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Elemental fluorine
Part 15. Selective direct fluorination of quinoline derivatives☆

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Abstract

Direct fluorination of various quinoline derivatives in acidic reaction media gives fluorinated quinoline products arising from electrophilic substitution processes.

Keywords: Direct selective fluorination; Elemental fluorine; Fluoroquinoline

1. Introduction

It is now well established that the incorporation of fluorine atoms into heterocyclic molecules can have a significant effect upon the chemical and biological properties of these systems [1]. This has been used to great effect in the development of various commercially important life-science products, such as 5-fluorouracil, 5-fluoroprimaquine and ciprofloxacin (Fig. 1), that owe their useful biological activity to the presence of a fluorine substituent located on the heterocyclic ring [1].

However, efficient synthesis of fluorinated heterocyclic derivatives is not trivial and presents a considerable challenge. Currently, various routes to fluoroheteroaromatic systems, involving the selective replacement of a leaving group by fluorine, are prevalent. The well established Balz–Schiemann process, involving treatment of a heteroaromatic diazonium salt with anhydrous hydrogen fluoride, has allowed the synthesis of, for example, various fluoro-pyridine and -quinoline derivatives [2]. Halogen exchange processes, in which nucleophilic displacement of chloride by fluoride ion occurs, is also widely used, but the harsh reaction conditions sometimes required prevent effective reaction. For both of these methods, appropriate chloro- and diazo-heteroaromatic substrates must first be synthesised and this can itself be problematic. An alternative approach to, for example, fluoroquinoline synthesis, involves annelation of the fluorinated benzenoid precursors, e.g. the Skraup synthesis, but, again, preparation of appropriate starting materials can be problematic.

Potentially, the most direct and efficient approach to the synthesis of fluoroheteroaromatic systems is the transformation of carbon–hydrogen to carbon–fluorine bonds upon fluorination by an electrophilic fluorinating agent. In this context, electrophilic reagents such as xenon difluoride [3], acetyl hypofluorite [4] and N–F reagents have been used to synthesise a very limited range of, for example, fluoroquinoline derivatives, with varying degrees of success. All of the aforementioned electrophilic reagents, however, are prepared from elemental fluorine and it is perhaps surprising that reports of syntheses of flurooheteroaromatic systems using fluorine are very few in number. This is despite the fact that 5-fluorouracil is prepared on a commercial scale using fluorine, demonstrating the opportunities provided by this approach. Various fluoro-pyridine [5] and -purine derivatives have been prepared by direct fluorination and, by a related, though conceptually very different approach, several 2-fluoroquinolines were synthesised by reaction with iodine monofluoride, prepared in situ from iodine and fluorine [6].

☆ For Part 14, see R.D. Chambers, A.M. Kenwright, M. Parsons, G. Sandford, J.S. Moilliet, J. Chem. Soc., Perkin Trans. 1 (2002) 2190–2197.

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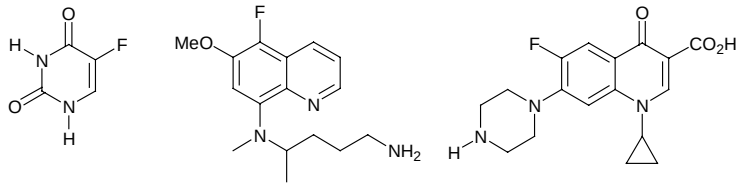


Fig. 1. Some commercially important fluoro-heterocyclic derivatives.

In this series, we are developing the use of elemental fluorine as a viable reagent for organic synthesis and we have described effective methodology for the preparation of various fluoro-aromatic [7,8], dicarbonyl and carbonyl derivatives. In particular, the beneficial role of using acidic media for direct fluorination processes has been emphasised [7] allowing effective selective synthesis of, for example, fluoro-aromatic systems. Here, we report our studies concerning the direct fluorination of quinoline derivatives with the possibility in mind of establishing the use of fluorine for the general synthesis of many fluoro-heteroaromatic systems.

2. Results and discussion

2.1. Synthesis

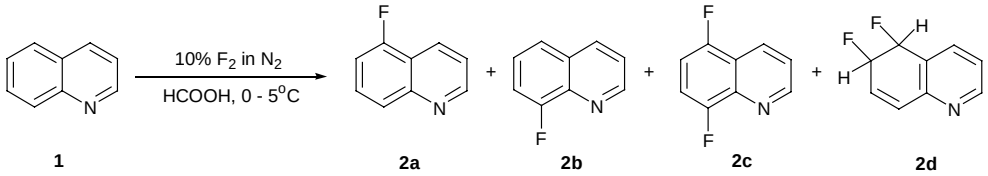
Since use of solvents with high relative permittivity, such as acetonitrile, formic and sulfuric acids has proved to be beneficial in direct fluorination reactions with aromatic substrates [7], we have assessed the effectiveness of these solvents for the fluorination of quinoline.

Reaction of quinoline **1** and fluorine in acetonitrile led to a crude mixture that contained many fluorinated products and considerable amounts of intractable tar, from which no useful product could be obtained. Similarly, using formic acid as solvent gave a complex mixture containing many fluorinated products and significant amounts of tar but, in this case, four major products **2a–d** could be identified by ^{19}F NMR. (Scheme 1). 5-Fluoro-**2a**, 8-fluoro-**2b**, 5,8-difluoro-quinoline-**2c** and the addition product **2d** were present in the crude reaction mixture in the ratio of 3.8:2.7:1:3.2 but in overall low yield. Column chromatography gave only an enriched sample of **2d** but the coupling patterns observed in both ^{1}H and ^{19}F NMR confirmed the structure. The three main monofluorinated products could not be isolated but were identified by ^{19}F NMR, by comparison with literature data and authentic samples.

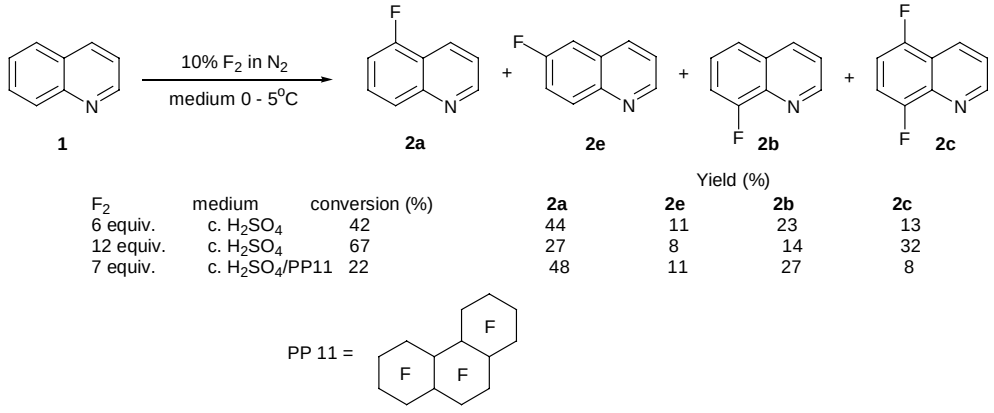
Concentrated sulfuric acid was found to be a much superior reaction medium because, essentially, no tar was formed upon passing fluorine, diluted to a 10% mixture (v/v) in nitrogen, through a solution of **1** at 0–5 °C. Although conversion of **1** was moderate, even after six equivalents of fluorine had been passed through the stirred reaction mixture, **2a–c** and **2e** were obtained in a total yield of 91% by ^{19}F NMR (Scheme 2). The reaction mixture was poured into water and neutralised (sodium bicarbonate) and, although separation of the fluorinated products was difficult, difluoro-quinoline **2c** was isolated and purified by column chromatography.

Proton/deuterium exchange studies in strong acid media have established [9] that, generally, the positional order of reactivity in quinoline towards electrophiles is 8 > 5, 6 > 7 > 3, whereby positions α to the hetero-ring are more readily attacked than β sites. More specifically, halogenation of quinoline by chlorine [10], bromine [11,12] and iodine [13] in sulfuric acid, gave the 5-, 8- and 5,8-halogenated quinolines as the major products. As can be seen from Scheme 2, the positional reactivity towards fluorine is in the order 5 > 8 > 6 in which sites α to the hetero-ring (5 and 8) are fluorinated almost exclusively. It seems reasonable, therefore, to conclude that fluorination of quinolines in a strongly acidic medium follows an electrophilic substitution process since the orientation of substitution parallels other halogenations.

The neutralisation of large quantities of sulfuric acid in the work-up stage by sodium bicarbonate is a limiting factor so we carried out the fluorination reaction in a medium consisting of sulfuric acid and a perfluorocarbon fluid (Flutec^{TM} PP11, 20% v/v) as an inert heat transfer and bulking agent. The product profile of the reaction was



Scheme 1.



F_2	medium	conversion (%)	Yield (%) 2a	2e	2b	2c
6 equiv.	c. H_2SO_4	42	44	11	23	13
12 equiv.	c. H_2SO_4	67	27	8	14	32
7 equiv.	c. H_2SO_4/PP11	22	48	11	27	8

PP 11 =

Scheme 2.

unaffected by the presence of the large volume of perfluorocarbon fluid and the work-up could be achieved more conveniently due to the lower quantity of acid present.

As a result of these studies, we adopted, as a medium of choice, either sulfuric acid or sulfuric acid/perfluorocarbon fluid for subsequent direct fluorination reactions of the following quinoline derivatives.

Having established that controlled, direct fluorination of **1** was possible using sulfuric acid, we then assessed the affect of substituents located on either the carbocyclic or heterocyclic ring of various quinoline substrates on the process. Fluorination of 2-chloro-**3** and 4-methyl-quinoline **4** in sulfuric acid and oleum/PP11 media, respectively, gave a mixture of four fluoroquinoline derivatives, **5a–d** and **6a–d**, respectively (Scheme 3). For both reactions, products were identified by ^{19}F NMR and GC/MS but, unfortunately, no individual fluorinated products **5a–d** or **6a–d** could be isolated pure from the crude mixtures. The presence of substituents on the heterocyclic ring of quinoline does not, therefore, appear to effect the regioselectivity of the fluorination reaction because a similar product profile is observed in fluorination of **3**, **4** and **1** itself (compare Schemes 2 and 3).

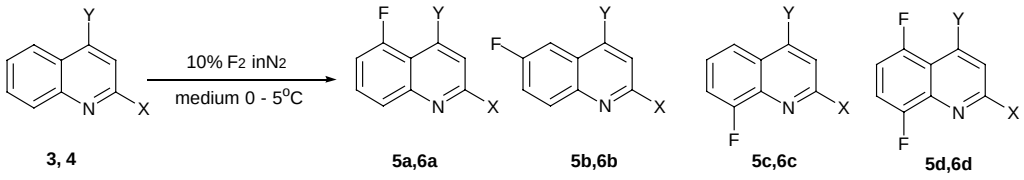
Fluorination of quinolines bearing electron withdrawing and/or electron releasing groups on the carbocyclic ring were next studied to determine the effect of ring substituents upon the fluorination process. Fluorination of various methyl-quinoline derivatives **7–9** were observed to be reasonably selective, although difluorination is a competing process, and all products could be isolated (Scheme 4). The regioselectivity of these reactions is also consistent with an electrophilic substitution process.

Unusually, 8-methylquinoline **8** gave a mixture containing both the 5-fluoroquinoline **12a** and a fluoro-ketone system **12b** while excess fluorine (12 equiv.) leads to an increase in the yield of **12b**. A mechanism for the formation of **12b**, requiring two equivalents of fluorine and nucleophilic attack by water in the reaction work-up to complete the transformation is given in Scheme 5.

Fluorination of 6-methoxyquinoline **13** gave either the 5-fluoroderivative **14a** or an α,α-difluoro-ketone **14b** in 74 and 26% yield, respectively (Scheme 6), upon reaction with three equivalents of fluorine in a very efficient, clean process and both products could be isolated by column chromatography. The yield of **14b** was increased simply by passing of a large excess of fluorine through the reaction mixture, and a mechanism for the formation of **14b** is outlined in Scheme 6.

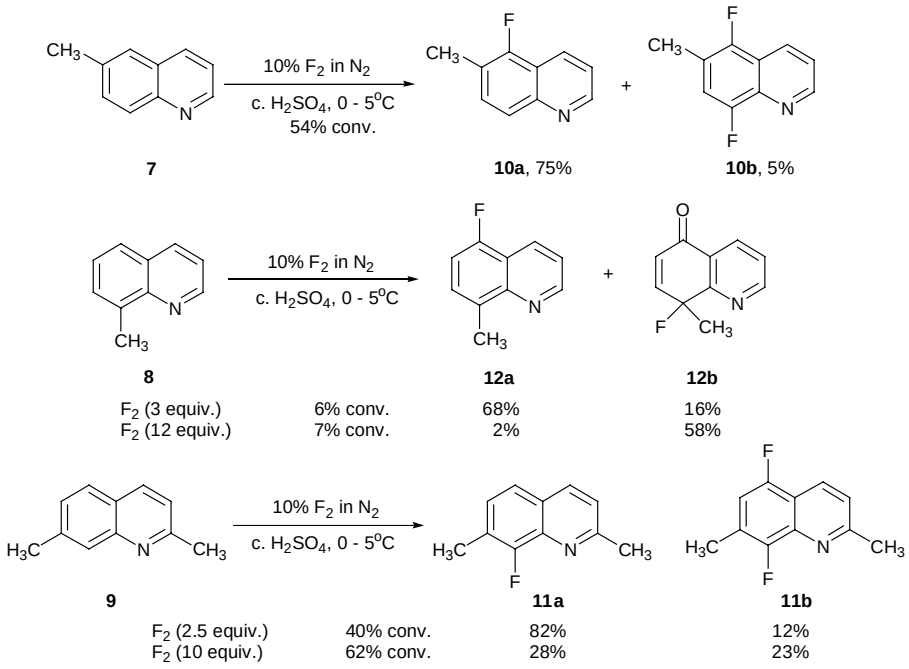
Similarly, the aldehyde **15** gave the corresponding difluoroketone **16b** (∼10 g scale) as a single, crude product, that was essentially pure, after reaction with excess fluorine (Scheme 7). The nitro-methoxy quinoline **17**, however, gave only the mono-fluorinated product **18** reflecting the deactivating influence of the nitro group on the second fluorine addition step (Scheme 7).

Quinoline derivatives with electron withdrawing substituents located on the carbocyclic ring were also fluorinated efficiently to give the products indicated in Scheme 8.

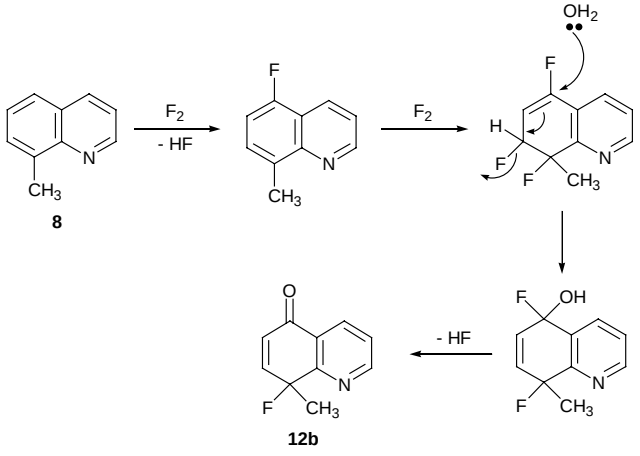


	F_2	medium	conversion (%)	Yield (%)			
3, X = Cl, Y = H	12 equiv.	oleum/PP11	68	**5a**, 25	**5b**,11	**5c**, 16	**5d**, 21
4, X = H, Y = CH_3	3 equiv.	c. H_2SO_4	26	**6a**, 48	**6b**, 14	**6c**, 23	**6d**, 6

Scheme 3.



Scheme 4.

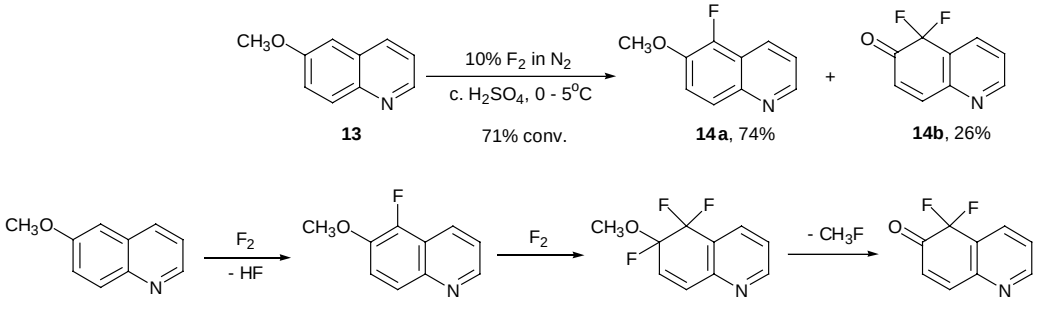


Scheme 5.

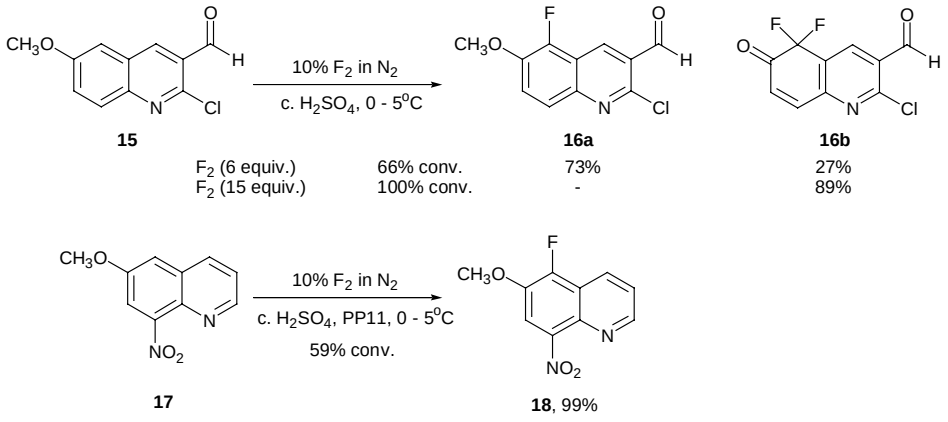
The direct fluorination reactions described above give rise to products that are all consistent with an electrophilic substitution process. Electron releasing groups (CH_3, OCH_3) gave products derived from substitution at positions *ortho* and *para* to the substituent, in which α positions are favoured over β sites if two sites are available. (e.g. **15** gives **16** rather than substitution at the 6-position). Fluorination of quinolines bearing electron withdrawing groups (NO_2) gave fluorination at sites *meta* to the substituent, as would be predicted for electrophilic substitution. These reactions further demonstrate that fluorine is a viable controllable reagent.

2.2. X-ray crystallography

The structures of several of the fluorinated products described above were confirmed by X-ray crystallography. Molecular structures are shown in Fig. 2 and the following



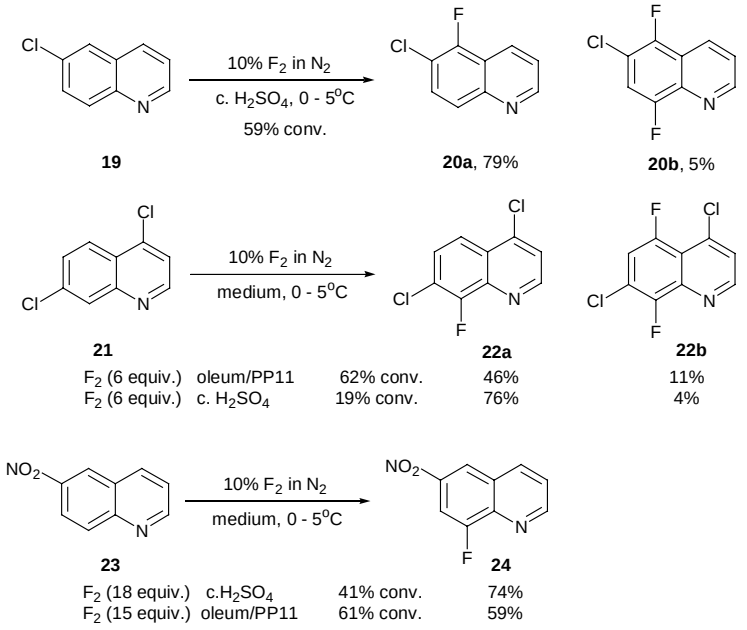
Scheme 6.



Scheme 7.

points are of note. In **12b**, the heterocycle is planar, while the carbocycle shows a small boat-like distortion, C(5), C(8) and O tilting out of the C(6), C(7), C(9), C(10) plane to the side of the methyl group, by 0.05, 0.08 and 0.13 Å, respectively. In **16a**, the formyl and methoxy groups are rotated out of the quinoline plane by 12.2 and 3.5°, respectively. In **16b**, the fused-ring system is planar, except the difluorinated atom C(5) which is tilted out of the plane by 0.07 Å; the formyl group lies in the same plane. The crystal of **17** was obtained as a solid solution of **18** (ca. 2.5%) in **17**, as indicated by the small but significant peak of electron density near H(5), which was interpreted and successfully refined as F(5) of **18** (all other atoms of either component share the same positions in the crystal lattice). The nitro-group is almost perpendicular to the quinoline plane (dihedral angle 88.4°), while the methoxy group lies in the latter plane. In the structure of pure **18**, the methoxy group also adopts an in-plane conformation, but differing from that in **17** by 180° rotation, while the inclination of the nitro group is reduced to 53.8°.

Crystallisation of **22a** produced a solid solution of **22b** in **22a** in a ca. 1:5 ratio. As in the case of **17/18**, the position 5 at the quinoline nucleus is shared by the F(5) substituent of **22b** (the occupancy of which was refined to 16.7 (8)%) and H(5) of **22a**, while the positions of all other atoms are the same for **22a** and **22b**. Molecules, related by the *b* translation, form continuous stacks with the interplanar separations of 3.38 Å. Each chlorine atom participates in two intra-stack contacts of 3.77 Å with its translational equivalents, and in one inter-stack contact $\mathrm{Cl}(4)\cdots\mathrm{Cl}(7)$ of 3.57 Å between stacks,



Scheme 8.

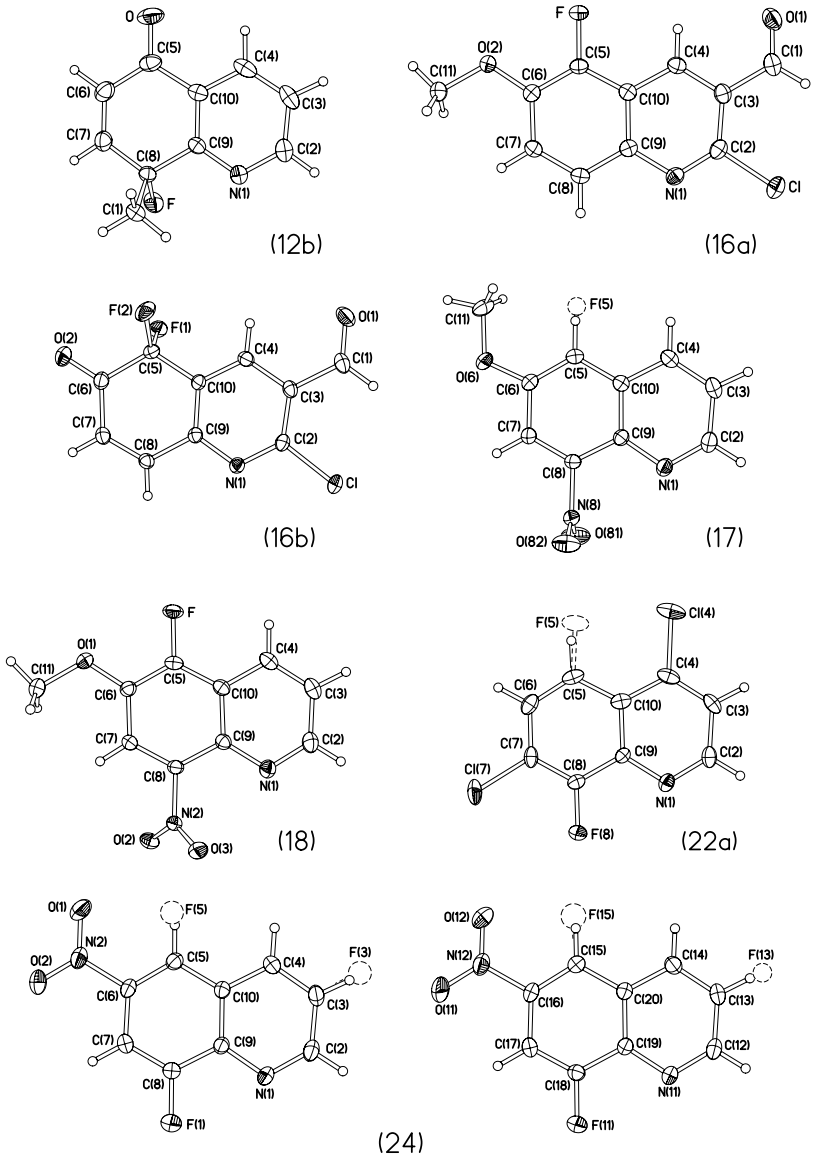


Fig. 2. X-ray molecular structures, showing displacement ellipsoids at 50% probability level. Atoms, belonging to impurities, are shown in dashed lines.

related via a *c* translation. These contacts, although exceeding the doubled van der Waals radius of Cl (1.76 Å), [14] indicate the usual tendency of chlorine atoms to ''stick together'' in a condensed phase [14,15]. These stacks form a layer, parallel to the (1 0 0) plane. All molecules within a layer are parallel to each other, but inclined by 53° to those of the adjacent layers (related via the *n* glide plane).

The asymmetric unit in the crystal of **24** comprises two molecules, both of which show traces of fluorine substitution in positions 3 and 5. The occupancies of 6% for F(3), F(5), F(13) and F(15) gave the best agreement with the data and the crystal can be described as a solid solution in **24** of 6% of 3,5,8-trifluoro-6-nitroquinoline, a minor by-product of the synthesis which was not isolated. In both independent molecules, the dihedral angles between the nitro group and the quinoline system are small, 3.2(1) and 4.1(1).

3. Experimental

3.1. General

All starting materials were obtained commercially (Sigma-Aldrich) and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. Spectral assignments were made with the aid of data collected by $^{1}H-^{1}H$ COSY and $^{1}H-^{13}C$ HETCOR experiments and coupling constants are given in Hz. Mass spectra were recorded on either a VG 7070E spectrometer or a Fissons VG Trio 1000 spectrometer coupled with a Hewlett-Packard 5890 series II gas chromatograph. Accurate mass measurements were performed by

the EPSRC National Mass Spectrometry service, Swansea, UK. Elemental analyses were obtained on either a Perkin-Elmer 240 or a Carlo Erba Elemental Analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was carried out on silica gel (Merck No. 1-09385, 230–400 mesh) and TLC analysis was performed on silica gel TLC plates using dichloromethane as eluant.

3.2. Reactions with elemental fluorine

3.2.1. General procedure

Elemental fluorine, as a 10% (v/v) mixture with nitrogen, was passed at a rate of ca. 50 ml min^{-1} through a stirred, cooled (0 °C) mixture which consisted of the substrate and the reaction medium. After addition of the fluorine, the reaction mixture was poured into water (1500 ml), neutralised ($NaHCO_3$) and extracted with dichloromethane (3×100 ml). The combined, dried ($MgSO_4$), organic extracts were evaporated to give a crude product. The composition of a weighed crude reaction mixture was determined by GC/MS analysis and the conversion of starting material was calculated from calibrated GC peak intensities. The amount of fluorinated product in the crude product was determined by adding a known amount of trifluoromethylbenzene to a weighed amount of the crude product mixture. Comparison of the relative intensities of the appropriate ^{19}F NMR resonances gave the yield of fluorinated derivative, based upon the conversion obtained above. Analytical samples of fluorinated products were obtained by either preparative scale GC or column chromatography. Yields of fluorinated products are quoted as yields based on the conversion of starting material.

For reactions involving the use of perfluorocarbon fluids (e.g. PP11) as reaction media, the following work-up procedure was used. The reaction was poured onto ice-water (400 ml) and the PP11 separated as a lower layer. The PP11 layer was further washed with water (50 ml), dried ($MgSO_4$) and re-used without further purification. The aqueous phase was neutralised with sodium hydrogencarbonate and extracted with dichloromethane. The combined extracts were dried over magnesium sulfate and solvent was removed by rotary evaporation to leave crude reaction product.

3.2.2. Fluorination of quinoline *1*: solvent survey

3.2.2.1. Acetonitrile. Quinoline **1** (2.0 g, 15 mmol) and fluorine (47 mmol, 3 equiv.) in acetonitrile (50 ml) gave a dark oil (13.0 g) and significant tar. Analysis of this crude product by ^{19}FF NMR showed a complex mixture of products that could not be identified and were not investigated further.

3.2.2.2. Formic acid. **1** (6.0 g, 45 mmol), formic acid (150 ml) and fluorine (90 mmol, 2 equiv.) gave a dark brown tar. ^{19}F NMR analysis showed the presence of four products; 5-fluoroquinoline **2a**, 8-fluoroquinoline 2b, 5,8-difluoroquinoline **2c** and 5,6-difluoro-5,6-dihydroquinoline **2d** in the ratio of 3.8:2.7:1:3.2. Conversion and yields could not be determined accurately due to the tar present in the crude product. Column chromatography over silica gel using diethyl ether as eluant gave only an enriched sample of 5,6-difluoro-5,6-dihydroquinoline **2d**; δ_H 5.28 (1H, ddt, $^1J_{HF}$ 49.2, $^3J_{FF}$ 17.2, $^3J_{HF}$ 4.4, H-6), 5.58 (1H, ddd, $^1J_{HF}$ 48.8, $^3J_{FF}$ 21.6, $^3J_{HF}$ 4.0, H-5), 6.39 (1H, m, H-7), 6.86 (1H, dd, $^3J_{HH}$ 10.0, $^4J_{HF}$ 2.8, H-8), 7.23 (1H, dd, $^3J_{HH}$ 7.6, $^3J_{HH}$ 4.8, H-3), 7.78 (1H, d, $^3J_{HH}$ 7.6, H-4), 8.56 (1H, d, $^3J_{HH}$ 4.8, H-2); δ_F –201.1 (1F, dm, $^2J_{HF}$ 49.6, F-6), −201.7 (1F, dd, $^2J_{HF}$ 48.1 $^3J_{FF}$ 11.7, F-5); δ_C 84.5 (dd, $^1J_{CF}$ 180.5, $^2J_{CF}$ 17.8, C-6), 87.7 (dd, $^1J_{CF}$ 185.9, $^2J_{CF}$ 18.2, C-5), 115.2 (d, $^2J_{CF}$ 20.5, C-4α), 122.9 (s, C-3), 127.2 (dd, $^2J_{CF}$ 18.2, $^3J_{CF}$ 6.1, C-7), 129.9 (d, $^3J_{CF}$ 7.9, C-8α), 133.3 (dd, $^3J_{CF}$ 9.2, $^4J_{CF}$ 1.6, C-8), 134.4 (d, $^3J_{CF}$ 6.1, C-4), 150.2 (d, $^5J_{CF}$ 2.2, C-2).

3.2.2.3. Sulfuric acid. **1** (4.0 g, 30 mmol), sulfuric acid (150 ml) and fluorine (360 mmol, 12 equiv.) gave a dark yellow oil (4.97 g, conv. 67%) that consisted of 5-fluoroquinoline **2a** (27%), 6-fluoroquinoline **2e** (8%), 8-fluoroquinoline **2b** (14%) and 5,8-difluoroquinoline **2c** (32%). Purification by column chromatography on silica gel using diethyl ether as elutant gave analytical samples of 5-fluoroquinoline **2a** as a yellow oil [2]; δ_H 7.03 (1 H, m, H-6), 7.25 (1H, dd, $^3J_{HH}$ 8.5,$^3J_{HH}$ 4.0, H-3), 7.46 (1 H, td, $^3J_{HH}$ 8.0, $^4J_{HF}$ 6.0, H-7), 7.77 (1 H, d, $^3J_{HH}$ 8.5, H-8), 8.23 (1 H, dm, $^3J_{HH}$ 8.5, H-4), 8.77 (1 H, dd, $^3J_{HH}$ 4.5, $^4J_{HH}$ 1.5, H-2); δ_F –123.3 (dd, $^3J_{HF}$ 9.4,$^4J_{HF}$ 5.6, F-5); δ_C 109.8 (d, $^2J_{CF}$ 18.9, C-6), 118.8 (d, $^2J_{CF}$ 16.5, C-4α), 120.9 (d, $^4J_{CF}$ 6.9, C-3), 125.0 (s, C-8), 128.7 (d, $^3J_{CF}$ 8.9, C-7), 129.0 (d, $^3J_{CF}$ 4.5, C-4), 148.6 (d, $^4J_{CF}$ 3.0, C-8α), 150.9 (s, C-2), 157.5 (d, $^1J_{CF}$ 255.0, C-5); *m/z* (EI^+) 147 (M^+, 100%); (Found: M^+ 147.048546. C_9H_6FN requires M^+ 147.048427); and, 8-fluoroquinoline **2b** as a yellow oil [2]; δ_H 7.33–7.21 (3 H, m, H-3,5,7), 7.43 (1 H, dm, $^3J_{HH}$ 8.0, H-6), 8.00 (1 H, dm, $^3J_{HH}$ 8.5, H-4), 8.81 (1 H, dm, $^3J_{HH}$ 4.0, H-2); δ_F −126.2 (dd, $^3J_{HF}$ 10.3, $^4J_{HF}$ 4.7, F-8); δ_C 113.1 (d, $^2J_{CF}$ 18.5, C-7), 121.7 (d, $^3J_{CF}$ 7.6, C-6), 123.1 (d, $^4J_{CF}$ 4.5, C-5), 126.0 (m, C-3), 129.4 (d, $^3J_{CF}$ 2.5, C-4α), 135.6 (s, C-4), 138.0 (d, $^2J_{CF}$ 12.0, C-8α), 150.1 (s, C-2), 157.6 (d, $^1J_{CF}$ 257.0, C-8); *m/z* (EI^+) 147 (M^+, 100%); (Found: M^+ 147.048437. C_9H_6FN requires M^+ 147.048427); and, 5,8-difluoroquinoline **2c** as a white solid [16]; mp 59–61 °C (hexane); δ_H 7.16 (1 H, td, $^3J_{HF}$ 8.5, $^3J_{HH}$ 4.0, H-6), 7.35 (1 H, td, $^3J_{HF}$ 9.5, $^3J_{HH}$ 4.5, H-7), 7.55 (1 H, dd, $^3J_{HH}$ 8.5, $^3J_{HH}$4.0, H-3), 8.43 (1 H, dm, $^3J_{HH}$ 8.5, H-4), 9.02 (1 H, dd, $^3J_{HH}$ 4.0, $^4J_{HH}$ 1.0, H-2); δ_F −127.4 (1 F, ddd, $^5J_{FF}$ 21.6, $^3J_{HF}$ 9.4, $^4J_{HF}$ 5.2, F-5), −130.2 (1 F, ddd, $^5J_{FF}$ 22.1, $^3J_{HF}$ 9.9, $^4J_{HF}$ 3.3, F-8); δ_C 109.5 (dd, $^2J_{CF}$ 22.0, $^3J_{CF}$ 7.7, C-6), 112.6 (dd, $^2J_{CF}$ 21.6, $^3J_{CF}$ 9.1, C-7), 120.0 (dd, $^2J_{CF}$ 18.3, $^3J_{CF}$ 2.7, C-4α), 122.1 (d, $^4J_{CF}$ 2.1, C-3), 129.5 (dd, $^2J_{CF}$ 3.7, $^4J_{CF}$ 2.4, C-4), 138.3 (m, C-8α), 151.3 (d, $^4J_{CF}$ 1.6, C-2), 153.5 (dd, $^1J_{CF}$ 250.1, $^4J_{CF}$ 3.8, C-5), 154.3 (dd, $^1J_{CF}$ 251.2, $^4J_{CF}$ 3.8, C-8); *m/z* (EI^+) 165 (M^+, 100%); (Found: M^+, 165.038984. $C_9H_5F_2N$ requires M, 165.039006). 6-Fluoroquinoline **2e** was not isolated but could be identified [2] in the ^{19}F NMR

spectrum of the crude reaction mixture; δ_F –114.3 (d, $^3J_{HF}$ 4.7, F-6).

3.2.2.4. Sulfuric acid/perfluorocaron fluid Flutec™ PP 11. **1** (4.0 g, 30 mmol), sulfuric acid (20 ml), Flutec™ PP11(80 ml) and fluorine (220 mmol, 7 equiv.) gave a dark yellow oil (8.26 g, conv. 22%) that consisted of 5-fluoroquinoline **2a** (48%), 6-fluoroquinoline **2e** (11%), 8-fluoroquinoline **2b** (27%) and 5,8-difluoroquinoline **2c** (8%); spectral data as above.

*3.2.3. Fluorination of 2-chloroquinoline **3***

2-Chloroquinoline 3 (2.5 g, 15 mmol), oleum (10 ml), PP11 (90 ml) and fluorine (180 mmol, 12 equiv.) qave a yellow oil (3.4 g, conv. 68%) that contained 2-chloro-5-fluoroquinoline [17] **5a** (25%); δ_F –122.4 (dd, $^3J_{HF}$ 10.2, $^4J_{HF}$ 6.4, F-5); 2-chloro-6-fluoroquinoline **5b** (11%); δ_F –113.2 (m, F-6); 2-chloro-8-fluoroquinoline **5c** (16%); δ_F –125.5 (dd, $^3J_{HF}$ 9.0, $^4J_{HF}$ 4.5, F-8); and, 2-chloro-5,8-difluoroquinoline **5d** (21%); δ_F –126.5 (1 F, ddd, $^5J_{FF}$ 21.1, $^3J_{HF}$ 8.3 $^4J_{HF}$ 4.5, F-5), –129.6 (1 F, ddd, $^5J_{FF}$ 22.0 $^3J_{HF}$ 9.2 $^4J_{HF}$ 2.8, F-8); which could not be separated from the reaction mixture.

*3.2.4. Fluorination of 4-methylquinoline **4***

4-Methylquinoline **4** (1.70 g, 12 mmol), sulfuric acid (150 ml) and fluorine (39 mmol, 3.25 equiv.) gave a dark oil (2.18 g, conv. 26%) which contained 5-fluoro-4-methylquinoline [18] **6a** (48%); δ_F –112.1 (m, F-5); 6-fluoro-4-methylquinoline [19] **6b** (14%); δ_F –113.7 (m, F-6); 8-fluoro-4-methylquinoline **6c** (23%); δ_F –125.7 (dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 5.5, F-8); and, 5,8-difluoro-4-methylquinoline **6d** (6%); δ_F –116.2 (1 F, m, F-5), –129.0 (1 F, ddd, $^5J_{FF}$ 22.0, $^3J_{HF}$ 9.2, $^4J_{HF}$ 3.8, F-8) which could not be separated from the reaction mixture.

*3.2.5. Fluorination of 6-methylquinoline **7***

6-Methylquinoline **7** (2.86 g, 20 mmol), sulfuric acid (150 ml) and fluorine (65 mmol, 3.25 equiv.) gave an orange oil (3.55 g, conv. 54%) that contained 5-fluoro-6-methyquinoline **10a** (75%) and 5,8-difluoro-6-methylquinoline **10b** (5%). Purification by column chromatography on silica gel using diethyl ether: hexane (4:1) as elutant, gave 5-fluoro-6-methylquinoline **10a** as a pale yellow oil; δ_H 2.37 (3 H, m, Me), 7.33 (1 H, m, H-3), 7.45 (1 H, td, $^4J_{HH}$ 8.0, $^4J_{HF}$ 3.2, H-7), 7.77 (1 H, dd, $^3J_{HH}$ 8.8, $^5J_{HF}$ 2.0, H-8), 8.27 (1 H, dd, $^3J_{HH}$ 8.4, $^4J_{HH}$ 2.0, H-4), 8.83 (1 H, br. m, H-2), δ_F –128.2 (d, $^4J_{HF}$ 8.6, F-5); δ_C 14.0 (d, $^3J_{CF}$ 3.5, Me), 118.6 (d, $^2J_{CF}$ 16.7, C-6), 119.4 (d, $^2J_{CF}$ 14.8, C-4α), 120.8 (d, $^4J_{CF}$ 3.0, C-3), 124.3 (d, $^4J_{CF}$ 4.2, C-8), 128.5 (d, $^3J_{CF}$ 5.4, C-4), 131.9 (d, $^3J_{CF}$ 6.1, C-7), 147.2 (d, $^4J_{CF}$ 2.7, C-8α), 149.9 (s, C-2), 156.6 (d, $^1J_{CF}$ 250.4, C-5); *m/z* (EI^+) 161 (M^+, 92%), 160 (100), 133 (63); found: $[M+H]^+$ 162.0719. $C_{10}H_9FN$ requires $[M+H]^+$ 162.0719; and, 5,8-difluoro-6-methylquinoline **10b** as a pale yellow solid; mp 81−82 °C; δ_H 2.43 (3 H, d, $^4J_{HF}$ 2.4, Me), 7.22 (1 H, dd, $^3J_{HF}$ 10.8, $^4J_{HF}$ 6.4, H-7), 7.48 (1 H, dd, $^3J_{HH}$ 8.4, $^3J_{HH}$ 4.4, H-3), 8.35 (1 H, dm, $^3J_{HH}$ 7.2, H-4), 8.93 (1 H, dm, $^3J_{HH}$ 4.4, H-2); δ_F –131.6 (1 F, dd, $^5J_{FF}$ 21.8, $^4J_{HF}$ 10.2, F-8), −132.3 (1 F, dm, $^5J_{FF}$ 21.8, F-5); δ_C 14.4 (d, $^3J_{CF}$ 3.4, $^4J_{CF}$ 0.8, Me), 115.6 (dd, $^2J_{CF}$ 20.8, $^3J_{CF}$ 5.6, C-4α), 119.7 (dd, $^2J_{CF}$ 18.2, $^3J_{CF}$ 5.0, C-7), 119.8 (d, $^2J_{CF}$ 18.3, C-6), 122.0 (d, $^4J_{CF}$ 2.3, C-3), 128.9 (dd, $^3J_{CF}$ 4.6, $^4J_{CF}$ 2.7, C-4), 136.9 (dd, $^2J_{CF}$ 13.7, $^3J_{CF}$ 3.0, C-8α), 150.3 (d, $^4J_{CF}$ 1.6, C-2), 150.7 (dd, $^1J_{CF}$ 246.2, $^4J_{HF}$ 3.1, C-5), 153.6 (dd, $^1J_{CF}$ 250.7, $^4J_{CF}$ 3.0, C-8); *m/z* (EI^+) 179 (M^+, 100%), 178 (91); (Found: M^+ 179.0549. $C_{10}H_7F_2N$ requires M^+ 179.0547).

*3.2.6. Fluorination of 8-methylquinoline **8***

8-Methylquinoline **8** (2.86 g, 20 mmol), sulfuric acid (150 ml) and fluorine (65 mmol, 3.25 equiv.) gave an orange oil (3.98 g, conv. 26%) which contained 5-fluoro-8-methylquinoline **12a** (68%) and 8-fluoro-8-methyl-8-hydroquinoline-5-one **12b** (16%). Purification by column chromatography on silica gel using diethyl ether: hexane (4:1) as elutant, gave *5-fluoro-8-methylquinoline* **12a** as a colourless oil; δ_H 2.74 (3 H, s, Me), 7.08 (1 H, dd, $^3J_{HH}$ 8.0, $^3J_{HF}$ 9.6, H-6), 7.43 (2 H, m, H-3,7), 8.38 (1 H, dd, $^4J_{HF}$ 8.4, $^3J_{HH}$ 1.6, H-4), 8.96 (1 H, dd, $^4J_{HH}$ 4.4, $^3J_{HH}$ 2.0, H-2); δ_F –126.9 (m, F-5); δ_C 17.6 (s, Me), 109.4 (d, $^2J_{CF}$ 18.6, C-6), 118.9 (d, $^2J_{CF}$ 16.3, C-4α), 120.7 (d, $^4J_{CF}$ 3.0, C-4), 128.4 (d, $^3J_{CF}$ 8.4, C-7), 129.3 (d, $^3J_{CF}$ 5.0, C-4), 132.7 (d, $^3J_{CF}$ 4.5, C-8α), 147.3 (d, $^4J_{CF}$ 2.7, C-8), 149.9 (s, C-2), 156.2 (d, $^1J_{CF}$ 250.7, C-5); *m/z* (EI^+) 161 (M^+, 100%), 160 (77); found: $[M+H]^+$ 162.0719. $C_{10}H_9FN$ requires $[M+H]^+$ 162.0719; and, 8-fluoro-8-methyl-8-hydroquinolin-5-one **12b** as a white solid; mp 68–70 °C; (Found: C, 67.5; H, 4.5; N, 8.0. $C_{10}H_8FNO$ requires C, 67.8; H, 4.5; N, 7.9%); δ_H 1.90 (3 H, d, $^3J_{HF}$ 21.2, Me), 6.44 (1 H, dd, $^3J_{HH}$ 10.4, $^4J_{HF}$ 1.2, H-6), 7.16 (1 H, dd, $^3J_{HH}$ 10.4, $^3J_{HF}$ 7.2, H-7), 7.49 (1 H, ddd, $^3J_{HH}$ 8.0, $^3J_{HH}$ 4.8, $^6J_{HF}$ 0.8, H-3), 8.36 (1 H, ddd, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6, $^5J_{HF}$ 0.8, H-4), 8.89 (1 H, dd, $^3J_{HH}$ 4.8, $^4J_{HH}$ 2.0, H-2); δ_F −144.4 (qd, $^3J_{HF}$ 20.3, $^3J_{HF}$ 5.6, F-8); δ_C 26.3 (d, $^2J_{CF}$ 28.8, Me), 87.4 (d, $^1J_{CF}$ 169.9, C-8), 124.4 (d, $^5J_{CF}$ 1.9, C-3), 125.2 (d, $^3J_{CF}$ 2.7, C-4α), 128.1 (d, $^3J_{CF}$ 7.6, C-6), 134.6 (s, C-4), 147.4 (d, $^2J_{CF}$ 22.0, C-7), 153.5 (d, $^4J_{CF}$ 1.6, C-2), 158.6 (d, $^2J_{CF}$ 16.3, C-8α), 183.9 (d, $^4J_{CF}$ 3.4, C-5); *m/z* (EI^+) 177 (M^+, 30%), 159 (100), 158 (78).

8 (2.02 g, 14 mmol) and fluorine (170 mmol, 12 equiv.) gave an orange oil (4.76 g, conv. 47%) which contained **12a** (12%) and **12b** (58%) by ^{19}F NMR analysis.

*3.2.7. Fluorination of 2,7-dimethylquinoline **9***

2,7-Dimethylquinoline **9** (1.5 g, 10 mmol), sulfuric acid (150 ml) and fluorine (50 mmol, 5 equiv.) gave a yellow solid (1.5 g, conv. 51%) which contained 8-fluoro-2,7-dimethylquinoline **11a** (61%) and 5,8-difluoro-2,7-dimethylquinoline **11b** (15%). Purification by column chromatography on silica gel using diethyl ether/hexane (4:1) as elutant, gave 8-fluoro-2,7-dimethylquinoline **11a** as a white solid; mp 90–92 °C; δ_H 2.38 (3 H, d, $^4J_{HF}$, 2.5, 7-Me), 2.68 (3 H, s, 2-Me), 7.20–7.14 (2 H, m, H-3,6), 7.34 (1 H, d, $^3J_{HH}$

4.0, H-5), 7.89 (1 H, dd, $^3J_{HH}$ 8.5, $^4J_{HH}$ 1.5, H-4); δ_F –131.8 (s, F-8); δ_C 14.6 (d, $^3J_{CF}$ 4.3, 7-Me), 25.5 (s, 2-Me), 122.0 (s, C-3), 122.1 (d, $^4J_{CF}$ 5.3, C-5), 123.3 (d, $^2J_{CF}$ 15.8, C-7), 126.2 (d, $^3J_{CF}$ 2.4, C-4α), 128.4 (d, $^3J_{CF}$ 4.8, C-6), 135.6 (d, $^4J_{CF}$ 3.4, C-4), 137.9 (d, $^2J_{CF}$ 11.9, C-8α), 155.1 (d, $^1J_{CF}$ 251.0, C-8), 159.2 (d, $^4J_{CF}$ 6.0, C-2); *m/z* (EI$^+$) 175 (M$^+$, 100%), 174 (79); M$^+$, 175.079991. $C_{11}H_{10}FN$ requires M, 175.079728; (Found: C, 74.91; H, 5.59; N, 7.87. $C_{11}H_{10}FN$ requires C, 75.41; H, 5.75; N, 7.99%); and, 5,8-difluoro-2,7-dimethylquinoline **11b** as a white solid; δ_H 2.46 (3 H, d, $^4J_{HF}$ 2.4, 7-Me), 2.78 (3 H, s, 2-Me), 6.95 (1 H, dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 5.2, H-6), 7.31 (1 H, d, $^3J_{HH}$ 8.8, H-3), 8.21 (1 H, d, $^3J_{HH}$ 8.8, H-4); δ_F –129.2 (1 F, dd, $^5J_{FF}$ 21.8, $^3J_{HF}$ 9.4, F-5), –135.9 (1 F, d, $^5J_{FF}$ 21.1, F-8); δ_C 14.9 (d, $^3J_{CF}$ 3.1, 7-Me), 25.6 (s, 2-Me), 111.5 (dd, $^2J_{CF}$ 21.4, $^3J_{CF}$ 4.6, C-6), 116.3 (dd, $^2J_{CF}$ 18.6, $^3J_{CF}$ 2.3, C-4α), 122.1 (d, $^4J_{CF}$ 2.2, C-3), 123.1 (dd, $^2J_{CF}$ 18.0, $^3J_{CF}$ 8.4, C-7), 129.3 (t, $^3J_{CF} = {}^4J_{CF}$ 2.7, C-4), 137.9 (dd, $^2J_{CF}$ 13.7, $^3J_{CF}$ 3.8, C-8α), 151.4 (dd, $^1J_{CF}$ 246.3, $^4J_{CF}$ 3.8, C-5), 152.8 (dd, $^1J_{CF}$ 249.0, $^4J_{CF}$ 3.8, C-8), 160.4 (s, C-2); *m/z* (EI$^+$) 193 (M$^+$, 100%); M$^+$, 193.070315. $C_{11}H_9F_2N$ requires M, 193.070306.

3.2.8. Fluorination of 6-methoxyquinoline **13**

6-Methoxyquinoline **13** (2.50 g, 16 mmol), sulfuric acid (150 ml) and fluorine (52 mmol, 3.25 equiv.) gave an orange oil (3.43 g, conv. 71%) that contained 5-fluoro-6-methoxyquinoline **14a** (74%) and 5,5-difluoro-5-hydroquinoline-6-one **14b** (26%). Purification by column chromatography on silica gel using diethyl ether as elutant, gave 5-fluoro-6-methoxyquinoline **14a** (1.1 g) as a white solid; mp 44–46 °C; (Found: C, 67.76; H, 4.56; N, 8.03. $C_{10}H_8FNO$ requires C, 67.79; H, 4.55; N, 7.91%); δ_H 7.36 (1 H, dd, $^3J_{HH}$ 8.4, $^5J_{HF}$ 4.0, H-8), 7.48 (1 H, t, $^3J_{HH} = {}^4J_{HF}$ 9.2, H-7), 7.85 (1 H, dm, $^3J_{HH}$ 9.2, H-3), 8.31 (1 H, dm, $^3J_{HF}$ 8.4, H-4), 8.78 (1 H, dd, $^4J_{HH}$ 4.0, $^3J_{HH}$ 1.6, H-2); δ_F –147.5 (s, F-5); δ_C 57.4 (d, $^4J_{CF}$ 1.1, MeO), 118.5 (d, $^3J_{CF}$ 2.7, C-7), 119.6 (d, $^2J_{CF}$ 13.7, C-4α), 121.2 (d, $^3J_{CF}$ 3.1, C-3), 125.4 (d, $^4J_{CF}$ 4.5, C-8), 128.0 (d, $^4J_{CF}$ 5.3, C-4), 143.1 (d, $^2J_{CF}$ 14.4, C-6), 143.2 (d, $^3J_{CF}$ 7.2, C-8α), 145.1 (d, $^1J_{CF}$ 250.0, C-5), 149.0 (s, C-2); *m/z* (EI$^+$) 177 (M$^+$, 100%), 134 (76); and, 5,5-difluoro-5-hydroquinolin-6-one **14b** (0.44 g) as a yellow solid; mp 105–107 °C; (Found: C, 59.68; H, 2.77; N, 7.82. C_9H_5FNO requires C, 59.68; H, 2.78; N, 7.73%); δ_H 6.46 (1 H, dt, $^3J_{HH}$ 10.4, $^4J_{HF}$ 4.0, H-7), 7.44 (1 H, dd, $^3J_{HH}$ 7.6, $^4J_{HH}$ 9.2, H-3), 7.64 (1 H, d, $^3J_{HH}$ 10.4, H-8), 8.10 (1 H, dm, $^4J_{HF}$ 8.1, H-4), 8.75 (1H, dq, $^3J_{HH}$ 4.8, $^4J_{HH}$ 1.2, H-2); δ_F –102.4 (2 F, s, F-5); δ_C 104.9 (t, $^1J_{CF}$ 245.0, C-5), 124.4 (s, C-3), 126.8 (t, $^3J_{CF}$ 2.7, C-7), 129.7 (t, $^2J_{CF}$ 24.3, C-4α), 134.7 (t, $^3J_{CF}$ 2.7, C-4), 146.9 (s, C-8), 149.3 (t, $^3J_{CF}$ 6.1, C-8α), 152.8 (t, $^5J_{CF}$ 1.9, C-2), 186.2 (t, $^2J_{CF}$ 24.2, C-6); *m/z* (EI$^+$) 181 (M$^+$, 100%), 153 (82).

3.2.9. Fluorination of 2-chloro-6-methoxyquinoline-3-carbaldehyde **15**

2-Chloro-6-methoxyquinoline-3-carbaldehyde **15** (1.5 g, 8 mmol), sulfuric acid (150 ml) and fluorine (48 mmol, 6 equiv) gave a yellow solid (1.6 g, conv. 66%) which contained 2-chloro-5-fluoro-6-methoxyquinoline-3-carbaldehyde **16a** (73%) and 2-chloro-5,5-difluoro-6-oxo-5-hydroquinoline-3-carbaldehyde **16b** (27%). Purification by column chromatography on silica gel using hexane: diethyl ether (7:3) then dichloromethane as elutant, gave 2-chloro-5-fluoro-6-methoxyquinoline-3-carbaldehyde **16a** as a yellow solid; mp 146–147°C; (Found: C, 54.87; H, 2.91; N, 5.80. $C_{11}H_7ClFNO_2$ requires C, 55.14; H, 2.94; N, 5.85%); δ_H 4.06 (3 H, s, OMe), 7.66 (1 H, t, $^3J_{HH} = {}^4J_{HF}$ 9.0, H-7), 7.83 (1 H, d, $^3J_{HH}$ 9.9, H-8), 8.91 (1 H, s, H-4), 10.52 (1 H, s, CHO); δ_F –141.8 (d, $^4J_{HF}$ 8.6, F-5); δ_C 57.5 (d, $^4J_{CF}$ 1.0, OMe), 118.3 (d, $^2J_{CF}$ 13.7, C-4α), 122.7 (d, $^3J_{CF}$ 2.8, C-7), 124.6 (d, $^4J_{CF}$ 4.5, C-8), 126.4 (d, $^3J_{CF}$ 2.3, C-8α), 133.2 (d, $^4J_{CF}$ 4.5, C-4), 143.6 (s, C-2), 144.4 (d, $^2J_{CF}$ 8.7, C-6), 146.7 (d, $^1J_{CF}$ 257.3, C-5), 148.5 (s, CHO), 188.6 (m, C-3); *m/z* (EI$^+$) 241 (M$^+$ [^{37}Cl], 75%), 240 (66), 239 (M$^+$ [^{35}Cl], 100), 241 (75), 238 (74), 224 (78), 196 (82), 175 (86), 168 (70), 132 (86); and, 2-chloro-5,5-difluoro-6-oxo-5-hydroquinoline-3-carbaldehyde **16b** as a yellow solid; mp 122–123 °C; (Found: C, 49.13; H, 1.59; N, 5.71. $C_{10}H_4ClF_2NO$ requires C, 49.31; H, 1.66; N, 15.60%); δ_H 6.64 (1 H, dt, $^3J_{HH}$ 10.0, $^4J_{HF}$ 2.5, H-7), 7.64 (1 H, d, $^3J_{HH}$ 10.5, H-8), 8.58 (1 H, s, H-4), 10.45 (1 H, s, CHO); δ_F –102.4 (2 F, s, F-5); δ_C 104.1 (t, $^1J_{CF}$ 248.1, C-5), 128.5 (s, C-2), 129.1 (t, $^2J_{CF}$ 25.1, C-4α), 130.0 (t, $^3J_{CF}$ 2.8, C-7), 136.7 (t, $^3J_{CF}$ 2.3, C-4), 143.9 (s, C-8), 153.3 (t, $^3J_{CF}$ 5.9, C-8α), 156.1 (s, CHO), 184.9 (t, $^2J_{CF}$ 24.3, C-6), 187.2 (m, C-3); *m/z* (EI$^+$) 245 (M$^+$ [^{37}Cl], 74%), 243 (M$^+$ [^{35}Cl], 100), 217 (60), 216 (67), 215 (80), 214 (97), 186 (86), 179 (51), 152 (68), 151 (88), 125 (65), 100 (52), 99 (67), 75 (81).

15 (10.4 g, 47 mmol), sulphuric acid (150 ml) and fluorine (707 mmol, 15 equiv.) gave a yellow solid (10.23 g, 100% conv.), which consisted of **16b** (10.23 g, 89%) as the sole product and no further purification was necessary; spectral and physical data as above.

3.2.10. Fluorination of 6-methoxy-8-nitroquinoline **17**

6-Methoxy-8-nitroquinoline **17** (0.5 g, 2.5 mmol), sulfuric acid (15 ml), PP11 (85 ml) and fluorine (36 mmol, 14 equiv.) gave a yellow/orange solid (0.45 g, conv. 59%) which contained 5-fluoro-6-methoxy-8-nitroquinoline **18** as the only product. Purification by column chromatography on silica gel using diethyl ether: hexane (9:1) as elutant, gave 5-fluoro-6-methoxy-8-nitroquinoline 18 (0.28 g) as a yellow solid; mp 154–155 °C; (Found: C, 53.8; H, 3.0; N, 12.4. $C_{10}H_7FNO_3$ requires C, 54.1; H, 3.2; N, 12.6%); δ_H 4.01 (3 H, d, $^5J_{HF}$ 0.8, OMe), 7.57 (1 H, dd, $^3J_{HH}$ 8.8, $^3J_{HH}$ 4.4, H-3), 8.01 (1 H, d, $^4J_{HF}$ 8.0, H-7), 8.44 (1 H, d, $^3J_{HH}$ 8.4, $^4J_{HH}$ 1.6, H-4), 9.01 (1 H, dd, $^3J_{HH}$ 4.4, $^4J_{HH}$ 1.6, H-2); δ_F –136.5 (d, $^4J_{HF}$ 7.9, F-5); δ_C 57.8 (s, OMe), 114.4 (d, $^3J_{CF}$ 3.6, C-7), 119.9 (d, $^2J_{CF}$ 14.2, C-4α), 122.8 (d, $^4J_{CF}$ 3.6, C-3), 128.4 (d, $^3J_{CF}$ 5.1, C-4), 134.8 (d, $^3J_{CF}$ 2.8, C-8α), 142.1 (d, $^2J_{CF}$ 10.6, C-6), 143.6 (s, C-8), 147.2 (d, $^1J_{CF}$ 259.7, C-5), 151.4 (s, C-2); *m/z* (EI$^+$) 222 (M$^+$, 100%), 192 (84), 133 (52).

3.2.11. Fluorination of 6-chloroquinoline **19**

6-Chloroquinoline **19** (2.35 g, 14 mmol), sulfuric acid (150 ml) and fluorine (168 mmol, 12 equiv.) gave a dark brown oil (3.29 g, conv. 59%) which contained 6-chloro-5-fluoroquinoline **20a** (79%) and 6-chloro-5,8-difluoroquinoline **20b** (5%); δ_F –128.3 (1 F, dd, $^5J_{FF}$ 19.9, $^3J_{HF}$ 9.6, F-8), –129.1 (1 F, dd, $^5J_{FF}$ 19.9, $^4J_{HF}$ 3.8, F-5). Purification by column chromatography using silica gel and diethyl ether as elutant, gave 6-chloro-5-fluoroquinoline **20a** as a white solid; δ_H 7.48 (1 H, dd, $^3J_{HH}$ 8.5, $^3J_{HF}$, 4.5, H-3), 7.65 (1 H, dd, $^3J_{HH}$ 9.0, $^4J_{HF}$ 8.0, H-7), 7.86 (1 H, dm, $^3J_{HH}$ 9.0, H-8), 8.39 (1 H, dm, $^3J_{HH}$ 8.5, H-4), 8.94 (1 H, dd, $^3J_{HH}$ 4.0, $^4J_{HH}$ 1.5, H-2); δ_F –124.2 (s, F-5); δ_C 116.5 (d, $^2J_{CF}$ 16.5, C-4α), 119.4 (d, $^2J_{CF}$ 15.5, C-6), 121.7 (d, $^4J_{CF}$ 7.9, C-3), 126.1 (d, $^4J_{CF}$ 4.5, C-8), 128.8 (d, $^4J_{CF}$ 4.0, C-4), 130.3 (d, $^3J_{CF}$ 2.9, C-7), 147.2 (d, $^3J_{CF}$ 2.4, C-8α), 151.2 (d, $^5J_{CF}$ 4.5, C-2), 152.9 (d, $^1J_{CF}$ 257.5, C-5), *m/z* (EI$^+$) 183 (M$^+${^{37}Cl}, 53%), 181 (M$^+${^{35}Cl}, 100%), 180 (66); (Found: M$^+$,183.006533. C9H5 ^{37}ClFN requires M$^+$, 183.006505; M$^+$, 181.009566. C_9H_5 ^{35}ClFN requires M$^+$, 181.009540).

3.2.12. Fluorination of 4,7-dichloroquinoline **21**

4,7-Dichloroquinoline **21** (2.4 g, 15 mmol), oleum (15 ml), PP11 (85 ml) and fluorine (180 mmol, 12 equiv.) gave an orange solid (3.3 g, conv. 62%) which contained 4,7-dichloro-8-fluoroquinoline **22a** (46%) and 4,7-dichloro-5,8-difluoroquinoline **22b** (11%); δ_F –114.8 (1 F, dd, $^5J_{FF}$ 20.3, $^3J_{HF}$ 11.7, F-5), 127.7 (1 F, d, $^5J_{FF}$ 20.3, F-8); *m/z* (EI$^+$) 235 (M$^+$ {^{35,37}Cl}, 54%), 233 (M$^+$ {^{35,35}Cl}, 100%), 198 (67); M$^+${^{35,35}Cl}, 232.961345. $C_9H_3{}^{35}Cl_2F_2N$ requires M, 232.961061. Purification using column chromatography on silica gel using diethyl ether: hexane (2:1) as elutant, gave 4,7-dichloro-8-fluoroquinoline **22a** as a white solid; δ_H 7.54 (1 H, d, $^3J_{HH}$ 4.4, H-3), 7.58 (1 H, dd, $^3J_{HH}$ 9.2, $^4J_{HF}$ 6.4, H-6), 7.92 (1 H, dd, $^3J_{HH}$ 9.2, $^5J_{HF}$ 2.0, H-5), 8.82 (1 H, d, $^3J_{HH}$ 4.0, H-2); δ_F –124.5 (s, F-8); δ_C 114.0 (d, $^2J_{CF}$ 27.3, C-8α), 119.9 (d, $^3J_{CF}$ 6.0, C-6), 121.3 (d, $^2J_{CF}$ 16.3, C-7), 123.1 (s, C-3), 128.7 (s, C-5), 139.7 (d, $^3J_{CF}$ 11.4, C-4α), 142.7 (d, $^4J_{CF}$ 3.8, C-4), 150.8 (s, C-2), 153.6 (d, $^1J_{CF}$ 257.5, C-8); *m/z* (EI$^+$) 217 (M$^+$ {^{35,37}Cl}, 75%), 215 (M$^+$ {^{35,35}Cl}, 100%), 180 (91), 145 (69); (Found: M$^+${^{35,35}Cl}, 214.971234. $C_9H_4{}^{35}Cl_2FN$ requires M, 214.970483).

3.2.13. Fluorination of 6-nitroquinoline **23**

6-Nitroquinoline **23** (2.8 g, 16 mmol), oleum (10 ml), PP11 (90 ml) and fluorine (240 mmol, 15 equiv.) at15 °C, gave a yellow solid (3.4 g, conv. 61%) which contained 8-fluoro-6-nitroquinoline **24** (59%). Purification by column chromatography on silica gel using dichloromethane: methanol (19:1) as elutant, gave 8-fluoro-6-nitroquinoline 24 as a yellow solid; δ_H 7.67 (1 H, dd, $^3J_{HH}$ 8.5, $^3J_{HH}$ 4.5, H-3), 8.17 (1 H, dd, $^3J_{HF}$ 10.0, $^4J_{HH}$ 2.5, H-7), 8.41 (1 H, dm, $^3J_{HH}$ 8.5, H-4), 8.62 (1 H, t, $^4J_{HH} = {}^5J_{HF}$ 2.0, H-5), 9.13 (1 H, dd, $^3J_{HH}$ 4.0, $^4J_{HH}$ 1.5, H-2); δ_F –119.5 (d, $^3J_{HF}$ 9.9, F-8); δ_C 108.0 (d, $^2J_{CF}$ 24.8, C-7), 120.0 (d, $^4J_{CF}$ 4.9, C-5), 123.9 (s, C-3), 128.2 (d, $^3J_{CF}$ 3.0, C-4α), 137.7 (d, $^4J_{CF}$ 3.1, C-4), 140.8 (d, $^2J_{CF}$ 12.2, C-8α), 145.0 (d, $^3J_{CF}$ 8.7, C-6), 153.8 (d, $^4J_{CF}$ 1.5, C-2), 158.0 (d, $^1J_{CF}$ 260.7, C-8); *m/z* (EI$^+$) 192

Table 1
Crystal data

	Compound						
	12b	**16a**	**16b**	**17**	**18**	**22a**	**24**
Formula	$C_{10}H_8FNO$	$C_{11}H_7ClFNO_2$	$C_{10}H_4ClF_2NO_2$	$C_{10}H_8N_2O_3$[a]	$C_{10}H_7FN_2O_3$	$C_9H_4Cl_2FN$[b]	$C_9H_5FN_2O_2$[c]
Formula weight	177.17	239.63	243.59	204.18	222.18	216.03	192.15
T (K)	110	120	120	120	120	120	120
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Triclinic
Space group	*Pbca* (# 61)	*P*21/*c* (# 14)	$P2_1/c$ (# 14)	$P2_1/c$ (# 14)	$P2_1/c$ (# 14)	$Pna2_1$ (# 33)	$P\bar{1}$ (No. 2)
a (Å)	11.426(1)	3.8149(4)	8.876(2)	6.714(2)	7.401(1)	23.335(4)	8.790(3)
b (Å)	6.726(1)	20.897(2)	6.093(2)	16.015(3)	16.214(6)	3.772(1)	9.748(3)
c (Å)	21.586(2)	12.275(1)	17.224(4)	8.624(2)	7.992(1)	9.601(2)	10.395(3)
α (°)	90	90	90	90	90	90	86.21(1)
β (°)	90	91.12(1)	91.56(1)	96.27(1)	108.19(2)	90	65.30(1)
γ (°)	90	90	90	90	90	90	77.07(1)
V (Å^3)	1658.9(3)	978.38(16)	931.2(4)	921.7(4)	911.1(4)	845.1(3)	788.3(4)
Z	8	4	4	4	4	4	4
Reflections collected	18687	13816	9784	11035	11044	9321	9714
Reflections unique	2219	2797	2473	2447	2430	2231	4146
R_{int}	0.038	0.048	0.020	0.033	0.030	0.067	0.028
Reflections with $I > 2\sigma(I)$	1776	1998	2286	2217	2133	1873	3355
R [$I > 2\sigma(I)$]	0.042	0.038	0.029	0.041	0.033	0.047	0.049
$wR(F^2)$, all reflections	0.125	0.105	0.081	0.122	0.102	0.100	0.141

[a] Contains 2.5% of 18; mean *fw* = 204.63.
[b] Contains 16.7(8)% of $C_9H_3Cl_2F_2N$ (**22b**), mean *fw* = 219.00.
[c] Contains ca. 6% of $C_9H_3F_3N_2O_2$, mean *fw* = 194.40.

(M^+, 100%), 146 (62), 134 (54), 126 (60); (Found: M^+ 192.0336. $C_9H_5FNO_2$ requires M^+ 192.0335).

3.3. X-ray crystallography

Diffraction experiments were carried out on a SMART 3-circle diffractometer with a 1K CCD area detector (6K CCD for **16a**), using Mo Kα radiation ($\bar{\lambda} = 0.71073$ Å). The crystals were cooled with a Cryostream open-flow N_2 cryostat (Oxford Cryosystems). Full sphere of reciprocal space to $2\theta \leq 58^\circ$ was covered by five sets of 0.3° ω scans, each set with different ϕ and/or 2θ angles (for **16a** with four sets to $2\theta \leq 60^\circ$). Reflection intensities were corrected for absorption for **16a** (semi-empirical method based on Laue equivalents [20]) and **22a** (numerical integration based on real crystal shape [21]). All structures were solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXTL software. [21] All H atoms were located in difference Fourier map. In **12b**, **16a**, **b**, **17** and **18** they were refined in isotropic approximation (except the disordered one in 17), in **22a** and **24** included in 'riding' model. Crystal data and experimental details are given in Table 1. The structures have been deposited at the Cambridge Crystallographic Data Centre, deposition numbers 209291-209297.

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