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Synthesis of (Mesylates) quinoline-5, 8-dione Precursor for Nucleophilic Fluorination Reaction

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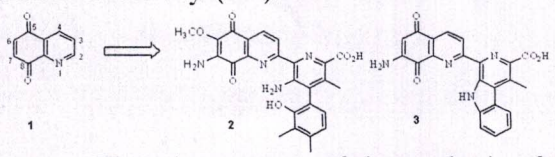
ABSTRACT

We have described a two-step method for the preparation of (Fluoropropyl)quinoline-5,8-dione. The sequence involved fluoride ion displacement of methanesulfonates (mesyltaes) of quinoline-5,8-dione derivatives, followed by the oxidative demethylation in using NBS in the presence of water and a catalytic amount of sulfuric acid. To develop positron emission tomography tracer for imaging of tumors, we described the efficient synthetic route for the preparation of fluoropropyl substituted quinolin-5,8-diones on C3, C4 and C6 position regioselectively using the corresponding mesylate precursors.

KEYWORDS: Quinoline-5,8-dione, Radiofluorination,

Introduction

The quinoline-5,8-diones (1-4) moiety is the principle structure have been the focus of a large number of studies because of their wide spectrum of biological activity[1]. Many structural variants of **1** showed that number of more complex antibiotic agents such as streptonigrin, streptonigrone, and lavendamycin, has been proposed to be important in determining their antitumor activity[2] (5-7).



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There is no report of the synthesis of a radiotracer with quinoline-5,8-dione derivatives which are the pharmacophore of streptonigrin and lavendamycin having [^{18}F]fluorine. Although positron-emitting radiopharmaceuticals labeled with the short lived positron emitting radionuclide fluorine-18 ($t_{1/2}$ = 110 min) are being increasingly used in clinical diagnosis, these are few chemical processes suitable for the introduction of fluorine-18 into the organic molecule are limited[3]. Many of the compounds are used in positron emission tomography (PET) contain sensitive functional groups, which further restrict the choice of the synthetic pathway (8-9). To be useful labeling method in PET, the synthesis of a radiotracer, including purification, usually has to be completed within three half-lives of the radionuclide. Consequently, a general method for incorporation of the radionuclide demands fast and efficient reactions that can be performed on a small scale and under mild conditions (10-11). To develop PET tracer for imaging of tumors, several [^{18}F]fluoropropylquinoline-5,8-dione derivatives were designed. 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.

Experimental Section.

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 spectra were recorded on a 600 MHz spectrometer.

Chemical shifts were reported in ´ 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.

Results and Discussion:

We now report the chemistry of these compounds and introduce efficient route by which a number of novel C-3, C-4, and C-6-substituted derivatives of quinoline-5,8-diones can be prepared.

A convenient method for the synthesis three of its allyl substituted 5,8-dimethoxyquinoline derivatives (**8, 16,** and **22**) as the key intermediate is shown in Scheme 1. The treatment of commercially available 2,5-dimethoxy aniline (**4**) with acroline via Doebner-Miller reaction using conc. HBr at 70 °C for 1 h provide the 5,8-dimethoxyquinoline (**5**) in 23% isolated yield[4]. The C3 and C6 position of bromo substituted 5,8-dimethoxyquinoline (**7, 21**) was synthesized by two way, first is treatment of **5** with NBS at 23 °C in methylene chloride for 12 h provide **21** in 61% isolated yield and second is overnight treatment of **5** with m-CPBA at 65 °C in chloroform provide the N-oxide **6**, which was brominated using $POBr_3$ at 60 °C in chloroform for 12 h gave the **7** in 23% isolated yield[5].

The 2,5-dimethoxy aniline **4** in trimethyl orthoformate was refluxed for 6 h provide **13** in 77% isolated yield. Thermolysis of **13** in diphenyl ether at 250 °C afforded quinolinone **14**, followed by the treatment with trifluoromethanesulfonic anhydride, 2,6-lutidine, and a catalytic amount of 4-(dimethylamino)pyridine in methylene chloride at 23 °C to give **15** in 52% isolated yield. The synthesis of the ally substituted at C3, C4 and C4

Reagents and conditions.

(i) (i) 1 M BH_3 in THF, 0 °C, 1 h. (ii) H_2O, 4 N NaOH, H_2O_2, 23 °C, 3 h, 61%; (j) MsCl, TEA, 23 °C, 1 h, 61%; (k) TBAF, *t*-amyl alc., 90 °C, 1 h, 95%; (l) NBS, H_2O, conc. H_2SO_4, 23 °C, 5 min, 90%.

The oxidative demethylation of 5,8-dimethoxyfluoropropyl quinoline derivatives to fluoropropyl quinoline-5,8-diones **12**, **20**, and **26** using NBS in the presence of water and a catalytic amount of sulfuric acid in THF also proceeded within 10 min. in 90% yield. It is impossible to oxidized mesylate 5,8-dimethoxyquinoline derivatives to quinoline-5,8-dione derivatives because bromination of the aromatic ring in addition to or instated of oxidative demythylation.

Conclusion:

In summary, Thus we have to introduced a fluoroalkyl group at C3, C4 and C6 position of Quinoline-5,8-dione and also synthesized methanesulfonates (mesyltaes) of quinoline-5,8-dione derivatives as a precursor for making ^{18}F-fluoride ion radiolabeling molecule, which applicable for Positron Emission Tomography (PET) imaging study. Therefore we described the efficient synthetic route to prepared mesylate-propylquinoline-5,8-dione derivatives at C3, C4 and C6 position of quinoline-5,8-diones by fluoride ion displacement and oxidative demethylation condition using NBS in the presence of water and catalytic sulforic acid.

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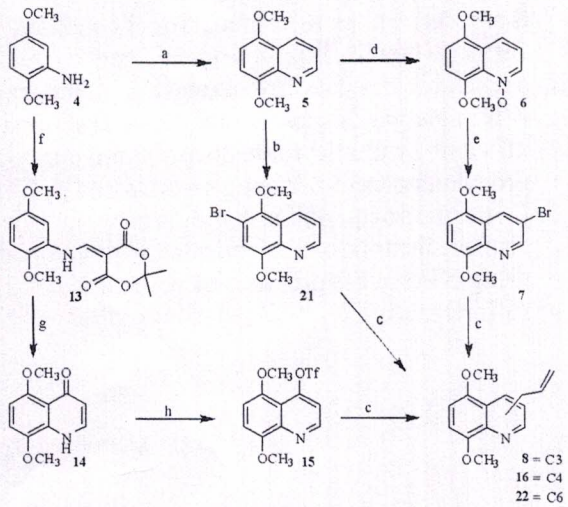
position of quinoline, compounds **7, 15,** and **21** is treated with allyltributyltin in the presence of Pd(PPh3)3 and lithium bromide in distilled THF gave the **8, 16,** and **22**.

Scheme 1:



Reagents and conditions.

(a)Acrolein, conc.HBr, 60 °C, 1 h, 23%;
(b) NBS, CH_2Cl_2, 23 °C, 12 h, 65%;
(c)
(i) LiBr, $Pd(PPh_3)_3$, THF, 30 °C, 30 min.
(ii) allyltributyltin, 85 °C, 24 h, 90%;
(d) *m*-CPBA, CH_2Cl_2, 65 °C, 24 h, 85%;
(e) $POBr_3$, chloroform, 60 °C, 12 h, 23%;
(f)(i) trimethylorthoformate, 90 °C, 2 h.
(ii) 2,2-dimethyl-1,3-dioxane-4,6-dione, 90 °C, 4 h, 77%;
(g) phenyl ether, 250 °C, 2 h, 80%;
(h) triflate anhydride, DMAP, 2,6-lutidine, CH_2Cl_2, 23 °C, 12 h, 52%.

The hydroxypropylquinoline derivatives **9, 17,** and **23** were prepared by hydroxylation of olefin (**8**, **16**, and **22**) with using boron-tetrahydrofuron complex, followed by mesylation of these alcohols afford a mesylates **10**, **18**, and **24**. The displacement reaction of these mesylated to fluoropropylquinoline derivatives **11**, **19**, and **25** using tetra n-butyl ammonium fluoride in ter-amyl alcohol at 100 °C for 1 h proceeded smoothly as shown (Scheme 2)[6] (12-13). Thus, much attention has been focused on the facile oxidation of fused 1,4-dimethoxybenzenes to 1,4-quinone. Although oxidation of 1,4-hydroxyquinones is much easier than that of 1,4-dimethoxybenzenes, however its process was failed to get an authentic sample because of fluorine was substituted to bromine under demythlation.

So the oxidative dimethylation affords quinines from dimethoxybenzenes using several oxidizing agents like ceric ammonium nitrate (CAN), argentic oxide, or conc. nitric acid (13-14). Ceric ammonium nitrate has been mostly used during over the last decade in the synthesis of quinines, especially oxidative demethylation of dimethoxybenzenes[7].

However, it has limited solubility in common organic solvents and sometimes it needed a cooxidant for oxidation like 2,6-dicarboxylic pyridine acid *N*-oxide (DCPNO) for oxidative demethylation of 5,8-dimethoxyquinoline derivatives to quinoline-5,8-dione derivatives[8].

There is an report to demonstrated mild oxidative dimethylation of fused 1,4-dimethoxybenzenes to 1,4-quinones using NBS in the presence of aqueous THF and a catalytic amount of sulfuric acid which gives good yield compare to other[9] (15-17).

Scheme 2: