4.1. INTRODUCTION

The amide moiety is an important constituent of many biologically significant compounds and an understanding of the formation, properties and reactions of amides is essential for future development in areas such as polypeptide and protein chemistry. Many amides exhibit pharmacological activities, which have inspired recent interest in their chemistry. Biological ramification apart, amides are of fundamental chemical interest because of conjugation between nitrogen lone-pair electrons and the carbonyl π-bond results in distinctive physical and chemical properties.¹

Amides are versatile organic compounds since all the three atoms in the O-C-N chain are potentially reactive. This results partly due to the delocalization of the π electrons along the O-C-N chain, and the ground state structure is a hybrid of the two resonance forms as shown below.

The majority of reactions of amides fall into two classes. The first involves nucleophilic attack by the oxygen atom or occasionally by the nitrogen atom on either positively charged or neutral reagents. The second and less common, process involves nucleophilic addition to the amide carbonyl group. Under the appropriate conditions amides behave either as weak bases or as very weak acids. They may therefore be regarded as feeble amphoteric compounds and this property is manifested in their ability to form hydrogen bonded complexes by self association and with other donors and acceptors. Many of the physical properties of amides can be understood in terms of delocalization of the nitrogen lone pair electrons into the π system of the carbonyl group. This produces partial double-bond character in the CO-NH bond and generate a 1,3-dipole, with nitrogen bearing the partial positive charge and oxygen the partial negative charge. The consequences of partial double bond character are the planar nature of the amide group and the existence of configurational isomers, whereas donor-acceptor properties of the amide moiety manifest in acid base and complexing interactions and a tendency to self associate are consequences of its dipolar structure. The versatility of the amide group in forming partial bonds with self and many other functional groups is partly responsible for the structural subtleties of the biologically important proton derivatives. The SAR also indicated that the major interactions of RT enzyme are through the amide group.²
4.2. APPLICATIONS

Benzoyl phenoxy acetamides play a vital role due to biodynamic activities such as analgesic, anticonvulsant and antiresperine. For example compound 62 has been explored as a significant antiresperine effect at 300 mg/kg in hypothermia test in mice.

![Image of compound 62]

They are also reported as antiulcerogenic and histamine H$_2$-receptor antagonist agents. Further, they are explored as potent β-adrenoceptor antagonist with moderate cardio selectivity and intrinsic sympathomimetic activity. Also they have showed gastric antisecretory and gastroprotective activities. A series of benzoyl phenoxy acetamides were synthesized and tested for their ability to inhibit RT activity of HIV-1. Compounds 1 and 63a showed more activity in the RT assay. To investigate whether the amide 64a is a likely site of metabolism, for the required activity, corresponding amine 63b and ketone 64a were synthesized.

![Image of compounds 63a and 63b]

The loss of activity associated with these modifications against HIV-1 RT suggests that the hydrogen bonding capabilities of the amide is a major determinant of the activity of 63a.
The bicyclic amide 64b exhibit good activity in antiviral assays and this suggests the amide hydrogen is not involved in hydrogen bonding to the enzyme and the major interaction is through the amide carbonyl.

Benzophenone analogues\textsuperscript{8-12} exhibit significant in vivo antitumour activity. These analogues isolated from natural plants like \textit{Garcinia assigu},\textsuperscript{13} \textit{Cudrania cochinchinensis},\textsuperscript{14} \textit{Cratoxylum sumatranum}\textsuperscript{15} have proved to be potential cancer preventive agents in many of the cancer cell lines. Besides the synthetic benzophenone analogues with amino acid and methoxy substituents at ortho and para position, respectively have been reported as potent cytotoxic agent against human cancer cell lines when compared with phenstatin, a benzophenone type combretastatin A-4 analogue. In addition, these compounds inhibited the in vitro tubulin polymerization and significantly arrested cells at the G2/M phase.\textsuperscript{16}

In particular, benzophenone analogues with amide moiety connected to the alkyl chain have been investigated as farnesyltransferase inhibitor which plays a role in cancer treatment.\textsuperscript{10} Recently a series of substituted benzophenone analogues, (2-aryloyl-4-methylphenoxy)acetamides were synthesized and evaluated for anti-tumor and proapoptotic effects in EAT cells.\textsuperscript{17}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Structural formula of compounds 64a and 64b.}
\end{figure}

Recently Romines \textit{et al}\textsuperscript{18} have synthesized a potential NNRTI 65. In particular, 65 have very low IC\textsubscript{50} values in antiviral assays: 0.5 nM against wild-type virus, 1 nM
against K103N and against Y181C. It has also demonstrated relatively low clearance in intravenous pharmacokinetic studies in three species and has been converted to a prodrug to increase its oral bioavailability, which progressed to phase 2 clinical trials.

The synthesis of new compounds that can be used as drugs in everyday life is one of the most important tasks of molecular design. In the light of these SAR observations it was planned to design, 2-(2-aryloxy)-N-phenyl-benzazole acetamides (68a-f) under scheme-5.

4.3. PLAN OF SYNTHESIS OF 2-[(2-ARYLAROXY)-N-PHENYL]-BENZAZOLE ACETAMIDES (69a-f)

Condensation of 2-(2-aryloxy)ethanoic acid (58a-c) with 4-amiobenzazole (68a-b) in presence of EDCI, catalytic amount of DMAP and dry dichloromethane afforded 2-[(2-aryloxy)-N-phenyl]-benzazole acetamides (69a-f) in good yield (scheme-5).
4.3.1. DISCUSSION ON THE EXPERIMENT LEADING TO THE SYNTHESIS OF 2-(4-AMINOPHENYL) BENZAZOLES (68a-b)

Benzazoles were prepared in various ways using appropriate 2-aminophenols or 2-aminothiophenols. Usually the simplest and most inexpensive process involves the reaction of an aminophenol or thiophenol with appropriate carboxylic acid. 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 benzazoles involves treatment of 2-aminophenol or 2-aminothiophenol with a selenoester/amide (in ethanol at room temperature for 4 days or under reflux in pyridine for 14 h)\textsuperscript{19} or with an acid fluoride/chloride.\textsuperscript{20} The other methodologies include the benzoxazole annulation by thermal/photochemical intramolecular aromatic nucleophilic substitution of 2-haloanilides in a basic medium,\textsuperscript{21} cyclodehydration with excess PPTS in xylene under reflux and intramolecular Mitsunoba reaction of 2-hydroxyanilide\textsuperscript{22} and acid catalyzed (with 2 equiv of p-TsoH in xylene under reflux for 2-72 h) deacylative condensation of the 2-acyloxyanilide.\textsuperscript{23} 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, SOCl$_2$/HF, PPh$_3$-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 benzazoles.

Hein \textit{et al}\textsuperscript{24} have synthesized 2-aryl substituted benzazoles by heating 2-aminophenol or 2-aminothiophenol 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-(4-aminophenyl) benzazoles (68a-b) were synthesized from 4-aminobenzoic acid\textsuperscript{66} and 2-aminophenol (67a-b). In a typical example, 68a was synthesized using equimolar mixture of 66 and 2-aminophenol 67a in presence of PPA at 220\textdegree C.
4.3.2. DISCUSSION ON THE EXPERIMENT LEADING TO THE SYNTHESIS OF 2-[(2-AROYLAROXY)-N-PHENYL]-BENZAZOLE ACETAMIDES (69a-f)

A variety of methods currently available for the synthesis of amides from carboxylic acids including the use of ion exchange resins,\textsuperscript{25} tetrachlorosilane,\textsuperscript{26} hexachlorocyclotriphosphazatriene,\textsuperscript{27} diethylphosphoryl cyanide,\textsuperscript{28} triphenyl phosphine in carbon tetrachloride,\textsuperscript{29} and triphenylphosphine ditriflate.\textsuperscript{30} A review\textsuperscript{31} is available on the various other reagents available for the synthesis of amides from carboxylic acids. Previously, Wyatt, \textit{et al}\textsuperscript{2} have been converted (2-aroyl-phenoxy)ethanoic acids to 2(2-aroyl-phenoxy)acetamides via acid chlorides using thionyl chloride and dry benzene. Many of the above available methods however, required relatively harsh reaction conditions, hazardous chemicals, and complex reagents and elaborate workup procedures. In contrast, Tani \textit{et al}\textsuperscript{32} have used boron trifluoride etherate to convert various carboxylic acids to respective amides in excellent yield. Though boron trifluoride etherate is having dehydrating and Lewis acid character, it is not considered as a useful reagent in the synthetic preparation of amides from carboxylic acids.\textsuperscript{33}

Recently, the use of EDCI in presence of catalytic amount of DMAP have been used for the preparation of amides have been reported.\textsuperscript{34,35} On the basis of previous reports 2-(2-aroylaroxy) acetamides (69a-f) were synthesized in good yield. In a typical example, 69a was obtained by stirring 58a (1 mmol) with 2-(4-amino-phenyl)benzoxazole 68a (1 mmol) in the presence of EDCI (1.2 mmol) as the carboxylate activator and DMAP as catalyst for 16 h. The structure of the compounds was elucidated by IR, \textsuperscript{1}H NMR and mass spectral analysis. Compound 68a is taken as a representative example of the acetamide series to discuss the spectral studies. The IR spectrum of 69a showed the absorption band in the region 1625, 1651, 1697 and 3325 cm\textsuperscript{-1} attributed to C=N, aromatic C=O, amide C=O and NH stretching frequencies, respectively. In the \textsuperscript{1}H NMR spectrum, it showed three singlets, two at the range $\delta$ 2.34, 2.42, and one at 4.7 attributed to two aromatic methyl and OCH\textsubscript{2} protons respectively. The signals due to fifteen aromatic protons appeared as four sets of doublets centered at $\delta$ 7.24 (J = 8.3 Hz), 7.76 (J = 8.5 Hz), 7.86 (J = 8.7 Hz) and 8.22 (J = 8.6 Hz) and a multiplet in the range 6.98-7.82. In addition, it showed a broad singlet at $\delta$ 9.6 attributed to amide proton. In mass spectrum, 69a did not show M$^+$ peak, instead showed an ion peak corresponding to M$^+$+1 peak, at m/z 477 with 100\% of relative abundance. The M$^+$+1 peak at mass 477 should have been formed by the abstraction of a hydrogen atom by the
M⁺ ion from the neutral molecule. Compounds 69b and 69c-f also showed M⁺+1 at m/z 497, 518, 493, 513 and 534 respectively, with relative intensities of 100% as base peaks.

4.4. EXPERIMENTAL SECTION

4.4.1. GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-(4-AMINOPHENYL) BENZAZOLES (68a-b)

A typical procedure is described for the synthesis of 2-(4-aminophenyl)benzoxazole (68a): To a mixture of 2-aminophenol 67a (2.12 g, 19.5 mmol) and 4-aminobenzoic acid 66 (2.74 g, 20 mmol) was added PPA (40 g). The mixture was stirred vigorously at 220 °C for 4 h, cooled and poured into 10% sodium carbonate solution. The suspension was stirred until gas evolution ceased and then filtered. The solid collected was washed with water (3 x 50 ml), and recrystallized from methanol-water to afford 68a as solid. Yield 2.93 g (72%). M.p. 182-184 °C; IR (Nujol): 1607 (C=N), 3466 cm⁻¹ (NH₂); ¹H NMR (CDCl₃): δ 4.05 (bs, 2H, NH₂), 6.75 (d, J = 8.7 Hz, 2H, Ar-H), 7.28-7.72 (m, 4H, Ar-H), 8.05 (d, J = 8.6 Hz, 2H, Ar-H); LC-MS: m/z 211 (M⁺+1, 100); Anal. Calcd. for C₁₃H₁₀N₂O: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.21; H, 4.72; N, 13.28%.

2-(4-Amino-phenyl)benzothiazole (68b): Obtained from 2-aminothiophenol 67b (2.43 g, 19.5 mmol) and 4-aminobenzoic acid 66 (2.74 g, 20 mmol) was added PPA (40 g). Yield 3.11 g (71%). M.p. 155-157 °C; IR (Nujol): 1589 (C=N), 3458 cm⁻¹ (NH₂); ¹H NMR (CDCl₃): δ 4.21 (bs, 2H, NH₂), 6.72 (d, J = 8.7 Hz, 2H, Ar-H), 7.33-8.01 (m, 4H, Ar-H), 7.85 (d, J = 8.6 Hz, 2H, Ar-H); LC-MS: m/z 227 (M⁺+1, 100); Anal. Calcd. for C₁₃H₁₀N₂S: C, 69.59; H, 4.45; N, 12.38; S, 14.17. Found: C, 69.53; H, 4.42; N, 12.23; S, 14.12%.
IR Spectrum of compound 69a
$^1$H NMR Spectrum of compound 69a
LC-Mass Spectrum of compound 69a
IR Spectrum of compound 69f
$^1$H NMR Spectrum of compound 69f
4.4.2. GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-{[2-AROYLAROXY]-N-PHENYL]BENZAZOLE ACETAMIDES (69a-f)

A typical procedure is described for the synthesis of 2-{[2-(4-methylbenzoyl)-4-methylphenoxy]-N-phenylbenzoxazole acetamide (69a):

To a solution of 58a (0.28 g, 1 mmol) in dry dichloromethane (10 ml) were added 1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide.HCl (0.23 g, 1.2 mmol) and catalytic amount of 4-dimthylaminopyridine followed by 2-(4-aminophenyl)benzoxazole 68a (0.21 g, 1 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic solution was washed with water (2 × 50 mL), dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate, 80:20) to afford 69a as white solid. Yield 0.35 g (75%). M.p. 169-171°C; IR (Nujol): 1625 (C=N), 1651 (C=O), 1697 (C=O of amide) 3325 cm$^{-1}$ (NH); $^1$H NMR (CDCl$_3$): δ 2.34 (s, 3H, CH$_3$), 2.42 (s, 3H, CH$_3$), 4.7 (s, 2H, OCH$_2$), 7.98-7.82 (m, 7H, Ar-H), 7.26 (d, J = 8.3 Hz, 2H, Ar-H), 7.76 (d, J = 8.5 Hz, 2H, Ar-H), 7.86 (d, J = 8.7 Hz, 2H, Ar-H), 8.22 (d, J = 8.6 Hz, 2H, Ar-H), 9.6 (bs, 1H, CONH); LC-MS: m/z 477 (M$^+$+1, 100); Anal. Calcd. for C$_{30}$H$_{24}$N$_2$O$_4$: C, 75.60; H, 5.08; N, 5.87. Found: C, 75.54; H, 5.02; N, 5.82%.

2-{[2-(4-Chlorobenzoyl)-4-methylphenoxy]-N-phenylbenzoxazole acetamide (69b): Obtained from 58b (0.3 g, 1 mmol), 2-(4-aminophenyl)benzoxazole 68a (0.21 g, 1 mmol), EDCI (0.23 g, 1.2 mmol) and catalytic amount of DMAP. Yield 0.35 g (72%). M.p. 184-186°C; IR (Nujol): 1620 (C=N), 1665 (C=O), 1705 (C=O of amide) 3340 cm$^{-1}$ (NH); $^1$H NMR (CDCl$_3$): δ 2.35 (s, 3H, CH$_3$), 4.72 (s, 2H, OCH$_2$), 7.0-8.2 (m, 15H, Ar-H), 9.62 (bs, 1H, CONH); LC-MS: m/z 497 (M$^+$+1, 100); Anal. Calcd. for C$_{29}$H$_{21}$ClN$_2$O$_4$: C, 70.09; H, 4.26; Cl, 7.13; N, 5.64. Found: C, 70.04; H, 4.21; Cl, 7.08; N, 5.59%.

2-{[2-(4-Chlorobenzoimid)-4-methylphenoxy]-N-phenylbenzoxazole acetamide (69c): Obtained from 58c (0.32 g, 1 mmol), 2-(4-aminophenyl)benzoxazole 68a (0.21 g, 1 mmol), EDCI (0.23 g, 1.2 mmol) and catalytic amount of DMAP. Yield 0.35 g (70%). M.p. 202-204°C; IR (Nujol): 1615 (C=N), 1670 (C=O), 1710 (C=O of amide) 3325 cm$^{-1}$ (NH); $^1$H NMR (CDCl$_3$): δ 4.75 (s, 2H, OCH$_2$), 7.05-8.23 (m, 15H, Ar-H), 9.62 (bs, 1H, CONH); LC-MS: m/z 518 (M$^+$+1, 100); Anal. Calcd. for C$_{28}$H$_{18}$ClN$_2$O$_4$: C, 64.98; H, 3.51; Cl, 13.70; N, 5.41. Found: C, 64.94; H, 3.46; Cl, 13.65; N, 5.37%.

96
2-[2-(4-Methylbenzoyl)-4-methylphenoxy]-N-phenylbenzothiazole acetamide (69d):
Obtained from 58a (0.3 g, 1 mmol), 2-(4-amino-phenyl)benzothiazole 68b (0.22 g, 1 mmol), EDCI (0.23 g, 1.2 mmol) and catalytic amount of DMAP. Yield 0.34 g (71%).
M.p. 178-180°C; IR (Nujol): 1592 (C=N), 1660 (C=O), 1695 (C=O of amide) 3310 cm⁻¹ (NH); ¹H NMR (CDCl₃): δ 2.35 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 4.65 (s, 2H, OCH₂), 7.05-8.13 (m, 15H, Ar-H), 9.56 (bs, 1H, CONH); LC-MS: m/z 493 (M⁺+1, 100); Anal. Calcd. for C₃₀H₂₄N₂O₃S: C, 73.15; H, 4.91; N, 5.69; S, 6.51. Found: C, 73.10; H, 4.86; N, 5.62; S, 6.46%.

2-[2-(4-Chlorobenzoyl)-4-methylphenoxy]-N-phenylbenzothiazole acetamide (69e):
Obtained from 58b (0.3 g, 1 mmol), 2-(4-amino-phenyl)benzothiazole 68b (0.22 g, 1 mmol), EDCI (0.23 g, 1.2 mmol) and catalytic amount of DMAP. Yield 0.35 g (70%).
M.p. 209-211°C; IR (Nujol): 1590 (C=N), 1658 (C=O), 1700 (C=O of amide) 3315 cm⁻¹ (NH); ¹H NMR (CDCl₃): δ 2.34 (s, 3H, CH₃), 4.69 (s, 2H, OCH₂), 7.06-8.14 (m, 15H, Ar-H), 9.55 (bs, 1H, CONH); LC-MS: m/z 513 (M⁺+1, 100); Anal. Calcd. for C₂₉H₂₁ClN₂O₃S: C, 67.90; H, 4.12; Cl, 6.90; N, 5.46; S, 6.25. Found: C, 67.84; H, 4.17; Cl, 6.86; N, 5.41; S, 6.21%.

2-[2-(4-Chlorobenzoyl)-4-chlorophenoxy]-N-phenylbenzothiazole acetamide (69f):
Obtained from 58c (0.32 g, 1 mmol), 2-(4-amino-phenyl)benzothiazole 68b (0.22 g, 1 mmol), EDCI (0.23 g, 1.2 mmol) and catalytic amount of DMAP. Yield 0.37 g (71%).
M.p. 221-223°C; IR (Nujol): 1589 (C=N), 1652 (C=O), 1690 (C=O of amide) 3308 cm⁻¹ (NH); ¹H NMR (CDCl₃): δ 4.74 (s, 2H, OCH₂), 7.07-8.15 (m, 15H, Ar-H), 9.54 (bs, 1H, CONH); LC-MS: m/z 534 (M⁺+1, 100); Anal. Calcd. for C₂₈H₁₈Cl₂N₂O₃S: C, 63.05; H, 3.40; Cl, 13.29; N, 5.24; S, 6.01. Found: C, 62.98; H, 3.36; Cl, 13.25; N, 5.19; S, 5.97%.

4.5. BIBLIOGRAPHY


