Novel selective Cox-2 inhibitors induce apoptosis in Caco-2 colorectal carcinoma cell line

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ABSTRACT
The cyclooxygenase-2 (COX-2) inhibitors including celecoxib inhibit cell growth and induce apoptosis in cancer cells. As COX-2 is over expressed in solid tumors such as colorectal cancer, it can be a suitable target for cancer treatment studies. In this study we designed and synthesized 4,5-bisaryl imidazolyl imidazoles as novel COX-2 inhibitors and evaluated their apoptosis inducing activities. The ability of our synthetic compounds to inhibit ovine COX-1 and COX-2 was determined using a colorimetric method. The expression of five apoptosis-related genes Bak-1, Bcl-x, BIRC (Survivin), TNFSF10 and CASP3 were evaluated by quantitative real-time PCR. Among our synthetic compounds (3a–c), 4,5-bis(4-methoxyphenyl)-1H-imidazol-2-yl derivative (compound 3c) exhibited the highest COX-1/COX-2 selectivity index (SI = 262.9) and lowest growth inhibition concentration (IC50 = 21.20 μM). In addition, compounds 3a–c could up-regulate pro-apoptotic genes and down-regulate anti-apoptotic genes. So, these synthetic compounds seem to be inducers of apoptosis in Caco-2 cell line. This study indicates that 4,5-bisaryl imidazolyl imidazole is a suitable scaffold to design COX-2 inhibitors and 4,5-bis(4-methoxyphenyl)-1H-imidazol-2-yl derivative exhibited highly COX-2 inhibitory potency and selectivity even more than celecoxib. It seems that it could induce apoptosis in Caco-2 colorectal carcinoma cell line.

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1. Introduction
Colorectal cancer, one of the leading causes of cancer deaths in both men and women is a major public health problem and its chemoprevention currently is an area of intense investigation. The cyclooxygenase enzyme includes two isoforms, COX-1 and COX-2. The enzyme COX-1 is responsible for protecting the gastric mucosa and maintaining homeostasis whereas COX-2 is mostly triggered by inflammation and carcinogenesis (Hawcroft et al., 2007; Riendeau et al., 2001). COX-2 is over-expressed in many solid tumors including colon, breast, prostate, liver and lung cancer and the increased expression of COX-2 also seems to prevent cancer cells from undergoing programmed cell death (Amir and Agrawal, 2005; Gasparini et al., 2003; Hawcroft et al., 2007). Model studies in laboratory animals have provided convincing evidence that administration of the NSAIDs inhibited chemically induced colon carcinogenesis (Agarwal et al., 2003). The chemo-preventive effects of NSAIDs and selective COX-2 inhibitors are believed to be related to their ability to induce apoptosis in colon epithelial cells, although the degree of apoptosis does not correlate directly with the chemo-preventive effect (Marx, 2001). The cyclooxygenases are responsible for conversion of arachidonic acid to prostanoids and their metabolites play a pivotal role in multiple physiologic and pathophysiologic processes.

Recent studies indicating the place of COX-2 inhibitors in cancer chemotherapy especially colon cancer (Ghodsi et al., 2010) still continues to attract investigations on development of COX-2 inhibitors. However, the recent market removal of rofecoxib and some other COX-2 inhibitors due to their adverse cardiovascular side effects (Mukherjee et al., 2001) clearly encourages the researchers to explore and evaluate alternative templates with COX-2 inhibitory effects.