Supplementary Information

α-Angelica Lactone in a New Role: Facile Access to N-Aryl Tetrahydroisoquinolinones and Isoindolinones via Organocatalytic α-CH₂ Oxygenation

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1. General information

All chemical were obtained from commercial supplier and were used without further purification unless otherwise stated. Flash column chromatography was performed on Merck flash silica gel 230-400 mesh size. Unless otherwise specified, all reactions were carried out in oven dried glass vials under open atmosphere. All the solvents were distilled prior to use. Analytical thin layer chromatography (TLC) was performed with Merck silica gel 60 F-254 aluminium-backed plates. Visualization on TLC was monitored by UV light. $^1$H and $^{13}$C spectra were recorded at 400, 500MHz and 101, 126 MHz respectively on bruker AV400 and AV500 Avance using CDCl$_3$ purchased from Merck/sigma as internal standard (CDCl$_3$ at 7.27 ppm for $^1$H and 77.00 ppm for $^{13}$C). All the NMR spectra were processed in either MestReNova or Bruker software. Chemical shifts ($\delta$) are given in ppm. High resolution mass spectroscopy (HRMS) was recorded using Q-exactive-orbitap spectrometer with electrospray ionization as ionization source.

2. Table S1: Solvent and base optimization$^a$

| S.no | Base  | Solvent | Catalyst | % of Yield$^c$ 2a |
|------|-------|---------|----------|------------------|
| 1    | -     | THF     | A        | no reaction      |
| 2    | DABCO | THF     | -        | no reaction      |
| 3$^b$| DABCO | THF     | A        | no reaction      |
| 4$^b$| DABCO | THF     | A        | no reaction      |
| 5    | DABCO | Toluene | A        | 76               |
| 6    | DABCO | CH$_3$CN| A        | trace            |
| 7    | DABCO | DMF     | A        | <10              |
| 8    | DABCO | DMSO    | A        | 11               |
| 9    | DABCO | MeOH    | A        | 13               |
| 10   | DABCO | Et$_2$O | A        | 56               |
| 11   | DABCO | MTBE    | A        | 45               |
| 12   | Et$_3$N| THF     | A        | 44               |
| 13   | NMM   | THF     | A        | 40               |
| 14   | Pyridine | THF | A        | 18               |
| 15   | Na$_2$CO$_3$ | THF | A        | trace            |

$^a$Reaction condition: 1a (0.1 mmol), DABCO (0.3 mmol), catalyst A (25 mol%), in THF (0.5 mL) at room temperature for 36 h under O$_2$ (balloon) atmosphere. $^b$Under argon and nitrogen (balloon) atmosphere. $^c$Isolated yields.

3. General procedure for the oxidation of N-aryl/heteroaryl tetrahydroisoquinolines and isoindolines

To a solution of N-aryl/heteroaryl tetrahydroisoquinolines$^1$ or N-aryl isoindolines$^1$ (0.1 mmol) and DABCO (0.3 mmol) in THF (0.5 mL) was added the $\alpha$-angelica lactone (25 mol%,
2.3 µL) at room temperature. The vial was equipped with balloon containing O₂ gas and the reaction mixture was stirred at room temperature for 36 h. The resulting reaction mixture was monitored by TLC and or ¹H NMR. Then reaction mixture was diluted with dichloromethane and washed with water. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The products were purified on a silica gel column using 20% pet ether/EtOAc.

4. Characterization of compounds

2-Phenyl-3,4-dihydroisoquinolin-1(2H)-one (2a): White solid (18.0 mg, 81%); TLC Rᵢ = 0.5 (20% EtOAc/Pet ether); ¹H NMR (500 MHz, CDCl₃) δ 8.16 (d, J = 7.5 Hz, 1H), 7.48-7.45 (m, 1H), 7.42-7.36 (m, 5H), 7.24 (d, J = 7.5 Hz, 2H), 4.00 (t, J = 6.1 Hz, 2H), 3.15 (t, J = 6.0 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 164.24, 143.15, 138.34, 132.06, 129.75, 128.94, 128.78, 127.22, 126.97, 126.28, 125.36, 49.45, 28.65. HRMS (ESI+) (m/z) calcd for C₁₅H₁₄NO [M+H] 224.1075 found 224.1070.

2-(4-(Trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2b): White solid (24.7 mg, 85%); TLC Rᵢ = 0.7 (20% EtOAc/Pet ether); ¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.4 Hz, 1H), 7.34-7.30 (m, 1H), 7.20-7.18 (m, 1H), 3.96 (t, J = 6.4 Hz, 2H), 3.09 (t, J = 6.3 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.24, 146.08, 138.26, 132.47, 129.26, 128.90, 128.02, 127.39, 127.08, 125.955 (q, J = 6.3 Hz), 125.12, 124.011 (q, J = 271.69 Hz), 49.10, 28.51. HRMS (ESI+) (m/z) calcd for C₁₆H₁₃F₃NO [M+H] 292.0949 found 292.0944.

2-(4-Acetylphenyl)-3,4-dihydroisoquinolin-1(2H)-one (2c): Yellow solid (20.9 mg, 79%); TLC Rᵢ = 0.4 (20% EtOAc/Pet ether); ¹H NMR (500 MHz, CDCl₃) δ 8.16 (d, J = 7.6 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.50 (dd, J = 18.9, 7.9 Hz, 3H), 7.41-7.38 (m, 1H), 7.26 (d, J = 6.8 Hz, 1H), 4.05 (t, J = 6.3 Hz, 2H), 3.17 (t, J = 6.2 Hz, 2H), 2.61 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 197.16, 164.16, 147.25, 138.28, 134.36, 132.45, 129.35, 129.08, 128.91, 127.36, 127.06, 124.60, 49.02, 28.50, 26.61. HRMS (ESI+) (m/z) calcd for C₁₇H₁₆NO₂ [M+H] 266.1181 found 266.1176.

2-(3-(Trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2d): Yellow oil (20.6 mg, 71%); TLC Rᵢ = 0.7 (20% EtOAc/Pet ether); ¹H NMR (500 MHz, CDCl₃) δ 8.15 (d, J = 7.6 Hz, 1H), 7.67 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.53 - 7.46 (m, 3H), 7.40-7.37 (m, 1H), 7.27 - 7.24 (m, 1H), 4.01 (t, J = 6.5 Hz, 2H), 3.16 (t, J = 6.4 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 164.29,
143.53, 138.30, 132.43, 131.29 (q, J = 32.4 Hz), 129.35, 129.25, 128.81, 128.65, 127.35, 127.11, 124.95, 122.78, 121.98, 49.21, 28.51. HRMS (ESI+) (m/z) calcd for C_{16}H_{13}F_{3}NO [M+H] 292.0949 found 292.0944.

2-(3,5-bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2e): Colourless oil (29.0 mg, 81%); TLC R_f = 0.7 (10% EtOAc/Pet ether); ^1H NMR (400 MHz, CDCl$_3$) δ 8.15 (d, J = 7.6 Hz, 1H), 7.90 (s, 2H), 7.74 (s, 1H), 7.54-7.50 (m, 1H), 7.42–7.39 (m, 1H), 7.31 – 7.24 (m, 1H), 4.07 (t, J = 6.2 Hz, 2H), 3.20 (t, J = 6.1 Hz, 2H). ^13C NMR (101 MHz, CDCl$_3$) δ 164.38, 144.28, 138.23, 132.87, 128.90, 128.68, 127.53, 127.23, 125.09, 124.46, 121.75, 119.39, 119.03, 49.01, 28.36. HRMS (ESI+) (m/z) calcd for C$_{17}$H$_{12}$F$_6$NO [M+H] 360.0823 found 360.0818.

2-(2-(Trifluoromethoxy)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2f): Yellow oil (15.9 mg, 52%); TLC R_f = 0.5 (20% EtOAc/Pet ether); ^1H NMR (400 MHz, CDCl$_3$) δ 8.14 (d, J = 7.7 Hz, 1H), 7.50–7.46 (m, 1H), 7.44–7.33 (m, 5H), 7.25 (d, J = 7.4 Hz, 1H), 3.88 (t, J = 6.0 Hz, 2H), 3.15 (s, 2H). ^13C NMR (101 MHz, CDCl$_3$) δ 164.15, 144.80, 138.63, 135.37, 132.29, 129.43, 129.10, 128.79, 128.68, 127.52, 127.13, 121.69, 49.38, 28.52. HRMS (ESI+) (m/z) calcd for C$_{16}$H$_{13}$F$_3$NO$_2$ [M+H] 308.0898 found 308.0893.

2-(2-Nitrophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2g): Yellow solid (13.9 mg, 52%); TLC R_f = 0.4 (20% EtOAc/Pet ether); ^1H NMR (500 MHz, CDCl$_3$) δ 8.18 (t, J = 2.0 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.51-7.47 (m, 1H), 7.44-7.41 (m, 1H), 7.33-7.30 (m, 1H), 7.20 (d, J = 7.6 Hz, 1H), 3.99 (t, J = 6.4 Hz, 2H), 3.12 (t, J = 6.4 Hz, 2H). ^13C NMR (126 MHz, CDCl$_3$) δ 164.33, 148.48, 144.00, 138.70, 135.42, 132.29, 129.43, 129.10, 128.79, 128.68, 127.52, 127.13, 121.69, 49.38, 28.52. HRMS (ESI+) (m/z) calcd for C$_{15}$H$_{13}$N$_2$O$_3$ [M+H] 269.0926 found 269.0921 and calcd for C$_{15}$H$_{12}$N$_2$O$_3$ [M+Na] 291.0746 found 291.0740.

2-(4-Chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2h): White solid (21.5 mg, 84%); TLC R_f = 0.6 (20% EtOAc/Pet ether); ^1H NMR (500 MHz, CDCl$_3$) δ 8.14 (d, J = 7.6 Hz, 1H), 7.49-7.46 (m, 1H), 7.39 – 7.31 (m, 5H), 7.24 (d, J = 7.5 Hz, 1H), 3.96 (t, J = 6.5 Hz, 2H), 3.14 (t, J = 6.4 Hz, 2H). ^13C NMR (126 MHz, CDCl$_3$) δ 164.22, 141.59, 138.26, 132.25, 131.57, 129.44, 128.99, 128.78, 127.29, 127.03, 126.57, 49.33, 28.55. HRMS (ESI+) (m/z) calcd for C$_{15}$H$_{13}$ClNO [M+H] 258.0686 found 258.0680.

2-(4-Bromophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2i): White solid (15.6 mg, 52%); TLC R_f = 0.6 (10% EtOAc/Hexane); ^1H NMR (400 MHz, CDCl$_3$) δ 8.14 (d, J = 7.6 Hz, 1H), 7.52 (d,
$J = 8.7$ Hz, 2H), 7.46 (d, $J = 7.3$ Hz, 1H), 7.39-7.36 (m, 1H), 7.26 (dd, $J = 14.5$, 8.1 Hz, 3H), 3.96 (t, $J = 6.4$ Hz, 2H), 3.14 (t, $J = 6.4$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.16, 142.09, 138.25, 132.28, 131.94, 129.41, 128.78, 127.30, 127.05, 126.89, 119.43, 49.26, 28.54. HRMS (ESI+) ($m/z$) calcld for C$_{15}$H$_{13}$BrNO [M+H] 302.0181 found 302.0175.

2-(4-Fluorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2j): White solid (19.0 mg, 79%); TLC R$_f$ = 0.6 (10% EtOAc/Hexane); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.15 (dd, $J = 7.7$, 0.9 Hz, 1H), 7.50-7.46 (m, 1H), 7.43 – 7.32 (m, 3H), 7.25 (d, $J = 8.9$ Hz, 1H), 7.13 – 7.07 (m, 2H), 3.98 – 3.94 (m, 2H), 3.15 (t, $J = 6.5$ Hz, 2H) $^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.47, 162.01, 159.57, 139.11, 138.33, 132.25, 129.56, 128.82, 127.36, 127.23, 127.14, 127.09, 115.96, 115.73, 49.65, 28.67. HRMS (ESI+) ($m/z$) calcld for C$_{15}$H$_{13}$FNO [M+H] 242.0976 and calcld for C$_{15}$H$_{12}$FNO [M+Na] 264.0795.

2-(3-Chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2k): White solid (20.0 mg, 78%); TLC R$_f$ = 0.6 (20% EtOAc/Pet ether); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.14 (d, $J = 7.7$ Hz, 1H), 7.49-7.46 (m, 1H), 7.41 (s, 1H), 7.39-7.36 (m, 1H), 7.34 – 7.28 (m, 2H), 7.23 (dd, $J = 11.1$, 7.9 Hz, 2H), 3.97 (t, $J = 6.4$ Hz, 2H), 3.14 (t, $J = 6.4$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.19, 144.18, 138.18, 134.35, 132.33, 129.82, 129.38, 128.82, 127.31, 127.06, 126.33, 125.57, 123.50, 49.30, 28.54. HRMS (ESI+) ($m/z$) calcld for C$_{15}$H$_{13}$CINO [M+H] 258.0680.

2-(3-Chloro-4-fluorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2l): White solid (23.1 mg, 84%); TLC R$_f$ = 0.8 (20% EtOAc/Pet ether); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.14 (d, $J = 7.6$ Hz, 1H), 7.50-7.46 (m, 2H), 7.40-7.37 (m, 1H), 7.28-7.24 (m, 2H), 7.19-7.16 (m, 1H), 3.96 (t, $J = 6.3$ Hz, 2H), 3.15 (t, $J = 6.1$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.33, 155.18 (d, $J = 249.4$ Hz), 139.57, 138.21, 132.40, 129.19, 128.80, 127.75, 127.35, 127.09, 125.27 (d, $J = 7.0$ Hz), 121.05 (d, $J = 18.7$ Hz), 116.57 (d, $J = 22.1$ Hz), 49.46, 28.52. HRMS (ESI+) ($m/z$) calcld for C$_{15}$H$_{12}$ONClF [M+H] 276.0586.

2-(4-(tert-butyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2m): White solid (22.8 mg, 82%); TLC R$_f$ = 0.7 (20% EtOAc/Pet ether); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.08 (d, $J = 7.6$ Hz, 1H), 7.36 (dd, $J = 17.7$, 7.5 Hz, 3H), 7.30-7.27 (m, 1H), 7.24 (d, $J = 8.6$ Hz, 2H), 7.17 – 7.14 (m, 1H), 3.90 (t, $J = 6.5$ Hz, 2H), 3.05 (t, $J = 6.4$ Hz, 2H), 1.25 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.34, 149.16, 140.50, 138.41, 132.05, 129.90, 128.81, 127.25, 127.02, 125.94, 124.82, 49.51, 34.63, 31.46, 28.71. HRMS (ESI+) ($m/z$) calcld for C$_{19}$H$_{22}$NO [M+H] 280.1701 found 280.1696 and calcld for C$_{19}$H$_{21}$NONa [M+Na] 302.1521 found 302.1515.
2-(p-tolyl)-3,4-dihydroisoquinolin-1(2H)-one (2m')

Yellow oil (19.9 mg, 84%); TLC Rf = 0.7 (20% EtOAc/Pet ether); 1H NMR (400 MHz, CDCl3) δ 8.07 (dd, J = 7.7, 1.1 Hz, 1H), 7.39-7.35 (m, 1H), 7.30-7.27 (m, 1H), 7.20 – 7.12 (m, 5H), 3.90 – 3.86 (m, 2H), 3.05 (t, J = 6.5 Hz, 2H), 2.28 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 164.36, 140.64, 138.40, 136.16, 132.04, 129.87, 129.64, 128.80, 127.25, 127.03, 125.30, 49.61, 28.72, 21.16. HRMS (ESI+) (m/z) calcd for C16H16NO [M+H] 238.1232 found 238.1226.

2-(m-tolyl)-3,4-dihydroisoquinolin-1(2H)-one (2n)

Yellow oil (19.9 mg, 84%); TLC Rf = 0.7 (20% EtOAc/Pet ether); 1H NMR (400 MHz, CDCl3) δ 8.07 (dd, J = 7.7, 1.1 Hz, 1H), 7.39-7.35 (m, 1H), 7.30-7.27 (m, 1H), 7.20 – 7.12 (m, 5H), 3.90 – 3.86 (m, 2H), 3.05 (t, J = 6.5 Hz, 2H), 2.28 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 164.33, 143.14, 138.91, 138.41, 132.09, 129.85, 128.90, 128.81, 127.27, 127.04, 126.30, 122.41, 49.60, 28.72, 21.53. HRMS (ESI+) (m/z) calcd for C16H16NO [M+H] 238.1232 found 238.1226.

2-(3-Methoxyphenyl)-3,4-dihydroisoquinolin-1(2H)-one (2o)

Yellow oil (14.9 mg, 59%); TLC Rf = 0.5 (20% EtOAc/Pet ether); 1H NMR (500 MHz, CDCl3) δ 8.15 (d, J = 7.7 Hz, 1H), 7.47 - 7.44 (m, 1H), 7.38 - 7.35 (m, 1H), 7.32 - 7.29 (m, 1H), 7.23 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.90 (dd, J = 8.3, 1.7 Hz, 1H), 3.96 (t, J = 6.5 Hz, 2H), 3.12 (t, J = 6.4 Hz, 2H). 13C NMR (126 MHz, CDCl3) δ 164.22, 160.00, 144.31, 138.33, 132.08, 129.73, 129.61, 128.75, 127.21, 126.99, 117.50, 112.18, 111.43, 55.40, 49.51, 28.63. HRMS (ESI+) (m/z) calcd for C16H16NO2 [M+H] 254.1181 found 254.1176.

2-(o-tolyl)-3,4-dihydroisoquinolin-1(2H)-one (2p)

Yellow oil (18.9 mg, 80%); TLC Rf = 0.7 (20% EtOAc/Pet ether); 1H NMR (400 MHz, CDCl3) δ 8.16 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.32 – 7.29 (m, 1H), 7.28 – 7.23 (m, 3H), 7.23 – 7.19 (m, 1H), 4.00 – 3.93 (m, 1H), 3.78 – 3.70 (m, 1H), 3.29 – 3.21 (m, 1H), 3.14 – 3.06 (m, 1H), 2.29 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 163.87, 142.15, 138.39, 135.38, 131.99, 131.05, 129.66, 128.70, 127.69, 127.21, 127.07, 127.02, 126.70, 49.38, 28.80, 18.17. HRMS (ESI+) (m/z) calcd for C16H16NO [M+H] 238.1232 found 238.1226.

2-(6-Bromopyridin-3-yl)-3,4-dihydroisoquinolin-1(2H)-one (2q)

White solid (22.9 mg, 76%); TLC Rf = 0.5 (30% EtOAc/Pet ether); 1H NMR (400 MHz, CDCl3) δ 8.42 (d, J = 2.7 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.71 (dd, J = 8.5, 2.8 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.41-7.37 (m, 1H), 7.28 – 7.25 (m, 1H), 4.02 (t, J = 6.4 Hz, 2H), 3.18 (t, J = 6.4 Hz, 2H). 13C NMR (101 MHz,
CDCl$_3$) $\delta$ 164.35, 145.99, 139.14, 138.31, 138.15, 135.41, 132.79, 128.92, 128.84, 127.85, 127.54, 127.28, 49.03, 28.45. HRMS (ESI+) ($m/z$) calcd for C$_{14}$H$_{12}$Br$_2$O [M+H] 303.0133 found 303.0128.

2-(Thiophen-3-yl)-3,4-dihydroisoquinolin-1(2H)-one (2r): White solid (16.9 mg, 74%); TLC R$_f$ = 0.6 (20% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14 (d, $J$ = 7.6 Hz, 1H), 7.47-7.44 (m, 1H), 7.38 (d, $J$ = 6.6 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.23 (d, $J$ = 7.4 Hz, 1H), 4.02 (t, $J$ = 6.5 Hz, 2H), 3.12 (t, $J$ = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 163.53, 141.23, 137.99, 132.10, 129.68, 128.70, 127.27, 126.90, 124.15, 123.87, 113.96, 48.98, 28.30. HRMS (ESI+) ($m/z$) calcd for C$_{13}$H$_{12}$NOS [M+H] 230.0640 found 230.0634.

2-(4-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (2s): White solid (16.4 mg, 52%); TLC R$_f$ = 0.4 (30% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.64 (s, 1H), 7.34 (dd, $J$ = 19.1, 8.6 Hz, 4H), 6.69 (s, 1H), 3.94 (d, $J$ = 8.0 Hz, 8H), 3.07 (t, $J$ = 6.2 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.23, 152.32, 148.17, 141.76, 132.10, 131.34, 128.91, 126.50, 121.87, 110.81, 109.23, 56.11, 49.52, 28.19. HRMS (ESI+) ($m/z$) calcd for C$_{17}$H$_{16}$ClNO$_3$ [M+H] 318.0897 found 318.0891.

6,7-dimethoxy-2-(p-tolyl)-3,4-dihydroisoquinolin-1(2H)-one (2t): Yellow solid (17.5 mg, 59%); TLC R$_f$ = 0.5 (40% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.66 (s, 2H), 7.23 (dd, $J$ = 18.6, 7.8 Hz, 9H), 6.69 (s, 2H), 3.94 (d, $J$ = 6.8 Hz, 16H), 3.06 (t, $J$ = 6.5 Hz, 4H), 2.36 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.27, 152.07, 148.09, 140.77, 135.87, 132.05, 129.49, 125.20, 122.33, 110.90, 109.21, 56.09, 49.74, 28.29, 21.04. HRMS (ESI+) ($m/z$) calcd for C$_{18}$H$_{20}$NO$_3$ [M+H] 298.1443 found 298.1438.

7-chloro-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2u): White solid (18.3 mg, 63%); TLC R$_f$ = 0.5 (20% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.11 (s, 1H), 7.41 (dd, $J$ = 20.4, 7.1 Hz, 3H), 7.33 (s, 2H), 7.20 (d, $J$ = 7.5 Hz, 1H), 3.97 (s, 2H), 3.12 (s, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 163.04, 141.23, 136.99, 135.47, 133.42, 132.20, 131.92, 130.99, 129.13, 128.73 128.52, 126.58, 49.27, 28.05. HRMS (ESI+) ($m/z$) calcd for C$_{15}$H$_{12}$ONCl$_2$ [M+H] 292.0296 found 292.0290.

7-Bromo-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2v): White solid (18.7 mg, 56%); TLC R$_f$ = 0.6 (20% EtOAc/Pet ether); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.26 (s, 1H), 7.58 (d, $J$ = 8.0 Hz, 1H), 7.38 (d, $J$ = 7.6 Hz, 2H), 7.31 (d, $J$ = 7.6 Hz, 2H), 3.95 (t, $J$ = 5.8 Hz, 2H), 3.09 (t, $J$ = 5.9 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 141.22, 136.99, 135.09, 131.89, 131.65,
131.19, 129.11, 128.80, 126.55, 121.15, 49.17, 28.07. HRMS (ESI+) (m/z) calcd for C_{15}H_{12}ON^{79}BrCl [M+H] 335.9791 found 335.9785 and calcd for C_{15}H_{12}ON^{81}BrCl [M+H] 337.9770 found 337.9765.

**2-(4-chlorophenyl)-8-nitro-3,4-dihydroisoquinolin-1(2H)-one (2w):** White solid (14.2 mg, 52%); TLC Rf = 0.4 (30% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.48 (d, J = 7.7 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 3.98 (t, J = 6.4 Hz, 2H), 3.50 (t, J = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.19, 147.51, 140.61, 134.00, 133.60, 132.15, 129.76, 129.22, 128.05, 127.73, 126.30, 48.17, 25.81.

HRMS (ESI+) (m/z) calcd for C$_{15}$H$_{12}$ON$_2$Cl [M+H] 303.0536 found 303.0531.

(S)-2-(4-Chlorophenyl)-3-(hydroxymethyl)-3,4-dihydroisoquinolin-1(2H)-one (2x): White solid (14.0 mg, 49%); TLC Rf = 0.6 (30% EtOAc/Pet ether); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.02 (d, J = 7.7 Hz, 1H), 7.48-7.45 (m, 1H), 7.35 (d, J = 8.7 Hz, 3H), 7.30–7.26 (m, 2H), 7.23 (d, J = 8.0 Hz, 1H), 4.06–4.01 (m, 1H), 3.67 (dd, J = 10.8, 4.8 Hz, 1H), 3.47 (ddd, J = 22.0, 13.3, 7.2 Hz, 2H), 3.19 (dd, J = 16.2, 1.9 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 163.87, 140.58, 136.17, 132.56, 129.41, 129.29, 128.83, 128.69, 128.51, 128.03, 127.28, 61.54, 60.47, 29.55.

HRMS (ESI+) (m/z) calcd for C$_{16}$H$_{14}$ClNO$_2$ [M+H] 288.0791 found 288.0786.

2-Phenylisoindolin-1-one (4a): Yellow solid (8.7 mg, 42%); TLC Rf = 0.5 (25% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.55-7.52 (m, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.39-7.35 (m, 2H), 7.19-7.10 (m, 1H), 4.81 (s, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.65, 140.19, 139.95, 139.56, 133.31, 132.18, 129.27, 128.49, 124.61, 124.28, 122.71, 119.61, 50.85. HRMS (ESI+) (m/z) calcd for C$_{14}$H$_{12}$NO [M+H] 210.0919 found 210.0913 and C$_{14}$H$_{11}$NO [M+Na] 232.0733.

2-(p-tolyl)isoindolin-1-one (4b): White solid (9.1 mg, 41%); TLC Rf = 0.5 (20% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.63-7.59 (m, 1H), 7.53 (d, J = 7.1 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 4.86 (s, 2H), 2.38 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.40, 140.15, 136.97, 134.24, 133.36, 131.78, 129.69, 128.34, 124.11, 122.57, 119.68, 50.90, 20.87. HRMS (ESI+) (m/z) calcd for C$_{15}$H$_{14}$NO [M+H] 224.1075 found 224.1070 and calcd for C$_{15}$H$_{13}$NO [M+Na] 246.0895 found 246.089.

2-(4-Chlorophenyl)isoindolin-1-one (4c): White solid (10.9 mg, 45%); TLC Rf = 0.5 (20% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.86 (d, J = 8.1 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.54 (dd, J = 11.0, 4.4 Hz, 1H), 7.46 (d, J = 6.7 Hz, 2H), 7.37 – 7.28 (m, 2H), 4.78 (s, 2H). $^{13}$C
NMR (101 MHz, CDCl₃) δ 167.63, 139.96, 138.18, 133.02, 129.65, 129.26, 128.63, 124.34, 122.73, 120.55, 50.75. HRMS (ESI+) (m/z) calcd for C₁₄H₁₁ClNO [M+H] 244.0529 found 244.0524.

2-(3,5-bis(trifluoromethyl)phenyl)isoindolin-1-one (4d): White solid (16.5 mg, 48%); TLC R₇ = 0.7 (20% EtOAc/Pet ether); ¹H NMR (400 MHz, CDCl₃) δ 8.43 (s, 2H), 7.96 (d, J = 7.0 Hz, 1H), 7.72 – 7.51 (m, 4H), 4.95 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 167.93, 140.97, 139.62, 133.09, 132.71, 132.21, 128.92, 124.60, 122.84, 118.35, 117.31, 50.46. HRMS (ESI+) (m/z) calcd for C₁₆H₁₀F₆NO [M+H] 346.0667 found 346.0661.

5. General procedure for the synthesis of Indoprofen (3e-5e)

(a) Synthesis of ethyl 2-(4-(isoindolin-2-yl)phenyl)propanoate (3e)

An oven-dried 50 mL two neck round bottom flask equipped with a magnetic stir bar was charged with (±)-BINAP (5 mol %) and purged with argon. Anhydrous toluene (2 mL) was added and the mixture was heated to 100 °C with vigorous stirring until a homogenous solution was obtained. The solution was cooled to room temperature, Pd(OAc)₂ (5 mol %) was added and the mixture was stirred vigorously for 1 min. Ethyl 2-(4-bromophenyl)propanoate (0.25 mmol), isoindoline (0.3 mmol) and potassium tert-butoxide (0.35 mmol) were added sequentially and the mixture was heated at 100 °C. After 30 min, the mixture was cooled to room temperature, diluted with EtOAc and filtered through celite and this crude reaction mixture was purified by flash chromatography to give a compound 3e.

(b) Synthesis of ethyl 2-(4-(1-oxoisooindolin-2-yl)phenyl)propanoate (4e)

To a solution of ethyl 2-(4-(isoindolin-2-yl)phenyl)propanoate 3e (0.1 mmol) and DABCO (0.3 mmol) in THF (0.5 mL) was added the α-angelica lactone (25 mol%, 2.3 µL) at room temperature. The vial was equipped with balloon containing O₂ gas and the reaction was stirred at room temperature for 36 h. The resulting reaction mixture was monitored by TLC and or ¹H NMR. Then reaction mixture was diluted with dichloromethane and washed with water. The
layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude products were purified on a silica gel column using pet ether/EtOAc which afforded compound 4e in 44% yield.

(c) **Synthesis of Indoprofen (5e)**

Ethyl 2-(4-(1-oxoisooindolin-2-yl)phenyl)propanoate 4e (9 mg, 0.03 mmol) was dissolved in MeOH (1 mL) and 2 M NaOH(aq) (1 mL) was added. THF was added until reaction mixture was clear. Reaction mixture was stirred at RT and followed by TLC. After reaction was completed, the mixture was acidified using 3 M HCl. Product was extracted with ethyl acetate and the combined EtOAc fractions were washed with brine and dried over MgSO$_4$. Solvent was removed and 8 mg of yellow solid of 5e was obtained.

6. **General procedure for the synthesis of Indobufen**$^{2,3}$ (3f-5f)

Performed as described above mentioned synthetic procedure of Indoprofen.

7. **Characterization of compounds 3e-5e and 3f-5f**

**Ethyl 2-(4-(isoindolin-2-yl)phenyl)propanoate (3e):** Yellow solid (57 mg, 64%); TLC R$_f$ = 0.8 (20% EtOAc/Pet ether); $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.40 – 7.12 (m, 6H), 6.78 – 6.46 (m, 2H), 4.64 (s, 4H), 4.24 – 3.96 (m, 2H), 3.64 (dd, $J$ = 14.3, 7.2 Hz, 1H), 1.48 (d, $J$ = 7.2 Hz, 3H), 1.22 (t, $J$ = 7.1 Hz, 3H). HRMS (ESI+) (m/z) calcd for C$_{19}$H$_{22}$NO$_2$ [M+H] 296.1651 found 296.1645.

**Ethyl 2-(4-(1-oxoisooindolin-2-yl)phenyl)propanoate (4e):** Yellow solid (13.6 mg, 44%); TLC R$_f$ = 0.7 (20% EtOAc/Pet ether); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.93 (d, $J$ = 7.3 Hz, 1H), 7.83 (d, $J$ = 8.5 Hz, 2H), 7.60 (d, $J$ = 6.5 Hz, 1H), 7.52 (d, $J$ = 7.5 Hz, 2H), 7.38 (d, $J$ = 8.8 Hz, 2H), 4.86 (s, 2H), 4.17 – 4.11 (m, 2H), 3.72 (d, $J$ = 7.2 Hz, 1H), 1.51 (d, $J$ = 7.0 Hz, 3H), 1.21 (d, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.60, 167.59, 140.17, 138.48, 136.87, 133.25,
132.18, 128.50, 128.33, 128.21, 128.06, 124.27, 122.72, 119.75, 60.91, 50.83, 45.09, 18.65, 14.22. HRMS (ESI+) (m/z) calcd for C\textsubscript{19}H\textsubscript{20}NO\textsubscript{3} [M+H] 310.1443 found 310.1438.

**Indoprofen (5e):** Yellow solid (12.0 mg, 98%); TLC R\textsubscript{f} = 0.5 (10% DCM/MeOH); \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \delta 12.33 (s, 1H), 7.86 (d, \textit{J} = 8.5 Hz, 2H), 7.79 (d, \textit{J} = 7.6 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.58 – 7.53 (m, 1H), 7.35 (dd, \textit{J} = 9.0, 2.1 Hz, 2H), 5.02 (s, 2H), 3.71 (d, \textit{J} = 7.1 Hz, 1H), 1.38 (d, \textit{J} = 7.0 Hz, 3H). HRMS (ESI+) (m/z) calcd for C\textsubscript{17}H\textsubscript{16}NO\textsubscript{3} [M+H] 282.1130 found 282.1125.

**Ethyl 2-(4-(isoindolin-2-yl)phenyl)butanoate (3f):** Yellow solid (47 mg, 61%); TLC R\textsubscript{f} = 0.7 (20% EtOAc/Pet ether); \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) \delta 7.32 (d, \textit{J} = 2.8 Hz, 4H), 7.26 (s, 1H), 7.20 (s, 1H), 6.64 (d, \textit{J} = 8.5 Hz, 2H), 4.64 (s, 4H), 4.14 (dd, \textit{J} = 14.2, 7.1 Hz, 3H), 3.54 (s, 2H), 1.26 (t, \textit{J} = 7.1 Hz, 6H). HRMS (ESI+) (m/z) calcd for C\textsubscript{20}H\textsubscript{24}NO\textsubscript{2} [M+H] 310.1807 found 310.1802.

**Ethyl 2-(4-(1-oxoisindolin-2-yl)phenyl)propanoate (4f):** Yellow solid (12.2 mg, 38%); TLC R\textsubscript{f} = 0.5 (25% EtOAc/Pet ether); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 7.96 – 7.90 (m, 1H), 7.86 – 7.81 (m, 2H), 7.64 – 7.58 (m, 1H), 7.54 – 7.49 (m, 2H), 7.35 (dd, \textit{J} = 8.9, 2.3 Hz, 2H), 4.87 (s, 2H), 4.16 (dd, \textit{J} = 14.4, 6.9 Hz, 3H), 3.63 (s, 2H), 1.27 (t, \textit{J} = 6.9 Hz, 6H). HRMS (ESI+) (m/z) calcd for C\textsubscript{20}H\textsubscript{21}NO\textsubscript{3} [M+H] 310.1807 found 310.1802.

**Indobufen (5f):** Yellow solid (10.9 mg, 98%); TLC R\textsubscript{f} = 0.5 (10% DCM/MeOH); \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \delta 7.80 (dd, \textit{J} = 13.4, 8.1 Hz, 3H), 7.69 – 7.65 (m, 2H), 7.55 (s, 1H), 7.31 (d, \textit{J} = 8.6 Hz, 2H), 5.02 (s, 2H), 3.50 (d, \textit{J} = 5.5 Hz, 3H), 1.23 (s, 3H). HRMS (ESI+) (m/z) calcd for C\textsubscript{18}H\textsubscript{18}NO\textsubscript{3} [M+H] 296.1287 found 296.1281 and calcd for C\textsubscript{18}H\textsubscript{17}NO\textsubscript{3} [M+Na] 318.1106 found 318.1101.

**8. Gram scale reaction procedure:** To a solution of 2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (1.5 g, 6.17 mmol) and DABCO (2.0 g, 18.51 mmol) in THF (35 mL) was added the \(\alpha\)-angelica lactone (25 mol%, 139 µL) at room temperature. The round bottom flask was equipped with balloon containing O\textsubscript{2} gas and the reaction mixture was stirred at room temperature for 48 h. The resulting reaction mixture was monitored by TLC and or GC-MS. Then reaction mixture was diluted with dichloromethane and washed with water. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The product was purified on a silica gel column using 20% pet ether/EtOAc in 81% (1.28g).
9. H$_2$O$^{18}$ experiment procedure

H$_2$O$^{18}$ was purchased from sigma Aldrich (catalog no: 329878-250mg) with 97% isotopic purity. The experiment was carried out according to the procedure reported for the oxidation of 1a to 2a using 4 equiv of H$_2$O$^{18}$ and 492 µL THF. The percentage of $^{18}$O enrichment was examined by mass spectrometry as shown in following spectra (S68). The calculated data showed no enrichment of $^{18}$O.

Reaction condition: 2-Phenyl-1, 2,3,4-tetrahydroisoquinoline (0.1 mmol), DABCO (0.3 mmol), α-angelica lactone (25 mol%, 2.3 µL) and THF (492 µL) and H$_2$O$^{18}$ (8 µL) were added in a schlenk tube inside the glove box. The reaction mixture stirred under O$_2$ (1 atm) at 25°C for 36 h. No isotopic enrichment in product 2a was determined by GCMS (shown in S68).

10. Mechanistic studies

a. HRMS of compound VI (after 3h of reaction time)
12. $^1$H NMR, $^{13}$C NMR, Mass spectra of compounds

$^1$H NMR of 2-phenyl-3, 4-dihydroisoquinolin-1(2H)-one (2a) in CDCl$_3$

$^{13}$C NMR of 2-phenyl-3, 4-dihydroisoquinolin-1(2H)-one (2a) in CDCl$_3$
HRMS of 2-phenyl-3, 4-dihydroisoquinolin-1(2H)-one (2a)

\[ \text{TT-1 #259 RT: 1.16 AV: 1 NL: 4.27E9} \]
\[ \text{T: FTMS + p ESI Full ms [100.0000-1500.0000]} \]

Relative Abundance

1H NMR of 2-(4-(Trifluoromethyl) phenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2b) in CDCl₃

\[ \text{144.9824 R=87102} \]
\[ \text{137.0249 R=69500} \]
$^{13}$C NMR of 2-(4-(Trifluoromethyl) phenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2b) in CDCl$_3$

HRMS of 2-(4-(Trifluoromethyl) phenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2b)
$^1$H NMR of 2-(4-Acetylphenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2c) in CDCl$_3$.

$^{13}$C NMR of 2-(4-Acetylphenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2c) in CDCl$_3$.
HRMS of 2-(4-Acetylphenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2c)

TT-10 #260 RT: 1.16 AV: 1 NL: 8.52E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]

1H NMR of 2-(3-(Trifluoromethyl) phenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2d) in CDCl₃
$^{13}$C NMR of 2-(3-(Trifluoromethyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2d) in CDCl$_3$

HRMS of 2-(3-(Trifluoromethyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2d)
$^1$H NMR of 2-(3, 5-bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2e) in CDCl$_3$ 

![H NMR spectrum of 2e](image)

$^{13}$C NMR of 2-(3, 5-bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2e) in CDCl$_3$ 

![C NMR spectrum of 2e](image)
HRMS of 2-(3, 5-bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2e)

1H NMR of 2-(2-(Trifluoromethoxy) phenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2f) in CDCl₃
$^{13}$C NMR of 2-(2-(Trifluoromethoxy) phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2f) in CDCl$_3$

![Chemical Structure of 2f]

HRMS of 2-(2-(Trifluoromethoxy) phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2f) in CDCl$_3$

TT-13 #262
RT: 1.17
AV: 1
NL: 3.66E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]
$^1$H NMR of 2-(2-Nitrophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2g) in CDCl$_3$

$^{13}$C NMR of 2-(2-Nitrophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2g) in CDCl$_3$
HRMS of 2-(2-Nitrophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2g)

2NO2NPH-O #256 RT: 1.14 AV: 1 NL: 2.62E8
T: FTMS + p ESI Full ms (100.0000-1500.0000)

1H NMR of 2-(4-Chlorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2h) in CDCl3
$^{13}$C NMR of 2-(4-Chlorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2h) in CDCl$_3$

HRMS of 2-(4-Chlorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2h)

**SI-25**
$^1$H NMR 2-(4-Bromophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2i) in CDCl$_3$

$^{13}$C NMR of 2-(4-Bromophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2i) in CDCl$_3$
HRMS of 2-(4-Bromophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2i)

$^1$H NMR of 2-(4-Fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2j) in CDCl$_3$
$^{13}$C NMR of 2-(4-Fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2j) in CDCl$_3$

HRMS of 2-(4-Fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2j)
$^1$H NMR of 2-(3-Chlorophenyl)-3, 4-dihydropseudoquinolin-1(2H)-one (2k) in CDCl$_3$

$^{13}$C NMR of 2-(3-Chlorophenyl)-3, 4-dihydropseudoquinolin-1(2H)-one (2k) in CDCl$_3$
HRMS of 2-(3-Chlorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2k)

$^{1}$H NMR of 2-(3-Chloro-4-fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2l) in CDCl$_3$
$^{13}$C NMR of 2-(3-Chloro-4-fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2l) in CDCl$_3$

HRMS of 2-(3-Chloro-4-fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2l)
$^1$H NMR of 2-(4-((tert-butyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2m) in CDCl$_3$

$^{13}$C NMR of 2-(4-((tert-butyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2m) in CDCl$_3$
HRMS of 2-(4-\textit{tert}-butyl phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2m)

1H NMR of 2-(\textit{p}-toly)-3, 4-dihydroisoquinolin-1(2H)-one (2m') in CDCl3
$^{13}$C NMR of 2-(p-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one (2m') in CDCl$_3$

HRMS of 2-(p-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one (2m'):
^1H NMR of 2-(m-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one (2n) in CDCl₃

^13C NMR of 2-(m-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one (2n) in CDCl₃
HRMS of 2-(m-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one (2n)

\[ \text{SI-36} \]

\[ \text{TT-3 #263 RT: 1.18 AV: 1 NL: 2.98E9} \]
\[ T: \text{FTMS } + \text{p ESI Full ms [100.0000-1500.0000]} \]

\[ \begin{align*}
\text{m/z} & \quad 238.1232 \quad R=73803 \\
\text{C} & \quad 16 \quad \text{H} \quad 16 \quad \text{O} \quad \text{N} = 238.1226 \quad 2.2825 \text{ ppm} \\
\text{220.1127} \quad R=72507 \\
\text{C} & \quad 16 \quad \text{H} \quad 14 \quad \text{N} = 220.1121 \quad 2.6333 \text{ ppm} \\
\text{200.0785} \quad R=75702 \\
\text{C}_8 \text{H}_{12} \text{O}_4 \text{N}_2 & = 200.0792 \quad -3.1819 \text{ ppm} \\
\text{249.1390} \quad R=76200 \\
\text{C} & \quad 17 \quad \text{H} \quad 17 \quad \text{N} \quad 2 = 249.1386 \quad 1.5964 \text{ ppm} \\
\text{207.5726} \quad R=45100 \\
\end{align*} \]

\[^1\text{H NMR of 2-(3-Methoxyphenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2o)} \text{ in CDCl}_3 \]
$^{13}$C NMR of 2-(3-Methoxyphenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2o) in CDCl$_3$

![NMR spectrum](image)

HRMS of 2-(3-Methoxyphenyl)-3, 4-dihydroisoquinolin-1(2H)-one (2o)

![HRMS spectrum](image)

| m/z       | Relative Abundance | Formula  | Mass (ppm) |
|-----------|--------------------|----------|------------|
| 254.1179  | 100                | C$_{16}$H$_{16}$O$_2$N | 1.2548 ppm |
| 238.1226  | 40                 | C$_{16}$H$_{16}$O$_2$N | 1.0650 ppm |
| 196.5680  | 20                 | C$_{16}$H$_{16}$O$_2$N |             |
| 176.0546  | 10                 | C$_{16}$H$_{16}$O$_2$N |             |
| 156.2150  | 5                  | C$_{16}$H$_{16}$O$_2$N |             |

TT: 5 #060  RT: 1.16  AV: 1  NL: 2.45E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]

SI-37
$^1$H NMR of 2-(o-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one (2p) in CDCl$_3$

$^{13}$C NMR of 2-(o-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one (2p) in CDCl$_3$
HRMS of 2-(o-tolyl)-3, 4-dihdroisoquinolin-1(2H)-one (2p)

T: FTMS + p ESI Full ms [100.0000-1500.0000]

1H NMR of 2-(6-Bromopyridin-3-yl)-3, 4-dihydroisoquinolin-1(2H)-one (2q) in CDCl₃
$^{13}$C NMR of 2-(6-Bromopyridin-3-yl)-3, 4-dihydroisoquinolin-1(2H)-one (2q) in CDCl$_3$

HRMS of 2-(6-Bromopyridin-3-yl)-3, 4-dihydroisoquinolin-1(2H)-one (2q)
$^1$H NMR of 2-(Thiophen-3-yl)-3, 4-dihydroisoquinolin-1(2H)-one (2r) in CDCl₃

$^{13}$C NMR of 2-(Thiophen-3-yl)-3, 4-dihydroisoquinolin-1(2H)-one (2r) in CDCl₃
HRMS of 2-(Thiophen-3-yl)-3, 4-dihydroisoquinolin-1(2H)-one (2r)

\[ \text{C}_{13}\text{H}_{12}\text{O}_3\text{N}_2\text{S} = 230.0634 \pm 1.1753 \text{ ppm} \]

1H NMR of 2-(4-Chlorophenyl)-6, 7-dimethoxy-3, 4-dihydroisoquinolin-1(2H)-one (2s) in CDCl₃
$^{13}$C NMR of 2-(4-Chlorophenyl)-6, 7-dimethoxy-3, 4-dihydroisoquinolin-1(2H)-one (2s) in CDCl$_3$

HRMS of 2-(4-Chlorophenyl)-6, 7-dimethoxy-3, 4-dihydroisoquinolin-1(2H)-one (2s)
$^1$H NMR of 2-(4-Chlorophenyl)-6, 7-dimethoxy-3, 4-dihydroisoquinolin-1(2H)-one (2t) in CDCl$_3$

$^{13}$C NMR of 2-(4-Chlorophenyl)-6, 7-dimethoxy-3, 4-dihydroisoquinolin-1(2H)-one (2t) in CDCl$_3$
HRMS of 2-(4-Chlorophenyl)-6, 7-dimethoxy-3, 4-dihydroisoquinolin-1(2H)-one (2t)

\[
\text{DiomeNpho-4ch3 #254 RT: 1.13 AV: 1 NL: 5.41E9}
\text{T: FTMS + p ESI Full ms [133.4000-2000.0000]}
\]

\[
\begin{align*}
298.1436 & \text{ R=66207} \\
C_{18}H_{20}O_3N & = 298.1438 -0.7222 \text{ ppm} \\
R=59707 & \text{ C}_{17}H_{17}O_3N = 283.1203 -0.8433 \text{ ppm} \\
R=49400 & \text{ C}_{17}H_{17}O_3N = 283.1203 -0.8433 \text{ ppm} \\
221.3202 & \text{ R=51100} \\
232.1567 & \text{ R=45700} \\
270.0492 & \text{ R=49700} \\
\end{align*}
\]

\[
1^H \text{ NMR of 7-chloro-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2u) in CDCl}_3
\]
$^{13}$C NMR of 7-chloro-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2u) in CDCl$_3$
$^1$H NMR of 7-Bromo-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2v) in CDCl$_3$

!![Chemical structure image]

$^{13}$C NMR of 7-Bromo-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2v) in CDCl$_3$

!![Chemical structure image]
HRMS of 7-Bromo-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2v)

1H NMR of 2-(4-chlorophenyl)-8-nitro-3,4-dihydroisoquinolin-1(2H)-one (2w) in CDCl₃
$^{13}$C NMR of 2-(4-chlorophenyl)-8-nitro-3,4-dihydroisoquinolin-1(2H)-one (2w) in CDCl$_3$

HRMS of 2-(4-chlorophenyl)-8-nitro-3,4-dihydroisoquinolin-1(2H)-one (2w)
\(^1\)H NMR of (S)-2-(4-Chlorophenyl)-3-(hydroxymethyl)-3, 4-dihydroisoquinolin-1(2H)-one (2x) in CDCl\(_3\)

\(^{13}\)C NMR of (S)-2-(4-Chlorophenyl)-3-(hydroxymethyl)-3, 4-dihydroisoquinolin-1(2H)-one (2x) in CDCl\(_3\)
HRMS of (S)-2-(4-Chlorophenyl)-3-(hydroxymethyl)-3, 4-dihydroisoquinolin-1(2H)-one (2x)

1H NMR of 2-Phenylisoindolin-1-one (4a) in CDCl₃
$^{13}$C NMR of 2-Phenylisoindolin-1-one (4a) in CDCl$_3$

HRMS of 2-Phenylisoindolin-1-one (4a)
$^1$H NMR of 2-$(p$-tolyl)$isoindolin$-1$-one (4b) in CDCl$_3$

$^{13}$C NMR of 2-$(p$-tolyl)$isoindolin$-1$-one (4b) in CDCl$_3$
HRMS of 2-(p-tolyl)isoindolin-1-one (4b)

$^{1}$H NMR of 2-(4-Chlorophenyl)isoindolin-1-one (4c) in CDCl$_3$
$^{13}$C NMR of 2-(4-Chlorophenyl)isoindolin-1-one (4c) in CDCl$_3$

HRMS of 2-(4-Chlorophenyl)isoindolin-1-one (4c)

4CLNPHII-O #289 RT: 1.29 AV: 1 NL: 4.14E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]
$^1$H NMR of 2-(3,5-bis(trifluoromethyl)phenyl)isoindolin-1-one (4d) in CDCl$_3$
HRMS of 2-(3,5-bis(trifluoromethyl)phenyl)isoindolin-1-one (4d)

\[
\text{**C}_{24}\text{H}_{16}\text{O}_{2}\text{N}_{2}\text{F}_{6} = 346.0661 \pm 1.7886 \text{ ppm}}
\]

\[
\begin{align*}
322.2007 & \text{ R=67287} \\
329.0046 & \text{ R=59452} \\
332.2007 & \text{ R=59452} \\
332.9476 & \text{ R=58602} \\
336.2319 & \text{ R=54100} \\
342.2075 & \text{ R=59452} \\
344.0223 & \text{ R=59452} \\
346.0655 & \text{ R=60887} \\
350.9865 & \text{ R=59802} \\
356.9087 & \text{ R=57902} \\
360.0303 & \text{ R=57206} \\
365.9236 & \text{ R=58602} \\
332.9476 & \text{ R=59452} \\
344.0223 & \text{ R=59452} \\
350.9865 & \text{ R=59802} \\
356.9087 & \text{ R=57902} \\
360.0303 & \text{ R=57206} \\
365.9236 & \text{ R=58602}
\end{align*}
\]

\[\text{RT: 1.25 AV: 1 NL: 1.74E7}
\]

\[\text{T: FTMS + p ESI Full ms [100.0000-1500.0000]}
\]

\[\text{**m/z** 325 330 335 340 345 350 355 ... 344.0223}
\]

\[\text{**R=55102**}
\]

1H NMR of Ethyl 2-(4-(isoindolin-2-yl)phenyl)propanoate (3e) in CDCl3
HRMS of Ethyl 2-(4-(isoindolin-2-yl) phenyl)propanoate (3e)

\[
\begin{align*}
&\text{MeEsterNPHII} \#627 \quad \text{RT: 2.84} \quad \text{AV: 1} \quad \text{NL: 1.79E9} \\
&T: \text{FTMS + p ESI Full ms [150.0000-1500.0000]}
\end{align*}
\]

\[
\begin{align*}
&C_{19} H_{22} O_2 N = 296.1645 \\
&1.18 \text{ ppm}
\end{align*}
\]

\[
\begin{align*}
&\text{C} \quad \text{H} \quad \text{O} \quad \text{N} = 254.1176 \\
&0.23 \text{ ppm}
\end{align*}
\]

\[
\begin{align*}
&C_{16} H_{16} O_2 N = 254.1176 \\
&477.1381 \quad R=48707 \\
&410.2321 \quad R=41400 \\
&338.3424 \quad R=27500 \\
&310.1436 \quad R=63807
\end{align*}
\]

\[1\text{H NMR of Ethyl 2-}(4-\text{(1-oxoisooindolin-2-yl) phenyl})\text{propanoate (4e) in CDCl}_3\]

\[
\begin{align*}
&\text{COOEt}
\end{align*}
\]

\[
\begin{align*}
&\text{COOEt}
\end{align*}
\]
$^{13}$C NMR of Ethyl 2-(4-(1-oxoisooindolin-2-yl) phenyl)propanoate (4e) in CDCl$_3$

HRMS of Ethyl 2-(4-(1-oxoisooindolin-2-yl) phenyl)propanoate (4e)
$^1$H NMR of Indoprofen (5e) in DMSO-$d_6$

HRMS of Indoprofen (5e)

Indoprofen #452  RT: 2.06  AV: 1  NL: 3.94E8
T: FTMS + p ESI Full ms [150.0000-1500.0000]
$^1$H NMR of Ethyl 2-(4-(isoindolin-2-yl) phenyl)butanoate (3f) in CDCl$_3$

HRMS of Ethyl 2-(4-(isoindolin-2-yl) phenyl)butanoate (3f)
$^1$H NMR Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl)butanoate (4f) in CDCl$_3$

HRMS of Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl)butanoate (4f) in CDCl$_3$
$^1$H NMR of Indobufen (5f) in DMSO-$d_6$

HRMS of Indobufen (5f)
13. Gram scale reaction crude GC-MS spectra of 2-(4-chlorophenyl)-1,2,3,4-tetrahydro isoquinolinolone (2h)
14. GC-MS spectrum of the reaction of $N$-phenyltetrahydroisoquinoline in the presence of H$_2$O$^{18}$
15. References

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