Chapter – 3A

Synthesis of different aliphatic chained benzofuran derivatives bridged with oxadiazole moiety
3A.1. Introduction

Benzofurans are very important compounds due to their broad spectrum of biological and pharmacological effects. They are considered as non-steroidal anti-inflammatory drugs (NSAID), where the action of (NSAID) is lowering the prostaglandin production through inhibition of cyclooxygenase (COX). Benzofurans are among the COX-2 inhibitors [1-3]. In addition, diverse pharmacological properties have been associated with benzofuran derivatives [4-8]. These include pesticidal [9], fungicidal, antimicrobial, antioxidant [10], anti-inflammatory [11], antihistaminic [12], antiallergic [13], antitumor [14], anticonvulsant and antinociceptive [15] activities containing a wide variety of pharmacological properties.

Some benzofurans [16-18] and its derivatives [19-21] are also associated with a broad spectrum of biological activities [22,23]. Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical and material interest, which is documented by a steadily increasing number of publications and patents. For instance, 2-amino-1,3,4-oxadiazoles act as muscle relaxants [24] and showed antimitotic activity [25]. Analgesic, antiinflammatory, anticonvulsive, diuretic and antiemetic properties are exhibited by 5-aryl-2-hydroxy-methyl-1,3,4-oxadiazole derivatives [26] and 2-hydroxy phenyl-1,3,4-oxadiazole was used as a hypnotic and sedative [27]. Some material applications of 1,3,4-oxadiazole derivatives lie in the fields of photosensitizers [28] and liquid crystals [29].

The common synthetic approaches to oxadiazoles [30,31] involved the cyclization of diacylhydrazines. A variety of reaction conditions influence the cyclization reaction. Typically, the reaction is promoted by heat and anhydrous reagents including thionyl
chloride[32,33], phosphorous oxychloride[34,35], phosphorous pentoxide[36], triphenyl phosphine[37], and triflic anhydride[38]. Alternative synthetic methods involved the reaction of carboxylic hydrazides with keteneylidene triphenylphosphorane[39] or base-promoted cyclization reaction of trichloroacetic acid hydrazones[40], which is a simple method for the synthesis of 1,3,4-oxadiazoles having phenol[41,42] or thiophenol group.

3A.1.1. Synthetic oxadiazoles derivatives

The 1,3,4-Oxadiazole derivatives have been widely studied in diverse areas of chemistry, in particular due to the electron-deficient properties of oxadiazole ring and their luminescent properties[43-46]. Some pharmaceutical products which contain the oxadiazole core includes Nesapidil(1), Furamizole(2) and Tiodazosin(3) [47]. However, the detailed discussion of such work is out of the scope of the present thesis, hence only the important reports mentioning the structures, biological activity and appropriate references are presented briefly in table-3A.1.
### Table-3A.1. Some important oxadiazole derivatives

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Structure</th>
<th>Application</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="Structure" /></td>
<td>Possess strong photoluminescent property and are completely soluble in organic solvents</td>
<td>48</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2" alt="Structure" /></td>
<td>Used widely for electron transport in organic light emitting diodes (OLED)</td>
<td>49</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3" alt="Structure" /></td>
<td>Its fluorescent sensing behavior towards Metal ions was investigated</td>
<td>50</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4" alt="Structure" /></td>
<td>Synthesis and characterisation</td>
<td>51</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image5" alt="Structure" /></td>
<td>Exhibited fluorescent and biological activity</td>
<td>52</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image6" alt="Structure" /></td>
<td>Microwave-assisted and possess antifungal activity</td>
<td>53</td>
</tr>
</tbody>
</table>
3A.1.2. Benzofuran compounds containing oxadiazole moiety

Hui-fang et al have reported that substituted benzofurans and benzothiophene compounds were found to be a new class of potential anabolic agents by enhancing BMP-2 expression[57]. The compounds represent potential leads in the development of a new class of anabolic agents. Some benzofuran compounds like compound 4 which are linked by a stilbene bridge to 3-phenyl-1,2,4-oxadiazolyl was used in optical brightening, especially for textile materials of synthetic polymers[58].
Morihisa, Saitoh and coworkers reported that, the Glycogen synthase kinase 3β (GSK-3β) inhibition is expected to be a promising therapeutic approach for treating Alzheimer’s disease. A series of 2-(1-benzofuran-5-yl)-1,3,4-oxadiazole 5 derivatives have been reported as potent and highly selective GSK-3β inhibitors [59,60].

Christopher et al synthesized some substituted 2-(4-hydroxyphenyl)-7-(1,3,4-oxadiazol-2-yl)-1-benzofuran-5-ol 6, benzofuran derivatives containing 1,3,4-oxadiazole ring, which are useful as estrogenic agent [61].
Ananta and coworkers reported the synthesis of 1,3,4-oxadiazoles by conventional and non-conventional methods[62].

In light of these observations and in continuation of our investigation on different benzofuran derivatives, we have synthesized some variant benzofuran derivatives containing 1,3,4-oxadiazole ring having different chain length.

3A.2. Present work

The various biological activities associated with compounds formed by the reaction of benzofuran with different fatty acid systems prompted us to investigate the synthesis and biological activities of oxadiazole derivatives involving benzo[b]furans. There are very less report on synthesis and biological studies of benzofuran containing oxadiazole.

In the present investigation, we focused our interest on the synthesis of 2-(1,3,4-oxadiazol-2-yl)-1-benzofuran-3-amine starting from the 2-hydroxy benzonitrile.

The synthetic strategy involved the following steps:

3. Condensation of compound 3 with different fatty acids to get 2-(5-substituted-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-amine.

Schematic representation of benzofuran-2-1,3,4-oxadiazol derivatives, given in the following scheme-2.

\[ \text{Scheme-2} \]

\[
\begin{align*}
\text{CN} & \quad \xrightarrow{\text{Ethyl chloroacetate, K}_2\text{CO}_3/\text{Acetone}} \quad \text{CN} \\
\text{OH} & \quad \xrightarrow{\text{DMF/Dry K}_2\text{CO}_3} \quad \text{OCH}_2\text{COOC}_2\text{H}_5 \\
\text{2} & \quad \xrightarrow{\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O, Dry Ethanol, } \Delta} \quad \text{3} \\
\text{4a-d} & \quad \xrightarrow{\text{POCl}_3} \quad \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}
\end{align*}
\]

where \( n=1,13,15, \) and 17

3A.2.1. Synthesis of salicylonitrile

The starting material salicylonitrile(1) was synthesized starting from salicylaldehyde. When salicylaldehyde was treated with hydroxylamine hydrochloride and 70% KOH in ethanol, it furnished the oxime, which upon further reaction with acetic anhydride at reflux temperature gave the intermediate product(1,2-benzoxazole). The intermediate was stirred in strong base like sodium ethoxide at room temperature for about 8hr and resulting mixture was neutralized with 30% HCl to yield desired product 1.
The structure of compound (1) was confirmed by comparing its physical constant with literature[63].

3A.2.2. Synthesis of ethyl 3-amino-1-benzofuran-2-carboxylate (2)

The condensation of salicylonitrile 1 with ethylchloroacetate in presence of anhydrous potassium carbonate in anhydrous acetone gave ethyl 2-cyanophenoxyacetate. The ring-closure of ethyl 2-cyanophenoxyacetate in anhydrous dimethyl formamide in presence of anhydrous potassium carbonate at steam bath temperature afforded ethyl 3-amino-2-benzofurancarboxylate 2 in good yield.
The structure of compound 2 was established by IR, NMR and mass spectral studies. The IR spectrum exhibited sharp absorption band at 3332 cm\(^{-1}\) due to NH\(_2\) and another absorption band at 1763 cm\(^{-1}\) due to ester carbonyl group. In the \(^1\)HNMR spectrum of compound 2, a triplet is displayed at \(\delta 1.43\) ppm due to 3 methyl protons, quartet at \(\delta 4.44\) ppm due to methylene protons, a broad singlet at \(\delta 4.96\) ppm due to two protons of \(-\text{NH}_2\) and a multiplet between \(\delta 7.22-7.55\) ppm due to four aromatic protons. The mass spectrum of compound 2 displayed a molecular ion peak M\(^+\) at m/z 206, which corresponds to the molecular weight of compound 2.
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2-(1,3,4-oxadiazol-2-yl)-1-benzofuran-3-aminoderivatives
Sample Name: Mobile A: 0.1% HCOOH in Water
Data File: Mobile B: 0.1% HCOOH in ACN
Acq.Method: AZ_BOS.obj
Instrument Code: SCIAD17-004

UV Detector: TIC

Peak no R.T Area % Area
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Peak ID Time
1 1.24
1: (Time: 1.24)

Peak ID Time
1: MS ES+ 1: (Time: 1.24)
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6.9e-007
100 163.0

m/z
500.0 1000.0 500.0

m/z
207.2 208.2

265.0 391.4 446.7 697.4 868.9

Range: 1.832e+2

Sample Report:

Page 1
3A.2.3. Synthesis of 3-amino-1-benzofuran-2-carbohydrazide (3)

3-Amino-1-benzofuran-2-carbohydrazide 3, which is used as a key intermediate, was prepared by the condensation reactions of ethyl 3-amino-1-benzofuran-2-carboxylate 2 with hydrazine hydrate in ethanol.

The structure of compound 3 was established by IR, $^1$HNMR and mass spectral data. The IR spectrum exhibited absorption bands at 3478 and 3359 cm$^{-1}$ due to -NH$_2$ and NHNH$_2$ respectively, another absorption band at 1632 cm$^{-1}$ due to carbonyl group. The $^1$HNMR spectrum of the compound 3 showed a singlet at δ 4.34 ppm due to 2 protons of -NH$_2$ another singlet at δ 5.95 ppm due to two protons of –NH$_2$ and one singlet at δ 9.17 ppm due to –NH proton. Its also displayed a multiplet between δ 7.22–7.85 ppm due to four aromatic protons. The mass spectrum of compound 3 displayed a molecular ion peak $M^+$ at m/z 192.
Chapter 3A

2-(1,3,4-oxadiazol-2-yl)-1-benzofuran-3-aminederivatives
Chapter 3a

2,4-Disubstituted 3-pyrimidin-3-amine derivatives

NAME: ERFPRO
PROCNO: 1
Date: 200X-02-06
Time: 15:12
INSTRUM: spect
PRF/CHN: 5 mm PABBO DM
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FIDRES: 0.259666 Hz
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TG: 200
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DE: 6.50 sec
TF: 99.50 F
D1: 1.7000000 sec
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F2: 4.00 ppm
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SI: 27.46
SF: 403.1500000 MHz
F1: 0
S2: 0
L1: 0.30 Hz
CR: 0
EC: 1.00
LC - MS Report

Method: ACIDIC M
Data File
Sample Name:
Acq. Date: 8/29/2009 6:18:48 PM
Instrument: Agilent 6330 Ion Trap
Analysis Info: V6

Print Date: 9/1/2009 12:09:51 PM

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3A.2.4. Synthesis of 2-(5-substituted-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-amine (4a-d)

When 3-amino-1-benzofuran-2-carbohydrazide (3) was treated with different fatty acids bearing different chain length (i.e. n=11, 13, 15, 17) in presence of POCl₃ we got corresponding 2-(5-substituted-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-amine derivatives (4a-d).

![Chemical structure](image)

The structure of compound 4(a-d) was established by IR, ¹H NMR and mass spectral studies. The IR spectrum of compound 4a exhibited absorption band at 3383 cm⁻¹ due to -NH₂ functionality and other absorption band at 1618, 1572 due to -C=N groups. The ¹H NMR spectrum of the compound 4a displayed six signals. A triplet at δ 0.86 ppm due to methyl protons, a multiplet at δ 1.27 ppm due to 27 protons of aliphatic chain of attached to oxadiazole ring, quintet at δ 2.43 ppm due to two methylene protons of -CH₂-CH₂- group and a triplet at δ 2.70 ppm due to CH₂ protons attached to oxadiazole ring. It also displayed a singlet at δ 5.95 ppm due to two -NH₂ protons and a multiplet between δ 7.51–8.08 ppm due to four aromatic protons. The mass spectrum of compound 4a displayed a molecular ion peak M⁺ at m/z 440, which corresponding to its molecular weight of compound 4a.
Chapter 3A

2-(1,3,4-oxadiazol-2-yl)-1-benzofuran-3-aminoderivatives
MASS REPORT

Data File: D:DATADEC08\8274066.D
Instrument: LC-MSD-Trap-XCT

Method: AT_3070FA.M
Sample Name: GI857456

[Graph showing mass spectra and molecular structure]

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Table 3A.2. Spectral data of synthesized compounds

<table>
<thead>
<tr>
<th>Com.</th>
<th>Structure</th>
<th>IR in cm$^{-1}$</th>
<th>$^1$H NMR in δ ppm</th>
<th>MS in m/z (M+1)</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>3332 (-NH$_2$), 1763 (C=O)</td>
<td>δ 1.43(t, 3H, -CH$_3$), δ 4.44 (q, 2H, -CH$_2$), δ 4.96 (s, 2H, -NH$_2$), δ 7.22–7.55 (m, 4H, Ar H)</td>
<td>205</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>3478(-NH$_2$), 3359(-NH NH$_2$) 1632 (C=O)</td>
<td>δ 4.34 (s, 2H, -NH$_2$), δ 5.59 (s, 2H, -NH$_2$), δ 9.17 (s, 1H, -NH), δ 7.22–7.85 (m, 4H, Ar H)</td>
<td>191</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td>3383(-NH$_2$) 1618, 1572(-C=N)</td>
<td>δ 0.86(t, 3H, -CH$_3$), δ 1.27 (m, 27H, -CH$_2$), δ 2.43 (m, 2H, -CH$_2$), δ 2.70 (t, 2H, -CH$_2$), δ 5.95 (s, -NH$_2$) δ 7.51–8.08 (4H, Ar H)</td>
<td>440</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td>3413(-NH$_2$) 1626, 1555(C=N)</td>
<td>δ 0.88(t, 3H, -CH$_3$), δ 1.38 (m, 24H, -CH$_2$), δ 2.48 (m, 2H, -CH$_2$), δ 2.80 (t, 2H, -CH$_2$), δ 5.01 (s, -NH$_2$) δ 7.25–8.32 (4H, Ar H)</td>
<td>411</td>
</tr>
<tr>
<td>4c</td>
<td></td>
<td>3386(-NH$_2$) 1620, 1568(C=N)</td>
<td>δ 0.86(t, 3H, -CH$_3$), δ 2.17 (m, 20H, -CH$_2$), δ 2.51 (m, 2H, -CH$_2$), δ 2.83 (t, 2H, -CH$_2$), δ 5.05 (s, -NH$_2$) δ 7.27–8.09 (4H, Ar H)</td>
<td>383</td>
</tr>
<tr>
<td>4d</td>
<td></td>
<td>3388(-NH$_2$) 1632, 1562(C=N)</td>
<td>δ 0.89(t, 3H, -CH$_3$), δ 1.40 (m, 16H, -CH$_2$), δ 2.46 (m, 2H, -CH$_2$), δ 2.85 (t, 2H, -CH$_2$), δ 5.02 (s, -NH$_2$) δ 7.26–8.10 (4H, Ar H)</td>
<td>355</td>
</tr>
</tbody>
</table>
3A.3. Experimental

3A.3.1. Synthesis of salicylonitrile (1)

The reaction mixture of salicylaldehyde (0.01 M, 1.22 g) with hydroxylamine hydrochloride (0.01 M, 0.69 g) in ethanol was refluxed for about 4 hr to offer oxime, as intermediate which was further treated with acetic anhydride to gave another 1,2-benzoxazole. The resulting product was treated with sodium ethoxide for about 2 hr, and after cooling, reaction mixture was neutralized with 30% HCl to get creamy white colored compound with good yield; m.p. 96-98 °C; crystallized from ethanol; C₇H₅NO.

3A.3.2. Synthesis of ethyl 3-amino-1-benzofuran-2-carboxylate (2)

Two steps were involved for the synthesis of ethyl 3-amino-1-benzofuran-2-carboxylate.

First step: To a solution of salicylonitrile 1 (0.1 mol, 11.9 g) in anhydrous acetone (150 ml), ethyl chloroacetate (0.1 mol, 12.5 g) and anhydrous potassium carbonate (30 g) were added and the mixture was heated under reflux for 8 hr. Potassium salts were filtered off. The filtrate upon removal of solvent gave ethyl 2-cyanophenoxyacetate as colorless solid was dried. 90% yield: m.p. 49-51 °C (lit, 49 °C).

Second step: To the reaction mixture of 2-cyanophenoxyacetate (14 g, 0.0683 mol) in anhydrous dimethyl formamide (100 ml), anhydrous potassium carbonate (15 g) was added and the mixture was heated on a steam bath for 8 hr. The reaction product was cooled and poured into cursed ice with stirring. The solid separated was collected and crystallized from ethanol as colorless compound, yield 96%; m.p. 70-72 °C (lit, 73 °C).

3A.3.3. Synthesis of 3-amino-1-benzofuran-2-carboxyhydrazide (3)

A mixture of ethyl 3-amino-1-benzofuran-2-carboxylate 2 (0.01 M, 2.05 g) and hydrazine hydrate (0.015 M, 0.75 g) in ethanol was refluxed for about 5 hr on water bath,
resulting 3-amino-1-benzofuran-2-carbohydrazide 3. The excess of solvent was distilled off and cooled to room temperature. The reaction mixture was poured onto ice cold water, filtered and crystallized using ethanol. Yield 92%; m.p. 97-99 °C.

3A.3.4. Synthesis of 2-(5-aliphatic-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-amine (4a-e)

General procedure:

An equimolar mixture of 3-amino-1-benzofuran-2-carbohydrazide (0.01 mol) (3) and variant aliphatic acid (0.01 mol) is taken in POCI₃ (5 ml) solvent. The reaction mixture was refluxed for about 18-23 hr, dry condition were maintained up to the end of the reaction by adapting guard tube to the condenser. Reaction mixture was cooled to room temperature and mixture was poured into ice cold water, neutralized with NaHCO₃ solution. Resulting compound was filtered, dried and recrystallized with ethyl acetate.

The physical data for synthesized compounds 4a-d is given in the table 3a.3.

Table 3A.3. Physical data for synthesized compounds 4a-d

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>M.P (°C)</th>
<th>Yield (%)</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C₁₇H₃₅</td>
<td>180-182</td>
<td>53</td>
<td>C₂₇H₄₉N₃O₂</td>
</tr>
<tr>
<td>4b</td>
<td>C₁₅H₃₁</td>
<td>174-176</td>
<td>48</td>
<td>C₂₅H₃₇N₃O₂</td>
</tr>
<tr>
<td>4c</td>
<td>C₁₃H₂₇</td>
<td>170-172</td>
<td>57</td>
<td>C₂₃H₃₅N₃O₂</td>
</tr>
<tr>
<td>4d</td>
<td>C₁₁H₂₃</td>
<td>166-168</td>
<td>55</td>
<td>C₂₁H₂₉N₃O₂</td>
</tr>
</tbody>
</table>
References:


