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Research Article

Synthesis of ^{18}F-labeled cyclooxygenase-2 (COX-2) inhibitor as a potential PET imaging agent

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Summary

A new PET tracer for COX-2 imaging, the 6-ethoxy-3-(4-methanesulfonylphenyl)-4-(4-[^{18}F]fluorophenyl)pyran-2-one ([^{18}F]EFMP), was synthesized. For F-18 radiolabeling, a trimethylammonium precursor and a brominated precursor were synthesized from 1,1,2,3-tetrachlorocycloprop-2-ene in 6 steps. The radiolabeling was achieved through nucleophilic substitution using no-carrier-added (n.c.a.) fluorine-18. Solid-phase extraction and semi-preparative-HPLC purification produced [^{18}F]EFMP in $14.6 \pm 3.3\%$ ($n = 4$) decay corrected radiochemical yield with a specific activity of 487 ± 85.1 ($n = 4$) Ci/mmol and greater than 98% radiochemical purity. Copyright © 2006 John Wiley & Sons, Ltd.

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Key Words: fluorine-18; COX-2 inhibitor; nucleophilic substitution

Introduction

Cyclooxygenase-2 (COX-2) is an enzyme that converts arachidonic acid to prostaglandin H_2. COX-2 is expressed in normal brain and kidney, activated macrophages, synoviocytes during inflammation, and malignant epithelial cells of several major cancers. COX-2 expression is stimulated by a number of inflammatory cytokines, growth factors, oncogenes, lipopolysaccharides, and tumor promoters.[1,2] Generally, COX-2 expression in humans is assessed by

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ex vivo laboratory analysis of tissue samples acquired by biopsy or autopsy.[3] Because COX-2 messenger RNA (mRNA) and protein are unstable, the accuracy of *ex vivo* COX-2 analysis strongly depends on the interval between tissue sampling and analysis.[4] A noninvasive imaging method to monitor COX-2 expression *in vivo* is thus needed to overcome this problem. *In vivo* imaging of COX-2 would also provide a valuable tool to gain more insight in pathophysiology of diseases involving COX-2. Over-expression of COX-2 in arthritis, organ rejection, myocardial infraction, cancer, pain sensation, stroke, and neurodegenerative diseases has been reported,[5–8] which makes COX-2 a potential target for therapeutic intervention and diagnosis based on noninvasive medical imaging technique such as positron emission tomography (PET). Although attempts have been made to develop PET probes for COX-2 imaging, currently no satisfactory COX-2 PET imaging agents are available for *in vivo* imaging of COX-2 expression. McCarthy *et al.*[9] reported the radiosynthesis of ^{18}F-SC58125 as a COX-2 PET tracer for investigation of the COX-2 pathway in inflammatory diseases. But, it showed high nonspecific binding *in vivo*, which would limit the usefulness of this imaging probe. de Vries *et al.*[10] reported [^{18}F]-Desbromo-DuP-697, another radiolabeled COX-2 inhibitor that was evaluated in a rat model for carrageenan-induced hyperalgesia, which exhibited substantial nonspecific uptake in fat and intestine. Isakson *et al.*[11] reported the synthesis of several labeled COX-2 inhibitors without demonstrating specific binding *in vivo*. Toyokuni *et al.*[12] reported the synthesis of [^{18}F]fluoromethyl analogue of valdecoxib, and biodistribution studies in mice revealed rapid defluorination and accumulation of the radioactive label in bone, which made it unfit for imaging to COX-2 in this species. However, studies in vervet monkeys revealed much later and much less prominent defluorination, suggesting its potential role for imaging in humans. More recently, F-18 labeled Rofecoxib,[13] C-11 labeled Celecoxib[14] and C-11 labeled Etoricoxib[15] have been synthesized as COX-2 selective radiotracers. However, *in vivo* studies have not been published with these compounds.

In this study, we investigated feasibility of labeling a new generation of COX-2 inhibitors as radiotracers for PET imaging to quantitatively assess COX-2 expression *in vivo*. We select to synthesize [^{18}F]EFMP, an F-18 labeled COX-2 inhibitor for PET imaging studies of COX-2 *in vivo*. The structure of the COX-2 inhibitor, 6-ethoxy-4-(4-fluorophenyl)-3-(4-methanesulfonyl-phenyl)-pyran-2-one (EFMP) is shown in Figure 1. It exhibits excellent potency ($IC_{50} = 0.10\,\mu M$) and selectivity ($SI = 2880$) for COX-2[16] better than Desbromo-DuP-697, SC-58125, etc. Its anti-inflammatory activity was also studied revealing a much better anti-inflammatory activity than that of the celecoxib.[16] The structure of EFMP permits incorporation of ^{18}F through a nucleophilic reaction between [^{18}F]fluorine and a trimethylammonium

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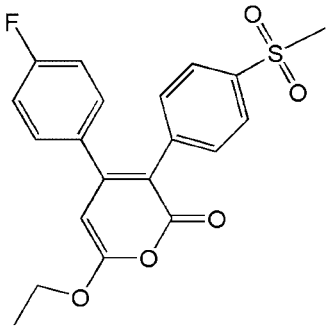

Figure 1. Selective COX-2 inhibitors: EFMP

precursor. This manuscript summarizes the radio-synthesis procedure. We plan to use microPET imaging along with other assays to extensively evaluate the potential of this new COX-2 imaging agent on mouse models in the near future. One of the models is transgenic, in which the erbB2/HER-2/neu oncogene was expressed under tissue-specific transcriptional control of the mouse mammary tumor virus promoter (MMTV-LTR) and represents a suitable model of mammary carcinogenesis paw. The relationship between COX-2 and breast cancer has been proposed,[17] and PET imaging using the new tracer reported here will directly measure COX-2 expression in breast cancer. Similar PET imaging will also be used for assessing COX-2 level in a mouse model of colorectal cancer since COX-2 is over-expressed in 85% of colon cancers.[18]

Results and discussion

For F-18 radiolabeling, the trimethylammonium precursor **5** and brominated precursor **3b**, were synthesized as depicted in Scheme 1. Aryltrimethylammonium is often used by many as a leaving group in the nucleophilic substitution of n.c.a. [^{18}F]fluoride.[19] Our initial strategy was to introduce trimethylammonium directly starting with dimethylaniline (Scheme 1, R = NMe_3). Unfortunately, when we tried to prepare 2-(4-dimethylamino-phenyl)-3-(4-methanesulfonyl-phenyl)-cycloprop-2-enone (**1c**) through tandem Friedel–Crafts arylation reaction of 1,1,2,3-tetrachlorocycloprop-2-ene with *N*,*N*-dimethylbenzenamine in the presence of $AlCl_3$, no product of **1c** was obtained. This might be due to the fact that the benzene ring of **1c** was not sufficiently active upon protonation of dimethylamine group in the presence of the acid solution. An alternative approach was then taken, in which 2-(4-bromo-phenyl)-3-(4-methanesulfonyl-phenyl)-cycloprop-2-enone **2b** was first prepared with a yield of 69.0%. The 4-(4-bromophenyl)-6-ethoxy-3-(4-methanesulfonyl-phenyl)-pyran-2-one **3b** was prepared with a yield of 17.2% by condensation of **2b** with a pyridinium salt **6** in the presence of

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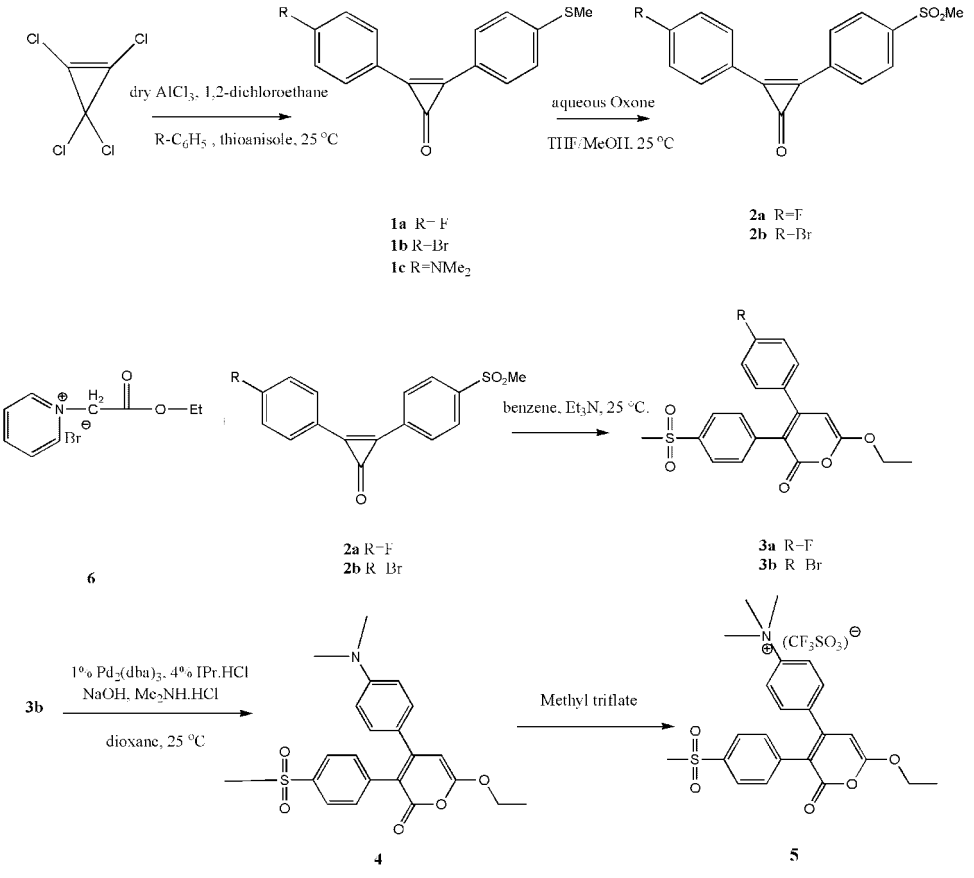

Scheme 1. Synthesis of 6-ethoxy-4-(4-fluorophenyl)-3-(4-methanesulfonyl-phenyl)-pyran-2-one (EFMP) and trimethylammonium precursor 5 and brominated precursor 3b

triethylamine. The pyridinium salt **6** was prepared from ethyl bromoacetate with pyridine according to a previously published method.[20]

For the synthesis of trimethylamino derivative **5**, palladium-catalyzed coupling reaction was used, which proved to be an efficient method for substitution of aryl halogen atoms by amine according to a previous report.[21] The palladium (0)/imidazolium salt catalyzed amination of aryl bromides was achieved at room temperature. To effectively accelerate the reaction rate, a palladium-substrate ratio of 1:2 was used and led to an isolated yield (30.3%). As shown in Scheme 1, 4-(4-dimethylamino-phenyl)-6-ethoxy-3-(4-methanesulfonyl-phenyl)-pyran-2-one **4** was prepared based on the amination reaction catalyzed by $Pd_2(dba)_3$/IPr.HCl. The treatment of **4** with methyl triflate thus produced the desired trimethylammonium salts **5**.

Following the production of [^{18}F]fluoride through ^{18}O(p,n) nuclear reaction, EFMP was radiolabeled by the nucleophilic substitution reaction using the

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Table 1. Effect of temperature of fluorination trimethylammonium salt in acetonitrile

Reaction time (min)	Temperature (°C)	Labeling yield (% ± SD) $n = 3$
20	100	28.4 ± 6.85
20	130	86.8 ± 2.01
20	140	75.1 ± 6.53

n represents number of runs, SD: standard deviation.

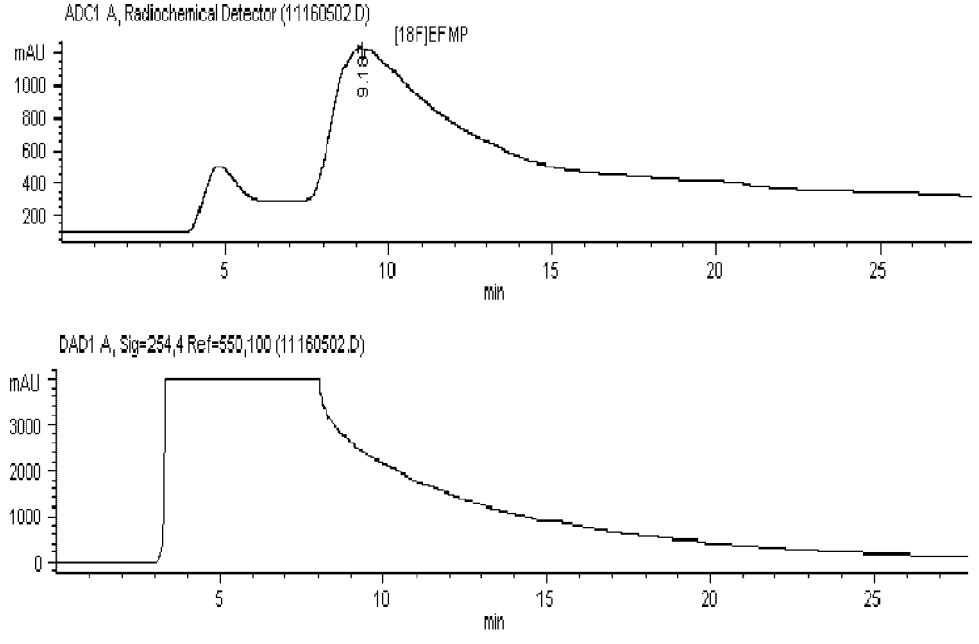

Figure 2. The separation of semi-preparative HPLC-chromatograms of [^{18}F]EFMP

trimethylammonium precursor in CH_3CN. The labeling yields at different temperatures were examined. It appeared that the labeling reaction at 130°C was appropriate for trimethylammonium substitution (Table 1). Following rapid Sep-Pak (C-18) extraction, the radiolabeled product was further purified by HPLC (Alltech Econosil C18, 250 × 10 mm, 5 mm column, 0.1% TFA: acetonitrile, 50:50 mixture as an eluent at a flow rate of 3.0 ml/min) with a radiochemical yield of 14.6 ± 3.3% ($n = 4$)(decay corrected) (Figure 2). The total synthesis took 60–70 min (EOB). The radiochemical purity of [^{18}F]EFMP was verified by co-elution of the radioactive peak with nonlabeled standard. The specific activity was determined at 487 ± 85.1 ($n = 4$) Ci/mmol at EOS.

Similarly, radiofluorination of brominated precursor was also studied in DMSO at 160°C. As shown in Scheme 2, [^{18}F]EFMP was obtained in 4%

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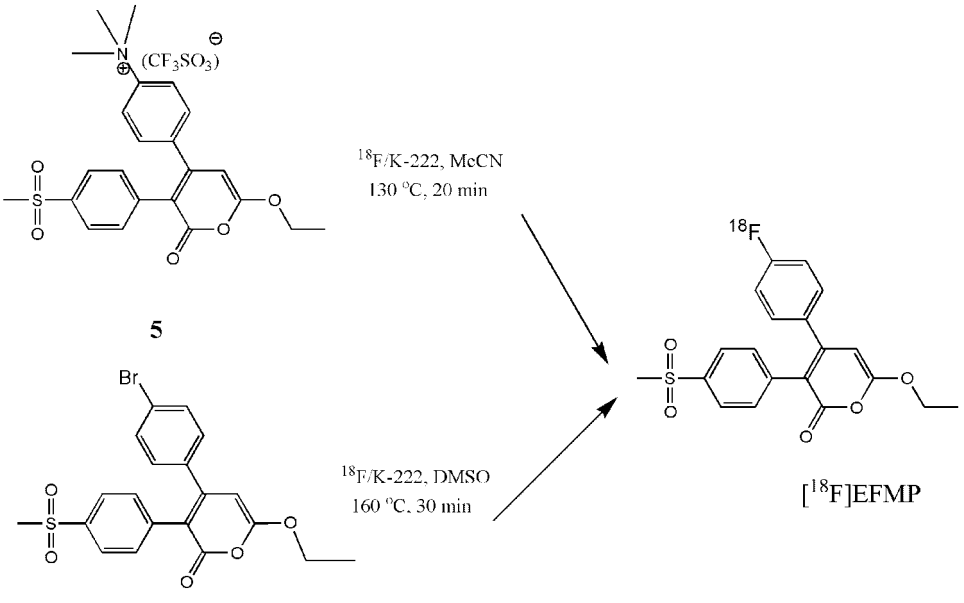

Scheme 2. Radiofluorination of trimethylammonium precursor and brominated precursor

radiochemical yield following purification by semi-preparative HPLC. However, this approach was not optimized as it was difficult to separate the brominated precursor from the final product, resulting in decreased specific activity of [^{18}F]EFMP.

Experimental

Materials and methods

Chemicals for the syntheses were purchased from commercial sources (Sigma-Aldrich) and were used without further purification. Solvents of the highest grade were used. Infrared (IR) spectra were recorded using a Digilab FTS-60 FTIR system. ^{1}H NMR spectra were obtained on a Varian Gemini-2000(200-MHz) instrument in $CDCl_3$ using tetramethylsilane as the internal standard. High-resolution mass-spectrometry (HRMS), fast atom bombardment (FAB) mode (glycerol matrix) was obtained at 20–40 eV on a Kratos MS-25A instrument. HPLC analysis and purification were performed on Hewlett-Packard 1050 using an in-line UV detector (254 nm), and a NaI crystal flow-count radioactivity detector (Beckman Model 170 Radioisotope Detector). A dose calibrator (model CRC-7, Capintec) was used for all radioactivity measurements. Compounds **1a**, **2a**, **3a** were synthesized according to previously reported procedures with some modification.[16] [^{18}F]fluoride was

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produced by bombardment of [^{18}O]H_2O using a Scanditronix MC-17 cyclotron. Flash chromatography was performed using silica gel (230–400 mesh, Merck).

Chemistry

2-(4-bromo-phenyl)-3-(4-methylthiophenyl)cycloprop-2-en-1-one (**1b**). To a suspension of dried $AlCl_3$ (4.50 g, 33 mmol) in 1,2-dichloroethane (80 ml) was added 1,1,2,3-Tetrachlorocycloprop-2-ene (5.31 g, 30 mmol) at 0°C. Under stirring bromobenzene (4.68 g, 30 mmol) was added to the reaction mixture. There action was allowed to proceed at 25°C for 24 h while the color of the reaction mixture was changed from yellow to red. Thioanisole (3.72 g, 30 mmol) was then added and the reaction mixture was stirred for an additional 24 h at 25°C, while the color of mixture was changed from red to deep green. Eventually green solid was precipitated. Ice water (100 g) was then added to the reaction mixture and the organic and aqueous layers were separated. The aqueous layer was extracted with 1,2-dichloroethane (2×40 ml), and the combined organic fractions were washed successively with $NaHCO_3$ (50 ml of 5% wt/vol) and water (50 ml) and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave the crude product as a yellow solid. Recrystallization of the mixture from MeOH-ether (twice) afforded 8.36 g (84.1%) of the product **1b**. IR(KBr): 1854 cm^{-1}(C=O), 1610 cm^{-1}(C=C); ^{1}H NMR($CDCl_3$): $\delta = 2.57$(s, 3 H, SCH_3), 7.34(dd, 2H, fluorophenyl H-3, H-5), 7.44(d, 2H, methylthiophenyl H-3, H-5), 7.76(d, 2H, methylthiophenyl H-3, H-5), 7.88(dd, 2H, fluorophenyl H-2, H-6).

2-(4-bromo-phenyl)-3-(4-methanesulfonyl-phenyl)-cycloprop-2-enone (**2b**). A solution of oxone (6.25 g, 10.1 mmol) in water (30 ml) was added slowly to a solution of **1b** (0.27 g, 8.1 mmol) dissolved in MeOH/THF (50 ml of 1:1, vol/vol) at ice-bath temperature. While stirring, the reaction mixture was allowed to warm to 25°C, and proceed for 24 h. White solid was then precipitated. Removal of the solvent *in vacuo* gave a residue, which was dissolved in water (25 ml) and $CHCl_3$ (100 ml). The organic phase was separated and washed with water and then brine before it was dried over Na_2SO_4. Removal of the solvent from the organic fraction *in vacuo* gave a light yellow solid that was purified by silica gel column chromatography using EtOAc-hexane (2:1, vol/vol) as eluents to afford 0.205 g (69%) of the product as white needle. IR(KBr): 1854 cm^{-1}(C=O), 1624 cm^{-1}(C=C); ^{1}H NMR($CDCl_3$): $\delta = 3.12$(s, 3H, SO_2CH_3), 7.75(dd, 2H, bromophenyl H-3, H-5), 7.82(d, 2H, methylsulfonyl-phenyl H-2, H-6), 8.08(dd, 2H, bromophenyl H-2, H-6), 8.14(d, 2H, methylsulfonylphenyl H-3, H-5). MS, m/z, M^+ 360.760, calculated for $C_{16}H_{11}{}^{77}BrO_3S$: 360.230.

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*N-(ethoxycarbonylmethyl)-pyridinium bromides (**6**)*. To a stirred solution of dry pyridine (9.0 ml, 11.0 mmol) in anhydrous THF (50 ml) was added ethyl bromoacetate (1.84 g, 11.0 mmol) under an argon atmosphere. The reaction mixture was stirred for 4 h at 25°C till white solid was precipitated. The solvent was removed *in vacuo*, and the solid product obtained was purified by recrystallization from methanol/ether to give 1.31 g (51.5%) of the product as white solid m.p.132–134°C (lit.,[20] 134–136°C); ^{1}H NMR(DMSO-d_6): $\delta = 1.23$(t, 3H, OCH_2CH_3), 4.25(q, 2H, OCH_2CH_3), 5.75 (s, 2H, N^+CH_2), 8.22(dd, 2H, pyridine H-3, H-5), 8.70(dd, 1H, pyridine H-4), 9.10(d, 2H, pyridine H-2, H-4).

*6-ethoxy-3-(4-methanesulfonylphenyl)-4-(4-bromophenyl)pyran-2-one(**3b**)*. To a solution of the N-(ethoxycarbonylmethyl)-pyridinium bromides (2.09 g, 8.5 mmol) in anhydrous benzene (150 ml) at 25°C was added dry triethylamine (3.3 ml, 23 mmol), followed by addition of **2b** (3.0 g, 8.3 mmol). The reaction mixture was stirred for 24 h at 25°C, while the color of the mixture was changed from yellow to deep green. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography using hexanes-ethyl acetate (5:5, v/v) as eluents to afford 637 mg (17.2%) of the product as green solid. IR (KBr): 1722 cm^{-1}(C=O), 1147 cm^{-1}(SO_2); ^{1}H NMR($CDCl_3$): $\delta = 1.49$(t, 3H, OCH_2CH_3), 3.05(s, 3H, SO_2CH_3), 4.38(q, 2H, OCH_2CH_3), 5.55(s, 1H, pyranone H-5), 6.95(dd, 2H, bromophenyl H-3, H-5), 7.30(dd, 2H, bromophenyl H-2, H-6), 7.38(d, 2H, methylsulfonylpheny H-2, H-6), 7.78(d, 2H, methylsulfonylpheny H-3, H-5). MS, m/z, M^+ 446.298, calculated for $C_{20}H_{17}{}^{77}BrO_5S$: 446.310.

*6-ethoxy-3-(4-methanesulfonylphenyl)-4-(4-dimethylamino-phenyl)pyran-2-one(**4**)*. The $Pd_2(dba)_3$ (6.6 mg, 0.0115 mmol) and 1Pr.HCl (19.6 mg, 0.046 mmol) were added into the mixture of 1,4,-dioxane (20 ml), NaOH (240 mg, 6.0 mmol), **3b** (520 mg, 1.15 mmol), and dimethylamine hydrochloride (123 mg, 1.5 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 24 h at room temperature. The mixture was then diluted with water then extracted with diethyl ether. The extracts were combined, washed with saturated saline solution, and then dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography, the desired product **4** was obtained in 30.3% yield as yellow solid. ^{1}H NMR($CDCl_3$): $\delta = 1.49$(t, 3H, OCH_2CH_3), 3.05(s, 3H, SO_2CH_3), 3.10(s, 6H, dimethylaminophenyl) 4.38(q, 2H, OCH_2CH_3), 5.55(s, 1H, pyranone H-5), 6.95(dd, 2H, dimethylaminophenyl H-3, H-5), 7.30(dd, 2H, dimethylaminophenyl H-2, H-6), 7.38(d, 2H, methylsulfonylpheny H-2, H-6), 7.78(d, 2H, methylsulfonylpheny H-3, H-5). MS, m/z, M^+ 413.230, calculated for $C_{22}H_{23}NO_5S$: 413.085.

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*6-ethoxy-3-(4-methanesulfonylphenyl)-4-(4-trimethylammonium trifluoromethane sulfonate phenyl)pyran-2-one(***5***)*. To a solution of **4** (40 mg, 0.07 mmol) dissolved in 5 ml of anhydrous methylene chloride was added methyl trifluoromethanesulfonate (9 µl, 0.08 mmol). The reaction solution was stirred at room temperature overnight. At the end of the reaction, the solvent was evaporated under reduced pressure and the residue was recrystallized from MeOH/Et_2O to give 12.3 mg (22.5%) of the product as brown solid. ^{1}H NMR($CDCl_3$): $\delta = 1.49$(t, 3H, OCH_2CH_3), 3.05(s, 3H, SO_2CH_3), 3.10(s, 9H, trimethylaminophenyl) 4.38(q, 2H, OCH_2CH_3), 5.55(s, 1H, pyranone H-5), 6.95(dd, 2H,trimethylaminophenyl H-3, H-5), 7.30(dd, 2H, trimethylaminophenyl H-2, H-6), 7.38(d, 2H, methylsulfonylpheny H-2, H-6), 7.78(d, 2H, methylsulfonylpheny H-3, H-5). MS, *m*/*z*, M^+ 577.233, calculated for $C_{24}H_{26}F_3NO_8S_2$: 577.590.

Radiosynthesis of 6-ethoxy-4-(4-[^{18}*F]fluorophenyl)-3-(4-methanesulfonyl-phenyl)-pyran-2-one ([*^{18}*F]EFMP)*. To a 10-ml V-vial containing 4.0 mg of potassium carbonate, 50 µl of water, and 22 mg of Kryptofix-2.2.2 in 200 µl of acetonitrile was added [^{18}F]fluoride. The water was then removed through evaporation with anhydrous acetonitrile under argon flow on a 120°C oil bath. To the above-mentioned test vial containing the anhydrous [^{18}F]fluoride ion was added 2 mg of precursor **5** dissolved in 0.5 ml of acetonitrile. The vial was sealed and heated on the oil bath at 130°C for 20 min. The reaction mixture was cooled to room temperature and diluted with 1.0 ml acetonitrile and passed through a C-18 Sep-Pak$^@$ cartridge activated with methanol and water. After the column was washed with 5 ml water, [^{18}F]EFMP was then eluted with 5 ml of acetonitrile. The solvent was removed under argon flow. Upon dissolving in HPLC mobile phase, the mixtures were injected onto the preparative HPLC column. Reversed phase semi-preparative HPLC (Alltech Econosil C18, 250 × 10 mm, 5 mm column) was performed with 0.1% TFA: acetonitrile, 50:50 mixtures as an eluent at a flow rate of 3.0 ml/min. The effluent in semi-preparative HPLC was monitored with an ultraviolet detector at 254 nm coupled with a gamma-radioactivity detector, and the radioactive fraction having a retention time of 7.8–9.2 min was collected in a flask. After collection and evaporation to dryness, the product was dissolved in 3.0 ml of sterile normal saline and filtered through a sterile 0.2 mm filter into a sterile evacuated vial. Radiochemical purity and specific activity of the product [^{18}F]EFMP was determined by analytical reversed phase HPLC (Alltech Econosil C18, 250 × 4.6 mm, 5 mm column).

Radiofluorination of the brominated precursor **3b** was conducted similarly. The reaction was conducted in DMSO at 160°C for 30 min. The reaction mixture was then cooled to room temperature and diluted with 1.0 ml water before being passed through a C-18 Sep-Pak$^@$ cartridge activated with

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methanol and water. The column was washed with 5.0 ml water. [^{18}F]EFMP was then eluted with 5 ml of acetonitrile and the solvent was removed under argon flow. After being dissolved in HPLC mobile phases, the crude product was injected onto the preparative HPLC column for further purification and analysis.

Conclusion

In summary, [^{18}F]EFMP, a potential F-18 labeled radiotracer for *in vivo* PET imaging of COX-2 expression, has been successfully synthesized via a trimethylammonium precursor. The radiosynthesis appeared to be superior to that via a brominated precursor. After short reaction and fast purification, the radiotracer was obtained with high specific activity and radiochemical and chemical purity.

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