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An efficient synthesis of ([^{18}F]fluoropropyl)quinoline-5,8-diones by rapid radiofluorination–oxidative demethylation

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ABSTRACT

Since many molecules bearing quinoline-5,8-dione or fused 1,4-quinone moieties possess a wide spectrum of biological activities, efficient methods for incorporation of fluorine-18 (F-18) into quinoline-5,8-diones have received considerable attention in positron emission tomography (PET) molecular imaging studies. In this paper, we describe an efficient synthetic route for the regioselective preparation of fluoropropyl-substituted quinoline-5,8-diones on the C3, C4, and C6 positions by *tert*-alcohol media fluorination, followed by oxidative demethylation of the corresponding dimethoxy compound using *N*-bromosuccinimide (NBS) in the presence of catalytic amounts of sulfuric acid. Moreover, F-18 labeled [^{18}F]fluoropropylquinoline-5,8-diones [^{18}F]**21**–**23** were prepared from the corresponding mesylate precursors by a method of rapid and efficient one-pot, two-step reactions: radiofluorination using TBA [^{18}F]F generated under no-carrier-added (NCA) conditions; oxidative demethylation, resulting in a 45% radiochemical yield of [^{18}F]**21**–**23** (decay-corrected) with a total synthesis time (including HPLC purification) of 75 min and high radiochemical purity (>99%), as well as high specific activity (~230 GBq/μmol).

1. Introduction

It is well-known that low fluorinated compounds have played a crucial role in the field of medicinal chemistry because of their physiological properties.[1] In particular, radiopharmaceuticals labeled with the short-lived positron-emitting radionuclide, in particular, fluorine-18 ($t_{1/2}$=110 min), are being increasingly used in clinical diagnosis, as well as the molecular imaging field[2] using positron emission tomography (PET) as a noninvasive molecular imaging protocol, which provides exciting opportunities to detect diseases in humans and monitor biological processes in living subjects.[3] However, suitable chemical processes for the introduction of fluorine-18 into organic molecules for preparation of radiotracers are often limited by: harsh labeling reaction conditions; the relative short half-life of fluorine-18; sensitive functional groups or chemical structure of the radiotracer molecules that can restrict the choice of potential synthetic pathways; synthesis of a radiotracer, including purification, usually should be completed within three half-lives of the radionuclide. Consequently, rapid and efficient protocols that can be performed on a trace level reaction scale, considering the specific activity of the radionuclide, are required for effective radiotracer preparation.[4]

A number of bioactive molecules bearing the quinoline-5,8-dione and fused 1,4-quinone moieties are widespread in nature and have received much interest given their wide spectra of biological activities, such as antitumor and antibacterial.[5] Thus, an efficient fluorine-18 labeling protocol for quinoline-5,8-diones would afford developmental opportunities of various new radiopharmaceuticals for PET. However, it is hard to introduce fluorine-18 (F-18) at specific sites of the quinoline-5,8-diones without their decomposition under standard F-18 labeling reaction conditions since the quinone moiety is easily reduced and attacked by nucleophiles.[6] Therefore, protection of the quinone moiety is required for the labeling reaction to proceed. It has been reported that oxidative demethylation of fused 1,4-dimethoxybezenes to 1,4-quinones using *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of H_2SO_4 can proceed nearly quantitatively within 5 min at room temperature.[7] Therefore, this oxidation method allowed this lab to design an efficient retrosynthetic route for the preparation of radiolabeled quinoline-5,8-diones with F-18 from 5,8-dimethoxyquinoline mesylate precursors via the [^{18}F]radiofluorination–oxidation reaction sequence as shown in Fig. 1. Herein, we report the efficient syntheses of fluoropropyl- or

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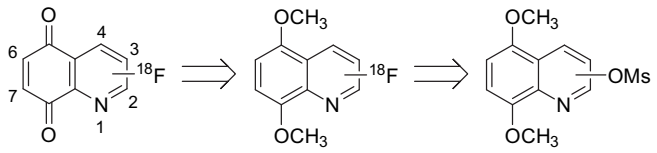
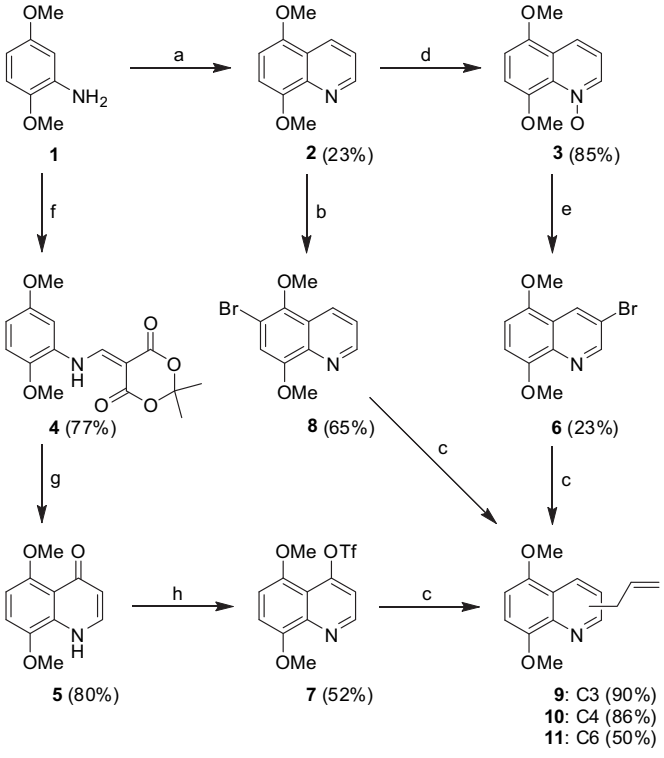


Fig. 1. Strategy for the preparation of radiolabeled quinoline-5,8-diones with fluorine-18.

[^{18}F]fluoropropyl-substituted quinoline-5,8-diones on the C3, C4, and C6 position using a one-pot, two-step radiofluorination–oxidative demethylation reaction sequence. This protocol afforded F-18 labeled quinoline-5,8-diones in high radiochemical yield with short reaction times.

2. Results and discussion

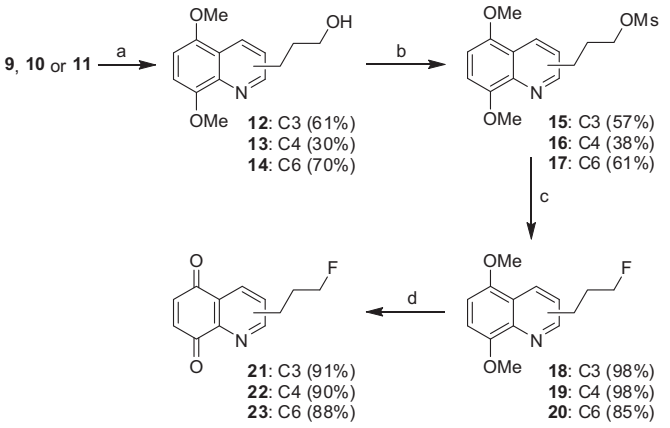
Scheme 1 illustrates the regioselective synthetic route for preparation of allylquinoline derivatives **9**–**11** as key intermediates for introduction of the fluoropropyl group at the C3, C4, and C6 positions of the quinoline-5,8-dione. 5,8-Dimethoxyquinoline (**2**) was prepared from commercially available 2,5-dimethoxyaniline (**1**) by the Skraup reaction.[8] A bromine could be incorporated at the C6 position of quinoline compound **2** by bromination with *N*-bromosuccinimide (NBS), affording 6-bromo-5,8-dimethoxyquinoline (**8**) in 65% yield. To introduce a bromine atom regioselectively at C3, oxidation of **2** to the corresponding *N*-oxide compound **3** with 3-chloroperoxybenzoic acid (*m*-CPBA) was followed by C3 bromination using phosphorus oxybromide to provide 3-bromo-5,8-dimethoxyquinoline (**6**). For placement of the trifluoromethanesufonyloxy group at the C4 position using the Stille reaction, 5,8-dimethoxy-4-quinolone (**5**) was prepared by treatment of **1** with Meldrum's acid[9]



Scheme 1. Synthesis of allyl-5,8-dimethoxylquinoline-5,8-diones as a key intermediate. Reagents: (a) acrolein, HBr, 60 °C, 1 h; (b) NBS, CH_2Cl_2, 25 °C, 12 h; (c) (i) LiBr, $Pd(PPh_3)_3$, THF, 30 °C, 30 min; (ii) allyltributyltin, 85 °C, 24 h; (d) *m*-CPBA, CH_2Cl_2, 65 °C, 24 h; (e) $POBr_3$, chloroform, 60 °C, 12 h; (f) (i) trimethylorthoformate, 90 °C, 2 h; (ii) 2,2-dimethyl-1,3-dioxane-4,6-dione, 90 °C, 4 h; (g) phenyl ether, 250 °C, 2 h; (h) triflic anhydride, DMAP, 2,6-lutidine, CH_2Cl_2, 23 °C, 12 h.

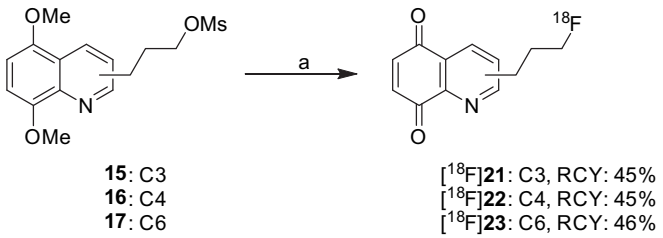
in trimethylorthoformate, followed by thermolysis of **4** at 250 °C in diphenyl ether; treatment of quinolone **5** with triflic anhydride afforded triflate **7**. Stille reaction[10] of **6**–**8** with allyltributyltin in the presence of tetrakis (triphenylphosphine palladium(0)) and lithium bromide provided the corresponding allyl-substituted quinoline compounds at the C3, C4, and C6 positions (**9**–**11**, 90, 86, and 50%, respectively).

The unlabeled fluoropropylquinoline-5,8-diones (**21**–**23**) and the mesylate precursors for the ^{18}F-labeled quinoline-5,8-dione derivatives were synthesized as shown in Scheme 2. Hydroboration[11] of allyl compounds **9**–**11**, followed by mesylation of alcohols **12**–**14**, provided the corresponding mesylate precursors **15**–**17**. The *tert*-alcohol media nucleophilic fluorination[12] of these precursors using tetrabutylammonium fluoride (TBAF) proceeded selectively, affording the desired fluoropropylquinolines **18**–**20** in very high yield. The oxidation reaction of fluoropropyl-5,8-dimethoxyquinolines **18**–**20** using NBS in the presence of catalytic amounts of sulfuric acid could be completed within 5 min at room temperature to give the fluoropropylquinoline-5,8-diones **21**–**23** in high yield. This highly efficient oxidative demethylation method allowed the dimethoxy group act as a good protecting group for the synthesis of quinolinediones labeled by short half-life radioisotopes.



Scheme 2. Synthesis of fluoropropylquinoline-5,8-diones. Reagents: (a) (i) 1.0 M BH_3 in THF, 0 °C, 1 h; (ii) H_2O, 4.0 N NaOH, H_2O_2, 23 °C, 3 h; (b) MsCl, TEA, 25 °C, 1 h; (c) TBAF, *tert*-amyl alcohol, 90 °C, 1 h; (d) NBS, H_2O, H_2SO_4, THF, 25 °C, 5 min.

[^{18}F]Fluoropropylquinoline-5,8-diones [^{18}F]**22**–**23** were generated by a one-pot, two-step procedure consisting of *tert*-alcohol media [^{18}F]fluorination and subsequent oxidative demethylation, as shown in Scheme 3. The final labeled products [^{18}F]**22**–**23** were prepared by radiofluorination of mesylate precursors **15**–**17** in *tert*-amyl alcohol at 100 °C for 20 min with TBA [^{18}F]F, generated under no-carrier-added (NCA) conditions, followed by, without any purification procedures, direct oxidation of F-18 labeled dimethoxy compounds [^{18}F]**18**–**20** with NBS in the presence of catalytic amounts of sulfuric acid at room temperature for 5 min. During the one-pot, two-step process, various reagents, chemicals, and *tert*-amyl alcohol for the [^{18}F]fluorination reaction did not inhibit oxidation at all. The labeled products [^{18}F]**22**–**23** were isolated by reversed-phase HPLC purification, each with high specific activities (~230 GBq/μmol), as described in the experimental section. The overall radiosyntheses of [^{18}F]**22**–**23** resulted in decay-corrected radiochemical yields of approximately 45%, with a total synthesis time (including HPLC purification) of 75 min from the end of bombardment through the one-pot, two-step reaction. The radiochemical purities of [^{18}F]**22**–**23**, which co-eluted on the analytical HPLC with an authentic sample of the corresponding unlabeled **22**–**23**, were >99%.



Scheme 3. Preparation of [^{18}F]fluoropropylquinoline-5,8-diones by one-pot, two-step reactions of radiofluorination and oxidative demethylation. Reagents: (a) (i) TBA [^{18}F]F, *tert*-amyl alcohol, 100 °C, 20 min; (ii) NBS, H_2O, H_2SO_4, THF, 25 °C, 5 min.

3. Conclusions

In summary, we have described an efficient synthetic route to regioselectively introduce a fluoropropyl group on the C3, C4, and C6 positions of quinoline-5,8-diones. In this route, the synthetic protocol of the protic media, fluorination–oxidative demethylation, described for preparation of the fluoroproylquinoline-5,8-diones, is sufficiently rapid and efficient and appears suitable for the synthesis of a variety of fused 1,4-quinone molecules labeled with the short half-life ($t_{1/2}$=110 min) radionuclide fluoride-18 for PET molecular imaging study. Furthermore, using this efficient one-pot, two-step protocol, synthesis of [^{18}F]fluoropropylquinoline-5,8-diones in high RCY within short reaction times proved possible.

4. Experimental section

4.1. General

Reagents and solvents are purchased from Sigma–Aldrich and used without further purification. Reaction progress was followed by TLC on 0.25 mm silica gel glass plates containing F-254 indicator. Visualization on TLC was monitored by UV light or radio-TLC scanner. Flash chromatography was performed using a 230–400 mesh silica gel (Merck KGaA). ^{1}H NMR spectra were recorded on a 600 MHz spectrometer. Chemical shifts were reported in δ units (ppm) relative to tetramethylsilane, and coupling constants were reported in hertz. ^{13}C NMR spectra were acquired at 125 MHz. Low- and high-resolution electron impact (EI, 70 eV) spectra were obtained. [^{18}F]Fluoride ion was produced from a cyclotron (KIRAMS 13 MeV, South Korea) using the ^{18}O(p,n)^{18}F nuclear reaction with 19 MeV proton irradiation of an enriched [^{18}O]H_2O target. High-performance liquid chromatography (HPLC) was performed with a spectra system (Thermo Scientific, Waltham, MA, USA) using a semipreparative column (C18 silica gel, 10 μm, 10×250 mm) and analytic column (C18 silica gel, 5 μm, 4.6×250 mm). The flow was 3 mL/min, with a mobile phase of 10 mM aqueous phosphoric acid/ethanol=75:25 (v/v). The eluent was simultaneously monitored with a UV detector (215 nm) and a NaI (Tl) radioactivity detector. Radioactivity was measured in a dose calibrator.

4.2. General procedure for the synthesis of 9–11

To a mixture of **6** (280 mg, 1.0 mmol) and lithium bromide (755 mg, 8.7 mmol) in dried THF (10 mL) under nitrogen atmosphere was added tetrakis(triphenylphosphine)palladium (60 mg, 5 mol%). The mixture was stirred at room temperature. After 40 min, a colorless solution was generated that was added to allyltributyltin (0.65 mL, 2.1 mmol). This mixture was heated at 80 °C for 24 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL), and the LiBrPd(II) complex removed by filtration. The filtrate was washed with 10% NaOH aqueous (2×15 mL), and the organic layer dried over Na_2SO_4. After the solvents were evaporated, the residue was purified by silica gel flash column chromatography (hexane/EtOAc=19:1) to give 3-allyl-5,8-dimethoxyquinoline (**9**) (215 mg, 90%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.55 (d, J=6.1 Hz, 2H), 3.92 (s, 3H), 4.00 (s, 3H), 5.08–5.13 (m, 2H), 5.96–6.03 (m, 1H), 6.71 (d, J=8.2 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 8.29 (s, 1H), 8.76 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 37.5, 55.8, 56.1, 103.8, 106.2, 117.0, 121.6, 129.7, 132.6, 133.2, 139.1, 148.5, 149.5, 150.1; FT-IR (KBr) 940, 982, 1463, 1478, 1602 cm^{-1}; MS (EI) m/z 229 (M^+), 214 (100); HRMS (EI) m/z calculated for $C_{14}H_{15}NO_2$ (M^+) 229.1103, found 229.1100.

*4.2.1. 4-Allyl-5,8-dimethoxyquinoline (**10**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.60–3.61 (m, 2H), 3.87 (s, 3H), 4.06 (s, 3H), 5.12–5.16 (m, 2H), 6.02–6.07 (m, 1H), 6.72 (d, J=8.2 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 7.48 (d, J=4.1 Hz, 1H), 8.72 (d, J=4.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.0, 56.1, 56.2, 105.7, 106.7, 120.0, 120.3, 129.4, 132.4, 141.6, 145.3, 149.2, 149.9, 150.2; FT-IR (KBr) 966, 1476, 1515, 1589, 1617 cm^{-1}; MS (EI) m/z 229 (M^+), 214 (100); HRMS (EI) m/z calculated for $C_{14}H_{15}NO_2$ (M^+) 229.1103, found 229.1107.

*4.2.2. 6-Allyl-5,8-dimethoxyquinoline (**11**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.60–3.61 (m, 2H), 3.87 (s, 3H), 4.06 (s, 3H), 5.12_5.16 (m, 2H), 6.02–6.07 (m, 1H), 6.85 (s, 1H), 7.45 (dd, J=13.0 , 4.1 Hz, 1H), 8.37 (dd, J=9.6 , 1.3 Hz, 1H), 8.89 (dd, J=9.4 , 1.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.9, 55.9, 62.7, 109.2, 116.4, 121.6, 124.0, 128.6, 130.7, 136.7, 139.8, 145.8, 148.8, 152.0; FT-IR (KBr) 920, 1503, 1504, 1593, 1618 cm^{-1}; MS (EI) m/z 229 (M^+), 214 (100); HRMS (EI) m/z calculated for $C_{14}H_{15}NO_2$ (M^+) 229.1103, found 229.1104.

4.3. General procedure for the synthesis of 12–14

To a solution of **9** (190 mg, 0.8 mmol) in dried THF (10 mL) at 0 °C under nitrogen atmosphere was added 1.0 M boran–tetrahydrofuran complex (1.3 mL, 1.3 mmol). After 1 h, water (1.0 mL) was added continuously to decompose the excess hydride. To the reaction mixture was added 4.0 N NaOH (2.0 mL), followed by addition of 28% hydrogen peroxide (3.0 mL) and stirred for 60 min. The crude product was extracted with EtOAc (2×5 mL) and washed (H_2O, brine). The organic layer was dried over Na_2SO_4. After removal of the solvent, silica gel flash column chromatography (hexane/EtOAc=1:5) gave 3-(3-hydroxypropyl)-5,8-dimethoxyquinoline (**12**) (125 mg, 61%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.89–1.93 (m, 2H), 2.84 (t, J=7.8 Hz, 2H), 3.64 (t, J=4.8 Hz, 2H), 3.87 (s, 3H), 3.96 (s, 3H), 6.66 (d, J=8.2 Hz, 1H), 6.78 (d, J=8.2 Hz, 1H), 8.27 (s, 1H), 8.74 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.5, 34.0, 55.8, 56.1, 61.9, 103.8, 106.0, 121.6, 129.7, 134.5, 139.0, 148.5, 149.5, 151.1; FT-IR (KBr) 920, 976, 1480, 1504, 1623, 1624 cm^{-1}; MS (EI) m/z 247 (M^+), 232 (100); HRMS (EI) m/z calculated for $C_{14}H_{17}NO_3$ (M^+) 247.1208, found 247.1207.

*4.3.1. 4-(3-Hydroxypropyl)-5,8-dimethoxyquinoline (**13**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.84–1.88 (m, 2H), 3.26 (t, J=7.6 Hz, 2H), 3.63 (t, J=6.2 Hz, 2H), 3.84 (s, 3H), 3.96 (s, 3H), 6.72 (d, J=8.2 Hz, 1H), 6.86 (d, J=8.2 Hz, 1H), 7.12 (d, J=4.1 Hz, 1H), 8.68 (d, J=4.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.3, 34.7, 55.8, 56.1, 62.5, 105.0, 106.7, 121.1, 123.1, 141.5, 149.0, 149.5, 149.9, 150.5; FT-IR (KBr) 971, 1403, 1468, 1521, 1610, 1617 cm^{-1}; MS (EI) m/z 247 (M^+), 232 (100); HRMS (EI) m/z calculated for $C_{14}H_{17}NO_3$ (M^+) 247.1208, found 247.1211.

*4.3.2. 6-(3-Hydroxypropyl)-5,8-dimethoxyquinoline (**14**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.92–1.97 (m, 2H), 2.92–2.97 (m, 2H), 3.59–3.62 (m, 2H), 3.90 (s, 3H), 4.07 (s, 3H), 6.84 (s, 1H), 7.47 (dd, J=12.3 , 4.1 Hz, 1H), 8.35 (dd, J=10.2, 2.0 Hz, 1H), 8.89 (dd, J=10.2, 2.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.9, 33.2, 56.1, 61.4, 62.7, 109.0, 121.7, 123.7, 130.3, 130.5, 139.7, 145.9, 148.8, 152.3; FT-IR (KBr) 953, 1474, 1505, 1620, 1622 cm^{-1}; MS (EI) m/z 247 (M^+), 232

(100); HRMS (EI) *m/z* calculated for $C_{14}H_{17}NO_3$ (M^+) 247.1208, found 247.1207.

4.4. General procedure for the synthesis of 15–17

To a solution of **12** (100 mg, 0.40 mmol) and triethylamine (0.12 mL, 0.80 mmol) in methylene chloride (10 mL) was added methanesulfonyl chloride (0.05 mL, 0.60 mmol) at 0 °C dropwise. After 1 h, the reaction mixture was quenched with H_2O. The reaction mixture was extracted with CH_2Cl_2 (1×3 mL). The organic layer was dried over Na_2SO_4. After removal of the solvent, silica gel flash column chromatography (hexane/EtOAc=1:4) gave 3-(3-methansulfonyloxypropyl)-5,8-dimethoxyquinoline (**15**) (76 mg, 57%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.09–2.13 (m, 2H), 2.89 (t, *J*=7.5 Hz, 2H), 2.94 (s, 3H), 3.89 (s, 3H), 3.97 (s, 3H), 4.19 (t, *J*=5.9 Hz, 2H), 6.69 (d, *J*=8.2 Hz, 1H), 6.83 (d, *J*=8.2 Hz, 1H), 8.29 (s, 1H), 8.74 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.2, 30.5, 37.5, 55.9, 56.1, 68.8, 104.2, 106.6, 121.5, 129.5, 133.0, 138.9, 148.4, 149.3, 150.5; FT-IR (KBr) 932, 979, 1480, 1543, 1607, 1623 cm^{-1}; MS (EI) *m/z* 325 (M^+), 310 (100); HRMS (EI) *m/z* calculated for $C_{15}H_{19}NO_5S$ (M^+) 325.0984, found 325.0982.

*4.4.1. 4-(3-Methansulfonyloxypropyl)-5,8-dimethoxyquinoline (**16**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.04–2.08 (m, 2H), 2.94 (s, 3H), 3.30 (t, *J*=7.5 Hz, 2H), 3.89 (s, 3H), 3.96 (s, 3H), 4.22 (t, *J*=6.2 Hz, 2H), 6.74 (d, *J*=8.2 Hz, 1H), 6.89 (d, *J*=8.2 Hz, 1H), 7.13 (d, *J*=10.6 Hz, 1H), 8.71 (d, *J*=10.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 31.2, 33.3, 37.4, 55.7, 56.2, 69.7, 105.1, 107.0, 120.8, 123.8, 141.6, 147.86, 149.1, 149.9, 150.3; FT-IR (KBr) 928, 980, 1502, 1504, 1594, 1620 cm^{-1}; MS (EI) *m/z* 325 (M^+), 310 (100); HRMS (EI) *m/z* calculated for $C_{15}H_{19}NO_5S$ (M^+) 325.0984, found 325.0982.

*4.4.2. 6-(3-Methansulfonyloxypropyl)-5,8-dimethoxyquinoline (**17**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.15–2.19 (m, 2H), 2.95 (t, *J*=7.5 Hz, 2H), 3.02 (s, 3H), 3.87 (s, 3H), 4.07 (s, 3H), 4.29 (t, *J*=6.2 Hz, 2H), 6.85 (s, 1H), 7.46 (dd, *J*=12.3 , 4.1 Hz, 1H), 8.35 (dd, *J*=10.3, 1.3 Hz, 1H), 8.90 (dd, *J*=10.3 , 1.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.2, 30.1, 37.4, 56.2, 62.5, 69.5, 109.0, 121.7, 124.0, 129.2, 130.6, 139.8, 146.2, 148.9, 152.2; FT-IR (KBr) 928, 978, 1471, 1503, 1594, 1620 cm^{-1}; MS (EI) *m/z* 325 (M^+), 310 (100); HRMS (EI) *m/z* calculated for $C_{15}H_{19}NO_5S$ (M^+) 325.0984, found 325.0980.

4.5. General procedure for the synthesis of 18–20

A mixture of **15** (40 mg, 0.12 mmol) and tetrabutylammonium fluoride hydrate (TBAF) (64 mg, 0.24 mmol) was dissolved in *tert*-amyl alcohol (3 mL) and heated at 80 °C for 2 h. The residue was extracted with EtOAc (3×5 mL), the organic layer dried over Na_2SO_4, evaporated, and purified by silica gel flash column chromatography (60% hexane/EtOAc=1:3) to give 3-(3-fluoropropyl)-5,8-dimethoxyquinoline (**18**) (30 mg, 98%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.99–2.07 (m, 2H), 2.88 (t, *J*=7.92 Hz, 2H), 3.88 (s, 3H), 3.96 (s, 3H), 4.42 (dt, *J*=47.4 , 5.8 Hz, 2H), 6.67 (d, *J*=8.3 Hz, 1H), 6.80 (d, *J*=8.3 Hz, 1H), 8.29 (s, 1H) 8.74 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.9 (d, *J*=5.7 Hz), 31.9 (d, *J*=20.1 Hz), 55.8, 56.1, 82.8 (d, *J*=165.2 Hz), 103.9, 106.2, 121.5, 129.5, 133.5, 139.2, 148.4, 149.6, 150.9; FT-IR (KBr) 914, 915, 1480, 1482, 1500, 1623 cm^{-1}; MS (EI) *m/z* 249 (M^+), 234 (100); HRMS (EI) *m/z* calculated for $C_{14}H_{16}NO_2F$ (M^+) 249.1165, found 249.1162.

*4.5.1. 4-(3-Fluoropropyl)-5,8-dimethoxyquinoline (**19**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.95–2.03 (m, 2H), 3.30 (t, *J*=7.5 Hz, 2H), 3.84 (s, 3H), 3.96 (s, 3H), 4.43 (dt, *J*=47.4 Hz, *J*=5.8 Hz, 2H), 6.72 (d, *J*=8.2 Hz, 1H), 6.87 (d, *J*=8.2 Hz, 1H), 7.13 (d, *J*=4.1 Hz, 1H) 8.70 (d, *J*=9.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 32.5 (d, *J*=4.3 Hz), 33.0 (d, *J*=18.7 Hz), 55.6, 56.2, 83.6 (d, *J*=165.2 Hz), 104.9, 106.7, 121.0, 123.8, 141.8, 148.5, 150.0, 150.4; FT-IR (KBr) 904, 910, 1467, 1570, 1616, 1621 cm^{-1}; MS (EI) *m/z* 249 (M^+), 234 (100); HRMS (EI) *m/z* calculated for $C_{14}H_{16}NO_2F$ (M^+) 249.1165, found 249.1162.

*4.5.2. 6-(3-Fluoropropyl)-5,8-dimethoxyquinoline (**20**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.06–2.15 (m, 2H), 2.95 (t, *J*=7.9 Hz, 2H), 3.88 (s, 3H), 4.07 (s, 3H), 4.53 (dt, *J*=47.4 , 5.8 Hz, 2H), 6.85 (s, 1H), 7.46 (dd, *J*=12.3 , 4.1 Hz, 1H), 8.36 (dd, *J*=10.3 , 1.3 Hz, 1H), 8.89 (dd, *J*=10.3, 1.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.9 (d, *J*=4.3 Hz), 31.4 (d, *J*=20.1 Hz), 56.1, 62.5, 83.4 (d, *J*=165.1 Hz), 109.0, 121.7, 124.0, 129.9, 130.6, 139.8, 146.2, 148.8, 152.1; FT-IR (KBr) 910, 912, 1470, 1504, 1619, 1621 cm^{-1}; MS (EI) *m/z* 249 (M^+), 234 (100); HRMS (EI) *m/z* calculated for $C_{14}H_{16}NO_2F$ (M^+) 249.1165, found 249.1162.

4.6. General procedure for the synthesis of 21–23

A solution of **18** (50 mg, 1.6 mmol) in THF (3.0 mL) was added to a well-stirred mixture of NBS (285 mg, 1.6 mmol) in a solution of THF (5.0 mL), H_2O (1.0 mL), and sulfuric acid (0.01 mL) at 20 °C. The mixture was stirred over 15 min and basified with aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3×5 mL). The organic layer was dried over Na_2SO_4. After removal of the solvent, silica gel flash column chromatography (hexane/EtOAc=1:4) gave 3-(3-fluoropropyl)quinoline-5,8-dione (**21**) (40 mg, 91%) as a tan solid; mp: 163–165 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.99–2.09 (m, 2H), 2.92 (t, *J*=7.5 Hz, 2H), 4.44 (dt, *J*=46.7 , 6.8 Hz, 2H), 7.19 (s, 1H), 7.51 (s, 1H), 8.17 (d, *J*=2.1 Hz, 1H), 8.25 (d, *J*=2.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.6 (d, *J*=4.3 Hz), 31.3 (d, *J*=20.1 Hz), 82.5 (d, *J*=166.6 Hz), 128.9, 133.8, 138.0, 139.2, 142.2, 145.8, 155.2, 183.2, 184.9; FT-IR (KBr) 937, 1590, 1687, 1716, 1782 cm^{-1}; MS (EI) *m/z* 219 (M^+), 191 (100); HRMS (EI) *m/z* calculated for $C_{12}H_{10}NO_2F$ (M^+) 219.0696, found 219.0692.

*4.6.1. 4-(3-Fluoropropyl)quinoline-5,8-dione (**22**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.99–2.09 (m, 2H), 3.25 (t, *J*=7.5 Hz, 2H), 4.47 (dt, *J*=47.4, 5.8 Hz, 2H), 7.10 (d, *J*=10.2 Hz, 1H), 7.40 (d, *J*=10.2 Hz, 1H), 7.46 (d, *J*=4.8 Hz, 1H), 8.83 (d, *J*=4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (d, *J*=4.1 Hz), 30.6 (d, *J*=20.0 Hz), 83.2 (d, *J*=165.4 Hz), 127.0, 130.7, 138.7, 141.2, 149.4, 153.6, 154.1, 176.4, 183.9; FT-IR (KBr) 937, 1530, 1627, 1716, 1776 cm^{-1}; MS (EI) *m/z* 219 (M^+), 198 (100); HRMS (EI) *m/z* calculated for $C_{12}H_{10}NO_2F$ (M^+) 219.0696, found 219.0697; mp: 180–182 °C.

*4.6.2. 6-(3-Fluoropropyl)quinoline-5,8-dione (**23**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.90–1.98 (m, 2H), 2.96 (t, *J*=7.5 Hz, 2H), 4.47 (dt, *J*=47.4, 5.4 Hz, 2H), 7.19 (s, 1H), 7.64 (t, *J*=12.4 Hz, 1H), 8.39 (t, *J*=9.6 Hz, 1H), 8.98 (d, *J*=4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.9 (d, *J*=4.2 Hz), 28.8 (d, *J*=21.4 Hz), 83.0 (d, *J*=166.6 Hz), 109.0, 127.8, 129.3, 134.8, 135.7, 147.6, 154.7, 183.4, 184.6; FT-IR (KBr) 936, 1581, 1676, 1715, 1780 cm^{-1}; MS (EI) *m/z* 219 (M^+), 198 (100); HRMS (EI) *m/z* calculated for $C_{12}H_{10}NO_2F$ (M^+) 219.0696, found 219.0697; mp: 156–158 °C.

4.7. General procedure for the labeling of [^{18}F]21–23

[^{18}F]Fluoride was produced in a cyclotron by the $^{18}O(p,n)^{18}F$ reaction. A volume of 100–200 μL of [^{18}F]fluoride (370 MBq) in water was added to a vacutainer containing *n*-Bu_4NHCO_3 (40% aq, 3.7 μL, 7.7 μmol). The azeotropic distillations were conducted with 200 μL aliquots of CH_3CN at 75 °C under a stream of nitrogen. A [^{18}F]fluoride displacement reaction of **10** (2.5 mg, 7.7 μmol) with *n*-Bu_4N [^{18}F]F in *tert*-amyl alcohol (500 μL) was carried out in a reaction vial at 100 °C for 20 min. After cooling to room temperature, a solution of NBS (5.6 mg, 30.7 μmol) in THF (300 μL), H_2O (100 μL), and sulfuric acid (50 μL) was added to the reaction mixture directly, and stirred for 5 min at room temperature. After the reaction mixture was basified with aqueous $NaHCO_3$, the solvent was removed with a gentle stream of nitrogen. The crude compound was injected onto a reversed-phase HPLC column with 10 mM aqueous phosphoric acid (1 mL) and

purified. The desired compound [^{18}F]**21** was collected from the HPLC (t_R=12.33 min; C18 silica gel, 10 μm, 4.6×250 mm; 10 mM aqueous phosphoric acid/ethanol=75:25 (v/v); 215 nm; 3 mL/min). For identification of the radioproduct, the collected HPLC fraction was co-injected with the cold compound **21**. The preparations of [^{18}F]**22**–**23** were followed with the same procedure with the preparations of [^{18}F]**21**. The total reaction time of [^{18}F]**21**–**23** was 75 min, and the overall decay-corrected radiochemical yield was approximately 45%. Specific activity was estimated by comparing UV peak intensity of the purified [^{18}F]-labeled compound with reference nonradioactive compounds of known concentrations. The specific activities of [^{18}F]**21**–**23** (in the range of 220–250 GBq/μmol) were obtained after purification on the HPLC column.

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Supplementary data

Detail procedures and characterization data including ^{1}H and ^{13}C NMR spectra of all new compounds, and HPLC chromatograms of ^{18}F-labeled derivatives [^{18}F]**21**–**23** are available free of charge via the internet at http://www.elsevier.com. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.057.

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