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N-CARBAMOYL ANALOGS OF ZAFIRLUKAST: POTENT RECEPTOR ANTAGONISTS OF LEUKOTRIENE D_4

Matthew F. Brown,* Anthony Marfat,* Gerard Antognoli, Robert J. Chambers, John B. Cheng, David B. Damon, Theodore E. Liston, Molly A. McGlynn, Stacie P. O'Sullivan, Brian S. Owens, Joann S. Pillar, John T. Shirley, and John W. Watson

Pfizer Central Research, Eastern Point Rd. Groton, CT 06340, U.S.A.

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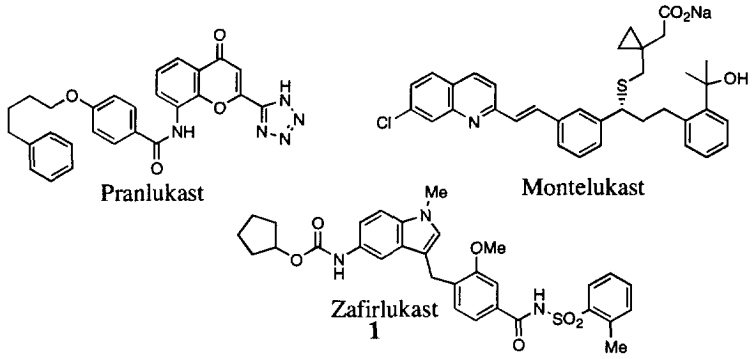
Abstract: Exploration of the indole nitrogen region of Zafirlukast (**1**) has uncovered a potent series of cysteinyl leukotriene D_4 (LTD_4) antagonists. These studies showed that a variety of functionality could be incorporated in this region of the molecule without sacrificing potency. Efforts to exploit this site in order to improve oral efficacy are discussed.

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) have been shown to be potent mediators of bronchoconstriction and increased vascular permeability, making them attractive targets for therapeutic intervention in the treatment of asthma.[1,2] The role that leukotriene D_4 plays in the pathogenesis of asthma has been validated recently by the success of a number of orally active leukotriene D_4 antagonists in clinical trials, including Montelukast,[3-5] Pranlukast[6,7] and Zafirlukast (**1**).[8-10] Herein, we describe our efforts toward the discovery of a potent series of leukotriene D_4 antagonists.



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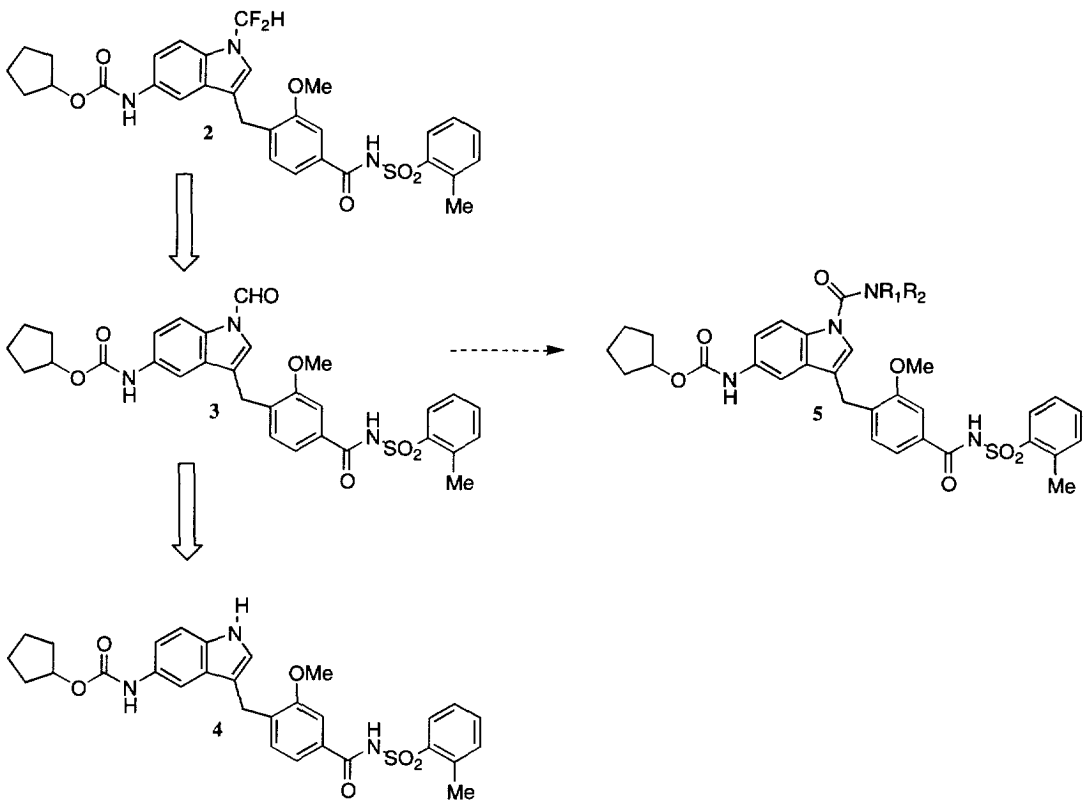
Our strategy involved expanding the known SAR of the aryl sulfonamide class of leukotriene D_4 antagonists exemplified by Zafirlukast (**1**). Several reports have shown that a variety of functionality appended to the indole nitrogen maintained potent in vitro activity.[11-13] Early on in our efforts, the difluoromethyl analog **2** was prepared and displayed potency equivalent to **1** in vitro in both a receptor binding assay,[14] as well as an LTD_4-dependent Ca^{2+} mobilization assay[15] (see Table 1). However, under simulated physiological conditions, hydrolysis of **2** to formamide **3** was observed.[16] Interestingly, **3** was shown to be potent in vitro and exhibited outstanding activity following oral administration in a guinea pig model of allergic airway obstruction.[17] However, **3** was found to be rather unstable, readily converting to the unsubstituted indole analog **4** in rat, monkey and human plasma (13-36% after 1 hour).

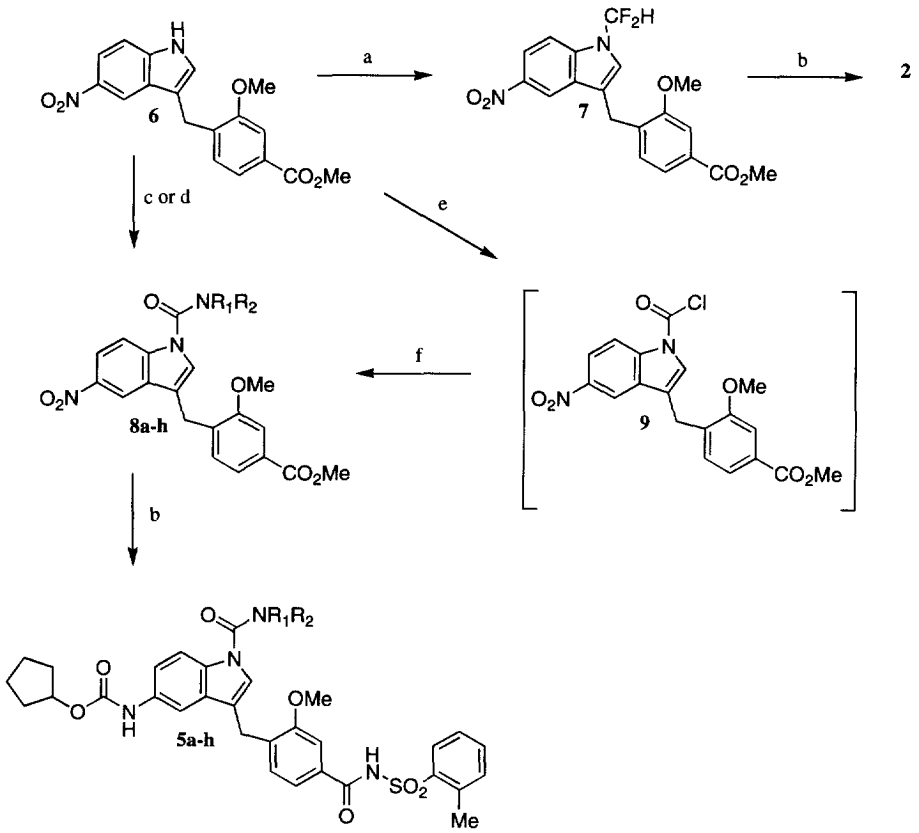
Encouraged by the efficacy of the N-formyl analog **3**, a series of N-carbamoyl substituted analogs (i.e., **5**) were prepared in an attempt to improve chemical stability.



Two general procedures were used to incorporate the carbamoyl functionality (see Scheme 1). Treatment of the 5-nitroindole intermediate **6**[11] with isocyanates in the presence of DMAP gave indoles **8** in good yield.

Alternatively, treatment of **6** with phosgene to generate indolyl chloride **9** followed by addition of primary or secondary amines provided N-carbamoyl compounds **8**. The N-formamide intermediate **8h** was prepared by treating indole **6** with chlorosulfonylisocyanate followed by aqueous NaOH. Conversion of **8a-h** to the aryl sulfonamides **5a-h** was carried out in a manner analogous to methods reported in the literature.[11]

Scheme 1[a]



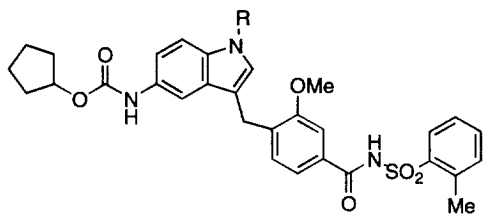
[a] (a) NaH, DMF, $CHClF_{2(g)}$, 5 min; (b) see ref 11; (c) RNCO, DMAP, CH_2Cl_2; (d) $ClSO_2NCO$, CH_2Cl_2, 5 days; 2 N NaOH, acetone; (e) phosgene (1.9 M in toluene), NEt_3, CH_2Cl_2; (f) R_1R_2NH, CH_2Cl_2

In general, this series of analogs are potent LTD_4 antagonists (see Table 1). For example, **5g** is fourfold more potent than **1** in the ^3H-LTD_4 binding assay and displays a tenfold improvement in functional activity (Ca^{2+} mobilization). Excellent in vitro potency was maintained in this series with a diverse array of substituents appended to the indole nitrogen. Brown et al.[12] have previously reported that attachment of a propionamide moiety to the indole nitrogen in a closely related chemical series gave enhanced in vitro potency. They proposed that this functionality may be directly interacting with the receptor by mimicking the C-1 carboxylic

acid of LTD_4. Regardless of how the indole nitrogen substituents improve receptor binding relative to **1**, we attempted to exploit this area of the molecule to enhance in vivo activity.

While achieving greater in vitro potency relative to Zafirlukast (**1**) was accomplished, improving efficacy in vivo was much more challenging. For example, the N-formamide analog **5h** was approximately fourfold more potent than **1** in vitro. However, **5h** was shown to be approximately twofold *less* potent than **1** when administered orally in the guinea pig efficacy model (see Table 1).

Table 1



Compound	R	^{3}H-LTD_4 Binding IC_{50} (nM)	Ca^{2+} Mobilization IC_{50}(nM)	Guinea pig efficacy model oral ED_{50} (mg/kg)
1	-CH_3 (Zafirlukast)	2	1	0.9 (2 h)
2	-CHF_2	1	0.4	58% inh. @ 1mg/kg(2 h)
3	-CHO	1	0.6	0.84 (1h)
4	-H	1	2	40% inh. @ 1 mg/kg (1 h)
5a	-$CONMe_2$	0.4	1	39% @ 1 mg/kg (1 h)
5b	-$CONEt_2$	0.5	0.8	1.2 (1 h)
5c	-$CONH(CH_2)_3Ph$	0.5	0.1	1.6 (1 h)
5d	-$CON(CH_3)(Ph)$	0.4	0.2	1.1 (2 h)
5e	-$CON(Ph)_2$	2.0	0.4	1.1 (2 h)
5f	-CO(morpholino)	0.4	2	8% @ 1 mg/kg (2 h)
5g	-$CONH(CH_2)_2N(CH_3)_2$	0.5	0.1	34% @ 1 mg/kg (1 h)
5h	-$CONH_2$	0.5	0.3	1.6 (1 h)

Pharmacokinetic studies were conducted with representative compounds to gain insight into the lack of improved in vivo efficacy. For example, after oral administration of **5h** to monkeys, no drug could be detected in the circulation. Low to moderate clearance of several of these analogs was observed following intravenous administration suggesting that absorption may be the limiting factor for this series. Follow-up studies in portal-vein cannulated dogs involving oral administration of analogs in PEG400 solutions confirmed this hypothesis as low portal and systemic plasma drug concentrations were detected. Attempts to enhance absorption by preparing analogs with improved aqueous solubility were not successful.[18]

In conclusion, a potent series of leukotriene D_4 receptor antagonists is described. While efforts to identify a compound with an acceptable pharmacokinetic profile were not successful, further exploration of indole N-substitution could potentially identify such an agent.

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15. The $[Ca^{2+}]i$ concentration in differentiated human monocytic U-937 cells was assessed using a the Ca^{2+} florescence probe, fura-2/AM according to a previous method, see: Winkler, J. D.; Sarau, H. M.; Foley, J. J.; Crooke, S. T. *J. Pharmacol. Exp. Therap.* **1988**, *247*, 54.

16. **2** was found to degrade to **3** (10%) and **4** (4%) after 1 hour in simulated gastric fluid.

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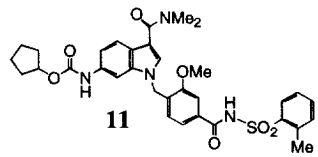
18. In a structurally related series, intraduodenal administration of the water soluble meglumine salt of **11** to monkeys resulted in poor systemic exposure, again suggesting poor absorption.



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