



Structure–activity relationship of *ortho*- and *meta*-phenol based LFA-1 ICAM inhibitors

Edward Yin-Shiang Lin*, Kevin M. Guckian, Laura Silvian, Donovan Chin, P. Ann Boriack-Sjodin, Herman van Vlijmen, Jessica E. Friedman, Daniel M. Scott

Research and Development, Biogen Idec Inc., 14 Cambridge Center, Cambridge, MA 02142, USA

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ABSTRACT

LFA-1 ICAM inhibitors based on *ortho*- and *meta*-phenol templates were designed and synthesized by Mitsunobu chemistry. The selection of targets was guided by X-ray co-crystal data, and led to compounds which showed an up to 30-fold increase in potency over reference compound **1** in the LFA-1/ICAM1-Ig assay. The most active compound exploited a new hydrogen bond to the I-domain and exhibited subnanomolar potency.

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LFA-1 (leukocyte function-associated antigen-1) is a cell surface adhesion protein expressed on all leukocytes, and plays a key role in the inflammatory process. Interaction of LFA-1 with its counter-receptors (intracellular adhesion molecules ICAM-1, -2, -3) promotes the migration of leukocytes to the site of inflammation. Blocking the LFA-1/ICAM interaction is of great interest and has potential in the treatment of autoimmune diseases.^{1–4}

Inhibition of the LFA-1/ICAM-1 interaction is possible at two sites, including the metal-ion dependent adhesion site (MIDAS) that is the location of the direct interaction between LFA-1 and the ICAMs. Alternatively, inhibitors may target the I-domain allosteric site (IDAS). Binding at this remote site prevents conformational changes in LFA-1 necessary for interaction with the ICAMs.^{5,6}

Previous studies at Abbott Laboratories^{7–13} had identified *p*-arylthio cinnamide compounds, as shown in Figure 1, that inhibit the interaction of LFA-1 and ICAM-1 at the allosteric site with moderate potency. This series of compounds is characterized by A and B phenyl rings, connected by a sulfide linker. Appended to the B-ring is a third ring (C-ring) linked via a *trans*-cinnamide moiety. These studies indicate that 2,3-bis(trifluoromethyl)phenyl and 4-carboxypiperidine were the preferred B- and C-rings, respectively. Compound **1** (Fig. 2) was among the most active¹² in inhibiting the interaction of LFA-1 and ICAM-1, and showed 12 nM potency in the LFA-1/ICAM1-Ig assay.⁹

The scope of this study is to improve on the potency of **1** by exploring the structure–activity relationship of substitution on

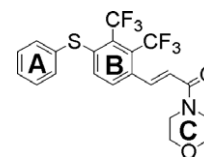


Figure 1. General structure for LFA-1 ICAM inhibitors.

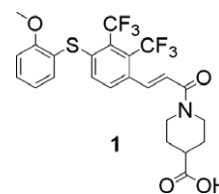


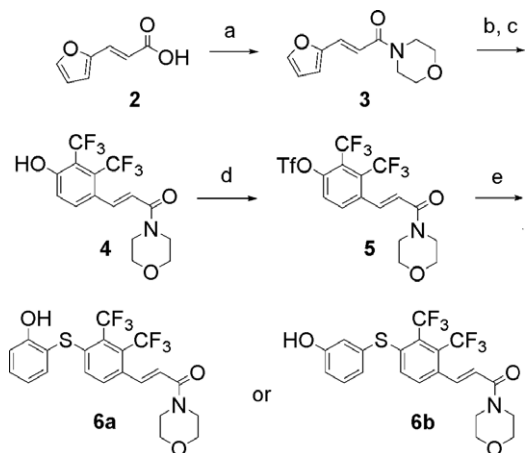
Figure 2. Abbott LFA-1 ICAM inhibitor compound **1**.

the A-ring, while the B- and C-rings are kept constant. Modeling studies suggested potential hydrophobic interactions and hydrogen bonding interactions when the A-ring is properly substituted at the *ortho*- or *meta*-position. This study intends to examine these interactions through the synthesis of appropriate A-ring ethers. Note that morpholine was chosen as a C-ring replacement for 4-carboxypiperidine, as this substitution simplifies the synthesis and had earlier been shown to result in no loss of potency.¹²

Previously reported chemistry^{14,15} (Scheme 1) was applied to prepare the common phenol intermediates, compounds **6a** and **6b**. Amide coupling of carboxylic acid **2** to morpholine gave amide **3**. Dienophile hexafluorobutyne was condensed with **3**, which was

* Corresponding author.

E-mail address: ted.lin@biogenidec.com (E.Y.-S. Lin).



Scheme 1. Synthetic scheme for preparation of **6a** and **6b**. Reagents and conditions: (a) i-SOCl₂, CH₂Cl₂, 0 °C to RT, o/n; ii-morpholine, CH₂Cl₂, RT, 2 h; (b) hexafluoro-2-butyne, dichloroethane, -78 °C to 115 °C, o/n; (c) boron trifluoride diethyl etherate, dichloroethane, reflux, 2 h; (d) triflic anhydride, pyridine, CH₂Cl₂, 0 °C to RT, 2 h; (e) 2-mercaptophenol or 3-mercaptophenol, K₂CO₃, acetone, reflux, 1 h.

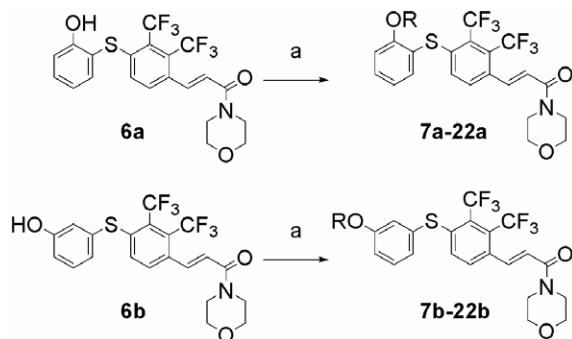
followed by Lewis-acid catalyzed rearrangement to give phenol **4**. Conversion of phenol **4** to the triflate **5** with triflic anhydride was followed by reaction with 2- or 3-mercaptophenol to give the key intermediates, **6a** and **6b**. Phenols **6a** and **6b** were found to be active in the LFA-1/ICAM1-Ig assay, with IC₅₀ of 9.7 and 17 nM, respectively.

From phenols **6a** and **6b**, elaboration to the A-ring ethers was accomplished by Mitsunobu reaction with the appropriate alcohols to give the ethers **7a–22a** and **7b–22b** (Scheme 2). Note that for certain multifunctional alcohols, a subsequent deprotection was required to complete the synthesis.

A series of saturated-ring alcohols was used and the data for the ether products is summarized in Table 1. Each ether shows moderate to high potency in the LFA-1/ICAM1-Ig assay.

In general, the *ortho*-substituted ethers (**7a–14a**) are either equipotent or more active than the *meta*-substituted analogs (**7b–14b**).¹⁶ The presence of a polar heteroatom in the ring increased potency, as the piperidine (**8a**, 2 nM) and tetrahydropyran compounds (**9a**, 2.5 nM) were more active than the corresponding cyclohexyl compound (**7a**, 8.9 nM). This suggests that a polar group in this position is preferred. This result is supported by the substituted cyclohexane compounds, **11a–14a**. Comparison of 4-methylcyclohexyl (*cis*-**11a**, 18 nM; *trans*-**12a**, 51 nM) and 4-carboxycyclohexyl (*cis*-**13a**, 4 nM; *trans*-**14a**, 1.8 nM) shows that the more polar 4-carboxycyclohexyl is favored.

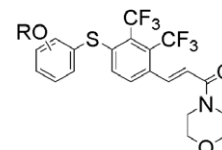
To complement the data on saturated ring ethers, a series of arylmethanols was used. These were chosen to determine the



Scheme 2. Synthetic scheme for preparation of **7a–22a** and **7b–22b**. Reagents and conditions: (a) R-OH, PPh₃, diisopropyl azodicarboxylate, THF, RT, o/n.

Table 1

Activity of ether compounds: saturated rings^a



R-	LFA-1 ICAM1-Ig IC ₅₀ (nM)			
		<i>ortho</i> -	<i>meta</i> -	
	7a	8.9	7b	530
	8a	2	8b	3.9
	9a	2.5	9b	34
	10a	55	10b	2.1
	11a	18	11b	860
	12a	51	12b	810
	13a	4	13b	3
	14a	1.8	14b	18

^a Assay performed as described in the Ref. 9.

effect of aryl rings on the structure–activity relationship, and to see the effect of inserting an additional methylene into the linker. The data for the ether products is summarized in Table 2. As in the previous series, the *ortho*-substituted ethers (**15a–20a**) were more potent than the *meta*-substituted analogs (**15b–20b**). As a whole, the series shows retention of activity, and in some cases improved activity relative to phenols **6a** or **6b**. Benzyl (**17a**, 24 nM) was tolerated but was less active than each of the pyridinemethyl isomers, **18a–20a**. This is consistent with the preference for polar substitutions.

3- and 4-pyridinemethyl-substituted, **19a** and **20a**, were the most active compounds in Table 2, and have IC₅₀ of 2.5 and 3.7 nM, respectively. Crystal structure of **19a** and LFA-1 complex (Fig. 3) suggests that no new hydrogen bonds are formed between the protein and the ether-modified A-ring of the small molecule; most of the improved potency is likely due to increased hydrophobic interactions. Note that in the co-crystal structure, the pyridine moiety is exposed to solvent, leading to the preference for pyridinemethyl over the less hydrophilic benzyl. Interestingly, the crystal structure showed that the pyridine ring of **19a** is in close proximity to the phenol OH of Tyr-257 (5.45 Å). Interaction of the small molecule with this residue directly (via a longer linker) or through a water molecule would be expected to increase potency significantly.

The saturated ring series led to the discovery of the polar 4-carboxy substitution. The unsaturated series confirmed the preference for substitution by polar groups and also suggested that an additional methylene in the linker could bring the compound into contact with Tyr-257. Close examination of the X-ray co-crystal structure suggested that the non-planar cyclohexane would be a better scaffold than the planar phenyl for reaching and interacting

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