Second-Generation Lymphocyte Function-Associated Antigen-1 Inhibitors: 1*H*-Imidazo[1,2-α]imidazol-2-one Derivatives

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A novel class of lymphocyte function-associated antigen-1 (LFA-1) inhibitors is described. Discovered during the process to improve the physicochemical and metabolic properties of BIRT377 (**1**, Figure 1), a previously reported hydantoin-based LFA-1 inhibitor, these compounds are characterized by an imidazole-based 5,5-bicyclic scaffold, the 1,3,3-trisubstituted 1*H*-imidazo[1,2-α]imidazol-2-one (i.e. structure **3**). The structure−activity relationship (SAR) shows that electron−withdrawing groups at C_5 on the imidazole ring benefit potency and that oxygen-containing functional groups attached to a C_5-sulfonyl or sulfonamide group further improve potency. This latter gain in potency is attributed to the interaction(s) of the functionalized sulfonyl/sulfonamide groups with the protein, likely polar−polar in nature, as suggested by SAR data. X-ray studies revealed that these bicyclic inhibitors bind to the I-domain of LFA-1 in a pattern similar to that of compound **1**.

Introduction

Lymphocyte function-associated antigen-1 (LFA-1) is a cellular adhesion molecule involved in many fundamental immunological processes, such as leukocyte trafficking, antigen presentation, B-cell activation, and activation of cytotoxic T lymphocytes.[1] LFA-1 inhibitors have attracted considerable attention in the pharmaceutical industry as potential therapeutic agents for immunological diseases.[2] An anti-LFA-1 antibody has been approved for treatment of psoriasis.[2c,e]

We previously reported the discovery of BIRT377 (**1**, Figure 1), a hydantoin-based reversible and specific small molecule inhibitor of LFA-1.[3] Shown to be an allosteric modulator that binds to the I-domain of LFA-1, compound **1** demonstrated good molecular and cellular potency and was orally active in a mouse model that measures inhibition of *Staphylococcal enterotoxin* superantigen (SEB) induced IL-2 production. However, this compound was poorly soluble in aqueous solution and was rapidly metabolized in a human liver microsome assay (Figure 1). Metabolite identification studies revealed that N_4-demethylation was the major metabolic pathway.[3,4] Developing second-generation LFA-1 inhibitors with improved solubility and metabolic stability therefore became the primary objective of our strucure−activity relationship (SAR) study.

Previous SAR studies on compound **1** showed that substitutions at N_4 and C_5 were well-tolerated.[4a] This prompted us to investigate bicyclic structures such as those depicted in Figure 2 (Structure **A**). Such structures would provide additional sites to incorporate solublizing groups[4b] and eliminate the possibility of N_4-demethylation. The nonhydantoin nature of structure **A** was also particularly attractive in that it would lead to a structurally novel class of LFA-1 inhibitors.

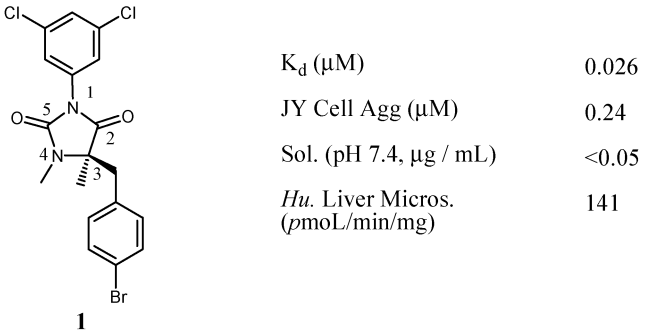

Figure 1. The profiles of compound **1**.

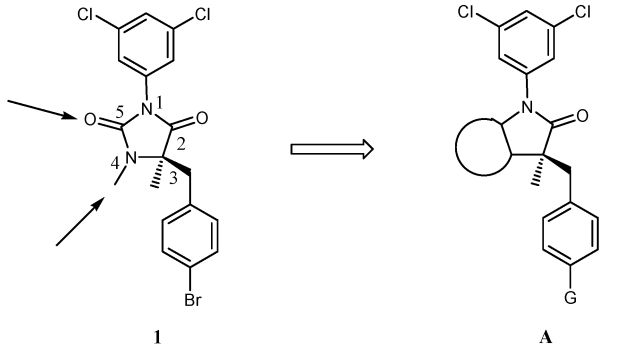

Figure 2.

To test if a second fused ring could be tolerated, a series of bicyclic analogues were synthesized. As shown in Figure 3, all four of the initially prepared compounds were active in the LFA-1/ICAM-1 binding assay,[5] indicating that the bicyclic structures were indeed acceptable. While compounds **4** and **5** were found to be unstable in aqueous solution,[6] compounds **2** and **3** were stable and therefore warranted further investigation.

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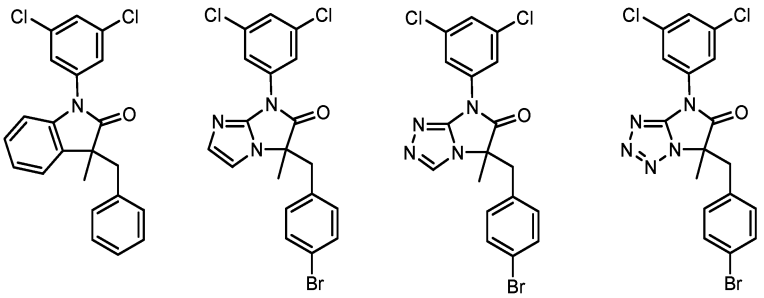
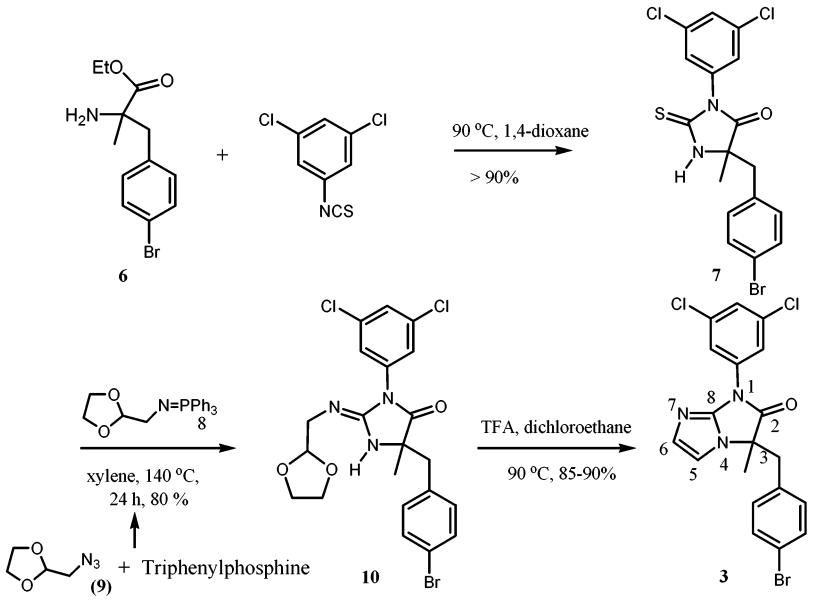


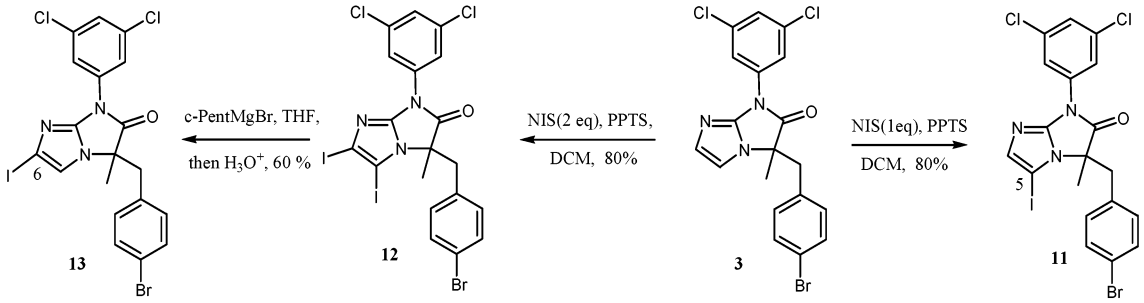
	2	**3**	**4**	**5**
K_d (μM)	**0.76 ±0.07**	**0.38 ±0.04**	**0.048 ±0.02**	**0.114 ±0.001**

Figure 3. Initial series of bicyclic analogues. K_ds are the dissociation constants obtained from the LFA-1/ICAM-1 binding assay.[5]

Scheme 1. Synthesis of the Bicyclic Compound **3**



Scheme 2. Regioselective Iodination of Compound **3**



In this and subsequent papers, we detail the SAR studies centered around structure **3** that led to the development of a novel class of potent LFA-1 inhibitors.[7]

Chemistry

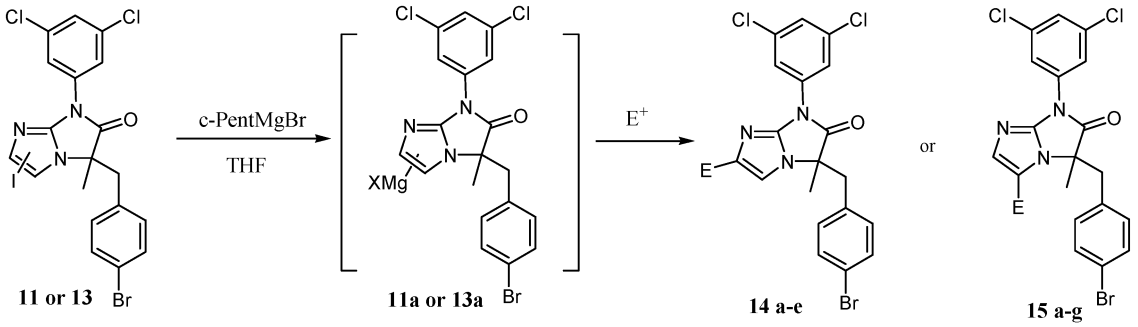
The syntheses of the compounds discussed in this paper are summarized in Schemes1−4.[8,9] Shown here as racemic syntheses, these schemes were also adapted for the preparation of the single enantiomers, using (*R*)- or (*S*)-enantiomers of amino ester **6**[10] as the starting material.

Reaction of amino ester **6** with 3,5-dichlorophenyl isothiocyanate afforded the thiohydantoin **7**. Compound **7** was then reacted with aza-phosphonium ylide **8**, generated in situ from triphenylphosphine, and azide **9**, to produce the guanidine derivative **10**. Compound **10** was subsequently cyclized to product **3** by treatment with trifluoroacetic acid (Scheme 1).

Substitution of the imidazole ring in compound **3** is summarized in Schemes 2−4. Compound **3** was treated with 1 equiv of *N*-iodosuccinimide (NIS) to give the C_5-iodide **11**. With 2 equiv of NIS, the compound was converted to the diiodide **12**, which was subsequently treated with cyclopentylmagnesium bromide followed by quenching with aqueous ammonium chloride to generate the C_6-iodide **13** (Scheme 2).

The two isomers of iodide were further functionalized via a magnesium−iodine exchange reaction.[11] Treat-

Scheme 3. Functionalization of the Imidazole Ring



Scheme 4. Synthesis of the C_5 Sulfones and Sulfonamides

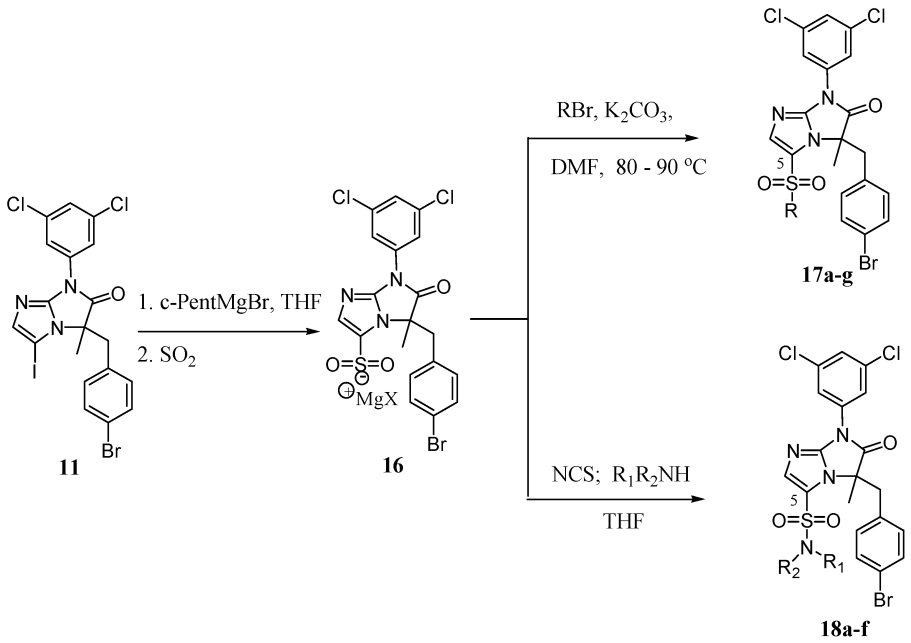
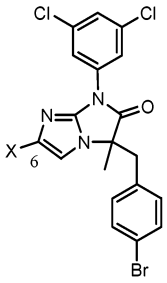


Table 1. Dissociation Constants of Compounds **14a**−**e**[a]



Compound	X	K_d (μM)	Compound	X	K_d (μM)
3	H	0.38 ± 0.04	**14c**	CN	0.28 ± 0.09
14a	Br	0.63*	**14d**	CO_2CH_3	1.62 ± 0.03
14b	I	>20*	**14e**	SO_2CH_3	0.92 ± 0.09

* Result from single test.

[a] Compounds are racemic.

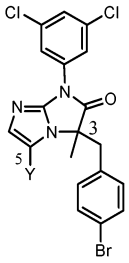
ment of iodides **11** or **13** with cyclopentylmagnesium bromide generated the metalated intermediates **11a** or **13a**, which were trapped in situ with a range of electrophilic reagents to provide compounds **14a**−**e** and **15a**−**g**, as shown in Tables 1 and 2.

The magnesium−iodide exchange reaction was modified for the synthesis of the sulfones and sulfonamides listed in Tables 3 and 4. As shown in Scheme 4, the metalated intermediate **11a** generated from iodide **11** was reacted with SO_2 to give the magnesium sulfinate salt **16**.[12] This sulfinate salt was in turn reacted with alkyl bromide/iodide to give sulfones **17a**−**g** (Tables 3 and 4). Alternatively, the magnesium sulfinate **16** was treated with *N*-chlorosuccinimide to generate in situ the sulfonyl chloride intermediate, which was reacted with amines to produce sulfonamides **18a**−**f** (Table 5).

Results and Discussion

Stereoselective Inhibition. It was previously established that the stereochemistry at C_3 in the hydantoin-based LFA-1 inhibitors was important for compound potency. For example, compound **1**, the (*R*)-enantiomer, was shown to be ∼35 times more potent

Table 2. Dissociation Constants of Compounds **15a**−**g**[a]

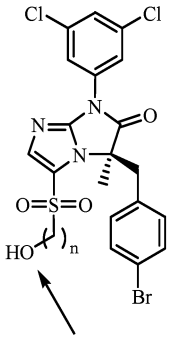


Compound	Y	K_d (μM)	Compound	Y	K_d (μM)
3	H	0.38 ± 0.04	**15d**	I (R)**	0.41 ± 0.15
15a	CH_3	0.34 ± 0.04	**15e**	CN	0.197*
15b	OMe	0.36*	**15f**	CO_2CH_3	0.243 ± 0.01
15c	Br(R)**	0.18 ± 0.02	**15g**	SO_2CH_3	0.074*

* Result from single test.
** 3-*(R)*-enantiomers.

[a] Compounds are racemic unless otherwise noted.

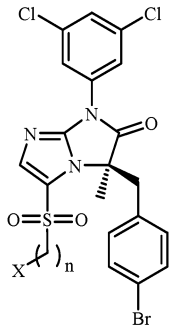
Table 3. Dissociation Constant for **17a**−**c**



New Binding Interaction?

Compounds	n	K_d (μM)
17a	2	0.043 ± 0.001
17b	3	0.013 ± 0.001
17c	4	0.011 ± 0.002
***(R)*-15g**	---	0.050 ± 0.014

Table 4. SAR at the New Binding Site



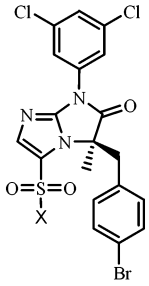
Compounds	n	X	K_d (μM)
17b	3	OH	0.011 ± 0.001
17d	3	OAc	0.014 ± 0.007
17e	3	OMe	0.020 ± 0.002
17c	4	OH	0.011 ± 0.002
17f	4	OAc	0.030 ± 0.014
17g	3	NH_2	0.171*
17h	3	NHMe	0.153*
17i	3	NHAc	0.034 ± 0.024

than its (*S*)-enantiomer.[3a,4a] The existence of the same C_3 chiral center in the bicyclic series led us to examine the stereochemical influence early on in the exploration of the SAR. The two enantiomers of compound **3**, (*R*)-**3** and (*S*)-**3**, were prepared and tested in the binding assay. While (*R*)-**3** produced a K_d of 172 nM, (*S*)-**3** was substantially less active (K_d > 7 μM). Thus, the stereoselective inhibition observed in the hydantoin series was retained in the bicyclic series (Figure 4).

Preliminary Profile of (*R*)-3. With molecular potency in the submicromolar range, compound (*R*)-**3** was deemed as a favorable SAR starting point and further profiled. In the JY cell aggregation assay,[13] known to be LFA-1 dependent, the compound generated an IC_{50} of 1.2 μM. However, in an experiment that measures SEB-induced IL-2 production in mice (oral dosing), the compound showed no inhibition at the dose of 100 mg/kg. Subsequent analysis revealed an extremely low plasma concentration that, together with a fast degradation rate (114 pmol/min/mg protein) in human liver microsomes, suggested metabolic instability as the cause of in vivo inefficacy. Thus, our effort focused on improving metabolic stability as well as increasing potency (Figure 5).

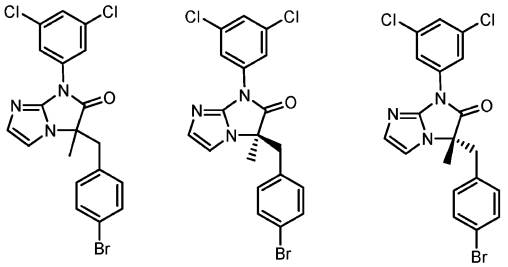
Although no metabolite information was available at the time, the imidazole moiety in (*R*)-**3** was considered a potential metabolic liability, due to its electron-rich nature and known sensitivity toward oxidation. It was reasoned that attaching functional groups to the imidazole ring would alter the electronic and steric environment and modulate the metabolic properties of the molecule. A search of substitutions capable of stabilizing the molecule as well as increasing compound potency was thus started.

Table 5. Dissociation Constants for Compounds **18a**−**f**



	X			
Compounds		**18a**	**18b**	**18c***
K_d (μM)		0.05*	0.023 ± 0.004	0.072
	X			
Compounds		**18d**	**18e**	**18f**
K_d (μM)		0.008 ± 0.003	0.011 ± 0.005	0.056 ± 0.001

* Result from single test



	3 (racemic)	*(R)*-**3**	*(S)*-**3**
K_d (μM)	**0.377 ± 0.04**	**0.172 ± 0.01**	**>7**

Figure 4. Stereoisomers of Compound **3**.

Structure−Activity Relationships. The initial series of compounds substituted at C_6 or C_5 are shown in Tables 1 and 2. As revealed by Table 1, substitutions at C_6 were generally not well tolerated. With the exception of the CN group, which had little influence on potency, all other substitutions reduced potency. At C_5 (Table 2), the electronic characters of the substituting groups proved important. While electron-rich groups (i.e., Me, OMe, and I) did not improve potency, the electron-withdrawing groups (i.e., CN, CO_2CH_3, and SO_2CH_3) did increase the potency. The most effective substitution was the C_5-methanesulfonyl group, the introduction of which resulted in a compound of 74 nM (**15g**).

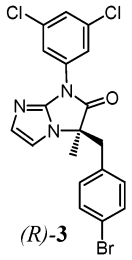
The (*R*)-enantiomer of compound **15g**, (*R*)-**15g**, was next synthesized and profiled. As shown in Figure 6, (*R*)-**15g** was 50 nM in the binding assay and 0.26 μM in JY cell aggregation assay, a considerable improvement compared to the unsubstituted compound (*R*)-**3** (Figure 1). More importantly, (*R*)-**15g** was found to be stable in a human liver microsome assay. In the mouse SEB/IL-2 experiment, the plasma concentration of (*R*)-**15g** 4 h after dosing was determined to be 2800 and 14 400 ng/mL at doses of 30 and 100 mg/kg, respectively, a striking improvement compared to that of (*R*)-**3**. Thus, introducing the methanesulfonyl group at C_5 had the double benefit of increasing compound potency as well as improving metabolic stability.

Despite of the good exposure level in mice, compound (*R*)-**15g** did not show in vivo efficacy in the mouse experiment, a result attributed to its insufficient potency in serum rich media. Additionally, the compound was shown to be poorly soluble, with a solubility of ∼0.1 μg/mL at pH 7.4. Thus, improving solubility and further increasing potency became our next objectives.

A New Binding Interaction. Our strategy for increasing the solubility of (*R*)-**15g** was to attach polar groups to the sulfonyl moiety. For this purpose, a series of sulfones containing ω-hydroxy groups was prepared, as shown in Table 3. The 2-hydroxy ethyl sulfone derivative **17a** (n = 2) produced a K_d of 43 nM, comparable to that of (*R*)-**15g**. When the OH group was further extended out, as in compounds **17b** and **17c** (n = 3 and 4), a marked increase in potency, to 13 and 11 nM, respectively, was observed. It appeared that the OH groups in **17b** and **17c**, located three and four carbons from the sulfur atom, picked up a new interaction.

Subsequent studies were designed to elucidate the nature of the newly discovered interaction(s). Replacing the OH groups in **17b** and **17c** with OAc or OMe produced compounds of comparable potency (**17d**−**f**), excluding the possibility that the OH groups in **17b** and **17c** were H-bond donors.[14] Substituting the OH group in **17b** with amino groups resulted in loss of potency (**17g** and **17h**),[15] indicating that oxygen atom(s) were required. Placing an acetyl group on the amino group in **17g** restored potency (**17i**, K_d = 34 nM), further demonstrating the essential role of oxygen atom(s) in the interaction. Although the exact nature of the interaction could not be deduced, it likely involves a polar−polar interaction(s) (Table 4).[16]

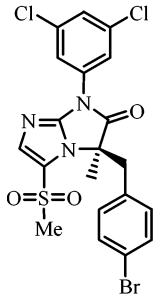
Further SAR studies focused on the directional preferences of the interaction. A series of cyclic analogues were synthesized and tested, as summarized in Table 5. The piperidine sulfonamide **18a** has a K_d of 50 nM, similar to the methyl sulfone derivative (*R*)-**15g**. When a hydroxy or carbonyl group was placed at the 4-position of the piperidine ring, a significant increase in potency was observed (**18d** or **18e**). Placing an OH at the 3-position had no beneficial effect (**18c**). The morpholine sulfonamide **18b**, with an ethereal oxygen at the 4-position, also showed a moderate gain in potency. An amino group, as in **18f**, showed no beneficial effect. Thus, a



(R)-**3**

K_d (μM)	0.172 ± 0.01
JY Agg. (μM)	1.2
Mouse SEB/IL-2	no inhibition @ 100 mg/kg
plasma con.(4 hs, *n*g/mL)	25 (30 mg / kg); 155 (100 mg / kg)
Hu. liver micros. (*p*mol/min/mg)	114

Figure 5. Profiles of *R*-**3**.

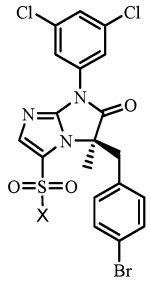


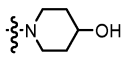
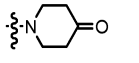
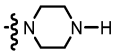
R-**15g**

K_d (μM)	0.050 ± 0.014
JY cell agg. (μM)	0.26 ± 0.07
Solubility (μg/mL, pH 7.4)	0.12
Hu. liver microsome (*p*mol/min/mg)	stable
Mouse SEB/IL-2	no inhibition @ 100 mg/kg
Plasma conc.(at 4 hr, *n*g / mL)	2800 (30 mg / kg); 14400 (100 mg / kg)

Figure 6. Profiles of compound (*R*)-**15g**.

Table 6. Cellular Activities for Selected Compounds



Compounds	X	K_d (μM)	K_d w/14% *hu.*serum (μM)	JY Agg. IC_{50} (μM)	SEB / IL-2 (hu. whole blood) IC_{50} (μM)
17b	$-(CH_2)_3OH$	0.011 ± 0.001	0.10*	0.09 ± 0.06	10.4*
17d	$-(CH_2)_3OAc$	0.014 ± 0.007	0.048*	0.37 ± 0.13	7.0*
17i	$-(CH_2)_3NHAc$	0.037 ± 0.024	0.074*	0.35 ± 0.03	9.5*
18d		0.009 ± 0.004	0.044*	0.03*	4.6 ± 0.8
18e		0.011 ± 0.005	0.30*	0.25 ± 0.06	5.5 ± 0.9
18f		0.056 ± 0.005	0.40*	0.38 ± 0.12	27.8*

* Result from single test.

proper orientation, in addition to the presence of oxygen atom, is required for an effective interaction.

Protein Binding Studies. With compounds of low nanomolar potency identified, we proceeded to the cellular level of compound evaluation. In the JY cell aggregation[13] assay, compounds with low nanomolar K_ds consistently generated IC_{50}s less than 1 μM. However, in a human whole blood assay,[5] which measures the SEB-induced IL-2 production, the IC_{50}s were well above the micromolar level (Table 6).

The discrepancies between the two cellular assays were attributed to protein binding. In a modified binding assay,[5,17] which included 1% of human plasma proteins during incubation, a dramatic reduction in binding potency was observed (Table 6, column 4). The presence of plasma proteins apparently reduced the free compound concentration and resulted in the lower observed potency. The same protein binding effect was likely to account for the lower potency in the whole blood assay. Studies on the SAR of protein binding will be reported shortly.

X-ray Crystallography Studies. The bicyclic class of LFA-1 inhibitors had been assumed to bind to the I-domain of LFA-1, similar to compound **1**.[3b] This was confirmed when the cocrystal structure of compound **17d** and I-domain was obtained, as presented in Figure 7. Similar to compound **1**,[3b] the N-1 dichlorophenyl moiety of **17d** was located in a hydrophobic pocket between α-helices 1 and 7 and β-strands 1, 3, and 4. The bromophenyl group at C_3 was oriented toward the two α-helices 1 and 7. However, the X-ray structure did not reveal the detailed binding pattern of the C_5-acetylpropylsulfonyl group, which was apparently responsible for the potency increase in **17d**. In Figure 7, the C_5 acetylpropylsulfonyl was shown to extend toward solvent, not in apparent contact with any amino

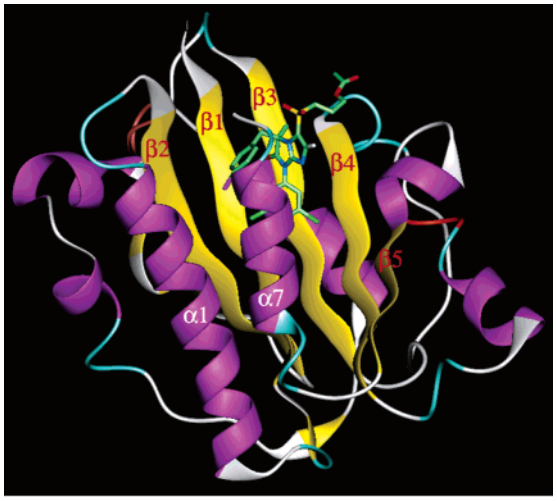


Figure 7. X-ray cocrystal structure of **17d** and the I-domain.

acid residues. One possibility is that the acetylpropylsulfonyl residue interacts with portions of LFA-1 outside of the I-domain.

Summary

We have identified a novel class of potent small molecule inhibitors of LFA-1. These compounds are characterized by the 1,3,3-trisubstituted 1*H*-imidazo-[1,2-α]imidazol-2-one scaffold. Substitution at C_5 with electron-withdrawing groups benefits potency. Certain functionalized sulfonyl or sulfonamide groups at this position further enhance potency by engaging in a new interaction not known previously. SAR data suggests that the new interaction most likely involves a polar−polar interaction(s). X-ray studies reveal that these compounds bind to the I-domain in a pattern similar to that of compound **1**.

Experimental Section

All reactions were carried out in oven or flame-dried glassware under nitrogen atmosphere in commercially supplied (EMS or Aldrich) dry solvents. Thin-layer chromatography was performed on Analtech or E-Merck silica gel TLC plates. Developed plates were visualized using 254 nm UV illumination or by PMA stain. Flash chromatography was performed using 230−400 mesh Merck silica gel.

^{1}H and ^{13}C NMR spectra were recorded on Bruker Ultra-Shield-400 MHz spectrometers in solvents as noted. IR spectra were recorded on a Nicolet Impact-410 instrument. Mass spectra were obtained on Micromass Platform LCZ mass spectrometers using either electrospray positive/negative ionizations or chemical ionization. Elemental analysis was performed by Quantitative Technologies, Whitehouse, NJ.

Synthesis of Compound 3 (Scheme 1). 5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (7). A solution of amino-ester **6** (3.40 g, 12.5 mmoL) and 3,5-dichlorophenylisothiocyanate (2.60 g, 12.7 mmoL) in 1,4-dioxane (15 mL) was heated at 90 °C overnight. The mixture was concentrated to give a thick oil, which was crystallized from EtOAc−hexane to give 5.0 g of thiohydantoin derivative **7**: yield 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (2H, d, J = 8 Hz), 7.48 (1H, s), 7.15 (2H, d, J = 8 Hz), 6.78 (2H, s), 3.22 (1H, d, J = 14 Hz), 3.05 (1H, d, J = 14 Hz), 1.70 (3H, s) ppm.

2-(Azidomethyl)[1,3]dioxolane (9). A mixture of 10.0 g (0.060 moL) of 2-(bromomethyl)-1,3-dioxolane and 20 g (0.3 moL) of sodium azide in 100 mL of DMSO was heated at 100 °C for 30 min. The mixture was then cooled to room temperature and poured into 200 mL of an ice−water mixture. The mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried, and concentrated to give azide **9** in quantitative yield: ^{1}H NMR ($CDCl_3$, 400 MHz) 5.10 (1H, t, J = 3.5 Hz), 4.15−4.08 (2H, m), 4.05−3.92 (2H, m), 3.35 (2H, d, J = 3.5 Hz) ppm.

5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-2-[(*E*)-[1,3]-dioxolan-2-ylmethylimino]-5-methylimidazolidin-4-one (10). To a solution of PPh_3 (2.36 g, 9.0 mmol) in toluene (20 mL) was added azide **9** (1.2 g, 9.0 mmol). After stirring at room temperature overnight, thiohydantoin **7** (2 g, 4.5 mmol) was added. The mixture was sealed under N_2 in a pressure tube and heated at 130−140 °C for 3−4 days. The mixture was then cooled to room temperature, concentrated, and purified by silica gel chromatography to give the product **10** (1.96 g, yield 85%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.35 (3H, m), 7.05 (2H, d, J = 8 Hz), 6.55 (2H, s), 5.05−4.92 (1H, m), 4.00−3.90 (4H, m), 3.82 (1H, m), 3.75−3.65 (1H, m), 3.55−3.45 (1H, m), 3.02 (2H, abq, J = 14, 22 Hz), 2.28 (1H, s), 1.58 (3H, s) ppm.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (3). To a solution of **10** in CH_2Cl_2 was added trifluoroacetic acid (TFA, 5−6 equiv). The mixture was heated under N_2 at 90 °C overnight. The mixture was then cooled to room temperature, diluted with EtOAc, washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography to give the title compound **3**: yield >85%; mp 36.0−37.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (2H, s), 7.35 (2H, d, J = 8.3 Hz), 7.00 (1H, s), 6.92 (1H, s), 6.81 (2H, d, J = 8.3 Hz), 3.32 (1H, d, J = 14.0 Hz), 3.18 (1H, d, J = 13.9 Hz), 1.80 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 M Hz) δ 174.3, 145.3, 134.8, 134.2, 131.5, 131.2, 130.6, 128.5, 126.6, 121.6, 119.8, 110.6, 65.5, 43.6, 22.7 ppm; mass spectrum (EI) m/z 449 (M^+). Anal. Calcd for $C_{19}H_{14}BrCl_2N_3O$: C, 50.58; H, 3.13; N, 9.31. Found: C, 50.64; H, 3.17; N, 9.12.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-iodo-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (11). To a solution of compound **3** (1.82 g, 4.04 mmol), in CH_2Cl_2 (20 mL), cooled to 0 °C was added in small portions *N*-iodosuccinimide (1.43 g, 6.04 mmol). Pyridinium *p*-toluenesulfonate (100 mg, 0.40 mmol) was added and the mixture was stirred at 0 °C for 3 h, during which time additional *N*-iodosuccinimide (400 mg, 1.68 mmol) was added to complete the reaction. The mixture was diluted with CH_2Cl_2, washed with 10% Na_2SO_3 solution, dried, and concentrated. The residue was purified by silica gel chromatography to give the title compound **11** (1.8 g): yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (2H, s), 7.39 (2H, d, J = 8.3 Hz), 7.30−7.32 (m, 1H), 7.01 (1H, s), 6.83 (2H, d, J = 8.3 Hz), 3.29 (1H, d, J = 13.9 Hz), 3.16 (1H, d, J = 14.0 Hz), 1.78 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3, 146.4, 135.5, 134.3, 131.9, 131.7, 131.2, 127.6, 122.4, 120.7, 116.8, 80.3, 66.8, 44.0, 23.2. ppm; mass spectrum (CI) m/z 576 ($M + H)^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5,6-diiodo-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (12). Diiodide **12** was synthesized from **3** using 2.2 mol equiv of *N*-iodosuccinimide by the same procedure as described above: yield 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.44 (2H, s), 7.35−7.25 (3H, m), 6.82 (2H, d, J = 8 Hz), 3.58 (1H, d, J = 14 Hz), 3.26 (1H, d, J = 14 Hz), 1.92 (3H, s) ppm.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-6-iodo-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (13/14b). To a solution of compound **12** (92 mg, 0.131 mmol) in THF (2 mL) at −30 °C was added cyclopentylmagnesium bromide (2.0 M in ether, 0.131 mL, 0.262 mmol) under nitrogen. The solution was stirred at −30 °C for 1.5 h before saturated NH_4Cl solution was added. The mixture was warmed to room temperature and extracted with EtOAc. The organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to give the iodide **13** (45 mg, yield 60%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (2H, s), 7.40 (2H, d, J = 8 Hz), 7.30 (1H, m), 7.04 (1H, s), 6.84 (2H, d, J = 8 Hz), 3.30 (1H, d, J = 14 Hz), 3.18 (1H, d, J = 14 Hz), 1.84 (3H, s) ppm.

Synthesis of Compounds 14a−14e and 15a−15 g (Tables 1 and 2). 6-Bromo-3-(4-bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (14a). Compound 14a was prepared from compound **3** and *N*-bromosuccinimide via the same procedure as for the preparation of iodide **13**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (2H, s), 7.40 (2H, d, J = 8 Hz), 7.30 (1H, m), 6.90 (1H, s), 6.85 (2H, d, J = 8 Hz), 3.30 (1H, d, J = 14 Hz), 3.15 (1H, d, J = 14 Hz), 1.81 (3H, s) ppm; mass spectrum (ES$^+$) m/z 528 (M + H)$^+$.

Synthesis of 14b: See Synthesis of Compound 13. General Procedure I. To a solution of the iodide **13 or 11** (1 equiv) in THF at −35 °C was added cyclopentylmagnesium bromide (2 M in ether, 3 equiv) under nitrogen. The solution was stirred at −35 °C for 1 h before an electrophilic reagent (5−8 equiv) was added. The mixture was stirred at −35 °C for 30 min and then at room temperature for 1 h. Saturated $NaHCO_3$ solution was added at 0 °C. The mixture was extracted with EtOAc, and the organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to give the products **14a−e** or **15a−g**.

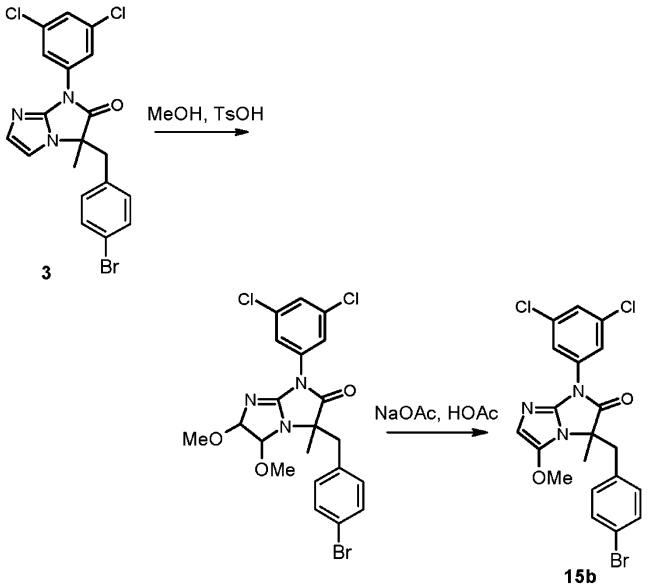
5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-α]imidazole-2-carbonitrile (14c). Compound **14c** was prepared from iodide **13** according to general procedure I, using tosyl cyanide as the electrophile: yield 38%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (2H, s), 7.46 (1H, s), 7.41 (2H, d, J = 8.3 Hz), 7.54 (1H, m), 6.81 (2H, d, J = 8.3 Hz), 3.36 (1H, d, J = 14.1 Hz), 3.20 (1H, d, J = 14.1 Hz), 1.85 (3H, s) ppm; mass spectrum (CI) m/z 475 (M + H)$^+$.

5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-α]imidazole-2-carboxylic Acid Methyl Ester (14d). Compound **14d** was prepared from iodide **13** according to general procedure I, using methyl chloroformate as the electrophile: yield 16%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (1H, s), 7.51 (2H, s), 7.38−7.34 (3H, m), 6.80 (2H, d, J = 8.3 Hz), 3.95 (3H, s), 3.37 (1H, d, J = 14.0 Hz), 3.20 (1H, d, J = 14.0 Hz), 1.85 (3H, s) ppm; mass spectrum (CI) m/z 508 (M + H)$^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-6-methanesulfonyl-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (14e). Compound **14e** was prepared from iodide **13** according to general procedure I, using methylsulfonyl chloride as the electrophile: yield 22%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (2H, s), 7.62 (1H, s), 7.40−7.36 (3H, m), 6.84 (2H, d, J = 8.2 Hz), 3.38 (1H, d, J = 14.1 Hz), 3.22 (1H, d, J = 14.0 Hz), 3.21 (3H, s), 1.86 (3H, s) ppm.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3,5-dimethyl-1*H*-imidazo[1,2-α]imidazol-2-one (15a). To a suspension of anhydrous LiCl (10.0 mg, 0.236 mmol) and CuCN (10.5 mg, 0.117 mmol) in THF (0.2 mL), cooled at −20 °C, was added CH_3MgBr (1.4 M in THF, 0.21 mL, 0.294 mmol) under N_2. The solution was stirred at −20 °C for 15 min. A solution of compound **11** (34 mg, 0.059 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at −20 °C for 2 h and then room temperature overnight before being quenched with saturated NH_4Cl at 0 °C. The mixture was extracted with EtOAc, dried with Na_2SO_4, and concentrated. The residue was purified with preparative thin-layer chromatography (prep-TLC) to give 2 mg (yield 6%) of **15a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (2H, s), 7.32−7.28 (3H, m), 6.74 (2H, d, J = 8 Hz), 6.65 (1H, s), 3.33 (1H, d, J = 14.0 Hz), 3.27 (1H, d, J = 14.0 Hz), 2.47 (3H, s), 1.98 (3H, s) ppm; mass spectrum (EI) m/z 463 (M + H)$^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-methoxy-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (15b). To a solution of compound **3** (80 mg) in methanol (2 mL) was added toluenesulfonic acid (2 mg). The mixture was stirred at room temperature overnight. The mixture was concentrated. The residue was redissolved in HOAc (1 mL). To this mixture was added NaOAc (anhydrous, 50 mg). The mixture was heated at 100 °C for 4 h. The mixture was concentrated, and the residue was taken up in EtOAc (5 mL). The mixture was filtered through a short silica gel plug, concentrated and purified by Prep-TLC using 33% ethyl acetate−hexane to give compound **15b** (22 mg, 26% two steps). M.p. 170.1−171.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (2H, s), 7.30 (3H, m), 6.82 (2H, d, J = 8 Hz), 6.10 (1H, s), 4.00 (3H, s), 3.35 (1H, d, J = 14 Hz), 3.28 (1H, d, J = 14 Hz), 1.82 (3H, s) ppm; mass spectrum (CI) m/z 480 (M + H)$^+$.



5-Bromo-3-(4-bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (15c). Compound **15c** was synthesized from compound (*R*)-**3** and *N*-bromosuccinimide according to the same procedure as the synthesis of iodide **11**: yield 85%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (2H, s), 7.35−7.26 (3H, m), 6.89 (1H, s), 6.85 (2H, d, J = 8 Hz), 3.54 (1H, d, J = 14 Hz), 3.32 (1H, d, J = 14 Hz), 1.98 (3H, s) ppm; mass spectrum (CI) m/z 528 (M + H)$^+$.

(*R*)-3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-iodo-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (15d) ((*R*)-Enantiomer of Iodide 11). See preparation of compound 11.

5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-α]imidazole-3-carbonitrile (15e). Compound **15e** was prepared from iodide **11** according to general procedure I, using tosylcyanide as the electrophile: yield 35%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (3H, m), 7.37−7.30 (3H, m), 6.84 (2H, d, J = 8.3 Hz), 3.48 (1H, d, J = 14.3 Hz), 3.41 (1H, d, J = 14.2 Hz), 1.99 (3H, s) ppm; mass spectrum (CI) m/z 475 (M + H)$^+$.

5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-α]imidazole-3-carboxylic Acid Methyl Ester (15f). Compound **15f** was prepared from iodide **11** according to general procedure I, using methyl chloroformate as the electrophile: yield 38%; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.61 (1H, s), 7.57 (2H, m), 7.35 (1H, s), 7.29 (2H, d, J = 8.0 Hz), 6.75 (2H, d, J = 8.0 Hz), 4.01 (3H, s), 3.86 (1H, d, J = 16.0 Hz), 3.34 (1H, d, J = 16.0 Hz), 1.99 (3H, s) ppm; mass spectrum (CI) m/z 508 (M + H)$^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-methylsulfonyl-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (15g). Compound **15g** was prepared from iodide **11** according to general procedure I, using methylsulfonyl chloride as the electrophile: yield 66%; mp 92−93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51(1H, s), 7.38 (2H, s), 7.33 (1H, s), 7.26 (2H, d, J = 8.2 Hz), 6.80 (2H, d, J = 8.3 Hz, 3.86 (1H, d, J = 13.9 Hz), 3.25 (3H, s), 3.24 (1H, d, J = 14 Hz), 2.03 (3H, s) ppm; mass spectrum (ES$^+$) m/z 528 (M + H)$^+$. Anal. Calcd for $C_{20}H_{16}BrCl_2N_3O_3S_1$: C, 45.39; H, 3.05; N, 7.94. Found, C, 45.64; H, 3.13; N, 7.95.

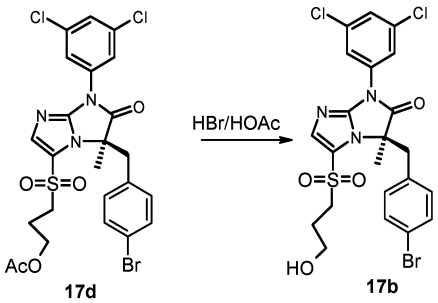
Alternative Synthesis of Compound 15g. Compound **15g** was also prepared from the magnesium sulfinate **16**, according to general procedure II (see below), using iodomethane as the alkylating reagent: yield 83%.

Bromomagnesium 5-(4-bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-α]-imidazole-3-sulfinate (16). A solution of compound **11** (2.5 g, 4.33 mmol) in 25 mL of THF was treated with cyclopentylmagnesium bromide (2.6 mL, 2 M, 5.2 mmol) at −40 °C under argon. The mixture was stirred at −40 °C for 40 min and then SO_2 was bubbled in over 1 min. The mixture was stirred at −40 °C for 15 min and then room temperature for 1 h before being concentrated. The residue was twice redissolved in fresh dry THF (25 mL each time) and concentrated to give 3.8 g of the solid magnesium salt **16**. The product thus obtained was assumed to be 70% pure based on theoretical yield and used in later reactions without further purification.

Synthesis of Compounds 17a−i (Tables 3 and 4) General Procedure II. The magnesium salt (*R*)-**16** (1 equiv) was dissolved in dry DMF. To this solution were added powdered potassium carbonate (3 equiv) and an alkyl bromide/iodide. The mixture was heated at 70−80 °C for 2−16 h until the reaction was complete. The mixture was then cooled to room temperature, diluted with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography to give sulfones **17a**−**g**.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-(2-hydroxyethanesulfonyl)-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (17a). The sulfinate salt (*R*)-**16** was reacted with 2-bromoethyl acetate according to general procedure II. Only the deacetylated product **17a** was isolated: yield 7.5%; mp 139.2−140.0; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (1H, s), 7.41 (2H, s), 7.38 (1H, s), 7.31 (2H, d, J = 8.1 Hz), 6.85 (2H, d, J = 8.2 Hz), 4.21−4.16 (2H, m), 3.89 (1H, d, J = 13.8 Hz), 3.58−3.47 (2H, m), 3.29 (1H, d, J = 13.9 Hz), 2.43 (1H, t, J = 5.2 Hz), 2.06 (3H, s) ppm; mass spectrum (ES$^+$) m/z 558 (M + H)$^+$. Anal. Calcd for $C_{21}H_{18}BrCl_2N_3O_4S_1 \cdot 0.5H_2O$: C, 44.39; H, 3.37; N, 7.39. Found: C, 44.47; H, 3.41; N, 7.39.

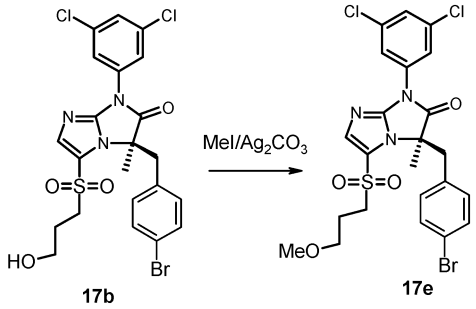
3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-(3-hydroxypropyl-1-sulfonyl)-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (17b). A solution **17d** (44 mg) in methanol was treated with 30% HBr/HOAc. The mixture was stirred at room temperature overnight and concentrated. The residue was diluted with CH_2Cl_2, washed with aq $NaHCO_3$, and concentrated. Purification by prep-TLC gave 13 mg of **17b**: yield 31%; mp 112.6−113.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (1H, s), 7.42 (2H, s), 7.37 (1H, s), 7.31 (2H, d, J = 8 Hz), 6.86 (2H, d, J = 8.3 Hz), 3.92 (1H, d, J = 13.8 Hz), 3.87−3.84 (2H, m), 3.53−3.40 (2H, m), 3.28 (1H, d, J = 13.8 Hz), 2.22−2.20 (2H, m), 2.06 (3H, s) ppm; mass spectrum (ES$^+$) m/z 573.9 (M + H)$^+$.



3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-(4-hydroxybutyl-1-sulfonyl)-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (17c). The acetate **17f** was hydrolyzed to **17c** using 30% HBr/HOAc in methanol in a similar procedure for the synthesis of **17b**: yield 84%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (1H, s), 7.42 (2H, s), 7.37 (1H, m), 7.32−7.29 (2H, m), 6.85 (2H, d, J = 8.3 Hz), 3.91 (1H, d, J = 13.9 Hz), 3.75 (2H, t, J = 6.0 Hz), 3.38−3.28 (2H, m), 3.27 (1H, d, J = 13.9 Hz), 2.05 (3H, s), 2.00−1.85 (2H, m), 1.85−1.70 (2H, m) ppm; mass spectrum (ES$^+$) m/z 586 (M + H)$^+$.

Acetic Acid 3-[5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-α]imidazolyl-3-sulfonyl]propyl Ester (17d). Compound **17d** was prepared from (*R*)-**16** and 3-bromopropyl acetate according to general procedure II: yield 43%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (1H, s), 7.41 (2H, s), 7.38 (1H, m), 7.31 (2H, d, J = 7.2 Hz), 6.84 (2H, d, J = 8.3 Hz), 4.27−4.21 (2H, m), 3.90 (1H, d, J = 13.9 Hz), 3.43−3.28 (2H, m), 3.27 (1H, d, J = 14.0 Hz), 2.34−2.25 (1H, m), 2.22−2.13 (1H, m), 2.10 (3H, s), 2.05 (3H, s) 2.00−1.75 (3H, m) ppm.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-(3-methoxypropyl-1-sulfonyl)-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (17e). To a solution of 20 mg (35 μmol) of **17b** in 2 mL of ether was added 0.1 mL (1.6 mmol) of MeI, 16 mg (70 mmol) of Ag_2O, and 19 mg of Ag_2CO_3. The mixture was stirred for 3 days. The mixture was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated and purified by silica gel Prep-TLC with 20% acetone−hexane to give 8 mg of **17e**: yield 39%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (1H, s), 7.41 (2H, s), 7.36 (1H, s), 7.31−7.27 (2H, m), 6.85 (2H, d, J = 8 Hz), 3.90 (1H, d, J = 14 Hz), 3.50 (2H, t, J = 6.0 Hz), 3.40−3.28 (5H, m), 3.25 (1H, d, J = 14 Hz), 2.25−2.10 (1H, m), 2.10−2.02 (1H, m), 2.02 (3H, s) ppm; mass spectrum (ES$^+$) m/z 586 (M + H)$^+$.



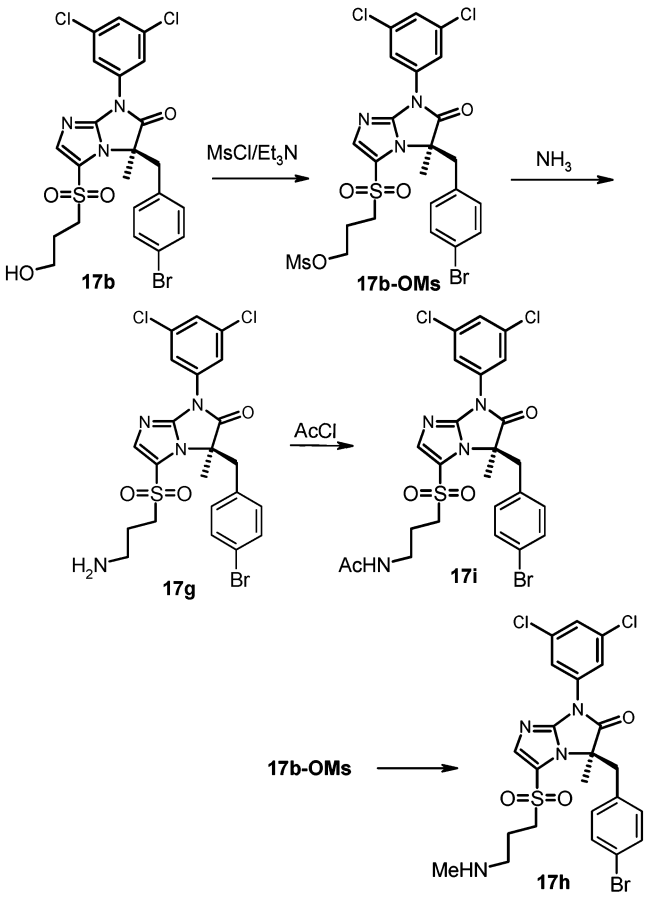
Acetic acid 4-[5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-α]imidazolyl-3-sulfonyl]butyl Ester (17f). Compound **17f** was prepared from (*R*)-**16** and 4-bromobutyl acetate according to general procedure II: yield 30%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (1H, s), 7.42 (2H, s), 7.37 (1H, m), 7.31 (2H, d, J = 8.3 Hz), 6.85 (2H, d, J = 8.3 Hz), 4.20−4.10 (2H, m), 3.90 (1H, d, J = 13.9 Hz), 3.30−3.20 (3H, m), 2.07 (3H, s), 2.10−2.00 (4H, m), 2.00−1.75 (3H, m) ppm; mass spectrum (ES$^+$) m/z 628 (M + H)$^+$.

Compounds **17g**−**i** were prepared according to the following scheme.

Methanesulfonic Acid 3-[5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo-[1,2-α]imidazolyl-3-sulfonyl]propyl Ester (17b-OMs). To a solution of 37 mg (64.5 μmol) of **17b** in 2 mL of CH_2Cl_2 at room temperature was added 20 μL (0.14 mmol) of triethylamine and 4 μL of methylsulfonyl chloride. The mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated NH_4Cl. The mixture was extracted with CH_2Cl_2, and the organic layer was dried and concentrated. The residue was purified by Prep-TLC with 5% MeOH−CH_2Cl_2 to give 30 mg of the mesylate **17b-OMs**.

5-(3-Aminopropyl-1-sulfonyl)-3-(4-bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-1*H*-imidazo[1,2-α]imidazol-2-one (17g). A solution of 53 mg (81 μmol) of **17b-OMs** in 2 mL of 2 M NH_3−EtOH was heated in a sealed tube at 80 °C overnight. The mixture was then cooled to room temperature and concentrated. The residue was purified by Prep-TLC using 5% MeOH−CH_2Cl_2 with 1% concentrated $NH_3 \cdot H_2O$ to give 31 mg of **17g**: yield 66.5%; mp 75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (1H, s), 7.42 (2H, m), 7.37 (1H, m), 7.30 (2H, d, J = 8.3 Hz), 6.85 (2H, d, J = 8.3 Hz), 3.91 (1H, d, J = 13.9 Hz), 3.50−3.32 (2H, m), 3.27 (1H, d, J = 13.9 Hz), 2.91 (2H, t, J = 6.5 Hz), 2.00−1.98 (4H, m), 1.98−1.87 (1H, m), ppm; mass spectrum (ES$^+$) m/z 571 (M + H)$^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-5-(3-methylaminopropyl-1-sulfonyl)-1*H*-imidazo[1,2-α]imidazol-2-one (17h). A solution of 20 mg (31 μmol) of **17b-OMs** in 2 mL of 2 M $MeNH_2$−MeOH was heated in a sealed tube at



70 °C overnight. The mixture was then cooled to room temperature and concentrated. The residue was purified by Prep-TLC using 5% MeOH−CH_2Cl_2 with 1% concentrated $NH_3 \cdot H_2O$ to give 3 mg of **17h**: yield 17%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (1H, s), 7.37 (2H, s), 7.33 (1H, s), 7.26 (2H, m), 6.90 (2H, m), 3.85 (1H, d, J = 14.9 Hz), 3.40−3.27 (2H, m), 3.23 (1H, d, J = 14.0 Hz), 2.85−2.78 (3H, m), 2.44 (3H, s), 2.45−2.00 (4H, m), 2.01 (3H, s) ppm.

***N*-{3-[5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-α]imidazolyl-3-sulfonyl]propyl}acetamide (17i).** To a solution of **17g** (23 mg, 40 μmol) in CH_2Cl_2 (2.5 mL) was added triethylamine (7 μL, 48 μmol) followed by acetyl chloride (3 μL, 48 μmol). The mixture was stirred at room temperature for 2 h. The reaction was then quenched by saturated ammonium chloride. The mixture was extracted with CH_2Cl_2 (3×), dried, and concentrated. The residue was purified by prep-TLC using 5% MeOH−CH_2Cl_2 to give compound **17i** (18 mg, yield 73%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (1H, s), 7.42 (2H, s), 7.36 (1H, s), 7.30 (2H, d, J = 8 Hz), 6.84 (2H, d, J = 8 Hz), 5.73 (1H, br s), 3.89 (1H, d, J = 14 Hz), 3.50−3.20 (5H, m), 2.20−2.05 (2H, m), 2.05 (3H, s) ppm; mass spectrum (ES$^+$) m/z 615 (M + H)$^+$.

Synthesis of Sulfonamides 18a−f (Tables 5). General Procedure III. To a stirred solution of *N*-chlorosuccinimide (1.5 equiv) in THF (10 mL) was added (*R*)-**16** (1.0 equiv) in portions at 0 °C. After the addition, the cooling bath was removed and the mixture was stirred at room temperature for 5 min. An amine R′R″NH (2−5 equiv) was added next. The reaction mixture was stirred for 1 h and quenched with saturated ammonium chloride at 0 °C. The mixture was extracted with EtOAc, washed successively with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography to afford the sulfonamides **18a−f.**

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-5-(piperidinyl-1-sulfonyl)-1*H*-imidazo[1,2-α]imidazol-2-one (18a). Compound **18a** was prepared according to general procedure III, using piperidine as the amine: yield 46%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (2H, s), 7.36 (2H, s), 7.30 (2H, d, J = 8.3 Hz), 6.87 (2H, d, J = 8.3 Hz), 3.89 (1H, d, J = 13.6 Hz), 3.33−3.15 (5H, m), 2.00 (3H, s), 1.78−1.68 (4H, m), 1.62−1.50 (2H, m) ppm; mass spectrum (ES$^+$) m/z 597 (M + H)$^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-5-(morpholinyl-4-sulfonyl)-1*H*-imidazo[1,2-α]imidazol-2-one (18b). Compound **18b** was prepared according to general procedure III, using morpholine as the amine: yield 21%; mp 76.1−77.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (2H, s), 7.40 (1H, s), 7.37 (1H, m), 7.31 (2H, d, J = 7 Hz), 6.86 (2H, d, J = 8.4 Hz), 3.88−3.85 (5H, m), 3.37−3.25 (5H, m), 2.02 (3H, s) ppm; mass spectrum (ES$^+$) m/z 599 (M + H)$^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-(3-hydroxypiperidinyl-1-sulfonyl)-3-methyl-1*H*-imidazo[1,2-α]-imidazol-2-one (18c). Compound **18c** was prepared according to general procedure III, using 3-hydroxypiperidine as the amine: yield 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.30 (6H, m), 6.87 (2H, d, J = 8.2 Hz), 4.00 (1H, br s), 3.86 (1H, d, J = 13.8 Hz), 3.60−3.51 (1H, m), 3.40−3.30 (1H, m), 3.26 (1H, d, J = 13.9 Hz), 3.24−3.06 (2H, m), 2.09 (3H, s), 2.09−1.62 (4H, m) ppm; mass spectrum (ES$^+$) m/z 613 (M + H)$^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-(4-hydroxypiperidinyl-1-sulfonyl)-3-methyl-1*H*-imidazo[1,2-α]-imidazol-2-one (18d). Compound **18d** was prepared according to general procedure III, using 4-hydroxypiperidine as the amine: yield 41%; mp 67.2−68.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (2H, s), 7.40 (1H, s), 7.36 (1H, m), 7.30 (2H, d, J = 8 Hz), 6.87 (2H, d, J = 8.4 Hz), 4.17 (1H, br s), 3.87 (1H, d, J = 13.8 Hz), 3.57−3.50 (3H, m), 3.27−3.24 (3H, m), 2.08−2.00 (2H, m), 2.02 (3H, s), 1.82−1.79 (2H, m) ppm; mass spectrum (ES$^+$) m/z 613 (M + H)$^+$.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-5-(4-oxopiperidinyl-1-sulfonyl)-1*H*-imidazo[1,2-α]imidazol-2-one (18e). Compound **18e** was prepared according to general procedure III, using 4-piperidone as the amine: yield 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (1H, s), 7.32 (2H, s), 7.30 (1H, m), 7.25 (2H, d, J = 8 Hz), 6.82 (2H, d, J = 8 Hz), 3.88 (1H, d, J = 14 Hz), 3.74−3.60 (4H, m), 3.22 (1H, d, J = 14 Hz), 2.65 (4H, m), 1.98 (3H, s) ppm.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-5-(piperazinyl-1-sulfonyl)-1*H*-imidazo[1,2-α]imidazol-2-one (18f). Compound **18f** was obtained according to general procedure III, using piperazine as the amine: yield 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (2H, m), 7.38 (1H, s), 7.36 (1H, m), 7.30 (2H, d, J = 8.3 Hz), 6.86 (2H, d, J = 8.3 Hz), 3.87 (1H, d, J = 14.0 Hz), 3.32−3.24 (5H, m), 3.08−3.03 (4H, m), 1.98 (3H, s) ppm; mass spectrum (CI) m/z 598 (M + H)$^+$.

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Supporting Information Available: Synthetic schemes, experimental procedures, and spectral data for compounds **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Springer, T. A. Adhesion receptors of the immune system. *Nature* **1990**, *346*, 425−434. (b) Gahmberg, C. G. Leukocyte adhesion: CD11/CD18 integrins and intercellular adhesion molecules. *Curr. Opin. Cell Biol.* **1997**, *9*, 643−650. (c) Vazeux, R.; Hoffman, P.; Tomfta, J.; Dkkinson, E.; Jasman, R.; St. John, T. and Gallatin, W. Cloning and characterization of a new intercellular adhesion molecule ICAM-R. *Nature* **1992**, *360*, 485−488.

(2) (a) Fischer, A.; Friedrich, W.; Fasth, A.; Blanche, S.; Le Deist, F.; Girault, D.; Veber, F.; Vossen, J.; Lopez, M.; Griscelli, C. Reduction of graft failure by a monoclonal antibody (anti-LFA-1 CD11a) after HLA nonidentical bone marrow transplantation in children with immunodeficiencies, osteopetrosis, and Fanco-

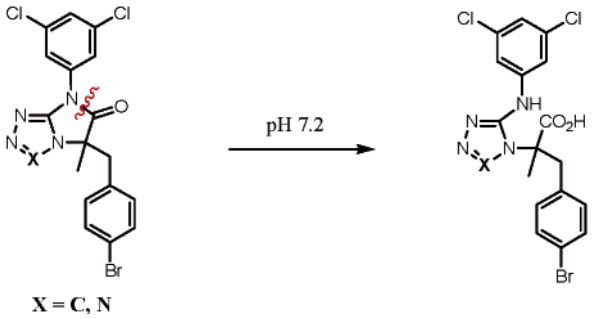
ni's anemia: A European Group for Immunodeficiency/European Group for Bone Marrow Transplantation report. *Blood* **1991**, *77*, 249−256. (b) Hourmant, M.; Le Mauff, B.; Le Meur, Y.; Dantal, J.; Cantarovich, D.; Giral, M.; Caudrelier, P.; Albericci, G.; Soulillou, J. Administration of an anti-CD11a monoclonal antibody in recipients of kidney transplantation: A pilot study. *Transplantation* **1994**, *58*, 377−380. (c) Gottlieb, A.; Krueger, J.; Bright, R.; Ling, M.; Lebwohl, M.; Kang, S.; Feldman, S.; Spellman, M.; Wittkowski, K.; Ochs, H. D.; Jardieu, P.; Bauer, R.; White, M.; Dedrick, R.; Garavoy, M. Effects of administration of a single dose of a humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. *J. Am. Acad. Dermatol.* **2000**, *42*, 428−435. (d) Sanfilippo, P. J.; Jetter, M. C.; Cordova, R.; Noe, R. A.; Chourmouzis, E.; Lau, C. Y. and Wang, E. Novel thiazole based heterocycles as inhibitors of LFA-1/ICAM-1 mediated cell adhesion. *J. Med. Chem.* **1995**, *38*, 1057−1059. (e) Efalizumab (Raptiva), a humanized anti-LFA-1 monoclonal antibody, was approved for the treatment of chronic moderate-to-severe psoriasis in October 2003.

(3) (a) Kelly, T.; Jeanfavre, D.; McNeil, D.; Woska, J.; Reilly, P.; Mainolfi, E.; Kishimoto, K.; Nabozny, G.; Zinter, R.; Bormann, B.-J.; Rothlein, R. Cutting Edge: A Small Molecule Antagonist of LFA-1-Mediated Cell Adhesion. *J. Immunol.* **1999**, *163*, 5173−5177. (b) Last-Barney, K.; Davidson, W.; Cardozo, M.; Frye, L.; Grygon, C.; Hopkins, J.; Jeanfavre, D.; Pav, S.; Qian, C.-g.; Stevenson, J.; Tong, L.; Zindell, R.; Kelly, T. Binding site elucidation of hydantoin-based antagonists of LFA-1 using multidisciplinary technologies: Evidence for the allosteric inhibition of a protein−protein interaction. *J. Am. Chem. Soc.* **2001**, *123*, 5643−5650.

(4) (a) Kelly, T.; et al. To be published. (b) As will be discussed in ref 4a, the 3,5-dichlorophenyl substituent at N_1 is critical for the activity. This precludes the option to improve the solubility by replacing the N_1-dichlorophenyl group. Alternative approaches such as incorporating solubilizing groups therefore are especially relevant in the current work.

(5) The LFA-1/ICAM-1 binding assay, JY cell aggregation assay, and human whole blood SEB/IL-2 assay were performed as previously described; see ref 3a.

(6) Compounds **4** and **5** were hydrolyzed to the corresponding ring-opened acids after 24 h at pH 7.4.

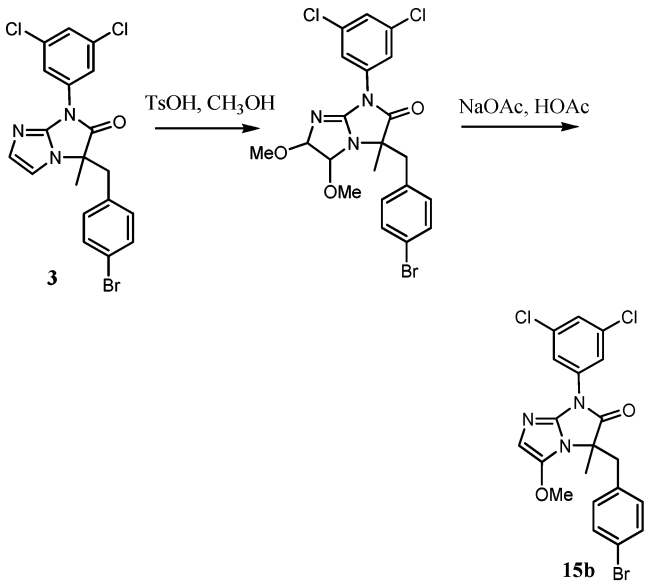


X = C, N

(7) The SAR of the 6,5-bicyclic structure **2** will be the topic of a separate publication.

(8) The details of the chemical synthesis outlined herein will be published in separate papers. Wu, J.-P.; et al. Manuscripts in preparation.

(9) (a) The chemical synthesis of compounds **4** and **5** are provided as Supporting Information. (b) Compound **15b** was synthesized as follows:



(10) The synthesis of the pure enantiomers of amino acid **6** has been previously reported. Yi, N. K. Self-regeneration of stereocenters: A practical enantiospecific synthesis of LFA-1 antagonist BIRT377. *Org. Lett.* **2000**, *2*, 2781−2783.

(11) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. Preparation of highly functionalized Grignard reagents by an iodine−magnesium exchange reaction and its application in solid-phase synthesis. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701−1703.

(12) The sulfinate **16** can be prepared in large quantity (procedure provided in Experimental Section) and stored in refrigerator for months without noticeable degradation.

(13) Rothlein, R.; Springer, T. A. The requirement for lymphocyte function-associated antigen 1 in homotypic leukocyte adhesion stimulated by phorbol ester. *J. Exp. Med.* **1986**, *163*, 1132−1149.

(14) The initial impression from Table 3 was that the OH groups in **17b** or **17c** acted as H-bond donors in a H-bonding interaction. This was proved incorrect by subsequent SAR data.

(15) The fact that the amino derivatives **17g** and **17h** were less potent than the methanesulfonyl derivative (*R*)-**15g** (50 nM) seemed to suggest the presence of positive charges on the protein near the sulfonyl binding site.

(16) (a) A H-bonding interaction where an oxygen atom functioning as a H-bond acceptor cannot be ruled out. (b) There were suggestions that the apparent increase in potency could be the entropic effect due to solvent exclusion. However, the fact that sulfonyl groups similar in size had different effects (compare **17g**,**h** vs **17b**,**d**,**e**,**i**; **18a** vs **18b**,**d**,**e**) and that the interaction has orientational preference (Table 5) argue against this suggestion.

(17) The protein shift assay is a modified binding assay in which 14% of human serum, corresponding to 1% of plasma protein, was added during incubation. The experiment details are otherwise identical to that described in ref 3a.

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