4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic Acid: A High Affinity, Competitive, Orally Active Leukotriene B_4 Receptor Antagonist

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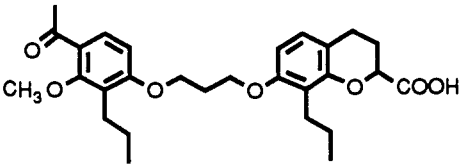
Leukotriene B_4 is a potent activator for polymorphonuclear (PMN) leukocytes.[1] It causes increased chemotactic and chemokinetic migration, aggregation, degranulation, lysosomal enzymes release, and free radical release. Because of these biological activities, LTB_4 may play an important role in inflammatory diseases in which elevated levels of LTB_4 have been detected, such as inflammatory bowel disease, rheumatoid arthritis, and psoriasis. The effects of LTB_4 are mediated through high- and low-affinity receptors on the surface of leukocytes. Since many receptor antagonists of other potent mediators have already demonstrated therapeutic value in man, the search for LTB_4 receptor antagonists represents a rational therapeutic approach to inflammatory diseases. In this communication, we report the discovery of a potent new LTB_4 antagonist.

Several LTB_4 receptor antagonists with a variety of biological activities have been reported in the literature. For example, SC-41930 (1), a well-studied LTB_4 antagonist with multiple biological activities, exhibits only moderate binding affinity (IC_{50} = 300 nM) to human neutrophils.[2] Upjohn reported a series of LTB_4 structure-based antagonists with IC_{50} values ranging from 80 to 400 nM, but most of the compounds appear to exhibit mixed agonist/antagonist activity.[3] Recently, Eli Lilly has reported LY 223982 (2) as a potent LTB_4 antagonist with an IC_{50} of 12 nM against human PMN LTB_4 receptors.[4] ONO-LB-457 (3), which has a similar but slightly modified structure, is also a high-affinity LTB_4 antagonist.[5] Interestingly, structure–activity relationship studies reveal that both of the acidic groups are required in the chemical series related to both 2 and 3 for high binding affinity. This is in contrast to the structural features of the natural ligand. We report here that RG 14893, 4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid (4), a compound currently being evaluated for clinical development, is a novel, high-affinity competitive LTB_4 receptor antagonist with oral activity.



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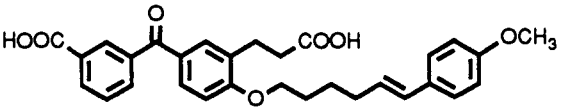

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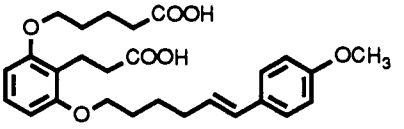

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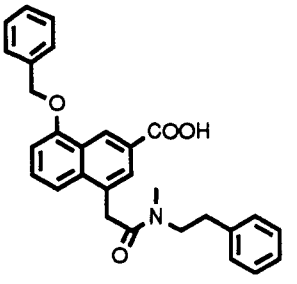

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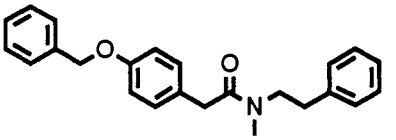

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The synthesis of 4 resulted from our initial observation that a simple phenacetamide derivative 5 displayed

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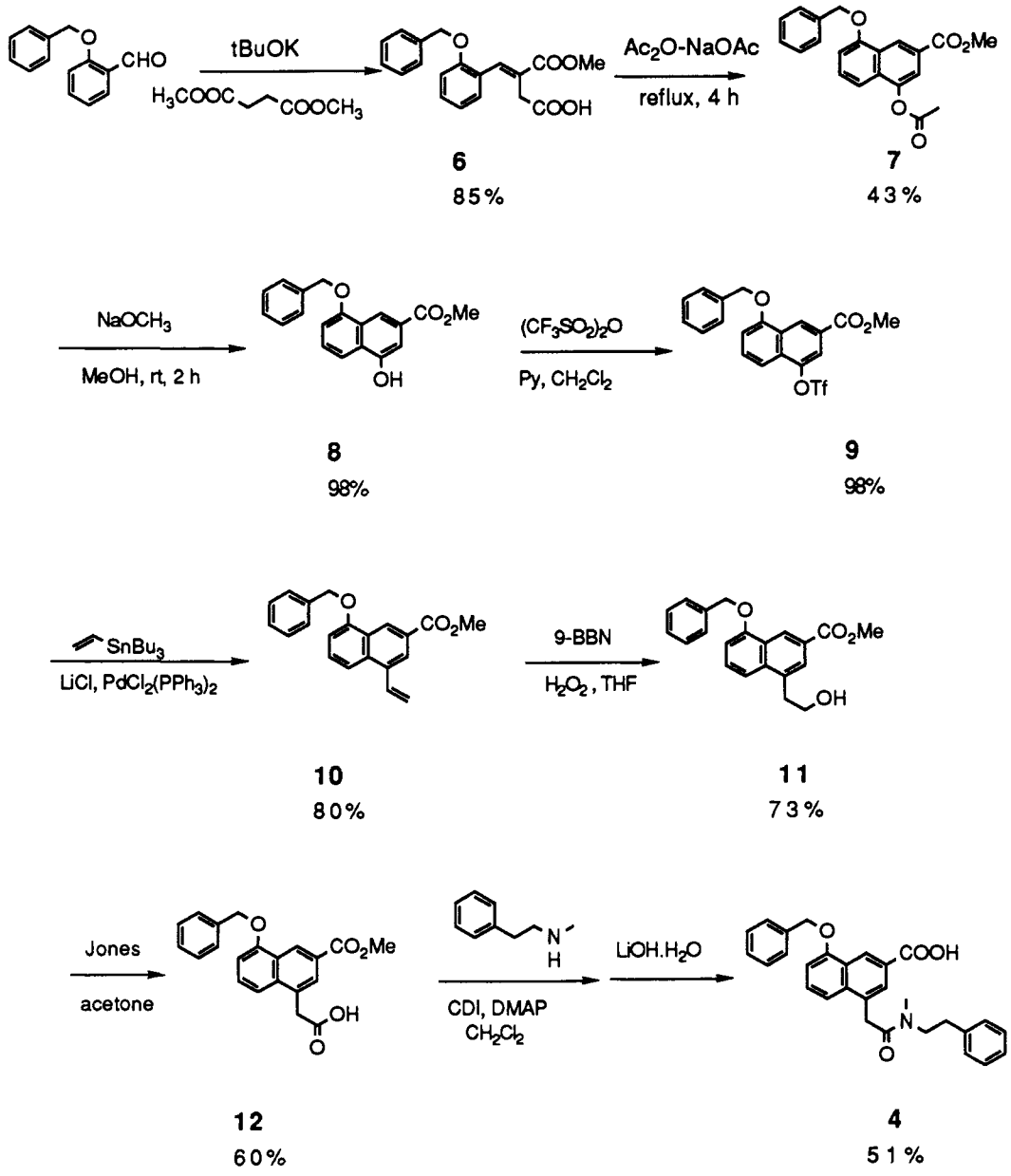
Scheme I



moderate binding affinity with an IC_{50} of 4.7 μM in a human PMN leukocyte LTB_4 receptor binding assay. A series of structure–activity relationship led to the synthesis of **4** (Scheme I). These studies include (a) establishing *N*-methyl-*N*-phenethylacetamide as key binding ligand to LTB_4 receptor, (b) addition of an acidic functional group to improve binding affinity (based on the chemical attributes of the LTB_4 molecule), (c) replacing the center phenyl ring with other aromatic moieties, and (d) optimizing the geometrical relationship of the functional groups. The Stobbe condensation of *o*-(benzyloxy)-benzaldehyde with dimethyl succinate gave **6** as mixtures of *E* and *Z* isomers which were used directly in the next step. Cyclization of **6** with Ac_2O–NaOAc provided the naphthalene derivative **7**.[6] After methanolysis, the resulting phenol **8** was converted to the triflate **9**. Palladium-catalyzed vinylation of **9** with vinyltributyltin gave **10**.[7] Hydroboration of **10** with 9-BBN followed by oxidation of **11** with Jones reagent provided **12**, which upon coupling with *N*-methylphenethylamine followed by base hydrolysis gave **4**[8] as a crystalline solid, mp 179–181 °C.

Initially, radioligand receptor binding assays using guinea pig (GP) spleen cell membrane LTB_4 receptors were employed to determine the affinity of compounds.[9] In this assay, **4** is an extremely potent LTB_4 antagonist with an IC_{50} of 0.36 ± 0.04 nM vs 0.5 nM ligand. Subsequent receptor binding studies reveal that **4** is also a potent inhibitor of the binding of [^{3}H]LTB_4 to human

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(8) ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.88, 2.91 (2 H, d, t), 2.98, 3.08 (3 H, d, t), 3.67 (2 H, m), 3.79, 4.12 (2 H, d, s), 5.29, 5.31 (2 H, d, s), 6.91, 6.93 (1 H, d, d), 7.12–7.54 (12 H, m), 7.82, 8.01 (1 H, d, s), 9.12, 9.14 (1 H, d, s). HR-EI-MS: *m/z* 453.1944.

(9) The guinea pig LTB_4 receptor binding assay is purchased as a kit from New England Nuclear Research Products (Catalog No. NED-005A).

whole cell neutrophils.[10] In this assay, 4 exhibits an IC_{50} of 4.7 ± 0.8 nM (n = 5) vs 0.5 nM ligand. By Scatchard analysis, 4 exhibits K_is of 0.14 and 2 nM for guinea pig and human PMN LTB_4 receptors, respectively. In a GP PMN aggregation assay,[11] 4 inhibits 1 nM LTB_4-induced aggregation with an IC_{50} of 0.8 nM. The inhibitory activity is dose-dependent and freely reversible. In addition, 4 exhibited no agonist activity at all concentrations evaluated in the aggregation assay. These results indicate that there is a good correlation between the binding affinity and functional antagonist activity of 4 against LTB_4 high-affinity receptors in guinea pigs.

The in vivo activity of 4 was evaluated in two different animal models. It has been shown that intradermal injection of LTB_4 induces neutrophil accumulation in the skin in animal models[12] and in man,[13] consistent with its in vitro chemotactic properties. When 4 is administered orally followed immediately by radiolabeled donor neutrophils and 1 μg of LTB_4 (id), it effectively inhibits the chemotaxis of ^{111}indium-labeled PMNs to the LTB_4-induced wheals in guinea pigs (ED_{50} = 0.14 mg/kg po).[14] The data confirmed that 4 is a potent, orally active antagonist of LTB_4 high-affinity receptors.

The effect of 4 on LTB_4-induced neutrophil functions in monkey was also studied.[15] Systemic administration of LTB_4 (0.3 μg/kg) to cynomolgus monkeys causes an immediate neutropenia followed by subsequent neutrophilia several minutes later. When administered intravenously at the dose of 3 mg/kg 2 min before challenge with LTB_4, 4, which has an IC_{50} of 9 nM in the monkey neutrophil LTB_4 receptor binding assay, inhibits neutropenia and neutrophilia (61% and 73%, respectively) in this model.

It has been more than a decade since LTB_4 was reported as a potent activator for PMN leukocytes, and only a very limited number of potent LTB_4 receptor antagonists have been reported in the literature. The role of LTB_4 in various disease states also remains to be established. We report here that 4, a novel and potent LTB_4 antagonist both in vitro and in vivo, has been selected for further development and potential clinical evaluation and expect that it will serve as a useful agent in elucidating the pathophysiological role of LTB_4 in human diseases. Details of the structure–activity relationships of this new series of LTB_4 antagonists will be described in forthcoming publications.

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