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SYNTHESIS AND IN VITRO PROFILE OF 7-SUBSTITUTED QUINOLINE CHROMANOLS AS NOVEL, NON-ACIDIC LTB4 ANTAGONISTS.

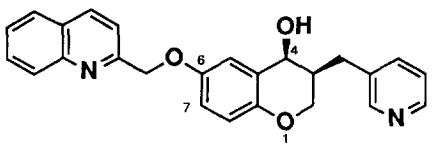
H. Masamune,* R. Breslow, J.B. Cheng, M.J. Conklyn, J.F. Eggler, A. Marfat, L.S. Melvin, J.S. Pillar, J.T. Shirley, H.J. Showell, and J.E. Tickner

Central Research Division, Pfizer, Inc., Groton, Connecticut 06340

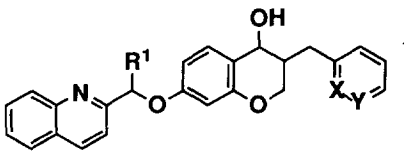
Abstract: The development of novel LTB_4 antagonists from a class of quinolylmethyl LTD_4 antagonists is described. These α-methyl quinolylmethyl chromanols were found to have good *in vitro* activity.

Leukotriene B_4 (LTB_4) is a potent chemotactic agent and is one of the derivatives of arachidonic acid, synthesized via the 5-lipoxygenase pathway.[1] It has a multitude of effects on different inflammatory cells, and hence, is implicated in a variety of inflammatory diseases[1] including rheumatoid arthritis.[2] Consequently, a number of potent and selective prototype LTB_4 receptor antagonists have been developed in the past few years.[3]

The vast majority of these agents are acidic and we were interested in developing a non-acidic antagonist.[4] Among other characteristics, such a compound may have different tissue distribution from an acidic agent and thus, be suitable for development in other therapeutic areas. The LTB_4 receptor antagonists reported in this manuscript evolved from research in the pulmonary area on leukotriene D_4 (LTD_4) receptor antagonists. During the course of that research, **1** was identified as an early development lead[5] and became the focus of SAR studies. Part of that investigation involved relocating the quinolinylmethylene oxygen sidechain to the 7 position of the chromanol, leading to the general structure **2**. While pursuit of these leads did not uncover agents with potentiated LTD_4 antagonist activity, some of these compounds possessed unexpected LTB_4 antagonist activity. This paper discusses some of our discoveries in this area.



1

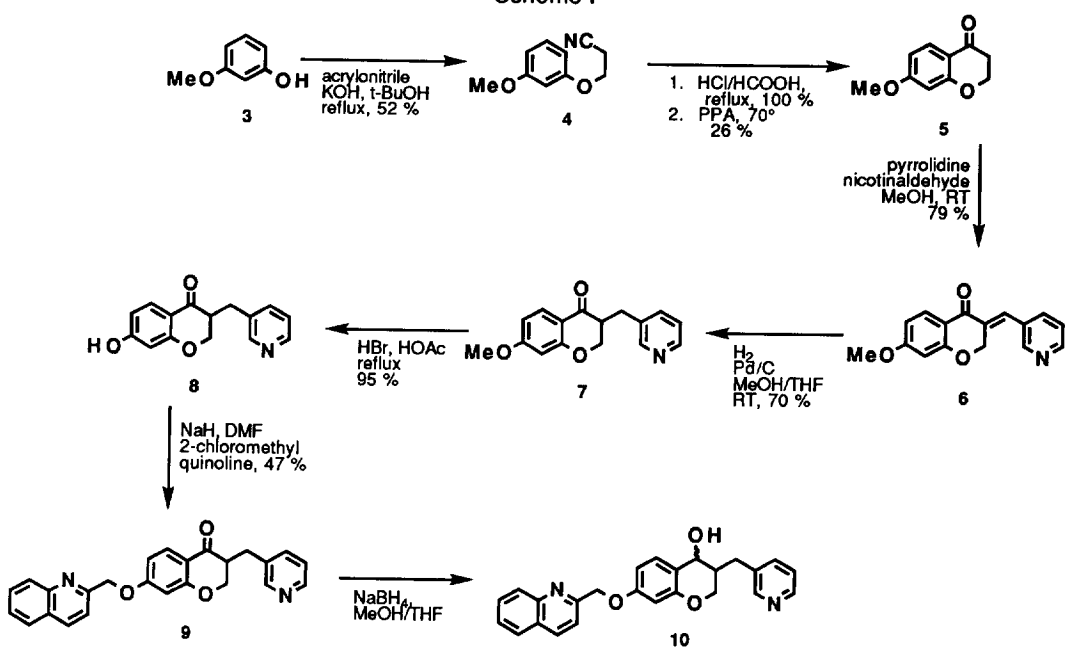


2

R^1 = H, methyl
if X = N, then Y = C
if Y = N, then X = C

The general route for synthesizing these compounds is illustrated in Scheme I.[6] In the final step, reduction of the ketone **9** with sodium borohydride afforded the chromanol product **10**, which upon purification by column chromatography provided the desired products **11** and **12** in 34% and 26% yield, respectively.

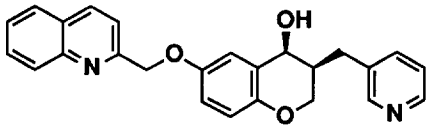
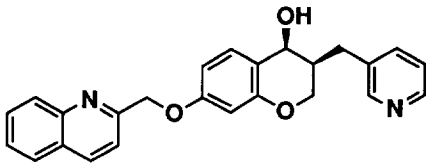
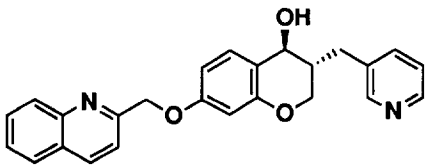
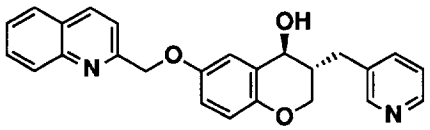
Scheme I



Initially, the goal was to explore the SAR around **1**, with the objective of potentiating the LTD_4 antagonist activity. Thus, both the *cis* and *trans* quinolylmethyl compounds **11** and **12** were evaluated for LTD_4 inhibitory activity as illustrated in Table I (the analogous 6-substituted chromanol **13** is shown for comparison).

As can be seen, there was no loss in the LTD_4 antagonist activity of **11** versus **1**, which encouraged further pursuit of this series. However, we were interested to note that the 7-substituted compounds retained the moderate LTB_4 antagonist activity of their 6-substituted counterparts. Since the 6-substituted compounds were being developed as LTD_4 antagonists,[5] and since we were also interested in pursuing a series of LTB_4 antagonists, we decided to focus on this 7-substituted series as potential lead structures.

TABLE I. Inhibition of LTD4 and LTB4 Receptor Binding for 6- and 7-Substituted Quinolylmethyl Chromanols.

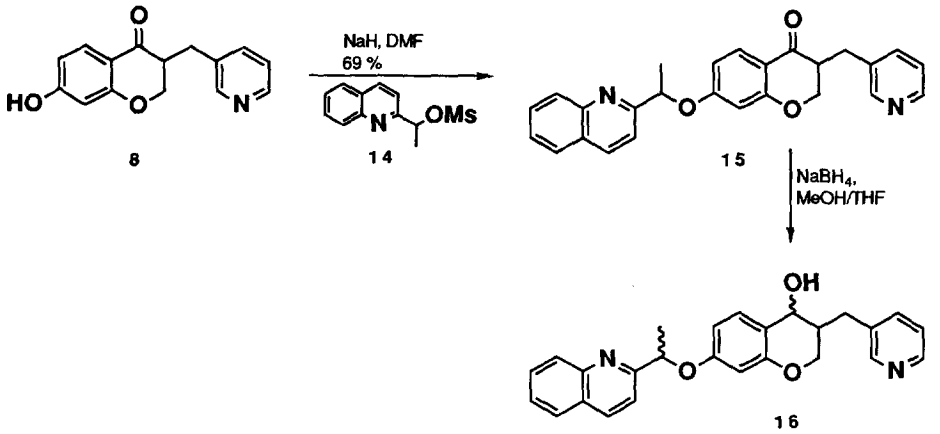
Example	Structure	LTD4[7] Ki (μM)[a]	LTB4[8] Ki (μM)[a]
1		1.6 ± 0.3	38 ± 17
11		1.3 ± 0.5	38 ± 37
12		4.1	39[b]
13		1.0 ± 0.2	16 ± 4

[a] Values are either individual determinations or mean ± SD of 2 or more assays.
[b] Measured in guinea pig binding assay; Kis found to be comparable to human assay.

We had found in our earlier work on the 6-substituted chromanols,[5] that placing a methyl group on the methylene α to the quinoline ring effectively eliminated all LTD4 antagonist activity. No determination was made as to the source of this effect, although it may be due to intolerance for steric hindrance on a critical sidechain. With the goal of developing a selective LTB4 antagonist, a brief program was undertaken to synthesize analogous α-methyl quinolylmethyl chromanols in the 7-substituted series. The general synthetic route to these α-methyl compounds utilizes quinolylethyl mesylate **14** to append the sidechain onto compound **8** (Scheme II). After reduction with sodium borohydride, separation of the resulting isomers via column chromatography provides the products illustrated in Table II. In addition, the *o*-substituted pyridine sidechains (from coupling with picolinaldehyde instead of nicotinaldehyde, see Scheme I) were synthesized in a similar manner to yield **20** and **21**. In the case of **18** and **19**, the two methyl isomers were separable by chromatography, although the stereochemistry of the methyl groups was not determined and are

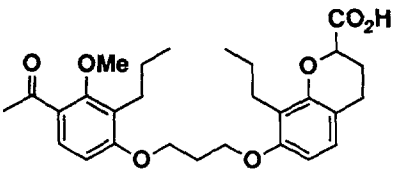
shown with an arbitrary assignment. The *cis* isomer **17**, as well as the two 2-pyridyl compounds **20** and **21**, were isolated as inseparable 50:50 mixtures at the α-methyl center.

Scheme II



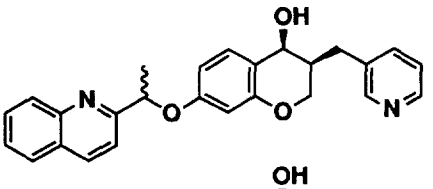
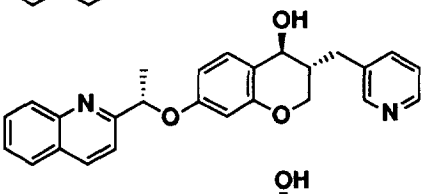
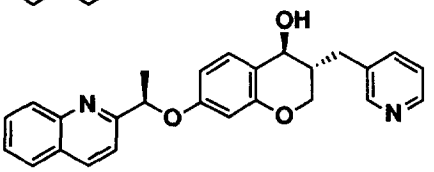
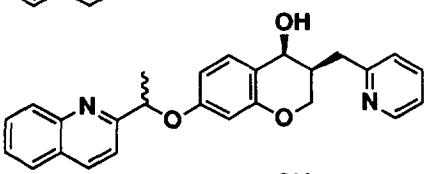
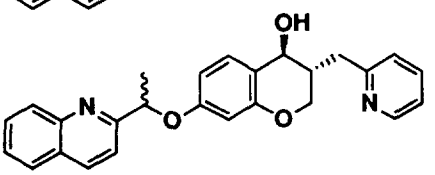
As expected, the addition of the α-methyl group greatly decreased the affinity of these compounds for the LTD_4 receptor. What was unexpected however, was the roughly 10- to 100-fold potentiation of LTB_4 antagonist activity generating K_i's now in the low micromolar range. While this was still 100 to 1000 fold less potent than many of the acidic LTB_4 receptor antagonists, we felt that this was of sufficient interest to warrant examination in the LTB_4-induced chemotaxis assay. Examination in this assay was also important to determine whether these compounds were agonists or antagonists; in fact, they were determined to be antagonists as measured by their inability to cause biological responses on their own.

Table III shows how these agents performed in the *in vitro* functional assay. As a comparative agent, SC-41,930 **22** a prototypical LTB_4 receptor antagonist (K_i = 0.28 μM in the [^{3}H]LTB_4 human neutrophil receptor binding assay) was also tested in the chemotaxis assay. We were excited to find that the micromolar potency in the binding assay translated well into the chemotaxis assay. Indeed, these compounds compared favorably *in vitro* with SC-41,930 **22**. However at this time, in view of the superior activity of another novel series of LTB_4 antagonists,[2] no further pursuit of these compounds is planned.



22

TABLE II. Inhibition of LTD_4 and LTB_4 Receptor Binding by α-Methyl Quinolylmethyl Chromanols.

Example	Structure	Yield in last step	LTD4[7] K_i (μM)[a]	LTB4[8] K_i (μM)[a]
17[9]		56 %	>50 (3)	5.2 ± 1.1
18[10]		18 %	>50 (5)	1.9 ± 1.3
19[10]		19 %	>50 (1)	0.33 ± 0.03
20[9]		45 %	>50 (3)	3.3 ± 1.3
21[9]		44 %	>50 (4)	0.24 ± 0.18

[a] Values are either individual determinations or mean ± SD of 2 or more assays. For those K_i's > 50 μM, the value in the parenthesis indicates the number of determinations.

TABLE III. Inhibition of Neutrophil Migration by α-Methyl Quinolylmethyl Chromanols

Example	LTB_4 Induced Chemotaxis[11] IC_{50} (μM)[a]
17	38 ± 18
18	6.1 ± 1.5
19	3.4 ± 1.6
20	14 ± 4
21	0.22 ± 0.03
22	0.14 ± 0.08

[a] Values are the mean ± SD of 2 or more assays.

In summary, the addition of a methyl group α to the quinoline ring was effective in attenuating the LTD_4 antagonist property of the 7-substituted chromanols while significantly enhancing the LTB_4 antagonist activity of this series. These α-methyl quinolylmethyl chromanols represent a novel, non-acidic class of LTB_4 antagonists.

References and Notes

1. For recent reviews, see a) Djuric, S. W.; Fretland, D. J.; Penning, T.D. *Drugs Fut.* **1992**, *17*, 819; b) Cohen, N.; Yagaloff, K. A. *Curr. Opin. Invest. Drugs* **1994**, *3*, 13.
2. For a discussion of one of Pfizer's candidates in this therapeutic area, see a) Koch, K.; Melvin, L. S., Jr.; Reiter, L. A.; Biggers, M. S.; Showell, H. J.; Griffiths, R. J.; Pettipher, R. E.; Cheng, J. B.; Milici, A. J.; Breslow, R.; Conklyn, M. J.; Farrell, C. A.; Smith, M. A.; Salter, E.; Doherty, N. S. *J. Med. Chem.*, in press; b) Griffiths, R. J.; Pettipher, E. R.; Koch, K.; Farrell, C. A.; Breslow, R.; Conklyn, M. J.; Smith, M. A.; Hackman, B.; Wimberly, D. J.; Milici, A. J.; Cheng, J. B.; Pillar, J. S.; Pazoles, C. J.; Doherty, N. S.; Melvin, L. S.; Reiter, L. A.; Biggers, M. S.; Falkner, F. C.; Mitchell, D. Y.; Liston, T. E.; Showell, H. J. *Proc. Natl. Acad. Sci., USA* **1995**, *92*, 517.
3. In addition to those compounds cited in refs. 1 and 2, recent antagonists are discussed in a) Wikel, J. H.; Sofia, M. J.; Saussy, D. L., Jr.; Bemis, K. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 795; b) Djuric, S. W.; Docter, S. H.; Yu, S. S.; Spangler, D.; Tsai, B. S.; Anglin, C. P.; Gaginella, T. S.; Kachur, J. F.; Keith, R. H.; Maziasz, T. J.; Villani-Price, D.; Rao, T. S.; Walsh, R. E.; Widomski, D. L.; Fretland, D. J. *ibid.* **1994**, *4*, 811; c) Kawakami, H.; Ohmi, N.; Nagata, H. *ibid.* **1994**, *4*, 1461; d) Harper, R. W.; Jackson, W. T.; Froelich, L. L.; Boyd, R. J.; Aldridge, T. E.; Herron, D. K. *J. Med. Chem.* **1994**, *37*, 2411; and e) Cohen, N.; Bizzaro, F. T.; May, W. P.; Toth, K.; Lee, F. K.; Heslin, P. H.; Holland, G. W.; Kwoh, S. C.; Franco, L. S.; Simko, B. A.; Yagaloff, K. A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2883.
4. For two other classes of non-acidic antagonists, see a) Boehm, J. C.; Gleason, J. G.; Pendrak, I.; Sarau, H. M.; Schmidt, D. B.; Foley, J. J.; Kingsbury, W. D. *J. Med. Chem.* **1993**, *36*, 3333 and b) *Drug News and Perspectives* **1993**, *6*, 108.
5. Eggler, J. F.; Marfat, A.; Masamune, H.; Melvin, L. S., Jr.; Carty, T. J.; Cheng, J. B. Unpublished results.
6. All chiral compounds described in this paper are racemates. All yields are unoptimized.
7. Cheng, J. B.; Pillar, J. S.; Conklyn, M. J.; Breslow, R.; Shirley, J. T.; Showell, H. J. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 664. The K_i for non-radioactive LTD_4 is 0.4 nM for comparison.
8. $[^3H]LTB_4$ human neutrophil receptor binding assay. The $[^3H]LTB_4$ human neutrophil receptor binding assay was performed as described by Lin, et. al. (*Prostaglandins* **1984**, *28*, 837) with the following changes: human neutrophils were used at a final density fo 2.5×10^6/mL, $[^3H]LTB_4$ at 0.3 nM and an incubation period of 30 min. The K_i for non-radioactive LTB_4 is 1.09 nM for comparison.
9. Mixture of both methyl stereoisomers.
10. Stereochemistry of methyl group not definitively assigned.
11. Human neutrophil isolation and chemotaxis assay. Human neutrophils were isolated from the blood of normal donors according to the method of Ferrante and Thong (*J. Immunol. Methods*, **1978**, *24*, 389). Purified PMNs were resuspended (2.5×10^6/mL) in Hanks buffer (supplemented with 10 mM HEPES) containing Mg^{+2} and Ca^{+2} and 2 mg/mL crystallized bovine serum albumin (BSA, Sigma, St. Louis, MO) and adjusted to pH 7.2. The chemotaxis assay was performed using a 48 well chamber apparatus (Neuroprobe, Cabin John, MD) with cellulose nitrate filters (pore size, 3.0 μM) as described by Harvath, et. al. (*J. Immunol.* **1987**, *139*, 3055). The total number of cells (observed at 400X magnification) migrating from 20 μM beneath the surface of the monolayer to the leading front (usually ~100-120 mM/60 min) at optimal chemotactic factor concentrations were either determined using an Optomax image analyzer (Optomax, Hollis, NH) or manually and provided an index of the chemotactic response. A concentration of LTB_4 (5 nM) giving ≥ 80 % of the maximal response was chosen against which serial dilution of compounds (present in both compartments of the chemotaxis chamber) were examined. In each experiment full concentration-responses for LTB_4 alone were assessed in order to determine the responsiveness of individual populations of neutrophils.

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