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Combinatorial and Rational Strategies To Develop Nonpeptidic α4β7-Integrin Antagonists from Cyclic Peptides

Dirk Gottschling, Jürgen Boer, Anja Schuster, Bernhard Holzmann, and Horst Kessler*

The development of low-molecular-weight, nonpeptidic, and orally available drugs starting from biologically active peptides or proteins is one of the great challenges in medicinal chemistry. Herein we present an example in which a biologically active tripeptide has been reduced to a dipeptide in which the activity has been retained. New concepts in the treatment of inflammatory diseases have recently emerged.[1] One promising target to treat inflammatory diseases in the intestine is the inhibition of the α4β7-integrin/MAdCAM-1 interaction (MAdCAM-1 = mucosal addressin cell-adhesion molecule 1) interaction.[2] In contrast to other cell adhesion molecules, MAdCAM-1 is expressed only on a few cell types.[3,4] The interference of the α4β7-integrin/MAdCAM-1 interaction, which selectively mediates lymphocyte recruitment to the mucosa-associated lymphoid tissues of the intestine, is not expected to affect other parts of the immune system. As a consequence, no systemic side effects should occur during this therapy. The potential value of this therapy has already been shown with antibodies in animal models of colitis.[5,6] Recently, we and others reported the synthesis of peptidic α4β7-integrin antagonists that contain the Leu-Asp-Thr (LDT) recognition sequence for α4β7-integrins.[7–10] In our previous work we showed that the amide bond between Thr^4 and Asp^5 in the cyclic peptide *cyclo*-(Phe[1]-Leu[2]-Asp[3]-Thr[4]-Asp[5]-D-Pro[6]) was not essential. Furthermore, Thr^4 could be substituted with Val without loss of biological activity. Therefore, we synthesized a library of cyclic hexapeptides of the general formula *cyclo*-(Phe-Leu-Asp-Xaa-Asp-D-Pro). The biological evaluation of the corresponding compounds with a cell adhesion assay showed that when Xaa = phenylalanine (see **1**) or phenylglycine (see **2**) the biological activity towards inhibiting the α4β7-integrin/MAdCAM-1 interaction was maintained (Table 1). Based on these results and on the results of Shroff et al.,[9,10] we developed a library illustrated in Figure 1. Four different building blocks **A**, **B**, **C,** and **D** were used. Starting from isoquinoline-3-carbonyl-Leu-Asp-Thr-OH (**3**)[10] only one building block was changed each time. The resulting library was consequently not completely combinatorial. The synthesis of these compounds was performed step-by-step in parallel on solid supports, according to the Fmoc-strategy.[11] The incorporation of fluoroaromatics as

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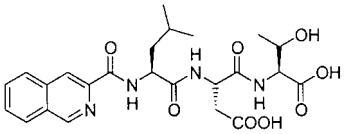
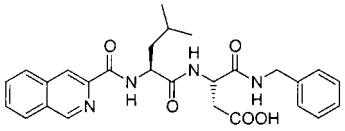
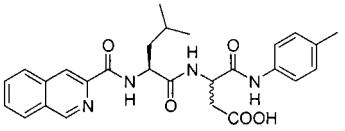
Table 1. Specific effects of peptidomimetics (1 mg mL^{-1}) on α4β7- and α4β1-integrin-mediated cell adhesion to MAdCAM-1 and VCAM-1.[a]

Structure	No.	Cell adhesion [%]		
		α4β7/MAdCAM-1	α4β7/VCAM-1	α4β1/VCAM-1
cyclo-(F-L-D-F-D-p)	**1**	59 ± 29	93 ± 9	81 ± 15
cyclo-(F-L-D-*Phg*-D-p)[b]	**2a**	38 ± 24	89 ± 2	80 ± 21
	2b	73 ± 20	101 ± 3	98 ± 3
	**3**[10]	48 ± 29	81 ± 4	NT[c]
	**4**	44 ± 21	67 ± 13	103 ± 1
	5a	53 ± 24	93 ± 18	101 ± 6
	**5b**	26 ± 7	51 ± 37	98 ± 13

[a] Cell adhesion is presented as a percentage of medium control. The data represents the mean ± standard deviation of three experiments, repeated three times. [b] Racemization occurred during synthesis. [c] NT = not tested.

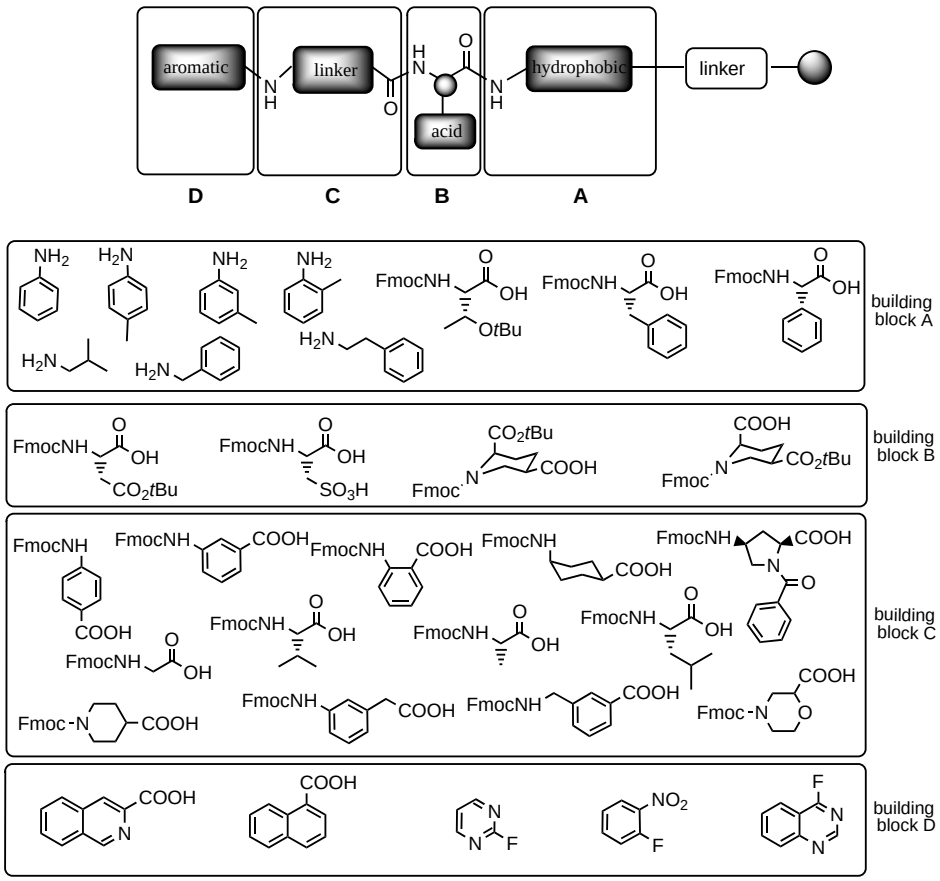


Figure 1. Building blocks used for the synthesis of a LDT-mimetic library.

building block **D** was achieved on solid supports by nucleophilic substitution.[12] The use of aniline derivatives as building block **A** afforded a fragment condensation of isoquinoline-3-carbonyl-Leu-Asp(O*t*Bu)-OH and the corresponding aniline derivative in solution. All compounds were purified by preparative HPLC and tested separately in a cell-adhesion assay.

For that purpose, the α4-integrin ligands MAdCAM-1 and VCAM-1 (VCAM-1 = vascular cell-adhesion molecule 1) were immobilized on microtiter plates and the adhesion of the lymphoid cell lines 38C13-β7 (α4β7^{pos}, α4β1^{neg}) and Jurkat (α4β1^{pos}, α4β7^{neg}) was analyzed in the presence or absence of the peptidomimetics at a concentration of 1 mg mL^{-1}. The inhibitory activity of the previously characterized α4β7-integrin antagonist *cyclo*-(Phe-Leu-Asp-Thr-Asp-D-Pro) was always measured at 1 mg mL^{-1} as a positive control.[7] The results of the biological evaluation of the library are summarized in Table 1. Only compounds of the general formula isoquinoline-3-carbonyl-Leu-Asp-Xbb-OH with Xbb = benzylamine (see **4**), aniline or *m*-, *o*-, *p*-toluidine (e.g. **5**) were able to inhibit the α4β7-integrin/MAdCAM-1 interaction. Notably, these compounds were highly selective, because they did not inhibit α4β1-integrin binding to VCAM-1 and only partially blocked α4β7-integrin/VCAM-1 interactions. In contrast to cyclic peptide **2a** (Xaa = Phg), the use of Xbb = Phg resulted in an inactive compound and in the case of Xbb = Phe the corresponding compound precipitated during biological evaluation. As Thr (building block **A**) could be substituted in compound **3** by an aromatic system, we tried to shift the phenyl ring along the peptide backbone. In medicinal

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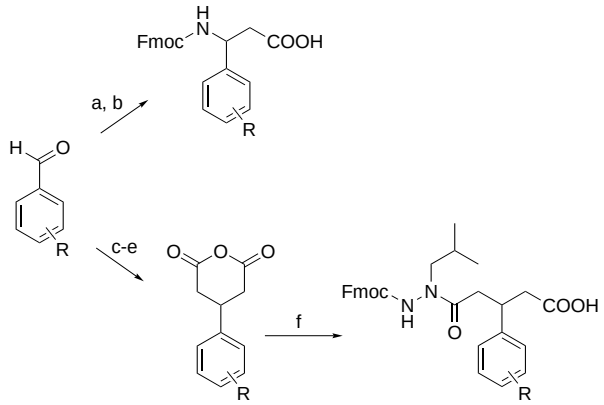
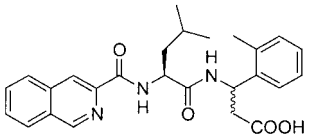
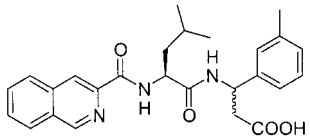
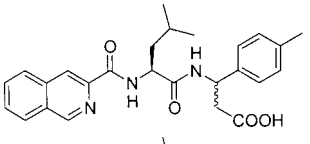
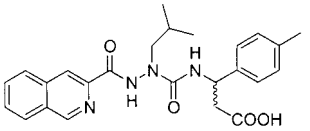
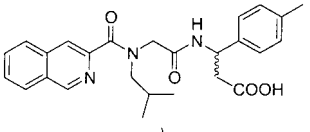
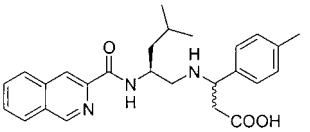
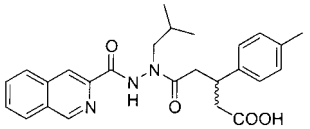
chemistry, it is sometimes possible to replace amide bonds by a phenyl ring, because of their similar structural properties.[13] We thus replaced the amide bond between Asp and Thr in compound **3** by a phenyl ring. We chose 3-amino-3-aryl-propionic acid as a mimic for the Asp-Thr-residue (Scheme 1).[14] 3-Amino-aryl-propionic acid-derivatives have already been shown to be useful building blocks for αvβ3-integrin antagonists.[15] Furthermore we synthesized (1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid as a conformationally constrained 3-amino arylpropionic acid derivative.[16] We also used phenylglycine and phenylalanine, which differ only in one methylene group from 3-amino arylpropionic acid, as dipeptide mimetics. Scheme 2 summarizes the Asp-Thr-dipeptide mimetics used. The biological evaluation of these compounds is shown in Table 2; only **6**, **7**, and **8** were able to mimic the Asp-Thr dipeptide residue and to inhibit α4β7-integrin/MAdCAM-1 interactions. As racemic 3-amino arylpropionic acid derivatives were used, both diastereoisomers of each compound were tested separately. Both isomers exhibited quantitative differences in their inhibitory efficacy, and we are thus currently focusing our attention on the determination of their stereochemistry. The substitution pattern of the phenyl ring appeared to have no influence on the biological activity. The 3-amino arylpropionic acid deriv-



Scheme 1. a) NH_4OAc, malonic acid, EtOH, 80 °C; b) Fmoc-Cl, $NaHCO_3$, dioxane, 0 °C; c) ethyl acetoacetate, piperidine, room temperature; d) KOH (20 M), 85 °C; e) acetic anhydride, 120 °C; f) *N*-Fmoc-*N*′-isopropylhydrazine, THF, 70 °C.

Table 2. Specific effects of compounds (1 mg mL^{-1}) that contain a dipeptide mimetic on α4β7- and α4β1-integrin-mediated cell adhesion to MAdCAM-1 and VCAM-1.[a]

Structure	No.	Cell adhesion [%]		
		$\alpha4\beta7$/MAdCAM-1	$\alpha4\beta7$/VCAM-1	$\alpha4\beta1$/VCAM-1
	**6a**	60 ± 26	79 ± 21	NT
	6b	19 ± 4	27 ± 6	NT
	**7a**	44 ± 1	66 ± 15	NT
	7b	15 ± 5	12 ± 4	NT
	**8a**	47 ± 8	65 ± 5	NT
	8b	18 ± 11	35 ± 11	NT
	**9**[c]	65 ± 14	102 ± 22	107 ± 6
	**10**[c]	100 ± 11	114 ± 2	111 ± 1
	**11a**	10 ± 4	41 ± 0	71 ± 14
	11b	11 ± 3	18 ± 6	19 ± 5
	**12**[c]	64 ± 2	91 ± 27	79 ± 24

[a] Cell adhesion is presented as a percentage of medium control. The data represents the mean ± standard deviation of three experiments, repeated three times. [b] NT = not tested. [c] Tested as a racemic mixture.

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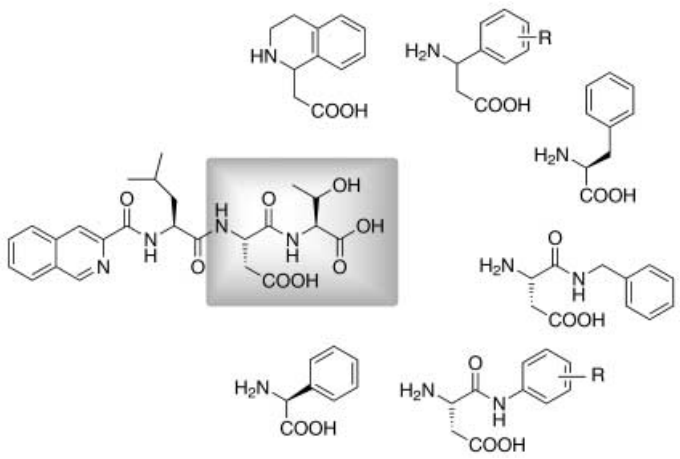

Scheme 2. Different building blocks were used as Asp-Thr dipeptide mimetics. Fmoc = 9-fluorenylmethoxycarbonyl.

atives **6**, **7**, and **8** were slightly less selective than the cyclic compound **2**. The use of (1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid, phenylglycine, or phenylalanine as Asp-Thr mimetics resulted in inactive compounds. To decrease the peptidic character of compound **8**, we used the corresponding azaamino acid azaLeu (**9**) and the peptoid building block Nleu (**10**) instead of Leu (Table 2). However, these modifications led to a significant loss of biological activity. Furthermore, the reduction of the amide bond between Leu and 3-amino-3-(4-methylphenyl)propionic acid in compound **8** resulted in biological active diastereoisomers (**11**). These compounds fulfill "Pfizer's rule of five"[17] (number of hydrogen donors: 3, number of hydrogen acceptors: 3, M_W: 433.5, log P: 4.19) and represent a promising starting point for further development. Scheme 3 summarizes the process of developing this compound.

We also used 3-phenylglutaric acid derivatives instead of the 3-amino arylpropionic acid residue (Scheme 1).[18] Recent work by our group has shown that 3-aryl-5-hydrazino-5-oxopentanoic acids represent a very promising pharmacophoric scaffold for αvβ3-integrin antagonists.[15] It seems, that compound **12** shows only a very weak inhibitory activity for the α4β7-integrin/MAdCAM-1 interaction. Nonetheless, it is conceivable that these compounds could be further optimized. In this case, the diacylhydrazine moiety would represent a universal scaffold for integrin antagonists. This would also support the assumption of Zheng and coworkers that αIIbβ3-integrin antagonists could be easily transformed into α4-integrin antagonists.[19]

In summary, we have shown that it is possible to develop low-molecular-weight, nonpeptidic α4β7-integrin antagonists by using rational and combinatorial strategies. In the post-genomic area, inhibition of protein–protein interactions becomes increasingly important as an independent approach to interfere with the function of defined target structures. We have demonstrated that the stepwise procedure: proteine-sequence→cyclic, constrained peptides→peptido-mimetics→nonpeptidic leads can be a valuable method to develop new drugs.

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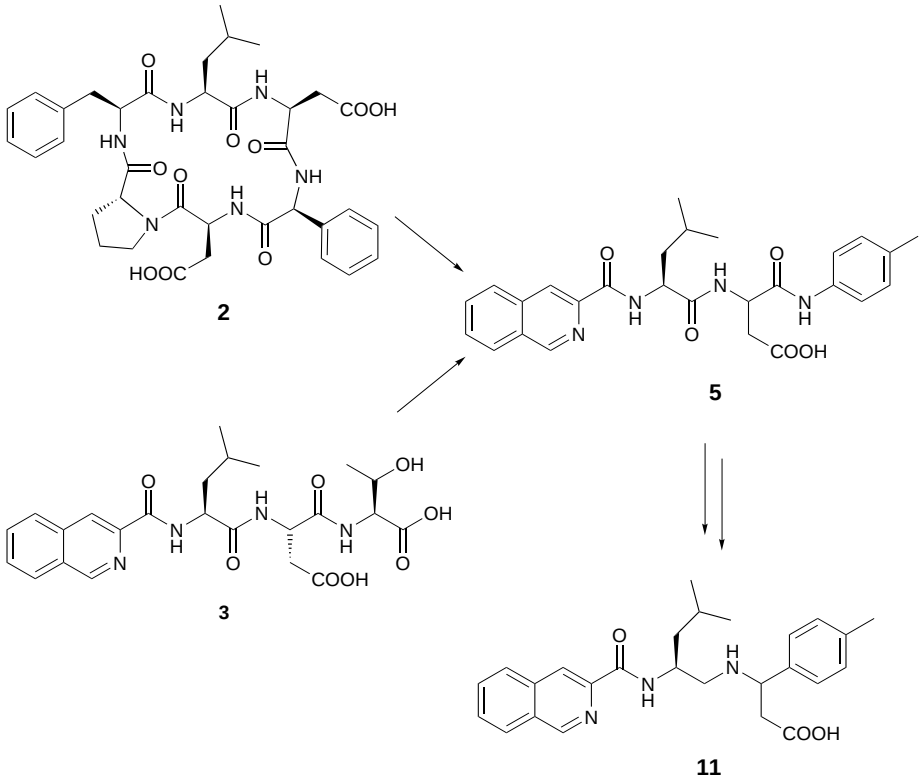

Scheme 3. Stepwise development of nonpeptidic α4β7-integrin antagonists.

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Tetraiodobutatriene: A New Cumulenic Carbon Iodide**

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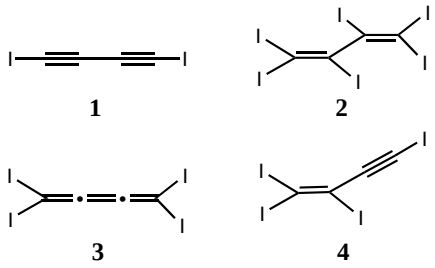
Diiodopolyynes such as **1** have attracted our attention as potential precursors to all-carbon molecules and materials. Lespieau and Prévost reported 75 years ago that diiodobutadiyne (**1**) reacts with molecular iodine to form hexaiodobutadiene (**2**).[1] Others repeated this experiment with similar results, each time obtaining a yellow solid that melted at about 165°.[2] We now present evidence that, under appropriate conditions, this same reaction can instead give cumulene **3**, which is stable, isolable, and fully characterized (Scheme 1).



Scheme 1. A family of carbon iodides C_4I_x.

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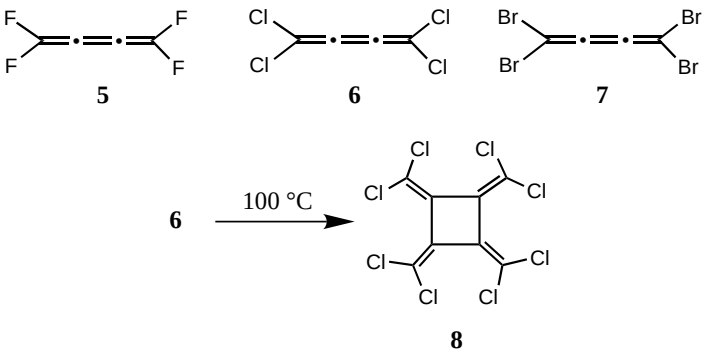
We recently synthesized two longer diiodopolyynes, C_6I_2 and C_8I_2,[3] and began exploring methods for the ordered polymerization of such iodine-capped polyynes. As part of our studies, we collected X-ray data on a crystal from a previously pure sample of **1** which had been sitting on a benchtop for several months. Instead of the expected butadiyne **1**, the sample contained novel butatriene **3**. Evidently, **1** (C_4I_2) can disproportionate over time to yield **3** (C_4I_4), with unknown carbon-rich by-products. However, the majority of crystals in the sample still contained **1** instead of **3**; the decomposition reaction had occurred in low overall yield.

Compound **3** is one of only a handful of halogenated cumulenes that have been characterized. Perfluorobutatriene **5** (Scheme 2) is extremely unstable; it reportedly explodes above its boiling point of −5 °C and decomposes even at −80 °C.[4] Perchlorobutatriene **6** is more stable (m.p. 59–60 °C), but like many cumulenes it dimerizes to form radialene **8** when heated.[5] Perbromobutatriene **7** has not been reported, and compound **3** is, to the best of our knowledge, the first known iodine-substituted cumulene of any sort.[6]



Scheme 2. Cumulenes **5** and **6** are known; **7** is not.

We have now found conditions which lead cleanly to **3** in good yield. Iodination of **1** in concentrated solution in hexanes produces a yellow precipitate after only a few minutes.[7] Filtration separates the solid from the solvent and any remaining I_2, leaving a yellow powder (m.p. 142–143 °C). As discussed below, mass spectrometry, IR and NMR spectroscopy, and X-ray diffraction studies all confirm that this material is cumulene **3**.

Without careful handling, however, compound **3** rapidly decomposes in solution to give **2**. The decomposition reaction occurs in pure solutions of **3**, suggesting a disproportionation mechanism, much like the observed decomposition of **1**. The simplest disproportionation of **3**, to give equal parts of **1** and **2**, would be endothermic by 9.1 kcal mol^{-1}, according to density-functional (B3LYP/LanL2DZ) calculations.[8] Furthermore, we found no evidence for the formation of **1** during the decomposition reaction. Thus far, we have been unable to identify the by-product(s) of this reaction.

The decomposition of **3** can be monitored by thin-layer chromatography (TLC; AlO_3/hexanes).[9] When **3** is dissolved in a variety of solvents (e.g., THF, CS_2), the diyne disappears over several minutes, while a new TLC spot appears simultaneously, corresponding to **2**. In some solvents (acetone, benzene, CCl_4), TLC indicates that **3** is stable unless exposed

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