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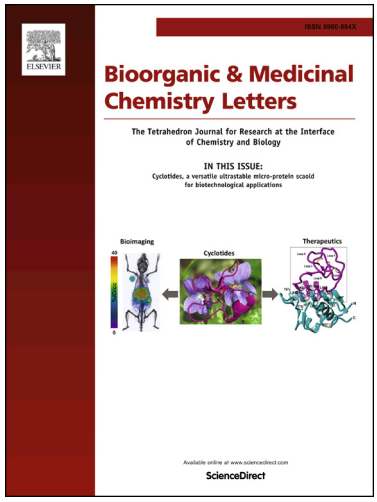

Discovery of {4-[4,9-bis(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid (GSK726701A), a novel EP_4 receptor partial agonist for the treatment of pain

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Discovery of {4-[4,9-bis(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid (GSK726701A), a novel EP_4 receptor partial agonist for the treatment of pain

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Abstract— A novel series of EP_4 agonists and antagonists have been identified, and then used to validate their potential in the treatment of inflammatory pain. This paper describes these novel ligands and their activity within a number of pre-clinical models of pain, ultimately leading to the identification of the EP_4 partial agonist GSK726701A.

Prostaglandin E2 (PGE_2) **1**, synthesised from arachidonic acid (AA) by the cyclooxygenase enzymes, is a ubiquitous mediator of mammalian physiology and pathophysiology.[1] Physiologically, PGE_2 contributes to the modulation of bone formation[2], gut homeostasis including pH control[3], renal function and blood pressure.[4] In addition PGE_2 is associated with the growth of certain cancers[5] and is a well characterised inflammatory mediator contributing to pain and inflammation.[6] To date, pharmacological intervention in the AA pathway has led to the discovery and commercialisation of NSAIDS and COX2 inhibitors.[7] However these drugs have a number of safety concerns associated with gastro-intestinal bleeding and damage and adverse cardiovascular events, respectively.[8]

The biological effects of PGE_2 are mediated by four G-protein coupled receptors designated $EP_{1\text{-}4}$.[9] Each of these receptors has characteristic distribution in various tissues and this feature, together with the paracrine nature of PGE_2, allows PGE_2 to play varied and sometimes opposing roles in the mammalian system. For example, PGE_2 is thought to act as a pro-inflammatory agent in the early stages of inflammation, while helping to promote inflammatory resolution at later time points[10] and these effects may be mediated by different receptor sub-types. Thus selectively targeting individual EP receptors offers the opportunity to intervene in pathophysiology with specificity and to potentially avoid toxicity.

As part of a wider investigation of the role of EP receptors in pain and inflammation, we initiated a programme to discover selective EP_4 ligands. We were particularly intrigued by seemingly conflicting roles of EP_4 in pain and inflammation. Studies have confirmed that PGE_2 acting on the EP_4 receptor can either stimulate or inhibit inflammation in concert with IFNγ.[11] Furthermore, EP_4 receptor knockout mice showed resistance to inflammation in a collagen induced arthritis model[12] and selective EP_4 antagonists show robust anti-inflammatory effects in vivo.[13] However, EP_4 agonists have also been reported to attenuate levels of the pro-inflammatory mediator TNFα in rats[14] and can potently suppress inflammation in an adjuvant induced arthritis model.[15]

The PGE_2 analogue ONO-4819CD (rivenprost) **2** has been in clinical development and was reported to have an

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