Efficient syntheses of 1,3-unsubstituted 1*H*-pyrazolo[3,4-*b*]quinolines

Arash Afghan, M. Mehdi Baradarani,[a]* and John A. Joule[b]

[a]*Department of Chemistry, Faculty of Science, University of Urmia, Urmia 57153-165, Iran*
[b]*The School of Chemistry, The University of Manchester, Manchester, M13 9PL, UK*
E-mail: mmbaradarani@yahoo.com

Abstract

The synthesis of pyrazolo[3,4-*b*]quinolines from 2-chloro-3-formylquinolines is described. Direct reaction of the chloro-aldehydes with hydrazine was unsuccessful, but a very efficient sequence was developed in which protection of the aldehyde group was followed by displacement of the halogen by hydrazine, release of the aldehyde then leading to spontaneous ring closure giving the tricycles. The products were obtained in excellent yields.

Keywords: 1*H*-Pyrazolo[3,4-*b*]quinolines, 2-chloro-3-formylquinolines, hydrazine, ethylene acetal, ethylene thioacetal

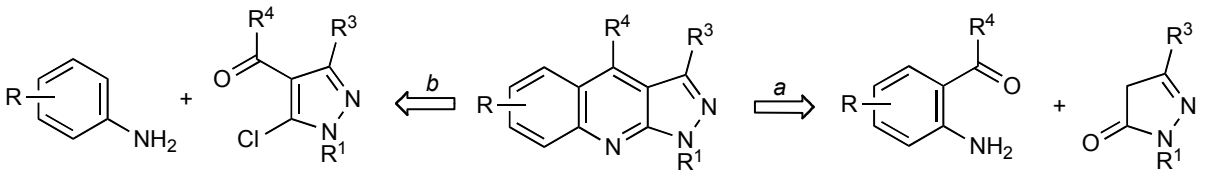
Introduction

1*H*-Pyrazolo[3,4-*b*]quinolines are of interest in a number of diverse contexts: for example as antiviral agents[1] in particular as inhibitors of *Herpex simplex* virus type 1 replication,[2] as activators of caspases and inducers of apoptosis,[3] as antimicrobial agents,[4-7] as parasiticidic agents,[8] as antimalarials,[9] in photoluminescence[10] and electroluminescence[11] studies, and in electroluminescent devices.[12] The use of 1*H*-pyrazolo[3,4-*b*]quinoline derivatives as optical brighteners has been long known[13] and interest in them as dyestuffs[14,15] and as colourants within polymers,[16] continues to the present.

Two main strategies have been employed for the synthesis of 1*H*-pyrazolo[3,4-*b*]quinolines: (1) some routes begin with a preformed pyrazole (or pyrazolone) the pyridine ring being constructed during the sequence; (2) other routes start from a preformed quinoline with the pyrazole ring being constructed during the sequence. The new work in this paper falls into the latter category.

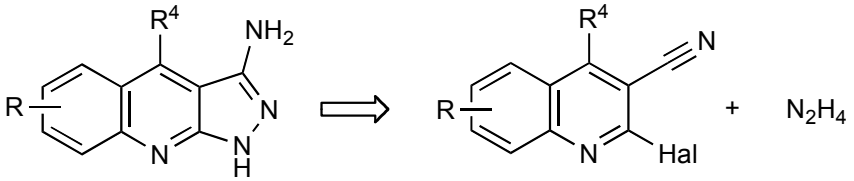
(1) The reaction of a 1*H*-pyrazol-5(4*H*)-one with an *ortho*-aminoaryl aldehyde or ketone (Scheme 1 route *a*) in a classic Friedländer quinoline synthesis has been used by several groups

for the assembly of 1*H*-pyrazolo[3,4-*b*]quinolines.[17-19] An alternative pyridine ring construction results from the condensation of a 5-halo-4-acylpyrazole with an aniline (Scheme 1 route *b*).[20,21] Less frequently employed routes which also start from preformed pyrazoles include the condensation of 5-aminopyrazoles with *ortho*-halo aromatic aldehydes,[22] the Friedel–Crafts type closure of an *ortho*-pyrazol-5-ylamino benzoic acid[9] and the condensation of 4-arylidenepyrazolin-5-ones with anilines.[23]



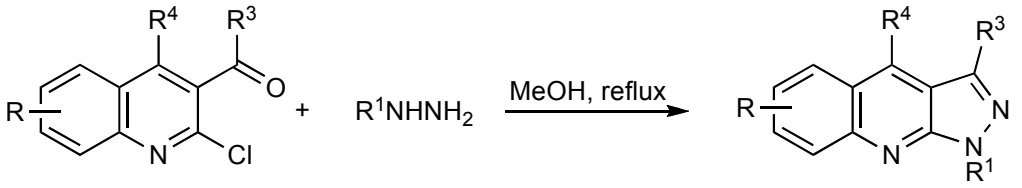
Scheme 1

(2) The reaction of 2-chloro-3-cyanoquinolines with hydrazine producing 3-amino-1*H*-pyrazolo[3,4-*b*]quinolines (Scheme 2) has been used widely.[7, 24-28]



Scheme 2

There has been a similar wide interest in the combination of 2-chloro-3-acylquinolines with hydrazine or arylhydrazines to form 1*H*-pyrazolo[3,4-*b*]quinolines. In particular, and partly because of the ready availability of 2-chloro-3-formylquinolines from Meth-Cohn's convenient and efficient synthesis of such molecules from acetanilides and the Vilsmeier reagent,[29] most work has involved these chloro-aldehydes, though these are easily converted into corresponding ketones by Grignard addition then oxidation of the resulting alcohol.[24,30] The reaction of such ketones with hydrazine or arylhydrazines produces 3-substituted 1*H*-pyrazolo[3,4-*b*]quinolines simply by refluxing in methanol (Scheme 3);[24,30] it was suggested[30] that the size of the ketone substituent favours formation of the *Z*-stereoisomer of a first-formed hydrazone, thus having the geometry required for a subsequent ring-closing displacement of the chloride.



Scheme 3

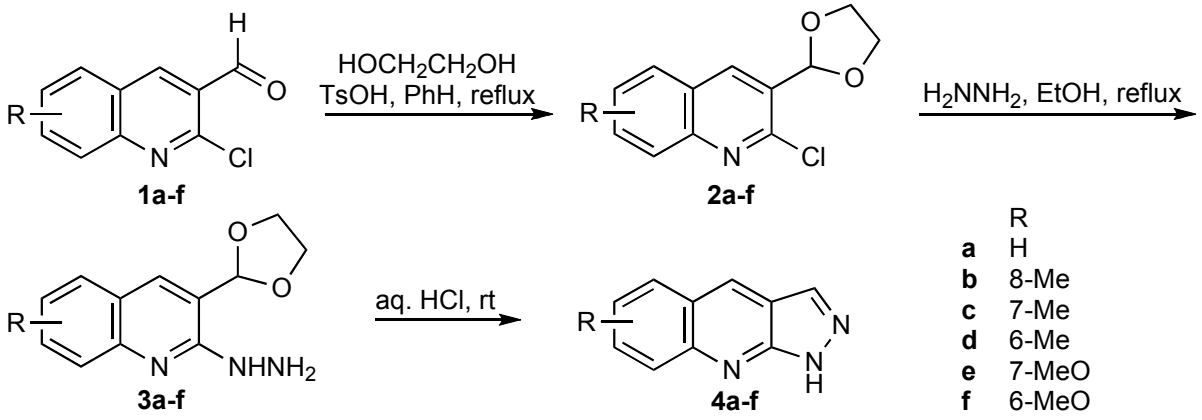
At the commencement of our work, there were conflicting reports as to the facility with which hydrazine and arylhydrazines would react, to give comparable products, with 2-chloro-3-*formyl*quinolines *i.e.* to produce 3-*unsubstituted* 1*H*-pyrazolo[3,4-*b*]quinolines. Thus, although some hetarylhydrazines were described as reacting with 6-bromo-[31] or 7-methoxy-[32] -2-chloro-3-formylquinolines in methanol at reflux or with microwave heating, other reports of attempts to bring about such cyclocondensations implied difficulties. It was shown[28] for example, that an *E*-hydrazone is formed from such chloro-aldehydes which would not ring-close in refluxing ethanol, having the inappropriate imine geometry, however other workers apparently did not encounter such difficulties using hydrazine hydrochlorides in refluxing ethanol for extended reaction times,[33] or reflux in acetonitrile.[34] Much more vigorous conditions can be applied to the interaction between 2-chloro-3-formylquinolines and hydrazine and arylhydrazines which overcome these difficulties: microwave heating with *p*-toluenesulfonic acid is recommended.[35] In a similar study, a 2-methylthio-3-benzoylquinoline formed the undesirable hydrazone isomer which would not ring close; here again, the difficulty was overcome by reacting the ketone with hydrazine using microwave heating in the presence of *p*-toluenesulfonic acid.[36]

A device which was utilised first by Meth-Cohn[39,37] and later by Singh[28] to avoid the difficulties associated with formation of the undesired geometrical isomer of the hydrazone, was to initially protect the aldehyde as an acetal thus forcing a first step to be nucleophilic displacement of the chloride by the hydrazine, hydrolytic release of the aldehyde then leading to the desired pyrazolo-quinoline.

Results and Discussion

Our aim in this work was develop a simple and mild procedure for the synthesis of 1,3-*unsubstituted* 1*H*-pyrazolo[3,4-*b*]quinolines (Scheme 4). We view such compounds as ideal starting materials for the flexible synthesis of a large range of substituted 1*H*-pyrazolo[3,4-*b*]quinolines through manipulations at N-1 and C-3. Benzene ring substituents will be provided by the 2-chloro-3-formylquinoline ring syntheses, which, it will be recalled, are absolutely straightforward using Meth-Cohn's procedure and start from simple and readily available benzenamines. Alkylations at N-1 will involve pyrazole ring anions which can be easily formed using a strong base and which react with alkylating agents.[38] *N*-Arylations will rely on highly efficient and well established copper-[39] or palladium-[40] -catalysed processes.

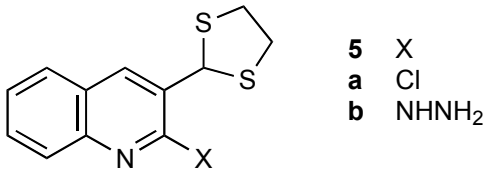
The introduction of substituents at C-3 will involve the intriguing prospect of developing further the relatively little explored electrophilic substitution of indazoles, in this case 7-azaindazoles. There is considerable interest in indazole analogues of the many biologically significant indoles, natural and synthetic, in the medicinal and biological fields. Halogenation of the target 1*H*-pyrazolo[3,4-*b*]quinolines, would be predicted to produce 3-halo-derivatives, with all the potential therein for formation of nucleophilic organometallic reagents or for use directly in cross-coupling processes.



Scheme 4

2-Chloro-3-formylquinolines **1a-f** were produced in good yields from precursor acetanilides (acetanilide itself, 2-methyl-, 3-methyl-, 4-methyl-, 3-methoxy- and 4-methoxyacetanilide).[29]

Reaction of **1a** with hydrazine produced a hydrazone which could not be cyclised by refluxing in ethanol. We concluded that the hydrazone had *E* geometry and thus was sterically prevented from attacking the quinoline C-2. In order to avoid this difficulty, each of the aldehydes was converted into an ethylene acetal **2**, and aldehyde **1a** was also converted into the corresponding thioacetal **5a**.



With the aldehyde masked, each of the chloro-quinolines **2a-f** and **5a** was reacted with hydrazine hydrate in refluxing ethanol, giving the quinolin-2-ylhydrazines **4a-f** and **5b** in good yields. Finally, mild aqueous acidic removal of the acetal protection from **3a-f** led directly, in one pot, to the cyclised 1*H*-pyrazolo[3,4-*b*]quinolines **4a-f**. This protocol is far superior to the bismuth trichloride method employed[28] for the comparable ring closure of two examples, **3a** and **3e**, and requires nothing more than simple basification at the end of the process to liberate the

product in more-or-less pure form. Removal of the thioacetal group from **5b** by treatment with copper(II) chloride and copper(II) oxide led, again in one pot, to the parent 1*H*-pyrazolo[3,4-*b*]quinoline **4a**; utilisation of a thioacetal has the advantage that its formation is faster than formation of the acetals, and its melting point higher than the those of the acetals, facilitating purification.

Conclusions

We have developed a practical and mild route to 1,3-doubly unsubstituted 1*H*-pyrazolo[3,4-*b*]quinolines. In future reports we shall describe our investigations of the substitution chemistry of these tricyclic heterocycles.

Experimental Section

General Experimental Procedures. All the 2-chloro-3-formylquinolines **(1a-f)** were prepared by the Meth-Cohn method.[29] Melting points were recorded on a Philip Harris C4954718 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer, at 300 MHz and 75 MHz respectively. Chemical shifts d are in parts per million (ppm) measured in $CDCl_3$ or DMSO-d_6 as solvent and relative to TMS as the internal standard. Infrared spectra were recorded on a Thermonicolet-Nexus 670 FT-IR instrument and elemental analyses were carried out on an Exeter analytical model CE440 (CHN) and a Leco elemental analyzer Truspec (CHNSO), and Cl was determined by Chemical Analyses Labs Ltd.

General method for the formation of ethylene acetals (2)
A solution of 2-chloro-3-formylquinoline (20 mmol) in benzene (100 mL) containing ethylene glycol (3.57 g, 3.2 mL, 57 mmol) and a crystal of toluene-*p*-sulfonic acid was heated under reflux using a Dean-Stark water separator until no more water collected in the side arm (5-12 h). The cooled solution was treated with saturated aqueous sodium carbonate (50 mL), dried and evaporated giving **2** which was recrystallised from petroleum (b.p. 100-120 ºC)-toluene.
2-Chloro-3-(1,3-dioxolan-2-yl)quinoline (2a). 85% yield. m.p. 46-48 ºC (lit. 59-60 °C). Anal. Calcd. for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; Cl, 15.04; N, 5.94% Found: C, 61.09; H, 4.34; Cl,14.91; N, 5.93%.
2-Chloro-3-(1,3-dioxolan-2-yl)-8-methylquinoline (2b). 85% yield. m.p. 88-90 ºC (lit.[41] 71-72 °C). Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; Cl, 14.20; N, 5.61% Found: C, 62.33; H, 4.78; Cl, 14.10; N, 5.54%.
2-Chloro-3-(1,3-dioxolan-2-yl)-7-methylquinoline (2c). 90% yield. m.p. 58-60 ºC. IR (KBr, cm^{-1}) ν 3060, 2971, 2887, 1626, 1599, 1494, 1330, 1101, 1038, 919, 809; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 4.08-4.21 (m, 4H), 6.21 (s, 1H), 7.38 (dd, J_1=8.4 Hz, J_2=1.8 Hz, 1H), 7.73 (d, J=8.4

Hz, 1H), 7.79 (7, *J*=1.8Hz, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.0, 65.5, 100.5, 124.9, 127.4, 127.6, 128.5, 129.5, 136.3, 141.7, 148.0, 149.2; Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; Cl, 14.20; N, 5.61% Found: C, 62.45; H, 4.91; Cl, 14.14; N, 5.60%.

2-Chloro-3-(1,3-dioxolan-2-yl)-6-methylquinoline (2d). 90% yield. m.p. 42-44 ºC. IR (KBr, cm^{-1}) ν 3063, 2953, 2889, 1598, 1567, 1422, 1332, 1104, 1013, 924, 824; ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 4.01-4.13 (m, 4H), 6.13 (s, 1H), 7.45 (d, *J*=8.4 Hz, 1H), 7.46 (s, 1H), 7.81 (d, *J*=8.4 Hz, 1H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.5, 65.5, 100.4, 126.8, 126.8, 127.8, 129.3, 133.2, 135.9, 137.2, 146.2, 148.2; Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; Cl, 14.20; N, 5.61% Found: C, 62.61; H, 4.85; Cl, 14.16; N, 5.51%.

2-Chloro-3-(1,3-dioxolan-2-yl)-7-methoxyquinoline (2e). 85% yield. m.p. 124-126 ºC. IR (KBr, cm^{-1}) ν 3006, 2981, 2937, 2880, 1621, 1496, 1336, 1229, 1098, 1030, 919, 850, 818; ^{1}H NMR ($CDCl_3$): δ 3.91 (s, 3H), 4.09-4.18 (m, 4H), 6.19 (s, 1H), 7.18 (dd, J_1=9.0 Hz, J_2=2.4 Hz, 1H), 7.32 (d, *J*=2.4 Hz, 1H), 7.69 (d, *J*=9 Hz, 1H), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 55.6, 65.5, 100.5, 106.4, 120.5, 122.0, 126.9, 129.0, 136.4, 149.6, 162.0; Anal. Calcd. for $C_{13}H_{12}ClNO_3$: C, 58.77; H, 4.55; Cl, 13.34; N, 5.27% Found: C, 58.91; H, 4.59; Cl, 13.41; N,5.24%.

2-Chloro-3-(1,3-dioxolan-2-yl)-6-methoxyquinoline (2f). 80% yield. m.p. 82-84 ºC (lit.[41] 79-80 °C). Anal. Calcd. for $C_{13}H_{12}ClNO_3$: C, 58.77; H, 4.55; Cl, 13.34; N, 5.27% Found: C, 58.81; H, 4.48 ; Cl, 13.30; N, 5.32%.

Synthesis of 2-chloro-3-(1,3-dithiolan-2-yl)quinoline (5a). To 2-chloro-3-formylquinoline (0.95 g, 5 mmol) and ethane-1,2-dithiol (0.46 g, 5 mmol) in dry benzene (20 mL) was added boron trifluoride-etherate (0.5 mL). A white precipitate formed and the reaction mixture was refluxed for 10 min. On cooling, a dark oil separated. The upper benzene layer was decanted and evaporated to give a pale yellow solid, and the dark oil was solidified with cold methanol to give further a further quantity. The two crops of solid were combined and recrystallised from methanol to give **5a** (1 g, 75%), m.p. 108-110 ºC. IR (KBr, cm^{-1}) ν 3062, 2937, 1583, 1561, 1487, 1373, 1329, 1130, 1029, 778, 754, 593; ^{1}H NMR ($CDCl_3$): δ 3.49 (m, 4H), 6.10 (s, 1H), 7.56 (ddd, J_1=8.1 Hz, J_2=6.9 Hz, J_3=1.2 Hz, 1H), 7.72 (ddd, J_1=8.4 Hz, J_2=6.9 Hz, J_3=1.5 Hz, 1H), 7.84 (d, *J*=8.1 Hz, 1H), 8.00 (d, *J*=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): 39.4, 52.3, 127.2, 127.3, 127.7, 128.1, 130.6, 133.6, 136.9, 146.8, 149.9; Anal. Calcd. for $C_{12}H_{10}ClNS_2$: C, 53.82; H, 3.76; Cl, 13.24; N, 5.23; S, 23.95% Found: C, 53.78; H, 3.80; Cl, 13.15; N, 5.35; S, 23.84%.

General method for the hydrazinolysis reactions giving 3

A solution of **2a-f** (20 mmol) and hydrazine hydrate 80% (12.5 g, 12.1 ml, 200 mmol) was heated under reflux for 24 h. Then cooled solution was evaporated and residue recrystallised from ethanol to give **3a-f** in high yields.

3-(1,3-Dioxolan-2-yl)-2-hydrazinoquinoline (3a) 80% yield. m.p. 68-70 ºC (lit.[28] 68 °C) IR (KBr, cm^{-1}) ν 3379, 3305, 31191, 3060, 2964, 2889, 1664, 1631, 1374, 1176, 1063, 750, 603, 477; ^{1}H NMR ($CDCl_3$): δ 4.05-4.16 (m, 4H), 4.73 (brs, NH_2), 5.85 (s, 1H), 7.28 (ddd, J_1=8.1 Hz, J_2=6.9 Hz, J_3=1.2 Hz, 1H), 7.59 (ddd, J_1=8.1 Hz, J_2=6.9 Hz, J_3=1.5 Hz, 1H), 7.66 (d, *J*=8.1 Hz,

1H), 7.78 (d, *J*=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): 65.0, 101.6, 119.0, 123.0, 123.4, 126.1, 127.9, 130.1, 135.1, 147.3, 156.4.

3-(1,3-Dioxolan-2-yl)-2-hydrazino-8-methylquinoline (3b) 80% yield. m.p. 98-100 ºC. IR (KBr, cm^{-1}) ν 3303, 3046, 2988, 2896, 2883, 1627, 1525, 1485, 1169, 1070, 1042, 979, 920, 752, 539; ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 1H), 4.08-4.14 (m, 4H), 4.28 (brs, 2H, NH_2), 6.79 (brs, 1H, NH), 5.87 (s, 1H), 7.19 (t, *J*=7.5 Hz, 1H), 7.47 (d, *J*=7.5 Hz, 1H), 7.52 (d, *J*=7.5 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 17.8, 65.0, 101.8, 118.5, 122.7, 123.1, 125.7, 130.2, 134.2, 135.4, 146.0, 155.4; Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13% Found: C, 63.54; H, 6.25; N, 17.11%.

3-(1,3-Dioxolan-2-yl)-2-hydrazino-7-methylquinoline (3c) 85% yield. m.p. 92-94 ºC. IR (KBr, cm^{-1}) ν 3390, 3290, 3196, 2965, 2887, 1626, 1515,1175, 1068, 981, 609; ^{1}H NMR ($CDCl_3$): δ 2.5 (s, 3H), 4.04-4.15 (m, 4H), 4.20-5.60 (brs, 2H, NH_2), 5.83 (s, 1H), 7.11 (dd, J_1=9 Hz, J_2=1.5 Hz, 1H), 7.54 (d, *J*=9 Hz, 1H), 7.58 (d, *J*=1.5 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 65.0, 101.8, 117.9, 121.2, 125.0, 125.6, 127.6, 135.0, 140.4, 147.5, 156.5; Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13% Found: C, 63.69; H, 6.21; N, 17.14%.

3-(1,3-Dioxolan-2-yl)-2-hydrazino-6-methylquinoline (3d) 80% yield. m.p. 84-86 ºC. IR (KBr, cm^{-1}) ν 3361, 3304, 2972, 2903, 1628, 1511, 1483, 1413, 1075, 933, 910, 816, 585; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H), 4.03-4.15 (m, 4H), 4.20-5.60 (brs, 2H, NH_2), 5.83 (s, 1H), 7.43 (d, *J*=9 Hz, 1H), 7.44 (s, 1H), 7.68 (d, *J*=9 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.2, 65.0, 101.7, 118.9, 123.3, 125.9, 127.1, 132.1, 132.5, 134.7, 145.6, 156.0; Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13% Found: C, 63.64; H, 6.09; N, 17.08%.

3-(1,3-Dioxolan-2-yl)-2-hydrazino-7-methoxyquinoline (3e) 85% yield. m.p. 116-118 ºC (lit.[28] 159-161 °C). IR (KBr, cm^{-1}) ν 3314, 3267, 2994, 2969, 2887, 1625, 1572, 1506, 1463, 1227, 1166, 1053, 854; ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H), 4.07-4.14 (m, 4H), 4.15-4.20 (brs, NH_2), 5.81 (s, 1H), 6.93 (dd, J_1=8.7 Hz, J_2=2.4 Hz, 1H), 7.16 (d, *J*=2.4 Hz), 7.53 (d, *J*=8.7 Hz), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 55.4, 65.0, 102.0, 105.6, 115.1, 116.0, 118.0, 129.0, 135.2, 149.1, 156.9, 161.5; Anal. (included because of the discrepancy of melting point with that previously reported[28]) Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08% Found: C, 59.91; H, 5.71; N, 16.17%.

3-(1,3-Dioxolan-2-yl)-2-hydrazino-6-methoxyquinoline (3f) 85% yield. m.p. 100-102 ºC. IR (KBr, cm^{-1}) ν 3305, 2987, 2961, 2878, 1615, 1519, 1408, 1359, 1226, 1063, 1034, 850, 580; ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H), 4.05-4.16 (m, 4H), 4.20-4.60 (brs, NH_2), 5.85 (s, 1H), 7.02 (d, *J*=2.7 Hz, 1H), 7.26 (dd, J_1=9Hz, J_2=2.7 Hz, 1H), 7.72 (d, *J*=9 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 5.5, 65.0, 101.6, 106.9, 119.3, 121.5, 123.9, 127.5, 134.2, 142.8, 155.3, 155.5; Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08% Found: C, 59.71; H, 5.76; N,16.20%.

Synthesis of 3-(1,3-dithiolan-2-yl)-2-hydrazinoquinoline (5b). A solution of **5a** (20 mmol) and hydrazine hydrate 80% (12.5 g, 12.1 mL, 200 mmol) was heated under reflux for 24 h. The cooled solution was evaporated and the residue recrystallised from ethanol to give **5b** in 70% yield. m.p. 156-158 ºC. IR (KBr, cm^{-1}) ν 3287, 3039, 2914, 1609, 1521, 1412, 748; ^{1}H NMR

($CDCl_3$): δ 3.36-3.53 (m, 4H), 4.50-5.50 (brs, NH_2), 5.75 (s, 1H), 7.25-7.30 (m, 1H), 7.55-7.60 (m, 1H), 7.64 (d, *J*=7.8 Hz), 7.76 (d, *J*=8.4 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 39.6, 52.9, 120.2, 123.1, 123.5, 125.7, 127.6, 130.0, 136.1, 146.4, 155.7; Anal. Calcd. for $C_{12}H_{13}N_3S_2$: C, 54.72; H, 4.97; N, 15.95; S, 24.35% Found: C, 54.61; H, 5.06; N, 16.09; S, 24.31%.

General method for the synthesis of 1*H*-pyrazolo[3,4-*b*]quinolines (4)

A solution of ***(3)*** (1 mmol) in aqueous 2*M* HCl (10 mL) was stirred at r.t. for 20 minutes. During this time a yellow to orange precipitate of hydrochloride salt of **4** was formed which was dissolved in water (10 mL). The acidic solution was neutralized with 2*M* NaOH and the resulting precipitate was filtered off and washed with water then recrystallized from ethanol to give pure **4**.

1*H*-Pyrazolo[3,4-*b*]quinoline (4a). 95% yield. m.p. 180-182 ºC (lit.[28] 159-161 °C). IR (KBr, cm^{-1}) ν 3122, 3055, 2970, 2847, 2786, 1627, 1583, 1506, 1284, 1116, 936, 747; ^1H NMR ($CDCl_3$): δ 7.51 (ddd, J_1=8.4 Hz, J_2=6.9 Hz, J_3=1.5 Hz, 1H), 7.83 (ddd, J_1=8.7 Hz, J_2=6.9 Hz, J_3=1.2 Hz, 1H), 8.03 (d, *J*=8.4 Hz, 1H), 8.27 (d, *J*=8.7 Hz, 1H), 8.73 (s, 1H), 13.36 (brs, NH); ^{13}C NMR ($CDCl_3$): δ 116.5, 123.9, 124.5, 127.8, 129.4, 130.9, 131.0, 134.6, 148.0, 151.9; Anal. (included because of the discrepancy of melting point with that previously reported[28]) Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84% Found: C, 71.10; H, 4.19; N, 24.73%.

8-Methyl-1*H*-pyrazolo[3,4-*b*]quinoline (4b). 90% yield. m.p. 164-166 ºC. IR (KBr, cm^{-1}) ν 3183, 3142, 3096, 3041, 2964, 2916, 1634, 931, 753; ^1H NMR ($CDCl_3$): δ 2.72 (s, 3H), 7.34 (t, *J*=6.9 Hz, 1H), 7.61 (d, *J*=6.9 Hz, 1H), 7.94 (d, *J*=6.9 Hz, 1H), 8.39 (s, 1H), 8.87 (s, 1H), 13.55 (s, NH); ^{13}C NMR ($CDCl_3$): δ 18.9, 116.0, 123.4, 124.2, 128.1, 130.4, 131.2, 134.3, 135.3, 147.4, 151.6; Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94% Found: C, 71.98; H, 5.01; N, 22.96%.

7-Methyl-1*H*-pyrazolo[3,4-*b*]quinoline (4c). 90% yield. m.p. 218-220 ºC (lit.[30] 144-145 °C). IR (KBr, cm^{-1}) ν 3124, 3095, 3053, 2949, 2913, 2851, 1624, 1583, 1505, 930; ^1H NMR ($CDCl_3$): δ 2.65 (s, 3H), 7.34 (d, *J*=8.4 Hz, 1H), 7.91 (d, *J*=8.4 Hz, 1H), 8.02 (s, 1H), 8.34 (s, 1H), 8.66 (s, 1H), 13.23 (brs, NH); ^{13}C NMR ($CDCl_3$): δ 22.3, 116.0, 122.8, 126.4, 126.6, 129.0, 130.5, 134.6, 141.7, 148.4, 152.1; Anal. (included because of the discrepancy of melting point with that previously reported[28]) Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94% Found: C, 72.13; H, 4.93; N, 22.98%.

6-Methyl-1*H*-pyrazolo[3,4-*b*]quinoline (4d). 95% yield. m.p. 264-266 ºC. IR (KBr, cm^{-1}) ν 3124, 3084, 3035, 2917, 28855, 1625 1582, 1509, 1130, 934, 826; ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H), 7.60 (dd, J_1=8.7 Hz, J_2=1.5 Hz, 1H), 7.84 (d, *J*=1.5 Hz, 1H), 7.87 (d, *J*=8.7 Hz, 1H), 8.37 (s, 1H), 8.78 (s, 1H), 13.57 (brs, NH); ^{13}C NMR ($CDCl_3$): δ 21.4, 116.3, 124.4, 127.9, 128.1, 129.8, 132.9, 133.4, 134.3, 146.9, 151.8; Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94% Found: C, 72.22; H, 5.02; N, 4.89%.

7-Methoxy-1*H*-pyrazolo[3,4-*b*]quinoline (4e). 90% yield. m.p. 232-234 ºC (lit.[28] 221-223 °C). IR (KBr, cm^{-1}) ν 3120, 3060, 3005, 2864, 1625, 1589, 1507, 1234, 1146, 935, 835; ^1H NMR ($CDCl_3$): δ 3.92 (s, 3H), 7.12 (dd, J_1=9 Hz, J_2=2.4 Hz), 7.28 (d, *J*=2.4 Hz), 7.99 (d, *J*=9Hz, 1H),

8.32 (s, 1H), 8.79 (s, 1H), 13.41 (s, NH); ^{13}C NMR ($CDCl_3$): δ 55.9, 105.4, 114.7, 117.9, 120.1, 130.6, 131.2, 134.5, 150.2, 152.4, 161.5.

6-Methoxy-1*H*-pyrazolo[3,4-*b*]quinoline (4f). 95% yield. m.p. 240-242 ºC. IR (KBr, cm^{-1}) ν 3123, 3096, 3002, 2965, 2932, 2828, 1632, 1587, 1509 122, 1168, 1123, 1030, 936, 914, 827; ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H), 7.41-7.45 (m, 2H), 7.89 (d, *J*=9.9 Hz, 1H), 8.34 (s, 1H), 8.75 (s, 1H), 13.47 (brs, NH); ^{13}C NMR ($CDCl_3$): δ 55.8, 106.1, 116.3, 124.8, 125.1, 128.7, 129.6, 133.8, 144.6, 151.2, 155.3; Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09% Found: C, 66.31; H, 4.51; N, 21.02%.

Synthesis of 1*H*-pyrazolo[3,4-*b*]quinoline (4a) from 3-(1,3-dithiolan-2-yl)-2-hydrazinoquinoline (5b)

In 50-mL flask fitted with a condenser and a dropping funnel was added cupric oxide (0.48 g, 6 mmol), anhydrous cupric chloride (1.61 g, 12 mmol) and acetone (40 mL). The resulting suspension was brought to reflux with vigorous stirring and a solution of **5b** (1.31 g, 5 mmol) in acetone (9 ml) and DMF (1 mLl) was added over 5 min. Reflux was maintained for 30 min then the mixture was cooled and filtered. The insoluble material was washed with dichloromethane (3×20 mL) and the combined organic layers were washed with aqueous sodium carbonate (50 ml), dried over sodium sulfate and filtered. Evaporation of the solvent gave **4a** as yellow powder in 85% yield.

Acknowledgements

The authors are grateful to the University of Urmia for financial support of this work.

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