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The reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones with dinucleophilic reagents: a convenient route to fluoroalkylated nitrogen-containing tricyclic compounds

Xian-Jin Yang, Jin-Tao Liu* and He-Jun Lu

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People's Republic of China

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Abstract—The reactions of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones (**2**) with hydrazine hydrate and phenyl hydrazine were investigated. The reaction of **2** with hydrazine hydrate in ethanol under reflux condition readily gave 2-fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones (**3**) in high yields. The reaction of **2** with phenyl hydrazine, however, resulted in the formation of 2-(2-phenyl-5-fluoroalkyl-2*H*-pyrazol-3-yl) benzoic acids (**7**). Further treatment of **7** with PPA gave 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones (**4**) in 65–80% overall yields.

1. Introduction

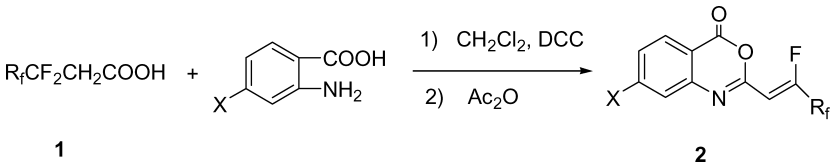
Many heterocyclic compounds containing fluorine or fluorocarbon groups showed potential biological activities and some of them had been employed in medicine and pesticides.[1] Thus to develop synthetic methods for fluorine-containing heterocyclic compounds has been a continuous subject of much research work in both organofluorine chemistry and organic synthesis. 4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones and 1-phenyl-4,9-dihydro-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones are important nitrogen-containing tricyclic compounds with unique biological properties, and their syntheses and properties have been studied in detail by Sircar and Catarzi respectively.[2,3] To our knowledge, little work was done on their fluorinated analogues due to the difficulty to synthesize these fluorine-containing heterocyclic compounds.

Recently, we developed a facile method for the preparation of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones (**2**) from 2,2-dihydropolyfluoroalkanoic acids (Scheme 1).[4] Compound **2** is a reactive intermediate with both C-2 and the unsaturated carbon with a fluorine atom in the alkenyl group readily attacked by nucleophilic reagent.[5–12] It was found that **2** reacted with some dinucleophilic reagents readily, for instance, hydrazine hydrate or phenyl hydrazine. The subsequent cyclization gave tricyclic compound, 2-fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones (**3**) and 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones (**4**) respectively. The results are reported in this paper.

2. Results and discussion

2.1. Reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones (2) with hydrazine hydrate

In the presence of Et_3N, compound **2** reacted readily with a little excess of hydrazine hydrate in ethanol under reflux to form a new compound as shown by TLC (Scheme 2). After workup, a white solid was obtained in high yield. The



1 2

Scheme 1.

Keywords: 2-(1-Hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones; Hydrazine hydrate; 2-Fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones; 3-Fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones; Phenyl hydrazine.
* Corresponding author. Tel.: +86-021-64163300-3533; fax: +86-021-64166128; e-mail address: jtliu@mail.sioc.ac.cn

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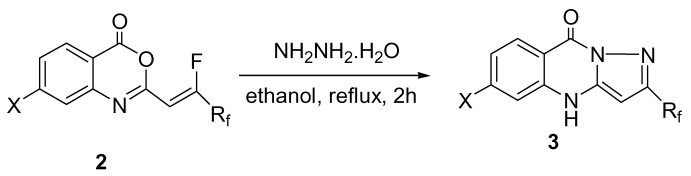


a : R_f = CF_2Cl, X = H; b : R_f = $(CF_2)_3F$, X = H; c : R_f = $(CF_2)_3Cl$, X = H;

d : R_f = $(CF_2)_5Cl$, X = H; e : R_f = $(CF_2)_3F$, X = Cl

Scheme 2.

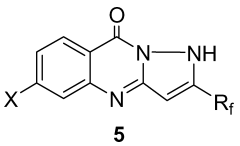


Figure 1.

in this reaction. The difference in spectra between the analogues of **3** and **5** are trivial in literature,[2,3,13–16] therefore it is difficult to determine the products' structures according to the above spectra. Fortunately a single crystal of compound **3e** was obtained and the X-ray crystallography assigned the structure as isomer **3** (Fig. 2). The results are summarized in Table 1.

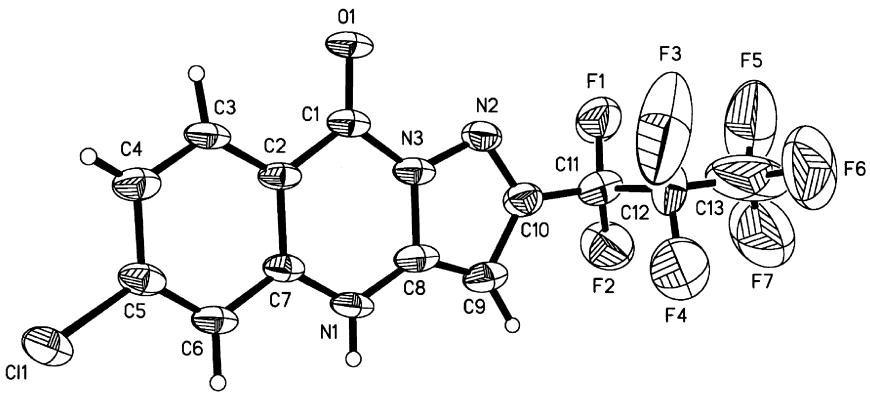


Figure 2. Molecular structure of compound **3e** (CCDC number: CCDC 219160).

Table 1. The Reaction of **2** with hydrazine hydrate

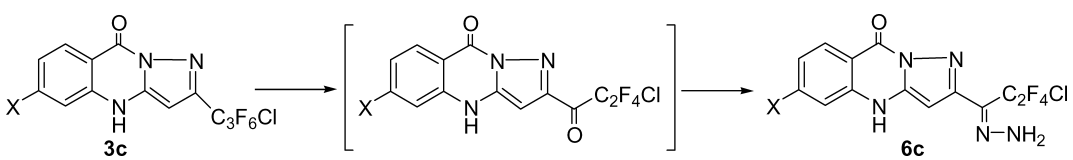
Entry	Substrate	R_f	X	Solvent	Product	Yield (%)
1	**2a**	CF_2Cl	H	EtOH	**3a**	96
2	**2a**	CF_2Cl	H	C_6H_6	**3a**	94
3	**2a**	CF_2Cl	H	DMF	**3a**	91
4	**2b**	$(CF_2)_2CF_3$	H	EtOH	**3b**	96
5	**2c**	$(CF_2)_3Cl$	H	EtOH	**3c**	96
6	**2d**	$(CF_2)_5Cl$	H	EtOH	**3d**	92
7	**2e**	$(CF_2)_2CF_3$	Cl	EtOH	**3e**	96

product is almost insoluble in chloroform, dichloromethane or benzene, but soluble in DMSO. Its ^{19}F NMR, ^{1}H NMR, HRMS and IR spectra indicated that it was a tricyclic compound with a fluoroalkyl substituent. According to the data, either 2-fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-one (**3**) or its isomer, compound **5** (Fig. 1), might be formed

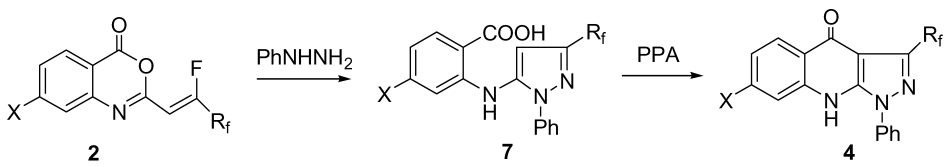
As shown in Table 1, both R_f and substituent X had little influence on the reaction result. Other solvents such as C_6H_6, MeCN and DMF may also be used. But for the reaction of **2c** compound **6c** was obtained as a by-product when longer time and excess hydrazine hydrate was used in the reaction of **2c** with hydrazine hydrate. This might be caused by the hydrolysis of the CF_2 group next to aromatic pyrazole ring[17,18] and the subsequent nucleophilic attack of hydrazine hydrate to the resulting carbonyl group (Scheme 3).

2.2. Reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones (2) with phenyl hydrazine

Under similar conditions the reaction of **2** with phenyl hydrazine, however, afforded the ring-opening product **7** as main product instead of the desired tricyclic compound as above (Scheme 4). As shown in Table 2, ethanol was the



Scheme 3.



b : R_f = (CF_2)$_3$F, X = H; c : R_f = (CF_2)$_3$Cl, X = H; e : R_f = (CF_2)$_3$F, X = Cl;

f : R_f = CF_3, X = H; g : R_f = CF_3, X = Cl; h : R_f = (CF_2)$_3$Cl, X = Cl

Scheme 4.

Table 2. The reaction of **2** with phenyl hydrazine

Entry	Substrate	R_f	X	Solvent	Product	Yield (%)
1	**2b**	$(CF_2)_2CF_3$	H	EtOH	**7b**	84
2	**2b**	$(CF_2)_2CF_3$	H	DMF	**7b**	43
3	**2b**	$(CF_2)_2CF_3$	H	PhH	**7b**	55
4	**2c**	$(CF_2)_3Cl$	H	EtOH	**7c**	82
5	**2e**	$(CF_2)_2CF_3$	Cl	EtOH	**7e**	76
6	**2f**	CF_3	H	EtOH	**7f**	75
7	**2g**	CF_3	Cl	EtOH	**7g**	72
8	**2h**	$(CF_2)_3Cl$	Cl	EtOH	**7h**	77

best solvent of all solvents tested. Usually better results were obtained when 1.2 equiv. of phenyl hydrazine was used and the yield of **7** decreased when more phenyl hydrazine was added. Treatment of compound **7** in polyphosphoric acid at 170 °C for about 4 h afforded the corresponding cyclization product, 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-one (**4**), in 91–95% yields. The reaction conditions must be controlled carefully for a good result. Higher temperature and longer reaction time would cause the reaction more complex and lower yields. The results are summarized in Table 3.

Table 3. Cyclization reaction of **7**

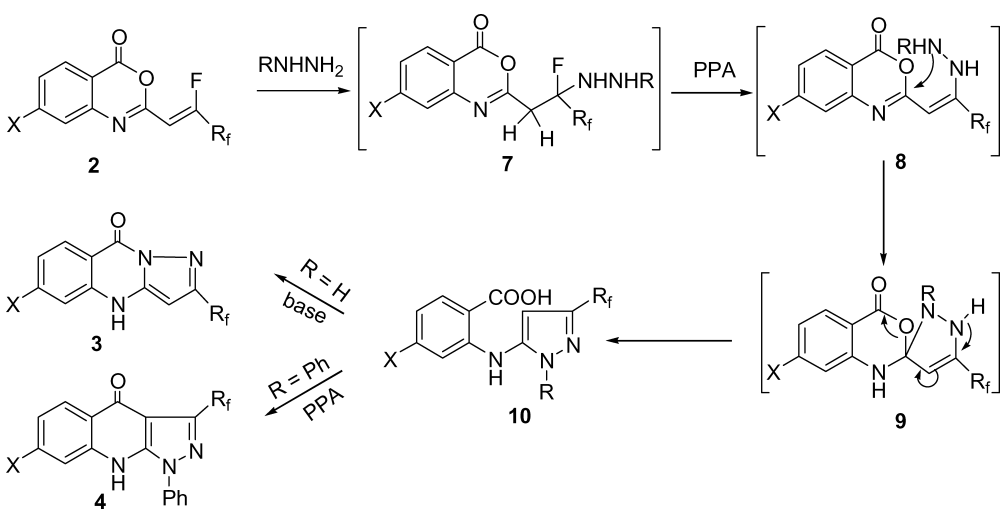
Entry	Substrate	R_f	X	Conditions	Product	Yield (%)
1	**7b**	$(CF_2)_3F$	H	PPA, 170 °C, 2 h	**4b**	95
2	**7f**	CF_3	H	PPA, 170 °C, 2 h	**4f**	92
3	**7f**	CF_3	H	PPA, 170 °C, 4 h	**4f**	85
4	**7f**	CF_3	H	PPA, 170 °C, 8 h	**4f**	77
5	**7g**	CF_3	Cl	PPA, 170 °C, 2 h	**4g**	91

2.3. Mechanism

A mechanism involving nucleophilic substitution and ring rearrangement was proposed for the formation of compound **3** and **4** as shown in Scheme 5. Nucleophilic attack of NH_2 to the unsaturated carbon with a fluorine atom in the alkenyl group of compound **2** followed by the elimination of a HF gave intermediate **8**. Next the carbon at 2-position in **8** was attacked by another nucleophilic nitrogen to give intermediate **9**, which underwent rearrangement to form the ring-opening intermediate **10**. For R=H, in the presence of Et_3N the condensation reaction between COOH and N–H in the pyrazole ring of intermediate **10** readily took place to give compound **3** as final product. In the case of phenyl hydrazine this condensation reaction did not occur since no N–H group in the pyrazole ring was present, and the condensation of COOH and C–H was difficult under the reaction conditions. Thus compound **7** was obtained in this step and underwent cyclization reaction under more vigorous conditions in PPA to give compound **4**.

3. Conclusions

In conclusion, the reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones with hydrazine hydrate and phenyl hydrazine was achieved under mild conditions,



Scheme 5.

providing a convenient method for the synthesis of two kinds of fluoroalkylated nitrogen-containing tricyclic compounds, 2-fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones and 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones. Further investigation on the reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones with other nucleophilic reagents is in progress.

4. Experimental

Melting points were uncorrected. IR spectra were taken on a Perkin–Elmer 983G IR spectrophotometer. ^{1}H NMR spectra were measured on a Bruker AM300 (300 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM300 (282 MHz) spectrometer, chemical shifts are reported as δ_{CFCl3} ($\delta_{CFCl3}=\delta_{TFA}-76.8$), negative for upfield shifts. Mass spectra were obtained on a Finnigan GC-MS 4021 spectrometer. X-ray data were measured at 293 K on a Bruker SMART CCD diffractomer with graphite monochromated Mo Kα radiation. Column chromatography was performed using silica gel H, particle size 10–40 μ.

4.1. Synthesis of 2-fluoroalkyl-*4H*-pyrazolo[5,1-*b*] quinazolin-9-ones (3)

Typical procedure. 1.0 mmol of **2**, 1.2 mmol of hydrazine hydrate and 1 mL of Et_3N in 10 mL of ethanol was stirred under reflux for about 2 h (monitored by TLC). After removal of the solvent, the solid residue obtained was purified by column chromatography (hexane/ethyl acetate=2:1) or by washing several times with chloroform and the subsequent recrystallization in ethanol to give **3**.

4.1.1. Compound 3a. White solid, mp 238–240 °C. IR (KBr, cm^{-1}): ν_{max} 3276, 3194, 3121, 2927, 2854, 1745, 1681, 1651, 1578, 1506, 1468, 1352, 1204, 1114, 990, 874, 748. ^{19}F NMR (acetone-d$_6$, δ, ppm): −67.8 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 8.21–8.16 (m, 1H), 7.72–7.64 (m, 1H), 7.40–7.34 (m, 1H), 7.26–7.21 (m, 1H), 6.27 (s, 1H), 2.70 (br, 1H). EI-MS *m*/*z*: 271 (M^++2, 22), 269 (M^+, 67), 234 (M^+-Cl, 72), 219 (M^+-CF_2, 24), 185 (M^+-CF_2Cl+1, 100). EI-HRMS calcd For $C_{11}H_6F_2N_3O$ (M^+-Cl): 234.0479. Found: 234.0457.

4.1.2. Compound 3b. White solid, mp 280–282 °C. IR (KBr, cm^{-1}): ν_{max} 3293, 3227, 3164, 1708, 1631, 1578, 1475, 1210, 1116, 989, 872, 751. ^{19}F NMR (acetone-d$_6$, δ, ppm): −81.1 (s, 3F), −112.8 (s, 2F), −127.1 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 8.21 (d, *J*=8.1 Hz, 1H), 7.73–7.68 (m, 1H), 7.40 (d, *J*=8.1 Hz, 1H), 7.27–7.22 (m, 1H), 6.33 (s, 1H), 2.70 (br, 1H). EI-MS *m*/*z*: 354 (M^++1, 100), 353 (M^+, 91), 335 (M^+-F, 14), 234 ($M^+-CF_2CF_3$, 30), 206 (61). EI-HRMS calcd for $C_{13}H_6F_7N_3O$: 353.0399. Found: 353.0417.

4.1.3. Compound 3c. White solid, mp 278–280 °C. IR (KBr, cm^{-1}): ν_{max} 3292, 3225, 3130, 1708, 1631, 1577, 1473, 1191, 1115, 756. ^{19}F NMR (acetone-d$_6$, δ, ppm): −68.4 (s, 2F), −110.8 (s, 2F), −122.1 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 8.28 (d, *J*=8.1 Hz, 1H), 7.80–7.74 (m, 1H), 7.49 (d, *J*=8.1 Hz, 1H), 7.34–7.29 (m, 1H), 6.18 (s, 1H), 3.20 (br, 1H). EI-MS *m*/*z*: 371 (M^++2, 32), 369 (M^+, 100), 334 (M^+-Cl, 20), 234 ($M^+-CF_2CF_2Cl$, 49), 206 (49). EI-HRMS calcd for $C_{13}H_6F_6N_3O$ (M^+-Cl): 334.0415. Found: 334.0431.

4.1.4. Compound 3d. White solid, mp 282–284 °C. IR (KBr, cm^{-1}): ν_{max} 3290, 3225, 1708, 1633, 1577, 1475, 1211, 1135, 1048, 973, 959, 752, 735. ^{19}F NMR (acetone-d$_6$, δ, ppm): −68.3 (s, 2F), −110.1 (s, 2F), −119.9 (s, 2F), −120.5 (s, 2F), −122.0 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 8.28 (d, *J*=8.1 Hz, 1H), 7.82–7.71 (m, 1H), 7.48 (d, *J*=8.1 Hz, 1H), 7.32–7.26 (m, 1H), 6.38 (s, 1H), 3.50 (br, 1H). EI-MS *m*/*z*: 471 (M^++2, 47), 469 (M^+, 100), 434 (M^+-Cl, 23), 234 ($M^+-CF_2CF_2CF_2CF_2Cl$, 62), 206 (37). Anal. calcd for $C_{15}H_6ClF_{10}N_3O$: C, 38.36; H, 1.29; N, 8.95. Found: C, 38.52; H, 1.53; N, 9.10.

4.1.5. Compound 3e. White solid, mp 288–290 °C. IR (KBr, cm^{-1}): ν_{max} 3280, 3196, 1645, 1347, 1272, 1224, 1110, 872, 756. ^{19}F NMR (acetone-d$_6$, δ, ppm): −80.2 (s, 3F), −107.3 (s, 2F), −126.8 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 7.09 (d, *J*=9.0 Hz, 1H), 6.35 (s, 1H), 6.21 (d, *J*=9.0 Hz, 1H), 5.45 (s, 1H). EI-MS *m*/*z*: 389 (M^++2, 41), 387 (M^+, 100), 268 (M^+-F, 34), 268 ($M^+-CF_2CF_3$). Anal. calcd for $C_{13}H_5ClF_7N_3O$: C, 40.28; H, 1.30; N, 10.84. Found: C, 40.20; H, 1.21; N, 10.81.

4.1.6. Compound 6c. White solid which decomposed at 280 °C. IR (KBr, cm^{-1}): ν_{max} 3498, 3406, 3294, 3104, 2966, 1668, 1641, 1562, 1117, 1091, 943, 753. ^{19}F NMR (acetone-d$_6$, δ, ppm): −68.6 (s, 2F), −106.2 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 11.01 (br, 2H), 9.01 (br, 1H), 8.32–8.28 (m, 1H), 7.82–7.77 (m, 1H), 7.49–7.47 (m, 1H), 7.36–7.31 (m, 1H), 6.16 (s, 1H). EI-MS *m*/*z*: 363 (M^++2, 24), 361 (M^+, 72), 333 (59), 248 (100), 228 (26), 326 (M^+-Cl, 23), 228 ($M^+-C_2F_4Cl$). Anal. calcd for $C_{13}H_8ClF_4N_5O$: C, 43.17; H, 2.23; N, 19.36. Found: C, 43.25; H, 2.24; N, 19.56.

4.2. Synthesis of 2-(2-phenyl-5-fluoroalkyl-2*H*-pyrazol-3-yl) benzoic acids (7)

Typical procedure. A mixture of 1.0 mmol of compound **2** and 1.2 mmol of phenyl hydrazine in 10 mL of ethanol was stirred under reflux for 4–5 h. After removal of the solvent, the solid residue was subjected to column chromatography (light petroleum/ethyl acetate=1:2) to give compound **7**.

4.2.1. Compound 7b. Yellow solid, mp 241–243 °C. IR (KBr, cm^{-1}): ν_{max} 3250, 1663, 1594, 1563, 1236, 1109, 893, 866, 741. ^{19}F NMR ($CDCl_3$, δ, ppm): −79.1 (s, 3F), −110.7 (s, 2F), −126.3 (s, 2F). ^{1}H NMR ($CDCl_3$, δ, ppm): 9.68 (s, 1H), 8.05 (dd, *J*=8.2, 1.2 Hz, 1H), 7.41–7.59 (m, 6H), 7.19 (d, *J*=8.2 Hz, 1H), 6.94 (t, *J*=7.8 Hz, 1H), 6.59 (s, 1H). EI-MS *m*/*z*: 447 (M^+, 65), 429 (M^+-OH-1, 100), 310 ($M^+-OH-CF_3CF_2$, 29), 260 ($M^+-OH-C_3F_7$-1, 35). EI-HRMS calcd for $C_{19}H_{12}F_7N_3O_2$: 447.0818. Found: 447.0832.

4.2.2. Compound 7c. Yellow solid, mp 238–239 °C. IR (KBr, cm^{-1}): ν_{max} 3246, 1663, 1595, 1561, 1455, 1263, 1241, 1195. ^{19}F NMR ($CDCl_3$, δ, ppm): −61.6 (s, 2F), −110.0 (s, 2F), −121.8 (s, 2F). ^{1}H NMR ($CDCl_3$, δ, ppm):

9.67 (s, 1H), 8.05 (dd, J=8.4, 1.2 Hz, 1H), 7.44–7.59 (m, 6H), 7.17 (d, J=8.4 Hz, 1H), 6.93 (t, J=7.7 Hz, 1H), 6.59 (s, 1H). EI-MS *m/z*: 465 (M^++2, 24), 463 (M^+, 69), 445 (M^+−OH-1, 100), 410 (M^+−OH−Cl-1, 7), 310 (M^+−OH−$ClCF_2CF_2$-1, 40), 260 (M^+−OH−$ClCF_3CF_2$-CF_2-1, 62). EI-HRMS calcd for: $C_{19}H_{12}ClF_6N_3O_2$: 463.0522. Found: 463.0486.

4.2.3. Compound 7e. Yellow solid, mp 251–254 °C. IR (KBr, cm^{-1}): ν_{max} 3255, 1665, 1587, 1234, 1186, 1112, 879, 764. ^{19}F NMR ($CDCl_3$, δ, ppm): −79.9 (s, 3F), −111.5 (s, 2F), −126.6 (s, 2F). ^1H NMR ($CDCl_3$, δ, ppm): 9.66 (s, 1H), 7.95 (d, J=8.6 Hz, 1H), 7.34–7.56 (m, 5H), δ 7.07 (d, J=1.8 Hz, 1H), 6.88 (dd, J=8.6, 1.8 Hz, 1H), 6.61 (s, 1H). EI-MS *m/z*: 483 (M^++2, 23) 481 (M^+, 65), 463 (M^+−OH-1, 100), 344 (M^+−OH−CF_3CF_2-1, 33), 294 (M^+−OH−$CF_3CF_2CF_2$-1, 43). Anal. calcd for $C_{19}H_{11}ClF_7N_3O_2$: C, 47.37; H, 2.30; N, 8.72. Found: C, 47.25; H, 2.41; N, 8.40.

4.2.4. Compound 7f. Yellow solid, mp 255–257 °C. IR (KBr, cm^{-1}): ν_{max} 3274, 1668, 1589, 1269, 1247, 1122, 970, 751. ^{19}F NMR ($CDCl_3$, δ, ppm): −61.6 (s, 3F). ^1H NMR ($CDCl_3$, δ, ppm): 9.69 (s, 1H), 8.04 (d, J=7.9 Hz, 1H), 7.42–7.58 (m, 6H), 7.20 (d, J=8.5 Hz, 1H), 6.93 (t, J=7.6 Hz, 1H), 6.57 (s, 1H). EI-MS *m/z*: 347 (M^+, 100), 329 (M^+−OH-1, 63), 260 (M^+−OH−CF_3-1, 15). EI-HRMS calcd for $C_{17}H_{12}F_3N_3O_2$: 347.0882. Found: 347.0858.

4.2.5. Compound 7g. Yellow solid, mp 263–264 °C. IR (KBr, cm^{-1}): ν_{max} 3285, 1663, 1603, 1585, 1241, 1149, 971, 759. ^{19}F NMR ($CDCl_3$, δ, ppm): −61.4 (s, 3F). ^1H NMR ($CDCl_3$, δ, ppm): 9.70 (s, 1H), 7.93 (d, J=7.5 Hz, 1H), 7.43–7.53 (m, 5H), 7.09 (s, 1H), 6.85 (d, J=7.5 Hz, 1H), 6.58 (s, 1H). EI-MS *m/z*: 383 (M^++2, 18), 381 (M^+, 52), 363 (M^+−OH-1, 100), 294 (M^+−OH−CF_3-1, 15). EI-HRMS calcd for $C_{17}H_9ClF_3N_3O$ (M^+−OH-1): 363.0386. Found: 363.0340.

4.2.6. Compound 7h. Yellow solid, mp 250–252 °C. IR (KBr, cm^{-1}): ν_{max} 3277, 1664, 1600, 1572, 1506, 1240, 1170, 1135, 821, 765. ^{19}F NMR ($CDCl_3$, δ, ppm): −65.5 (s, 2F), −108.8 (s, 2F), −120.1 (s, 2F). ^1H NMR ($CDCl_3$, δ, ppm): 9.67 (s, 1H), 7.95 (d, J=8.6 Hz, 1H), 7.45–7.55 (m, 5H), 7.07 (s, 1H), 6.89 (d, J=8.6 Hz, 1H), 6.61 (s, 1H). EI-MS *m/z*: 497 (M^+, 55), 481 (M^+−OH+1, 66), 480 (M^+−OH, 47), 479 (M^+−OH-1, 100), 444 (M^+−OH−Cl-1, 8), 344 (M^+−OH−$ClCF_2CF_2$-1, 40). EI-HRMS calcd for $C_{19}H_{11}Cl_2F_6N_3O_2$: 497.0133. Found: 497.0131.

4.3. Synthesis of 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones (4)

Typical procedure. A mixture of 0.5 g of **7** and 10 g of PPA was stirred for 3–4 h at 170 °C. After cooling the reaction mixture was neutralized with aqueous 2 N NaOH to pH=7, extracted with ethyl ether (15 mL×3). The combined organic phase was washed with water and saturated NaCl solution twice respectively, dried over anhydrous Na_2SO_4. After removal of solvent, the solid residue was purified by column chromatography (hexane/ethyl acetate=3:1) to give compound **4**.

4.3.1. Compound 4b. Yellow solid, mp 250–253 °C. IR (KBr, cm^{-1}): ν_{max} 3198, 1627, 1593, 1233, 1117, 759. ^{19}F NMR (acetone-d_6, δ, ppm): −81.3 (s, 3F), −109.1 (s, 2F), −126.3 (s, 2F). ^1H NMR (acetone-d_6, δ, ppm): 8.42 (d, J=7.3 Hz, 1H), 7.88 (dd, J=8.8 Hz, 1.7 Hz, 1H), 7.68–7.78 (m, 6H), 7.38–7.42 (m, 1H), 3.10 (br, 1H). EI-MS *m/z*: 429 (M^+, 100), 310 (M^+−CF_2CF_3, 43). EI-HRMS calcd for $C_{19}H_{10}F_7N_3O$: 429.0712. Found: 429.0709.

4.3.2. Compound 4f. Yellow solid, mp 265–267 °C. IR (KBr, cm^{-1}): ν_{max} 3186, 1628, 1593, 1233, 758. ^{19}F NMR (acetone-d_6, δ, ppm): −63.4 (s, 3F). ^1H NMR (acetone-d_6, δ, ppm): 8.41 (d, J=8.0 Hz, 1H), 7.87 (dd, J=8.4, 1.4 Hz, 1H), 7.63–7.78 (m, 6H), 7.38–7.43 (m, 1H), 3.30 (br, 1H). EI-MS *m/z*: 329 (M^+, 100), 260 (M^+−CF_3, 8), 243 (45). EI-HRMS calcd for $C_{17}H_{10}F_3N_3O$: 329.0776. Found: 329.0766.

4.3.3. Compound 4g. Yellow solid, mp 271–272 °C. IR (KBr, cm^{-1}): ν_{max} 3168, 1631, 1596, 1139, 931. ^{19}F NMR (acetone-d_6, δ, ppm): −62.8 (s, 3F). ^1H NMR (acetone-d_6, δ, ppm): 8.33 (d, J=8.7 Hz, 1H), 7.62–7.85 (m, 6H), 7.35 (dd, J=8.7, 1.9 Hz, 1H), 3.15 (br, 1H). EI-MS *m/z*: 365 (M^++2, 37), 363 (M^+, 100), 328 (M^+−Cl, 17), 294 (M^+−CF_3, 8). EI-HRMS calcd for $C_{17}H_9ClF_3N_3O$: 363.0386. Found: 363.0382.

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