

An Unexpected Three-component Reaction of 2-Alkylencyclobutanone, *N'*-(2-Alkynylbenzylidene)hydrazide with Water

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Supporting Information

1. General experimental methods (S2).
2. General experimental procedure and characterization data (S2-S12).
3. ¹H and ¹³C NMR spectra of compounds **3** (S13 –S52).

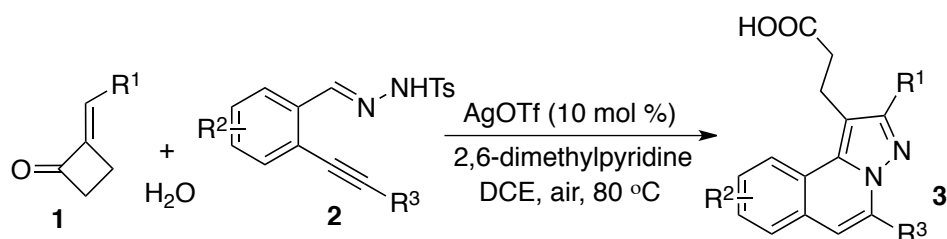
General experimental methods:

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63µm, 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 at 25–35°C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II Instrument.

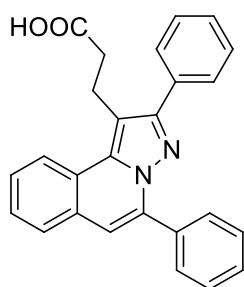
General experimental procedure for the synthesis of 2-alkylenecyclobutanone

$\text{Ca}(\text{OH})_2$ (10 mol %) was added to a solution of aldehyde (1.0 equiv) in ethanol. Then cyclobutanone (3.0 equiv) was injected via a syringe at N_2 atmosphere. The mixture was stirred at 80 °C for about 24 hours. After completion of conversion indicated by TLC, the solvent was evaporated under vacuum and the residue was purified through flash column chromatogram (petroleum ether: EtOAc 12:1) to give the desired 2-alkylenecyclobutanone. (ref: L. Yu, Y. Wu, H. Cao, X. Zhang, X. Shi, J. Luan, T. Chen, Y. Pan and Q. Xu, *Green Chem.* 2014, **16**, 287.)

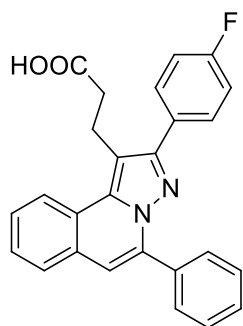
General experimental procedure for the three-component reaction of 2-alkylenecyclobutanone, N' -(2-alkynylbenzylidene)hydrazide with water



Silver triflate (10 mol %) was added to a solution of *N'*-(2-alkynylbenzylidene)hydrazide **2** (0.5 mmol, 1.0 equiv) in DCE (4.0 mL) at 80 °C. After 1 hour, 2-alkylenecyclobutanone **1** (1.0 mmol, 2.0 equiv), 2,6-dimethylpyridine (2.0 equiv) and water (0.18 mL, 20.0 equiv) were added to the above suspension and the mixture was stirred under reflux. After completion of the reaction as indicated by TLC, the solvent was evaporated and the residue was purified directly by flash column chromatograph (*n*-hexane/ethyl acetate = 2:1) to give the corresponding product **3**.



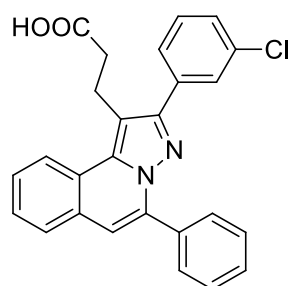
3-(2,5-Diphenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3a**). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.41 (s, 1H), 8.32 (d, *J* = 6.9 Hz, 1H), 7.95-7.94 (m, 3H), 7.70-7.64 (m, 4H), 7.53-7.48 (m, 6H), 7.32 (s, 1H), 3.40 (m, 2H), 2.68 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 174.0, 151.9, 137.9, 135.8, 133.8, 133.6, 129.9, 129.7, 129.6, 129.3, 129.0, 128.6, 128.3, 128.3, 128.1, 126.1, 124.5, 122.9, 113.3, 111.6, 34.6, 20.6. HRMS (ESI) calcd for C₂₆H₂₁N₂O₂⁺: 393.1598 (M + H⁺), found: 393.1600.



3-(2-(4-Fluorophenyl)-5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3b**).

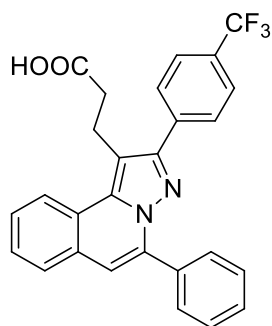
^1H NMR (400 MHz, DMSO- d_6): δ 12.40 (s, 1H), 8.31 (d, $J = 7.5$ Hz, 1H), 7.94 (m, 3H), 7.76-7.63 (m, 4H), 7.53 (m, 3H), 7.36-7.32 (m, 2H), 3.37 (m, 2H), 2.67 (m, 2H).

^{13}C NMR (100 MHz, DMSO- d_6): δ 173.9, 162.5 (d, $J_{\text{CF}} = 244.0$ Hz), 151.0, 137.8, 135.8, 133.8, 131.4 (d, $^3J_{\text{CF}} = 8.2$ Hz), 129.9, 129.7 (d, $^2J_{\text{CF}} = 15.4$ Hz), 128.6, 128.3 (d, $^3J_{\text{CF}} = 5.5$ Hz), 128.2, 126.1, 124.5, 122.9, 115.9 (d, $^2J_{\text{CF}} = 21.3$ Hz), 113.3, 111.6, 34.5, 20.5. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{20}\text{FN}_2\text{O}_2^+$: 411.1503 ($\text{M} + \text{H}^+$), found: 411.1514.

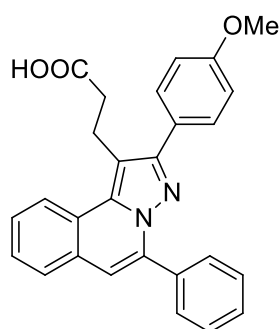


3-(2-(3-Chlorophenyl)-5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3c**).

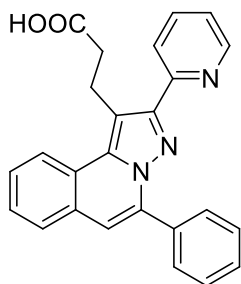
^1H NMR (400 MHz, DMSO- d_6): δ 12.38 (s, 1H), 8.29 (d, $J = 8.0$ Hz, 1H), 7.93-7.90 (m, 3H), 7.69-7.58 (m, 4H), 7.54-7.51 (m, 5H), 7.32 (s, 1H), 3.36 (t, $J = 8.2$ Hz, 2H), 2.65 (t, $J = 7.8$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 173.9, 150.4, 137.8, 135.9, 133.7, 130.9, 129.9, 129.7, 129.6, 129.3, 128.9, 128.6, 128.4, 128.3, 128.2, 127.9, 124.4, 122.9, 113.6, 111.9, 34.4, 20.5. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{20}\text{ClN}_2\text{O}_2^+$: 427.1208 ($\text{M} + \text{H}^+$), found: 427.1204.



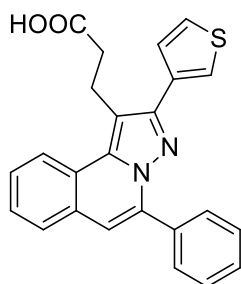
3-(5-Phenyl-2-(4-(trifluoromethyl)phenyl)pyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3d**). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.38 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.95-7.90 (m, 3H), 7.84 (m, 4H), 7.69-7.67 (m, 1H), 7.64-7.62 (m, 1H), 7.52-7.51 (m, 3H), 7.34 (s, 1H), 3.38 (t, *J* = 8.1 Hz, 2H), 2.67 (t, *J* = 8.1 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 173.9, 150.4, 137.8, 135.9, 133.7, 130.9, 129.9, 129.7, 129.6, 129.3, 128.9, 128.6, 128.4, 128.3, 128.2, 127.9, 124.4, 122.9, 113.6, 111.9, 34.4, 20.5. HRMS (ESI) calcd for C₂₇H₂₀F₃N₂O₂⁺: 461.1471 (M + H⁺), found: 461.1487.



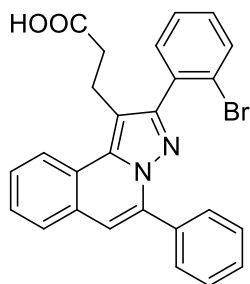
3-(2-(4-Methoxyphenyl)-5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3e**). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.38 (s, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 7.92-7.91 (m, 3H), 7.68-7.66 (m, 1H), 7.62-7.60 (m, 1H), 7.56-7.49 (m, 5H), 7.28 (s, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.36 (t, *J* = 8.4 Hz, 2H), 2.64 (t, *J* = 8.0 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 174.0, 159.6, 151.7, 137.9, 135.7, 133.9, 130.5, 129.9, 129.7, 129.6, 128.5, 128.3, 128.0, 125.9, 124.5, 122.8, 114.4, 113.0, 111.3, 55.6, 34.6, 20.7. HRMS (ESI) calcd for C₂₇H₂₃N₂O₃⁺: 423.1703 (M + H⁺), found: 423.1693.



3-(5-Phenyl-2-(pyridin-2-yl)pyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3f**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.28 (s, 1H), 8.69-8.68 (m, 1H), 8.36 (d, J = 8.1 Hz, 1H), 7.94-7.89 (m, 4H), 7.86-7.82 (m, 1H), 7.68 (t, J = 7.4 Hz, 1H), 7.61-7.51 (m, 4H), 7.34-7.34 (m, 1H), 7.31 (s, 1H), 3.76 (t, J = 8.2 Hz, 2H), 2.73 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 174.5, 153.6, 149.5, 149.1, 137.8, 137.2, 136.2, 133.7, 129.9, 129.7, 129.6, 128.6, 128.4, 128.4, 128.2, 124.8, 123.2, 122.8, 113.8, 113.6, 34.5, 20.8. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{20}\text{N}_3\text{O}_2^+$: 394.1550 ($\text{M} + \text{H}^+$), found: 394.1567.

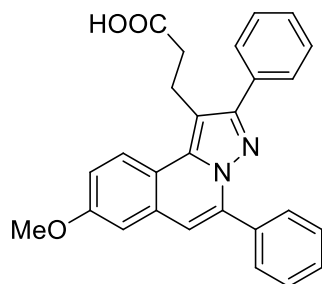


3-(5-Phenyl-2-(thiophen-3-yl)pyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3g**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.40 (s, 1H), 8.31 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 7.4 Hz, 3H), 7.83-7.82 (m, 1H), 7.69-7.62 (m, 3H), 7.55-7.51 (m, 3H), 7.46-7.45 (m, 1H), 7.30 (s, 1H), 3.44 (t, J = 8.3 Hz, 2H), 2.67 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 174.1, 147.5, 137.8, 135.8, 134.2, 133.8, 129.9, 129.7, 129.6, 128.6, 128.5, 128.4, 128.3, 128.1, 126.9, 124.4, 124.2, 122.8, 113.2, 111.6, 34.4, 20.7. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{19}\text{N}_2\text{O}_2\text{S}^+$: 399.1162 ($\text{M} + \text{H}^+$), found: 399.1158.

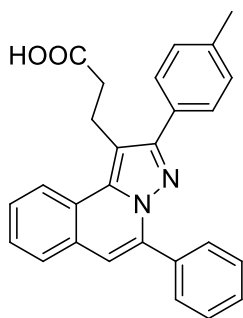


3-(2-(2-Bromophenyl)-5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3h**).

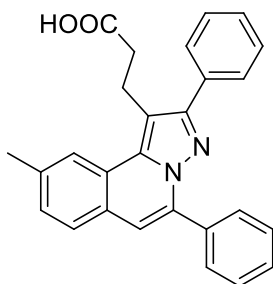
^1H NMR (400 MHz, DMSO- d_6): δ 12.27 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.98-7.91 (m, 3H), 7.80-7.65 (m, 3H), 7.52-7.43 (m, 6H), 7.37 (s, 1H), 3.14-3.13 (m, 2H), 2.50 (m, 2H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 173.8, 152.0, 137.9, 135.1, 134.6, 133.7, 133.0, 132.9, 131.1, 129.8, 129.7, 128.6, 128.5, 128.3, 128.0, 126.1, 124.4, 124.3, 123.0, 120.5, 113.3, 112.5, 34.2, 20.8. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{20}\text{BrN}_2\text{O}_2^+$: 471.0703 ($\text{M} + \text{H}^+$), found: 471.0711.



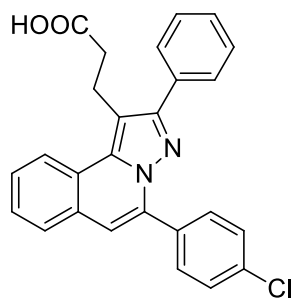
3-(8-Methoxy-2,5-diphenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3i**). ^1H NMR (400 MHz, DMSO- d_6): δ 12.35 (s, 1H), 8.21 (d, J = 8.9 Hz, 1H), 7.92-7.91 (m, 2H), 7.62-7.60 (m, 2H), 7.53-7.42 (m, 7H), 7.31 (d, J = 7.2 Hz, 1H), 7.26 (s, 1H), 3.90 (s, 3H), 3.32 (t, J = 8.2 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 173.5, 158.4, 151.4, 137.7, 135.5, 133.4, 133.2, 131.1, 129.3, 129.1, 128.8, 128.4, 128.1, 128.0, 124.0, 118.0, 117.0, 112.5, 109.6, 109.3, 55.3, 34.1, 20.0. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{23}\text{N}_2\text{O}_3^+$: 423.1703 ($\text{M} + \text{H}^+$), found: 423.1716.



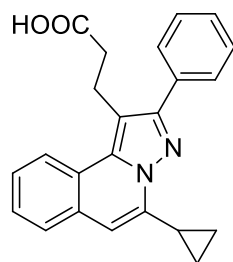
3-(5-Phenyl-2-(*p*-tolyl)pyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3j**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.43 (s, 1H), 8.28 (d, $J = 5.6$ Hz, 1H), 7.89 (m, 3H), 7.66-7.49 (m, 7H), 7.25 (m, 3H), 3.36 (m, 2H), 2.64 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 174.0, 151.9, 137.9, 135.7, 133.9, 130.7, 129.8, 129.7, 129.5, 129.2, 128.5, 128.2, 128.0, 124.5, 122.8, 113.1, 111.5, 34.6, 21.3, 20.7. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{23}\text{N}_2\text{O}_2^+$: 407.1754 ($\text{M} + \text{H}^+$), found: 407.1731.



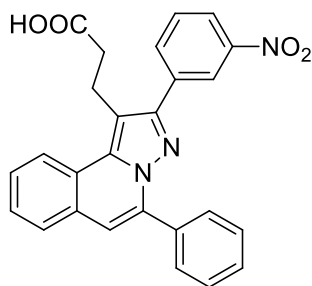
3-(9-Methyl-2,5-diphenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3k**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.41 (s, 1H), 8.09 (s, 1H), 7.90 (d, $J = 6.5$ Hz, 2H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.63-7.61 (m, 2H), 7.51-7.41 (m, 7H), 7.24 (s, 1H), 3.36 (t, $J = 8.4$ Hz, 2H), 2.65 (d, $J = 7.7$ Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 173.6, 151.1, 137.4, 136.6, 135.1, 133.4, 133.1, 129.3, 129.2, 128.9, 128.8, 128.5, 128.0, 127.6, 127.0, 125.6, 124.1, 122.2, 112.7, 111.0, 34.3, 21.5, 20.2. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{23}\text{N}_2\text{O}_2^+$: 407.1754 ($\text{M} + \text{H}^+$), found: 407.1746.



3-(5-(4-Chlorophenyl)-2-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3l**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.69 (s, 1H), 8.30 (d, $J = 7.9$ Hz, 1H), 7.97-7.93 (m, 4H), 7.70 (t, $J = 7.6$ Hz, 1H), 7.63-7.44 (m, 7H), 7.35 (s, 1H), 3.36-3.34 (m, 2H), 2.64 (t, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 173.4, 166.4, 151.4, 137.7, 136.1, 135.3, 133.8, 133.0, 132.0, 131.2, 131.0, 128.8, 128.6, 128.5, 128.1, 127.7, 124.1, 122.4, 113.0, 111.2, 34.0, 20.1. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{20}\text{ClN}_2\text{O}_2^+$: 427.1208 ($\text{M} + \text{H}^+$), found: 427.1205.

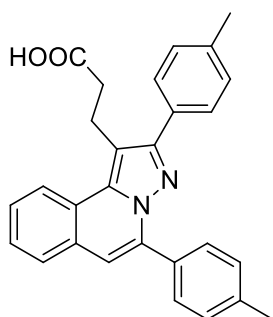


3-(5-Cyclopropyl-2-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3m**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.35 (s, 1H), 8.24 (d, $J = 7.8$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 1H), 7.70 (d, $J = 7.3$ Hz, 2H), 7.61-7.46 (m, 5H), 6.92 (s, 1H), 3.36 (t, $J = 8.4$ Hz, 2H), 2.73-2.71 (m, 1H), 2.63 (t, $J = 7.8$ Hz, 2H), 1.13-1.11 (m, 2H), 0.96-0.95 (m, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 174.0, 151.7, 140.9, 135.2, 133.8, 129.8, 129.3, 129.0, 128.5, 127.9, 127.5, 127.4, 123.7, 122.8, 111.5, 106.7, 34.7, 20.6, 11.3, 7.8. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_2^+$: 357.1598 ($\text{M} + \text{H}^+$), found: 357.1602.

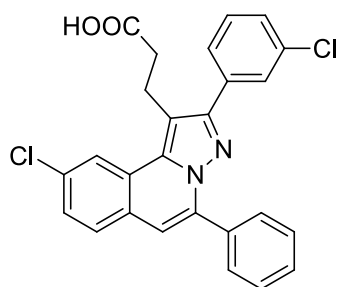


3-(2-(3-Nitrophenyl)-5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3n**).

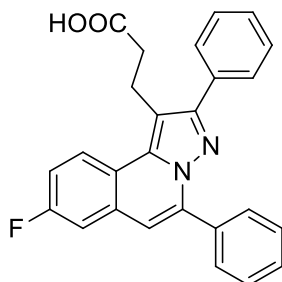
^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.36 (s, 1H), 8.41 (s, 1H), 8.30 (d, $J = 9.0$ Hz, 2H), 8.11-8.10 (m, 1H), 7.97-7.92 (m, 3H), 7.82-7.64 (m, 3H), 7.54 (m, 3H), 7.37 (s, 1H), 3.40 (m, 2H), 2.70 (m, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 173.3, 149.0, 147.8, 137.3, 135.5, 135.0, 134.7, 133.1, 130.1, 129.3, 129.2, 129.2, 128.1, 128.0, 127.8, 123.9, 123.0, 122.7, 122.4, 113.4, 111.6, 33.8, 19.8. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{20}\text{N}_3\text{O}_4^+$: 438.1448 ($\text{M} + \text{H}^+$), found: 438.1443.



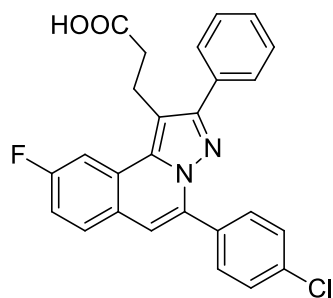
3-(2,5-Di-*p*-tolylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3o**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.35 (s, 1H), 8.29 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 7.6$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 2H), 7.69-7.61 (m, 2H), 7.50 (d, $J = 7.9$ Hz, 2H), 7.34-7.28 (m, 5H), 3.36 (m, 2H), 2.63 (t, $J = 8.0$ Hz, 2H), 2.39 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 173.4, 151.3, 138.6, 137.4, 137.3, 135.2, 130.4, 130.2, 129.3, 129.2, 129.0, 128.7, 128.6, 128.6, 127.7, 127.6, 123.9, 122.3, 112.2, 110.9, 34.1, 20.9, 20.8, 20.1. HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{25}\text{N}_2\text{O}_2^+$: 421.1911 ($\text{M} + \text{H}^+$), found: 421.1929.



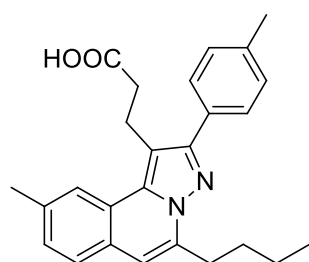
3-(9-Chloro-2-(3-chlorophenyl)-5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3p**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.43 (s, 1H), 8.17 (s, 1H), 7.91-7.86 (m, 3H), 7.61-7.56 (m, 3H), 7.53-7.48 (m, 5H), 7.30 (s, 1H), 3.30 (t, $J = 8.4$ Hz, 2H), 2.61 (t, $J = 7.8$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 173.3, 149.9, 137.6, 134.9, 134.3, 133.2, 132.8, 132.3, 130.4, 129.6, 129.3, 128.2, 128.1, 127.8, 127.3, 124.8, 121.6, 112.4, 112.0, 33.8, 19.8. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}_2^+$: 461.0818 ($\text{M} + \text{H}^+$), found: 461.0823.



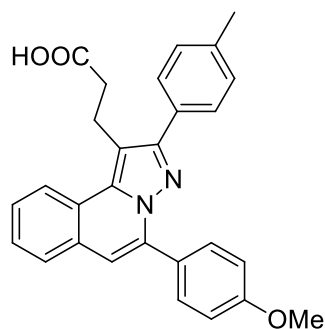
3-(8-Fluoro-2,5-diphenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3q**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.38 (s, 1H), 8.31-8.27 (m, 1H), 7.89-7.88 (m, 2H), 7.76-7.63 (m, 1H), 7.62-7.60 (m, 2H), 7.50-7.42 (m, 7H), 7.27 (s, 1H), 3.32 (t, $J = 8.1$ Hz, 2H), 2.62 (t, $J = 7.8$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 173.4, 160.8 (d, $J_{\text{CF}} = 244.3$ Hz), 151.6, 138.3, 135.0, 133.0 (d, $^4J_{\text{CF}} = 2.5$ Hz), 131.3 (d, $^3J_{\text{CF}} = 9.4$ Hz), 129.3, 129.3, 128.8, 128.5, 128.1, 125.0 (d, $^3J_{\text{CF}} = 8.6$ Hz), 120.8, 116.0 (d, $^2J_{\text{CF}} = 23.4$ Hz), 112.4 (d, $^2J_{\text{CF}} = 21.8$ Hz), 111.9, 110.8, 33.9, 20.0. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{20}\text{FN}_2\text{O}_2^+$: 411.1503 ($\text{M} + \text{H}^+$), found: 411.1514.



3-(5-(4-Chlorophenyl)-9-fluoro-2-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3r**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.42 (s, 1H), 7.93-7.88 (m, 4H), 7.61-7.59 (m, 2H), 7.54-7.44 (m, 6H), 7.30 (s, 1H), 3.30-3.28 (m, 2H), 2.59 (t, $J = 7.8$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 173.4, 161.2 (d, $J_{\text{CF}} = 243.8$ Hz), 151.3, 134.6 (d, $^4J_{\text{CF}} = 3.2$ Hz), 133.7, 132.8, 131.8, 131.1, 130.4 (d, $^3J_{\text{CF}} = 8.9$ Hz), 129.2, 128.7, 128.5, 128.1, 125.8, 125.6, 125.1 (d, $^3J_{\text{CF}} = 9.3$ Hz), 116.0 (d, $^2J_{\text{CF}} = 23.0$ Hz), 112.4, 111.8, 107.8 (d, $^2J_{\text{CF}} = 23.89$ Hz), 34.1, 19.8. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{19}\text{ClFN}_2\text{O}_2^+$: 445.1114 ($\text{M} + \text{H}^+$), found: 445.1115.



3-(5-Butyl-9-methyl-2-(*p*-tolyl)pyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3s**). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.36 (s, 1H), 8.03 (s, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.55 (d, $J = 7.5$ Hz, 2H), 7.37 (d, $J = 7.9$ Hz, 1H), 7.30 (d, $J = 7.4$ Hz, 2H), 6.95 (s, 1H), 3.31 (t, $J = 7.8$ Hz, 2H), 3.04 (t, $J = 7.1$ Hz, 2H), 2.60 (t, $J = 7.5$ Hz, 2H), 2.48 (s, 3H), 2.37 (s, 3H), 1.80-1.76 (m, 2H), 1.43-1.37 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 173.6, 150.8, 137.7, 137.2, 136.3, 134.5, 130.5, 129.0, 128.6, 128.5, 126.9, 126.8, 123.5, 122.0, 110.6, 109.3, 34.3, 29.8, 28.4, 21.9, 21.4, 20.8, 20.3, 13.7. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_2^+$: 401.2224 ($\text{M} + \text{H}^+$), found: 401.2232.



3-(5-(4-Methoxyphenyl)-2-(*p*-tolyl)pyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (**3t**). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.36 (s, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.92-7.88 (m, 3H), 7.69-7.59 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.26 (s, 1H), 7.07 (t, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 3.36-3.34 (m, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.37 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 173.5, 159.8, 151.3, 137.3, 137.2, 135.2, 130.8, 130.3, 129.4, 129.0, 128.7, 127.6, 127.5, 125.5, 123.7, 122.3, 113.4, 111.8, 110.9, 55.2, 34.1, 20.8, 20.1. HRMS (ESI) calcd for C₂₈H₂₅N₂O₃⁺: 437.1860 (M + H⁺), found: 437.1867.

