Available online at www.sciencedirect.com
ScienceDirect
Nuclear Medicine and Biology 36 (2009) 869–876
NUCLEAR MEDICINE — AND — BIOLOGY
www.elsevier.com/locate/nucmedbio

Synthesis and evaluation of a radioiodinated lumiracoxib derivative for the imaging of cyclooxygenase-2 expression

Yuji Kuge[a,b,*], Naoyuki Obokata[a], Hiroyuki Kimura[a], Yumiko Katada[a], Takashi Temma[a], Yukihiko Sugimoto[c], Kazuki Aita[a,d], Koh-ichi Seki[d], Nagara Tamaki[e], Hideo Saji[a]

[a]*Department of Patho-Functional Bioanalysis, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan*
[b]*Department of Tracer Kinetics and Bioanalysis, Graduate School of Medicine, Hokkaido University, Sapporo 060-8638, Japan*
[c]*Department of Physiological Chemistry, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan*
[d]*Central Institute of Isotope Science, Hokkaido University, Sapporo 060-8638, Japan*
[e]*Department of Nuclear Medicine, Graduate School of Medicine, Hokkaido University, Sapporo 060-8638, Japan*

Received 18 February 2009; received in revised form 14 July 2009; accepted 26 July 2009

Abstract

Introduction: Despite extensive attempts to develop cyclooxygenase (COX)-2 imaging radiotracers, no suitable positron emission tomography (PET)/single photon emission computed tomography (SPECT) tracers are currently available for in vivo imaging of COX-2 expression. The aims of this study were to synthesize and evaluate a radioiodinated derivative of lumiracoxib, 2-[(2-fluoro-6-iodophenyl)-amino]-5-methylphenylacetic acid (FIMA), which is structurally distinct from other drugs in the class and has weakly acidic properties, as a SPECT tracer for imaging COX-2 expression.

Methods: The COX inhibitory potency was assessed by measuring COX-catalyzed oxidation with hydrogen peroxide. Cell uptake characteristics of ^{125}I-FIMA were assessed in control and linterfero/interferon-γ-stimulated macrophages. The biodistribution of ^{125}I-FIMA was determined by the ex vivo tissue counting method in rats.

Results: The COX-2 inhibitory potency of FIMA (IC_{50}=2.46 μM) was higher than that of indomethacin (IC_{50}=20.9 μM) and was comparable to lumiracoxib (IC_{50}=0.77 μM) and diclofenac (IC_{50}=0.98 μM). The IC_{50} ratio (COX-1/COX-2=182) indicated FIMA has a high isoform selectivity for COX-2. ^{125}I-FIMA showed a significantly higher accumulation in COX-2 induced macrophages than in control macrophages, which decreased with nonradioactive FIMA in a concentration dependent manner. The biodistribution study showed rapid clearance of ^{125}I-FIMA from the blood and most organs including the liver and kidneys. No significant in vivo deiodination was observed with radioiodinated FIMA.

Conclusions: FIMA showed high inhibitory potency and selectivity for COX-2. Radioiodinated FIMA showed specific accumulation into COX-2 induced macrophages, no significant in vivo deiodination and rapid blood clearance. Radioiodinated FIMA deserves further investigation as a SPECT radiopharmaceutical for imaging COX-2 expression.

Keywords: Cyclooxygenase-2; Inhibitor; Radioiodination; SPECT; Radiopharmaceutical

1. Introduction

Cyclooxygenases (COXs) are the key rate-limiting enzymes in the conversion of arachidonic acid to prostaglandins and thromboxanes. To date, at least two distinct isoforms of the COXs, a constitutive isoform (COX-1) and an inducible isoform (COX-2), and several of their variants have been discovered [1]. COX-2 plays important roles in response to inflammatory stimuli and has been implicated in a number of pathological processes including many human cancers, atherosclerosis and cerebral and cardiac ischemia [2–5]. We have also reported the association of COX-2 expression with cerebral ischemia and

* Corresponding author. Department of Tracer Kinetics and Bioanalysis, Graduate School of Medicine, Hokkaido University, Sapporo 060-8638, Japan. Tel.: +81 11 706 5085, fax: +81 11 706 7155.
E-mail address: kuge@med.hokudai.ac.jp (Y. Kuge).

0969-8051/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.nucmedbio.2009.07.006

atherosclerosis using rodent and primate models of these diseases [6–11].

Accordingly, noninvasive imaging of COX-2 expression would be useful for early diagnosis and for monitoring the progression and treatment efficacy for such diseases [12,13]. In this regard, several COX-2 inhibitors including ^{18}F-SC58125, ^{18}F-desbromo-DuP-697, ^{11}C-celecoxib, ^{11}C-rofecoxib and ^{123}I-celecoxib analogues have been radiolabeled and evaluated as potential tracers for positron emission tomography (PET) and single photon emission tomography (SPECT) [14–24] (Fig. 1). We have contributed to this area with the synthesis and preliminary evaluation of radioiodinated celecoxib analogues [22]. Results, however, have not been entirely consistent between laboratories due to what is generally ascribed to the relatively high nonspecific binding of these compounds [23–26]. The effect of this high nonspecific binding on results appears to be largely dependent on experimental conditions and could cause inconsistent findings. Thus, no appropriate PET/SPECT tracers are currently available for in vivo imaging of COX-2 expression [23–25]. In the search for suitable PET/SPECT tracers for COX-2 imaging, attempts have recently been made to radiolabel new generation COX-2 inhibitors which have greater inhibitory potencies and selectivities for COX-2 [25–27]. However, to date, the radiolabeled COX-2 inhibitors evaluated as PET/SPECT tracers exclusively possess the same basic skeleton, a cyclic core with two vicinal aryl rings.

Another new generation COX-2 selective inhibitor, lumiracoxib, is structurally distinct from other drugs in the class and has weakly acidic properties [28–31]. The K_i and IC_{50} values of lumiracoxib for COX-2 are better than or comparable to those of other COX-2 inhibitors including celecoxib [28]. Lumiracoxib is distributed and retained in inflamed tissues while being rapidly cleared from plasma with a short elimination half-life [30–32]. Thus, we selected lumiracoxib as a lead compound for a potential COX-2 imaging tracer. In this study, a radioiodinated derivative of lumiracoxib, 2-[(2-Fluoro-6-iodophenyl)-amino]-5-methyl-phenylacetic acid (FIMA) was synthesized and its potential as an imaging tracer was assessed in both in vitro and in vivo experiments.

2. Materials and methods

2.1. General

Sodium ^{125}I-iodide (642.8 GBq/mg) was purchased from Perkin Elmer Life and Analytical Sciences (Boston, MA, USA). All chemicals used were of reagent grade.

Proton and carbon nuclear magnetic resonance spectra were recorded on a JMM-ECA500KP spectrometer (JEOL, Tokyo, Japan). The chemical shifts are reported in parts per million (ppm) downfield from an internal tetramethylsilane standard. Mass spectra were recorded with a JMS-HX/HX110A, JMS-SX102AQQ or JMS-GC-mate spectrometer (JEOL).

2.2. Synthesis

2.2.1. Synthesis of FIMA (5)

FIMA was synthesized according to the procedure outlined in Fig. 2.

Compound **2** was synthesized in three steps according to the method reported by Acemoglu et al. [33]. Briefly, *p*-iodotoluene (189 μl, 1.4 mmol) was coupled with 2-bromo-6-fluoroaniline (158 μl, 1.4 mmol), utilizing the Pd(0) catalyzed Buchwald–Hartwig reaction, to give 1 as a colorless oil with a yield of 27%. Compound **1** (771.5 mg, 2.75 mmol) was acylated with bromoacetyl bromide (288 μl, 3.30 mmol) and then subjected to a Friedel-Crafts alkylation to obtain **2** as a yellowish powder with a yield of 39% (Mp, 118–120°C).

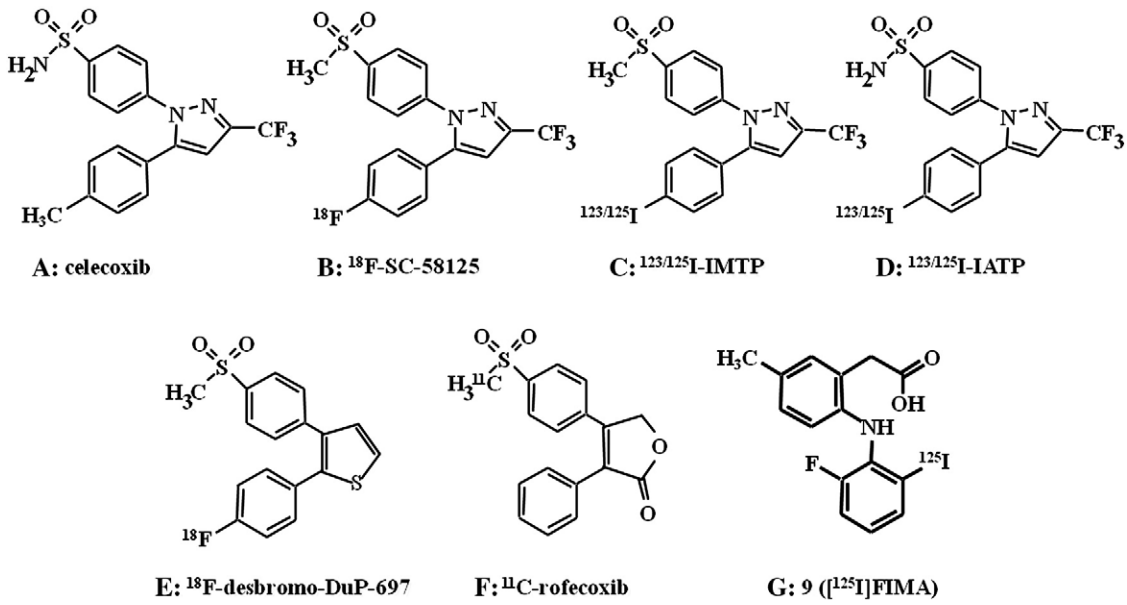

Fig. 1. Chemical structures of radiolabeled COX-2 inhibitors.