Supporting Information
for DOI: 10.1055/s-0030-1259704
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Rapid Access to
\textit{H}-Pyrazolo[5,1-\textit{a}]isoquinolines via Sequential
Reaction of
\textit{N'}-(2-Alkynylbenzylidene)hydrazide

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Supporting Information

1. General experimental methods (S2)
2. General experimental procedure and characterization data (S2-S14)
3. $^1$H and $^{13}$C NMR spectra of compound 3 and 4 (S15-S64)
General experimental methods:

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All reactions were performed in reaction tubes. The Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 µm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25-35°C. DCE was distilled from CaH₂ suspension after stirred at r.t. overnight followed by refluxed for 2 hs under N₂. Other commercial reagents and solvents were used as received. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale.

General procedure for the one-pot reaction of N'- (2-alkynylbenzylidene)hydrazide 1, bromine, methanol, and α,β-unsaturated aldehyde 2

Bromine (0.3 mmol, 1.0 equiv) in 2.0 mL of CH₂Cl₂ was added dropwisely to a mixture of N'- (2-alkynylbenzylidene)hydrazide 1 (0.30 mmol) in CH₂Cl₂ (4.0 mL). The reaction was stirred at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was then diluted with CH₂Cl₂ (25 mL), washed with saturated aqueous Na₂S₂O₃ (25 mL), dried (Na₂SO₄) and filtered. The solvent was then evaporated and the residue was dissolved in 2.0 mL of CCl₄. Then α,β-unsaturated aldehyde 2 (0.36 mmol, 1.2 equiv), methanol (0.2 mL) and DBU (2.0 equiv) were added. The mixture was heated to 50 °C for a period of time. After completion of the reaction as indicated by TLC, the solvent was concentrated under
vacuum, and the crude mixture was directly purified by column chromatography on silica gel (PE : DCM = 4:1 to 1:1) to afford the desired product 3.

**6-Bromo-1-(methoxy(phenyl)methyl)-5-phenylpyrazolo[5,1-a]isoquinoline \( (3a) \):**
Yield: 80%; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.33-8.25 (m, 2H), 7.68-7.54 (m, 6H), 7.53-7.45 (m, 4H), 7.39-7.29 (m, 3H), 5.90 (s, 1H), 3.50 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 56.9, 78.9, 110.0, 115.8, 124.5, 125.4, 127.4, 127.7, 128.1, 128.4, 128.5, 128.6, 128.7, 128.8, 129.6, 130.1, 134.5, 135.1, 138.0, 139.9, 142.5; HRMS calcd. for C\(_{25}\)H\(_{19}\)BrN\(_2\)O\(^+\) [M+H]\(^+\): 443.0759, found 443.0738.

**6-Bromo-1-(methoxy(p-tolyl)methyl)-5-phenylpyrazolo[5,1-a]isoquinoline \( (3b) \):**
Yield: 51%; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.32-8.24 (m, 2H), 7.66-7.49 (m, 8H), 7.37-7.33 (m, 2H), 7.18-7.15 (m, 2H), 5.86 (s, 1H), 3.47 (s, 3H), 2.34 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 21.2, 56.8, 78.7, 109.9, 116.0, 124.3, 125.4, 127.4, 127.7, 127.9, 128.4, 128.5, 128.7, 128.8, 129.2, 129.5, 130.1, 134.6, 135.1, 137.0, 137.7, 142.4; HRMS calcd. for C\(_{26}\)H\(_{21}\)BrN\(_2\)O\(^+\) [M+H]\(^+\): 457.0916, found 457.0899.

**6-Bromo-1-(methoxy(4-methoxyphenyl)methyl)-5-phenylpyrazolo[5,1-a]isoquinoline \( (3c) \):**
Yield: 54%; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.31-8.24 (m, 2H), 7.68 (s, 1H), 7.67-7.50 (m, 7H), 7.39-7.37 (m, 2H), 6.91-6.88 (m, 2H), 5.84 (s, 1H), 3.79 (s, 3H),
3.47 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 55.3, 56.7, 77.8, 109.9, 113.9, 116.1, 124.5, 125.4, 127.7, 128.4, 128.5, 128.8, 129.5, 130.1, 132.0, 134.5, 134.9, 136.0, 138.0, 142.3, 149.9, 159.4; HRMS calcd. for C$_{26}$H$_{21}$BrN$_2$O$_2$ $\left[M+H\right]^+$: 473.0865, found 473.0886.

6-Bromo-1-((4-bromophenyl)(methoxy)methyl)-5-phenylpyrazolo[5,1-$a$]isoquinoline (3d): Yield: 87%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.28-8.25 (m, 2H), 7.68 (s, 1H), 7.63-7.46 (m, 9H), 7.35-7.33 (m, 2H), 5.85 (s, 1H), 3.48 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 56.9, 77.9, 110.2, 115.0, 121.9, 124.3, 125.4, 127.8, 128.5, 128.7, 128.8, 129.1, 129.6, 130.1, 131.7, 132.5, 134.4, 135.1, 139.2, 142.4, 151.2; HRMS calcd. for C$_{25}$H$_{18}$Br$_2$N$_2$O $\left[M+H\right]^+$: 520.9864, found 520.9865.

6-Bromo-1-(methoxy(pyridin-3-yl)methyl)-5-phenylpyrazolo[5,1-$a$]isoquinoline (3e): Yield: 78%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.73 (s, 1H), 8.53 (d, $J$ = 3.64 Hz, 1H), 8.27-8.24 (m, 2H), 7.80-7.72 (m, 2H), 7.66-7.51 (m, 7H), 7.29-7.25 (m, 1H), 5.94 (s, 1H), 3.49 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 56.9, 76.7, 110.3, 114.3, 123.5, 124.1, 125.3, 127.9, 128.6, 128.8, 128.86, 128.9, 129.6, 130.1, 130.2, 134.9, 135.2, 135.8, 138.0, 142.4, 149.0, 149.3; HRMS calcd. for C$_{24}$H$_{18}$BrN$_3$O $\left[M+H\right]^+$: 444.0711, found 444.0691.

6-Bromo-5-butyl-1-(methoxy(phenyl)methyl)pyrazolo[5,1-$a$]isoquinoline (3g): Yield:
70%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.25-8.22 (m, 1H), 8.17 (d, $J = 7.36$ Hz, 1H), 7.64 (s, 1H), 7.63-7.51 (m, 2H), 7.49-7.45 (m, 2H), 7.41-7.29 (m, 3H), 5.87 (s, 1H), 3.52 (t, $J = 7.36$ Hz, 2H), 3.48 (s, 3H), 1.79-1.77 (m, 2H), 1.58-1.52 (m, 2H), 0.98 (t, $J = 7.36$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.0, 22.9, 28.9, 31.7, 56.8, 78.2, 108.8, 115.8, 123.7, 125.0, 127.1, 127.4, 127.5, 128.0, 128.3, 128.6, 128.8, 134.6, 139.5, 140.0, 141.8; HRMS calcd. for C$_{23}$H$_{23}$BrN$_2$O$^+$ [M+Na]$^+$: 445.0891, found 445.0893.

![Chemical structure of 6-Bromo-5-butyl-1-(methoxy(pyridin-3-yl)methyl)pyrazolo[5,1-a]isoquinoline (3h)]

6-Bromo-5-butyl-1-(methoxy(pyridin-3-yl)methyl)pyrazolo[5,1-a]isoquinoline (3h):
Yield: 56%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.90-8.50 (br, 2H), 8.19-8.14 (m, 2H), 7.79-7.75(m, 1H), 7.74 (s, 1H), 7.61-7.57 (m, 1H), 7.52-7.48 (m, 1H), 7.32-7.27 (m, 1H), 5.91 (s, 1H), 3.54 (t, $J = 7.56$ Hz, 2H), 3.47 (s, 3H), 1.81-1.72 (m, 2H), 1.60-1.49 (m, 2H), 0.98 (t, $J = 7.56$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.0, 22.9, 28.9, 31.7, 56.9, 76.6, 109.1, 114.2, 123.4, 125.0, 127.2, 127.6, 128.5, 128.8, 134.7, 135.0, 139.6, 141.7, 148.9, 149.1; HRMS calcd. for C$_{22}$H$_{22}$BrN$_3$O$^+$ [M+H]$^+$: 424.1024, found 424.1014.

![Chemical structure of 6-Bromo-1-(methoxy(phenyl)methyl)-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (3i)]

6-Bromo-1-(methoxy(phenyl)methyl)-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (3i):
Yield: 80%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.15-8.10 (m, 2H), 7.61-7.42 (m, 9H), 7.41-7.36 (m, 2H), 7.34-7.29 (m, 1H), 5.88 (s, 1H), 3.52 (s, 3H), 2.54 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.8, 56.8, 79.3, 109.9, 115.9, 124.4, 125.3, 126.7, 127.5, 127.6, 128.0, 128.5, 128.7, 128.8, 129.5, 129.9, 130.2, 134.5, 134.9, 138.5, 140.0, 142.2; HRMS calcd. for C$_{26}$H$_{21}$BrN$_2$O$^+$ [M+H]$^+$: 457.0916, found 457.0897.
6-Bromo-1-(methoxy(p-tolyl)methyl)-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (3j): Yield: 44%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.14-8.09 (m, 2H), 7.60 (s, 1H), 7.58-7.44 (m, 6H), 7.38-7.36 (m, 2H), 7.19-7.16 (m, 2H), 5.84 (s, 1H), 3.49 (s, 3H), 2.55 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.2, 21.8, 56.7, 78.3, 109.8, 116.1, 124.4, 125.3, 126.7, 127.5, 127.6, 128.71, 128.77, 129.2, 129.4, 129.9, 130.2, 134.5, 134.8, 136.9, 137.7, 138.4, 142.1; HRMS calcd. for C$_{27}$H$_{23}$BrN$_2$O$^+$ [M+H]$^+$: 471.1072, found 471.1079.

6-Bromo-1-(methoxy(4-methoxyphenyl)methyl)-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (3k): Yield: 40%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.12 (d, $J = 8.72$ Hz, 1H), 8.05 (s, 1H), 7.61 (s, 1H), 7.59-7.44 (m, 6H), 7.41-7.38 (m, 2H), 6.91-6.89 (m, 2H), 5.82 (s, 1H), 3.80 (s, 3H), 3.48 (s, 3H), 2.53 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.8, 55.3, 56.6, 78.4, 109.8, 113.9, 116.2, 124.4, 125.3, 127.5, 128.71, 128.77, 128.8, 129.4, 129.9, 130.2, 132.1, 134.5, 134.7, 137.1, 138.4, 142.0, 159.3; HRMS calcd. for C$_{27}$H$_{23}$BrN$_2$O$_2$$^+$ [M+Na]$^+$: 509.0841, found 509.0852.

6-Bromo-1-((4-bromophenyl)(methoxy)methyl)-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (3l): Yield: 73%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.14 (d, $J = 8.24$ Hz, 1H), 8.04 (s, 1H), 7.61 (s, 1H), 7.59-7.44 (m, 8H), 7.38-7.34 (m, 2H), 5.84 (s, 1H), 3.49 (s, 3H), 2.53 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.8, 56.8, 78.4, 110.2, 115.0,
121.9, 124.2, 125.3, 126.7, 127.7, 128.7, 129.1, 129.5, 130.1, 130.3, 131.6, 134.42, 135.0, 137.1, 138.6, 139.3, 142.2; HRMS calcd. for C_{26}H_{20}Br_2N_2O^+[M+Na]^+: 556.9840, found 556.9811.

![Chemical structure]

6-Bromo-1-(methoxy(pyridin-3-yl)methyl)-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (3m): Yield: 63%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.74 (s, 1H), 8.55 (d, $J = 4.12$ Hz, 1H), 8.12 (d, $J = 8.24$ Hz, 1H), 8.03 (s, 1H), 7.80-7.72 (m, 1H), 7.66 (s, 1H), 7.61-7.48 (m, 5H), 7.47-7.43 (m, 1H), 7.31-7.26 (m, 1H), 5.92 (s, 1H), 3.50 (s, 3H), 2.51 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.8, 56.9, 76.5, 110.3, 114.3, 123.5, 124.1, 125.2, 126.8, 127.7, 128.7, 128.8, 129.5, 130.2, 134.4, 134.9, 135.0, 135.9, 137.1, 138.7, 142.2, 149.0, 149.3; HRMS calcd. for C$_{25}$H$_{20}$BrN$_3$O$^+[M+H]^+$: 365.1654, C$_{21}$H$_{17}$BrN$_2$O$^+[M+H]^+$: 458.0868, found 458.0836.

![Chemical structure]

6-Bromo-5-cyclopropyl-8-fluoro-1-(methoxy(pyridin-3-yl)methyl)pyrazolo[5,1-a]isoquinoline (3n): Yield: 54%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.69 (s, 1H), 8.54 (d, $J = 3.64$ Hz, 1H), 8.18 (dd, $J = 5.48$, 9.16 Hz, 1H), 7.89 (dd, $J = 2.28$, 10.52 Hz, 1H), 7.76 (s, 1H), 7.74-7.69 (m, 1H), 7.30-7.25 (m, 1H), 7.24-7.17 (m, 1H), 5.85 (s, 1H), 3.45 (s, 3H), 2.42-2.31 (m, 1H), 1.41-1.281 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 10.1, 14.3, 56.8, 76.6, 110.8, 112.9 (d, $J = 27.75$ Hz), 113.3, 116.4 (d, $J = 22.88$ Hz), 120.1, 123.5, 127.8, 131.5, 134.8, 134.9, 135.7, 139.2, 142.0, 148.9, 149.3, 162.3 (d, $^1$J = 247.90 Hz); HRMS calcd. for C$_{21}$H$_{17}$BrFN$_3$O$^+[M+H]^+$: 426.0617, found 426.0611.
6-Bromo-5-cyclopropyl-9-fluoro-1-(methoxy(phenyl)methyl)pyrazolo[5,1-a]isoquinoline (3o): Yield: 50%; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.23-8.19 (dd, \(J = 5.48, 9.16\) Hz, 1H), 7.97-7.93 (dd, \(J = 2.76, 10.52\) Hz, 1H), 7.60 (s, 1H), 7.47-7.44 (m, 2H), 7.42-7.27 (m, 4H), 5.78 (s, 1H), 3.47 (s, 3H), 2.34-2.26 (m, 1H), 1.38-1.31 (m, 2H), 1.27-1.22 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 10.0, 10.1, 13.9, 56.7, 78.9, 110.6 (d, \(J = 24.39\) Hz), 116.2, 116.6 (d, \(J = 22.89\) Hz), 125.0, 125.6, 127.4, 128.1, 128.6, 129.5, 129.6, 134.3, 137.4, 139.6, 141.6, 161.8 (d, \(J = 245.99\) Hz); HRMS calcd. for C\(_{22}\)H\(_{18}\)BrFN\(_2\)O\(^+\)[M+H]\(^+\): 425.0665, found 425.0630.

6-Bromo-1-((4-bromophenyl)(methoxy)methyl)-5-cyclopropyl-9-fluoropyrazolo[5,1-a]isoquinoline (3p): Yield: 60 %; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.20 (dd, \(J = 5.52, 9.16\) Hz, 1H), 7.90 (dd, \(J = 2.76, 10.08\) Hz, 1H), 7.64 (s, 1H), 7.52-7.46 (m, 2H), 7.34-7.29 (m, 3H), 5.73 (s, 1H), 3.45 (s, 3H), 2.35-2.27 (m, 1H), 1.39-1.33 (m, 2H), 1.27-1.23 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 10.0, 10.1, 14.0, 56.7, 77.9, 110.6 (d, \(J = 24.79\) Hz), 111.2, 115.4, 116.8 (d, \(J = 23.84\) Hz), 122.0, 124.7, 125.6, 129.0, 129.6, 131.7, 134.3, 137.4, 138.9, 141.6, 161.8 (d, \(J = 245.99\) Hz). HRMS calcd. for C\(_{22}\)H\(_{17}\)BrFN\(_2\)O\(^+\)[M+H]\(^+\): 502.9770, found 502.9763.

A solution of \textit{H}-pyrazolo[5,1-\textit{a}]isoquinoline 3 (0.1 mmol), arylboronic acid (0.12 mmol, 1.2 equiv), K$_2$CO$_3$ (0.2 mmol, 2.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.01 mmol, 10 mol \%) in 0.8 mL of DMF-H$_2$O (5:1, v/v ) was stirred at 50 °C for about 8-10 hours under N$_2$ atmosphere. After completion of the reaction as indicated by TLC, water (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL \times 3). The combined organic layer was washed with brine (15 mL), dried over Na$_2$SO$_4$. Evaporation of the solvent followed by purification on silica gel provided the corresponding product 4.

1-(Methoxy(phenyl)methyl)-5,6-diphenylpyrazolo[5,1-\textit{a}]isoquinoline (4a): Yield: 99%; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.35 (d, $J = 8.24$ Hz, 1H), 7.67 (s, 1H), 7.56-7.50 (m, 4H), 7.43-7.36 (m, 5H), 7.33-7.23 (m, 6H), 7.21-7.16 (m, 3H), 5.97 (s, 1H), 3.53 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 56.9, 79.0, 115.4, 124.5, 124.6, 125.2, 126.7, 127.4, 127.5, 127.6, 127.9, 128.0, 128.1, 128.4, 128.5, 130.7, 130.8, 131.6, 133.3, 135.3, 136.2, 136.6, 140.3, 142.0; HRMS calcd. for C$_{31}$H$_{24}$N$_2$O$^+$ [M + H]$^+$: 441.1967, found 441.1958.
1-(Methoxy(phenyl)methyl)-5-phenyl-6-p-tolylrazolo[5,1-a]isoquinoline (4b): Yield: 98%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.37 (d, $J = 8.24$ Hz, 1H), 7.69 (s, 1H), 7.56-7.52 (m, 3H), 7.46-7.37 (m, 4H), 7.35-7.27 (m, 6H), 7.11-7.07 (m, 4H), 5.98 (s, 1H), 3.54 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.3, 56.9, 78.9, 115.3, 124.5, 124.6, 125.1, 127.3, 127.5, 127.6, 127.9, 128.0, 128.3, 128.5, 128.8, 128.9, 130.9, 130.9, 131.4, 133.1, 133.5, 135.3, 136.6, 140.3, 142.0; HRMS calcd. for C$_{32}$H$_{26}$N$_2$O$^+$ [M + H]$^+$: 455.2123, found 455.2108.

1-(Methoxy(phenyl)methyl)-6-(4-methoxyphenyl)-5-phenylrazolo[5,1-a]isoquinoline (4c): Yield: 90%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.35 (d, $J = 8.24$ Hz, 1H), 7.67 (s, 1H), 7.58-7.50 (m, 3H), 7.48-7.36 (m, 4H), 7.34-7.27 (m, 6H), 7.12-7.06 (m, 2H), 6.84-6.80 (m, 2H), 5.97 (s, 1H), 3.78 (s, 3H), 3.53 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 55.2, 56.9, 79.1, 113.6, 115.3, 124.2, 124.5, 125.1, 126.9, 127.3, 127.5, 127.6, 127.9, 128.1, 128.3, 128.4, 128.5, 130.8, 132.6, 132.6, 136.8, 140.3, 142.0, 158.6; HRMS calcd. for C$_{32}$H$_{26}$N$_2$O$_2$$^+$ [M + H]$^+$: 471.2073, found 471.2052.
1-(Methoxy(phenyl)methyl)-5-phenyl-6-(4-(trifluoromethyl)phenyl)pyrazolo[5,1-a]isoquinoline (4d): Yield: 94%; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \ 8.39\) (d, \(J = 7.76\) Hz, 1H), 7.71 (s, 1H), 7.62-7.50 (m, 6H), 7.48-7.39 (m, 3H), 7.38-7.28 (m, 8H), 5.98 (s, 1H), 3.54 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta \ 56.9, 78.9, 115.7, 123.1, 124.6, 125.1, 125.4, 126.2, 126.3\ (q, \(^1J = 270\) Hz), 127.5, 127.7, 127.8, 128.0, 128.2, 128.6, 128.8, 129.5 (q, \(^2J = 33\) Hz), 130.1, 130.7, 132.0, 132.7, 135.4, 136.9, 140.2, 140.3, 142.4; HRMS calcd. for C\(_{32}\)H\(_{23}\)F\(_3\)N\(_2\)O\(_2\)\([M + H]^+\): 509.1841, found 509.1822.

1-(Methoxy(pyridin-3-yl)methyl)-5,6-diphenylpyrazolo[5,1-a]isoquinoline (4e): Yield: 98%; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \ 8.75\) (d, \(J = 1.36\) Hz, 1H), 8.54 (dd, \(^1J = 1.36, 4.60\) Hz, 1H), 8.29 (d, \(J = 8.28\) Hz, 1H), 7.84-7.80 (m, 1H), 7.77 (s, 1H), 7.54-7.49 (m, 1H), 7.43-7.41 (m, 2H), 7.34-7.23 (m, 9H), 7.21-7.17 (m, 2H), 6.00 (s, 1H), 3.53 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta \ 56.9, 76.7, 113.8, 123.5, 124.2, 124.9, 125.1, 127.3, 127.5, 127.8, 128.0, 128.1, 128.2, 128.5, 130.7, 130.8, 131.5, 133.2, 135.0, 135.4, 136.1, 136.2, 136.6, 142.0, 149.1, 149.2; HRMS calcd. for C\(_{30}\)H\(_{23}\)N\(_3\)O\(_2\)\([M + H]^+\): 442.1919, found 442.1896.

1-(Methoxy(phenyl)methyl)-9-methyl-5,6-diphenylpyrazolo[5,1-a]isoquinoline (4f):
Yield: 96%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.16 (s, 1H), 7.63 (s, 1H), 7.58-7.53 (m, 2H), 7.44-7.37 (m, 2H), 7.35-7.23 (m, 1H), 7.22-7.15 (m, 2H), 5.97 (s, 1H), 3.56 (s, 3H), 2.52 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.8, 56.8, 79.1, 115.5, 124.5, 124.6, 125.1, 126.6, 127.2, 127.5, 127.9, 128.0, 128.1, 128.3, 128.6, 129.0, 130.9, 131.5, 131.6, 133.4, 135.1, 135.7, 136.4, 137.2, 140.4, 141.8; HRMS calcd. for C$_{32}$H$_{26}$N$_2$O$^+$ [M + H]$^+$: 455.2123, found: 455.2091.

![Structure 4g](image)

1-(Methoxy(pyridin-3-yl)methyl)-9-methyl-5,6-diphenylpyrazolo[5,1-a]isoquinoline (4g): Yield: 93%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.76 (s, 1H), 8.07 (s, 1H), 7.87-7.05 (m, 1H), 7.71 (s, 1H), 7.34-7.22 (m, 1H), 7.19-7.14 (m, 2H), 5.99 (s, 1H), 3.54 (s, 3H), 2.47 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.8, 56.9, 76.7, 113.9, 123.4, 124.2, 124.8, 125.0, 126.7, 127.2, 128.0, 128.1, 128.4, 128.5, 129.2, 130.9, 131.5, 133.2, 135.0, 135.2, 135.8, 136.2, 137.4, 141.8, 149.1, 149.2; HRMS calcd. for C$_{31}$H$_{25}$N$_3$O$^+$ [M + H]$^+$: 456.2076, found 456.2063.

![Structure 4h](image)

5-Cyclopropyl-9-fluoro-1-(methoxy(phenyl)methyl)-6-phenylpyrazolo[5,1-a]isoquinoline (4h): Yield: 83%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.99 (dd, $J = 0.68$, 2.63 Hz, 1H), 7.66 (s, 1H), 7.53-7.45 (m, 5H), 7.43-7.37 (m, 2H), 7.36-7.31 (m, 4H), 7.14-7.07 (m, 1H), 5.86 (s, 1H), 3.51 (s, 3H), 2.18-2.10 (m, 1H), 0.89-0.80 (m, 2H), 0.66-0.58 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 8.27, 12.1, 56.7, 78.9, 110.4 (d, $J = 23.84$ Hz), 115.7 (d, $J = 21.93$ Hz), 123.9, 125.1, 126.8, 127.1, 127.5, 127.7, 128.0, 128.3, 128.4, 128.5, 128.6, 131.3, 135.8, 136.7, 140.0, 141.4, 161.2 (d, $J = 245.04$ Hz); HRMS calcd. for C$_{28}$H$_{23}$FN$_2$O$^+$ [M + Na]$^+$: 445.1692, found 445.1674.
1-(Biphenyl-4-yl(methoxy)methyl)-9-methyl-5,6-diphenylpyrazolo[5,1-α]isoquinoline (4i): Yield: 98%; 1H NMR (400 MHz, CDCl₃): δ 8.18 (s, 1H), 7.72 (s, 1H), 7.66-7.60 (m, 6H), 7.47-7.41 (m, 2H), 7.36-7.22 (m, 11H), 7.21-7.15 (m, 2H), 6.01 (s, 1H), 3.58 (s, 3H), 2.52 (s, 3H); 13C NMR (100 MHz, CDCl₃): δ 21.8, 56.9, 78.9, 115.3, 124.5, 125.1, 126.6, 127.20, 127.24, 127.27, 127.4, 128.0, 128.1, 128.3, 128.6, 128.8, 129.1, 130.9, 131.5, 133.4, 135.1, 135.8, 136.4, 137.3, 139.5, 140.7, 140.9, 141.8; HRMS calcld. for C₃₈H₃₀N₂O⁺ [M + H]⁺: 531.2436, found 531.2417.

A mixture of compound 3a (0.1 mmol), K₂CO₃ (0.2 mmol, 2.0 equiv), PdCl₂(PPh₃)₂ (10 mol %), PPh₃ (0.4 equiv), and n-butyl acrylate (0.2 mmol, 2.0 equiv) in 1.0 mL of anhydrous DMF was heated to reflux for 24 hours under N₂ atmosphere. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature. The reaction was quenched with water (10 mL) and the reaction mixture was extracted with ethyl acetate (8 mL × 3). The combined organic layer was washed with brine (20 mL × 2), dried over Na₂SO₄. Evaporation of the solvent followed by purification on silica gel provided the corresponding product 4j as a white solid.

(E)-Butyl 3-(1-(methoxy(phenyl)methyl)-5-phenylpyrazolo[5,1-α]isoquinolin-6-yl)acrylate (4j): Yield: 80%; 1H NMR (400 MHz, CDCl₃): δ 8.36-8.32 (m, 1H), 8.09-8.05 (m, 1H), 7.72 (d, J = 16.04 Hz, 1H), 7.67 (s, 1H), 7.61-7.58 (m, 2H), 7.53-7.44 (m, 7H),
7.40-7.29 (m, 3H), 6.04 (d, $J = 16.04$ Hz, 1H), 5.91 (s, 1H), 4.13 (t, $J = 6.88$ Hz, 2H), 3.50 (s, 3H), 1.65-1.57 (m, 2H), 1.39-1.30 (m, 2H), 0.92 (t, $J = 7.32$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 13.8, 19.2, 30.7, 56.9, 64.5, 79.0, 115.9, 117.5, 124.7, 125.1, 125.7, 127.4, 127.8, 128.0, 128.3, 128.5, 128.6, 128.7, 129.5, 130.6, 132.5, 135.3, 137.8, 139.9, 140.0, 143.0, 166.3; HRMS calcd. for C$_{32}$H$_{30}$N$_2$O$_3$ $^{[M + H]}$: 491.2335, found 491.2312.
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