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# Structure–activity relationship (SAR) of the α-amino acid residue of potent tetrahydroisoquinoline (THIQ)-derived LFA-1/ICAM-1 antagonists

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ABSTRACT

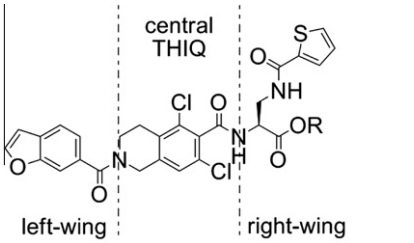
This letter describes the structure–activity relationship (SAR) of the 'right-wing' α-amino acid residue of potent tetrahydroisoquinoline (THIQ)-derived LFA-1/ICAM-1 antagonists. Novel (*S*)-substituted heteroaryl-bearing α-amino acids have been identified as replacements of the 'right-wing' (*S*)-2,3-diaminopropanoic acid (DAP) moiety. Improvement of potency in the Hut-78 assay in the presence of 10% human serum has also been achieved.



The interaction between leukocyte function-associated antigen-1 (LFA-1, αLβ2, CD11a/CD18) and intercellular adhesion molecule-1 (ICAM-1, CD54) supports inflammatory and specific T-cell regulated immune responses by mediating cell adhesion, leukocyte extravasation, migration, antigen presentation, formation of the immunologic synapse, and augmentation of T-cell receptor signaling.[1–3] This interaction has been directly implicated in a wide range of immunoregulatory disorders,[4] such as arthritis, psoriasis/atopic dermatitis, graft rejection, and ocular diseases, such as dry eye and diabetic retinopathy. Therefore, much effort has been expended in discovering small molecule-based LFA-1/ICAM-1 antagonists as potential therapeutics for treating these diseases.[5–10]

Recently, we have disclosed the discovery of a novel series of potent tetrahydroisoquinoline (THIQ)-derived LFA-1/ICAM-1 antagonists[11] exemplified by **1a**,**b** (Fig. 1), which have demonstrated good mouse and rat pharmacokinetic (PK) profiles and in vivo efficacy in a thioglycollate-induced murine peritonitis model. However, as noted in our previous Letter, further evaluation of the biological properties of **1a**,**b** and their close analogs revealed a significant reduction of antagonist activity in the presence of either human or fetal bovine serum, decreasing their likelihood of in vivo efficacy. As part of the efforts to address such an issue, we performed extensive SAR studies of the 'right-wing' amino acid residue of THIQ-derived LFA-1/ICAM-1 antagonists. Herein, we report the identification of novel (*S*)-substituted heteroaryl-bearing α-amino acids as replacements of the (*S*)-2,3-diaminopropanoic acid (DAP) moiety, which resulted in a significant improvement of potency in the Hut-78 assay[11a] in the presence of 10% human serum.

Schemes 1 and 2 describe synthetic approaches to representative functionalized L-α-amino acid derivatives, which are introduced onto the THIQ scaffold following our previously reported protocol.[11]




**1a** R = H Hut-78 $IC_{50}$ = 0.005 μM
Hut-78-10%HS $IC_{50}$ = 0.95 μM
**1b** R = Et

**Figure 1.** Representative THIQ-derived LFA-1/ICAM-1 antagonists **1a**,**b**.

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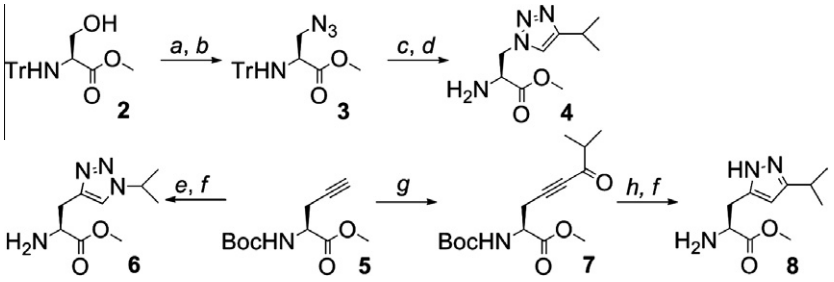
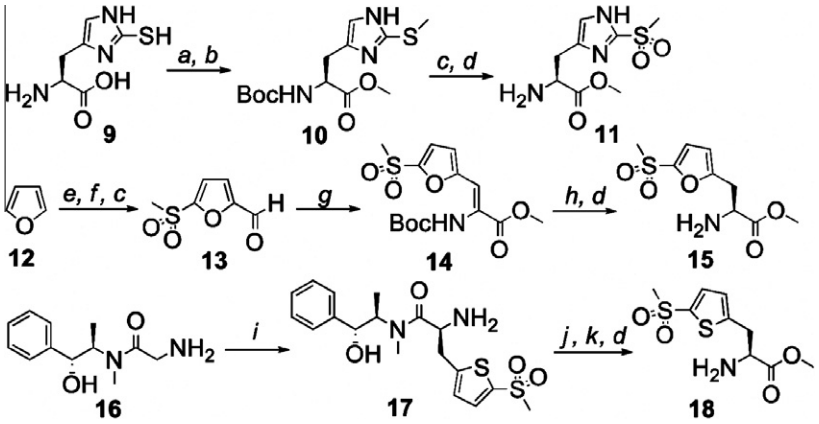


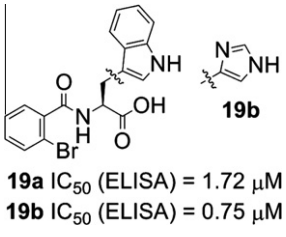
**Scheme 1.** Reagents and conditions: (a) MsCl, $Et_3N$, $CH_2Cl_2$, 90% yield; (b) $NaN_3$, DMF, 60 °C, 75% yield; (c) CuI (0.1 equiv), DIEA (0.1 equiv), 3-methylbut-1-yne (2.0 equiv), $CH_3CN$, rt, 65% yield; (d) 2.0 N HCl in ether, rt, quantitative yield; (e) CuI (0.1 equiv), DIEA (0.1 equiv), isopropyl azide (10 equiv), $CH_3CN$, rt, 75% yield; (f) 4.0 N HCl in dioxane, rt, quantitative yield; (g) isobutyryl chloride, $Pd(PPh_3)_2Cl_2$, $Et_3N$, CuI, toluene, $N_2$, 80% yield; (h) $NH_2NH_2$, MeOH, 0 °C to rt, 65% yield.



**Scheme 2.** Reagents and conditions: (a) $H_2SO_4$, MeOH, rt; 50 °C; (b) $Boc_2O$, $K_2CO_3$, THF/$H_2O$, 56% yield (two steps); (c) *m*-CPBA, DCM, quantitative yield; (d) 4.0 N HCl in dioxane, quantitative yield; (e) *n*-BuLi, −78 °C, THF; $CH_3SSCH_3$, −78 °C to rt, 55% yield; (f) *n*-BuLi, −78 °C, THF; dry DMF, −78 °C to rt, 65% yield; (g) (±)-*N*-Boc-α-phosphonoglycine trimethyl ester, *N*,*N*,*N*′,*N*′-tetramethylguanidine, DCM, −35 °C to rt, 70% yield; (h) (+)-bis (2*S*,5*S*)-2,5-dimethylphospholano)benzene(cyclooctadiene)-rodhium(I) tetrafluoroborate (0.01 equiv), MeOH, 45 psi $H_2$, 75% yield; (i) LiHMDS, LiCl, 2-chloromethyl-5-methanesulfonylthiophene, 0 °C, 70% yield; (j) 1.0 N NaOH, reflux; $Boc_2O$, $NaHCO_3$, dioxane/$H_2O$, 95% yield; (k) $TMSCHN_2$, DCM, rt, quantitative yield.

As shown in Scheme 1, commercially available functionalized L-serine **2** is readily converted to its azide derivative **3**, which undergoes a copper catalyzed [3+2] cycloaddition,[12] followed by *N*-trityl deprotection to give triazole-bearing α-amino acid methyl ester **4**. Compound **6**, the regio-isomer of **4** is prepared similarly using functionalized L-propargylglycine **5** as the starting material. Compound **5** may also be used in a Pd-catalyzed coupling with isobutyryl chloride to give **7**, which is treated with hydrazine, followed by *N*-Boc deprotection to yield pyrazole-containing α-amino acid derivative **8**.

2-Methylsulfonyl-substituted L-histidine derivative **11** is prepared using commercially available 2-mercapto-L-histidine (**9**) as the starting material, following a sequence of transformations as outlined in Scheme 2.[11a,13] 2-Methylsulfonylfuryl substituted L-alanine methyl ester (**15**) is synthesized using asymmetric hydrogenation[14] of a dehydrated amino acid intermediate **14**, while the corresponding thiophene analog **18** is obtained using an asymmetric alkylation approach reported by Myers et al.[15]

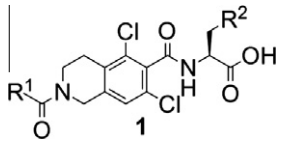


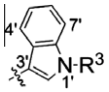
**19a** $IC_{50}$ (ELISA) = 1.72 μM
**19b** $IC_{50}$ (ELISA) = 0.75 μM

**Figure 2.** Representative *N*-benzoyl amino acid derived LFA-1/ICAM-1 antagonists **19a**,**b**.

In our previous Letter,[11b] we disclosed that THIQ analogs bearing non-DAP 'right-wing' residues, such as L-tryptophan, showed low micromolar potency in the Hut-78 assay. This result is consistent with previous observations[8b] with *N*-benzoyl amino acids-based LFA-1/ICAM-1 antagonists (Fig. 2) that were thought to have the same binding mode as the THIQ chemotype. Although L-tryptophan derivative **1d** (Table 1, entry 3) has much weaker affinity in comparison to its corresponding DAP-bearing analog **1c** (entry 2), it has less peptide characteristic and the potency of this non-DAP analog could potentially be improved by modifying the indole moiety. As summarized in Table 1, when the free –NH of **1d** is acetylated, the resulting compound (**1e**) retains potency (entry 4). Interestingly, when the free –NH of **1d** is capped with a methylsulfonyl (–$SO_2$Me) moiety, significant improvement of the potency is observed (entry 5). However, replacing the –$SO_2$Me residue with a –$SO_2NH_2$ moiety results in a substantial decrease in potency (entry 6). Also, introduction of a methyl group at either C-5′ (**1i**) (entry 8) or -6′ (**1j**) (entry 9) position of the indole moiety of **1f** affords low nanomolar compounds, comparable to the potency of DAP derivative **1c** in the Hut-78 assay. Methyl substitution at the C-4′ position (**1h**) (entry 7) is not well tolerated while the substitution at the C-7′ position (**1k**) (entry 10) seems to retain potency. Unfortunately, there is still a drastic decrease in potency of these compounds in the presence of 10% human serum (entries 8–10). Presumably, the hydrophobic nature of the indole moiety contributes to high protein binding of the molecule, which is detrimental to potency in the presence of human serum.

**Table 1**
SAR of α-amino acid residue of the THIQ-derived LFA-1/ICAM-1 antagonists




| Entry | Compd | $R^1$ | $R^2$ | | Hut-78 $IC_{50}$[a] (μM) | Hut-78-10% HS[b] $IC_{50}$ (μM) | Rat iv PK[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | $t_{1/2}$ (h) | CL (mL/min/kg) | AUC (h ng/mL) |
| 1 | **1a** | 6-Benzofuryl | –NHCO(thien-2-yl) | | 0.005 | 0.95 | 3.0 | 3.2 | 5495 |
| 2 | **1c** | 4-Chlorophenyl | –NHCO(thien-2-yl) | | 0.022 | 1.5 | 1.4 | 31 | 580 |
| 3 | **1d** | 4-Chlorophenyl |  | $R^3$ = H | 0.81 | —[d] | — | — | — |
| 4 | **1e** | 4-Chlorophenyl | | $R^3$ = –Ac | 0.82 | — | — | — | — |
| 5 | **1f** | 4-Chlorophenyl | | $R^3$ = $–SO_2Me$ | 0.10 | 25 | — | — | — |
| 6 | **1g** | 4-Chlorophenyl | | $R^3$ = $–SO_2NH_2$ | >1.0 | — | — | — | — |
| 7 | **1h** | 4-Chlorophenyl | | $R^3$ = $–SO_2Me$; 4′-Me | >1.0 | — | — | — | — |
| 8 | **1i** | 4-Chlorophenyl | | $R^3$ = $–SO_2Me$; 5′-Me | 0.026 | 11 | — | — | — |
| 9 | **1j** | 4-Chlorophenyl | | $R^3$ = $–SO_2Me$; 6′-Me | 0.039 | 25 | — | — | — |
| 10 | **1k** | 4-Chlorophenyl | | $R^3$ = $–SO_2Me$; 7′-Me | 0.14 | 25 | — | — | — |
| 11 | **1l** | 4-Chlorophenyl | 1*H*-imidazol-4-yl | | 0.43 | — | — | — | — |
| 12 | **1m** | 4-Chlorophenyl | 1-Me-1*H*-imidazol-4-yl | | 0.56 | — | — | — | — |
| 13 | **1n** | 4-Chlorophenyl | 1-*i*-Pr-1*H*-imidazol-4-yl | | 0.17 | — | — | — | — |
| 14 | **1o** | 4-Chlorophenyl | 1-Ph-1*H*-imidazol-4-yl | | >1.0 | — | — | — | — |
| 15 | **1p** | 4-Chlorophenyl | 1-*i*-Pr-1*H*-1,2,3-triazol-4-yl | | 0.059 | 1.0 | 2.3 | >60 | 1412 |
| 16 | **1q** | 4-Chlorophenyl | 4-*i*-Pr-1*H*-1,2,3-triazol-1-yl | | 0.31 | — | — | — | — |
| 17 | **1r** | 4-Chlorophenyl | 5-*i*-Pr-1*H*-pyrazol-3-yl | | 0.25 | — | — | — | — |
| 18 | **1s** | 4-Chlorophenyl | 5-*i*-Pr-thiazol-2-yl | | >1.0 | — | — | — | — |
| 19 | **1t** | 4-Chlorophenyl | 3-*i*-Pr-phen-3-yl | | 0.01 | >10 | — | — | — |
| 20 | **1u** | 2-Benzofuryl | 1-*i*-Pr-1*H*-1,2,3-triazol-4-yl | | 0.005 | 0.19 | — | — | — |
| 21 | **1v** | 6-Benzofuryl | 1-*i*-Pr-1*H*-1,2,3-triazol-4-yl | | 0.019 | 0.95 | 0.97 | 26 | 3680 |
| 22 | **1w** | 2-Pyrazolo[1,5-*a*]pyridyl | 1-*i*-Pr-1*H*-1,2,3-triazol-4-yl | | 0.007 | 0.26 | — | — | — |
| 23 | **1x** | 6-Benzofuryl | 2-Methylsulfonyl-1*H*-imidazol-5-yl | | 0.030 | 0.56 | — | — | — |
| 24 | **1y** | 6-Benzofuryl | 2-Methylsulfonylfur-5-yl | | 0.0012 | 0.096 | 0.43 | 60 | 1514 |
| 25 | **1z** | 6-Benzofuryl | 2-Methylsulfonylthien-5-yl | | 0.15 | — | — | — | — |
| 26 | **1α** | 6-Benzofuryl | 1-Methylsulfonylpyrrolid-3-yl | | 1.0 | — | — | — | — |

[a] The $IC_{50}$ value is an average of three titrations with eight concentration points.
[b] Human 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.

Burdick et al. reported that their L-histidine derivative has comparable potency to its corresponding L-tryptophan analog (Fig. 2, **19a** vs **19b**).[8b] As expected, this trend was also observed on our THIQ series compounds (**1d** vs **1l**) (entries 3 and 11). Next, several readily available N-substituted THIQ analogs were prepared to obtain preliminary SAR on the imidazole moiety (entries 12–14), which led to the identification of *N*-isopropyl (-*i*Pr) substituted analog **1n** (entry 13) with slightly improved affinity relative to **1l** (entry 11). Subsequently, several **1n** close derivatives were prepared by replacing the imidazole residue with other five- and six-membered aromatic moieties, such as triazole, thiazole, pyrazole, and phenyl (entries 15–19). Interestingly, triazole-bearing analog **1p** (entry 15) and phenyl-bearing analog **1t** (entry 19) demonstrated significant improvement of potency in the Hut-78 assay. However, only **1p** retained good activity in the presence of 10% human serum, while **1t** completely lost its potency under the same condition. Moreover, both **1p** and its 2-benzofuryl (**1u**), 6-benzofuryl (**1v**) and 2-pyrazolo[1,5-*a*]pyridyl (**1w**) analogs (entries 20–22) have comparable or improved potency to the corresponding DAP derivatives **1a** (entry 1) and **1c** (entry 2) in both assays.

Compounds **1p** (entry 15) and **1v** (entry 21) were further evaluated to determine their preliminary pharmacokinetic properties. Despite evidence of good stability in rat liver microsomes,[16] both **1p** and **1v** are rapidly cleared in rat. Compound **1p** does have a reasonable half life ($t_{1/2}$ = 2.3 h), but its clearance is greater than the liver blood flow of rat. Similar to the pair of DAP derivatives **1a** (entry 1) and **1c** (entry 2), **1v** demonstrates lower CL and higher area under curve (AUC) as compared to **1p**. It should be noted that the overall rat iv profile of **1v** is inferior to that of the corresponding DAP analog **1a**.

The SAR of *N*-$SO_2Me$ L-tryptophan derivatives and -*i*Pr substituted azole-bearing analogs led us to explore –$SO_2Me$ substituted heteroaryl analogs. As summarized in Table 1, 2-methylsulfonylimidazole analog **1x** (entry 23) shows comparable potency to *N*-*i*Pr substituted triazole derivative **1v** (entry 21) in the Hut-78 assay in the presence of 10% human serum. Interestingly, the corresponding furan analog **1y** (entry 24) demonstrates a significant improvement in potency[17]; however, the corresponding thiophene analog **1z** (entry 25) is less active relative to both **1x** and **1y**. Moreover, the non-aromatic *N*-$SO_2Me$ substituted pyrrolidine analog (**1α**) (entry 26) is much less potent than the corresponding aromatic ones. Similar to **1v**, **1y** is stable in both rat and human liver microsomes.[16] However, a rat iv PK study shows that **1y** has a short $t_{1/2}$ and high CL with total exposure similar to **1p** (entry 15) as indicated by AUC.

In summary, we have successfully identified a number of DAP replacements bearing functionalized heteroaryl moieties during

SAR studies of the 'right-wing' α-amino acid residue of potent THIQ-derived LFA-1/ICAM-1 antagonists. Several compounds possessing these amino acids have good potency in the Hut-78 assay in the presence of 10% human serum. However, these potent LFA-1/ICAM-1 antagonists generally have inferior PK profiles in rat comparing to the corresponding DAP derivatives. Future work will be focused on optimizing analogs bearing the $-SO_2Me$ substituted DAP replacements and potentially applying this type of compounds in treatment of human immunoregulatory disorders, which will be reported in due course.

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13. For the transformation of **9**–**10**, it can be done through either a two-step sequence as shown in Scheme 2 or a three-step sequence by initially methylating the –SH with MeI in the presence of $K_2CO_3$ in acetone, followed by esterification and Boc-protection. For $H_2SO_4$ mediated methylation of –SH in MeOH, also see, Shimizu, M.; Shimazaki, T.; Kon, Y.; Konakaharab, T. *Heterocycle* **2010**, *81*, 43.
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16. Compounds **1p**, **1v** and **1y** were evaluated in liver microsomal stability assays. The tested compounds were incubated with rat or human liver microsomes in the presence of NADPH and $MgCl_2$ solution. Samples were taken at 0, 30, and 60 min three time points and tested on LC/MS. The data were reported as a ratio of the peak area at 30 min or 60 min relative to the one at 0 min. Lidocaine and Dextromethorphan were used as positive controls. **1p**: 92% at 30 min in human liver microsomes (HLM); **1v**: >95% at 30 min in rat liver microsomes (RLM) and 86% at 30 min in HLM; and **1y**: >65% at 30 min in RLM and >95% at 30 min in HLM.
17. In general, analogs bearing the 'right-wing' amino acid moiety of **1y** and various 'left-wing' residues show better potency relative to the corresponding DAP analogs in either the Hut-78 or Staphylococcal Enterotoxin B (SEB)-stimulated T-cell activation assay in the presence of either human or fetal bovine serum. The data are not shown.