Acid and Solvent Effects on the Regioselectivity of Minisci-Type Addition to Quinolines Using Amino-Acid-Derived Redox Active Esters

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General information

**NMR Spectra:** $^1$H NMR spectra were recorded on a Bruker DRX-400 (400 MHz), Bruker QNP Cryoprobe (400 MHz) or Bruker Advance DRX-600 (600 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) and the spectra are calibrated to the residual protic form of the deuterated solvent (7.26 ppm in CDCl$_3$; 2.05 ppm in (CH$_3$)$_2$CO; 5.32 ppm in CD$_2$Cl$_2$). Multiplicity was reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad. Coupling constants ($J$) are given in hertz (Hz) to 1 decimal place calculated on Bruker TopSpin 3.2. The centre of each peak is recorded with the exception of multiplet signals where a range of ppm values are given. $^{13}$C NMR were recorded on a DRX-400 (400 MHz), Bruker QNP Cryoprobe (400 MHz), spectrometer with complete proton decoupling. Chemical shifts are reported in ppm and the spectra are calibrated to the deuterated solvent as the internal deuterium lock (77.16 ppm in CDCl$_3$; 29.84 ppm in (CH$_3$)$_2$CO; 53.84 ppm in CD$_2$Cl$_2$). $^{13}$C signals are reported to 1 decimal place unless otherwise stated.

**Infrared (IR) spectroscopy:** Perkin Elmer Spectrum.

One FT infra-red spectrophotometer sampling accessory, scanning from 4000-600 cm$^{-1}$. IR absorption maxima ($v_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$).

**Reagents:** All reagents, unless otherwise specified, were used as supplied from commercial sources without further purification.

**High Resolution Mass Spectrometry (HRMS):** Measurements were recorded on a Waters Micromass LCT Premier spectrometer using a positive electrospray ionisation (ESI$^+$). Measured values are reported to 4 decimal places and are within ±5 ppm of the calculated value. The calculated values are based on the most abundant isotope.
General Procedures:

General Procedure for synthesis of redox-active esters (RAEs)

A round bottom flask was charged with N-acetyl-protected amino acid (1.0 equiv.), N-hydroxyphthalimide (NHPI, 1.1 equiv.), N,N'-dicyclohexylcarbodiimide (DCC, 1.2 equiv.) and DMAP (0.1 equiv.). CH$_2$Cl$_2$ (0.2 M) was added at room temperature (RT). The mixture was allowed to stir until all the acid was consumed (as indicated by TLC). The resulting mixture was quickly filtered and the solid residue was rinsed with more CH$_2$Cl$_2$. The filtrate was concentrated in vacuo and purified as detailed to afford the corresponding redox-active ester (RAE).

General procedure A

Sequentially, N-heteroarene (0.20 mmol, 2.0 equiv.), redox-active ester (0.10 mmol, 1.0 equiv.), 4CzIPN (1.6 mg, 0.002 mmol, 2 mol%), and p-toluenesulfonic acid (1.9 mg, 0.01 mmol, 10 mol%) were added to a 4 ml crimp top vial containing a stirrer bar. The vial was sealed with a crimp seal, evacuated and refilled with argon three times. Anhydrous, freshly argon-sparged solvent (2.0 mL) was then added via syringe and the top wrapped with Parafilm. The reaction mixture was stirred under irradiation with blue LEDs for 14 h. The apparatus was maintained at approximately room temperature by use of a desk fan close to the vials. The solvent was removed under a stream of compressed air and the crude residue was purified via flash column chromatography on silica gel.

General procedure B

Sequentially, N-heteroarene (0.20 mmol, 2.0 equiv.), redox-active ester (0.10 mmol, 1.0 equiv.), 3DPAFIPN (1.3 mg, 0.002 mmol, 2 mol%), and 2,4,6-triisopropylsulfonic acid (1.3 mg, 0.01 mmol, 10 mol%) were added to a 4 ml crimp top vial containing a stirrer bar. The vial was sealed with a crimp seal, evacuated and refilled with argon three times. Anhydrous, freshly argon-sparged solvent (2.0 mL) was then added via syringe and the top wrapped with Parafilm. The reaction mixture was stirred under irradiation with blue LEDs for 14 h. The apparatus was maintained at approximately room temperature by use of a desk fan close to the vials. The solvent was removed under a stream of compressed air and the crude residue was purified via flash column chromatography on silica gel.

Important Note: After purification on silica, product fractions were sometimes found to contain some phosphoric acid catalyst and/or photoredox catalyst and could be subjected to the following procedure to remove these impurities. Post column fractions containing photocatalyst or active ester were concentrated in vacuo and the resultant residue suspended in diethyl ether (5 mL) and shaken with 3 M HCl (5 mL). The two phases were separated and the aqueous phase was then washed with diethyl ether (1 x 5 mL), basified to pH 10 using solid sodium carbonate and extracted with CH$_2$Cl$_2$ until no product remained in the aqueous layer.
Synthesis of redox-active esters

1,3-dioxoisindolin-2-yl acetylphenylalaninate (2a)

Following general procedure with N-acetyl-L-phenylalanine (2.0 g, 9.6 mmol). The crude product was precipitated out of EtOAc to give 2 (2.15 g, 6.10 mmol, 64%) as a white solid.

$^1$H NMR (CDCl$_3$, 600 MHz) $\delta$H 7.93 (m, 2H), 7.83 (m, 2H), 7.38 – 7.31 (m, 5H), 5.82 (d, $J = 8.2$ Hz, 1H), 5.39 (td, $J = 8.3$, 5.8 Hz, 1H), 3.39 (dd, $J = 14.2$, 6.2 Hz, 1H), 3.33 (dd, $J = 14.2$, 5.4 Hz, 1H), 2.02 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 400 MHz) $\delta$C 169.6, 168.6, 160.6, 135.0, 134.5, 129.7, 128.9, 128.8, 127.6, 124.3, 51.1, 37.8, 23.1.

Data is in accordance with those previously recorded.$^1$

1,3-dioxoisindolin-2-yl acetylvalinate (2b)

Following general procedure with N-acetyl valine (1.0 g, 6.3 mmol). The crude product was purified via flash column chromatography on silica gel (1:1 40-60 petroleum ether / ethyl acetate) to give 2a (1.45 g, 4.77 mmol, 75%) as a white solid.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$H 7.93 – 7.91 (m, 2H), 7.84 – 7.82 (m, 2H), 5.94 (br d, $J = 9.4$ Hz, 1H), 5.06 (dd, $J = 8.99$, 4.16 Hz, 1H), 2.46–2.38 (m, 1H), 2.11 (s, 3H), 1.13 (d, $J = 6.90$ Hz, 6H). $^{13}$C NMR (CDCl$_3$, 400 MHz) $\delta$C 169.8, 168.7, 161.3, 135.0, 128.8, 124.1, 55.5, 30.9, 23.2, 18.7, 17.9.

Data is in accordance with those previously recorded.$^1$

5-(tert-butyl) 1-(1,3-dioxoisindolin-2-yl) acetylglutamate (2c)

Following general procedure with (S)-2-acetamido-5-(tert-butoxy)-5-oxopentanoic acid (500 mg, 2.04 mmol). The crude product was purified via flash column chromatography on deactivated silica (35% w.t. H$_2$O) eluting with 30% ethyl acetate in 40-60 petroleum ether to give 2c (593 mg, 1.52 mmol, 76%) as a white solid.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$H 7.93 – 7.91 (m, 2H), 7.83 – 7.81 (m, 2H), 6.53 (d, $J = 7.73$ Hz, 1H), 5.06 (td, $J = 8.0$, 5.0 Hz, 1H), 2.62 – 2.47 (m, 2H), 2.40 – 2.31 (m, 1H), 2.29 – 2.20 (m, 1H), 2.08 (s, 3H), 1.49 (s, 9H). $^{13}$C NMR (CDCl$_3$, 400 MHz) $\delta$C 172.5, 170.0, 168.7, 161.4, 134.9, 128.8, 124.1, 81.3, 50.4, 31.1, 28.1, 27.1, 22.9.

Data is in accordance with those previously recorded.$^1$
1,3-dioxoisindol-2-yl acetylmethioninate (2d)

Following general procedure with N-acetyl methionine (1.00 g, 5.23 mmol). The crude product was purified via flash column chromatography on deactivated silica (35% wt. H₂O) eluting with 30% ethyl acetate in 40-60 petroleum ether to give 2d (729 mg, 2.17 mmol, 42%) as a white solid.

1H NMR (CDCl₃, 400 MHz) δ 7.91 – 7.88 (m, 2H), 7.85 – 7.80 (m, 2H), 6.25 (br d, J = 8.1 Hz, 1H), 5.26 – 5.21 (m, 1H), 2.74 – 2.70 (m, 2H), 2.37 – 2.30 (m, 1H), 2.28 – 2.21 (m, 1H), 2.17 (s, 3H), 2.08 (s, 3H).

13C NMR (CDCl₃, 400 MHz) δ 169.7, 168.8, 161.4, 134.9, 128.8, 124.1, 50.0, 31.9, 29.6, 23.0, 15.5.

Data is in accordance with those previously recorded. ¹
Synthesis of products

**N-((2-phenyl-1-(quinolin-4-yl)ethyl)acetamide (3a)**

General procedure A was followed with quinoline (65 mg, 0.5 mmol) and 2a (68 mg, 0.25 mmol) in DMA as a solvent. The crude mixture (7.6:1 C4:C2 NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3a as a major regioisomer (47 mg, 0.16 mmol, 32%) as a yellow oil.

$^1$H NMR (CDCl3, 400 MHz) $\delta$H 8.82 (d, $J$ = 4.5 Hz, 1H), 8.19 (d, $J$ = 8.5 Hz, 1H) 8.15 (d, $J$ = 8.3 Hz, 1H), 7.75 (t, $J$ = 7.6 Hz, 1H), 7.61 (t, $J$ = 7.3 Hz, 1H), 7.29 - 7.19 (m, 4H), 7.09 (d, $J$ = 7.1 Hz, 2H), 6.15 (quar., $J$ = 6.9 Hz, 1H), 6.04 (d, $J$ = 8.1 Hz, 1H), 3.35 (dd, $J$ = 5.7, 14 Hz, 1H), 3.16 (dd, $J$ = 7.5, 14.4 Hz, 1H), 1.98 (s, 3H).

$^{13}$C NMR (CDCl3, 400 MHz) $\delta$C 169.3, 149.9, 148.5, 147.0, 136.4, 130.4, 129.4, 128.6, 127.0, 126.0, 122.9, 117.6, 49.4, 41.1, 23.2.

Data is in accordance with those previously recorded.

**N-((2-phenyl-1-(quinolin-2-yl)ethyl)acetamide (4a)**

General procedure B was followed with quinoline (26 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in toluene as a solvent. The crude mixture (1:7.3 C4:C2 NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 4a as a major regioisomer (13 mg, 0.045 mmol, 45%) as a yellow oil.

$^1$H NMR (CDCl3, 600 MHz) $\delta$H 8.03 (d, $J$ = 8.1 Hz, 1H), 7.97 (d, $J$ = 8.3 Hz, 1H), 7.78 (d, $J$ = 7.7 Hz, 1H), 7.71 (t, $J$ = 8.1 Hz, 1H), 7.53 (t, $J$ = 7.8 Hz, 1H), 7.15-7.12 (m, 3H), 6.96-6.92 (m, 3H), 5.45 (td, $J$ = 7.8, 5.1 Hz, 1H), 3.38 (dd, $J$ = 13.8, 5.2 Hz, 1H), 3.13 (dd, $J$ = 13.3, 8.1, 1H), 2.09 (s, 3H). $^{13}$C NMR (CDCl3, 400 MHz) $\delta$C 169.4, 159.1, 147.4, 137.1, 136.1, 129.7, 129.6, 128.9, 128.1, 127.7, 127.4, 126.4, 126.4, 120.8, 55.6, 42.4, 23.6.

Data is in accordance with those previously recorded.

**N-((2-methyl-1-(quinolin-4-yl)propyl)acetamide (3b)**

General procedure A was followed with quinoline (65 mg, 0.5 mmol) and 2b (75 mg, 0.25 mmol) in DMA as a solvent. The crude mixture (3.2:1 C4:C2 NMR ratio) was purified via flash column chromatography
(100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3b as a major regioisomer (19 mg, 0.078 mmol, 32%)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.85 (d, $J = 4.5$ Hz, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 8.12 (d, $J = 8.5$ Hz, 1H), 7.74 – 7.70 (m, 1H), 7.61 – 7.57 (m, 1H), 7.27 – 7.25 (m, 1H), 6.01 (br d, $J = 8.9$ Hz, 1H), 5.65 (dd, $J = 8.4, 8.4$ Hz, 1H), 2.27 (sept, $J = 6.7$ Hz, 1H), 2.02 (s, 3H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz) $\delta$ 169.5, 149.8, 148.6, 147.8, 130.2, 129.4, 126.9, 126.7, 123.4, 117.7, 53.7, 32.6, 23.3, 20.2, 18.2.

FTIR (v max, cm$^{-1}$): 3750, 3296, 2966, 1647, 1548, 1371, 756. HRMS m/z: [M+H]$^+$ calculated for [C$_{15}$H$_{19}$N$_2$O]$^+$ expect 243.1492; found 243.1483.

$N$-(2-methyl-1-quinolin-2-yl)propylacetamide (4b)

General procedure B was followed with quinoline (26 mg, 0.2 mmol) and 2b (30.4 mg, 0.1 mmol) in dioxane as a solvent. The crude mixture (1:9.3 C$_4$:C$_2$ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 4b as a major regioisomer (7.8 mg, 0.032 mmol, 32%) as a white solid.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.10 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 8.5$ Hz, 1H), 7.81 (d, $J = 7.7$ Hz, 1H), 7.53 (t, $J = 6.9$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.10 (d, $J = 7.8$ Hz, 1H), 5.11 (dd, $J = 6.3, 8.5$ Hz, 1H), 2.24 (sept, $J = 6.7$ Hz, 1H), 2.10 (s, 3H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz) $\delta$ 169.7, 159.7, 147.4, 136.2, 129.5, 128.9, 127.7, 127.3, 126.3, 121.3, 59.0, 34.3, 23.6, 19.3, 18.4. FTIR (v max, cm$^{-1}$): 3290, 2961, 2925, 2367, 1648, 1503, 1429, 1372, 823, 754. HRMS m/z: [M+H]$^+$ calculated for [C$_{15}$H$_{19}$N$_2$O]$^+$ expect 243.1492; found 243.1484.

Tert-butyl 4-acetamido-4-quinolin-4-yl)butanoate (3c)

General procedure A was followed with quinoline (26 mg, 0.2 mmol) and 2c (39 mg, 0.1 mmol) in 10% water in DMA as a solvent. The crude mixture (5.3:1 C$_c$:C$_2$ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3c as a major regioisomer (27.4 mg, 0.083 mmol, 33%) as a white solid.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.84 (d, $J = 4.5$ Hz, 1H), 8.12 (t, $J = 8.3$ Hz, 2H), 7.71 (td, $J = 6.9, 1.3$ Hz, 1H), 7.59 (td, $J = 6.9, 1.3$ Hz, 1H), 7.32 (d, $J = 4.5$ Hz, 1H), 6.57 (d, $J = 7.5$ Hz, 1H), 5.77 (dt, $J = 8.3, 5.3$ Hz, 1H), 2.40 – 2.35 (m, 2H), 2.22 – 2.15 (m, 2H), 2.00 (s, 3H) 1.45 (s, 9H). $^{13}$C NMR (CDCl$_3$, 400 MHz) $\delta$ 173.1, 169.5, 150.1, 148.6, 147.6, 130.3, 129.4, 127.0, 126.1, 123.1, 117.3, 81.2, 48.8, 32.3, 29.7, 28.1, 23.3. FTIR (v max,
Tert-butyl 4-acetamido-4-(quinolin-2-yl)butanoate (4c)

General procedure B was followed with quinoline (26 mg, 0.2 mmol) and 2c (39 mg, 0.1 mmol) in toluene as a solvent. The crude mixture (1:4 C₂: C₄ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 4c as a major regioisomer (10.5 mg, 0.032 mmol, 32%) as a white solid.

\[ \text{H NMR (CDCl}_3, 400 MHz) \delta 8.14 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.72 (br t, J = 7.5 Hz, 1H), 7.54 (br t, J = 7.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 5.31 (dt, J = 7.1, 5.1 Hz, 1H), 2.35 – 2.27 (m, 2H), 2.18 – 2.17 (m, 1H), 2.11 (s, 3H), 1.38 (s, 9H).]  

\[ \text{C NMR (CDCl}_3, 400 MHz) \delta 172.5, 169.7, 159.5, 147.3, 136.9, 129.7, 128.9, 127.7, 127.4, 126.4, 120.2, 80.4, 53.4, 31.5, 28.0, 23.6. \]

FTIR (ν max, cm⁻¹): 3672, 3288, 2927, 1726, 1649, 1505, 1367, 1152, 833, 757. HRMS m/z: [M+H]⁺ calculated for [C₁₉H₂₄N₂O₃]⁺ expect 329.1865; found 329.1855.

N-(3-(methylthio)-1-(quinolin-4-yl)propyl)acetamide (3d)

General procedure A was followed with quinoline (26 mg, 0.2 mmol) and 2d (mg, 0.1 mmol) in 10% water in DMA as a solvent. The crude mixture (5.8:1 C₂: C₄ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3d as a major regioisomer (29.6 mg, 0.11 mmol, 43%) as a white solid.

\[ \text{H NMR (CDCl}_3, 400 MHz) \delta 8.85 (d, J = 4.5 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 8.3, 7.2 Hz, 1H), 7.60 (dd, J = 8.2, 7.6 Hz, 1H), 7.32 (d, J = 4.5 Hz, 1H), 6.22 (d, J = 8.3 Hz, 1H), 5.97 (quin., J = 5.4 Hz, 1H), 2.60 – 2.52 (m, 2H), 2.29 – 2.23 (m, 1H), 2.20 – 2.14 (m, 1H), 2.13 (s, 3H), 2.02 (s, 3H).]  

\[ \text{C NMR (CDCl}_3, 400 MHz) \delta 169.4, 150.0, 148.6, 147.1, 130.3, 129.5, 127.2, 126.1, 123.1, 117.3, 47.9, 34.5, 30.9, 23.3, 15.7. \]

FTIR (ν max, cm⁻¹): 3269, 3049, 2524, 2853, 1651, 1544, 1508, 1426, 1371, 1027, 848, 764. HRMS m/z: [M+H]⁺ calculated for [C₁₅H₁₉N₂O₃]⁺ expect 275.1218; found 275.1214.
**N-(1-(6-fluoroquinolin-4-yl)-2-phenylethyl)acetamide (3f)**

![Chemical structure of 3f]

General procedure A was followed with 6-fluoroquinoline (29 mg, 0.2 mmol) and 2d (35 mg, 0.1 mmol) in DMSO as a solvent. The crude mixture (6:1 C₆C₂ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3f as a major regioisomer (20 mg, 0.065 mmol, 65%) as a white solid.

\[ ^1H \text{ NMR (CDCl}_3, 400 MHz) \delta_{H} 8.78 (d, J = 4.0 Hz, 1H), 8.13 (dd, J = 9.2, 5.7 Hz, 2H), 7.77 (dd, J = 10.0, 2.6 Hz, 1H), 7.49 (td, J = 9.2, 2.6 Hz, 1H), 7.28 – 7.20 (m, 4H), 7.05 (d, J = 7.8 Hz, 2H), 5.95 – 5.93 9 (m, 2H), 3.29 (dd, J = 13.8, 5.9 Hz, 1H), 3.12 (dd, J = 14.3, 7.2 Hz, 1H), 1.97 (s, 3H). \]

\[ ^{13}C \text{ NMR (CDCl}_3, 400 MHz) \delta_{C} 169.3, 161.9, 159.5, 149.1, 146.7, 145.7, 136.0, 129.1, 128.7, 127.2, 126.3, 119.8, 119.5, 118.3, 106.9, 106.6, 49.6, 40.9, 23.2. \]

FTIR (ν max, cm⁻¹): 3274, 2161, 1966, 1642, 1542, 1510, 1463, 1378, 1300, 1220, 1163, 1108, 854, 741, 698. HRMS m/z: [M+H]⁺ calculated for [C₁₉H₁₇FNO]⁺ expect 309.1403; found 309.1407.

**N-(1-(6-fluoroquinolin-2-yl)-2-phenylethyl)acetamide (4d)**

![Chemical structure of 4d]

General procedure B was followed with 6-fluoroquinoline (29 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in dioxane as a solvent. The crude mixture (1:7.8 C₆C₂ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 4d as a major regioisomer (12 mg, 0.039 mmol, 39%) as a white solid.

\[ ^1H \text{ NMR (CDCl}_3, 400 MHz) \delta_{H} 8.03 (dd, J = 9.4, 5.4 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.48 (td, J = 8.9, 2.8 Hz, 1H), 7.40 (dd, J = 8.8, 2.8 Hz, 1H), 7.16 – 7.11 (m, 4H), 6.97 (d, J = 8.5 Hz, 1H), 6.94 – 6.92 (m, 2H), 5.45 (td, J = 7.8, 5.1 Hz, 1H), 3.36 (dd, J = 13.2, 5.1 Hz, 1H), 3.14 (dd, J = 13.2, 8.2 Hz, 1H), 2.09 (s, 3H). \]

\[ ^{13}C \text{ NMR (CDCl}_3, 400 MHz) \delta_{C} 169.4, 159.9, 158.6, 144.5, 137.0, 135.5, 131.4, 131.3, 129.6, 128.2, 127.9, 126.5, 121.6, 110.8, 110.6, 55.5, 42.3, 23.6. \]

Data is in accordance with those previously recorded.¹

**N-(1-(6-chloroquinolin-4-yl)-2-phenylethyl)acetamide (3g)**

![Chemical structure of 3g]
General procedure A was followed with 6-chloroquinoline (33 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in DMSO as a solvent. The crude mixture (4.3:1 C\textsubscript{6}C\textsubscript{2} NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3g as a major regioisomer (15 mg, 0.046 mmol, 47%) as a white solid.

\[ \text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz)} \delta 8.81 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 2.2 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.65 (dd, J = 9.0, 2.2 Hz, 1H), 7.28 – 7.23 (m, 4H), 7.19 (d, J = 4.6 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 5.98 (quar., J = 6.6 Hz, 1H), 5.90 (br d, J = 7.3 Hz, 1H), 3.29 (dd, J = 13.7, 5.5 Hz, 1H), 3.13 (dd, J = 13.8, 6.6 Hz, 1H), 1.98 (s, 3H).
\[ \text{\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz)} \delta 169.3, 150.1, 146.9, 146.5, 135.9, 133.0, 131.9, 130.3, 129.1, 128.7, 127.3, 126.7, 122.1, 118.4, 49.5, 41.2, 23.2. \]

General procedure A was followed with 6-chloroquinoline (41.6 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in DMSO as a solvent. The crude mixture (4.6:1 C\textsubscript{6}C\textsubscript{2} NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3h as a major regioisomer (17 mg, 0.046 mmol, 46%) as a white solid.

\[ \text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz)} \delta 8.82 (d, J = 4.5 Hz, 1H), 8.28 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 8.9 Hz, 1H), 7.79 (dd, J = 9.0, 1.9 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.18 (d, J = 4.5 Hz, 1H), 7.02 (d, J = 5.3 Hz, 2H), 5.98 (quar., J = 6.7 Hz, 1H), 5.91 (d, J = 7.4 Hz, 1H), 3.29 (dd, J = 14.2, 6.0 Hz, 1H), 3.13 (dd, J = 14.1, 7.1 Hz, 1H), 1.99 (s, 3H).
\[ \text{\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz)} \delta 169.3, 150.2, 147.1, 146.5, 135.8, 132.9, 132.0, 129.2, 128.7, 127.3, 127.2, 125.4, 121.3, 118.3, 49.5, 41.2, 23.2. \]

General procedure B was followed with 6-bromoquinoline (41.6 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in dioxane as a solvent. The crude mixture (1:9 C\textsubscript{6}C\textsubscript{2} NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3h as major regioisomer (17 mg, 0.046 mmol, 46%) as a white solid.

\[ \text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz)} \delta 8.82 (d, J = 4.5 Hz, 1H), 8.28 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 8.9 Hz, 1H), 7.79 (dd, J = 9.0, 1.9 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.18 (d, J = 4.5 Hz, 1H), 7.02 (d, J = 5.3 Hz, 2H), 5.98 (quar., J = 6.7 Hz, 1H), 5.91 (d, J = 7.4 Hz, 1H), 3.29 (dd, J = 14.2, 6.0 Hz, 1H), 3.13 (dd, J = 14.1, 7.1 Hz, 1H), 1.99 (s, 3H).
\[ \text{\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz)} \delta 169.3, 150.2, 147.1, 146.5, 135.8, 132.9, 132.0, 129.2, 128.7, 127.3, 127.2, 125.4, 121.3, 118.3, 49.5, 41.2, 23.2. \]

General procedure B was followed with 6-bromoquinoline (41.6 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in dioxane as a solvent. The crude mixture (1:9 C\textsubscript{6}C\textsubscript{2} NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 4e as major regioisomer (16 mg, 0.041 mmol, 43%) as a white solid.
**N-(1-(7-bromoquinolin-4-yl)-2-phenylethyl)acetamide (3i)**

![Diagram](image)

General procedure A was followed with 7-bromoquinoline (41.6 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in DMSO as a solvent. The crude mixture (4.2:1 C₄:C₂ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3i as major regioisomer (21.7 mg, 0.059 mmol, 51%) as a white solid.

**General Procedure A**

1H NMR (CDCl₃, 400 MHz) δH 8.82 (d, J = 4.5 Hz, 1H), 8.31 (d, J = 2.0 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.66 (dd, J = 9.0, 2.0 Hz, 1H), 7.25 – 7.21 (m, 4H), 7.04 (d, J = 8.0 Hz, 2H), 6.06 (quar., J = 7.3 Hz, 1H), 5.88 (d, J = 7.7 Hz, 1H), 3.29 (dd, J = 14.2, 6.4 Hz, 1H), 3.14 (dd, J = 14.2, 7.4 Hz, 1H), 1.97 (s, 3H). 13C NMR (CDCl₃, 400 MHz) δC 169.3, 150.9, 149.2, 147.4, 136.0, 132.6, 130.5, 129.1, 128.7, 127.2, 124.8, 124.5, 123.6, 117.9, 49.2, 41.1, 23.2. FTIR (ν max, cm⁻¹): 3284, 2923, 2169, 1651, 1599, 1549, 1493, 1373, 1305, 1098, 886, 826, 744, 702. HRMS m/z: [M+H]^+ calculated for [C₁₉H₁₇BrN₂O]⁺ expect 369.0603, found 369.0592.

**N-(1-(6-methoxyquinolin-4-yl)-2-phenylethyl)acetamide (3e)**

![Diagram](image)

General procedure A was followed with 6-methoxyquinoline (31.8 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in DMSO as a solvent. The crude mixture (4.3:1 C₄:C₂ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 3e as major regioisomer (18 mg, 0.056 mmol, 56%) as a white solid.

**General Procedure A**

1H NMR (DMSO-d₆, 400 MHz) δH 8.71 (d, J = 4.5 Hz, 1H), 8.59 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 4.5 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.38 (dd, J = 8.9, 2.7 Hz, 1H), 7.30 – 7.23 (m, 4H), 7.17 (d, J = 7.0 Hz, 1H), 5.72 (td, J = 8.9, 5.4 Hz, 1H), 3.88 (s, 3H), 3.16 (dd, J = 14.0, 5.4 Hz, 1H), 3.06 (dd, J = 13.9, 4.8 Hz, 1H), 1.79 (s, 3H). 13C NMR (DMSO-d₆, 400 MHz) δC 169.0, 157.7, 148.1, 147.4, 144.3, 138.8, 131.7, 129.5,
128.7, 127.3, 126.8, 121.9, 118.8, 102.1, 55.9, 49.9, 23.0. FTIR (ν max, cm⁻¹): 3285, 3064, 2926, 1727, 1649, 1622, 1505, 1454, 1372, 1264, 1230, 1171, 1112, 1030, 909, 879, 831, 733, 699. HRMS m/z : [M+H]+ calculated for [C₂₀H₁₇N₂O₂]+ expect 321.1603; found 321.1609.

**N-(1-(6-methoxyquinolin-2-yl)-2-phenylethyl)acetamide (4f)**

General procedure B was followed with 6-methoxyquinoline (31.8 mg, 0.2 mmol) and 2a (35 mg, 0.1 mmol) in dioxane as a solvent. The crude mixture (1:7.9 C₆:C₂ NMR ratio) was purified via flash column chromatography (100% 40-60 petroleum ether to 3% MeOH in EtOAc) to give product 4f as a major regioisomer (13 mg, 0.041 mmol, 41%) as a white solid.

¹H NMR (CDCl₃, 400 MHz) δH 7.92 (d, J = 9.2 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.36 (dd, J = 9.2, 2.8 Hz, 1H), 7.19 – 7.13 (m, 4H), 7.04 (d, J = 2.7 Hz, 1H), 6.93 - 6.92 (m, 2H), 6.89 (d, J = 8.4 Hz, 1H), 5.40 (td, J = 7.8, 5.0 Hz, 1H), 3.93 (s, 3H), 3.35 (dd, J = 13.1, 5.0 Hz, 1H), 3.12 (dd, J = 13.2, 8.2 Hz, 1H), 2.08 (s, 3H). ¹³C NMR (CDCl₃, 400 MHz) δC 169.3, 157.7, 156.5, 137.2, 134.9, 130.3, 129.7, 128.3, 128.1, 126.4, 122.3, 121.1, 105.1, 55.5, 55.5, 42.4, 23.6.

Data is in accordance with those previously recorded.¹

1. Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. *Science* 2018, 360, (6387), 419-422.
$^1$H NMR spectrum (CDCl$_3$, 600 MHz) 1,3-dioxoisindolin-2-yl acetylphenylalaninate (2a)
$^{13}$C NMR spectrum (CDCl$_3$, 600 MHz) 1,3-dioxoisooindolin-2-yl acetylphenylalaninate (2a)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) of 1,3-dioxoisindolin-2-yl acetylvalinate (2b)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) of 1,3-dioxoisooindolin-2-yl acetylvalinate (2b)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) 5-(tert-butyl) 1-(1,3-dioxoisindolin-2-yl) acetylglutamate (2c)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) 5-(tert-butyl) 1-(1,3-dioxoisooindolin-2-yl) acetylglutamate (2c)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) 1,3-dioisoindolin-2-yl acetylmethioninate (2d)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) 1,3-dioxoisooindolin-2-yl acetylmethioninate (2d)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) N-(-2-phenyl-1-(quinolin-4-yl)ethyl)acetamide (3a)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) $N$-(2-phenyl-1-(quinolin-4-yl)ethyl)acetamide (3a)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) $N$-(-2-phenyl-1-(quinolin-2-yl)ethyl)acetamide (4a)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-(-2-phenyl-1-(quinolin-2-yl)ethyl)acetamide (4a)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) $N$-(2-methyl-1-(quinolin-4-yl)propyl)acetamide (3b)
\(^{13}\)C NMR spectrum (CDCl\(_3\), 400 MHz) \(N\)-(2-methyl-1-(quinolin-4-yl)propyl)acetamide (3b)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) $N$-(2-methyl-1-(quinolin-2-yl)propyl)acetamide (4b)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-(2-methyl-1-(quinolin-2-yl)propyl)acetamide (4b)

\[
\text{N} \quad \text{NHAc}
\]
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) of tert-butyl 4-acetamido-4-(quinolin-4-yl)butanoate (3c)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) of tert-butyl 4-acetamido-4-(quinolin-4-yl)butanoate (3c)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) tert-butyl 4-acetamido-4-(quinolin-2-yl)butanoate (4c)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) tert-butyl 4-acetamido-4-(quinolin-2-yl)butanoate (4c)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) $N$-(3-(methylthio)-1-(quinolin-4-yl)propyl)acetamide (3d)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-(3-(methylthio)-1-(quinolin-4-yl)propyl)acetamide (3d)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(6-fluoroquinolin-4-yl)-2-phenylethyl)acetamide (3f)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(6-fluoroquinolin-4-yl)-2-phenylethyl)acetamide (3f)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) of N-(1-(6-fluoroquinolin-2-yl)-2-phenylethyl)acetamide (4d)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) of $N$-(1-(6-fluoroquinoxalin-2-yl)-2-phenylethyl)acetamide (4d)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(6-chloroquinolin-4-yl)-2-phenylethyl)acetamide (3g)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(6-chloroquinolin-4-yl)-2-phenylethyl)acetamide (3g)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) \( N\)-(1-(6-bromoquinolin-4-yl)-2-phenylethyl)acetamide (3h)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(6-bromoquinolin-4-yl)-2-phenylethyl)acetamide (3h)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(6-bromoquinolin-2-yl)-2-phenylethyl)acetamide (4e)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(6-bromoquinolin-2-yl)-2-phenylethyl)acetamide (4e)
$^{1}\text{H NMR spectrum (CDCl}_3, 400 \text{ MHz)} \ N-(1-(7\text{-bromoquinolin-4-yl})-2\text{-phenylethyl})\text{acetamide (3i)}}$
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(7-bromoquinolin-4-yl)-2-phenylethyl)acetamide (3i)
$^{1}H$ NMR spectrum (CDCl$_3$, 400 MHz) $N$-(1-(6-methoxyquinolin-4-yl)-2-phenylethyl)acetamide (3e)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-$(1$-(6-methoxyquinolin-4-yl)$-2$-phenylethyl)acetamide (3e)
$^1$H NMR spectrum (CDCl$_3$, 400 MHz) \( N\)-(1-(6-methoxyquinolin-2-yl)-2-phenylethyl)acetamide \(4f\)
$^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) $N$-\{1-(6-methoxyquinolin-2-yl)-2-phenylethyl\}acetamide (4f)