Tetrahedron 68 (2012) 4501–4505

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Double-sided α-helix mimetics

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ARTICLE INFO

Article history:
Received 6 October 2011
Received in revised form 2 November 2011
Accepted 4 November 2011
Available online 12 November 2011

Keywords:
Foldamer
Helical structure
Peptidomimetic
Proteomimetic
Protein–protein interaction

ABSTRACT

The design and synthesis of substituted bis- and tris-benzamides is reported in which the projection of side-chain residues on both sides of an α-helix is reproduced. The scaffold is conformationally constrained by a series of intramolecular hydrogen bonds, allowing for spatial and angular mimicry of the *i*, *i*+2, *i*+4 and *i*+6 side-chains in the case of the bis-benzamide, and may be extended to higher-order oligomers.

1. Introduction

Protein–protein interactions (PPIs) are responsible for diverse biological functions ranging from signal transduction to immune response.[1] Among protein secondary structures, α-helices form the largest class and are responsible for a multitude of PPIs and the stability of higher-order structures.[2] Hence, the design of α-helix mimetics as inhibitors of aberrant interactions is a promising strategy that has attracted wide attention from the synthetic community. There are many reports in which both peptidic[3] and non-peptidic[4] oligomers project substituents in the correct spatial and angular orientation to mimic the side-chains of one face of an α-helix—frequently those of the *i*, *i*+4 and *i*+7 residues. Non-peptidic scaffolds include indanes, terphenyls, terpyridyls and polycylic ethers.[4e] In a related approach, hydrogen-bond-constrained scaffolds including enaminones,[5] benzoylureas, tris-pyridylamides and tris-benzamide have been developed as more accessible mimetics in which the syntheses are simplified and the biological properties improved (Fig. 1a,b, Ref. 4b and refs therein).

Whilst there are a growing number of synthetic scaffolds for the mimicry of side-chains on a single face of an α-helix, there have been very few examples in which the side-chain projection of two faces is reproduced.[6] Of these approaches, many do not allow extension to higher-order oligomers in which more than three or four side-chains are mimicked. The side-chains projecting from the exterior face of an α-helix have been widely implicated in the binding of multiple proteins and in bacterial cell wall sensing. Hrs-UIM (hepatocyte growth factor-regulated tyrosine kinase substrate-ubiquitin interacting motif),[7] golgi associated protein

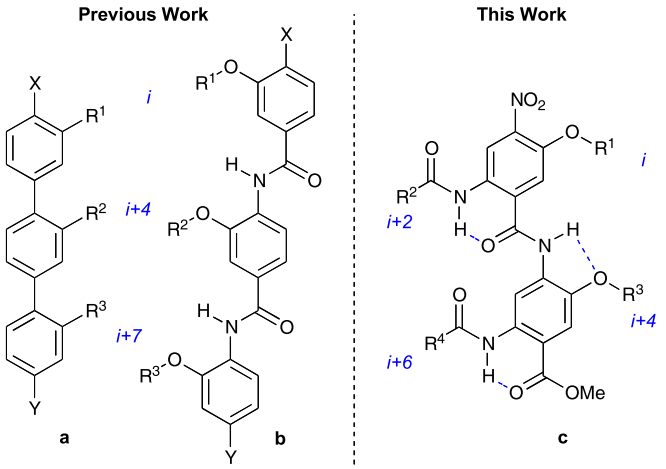

Fig. 1. Functionalized single- and double-sided α-helix mimetics: (a) terphenyl; (b) tris-benzamide; (c) bis-benzamide.

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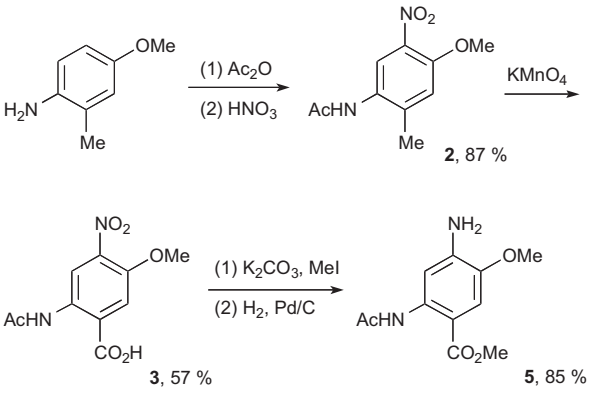
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.11.010

Arf-GAP1[8] and glucagon like peptide-1 (GLP-1)[9] depend of residues of both faces of the α-helix for their function. Antimicrobial peptides (magainins, defensins and protegrins) have one side of their backbone composed of cationic groups to interact with anionic phospholipids and lipopolysaccharides on the bacterial cell wall, and another side composed of hydrophobic groups to facilitate penetration of the bacterial membrane.[10]

With the goal of creating a novel scaffold for simultaneous mimicry of two faces of an α-helix, we have designed a series of double-sided mimetics based on our benzamide scaffold[11] (Fig. 1c). We anticipated that this design would adopt a constrained conformation due to intramolecular H-bonding between the amide N–H and *ortho*-alkoxy group, and mimic of the *i*, *i*+2, *i*+4 and *i*+6 residues of an α-helix. The two oligomer precursors originate from a common intermediate and may be connected via nucleophilic attack of an aromatic amine on an activated carboxyl group. A range of acyl groups, potentially including amino acids, may be incorporated in the *i*+2 and *i*+6 positions.

2. Results and discussion

Synthesis of carboxylic acid monomer **3** from 2-amino-5-hydroxybenzoic acid or 4-chloro-2-methylaniline was poor yielding; however a robust three-step procedure was established starting from *m*-cresidine in 50% overall yield (Scheme 1). Esterification of the carboxylic acid and reduction of the nitro-group gave amine **5** in 85% yield, setting the stage for coupling with **3** to form bis-benzamide **10**.



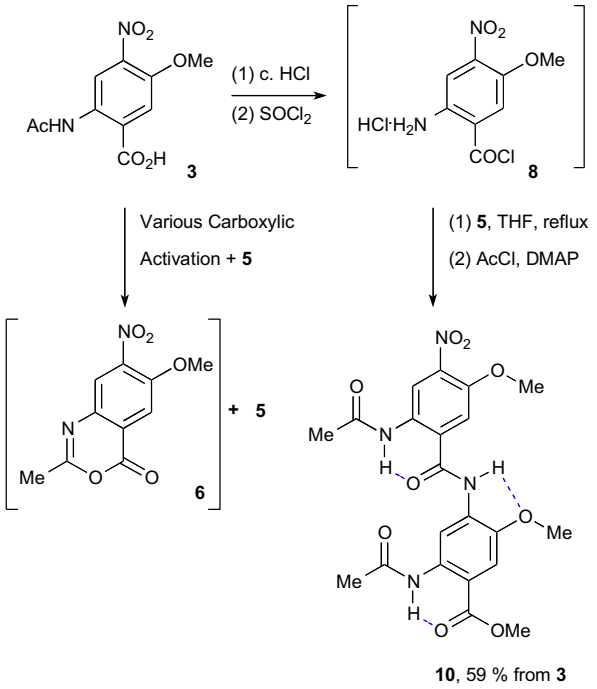
Scheme 1. Synthesis of building blocks.

Activation of **3** as an acid chloride, or the use of coupling agents such as DCC, EDCI, HATU, gave an intermediate thought to be benzoxazinone **6** and recovered amine **5**.

As an alternative we protected the amino group of **3** as the hydrochloride salt (**7**, not shown) prior to carboxyl activation coupling in refluxing tetrahydrofuran and reacylation with acetyl chloride. Overall this represents a modular and scalable six-step bis-benzamide synthesis from *m*-cresidine (Scheme 2).

The single crystal X-ray structure of bis-benzamide **10**[12a] confirms the presence of hydrogen bonds between side-chain N–Hs and the adjacent carbonyls of 1.9 and 2.0 Å, and between the main-chain N–H and *ortho*-alkoxy group of 2.1 Å in the solid state. These appear to provide a conformationally constrained scaffold in which substituent projection is in good agreement with the *i*, *i*+2, *i*+4 and *i*+6 side-chains of an α-helix; i.e., two residues on one face of an α-helix and two residues on the other face (Fig. 2).

Our synthetic strategy enabled us to synthesize heterodimers where, following amide bond formation, the free amino group may be decorated with a variety of different acyl groups to generate bis-benzamides bearing different side-chains (Scheme 3).[12b]



Scheme 2. Synthesis of functionalized bis-benzamide bearing four side-chains.

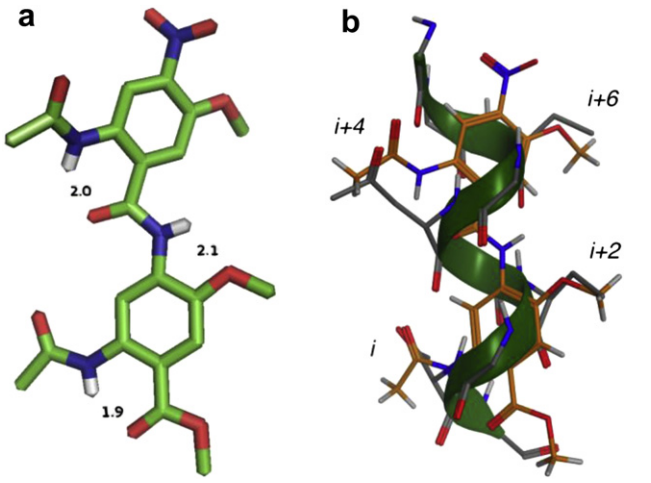


Fig. 2. (a) X-ray crystal structure of bis-benzamide **10**. (b) Substituents of bis-benzamide X-ray structure (orange) fitting the side-chains of an α-helix (grey, green ribbon) with a root-mean-square deviation of 0.434 Å.[13]

Following our standard protocol for benzamide formation, reduction of nitro-substituted bis-benzamide **10**, coupling with acid chloride **8** and acylation gave hexa-substituted tris-benzamide **16** (Scheme 4). This molecule has substituents mimicking the side-chain positions of the *i*, *i*+2, *i*+4, *i*+6, *i*+8 and *i*+10 positions.

3. Conclusions

In summary, we have designed a modular and scalable route to conformationally constrained double-sided benzamide α-helix mimetics and have efficiently synthesized a range of heterodimeric bis-benzamides and a tris-benzamide bearing six side-chains. The synthesis is amenable to extension of these mimetics to higher oligoamides and to molecules with a broad array of *N*-acyl groups.