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Synthesis of fluorinated 2-phenyl-4-quinolones from pyrrole-2,3-diones †

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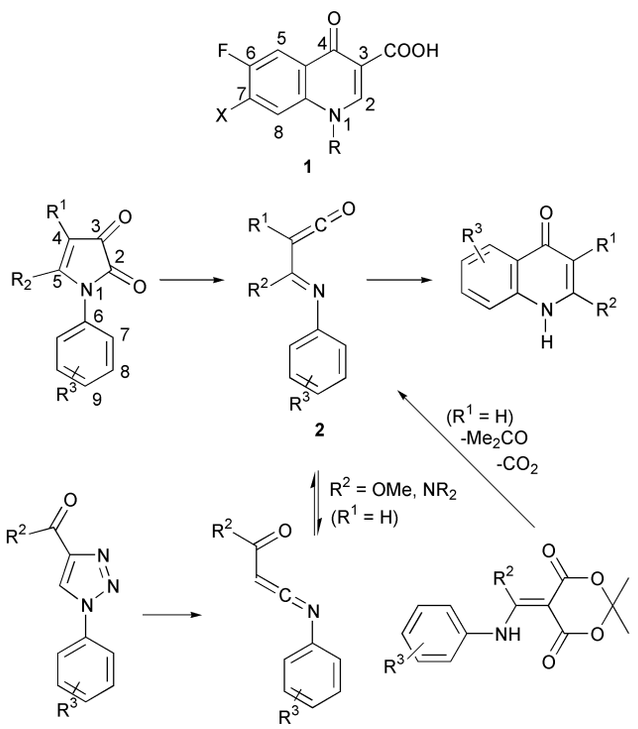
A series of substituted 2-phenyl-4-quinolones **8**–**11** have been synthesized in good yields *via* flash vacuum thermolysis (FVT) of 1-aryl-4-cyano-5-phenylpyrrole-2,3-diones **7a**–**e** and 1-aryl-4-methoxycarbonyl-5-phenylpyrrole-2,3-diones **7f**–**j**. The pyrrolediones **7** were prepared from amines **3** and benzoylacetonitriles **5a**–**e** or methyl 3-arylamino-3-phenylprop-2-enoates **5f**–**j**.

Introduction

Over the past two decades quinolone antibiotics of type **1** have received considerable attention and resulted in an enormous amount of research on new structural modifications to improve the overall spectrum of antibacterial activity. Worldwide efforts have delivered highly successful antibiotics such as ciprofloxacin (**1**, R = cyclopropyl; X = piperazinyl) and norfloxacin (**1**, R = ethyl; X = piperazinyl),[1,2] related naphthyridone antibiotics such as enoxacin[3] and trovafloxacin,[4] and several other drugs.[5] Recent literature indicates that there is a number of new fluoroquinolone drugs in very late clinical development.[6] A typical requirement for high antibiotic activity is a carboxylic acid function in position 3 and a fluorine in position 6 of the quinolone ring. A saturated heterocyclic amine group is usually present in position 7. In the course of our research on the rearrangements and cyclization of ketenes, we have found that imidoylketenes **2** can be generated in several different ways, *viz*. by rearrangement of oxoketenimines formed from triazoles,[7] from 5-aminomethylene-derivatives of Meldrum's acid derivatives,[8] and by CO extrusion from pyrrole-1,2-diones.[9] The imidoylketenes cyclize efficiently to 4-quinolones. Here we report the synthesis of a series of (7,8-substituted) 2-phenyl-6-fluoro-4-quinolones **8**–**11** by means of flash vacuum thermolysis (FVT) of pyrrolediones **7**. It has been shown in another context that 2-phenylquinolones are efficient cytotoxic agents against human lung carcinoma.[10]



Results and discussion

Reaction of substituted anilines **3a**–**e** with benzoylacetonitrile **4a** and methyl benzoylacetate **4f** in AcOH at 80 °C without solvent afforded the corresponding cinnamic nitriles **5a**–**e** (enamino esters) and propionates **5f**–**j** in yields of 52–87% (Table 1). Treatment with oxalyl chloride afforded the pyrrolediones **7**. It has been reported that HCl evolved during the reaction could cause partial decomposition of the pyrrolediones to tetrahydrofurantrione derivatives **6** when phenyl and aliphatic amines were used (Scheme 1).[11] Indeed, in some of our initial reactions with **5i**,**j** we obtained only the colourless triones (**6i**,**j**) in place of the usually brightly coloured pyrrolediones. This problem was overcome by adding the oxalyl chloride at −50 °C, and the products **7a**–**j** were obtained in excellent yields (82–94%). Yields, analytical data and characteristic IR frequencies are reported in Table 2.

Table 1 Yields and physical data for methyl 3-arylamino-3-phenylprop-2-enoates **5f**–**j** and nitriles **5a**–**e**

Compd.	Yield (%)	Mp/°C
5a	75	142–144
5b	78	134–136
5c	81	154–156
5d	80	151–152
5e	45	oil
5f	82	91–93
5g	70	46–48
5h	87	96–98
5i	56	oil
5j	52	oil

The IR spectra of pyrrolediones **7a**–**e** displayed characteristic absorption at 2219–2228 cm^{-1} due to the CN stretching

† Electronic supplementary information (ESI) available: spectroscopic data of compounds **5**–**11** (Tables S1–S3). See http://www.rsc.org/suppdata/p1/b2/b202128e/

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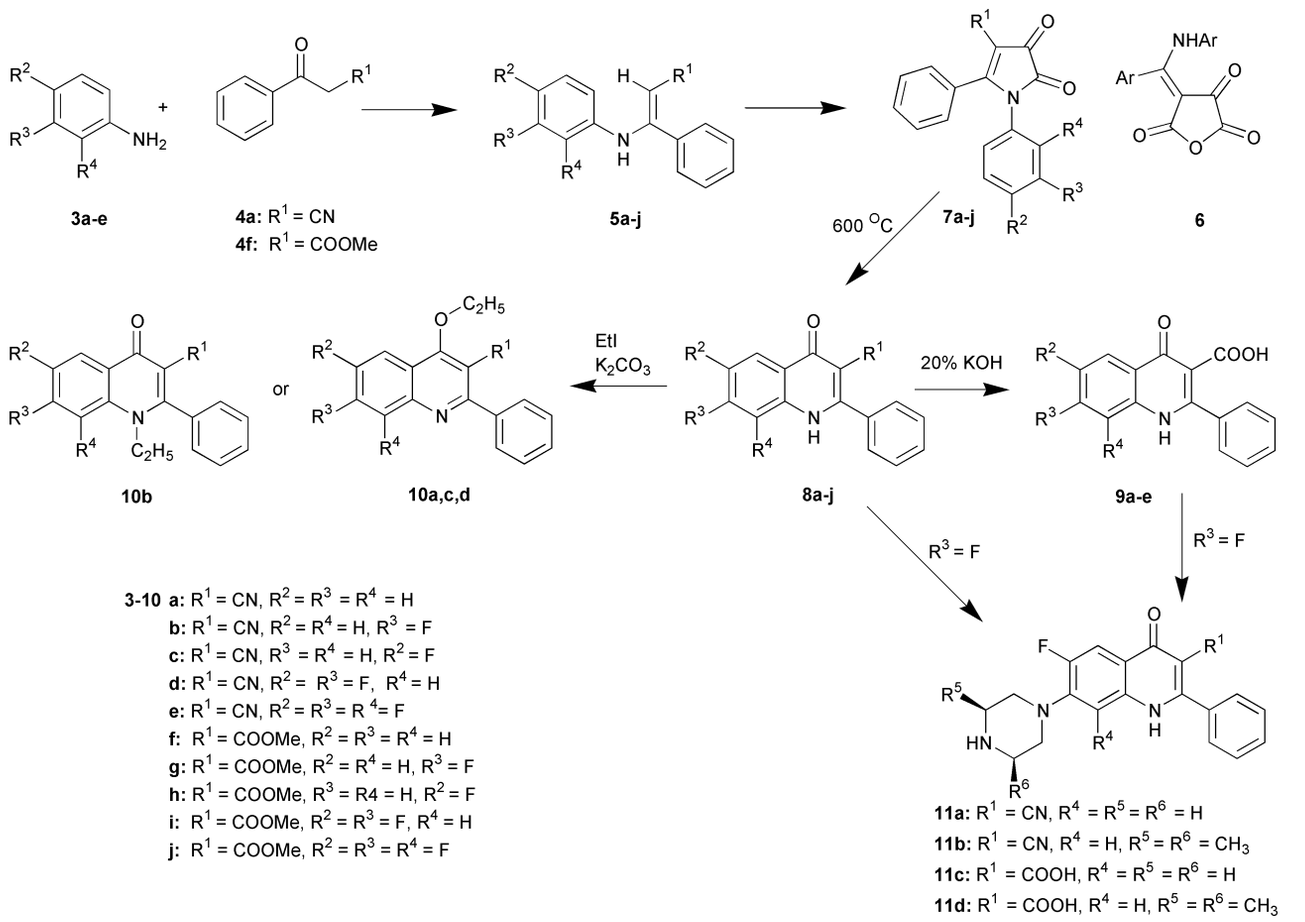
Table 2 Yields and physical data for the 1-aryl-4-cyano-5-phenylpyrrole-2,3-diones **7a–e** and 1-aryl-4-methoxycarbonyl-5-phenylpyrrole-2,3-diones **7f–j**

Compd.	Yield (%)	Mp/°C	Molecular formula	Calcd (%) (Found) C	H	N	ν_{max}/cm^{-1} IR
7a	75	224–226[14]	$C_{17}H_{10}N_2O_2$	74.45 (74.31)	3.65 (3.62)	10.22 (10.00)	2222, 1769, 1724
7b	82	207–209	$C_{17}H_9N_2O_2F$	69.86 (69.95)	3.08 (3.08)	9.59 (9.57)	2228, 1773, 1719
7c	85	187–189	$C_{17}H_9N_2O_2F$	69.86 (69.84)	3.08 (3.07)	9.59 (9.57)	2219, 1773, 1727
7d	87	171–173	$C_{17}H_8N_2O_2F_2$	65.67 (65.80)	2.58 (2.58)	8.96 (9.03)	2223, 1783, 1735
7e	94	151–153	$C_{17}H_7N_2O_2F_3$	61.89 (62.20)	2.06 (2.13)	8.48 (8.54)	2225, 1773, 1735
7f	86	221–223	$C_{18}H_{13}NO_4$	70.36 (70.14)	4.23 (4.46)	4.56 (4.91)	1769, 1727, 1714
7g	89	218–220	$C_{17}H_{12}NO_4F$	66.46 (66.56)	3.69 (3.74)	4.30 (4.25)	1771, 1731, 1712
7h	83	172–174	$C_{17}H_{12}NO_4F$	66.46 (66.30)	3.69 (3.74)	4.30 (4.24)	1773, 1727, 1719
7i	84	179–181	$C_{17}H_{11}NO_4F_2$	62.97 (63.09)	3.20 (3.24	4.08 (3.95)	1773, 1735, 1723
7j	86	147–149	$C_{17}H_{10}NO_4F_3$	59.83 (59.79)	2.77 (2.66)	3.88 (3.82)	1778, 1741, 1724



3-10 a: R^1 = CN, R^2 = R^3 = R^4 = H
b: R^1 = CN, R^2 = R^4 = H, R^3 = F
c: R^1 = CN, R^3 = R^4 = H, R^2 = F
d: R^1 = CN, R^2 = R^3 = F, R^4 = H
e: R^1 = CN, R^2 = R^3 = R^4 = F
f: R^1 = COOMe, R^2 = R^3 = R^4 = H
g: R^1 = COOMe, R^2 = R^4 = H, R^3 = F
h: R^1 = COOMe, R^3 = R4 = H, R^2 = F
i: R^1 = COOMe, R^2 = R^3 = F, R^4 = H
j: R^1 = COOMe, R^2 = R^3 = R^4 = F

Scheme 1

vibration, and at 1720–1780 cm^{-1} due to the five-membered ring dione. Similar absorptions were observed for **7f–j** at 1710–1775 cm^{-1}. The ^{13}C NMR spectra of **7a–e** displayed characteristic peaks at δ 175–176, 155.5–156.3 and 87.5–88.5 due to the two carbonyls and the CN group, respectively.[12] The 9-fluoro derivative **7c** exhibits doublets due to carbon–fluorine couplings in the ^{13}C NMR spectrum. The doublet at δ 129.0 ppm was assigned to the C-7 (J_{CF} = 9 Hz), a doublet at δ 116.9 ppm to C-8 (J_{CF} = 23 Hz), and a doublet at 162.4 ppm to C-9 (J_{CF} = 250 Hz), on the basis of chemical shifts, coupling constants, and a DEPT experiment. Likewise, signals were observed for **7f–j** at δ 177–178.0, 156–157, 161–161.5 and 51.8 due to C-4, C-5, ester C=O, and CH_3, respectively (Table S1).

FVT of compounds **7** at 500 °C yielded quinolones **8** in yields of 60–88% (Table 3). Alkaline hydrolysis of **8a–e** resulted in 4-oxoquinoline-3-carboxylic acids **9a–e**. The ^{1}H NMR spectra of the quinolones **8** and **9** showed characteristic signals at δ 12.7–13.1 due to N–H, and 7.25–8.40 (m) due to aromatic protons. The ^{13}C NMR spectra of compounds **8a–e** displayed signals at δ 172–175 (C=O), 116–117 (CN). The ^{13}C NMR spectrum of the 6-fluoro compound **8c** displayed doublets due to carbon–fluorine couplings. The doublet at δ 122.1 ppm was assigned to the C-5 (J_{CF} = 25.3 Hz), a doublet at 159.4 ppm to C-6 (J_{CF} = 243 Hz), a doublet at 109.3 to C-7 (J_{CF} = 22.9 Hz), and a doublet at 122.4 to C-8 (J_{CF} = 8.6 Hz) on the basis of chemical shifts, coupling constants, and a DEPT experiment. The ^{13}C NMR spectra of compounds **9a–e** showed signals at δ 176–179 (C=O) and 165–165.3 (COOH) (Table S2).

Alkylation of **8a–d** with ethyl iodide in the presence of potassium carbonate yielded the *O*-ethyl derivatives **10a**,**c**,**d** (16–30%) and only in one case the *N*-ethyl compound, **10b**. The methylation of 2-phenylquinolines with methyl iodide was reported to yield a mixture of *N* and *O*-alkylated products, but when ethyl or higher alkyl halides were used, only the *O*-alkylated derivative was obtained.[10] The ^{1}H NMR spectra of

Table 3 Yields and physical data for the 2-phenyl-4-quinolones **8**–**10**

Comd.	Yield (%)	Mp/°C	Molecular formula	Calcd (%) (Found)			
				C	H	N	M^+
8a	87	[a]	$C_{16}H_{10}N_2O$	78.02 (77.82)	4.10 (4.08)	11.38 (11.35)	246.0793
8b	81	[a]	$C_{16}H_9N_2OF$	72.72 (72.95)	3.41 (3.38)	10.60 (10.58)	264.0697
8c	77	[a]	$C_{16}H_9N_2OF$	72.72 (72.73)	3.41 (3.41)	10.60 (10.39)	264.0697
8d	80	[a]	$C_{16}H_8N_2OF_2$	68.08 (68.06)	2.83 (2.80)	9.93 (9.76)	282.0611
8e	77	[a]	$C_{16}H_7N_2OF_3$	64.00 (64.09)	2.33 (2.19)	9.33 (9.27)	300.0515
9a	70	[a]	$C_{16}H_{11}NO_3$	72.45	4.15	5.28	265.0730
9b	88	[a]	$C_{16}H_{10}NO_3F$	67.84	3.53	4.95	283.0661
9c	60	[a]	$C_{16}H_{10}NO_3F$	67.84 (67.97	3.53 (3.31)	4.95 (4.78)	283.0651
9d	65	[a]	$C_{16}H_9NO_3F_2$	63.78	3.00	4.65	301.0552
9e	86	[a]	$C_{16}H_8NO_3F_3$	60.19	2.50	4.39	319.0437
10a	30	124–126	$C_{18}H_{14}N_2O$	78.83 (78.87)	5.11 (5.00)	10.22 (10.00)	274.1105
10b	17	125–127	$C_{18}H_{13}N_2OF$	73.97(73.96)	4.45 (4.32)	9.59 (9.48)	292.104
10c	27	151–153	$C_{18}H_{13}N_2OF$	73.97(74.29	4.45 (4.45	9.59 (9.48)	292.1013
10d	16	137–139	$C_{18}H_{12}N_2OF_2$	69.67 (69.89)	3.87 (3.85)	9.03 (8.80)	310.0918

[a] > 300 °C.

the ethylated products **10a**–**d** displayed signals at δ 1.3–1.6 (t, 3H) and δ 4.1–4.8 (q, 4H) which are readily assignable to the ethyl group (Table S2). The ^{13}C NMR spectra of compounds **10a**,**c** and **10d** displayed signals at δ 167–168 (C–O), 116.6–117.7 (CN), 71 (CH_2) and 15.7 (CH_3), revealing that they are *O*-alkylated products. In contrast, compound **10b** displayed signals at δ 173.5 (C=O), 105.1 (CN), 44.9 (CH_2) and 14.1 (CH_3), corresponding to an *N*-alkylated product. The IR spectrum of **10b** clearly shows the presence of a C=O absorption at 1622 cm^{-1}. We could not isolate even small amounts of alkylated products from **8e** and **9a**–**e**.

The literature reveals that the most successful antibacterial quinolones are substituted with piperazinyl, or pyrrolidinyl groups at position 7.[5] The condensation of compounds **8d** and **9d** with piperazine and *cis*-2,6-dimethylpiperazine in pyridine gave the substituted quinolones **11** in 20–30% yields. The IR spectra of **11a** and **11b** displayed characteristic absorptions at *ca*. 3440–3480, 2220, and 1637 cm^{-1} due to NH, CN, and CO groups, respectively. The presence of the piperazine moiety in **11a** was confirmed by its ^{1}H NMR spectrum showing an eight proton signal at δ 3.0. Similarly, the *cis*-3,5-dimethylpiperazinyl moiety in **11b** gave rise to a doublet at δ 0.47 due to 2 × CH_3, followed by a triplet at 1.85 (2 × CH) and a doublet at 2.82 (2 × CH_2). The ^{13}C NMR spectrum displayed prominent signals at δ 41.7 and 41.8 due to the piperazine methylene groups and at 105.1 and 173.6 due to CN and CO groups, respectively. Readily assignable doublets due to C–F coupling were observed for **11b** at δ 110.2 ppm (J_{CF} = 23.2 Hz), 151.6 (J_{CF} = 244.6 Hz), 144.8 (J_{CF} = 10.5 Hz), and 116.1 (J_{CF} = 7 Hz) and assigned to C-5, C-6, C-7, and C-8, respectively. Similar data were obtained for compounds **11a** and **11c**,**d** (Table S3).

In conclusion, FVT of pyrrole-2,3-diones **7** allows the preparation of fluorinated 2-phenyl-4-quinolones which are, in turn, precursors of variously substituted 2-phenylquinolones.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer 1700 or 2000 FTIR spectrometer, NMR spectra on a Bruker AC2000 (200 Hz), and mass spectra (70 eV) on a Kratos MS25RFA instrument. Column chromatography was performed on silica gel (200–400 mesh). GCMS was carried out using a capillary column BP5 (0.25 mm × 30 m × 0.25 μm) with a pressure of 20 psi and He as the carrier gas. The FVT apparatus was as previously reported for preparative scale work (77 K isolation).[13] The substituted anilines, benzoylacetonitrile and methyl benzoylacetate are commercially available.

General procedure for the preparation of 3-aryl-3-phenylaminopropenenitriles 5a–e

A solution of substituted arylamines **3a**–**e** (10 mmol), benzoylacetonitrile **4a** (50 mmol), and AcOH (50 mmol) was warmed at 80 °C for 3 h. The progress of the reaction was monitored by GCMS to check for the absence of starting material **4a**. The reaction mixture was then cooled to room temperature. Solids precipitated at room temperature in the cases where **3a**,**c**,**d** were used. In the other cases the mixture was diluted with benzene (20 cm^3), stirred, filtered, and the solid was washed with benzene and dried. The filtrate, or the reaction mixture where no solid precipitated, was diluted with water (50 cm^3) and extracted with CH_2Cl_2. The organic layer was washed with 10% HCl, and then with saturated NaCl solution, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography on silica gel using benzene as eluent. Yields and data are reported in Table 1.

General procedure for the preparation of methyl 3-aryl-3-arylaminoprop-2-enoates 5f–j

A solution of substituted arylamines **3a**–**e** (10 mmol), methyl benzoylacetate **4f** (50 mmol), and AcOH (50 mmol) was stirred at 80 °C for 3 h, diluted with water (50 cm^3), and extracted with CH_2Cl_2 (3 × 25 cm^3). The combined organic phase was washed with 10% HCl, brine, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography on silica gel using $CHCl_3$ as eluent. Yields and melting points are reported in Table 1.

General procedure for the preparation of 1-aryl-4-cyano-5-phenylpyrrole-2,3-diones 7a–e

To a solution of **5a** (1.5 g, 6.8 mmol) in dry ether (30 cm^3) was added oxalyl chloride (0.95 g, 7.48 mmol) at 5 °C. The reaction mixture was brought to room temperature and stirred for 1 h. The precipitated solid was filtered and washed with dry ether (10 cm^3) to give **7a**. For each compound **5b**–**e** the method was similar to that described for **5a**, except that after addition of oxalyl chloride, the mixture was brought to reflux slowly and stirred for 1 h. Yields, melting points, analytical data and IR frequencies of the CN and CO groups are given in Table 2.

General procedure for the preparation of 1-aryl-4-methoxycarbonyl-5-phenylpyrrole-2,3-diones 7f–j

To a solution of **5f** (2 g, 7.9 mmol) in dry ether (40 cm^3) was added oxalyl chloride (1.1 g, 8.7 mmol) slowly at −50 °C. The reaction mixture was stirred at −40 °C for 1 h. The usual

workup as above gave 2.1 g (86%) of **7f**. For the compounds **5g–j**, the method was similar to that described for **5f**, except that after the addition of oxalyl chloride, the reaction mixture was brought to −10 °C in the course of 1 h and stirred for an additional 1 h. In the case of compound **5j**, the reaction mixture was brought to room temperature in the course of 1 h and then stirred for an additional 1 h. Yields, melting points, analytical data and IR frequencies of the CO groups are given in Table 2, and spectroscopic data in Table S1.

General procedure for the preparation of 6,7,8-substituted-3-cyano-2-phenyl-4-quinolones 8a–e

Compounds **7a–e** (0.3–1 mmol) were vaporized at 110–120 °C (depending on volatility) into the pyrolysis tube at 500 °C in the course of 4 h. The pyrolysates were condensed on a liq. N_2 cold finger at 77 K. Upon completion of the pyrolysis, the system pressure was equalised with N_2. The products collected from the cold finger were stirred with acetone, the insoluble solids were filtered and recrystallized from $CHCl_3$–MeOH (3 : 1). Yields, melting points and analytical data are reported in Table 3, and spectroscopic data in Table S2.

General procedure for the preparation of 6,7,8-substituted-1,4-dihydro-4-oxo-2-phenylquinoline-3-carboxylic acids 9a–e

The crude solids obtained by a procedure similar to that described above for the cyanoquinolones using compounds **7f–j** were stirred with 20% KOH (5 cm^3) at 80 °C for 3 h. After the reaction, the insoluble solids were filtered and the filtrate was acidified with 10% HCl. The precipitated solid was filtered, washed with water, and dried to give the compounds **9a–e**. Yields and analytical data are reported in Table 3, and spectroscopic data in Table S2.

General procedure for the preparation of 6,7-substituted 3-cyano-1-ethyl-2-phenyl-4-quinolone 10b or 6,7-substituted 3-cyano-4-ethoxy-2-phenyl-4-quinolones 10a,c,d

(a) A mixture containing 150 mg (0.61 mmol) of **8a**, 165 mg (1.22 mmol) of K_2CO_3, and 5 cm^3 of DMF was heated at 100 °C for 30 minutes with stirring. To this mixture was added 285 mg (1.83 mmol) of ethyl iodide. The resulting mixture was allowed to stir at the same temperature for 3 h and filtered to remove insoluble materials. The filtrate was concentrated to dryness in a vacuum. The residue was taken up in water (10 cm^3) and the solid which separated was filtered and washed with water, dried, and chromatographed on silica gel with benzene–chloroform (1 : 1) to give **10a**. Yields and analytical data for **10a–d** are reported in Table 3, and spectroscopic data in Table S2.

(b) To a solution of **8a** (60 mg, 0.23 mmol) in dry THF (5 cm^3) was added butyllithium (0.23 mmol) at −50 °C. The turbid mixture was clear when brought to room temperature. Ethyl iodide (18 mg, 0.23 mmol) was added at room temperature and the mixture was stirred for 10 h at reflux temperature. The yield of **10a** was 10%.

General procedure for the preparation of 7-substituted-3-cyano-6-fluoro-1,4-dihydro-2-phenyl-4-quinolones or 7-substituted-1,4-dihydro-6-fluoro-4-oxoquinoline-3-carboxylic acids 11

A mixture of **8d** (200 mg, 0.71 mmol), piperazine (305 mg, 3.5 mmol), and pyridine (5 cm^3) was heated 115 °C with stirring. After 12 h, the mixture was evaporated to dryness. The solid residue was quenched with water (5 cm^3) and neutralized with AcOH to give a cream solid (40 mg, 16%) identified as **11a**, mp > 300 °C; IR (KBr) ν 3483, 2220, 1638, 1576, 1491, 1259, 1170, 1126, 1037, 1009, 794, 690 cm^{-1}; δ_H(200 MHz; DMSO-d_6) 2.49–3.46 (m, 8H), 7.0–7.04 (d, 1H), 7.59–7.77 (m, 6H), 12.3 (br s); ^{13}C NMR: See Table S3; Found M^+, 348.1388. $C_{20}H_{17}N_4OF$ requires M^+, 348.1386.

Compounds **11b–d** were analogously prepared using piperazine and *cis*-2,6-dimethylpiperazine. Data are reported below.

3-Cyano-6-fluoro-2-phenyl-7-(*cis*-3,5-dimethylpiperazin-1-yl)-4-quinolone 11b. Light brown solid (20 mg, 30%) mp > 300 °C, IR (KBr) ν 3443, 2221, 1637, 1571, 1491, 1384, 1273, 1101, 794, 768, 699 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.47 (d, 6H), 1.85 (t, 2H), 2.82 (d, 4H), 6.52–6.56 (m, 1H), 6.87–6.89 (m, 2H), 6.97–7.04 (s, 1H), 7.08–7.11 (m, 3H); ^{13}C NMR: See Table S3; Found: M^+, 376.1736. $C_{22}H_{21}N_4OF$ requires, 376.1699.

6-Fluoro-1,4-dihydro-4-oxo-2-phenyl-7-(piperazin-1-yl)quinoline-3-carboxylic acid 11c. Pale brown solid, (26 mg, 25%); mp > 300 °C IR(KBr) ν 3456, 1636, 1597, 1488, 1383, 1291, 1260, 890, 771, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.49–3.19 (m, 8H), 7.27–7.99 (m, 7H); ^{13}C NMR: See Table S3; Found: [$M^+ - CO_2$] 323.1426. $C_{19}H_{18}N_3OF$ requires [$M^+ - CO_2$] 323.1423.

6-Fluoro-1,4-dihydro-4-oxo-2-phenyl-7-(*cis*-2,6-dimethylpiperazin-1-yl)quinoline-3-carboxylic acid 11d. Cream solid (25 mg, 19%); mp > 300 °C IR(KBr) ν 3452, 1639, 1573, 1513, 1478, 1384, 1272, 1178, 1100, 1048 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.58 (d, 6H), 1.85 (t, 2H), 2.05 (s, 4H), 7.3–7.9 (m, 7H), 11.6 (br s); ^{13}C NMR: See Table S3; Found: [$M^+ - CO_2$] 351.1687. $C_{21}H_{22}N_3OF$ requires [$M^+ - CO_2$] 351.1754.

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References

1 D. Niccolai, L. Tarsi and R. J. Thomas, *Chem. Commun.*, 1997, 2333–2342.
2 K. Grohe, *Chem. Brit.*, 1992, 34.
3 J. Matsumoto, T. Miyamoto, A. Minamida, Y. Nishimura, H. Egawa and H. Nishimura, *J. Med. Chem.*, 1984, **27**, 292.
4 E. Vilsmaier and T. Goertz, *Synthesis*, 1998, 739 and references therein.
5 Y. Kimura, S. Atarashi, K. Kowakami, K. Sato and I. Hayakawa, *J. Med. Chem.*, 1994, **37**, 3344 and references therein.
6 S. J. Brickner, *Chem. Ind. (London)*, 1997, 131.
7 B. E. Fulloon and C. Wentrup, *J. Org. Chem.*, 1996, **61**, 1363; V. V. Ramana Rao and C. Wentrup, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2583.
8 C. Wentrup, V. V. Ramana Rao, W. Frank, B. E. Fulloon, D. W. J. Moloney and T. Mosandl, *J. Org. Chem.*, 1999, **64**, 3608.
9 B. Fulloon, H. A. A. El-Nabi, G. Kollenz and C. Wentrup, *Tetrahedron Lett.*, 1995, **36**, 6547; H. Briehl, A. Lukosch and C. Wentrup, *J. Org. Chem.*, 1984, **49**, 2772.
10 S.-C. Kuo, H.-Z. Lee, J.-P. Juang, Y.-T. Lin, T.-S. Wu, J.-J. Chang, D. Lednicer, K. D. Paull, C. M. Lin, E. Hamel and K.-H. Lee, *J. Med. Chem.*, 1993, **36**, 1146.
11 T. Sano, Y. Horiguchi, J. Toda, K. Imafuku and Y. Tsuda, *Chem. Pharm. Bull.*, 1984, **121**, 497.
12 For the ^{13}C NMR spectra of pyrrolediones see G. Kollenz, G. Penn, W. Ott, K. Peters, E.-M. Peters and H. G. von Schnering, *Chem. Ber.*, 1984, **117**, 1310; K. P. Netsch, PhD Thesis, Universität Marburg, Germany, 1985.
13 A. Kuhn, C. Plüg and C. Wentrup, *J. Am. Chem. Soc.*, 2000, **122**, 1945; C. Wentrup, R. Blanch, H. Briehl and G. J. Gross, *J. Am. Chem. Soc.*, 1988, **110**, 1874.
14 W. Zankowska-Jasinska, J. Golus, Z. Kamela and A. Kolasa, *Pol. J. Chem.*, 1987, **61**, 141.