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Synthesis and evaluation of radioiodinated cyclooxygenase-2 inhibitors as potential SPECT tracers for cyclooxygenase-2 expression

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Abstract

Although several COX-2 inhibitors have recently been radiolabeled, their potential for imaging COX-2 expression remains unclear. In particular, the sulfonamide moiety of COX-2 inhibitors may cause slow blood clearance of the radiotracer, due to its affinity for carbonic anhydrase (CA) in erythrocytes. Thus, we designed a methyl sulfone-type analogue, 5-(4-iodophenyl)-1-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl-1*H*-pyrazole (IMTP). In this study, the potential of radioiodinated IMTP was assessed in comparison with a ^{125}I-labeled celecoxib analogue with a sulfonamide moiety (^{125}I-IATP).

Methods: The COX inhibitory potency was assessed by measuring COX-catalyzed oxidation by hydrogen peroxide. The biodistribution of ^{125}I-IMTP and ^{125}I-IATP was determined by the ex vivo tissue counting method in rats. Distribution of the labeled compounds to rat blood cells was measured.

Results: The COX-2 inhibitory potency of IMTP (IC_{50}=5.16 μM) and IATP (IC_{50}=8.20 μM) was higher than that of meloxicam (IC_{50}=29.0 μM) and comparable to that of SC-58125 (IC_{50}=1.36 μM). The IC_{50} ratios (COX-1/COX-2) indicated the high isoform selectivity of IMTP and IATP for COX-2. Significant levels of ^{125}I-IMTP and ^{125}I-IATP were observed in the kidneys and the brain (organs known to express COX-2). The blood clearance of ^{125}I-IMTP was much faster than that of ^{125}I-IATP. Distribution of ^{125}I-IATP to blood cells (88.0%) was markedly higher than that of ^{125}I-IMTP (18.1%), which was decreased by CA inhibitors.

Conclusions: Our results showed a high inhibitory potency and selectivity of IMTP for COX-2. The substitution of a sulfonamide moiety to a methyl sulfone moiety effectively improved the blood clearance of the compound, indicating the loss of the cross reactivity with CA in ^{125}I-IMTP. ^{123}I-IMTP may be a potential SPECT radiopharmaceutical for COX-2 expression.

Keywords: Cyclooxygenase-2 (COX-2); Inhibitor; Radioiodination; SPECT; Radiopharmaceutical

1. Introduction

Cyclooxygenases (COXs) catalyse the key rate-limiting step in the conversion of arachidonic acid into prostaglandins and thromboxanes. To date, at least 2 distinct isoforms of the COXs—a constitutive form (COX-1) and an inducible isoform (COX-2)—and several of their variants have been discovered [1]. COX-1 is constitutively expressed in most tissues and is responsible for maintaining homeostasis, whereas COX-2 is induced in response to inflammatory stimuli. Besides being associated with inflammation, COX-2 has been implicated in a number of pathological processes, including many human cancers, atherosclerosis, and cerebral and cardiac ischemia [2–5]. We also reported

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the neuronal expression of COX-2 in rodent and primate models of cerebral ischemia [6–10].

Accordingly, the noninvasive imaging of COX-2 expression should help in understanding the pathophysiology of the diseases and contribute to the clinical use of COX-2 inhibitors [11]. In this regard, several COX-2 inhibitors were recently radiolabeled with F-18 and their potentials for positron emission tomography (PET) tracers were preliminarily evaluated [12–14]. The results for the potentials of these labeled compounds, however, are not necessarily consistent from one laboratory to another. In addition, the short half-life of ^{18}F may hamper the determination of the specific binding of the tracer to COX-2, because it is known that the COX-2 inhibitors show time-dependent inhibition of COX-2 [11]. The longer half-lives of single photon emission tomography (SPECT) nuclides, such as Tc-99m or I-123, may be more suitable for radiotracers to image COX-2. From these points of view, we intended to develop radioiodinated COX-2 inhibitors as SPECT tracers for imaging COX-2 expression.

As for SPECT tracers, Yang et al. [15] proposed a ^{99m}Tc-labeled celecoxib (celebrex) analogue as a potential tracer for COX-2 expression. Kabalka et al. [16] recently reported the radiosynthesis of a ^{123}I-labeled celecoxib analogue. However, the detailed characteristics of these tracers, including affinity and selectivity to COX-2, have not

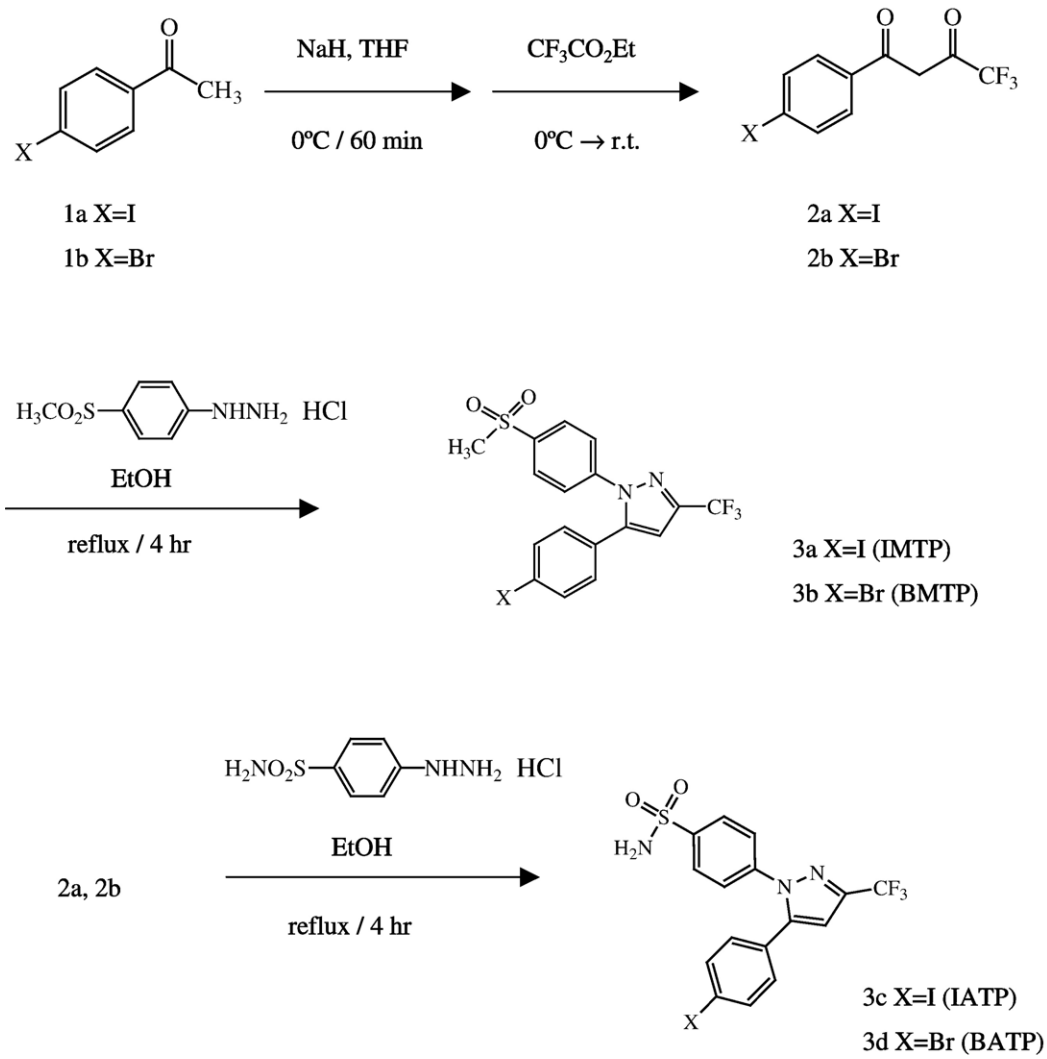

Fig. 1. Synthesis of IMTP (compound **3a**), BMTP (compound **3b**), IATP (compound **3c**) and BATP (compound **3d**).
Compound 1a, iodoacetophenone
Compound 1b, bromoacetophenone
Compound 2a, 4,4,4-trifluoro-1-(4-iodophenyl)-butane-1,3-dione
Compound 2b, 4,4,4-trifluoro-1-(4-bromophenyl)-butane-1,3-dione
Compound 3a, 5-(4-iodophenyl)-1-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole
Compound 3b, 5-(4-bromophenyl)-1-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole
Compound 3c, 5-(4-iodophenyl)-1-[4-(aminosulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole
Compound 3d, 5-(4-bromophenyl)-1-[4-(aminosulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole