S-1 [10:00～10:30]

4,5-Diaryl-2,2-Dimethyl-3(*2H*)Furanone Derivatives as COX-2 Inhibitors -Next Generation Anti-Arthritis Candidate-

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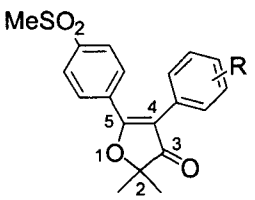
Inflammation is an outcome or an end effect of disruption of complex immunological balance. A variety of approaches to control immunological unbalance have been tried, and some of them are in practice in the clinic. Since inflammatory disorders are reflection of very complex immunological responses, it should be difficult to have such disorders under complete control. Thus, most of the drugs, being marketed and under development, possess some degrees of undesired side effects originating from disruption of immunological balance. Steroids are excellent drugs suppressing inflammation in short term, however, long-term use of steroids would incur a serious side effect of "rebound". Another example is TNF-α-neutralizing agents, such as enbrel and infliximab. TNF-α has been known to play a key role in the exacerbation of inflammation, and knock-out of TNF-α is regarded essential to control of chronic inflammation. The TNF-α-neutralizing drugs in the market are regarded very efficient in the management of rheumatoid arthritis. Upon long term use, however, those drugs cause sepsis to a certain proportion of patients. It is ironical that a high plasma level of TNF-α is known to be responsible for sepsis, and that the drugs scavenging TNF-α cause sepsis. The above two examples illustrate well the difficulty of discovering an anti-inflammatory drug without unwanted immunological side effects. An anti-inflammatory drug would make a case in the market, as long as the drug has huge therapeutic benefits compared to its expected but unwanted immunological side effects, where cyclooxygenase-2 inhibitors are positioning. In this presentation, will be

discussed general aspects of cyclooxygenase-2 inhibition in conjunction with 3(*2H*)furanone derivatives, a novel class of COX-2 inhibitors.

Cyclooxygenases are a family of enzymes, which convert arachidonic acid into prostaglandins responsible for bodily homeostasis as well as inflammation. There are at least two kinds of cycloxygenase, cyclooxygease-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutively expressed and involved in bodily homeostasis, especially gastrointestinal integrity. On the other hand, COX-2 is induced upon inflammatory stimuli. COX-2 activity is essential to bodily defense, however, overt expression of COX-2 could lead to undesirable inflammatory situations such as oesteoarthritis, rheumatoid arthiritis, inflammatory bowel disease, pains and so on.[1]

Activity of cyclooxygenases was traditionally controlled by non-steroidal antiinflammatory drugs (NSAIDs), such as aspirin, naproxen, ibuprofen, diclofenac, *etc.* Those NSAIDs are good antiinflammatories as well as analgesics. Unfortunately, traditional NSAIDs inhibit both COX-1 and COX-2 at clinical doses. It is widely accepted that inhibition of COX-1 could lead to life-threatening gastrointestinal toxicity of perforation, ulceration and bleeding (PUB), which has limited use of traditional NSAIDs despite their superb antiinflammatory and analgesic potency.[2]



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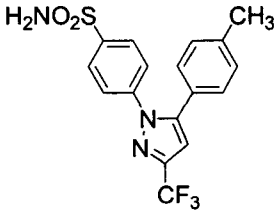
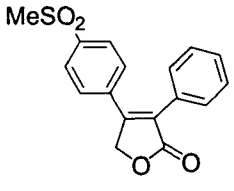


Celecoxib



Rofecoxib

Since the identification of COX-2 enzyme about a decade ago, lots of R&D efforts have been dedicated to discover COX-2 selective inhibitors. Currently there are two COX-2 inhibitors in the market, celecoxib and vioxx. Meeting the expectations of clinicians, the COX-2 inhibitors indeed show gastric safety profiles far better than traditional NSAIDs. The blockbuster COX-2 inhibitors manifested gastric safety as well as antiinflammatory potency, however, they are unlikely to enjoy long-term success in

the market. In case of celecoxib, high dose is posing a real problem for chronic use by eldery arthritis patients, who are often metabolically insufficient. Furthermore pain suppression profile doesn't seem to lean toward celecoxib. On the other hand, the unexpected and dangerous cardiovascular episodes would hamper the success of rofecoxib.[3] Thus, a next generation COX-2 drug needs to have safety profile comparable to celcoxib, maintaining potency of rofecoxib.

In this paper, will be presented pharmacological profiles for a novel class of 2,2-dimethyl-4,5-diaryl-3(*2H*)furanone derivatives (**1**), which are orally active, highly potent and selective COX-2 inhibitors. As indicated in Table 1, the furanone derivatives possess COX-2 selectivity comparable to celecoxib.

Table 1. *In vitro* COX-1/COX-2 activities against mouse peritoneal macrophages.

Entry	R	IC_{50} (μg/ml)		**COX-2 selectivity over COX-1**
		COX-2	COX-1	
1a	H	0.05	3	60
1b	3-CF_3	0.05	3	60
1c	3-F	0.02	5	250
1d	3-F, 5-F	0.03	20	667
Celecoxib		0.02	1.86	93
Rofecoxib		0.06	>100	>1667

On the other hand, the antiinflammatory potency of **1** is much stronger than celecoxib, as shown by an animal model of adjuvant arthritis.[4] The impressively high adjuvant arthritis potency of **1** should be the strongest among the reported COX-2 inhibitors (Table 2). Often adjuvant arthritis ED50 can be misleading when a compound has very slow in vivo clearance. The tested compounds do have a reasonable range of plasma clearance half-life in the rat, suggesting those compounds are developable from pharmacokinetic considerations. Thus, 3(*2H*)furanone derivatives should be promising development candidates for next generation anti-arthritis medications.

Table 2. Antiinflammatory activities by adjuvant arthritis (therapeutic model/SD rats)

Entry	Adjuvant Arthritis ED_{50} (mg/kg/day), QD
1b	0.06
1c	0.08
1d	0.03
Celecoxib	0.2

3(*2H*)furanone derivatives **1** were originally prepared by a scheme involving Suzuki Coupling as a key reaction for generating structural diversity.[5] However, an efficient synthetic approach will be presented, which is believed to be suitable for GMP-compatible scale-up preparation of 3(*2H*)furanone derivatives **1**.

References

1. Hia, T.; Nielson, T. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7384

2. Reitz, D. B.; Seibert, K. *Ann. Rep. Med. Chem.* **1995**, *30*, 179.

3. *Scripp* **2000**, *2554*, 20.

4. Lewis, E. J.; Bishop, J.; Aspinall, S. *J. Inflamm. Res.* **1998**, *47*, 26.

5. Shin, S. S.; Noh, M.-S.; Byun, Y. J.; Choi, J. K.; Kim, J. Y.; Lim, K. M.; Ha, J.-Y.; Kim, J. K.; Lee, C.-H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 165.