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Registry No. (±)-1, 97275-04-2; (±)-1 (free base), 97233-26-6; (±)-2, 52661-17-3; (±)-3, 95526-41-3; (±)-4, 95671-24-2; 5, 5279-03-8; 6, 95526-48-0.

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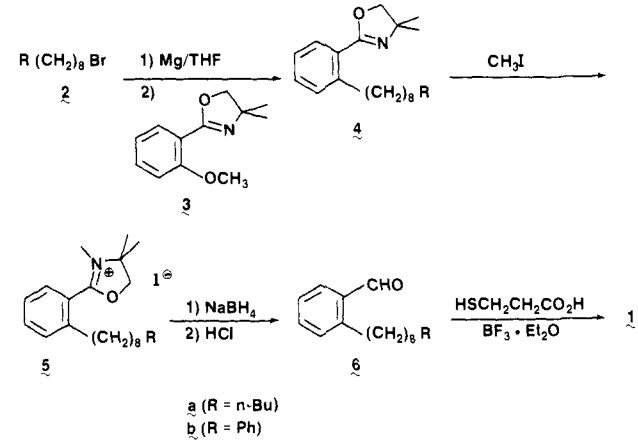
Synthesis and Pharmacological Characterization of 5-(2-Dodecylphenyl)-4,6-dithianonanedioic Acid and 5-[2-(8-Phenyloctyl)phenyl]-4,6-dithianonanedioic Acid: Prototypes of a Novel Class of Leukotriene Antagonists

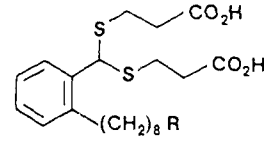
Sir:

As a result of some elegant studies in structural elucidation and chemical synthesis,[1-3] leukotrienes C_4, D_4, and E_4 are now recognized as the components of slow-reacting substance of anaphylaxis. Released upon antigenic stimulation of sensitized human and animal lung tissue,[3,4] they cause potent bronchoconstriction,[5] increased microvascular permeability,[6,7] and altered mucous production and transport.[8] Consequently, it is generally believed that these leukotrienes play a key role in the pathophysiology of allergic asthma and other immediate hypersensitivity diseases and that a leukotriene antagonist would provide novel and effective therapy for such conditions.

Scheme I



Chemical efforts in our laboratories, guided by the structures of the natural leukotrienes, have resulted in the synthesis and pharmacological characterization of 4(*R*)-hydroxy-5(*S*)-(cysteinylglycyl)-6(*Z*)-nonadecenoic acid[9,10] and its analogues[11,12] as leukotriene antagonists on airway and vascular smooth muscle. Although these compounds represent the first examples of leukotriene analogues having antagonist activity, their potency is generally modest and their duration of action in vivo is brief. In addition, some are partial agonists, possessing varying degrees of contractile activity. Further research has led to the discovery that certain 5-aryl-4,6-dithianonanedioic acids comprise a novel class of selective leukotriene antagonists having potent in vitro and in vivo activity of considerable duration, in addition to being completely devoid of agonist activity. Two prototypical members of this class, 5-(2-dodecylphenyl)-4,6-dithianonanedioic acid (**1a**, SK&F 102081) and 5-[2-(8-phenyloctyl)phenyl]-4,6-dithianonanedioic acid (**1b**, SK&F 102922) are the subjects of this paper.



1a, R = n-Bu
1b, R = Ph

Chemistry. Compounds **1a** and **1b** were readily prepared from aldehydes **6a** and **6b**, respectively, by reaction with 2.1 equiv of 3-mercaptopropionic acid (1 equiv of BF_3·Et_2O, CH_2Cl_2, 0 °C, 10 min; **1a**, mp 34–38 °C, 89%; **1b**, mp 59–60 °C, 89%).[13] The aldehydes, in turn, were

(1) Murphy, R. C.; Hammarstrom, S.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4275.
(2) Morris, H. R.; Taylor, G. W.; Piper, P. J.; Samhoun, M. N.; Tippins, J. R. *Prostaglandins* **1980**, *19*, 185.
(3) Lewis, R. A.; Austen, K. F.; Drazen, J. M.; Clark, D. A.; Marfat, A.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3710.
(4) Dahlen, S. E.; Hansson, G.; Hedqvist, P.; Bjorck, T.; Granstrom, E.; Dahlen, B. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 1712.
(5) Dahlen, S. E.; Hedqvist, P.; Hammarstrom, S.; Samuelsson, B. *Nature (London)* **1980**, *288*, 484.
(6) Peck, M. J.; Piper, P. G.; Williams, T. J. *Prostaglandins* **1981**, *21*, 315.
(7) Woodward, D. F.; Weichman, B. M.; Gill, C. A.; Wasserman, M. A. *Prostaglandins* **1983**, *25*, 131.
(8) Marom, Z.; Shelhamer, J. H.; Bach, M. K.; Morton, D. R.; Kaliner, M. *Am. Rev. Respir. Dis.* **1982**, *126*, 449.
(9) Gleason, J. G.; Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Holden, D.; Osborn, R. R.; Zabko-Potapovich, B.; Berkowitz, B.; Wasserman, M. A. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 732.
(10) Weichman, B. M.; Wasserman, M. A.; Holden, D. A.; Osborn, R. R.; Woodward, D. F.; Ku, T. W.; Gleason, J. G. *J. Pharmacol. Exp. Ther.* **1983**, *227*, 700.
(11) Perchonock, C. D.; Uzinskas, I.; Ku, T. W.; McCarthy, M. E.; Bondinell, W. E.; Volpe, B. W.; Gleason, J. G.; Weichman, B. M.; Muccitelli, R. M.; DeVan, J. F.; Tucker, S. S.; Vickery, L. M.; Wasserman, M. A. *Prostaglandins* **1985**, *29*, 75.
(12) Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Gleason, J. G. *J. Med. Chem.*, in press.

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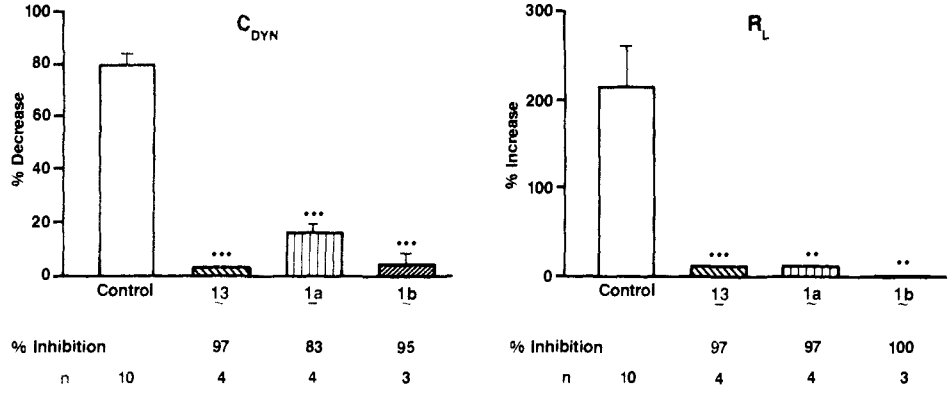
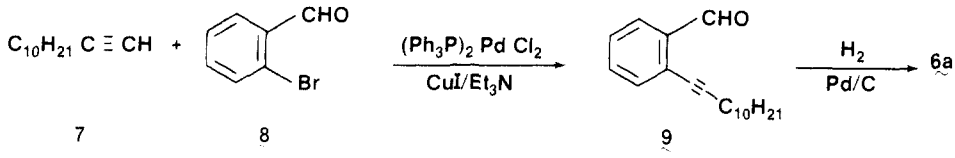
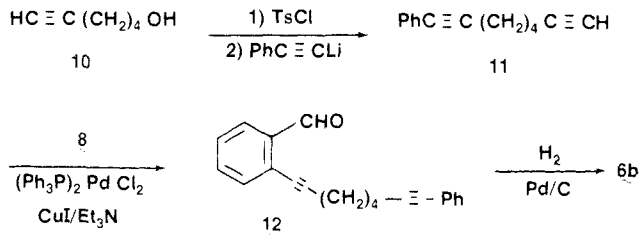


Figure 1. Comparison of the antagonistic effects of **1a**, **1b**, and **13** (5 mg/kg, iv) on LTD_4 (0.17 μg/kg, iv) induced changes in dynamic lung compliance (C_{DYN}) and airway resistance (R_L) in anesthetized guinea pigs. The results are the mean percentage changes ± SEM of three to four animals each, with statistical significance achieved at the indicated level (unpaired t test): (**) $p \leq 0.025$, (***) $p \leq 0.01$.

Scheme II



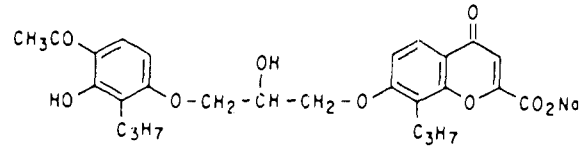
Scheme III



synthesized by either of two methods. The first procedure (Scheme I) utilized the oxazoline methodology developed by Meyers et al.[14] Thus, bromides **2a** and **2b**[15] were converted to their Grignard reagents, which were reacted with 2-(2-methoxyphenyl)oxazoline **3** (THF, room temperature, 20 h) to afford **4a** (97%) and **4b** (69%). Quaternization in refluxing methyl iodide (18 h) produced **5a** (mp 78–82 °C, 88%) and **5b** (mp 76.5–78 °C, 83%), which were subjected to a reduction–hydrolysis sequence[16] (4 equiv of $NaBH_4$, MeOH, 0 °C, 30 min; HCl, H_2O, acetone, room temperature, 18 h) to yield **6a**[17] (63%) and **6b**[18] (65%).

Alternatively, the aldehydes could be prepared through palladium-catalyzed coupling processes[19] (Schemes II and III). Coupling of 1-dodecyne (**7**) and 2-bromobenzaldehyde (**8**) ($(Ph_3P)_2PdCl_2$, CuI, Et_3N, reflux, 30 min) afforded a 91% yield of **9**, which was catalytically reduced to **6a** (H_2/Pd–C, EtOAc; 96%). Alkylation of lithium phenylacetylide with the tosylate derived from 5-hexyn-1-ol (**10**) (1.2 equiv of HMPA, THF, room temperature, 18 h) afforded the diacetylene **11** (74% from **10**), which was coupled with **8** to produce **12** (69%). Hydrogenation of **12** then yielded **6b** (98%).

Pharmacology. Compounds **1a** and **1b** were examined pharmacologically[20] in vitro and in vivo and compared to the standard leukotriene antagonist **13** (FPL 55712).[21] On



13

the isolated guinea pig trachea, LTD_4 elicited a concentration-dependent contraction of the tissue within the concentration range of 0.1 nM–10 μM, with a maximal response equivalent to 67% of carbachol (10 μM). Pretreatment of the tracheal strips with 10 μM solutions of either **1a**, **1b**, or **13** caused a significant, competitive antagonism of the LTD_4-induced contraction, as reflected by a parallel shift of the concentration–response curves. Calculations of the negative logarithm of the antagonist dissociation constant ($-\log K_B$) indicate that **1b** (6.7 ± 0.1) is comparable in activity to **13** (6.8), whereas **1a** (6.0 ± 0.1) is somewhat less potent. The selectivity of **1a** and **1b** toward LTD_4 was indicated by their inability to antagonize the action of other contractile agents, e.g., KCl, histamine, PGD_2, $PGF_{2\alpha}$, and a TxA_2 mimetic (U-44069) (data not shown).

When these antagonists were administered intravenously to anesthetized, spontaneously breathing guinea pigs at a dose of 5 mg/kg, they provided excellent protection

(13) All compounds were characterized by IR and NMR spectroscopy. Elemental analyses were within 0.4% of the theoretical values except where noted otherwise.
(14) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.
(15) Prepared from 8-phenyloctanol with 1.2 equiv each of Ph_3P and CBr_4 (CH_2Cl_2, 0 °C, 1 h; 94%). Anal. ($C_{14}H_{21}Br$) H; C: calcd, 62.46; found, 61.83.
(16) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531.
(17) Anal. ($C_{19}H_{30}O$) H; C: calcd, 83.15; found, 82.59.
(18) Anal. ($C_{21}H_{26}O$) H; C: calcd, 85.67; found, 85.22.
(19) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.
(20) For pharmacological and statistical methods, see ref 10.
(21) Augstein, J.; Farmer, J. B.; Lee, T. B.; Sheard, P.; Tattersall, M. L. *Nat. New Biol.* **1973**, *245*, 215.

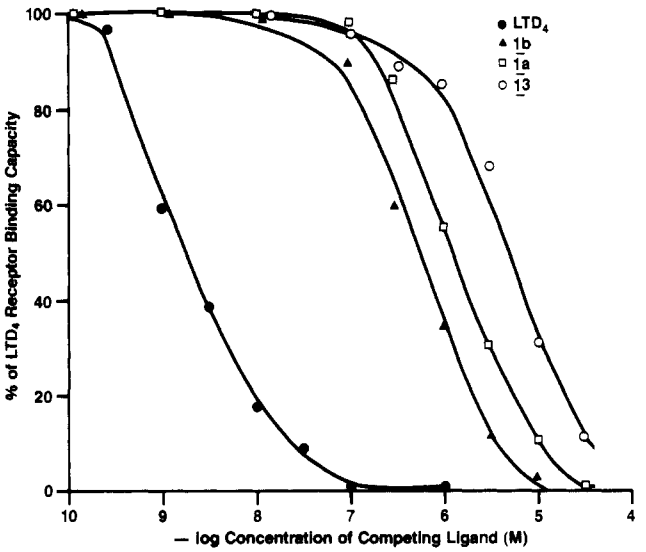


Figure 2. Competition of [^{3}H]LTD_4 binding to guinea pig lung receptors with LTD_4, **1a**, **1b**, and **13**. Standard error of each point was 3–5% of the mean.

against the changes in airway resistance (R_L) and dynamic lung compliance (C_{DYN}) induced by a subsequent (1 min) challenge with LTD_4 (0.17 μg/kg, iv) (Figure 1). Similarly, aerosols of **1a** (0.4%, 100×, Bird respirator), **1b** (0.4%, 100×, Monaghan nebulizer), and **13** (0.1%, 100×, Bird respirator) were effective antagonists of bronchoconstriction induced by aerosol LTD_4 (0.005–0.01 mg/mL, 5×) in the guinea pig, all having a duration of action of at least 30 min (data not shown).

That **1a** and **1b** are acting at the receptor level is indicated by the data in Figure 2, which shows the ability of these compounds to bind to the LTD_4 receptor in guinea pig lung.[22] Compounds **1a** and **1b** displaced [^{3}H]LTD_4 from receptor sites on lung membranes with K_i values of 445 ± 48 and 245 ± 32 nM, respectively. This contrasts with the standard leukotriene antagonist **13**, which has in vitro activity comparable to that of **1b** but considerably lower receptor affinity (K_i = 2.2 ± 0.2 μM).

Thus, **1a** and **1b** are potent and selective in vitro and in vivo antagonists of LTD_4, exerting their effect at the receptor level. They represent prototypes of a novel class of leukotriene antagonists that may prove to be of benefit in the treatment of bronchial asthma and other immediate hypersensitivity diseases.

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Registry No. **1a**, 96964-39-5; **1b**, 96964-40-8; **2a**, 143-15-7; **2b**, 54646-75-2; **3**, 57598-33-1; **4a**, 96964-41-9; **4b**, 96964-42-0; **5a**, 96998-81-1; **5b**, 96964-43-1; **6a**, 96964-44-2; **6b**, 96964-45-3; **7**, 765-03-7; **8**, 6630-33-7; **9**, 96964-46-4; **10**, 928-90-5; **11**, 96964-47-5; **12**, 96964-48-6; 3-mercaptopropionic acid, 107-96-0; lithium phenylacetylide, 4440-01-1.

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(22) For characterization of this receptor, see: Mong, S.; Wu, H. L.; Hogaboom, G. K.; Clark, M. A.; Crooke, S. T. *Eur. J. Pharmacol.* **1984**, *102*, 1.