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A Novel Synthesis of 2-Fluoroalkyl Quinolines

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Summary. 2-Fluoroalkyl quinolines are prepared by reacting aniline with α-fluoroalkyl aldehydes or α-fluoroalkyl cyclohexanones in the presence of acetic acid. Under the same reaction condition, 2-aminophenol gives the corresponding 2-fluoroalkyl-8-quinolinols; in some cases, 2-fluoroalkyl benzoxazoles are also formed as minor products.

Keywords. α-Fluoroalkyl aldehyde; α-Fluoroalkyl cyclohexanone; Aniline; 2-Fluoroalkyl quinoline; 2-Fluoroalkyl benzoxazole; Acetic acid.

Eine neue Synthese von 2-Fluoralkylchinolinen

Zusammenfassung. 2-Fluoralkylchinoline werden durch Reaktion von Anilin mit α-Fluoraldehyden oder α-Fluorcyclohexanonen in Gegenwart von Essigsäure dargestellt. Unter denselben Reaktionsbedingungen gibt 2-Aminophenol die entsprechenden 2-Fluoralkyl-8-chinolinole; in manchen Fällen werden 2-Fluoralkylbenzoxazole als Nebenprodukte gebildet.

Introduction

The incorporation of a fluorine atom or a fluoroalkyl group into quinoline and its derivatives is of considerable importance due to the biological activities of the resulting products [1]. Various methods have been reported for the synthesis of these compounds, such as the electrochemical process of introducing -CF_3 into quinolines [2] and the cyclization of fluorine-containing building blocks [3, 4]. Recently, *Linderman et al*. have reported the synthesis of 2-trifluoromethyl quinoline from the reaction of EtOH=CHCOCF_3 with aniline followed by treatment with PCl_3 [5]. During our studies on α-fluoroalkyl aldehydes [6] we have found that these compounds readily react with ethylenediamine to afford 5-fluoralkyl-1,4-diazepines [7]. In continuation, of our work on fluorinated aldehydes and fluorinated cyclohexanones [8] we recently found that they can be reacted with aniline and its derivatives to yield 2-fluoroalkyl substituted quinolines. Here we wish to report these results.

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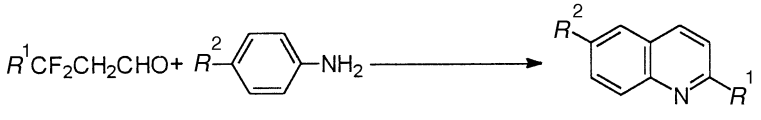
Results and Discussion

α-Fluoroalkyl aldehydes of the type R^1 CF_2CH_2CHO (**1**) which can be prepared by treatment of R^1CF_2X with $EtOCH{=}CH_2$ were mixed with two mole equivalents aniline and refluxed in acetic acid for 8 h to afford the 2-fluoralkyl quinolines **3** in about 60% yield (Scheme 1).

The fluoroalkyl group in **3** is located at position 2 as deduced by comparison of the ^{13}C NMR chemical shifts with reported values [5]. The influence of the substituent on the aromatic ring of aniline is evident; 4-methyl-or 4-hydroxyaniline react smoothly with **1a** to from the desired products, whereas 4-nitroaniline or 4-aminobenzoic acid did not. Even under higher reaction temperature and longer reaction time no reaction occurred. The length of the fluoroalkyl chain and the presence of chlorine or bromine in ω-position showed little effect on the reaction, and all substrates afforded products **3** in nearly equal yield. Acetic acid proved to be the best solvent. Other solvents such as ethanol, acetonitrile, *THF*, and 1,4-dioxane gave complex mixtures.

3,3-Dihalo-4,4,4-trifluorobutylaldehyde (CF_3CXYCH_2CHO, **4**), formed by treatment of the corresponding fluoro-halo ethane CF_3CXY_2 with ethyl vinyl ether, reacted with aniline in the same way as **1**. All educts resulted in product **3a** as shown in Scheme 2.



1a-e

	R^1
a	CF_3
b	$ClCF_2$
c	$BrCF_2$
d	$Cl(CF_2)_3$
e	$CF_3(CF_2)_4$

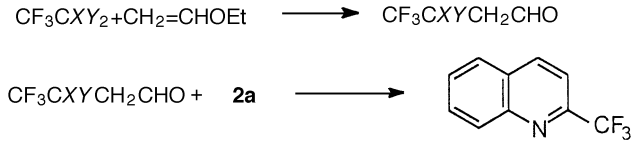
2a-c

	R^2
a	H
b	OH
c	CH_3

3

	R^1	R^2
a	CF_3	H
b	CF_3	OH
c	CF_3	CH_3
d	$ClCF_2$	H
e	$BrCF_2$	H
f	$Cl(CF_2)_3$	H
g	$CF_3(CF_2)_4$	H

Scheme 1

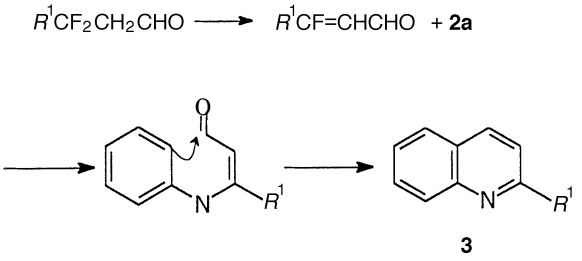


4a-c

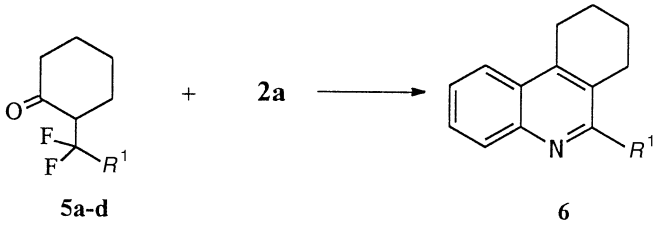
	X	Y
a	F	Br
b	Cl	Cl
c	Br	Br

3a

Scheme 2



Scheme 3



	R^1
a	CF_3
b	$ClCF_2$
c	$Cl(CF_2)_3$
d	$CF_3(CF_2)_4$

Scheme 4

A possible reaction pathway for the formation of **3** might be formulated as displayed in Scheme 3. It was found that α-fluoroalkyl cyclohexanones undergo a similar reaction with aniline to afford 2-fluoroalkyl-3,4-cyclohexa-quinolines (Scheme 4).

Products **6** are solids and easy to crystallize from C_6H_6:$CHCl_3 = 1{:}1$. Their structures were fully characterized by spectroscopic data, elemental analyses, and an X-ray diffraction analysis of compound **6a** (Fig. 1).

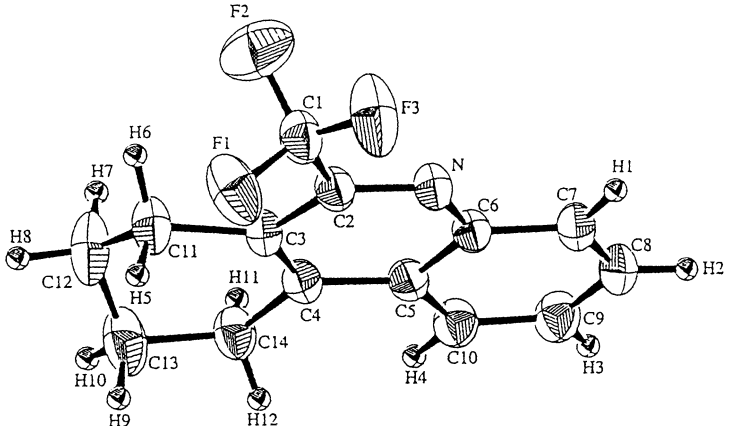


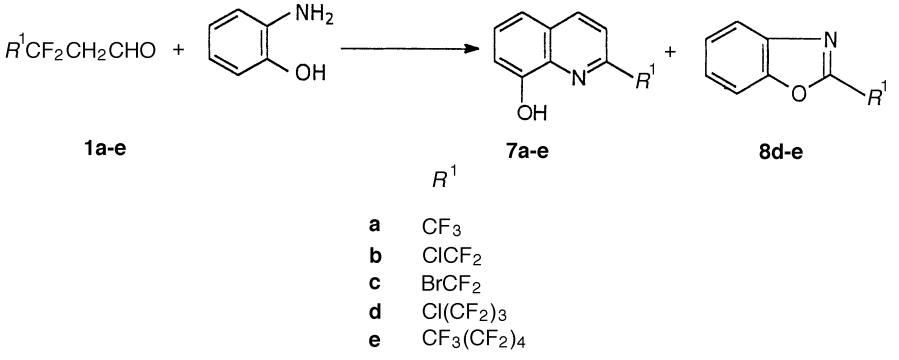
Fig. 1. The structure of compound

Table 1. Selected bond lengths (Å) and bond angles (°) of compound **6a**

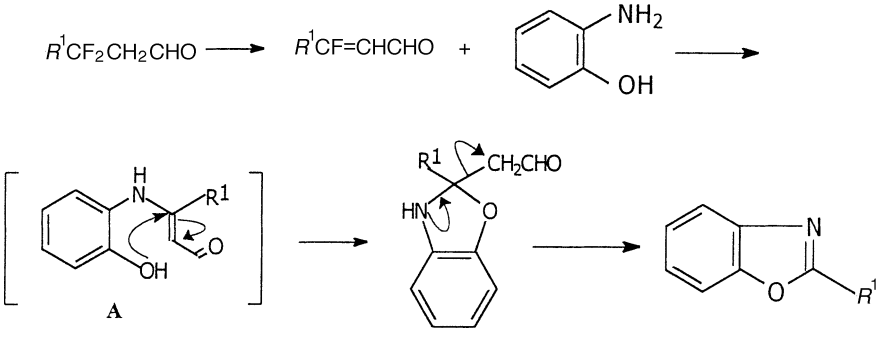
Bond lengths		Bond angles	
C(2)–N	1.311(3)	C(2)–N–C(6)	117.2(2)
C(6)–N	1.369(3)	C(4)–C(5)–C(6)	118.9(2)
C(1)–C(2)	1.510(4)	C(2)–C(3)–C(4)	117.0(2)
C(2)–C(3)	1.422(3)	C(4)–C(3)–C(11)	121.6(2)
C(4)–C(5)	1.428(3)	N–C(2)–C(1)	112.8(2)
C(3)–C(11)	1.517(4)	N–C(2)–C(3)	126.1(2)
C(5)–C(6)	1.414(3)	N–C(6)–C(5)	121.8(2)
C(3)–C(4)	1.377(4)	N–C(6)–C(7)	117.6(2)

In the case a fluoroalkyl ester was used, the corresponding 2-fluoroalkyl-4-*o*-methyl substituted quinoline derivatives could not be obtained.

As discussed above, 4-aminophenol reacted with **1a** to afford 2-trifluoromethyl-6-hydroxy-quinolines. 2-Aminophenol behaved similarly when reacted with **1a–c** to yield the corresponding 2-fluoroalkyl-8-quinolines which are of interest due to their bioactivity. However, to our knowledge only one patent [9] is concerned with their synthesis so far. It seems noteworthy that when 2-aminophenol was treated with aldehydes **1d** or **1e**, whose fluoroalkyl chain is longer, two products were formed. In addition to the quinolines **7**, 2-fluoroalkyl-benzoxazoles **8** were obtained as byproducts (Scheme 5). The formation of **8** could be attributed to an



Scheme 5



Scheme 6

attack of the -OH group on the olefinic carbon atom of intermediate **A** (Scheme 6). However, no attempts have been undertaken to explain why the reaction of 2-aminophenol with **1a–c** did not give the corresponding benzoxazoles **8** with $R^1 = CF_2X (X = F, Cl, Br)$. The reactions of **1** with *o*-phenylenediamine or 2-aminothiophenol will be published elsewhere.

Experimental

All melting points uncorrected. IR spectra were measured with a Shimadzu IR-440 spectrometer (KBr pellets for solids, films for liquids). ^{1}H NMR spectra were recorded at 90 and 300 MHz ^{13}C NMR spectra at 75.6 MHz on JEOL FX-90Q and Bruker AM 300 instruments, respectively using *TMS* as internal standard and $CDCl_3$ as solvent unless otherwise noted. ^{19}F NMR spectra were recorded on a Varian EM-360L spectrometer at 56.4 MHz using *TFA* as external standard and $CDCl_3$ as solvent unless otherwise noted (positive values for upfield shifts). MS and HRMS: Finnigan GC-MS-4021 spectrometer; elemental analyses: Elemental Analysis Group of SIOC. The results (C, H, N, F) were in good agreement with the calculated values.

General procedure for the preparation of 2-fluoroalkyl-substituted quinolines

Compound **1a** (10 mmol) and aniline (20 mmol) were dissolved in 40 cm^3 acetic acid. After refluxing at 120°C for 8 h the mixture was cooled, poured into 50 cm^3 ice water, and extracted with diethyl ether (3×40 cm^3). The organic extracts were combined, washed with aq. $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed by distillation and the crude product was further purified by flash chromatography using petroleum ether (b.p.: 60–90°C) and ethyl acetate as eluents (10:1 by volume).

General procedure for the preparation of 2-fluoroalkyl-benzoxazoles and 2-fluoroalkyl-8-hydroxyquinolines

A mixture of 2.8 g **1d** (10 mmol), 2.2 g *o*-hydroxylaniline (20 mmol), and 20 cm^3 acetic acid was refluxed for 6 h. The reaction mixture was poured into a 150 ml beaker containing 50 cm^3 ice water and extracted with ether (3×30 cm^3). The organic layer was washed with $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was removed by distillation, and the crude product was further purified by flash chromatography using petroleum ether (b.p.: 60–90°C) and ethyl acetate as eluents (10:1 by volume) to give **7d** (1.5 g) and **8d** (0.4 g).

2-Trifluoromethyl-quinoline (**3a**; $C_{10}H_6F_3N$)

Yield: 60%; m.p.: 55–56°C; ^{1}H NMR (CD_3COCD_3, δ, 300 MHz): 8.34 (d, $J = 8.5$ Hz, 1H), 8.23 (d, $J = 8.5$ Hz, 1H), 7.90 (d, $J = 8.3$ Hz, 1H), 7.82 (t, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.67 (t, $J = 8.0$ Hz, 1H) ppm; ^{13}C NMR (CD_3COCD_3, δ, 75 MHz): 147.58, (q, $^2J_{CF} = 0.4$ Hz), 147.25, 138.16, 130.87, 130.18, 128.93, 128.65, 127.73, 121.65 (q, $^1J_{CF} = 3.7$ Hz), 116.82 ppm; ^{19}F NMR (CD_3COCD_3, δ, 54.6 MHz): −10.0 (s, CF_3) ppm; IR $\nu = 3060$, 1620, 1599, 1573, 1566, 1510, 1479, 1434, 1379, 1344, 1299, 1251, 1216, 1175, 1120, 1087 cm^{-1}; MS: m/z (%) = 197 (M^+, 100), 178 (M^+-F, 9.56), 128 (M^+-CF_3, 49); HRMS: calc. for $C_{10}H_6F_3N$: 197.0453, found: 197.0458.

2-Trifluoromethyl-6-hydroxylquinoline (**3b**; $C_{10}H_6F_3NO$)

Yield: 75%; m.p.: 47–49°C; ^{1}H NMR (CD_3COCD_3, δ, 300 MHz): 8.39 (d, $J = 8.7$ Hz, 1H), 8.06 (d, $J = 9.2$ Hz, 1H), 7.77 (d, $J = 8.6$ Hz, 1H), 7.56 (dd, $J_1 = 9.2$ Hz, $J_2 = 2.7$ Hz, 1H), 7.25 (d, $J = 2.7$ Hz,

1H) ppm; ^{19}F NMR (CD_3COCD_3, δ, 54.6 MHz): −9.0 (s, CF_3) ppm; IR: $\nu = 3107$, 1622, 1527, 1481, 1436, 1398, 1352, 1328, 1304, 1231, 1184, 1154, 1127, 1095 cm^{-1}; MS: *m/z* (%) = 213 (M^+, 100), 194 (M^+-F, 9.07).

2-Trifluoromethyl-6-methylquinoline (**3c**; $C_{11}H_8F_3N$)

Yield: 62%; oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.22 (d, $J = 8.5$ Hz, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 7.67 (d, $J = 8.5$ Hz, 1H), 7.63 (m, 2H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): −9.7 (s, CF_3) ppm; IR: $\nu = 1504$, 1348, 1339, 1307, 1195, 1132, 1117, 1087, cm^{-1}; MS: *m/z* (%) = 211 (M^+, 100), 191 (M^+-1-F, 9.07), 142 (M^+-CF_3, 24.46).

2-Chlorodifluoromethyl-quinoline (**3d**; $C_{10}H_6F_2NCl$)

Yield: 62%; m.p.: 27–29°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.33 (d, $J = 8.5$ Hz, 1H), 8.22 (d, $J = 8.5$ Hz, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.81 (t, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 7.66 (t, $J = 8.0$ Hz, 1H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): −23.5 (s, CF_2Cl) ppm; IR: $\nu = 3064$, 1948, 1836, 1637, 1619, 1596, 1568, 1506, 1496, 1431, 1378, 1348, 1309, 1290, 1273, 1245, 1207, 1125, 1070, 1017 cm^{-1}; MS: *m/z* (%) = 213 (M^+, 50.98), 178 (M^+-Cl, 100), 128 (M^+-CF_2Cl, 48.09); HRMS: calc. for $^{35}ClC_{10}H_6F_2N$: 213.0157, found: 213.0157.

2-Bromodifluoromethyl-quinoline (**3e**; $C_{10}H_6F_2NBr$)

Yield: 58%; m.p.: 30–32°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.33 (d, $J = 8.5$ Hz, 1H), 8.22 (d, $J = 8.5$ Hz, 1H), 7.90 (d, $J = 8.3$ Hz, 1H), 7.81 (t, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 7.66 (t, $J = 8.0$ Hz, 1H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): −27.5 (s, CF_2Br) ppm; IR: $\nu = 1618$, 1595, 1504, 1467, 1430, 1376, 1346, 1309, 1291, 1268, 1247, 1214, 1148, 1127, 1081, 1017 cm^{-1}; MS: *m/z*(%) = 259 (5.13), 257 (5.33), 178 (M^+-Br, 100), 128 (M^+-CF_2Br, 34.59); HRMS: calc. for $^{79}BrC_{10}H_6F_2N$: 256.9652, found: 256.9654.

2-(1,1,2,2,3,3-Hexafluoro-3-chloropropyl)-quinoline (**3f**; $C_{12}H_6F_6NCl$)

Yield: 64%; m.p.: 38–39°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.33 (d, $J = 8.5$ Hz, 1H), 8.25 (d, $J = 8.5$ Hz, 1H), 7.90 (d, $J = 8.3$ Hz, 1H), 7.82 (t, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 7.69 (t, $J = 8.0$ Hz, 1H) ppm; ^{19}F NMR ($CDCl_3$, 54.6 MHz): −10.7 (s, CF_2Cl), 35.3 (m, CF_2), 42.6 (m, CF_2) ppm; IR: $\nu = 3060$, 1622, 1597, 1573, 1508, 1475, 1432, 1378, 1318, 1301, 1254, 1191, 1134, 1118, 1010 cm^{-1}; MS: *m/z* (%) = 313 (M^+, 13.34), 278 (M^+-Cl, 6.83), 178 (M^+-C_2F_4Cl, 100), 128 (M^+-C_3F_6Cl, 53.46); HRMS: calc. for $^{35}ClC_{12}H_6F_6N$: 313.0093, found: 313.0092.

2-Perfluoroheptyl-quinoline (**3g**; $C_{14}H_6F_{11}N$)

Yield: 65%; m.p.: 43–44°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.35 (d, $J = 8.5$ Hz, 1H), 8.26 (d, $J = 8.5$ Hz, 1H), 7.91 (d, $J = 8.3$ Hz, 1H), 7.83 (t, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.68 (t, $J = 8.0$ Hz, 1H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): 3.5 (s, 3F), 36.2 (m, 2F), 44.7 (m, 4F), 49.0 (m, 2F) ppm; IR: $\nu = 3057$, 3028, 1599, 1573, 1509, 1472, 1434, 1363, 1317, 1296, 1242, 1205, 1189, 1162, 1138, 1109, 1091 cm^{-1}; MS: *m/z* (%) = 397 (M^+, 33.77), 378 (M^+-F, 6.83), 178 (M^+-C_4F_9, 100), 128 (M^+-C_5F_{11}, 35.54).

7,8,9,10-Tetrahydro-6-trifluoromethylphenanthridine (**6a**; $C_{14}H_{12}F_3N$)

Yield: 66%; m.p.: 116–117°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.13 (d, $J = 8.5$ Hz, 1H), 7.94 (d, $J = 8.5$ Hz, 1H), 7.70 (t, $J = 7.5$ Hz, 1H), 7. (t, $J = 7.5$ Hz, 1H), 3.17 (t, $J = 6.0$ Hz, 2H), 3.03 (t,

$J = 6.0$ Hz, 2H), 1.92 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 146.31 (q, $^2J_{CF} = 0.4$ Hz), 144.71, 144.09, 130.67, 129.14, 128.38, 127.45, 122.56, 122.36 (q, $^1J_{CF} = 3.7$ Hz), 25.95, 24.96, 22.01, 21.75 ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): -12.0 (s, CF_3) ppm; IR: $\nu = 2952$, 2877, 1571, 1501, 1462, 1434, 1369, 1360, 1341, 1325, 1289, 1252, 1192, 1174, 1157, 1126, 1096, 1078 cm^{-1}; MS: *m/z* (%) = 251 (M^+, 100), 232 (M^+-F, 5.30), 182 (M^+-CF_3, 14.05); X-ray data: triclinic, $a = 8.261(2)$, $b = 10.358(2)$, $c = 7.452(3)$ Å, $\alpha = 98.02(2)$, $\beta = 114.83(2)$, $\gamma = 84.42(2)^\circ$, $V = 572.5(3)$ Å^3, $D_c = 1.46$ g/cm^3; crystal dimensions: $0.20 \times 0.20 \times 0.40$ mm. Data were measured at 293 K on a Rigaku AFC7R diffractomer with graphite monochromated MoK_α radiation and a 12 kW rotating anode generator.

7,8,9,10-Tetrahydro-6-chlorodifluoromethylphenanthridine (**6b**; $C_{14}H_{12}ClF_2N$)

Yield: 68%; m.p.: 102–104°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.15 (d, $J = 8.5$ Hz, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.71 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 3.21 (t, $J = 6.0$ Hz, 2H), 3.13 (t, $J = 6.0$ Hz, 2H), 1.95 (m, 4H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): -25.0 (s, CF_2Cl) ppm; IR: $\nu = 2954$, 2870, 1579, 1568, 1499, 1459, 1431, 1380, 1367, 1346, 1335, 1317, 1284, 1245, 1188, 1149, 1133, 1094, 1085, 1078, 1029 cm^{-1}; MS: *m/z* (%) = 267 (M^+, 82.47), 232 (M^+-Cl, 100).

7,8,9,10-Tetrahydro-6-(1,1,2,2,3,3-hexafluoro-3-chloropropyl)-phenanthridine (**6c**; $C_{16}H_{12}F_6NCl$)

Yield: 68%; m.p.: 50–52°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.14 (d, $J = 8.5$ Hz, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 8.0$ Hz, 1H), 3.21 (t, $J = 6.0$ Hz, 2H), 3.06 (t, $J = 6.0$ Hz, 2H), 1.89 (m, 4H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): -11.5 (s, CF_2Cl), 28.3 (m, CF_2), 40.5 (m, CF_2) ppm; IR: $\nu = 2950$, 2926, 2864, 1828, 1616, 1574, 1498, 1459, 1450, 1437, 1425, 1413, 1366, 1343, 1318, 1290, 1241, 1191, 1181, 1159, 1143, 1126, 1114, 1084, 1038, 1013 cm^{-1}; MS: *m/z* (%) = 367 (M^+, 100), 339 (M^+-C_2H_4, 41.07), 332(M^+-Cl, 23.19), 232 (M^+-C_2F_4Cl, 95.88); HRMS: calc. for $^{35}ClC_{16}H_{12}F_6N$: 367.0563, found: 367.0565.

7,8,9,10-Tetrahydro-6-perfluoropentyl-phenanthridine (**6d**; $C_{16}H_{12}F_6NCl$)

Yield: 64%; m.p.: 36–37°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.12 (d, $J = 8.5$ Hz, 1H), 7.98 (d, $J = 8.5$ Hz, 1H), 7.71 (t, $J = 7.5$ Hz, 1H), 7.63 (t, $J = 7.5$ Hz, 1H), 3.22 (t, $J = 6.0$ Hz, 2H), 3.08 (t, $J = 6.0$ Hz, 2H), 1.93 (m, 4H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): 3.2 (s, 3F), 28.9 (m, 2F), 41.8 (m, 2F), 43.0 (m, 2F), 48.7 (m, 2F) ppm; IR: $\nu = 2957$, 2878, 1575, 1503, 1464, 1440, 1352, 1322, 1297, 1286, 1236, 1202, 1161, 1149, 1133, 1087, 1077, 1066, 1016 cm^{-1}; MS: *m/z* (%) = 451 (M^+, 100), 432 (M^+-F, 21.34), 423 (M^+-C_2H_4, 25.53), 232 (M^+-C_4F_9, 86.93); HRMS: calc. for $C_{18}H_{12}F_{11}N$: 451.0795, found: 451.0764.

2-Trifluoromethyl-8-hydroxy-quinoline (**7a**; $C_{10}H_6F_3NO$)

Yield: 60%; m.p.: 40–42°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.29 (d, $J = 8.6$ Hz, 1H), 7.71, (d, $J = 8.6$ Hz, 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.25 (d, $J = 7.6$ Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 145.76 (q, $^2J_{CF} = 0.4$ Hz), 145.52, 138.24, 137.21, 130.14, 129.30, 121.53 (q, $^1J_{CF} = 3.7$ Hz), 117.91, 117.49, 111.61 ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): -10.0 (s, CF_3) ppm; IR: $\nu = 3230$, 2966, 1629, 1556, 1469, 1450, 1262, 1096, 1027 cm^{-1}; MS: *m/z* = 213 (M^+, 73.57), 194 (M^+-F, 11.08), 165 (M^++1-CF_3, 100); HRMS: calc. for $C_{10}H_6F_3NO$: 213.0404, found: 213.0386.

2-Chlorodifluoromethyl-8-hydroxy-quinoline (**7b**; $C_{10}H_6F_2NOCl$)

Yield: 62%; m.p.: 46–48°C; ^{1}H NMR (CD_3COCD_3, δ, 300 MHz): 8.61 (d, $J = 8.7$ Hz, 1H), 7.89 (d, $J = 8.7$ Hz, 1H), 7.63 (t, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 8.1$ Hz, 1H), 7.26 (d, $J = 7.4$ Hz, 1H), 3.48

(s, -OH) ppm; ^{19}F NMR (CD_3COCD_3, δ, 54.6 MHz): −22.0 (s, CF_2Cl) ppm; IR: $\nu = 3230$, 1629, 1556, 1469, 1450, 1321, 1289, 1262, 1135, 1096, 1029 cm^{-1}; MS: $m/z = 229$ (M^+, 100), 194 (M^+-Cl, 87.09), 144 (M^+-CF_2Cl, 14.26); HRMS: calc. for $^{35}ClC_{10}H_6F_2NO$: 229.0106, found: 229.0133.

2-Bromodifluoromethyl-8-hydroxy-quinoline (**7c**; $C_{10}H_6F_2NOBr$)

Yield: 58%; m.p.: 41–42°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.32 (d, $J = 8.6$ Hz, 1H), 7.95 (s, -OH), 7.74 (d, $J = 8.6$ Hz, 1H), 7.59 (t, $J = 8.0$ Hz, 1H), 7.41 (d, $J = 8.1$ Hz, 1H), 7.27 (d, $J = 7.4$ Hz, 1H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): −27.3 (s, CF_2Br) ppm; IR: $\nu = 3427$, 1578, 1510, 1475, 1405, 1365, 1335, 1298, 1261, 1246, 1214, 1134, 1083, 1042 cm^{-1}; MS: $m/z = 275$ (29.58), 273 (28.59), 194 (M^+-Br, 100), 144 (M^+-CF_2Br, 18.08); HRMS. calc. for $^{79}BrC_{10}H_6F_2NO$: 272.9600, $^{81}BrC_{10}H_6F_2NO$: 274.9580, found: 274.9625, 274.9563.

2-(1,1,2,2,3,3-Hexafluoro-3-chloro-propyl)-8-hydroxy-quinoline (**7d**; $C_{12}H_6F_6NOCl$)

Yield: 46%; oil; ^{1}H NMR (CD_3COCD_3, δ, 300 MHz): 8.60 (d, $J = 8.6$ Hz, 1H), 7.86 (d, $J = 8.6$ Hz, 1H), 7.60 (t, $J = 8.0$ Hz, 1H), 7.53 (m, 1H), 7.29 (m, 1H), 3.42 (s, -OH), ^{19}F NMR (CD_3COCD_3, δ, 300 MHz): −10.0 (s, CF_2Cl), 36.3 (m, CF_2), 43.7 (m, CF_2) ppm; IR: $\nu = 3453$, 3059, 2931, 1633, 1579, 1476, 1367, 1309, 1246, 1184, 1129, 1100 cm^{-1}; MS: $m/z = 329$ (M^+, 87.19), 294 (M^+-Cl, 17.26), 194 (M^+-C_2F_4Cl, 100), 144 (M^+-C_3F_6Cl, 16.98); HRMS; calc. for $^{35}ClC_{12}H_6F_6NO$: 329.0043, found: 329.0028.

2-Perfluoropentyl-8-hydroxy-quinoline (**7e**; $C_{14}H_6F_{11}NO$)

Yield: 48%; m.p.: 53–54°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.37 (d, $J = 8.6$ Hz, 1H), 7.77 (d, $J = 8.6$ Hz, 1H), 7.62 (t, $J = 8.0$ Hz, 1H), 7.59 (m, 1H), 7.29 (m, 1H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): 3.3 (s, 3F), 35.5 (m, 2F), 44.7 (m, 4F), 48.7 (m, 2F) ppm; IR: $\nu = 3439$, 1636, 1581, 1508, 1473, 1363, 1331, 1305, 1238, 1195, 1164, 1143, 1116, 1088 cm^{-1}; MS: $m/z = 413$ (M^+, 87.05), 394 (M^+-Cl, 12.25), 194 (M^+-C_4F_9, 100), 144 (M^+-C_5F_{11}, 18.79); HRMS: calc. for $C_{14}H_6F_{11}NO$: 413.0278, found: 413.0281.

2-(1,1,2,2,3,3-Hexafluoro-3-chloro-propyl)-benzoxazole (**8d**; $C_{10}H_4F_6NOCl$)

Yield: 14%; oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.91 (m, 1H), 7.68 (m, 1H), 7.57 (m, 2H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): −9.0 (s, CF_2Cl), 36.0 (m, CF_2), 44.5 (m, CF_2) ppm; IR: $\nu = 1616$, 1573, 1480, 1359, 1312, 1239, 1193, 1135, 1113, 1101, 1013 cm^{-1}; Ms: $m/z = 303$ (M^+, 37.66), 268 (M^+-Cl, 13.45), 168 (M^+-C_2F_4Cl, 100); HRMS: calc. for $^{35}ClC_{10}H_4F_6NO$: 302.9886, found: 302.9892.

2-(Perfluoropentyl)-benzoxazole (**8e**; $C_{12}H_4F_{11}NO$)

Yield: 16%; oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.92 (m, 1H), 7.69 (m, 1H), 7.58 (m, 2H) ppm; ^{19}F NMR ($CDCl_3$, δ, 54.6 MHz): 3.3 (s, 3F), 35.5 (m, 2F), 44.7 (m, 4F), 48.7 (m, 2F) ppm; IR: $\nu = 1616$, 1573, 1481, 1452, 1363, 1311, 1240, 1207, 1144, 1129, 1109, 1097, 1072, 1049, 1004 cm^{-1}; MS: $m/z = 387$ (M^+, 52.37), 368 (M^+-F, 14.49), 168 (M^+-C_4F_9, 100); HRMS: calc. for $C_{12}H_4F_{11}NO$: 387.0116, found: 387.0111.

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