A convenient synthesis of 2-(*F*-alkyl)-4-hydroxyquinolines [1]

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Abstract

A convenient new route to 2-(*F*-alkyl)-4-hydroxyquinolines has been developed. In the presence of triethylamine, treatment of ethyl 2,2-dihydropolyfluoroalkanoates with aromatic amines in acetonitrile at 70 °C led to a mixture of the corresponding enamines and imines, which was cyclized in polyphosphoric acid (PPA) at 170 °C to give 2-(*F*-alkyl)-4-hydroxyquinolines in good yield.

Introduction

Because of their potential biological activity [2], considerable interest has been directed towards the synthesis of fluorinated heteroaromatic compounds such as quinolines [3], coumarin [4], pyrrole and 2*H*-pyrrole [5], pyrazole and isoxazole [6], indole [7], etc. Cambon and coworkers reported the synthesis of 2-(*F*-alkyl)-quinolines using *F*-alkynyl esters as starting materials [3c], but the preparation of the latter was not easy [3c, 8]. In a previous report [9], we described the development of a new efficient method for the preparation of ethyl 2,2-dihydropolyfluoroalkanoates from readily available polyfluoroalkyl iodides. In the presence of base, the former readily eliminated HF to give the corresponding alkenoates which might undergo Michael-addition reactions with nucleophiles. Thus, it is conceivable that ethyl 2,2-dihydropolyfluoroalkanoates may be used directly as versatile intermediates for the synthesis of *F*-alkyl-substituted heterocyclic compounds. We now wish to report the results on the synthesis of 2-(*F*-alkyl)-4-hydroxyquinolines from ethyl 2,2-dihydropolyfluoroalkanoates.

Results and discussion

Of the various solvents tested for the Michael-addition reaction of anilines to 2,2-dihydropolyfluoroalkanoates in the presence of triethylamine, it was found that acetonitrile and dimethylformamide were suitable whereas the reaction proceeded very slowly in tetrahydrofuran or other ether solvents. The reaction of a variety of anilines with ethyl 2,2-dihydropolyfluoroalkanoates in acetonitrile at 70 °C in the presence of triethylamine provided a mixture of the corresponding enamines and imines in good yield. The ratio of products was easily determined from their ^{1}H NMR and ^{19}F NMR spectra (see Table 1). Cyclization of these mixtures took place smoothly in polyphosphoric acid (PPA) at 170 °C, providing the corresponding 2-(*F*-alkyl)-4-hydroxyquinolines in high yield.

TABLE 1. Synthesis of 2-(*F*-alkyl)-4-hydroxyquinolines

R	R_F	Intermediates **2–6**			Yield of substituted quinolines (%)[c]	
			Yield (%)[a]	Ratio of enamines/imines[b]		
CH_3	$ClCF_2$	**2a**	87	53:47	**7a**	97
	$Cl(CF_2)_3$	**2b**	92	31:69	**7b**	96
	$Cl(CF_2)_5$	**2c**	89	29:71	**7c**	96
	$BrCF_2$	**2d**	83	54:46	**7d**	83
	CF_3	**2e**	88	88:12	**7e**	89
H	$ClCF_2$	**3a**	81	46:54	**8a**	96
	$Cl(CF_2)_3$	**3b**	85	27:73	**8b**	94
	$Cl(CF_2)_5$	**3c**	85	27:73	**8c**	94
	$BrCF_2$	**3d**	77	58:42	**8d**	92
Cl	$Cl(CF_2)_3$	**4b**	76	36:64	**9b**	94
	$Cl(CF_2)_5$	**4c**	67	33:67	**9c**	93
	$BrCF_2$	**4d**	63	42:58	**9d**	93
	CF_3	**4e**	65	88:12	**9e**	80
F	$Cl(CF_2)_5$	**5c**	80	36:64	**10c**	88
	CF_3	**5e**	51	80:20	**10e**	80
I	$ClCF_2$	**6a**	78	63:37	**11a**	89

[a]isolated yield.
[b]Based on ^{1}H NMR and ^{19}F NMR spectra.
[c]Isolated yield based on **2–6**.

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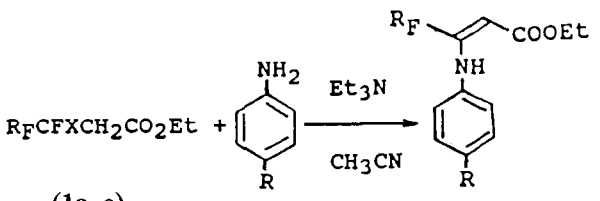
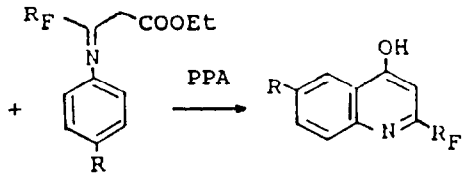


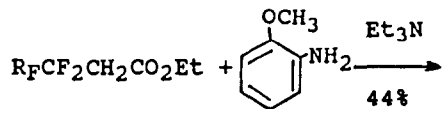
(1a–e)



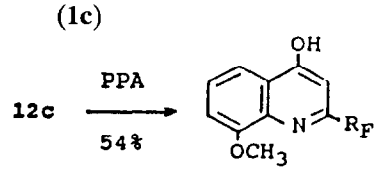
(2–6) (7–11)

a: $R_F = ClCF_2$, X = F — **2** and **7**: R = CH_3
b: $R_F = Cl(CF_2)_3$, X = F — **3** and **8**: R = H
c: $R_F = Cl(CF_2)_5$, X = F — **4** and **9**: R = Cl
d: $R_F = BrCF_2$, X = F — **5** and **10**: R = F
e: $R_F = CF_3$, X = Br — **6** and **11**: R = I

It has been shown that the Michael-addition reaction of *o*-methoxyaniline with **1c** occurs only with considerable difficulty to give the corresponding addition product in a somewhat lower yield, probably due to steric effects. Almost no addition product was obtained when *p*-nitroaniline and methyl *p*-aminobenzoate were used as nucleophiles.

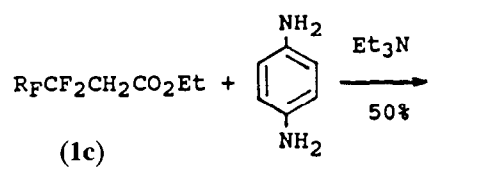


(1c)

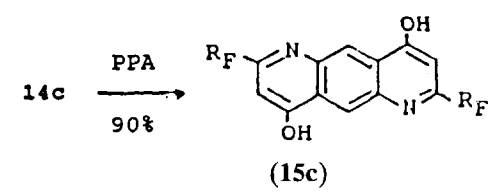


(13c)

1,4-Phenylenediamine reacted with 2 equiv. of **1c** followed by cyclization with PPA under the same conditions to give a tricyclic product (**15c**).

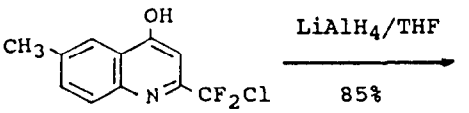


(1c)

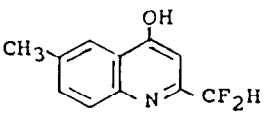


(15c)

2-Chlorodifluoromethyl-substituted 4-hydroxyquinoline was readily reduced with $LiAlH_4$ in refluxing THF to produce the corresponding difluoromethyl derivative in high yield. These reactions may be used as a useful alternative route to 2-difluoromethyl-substituted quinoline, thus:



(7a)



(16)

In conclusion, we have developed a new convenient method for the synthesis of 2-(*F*-alkyl)-substituted quinolines derived from 2,2-dihydropolyfluoroalkanoates. Further study on the synthesis of other heteroaromatic compounds using 2,2-dihydropolyfluoroalkanoates as starting materials is under way.

Experimental

All melting points were uncorrected. IR spectra were measured with an IR-440 spectrometer, using liquid films or KBr pellets for solids. ^1H NMR spectra were recorded on Varian EM-360A (60 MHz), FX-90Q (90 MHz) spectrometers using TMS as internal standard and ^{19}F NMR spectra were recorded on a Varian EM-360L spectrometer (56.4 MHz) using TFA as external standard. In ^{19}F NMR spectra, chemical shifts (in ppm) were positive for upfield shifts and the values are reported as $\delta CFCl_3 (\delta CFCl_3 = \delta TFA + 76.8)$. Mass spectra were taken on a Finnegan GC–MS 4021 spectrometer. Column chromatography was performed using silica gel H, particle size 10–40 μm.

Preparation of the mixture of enamine and imine (2–6, 12c, 14c)

Typical procedure

A mixture consisting of 5 mmol of 2,2-dihydropolyfluoroalkanoate, 7.5 mmol of aniline, 15 mmol of Et_3N and 5 ml of CH_3CN was stirred at 70 °C for 6 h. The mixture was then neutralized with aqueous 1 N HCl solution and extracted with ether. The ethereal layer was washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using petroleum ether/ethyl acetate = 25:1 as eluant to give a mixture of enamine and imine.

Compound **2a**: ^{1}H NMR ($CDCl_3$) δ: 1.16–1.37 (3H, m, CH_2CH_3); 2.32 (3H, s, Ar−CH_3); 3.48 (s, CH_2CO in imine); 4.01–4.30 (2H, m, CH_2CH_3); 5.30 (s, =CH in enamine); 6.72–7.18 (4H, m, Ar−H); 9.72 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 50.3 (s, $ClCF_2$ in enamine); 59.4 (s, $ClCF_2$ in imine) ppm. IR ν_{max} (cm^{-1}): 3250 (NH); 1740 (C=O); 1670 (C=N); 1630 (C=C); 1100–1280 (C−F). MS *m/z*: 289 (M^+); 204 ($M^+ - CF_2Cl$); 158 ($M^+ - CF_2Cl - EtOH$). Analysis: Calc. for $C_{13}H_{14}ClF_2NO_2$: C, 53.90; H, 4.87; N, 4.83; F, 13.12%. Found: C, 53.51; H, 4.79; N, 4.89; F, 13.52%.

Compound **2b**: ^{1}H NMR ($CDCl_3$): 1.17–1.36 (3H, m, CH_2CH_3); 2.32 (3H, s, Ar−CH_3); 3.45 (s, CH_2CO in imine); 4.03–4.26 (2H, m, CH_2CH_3); 5.36 (s, =CH in enamine); 6.68–7.19 (4H, m, Ar−H); 9.30 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 66.8 (2F, s, CF_2Cl); 108.2 (s, C=CCF_2 in enamine); 113.2 (s, N=CCF_2 in imine); 119.3 (s, other CF_2 in enamine); 119.8 (s, other CF_2 in imine) ppm. IR ν_{max} (cm^{-1}): 1740 (C=O); 1670 (C=N); 1630 (C=C); 1100–1240 (C−F). Analysis: Calc. for $C_{15}H_{14}ClF_6NO_2$: C, 46.23; H, 3.62; N, 3.59; F, 29.25%. Found: C, 46.03; H, 3.59; N, 3.70; F, 29.33%.

Compound **2c**: ^{1}H NMR ($CDCl_3$) δ: 1.16–1.35 (3H, m, CH_2CH_3); 2.32 (3H, s, Ar−CH_3); 3.46 (s, CH_2CO in imine); 4.02–4.26 (2H, m, CH_2CH_3); 5.36 (s, =CH in enamine); 6.68–7.22 (4H, m, Ar−H); 9.28 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.5 (2F, s, CF_2Cl); 108.6 (s, C=CCF_2 in enamine); 113.4 (s, N=CCF_2 in imine); 120.0–120.8 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 1740 (C=O); 1680 (C=N); 1630 (C=C); 1110–1220 (C−F). Analysis: Calc. for $C_{17}H_{14}ClF_{10}NO_2$: C, 41.69; H, 2.88; N, 2.86; F, 38.79%. Found: C, 41.98; H, 2.85; N, 3.08; F, 39.29%.

Compound **2d**: ^{1}H NMR ($CDCl_3$) δ: 1.11–1.40 (3H, m, CH_2CH_3); 2.32 (3H, s, Ar−CH_3); 3.52 (s, $COCH_2$ in imine); 4.03–4.28 (2H, m, CH_2CH_3); 5.30 (s, =CH in enamine); 6.63–7.26 (4H, m, Ar−H); 9.72 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 46.2 (s, $BrCF_2$ in enamine); 55.6 (s, $BrCF_2$ in imine) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1740 (C=O); 1670 (C=N); 1620 (C=C); 1140–1240 (C−F). MS *m/z*: 335 ($M^+ + 2$); 333 (M^+); 289 ($M^+ - EtOH$); 204 ($M^+ - BrCF_2$). Analysis: Calc. for $C_{13}H_{14}BrF_2NO_2$: C, 46.73; H, 4.22; N, 4.19; F, 11.37%. Found: C, 46.78; H, 4.10; N, 4.02; F, 11.88%.

Compound **2e**: ^{1}H NMR ($CDCl_3$) δ: 1.15–1.39 (3H, m, CH_2CH_3); 2.30 (3H, s, Ar−CH_3); 3.40 (s, $COCH_2$ in imine); 4.01–4.35 (2H, m, CH_2CH_3); 5.31 (s, =CH in enamine); 6.76–7.20 (4H, m, Ar−H); 9.75 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 63.5 (s, CF_3 in enamine); 72.4 (s, CF_3 in imine) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1740 (C=O); 1680 (C=N); 1630 (C=C); 1120–1220 (C−F). MS *m/z*: 273 (M^+); 227 ($M^+ - EtOH$); 158 ($M^+ - CF_3 - EtOH$). Analysis: Calc. for $C_{13}H_{14}ClF_3NO_2$: C, 57.14; H, 5.16; N, 5.13; F, 20.86%. Found: C, 56.89; H, 4.78; N, 4.88; F, 20.92%.

Compound **3a**: ^{1}H NMR ($CDCl_3$) δ: 1.12–1.34 (3H, m, CH_2CH_3); 3.45 (s, $COCH_2$ in imine); 3.98–4.28 (2H, m, CH_2CH_3); 5.33 (s, =CH in enamine); 6.80–7.33 (5H, m, Ar−H); 9.76 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 50.8 (s, CF_2Cl in enamine); 60.0 (s, CF_2Cl in imine) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1740 (C=O); 1670 (C=N); 1620 (C=C); 1100–1260 (C−F). MS *m/z*: 275 (M^+); 230 ($M^+ - OEt$); 190 ($M^+ - CF_2Cl$); 144 ($M^+ - CF_2Cl - EtOH$). Analysis: Calc. for $C_{12}H_{12}ClF_2NO_2$: C, 52.28; H, 4.39; N, 5.08; F, 13.78%. Found: C, 51.70; H, 4.32; N, 5.02; F, 14.34%.

Compound **3b**: ^{1}H NMR ($CDCl_3$) δ: 1.16–1.32 (3H, m, CH_2CH_3); 3.43 (s, $COCH_2$ in imine); 4.01–4.25 (2H, m, CH_2CH_3); 5.42 (s, =CH in enamine); 6.72–7.35 (5H, m, Ar−H); 9.19 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 66.5 (2F, s, CF_2Cl); 108.3 (s, C=CCF_2 in enamine); 113.2 (s, N=CCF_2 in imine); 119.6 (2F, s, other CF_2) ppm. IR ν_{max} (cm^{-1}): 1740 (C=O); 1680 (C=N); 1620 (C=C); 1120–1280 (C−F). Analysis: Calc. for $C_{14}H_{12}ClF_6NO_2$: C, 44.67; H, 3.22; N, 3.73; F, 30.34%. Found: C, 44.17; H, 3.41; N, 3.82; F, 31.32%.

Compound **3c**: ^{1}H NMR ($CDCl_3$) δ: 1.16–1.31 (3H, m, CH_2CH_3); 3.42 (s, $COCH_2$ in imine); 4.10–4.20 (2H, m, CH_2CH_3); 5.41 (s, =CH in enamine); 6.76–7.41 (5H, m, Ar−H); 9.17 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.5 (2F, s, CF_2Cl); 108.7 (s, C=CCF_2 in enamine); 113.5 (s, N=CCF_2 in imine); 119.8–120.6 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 1740 (C=O); 1680 (C=N); 1620 (C=C); 1140–1240 (C−F). Analysis: Calc. for $C_{16}H_{12}ClF_{10}NO_2$: C, 40.40; H, 2.72; N, 2.94; F, 39.94%. Found: C, 40.24; H, 2.45; N, 2.94; F, 40.92%.

Compound **3d**: ^{1}H NMR ($CDCl_3$) δ: 1.11–1.41 (3H, m, CH_2CH_3); 3.50 (s, $COCH_2$ in imine); 3.97–4.38 (2H, m, CH_2CH_3); 5.35 (s, =CH in enamine); 6.81–7.39 (5H, m, Ar−H); 9.75 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 47.0 (s, $BrCF_2$ in enamine); 55.9 (s, $BrCF_2$ in imine) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1740 (C=O); 1670 (C=N); 1620 (C=C); 1100–1200 (C−F). MS *m/z*: 321 ($M^+ + 2$); 319 (M^+); 276 ($M^+ - OEt$); 240 ($M^+ - Br$); 190 ($M^+ - CF_2Br$). Analysis: Calc. for $C_{12}H_{12}BrF_2NO_2$: C, 45.02; H, 3.78; N, 4.38; F, 11.87%. Found: C, 45.55; H, 3.67; N, 4.33; F, 12.83%.

Compound **4b**: ^{1}H NMR ($CDCl_3$) δ: 1.16–1.36 (3H, m, CH_2CH_3); 3.22 (s, $COCH_2$ in imine); 4.04–4.27 (2H, m, CH_2CH_3); 5.44 (s, =CH in enamine); 6.73–7.37 (4H, m, Ar−H); 9.11 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 66.5 (2F, s, CF_2Cl); 108.1 (s, C=CCF_2 in enamine); 112.9 (s, N=CCF_2 in imine); 119.8 (2F, s, other CF_2) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1730 (C=O); 1680 (C=N); 1630 (C=C); 1100–1220 (C−F). Analysis: Calc. for $C_{11}H_{11}Cl_2F_6NO_2$: C, 41.00; H, 2.70;

N, 3.42; F, 27.79%. Found: C, 40.47; H, 2.34; N, 3.25; F, 28.03%.

Compound **4c**: ^{1}H NMR ($CDCl_3$) δ: 1.16–1.39 (3H, m, CH_2CH_3); 3.44 (s, $COCH_2$ in imine); 4.04–4.28 (2H, m, CH_2CH_3); 5.26 (s, =CH in enamine); 6.75–7.39 (4H, m, Ar–H); 9.11 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.5 (2F, s, CF_2Cl); 108.9 (s, C=CCF_2 in enamine); 113.6 (s, N=CCF_2 in imine); 118.9–119.6 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 1730 (C=O); 1680 (C=N); 1630 (C=C); 1100–1200 (C–F). MS *m/z*: 509 (M^+); 463 ($M^+ - EtOH$); 224 ($M^+ - C_5F_{10}Cl$); 178 ($M^+ - C_5F_{10}Cl - EtOH$). Analysis: Calc. for $C_{16}H_{11}Cl_2F_{10}NO_2$: C, 37.67; H, 2.17; N, 2.75; F, 37.24%. Found: C, 37.58; H, 2.23; N, 2.80; F, 38.29%.

Compound **4d**: ^{1}H NMR ($CDCl_3$) δ: 1.12–1.45 (3H, m, CH_2CH_3); 3.49 (s, $COCH_2$ in imine); 4.01–4.33 (2H, m, CH_2CH_3); 5.34 (s, =CH in enamine); 6.79–7.42 (4H, m, Ar–H); 9.68 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 46.8 (s, $BrCF_2$ in enamine); 55.8 (s, $BrCF_2$ in imine) ppm. IR ν_{max} (cm^{-1}): 1740 (C=O); 1670 (C=N); 1630 (C=C); 1120–1220 (C–F). MS *m/z*: 355 ($M^+ + 2$); 353 (M^+); 309 ($M^+ - OEt$); 224 ($M^+ - CF_2Br$). Analysis: Calc. for $C_{12}H_{11}BrF_2NO_2$: C, 40.65; H, 3.13; N, 3.95; F, 10.72%. Found: C, 41.09; H, 3.14; N, 3.82; F, 11.56%.

Compound **4e**: ^{1}H NMR ($CDCl_3$) δ: 1.16–1.32 (3H, m, CH_2CH_3); 3.36 (s, $COCH_2$ in imine); 4.00–4.29 (2H, m, CH_2CH_3); 5.28 (s, =CH in enamine); 6.96–7.32 (4H, m, Ar–H); 9.64 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 62.8 (s, CF_3 in enamine); 72.1 (s, CF_3 in imine) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1660 (C=N); 1620 (C=C); 1130–1230 (C–F). MS *m/z*: 293 (M^+); 247 ($M^+ - EtOH$); 178 ($M^+ - EtOH - CF_3$). Analysis: Calc. for $C_{12}H_{11}ClF_3NO_2$: C, 49.08; H, 3.78; N, 4.77; F, 19.41%. Found: C, 49.11; H, 3.75; N, 4.70; F, 19.22%.

Compound **5c**: ^{1}H NMR ($CDCl_3$) δ: 1.14–1.32 (3H, m, CH_2CH_3); 3.43 (s, $COCH_2$ in imine); 4.02–4.25 (2H, m, CH_2CH_3); 5.36 (s, =CH in enamine); 6.72–7.20 (4H, m, Ar–H); 9.28 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 68.1 (2F, s, CF_2Cl); 110.1 (s, C=CCF_2 in enamine); 117.2 (s, N=CCF_2 in imine); 114.1 (1F, s, Ar–F); 120.8–121.4 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1730 (C=O); 1680 (C=N); 1630 (C=C); 1120–1220 (C–F). MS *m/z*: 493 (M^+); 448 ($M^+ - OEt$); 208 ($M^+ - C_5F_{10}Cl$); 162 ($M^+ - C_5F_{10}Cl - EtOH$). Analysis: Calc. for $C_{16}H_{11}ClF_{11}NO_2$: C, 38.93; H, 2.25; N, 2.84; F, 42.33%. Found: C, 38.39; H, 2.11; N, 2.49; F, 42.26%.

Compound **5e**: ^{1}H NMR ($CDCl_3$) δ: 1.20–1.44 (3H, m, CH_2CH_3); 3.48 (s, $COCH_2$ in imine); 4.06–4.43 (2H, m, CH_2CH_3); 5.38 (s, =CH in enamine); 6.96–7.31 (4H, m, Ar–H); 9.72 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 62.8 (s, CF_3 in enamine); 71.8 (s, CF_3 in imine); 114.5 (1F, s, Ar–F) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1680 (C=N); 1640 (C=O); 1120–1220 (C–F). MS *m/z*: 277 (M^+). Analysis: Calc. for $C_{12}H_{11}F_4NO_2$: C, 51.99; H, 4.00; N, 5.05; F, 27.41%. Found: C, 51.78; H, 3.95; N, 4.99; F, 27.41%.

Compound **6a**: ^{1}H NMR ($CDCl_3$) δ: 1.12–1.37 (3H, m, CH_2CH_3); 3.42 (s, $COCH_2$ in imine); 3.99–4.34 (2H, m, CH_2CH_3); 5.34 (s, =CH in enamine); 6.85–7.66 (4H, m, Ar–H); 9.66 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 50.4 (s, CF_2Cl in enamine); 59.9 (s, CF_2Cl in imine) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1740 (C=O); 1670 (C=N); 1630 (C=C); 1100–1200 (C–F). MS *m/z*: 401 (M^+); 316 ($M^+ - CF_2Cl$); 270 ($M^+ - CF_2Cl - EtOH$). Analysis: Calc. for $C_{12}H_{11}ClF_2INO_2$: C, 35.89; H, 2.76; N, 3.49; F, 9.46%. Found: C, 35.79; H, 2.84; N, 3.31; F, 10.07%.

Compound **12c**: ^{1}H NMR ($CDCl_3$) δ: 1.16–1.38 (3H, m, CH_2CH_3); 3.40 (s, $COCH_2$ in imine); 3.77–3.82 (3H, d, OCH_3 in enamine and imine); 4.00–4.34 (2H, m, CH_2CH_3); 5.40 (s, =CH in enamine); 6.82–7.24 (4H, m, Ar–H); 8.60 (br., NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.4 (2F, s, CF_2Cl); 112.0 (s, C=CCF_2 in enamine); 113.5 (s, N=CCF_2 in imine); 119.8–120.9 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1740 (C=O); 1680 (C=N); 1630 (C=C); 1120–1250 (C–F). MS *m/z*: 505 (M^+). Analysis: Calc. for $C_{17}H_{14}ClF_{10}NO_3$. C, 40.37; H, 2.79; N, 2.77%. Found: C, 40.75; H, 2.72; N, 2.95%.

Compound **14c**: ^{1}H NMR ($CDCl_3$) δ: 1.18–1.37 (6H, m, 2×CH_2CH_3); 3.48 (s, 2×$COCH_2$ in imine); 4.06–4.29 (4H, m, 2×CH_2CH_3); 5.44 (s, =CH×2 in enamine); 6.75–7.25 (4H, m, Ar–H); 9.27 (br., 2×NH in enamine) ppm. ^{19}F NMR ($CDCl_3$) δ: 67.5 (4F, s, 2×CF_2Cl); 117.9 (s, 2×C=CCF_2 in enamine); 122.8 (s, 2×N=CCF_2 in imine); 129.2–129.9 (12F, m, other 6×CF_2) ppm. IR ν_{max} (cm^{-1}): 3200 (NH); 1730 (C=O); 1680 (C=N); 1630 (C=C); 1120–1220 (C–F). MS *m/z*: 874 ($M^+ + 2$); 587 ($M^+ - C_5F_{10}Cl$); 541 ($M^+ - C_5F_{10}Cl - EtOH$). Analysis: Calc. for $C_{26}H_{18}Cl_2F_{20}N_2O_4$: C, 35.76; H, 2.08; N, 3.21; F, 43.51%. Found: C, 35.72; H, 1.72; N, 2.90; F, 44.38%.

Preparation of 2-(F-alkyl)-4-hydroxyquinolines (7–11, 13c, 15c)

Typical procedure

The mixture of enamine and imine (1 g) and polyphosphoric acid (PPA) (10 g) was stirred at 170 °C for 2 h. After cooling to room temperature, it was neutralized with aqueous 2 N NaOH solution and extracted with ether. The organic layer was washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. Removal of solvent followed by recrystallization from ethanol gave the pure 2-(*F*-alkyl)-quinolines.

Compound **7a**: M.p. 224–226 °C. ^{1}H NMR (CD_3OD) δ: 2.65 (3H, s, Ar–CH_3); 6.90 (1H, s, H in position 3); 7.74–8.14 (3H, m, Ar–H) ppm. ^{19}F NMR (CD_3OD) δ: 56.6 (s, CF_2Cl) ppm. IR ν_{max} (cm^{-1}): 3420 (OH); 1570–1610 (Ar); 1150–1220 (C–F). MS *m/z*: 243 (M^+);

85 ($ClCF_2^+$). Analysis: Calc. for $C_{11}H_8ClF_2NO$: C, 54.23; H, 3.31; N, 5.75; F, 15.60%. Found: C, 54.19; H, 3.27; N, 5.23; F, 15.75%.

Compound **7b**: M.p. 196–198 °C. ^1H NMR (CD_3OD) δ: 2.62 (3H, s, Ar−CH_3); 6.92 (1H, s, H in position 3); 7.66–8.13 (3H, m, Ar−H) ppm. ^{19}F NMR (CD_3OD) δ: 68.4 (2F, s, CF_2Cl); 114.8 (2F, s, =C−CF_2); 121.5 (2F, s, other CF_2) ppm. IR ν_{max} (cm^{-1}): 3420 (OH); 1560–1610 (Ar); 1120–1200 (C−F). Analysis: Calc. for $C_{13}H_8ClF_6NO$: C, 45.44; H, 2.35; N, 4.08; F, 33.17%. Found: C, 45.57; H, 2.36; N, 4.20; F, 33.07%.

Compound **7c**: M.p. 201–203 °C. ^1H NMR (DMSO-d_6) δ: 2.48 (3H, s, Ar−CH_3); 7.07 (1H, s, H in position 3); 7.55–7.94 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 69.5 (2F, s, CF_2Cl); 115.3 (2F, s, =C−CF_2); 121.3–122.5 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 3420 (OH); 1570–1620 (Ar); 1140–1220 (C−F). Analysis: Calc. for $C_{15}H_8ClF_{10}NO$: C, 40.61; H, 1.82; N, 3.16; F, 42.82%. Found: C, 40.58; H, 1.61; N, 2.98; F, 43.09%.

Compound **7d**: M.p. 217–219 °C. ^1H NMR (DMSO-d_6) δ: 2.55 (3H, s, Ar−CH_3); 7.05 (1H, s, H in position 3); 7.64–8.06 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO−d_6) δ: 49.3 (s, CF_2Br) ppm. IR ν_{max} (cm^{-1}): 3420 (OH); 1560–1620 (Ar); 1140–1220 (C−F). MS *m/z*: 289 (M^+ +2); 287 (M^+); 208 (M^+ − Br); 158 (M^+ − CF_2Br). Analysis: Calc. for $C_{11}H_8BrF_2NO$: C, 45.86; H, 2.80; N, 4.86; F, 13.19%. Found: C, 45.90; H, 2.65; N, 4.66; F, 13.51%.

Compound **7e**: M.p. 247–249 °C. ^1H NMR (DMSO-d_6) δ: 2.50 (3H, s, Ar−CH_3); 7.02 (1H, s, H in position 3); 7.60–8.02 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 65.7 (s, CF_3) ppm. IR ν_{max} (cm^{-1}): 3430 (OH); 1570–1630 (Ar); 1150–1250 (C−F). MS *m/z*: 227 (M^+); 158 (M^+ − CF_3). Analysis: Calc. for $C_{11}H_8F_3NO$: C, 58.16; H, 3.55; N, 6.17; F, 25.09%. Found: C, 58.33; H, 3.73; N, 5.96; F, 25.29%.

Compound **8a**: M.p. 201–203 °C. ^1H NMR (CD_3OD) δ: 6.92 (1H, s, H in position 3); 7.56–8.44 (4H, m, Ar−H) ppm. ^{19}F NMR (CD_3OD) δ: 57.6 (s, CF_2Cl) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1580–1620 (Ar); 1140–1250 (C−F). MS *m/z*: 229 (M^+). Analysis: Calc. for $C_{10}H_6ClF_2NO$: C, 52.31; H, 2.63; N, 6.10; F, 16.55%. Found: C, 52.20; H, 2.34; N, 5.89; F, 16.96%.

Compound **8b**: M.p. 185–187 °C. ^1H NMR (DMSO-d_6) δ: 7.04 (1H, s, H in position 3); 7.52–8.24 (4H, m, Ar−H) ppm. ^{19}F NMR (DMSO-D_6) δ: 66.4 (2F, s, CF_2Cl); 111.4 (2F, s, =C−CF_2); 129.8 (2F, s, other CF_2) ppm. IR ν_{max} (cm^{-1}) 3440 (OH); 1520–1620 (Ar); 1120–1220 (C−F). Analysis: Calc. for $C_{12}H_6ClF_6NO$: C, 43.73; H, 1.83; N, 4.25; F, 34.58%. Found: C, 43.53; H, 1.53; N, 4.07; F, 34.76%.

Compound **8c**: M.p. 201–203 °C. ^1H NMR (DMSO-d_6) δ: 7.02 (1H, s, H in position 3); 7.60–8.28 (4H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 67.5 (2F, s, CF_2Cl); 111.6 (2F, s, =C−CF_2); 119.4–120.4 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 3420 (OH); 1520–1620 (Ar); 1140–1210 (C−F). Analysis: Calc. for $C_{14}H_6ClF_{10}NO$: C, 39.14; H, 1.41; N, 3.26; F, 44.64%. Found: C, 38.94; H, 1.49; N, 3.25; F, 44.64%.

Compound **8d**: M.p. 205–207 °C. ^1H NMR (DMSO-d_6) δ: 6.97 (1H, s, H in position 3); 7.56–8.27 (4H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 50.5 (s, $BrCF_2$) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1520–1620 (Ar); 1140–1220 (C−F). MS *m/z*: 275 (M^+ +2); 273 (M^+); 194 (M^+ − Br); 144 (M^+ − CF_2Br). Analysis: Calc. for $C_{10}H_6BrF_2NO$: C, 44.83; H, 2.21; N, 5.11; F, 13.87%. Found: C, 44.54; H, 2.29; N, 5.21; F, 14.62%.

Compound **9b**: M.p. 242–244 °C. ^1H NMR (CD_3OD) δ: 7.04 (1H, s, H in position 3); 7.79–8.33 (3H, m, Ar−H) ppm. ^{19}F NMR (CD_3OD) δ: 68.5 (2F, s, CF_2Cl); 114.6 (2F, s, =CF−CF_2); 121.5 (2F, s, other CF_2) ppm. IR ν_{max} (cm^{-1}): 3420 (OH); 1560–1620 (Ar); 1120–1220 (C−F). Analysis: Calc. for $C_{12}H_5Cl_2F_6NO$: C, 39.59; H, 1.38; N, 3.85; F, 31.31%. Found: C, 39.57; H, 1.61; N, 4.07; F, 32.44%.

Compound **9c**: M.p. 261–263 °C. ^1H NMR (DMSO-d_6) δ: 7.07 (1H, s, H in position 3); 7.70–8.13 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 68.3 (2F, s, CF_2Cl); 112.8 (2F, s, =C−CF_2); 120.2–121.3 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 3420 (OH); 1580–1620 (Ar); 1140–1220 (C−F). MS *m/z*: 463 (M^+); 228 (M^+ − $C_5F_{10}Cl$). Analysis: Calc. for $C_{14}H_5Cl_2F_{10}NO$: C, 36.23; H, 1.09; N, 3.02; F, 40.94%. Found: C, 36.36; H, 1.02; N, 2.68; F, 41.91%.

Compound **9d**: M.p. 223–225 °C. ^1H NMR (DMSO-d_6) δ: 7.13 (1H, s, H in position 3); 7.64–8.18 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 68.4 (s, CF_2Br) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1510–1630 (Ar); 1160–1250 (C−F). MS *m/z*: 309 (M^+ +2); 307 (M^+); 228 (M^+ − Br); 178 (M^+ − CF_2Br). Analysis: Calc. for $C_{10}H_5BrClF_2NO$: C, 38.93; H, 1.63; N, 4.54; F, 12.32%. Found: C, 39.25; H, 1.43; N, 4.33; F, 12.88%.

Compound **9e**: M.p. 272–274 °C. ^1H NMR (DMSO-d_6) δ: 7.07 (1H, s, H in position 3); 7.74–8.28 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 66.2 (s, CF_3) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1510–1630 (Ar); 1140–1230 (C−F). MS *m/z*: 247 (M^+). Analysis: Calc. for $C_{10}H_5ClF_3NO$: C, 48.51; H, 2.04; N, 5.66; F, 23.02%. Found: C, 48.46; H, 1.96; N, 5.35; F, 22.39%.

Compound **10c**: M.p. 218–220 °C. ^1H NMR (DMSO-d_6) δ: 7.00 (1H, s, H in position 3); 7.72–8.12 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 68.4 (2F, s, CF_2Cl); 111.1 (1F, s, Ar−F); 112.6 (2F, s, =C−CF_2); 120.2–121.2 (6F, m, other 3×CF_2) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1520–1620 (Ar); 1140–1220 (C−F). MS *m/z*: 447 (M^+); 428 (M^+ − F); 412 (M^+ − Cl); 162 (M^+ − $C_5F_{10}Cl$). Analysis: Calc. for $C_{14}H_5ClF_{11}NO$: C, 37.56; H, 1.21; N, 3.13; F, 46.69%. Found: C, 37.84; H, 1.01; N, 3.12; F, 46.62%.

Compound **10e**: M.p. 254–256 °C. ^{1}H NMR (DMSO-d_6) δ: 7.07 (1H, s, H in position 3); 7.60–8.12 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 67.5 (3F, s, CF_3); 111.2 (1F, s, Ar−F) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1520–1620 (Ar); 1140–1240 (C−F). MS *m/z*: 231 (M^+); 212 ($M^+ - F$); 162 ($M^+ - CF_3$). Analysis: Calc. for $C_{10}H_5F_4NO$: C, 51.96; H, 2.18; N, 6.06; F, 32.88%. Found: C, 51.83; H, 2.09; N, 5.81; F, 32.84%.

Compound **11a**: M.p. 274–276 °C. ^{1}H NMR (DMSO-d_6) δ: 7.04 (1H, s, H in position 3); 7.66–8.52 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 53.6 (s, CF_2Cl) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1560–1630 (Ar); 1140–1220 (C−F). MS *m/z*: 355 (M^+); 320 ($M^+ - Cl$); 270 ($M^+ - CF_2Cl$); 228 ($M^+ - I$). Analysis: Calc. for $C_{10}H_5ClF_2INO$: C, 33.79; H, 1.42; N, 3.94; I, 35.70%. Found: C, 33.57; H, 1.13; N, 3.77; I, 35.72%.

Compound **13c**: M.p. 128–130 °C. ^{1}H NMR (DMSO-d_6) δ: 3.86 (3H, s, OCH_3); 7.08 (1H, s, H in position 3); 7.18–7.75 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 67.8 (2F, s, CF_2Cl); 111.8 (2F, s, $=C-CF_2$); 119.6–120.5 (6F, m, other $3\times CF_2$) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1530–1630 (Ar); 1140–1220 (C−F). MS *m/z*: 459 (M^+); 444 ($M^+ - CH_3$). Analysis: Calc. for $C_{15}H_8ClF_{10}NO_2$: C, 39.19; H, 1.75; N, 3.05%. Found: C, 39.30; H, 1.68; N, 2.99%.

Compound **15c**: M.p. 203–205 °C. ^{1}H NMR (DMSO-d_6) δ: 7.11 (2H, s, 2H in positions 3 and 7); 8.22 (2H, s, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 68.8 (4F, s, $2\times CF_2Cl$); 115.1 (4F, s, $2\times =C-CF_2$); 120.9–122.0 (12F, m, other $6\times CF_2$) ppm. IR ν_{max} (cm^{-1}): 3400 (OH); 1560–1640 (Ar); 1130–1230 (C−F). MS *m/z*: 780 (M^+); 545 ($M^+ - C_4F_8Cl$). Analysis: Calc. for $C_{22}H_6Cl_2F_{20}N_2O_2$: C, 33.83; H, 0.77; N, 3.59; F, 48.64%. Found: C, 33.52; H, 0.93; N, 3.61; F, 48.56%.

Preparation of compound 16

A mixture consisting of 5 mmol of **7a** and 20 mmol of $LiAlH_4$ was refluxed in anhydrous THF for 10 h. After the usual work-up, the crude product was recrystallized from ethanol to give compound **16** in 71% yield.

Compound **16**: M.p. 250–252 °C. ^{1}H NMR (DMSO-d_6) δ: 2.46 (3H, s, Ar−CH_3); 6.55 (1H, s, H in position 3); 6.80–7.34 (1H, t, CF_2H, $^2J_{HF}=54.0$ Hz); 7.56–7.95 (3H, m, Ar−H) ppm. ^{19}F NMR (DMSO-d_6) δ: 115.8–116.7 (2F, d, CF_2H, $^2J_{HF}=54.0$ Hz) ppm. IR ν_{max} (cm^{-1}): 1540–1640 (Ar); 1150–1250 (C−F). MS *m/z*: 209 (M^+); 189 ($M^+ - HF$); 158 ($M^+ - CF_2H$). Analysis: Calc. for $C_{11}H_9F_2NO$: C, 63.16; H, 4.34; N, 6.70; F, 18.16%. Found: C, 63.11; H, 4.29; N, 6.49; F, 17.92%.

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