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Communications to the Editor

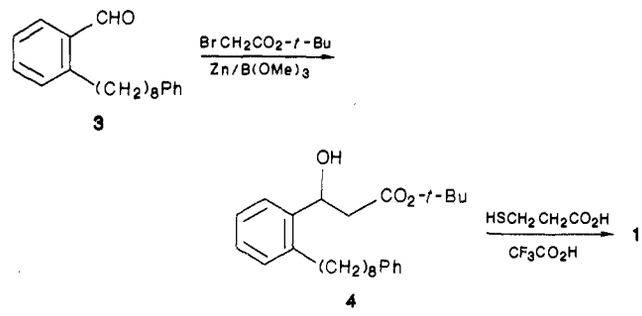
High-Affinity Leukotriene Receptor Antagonists. Synthesis and Pharmacological Characterization of 2-Hydroxy-3-[(2-carboxyethyl)thio]-3-[2-(8-phenyloctyl)phenyl]propanoic Acid

Sir:

The leukotrienes (LTC_4, LTD_4, and LTE_4) have been the focus of intensive research since their identification as the biologically active components of slow reacting substance of anaphylaxis.[1-3] Released by sensitized human and animal lung tissue,[3,4] these natural substances produce prolonged bronchoconstriction,[5] increased microvascular permeability,[6,7] and enhanced mucus production.[8] They have been implicated in a wide variety of immediate hypersensitivity diseases, including asthma, and have also been associated with nonimmunological pulmonary, cardiovascular, and renal diseases.[9,10]

Most of the pharmacological effects of the leukotrienes appear to be receptor mediated, and [^{3}H]LTD_4-specific binding sites (receptors) have been identified and characterized in human[11] and animal tissues.[12-14] A number of leukotriene antagonists have been reported,[15-17] most of which bear a close structural similarity with the initial prototype antagonist, FPL 55712.[18] However, these compounds do not exhibit high affinity for LTD_4 receptors (K_i = 0.5–5 μM).

Scheme I



Chemical efforts in our laboratories have focused on the design and synthesis of high affinity peptidoleukotriene receptor antagonists. This research has been guided by two key observations. First, 2-norleukotrienes, in which the spacial separation between the eicosanoid carboxyl and thioether functionality of the natural leukotrienes is shortened by one methylene residue, exhibit antagonist properties.[19-21] Second, the unsaturated triene moiety of LTD_4 may be replaced by a (phenyloctyl)phenyl group, which confers improved chemical and metabolic stability without significant loss of receptor affinity.[22] These early studies were not definitive with respect to the importance of the C-5 hydroxyl of LTD_4 for receptor affinity. Deletion of this hydroxyl in antagonist analogues had little effect on potency.[20,23] In contrast, the agonist potency of LTD_1 is significantly diminished on deletion of the C-5 hydroxyl.[24] Further studies in our laboratories have led to the

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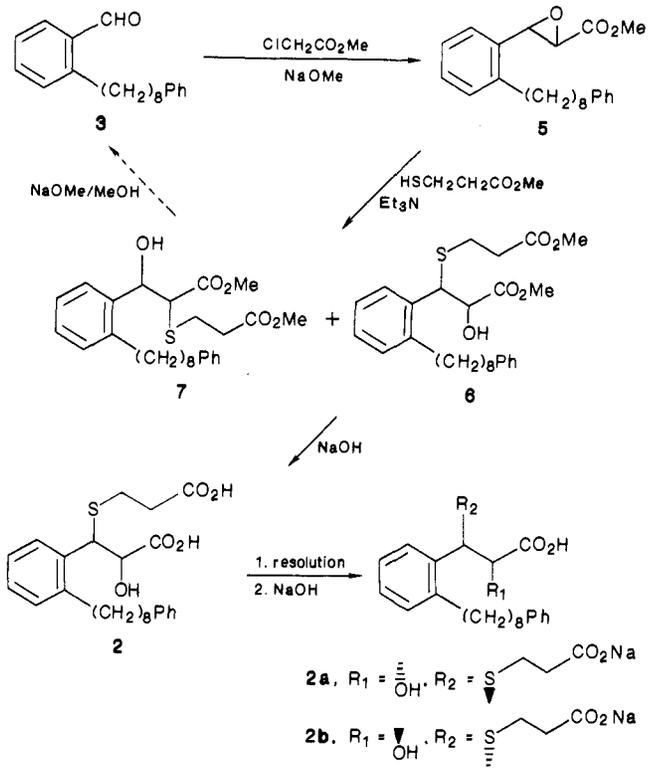
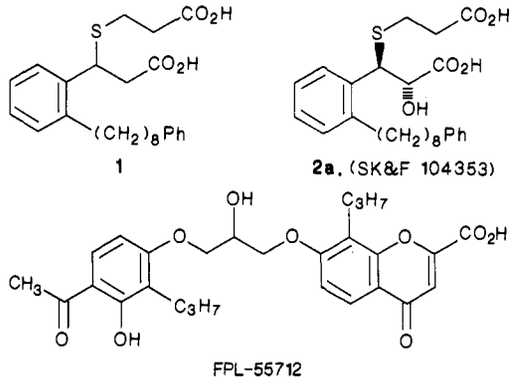
Scheme II

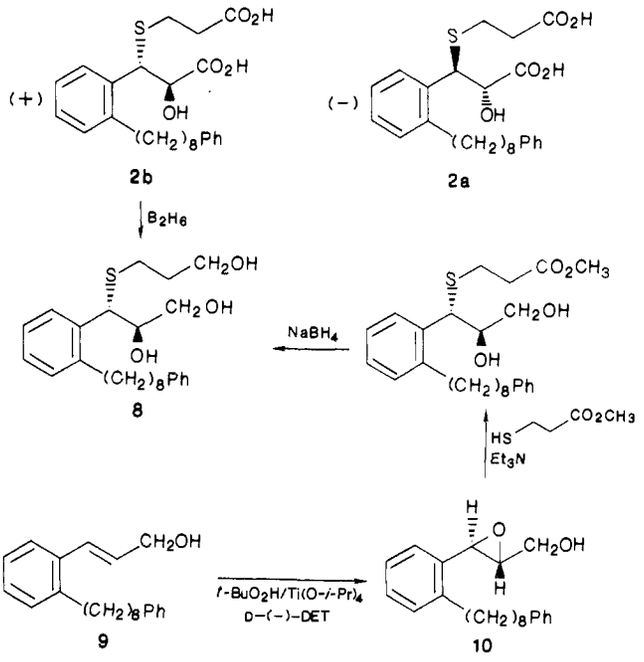


discovery of a series of [(phenyloctyl)phenyl]propionic acids as novel, potent, specific, high-affinity peptidoleukotriene receptor antagonists. The syntheses and pharmacological profile of two members of this class, 3-[(2-carboxyethyl)thio]-3-[2-(8-phenyloctyl)phenyl]-propionic acid (**1**) and 2(*S*)-hydroxy-3(*R*)-[(2-carboxyethyl)thio]-3-[2-(8-phenyloctyl)phenyl]propionic acid (**2a**, SK&F 104353) are described in this paper.



Chemistry.[25] Compound **1** was prepared from (phenyloctyl)benzaldehyde (**3**)[22] as depicted in Scheme I. Trimethyl borate promoted Reformatsky[26] reaction of **3** with *tert*-butyl bromoacetate (THF, room temperature, 24 h) afforded the 3-hydroxyarylpropionic ester **4**. Displacement of the hydroxyl with mercaptopropionic acid proceeded with simultaneous cleavage of the *tert*-butyl ester (2:1 TFA, CH_2Cl_2, 0 °C, 5 h); conversion to the salt (K_2CO_3, reverse-phase chromatography) afforded the di-

Scheme III. Determination of Absolute Stereochemistry



potassium salt of **1** (mp 270 °C).

The 2-hydroxy analogue **2** was prepared as shown in Scheme II. Darzens condensation of **3** with methyl chloroacetate (1.5 equiv of NaOMe, ether, 0 °C, 2.5 h) afforded the trans-epoxy ester **5** which, on reaction with methyl mercaptopropionate (Et_3N, MeOH, room temperature, 18 h), gave a 1:1 mixture of regioisomers **6** and **7**. Treatment of the mixture of regioisomers with methoxide effected a retro-aldol degradation of the undesired isomer **7**, affording **6** and recovered aldehyde **3**. Ester hydrolysis of **6** (NaOH, MeOH, room temperature) afforded racemic **2**, which was resolved as the α-methyl-4-bromobenzylamine salt to give, after conversion to their respective disodium salts (NaOH, MeOH), the enantiomers **2a** ($[\alpha]^{24}_D$ −47.0° (*c* 1, H_2O)) and **2b** ($[\alpha]^{24}_D$ +46.6°).

Determination of absolute configuration (Scheme III) was carried out on the dextrorotatory isomer **2b**. Thus, diborane reduction of **2b** afforded the triol **8** which was identical (NMR, IR, $[\alpha]_D$) to the 2(*R*),3(*S*)-triol prepared by the following independent chiral synthesis.[27] Sharpless chiral epoxidation[28] of 2-(phenyloctyl)cinnamyl alcohol **9** (*t*-BuO_2H/Ti(*i*-OPr)$_4$/D-(−)-diethyl tartrate, CH_2Cl_2) afforded the 2(*R*),3(*R*)-epoxide **10**, which on reaction with mercaptide and subsequent ester reduction ($NaBH_4$, THF/H_2O) provided the necessary triol **8**.

Pharmacology. Compounds **1**, **2a**, and **2b** were evaluated pharmacologically in vitro and in vivo and compared to the standard antagonist FPL 55712.[18] Compound **1** competed for specific [^{3}H]LTD_4 binding sites on guinea pig lung membranes with a K_i of 60 ± 8 nM. Introduction of a hydroxyl group adjacent to the carboxylate function significantly enhanced receptor affinity. Thus, **2a**, which possesses absolute stereochemistry identical with the natural agonist LTD_4, exhibited high affinity for the receptor (K_i = 5 ± 2 nM), while the enantiomer **2b** exhibited significantly reduced affinity (K_i = 180 ± 24 nM).[29] These

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(25) Satisfactory elemental analyses were obtained for all new compounds. All synthetic intermediates were characterized spectroscopically.

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(27) The assignment of the absolute configuration of **2a** and **2b** is based on the well-documented Sharpless asymmetric epoxidation of allylic alcohols.[28]

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Table I. In Vitro Antagonist Potency

	pK_b[a]			
	guinea pig trachea		human bronchus	
compd	vs. LTD_4	vs. LTC_4[b]	vs. LTD_4	vs. LTC_4[b]
1	7.0	5.1	c	c
2a	8.6	<5.4	8.2	8.3
2b	6.1	c	c	c
FPL 55712	6.7	4.9	5.8	6.4

[a] pK_b values for all compounds were calculated at 10 μM except for **2a** (3 μM). [b] Experiments conducted in the presence of 45 mM L-serine borate complex to inhibit the conversion of LTC_4 to LTD_4. [c] Not performed.

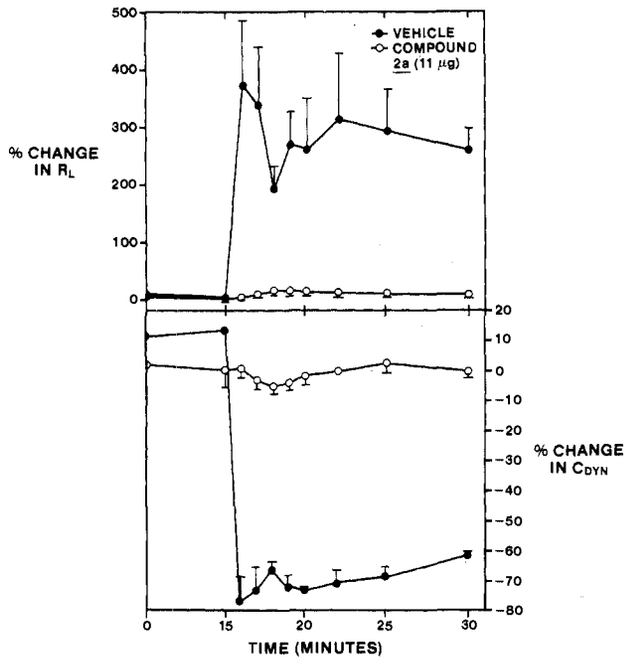

Figure 1. Inhibitory effect of aerosolized **2a** on bronchoconstriction induced by aerosolized LTD_4 in the anesthetized guinea pig; (●) control response to LTD_4 (10 ng/animal); (○) **2a** (11 μg/animal) administered 15 min prior to LTD_4 challenge (10 ng).

results are indicative of a highly stereospecific interaction of the antagonist with the receptor and are similar to those reported previously for LTD_4-receptor interactions.[12] These data contrast with the relatively low affinity (K_i = 1200 nM) observed for the standard antagonist FPL 55712. Similar results are also observed for **2a** in competing for [^{3}H]LTD_4 human lung membrane binding sites (K_i = 10 ± 3 nM).

(29) The observed receptor antagonist activity of **2b** (98% ee) may, in part, result from incomplete resolution of **2**.

The ability of these compounds to antagonize LTC_4- and LTD_4-induced contractions of guinea pig and human airway smooth muscle is illustrated in Table I. Compound **2a** antagonized LTD_4-induced contractions of the guinea pig trachea in a potent and competitive manner[30] with a pA_2 = 8.6, but was essentially without effect on LTC_4-induced contractions of this tissue. However, on isolated human bronchial tissue, **2a** exhibited potent antagonism of contractions induced by either LTD_4 (pA_2 = 8.2, slope = 1.14, n = 5) or LTC_4 (pK_b = 8.3). Compound **1** was 10-fold less potent than **2a**, but was considerably more potent than FPL 55712. The enantiomer **2b** was weakly active, consistent with its observed lower affinity for the receptor.[29] Neither **1** nor **2a** elicited a contraction of either guinea pig tracheal or human bronchial tissue at concentrations as high as 10 μM. Thus, neither compound appears to exhibit partial agonist properties. Moreover, **2a** (10 μM) had no effect on contractions induced by KCl, histamine, carbachol, PGD_2, or the TxA_2 mimic U-44069.

When administered as an aerosol, **2a** (0.03%, 100 breaths, 11 μg total dose) provided complete protection against the changes in airway resistance (R_L) and dynamic lung compliance (C_{DYN}) induced by aerosolized LTD_4 (0.5 μg/mL, 5 breaths, 10 ng) in anesthetized guinea pigs (Figure 1).

Thus, **2a** is a high-affinity leukotriene receptor antagonist, exhibiting potent in vitro and in vivo inhibition of leukotriene-mediated bronchoconstriction. The deshydroxy analogue **1** is similarly an effective antagonist, although with somewhat diminished potency. These compounds represent a novel class of high-affinity leukotriene receptor antagonists that may prove to be of benefit in the treatment of bronchial asthma and other immediate hypersensitivity diseases.

(30) Competitiveness was supported by the observation of parallel shifts in the LTD_4 dose–response curves over a 100-fold concentration range (0.03–3 μM), which, by Schild analysis, afforded a pA_2 = 8.6 and a slope of 0.98 (n = 4).

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