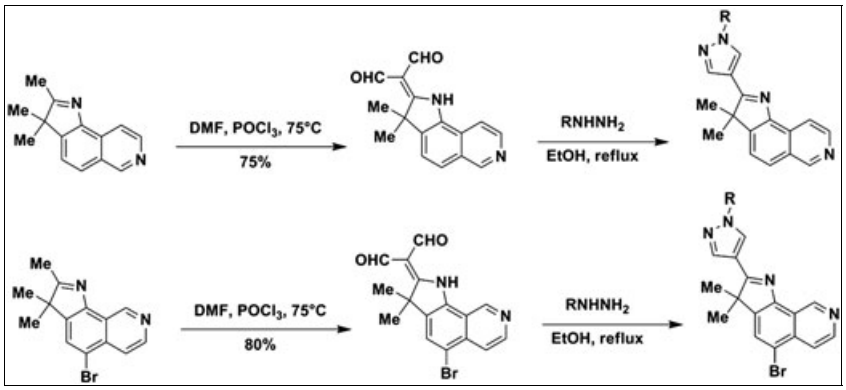
Arash Afghan,[a]* Laia Roohi,[b] Mehdi M. Baradarani,[b] and John A. Joule[c]

[a]Department of Chemical Engineering, Urmia University of Technology, Urmia 57155-419, Iran
[b]Department of Chemistry, Faculty of Science, University of Urmia, Urmia 57153-165, Iran
[c]The School of Chemistry, The University of Manchester, Manchester M13 9PL, UK
*E-mail: a.afghan@che.uut.ac.ir

Received December 7, 2011
DOI 10.1002/jhet.1735
Published online 3 December 2013 in Wiley Online Library (wileyonlinelibrary.com).



Isoquinolin-5-ylhydrazinium chloride **13** and 5-bromoisoquinolin-8-ylhydrazinium chloride **14** were converted *via* Fischer syntheses with 3-methylbutan-2-one into indolenines, 2,3,3-trimethyl-3*H*-pyrrolo[2,3-*f*] isoquinoline **15** and 5-bromo-2,3,3-trimethyl-3*H*-pyrrolo[3,2-*h*]isoquinoline **16**, respectively. Exposure of the indolenines to the Vilsmeier reagent produced diformyl compounds **17** and **18**, which reacted with arylhydrazines to give the corresponding pyrazoles **19a–i** and **20a–g**. Reaction of **17** with thiourea gave a pyrimidine-2(1*H*)-thione **23** or with hydroxylamine hydrochloride, an isoxazole **24**.

J. Heterocyclic Chem., **51**, 706 (2014).

INTRODUCTION

The recognition of the power of the species produced by the combination of phosphoryl chloride with the amide of a secondary amine (*N*-methylformanilide and *N,N*-dimethylformamide have been most often utilized) has its origins in a paper in 1896 [1]. Later, work by Fischer, Muller and Vilsmeier [2], and then by Vilsmeier and Haack [3], and later by the groups of Arnold [4] and Meth-Cohn [5] clarified the process and made it into a widely used regimen for acylation, especially formylation of reactive aromatic and hetero-aromatic compounds, and indeed nonaromatic compounds [6].

In 1959, Fritz [7] reported the *N*-formylation of the 3,3-disubstituted 3*H*-indole (indolenine) **1** giving **2** using the Vilsmeier reagent from DMF and $POCl_3$. Further reaction of **2** with the Vilsmeier reagent and hydrolysis produced **4**. Formation of this product probably involves the intermediacy of **3**, from which the *N*-formyl group is hydrolytically removed. The enamine **5** was directly *C*-formylated, producing **6** (Scheme 1).

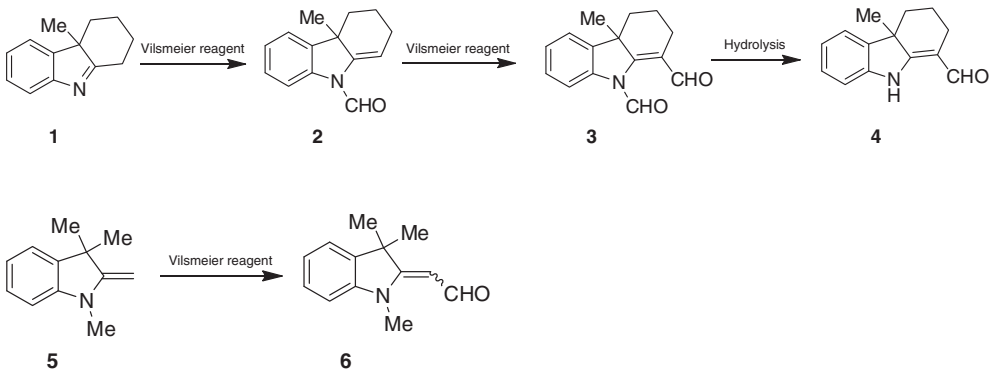
We recently described the reaction of indolenines **7** and some pyridoindolenines, with the Vilsmeier reagent formed from *N,N*-dimethylformamide and phosphorus oxychloride to produce aminomethylene malondialdehydes such as **8** [8–10]. Additionally, we showed that these intriguing polyfunctional compounds reacted well with hydrazine or arylhydrazines to produce corresponding pyrazoles **9**, with migration of the exocyclic double bond back into the pyrrole ring, thus restoring the indolenine structure from which the sequence started [8–11] (Scheme 2).

For the mechanism of formation of the aminomethylene malondialdehydes, we suggested that a small equilibrium concentration of an enamine tautomer **11** is successively C-substituted twice and thus, before hydrolysis during work-up, species **12** is present (Scheme 3). We propose that a comparable mechanism operates in the work described in the following paragraphs.

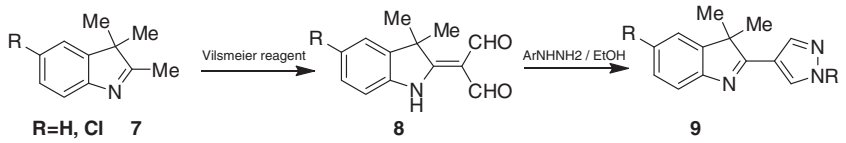
RESULTS AND DISCUSSION

Diazotisation of 5-aminoisoquinoline and 5-bromo-8-aminoisoquinoline, then reduction of the diazonium salts with tin(II) chloride, produced the corresponding hydrazinium chlorides **13** and **14**. Reaction of isoquinolin-5-ylhydrazinium chloride **13** with isopropyl methyl ketone in a Fischer reaction produced the indolenine 2,3,3-trimethyl-3*H*-pyrrolo[2,3-*f*] isoquinoline **15** in good yield. Similarly, 5-bromoisoquinolin-8-yl hydrazinium chloride **14** reacted with isopropyl methyl ketone in hot acetic acid to give 5-bromo-2,3,3-trimethyl-3*H*-pyrrolo[3,2-*h*]isoquinoline **16** (Scheme 4). The structures of

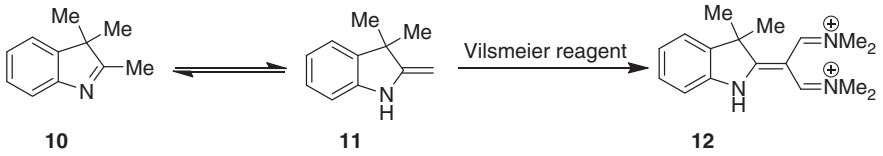
Scheme 1



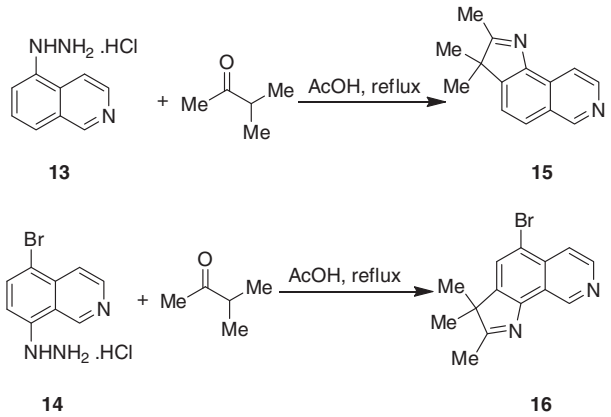
Scheme 2



Scheme 3



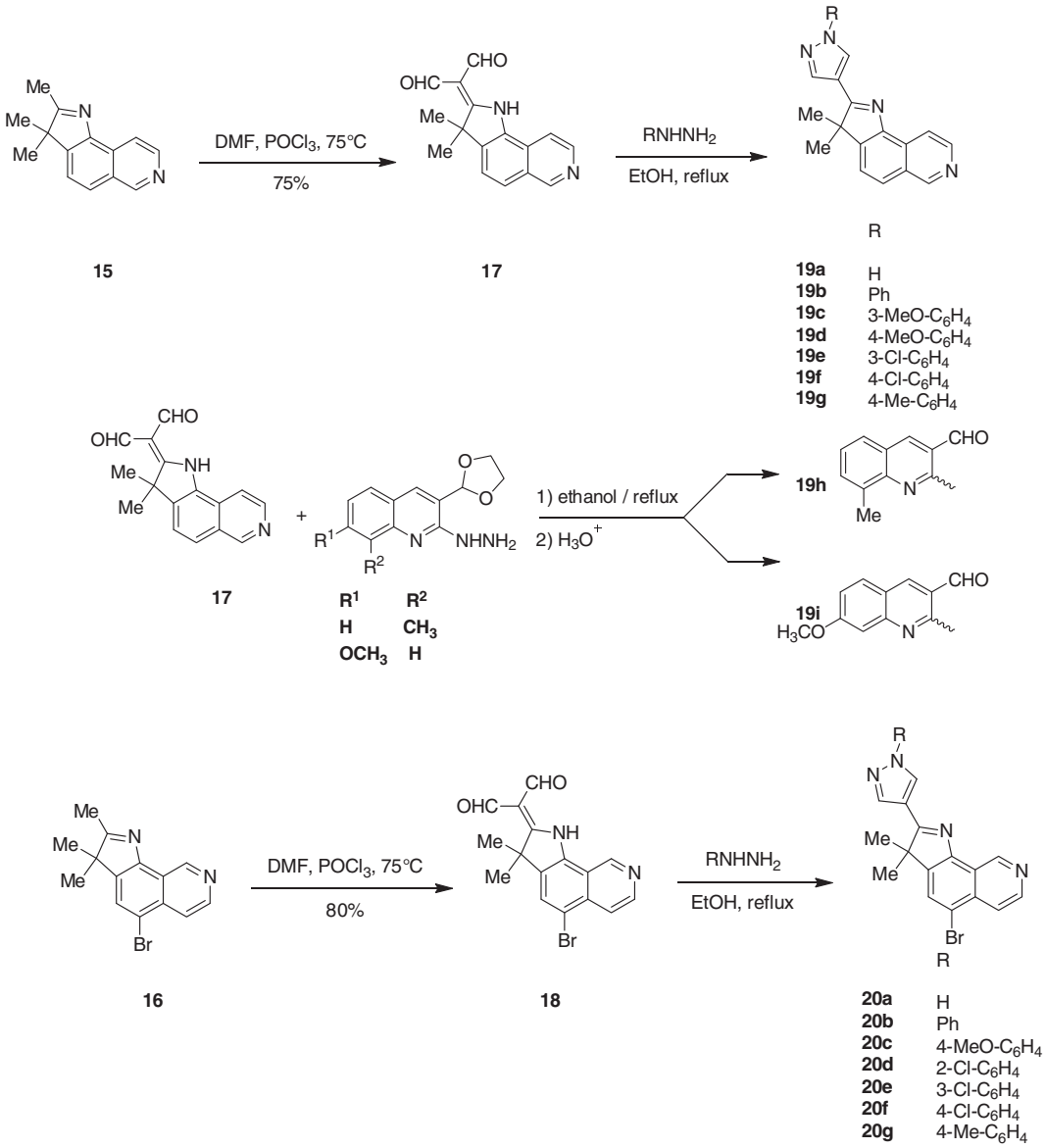
Scheme 4



the two pyridoindolenines were evident from their NMR data: there were six-hydrogen singlets for the geminal methyl groups, at δ 1.36 and 1.39 ppm for **15** and **16**, and three-hydrogen singlet signals for the imine-methyl groups, resonating at δ 2.39 and 2.42 ppm, respectively. Each compound had an AB system for the *ortho*-related isoquinoline-3- and 4-protons, in addition to singlet signals for the isoquinoline C-1-protons.

Each of the pyridoindolenines **15**,**16** was now reacted with the Vilsmeier reagent, and diformyl compounds **17**,**18** were obtained in yields of 75% and 80%, respectively (Scheme 5). The structures of the aminomethylene malondialdehydes rest on the observation of two 1-hydrogen singlets at δ 9.80 and δ 9.85 for **17**, and δ 9.83 and δ 9.88 for **18** corresponding to aldehyde protons. Absorptions at 3140 cm^{-1} and 3165 cm^{-1} for **17** and **18**, respectively, were evidence for the presence of N–H bonds, further confirmed by ^{1}H NMR signals for the N-hydrogens appearing at δ 14.30 (**17**) and δ 14.55 (**18**), respectively. As in our previous work, the aminomethylene malondialdehydes reacted efficiently with hydrazine and various arylhydrazines at reflux conditions to give pyrazoles **19a–i** and **20a–g**, with migration of the exocyclic double bond to reform the imine unit (Scheme 5). For pyrazoles

Scheme 5



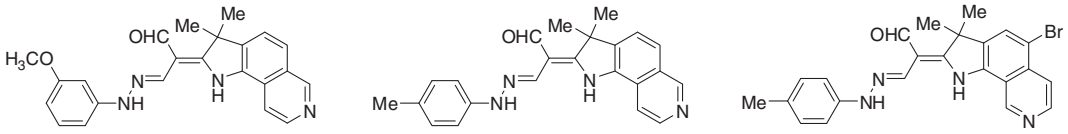
19a–i, the protons of the newly formed five-membered heterocyclic ring resonated in the range δ 8.38–8.80 and for the pyrazoles **20a–g** in the range δ 8.37–8.71.

In some cases, the reaction of diformyl compounds **17**,**18** with arylhydrazines in ethanol at room temperature produced sharp melting mono-arylhydrazones **21a–b** and **22** in excellent yields, which converted into corresponding pyrazoles at reflux conditions. It was not possible to ascertain which carbonyl group had reacted (Scheme 6). The ^{1}H NMR spectra of compounds **21c**, **21g** and **22g** confirmed the presence of a single isomer (*cis* or *trans*) in each case [one possibility is shown below in each case]; the N-hydrogen protons resonated in the range δ 7.54–7.74 and imine C-hydrogens in the range δ 12.90–16.02.

The reaction of dialdehyde **17** with thiourea in presence of HCl(aq.) for 2 days at room temperature produced pyrimidine thione **23** (Scheme 7). The structure of thione **23** was evident from its NMR data, a two-hydrogen singlet for the pyrimidine ring protons at δ 9.86, further confirmed by a ^{13}C NMR signal at δ 189.92 for the thione group. Absorptions at 2736 cm^{-1} and 1194 cm^{-1} were evidence for existence of two tautomers, one with an S–H (thiol) and one having a C=S (thione) group.

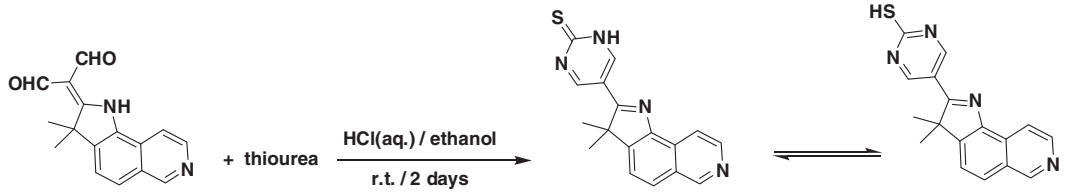
Finally, the reaction of dialdehyde **17** with hydroxylamine in ethanol at room temperature for 2 days led to isoxazole derivative **24**. Attempt to formation of a comparable isoxazole from dialdehyde **18** under the same conditions produced **25** (or its geometrical isomer) (Scheme 8).

Scheme 6



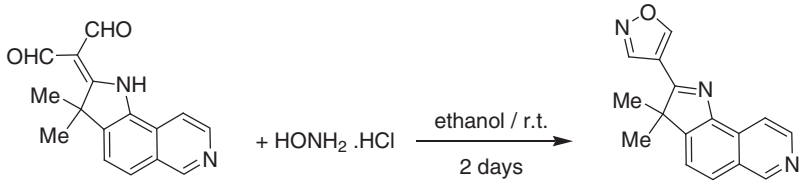
21c **21g** **22g**

Scheme 7

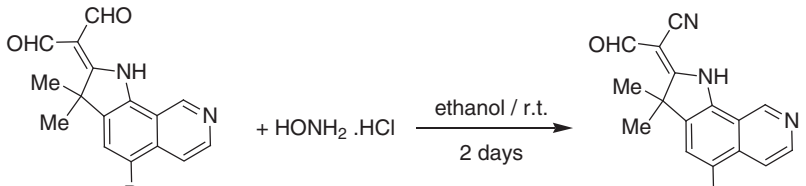


17 **23**

Scheme 8



17 24



18 25

The structure of the isoxazole ring in **24** rests on the observation of two 1-hydrogen singlets at δ 9.90 and δ 10.05. The structure of **25** was evident from its molecular formula, a singlet at δ 9.51 assigned to a CHO group and the NH proton resonance at δ 16.12. Absorptions at 3201 cm^{-1} and 1905 cm^{-1} were evidence for the presence of NH and CN functionalities, respectively.

CONCLUSION

Diformyl Compounds **17**,**18** were synthesized in good yields by Vilsmeier–Haack formylation of pyridoindolenines **15**,**16**. Their condensation with hydrazine and various arylhydrazines afforded corresponding pyrazole derivatives. Also, reaction of **17** with thiourea and hydroxylamine hydrochloride produced thiopyrimidone and isoxazole derivatives, respectively. On the other hand, condensation of **18** with hydroxylamine hydrochloride afforded 3-oxopropanenitrile derivative **25**.

EXPERIMENTAL

General. Melting points were recorded on an electrothermal IA 9200 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer

(Brucker, Karlsruhe, Germany), at 300 MHz and 75 MHz, respectively. Chemical shifts δ are in parts per million (ppm) measured in $CDCl_3$ and DMSO-d_6 as solvents and relative to TMS as the internal standard. Infrared spectra were recorded on a Thermonicolet-Nexus 670 FTIR instrument (Thermonicolet, USA). Microanalyses were performed on a Leco Analyzer 932 (Leco, USA).

General procedure for synthesis of (15) and (**16**). A mixture of isoquinolinyl hydrazine hydrochloride (5 g, 31 mmol) and isopropyl methyl ketone (6.52 mL, 60 mmol) was heated at reflux in acetic acid (30 mL) for 3 h and then cooled, diluted with water (50 mL) and neutralized with solid Na_2CO_3; then the crude product precipitated, was filtered off and washed with water, then recrystallized from ethanol to give the pure compound.

2,3,3-Trimethyl-3H-pyrrolo-[2,3-f]isoquinoline (15). Yield of 75%; mp 111–116 °C; FTIR (KBr, cm^{-1}) ν_{max} 3000, 2966, 2924, 1628, 1579, 1668, 1283, 847, 709; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 6H), 2.39 (s, 3H), 7.55 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 5.4 Hz, 1H), 8.58 (d, J = 5.4 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.61, 18.32, 54.00, 115.09, 119.77, 124.18, 127.81, 127.99, 141.98, 145.50, 146.79, 151.38, 188.45; *Anal*. Calcd. for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32% found: C, 79.85; H, 6.68; N, 13.24%.

5-Bromo-2,3,3-Trimethyl-3H-pyrrolo-[3,2-h]isoquinoline (16). Yield of 80%; mp 82–84 °C; FTIR (KBr, cm^{-1}) ν_{max} 3036, 2964, 2926, 2865, 1618, 1608, 1582, 1649, 809; ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 6H), 2.42 (s, 3H), 6.68 (s, 1H), 8.03 (d, J = 6.0 Hz, 1H), 8.66 (d, J = 6.0 Hz, 1H), 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.69, 19.39, 55.15, 118.15, 119.59, 124.42, 127.72, 128.01, 133.12, 143.47, 143.76, 149.16, 190.84; *Anal*. Calcd. for $C_{14}H_{16}BrN_2$: C, 58.15; H, 4.53; N, 9.69% found: C, 58.09; H, 4.41; N, 9.62%.

General procedure for synthesis of (17) and (**18**). To *N,N*-dimethylformamide (16.8 mL, 180 mmol) cooled in an ice bath was added dropwise phosphorus oxychloride (5.48 mL, 60 mmol) with stirring at below 5 °C. After this addition, indolenine (20 mmol) was added slowly. The cooling bath was removed, and the reaction mixture was stirred at 75 °C for 6 h. The resulting solution was added to ice-cooled water and made alkaline with NaOH (aq.) solution (pH = 8–9). The resulting precipitate was collected by filtration, dried in air and recrystallized from ethanol to give pure malondialdehyde.

2-(3,3-dimethyl-1H-pyrrolo[2,3-f]-isoquinolin-2(3H)-ylidene) malonaldehyde (17). Yield of 85%; mp 188–190 °C; FTIR (KBr, cm^{-1}) ν_{max} 3140, 3055, 2964, 2868, 1682, 1660, 1647, 1514, 1164, 831, 769; ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 6H), 7.62 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 8.67 (d, J = 6.0 Hz, 1H), 9.34(s,1H), 9.80 (s, CHO), 9.85 (s, CHO), 14.30 (bs, NH); ^{13}C NMR ($CDCl_3$): δ 19.53, 52.71, 110.14, 116.82, 120.92, 119.91, 125.91, 128.40, 133.73, 141.30, 144.07, 153.09, 189.79, 187.67, 192.72; *Anal*. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52% found: C, 72.09; H, 5.33; N, 10.49%.

2-(5-bromo-3,3-dimethyl-1H-pyrrolo[3,2-H]isoquinolin-2(3H)-ylidene)malonaldehyde (18). Yield of 87%; mp 180–182 °C; FTIR (KBr, cm^{-1}) ν_{max} 2966, 2869, 2767, 1681, 1661, 1606, 1511, 1271, 1079, 1034, 886; ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 6H), 7.78 (s, 1H), 8.09 (d, J = 6.0 Hz, 1H), 8.75 (d, J = 6.0 Hz, 1H), 9.49 (s, 1H), 9.83 (s, CHO), 9.88 (s, CHO), 14.55 (bs, NH); ^{13}C NMR ($CDCl_3$): δ 19.68, 52.39, 110.37, 118.70, 124.40, 127.97, 128.28, 133.25, 138.30, 144.87, 145.15, 146.31,189.83, 187.57, 192.81; *Anal*. Calcd. for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12% found: C, 55.65; H, 3.79; N, 8.09%.

General procedure for synthesis of (19a–i) and (**21a–g**). A mixture of the diformyl compound **17/18** (0.7 mmol) and hydrazine hydrate (80% w/w, 0.18 g, 3.5 mmol), or aryl hydrazine (0.7 mmol), in absolute ethanol (15 mL) was heated with stirring at reflux for 3–5 h. After cooling and concentrating the solution, the resulting crystals were collected by filtration and recrystallized from EtOH to give the corresponding pyrazoles.

3,3-dimethyl-2-(1H-pyrazol-4-yl)-3H-pyrrolo[2,3-f]isoquinoline (19a). Yield of 95%; mp 234.6–237.4 °C; FTIR (KBr, cm^{-1}) ν_{max} 3110, 2967, 2927, 1652, 1633, 1582, 1670, 1163, 941, 718; ^{1}H NMR ($CDCl_3$): δ 1.56 (s, 6H), 7.63 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 6.0 Hz, 1H), 8.62 (d, J = 6.0 Hz, 1H), 8.38 (s, 2H, pyrazole), 11–14 (bs, NH); ^{13}C NMR ($CDCl_3$): δ 24.1, 54.57, 116.06, 116.59, 120.57, 125.23, 129.03, 129.35, 133.50, 142.78, 147.03, 148.36, 152.36, 189.86; *Anal*. Calcd. for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36% found: C, 73.15; H, 5.31; N, 21.29%.

3,3-dimethyl-2-(1-phenyl-1H-pyrazol-4-yl)-3H-pyrrolo[2,3-f] isoquinoline (19b). Yield of 82%; mp 181.5–182.5 °C; FTIR (KBr, cm^{-1}) ν_{max} 3049, 2965, 2926, 1631, 1599, 1577, 1560, 1669, 1280, 951, 757; ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 6H), 7.39 (tt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.54 (t, J = 8.4 Hz, 2H), 7.66 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 8.40 (s, 1H, pyrazole), 8.34 (d, J = 5.7 Hz, 1H), 8.64 (d, J = 5.7 Hz, 1H), 8.69 (s,1H, pyrazole), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.077, 54.58, 113.59, 118.23, 119.58, 120.55, 120.96, 125.96, 127.14, 129.03, 129.47, 129.64, 139.54, 140.67, 143.90, 147.12, 148.44, 152.30, 189.24; *Anal*. Calcd. for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.56% found: C, 77.99; H, 5.32; N, 16.54%.

2-(1-(3-methoxyphenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinoline (19c). Yield of 84%; mp 185.5–186.5 °C; FTIR (KBr, cm^{-1}) ν_{max} 3081, 2975, 2925, 1631, 1610, 1573, 1556, 1495, 1268, 938, 833; ^{1}H NMR ($CDCl_3$): δ 1.59 (s, 6H), 3.88 (s, 3H), 6.89 (d, J = 7.5 Hz, 1H), 7.32–7.41 (m,3H), 7.61 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 8.37 (s, 1H, pyrazole), 8.40 (bs, 1H),8.66 (s, 1H, pyrazole), 8.66 (s, 1H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.04, 54.54, 55.57, 105.49, 111.46, 113.23, 116.56, 118.16, 120.49, 125.34, 127.19, 129.34, 130.38, 140.60, 142.97, 147.01, 148.39, 152.38, 160.63, 189.15; *Anal*. Calcd. for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21% found: C, 75.01; H, 5.43; N, 15.18%.

2-(1-(4-methoxyphenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinoline (19d). Yield of 80%; mp 253.0–255.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 3075, 2999, 2967, 1644, 1567, 1524, 1504, 1253, 950, 833; ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 6H), 3.90 (s, 3H), 7.06 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 8.1 Hz, 1H), 8.24 (d, J = 8.1 Hz, 1H), 8.39 (s, 1H, pyrazole) , 8.59 (d, J = 6.0 Hz, 1H),8.77 (s, 1H, pyrazole), 8.99(d, J = 6.0 Hz, 1H), 9.59 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.00, 55.39, 55.66, 114.81, 118.10, 118.37, 124.19, 127.35, 127.44, 128.32, 132.82, 140.64, 146.19, 159.30, 181.47; *Anal*. Calcd. for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21% found: C, 74.89; H, 5.43; N, 15.20%.

2-(1-(3-chlorophenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinoline (19e). Yield of 80%; mp 239.2–241.2 °C; FTIR (KBr, cm^{-1}) ν_{max} 3049, 2972, 2931, 1645, 1486, 1676, 768; ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 6H), 7.39 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.88 (s, 1H), 7.99 (d, J = 8.1 Hz,1H), 8.30(d, J = 8.1 Hz,1H), 8.43 (s, 1H),8.60(d, J = 6 Hz, 1H), 8.80 (s, 1H), 8.99 (d, J = 6 Hz,1H), 9.67 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 23.83, 55.55, 118.58, 120.00, 118.32, 124.48, 127.86, 160.81, 161.39, 165.63, 140.16, 141.27, 146.28, 181.15; *Anal*. Calcd. for $C_{22}H_{17}ClN_4$: C, 70.87; H, 4.60; N, 15.03% found: C, 70.81; H, 4.59; N, 15.01%.

2-(1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo [2,3-f]isoquinoline (19f). Yield of 75%; mp 252.5–253.5 °C; FTIR (KBr, cm^{-1}) ν_{max} 3038, 2961, 2867, 1644, 1602, 1574, 1555, 1497, 1675, 952, 823; ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 6H), 7.53 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.91 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.24 (s, 1H, pyrazole), 8.59 (d, J = 6.0 Hz, 1H),8.80 (s, 1H, pyrazole), 8.97(d, J = 6.0 Hz, 1H), 9.57 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 23.23, 55.69, 117.76, 120.26, 121.20, 124.89, 127.73, 128.25, 129.10, 129.98, 130.58, 131.85, 132.14, 133.50, 138.33, 141.98, 148.32, 153.35, 181.39; *Anal*. Calcd. for $C_{22}H_{17}ClN_4$: C, 70.87; H, 4.60; N, 15.03% found: C, 70.69; H, 4.49; N, 14.98%.

***2-(1-(4-methylphenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo [2,3-f]*isoquinoline (19g).** Yield of 86%; mp 191.0–192.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 3040, 2968, 1630, 1577, 1561, 1520, 953, 941, 843, 819; ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 6H), 2.43 (s, 3H), 7.32 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.1 Hz, 1H), 8.38 (s,1H, pyrazole), 8.41 (d, J = 5.7 Hz, 1H), 8.64 (d, J = 5.7 Hz, 1H), 8.65 (s, 1H, pyrazole), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.02, 24.12, 54.53, 116.40, 118.03, 119.50, 120.44, 125.23, 127.05, 129.06, 129.35, 130.14, 137.30, 137.40, 140.42, 143.18, 146.91, 148.47, 152.52, 189.27; *Anal*. Calcd. for $C_{23}H_{20}N_4$: C, 78.38; H, 5.72; N, 15.90% found: C, 78.31; H, 5.69; N, 15.84%.

2-(4-(3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinolin-2-yl)-1H-pyrazol-1-yl)-8-methylquinoline-3-carbaldehyde (19h). Yield of 78%; mp 266.0–268.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 3046, 2964, 2924, 1697, 1631, 1616, 1591, 1492, 1433, 955, 759; ^{1}H NMR ($CDCl_3$): δ 1.68 (s, 6H), 2.85 (s,3H), 7.51 (t, J = 8.1 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.71 (s, 1H), 7.80 (s,1H), 7.89 (d, J = 8.1 Hz, 1H), 8.41 (d, J = 5.7 Hz, 1H), 8.55 (s, 1H, pyrazole), 8.63 (d, J = 5.7 Hz, 1H), 8.75 (s, 1H, pyrazole), 9.29 (s, 1H), 9.37 (s, 1H), 10.80 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 18.75, 24.14, 54.69, 116.44, 118.30, 120.46, 122.79, 125.69, 126.51,127.22, 127.34, 128.69, 129.00, 129.42, 133.14, 136.72, 141.23, 142.63, 143.18, 146.66, 146.91, 147.15, 148.26, 152.45, 188.68, 190.11; *Anal.* Calcd. for $C_{27}H_{21}N_5O$: C, 75.16; H, 4.91; N, 16.23% found: C, 75.03; H, 4.83; N, 16.19%.

2-(4-(3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinolin-2-yl)-1H-pyrazol-1-yl)-7-methoxyquinoline-3-carbaldehyde (19i). Yield of 80%; mp 236.0–238.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 3046, 2964, 2924, 1697, 1631, 1616, 1591, 1492, 1433, 955, 759; ^{1}HNMR ($CDCl_3$): δ 1.55 (s, 6H), 3.91 (s, 3H), 7.13 (s, 1H), 7.29(s, 1H), 7.53(d, J = 7.8 Hz, 1H), 7.73–7.80(m, 2H), 8.30 (s, 1H), 8.46 (s,1H), 8.52 (s, 1H), 8.63 (s, 1H), 9.19 (m,2H),10.65(s, 1H, CHO); ^{13}CNMR ($CDCl_3$): δ 24.07,54.67,55.84,106.67, 116.48, 118.32, 120.43, 120.99, 121.06, 121.87, 125.64, 128.81, 129.51, 130.53, 140.39, 142.87, 143.25, 147.16, 148.38, 148.92, 150.19,163.85, 170.79, 173.10, 188.67, 189.98; *Anal*. Calcd. for $C_{27}H_{21}N_5O_2$: C, 72.47; H, 4.73; N, 15.65% found: C, 72.41; H, 4.69; N, 15.61%.

5-bromo-3,3-dimethyl-2-(1H-pyrazol-4-yl)-3H-pyrrolo[3,2-h] isoquinoline (20a). Yield of 92%; mp 245–246 °C; FTIR (KBr, cm^{-1}) ν_{max} 3185, 2970, 1623, 1586, 1649, 1276, 938, 812; ^{1}H NMR (DMSO-d_6): δ 1.53 (s, 6H), 7.96(dd, J_1 = 6.0 Hz, J_2 = 0.6 Hz, 1H), 8.23 (s, 1H), 8.50 (s, 2H, pyrazole), 8.64 (d, J = 6.0 Hz, 1H), 9.86 (d, J = 0.6 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 23.81, 54.78, 115.06, 116.98, 121.75, 125.61, 125.77, 132.62, 144.31, 145.19, 149.08, 149.20, 182.48; *Anal*. Calcd. for $C_{16}H_{13}BrN_4$: C, 56.32;H, 3.84;N, 16.42% found: C, 56.18; H, 3.79; N, 16.31%.

5-bromo-3,3-dimethyl-2-(1-phenyl-1H-pyrazol-4-yl)-3H-pyrrolo [3,2-h]isoquinoline (20b). Yield of 78%; mp 298.5–300.5 °C; FTIR (KBr, cm^{-1}) ν_{max} 3055, 2964, 1624, 1601, 1579, 1566, 1419, 1646, 938, 756; ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 6H), 7.40 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.81(s, 1H), 7.83(t, J = 8.4 Hz, 2H), 8.04(d, J = 6.0 Hz, 1H), 8.40 (s, 1H, pyrazole), 8.70 (d, J = 6.0 Hz, 1H), 8.71 (s, 1H, pyrazole), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.14, 54.50, 118.049, 118.03, 119.63, 119.25, 123.99, 127.42, 127.55, 129.66, 133.26, 139.46, 140.68, 143.94, 149.18, 149.48, 180.27; *Anal*. Calcd. for $C_{22}H_{17}BrN_4$: C, 63.32; H, 4.11; N, 13.43% found: C, 63.19; H, 4.03; N, 13.29%.

5-bromo-2-(1-(4-methoxyphenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo[3,2-h]isoquinoline (20c). Yield of 85%; mp 198.0–199.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 3108, 2998, 1625, 1582, 1524, 1503, 1648, 1267, 1253, 1183, 826; ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 6H), 3.89 (s, 3H), 7.04 (d, J = 9.0 Hz, 2H), 7.72 (d, J = 9.0 Hz, 2H), 7.81 (s, 1H), 8.05 (d, J = 6 Hz,1H), 8.35 (s, 1H, pyrazole), 8.63 (s, 1H, pyrazole), 8.69(d, J = 6 Hz,1H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.18, 54.50, 55.62, 114.72, 117.19, 117.66, 121.27, 122.19, 124.17, 127.40, 127.51, 133.11, 133.29, 140.30, 143.51, 144.07, 149.30, 159.04, 180.53; *Anal*. Calcd. for $C_{23}H_{19}BrN_4O$: C, 61.75; H, 4.28; N, 12.52% found: C, 61.71; H, 4.19; N, 12.49%.

5-bromo-2-(1-(2-chlorophenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo[3,2-h]isoquinoline (20d). Yield of 76%; mp 184.0–185.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 2966, 2926, 1625, 1587, 1488, 1649, 1275, 750; ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 6H), 7.43 (td, J_1 = 7.5 Hz, J_2 = 2.1 Hz, 1H), 7.47 (td, J_1 = 7.5 Hz, J_2 = 2.1 Hz, 1H), 7.60 (dd, J_1 = 7.5 Hz, J_2 = 2.1 Hz, 1H), 7.70 (dd, J_1 = 7.5 Hz , J_2 = 2.1 Hz, 1H), 7.83 (s, 1H), 8.07 (d, J = 6 Hz, 1H), 8.47 (s, 1H, pyrazole), 8.63 (s, 1H, pyrazole), 8.68 (d, J = 6.0 Hz, 1H), 10.08 (s,1H); ^{13}C NMR ($CDCl_3$): δ 24.15, 54.59, 118.20, 118.38, 119.19, 124.41, 127.53, 127.70, 127.93, 128.34, 129.84, 130.86, 132.02, 133.36, 137.47, 140.77, 143.03, 144.25, 149.11, 149.42, 180.38.; *Anal*. Calcd. for $C_{22}H_{16}BrClN_4$: C, 58.49; H, 3.57; N, 12.40% found: C, 58.31; H, 3.51; N, 12.34%.

5-bromo-2-(1-(3-chlorophenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo-[3,2-h]isoquinoline (20e). Yield of 80%; mp 240.0–241.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 2969, 2930, 1625, 1593, 1495, 1648, 1276, 947, 827; ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 6H), 7.36 (ddd, J_1 = 8.1 Hz, J_2 = 2.1 Hz, J_3 = 0.9 Hz, 1H), 7.46 (t, J = 8.1 Hz, 1H), 7.72 (ddd, J_1 = 8.1 Hz, J_2 = 2.1 Hz, J_3 = 0.9 Hz, 1H), 7.83 (s, 1H), 7.87 (t, J = 1.8 Hz, 1H), 8.06 (dd, J_1 = 6 Hz, J_2 = 0.6 Hz, 1H), 8.39(s,1H, pyrazole), 8.68(s, 1H), 8.69 (d, J = 6.0 Hz, 1H), 10.07 (d, J = 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.07, 54.56, 117.24, 117.43, 118.41, 119.88, 119.19, 124.18, 127.34, 127.52, 130.70, 133.34, 135.55, 140.33, 141.04, 143.51, 144.12,149.18, 149.23, 180.03; *Anal.* Calcd. for $C_{22}H_{16}BrClN_4$: C, 58.49; H, 3.57; N, 12.40% found: C, 58.43; H, 3.55; N, 12.31%.

5-bromo-2-(1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo[3,2-h]isoquinoline (20f). Yield of 80%; mp 247.5–248.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 2969, 2930, 1625, 1593, 1495, 1648, 1276, 947, 827; ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 6H), 7.61 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.82(s, 1H), 8.06 (d, J = 6 Hz, 1H), 8.38 (s, 1H, pyrazole), 8.69(s, 1H, pyrazole), 8.70 (d, J = 6.0 Hz, 1H), 10.07 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.07, 54.55, 117.26, 118.32, 120.72, 122.20, 124.20, 127.32, 127.70, 129.78, 133.18, 133.34, 137.96, 140.86, 143.46, 144.12, 149.20, 180.14; *Anal.* Calcd. for $C_{22}H_{16}BrClN_4$: C, 58.49; H, 3.57; N, 12.40% found: C, 58.41; H, 3.52; N, 12.29%.

5-bromo-2-(1-(4-methylphenyl)-1H-pyrazol-4-yl)-3,3-dimethyl-3H-pyrrolo[3,2-h]isoquinoline (20g). Yield of 80%; mp 198.0–199.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 3035, 2968, 2920, 1625, 1580, 1519, 1425, 1647, 1275, 1188, 951; ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 6H), 2.43 (s, 3H), 7.33 (d, J = 8.1 Hz, 2H), 7.70

(d, $J = 8.1$ Hz, 2H), 7.80 (s, 1H), 8.03 (d, $J = 6$ Hz,1H), 8.37 (s, 1H, pyrazole), 8.67 (s, 1H, pyrazole), 8.69 (d, $J = 6.0$ Hz, 1H), 10.07(d, $J = 0.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.01, 24.18, 54.48, 117.04, 117.79, 119.55, 122.23, 123.99, 127.37, 127.44, 130.16, 133.24, 137.19, 137.54, 140.44, 143.98, 149.19, 149.48, 180.38; *Anal.* Calcd. for $C_{23}H_{19}BrN_4$: C, 64.05; H, 4.44; Br, 18.53; N, 12.99% found: C, 63.97; H, 4.34; N, 13.02%.

General procedure for synthesis of (21c, **21g** and **22**). A mixture of the diformyl compound **16** or **17** (0.57 mmol) and aryl hydrazine (0.57 mmol) in absolute ethanol (15 mL) was stirred at RT overnight. After cooling and concentrating the solution, the resulting crystals were collected by filtration, air dried and washed with cold EtOH.

2-(3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinolin-2-yl)-2-(2-(3-methoxyphenyl) hydrazono)acetaldehyde (21c). Yield of 70%; mp 151.5–152.5 °C; FTIR (KBr, cm^{-1}) ν_{max} 3283, 3957, 2959, 2831, 1630, 1578, 1566, 1670, 1269, 1155, 680; ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 6H), 3.91 (s, 3H), 6.52 (dd, $J_1 = 8.1$ Hz, $J_2 = 2.1$ Hz, 1H), 6.67 (dd, $J_1 = 8.1$ Hz, $J_2 = 2.1$ Hz, 1H), 6.84 (t, $J = 2.4$ Hz, 1H), 7.29 (d, $J = 7.8$ Hz, 1H),7.60 (d, $J = 8.4$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 7.74 (bs, NH, 1H), 7.91 (d, $J = 6$ Hz, 1H), 8.62 (d, $J = 6$ Hz, 1H), 8.39 (s, 1H), 9.32 (s, 1H), 10.10 (s, 1H), 12.90 (bs, NH,1H); ^{13}C NMR ($CDCl_3$): δ 28.49, 50.18, 55.44, 99.57, 104.29, 105.69, 106.18, 114.50, 120.98, 119.25, 123.42, 128.64, 130.34, 135.46, 137.95, 139.55, 143.44, 146.25, 153.06, 161.19, 181.29, 184.66; *Anal.* Calcd. for $C_{23}H_{22}N_4O$: C, 71.48; H, 5.74; N, 14.50% found: C, 71.07; H, 5.40; N, 15.01%.

2-(3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinolin-2-yl)-2-(2-(4-methylphenyl)hydrazono)-acetaldehyde (21g). Yield of 70%; mp 140.0–141.5 °C; FTIR (KBr, cm^{-1}) ν_{max} 3268, 2974, 2931, 1602, 1580, 1560, 1670, 1264, 679; ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 6H), 2.38 (s, 3H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.57 (bs, NH, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 8.41 (d, $J = 5.7$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 8.37 (s, 1H), 8.64 (d, $J = 5.7$ Hz, 1H), 9.33 (s, 1H), 10.09 (s, 1H), 12.91 (bs, NH, 1H); ^{13}C NMR ($CDCl_3$): δ 20.64, 50.16, 106.30, 112.76, 114.14, 118.08, 119.19, 123.37, 128.65, 129.80, 129.99, 135.51, 137.64, 139.60, 142.75, 143.33, 153.18, 181.14, 184.66; *Anal.* Calcd. for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.99; N, 15.12% found: C, 74.11; H, 5.63; N, 15.60%.

2-(5-bromo-3,3-dimethyl-3H-pyrrolo[3,2-H]isoquinolin-2-yl)-2-(2-(p-tolyl) hydrazono)acetaldehyde (22g). Yield of 65%; mp 230.5–232.5 °C; FTIR (KBr, cm^{-1}) ν_{max} 3273, 3120, 2966, 1634, 1612, 1597, 1564, 1657, 1267, 1182, 811; ^{1}H NMR ($CDCl_3$): δ 1.81 (s, 6H), 2.34 (s, 3H), 7.05 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.55 (bs, NH, 1H), 7.73 (s,1H), 8.06 (dd, $J_1 = 6$ Hz, $J_2 = 0.6$ Hz, 1H), 8.33 (s, 1H), 8.72 (d, $J = 6.0$ Hz, 1H), 9.51 (s, 1H, CHO), 10.10 (d, $J = 0.6$ Hz,1H), 16.02 (bs, NH, 1H); ^{13}C NMR ($CDCl_3$): δ 20.57, 28.66, 58.44, 106.89, 112.76, 115.94, 118.70, 124.59, 125.23, 130.12, 130.18,133.18, 136.83, 137.23, 142.41, 144.46, 146.68, 180.50, 184.75; *Anal.* Calcd. for $C_{23}H_{21}BrN_4O$: C, 61.48; H, 4.71; N, 12.47% found: C, 61.60; H, 4.39; N, 12.81%.

5-(3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinolin-2-yl)pyrimidine-2(1H)-thione(23). A solution of **18** (0.2 g, 0.7 mol) and thiourea (0.053 g, 0.7 mol) in absolute ethanol (15 mL) was treated with concentrated hydrochloric acid (1 mL), and reaction mixture was stirred at RT for 2 days. After solvent evaporated, water was added to the residue, and solution neutralized by solid NaOH. Obtained solid filtered off, washed with water and dried in air. The crude product was purified by recrystallization from EtOH. 85% yield; mp 256–258 °C; FTIR (KBr, cm^{-1}) ν_{max} 3056, 2968, 2873, 2736(SH), 1673, 1647, 1687, 1194(C = S), 1168; ^{1}H NMR (DMSO-d_6): δ 1.19 (s, 6H), 8.19 (d, $J = 8.1$ Hz, 1H), 8.37(d, $J = 8.1$ Hz, 1H), 8.62 (d, $J = 6.2$ Hz, 1H), 8.69 (d, $J = 6.2$ Hz, 1H), 9.82 (s, 1H), 9.86 (s, 2H), 13.73 (bs, NH); ^{13}C NMR (DMSO-d_6): δ 19.92, 56.57, 110.45, 119.31, 119.10, 124.42, 124.51, 124.91, 127.59, 128.32, 128.58, 134.95, 134.98, 145.90,149.45, 152.90, 188.70, 189.92(C = S); *Anal.* Calcd. for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29; S, 10.47% found: C, 66.59; H, 4.54; N, 18.18; S, 10.43%.

General procedure for synthesis of (24 and **25**). A solution of **17**,**18** (0.7 mol) and hydroxylamine hydrochloride (0.048 g, 0.7 mol) in absolute ethanol (15 mL) was stirred at RT for 2 days. After this time, a yellow precipitate had formed and was filtered off, washed with water and dried in air. The crude products **24**,**25** were purified by recrystallization from EtOH.

4-(3,3-dimethyl-3H-pyrrolo[2,3-f]isoquinolin-2-yl)isoxazole (24). Yield of 65%; mp 295 °C (dec.); FTIR (KBr, cm^{-1}) ν_{max} 3099, 3055, 3029, 2975, 1634, 1608, 1554, 1680, 1129, 825; ^{1}H NMR (DMSO-d_6): δ 1.57 (s, 6H), 8.28 (d, $J = 8.4$ Hz, 1H), 8.47 (d, $J = 8.4$ Hz, 1H), 8.73 (s, 2H), 9.36(s,1H), 9.90 (s, 1H), 10.05 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 19.82, 56.01, 114.66, 120.10, 124.92, 127.71, 129.18, 160.89, 163.93, 147.74, 148.77, 149.28, 153.43, 160.45, 189.19; *Anal.* Calcd. For $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96% found: C, 72.91; H, 4.89; N, 15.91%.

2-(5-bromo-3,3-dimethyl-1H-pyrrolo[3,2-h]isoquinolin-2(3H)-ylidene)-3-oxopropanenitrile (25). Yield of 70%; mp 292.0–293.0 °C; FTIR (KBr, cm^{-1}) ν_{max} 3201 (NH), 3059, 2205 (CN), 1648, 1631, 1544, 1388, 1361, 1165, 887, 758; ^{1}H NMR ($CDCl_3$): δ 1.81 (s, 6H), 7.76 (s, 1H), 8.09 (d, $J = 6.0$ Hz, 1H), 8.75 (d, $J = 6.0$ Hz,1H), 9.44 (s, 1H), 9.51 (s, 1H, CHO), 13.10 (bs, NH, 1H); ^{13}C NMR ($CDCl_3$): δ 23.36, 50.89, 115.90, 118.69, 124.32, 127.80, 133.34, 134.70, 135.66, 144.99, 146.20, 178.32, 188.04; *Anal.* Calcd. for $C_{16}H_{12}BrN_3O$: C, 56.16; H, 3.53; N, 12.28% found: C, 56.12; H, 3.52; N; 12.19%.

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

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