6-Methoxy-2-oxo-1,2-dihydroquinoline-3,4-dicarbonitriles, A Red Compound Class with Solvent and pH Independent Green Fluorescence Maxima

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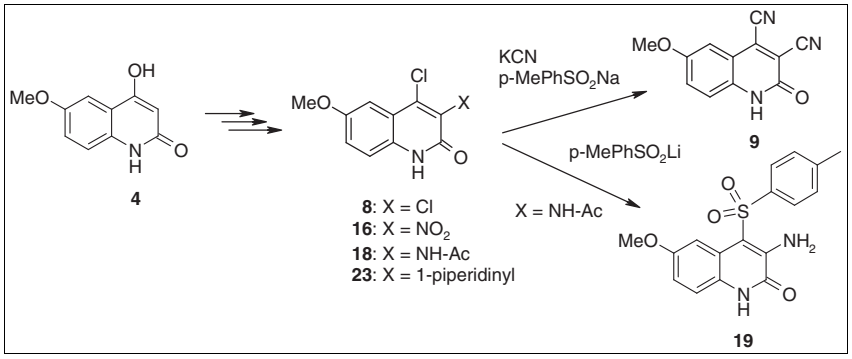

The sodium *p*-toluenesulfinate mediated reaction of potassium cyanide with 4-chlorocarbostyrils **8**, **16**, **18**, and **23** gave in all cases the highly fluorescent and stable 6-methoxy-2-oxoquinoline-3,4-dicarbonitrile **9** (λ_{exc} 460 nm and λ_{em} 545 nm). This is remarkable, because starting carbostyrils **8**, **16**, **18**, and **23** had a chloro substituent, a nitro substituent, an acetylamino substituent, or a piperidinyl substituent in position 3. Hence, we observed not only a substitution of the 4-chloro and expected 3-chloro substituents by the cyanide nucleophile but also an exchange of a nitro substituent, an acetylamino substituent, and a piperidinyl substituent in position 3. The multistep insertion of substituents leading to **8**, **16**, **18**, and **23** started from 4-hydroxy-6-methoxyquinolone **4**, easily obtained from *p*-anisidine and malonic acid. Substitutions in position 3 gave 4-hydroxy-3-nitro and 3-chloro intermediates, which were converted to 3,4-dichlorocarbostyril **8** and 4-chloro-3-nitrocarbostyril **16**. Reduction of the 3-nitro intermediate led to the 3-acetylamino analog and subsequent chlorination led to 3-acetylamino-4-chlorocarbostyril **18**. 4-Chloro-3-piperidinylcarbostyril **23** was obtained from intermediate 3,3-dichloroquinolinedione by subsequent amination, reduction and chlorination. Further, 3-acetylamino-4-chlorocarbostyril **18** gave with lithium *p*-toluenesulfinate highly fluorescent 3-amino-6-methoxy-4-p-tolylsulfonylquinolone **19**.

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INTRODUCTION

In earlier investigations, we have shown that 6,7-dimethoxy-4-trifluoromethylcarbostyrils [1] and 4-cyano-6,7-dimethoxycarbostyrils [2] are highly fluorescent compounds with emission values up to 440 nm, and high quantum yields up to 0.6. Together with further properties such as a high thermal and photochemical stability and no oxygen quenching make them very useful as new fluorophors (e.g. shown in Ref. [3]) suitable to outclass similar and wide-used coumarin derivatives [4]. In a recent project, we reported about the interesting fluorescence properties of 3-aryl-4-cyano-6-methoxycarbostyrils [5] with excitation wavelengths above 400 nm and emission wavelengths above 500 nm, with quantum yields of about $\Phi = 0.23$. Attempts for a fine tuning of these values with donor and acceptor substituents at the aryl nucleus in position 3 showed no significant effect (the emission values range between 503 and 510 nm).

In this communication, we report about our investigation on the synthesis of derivatives of 4-cyano-6-methoxycarbostyrils containing a variety of substituents in position 3 to study the influence of donor and acceptor groups on the electronic spectra.

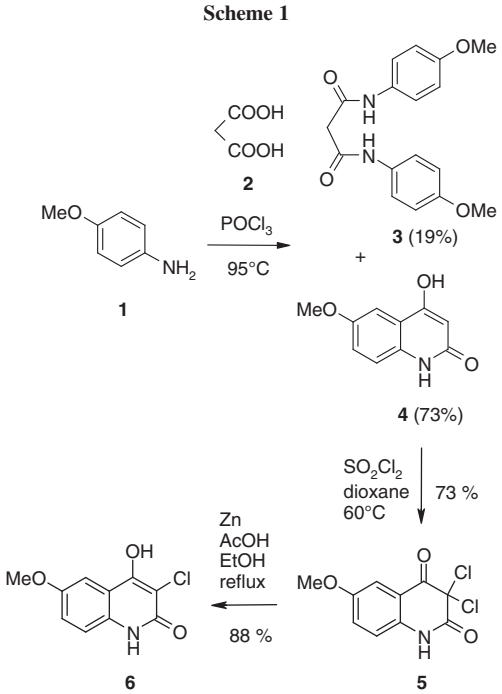
RESULTS AND DISCUSSION

Synthesis. 4-Hydroxy-6-methoxy-2-quinolone (**4**) serves as starting compound for the planned multistep syntheses of the desired fluorescent 4-cyano-6-methoxycarbostyrils. In the literature, several syntheses for quinolone **4** are published, starting from *p*-anisidine (**1**) that cyclized to the quinoline nucleus either with diethylmalonate [6], malonic acid [7], or Meldrum's acid [8]; another approach to **4** was reported starting from 5-methoxy-nitrobenzoyl chloride and diethyl malonate followed by reduction [9]. Our approach started from *p*-anisidine (**1**) and malonic acid (**2**) using phosphoryl chloride as cyclization agent similar as described in Refs. [7,10]. Phosphoryl chloride is reported to act in two

steps, first to convert malonic acid (**2**) to a reactive malonic-halfamide intermediate, and then as cyclocondensation agent for the acylation at the reactive aromatic amine **1**. In the literature [7,10], quinolone **4** was obtained in 63% yield; and as by-product, *N*,*N*′-bis(4-methoxyphenyl)malonamide **(3)** was obtained in 32% yield. Optimization attempts by changing the ratio of *p*-anisidine, malonic acid, and phosphoryl chloride, reaction time and work-up gave best results when only a small excess of phosphoryl chloride and a reaction temperature of 90–95 °C for 90 min were used, then pouring the mixture onto ice water and doing work-up by dissolving the crude material in a large excess of 1 *M* sodium hydroxide solution. In this case, **4** was obtained in 73% yield together with 19% of the dianilide **3** as by-product. Scheme 1.

In order to introduce electron acceptor substituents in position 3 of quinolone **4**, two approaches were chosen: chlorination and nitration. Electrophilic chlorination with sulfuryl chloride provides a Cl^+ source known to give in similar systems 3,3-dichloroquinolinediones [11]; a radical process can be ruled out because all requirements for this reaction type such as high temperature, radical starters, or light irradiation were missing. In contrast, reactive 4-hydroxyquinolones and similar systems are known to need cooling to avoid multi-chlorination [11]. The chlorination of **4** was carried out in dioxane keeping the temperature at 40–50 °C by dropwise addition of sulfuryl chloride. The reaction temperature must be kept below 60 °C because otherwise many unwanted by-products were formed—mainly chlorinations at the reactive benzene nucleus [11]—which were difficult to separate. As product, 3,3-dichloro-6-methoxyquinolinedione **5** was isolated in 73% yield, showing two expected carbonyl signals at 1725 and 1688 cm^{-1}. Reduction of **5** with zinc dust in refluxing ethanolic acetic acid gave a selective removal of one chloro substituent to form 3-chloro-4-hydroxy-6-methoxyquinolone **6** in an excellent yield of 89%. The end of the monodechlorination is shown when the yellow color of the reaction mixture changes to a greenish color. This must be observed carefully because otherwise the addition of more zinc dust results in the removal of the second chloro substituent, and the pre-starting material, 4-hydroxyquinolone **4**, is formed back.

Scheme 1



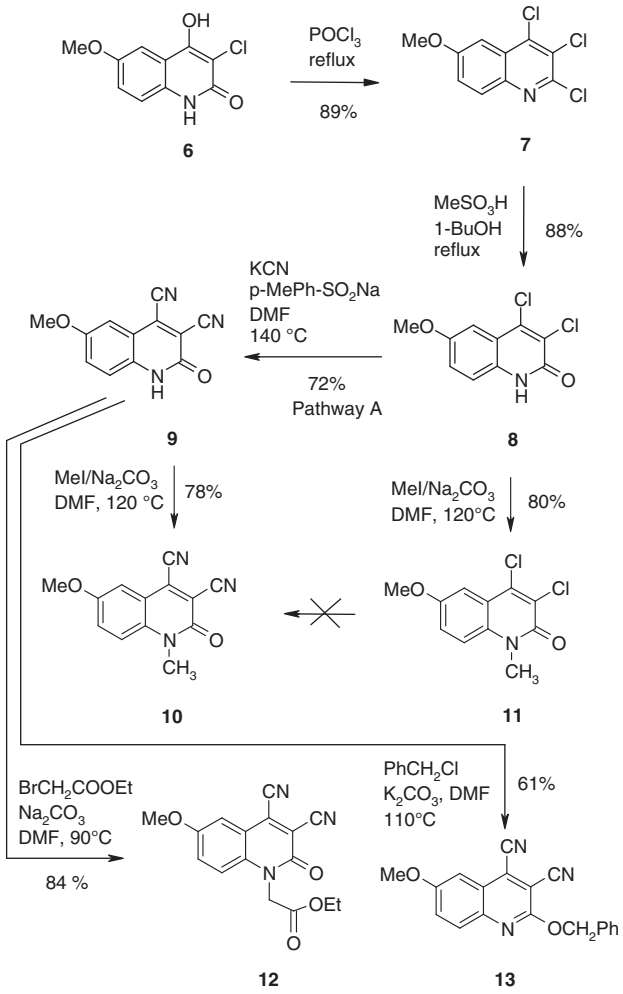
The next step in the reaction sequence was the exchange of the rather inreactive hydroxy group in position 4 against a better leaving group. Our earlier investigations revealed that a 4-chloro group would be the best choice, both in synthesis, stability and then in further exchange reactions [2,5]. The transformation of **6** to the intended reactive 4-chloroquinolone **8** needed two steps, because a single regioselective substitution of the 4-hydroxy group of **6** could not be performed: with phosphoryl chloride, the completion of the reaction resulted in the formation of 2,3,4-trichloroquinoline **7** in excellent yields, confirmed by the lack of the carbonyl function at position 2 in the IR spectra.

In order to obtain a regioselective hydrolysis of the chlorine at position 2 of the quinoline nucleus in acidic media such as methanesulfonic acid, a number of solvents had to be tested to form 3,4-dichloroquinolone **8**. The conditions we have described for similar systems [2] using ethanol as the solvent gave here a mixture of compounds. Among a series of solvents, we found that refluxing 1-butanol revealed the best results in yields and purity for 3,4-dichloroquinolone **8**, whereas higher boiling solvents (e.g. DMF or dodecanol) caused a partial hydrolysis of both chloro substituents back to its oxygen origins. Methanesulfonic acid in 1-butanol [5] attacked regioselectively the 2-chloro function to form back the 2-oxo function producing 3,4-dichloroquinolone **8** in excellent yields (IR: C=O at 1657 cm^{-1}, ^{1}H NMR: NH at 12.47 ppm). 3,4-Dichloroquinolone **8** served now as reactive starting material for the introduction of the cyano substituent in position 4. Scheme 2

Recently, we were able to show that the introduction of cyano substituents into 4-chloroquinolones was performed with best results from potassium cyanide using *p*-toluenesulfinate as catalyst, forming reactive intermediates [2, and references cited therein].

Other approaches described in the literature such as the reaction with copper(II) cyanide according to the Rosenmund–Brown aromatic cyanation gave low yields and impure products [2, and references cited therein]; the use of crown ethers gave no products. The treatment of 3,4-dichloroquinolone **8** with dry potassium cyanide in the presence of dry sodium *p*-toluenesulfinate in dry dimethylformamide gave at

Scheme 2



140 °C after some hours a mixture of fluorescent compounds. Prolongation of the reaction time resulted in the formation of one single compound showing a strong fluorescence in the green region. Surprisingly, after work-up and analytical evaluation, we found that not only the chloro substituent in position 4 but also the chloro substituent in position 3 was exchanged against a cyano group to yield 6-methoxy-2-oxo-1,2-dihydroquinoline-3,4-dicarbonitrile (**9**). The IR spectra of **9** showed the cyano signal at 2228 cm^{-1} and the lactam carbonyl signal at 1650 cm^{-1}. In the ^{13}C NMR spectra, a signal for the cyano group at 118.8 ppm with intensity of signals twice the usual size was visible. Mass spectra gave a molecular mass of 225 and also elemental analysis gave the correct values for **9**.

In a further continuation of this project, the introduction of linker groups into compound **9** at N-1 is planned, similar to earlier investigations [1,2]. As model compounds for testing the reaction conditions and fluorescence properties of N-alkylated derivatives of **9**, we selected two pathways: either performing the alkylation step at precursor dichloroquinolone **8** with iodomethane, and then reacting the N-methyl derivative **11** with potassium cyanide, or in a reversed order, by alkylation of dicyanoquinolone **9** with iodomethane. The result was that the reaction of the N-alkylated dichloroquinolone **11** obtained from **8** with iodomethane and sodium carbonate in dimethylformamide gave with potassium cyanide only mixtures, whereas N-alkylation of dicyanoquinolone **9** produced in excellent yields N-methylquinolone **10**. In the same manner, the alkylation of dicyanoquinolone **9** with ethyl bromoacetate gave in excellent yields ethyl (3,4-dicyano-2-oxoquinolin-1-yl)acetate **12**. On the other hand, alkylation of dicyanoquinolone **9** with benzylchloride attacked under similar conditions the tautomeric 2-oxo/2-hydroxy group and gave the isomeric product, 2-benzyloxy-6-methoxyquinoline-3,4-dicarbonitrile (**13**); no N-benzyl product could be detected.

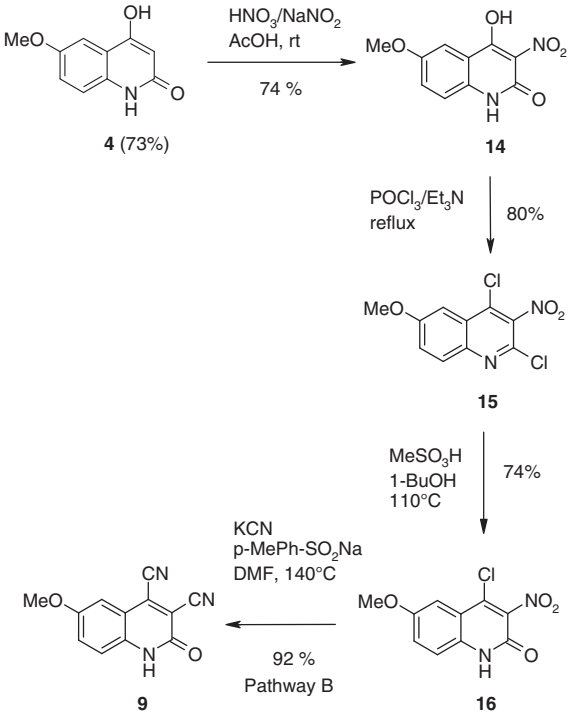
Another well-known electrophilic substitution at position 3 of hydroxyquinolone **4** is the nitration reaction, because the products reveal many biological activities [8,12]. The nitration was performed under mild reaction conditions at room temperature with nitric acid in acetic acid using sodium nitrite as catalyst [13], which prevents by-products such as benzo-nitrated quinolones formed with higher reaction temperatures. 4-Hydroxy-3-nitroquinolone **14** was obtained in a pure form and in good yields by this method. The reaction with phosphoryl chloride gave again a bis-chlorination and yielded the dichloroquinoline **15**. The addition of triethylamine both accelerated the reaction and increased the yield obviously because hydrogen bondings between the 4-hydroxy and the 3-nitro group were destructed. Similar as described for compound **8**, 4-chloro-3-nitroquinolone **16** was obtained by regioselective hydrolysis at position 2 with methanesulfonic acid in 1-butanol. Scheme 3.

The reaction of the **16** with dry potassium cyanide in the presence of dry sodium *p*-toluenesulfinate in dry dimethylformamide gave at 140 °C already after 2–3 h reaction time, a single product with strong green fluorescence properties. After work-up and interpretation of the spectra, it was obvious that again the same product as obtained from **8**, namely 6-methoxy-2-oxo-1,2-dihydroquinoline-3,4-dicarbonitrile (**9**) was isolated in excellent yields. This fact means that again also the substituent in position 3, the nitro group, was exchanged against the cyano substituent.

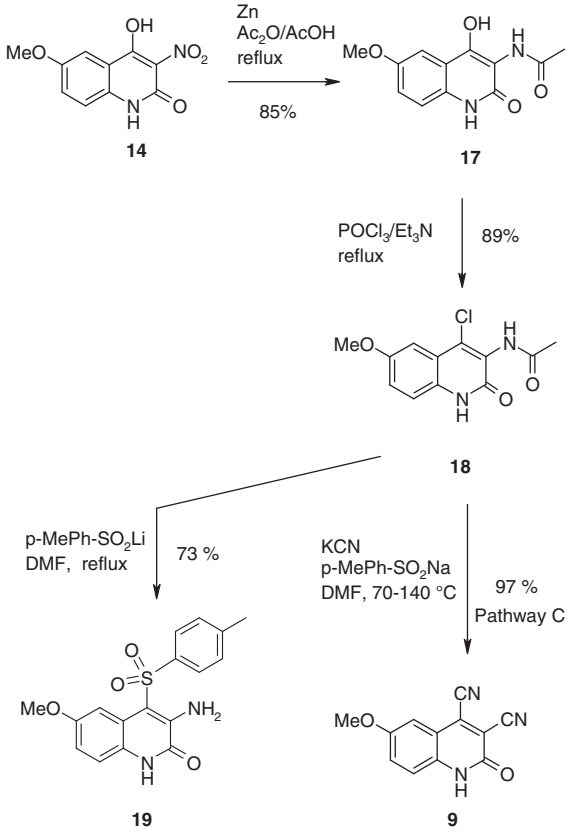
Both investigated electron-withdrawing substituents in position 3, the 3-chloro and the 3-nitro group, did not allow us to perform the introduction of a single cyano group in position 4. However, on the other hand, we fortunately obtained in this way a 4-cyano compound having additionally the 3-cyano group that allowed us to study the effect of a strong electron withdrawing group in *ortho* neighborhood.

In the next step, we planned the synthesis of 6-methoxy-2-quinolones having an electron-donor group in position 3. The first reaction sequence started from 4-hydroxy-3-

Scheme 3



Scheme 4



nitroquinolone **14**, where the 3-nitro group was reduced with zinc in acetic acid as mild reduction agent. Other agents such as sodium dithionite gave no satisfying results [14]. The resulting 3-amino group is not very stable and was therefore stabilized by acetylation [15] to give in excellent yields 3-acetylamino-4-hydroxyquinolone **17**. Chlorination with phosphoryl chloride using again triethylamine as catalyst gave surprisingly only a selective monochlorination in position 4 probably caused by hydrogen bondings between the acetyl and the hydroxy group. A dichlorination at the 2- and 4-position as observed with 3-nitroquinolone **14** did not take place. As product, 3-acetylamino-4-chloroquinolone **18** was obtained in excellent yield. Scheme 4.

The reaction of 4-chloroquinolone **18** with dry potassium cyanide in the presence of dry sodium *p*-toluenesulfinate in dry dimethylformamide gave again at 140 °C after 45 h reaction time 6-methoxy-2-oxo-1,2-dihydroquinoline-3,4-dicarbonitrile (**9**) in excellent yields by cleavage of the acetylamino group. Shorter reaction time or lower temperatures resulted in a mixture of a number of fluorescent compounds, with **18** as the main product (65–86%).

Recently, we found in first experiments that quinoline-tosylates and quinoline-sulfones are a new class of fluorescent compounds [16]. Attempts to produce that class of compounds from nitro derivatives such as 2,4-dichloroquinoline **15** or 4-chloroquinolone **16** with sodium *p*-toluenesulfinate were unsuccessful because no reaction was observed. When lithium *p*-toluenesulfinate was used in this reaction, a mixture of fluorescent compounds was produced; however, we could not isolate a pure product because of persistent co-crystallization and the almost equal chromatographic properties. The reaction of hydroxy-nitroquinolone **14** or acetylamino-hydroxyquinolone **17** with tosylchloride gave mixtures of several ditosylates that could not be isolated in a pure form; similar results were obtained in the reaction of **14** or **17** with methylbenzenesulfonyl chloride [17]. 3-Acetylamino-4-chloroquinolone **18** reacted with lithium *p*-toluenesulfinate in refluxing dry dimethylformamide in good yields to the sulfone **19** by cleavage of the acetyl group. This compound showed as expected a strong fluorescence already visible during TLC detection. The structural elucidation by IR and ^{1}H NMR spectra gave the expected signals of lactam, methoxy and NH groups. The ^{13}C NMR spectra favor the sulfone structure (and not the possible sulfinyloxy derivative) because only two signals can be assigned to a C–O bonding: 156.2 ppm (2-CO) and 155.1 ppm (6-O). A third C–O signal supporting the structure of a 4-sulfinyloxy derivative is missing. This result is supported by findings in the literature, which favor the formation of sulfones from arylsulfinates and activated halogenoarenes. [18].

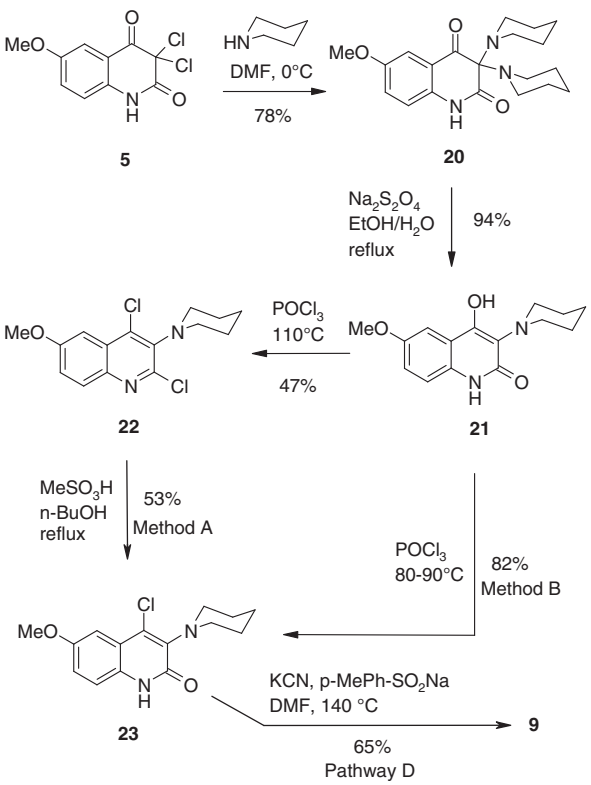
A further approach to obtain a 4-cyanoquinolone with an electron-donor group in position 3 was planned via a 3-*N*,*N*-disubstituted aminoquinolone. Adapting a literature-known reaction sequence for the introduction of piperidinyl

substituents [19], we started from dichloroquinolinedione **5**, which gave by reaction with piperidine already at 0 °C 3,3-dipiperidinylquinolinedione **20**. Reductive cleavage of one piperidinyl substituent with sodium dithionite gave 4-hydroxy-3-piperidinylquinolone **21**. The reaction with phosphoryl chloride formed—similar as observed in **6** and **14**—the 2,4-dichloro-3-piperidinylquinoline **22**, which was regioselectively hydrolyzed with methanesulfonic acid to 4-chloro-3-piperidinylquinolone **23**. Scheme 5

When 4-chloro-3-piperidinylquinolone **23** reacted with dry potassium cyanide in the presence of dry sodium *p*-toluenesulfinate in dry dimethylformamide at 140–150 °C, after a reaction time of several days, a mixture of a number of fluorescent and decomposition products was obtained. Among them again quinoline-3,4-dicarbonitrile **9** could be isolated in 65% yield; a further very strong fluorescent product was isolated via HPLC separation, which showed very interesting fluorescence properties, with again an absorption maximum at 450 nm and an emission maximum at 570 nm, and an excellent quantum yield of $\Phi = 0.79$. However, separation of a sufficiently pure product and structural elucidation was not successful.

Electronic spectra. 6-Methoxy-2-oxo-1,2-dihydroquinoline-3,4-dicarbonitrile (3,4-dicyano-6-methoxycarbostyril) (**9**) is our hitherto most advanced push–pull substituted fluorescent carbostyril. The single methoxy group in 6-position in combination with the 2 cyano groups in position 3 and 4 causes a strong red shift compared with analogs we have investigated in recent years [1,2,5], which makes this structure very interesting for fluorescence investigations. The fluorescence measurement with an excitation wavelength of $\lambda_{exc} = 460$ nm produces an emission wavelength of $\lambda_{em} = 545$ nm, which means a further red shift of about 40–50 nm compared with our most long-wave fluorescent compounds, 3-aryl-4-cyano-6-methoxycarbostyrils [5]. The quantum yield, however, gave a value of $\Phi_F = 0.13$, which is no improvement compared with the recently investigated compounds. N-Alkyl derivatives of the dicyanocarbostyril, such as N-methylquinolone **10** and quinolinyl-N-acetate **12**, showed similar values of 543 and 535 nm, however, with similar low quantum yields. These results show that the intended use of N-alkyl linkers do not influence the photophysical properties. Further investigations on photophysical properties revealed that in structures **9**, **10**, and **12** there is nearly no solvent dependance visible (e.g. $\lambda_{em} = 535$ nm in dimethylsulfoxide and $\lambda_{em} = 550$ nm in acetonitrile for **12**) and also no pH dependance and oxygen quenching was observed. 3-Amino-4-p-tolylsulfonylquinolone **19** shows a blue shifted fluorescence maximum at 455 nm, together with a comparable quantum yield of $\Phi_F = 0.10$. The blue shift seems to be caused at least in part by the 3-amino group as donor substituent [16].

Scheme 5



CONCLUSIONS

Quinoline-4-carbonitriles with different electron acceptor and donor substituents in position 3 for comparison of the fluorescence properties were not obtained, because in all cases not only the substituent in 4-position but also the substituent in 3-position were exchanged during the reaction with potassium cyanide and toluenesulfinate against a further cyano substituent. So in all cases, quinoline-3,4-dicarbonitrile **9** was obtained as the main product. Milder reaction conditions resulted only in mixtures of intermediate compounds. The fluorescent properties show in both compounds a dramatic red shift up to the green area of 560 nm influenced by the 3-cyano substituent, however, accompanied with a rather low quantum yield of max. $\Phi_F = 0.13$. With lithium *p*-toluenesulfinate we obtained from 4-chloro substituted **18**, a new representative of push–pull substituted fluorescent carbostyrils, 4-p-tolylsulfonylquinolone **19**, which will be further investigated.

EXPERIMENTAL

General. Melting points were determined in open capillary tubes using a Stuart SMP3 Melting Point Apparatus (Bibby Scientific Limited, Stone, Staffordshire, UK). IR spectra were recorded either with a Mattson Galaxy Series FTIR 7020 instrument (Mattson Instruments, Ltd. Milton Keynes, England) in potassium bromide disks, or with a Bruker Alpha-P (Bruker

GmbH, Karlsruhe, Germany) with Attenuated Total Reflectance (ATR) measurement, using a reflexion method. NMR spectra were recorded either on a Bruker AMX 360 instrument (Bruker GmbH, Karlsruhe, Germany) (360 MHz ^{1}H, 90 MHz ^{13}C), or on a Bruker Avance III instrument (Bruker GmbH, Karlsruhe, Germany) (300 MHz ^{1}H), or on a Bruker Avance DRX 500 instrument (Bruker GmbH, Karlsruhe, Germany) (500 MHz ^{1}H, 125 MHz ^{13}C). Chemical shifts are given in parts per million (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 an HP 1100 LC/MSD mass spectral instrument (Agilent Technologies, Santa Clara, California, USA) (either positive or negative atmospheric pressure chemical ionization (APCI) ion source, 50–200 V, nitrogen, or atmospheric pressure-electrospray (AP–ES) electrospray method). UV/Vis spectra were recorded with a Shimadzu UV/Vis scanning spectrophotometer UV-2101 PC (Shimadzu Corp., Kyoto, Japan); concentration: 1×10^{-4} M. Fluorescence data: excitation and emission spectra were recorded with a Perkin–Elmer LS50B luminescence spectrometer (Perkin Elmer Corp., Waltham, Massachusetts, USA). 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 $(n_{water}/n_{solvent})^2$ [4c,d]. Analytical HPLC was performed on a Shimadzu LC 20 system (Shimadzu Corp., Kyoto, Japan) equipped with a diode array detector (215 and 254 nm) on a Pathfinder AS reversed phase (4.6150 mm, 5 μm) column, running mainly in acetonitrile/water gradient (30–100% acetonitrile). Dry column flash chromatography [20] 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 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.

N,N′-Bis(4-methoxyphenyl)malonamide (3). This compound was obtained as insoluble solid by-product during the work-up of 4-hydroxyquinolone **4**. The solid was recrystallized from acetic acid/methanol (1:3). The yield was 9.21 g (19%), gray prisms, mp 228–231 °C (acetic acid/methanol), lit. mp 226–240 °C [6a,7,21]. IR (KBr): 3435 m, 1655 w, 1620 s, 1588 s cm^1. ^{1}H NMR (360 MHz, $CDCl_3$): δ 3.49 (s, 2H, CH_2), 3.81 (s, 6H, 2 MeO), 6.88 (d, J = 8.8 Hz, 4H, ArH), 7.45 (d, J = 8.8 Hz, 4H, ArH), 8.64 (s, 2H, NH).

4-Hydroxy-6-methoxyquinolin-2(1H)-one (4). A mixture of *p*-anisidine (**1**) (19.00 g, 154 mmol) and dry malonic acid (**2**) (23.0 g, 220 mmol) in phosphoryl chloride (40.0 g, 260 mmol) was heated under stirring for 90 min in an open flask to 95 °C, then cooled to 20 °C, poured onto ice/water (500 mL) and filtered by suction. The precipitate was dissolved in aq. sodium hydroxide (1 L, 1 M) at 60 °C. The remaining insoluble *N,N′*-bis(4-methoxyphenyl) malonamide (**3**) was filtered off. 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 21.55 g (73%), yellow prisms, mp 324–328 °C (methanol), lit. mp 298–320 °C [6–9]. IR (ATR): 3434 m, 3290 s, 1663 w, 1642 s, 1616 w, 1602 w cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (s, 3H, MeO), 5.79 (s, 1H, 3-H), 7.14 (dd, J = 8.9 + 2.7 Hz, 1H, 7-H), 7.20 (d, J = 8.8 Hz, 1H, 8-H), 7.21 (d, J = 2.8 Hz, 1H, 5-H), 11.08 (s, 1H, NH).

3,3-Dichloro-6-methoxyquinoline-2,4(1H,3H)-dione (5). A suspension of 4-hydroxyquinolone **4** (35.00 g, 183 mmol) in dioxane (400 mL) was warmed to 40–50 °C; and then under vigorous stirring, sulfuryl chloride (60.0 g, 0.44 mol) was added dropwise keeping the temperature between 50–60 °C. The reaction mixture was then cooled to 20 °C and filtered. The filtrate was poured onto ice/water (1.5 L) under stirring, and the precipitate filtered by suction, washed with water and dried at 40 °C under reduced pressure. The product was pure enough for further reactions. The yield was 34.96 g (73%), yellow prisms, mp 219–223 °C (ethanol), lit. mp 215–216 °C [7]. IR (KBr): 3434 m, 3198 m, 3076 m, 2976 m, 2915 m, 1725 s, 1688 s, 1622 m cm^{-1}. ^{1}H NMR (360 MHz, DMSO-d_6): δ 3.79 (s, 3H, MeO), 7.07 (d, J = 8.5 Hz, 1H, 8-H), 7.28 (d, J = 2.8 Hz, 1H, 5-H), 7.30 (dd, J = 8.6 + 2.9 Hz, 7-H), 11.27 (s, 1H, NH).

3-Chloro-4-hydroxy-6-methoxyquinolin-2(1H)-one (6). To a solution of 3,3-dichloroquinolinedione **5** (5.25 g, 20.2 mmol) in ethanol (50 mL) and acetic acid (25 mL), zinc-dust (5.23 g, 80 mmol) was added in small portions, whereas the solution was kept to boiling. The yellow solution got decolorized (from yellow to gray-greenish), which indicated the end of reaction. The solution was cooled to room temperature and filtered from insoluble zinc reagents. To the filtrate, ice/water (500 mL) was added. The colorless precipitate was filtered by suction, washed with water, and dried at 40 °C under reduced pressure. The yield was 4.02 g (88%), colorless powder, mp 270–273 °C (ethanol). IR (KBr): 3432 m, 1633 w, 1586 s cm^{-1}. ^{1}H NMR (360 MHz, DMSO-d_6): δ 3.68 (s, 3H, MeO), 7.00 (dd, J = 8.7 + 2.6 Hz, 1H, 7-H), 7.12 (d, J = 8.8 Hz, 1H, 8-H), 7.41 (d, J = 2.5 Hz, 1H, 5-H), 10.84 (s, 1H, NH). *Anal.* Calcd. for $C_{10}H_8ClNO_3$ (225.63): C, 53.23; H, 3.57; N, 6.21. Found: C, 53.47; H, 3.29; N, 5.98.

2,3,4-Trichloro-6-methoxyquinoline (7). A solution of 3-chloroquinolone **6** (6.00 g, 26.6 mmol) in phosphoryl chloride (40.0 g, 0.26 mol) was heated under reflux for 8 h. The excess of phosphoryl chloride was removed under reduced pressure, the residue poured onto ice/water (300 mL) and brought to pH = 4–6 with aq. sodium hydroxide (5 *M*). The precipitate was filtered by suction and washed with water and the solid dried at 40 °C under reduced pressure. The yield was 6.24 g (89%), beige powder, mp 276–279 °C (toluene). IR (ATR): 3012 w, 2944 w, 1619 m, 1546 m cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.97 (s, 1H, MeO), 7.40 (d, J = 2.8 Hz, 1H, 5-H), 7.57 (dd, J = 9.2 + 2.7 Hz, 1H, 7-H), 7.96 (d, J = 9.2 Hz, 1H, 8-H). *Anal.* Calcd for $C_{10}H_6Cl_3NO$ (262.52): C, 45.75; H, 2.30; N, 5.34. Found: C, 45.71; H, 2.44; N, 5.27.

3,4-Dichloro-6-methoxyquinolin-2(1H)-one (8). A solution of trichloroquinoline **7** (6.50 g, 24.8 mmol) and 70% methanesulfonic acid (10.0 g, 0.07 mol) in 1-butanol (130 mL) was heated under reflux for 45 h. The mixture was cooled to 20 °C, poured onto ice/water (50 mL), brought to pH = 4–6 with aq. sodium hydroxide (2 *M*) and filtered by suction. The solid was washed with water and dried at 40 °C under reduced pressure. The yield was 5.33 g (88%), beige prisms, mp 264–265 °C (xylene). IR (KBr): 3467 m, 2840 m, 1657 s, 1599 s cm^{-1}. ^{1}H NMR (360 MHz, DMSO-d_6): δ 3.83 (s, 3H, MeO), 7.25 (d, J = 2.2 Hz, 1H, 5-H), 7.30 (dd, J = 8.9 + 2.4 Hz, 1H, 7-H), 7.36 (d, J = 8.9 Hz, 1H, 8-H), 12.47 (s, 1H, NH). *Anal.* Calcd for $C_{10}H_7Cl_2NO_2$ (244.08): C, 49.21; H, 2.89; N, 5.74. Found: C, 49.24; H, 2.83; N, 5.68.

6-Methoxy-2-oxo-1,2-dihydroquinoline-3,4-dicarbonitrile (9). **Pathway A:** A mixture of 3,4-dichloroquinolone **8** (619 mg, 2.54 mmol), sodium *p*-toluenesulfinate (950 mg, 5.34 mmol), and potassium cyanide (410 mg, 6.35 mmol) in dry dimethylformamide (15 mL) was heated to 140 °C for 46 h with vigorous stirring. The resulting solution was cooled to 20 °C and poured onto ice/water

(500 mL). The obtained solid was filtered by suction, washed with water, and dried at 40 °C under reduced pressure. The yield was 408 mg (72%), red prisms, mp 302–306 °C (acetone).

Pathway B: A mixture of 4-chloro-3-nitroquinolone **16** (32 mg, 0.13 mmol), potassium cyanide (30 mg, 0.46 mmol), and sodium *p*-toluenesulfinate (50 mg, 0.28 mmol) in dry dimethylformamide (1 mL) was heated to 140 °C for 2.5 h and worked up using the procedure described for pathway A. The yield was 26 mg (92%), red prisms, mp 301–304 °C (acetonitrile).

Pathway C: A mixture of N-(4-chloroquinolin-3-yl)acetamide **18** (1.67 g, 6.6 mmol), potassium cyanide (1.02 g, 15.7 mmol), and sodium *p*-toluenesulfinate (2.34 g, 13.1 mmol) in dry dimethylformamide (38 mL) was heated to 140 °C for 45 h with vigorous stirring and worked up using the procedure described for pathway A. The yield was 1.37 g (97%), red prisms, mp 300–302 °C (acetonitrile).

Pathway D: A mixture of 4-chloro-3-piperidinylquinolone **23** (340 mg, 1.16 mmol), sodium *p*-toluenesulfinate (440 mg, 2.47 mmol), and potassium cyanide (200 mg, 3.07 mmol) in dry dimethylformamide (7 mL) was heated to 140 °C for 5 days with vigorous stirring and worked up using the procedure described for pathway A. The yield was 171 mg (65%), red-green prisms, mp 297–300 °C (acetonitrile).

IR (KBr): 2972–2742 w, br, 2228 w, 1650 s, 1615 w, 1555 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.88 (s, 3H, MeO), 7.12 (d, $J = 2.7$ Hz, 1H, 5-H), 7.42 (d, $J = 9.2$ Hz, 1H, 8-H), 7.52 (dd, $J = 9.2 + 2.7$ Hz, 1H, 7-H), 13.08 (s, 1H, NH). ^{13}C NMR (90 MHz, DMSO-d_6): δ 56.3 (MeO), 106.5 (3-C), 113.4 (8-C), 114.6 (10-C), 116.7 (5-C), 118.8 (3-CN, 4-CN), 126.4 (7-C), 129.5 (9-C), 135.8 (4-C), 156.1 (6-C), 157.0 (2-C═O). UV (DMSO): λ (ε, $M^{-1}cm^{-1}$) = 319, 460 (7310, 4760) nm. Fluorescence (DMSO): λ (Φ_F) = 545 (0.13). MS (API-ESI neg): *m/z* (%) = 225 (15, M), 224 (100, M − 1), 209 (6, M − 16). MS (API–ESI pos): *m/z* (%) = 264 (17, M + K), 248 (100 M + Na), 226 (8, M + 1). *Anal*. Calcd for $C_{12}H_7N_3O_2$ (225.21): C, 64.00; H, 3.13; N, 18.66. Found: C, 63.70; H, 3.00; N, 18.33.

6-Methoxy-1-methyl-2-oxo-1,2-dihydroquinoline-3,4-dicarbonitrile (10). A mixture of quinoline-3,4-dicarbonitrile **9** (421 mg, 1.87 mmol), iodomethane (685 mg, 4.83 mmol), and dry sodium carbonate (590 mg, 5.56 mmol) in dry dimethylformamide (17 mL) was heated to 120 °C for 25 min. The solution was cooled to 20 °C and poured onto ice/water (50 mL). The obtained solid was filtered by suction, washed with water, and dried at 40 °C under reduced pressure. The yield was 347 mg (78%), red prisms, mp 219–223 °C (ethanol). IR (KBr): 3459–3438 w, br, 3026 w, 2238 w, 1657 s, 1586 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.70 (s, 3H, NMe), 3.91 (s, 3H, MeO), 7.21 (d, $J = 2.3$ Hz, 1H, 5-H), 7.61 (dd, $J = 9.4 + 2.5$ Hz, 1H, 7-H), 7.76 (d, $J = 9.4$ Hz, 1H, 8-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 31.5 (NMe), 56.1 (MeO), 107.29 (ArC), 112.5 (ArC), 113.3 (ArC), 114.6 (ArC), 117.3 (CN), 118.9 (CN), 125.8 (ArC), 128.5 (ArC), 136.5 (ArC), 155.9 (6-C), 156.7 (2-C═O). UV (DMSO): λ (ε, $M^{-1}cm^{-1}$) = 321, 459 (8600, 5720) nm. Fluorescence (DMSO): λ (Φ_F) = 543 (0.08). MS (API–ESI pos): *m/z* (%) = 278 (11, M + K), 262 (100, M + Na), 240 (47, M + 1). *Anal*. Calcd for $C_{13}H_9N_3O_2$ (239.24): C, 65.27; H, 3.79; N, 17.56. Found: C, 65.10; H, 3.59; N, 17.17.

3,4-Dichloro-6-methoxy-1-methylquinolin-2(1H)-one (11). A mixture of 3,4-dichloroquinolone **8** (945 mg, 3.87 mmol), iodomethane (1.60 g, 11.3 mmol), and dry sodium carbonate (1.03 g, 9.7 mmol) in dry dimethylformamide (20 mL) was heated to 120 °C for 25 min, and worked up as described for 1-methylquinoline-3,4-dicarbonitrile **10**. The yield was 798 mg (80%), light yellow prisms, mp 170–179 °C (methanol). IR (ATR): 2998 w, 1644 s, 1585 w cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.67 (s, 3H, NMe), 3.85 (s, 3H, MeO), 7.31 (d, $J = 2.7$ Hz, 1H, 5-H), 7.36 (dd, $J = 9.2 + 2.7$ Hz, 1H, 7-H), 7.57 (d, $J = 9.2$ Hz, 1H, 8-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 31.5 (NMe), 56.1 (MeO), 107.7 (ArC), 117.7 (ArC), 118.8 (ArC), 121.1 (ArC), 126.1 (ArC), 132.5 (ArC), 139.8 (4-C), 155.5 (6-C), 156.2 (2-C═O). *Anal*. Calcd. for $C_{11}H_9Cl_2NO_2$ (258.11): C; 51.19 H, 3.51; N, 5.43. Found: C, 51.06; H, 3.37; N, 5.41.

Ethyl (3,4-Dicyano-6-methoxy-2-oxoquinolin-1(2H)-yl)-acetate (12). A mixture of quinoline-3,4-dicarbonitrile **9** (500 mg, 2.22 mmol), ethyl bromoacetate (910 mg, 5.4 mmol), and dry sodium carbonate (710 mg, 6.7 mmol) in dry dimethylformamide (15 mL) was heated to 90 °C for 15 min. The solution was cooled to room temperature and poured onto ice/water (5 mL). The resulting precipitate was filtered by suction, washed with water, and dried at 40 °C under reduced pressure. The yield was 579 mg (84%), yellow prisms, mp 216−219 °C (ethanol). IR (KBr): 3143 w, 2230 w, 1746 s, 1656 s, 1557 s cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.22 (t, $J = 7.0$ Hz, 3H, Me), 3.92 (s, 3H, MeO), 4.17 (q, $J = 7.0$ Hz, 2H, CH_2), 5.20 (s, 2H, NCH_2), 7.26 (d, $J = 2.7$ Hz, 1H, 5-H), 7.60 (dd, $J = 9.4 + 2.8$ Hz, 1H, 7-H), 7.73 (d, $J = 9.5$ Hz, 1H, 8-H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 14.5 (Me), 45.6 (NCH_2), 56.4 (MeO), 62.1 (OCH_2), 108.5 (ArC), 112.0 (ArC), 113.2 (ArC), 114.2 (ArC), 117.4 (CN), 118.6 (CN), 125.9 (ArC), 129.8 (ArC), 135.9 (4-C), 156.2 (6-C), 156.6 (2-C═O), 167.6 (ester-C═O). UV (DMSO): λ (ε, $M^{-1}cm^{-1}$) = 321, 451 (10000, 9440) nm. Fluorescence (DMSO): λ (Φ_F) = 535 (0.15). UV (MeCN): λ (ε, $M^{-1}cm^{-1}$) = 319, 455 (9440, 5400) nm. Fluorescence (MeCN): λ (Φ_F) = 550 (0.02). MS (API–ESI pos): *m/z* (%) = 305 (51, M + K), 334 (100, M + Na), 312 (62, M + 1). *Anal*. Calcd for $C_{16}H_{13}N_3O_4$ (311.30): C, 61.73; H, 4.21; N, 13.50. Found: C, 61.48; H, 4.06; N, 13.34.

2-Benzyloxy-6-methoxyquinoline-3,4-dicarbonitrile (13). A mixture of quinoline-3,4-dicarbonitrile **9** (900 mg, 4.00 mmol), potassium carbonate (750 mg, 5.4 mmol), and benzylchloride (880 mg, 6.8 mmol) in dry dimethylformamide (65 mL) was heated slowly to 80 °C, then the mixture was kept at this temperature for 3 h until TLC showed no more starting material. Then the temperature was raised to 110 °C for 2 h. The solution was filtered while still hot and the solvent removed under reduced pressure. A thick brown oil was obtained, which crystallized after standing overnight. The solid was purified by dry flash column chromatography using toluene/dichloromethane (3:1) as eluent. The yield was 768 mg (61%), yellow prisms, mp 318–323 °C (toluene/dichloromethane 3:1). IR (KBr): 3435 s, 2924 w, 2231 w, 1620 w, 1584 m cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.98 (s, 3H, MeO), 5.61 (s, 2H, CH_2), 7.30–7.55 (m, 5H, PhH), 7.58 (d, $J = 1.6$ Hz, 1H, 5-H), 7.70 (dd, $J = 9.3 + 2.8$ Hz, 1H, 7-H), 7.96 (d, $J = 9.2$ Hz, 1H, 8-H). *Anal*. Calcd. for $C_{19}H_{13}N_3O_2$ (315.33): C, 72.37; H, 4.16; N, 13.33. Found: C, 72.58; H, 4.01; N, 13.67.

4-Hydroxy-6-methoxy-3-nitroquinolin-2(1H)-one (14). To a mixture of 4-hydroxyquinolone **4** (17.40 g, 90.9 mmol) in glacial acetic acid (200 mL) at room temperature, a mixture of concentrated nitric acid (20 mL) and sodium nitrite (0.85 g, 12.32 mmol, 0.14 eq.) was added within 2 min. A strong exothermic reaction started and the starting material dissolved, followed immediately by precipitation of the product. The mixture was stirred for 45 min at ambient temperature and then

poured onto ice/water (1.5 L), stirred, filtered by suction, and the precipitate washed with water. The solid was dried at 40 °C under reduced pressure and then recrystallized from methanol. The yield was 16.01 g (74%), orange prisms, mp 254–257 °C (methanol). IR (KBr): 3001 m, 2896 m, 2847 m, 1668 s, 1636 w, 1609 s cm^{-1}. ^{1}H NMR (360 MHz, DMSO-d_6): δ 3.81 (s, 3H, MeO), 7.28 (d, J = 8.9 Hz, 1H, 8-H), 7.31 (dd, J = 9.1 + 2.5 Hz, 1H, 7-H), 7.49 (d, J = 2.2 Hz, 1H, 5-H), 11.89 (s, 1H, NH). *Anal*. Calcd. for $C_{10}H_8N_2O_5$ (236.19): C, 50.85; H, 3.41; N, 11.86. Found: C, 50.63; H, 3.67; N, 12.02.

2,4-Dichloro-6-methoxy-3-nitroquinoline (15). A solution of 3-nitroquinolone **14** (3.63 g, 15.37 mmol) and dry triethylamine (2.52 mL) in phosphoryl chloride (18.9 mL) was heated under reflux for 2 h. The excess phosphoryl chloride was removed under reduced pressure. The residue was poured onto ice/water (400 mL) and the solution brought to pH = 4–6 with aqueous sodium hydroxide (5 *M*). The residue was filtered by suction, washed with water, and the remaining solid dried at 40 °C under reduced pressure. The yield was 3.34 g (80%), brown prisms, mp 195–196 °C (dioxane). IR (ATR): 3120 w, 3077 w, 2971 w, 2936 w, 1680 sh, 1616 m cm^{-1}. ^{1}H NMR (360 MHz, DMSO-d_6): δ 4.01 (s, 3H, MeO), 7.52 (d, J = 2.6 Hz, 1H, 5-H), 7.73 (dd, J = 9.4 + 2.5 Hz, 1H, 7-H), 8.10 (d, J = 9.4 Hz, 1H, 8-H). *Anal*. Calcd. for $C_{10}H_6Cl_2N_2O_3$ (273.08): C, 43.98; H, 2.21; N, 10.26. Found: C, 44.27; H, 2.50; N, 10.02.

4-Chloro-6-methoxy-3-nitroquinolin-2(1H)-one (16). A solution of 2,4-dichloroquinoline **15** (5.10 g, 18.67 mmol) and 70% methanesulfonic acid (15.0 g, 0.11 mol) in 1-butanol (100 mL) was heated to 110 °C for 20 h. The mixture was cooled to room temperature and the solid (mainly 4-hydroxyquinolone **14**) was filtered off. The filtrate was poured onto ice/water (300 mL), the solution brought to pH = 4–6 with aq. sodium hydroxide (2 *M*), the precipitate filtered by suction, washed with water, and dried at 40 °C under reduced pressure. The remaining solid was purified by dry flash column chromatography using ethyl acetate as eluent. The yield was 3.52 g (74%), yellow prisms, mp 274–276 °C (chloroform/acetone 3:7). IR (KBr): 3437 m, 2866 m, 1663 s, 1626 w, 1596 w cm^{-1}. ^{1}H NMR (360 MHz, DMSO-d_6): δ 3.87 (s, 3H, MeO), 7.33 (d, J = 2.4 Hz, 1H, 5-H), 7.44–7.47 (m, 2H, 7-H and 8-H), 12.97 (s, 1H, NH). MS (APCI pos): *m/z* (%) = 257 (30, M + 3), 256 (10, M + 2), 255 (100, M + 1). MS (APCI neg): *m/z* (%) = 255 (34, M + 1), 254 (10, M), 253 (100, M − 1). *Anal*. Calcd. for $C_{10}H_7ClN_2O_4$ (254.63): C, 47.17; H, 2.77; N, 11.00. Found: C, 47.26; H, 2.62; N, 10.87.

N-(4-Hydroxy-6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl) acetamide (17). To a solution of 3-nitroquinolone **14** (1.50 g, 6.48 mmol) in acetic acid (50 mL), zinc-dust (2.60 g, 38.90 mmol, 6 eq.) was added in portions until the yellow colored mixture was decolorized. The reaction mixture was then heated under reflux for 15 min. Acetic anhydride (33 mL) was now added, and the mixture heated under reflux for further 15 min. The formed zinc salt was filtered off by suction while hot, and the filtrate taken to dryness under reduced pressure. The remaining residue was dissolved in aq. sodium hydroxide (100 mL, 1 *M*) and stirred for 10 min at room temperature. The solution was filtered and the filtrate acidified with conc. hydrochloric acid to pH = 1–2 under stirring. The precipitate was filtered by suction, washed with water, and dried at 40 °C under reduced pressure. The yield was 1.37 g (85%), beige prisms, mp 304–306 °C (toluene). IR (ATR): 3434 m, 3326 m, 2964 m, 2913 m, 2837 m, 1654 w, 1640 w, 1615 s cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H, Me), 3.79 (s, 3H, MeO), 7.13 (dd, J = 9.0 + 2.7 Hz, 1H, 7-H), 7.22 (d, J = 9.0 Hz, 1H, 8-H), 7.27 (d, J = 2.7 Hz, 1H, 5-H), 9.73 (s, 1H, NHAc), 11.74 (s, 1H, NH), 11.98 (s, 1H, OH). *Anal*. Calcd for $C_{12}H_{12}N_2O_4$ (248.24): C, 58.06; H, 4.87; N, 11.28. Found: C, 57.92; H, 4.62; N, 11.01.

N-(4-Chloro-6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl) acetamide (18). To a solution of N-(4-hydroxyquinolinyl) acetamide **17** (5.50 g, 22.2 mmol) in phosphoryl chloride (45.0 g, 0.29 mmol), dry triethylamine was added (2.70 g, 26.6 mmol), then the solution was heated under reflux for 1 h. The excess phosphoryl chloride was removed under reduced pressure, the residue poured onto ice/water (400 mL) and brought to pH = 4–6 with sodium hydroxide (2 *M*). The mixture was filtered by suction, the solid washed with water, and dried at 40 °C under reduced pressure. The yield was 5.25 g (89%), dark-brown powder, mp 283–285 °C (dioxane). IR (ATR): 3435 m, 3225 m, 3010 w, 2937 w, 1651 s, 1620 m cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.05 (s, 3H, Me), 3.84 (s, 3H, MeO), 7.25 (d, J = 2.4 Hz, 1H, 5-H), 7.31–7.35 (m, 2H, 7-H and 8-H), 9.60 (s, 1H, NHAc), 12.18 (s, 1H, NH). MS (APCI pos): *m/z* (%) = 269 (30, M + 3), 268 (12, M + 2), 267 (100, M + 1), 225 (8, M − 42), *Anal*. Calcd for $C_{12}H_{11}ClN_2O_3$ (266.69): C, 54.05; H, 4.16; N, 10.50. Found: C, 54.30; H, 3.97; N, 10.46.

3-Amino-6-methoxy-4-[(4-methylphenyl)sulfonyl]quinolin-2 (1H)-one (19). To a solution of *N*-(4-chloroquinolin-3-yl) acetamide **18** (150 mg, 0.56 mmol) in dry dimethylformamide (11 mL), lithium *p*-toluenesulfinate (140 mg, 0.88 mmol) was added and the reaction mixture heated under reflux for 16 h, then cooled to room temperature and poured onto ice/water (50 mL). The obtained solid was filtered by suction, washed with water, and dried. The remaining solid was purified by dry flash column chromatography using chloroform/acetone (8:2) as eluent. The yield was 140 mg (73%), yellow prisms, mp 245–247 °C (toluene). IR (ATR): 3475 s, 3360 s, 2837 s, br, 1671 s, 1593 s, sh, 1572 s cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 3H, Me), 3.66 (s, 3H, MeO), 6.80 (dd, J = 9.0 + 2.4 Hz, 1H, 7-H), 7.13 (d, J = 9.9 Hz, 1H, 8-H), 7.38 (d, J = 8.1 Hz, 2H$_{BB'}$, Ar–H), 7.44 (d, J = 2.4 Hz, 1H, 5-H), 7.82 (d, J = 8.4 Hz, 2 H$_{AA'}$, Ar–H), 12.27 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5 (Me), 55.7 (MeO), 106.2 (3-C), 106.8 (5-C), 113.1 (7-C), 117.1 (ArC), 117.1 (8-C), 124.9 (ArC), 126.5 (2 × ArC$_{BB'}$), 130.5 (2 × ArC$_{AA'}$), 139.6 (ArC), 141.8 (ArC), 144.9 (ArC), 155.1 (6-C), 156.2 (2-C=O). UV (ethanol): λ (ε, M^{-1}cm^{-1}) = 356 (14500) nm. Fluorescence (ethanol): λ (Φ_F) = 455 (0.10). UV (DMSO): λ (ε, M^{-1}cm^{-1}) = 354 nm. MS (API–ESI pos): *m/z* (%) = 377 (95, M + 33), 367 (100, M + Na). MS (API–ESI neg): *m/z* (%) = 452 (35, M + 108), 343 (100, M − 1). *Anal*. Calcd. for $C_{17}H_{16}N_2O_4S$ (344.38): C, 59.29; H, 4.68; N, 8.13. Found: C, 59.69; H, 4.46; N, 7.99.

6-Methoxy-3,3-di(piperidin-1-yl)quinoline-2,4(1H,3H)-dione (20). To a solution of 3,3-dichloroquinolinedione **5** (4.60 g, 17.7 mmol) in dry dimethylformamide (20 mL), piperidine (10.0 g, 117 mmol) was added at 0 °C, which gave a dark colored mixture. The temperature raised to 35 °C, and piperidine hydrochloride precipitated. The mixture was stirred for 30 min, cooled to 0 °C, and water (80 mL) was added dropwise to give a precipitate, which was filtered by suction. The solid was washed with water and dried at 40 °C under reduced pressure. The yield was 4.92 g (78%), yellow-green prisms, mp 162–164 °C

(ethanol). IR (KBr): 3435 s, 3202 m, 2932 s, 2851 m, 1688 s, 1657 s, 1616 w cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): δ 1.47–1.54 (m, 12H, 6 piperidine-CH_2), 2.62–2.64 (m, 8H, 4 piperidine-N–CH_2), 3.86 (s, 3H, MeO), 6.82 (d, $J = 8.7$ Hz, 1H, 8-H), 7.11 (dd, $J = 8.7 + 2.7$ Hz, 1H, 7-H), 7.39 (d, $J = 2.7$ Hz, 1H, 5-H), 8.36 (s, 1H, NH). *Anal*. Calcd. for $C_{20}H_{27}N_3O_3$ (357.46): C, 67.20; H, 7.61; N, 11.76. Found: C, 67.59; H, 7.23; N, 11.39.

4-Hydroxy-6-methoxy-3-(piperidin-1-yl)quinolin-2(1H)-one (21). To a refluxing solution of 3,3-di(piperidinyl) quinolinedione **20** (2.00 g, 5.60 mmol) in water/ethanol (1:1, 32 mL), sodium dithionite (2.00 g, 11.5 mmol) was added and the mixture stirred and heated for 30 min under reflux, then cooled to 5 °C and kept 2 h at this temperature. The product precipitated, was filtered by suction, washed with water and dried at 40 °C under reduced pressure. The product was sufficient pure for further reactions. The yield was 1.44 g (94%), beige prisms, mp 228–231°C. IR (KBr): 3439 m, 2991 m, 2952 m, 2851 m, 1638 s, 1597 s cm^{-1}. ^1H NMR (360 MHz, DMSO-d_6): δ 1.50–1.52 (m, 2 H, 1 piperidine-CH_2), 1.70–1.80 (m, 4H, 2 piperidine-CH_2), 3.39 (s, 3H, MeO), 3.73–3.76 (m, 4H, 2 piperidine-N–CH_2), 7.04 (dd, $J = 8.8 + 2.8$ Hz, 1H, 7-H), 7.10 (d, $J = 8.8$ Hz, 1H, 8-H), 7.28 (d, $J = 2.7$ Hz, 1H, 5-H), 10.66 (s, 1H, NH). MS (APCI neg): *m/z* (%) = 274 (5, M), 273 (100, M – 1). MS (APCI pos): *m/z* (%) = 276 (18, M + 2), 275 (100, M + 1). *Anal*. Calcd. for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N; 10.21. Found: C, 65.67; H, 6.37; N, 10.22.

2,4-Dichloro-6-methoxy-3-(piperidin-1-yl)quinoline (22). A solution of 4-hydroxy-3-piperidinylquinolone **21** (905 mg, 3.30 mmol) in phosphoryl chloride (15.0 g, 96.5 mmol) was heated under reflux for 8 h and worked up as described for trichloroquinoline **7**. The yield was 482 mg (47%), brown prisms, mp 182–185 °C (methanol). IR (KBr): 3433 m, 2932 m, 2847 w, 1620 s, 1556 w cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): δ 1.66–1.81 (m, 6H, 3 piperidine-CH_2), 3.23–3.25 (m, 4H, 2 piperidine-N–CH_2), 3.97 (s, 3H, MeO), 7.30 (dd, $J = 9.1 + 2.6$ Hz, 1H, 7-H), 7.39 (d, $J = 2.4$ Hz, 1H, 5-H), 7.86 (d, $J = 9.2$ Hz, 1H, 8-H). *Anal*. Calcd. for $C_{15}H_{16}Cl_2N_2O$ (311.21): C, 57.89; H, 5.18; N, 9.00. Found: C, 57.76; H, 5.34; N, 9.18.

4-Chloro-6-methoxy-3-(piperidin-1-yl)quinolin-2(1H)-one (23).

Method A: A solution of 2,4-dichloro-3-(piperidin-1-yl) quinoline **22** (2.00 g, 6.43 mmol) and 70% methanesulfonic acid (1.5 g, 10.9 mmol) in 1-butanol (15 mL) was heated under reflux for 48 h and worked up as described for dichloroquinolone **8**. The yield was 997 mg (53%), pale green prisms, mp 210–214 °C (ethanol).

Method B: A solution of 4-hydroxy-3-(piperidin-1-yl) quinolone **21** (1.00 g, 3.65 mmol) in phosphoryl chloride (13.0 g, 84 mmol) was heated at 80 °C for 25 min and worked up as described for trichloroquinoline **7** to form directly 4-chloroquinolone **23**. The yield was 875 mg (82%), pale green prisms, mp 213–216 °C (ethanol). IR (KBr): 3454 s, 2840 m, 1643 s, 1599 w cm^{-1}. ^1H NMR (360 MHz, DMSO-d_6): δ 1.56–1.60 (m, 6H, 3 piperidine-CH_2), 3.12–3.14 (m, 4H, 2 piperidin-N–CH_2), 3.82 (s, 3H, MeO), 7.11 (dd, $J = 8.8 + 2.7$ Hz, 1H, 7-H), 7.22 (d, $J = 8.9$ Hz, 1H, 8-H), 7.26 (d, $J = 2.7$ Hz, 1H, 5-H), 11.83 (s, 1H, NH). MS (APCI pos): *m/z* (%) = 295 (33, M + 3), 294 (20, M + 2), 293 (100, M + 1). $C_{15}H_{17}ClN_2O_2$ (292.77): C, 61.54; H, 5.85; N, 9.57. Found: C, 61.23; H, 5.98; N, 9.75.

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REFERENCES AND NOTES

[1] (a) Badgujar, N. S.; Pazicky, M.; Traar, P.; Terec, A.; Uray, G.; Stadlbauer, W. Eur J Org Chem 2006, 2715; (b) Uray, G.; Badgujar, N. S.; Kováčková, S.; Stadlbauer, W. J Heterocyclic Chem 2008, 45, 165; (c) Stadlbauer, W.; Avhale, A. B.; Badgujar, N. S.; Uray, G.; J Heterocyclic Chem 2009, 46, 415;

[2] Avhale, A. B.; Prokopcová, H.; Šefčovičová, J.; Steinschifter, W.; Täubl, A. E.; Uray, G.; Stadlbauer, W. Eur J Org Chem 2008, 563.

[3] Kramer, R. A.; Flehr, R.; Lay, M.; Kumke, M. U.; Bannwarth, W. Helv Chim Acta 2009, 92, 1933.

[4] (a) Piszczek, G.; Maliwal, B. P.; Gryczynski, I.; Jonathan, D.; Lakowicz, J. R. J Fluorescence 2001, 11, 101; (b) Schiedel, M. S.; Briehn, C. A.; Bäuerle, P. Angew Chem Int Ed 2001, 40, 4677; (c) Christie, R. M.; Lui, C.-H. Dyes Pigm 1999, 42, 85; (d) Eggeling, C.; Widengren, R. R. J.; Seidel, C. A. M. Anal Chem 1998, 70, 2651; (e) Christie, R. M. Rev Prog Coloration 1993, 23, 1; (f) Haughland, R. P. In Handbook of Fluorescence Probes and Research Chemicals; Larison, K., Ed.; Molecular Probes Inc: Eugene, USA, 1992; (g) Raue R. In Ullmanns Encyclopedia of Industrial Chemistry; Elvers, B.; Hawkins, S.; Schulz, G., Eds.; VCH: Weinheim, 1990; Vol A15, 5th ed, p 155; (h) Organic Luminescent Materials; Krasovitskii, B. M.; Bolotin, B. M., Eds.; Wiley-VCH: Weinheim, 1988; (i) Siegrist, A. E.; Hefti, H.; Meyer, H. R.; Schmidt, E. Rev Prog Coloration 1987, 17, 39; (j) Brackmann, U. in Lambdachrome Laser Dyes; Lambda Physik GmbH: Göttingen, 1986; (k) Wolfbeis, O. S. In Molecular Spectroscopy: Methods and Applications; Schulman, S. G., Ed.; John Wiley and Sons: New York, 1985; chapter 3; (l) Gold, H. In Environmental Quality and Safety, Supplement Volume IV: The Chemistry of Fluorescent Whitening Agents; Anliker, R.; Müller, G.; Raab, R.; Zinkernagel, R., Eds.; Georg Thieme: Stuttgart, 1975; p 25.

[5] Enoua, G. C.; Uray, G.; Stadlbauer, W. J Heterocyclic Chem 2012, 49, 1415.

[6] (a) Shobana, N.; Yeshosda, P.; Shanmugam, P. Tetrahedron 1989, 45, 757; (b) Nadaraj, V.; Selvi, S. T.; Sasi, R. Arkivoc 2006, 10, 82.

[7] Ziegler, E.; Forraita, H. G.; Kappe, T. Monatsh Chem 1967, 98, 324.

[8] Gao, W. T.; Hou, W. D.; Zheng, M. R.; Tang, L. J. Synth Commun 2010, 40, 732.

[9] Berinzaghi, B.; Muruzabal, A.; Labriola, R.; Deulofeu, V. J Org Chem 1945, 10, 181.

[10] Ziegler, E.; Junek, H.; Nölken, E.; Gelfert, K.; Salvador, R. Monatsh Chem 1961, 92, 814.

[11] (a) Stadlbauer, W.; Laschober, R.; Lutschounig, H.; Schindler, G.; Kappe, T. Monatsh Chem 1992, 123, 617; (b) Ziegler, E.; Kappe, T. Monatsh Chem 1964, 94, 447; (c) Ziegler, E.; Salvador, R.; Kappe, T. Monatsh Chem 1962, 93, 1376; (d) Malle, E.; Stadlbauer, W.; Ostermann, G.; Hofmann, B.; Leis, H. J.; Kostner, G. M. Eur J Med Chem 1990, 25, 137; (e) Laschober, R.; Stadlbauer, W. Liebigs Ann Chem 1990, 1083; (f) Ziegler, E.; Kappe, T. Monatsh Chem 1963, 94, 447.

[12] (a) Hwang, K. J. Arch Pharm Res 2000, 23, 31; (b) Mcleod, A. M.; Grimwood, S.; Barton, C.; Bristow, L., Saywell, K. L.; Marshall, G. R.; Ball, R. G. J Med Chem 1995, 38, 2239; (c) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R.; Mawer I. M.; Thomas, S., Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. J Med Chem 1993, 36, 3397; (d) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Moyes, C. R.; Duncton, M.; Hudson, M. L.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. J Med Chem 1997, 40, 754; (e) Meldrum, B. S. Excitatory Amino Acid Antagonists, Blackwell Scientific: Oxford, 1991; (f) Cai, S. X.; Zhou, Z. L.; Huang, J. C.; Whittemore, E. R.; Egbuwoku, Z. O.; Hawkinson, J. E.; Woodward, R. M.; Weber, E.; Keana, J. F. W. J Med Chem 1996, 39, 4682; (g) Buckle, D. E.; Cantello, B. C. C.; Smith, H.; Spicer, B. A. J Med Chem 1975, 18, 726.

[13] (a) Seidenfaden, W.; Pawellek, D. in Houben-Weyl, Methoden der Org. Chem.; Müller, E., Ed.; Georg Thieme: Stuttgart, 1971; Vol 10/1,

4th ed, p 849; (b) Roschger, P.; Fiala, W.; Stadlbauer, W. J Heterocyclic Chem 1992, 29, 225.

[14] Steinschifter, W.; Fiala, W.; Stadlbauer, W. J. Heterocyclic Chem, 1994, 31, 1647.

[15] (a) Gabriel, S. Ber Dtsch Chem Ges 1918, 51, 1501; (b) Lang, G. PhD thesis, Karl-Franzens University of Graz/Austria, 1972.

[16] Lahm, G. Master thesis, Karl-Franzens University of Graz / Austria, 2011.

[17] Shaugnessy, K. H.; Kim, P.; Hartwig, J. F. J Am Chem Soc 1999, 121, 39.

[18] (a) Schank, K. Liebigs Ann Chem 1967, 702, 75; (b) Neumoyer, C. R.; Armstutz, A. D. J Am Chem Soc 1959, 72, 1424; (c) Ullmann, F.; Lehner, A. Ber Dtsch Chem Ges 1905, 38, 729; (d) Fuller, A. T.; Tonkin, J. M., Walker, J. J Chem Soc 1945, 633; (e) Ullmann, F., Pasdermadjia, G. Ber Dtsch Chem Ges 1901, 34, 1150; (f) Holt, S.; Mason, F. A. J Chem Soc 1931, 377; (g) Roblin Jr, R. O.; Williams, J. H.; Anderson, G. W. J Am Chem Soc 1941, 63, 1930; (h) Ferry, C. W.; Buck, J.; Baltzly, R. Org Synth 1941, 22, 31.

[19] (a) Kappe, T.; Lender, E.; Ziegler, E. Monatsh Chem 1968, 99, 2157; (b) Kappe, T; Hariri, M.; Pongratz, E. Monatsh Chem 1981, 112, 1211.

[20] Harwood, L. M. Aldrichim Acta 1985, 18, 25.

[21] (a) Kutney, G. W.; Still, I. W. Can J Chem 1980, 58, 1233; (b) Pauw, E. A. Rec Trav Chim Pays-Bas Belg 1936, 55, 215; (c) Vaughan, W. R. J Am Chem Soc 1946, 68, 324; (d) Barnikow, G. J. Prakt Chem 1966, 34, 251; (e) Sen, A. K., Basu, U. P. J Indian Chem Soc 1957, 34, 906; (f) Sechi, M.; Azzena, U.; Delussu, M. P.; Dallocchio, R.; Dessi, A.; Cosseddu, A.; Pala, N.; Neamati, N. Molecules 2008, 13, 2442.