SUPPORTING INFORMATION

Access to 1-Amino-3,4-dihydroisoquinolines via Palladium-Catalyzed C-H Bond Aminoimidoylation Reaction from Functionalized Isocyanides

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Contents

I. General Information ............................................................................................................2
II. General Procedure ..............................................................................................................2
III. Characterization Data .........................................................................................................3
IV. References ..........................................................................................................................19
V. Copies of $^1$H and $^{13}$C NMR Spectra ............................................................................20

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I. General Information

$^1$H NMR (400 MHz) and $^{13}$C NMR (125 MHz) were registered on 400 MHz and 500 MHz spectrometers. Chemical shifts were reported in units (ppm) by assigning TMS resonance in the $^1$H spectrum as 0.00 ppm, CDCl$_3$ resonance in the $^{13}$C spectrum as 77.0 ppm. All coupling constants ($J$ values) were reported in Hertz (Hz). NMR analysis was carried out at 298 K unless noted otherwise. HRMS was obtained on an ESI-LC-MS/MS spectrometer.

II. General Procedure

**General procedure:** An oven-dried 25 mL schlenk tube charged with Pd(OAc)$_2$ (0.01 mmol, 2.24 mg), PPh$_3$ (0.02 mmol, 5.24 mg), Cs$_2$CO$_3$ (0.1 mmol, 32.6 mg) and 2 (0.15 mmol) was refilled with Ar for 3 times. Then a solution of pivalic acid (0.06 mmol, 7 uL) in 0.5 mL of dioxane was added by syringe and the tube was placed in an 110 °C oil-bath. A solution of 1 (0.1 mmol) in 1.0 mL of dioxane was added dropwise within 1 h by a syringe pump to the reaction mixture. After reacting for another 1-2 h, the reaction was completed. The crude reaction mixture was extracted with EA (20 mL × 3) and washed with brine (20 mL). The organic phase was concentrated in vacuo and the residue was purified by silica gel flash column chromatography to afford the corresponding amino substituted isoquinolines 3.
III. Characterization Data

ethyl 3-benzyl-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3a)
Prepared from ethyl 2-benzyl-2-isocyano-3-phenylpropanoate (29.3 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 3a as a light yellow oil (30 mg, 0.080 mmol, 80% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.40 (d, $J = 7.4$ Hz, 1H), 7.33-7.29 (m, 1H), 7.26-7.19 (m, 7H), 3.94-3.88 (m, 2H), 3.88-3.78 (m, 4H), 3.38-3.24 (m, 4H), 3.13-3.02 (m, 3H), 2.73 (d, $J = 15.2$ Hz, 1H), 0.96 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$174.1, 161.8, 138.4, 137.4, 130.8, 130.4, 128.8, 127.8, 126.8, 126.6, 126.2, 125.1, 66.9, 65.9, 60.7, 49.3, 44.5, 35.2, 14.1; HRMS: calcd for C$_{23}$H$_{26}$N$_2$O$_3$ (M+H$^+$) 379.2016; found 379.2014.

ethyl 7-methyl-3-(4-methylbenzyl)-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3b)
Prepared from ethyl 2-isocyano-2-(4-methylbenzyl)-3-(p-tolyl)propanoate (32.1 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 3b as a colorless oil (29 mg, 0.072 mmol, 72% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.19 (s, 1H), 7.14-7.07 (m, 4H), 7.05 (d, $J = 7.8$ Hz, 2H), 3.96-3.90 (m, 2H), 3.89-3.78 (m, 4H), 3.38-3.32 (m, 2H), 3.29-3.23 (m, 2H), 3.07-2.95 (m, 3H), 2.68 (d, $J = 15.2$ Hz, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 0.99 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.3, 161.9, 136.2, 135.9, 135.3,
ethyl 7-(tert-butyl)-3-(4-(tert-butyl)benzyl)-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3c)
Prepared from dimethyl ethyl 2-(4-(tert-butyl)benzyl)-3-(4-(tert-butyl)phenyl)-2-isocyanopropanoate (40.6 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 8) furnished the product 3c as colorless oil (35 mg, 0.071 mmol, 71% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44 (s, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.24 (d, $J = 6.9$ Hz, 2H), 3.97-3.88 (m, 2H), 3.87-3.79 (m, 4H), 3.39-3.33 (m, 2H), 3.31-3.25 (m, 2H), 3.08-3.00 (m, 2H), 2.97 (d, $J = 13.2$ Hz, 1H), 2.72 (d, $J = 15.3$ Hz, 1H), 1.31 (s, 9H), 1.29 (s, 9H), 0.93 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.3, 161.9, 149.5, 149.2, 135.3, 134.2, 130.3, 128.3, 127.2, 124.6, 124.4, 123.1, 66.8, 66.1, 60.5, 49.4, 43.7, 34.6, 34.4, 34.3, 31.4, 31.3, 13.9; HRMS: calcd for C$_{31}$H$_{42}$N$_2$O$_3$ (M+H$^+$) 491.3268; found 491.3256.

ethyl 7-fluoro-3-(4-fluorobenzyl)-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3d)
Prepared from ethyl 2-(4-fluorobenzyl)-3-(4-fluorophenyl)-2-isocyanopropanoate (32.9 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5
equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 8) furnished the product 3d as a colorless oil (26 mg, 0.063 mmol, 63% yield). 1H NMR (500 MHz, CDCl$_3$): $\delta$ 7.25-7.22 (m, 2H), 7.18-7.15 (m, 1H), 7.10-7.08 (m, 1H), 7.05-7.00 (m, 1H), 6.95-6.91 (m, 2H), 3.91-3.85 (m, 4H), 3.81-3.77 (m, 2H), 3.36-3.32 (m, 2H), 3.24-3.20 (m, 2H), 3.07-3.04 (m, 3H), 2.66 (d, $J$ = 15.1 Hz, 1H), 0.95 (t, $J$ = 7.1 Hz, 3H); 13C NMR (125 MHz, CDCl$_3$): $\delta$173.6, 161.9 (d, $J$ = 242.5 Hz), 161.5 (d, $J$ = 243.8 Hz), 161.1 (d, $J$ = 2.5 Hz), 133.5 (d, $J$ = 2.5 Hz), 132.8 (d, $J$ =3.8Hz), 132.2 (d, $J$ = 7.5Hz), 129.9 (d, $J$ = 7.5 Hz), 126.5 (d, $J$ = 7.5 Hz), 117.2 (d, $J$ =21.3 Hz), 114.5 (d, $J$ = 21.3 Hz), 113.1 (d, $J$ = 22.5 Hz), 66.7, 66.1, 60.8, 49.2, 43.9, 34.9, 13.9; HRMS: calcd for C$_{23}$H$_{24}$F$_2$N$_2$O$_3$ (M+H$^+$) 415.1828; found 415.1823.

![Structure of ethyl 7-chloro-3-(4-chlorobenzyl)-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3e)](image)

ethyl 7-chloro-3-(4-chlorobenzyl)-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3e)

Prepared from ethyl 2-(4-chlorobenzyl)-3-(4-chlorophenyl)-2-isocyanopropanoate (36.2 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 8) furnished the product 3h as colorless oil (32 mg, 0.070 mmol, 70% yield). 1H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35(d, $J$ = 2.1Hz, 1H), 7.29(dd, $J$ = 8.1, 2.1Hz, 1H), 7.21-7.16 (m, 4H), 7.14(d, $J$ = 8.1Hz, 1H), 3.93-3.85(m, 4H), 3.82-3.77(m, 2H), 3.37-3.30(m, 2H), 3.24-3.18(m, 2H), 3.11-3.03 (m, 3H), 2.65(d, $J$ = 15.1 Hz, 1H), 0.95 (t, $J$ = 7.1 Hz, 3H); 13C NMR (125 MHz, CDCl$_3$): $\delta$ 173.5, 160.9, 136.4, 135.7, 132.7, 132.6, 132.2, 130.4, 129.9, 127.9, 126.5, 126.3, 66.8, 65.9, 60.9, 49.3, 44.2, 35.2, 14.1; HRMS: calcd for C$_{23}$H$_{24}$Cl$_2$N$_2$O$_3$ (M+H$^+$) 447.1237; found 447.1240.
ethyl 1-morpholino-7-(trifluoromethyl)-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroisoquinoline-3-carboxylate (3f)

Prepared from ethyl 2-isocyano-2-(4-(trifluoromethyl)benzyl)-3-(4-(trifluoromethyl)phenyl)propanoate (42.9 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 8) furnished the product 3f as a light yellow oil (48 mg, 0.093 mmol, 93% yield). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.62 (s, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.51 (d, $J = 8.1$ Hz, 2H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 7.9$ Hz, 1H), 3.91-3.86 (m, 3H), 3.86-3.78 (m, 3H), 3.38-3.33 (m, 2H), 3.25-3.15 (m, 5H), 2.76 (d, $J = 15.3$ Hz, 1H), 0.89 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ$^{13}$C NMR (125 MHz, CDCl$_3$): δ 172.1, 160.9, 141.8, 141.0, 131.1, 134.2, 132.9, 131.1, 129.5 (q, $J = 32.5$ Hz), 128.7 (q, $J = 31.3$ Hz), 126.9 (q, $J = 2.5$ Hz), 124.7 (q, $J = 3.8$ Hz), 124.4 (q, $J = 270.8$ Hz), 123.8 (q, $J = 276.3$ Hz), 66.6, 65.6, 61.0, 49.2, 44.7, 35.8, 13.8; HRMS: calcd for C$_{25}$H$_{24}$F$_6$N$_2$O$_3$ (M+H$^+$) 515.1764; found 515.1756.

3-ethyl 7-methyl 3-(4-(methoxycarbonyl)benzyl)-1-morpholino-3,4-dihydroisoquinoline-3,7-dicarboxylate (3g)

Prepared from dimethyl 4,4'-(2-(ethoxycarbonyl)-2-isocyanopropane-1,3-diyldibenzoate (40.9 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 2) furnished the product 3g as colorless oil (33 mg, 0.067 mmol, 67% yield). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.04 (s, 1H), 7.99 (d, $J = 7.8$ Hz, 1H), 7.92 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 7.8$ Hz,
(3h)

Prepared from ethyl 2-isocyano-2-(4-nitrobenzyl)-3-(4-nitrophenyl)propanoate (38.3 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 3e as a light yellow oil (26 mg, 0.056 mmol, 56% yield). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.23 (s, 1H), 8.20 (d, $J = 8.2$ Hz, 1H), 8.13 (d, $J = 8.6$ Hz, 2H), 7.50 (d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 8.2$ Hz, 1H), 3.95-3.88 (m, 2H), 3.88-3.79 (m, 4H), 3.41-3.34 (m, 3H), 3.29-3.19 (m, 4H), 2.80 (d, $J = 15.4$ Hz, 1H), 0.90 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 172.4, 160.5, 147.2, 147.1, 144.8, 144.6, 131.7, 129.5, 125.9, 125.1, 122.9, 121.1, 66.5, 65.6, 61.3, 49.1, 44.9, 36.5, 13.9; HRMS: calcd for C$_{23}$H$_{24}$N$_4$O$_7$ (M+H$^+$) 469.1718; found 469.1719.

(3i)

Prepared from ethyl 2-(2-chlorobenzyl)-3-(2-chlorophenyl)-2-isocyanopropanoate (36.2 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5
equiv) according to the general procedure. Column chromatography purification (EtOAc: petroleum ether 1 : 4) furnished the product 3i as a colorless oil (26 mg, 0.058 mmol, 58% yield). $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.53 (d, $J$ = 7.1 Hz, 1H), 7.36 (d, $J$ = 7.9 Hz, 1H), 7.33-7.28 (m, 2H), 7.19-7.10 (m, 3H), 4.02-3.90 (m, 2H), 3.87-3.82 (m, 2H), 3.79-3.73 (m, 2H), 3.51 (d, $J$ = 15.9 Hz, 1H), 3.44 (d, $J$ = 13.7 Hz, 1H), 3.38 (d, $J$ = 13.7 Hz, 1H), 3.35-3.30 (m, 2H), 3.23-3.17 (m, 2H), 2.67 (d, $J$ = 15.9 Hz, 1H), 0.99 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.6, 161.6, 136.3, 135.4, 135.2, 133.9, 133.2, 131.1, 129.3, 127.9, 127.3, 126.8, 126.1, 124.6, 66.9, 65.7, 61.0, 49.3, 41.1, 32.1, 13.9; HRMS: calcd for C$_{23}$H$_{24}$Cl$_2$N$_2$O$_3$ (M+H$^+$) 447.1237; found 447.1230.

ethyl 1-morpholino-5-(trifluoromethyl)-3-(2-(trifluoromethyl)benzyl)-3,4-dihydroisoquinoline-3-carboxylate (3j)

Prepared from ethyl 2-isocyano-2-(2-(trifluoromethyl)benzyl)-3-(2-(trifluoromethyl)phenyl)propanoate (42.9 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc: petroleum ether 1 : 4) furnished the product 3j as a colorless oil (42 mg, 0.082 mmol, 82% yield). $^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.03 (d, $J$ = 7.9 Hz, 1H), 7.64-7.60 (m, 3H), 7.44 (t, $J$ = 7.6 Hz, 1H), 7.36 (t, $J$ = 7.8 Hz, 1H), 7.30 (t, $J$ = 7.7 Hz, 1H), 3.91-3.84 (m, 3H), 3.83-3.76 (m, 3H), 3.57 (d, $J$ = 14.7 Hz, 1H), 3.51 (d, $J$ = 16.0 Hz, 1H), 3.46 (d, $J$ = 14.9 Hz, 1H), 3.46 (d, $J$ = 14.9 Hz, 1H), 3.37-3.32 (m, 2H), 3.23-3.19 (m, 2H), 2.62 (d, $J$ = 16.0 Hz, 1H), 0.89 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 172.9, 161.5, 136.7 (q, $J$ = 1.3Hz), 136.3 (q, $J$ = 1.3Hz), 132.7, 130.9, 129.55, 129.51 (q, $J$ = 28.8Hz), 129.0 (q, $J$ = 30.0Hz), 127.4 (q, $J$ = 5.0Hz), 126.5, 126.4, 126.0, 125.7 (q, $J$ = 5.0Hz), 124.5 (q, $J$ = 272.6Hz), 123.8 (q, $J$ = 272.6Hz), 66.7, 64.8, 61.0, 49.1, 40.1, 32.8, 13.5; HRMS: calcd for C$_{23}$H$_{24}$F$_6$N$_2$O$_3$(M+H$^+$) 515.1764; found 515.1765.
ethyl 5-chloro-3-(2-chloro-4-fluorobenzyl)-7-fluoro-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3k)

Prepared from ethyl 2-(2-chloro-4-fluorobenzyl)-3-(2-chloro-4-fluorophenyl)-2-isocyanopropanoate (39.8 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 3k as a colorless oil (34 mg, 0.070 mmol, 70% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.52 (dd, $J = 8.4, 6.6$ Hz, 1H), 7.14 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.07 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.02 (dd, $J = 8.5, 2.1$ Hz, 1H), 6.89 (dt, $J = 8.3, 2.3$ Hz, 1H), 4.01-3.89 (m, 2H), 3.87-3.83 (m, 2H), 3.79-3.74 (m, 2H), 3.48 (d, $J = 15.8$ Hz, 1H), 3.39-3.36 (m, 2H), 3.32-3.28 (m, 2H), 3.19-3.15 (m, 2H), 2.57 (d, $J = 15.6$ Hz, 1H), 1.01 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.0, 160.8 (d, $J = 1.3$Hz), 161.2 (d, $J = 247.5$Hz), 160.7 (d, $J = 247.5$Hz), 135.6(d, $J = 10.0$Hz), 134.4 (d, $J = 8.8$Hz), 133.8 (d, $J = 8.8$Hz), 131.7 (d, $J = 3.8$Hz), 130.8 (d, $J = 3.8$Hz), 127.6 (d, $J = 6.3$Hz), 118.4 (d, $J = 25.0$Hz), 116.3 (d, $J = 25.0$Hz), 113.3 (d, $J = 21.3$Hz), 111.9 (d, $J = 22.5$Hz), 66.6, 65.6, 61.1, 49.2, 40.2, 31.6, 13.9; HRMS: calcd for C$_{23}$H$_{22}$Cl$_2$F$_2$N$_2$O$_3$(M+H$^+$) 483.1048; found 483.1045.

ethyl 3-(2,4-difluorobenzyl)-5,7-difluoro-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3l)

Prepared from ethyl 2-(2,4-difluorobenzyl)-3-(2,4-difluorophenyl)-2-isocyanopropanoate (36.5 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column
chromatography purification (EtOAc : petroleum ether 1 : 8) furnished the product 3l as a colorless oil (22 mg, 0.049 mmol, 49% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.34 (q, \(J = 8.4\) Hz, 1H), 6.91 (d, \(J = 8.4\) Hz, 1H), 6.83 (dt, \(J = 8.4, 2.3\) Hz 1H), 6.79-6.71 (m, 2H), 4.01-3.92 (m, 2H), 3.87-3.82 (m, 2H), 3.79-3.75 (m, 2H), 3.33-3.26 (m, 3H), 3.21-3.17 (m, 4H), 2.53 (d, \(J = 15.6\) Hz, 1H), 1.03 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 173.2, 162.1 (dd, \(J = 247.5, 12.5\) Hz), 161.6 (dd, \(J = 246.2, 11.3\) Hz), 161.4 (dd, \(J = 242.5, 12.5\) Hz), 160.4, 160.2 (dd, \(J = 247.5, 11.3\) Hz), 133.7 (dd, \(J = 10.0, 6.3\) Hz), 127.4 (dd, \(J = 7.5, 7.5\) Hz), 120.8 (dd, \(J = 18.8, 3.8\) Hz), 119.8 (dd, \(J = 16.3, 3.8\) Hz), 110.7 (dd, \(J = 20.0, 2.5\) Hz), 109.3 (dd, \(J = 23.8, 3.8\) Hz), 105.7 (dd, \(J = 25.6, 25.6\) Hz), 103.4 (dd, \(J = 26.3, 26.3\) Hz), 66.7, 65.2, 61.2, 49.2, 36.8, 27.2, 14.0; HRMS: calcd for C\(_{23}\)H\(_{22}\)F\(_4\)N\(_2\)O\(_3\) (M+H\(^+\)) 451.1639; found 451.1634.

![Chemical Structure](image)

**ethyl 6-chloro-3-(3-chlorobenzyl)-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate(3m)**

Prepared from ethyl 2-(3-chlorobenzyl)-3-(3-chlorophenyl)-2-isocyanopropanoate (36.2 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 3m as a colorless oil (28 mg, 0.063 mmol, 63% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.45 (s, 1H), 7.35-7.33 (m, 1H), 7.20 (d, \(J = 7.3\) Hz, 1H), 3.99-3.94 (m, 3H), 3.85-3.81 (m, 4H), 3.36-3.22 (m, 3H), 3.13 (d, \(J = 14.1\) Hz, 2H), 2.68 (d, \(J = 14.7\) Hz, 1H), 0.95 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 173.6, 159.3, 141.5, 139.3, 133.5, 131.4, 131.2, 130.6, 130.1, 129.0, 128.9, 127.2, 126.8, 124.6, 66.7, 66.0, 60.8, 44.8, 38.5, 29.8, 13.9; HRMS: calcd for C\(_{23}\)H\(_{24}\)Cl\(_2\)N\(_2\)O\(_3\) (M+H\(^+\)) 447.1237; found 447.1234.
methyl 3-benzyl-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3n)
Prepared from methyl 2-benzyl-2-isocyano-3-phenylpropanoate (27.9 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 3n as a colorless oil (32 mg, 0.088 mmol, 88% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.41 (d, $J$ = 7.74 Hz, 1H), 7.35-7.31 (m, 1H), 7.27-7.22 (m, 4H), 7.21-7.17 (m, 3H), 3.87-3.79 (m, 4H), 3.49 (s, 3H), 3.35-3.22 (m, 4H), 3.10-2.96 (m, 3H), 2.75 (d, $J$ = 15.3 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.7, 161.8, 138.3, 137.2, 130.7, 130.5, 128.8, 127.9, 126.8, 126.3, 124.9, 66.9, 66.2, 52.1, 49.3, 44.3, 34.8; HRMS: calcd for C$_{22}$H$_{24}$N$_2$O$_3$ (M+H$^+$) 365.1860; found 365.1862.

(3-benzyl-1-morpholino-3,4-dihydroisoquinolin-3-yl)(morpholino)methanone (3o)
Prepared from 2-benzyl-2-isocyano-1-morpholino-3-phenylpropan-1-one (33.4 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 2) furnished the product 3o as a colorless oil (36 mg, 0.086 mmol, 86% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36-7.32 (m, 2H), 7.29-7.20 (m, 5H), 7.19-7.16 (m, 2H), 4.25-4.23 (brs, 1H), 3.88-3.76 (m, 4H), 3.59 (brs, 2H), 3.38 (brs, 2H), 3.33-3.27 (m, 5H), 3.18-3.13 (m, 3H), 3.04 (d, $J$ = 13.2 Hz, 1H), 2.97 (d, $J$ = 13.2 Hz, 1H), 2.68 (d, $J$ = 15.0 Hz, 1H), 0.96 (t, $J$ = 7.08 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 172.1, 160.6, 140.3, 137.3, 130.8, 129.3, 128.0, 126.8, 126.4, 125.8, 124.4, 67.9, 66.8, 49.2, 44.5, 36.6; HRMS: calcd for C$_{25}$H$_{29}$N$_3$O$_3$(M+H$^+$) 420.2282; found
ethyl 3-isobutyl-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3p)
Prepared from ethyl 2-benzyl-2-isocyano-4-methylpentanoate (26 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 8 : 1) furnished the product 3p as colorless oil (23 mg, 67% yield). (new compound). ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.41 (m, 1H), 7.34-7.25 (m, 2H), 7.20 (d, J = 6.8 Hz, 1H), 4.01-3.94 (m, 2H), 3.91-3.80 (m, 4H), 3.38-3.25 (m, 4H), 3.06 (d, J = 15.2 Hz, 1H), 2.76 (d, J = 15.2 Hz, 1H), 1.95-1.86 (m, 1H), 1.81-1.77 (m, 1H), 1.69-1.64 (m, 1H), 1.04 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 161.4, 138.0, 130.1, 128.4, 126.7, 126.0, 125.0, 66.8, 64.6, 60.5, 49.1, 47.4, 37.2, 24.9, 24.2, 23.8, 14.0. HRMS (ESI) calcd for C₂₀H₂₈N₂O₃ [M+H]^+: 345.2173, Found: 345.2175.

ethyl 3-isopropyl-1-morpholino-3,4-dihydroisoquinoline-3-carboxylate (3q)
Prepared from ethyl 2-benzyl-2-isocyano-3-methylbutanoate (25 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 8 : 1) furnished the product 3q as colorless oil (16 mg, 50% yield). (new compound). ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.39 (m, 1H), 7.32-7.21 (m, 3H), 3.93-3.86 (m, 4H), 3.81-3.76 (m, 2H), 3.47-3.41 (m, 2H), 3.26-3.21 (m, 2H), 2.99 (d, J = 14.8 Hz, 1H), 2.82 (d, J = 14.8 Hz, 1H), 2.24-2.17 (m, 1H), 1.04 (dd, J = 6.8, 3.6 Hz, 6H), 0.94 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 161.8, 138.6, 130.0, 128.4,
ethyl 3-benzyl-1-(piperidin-1-yl)-3,4-dihydroisoquinoline-3-carboxylate (4a)
Prepared from ethyl 2-benzyl-2-isocyano-3-phenylpropanoate (29.3 mg, 0.1 mmol, 1.0 equiv) and piperidin-1-yl benzoate (30.75 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 2) furnished the product 4a as a light yellow oil (35 mg, 0.092 mmol, 92% yield). \(^1\text{H} \text{NMR} \ (500 \text{ MHz, CDCl}_3)\): \(\delta 7.41 \ (d, \ J = 7.43 \text{ Hz, 1H}), 7.31-7.28 \ (m, 1H), 7.26-7.21 \ (m, 5H), 7.20-7.17 \ (m, 2H), 3.30-3.21 \ (m, 4H), 3.11 \ (d, \ J = 13.2 \text{ Hz, 1H}), 3.05 \ (d, \ J = 15.1 \text{ Hz, 1H}), 2.98 \ (d, \ J = 13.2 \text{ Hz, 1H}), 2.73 \ (d, \ J = 15.1 \text{ Hz, 1H}), 1.72-1.65 \ (m, 6H), 0.96 \ (t, \ J = 7.15 \text{ Hz, 3H})\); \(^{13}\text{C} \text{NMR} \ (125 \text{ MHz, CDCl}_3)\): \(\delta 174.4, 162.4, 138.3, 137.6, 130.8, 129.9, 128.6, 127.8, 126.6, 126.5, 126.4, 125.9, 65.9, 60.6, 49.7, 44.5, 35.2, 26.0, 25.2, 14.1\); HRMS: calcd for C\(_{24}\)H\(_{28}\)N\(_2\)O\(_2\) (M+H\(^+\)) 377.2224; found 377.2223.

ethyl 3-benzyl-1-(4-methylpiperidin-1-yl)-3,4-dihydroisoquinoline-3-carboxylate (4b)
Prepared from ethyl 2-benzyl-2-isocyano-3-phenylpropanoate (29.3 mg, 0.1 mmol, 1.0 equiv) and 4-methylpiperidin-1-yl benzoate (32.85 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 4b as a colorless oil (26 mg, 0.067 mmol,
67% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.41 (d, $J = 7.45$ Hz, 1H), 7.30-7.28 (m, 1H), 7.26-7.23 (m, 5H), 7.19-7.17 (m, 2H), 3.94-3.80 (m, 4H), 3.11 (d, $J = 13.2$ Hz, 1H), 3.05 (d, $J = 15.0$ Hz, 1H), 2.98 (d, $J = 13.2$ Hz, 1H), 2.80-2.70 (m, 2H), 2.66-2.61 (m, 1H), 1.72-1.58 (m, 3H), 1.45-1.37 (m, 1H), 1.35-1.23 (m, 1H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.96 (t, $J = 7.10$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.3, 162.1, 138.1, 137.5, 130.7, 129.8, 128.4, 127.7, 126.5, 126.3, 125.8, 65.9, 60.5, 49.1, 48.7, 44.3, 35.0, 34.3, 34.1, 31.5, 22.1, 13.9; HRMS: calcd for C$_{25}$H$_{30}$N$_2$O$_2$ (M+H$^+$) 391.2380; found 391.2371.

![ethyl 3-benzyl-1-(4-(ethoxycarbonyl)piperidin-1-yl)-3,4-dihydroisoquinoline-3-carboxylate (4c)](image)

Prepared from ethyl 2-benzyl-2-isocyano-3-phenylpropanoate (29.3 mg, 0.1 mmol, 1.0 equiv) and ethyl 1-(benzoyloxy)piperidine-4-carboxylate (41.55 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 4c as a colorless oil (31 mg, 0.069 mmol, 69% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.40 (d, $J = 7.25$ Hz, 1H), 7.31-7.29 (m, 1H), 7.26-7.22 (m, 5H), 7.20-7.18 (m, 2H), 4.18 (q, $J = 7.10$ Hz, 2H), 3.95-3.80 (m, 4H), 3.12-2.97 (m, 3H), 2.86-2.72 (m, 3H), 2.51 (brs, 1H), 2.02-1.92 (m, 3H), 1.88-1.80 (m, 1H), 1.29 (t, $J = 7.25$ Hz, 1H), 0.95 (t, $J = 7.10$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 175.2, 174.3, 162.1, 138.3, 137.4, 130.8, 130.2, 128.7, 127.9, 126.8, 126.5, 126.3, 125.6, 65.9, 60.7, 60.6, 48.4, 48.0, 44.4, 41.9, 35.1, 28.3, 28.2, 14.4, 14.0; HRMS: calcd for C$_{27}$H$_{32}$N$_2$O$_4$ (M+H$^+$) 449.2435; found 449.2431.

![ethyl 3-benzyl-1-(4-(ethoxycarbonyl)piperidin-1-yl)-3,4-dihydroisoquinoline-3-carboxylate (4c)](image)
ethyl 3-benzyl-1-(4-methoxypiperidin-1-yl)-3,4-dihydroisoquinoline-3-carboxylate (4d)
Prepared from ethyl 2-benzyl-2-isocyano-3-phenylpropanoate (29.3 mg, 0.1 mmol, 1.0 equiv) and 4-methoxypiperidin-1-yl benzoate (35.25 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 2) furnished the product 4d as a colorless oil (27 mg, 0.067 mmol, 67% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.40 (d, J = 7.40 \text{ Hz}, 1\text{H}), 7.31-7.29 (m, 1\text{H}), 7.26-7.23 (m, 5\text{H}), 7.20-7.18 (m, 2\text{H}), 3.93-3.86 (m, 2\text{H}), 3.71(brs, 2\text{H}), 3.39 (s, 4\text{H}), 3.12-2.97 (m, 4\text{H}), 2.92-2.87 (m, 1\text{H}), 2.73(d, J = 15.1 \text{ Hz}, 1\text{H}), 2.04-1.97 (m, 2\text{H}), 1.75-1.63 (m, 3\text{H}), 0.95 (t, J = 7.10 \text{ Hz}, 3\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 174.3, 161.8, 138.3, 137.5, 130.8, 130.2, 128.7, 127.8, 126.7, 126.5, 126.3, 125.7, 66.0, 60.6, 55.7, 46.4, 46.2, 44.5, 35.3, 30.9, 30.8, 14.0; HRMS: calcd for C\(_{25}\)H\(_{30}\)N\(_2\)O\(_3\) (M+H\(^+\)) 407.2329; found 407.2331.

![Structure of 4d]

ethyl 3-benzyl-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3,4-dihydroisoquinoline-3-carboxylate (4e)
Prepared from ethyl 2-benzyl-2-isocyano-3-phenylpropanoate (29.3 mg, 0.1 mmol, 1.0 equiv) and 1, 4-dioxa-8-azaspiro[4.5]decan-8-yl benzoate (39.45 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 2) furnished the product 4e as a colorless oil (42 mg, 0.096 mmol, 96% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.39 (d, J = 7.55 \text{ Hz}, 1\text{H}), 7.31-7.28 (m, 1\text{H}), 7.26-7.21 (m, 5\text{H}), 7.19-7.17 (m, 2\text{H}), 3.99 (s, 4\text{H}), 3.92-3.85(m, 2\text{H}), 3.49-3.38 (m, 4\text{H}), 3.10(d, J = 13.1 \text{ Hz}, 1\text{H}), 3.06(d, J = 15.1 \text{ Hz}, 1\text{H}), 3.01(d, J = 13.1 \text{ Hz}, 1\text{H}), 2.71(d, J = 15.1 \text{ Hz}, 1\text{H}), 1.90-1.75 (m, 4\text{H}), 0.93 (t, J = 7.14 \text{ Hz}, 3\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 174.2, 161.4, 138.3, 137.5, 130.8, 130.1, 128.6, 127.8, 126.7, 126.5, 126.2, 125.7, 107.9, 66.1, 64.5, 60.6, 46.5, 44.7, 35.4, 34.8, 14.0; HRMS: calcd for C\(_{26}\)H\(_{30}\)N\(_2\)O\(_4\) (M+H\(^+\)) 435.2278; found 435.2273.
ethyl 3-benzyl-1-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3,4-dihydroisoquinoline-3-carboxylate (4f)

Prepared from ethyl 2-benzyl-2-isocyano-3-phenylpropanoate (29.3 mg, 0.1 mmol, 1.0 equiv) and tert-butyl 4-(benzoyloxy)piperazine-1-carboxylate (45.9 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 4f as a colorless oil (47 mg, 0.099 mmol, 99% yield). 

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39 (d, $J = 7.6$ Hz, 1H), 7.30-7.33 (m, 1H), 7.25-7.27 (m, 1H), 7.23-7.24 (m, 4H), 7.16-7.21 (m, 2H), 3.86-3.98 (m, 2H), 3.56-3.61 (m, 2H), 3.49-3.54 (m, 2H), 3.28-3.33 (m, 2H), 3.21-3.26 (m, 2H), 3.05-3.11 (m, 2H), 3.02 (d, $J = 13.1$ Hz, 1H), 2.73 (d, $J = 15.1$ Hz, 4H), 1.49 (s, 9H), 0.95 (t, $J = 7.2$ Hz, 3H); 

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.1, 161.7, 155.1, 138.3, 137.3, 130.8, 130.4, 128.7, 127.8, 126.8, 126.5, 126.1, 125.2, 79.9, 65.9, 60.7, 48.5, 44.4, 35.2, 28.6, 14.0; HRMS: calcd for C$_{28}$H$_{35}$N$_3$O$_4$ (M+H$^+$) 478.2700; found 478.2700.

ethyl 3-benzyl-1-(diethylamino)-3,4-dihydroisoquinoline-3-carboxylate (4g)

Prepared from ethyl 2-benzyl-2-isocyano-3-phenylpropanoate (29.3 mg, 0.1 mmol, 1.0 equiv) and O-benzoyl-$N,N$-diethylhydroxylamine (28.95 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 1 : 4) furnished the product 4g as a colorless oil (25 mg, 0.069 mmol, 69% yield). 

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.40 (d, $J = 7.6$ Hz, 1H), 7.32 (d, $J = 7.3$ Hz, 2H), 7.28-7.21 (m, 4H), 7.17 (t, $J = 6.7$ Hz, 2H), 3.81 (q, $J = 7.1$ Hz, 2H), 3.46-3.38 (m, 2H), 3.25-3.18 (m, 2H), 3.13 (d, $J = 13.1$ Hz, 1H), 3.09-3.04 (m, 2H), 2.67 (d, $J = 14.9$ Hz, 1H), 1.14 (t, $J = 7.0$ Hz, 6H), 0.88 (t, $J = 7.1$ Hz, 3H);
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.6, 160.8, 138.3, 137.8, 130.9, 129.7, 128.4, 127.7, 126.8, 126.5, 126.4, 126.0, 66.5, 60.4, 45.3, 43.6, 35.9, 13.9, 13.1; HRMS: calcd for C$_{23}$H$_{28}$N$_2$O$_2$ (M+H$^+$) 365.2224; found 365.2219.

ethyl 1-morpholino-3-phenyl-3,4-dihydroisoquinoline-3-carboxylate (6)
Prepared from ethyl 2-isocyano-2,3-diphenylpropanoate (27.9 mg, 0.1 mmol, 1.0 equiv) and morpholino benzoate (31.05 mg, 0.15 mmol, 1.5 equiv) according to the general procedure. Column chromatography purification (EtOAc : petroleum ether 8 : 1) furnished the product 6 as colorless oil (14 mg, 37% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78-7.76 (m, 2H), 7.46-7.45 (m, 1H), 7.38-7.26 (m, 6H), 3.97-3.91 (m, 4H), 3.89-3.84 (m, 2H), 3.68-3.65 (m, 1H), 3.55-3.50 (m, 2H), 3.42-3.37 (m, 2H), 3.06-3.02 (m, 1H), 0.96 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.2, 162.1, 142.6, 138.6, 130.5, 128.7, 128.2, 127.2, 126.7, 126.6, 126.1, 125.0, 66.8, 61.0, 49.2, 37.6, 13.8. HRMS calcd for C$_{22}$H$_{24}$N$_2$O$_3$ [M+H]$^+$: 365.1860, Found: 365.1866.

(3-benzyl-1-morpholino-3,4-dihydroisoquinolin-3-yl)methanol (8)
To an oven-dried flask containing 3a (37.8 mg) was added 1.0 mL of anhydrous THF under argon. The mixture was cooled to 0 °C in an ice-water bath. To the solution was added a solution of LiAlH$_4$ (50 uL, 0.12 mmol, 2.4 M in THF) dropwise. The resulting mixture was warmed to room temperature and stirred for 1 h. Then the reaction was quenched with aqueous NH$_4$Cl solution and extracted with DCM for three times. Column chromatography purification (EtOAc : petroleum ether 1 : 1) furnished the product 8 as colorless oil (23.5 mg, 70% yield). $^1$H NMR (400 MHz,
CDCl$_3$ $\delta$ 7.53-7.46 (m, 2H), 7.38-7.16 (m, 6H), 7.02-7.01 (m, 2H), 3.96-3.93 (m, 2H), 3.85-3.80 (m, 2H), 3.73 (s, 1H), 3.41-3.17 (m, 6H), 2.77 (d, $J$ = 13.2 Hz, 1H), 2.54-2.46 (m, 2H), 2.13 (d, $J$ = 12.8 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.3, 138.4, 137.5, 130.8, 130.4, 129.4, 129.3, 128.0, 126.7, 126.2, 66.8, 60.0, 49.4, 37.7, 32.0. HRMS calcd for C$_{21}$H$_{24}$N$_2$O$_2$ [M+H]$^+$: 337.1911, Found: 337.1915.

**3-(3-benzyl-1-morpholino-3,4-dihydroisoquinolin-3-yl)pentan-3-ol (9)**

To an oven-dried flask containing 3a (37.8 mg) was added 1.0 mL of anhydrous THF under argon. The mixture was cooled to 0 °C in an ice-water bath. To the solution was added a solution of EtMgBr (300 uL, 0.3 mmol, 1.0 M in THF) dropwise. The resulting mixture was stirred at 0 °C for 3 h. Then the reaction was quenched with aqueous NH$_4$Cl solution and extracted with DCM for three times. Column chromatography purification (EtOAc : petroleum ether 1 : 1) furnished the product 9 as colorless oil (17.6 mg, 45% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.21-7.17 (m, 1H), 7.09-7.07 (m, 1H), 6.96-9.92 (m, 1H), 6.89-6.82 (m, 4H), 6.65-6.63 (m, 2H), 3.91-3.85 (m, 2H), 3.77-3.72 (m, 2H), 3.35-3.30 (m, 2H), 3.18-3.03 (m, 4H), 2.85-2.81 (m, 1H), 2.67-2.66 (m, 1H), 2.04-1.95 (m, 1H), 1.87-1.78 (m, 1H), 1.66-1.60 (m, 4H), 1.11 (t, $J$ = 7.6 Hz, 3H), 1.01 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.1, 138.5, 130.4, 128.5, 126.7, 125.9, 125.7, 124.9, 77.8, 66.8, 65.1, 49.4, 41.0, 33.4, 27.9, 26.5, 9.8, 9.3. HRMS calcd for C$_{25}$H$_{32}$N$_2$O$_2$ [M+H]$^+$: 393.2537, Found: 393.2535.

**IV. References**

V. Copies of $^1$H and $^{13}$C NMR Spectra

3a
3c
3i
3p