Bioorganic & Medicinal Chemistry 25 (2017) 1875–1880

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Incorporation of arginine mimetic residue into peptides for recognition of double stranded nucleic acid structure: Binding and aggregation studies

Mao Li [a,1], Marija Matković [b,1], Ivo Piantanida [b,*], Carsten Schmuck [a,*]

[a] Institute for Organic Chemistry, University of Duisburg-Essen, 45117 Essen, Germany
[b] Division of Organic Chemistry & Biochemistry, Ruđer Bošković Institute, P.O. Box 180, 10002 Zagreb, Croatia

A R T I C L E I N F O

Article history:
Received 8 December 2016
Revised 27 January 2017
Accepted 2 February 2017
Available online 6 February 2017

Keywords:
Arginine mimic
Polynucleotide binding
DNA/RNA recognition
Hydrogen bonds
Ion pair

A B S T R A C T

An arginine mimetic, featuring a guanidiniocarbonypyrrol as artificial anion binding site (GCP), was introduced into short peptides to study their binding and aggregation with double stranded DNA and RNA. While the incorporation of this GCP modification did not significantly change the overall binding affinity for DNA/RNA, their interactions were more sensitive with respect to the type of polynucleotides. Peptide **4**, with four GCP modifications, exhibited amazing fluorescent selectivity for AU- and (to a lesser extent) AT- sequences. GC-containing DNA showed much lower response. Additionally, exclusively tri-GCP modified peptide **3** showed intriguing exciton-coupled bisignate ICD bands for all studied DNA/RNA which suggested that a well-defined GCP-dimer bound into DNA/RNA groove..

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Molecular recognition between peptides and nucleic acids is the central event in biological system.[1–3] Understanding of such events has profound significance for biochemical and medical applications. In nature, proteins with high content of cationic amino residues such as lysine, histidine and arginine are crucial for DNA recognition processes.[4–6] A typical example is protamine, which is a small, highly positively charged peptide used by cells to condense DNA at very high density in sperm nuclei.[7–10] The exclusive use of arginine in protamine suggests that the guanidinium cation in the side chain of arginine plays a crucial role in the binding and condensation process. For instance, of the 32 amino acids of salmon protamine, 21 are arginine residues.[11] Bovine protamine has 26 arginines of its 50 total amino acids and human protamines also consist half of arginine residues in their sequences.[11,12] The guanidinium cation, with a pK_a around 12–13, is positively charged under physiological conditions. Moreover, guanidinium cations can form bidentate hydrogen bonds with the phosphate linkage in DNA backbone.[13] The hydrogen bonding ability of guanidinium most likely endows arginine residues with a superior binding affinity for DNA in comparison to lysine residues, which possess only simple ammonium cations.

A number of synthetic nucleic acid binding motifs were developed in recent years.[14] Diarylamidines (such as DAPI and pentamidine) are now routinely used in molecular biology for DNA staining.[15] Another example is Distamycin A, a tri-(*N*-methylpyrrole) peptide, which binds to AT- rich DNA in the minor groove.[16,17] However, rationally designed peptides equipped with arginine mimetics are still rarely reported. We previously reported a guanidiniocarbonypyrrol (abbreviated GCP) moiety which showed enhanced oxoanion binding ability relative to simple guanidinium cations in water.[18] GCP can form H-bond assisted ion pairs with oxoanions such as carboxylate and phosphate. We have demonstrated that this tailor made anion binding motif can be conjugated with aryl derivatives which showed interesting properties in DNA/RNA recognition.[19–21] Incorporation of the GCP moiety in peptides has also shown to be rather effective in biological applications including gene delivery and cellular uptake.[22,23] We thus hypothesized that the introduction of GCP moieties in the side chain of peptides as arginine mimetics could provide interesting properties in the recognition between these peptides and double stranded (ds-) nucleic acids.

* Corresponding authors.
E-mail address: carsten.schmuck@uni-due.de (C. Schmuck).
[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.bmc.2017.02.006
0968-0896/© 2017 Elsevier Ltd. All rights reserved.

2. Results and discussion

2.1. Design and synthesis of peptides

A series of peptides with different numbers of GCP modifications were thus designed and synthesized (Fig. 1). Peptide **1** and **4** were tetra peptides with one and four GCP modifications, respectively. Dipeptides **2** and **3** were also designed to examine the influence of the number of GCP modifications on DNA/RNA binding. Tetra arginine peptide **5** was synthesized as control. The synthesis of peptides **4** and **5** has been reported previously.[22] Peptide **1** was obtained by Fmoc solid phase synthesis as shown in Scheme 1. Briefly, rink amide MBHA resin was attached consecutively with Fmoc-Lys(Boc)-OH and finally with Fmoc-Lys(Alloc)-OH. Alloc protection group was removed by the treatment with $Pd(PPh_3)_4$ and afterwards GCP was coupled to the free amino group of the side chain of lysine. Subsequently deprotection and cleavage gave rise to the desired crude product **1**. The crude product was purified with MPLC and the purity was check by analytical HPLC. The final product **1** was identified with MALDI-Tof mass spectrometry and NMR. GCP modified dipeptides **2** and **3** were also synthesized with similar strategy (see experimental section).

2.2. Physiochemical properties of peptides 1 – 5 in aqueous solution

Peptides **1** – **5** were well soluble in aqueous solutions, which were stable over long period of time when kept at +8 °C. The absorbency of buffered solution of the compounds is proportional to their concentration within the used concentration range, the absorption maxima and the corresponding molar absorptivities (ε) are given in Table 1. On the temperature increase up to 95 °C, changes of UV/Vis spectra were only minor at maximum wave-

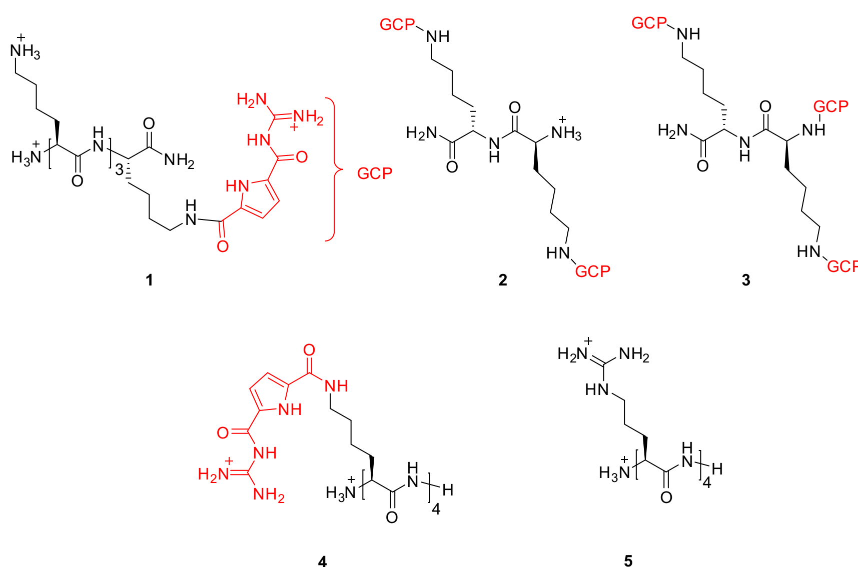
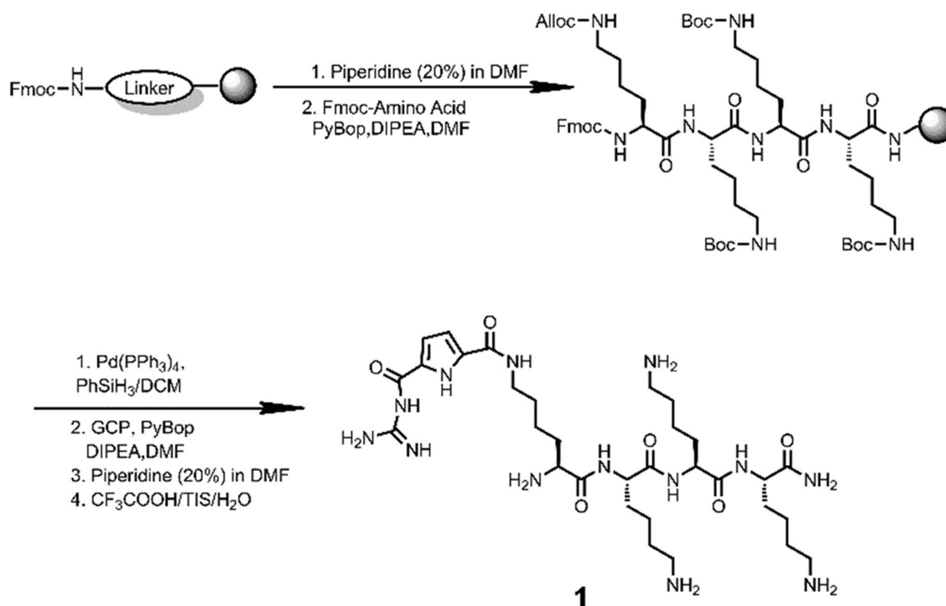


Fig. 1. Chemical structure of GCP modified peptides **1** – **4** as well as control peptide **5**. GCP moiety is highlighted in red.



Scheme 1. Solid phase synthesis of **1**.

Download English Version:

https://daneshyari.com/en/article/7776070

Download Persian Version:

https://daneshyari.com/article/7776070

Daneshyari.com