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SYNTHESIS OF 5*H*-PYRAZOLO[4,3-*c*]QUINOLINES

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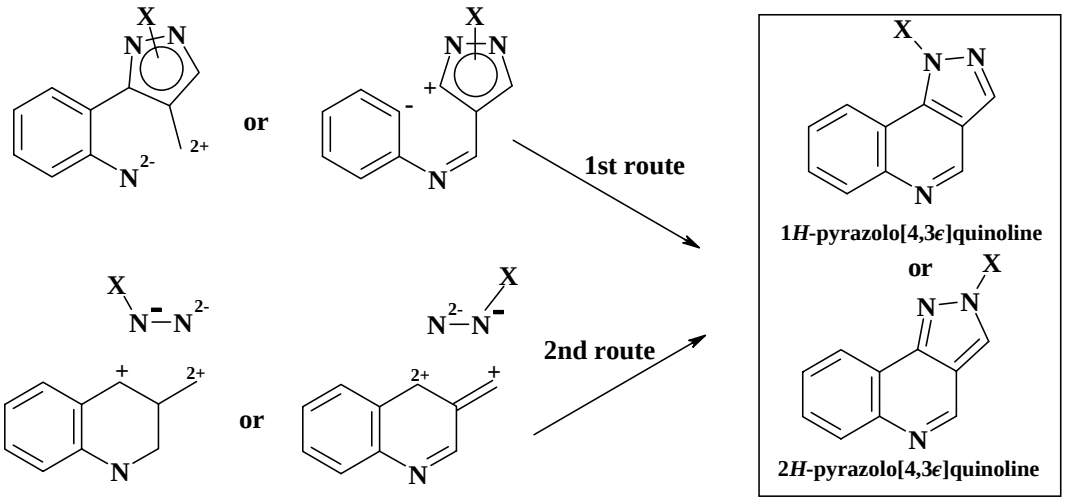
Abstract – A convenient synthesis of 3-aryl-5*H*-pyrazolo[4,3-*c*]quinolines is described. The key reactions include alkylation of 3-aroyl-1*H*-quinolin-4-ones with alkyl halides in DMF in the presence of sodium hydride, followed by hydrazine-mediated cyclization of the alkylated products in acetic acid.

INTRODUCTION

Structural analogues of pyrazolo[4,3-*c*]quinoline have been studied for their biological activities as acetylcholinesterase inhibitors,[1] interleukin 1 antagonists,[2] PDE 4 inhibitors,[3] anti-inflammatory agents[2,4,5] and gastric H+/K+-ATPase inhibitors.[6] Ability to displace specific flunitrazepam binding,[7] as well as antimalarial, anti-allergic, and antiviral activities[4,5] has also been investigated. According to these examples, pyrazolo[4,3-*c*]quinolines represent promising synthetic targets. Development of efficient synthetic approaches to the related molecular scaffolds will provide a valuable source of novel physiologically active agents.

Depending on the substitution pattern, two synthetic approaches were described to construction of the pyrazolo[4,3-*c*]quinoline scaffold (Scheme 1). The first possible route involves formation of the pyridine ring starting from substituted pyrazoles.[7-11] An alternative approach is based on assembly of the pyrazole heterocycle *via* hydrazine condensation in a late stage of the sequence.[1-3,5,6,12] For the synthesis of diverse 5-substituted pyrazolo[4,3-*c*]quinolines, the second strategy seems to be the method of choice. The first approach is less suitable because of poor availability of appropriate initial reagents. On the other hand, alkylation of *N*-unsubstituted 1*H*-pyrazolo[4,3-*c*]quinolines affords only *N*1-alkylated derivatives,[13] and, therefore, selective *N*5-alkylation is problematic.



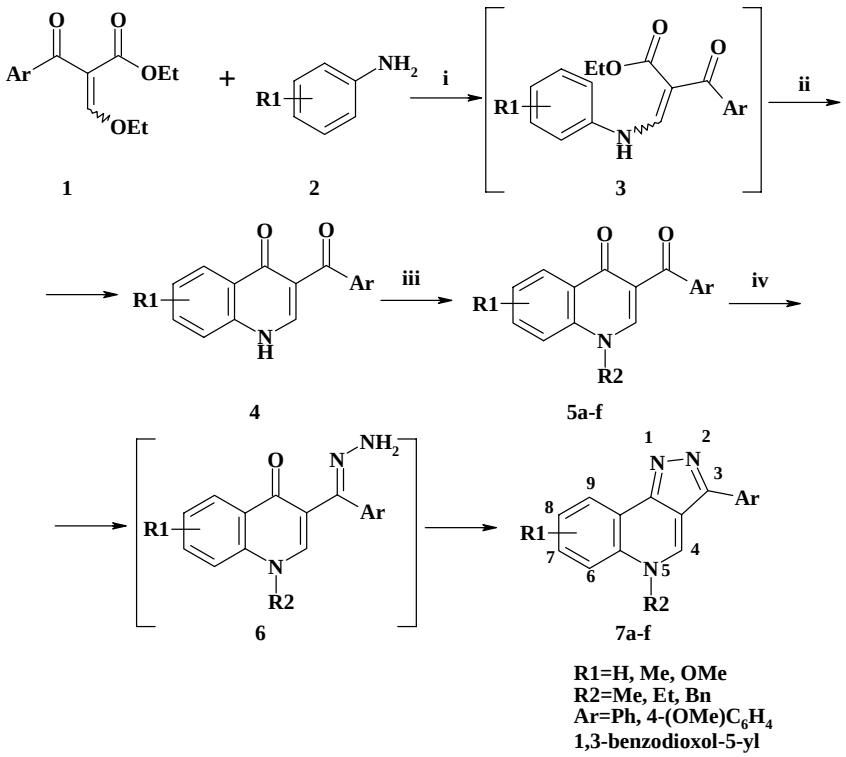
Scheme 1

In this work, we used the second strategy for the synthesis of a series of novel *N*5-substituted 3-aryl-5*H*-pyrazolo[4,3-*c*]quinolines of general formula (**7a-f**) (Scheme 2). The key intermediates (**4**) were obtained by Gould-Jacobs reaction of ethoxymethylenearoylacetates (**1**) with substituted anilines (**2**) using a reported procedure.[14] 3-Aroyl-1*H*-quinolin-4-ones (**4**) were alkylated by the treatment with alkylhalides in DMF in the presence of sodium hydride. Under the described conditions, only *N*-alkylated products (**5a-f**) were formed in high yields (85-92%). The assembly of 3-aryl-5*H*-pyrazolo[4,3-*c*]quinoline heterocyclic system was achieved by condensation of **5a-f** with hydrazine in the boiling acetic acid. The reaction proceeded in high yields (78-97%) *via* the hydrazone intermediates (**6**), which could not be isolated from the reaction mixture due to their high reactivity. In summary, using the described reactions, compounds (**5a-f**) and (**7a-f**) were obtained in high yields as pure crystalline products (Table 1).

The assignment of these structures was made on the basis of IR, ^{1}H NMR and UV spectral data. The UV spectra of *N*-alkylated quinolin-4-ones (**5a-f**) indicated the presence of absorption bands in the area of 233-350 nm. One of these bands with the maximum at 325 nm, which is characteristic of quinolones, is almost unaffected by different substituents R1, R2 and Ar. Compounds (**7a-f**) representing another chromophore system reveal a different UV absorption pattern. For these compounds, additional conjugation leads to longer wavelength characteristic absorption resulting in the bright yellow color with a maximum at 400 nm. The nature of substituents influences UV absorption in the long-wave area. Thus, electron donating R1 substituents of the quinoline ring cause a hypsochromic shift, while introduction of electron donating substituents in the aryl fragment results in the opposite bathochromic effect.

^{1}H NMR spectra of compounds (**5a-f**) and (**7a-f**) showed characteristic signals from protons of the 1*H*-quinolin-4-one and 5*H*-pyrazolo[4,3-*c*]quinoline heterocycles in the range of δ 7.0 – 10.0. The transformation of **5a-f** into **7a-f** is accompanied by a downfield shift of these protons which is related to

π–electron deficient nature of pyrazole ring. This shift (Δδ = 1.10 - 1.65 ppm) is particularly clear for the proton at C2 of the quinoline ring observed as a singlet in the range of 8.42 – 8.63 and 9.60 – 10.07 for **5a-f** and **7a-f**, respectively.



i: *i*-PrOH, reflux, 40 min; **ii**: reflux, 50 min; **iii**: R2-Cl, DMF, NaH, 70°C, 4 h;
iv: $N_2H_4 \cdot H_2O$, AcOH, reflux, 3.5 h.

Scheme 2

IR spectra of compounds (**5a-f**) and (**7a-f**) revealed the presence of absorption bands consistent with the assigned structures. The transformation of quinolin-4-ones (**5a-f**) into **7a-f** can be confirmed by the disappearance of absorption bands from carbonyl groups in the IR spectra characteristic of quinolin-4-ones (**5a-f**).

CONCLUSIONS

We have developed an efficient synthetic approach to novel substituted 5*H*-pyrazolo[4,3-*c*]quinoline derivatives featuring hydrazine-mediated cyclization of 3-aroyl-1*H*-quinolin-4-ones as the key step to assemble the pyrazolo[4,3-*c*]quinoline heterocyclic system. Considering the availability of initial reactants, convenient synthesis and isolation of products, and the overall excellent chemical yields of these transformations, this route provides a valuable synthetic approach to variously substituted pyrazolo[4,3-*c*]quinolines.

Table 1. Yields and melting points of the synthesized compounds.

Product	Ar	R1	R2	Yield, % last reaction/overall	mp, °C
5a	Ph	6-Me	Bn	90/57	223-224
5b	Ph	5,7-diOMe	Bn	92/43	205-206
5c	4-(OMe)C_6H_4	6-OMe	Bn	91/55	178-179
5d	4-(OMe)C_6H_4	6-Me	Bn	87/53	224-225
5e	1,3-benzodioxol-5-yl	H	Bn	88/42	194-195
5f	Ph	H	Me	92/65	219-220
5g	Ph	H	Et	85/62	116-117
7a	Ph	8-Me	Bn	80/45	233-234
7b	Ph	7,9-diOMe	Bn	93/40	177-178
7c	4-(OMe)C_6H_4	8-OMe	Bn	97/50	204-205
7d	4-(OMe)C_6H_4	8-Me	Bn	83/41	157-158
7e	1,3-benzodioxol-5-yl	H	Bn	78/35	212-213
7f	Ph	H	Me	80/50	256-257
7g	Ph	H	Et	75/41	243-244

EXPERIMENTAL

General Information. Melting points were measured on Koeffler melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H NMR spectra were recorded on Bruker-200 (200 MHz) spectrometer in DMSO-d_6 using TMS as an internal standard, the chemical shifts are given in δ units (ppm). UV absorption spectra were recorded on Specord M-40 spectrophotometer in *i*-PrOH in the area of 208 - 500 nm (λ (nm) (ε·10^{-3} (l/(mol·cm))). IR spectra were recorded on Specord M80 spectrometer in the area of 400 – 4000 cm^{-1} in KBr pellets. Elementary analyses were performed at Analytical Laboratory of the Institute of Single Crystals (Ukrainian Academy of Sciences). Substituted 3-aroyl-1*H*-quinolin-4-ones (**4**) were prepared from the corresponding ethoxymethylenearoylacetates (**1**) and substituted anilines (**2**) using a previously described approach.[14]

General Procedure for Synthesis of Substituted 1*H*-quinolin-4-ones (**5a-g**).

Sodium hydride (60% dispersion in mineral oil) (208 mg, 5.2 mmol) was added to a solution of the corresponding 3-aroyl-1*H*-quinolin-4-one (**4**) (4 mmol) in anhydrous DMF (15 mL) and the mixture was stirred at rt for 30 min. Then the reaction mixture was heated to 40ºC and the corresponding chloride R2-Cl

(5.2 mmol) was slowly added. The resulting mixture was stirred for 4 h at 70ºC, cooled to rt and diluted with water (45 mL). The formed precipitate was filtered off, washed with *i*-PrOH and hexane and recrystallized from *i*-PrOH/DMF to afford pure **5a-g** in 85-92% yield. The yields and melting points for **5a-g** are given in Table 1. *3-Benzoyl-1-benzyl-6-methyl-1H-quinolin-4-one* (**5a**): ^{1}H NMR (DMSO-d_6), δ (ppm): 8.61 (s, 1H, H-2), 8.00 (s, 1H, ArH), 7.82-7.74 (m, 2H, ArH), 7.66-7.22 (m, 10H, ArH), 5.64 (s, 2H, CH_2), 2.38 (s, 3H, CH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 237(24.9), 325(13.8); IR (KBr), ν (cm^{-1}): 1638 (C=O); 1607 (C=C). *Anal*. Calcd for $C_{24}H_{19}NO_2$: C 81,56; H 5,42; N 3,96. Found: C 81,32; H 5,28; N 4,05.

3-Benzoyl-1-benzyl-5,7-dimethoxy-1H-quinolin-4-one (**5b**): ^{1}H NMR (DMSO-d_6), δ (ppm): 8.42 (s, 1H, H-2), 7.72 (d, 2H, *J*=7.4 Hz, ArH), 7.62-7.22 (m, 8H, ArH), 6.5 (s, 1H, ArH), 6.44 (s, 1H, ArH), 5.54 (s, 2H, CH_2), 3.73 (s, 6H, 2(OCH_3)); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 239(37.1), 270(40.3), 322(20.0); IR (KBr), ν (cm^{-1}): 1646, 1629 (C=O); 1606 (C=C). *Anal*. Calcd for $C_{25}H_{21}NO_4$: C 75,17; H 5,30; N 3,51. Found: C 75,37; H 5,35; N 3,57.

1-Benzyl-6-methoxy-3-(4-methoxybenzoyl)-1H-quinolin-4-one (**5c**): ^{1}H NMR (DMSO-d_6), δ (ppm): 8.57 (s, 1H, H-2), 7.77 (d, 2H, *J*=8.8 Hz, ArH), 7.70-7.55 (m, 2H, ArH), 7.42-7.15 (m, 6H, ArH), 7.00 (d, 2H, *J*=8.8 Hz, ArH), 5.70 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 233(35.3), 327(19.8); IR (KBr), ν (cm^{-1}): 1648, 1625 shoulder (C=O); 1607 (C=C). *Anal*. Calcd for $C_{25}H_{21}NO_4$: C 75,17; H 5,30; N 3,51. Found: C 75,00; H 5,17; N 3,48.

1-Benzyl-3-(4-methoxybenzoyl)-6-methyl-1H-quinolin-4-one (**5d**): ^{1}H NMR (DMSO-d_6), δ (ppm): 8.63 (s, 1H, H-2), 8.00 (s, 1H, ArH), 7.77 (d, 2H, *J*=8.8 Hz, ArH), 7.62-7.45 (m, 2H, ArH), 7.40-7.17 (m, 5H, ArH), 7.00 (d, 2H, *J*=8.8 Hz, ArH), 5.65 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 231(22.1), 323(14.1); IR (KBr), ν (cm^{-1}): 1639, 1625 (C=O); 1606 (C=C). *Anal*. Calcd for $C_{25}H_{21}NO_3$: C 78,31; H 5,52; N 3,65. Found: C 78,39; H 5,69; N 3,73.

1-Benzyl-3-(1,3-benzodioxol-5-yl)-1H-quinolin-4-one (**5e**): ^{1}H NMR (DMSO-d_6), δ (ppm): 8.62 (s, 1H, H-2), 8.21 (d, 1H, *J*=8.0 Hz, ArH), 7.75-7.60 (m, 2H, ArH), 7.47-7.22 (m, 8H, ArH), 6.98 (d, 1H, *J*=8.2Hz, ArH), 6.12 (s, 2H, CH_2), 5.65 (s, 2H, CH_2); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 235(51.9), 269(10.8), 323(36.7); IR (KBr), ν (cm^{-1}): 1630 (C=O); 1599 (C=C). *Anal*. Calcd for $C_{24}H_{17}NO_4$: C 75,19; H 4,47; N 3,65. Found: C 75,34; H 4,53; N 3,62.

3-Benzoyl-1-methyl-1H-quinolin-4-one (**5f**): ^{1}H NMR (DMSO-d_6), δ (ppm): 8.47 (s, 1H, H-2), 8.20 (d, 1H, *J*=7.9 Hz, ArH), 7.90-7.65 (m, 4H, ArH), 7.62-7.34 (m, 4H, ArH), 3.94 (s, 3H, CH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 239(29.6), 322(20.3); IR (KBr), ν (cm^{-1}): 1639, 1622 (C=O); 1606 (C=C). *Anal*. Calcd for $C_{17}H_{13}NO_2$: C 77,55; H 4,98; N 5,32. Found: C 77,30; H 4,75; N 5,23.

3-Benzoyl-1-ethyl-1H-quinolin-4-one (**5g**): ^{1}H NMR (DMSO-d_6), δ (ppm): 8.50 (s, 1H, H-2), 8.20 (d, 1H, *J*=7.9 Hz, ArH), 7.90-7.65 (m, 4H, ArH), 7.62-7.34 (m, 4H, ArH), 4.42 (q, 2H, *J*=6.7 Hz, CH_2), 1.37 (t, 3H, *J*=6.7 Hz, CH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 239(33.3), 322(20.3); IR (KBr), ν (cm^{-1}): 1639, 1622 (C=O); 1599 (C=C). *Anal*. Calcd for $C_{18}H_{15}NO_2$: C 77,96; H 5,45; N 5,05. Found: C 78,25; H 5,63; N 5,13.

General Procedure for Synthesis of Substituted 5*H*-pyrazolo[4,3-*c*]quinolines (**7a-g**).

30% hydrazine hydrate (500 mL, 3 mmol) was added to a solution of **5a-g** (2 mmol in acetic acid (10 mL), and the resulting mixture was heated under reflux for 3.5 h. The mixture was cooled to rt, and 20% aqueous sodium hydroxide (30 mL) was added. The formed precipitate was filtered off, washed with water and recrystallized from 50% aqueous isopropanol to afford pure **7a-g** in 75-97% yield. The yields and melting points for **7a-g** are given in Table 1.

5-Benzyl-8-methyl-3-phenyl-5H-pyrazolo[4,3-c]quinoline (**7a**): ^{1}H NMR (DMSO-d_6), δ (ppm): 9.80 (s, 1H, H-4), 8.48 (s, 1H, ArH), 8.15 (d, 2H, *J*=7.6 Hz, ArH), 7.87 (d, 1H, *J*=9.2 Hz, ArH), 7.60-7.16 (m, 9H, ArH), 6.10 (s, 2H, CH_2), 2.52 (s, 3H, CH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 270(21.2), 339(6.8), 388(8.9); IR (KBr), ν (cm^{-1}): 1606 (C=C). *Anal*. Calcd for $C_{24}H_{19}N_3$: C 82,49; H 5,48; N 12,03. Found: C 82,36; H 5,30; N 12,08.

5-Benzyl-7,9-dimethoxy-3-phenyl-5H-pyrazolo[4,3-c]quinoline (**7b**): ^{1}H NMR (DMSO-d_6), δ (ppm): 10.07 (s, 1H, H-4), 8.23-8.06 (m, 2H, ArH), 7.66-7.45 (m, 3H, ArH), 7.40-7.24 (m, 5H, ArH), 7.07 (s, 1H, ArH), 7.00 (s, 1H, ArH), 6.20 (s, 2H, CH_2), 4.12 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 240(24.4), 267(21.6), 290(15.8), 345(7.4); IR (KBr), ν (cm^{-1}): 1607 (C=C). *Anal*. Calcd for $C_{25}H_{21}N_3O_2$: C 75,93; H 5,35; N 10,63. Found: C 76,31; H 5,65; N 10,70.

5-Benzyl-8-methoxy-3-(4-methoxybenzoyl)-5H-pyrazolo[4,3-c]quinoline (**7c**): ^{1}H NMR (DMSO-d_6), δ (ppm): 9.70 (s, 1H, H-4), 8.08 (d, 2H, *J*=8.4 Hz, ArH), 8.01 (d, 1H, *J*=2.6 Hz, ArH), 7.90 (d, 2H, *J*=8.8 Hz, ArH), 7.38-7.16 (m, 6H, ArH), 7.02 (d, 2H, *J*=8.4 Hz, ArH), 6.05 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 230(39.7), 266(17.4), 395(6.7); IR (KBr), ν (cm^{-1}): 1610 (C=C). *Anal*. Calcd for $C_{25}H_{21}N_3O_2$: C 75,93; H 5,35; N 10,63. Found: C 75,20; H 5,49; N 10,55.

5-Benzyl-3-(4-methoxyphenyl)-8-methyl-5H-pyrazolo[4,3-c]quinoline (**7d**): ^{1}H NMR (DMSO-d_6), δ (ppm): 9.77 (s, 1H, H-4), 8.44 (s, 1H, ArH), 8.06 (d, 2H, *J*=8.4 Hz, ArH), 7.84 (d, 1H, *J*=8.8 Hz, ArH), 7.52 (d, 1H, *J*=8.8 Hz, ArH), 7.38-7.16 (m, 5H, ArH), 7.06 (d, 2H, *J*=8.4 Hz, ArH), 6.07 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 2.49 (s, 3H, CH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 236(25.0), 265(13.2),

339(4.1), 397(6.0); IR (KBr), ν (cm^{-1}): 1609 (C=C). *Anal*. Calcd for $C_{25}H_{21}N_3O$: C 79,13; H 5,58; N 11,07. Found: C 78,98; H 5,52; N 11,00.

5-Benzyl-3-(1,3-benzodioxol-5-yl)-5H-pyrazolo[4,3-c]quinoline (**7e**): ^{1}H NMR (DMSO-d_6), δ (ppm): 9.80 (s, 1H, H-4), 8.22-8.57 (m, 1H, ArH), 8.00-7.87 (m, 1H, ArH), 7.73-7.57 (m, 4H, ArH), 7.40-7.17 (m, 5H, ArH), 7.05 (d, 1H, *J*=8.4 Hz, ArH), 6.10 (s, 4H, 2(CH_2)); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 228(26.2), 274(15.5), 323(6.3), 400(6.2); IR (KBr), ν (cm^{-1}): 1608 (C=C). *Anal*. Calcd for $C_{24}H_{17}N_3O_2$: C 75,98; H 4,52; N 11,07. Found: C 75,23; H 4,27; N 11,06.

5-Methyl-3-phenyl-5H-pyrazolo[4,3-c]quinoline (**7f**): ^{1}H NMR (DMSO-d_6), δ (ppm): 9.60 (s, 1H, H-4), 8.76-8.58 (m, 1H, ArH), 8.25-7.98 (m, 3H, ArH), 7.88-7.65 (m, 2H, ArH), 7.58-7.30 (m, 3H, ArH), 4.34 (s, 3H, CH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 232(26.4), 274(18.0), 334(5.9), 384(6.8); IR (KBr), ν (cm^{-1}): 1614 (C=C). *Anal*. Calcd for $C_{17}H_{13}N_3$: C 78,74; H 5,05; N 16,20. Found: C 78,65; H 5,03; N 16,30.

5-Ethyl-3-phenyl-5H-pyrazolo[4,3-c]quinoline (**7g**): ^{1}H NMR (DMSO-d_6), 9.60 (s, 1H, H-4), 8.76-8.58 (m, 1H, ArH), 8.25-7.98 (m, 3H, ArH), 7.88-7.65 (m, 2H, ArH), 7.58-7.30 (m, 3H, ArH), 4.85 (q, 2H, *J*=6.7 Hz, CH_2), 1.52 (t, 3H, J=6.7 Hz, CH_3); UV/VIS (*i*-PrOH), λ (nm) (ε·10^{-3} (l/(mol·cm)): 231(27.7), 272(18.2), 334(6.0), 387(6.8); IR (KBr), ν (cm^{-1}): 1613 (C=C). *Anal*. Calcd for $C_{18}H_{15}N_3$: C 79,10; H 5,53; N 15,37. Found: C 79,16; H 5,79; N 15,42.

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