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Research Article

Synthesis of [^{11}C]celecoxib: a potential PET probe for imaging COX-2 expression

Jaya Prabhakaran[1], Vattoly J. Majo[1], Norman R. Simpson[2,3], Ronald L. Van Heertum[3], J. John Mann[1,2,3] and J. S. Dileep Kumar[1,2,*]

[1] *Department of Psychiatry, Columbia University, New York, NY 10032, USA*
[2] *Division of Neuroscience, New York State Psychiatric Institute, 1051 Riverside Drive, Box 42, New York, NY 10032, USA*
[3] *Department of Radiology, Columbia University, New York, NY 10032, USA*

Summary

[^{11}C]Labeling of celecoxib, a COX-2 selective inhibitor and prescription drug for arthritis and pain has been achieved. The precursor molecule for the radiolabeling was synthesized from 4-bromoacetophenone in 4 steps with 23% overall yield. Stille reaction of N-[*bis*-(4-methoxyphenyl)phenylmethyl]-4-[5-(4-tributylstannylphenyl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (**5**) with methyl iodide in presence of catalytic amounts of $Pd_2(dba)_3$, tri-*o*-tolylphosphine, CuCl and excess of K_2CO_3 in DMF followed by deprotection of the sulfonamide with 20% trifluoroaceticacid yielded 4-(5-*p*-tolyl-3-trifluoromethylpyrazol-1-yl)benzenesulfonamide or celecoxib (**6**) in 30% yield. However, under identical conditions, synthesis of [^{11}C]celecoxib ([^{11}C]**6**) was unsuccessful. Instead, trapping [^{11}C]CH_3I in an argon purged solution of catalytic amounts of $Pd_2(dba)_3$ and tri-*o*-tolylphosphine followed by the addition of the precursor **5** in DMF under argon and heating the mixture at 135°C for 4 min resulted in the incorporation of [^{11}C]CH_3 group. Removal of the dimethoxytrityl (DMT) with 20% trifluoroacetic acid afforded [^{11}C]celecoxib in 40 min (EOB) and 8 ± 2% yield (EOB) along with a specific activity of 1080 ± 180 Ci/mmol ($n = 6$) (EOB).

Key Words: celecoxib; COX-2 expression; prostaglandins; NSAIDs; PET ligand

*Correspondence to: J. S. Dileep Kumar, Department of Psychiatry and Division of Neuroscience, Columbia University and New York State Psychiatric Institute, 1051 Riverside Drive, PO Box 42, New York, NY 10032, USA. E-mail: dk2038@columbia.edu

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Introduction

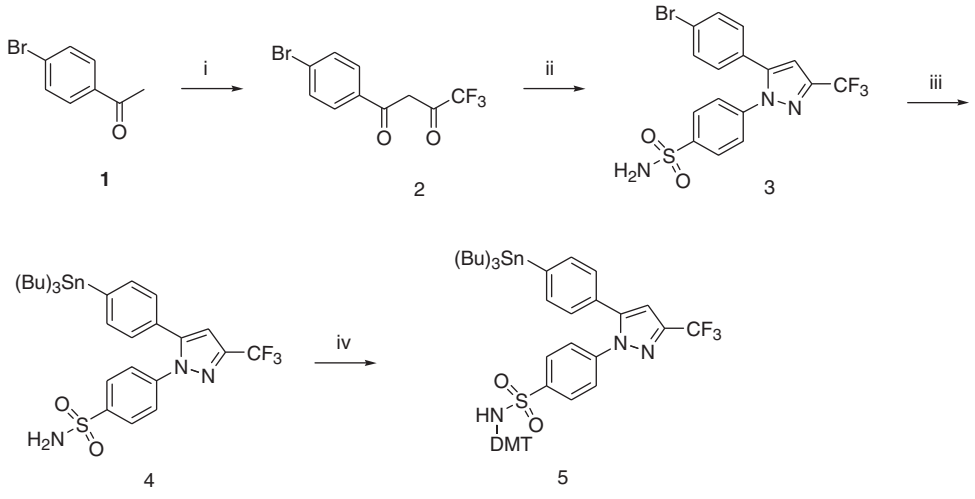
Cyclooxygenase (COX) is the key enzyme involved in the biosynthesis of prostaglandins, prostacyclins and thromboxanes from arachidonic acid.[1] There are three isoforms of COX. COX-1 is constitutively expressed in many tissues and is responsible for the production of prostanoids associated with normal homeostatic functions.[2] In most tissues, COX-2 is mainly induced by inflammatory stimuli except for heart, kidney and brain.[3] COX-3 has been more recently identified and is believed to be the isoform that mediates the antipyretic action of aspirin and other antipyretic analgesics.[4] The discovery of COX-2 led to a new generation of drugs called non-steroidal anti-inflammatory drugs (NSAIDs) that selectively inhibit COX-2.[5–8] COX-2 over expression contributes to the pathogenesis of arthritis, organ rejection, myocardial infraction, cancer, pain sensation, stroke and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.[9–12] To examine the role of COX-2 in these conditions, it would be of great advantage to quantitatively monitor COX-2 expression *in vivo*, non-invasively and repeatedly over time. We therefore, sought to develop specific PET imaging probes that target COX-2 enzyme. Such PET tracers are powerful tools for relating therapeutic effect of NSAIDs to enzyme blockade, and to blood level of medication as well as to evaluate the side effects of NSAID medications in cardiac, renal and reproductive functions.

Efforts undertaken, prior to our studies, to develop a successful PET probe for COX-2 expression by several other groups were unsuccessful or have not published any *in vivo* image data so far.[13–17] Development of a PET tracer with high specific binding to COX-2 would therefore be useful and in this report we describe the radiolabeling of celecoxib, the known and safe COX-2 inhibitor. Our rodent studies with [^{18}F]celecoxib resulted in de[^{18}F]fluorination *in vivo* and hence we pursued the synthesis of [^{11}C]celecoxib as a potential marker for COX-2 expression.[18] The synthesis of [^{11}C]celecoxib and its radiolabeling precursor are described herein.

Results and discussion

The synthesis of [^{11}C]celecoxib (**6**) was achieved through the precursor N-[*bis*-(4-methoxyphenyl)phenylmethyl]-4-[5-(4-tributylstannylphenyl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (**5**). Attempts to synthesize sulfonamide **5** by the condensation of 4,4,4-trifluoro-1-[4-(tributylstannyl)phenyl] butane-1,3-dione with 4-sulfonamidophenylhydrazine hydrochloride resulted in destannylation. We therefore pursued the strategy of introducing the stannyl group after the formation of the pyrazole ring (Scheme 1).

Towards this, compound **1** was first condensed with N-trifluoroacetylimidazole using NaHMDS as the base in THF at –78°C to room temperature. This afforded 1-(4-bromophenyl)-4,4,4-trifluorobutane-1,3-dione (**2**) in 84%



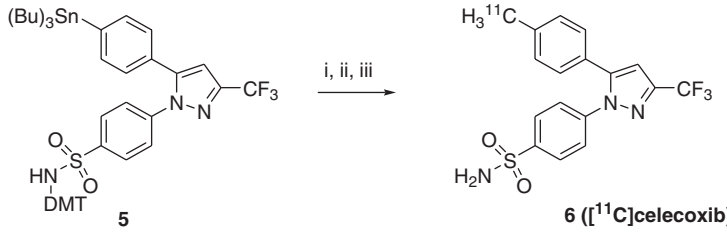
Scheme 1. Synthesis of [^{11}C]celecoxib precursor: (i) NaHMDS, N-trifluoroacetylimidazole, THF, −78°C ∼ rt, 12 h, 84%; (ii) 4-sulfonamidophenylhydrazine. HCl, ethanol, 90°C, 75%; (iii) $Pd(PPh_3)_4$, hexabutylbisstannane, dioxane, 90°C, 24 h, 51%; (iv) DMT-Cl, triethylamine, DCM, rt. 72%

yield which was then refluxed with 4-sulfonamidophenylhydrazinehydrochloride in ethanol to obtain 4-[5-(4-bromophenyl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (**3**) in 75% yield. The introduction of the tributylstannyl group to bromopyrazole **3** was then accomplished in 51% yield using tetrakistriphenylphosphine palladium and hexa-*n*-butyl-bisstannane in refluxing dioxane under argon.[19] Using the tributyltinpyrazolesulfonamide **4** thus obtained, we attempted the synthesis of celecoxib using a protocol described by Suzuki *et al.*[20,21] This involves the use of catalytic amounts of $Pd_2(dba)_3$, tri-*o*-tolylphosphine, CuCl and K_2CO_3 in DMF. This reaction resulted in a mixture of products and the major products isolated from this reaction were identified as 4-(5-phenyl-3-trifluoromethylpyrazol-1-yl)benzenesulfonamide (destannylated **4**) and the starting material **4** itself by ^{1}HNMR. We attribute this failure to a possible interaction of copper reagents with the free sulfonamide group or pyrazole ring of the precursor molecule **4**. Therefore, the sulfonamide group of **4** was protected using dimethoxytrityl (DMT) group to obtain pyrazole derivative **5** as the precursor for radiosynthesis in 72% yield.

It is to be noted that under palladium catalyzed conditions, the DMT protective group is eliminated when stirred for longer period of time and hence the protection of the sulfonamide group has to follow the stannylation reaction that utilizes palladium catalyst. The bulky DMT group also possibly provides sufficient steric hindrance around the sulfonamide group preventing

the incorporation of methyl iodide on the sulfonamide nitrogen atom. DMT group can also be cleaved under relatively milder conditions in 2 min and therefore it appears to be ideal for sulfonamide protection while conducting ^{11}C-methylation reactions. The reaction of DMT-stannane **5** with CH_3I in presence of catalytic amounts of $Pd_2(dba)_3$, tri-*o*-tolylphosphine, CuCl and K_2CO_3 in DMF yielded celecoxib (30% yield) using a two-pot strategy described by Bjorkman *et al.*[22] This involves reacting methyl iodide with a DMF solution of $Pd_2(dba)_3$ and (*o*-tolyl)$_3$P purged with argon for 15 min followed by stirring with a mixture of copper salt, the tin precursor and potassium carbonate in DMF under argon. However, the radiosynthesis of [^{11}C]celecoxib was unsuccessful under these conditions with [^{11}C]CH_3I or [^{11}C]CH_3OTf. In the absence of copper and base the reaction was achieved by initially trapping [^{11}C]CH_3I for 5 min in a solution of catalytic amounts of $Pd_2(dba)_3$ and (*o*-tolyl)$_3$P in DMF, purged with argon for 15 min. To this mixture a DMF solution of the precursor **5** purged with argon for 15 min was added and the mixture was heated at 135°C for 4 min. Subsequent removal of the DMT group with 20% trifluoroacetic acid in dichloromethane (0.8 ml) followed by reverse-phase HPLC purification and isolation using C-18 Sep Pak® afforded [^{11}C]celecoxib ([^{11}C]**6**) (Scheme 2). The average yield of [^{11}C]celecoxib was 8% ($n = 6$, SD = 2) at EOB with >99% chemical and radiochemical purity. The chemical identity of [^{11}C]celecoxib was additionally confirmed using analytical HPLC by co-injecting with non-radioactive celecoxib. The specific activity of [^{11}C]celecoxib was calculated based on a standard mass curve using HPLC technique and was found to be 1080 Ci/mmol ($n = 6$, SD = 180).

Yield and specific activity of [^{11}C]celecoxib were found to be highly dependent on the rate of trans-metallation of the tin precursor with the palladium reagent produced *in situ*. To achieve consistency of yield and specific activity, the integrity of reagents must be maintained in the highest quality for each synthesis. The detection of palladium or tin impurities in the formulated radioligand solution may be necessary to use [^{11}C]celecoxib in



Scheme 2. Radiosynthesis of [^{11}C]celecoxib: (i) $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, [^{11}C]CH_3I, DMF, 135°C, 4 min; (ii) TFA (20% in DCM), 60°C, 5 min; (iii) Preparative HPLC

human subjects. Our estimation of the residual amount of palladium and tin using atomic absorption spectroscopy (AAS) in the purified [^{11}C]celecoxib was found to be <31 and <39 ppb, respectively.

Experimental section

Melting points were determined on a Fisher Melting point apparatus and are uncorrected. ^{1}H and ^{19}F NMR spectra were recorded on a Bruker PPX 300 MHz spectrometer and Bruker PPX 282.5 MHz spectrometer, respectively. Spectra were recorded in $CDCl_3$ and chemical shifts are reported in ppm relative to TMS for ^{1}H and $CFCl_3$ for ^{19}F as internal standards. The mass spectra were recorded on JKS-HX 11UHF/HX110 HF Tandem Mass Spectrometer in the FAB+ mode. The HPLC analyses were performed using Waters 1525 HPLC system (column: Phenomenex, Prodigy ODS(3) 4.6×250 mm, 5 μm for analytical and Phenomenex C18, 10×250 mm, 10 μm for semi preparative RP-HPLC). Flash column chromatography was performed on silica gel (Fisher 200–400 mesh) using the solvent system indicated. The [^{11}C]MeOTf and [^{11}C]CH_3I were synthesized from [^{11}C]CO_2 according to a reported procedure.[23,24] Elemental analyses of the reported compounds and the residual amount of palladium and tin in the purified [^{11}C]celecoxib were performed using atomic absorption spectroscopy (AAS) by the service of Galbraith Laboratories Inc., Knoxville, TN, USA.

1-(4-Bromophenyl)-4,4,4-trifluorobutane-1,3-dione (**2**)

4′-Bromoacetophenone (**1**, 400 mg, 2.01 mmol) was dissolved in anhydrous THF (4.0 ml) and 1 M NaHMDS (3.0 ml, 3.0 mmol) was added to it at –78°C. The solution was warmed to 0°C and stirred for 45 min followed by the addition of N-trifluoroacetylimidazole (394 mg, 2.4 mmol) in THF (1.5 ml) after cooling to –78°C. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched by adding brine, and the products were extracted into ethyl acetate (4×25 ml). The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by silica gel column chromatography using a gradient of 20–50% ethyl acetate in hexane to obtain the title compound in 84% yield (500 mg).

2: ^{1}H NMR ($CDCl_3$) δ: 7.80 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 2H), 6.53 (s, 2H); ^{19}F NMR ($CDCl_3$) δ: −75.511(s); HRMS (EI^+) calculated for: $C_{10}H_6O_2BrF_3$: 293.9502; found 293.9493.

4-[5-(4-Bromophenyl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (**3**)

A solution of 1,3-diketone, **2** (545 mg, 1.85 mmol) and 4-sulfonamidophenylhydrazine hydrochloride (497 mg, 2.22 mmol) in absolute ethanol (6.0 ml) was

refluxed for 24 h. The solvent was evaporated under reduced pressure and the products were purified by silica gel column chromatography. The desired product **8** was obtained in 75% yield (663 mg) as a yellow solid upon elution with 1:1 ethyl acetate and hexane.

3: m.p: 60–65°C (decomposed); ^{1}H NMR ($CDCl_3$) δ: 7.80 (d, $J = 7$ Hz, 2H), 7.49–7.42 (m, 4H), 7.09 (m, 2H), 6.7 (s, 1H), 5.39 (brs, 2H); ^{19}F NMR ($CDCl_3$) δ: −61.493 (s); HRMS (FAB^+) calculated for: $C_{16}H_{12}O_2N_3BrF_3S$: 447.2554; Found: 447.2542.

4-[5-(4-Tributylstannylphenyl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (**4**)

A solution of 4-bromobenzenesulfonamide **3** (68 mg, 0.15 mmol) in anhydrous dioxane (0.5 ml) was added to $Pd(PPh_3)_4$ (18 mg, 0.015 mmol) under argon. To this mixture a solution of hexabutylbisstannane (265 mg, 0.5 mmol) was added in 1 ml dioxane. The mixture was heated at 90°C under argon atmosphere for 24 h. Aqueous KF solution (1 ml) was added to remove the tin impurities. The products were extracted into ethyl acetate and the ethyl acetate layer was washed with water and brine. The solvent was evaporated under reduced pressure and the product was purified by silica gel column chromatography using 25% ethyl acetate in hexane as the eluent. A colorless paste was obtained in 51% yield (50 mg).

4: ^{1}H NMR ($CDCl_3$) δ: 7.85 (d, $J = 8$ Hz, 2H), 7.42 (m, 4H), 7.15 (d, $J = 8$ Hz, 2H), 6.69 (s, 1H), 5.26 (s, 2H), 1.59–0.79 (m, 27H); ^{19}F NMR ($CDCl_3$) δ: −61.48 (s); HRMS (FAB^+) calculated for: $C_{28}H_{39}O_2N_3F_3SSn$: 657.4078; Found: 657.4087.

N-[Bis-(4-methoxyphenyl)phenylmethyl]-4-[5-(4-tributylstannylphenyl)-3-trifluoromethyl-pyrazol-1-yl]benzenesulfonamide (**5**)

The sulfonamide **4** (20 mg, 0.03 mmol) was dissolved in dichloromethane (1.0 ml) followed by the subsequent addition of DMT-Cl (12.2 mg, 0.036 mmol) and triethylamine (10.0 µl, 0.075 mmol). The reaction mixture was stirred at room temperature for 30 min and the solvent was evaporated. The crude mixture was purified by silica gel column chromatography using 20% ethyl acetate in hexane as the eluent. The DMT protected compound **5** was obtained in 72% yield (21.0 mg).

5: m.p: 44–47°C (decomposed); ^{1}H NMR ($CDCl_3$) δ: 7.46–7.08 (m, 17H), 6.72–6.65 (m, 5H), 5.79 (s, 1H), 3.8 (brs, 6 H), 1.51–0.85 (m, 27H); ^{19}F NMR ($CDCl_3$) δ: −61.50 (s); HRMS (FAB^+) calculated for: $C_{49}H_{57}O_4N_3F_3SSn$: 959.7805; Found: 959.7826; Analytically Calculated for $C_{49}H_{57}O_4N_3F_3SSn$: C 61.39; H 5.89; N 4.38. Found: C 61.30; H 5.76; N 4.35.

Synthesis of celecoxib

$Pd_2(dba)_3$, (5.70 mg, 0.0062 mmol) and tri-*o*-tolylphosphine (7.5 mg, 0.025 mmol) were dissolved in DMF (0.4 ml) and the solution was purged with argon for 15 min under argon. In a separate flask CuCl (12.30 mg, 0.12 mmol) and K_2CO_3 (1.7 mg, 0.01 mmol) were taken in 0.4 ml of DMF and purged with argon for 10 min followed by the addition of the stannyl precursor **5** (30.0 mg, 0.031 mmol) in DMF (0.5 ml) under argon atmosphere. Methyl iodide (3.70 ml, 0.031 mmol) in 20 ml DMF was added to the flask containing $Pd_2(dba)_3$ and tri-*o*-tolylphosphine and the mixture was kept for 5 min followed by transferring it to the second flask. The combined reaction mixture was heated at 60°C for 30 min. The reaction was cooled to room temperature and 20% TFA in dichloromethane was added to it. The solids were filtered out and water (10.0 ml) was added to the reaction mixture. The products were extracted into ethyl acetate and the ethyl acetate layer was dried over anhydrous $MgSO_4$. Purification of the product by silica gel column chromatography using a gradient of 30–40% ethyl acetate in hexane afforded 4-(5-*p*-tolyl-3-trifluoromethyl-pyrazol-1-yl)benzenesulfonamide (celecoxib, **6**) in 30% yield (3.8 mg). The formation of celecoxib was characterized based on comparing HPLC retention time and ^{1}H NMR analyses of the authentic compound.

Radiosynthesis of [^{11}C]celecoxib

[^{11}C]MeI was purged through a solution of 1 mg of $Pd_2(dba)_3$ and 1.3 mg of $(o\text{-tolyl})_3P$ in 0.5 ml DMF for 5 min in an atmosphere of argon at room temperature. The solution was kept for additional 2 min and treated with an argon purged solution of 1 mg of precursor **5** in 0.4 ml of DMF. The resulting mixture was allowed to react at 135°C for 4 min and allowed to cool to room temperature. One milliliter of 20% trifluoroacetic acid in dichloromethane was added to the reaction mixture and the solution was heated at 60°C for 5 min with a slow stream of argon to remove dichloromethane. The resulting solution was passed though a nylon filter (0.2 μM) to remove the precipitated palladium. The filtrate was diluted with 20 ml deionized water and passed through a C-18 Sep Pak®. The Sep Pak® was eluted with 2 ml acetonitrile and injected into an HPLC column (mobile phase: 50:49:1, acetonitrile: water: acetic acid, flow rate: 10 ml/min) and the product fraction was collected between 9 and 10 min based on a γ-detector. The collected fraction was then diluted with deionized water (100 ml), passed through a C-18 Sep Pak® and washed twice with water (2×20 ml) to ensure the complete removal of acetic acid. Reconstitution of the product in ethanol afforded [^{11}C]celecoxib in 8% yield (EOB, based on [^{11}C]MeI).[21] A small portion of the product was analyzed with analytical HPLC (mobile phase: 50:49:1, acetonitrile: water:

acetic acid, flow rate: 2 ml/min, rt: 8 min) to obtain chemical, radiochemical purities and for specific activity measurements.

Conclusion

A Stille type radiosynthesis of [^{11}C]celecoxib has been achieved. The precursor molecule for the radiolabeling was synthesized from 4′-bromoacetophenone in 4 steps with an overall yield of 23%. Reaction of radiolabeling precursor **5** with [^{11}C]MeI in presence of catalytic amounts of $Pd_2(dba)_3$ and tri-*o*-tolylphosphine provided [^{11}C]celecoxib in an average yield of $8 \pm 2\%$ at EOB with excellent chemical and radiochemical purity. [^{11}C]celecoxib, the COX-2 selective inhibitor radioligand, may be used as a potential marker for labeling COX-2 with PET.

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