# o-Phenylphenols: Potent and Orally Active Leukotriene $B_4$ Receptor Antagonists

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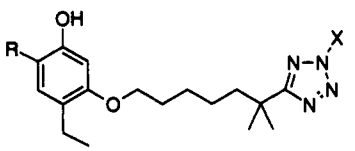
Leukotriene $B_4$ ($LTB_4$) has received much attention as a mediator of inflammatory cell function. Via G-protein-coupled receptor-mediated events, this eicosanoid was shown to be a potent chemoattractant for neutrophils and eosinophils.[1] $LTB_4$ has demonstrated the ability to enhance cell–cell recognition by the up-regulation of CD11b/CD18 adhesion molecules[2] and to initiate neutrophil aggregation,[3] calcium mobilization,[4] superoxide release,[4] and the release of degradative enzymes.[1,5] Along with the presence of inflammatory cells, $LTB_4$ was found to be present at high concentrations in bronchoalveolar lavage fluid of asthmatics,[6] skin lesions of psoriatics,[7] synovial fluid of arthritics,[7b] and rectal dialysates of patients with inflammatory bowel disease.[8] Consequently, this product of arachidonic acid metabolism may play an important proinflammatory role in disease. However, in order to clearly define the role of $LTB_4$ in human inflammatory disease, potent, selective, and bioavailable antagonists are needed.

A number of reports have disclosed the discovery and development of novel $LTB_4$ receptor antagonists.[9] We previously reported that the *o*-acetyl group of the 1,2,4,5-substituted hydroxyacetophenone $LTB_4$ receptor antagonist 1 (LY255283)[9a] could be replaced by an alkoxy[10] or alkyl[11] moiety to give antagonists with enhanced receptor binding and functional antagonistic profiles. However, although these alkyl and alkoxy analogues **2** and **3** showed good *in vivo* activity when administered via the intravenous route, they were not particularly potent as oral agents ($ED_{50}$s > 10 mg/kg).[12] Consequently, we chose to further extend the SAR of the ortho phenolic substituent. We report here on the discovery of *o*-phenylphenols as exceptionally potent $LTB_4$ receptor antagonists.




**1** R = $CH_3C(O)$, X = H (LY255283)

**2** R = $CH_3CH_2CH_2$, X = $Na^+$ (LY303552)

**3** R = $CH_3CH_2O$, X = $Na^+$ (LY247833)

Our synthetic strategy for the preparation of 1,2,4,5-substituted phenylphenol $LTB_4$ receptor antagonists required that we develop the ability to introduce ortho to the phenol phenyl groups containing varied substituents. Our synthetic analysis of this problem envisioned that the phenylphenol core could be constructed by appending the *o*-phenyl substituent via an organometallic coupling. Consequently, this strategy required the synthesis of the tetrasubstituted aryl bromide intermediate **7** as outlined in Scheme I. In this approach, the *gem*-dimethyl nitrile chain of **7** served as the precursor to the tetrazole acid moiety. This key intermediate was obtained from 4-(benzyloxy)-2-hydroxyacetophenone (**4**).[13] Alkylation of the remaining free phenol with 6-cyano-1-chloro-6-methylheptane produced compound **5**. Ketone reduction with $Et_3SiH$[14] and aryl bromination gave the desired aryl bromide **7**.

While maintaining the [6-methyl-6-(2*H*-tetrazol-5-yl)-heptyl]oxy moiety as the acid unit, the effect of varying the *o*-phenyl ring substituent on receptor binding was investigated. As demonstrated in Scheme II, the *o*-phenol substituent was attached to the aryl bromide **7** either via a Suzuki coupling[15] utilizing a substituted boronic acid[16] or in the case of the *m*-$CF_3$ and pyridyl analogues, the coupling was accomplished by first preparing the arylzinc reagent of **7** and reacting with either 1-bromo-3-(trifluoromethyl)benzene or 2-bromopyridine in the presence of a Pd(0) catalyst.[17] These couplings were accomplished in 40–97% yields. Phenol deprotection and elaboration of the nitrile to the tetrazole acid provided the desired phenylphenol antagonists **10a–l**.[18]

Substitution of a phenyl moiety ortho to the phenol group of the 1,2,4,5-substituted phenol class of $LTB_4$ receptor antagonists had a significant effect on both receptor binding potency and *in vitro* functional antagonism of both human neutrophil and guinea pig lung membrane receptors (Table I). Comparison of the *o*-phenyl analogue **10a** to either the *o*-acetyl, **1**, -alkyl, **2**, or -alkoxy, **3**, derivatives demonstrated that the phenyl group was superior to the other *o*-phenol substituents. A 2.8- and 3.2-fold improvement in the respective human neutrophil[20] and guinea pig lung membrane receptor binding[21] potencies was observed. We saw a similar improvement in the ability of **10a** to antagonize $LTB_4$-induced functional responses in human neutrophils and guinea pig lung tissues. Relative to the *n*-propyl analogue **2**, phenylphenol **10a** was 5-fold more potent at inhibiting the up-regulation of CD11b/CD18 adhesion molecules on human neutrophils[2] and in its ability to inhibit $LTB_4$-induced contraction of guinea pig lung parenchymal strips.[21] Also, Schild analysis of the antagonism of the latter indicated that phenylphenol **10a** competed with $LTB_4$ for a common receptor site with a $pA_2$ value of 8.46 and a Schild plot slope of $-1.06 \pm 0.12$, thus indicating a purely competitive antagonism.[22]

We investigated the effect of *o*-phenyl ring substitution on receptor binding (Table II). It was clear that for optimal binding to both the human neutrophil receptor and guinea pig lung membrane receptor an unsubstituted (**10a**) or *p*-fluoro-substituted phenyl ring (**10e**) was preferred. It was also apparent that the guinea pig lung membrane receptor was more discriminating in regard to the substitution of the *o*-phenyl ring than was the human neutrophil receptor. For the guinea pig lung receptor, ortho and meta substitution of any kind (except *m*-F) decreased receptor binding. However, the human neutrophil receptor tolerated *p*-methyl (**10b**), -methoxy (**10g**),

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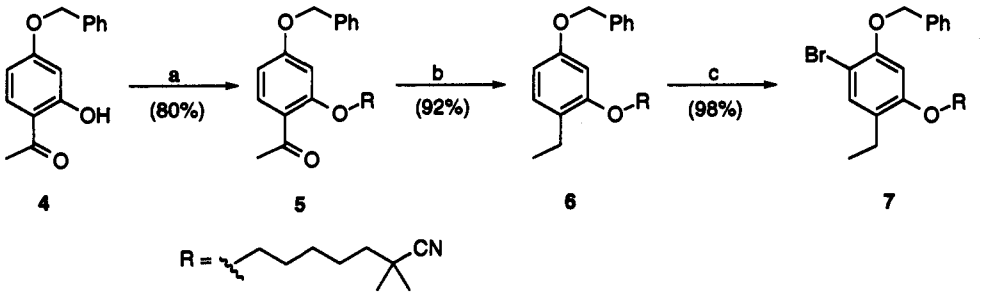
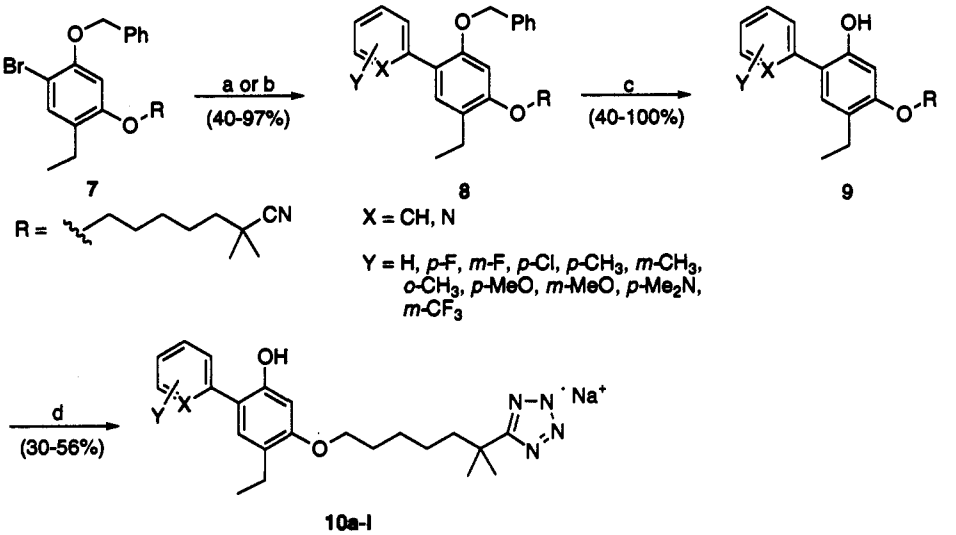
**Scheme I**[a]



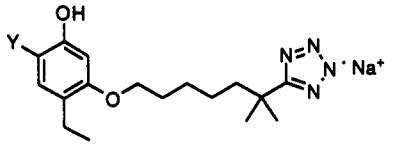

[a] Reagents: (a) 6-cyano-1-chloro-6-methylheptane,[9a] DMF, KI, $K_2CO_3$, Δ; (b) $Et_3SiH$, TFA, $CCl_4$, 25 °C; (c) NBS, $CCl_4$, 25 °C.

**Scheme II**[a]




[a] Reagents: (a) arylboronic acid, $Pd(PPh_3)_4$ (cat.), benzene, EtOH, $Na_2CO_3$(aq), Δ; (b) (1) tBuLi, THF, −78 °C, (2) $ZnCl_2$, (3) aryl halide; (c) 10% Pd/C, EtOAc, $H_2$(g) 1 atm or $BBr_3$, $CH_2Cl_2$; (d) (1) $NaN_3$, diglyme, (dimethylamino)ethanol hydrochloride, 135 °C, (2) NaOH(aq), CHP-20 chromatography.

**Table I.** The Effect of the *o*-Phenol Substituent of 1,2,4,5-Substituted Phenol $LTB_4$ Receptor Antagonists on Receptor Binding and Functional Antagonism in Human Neutrophils and Guinea Pig Lung Tissues




| compd no. | Y | human neutrophil binding[23] $IC_{50}$ (nM) | guinea pig lung membrane binding[a] $K_i$ (nM) | human neutrophil CD11b/CD18 integrin up-regulation[24] $IC_{50}$ (nM) | guinea pig lung parenchyma strip contraction[a] $pK_B$ |
|---|---|---|---|---|---|
| 1[b] | $CH_3C(O)$ | 85.1 ± 7.9 | 77.9 ± 10.4 | 2874 ± 470 | 6.7 ± 0.2 |
| 2 | $CH_3(CH_2)_2$ | 9.3 | 14.2 ± 6.3 | 161 | 7.6 ± 0.4 |
| 3 | $CH_3CH_2O$ | 8.4 | 14.2 ± 2.9 | 206 | 6.6 ± 0.1 |
| 10a | Ph | 3.0 ± 0.1 | 4.4 ± 1.0 | 31.5 ± 3.4 | 8.3 ± 0.4 |

[a] For assay conditions see ref 21. [b] Tested as the free acid.

and -chloro (**10k**) and *m*-methoxy (**10h**) groups. In this system, substitution of a pyridine ring (compound **10l**) for the *o*-phenyl ring was detrimental to receptor binding and was therefore not a good isosteric replacement for phenyl. It is possible to speculate that when comparing the receptor binding potencies of the various substituted *o*-phenylphenol antagonists **10a–l**, the differences observed between the human neutrophil and guinea pig lung membrane receptor binding data many be attributed to a difference in either species or cell specific differences in receptor structure.

We compared the ability of the most potent tetrazole acid receptor ligands **10a** (LY280748) and **10e** (LY306669) to antagonize $LTB_4$-induced functional responses. Compound **10e** was 2.4-fold more effective than **10a** at antagonizing the human neutrophil CD11b/CD18 integrin up-regulation response, but the two agents were equally effective at inhibiting the guinea pig lung parenchyma tissue contraction (Table III). The discrepancy in correlation between the human neutrophil receptor binding and the antagonism of CD11b/CD18 integrin up-regulation data for compounds **10a** and **10e** may be explained by a difference in either receptor subtype selectivity or a compound preference for one particular affinity state of the receptor.[25]

*In vivo* via a receptor-mediated mechanism, $LTB_4$ is known to induce bronochoconstriction in guinea pig airways.[26] In a guinea pig model of $LTB_4$-induced airway obstruction,[27] phenylphenols **10a** and **10e** were shown to be extremely potent antagonists (see Figure 1). The

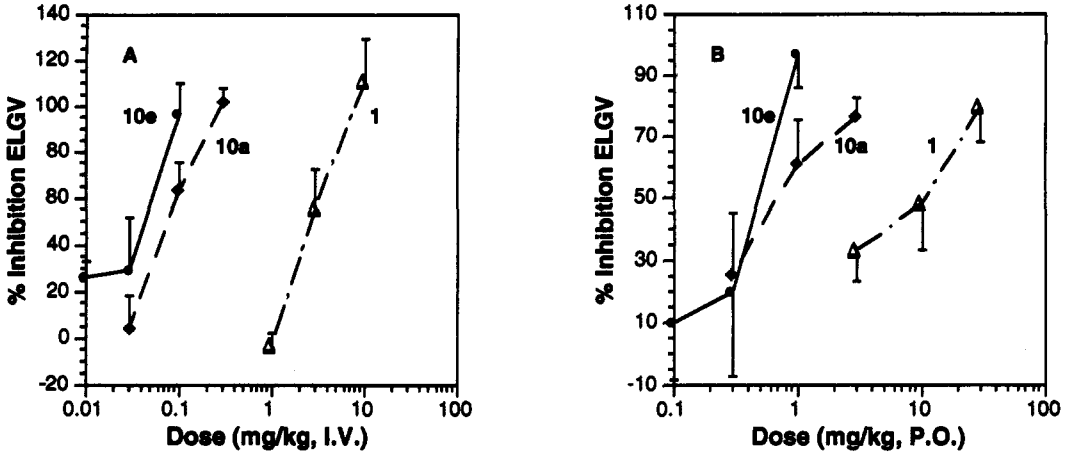
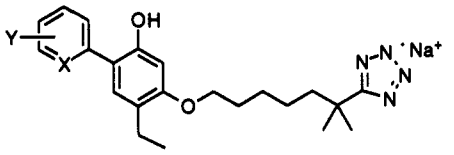



**Figure 1.** *In vivo* antagonism of $LTB_4$-induced bronchoconstriction in guinea pig aiways by phenylphenol $LTB_4$ receptor antagonists. (A) Effect of intravenously administered **1**, **10a**, and **10e** on inhibition of $LTB_4$-induced increases in excised lung gas volumes (ELGV). Intravenous doses were given 5 min before a 3.0 μg/kg iv $LTB_4$ challenge. (B) Effect of orally administered **1**, **10a**, and **10e** on inhibition of $LTB_4$-induced increases in ELGV. Oral doses were administered 2 h prior to a 3.0 μg/kg iv $LTB_4$ challenge. In all cases animals were killed 1 min after challenge and ELGV measured as an index of severity of airway obstruction at death. Values are means ± SEM of 3–14 guinea pigs per group.

**Table II.** Inhibition of [$^3$H]$LTB_4$ Receptor Binding to Human Neutrophils and Guinea Pig Lung Membrane Receptors by *o*-Phenylphenol $LTB_4$ Receptor Antagonists



| compd no. | X | Y | human neutrophil binding[23] $IC_{50}$ (nM) | guinea pig lung membrane binding[a] $K_i$ (nM) |
|---|---|---|---|---|
| **10a** | CH | H | 3.0 ± 0.1 | 4.5 ± 1.0 |
| **10b** | CH | *p*-$CH_3$ | 4.0 | 37.3 ± 6.6 |
| **10c** | CH | *m*-$CH_3$ | 8.0 | 72.2 ± 17.3 |
| **10d** | CH | *o*-$CH_3$ | 11 | 70.3 ± 14.3 |
| **10e**[b] | CH | *p*-F | 2.8 | 3.7 ± 1.0 |
| **10f**[b] | CH | *m*-F | 3.0 | 6.2 ± 1.9 |
| **10g** | CH | *p*-MeO | 2.9 | 54.6 ± 11.9 |
| **10h** | CH | *m*-MeO | 4.0 | 21.0 ± 5.6 |
| **10i** | CH | *p*-$Me_2N$ | 15.8 | 85.9 ± 28.0 |
| **10j** | CH | *m*-$CF_3$ | 33.2 | 76.9 ± 2.02 |
| **10k** | CH | *p*-Cl | 5.0 | 25.0 ± 8.8 |
| **10l** | N | H | 453 | 196 ± 39.4 |

[a] For assay conditions, see ref 21. [b] Tested as the free acid.

**Table III.** Antagonism of $LTB_4$-induced Human Neutrophil CD11b/CD18 Integrin Up-Regulation and Guinea Pig Lung Parenchyma Strip Contraction by Phenylphenol $LTB_4$ Receptor Antagonists

| compd no. | human neutrophil CD11b/CD18 integrin up-regulation[24] $IC_{50}$ (nM) | guinea pig lung parenchyma strip contraction[a] $pK_B$ |
|---|---|---|
| **10a** | 31.5 ± 3.4 | 8.3 ± 0.4 |
| **10e**[b] | 13.1 ± 0.5 | 8.3 ± 0.2 |

[a] For assay conditions, see ref 21. [b] Tested as the free acid.

relative *in vivo* activities of these antagonists when administered intravenously ($ED_{50}$(**10a**) = 0.05 mg/kg, $ED_{50}$(**10e**) = 0.03 mg/kg) correlated extremely well with both the guinea pig receptor binding and guinea pig lung parenchyma tissue contraction potencies. As shown in Figure 1, these compounds were also very efficacious when given orally ($ED_{50}$(**10a**) = 0.70 mg/kg, $ED_{50}$(**10e**) = 0.56 mg/kg). Each of these antagonists demonstrated a dramatic improvement in oral activity over earlier studied 1,2,4,5-substituted phenol tetrazole acid $LTB_4$ receptor antagonists.

In summary, we have discovered a novel class of *o*-phenylphenol leukotriene $B_4$ receptor antagonists with exceptional *in vitro* and *in vivo* potencies. This class of compounds has been selected for further development and will hopefully be useful in delineating the role of $LTB_4$ in human inflammatory diseases. A detailed description of the structure–activity relationships and development of this class of antagonists will be the subject of future disclosures.

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**Supplementary Material Available:** Experimental procedures and spectral data for compounds **5**–**10a**–**l** are presented (14 pages). Ordering information is given on any current masthead page.

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(16) Boronic acids which were not commercially available were prepared by one of two methods. **Method A.** An aryl bromide in THF at −78 °C under a nitrogen atmosphere was metalated with tBuLi (2 equiv). To a solution of $B(OiPr)_3$ in THF at −78 °C added the aryllithium reagent and after 15 min warmed to room temperature and stirred for 15 min. Subsequently, the reaction mixture was diluted with EtOAc and agitated with 10% aqueous HCl. The organic layer was dried, filtered, and concentrated. The resulting boronic acid was recrystallized from hexane and EtOAc. **Method B.** An aryl iodide or aryl bromide was metalated with tBuLi (2 equiv). Trimethylsilyl chloride (1.8 equiv) was added to the reaction at −78 °C, and then the reaction was allowed to warm to 25 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The EtOAc extract was dried, filtered, and concentrated. The crude arylsilane was dissolved in $CH_2Cl_2$ cooled to −78 °C and treated with $BBr_3$ (1 equiv). The reaction mixture was stirred at room temperature for 15 h, recooled to −78 °C, and treated with MeOH (excess). The reaction mixture was stirred at room temperature for 30 min and then diluted with $CH_2Cl_2$ and washed with aqueous 5 N HCl. The crude boronic acid was recrystallized from hexane and EtOAc. Sharp, M. J.; Cheng, W.; Snieckus, V. Synthetic Connections to the Aromatic Directed Metalation Reaction. Functionalized Aryl Boronic Acids by IPSO Borodesilylation. General Synthesis of Unsymmetrical Biphenyls and m-Terphenyls. *Tetrahedron Lett.* 1987, *28*, 5093–5096.

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(24) Concentration of preincubated antagonist (15 min at room temperature) required to provide 50% inhibition of the up-regulated CD11b/CD18 expression of human neutrophils, activated with $1 \times 10^{-9}$ M $LTB_4$ (30 min at 37 °C). CD11b/CD18 expression was determined flow cytometrically by measuring single cell fluorescence of specific monoclonal antibody-reacted cells. See ref 2.

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