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Discovery of tetrahydroisoquinoline (THIQ) derivatives as potent and orally bioavailable LFA-1/ICAM-1 antagonists

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ABSTRACT

This letter describes the discovery of a novel series of tetrahydroisoquinoline (THIQ)-derived small molecules that potently inhibit both human T-cell migration and super-antigen induced T-cell activation through disruption of the binding of integrin LFA-1 to its receptor, ICAM-1. In addition to excellent in vitro potency, **6q** shows good pharmacokinetic properties and its ethyl ester (**6t**) demonstrates good oral bioavailability in both mouse and rat. Either intravenous administration of **6q** or oral administration of its ethyl ester (**6t**) produced a significant reduction of neutrophil migration in a thioglycollate-induced murine peritonitis model.

Integrin-mediated, cell–cell adhesive interactions between leukocytes and endothelial cells effect both T-cell trafficking, migration, priming, and activation, and as such are believed to be critical to the initiation and maintenance of immune responses.[1–3] A heterodimeric member of the β_2 family of integrins, leukocyte function-associated antigen-1 (LFA-1, $\alpha_L\beta_2$, CD11a/CD18) plays a key role in inflammation and other T-cell specific immune responses through mediating cell adhesion, leukocyte extravasation and migration, antigen presentation, and augmentation of T-cell receptor signaling.[4] The interaction between LFA-1 and intercellular adhesion molecule-1 (ICAM-1, CD54) is implicated in numerous immunoregulatory diseases, such as graft rejection, arthritis, and psoriasis. In vivo studies using anti-LFA-1 antibodies or LFA-1-deficient mice suggest that inhibition of the binding of LFA-1 to ICAM-1 has the potential for treating these diseases.[5–10] In 2003, humanized monoclonal anti-LFA-1 antibody efalizumab (Raptiva®) was approved for the treatment of psoriasis, and was reported to be effective in the treatment of transplant rejection.[11] Thus, the efficacy of efalizumab provides an important proof-of-principle for LFA-1 as a viable therapeutic target. However, efalizumab had to be administered by subcutaneous injection and was expensive to produce. Also, long term use of efalizumab has caused undesirable side effects.[12] Therefore, discovery of small molecule-based LFA-1 antagonists[13–21] has been the subject of an extensive commitment by the pharmaceutical industry.

A variety of potent small molecules (Fig. 1) have been reported to bind to either direct[16d] or allosteric (IDAS)[13–15] competitive binding sites within LFA-1's inserted I-domain. For example, ^{1}H NMR or a combination of immunochemical and molecular modeling studies showed hydantoin derivatives, such as **1**[13a] and **2**,[14b] and diphenyl sulfide analog, such as **3**,[15a] bind at the IDAS. In contrast, a fluorescein labeling study demonstrated that *N*-benzoyl amino derivative **4** directly inhibits the interaction of LFA-1 and ICAM-1 by binding to a high-affinity site on LFA-1. This binding site overlaps with the ICAM-1 binding site on the α-subunit of LFA-1, which has previously been localized to the I-domain.[16d] Many of these small molecules have excellent in vitro and in vivo properties. Moreover, an antagonist (**IC747**)[22] related to **3** was advanced as far as Phase IIb human clinical trials in patients with moderate to severe psoriasis. Herein, we present the discovery of a novel series of tetrahydroisoquinoline (THIQ)-derived antagonists that potently inhibit the adhesion of human lymphoma T-cells (Hut-78 cells) to immobilized ICAM-1. This inhibition results from disruption of the binding of LFA-1 to ICAM-1, since LFA-1 is the dominant ICAM-1 binding integrin expressed on the surface of Hut-78 cells.[1]

In comparison to those reported I-domain allosteric compounds, direct competitive antagonists seemed to have considerably better in vitro potency as suggested by those *N*-benzoyl

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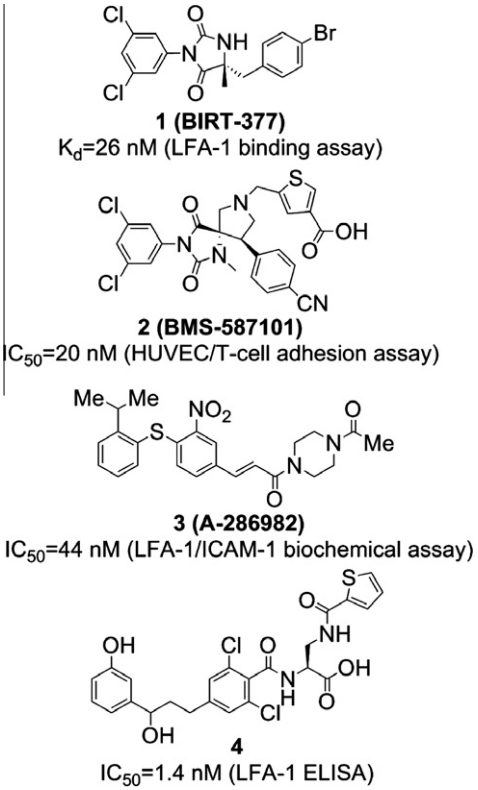


Figure 1. Representative LFA-1/ICAM-1 antagonists.

amino acid-derived analogs.[16a] Moreover, the binding site of these direct competitive LFA-1 antagonists was a newly identified one and no compounds that bind to this site had been advanced to clinical trials when we initiated this project.[23] Therefore, the direct competitive binding site represented an attractive binding site to allow us develop novel LFA-1 antagonists.

In addition to **4**,[16a] Burdick et al.[24] disclosed a number of new scaffolds, including **5** (Fig. 2), using an amide bond instead of an alkyl chain to connect the 'left-wing' and the central 4-substituted-2,6-dichlorobenzoic acid moiety. As suggested by the superimposed structure of **4** on the crystal structure of the first domain of ICAM-1[13a,16a] and SAR of derivatives related to **4** and **5**, the 'left-wing' and 'right-wing' are two key binding fragments to the protein; the central 2,6-dichlorobenzoyl moiety is critical to define

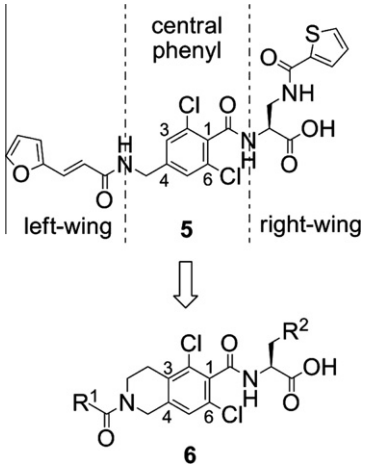


Figure 2. Evolution of novel THIQ-derived LFA-1/ICAM-1 antagonists.

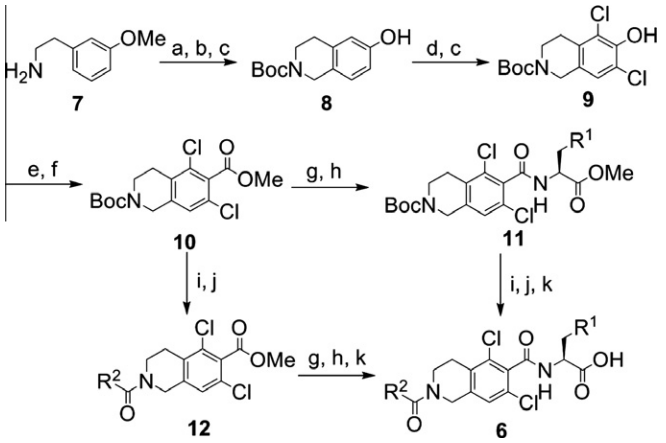
a preferred conformation of 'right-wing'; and various linkages can be tolerated to connect the 'left-wing' to the central functionalized phenyl moiety without affecting the potency of binding affinity.[16a,24] Hence, we designed a novel series of LFA-1 antagonists using a bicyclic tetrahydroisoquinoline (THIQ) central scaffold to link both 'left-wing' and 'right-wing'. As shown in Figure 2, assumed the amide bond of **5** was not critical to the binding affinity, its –NH could be cyclized with the phenyl residue at C3 position to give a novel series of THIQ-derived LFA-1 antagonists (**6**)[25] (Fig. 2).

Preparations of the THIQ scaffold and its derivatives as LFA-1 antagonists were carried out as shown in Scheme 1. Commercially available **7** was refluxed with aqueous formaldehyde (37 wt %) under an acidic condition,[26] followed by treatment with 48% aqueous HBr[27] and subsequent *N*-Boc protection, to give **8** in quantitative yield. Reaction of **8** and surfuryl chloride in acetic acid and *N*-Boc protection afforded **9** in 85% yield. Subsequently, **9** was converted to its corresponding triflate, which underwent a palladium-catalyzed carbonylation to generate **10** in 56% yield. Finally, **6a–t** bearing various R^1 and R^2 moieties were readily assembled via either **11** or **12** by employing different sequences of Boc-deprotection, amide formation, and saponification.

Compounds **6a–t** were first evaluated in a cellular adhesion assay by measuring inhibition of the binding of Hut-78 cells to immobilized ICAM-1.[25] Compounds demonstrating good potency (IC_{50} $\leqslant$100 nM) were subsequently evaluated in a Staphylococcal Enterotoxin B (SEB)-stimulated T-cell activation assay in the presence of 10% fetal bovine serum (FBS).[28] Reduced activities in SEB assay relative to Hut-78 assay were anticipated partly due to potential serum protein bindings.[29] Compounds showing potent antagonism of LFA-1/ICAM-1 interaction in Hut-78 assay ($\leqslant$30 nM) and good inhibition of T-cell activation in SEB assay ($\leqslant$500 nM) were advanced into pharmacokinetic (PK) profiling in rat.

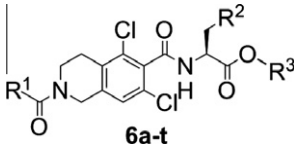
As expected, **6a** shows good potency in Hut-78 assay (Table 1, entry 1). Although **6a** is less potent than the corresponding reference compound **5** (IC_{50} = 0.005 μM in Hut-78 assay), it demonstrates THIQ is a viable scaffold. Encouraged by this positive result, we initiated SAR study to understand the impact of R^1 and R^2 on the potency.

Interestingly, the (*E*)-(2-furyl)vinyl residue of **6a** can be readily replaced with an un-substituted phenyl moiety (**6b**) (entry 2) without affecting the activity in Hut-78 assay. Also, **6b** shows reasonably good potency in SEB assay. Next, SAR on the phenyl residue was performed. In general, *ortho*-substitution on the phenyl



Scheme 1. Reagents and conditions: (a) 37 wt % aq formaldehyde, 1.0 N aq HCl, reflux; (b) HBr (48%), reflux, 16 h; (c) Boc_2O, 2 M aq Na_2CO_3, THF, rt, 5 h; (d) SO_2Cl_2 (3 equiv), AcOH/DCM, 0 °C to rt, 16 h; (e) Tf_2O, py/DCM, 0 °C to rt, 4 h; (f) $Pd(OAc)_2$ (0.1 equiv), dppp (0.1 equiv), CO (1 atm), TEA, DMF/MeOH, 65–70 °C, 14 h; (g) LiI (10 equiv), py, 100 °C; (h) amino acid methyl ester, HATU, DIEA, DMF, rt, 16 h; (i) TFA, DCM, rt; (j) R^2COOH, HATU, DIEA, DMF, 45 °C; (k) LiOH, THF/H_2O, rt.

Table 1
In vitro and in vivo properties of **6a–t**



6a-t

Entry	Compd	R^1	R^2	R^3	Hut-78 IC_{50}[a] (μM)	SEB-10% FBS[b] IC_{50} (μM)	Rat iv PK[c]		
							$t_{1/2}$ (h)	CL (mL/min/kg)	AUC (h ∗ ng/mL)
1	**6a**	(*E*)-(2-Furyl)vinyl	–NHCO(2-thienyl)	H	0.025	—[d]	—	—	—
2	**6b**	Phenyl	–NHCO(2-thienyl)	H	0.079	1.2	—	—	—
3	**6c**	2-Methylphenyl	–NHCO(2-thienyl)	H	0.46	—	—	—	—
4	**6d**	3-Methylphenyl	–NHCO(2-thienyl)	H	0.090	—	—	—	—
5	**6e**	4-Methylphenyl	–NHCO(2-thienyl)	H	0.010	1.6	—	—	—
6	**6f**	3-Chlorophenyl	–NHCO(2-thienyl)	H	0.066	0.24	1.1	>60	120
7	**6g**	4-Chlorophenyl-	–NHCO(2-thienyl)	H	0.022	0.43	1.4	31	580
8	**6h**	4-Chlorophenyl-	$–NH_2$	H	>1.0	—	—	—	—
9	**6i**	4-Chlorophenyl-	–NHAc	H	0.62	—	—	—	—
10	**6j**	4-Chlorophenyl-	–NHCO*c*-Hex	H	0.54	—	—	—	—
11	**6k**	4-Chlorophenyl-	–NHCOPhenyl	H	0.029	0.55	0.7	>60	487
12	**6l**	4-Chlorophenyl-	–NHCO(2-furyl)	H	0.051	3.8	—	—	—
13	**6m**	4-Chlorophenyl-	-3-Hydroxyphenyl	H	>1.0	—	—	—	—
14	**6n**	4-Chlorophenyl-	-3-Indolyl	H	0.81	—	—	—	—
15	**6o**	Methyl	–NHCO(2-thienyl)	H	>1.0	—	—	—	—
16	**6p**	*c*-Hex	–NHCO(2-thienyl)	H	>1.0	—	—	—	—
17	**6q**	6-Benzofuryl	–NHCO(2-thienyl)	H	0.009	0.26	3.0	3.2	5495
18	**6r**	[2,3]-*2H*-6-Benzofuryl	–NHCO(2-thienyl)	H	0.013	0.65	1.1	19	4867
19	**6s**	2-Benzofuryl	–NHCO(2-thienyl)	H	0.005	0.069	1.5	>60	1260
20	**6t**	6-Benzofuryl	–NHCO(2-thienyl)	Et	—	—	2.8[e]	5.0[e]	16,850[e]

[a] The IC_{50} value is an average of three titrations with eight concentration points.
[b] Fetal bovine serum.
[c] PK experiments were carried out with a single dose of 5 mg/kg of a testing compound using a group of three male Sprague–Dawley rats.
[d] Not determined.
[e] The compound was administered in ester form, which was rapidly hydrolyzed in vivo to parent acid **6q**, so the data presented are for measured **6q**.

residue has a negative effect on the potency (entry 3) while both *meta*- and *para*-substitutions can be tolerated (entries 4–7). Rat intravenous (iv) PK profiling indicates that the *p*-Cl substituted analog (**6g**) (entry 7) has better PK properties than the corresponding *m*-Cl substituted analog (**6f**) (entry 6). For these L-2,3-diaminopropionic acid (DAP) derived analogs, the free β-amine residue is preferred to be capped as an aromatic amide instead of an aliphatic amide (entries 8–12). Predictably, the thienyl residue of **6g** could be replaced with a phenyl group (**6k**) to maintain the potency (entry 11); however, **6k** showed an inferior rat iv PK profile to that of **6g**. Additionally, replacement of the thienyl moiety of **6g** with a furyl residue was tolerated in Hut-78 assay, but there was a significant decrease of the potency in SEB assay. It is worth mentioning that initial attempts to replace DAP with other amino acids with less peptide characteristics were not fruitful (entries 13–14).

With **6g** in hand, our efforts were then directed to further study the SAR of 'left-wing' residue R^1. In general, aliphatic residues showed reduced potency relative to aromatic ones (entries 15–16). When a fused 6-benzofuryl moiety (**6q**) was used, significant improvement of the potency in Hut-78 assay was observed (entry 17). Moreover, the corresponding saturated dihydrobenzofuran derivative (**6r**) demonstrated comparable potency in both Hut-78 and SEB assays (entry 18); however, its rat iv PK profile was inferior to that of **6q**. Although substantial improvement of the potency in SEB assay was achieved by replacing the 6-benzofuryl residue of **6q** with a 2-benzofuryl moiety (**6s**), the rat iv PK profile of **6s** was unfavorable (entry 19).

The SAR on both 'left-wing' and 'right-wing' of these THIQ-derived LFA-1/ICAM-1 antagonists is similar to those compounds disclosed by Burdick et al.[16a–c] suggesting they have similar binding mode to LFA-1.

Poor cellular permeability was found with these THIQ-derived analogs bearing a DAP residue, possibly due to the presence of a free carboxylic acid moiety.[30] Therefore, a prodrug strategy was then applied to improve the oral bioavailability of **6q**. Compound **6q** was subsequently converted to its ethyl ester (**6t**), which showed significant improvement of cell permeability relative to **6q**, determined by MDCK assay (P_{app} 8.5×10^{-6} cm/s (A/B) and 10×10^{-6} cm/s (B/A) for **6t**; and P_{app} 0.34×10^{-6} cm/s (A/B) and 0.3×10^{-6} cm/s (B/A) for **6q**). After iv administration of **6t** in rat, only parent acid **6q** was detected in the blood samples from the PK study. Interestingly, even though the ethyl ester was rapidly hydrolyzed in vivo, significantly enhanced rat iv PK profile was observed for **6t** when compared to **6q** (entry 20 vs entry 17, Table 1), with a much higher area under the curve (AUC) while maintaining similar half life ($t_{1/2}$) and clearance (CL). Possibly, the ethyl ester prodrug (**6t**) has wider distribution in rat than the free carboxylic acid (**6q**) after iv administration.

More importantly, **6t** is orally bioavailable in both mouse ($F = 27\%$ at 20 mg/kg and $F = 31\%$ at 100 mg/kg) and rat ($F = 18\%$ at 20 mg/kg), and demonstrates dose-linear PK profiles in mouse (Table 2).

Finally, the in vivo efficacy of **6q** and **6t** was evaluated with a thioglycollate-induced murine peritonitis model.[31] Compound **6q** was intravenously administrated in one experiment, while its ethyl

Table 2
Oral PK profiles of **6t** in rat and mouse[a,b]

Species	Dose (mg/kg)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h ∗ ng/mL)	F (%)
Rat	20	0.8	3395	13,853	18
Mouse	20	0.8	2117	5545	27
Mouse	100	1	8460	31,895	31

[a] PK experiments were carried out using male Sprague–Dawley rats or female C57BL/6 mice administrated orally with a single given dose of **6t**.
[b] Compound **6t** was rapidly hydrolyzed in vivo to parent acid **6q**, so the data presented are for measured **6q**.

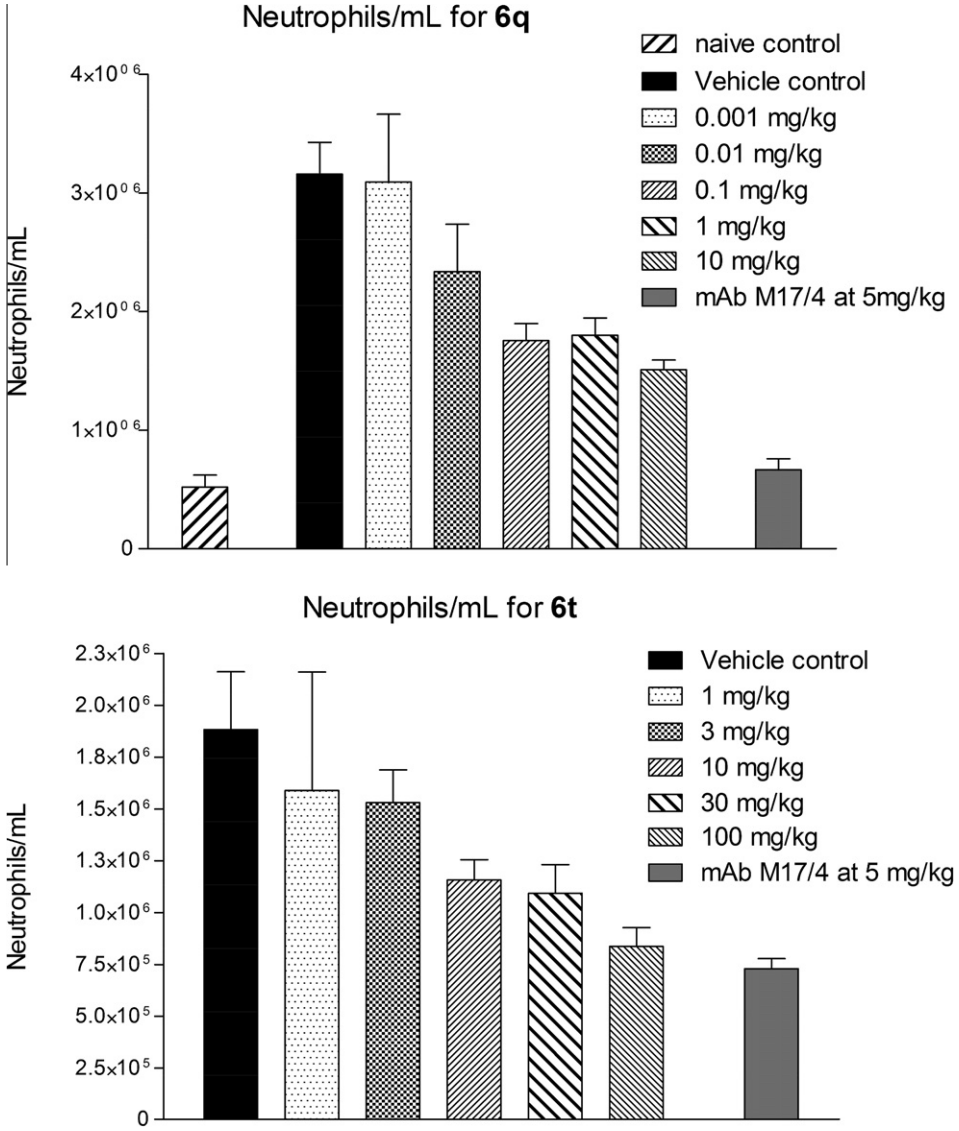


Chart 1. Efficacy of **6q** and its ethyl ester (**6t**) in a thioglycollate-induced murine peritonitis model. Experiments were carried out using a group of eight female c57Bl/6 mice administrated iv for **6q** and po for its ethyl ester (**6t**) at different levels 15 min prior to intraperitoneal (ip) injection of thioglycollate. Blood samples were collected 4 h post ip injection of thioglycollate and neutrophils were counted.

ester prodrug (**6t**) was orally dosed in parallel. For comparison, a murine LFA-1 antibody, mAb M 17/4, was dosed at 5 mg/kg as a positive control. As shown in Chart 1, preliminary data indicated that both **6q** and its ethyl ester prodrug (**6t**) had dose-dependent inhibition of neutrophil recruitment with ED_{50}'s of 0.038 mg/kg and 6.4 mg/kg, respectively.

In summary, we successfully discovered a novel series of tetrahydroisoquinoline (THIQ)-derived LFA-1/ICAM-1 antagonists. Compound **6q** not only has good in vitro potency and PK parameters, but also possesses encouraging in vivo efficacy in a thioglycollate-induced murine peritonitis model. Its ethyl ester prodrug (**6t**) demonstrates moderate oral bioavailability in both mouse and rat. The discovery of **6q** and its ethyl ester prodrug (**6t**) has justified further studies of this novel series of potent LFA-1/ICAM-1 antagonists.

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References and notes

1. Butcher, E. C. *Cell* **1991**, *67*, 1033.
2. Springer, T. A. *Annu. Rev. Physiol.* **1995**, *57*, 827.
3. Ali, H.; Haribabu, B.; Richardson, R. M.; Snyderman, R. *Med. Clin. North Am.* **1997**, *81*, 1.
4. Gahmberg, C. G. *Curr. Opin. Cell Biol.* **1997**, *9*, 643.
5. Bevilacqua, M. P.; Nelson, R. M.; Mannori, G. *Annu. Rev. Med.* **1994**, *45*, 361.
6. Huang, Y.-W.; Baluna, R.; Visetta, E. S. *Histol. Hitopathol.* **1997**, *12*, 467.
7. Cornejo, C. J.; Winn, R. K.; Harlan, J. M. *Adv. Pharmacol.* **1997**, *39*, 99.
8. Henricks, P. A.; Nijkamp, F. P. *Eur. J. Pharmacol.* **1998**, *344*, 1.
9. Yusuf-Makagiansar, H.; Anderson, M. E.; Yakovleva, T. V.; Murray, J. S.; Siahaan, T. J. *Med. Res. Rev.* **2002**, *22*, 146.
10. Nicolls, M. R.; Gill, R. G. *Am. J. Transplant.* **2006**, *6*, 27.
11. (a) Dedrick, R. L.; Walicke, P.; Garovoy, M. *Transpl. Immunol.* **2002**, *9*, 181; (b) Cather, J. C.; Cather, J. C.; Menter, A. *Expert Opin. Biol. Ther.* **2003**, *3*, 361.
12. Post-market findings have shown that long term use of efalizumab causes severe side effects, including lymphoma, meningitis, progressive multifocal leukoencephalopathy (PML), and sepsis etc. Recently, Genentech, the manufacturer of the efalizumab, announced that it has begun a voluntary, phased withdrawal of the product from the US market. For more information, see http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149561.htm.
13. (a) Kelly, T. A.; Jeanfavre, D. D.; McNeil, D. W.; Woska, J. R., Jr.; Reilly, P. L.; Mainolfi, E. A.; Kishimoto, K. M.; Nabozny, G. H.; Zinter, R.; Bormann, B.-J.; Rothlein, R. *J. Immunol.* **1999**, *163*, 5173; (b) Last-Barney, K.; Davidson, W.; Cardozo, M.; Frye, L. L.; Grygon, C. A.; Hopkins, J. L.; Jeanfavre, D. D.; Pav, S.;

Qian, C.; Stevenson, J. M.; Tong, L.; Zindell, R.; Kelly, T. A. *J. Am. Chem. Soc.* **2001**, *123*, 5643; (c) Panzenbeck, M. J.; Jeanfavre, D. D.; Kelly, T. A.; Lemieux, R.; Nabozny, G.; Reilly, P. L.; Desai, S. *Eur. J. Pharmacol.* **2006**, *534*, 233; (d) Caviness, G. O.; Labadia, M. E.; Giblin, P. A.; Woska, J. R., Jr.; Last-Barney, K.; Jeanfavre, D. D.; Morelock, M. M. *Biochem. Phacmacol.* **2007**, *74*, 98.

14. (a) Potin, D.; Launay, M.; Nicolai, E.; Fabreguette, M.; Malabre, P.; Caussade, F.; Besse, D.; Skala, S.; Stetsko, D. K.; Todderud, G.; Beno, B. R.; Cheney, D. L.; Chang, C. J.; Sheriff, S.; Hollenbaugh, D. L.; Barrish, J. C.; Iwanowicz, E. J.; Suchard, S. J.; Murali Dhar, T. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1161; (b) Potin, D.; Launay, M.; Monatlik, F.; Malabre, P.; Fabreguettes, M.; Fouquet, A.; Maillet, M.; Nicolai, E.; Dorgeret, L.; Chevallier, F.; Besse, D.; Dufort, M.; Caussade, F.; Ahmad, S. Z.; Stetsko, D. K.; Skala, S.; Davis, P. M.; Balimane, P.; Patel, K.; Yang, Z.; Marathe, P.; Postelneck, J.; Townsend, R. M.; Goldfarb, V.; Sheriff, S.; Einspahr, H.; Kish, K.; Malley, M. F.; DiMarco, J. D.; Gougoutas, J. Z.; Kadiyala, P.; Cheney, D. L.; Tejwani, R. W.; Murphy, D. K.; Mcintyre, K. W.; Yang, X.; Chao, S.; Leith, L.; Xiao, Z.; Mathur, A.; Chen, B.-C.; Wu, D.-R.; Traeger, S. C.; McKinnon, M.; Barrish, J. C.; Robl, J. A.; Iwanowicz, E. J.; Suchard, S. J.; Murali Dhar, T. G. *J. Med. Chem.* **2006**, *49*, 6946; (c) Dodd, D. S.; Sheriff, S.; Chang, C. J.; Stetsko, D. K.; Phillips, L. M.; Zhang, Y.; Launay, M.; Potin, D.; Vaccaro, W.; Poss, M. A.; McKinnon, M.; Barrish, J. C.; Suchard, S. J.; Murali Dhar, T. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1908; (d) Tran, S. B.; Maxwell, B. D.; Chen, S.-Y.; Bonacorsi, S. J.; Leith, L.; Ogan, M.; Rinehart, J. K.; Balasubramanian, B. *J. Labelled Compd. Rad.* **2009**, *52*, 236.
15. (a) Liu, G.; Link, J. T.; Pei, Z.; Reilly, E. B.; Leitza, S.; Nguyen, B.; Marsh, K. C.; Okasinski, G. F.; von Geldern, T. W.; Ormes, M.; Fowler, K.; Gallatin, M. *J. Med. Chem.* **2000**, *43*, 4025; (b) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, R.; DeVries, P.; Leitza, S.; Reilly, E. B.; Okasinski, G. F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202; (c) Pei, Z.; Xin, Z.; Liu, G.; Li, Y.; Reilly, E. B.; Lubbers, N. L.; Huth, J. R.; Link, J. T.; von Geldern, T. W.; Cox, B. F.; Leitza, S.; Gao, Y.; Marsh, K. C.; DeVries, P.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 2913; (d) Winn, M.; Reilly, E. B.; Liu, G.; Huth, J. R.; Jae, H.-S.; Freeman, J.; Pei, Z.; Xin, Z.; Lynch, J.; Kester, J.; von Geldern, T. W.; Leitza, S.; DeVries, P.; Dickinson, R.; Mussatto, D.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 4393; (e) Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973; (f) Wang, G. T.; Wang, S.; Gentles, R.; Sowin, T.; Leitza, S.; Reilly, E. B.; von Geldern, T. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 195.
16. (a) Gadek, T. R.; Burdick, D. J.; McDowell, R. S.; Stanley, M. S.; Marsters, J. C., Jr.; Paris, K. J.; Pare, D. A.; Reynolds, M. E.; Ladner, C.; Zioncheck, K. A.; Lee, W. P.; Gribling, P.; Dennis, M. S.; Skelton, N. J.; Yumas, D. B.; Clark, K. R.; Keatinh, S. M.; Beresini, M. H.; Tilley, J. W.; Presta, L. G.; Bodary, S. C. *Science* **2002**, *295*, 1086; (b) Burdick, D. J.; Paris, K.; Weese, K.; Stanley, M.; Beresini, M.; Clark, K.; McDowell, R. S.; Marsters, J. C., Jr.; Gadek, T. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1015; (c) Burdick, D. J.; Marsters, J. C., Jr.; Aliagas-Martin, I.; Stanley, M.; Beresini, M.; Clark, K.; McDowell, R. S.; Gadek, T. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2055; (d) Keating, S. M.; Clark, K. R.; Stefanich, L. D.; Arellano, F.; Edwards, C. P.; Bodary, S. C.; Spencer, S. A.; Gadek, T. R.; Marsters, J. C., Jr.; Beresini, M. H. *Protein Sci.* **2006**, *15*, 290; (e) Khojasteh, S. C.; Leipold, D. D.; Lai, F.; La, H.; Baumgardner, M. J.; Desino, K. E.; Gudmundsson, O. S.; Bloedow, D. C.; Bodary, S. C.; Reynolds, M. E.; Gadek, T. R.; Kenkare-Mitra, S. *Xenobiotica* **2008**, *38*, 340.
17. Wattanasin, S.; Albert, R.; Ehrhardt, C.; Roche, D.; Sabio, M.; Hommel, U.; Welzenbach, K.; Weitz-Schmidt, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 499.
18. Wattanasin, S.; Kallen, J.; Myers, S.; Guo, Q.; Sabio, M.; Ehrhardt, C.; Albert, R.; Hommel, U.; Weckbecker, G.; Welzenbach, K.; Weitz-Schmidt, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1217.
19. Shoda, M.; Harada, T.; Yano, K.; Stahura, F. L.; Himeno, T.; Shiojiri, S.; Kogami, Y.; Kouji, H.; Bajorath, J. *ChemMedChem* **2007**, *2*, 515.
20. Shimaoka, M.; Springer, T. A. *Nat. Rev. Drug Discov.* **2003**, *2*, 703.
21. Liu, G. *Expert Opin. Ther. Pat.* **2001**, *11*, 1383.
22. Gniadecki, R.; Zachariae, C.; Calverley, M. *Acta Derm. Venereol.* **2002**, *82*, 401.
23. There were no LFA-1 antagonists derived from *N*-benzoyl amino acid advanced to clinical trials reported when we initiated this program in late 2002. SARCode, Inc. in-licensed Sunesis Pharmaceuticals, Inc.'s LFA-1 program in 2007 and has recently completed two Phase II clinical trials of SAR 1118 in patients with dry eyes and/or allergic conjunctivitis. For related press release, please see http://www.sarcode.com/news.html and for information on clinical trial status of SAR 1118, please see http://clinicaltrials.gov/ct2/results?term=SAR+1118.
24. (a) Burdick, D. J. WIPO Patent Appl. WO1999/49856; (b) Burdick, D. J.; Gadek, T. R.; Marsters, J. C., Jr.; Oare, D.; Reynolds, M. E.; Stanley, M. S. WIPO Patent Appl. WO2002/059114.
25. Shen, W.; Barr, K. J.; Oslob, J. D.; Zhong, M. WIPO Patent Appl. WO2005/044817.
26. Buck, J. S. *J. Am. Chem. Soc.* **1934**, *56*, 1769.
27. Sall, D. J.; Grunewald, G. L. *J. Med. Chem.* **1987**, *30*, 2208.
28. (a) Baker, M.; Gutman, D. M.; Papageorgiou, A. C.; Collins, C. M.; Acharya, K. R. *Protein Sci.* **2001**, *10*, 1268; (b) Neill, R. J.; Jett, M.; Crane, R.; Wootres, J.; Welch, C.; Hoover, D.; Gemski, P. *Infect. Immun.* **1996**, *64*, 3007.
29. Those active compounds in Hut-78 assay are also less potent in the presence of 10% fetal bovine serum (FBS). This suggests that the decrease of potency is possibly due to serum protein binding.
30. Selected compounds were tested in MDCK permeability assay and all showed poor permeability (MDCK P_{app} $<1 \times 10^{-6}$ cm/s (A/B and B/A)).
31. Shaw, D. R.; Griffin, F. M., Jr. *J. Immunol.* **1982**, *128*, 433.