NEW DRUGS

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This issue new drugs provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications.

Selective COX-2 inhibitors

The widely used nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase (COX) which converts arachidonic acid into prostaglandins (PGs). COX exists in at least two isoforms. COX-1 (constitutive isoform) is present constitutively under physiological condition. COX-2 (inducible isoform) is induced in various cell types by mitogens and cytokines including endotoxin. The marketed NSAIDs are differential effects on COX-1 and COX-2. PGs produced by COX-1 have important role in normal platelet, gastric and renal function. As a consequence, inhibition of COX-1 results in unwanted side effects. The developing selective COX-2 inhibitors may offer an advantage over the existing non-selective NSAIDs by reducing the associated renal and gastric toxicity.

Some of these new drugs are:

1. A novel series of 1,2-diarylcyclobutenes has evaluated as potential selective COX-2 inhibitors. 4,4-dimethyl-2-phenyl-3-[4-(methylsulphonyl)phenyl]cyclobutenone (figure 1) was shown to be particularly selective for COX-2 and orally active in the rat paw edema model (ED_{50} = 2.4 mg/kg). (Friesen and coworkers. *Bioorg Med Chem Lett* 1996; **6:** 2677-2682).

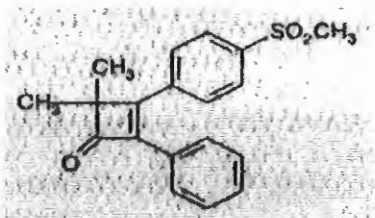

figure 1

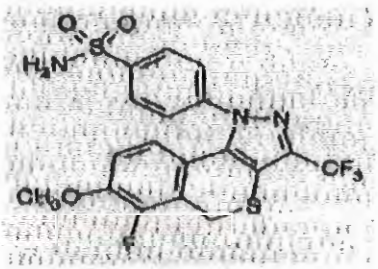

figure 2

2. The agents based on the synthesis and evaluation of series of 1,5-diarylpyrazones containing either a sulphone or sulphonamide moiety as COX-1 and COX-2 inhibitors have been described. The series of benzothiopyrano-pyrazoles, exemplified by figure 2, were found to be both selective COX-2 inhibitors *in vitro* and antiinflammatory agents *in vitro* in the air-pouch model of inflammation. (Bertenshaw and coworkers. *Bioorg Med Chem Lett* 1996; **6:** 2827-2830).

3. DuPont Merck (Wilmington, DE, USA) has described the new class of COX-2 inhibitors, the terphe-nyls, which they discovered while seeking to improve the in vitro selectivity of their selective COX-2 inhibitor, diarylthio-phen (figure 3 DuP697). The terphenyl compound (figure 4) was identified as a potential lead compound having good COX-2 selectivity and a better pharma-cokinetic profile than DuP697. (Pinto and coworkers. *Bioorg Med Chem Lett* 1996; **6:** 2907-2912).

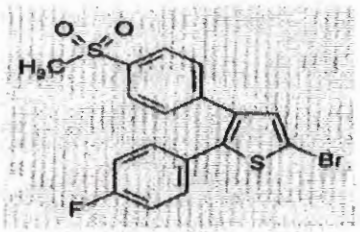

figure 3

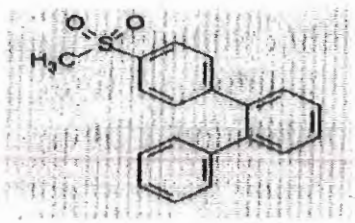

figure 4

4. The agents based on the synthesis and evaluation of a series of 3,4-diarylpyrazoles as potential COX-2 inhibitors have been described. A number of these compounds, exemplified by figure 5, were found to be potent selective inhibitors of COX-2 and shown to have oral antiinflammatory activity in a rat carrageenan-induced foot pad edema assay. (Pinning and coworkers. *Bioorg Med Chem Lett* 1996; **7:** 2122-2124).

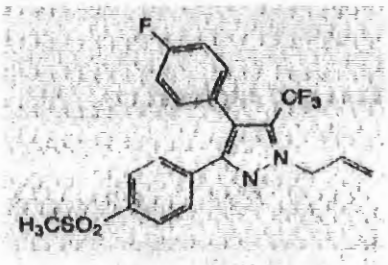

figure 5

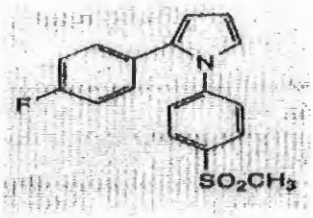

figure 6

5. A group from Searle Research and Development (Skokie, IL, USA) have described the identification of 1,2-diarylpyrroles as potent, selective inhi-bitors of COX-2 (IC_{50} = 15-100 nM). In vivo testing of these compounds in the rat carrageenan induced paw edema model established that the compounds were orally active anti-inflammatory compounds with the most potent inhibitor of edema (figure 6) having an ED_{50} of 4.7 mg/kg and a 200-fold selectivity for COX-2 over COX-1. (Khanne and coworkers. *J Med Chem* 1997; **40:** 1619-1633).

6. The agents based on the synthesis and evaluation of 1,2-diaryl-imidazoles as COX-2 inhibitors have been described. These compounds were also found to be potent and highly selective inhibitors of the human COX-2 enzyme. Several of these com-pounds, exemplified by figure 7, were found to exhibit excellent inhibition in the adjuvant-induced arthritis model (ED_{50} = 0.02 mg/kg). The 1,2-diarylimidazoles were also shown to inhibit carrageenan-induced rat paw edema and hyperalgesia, with several orally active compounds showing no gastrointestinal toxicity in either the rat or mouse at up to 200 mg/kg, suggesting that these compounds offer potential as anti-inflammatory agents with reduced side effects. (Khanne and coworkers. *J Med Chem* 1997; **40:** 1634-1647).

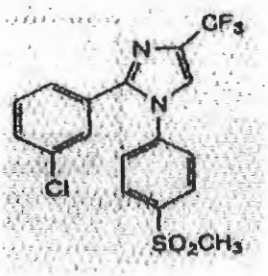

figure 7