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Regioselective synthesis of 4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]-quinolin-5(6*H*)-ones. Mechanism and structural analysis

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Abstract—Reactions of 5-amino-3-methyl-1*H*-pyrazole with dimedone and aldehydes afford regioselectivelly tricyclic linear 3,7,7-trimethyl-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-ones in good yields. Several aspects on this regioselective reaction, such as the reaction mechanism and structural studies of the predominant tautomeric form, are treated.

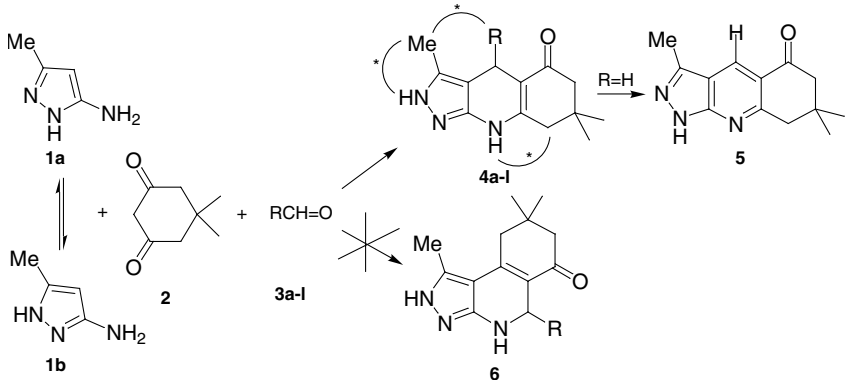
1. Introduction

Pyrazolo[3,4-*b*]quinolines are of interest as possible antiviral agents.[1] Some derivatives exhibit parasiticidic properties[2] and have been studied as potential antimalarial agents.[3] Others have shown bactericidal activity,[4] and also used as vasodilators[5] or evaluated for enzymatic inhibitory activity.[6]

Friedländer condensation could seem in a first instance the simplest route to prepare pyrazolo[3,4-*b*]quinolines using an *o*-aminobenzaldehyde and the appropriate pyrazolin-5-one. But this reaction affords several by-products along with the desired pyrazoloquinoline.[7–9] Another alternative is the Vilsmeier–Haack formylation of 5-(*p*-chloroanilino)-1-phenylpyrazolin-3-one.[10]

Previously we have reported an efficient and versatile synthesis of novel tetrahydro-pyrimido- and tetrahydropyrazolo[3,4-*b*]quinolinones from appropriates pyrimidine and pyrazole amines, respectively,[11–16] to which the quinoline ring is annelated, using dimedone (**2**) and substituted benzaldehyde **3**.

Here, we report a complementary and more exhaustive study on that reaction, using 5(3)-amino-3(5)-methylpyrazole (**1**) and the mentioned reactants **2** and **3**. The



Scheme 1. Synthesis of pyrazolo[3,4-*b*]quinolines **4** and **5**. **4a** R = C_6H_5; **4b** R = 4-$CH_3C_6H_4$; **4c** R = 4-$CH_3OC_6H_4$; **4d** R = 4-ClC_6H_4; **4e** R = 4-BrC_6H_4; **4f** R = 4-$O_2NC_6H_4$; **4g** R=4-$(CH_3)_2NC_6H_4$; **4h** R=3,4,5-tri$CH_3OC_6H_2$; **4i** R=C_6H_5CH=CH-; **4j** R=3-pyridinyl; **4k** R=β-naphthalenyl; **4l** R=H; *=NOESY correlations.

Keywords: regioselective pyrazole cyclocondensation; pyrazolo[3,4-*b*]quinoline; tautomerism.
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Table 1. ^{1}H NMR chemical shifts (δ in ppm) of compounds **4a–k** and **5**

Compound	3-CH_3 s	CMe_2 s	2-H s	4-H s	6-H d[a]	8-H d[a]	9-H s	4-Aryl *o–m*
4a	1.89	0.94	11.73	4.93	1.95	2.42	9.68	7.01–7.19
		1.00			2.12	2.44		
4b[b]	1.89	0.93	11.70	4.88	1.92	2.40	9.64	6.98–7.01
		1.00			2.13	2.43		
4c[c]	1.87	0.92	11.70	4.87	1.89	2.39	9.63	6.74–7.01
		0.99			2.10	2.41		
4d	1.89	0.93	11.78	4.97	1.95	2.38	9.74	7.14–7.23
		1.00			2.12	2.46		
4e	1.89	0.93	11.79	4.92	1.94	2.41	9.74	7.08–7.36
		1.00			2.12	2.44		
4f	1.88	0.93	11.85	5.09	1.95	2.45	9.87	7.40–8.08
		1.01			2.13	2.49		
4g[d]	1.90	0.94	11.66	4.81	1.95	2.38	9.58	6.54–6.93
		1.00			2.13	2.41		
4h[e]	2.02	1.04	11.73	4.91	2.08	2.40	9.66	6.43
					2.17	2.50		
4i[f]	2.10	1.00	11.84	4.60	2.13 (s)	2.36 (s)	9.61	7.15–7.26
4j	1.88	0.92	11.82	4.97	1.95	2.41	9.80	7.20 (1H)
		1.00			2.13	2.47		7.44 (1H)
								8.26 (1H)
								8.38 (1H)
4k	1.95	0.94	11.73	5.12	1.92	2.40	9.72	7.25–7.31 (1H)
		1.01			2.13	2.46		7.35–7.47 (2H)
								7.63–7.83 (4H)
5	2.52	1.04 (6H)	13.39	8.66	2.58 (s)	3.05 (s)	–	–

[a] Those protons are diasterotopics appearing as typical geminal doublets protons with J=16 Hz in both cases.
[b] Ar–CH_3 2.19 ppm.
[c] Ar–OCH_3 3.64 ppm.
[d] Ar–$N(CH_3)_2$ 2.79 ppm.
[e] Ar–$(OCH_3)_3$ 3.58 (3H) and 3.67 (6H) ppm.
[f] C_6H_5–CH_α=CH_β–, 6.05 (H_α, d, $J_{\alpha,\beta}$=16 Hz) and 6.21 (H_β, dd, $J_{\beta,4}$=6 Hz) ppm.

mechanism has been proved via synthesis of a proposed intermediate and analysis of its evolution, and a deeper structural analysis has been carried out to determine the preferred tautomeric form of the final product both in solution and in solid state.

2. Results and discussion

The preparation of tetrahydropyrazolo[3,4-*b*]quinolin-5(6*H*)-ones **4a–k** has been accomplished by reacting equimolar amounts of 5(3)-amino-3(5)-methylpyrazole (**1**) with

Table 2. ^{13}C NMR chemical shifts (δ ppm, in DMSO-d_6) of compounds **4a–k** and **5**

	4a	**4b**[a]	**4c**[b]	**4d**	**4e**	**4f**	**4g**[c]	**4h**[d]	**4i**[e]	**4j**[f]	**4k**[g]	**5**
CH_3	9.3	9.3	9.3	9.1	9.3	9.2	0.93	9.6	9.4	9.2	9.3	12.1
CMe_2	26.8	26.8	26.8	26.8	26.8	26.7	26.8	26.4	27.2	26.8	26.7	27.7
	28.8	28.8	28.8	28.7	28.7	28.6	28.8	29.1	28.3	28.6	28.8	
C-3	134.8	134.6	134.7	134.9	135.0	135.3	134.5	135.1	137.2	135.0	135.1	143.7
C-3a	103.8	104.0	104.1	103.3	103.2	102.4	104.4	103.7	100.7	102.9	103.5	113.4
C-4	35.0	34.6	34.0	38.6	38.6	35.8	33.8	35.2	31.8	38.6	38.6	129.3
C-4a	106.9	107.1	107.2	106.5	106.5	105.9	107.4	106.5	104.8	106.0	106.7	120.9
C-5	192.7	192.7	192.7	192.7	192.7	192.3	192.7	192.9	193.0	192.7	192.8	196.6
C-6	50.3	50.4	50.4	50.3	50.3	50.2	50.5	50.3	50.5	50.2	50.4	51.5
C-7	31.8	31.8	31.8	34.6	31.8	31.9	31.8	31.7	31.7	31.8	31.8	32.4
C-8	40.9	40.9	40.9	40.9	40.9	40.9	40.9	40.9	41.0	40.9	40.9	46.3
C-8a	152.7	152.5	152.4	152.8	153.0	155.8	152.2	153.0	152.9	153.1	152.8	161.7
C-9a	146.1	146.2	146.2	146.1	146.1	146.0	146.3	146.0	146.6	146.1	146.2	153.2
Aryl												
i	148.3	145.4	140.6	129.1	146.1	145.1	136.8	144.3	135.4			
o	127.6	128.2	127.9	128.9	130.5	128.3	127.5	104.1	128.4			
m	127.1	127.0	112.9	127.6	129.4	123.1	112.0	152.3	125.8			
p	125.1	133.8	156.7	147.2	147.8	153.3	148.2	134.8	133.0			

[a] Ar–CH_3 20.5 ppm.
[b] Ar–OCH_3 54.7 ppm.
[c] Ar–$N(CH_3)_2$ 40.3 and 40.9 ppm.
[d] Ar–$(OCH_3)_3$ 55.5 and 59.7 ppm.
[e] –CH=CH– 126.5 and 126.7 ppm.
[f] 148.5, 143.3, 134.4, 123.1 and 146.4 ppm for C-2, C-3, C-4, C-5 and C-6 for pyridine ring, respectively.
[g] 124.6, 124.8, 125.6, 126.4, 127.2, 127.3, 127.4, 131.3, 132.7, and 135,1 ppm for naphthalene ring carbon.

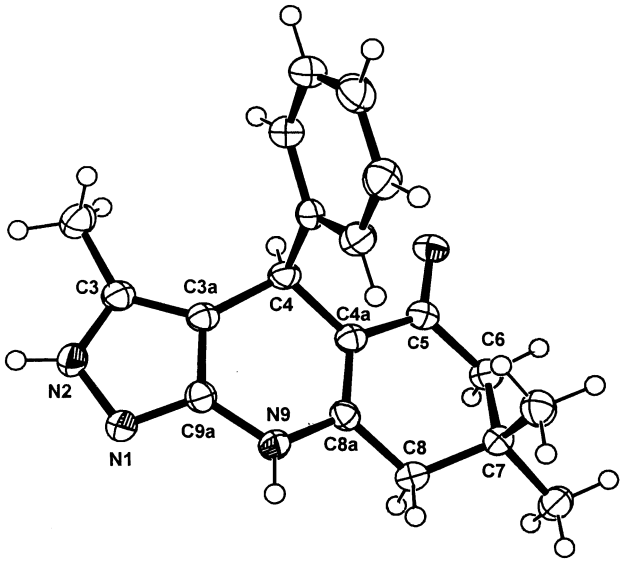
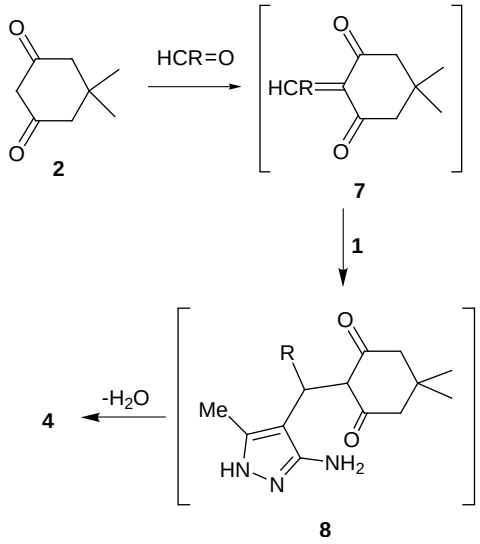


Figure 1. The asymmetric unit of compound **4a**. Displacement ellipsoids are drawn at the 50% probability level.

dimedone (**2**) and the aldehydes (**3**) in absolute ethanol to reflux for 20–50 min (Scheme 1). The reaction products were easily isolated in good yields as stable crystalline solids and purified by recrystallization from ethanol.

This one step cyclocondensation reaction leads to regioselective linear tricyclic **4**. In all cases the reaction gave a single product and the structures were assigned by spectroscopic and analytical methods (^{1}H-, ^{13}C NMR and MS, see Section 4).

The NMR spectroscopic data are consistent with structures **4**. Regarding to the heterocyclic nucleus, for example compound **4e** exhibits a ^{1}H NMR spectrum (see Table 1) with three relatively sharp singlets at 11.79, 9.74 and 4.92 ppm, integrals ratio 1:1:1, the two formers are exchangeable proton signals, and are readily assigned to the two NH-groups, 1(2)-NH and 9-NH, respectively; and the latter to H-4; another two couples of doublets appear



Scheme 2. Mechanism to pyrazolo[3,4-*b*]pyridines.

around 2.00 and 2.40 ppm corresponding to the diastereotopic CH_2-groups at position 6 and 8, respectively.

The whole carbon skeleton was assigned using ^{13}C NMR spectra (Table 2), combining with DEPT, and two dimensional ^{1}H, ^{13}C shift correlation HMQC and HMBC experiments. Compounds **4a**–**k** show in their ^{13}C NMR spectra the signals for C-8a and C-9a at higher δ values 145.8–155.8 ppm than those for carbon atoms C-3a and C-4a at δ values, 110.7–103.7 and 101.7–106.5 ppm, respectively, that is due to the influence of the linked nitrogen.

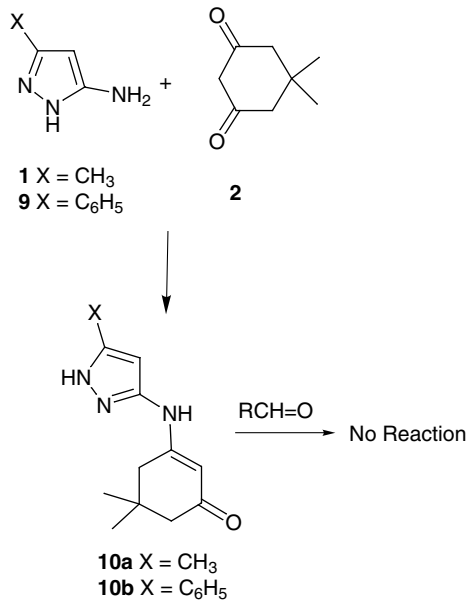
Both the linear tricyclic structure vs the non-linear **6**, and the 2*H* tautomer are supported by NOESY experiments. For example, in the experiments for **4d** and **4h**, correlation between protons at 2.40 ppm, corresponding to C(8)H_2, and at 9.74 ppm, N(9)–H, corroborates the linear tricyclic structure. And another correlation between the signal of the methyl hydrogens attached to the pyrazole ring at 1.89 ppm with the exchangeable proton signal at 11.79 ppm, confirms that the preferred tautomer in DMSO solution is the 2*H*. (See * in Scheme 1.)

Solid state gives unambiguous proof of the above features, and the isolation of unique crystals for compounds **4a**,**c**,**e** and **k** permitted the determination of their crystal structure from X-ray diffraction analysis.[17–20] All those crystal structures present similar crystal features and just the perspective view of one of those is shown as an example in Fig. 1. This figure displays the linear tricyclic structure and the 2*H*-tautomer, being that hydrogen withdrawn from the difference map.

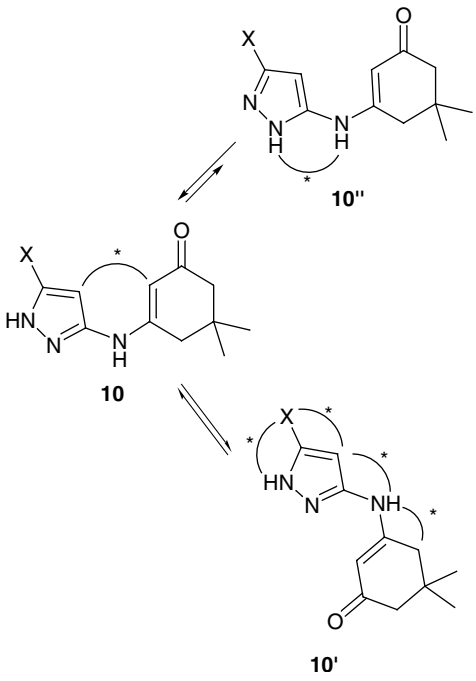
Regarding to the mass spectra, all products **4** exhibit similar behavior in their fragmentation, showing the molecular peak along with a typical loss of the aryl group at position 4 as the base peak. It is important to remark that the reaction of amine **1** with formaldehyde and dimedone under the same conditions led to the formation of the aromatized product **5** (see Scheme 1), differing to the other aldehydes; and it was impossible to isolate the intermediate product as **4**. The presumable tautomer for this aromatic compound **5** is the 1*H*, which is supported by the no NOESY correlation between the N–H and C(3)–CH_3 signals, otherwise observed for **4**. This is probably the stablest form in such a heterocyclic system.[16]

In Scheme 2, we postulate a mechanism for the cyclocondensation between aminopyrazole, dimedone and an aldehyde to provide pyrazolo[3,4-*b*]quinolines. Firstly, we assume that the initial step is a Knoevenagel condensation between **2** and **3**, resulting the adduct **7**, (compounds such as **7** were isolated as a by-product in some reactions), which suffers a Michael addition of the aminopyrazole **1** to the C=C bond of **7**. The Michael adduct **8** undergoes a cyclocondensation reaction through amino and carbonyl to render compounds **4**.

Other possible explanation for this reaction is shown in Scheme 3, where a condensation between **1** and **2** is postulated as the initial step, affording the enamine **10** which then reacts with the corresponding aldehyde. To check this possibility we first synthetized the enamines **10a**,**b** by reaction of



Scheme 3. Proofs to discard an alternative mechanism via enamine pyrazole **10** intermediate.



Scheme 5. Tautomeric and conformational equilibria in enamine pyrazoles **10**.

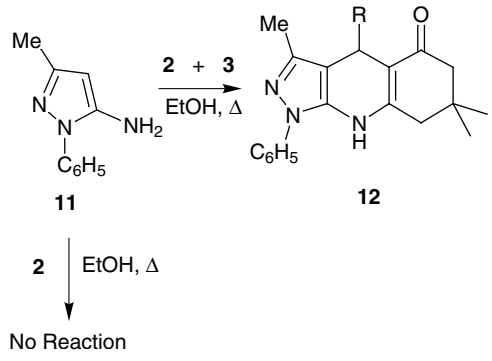
equimolar amounts of dimedone **2** and amine **1** and **9** (5(3)-amino-3(5)-phenylpyrazole), respectively, by heating in ethanol. However, when we tried to react enamines **10** to an aldehyde in the above reaction conditions, reaction did not proceed.

The above fact together with that the compound 5-amino-3-methyl-1-phenylpyrazole (**11**) did not react with dimedone (**2**) in the reaction condition, but afforded the final product as **4** (see Scheme 4)[12] permit us to discard the mechanism described in Scheme 3 as a reaction pathway and encourage us to consider that illustrated in the Scheme 2, furthermore the intermediate **7** was detected in the reaction process.

The enamine intermediates **10a**,**b** were also fully characterized by spectroscopic and analytical methods. Both one (^{1}H, ^{13}C and DEPT) and two dimensional (homonuclear COSY and NOESY, and heteronuclear HMQC and HMBC) NMR spectroscopic experiments were used for a complete structural determination. ^{1}H-, ^{13}C NMR and NOESY experiments show several equilibria involving both tautomerism in the pyrazole ring and conformational by rotation C3′–N3 as displayed in Scheme 5. Some signals in the ^{1}H- and ^{13}C NMR spectra are found wider than expected, which indicates the presence of that conformational equilibrium. (See Fig. 2.)

The qualitative ratio of those isomers are based on the intensity of the NOESY correlation signals, i.e. the correlation between H-4′ with H–N(3) has similar intensity order to that of H-4′ with H-2, which permits us to say that the conformational equilibrium in the 5-methylpyrazole tautomer (**10′**=**10**) is nearly fifty–fifty; however the tautomeric equilibrium of **10a** (X:CH$_3$) shows a minor NOESY correlation between the two NH protons but not NH (pyrazole) with H-2, indicating the 3-methylpyrazole tautomer in the conformation **10″**, drawn in Scheme 5, having a minor proportion.

In addition both compounds were crystallized and examined by X-ray diffraction (Fig. 3), resulting the isomer **10** in crystalline state.[21,22]



Scheme 4. Proofs to discard a first step of condensation between aminopyrazole and dimedone.

3. Conclusions

The three components one step cyclocondensation between dimedone, aldehydes and aminopyrazoles goes on through a first Knoevenagel condensation followed by a Michael addition of the aminopyrazole to the Knoevenagel adducts, and a further cyclization to afford the pharmaceutical interesting tetrahydropyrazolo[3,4-*b*]quinolines. NOESY experiments and X-ray analysis of compounds **4** both conclude in the 2*H*-tautomer as the preferred form, although the 1*H*- is the preferred for the aromatized compound **5**.

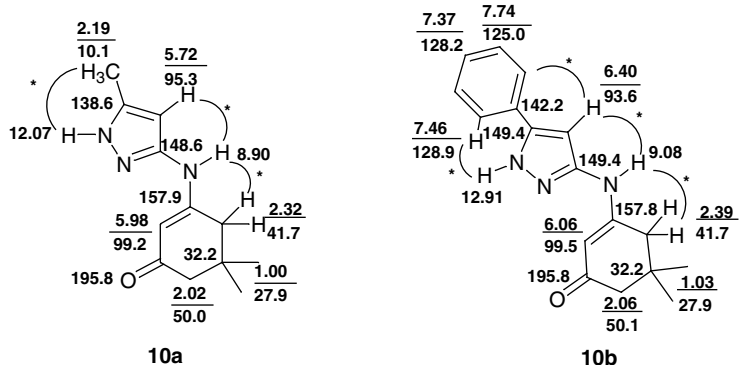


Figure 2. ^{1}H- and ^{13}C NMR data of **10a**,**b** in DMSO-d_6 (chemical shifts δ related to TMS as internal standard; the * indicate the most important nuclear Overhauser effects).

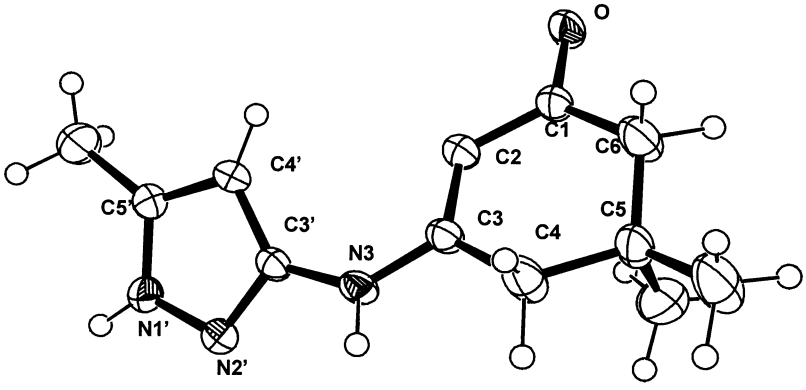


Figure 3. The asymmetric unit of compound **10a**. Displacement ellipsoids are drawn at the 50% probability level.

4. Experimental

4.1. General methods

Melting points were taken on a Buchi melting point apparatus and were uncorrected. The IR spectra were obtained in potassium bromide pellets with a Perkin–Elmer 599B spectrometer. The ^{1}H- and ^{13}C NMR spectra were run on a Bruker AVANCE DPX 300 spectrometer in DMSO-d_6 using TMS as internal standard. The mass spectra were recorded on a Fisons-Platform interface APCI in MeOH. The elemental analyses have been obtained using a LEGO CHNS-900 equipment.

4.2. General procedure for the synthesis of 4-aryl-3,7,7-trimethyl-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]-quinolin-5(6*H*)-ones 4a–k

A solution of 5-aminopyrazole **1** (1 mmol), dimedone **2** (1 mmol) and benzaldehyde **3** (1 mmol) in absolute ethanol (15 mL) was heated to reflux for 20–50 min (TLC control). The cyclizated products **4** were isolated by cooling down the reaction mixture, followed by filtration, washed with ethanol, and recrystallized from ethanol.

4.2.1. 3,7,7-Trimethyl-4-phenyl-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4a. This compound was obtained according to general procedure as white crystals. Mp 229°C, yield 60%. The mass spectrum shows the following peaks: MS: (70 eV) *m*/*z* (%)=309 (9), 308 (45), 307 (47, M^+), 230 (100, $M^+-4\text{-}C_6H_5$), 77 (22). Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.12; H, 6.95; N, 13.56.

4.2.2. 3,7,7-Trimethyl-4-(4-methylphenyl)-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4b. This compound was obtained according to general procedure as white crystals. Mp 309–310°C, yield 75%. The mass spectrum shows the following peaks: MS: (70 eV) *m*/*z* (%)=323 (5), 322 (30), 321 (52, M^+), 230 (100, $4\text{-}CH_3C_6H_4$). Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.84, H, 7.15; N, 13.14.

4.2.3. 4-(4-Methoxyphenyl)-3,7,7-trimethyl-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4c. This compound was obtained according to general procedure as white crystals. Mp 297°C, yield 61%. The mass spectrum shows the following peaks: MS: (70 eV) *m*/*z* (%)=339 (2), 338 (14), 337 (61, M^+), 230 (100, $M^+-4\text{-}CH_3OC_6H_4$), 77 (5). Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87 N, 12.45. Found: C, 71.22; H, 6.81; N, 12.32.

4.2.4. 4-(4-Chlorophenyl)-3,7,7-trimethyl-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4d. This compound was obtained according to general procedure as white crystals. Mp 304–305°C, yield 73%. The mass spectrum shows the following peaks: MS: (70 eV) *m*/*z* (%)=343/341 (14/45, M^+), 230 (100, $M^+-4\text{-}ClC_6H_4$). Anal. Calcd for $C_{19}H_{20}ClN_3O$: C, 66.76; H, 5.90; N, 12.29. Found: C, 66.65; H, 5.77; N, 12.20.

4.2.5. 4-(4-Bromophenyl)-3,7,7-trimethyl-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4e. This compound was obtained according to general procedure as white crystals. Mp 314–315°C, yield 70%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=387/385 (31/31, M^+), 230 (100, $M^+-4\text{-}BrC_6H_4$), 174 (9), 146 (11), 41 (18). Anal. Calcd for $C_{19}H_{20}BrN_3O$: C, 59.08; H, 5.22; N, 10.88. Found: C, 59.15; H, 5.13; N, 10.72.

4.2.6. 3,7,7-Trimethyl-4-(4-nitrophenyl)-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4f. This compound was obtained according to general procedure as yellow crystals. Mp 299–301°C, yield 67%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=353 (17), 352 (38, M^+), 230 (100, $M^+-4\text{-}O_2NC_6H_4$), 171 (11), 146 (12), 41 (10). Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.73; N, 15.90. Found: C, 64.65; H, 5.83; N, 15.78.

4.2.7. 3,7,7-Trimethyl-4-(4-dimethylaminophenyl)-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4g. This compound was obtained according to general procedure as white crystals. Mp 257°C, yield 80%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=351 (2), 350 (100, M^+), 230 (100, $M^+-4\text{-}(CH_3)_2NC_6H_4$), 121 (33), 77 (10). Anal. Calcd for $C_{21}H_{26}N_4O$: C, 71.97; H, 7.48; N, 15.99. Found: C, 71.82; H, 7.39; N, 16.03.

4.2.8. 4-(3,4,5-Trimethoxyphenyl)-3,7,7-trimethyl-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4h. This compound was obtained according to general procedure as white crystals. Mp 318–320°C, yield 72%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=397 (69, M^+), 366 (13), 230 (100, $M^+-3,4,5\text{-}(CH_3O)_3C_6H_2$). Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.55; H, 6.76; N, 10.44.

4.2.9. 3,7,7-Trimethyl-4-(β-stiryl)-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4i. This compound was obtained according to general procedure as white crystals. Mp 313–314°C, yield 67%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=334 (21), 33 (55, M^+), 242 (100, $M^+-C_7H_7$), 230 (31, $M^+-C_6H_5CH{=}CH$), 77 (10). Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.52; H, 6.86; N, 12.78.

4.2.10. 3,7,7-Trimethyl-4-(3-pyridinyl)-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4j. This compound was obtained according to general procedure as white crystals. Mp 306–308°C, yield 64%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=309 (14), 308 (55, M^+), 231 (16), 230 (100, $M^+-C_6H_4N$). Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.11; H, 6.54; N, 18.17. Found: C, 70.15; H, 6.58; N, 18.33.

4.2.11. 3,7,7-Trimethyl-4-(β-naphthalenyl)-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 4k. This compound was obtained according to general procedure as white crystals. Mp 329°C, yield 65%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=359 (1), 358 (9), 357 (35, M^+), 230 (100, M^+-naphthalenyl). Anal. Calcd for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49; N, 11.76. Found: C, 77.40; H, 6.57; N, 11.63.

4.2.12. Synthesis of 3,7,7-trimethyl-7,8-dihydro-1*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one 5. This compound was obtained according to general procedure as white crystals. Mp 284–285°C, yield 87%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=231 (1), 230 (12), 229 (59, M^+), 173 (56). Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.25; H, 6.43; N, 18.20.

4.3. Synthesis of compounds 10

A solution of 5-amino-3-methylpyrazole (**1**) or 5-amino-3-phenylpyrazole (**9**) (1 mmol) and dimedone (**2**) (1 mmol) in absolute ethanol (15 ml) was heated to reflux for 25 min. The formed solid was isolated by filtration, then washed with ethanol and recrystallized from ethanol.

4.3.1. 5,5-Dimethyl-3-(5-methyl-1*H*-pirazol-3-ylamino)-cyclohex-2-en-1-one 10a. This compound was obtained according to general procedure as yellow crystals. Mp 245°C, yield 87%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=222 (1), 221 (14), 220 (88), 219 (56, M^+), 204 (40), 191 (31), 163 (37), 135 (100), 108 (52). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.65; H, 7.73; N, 19.09.

4.3.2. 5,5-Dimethyl-3-(5-phenyl-1*H*-pirazol-3-ylamino)-cyclohex-2-en-1-one 10b. This compound was obtained according to general procedure as yellow crystals. Mp 229°C, yield 80%. The mass spectrum shows the following peaks: MS: (70 eV) *m/z* (%)=283 (3), 282 (18), 281 (51, M^+), 266 (59), 253 (22), 225 (36), 196 (100), 77 (24). Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.45; H, 6.73; N, 14.90.

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