

Multimeric Presentation of RGD Peptidomimetics Enhances Integrin Binding and Tumor Cell Uptake

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Abstract: The use of multimeric ligands is considered as a promising strategy to improve tumor targeting for diagnosis and therapy. Herein, tetrameric RGD peptidomimetics were designed to target $\alpha_v\beta_3$ integrin-expressing tumor cells. These compounds were prepared *via* an oxime chemoselective assembly of *cyclo*(DKP-RGD) ligands and a cyclodecapeptide scaffold that allows a tetrameric presentation. The resulting tetrameric RGD peptidomimetics were shown to improve $\alpha_v\beta_3$ integrin binding compared to the monomeric form. Interestingly, these compounds were also able to enhance tumor cell endocytosis in the same way as tetrameric RGD peptides. Altogether, the results show the potential of the tetrameric *cyclo*(DKP-RGD) ligands for *in vivo* imaging and drug delivery.

Introduction

Multivalent interactions play a key role in numerous biological processes including antibody-antigen, virus-cell, and cell-cell recognition.^[1] In particular, multivalent interactions enhance the avidity of multimeric species, resulting in an increased binding affinity compared to each individual binding unit.^[2] As an application of this concept to tumor-targeted therapy or diagnosis, multivalency could improve the tumor targeting performance of Small Molecule - Drug Conjugates (SMDCs), potentially approaching the well-known selectivity and binding strength of Antibody - Drug Conjugates (ADCs).^[3] To date, multivalency has found application in targeting agents for imaging, drug delivery or a combination thereof.^[4] Among relevant biological targets, the $\alpha_v\beta_3$ integrin subclass has received special attention as it is involved in tumor development including melanoma, prostate, breast, pancreatic carcinoma, and aggressive metastatic cancers.^[5] As $\alpha_v\beta_3$ -expressing cells interact with the extracellular matrix *via* the recognition of the ubiquitous sequence RGD (Arg-Gly-Asp), much research effort

has been devoted to the design of RGD peptides^[6] and peptidomimetics^[7] that display this triad sequence. Various molecular scaffolds were used to construct multivalent ligands varying in size, shape and physico-chemical properties.^[8] The design of RGD clusters appears to be a prerequisite for effective integrin recognition.^[9] For a decade, the Grenoble group has shown that a cyclodecapeptide scaffold, named RAFT (Regioselectively Addressable Functionalized Template), exhibits suitable properties to design multivalent ligands.^[10] The benefit of RAFT-supported tetrameric RGD compounds for tumor therapy has been recently reported.^[11]

Taking advantage of the cyclodecapeptide RAFT scaffold, herein we describe the modular synthesis and the *in vitro* characterization of tetrameric RGD peptidomimetic **1** (Figure 1). For this purpose, we exploited *cyclo*(DKP-RGD) peptidomimetic **2** derived from *trans*-diketopiperazine (DKP). This compound was shown to be highly specific for $\alpha_v\beta_3$ integrin with nanomolar IC₅₀ values.^[7e] The DKP 6-membered ring has been incorporated in the ligand structure to reduce its susceptibility to proteolytic degradation and to diminish conformational flexibility. Moreover, the presence of groups that can act as H-bond donors (amide proton) or acceptors (amide carbonyl groups) allows for potentially favorable interactions of the DKP scaffold with biological targets. In the last decade, the Milan group has designed and synthesized several SMDCs employing the *cyclo*(DKP-RGD) ligand as recognition unit, confirming its potential for the selective delivery of cytotoxic agents.^[12]

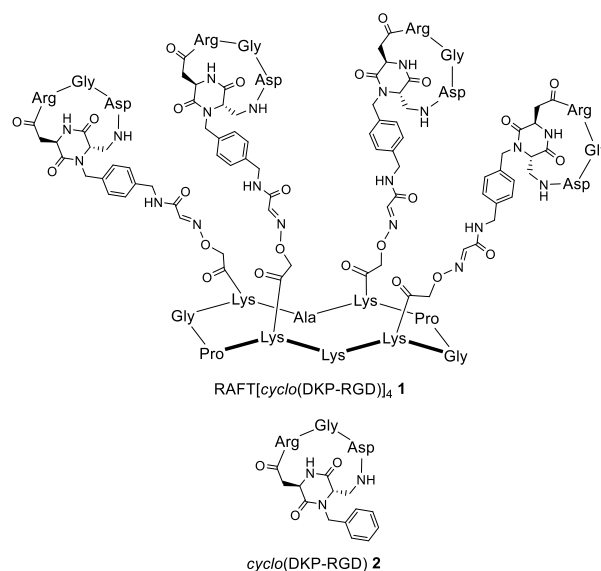


Figure 1. Molecular structure of the $\alpha_v\beta_3$ integrin tetrameric and monomeric *cyclo*(DKP-RGD) containing ligands (**1** and **2**).

Results and Discussion

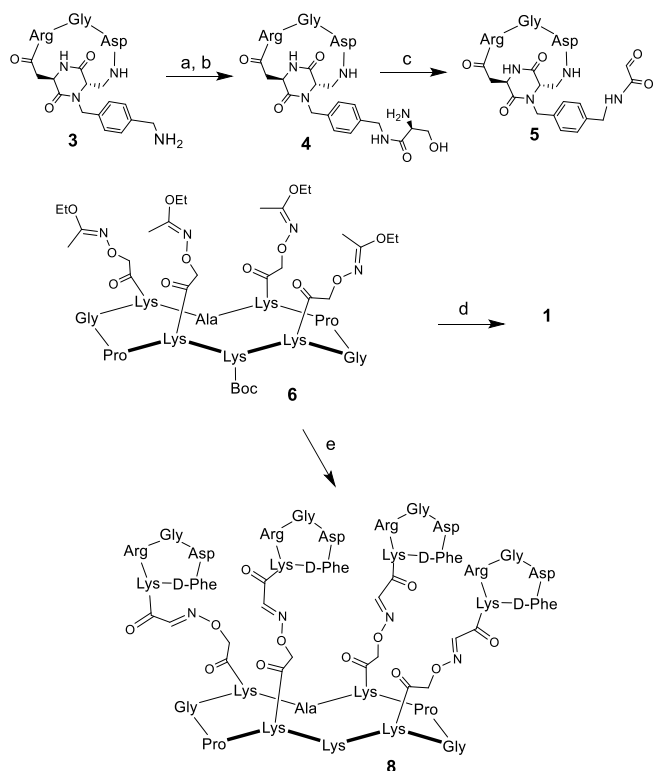
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Access to multimeric compound **1** was carried out following Scheme 1, using the highly chemoselective and efficient oxime ligation protocol. For this purpose, a serine residue was introduced into the RGD peptidomimetic **3**, the functionalized version of compound **2**, bearing an amino moiety suitable for conjugation.^[12a] Oxidative cleavage with sodium periodate of the amino-alcohol moiety of serine-containing peptidomimetic **4** afforded the desired glyoxylyl RGD compound **5** in good overall yield (74%). In parallel, cyclodecapeptide **6** was prepared by a combination of SPPS (solid phase peptide synthesis) and solution strategy.^[13] The 1-ethoxyethylidene group was selected to protect the aminoxy functions due to its stability under SPPS conditions and easy removal under the mild acidic conditions used for the oxime ligation. Then, one-pot aminoxy deprotection of **6** and subsequent ligation of aldehyde containing-compound **5** were performed in an aqueous trifluoroacetic acid solution, affording the expected tetrameric RAFT[*cyclo*(DKP-RGD)]₄ peptidomimetic **1** in 44% yield after RP-HPLC purification. Compound **1** was characterized by ESI-MS and the observed *m/z* was found in excellent agreement with the calculated value (see the Supporting Information).



Scheme 1. Synthesis of tetrameric RAFT[*cyclo*(DKP-RGD)]₄ ligand **1** and tetrameric RAFT[*cyclo*(RGDfK)]₄ ligand **8**. Reagents and conditions: a) Boc-Ser(*t*-Bu)-O-NHS, DMF, DIPEA, RT, 2 h; b) TFA/H₂O (19/1), RT, 2 h; c) NaIO₄, H₂O, RT, 20 min; d) **5**, TFA/H₂O (7/3), RT, 30 min; e) *cyclo*(RGDfK)-CO-CHO, RT, 30 min.

In parallel, control compounds such as the monomeric *cyclo*(DKP-RGD) **2**,^[7e] *cyclo*(DKP-RβAD) **7**,^[14] and the peptidic analog RAFT[*cyclo*(RGDfK)]₄ **8**^[9d] were prepared as previously

described. It is important to note that incorporation of β-alanine (βA) instead of glycine within the RGD sequence is known to result in a complete loss of biological activity.^[9d,14]

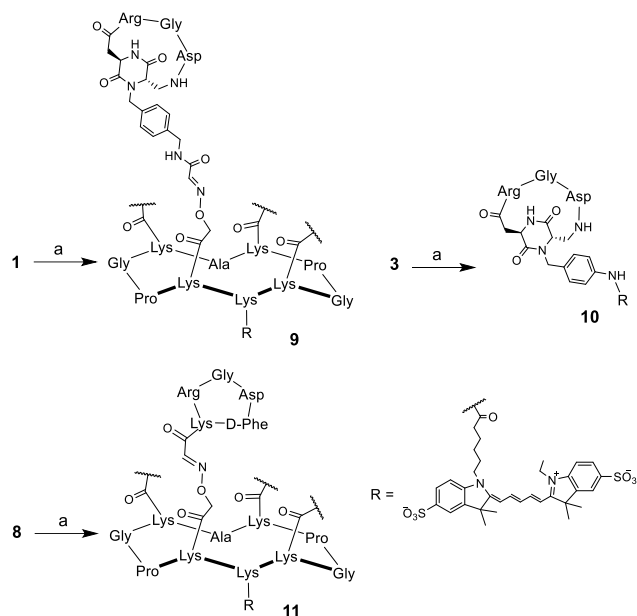
The compounds were then examined *in vitro* for their ability to inhibit biotinylated vitronectin binding to the purified α_vβ₃ receptor. Experiments were performed by incubating immobilized integrin with solutions of the compounds at different concentrations (10⁻¹² to 10⁻⁵ M) in the presence of biotinylated vitronectin (1 μg·mL⁻¹). The IC₅₀ values are shown in Table 1. As expected, the control compound *cyclo*(DKP-RβAD) **7** displayed strongly reduced binding affinity, that is three orders of magnitude lower than *cyclo*(DKP-RGD) **2**. Interestingly, while functionalization of the parent *cyclo*(DKP-RGD) ligand **2** with the *p*-aminomethyl group, leading to amine **3** and derivatives, generally results in a lower α_vβ₃ integrin binding affinity (e.g. IC₅₀ of amine **3** = 26.4 ± 3.7 nM),^[12a] the tetrameric RAFT[*cyclo*(DKP-RGD)]₄ peptidomimetic **1** showed subnanomolar affinity, with an IC₅₀ lower than that of monomeric *cyclo*(DKP-RGD) **2** (4.5-fold decrease of IC₅₀). This result highlights the improvement of the binding affinity through multiple presentation of the integrin ligand. However, we found that the binding potency of peptidomimetic **1** is lower than that of the peptidic analog **8**, paralleling the relative affinity of the respective monomeric ligands [cf. the IC₅₀ value of *cyclo*(DKP-RGD) **2** = 4.5 ± 1.1 nM with that of *cyclo*(RGDfK) = 1.4 ± 0.2 nM].^[15] Based on previous studies, optimization of the linker lengths could be important to improve biological activity.^[16]

Table 1. Inhibition of biotinylated vitronectin binding to the α_vβ₃ receptor.

Compound	Structure	α _v β ₃ IC ₅₀ [nm] ^[a]
1	RAFT[<i>cyclo</i> (DKP-RGD)] ₄	0.98 ± 0.27
2	<i>cyclo</i> (DKP-RGD)	4.5 ± 1.1 ^[b]
7	<i>cyclo</i> (DKP-RβAD)	1550 ± 226 ^[c]
8	RAFT[<i>cyclo</i> (RGDfK)] ₄	0.18 ± 0.01

[a] IC₅₀ values were calculated as the concentration of compound required for 50% inhibition of biotinylated vitronectin binding, as estimated by GraphPad Prism software. All values are the arithmetic mean ± the standard deviation (SD) of triplicate determinations; [b] see ref.^[7e]; [c] see ref.^[14].

To evaluate the interactions of the RAFT[*cyclo*(DKP-RGD)]₄ peptidomimetic with cancer cells, we introduced a near-infra red (NIR) fluorescent reporter such as Cyanine 5 (Cy5) (Scheme 2). Cy5 dye was conjugated to the lysine side-chain of compounds **1** and **8**, and to the exocyclic amino group of **3** under neutral conditions (pH 8.0), affording the fluorescent conjugates **9-11** in good yields after RP-HPLC purification. Fluorescent compounds were characterized by ESI-MS: *m/z* were found to be in agreement with the calculated values (see the Supporting Information).



Scheme 2. Synthesis of fluorescent compounds **9-11**. Reagents and conditions: a) Cy5-NHS, DIPEA (pH 8.0), DMF, 3 h, RT.

The recognition potency of the different compounds was determined by using flow cytometry assays (Figure 2). For this purpose, human U87 glioblastoma and M21 melanoma that express $\alpha_v\beta_3$ integrin to a similar extent (see Figure S1 in the Supporting Information), and the α_v -negative variant M21-L cell lines were chosen. As observed with the $\alpha_v\beta_3$ receptor (Table 1), we confirmed the high potency of the fluorescent RAFT[*cyclo*(DKP-RGD)]₄ **9** compared to the monovalent analog *cyclo*(DKP-RGD) **10**, using U87 glioblastoma in particular and, to a lesser degree, M21 melanoma cell lines. It is worth mentioning the comparable biological activity of both tetrameric RGD compounds **9** and **11**, which highlights the biological potential of **9** for tumor targeting. In contrast, compound **10** may be less efficient on different cell lines expressing similar levels of integrin $\alpha_v\beta_3$ because this receptor may not behave identically in each cell line. As expected, only low binding was observed on the M21-L α_v -negative control cell line (Figure 2c).

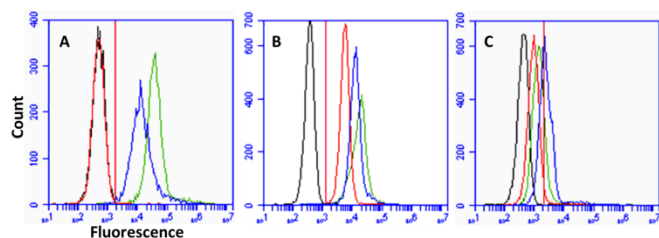


Figure 2. Flow cytometry analysis of A) U87, B) M21, and C) M21L. Experiments were performed by incubating cells with 0.5 μM of compounds **9** (blue plot), **10** (red plot), **11** (green plot) and without compound (black plot) in Dulbecco's modified eagle medium (DMEM) for 30 min at 37°C.

To further investigate the potential of DKP-compound for drug delivery, we examined the behavior of compounds **9-11** in the presence of cells expressing $\alpha_v\beta_3$ integrin, by using confocal microscopy. As shown in Figure 3, NIR fluorescent compounds were detected in the cytoplasm with the presence of small vesicles. Weak signal was observed when cells were incubated with fluorescent monomeric *cyclo*(DKP-RGD) **10** (Figure 3c) reinforcing the observation that the multimeric presentation clearly improves cell targeting. Similar uptake was found for tetrameric RGD compounds **9** and **11**. Moreover, the presence of small vesicles suggests that the internalization occurs *via* classical pathways observed for RGD compounds [9d,17] and natural ligands such as vitronectin.[18] We obtained similar results when M21 cells were incubated with compounds **9-11** (see Figure S2 in the Supporting Information). Notably, the presence of the fluorescent conjugates **9-11** was never detected in the nuclei of U87 and M21 cells.

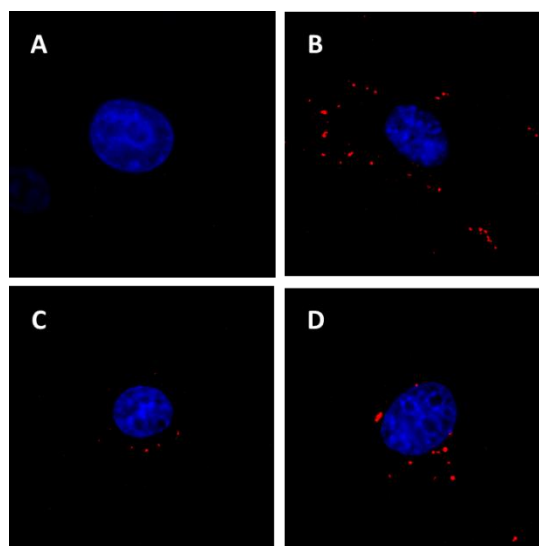


Figure 3. Representative fluorescence confocal images from living U87 cells (10^5 cells/mL) incubated for 30 min at 37°C a) without compound, b) with **9** (0.5 μM), c) with **10** (0.5 μM), and d) with **11** (0.5 μM). Nucleus was stained by using Hoechst 33342 dye.

Conclusions

In recent years, much research effort has been devoted to improve the tumor-targeting properties of RGD compounds.[19] In particular, multimeric systems were shown to give superior *in vivo* pharmacokinetics than monomeric RGD peptides. In the present work, tetrameric RAFT[*cyclo*(DKP-RGD)]₄ peptidomimetics were prepared through a convergent synthetic scheme. We have shown that this multimeric design results in improved $\alpha_v\beta_3$ integrin binding and stronger cancer cell uptake. Altogether, our results demonstrate the potential of the tetrameric RAFT[*cyclo*(DKP-RGD)]₄ peptidomimetics for *in vivo* imaging and drug delivery. The use of *cyclo*(DKP-RGD)-based peptidomimetics instead of traditional RGD peptides should also provide interesting properties such as increased stability towards

proteolytic degradation and a better pharmacokinetic perspective. Additional *in vivo* experiments in mice concerning pharmacokinetic assessment are in progress and will be reported in due course.

Experimental Section

All compounds were prepared according to literature procedures. Compounds **2**, **7**, **8**, and **11** were prepared as previously described.^[7e,9d,14] Detailed procedures of compounds **1**, **9** and **10**, analytical data and biological experiments are reported in the Supporting Information.

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Keywords: peptidomimetics • multivalency • RGD peptide • cell targeting • integrin

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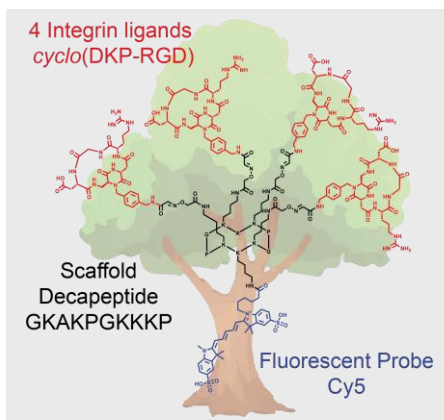
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Multiplicity makes for strength.

Multimeric presentation can effectively increase the strength of peptidomimetic ligand - receptor interactions and enhance tumor cell uptake.



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Multimeric Presentation of RGD Peptidomimetics Enhances Integrin Binding and Tumor Cell Uptake
