Ruthenium(II)-catalyzed remote C-H addition of 8 aminoquinoline amide to activated aldehyde

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Table of Contents

<table>
<thead>
<tr>
<th>Content</th>
<th>Page no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General Information……………………..</td>
<td>S2</td>
</tr>
<tr>
<td>2. Typical experimental procedure for the compound 3a……</td>
<td>S2</td>
</tr>
<tr>
<td>3. Characterization data for the synthesized compounds (3a-3s and 5a, 5b) ….</td>
<td>S3-S13</td>
</tr>
<tr>
<td>4. References……………….</td>
<td>S13</td>
</tr>
<tr>
<td>5. Structure Determination (X-ray crystallographic data for 3d):</td>
<td>S13-S14</td>
</tr>
<tr>
<td>6. NMR spectra for the synthesized products………………………..</td>
<td>S15-S57</td>
</tr>
</tbody>
</table>
1. General Information:

All reagents were purchased from commercial sources and used without further purification. $^1$H NMR spectra were determined on 400 MHz spectrometer as solutions in CDCl$_3$. Chemical shifts were expressed in parts per million ($\delta$) and the signals were reported as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), and coupling constants ($J$) were given in Hz. $^{13}$C{$^1$H} NMR spectra were recorded at 100 MHz in CDCl$_3$ solution. Chemical shifts as internal standard were referenced to CDCl$_3$ ($\delta =$ 7.26 for $^1$H and $\delta =$ 77.16 for $^{13}$C{$^1$H} NMR) as internal standard. TLC was done on silica gel coated glass slide. All solvents were dried and distilled before use. Commercially available solvents were freshly distilled before the reaction. All reactions involving moisture sensitive reactants were executed using oven dried glassware. All the 8-aminoquinoline amides were prepared by the reported method.[1]

2. Typical experimental procedure for the compound ethyl 2-(8-benzamidoquinolin-5-yl)-2-hydroxyacetate (3a):

$N$-(Quinolin-8-yl)benzamide (1a) (0.2 mmol, 49.6 mg), ethyl glyoxalate solution (2a) (2 equiv., 40.8 mg), [Ru($p$-Cy)Cl$_2$)$_2$ (5 mol%, 3.06 mg), AgSbF$_6$ (10 mol%, 6.86 mg), and NaOAc (2 equiv., 32.8 mg) was taken in a reaction tube with cap. Then 1,2-DCE (2 mL) was added to it and stirred at 100°C for 8 h. After completion of the reaction (TLC), the reaction mixture was quenched with water (2 mL). The reaction mixture was then extracted with ethyl acetate. The organic phase was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to get the crude residue which was purified by column chromatography on silica gel (60-120 mesh) using petroleum ether:ethyl acetate = 4:1 as an eluent to afford the pure product (3a) (51.8 mg, 74%) as a light yellow gummy mass.
3. Characterization data for the synthesized compounds (3a-3s and 5a, 5b):

**Ethyl 2-(8-benzamidoquinolin-5-yl)-2-hydroxyacetate (3a):** Light yellow gummy mass (74%, 51.8 mg); 
R<sub>f</sub> = 0.45 (PE:EA = 80:20); ¹H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.82 (s, 1H), 8.89-8.85 (m, 2H), 8.57 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 8.08-8.06 (m, 2H), 7.60-7.50 (m, 5H), 5.68 (s, 1H), 4.28-4.17 (m, 2H), 3.67 (br s, 1H), 1.14 (t, J = 7.2 Hz, 3H); ¹³C {¹H} NMR (100 MHz, CDCl<sub>3</sub>): δ 173.9, 165.6, 148.2, 139.1, 135.1, 135.0, 133.1, 132.0, 128.9, 128.2, 127.6, 127.4, 126.2, 121.9, 115.7, 71.5, 62.6, 14.1; Anal. Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C, 68.56; H, 5.18; N, 8.00%; Found: C, 68.80; H, 5.11; N, 8.12%.

**Ethyl 2-hydroxy-2-(8-(3-methylbenzamido)quinolin-5-yl)acetate (3b):** Light yellow gummy mass (76%, 55.4 mg); 
R<sub>f</sub> = 0.55 (PE:EA = 75:25); ¹H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.77 (s, 1H), 8.88-8.85 (m, 2H), 8.56 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.87-7.84 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.52-7.49 (m, 1H), 7.44-7.38 (m, 2H), 5.68 (s, 1H), 4.29-4.12 (m, 2H), 3.69 (br s,1H), 2.47 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); ¹³C {¹H} NMR (100 MHz, CDCl<sub>3</sub>): δ 173.8, 165.9, 148.2, 139.1, 138.8, 135.4, 135.1, 132.8, 128.8, 128.2, 127.6, 126.2, 124.3, 121.9, 115.8, 71.5, 62.5, 21.6, 14.1; Anal. Calcd for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>: C, 69.22; H, 5.53; N, 7.69%; Found: C, 69.40; H, 5.58; N, 7.77%.
Ethyl 2-hydroxy-2-(8-(4-methylbenzamido)quinolin-5-yl)acetate (3c): White solid (82%, 59.7 mg); $R_f = 0.45$ (PE:EA = 80:20); M.p. 89-90 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.79 (s, 1H), 8.89-8.86 (m, 2H), 8.56 (dd, $J = 8.4$ Hz, 1.6 Hz, 1H), 7.98-7.96 (m, 2H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.53-7.50 (m, 1H), 7.34 (d, $J = 8.0$ Hz, 2H), 5.68 (s, 1H), 4.28-4.14 (m, 2H), 3.60 (br s, 1H), 2.45 (s, 3H), 1.14 (t, $J = 7.2$ Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$): δ 173.9, 165.6, 148.2, 142.6, 139.2, 135.5, 133.1, 132.3, 129.6, 128.0, 127.7, 127.4, 126.2, 121.9, 115.7, 71.5, 62.6, 21.6, 14.1; Anal. Calcd for C$_{21}$H$_{20}$N$_2$O$_4$: C, 69.22; H, 5.53; N, 7.69%; Found: C, 69.01; H, 5.61; N, 7.60%.

Ethyl 2-hydroxy-2-(8-(4-methoxybenzamido)quinolin-5-yl)acetate (3d): White solid (78%, 59.4 mg); $R_f = 0.50$ (PE:EA = 70:30); M.p. 85-86 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.70 (s, 1H), 8.83-8.78 (m, 2H), 8.55 (dd, $J = 8.8$ Hz, 1.2 Hz, 1H), 8.03-7.99 (m, 2H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.49-7.45 (m, 1H), 7.02-6.99 (m, 2H), 5.66 (s, 1H), 4.27-4.10 (m, 2H), 3.87 (s, 4H), 1.12 (t, $J = 7.2$ Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$): δ 173.7, 165.1, 162.6, 148.1, 139.0, 135.4, 133.2, 129.2, 128.0, 127.5, 127.2, 126.1, 121.8, 115.5, 114.1, 71.5, 62.4, 55.5, 14.0; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{21}$H$_{20}$N$_2$O$_5$: 381.1445; found: 381.1449.
Ethyl 2-(8-(4-fluorobenzamido)quinolin-5-yl)-2-hydroxyacetate (3e): White solid (68%, 50.0 mg); R_f = 0.55 (PE:EA = 75:25); M.p 102-103 °C; ¹H NMR (400 MHz, CDCl₃): δ 10.77 (s, 1H), 8.87-8.84 (m, 2H), 8.57 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.10-8.06 (m, 2H), 7.60 (d, J = 8.0 Hz, 1H), 7.54-7.51 (m, 1H), 7.24-7.20 (m, 2H), 5.64 (s, 1H), 4.26-4.16 (m, 2H), 3.64 (br s, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 173.9, 164.5, 148.2, 139.1, 134.2 (J_C,F = 200.0 Hz), 131.3 (J_C,F = 4.0 Hz), 129.89, 129.81, 128.3, 127.6, 126.2, 122.0, 116.1, 115.9, 115.8, 71.5, 62.6, 14.1; Anal. Calcd for C₂₀H₁₇FN₂O₄: C, 65.21; H, 4.65; N, 7.60%; Found: C, 65.05; H, 4.59; N, 7.51%.

Ethyl 2-(8-(3-chlorobenzamido)quinolin-5-yl)-2-hydroxyacetate (3f): White solid (72%, 55.3 mg); R_f = 0.55 (PE:EA = 80:20); M.p. 94-95 °C; ¹H NMR (400 MHz, CDCl₃): δ 10.76 (s, 1H), 8.87 (dd, J = 4.4 Hz, 1.6 Hz, 1H), 8.83 (d, J = 8.0 Hz, 1H), 8.57 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 8.04 (t, J = 2.0 Hz, 1H), 7.94-7.91 (m, 1H), 7.60-7.46 (m, 4H), 5.68 (d, J = 3.2 Hz, 1H), 4.27-4.14 (m, 2H), 3.70 (d, J = 4.0 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 173.8, 164.1, 148.3, 139.0, 136.8, 135.1, 135.0, 133.2, 132.1, 130.2, 128.6, 127.8, 127.5, 126.2, 125.4, 122.0, 115.9, 71.4, 62.6, 14.1; Anal. Calcd for C₂₀H₁₇ClN₂O₄: C, 62.42; H, 4.45; N, 7.28%; Found: C, 62.25; H, 4.55; N, 7.39%.
**Ethyl 2-(8-(4-chlorobenzamido)quinolin-5-yl)-2-hydroxyacetate (3g):** White solid (76%, 58.4 mg); $R_f = 0.50$ (PE:EA = 75:25); M.p. 131-132 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.77 (s, 1H), 8.86-8.82 (m, 2H), 8.57 (dd, $J = 8.8$ Hz, 1.6 Hz, 1H), 8.01-7.98 (m, 2H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.53-7.49 (m, 3H), 5.67 (d, $J = 3.6$ Hz, 1H), 4.27-4.14 (m, 2H), 3.69 (d, $J = 4.4$ Hz, 1H), 1.14 (t, $J = 7.2$ Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$): $\delta$ 173.8, 164.5, 148.2, 139.0, 138.3, 135.1, 133.4, 133.2, 129.2, 128.8, 128.5, 127.5, 126.2, 122.0, 115.8, 71.5, 62.6, 14.1; Anal. Calcd for C$_{20}$H$_{17}$ClN$_2$O$_4$: C, 62.42; H, 4.45; N, 7.28%; Found: C, 62.60; H, 4.49; N, 7.19%.

**Ethyl 2-(8-(2-bromobenzamido)quinolin-5-yl)-2-hydroxyacetate (3h):** Yellow gummy mass (65%, 55.8 mg); $R_f = 0.45$ (PE:EA = 80:20); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.86 (s, 1H), 8.93 (d, $J = 8.0$ Hz, 1H), 8.89 (dd, $J = 4.4$ Hz, 1.6 Hz, 1H), 8.64 (dd, $J = 8.8$ Hz, 1.6 Hz, 1H), 8.09-8.07 (m, 2H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.60-7.56 (m, 3H), 6.52 (s, 1H), 4.26-4.11 (m, 2H), 1.15 (t, $J = 7.2$ Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$): $\delta$ 170.4, 169.0, 165.7, 148.4, 139.0, 136.0, 135.0, 134.4, 133.3, 132.1, 129.2, 129.0, 127.4, 126.3, 124.1, 122.3, 115.8, 72.6, 62.1, 14.1; Anal. Calcd for C$_{20}$H$_{17}$BrN$_2$O$_4$: C, 55.96; H, 3.99; N, 6.53%; Found: C, 55.81; H, 3.93; N, 6.63%. 
**Ethyl 2-(8-(4-bromobenzamido)quinolin-5-yl)-2-hydroxyacetate (3i):** Yellow solid (70%, 60.1 mg); R$_f$ = 0.50 (PE:EA = 80:20); M.p. 134-135 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.79 (s, 1H), 8.87-8.84 (m, 2H), 8.57 (dd, $J = 8.8$ Hz, 1.6 Hz, 1H), 7.95-7.92 (m, 2H), 7.70-7.67 (m, 2H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.55-7.51 (m, 1H), 5.68 (d, $J = 3.6$ Hz, 1H), 4.30-4.13 (m, 2H), 3.60 (d, $J = 4.0$ Hz, 1H), 1.14 (t, $J = 7.2$ Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$): δ 173.8, 164.6, 148.3, 139.1, 135.1, 133.9, 133.2, 132.2, 129.0, 128.5, 127.6, 126.8, 126.2, 122.0, 115.9, 71.5, 62.6, 14.1; Anal. Calcd for C$_{20}$H$_{17}$BrN$_2$O$_4$: C, 55.96; H, 3.99; N, 6.53%; Found: C, 56.14; H, 4.06; N, 6.41%.

**Ethyl 2-hydroxy-2-(8-(4-iodobenzamido)quinolin-5-yl)acetate (3j):** White solid (72%, 68.7 mg); R$_f$ = 0.50 (PE:EA = 70:30); M.p. 155-156 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.77 (s, 1H), 8.85-8.81 (m, 2H), 8.56 (d, $J = 8.4$ Hz, 1H), 7.88 (dd, $J = 8.4$ Hz, 1.6 Hz, 2H), 7.77 (dd, $J = 8.4$ Hz, 2.0 Hz, 2H), 7.58 (dd, $J = 8.0$ Hz, 2.8 Hz, 1H), 7.53-7.49 (m, 1H), 5.67 (s, 1H), 4.27-4.12 (m, 2H), 3.70 (d, $J = 11.6$ Hz, 1H), 1.13 (t, $J = 7.2$ Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$): δ 173.8, 164.8, 148.2, 139.0, 138.1, 135.0, 134.4, 133.2, 128.9, 128.5, 127.5, 126.2, 122.0, 115.8, 99.2, 71.4, 62.5, 14.0; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{20}$H$_{17}$IN$_2$O$_4$: 477.0306; found: 477.0302.
Ethyl 2-hydroxy-2-(8-(3-(trifluoromethyl)benzamido)quinolin-5-yl)acetate (3k): White solid (61%, 51.0 mg); \( R_f = 0.55 \) (PE:EA = 80:20); M.p. 102-103 °C; \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 10.85 (s, 1H), 8.88-8.85 (m, 2H), 8.58 (dd, \( J = 8.8 \) Hz, 1.6 Hz, 1H), 8.33 (s, 1H), 8.23 (d, \( J = 7.6 \) Hz, 1H), 7.84 (d, \( J = 8.0 \) Hz, 1H), 7.69 (t, \( J = 8.0 \) Hz, 1H), 7.61 (d, \( J = 8.4 \) Hz, 1H), 7.55-7.52 (m, 1H), 5.69 (s, 1H), 4.30-4.13 (m, 2H), 3.66 (br s, 1H), 1.14 (t, \( J = 7.2 \) Hz, 3H); \( ^{13}\text{C} \{^1\text{H} \} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 173.8, 164.1, 148.4, 139.1, 135.9, 134.9, 133.3, 131.7, 131.4, 130.4, 129.5, 128.7, 128.6 (\( J_{\text{CF}} = 8.0 \) Hz, 5.0 Hz), 127.5, 126.2, 124.7 (\( J_{\text{CF}} = 8.0 \) Hz, 5.0 Hz), 122.1, 116.0, 71.4, 62.6, 14.1; Anal. Calcd for C\(_{21}\)H\(_{17}\)F\(_3\)N\(_2\)O\(_4\): C, 60.29; H, 4.10; N, 6.70%; Found: C, 60.48; H, 4.18; N, 6.61%.

Ethyl 2-(8-([1,1'-biphenyl]-4-carboxamido)quinolin-5-yl)-2-hydroxyacetate (3l): White solid (77%, 65.6 mg); \( R_f = 0.45 \) (PE:EA = 75:25); M.p. 92-93 °C; \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 10.87 (s, 1H), 8.91-8.88 (m, 2H), 8.58 (dd, \( J = 8.8 \) Hz, 1.6 Hz, 1H), 8.16-8.14 (m, 2H), 7.79-7.76 (m, 2H), 7.67-7.65 (m, 2H), 7.61 (d, \( J = 8.0 \) Hz, 1H), 7.55-7.47 (m, 3H), 7.43-7.39 (m, 1H), 5.69 (s, 1H), 4.29-4.15 (m, 2H), 3.65 (br s, 1H), 1.15 (t, \( J = 7.2 \) Hz, 3H); \( ^{13}\text{C} \{^1\text{H} \} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 173.9, 165.3, 148.2, 144.8, 140.1, 139.1, 135.4, 133.7, 133.2, 129.1, 128.2, 127.9,
127.7, 127.6, 127.3, 126.2, 122.0, 115.8, 71.5, 62.6, 14.1; Anal. Calcd for C_{26}H_{22}N_{2}O_{4}: C, 73.23; H, 5.20; N, 6.57%; Found: C, 73.39; H, 5.13; N, 6.46%.

![Ethyl 2-(8-(furan-2-carboxamido)quinolin-5-yl)-2-hydroxyacetate (3m):](image)

**Ethyl 2-(8-(furan-2-carboxamido)quinolin-5-yl)-2-hydroxyacetate (3m):** White solid (79%, 53.7 mg); R_f = 0.45 (PE:EA = 80:20); M.p. 112-113 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.84 (s, 1H), 8.90 (dd, \(J = 4.0\) Hz, 1.6 Hz, 1H), 8.82 (d, \(J = 8.0\) Hz, 1H), 8.56 (dd, \(J = 8.8\) Hz, 1.6 Hz, 1H), 7.63 (t, \(J = 1.2\) Hz, 1H), 7.58 (d, \(J = 8.0\) Hz, 1H), 7.54-7.51 (m, 1H), 7.30 (d, \(J = 3.6\) Hz, 1H), 6.59 (dd, \(J = 3.6\) Hz, 1.6 Hz, 1H), 5.68 (d, \(J = 3.2\) Hz, 1H), 4.28-7.14 (m, 2H), 3.60 (d, \(J = 4.0\) Hz, 1H), 1.14 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C\{\(^1\)H\} NMR (100 MHz, CDCl\(_3\)): \(\delta\) 173.9, 156.5, 148.3, 144.7, 139.0, 135.0, 133.1, 128.3, 127.5, 126.2, 122.0, 115.9, 115.4, 112.6, 71.5, 62.6, 14.1; Anal. Calcd for C_{18}H_{16}N_{2}O_{5}: C, 63.53; H, 4.74; N, 8.23%; Found: C, 63.32; H, 4.79; N, 8.31%.

![Ethyl 2-(8-(cyclohexanecarboxamido)quinolin-5-yl)-2-hydroxyacetate (3n):](image)

**Ethyl 2-(8-(cyclohexanecarboxamido)quinolin-5-yl)-2-hydroxyacetate (3n):** White solid (72%, 51.3 mg); R_f = 0.55 (PE:EA = 80:20); M.p. 153-154 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.96 (s, 1H), 8.81 (dd, \(J = 4.0\) Hz, 1.6 Hz, 1H), 8.73 (d, \(J = 8.0\) Hz, 1H), 8.53 (dd, \(J = 8.4\) Hz, 1.6 Hz, 2H), 7.53-7.47 (m, 2H), 5.64 (s, 1H), 4.25-4.12 (m, 1H), 3.66 (br s, 1H), 2.49-2.42 (m, 1H), 2.08-2.04 (m, 2H), 1.88-1.84 (m, 2H), 1.74-1.70 (m, 1H), 1.66-1.56 (m, 2H), 1.42-1.26 (m, 3H), 1.12 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C\{\(^1\)H\} NMR (100 MHz, CDCl\(_3\)): 175.1, 173.9, 148.0, 138.8, 135.4,
133.1, 127.8, 127.6, 126.1, 121.8, 115.6, 71.5, 62.5, 47.0, 29.8, 25.8, 14.0; Anal. Calcd for 
C_{20}H_{24}N_{2}O_{4}: C, 67.40; H, 6.79; N, 7.86%; Found: C, 67.63; H, 6.87; N, 7.72%.

**Ethyl 2-(8-acetamidoquinolin-5-yl)-2-hydroxyacetate (3o):** White solid (74%, 42.6 mg); R_{f} = 0.45 (PE:EA = 75:25); M.p. 191-192 °C; ^1H NMR (400 MHz, CDCl_{3}): δ 9.86 (s, 1H), 8.81 (dd, J = 4.0 Hz, 1.6 Hz, 1H), 8.71 (d, J = 8.0 Hz, 1H), 8.54 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.54-7.48 (m, 2H), 5.65 (s, 1H), 4.26-4.11 (m, 2H), 2.34 (s, 3H), 3.58 (br s, 1H), 1.13 (t, J = 7.2 Hz, 3H); ^13C{^1H} NMR (100 MHz, CDCl_{3}): δ 173.8, 168.9, 147.9, 138.5, 135.2, 133.0, 127.8, 127.5, 126.0, 121.7, 115.5, 71.3, 62.4, 25.1, 13.9; Anal. Calcd for C_{15}H_{16}N_{2}O_{4}: C, 62.49; H, 5.59; N, 9.72%; Found: C, 62.30; H, 5.63; N, 9.81%.

**Ethyl 2-(8-butyramidoquinolin-5-yl)-2-hydroxyacetate (3p):** Yellow gummy mass (79%, 49.9 mg); R_{f} = 0.55 (PE:EA = 70:30); ^1H NMR (400 MHz, CDCl_{3}): δ 9.89 (s, 1H), 8.81 (dd, J = 4.0 Hz, 1.6 Hz, 1H), 8.74 (d, J = 8.4 Hz, 1H), 8.53 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.51-7.48 (m, 1H), 5.65 (s, 1H), 4.26-4.13 (m, 2H), 3.55 (br s, 1H), 2.54 (t, J = 7.6 Hz, 2H), 1.89-1.80 (m, 2H), 1.13 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.6 Hz, 3H); ^13C{^1H} NMR (100 MHz, CDCl_{3}): δ 173.9, 172.0, 148.0, 138.7, 135.4, 133.1, 127.8, 127.7, 126.1, 121.8, 115.6, 71.5, 62.6,
40.3, 19.2, 14.1, 13.9; Anal. Calcd for C_{17}H_{20}N_{2}O_{4}: C, 64.54; H, 6.37; N, 8.86%; Found: C, 64.36; H, 6.43; N, 8.75%.

**Ethyl 2-hydroxy-2-(8-pivalamidoquinolin-5-yl)acetate (3q):** Yellow gummy mass (80%, 52.8 mg); R<sub>f</sub> = 0.50 (PE:EA = 75:25); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.35 (s, 1H), 8.82 (dd, <i>J</i> = 4.4 Hz, 1.6 Hz, 1H), 8.74 (d, <i>J</i> = 8.0 Hz, 1H), 8.53 (dd, <i>J</i> = 8.8 Hz, 1.6 Hz, 1H), 7.54 (d, <i>J</i> = 8.0 Hz, 1H), 7.50-7.47 (m, 1H), 5.64 (s, 1H), 4.25-4.14 (m, 2H), 3.55 (br s, 1H), 1.41 (s, 9H), 1.12 (t, <i>J</i> = 7.2 Hz, 3H); <sup>13</sup>C<sup>{1}H</sup> NMR (100 MHz, CDCl<sub>3</sub>): δ 177.5, 173.9, 148.1, 139.1, 135.5, 133.0, 127.74, 127.70, 126.1, 121.8, 115.4, 71.5, 62.5, 40.5, 27.8, 14.0; Anal. Calcd for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C, 65.44; H, 6.71; N, 8.48%; Found: C, 65.59; H, 6.67; N, 8.40%.

4-Methyl-N-(5-(2,2,2-trifluoro-1-hydroxyethyl)quinolin-8-yl)benzamide (3r): White solid (61%, 43.9 mg); R<sub>f</sub> = 0.50 (PE:EA = 80:20); M.p. 178-179 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.71 (s, 1H), 8.82 (dd, <i>J</i> = 4.4 Hz, 1.6 Hz, 1H), 8.75 (d, <i>J</i> = 8.0 Hz, 1H), 8.50 (d, <i>J</i> = 8.4 Hz, 1H), 7.91 (d, <i>J</i> = 8.0 Hz, 2H), 7.75 (d, <i>J</i> = 8.0 Hz, 1H), 7.48-7.44 (m, 1H), 7.34 (d, <i>J</i> = 8.0 Hz, 2H), 5.63 (q, <i>J</i> = 6.8, 1H), 3.82 (br s, 1H), 2.46 (s, 3H); <sup>13</sup>C<sup>{1}H</sup> NMR (100 MHz, CDCl<sub>3</sub>): δ 165.8, 148.2, 142.9, 138.6, 135.7, 132.9, 131.9, 129.7, 128.2, 127.4, 126.2 (<i>J</i><sub>C-F</sub> = 22.0 Hz),
124.1, 123.3, 122.0, 115.6, 70.4 \((J_{C-F} = 66.0 \text{ Hz}, 33.0 \text{ Hz})\), 21.7 ; Anal. Calcd for \(C_{19}H_{15}F_{3}N_{2}O_{2}\): C, 63.33; H, 4.20; N, 7.77%; Found: C, 63.54; H, 4.26; N, 7.89%.

\[
\begin{align*}
\text{N-(5-(2,2,2-trifluoro-1-hydroxyethyl)quinolin-8-yl)cyclohexanecarboxamide (3s):} & \\
& \text{White solid (69%, 48.6 mg); } R_f = 0.55 \text{ (PE:EA = 80:20); M.p. 142-1432 °C; } \text{\(^1\)H NMR (400 MHz, CDCl}_3):} \\
& \delta 9.98 \text{ (s, 1H), 8.81 (dd, } J = 4.4 \text{ Hz, 1.6 Hz, 1H), 8.68 (d, } J = 8.0 \text{ Hz, 1H), 8.55 (d, } J = 8.4 \text{ Hz, 1H), 7.73 (d, } J = 8.0 \text{ Hz, 1H), 7.52-7.49 (m, 1H), 5.64 (q, } J = 6.8 \text{ Hz, 1H), 3.72 (br s, 1H), 2.48-2.40 (m, 1H), 2.06-2.02 (m, 2H), 1.88-1.84 (m, 2H), 1.74-1.72 (m, 1H), 1.63-1.54 (m, 2H), 1.41-1.29 (m, 3H); } \text{\(^{13}\)C\{\(^1\)H\} NMR (100 MHz, CDCl}_3):} \\
& \delta 175.4, 148.1, 138.4, 135.8, 132.9, 128.2, 126.2 \text{ (} J_{C-F} = 19.0 \text{ Hz), 123.8, 123.3, 121.9, 115.6, 70.4 \text{ (} J_{C-F} = 65.0 \text{ Hz, 33.0 Hz), 47.0, 29.8, 29.7, 25.8; Analyst. Calcd for } C_{18}H_{19}F_{3}N_{2}O_2: C, 61.36; H, 5.44; N, 7.95%; Found: C, 61.50; H, 5.49; N, 8.02%.}
\end{align*}
\]

\[
\begin{align*}
\text{Ethyl 2-(8-benzamido-7-methylquinolin-5-yl)-2-hydroxyacetate (5a):} & \\
& \text{Yellow gummy mass (81%, 59.0 mg); } R_f = 0.50 \text{ (PE:EA = 80:20); } \text{\(^1\)H NMR (400 MHz, CDCl}_3):} \\
& \delta 9.57 \text{ (s, 1H), 8.79 (dd, } J = 4.4 \text{ Hz, 1.6 Hz, 1H), 8.50 (dd, } J = 8.8 \text{ Hz, 1.6 Hz, 1H), 8.09-8.07 (m, 2H), 7.60-7.56 (m, 1H), 7.54-7.50 (m, 3H), 7.43-7.40 (m, 1H), 5.70 (s, 1H), 4.32-4.09 (m, 2H), 3.74 (br s, 1H), 2.52 (s, 3H), 1.16 (t, } J = 7.2 \text{ Hz, 3H); } \text{\(^{13}\)C\{\(^1\)H\} NMR (100 MHz, CDCl}_3):} \\
& \delta 173.7, 166.0, 148.7, 142.6,}
\end{align*}
\]
134.6, 133.1, 132.4, 132.1, 130.8, 130.5, 128.8, 128.0, 124.7, 120.9, 71.0, 62.7, 20.6, 14.1; Anal. Calcd for C_{21}H_{20}N_{2}O_{4}: C, 69.22; H, 5.53; N, 7.69%; Found: C, 69.01; H, 5.63; N, 7.57%.

**Ethyl 2-(8-(4-chlorobenzamido)-7-methylquinolin-5-yl)-2-hydroxyacetate (5b):** White solid (75%, 59.7 mg); R_f = 0.50 (PE:EA = 80:20); M.p. 162-163 °C; ^1H NMR (400 MHz, CDCl_3): δ 9.62 (s, 1H), 8.77 (dd, J = 4.4 Hz, 1.6 Hz, 1H), 8.48 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.02-7.99 (m, 2H), 7.52 (s, 1H), 7.49-7.45 (m, 2H), 7.42-7.39 (m, 1H), 5.68 (s, 1H), 4.29-4.10 (m, 2H), 3.70 (br s, 1H), 2.50 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^13C{^1H} NMR (100 MHz, CDCl_3): δ 173.7, 164.9, 148.9, 142.8, 138.3, 133.1, 132.8, 132.3, 131.0, 130.4, 129.4, 129.0, 128.7, 124.6, 121.0, 71.0, 62.7, 20.6, 14.1; Anal. Calcd for C_{21}H_{19}ClN_{2}O_{4}: C, 63.24; H, 4.80; N, 7.02%; Found: C, 63.09; H, 4.71; N, 7.15%.

4. References:


5. Structure Determination (X-ray crystallographic data for 3d):

The white crystals of 3d was obtained by crystallization from a solution in dichloromethane/petroleum ether after purification by column chromatography. Chemical Formula: C_{21}H_{20}N_{2}O_{5}.
ORTEP (with 50% probability) diagram for the structure ethyl 2-hydroxy-2-(8-(4-methoxybenzamido)quinolin-5-yl)acetate (3d).

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The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication with a CCDC reference number CCDC 1831821.
6. NMR spectra for the synthesized products