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Photochemistry of some non zwitterionic fluoroquinolones

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ABSTRACT

Two non zwitterionic analogues of fluoroquinolone drugs, viz. 1-ethyl-7-piperidino-8-fluoroquinol-4-one-3-carboxylic acid and 1-ethyl-7-piperidino-6,8-difluoroquinol-4-one-3-carboxylic acids have been synthesized and their photochemistry has been investigated. Both compound undergo photoheterolysis of the C_8—F bond generating a triplet cation that either inserts into the 1-alkyl chain or is trapped or reduced by external nucleophiles. The reaction is analogous to that observed with the corresponding (zwitterionic) 7-piperazino derivatives, but the quantum yield is ca five times lower. This supports the rationalization that in the latter case assistance to defluorination by the N^+—H bond has a determining role.

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1. Introduction

Fluoroquinolones (ArF) are antimicrobial agents and are derivatives of 4-quinolone, in many cases 1-alkyl-6-fluoro-7-dialkylaminoquinol-4-one-3-carboxylic acids (**1**). Several molecules of this family have found large therapeutic use in view of the excellent properties and the limited side effects. A negative aspect that many of such drugs share, however, is that these cause some form of skin photosensitization, or photoallergy [1–4] or even exert a photomutagenic effect [5–7]. These phenomena have been related to two alternative mechanisms, viz. either oxygen sensitization (Eq. (1)) or fragmentation of the molecule, which resulted in the generation of aggressive intermediates that may damage some cell component (Eq. (2)).

$$\mathrm{ArF} + h\nu + \mathrm{O_2} \rightarrow {}^1\mathrm{O_2} \quad (1)$$

$$\mathrm{ArF} + h\nu \rightarrow \text{fragments} \quad (2)$$

The first path is certainly operative. Singlet oxygen generation (path 1) is observed, though to a various degree, with most, if not all aromatic compounds. Oxygen sensitization with ArF acting as sensitizers according to Eq. (1) is possible and indeed this process has been demonstrated for a number of fluoroquinolones [8]. Singlet oxygen is the active "drug" in photodynamic therapy. It appears thus likely that this mechanism is active also with these compounds and justifies at least a part of the phototoxic effect.

However, ordering these drugs according to the efficiency in producing singlet oxygen does not fit with the order of toxicity, which suggest that a different mechanism may participate. Such a mechanism would obviously depend on the structure of the specific molecule. Actually, detailed studies by a few laboratories, including our own, demonstrated that fluoroquinolones undergo photofragmentation reactions [9–16]. Different processes have been recognized, widely depending on structure. In particular, the derivatives bearing an additional fluorine atom in position 8 (besides that in position 6, common to all of these derivatives) showed a peculiar behaviour with heterolysis of the C_8—F bond from the triplet state (Eq. (3)) [12,15,16].

$$\mathrm{ArF} + h\nu \rightarrow {}^3\mathrm{ArF} \rightarrow {}^3\mathrm{Ar^+} + \mathrm{F^-} \quad (3)$$

This reaction generated a heteroaryl cation in the triplet state. As it has been demonstrated both for fluoroquinolones [15] and for simple models such as electron-donating substituted phenyl fluorides, [17,18] this intermediate has a radical/radical cation character (see formula below).

This is because one of the two unpaired electrons occupies the (in plane) sp^2 orbital at the divalent carbon, while the other one is delocalized over the π system, see formula above). Despite the positive charge, the chemical behaviour of this species is thus reminiscent of that of triplet carbenes and not of that of aliphatic carbocations.

The molecules that show photochemical heterolysis according to Eq. (3) all have in common, besides the fluorine in 8, a piperazino

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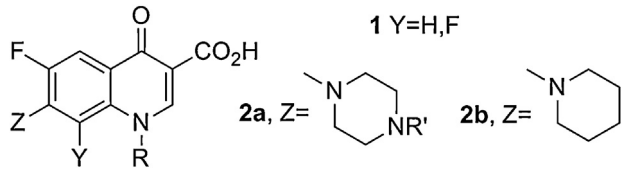


Chart 1.

group in position 7 (**2a**, Chart 1). The presence of a basic nitrogen (N—4′ of the piperazine side-chain) and of the carboxyl group in position 3 makes the zwitterionic form of such a compound predominating at neutral pH. This may be a determining parameter, since several investigations suggested that the photophysical and photochemical properties of fluoroquinolones depend on the ionic form present [19–21].

2. Results and discussion

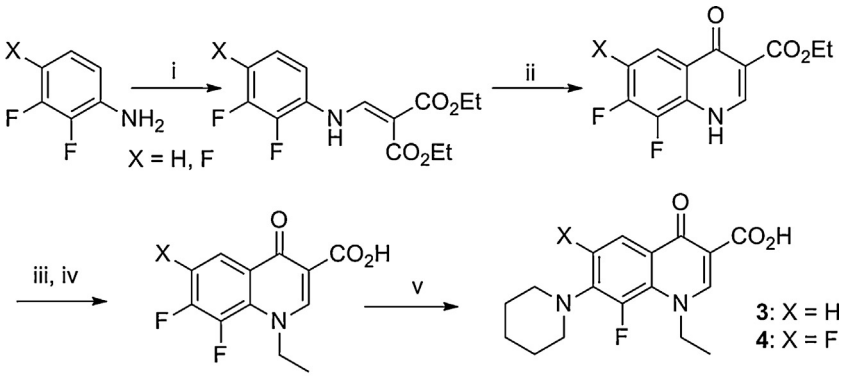
In view of the above considerations and in the frame of our continuing interest in the photochemistry of these drugs, we deemed appropriate to extend gradually the investigation by introducing some structure changes that may alter the key characteristics. The study reported below involves the effect caused by substituting a 1′-piperidino (see formula **2b**) for the 1′-piperazino (**2a**) side-chain (Chart 1). In this way, the most basic centre was removed, leaving only the less basic nitrogen atom (N—1′) adjacent to the expected reactive site, the C—F bond in position 8. Therefore, such compounds do not have a zwitterionic structure in solution. We were curious to test whether the change in the electronic distribution with respect to the piperazino substituted fluoroquinolones may cause some effect on the photochemistry.

The molecules chosen were 1-ethyl-8-fluoro-4-oxo-7-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (**3**; see Scheme 1) and 1-ethyl-6,8-difluoro-4-oxo-7-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (**4**). These were synthesized through suitable modifications of known general synthetic schemes for these compounds (see Scheme 1). This involved condensation of the appropriate aniline with ethoxymethylenemalonate, thermal cyclization, *N*-alkylation, hydrolysis of the ester group and aromatic nucleophilic substitution (24 and 29% yield over five steps, see Section 4). Titration showed two acidity constants for compound **3** (in parenthesis for **4**) pK_{a1} 5.1 (4.7) and pK_{a2} 7.7 (7.49).

Irradiation of compound **3** in a water-acetonitrile 2 to 3 mixture led to complete consumption and the formation of a single HPLC detected product (quantum yield of decomposition $\Phi_R = 0.01$). This was isolated in quantitative yield by evaporation of acetonitrile (MeCN) and chloroform extraction and was recognized by the characteristic CH_2CH_2 signal and by the modification of the aromatic part of the NMR spectrum as pyrroloquinolone **5**. The photochemistry was then explored in the presence of various additives. In the presence of 0.05 M KBr the course of the reaction changed and again a single product was isolated in quantitative yield. Elemental and spectroscopic data showed that this was the 8-bromoquinolone **6**. The irradiation with other halides gave different results. In the presence of 0.05 M KCl some of the corresponding 8-chloro derivative (**7**) was formed, as deduced from HPLC/Mass examination, at the expenses of tricyclic **5**, which was still generated to a certain extent, however. Furthermore, compound **7** suffered secondary photodegradation at a rate comparable with its formation, giving the dehalogenated compound **8** (see below). On the other hand, 0.05 M KI led to a single compound in 83% yield that had incorporated a iodine atom, but this was not the analogue of **6**, but rather the 1-(2-iodoethyl)quinolone **9**, as demonstrated by the spectroscopic properties. In addition to the experiments in halide solution, irradiation in the presence of 0.05 M Na_2SO_3 was also carried out and gave a single main product (in a sample containing some contaminant) recognized as the dehalogenated compound **8**. Finally, an organic trap was tested, viz. pyrrole. In the presence of either 0.05 or 0.1 M of this heterocycle, a mixture of tricyclic heterocyclic **5** and reduced **8** was formed. This mixture contained also minor amounts of two products resulting, as judged from the mass analysis, by pyrrole incorporation and HF elimination. (Scheme 2).

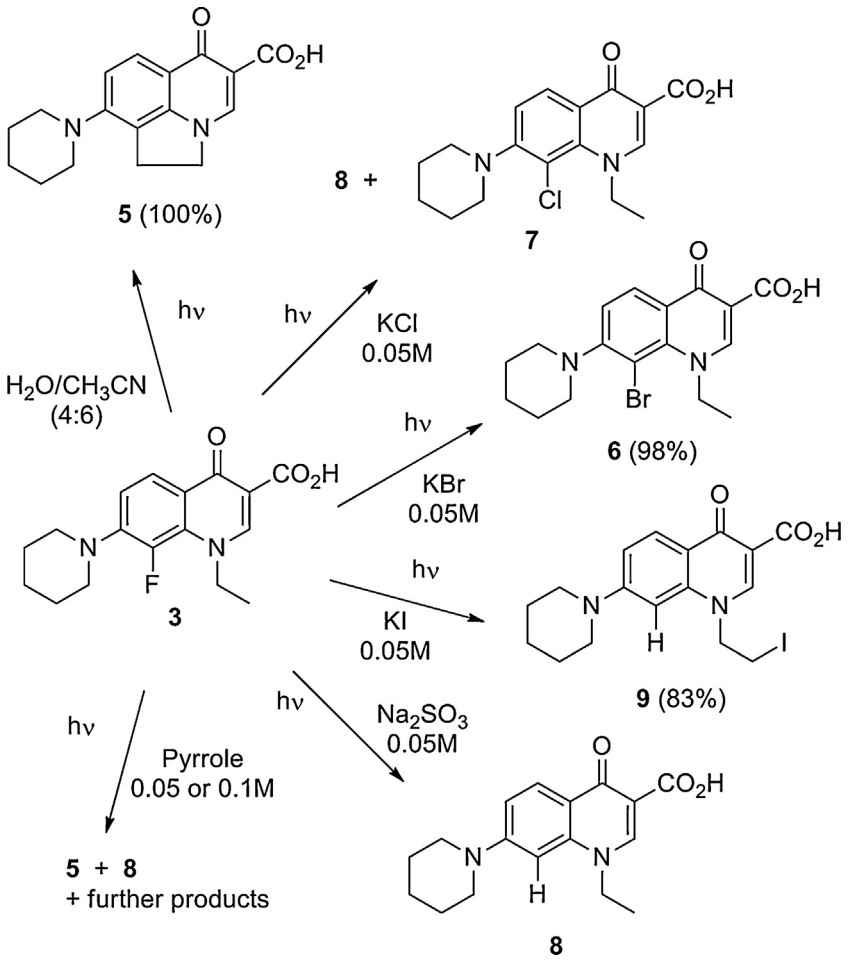
The 6,8-difluoroquinolone **4** was then examined under the same conditions as **3** and likewise reacted by irradiation in water ($\Phi_R = 0.005$), whereupon it gave quantitatively pyrroloquinolone **10** (6-fluoro analogue of **5**). The photochemistry was explored by HPLC/mass under a few further conditions. In particular in the presence of chloride the corresponding 8-chloroquinolone (analogue of **7**) appeared to be formed and with pyrrole a mixture of compound **10** and the product of reductive dehalogenation (6-fluoro analogue of **8**) were formed, with barely a trace of pyrrole incorporating quinolones.

The absorption spectrum of compounds **3** and **4** is typical of fluoroquinolones, with intense band centred around 290 and 320 nm and extending to 400 nm (Fig. 1). The fluorescence spectrum (Fig. 2) and quantum yield of compounds **3** and **4** as well as of the corresponding piperazino derivatives **11** and **12** was measured. It appears that piperazino derivatives emit more intensely, by a factor of 3, and that introduction of a second fluorine in 6 decreases the emission, again by a factor of ca. 3 (see Table 1).



i, $EtOCH(CO_2Et)$, 120°C; ii, Ph_2O, reflux; iii, EtI, K_2CO_3, DMF, 120°C; iv, AcOH, 100°C; v, piperidine, DBU, MeCN, rT

Scheme 1. Synthesis of compounds **3** and **4**.



Scheme 2. Photoproducts obtained from compound **3** by irradiation under different conditions.

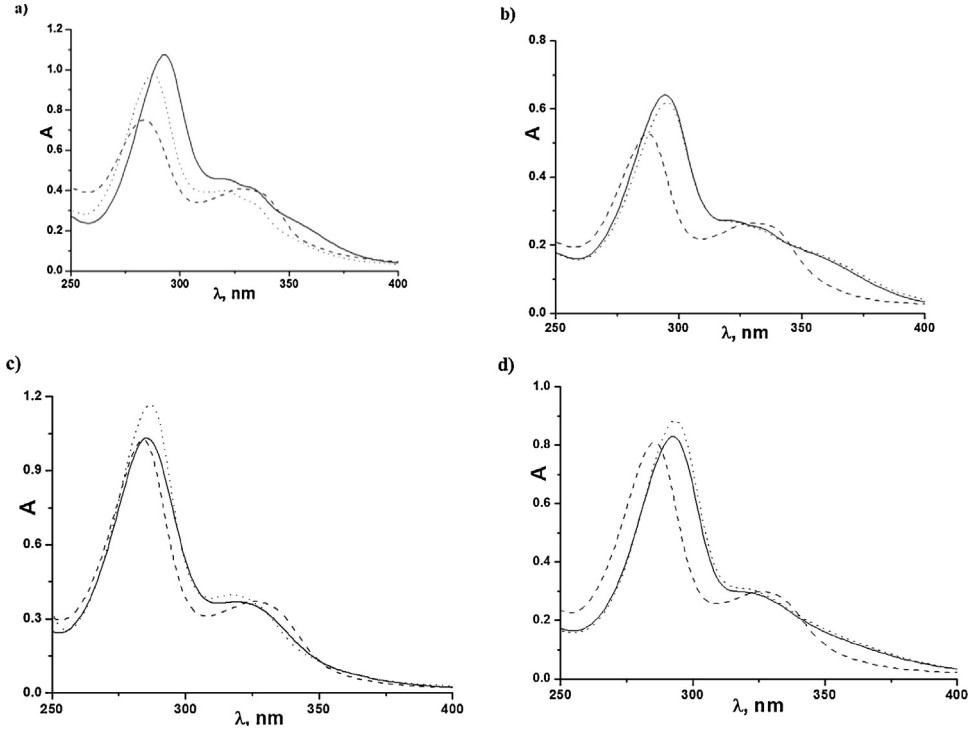


Fig. 1. UV–vis spectra of a 2.5×10^{-5} M solution of fluoroquinolones (a) **12**, (b) **4**, (c) **11** and (d) **3** in MeCN–H_2O 6–4 at pH = 2.5 (dotted line), pH = 7 (continuous line) and pH = 12 (dashed line).

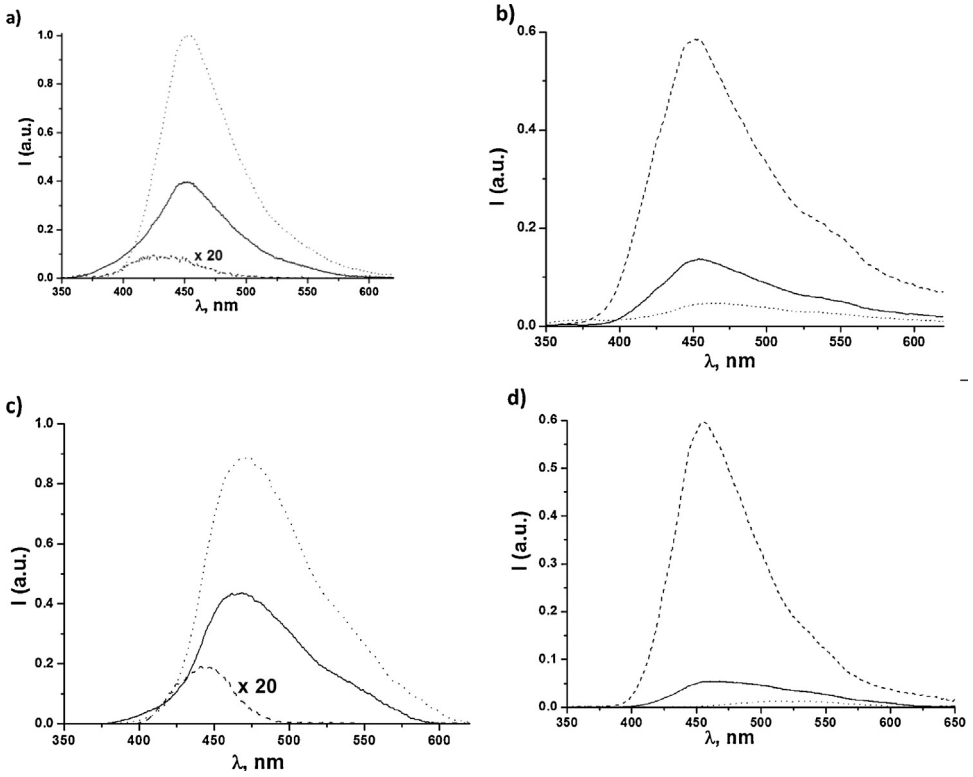
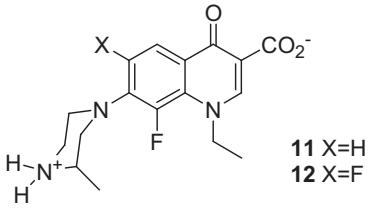


Fig. 2. Fluorescence spectra of a 2.5×10^{-5} M solution of fluoroquinolones (a) **12**, (b) **4**, (c) **11** and (d) **3** in in MeCN–H_2O 6–4 at pH = 2.5 (dotted line), pH = 7 (continuous line) and pH = 12 (dashed line).

As for the pH dependence, the significant point in this connection is that the fluorescence of compounds **3** and **4**, where only a weakly basic aromatic amino group is present, increases under basic condition with respect to the neutral conditions, while it markedly decreases with compounds **11** and **12**, where a more basic aliphatic amino group is present and where at neutral pH the zwitterion form (protonated at the 4′ position) certainly predominates. The emission is reasonably attributed to the fluoroquinolonecarboxylate moiety and is quenched at high pH when the amino group is liberated with **11** and **12**. This does not happen with **3** and **4**, which are not protonated under neutral conditions.



11 X=H
12 X=F

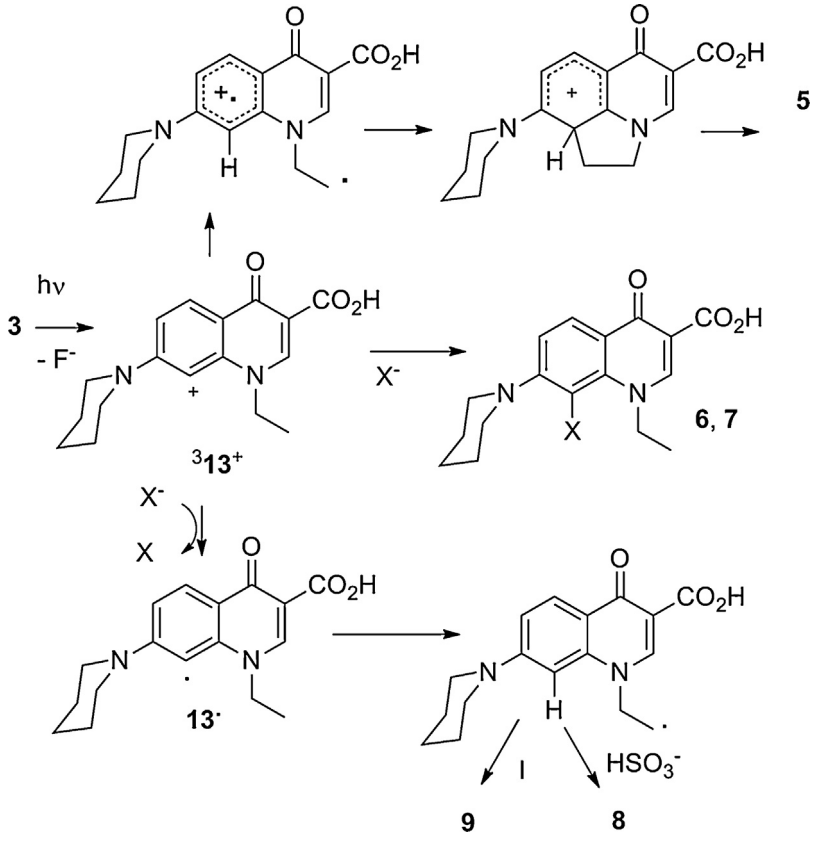
The product study reported above well fits with the previously formulated generalization about the photochemistry of 6,8-fluoroquinolones. The reaction course remains the same in the non-zwitterionic fluoroquinolones. Just as in the case of previously examined compound bearing a piperazino side-chain, irradiation gives cyclization onto the N-ethyl chain. Compounds **3** and **4** are not sufficiently soluble in water to allow for a detailed examination of their photochemistry but, as checked with compounds **11** and **12**, the chemical path in MeCN–H_2O 3–2 is the same as in neat water, although the reaction quantum yield is lowered. The key step is selective dehalogenation from position 8, as here confirmed for the case of products **3** and **4**, via the triplet state (see Scheme 3). The corresponding cation is thus formed in the triplet state ^{3}**13**$^+$. As mentioned in the introduction, this species is not a localized carbocation, but rather has a radical/radical cation nature. Thus, it does not add to water but rather abstracts hydrogen from the accessible methyl group and cyclizes to the observed pyrroloquinolones. A charged nucleophile however does add, as previously observed for related compounds such as **12**, and both the 8-chloro and the 8-bromo derivatives are formed in this way.

The other characteristics of intermediate ^{3}**13**$^+$ (and in general of aryl cations) [17] is that of a strong oxidant. In this case, electron transfer from a soft nucleophile such as iodide leads to radical **13**$^\cdot$ This in turn abstracts hydrogen before recombining with a iodine atom, resulting in the incorporation of the halogen into the side chain. As one would expect, when such as good reducing agent as sulfite anion is used, the initial ET transfer step is followed by reduction of the radical. A redox process occurs also with pyrrole, where however recombination fails and neat reduction takes place (a small amount of pyrrole-containing products is formed from **3**, and mere traces from **4**).

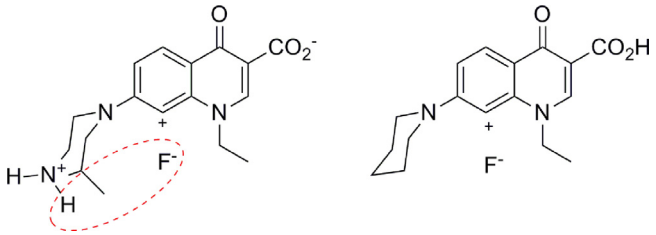
Thus, the chemistry via triplet cation previously observed for piperazino fluoroquinolones is maintained, the intermediate ^{3}**13**$^+$ arising from the piperidino analogue **3** (and similarly from **4**). The competition between attack to the neighbouring *N*-ethyl chain and external molecules behaving as nucleophile or as reducing agent (to yield radical **13**$^\bullet$) determines the product distribution, which remains qualitatively the same, though with some shift in the yields. The difference rather lies in the marked drop in the quantum yield of reaction that is lower by a factor of ca. 5 with respect to the piperazino analogues. A rationalization we propose has to do

Table 1
Fluorescence and reaction quantum yield in MeCN–water 3–2 mixture.

Compounds	Φ_F	Φ_R
3	0.13	0.01
4	0.03	0.005
11	0.33	0.055
12	0.13	0.027



Scheme 3. Key steps in the photochemistry of compound **3**.



Scheme 4. Cleavage of C—F bond.

with the nature of the first step of the reaction. Heterolysis of such a strong bond as C—F, particularly from $\pi\pi^*$ states such as those of fluoroquinolones, involves a complex rearrangement of the electronic structure and a key contribution is given by the formation of HF. Now, piperazine derivatives are zwitterions at neutral pH, whereas piperidino derivatives are neutral. Cleavage of the strong C—F bond would thus be favoured by the ionic environment in the first case, where a N^+—H bond acts as proton donor, but not in the latter one (Scheme 4).

3. Conclusions

The results above extend the knowledge on the role of heteroaryl cations in the photochemistry of fluoroquinolones. A novel feature is introduced in the mechanistic picture, by demonstrating the participation of the protonated piperazine in assisting heterolysis of C—F bond in zwitterionic compounds. In that case the key defluorination step is five times more efficient than in non zwitterionic piperidino derivatives that lack this feature.

4. Experimental

4.1. Synthesis of 1-ethyl-8-fluoro-4-oxo-7-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (3) and 1-ethyl-6,8-difluoro-4-oxo-7-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (4) (see Scheme 5)

4.1.1. Step a [22]

A mixture of aniline **14** (10 mmol) and diethyl ethoxymethylenemalonate (2.1 ml, 10.5 mmol) was stirred at 120 °C for 2.5 h. Ethanol was evaporated and the resulting solid was crystallized from hexane to give products **15** as colourless solids.

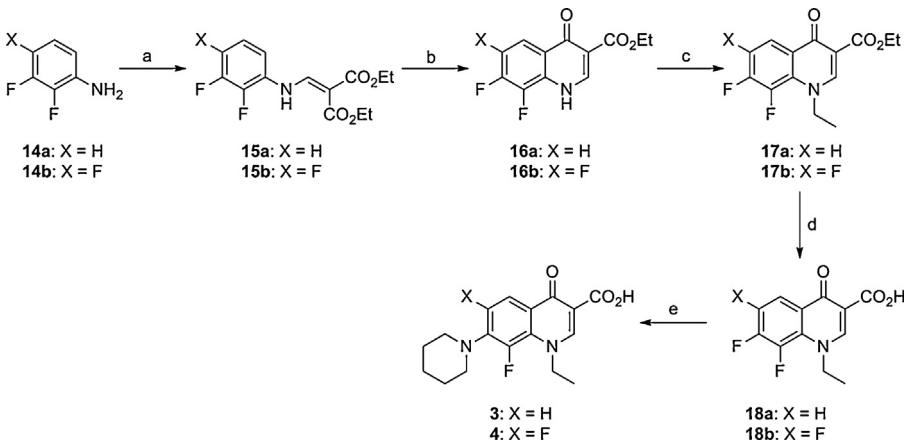
15a: m.p. 85–87 °C. ^{1}H NMR ($CDCl_3$) δ 11.10 (d, 1H, J = 10 Hz), 8.60 (d, 1H, J = 10 Hz), 7.10–6.90 (m, 3H), 4.3 (m, 4H), 1.4 (m, 6H). IR (nujol) 1686. ESI-MS m/z (%) 300.2 ($[M+1]^+$, 100). Anal. calcd for $C_{14}H_{15}F_2NO_4$, C 56.19, H 5.05, N, 4.68 found C 56.0, H 5.2, N 4.4.

15b: ^{1}H NMR ($CDCl_3$) δ 11.00 (d, 1H, J = 13 Hz), 8.40 (d, 1H, J = 13 Hz), 7.00 (m, 2H), 4.40–4.15 (m, 4H), 1.40–1.25 (m, 6H). IR (nujol) 1699, 1652.

4.1.2. Step b [22]

Compound **15** (1.7 mmol) and diphenyl ether (3.5 ml) were refluxed for 15–20 min. After cooling down to r.t., the resulting precipitate was collected by filtration and crystallized from ethanol, affording a colourless solid, **16**.

16a: m.p. >250 °C. ^{1}H NMR (D_2O) δ 8.00 (s, 1H), 7.30 (m, 1H), 6.50 (m,1H), 4.20 (q, 2H, J = 7.2 Hz), 1.30 (t, 3H, J = 7.2 Hz). IR (nujol) 1718. ESI-MS m/z (%) 254.1 ($[M+1]^+$, 100). Anal calcd for $C_{12}H_9F_2NO_3$, C 56.92, H 3.58, N 5.53, found C 56.7, H 3.8, N 5.5.



Scheme 5. Synthesis of 1-ethyl-8-fluoro-4-oxo-7-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **(3)** and 1-ethyl-6,8-difluoro-4-oxo-7-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **(4)**.

16b: ^{1}H NMR (CD_3OD) δ 8.65 (s, 1H), 8.00 (t, 1H, *J* = 8 Hz), 4.35 (q, 2H, *J* = 7 Hz), 1.35 (t, 3H, *J* = 7 Hz). IR (nujol) 1717.

4.1.3. Step c [22]

Derivative **16** (6.12 mmol), K_2CO_3 (2.1 g, 15.3 mmol), ethyl iodide (2.47 ml, 30.6 mmol) and DMF (8 ml) were placed in a flask and stirred at 120 °C for 2 h. The mixture was filtered hot, to remove potassium salts, and the salts were washed with ethanol. The organic phases were cooled down to r.t. and the resulting precipitate (**17**) was collected by filtration and used in the next step without further purification.

17a: m.p. 158–160 °C. ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1H), 8.10 (m, 1H), 7.10 (m,1H), 4.30 (m, 4H), 1.40 (m, 6H). IR (nujol) 1678. ESI-MS *m*/*z* (%) 282.1 ($[M+1]^+$, 100). Anal. calcd for $C_{14}H_{13}F_2NO_3$, C 59.79, H 4.66, N 4.98, found C 59.7, H 4.7, N 5.1.

17b: ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 8.20 (t, 1H, *J* = 8 Hz), 4.50–4.30 (m, 4H), 1.55 (t, 3H, *J* = 7 Hz), 1.40 (t, 3H, *J* = 7 Hz).

4.1.4. Step d [23]

Compound **17** (7.4 mmol) was dissolved in acetic acid (40 ml) and heated at 100 °C.

3 N HCl (20 ml) was added dropwise over 2 h and the final solution was stirred at 100 °C for 2 more hours, then cooled down slowly to r.t. Water was added and the resulting precipitate was collected by filtration, washed with cold water, 2-propanol and diethyl ether to give **5** as a colourless solid.

18a: m.p. 217–219 °C. ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1H), 8.40 (m, 1H), 7.50 (m,1H), 4.60 (q, 2H, *J* = 6.6 Hz), 1.6 (t, 3H, *J* = 6.6 Hz). IR (nujol) 1653. ESI-MS *m*/*z* (%) 254.1 ($[M+1]^+$, 100). Anal. calcd for $C_{12}H_9F_2NO_3$, C 56.92, H 3.58, N 5.53, found C 56.9, H 3.6, N 5.4.

18b: ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.25 (dt, 1H, *J* = 8 and 2 Hz), 4.65–4.50 (m, 2H), 1.75–1.55 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 176.0, 165.7, 150.6 (CH), 149.0 (dd, *J* = 260 and 15 Hz)), 144.4 (dd, *J* = 260 and 15 Hz), 143.6 (t, *J* = 260 Hz), 126.6, 123.2, 109.4 (d, CH, *J* = 19 Hz), 108.9, 54.3 (d, CH_2, *J* = 15 Hz), 16.1 (d, CH_3, *J* = 4.5 Hz). IR (nujol) 1726.

4.1.5. Step e [23]

Compound **18** (4 mmol) was suspended in acetonitrile (12 ml). A solution of piperidine (0.42 ml, 4.2 mmol) and DBU (0.6 ml, 4 mmol) in acetonitrile (6 ml) was added, under stirring, to the starting suspension. The resulting mixture was refluxed for 2.5 h, then stirred at r.t. overnight.

The precipitate was collected by filtration and washed with acetonitrile (12 ml), 80% aqueous acetonitrile (4.5 ml), ethanol (12 ml) and diethyl ether (45 ml), affording products **3** or respectively **4.**

3: Colourless solid, m.p. 225–226 °C. ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.20 (d, 1H, *J* = 9 Hz), 7.20 (t, 1H, *J* = 9 Hz), 4.60–4.45 (m, 2H), 3.35–3.20 (m, 4H), 1.90–1.65 (m, 6H), 1.60 (t, 3H, *J* = 7 Hz). ^{13}C NMR ($CDCl_3$) δ 177.2, 167.0, 150.2 (CH), 145.9, 143.1 (q, *J* = 245 Hz), 129.8, 122.9 (CH), 120.9, 117.9 (CH), 108.0, 54.6 (d, CH_2, *J* = 16 Hz), 51.7 (2 × CH_2), 25.9 (2 × CH_2), 24 (CH_2), 16.2 (d, CH_3, *J* = 4 Hz). IR (nujol) 1722. Anal. calcd for $C_{17}H_{19}FN_2O_3$, C 64.14, H 6.02, N 8.80, found C 63.5, H 6.9, N 8.9.

4: [24] Colourless solid, m.p. >250 °C. ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 7.90 (dd, 1H, *J* = 2 and 12 Hz), 4.60–4.40 (m, 2H), 3.40 (bs, 4H), 1.85–1.65 (m, 6H), 1.60 (dt, 3H, *J* = 1 and 7 Hz). ^{13}C NMR ($CDCl_3$) δ 176.2, 166.7, 155.2 (dd, *J* = 7 and 250 Hz), 149.7 (CH), 145.6 (d, *J* = 245 Hz), 135.4, 127.0 (d, *J* = 40 Hz), 120.5, 108.1 (dd, *J* = 3 and 23 Hz), 107.9 (CH), 54.4 (d, CH_2, *J* = 16 Hz), 52.2 (2 × CH_2), 26.4 (2 × CH_2), 24.0 (CH_2), 16.2 (d, CH_3, *J* = 4 Hz). IR (nujol) 1720. Anal. calcd for $C_{17}H_{18}F_2N_2O_3$, C 60.71, H 5.39, N 8.33, found C 61.3, H 4.9, N 8.2.

4.2. Reaction quantum yields

Reaction quantum yields were measured on 2-ml degassed samples, in 1-cm optical path spectrophotometric cuvettes, irradiating with a 150 W high-pressure mercury arc and an interference filter (317 nm). Consumption of the starting compound was assessed by HPLC (Discovery® HS C18, 250 × 4.6 mm, 5 μm, pH 2.5 water/acetonitrile (from 50:50 to 45:55) as eluant, flow 1–1.2 ml/min, λ = 285 nm). The light flux was measured by ferrioxalate actinometry.

4.3. Fluorescence quantum yields

Fluorescence quantum yields were measured by means of a Perkin Elmer LS55 spectrofluorimeter by using quinine sulphate as the standard.

4.4. Titration

pKa values were measured by titration with a dilute NaOH solution by using a Model 121 Microcomputer pHmeter.

4.5. Preparative irradiations

4.5.1. Irradiation of compounds *3*,*4* in H_2O/CH_3CN (4:6)

A solution of either **3** or **4** (2 × 0.1 mmol, 3.5×10^{-4} M) in H_2O/CH_3CN (4:6) was placed in an immersion-well apparatus (2 × 300 ml), stirred and flushed with argon for 20 min, then

irradiated with a 125 W medium-pressure mercury lamp through Pyrex, while maintaining the argon flow. The reaction was monitored by HPLC.

After irradiation, acetonitrile was removed under vacuum and the aqueous phase was extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated. The remaining yellow solids were washed with diethyl ether.

5: Yellow solid, m.p. 198–200 °C. ^{1}H NMR (CD_3CN) δ 8.70 (s, 1H), 7.90 (d, 1H, *J* = 9 Hz), 7.10 (d, 1H, *J* = 9 Hz), 4.60 (t, 2H, *J* = 8 Hz), 3.50 (t, 2H, *J* = 8 Hz), 3.40–3.30 (m, 4H), 1.80–1.60 (m, 6H). ^{13}C NMR (CD_3CN) δ 177.3, 167.5, 152.0, 146.0, 143.3 (CH), 127.3, 123.6 (CH), 117.8 (CH), 115.8, 108.0, 52.3 (CH_2), 49.9 ($2 \times CH_2$), 28.6 (CH_2), 25.8 ($2 \times CH_2$), 24.0 (CH_2). IR (nujol) 1731, 1637. Anal. calcd for $C_{17}H_{18}N_2O_3$, C 68.44, H 6.08, N 9.39, found C 67.6, H 6.5, N 9.2.

6-F analogue of **5** Yellow solid, decomposed without melting. ^{1}H NMR (DMSO-d_6) δ 9.00 (s, 1H), 7.60 (d, 1H, *J* = 12.6 Hz), 4.70 (t, 2H, *J* = 7.4 Hz), 3.70 (t, 2H, *J* = 7.4 Hz), 3.40–3.20 (m, 4H), 1.80–1.55 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 176.2, 166.6, 156.0 (d, *J* = 245 Hz), 143.6 (CH), 142.0, 124,4, 116.1, 107.8, 107.7, 107.4, 52.7 (CH_2), 51.0 ($2 \times CH_2$), 28.0 (CH_2), 26.1 ($2 \times CH_2$), 23.6 (CH_2). IR (nujol) 1728, 1634. Anal. calcd for $C_{17}H_{17}FN_2O_3$, C 64.55, H 5.42, found C 64.1, H 5.7, N 8.86.

4.5.2. Irradiation of compound 3 with KI 0.05 M

A solution of **3** (2×0.1 mmol, 3.5×10^{-4}M) and potassium iodide (2×15 mmol, 0.05 M) in H_2O/CH_3CN (4:6) was placed in an immersion-well apparatus (2×300 ml), stirred and flushed with argon for 20 min, then irradiated with a 125 W medium-pressure mercury lamp through Pyrex, while maintaining the argon flow. The reaction was monitored by HPLC, showing complete consumption of **3** after 45 min.

The irradiated solutions were collected together and acetonitrile was removed under vacuum. The remaining aqueous phase was extracted with chloroform, affording **9** as a yellow solid (78 mg, 83% yield).

9: Yellow solid, decomposed without melting. ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1H), 8.10 (d, 1H, *J* = 9 Hz), 7.30 (d, 1H, *J* = 9 Hz), 6.85 (s, 1H), 4.80 (t, 2H, *J* = 6 Hz), 3.60 (t, 2H, *J* = 6 Hz), 3.50 (bs, 4H), 1.60 (bs, 6H). ^{13}C NMR (DMSO-d_6) δ 176.5, 166.5, 154.4, 149.3 (CH), 141.0, 127.2 (CH), 115.4, 114.7 (CH), 106.1, 97.5 (CH), 53.9 (CH_2), 47.9 (CH_2), 24.9 (CH_2), 23.9 (CH_2), 3.4 (CH_2). IR (nujol) 1702, 1623. Anal. calcd for $C_{17}H_{19}IN_2O_3$, C 47.90, H 4.49, N 6.57, found C 48.2, H 4.1, N 6.7.

4.5.3. Irradiation of compound 3 with KBr 0.05 M

A solution of **3** (2×0.1 mmol, 3.5×10^{-4}M) and potassium bromide (2×15 mmol, 0.05 M) in H_2O/CH_3CN (4:6) was placed in an immersion-well apparatus (2×300 ml), stirred and flushed with argon for 20 min, then irradiated with a 125 W medium-pressure mercury lamp through Pyrex, while maintaining the argon flow. The reaction was monitored by HPLC, showing complete consumption of **3** after 110 min.

The irradiated solutions were collected together and acetonitrile was removed under vacuum. The remaining aqueous phase was extracted with chloroform, affording **6** as a pale yellow solid (74 mg, 98% yield).

6: Pale yellow solid, decomposed without melting. ^{1}H NMR (DMSO-d_6) δ 8.90 (s, 1H), 8.30 (d, 1H, *J* = 9 Hz), 7.40 (d, 1H, *J* = 9 Hz), 4.85 (q, 2H, *J* = 7 Hz), 3.25–3.15 (m, 4H), 1.80–1.55 (m, 6H), 1.35 (t, 3H, *J* = 7 Hz). ^{13}C NMR (DMSO-d_6) δ 176.8, 165.5, 158.6, 152.5 (CH), 141.6, 126.7 (CH), 123.2, 119.0 (CH), 108.4, 104.0, 52.9 ($2 \times CH_2$), 52.5 (CH_2), 25.6 ($2 \times CH_2$), 23.5 (CH_2), 15.1 (CH_3). IR (nujol) 1720, 1605. Anal. calcd for $C_{17}H_{19}BrN_2O_3$, C 53.83, H 5.05, N 7.39, found C 54.0, H 4.9, N 7.2.

4.5.4. Irradiation of compound 3 with Na_2SO_3 0.05 M

A solution of **3** (2×0.1 mmol, 3.5×10^{-4}M) and sodium sulphite (2×15 mmol, 0.05 M) in H_2O/CH_3CN (4:6) was placed in an immersion-well apparatus (2×300 ml), stirred and flushed with argon for 20 min, then irradiated for 30 minutes, with a 125 W medium-pressure mercury lamp through Pyrex, while maintaining the argon flow.

The irradiated solutions were collected together and acetonitrile was removed under vacuum. The remaining aqueous phase was extracted with chloroform, affording 55 mg of a dark yellow residue, containing **8** as the main product.

8 (from the mixture): ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1H), 8.10 (d, 1H, *J* = 9 Hz), 7.30 (dd, 1H, *J* = 9 and 1.6 Hz), 6.90 (d, 1H, *J* = 1.6 Hz), 4.50 (q, 2H, *J* = 7 Hz), 3.30 (bs, 4H), 1.65 (bs, 6H), 1.40 (t, 3H, *J* = 7 Hz).

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