Letters

Discovery and Development of 5-[(5*S*,9*R*)-9-(4-Cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl-methyl]-3-thiophenecarboxylic Acid (BMS-587101)—A Small Molecule Antagonist of Leukocyte Function Associated Antigen-1†

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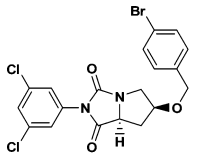
Abstract: LFA-1 (leukocyte function-associated antigen-1), is a member of the β2-integrin family and is expressed on all leukocytes. This letter describes the discovery and preliminary SAR of spirocyclic hydantoin based LFA-1 antagonists that culminated in the identification of analog **8** as a clinical candidate. We also report the first example of the efficacy of a small molecule LFA-1 antagonist in combination with CTLA-4Ig in an animal model of transplant rejection.

Leukocyte function-associated antigen-1 (LFA-1), also known as CD11a/CD18 and $\alpha_L\beta_2$, is a β_2-integrin expressed on all leukocytes.[1] The major ligand for LFA-1 is intercellular adhesion molecule-1 (ICAM-1), which is expressed on the surface of many cell types including endothelial cells and other leukocytes. The LFA-1/ICAM interaction promotes tight adhesion between activated leukocytes and the endothelium, as well as between T cells and antigen-presenting cells. LFA-1 is expressed in a low affinity state on unactivated cells and switches to a high affinity state following cell activation.[2] The amino-terminal region of the CD11a (α_L) subunit of LFA-1 contains an inserted domain (termed the I-domain) that contains both a metal ion-dependent adhesion site (MIDAS) that directly interacts with ICAM-1, and an I-domain allosteric site (IDAS) that indirectly affects the conformation of the MIDAS to regulate the affinity of LFA-1. Specifically, a change in the IDAS, from a closed to an open conformation, results in high affinity LFA-1/ICAM-1 interactions. In vivo studies using anti-LFA-1 antibodies or conducted in LFA-1-deficient mice demonstrate that LFA-1 plays a critical role in leukocyte extravasation in recruitment models.[3]

Clinical trials using the humanized anti-LFA-1 antibody efalizumab, provide excellent proof-of-principle for this target in psoriasis.[4] Because of the strong validation from both animal models and clinical trials, there has been an intense effort to identify orally available small molecule inhibitors of LFA-1 as potential therapeutic agents.[5]

We reported earlier on the design, synthesis, and SAR of bicyclic hydantoins as LFA-1 antagonists **1**.[6] In this letter, we report on the synthesis and SAR of spirocyclic pyrrolidine-based LFA-1 antagonists **3**, which eventually led to the identification of the clinical compound **8** (BMS-587101).



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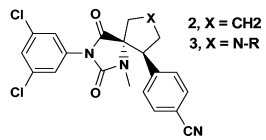

Although spirocyclic hydantoins of type **2** were prepared initially[7] and were potent LFA-1 antagonists (HUVEC[a]: T-cell $IC_{50} = 8 \pm 1$ nM; see Table 1), these compounds were not pursued because of poor physicochemical properties (high log *P*) and profiling issues (CYP inhibition and microsomal stability). The X-ray cocrystal structures of spirocyclic hydantoins of type **2** with the I-domain of LFA-1,[8] revealed that these compounds bind to the IDAS of the I-domain. In addition, the crystal structures also suggested that substituents anchored off the cyclopentane ring system of analog **2**, would project into solvent. Subsequent strategies therefore focused on leveraging the X-ray crystal structure information to optimize the physicochemical and profiling parameters of the spirocyclic hydantoin class of LFA-1 antagonists, while maintaining potency. We reasoned that introducing a nitrogen atom into the cyclopentane ring of analog **2** would give us a handle to introduce various substituents for modulating the potency and physicochemical and profiling parameters of the series. Because extensive SAR in the bicyclic hydantoin **1** and spriocyclic hydantoin **2** series suggested that the 3,5-dichlorophenyl, *N*-methyl, and 4-cyanophenyl moieties to be optimum, the general synthetic protocol for the spirocylic pyrrolidine analogs **3**, as outlined in Scheme 1, is shown with these optimized groups in place.

Knoevenagel condensation of **4** with 4-cyanobenzaldehyde gave the thermodynamically more stable benzylidene hydantoin

† Pdb ID code 2ICA.

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[a] Abbreviations: HUVEC, human umbilical vein endothelial cells; APC, antigen presenting cells; hERG, human ether-a-go-go-related gene.

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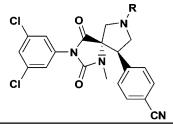
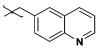
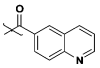
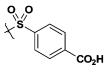
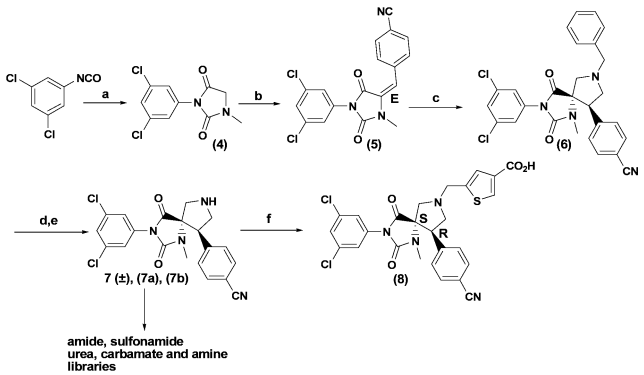
Table 1. In Vitro Potency of Spirocyclic Pyrrolidine Analogs in the HUVEC/T-Cell Adhesion Assay[a]



cmpd	R	HUVEC/T-cell IC50 nM
2		8 ± 1
9		15 ± 2
10		14 ± 2
11		6 ± 1
12		3 ± 1
13		30 ± 7
14		164 ± 27
15		12 ± 2

[a] All compounds are racemic. The relative stereochemistry is shown. IC_{50} values are shown as mean values of three or more determinations.

Scheme 1[a]



[a] Reagents and conditions: (a) sarcosine ethyl ester, NaOH, THF/H_2O, 96%; (b) 4-cyanobenzaldehyde, β-alanine, AcOH, reflux, 35% or 4-cyanobenzaldehyde, pyrrolidine/EtOH, 78 °C 18 h, 85%; (c) *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine, THF, TFA, 0 °C to rt, 18 h, 70%; (d) 1,2-dichloroethane, 1-chloroethyl chloroformate, 5 °C, to rt, 18 h, MeOH, reflux, 3 h, 50−85%; (e) Chiralpak-AD column, CO_2/MeOH, ∼100% desired enantiomer; (f) 5-formyl-3-thiophenecarboxylic acid, $Na(OAc)_3BH$, Na_2SO_4, 1,2-dichloroethane, 75−90%.

5, which crystallized out of the reaction mixture as a single diastereomer having the desired *E*-stereochemistry around the double bond. The double bond geometry is critical in that it dictates the stereochemistry in the subsequent azomethine ylide cycloaddition step with commercially available *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine precursor, to yield compound **6** as a single diasteromer.

N-Debenzylation employing modified Von Braun conditions afforded the des-benzyl analog **7**, which served as an excellent substrate for the generation of a large number of amide, carbamate, sulfonamide, urea, and amine libraries. For the preparation of homochiral analogs, compound **7** was separated into its individual enantiomers using a Chiralpak-AD column under supercritical fluid chromatography (SFC) conditions. Compounds were then tested in a cell−cell-based adhesion assay employing primary human T and endothelial cells. Table 1 outlines the preliminary SAR and in vitro potency of the spirocyclic pyrrolidine-based LFA-1 antagonists in the HUVEC/T-cell adhesion assay (see Supporting Information).

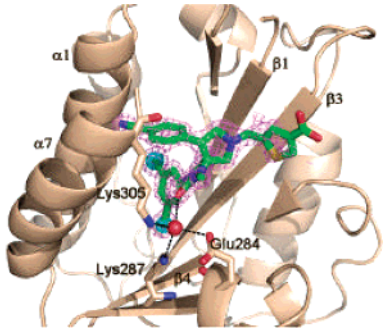


Figure 1. X-ray cocrystal structure of compound **8** with the I-domain of LFA-1. Also shown is the initial electron density (magenta, 2Fo-Fc 1σ; cyan, Fo-Fc 8σ) prior to fitting compound **8**.

The SAR trends from various libraries suggested that a variety of groups anchored off the pyyrolidine nitrogen are tolerated and led to potent LFA-1 antagonists. This was consistent with our hypothesis that groups anchored off the spirocyclic pyrrolidine are projected into solvent and may not be interacting with any specific regions of the protein. Because a number of compounds were active in the cell−cell-based adhesion assay, a second, cell-based, functional assay was employed to progress compounds. Because it is well-known[9] that LFA-1 present on the surface of T cells can mediate adhesion as well as provide optimum costimulatory signals in combination with CD28/CD80 or CD28/CD86 for T-cell proliferation, we evaluated the effect of these compounds on their ability to inhibit APC-dependent T-cell proliferation in vitro using a one-way mixed lymphocyte reaction (MLR) assay (see Supporting Information). Compounds that were active in the MLR assay were then subjected to screening in advanced in vitro profiling assays (CYP inhibition, microsomal stability, hERG, etc.) and pharmacokinetic (PK) analysis. Based on the analysis of the data from a number of compounds in the aforementioned assays, analog **8** emerged as the leading candidate for nomination based on its in vitro/in vivo potency, excellent PK profile in preclinal species and optimal physicochemical and profiling properties (vide infra).

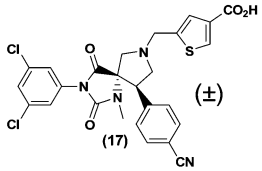
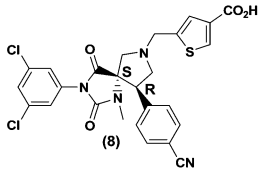
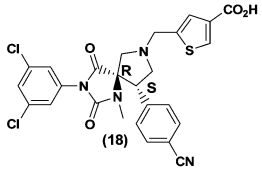
Figure 1 shows the X-ray cocrystal structure of compound **8** complexed with the I-domain of LFA-1 determined at 1.6 Å resolution.

The X-ray crystal structure reveals that most of the interactions of the ligand with the protein are hydrophobic in nature except for the interaction of the urea carbonyl with Lys287, Lys305, and Glu284 via a water molecule. The N-3 dichlorophenyl group occupies a hydrophobic pocket between α-helices 1 and 7 and β-strands 1, 3, and 4. As is evident from the crystal structure, the thiophene carboxylic acid moiety is projected into solvent and does not appear to interact with any residues of the I-domain, thus confirming our earlier hypothesis. The X-ray cocrystal structure also allowed us for the first time to assign the absolute configuration at the spirocyclic carbon atom as (*S*) and at the carbon bearing the 4-cyanophenyl residue as (*R*). This was later confirmed through the single-crystal X-ray analysis for compound **8** using anomalous scattering methods (data not shown).

Table 2 summarizes the in vitro potency of analog **8** and its enantiomer **18** in the human and mouse adhesion assays (HUVEC/T-cell and bEND assays respectively) and the MLR assay.

As is evident from Table 2, **8** is a potent inhibitor of LFA-1-mediated adhesion in the T-cell/HUVEC adhesion assay. Its enantiomer **18** as expected is significantly less potent in this assay. The activity of **8** on APC-dependent T-cell proliferation

Table 2. In Vitro Activity of Compound **8** and Enantiomer **18** in the In Vitro Adhesion and MLR Assays

cmpd.	HUVEC/ T-cell IC_{50} (nM)	bEND IC_{50} (nM)	MLR IC_{50} (nM)
 (±) (17)	21 ± 2	ND[a]	ND[a]
 (8)	20 ± 1	150±15	280±20
 (18)	320 ± 125	3000 ± 1300	ND[a]

[a] Not determined.

Table 3. PK Parameters for Compound **8** in Mouse and Dog

parameter	mouse[a]	dog[b]
po dose (mg/kg)	1[c]	10[d]
iv dose (mg/kg)	1[c]	5[d]
C_{max} (μM), po	0.083	18.9 ± 2.7
T_{max} (h), po	0.25	2.0 ± 0.0
AUC (μM × h), po	0.306[e]	115 ± 2[f]
$t_{1/2}$ (h), iv	5.4	3.5 ± 1.0
MRT (h), iv	4.4	3.3 ± 1.1
Cl (mL/min/kg), iv	32	3.6 ± 0.5
V_{ss} (L/kg), iv	8.5	0.7 ± 0.1
F_{po} (%)	41	100

[a] Composition serum concentration-time profiles were constructed for the PK analysis. [b] Average of three animals with associated standard deviations. [c] Vehicle: 15% pluronic F-68 in water. [d] Vehicle: PEG400 + water (1:1). [e] $AUC_{(0-8h)}$. [f] $AUC_{(0-24h)}$.

was evaluated in vitro using a one-way MLR assay. In contrast to the adhesion assay, the MLR assay was conducted in the presence of 10% serum. In this assay, **8** is a moderately potent inhibitor of LFA-1-mediated T-cell proliferation, with an IC_{50} of 280 ± 20 nM. During the course of our studies, it became clear that many of our program compounds exhibited a greater potency toward inhibition of human LFA-1 vs rodent LFA-1.[10] Because of these cross species issues with LFA-1 antagonists, we introduced a mouse−specific adhesion assay that employed mouse splenocytes and a mouse ICAM-1 expressing cell line, bEND.3, into our screening strategy (see Supporting Information). Analog **8** was among the first compounds in the spirocyclic pyrrolidine series of LFA-1 antagonists to show activity in this assay, with an IC_{50} of 150 ± 15 nM—about 7−10-fold higher than in the human T-cell/HUVEC adhesion assay.

The moderate potency of analog **8** in the in vitro mouse adhesion assay, good PK in several preclinical species (mouse and dog PK shown in Table 3), and a very clean profile in various in vitro profiling assays (partial list shown in Table 4) prompted us to test the compound in two in vivo models of inflammation.

Two different in vivo models were chosen to address two important aspects of LFA-1 function, leukocyte recruitement,

Table 4. Partial In Vitro Profiling Data for Compound **8**

parameter	result
metabolism	Low turnover rates in liver microsomes and hepatocytes (m, h, d, r, and c)[a]
CYP inhibition[b]	>40 μM 1A2, 2C9, 2C19, 2D6, 3A4
mutagenicity	Ames negative
hERG	24% inhib. @ 30 μM

[a] m = mouse, h = human, d = dog, r = rat, c = cynomolgus monkey. [b] CYP = cytochrome P450.

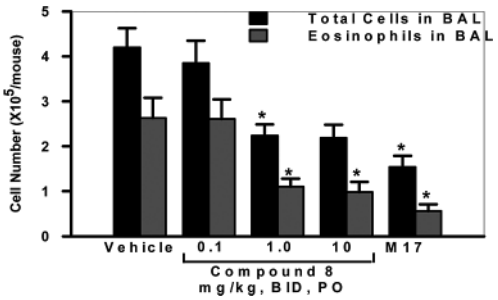


Figure 2. In vivo activity of compound **8** in the mouse ovalbumin-induced lung inflammation model.

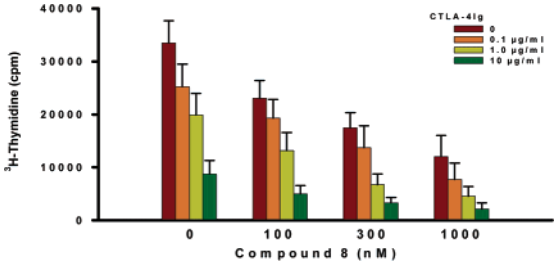


Figure 3. Compound **8** in combination with CTLA-4Ig inhibits proliferation in a primary MLR.

and T-cell activation: (i) a mouse ovalbumin-induced lung inflammation model and (ii) a mouse heart-to-ear nonvascularized allograft transplant model.

In the mouse ovalbumin-induced lung inflammation model, the ability of compound **8** to block eosinophil accumulation in airways as measured in bronchoalveolar lavage (BAL) fluid was evaluated at 0, 0.1, 1.0, and 10 mg/kg. Significant inhibition ($p < 0.05$ vs vehicle) of eosinophil accumulation was seen at doses of 1.0 mg/kg BID (Figure 2), which was similar to that seen with the antimouse LFA-1 antibody, M17, that was used as the positive control in the experiment. As expected, analog **18**, the enantiomer of analog **8**, was significantly less-potent in this assay, being active only at 50 mg/kg BID (data not shown).

It is well-documented in the literature that LFA-1 plays a central role in the formation and maintenance of the immunological synapse,[9] and an appreciation of the role of LFA-1 as a costimulatory molecule has increased as the characteristics of its function have become better understood. For example, the combination of cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin fusion protein (CTLA-4Ig) with an antimouse LFA-1 antibody has been reported to induce long-term acceptance of cardiac and skin allograft survival.[11,12]

This is consistent with the finding that optimal costimulation of naïve $CD4^+$ T cells in vitro occurs when both B7 and ICAM-1 on APCs are engaged.[13] Consistent with these findings, compound **8** in combination with CTLA-4Ig demonstrated an additive effect in an in vitro MLR response (Figure 3). More importantly, in the in vivo mouse heart-to-ear nonvascularized allograft transplant model,[14] the combination of compound **8** dosed 100 mg/kg BID with a suboptimal dose of CTLA-4Ig

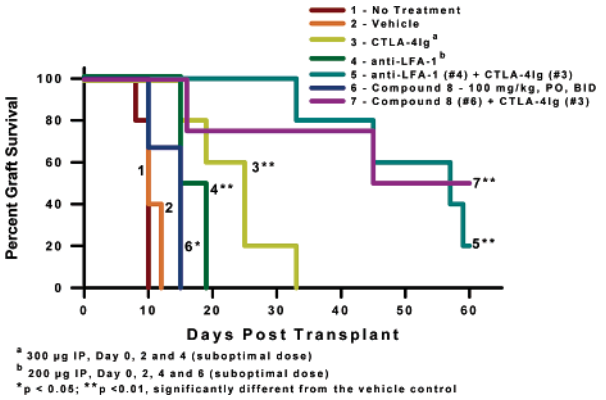


Figure 4. In vivo activity of compound **8** in a mouse cardiac allograft transplant model, with C57BL/6 mice as donors and BALB/c mice as recipients.

increased graft survival substantially beyond that seen with compound **8** or CTLA-4Ig alone (Figure 4). This is similar to the synergy we observed with CTLA-4Ig using a suboptimal dosing regimen of anti-LFA-1 antibody. To the best of our knowledge, this represents the first example of the efficacy of a small molecule LFA-1 antagonist in combination with a CD28 dependent costimulation blocker (CTLA-4Ig) in an animal model of transplant rejection.

In summary, a novel series of spirocyclic pyrrolidine-based LFA-1 antagonists have been identified. Structure−activity relationship studies led to the discovery of 5-[(5*S*,9*R*)-9-(4-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl-methyl]-3-thiophenecarboxylic acid **8**, which showed efficacy in in vivo models of inflammation. On the basis of its excellent in vitro potency, in vivo activity, PK, and safety profile, compound **8** was advanced into clinical trials.[15]

Supporting Information Available: Experimental procedures and characterization data for compounds **4**−**18**. Table of combustion analysis or HPLC analysis data for key compounds. Detailed description of pharmacological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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