3-Aryl-6-methoxy-2-oxo-1,2-dihydroquinoline-4-carbonitriles as Solvent and pH Independent Green Fluorescent Dyes

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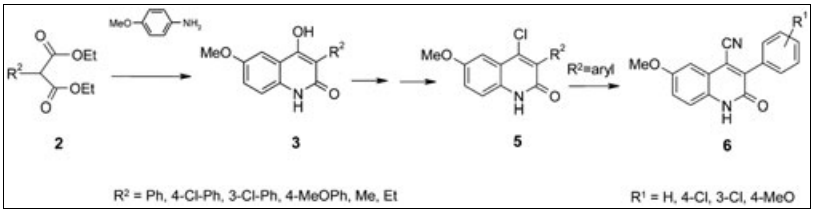

Highly fluorescent and stable 3-aryl-6-methoxy-2-oxoquinoline-4-carbonitriles **6** (λ_{exc} = 408 nm and λ_{em} = 510 nm) were synthesized starting from appropriate arylmalonates **2**. Ring closure reaction with *p*-anisidine gave 4-hydroxyquinolones **3**, which could be bis-chlorinated to yield quinolines **4**. Regioselective hydrolysis produced reactive 4-chloroquinolones **5**, which were converted to green fluorescent 4-cyano quinolones **6** using toluenesulfinates as catalysts.

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INTRODUCTION

We have shown that 6,7-dimethoxy-4-trifluoromethylcarbostyrils [1] and 4-cyano-6,7-dimethoxycarbostyrils [2] are highly fluorescent dyes. Compared with previously known substitution patterns they show red-shifted absorption and emission wavelengths up to 410 and 460 nm, respectively. Together with quantum yields up to 0.6, these parameters are fairly solvent and pH independent. Hence, they are suitable to outclass widely used coumarin dyes [3]. Furthermore, these 6,7-4 push–pull substituted quinolone dyes show high thermal and photochemical stability and no oxygen quenching different from many other fluorophores. Recently, another work group incorporated our 4-trifluoromethyl and 4-cyanocarbostyrils into peptides and got an efficient fluorescence-resonance-energy transfer (FRET) system [4].

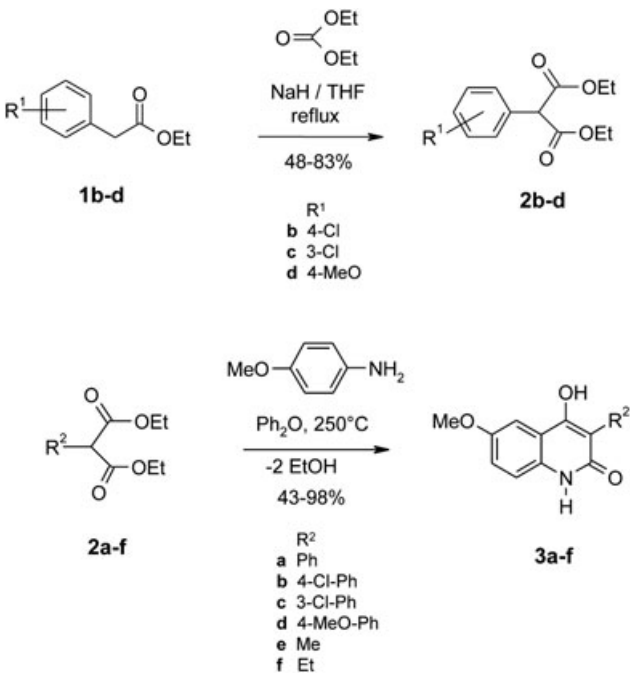
In this communication, we describe an investigation on 6-methoxy-2-oxo-1,2-dihydro-quinoline-4-carbonitriles (4-cyano-6-methoxycarbostyrils) having 3-aryl- and 3-alkyl substituents, and compare the electronic spectra with the 6,7-dimethoxy derivatives. Synthesis of 3-aryl and 3-alkyl-4-hydroxy-6-methoxy-2-quinolones **3** was planned to proceed *via* the reaction of corresponding aryl- and alkylmalonates with *p*-anisidine. Final conversion of the 4-hydroxy to the cyano group should give strongly fluorescent carbostyril derivatives **6**.

RESULTS AND DISCUSSION

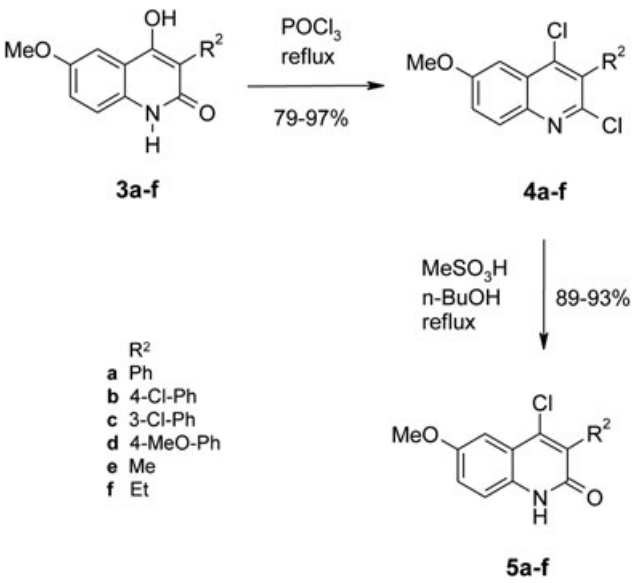
Synthesis. The key step in the reaction sequence for the ring closure reaction to 3-aryl-4-hydroxy-6-methoxy-2-quinolones **3** involves the use of 2-arylmalonates **2**, obtained either by a Claisen condensation reaction type [5], or *via* C C couplings of malonates with arylhalogenides using metal catalysts [6]. We started the reaction from commercially available arylacetates **1b–d** utilizing the Claisen condensation pathway. The literature describes several variants for the preparation of **2** by Claisen condensation from **1**, e.g., *via* oxaloesters [5a–d], or by condensation reaction with diethyl carbonate [5e–g] or other similar methods. In this work, the diethyl carbonate method from ref. [5f] was applied. Arylmalonates **2b–d** were synthesized from arylacetates **1b–d** having a 4-chloro-, a 3-chloro-, and a 4-methoxy substituent in the aryl ring. The reaction with diethyl carbonate was promoted by sodium hydride as a strong base and gave yields within 48–83% (Scheme 1).

The arylmalonates **2a–d** readily underwent cyclization with *p*-anisidine to 3-aryl-4-hydroxy-6-methoxy-2(1H)-quinolones **3a–d** in 73–98% yields. The cyclocondensation step is known to proceed in two steps, having as the key reaction the thermolytic formation of a ketene intermediate [7], which attacks easily the aryl nucleus at elevated temperatures and gives the quinoline ring by cyclization reaction. In the same manner, 3-methyl- and 3-ethyl-4-hydroxy-6-methoxy-2(1H)-quinolones **3e**,**f** were obtained from 2-methyl- or 2-ethylmalonates **2e**,**f** and *p*-anisidine in 94 and 43% yield, respectively. ^{1}H NMR spectroscopic data proved the structures by the singlet signals of 1-NH and 4-OH (~ 10.20 and ~ 11.30 ppm) and by the 5-H, 7-H, and 8-H signals (~ 7.35 ppm, doublet with 2.5 Hz; ~ 7.15 ppm, doubled doublet with 9 and 2.5 Hz; ~ 7.25 ppm, doublet with 9 Hz), together with the 6-methoxy signal as a singlet at ~ 3.80 ppm.

Scheme 1

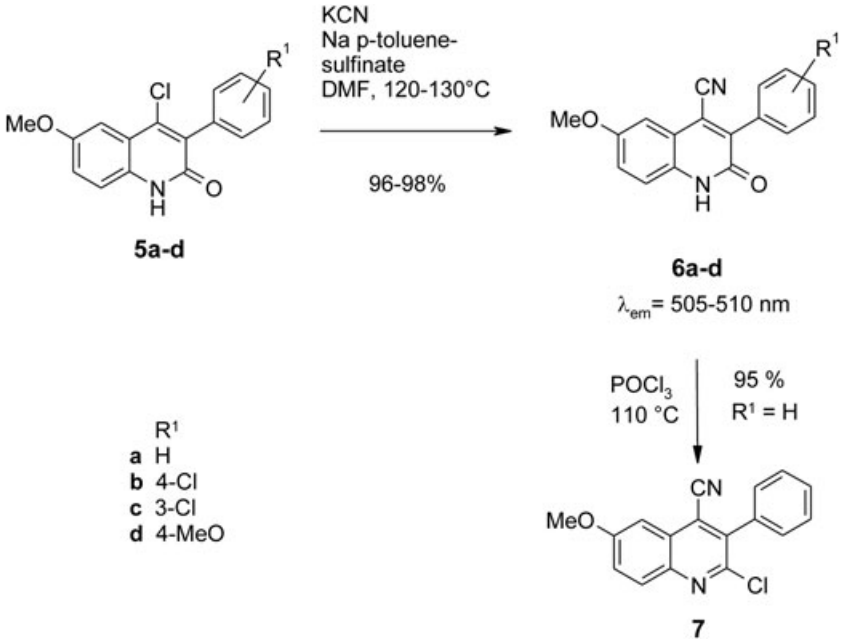


Scheme 2

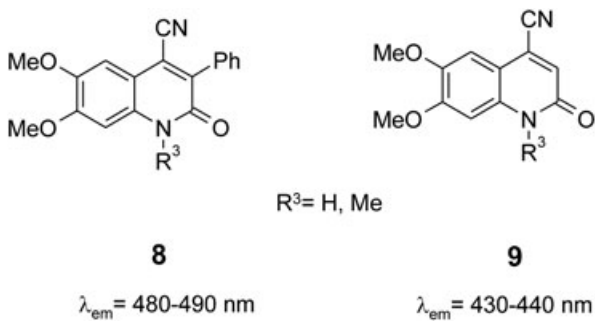


The next step in our reaction sequence was the introduction of a usable leaving group in position 4 instead of the 4-hydroxy group in quinolone **3**. In earlier investigations, we found a 4-chloro substituent to have the best properties, both in the synthesis and stability, and then in further exchange reactions [2]. The transformation to the desired reactive 4-chloroquinolone **5** was achieved in two steps, because a single substitution of the 4-hydroxy group of **3** to a 4-chloro-substituent in **5** could not be performed regioselectively: with phosphoryl chloride, in all attempts also the enolizable 2-oxo group was replaced at least partially by chlorination, and the completion of the reaction resulted in the formation of 2,4-dichloroquinolines **4a–f** in excellent yields, confirmed by the lack of the carbonyl function in position 2 in the IR spectra. The reaction time for a complete conversion was strongly dependent on the substituent in position 3: the 3-aryl substituent caused a rather high

Scheme 3



Scheme 4



reactivity with best results observed in the phenyl and *p*-chlorophenyl derivatives **3a,b**, similar but lower reactivity in *p*-methoxy- and *m*-chlorophenyl derivatives **3c,d** and rather low reactivity in the 3-alkyl derivatives **3e,f** (Scheme 2).

As shown in earlier investigations [2], it is possible to hydrolyze regioselectively the chloro function in position 2 of dichloroquinolines **4** in acidic media such as methanesulfonic acid to get back the 2-oxo function. The slightly lower reactivity of **4** caused probably by the 6-methoxy group demanded higher reaction temperatures: so we replaced the solvent ethanol by *n*-butanol, which allowed us to convert the dichloro derivatives **4** in good to excellent yields to 4-chloro-2-quinolones **5a–f**. The infrared spectral data of **5** revealed the 2-oxo-function (~ 1650 cm^{-1}), and in the ^1H NMR spectra the NH signals were visible again at ~ 12.00 ppm. 4-Chloroquinolones **5** should now serve as reactive starting material for the introduction of the cyano substituent in position 4.

A simple nucleophilic substitution of the 4-chloro function in **5** by the cyano group using a reaction with potassium or sodium cyanide was unsuccessful, also in the presence of different crown ethers. Attempts with the Rosenmund–Braun aromatic cyanation [8] with copper(I) cyanide gave a mixture of fluorescent compounds, but separation attempts failed. A method we have recently used successfully for such reactions [2] was the addition of sodium *p*-toluenesulfinate as reaction mediator to the reaction mixture of 4-chloroquinolones and potassium cyanide in dimethylformamide. The application of this method in the reaction of **5** gave with all 3-arylsubstituted quinolones **5a–d** the 4-cyanoquinolones **6a–d** in excellent yields. The different substituents at the aryl moiety did not affect the reactivity and yield of **5a–d**. The successful exchange was already visible in the TLC control: the newly formed cyano product **6** gave a strong greenish fluorescent spot, which made it easy to follow the reaction. IR spectra showed besides the strong carbonyl signal at about 1660 cm^{-1} a weak signal for the cyano group at about 2230 cm^{-1}. The ^1H and ^{13}C NMR spectra showed all relevant signals, and mass spectra using either APCI or ESI methods gave the parent peaks with 100%. On the other hand, however, the exchange of the chloro group in 3-alkylquinolones **5e,f** was unsuccessful with all methods, and no conversion to any fluorescent new compound could be detected (Scheme 3).

The chlorination of cyanoquinolone **6a** gave in excellent yields the 2-chloroquinoline-4-carbonitrile **7**. No reaction took place at the 4-position, which is visible in the IR spectra, because the 2-carbonyl signal disappeared, whereas the nitrile signal at 2236 cm^{-1} remained unchanged. This shows the stability of this class of compounds **6**, which makes them useful as stable fluorescent probes. The strong fluorescence of **6a** disappeared nearly completely when the compound was converted to quinoline **7**, which demonstrates the importance of the carbostyril (2-quinolone) structure element for fluorescence properties.

Electronic spectra. The aim of this investigation was the comparison of 3-aryl-4-cyano-6-methoxy-carbostyrils **6** having different substituents at the 3-aryl ring, to get information on the influence of substituents in 3-position on the fluorescence properties of this compound class. This class of compounds was hitherto not described by other groups. In ref. [2], we have described one similar type of compounds, 6,7-dimethoxy-1-methyl-2-oxo-3-phenyl-1,2-dihydroquinoline-4-carbonitriles **8**. Fluorescence measurement of these compounds shows an excitation wavelength of λ_{exc} = 380–390 nm and an emission wavelength of λ_{em} = 480–490 nm, which means a red shift of about 50 nm caused by the phenyl group, compared with 3-unsubstituted 6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-4-carbonitriles **9** (λ_{exc} at 380–390 nm, λ_{em} at 430–440 nm; Scheme 4).

Surprisingly, compared with 6,7-dimethoxy derivatives **8** the single 6-methoxy group in this 4-cyano-3-phenylcarbostyrils **6** causes a more efficient red shift. Already 4-hydroxy-6-methoxy-3-(4-chlorophenyl)-carbostyril (**3b**) shows a blue fluorescence with λ_{exc} at 352 nm and λ_{em} at 416 nm.

6-Methoxy-2-oxo-3-phenyl-1,2-dihydroquinoline-4-carbonitrile (**6a**) with no substituent in the 3-aryl ring shows fluorescence values of λ_{exc} at 405 nm and λ_{em} at 505 nm; a similar value (λ_{exc} at 405 nm and λ_{em} at 503 nm) was observed with the 4-methoxyphenyl derivative **6d**. Both chlorophenyl derivatives **6b** and **6c** gave slightly red shifted values (λ_{exc} at 406 and 408 nm, and λ_{em} at 510 nm), but no significant change in the wavelengths was visible as one could assume. Investigations in different solvents revealed that electronic spectra of structures **6** are almost not influenced (e.g., λ_{em} at 505 nm in DMSO, and λ_{em} at 500 nm in water for **6d**), and also no pH dependence and oxygen quenching was observed.

CONCLUSIONS

The synthesis of 6-methoxy-2-oxo-3-aryl-1,2-dihydroquinoline-4-carbonitriles **6** could be performed in a five-step synthesis starting from arylacetates **1** in a good overall yield. The resulting quinoline-4-carbonitriles **6** showed

very useful fluorescence properties: Excitation is possible in visible light (above 400 nm), and emission can be measured above 500 nm (in the green region), which means a Stokes' shift of about 100 nm. The introduction of electron-pushing or pulling substituents at the 3-aryl ring has no significant effect on the fluorescence values of **6a–d**. One disadvantage of the 6-methoxycarbostyril substitution pattern was observed throughout: compared with dimethoxy derivatives **8** and **9** (Φ = 0.5 and 0.4), in 3-aryl-6-methoxy derivatives **6** fluorescence quantum yields are lower (Φ = 0.05–0.23).

EXPERIMENTAL

General. Melting points were determined in open capillary tubes using a Stuart SMP3 Melting Point Apparatus. IR spectra were recorded with a Mattson Galaxy Series FTIR 7020 instrument in potassium bromide discs, or with a Bruker Alpha-P with attenuated total reflectance (ATR) measurement, using a reflexion method. NMR spectra were recorded on a Bruker AMX 360 instrument (360 MHz ^{1}H, 90 MHz ^{13}C), or on a Bruker Avance III instrument (300 MHz ^{1}H), or on a Bruker Avance DRX 500 instrument (500 MHz ^{1}H, 125 MHz ^{13}C). Chemical shifts are given in ppm (δ) from the internal TMS standard. Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna, Austria. Mass spectra were obtained from a HP 1100 LC/MSD mass spectral instrument (positive or negative APCI ion source, 50–200 V, nitrogen, or AP-ES electrospray method). UV/Vis spectra were recorded with a Shimadzu UV/Vis scanning spectrophotometer UV-2101 PC; concentration: 1×10^{-4} M. Fluorescence data: Excitation and emission spectra were recorded with a Perkin-Elmer LS50B luminescence spectrometer. Determination of quantum yields: emission signals were set in relation to the known area of the emission signal of quinine sulfate at pH = 1. Corrections were made for other solvents by using the factor $(n\text{water}/n\text{solvent})^2$ [3c,e]. Analytical HPLC was performed on a Shimadzu LC 20 system equipped with a diode array detector (215 and 254 nm) on a Pathfinder AS reversed phase (4.6150 mm, 5 μm) column, running an acetonitrile/water gradient (30–100% acetonitrile). Dry column flash chromatography [9] was carried out on silica gel 60 H (5–40 μm) (Merck, Darmstadt, Germany). All reactions were monitored by thin layer chromatography on 0.2-mm silica gel F 254 plates (Merck, Darmstadt, Germany) using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

Ethyl (4-chlorophenyl)acetate (1b), ethyl (3-chlorophenyl) acetate (1c), and ethyl (4-methoxyphenyl)acetate (1d). Ethyl (4-chlorophenyl)acetate (**1b**), ethyl (3-chlorophenyl)acetate (**1c**), and ethyl (4-methoxyphenyl)acetate (**1d**) are commercially available.

Diethyl phenylmalonate (2a). Diethyl phenylmalonate (**2a**) is commercially available.

General procedure for the preparation of diethyl arylmalonates (2b–d). To a mixture of sodium hydride (60% in mineral oil; 15.00 g, 375 mmol) and diethyl carbonate (57.50 g, 59.0 mL, 487 mmol) in dry tetrahydrofuran (120 mL), was added dropwise a solution of the appropriate ethyl arylacetate **1b–d** (95 mmol) in dry tetrahydrofuran (40 mL). The mixture was heated under reflux for the time given, cooled to 20°C, and neutralized with a saturated aq. ammonium chloride (150 mL). The organic phase was separated and the aqueous phase extracted with diethylether (2 × 150 mL). The combined organic phases were washed with saturated aq. $NaHCO_3$ (150 mL) and brine (150 mL), and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by distillation under reduced pressure.

Diethyl (4-chlorophenyl)malonate (2b). From (4-chlorophenyl) acetate **1b** (18.85 g, 95 mmol; reaction time: 2 h). The yield was 21.34 g (83%), colorless oil, bp 170–180°C/27 mbar, lit. bp 116–180°C/0.05–25 mmHg [5c,e,g, 6a, 10b–d].

Diethyl (3-chlorophenyl)malonate (2c). From (3-chlorophenyl) acetate **1c** (18.85 g, 95 mmol; reaction time: 7 h), the yield was 12.34 g (48%), colorless oil, bp 178–184°C/22.7 mbar, lit. bp 145–178°C/1.2–17 mmHg [5c,f, 6a,b,i].

Diethyl (4-methoxyphenyl)malonate (2d). From (4-methoxyphenyl)acetate **1d** (18.35 g, 95 mmol; reaction time: 87 h), the yield was 17.37 g (69%), clear yellow oil, bp 190–206°C/36.5 mbar, lit. bp 136–198°C/0.05–13 mmHg [5d,i, 6d–h, 10a, 11a–c].

Diethyl methylmalonate (2e) and diethyl ethylmalonate (2f). Diethyl methylmalonate (**2e**) and diethyl ethylmalonate (**2f**) are commercially available.

4-Hydroxy-6-methoxy-3-phenylquinolin-2(1H)-one (3a). A solution of *p*-anisidine (10.01 g, 81.4 mmol) and phenylmalonate **2a** (19.34 g, 82 mmol) in diphenyl ether (50 mL) was heated under reflux at about 250–300°C for 3 h. During this time, ethanol (6.0 mL, 103 mmol) was liberated. The solution was cooled to 20°C, diluted with cyclohexane (25 mL) and filtered by suction. The solid was dissolved in warm aq. sodium hydroxide (250 mL, 1*M*) and filtered. To the alkaline filtrate, concentrated hydrochloric acid was added until pH = 1–2 was reached, the precipitate filtered by suction, washed with water, and dried at 40°C under reduced pressure. The yield was 21.09 g (97%), colorless prisms, mp 324–327°C (ethanol), lit. mp 319–326°C [12b].

3-(4-Chlorophenyl)-4-hydroxy-6-methoxyquinolin-2(1H)-one (3b). *p*-Anisidine (1.68 g, 13.7 mmol) and *p*-chlorophenyl malonate **2b** (3.70 g, 13.7 mmol) in diphenyl ether (16 mL) were brought to reaction and worked up as described for **3a**. The yield was 3.27 g (79%), colorless prisms, mp 347–355°C (ethanol). IR (KBr): 2949 s, 1648 s (amide-C O), 1607 s, 1585 s cm^{-1}. ^{1}H NMR (300 MHz; DMSO-d_6): δ 3.79 (s, 3 H, MeO), 7.17 (dd, J = 8.9 + 2.7 Hz, 1 H, 7-H), 7.24 (d, J = 8.9 Hz, 1 H, 8-H), 7.39 (d, J = 8.8 Hz, 2 H, $ArH_{AA'}$), 7.44 (d, J = 2.6 Hz, 1 H, 5-H), 7.45 (d, J = 8.8 Hz, 2 H, $ArH_{BB'}$), 10.20 (s, 1 H, 1-NH), 11.42 (s, 1 H, OH). UV (DMSO): λ (ε, M^{-1} cm^{-1}) = 352 (8720) nm. Fluorescence (DMSO): λ (Φ_F) = 416 (0.03). Anal. calcd for $C_{16}H_{12}ClNO_3$ (301.73): C, 63.69; H, 4.01; N, 4.64. Found: C, 63.56; H, 3.83; N, 4.63.

3-(3-Chlorophenyl)-4-hydroxy-6-methoxyquinolin-2(1H)-one (3c). *p*-Anisidine (5.27 g, 42.9 mmol) and *m*-chlorophenyl malonate **2c** (11.59 g, 42.9 mmol) in diphenyl ether (50 mL) were brought to reaction and worked up as described for **3a**. The yield was 9.41 g (73%), colorless prisms, mp 322–325°C (ethanol). IR (KBr): 2964 s, 1644 m (amide-C O), 1607 s, 1587 w cm^{-1}. ^{1}H NMR (300 MHz; DMSO-d_6): δ 3.79 (s, 3 H, MeO), 7.18 (dd, J = 8.9 + 2.4 Hz, 1 H, 7-H), 7.25 (d, J = 8.9 Hz, 1 H, 8-H), 7.37 (s, 1 H, ArH), 7.34–7.42 (m, 3 H, ArH), 7.45 (d, J = 2.0 Hz, 1 H, 5-H), 10.30 (s,

1 H, NH), 11.44 (s, 1 H, OH). Anal. calcd for $C_{16}H_{12}ClNO_3$ (301.73): C, 63.69; H, 4.01; N 4.64. Found: C, 63.67; H, 3.78; N, 4.63.

4-Hydroxy-6-methoxy-3-(4-methoxyphenyl)quinolin-2(1H)-one (3d). *p*-Anisidine (5.30 g, 43.1 mmol) and (*p*-methoxyphenyl) malonate **2d** (11.46 g, 42.8 mmol) in diphenyl ether (50 mL) were brought to reaction and worked up as described for **3a**. The yield was 12.59 g (98%), colorless prisms, mp 325–328°C (ethanol). IR: 3435 m, 2958 m, 1647 m (amide-C O), 1611 s, 1587 w cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ 3.78 (s, 3 H, 6-MeO), 3.79 (s, 3 H, Ar-MeO), 6.96 (d, *J* = 8.8 Hz, 2 H, $ArH_{BB'}$), 7.14 (dd, *J* = 8.9 + 2.7 Hz, 1 H, 7-H), 7.23 (d, *J* = 8.9 Hz, 1 H, 8-H), 7.30 (d, *J* = 8.8 Hz, 2 H, $ArH_{AA'}$), 7.44 (d, *J* = 2.6 Hz, 1 H, 5-H), 10.00 (s, 1 H, NH), 11.33 (s, 1 H, OH). Anal. calcd for $C_{17}H_{15}NO_4$ (297.31): C, 68.68, H, 5.09; N 4.71. Found: C, 68.31; H, 4.86; N, 4.72.

4-Hydroxy-6-methoxy-3-methylquinolin-2(1H)-one (3e). *p*-Anisidine (10.00 g, 81.3 mmol) and methylmalonate **2e** (14.0 mL, 81 mmol) in diphenyl ether (50 mL) were brought to reaction and worked up as described for **3a**. The yield was 15.71 g (94%), colorless prisms, mp 234–236°C (ethanol). IR: 3431 s, 1647 s (amide-C O), 1612 s cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ 1.99 (s, 3 H, Me), 3.78 (s, 3 H, MeO), 7.08 (dd, *J* = 8.9 + 2.7 Hz, 1 H, 7-H), 7.19 (d, *J* = 8.9 Hz, 1 H, 8-H), 7.34 (d, *J* = 2.7 Hz, 1 H, 5-H), 10.03 (s, 1 H, NH), 11.22 (s, 1 H, OH). Anal. calcd for $C_{11}H_{11}NO_3$ (205.22): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.32; H, 5.26; N, 6.85.

3-Ethyl-4-hydroxy-6-methoxyquinolin-2(1H)-one (3f). *p*-Anisidine (12.50 g, 101 mmol) and diethyl ethylmalonate (**2f**: 18.0 mL, 101 mmol) in diphenyl ether (50 mL) were brought to reaction and worked up as described for **3a**. The yield was 9.50 g (43%), colorless prisms, mp 160–162°C (ethanol), lit. mp 172°C [12a].

2,4-Dichloro-6-methoxy-3-phenylquinoline (4a). A solution of 3-phenylquinolone **3a** (18.50 g, 69.3 mmol) in phosphorylchloride (80 mL) was heated under reflux for 8 h. The excess of phosphorylchloride was removed under reduced pressure, the residue poured onto ice/water (300 mL), brought to pH = 4–6 with aq. sodium hydroxide (5 *M*), filtered by suction, and washed with water. The solid was dried at 40°C under reduced pressure. The yield was 20.41 g (97%), colorless prisms, mp 220–222°C (ethanol). IR (KBr): 3438 m, 1620 m, 1572 m cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 3.97 (s, 3 H, MeO), 7.39–7.40 (m, 1 H, 7-H), 7.42 (d, *J* = 1.8 Hz, 1 H, 5-H), 7.48–7.62 (m, 5 H, PhH), 8.02 (d, *J* = 9.2 Hz, 1 H, 8-H). Anal. calcd for $C_{16}H_{11}Cl_2NO$ (304.18): C, 63.18; H, 3.65; N, 4.60. Found: C, 63.05; H, 3.44; N, 4.58.

2,4-Dichloro-3-(4-chlorophenyl)-6-methoxyquinoline (4b). 3-(4-Chlorophenyl)quinolone **3b** (13.38 g, 44.4 mmol) in phosphorylchloride (70 mL) was brought to reaction (reaction time: 8 h) and worked up as described for **4a**. The yield was 12.91 g (86%), colorless prisms, mp 167–170°C (ethanol). IR (KBr): 3503 w, 1687 w, 1619 s, 1567 m cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ 3.96 (s, 3 H, MeO), 7.45 (d, *J* = 1.8 Hz, 1 H, 5-H), 7.47 (d, *J* = 8.2 Hz, 2 H, $ArH_{BB'}$), 7.59 (d, *J* = 9,2 + 2.0 Hz, 1 H, 7-H), 7.63 (d, *J* = 8.2 Hz, 2 H, $ArH_{AA'}$), 7.99 (d, *J* = 9.2 Hz, 1 H, 8-H). Anal. calcd for $C_{16}H_{10}Cl_3NO$ (338.62): C, 56.75; H, 2.98; N, 4.14. Found: C, 56.70; H, 2.77; N, 4.14.

2,4-Dichloro-3-(3-chlorophenyl)-6-methoxyquinoline (4c). 3-(3-Chlorophenyl)-6-methoxyquinolone **3c** (7.00 g, 23.2 mmol) in phosphorylchloride (30 mL) was brought to reaction (reaction time: 12 h) and worked up as described for **4a**. The yield was 7.60 g (97%), beige prisms, mp 215–217°C (ethanol). IR (KBr): 3073 w, 1618 w, 1599 s, 1567 m cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ 3.97 (s, 3 H, MeO), 7.41–7.42 (m, 1 H, ArH), 7.48 (d, *J* = 2.6 Hz, 1 H, 5-H), 7.58–7.60 (m, 3 H, ArH), 7.62 (dd, *J* = 9.2 + 2.6 Hz, 1 H, 7-H), 8.02 (d, *J* = 9.2 Hz, 1 H, 8-H). Anal. calcd for $C_{16}H_{10}Cl_3NO$ (338.62): C, 56.75; H, 2.98; N, 4.14. Found: C, 56.46; H, 2.66; N, 4.09.

2,4-Dichloro-6-methoxy-3-(4-methoxyphenyl)quinoline (4d). 3-(4-Methoxyphenyl)quinolone **3d** (11.10 g, 37.4 mmol) in phosphorylchloride (45 mL) was brought to reaction (reaction time: 12 h) and worked up as described for **4a**. The yield was 9.77 g (79%), colorless prisms, mp 169–170°C (ethanol). IR: 3439 s, 1617 s, 1565 m cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ 3.83 (s, 3 H, 6-MeO), 3.95 (s, 3 H, Ar-MeO), 7.08 (d, *J* = 8.7 Hz, 2 H, $ArH_{BB'}$), 7.32 (d, *J* = 8.6 Hz, 2 H, $ArH_{AA'}$), 7.44 (d, *J* = 2.6 Hz, 1 H, 5-H), 7.56 (dd, *J* = 9.2 + 2.7 Hz, 1 H, 7-H), 7.97 (d, *J* = 9.2 Hz, 1 H, 8-H). Anal. calcd for $C_{17}H_{13}Cl_2NO_2$ (334.20): C, 61.10; H, 3.92; N, 4.19. Found: C, 61.08; H, 3.72; N, 4.17.

2,4-Dichloro-6-methoxy-3-methyl-quinoline (4e). 3-Methylquinolone **3e** (9.50 g, 46.3 mmol) in phosphorylchloride (54 mL) was brought to reaction (reaction time: 24 h) and worked up as described for **4a**. The yield was 10.28 g (92%), light yellow prisms, mp 149–151°C (ethanol). IR (KBr): 3459 s, 1622 m, 1572 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.60 (s, 3 H, Me), 3.95 (s, 3 H, MeO), 7.40 (d, *J* = 2.7 Hz, 1 H, 5-H), 7.49 (dd, *J* = 9.2 + 2.8 Hz, 1 H, 7-H), 7.91 (d, *J* = 9.1 Hz, 1 H, 8-H). Anal. calcd for $C_{11}H_9Cl_2NO$ (242.11): C, 54.57; H, 3.75; N, 5.79. Found: C, 54.36; H, 3.55; N, 5.69.

2,4-Dichloro-3-ethyl-6-methoxyquinoline (4f). 3-Ethylquinolone **3f** (3.15 g, 14.4 mmol) in phosphorylchloride (17 mL) was brought to reaction (reaction time: 24 h) and worked up as described for **4a**. The yield was 3.09 g (84%), colorless prisms, mp 115–118°C (ethanol). IR (ATR): 3038 w, 1619 m, 1568 m cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.20 (t, *J* = 7.4 Hz, 3 H, Me), 3.00 (q, *J* = 7.2 Hz, 2 H, CH_2), 3.94 (s, 3 H, MeO), 7.35 (s, 1 H, 5-H), 7.47 (d, *J* = 8.8 Hz, 7-H), 7.86 (d, *J* = 8.8 Hz, 1 H, 8-H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 12.8 (Me), 25.3 (MeO), 56.2 (CH_2), 102.6 (ArC), 123.7 (ArC), 126.9 (ArC), 130.5 (ArC), 133.6 (ArC), 140.6 (4-C), 141.8 (9-C), 147.8 (2-C), 159.3 (6-C). Anal. calcd for $C_{12}H_{11}Cl_2NO$ (256.13): C, 56.27, H, 4.33; N; 5.47. Found: C, 56.10; H, 4.13; N, 5.43.

4-Chloro-6-methoxy-3-phenylquinolin-2(1H)-one (5a). 3-Phenylquinoline **4d** (7.00 g, 23.0 mmol) and methanesulfonic acid (11.5 mL, 70% in water) in 1-butanol (100 mL) were heated under reflux for 30 h. The mixture was cooled to 20°C, poured into ice/water (100 mL), and brought to pH = 4–6 with sodium hydroxide (2 *M*). The solid was filtered off by suction, washed with water, and dried at 40°C under reduced pressure. The yield was 5.86 g (89%), colorless prisms, mp 278–281°C (ethanol). IR (ATR): 3437 m, 3192 s, 1640 s (amide-C O), 1595 m cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.38 (s, 3 H, MeO), 7.29–7.48 (m, 8 H, 5-H, 7-H 8-H, PhH), 12.14 (s, 1 H, NH). Anal. calcd for $C_{16}H_{12}ClNO_2$ (285.73): C, 67.26; H, 4.23; N, 4.90. Found: C, 67.25; H, 3.99; N, 4.90.

4-Chloro-3-(4-chlorophenyl)-6-methoxyquinolin-2(1H)-one (5b). 3-(4-Chlorophenyl)quinoline **4b** (6.00 g, 17.7 mmol) and methanesulfonic acid (6.0 mL, 70% in water) in 1-butanol (60 mL) were heated under reflux for 45 h and worked up following the method described for **5a**. The yield was 5.33 g (94%) beige prisms, mp 296–298°C (ethanol). IR (KBr): 3427 m, 2848 s, 1666 s (amide-C O), 1624 w, 1593 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3 H, MeO), 7.30–7.35 (m. 3 H, 5-

H, 7-H and 8–H), 7.49 (d, J = 7.7 Hz, 2 H, $ArH_{AA'}$), 7.52 (d, J = 7.8 Hz, 2 H, $ArH_{BB'}$), 12.18 (s, 1 H, NH). Anal. calcd for $C_{16}H_{11}Cl_2NO_2$ (320.18): C 60.02, H 3.46, N 4.37. Found: C 60.23, H 3.39, N 4.36.

4-Chloro-3-(3-chlorophenyl)-6-methoxyquinolin-2(1H)-one (5c). 3-(3-Chlorophenyl)quinoline **4c** (6.00 g, 17.7 mmol), and methanesulfonic acid (3.0 mL, 70% in water) in 1-butanol (50 mL) were heated under reflux for 45 h and worked up following the method described for **5a**. The yield was 5.10 g (90%), beige prisms, mp 285–288°C (ethanol). IR (KBr): 2832 w, 1658 s (amide-C O), 1623 m, 1500 m cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3 H, MeO), 7.32–7.33 (m, 3 H, ArH), 7.37 (d, J = 8.6 Hz, 1 H, 8-H), 7.44 (s, 1 H, ArH), 7.43–7.50 (m, 2 H, 5-H, and 7-H), 12.21 (s, 1 H, NH). Anal. calcd for $C_{16}H_{11}Cl_2NO_2$ (320.18): C, 60.02; H, 3.46; N, 4.37. Found: C, 59.90; H, 3.31; N, 4.35.

4-Chloro-6-methoxy-3-(4-methoxyphenyl)quinolin-2(1H)-one (5d). 3-(4-Methoxyphenyl)quinoline **4a** (7.40 g, 22.2 mmol) and methanesulfonic acid (8.0 mL, 70% in water) in 1-butanol (80 mL) were heated under reflux for 48 h and worked up following the method described for **5a**. The yield was 6.47 g (93%), beige prisms, mp 275–277°C (ethanol). IR (ATR): 3435 m, 3179 m, 1649 s (amide-C O), 1622 w, 1609 w, 1595 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 3 H, 6-MeO), 3.83 (s, 3 H, Ar-MeO), 7.01 (d, J = 8.7 Hz, 2 H, $ArH_{AA'}$), 7.27–7.36 (m, 5 H, 5-H, 7-H, 8-H, $ArH_{BB'}$), 12.09 (s, 1 H, NH). Anal. calcd for $C_{17}H_{14}ClNO_3$ (315.76): C, 64.67, H, 4.47, N, 4.44. Found: C, 64.48, H, 4.27, N, 4.42.

4-Chloro-6-methoxy-3-methylquinolin-2(1H)-one (5e). 3-Methylquinoline **4e** (8.50 g, 35.1 mmol) and methanesulfonic acid (7.0 mL, 70% in water) in ethanol (80 mL) were heated under reflux for 48 h and worked up following the method described for **5a**. The yield was 7.19 g (92 %), light yellow prisms, mp 253–256°C (ethanol). IR (KBr): 3431 m, 2842 m, 1649 s (amide-C O), 1625 sh, 1600 sh, 1566 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3 H, Me), 3.81 (s, 3 H, MeO), 7.18–7.23 (m, 2 H, 5-H and 7-H), 7.30 (d, J = 8.7 Hz, 1 H, 8-H), 11.95 (s, 1 H, NH). Anal. calcd for $C_{11}H_{10}ClNO_2$ (223.66): C, 59.07; H, 4.51; N, 6.26. Found: C, 58.95; H, 4.32; N, 6.17.

4-Chloro-3-ethyl-6-methoxyquinolin-2(1H)-one (5f). 3-Ethylquinoline **4f** (2.15 g, 8.40 mmol) and 70% methanesulfonic acid (2.0 mL) in 1-butanol (20 mL) was heated under reflux for 48 h and worked up following the method described for **5a**. The yield was 1.59 g (80%), colorless prisms, mp 215–218°C (ethanol). IR (ATR): 2867 m, 2722 m, 1651 s (amide-C O), 1620 sh, 1597 s cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.07 (t, J = 7.4 Hz, 3 H, Me), 2.72 (q, J = 7.4 Hz, 2 H, CH_2), 3.81 (s, 3 H, MeO), 7.19 (dd, J = 8.7 + 2.8 Hz, 1 H, 7-H), 7.22 (d, J = 2.3 Hz, 1 H, 5-H), 7.28 (d, J = 8.7 Hz, 1 H, 8-H), 11.95 (s, 1 H, NH). ^{13}C NMR (90 MHz, DMSO-d_6): δ 12.5 (Me), 21.9 (CH_2), 55.9 (MeO), 106.5 (ArC), 117.3 (ArC), 118.7 (ArC), 120.2 (ArC), 131.8 (ArC), 134.2 (ArC), 139.8 (4-C), 155.0 (6-C), 160.9 (2-C O). Anal. calcd for $C_{12}H_{12}ClNO_2$ (237.69): C, 60.64; H, 5.09; N, 5.89. Found: C, 60.43; H, 4.89; N, 5.82.

6-Methoxy-2-oxo-3-phenyl-1,2-dihydroquinoline-4-carbonitrile (6a). A mixture of 3-phenylquinolone **5a** (3.00 g, 10.51 mmol), sodium *p*-toluenesulfinate (1.87 g, 10.51 mmol) and dry potassium cyanide (2.00 g, 30.8 mmol) in dry dimethylformamide (63 mL) was heated at 120°C for 45 h with vigorous stirring. The solution was cooled to 20°C, poured into ice/water (100 mL) and acidified with concentrated hydrochloric acid to pH = 1–2. The solid was filtered off by suction, washed with water and dried at 40°C under reduced pressure. The yield was 2.76 g (95 %), yellow prisms, mp 263–265° C (acetone). IR (KBr): 3449 s, 2849 m, 2236 w (CN), 1667 s (amide-C O), 1624 w, 1602 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.82 (s, 3 H, MeO), 7.11 (d, J = 2.5 Hz, 1 H, 5-H), 7.30 (dd, J = 9.0 + 2.6 Hz, 1 H, 7-H), 7.35 (d, J = 9.0 Hz, 1 H, 8-H), 7.48–7.50 (m, 3 H, PhH), 7.59 (dd, J = 7.5 + 2.4 Hz, 2 H, PhH), 12.44 (s, 1 H, NH). ^{13}C NMR (90 MHz, DMSO-d_6): δ 55.9 (Me), 106.6 (ArC), 115.2 (ArC), 117.7 (ArC), 119.2 (CN), 121.5 (ArC), 128.4 (PhC), 129.8 (2 $ArC_{AA'}$), 130.4 (2 $ArC_{BB'}$), 133.2 (9-C), 133.7 (PhC), 141.1 (3-C), 155.4 (6-C O), 159.3 (amide-C O at C-2). UV (DMSO): λ (ε, M^{-1} cm^{-1}) = 402 (4850) nm; UV (water): λ (ε, M^{-1} cm^{-1}) = 400 (5100) nm. Fluorescence (DMSO): λ (Φ_F) = 505 (0.06); Fluorescence (water): λ (Φ_F) = 500 (0.05). MS (APCI, pos): m/z (%) = 277 (100, M + 1). MS (APCI, neg): m/z (%) = 276 (19, M), 275 (100, M − 1). Anal. calcd for $C_{17}H_{12}N_2O_2$ (276.30): C, 73.90; H, 4.38; N, 10.14. Found: C, 73.62; H, 4.11; N, 9.92.

3-(4-Chlorophenyl)-6-methoxy-2-oxo-1,2-dihydroquinoline-4-carbonitrile (6b). A mixture of 3-(4-chlorophenyl)quinolone **5b** (1.60 g, 5.10 mmol), sodium *p*-toluenesulfinate (0.89 g, 5.10 mmol), and dry potassium cyanide (0.81 g, 12.51 mmol) in dry dimethylformamide (30 mL) was heated to 120°C for 63 h and worked up following the method described for **6a**. The yield was 1.52 g (98 %), yellow prisms, mp 332–333.5°C (acetone). IR (ATR): 3434 m, 2231 w (CN), 1670 s (amide-C O), 1623 w, 1607 w, 1595 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3 H, MeO), 7.15 (d, J = 2.1 Hz, 1 H, 5-H), 7.35 (dd, J = 9.1 + 2.3 Hz, 1 H, 7-H), 7.41 (d, J = 9.0 Hz, 1 H, 8-H), 7.58 (d, J = 8.6 Hz, 2 H, $ArH_{AA'}$), 7.63 (d, J = 8.6 Hz, 2 H, $ArH_{BB'}$), 12.50 (s, 1 H, NH). ^{13}C NMR (90 MHz, DMSO-d_6): δ 56.1 (MeO), 106.7 (10-C), 115.2 (5-C), 117.4 (4-C), 117.8 (7-C), 119.5 (CN), 121.8 (8-C), 130.8 (2 $ArC_{BB'}$), 132.4 (2 $Ar_{AA'}$), 132.6 (9-C), 133.4 (aryl-C), 134.7 (aryl-C), 139.9 (3-C), 155.5 (6-C O), 159.1 (amide-C O at C-2). UV (DMSO): λ (ε, M^{-1} cm^{-1}) = 311, 406 (9270, 6840) nm. Fluorescence (DMSO): λ (Φ_F) = 510 (0.23). MS (ESI, neg): m/z (%) = 310 (35, M), 309 (100, M − 1). Anal. calcd. for $C_{17}H_{11}ClN_2O_2$ (310.75): C, 65.71; H, 3.57; N, 9.01. Found: C, 66.09; H, 3.18; N, 8.63.

3-(3-Chlorophenyl)-6-methoxy-2-oxo-1,2-dihydroquinoline-4-carbonitrile (6c). A mixture of 3-(3-chlorophenyl)quinolone **5c** (2.50 g, 7.81 mmol), sodium *p*-toluenesulfinate (1.60 g, 8.98 mmol) and dry potassium cyanide (1.70 g, 26.2 mmol) in dry dimethylformamide (50 mL) was heated to 130°C for 43 h and worked up following the method described for **6a**. The yield was 2.35 g (97%), greenish prisms, mp 328–330°C (acetone). IR (ATR): 2823 m, 2230 w (CN), 1661 s (amide-C O), 1623 m, 1501 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.86 (s, 3 H, MeO), 7.18 (d, J = 2.0 Hz, 1 H, 5-H), 7.37 (dd, J = 9.1 + 2.3 Hz, 1 H, 7-H), 7.41 (d, J = 9.0 Hz, 1 H, 8-H), 7.57 (m, 3 H, ArH), 7.70 (s, 1 H, ArH), 12.54 (s, 1 H, NH). UV (DMSO): λ (ε, M^{-1} cm^{-1}) = 310, 408 (7080, 5500) nm. Fluorescence (DMSO): λ (Φ_F) = 510 (0.11). Anal. calcd for $C_{17}H_{11}ClN_2O_2$ (310.74): C, 65.71; H, 3.57; N, 9.01. Found: C, 65.30; H, 3.45; N 8.86.

6-Methoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-4-carbonitrile (6d). A mixture of 3-(4-methoxyphenyl)quinolone **5d** (1.60 g, 5.11 mmol), sodium *p*-toluenesulfinate (0.91 g, 5.10 mmol), and dry potassium cyanide (1.00 g, 15.3 mmol) in dry dimethylformamide (30.0 mL) was heated to 120°C for 72 h and worked up following the method described for **6a**. The yield was 1.50 g (96 %), yellow prisms, mp 275–278°C (acetone). IR (KBr): 3432 m, 2839 m, 2229 w (CN), 1658 s (amide-C O), 1624 m,

1606 s, 1574 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3 H, ArOMe), 3.85 (s, 3 H, 6-MeO), 7.06 (d, J = 8.7 Hz, 2 H, $ArH_{BB'}$), 7.16 (d, J = 2.4 Hz, 1 H, 5-H), 7.32 (dd, J = 9.0 + 2.4 Hz, 1 H, 7-H), 7.38 (d, J = 9.0 Hz, 1 H, 8-H), 7.58 (d, J = 8.6 Hz, 2 H, $ArH_{AA'}$), 12.41 (s, 1 H, NH). ^{13}C NMR (90 MHz, DMSO-d_6): δ 55.7 (MeO at C-6), 55.9 (4-MeO at Ph), 106.6 (ArC), 113.8 (2 $ArC_{AA'}$), 115.6 (ArC), 117.6 (ArC), 118.3 (CN), 121.2 (ArC),125.7 (ArC), 132.1 (2 $ArC_{BB'}$), 132.9 (ArC), 140.8 (ArC), 155.4 (6-C O), 159.4 (4-C at Ph), 160.7 (amide-C O at C-2). UV (DMSO): λ (ε, M^{-1} cm^{-1}) = 341, 405 (8490, 10370) nm. Fluorescence (DMSO): λ (Φ_F) = 503 (0.20). MS (ESI, neg): m/z (%) = 306 (21, M), 305 (100, M − 1). Anal. calcd for $C_{18}H_{14}N_2O_3$ (306.32): C, 70.58; H, 4.61; N, 9.15. Found: C, 70.19; H, 4.40; N, 9.01.

2-Chloro-6-methoxy-3-phenylquinoline-4-carbonitrile (7). A solution of 3-phenylquinoline-4-carbonitrile **6d** (1.37 g, 5.00 mmol) in phosphorylchloride (6.0 mL) was heated under reflux at 110°C for 12 h. The solution was cooled to 50°C and the excess amount of phosphorylchloride was removed under reduced pressure. The residue was poured onto ice/water (100 mL), filtered by suction and washed with water. The yield was 1.39 g (95%), yellowish prisms, mp 242–245°C (ethanol). IR (KBr): 3439 s, 2236 w (CN), 1618 m, 1561 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 4.00 (s, 3 H, MeO), 7.36 (d, J = 2.7 Hz, 1 H, 5-H), 7.59 (s, 5 H, PhH), 7.68 (dd, J = 9.3 + 2.7 Hz, 1 H, 7-H), 8.11 (d, J = 9.3 Hz, 1 H, 8-H). Anal. calcd for $C_{17}H_{11}ClN_2O$ (294.74): C, 69.28; H, 3.76; N, 9.50. Found: C, 69.67; H, 3.38; N, 9.12.

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