DBU-promoted cyclization of vinyl isocyanides with ethers via functionalization of C(sp$^3$)–H bond for the synthesis of isoquinolines

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1. General information

Vinyl isocyanide 1 were synthesized according to literature. The other reagents were obtained from commercial suppliers and used without further purification. The reactions were conducted under an atmosphere of N\textsubscript{2} and were monitored by TLC. Solvents were dried and distilled prior to use. Flash chromatography was performed using silica gel 60 (300–400 mesh). \textsuperscript{1}H, \textsuperscript{13}C and \textsuperscript{19}F NMR spectra were recorded on a Bruker AVANCE400M spectrometer. Melting points were uncorrected. Infrared spectra were obtained on a Bruker Vector 22 in KBr pellets. HRMS were conducted on an Agilent 6540Q-TOF LC/MS equipped with an electrospray ionization (ESI) probe operating in positive or negative ion mode.

Reference

2. General procedure for radical cyclization between vinyl isocyanide with ethers

Into an oven-dried reaction vial flushed with N\textsubscript{2} was added methyl 2-isocyano-3,3-diphenylacrylate (1a) (0.2 mmol), 1,4-dioxane (2a, 2 mL), TBPB (0.2 mmol), DBU (0.06 mmol). Then the reaction mixture was stirred for 12 hours at 120 °C under nitrogen atmosphere. After cooling, dichloromethane (30 mL) was added into the reaction, and the mixture was washed with saturated K\textsubscript{2}CO\textsubscript{3} solution (1 × 20 mL), water (1 × 30 mL) and brine solution (1 × 30 mL). After drying over anhydrous Na\textsubscript{2}SO\textsubscript{4}, solvent was removed. The crude mixture was charged onto silica gel and purified by flash chromatography to furnish the corresponding product 3aa.
3. ESI-Mass analysis of 4

A mixture of methyl 2-isocyano-3,3-diphenylacrylate (1a, 0.2 mmol), 1,4-dioxane (2a, 2 mL), TBPB (0.2 mmol), DBU (0.06 mmol) and TEMPO (0.4 mmol) was stirred at 120 °C under nitrogen atmosphere. After 12 h, the reaction mixture was subjected to ESI-mass (positive mode) spectroscopic analysis. Copied below is the ESI-mass spectrum we obtained. LCMS (ESI) for 4: calcd for C_{13}H_{26}NO_{3} [M+H]^+ 244.19, found 244.10.
4. KIE studies of the cyclization reaction

\[ \text{1a, 0.2 mmol} \]

\[ \begin{align*}
\text{2b, 1 mL} & \quad \text{TBPB (1.0 equiv)} \\
& \quad \text{DBU (30 mol %)} \\
& \quad 120 ^\circ \text{C, 12 h, N}_2 \\
\end{align*} \]

\[ \text{3ab} \quad \text{3ab} : [\text{D}3\text{ab}] = 4.35:1 \]

\[ 78\% \text{ yield} \]

\[ \begin{align*}
\text{1b} : [\text{D}1\text{b}] = 1 : (1.23-1) = 4.35 : 1 \\
\text{3ab} = [\text{D}3\text{ab}] \\
\text{3ab} = [\text{D}3\text{ab}] \\
\text{3ab} = [\text{D}3\text{ab}] \\
\text{3ab} = [\text{D}3\text{ab}] \\
\text{3ab} = [\text{D}3\text{ab}] \\
\text{3ab} = [\text{D}3\text{ab}] \\
\end{align*} \]
5. Characterization data of compounds 3

**Methyl 1-(1,4-dioxan-2-yl)-4-phenylisoquinoline-3-carboxylate (3aa):** Colorless oil (57.2 mg, 82% yield), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.53 (d, $J=8.4$ Hz, 1H), 7.70 (m, 1H), 7.64 (m, 2H), 7.47 (m, 3H), 7.31 (m, 2H), 5.45 (dd, $J=9.5, 3.2$ Hz, 1H), 4.32 (qd, $J=12.0, 6.4$ Hz, 2H), 4.11 (m, 2H), 3.90 (dd, $J=8.0, 2.2$ Hz, 2H), 3.66 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.6, 155.7, 140.9, 136.3, 135.9, 133.9, 130.6, 129.8, 129.6, 128.5, 128.2, 128.0, 127.2, 127.1, 125.5, 76.6, 69.8, 67.7, 66.5, 52.3. IR (cm$^{-1}$): $\nu$ 2955, 2926, 2858, 1732, 1506, 1437, 1396, 1328, 1239, 1170, 1120, 1092, 913, 774, 699. HRMS (ESI): calcd for C$_{21}$H$_{19}$NO$_4$Na [M+Na]$^+$ 372.1212, found: 372.1214.

**Methyl 4-phenylisoquinoline-3-carboxylate (3aa'):** White solid, mp 86-88 °C, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.34 (s, 1H), 8.09 (dd, $J=6.8, 1.9$ Hz, 1H), 7.68 (m, 3H), 7.51 (m, 3H), 7.34 (m, 2H), 3.76 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.1, 151.8, 140.9, 136.0, 134.9, 131.1, 129.5, 129.04, 128.8, 128.5, 128.0, 127.6, 126.6, 52.5. IR (cm$^{-1}$): $\nu$ 2952, 2921, 2850, 1728, 1564, 1502, 1448, 1433, 1376, 1332, 1288, 1222, 1158, 1101, 982, 773, 710, 585. HRMS (ESI): calcd for C$_{17}$H$_{14}$NO$_2$ [M+H]$^+$ 264.1025, found: 264.1019.
Methyl 1-(1,4-dioxan-2-yl)-7-fluoro-4-(4-fluorophenyl)isoquinoline-3-carboxylate (3ba): White solid (50.8 mg, 66% yield), mp 157-160 °C, $^1$H NMR (400 MHz, CDCl$_3$) δ 8.20 (dd, $J = 10.0$, 2.5 Hz, 1H), 7.63 (dd, $J = 9.3$, 5.5 Hz, 1H), 7.43 (ddd, $J = 9.4$, 8.0, 2.6 Hz, 1H), 7.27 (m, 2H), 7.19 (t, $J = 8.3$ Hz, 2H), 5.33 (ddd, $J = 7.6$, 5.0 Hz, 1H), 4.30 (m, 2H), 4.10 (m, 2H), 3.90 (m, 2H), 3.70 (s, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -108.06, -113.27. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.2, 162.7 (d, $J = 247.9$ Hz), 161.6 (d, $J = 251.9$ Hz), 155.4 (d, $J = 5.6$ Hz), 140.4 (d, $J = 2.5$ Hz), 133.5, 133.0 (d, $J = 1.3$ Hz), 131.5 (d, $J = 8.0$ Hz), 131.5, 131.3 (d, $J = 8.2$ Hz), 129.8 (d, $J = 8.9$ Hz), 128.5 (d, $J = 9.1$ Hz), 121.2 (d, $J = 25.1$ Hz), 115.5 (d, $J = 21.6$ Hz), 109.8 (d, $J = 22.4$ Hz), 76.8, 69.5, 67.6, 66.5, 52.4. IR (cm$^{-1}$): ν 3092, 2984, 2912, 2859, 1736, 1623, 1604, 1516, 1440, 1404, 1375, 1292, 1228, 1188, 1167, 1116, 1089, 1051, 960, 912, 887, 849, 795, 698. HRMS (ESI): calcd for C$_{21}$H$_{17}$F$_2$NO$_4$Na [M+Na]$^+$ 408.1023, found: 408.1023.

Methyl 7-chloro-4-(4-chlorophenyl)-1-(1,4-dioxan-2-yl)isoquinoline-3-carboxylate (3ca):

Yellow solid (58.3 mg, 70% yield), mp 178-180 °C, $^1$H NMR (400 MHz, CDCl$_3$) δ 8.53 (d, $J = 1.8$ Hz, 1H), 7.59 (dd, $J = 9.1$, 2.0 Hz, 1H), 7.54 (d, $J = 9.0$ Hz, 1H), 7.48
(d, $J = 8.0$ Hz, 2H), 7.23 (m, 2H), 5.35 (dd, $J = 7.9$, 4.8 Hz, 1H), 4.29 (m, 2H), 4.11 (m, 2H), 3.90 (m, 2H), 3.71 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.9, 155.3, 140.8, 134.9, 134.6, 134.5, 133.8, 132.8, 131.8, 131.0, 130.9, 128.7, 128.5, 127.9, 124.9, 76.5, 69.5, 67.6, 66.5, 52.5. IR (cm$^{-1}$): $\nu$ 3085, 2974, 2948, 2858, 1735, 1598, 1552, 1498, 1434, 1402, 1291, 1234, 1167, 1117, 1093, 1084, 1030, 948, 909, 884, 839, 783. HRMS (ESI): calcd for C$_{21}$H$_{17}$Cl$_2$NO$_4$Na [M+Na]$^+$ 440.0432, found: 440.0432.

**Methyl 7-bromo-4-(4-bromophenyl)-1-(1,4-dioxan-2-yl)isoquinoline-3-carboxylate (3da):**

Yellow solid (73.5 mg, 73% yield), mp 67-69 °C, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.70 (d, $J = 1.8$ Hz, 1H), 7.72 (dd, $J = 9.0$, 1.9 Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 9.0$ Hz, 1H), 7.16 (q, $J = 3.6$ Hz, 2H), 5.35 (dd, $J = 7.9$, 4.8 Hz, 1H), 4.29 (m, 2H), 4.11 (m, 2H), 3.90 (m, 2H), 3.72 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.9, 155.2, 140.7, 134.7, 134.3, 134.3, 132.8, 131.6, 131.3, 131.1, 128.5, 128.2, 128.2, 123.4, 122.7, 76.4, 69.5, 67.6, 66.5, 52.5. IR (cm$^{-1}$): $\nu$ 2949, 2924, 2860, 1733, 1492, 1436, 1391, 1307, 1230, 1165, 1120, 1011, 957, 822, 802, 775, 728. HRMS (ESI): calcd for C$_{21}$H$_{17}$Br$_2$NO$_4$Na [M+Na]$^+$ 527.9422, found: 527.9418.
Methyl 1-(1,4-dioxan-2-yl)-7-methyl-4-(p-tolyl)isoquinoline-3-carboxylate (3ea): Colorless solid (66.3 mg, 88%), mp 179-181 °C, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.22 (s, 1H), 7.57 (d, $J = 8.7$ Hz, 1H), 7.45 (d, $J = 8.3$ Hz, 1H), 7.28 (t, $J = 5.8$ Hz, 2H), 7.18 (d, $J = 7.4$ Hz, 2H), 5.43 (dd, $J = 9.6$, 2.7 Hz, 1H), 4.29 (m, 2H), 4.11 (m, 2H), 3.91 (m, 2H), 3.69 (s, 3H), 2.59 (s, 3H), 2.45 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.7, 154.5, 140.1, 138.8, 137.6, 134.7, 134.1, 133.0, 132.7, 129.6, 129.4, 128.9, 127.4, 127.0, 124.1, 76.3, 69.8, 67.6, 66.5, 52.2, 22.20, 21.4. IR (cm$^{-1}$): $\nu$ 2945, 2918, 2850, 1733, 1518, 1434, 1405, 1328, 1299, 1237, 1168, 1120, 1088, 1052, 1027, 1000, 950, 913, 886, 829, 726. HRMS (ESI): calcd for C$_{23}$H$_{23}$NO$_4$Na [M+Na]$^+$ 400.1525, found: 400.1520.

Methyl 1-(1,4-dioxan-2-yl)-7-methoxy-4-(4-methoxyphenyl)isoquinoline-3-carboxylate (3fa): Colorless oil (57.2 mg, 70%), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 2.5$ Hz, 1H), 7.59 (d, $J = 9.3$ Hz, 1H), 7.28 (m, 1H), 7.21 (d, $J = 6.6$ Hz, 2H), 7.01 (d, $J = 8.0$ Hz, 2H), 5.37 (dd, $J = 9.6$, 3.0 Hz, 1H), 4.31 (m, 2H), 4.10 (m, 2H), 3.99 (s, 3H), 3.91 (m, 1H), 3.88 (s, 3H), 3.83 (m, 1H), 3.69 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 167.8, 159.4, 159.2, 153.5, 139.2, 134.0, 132.0, 130.9, 130.7, 128.9, 128.2, 122.9, 113.7, 103.7, 76.9, 69.6, 67.6, 66.6, 55.5, 55.3, 52.3. IR (cm$^{-1}$): $\nu$ 2950,
Methyl 1-(1,4-dioxan-2-yl)-4-(4-fluorophenyl)-7-methoxyisoquinoline-3-carboxylate (3ga): Colorless oil, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.17 (dd, \(J = 10.0, 2.3 \text{ Hz}, 1\text{H})\), 7.72 (dd, \(J = 9.3, 5.6 \text{ Hz}, 1\text{H})\), 7.41 (m, 1H), 7.22 (d, \(J = 6.6 \text{ Hz}, 2\text{H})\), 7.02 (d, \(J = 7.9 \text{ Hz}, 2\text{H})\), 5.32 (dd, \(J = 7.9, 4.7 \text{ Hz}, 1\text{H})\), 4.29 (m, 2H), 4.09 (m, 2H), 3.89 (m, 5H), 3.70 (s, 3H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -108.62. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.6, 161.5 (d, \(J = 251.3 \text{ Hz})\), 159.6, 154.8 (d, \(J = 5.6 \text{ Hz})\), 140.8 (d, \(J = 2.5 \text{ Hz})\), 133.7, 133.5 (d, \(J = 1.1 \text{ Hz})\), 130.9 (d, \(J = 17.9 \text{ Hz})\), 130.1 (d, \(J = 8.9 \text{ Hz})\), 128.5 (d, \(J = 9.1 \text{ Hz})\), 127.5, 120.9 (d, \(J = 25.1 \text{ Hz})\), 113.8, 109.6 (d, \(J = 22.3 \text{ Hz})\), 76.9, 69.5, 67.6, 66.5, 55.3, 52.4. IR (cm\(^{-1}\)): \(\nu\) 2952, 2924, 2856, 1735, 1624, 1558, 1517, 1441, 1398, 1235, 1191, 1164, 1117, 1089, 1033, 911, 771, 700. HRMS (ESI): calcd for C\(_{22}\)H\(_{20}\)FNO\(_5\)Na [M+Na]\(^+\) 420.1223, found: 420.1223.

Methyl 1-(1,4-dioxan-2-yl)-7-fluoro-4-(4-methoxyphenyl)isoquinoline-3-carboxylate (3ha): Colorless solid, mp 87-90 °C, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.80 (d, \(J = 2.5 \text{ Hz}, 1\text{H})\), 7.50 (d, \(J = 9.3 \text{ Hz}, 1\text{H})\), 7.30 (dd, \(J = 9.3, 2.5 \text{ Hz}, 1\text{H})\), 7.25 (m,
2H), 7.18 (t, J = 8.3 Hz, 2H), 5.38 (dd, J = 9.6, 3.0 Hz, 1H), 4.31 (ddd, J = 15.0, 12.0, 6.4 Hz, 2H), 4.11 (m, 2H), 4.01 (s, 3H), 3.90 (m, 2H), 3.69 (d, J = 6.8 Hz, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -113.90. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.4, 162.6 (d, J = 247.2 Hz), 159.4, 154.0, 138.8, 133.5, 132.1 (d, J = 3.5 Hz), 131.8, 131.4 (d, J = 8.0 Hz), 131.2 (d, J = 8.1 Hz), 128.9, 128.6, 115.3 (d, J = 21.6 Hz), 103.8, 76.8, 69.6, 67.6, 66.6, 55.5, 52.3. IR (cm$^{-1}$): ν 2954, 2918, 2815, 1720, 1618, 1515, 1466, 1415, 1396, 1378, 1328, 1303, 1227, 1160, 1119, 1089, 1025, 1002, 911, 840, 802. HRMS (ESI): calcd for C$_{22}$H$_{20}$FNO$_5$Na [M+Na]$^+$ 420.1223, found: 420.1221.

![Ethyl 1-(1,4-dioxan-2-yl)-4-phenylisoquinoline-3-carboxylate (3ia): Colorless oil](image)

Ethyl 1-(1,4-dioxan-2-yl)-4-phenylisoquinoline-3-carboxylate (3ia): Colorless oil (53.7 mg, 74% yield), $^1$H NMR (400 MHz, CDCl$_3$) δ 8.53 (d, J = 8.3 Hz, 1H), 7.67 (m, 3H), 7.48 (m, 3H), 7.33 (m, 2H), 5.44 (dd, J = 9.5, 3.1 Hz, 1H), 4.33 (m, 2H), 4.09 (m, 4H), 3.89 (d, J = 5.8 Hz, 2H), 0.96 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.3, 155.7, 141.4, 136.2, 136.0, 133.4, 130.5, 123.0, 129.8, 128.3, 128.2, 128.0, 127.2, 126.9, 125.6, 76.5, 69.7, 67.7, 66.5, 61.2, 13.6. IR (cm$^{-1}$): ν 2961, 2919, 2855, 1729, 1558, 1456, 1443, 1404, 1328, 1291, 1256, 1237, 1227, 1181, 1119, 1091, 1031, 915, 883, 765, 699. HRMS (ESI): calcd for C$_{22}$H$_{21}$NO$_4$Na [M+Na]$^+$ 386.1368, found: 386.1366.
Ethyl 1-(1,4-dioxan-2-yl)-7-methoxy-4-(4-methoxyphenyl)isoquinoline-3-carboxylate (3ja): Light yellow solid (47.3 mg, 56%), mp 130-132 °C, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.77 (d, \(J = 2.0\) Hz, 1H), 7.60 (d, \(J = 9.3\) Hz, 1H), 7.25 (m, 3H), 7.00 (d, \(J = 8.1\) Hz, 2H), 5.37 (dd, \(J = 9.5, 2.7\) Hz, 1H), 4.32 (m, 2H), 4.10 (m, 2H), 3.97 (d, \(J = 13.2\) Hz, 3H), 3.88 (m, 5H), 1.03 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.6, 159.4, 159.1, 153.6, 139.9, 133.4, 131.9, 131.1, 130.8, 128.8, 128.7, 128.3, 122.8, 113.7, 103.7, 74.9, 69.6, 67.6, 67.1, 66.6, 66.4, 61.1, 55.5, 55.4, 13.8. IR (cm\(^{-1}\)): \(\nu\) 2965, 2924, 2834, 1731, 1609, 1515, 1452, 1419, 1382, 1290, 1246, 1220, 1114, 1092, 1026, 839, 810, 564. HRMS (ESI): calcd for C\(_{24}\)H\(_{25}\)NO\(_6\)Na [M+Na]\(^+\) 446.1580, found: 446.1577.

Ethyl 1-(1,4-dioxan-2-yl)-7-fluoro-4-(4-fluorophenyl)isoquinoline-3-carboxylate (3ka): Colorless oil (51.8 mg, 65%), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.19 (dd, \(J = 10.0, 2.5\) Hz, 1H), 7.63 (dd, \(J = 9.3, 5.5\) Hz, 1H), 7.43 (ddd, \(J = 9.3, 7.9, 2.6\) Hz, 1H), 7.29 (m, 2H), 7.19 (m, 2H), 5.32 (m, 1H), 4.32 (m, 2H), 4.10 (m, 4H), 3.88 (m, 2H), 1.04 (t, \(J = 7.1\) Hz, 3H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -108.33, -113.41. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.9, 162.8 (d, \(J = 247.9\) Hz), 161.5 (d, \(J = 251.6\) Hz), 155.4 (d, \(J = 5.7\) Hz), 141.1 (d, \(J = 2.4\) Hz), 133.4, 132.4, 131.61 (d, \(J = 8.1\) Hz), 131.6 (d, \(J = 3.4\) Hz).
Hz), 131.4 (d, J = 8.1 Hz), 129.6 (d, J = 8.9 Hz), 128.4 (d, J = 9.2 Hz), 121.1 (d, J = 25.2 Hz), 115.4 (d, J = 21.7 Hz), 109.9 (d, J = 22.4 Hz), 76.7, 69.5, 67.6, 66.5, 61.4, 13.8. IR (cm\(^{-1}\)):\(\nu\) 3075, 2962, 2917, 2855, 1731, 1624, 1603, 1516, 1463, 1401, 1323, 1289, 1266, 1116, 1026, 911, 880, 839. HRMS (ESI): calcd for \(\text{C}_{22}\text{H}_{19}\text{F}_{2}\text{NO}_{4}\text{Na} [\text{M+Na}]^+\) 422.1180, found: 422.1180.

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\text{Methyl 1-}(\text{1,4-dioxan-2-yl})-4\text{-methylisoquinoline-3-carboxylate (3la):}\]
White solid (29.2 mg, 51% yield), mp 148-151 °C, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.49 (d, \(J = 8.4\) Hz, 1H), 8.14 (d, \(J = 8.4\) Hz, 1H), 7.78 (t, \(J = 7.6\) Hz, 1H), 7.70 (t, \(J = 7.5\) Hz, 1H), 5.36 (dd, \(J = 9.6, 2.7\) Hz, 1H), 4.23 (m, 2H), 4.07 (m, 5H), 3.87 (m, 2H), 2.82 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.0, 154.0, 140.7, 136.6, 130.4, 129.4, 128.3, 127.0, 126.0, 124.8, 76.7, 69.8, 67.6, 66.5, 52.6, 14.4. IR (cm\(^{-1}\)):\(\nu\) 2976, 2926, 2856, 1727, 1431, 1332, 1254, 1242, 1198, 1166, 1118, 1100, 1062, 1053, 1027, 913, 880, 865, 764. HRMS (ESI): calcd for \(\text{C}_{16}\text{H}_{17}\text{NO}_{4}\text{Na} [\text{M+Na}]^+\) 310.1055, found: 310.1052.

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\text{Methyl 4-phenyl-1-}(\text{tetrahydrofuran-2-yl})\text{-isoquinoline-3-carboxylate (3ab):}\]
Colorless oil (57.2 mg, 86%), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.53 (d, \(J = 8.3\) Hz, 1H), 7.67 (m, 3H), 7.48 (m, 3H), 7.33 (m, 2H), 5.73 (t, \(J = 7.0\) Hz, 1H), 4.16 (dd, \(J = 14.5, 7.5\) Hz, 1H), 4.04 (td, \(J = 7.9, 6.1\) Hz, 1H), 3.66 (s, 3H), 2.81 (ddd, \(J = 15.6, 12.6, 7.2\) Hz, 1H), 2.41 (m, 1H), 2.18 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.8, 158.8,
140.4, 136.3, 136.2, 133.5, 130.3, 129.9, 128.3, 128.2, 127.9, 127.2, 127.0, 125.8, 79.8, 69.1, 52.2, 29.8, 26.2. IR (cm⁻¹): ν 3058, 3027, 2950, 2873, 1737, 1614, 1558, 1505, 1445, 1396, 1327, 1234, 1166, 1117, 1055, 991, 918, 771, 700.


Methyl 7-fluoro-4-(4-fluorophenyl)-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3bb): Yellow solid (37.6 mg, 51% yield), mp 96-98 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.19 (dd, J = 10.1, 2.5 Hz, 1H), 7.61 (dd, J = 9.3, 5.6 Hz, 1H), 7.41 (m, 1H), 7.29 (m, 2H), 7.19 (m, 2H), 7.18 (m, 2H), 5.60 (t, J = 7.1 Hz, 1H), 4.14 (dd, J = 14.6, 7.4 Hz, 1H), 4.04 (dd, J = 14.1, 7.9 Hz, 1H), 3.70 (s, 3H), 2.79 (td, J = 15.7, 7.5 Hz, 1H), 2.40 (td, J = 12.7, 7.5 Hz, 1H), 2.17 (m, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ -109.41, -114.38. ¹³C NMR (101 MHz, CDCl₃) δ 167.5, 162.6 (d, J = 247.7 Hz), 161.5 (d, J = 251.5 Hz), 158.5 (d, J = 5.6 Hz), 140.1, 132.5, 131.8 (d, J = 3.6 Hz), 131.5 (d, J = 8.1 Hz), 131.3 (d, J = 8.1 Hz), 129.7 (d, J = 8.9 Hz), 128.5 (d, J = 9.0 Hz), 120.9 (d, J = 25.0 Hz), 115.5 (d, J = 21.6 Hz), 110.1 (d, J = 22.3 Hz), 80.2, 69.1, 52.4, 29.7, 26.1. IR (cm⁻¹): ν 2954, 2928, 2873, 1736, 1624, 1603, 1516, 1501, 1439, 1399, 1312, 1237, 1197, 1160, 1114, 1056, 1017, 840, 521. HRMS (ESI): calcd for C₂₁H₁₇F₂NO₃Na [M+Na]⁺ 392.1074, found: 392.1074.
Methyl 7-chloro-4-(4-chlorophenyl)-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3cb): Yellow oil (48.1 mg, 60% yield), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.55 (d, $J = 1.4$ Hz, 1H), 7.57 (m, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 7.24 (m, 2H), 5.63 (t, $J = 6.9$ Hz, 1H), 4.13 (dd, $J = 14.6$, 7.3 Hz, 1H), 4.05 (dd, $J = 14.0$, 7.7 Hz, 1H), 3.72 (s, 3H), 2.80 (td, $J = 15.2$, 7.5 Hz, 1H), 2.40 (dt, $J = 12.3$, 7.4 Hz, 1H), 2.17 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.2, 158.4, 140.5, 134.7, 134.6, 134.3, 134.2, 132.3, 131.5, 131.1, 130.9, 128.7, 128.6, 128.4, 128.0, 125.3, 79.8, 69.1, 52.5, 29.7, 26.1. IR (cm$^{-1}$): $\nu$ 3086, 2950, 2872, 2688, 2560, 1772, 1732, 1591, 1567, 1555, 1496, 1455, 1437, 1309, 1230, 1165, 1092, 1056, 1017, 837, 803. HRMS (ESI): calcd for C$_{21}$H$_{17}$Cl$_2$NO$_3$Na [M+Na]$^+$ 424.0483, found: 424.0482.

Methyl 7-bromo-4-(4-bromophenyl)-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3db): light yellow oil (64.4 mg, 66% yield), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.73 (d, $J = 1.8$ Hz, 1H), 7.70 (m, 1H), 7.63 (m, 2H), 7.44 (d, $J = 9.0$ Hz, 1H), 7.18 (m, 2H), 5.63 (t, $J = 7.0$ Hz, 1H), 4.08 (m, 2H), 3.72 (s, 3H), 2.80 (m, 1H), 2.40 (m, 1H), 2.17 (m, 2H). $^{13}$C NMR (101MHz, CDCl$_3$) $\delta$ 167.2, 158.4, 140.4, 134.7, 134.6, 134.1, 132.4, 131.6, 131.4, 131.2, 128.6, 128.4, 128.3, 123.1, 122.5, 79.8, 69.1, 52.4, 29.7, 26.1. IR (cm$^{-1}$): $\nu$ 3084, 2950, 2872, 2688, 2560, 2248, 1772, 1732, 1591,

Methyl 7-methyl-1-(tetrahydrofuran-2-yl)-4-(p-tolyl)isoquinoline-3-carboxylate (3eb): Colorless oil (59.2 mg, 82 %), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.25 (s, 1H), 7.55 (d, \(J = 8.7\) Hz, 1H), 7.43 (dd, \(J = 8.7, 1.4\) Hz, 1H), 7.27 (t, \(J = 6.8\) Hz, 2H), 7.19 (t, \(J = 8.2\) Hz, 2H), 5.71 (t, \(J = 7.0\) Hz, 1H), 4.14 (dd, \(J = 14.5, 7.4\) Hz, 1H), 4.04 (td, \(J = 7.9, 6.2\) Hz, 1H), 3.69 (s, 3H), 2.83 (m, 1H), 2.56 (s, 3H), 2.44 (s, 3H), 2.37 (m, 1H), 2.18 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.0, 158.7, 139.6, 138.5, 137.5, 134.7\(\nu\), 133.7, 133.4, 132.4, 129.7, 129.4, 128.9, 128.9, 127.5, 127.0, 124.6, 79.5, 69.0, 52.2, 29.6, 26.2, 22.2, 21.4. IR (cm\(^{-1}\)): \(\nu\) 2949, 2924, 2869, 1737, 1622, 1518, 1436, 1397, 1321, 1233, 1167, 1120, 1055, 1024, 1008, 962, 832, 819, 747. HRMS (ESI): calcd for C_{23}H_{23}NO_{3}Na [M+Na]^+ 384.1577, found: 384.1576.

Ethyl 4-phenyl-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3ib): Colorless oil (43.0 mg, 62%), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.46 (d, \(J = 8.2\) Hz, 1H), 7.57 (m, 3H), 7.40 (m, 3H), 7.27 (m, 2H), 5.67 (t, \(J = 7.0\) Hz, 1H), 4.01 (m, 4H), 2.77 (m, 1H), 2.32 (m, 1H), 2.12 (m, 2H), 0.89 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (101 MHz,
Methyl 4-phenyl-1-(tetrahydro-2H-pyran-2-yl)isoquinoline-3-carboxylate (3ac):
Colorless oil (38.1 mg, 55% yield), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.69 (d, $J$ = 8.3 Hz, 1H), 7.64 (m, 3H), 7.46 (m, 3H), 7.32 (m, 2H), 5.18 (dd, $J$ = 11.3, 2.2 Hz, 1H), 4.23 (m, 1H), 3.79 (td, $J$ = 11.6, 2.1 Hz, 1H), 3.66 (s, 3H), 2.32 (m, 1H), 2.08 (m, 2H), 1.84 (m, 2H), 1.69 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.7, 159.3, 140.6, 136.5, 136.3, 133.6, 130.3, 129.8, 129.7, 128.2, 128.1, 128.0, 127.9, 127.0, 126.9, 126.3, 81.4, 69.4, 52.3, 30.4, 26.0, 23.7. IR (cm$^{-1}$): $\nu$ 3057, 2924, 2851, 1735, 1682, 1613, 1556, 1505, 1443, 1377, 1337, 1232, 1166, 1084, 1042, 1003, 906, 770, 700. HRMS (ESI): calcd for C$_{22}$H$_{21}$NO$_3$Na [M+Na]$^+$ 370.1419, found: 370.1415.

Methyl 1-(benzo[d][1,3]dioxol-2-yl)-4-phenylisoquinoline-3-carboxylate (3ad):
Yellow solid (19.2 mg, 25% yield), mp 177-179 °C, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$
8.18 (d, J = 8.2 Hz, 1H), 7.57 (m, 3H), 7.43 (d, J = 6.2 Hz, 3H), 7.31 (s, 1H), 7.27 (d, J = 7.1 Hz, 2H), 6.91 (s, 4H), 3.63 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.0, 150.8, 146.2, 139.3, 136.0, 135.5, 134.6, 129.9, 128.5, 128.2, 127.3, 127.2, 126.4, 125.7, 123.8, 121.3, 111.5, 108.3, 51.5. IR (cm$^{-1}$): $\nu$ 3033, 2950, 2920, 2851, 1732, 1561, 1482, 1452, 1434, 1348, 1318, 1231, 1192, 1166, 1089, 1024, 983, 937, 743, 670. HRMS (ESI): calcd for C$_{24}$H$_{17}$NO$_4$Na [M+Na]$^+$ 406.1055, found: 406.1053.

Methyl 4-phenyl-1-(tetrahydrothiophen-2-yl)isoquinoline-3-carboxylate (3ae): Colorless oil (20.9 mg, 30%), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.27 (d, J = 8.3 Hz, 1H), 7.68 (m, 1H), 7.62 (m, 2H), 7.49 (m, 3H), 7.32 (m, 2H), 5.33 (t, J = 6.4 Hz, 1H), 3.64 (s, 3H), 3.12 (m, 3H), 2.58 (dt, J = 12.2, 6.2 Hz, 1H), 2.33 (td, J = 12.3, 6.3 Hz, 1H), 2.24 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.9, 160.3, 140.8, 136.2, 136.0, 132.5, 130.3, 129.9, 129.7, 128.3, 128.2, 127.9, 127.2, 125.1, 52.1, 48.7, 34.2, 33.8, 31.4. IR (cm$^{-1}$): $\nu$ 3063, 2947, 2858, 1732, 1644, 1573, 1557, 1506, 1443, 1393, 1329, 1229, 1190, 1167, 1032, 770, 700. HRMS (ESI): calcd for C$_{21}$H$_{15}$NO$_2$SNa [M+Na]$^+$ 372.1212, found: 372.1210.

Methyl 4-phenyl-1-(1-propoxypropyl)isoquinoline-3-carboxylate (3af): Colorless oil (37.2 mg, 51% yield). (major isomer) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.95 (m, 1H),
7.64 (m, 3H), 7.48 (m, 3H), 7.36 (m, 2H), 4.91 (dd, J = 8.8, 5.4 Hz, 1H), 3.66 (s, 3H),
3.45 (dt, J = 9.1, 6.6 Hz, 1H), 3.36 (dt, J = 9.2, 6.6 Hz, 1H), 2.22 (m, 1H), 2.01 (m,
1H), 1.61 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (101
MHz, CDCl$_3$) $\delta$ 166.9, 160.3, 139.8, 135.3, 135.2, 132.0, 129.4, 128.8, 128.7, 127.2,
126.9, 126.7, 125.9, 125.7, 125.3, 86.6, 70.4, 51.3, 28.4, 22.2, 10.0, 9.7. IR (cm$^{-1}$): $\nu$
3059, 2964, 2935, 2875, 1738, 1556, 1505, 1445, 1435, 1379, 1346, 1313, 1298, 1282,
127.9, 127.8, 127.0, 126.7, 126.3, 86.1, 69.4, 52.3, 38.6, 32.1, 19.9, 19.4, 14.0, 13.9.
IR (cm$^{-1}$): $\nu$ 3059, 2964, 2935, 2875, 1738, 1556, 1505, 1445, 1435, 1379, 1346,

![Structure](image)

**Methyl 1-(1-butoxybutyl)-4-phenylisoquinoline-3-carboxylate (3ag1):** Colorless oil (46 mg, 58% yield). (major isomer) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.96 (m, 1H),
7.64 (m, 3H), 7.48 (m, 3H), 7.35 (m, 2H), 4.99 (dd, J = 9.1, 5.1 Hz, 1H), 3.65 (s, 3H),
3.47 (m, 1H), 3.39 (m, 1H), 2.18 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.57 (m, 2H),
1.43 (m, 1H), 1.35 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). $^{13}$C
NMR (101 MHz, CDCl$_3$) $\delta$ 168.0, 161.5, 140.8, 136.4, 136.2, 133.0, 130.4, 129.8,
129.8, 128.2, 127.9, 127.8, 127.0, 126.7, 126.3, 86.1, 69.4, 52.3, 38.6, 32.1, 19.9, 19.4,
14.0, 13.9. IR (cm$^{-1}$): $\nu$ 2958, 2931, 2871, 1739, 1613, 1505, 1463, 1445, 1379, 1346,
1313, 1239, 1222, 1167, 1115, 1094, 773, 700. HRMS (ESI): calcd for C$_{25}$H$_{29}$NO$_3$Na
Methyl 1-(4-butoxybutan-2-yl)-4-phenylisoquinoline-3-carboxylate (3ag2):
Colorless oil (3.4 mg, 4% yield). (minor isomer) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.39 (m, 1H), 7.64 (m, 3H), 7.47 (m, 3H), 7.36 (m, 2H), 4.10 (dd, $J = 13.9$, 6.9 Hz, 1H), 3.65 (s, 3H), 3.53 (dt, $J = 9.7$, 6.0 Hz, 1H), 3.34 (m, 3H), 2.39 (m, 1H), 2.04 (m, 1H), 1.52 (m, 2H), 1.48 (d, $J = 6.8$ Hz, 3H), 1.34 (m, 2H), 0.89 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.4, 163.9, 140.5, 135.4, 134.7, 130.1, 129.0, 128.9, 127.2, 127.1, 126.9, 126.8, 126.2, 126.0, 123.9, 69.6, 67.8, 51.1, 35.3, 31.8, 30.9, 19.5, 18.4, 12.9. IR (cm$^{-1}$): $\nu$ 2959, 2930, 2870, 1739, 1556, 1506, 1446, 1395, 1328, 1232, 1168, 1115, 1031, 771, 700. HRMS (ESI): calcd for C$_{25}$H$_{29}$NO$_3$Na [M+Na]$^+$ 414.2045, found: 414.2043.

Methyl 1-(2-methyltetrahydrofuran-2-yl)-4-phenylisoquinoline-3-carboxylate (3ah1):
White solid (33.1 mg, 48% yield), mp 119-121°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.07 (m, 1H), 7.53 (m, 3H), 7.39 (m, 3H), 7.26 (d, $J = 7.1$ Hz, 2H), 4.02 (m, 1H), 3.69 (m, 1H), 3.57 (s, 3H), 3.42 (m, 1H), 1.91 (m, 3H), 1.75 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.1, 162.9, 139.9, 136.8, 136.4, 132.8, 129.9, 129.8, 128.2, 128.2, 128.1, 127.8, 127.5, 127.0, 126.7, 88.5, 68.1, 52.1, 37.4, 28.4, 25.2. IR (cm$^{-1}$): $\nu$ 2974, 2948, 2867, 1728, 1505, 1445, 1396, 1370, 1237, 1168, 1116, 1030, 913, 783, 710. HRMS (ESI): calcd for C$_{25}$H$_{21}$NO$_3$Na [M+Na]$^+$ 370.1419, found:
Methyl 1-(5-methyltetrahydrofuran-2-yl)-4-phenylisoquinoline-3-carboxylate (3ah2): Colorless oil (25.1 mg, 36% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.54 (d, $J$ = 8.3 Hz, 1H), 7.65 (m, 3H), 7.47 (m, 3H), 7.33 (m, 2H), 5.88 (t, $J$ = 7.0 Hz, 1H), 4.43 (m, 1H), 3.66 (s, 3H), 2.84 (m, 1H), 2.34 (m, 2H), 1.80 (m, 1H), 1.37 (d, $J$=6.1, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.9, 167.8, 159.3, 158.7, 140.4, 140.3, 136.4, 136.3, 136.3, 133.7, 133.4, 130.3, 129.9, 129.8, 129.6, 128.3, 128.2, 128.1, 127.9, 127.3, 127.2, 127.0, 126.0, 125.8, 80.5, 79.1, 76.0, 52.2, 34.0, 33.1, 30.4, 30.0, 21.4, 21.2. IR (cm$^{-1}$): $\nu$ 2965, 2928, 2870, 1738, 1557, 1505, 1445, 1379, 1326, 1235, 1167, 1116, 1077, 994, 771, 700. HRMS (ESI): calcd for C$_{22}$H$_{21}$NO$_3$Na [M+Na]$^+$ 370.1419, found: 370.1419.
6. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra for compound 3

$^1\text{H}$ NMR and $^{13}\text{C}$ NMR spectrum of 3aa
$^1$H NMR and $^{13}$C NMR spectrum of 3aa'}
$^1$H NMR and $^{13}$C NMR spectrum of 3ba
$^1$H NMR and $^{13}$C NMR spectrum of 3ca
$^1$H NMR and $^{13}$C NMR spectrum of 3da
$^1$H NMR and $^{13}$C NMR spectrum of 3ea
$^1$H NMR and $^{13}$C NMR spectrum of 3fa
$^1$H NMR and $^{13}$C NMR spectrum of 3ga
$^1$H NMR and $^{13}$C NMR spectrum of 3ha
$^1$H NMR and $^{13}$C NMR spectrum of 3ia
$^1$H NMR and $^{13}$C NMR spectrum of 3ja
$^1$H NMR and $^{13}$C NMR spectrum of 3ka
$^1$H NMR and $^{13}$C NMR spectrum of 3la
$^1$H NMR and $^{13}$C NMR spectrum of 3ab
$^1$H NMR and $^{13}$C NMR spectrum of 3bb
$^1$H NMR and $^{13}$C NMR spectrum of 3cb
$^1$H NMR and $^{13}$C NMR spectrum of 3db
$^1$H NMR and $^{13}$C NMR spectrum of 3eb
$^1$H NMR and $^{13}$C NMR spectrum of 3ib
$^1$H NMR and $^{13}$C NMR spectrum of 3ac
$^1$H NMR and $^{13}$C NMR spectrum of 3ad
$^1$H NMR and $^{13}$C NMR spectrum of 3ae
$^1$H NMR and $^{13}$C NMR spectrum of 3af
$^1$H NMR and $^{13}$C NMR spectrum of 3ag1
$^1$H NMR and $^{13}$C NMR spectrum of 3ag2
$^1$H NMR and $^{13}$C NMR spectrum of 3ah1
$^1$H NMR and $^{13}$C NMR spectrum of 3ah2