GS04-6 Significance and creation of novel cyclooxygenase-1(COX-1) selective inhibitors

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Analgesic agents are very important to reduce physical and mental pains for the patients to achieve a better quality of life. To relieve these pains, non-steroidal anti-inflammatory drugs (NSAIDs) are in heavy usage. However, stomach irritation is caused as a major side effect by NSAIDs. Most NSAIDs inhibit cyclooxygenases (COXs), which have three subtypes. In general, the gastric disturbance was thought to be inhibition of COX-1 on the stomach mucous membrane by NSAIDs. Consequently, development of COX-1-selective inhibitors have delayed and much attention was attracted to COX-2-selective inhibitors. However, NSAIDs-induced gastric damage was reported not to be induced only by either COX-1 or COX-2 inhibition. Therefore, the idea of gastric disturbance caused by inhibition of COX-1 was questioned. We have reported the development of COX-1-selective inhibitor TFAP, which shows analgesic activity without causing gastric damage（*J. Med. Chem.* 2008, *51,* 2400.）. However, TFAP colors urine with its metabolite. In addition, analgesic activity of TFAP is weaker than that of indomethacin. Therefore, we designed new COX-1-selective inhibitors, the ABEX series, in order to avoid colored urine by converting a diaminopyridine skeleton which is thought as a cause of colored urine by TFAP. As a result of synthesis, *in vitro* and *in vivo* research of the ABEX series, we found novel COX-1 selective inhibitors which show better analgesic activity than indomethacin, and show no colored urine. In this symposium, we will present the research background and novel *in vivo* active COX-1 selective inhibitors.