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N-ARYL CINNAMIDES: A NOVEL CLASS OF RIGID AND HIGHLY POTENT LEUKOTRIENE B_4 RECEPTOR ANTAGONISTS

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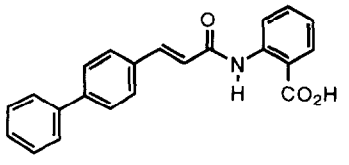
Abstract: A series of N-aryl cinnamides has been prepared and assayed for antagonism of the leukotriene B_4 receptor. Several compounds in this series were found to be highly potent antagonists of the human neutrophil receptor, based on a whole cell binding assay, as well as a neutrophil aggregration assay. This series is unique among LTB_4 antagonists, due to its high degree of rigidity. © 1997 Elsevier Science Ltd.

Introduction: Leukotriene B_4 (LTB_4), a product of arachidonic acid metabolism, is a potent mediator of inflammation, exerting its effects primarily through the recruitment and activation of neutrophils.[1] LTB_4 has been postulated to play a role in a variety of diseases, including rheumatoid arthritis,[2] psoriasis,[3] inflammatory bowel disease[4] and inflammatory lung diseases such as adult respiratory distress syndrome (ARDS) and asthma.[5] Due to the therapeutic potential of a potent and selective LTB_4 antagonist, many research groups have been involved in the discovery and study of such agents.[6]

As part of Novartis' (formerly Ciba's) long-standing effort within this area of research, our laboratories have investigated a series of N-(carboxyaryl)-phenylcinnamides. Beginning with the weakly active lead compound **1**, a number of closely related compounds were prepared in order to characterize the SAR of this class of antagonists. Optimization of this series eventually afforded compound **2**, which showed potent in vitro activity (vide infra). The SAR of this series will be discussed herein.



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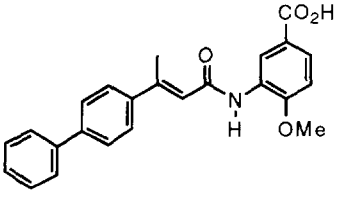
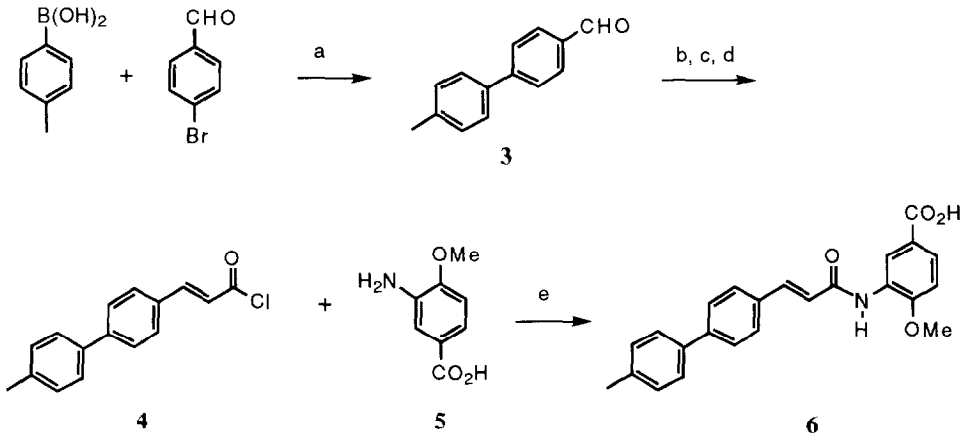


2

Chemistry: The syntheses of all compounds were carried out using the same general protocol, which is exemplified for compound **6**, as shown in Scheme 1. The biphenyl aldehyde **3** was prepared through a Suzuki coupling[7] and was then subjected to Horner - Emmons olefination to provide the desired cinnamate ester. The ester was then converted to acid chloride **4**, and coupled to the aniline **5**.

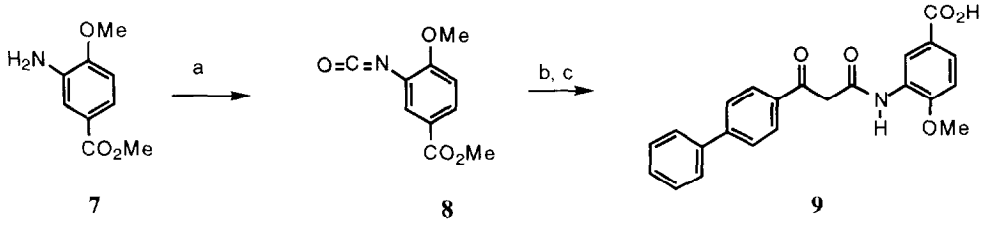
Scheme 1



Reagents: (a) $(Ph_3P)_2PdCl_2$, K_2CO_3, toluene, reflux; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (c) 1 N NaOH, THF, MeOH, reflux, then 1 N HCl; (d) $(COCl)_2$, DMF, CH_2Cl_2, 25 °C; (e) THF, Et_3N, 25 °C.

The β-ketoamide **9** was prepared by reaction of the enolate of acetylbiphenyl with isocyanate **8** (prepared from aniline **7**), as shown in Scheme 2.[8]

Scheme 2

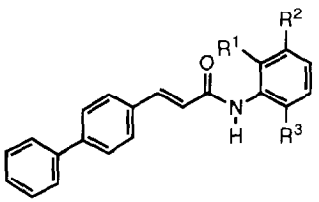


Reagents: (a) triphosgene, Et_3N, CH_2Cl_2; (b) 4-acetylbiphenyl, LDA, THF, -78 °C; (c) 1 N NaOH, THF, MeOH, reflux, then 1 N HCl.

Results: All compounds were tested in two in vitro assays. The binding affinity of the compounds to the LTB_4 receptor was determined by measuring the displacement of ^{3}[H]-LTB_4 from isolated neutrophils.[9] In order to confirm that the compounds inhibited neutrophil function, inhibition of LTB_4 induced neutrophil aggregation was also measured.[10] Human neutrophils were used in both assays. All assays were run with an n = 3 (except where noted otherwise), and the results of these assays are reported in Tables 1, 2 and 3.

The SAR of the anilide ring was explored first (Table 1). Compound **1**, the initial lead, displayed moderate in vitro potency. Moving the carboxylate from the *ortho*- to the *meta*-position had only a modest effect on activity (compound **10**). An interesting effect was noted with introduction of oxygenation *ortho* to the anilide nitrogen. Incorporation of a methoxy group into compound **10** at this position led to a significant increase in potency (compound **11**). However, *ortho*-methoxy substitution on compound **1** sharply reduces activity (compound **12**). This may be due to increased steric crowding around the anilide moiety (see discussion below). The inactivity of compound **13** clearly demonstrates the need for a negatively ionizable substituent, a feature common to almost all known LTB4 antagonists.[6] Reflecting a trend seen with other LTB4 antagonists,[6] tetrazole **14** functions as a good bioisostere for the carboxylic acid, leading to a significant enhancement in potency. The unique role of the methoxy group in compound **11** was highlighted by the diminshed potency of both the ethoxy and chloro analogs of **11** (compounds **15** and **16**, resp.)

Table 1: SAR of anilide fragment of series.



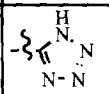
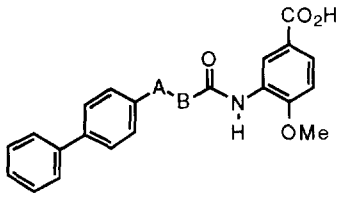
Compound #	R^1	R^2	R^3	Binding IC_{50} (nM)	Aggreg. IC_{50} (nM)
1	CO_2H	H	H	830 ± 25	3417 ± 1070
10	H	CO_2H	H	1180 ± 40	1021 ± 283
11	H	CO_2H	OMe	68.2 ± 2.9	83 ± 20
12	CO_2H	H	OMe	1180 ± 40	1021 ± 283
13	H	H	OMe	> 10,000	-
14	H		OMe	16.7 ± 0.5	30 ± 12
15	H	CO_2H	OEt	190 (n = 1)	173 (n = 1)
16	H	CO_2H	Cl	908 (n = 1)	429 (n = 1)

Table 2: SAR for 2-atom linker.

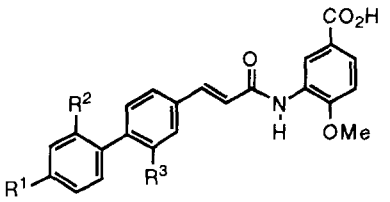


Compound #	A-B	Binding IC_{50} (nM)	Aggreg. IC_{50} (nM)
11	CH=CH	68.2 ± 2.9	83 ± 20
17	CH_2-CH_2	1510 ± 140	2409 ± 743
18		932 ± 45	839 ± 203
9	C(O)-CH_2	784 ± 33	249 ± 134
2	C(Me)=CH	15.9 ± 1.3	42 ± 23

The SAR of the olefin linker was next examined, using compound **11** as a starting point (Table 2). Hydrogenation of the double bond of **11** (H_2, Pd/C, EtOH) yielded the much less active compound **17**. It was reasoned that the rigidity of a trans cyclopropyl group would more closely mimic the behavior of the olefin and therefore, compound **18** was prepared.[11] While this change brought out a modest increase in potency in comparison to compound **11**, the activity was still well below that of the unsaturated analog. Replacement of the cinnamide with a β-ketoamide (anticipating that the enolic tautomer of the compound would be bioisosteric to the cinnamide) yielded the weakly active compound **9**. The incorporation of a β-methyl group on the olefin (compound **2**) led to a 2- to 4-fold increase in receptor binding in comparison to compound **11**. Compound **2** was found to be the most potent carboxylate prepared within the series.

The biphenyl group was found to be particularly sensitive to substitution (Table 3). As exemplified by compounds **19** and **20**, substitution on either phenyl ring ortho to the biphenyl junction greatly diminishes activity. Methylation at the para-position of the distal phenyl ring (compound **6**) compromises activity, albeit to a lesser extent.

Table 3: SAR for biphenyl group.



Compound #	R^1	R^2	R^3	Binding IC_{50} (nM)	Aggreg. IC_{50} (nM)
1	H	H	H	68.2 ± 2.9	83 ± 20
6	Me	H	H	276 ± 29	103 ± 33
19	H	Me	H	4570 ± 500	6587 ± 1263
20	H	H	Me	1220 ± 70	2161 ± 842

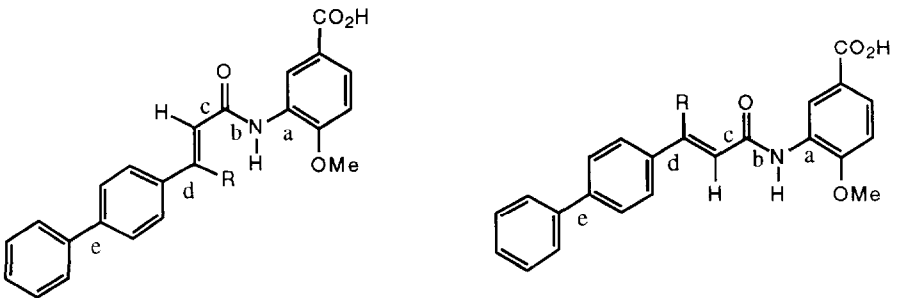
Discussion: As detailed above, a relatively small and rigid cinnamide was optimized to provide low-nanomolar antagonists of the LTB_4 receptor. This series of antagonists is unique in comparison to other reported classes of LTB_4 antagonists. While virtually all nanomolar antagonists have significant conformational flexibility (at least one 3-atom saturated chain in the molecule),[6,12] this series is highly rigid, containing only 3 rotatable bonds in the entire molecule (discounting phenyl ring substituents). As a result, we have been able to utilize the SAR thus far obtained to suggest conformational requirements for receptor binding within this series.

One would anticipate that the amide bond (bond **b**, Fig.1) would strongly prefer an E-orientation.[13] In addition, molecular mechanics calculations reveal a strong preference for planarity around bond **a** (a prediction reinforced by the lack of activity of the highly encumbered compound **12**).[14] Of the two coplanar orientations available to bond **a**, the one displayed in Figure 1 appears to be strongly favored,[13] primarily because of the availability of an intramolecular hydrogen bond (which is not available in the less potent des-methoxy compound **6**!). It is conceivable that the methoxy group improves the potency of compound **12** by affecting the pK_a of the carboxylate or anilide proton. Nonetheless, the calculated preference for the intramolecularly H-bonded conformation, along with the reduced potency of **15** (in which the methyl to ethyl substitution would be expected to exert a steric rather than electronic effect) seem to support the hypothesis that this is the preferred conformation. Bond **c** is also expected to prefer a planar orientation, on the basis of molecular mechanics calculations, although it is not clear whether the s-*trans* (conformation **A**) or the s-*cis* (conformation **B**) is preferred.[14] The sharp drop in potency upon methylation of either interior position of the biphenyl system seems to suggest that the preferred orientation of the phenyl groups is nearly planar. This leaves bond **d** as the only rotatable bond whose conformation cannot be relatively well defined!

Although the bound conformation of any molecule may differ significantly from the ground state of the free compound, the strong energy preferences for the orientations discussed (> 5 kcal/mol energy penalty for >45° bond rotation for bonds **a**, **b**, and **c**)[14] tend to indicate that this molecule is rigid enough to resist significant deformation on binding. With this analysis in hand, we can postulate that the most probable bound

conformation of these inhibitors as either A or B. Although this does not absolutely define the binding mode of the antagonist, it does provide a reasonable model, which can be tested and refined as other antagonists are prepared. We consider it imprudent to apply the results described herein to the analysis of receptor binding for other LTB_4 antagonists, or for LTB_4 itself, due to the uniqueness of this series. However, this information is currently being applied to the discovery of new LTB_4 antagonists based on this template.

Figure 1



conformation **A** conformation **B**

References:

1. Ford-Hutchinson, A. W. *Crit. Rev. in Immunol.* **1990**, *10*, 1.
2. Ahmadzaden, N.; Shingu, M.; Nobunaga, M.; Towara, T. *Inflammation* **1991**, *15*, 497.
3. Grabbe, J.; Czarnetzki, B. M.; Rosenbach, T.; Mardin, M. *J. Invest. Dermatol.* **1984**, *82*, 477.
4. Clapp, N.; Henke, M.; Hansard, R.; Carson, R.; Widomski, D.; Anglin, C.; Walsh, R.; Djuric, S.; Fretland, D. *Agents Actions* **1994**, *41*, C-254.
5. Yoshimura, K.; Nakagawa, S.; Koyama, S.; Kobayashi, T.; Homma, T. *J. Appl. Physiol.* **1993**, *74*, 2174.
6. Cohen, N.; Yagaloff, K. A. *Curr. Opin. Invest. Drugs* **1994**, *3*, 13.
7. Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.
8. Hendi, S. B.; Hendi, M. S.; Wolfe, J. F. *Synth. Comm.* **1987**, *17*, 13
9. Jackson, R. H.; Morrissey, M. M.; Sills, M. A.; Jarvis, M. F. *J. Pharm. Exp. Ther.* **1992**, *262*, 80.
10. Ford-Hutchinson, A. W.; Evans, J. F. *Methods in Enzymology* **1988**, *162*, 72.
11. Arnold, C.; Thatcher, D. N. *J. Org. Chem.* **1969**, *34*, 1141.
12. Koch, K.; Melvin, L. S.; Reither, L. A.; Biggers, M. S.; Showell, H. J.; Griffiths, R. J.; Pettipher, E. R.; Cheng, J. B.; Milici, A. J.; Breslow, R.; Concklyn, M. J.; Smith, M. A.; Hackman, B. C.; Doherty, N. S.; Salter, E.; Farrell, C. A.; Schulte, G. *J. Med. Chem.* **1994**, *75*, 3197. This paper describes a fairly rigid hydroxychromane antagonist, which, interestingly, contains a biphenyl substituent. Since no SAR on this series has been published, it is not possible to compare its binding requirements to that of the series reported herein.
13. Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517
14. All molecular mechanics calculations were carried out using the Cache molecular modeling package. Structures were minimized via the conjugate gradient method, using MM2 force field parameters. Multiple pass sequential searches were performed on each molecule to identify the global minimum.

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