0.2 g, 1 mmol) and anhydrous potassium carbonate (7.33 g, 0.056 mol) in presence of dry acetone as white solid. Yield 0.38 g (76%). M.p. 163-165°C; IR (Nujol): 1612 (C=N), 1655 (C=O); ¹H NMR (CDCl₃): δ 5.34 (s, 2H, OCH₂), 5.54 (s, 2H, NCH₂), 7.16-7.72 (m, 15H, Ar-H), 12; LC-MS: m/z 505 (M⁺, 50); Anal. Calcd. for C₂₈H₁₉ClFN₂O₂: C, 66.54; H, 3.79; Cl, 13.96; F, 3.71; N, 5.50%.

3.5. BIBLIOGRAPHY


