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Cascade bicyclization of triethylammonium thiolates with hydrazines: efficient access to pyrazolo[3,4-*c*]quinolines

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Abstract

A new bicyclization strategy has been established, allowing a flexible and practical approach to 33 examples of pyrazolo[3,4-*c*]quinolines from low-cost and readily accessible triethylammonium thiolates with hydrazines. Notably features of this work include broad functional group compatibility, mild reaction conditions and good reaction yields.

Graphical Abstract

Introduction

Quinolines are an important class of aza-heterocycles that are widely distributed in numerous natural products¹ and synthetically interesting substances including medicinal agents² and functional materials.³ Among the family of fused quinolines, pyrazolo[3,4-*c*]quinolines have been displayed significant biological activities, such as good affinity and selectivity for adenosine A3 receptors (Figure 1, type i),⁴ benzodiazepine receptor activity (type ii),⁵ adenosine receptor antagonists⁶ and NMDA receptor inhibition (type iii).⁷ Accordingly, the construction of functional pyrazolo[3,4-*c*]quinolines has unarguably become an important pursuit of the goal by chemists. Traditionally, three general strategies have been reported including the direct functionalization of the pyrazolo[3,4-*c*]quinolone,⁸

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the merging of a pyrazole ring into the pre-existing indole and quinoline skeletons,⁹ and the multistep cyclizations of anilines and pyrazole precursor¹⁰ as well as domino cyclization of (indol-3-yl)-2-oxoacetates with hydrazines.¹¹ Very recently, Li and co-workers report a dehydrogenative [2 + 2 + 1] heteroannulation of *N*-(*o*-alkenylaryl) imines for accessing pyrazolo[3,4-*c*]quinolines.¹² Despite these limited advances, to the best of our knowledge, a one-pot synthesis of pyrazolo[3,4-*c*]quinolines *via* a metal-free domino transannulation strategy involving sequential C-S and C-N bond cleavage has not been documented yet.

Bicyclization cascades have emerged as effective methods for the assembly of complex cyclic structures by the combination of several distinct reactions into a one-pot transformation.¹³ Such reactions features annulation efficiency, bond forming efficiency and high levels of structural complexity.¹⁴ In recent years, our laboratories have focused on the development of bicyclization cascades for multiple ring constructions.¹⁵ Recently, we have reported a I₂/O₂-enabled cross-dehydrogenative coupling (CDC) between the preformed triethylammonium thiolates and simple arylhydrazines, allowing direct N-S bond-formation to access functionalized 1,2,3-thiadiazoles (Scheme 1a).¹⁶ To continue this project, hydrazine hydrate was used as replacement for arylhydrazines to investigate its synthetic utilization. Interestingly, instead of the expected 1,2,3-thiadiazole products, the reaction occurred in a completely different direction, affording the unexpected pyrazolo[3,4-*c*]quinolines through bicyclization cascades (Scheme 1b). Herein, we reported this interesting observation.

Results and discussion

To develop this new bicyclization cascade, we began our investigation with condition optimization by reacting triethylammonium thiolates **1a**¹⁷ with hydrazine hydrate **2a** in THF at 100 °C under air conditions. As illustrated in Table 1, the expected product **3a** was obtained with 17% yield (entry 1). Subsequently, we investigated the solvent effect for this transformation with use of various polar solvents such as 1,2-dichloroethane (DCE), MeCN, ethyl acetate (EA), EtOH and 1,4-dioxane. The use of 1,2-dichloroethane (DCE), MeCN and ethyl acetate (EA) all generated a slightly higher yields compared with THF, but still with low yields (entries 2–4). This reaction worked more efficiently in EtOH, giving access to the corresponding product **3a** in 57% yield (entry 5). Gratifyingly, 1,4-dioxane showed a best performance, affording product **3a** in 66% isolated yield (entry 6). It was found that the reaction temperatures critically affected the reaction efficiency (entries 6–9). Increasing the reaction temperature facilitate the reaction process and the higher 81% yield was obtained with reaction temperature being at 120 °C. Unfortunately, further increase of temperature to 130 °C failed to improve the conversion (entry 9). The reaction of **1a** and **2a** was performed in 1,4-dioxane at 120 °C using 10 mol% I₂ as a catalyst, and the desired product **3a** was obtained in 80% yield (entry 10), indicating that this reaction did not demand molecular iodine catalyst.

With the optimal reaction conditions for bicyclization processes in hand (Table 1, entry 8), we then set out to evaluate the scope of these transformations by allowing a variety of structurally diverse triethylammonium thiolate **1** to react with hydrazine hydrate **2a**. The results are summarized in Scheme 2. As anticipated, substituents resided at different

positions on the phenyl ring (Ar) did not hamper the reaction process. The variants of substituents including Cl, Br, NO₂, Me and MeO can tolerate the conditions well. It seemed that there was no evident difference among substrates carrying electron-donating or electron-withdrawing groups in terms of reactivity, and all of them offered good yields of the pyrazolo[3,4-*c*]quinoline products **3a–3h**. Among them, even for a challenging case in which a strong electron-withdrawing effect NO₂ exists on the *p*-position was well-suited for this present transformation, converting into the corresponding product **3d** in a 70% yields. Therefore, the electronic nature and the position of the substituents linked to the phenyl moiety (Ar) imposed little effect on the reaction efficiency. Next, we turned our attention to investigate the electronic properties of indolin-2-one moiety (R). Different groups such as electron-withdrawing (F, Cl, Br) and electron-donating (Me) situated in 5-, 6- or 7-position of indolin-2-one ring were proven to be suitable for this domino process, providing the desired products **3i–ee** with yields from 71% to 93% yields.

After the successful utilization of diverse triethylammoniumthiolate **1** with hydrazine hydrate, we then explored the feasibility of this transformation using alkylated hydrazines. As illustrate in Scheme 3, firstly, we selected (2,2,2-trifluoroethyl)hydrazine (**2b**) to replace hydrazine hydrate, which enabled its bicyclization cascades to deliver the trifluoroethylated product **3ff** in a 73% yield. Both 2-hydrazinylethanol (**2c**) and 2-hydrazinylethanethiol (**2d**) could be accommodated, confirming the reaction efficiency, as products **3gg** and **3hh** were afforded in 64% and 60% yields, respectively. Unfortunately, when benzyl (**2e**), *t*-butyl (**2f**) or cyclopropyl (**2g**) counterparts were employed, only trace amount of products were detected and failed to be isolated. In comparison with the successful alkylhydrazine substrates, substrates **2e–2g** have no hydrogen bonding acceptor moieties, so they are ineffective in this transformation.

The structural elucidation of the products was determined from its IR, ¹H NMR, ¹³C NMR, and HRMS spectra. The structural was unequivocally determined by X-ray diffraction of single crystals that were obtained by slow evaporation of the solvent, as in the cases of product **3c** (Figure 2).

Although a detailed mechanism for the formation of products **3** is not yet clear to us, on the basis of all the above results, a plausible mechanism for the domino bicyclization cascades is proposed in Scheme 4. Frist, intermolecular proton exchange between **1** and **2** occurs, leading to intermediates **A** and hydrazine anion. Next, intermediates **A** undergo tautomerization and selective nucleophilic addition of hydrazine anion to thiocarbonyls, due to inductive effect ortho-carbonyl group, give intermediates **B**, followed by second nucleophilic addition (**B** to **C**) and ring-opening of indolin-2-one (**C** to **D**) to yield intermediates **D**. Eventually, intermediates **D** are converted into the final products **3** through a continuous cyclization-dehydration (**D** to **E**), elimination of hydrogen sulfide (**E** to **F**) and keto-enol tautomerization (**F** to **3**) sequence.

Conclusions

In summary, we have established a new, flexible and practical bicyclization cascade between triethylammonium thiolates and hydrazines for the synthesis of a wide range of

pyrazolo[3,4-*c*]quinolines through sequential C-N and C-S bond cleavage under mild metal-free conditions. Significant features of this work include applicable to one-pot methodology, broad functional group compatibility and good reaction yields. We believe this methodology may be of value to others seeking original synthetic fragments with unique activities for medicinal and pharmaceutical studies.

Experiment

General Information

Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1} . ^1H NMR (^{13}C NMR) spectra were measured on a Bruker DPX 400 MHz spectrometer in $\text{DMSO}-d_6$ with chemical shift (δ) given in ppm relative to TMS as internal standard [(s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet), coupling constant (Hz)]. HRMS (ESI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General Procedure for the Synthesis of Products 3—Example for the synthesis of **3a**: In a typical experiment procedure, triethylammonium (*E*)-2-oxo-1-(2-oxoindolin-3-ylidene)-2-phenylethanethiolate **1a** (1.0 mmol, 382 mg), 55% hydrazinium hydroxide **2a** (2.0 mmol, 183 mg) were introduced in a sealed 10 mL reaction tube, and 1,4-dioxane (2.0 mL) were then successively added. The mixture stirred at 120 °C for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was down to room temperature. Then, the solvent was removed under vacuum, and the residue was purified by column chromatography (eluents, petroleum ether/ethyl acetate) to afford the pure product **3a**.

4-Phenyl-3H-pyrazolo[3,4-*c*]quinolin-1-ol (3a): A yellow solid; 211 mg; 81% yield; Mp: 265–267 °C; IR (KBr, ν , cm^{-1}): 3300, 2955, 1618, 1573, 1519, 1476, 1450, 1392, 1319; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.75 (s, 1H, NH), 11.31 (s, 1H, OH), 8.45–8.42 (m, 1H, ArH), 8.12 (d, 3H, $J = 7.2$ Hz, ArH), 7.69–7.65 (m, 1H, ArH), 7.63–7.57 (m, 4H, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 141.9, 137.2, 130.3, 129.6, 129.3, 129.0, 127.8, 126.3, 122.8, 122.5; HRMS (ESI): m/z calcd for: $\text{C}_{16}\text{H}_{10}\text{N}_3\text{O}$, 260.0824 $[\text{M}-\text{H}]^-$; found: 260.0820.

4-(3-Chlorophenyl)-3H-pyrazolo[3,4-*c*]quinolin-1-ol (3b): A white solid; 221 mg; 75% yield; Mp: 250–251 °C; IR (KBr, ν , cm^{-1}): 3317, 2963, 1630, 1599, 1580, 1518, 1471, 1450, 1390, 1341, 1328, 1303; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.86 (s, 1H, NH), 11.37 (s, 1H, OH), 8.44 (d, 1H, $J = 8.0$ Hz, ArH), 8.15–8.08 (m, 3H, ArH), 7.69 (t, 1H, $J = 7.2$ Hz, ArH), 7.65–7.64 (m, 2H, ArH), 7.62 (d, 1H, $J = 6.8$ Hz, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 141.9, 139.2, 134.1, 131.1, 130.2, 129.8, 128.6, 128.1, 127.7, 126.4, 122.8, 122.7; HRMS (ESI): m/z calcd for: $\text{C}_{16}\text{H}_9\text{ClN}_3\text{O}$, 294.0434 $[\text{M}-\text{H}]^-$; found: 294.0438.

4-(4-Bromophenyl)-3H-pyrazolo[3,4-*c*]quinolin-1-ol (3c): A pale yellow solid; 288 mg; 85% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3450, 2982, 1618, 1584, 1548, 1523, 1487,

1450, 1402, 1336, 1314; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.80 (s, 1H, NH), 11.35 (s, 1H, OH), 8.43 (d, 1H, $J = 7.6$ Hz, ArH), 8.14–8.08 (m, 3H, ArH), 7.82 (d, 2H, $J = 8.4$ Hz, ArH), 7.68 (t, 1H, $J = 7.2$ Hz, ArH), 7.62 (t, 1H, $J = 7.2$ Hz, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 141.8, 136.3, 132.2, 131.0, 129.6, 128.0, 126.5, 123.9, 122.9, 122.6; HRMS (ESI): m/z calcd for: $\text{C}_{16}\text{H}_9\text{BrN}_3\text{O}$, 337.9929 $[\text{M}-\text{H}]^-$; found: 337.9916.

4-(4-Nitrophenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3d): A yellow solid; 214 mg; 70% yield; Mp: 283–285 °C; IR (KBr, ν , cm^{-1}): 3431, 3032, 1621, 1579, 1536, 1469, 1457, 1438, 1396, 1340, 1312; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.92 (s, 1H, NH), 11.45 (s, 1H, OH), 8.47–8.40 (m, 5H, ArH), 8.17 (d, 1H, $J = 7.6$ Hz, ArH), 7.74–7.70 (m, 1H, ArH), 7.67–7.63 (m, 1H, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 148.5, 143.1, 141.8, 130.4, 129.9, 128.6, 126.6, 124.3, 122.9; HRMS (ESI): m/z calcd for: $\text{C}_{16}\text{H}_9\text{N}_4\text{O}_3$, 305.0675 $[\text{M}-\text{H}]^-$; found: 305.0668.

4-(p-Tolyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3e): A white solid; 228 mg; 83% yield; Mp: 270–272 °C; IR (KBr, ν , cm^{-1}): 3447, 3031, 1611, 1585, 1569, 1543, 1526, 1506, 1465, 1415, 1388, 1319, 1301; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.71 (s, 1H, NH), 11.29 (s, 1H, OH), 8.43 (d, 1H, $J = 7.6$ Hz, ArH), 8.11 (d, 1H, $J = 8.0$ Hz, ArH), 8.04 (d, 2H, $J = 7.2$ Hz, ArH), 7.65 (t, 1H, $J = 6.8$ Hz, ArH), 7.60 (t, 1H, $J = 8.4$ Hz, ArH), 7.43 (d, 2H, $J = 8.0$ Hz, ArH), 2.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 141.9, 140.0, 134.4, 129.8, 129.5, 128.9, 127.6, 126.3, 122.8, 122.4, 21.5; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{12}\text{N}_3\text{O}$, 274.0981 $[\text{M}-\text{H}]^-$; found: 274.0977.

4-(4-Methoxyphenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3f): A pale pink solid; 233 mg; 80% yield; Mp: 290–292 °C; IR (KBr, ν , cm^{-1}): 3437, 2955, 1606, 1574, 1535, 1510, 1466, 1441, 1421, 1392, 1313; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.71 (s, 1H, NH), 11.27 (s, 1H, OH), 8.40 (d, 1H, $J = 7.2$ Hz, ArH), 8.10 (t, 3H, $J = 8.4$ Hz, ArH), 7.65–7.57 (m, 2H, ArH), 7.16 (d, 2H, $J = 8.8$ Hz, ArH), 3.88 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 161.1, 142.0, 130.5, 129.7, 129.4, 127.4, 126.2, 122.8, 122.3, 114.7, 55.9; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{12}\text{N}_3\text{O}_2$, 290.0930 $[\text{M}-\text{H}]^-$; found: 290.0938.

4-(3-Methoxyphenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3g): A white solid; 213 mg; 73% yield; Mp: 251–253 °C; IR (KBr, ν , cm^{-1}): 3411, 3002, 1656, 1585, 1542, 1522, 1488, 1466, 1429, 1388, 1309; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.75 (s, 1H, NH), 11.32 (s, 1H, OH), 8.43 (d, 1H, $J = 8.0$ Hz, ArH), 8.12 (d, 1H, $J = 8.0$ Hz, ArH), 7.67 (t, 2H, $J = 6.8$ Hz, ArH), 7.61 (t, 2H, $J = 7.6$ Hz, ArH), 7.53 (t, 1H, $J = 8.0$ Hz, ArH), 7.17–7.14 (m, 1H, ArH), 3.91 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 159.9, 141.7, 138.5, 130.5, 129.6, 127.9, 126.4, 122.8, 122.5, 121.3, 116.5, 113.8, 55.7; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{12}\text{N}_3\text{O}_2$, 290.0930 $[\text{M}-\text{H}]^-$; found: 290.0941.

4-(Naphthalen-2-yl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3h): A pale yellow solid; 236 mg; 76% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3422, 2983, 1619, 1596, 1580, 1515, 1482, 1447, 1387, 1321; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 13.11 (s, 1H, NH), 11.60 (s, 1H, OH), 8.73 (s, 1H, ArH), 8.40 (d, 1H, $J = 2.4$ Hz, ArH), 8.31 (d, 1H, $J = 8.0$ Hz, ArH), 8.19–8.14 (m, 3H, ArH), 8.06–7.98 (m, 2H, ArH), 7.66–7.64 (m, 3H, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.4, 134.1, 133.2, 132.2, 131.6, 129.6, 129.0, 128.9, 128.1,

127.8, 127.2, 127.0, 126.7, 126.2, 123.5, 121.7; HRMS (ESI): m/z calcd for: $C_{20}H_{12}N_3O$, 310.0981 $[M-H]^-$; found: 310.0993.

8-Fluoro-4-phenyl-3H-pyrazolo[3,4-c]quinolin-1-ol (3i): A pale yellow solid; 232 mg; 83% yield; Mp: 279–281 °C; IR (KBr, ν , cm^{-1}): 3299, 3058, 1625, 1574, 1542, 1520, 1464, 1448, 1396, 1329; 1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 12.85 (s, 1H, NH), 11.47 (s, 1H, OH), 8.19–8.10 (m, 3H, ArH), 8.05–8.02 (m, 1H, ArH), 7.64–7.57 (m, 3H, ArH), 7.50–7.45 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.1 ($^1J_{CF}$ = 243.7 Hz), 157.3, 145.6, 138.9, 137.0, 134.0, 132.3 ($^5J_{CF}$ = 9.7 Hz), 130.4, 129.3, 128.9, 123.6 ($^4J_{CF}$ = 10.9 Hz), 115.2 ($^2J_{CF}$ = 24.5 Hz), 109.3, 107.0 ($^3J_{CF}$ = 23.3 Hz); HRMS (ESI): m/z calcd for: $C_{16}H_9FN_3O$, 278.0730 $[M-H]^-$; found: 278.0726.

4-(4-Chlorophenyl)-8-fluoro-3H-pyrazolo[3,4-c]quinolin-1-ol (3j): A white solid; 272 mg; 87% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3416, 2971, 1629, 1585, 1569, 1551, 1530, 1493, 1474, 1441, 1407, 1387, 1337, 1318; 1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 12.88 (s, 1H, NH), 11.54 (s, 1H, OH), 8.16–8.11 (m, 3H, ArH), 8.03–8.00 (m, 1H, ArH), 7.65 (d, 2H, J = 8.8 Hz, ArH), 7.48–7.43 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.2 ($^1J_{CF}$ = 244.0 Hz), 138.8, 135.7, 135.2, 132.2 ($^5J_{CF}$ = 9.8 Hz), 130.7, 129.3, 123.7 ($^4J_{CF}$ = 11.1 Hz), 115.3 ($^2J_{CF}$ = 24.2 Hz), 107.0 ($^3J_{CF}$ = 23.4 Hz); HRMS (ESI): m/z calcd for: $C_{16}H_8ClFN_3O$, 312.0340 $[M-H]^-$; found: 312.0331.

4-(3-Chlorophenyl)-8-fluoro-3H-pyrazolo[3,4-c]quinolin-1-ol (3k): A white solid; 238 mg; 76% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3443, 3029, 1629, 1587, 1550, 1529, 1483, 1438, 1413, 1385, 1372, 1337, 1314; 1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 12.96 (s, 1H, NH), 11.51 (s, 1H, OH), 8.19–8.16 (m, 1H, ArH), 8.11–8.00 (m, 3H, ArH), 7.64–7.61 (m, 2H, ArH), 7.50–7.45 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.3 ($^1J_{CF}$ = 244.2 Hz), 138.8, 138.7, 134.1, 132.3 ($^5J_{CF}$ = 9.6 Hz), 131.1, 130.3, 128.6, 127.7, 123.8 ($^4J_{CF}$ = 11.6 Hz), 115.4 ($^2J_{CF}$ = 24.2 Hz), 107.0 ($^3J_{CF}$ = 23.3 Hz); HRMS (ESI): m/z calcd for: $C_{16}H_8ClFN_3O$, 312.0340 $[M-H]^-$; found: 312.0336.

4-(4-Bromophenyl)-8-fluoro-3H-pyrazolo[3,4-c]quinolin-1-ol (3l): A white solid; 303 mg; 85% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3432, 2938, 1626, 1582, 1563, 1546, 1490, 1437, 1404, 1318; 1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 12.87 (s, 1H, NH), 11.51 (s, 1H, OH), 8.13–8.03 (m, 4H, ArH), 7.78 (s, 2H, ArH), 7.45 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.2 ($^1J_{CF}$ = 244.0 Hz), 138.8, 136.0, 132.2 ($^5J_{CF}$ = 8.2 Hz), 131.0, 124.0, 123.7 ($^4J_{CF}$ = 11.2 Hz), 115.4 ($^2J_{CF}$ = 24.6 Hz), 107.0 ($^3J_{CF}$ = 23.3 Hz); HRMS (ESI): m/z calcd for: $C_{16}H_8BrFN_3O$, 355.9835 $[M-H]^-$; found: 355.9847.

8-Fluoro-4-(*p*-tolyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3m): A white solid; 261 mg; 89% yield; Mp: 282–284 °C; IR (KBr, ν , cm^{-1}): 3465, 3014, 1628, 1582, 1566, 1545, 1526, 1510, 1468, 1432, 1411, 1386, 1334, 1320; 1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 12.81 (s, 1H, NH), 11.45 (s, 1H, OH), 8.17–8.13 (m, 1H, ArH), 8.04–8.01 (m, 3H, ArH), 7.49–7.44 (m, 1H, ArH), 7.41 (d, 2H, J = 8.0 Hz, ArH), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.0 ($^1J_{CF}$ = 243.4 Hz), 157.3, 145.6, 140.1, 139.0, 134.3, 134.0, 132.2 ($^5J_{CF}$ = 9.7 Hz), 129.9, 128.8, 123.5 ($^4J_{CF}$ = 10.4 Hz), 115.1 ($^2J_{CF}$ = 23.8 Hz), 109.3,

106.9 ($^3J_{\text{CF}} = 23.3$ Hz), 21.5; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{11}\text{FN}_3\text{O}$, 292.0886 $[\text{M-H}]^-$; found: 292.0897.

8-Fluoro-4-(4-methoxyphenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3n): A white solid; 272 mg; 88% yield; Mp: 277–279 °C; IR (KBr, ν , cm^{-1}): 3376, 2936, 1626, 1609, 1540, 1533, 1472, 1465, 1457, 1437, 1388, 1339, 1319; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.81 (s, 1H, NH), 11.45 (s, 1H, OH), 8.14–8.09 (m, 3H, ArH), 8.03–8.00 (m, 1H, ArH), 7.47–7.41 (m, 1H, ArH), 7.14 (d, 2H, $J = 8.8$ Hz, ArH), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 161.1, 160.9 ($^1J_{\text{CF}} = 243.1$ Hz), 157.3, 145.3, 138.9, 134.0, 131.9 ($^5J_{\text{CF}} = 9.6$ Hz), 130.4, 129.5, 123.3 ($^4J_{\text{CF}} = 11.0$ Hz), 115.0 ($^2J_{\text{CF}} = 24.3$ Hz), 114.6, 109.2, 106.9 ($^3J_{\text{CF}} = 23.2$ Hz), 55.8; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{11}\text{FN}_3\text{O}_2$, 308.0836 $[\text{M-H}]^-$; found: 308.0845.

8-Fluoro-4-(3-methoxyphenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3o): A white solid; 226 mg; 73% yield; Mp: 287–289 °C; IR (KBr, ν , cm^{-1}): 3274, 2948, 1625, 1589, 1534, 1491, 1481, 1456, 1444, 1421, 1396, 1339, 1317; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.85 (s, 1H, NH), 11.47 (s, 1H, OH), 8.19–8.16 (m, 1H, ArH), 8.04–8.01 (m, 1H, ArH), 7.66–7.60 (m, 2H, ArH), 7.54–7.46 (m, 2H, ArH), 7.17–7.14 (m, 1H, ArH), 3.90 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 161.1 ($^1J_{\text{CF}} = 243.4$ Hz), 138.8, 138.4, 132.3 ($^5J_{\text{CF}} = 9.9$ Hz), 130.5, 123.6 ($^4J_{\text{CF}} = 10.2$ Hz), 121.3, 116.5, 115.2 ($^2J_{\text{CF}} = 24.9$ Hz), 113.7, 107.0 ($^3J_{\text{CF}} = 23.4$ Hz), 55.7; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{11}\text{FN}_3\text{O}_2$, 308.0836 $[\text{M-H}]^-$; found: 308.0847.

8-Chloro-4-phenyl-3H-pyrazolo[3,4-c]quinolin-1-ol (3p): A white solid; 236 mg; 80% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3455, 2958, 1615, 1589, 1574, 1516, 1455, 1387, 1322, 1297; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.91 (s, 1H, NH), 11.52 (s, 1H, OH), 8.36 (d, 1H, $J = 2.4$ Hz, ArH), 8.14–8.11 (m, 3H, ArH), 7.64–7.63 (m, 1H, ArH), 7.62–7.60 (m, 3H, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.5, 136.9, 132.1, 131.6, 130.5, 129.3, 129.0, 126.6, 123.5, 121.6; HRMS (ESI): m/z calcd for: $\text{C}_{16}\text{H}_9\text{ClN}_3\text{O}$, 294.0434 $[\text{M-H}]^-$; found: 294.0421.

8-Chloro-4-(*p*-tolyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3q): A white solid; 266 mg; 86% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3418, 2976, 1654, 1611, 1586, 1567, 1542, 1478, 1419, 1387, 1318; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.86 (s, 1H, NH), 11.50 (s, 1H, OH), 8.35 (d, 1H, $J = 2.4$ Hz, ArH), 8.10 (d, 1H, $J = 8.8$ Hz, ArH), 8.02 (d, 2H, $J = 6.4$ Hz, ArH), 7.61–7.58 (m, 1H, ArH), 7.41 (d, 2H, $J = 8.0$ Hz, ArH), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.4, 140.3, 134.2, 131.9, 131.5, 129.9, 128.9, 126.5, 123.4, 121.6, 21.5; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{11}\text{ClN}_3\text{O}$, 308.0591 $[\text{M-H}]^-$; found: 308.0583.

8-Chloro-4-(4-methoxyphenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3r): A white solid; 276 mg; 85% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3449, 2933, 1604, 1584, 1572, 1546, 1507, 1428, 1414, 1384, 1333, 1319; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.87 (s, 1H, NH), 11.50 (s, 1H, OH), 8.33 (d, 1H, $J = 2.4$ Hz, ArH), 8.11–8.06 (m, 3H, ArH), 7.60–7.57 (m, 1H, ArH), 7.15 (d, 2H, $J = 8.4$ Hz, ArH), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 161.3, 140.4, 131.7, 131.3, 130.5, 129.4, 126.5, 123.3, 121.6,

114.7, 55.9; HRMS (ESI): m/z calcd for: $C_{17}H_{11}ClN_3O_2$, 324.0540 $[M-H]^-$; found: 324.0535.

8-Bromo-4-phenyl-3H-pyrazolo[3,4-c]quinolin-1-ol (3s): A white solid; 275 mg; 81% yield; Mp: $>300^\circ\text{C}$; IR (KBr, ν , cm^{-1}): 3444, 3018, 1614, 1585, 1573, 1544, 1515, 1495, 1455, 1422, 1386, 1319; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.93 (s, 1H, NH), 11.54 (s, 1H, OH), 8.52 (d, 1H, $J = 2.0$ Hz, ArH), 8.11 (s, 2H, ArH), 8.05 (d, 1H, $J = 8.8$ Hz, ArH), 7.75-7.72 (m, 1H, ArH), 7.62 (d, 1H, $J = 2.4$ Hz, ArH), 7.61 (d, 2H, $J = 2.0$ Hz, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.6, 136.8, 131.7, 130.6, 129.3, 129.0, 124.8, 124.0, 120.8; HRMS (ESI): m/z calcd for: $C_{16}H_9\text{BrN}_3\text{O}$, 337.9929 $[M-H]^-$; found: 337.9938.

8-Bromo-4-(4-chlorophenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3t): A white solid; 313 mg; 84% yield; Mp: $>300^\circ\text{C}$; IR (KBr, ν , cm^{-1}): 3442, 2968, 1614, 1583, 1566, 1540, 1519, 1491, 1449, 1405, 1385, 1328, 1314; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.93 (s, 1H, NH), 11.55 (s, 1H, OH), 8.50 (d, 1H, $J = 1.6$ Hz, ArH), 8.13 (d, 2H, $J = 6.4$ Hz, ArH), 8.02 (d, 1H, $J = 8.8$ Hz, ArH), 7.73-7.70 (m, 1H, ArH), 7.65 (d, 2H, $J = 8.4$ Hz, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.4, 135.6, 135.4, 131.7, 130.8, 129.3, 124.8, 124.0, 121.0; HRMS (ESI): m/z calcd for: $C_{16}H_8\text{BrClN}_3\text{O}$, 371.9540 $[M-H]^-$; found: 371.9557.

8-Bromo-4-(4-bromophenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3u): A pale pink solid; 335 mg; 80% yield; Mp: $>300^\circ\text{C}$; IR (KBr, ν , cm^{-1}): 3450, 3010, 1714, 1582, 1563, 1537, 1514, 1486, 1447, 1422, 1400, 1381, 1315; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.94 (s, 1H, NH), 11.57 (s, 1H, OH), 8.51 (d, 1H, $J = 2.0$ Hz, ArH), 8.04 (d, 3H, $J = 8.8$ Hz, ArH), 7.80 (d, 2H, $J = 8.8$ Hz, ArH), 7.75-7.72 (m, 1H, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.5, 136.0, 132.2, 131.8, 131.0, 129.3, 124.8, 124.1, 121.0; HRMS (ESI): m/z calcd for: $C_{16}H_8\text{Br}_2\text{N}_3\text{O}$, 417.9014 $[M-H]^-$; found: 417.9029.

8-Bromo-4-(*p*-tolyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3v): A pale yellow solid; 307 mg; 87% yield; Mp: $>300^\circ\text{C}$; IR (KBr, ν , cm^{-1}): 3442, 2917, 1614, 1582, 1566, 1541, 1506, 1450, 1409, 1384, 1329, 1316; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.88 (s, 1H, NH), 11.51 (s, 1H, OH), 8.50 (d, 1H, $J = 2.0$ Hz, ArH), 8.03 (d, 3H, $J = 8.8$ Hz, ArH), 7.73-7.70 (m, 1H, ArH), 7.42 (d, 2H, $J = 8.0$ Hz, ArH), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.6, 140.3, 134.1, 131.6, 129.9, 129.2, 128.9, 124.7, 123.9, 120.5, 21.5; HRMS (ESI): m/z calcd for: $C_{17}H_{11}\text{BrN}_3\text{O}$, 352.0086 $[M-H]^-$; found: 352.0097.

8-Bromo-4-(4-methoxyphenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3w): A pale yellow solid; 306 mg; 83% yield; Mp: $>300^\circ\text{C}$; IR (KBr, ν , cm^{-1}): 3438, 2932, 1604, 1583, 1571, 1543, 1506, 1452, 1413, 1385, 1332, 1318; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.87 (s, 1H, NH), 11.49 (s, 1H, OH), 8.50 (d, 1H, $J = 2.0$ Hz, ArH), 8.11 (d, 2H, $J = 8.0$ Hz, ArH), 8.00 (d, 1H, $J = 8.8$ Hz, ArH), 7.70-7.68 (m, 1H, ArH), 7.14 (d, 2H, $J = 8.8$ Hz, ArH), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 161.3, 157.1, 146.4, 140.6, 134.2, 131.5, 130.6, 129.3, 129.2, 124.7, 123.8, 120.3, 114.7, 108.4, 55.8; HRMS (ESI): m/z calcd for: $C_{17}H_{11}\text{BrN}_3\text{O}_2$, 368.0035 $[M-H]^-$; found: 368.0023.

6,8-Dimethyl-4-phenyl-3H-pyrazolo[3,4-c]quinolin-1-ol (3x): A pale yellow solid; 228 mg; 79% yield; Mp: 265–267 °C; IR (KBr, ν , cm^{-1}): 3414, 2948, 1620, 1589, 1575, 1526, 1494, 1470, 1451, 1417, 1381, 1346, 1318; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.64 (s, 1H, NH), 11.28 (s, 1H, OH), 8.17 (d, 2H, $J = 7.2$ Hz, ArH), 8.10 (s, 1H, ArH), 7.63–7.59 (m, 2H, ArH), 7.58–7.54 (m, 1H, ArH), 7.30 (s, 1H, ArH), 2.77 (s, 3H, CH_3), 2.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 157.4, 150.4, 143.4, 139.0, 137.8, 136.9, 134.2, 130.0, 129.3, 128.9, 128.7, 122.5, 120.1, 109.7, 22.0, 18.9; HRMS (ESI): m/z calcd for: $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}$, 288.1137 $[\text{M}-\text{H}]^-$; found: 288.1131.

8-Methyl-4-phenyl-3H-pyrazolo[3,4-c]quinolin-1-ol (3y): A pale yellow solid; 242 mg; 88% yield; Mp: 268–270 °C; IR (KBr, ν , cm^{-1}): 3346, 2955, 1626, 1575, 1538, 1514, 1451, 1380, 1328, 1309; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.68 (s, 1H, NH), 11.28 (s, 1H, OH), 8.23 (s, 1H, ArH), 8.11 (d, 2H, $J = 6.8$ Hz, ArH), 8.01 (d, 1H, $J = 8.4$ Hz, ArH), 7.62–7.59 (m, 3H, ArH), 7.45–7.42 (m, 1H, ArH), 2.56 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.4, 137.3, 130.1, 129.4, 129.3, 128.9, 128.1, 122.5, 122.2, 22.0; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{12}\text{N}_3\text{O}$, 274.0981 $[\text{M}-\text{H}]^-$; found: 274.0987.

8-Methyl-4-(*p*-tolyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3z): A white solid; 269 mg; 93% yield; Mp: 286–288 °C; IR (KBr, ν , cm^{-1}): 3442, 2970, 1614, 1587, 1540, 1508, 1386, 1338, 1320, 1308; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.65 (s, 1H, NH), 11.29 (s, 1H, OH), 8.22 (s, 1H, ArH), 8.03–7.98 (m, 3H, ArH), 7.43–7.39 (m, 3H, ArH), 2.55 (s, 3H, CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 140.4, 139.8, 137.1, 134.6, 129.8, 129.3, 128.8, 128.0, 122.4, 122.2, 21.9, 21.4; HRMS (ESI): m/z calcd for: $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}$, 288.1137 $[\text{M}-\text{H}]^-$; found: 288.1143.

4-(4-Methoxyphenyl)-8-methyl-3H-pyrazolo[3,4-c]quinolin-1-ol (3aa): A pale yellow solid; 275 mg; 90% yield; Mp: 252–254 °C; IR (KBr, ν , cm^{-1}): 3425, 2967, 1662, 1608, 1588, 1574, 1538, 1509, 1439, 1420, 1387, 1339, 1321, 1308; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.65 (s, 1H, NH), 11.26 (s, 1H, OH), 8.20 (s, 1H, ArH), 8.09 (d, 2H, $J = 7.6$ Hz, ArH), 7.97 (d, 1H, $J = 8.4$ Hz, ArH), 7.42–7.40 (m, 1H, ArH), 7.14 (d, 2H, $J = 8.8$ Hz, ArH), 3.87 (s, 3H, OCH_3), 2.54 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 161.0, 140.4, 136.9, 130.3, 129.8, 129.2, 128.0, 122.2(5), 122.1(7), 114.6, 55.8, 21.9; HRMS (ESI): m/z calcd for: $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}_2$, 304.1086 $[\text{M}-\text{H}]^-$; found: 304.1072.

7-Chloro-4-phenyl-3H-pyrazolo[3,4-c]quinolin-1-ol (3bb): A white solid; 233 mg; 79% yield; Mp: 275–277 °C; IR (KBr, ν , cm^{-1}): 3420, 2976, 1660, 1613, 1583, 1547, 1512, 1493, 1415, 1378; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 12.89 (s, 1H, NH), 11.45 (s, 1H, OH), 8.43 (d, 1H, $J = 8.8$ Hz, ArH), 8.16–8.13 (m, 3H, ArH), 7.73–7.70 (m, 1H, ArH), 7.64–7.62 (m, 3H, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) (δ , ppm): 142.6, 136.8, 130.7, 130.4, 129.3, 129.1, 128.4, 128.0, 124.5, 121.2; HRMS (ESI): m/z calcd for: $\text{C}_{16}\text{H}_9\text{ClN}_3\text{O}$, 294.0434 $[\text{M}-\text{H}]^-$; found: 294.0427.

7-Bromo-4-(3-chlorophenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3cc): A pale pink solid; 265 mg; 71% yield; Mp: 268–270 °C; IR (KBr, ν , cm^{-1}): 3429, 2958, 1711, 1581, 1536, 1512, 1467, 1437, 1376, 1335; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 13.00 (s, 1H, NH), 11.68 (s, 1H, OH), 8.36 (d, 1H, $J = 8.8$ Hz, ArH), 8.30 (s, 1H, ArH), 8.20–8.14 (m, 2H,

ArH), 7.81 (d, 1H, $J = 8.0$ Hz, ArH), 7.66–7.62 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 157.3, 150.4, 142.6, 138.9, 134.0, 131.6, 131.1, 130.8, 130.4, 128.8, 127.8, 124.5, 120.6; HRMS (ESI): m/z calcd for: $\text{C}_{16}\text{H}_8\text{BrClN}_3\text{O}$, 371.9540 $[\text{M}-\text{H}]^-$; found: 371.9552.

7-Bromo-4-(4-methoxyphenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3dd): A white solid; 317 mg; 86% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3407, 2995, 1604, 1580, 1568, 1544, 1505, 1475, 1456, 1439, 1379, 1337, 1313; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 12.86 (s, 1H, NH), 11.44 (s, 1H, OH), 8.33 (d, 1H, $J = 8.8$ Hz, ArH), 8.26 (d, 1H, $J = 1.6$ Hz, ArH), 8.11 (d, 2H, $J = 6.0$ Hz, ArH), 7.79–7.77 (m, 1H, ArH), 7.16 (d, 2H, $J = 8.8$ Hz, ArH), 3.88 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.4, 143.0, 131.3, 130.6, 130.2, 129.3, 124.6, 121.2, 118.6, 114.7, 55.9; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{11}\text{BrN}_3\text{O}_2$, 368.0035 $[\text{M}-\text{H}]^-$; found: 368.0029.

7-Bromo-4-(3-methoxyphenyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3ee): A white solid; 295 mg; 80% yield; Mp: 260–262 °C; IR (KBr, ν , cm^{-1}): 3406, 2938, 1602, 1588, 1540, 1520, 1488, 1466, 1449, 1438, 1306; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 12.88 (s, 1H, NH), 11.46 (s, 1H, OH), 8.35 (d, 1H, $J = 8.8$ Hz, ArH), 8.30 (d, 1H, $J = 1.6$ Hz, ArH), 7.83–7.81 (m, 1H, ArH), 7.67–7.61 (m, 2H, ArH), 7.53 (t, 1H, $J = 8.0$ Hz, ArH), 7.18–7.16 (m, 1H, ArH), 3.90 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 159.9, 142.9, 138.2, 131.6, 130.6, 130.5, 124.7, 121.5, 121.4, 118.6, 116.8, 113.9, 55.7; HRMS (ESI): m/z calcd for: $\text{C}_{17}\text{H}_{11}\text{BrN}_3\text{O}_2$, 368.0035 $[\text{M}-\text{H}]^-$; found: 368.0022.

8-Chloro-4-phenyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3ff): A purple solid; 275 mg; 73% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3381, 3016, 1656, 1621, 1597, 1529, 1490, 1459, 1428, 1343; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.47–8.45 (m, 3H, ArH), 8.06 (d, 1H, $J = 8.8$ Hz, ArH), 7.65–7.62 (m, 3H, ArH), 7.58–7.55 (m, 1H, ArH), 5.17–5.10 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 149.7, 139.9, 135.7, 132.9, 131.1, 130.5, 129.5, 129.0, 128.3, 126.3, 125.5, 124.7, 122.8, 120.9, 66.8, 46.7 ($J_{\text{CF}} = 31.1$ Hz); HRMS (ESI): m/z calcd for: $\text{C}_{18}\text{H}_{10}\text{ClF}_3\text{N}_3\text{O}$, 376.0465 $[\text{M}-\text{H}]^-$; found: 376.0472.

8-Fluoro-3-(2-hydroxyethyl)-4-phenyl-3H-pyrazolo[3,4-c]quinolin-1-ol (3gg): An orange solid; 207 mg; 64% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3430, 3317, 2955, 1636, 1580, 1561, 1542, 1483, 1430, 1421, 1381, 1313; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 9.25 (s, 1H, OH), 8.17–8.13 (m, 3H, ArH), 7.71–7.68 (m, 1H, ArH), 7.60 (t, 2H, $J = 7.2$ Hz, ArH), 7.54–7.48 (m, 2H, ArH), 5.04 (t, 1H, $J = 5.6$ Hz, OH), 4.95 (t, 2H, $J = 5.6$ Hz, CH_2), 4.14–4.10 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 156.8 ($^1J_{\text{CF}} = 232.9$ Hz), 153.4, 142.8, 136.3, 134.1 ($^5J_{\text{CF}} = 5.0$ Hz), 129.6, 127.0, 122.4 ($^3J_{\text{CF}} = 10.4$ Hz), 120.1, 119.8, 119.6 ($^4J_{\text{CF}} = 9.2$ Hz), 109.2 ($^2J_{\text{CF}} = 23.8$ Hz), 59.1, 58.0; HRMS (ESI): m/z calcd for: $\text{C}_{18}\text{H}_{13}\text{FN}_3\text{O}_2$, 322.0992 $[\text{M}-\text{H}]^-$; found: 322.0981.

4-(4-Bromophenyl)-3-(2-mercaptoethyl)-3H-pyrazolo[3,4-c]quinolin-1-ol (3hh): An orange solid; 239 mg; 60% yield; Mp: >300 °C; IR (KBr, ν , cm^{-1}): 3362, 3018, 1639, 1612, 1552, 1539, 1460, 1409, 1340, 1337; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 9.20 (s, 1H, OH), 8.32 (d, 1H, $J = 8.0$ Hz, ArH), 8.13 (d, 2H, $J = 8.4$ Hz, ArH), 7.79 (d, 2H, $J = 8.4$ Hz,

ArH), 7.68 (d, 1H, $J = 8.0$ Hz, ArH), 7.66-7.62 (m, 1H, ArH), 7.27-7.24 (m, 1H, ArH), 5.06 (s, 1H, OH), 4.95 (t, 2H, $J = 5.6$ Hz, CH₂), 4.12 (t, 2H, $J = 5.2$ Hz, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm): 155.4, 153.5, 143.4, 136.2, 133.5, 131.4, 129.7, 129.6, 127.0, 123.7, 123.5, 123.4, 120.3, 120.1, 59.1, 58.1; HRMS (ESI): *m/z* calcd for: C₁₈H₁₃BrN₃OS, 397.9963 [M-H]⁻; found: 397.9955.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

1. Kouznetsov VV, Mendez LY, Gomez CM. *Curr Org Chem.* 2005; 9:141.
2. (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles.* 2. Wiley-VCH; Weinheim, Germany: 2003. (b) Michael JP. *Nat Prod Rep.* 2008; 25:166. [PubMed: 18250901] (c) Egan TJ, Ross DC, Adams PA. *FEBS Lett.* 1994; 352:54. [PubMed: 7925942] (d) Vu AT, Cohn ST, Manas ES, Harris HA, Mewshaw RE. *Bioorg Med Chem Lett.* 2005; 15:4520. [PubMed: 16098741] (e) Kaschula CH, Egan TJ, Hunter R, Basilico N, Parapini S, Taramelli D, Pasini E, Monti D. *J Med Chem.* 2002; 45:3531. [PubMed: 12139464] (f) Foley M, Tilley L. *Pharmacol Ther.* 1998; 79:55. [PubMed: 9719345] (g) Solomon VR, Lee H. *Curr Med Chem.* 2011; 18:1488. [PubMed: 21428893]
3. (a) Tokoro Y, Nagai A, Kokado K, Chujo Y. *Macromolecules.* 2009; 42:2988. (b) Jegou G, Jenekhe SA. *Macromolecules.* 2001; 34:7926. (c) Kim JI, Shin IS, Kim H, Lee JK. *J Am Chem Soc.* 2005; 127:1614. [PubMed: 15700976] (d) Tong H, Wang L, Jing X, Wang F. *Macromolecules.* 2003; 36:2584.
4. (a) Baraldi PG, Borea PA. *Trends Pharmacol Sci.* 2000; 21:456. [PubMed: 11121831] (b) Coletta V, Catarzi D, Varano F, Cecchi L, Filacchioni G, Martini C, Trincavelli L, Lucacchini A. *J Med Chem.* 2000; 43:3118. [PubMed: 10956220]
5. (a) Palazzino G, Cecchi L, Melani F, Colotta V, Filacchioni G, Martini C, Lucacchini A. *J Med Chem.* 1987; 30:1737. [PubMed: 2821257] (b) Catarzi D, Coletta V, Varano F, Cecchi L, Filacchioni G, Galli A, Costagli C. *Arch Pharm Pharm Med Chem.* 1997; 330:383.
6. Colotta V, Catarzi D, Varano F, Cecchi L, Filacchioni G, Martini C, Trincavelli L, Lucacchini A. *J Med Chem.* 2000; 43:3118. [PubMed: 10956220]
7. MacLeod AM, Grimwood S, Barton C, Bristow L, Saywell KL, Marshall GR, Ball RG. *J Med Chem.* 1995; 38:2239. [PubMed: 7783155]
8. (a) Pawlas J, Vedso P, Jakobsen P, Huusfeldt PO, Begtrup M. *J Org Chem.* 2000; 65:9001. [PubMed: 11149843] (b) Pawlas J, Vedso P, Jakobsen P, Huusfeldt PO, Begtrup M. *J Org Chem.* 2002; 67:585. [PubMed: 11798334] (c) Pawlas J, Greenwood J, Vedso P, Liljefors T, Jakobsen P, Huusfeldt PO, Begtrup M. *J Chem Soc, Perkin Trans 1.* 2001; 8:861.
9. (a) Kolotaev AV, Belen'kii LI, Kononikhin AS, Krayushkin MM. *Russ Chem Bull, Int Ed.* 2006; 55:892. (b) Cajipe GJB, Landen G, Semler B, Moore HW. *J Org Chem.* 1975; 40:3874. (c) Hosokawa T, Matsumura A, Katagiri T, Uneyama K. *J Org Chem.* 2008; 73:1468. [PubMed: 18205387]
10. (a) Eskildsen J, Ostergaard N, Vedso P, Begtrup M. *Tetrahedron.* 2002; 58:7635. (b) Pawlas J, Vedso P, Jakobsen P, Huusfeldt PO, Begtrup M. *J Org Chem.* 2001; 66:4214. [PubMed: 11397156] (c) Palazzino G, Cecchi L, Melani F, Colotta V, Filacchioni G, Martini C, Lucacchini A. *J Med Chem.* 1987; 30:1737. [PubMed: 2821257]
11. (a) Almstetter, M.; Thormann, M.; Tremel, A.; Koestler, R.; Yehia, N. *PCT Int Appl WO.* 2014060113. 2014. (b) Yoo E, Salunke DB, Sil D, Guo X, Salyer ACD, Hermanson AR, Kumar

- M, Malladi SS, Balakrishna R, Thompson WH, Tanji H, Ohto U, Shimizu T, David SA. *J Med Chem.* 2014; 57:7955. [PubMed: 25192394] (c) Almstetter, M.; Thormann, M.; Trembl, A.; Koestler, R.; Yehia, N. *PCT Int Appl WO.* 2012143143. 2012. (d) Lenzi O, Colotta V, Catarzi D, Varano F, Squarzialupi L, Filacchioni G, Varani K, Vincenzi F, Borea PA, Ben DD, Lambertucci C, Cristalli G. *Bioorg Med Chem.* 2011; 19:3757. [PubMed: 21616671] (e) Borchardt, A.; Davis, R.; Beauregard, C.; Becker, D.; Gamache, D.; Noble, SA.; Hellberg, MR.; Klimko, PG.; Qui, Z.; Payne, JE.; Yanni, J. *PCT Int Appl WO.* 2011112731. 2011. (f) Danielson ME, Hays DS, Kshirsagar TA, Haraldson CA, Lundquist GD, Wurst JR, Lindstrom KJ, Mackey SS, Willie DJ, Heppner PD, Leir CM, Benson KE. *J Org Chem.* 2007; 72:4570. [PubMed: 17506580] (g) Colotta V, Catarzi D, Varano F, Capelli F, Lenzi O, Filacchioni G, Martini C, Trincavelli L, Ciampi O, Pugliese AM, Pedata F, Schiesaro A, Morizzo E, Moro S. *J Med Chem.* 2007; 50:4061. [PubMed: 17665891] (h) Merrill, BA.; Danielson, ME.; Hays, DS.; Amos, DT.; Heppner, PD.; Kshirsagar, TA.; Lundquist, GDJ.; Moser, WH. *PCT Int Appl WO.* 2006107771. 2006. (i) Hays, DS.; Prince, RB.; Haraldson, CA.; Bonk, JD. *PCT Int Appl, WO.* 2006107851. 2006. (j) Kolotaev AV, Belen'kii LI, Kononikhin AS, Krayushkin MM. *Russ Chem Bull, Int Ed.* 2006; 55:892.(k) Cusmano G, Macaluso G, Vivona N, Ruccia M. *Heterocycles.* 1986; 24:3181.
12. Deng GB, Li HB, Yang XH, Song RJ, Hu M, Li JH. *Org Lett.* 2016; 18:2012. [PubMed: 27123866]
13. (a) Domling A, Wang W, Wang K. *Chem Rev.* 2012; 112:3083. [PubMed: 22435608] (b) Zhu YL, Jiang B, Hao WJ, Qiu JK, Sun J, Wang DC, Wei P, Wang AF, Li G, Tu SJ. *Org Lett.* 2015; 17:6078. [PubMed: 26618403] (c) Chen ZZ, Liu S, Hao WJ, Xu G, Wu S, Miao JN, Jiang B, Wang SL, Tu SJ, Li G. *Chem Sci.* 2015; 6:6654. [PubMed: 26568814] (d) Gao Q, Zhou P, Liu F, Hao WJ, Yao C, Jiang B, Tu SJ. *Chem Commun.* 2015; 51:9519.
14. (a) Vlaar T, Maes BU, Ruijter E, Orru RV. *Angew Chem Int Ed.* 2013; 52:7084.(b) Rotstein BH, Zaretsky S, Rai V, Yudin AK. *Chem Rev.* 2014; 114:8323. [PubMed: 25032909] (c) Wu YN, Fu R, Wang NN, Hao WJ, Li G, Tu SJ, Jiang B. *J Org Chem.* 2016; 81:4762. [PubMed: 27176454] (d) Sun J, Qiu JK, Jiang B, Hao WJ, Guo C, Tu SJ. *J Org Chem.* 2016; 81:3321. [PubMed: 26991413]
15. (a) Gao Q, Hao WJ, Liu F, Tu SJ, Wang SL, Li G, Jiang B. *Chem Commun.* 2016; 52:900.(b) Zhou P, Hao WJ, Zhang JP, Jiang B, Li G, Tu SJ. *Chem Commun.* 2015; 51:13012.(c) Fan W, Ye Q, Xu HW, Jiang B, Wang SL, Tu SJ. *Org Lett.* 2013; 15:2258. [PubMed: 23597067] (d) Jiang B, Ye Q, Fan W, Wang SL, Tu SJ, Li G. *Chem Commun.* 2014; 50:6108.(e) Qiu JK, Jiang B, Zhu YL, Hao WJ, Wang DC, Sun J, Wei P, Tu SJ, Li G. *J Am Chem Soc.* 2015; 137:8928. [PubMed: 26131954]
16. Fan W, Li Q, Li Y, Sun H, Jiang B, Li G. *Org Lett.* 2016; 18:1258. [PubMed: 26927417]
17. The preparation of triethylammonium thiolates, see: Jiang B, Tu XJ, Wang X, Tu SJ, Li G. *Org Lett.* 2014; 16:3656. [PubMed: 24988049]

Figure 1.
Several representative bioactive pyrazolo[3,4-c]quinolines

Figure 2.
X-Ray structure of **3c**

This work

Scheme 1.
Synthesis of pyrazolo[3,4-*c*]quinolones

Scheme 2.

Substrate scope for synthesis of **3a-ee**. Reaction conditions: all the reactions were performed with **1** (1.0 mmol), **2a** (2.0 mmol), and 1,4-dioxane (2.0 mL) in the sealed reaction tube at 120 °C under air conditions for 24 h. Isolated yield is based on **1**.

Scheme 3.

Substrate scope for synthesis of **3ff-kk**. Reaction conditions: all the reactions were performed with **1** (1.0 mmol), **2** (2.0 mmol), and 1,4-dioxane (2.0 mL) in the sealed reaction tube at 120 °C under air conditions for 24 h. Isolated yield is based on **1**.

Scheme 4.
Proposed mechanisms for forming products 3

Table 1Optimization of the reaction conditions^a

Entry	Solvent	<i>T</i> (°C)	Yield (%) ^b
1	THF	100	17
2	DCE	100	28
3	MeCN	100	23
4	EA	100	31
5	EtOH	100	57
6	1,4-dioxane	100	66
7	1,4-dioxane	110	70
8	1,4-dioxane	120	81
9	1,4-dioxane	130	77
10	1,4-dioxane	120	80 ^c

^aReaction conditions: all the reactions were performed with **1a** (1.0 mmol), **2a** (2.0 mmol), solvent (2.0 mL) in the sealed reaction tube under air conditions for 24 h.

^bIsolated yield based on **1a**.

^cuse of 10 mol% I_2 .