

Supporting Information

for

Synthesis of 2-trifluoromethylpyrazolo[5,1-*a*]isoquinolines via silver triflate-catalyzed or electrophile-mediated one-pot tandem reaction

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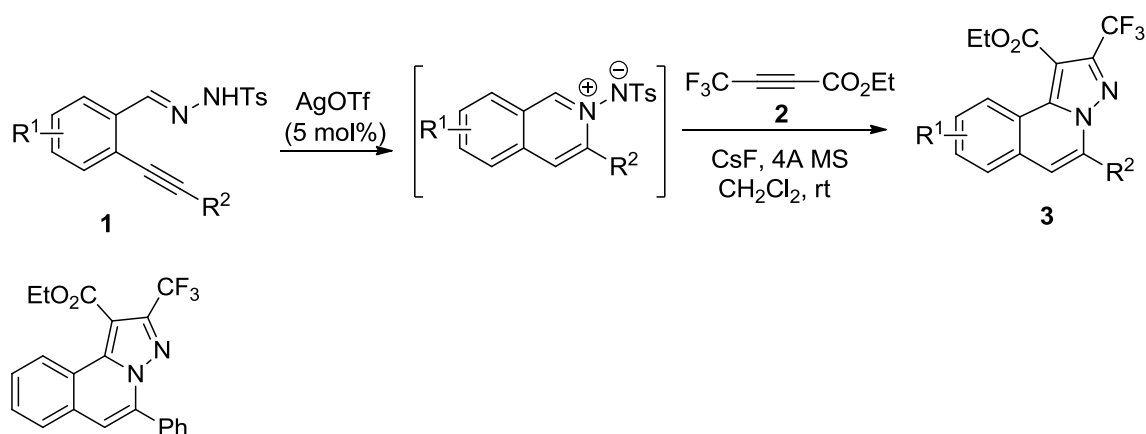
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Characterization data and NMR spectra

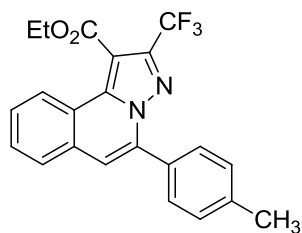
1. General procedure and characterization data for compounds **3** and **4** S2–S13
2. NMR spectra of all compounds. S14–S32

General procedure for the silver triflate-catalyzed one-pot tandem reaction of N'-(2-alkynylbenzylidene)-hydrazide **1** with ethyl 4,4,4-trifluorobut-2-ynoate **2** : A mixture of N'-(2-alkynylbenzylidene)hydrazide **1** (0.30 mmol, 1.0 equiv.) and silver triflate (5 mol%) in anhydrous dichloromethane (3.0 mL) was stirred at room temperature for overnight. Then a solution of ethyl 4,4,4-trifluorobut-2-ynoate (0.60 mmol, 2.0 equiv.) in dichloroethane (2.0 mL), 4A MS (75 mg) and CsF (0.45 mmol, 1.5 equiv.) were added, stirred for another 3 h. After completion of the reaction as indicated by TLC, the reaction mixture was purified by flash column chromatography on silica gel to provide the corresponding product **3**.



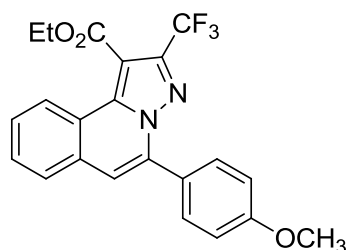
Ethyl 5-phenyl-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3a**)

Isolated (R_f = 0.7, EtOAc–petroleum ether = 1:10) as a colorless solid (105 mg, 91% yield), mp: 147-148 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.46 (t, *J* = 7.2 Hz, 3H), 4.49 (q, *J* = 7.2 Hz, 2H), 7.25 (s, 1H), 7.46-7.54 (m, 3H), 7.57-7.64 (m, 2H), 7.71-7.76 (m, 1H), 7.80-7.85 (m, 2H), 9.17 (d, *J* = 9.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 61.7, 106.3, 116.6, 121.0 (q, ¹*J*_{C-F} = 269.0 Hz), 123.2, 126.3, 127.5, 128.1, 128.4, 129.7, 129.8, 130.0, 130.6, 132.4, 137.9, 140.1, 143.1 (q, ²*J*_{C-F} = 37.0 Hz), 163.4; HRMS calcd. For C₂₁H₁₆F₃N₂O₂ [M+H]⁺: 385.1164, Found: 385.1167.



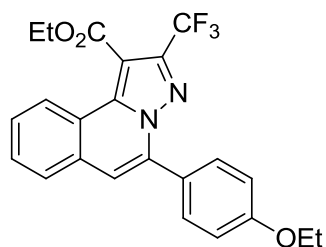
Ethyl 5-(p-tolyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3b**)

Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a colorless solid (102 mg, 86% yield), mp: 133-134 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.46 (t, $J = 7.2$ Hz, 3H), 2.43 (s, 3H), 4.49 (q, $J = 7.2$ Hz, 2H), 7.23 (s, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.57-7.63 (m, 2H), 7.72 (d, $J = 8.0$ Hz, 3H), 9.16 (d, $J = 8.8$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 13.9, 21.5, 61.7, 106.2, 116.2, 121.1 (q, $^1J_{\text{C-F}} = 269.0$ Hz), 123.1, 126.3, 127.4, 127.9, 129.1, 129.4, 129.6, 129.9, 130.7, 138.0, 139.9, 140.1, 143.0 (q, $^2J_{\text{C-F}} = 37.0$ Hz), 163.4; HRMS calcd. For. $\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 421.1140, Found: 421.1155.

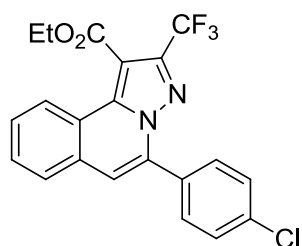


Ethyl 5-(4-methoxyphenyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3c**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a colorless solid (93.1 mg, 75% yield); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.38 (t, $J = 7.2$ Hz, 3H), 3.78 (s, 3H), 4.49 (q, $J = 7.2$ Hz, 2H), 6.93 (d, $J = 7.2$ Hz, 2H), 7.12 (s, 1H), 7.48-7.54 (m, 2H), 7.62 (d, $J = 7.2$ Hz, 2H), 7.70 (d, $J = 8.8$ Hz, 2H), 9.07 (d, $J = 7.2$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 13.9, 55.4, 61.7, 106.2, 113.8, 115.8, 121.1 (q, $^1J_{\text{C-F}} = 269.0$ Hz), 123.0, 124.6, 126.2, 127.3, 127.8, 129.8, 130.7, 131.1, 137.7, 140.1, 142.9

(q, $^2J_{C-F} = 37.0$ Hz), 160.7, 163.4; HRMS calcd. For $C_{22}H_{17}F_3KN_2O_3$ $[M+K]^+$: 453.0823, Found: 453.0850.

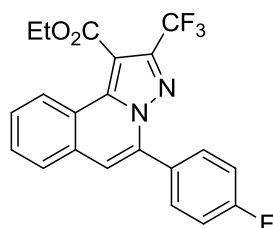


Ethyl 5-(4-ethoxyphenyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3d**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a colorless solid (114 mg, 89% yield), mp: 137-138 °C; 1H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, $J = 6.8$ Hz, 3H), 1.47 (t, $J = 6.8$ Hz, 3H), 4.12 (q, $J = 6.8$ Hz, 2H), 4.50 (q, $J = 7.2$ Hz, 2H), 7.03 (d, $J = 8.0$ Hz, 2H), 7.26 (s, 1H), 7.60-7.68 (m, 2H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.4$ Hz, 2H), 9.18 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.8, 61.7, 63.6, 106.2, 114.3, 115.7, 121.1 (q, $^1J_{C-F} = 268.0$ Hz), 123.0, 124.4, 126.2, 127.3, 127.7, 129.8, 130.8, 131.1, 137.8, 140.1, 143.0 (q, $^2J_{C-F} = 37.0$ Hz), 160.1, 163.4; HRMS calcd. For $C_{23}H_{20}F_3N_2O_3$ $[M+H]^+$: 429.1426, Found: 429.1434.

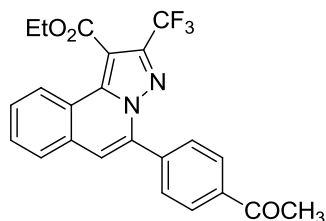


Ethyl 5-(4-chlorophenyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3e**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a colorless solid (106 mg, 85% yield), mp: 174-175 °C; 1H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, $J = 6.8$ Hz, 3H), 4.50 (q, $J = 6.8$ Hz, 2H), 7.29 (s, 1H), 7.50 (d, $J = 8.0$ Hz, 2H), 7.65-7.73 (m, 2H), 7.80 (d, $J = 8.8$ Hz, 3H), 9.21 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 13.8, 61.7, 106.5, 116.6, 120.8 (q, $^1J_{C-F} = 268.0$ Hz), 123.4, 126.4, 127.5, 128.4, 128.7, 130.1, 130.4, 130.8, 131.0, 135.8, 136.8, 140.1, 143.1 (q, $^2J_{C-F} = 37.0$ Hz), 163.3; HRMS calcd. For $C_{21}H_{14}ClF_3N_2NaO_2$ $[M+Na]^+$: 441.0594, Found: 441.0599.

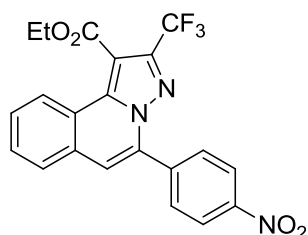


Ethyl 5-(4-fluorophenyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3f**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:5) as a yellow solid (96 mg, 80% yield); 1H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, $J = 7.2$ Hz, 3H), 4.50 (q, $J = 7.2$ Hz, 2H), 7.21 (t, $J = 8.8$ Hz, 2H), 7.26 (s, 1H), 7.63-7.68 (m, 2H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.81-7.88 (m, 2H), 9.19 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 61.8, 106.4, 115.6 (d, $^2J_{C-F} = 22.0$ Hz), 116.5, 121.0 (q, $^1J_{C-F} = 269.0$ Hz), 123.3, 126.3, 127.5, 128.2, 128.4, 130.0, 130.5, 131.7 (d, $^3J_{C-F} = 8.0$ Hz), 136.9, 140.1, 143.1 (q, $^2J_{C-F} = 37.0$ Hz), 163.3, 163.5 (d, $^1J_{C-F} = 249.0$ Hz); HRMS calcd. for $C_{21}H_{15}F_4N_2O_2$ $[M+H]^+$: 403.1070, Found: 403.1064.

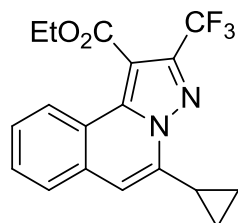


Ethyl 5-(4-acetylphenyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3g**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a colorless solid (111 mg, 87% yield), mp: 167-168 °C; 1H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, $J = 6.8$ Hz,

3H), 2.67 (s, 3H), 4.50 (q, $J = 7.2$ Hz, 2H), 7.33 (s, 1H), 7.63-7.69 (m, 2H), 7.75-7.80 (m, 1H), 7.94 (d, $J = 8.0$ Hz, 2H), 8.08 (d, $J = 7.6$ Hz, 2H), 9.19 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 26.7, 61.7, 106.4, 117.1, 120.8 (q, $^1J_{\text{C-F}} = 269.0$ Hz), 123.4, 126.3, 127.6, 128.2, 128.5, 129.8, 130.0, 130.2, 136.6, 137.6, 140.0, 143.0 (q, $^2J_{\text{C-F}} = 37.0$ Hz), 163.1, 197.4; HRMS calcd. for $\text{C}_{23}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 427.1270, Found: 427.1276.

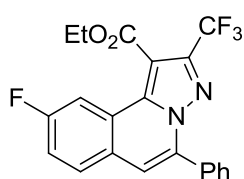


Ethyl 5-(4-nitrophenyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3h**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:5) as a pale yellow solid (60.5 mg, 47% yield), mp: 182-183 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.46 (t, $J = 7.2$ Hz, 3H), 4.49 (q, $J = 7.2$ Hz, 2H), 7.27 (s, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.61-7.70 (m, 2H), 7.72-7.81 (m, 3H), 9.18 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 61.7, 106.4, 116.6, 120.9 (q, $^1J_{\text{C-F}} = 269.0$ Hz), 123.3, 126.3, 127.5, 128.3, 128.7, 130.0, 130.4, 130.7, 131.0, 135.8, 136.7, 140.1, 143.1 (q, $^2J_{\text{C-F}} = 37.0$ Hz), 163.3; HRMS calcd. for $\text{C}_{21}\text{H}_{15}\text{F}_3\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 430.1015, Found: 430.1021.



Ethyl 5-cyclopropyl-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**3i**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a colorless solid (94 mg, 90%

yield), mp: 75-76 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.80-0.90 (m, 2H), 1.13 (d, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 6.4 Hz, 3H), 2.60-2.65 (m, 1H), 4.40 (d, *J* = 6.4 Hz, 2H), 6.73 (s, 1H), 7.35-7.54 (m, 3H), 9.05 (d, *J* = 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 7.6, 11.1, 13.9, 61.6, 106.2, 110.4, 121.2 (q, ¹*J*_{C-F} = 268.0 Hz), 122.5, 126.2, 126.7, 127.2, 129.6, 130.5, 139.5, 140.7, 143.0 (q, ²*J*_{C-F} = 37.0 Hz), 163.4; HRMS calcd. For C₁₈H₁₅F₃N₂NaO₂ [M+Na]⁺: 371.0983, Found: 371.0991.

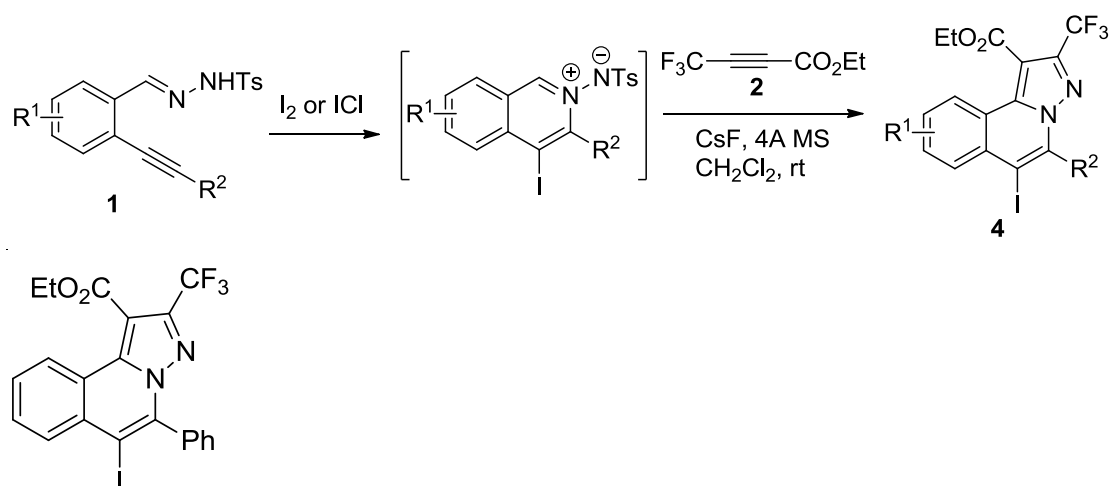


Ethyl 9-fluoro-5-phenyl-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate

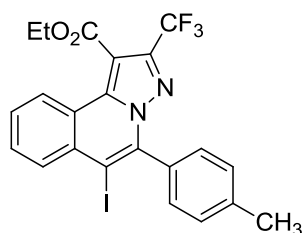
(3j) Isolated (R_f = 0.6, EtOAc–petroleum ether = 1:10) as a colorless solid (53 mg, 44% yield), mp: 161-162 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.46 (t, *J* = 7.2 Hz, 3H), 4.50 (q, *J* = 7.2 Hz, 2H), 7.30 (s, 1H), 7.44 (dt, *J* = 2.4, 8.4 Hz, 1H), 7.50-7.56 (m, 3H), 7.78-7.85 (m, 3H), 9.09 (dd, *J* = 2.0, 10.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.8, 61.8, 106.8, 112.2 (d, ²*J*_{C-F} = 26.0 Hz), 115.8, 118.9 (d, ²*J*_{C-F} = 26.0 Hz), 120.9 (d, ¹*J*_{C-F} = 268.0 Hz), 124.7 (d, ³*J*_{C-F} = 11.0 Hz), 127.3, 128.4, 129.6 (d, ³*J*_{C-F} = 9.0 Hz), 129.7, 129.8, 132.2, 137.5, 139.5, 143.4 (d, ²*J*_{C-F} = 37.0 Hz), 161.7 (d, ¹*J*_{C-F} = 247.0 Hz), 163.0; HRMS calcd. for C₂₁H₁₅F₄N₂O₂ [M+H]⁺: 403.1070, Found 403.1064.

General procedure for the electrophile-mediated one-pot tandem reaction of N²-(2-alkynylbenzylidene)-hydrazide **1** with ethyl 4,4,4-trifluorobut-2-ynoate **2** : A mixture of N²-(2-alkynylbenzylidene)hydrazide **1** (0.30 mmol, 1.0 equiv.) and

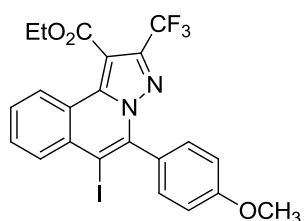
electrophiles (I₂ or ICl) (0.36 mmol, 1.2 equiv.) in anhydrous dichloromethane (3.0 mL) was stirred at room temperature for overnight. Then a solution of ethyl 4,4,4-trifluorobut-2-ynoate (0.60 mmol, 2.0 equiv.) in dichloroethane (2.0 mL), 4A MS (75 mg) and CsF (0.45 mmol, 1.5 equiv.) were added, stirred for another 3 h. After completion of the reaction as indicated by TLC, the reaction mixture was purified by flash column chromatography on silica gel to provide the corresponding product **4**.



Ethyl 6-iodo-5-phenyl-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4a**) Isolated (R_f = 0.7, EtOAc–petroleum ether = 1:10) as a yellow solid (119 mg, 78% yield); ¹H NMR (400 MHz, CDCl₃) δ 1.44 (t, *J* = 7.2 Hz, 3H), 4.49 (q, *J* = 7.2 Hz, 2H), 7.38-7.45 (m, 2H), 7.51-7.61 (m, 3H), 7.63-7.74 (m, 2H), 8.24 (d, *J* = 8.0 Hz, 1H), 9.17 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.8, 61.9, 92.4, 106.2, 120.7 (q, ¹*J*_{C-F} = 270.0 Hz), 123.0, 126.5, 128.7, 129.1, 129.8, 130.3, 131.0, 131.4, 133.5, 136.8, 139.2, 140.9, 143.2 (q, ²*J*_{C-F} = 38.0 Hz), 163.3; HRMS calcd. for C₂₁H₁₅F₃IN₂O₂ [M+H]⁺: 511.0130, Found 511.0125.



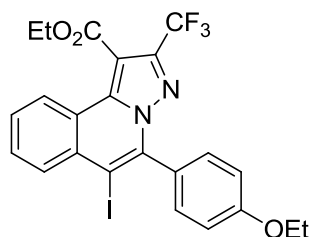
Ethyl 6-iodo-5-(p-tolyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4b**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a yellow solid (141 mg, 90% yield), mp: 165-166 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.44 (t, $J = 7.2$ Hz, 3H), 2.48 (s, 3H), 4.48 (q, $J = 7.2$ Hz, 2H), 7.30 (d, $J = 7.6$ Hz, 2H), 7.37 (d, $J = 7.6$ Hz, 2H), 7.63-7.71 (m, 2H), 8.22 (d, $J = 8.0$ Hz, 1H), 9.14 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.7, 21.6, 61.7, 92.4, 106.1, 120.6 (q, $^1J_{\text{C-F}} = 269.0$ Hz), 122.8, 126.3, 126.9, 128.8, 129.3, 130.0, 130.8, 131.3, 133.4, 133.7, 139.1, 139.7, 140.9, 143.0 (q, $^2J_{\text{C-F}} = 37.0$ Hz), 163.2; HRMS calcd. for $\text{C}_{22}\text{H}_{16}\text{F}_3\text{IN}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 547.0126, found 547.0101.



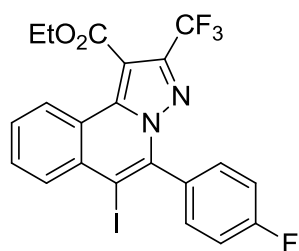
Ethyl 6-iodo-5-(4-methoxyphenyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4c**) Isolated ($R_f = 0.5$, EtOAc–petroleum ether = 1:20) as a yellow solid (130 mg, 80% yield), mp: 154-155 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.44 (t, $J = 7.2$ Hz, 3H), 3.92 (s, 3H), 4.49 (q, $J = 7.2$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.68-7.76 (m, 2H), 8.27 (d, $J = 8.0$ Hz, 1H), 9.17 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 55.3, 61.9, 92.9, 106.2, 114.0, 119.7 (q, $^1J_{\text{C-F}} = 269.0$ Hz), 123.0, 126.4, 129.0, 129.1, 131.0, 131.6, 131.8, 133.6, 139.2, 140.9, 143.0 (q,

$^2J_{C-F} = 37.0$ Hz), 160.5, 163.4; HRMS calcd. for $C_{22}H_{17}F_3IN_2O_3$ $[M+H]^+$: 541.0236,

Found 541.0230.

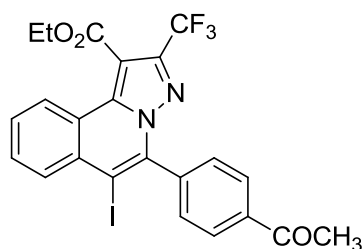


Ethyl 5-(4-ethoxyphenyl)-6-iodo-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4d**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a yellow solid (145 mg, 88% yield); 1H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, $J = 6.8$ Hz, 3H), 1.47 (t, $J = 6.8$ Hz, 3H), 4.13 (q, $J = 7.2$ Hz, 2H), 4.48 (d, $J = 7.2$ Hz, 2H), 7.06 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 7.64-7.69 (m, 2H), 8.20 (d, $J = 8.0$ Hz, 1H), 9.14 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 13.8, 60.7, 62.4, 91.8, 105.1, 113.3, 119.7 (q, $^1J_{C-F} = 269.0$ Hz), 121.8, 125.3, 127.7, 127.8, 129.8, 130.4, 130.8, 132.4, 138.1, 139.8, 142.0 (q, $^1J_{C-F} = 37.0$ Hz), 158.8, 162.2; HRMS calcd. for $C_{23}H_{19}F_3IN_2O_3$ $[M+H]^+$: 555.0392, Found 555.0387 .

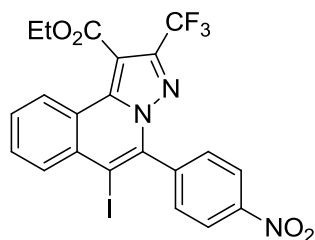


Ethyl 5-(4-fluorophenyl)-6-iodo-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4e**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a yellow solid (97 mg, 62% yield), mp: 197-198 °C; 1H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, $J = 7.2$ Hz, 3H), 4.48 (q, $J = 7.2$ Hz, 2H), 7.26 (t, $J = 8.4$ Hz, 2H), 7.36-7.45 (m, 2H), 7.64-7.72 (m, 2H), 8.20 (d, $J = 7.6$ Hz, 1H), 9.15 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100

MHz, CDCl₃) δ 13.8, 61.9, 92.8, 106.3, 116.0 (d, $^2J_{C-F} = 22.0$ Hz), 120.7 (q, $^1J_{C-F} = 269.0$ Hz), 123.0, 126.5, 129.2, 131.1, 131.3, 132.5 (d, $^3J_{C-F} = 9.0$ Hz), 132.7, 133.5, 139.2, 139.9, 143.3 (q, $^2J_{C-F} = 37.0$ Hz), 163.2, 163.4 (d, $^1J_{C-F} = 249.0$ Hz); HRMS calcd. for C₂₁H₁₄F₄IN₂O₂ [M+H]⁺: 529.0036, Found 529.0031.

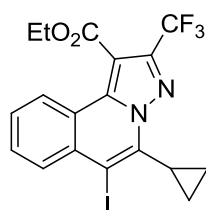


Ethyl 5-(4-acetylphenyl)-6-iodo-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4f**) Isolated (Rf = 0.7, EtOAc–petroleum ether = 1:10) as a yellow solid (139 mg, 84% yield); ¹H NMR (400 MHz, CDCl₃) δ 1.35 (t, $J = 7.2$ Hz, 3H), 2.62 (s, 3H), 4.40 (q, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.60-7.70 (m, 2H), 8.08 (d, $J = 8.0$ Hz, 2H), 8.16 (d, $J = 8.0$ Hz, 1H), 9.10 (d, $J = 8.0$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.8, 26.8, 61.9, 92.0, 106.4, 120.6 (q, $^1J_{C-F} = 269.0$ Hz), 123.1, 126.6, 128.7, 129.4, 130.8, 131.2, 132.7, 133.5, 137.8, 139.2, 139.8, 141.0, 143.4 (q, $^2J_{C-F} = 38.0$ Hz), 163.1, 197.5; HRMS calcd. for C₂₃H₁₇F₃IN₂O₃ [M+H]⁺: 553.0236, Found 553.0230.

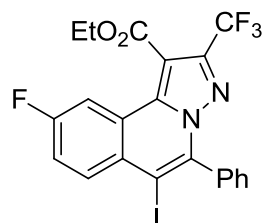


Ethyl 6-iodo-5-(4-nitrophenyl)-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4g**) Isolated (Rf = 0.7, EtOAc–petroleum ether = 1:10) as a colorless solid (83.2 mg, 50% yield); ¹H NMR (400 MHz, CDCl₃) δ 1.45 (t, $J = 7.2$ Hz, 3H),

4.49 (q, $J = 7.2$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 2H), 7.70-7.79 (m, 2H), 8.27 (d, $J = 8.0$ Hz, 1H), 9.19 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 12.8, 60.9, 91.5, 105.3, 115.5, 119.6 (q, $^1J_{\text{C-F}} = 269.0$ Hz), 122.1, 125.5, 128.1, 128.6, 130.2, 130.8, 132.5, 133.9, 134.8, 138.1, 138.7, 142.3 (q, $^2J_{\text{C-F}} = 37.0$ Hz), 162.2; HRMS calcd. for $\text{C}_{21}\text{H}_{14}\text{F}_3\text{IN}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 555.9981, Found: 555.9989.



Ethyl 5-cyclopropyl-6-iodo-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4h**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a colorless solid (122 mg, 85% yield), mp: 102-103 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.16 (t, $J = 5.6$ Hz, 2H), 1.42-1.50 (m, 5H), 2.28-2.32 (m, 1H), 4.49 (q, $J = 7.2$ Hz, 2H), 7.58 (t, $J = 7.2$ Hz, 1H), 7.65 (t, $J = 7.6$ Hz, 1H), 8.18 (d, $J = 8.0$ Hz, 1H), 9.05 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 12.5, 13.8, 18.3, 61.7, 93.9, 105.9, 120.9 (q, $^1J_{\text{C-F}} = 268.0$ Hz), 122.2, 126.1, 128.4, 130.6, 131.5, 132.5, 139.1, 140.2, 142.5 (q, $^2J_{\text{C-F}} = 37.0$ Hz), 163.3; HRMS calcd. for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{IN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 475.0130, Found: 475.0125.



Ethyl 9-fluoro-6-iodo-5-phenyl-2-(trifluoromethyl)pyrazolo[5,1-a]isoquinoline-1-carboxylate (**4i**) Isolated ($R_f = 0.7$, EtOAc–petroleum ether = 1:10) as a colorless

solid (79 mg, 50% yield); ^1H NMR (400 MHz, CDCl_3) δ 1.44 (t, $J = 7.2$ Hz, 3H), 4.48 (q, $J = 7.2$ Hz, 2H), 7.37-7.48 (m, 3H), 7.52-7.65 (m, 3H), 8.27 (dd, $J = 5.2, 8.8$ Hz, 1H), 9.11 (d, $J = 10.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 62.0, 91.3, 106.6, 112.2 (d, $^2J_{\text{C-F}} = 26.0$ Hz), 119.5 (d, $^2J_{\text{C-F}} = 23.0$ Hz), 120.6 (q, $^1J_{\text{C-F}} = 269.0$ Hz), 124.1 (d, $^3J_{\text{C-F}} = 10.0$ Hz), 128.2, 128.7, 129.9, 130.3, 136.1 (d, $^3J_{\text{C-F}} = 8.0$ Hz), 136.6, 138.7, 140.4, 143.5 (q, $^2J_{\text{C-F}} = 38.0$ Hz), 162.2 (d, $^1J_{\text{C-F}} = 248.0$ Hz), 162.9; HRMS calcd. for $\text{C}_{21}\text{H}_{14}\text{F}_4\text{IN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 529.0036, Found: 529.0035.

