

# 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-dihydropolyfluoroal-

kanoates 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 <sup>1</sup>H NMR and <sup>19</sup>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

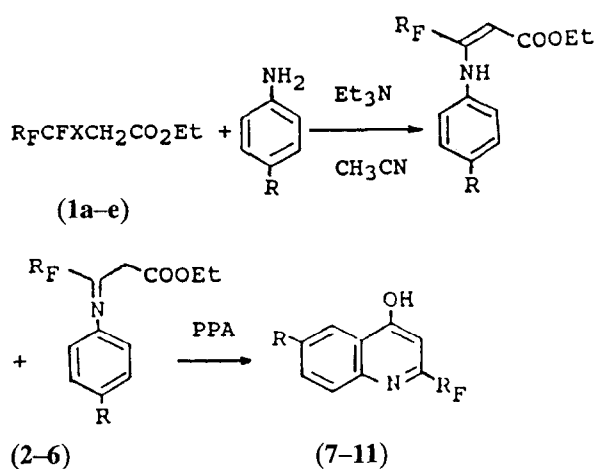
| R               | R <sub>F</sub>                    | Intermediates 2–6 |                        |                                           | Yield of substituted quinolines (%) <sup>c</sup> |    |
|-----------------|-----------------------------------|-------------------|------------------------|-------------------------------------------|--------------------------------------------------|----|
|                 |                                   |                   | Yield (%) <sup>a</sup> | Ratio of enamines/<br>imines <sup>b</sup> |                                                  |    |
| CH <sub>3</sub> | ClCF <sub>2</sub>                 | <b>2a</b>         | 87                     | 53:47                                     | <b>7a</b>                                        | 97 |
|                 | Cl(CF <sub>2</sub> ) <sub>3</sub> | <b>2b</b>         | 92                     | 31:69                                     | <b>7b</b>                                        | 96 |
|                 | Cl(CF <sub>2</sub> ) <sub>5</sub> | <b>2c</b>         | 89                     | 29:71                                     | <b>7c</b>                                        | 96 |
|                 | BrCF <sub>2</sub>                 | <b>2d</b>         | 83                     | 54:46                                     | <b>7d</b>                                        | 83 |
|                 | CF <sub>3</sub>                   | <b>2e</b>         | 88                     | 88:12                                     | <b>7e</b>                                        | 89 |
| H               | ClCF <sub>2</sub>                 | <b>3a</b>         | 81                     | 46:54                                     | <b>8a</b>                                        | 96 |
|                 | Cl(CF <sub>2</sub> ) <sub>3</sub> | <b>3b</b>         | 85                     | 27:73                                     | <b>8b</b>                                        | 94 |
|                 | Cl(CF <sub>2</sub> ) <sub>5</sub> | <b>3c</b>         | 85                     | 27:73                                     | <b>8c</b>                                        | 94 |
|                 | BrCF <sub>2</sub>                 | <b>3d</b>         | 77                     | 58:42                                     | <b>8d</b>                                        | 92 |
| Cl              | Cl(CF <sub>2</sub> ) <sub>3</sub> | <b>4b</b>         | 76                     | 36:64                                     | <b>9b</b>                                        | 94 |
|                 | Cl(CF <sub>2</sub> ) <sub>5</sub> | <b>4c</b>         | 67                     | 33:67                                     | <b>9c</b>                                        | 93 |
|                 | BrCF <sub>2</sub>                 | <b>4d</b>         | 63                     | 42:58                                     | <b>9d</b>                                        | 93 |
|                 | CF <sub>3</sub>                   | <b>4e</b>         | 65                     | 88:12                                     | <b>9e</b>                                        | 80 |
| F               | Cl(CF <sub>2</sub> ) <sub>5</sub> | <b>5c</b>         | 80                     | 36:64                                     | <b>10c</b>                                       | 88 |
|                 | CF <sub>3</sub>                   | <b>5e</b>         | 51                     | 80:20                                     | <b>10e</b>                                       | 80 |
| I               | ClCF <sub>2</sub>                 | <b>6a</b>         | 78                     | 63:37                                     | <b>11a</b>                                       | 89 |

<sup>a</sup>Isolated yield.

<sup>b</sup>Based on <sup>1</sup>H NMR and <sup>19</sup>F NMR spectra.

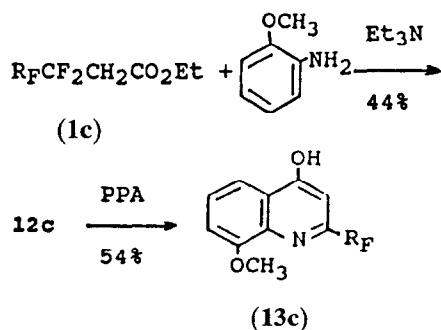
<sup>c</sup>Isolated yield based on 2–6.

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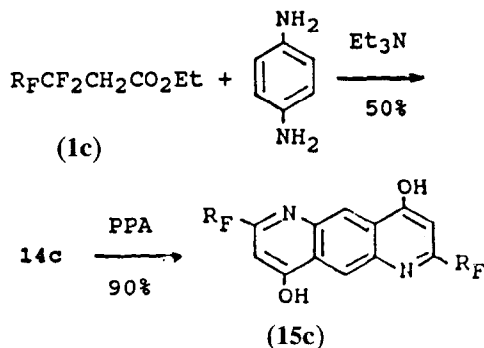


- a:  $R_F = \text{ClCF}_2$ ,  $X = \text{F}$       2 and 7:  $R = \text{CH}_3$   
 b:  $R_F = \text{Cl}(\text{CF}_2)_3$ ,  $X = \text{F}$       3 and 8:  $R = \text{H}$   
 c:  $R_F = \text{Cl}(\text{CF}_2)_5$ ,  $X = \text{F}$       4 and 9:  $R = \text{Cl}$   
 d:  $R_F = \text{BrCF}_2$ ,  $X = \text{F}$       5 and 10:  $R = \text{F}$   
 e:  $R_F = \text{CF}_3$ ,  $X = \text{Br}$       6 and 11:  $R = \text{I}$

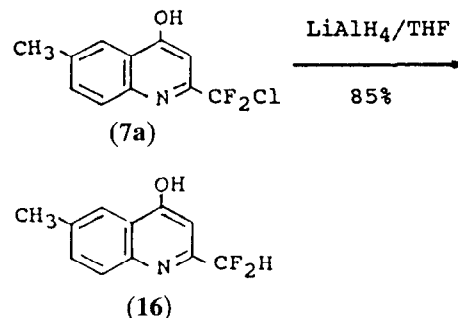
It has been shown that the Michael-addition reaction of *o*-methoxyaniline with **1c** occurs only with considerable difficulty to give the corresponding addition product in a somewhat lower yield, probably due to steric effects. Almost no addition product was obtained when *p*-nitroaniline and methyl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



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



2-Chlorodifluoromethyl-substituted 4-hydroxyquinoline was readily reduced with  $\text{LiAlH}_4$  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:



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.  $^1\text{H}$  NMR spectra were recorded on Varian EM-360A (60 MHz), FX-90Q (90 MHz) spectrometers using TMS as internal standard and  $^{19}\text{F}$  NMR spectra were recorded on a Varian EM-360L spectrometer (56.4 MHz) using TFA as external standard. In  $^{19}\text{F}$  NMR spectra, chemical shifts (in ppm) were positive for upfield shifts and the values are reported as  $\delta\text{CFCl}_3$  ( $\delta\text{CFCl}_3 = \delta\text{TFA} + 76.8$ ). Mass spectra were taken on a Finnegan GC-MS 4021 spectrometer. Column chromatography was performed using silica gel H, particle size 10–40  $\mu\text{m}$ .

### 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  $\text{Et}_3\text{N}$  and 5 ml of  $\text{CH}_3\text{CN}$  was stirred at 70  $^\circ\text{C}$  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  $\text{Na}_2\text{SO}_4$ . 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.16–1.37 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 2.32 (3H, s, Ar- $\text{CH}_3$ ); 3.48 (s,  $\text{CH}_2\text{CO}$  in imine); 4.01–4.30 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.30 (s, =CH in enamine); 6.72–7.18 (4H, m, Ar-H); 9.72 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 50.3 (s,  $\text{ClCF}_2$  in enamine); 59.4 (s,  $\text{ClCF}_2$  in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3250 (NH); 1740 (C=O); 1670 (C=N); 1630 (C=C); 1100–1280 (C-F). MS  $m/z$ : 289 ( $\text{M}^+$ ); 204 ( $\text{M}^+ - \text{CF}_2\text{Cl}$ ); 158 ( $\text{M}^+ - \text{CF}_2\text{Cl} - \text{EtOH}$ ). Analysis: Calc. for  $\text{C}_{13}\text{H}_{14}\text{ClF}_2\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.17–1.36 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 2.32 (3H, s, Ar- $\text{CH}_3$ ); 3.45 (s,  $\text{CH}_2\text{CO}$  in imine); 4.03–4.26 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.36 (s, =CH in enamine); 6.68–7.19 (4H, m, Ar-H); 9.30 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 66.8 (2F, s,  $\text{CF}_2\text{Cl}$ ); 108.2 (s, C=CCF<sub>2</sub> in enamine); 113.2 (s, N=CCF<sub>2</sub> in imine); 119.3 (s, other CF<sub>2</sub> in enamine); 119.8 (s, other CF<sub>2</sub> in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1740 (C=O); 1670 (C=N); 1630 (C=C); 1100–1240 (C-F). Analysis: Calc. for  $\text{C}_{15}\text{H}_{14}\text{ClF}_6\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.16–1.35 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 2.32 (3H, s, Ar- $\text{CH}_3$ ); 3.46 (s,  $\text{CH}_2\text{CO}$  in imine); 4.02–4.26 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.36 (s, =CH in enamine); 6.68–7.22 (4H, m, Ar-H); 9.28 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 67.5 (2F, s,  $\text{CF}_2\text{Cl}$ ); 108.6 (s, C=CCF<sub>2</sub> in enamine); 113.4 (s, N=CCF<sub>2</sub> in imine); 120.0–120.8 (6F, m, other  $3 \times \text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1740 (C=O); 1680 (C=N); 1630 (C=C); 1110–1220 (C-F). Analysis: Calc. for  $\text{C}_{17}\text{H}_{14}\text{ClF}_{10}\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.11–1.40 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 2.32 (3H, s, Ar- $\text{CH}_3$ ); 3.52 (s,  $\text{COCH}_2$  in imine); 4.03–4.28 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.30 (s, =CH in enamine); 6.63–7.26 (4H, m, Ar-H); 9.72 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 46.2 (s,  $\text{BrCF}_2$  in enamine); 55.6 (s,  $\text{BrCF}_2$  in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1740 (C=O); 1670 (C=N); 1620 (C=C); 1140–1240 (C-F). MS  $m/z$ : 335 ( $\text{M}^+ + 2$ ); 333 ( $\text{M}^+$ ); 289 ( $\text{M}^+ - \text{EtOH}$ ); 204 ( $\text{M}^+ - \text{BrCF}_2$ ). Analysis: Calc. for  $\text{C}_{13}\text{H}_{14}\text{BrF}_2\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.15–1.39 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 2.30 (3H, s, Ar- $\text{CH}_3$ ); 3.40 (s,  $\text{COCH}_2$  in imine); 4.01–4.35 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.31 (s, =CH in enamine); 6.76–7.20 (4H, m, Ar-H); 9.75 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 63.5 (s,  $\text{CF}_3$  in enamine); 72.4 (s,  $\text{CF}_3$  in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1740 (C=O); 1680 (C=N); 1630 (C=C); 1120–1220 (C-F). MS  $m/z$ : 273 ( $\text{M}^+$ ); 227 ( $\text{M}^+ - \text{EtOH}$ ); 158 ( $\text{M}^+ - \text{CF}_3 - \text{EtOH}$ ). Analysis: Calc. for

$\text{C}_{13}\text{H}_{14}\text{ClF}_3\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.12–1.34 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.45 (s,  $\text{COCH}_2$  in imine); 3.98–4.28 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.33 (s, =CH in enamine); 6.80–7.33 (5H, m, Ar-H); 9.76 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 50.8 (s,  $\text{CF}_2\text{Cl}$  in enamine); 60.0 (s,  $\text{CF}_2\text{Cl}$  in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1740 (C=O); 1670 (C=N); 1620 (C=C); 1100–1260 (C-F). MS  $m/z$ : 275 ( $\text{M}^+$ ); 230 ( $\text{M}^+ - \text{OEt}$ ); 190 ( $\text{M}^+ - \text{CF}_2\text{Cl}$ ); 144 ( $\text{M}^+ - \text{CF}_2\text{Cl} - \text{EtOH}$ ). Analysis: Calc. for  $\text{C}_{12}\text{H}_{12}\text{ClF}_2\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.16–1.32 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.43 (s,  $\text{COCH}_2$  in imine); 4.01–4.25 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.42 (s, =CH in enamine); 6.72–7.35 (5H, m, Ar-H); 9.19 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 66.5 (2F, s,  $\text{CF}_2\text{Cl}$ ); 108.3 (s, C=CCF<sub>2</sub> in enamine); 113.2 (s, N=CCF<sub>2</sub> in imine); 119.6 (2F, s, other CF<sub>2</sub>) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1740 (C=O); 1680 (C=N); 1620 (C=C); 1120–1280 (C-F). Analysis: Calc. for  $\text{C}_{14}\text{H}_{12}\text{ClF}_6\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.16–1.31 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.42 (s,  $\text{COCH}_2$  in imine); 4.10–4.20 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.41 (s, =CH in enamine); 6.76–7.41 (5H, m, Ar-H); 9.17 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 67.5 (2F, s,  $\text{CF}_2\text{Cl}$ ); 108.7 (s, C=CCF<sub>2</sub> in enamine); 113.5 (s, N=CCF<sub>2</sub> in imine); 119.8–120.6 (6F, m, other  $3 \times \text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1740 (C=O); 1680 (C=N); 1620 (C=C); 1140–1240 (C-F). Analysis: Calc. for  $\text{C}_{16}\text{H}_{12}\text{ClF}_{10}\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.11–1.41 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.50 (s,  $\text{COCH}_2$  in imine); 3.97–4.38 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.35 (s, =CH in enamine); 6.81–7.39 (5H, m, Ar-H); 9.75 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 47.0 (s,  $\text{BrCF}_2$  in enamine); 55.9 (s,  $\text{BrCF}_2$  in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1740 (C=O); 1670 (C=N); 1620 (C=C); 1100–1200 (C-F). MS  $m/z$ : 321 ( $\text{M}^+ + 2$ ); 319 ( $\text{M}^+$ ); 276 ( $\text{M}^+ - \text{OEt}$ ); 240 ( $\text{M}^+ - \text{Br}$ ); 190 ( $\text{M}^+ - \text{CF}_2\text{Br}$ ). Analysis: Calc. for  $\text{C}_{12}\text{H}_{12}\text{BrF}_2\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.16–1.36 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.22 (s,  $\text{COCH}_2$  in imine); 4.04–4.27 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.44 (s, =CH in enamine); 6.73–7.37 (4H, m, Ar-H); 9.11 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 66.5 (2F, s,  $\text{CF}_2\text{Cl}$ ); 108.1 (s, C=CCF<sub>2</sub> in enamine); 112.9 (s, N=CCF<sub>2</sub> in imine); 119.8 (2F, s, other CF<sub>2</sub>) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1730 (C=O); 1680 (C=N); 1630 (C=C); 1100–1220 (C-F). Analysis: Calc. for  $\text{C}_{11}\text{H}_{11}\text{Cl}_2\text{F}_6\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.16–1.39 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.44 (s,  $\text{COCH}_2$  in imine); 4.04–4.28 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.26 (s,  $=\text{CH}$  in enamine); 6.75–7.39 (4H, m, Ar–H); 9.11 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 67.5 (2F, s,  $\text{CF}_2\text{Cl}$ ); 108.9 (s,  $\text{C}=\text{CCF}_2$  in enamine); 113.6 (s,  $\text{N}=\text{CCF}_2$  in imine); 118.9–119.6 (6F, m, other  $3\times\text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1730 ( $\text{C}=\text{O}$ ); 1680 ( $\text{C}=\text{N}$ ); 1630 ( $\text{C}=\text{C}$ ); 1100–1200 ( $\text{C}-\text{F}$ ). MS  $m/z$ : 509 ( $\text{M}^+$ ); 463 ( $\text{M}^+ - \text{EtOH}$ ); 224 ( $\text{M}^+ - \text{C}_5\text{F}_{10}\text{Cl}$ ); 178 ( $\text{M}^+ - \text{C}_5\text{F}_{10}\text{Cl} - \text{EtOH}$ ). Analysis: Calc. for  $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{F}_{10}\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.12–1.45 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.49 (s,  $\text{COCH}_2$  in imine); 4.01–4.33 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.34 (s,  $=\text{CH}$  in enamine); 6.79–7.42 (4H, m, Ar–H); 9.68 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 46.8 (s,  $\text{BrCF}_2$  in enamine); 55.8 (s,  $\text{BrCF}_2$  in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1740 ( $\text{C}=\text{O}$ ); 1670 ( $\text{C}=\text{N}$ ); 1630 ( $\text{C}=\text{C}$ ); 1120–1220 ( $\text{C}-\text{F}$ ). MS  $m/z$ : 355 ( $\text{M}^+ + 2$ ); 353 ( $\text{M}^+$ ); 309 ( $\text{M}^+ - \text{OEt}$ ); 224 ( $\text{M}^+ - \text{CF}_2\text{Br}$ ). Analysis: Calc. for  $\text{C}_{12}\text{H}_{11}\text{BrF}_2\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.16–1.32 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.36 (s,  $\text{COCH}_2$  in imine); 4.00–4.29 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.28 (s,  $=\text{CH}$  in enamine); 6.96–7.32 (4H, m, Ar–H); 9.64 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 62.8 (s,  $\text{CF}_3$  in enamine); 72.1 (s,  $\text{CF}_3$  in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1660 ( $\text{C}=\text{N}$ ); 1620 ( $\text{C}=\text{C}$ ); 1130–1230 ( $\text{C}-\text{F}$ ). MS  $m/z$ : 293 ( $\text{M}^+$ ); 247 ( $\text{M}^+ - \text{EtOH}$ ); 178 ( $\text{M}^+ - \text{EtOH} - \text{CF}_3$ ). Analysis: Calc. for  $\text{C}_{12}\text{H}_{11}\text{ClF}_3\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.14–1.32 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.43 (s,  $\text{COCH}_2$  in imine); 4.02–4.25 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.36 (s,  $=\text{CH}$  in enamine); 6.72–7.20 (4H, m, Ar–H); 9.28 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 68.1 (2F, s,  $\text{CF}_2\text{Cl}$ ); 110.1 (s,  $\text{C}=\text{CCF}_2$  in enamine); 117.2 (s,  $\text{N}=\text{CCF}_2$  in imine); 114.1 (1F, s, Ar–F); 120.8–121.4 (6F, m, other  $3\times\text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1730 ( $\text{C}=\text{O}$ ); 1680 ( $\text{C}=\text{N}$ ); 1630 ( $\text{C}=\text{C}$ ); 1120–1220 ( $\text{C}-\text{F}$ ). MS  $m/z$ : 493 ( $\text{M}^+$ ); 448 ( $\text{M}^+ - \text{OEt}$ ); 208 ( $\text{M}^+ - \text{C}_5\text{F}_{10}\text{Cl}$ ); 162 ( $\text{M}^+ - \text{C}_5\text{F}_{10}\text{Cl} - \text{EtOH}$ ). Analysis: Calc. for  $\text{C}_{16}\text{H}_{11}\text{ClF}_{11}\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.20–1.44 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.48 (s,  $\text{COCH}_2$  in imine); 4.06–4.43 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.38 (s,  $=\text{CH}$  in enamine); 6.96–7.31 (4H, m, Ar–H); 9.72 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 62.8 (s,  $\text{CF}_3$  in enamine); 71.8 (s,  $\text{CF}_3$  in imine); 114.5 (1F, s, Ar–F) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1680 ( $\text{C}=\text{N}$ ); 1640 ( $\text{C}=\text{O}$ ); 1120–1220 ( $\text{C}-\text{F}$ ).

MS  $m/z$ : 277 ( $\text{M}^+$ ). Analysis: Calc. for  $\text{C}_{12}\text{H}_{11}\text{F}_4\text{NO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.12–1.37 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.42 (s,  $\text{COCH}_2$  in imine); 3.99–4.34 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.34 (s,  $=\text{CH}$  in enamine); 6.85–7.66 (4H, m, Ar–H); 9.66 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 50.4 (s,  $\text{CF}_2\text{Cl}$  in enamine); 59.9 (s,  $\text{CF}_2\text{Cl}$  in imine) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1740 ( $\text{C}=\text{O}$ ); 1670 ( $\text{C}=\text{N}$ ); 1630 ( $\text{C}=\text{C}$ ); 1100–1200 ( $\text{C}-\text{F}$ ). MS  $m/z$ : 401 ( $\text{M}^+$ ); 316 ( $\text{M}^+ - \text{CF}_2\text{Cl}$ ); 270 ( $\text{M}^+ - \text{CF}_2\text{Cl} - \text{EtOH}$ ). Analysis: Calc. for  $\text{C}_{12}\text{H}_{11}\text{ClF}_2\text{INO}_2$ : 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.16–1.38 (3H, m,  $\text{CH}_2\text{CH}_3$ ); 3.40 (s,  $\text{COCH}_2$  in imine); 3.77–3.82 (3H, d,  $\text{OCH}_3$  in enamine and imine); 4.00–4.34 (2H, m,  $\text{CH}_2\text{CH}_3$ ); 5.40 (s,  $=\text{CH}$  in enamine); 6.82–7.24 (4H, m, Ar–H); 8.60 (br., NH in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 67.4 (2F, s,  $\text{CF}_2\text{Cl}$ ); 112.0 (s,  $\text{C}=\text{CCF}_2$  in enamine); 113.5 (s,  $\text{N}=\text{CCF}_2$  in imine); 119.8–120.9 (6F, m, other  $3\times\text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1740 ( $\text{C}=\text{O}$ ); 1680 ( $\text{C}=\text{N}$ ); 1630 ( $\text{C}=\text{C}$ ); 1120–1250 ( $\text{C}-\text{F}$ ). MS  $m/z$ : 505 ( $\text{M}^+$ ). Analysis: Calc. for  $\text{C}_{17}\text{H}_{14}\text{ClF}_{10}\text{NO}_3$ : C, 40.37; H, 2.79; N, 2.77%. Found: C, 40.75; H, 2.72; N, 2.95%.

Compound **14c**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.18–1.37 (6H, m,  $2\times\text{CH}_2\text{CH}_3$ ); 3.48 (s,  $2\times\text{COCH}_2$  in imine); 4.06–4.29 (4H, m,  $2\times\text{CH}_2\text{CH}_3$ ); 5.44 (s,  $=\text{CH}\times 2$  in enamine); 6.75–7.25 (4H, m, Ar–H); 9.27 (br.,  $2\times\text{NH}$  in enamine) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 67.5 (4F, s,  $2\times\text{CF}_2\text{Cl}$ ); 117.9 (s,  $2\times\text{C}=\text{CCF}_2$  in enamine); 122.8 (s,  $2\times\text{N}=\text{CCF}_2$  in imine); 129.2–129.9 (12F, m, other  $6\times\text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3200 (NH); 1730 ( $\text{C}=\text{O}$ ); 1680 ( $\text{C}=\text{N}$ ); 1630 ( $\text{C}=\text{C}$ ); 1120–1220 ( $\text{C}-\text{F}$ ). MS  $m/z$ : 874 ( $\text{M}^+ + 2$ ); 587 ( $\text{M}^+ - \text{C}_5\text{F}_{10}\text{Cl}$ ); 541 ( $\text{M}^+ - \text{C}_5\text{F}_{10}\text{Cl} - \text{EtOH}$ ). Analysis: Calc. for  $\text{C}_{26}\text{H}_{18}\text{Cl}_2\text{F}_{20}\text{N}_2\text{O}_4$ : 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  $\text{Na}_2\text{SO}_4$ . Removal of solvent followed by recrystallization from ethanol gave the pure 2-(*F*-alkyl)-quinolines.

Compound **7a**: M.p. 224–226 °C.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 2.65 (3H, s, Ar– $\text{CH}_3$ ); 6.90 (1H, s, H in position 3); 7.74–8.14 (3H, m, Ar–H) ppm.  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 56.6 (s,  $\text{CF}_2\text{Cl}$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3420 (OH); 1570–1610 (Ar); 1150–1220 ( $\text{C}-\text{F}$ ). MS  $m/z$ : 243 ( $\text{M}^+$ );

85 ( $\text{ClCF}_2^+$ ). Analysis: Calc. for  $\text{C}_{11}\text{H}_8\text{ClF}_2\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 2.62 (3H, s, Ar- $\text{CH}_3$ ); 6.92 (1H, s, H in position 3); 7.66–8.13 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 68.4 (2F, s,  $\text{CF}_2\text{Cl}$ ); 114.8 (2F, s,  $=\text{C}-\text{CF}_2$ ); 121.5 (2F, s, other  $\text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3420 (OH); 1560–1610 (Ar); 1120–1200 (C-F). Analysis: Calc. for  $\text{C}_{13}\text{H}_8\text{ClF}_6\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 2.48 (3H, s, Ar- $\text{CH}_3$ ); 7.07 (1H, s, H in position 3); 7.55–7.94 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 69.5 (2F, s,  $\text{CF}_2\text{Cl}$ ); 115.3 (2F, s,  $=\text{C}-\text{CF}_2$ ); 121.3–122.5 (6F, m, other  $3 \times \text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3420 (OH); 1570–1620 (Ar); 1140–1220 (C-F). Analysis: Calc. for  $\text{C}_{15}\text{H}_8\text{ClF}_{10}\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 2.55 (3H, s, Ar- $\text{CH}_3$ ); 7.05 (1H, s, H in position 3); 7.64–8.06 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 49.3 (s,  $\text{CF}_2\text{Br}$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3420 (OH); 1560–1620 (Ar); 1140–1220 (C-F). MS  $m/z$ : 289 ( $\text{M}^+ + 2$ ); 287 ( $\text{M}^+$ ); 208 ( $\text{M}^+ - \text{Br}$ ); 158 ( $\text{M}^+ - \text{CF}_2\text{Br}$ ). Analysis: Calc. for  $\text{C}_{11}\text{H}_8\text{BrF}_2\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 2.50 (3H, s, Ar- $\text{CH}_3$ ); 7.02 (1H, s, H in position 3); 7.60–8.02 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 65.7 (s,  $\text{CF}_3$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3430 (OH); 1570–1630 (Ar); 1150–1250 (C-F). MS  $m/z$ : 227 ( $\text{M}^+$ ); 158 ( $\text{M}^+ - \text{CF}_3$ ). Analysis: Calc. for  $\text{C}_{11}\text{H}_8\text{F}_3\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 6.92 (1H, s, H in position 3); 7.56–8.44 (4H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 57.6 (s,  $\text{CF}_2\text{Cl}$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1580–1620 (Ar); 1140–1250 (C-F). MS  $m/z$ : 229 ( $\text{M}^+$ ). Analysis: Calc. for  $\text{C}_{10}\text{H}_6\text{ClF}_2\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 7.04 (1H, s, H in position 3); 7.52–8.24 (4H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 66.4 (2F, s,  $\text{CF}_2\text{Cl}$ ); 111.4 (2F, s,  $=\text{C}-\text{CF}_2$ ); 129.8 (2F, s, other  $\text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3440 (OH); 1520–1620 (Ar); 1120–1220 (C-F). Analysis: Calc. for  $\text{C}_{12}\text{H}_6\text{ClF}_6\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 7.02 (1H, s, H in position 3); 7.60–8.28 (4H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 67.5 (2F, s,

$\text{CF}_2\text{Cl}$ ); 111.6 (2F, s,  $=\text{C}-\text{CF}_2$ ); 119.4–120.4 (6F, m, other  $3 \times \text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3420 (OH); 1520–1620 (Ar); 1140–1210 (C-F). Analysis: Calc. for  $\text{C}_{14}\text{H}_6\text{ClF}_{10}\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 6.97 (1H, s, H in position 3); 7.56–8.27 (4H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 50.5 (s,  $\text{BrCF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1520–1620 (Ar); 1140–1220 (C-F). MS  $m/z$ : 275 ( $\text{M}^+ + 2$ ); 273 ( $\text{M}^+$ ); 194 ( $\text{M}^+ - \text{Br}$ ); 144 ( $\text{M}^+ - \text{CF}_2\text{Br}$ ). Analysis: Calc. for  $\text{C}_{10}\text{H}_6\text{BrF}_2\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 7.04 (1H, s, H in position 3); 7.79–8.33 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 68.5 (2F, s,  $\text{CF}_2\text{Cl}$ ); 114.6 (2F, s,  $=\text{C}-\text{CF}_2$ ); 121.5 (2F, s, other  $\text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3420 (OH); 1560–1620 (Ar); 1120–1220 (C-F). Analysis: Calc. for  $\text{C}_{12}\text{H}_5\text{Cl}_2\text{F}_6\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 7.07 (1H, s, H in position 3); 7.70–8.13 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 68.3 (2F, s,  $\text{CF}_2\text{Cl}$ ); 112.8 (2F, s,  $=\text{C}-\text{CF}_2$ ); 120.2–121.3 (6F, m, other  $3 \times \text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3420 (OH); 1580–1620 (Ar); 1140–1220 (C-F). MS  $m/z$ : 463 ( $\text{M}^+$ ); 228 ( $\text{M}^+ - \text{C}_5\text{F}_{10}\text{Cl}$ ). Analysis: Calc. for  $\text{C}_{14}\text{H}_5\text{Cl}_2\text{F}_{10}\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 7.13 (1H, s, H in position 3); 7.64–8.18 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 68.4 (s,  $\text{CF}_2\text{Br}$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1510–1630 (Ar); 1160–1250 (C-F). MS  $m/z$ : 309 ( $\text{M}^+ + 2$ ); 307 ( $\text{M}^+$ ); 228 ( $\text{M}^+ - \text{Br}$ ); 178 ( $\text{M}^+ - \text{CF}_2\text{Br}$ ). Analysis: Calc. for  $\text{C}_{10}\text{H}_5\text{BrClF}_2\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 7.07 (1H, s, H in position 3); 7.74–8.28 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 66.2 (s,  $\text{CF}_3$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1510–1630 (Ar); 1140–1230 (C-F). MS  $m/z$ : 247 ( $\text{M}^+$ ). Analysis: Calc. for  $\text{C}_{10}\text{H}_5\text{ClF}_3\text{NO}$ : 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.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 7.00 (1H, s, H in position 3); 7.72–8.12 (3H, m, Ar-H) ppm.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 68.4 (2F, s,  $\text{CF}_2\text{Cl}$ ); 111.1 (1F, s, Ar-F); 112.6 (2F, s,  $=\text{C}-\text{CF}_2$ ); 120.2–121.2 (6F, m, other  $3 \times \text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1520–1620 (Ar); 1140–1220 (C-F). MS  $m/z$ : 447 ( $\text{M}^+$ ); 428 ( $\text{M}^+ - \text{F}$ ); 412 ( $\text{M}^+ - \text{Cl}$ ); 162 ( $\text{M}^+ - \text{C}_5\text{F}_{10}\text{Cl}$ ). Analysis: Calc. for  $\text{C}_{14}\text{H}_5\text{ClF}_{11}\text{NO}$ : 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.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 7.07 (1H, s, H in position 3); 7.60–8.12 (3H, m, Ar–H) ppm.  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta$ : 67.5 (3F, s,  $\text{CF}_3$ ); 111.2 (1F, s, Ar–F) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1520–1620 (Ar); 1140–1240 (C–F). MS  $m/z$ : 231 ( $\text{M}^+$ ); 212 ( $\text{M}^+ - \text{F}$ ); 162 ( $\text{M}^+ - \text{CF}_3$ ). Analysis: Calc. for  $\text{C}_{10}\text{H}_5\text{F}_4\text{NO}$ : 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.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 7.04 (1H, s, H in position 3); 7.66–8.52 (3H, m, Ar–H) ppm.  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta$ : 53.6 (s,  $\text{CF}_2\text{Cl}$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1560–1630 (Ar); 1140–1220 (C–F). MS  $m/z$ : 355 ( $\text{M}^+$ ); 320 ( $\text{M}^+ - \text{Cl}$ ); 270 ( $\text{M}^+ - \text{CF}_2\text{Cl}$ ); 228 ( $\text{M}^+ - \text{I}$ ). Analysis: Calc. for  $\text{C}_{10}\text{H}_5\text{ClF}_2\text{INO}$ : 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.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 3.86 (3H, s,  $\text{OCH}_3$ ); 7.08 (1H, s, H in position 3); 7.18–7.75 (3H, m, Ar–H) ppm.  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta$ : 67.8 (2F, s,  $\text{CF}_2\text{Cl}$ ); 111.8 (2F, s,  $=\text{C}-\text{CF}_2$ ); 119.6–120.5 (6F, m, other  $3 \times \text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1530–1630 (Ar); 1140–1220 (C–F). MS  $m/z$ : 459 ( $\text{M}^+$ ); 444 ( $\text{M}^+ - \text{CH}_3$ ). Analysis: Calc. for  $\text{C}_{15}\text{H}_8\text{ClF}_{10}\text{NO}_2$ : 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.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 7.11 (2H, s, 2H in positions 3 and 7); 8.22 (2H, s, Ar–H) ppm.  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta$ : 68.8 (4F, s,  $2 \times \text{CF}_2\text{Cl}$ ); 115.1 (4F, s,  $2 \times =\text{C}-\text{CF}_2$ ); 120.9–122.0 (12F, m, other  $6 \times \text{CF}_2$ ) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3400 (OH); 1560–1640 (Ar); 1130–1230 (C–F). MS  $m/z$ : 780 ( $\text{M}^+$ ); 545 ( $\text{M}^+ - \text{C}_4\text{F}_8\text{Cl}$ ). Analysis: Calc. for  $\text{C}_{22}\text{H}_6\text{Cl}_2\text{F}_{20}\text{N}_2\text{O}_2$ : 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  $\text{LiAlH}_4$  was refluxed in anhydrous THF for 10 h.

After the usual work-up, the crude product was re-crystallized from ethanol to give compound **16** in 71% yield.

Compound **16**: M.p. 250–252 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 2.46 (3H, s, Ar– $\text{CH}_3$ ); 6.55 (1H, s, H in position 3); 6.80–7.34 (1H, t,  $\text{CF}_2\text{H}$ ,  $^2J_{\text{HF}} = 54.0$  Hz); 7.56–7.95 (3H, m, Ar–H) ppm.  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta$ : 115.8–116.7 (2F, d,  $\text{CF}_2\text{H}$ ,  $^2J_{\text{HF}} = 54.0$  Hz) ppm. IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 1540–1640 (Ar); 1150–1250 (C–F). MS  $m/z$ : 209 ( $\text{M}^+$ ); 189 ( $\text{M}^+ - \text{HF}$ ); 158 ( $\text{M}^+ - \text{CF}_2\text{H}$ ). Analysis: Calc. for  $\text{C}_{11}\text{H}_9\text{F}_2\text{NO}$ : 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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