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Amino-substituted heterocycles as isosteres of *trans*-cinnamides: design and synthesis of heterocyclic biaryl sulfides as potent antagonists of LFA-1/ICAM-1 binding

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Abstract—2-Amino-4-phenyl pyridine and, to a lesser extent, 4-amino-6-phenyl pyrimidine, were established as isosteres of *trans*-cinnamide moiety. Applying this isosterism to previously reported *p*-arylthio cinnamides resulted in the identification of 4-amino-6-(*p*-arylthio)phenyl-pyrimidines and 2-amino-4-(*p*-arylthio)phenyl-pyridines as potent antagonists of LFA-1/ICAM-1 binding.

Adhesion-mediated leukocyte emigration is a mechanism of host defense following inflammation, injury or infection.[1,2] During this process, circulating leukocytes are attracted to the injury or infection site and cross the vascular endothelium wall to enter the surrounding tissues, where the leukocytes neutralize the pathogens and carry out regulated tissue destruction. However, over activation of this process leads to untoward tissue damage, as found in many inflammatory diseases and reperfusion injury such as ischemia following stroke, myocardial infarction and trauma. At the molecular level, the recruitment of leukocytes is primarily mediated by the interaction between leukocyte-function-associated antigen-1 (LFA-1, also known as CD11a/CD18 or $\alpha_v\beta_2$ integrin) on leukocytes and intercellular adhesion molecule-1 (ICAM-1, also known as CD54) on endothelial cells.[1,2] Thus, inhibition of LFA-1/ICAM-1 binding represents a potential therapeutic target for these conditions.[3]

Our laboratories have reported several series of *p*-arylthio *trans*-cinnamides, represented by structure **1** and exemplified by compound **2** (Fig. 1), as potent antagonists of LFA-1/ICAM-1 interaction.[3] Starting from a high throughput screening lead, extensive medicinal chemistry effort led to the identification of several subseries of compounds with potent LFA-1/ICAM-1 antagonist activity, good solubility and pharmacokinetic properties.[4–7] During the course of the project, the metabolic stability of the *trans*-cinnamide moiety became a concern, since incubating one analog of *p*-arylthio *trans*-cinnamides with rat and human liver microsomes resulted in cinnamide isomerization and subsequent degradation. Thus, we undertook an effort to identify replacements of the *trans*-cinnamide moiety, even though it was ultimately proven that the cinnamide was sufficiently stable. Toward this end, diarylsulfide *trans*-cyclopropylamides **3** (Fig. 1) have been reported by Link et al.[8] This class of compounds, in which the olefin bond of the cinnamide was replaced with a cyclopropyl ring, have been shown to have LFA-1/ICAM-1 antagonist activity comparable with the analogous cinnamides **1**. Alternatively, we envisioned that properly substituted heterocycles depicted by **4** (Fig. 1), such as 4-amino-6-(*p*-arylthio)phenyl-pyrimidine or 2-amino-4-(*p*-arylthio)phenyl-pyridine, could serve as isosteres of **1**. Based on both electronic and steric considerations, these moieties could potentially replace both the olefin bond and the carbonyl of the *trans*-cinnamide moiety. We report our findings in this paper.

Our attention was first focused on 4-amino-6-(*p*-arylthio)phenyl-pyrimidines **10** which were synthesized

Keywords: *trans*-Cinnamide isostere; Cell adhesion; LFA-1/ICAM-1 binding.
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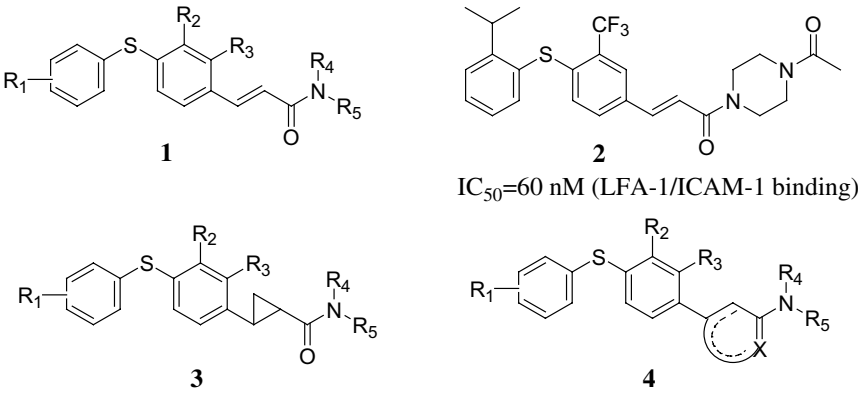
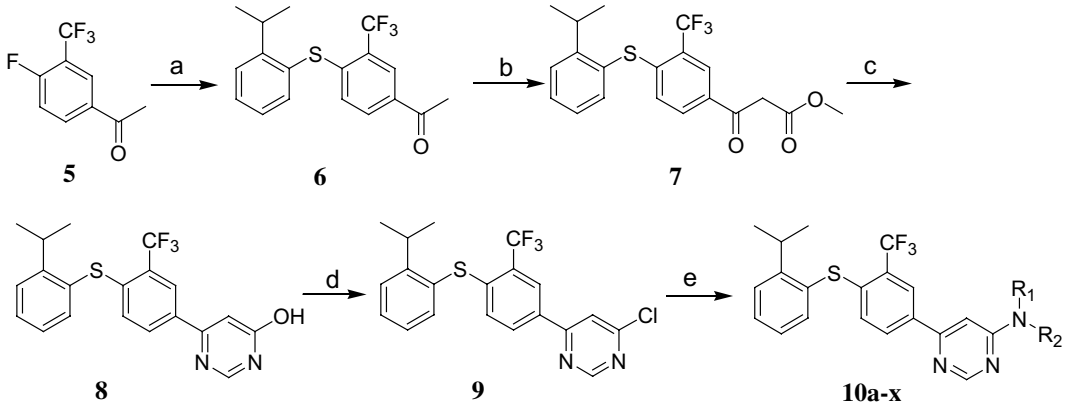


Figure 1.



Scheme 1. (a) *o-iso*-Propyl thiophenol, Cs_2CO_3, DMF, rt 16 h, 90–100%. (b) NaH, $CO(OEt)_2$, THF, rt 2 h, 76%. (c) $HC(NH)NH_2$, 20% HOAc, DMF, 120 °C, 3 days, 14%. (d) $POCl_3$, 60 °C, 1 h, 51%. (e) R_1R_2NH, DMF, 80 °C, 16 h, 70–80%.

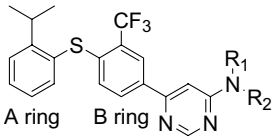
according to Scheme 1. Reaction of 2-*iso*-propyl thiophenol with 1-fluoro-2-trifluoromethyl-4-acetyl benzene **5** under basic conditions gave the diaryl sulfide **6**, which was converted to the β-ketoester **7** by treating with diethyl carbonate under basic conditions. Condensation of **7** with formamidine gave the hydroxyl-pyrimidine **8** in low yield. The key common intermediate, chloropyrimidine **9**, was then obtained by treating **8** with phosphoryl chloride. Displacement of the chloride of **9** with a selected set of amines was carried out in a parallel synthesis mode to rapidly prepare a set of analogs **10a**–**x**.[9]

The LFA-1/ICAM-1 antagonist activity of **10a**–**x** is summarized in Table 1.[10] The decision to fix the A-ring substitution as *o-iso*-propyl and B-ring substitution as *o*-trifluoromethyl (*ortho* to the sulfur) was based on the SAR results of the cinnamide series, as was the selection of the amines.[4,6] Where a direct comparison is available, the data (Table 1) indicated that the pyrimidine ring of **10** is a reasonable isostere of the *trans*-cinnamide moiety of **1**, even though the potency is typically reduced by 2- to 4-fold. Thus, compound **10a** showed an IC_{50} of 200 nM, comparing to 60 nM for the corresponding *trans*-cinnamide analog, compound **10e** exhibited an IC_{50} of 320 nM, comparing to 80 nM for the corresponding *trans*-cinnamide analog, and compound **10w** showed an IC_{50} of 680 nM, comparing with 480 nM for the corresponding *trans*-cinnamide analog. Consistent with the SAR of the cinnamide series,[4,6] substitution on the amino nitrogen of **10** with acidic residues, such as in **10m**, **10n**, **10o** and **10p**, gave more potent inhibitors.

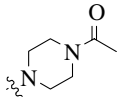
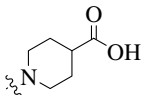
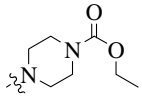
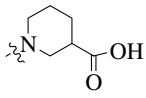
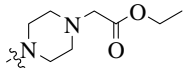
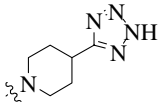
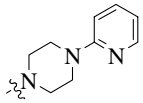
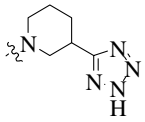
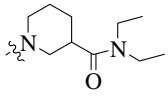
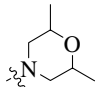
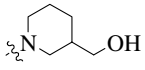
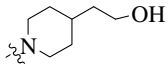
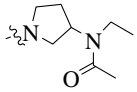
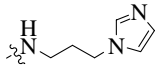
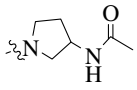
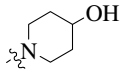
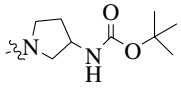
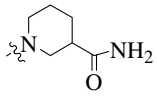
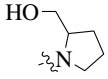
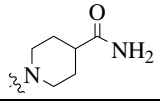
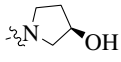
We then turned our attention to 2-amino-4-(*p*-arylthio)phenyl-pyridines. Three different series of pyridine derivatives were synthesized, with the B ring substitution fixed as trifluoromethyl *ortho* to the sulfur, and the A ring being *o-iso*-propylphenyl (**16a**–**ab**), *o*-methoxyphenyl (**17a**–**p**) and 3,4-ethylenedioxyphenyl (**18a**–**p**). These compounds were synthesized as illustrated in Scheme 2. The pyridyl biaryl **12** was prepared via the Suzuki coupling of pyridine-4-boronic acid with 1-fluoro-2-trifluoromethyl-4-bromo benzene. Oxidation of **12** with hydrogen peroxide catalyzed by methyltrioxorhenium (VII) gave the *N*-oxide **13**, which was reacted with appropriate thiophenols to give the diaryl sulfide pyridine oxides **14a**–**c**. Treating **14a**–**c** with phosphoryl chloride gave 2-chloropyridines **15a**–**c**. Displacement of the chloride of **15a**–**c** with a set of selected amines gave the desired compounds **16a**–**ab**, **17a**–**p** and **18a**–**p**.

The LFA-1/ICAM-1 antagonist IC_{50}'s of the representative pyridine derivatives were shown in Tables 2 and 3. In the *o-iso*-propyl phenylthio series (**16**), comparison of **16t** and **16x** with the corresponding *trans*-cinnamide analogs (Table 2) revealed that the pyridine derivatives were essentially equipotent with the analogous *trans*-

Table 1. Structure–activity relationships of 4-amino-6-(*p*-arylthiophenyl)-pyrimidines

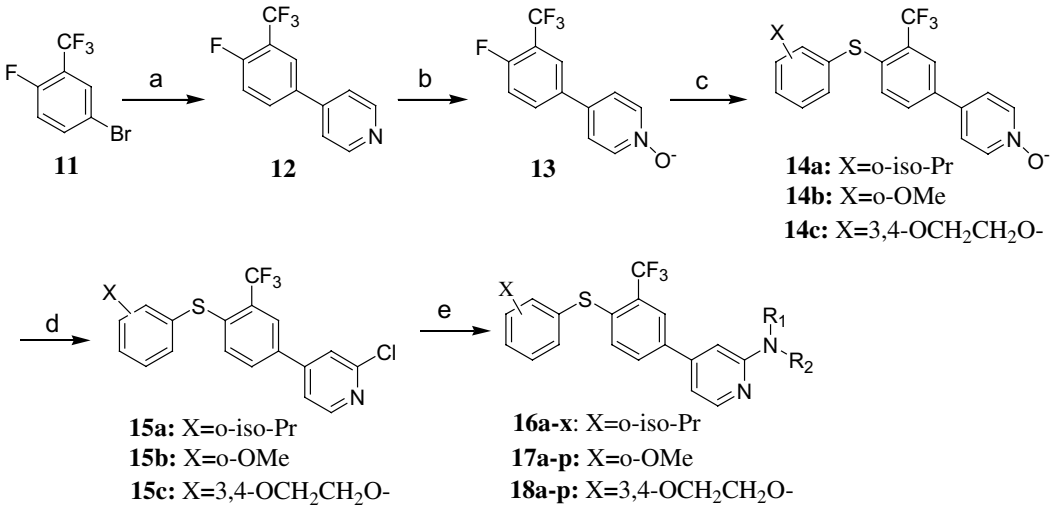


10a-x

Compound	–NR_1R_2	IC_{50} (nM)[a] LFA-1/ICAM-1	Compound	–NR_1R_2	IC_{50} (nM)[a] LFA-1/ICAM-1
10a		200 (60 nM)[c]	**10m**		120[b]
10b		470	**10n**		120[b]
10c		420	**10o**		108[b]
10d		1270	**10p**		51[b]
10e		320 (80 nM)[c]	**10q**		620
10f		490	**10r**		230[b]
10g		740	**10s**		230[b]
10h		680	**10t**		300
10i		760	**10u**		220[b]
10j		228[b]	**10v**		550
10k		340	**10w**		680 (480)[c]
10L		230	**10x**		158

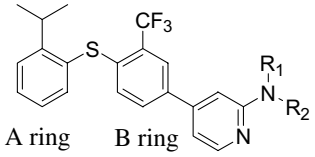
[a] The IC_{50} reported is the result of single determination unless noted.
[b] Average of two determinations.
[c] Number in parenthesis is the IC_{50} of the corresponding *trans*-cinnamide analog.

cinnamides. Further analysis of the data showed that the pyridine derivatives **16** (Table 2) were typically ~3-times more potent than the the analogous pyrimidine derivatives **10** (Table 1), as indicated by the comparison of **16g** with **10j**, **16j** with **10m**, **16k** with **10m**, **16m** with **10o**, **16n** with **10L** and **16z** with **10u**. The data (Table 2) also indicated a strong preference for polar and acidic substituents on the amino nitrogen. Thus, compounds with hydrophobic substituents at this position (**16b–f**, **16o–r**) were essentially inactive, while several compounds with acidic substituents (**16j**, **16k**, **16L**, **16m** and **16y**) showed $IC_{50} < 50$ nM, consistent with the previous reports on the *trans*-cinnamides.[4,5] The data for the *o*-methoxyphenylthio series (**17**) and 3,4-ethylenedioxyphenylthio series (**18**) in Table 3 similarly indicated that 2-aminopyridine derivatives were good mimics of



Scheme 2. (a) Pyridine-4-boronic acid, *n*-PrOH, H_2O, $Pd(OAc)_2$, Ph_3P, reflux, 4 h, 82%. (b) CH_3ReO_3, H_2O_2, CH_2Cl_2, rt, 16 h, 94%. (c) Cs_2CO_3, DMA, thiophenol, 100 °C, 16 h, 77–90%. (d) $POCl_3$, 100 °C, 10 h, 60–82%. (e) R_1R_2NH, DMSO, 140 °C, 16 h, 60–85%.

Table 2. Structure–activity relationships of 2-amino-4-[3′-trifluoromethyl-4′-(*o-iso*-propylphenylthio)]-pyridines



16a-ab

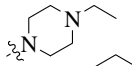
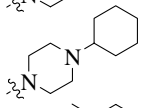
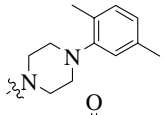
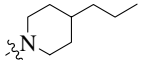
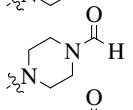
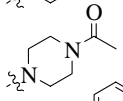
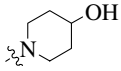
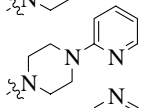
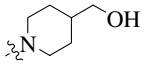
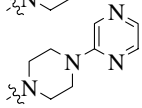
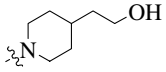
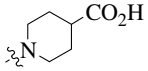
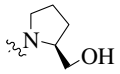
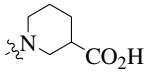
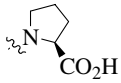
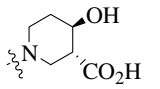
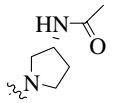
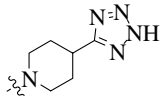
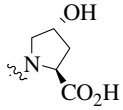
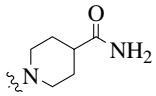
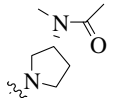
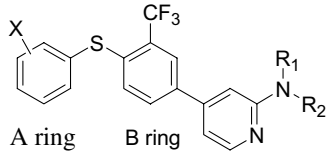
Compound	–NR_1R_2	IC_{50} (nM)[a] LFA-1/ICAM-1	Compound	–NR_1R_2	IC_{50} (nM)[a] LFA-1/ICAM-1
16a		250	**16o**		58% inhi. @ 1 μM
16b		1000	**16p**		54% inhi. @ 1 μM
16c		34% inhi. @ 1 μM	**16q**		21% inhi. @ 1 μM
16d		40% inhi. @ 1 μM	**16r**		0% inhi. @ 1 μM
16e		8% inhi. @ 1 μM	**16s**		165
16f		22% inhi. @ 1 μM	**16t**		93 (60)[b]
16g		76	**16u**		40% inhi. @ 1 μM
16h		160	**16v**		82% inhi. @ 1 μM
16i		160	**16w**		93
16j		42 (50)[b]	**16x**		264 (480)[b]
16k		43 (30)[b]	**16y**		26

Table 2 (*continued*)

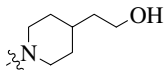
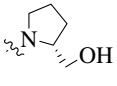
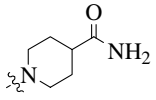
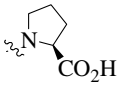
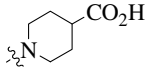
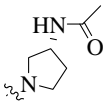
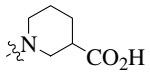
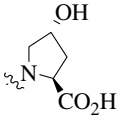
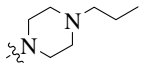
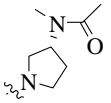
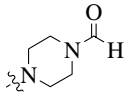
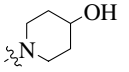
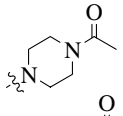
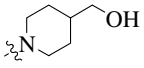
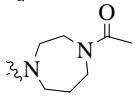
Compound	$-NR_1R_2$	IC_{50} (nM)[a] LFA-1/ICAM-1	Compound	$-NR_1R_2$	IC_{50} (nM)[a] LFA-1/ICAM-1
16L		43	**16z**		62
16m		51	**16aa**		90
16n		73	**16ab**		112

[a] The IC_{50}'s are the results of single determination.
[b] Number in parenthesis is the IC_{50} of the corresponding *trans*-cinnamide analog.

Table 3. Structure–activity relationships of 2-amino-4-(*p*-arylthio)phenyl-pyridines



17a-p: X=*o*-OMe
18a-p: X=3,4-OCH_2CH_2O

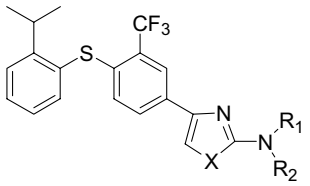
Compound	$-NR_1R_2$	IC_{50} (nM)[a] LFA-1/ICAM-1	Compound	$-NR_1R_2$	IC_{50} (nM)[a] LFA-1/ICAM-1
17a		77	**17i**		111
18a		126	**18i**		132
17b		331	**17j**		140
18b		510	**18j**		140
17c		80	**17k**		113
18c		147	**18k**		71 (50)[b]
17d		88	**17L**		122
18d		112	**18L**		76 (30)[b]
17e		214	**17m**		900
18e		192	**18m**		747
17f		88	**17n**		186
18f		168	**18n**		351
17g		128	**17o**		121
18g		300	**18o**		131 (60)[b]
17h		80	**17p**		168
18h		390	**18p**		365

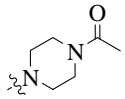
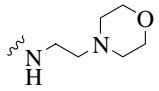
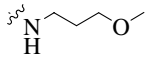
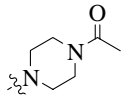
[a] All the IC_{50}'s are the average of two determinations.
[b] Number in parenthesis is the IC_{50} of the corresponding *trans*-cinnamide analog.

the *trans*-cinnamides **1**. However, the *o*-methoxy- and the 3,4-ethylenedioxy-substitution on the A ring appears to be less optimal than the *o-iso*-propyl.

We also examined five-membered ring heterocycles as the replacement of the *trans*-cinnamide moiety of **1**. A set of thiazole derivatives were synthesized according to Scheme 3, involving the bromination of disulfide methyl ketone **6** and condensation of the resulting α-bromomethyl ketone with thioureas to give the desired 2-amino-4-(*p*-arylthio)phenyl-thiazoles **20a–d**. The LFA-1/ICAM-1 antagonist activity of representative

Table 4. Structure–activity relationships of 2-amino-4-(*p*-arylthio)-phenyl-thiazoles



Compound	X	$-NR_1R_2$	IC_{50} (nM)[a] LFA-1/ICAM-1
20a	S		3000 (60)[b]
20b	S		40 % inhi. @ 20 μM
20c	S		12,000
20d	S		10,500
21a	O		2500 (60)[b]
21b	O		15,000
21c	O		3600

[a] All the inhibition data are the average of two determinations.
[b] Number in parenthesis is the IC_{50} of the corresponding *trans*-cinnamide analog.

thiazole derivatives (Table 4) clearly indicated that the 2-amino-thiazole moiety is not a good isostere of the *trans*-cinnamide of **1**. A small set of oxazole derivatives (**21a**–**c**) were also prepared and found much less potent than the corresponding *trans*-cinnamides (Table 4). The fact that five-membered ring heterocycles gave much less active compounds is likely due to the fact that five-membered ring heterocylces as in **20a**–**d or 21a**–**c** do not mimic the geometry of *trans*-cinnamide as closely as six-membered ring as in **10** or **16**–**18**. However, an electronic effect cannot be ruled out, since the location of the N atom in the heterocycles of **20a**–**d** and **21a**–**c** has been shifted. Properly substituted pyrrole, imidazole or pyrazole would resolve this ambiguity.

Compound **10n** and **10p** were tested in a cell-based adhesion assay measuring the adherence of LFA-1 expressing JY8 cells to immobilized ICAM-1, giving a EC_{50} of 90 nM and 20 nM, respectively.

In summary, we have established 2-amino-4-phenyl pyridine and, to a lesser extent, 4-amino-6-phenyl pyrimidine as isosteres of *trans*-cinnamide moiety, leading to the identification of 4-amino-6-(*p*-arylthio)-phenyl-pyrimidines and 2-amino-4-(*p*-arylthio)phenyl-pyridines as potent antagonists of LFA-1/ICAM-1 binding.

References and notes

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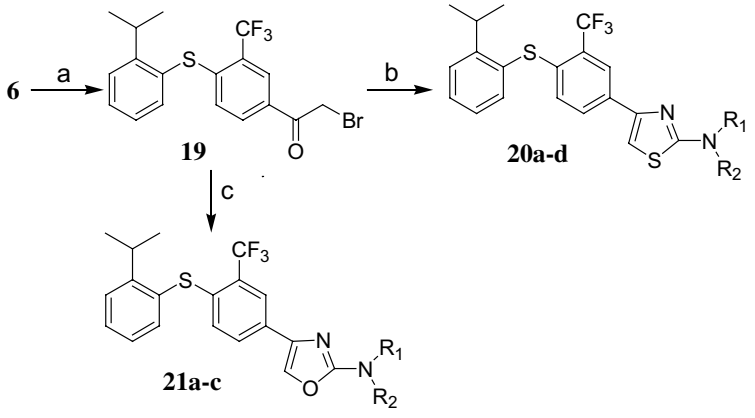

Scheme 3. (a) $(n\text{-Bu})_4NBr_3$, MeOH, CH_2Cl_2, rt 16 h, 100%. (b) $H_2NC(S)NR_1R_2$, DMF, rt 16 h, 40–90%. (c) $H_2NC(O)NR_1R_2$, DMF, 100 °C, 24 h, 20–60%.

Geldern, T. W.; Leitza, S.; DeVries, P.; Dickinson, R.; Mussatto, D.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 4393.
8. Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973.
9. All the compounds used for biological testing were purified by reverse-phase HPLC. The identity and purity were established by ^{1}H NMR and MS spectra and HPLC analysis.
10. The LFA-1/ICAM-1 binding assay and the JY-8 cell adhesion assay were described in Ref. 4.