Synthesis of Radiolabeled ^{18}F-Fluoropropyl quinoline-5,8-diones under no-carrier-added (NCA) condition.

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Abstract:

We have described F-18 labeled [^{18}F]fluoropropylquinoline-5,8-diones [^{18}F]were prepared from the corresponding mesylate precursors by the radiofluorination with TBA[^{18}F]F generated under no-carrier-added (NCA) conditions, followed by direct oxidation reaction of the corresponding F-18 labeled dimethoxy compounds, resulting in 55% radiochemical yield of [^{18}F]27-29 (decay corrected) with total synthesis time (including the HPLC purification) of 65 min and high radiochemical purity (> 99%) as well as high specific activity (approximately 250 GBq/μmol).

Keywords: *Quinoline, Radiochemistry, Fluorine-18, Positron emission tomography (PET).*

Introduction:

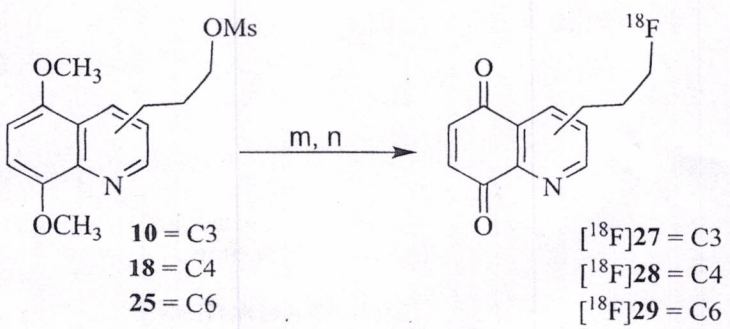
The quinoline-5,8-diones derivatives is the main structure have been the centre of interest to a large number of studies because of their large area of biological activity. Many structural version of quinolone derivatives showed that number of more complex antibiotic agents such as streptonigrin, streptonigrone, and lavendamycin, has been bring forward to be important in resolved their antitumor activity.

There is no evidance of the synthesis of a radiolabeled with quinoline-5,8-dione derivatives which are the pharmacophore of streptonigrin and lavendamycin with [^{18}F]fluorine radiostope. Despite the fact that positron-emitting tomography of radiopharmaceuticals labeled with the short lived positron emitting radionuclide like fluorine-18 which have half-life period is $t_{1/2}$ = 110 min are being gradually more used in clinical diagnosis, these are some chemical procedure suitable for the formation of fluorine-18 into the organic molecule in drugs. Several of the compounds are used in positron emission tomography (PET) contain active radioisotope functional groups, which further limit the choice of the synthetic pathway. The abality of beging put labeling method in radiofluoration, the synthesis of a radiotracer, including purification, usually has to be completed within short time compare with half-lives of the radionuclide. Accordingly, a general method for introduction of the radionuclide quickly and efficient reactions with purification that can be performed on a small scale and under mild conditions within time. To improve or grow radio tracer for imaging of body organs specially tumor, several [^{18}F]fluoropropylquinoline-5,8-dione derivatives were synthesised. Considering pharmacophore and stability of target in vitro and in vivo, the structure of quinoline-5,8-dione derivatives with [^{18}F]fluoropropyl group at C3, C4 and C6 positions are prepared for the synthesis of radiolabeled quinolone derivatives.

Result and Discussion:

The preparation of [^{18}F]fluoropropylquinoline-5,8-dione at C3, C4, and C6 position ([^{18}F]27, [^{18}F]28, and [^{18}F]29) was carried out in one-pot reaction: the displacement [^{18}F]fluoride ion using activated n-Bu4N[^{18}F]F complex reaction with mesylate 10, 18, and 24 in tert-amyl alcohol at 100 °C for 20 min and the second radiochemical step is the oxidative demethylation using NBS in the presence of water and a catalytic amount of sulfuric acid in THF proceeded for 5 min at room temperature.

Scheme 1.



10 = C3
18 = C4
25 = C6

[^{18}F]**27** = C3
[^{18}F]**28** = C4
[^{18}F]**29** = C6

Reagents and conditions: (m) n-Bu$_4$N^{18}F, t-amyl alc., 100 °C, 20 min; (n) NBS, H_2O, conc. H_2SO_4, 23 °C, 5 min.

[^{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 (37-370 MBq) in water was added to a vacutainter containing n-Bu$_4$NHCO$_3$ (40% aq, 3.7 μL,

7.68 μmol). The azeotropic distillations were conducted with 200 μL aliquots of CH3CN at 75 °C under a stream of nitrogen. A [^{18}F]fluoride displacement reaction of 10 (2.5 mg, 7.68 μmol) with n-Bu_4N[^{18}F]F in tert-amyl alcohol (500μL) 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, 30.73 μmol) in THF (300 μL), H_2O (100 μL) and a catalytic amount of sulfuric acid (50 μL) was added. The reaction mixture was stirred for 5 min at room temperature. After the content was basified with aqueous $NaHCO_3$ (pH = 5 - 6). The solvent was removed with a gentle stream of nitrogen. The crude compound was injected onto reverse-phase HPLC with the help of 10mM aqueous phosphoric acid (1 mL) and purified. The desired compounds [^{18}F]27 was collected from HPLC (tR = 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 the identification of the radioproduct, the collected HPLC fraction was coinjected with the cold compound 12. The labeling of [^{18}F]27-29 was followed with the same procedure. The total reaction time of [^{18}F]27- 29 was 75 min, and the overall decay-corrected radiochemical yield was about 40-50%. Specific activity at the end of synthesis was calculated by relating radioactivity to the mass associated with the UV absorbance (215 nm) peak of cold compound.

Experimental Section:

Reagents and solvents are purchased from Sigma-Aldrich and used without further purification. [^{18}F]Fluoride ion was produced from a cyclotron (KIRAMS 13 MeV, South Korea) using the ^{18}O(p,n)18F nuclear reaction with 19 MeV proton irradiation of an enriched [^{18}O]H2O target. High performance liquid chromatography (HPLC) was performed with spectra system SCM100 degasser, P4000 pump, and UV/vis 3000 detector (Thermo Scientific, Waltham, MA) using Hypersil gold semipreparative column (C18 silica gel, 10 μm, 10 × 250 mm) and analytic column (C18 silica gel, 5 μm, 4.6 × 250 mm). ChromQuest 4.2 software was used to record chromatogram. The flow was 4 mL/min, with the mobile phase 10mM aqueous phosphoric acid/ethanol = 75:25 (v/v, pH 2.25). The eluant was simultaneously monitored by a UV detector (215 nm) and a NaI(Tl) radioactivity detector. Radioactivity was measured in a dose calibrator.

Conclusion:

The In summary, we have described the synthesis of a variety of fused 1,4-quinone molecules labeled with short half-life (t1/2 = 110 min) radionuclide fluoride-18 for PET molecular imaging study. We have obtained [^{18}F]27-29 in 45, 45, and 46% yields, respectively with radiochemical purity (> 99%) and high specific activity ([^{18}F]27; 230 GBq/μmol, [^{18}F]28; 220 GBq/μmol, [^{18}F]29; 240 GBq/μmol). The overall radiosynthesis of [^{18}F]27-29 with a total synthesis time (including the HPLC purification) was about 75 min..

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