Synthesis of Novel Conformationally Constrained Pyrazolo[4,3-*c*]quinoline Derivatives as Potential Ligands for the Estrogen Receptor

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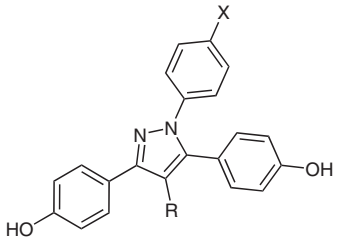
Abstract: The preparation of three novel classes of pyrazolo[4,3-*c*]quinoline derivatives is reported. The easily accessible 2,3-dihydro-1*H*-quinolin-4-ones were used as the starting materials and were functionalized with three different acylating agents affording their respective constrained core substrates. The latter by condensation with phenyl(or 4-methoxyphenyl)hydrazines and subsequent debenzylation or demethylation provided the desired pyrazole derivatives. Some interesting features emerged with respect to the regioselectivity and mechanism of these reactions.

Key words: quinolines, fused ring-systems, acylations, pyrazole, estrogens

Estrogens are known to exert various biological effects via their molecular target, the estrogen receptor (ER). The latter functions as a ligand-activated transcriptional regulator that binds with a wide range of steroidal and non-steroidal ligands.[1] In this context, the high ER affinity synthetic estrogens – especially those of a non-steroidal nature – generally retain the phenolic function of natural estradiol but exhibit tolerance with regard to their structural motifs. Thus, they can encompass either simple acyclic core structures of various lengths and sizes and/or a wide ring-size range of fused or non-fused carbocyclic and heterocyclic systems.[2–4]

An appreciable number of these ligands have been utilized as hormonal agents, exhibiting mixed agonist-antagonist and tissue selective activities that are useful in hormone replacement therapy, fertility regulation, and the prevention or treatment of breast cancer.[5–8] Some of these agents (Selective Estrogen Receptor Modulators, SERMs) display a mixed endocrine profile that is expressed by agonistic or antagonistic activity, depending on the tissue target.[9] The characterization of a second form of estrogen receptor (ERβ subtype), by Gustafsson and coworkers,[10–12] directed research interest towards the synthesis of ligands able to selectively activate or inhibit each of the ER subtypes.

In the course of investigations aimed at developing novel SERMs that possess high affinity and selectivity for an ER subtype, a broad variety of diverse ligands have been considered. Among them, 1,3,5-triaryl-4-alkyl substituted pyrazole derivatives, exemplified by the propylpyrazole triol (PPT, Figure 1), have emerged as particularly interesting targets. The latter was found to possess particularly high ERα-selective binding affinity and potency.[13–15] On the other hand, other research groups have reported that the substitution pattern of the pyrazole derivatives[16] greatly affects their binding affinity to the ERβ.



R = *n*-Pr, X = H
R = *n*-Pr, X = OH (PPT)
R = Et, X = H
R = Et, X = OH

Figure 1 1,3,5-Triaryl-4-alkyl substituted pyrazole derivatives.

We were interested in investigating the ER binding selectivity pattern, and thus envisioned the synthesis of novel fused pyrazolo[4,3-*c*]quinoline derivatives. Recent reports have established that similar ring systems display significant biological activities, such as good affinity and/or selectivity to adenosine, benzodiazepine, and NMDA receptors.[17–19] The rationale to design these molecules is to combine in a single molecule the known pharmacophore quinoline ring with a tetrasubstituted pyrazole ring backbone that inherently displays high affinity and selectivity to the ER. This was achieved through the initial preparation of the 2,3-dihydro-1*H*-quinolin-4-one moiety,[20–22] providing the constrained core substrate for the consecutive construction of the desired substituted pyrazole derivatives. Herein, we describe the substrate-dependent/directed regioselective synthesis of various pyrazolo[4,3-*c*]quinolines, that can act as potential ligands for the estrogen receptor.

1-Benzyl-7-methoxy-2,3-dihydro-1*H*-quinolin-4-one (**3**) was synthesized via condensation of *m*-anisidine with acrylic acid and subsequent acid-promoted ring closure.[20] On the other hand, the condensation of *m*-anisidine with ethylacetoacetate provided the corresponding enamine, which by subsequent hydrogenation furnished compound

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1. The latter was cyclized in a solution of polyphosphonic acid (PPA) to give the corresponding qionolin-4-one **2**, which after benzylation produced the 1-benzyl-7-methoxy-2-methyl-2,3-dihydro-1*H*-quinolin-4-one (compound **4**; Scheme 1).

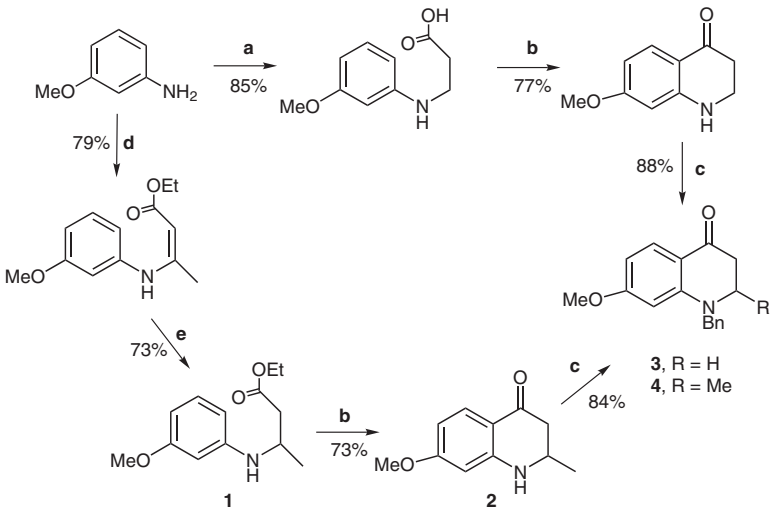
A general route to access the target pyrazole derivatives is via α-acylation of the corresponding quinolinone substrate and the subsequent condensation with a phenylhydrazine derivative. However, the outcome of this acylation reaction depends greatly on the nature of both the quinolinone substrate and the acylating agent.[23] In this context, three distinct pathways were investigated.

The first pathway involves the formylation of quinolinone which afforded the hydroxymethylene quinolin-4-ones **5a** and **5b**. Double condensation of the latter with phenyl (or 4-methoxyphenyl)hydrazine furnished predominantly the pyrazoles **6a–c** (Scheme 2), while only a small amount (2–13%) of the regioisomeric pyrazoles **6d–f** was obtained. The regioselectivity of this condensation may be rationalized considering that the formyl carbons of compounds **5** react predominantly with the most nucleophilic terminal NH_2 of phenylhydrazines to form an imine intermediate. The latter by intramolecular ring closure provided the corresponding quinolinone derivatives.

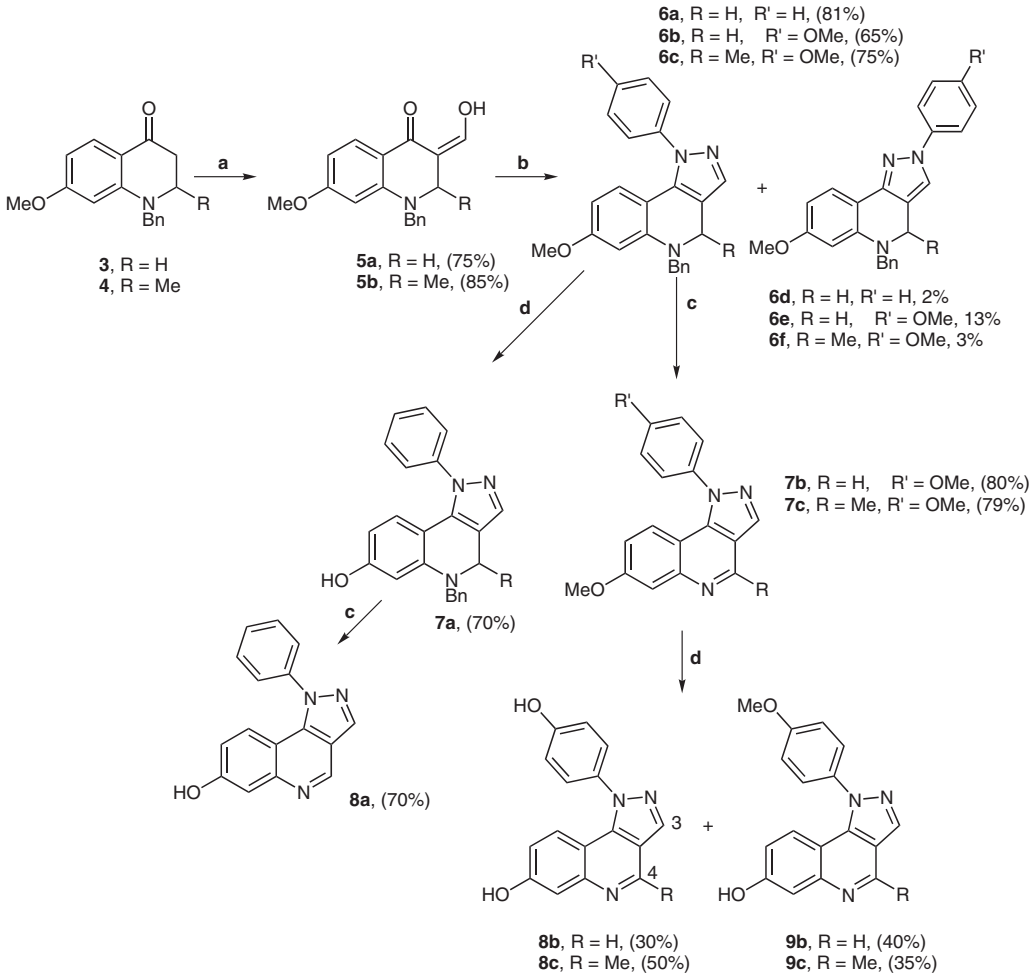
Subsequently, the initial demethylation of quinoline **6a** and the removal of the benzyl protecting group resulted in the aromatization of the molecule to afford the desired pyrazolo[4,3-*c*]quinolinone derivative **8a**. Similar results were obtained by performing the aromatization before the demethylation reaction (pyrazoles **8b**, **8c** and **9b**, **9c**).

The configuration of the pyrazole products was elucidated, through 2D NOE NMR spectroscopy. More specifically, the assigned stereochemistry of compounds **6a–c** is consistent with the observed strong cross peak between H-9 and the phenyl group. On the contrary, for compounds **6d–f** the observed enhancement of the phenyl protons corresponds to H-3. These results were further confirmed by gradient inverse-detected long range ^{1}H-^{15}N correlation experiments. In this regard, for compound **7b** a four-bond correlation was observed between the aromatic proton H-9 (7.36 ppm) and the nitrogen atom that resonates at 198.7 ppm. The latter corresponds to the shielded N-1, which also correlates with the aromatic protons of the *N*-(*p*-methoxyphenyl) ring. It must also be noted that according to the assigned structure the other two nitrogen atoms bear double bonds and resonate at 294.8 and 324.6 ppm.

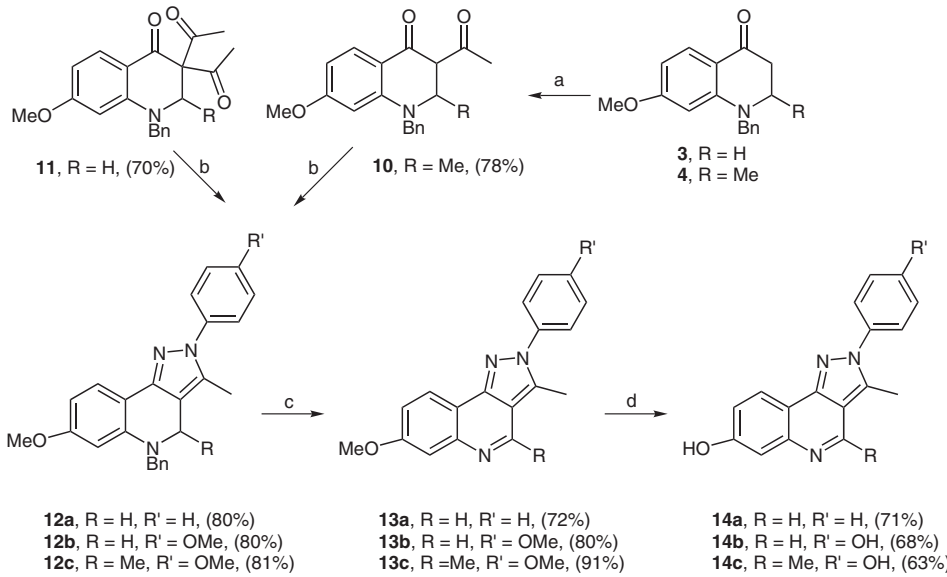
The second pathway involves the reaction of lithium enolates of quinolin-4-ones with pyruvonitrile. More specifically, the reaction of compound **3** furnished exclusively the diacetylation product **11**, presumably because of the increased acidity of its α-hydrogens. However, in the case of the 2-methyl-substituted derivative, it is evident that the presence of a bulky methyl group on the vicinal C-2 hinders the addition of a second acetyl group, leading to the formation of 1,3-diketone **10** as the only product (Scheme 3). In both cases, however, some of the starting material (22–29%) was recovered intact. Finally, the condensation of carbonyl intermediates **10** and **11** with phenylhydrazines led to the exclusive formation of the pyrazole regioisomers **14a–c**, as depicted in Scheme 3. The regioselectivity of compounds **14a–c** was confirmed to be in accordance with the previously described spectroscopy experiments. More specifically, for compound **14a**, 2D NOE showed a strong cross-peak between the pyrazole methyl group and the N-aryl hydrogens, as well as the absence of enhancement with H-9, are indicative of the assigned regiochemistry. This assignment was confirmed by ^{1}H–^{15}N correlation experiments. The aromatic proton H-9 (7.36 ppm) showed a characteristic four-bond correlation with the nitrogen atom that resonates at 290.3 ppm, corresponding to the deshielded N-1 atom bearing a double bond.



Scheme 1 *Reagents and conditions*: (a) acrylic acid (1.5 equiv), toluene, reflux; (b) PPA, 90 °C; (c) K_2CO_3, BnBr, DMF, 60 °C; (d) $CH_3COCH_2CO_2Et$, AcOH; (e) Pd/C, H_2, MeOH.



Scheme 2 *Reagents and conditions*: (a) NaH, HCOOEt, DMF, THF; (b) R′$C_6H_4NHNH_2$·HCl, DMF–THF 3:1, 120 °C; (c) Pd/C, H_2, MeOH or EtOAc–AcOH; (d) BBr_3, CH_2Cl_2, –78 °C.

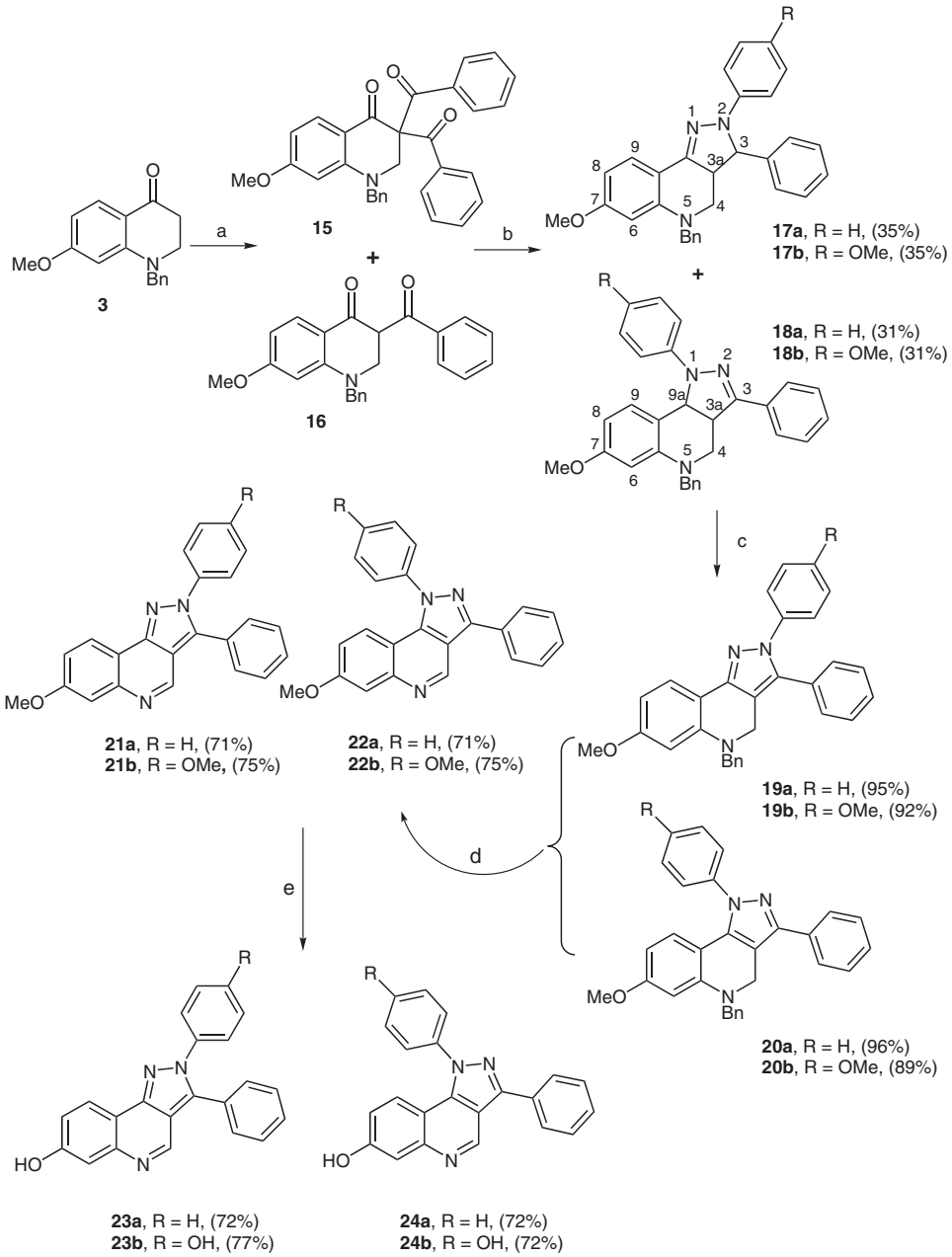


Scheme 3 *Reagents and conditions*: (a) LHMDS, CH_3COCN THF; (b) R′$C_6H_4NHNH_2$·HCl, DMF–THF (3:1), 120 °C; (c) Pd/C, H_2, MeOH or EtOAc; (d) BBr_3, CH_2Cl_2, –78 °C.

The third synthetic route, which is presented in Scheme 4, involves the acylation of the lithium enolate of 1-benzyl-7-methoxy-2,3-dihydro-1*H*-quinolin-4-one (**3**) with benzoyl cyanide to produce an inseparable mixture (Scheme 4) of triketone **15** and 1,3-diketone **16** (**15/16**, 5:1). These derivatives were identified and analyzed after separation by semi-preparative HPLC.

Since the main goal of this synthetic route was the preparation of pyrazole derivatives, a mixture of **15** and **16** was condensed with phenylhydrazine to give a 1:1 mixture of **17a** and its regioiosmer **18a**, which were separated by preparative HPLC. Condensation of the same mixture with 4-methoxyphenylhydrazine produced a similar mixture of compounds **17b** and **18b**. The regioselectivity of compounds **17** and **18** was assigned based on gradient-inverse-detected long-range ^{1}H–^{15}N correlation experiments. For example, for compound **17b** we observed a four bond correlation between the aromatic proton H-9 (6.67 ppm) and the deshielded nitrogen atom N-1 (291.8 ppm), which bears a double bond. On the contrary, for compound **18b**, this four-bond correlation was observed with a shielded nitrogen atom, indicating that N-1 does not bear a double bond.

The manganese dioxide oxidation of these compounds provided in almost quantitative yield the respective pyrazoles **19a**, **19b**, **20a**, **20b**. Finally, debenzylation (aroma-



Scheme 4 *Reagents and conditions*: (a) LHMDS, C_6H_4COCN, THF; (b) $R'C_6H_4NHNH_2 \cdot HCl$, DMF–THF (3:1), 120 °C; (c) MnO_2, benzene, 100 °C; (d) Pd/C, H_2, MeOH or EtOAc; (e) BBr_3, CH_2Cl_2, –78 °C.

tization) and subsequent removal of the methoxy protecting groups produced in good yields the conformationally constrained pyrazoles **23a**, **23b**, **24a**, **24c**. It is noteworthy that the configuration of compounds **23a**, **23b** and **24a**, **24b** were elucidated considering the chemical shift of N-1, since this nitrogen atom correlates (through three or four bonds) with the aromatic proton H-9 or the aromatic protons of the *N*-(phenyl) or the *N*-(*p*-hydroxyphenyl) ring. More specifically, in the case of compounds **23a** and **23b**, the nitrogen atom N-1 is deshielded (297 ppm), presumably because of the attached double bond. On the contrary, in compounds **24a** and **24b** the nitrogen atom (N-1) does not bear a double bond and thus resonates at 209 ppm. The latter configuration assignment is reinforced by the observed correlation between the N-1 and all N-attached phenolic protons.

All anhydrous reactions were carried out under an argon atmosphere. Solvents were dried by distillation prior to use. Starting materials were purchased from Aldrich (analytical reagent grades) and were used without further purification. Analytical TLC was conducted on Merck glass plates coated with silica gel 60 F_{254} and spots were visualized with UV light and/or an alcohol solution of anisaldehyde. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh).

Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^{1}H and 2D NMR spectra were recorded at 400 MHz on a Bruker DRX-400 spectrometer in the indicated solvents. The chemical shifts are reported in ppm with TMS as an internal standard. IR spectra were obtained on a Nicolet Magna 750, series II spectrometer.

HPLC separations were performed using a Hewlett Packard 1100 series instrument with a variable wavelength UV detector coupled to a HP ChemStation utilizing the manufactorer's software package (version 5.01). A Kromasil column with pore size 100 Å, internal diameter of 5 μm, and a C-18 bond phase was used. Compounds **15** and **16** were eluted with H_2O–MeCN (30:70) at a flow rate of 1.6 mL/min. Compounds **17** and **18** were eluted with H_2O–MeCN (50:50) at a flow rate of 3 mL/min.

The ^{1}H–^{15}N GHMQC spectral data were acquired as 3072 × 400 data points with a total of 290 transients accumulated/t_1 increment. Pulse widths were 8.55 μs for ^{1}H and 27.7 μs for the ^{15}N at 0 and –3 dB. The F1 spectral window employed was set from 100–400 ppm. Pulsed field gradients, gt1–gt3, had durations of 0.8 ms. Gradient pairs were optimized as 70:30:50 for ^{15}N spectroscopy.

3-(3-Methoxyphenylamino)butyric Acid Ethyl Ester (1)

3-(3-Methoxyphenylamino)but-2-enoic acid ethyl ester (4.0 g, 17 mmol) was dissolved in MeOH (80 mL) and hydrogenated over 10% Pd/C (0.4 g) at 1 atm for 8 h in the absence of sunlight. The mixture was filtered through celite, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (EtOAc–hexane, 1:1) afforded the title compound as an off-white oil; yield: 2.94 g (73%).

IR (neat): 3230, 1729 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.28 (d, 3 H, *J* = 7.1 Hz, $CHCH_3$), 2.32 (dd, *J* = 14.9, 5.1 Hz, 1 H, $COCHHCHCH_3$), 2.36 (dd, *J* = 14.9, 5.1 Hz, 1 H, $COCHHCHCH_3$), 3.74 (s, 3 H, OCH_3), 3.79 (s, 1 H, NH), 3.81–3.84 (m, 1 H, $CHCH_3$), 4.11 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.00 (d, *J* = 2.2 Hz, 1 H, H-2′), 6.03 (d, *J* = 8.8, 1.4 H, H-6′), 6.30 (dd, *J* = 8.8, 2.2 Hz, 1 H, H-4′), 7.06 (dd, *J* = 8.8, 8.8 Hz, 1 H, H-5′).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.28; H, 7.31; N, 6.60.

7-Methoxy-2-methyl-2,3-dihydro-1*H*-quinolin-4-one (2)

PPA (10 g) was heated to 90 °C with mechanical stirring. Ester **1** (0.5 g, 2.1 mmol) was added in one portion, and the mixture was stirred for 2 h. After cooling to 60 °C, ice (50 g) was added and the reaction mixture was stirred until the reaction was complete (ca. 15 min). Then the product was extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with H_2O (30 mL) and aq NaOH (5%, 15 mL). Then the organic layer was washed with H_2O (20 mL) until the pH of the solution was neutral. The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting brown oil was purified by flash column chromatography (EtOAc–hexane 1:1) to afford the title compound as a yellow solid; yield: 0.29 g (73%); mp 137–138 (dec.).

IR (neat): 3230, 1681 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.21 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 2.49 (dd, *J* = 6.8, 2.9 Hz, 1 H, H-3), 3.02 (dd, *J* = 11.3, 5.9 Hz, 1 H, H-3), 3.43 (m, 1 H, H-2), 3.77 (s, 3 H, OCH_3), 4.25 (s, 1 H, NH), 6.05 (d, *J* = 2.2 Hz, 1 H, H-8), 6.30 (dd, *J* = 8.8, 2.2 Hz, 1 H, H-6), 7.76 (d, *J* = 8.8 Hz, 1 H, H-5).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.89; H, 7.91; N, 5.80.

1-Benzyl-7-methoxy-2,3-dihydro-1*H*-quinolin-4-one (3)[20]

^{1}H NMR ($CDCl_3$): δ = 2.68 (t, *J* = 7.1 Hz, 2 H, H-3), 3.56 (t, *J* = 7.1 Hz, 2 H, H-2), 3.69 (s, 3 H, OCH_3), 4.52 (s, 2 H, NCH_2), 6.09 (d, *J* = 2.5 Hz, 1 H, H-8), 6.32 (dd, *J* = 8.7, 2.5 Hz, 1 H, H-6), 7.23–7.37 (m, 5 H, Ar), 7.87 (d, *J* = 8.7 Hz, 1 H, H-5).

1-Benzyl-7-methoxy-2-methyl-2,3-dihydro-1*H*-quinolin-4-one (4)[20]

^{1}H NMR ($CDCl_3$): δ = 1.21 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 2.49 (dd, *J* = 6.8, 2.9 Hz, 1 H, H-3), 3.02 (dd, *J* = 11.3, 5.9 Hz, 1 H, H-3), 3.68 (s, 3 H, OCH_3), 3.81 (m, 1 H, H-2), 4.35 (d, *J* = 16.5 Hz, 1 H, NC*H*HPh), 4.64 (d, *J* = 16.5 Hz, 1 H, NCH*H*Ph), 6.01 (d, *J* = 2.4 Hz, 1 H, H-8), 6.28 (dd, *J* = 8.8, 2.4 Hz, 1 H, H-6), 7.23–7.37 (m, 5 H, Ph), 7.87 (d, *J* = 8.8 Hz, 1 H, H-5).

Formylation of 2,3-Dihydro-1*H*-quinolin-4-ones; General Procedure

To a stirred solution of NaH (60% dispersion in oil, 1.5 mmol) in anhyd DMF (4 mL) under a N_2 atmosphere, was added a solution of the corresponding quinolinone (1.5 mmol) in anhyd THF (8 mL) dropwise. After stirring for 4 h, HCOOEt (1.64 mmol) was added, and the mixture was stirred for an additional 4 h. A sat. solution of NH_4Cl (10 mL) was added to quench the reaction and the product was extracted with EtOAc (2 × 20 mL). The combined organic layers were concentrated under vacuum; the resulting orange solid was purified by flash chromatography (EtOAc–hexane, 4:1) and recrystallized (Et_2O) to furnish the desired product.

***N*-Benzyl-3-hydroxymethylene-7-methoxy-2,3-dihydro-1*H*-quinolin-4-one (5a)**

Quinolinone **3** (2.0 g, 7.5 mmol) was reacted according to the general procedure to afford **5a** as a yellow solid; yield: 1.65 g (75%); mp 187–189 (dec.).

IR (neat): 3487, 1679 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.71 (s, 3 H, OCH_3), 4.09 (s, 2 H, H-2), 4.48 (s, 2 H, NCH_2), 6.09 (d, *J* = 2.5 Hz, 1 H, H-8), 6.33 (dd, *J* = 8.7, 2.5 Hz, 1 H, H-6), 7.25–7.37 (m, 5 H, Ph), 7.72 (s, 1 H, C=CH), 7.83 (d, *J* = 8.7 Hz, 1 H, H-5), 14.70 (br s, 1 H, OH).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.44; H, 5.91; N, 4.59.

1-Benzyl-3-hydroxymethylene-7-methoxy-2-methyl-2,3-dihydro-1*H*-quinolin-4-one (5b)

Quinolinone **4** (2 g, 7.11 mmol) was reacted according to the general procedure to afford **5b** as a light-yellow crystalline solid; yield: 1.87 g (85%); mp 178–180 (dec.).

IR (neat): 3415, 1672 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.27 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$), 3.69 (s, 3 H, OCH_3), 4.20 (q, *J* = 6.3 Hz, 1 H, H-2), 4.38 (d, *J* = 16.0 Hz, 1 H, NC*H*H), 4.51 (d, *J* = 16.0 Hz, 1 H, NCH*H*), 6.02 (d, *J* = 1.9 Hz, 1 H, H-8), 6.33 (dd, *J* = 9, 1.9 Hz, 1 H, H-6), 7.28–7.37 (m, 5 H, Ph), 7.81 (d, *J* = 9.0 Hz, 1 H, H-5), 7.98 (s, 1 H, C=CH), 14.75 (br s, 1 H, OH).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.64; H, 6.06; N, 4.67.

Acylation of Quinolin-4-ones; General Procedure

A solution of the appropriate 2,3-dihydro-1*H*-quinolin-4-one (0.71 mmol) in THF (10 mL) was added dropwise to a stirred solution of LHMDS (1 M, THF; 0.71 mmol) over a period of 30 min. The resulting solution was stirred for a further 15 min prior to the addition of a solution of the acylating agent (0.71 mmol) in THF (2 mL). The reaction mixture was stirred for 30 min, quenched with a solution of NH_4Cl (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic solvents were dried over $MgSO_4$, concentrated under vacuum, and the residue was purified by chromatography.

3-Acetyl-1-benzyl-7-methoxy-2,3-dihydro-1*H*-quinolin-4-one (10)

Column chromatography (EtOAc–hexanes, 1:4) gave unreacted quinolinone **4** (22%) and, after recrystalization (Et_2O), the desired diketone **10** as a yellowish solid; yield: 0.18 g (78%); mp 113–114 (dec.).

IR (neat): 1703, 1695 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.27 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.98 (s, 3 H, $COCH_3$), 3.69 (s, 3 H, OCH_3), 4.28 (q, *J* = 7.1 Hz, 1 H, H-4), 4.34 (d, *J* = 15.3 Hz, 1 H, NCH_2), 4.65 (d, *J* = 15.3 Hz, 1 H, NCH_2), 4.78 (d, *J* = 7.1 Hz, 1 H, H-3), 5.99 (d, *J* = 2.2 Hz, 1 H, H-8), 6.31 (dd, *J* = 8.8, 2.2 Hz, 1 H, H-6), 7.24–7.27 (m, 1 H, Ph), 7.30–7.36 (m, 4 H, Ph), 7.79 (d, *J* = 8.8 Hz, 1 H, H-5).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.11; H, 6.69; N, 4.41.

3,3-Diacetyl-1-benzyl-7-methoxy-2,3-dihydro-1*H*-quinolin-4-one (11)

Column chromatography (EtOAc–hexanes, 1:4) gave unreacted quinolinone **3** (29%) and, after recrystalization (Et_2O), the desired triketone **11** as a yellowish solid; yield: 0.29 g (70%); mp 97–98 (dec.).

IR (neat): 1700 (br), 1693 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.22 (s, 3 H, $COCH_3$), 2.85 (s, 3 H, $COCH_3$), 3.44 (s, 2 H, H-2), 3.80 (s, 3 H, OCH_3), 4.39 (d, *J* = 16.1 Hz, 1 H, NHHPh), 4.56 (d, *J* = 16.1 Hz, 1 H, NHHPh), 6.71 (d, *J* = 2.1 Hz, 1 H, H-8), 7.01 (dd, *J* = 8.5, 2.1 Hz, 1 H, H-6), 7.32–7.40 (m, 5 H, Ph), 7.70 (d, *J* = 8.5 Hz, 1 H, H-5).

Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.65; H, 5.85; N, 4.15.

3,3-Dibenzoyl-1-benzyl-7-methoxy-2,3-dihydro-1*H*-quinolin-4-one (15) and 3-Benzoyl-1-benzyl-7-methoxy-2,3-dihydro-1*H*-quinolin-4-one (16)

Column chromatography (EtOAc–hexanes, 1:4) gave unreacted quinolinone **3** (15%) and an inseparable mixture of triketone **15** and diketone **16** (0.29 g), which were separated by semi-preparative HPLC.

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IR (neat): 1694 (br) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 4.25 (s, 2 H, H-2), 4.43 (s, 2 H, NCH_2), 6.09 (d, *J* = 2.1 Hz, 1 H, H-8), 6.39 (dd, *J* = 8.5, 1.7 Hz, 1 H, H-6), 7.25–7.39 (m, 12 H, Ph), 7.47 (t, *J* = 8.7 Hz, 1 H, Ph), 7.89 (t, *J* = 8.7 Hz, 1 H, Ph), 7.92 (d, *J* = 8.5 Hz, 1 H, H-5), 8.01 (d, *J* = 8.2 Hz, 1 H, Ph).

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^1H NMR ($CDCl_3$): δ = 3.71 (m, 1 H, H-2), 3.72 (m, 1 H, H-2), 3.78 (s, 3 H, OCH_3), 4.12 (t, *J* = 2.1 Hz, 1 H, H-3), 4.43 (s, 2 H, CH_2N), 6.09 (d, *J* = 2.1 Hz, 1 H, H-8), 6.39 (dd, *J* = 8.5, 1.7 Hz, 1 H, H-6), 7.25–7.39 (m, 8 H, Ar), 7.55 (t, 1 H, *J* = 8.7 Hz, Ar), 7.91 (t, 1 H, *J* = 8.7 Hz, Ar), 8.42 (d, *J* = 8.5 Hz, 1 H, Ar).

Pyrazole Synthesis; General Procedure

To a solution of the appropriate quinolin-4-one substrate (1.0 mmol; keto, diketo, or hydroxymethylene derivative) in DMF (30 mL) and THF (10 mL) was added the appropriate phenylhydrazine hydrochloride (3–5 equiv). The mixture was heated at reflux (oil bath temperature 120 °C) until the starting material had disappeared (TLC analysis). The reaction mixture was then allowed to cool to r.t. and diluted with H_2O (30 mL). The product was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with a sat. solution of LiCl (25 mL), a sat. solution of $NaHCO_3$ (25 mL), and brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product as an oil, which was purified by flash chromatography or by filtration through a short plug of silica gel (EtOAc–hexanes).

5-Benzyl-7-methoxy-1-phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (6a)

Quinolinone **5a** and phenylhydrazine hydrochloride were reacted according to the general procedure. Flash chromatography (EtOAc–hexanes, 1:4) gave **6a** as an amorphous yellow solid; yield: 0.37 g (81%); mp 124–125 (dec.).

^1H NMR ($CDCl_3$): δ = 3.63 (s, 3 H, OCH_3), 4.47 (s, 2 H, H-2), 4.53 (s, 2 H, NCH_2), 6.01 (dd, *J* = 8.7, 2.3 Hz, 1 H, H-8), 6.22 (d, *J* = 2.3 Hz, 1 H, H-6), 6.67 (d, *J* = 8.7 Hz, 1 H, H-9), 7.23–7.27 (m, 2 H, Ph), 7.34 (m, 3 H, Ph), 7.42 (s, 1 H, H-3), 7.45–7.52 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 53.3 (C-4), 57.1 (OCH_3), 62.9 (NCH_2), 97.2 (C-6), 105.2 (C-8), 115.8, 117.9, 119.3, 123.6, 125.5, 129.2 (C-9), 132.2, 137.8, 144.4 (C=N), 146.3, 172.2 (C-7).

Anal. Calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44. Found: C, 78.32; H, 5.87; N, 11.27.

5-Benzyl-7-methoxy-1-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (6b) and 5-Benzyl-7-methoxy-2-(4-methoxyphenyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*] quinoline (6e)

Quinolinone **5a** and 4-methoxyphenylhydrazine hydrochloride were reacted according to the general procedure. Flash chromatography (EtOAc–hexanes, 1:4) gave **6b** and **6e** as amorphous yellow solids.

6b

Yield: 65%.

^1H NMR ($CDCl_3$): δ = 3.66 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.53 (s, 2 H, H-4), 4.57 (s, 2 H, NCH_2), 6.06 (dd, *J* = 8.8, 2.4 Hz, 1

H, H-8), 6.26 (d, *J* = 2.4 Hz, 1 H, H-6), 6.70 (d, *J* = 8.3 Hz, 2 H, Ph), 7.03 (d, *J* = 8.8 Hz, 1 H, H-9), 7.35–7.38 (m, 3 H, Ph), 7.41–7.44 (m, 4 H, Ph), 7.45 (s, 1 H, H-3).

^{13}C NMR ($CDCl_3$): δ = 53.9 (C-4), 57.3 (OCH_3), 58.1 (OCH_3), 62.9 (NCH_2), 97.9 (C-6), 105.2 (C-8), 115.8, 117.9 (C=C), 118.1, 119.2, 123.6, 126.5, 130.2 (C-9), 132.2, 136.8, 145.1 (C=N), 146.3, 161.2 (*C*OCH_3), 170.1 (C-7).

Anal. Calcd for $C_{25}H_{23}N_3O_2$: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.72; H, 5.97; N 10.47.

6e

Yield: 13%.

^{1}H NMR ($CDCl_3$): δ = 3.68 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.49 (s, 2 H, H-4), 4.59 (s, 2 H, NCH_2), 6.26 (d, *J* = 2.1 Hz, 1 H, H-6), 6.36 (dd, *J* = 8.8, 2.1 Hz, 1 H, H-8), 6.98 (d, *J* = 8.3 Hz, 1 H, H-9), 7.13 (d, *J* = 8.3 Hz, 2 H, Ph) 7.32–7.37 (m, 5 H, Ph), 7.53 (s, 1 H, H-3), 7.63 (d, *J* = 8.3 Hz, 2 H, Ph).

Anal. Calcd for $C_{25}H_{23}N_3O_2$: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.37; H, 5.96; N, 10.35.

5-Benzyl-7-methoxy-1-(4-methoxyphenyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (6c)

Quinolinone **5b** and 4-methoxyphenylhydrazine hydrochloride were reacted according to the general procedure. Flash chromatography (EtOAc–hexanes, 3:7) gave **6c** as an amorphous yellow solid; yield: 90 mg (75%).

^{1}H NMR ($CDCl_3$): δ = 1.27 (d, *J* = 6.2 Hz, 3 H, CHC*H*$_3$), 3.59 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.51 (d, *J* = 16.1 Hz, 1 H, NCH*H*), 4.68 (d, *J* = 16.1 Hz, 1 H, NC*H*H), 4.85 (q, *J* = 6.2 Hz, 1 H, H-4), 6.03 (dd, *J* = 8.8, 2.3 Hz, 1 H, H-8), 6.19 (d, *J* = 2.3 Hz, 1 H, H-6), 6.67 (d, *J* = 8.8 Hz, 1 H, H-9), 7.09 (d, *J* = 9.1 Hz, 2 H, Ph), 7.24 (t, *J* = 7.3 Hz, 1 H, Ph), 7.31–7.41 (m, 6 H, Ph), 7.43 (s, 1 H, H-3).

^{13}C NMR ($CDCl_3$): δ = 23.1 (C*C*H_3), 52.9 (C-4), 56.2 (OCH_3), 56.9 (OCH_3), 59.9 (NCH_2), 98.4 (C-6), 105.2 (C-8), 115.1, 117.9 (*C*=C), 120.1, 125.5, 127.4, 128.5, 130.2 (C-9), 132.2, 136.8, 142.3 (C=N), 146.3, 163.1 (*C*OCH_3), 166.1 (C-7).

Anal. Calcd for $C_{26}H_{25}N_3O_2$: C, 75.89; H, 6.12; N, 10.21. Found: C, 75.75; H, 5.94; N, 10.07.

5-Benzyl-7-methoxy-3-methyl-2-phenyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (12a)

Quinolinone **11** and phenylhydrazine hydrochloride were reacted according to the general procedure. Flash chromatography (EtOAc–hexanes, 1:4) gave **12a** as an amorphous yellow solid; yield: 0.14 g (80%); mp 139–142 (dec.).

^{1}H NMR ($CDCl_3$): δ = 2.19 (s, 3 H, CH_3) 3.63 (s, 3 H, OCH_3), 4.47 (s, 2 H, H-4), 4.53 (s, 2 H, CH_2N), 5.97 (dd, *J* = 8.4, 2.1 Hz, 1 H, H-8), 6.19 (d, *J* = 2.1 Hz, 1 H, H-6), 6.63 (d, *J* = 8.4 Hz, 1 H, H-9), 7.28–7.35 (m, 5 H, Ph), 7.44–7.51 (m, 5 H, Ph).

Anal. Calcd for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.00; N, 11.02. Found: C, 78.92; H, 5.85; N, 11.17.

5-Benzyl-7-methoxy-2-(4-methoxyphenyl)-3-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (12b)

Quinolinone **11** and 4-methoxyphenylhydrazine hydrochloride were reacted according to the general procedure. Flash chromatography (EtOAc–hexanes, 1:4) gave **12b** as an amorphous yellow solid; yield: (80%).

^{1}H NMR ($CDCl_3$): δ = 2.22 (s, 3 H, CH_3) 3.64 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.43 (s, 2 H, H-4), 4.55 (s, 2 H, NCH_2), 6.02 (dd, *J* = 8.3, 2.1 Hz, 1 H, H-8), 6.19 (d, *J* = 2.1 Hz, 1 H, H-6), 6.71 (d, *J* = 8.3 Hz, 1 H, H-9), 6.85 (d, *J* = 8.2 Hz, 2 H, Ph), 7.29–7.34 (m, 2 H, Ph), 7.44–7.51 (m, 5 H, Ph).

Anal. Calcd for $C_{26}H_{25}N_3O_2$: C, 75.89; H, 6.12; N, 10.21. Found: C, 75.75; H, 6.02; N, 10.39.

5-Benzyl-7-methoxy-2-(4-methoxyphenyl)-3,4-dimethyl-4,5-dihydro-2*H*-pyrazolo [4,3-*c*]quinoline (12c)

Quinolinone **10** and 4-methoxyphenylhydrazine hydrochloride were reacted according to the general procedure. Flash chromatography (EtOAc–hexanes, 1:4) gave **12c** as an amorphous yellow solid; yield: 81%; mp 177–179 (dec.).

^{1}H NMR ($CDCl_3$): δ = 1.27 (d, *J* = 6.2 Hz, 3 H, CH_3), 2.88 (s, 3 H, CH_3), 3.54 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.36 (d, *J* = 15.8 Hz, 1 H, NCH*H*), 4.52–4.58 (m, 2 H, NC*H*H, H-4), 5.95 (dd, *J* = 8.5, 2.3 Hz, 1 H, H-8), 6.07 (d, *J* = 2.3 Hz, 1 H, H-6), 6.62 (d, *J* = 8.8 Hz, 1 H, H-9), 6.90 (d, *J* = 9.1 Hz, 2 H, Ph), 7.18 (d, *J* = 9.1 Hz, 2 H, Ph), 7.22–7.33 (m, 5 H, Ph).

Anal. Calcd for $C_{27}H_{27}N_3O_2$: C, 76.21; H, 6.40; N, 9.87. Found: C, 76.09; H, 6.54; N, 10.03.

5-Benzyl-7-methoxy-2,3-diphenyl-3,3a,4,5-tetrahydro-2*H*-pyrazolo[4,3-*c*]quinoline (17a) and 5-Benzyl-7-methoxy-1,3-diphenyl-3a,4,5,9a-tetrahydro-1*H*-pyrazolo[4,3-*c*]quinoline (18a)

A mixture of triketone **15** and diketone **16** (0.28 g), and phenylhydrazine hydrochloride (0.34 g, 2.2 mmol) were reacted according to the general procedure. Preparative HPLC (H_2O–MeCN, 1:1) gave **17a** and **18a** as yellow amorphous solids.

17a

Yield: 90 mg (35%); t_R 14.7 min.

^{1}H NMR ($CDCl_3$): δ = 3.62 (s, 3 H, OCH_3), 3.65–3.68 (m, 1 H, H-4), 3.78–3.81 (m, 1 H, H-4), 3.95 (ddd, *J* = 3.1 Hz, 1 H, H-3$_a$), 4.78 (d, *J* = 16.7 Hz, 1 H, NCH_2), 4.87 (d, *J* = 16.7 Hz, 1 H, NCH_2), 5.36 (d, *J* = 3.1 Hz, 1 H, H-3), 5.97 (dd, *J* = 8.2, 2.2 Hz, 1 H, H-8), 6.19 (d, *J* = 2.2 Hz, 1 H, H-6), 6.67 (d, *J* = 8.8 Hz, 1 H, H-9), 7.26–7.33 (m, 5 H, Ph), 7.36–7.39 (m, 3 H, Ph), 7.43–7.49 (m, 3 H, Ph), 7.54 (d, *J* = 7.0 Hz, 2 H, Ph), 7.74 (d, *J* = 7.0 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 45.6 (C-3$_a$), 52.9 (C-4), 54.3 (C-3), 58.5 (OCH_3), 59.9 (NCH_2), 98.4 (C-6), 105.2 (C-8), 110.2, 112.4, 116.1, 126.9, 127.4, 128.1, 128.5, 129.5, 132.2, 134.1 (C-9), 136.8, 144.2, 146.3, 153.4 (C=N), 169.2 (C-7).

^{1}H–^{15}N NMR ($CDCl_3$): δ = 292.3 (N-1), 194.2 (N-2), 322.6 (N-5).

Anal. Calcd for $C_{30}H_{27}N_3O$: C, 80.87; H, 6.11; N, 9.43. Found: C, 81.05; H, 6.24; N, 9.32.

18a

Yield: 90 mg (35%); t_R 19.9 min.

^{1}H NMR ($CDCl_3$): δ = 3.61–3.65 (m, 1 H, H-4), 3.67–3.70 (m, 4 H, OCH_3, H-4), 3.92 (q, *J* = 7.0 Hz, 1 H, H-3$_a$), 4.63 (d, *J* = 8.3 Hz, 1 H, H-9$_a$), 4.75 (d, *J* = 14.9 Hz, 1 H, NCH*H*), 4.87 (d, *J* = 14.9 Hz, 1 H, NC*H*H), 6.08 (dd, *J* = 8.3, 2.2 Hz, 1 H, H-8), 6.38 (d, *J* = 2.2 Hz, 1 H, H-6), 6.75 (d, *J* = 8.8 Hz, 1 H, H-9), 7.26–7.31 (m, 4 H, Ph), 7.34–7.38 (m, 2 H, Ph), 7.42–7.48 (m, 5 H, Ph), 7.51–7.58 (m, 4 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 48.6 (C-9$_a$), 52.9 (C-4), 58.5 (OCH_3), 63.2 (NCH_2), 97.9 (C-6), 105.2 (C-8), 110.2, 112.4, 116.1, 126.9, 127.4, 128.1, 128.5, 129.5, 130.1, 132.9, 133.8 (C-9), 138.4, 145.4, 146.8, 154.9 (C-3), 162.5 (C-7).

^{1}H–^{15}N NMR (acetone-d_6): δ = 197.7 (N-1), 295.5 (N-2), 323.4 (N-5).

Anal. Calcd for $C_{30}H_{27}N_3O$: C, 80.87; H, 6.11; N, 9.43. Found: C, 81.01; H, 6.22; N, 9.29.

5-Benzyl-7-methoxy-2-(4-methoxyphenyl)-3-phenyl-3,3a,4,5-tetrahydro-2*H*-pyrazolo[4,3-*c*]quinoline (17b) and 5-Benzyl-7-methoxy-1-(4-methoxyphenyl)-3-phenyl-3a,4,5,9a-tetrahydro-1*H*-pyrazolo[4,3-*c*]quinoline (18b)

A mixture of triketone **15**, diketone **16**, and 4-methoxyphenylhydrazine hydrochloride were reacted according to the general procedure. Preparative HPLC (H_2O–MeCN, 1:1) gave **17b** and **18b** as yellow amorphous solids.

17b

Yield: (31%); t_R13.7 min.

^{1}H NMR ($CDCl_3$): δ = 3.63 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.66–3.69 (m, 1 H, H-4), 3.79–3.81 (m, 1 H, H-4), 3.96 (m, 1 H, H-3_a), 4.81 (d, *J* = 16.7 Hz, 1 H, NCH*H*), 4.89 (d, *J* = 16.7 Hz, 1 H, NC*H*H), 5.36 (d, *J* = 3.1 Hz, 1 H, H-3), 5.99 (dd, *J* = 8.2, 2.2 Hz, 1 H, H-8), 6.28 (d, *J* = 2.2 Hz, 1 H, H-6), 6.67 (d, *J* = 8.8 Hz, 1 H, H-9), 7.26–7.31 (m, 5 H, Ph), 7.33–7.39 (m, 3 H, Ph), 7.43–7.49 (m, 2 H, Ph), 7.57 (d, *J* = 7.0 Hz, 2 H, Ph), 7.76 (d, *J* = 7.0 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 45.6 (C-3_a), 52.9 (C-4), 54.3 (C-3), 57.6 (OCH_3), 57.9 (OCH_3), 61.3 (NCH_2), 100.1 (C-6), 105.2 (C-8), 110.2, 113.7, 115.3, 127.4, 128.7, 129.2, 129.8, 132.2, 132.7 (C-9), 136.8, 144.2, 145.6, 151.9 (*C*OCH_3), 157.9 (C=N), 170.1 (C-7).

^{1}H–^{15}N NMR ($CDCl_3$): δ = 291.8 (N-1), 193.1 (N-2), 322.2 (N-5).

Anal. Calcd for $C_{31}H_{29}N_3O_2$: C, 78.29; H, 6.15; N, 8.84. Found: C, 78.49; H, 6.29; N, 8.99

18b

Yield: 31%; t_R 19.1 min.

^{1}H NMR ($CDCl_3$): δ = 3.61–3.68 (m, 1 H, H-4), 3.67–3.70 (m, 4 H, OCH_3, H-4), 3.72 (s, 3 H, OCH_3) 3.96 (q, *J* = 7.0 Hz, 1 H, H-3_a), 4.69 (d, *J* = 8.3 Hz, 1 H, H-9_a), 4.77 (d, *J* = 14.9 Hz, 1 H, NCH*H*), 4.87 (d, *J* = 14.9 Hz, 1 H, NC*H*H), 6.12 (dd, *J* = 8.3, 2.2 Hz, 1 H, H-8), 6.37 (d, *J* = 2.2 Hz, 1 H, H-6), 6.76 (d, *J* = 8.8 Hz, 1 H, H-9), 7.26–7.31 (m, 4 H, Ph), 7.34–7.38 (m, 2 H, Ph), 7.42–7.48 (m, 4 H, Ph), 7.63 (d, *J* = 7.3 Hz, 2 H, Ph), 7.83 (d, *J* = 7.3 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 46.4 (C-3_a), 48.9 (C-9_a), 54.4 (C-4), 57.6 (OCH_3), 57.9 (OCH_3), 61.3 (NCH_2), 100.1 (C-6), 105.2 (C-8), 110.2, 113.7, 115.8, 127.8, 128.7, 129.2, 129.8, 130.7 (C-9), 132.2, 138.4, 144.9, 151.2 (*C*OCH_3), 155.6 (C-3), 162.3 (C-7).

^{1}H–^{15}N NMR ($CDCl_3$): δ = 198.2 (N-1), 296.5 (N-2), 325.9 (N-5).

Anal. Calcd for $C_{31}H_{29}N_3O_2$: C, 78.29; H, 6.15; N, 8.84. Found: C, 78.12; H, 6.29; N, 9.02.

Oxidation; General Procedure

To a stirred solution of tetrahydro-2*H*-pyrazolo[4,3-*c*]quinoline (0.45 mmol) in anhyd benzene (25 mL) was added MnO_2 (0.51 g, 5.85 mmol). A Dean–Stark trap was attached, the solution was heated to 100 °C for 2 h, cooled to r.t., filtered through celite, and concentrated. The crude product was purified by chromatography (EtOAc–hexanes, 1:4) to afford the desired pyrazole derivatives.

5-Benzyl-7-methoxy-2,3-diphenyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (19a)

Quinoline **17a** was oxidized according to the general procedure to give **19a** as an amorphous yellow solid; yield: 0.19 g (95%).

^{1}H NMR ($CDCl_3$): δ = 3.62 (s, 3 H, OCH_3), 4.23 (s, 2 H, H-4), 4.72 (d, *J* = 16.7 Hz, 1 H, NCH*H*), 4.82 (d, *J* = 16.7 Hz, 1 H, NC*H*H), 6.05 (dd, *J* = 8.7, 2.1 Hz, 1 H, H-8), 6.21 (d, *J* = 2.1 Hz, 1 H, H-6), 6.81 (d, *J* = 8.7 Hz, 1 H, H-9), 7.29–7.34 (m, 4 H, Ph), 7.39–7.43 (m, 4 H, Ph), 7.45 (d, *J* = 7.7 Hz, 2 H, Ph), 7.48–7.56 (m, 3 H, Ph), 7.73 (d, *J* = 7.7 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 44.4 (C-4), 58.5 (OCH_3), 63.9 (NCH_2), 98.4 (C-6), 105.2 (C-8), 110.8, 113.2, 117.6 (C=C), 120.1, 126.5, 127.2, 128.1, 128.6, 129.5, 130.1, 133.1 (C-9), 136.8, 138.9, 144.2 (C-3), 146.3, 157.4 (C=N), 165.2 (C-7).

Anal. Calcd for $C_{30}H_{25}N_3O$: C, 81.24; H, 5.68; N, 9.47. Found: C, 81.02; H, 5.49; N, 9.65.

5-Benzyl-7-methoxy-2-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (19b)

Quinoline **17b** was oxidized according to the general procedure to give **19b** as an amorphous yellow solid; yield: 0.18 g (92%).

^{1}H NMR ($CDCl_3$): δ = 3.62 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 4.23 (s, 2 H, H-4), 4.72 (d, *J* = 16.7 Hz, 1 H, NCH*H*), 4.82 (d, *J* = 16.7 Hz, 1 H, NC*H*H), 5.99 (dd, *J* = 8.7, 2.1 Hz, 1 H, H-8), 6.18 (d, *J* = 2.1 Hz, 1 H, H-6), 6.76 (d, *J* = 8.7 Hz, 1 H, H-9), 6.92 (d, *J* = 7.7 Hz, 2 H, Ph), 7.22 (d, *J* = 7.7 Hz, 2 H, Ph), 7.27–7.33 (m, 4 H, Ph), 7.43–7.52 (m, 3 H, Ph), 7.63–7.72 (m, 3 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 45.5 (C-4), 56.9 (OCH_3), 57.2 (OCH_3), 63.9 (NCH_2), 100.3 (C-6), 106.2 (C-8), 110.8, 113.2, 113.9, 118.1 (C=C), 120.1, 126.5, 128.1, 128.6, 129.5, 130.4 (C-9), 131.7, 137.3, 138.8, 144.9 (C-3), 146.3, 157.4 (C=N), 161.5 (*C*OCH_3), 165.2 (C-7).

Anal. Calcd for $C_{31}H_{27}N_3O_2$: C, 78.62; H, 5.75; N, 8.87. Found: C, 78.82; H, 5.56; N, 8.77.

5-Benzyl-7-methoxy-1,3-diphenyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (20a)

Quinoline **18a** was oxidized according to the general procedure to give **20a** as an amorphous yellow solid; yield: 0.1 g (96%).

^{1}H NMR ($CDCl_3$): δ = 3.63 (s, 3 H, OCH_3), 4.27 (s, 2 H, H-4), 4.74 (s, 2 H, NCH_2), 6.04 (dd, 1 H, *J* = 8.8, 2.2 Hz, H-8), 6.20 (d, 1 H, *J* = 2.2 Hz, H-6), 6.77 (d, 1 H, *J* = 8.8 Hz, H-9), 7.29–7.41 (m, 8 H, Ph), 7.44–7.56 (m, 3 H, Ph), 7.59 (d, *J* = 7.2 Hz, 2 H, Ph), 7.73 (d, *J* = 7.2 Hz, 2 H, Ph).

Anal. Calcd for $C_{30}H_{25}N_3O$: C, 81.24; H, 5.68; N, 9.47. Found: C, 80.99; H, 5.54; N, 9.65.

5-Benzyl-7-methoxy-1-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (20b)

Quinoline **18b** was oxidized according to the general procedure to give **20b** as an amorphous yellow solid; yield: 0.16 g (89%).

^{1}H NMR ($CDCl_3$): δ = 3.62 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 4.19 (s, 2 H, H-4), 4.69 (d, *J* = 16.7 Hz, 1 H, NCH*H*), 4.78 (d, *J* = 16.7 Hz, 1 H, NC*H*H), 6.07 (dd, *J* = 8.7, 2.1 Hz, 1 H, H-8), 6.22 (d, *J* = 2.1 Hz, 1 H, H-6), 6.88 (d, *J* = 8.7 Hz, 1 H, H-9), 6.94 (d, *J* = 7.9 Hz, 2 H, Ph), 7.20 (d, *J* = 7.9 Hz, 2 H, Ph), 7.29–7.33 (m, 3 H, Ph), 7.45–7.52 (m, 4 H, Ph), 7.63–7.72 (m, 3 H, Ph).

Anal. Calcd for $C_{31}H_{27}N_3O_2$: C, 78.62; H, 5.75; N, 8.87. Found: C, 78.43; H, 5.63; N, 8.71.

Hydrogenolysis; General Procedure

Pyrazolo[4,3-*c*]quinolines (0.2 mmol) in MeOH (18 mL) or MeOH–AcOH (5:1, 25 mL) were hydrogenated over 10% Pd/C (10 mg) at 1 atm in the absence of sunlight. The progress of the reaction was monitored by TLC, when the reaction was complete the resulting mixture was filtered through celite, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc–hexanes) gave the desired products as yellow solids, which were recrystallized (CH_2Cl_2–MeOH or Et_2O) to afford pale-yellow/white needles.

7-Methoxy-2,3-diphenyl-2*H*-pyrazolo[4,3-*c*]quinoline (21a)

Pyrazolo[4,3-*c*]quinoline **19a** in MeOH was hydrogenated according to the general procedure. Flash chromatography (EtOAc–hexanes, 1:9) and recrystallization (Et_2O) gave **21a** as a yellow solid; yield: 71%; mp 144–145 (dec.).

^{1}H NMR ($CDCl_3$): δ = 3.70 (s, 3 H, OCH_3), 6.84 (d, *J* = 2.4 Hz, 1 H, H-6), 7.09 (dd, *J* = 8.9, 2.4 Hz, 1 H, H-8), 7.26 (d, *J* = 8.9 Hz, 1 H, H-9), 7.31–7.38 (m, 6 H, Ph), 7.41–7.48 (m, 4 H, Ph), 8.30 (s, 1 H, H-4).

Anal. Calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.76; H, 4.77; N, 11.83.

7-Methoxy-2-(4-methoxyphenyl)-3-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline (21b)

Pyrazolo[4,3-*c*]quinoline **19b** in MeOH was hydrogenated according to the general procedure. Flash chromatography (EtOAc–hexanes, 1:9) and recrystallization (Et_2O) gave **21b** as a yellow solid; yield: 75%; mp 204–205 (dec.).

^{1}H NMR ($CDCl_3$): δ = 3.69 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 6.89 (d, *J* = 2.3 Hz, 1 H, H-6), 6.96 (d, *J* = 8.2 Hz, 2 H, Ph), 7.10 (dd, *J* = 8.8, 2.3 Hz, 1 H, H-8), 7.22 (d, *J* = 8.2 Hz, 2 H, Ph), 7.29 (d, *J* = 8.8 Hz, 1 H, H-9), 7.33–7.35 (m, 3 H, Ph), 7.40–7.43 (m, 2 H, Ph), 8.25 (s, 1 H, H-4).

Anal. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.74; H, 5.20; N, 11.15.

7-Methoxy-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline (22a)

Pyrazolo[4,3-*c*]quinoline **20a** in MeOH was hydrogenated according to the general procedure. Flash chromatography (EtOAc–hexanes, 3:2) and recrystallization (CH_2Cl_2–MeOH) gave **22a** as white needles; yield: 71%.

^{1}H NMR ($CDCl_3$): δ = 3.70 (s, 3 H, OCH_3), 6.79 (d, *J* = 2.4 Hz, 1 H, H-6), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1 H, H-8), 7.26 (d, *J* = 8.9 Hz, 1 H, H-9), 7.36–7.44 (m, 5 H, Ph), 7.49–7.53 (m, 3 H, Ph), 7.55–7.59 (m, 2 H, Ph), 8.36 (s, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 44.7 (C-4), 58.5 (OCH_3), 61.9 (NCH_2), 98.4 (C-6), 103.6 (C-8), 113.2, 117.6 (C=C), 117.9, 120.1, 126.5, 127.2, 128.1, 128.6, 129.5, 130.1, 133.1 (C-9), 136.8, 137.6, 139.5, 145.3, 146.3, 157.9 (C=N), 164.2 (C-7).

Anal. Calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.41; H, 4.76; N, 12.14.

7-Methoxy-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline (22b)

Pyrazolo[4,3-*c*]quinoline **20b** in MeOH was hydrogenated according to the general procedure. Flash chromatography (EtOAc–hexanes, 3:2) and recrystallization (CH_2Cl_2–MeOH) gave **22b** as white needles; yield: 75%.

^{1}H NMR ($CDCl_3$): δ = 3.65 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 6.89 (d, *J* = 2.3 Hz, 1 H, H-6), 6.92 (d, *J* = 8.2 Hz, 2 H, Ph), 7.15 (dd, *J* = 8.7, 2.3 Hz, 1 H, H-8), 7.30 (d, *J* = 8.7 Hz, 1 H, Ph), 7.35 (d, *J* = 8.8 Hz, 1 H, H-9), 7.37–7.40 (m, 2 H, Ph), 7.42–7.48 (m, 4 H, Ph), 8.21 (s, 1 H, H-4).

Anal. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.77; H, 4.88; N, 10.86.

1-Phenyl-1*H*-pyrazolo[4,3-*c*]quinolin-7-ol (8a)

Pyrazolo[4,3-*c*]quinoline **7a** in MeOH was hydrogenated according to the general procedure. Flash chromatography (EtOAc–hexanes, 3:2) and recrystallization (CH_2Cl_2–MeOH) gave **8a** as white needles; yield: 70%; mp 181–182 (dec.).

^{1}H NMR (DMSO-d_6): δ = 6.92 (dd, *J* = 8.9, 2.4 Hz, 1 H, H-8), 7.30 (d, *J* = 8.9 Hz, 1 H, H-9), 7.42 (d, *J* = 2.4 Hz, 1 H, H-6), 7.61–7.68 (m, 5 H, Ph), 8.48 (s, 1 H, H-3), 9.18 (s, 1 H, H-4), 10.18 (br s, 1 H, HH).

Anal. Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.69; H, 4.42; N, 15.93.

7-Methoxy-1-(4-methoxyphenyl)-1*H*-pyrazolo[4,3-*c*]quinoline (7b)

Pyrazolo[4,3-*c*]quinoline **6b** (0.16 g, 0.4 mmol) in MeOH–AcOH (5:1, 45 mL) was hydrogenated according to the general procedure for 1.5 h. Flash chromatography (EtOAc–hexanes, 3:2) and recrystalization (CH_2Cl_2–acetone) gave **7b** as a yellow solid; yield: 98 mg (80%); mp 139–141 (dec.).

^{1}H NMR (acetone-d_6): δ = 3.87 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 7.09 (dd, *J* = 8.3, 2.4 Hz, 2 H, Ar), 7.16 (d, *J* = 8.8 Hz, 2 H, Ar), 7.36 (d, *J* = 8.3 Hz, 1 H, H-9), 7.52–7.58 (m, 2 H, Ar), 8.49 (s, 1 H, H-4), 9.21 (s, 1 H, H-3).

^{13}C NMR (acetone-d_6): δ = 57.6 (OCH_3), 58.3 (OCH_3), 109.1 (C-6), 115.8, 117.9 (*C*=C), 118.1, 118.8 (C-8), 119.9, 123.6, 124.5, 130.5 (C-9), 137.2, 147.1 (C=N), 152.5 (C-4), 161.2 (*C*OCH_3), 162.8 (C-7).

^{1}H–^{15}N NMR (acetone-d_6): δ = 198.7 (N-1), 294.8 (N-2), 324.6 (N-5).

Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 71.09; H, 4.72; N, 13.92.

7-Methoxy-1-(4-methoxyphenyl)-4-methyl-1*H*-pyrazolo[4,3-*c*]quinoline (7c)

Pyrazolo[4,3-*c*]quinoline **6c** (80 mg, 0.19 mmol) in MeOH–AcOH (5:1, 20 mL) was hydrogenated according to the general procedure. Flash chromatography (EtOAc–hexanes, 3:2) gave **7c** as a dark-yellow crystalline solid; yield: 49 mg (79%); mp 187–189 (dec.).

^{1}H NMR ($CDCl_3$): δ = 2.62 (s, 3 H, CH_3), 3.61 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.89 (d, *J* = 9.1 Hz, 2 H, Ph), 7.02 (dd, *J* = 8.9, 2.4 Hz, 1 H, H-8), 7.25 (d, *J* = 8.9 Hz, 1 H, H-9), 7.29 (d, *J* = 9.1 Hz, 2 H, Ph), 7.53 (d, *J* = 2.4 Hz, 1 H, H-6), 8.63 (s, 1 H, H-3).

^{13}C NMR ($CDCl_3$): δ = 20.1 (C*C*H_3), 56.9 (OCH_3), 57.3 (OCH_3), 109.1 (C-6), 115.8, 116.2, 117.9 (*C*=C), 118.5 (C-8), 119.9, 123.6, 124.5, 128.2 (C-9), 132.2, 135.4, 142.2 (C-3), 147.1 (C=N), 156.5 (C-4), 159.7 (*C*OCH_3), 162.4 (C-7).

^{1}H–^{15}N NMR (acetone-d_6): δ = 197.6 (N-1), 292.8 (N-2), 321.7 (N-5).

Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.58; H, 5.29; N, 13.30.

7-Methoxy-3-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline (13a)

Pyrazolo[4,3-*c*]quinoline **12a** (0.1 g, 0.26 mmol) in MeOH (20 mL) was hydrogenated according to the general procedure. Flash chromatography (EtOAc–hexanes, 2:3) gave **7c** as a dark-yellow crystalline solid; yield: 54 mg (72%); mp 135–137 (dec.).

^{1}H NMR ($CDCl_3$): δ = 2.72 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 6.99 (dd, *J* = 8.4, 2.1 Hz, 1 H, H-8), 7.17 (d, *J* = 2.1 Hz, 1 H, H-6), 7.21–7.28 (m, 5 H, Ph), 7.49 (d, *J* = 8.4 Hz, 1 H, H-9), 8.27 (s, 1 H, H-4).

^{13}C NMR ($CDCl_3$): δ = 7.8 (C*C*H_3), 56.9 (OCH_3), 110.1 (C-6), 118.1, 119.2, 120.5 (C-8), 122.2, 123.6, 124.5, 128.2 (C-9), 132.2, 138.7, 140.9 (C-3), 147.2, 151.5 (C-4), 159.8 (C-7).

Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.50; H, 5.36; N, 14.39.

5-Benzylo-7-methoxy-2-(4-methoxyphenyl)-3-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (13b)

Pyrazolo[4,3-*c*]quinoline **12b** (0.1 g, 0.24 mmol) in MeOH (20 mL) was hydrogenated according to the general procedure. Purification by flash chromatography (EtOAc–hexanes, 2:3) afforded **13b** as yellowish needles; yield: 80%.

^{1}H NMR ($CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 3.63 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 4.47 (s, 2 H, H-4), 5.97 (dd, *J* = 8.4, 2.1 Hz, 1 H, H-

8), 6.19 (d, *J* = 2.1 Hz, 1 H, H-6), 6.63 (d, *J* = 8.4 Hz, 1 H, H-9), 7.18 (d, *J* = 8.7 Hz, 2 H, Ph), 7.40–7.42 (d, *J* = 8.7 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 6.7 (CH_3), 56.9 (OCH_3), 58.5 (OCH_3), 109.1 (C-6), 113.8, 118.1, 119.2, 120.5 (C-8), 122.2, 123.6, 125.7, 128.2 (C-9), 132.7, 138.7, 140.9 (C-3), 149.8, 153.2 (C-4), 159.6 (*C*OCH_3), 161.9 (C-7).

Anal. Calcd for $C_{18}H_{15}N_3O$: C, 75.89; H, 6.12; N, 10.21. Found: C, 75.75; H, 5.95; N, 10.39.

7-Methoxy-2-(4-methoxyphenyl)-3,4-dimethyl-2*H*-pyrazolo[4,3-*c*]quinoline (13c)

Pyrazolo[4,3-*c*]quinoline **12c** (24 mg, 0.06 mmol) in MeOH–AcOH (5:1, 25 mL) was hydrogenated according to the general procedure. Purification by flash chromatography (EtOAc–hexanes, 1:1) afforded **13c** as a yellowish solid; yield: 91%.

^{1}H NMR ($CDCl_3$): δ = 2.71 (s, 3 H, CH_3), 2.90 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 7.01 (dd, *J* = 8.9, 2.7 Hz, 1 H, H-8), 7.19 (d, *J* = 8.9 Hz, 2 H, Ph), 7.25 (d, *J* = 8.9 Hz, 1 H, H-9), 7.46 (d, *J* = 2.7 Hz, 1 H, H-6), 7.52 (d, *J* = 8.9 Hz, 2 H, Ph).

Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 4.95; N, 13.76. Found: C, 72.25; H, 4.84; N, 13.61.

Demethylation; General Procedure

To a stirred solution of methyl-protected pyrazole (1 equiv) in CH_2Cl_2 (35 mL/mmol) at –78 °C, a solution of BBr_3 (1 M, CH_2Cl_2; 10–15 equiv) was added dropwise. After complete addition of BBr_3, the reaction was maintained at –78 °C for 1 h and then the temperature was allowed to rise to r.t. and stirring continued for an additional 16 h. The mixture was cooled to 0 °C and carefully quenched with H_2O (15–25 mL). The product was then extracted with EtOAc (3 × 20 mL) and the organic layers were dried over $MgSO_4$. After removal of the solvent the crude phenolic products were purified by flash chromatography and/or recrystallization (MeOH–CH_2Cl_2 or Et_2O).

5-Benzyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinolin-7-ol (7a)

A stirred CH_2Cl_2 solution of **6a** (100 mg, 0.27 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (EtOAc–hexanes, 2:3) afforded a yellow solid which was recrystallized (Et_2O) to afford the title compound as small off-white crystals; yield: 67 mg (70%); mp 169–171 (dec.).

^{1}H NMR (acetone-d_6): δ = 4.52 (s, 2 H, H-4), 4.55 (s, 2 H, HCH_2), 5.95 (dd, *J* = 8.7, 2.1 Hz, 1 H, H-8), 6.22 (d, *J* = 2.1 Hz, 1 H, H-6), 6.56 (d, *J* = 8.7 Hz, 1 H, H-9), 7.24–7.28 (m, 1 H, Ph), 7.31–7.40 (m, 4 H, Ph), 7.41 (s, 1 H, H-3), 7.45–7.55 (m, 5 H, Ph).

^{13}C NMR (acetone-d_6): δ = 52.9 (C-4), 61.2 (NCH_2), 99.7 (C-6), 104.4 (C-8), 115.1, 118.5 (*C*=C), 120.1, 125.5, 127.4, 128.5, 128.9, 129.3 131.1 (C-9), 132.2, 136.8, 142.3 (C=N), 145.4, 160.1 (C-7).

^{1}H–^{15}N NMR (acetone-d_6): δ = 199.8 (N-1), 295.2 (N-2), 327.6 (N-5).

Anal. Calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.84. Found: C, 78.28; H, 5.31; N, 11.71.

1-(4-Hydroxyphenyl)-1*H*-pyrazolo[4,3-*c*]quinolin-7-ol (8b) and 1-(4-Methoxyphenyl)-1*H*-pyrazolo[4,3-*c*]quinolin-7-ol (9b)

A stirred CH_2Cl_2 solution of **7b** (60 mg, 0.2 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (MeOH–CH_2Cl_2, 1:20) gave **8b** and **9b** as yellow solids, which were recrystallized (Et_2O) to afford the title compounds as small off-white crystals.

8b

Yield: 16 mg (30%); mp 271–272 (dec.).

^{1}H NMR (DMSO-d_6): δ = 6.99 (d, *J* = 8.9 Hz, 2 H, Ph), 7.03 (d, *J* = 2.1 Hz, 1 H, H-6), 7.34 (d, *J* = 8.9 Hz, 1 H, H-9), 7.40 (dd, *J* = 8.9, 2.1 Hz, 1 H, H-8), 7.42 (d, *J* = 8.9 Hz, 2 H, Ph), 8.44 (s, 1 H, H-3), 9.17 (s, 1 H, H-4), 10.19 (br s, 2 H, OH).

Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.52; H, 4.14; N, 14.97.

9b

Yield: 22 mg (40%); mp 241–243 (dec.).

^{1}H NMR (DMSO-d_6): δ = 3.89 (s, 3 H, OCH_3), 7.05 (d, *J* = 8.5 Hz, 2 H, Ph), 7.17 (dd, *J* = 9.2, 2.4 Hz, 1 H, H-8), 7.41 (d, *J* = 9.2 Hz, 1 H, H-9), 7.45 (d, *J* = 8.5 Hz, 2 H, Ph), 7.59 (d, *J* = 2.4 Hz, 1 H, H-6), 8.71 (s, 1 H, H-4), 9.24 (s, 1 H, H-4), 10.19 (br s, 1 H, OH).

Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.95; H, 4.37; N, 14.56.

1-(4-Hydroxyphenyl)-4-methyl-1*H*-pyrazolo[4,3-*c*]quinolin-7-ol (8c) and 1-(4-Methoxyphenyl)-4-methyl-1*H*-pyrazolo[4,3-*c*]quinolin-7-ol (9c)

A stirred CH_2Cl_2 solution of **7c** (60 mg, 0.19 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (MeOH–CH_2Cl_2, 1:20) gave **8c** and **9c** as yellow solids, which were recrystallized (Et_2O) to afford the title compounds as small off-white crystals.

8c

Yield: 50% yield; mp 221–222 (dec.).

^{1}H NMR (DMSO-d_6): δ = 2.55 (s, 3 H, CH_3), 6.87 (d, *J* = 8.5 Hz, 2 H, Ph), 7.17 (dd, *J* = 9.2, 2.4 Hz, 1 H, H-8), 7.25 (d, *J* = 8.5 Hz, 2 H, Ph), 7.41 (d, *J* = 9.2 Hz, 1 H, H-9), 7.59 (d, *J* = 2.4 Hz, 1 H, H-6), 8.11 (s, 1 H, H-3), 9.05 (br s, 1 H, OH), 9.15 (br s, 1 H, OH).

Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.92; H, 4.61; N, 14.28.

9c

Yield: 35%; mp 191–193 (dec.).

^{1}H NMR (DMSO-d_6): δ = 2.59 (s, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 7.06 (d, *J* = 8.5 Hz, 2 H, Ph), 7.17 (dd, *J* = 9.2, 2.4 Hz, 1 H, H-8), 7.41 (d, *J* = 9.2 Hz, 1 H, H-9), 7.45 (d, *J* = 8.5 Hz, 2 H, Ph), 7.59 (d, *J* = 2.4 Hz, 1 H, H-6), 8.59 (s, 1 H, H-3), 10.21 (br s, 1 H, OH).

Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.96; H, 4.79; N, 13.63.

3-Methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]quinolin-7-ol (14a)

A stirred CH_2Cl_2 solution of **13a** (0.1 g, 0.34 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (EtOAc–hexanes, 2:1) afforded **14a** as white needles; yield: 71%; mp 211–213 (dec.).

^{1}H NMR (acetone-d_6): δ = 2.68 (s, 3 H, CH_3), 6.75 (d, *J* = 8.3 Hz, 2 H, Ph), 6.89 (dd, *J* = 8.4, 2.1 Hz, 1 H, H-8), 7.13 (d, *J* = 2.1 Hz, 1 H, H-6), 7.20 (d, *J* = 8.3 Hz, 2 H, Ph), 7.33 (m, 1 H, Ph), 7.53 (d, *J* = 8.4 Hz, 1 H, H-9), 7.92 (s, 1 H, H-4).

^{13}C NMR (DMSO-d_6): δ = 6.2 (C=C*C*H_3), 108.2 (C-6), 116.4, 117.9 (*C*=C), 118.7 (C-8), 119.6, 123.6, 124.5, 128.2 (C-9), 129.4, 130.7, 134.8, 140.2 (C-3), 147.8, 152.9 (C-4), 158.9 (C-7).

^{1}H–^{15}N NMR (acetone-d_6): δ = 290.3 (N-1), 195.4 (N-2), 319.5 (N-5).

Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 73.93; H, 4.52; N, 15.43.

2-(4-Hydroxyphenyl)-3-methyl-2*H*-pyrazolo[4,3-*c*]quinolin-7-ol (14b)

A stirred CH_2Cl_2 solution of **13b** (0.1 g, 0.32 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (EtOAc–hexanes, 2:1) afforded **14b** as white needles; yield: 68%); mp 321–322 (dec.)

^{1}H NMR (DMSO-d_6): δ = 2.68 (s, 3 H, CH_3), 6.75 (d, *J* = 8.3 Hz, 2 H, Ph), 7.01 (dd, *J* = 8.4, 2.1 Hz, 1 H, H-8), 7.13 (d, *J* = 2.1 Hz, 1 H, H-6), 7.20 (d, *J* = 8.3 Hz, 2 H, Ph), 7.45 (d, *J* = 8.4 Hz, 1 H, H-9), 7.95 (s, 1 H, H-4).

^{1}H–^{15}N NMR (DMSO-d_6): δ = 294.9 (N-1), 197.2 (N-2), 323.9 (N-5).

Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.85; H, 4.65; N, 14.34.

2-(4-Hydroxyphenyl)-3,4-dimethyl-2*H*-pyrazolo[4,3-*c*]quinolin-7-ol (14c)

A stirred CH_2Cl_2 solution of **13c** (15 mg, 0.04 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (CH_2Cl_2–MeOH, 97:3) afforded **14c** as a yellowish solid; yield: 63%.

^{1}H NMR (DMSO-d_6): δ = 2.71 (s, 3 H, CH_3), 2.90 (s, 3 H, CH_3), 7.01 (dd, *J* = 8.9, 2.7 Hz, 1 H, H-8), 7.20 (d, *J* = 8.9 Hz, 2 H, Ph), 7.25 (d, *J* = 8.9 Hz, 1 H, H-9), 7.38 (d, *J* = 2.7 Hz, 1 H, H-6), 7.52 (d, *J* = 8.9 Hz, 2 H, Ph), 8.52 (br s, 2 H, OH).

^{13}C NMR (DMSO-d_6): δ = 6.8 (C=C*C*H$_3$), 19.9 (N=C*C*H$_3$), 108.2 (C-6), 116.4, 116.9, 117.9 (*C*=C), 118.7 (C-8), 119.9, 123.6, 124.5, 128.2 (C-9), 132.2, 135.4, 140.8 (C-3), 147.8, 158.1 (C-7), 160.2 (C-4).

^{1}H–^{15}N NMR (DMSO-d_6): δ = 295.1 (N-1), 196.2 (N-2), 324.8 (N-5).

Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.96; H, 4.75; N, 13.54.

2,3-Diphenyl-2*H*-pyrazolo[4,3-*c*]quinolin-7-ol (23a)

A stirred CH_2Cl_2 solution of **21a** (0.1 g, 0.29 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (CH_2Cl_2–MeOH, 97:3) afforded **23a** as an off-white solid; yield: 72%.

^{1}H NMR (acetone-d_6): δ = 7.09 (dd, *J* = 8.8, 2.2 Hz, 1 H, H-8), 7.22 (d, *J* = 2.2 Hz, 1 H, H-6), 7.32–7.37 (m, 4 H, Ph), 7.42 (d, *J* = 8.2 Hz, 2 H, Ph), 7.46–7.51 (m, 4 H, Ph), 7.58 (d, *J* = 8.8 Hz, 1 H, H-9), 8.82 (s, 1 H, H-4).

Anal. Calcd for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.51; H, 4.63; N, 12.19.

2-(4-Hydroxyphenyl)-3-phenyl-2*H*-pyrazolo[4,3-*c*]quinolin-7-ol (23b)

A stirred CH_2Cl_2 solution of **21b** (0.1 g, 0.27 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (CH_2Cl_2–MeOH, 97:3) afforded **23b** as off-white needles; yield: 77%.

^{1}H NMR (DMSO-d_6): δ = 6.82 (d, *J* = 7.8 Hz, 2 H, Ph), 7.02 (dd, *J* = 8.6, 1.9 Hz, 1 H, H-8) 7.14 (d, *J* = 7.8 Hz, 2 H, Ph), 7.30–7.35 (m, 5 H, Ph), 7.39 (d, *J* = 8.6 Hz, 1 H, H-9), 7.43 (d, *J* = 1.9 Hz, 1 H, H-6), 8.92 (s, 1 H, H-4), 9.15 (s, 2 H, OH).

Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.98; H, 4.39; N, 12.06.

1,3-Diphenyl-1*H*-pyrazolo[4,3-*c*]quinolin-7-ol (24a)

A stirred CH_2Cl_2 solution of **22a** (0.1 g, 0.29 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (CH_2Cl_2–MeOH, 97:3) afforded **24a** as an off-white solid; yield: 72%.

^{1}H NMR (acetone-d_6): δ = 7.09 (dd, *J* = 8.8, 2.2 Hz, 1 H, H-8), 7.22 (d, *J* = 2.2 Hz, 1 H, H-6), 7.32–7.37 (m, 6 H, Ph), 7.46–7.51 (m, 4 H, Ph), 7.58 (d, *J* = 8.8 Hz, 1 H, H-9), 8.32 (s, 1 H, H-4), 9.19 (s, 1 H, OH).

Anal. Calcd for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.31; H, 4.60; N, 12.74.

1-(4-Hydroxyphenyl)-3-phenyl-1*H*-pyrazolo[4,3-*c*]quinolin-7-ol (24b)

A stirred CH_2Cl_2 solution of **22b** (0.1 g, 0.27 mmol) was deprotected using BBr_3 according to the general demethylation procedure. Flash chromatography (CH_2Cl_2–MeOH, 97:3) afforded **24b** as an off-white solid; yield: 72%.

^{1}H NMR (DMSO-d_6): δ = 6.69 (d, *J* = 8.7 Hz, 2 H, Ph), 6.98 (d, *J* = 8.7 Hz, 2 H, Ph), 7.15 (dd, *J* = 8.6, 1.9 Hz, 1 H, H-8) 7.39 (d, *J* = 8.6 Hz, 1 H, H-9), 7.43 (d, *J* = 1.9 Hz, 1 H, H-6), 8.60 (s, 1 H, H-4).

Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.58; H, 4.43; N, 11.65.

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