Chapter-2

Synthesis of 5-((2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols
Introduction

There is a growing interest over the past years for the synthesis of benzimidazole based heterocycles due to the crucial role of benzimidazole unit in the functions of biologically important molecules. They are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio. Nowadays many infectious microbial diseases causing problems worldwide because of resistance to number of antimicrobial agents.

Five membered heterocyclic compounds show various types of biological activities, among them substituted oxadiazoles display wide spectrum of activities. 1,3,4-oxadiazoles have attracted an interest in medicinal chemistry as ester and amide bioisoesters for a number of biological targets. Moreover, these compounds have also demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields such as antibacterial, antifungal, anti-inflammatory, antimitotic, antiarrhythmic, and insecticidal activities.

The therapeutic importance of these rings prompted us to develop selective molecules in which a substituent could be arranged in a pharmacophoric pattern to display higher pharmacological activities.

Present Work

This chapter concerns with the synthesis of 2-(substituted phenoxy methyl)-1H-benzo[d]imidazoles (3a-f), ethyl 2-(2-(substituted phenoxy methyl)-1H-benzo[d]imidazol-1-yl)acetates (4a-f), 2-(2-(substituted phenoxy methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazides (5a-f), 5-((2-(substituted phenoxy methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols (6a-f).
Initially compounds 2a-f, aryloxy acetic acid derivative\textsuperscript{14,15} of substituted phenols were synthesized and these were the starting materials in the current chapter. Substituted 2-phenoxyacetic acids 2a-f on reaction with o-phenylenediamine yields 2-(substituted phenoxy)methyl\textsuperscript{16-18} (3a-f). In the IR spectrum of 3a, a stretching band at around 3485 cm\textsuperscript{-1} was due to N-H group while another stretching band at 1632 was attributed to C=N. \textsuperscript{1}H NMR spectrum showed a singlet at \(\delta\) 4.58 to account for NH. A singlet at 5.33 accounts for CH\(_2\). The above said spectral data confirms the formation of an imidazole in 3a.

**Characterization data of 3a-f**

\textbf{2-(phenoxy)methyl-\textit{1}H-benzo[\textit{d}]imidazole (3a)}

Yield 80\%, m.p. 130-132\(^\circ\)C.

IR (KBr)\(v_{\max}\) : 3485 (N-H stretching), 1632 (C=N stretching), 1588 (C=C stretching in aromatics), 1166, 1053 (sp\(^2\)/sp\(^3\) C-O stretching) cm\textsuperscript{-1}.
$^1$H NMR (DMSO-d$_6$): $\delta$ 4.58 (s, 1H, NH), 5.33 (s, 2H, OCH$_2$), 6.89-7.04 (m, 3H, ArH), 7.14 (d, J = 8 Hz, 2H, ArH), 7.26-7.34 (m, 2H, ArH), 7.59-7.64 (m, 2H, ArH) ppm.

$^{13}$C NMR (DMSO-d$_6$): $\delta$ 68.4 (OCH$_2$), 114.6, 115.1, 121.3, 123.6, 129.7, 134.5 (2C), 141.9, 156.4 (aromatic and benzimidazole carbons) ppm.

MS m/z: found 224 [M$^+$]; calcd. 224. Anal. C$_{14}$H$_{12}$N$_2$O. Found C 74.16 (74.98), H 5.24 (5.39), N 11.98 (12.49).

2-((o-tolyloxy)methyl)-1H-benzo[d]imidazole (3b)

Yield 70%, m.p. 182-184ºC.

IR (KBr)$\nu_{\text{max}}$: 3498 (N-H stretching), 2904 (C-H stretching in CH$_3$/CH$_2$), 1648 (C=N stretching), 1580 (C=C stretching in aromatics), 1170,1061 (sp$^2$/sp$^3$ C-O stretching) cm$^{-1}$.

$^1$H NMR (DMSO-d$_6$): $\delta$ 2.23 (s, 3H, CH$_3$), 4.55 (s, 1H, NH), 5.32 (s, 2H, OCH$_2$), 6.76 (d, J = 8 Hz, 1H, ArH), 6.82 (d, J = 8 Hz, 1H, ArH), 6.89 (d, J = 8 Hz, 1H, ArH), 7.08 (d, J = 8 Hz, 1H, ArH), 7.18 (dd, J = 3.6 Hz, 2H, ArH), 7.56 (dd, 2H, ArH) ppm.

$^{13}$C NMR (DMSO-d$_6$): $\delta$ 12.8 (CH$_3$), 65.6 (OCH$_2$), 114.8, 115.4, 121.1, 123.2, 124.8, 126.9, 130.2, 132.6 (2C), 133.8, 156.3 (aromatic and benzimidazole carbons) ppm.

MS m/z: found 238 [M$^+$]; calcd. 238. Anal. C$_{15}$H$_{14}$N$_2$O. Found C 74.98 (75.6), H 5.88 (5.92), N 11.69 (11.76).
2-((m-tolyloxy)methyl)-1H-benzo[d]imidazole (3c)

Yield 65%, m.p. 138-140°C.

IR (KBr)\(\nu_{\text{max}}\) : 3478 (N-H stretching), 2940 (C-H stretching in CH\(_3\)/CH\(_2\)), 1628 (C=N stretching), 1570 (C=C stretching in aromatics), 1142,1058 (sp\(^2\)/sp\(^3\) C-O stretching) cm\(^{-1}\).

\(^1\)H NMR (DMSO-d\(_6\)) : \(\delta\) 2.32 (s, 3H, CH\(_3\)), 4.64 (s, 1H, NH), 5.63 (s, 2H, OCH\(_2\)), 6.80-6.98 (m, 3H, ArH), 7.16-7.27 (d, J = 8 Hz, 1H, ArH), 7.32-7.45 (m, 1H, ArH), 7.53-7.56 (m, 1H, ArH), 7.73-7.80 (m, 1H, ArH), 7.81-7.83 (m, 1H, ArH) ppm.

\(^{13}\)C NMR (DMSO-d\(_6\)) : \(\delta\) 20.6 (CH\(_3\)), 64.3 (OCH\(_2\)), 112.4, 113.3, 115.8, 121.5, 123.4, 129.8, 132.4 (2C), 133.8, 135.6, 158.6 (aromatic and benzimidazole carbons) ppm.

MS m/z: found 238 [M\(^+\)]; calcd. 238. Anal. C\(_{15}\)H\(_{14}\)N\(_2\)O. Found C 74.96 (75.60), H 5.86 (5.92), N 11.72 (11.76).

2-((p-tolyloxy)methyl)-1H-benzo[d]imidazole (3d)

Yield 95%, m.p. 164-166°C.

IR (KBr)\(\nu_{\text{max}}\) : 3427 (N-H stretching), 2916 (C-H stretching in CH\(_3\)/CH\(_2\)), 1611 (C=N stretching), 1589 (C=C stretching in aromatics), 1178,1056 (sp\(^2\)/sp\(^3\) C-O stretching) cm\(^{-1}\).
1H NMR (DMSO-d$_6$) : δ 2.28 (s, 3H, CH$_3$), 4.65 (s, 1H, NH), 5.36 (s, 2H, OCH$_2$), 6.88-6.90 (d, J = 8 Hz, 2H, ArH), 7.08-7.10 (d, J = 8 Hz, 2H, ArH), 7.27 (t, J = 3.2 Hz, 2H, ArH), 7.59-7.62 (dd, J = 3.2 Hz, 2H, ArH) ppm.

13C NMR (DMSO-d$_6$): δ 20.5 (CH$_3$), 64.2 (OCH$_2$), 114.6, 115.3, 123.4, 130.2 (2C), 130.4 (2C), 131.6, 155.7 (aromatic and benzimidazole carbons) ppm.

MS m/z: found 238 [M$^+$]; calcd. 238. Anal. C$_{15}$H$_{14}$N$_2$O. Found C 74.99 (75.60), H 5.88 (5.92), N 11.64 (11.76).

2-((2-chlorophenoxy)methyl)-1H-benzo[d]imidazole (3e)

Yield 84%, m.p. 186-188ºC.

IR (KBr)$\nu_{\text{max}}$: 3451 (N-H stretching), 3024 (C-H stretching in aromatics), 1641 (C=N stretching), 1586 (C=C stretching in aromatics), 1121,1093 (sp$^2$/sp$^3$ C-O stretching) 1042 (C-Cl stretching in aromatics) cm$^{-1}$.

1H NMR (DMSO-d$_6$) : δ 4.57 (s, 1H, NH), 5.34 (s, 2H, CH$_2$O), 6.79 (d, J = 8 Hz, 1H, ArH), 6.84 (d, J = 8 Hz, 1H, ArH), 7.04 (d, J = 8 Hz, 1H, ArH), 7.14 (d, J = 8 Hz, 1H, ArH), 7.19 (dd, J = 3.2 Hz, 2H, ArH), 7.58 (dd, J = 3.2 Hz, 2H, ArH) ppm.

13C NMR (DMSO-d$_6$): δ 65.8 (OCH$_2$), 114.6, 115.6, 121.4, 123.5, 125.2, 127.1, 130.4 (2C), 132.9, 134.2, 156.8 (aromatic and benzimidazole carbons) ppm.

MS m/z: found 260 [M+2], 258 [M$^+$]; calcd. 258. Anal. C$_{14}$H$_{11}$N$_2$OCl. Found C 63.78 (65.00), H 4.27 (4.29), N 10.79 (10.83).

2-((4-chlorophenoxy)methyl)-1H-benzo[d]imidazole (3f)

Yield 80%, m.p. 172-174ºC.
IR (KBr)ν_{max} : 3468 (N-H stretching), 2920 (C-H stretching in CH₃/CH₂), 1621 (C=N stretching), 1592 (C=C stretching in aromatics), 1146, 1121 (sp²/sp³ C-O stretching), 1033 (C-Cl stretching in aromatics) cm⁻¹.

¹H NMR (DMSO-d₆) : δ 4.66 (s, 1H, NH), 5.38 (s, 2H, OCH₂), 6.75 (d, J = 8 Hz, 2H, ArH), 7.18 (d, J = 8 Hz, 2H, ArH), 7.29 (t, J =3.2 Hz, 2H, ArH), 7.82 (dd, J = 3.2 Hz, 2H, ArH) ppm.

¹³C NMR (DMSO-d₆): δ 68.6 (OCH₂), 115.4, 115.8, 123.6, 126.8, 130.0, 130.4 (2C), 140.8, 156.4 (aromatic and benzimidazole carbons) ppm.

MS m/z: found 260 [M+2], 258 [M⁺]; calcd. 258. Anal. C₁₄H₁₁N₂OCl. Found C 63.82 (65.0), H 4.26 (4.29), N 10.79 (10.83).

2-(substituted phenoxy)methyl-1H-benzo[d]imidazoles (3a-f) on reaction with ethyl chloroacetate in DMSO yields ethyl 2-(2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4a-f). In the IR spectrum of 4a, a strong absorption band for carbonyl group at 1742 cm⁻¹ confirms the formation of acetate.

¹H NMR spectrum showed a 3H triplet at δ 1.23 and 2H quartet at 4.18 corresponding to CH₃-CH₂ group. The singlet at 5.12 corresponds to CH₂ and the singlet at 5.51 corresponds to CH₂O respectively. The disappearance of singlet at around δ 4.58 (corresponding to NH in 3a-f) confirms that an acetate group substitute the proton on nitrogen of imidazole.
Characterization data of 4a-f

*Ethyl 2-(2-(phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4a)*

Yield 88%, m.p. 108-110°C.

IR (KBr)νmax : 1742 (C=O stretching in esters), 1622 (C=N stretching), 1564 (C=C stretching in aromatics), 1242, 1016 (sp²/sp³ C-O stretching) cm⁻¹.

¹H NMR (DMSO-d₆) : δ 1.23 (t, J = 8 Hz, 3H, ester CH₃), 4.18 (q, J = 8 Hz, 2H, ester CH₂), 5.12 (s, 2H, CH₂), 5.51 (s, 2H, CH₂O), 6.95 (d, 2H, ArH), 7.04 (d, 1H, Ar-H), 7.21 (dd, 2H, ArH), 7.23-7.25 (m, 2H, ArH), 7.48 (dd, 2H, ArH) ppm.

¹³C NMR (DMSO-d₆): δ 14.3 (ester CH₃), 50.9 (CH₂), 61.3 (ester CH₂), 69.2 (OCH₂), 114.5, 115.1, 121.3, 123.2, 129.8, 134.4, 140.1, 141.7, 158.2 (aromatic and benzimidazole carbons), 166.8 (C=O) ppm.

MS m/z: found 310 [M⁺]; calcd. 310. Anal. C₁₈H₁₈N₂O₃. Found C 69.28 (69.66), H 5.78 (5.85), N 8.86 (9.03).

*Methyl 2-(2-((o-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4b)*

Yield 80%, m.p. 116-118°C.
IR (KBr)ν max : 2940 (sp³ C-H stretching in CH₃/CH₂), 1742 (C=O stretching in esters), 1618 (C=N stretching), 1560 (C=C stretching in aromatics), 1245,1161 (sp²/sp³ C-O stretching) cm⁻¹.

¹H NMR (DMSO-d₆) : δ 1.16 (t, J = 7 Hz, 3H, ester CH₃), 2.22 (s, 3H, CH₃), 4.13 (q, J = 7 Hz, 2H, ester CH₂), 5.08 (s, 2H, CH₂), 5.43 (s, 2H, CH₂O), 6.88 (m, 1H, ArH), 7.06-7.17 (m, 3H, ArH), 7.31-7.33 (m, 2H, ArH), 7.80-7.82 (dd, 2H, ArH) ppm.

¹³C NMR (DMSO-d₆): δ 14.2 (ester CH₃), 14.6 (CH₃), 51.3 (CH₂), 61.2 (ester CH₂), 66.8 (OCH₂), 114.5, 115.8, 121.2, 122.8, 124.4, 126.7, 130.8, 134.5, 139.2, 141.3, 159.2 (aromatic and benzimidazole carbons), 166.5 (C=O) ppm.

MS m/z: found 324 [M⁺]; calcd. 324. Anal. C₁₉H₂₀N₂O₃. Found C 69.61 (70.35), H 6.19 (6.21), N 8.61 (8.64).

**Methyl 2-((m-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4c)**

Yield 65%, m.p. 92-94ºC.

IR (KBr)ν max : 2911 (sp³ C-H stretching in CH₃/CH₂), 1752 (C=O stretching in esters), 1634 (C=N stretching), 1572 (C=C stretching in aromatics), 1258,1152 (sp²/sp³ C-O stretching) cm⁻¹.

¹H NMR (DMSO-d₆) : δ 1.16 (t, J = 8 Hz, 3H, ester CH₃), 2.32 (s, 3H, CH₃), 4.14 (q, J = 8 Hz, 2H, ester CH₂), 4.95 (s, 2H, CH₂), 5.62 (s, 2H, OCH₂), 6.80-6.98 (m, 3H, ArH), 7.16-7.27 (m, 1H, ArH), 7.32-7.45 (m, 1H, ArH), 7.53-7.56 (m, 1H, ArH), 7.73-7.80 (m, 1H, ArH), 7.81-7.83 (m, 1H, ArH) ppm.
\(^{13}\)C NMR (DMSO-d\(_6\)): \(\delta\) 14.3 (ester CH\(_3\)), 24.8 (CH\(_3\)), 51.1 (CH\(_2\)), 61.3 (ester CH\(_2\)), 66.5 (OCH\(_2\)), 111.6, 113.3, 115.1, 121.6, 123.5, 129.5, 134.5, 139.2, 139.6, 141.8, 160.9 (aromatic carbons), 168.5 (C=O) ppm.

MS m/z: found 324 [M\(^+\)]; calcd. 324. Anal. C\(_{19}\)H\(_{20}\)N\(_2\)O\(_3\). Found C 69.43 (70.35), H 6.18 (6.21), N 8.60 (8.64).

**Methyl 2-(2-((m-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4d)**

Yield 85%, m.p. 118-120ºC.

IR (KBr)\(v_{\text{max}}\): 2981 (sp\(^3\) C-H stretching in CH\(_3\)/CH\(_2\)), 1739 (C=O stretching in esters), 1612 (C=N stretching), 1588 (C=C stretching in aromatics), 1239,1019 (sp\(^2\)/sp\(^3\) C-O stretching) cm\(^{-1}\).

\(^1\)H NMR (DMSO-d\(_6\) ) : \(\delta\) 1.22 (t, \(J = 8\) Hz, 3H, ester CH\(_3\) ), 2.28 (s, 3H, CH\(_3\)), 4.20 (q, \(J = 8\) Hz, 2H, ester CH\(_2\)), 5.13 (s, 2H, CH\(_2\)), 5.60 (s, 2H, CH\(_2\)O), 6.95 (d, 2H, ArH), 7.10 (d, 2H, ArH), 7.26 (dd, 2H, ArH), 7.41 (dd, 2H, ArH) ppm.

\(^{13}\)C NMR (DMSO-d\(_6\)): \(\delta\) 14.1 (ester CH\(_3\)), 24.1 (CH\(_3\)), 51.4 (CH\(_2\)), 61.5 (ester CH\(_2\)), 66.7 (OCH\(_2\)), 114.3, 115.6, 123.2, 130.3, 130.8, 134.2, 139.2, 141.6, 157.8 (aromatic and benzimidazole carbons), 166.4 (C=O) ppm.

MS m/z: found 324 [M\(^+\)]; calcd. 324. Anal. C\(_{19}\)H\(_{20}\)N\(_2\)O\(_3\). Found C 69.65 (70.35), H 6.19 (6.21), N 8.62 (8.64).

**Methyl 2-(2-((2-chlorophenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4e)**

Yield 83%, m.p. 134-136ºC.
IR (KBr)\(v_{\text{max}}\): 2976 (sp\(^3\) C-H stretching in CH\(_3\)/CH\(_2\)), 1736 (C=O stretching in esters), 1614 (C=N stretching), 1583 (C=C stretching in aromatics), 1248,1161 (sp\(^2\)/sp\(^3\) C-O stretching), 1036 (C-Cl stretching in aromatics) cm\(^{-1}\).

\(^1\)H NMR (DMSO-d\(_6\)) : \(\delta\) 1.16 (t, J = 8 Hz, 3H, ester CH\(_3\)), 4.13 (q, J = 8 Hz, 2H, ester CH\(_2\)), 5.09 (s, 2H, CH\(_2\)), 5.45 (s, 2H, OCH\(_2\)), 6.72 (m, 1H, ArH), 7.07-7.16 (m, 3H, ArH), 7.29-7.32 (m, 2H, ArH), 7.78-7.80 (dd, 2H, ArH) ppm.

\(^{13}\)C NMR (DMSO-d\(_6\)) : \(\delta\) 14.3 (ester CH\(_3\)), 51.4 (CH\(_2\)), 61.8 (ester CH\(_2\)), 65.2 (OCH\(_2\)), 115.6, 115.8, 122.6, 122.8, 123.2, 128.1, 130.2, 134.6, 139.5, 141.8, 154.8 (aromatic and benzimidazole carbons), 166.5 (C=O) ppm.

MS m/z: found 346 [M+2], 344 [M\(^+\)]; calcd. 344. Anal. C\(_{18}\)H\(_{17}\)N\(_2\)O\(_3\)Cl. Found C 61.76 (62.70), H 4.95 (4.97), N 8.11 (8.12).

**Methyl 2-(2-((4-chlorophenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4f)**

Yield 75%, m.p. 120-122ºC.

IR (KBr)\(v_{\text{max}}\): 2992 (sp\(^3\) C-H stretching in CH\(_3\)/CH\(_2\)), 1780 (C=O stretching in esters), 1630 (C=N stretching), 1570 (C=C stretching in aromatics), 1236,1147 (sp\(^2\)/sp\(^3\) C-O stretching), 1025 (C-Cl stretching in aromatics) cm\(^{-1}\).

\(^1\)H NMR (DMSO-d\(_6\)) : \(\delta\) 1.22 (t, J = 8 Hz, 3H, ester CH\(_3\)), 4.21 (q, J = 8 Hz, 2H, ester CH\(_2\)), 5.13 (s, 2H, CH\(_2\)), 5.60 (s, 2H, OCH\(_2\)), 7.03 (d, 2H, ArH), 7.18 (d, 2H, ArH), 7.26 (dd, 2H, ArH), 7.41 (dd, 2H, ArH) ppm.
$^{13}$C NMR (DMSO-d$_6$): $\delta$ 14.3 (ester CH$_3$), 51.4 (CH$_2$), 60.8 (ester CH$_2$), 66.2 (OCH$_2$), 115.9, 123.2, 126.8, 130.2, 134.5, 139.0, 141.3, 160.1 (aromatic and benzimidazole carbons), 166.8 (C=O) ppm.

MS m/z: found 346 [M+2], 344 [M$^+$]; calcd. 344. Anal. C$_{18}$H$_{17}$N$_2$O$_3$Cl. Found C 61.84 (62.70), H 4.94 (4.97), N 8.09 (8.12).

Ethyl 2-(2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4a-f) on reaction with hydrazine hydrate yields 2-(2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazides (5a-f). In the IR spectrum of (5a), broad stretching band at around 3254 cm$^{-1}$ was due to hydrazide NH while strong stretching at 1754 was attributed to amide carbonyl. $^1$H NMR spectrum showed singlets at $\delta$ 3.94 and 7.62 which were accounted for NH$_2$ and NH respectively. The singlet at 4.95 corresponds to CH$_2$ and another singlet at 5.33 corresponds to CH$_2$O respectively.

Characterization data of 5a-f

2-(2-(phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5a)

Yield 93%, m.p. 162-164ºC.
IR (KBr) $v_{\text{max}}$: 3254 (N-H stretching), 1754 (C=O stretching), 1669 (C=N stretching), 1412 (C-N stretching) cm$^{-1}$.

$^1$H NMR (DMSO-d$_6$): $\delta$ 3.94 (s, broad, 2H, NH$_2$), 4.95 (s, 2H, NCH$_2$), 5.33 (s, 2H, CH$_2$O), 6.97 (d, J = 8 Hz, 2H, ArH), 7.04 (d, J = 8.4 Hz, 1H, ArH), 7.23 (dd, 2H, ArH), 7.28 (d, J = 2.4 Hz, 2H, ArH), 7.51 (dd, 2H, Ar-H), 7.62 (s, 1H, NH) ppm.

$^{13}$C NMR (DMSO-d$_6$): $\delta$ 35.2 (CH$_3$), 69.2 (OCH$_2$), 114.5, 115.4, 121.2, 123.5, 129.7, 134.4, 141.2, 141.5, 158.6 (aromatic and benzimidazole carbons), 165.2 (C=O) ppm.

MS m/z: found 296 [M$^+$]; calcd. 296. Anal. C$_{16}$H$_{16}$N$_4$O$_2$. Found C 64.21 (64.85), H 5.39 (5.44), N 18.78 (18.91).

2-(2-((o-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5b)

Yield 70%, m.p. 136-138ºC.

IR (KBr) $v_{\text{max}}$: 3278 (N-H stretching), 3061 (C-H stretching in aromatics), 1739 (C=O stretching), 1667 (C=N stretching), 1415 (C-N stretching) cm$^{-1}$.

$^1$H NMR (DMSO-d$_6$): $\delta$ 2.23 (s, 3H, CH$_3$), 3.94 (s, broad, 2H, NH$_2$), 5.08 (s, 2H, NCH$_2$), 5.43 (s, 2H, OCH$_2$), 6.88-6.92 (d, J = 16 Hz, 1H, ArH), 7.06-7.10 (d, J = 16 Hz, 1H, ArH), 7.14-7.17 (d, J = 12 Hz, 2H, ArH), 7.28-7.38 (2dd, 4H, ArH), 7.82 (t, J = 2.4 Hz, 1H, NH) ppm.

$^{13}$C NMR (DMSO-d$_6$): $\delta$ 14.6 (CH$_3$), 37.5 (CH$_2$), 66.8 (OCH$_2$), 114.0, 115.5, 121.5, 123.5, 125.1, 127.2, 130.4, 134.5, 139.5, 142.2, 158.9 (aromatic and benzimidazole carbons), 165.2 (C=O) ppm.
MS m/z: found 310 [M⁺]; calcd. 310. Anal. C₁₇H₁₈N₄O₂. Found C 64.68 (65.79), H 5.83 (5.85), N 18.19 (18.25).

2′-(2-((m-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5c)

Yield 72%, m.p. 156-158°C.

IR (KBr)ν\text{max} : 3271 (N-H stretching), 3074 (C-H stretching in aromatics), 1780 (C=O stretching), 1642 (C=N stretching), 1448 (C-N stretching) ppm.

$^1$HMR (DMSO-d$_6$) : δ 2.32 (s, 3H, CH₃), 3.92 (s, broad, 2H, NH₂), 4.95 (s, 2H, NCH₂), 5.62 (s, 2H, CH₂O), 6.80-6.98 (m, 3H, ArH), 7.16-7.27 (m, 1H, ArH), 7.32-7.45 (m, 1H, ArH), 7.53-7.56 (m, 1H, ArH), 7.73-7.80 (m, 1H, ArH), 7.81-7.82 (m, 1H, ArH), 7.83 (s ,1H, NH) ppm.

$^{13}$C NMR (DMSO-d$_6$): δ 25.1 (CH₃), 33.6 (CH₂), 66.5 (OCH₂), 111.5, 113.5, 115.2, 121.6, 123.8, 130.2, 134.6, 139.5, 140.2, 141.8, 160.9 (aromatic and benzimidazole carbons), 165.2 (C=O) ppm.

MS m/z: found 310 [M⁺]; calcd. 310. Anal. C₁₇H₁₈N₄O₂. Found C 64.73 (65.79), H 5.81 (5.85), N 18.21 (18.25).

2′-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5d)

Yield 95%, m.p. 184-186°C.

IR (KBr)ν\text{max} : 3428 (N-H stretching), 2916 (C-H stretching in aromatics), 1739 (C=O stretching), 1611 (C=N stretching), 1428 (C-N stretching), 1233, 1057 (sp²/sp³ C-O stretching) cm⁻¹.
\[^1\]HMR (DMSO-d\textsubscript{6}) : \(\delta 2.22\) (s, 3H, CH\textsubscript{3}), 3.97 (s, broad, 2H, NH\textsubscript{2}), 4.94 (s, 2H, NCH\textsubscript{2}), 5.34 (s, 2H, CH\textsubscript{2}O), 6.97-6.98 (d, 2H, ArH), 7.08-7.10 (d, 2H, ArH), 7.20-7.28 (dd, 2H, ArH), 7.50-7.52 (dd, 2H, ArH), 7.63-7.68 (s ,1H, NH) ppm.

\[^{13}\]C NMR (DMSO-d\textsubscript{6}): \(\delta 24.1\) (CH\textsubscript{3}), 33.5 (CH\textsubscript{2}), 66.8 (OCH\textsubscript{2}), 114.5, 115.1, 115.2, 123.5, 130.5 ,130.8, 134.5, 140.2, 141.2, 158.3 (aromatic and benzimidazole carbons), 165.9 (C=O) ppm.

MS m/z: found 311 [M+H]; calcd. 310. Anal. C\textsubscript{17}H\textsubscript{18}N\textsubscript{4}O\textsubscript{2}. Found C 64.68 (65.79), H 5.83 (5.85), N 18.19 (18.25).

2'-\((2-(2-chlorophenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5e)

Yield 85%, m.p. 142-144ºC.

IR (KBr)\(v_{\text{max}}\): 3264 (N-H stretching), 3058 (C-H stretching in aromatics), 1760 (C=O stretching), 1648 (C=N stretching), 1456 (C-N stretching), 1028 (C-Cl stretching in aromatics) cm\textsuperscript{-1}.

\[^1\]HMR (DMSO-d\textsubscript{6}) : \(\delta 3.86\) (s, broad, 2H, NH\textsubscript{2}), 5.06 (s, 2H, NCH\textsubscript{2}), 5.43 (s, 2H, CH\textsubscript{2}O), 6.86-6.94 (d, 1H, ArH), 7.08-7.12 (d, 1H, ArH), 7.02 (d, 1H, ArH), 7.17 (d ,1H, ArH), 7.28-7.38 (2dd, 4H, ArH), 7.82 (s, 1H, NH) ppm.

\[^{13}\]C NMR (DMSO-d\textsubscript{6}): \(\delta 33.5\) (CH\textsubscript{2}), 66.0 (OCH\textsubscript{2}), 115.5, 115.8, 122.8, 122.9, 123.0, 123.5, 127.8, 129.8, 134.5, 139.2, 141.8, 154.8 (aromatic and benzimidazole carbons), 165.2 (C=O) ppm.

MS m/z: found 332 [M+2], 330 [M\textsuperscript{+}]; calcd. 330. Anal. C\textsubscript{16}H\textsubscript{15}N\textsubscript{4}O\textsubscript{2}Cl. Found C 57.64 (58.10), H 4.54 (4.57), N 16.73 (16.94).
2-(2-(4-chlorophenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5f)

Yield 82%, m.p. 190-192°C.

IR (KBr) νmax: 3245 (N-H stretching), 3078 (C-H stretching in aromatics), 1742 (C=O stretching), 1652 (C=N stretching), 1448 (C-N stretching), 1015 (C-Cl stretching in aromatics) cm⁻¹.

¹H NMR (DMSO-d₆): δ 3.94 (s, broad, 2H, NH₂), 4.92 (s, 2H, NCH₂), 5.31 (s, 2H, CH₂O), 6.94-6.96 (d, 2H, ArH), 7.15-7.17 (d, 2H, ArH), 7.20-7.24 (dd, 2H, ArH), 7.48-7.52 (dd, 2H, ArH), 7.59-7.62 (s, 1H, NH) ppm.

¹³C NMR (DMSO-d₆): δ 32.4 (CH₂), 66.1 (OCH₂), 115.4, 115.9, 123.4, 126.8, 130.2, 134.5, 140.4, 141.9, 160.3 (aromatic and benzimidazole carbons), 164.8 (C=O).

MS m/z: found 332 [M+2], 330 [M⁺]; calcd. 330. Anal. C₁₆H₁₅N₄O₂Cl. Found C 57.78 (58.10), H 4.53 (4.57), N 16.78 (16.94).

2-(2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)acetohydrazides (5a-f) on reaction with carbon disulfide in KOH yields 5-((2-(substituted phenoxymethyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols (6a-f). Lack of ¹H NMR resonances observed with NH and NH₂ groups in the spectrum of 6a confirm that ring closure starting from 5a resulted in the formation of 1,3,4-oxadiazole ring. This was further substantiated by a weak absorption band in IR at 2842 cm⁻¹ corresponding to SH stretching in thiols and a broad singlet at δ 3.67 in ¹H NMR for SH.
Characterization data of 6a-6f

5-((2-(phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6a)

Yield 96%, m.p. 154-156°C.

IR (KBr)νmax : 2842 (S-H stretching in thiols), 1634 (C=N stretching), 1564 (C=C stretching in aromatics), 1241, 1063 (sp²/sp³ C-O stretching) cm⁻¹.

¹H NMR (DMSO-d₆) : δ 3.67 (hump, 1H, SH), 5.21 (s, 2H, NCH₂), 5.35 (s, 2H, CH₂O), 6.96 (d, J = 8.4 Hz, 2H, ArH), 7.06 (d, 1H, Ar-H), 7.24 (dd, 2H, ArH), 7.32 (d, J = 8 Hz), 2H, ArH), 7.52 (dd, 2H, ArH) ppm.

¹³C NMR (DMSO-d₆): δ 48.5 (CH₂), 69.6 (OCH₂), 114.9, 116.8, 121.2, 123.4, 129.9, 133.6, 138.2, 141.8, 158.3 (aromatic and benzimidazole carbons), 164.4, 165.6 (oxadiazole carbons) ppm.

MS m/z: found 338 [M⁺]; calcd. 338. Anal. C₁₇H₁₄N₄O₂S. Found C 63.89 (64.34), H 3.98 (4.17), N 16.37 (16.56).
5-((2-((o-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6b)

Yield 84%, m.p. 158-160ºC.

IR (KBr)\text{v}_{\text{max}}: 2780 (S-H stretching in thiols), 1632 (C=N stretching), 1580 (C=C stretching in aromatics), 1256, 1095 (sp^2/sp^3 C-O stretching) cm\(^{-1}\).

\(^1\text{H}\text{ NMR (DMSO-d}_6): \delta 2.14 (s, 3H, CH}_3\), 3.63 (hump, 1H, SH), 5.22 (s, 2H, NCH\(_2\)), 5.41 (s, 2H, CH\(_2\)O), 6.87 (d, J = 11.2 Hz, 1H, ArH), 7.13-7.17 (m, 3H, ArH), 7.25-7.33 (dd, 2H, ArH), 7.60-7.71 (dd, 2H, ArH) ppm.

\(^{13}\text{C NMR (DMSO-d}_6): \delta 14.9 (CH}_3\), 45.8 (CH\(_2\)), 70.1 (OCH\(_2\)), 114.5, 115.5, 121.3, 123.4, 124.8, 126.9, 130.5, 134.6, 139.2, 141.9, 159.1 (aromatic and benzimidazole carbons), 164.8, 165.2 (oxadiazole carbons) ppm.

MS m/z: found 352 [M^+]; calcd. 352. Anal. C\(_{18}\)H\(_{16}\)N\(_4\)O\(_2\)S. Found C 60.98 (61.35), H 4.56 (4.58), N 15.6 (15.9).

5-((2-((m-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6c)

Yield 80%, m.p. 172-174ºC.

IR (KBr)\text{v}_{\text{max}}: 2810 (S-H stretching in thiols), 1651 (C=N stretching), 1572 (C=C stretching in aromatics), 1214, 1068 (sp^2/sp^3 C-O stretching) ppm.

\(^1\text{H NMR (DMSO-d}_6): \delta 2.32 (s, 3H, CH}_3\), 3.90 (hump, 1H, SH), 5.47 (s, 2H, NCH\(_2\)), 5.62 (s, 2H, CH\(_2\)O), 6.80-6.98 (m, 3H, ArH), 7.16-7.27 (m, 1H, ArH),
7.32-7.45 (m, 1H, ArH), 7.53-7.56 (m, 1H, ArH), 7.73-7.80 (m, 1H, ArH), 7.81-7.83 (m, 1H, ArH) ppm.

\(^{13}\)C NMR (DMSO-d\(_6\)) \(\delta\) 24.8 (CH\(_3\)), 45.8 (CH\(_2\)), 66.8 (OCH\(_2\)), 111.5, 113.4, 115.8, 121.5, 123.6, 130.3, 134.5, 139.2, 139.6, 141.8, 160.7 (aromatic and benzimidazole carbons), 165.5, 166.4 (oxadiazole carbons) ppm.

MS m/z: found 352 [M\(^+\)]; calcd. 352. Anal. C\(_{18}\)H\(_{16}\)N\(_4\)O\(_2\)S. Found C 60.56 (61.35), H 4.55 (4.58), N 15.4 (15.9).

\(5\)-((2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6d)

Yield 95%, m.p. 180-182°C.

IR (KBr)\(\nu_{\text{max}}\) : 2856 (S-H stretching in thiols), 1612 (C=N stretching), 1571 (C=C stretching in aromatics), 1238, 1070 (sp\(^2\)/sp\(^3\) C-O stretching) cm\(^{-1}\).

\(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) 2.31 (s, 3H, CH\(_3\)), 3.68 (hump, 1H, SH), 5.24 (s, 2H, NCH\(_2\)), 5.34 (s, 2H, CH\(_2\)O), 6.97-6.99 (d, 2H, ArH), 7.09 (d, J = 8 Hz, 2H, ArH), 7.20-7.28 (dd, 2H, ArH), 7.50-7.52 (dd, 2H, ArH) ppm.

\(^{13}\)C NMR (DMSO-d\(_6\)) \(\delta\) 24.9 (CH\(_3\)), 46.5 (CH\(_2\)), 68.5 (OCH\(_2\)), 115.1, 116.8, 123.5, 130.3, 130.9, 135.2, 140.3, 141.8, 158.2 (aromatic and benzimidazole carbons), 164.2, 165.8 (oxadiazole carbons) ppm.

MS m/z: found 352 [M\(^+\)]; calcd. 352. Anal. C\(_{18}\)H\(_{16}\)N\(_4\)O\(_2\)S. Found C 60.84 (61.35), H 4.57 (4.58), N 15.6 (15.9).
5-((2-((2-chlorophenoxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6e)

Yield 80%, m.p. 170-172°C.

IR (KBr)\(\nu_{\text{max}}\): 2854 (S-H stretching in thiols), 1647 (C=N stretching), 1586 (C=C stretching in aromatics), 1248, 1056 (sp\(^2\)/sp\(^3\) C-O stretching), 1012 (C-Cl stretching in aromatics) ppm.

\(^1\)H NMR (DMSO-\(d_6\)) : \(\delta\) 3.65 (hump, 1H, SH), 5.24 (s, 2H, NCH\(_2\)), 5.43 (s, 2H, CH\(_2\)O), 6.87-6.89 (d, 1H, ArH), 7.18-7.21 (m, 3H, ArH), 7.28-7.32 (dd, 2H, ArH), 7.68-7.72 (dd, 2H, ArH) ppm.

\(^{13}\)C NMR (DMSO-\(d_6\)) : \(\delta\) 45.9 (CH\(_2\)), 66.5 (OCH\(_2\)), 115.8, 123.0, 123.8, 123.9, 128.1, 130.2, 134.5, 139.3, 141.8, 154.9 (aromatic and benzimidazole carbons), 164.8, 165.9 (oxadiazole carbons) ppm.

MS m/z: found 380 [M+2], 372 [M\(^+\)]; calcd. 372. Anal. C\(_{17}\)H\(_{13}\)N\(_4\)O\(_2\)SCl. Found C 53.89 (54.77), H 3.50 (3.51), N 9.48 (9.51).

5-((2-((4-chlorophenoxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6f)

Yield 75%, m.p. 186-188°C.

IR (KBr)\(\nu_{\text{max}}\): 2842 (S-H stretching in thiols), 1648 (C=N stretching), 1574 (C=C stretching in aromatics), 1264, 1076 (sp\(^2\)/sp\(^3\) C-O stretching), 1005 (C-Cl stretching in aromatics) cm\(^{-1}\).
\( ^1H \) NMR (DMSO-\( d_6 \)) : \( \delta \ 3.66 \) (hump, 1H, SH), 5.24 (s, 2H, NCH\(_2\)), 5.38 (s, 2H, CH\(_2\)O), 6.98 (d, 2H, ArH), 7.11 (d, J =8 Hz, 2H, ArH), 7.19-7.26 (dd, 2H, ArH), 7.48-7.52 (dd, 2H, ArH) ppm.

\( ^{13}C \) NMR (DMSO-\( d_6 \)) : \( \delta \ 45.8 \) (CH\(_2\)), 66.9 (OCH\(_2\)), 116.2, 116.9, 123.4, 126.8, 130.3, 134.8, 139.5, 141.8, 159.1 (aromatic and benzimidazole carbons), 164.1, 165.9 (oxadiazole carbons) ppm.

MS m/z: found 380 [M+2], 372 [M\(^+\)]; calcd. 372. Anal. C\(_{17}\)H\(_{13}\)N\(_4\)O\(_2\)SCl. Found C 53.76 (54.77), H 3.49 (3.51), N 9.49 (9.51).
Experimental

Synthesis of substituted 2-phenoxyacetic acid derivatives (2a-f)

Synthesis of 2-phenoxyacetic acid (2a)

1 g of phenol (1a) was taken in a boiling test tube dissolved in 3.5 mL of 33% NaOH and 2.5 mL of 50% solution of monochloroacetic acid was added. The tube was loosely stoppered and heated on a boiling water bath for about 30 minutes. Cooled and then added dilute hydrochloric acid till the solution was acidic. The precipitate of aryloxyacetic acid\textsuperscript{14, 15} was filtered, washed with water and recrystallized from water to afford 2a. The melting points of the products obtained were compared with the literature values. Compounds (2b-f) were synthesized on the same lines.

Synthesis of 2-(substituted phenoxyethyl)-1H-benzo[d]imidazoles, (3a-f)

Synthesis of 2-(phenoxymethyl)-1H-benzo[d]imidazole, (3a)

The mixture of o-phenylenediamine (0.09 mol) and 2-phenoxyacetic acid 2 (0.1 mol) was dissolved in 4N HCl (10 mL) and refluxed at 100°C for 5 hr. The completion of reaction was checked by TLC. The reaction mixture was cooled to room temperature, poured into ice cold water and neutralized with dilute NaOH solution to get 2-(phenoxymethyl)-1H-benzo[d]imidazole,\textsuperscript{16-18} 3a. The separated solid was filtered, washed with ice cold water, dried and purified by recrystallization from ethanol. Compounds (3b-f) were synthesized on the same lines.
Synthesis of Ethyl 2-(2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetates, 4a-4f

Synthesis of Ethyl 2-(2-(phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate, (4a)

A mixture of 2-(phenoxy)methyl)-1H-benzo[d]imidazole (0.01 mol), Ethylchloroacetate (0.01 mol), anhydrous K$_2$CO$_3$ (1.38 g, 0.01 mol) and DMF was stirred at room temperature for 8 hr. The reaction mixture was diluted with ice-cold water. The separated solid was filtered, washed with water and recrystallized from ethanol to afford 4a. Compounds (4b-f) were prepared on the same lines.

Synthesis of 2-(2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazides (5a-f)

Synthesis of 2-(2-(phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5a)

A solution of Ethyl 2-(2-(phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate, 4a (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (25 mL) was refluxed for 5 hr. The reaction mixture was cooled and poured into ice-cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford 5a. Compounds (5b-f) were prepared on the same lines.

Synthesis of 5-((2-(substituted phenoxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols (6a-f)
Synthesis of 5-((2-(phenoxymethyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6a)

A mixture of 2-(2-(phenoxymethyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide 5a (0.01 mol), KOH (0.56 g, 0.01 mol) and 10 mL of carbon disulfide were refluxed in 50 mL of 95% ethanol for 8 hr. The resultant mixture was concentrated and cooled to room temperature. Then it was acidified with dilute HCl. The solid mass thus separated out was filtered, dried and purified by recrystallization from ethanol to afford 6a. Compounds (6b-f) were prepared on the same lines.

Fig 2.1 IR Spectrum of 2-((p-tolyloxy)methyl)-1H-benzo[d]imidazole (3d)
Fig 2.2 $^1$H NMR Spectrum of 2-((p-tolyloxy)methyl)-1H-benzo[d]imidazole (3d)
Fig 2.3 $^{13}$C NMR Spectrum of 2-((p-tolyloxy)methyl)-1H-benzo[d]imidazole (3d)
Fig 2.4 IR Spectrum of Methyl 2-((m-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4d)
Fig 2.5 $^1$H NMR Spectrum of Methyl 2-(2-((o-tolyloxy)methyl)-1H-benzo[\textit{d}]imidazol-1-yl)acetate (4b)
Fig 2.6 $^1$H NMR Spectrum of Methyl 2-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetate (4d)
Fig 2.7 IR Spectrum of 2'-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5d)
Fig 2.8 $^1$H NMR Spectrum of 2-((o-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5b)
Fig 2.9 Mass Spectrum of 2’-(2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (5d)
Fig 2.10 IR Spectrum of 5-((2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6d)
Fig 2.11 $^1$H NMR Spectrum of 5-((2-((o-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6b)
Fig 2.12 $^1$H NMR Spectrum of 5-((2-((m-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6c)
Fig 2.13 $^{13}$C NMR Spectrum of 5-((2-((p-tolyloxy)methyl)-1$H$-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6d)
Fig 2.14 Mass Spectrum of 5-((2-((p-tolyloxy)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (6d)
References


