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Research Article

Synthesis of an iodine-123-labeled celecoxib analogue: a potential spect agent

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Summary

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl]-benzenesulfonamide) is an effective inhibitor of the cyclooxygenase-2 (COX-2). The synthesis of a no-carrier-added iodine-123-labeled analogue of celecoxib was accomplished in four steps for potential use in single photon tomography. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: celecoxib; SPECT; radioiodination; radio-TLC; colon cancer

Introduction

The arachidonic acid (AA)-metabolizing enzyme cyclooxygenase-2 (COX-2) is frequently but not always over-expressed in adenocarcinomas of the lungs, pancreas, colon, stomach, breast and prostate, leading to the increased formation of AA-metabolites that stimulate tumor growth.[1,2] *In vitro* studies with cell lines derived from such cancers and experiments in relevant animal models as well as epidemiological studies in humans have provided evidence that non-selective COX inhibitors (e.g. aspirin, ibuprofen) as well as selective COX-2 inhibitors (e.g. celecoxib) can significantly reduce the risk for the development of this cancer family.[3–14] COX-2 inhibitors are therefore currently being tested in cancer prevention and treatment trials. COX-2 inhibitors are also widely used for treatment of arthritis[15,16] and they are being tested as preventive agents for Alzheimer's disease.[17]

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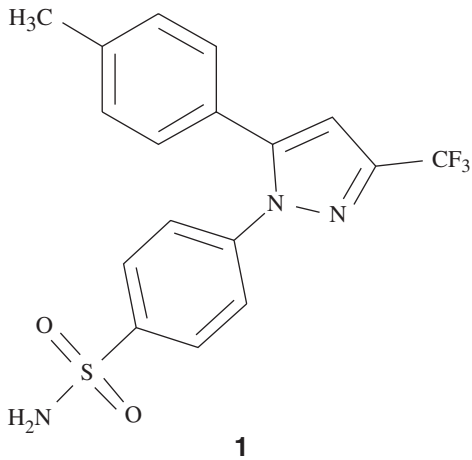

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Figure 1. Structure of celecoxib

A potential problem with the chronic use of COX-2 agents is the fact that physiological levels are necessary to ensure the proper balance of AA-metabolites that are critical mediators of cardiovascular and kidney function as well as platelet aggregation.[18,19] Recent reports have revealed that chronic use of the selective COX-2 inhibitor VIOXX significantly increased cardiovascular mortality.[19,20] This finding emphasizes the need to monitor COX-2 levels in patients subjected to chronic treatments with this family of drugs prior to therapy as well as during treatment. Non-invasive nuclear medicine imaging with a suitable radiolabeled COX-2 inhibitor would be an ideal tool to achieve this goal. Our research efforts have focused on the synthesis of a no-carrier-added radioiodinated analogue of celecoxib (**1**, Figure 1) for use as a single photon emission tomography (SPECT) imaging agent.

Results and discussion

The iodine-123-labeled 4-iodo analogue of celecoxib (**2**, Figure 2) was chosen for the study, based on the fact that substitution of a halogen for the 4-methyl group did not significantly alter the COX-2/COX-1 selectivity in the initial report. Thus, the chloro analogue of **1** showed a binding affinity of $K_i = 0.01$ and 17.8 μM for COX-2 and COX-1, respectively. Thus, the 4-chloro analogue proved to be more selective than celecoxib, which showed a binding affinity of $K_i = 0.04$ and 15.0 μM for COX-2 and COX-1.[21]

The synthesis of the no-carrier-added iodine-123-labeled analogue of celecoxib, **2**, is outlined in Scheme 1. 4-Iodoacetophenone, **3**, was converted into the requisite tin precursor in three steps. The initial reaction involving conversion of **3** to **4**, in the presence of NaOMe/MeOH proceeded in good yield (79%). Intermediate **4** was refluxed with 4-(sulfamoylphenyl)hydrazine hydrochloride in ethanol to give **5** in 91% yield.[21] Compound **5** was subjected

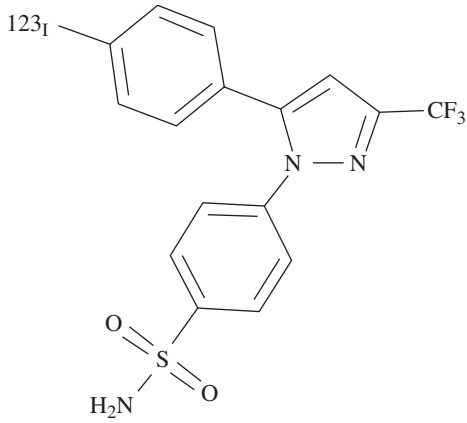

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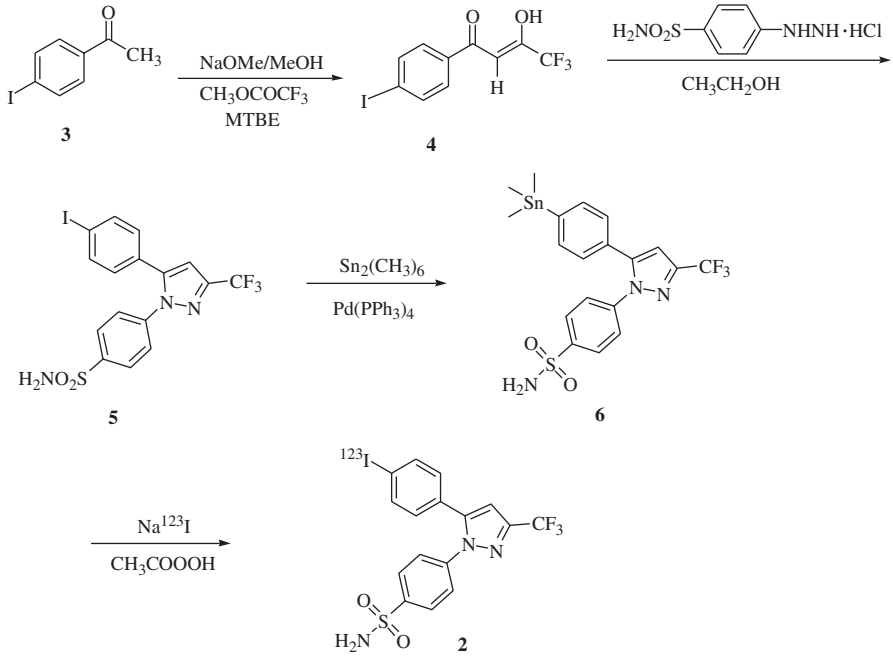
Figure 2. Radioiodinated analogue of celecoxib



3 4 5 6 2

Scheme 1. Synthesis of analogue 2

to a palladium-catalyzed deiodostannylation using hexamethylditin and tetrakis(triphenylphosphine)palladium(0) in refluxing dioxane to generate **6** in 90% yield.[22] The no-carrier-added radioiodination of trimethylstannyl derivative **6** was conducted by conventional electrophilic iododestannylation using $Na^{123}I$ and dilute peracetic acid, which produced **2** in a decay corrected radiochemical yield of 90% and a radiochemical purity $>98\%$. Product purification can be achieved by thin layer chromatography (silica gel, ethyl

ether/hexane = 3:1) since the R_f of **2** (0.61) is significantly different from that of tin precursor **6** (0.72).

Experimental

Elemental analyses were performed by Atlantic Micro Labs, Inc., Norcross Georgia. Melting points were recorded on an electrothermal Digital Melting Point Apparatus and are uncorrected. ^{1}H and ^{13}C spectra were recorded on a Bruker AC 250 MHz NMR spectrometer. The chemical shift values are expressed in parts per million (δ) relative to tetramethylsilane. Radio thin layer chromatography was carried out using a Bioscan, AR-2000 imaging scanner. All starting materials were purchased from Aldrich Chemical Company. $Na^{123}I$ was obtained from Nordion Inc., Vancouver, Canada. All reactions were carried out using dry solvents under an inert atmosphere.

*4,4,4-Trifluoro-1-(4-iodophenyl)-butane-1,3-dione (**4**)*

To a solution of methyl trifluoroacetate (4.23 g, 33.0 mmol) in 60 ml of methyl *tert*-butyl ether (MTBE) was added a 25% solution of NaOMe in MeOH (8.82 ml, 39.0 mmol). A solution of 4-iodoacetophenone (7.38 g, 30.0 mmol) in 115 ml of MTBE was then added dropwise to the mixture using an addition funnel. After stirring for 48 h at room temperature, 3 N HCl (14.0 ml) was added and the organic layer extracted into ether, washed with water and then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a brownish solid that was recrystallized from isooctane to yield 8.11 g (79%) of product. m.p. 37°C; ^{1}H NMR ($CDCl_3$) δ 6.53(s, 1H), 7.64 (d, 2H, J = 8.5 Hz), 7.87 (d, 2H, J = 8.6 Hz); ^{13}C NMR($CDCl_3$) δ 92.2, 102.2, 117.0, 128.8, 132.3, 138.4, 177.5, 185.1. Analytically calculated for $C_{10}H_6F_3IO_2$: C, 35.11; H, 1.77; I, 37.10. Found: C, 35.19; H, 1.74; I, 36.90.

*4-[5-(4-Iodophenyl)-3-trifluoromethyl-pyrazol-1-yl]benzenesulfonamide (**5**)*

To a stirred solution of diketone **4** (4.10 g, 12.0 mmol) in 120 ml of ethanol was added 4-(sulfamoylphenyl)hydrazine hydrochloride (2.95 g, 13.2 mmol). The mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a pale brown solid. The crude product was purified by column chromatography (30% ethyl acetate in hexane) to give 5.39 g (91%) of **5** as a white solid. m.p. 180°C; ^{1}H NMR ($CDCl_3$) δ 5.04 (s, 2H), 6.78 (s, 1H), 6.97 (d, 2H, J = 8.4 Hz), 7.46 (d, 2H, J = 8.7 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.93 (d, 2H, J = 8.7 Hz); ^{13}C NMR($CDCl_3$) δ 95.9, 106.6, 116.6, 125.6, 127.6, 128.0, 130.3, 138.3, 141.8, 142.1, 144.0, 144.9. Analytically calculated for $C_{16}H_{11}F_3IN_3O_2S$: C, 38.96; H, 2.25; N, 8.52; I, 25.73. Found: C, 38.98; H, 2.26; N, 8.42; I, 25.49.

4-[5-(4-Trimethylstynnyltinphenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide (**6** *)*

Hexamethylditin (0.98 g, 3.0 mmol) and **5** (0.99 g, 2.0 mmol) were added sequentially to a suspension of tetrakis(triphenylphosphine)palladium (0) (0.10 g, 0.09 mmol) in anhydrous 1,4-dioxane (15 ml). The reaction mixture was stirred at reflux under nitrogen for 0.5 h. After cooling, the mixture was filtered, the insoluble black material was washed with dioxane (20 ml) and the dioxane layers were combined. Removal of dioxane solvent gave a gummy residue, which was purified by chromatography (silica gel, ethyl acetate: hexane (1:1). The solid product was recrystallized from ethyl acetate/ petroleum ether. Yield (0.95 g, 90%); m.p. 88°C; $R_f = 0.72$ (silica gel, ethyl ether:hexane = 3:1). ^{1}H NMR ($CDCl_3$) δ 0.30 (s, 9H), 5.47 (brs, 2H), 6.75 (s, 1H), 7.15 (d, 2H, $J = 8.1$ Hz), 7.45 (d, 2H, $J = 8.5$ Hz), 7.50 (d, 2H, $J = 7.9$ Hz), 7.69 (d, 2H, $J = 8.5$ Hz); ^{13}C NMR($CDCl_3$) δ −6.6, 106.5, 125.5, 127.4, 128.0, 128.1, 136.4, 141.5, 142.3, 143.7, 144.3, 145.0, 145.3. Analytically calculated for $C_{19}H_{20}F_3N_3O_2SSn$: C, 43.04; H, 3.80; N, 7.93. Found: C, 43.02; H, 3.78; N, 7.94.

*4-[5-(4-[^{123}I]Iodophenyl)-3-trifluoromethyl-pyrazol-1-yl]benzenesulfonamide (***2***)*
Precursor **6** (2.8 mg, 5.2 μmol, in 100 μl methanol) was placed in a 2 ml Wheaton vial containing no-carrier-added Na^{123}I (37 MBq in 0.1% aqueous NaOH). To this was added peracetic acid (100 μl, 0.3% solution in methanol). The reaction vial was sealed, covered with aluminum foil and the mixture stirred for 5 min at room temperature. A drop of 10% aqueous sodium thiosulfate was added to decompose the excess iodine and the radioiodinated product was isolated by passing it through a silica gel Sep-pak using ethyl acetate:hexane (2:1) as eluent. This process removed all ionic materials including residual iodide. Product separation and radiochemical purity of the product were achieved using radio-TLC (aluminum-backed silica gel plate, ethyl ether:hexane = 3:1); $R_f = 0.61$. The decay-corrected radiochemical yield was determined to be 90% and radiochemical purity was > 98%. The total synthesis time was 15 min.

Conclusion

In summary, a no-carrier-added iodine-123-labeled analogue of celecoxib, **2**, a potential SPECT agent for imaging a variety of cancers, was synthesized via iododestannylation in excellent yield and high radiochemical purity.

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References

1. Hida T, Yatabe Y, Achiwa H, Muramatsu H, Kozaki K, Nakamura S, Ogawa M, Mitsudomi T, Sugiura T, Takahashi T. *Cancer Res* 1998; **58**: 3761–3764.
2. Hong SH, Avis I, Vox MD, Martinez A, Treston AM, Mulshine JL. *Cancer Res* 1999; **59**: 2223–2228.
3. Baek SJ, Kim KS, Nixon JB, Wilson LLC, Eling TE. *Mol Pharmacol* 2001; **59**: 901–909.
4. Castonguay A, Rioux N, Duperron C, Jalbert G. *Exp Lung Res* 1998; **24**: 605–615.
5. Harris RE, Beebe-Donk J, Schuller HM. *Oncol Rep* 2002; **9**: 693–695.
6. Molina MA, Sitja-Arnau M, Lemoine MG, Frazier ML, Sinicrope FA. *Cancer Res* 1999; **59**: 4356–4362.
7. Schuller HM, Weddle DL, Zhang L, Walker K, Miller MS, Castonguay A. *Proc Am Assoc Cancer Res* 2002; **43**: 3201.
8. Rioux N, Castonguay A. *Cancer Res* 1998; **58**: 5354–5360.
9. Soriano AF, Helfrich B, Chan DC, Heasley LE, Bunn Jr Pa, Chou TC. *Cancer Res* 1999; **59**: 6178–6184.
10. Weddle DL, Tithoff P, Williams M, Schuller HM. *Carcinogenesis* 2001; **22**: 473–479.
11. Schuller HM, Tithof PK, Williams M, Plummer III H. *Cancer Res* 1999; **59**: 4510–4515.
12. Cakir Y, Plummer III HK, Tithof PK, Schuller HM. *Int J Oncol* 2002; **21**: 153–157.
13. Koehne CH, Dubois RM. *Semin Oncol* 2004; **31**: 12–21.
14. Roberts EG, Vona-Davis L, Riggs DR, Jackson BJ, Hohseni H, Kandzari SJ, McFadden DW. *W Va Med J* 2004; **100**: 96–101.
15. Fenton C, Keating GM, Wagstaff AJ. *Drugs* 2004; **64**: 1231–1261.
16. Wigand R, Wehling M, Brauer HG, Stridde E, Vergin H, May M. *Deut Med Wochenschr* 2004; **129**: 1188–1192.
17. Hoozemans JJ, Veerhuis R, Rozemuller AJ, Eikelenboom P. *Curr Drug Targets* 2003; **4**: 461–468.
18. Walker T. *J Obstet Gynaecol* 1999; **19**: 56–58.
19. Krum H, Liew D, Aw J, Haas S. *Expert Rev Cardiovasc Ther* 2004; **2**: 265–270.
20. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. *Lancet* 2004; **364** (early online publication).
21. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers RS, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn JN, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang YY, Isakson PC. *J Med Chem* 1997; **40**: 1347–1365.
22. Akula MR, Kabalka GW. *J Label Compd Radiopharm* 1999; **42**: 959–964.

