CHAPTER IV

SYNTHESIS OF N-(BENZYOXY)-2-(4-H/METHYL-COUMARIN-4/6/7-YLOXY) ACETAMIDES:

Substituted N-(benzyloxy)-amides:
Recent reports suggest that N-(benzyloxy)-benzamide (I) and its analogues with the O-benzylhydroxylamine moiety (-CONHOCH<sub>2</sub>-Ar) possess antibacterial, hericidical and enzyme inhibiting activities<sup>1-4</sup>. The pharmacophore (-CONHOCH<sub>2</sub>-) is generally considered to be the bioisosteric analog of (-CONHCH<sub>2</sub>CH<sub>2</sub>-) in drug design<sup>5</sup>.

![Chemical Structure](image)

Hydroxamic acids (-CONHOH) are important components of many chemotherapeutic agents such as the succinate-based matrix metalloproteinase (MMP) inhibitors<sup>6</sup>, class I/II histone deacetylase (HDAC) inhibitors<sup>7</sup> and iron-containing antibiotics<sup>8</sup>. Also hydroxamic acid analogues are important targets for the medicinal chemist because of the intrinsic chelating properties of this functional group with Zn<sup>2+</sup> at the active site of metalloproteins<sup>9,10</sup>. Recently various methods have been reported for the preparation of hydroxamic acids starting from carboxylic acids or their derivatives<sup>11</sup> and N-acyloazolidinones<sup>12</sup>. The solution-phase hydroxyamination of esters is generally achieved via a two-step sequence; firstly preparation of a salt of hydroxylamine followed by addition of the ester in alcohol as solvent<sup>13</sup> or activation of the acid by reaction with an acyl chloride or mixed anhydride and quenching with O-protected hydroxylamine derivatives<sup>14</sup>.
PAST WORK:
Literature methods for the synthesis of O-alkyl hydroxamic acids are reviewed here.

METHODS FOR THE SYNTHESIS OF O-ALKYL HYDROXAMIC ACID ANALOGUES:

1) Synthesis of hydroxamic acid analogues via acid chloride method:
Agirbas et al reported the novel and facile procedure for the synthesis of O-alkyl hydroxamic acid analogues (4) of substituted pyrrole-2-carboxylic acid (2) and tested against various fungi in vitro.

Scheme 1:

\[
\begin{align*}
(2) \quad \text{(2)} & \xrightarrow{(\text{COCl})_2, \text{DCM/DMF}} (3) \\
(3) & \xrightarrow{\text{RCH}_2\text{ONH}_2, \text{Pyridine}} (4)
\end{align*}
\]

2) Synthesis and utilization of a novel coupling reagent for the preparation of O-alkyl hydroxamic acids:
Shinde et al reported an efficient novel reagent phosphoric acid diethyl ester 2-phenyl-benzimidazol-1-yl ester and its applicability was demonstrated for the preparation of O-alkyl hydroxamic acids (7). The O-alkyl hydroxamic acids (7) of N-protected amino acids were also synthesized.

Scheme 2:

\[
\begin{align*}
(5) & \quad (6) \\
R_1 = \text{Sub. phenyl} & \quad R_2 = \text{Benzyl, allyl, ethyl} \\
\text{Reagent} = & \quad \text{Reagent} = (\text{Ph})_2\text{P(O)}_2\text{OEt}
\end{align*}
\]
3) Synthesis of hydroxamic acid via hydrogenolysis:
Miller \(^{17}\) et al reported the synthesis of hydroxamic acid (10) via oxyamide route by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) mediated coupling of anthranilic acid (8) and O-benzyl hydroxylamine (10). The desired O-benzyl hydroxamate was obtained in 71% yield without the use of any protecting groups on the anthranilic acid nitrogen. Removal of the benzyl group under hydrogenolysis conditions gave a 99% yield of hydroxamic acid.

Scheme 3:

4) Synthesis of hydroxamic acid via mechanochemistry:
Lamaty \(^{18}\) et al reported the synthesis of various amides by avoiding the use of any organic solvent from activation of carboxylic acids with CDI to isolation of the amides. Mechano chemistry was the key point of the process allowing rapid formation of the amide bond and efficient water-based purification of the final products.

Scheme 4:

5) N-[(Diphenoxyphosphoryl)oxy]-2-phenyl-1H-benzimidazole as a versatile reagent for the synthesis of O-alkylhydroxamic acid:
Shinde \(^{19}\) et al reported the synthesis of an efficient novel reagent N-[(Diphenoxyphosphoryl)-oxy]-2-phenyl-1H-benzimidazole and its applicability was demonstrated for the preparation of O-alkyl hydroxamic acids.
Scheme 5:

\[ \text{R}_1 \text{OH} + \text{H}_2 \text{N}^\text{O} \text{R}_2 \xrightarrow{\text{Reagent}} \text{R}_1 \text{N}^\text{O} \text{R}_2 \]

\[ \text{Reagent} = \]

R\(_1\) = Sub. phenyl  
R\(_2\) = Benzyl, allyl, ethyl

PRESENT WORK:

Considering the potential antifungal activity of the coumarin derivatives and the fungicidal activity contribution of the O-benzylhydroxylamine group to the N-(benzyloxy)-benzamide derivatives a series of new O-alkyl hydroxamic acid analogues were designed, synthesized and tested against various fungi in vitro. Since the objective of the present work is to develop O-alkyl hydroxamic acids of substituted coumarin-4,6,7-yloxy acids at 4,6,7 positions, hydroxy coumarins (16-18) were first synthesized by the Pechmann condensation. These on reaction with ethylbromoacetate in presence of K\(_2\)CO\(_3\)/acetone to furnish O-alkylated esters (19-21) which on base hydrolysis gave substituted coumarin 4,6,7-yloxyacetic acids (22-24). Substituted benzylhalides (26-31) reacted with N-hydroxy phthalimide (25) and subsequent reaction with hydrazine hydrate gave O-(substituted benzyl)-hydroxylamines (33-38). Coumarin acetic acids (22-24) were coupled with hydroxylamines (33-38) via acid chloride method to achieve a series of N-(benzyloxy)-2-(4-H/Methyl-coumarin-4/6/7-yloxy)-acetamides (39-44), (45-50), (51-56).

Synthesis of N-(benzyloxy)-2-(4-H/Methyl-coumarin-4/6/7-yloxy)-acetamides involves 5 steps.

1) Synthesis of hydroxy coumarins (16-18)
2) Synthesis of O-alkylated hydroxy coumarins (19-21)
3) Synthesis of coumarin-4,6,7-yloxy acetic acids (22-24)

4) Synthesis of O-(substituted benzyl)-hydroxylamines (33-38)

5) Synthesis of N-(benzoyloxy)-2-(4-H/Methyl-coumarin-4/6/7-yloxy)-acetamides (39-44), (45-50), (51-56).

5a) Synthesis of N-(benzylxyloxy)-2-(coumarin-4-yloxy)-acetamides (39-44)

5b) Synthesis of N-(benzylxyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamides (45-50)

5c) Synthesis of N-(benzylxyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (51-56)

1) Synthesis of substituted hydroxy coumarins (16-18) and 2) O-alkylated substituted hydroxy coumarins (19-21) were described in Chapter III.

3) Synthesis of coumarin-4,6,7-yloxy acetic acids (22-24):

Coumarin-4,6,7-yloxyaceticacids (22-24) were synthesized from the base hydrolysis of O-alkylated hydroxy coumarin esters (19-21) with NaOH in EtOH at RT.

**Scheme 6: Synthesis of coumarin-4,6,7-yloxy acetic acids (22-24):**

![Scheme 6](image)

19) $R_1 = OCH_2COOEt, R_2 = R_3 = H$ \[\rightarrow\] 22) $R_1 = OCH_2COOH, R_2 = R_3 = H$

20) $R_2 = OCH_2COOEt, R_1 = CH_3, R_3 = H$ \[\rightarrow\] 23) $R_2 = OCH_2COOH, R_1 = CH_3, R_3 = H$

21) $R_3 = OCH_2COOEt, R_1 = CH_3, R_2 = H$ \[\rightarrow\] 24) $R_3 = OCH_2COOH, R_1 = CH_3, R_2 = H$

2-(4-Methyl-coumarin-7-yloxy)-acetic acid (24) is characterized from its spectral data. In $^1$H NMR spectrum (CDCl$_3$, 400 MHz) (Fig 4.1) the 4-CH$_3$, 7-OCH$_2$ protons appeared at $\delta$ 2.39 (s), 4.84 (s) and coumarin protons at 6.22 (s, H-3), 6.96 (s, H-8), 6.96 (d, J=8Hz, H-6), 7.68 (d, J=8.8Hz, H-5).
4) Synthesis of O-(substituted benzyl)-hydroxylamines (33-38):

N-Hydroxy phthalimide (25) was alkylated with substituted benzylhalides (26-31) in the presence of K₂CO₃ and DMF at RT. These are reacted with hydrazine hydrate in ethanol at reflux temperature to give O-(substituted benzyl)-hydroxylamines (33-38).

Scheme 7: Synthesis of O-(substituted benzyl)-hydroxylamines (33-38):

O-(4-Fluorobenzyl)-hydroxylamine (33) is characterized from its spectral data. In ¹H NMR (CDCl₃, 400 MHz) (Fig.4.2) -NH₂ & -CH₂ protons appeared at δ 5.4 (bs), 4.62 (s) and aromatic protons at 7.11-7.14 (m, H-3 & H-5), 7.32-7.37 (m, H-2 & H-6).

5) Synthesis of N-benzyloxy-2-(4-H/methyl-coumarin-4/6/7-yloxy)-acetamides (39-44), (45-50), (51-56):

5a) Synthesis of N-benzyloxy-2-(coumarin-4-yloxy)-acetamides (39-44):

N-(Benzyloxy)-2-(coumarin-4-yloxy)-acetamides (39-44) were synthesized from the amide coupling of 2-(coumarin-4-yloxy)-acetic acid (22) with O-substituted benzylhydroxylamines (33-38) via acid chloride method at RT. These were purified by acid-base workup and characterized from their spectra.
Scheme 8: Synthesis of \textit{N}-benzyloxy-2-(coumarin-4-yloxy)-acetamides (39-44):

\[
\begin{array}{c}
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
7 & 8 & 8a & 1 & 2 & 3 & 4 & 4a & 5 & 6 & 4 & 4 \\
7 & 8 & 8a & 1 & 2 & 3 & 4 & 4a & 5 & 6 & 4 & 4 \\
\end{array}
\]

\[
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
7 & 8 & 8a & 1 & 2 & 3 & 4 & 4a & 5 & 6 & 4 & 4 \\
7 & 8 & 8a & 1 & 2 & 3 & 4 & 4a & 5 & 6 & 4 & 4 \\
\end{array}
\]

33, 39) \( R = 4\text{-}F \) 34, 41) \( R = 4\text{-}\text{Cl} \) 35, 43) \( R = 4\text{-}\text{Br} \)
36, 40) \( R = 2\text{-}F \) 37, 42) \( R = 2,4\text{-}\text{Dichloro} \) 38, 44) \( R = 2\text{-}\text{CN} \)

\( 39\text{-}44 \)

\text{N-(4-Fluorobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (39) is characterized from its spectral data. In its } \textsuperscript{1}H\text{ NMR (CDCl\textsubscript{3}, 400 MHz) (Fig-4.3) the newly formed amide proton appeared at } \delta \text{ 11.59 (s, O=C-NH), 4-OCH} & 2' \text{ appeared at 4.79 (s), 4.85 (s) and other protons at 5.86 (s, H-3), 7.19-7.24 (m, H-3' & H-5'), 7.38-7.5 (m, H-2', H-3' & H-6, H-8), 7.67-7.71 (m, H-7), 7.96 (d, J=9.2Hz, H-5).}

In the \textsuperscript{13}C\text{ NMR (CDCl\textsubscript{3}, 100.6 MHz) (Fig-4.4) the newly formed amide carbon appeared at } \delta \text{ 163.5 (O=C-NH), other carbons appeared at 164.7 (C-4), 161.8 (2-C=O), 153.1 (C-8a), 133.3 (C-1'), 132.3 (C-3' & C-5'), 131.7 (C-7), 124.8 (C-4'), 123.9 (C-2' & C-6'), 116.8 (C-6), 115.7 (C-5), 115.3 (C-4a), 115.3 (C-8), 91.7 (C-3), 76.7 (1'-CH} & 2), 66.8 (4-OCH} & 2).

The DIPMS of 39 (Fig-4.5) showed the quasi-molecular ion peak at m/z 344 (M+1).

5b) Synthesis of \textit{N}-benzyloxy-2-(4-methyl-coumarin-6-yloxy)-acetamides (45-50):

\text{N-benzyloxy-2-(4-methyl-coumarin-6-yloxy)-acetamides (45-50) were synthesized from the amide coupling of 2-(4-methyl-coumarin-6-yloxy)-acetic acid (23) and O-substituted benzylhydroxylamine (33-38) via acid chloride method at RT. These were purified by acid-base workup and characterized from their spectra.}
Scheme 9: Synthesis of N-(benzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamides (45-50):

N-(4-Fluorobenzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (45) is characterized from its spectral data. In $^1$H NMR (CDCl$_3$, 400 MHz) (Fig-4.6) the newly formed amide proton appeared at $\delta$ 9.15 (s, O=C-NH). 4-CH$_3$, 6-OCH$_2$ & 1'-OCH$_2$ appeared at 2.38 (s), 4.61 (s) and 4.95 (s). Other protons appeared at 6.3 (s, H-3), 7.01-7.06 (m, H-5 & H-7, H-3' & H-5'), 7.24 (d, J=1.6Hz, H-2'), 7.37-7.41 (m, H-8 & H-6').

In the $^{13}$C NMR (CDCl$_3$, 100.6 MHz) (Fig-4.7), the newly formed amide carbon appeared at $\delta$ 164.9 (O=C-NH), other carbons appeared at 161.3 (C-4'), 160.2 (2-C=O), 154.3 (C-6), 153.2 (C-4), 148.1 (C-8a), 132.4 (C-1'), 131.5 (C-2' & C-6'), 120.5 (C-8), 120.0 (C-4a), 117.9 (C-3' & C-5'), 115.6 (C-7), 115.4 (C-3), 109.9 (C-5), 91.7 (1'-CH$_2$), 76.7 (6-OCH$_3$), 66.8 (4-CH$_3$).

The DIPMS of 45 (Fig-4.8) showed the quasi-molecular ion peak at m/z 358.4 (M+1).

5c) Synthesis of N-(benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (51-56):

N-(Benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (51-56) were synthesized from the amide coupling of 2-(4-methyl-coumarin-7-yloxy)-acetic acid (24) and O-substituted benzylhydroxylamines (33-38) via acid chloride method at RT. These were purified by acid-base workup and characterized from their spectra.
Scheme 10: Synthesis of N-(benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (51-56):

![Diagram of synthesis]

N-(4-Fluorobenzylxylo)-2-(4-methyl-coumarin-7-yloxy)-acetamide (51) is characterized from its spectral data. In $^1$H NMR (CDCl$_3$, 400 MHz) (Fig-4.9) the newly formed amide proton appeared at $\delta$ 9.13 (s, O=C-NH); 4-CH$_3$, 7-OCH$_2$ & 1'-OCH$_2$ appeared at 2.4 (s), 4.62 (s) & 4.95 (s), other protons appeared at 6.17 (s, H-3), 6.81 (s, H-8), 6.83 (d, J=2.4Hz, H-6), 7.01-7.05 (m, H-3' & H-5'), 7.37-7.4 (m, H-2' & H-6'), 7.51 (d, J=8.8Hz, H-5).

In the $^{13}$C NMR (CDCl$_3$, 100.6 MHz) (Fig-4.10) the newly formed amide carbon appeared at $\delta$ 164.6 (O=C-NH), other carbons appeared at 161.3 (C-4'), 161.0 (C-7), 160.4 (2-C=O), 154.9 (C-8a), 153.7 (C-4), 131.6 (C-1'), 131.5 (C-2' & C-6'), 126.9 (C-5), 115.6 (C-3' & C-5'), 114.4 (C-3), 112.8 (C-4a), 111.9 (C-6), 102.0 (C-8), 91.7 (1'-CH$_2$), 76.7 (7-OCH$_2$), 66.8 (4-CH$_3$).

The DIPMS of 51 (Fig-4.11) showed the quasi-molecular ion peak at m/z 358 (M+1).

The biological screening for endocrine, cardiovascular, oncology, neuroscience and tuberculosis, antibacterial and antifungal activity of N-(benzyloxy)-2-(coumarin-4-yloxy)-acetamides (39-44), N-(benzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamides (45-50), N-(benzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamides (51-56) with OIDD-Eli Lilly initiative are described in Chapter-VI.
Experimental Section:

1) Synthesis of substituted hydroxy coumarins (16-18) and 2) O-alkylated substituted hydroxy coumarins (19-21) were described in Chapter III.

3) Synthesis of coumarin-4,6,7-yloxy acetic acids (22-24):

i) Synthesis of 2-(coumarin-4-yloxy)-acetic acid (22):

A solution of ethyl-2-(coumarin-4-yloxy) acetate (19) (5g, 20.1 mmol) and 5% NaOH (5 mL) in ethanol (25 mL) was stirred under reflux temperature for 2 h. After removal of the solvent the residue was dissolved in water and acidified with HCl (6M). The white solid (22) collected by filtration washed with cool water, dried and crystalised from ethanol.

Yield= 3g, m.p. 185-186 °C (Lit.20 187-188 °C)

$^1$H NMR (CDCl$_3$, 400 MHz): δ 4.82 (s, 4-OCH$_2$), 5.79 (s, H-3), 7.38-7.43 (m, H-6 & H-8), 7.64-7.68 (m, H-7), 7.88-7.92 (m, H-5).

IR (KBr): 1725 (CO lactone), 3200-2500 (-COOH) cm$^{-1}$.

ii) 2-(4-Methyl-coumarin-6-yloxy)-acetic acid (23):

m.p. 192-193 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.37 (s, 3H), 4.48 (s, 6-OCH$_2$), 5.92 (s, H-3), 7.07 (dd, J=8.3Hz, J=2.2Hz, H-7), 7.21 (dd, J=8.3Hz, J=4.2Hz, H-8), 7.51 (dd, J=4.2Hz, J=2.2Hz, H-5).

IR (KBr): 1730 (-CO lactone), 3200-2500 (-COOH) cm$^{-1}$.
iii) 2-(4-Methyl-coumarin-7-ylxy)-acetic acid²⁰ (24):

```
\[O
\begin{array}{c}
\text{HO} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]
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m.p. 205-206 °C (Lit²⁰ 207-208 °C)

¹H NMR (CDCl₃, 400 MHz): δ 2.39 (s, 4-CH₃), 4.82 (s, 7-OCH₂), 6.22 (s, H-3), 6.97-7.02 (m, H-6 & H-8), 7.69 (d, J=8.5Hz, H-5).

¹³C NMR (CDCl₃, 100.6 MHz): δ 169.6 (O=C-OH), 160.8 (C-7), 160.2 (2-C=O), 154.5 (C-8a), 153.3 (C-4), 126.5 (C-5), 113.5 (C-3), 112.2 (C-4a), 111.3 (C-6), 101.5 (C-8), 64.9 (7-OCH₂), 18.1 (4-CH₃).

IR (KBr): 1735 (-CO lactone), 3200-2500 (-COOH) cm⁻¹.

4) Synthesis of O-(substituted benzyl)-hydroxylamines²¹ (33-38):

i) Synthesis of O-(4-fluorobenzyl)-hydroxylamine (33):

```
\begin{array}{c}
\text{NH}_2 \\
\text{O} \\
\text{F} \\
\end{array}
```

To N-Hydroxy phthalimide (25) (3g, 18.3 mmol) dissolved in DMF (30 mL) was added K₂CO₃ (5.07g, 36.7 mmol) and stirred for 10-15 min at RT. 4-Fluorobenzylchloride (26) (3.19g, 22.1 mmol) added and stirred for 2 h at RT. After completion of the reaction by TLC reference reaction mixture was poured on ice water, solid filtered and taken into 60 mL of ethanol. Hydrazine hydrate (3 mL) was added, refluxed for 1 h. Precipitated solid was filtered and washed with 30 mL of ethanol. Filterate concentrated, taken into 100 mL of ethylacetate, washed with (2x60) mL of H₂O. Organic layer dried over Na₂SO₄, concentrated to give the oxyamine (33) (liquid). Yield = 2.1g

¹H NMR (CDCl₃, 400 MHz): δ 4.6 (s, -OCH₂), 5.4 (bs, -NH₂), 7.1-7.14 (m, H-3 & H-5), 7.3-7.33 (m, H-2 & H-6).
ii) O-(2-fluorobenzyl)-hydroxylamine (34):

\[
\begin{align*}
\text{NH}_2 \\
\text{O} \\
\text{F}
\end{align*}
\]

\(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 4.6 (s, -OCH\(_2\)), 5.4 (bs, -NH\(_2\)), 6.95-7.09 (m, H-5 & H-6), 7.36-7.39 (m, H-3 & H-4).

iii) O-(4-chlorobenzyl)-hydroxylamine (35):

\[
\begin{align*}
\text{NH}_2 \\
\text{O} \\
\text{Cl}
\end{align*}
\]

\(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 4.79 (s, -OCH\(_2\)), 5.4 (bs, -NH\(_2\)), 7.3 (d, J=8Hz, H-3 & H-5), 7.42 (d, J=7.5Hz, H-2 & H-6).

iv) O-(2,4-dichlorobenzyl)-hydroxylamine (36):

\[
\begin{align*}
\text{NH}_2 \\
\text{O} \\
\text{Cl} \\
\text{Cl}
\end{align*}
\]

\(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 4.79 (s, -OCH\(_2\)), 5.4 (bs, -NH\(_2\)), 7.18 (dd, J=8.1Hz, J=1.6Hz H-6), 7.2 (dd, J=5.4Hz, J=1.6Hz, H-5), 7.53 (s, H-3).
v) O-(4-bromobenzyl)-hydroxylamine (37):

\[
\begin{align*}
\text{NH}_2 \\
\text{O} \\
\text{Br}
\end{align*}
\]

\(^1\text{H} \text{NMR (CDCl}_3, 400 \text{ MHz}): \delta \ 4.72 \ (s, -\text{OCH}_2), 5.1 \ (bs, -\text{NH}_2), 7.31 \ (d, J=8.2Hz, H-3 \ & H-5), 7.4 \ (d, J=8.2Hz, H-2 \ & H-6).

vi) O-(2-cyanobenzyl)-hydroxylamine (38):

\[
\begin{align*}
\text{NH}_2 \\
\text{O} \\
\text{CN}
\end{align*}
\]

\(^1\text{H} \text{NMR (CDCl}_3, 400 \text{ MHz}): \delta \ 4.56 \ (s, -\text{OCH}_2), 5.2 \ (bs, -\text{NH}_2), 6.85-7.19 \ (m, H-5 \ & H-6), 7.26-7.39 \ (m, H-3 \ & H-4).

5a) Synthesis of N-benzyloxy-2-(coumarin-4-yloxy)-acetamides (39-44):

i) Synthesis of N-(4-fluorobenzyl)oxy)-2-(coumarin-4-yloxy)-acetamide (39):
To a stirred solution of 2-(coumarin-4-yloxy)-acetic acid (22) (150mg, 0.68 mmol) in chloroform (15 mL) was added catalytic amount of DMF. Thionyl chloride (1.5 mL) was added dropwise and stirred for 2 h at reflux temperature. Solvents were removed under vacuum, acid chloride was dissolved in CHCl₃ (15 mL) and kept aside under N₂ atmosphere. O-(4-fluorobenzyl)-hydroxylamine (33) (114mg, 0.81 mmol) was dissolved in chloroform (15 mL). To this catalytic amount of pyridine was added. Acid chloride dissolved in chloroform was added dropwise to the oxyamine at RT and stirring continued for 1 h. After completion of the reaction by TLC reference, water (30 mL) was added and layers separated. Organic layer was washed with 1N HCl (30 mL), 10% NaHCO₃ (30 mL), brine solution (30 mL), dried over Na₂SO₄ and concentrated to yield the crude oxyamide. Crude oxyamide (39) was taken into 15mL of diethylether, stirred for 30 min. Filtered the solid to get pure compound as light brown solid (39).

Yield = 120mg, m.p. 163-165 °C

¹H NMR (CDCl₃, 400 MHz): δ 4.79 (s, 4-OCH₂), 4.85 (s, 1'-OCH₂), 5.86 (s, H-3), 7.19-7.24 (m, H-3' & H-5), 7.38-7.5 (m, H-2', H-3' & H-6, H-8), 7.67-7.71 (m, H-7), 7.96 (d, J=9.2Hz, H-5), 11.59 (s, C=ONH).

¹³C NMR (DMSO-d₆, 100.6 MHz) : δ 66.8 (4-OCH₂), 76.7 (1'-OCH₂), 91.7 (C-3), 115.3 (C-8), 115.3 (C-4a), 115.7 (C-5), 116.8 (C-6), 123.9 (C-2' & C-6'), 124.8 (C-4'), 131.7 (C-7), 132.3 (C-3' & C-5'), 133.3 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 164.7 (C-4), 163.5 (O=C-NH).

DIPMS: m/z at 344 (M+1).

IR (KBr): 1186 (C-O-C), 1672 (-CONH), 1724 (-C=O), 3179 (-CONH) cm⁻¹.

Employing the similar procedure as mentioned for 39, compounds 40-44 were obtained from 22 as solids.
ii) N-(2-Fluorobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (40):

Brown solid, m.p. 140-142 °C

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 4.65 (s, 4-OCH$_2$), 5.15 (s, 1'-OCH$_2$), 5.64 (s, H-3), 7.04-7.34 (m, H-5', H-6 & H-6'), 7.37-7.51 (m, H-8 & H-3'), 7.68-7.71 (m, H-4' & H-7), 7.78-7.81 (m, H-5), 11.59 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): $\delta$ 66.8 (4-OCH$_2$), 76.7 (1'-OCH$_2$), 91.7 (C-3), 115.9 (C-3'), 116.8 (C-4a), 122.8 (C-8), 123.0 (C-5), 123.9 (C-5'), 124.6 (C-6), 124.9 (C-1'), 131.5 (C-7), 132.5 (C-6'), 133.3 (C-4'), 133.3 (C-8a), 153.1 (C-2'), 161.8 (2-C=O), 163.6 (O=C-NH), 164.7 (C-4).

DIPMS: m/z at 344 (M+1).

IR (KBr): 1027 (C-O-C), 1621 (-CONH), 1712 (-C=O), 3087 (-CONH) cm$^{-1}$.

iii) N-(4-Chlorobenzyloxy)-2-(coumarin-4-yloxy)-acetamide (41):
Off-white solid, m.p. 218-220 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 4.79 (s, 4-OCH$_2$), 4.86 (s, 1'-OCH$_2$), 5.86 (s, H-3), 7.38-7.42 (m, H-2', H-6' & H-3'), 7.43-7.46 (m, H-5' & H-6, H-8), 7.67-7.69 (m, H-7), 7.96 (d, J=7.6Hz, H-5), 11.59 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 66.8 (4-OCH$_2$), 76.6 (1'-OCH$_2$), 91.8 (C-3), 115.3 (C-8), 116.8 (C-4a), 123.9 (C-5), 124.6 (C-6), 128.8 (C-7), 131.2 (C-3' & C-5'), 133.4 (C-2' & C-6'), 133.5 (C-4'), 135.1 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 163.5 (O=C-NH), 164.7 (C-4).

DIPMS: m/z at 360 (M+1), 362 (M+1+2)

IR (KBr): 1077 (C-O-C), 1669 (CONH), 1728 (C=O), 3176 (CONH) cm$^{-1}$.

iv) N-(2,4-Dichlorobenzoyloxy)-2-(coumarin-4-yloxy)-acetamide (42):

White solid, m.p. 167-169 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 4.78 (s, 4-OCH$_2$), 4.97 (s, 1'-OCH$_2$), 5.85 (s, H-3), 7.37-7.47 (m, H-5', H-6' & H-8), 7.58-7.7 (m, H-3' & H-6, H-7), 7.93 (d, J=7.2Hz, H-5), 11.59 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 66.7 (4-OCH$_2$), 73.7 (1'-OCH$_2$), 91.7 (C-3), 115.3 (C-8), 116.8 (C-4a), 123.8 (C-5), 124.6 (C-6), 127.8 (C-5'), 129.3 (C-7), 132.8 (C-6'), 133.2 (C-3'), 133.3 (C-2'), 134.4 (C-4'), 134.8 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 163.7 (O=C-NH), 164.7 (C-4).

DIPMS: m/z at 394 (M+1), 396 (M+1+2).

IR (KBr): 1029 (C-O-C), 1669 (-CONH), 1714 (-C=O), 3086 (-CONH) cm$^{-1}$. 
v) N-(4-Bromobenzylxylo)-2-(coumarin-4-yloxy)-acetamide (43):

Light orange solid, m.p. 228-230 °C

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 4.78 (s, 4-OCH$_2$), 4.84 (s, 1'-OCH$_2$), 5.86 (s, H-3), 7.38-7.43 (m, H-2', H-6' & H-6, H-8), 7.58-7.6 (m, H-3' & H-7, H-5'), 7.95 (d, J=7.2Hz, H-5), 11.59 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): $\delta$ 66.8 (4-OCH$_2$), 76.7 (1'-OCH$_2$), 91.8 (C-3), 115.3 (C-8), 116.8 (C-4a), 122.1 (C-4'), 123.9 (C-5), 124.6 (C-6), 131.5 (C-7), 131.7 (C-2' & C-6'), 133.4 (C-3' & C-5'), 135.5 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 163.5 (O=C-NH), 164.7 (C-4).

DIPMS: m/z at 404 (M+1), 406 (M+1+2).

IR (KBr): 1072 (C-O-C), 1628 (-CONH), 1728 (-C=O), 3175 (-CONH) cm$^{-1}$.

vi) N-(2-Cyanobenzylxylo)-2-(coumarin-4-yloxy)-acetamide (44):
Off white solid, m.p. 150-151 °C

\(^1\)H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 4.77 (s, 4-OCH\textsubscript{2}), 5.05 (s, 1'-OCH\textsubscript{2}), 5.83 (s, H-3), 7.37-7.41 (m, H-6' & H-8), 7.6-7.69 (m, H-4', H-5' & H-7, H-6), 7.8-7.85 (m, H-3' & H-5), 11.59 (s, O=C-NH).

\(^{13}\)C NMR (DMSO-d\textsubscript{6}, 100.6 MHz): \(\delta\) 66.8 (4-OCH\textsubscript{2}), 76.7 (1'-OCH\textsubscript{2}), 91.7 (C-3), 112.5 (C-2'), 115.3 (-CN), 116.9 (C-8), 117.7 (C-4a), 123.9 (C-5), 124.6 (C-6), 129.9 (C-6'), 131.3 (C-7), 133.5 (C-4'), 133.6 (C-3'), 133.7 (C-5'), 139.1 (C-1'), 153.1 (C-8a), 161.8 (2-C=O), 163.8 (O=C-NH), 164.7 (C-4).

DIPMS: m/z at 351 (M+1).

IR (KBr): 1022 (C-O-C), 1622 (-CONH), 1714 (-C=O), 2232 (-CN), 3093 (-CONH) cm\(^{-1}\).

5b) Synthesis of N-benzyloxy-2-(4-methyl-coumarin-6-yloxy)-acetamides (45-50):

i) Synthesis of N-(4-fluorobenzyloxy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (45):

To a stirred solution of 2-(4-methyl-coumarin-6-yloxy)-acetic acid (23) (150mg, 0.6 mmol) in chloroform (15 mL) was added catalytic amount of DMF. Thionyl chloride (1.5 mL) was added dropwise and stirred for 2 h at reflux temperature. Solvents were removed under vaccum, acid chloride was dissolved in CHCl\textsubscript{3} (15 mL) and kept aside under N\textsubscript{2} atmosphere. O-(4-fluorobenzyl)-hydroxylamine (33) (107mg, 0.7 mmol) was dissolved in chloroform (15 mL). To this catalytic amount of pyridine was added. Acid chloride dissolved in chloroform was added dropwise to the oxyamine at RT and continued for 1 h. After completion of the reaction by TLC reference, water (30 mL) was added and layers separated. Organic layer was washed with 1N HCl (30 mL), 10% NaHCO\textsubscript{3} (30 mL), brine solution (30 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. Crude oxyamide (45) was taken into 15 mL of diethylether, stirred for 30 min and filtered.
White solid, yield = 150mg; m.p 120-121 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.39 (s, 4-CH$_3$), 4.61 (s, 6-OCH$_2$), 4.95 (s, 1'-OCH$_2$), 6.3 (s, H-3), 7.01-7.06 (m, H-3' & H-5', H-5 & H-7), 7.24 (d, J=9.2Hz, H-2'), 7.37-7.41 (m, H-6' & H-8), 9.15 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 18.5 (4-CH$_3$), 66.8 (6-OCH$_2$), 76.6 (1'-OCH$_2$), 109.9 (C-5), 115.4 (C-3), 115.6 (C-7), 117.9 (C-3' & C-5'), 120.0 (C-4a), 120.5 (C-8), 131.5 (C-2' & C-6'), 132.4 (C-1'), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 161.3 (C-4'), 164.9 (O=C-NH).

DIPMS: m/z at 358.4 (M+1).

IR (KBr): 1052 (C-O-C), 1571 (CONH), 1675 (C=O), 3271 (CONH) cm$^{-1}$.

Employing the similar procedure as mentioned for 45, compounds 46-50 were obtained.

ii) N-(2-fluorobenzylxoy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (46):

![Chemical Structure]

White solid, m.p 150-151 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.41 (s, 4-CH$_3$), 4.62 (s, 6-OCH$_2$), 5.07 (s, 1'-OCH$_2$), 6.31 (s, H-3), 7.02-7.14 (m, H-5' & H-6', H-5 & H-7), 7.26 (d, J=8.8Hz, H-3'), 7.34-7.37 (m, H-4'), 7.43 (dd, J=1.6Hz, J=1.6Hz, H-8), 9.15 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 18.0 (4-CH$_3$), 66.7 (6-OCH$_2$), 70.9 (1'-OCH$_2$), 109.9 (C-5), 115.2 (C-3), 115.8 (C-7), 117.8 (C-3'), 117.9 (C-4a), 120.0 (C-5'), 120.5 (C-8), 124.8 (C-1'), 131.2 (C-6'), 131.3 (C-4'), 132.3 (C-8a), 148.1 (C-4), 153.3 (C-6), 154.4 (C-2'), 160.2 (2-C=O'), 165.0 (O=C-NH).

DIPMS: m/z at 358.3 (M+1).

IR (KBr): 1062 (C-O-C), 1682 (-CONH), 1715 (-C=O), 3314 (-CONH) cm$^{-1}$. 
iii) N-(4-chlorobenzylxylo)-2-(4-methyl-coumarin-6-yloxy)-acetamide (47):

White solid, m.p. 115-117 °C

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.39 (s, 4-CH$_3$), 4.61 (s, 6-OCH$_2$), 4.95 (s, 1'-OCH$_2$), 6.3 (s, H-3), 6.99-7.01 (m, H-5 & H-7), 7.24 (d, J=9.2Hz, H-2'), 7.37-7.45 (m, H-5', H-3' & H-6' & H-8), 9.07 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): $\delta$ 18.5 (4-CH$_3$), 66.8 (6-OCH$_2$), 76.6 (1'-OCH$_2$), 109.92 (C-5), 115.4 (C-3), 115.6 (C-7), 117.9 (C-3' & C-5'), 120.0 (C-4a), 120.5 (C-8), 131.5 (C-2' & C-6'), 132.4 (C-1'), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 161.3 (C-4'), 164.9 (O=C-NH).

DIPMS: m/z at 374.3 (M+1), 376.3 (M+1+2)

IR (KBr): 1088 (C-O-C), 1678 (-CONH), 1712 (-C=O), 3323 (-CONH) cm$^{-1}$

iv) N-(2,4-dichlorobenzylxylo)-2-(4-methyl-coumarin-6-yloxy)-acetamide (48):
White solid, m.p. 150-151 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.4 (s, 4-CH$_3$), 4.62 (s, 6-OCH$_2$), 5.09 (s, 1’-OCH$_2$), 6.32 (s, H-3), 7.02 (s, H-5), 7.07 (d, J=8.8Hz, H-7), 7.25-7.29 (m, H-5’ & H-6’), 7.47-7.45 (m, H-3’ & H-8), 9.12 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 18.5 (4-CH$_3$), 66.8 (6-OCH$_2$), 76.6 (1’-OCH$_2$), 109.9 (C-5), 115.2 (C-3), 117.9 (C-7), 120.0 (C-4a), 120.5 (C-8), 127.8 (C-5’), 129.2 (C-6’), 132.8 (C-3’), 132.9 (C-2’), 134.2 (C-4’), 134.5 (C-1’), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 165.1 (O=C-NH).

DIPMS: m/z at 408.3 (M+1), 410.3 (M+1+2)

IR (KBr): 1058 (C=O-C), 1692 (-CONH), 1730 (-C=O), 3313 (-CONH) cm$^{-1}$.

v) N-(4-Bromobenzylxylo)-2-(4-methyl-coumarin-6-yloxy)-acetamide (49):

Orange solid, m.p. 155-156 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.4 (s, 4-CH$_3$), 4.61 (s, 6-OCH$_2$), 4.93 (s, 1’-OCH$_2$), 6.32 (s, H-3), 7.01-7.06 (m, H-5 & H-7), 7.26-7.29 (m, H-8, H-2’ & H-6’), 7.47-7.5 (d, J=8.4Hz, H-5’ & H-3’), 9.01 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 18.6 (4-CH$_3$), 66.8 (6-OCH$_2$), 76.6 (1’-OCH$_2$), 109.9 (C-5), 115.2 (C-3), 117.9 (C-7), 120.0 (C-4a), 120.5 (C-8), 122.0 (C-8), 131.3 (C-2’ & C-6’), 131.6 (C-3’ & C-5’), 135.6 (C-1’), 148.1 (C-8a), 153.2 (C-4), 154.3 (C-6), 160.2 (2-C=O), 165.0 (O=C-NH).

DIPMS: m/z at 419.2 (M+1), 421.2 (M+2)

IR (KBr): 1065 (C-O-C), 1680 (-CONH), 1715 (-C=O), 3329 (-CONH) cm$^{-1}$.
vi) N-(2-cyanobenzylxoy)-2-(4-methyl-coumarin-6-yloxy)-acetamide (50):

White solid, m.p. 181-182 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.41 (s, 4-CH$_3$), 4.64 (s, 6-OCH$_2$), 5.19 (s, 1'-OCH$_2$), 6.3 (s, H-3), 7.06-7.12 (m, H-5 & H-7), 7.26 (d, J=9.2Hz, H-3'), 7.34-7.38 (m, H-6'), 7.64-7.7 (m, H-8, H-4' & H-5'), 9.43 (s, O=C-NH).
$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 18.7 (4-CH$_3$), 66.7 (6-OCH$_2$), 74.8 (1'-OCH$_2$), 109.9 (C-5), 112.2 (C-2'), 115.2 (C-3), 117.7 (C-7), 117.9 (-CN), 119.9 (C-4a), 120.5 (C-8), 129.8 (C-6'), 131.2 (C-4'), 133.7 (C-3'), 133.8 (C-5'), 139.3 (C-1'), 148.1 (C-8a), 153.3 (C-4), 154.3 (C-6), 160.2 (2-C=O), 165.2 (O=C-NH).

DIPMS: m/z at 365.4 (M+1).

IR (KBr): 1064 (C-O-C), 1681 (-CONH), 1709 (-C=O), 2225 (CN), 3273 (-CONH) cm$^{-1}$.

5c) Synthesis of N-benzyloxy-2-(4-methyl-coumarin-7-yloxy)-acetamides (51-56):
i) N-(4-fluorobenzylxoy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (51):

To a stirred solution of 2-(4-methyl-coumarin-7-yloxy)-aceticacid (24) (150mg, 0.64mmol) in chloroform (15 mL) was added catalytic amount of DMF. Thionyl chloride (1.5 mL) was added dropwise and stirred for 2 h at reflux temperature. Solvents were
removed under vaccum, acidchloride was dissolved in CHCl$_3$ (15 mL) and kept aside under N$_2$ atmosphere. O-(4-fluorobenzyl)-hydroxylamine (33) (107mg, 0.76 mmol) was dissolved in chloroform (15 mL). To this catalytic amount of pyridine was added. Acid chloride dissolved in chloroform was added dropwise to the oxyamine at RT and continued for 1 h. After completion of the reaction by TLC reference, water (30 mL) was added and layers separated. Organic layer was washed with 1N HCl (30 mL), 10% NaHCO$_3$ (30 mL), brine solution (30 mL), dried over Na$_2$SO$_4$ and concentrated to yield the crude oxyamide (51).

Crude oxyamide (51) was taken into 15 mL of diethylether, stirred for 30 min and filtered orange solid, yield = 165mg, m.p.156-158 °C

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.4 (s, 4-CH$_3$), 4.62 (s, 7-OCH$_2$), 4.95 (s, 1'-OCH$_2$), 6.17 (s, H-3), 6.81 (s, H-8), 6.83 (d, J=2.4Hz, H-6), 7.01-7.05 (m, H-3' & H-5'), 7.37-7.4 (m, H-2' & H-6'), 7.51 (d, J=8.8Hz, H-5), 9.13 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz) : $\delta$ 18.5 (4-CH$_3$), 66.3 (7-OCH$_2$), 76.6 (1'-OCH$_2$), 102.1 (C-8), 112.8 (C-6), 114.1 (C-4a), 115.6 (C-3), 126.9 (C-3' & C-5'), 131.5 (C-5), 131.6 (C-2' & C-6'), 132.4 (C-1'), 153.7 (C-4), 154.9 (C-8a), 160.4 (2-C=O), 161.1 (C-7), 161.3 (C-4'), 164.6 (O=C-NH).

DIPMS: m/z at 358 (M+1).

IR (KBr): 1077 (C-O-C), 1679 (-CONH), 1716 (-C=O), 3320 (-CONH) cm$^{-1}$.

Employing the similar procedure as mentioned for 51, compounds 52-56 were obtained.

ii) N-(2-fluorobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (52):

Orange solid, m.p. 162-163 °C

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.4 (s, 4-CH$_3$), 4.62 (s, 7-OCH$_2$), 5.07 (s, 1'-OCH$_2$), 6.17 (s, H-3), 6.81 (s, H-8), 7.26 (dd, J=2.8Hz, J=2.8Hz, H-6), 7.06-7.08 (m, H-5'), 7.14 (d, J=7.2Hz, H-6'), 7.34 (d, J=6.8Hz, H-3'), 7.42-7.46 (m, H-4'), 7.52 (d, J=8.8Hz, H-5), 9.24 (s, O=C-NH).
$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 18.5 (4-CH$_3$), 66.2 (7-OCH$_2$), 70.9 (1'-OCH$_2$), 101.9 (C-8), 111.9 (C-6), 112.8 (C-4a), 114.1 (C-3), 115.9 (C-3'), 122.9 (C-5'), 123.0 (C-5), 124.8 (C-1'), 126.9 (C-6'), 131.3 (C-4'), 132.4 (C-4), 153.7 (C-8a), 154.9 (C-2'), 161.0 (2C=O), 162.5 (C-7), 164.7 (O=C-NH).

DIPMS: m/z at 358 (M+1).

IR (KBr): 1079 (C-O-C), 1681 (-CONH), 1715 (-C=O), 3323 (-CONH) cm$^{-1}$

iii) N-(4-chlorobenzylxoxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (53):

![Chemical Structure](image)

Orange solid, m.p. 156-157 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.41 (s, 4-CH$_3$), 4.62 (s, 7-OCH$_2$), 4.95 (s, 1'-OCH$_2$), 6.17 (s, H-3), 6.8-6.83 (m, H-6 & H-8), 7.3-7.35 (m, H-2' & H-6', H-3' & H-5'), 7.51 (d, J=8.8Hz, H-5), 9.12 (s, O=C-NH).

$^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 18.6 (4-CH$_3$), 66.2 (7-OCH$_2$), 76.5 (1'-OCH$_2$), 101.9 (C-8), 111.9 (C-6), 114.1 (C-4a), 126.9 (C-3), 128.9 (C-5), 129.0 (C-3' & C-5'), 131.1 (C-2' & C-6'), 133.4 (C-4'), 135.2 (C-1'), 153.7 (C-4), 154.9 (C-8a), 160.5 (2-C=O), 161.0 (C-7), 164.6 (O=C-NH).

DIPMS: m/z at 374 (M+1), 376 (M+2).

IR (KBr): 1080 (C-O-C), 1684 (-CONH), 1716 (-C=O), 3322 (-CONH) cm$^{-1}$.

iv) N-(2,4-dichlorobenzylxoxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (54):

![Chemical Structure](image)

Orange solid, yield = 75%; m.p. 190-191 °C
\( ^1H \) NMR (CDCl\(_3\), 400 MHz): \( \delta \) 2.42 (s, 4-CH\(_3\)), 4.58 (s, 7-OCH\(_2\)), 5.04 (s, 1'-OCH\(_2\)), 6.15 (s, H-3), 6.85 (s, H-8), 6.9 (d, \( J=8.4Hz \), H-6), 7.25 (d, \( J=6.4Hz \), H-5'), 7.38 (d, \( J=8.8Hz \), H-6'), 7.48 (d, \( J=8Hz \), H-5), 7.55 (s, H-3'), 11.07 (s, O=C-NH).

\( ^{13}C \) NMR ((DMSO-d\(_6\), 100.6 MHz): \( \delta \) 14.4 (4-CH\(_3\)), 66.2 (7-OCH\(_2\)), 73.7 (1'-OCH\(_2\)), 101.9 (C-8), 111.9 (C-6), 112.8 (C-4a), 114.1 (C-3), 126.9 (C-5), 127.8 (C-5'), 129.2 (C-6'), 132.9 (C-3'), 133.0 (C-2'), 134.3 (C-4'), 134.6 (C-1'), 153.7 (C-4), 154.9 (C-8a), 160.4 (2-C=O), 161.0 (C-7), 164.8 (O=C-NH).

DIPMS: m/z at 408 (M+1), 410 (M+1+2)

IR (KBr): 1080 (C=O-C), 1683 (-CONH), 1718 (-C=O), 3317 (-CONH) cm\(^{-1}\)

v) N-(4-bromobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (55):

Orange solid, m.p. 176-177 °C

\( ^1H \) NMR (CDCl\(_3\), 400 MHz): \( \delta \) 2.41 (s, 4-CH\(_3\)), 4.62 (s, 7-OCH\(_2\)), 4.93 (s, 1'-OCH\(_2\)), 6.17 (s, H-3), 6.81-6.83 (m, H-6 & H-8a), 7.27 (d, \( J=6.8Hz \), H-2'), 7.45-7.51 (m, H-5 & H-5', H-3' & H-6'), 9.22 (s, O=C-NH).

\( ^{13}C \) NMR (DMSO-d\(_6\), 100.6 MHz): \( \delta \) 18.5 (4-CH\(_3\)), 66.2 (7-OCH\(_2\)), 76.6 (1'-OCH\(_2\)), 102.0 (C-8), 111.9 (C-6), 112.8 (C-4a), 114.1 (C-3), 122.0 (C-4'), 126.9 (C-5), 131.4 (C-2' & C-6'), 133.8 (C-3' & C-5'), 135.6 (C-1'), 153.7 (C-4), 154.9 (C-8a), 160.5 (2-C=O), 161.0 (C-7), 164.6 (O=C-NH).

DIPMS: m/z at 418 (M+1), 420 (M+1+2).

IR (KBr): 1073 (C=O-C), 1684 (-CONH), 1717 (-C=O), 3325 (-CONH) cm\(^{-1}\)
vi) N-(2-cyanobenzyloxy)-2-(4-methyl-coumarin-7-yloxy)-acetamide (56):

Orange solid, m.p. 162-163 °C

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.41 (s, 4-CH$_3$), 4.6 (s, 7-OCH$_2$), 5.15 (s, 1'-OCH$_2$), 6.16 (s, H-3), 6.84 (s, H-8), 6.91 (dd, J=2.4Hz, J=2.4Hz, H-6), 7.48-7.51 (m, H-3'), 7.53 (d, J=8.8Hz, H-5), 7.62-7.72 (m, H-4', H-5' & H-6'), 10.96 (s, O=C-NH).

$^{13}$C NMR (DMSO-d$_6$, 100.6 MHz): δ 18.6 (4-CH$_3$), 66.2 (7-OCH$_2$), 74.9 (1'-OCH$_2$), 101.9 (C-8), 111.9 (C-6), 112.8 (C-2'), 114.1 (C-4a), 117.7 (C-3), 126.9 (-CN), 129.8 (C-5), 131.1 (C-6'), 133.4 (C-4'), 133.7 (C-3'), 133.8 (C-5'), 139.2 (C-1'), 153.7 (C-4), 154.1 (C-8a), 160.5 (2-C=O), 161.0 (C-7'), 164.8 (O=C-NH).

DIPMS: m/z at 365 (M+1).

IR (KBr): 1080 (C-O-C), 1684 (-CONH), 1714 (-C=O), 2226 (-CN), 3310 (-CONH) cm$^{-1}$. 
References:


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