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Constraining the amide bond in N-Sulfonylated dipeptide VLA-4 antagonists

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Abstract—The integrin VLA-4 is implicated in several inflammatory disease states. In search of non-peptidic antagonists of VLA-4, rotational constraints were imposed on the amide bond of prototypical N-sulfonylated dipeptide VLA-4 antagonists. By judicious structural modification of the side chains, trisubstituted imidazoles with moderate binding potencies were obtained, for example, **19**, VLA-4 IC_{50} = 237 nM.

The integrin VLA-4 (very late antigen-4; $\alpha_4\beta_1$, CD49d/CD29) is a heterodimeric cell surface glycoprotein transmembrane receptor.[1] Expressed on all leukocytes except platelets and neutrophils, it is a key mediator in cell–cell and cell–matrix interactions. It is involved in leukocyte recruitment, activation, proliferation, and differentiation during normal and/or pathophysiological processes. Blockade of the interaction between VLA-4 and its ligands, vascular cell adhesion molecule-1 (VCAM-1) and CS-1, an alternatively spliced form of fibronectin, may reduce the vascular extravasation of inflammatory cells into tissues during prolonged inflammation.[2]

Recent Phase III clinical data of natalizumab, the humanized anti-α4 antibody, in multiple sclerosis validate the potential for α4 integrin antagonists in human disease.[3] In addition, peptidyl VLA-4 antagonists have proven effective in several animal models of inflammation and autoimmune diseases.[4] These results led to much effort in the development of small molecule VLA-4 antagonists.[5]

Initial efforts at Merck led to derivatives such as **1a** (IC_{50} = 1.4 nM),[6b] **1b** (IC_{50} = 0.64 nM),[6a] and **1c** (IC_{50} = 0.56 nM),[6a] all containing a central amide bond. Indeed, the equivalent of this amide bond is featured in many of the VLA-4 antagonists that have been identified, for example, **2**, **3**.[5a,c] We were interested in transforming compound **1** into active compounds where the amide bond is incorporated into various cyclic structures as shown in Figure 1. The first route (I) connected the amide nitrogen to the C-3 position of the proline

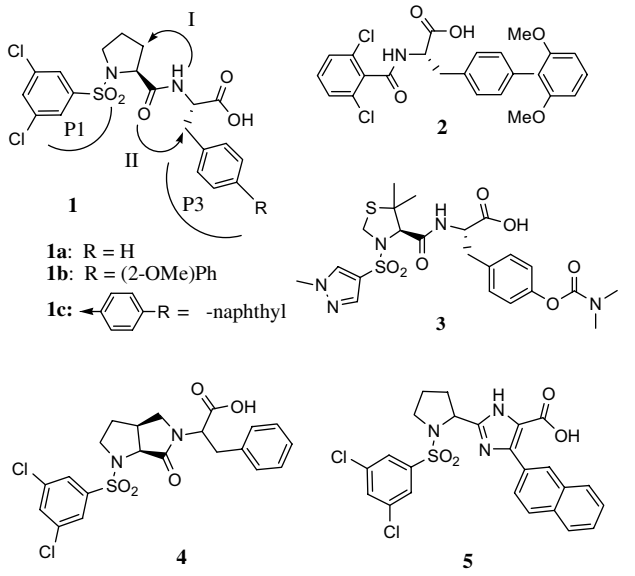

Figure 1.

Keywords: VLA-4; Peptide bond mimetic; Bicyclic VLA-4 antagonists; Imidazole VLA-4 antagonists.
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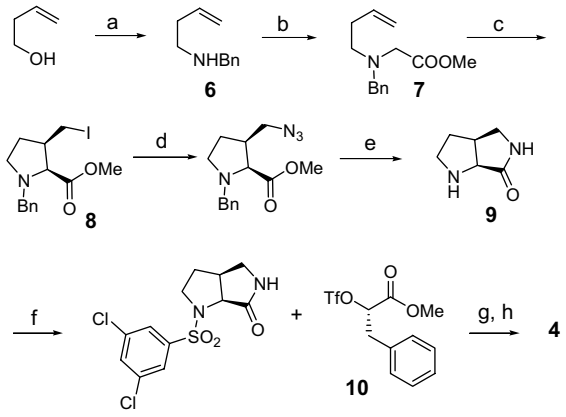
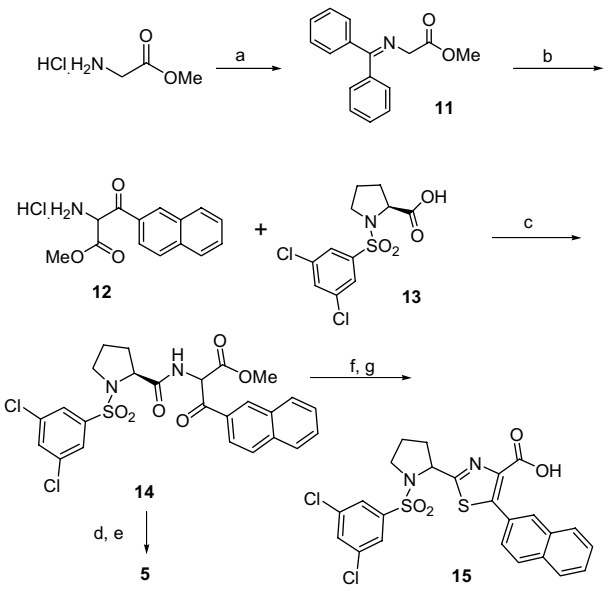


Scheme 1. Reagents and conditions: (a) i—MsCl, NEt_3, DCM; ii—$BnNH_2$, 80%; (b) $BrCH_2CO_2Me$, NEt_3, DMSO, rt, 12 h, 69%; (c) i—LDA, −78 °C; ii—$ZnBr_2$, −90 °C; iii—I_2, 80%; (d) NaN_3, DMF, rt, 16 h, 71%; (e) H_2, Pd/C, EtOAc, 98%. H_2, Pd/C, formic acid, MeOH, 99%; (f) $(3,5\text{-}Cl_2)C_6H_3SO_2Cl$, $NEt(iPr)_2$, DMAP, DCM/THF (1:1), 41%; (g) NaH, THF/DMF, 51%; (h) NaOH/MeOH, 94%.



Scheme 2. Reagents and conditions: (a) $(C_6H_5)_2C{=}NH$, DCM, rt, 77%; (b) KO-*t*-Bu, THF, −70 °C, β-naphthyl-COCl; 2 N HCl, 92%; (c) NMM, THF; *t*-Bu-OCOCl, NMM, −20 °C, 74%; (d) NH_4OAc, HOAc, 3A sieves, xylene, reflux, 16 h, 55%; (e) excess TMSI, 100 °C, 1–3 h, 40%; (f) Lawesson's Reagent, THF, 3A sieves, reflux, 14 h. 69%; (g) 2 equiv NaOH/MeOH, rt, 50%.

(P2) via a carbon bridge, as in **4**.[7] The second approach (II) incorporated the amide bond and the β-carbon of the P3 side chain into a 5-membered heteroaryl ring, as in **5**.[8] Both approaches introduced a considerable amount of conformational restriction to the resulting non-peptidic entities. Herein, we describe the effects of such constraints on receptor-ligand binding in this class of VLA-4 antagonists.

Compound **4**, the target from route I, contains a novel diaza-5,5-fused ring system which provided considerable synthetic challenges. The successful route began with the conversion of homoallylic alcohol to the corresponding homoallylic benzylamine **6**,[9] which was reacted with methyl bromoacetate to yield the key intermediate **7** (Scheme 1). Deprotonation of **7** was followed by the putative complexation of the resulting enolate oxygen, amine nitrogen, and the homoallyl double bond with zinc bromide.[10] Subsequent treatment with iodine provided the substituted proline methyl ester **8**, possessing an iodomethyl group. The iodo functionality was converted to an azide[11] which was hydrogenated to compound **9**, containing the desired restricted amide bond. Thus, the transformation from **8** to the strained, unsubstituted 5,5-fused ring system **9** was achieved in one pot via reductive cyclization followed by N-debenzylation.[12]

Subsequently, the 3,5-dichlorobenzenesulfonyl moiety (P1) was attached to the pyrrolidine nitrogen. Alkylation of the lactam nitrogen with the triflate of methyl (L)-3-phenyllactate **10** (obtained from methylation of (L)-3-phenyllactic acid and sulfonylation of the hydroxyl group) followed by base hydrolysis of the methyl ester provided the racemate **4**.

The imidazole **5** was prepared as shown in Scheme 2. Glycine methyl ester was converted to its benzophenone Schiff base **11**.[13] Addition of the corresponding potassium enolate to a solution of β-naphthoyl chloride at −70 °C provided the α-imino-β-keto compound which was hydrolyzed to intermediate **12**. Mixed anhydride coupling of **13** (prepared from proline *t*-butyl ester by N-sulfonylation and ester hydrolysis) with **12** provided the key intermediate **14**.[14] The imidazole ring formation was achieved by treatment of **14** with acidic ammonium acetate in refluxing xylene. Removal of the methyl ester was best accomplished by treatment with iodotrimethylsilane, providing the imidazole **5**.

The corresponding oxazole methyl ester was prepared by treating a solution of **14** and DBU in a mixture of carbon tetrachloride, pyridine, and acetonitrile with triphenylphosphine.[15] Unfortunately this compound could not be hydrolyzed to the corresponding acid cleanly under a variety of conditions. In contrast, treatment of **14** with Lawesson's reagent followed by base hydrolysis readily provided the thiazole **15**.

Compounds **16**–**20** were prepared from iminoglycine **11** using sequences analogous to Scheme 2 by the appropriate choice of acylating agent (in step b) and *N*-sulfonylated amino acid (in step c) for amide coupling.

The $\alpha_4\beta_1$ integrin binding affinity of the reported compounds was assessed by measuring the reduction in binding of ^{125}I-VCAM-Ig to a suspension of Jurkat cells in the presence of the test compound as described previously.[6c] All test compounds were assayed at least in duplicate.

The data in Table 1 show that a significant amount of binding was lost by the introduction of conformation constraints via route I or route II (Fig. 1) relative to the parent dipeptides (**1a** vs **4**, and **1c** vs **5**, **15**). Also, N-methylation of the amide bond N—H in **1b** resulted in a compound with IC_{50} of 2400 nM, equivalent to a