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Facile and regioselective synthesis of 4-fluoroalkyl-2-quinolinol

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Abstract

4-Fluoroalkyl-2-quinolinols were regioselectively synthesized in moderate to high yields by acid-assisted intramolecular ring-closure reaction of the corresponding *N*-aryl-3-oxa-polyfluoroalkanamides prepared from 2,2-dihydropolyfluoroalkanoic acids in two steps.

Keywords: 4-Fluoroalkyl-2-quinolinol; 2,2-Dihydropolyfluoroalkanoic acids; Synthesis

1. Introduction

Because of the unique biological activities imparted by fluorine, the development of new methodologies for the synthesis of fluorine-containing heterocyclic compounds continues to arise considerable interest [1–6]. Quinolines have been an important class of heterocycles, and some fluorine-containing quinolines have been found to possess special biological properties. For example, mefloquine, a trifluoromethylated quinoline, has been used as an antimalarial agent in response to increased resistance to existing drugs [7]. In the past few decades many approaches to fluorine-containing quinolines were reported and most work involved 2-fluoroalkyl-substituted quinolines [8–14]. The synthesis of 4-fluoroalkyl quinoline and its derivatives was less studied [15]. In the present paper we wish to report a facile and regioselective method for the synthesis of 4-fluoroalkyl-2-quinolinols and their derivatives from 2,2-dihydropolyfluoroalkanoic acids.

2. Results and discussion

2,2-Dihydropolyfluoroalkanoic acids (**1a–c**) were prepared readily through the sodium dithionite-initiated addition reaction of per(poly)fluoroalkyl iodides with ethyl vinyl ether and the following oxidation [16]. In the presence of DCC (*N,N'*-dicyclohexylcarbodiimide), **1** reacted with anilines to give the corresponding amides, which eliminated a hydrofluoride with Et_3N and $NaHCO_3$ to give *N*-aryl-3-fluoro-3-fluoroalkyl-2-propen-2-amides (**3**) in high yields (Scheme 1).

As shown in Scheme 2, compound **3** could undergo Michael addition with pyrrolidine. After hydration of the adduct, *N*-aryl-3-oxa-polyfluoroalkanamides (**4**) were obtained in high yields. Acid-assisted ring-closure of compound **4** was conducted in the presence of polyphosphoric acid (PPA) at 165–170°C. The reaction was complete in 5–9 h, giving the corresponding 4-fluoroalkyl-2-quinolinols regioselectively (**5**). The results are summarized in Table 1.

Steric effect played an important role in the above reactions. The *p*- and *m*-substituted anilines gave satisfactory results and only one of the two possible products was isolated with ring-closure taking place at the *p*-position of the substituent when a *m*-substituted aniline was used. In the case of *o*-substituted anilines, only trace cyclic products were obtained. Anilines bearing strong electron-withdrawing groups such as nitro also gave poor results. The length of fluoroalkyl groups also affects the yield of the ring-closure reaction, and better results were obtained with the trifluoromethyl group.

Similarly, tricyclic compound, **7b** was obtained from α-aminonaphthlene (**8**) by the following reactions (Scheme 3).

In summary, intramolecular ring-closure reaction of *N*-aryl-3-oxa-polyfluoroalkanamides obtained from 2,2-dihydropolyfluoroalkanoic acids was achieved in the presence of polyphosphoric acid, providing a convenient method for the synthesis of 4-fluoroalkyl-2-quinolinols and their derivatives.

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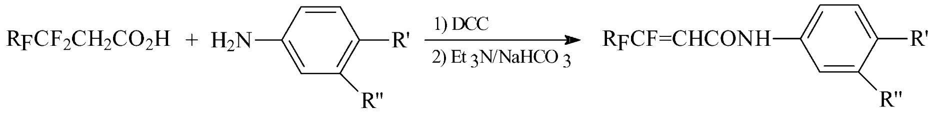


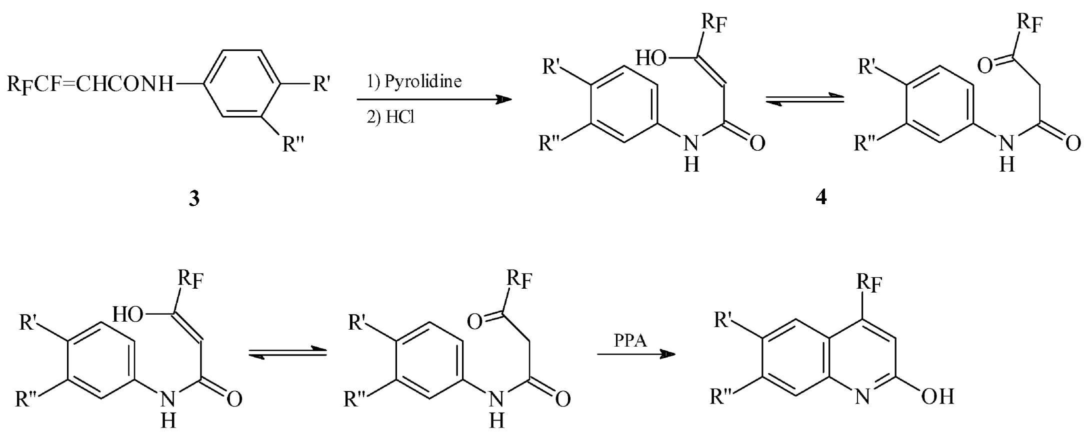
1a-c **2d-j** **3**

R_F = a, CF_3; b, $Cl(CF_2)_3$; c, $CF_3(CF_2)_4$

2d, R' = R'' = H; 2e, R' = Br, R'' = H; 2f, R' = H, R'' = CH_3

2g, R' = H, R'' = Cl; 2h, R' = Cl, R'' = H; 2i, R' = CH_3, R'' = H; 2j, R' = I, R'' = H

Scheme 1.



3 **4** **4** **5**

R_F = a, CF_3; b, $Cl(CF_2)_3$; c, $CF_3(CF_2)_4$

Scheme 2.

Table 1
Synthesis of 4-fluoroalkyl-2-quinolinols

Entry	Fluorinated acids	$ArNH_2$			Isolated yield (%)	
			R′	R″	3	5
1	**1a**	**2d**	H	H	**3ad**, 99.0	**5ad**, 84.0
2	**1b**	**2d**	H	H	**3bd**, 99.0	**5bd**, 70.5
3	**1c**	**2d**	H	H	**3cd**, 98.0	**5cd**, 68.5
4	**1a**	**2e**	Br	H	**3ae**, 99.0	**5ae**, 80.0
5	**1b**	**2e**	Br	H	**3be**, 98.5	**5be**, 59.5
6	**1c**	**2e**	Br	H	**3ce**, 97.0	**5ce**, 62.0
7	**1a**	**2f**	H	CH_3	**3af**, 99.5	**5af**, 82.5
8	**1b**	**2f**	H	CH_3	**3bf**, 99.5	**5bf**, 58.0
9	**1c**	**2f**	H	CH_3	**3cf**, 99.0	**5cf**, 56.5
10	**1b**	**2g**	H	Cl	**3bg**, 99.0	**5bg**, 58.5
11	**1a**	**2h**	Cl	H	**3ah**, 99.5	**5ah**, 80.5
12	**1b**	**2h**	Cl	H	**3bh**, 99.5	**5bh**, 61.0
13	**1c**	**2h**	Cl	H	**3ch**, 99.0	**5ch**, 65.4
14	**1a**	**2i**	CH_3	H	**3ai**, 99.0	**5ai**, 85.0
15	**1b**	**2i**	CH_3	H	**3bi**, 98.5	**5bi**, 62.5
16	**1c**	**2i**	CH_3	H	**3ci**, 98.5	**5ci**, 66.0
17	**1b**	**2j**	I	H	**3bj**, 97.0	**5bj**, 33.5[a]
18	**1b**	**8**			**6b**, 95.0	**7b**, 56.3

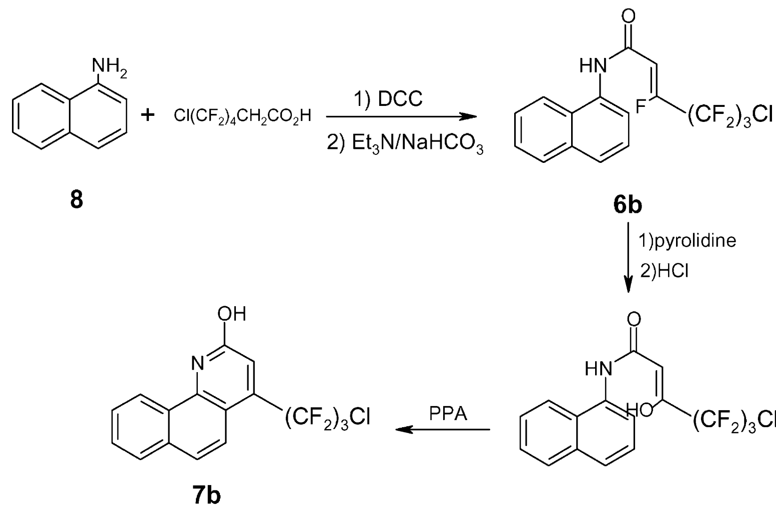
[a] 30.0% of **5bd** was isolated in addition to 33.5% of **5bj**.

3. Experimental

Melting points were uncorrected. IR spectra were measured with an IR-440 spectrometer and a Perkin-Elmer 983G IR spectrophotometer, using liquid films and KBr pellets for solids. ^1H NMR spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were recorded on a Varian EM-360L (56.4 MHz) spectrometer using TFA as external standard. In ^{19}F NMR spectra, chemical shifts (ppm) are regarded as positive for upfield shifts and the values are reported as δ_{CFCl_3} ($\delta_{CFCl_3} = \delta_{TFA} + 76.8$). Mass spectra were taken on a GC–MS 4021 spectrometer. Column chromatography was performed using silica gel H, particle size 10–40 μm.

3.1. Preparation of compound 3

Typical procedure: a mixture of 2,2-dihydropolyfluoroalkanoic acid (**1**, 5 mmol), anilne (**2**, 5 mmol), DCC (5 mmol) and CH_2Cl_2 (25 ml) was stirred at room temperature for 5–8 h. Then Et_3N (10 mmol) and $NaHCO_3$ (10 mmol) was added and the resulting mixture was stirred



Scheme 3.

under reflux for 5 h. After reaction, the reaction mixture was filtered by suction. Solvent was removed from the filtrate by evaporation and the crude product was purified by flash chromatography using petroleum ether and ethyl acetate (5:1) as eluent to give compound **3** as white solids.

Compound **3ad**: mp 110–111.5°C. ^{1}H NMR ($CDCl_3$) δ: 7.95 (1H, s, NH), 7.52 (2H, d, $J = 7.6$ Hz, ArH-2,6), 7.34 (2H, t, $J = 7.6$ Hz, ArH-3,5), 7.18 (1H, t, $J = 7.6$ Hz, ArH-4), 6.09 (1H, d, $J = 32.8$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 72.2 (3F, s, CF_3), 119.1 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 3308 (N–H), 1660 (C=O), 1200 (C–F); MS *m/z*: 233 (M^+), 214 ($M^+ - $F), 93 [$M^+ - Cl(CF_2)_3$CF=CHCO + 1]. Anal.: found: C, 51.59; H, 3.08; N, 5.84. $C_{10}H_7F_4NO$ requires: C, 51.51; H, 3.03; N, 6.01%.

Compound **3bd**: mp 112–114°C. ^{1}H NMR ($CDCl_3$) δ: 7.71 (1H, s, NH), 7.54 (2H, d, $J = 7.8$ Hz, ArH-2,6), 7.36 (2H, t, $J = 7.8$ Hz, ArH-3,5), 7.18 (1H, t, $J = 7.8$ Hz, ArH-4), 6.15 (1H, d, $J = 31.3$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 68.8 (2F, s, $ClCF_2$), 116.0 (1F, m, =CF), 118.3 (2F, m, CF_2), 122.1 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3282 (N–H), 1702 (C=O), 1126–1189 (C–F); MS *m/z*: 351, 349 (M^+), 93 [$M^+ - Cl(CF_2)_3$CF=CHCO + 1]. Anal.: found: C, 41.80; H, 1.90; N, 4.00. $C_{12}H_7ClF_7NO$ requires: C, 41.20; H, 2.00; N, 4.01%.

Compound **3cd**: mp 108–109°C. ^{1}H NMR ($CDCl_3$) δ: 7.91 (1H, s, NH), 7.51 (2H, d, $J = 7.6$ Hz, ArH-2,6), 7.33 (2H, t, $J = 7.6$ Hz, ArH-3,5), 7.16 (1H, t, $J = 7.6$ Hz, ArH-4), 6.18 (1H, d, $J = 30.5$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.8 (3F, s, CF_3), 113.4 (1F, m, =CF), 117.4–123.3 (8F, m, 4CF_2) ppm; IR ν_{max} (cm^{-1}): 3342 (N–H), 1702 (C=O), 1143–1201 (C–F); MS *m/z*: 433 (M^+), 93 [$M^+ - CF_3(CF_2)_4$-CHCO + 1]. Anal.: found: C, 39.04; H, 1.69; N, 3.36. $C_{14}H_7F_{12}NO$ requires: C, 38.82; H, 1.63; N, 3.23%.

Compound **3ae**: mp 118–119°C. ^{1}H NMR ($CDCl_3$) δ: 7.76 (1H, s, NH), 7.46 (4H, m, ArH), 6.10 (1H, d, $J = 33.1$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 72.0 (3F, s, CF_3), 118.7 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 3291 (N–H), 1652 (C=O), 1200 (C–F); MS *m/z*: 313, 311 (M^+), 171 ($M^+ - CF_3$CF=CHCO + 1). Anal.: found: C, 38.74; H, 2.16; N, 4.39. $C_{10}H_6BrF_4NO$ requires: C, 38.49; H, 1.94; N, 4.49%.

Compound **3be**: mp 138–140°C. ^{1}H NMR ($CDCl_3$) δ: 7.86 (1H, s, NH), 7.37–7.51 (4H, m, ArH), 6.12 (1H, d, $J = 32.3$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 67.1 (2F, s, $ClCF_2$), 113.8 (1F, m, CF), 117.1 (2F, m, CF_2), 120.6 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3286 (N–H), 1709 (C=O), 1131–1259 (C–F); MS *m/z*: 431, 429, 427 (M^+), 171 [$M^+ - Cl(CF_2)_3$CF=CHCO + 1]. Anal.: found: C, 33.78; H, 1.63; N, 3.35. $C_{12}H_6BrClF_7NO$ requires: C, 33.63; H, 1.41; N, 3.27%.

Compound **3ce**: mp 123–124°C. ^{1}H NMR ($CDCl_3$) δ: 7.75 (1H, s, NH), 7.39–7.48 (4H, m, ArH), 6.12 (1H, d, $J = 31.4$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.9 (3F, s, CF_3), 113.0 (1F, m, =CF), 117.8–125.5 (8F, m, 4CF_2) ppm; IR ν_{max} (cm^{-1}): 3321 (N–H), 1701 (C=O), 1141–1201 (C–F); MS *m/z*: 513, 511 (M^+), 171 [$M^+ - CF_3(CF_2)_4$CF=CHCO + 1]. Anal.: found: C, 33.15; H, 1.40; N, 3.03. $C_{14}H_6BrF_{12}NO$ requires: C, 32.84; H, 1.18; N, 2.74%.

Compound **3af**: mp 124–125°C. ^{1}H NMR ($CDCl_3$) δ: 8.34 (1H, s, NH), 7.36 (1H, s, ArH-2), 7.30 (1H, d, $J = 7.2$ Hz, ArH-6), 7.21 (1H, t, $J = 7.2$ Hz, ArH-5), 6.98 (1H, d, $J = 7.2$ Hz, ArH-4), 6.09 (1H, d, $J = 32.7$ Hz, =CH), 2.32 (3H, s, CH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 71.9 (3F, s, CF_3), 119.2 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 3158 (N–H), 1618 (C=O), 1201 (C–F); MS *m/z*: 247 (M^+); 107 ($M^+ - CF_3$CF=CHCO + 1). Anal.: found: C, 53.44; H, 3.74; N, 5.61. $C_{11}H_9F_4NO$ requires: C, 53.45; H, 3.67; N, 5.67%.

Compound **3bf**: mp 88–89°C. ^{1}H NMR ($CDCl_3$) δ: 8.20 (1H, s, NH), 7.35 (1H, s, ArH-2), 7.31 (1H, d, $J = 7.6$ Hz, ArH-6), 7.19 (1H, t, $J = 7.6$ Hz, ArH-5), 6.97 (1H, d, $J = 7.6$ Hz, ArH-4), 6.17 (1H, d, $J = 30.6$ Hz, =CH), 2.35 (3H, s, CH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 66.9 (2F, s, $ClCF_2$), 113.8 (1F, m, =CF), 116.8 (2F, m, CF_2), 120.3 (2F, m, CF_2)

ppm; IR ν_{max} (cm^{-1}): 3295 (N–H), 1702 (C=O), 1127–1180 (C–F); MS *m/z*: 365, 363 (M^+), 107 [$M^+ - Cl(CF_2)_3$-CHCO + 1]. Anal.: found: C, 43.09; H, 2.44; N, 3.97. $C_{13}H_9ClF_7NO$ requires: C, 42.94; H, 2.49; N, 3.85%.

Compound **3cf**: mp 101–102°C. ^{1}H NMR ($CDCl_3$) δ: 7.93 (1H, s, NH), 7.36 (1H, s, ArH-2), 7.31 (1H, d, $J = 7.8$ Hz, ArH-6), 7.21 (1H, t, $J = 7.8$ Hz, ArH-5), 6.98 (1H, d, $J = 7.8$ Hz, ArH-4), 6.18 (1H, d, $J = 31.3$ Hz, =CH), 2.36 (3H, s, CH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.8 (3F, s, CF_3), 113.3 (1F, m, CF), 117.6–123.1 (8F, m, $4CF_2$) ppm; IR ν_{max} (cm^{-1}): 3295 (N–H), 1701 (C=O), 1141–1199 (C–F); MS *m/z*: 447 (M^+), 107 [$M^+ - CF_3(CF_2)_4CF$=CHCO + 1]. Anal.: found: C, 40.75; H, 2.27; N, 3.42. $C_{15}H_9F_{12}NO$ requires: C, 40.29; H, 2.03; N, 3.13%.

Compound **3bg**: mp 102–104°C. ^{1}H NMR ($CDCl_3$) δ: 7.89 (1H, s, NH), 7.65 (1H, s, ArH-2), 7.37 (1H, d, $J = 8.0$ Hz, ArH-6), 7.26 (1H, t, $J = 8.0$ Hz, ArH-5), 7.14 (1H, d, $J = 8.0$ Hz, ArH-4), 6.17 (1H, d, $J = 32.3$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 66.8 (2F, s, $ClCF_2$), 112.9 (1F, m, =CF), 117.0 (2F, m, CF_2), 120.4 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3297 (N–H), 1705 (C=O), 1123–1181 (C–F); MS *m/z*: 387, 385, 383 (M^+), 127 [$M^+ - Cl(CF_2)_3CF$=CHCO + 1]. Anal.: found: C, 37.83; H, 1.77; N, 3.79. $C_{12}H_6Cl_2F_7NO$ requires: C, 37.53; H, 1.57; N, 3.65%.

Compound **3ah**: mp 120–122°C. ^{1}H NMR ($CDCl_3$) δ: 7.75 (1H, s, NH), 7.46 (4H, m, ArH), 6.10 (1H, d, $J = 33.1$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 72.9 (3F, s, CF_3), 118.6 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 3264 (N–H), 1653 (C=O), 1193 (C–F); MS *m/z*: 269, 267 (M^+), 248 ($M^+ - F$), 127 ($M^+ - CF_3CF$=CHCO + 1). Anal.: found: C, 44.92; H, 2.33; N, 5.19. $C_{10}H_6ClF_4NO$ requires: C, 44.88; H, 2.26; N, 5.23%.

Compound **3bh**: mp 130–132°C. ^{1}H NMR ($CDCl_3$) δ: 7.89 (1H, s, NH), 7.48 (2H, d, $J = 8.8$ Hz, ArH-2,6), 7.30 (2H, d, $J = 8.8$ Hz, ArH-3,5), 6.15 (1H, d, $J = 29.8$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 68.8 (2F, s, $ClCF_2$), 117.4 (1F, m, CF), 118.2 (2F, m, CF_2), 122.0 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3282 (N–H), 1702 (C=O), 1125–1189 (C–F); MS *m/z*: 387, 385, 383 (M^+), 127 [$M^+ - Cl(CF_2)_3CF$=CHCO + 1]. Anal.: found: C, 37.50; H, 1.67; N, 3.47. $C_{12}H_6Cl_2F_7NO$ requires: C, 37.53; H, 1.57; N, 3.65%.

Compound **3ch**: mp 111–112°C. ^{1}H NMR ($CDCl_3$) δ: 7.96 (1H, s, NH), 7.50 (2H, d, $J = 8.6$ Hz, ArH-2,6), 7.30 (2H, d, $J = 8.6$ Hz, ArH-3,5), 6.15 (1H, d, $J = 8.6$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.7 (3F, s, CF_3), 113.0 (1F, m, =CF), 117.5–125.2 (8F, m, $4CF_2$) ppm; IR ν_{max} (cm^{-1}): 3301 (N–H), 1701 (C=O), 1142–1203 (C–F); MS *m/z*: 469, 467 (M^+), 127 [$M^+ - CF_3(CF_2)_4CF$=CHCO + 1]. Anal.: found: C, 36.11; H, 1.49; N, 3.00. $C_{14}H_6ClF_{12}NO$ requires: C, 35.96; H, 1.29; N, 3.00%.

Compound **3ai**: mp 121–123°C. ^{1}H NMR ($CDCl_3$) δ: 7.93 (1H, s, NH), 7.39 (2H, d, $J = 8.4$ Hz, ArH-2,6), 7.12 (2H, d, $J = 8.4$ Hz, ArH-3,5), 6.08 (1H, d, $J = 32.7$ Hz, =CH), 2.32 (3H, s, CH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 72.2 (3F, s, CF_3), 119.3 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 3321 (N–H), 1648 (C=O), 1208 (C–F); MS *m/z*: 247 (M^+); 107 ($M^+ - CF_3CF$=CHCO + 1). Anal.: found: C, 53.52; H, 3.68; N, 5.69. $C_{11}H_9F_4NO$ requires: C, 53.45; H, 3.67; N, 5.67%.

Compound **3bi**: mp 115–117°C. ^{1}H NMR ($CDCl_3$) δ: 8.27 (1H, s, NH), 7.37 (2H, d, $J = 8.3$ Hz, ArH-2,6), 7.10 (2H, d, $J = 8.3$ Hz, ArH-3,5), 6.14 (1H, d, $J = 32.3$ Hz, =CH), 2.37 (3H, s, CH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 67.2 (2F, s, $ClCF_2$), 113.0 (1F, m, =CF), 116.5 (2F, m, CF_2), 120.4 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3287 (N–H), 1703 (C=O), 1129–1191 (C–F); MS *m/z*: 365, 363 (M^+), 107 [$M^+ - Cl(CF_2)_3$-CHCO + 1]. Anal.: found: C, 43.03; H, 2.49; N, 3.97. $C_{13}H_9ClF_7NO$ requires: C, 42.94; H, 2.49; N, 3.85%.

Compound **3ci**: mp 105–106°C. ^{1}H NMR ($CDCl_3$) δ: 7.98 (1H, s, NH), 7.40 (2H, d, $J = 8.2$ Hz, ArH-2,6), 7.12 (2H, d, $J = 8.2$ Hz, ArH-3,5), 6.15 (1H, d, $J = 32.9$ Hz, =CH), 2.32 (3H, s, CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 80.0 (3F, s, CF_3), 117.5 (1F, m, =CF), 122.0–125.7 (8F, m, $4CF_2$) ppm; IR ν_{max} (cm^{-1}): 3337 (N–H), 1702 (C=O), 1143–1200 (C–F); MS *m/z*: 447 (M^+), 107 [$M^+ - CF_3(CF_2)_4CF$=CHCO + 1]. Anal.: found: C, 40.60; H, 2.39; N, 3.48. $C_{15}H_9F_{12}NO$ requires: C, 40.29; H, 2.03; N, 3.13%.

Compound **3bj**: mp 152–153°C. ^{1}H NMR ($CDCl_3$) δ: 7.82 (1H, s, NH), 7.65 (2H, d, $J = 8.3$ Hz, ArH-2,6), 7.31 (2H, d, $J = 8.3$ Hz, ArH-3,5), 6.10 (1H, d, $J = 33.1$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 68.3 (2F, s, $ClCF_2$), 114.8 (1F, m, =CF), 118.0 (2F, m, CF_2), 121.8 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3313 (N–H), 1697 (C=O), 1124–1177 (C–F); MS *m/z*: 477, 475 (M^+), 219 [$M^+ - Cl(CF_2)_3CF$=CHCO + 1]. Anal.: found: C, 30.22; H, 1.47; N, 3.13. $C_{12}H_6ClF_7INO$ requires: C, 30.28; H, 1.27; N, 2.95%.

Compound **6b**: mp 133–135°C. ^{1}H NMR ($CDCl_3$) δ: 8.50 (1H, s, NH), 7.24–8.00 (7H, m, ArH), 6.31 (1H, d, $J = 33.1$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 66.8 (2F, s, $ClCF_2$), 113.8 (1F, m, CF), 116.6 (2F, m, CF_2), 120.2 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3272 (N–H), 1701 (C=O), 1547–1648 (ArH, C–H), 1129–1184 (C–F); MS *m/z*: 401, 399 (M^+), 143 [$M^+ - Cl(CF_2)_3CF$=CHCO + 1]. Anal.: found: C, 48.17; H, 2.38; N, 3.52. $C_{16}H_9ClF_7NO$ requires: C, 48.08; H, 2.27; N, 3.50%.

3.2. Preparation of 4-fluoroalkyl-2-quinolinols (5)

A typical procedure was as follows: a mixture of **3** (5 mmol), pyrrolidine (10 mmol) and CH_2Cl_2 (25 ml) was stirred under reflux for 1–2 h. Then the mixture was cooled to room temperature and 10 ml of 2N hydrochloride acid was added. The resulting mixture was stirred for 1 h at room temperature and separated. The organic layer was washed with water and saturated NaCl solution and dried over anhydrous sodium sulfate. Removal of CH_2Cl_2 gave the crude product of compound **4**, which was used directly in the next step without further purification.

The above crude product of **4** (1.0 g) and 20 g of PPA was heated with stirring at 165–170°C for 6–8 h. The mixture was cooled to room temperature, diluted with water, and neutralized to pH = 7. The resulting mixture was extracted with ether for three times. The combined etheral solution was washed with water and saturated NaCl solution, and dried over anhydrous sodium sulfate. Removal of the solvent followed by column chromatography using petroleum ether and ethyl acetate (5:1) as eluent gave compounds **5** as white solids.

Compound **5ad**: mp 215–216°C. ^{1}H NMR (CD_3COCD_3) δ: 7.35–7.82 (4H, m, ArH), 6.98 (1H, s, ArH-3), 3.34 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 63.3 (3F, s, CF_3) ppm; IR ν_{max} (cm^{-1}): 3431 (O–H), 1411–1671 (ArH, C–H), 1262 (C–F), 1127 (C–O); MS *m/z*: 213 (M^+). Anal.: found: C, 56.12; H, 2.88; N, 6.46. $C_{10}H_6F_3NO$ requires: C, 56.35; H, 2.84; N, 6.57%.

Compound **5bd**: mp 180–181°C. ^{1}H NMR (CD_3COCD_3) δ: 7.50–8.42 (4H, m, ArH), 6.86 (1H, s, ArH), 2.65 (1H, s, OH) ppm. ^{19}F NMR (CD_3COCD_3) δ: 67.8 (2F, s, $ClCF_2$), 113.5 (2F, s, $ArCF_2$), 121.1 (2F, s, CF_2) ppm; IR ν_{max} (cm^{-1}): 3360 (O–H), 1470–1640 (ArH, C–H), 1120–1200 (C–F); MS *m/z*: 331, 329 (M^+), 294 ($M^+ - Cl$), 194. Anal.: found: C, 43.91; H, 2.02; N, 4.29. $C_{12}H_6ClF_6NO$ requires: C, 43.73; H, 1.83; N, 4.25%.

Compound **5cd**: mp 201–202°C. ^{1}H NMR (CD_3COCD_3) δ: 7.66–8.42 (4H, m, ArH), 7.10 (1H, s, ArH-3), 3.07 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 81.8 (3F, s, CF_3), 114.0 (2F, s, $ArCF_2$), 122.6–126.9 (6F, m, $3CF_2$) ppm; IR ν_{max} (cm^{-1}): 3400 (O–H), 1439–1630 (ArH, C–H), 1185–1230 (C–F); MS *m/z*: 413 (M^+), 394 ($M^+ - F$), 194. Anal.: found: C, 40.74; H, 1.66; N, 3.18. $C_{15}H_6F_{12}NO$ requires: C, 40.29; H, 2.03; N, 3.13%.

Compound **5ae**: mp 201–203°C. ^{1}H NMR (CD_3COCD_3) δ: 7.96–8.42 (3H, m, ArH), 7.17 (1H, s, ArH-3), 3.56 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 62.3 (3F, s, CF_3) ppm; IR ν_{max} (cm^{-1}): 3435 (O–H), 1467–1611 (ArH, C–H), 1196 (C–F), 1150 (C–O); MS *m/z*: 293, 291 (M^+). Anal.: found: C, 41.50; H, 2.02; N, 4.61. $C_{10}H_5BrF_3NO$ requires: C, 41.12; H, 1.72; N, 4.80%.

Compound **5be**: mp 210–212°C. ^{1}H NMR (CD_3SOCD_3) δ: 7.86–8.31 (3H, m, ArH), 7.00 (1H, s, ArH-3), 2.95 (1H, s, OH) ppm; ^{19}F NMR (CD_3SOCD_3) δ: 67.8 (2F, s, $ClCF_2$), 113.7 (2F, s, $ArCF_2$), 121.3 (2F, s, CF_2) ppm. IR ν_{max} (cm^{-1}): 3350 (O–H), 1455–1620 (ArH, C–H), 1100–1160 (C–F); MS *m/z*: 412, 410, 408 (M^+). Anal.: found: C, 35.33; H, 1.34; N, 3.43. $C_{12}H_5BrClF_6NO$ requires: C, 35.28; H, 1.23; N, 3.43%.

Compound **5ce**: mp 215–217°C. ^{1}H NMR (CD_3COCD_3) δ: 7.99–8.46 (3H, m, ArH), 7.36 (1H, s, ArH-3), 2.93 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 81.7 (3F, s, CF_3), 114.1 (2F, s, $ArCF_2$), 122.8 (4F, m, $2CF_2$), 127.1 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3300 (O–H), 1460–1620 (ArH, C–H), 1130–1220 (C–F); MS *m/z*: 493, 491 (M^+). Anal.: found: C, 36.14; H, 1.79; N, 2.83. $C_{14}H_5BrF_{11}NO$ requires: C, 36.17; H, 1.62; N, 2.85%.

Compound **5af**: mp 193–194°C. ^{1}H NMR (CD_3SOCD_3) δ: 7.60 (1H, d, $J = 8.2$ Hz, ArH-5), 7.23 (1H, s, ArH-8), 7.14 (1H, d, $J = 8.2$ Hz, ArH-6), 6.90 (1H, s, ArH-3), 3.41 (1H, s, OH), 2.42 (3H, s, CH_3) ppm; ^{19}F NMR (CD_3SOCD_3) δ: 61.7 (3F, s, CF_3) ppm; IR ν_{max} (cm^{-1}): 3425 (O–H), 1421–1677 (ArH, C–H), 1188 (C–F); MS *m/z*: 227 (M^+). Anal.: found: C, 58.33; H, 3.58; N, 5.99. $C_{11}H_8F_3NO$ requires: C, 58.16; H, 3.55; N, 6.17%.

Compound **5bf**: mp 195–196°C. ^{1}H NMR (CD_3COCD_3) δ: 7.75 (1H, d, $J = 8.5$ Hz, ArH-5), 7.32 (1H, s, ArH-8), 7.18 (1H, d, $J = 8.5$ Hz, ArH-6), 6.86 (1H, s, ArH-3), 2.93 (1H, s, OH), 2.46 (3H, s, CH_3) ppm; ^{19}F NMR (CD_3COCD_3) δ: 86.1 (2F, s, $ClCF_2$), 107.8 (2F, s, $ArCF_2$), 119.5 (2F, s, CF_2) ppm; IR ν_{max} (cm^{-1}): 3350 (O–H), 1620–1685 (ArH, C–H), 1100–1210 (C–F); MS *m/z*: 345, 343 (M^+). Anal.: found: C, 45.58; H, 2.50; N, 4.32. $C_{13}H_8ClF_6NO$ requires: C, 45.44; H, 2.35; N, 4.08%.

Compound **5cf**: mp 190–191°C. ^{1}H NMR (CD_3COCD_3) δ: 8.24 (1H, d, $J = 8.8$ Hz, ArH-5), 7.92 (1H, s, ArH-8), 7.56 (1H, d, $J = 8.8$ Hz, ArH-6), 7.25 (1H, s, ArH-3), 2.95 (1H, s, OH), 2.55 (3H, s, CH_3) ppm; ^{19}F NMR (CD_3COCD_3) δ: 81.5 (3F, s, CF_3), 108.9 (2F, s, $ArCF_2$), 117.4–120.8 (6F, m, $3CF_2$) ppm; IR ν_{max} (cm^{-1}): 3400 (O–H), 1525–1630 (ArH, C–H), 1125–1230 (C–F); MS *m/z*: 427 (M^+), 408 ($M^+ - F$). Anal.: found: C, 42.83; H, 2.24; N, 3.30. $C_{15}H_8F_{11}NO$ requires: C, 42.67; H, 1.89; N, 3.28%.

Compound **5bg**: mp 250–252°C. ^{1}H NMR (CD_3COCD_3) δ: 8.32 (1H, d, $J = 8.0$ Hz, ArH-5), 8.08 (1H, s, ArH-8), 7.74 (1H, d, $J = 8.0$ Hz, ArH-6), 7.36 (1H, s, ArH-3), 3.15 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 66.7 (2F, s, $ClCF_2$), 113.0 (2F, s, $ArCF_2$), 120.9 (2F, s, CF_2) ppm; IR ν_{max} (cm^{-1}): 3350 (O–H), 1450–1635 (ArH, C–H), 1110–1185 (C–F); MS *m/z*: 367, 365, 363 (M^+). Anal.: found: C, 39.07; H, 1.90; N, 3.38. $C_{12}H_5Cl_2F_6NO$ requires: C, 39.39; H, 1.88; N, 3.35%.

Compound **5ah**: mp 189–190°C. ^{1}H NMR (CD_3COCD_3) δ: 7.35–7.64 (3H, m, ArH), 7.05 (1H, s, ArH-3), 3.14 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 63.9 (3F, s, CF_3) ppm; IR ν_{max} (cm^{-1}): 3441 (O–H), 1432–1614 (ArH, C–H), 1176 (C–F), 1140 (C–O); MS *m/z*: 249, 247 (M^+). Anal.: found: C, 48.44; H, 2.16; N, 5.49. $C_{10}H_5ClF_3NO$ requires: C, 48.51; H, 2.04; N, 5.66%.

Compound **5bh**: mp 238–240°C. ^{1}H NMR (CD_3COCD_3) δ: 8.26 (1H, s, ArH-5), 8.05 (1H, d, $J = 9.0$ Hz, ArH-8), 7.85 (1H, d, $J = 9.0$ Hz, ArH-7), 7.24 (1H, s, ArH-3), 3.46 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 67.2 (2F, s, $ClCF_2$), 112.9 (2F, s, $ArCF_2$), 120.4 (2F, s, CF_2) ppm; IR ν_{max} (cm^{-1}): 3400 (O–H), 1460–1635 (ArH, C–H), 1110–1195 (C–F); MS *m/z*: 367, 365, 363 (M^+). Anal.: found: C, 39.61; H, 1.51; N, 3.80. $C_{12}H_5Cl_2F_6NO$ requires: C, 39.59; H, 1.38; N, 3.85%.

Compound **5ch**: mp 250–252°C. ^{1}H NMR (CD_3COCD_3) δ: 8.27 (1H, s, ArH-5), 8.08 (1H, d, $J = 8.9$ Hz, ArH-8), 7.88 (1H, d, $J = 8.9$ Hz, ArH-7), 7.33 (1H, s, ArH-3), 3.10 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 81.3 (3F, s, CF_3), 113.8 (2F, s, $ArCF_2$), 122.3–127.0 (6F, m, $3CF_2$) ppm; IR ν_{max} (cm^{-1}): 3350 (O–H), 1490–1600 (ArH, C–H), 1110–1180 (C–F); MS *m/z*: 449, 447 (M^+). Anal.: found: C, 38.44; H, 1.48; N, 3.10. $C_{14}H_5ClF_{11}NO$ requires: C, 38.56; H, 1.13; N, 3.13%.

Compound **5ai**: mp 205–206.5°C. ^{1}H NMR (CD_3SOCD_3) δ: 7.32–7.47 (3H, m, ArH), 6.93 (1H, s, ArH-3), 3.34 (1H, s, OH), 2.36 (3H, s, CH_3) ppm; ^{19}F NMR (CD_3SOCD_3) δ: 61.7 (3F, s, CF_3) ppm; IR ν_{max} (cm^{-1}): 3439 (O–H), 1435–1677 (ArH, C–H), 1267 (C–F), 1126 (C–O); MS *m/z*: 227 (M^+). Anal.: found: C, 58.36; H, 3.54; N, 5.89. $C_{11}H_8F_3NO$ requires: C, 58.16; H, 3.55; N, 6.17%.

Compound **5bi**: mp 205–206°C. ^{1}H NMR (CD_3COCD_3) δ: 8.10 (1H, s, ArH), 7.95 (1H, d, $J = 8.6$ Hz, ArH), 7.75 (1H, d, $J = 8.6$ Hz, ArH), 7.27 (1H, s, ArH), 3.62 (1H, s, OH), 2.60 (3H, s, CH_3) ppm; ^{19}F NMR (CD_3COCD_3) δ: 67.8 (2F, s, CF_2Cl), 113.1 (2F, s, $ArCF_2$), 120.9 (2F, s, CF_2) ppm; IR ν_{max} (cm^{-1}): 3400 (O–H), 1595–1680 (ArH, C–H), 1100–1180 (C–F); MS *m/z*: 345, 343 (M^+). Anal.: found: C, 45.78; H, 2.37; N, 4.18. $C_{13}H_8ClF_6NO$ requires: C, 45.44; H, 2.35; N, 4.08%.

Compound **5ci**: mp 210–212°C. ^{1}H NMR (CD_3COCD_3) δ: 8.07 (1H, s, ArH-5), 7.92 (1H, d, $J = 8.4$ Hz, ArH-8), 7.72 (1H, d, $J = 8.4$ Hz, ArH-7), 7.25 (1H, s, ArH-3), 2.65 (1H, s, OH), 2.56 (3H, s, CH_3) ppm; ^{19}F NMR (CD_3COCD_3) δ: 81.3 (3F, s, CF_3), 113.5 (2F, s, $ArCF_2$), 122.4 (4F, m, $2CF_2$), 126.6 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 3350 (O–H), 1500–1600 (ArH, C–H), 1130–1225 (C–F); MS *m/z*: 427 (M^+), 408 ($M^+ - F$). Anal.: found: C, 42.23; H, 2.11; N, 3.25. $C_{15}H_8F_{11}NO$ requires: C, 42.17; H, 1.89; N, 3.28%.

Compound **5bj**: mp 216–218°C. ^{1}H NMR (CD_3COCD_3) δ: 8.68 (1H, s, ArH-5), 8.14 (1H, d, $J = 7.0$ Hz, ArH-8), 7.85 (1H, d, $J = 7.0$ Hz, ArH-7), 7.15 (1H, s, ArH-3), 3.57 (1H, s, OH) ppm. ^{19}F NMR (CD_3COCD_3) δ: 67.5 (2F, s, $ClCF_2$), 113.4 (2F, s, $ArCF_2$), 120.8 (2F, s, CF_2) ppm; IR ν_{max} (cm^{-1}): 3350 (O–H), 1460–1625 (ArH, C–H), 1110–1180 (C–F); MS *m/z*: 457, 455 (M^+), 420 ($M^+ - Cl$), 320 ($M^+ - ClCF_2CF_2$). Anal.: found: C, 31.60; H, 1.33; N, 3.12. $C_{12}H_5ClF_6INO$ requires: C, 31.64; H, 1.11; N, 3.07%.

Compound **7b**: mp 240–242°C. ^{1}H NMR (CD_3COCD_3) δ: 9.25 (1H, m, ArH), 7.42–8.26 (6H, m, ArH), 3.00 (1H, s, OH) ppm; ^{19}F NMR (CD_3COCD_3) δ: 67.5 (2F, s, $ClCF_2$), 112.4 (2F, s, $ArCF_2$), 120.6 (2F, s, CF_2) ppm; IR ν_{max} (cm^{-1}): 3400 (O–H), 1520–1620 (ArH, C–H), 1115–1170 (C–F); MS *m/z*: 381, 379 (M^+), 360 ($M^+ - F$). Anal.: found: C, 50.94; H, 2.33; N, 3.73. $C_{16}H_8ClF_6NO$ requires: C, 50.61; H, 2.12; N, 3.69%.

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