quantitative structure activity relationship (QSAR) models and applied them to combinatorial libraries built around scaffolds that had not been thoroughly explored.

Candidates from those virtual libraries were screened in silico for activity, selectivity, and ADMET liabilities. A few of the most attractive candidates were synthesized and tested in relevant biological assays, and their ADMET properties were measured; all were active and ADMET properties were in reasonable agreement with prediction.

2 Proof-of-Concept Target Selection

Cyclooxygenase is involved in the production of prostaglandins, which mediate a wide range of biological responses, including inflammation, constriction and dilation of vascular smooth muscle, aggregation of platelets, and regulation of gastric acid secretion. All COX isoforms convert arachidonic acid into prostaglandin H_2 (PGH_2) which can then be converted to other prostaglandins such as PGD_2, PGE_2, PGI_2, (prostacyclin), and TXA_2 (thromboxane) by other enzymes. The COX-1 isoform is constitutively expressed in many tissues and is the predominant form in the gastric mucosa and kidneys. Inhibition of COX-1 reduces levels of PGE_2 and PGI_2 which can contribute to gastric ulceration. COX-2 is an inducible isoform of cyclooxygenase that is elevated during inflammation.

When COX-2 was discovered in the 1990s, pharmaceutical companies raced to develop COX-2 inhibitors that were selective over COX-1 in order to alleviate pain without the risk of gastric problems associated with COX-1 inhibition. The compounds shown in Fig. 1 are COX-2-selective inhibitors that were approved in the late 1990s and early 2000s.

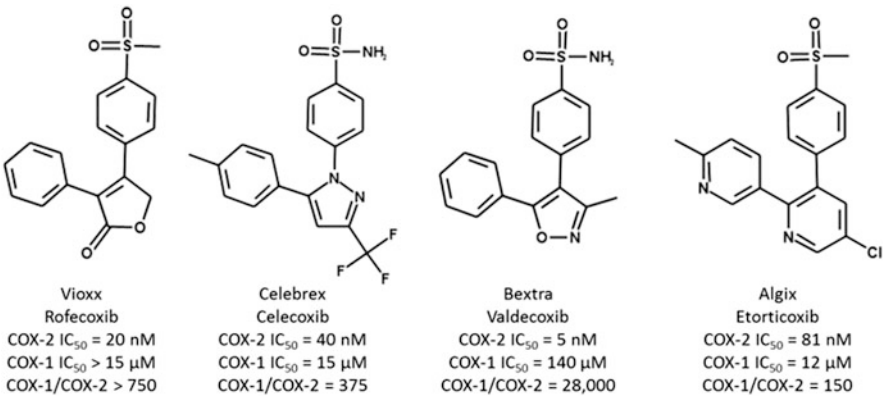

Fig. 1 Literature COX-1 and COX-2 IC_{50} values and selectivities for COX-2-selective inhibitors: Vioxx (Prasit et al. 1999), Celebrex (Penning et al. 1997), Bextra (Talley et al. 2000), and Algix (Friesen et al. 1998). Vioxx and Bextra were removed from the US market. Algix is approved in Europe but not in the USA