Pimarane Cyclooxygenase 2 (COX-2) Inhibitor and its Structure-Activity Relationship

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The cyclooxygenase enzymes catalyze the oxidative conversion of arachidonic acid into prostaglandin H2 which mediates both beneficial and pathodological effects. The COX-1, which is constitutively expressed in most tissues and in blood platelets, is responsible for the physiological production of prostaglandins whereas the expression of COX-2 isoform is induced in response to inflammatory stimuli such as cytokines. Thus, the identification of a novel COX-2 selective inhibitor should offer an excellent anti-inflammatory activity with minimal side effects including gastrointestinal toxicity. Recently, we have reported the isolation of a novel pimarane diterpene, acanthoic acid, from the Korean medicinal plant which has been traditionally used for treating rheumatism. In particular, acanthoic acid turned out to be biologically attractive because it has been shown to exhibit an excellent suppression of inter-leukin-1 (IL-1) and tumor necrosis factor-a (TNF-a) which are major proinflammatory cytokines. More recently, the COX-2 inhibitory activities of acanthoic acid have also been investigated by us as an extension of the studies on its anti-inflammatory effects as well as therapeutic utilities. We herein report acanthoic acid as a novel COX-2 inhibitor and its SAR. In addition, the interaction mode of acanthoic acid with the COX-2 active site and the highly bioactivity-enhanced acanthoic acid analogues are reported.