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RESEARCH PAPER

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Design of selective COX-2 inhibitors in the (aza)indazole series. Chemistry, *in vitro* studies, radiochemistry and evaluations in rats of a [^{18}F] PET tracer

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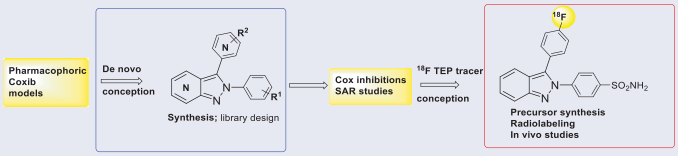
ABSTRACT

A series of novel derivatives exhibiting high affinity and selectivity towards the COX-2 enzyme in the (aza) indazole series was developed. A short synthetic route involving a bromination/arylation sequence under microwave irradiation and direct C–H activation were established in the indazole and azaindazole series respectively. *In vitro* assays were conducted and structural modifications were carried out on these scaffolds to furnish compound **16** which exhibited effective COX-2 inhibitory activity, with IC_{50} values of 0.409 μM and an excellent selectivity versus COX-1. Radiolabeling of this most potent derivative [^{18}F]**16** was achieved after boron ester release and the tracer was evaluated *in vivo* in a rat model of neuroinflammation. All chemistry, radiochemistry and biological experimental data are discussed.

GRAPHICAL ABSTRACT



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Introduction

An inflammatory reaction is a ubiquitous effective protective mechanism, which includes the cascade activation of coordinated chemical and cellular events. The role of inflammation is to restore tissue homeostasis[1]. However, it can have either a beneficial effect when it promotes repair or adverse consequences when it is excessive or long-lasting. Compared to other organs, the brain is characterised by a low regenerative capacity and specific immune processes due to the presence of the blood-brain-barrier (BBB). The immune response of the brain to various injuries is called neuroinflammation, and includes a number of events, the main one being the activation of microglial cells[2]. During this process, microglia change from a resting to an activated state, which can either mediate protective and regenerating mechanisms or on the contrary aggravate injury, contributing to neurodegeneration[3]. Neuroinflammation is involved in a number of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) as well as in several neuropsychiatric disorders such as autism, schizophrenia, and depression[4–6]. The *in vivo* detection and quantification of neuroinflammation in several brain diseases can therefore, be of high value for a better understanding of pathophysiological mechanisms, early diagnosis, and identification of new therapeutic approaches. In this context, a large panel of molecular targets can be envisaged for positron emission tomography (PET) exploration[7].

Among all the molecular pathways involved in the inflammation process, the cyclooxygenase (COX) enzyme that contributes to the subsequent production of prostaglandins clearly plays a central role. COX-2 is an inducible enzyme, which is expressed at high concentrations at inflammation sites and malignant transformations compared to most normal tissues. This, associated with the availability of COX-2-selective inhibitors, makes this enzyme an ideal target in order to image inflammation[8,9].

Several selective COX-2 inhibitors have been reported in the literature, among them, the Coxib family (celecoxib, rofecoxib), a non-steroidal anti-inflammatory drug class (NSAIDs) which has been extensively studied[10]. Several [^{18}F]PET radiotracers to image COX-2 have been developed over the past decade (Figure 1)[8,9]. Although some of them have proved useful to explore inflammation in a pre-clinical colorectal cancer model, no specific COX-2 radiotracers are available to visualise brain inflammation because of a poor brain penetrance which remains the main challenge for all PET agents targeting the central nervous system (CNS)[11,12].

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