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THE DISCOVERY OF CP-96,021 AND CP-96,486, BALANCED, COMBINED, POTENT AND ORALLY ACTIVE LEUKOTRIENE D4 (LTD4)/PLATELET ACTIVATING FACTOR (PAF) RECEPTOR ANTAGONISTS.

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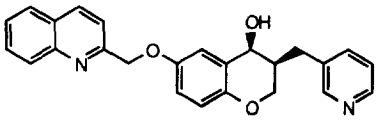
Abstract: The combination of key structural pharmacophores found in known leukotriene D4 (LTD4) receptor antagonists with those of potent platelet activating factor (PAF) receptor antagonist **UK-74,505** has led to the synthesis of hybrid compounds **CP-96,021** and **CP-96,486**. These compounds represent the first known balanced, combined and orally active LTD4/PAF receptor antagonists.

Asthma is a chronic inflammatory disease of the lung characterized by periodic acute bronchoconstrictive episodes, damaged airway epithelium, mucosal edema, hypersecretion of mucus and submucosal infiltration of eosinophils and neutrophils. Both the airway obstruction and the cellular infiltration are stimulated by various chemical mediators released within the lung during acute asthmatic attacks. Two such mediators are peptido leukotriene D4 (LTD4) and platelet activating factor (PAF). Since the discovery and elucidation of their chemical structures over a decade ago, both leukotrienes (LT's) [1,2,3] as well as platelet activating factor (PAF) [2,3,4] have been implicated as primary mediators in the pathogenesis of a variety of inflammatory diseases, including allergy, inflammation, asthma, gastrointestinal diseases and septic shock.

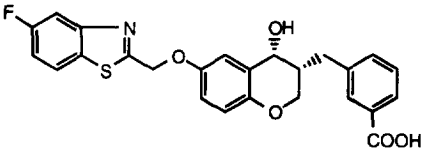
Numerous specific LTD4 antagonists have been prepared and advanced into clinical studies as documented by an ever increasing body of literature. [5] Recent clinical studies with specific LTD4 receptor antagonists **MK 571, MK 679** (Verlukast), [6] **ONO 1078**, [7] **ICI 204,219** (Accolate), [8] **RG 12525** ,[9] and **SK&F 104,058** [10] have been encouraging, demonstrating beneficial roles of LTD4-antagonists in human bronchial asthma. Numerous specific PAF antagonists have also been synthesized and advanced into clinical studies, and are being evaluated in both pulmonary as well as reperfusion injury diseases. [11] Suggestions have been made that PAF antagonists will be useful for controlling asthmatic disease [12], although clinical results available to this date have not been as encouraging as those with specific LTD4 antagonists.

Since asthma is a highly complex disease in which various cells and mediators interact during the disease process we felt that multimediator-type compounds antagonizing both LTD4 and PAF receptors may be clinically more advantageous than single-mediator compounds. We were encouraged by the report of O'Donnell and Welton [2] which demonstrated that the combination of a specific LTD4 antagonist and a specific PAF antagonist affords synergetic protection against systemic anaphylaxis in guinea pigs. As suggested by these and other workers, [5,9,12] it appeared that successful therapeutic strategies for a complex disease such as asthma may in fact require antagonism of multiple mediators. Recognizing this possibility we sought the synthesis of a single agent which would contain both LTD4 and PAF antagonist pharmacophores. To our knowledge no such agents have been reported, although the recent publication of the antihistamine agent

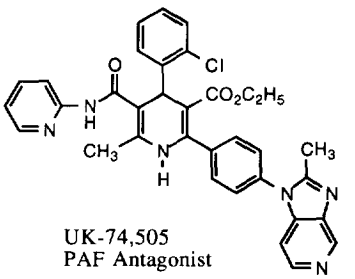
mequitazine [13] suggests that its antiallergic activity might be due in part to its ability to antagonize LT's and PAF in addition to its ability to inhibit histamine release from mast cells.



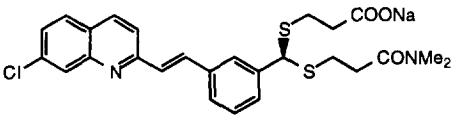
CP-80,798
LTD_4 Antagonist



CP-85,958
LTD_4 Antagonist



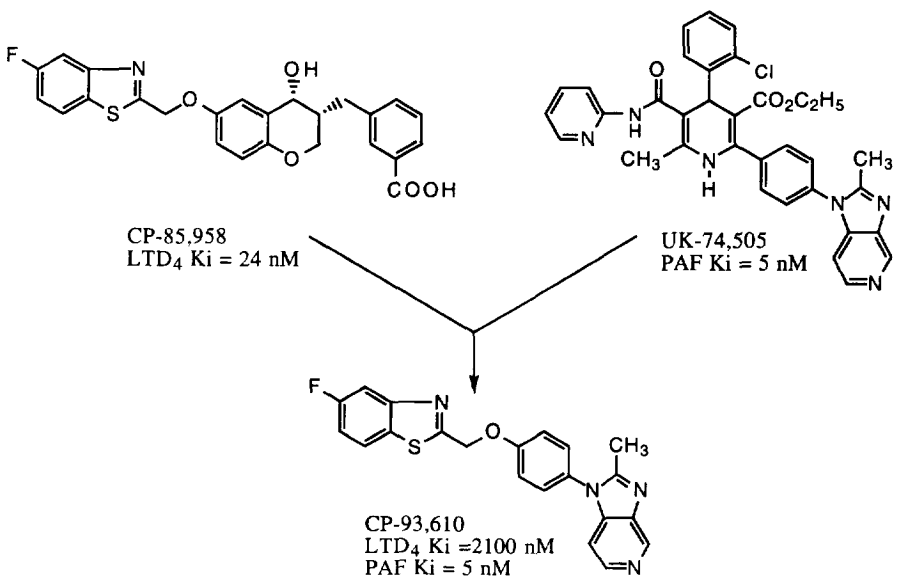
UK-74,505
PAF Antagonist



MK-0679 (Verlukast)
LTD_4 Antagonist

Our efforts in seeking specific PAF antagonists e.g. **UK-74,505** [14] as well as specific LTD4 antagonists such as **CP-80,798** and **CP-85,958** have been reported [15]. In seeking dual antagonists we have made use of our own extensive SAR derived from work on specific LTD4 and PAF antagonists as well as SAR from styryl quinoline LTD4 antagonists such as Verlukast and related compounds. [6,16] Initial attempts to prepare a combined LTD4/PAF antagonist called for combination of the benzothiazole portion of specific LTD4 antagonist **CP-85,958** with the PAF pharmacophore of **UK-74,505** (N-phenyl-2-methyl-5-azabenzimidazole), resulting in the synthesis of hybrid analog **CP-93,610**. Although excellent PAF antagonistic activity was obtained (PAF K_i=5 nM), only weak LTD4 activity at 2100 nM was observed in the guinea pig LTD4 receptor binding assay (Scheme I).

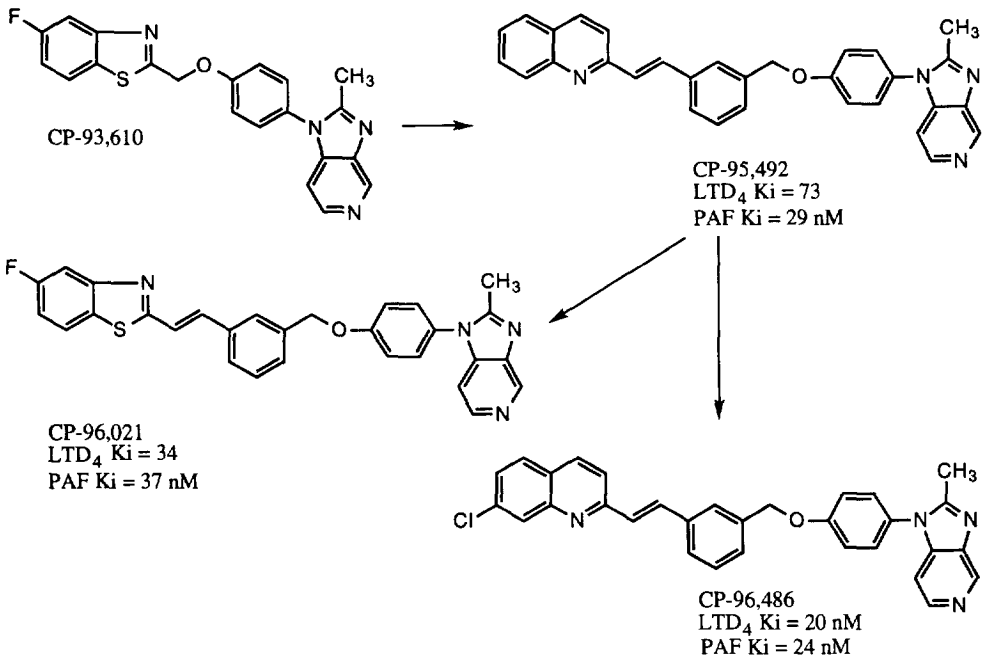
Scheme I



We recognized that numerous existing LTD4 antagonists, including **MK 0679, SR 2640, RG 12525,** and our own **CP-85,958**, contained a phenyl ring linking their respective heteroaromatic and acidic moieties. The effect of additional phenyl ring on a increased receptor binding affinity by increasing the lipophilicity of the molecule has been well documented [9a]. These facts led us to examine if a phenyl spacer group inserted between the LTD4 and PAF pharmacophores in **CP-93,610** would result in increased LTD4 binding affinity [17], resulting in a potent, *balanced* LTD4/PAF antagonist.

Accordingly, further structural modifications of **CP-93,610** led to the synthesis of styryl quinoline analog **CP-95,492**, which showed nearly balanced LTD4/PAF antagonistic activity K_i's of 73 and 29 nM respectively. Further modification of **CP-95,492** incorporated the optimal LTD4 pharmacophore heterocycles (5-fluorobenzothiazole and 7-chloroquinoline), leading to the synthesis of **CP-96,021** and **CP-96,486**, analogs with potent and balanced LTD4/PAF antagonistic activity [18] (Scheme II).

Scheme II



Extensive *in vitro* and *in vivo* pharmacology data have confirmed that both **CP-96,021** and **CP-96,486** are balanced antagonists of both LTD_4 and PAF receptors (Table 1). *In vitro,* **CP-96,021** antagonized ^3H-LTD_4 binding to guinea pig lung membranes [20] and ^3H-PAF binding to rabbit platelets [21] with K_i's of 34 and 37 nM respectively, whereas **CP-96,486** possessed K_i's of 20 and 24 nM respectively. The specificity of these compounds was further demonstrated in assays of ligand binding to alpha$_{1\&2}$, beta, dopamine$_2$, adenosine$_1$, 5-HT$_{1\&2}$, H_1, muscarinic, μ opiate, and GABA receptors, where they expressed IC_{50}'s greater than 10 μM. *In vivo*, CP-96,021 inhibited iv LTD_4- and iv PAF-induced bronchoconstriction in guinea pigs [22] with ED_{50}'s of 0.46 and 0.16 mg/kg p.o. respectively, whereas **CP-96,486** possessed ED_{50}'s of 0.27 and 0.26 mg/kg p.o. respectively. Evidence that these *in vivo* bronchoprotective effects were specific was provided by the failure of either compound to block aerosolized methacholine induced bronchoconstriction in this species. **CP-96,021** and **CP-96,486** effectively blocked the combined airway obstructive effects of endogenously released PAF and LTD_4 stimulated by aerosolized antigen challenge in guinea pigs [23] with ED_{50}'s of 1.8 and 1.7 mg/kg p.o. respectively. Biological data for reference compounds, specific LTD_4 antagonist ICI-204,219 and specific PAF antagonist UK-74,505, is provided in Table 1 for comparative purpose.

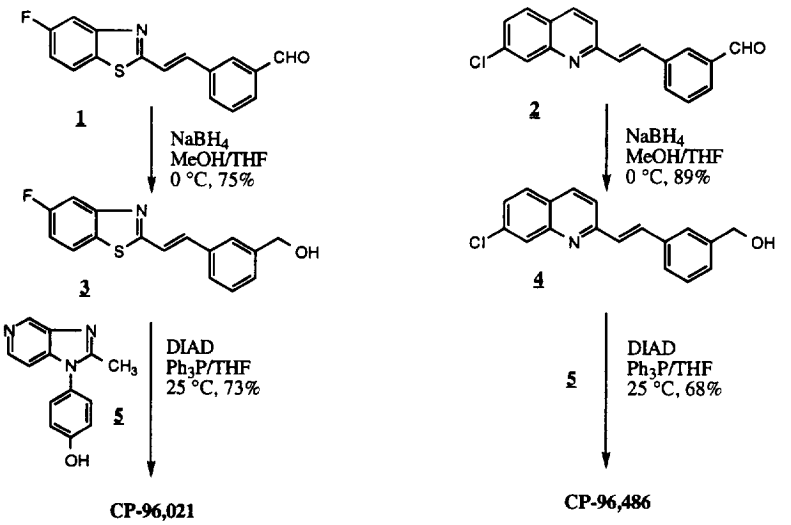
Table 1: Comparison of *in vitro* and *in vivo* properties of **CP-96,021**, **CP-96,486, ICI-204,219** and **UK-74,505**[a]

Test System	CP-96,021	CP-96,486	ICI-204,219	UK-74,505
LTD_4 Binding K_i (nM)[b]	34 ± 5	20 ± 2	2.3 ± 0.4	>30,000
PAF Binding K_i (nM)[b]	37 ± 12	24 ± 7	>50,000	5.0 ± 3
i.v. LTD_4 ED_{50} (mg/kg)	0.46 (4)[c]	0.27 (6)[c]	0.21(8)[c]	NT[d]
i.v. PAF ED_{50} (mg/kg)	0.16 (12)[c]	0.26 (8)[c]	NT[d]	0.33 (8)[c]
Aerosol Antigen ED_{50} (mg/kg)[b]	1.8 ± 0.3	1.7 ± 0.3	3.5	1.90

a) For pharmacological data of CP-85,958 see proceeding paper in this journal.
b) Values are shown as the mean ± S.E.M. (n = 3).
c) Numbers of pairs of animals used to construct a dose response curve.
d) Compounds not tested.

CP-96,021 and **CP-96,486** were prepared in a straightforward manner as illustrated in Scheme III. Briefly, reduction of readily available aldehydes **1** [18] and **2** [18,19] with sodium borohydride provides corresponding alcohols **3** and **4** which were coupled with PAF pharmacophore 4-(2-methyl-1H-imidazo[4,5-c]pyridine-1-yl-phenol **5** [18] to give the final products.

Scheme III.



In conclusion, preparation of hybrid structures which combine LTD4 antagonist pharmacophores with PAF antagonist pharmacophore results in the synthesis of unique compounds possessing dual and balanced antagonistic properties. To our knowledge, **CP-96,021** and **CP-96,486** represent the first known examples of a single compound possessing potent, dual and balanced LTD4/PAF antagonistic activity. Based on the uniqueness of this approach and the roles each mediator plays in pulmonary diseases, these and related compounds offer excellent potential to be developed as oral as well as aerosol agents for the treatment of asthma. **CP-96,021** and **CP-96,486** could also provide benefit in other maladies such as shock, trauma, stroke, and coronary reperfusion injury, all of which are believed to be PAF or leukotriene dependent. The availability of combined, balanced and orally active LTD4/PAF antagonists should therefore offer an additional and unique clinical opportunity in further defining the precise roles of LT's and PAF in the complex and chronic allergic inflammatory diseases. Full pharmacological/pharmacokinetic properties of **CP-96,021** and **CP-96,486** will be reported shortly.

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