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3-SUBSTITUTED-4-HYDROXY-7-CHROMANYLACETIC ACID DERIVATIVES AS ANTAGONISTS OF THE LEUKOTRIENE B_4 (LTB_4) RECEPTOR

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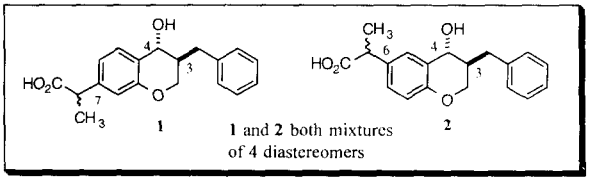
Abstract: The SAR of a series of 7-chromanylacetic acids has been investigated with the aim of identifying potent and selective LTB_4 receptor antagonists. We found optimal activity in derivatives with α,α-disubstitution on the acetic acid and a C-4 hydroxy group and a C-3 lipophilic group on the chromane ring. CP-105696 (**43**), which contains a 4-phenylbenzyl C-3 substituent, was selected for development. © 1997 Elsevier Science Ltd.

LTB_4 is a potent chemoattractant for granulocytes (e.g., neutrophils and eosinophils) and stimulates functional responses such as secretion and cytokine synthesis in these cells as well as in mononuclear cells and lymphocytes. Its presence in relevant tissues has implicated it to be a likely mediator in a number of inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and asthma. Receptor antagonists of LTB_4 are thus expected to be useful therapeutics for these diseases. To date, compounds from several structural classes have been discovered to display LTB_4 antagonism.[1]

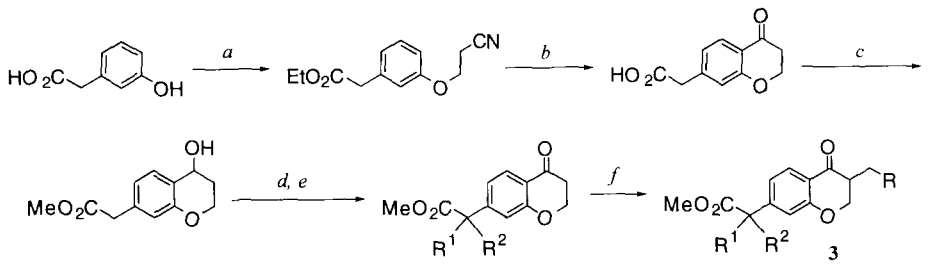
During the course of our investigations on leukotriene D_4 antagonists, we observed that certain chromanol derivatives displayed modest LTB_4 antagonism in addition to LTD_4 antagonism. We also noted that of all the NSAIDs examined, only the propionic acid class showed any significant parallel between their ability to block [^{3}H] LTB_4 binding to high affinity receptors on guinea pig spleen membranes and their ability to inhibit LTB_4-induced human neutrophil chemotaxis.[2] These observations led us to prepare hybrid molecules with the aim of identifying potent and selective LTB_4 antagonists. Accordingly, the propionic acid derivatives **1** and **2** were prepared. Their evaluation revealed that the former, the 7-substituted chromanol, had sub-micromolar LTB_4 antagonism on human neutrophils (0.79 μM ± 0.58) and very weak LTD_4 antagonism (>100 μM). The latter was inactive at both receptors. In addition to its ability to block ligand binding, **1** displayed inhibitory activity in the human neutrophil chemotaxis assay (Table 1) and even more compelling, exhibited oral activity against LTB_4-induced neutrophil infiltration in the guinea pig lung.[3] These promising properties led us to investigate the structural class further with the aim of identifying more potent LTB_4 antagonists. Herein we report the details of this investigation which ultimately led to the identification of CP-105696 as a potent and selective LTB_4 antagonist.[4]



The fully substituted chromanone intermediates (e.g., **3**) were synthesized by a palladium-catalyzed coupling of a silyl ketene acetal with a 7-triflyl-substituted chromanone as previously described[4] or by a multi-step sequence that began with (3-hydroxyphenyl)acetic acid (Scheme 1). In the latter sequence, variation of the structure was readily achieved by alkylating the intermediate TBDMS protected chromanol with various

alkylating agents or by condensing the intermediate chromanone with various aldehydes. Subsequent reduction, resolution (when performed), and saponification gave the target compounds.[4]

Scheme 1



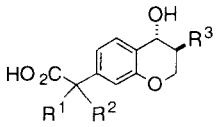
Reagents and yields: (a) i: EtOH, H^+, ii: acrylonitrile, 60% two steps; (b) i: formic acid, reflux, ii: polyphosphoric acid, 19% two steps; (c) i: dimethyl sulfate, ii: sodium borohydride, 75% two steps; (d) i: TBDMS-Cl, ii: NaH, R^1X, R^2X, iii: 4 N HCl/THF, 33% three steps for R^1X, R^2X = MeI; (e) MnO_2, 84% for R^1, R^2 = CH_3 ; (f) i: RCHO, pyrrolidine, ii: H_2/Pd-C, EtOAc, 71% two steps for R^1, R^2 = -$(CH_2)_4$- and R = Ph.

Although the lead compound was specifically designed to contain a propionic acid moiety, the presence of this functionality added a third stereocenter to the molecule. In an effort to reduce the stereochemical complexity of the series, this stereocenter was eliminated by preparing the corresponding unsubstituted and dimethyl substituted acetic acid analogs. The unsubstituted derivatives, compounds **4** and **5** (Table 1), were somewhat less active than **1** while the dimethyl substituted analog (**6**) was notably more potent as a receptor antagonist against the LTB_4 receptors on guinea pig spleen membranes.[5] Its potency against human neutrophil chemotaxis was likewise comparatively enhanced. Thus, even though the propionic acid functionality was a key element of our initial rationale, this early result demonstrated that its presence was not key to activity. Further investigation of disubstituted acetic acid derivatives revealed that the larger, more hindered compounds were the most active. The diethyl analog (**9**) was about 4 times more potent than **6**. The cyclopentyl and cyclohexyl derivatives, **11** and **14**, respectively, were essentially equiactive to **9** while the smaller cyclobutyl analog **10** was less potent and closer in activity to the dimethyl analog **6**.

Although the presence specifically of a propionic acid at C-7 of the chromanol was not necessary, the presence of an acidic function was. Thus, the alcohols **17** and **18** (Table 2) were essentially inactive as were the 7-unsubstituted and 7-isopropyl analogs, **19** and **20**, respectively. Conversion of the acidic group of **6** into a secondary or tertiary amide as in **21** and **22** led to great diminution of binding activity. The acidic function could be moved one methylene group further from the chromanol nucleus without affecting activity (compare **23** to **4**); however, bringing it closer to the chromanol nucleus as in **24** greatly reduced inhibition of chemotaxis. Replacement of the carboxylic acid function of the cyclopentyl acetic acid derivative **11** with a tetrazole demonstrated that the acidic group in this region of the molecule need not be a carboxylic acid as **25** was equipotent to **11** as a receptor antagonist.

Very early in our investigation we found that the 3,4-*trans* diastereomers of the chromanols were more potent than the corresponding *cis* compounds. For example, the *cis* analog of **6** was 33 times less potent as a receptor antagonist and 5 times less active at inhibiting neutrophil chemotaxis (IC_{50}'s for the two assays respectively, 40.0 μM and 12.5 ± 3.5 μM). Likewise the *cis* analog of **11** was 11 times and 7 times less potent

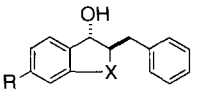
Table 1[a]



Cpd #	R^1/R^2	# of isomers or rotation[b]	R^3	GPS binding IC_{50} (μM)[c]		Chemotaxis IC_{50} (μM)[d]	
4	H-/H-	+38.5°	$PhCH_2$-	25.0	(± 7.1)	12.0	(± 8.5)
5	"	-38.9°	"	30.0		34.0	(± 22.6)
1	CH_3-/H-	4	"	13.0		16.4	(± 5.5)
6	CH_3-/CH_3-	2	"	1.2		2.4	(± 0.8)
7	"	+32.3°	"	2.3		5.7	(± 3.5)
8	"	-33.8°	"	1.3		3.4	(± 2.0)
9	Et-/Et-	2	"	0.29		0.17	
10	-$(CH_2)_3$-	2	"	2.7	(± 0.1)	14.0	
11	-$(CH_2)_4$-	2	"	0.32	(± 0.01)	0.16	(± 0.04)
12	"	+29.9°	"	0.42	(± 0.12)	0.078	(± 0.026)
13	"	-30.2°	"	0.29	(± 0.10)	0.098	(± 0.010)
14	-$(CH_2)_5$-	2	"	0.20		0.38	(± 0.11)
15	"	+6.8°	"	0.24	(± 0.06)	0.23	
16	"	-10.2°	"	0.25		0.17	
28	CH_3-/H-	4	(3-MeO)$PhCH_2$-	53.0		12.2	(± 0.4)
29	"	4	(4-MeO)$PhCH_2$-	12.0		18.5	(± 2.1)
30	CH_3-/CH_3-	2	(3-F)$PhCH_2$-	6.0		9.4	
31	"	2	(4-Cl)$PhCH_2$-	4.0		5.4	
32	"	2	(2,4-diF)$PhCH_2$-	8.0		6.2	
33	"	2	2-pyridylCH_2-	8.0		2.6	
34	"	2	cyclohexylCH_2-	34.0		20.0	
35	-$(CH_2)_4$-	2	(4-CF_3)$PhCH_2$-	12.0		6.0	
36	"	2	(2,4-diF)$PhCH_2$-	2.0		1.0	
37	"	2	2-thienylCH_2-	0.65		0.33	
38	"	2	2-quinolinylCH_2-	8.8		>50.0	
39	"	2	PhS-	0.56		0.50	
40	"	2	$PhCH_2CH_2$-	0.49	(± 0.01)	0.30	
41	"	2	$PhCH_2CH_2CH_2$-	2.7		4.2	
42	"	2	(4-Ph)$PhCH_2$-	0.0056	(± 0.0038)	0.0035	(± 0.0020)
43	"	+22.0°	"	0.0064	(± 0.0022)	0.0050	(± 0.0020)
44	"	-22.0°	"	0.0032	(± 0.0014)	0.0037	(± 0.0034)
45	"	2	(4-Ph)$PhCH_2CH_2$-	3.2		5.8	
46	"	2	$(Ph)_2CH$-	5.4		10	

[a]values are either individual determinations or mean ± SD of 2 or more assays, [b]2 - racemate; 4 - mixture of 2 diastereomeric racemates; all optical rotations: c=1 (MeOH), [c]inhibition of LTB_4 binding to guinea pig spleen derived receptors, assay performed as described in ref 5, [d]inhibition of LTB_4-induced chemotaxis of isolated human neutrophils, assay performed as described in ref 6.

Table 2[a]



Cpd #	R	X	GPS binding IC_{50} (μM)[b]	Chemotaxis IC_{50} (μM)[c]
17	$HOCH_2$-	$-OCH_2-$	>100	>50
18	$HOCH_2CH_2$-	$-OCH_2-$	>100	>50
19	H-	$-OCH_2-$	100	>50
20	$(CH_3)_2CH$-	$-OCH_2-$	100	7.2
21	$CH_3NHCOC(CH_3)_2$-	$-OCH_2-$	>100	1.5[d]
22	$(CH_2)_4NCOC(CH_3)_2$-	$-OCH_2-$	40.0	1.7[d]
23	$HO_2CCH_2CH_2$-	$-OCH_2-$	12.0 (± 1.4)	16.0
24	HO_2C-	$-OCH_2-$	20.0	>100
25	$N_4CC(CH_2)_4$-	$-OCH_2-$	0.35	1.5
26	$HO_2CC(CH_2)_4$-	$-CH_2CH_2-$	0.68	1.5
27	$HO_2CC(CH_2)_4$-	$-CH_2-$	3.6	0.84

[a]*see Table 1, footnote a, all compounds racemic,* [b]*see Table 1, footnote c,* [c]*see Table 1, footnote d,* [d]*see ref 7.*

in the two assays (IC_{50}'s 3.4 μM and 1.1 μM, respectively). Removing the 4-hydroxy group diminished but did not eliminate activity; the 4-deoxy analog of **6** was 14 times and 10 times less potent in the two assays (IC_{50}'s 17.0 μM and 25.0 μM, respectively).

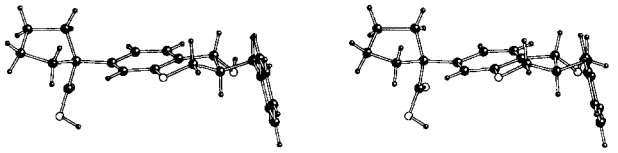
While the ring oxygen of the chromanol may be imparting favorable physical properties to the series and in particular, enhancing the compounds' water solubility (e.g., clogP of **11** = 3.64), the observation that the more lipophilic tetralone derivative **26** (clogP = 4.75) was only slightly less active as a receptor antagonist suggests that the ring oxygen is not directly involved in recognition of the molecules at the receptor. Reducing the ring size from 6 to 5 as in the indanone derivative **27** leads to a more substantial decrease in receptor binding indicating that the C-3 and C-4 substituents are more favorably oriented when on a 6-membered ring.

Initial exploration of the SAR on the C-3 side chain involved placing substituents on the benzyl group. This revealed that neither electron donating (compare **28** and **29** to **1**, Table 1) nor electron withdrawing groups (compare **30**, **31** and **32** to **6**, and **35** and **36** to **11**) conferred enhanced receptor binding. In most cases the effect of such substituents was to slightly reduce receptor affinity. Replacement of the benzyl group with heterocyclic functionality such as 2-pyridylmethyl (**33**), 2-thienylmethyl (**37**), or 2-quinolinylmethyl (**38**) similarly did not enhance activity, although the thienylmethyl derivative was quite similar in potency to the corresponding benzyl analog **11**. Reduction of the benzyl group to a cyclohexylmethyl substituent led to a significant drop in potency (compare **34** to **6**).

Improved activity was ultimately uncovered in analogs with more lipophilic substituents at C-3; however, the SAR was still very narrow. Replacing the benzyl methylene with a sulfur atom (**39**) or with two methylene units (**40**) led to little change in activity as compared to **11**. Moving the lipophilic phenyl group further from the chromanol nucleus through the introduction of a three methylene unit spacer (**41**) led to a drop

in potency. In contrast to this latter result, extending the range of the lipophilic C-3 side-chain by placing a 4-phenyl group on the benzyl group led to a dramatic increase in activity and yielded the most potent racemate in the series. Thus, the 4-phenyl substituted compound **42** was 57 times more potent than **11** as a receptor antagonist and 46 times more potent as an inhibitor of human neutrophil chemotaxis. Remarkably, moving the 4-phenylphenyl group one additional methylene group further from the chromanol nucleus as in **45** led to an ~1000-fold drop in activity. The essentially equally lipophilic, diphenylmethyl analog **46** was much less active than **42** (clogP's: **42**, 5.53; **46**, 5.08) showing that the activity was specific to the structure and not just dependent on high lipophilicity.

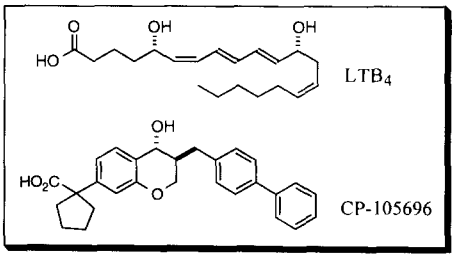
In order to establish the stereospecificity of **42**'s activities, we resolved this potent antagonist through the preparation of a diastereomeric ester as previously described.[4] Evaluation revealed that the two isomers, **43** and **44**, were equally potent in both assays, a not unexpected result given that the resolution of other compounds in the series likewise showed the enantiomers to have nearly equal activities (compare **4** and **5**, **7** and **8**, **12** and **13**, and **15** and **16**). An X-ray structure of **12** shows the C-3 and C-4 chromanol substituents to have a dihedral angle of nearly 60° with the C-3 benzyl group being equatorially situated. Comparison of



Stereoview of the X-ray Crystal Structure of **12**, *Viewing Down the C-3/C-4 Bond*

models of the enantiomers shows that while the C-3 benzyl groups can easily occupy the same space, the C-4 hydroxy substituents will be oriented in different directions. The essentially equal activity of the enantiomers coupled with the observation that 3,4-*cis* isomers and a 4-deoxy derivative are all about an order of magnitude less potent than the corresponding 3,4-*trans* isomers suggests that the role of the C-4 hydroxy group is primarily conformational, stabilizing the equatorial disposition of the C-3 substituent. Calculations to establish this point showed that the conformation displayed by **12** in its X-ray crystal structure was one of three accessible conformations and that similar conformations were accessible to the essentially equally active thioether **39** and tetralone derivative **26**.[8] In the case of **39**, this conformation was the only one readily accessible, an observation supporting the hypothesis. However, the hypothesis was not supported by the observation that comparable conformations were accessible to the less active 3,4-*cis* isomers and 4-deoxy derivative. Thus, the C-4 hydroxy group probably plays more of a role than one of simply stabilizing a preferred conformation.

The highly lipophilic nature of **42** and its enantiomers and the apparent juxtaposition of the compounds' functionality to that of LTB_4 leads one to speculate that this antagonist and the native agonist bind to the receptor with a similar orientation. Such speculation is supported by the very narrow SAR of the C-3 substituent which is consistent with the large changes in activity that are found in analogs of LTB_4 in which the terminal lipophilic tail is either truncated or extended.[9]



Likewise the loss in activity observed upon converting the carboxylic acid function into an amide is similar for LTB_4 and our series.[10] The SAR of the C-4 hydroxy group also supports such a postulated overlap in that this functionality and the C-5 hydroxy group of LTB_4 are not critical for activity; their elimination in both instances leads only to an ~10-fold loss in potency.[11,12]

In conclusion, we have described the optimization of LTB_4 receptor antagonist activity in a series of 7-chromanylacetic acid derivatives which led to the identification of **43**, (3*S*,4*R*)-[3-(4-phenylbenzyl)-4-hydroxychroman-7-yl]cyclopentane carboxylic acid (CP-105696), as a potent antagonist of ligand binding and inhibitor of human neutrophil chemotaxis. The positive findings obtained upon further examination of CP-105696 in other relevant pharmacodynamic and efficacy assays[6,13] led us to advance this compound into clinical trials; however, issues related to its exceptionally long half-life[14] led to suspension of its development.

Acknowledgment. *We thank Drs. Ralph P. Robinson and Kim F. McClure for their review of the manuscript and Dr. Jon Bordner and Debra L. DeCosta for determining the X-ray structure of* **12**.

References and Notes:

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7. Compounds **21** and **22** may display comparatively potent chemotactic activity by virtue of their being converted to **6** under the conditions of the assay. This possibility was not specifically examined.
8. Conformations for compounds **11**, **26**, **27**, **37**, **39**, the 3,4-*cis* analog of **11**, and the 4-deoxy analog of **6** were generated using a stochastic search method implemented in the Sybyl program (Tripos, Inc.; St. Louis, MO). For consistency, the substituent at the 7-position of each chromanol analogue was removed. Each conformer was optimized by *ab initio* methods using first the 3-21G and then the 6-31G(d) basis sets as implemented in the Spartan program (Wavefunction, Inc.; Irvine, CA).
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