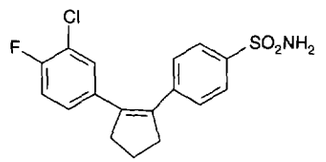
In particular, compound **5** was also found to be orally active in the rat carrageenan-induced paw oedema model and rat adjuvant arthritis model without apparent gastrointestinal toxicity. These studies indicate that this class of COX-2 inhibitor may have advantages over the existing treatments for acute and chronic inflammatory diseases.

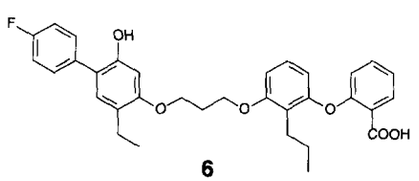


5

Leukotriene B_4 receptor antagonist

Elevated levels of leukotriene B_4 (LTB_4) are associated with diseases such as psoriasis, rheumatoid arthritis, asthma and inflammatory bowel disease and are known to cause degranulation, aggregation, chemotaxis and chemokinesis of polymorphonuclear leukocytes. LTB_4 antagonists may therefore also have utility as anti-inflammatory agents. Sawyer, J.S. and coworkers [*J. Med. Chem.* (1995) 38, 4411–4432] describe the discovery of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-phenoxy]benzoic acid **6** as such an agent.

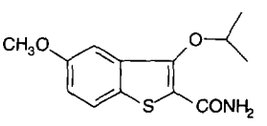
This compound was shown to: (i) bind strongly to human neutrophils (IC_{50} = 17 ± 4.6 nM) and guinea pig lung tissue (IC_{50} = 6.6 ± 0.71 nM); (ii) inhibit the leukotriene LTB_4-induced expression of the CD11b/CD18 receptor on human neutrophils (IC_{50} = 3.3 ± 0.81 nM) and leukotriene B_4-induced contraction of guinea pig lung parenchyma (pK_B = 8.7 ± 0.16); and (iii) inhibit leukotriene LTB_4-induced airway obstruction *in vivo* in the guinea pig. The compound is currently in phase I studies for a range of inflammatory diseases.



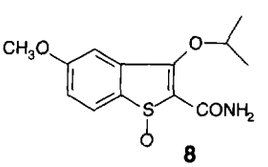
6

Novel cell adhesion inhibitors

The upregulation of the specific endothelial cell surface proteins E-selectin, ICAM-1 and VCAM-1 on exposure to an inflammatory stimulus facilitates the adherence of neutrophils to the vascular endothelium and the subsequent migration of neutrophils from the vasculature into the surrounding tissue, leading to swelling and pain. Previous studies have shown that the inhibition of the upregulation of these adhesion proteins by 3-alkoxybenzo[*b*]thiophene-2-carboxamides, such as **7**, decreases the adherence of neutrophils to the endothelium.



7



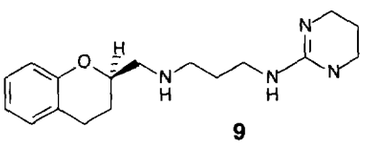
8

An extension of this work has recently shown that related benzofurans, naphthalenes and indoles also reduce the adhesion of neutrophils and monocytes to the inflammatory activated endothelium by modifying the expression of these adhesion proteins [Boschelli, D.H. *et al.*, *J. Med. Chem.* (1995) 38, 4597–4614]. The lead compound **8** was shown to be orally active in a number of inflammatory models with the activity residing in the *S*-enantiomer.

Novel non-indole $5\text{-}HT_{1D}$ agonists

Most of the $5\text{-}HT_{1D}$ agonists to emerge since the discovery of sumatriptan have been substituted indoles. Van Lommen, G. and coworkers [*Bioorg. Med. Chem. Lett.* (1995) 5, 2649–2654] describe the discovery of a series of new non-indole $5HT_{1D}$ agonists.

The most potent of these compounds was compound **9**, alniditan, which was found to be at least tenfold more effective than sumatriptan at inducing constriction of dog saphenous vein segments and the pig basilar artery. The authors report that this compound is presently undergoing clinical trials as a potential antimigraine agent.

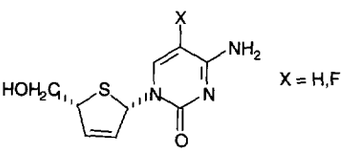


9

Antiviral evaluation of thionucleosides

Young, R.J. and coworkers [*Bioorg. Med. Chem. Lett.* (1995) 5, 2599–2604] report the synthesis and evaluation of enantiomeric 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxy-4′-thionucleosides as potential chemotherapeutic agents for the treatment of viral infections. The synthesis involved the use of chiral thiolactones to produce both enantiomers of the pyrimidine 2′,3′-dideoxy-4′-thio series. All of the compounds were screened *in vitro* for antiviral activity against a range of viruses.

The L-d4-cytidine analogues **10** were found to inhibit both the replication of the HIV and hepatitis B virus *in vitro*.



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