Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 17, pp. 2077-2082, 1994

0960-894X/94 $7.00+0.00

0960-894X(94)00290-8

STRUCTURAL ANALOGUES OF LY292728, A HIGHLY POTENT XANTHONE DICARBOXYLIC ACID LEUKOTRIENE B_4 RECEPTOR ANTAGONIST: SPATIAL POSITIONING OF THE SECONDARY ACID GROUP

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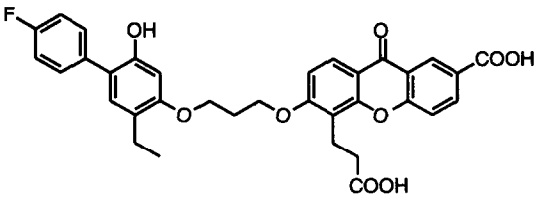
Abstract: We report the preparation and pharmacologic activity of three spatial analogues of LY292728, a highly potent xanthone dicarboxylic LTB_4 receptor antagonist. Molecular modeling of these compounds has helped to further elucidate the nature of the secondary acid binding site of the LTB_4 receptor.

We recently reported on the synthesis and biological evaluation of LY292728 (**1**), an exceedingly potent biphenyl-substituted xanthone dicarboxylic acid LTB_4 receptor antagonist.[1] Originally derived from the confluence of two separate structure-activity relationships,[2] **1** has



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demonstrated in vivo activity upon aerosol administration against LTB_4-induced airway constriction in the guinea pig.[1] Of particular note is the requirement of a secondary (aromatic) acid group for maximum receptor affinity.[1,2a,2c] In keeping with our continuing efforts to develop potent antagonists to LTB_4,[3] a lipid mediator implicated in a wide variety of inflammatory diseases,[4] we have constructed and evaluated in vitro three analogues of **1** which feature a selection of flexible scaffolding, each incorporating a secondary carboxylic acid.

Our original design for non-xanthone analogues of **1** envisioned alkyne **9** and diaryl ether **15** as appropriate targets. Simple inspection of molecular models confirmed that each of these molecules was capable of delivering the secondary carboxylic acid to the appropriate position while providing a degree of flexibility unavailable to the parent xanthone. As illustrated in Scheme 1, synthesis of **9** began with 4-iodophenol (**2**) and the now standard acid-catalyzed addition and Claisen rearrangement of triethyl orthoacrylate.[5] Contrary to our earlier

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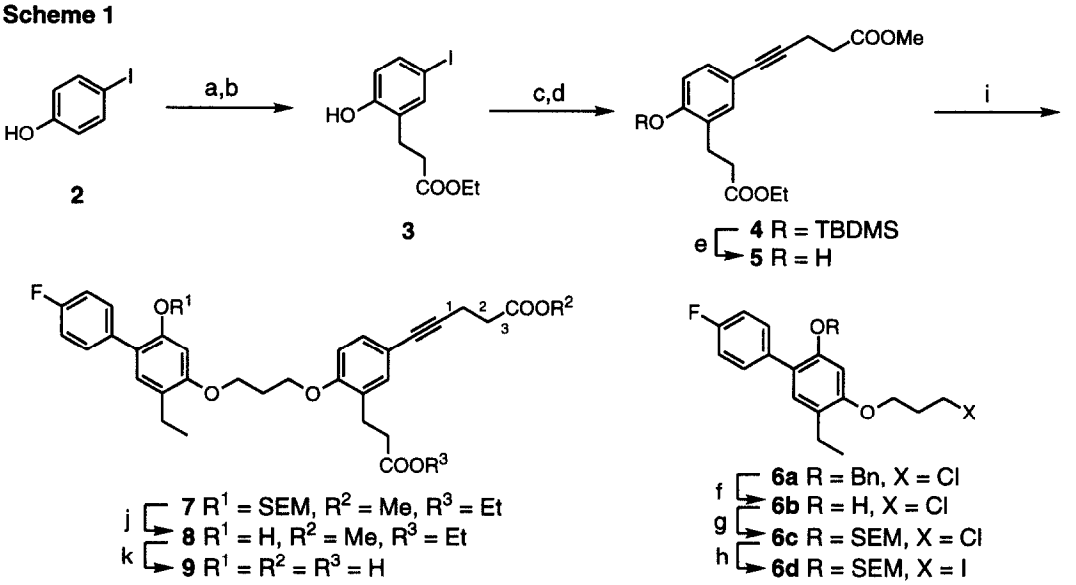
Scheme 1



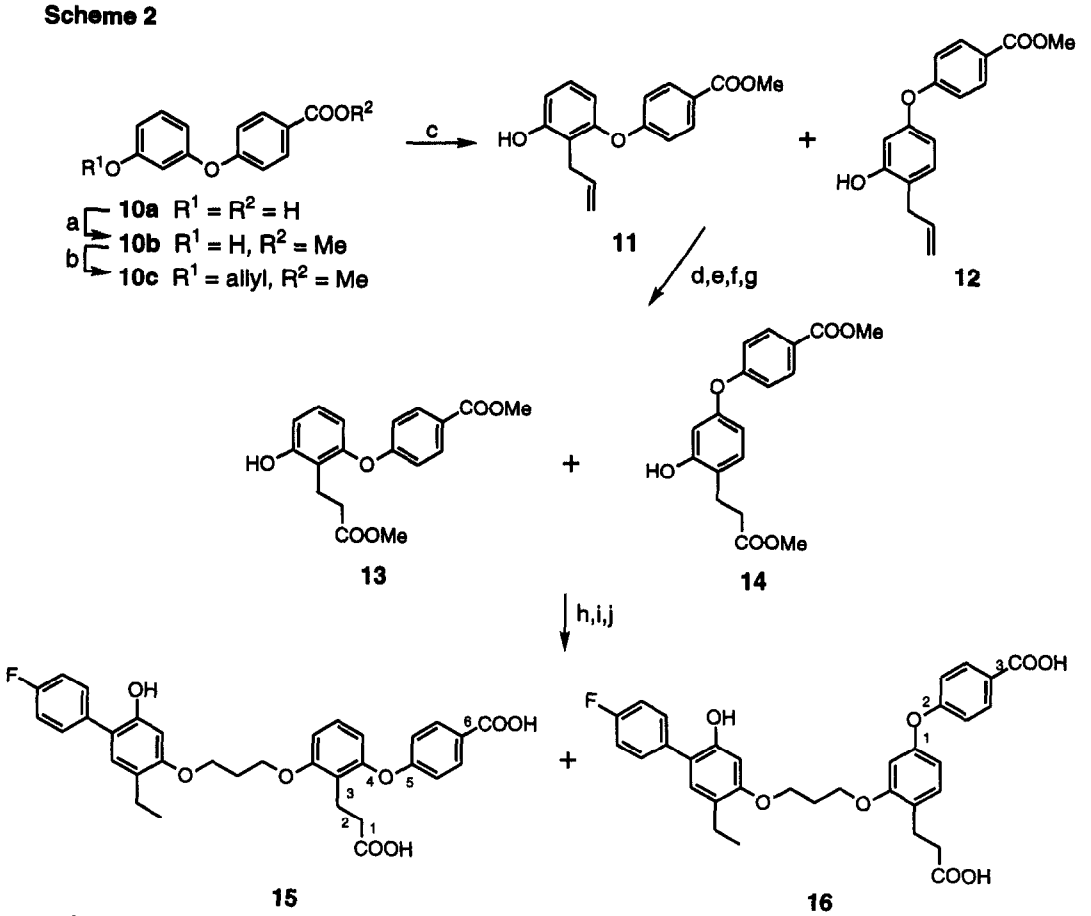
a) triethylorthoacrylate, pivalic acid, toluene; b) aq HCl, THF (28%, two steps); c) TBDMSCl, imidazole, THF (95%); d) methyl 4-pentynoate, diethylamine, $Pd(PPh_3)_2Cl_2$ (cat.), CuI (58%); e) TBAF, THF (41%); f) H_2, 10% Pd(C), EtOAc (98%); g) diisopropylamine, SEMCl, CH_2Cl_2, 0 °C (86%); h) NaI, 2-butanone, reflux (100%); i) **6d**, K_2CO_3, DMF (49%); j) TBAF, THF (95%); k) aq NaOH, MeOH, THF (89%)

experience, formation and acid catalyzed opening of the lactal to the required propanoic ester proceeded in remarkably poor yield. This sequence has previously been used to cleanly prepare the xanthone portion of **1**, a system devoid of a reactive halogen as is found in **2**.[2b] Protection of the resulting phenol **3** as the TBDMS ether, followed by a modified Cassar/Heck coupling[6] and deprotection,[7] led to alkyne intermediate **5**. Coupling of **5** to SEM-protected biphenyl **6d** (formed from routine halogen and protecting group exchange operations on **6a**[8]) provided compound **7**, from which the protecting groups were exhaustively removed in two steps to provide the target **9**.

Scheme II depicts the synthesis of diaryl ether **15**, which proceeded through the thermal Claisen rearrangement of allyl ether **10c**[2b] to produce phenols **11** and **12** in a ratio of 1:1.5 (attempted condensation and rearrangement of methyl 4-(3-hydroxyphenoxy)benzoate with triethyl orthoacrylate as described above gave exclusively the regioisomer corresponding to compound **12**). As separation of the isomers proved extremely difficult, the mixture was progressed to **15** beginning with the usual hydroboration/oxidation/esterfication sequence[2b] to convert the allyl side chain to methyl propanoate (compounds **13** and **14**). Alkylation of the mixture with intermediate **6a**,[1] followed by debenzylation and hydrolysis, produced isomeric diacids **15** and **16**, which were separated at this point by silica gel chromatography.

As indicated in Table 1, in vitro evaluation of compounds **9** and **15** revealed that both analogues possess extremely potent activity. Each inhibited the binding of $[^3H]LTB_4$ to human

Scheme 2



a) HCl, MeOH (85%); b) NaH, allyl bromide, THF, DMSO (96%); c) neat, 220 °C (92%); d) 9-BBN, THF (92%); e) H_2O_2 (100%); f) Jones reagent; g) H_2SO_4, MeOH (30%, 2 steps); h) **6a**, K_2CO_3, DMF (70%); i) H_2, 10% Pd(C)(100%); j) aq.NaOH, MeOH, THF (83%)

neutrophils with a K_i value of 1.1 nM, while an approximately 10-fold greater activity was observed at inhibiting binding to guinea pig lung membranes, a result consistent with our earlier findings with xanthone **1**. We also examined compound **16**, which proved to be 40- to 200-fold less active in inhibiting [^{3}H]LTB_4 binding than **9** and **15**, and is therefore apparently unable to bind to the secondary acid binding site of the receptor. These results reinforce the conclusions derived from our earlier observations relative to antagonists which are deficient in an ability to access this secondary site.[1,2b] Of particular interest was the activity demonstrated by these compounds in the inhibition of LTB_4-induced expression of the CD11b/CD18 adhesion receptor. While analogues **9** and **15** possessed potency similar to that observed for xanthone **1**, compound **16** was found to be significantly less active. This is in

Table 1. Inhibition of Specific Binding of [^{3}H]LTB_4 and LTB_4-mediated Up-regulation of Human Neutrophil CD11b/CD18 by Compounds **1**, **9**, **15**, and **16**.

Cmpd	Human Neutrophil (K_i, nM)[9]	Guinea-pig Lung Membranes (K_i, nM)[10]	Human Neutrophil CD11b /CD18 Up-regulation (IC_{50}, nM)[11]
1	0.47[1]	0.040 ± 0.016[1]	1.2 ± 0.10[1]
9[a]	1.1	0.073 ± 0.021	4.7
15	1.1	0.14 ± 0.012	2.6
16	39	14 ± 0.39	1800
LTB_4	1.9 ± 0.050	0.12 ± 0.015	--

a) Tested as the disodium salt.

marked contrast to analogues of **1** which, although lacking the aromatic carboxylic acid, have almost identical CD11b/CD18 activity.[1] This suggests that the position of the phenoxy group may hinder binding of **16** to the receptor sub-type responsible for CD11b/CD18 up-regulation.

A conformational analysis study featuring vector mapping of the secondary acid moiety of **9**, **15**, and **16** was executed using SYBYL 6.0 (Tripos Associates, St. Louis, MO). Each molecule was initially built and minimized as the dicarboxylate (bearing Gasteiger-Marsili charges) using the MAXIMIN2 routine. Minimization was accomplished in vacuo with the inclusion of electrostatic terms. Rotational bonds (examined through a full 360°) and angle increments of each compound were assigned as follows: **9**, bonds 1 and 2 = 10°, bond 3 = 30°; **15**, bonds 1, 2, 3, and 6 = 30°, bonds 4 and 5 = 10°; **16**, bonds 1 and 2 = 10°, bond 3 = 30°. Rotatable bonds defining the propanoic acid side chain were only driven for compound **15** due to the close proximity of the pendant carboxy-substituted phenoxy group. As we have observed in the modeling of similar systems, the orthogonal disposition of the propanoic acid group remained constant over all conformations generated. Use of the SEARCH routine produced a series of conformations for each molecule using cut-off energies ranging from 0.5 to 2.5 kcal/mol. Mapping of the spatial disposition of the secondary carboxylate manifold, defined as a vector connecting both oxygen atoms of the carboxyl group, provided a discrete array for each molecule which could be compared directly with the fixed group of xanthone **1**.

Panels A, B, and C in Figure 1 display representative low energy conformations of compounds **9**, **15**, and **16**, respectively, superimposed with their corresponding secondary carboxylate vector maps. All three analogues, together with a minimized model of xanthone **1** containing no rotatable bonds (panel D), were aligned in a common orientation with the FIT routine employing three discreet points. As can be seen in panel A, the pentynoic scaffolding of compound **9** constrains the secondary carboxyl group predominantly to a focused, disk-shaped cloud. Similarly, a well defined scatter is also observed in the vector map of compound **15** (panel B), due primarily to steric interactions involving the propanoic side chain. As predicted, the vector map of compound **16** encompasses a wide pattern characteristic of a high degree of conformational flexibility (panel C). Panel D illustrates a composite of these vector maps overlaid with xanthone **1**. The area of overlap between the maps of compound **9** (purple)

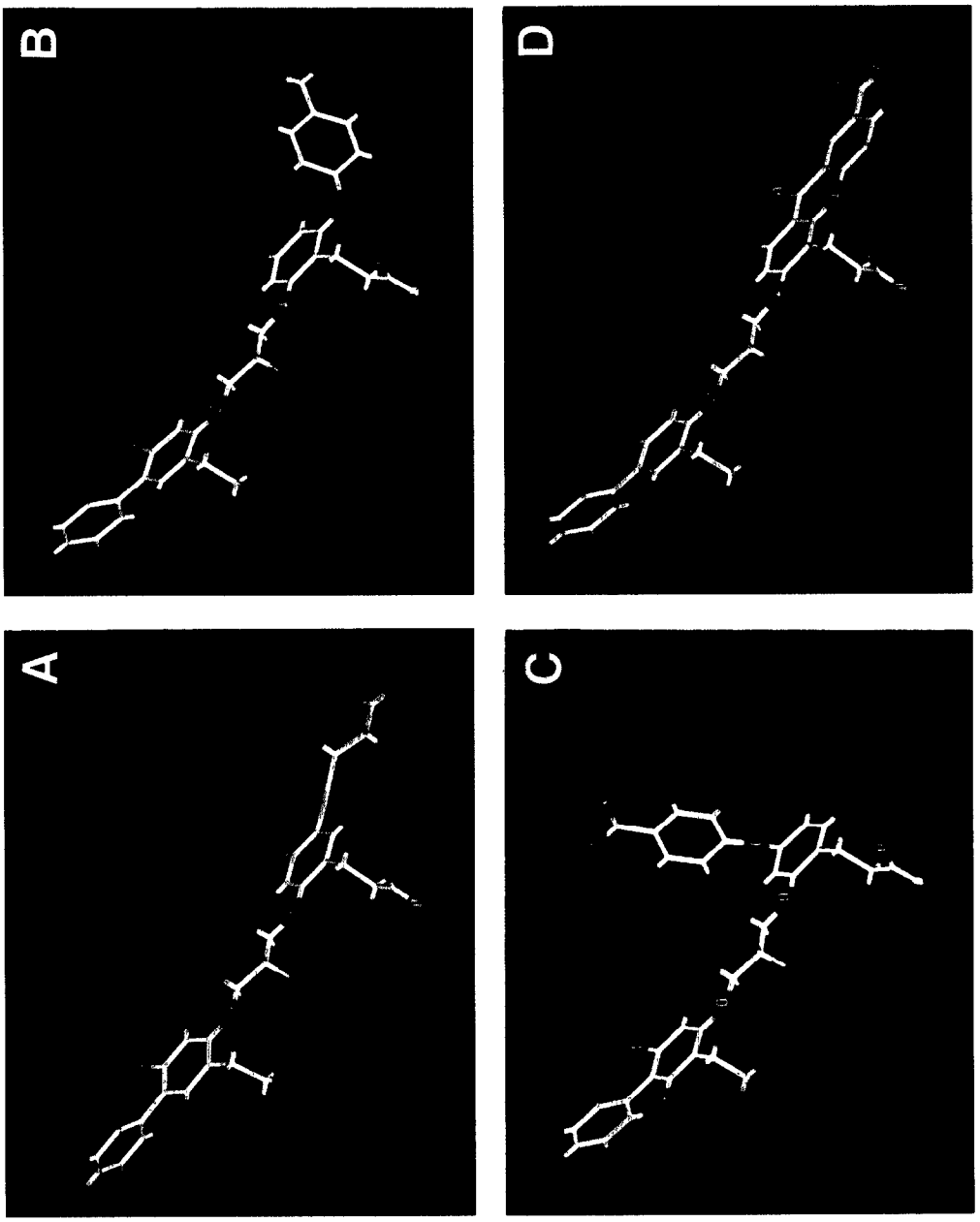


Figure 1. Conformational analysis of compounds **9** (A), **15** (B), and **16** (C), together with **1** (D).

and compound **15** (red) defines the minimum requirements for spatial disposition of the secondary carboxylate relative to the corresponding receptor pharmacophore. The oxygen atoms of the secondary carboxylate of xanthone **1** (panel D) reside in the midst of the purple/red area. Note that the space available to the secondary carboxylate of compound **16** (blue) does not share congruency with this region, although it does overlap a portion of the compound **9** map.

Acknowledgements: We thank Drs. D. K. Herron and M. O. Chaney for helpful discussions regarding SYBYL 6.0.

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(9) Assay conditions are described in references 5b and 8. For each compound, an inhibition response study was done in triplicate on cells from a single individual. Standard errors for the IC_{50} values can be estimated from standard deviations of IC_{50} values obtained for six reference LTB_4 receptor antagonists whose effects were measured on cells from five individuals. The average standard deviation was 15 ± 4% of the mean IC_{50}.

(10) Values are the averages of three determinations; for assay conditions see: Silbaugh, S. A., Stengel, P. W.; Cockerham, S. L.; Roman, C. R.; Saussy, D. L., Jr., Spaethe, S. M., Goodson, T.; Herron, D. K , Fleisch, J. H. *Eur. J. Pharmacol.* **1992**, *223*, 57.

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(*Received in USA* 9 *May* 1994; *accepted* 19 *July* 1994)