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REVIEW ARTICLE

Foldamers containing γ-amino acid residues or their analogues: structural features and applications

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Abstract Over the past 20 years, the field of foldamers has rapidly increased. Many β-peptides have already been described and shown interesting properties. γ-Peptides have more recently emerged but seem to be very interesting as well. In this review, we will cover every peptidomimetic oligomer that contains a γ-amino acid or an analogue and presents a structural feature. It includes γ-peptides but also hybrid α–γ peptides, β–γ peptides and analogues such as oligoureas or aminoxy acids. We will present the biological properties of these oligomers.

Keywords Gamma-amino acid · Gamma-peptide · Foldamer · Hybrid peptide · Secondary structure

Introduction

Proteins are essential biomacromolecules that participate in almost every process within cells. As their function is related to their structure, a great effort has been made to gain deeper insights into the determination of their structures and in the processes of folding. A part of this challenging problem is to build new small oligomers that adopt a well-defined conformation in solution. A new field of research, the foldamers, has emerged during the last 20 years. The term foldamer was proposed by Gellman in 1996 to describe "any polymer with strong tendency to adopt a specific compact conformation" (Appella et al. 1996; Gellman 1998). Later on, Moore proposed the following narrower definition: "any oligomer that folds into a conformationally ordered state in solution, the structures of which are stabilized by a collection of noncovalent interactions between nonadjacent monomer units" (Hill et al. 2001). This definition covers both "single-stranded foldamers that only fold and multiple-stranded foldamers that both associate and fold". This definition seems to be a little restrictive for several reasons. First, many efforts have been devoted to determine the structures of synthetic oligomers in the solid state. Second, by specifying "noncovalent interactions", the definition obviously excludes the polyproline helices or their mimics, and it seems that this type of structure also contributes (as well as the other helices, sheets and turns) to the secondary structures adopted by proteins. Therefore, we will prefer the following shorter definition: "any oligomer that folds in a conformationally ordered state", and we will present oligomers that are folded in the solid state (even though a structure in solution is not always clearly demonstrated), and also oligomers that tend to adopt extended structures similar to polyprolines.

In this review, we will cover every peptidomimetic oligomer (excluding abiotic oligomers containing an aromatic ring in the skeleton or nucleotidomimetic oligomers) that contains a γ-amino acid or an analogue of a γ-amino acid. By analogue, we mean a compound in which the nitrogen atom is separated from the carbonyl group by three atoms (including, for instance, the oligoureas and the β-aminoxy acids). We will also describe some cyclic oligomers that both fold and above all associate. We will present the structures observed for homogeneous and heterogeneous oligomers and their analogues before describing the biological properties and applications of these foldamers. Several reviews have covered some parts of

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this subject (Goodman et al. 2007; Hecht and Huc 2007; Seebach et al. 2004a, b, 2006; Stigers et al. 1999; Vasudev et al. 2011) and we will focus mostly on work published since Moore's review in 2001.

Homogeneous oligomers containing γ-amino acids

After three decades of studies on homogeneous oligomers containing β-amino acids, molecules based on γ-amino acids were investigated. Although this homologation reduces (for an oligomer of the same length) the number of potential hydrogen bonds, the γ-peptides have shown their capability to adopt various stable conformations, such as helices, sheets and turn.

In 1998, Seebach and Hannessian reported simultaneously that homogeneous oligomers containing monosubstituted γ-amino acids can form stable helical conformations in solution. Seebach synthesized hexamer **1** and performed extensive 2D-NMR studies in pyridine-d_5 (Hintermann et al. 1998). Many NOEs were extracted from the ROESY spectra and used as distance restraints in a simulated annealing protocol. The secondary structure obtained was a right-handed helix stabilized by H-bonds between the carbonyl group of residue *i* and the NH group of residue ($i + 3$) (Fig. 1). Moreover, the same NOEs were also present in CD_3OH, although a smaller dispersion of chemical shifts was observed. Thus, this 14 helix, possessing the same screw sense and polarity as the α-helix of α-peptides, is also populated in CD_3OH.

Hanessian et al. (1998) also described the same 14 helices (helices with C_{14} pseudocycles) for compounds **2**, **3** and **4**. In these cases, a tetramer is sufficient to observe the helix formation (Fig. 1). The structure determination was achieved through 2D-NMR studies in pyridine-d_5 (NOE-derived distances and coupling constant-derived dihedral angles were included in a restrained molecular dynamics simulated annealing protocol). Moreover, for peptides **2** and **3**, temperature-dependence experiments, as well as DMSO-d_6 titration experiments confirmed this conformation.

Hofmann later performed calculations on unsubstituted and monosubstituted γ-peptides (with one methyl group on the α-, β- or γ-position), employing ab initio MO theory at various levels of approximation (Baldauf et al. 2003, 2005). He showed that the observed 14-helix conformation and the 9-helix were the most stable conformations. He also claimed that for unsubstituted and monosubstituted γ-peptides, mixed helices could also be observed (Baldauf et al. 2004). In these cases, the most stable helices are the 22/24 and the 14/12 helices. The hydrogen bonds are oriented alternately in opposite directions leading to a small helix dipole (Fig. 2). These mixed helices should then be favored in less polar media.

As predicted by Hofmann, a 9 helix has been observed in other monosubstituted γ-peptides. In fact, Kunwar showed that tetramer **5** and hexamer **6** [alternating a C-linked carbo-γ^4-amino acid and γ-aminobutyric acid (GABA)] form a 9 helix in $CDCl_3$ (Fig. 3). To determine this conformation, extensive NMR studies were performed (including NOESY, ROESY, DMSO-d_6 titration experiments) and the resulting data were used to achieve restrained MD calculations (Sharma et al. 2006a).

On the contrary, monosubstituted hexamers **7** and **8** (Fig. 4) showed limited dispersion of the chemical shifts, probably indicating the absence of secondary structure in solution (Seebach et al. 2002).

Disubstituted γ-peptides have also been investigated. Balaram, for instance, synthesized many peptides incorporating the quaternary achiral Gabapentin residue (Gpn; Fig. 5), in homogeneous and heterogeneous peptides (see below). He thus obtained a crystallographic structure of dimer **9** (Boc-Gpn-Gpn-NHMe) and tetramer **10** (Boc-Gpn-Gpn-Gpn-Gpn-NHMe). The tetramer formed a 9 helix stabilized by three hydrogen bonds. For dimer **9**, he also identified a conformation stabilized by two C_9 hydrogen bonds between the C=O moiety of residue *i* and the NH group of the residue ($i + 2$). Nevertheless, in that case, the backbone torsion angles are different and the folded conformation is a C_9 ribbon (Vasudev et al. 2005). The same C_9 hydrogen bond around the Gpn residue ($i + 1$), between the C=O moiety of residue *i* and the NH group of the residue ($i + 2$), was also observed in the crystallographic structures of other small oligomers regardless of the other residue: Boc-Gpn-Aib-OH, Piv-Pro-Gpn-Val-OMe,

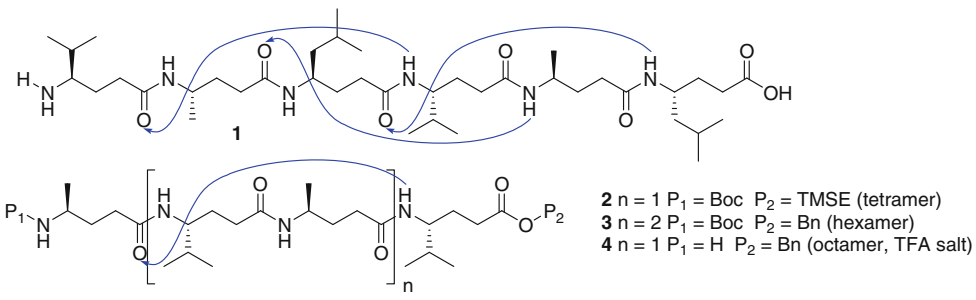


Fig. 1 γ^4-peptides forming 14 helices (H-bond $i + 3 \rightarrow i$ are shown with *curved arrows*). *TMSE* trimethylsilylethyl

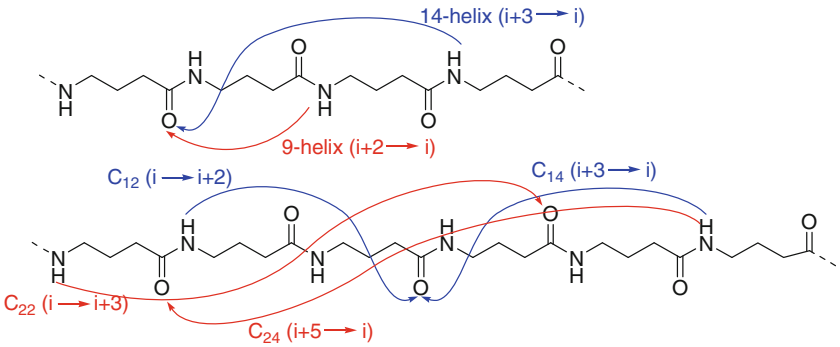


Fig. 2 H-bonding in 14 helix or 9 helix (*top*) and in mixed helices: 14/12 helix or 24/22 helix (*bottom*)

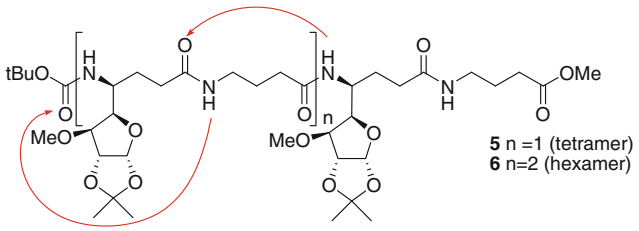


Fig. 3 9 helix of tetramer **5** and hexamer **6** (all NH, except NH(1), participate in H-bonding)

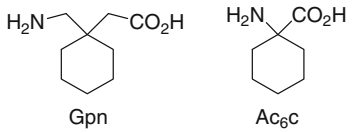


Fig. 5 Structures of Gpn ($\gamma^{3,3}$-amino acid) and of Ac_6c residues

Boc-Gpn-Gpn-Leu-OMe, Boc-Ac_6c-Gpn-OH [Ac_6c stands for 1-(aminomethyl)cyclohexaneacetic acid], and Boc-Val-Pro-Gpn-OH (Vasudev et al. 2007).

Disubstituted $\gamma^{2,4}$-amino acids have also been used for γ-peptide elaboration. This additional substitution reduces the number of accessible conformations for the backbone. In fact, only two of the nine possible conformers for a γ-residue do not possess unfavorable *syn*-pentane interactions (Fig. 7). Thus, Hanessian synthesized tetramers **11**, **13** and hexamer **12** and concluded that they all adopt a right-handed 14-helix conformation in pyridine-d_5. Structures of compounds **11** and **12** were determined using a restrained molecular dynamics simulated annealing protocol (temperature-dependence experiments and DMSO-d_6 titration experiments were also performed, Hanessian et al. 1998) and for compound **13**, long-range NOE data and temperature-dependence experiments corroborate the same 14-helix formation (Hannessian et al. 1999). On the contrary, hexamer **14**, which possesses the opposite relative configuration, presents no helical conformation (Fig. 6).

This behavior has been rationalized by Seebach and Hoffmann (Hoffmann et al. 1999; Hoffmann 2000; Brenner and Seebach 2001a). In fact, a disubstituted $\gamma^{2,4}$-amino acid **A** can adopt a conformation found in the 14 helix (conformation II), whereas for compound **B**, this type of conformation is destabilized by a *syn*-pentane repulsive interaction (conformation V). Compound **B** should be able to adopt a turn conformation (conformations III and IV; Fig. 7).

In fact, a turn conformation has been identified by Hanessian and Seebach. Tetrapeptide **15** forms a reverse turn in pyridine-d_5, as suggested by NOE data and deuterium exchange (Hanessian et al. 1999). Crystallographic structures of heterochiral dipeptides **16** and **17** clearly indicate the same conformation (Fig. 8; Brenner and Seebach 2001a), which should be retained in solution (for compound **16**, an NOE was observed between NH group of the terminal methylamide group and H–C(γ) of residue 1, and between H–C(γ) of residue 1 and H–C(α) of residue 2 in CD_3OH), according to ROESY analysis.

Other disubstituted γ-peptides possessing a hydroxyl moiety have been synthesized, although only the CD spectra of these peptides (**18**–**22**; Fig. 9) were studied in acetonitrile, MeOH and water. As no specific CD pattern in the field of γ-peptide can be related to a secondary structure, no firm conclusion can be drawn, but the fact that modifications of the CD curves are observed when changing the solvent may suggest the presence of a preferred secondary structure (Brenner and Seebach 2001b).

Trisubstituted $\gamma^{2,3,4}$-peptides have also been studied (Seebach et al. 2001, 2002). Peptides **23** and **24** possess the same 2,4-relative configuration as compounds **11**–**13**, and they also form a 14 helix (the opposite 2,4-absolute configuration of **23** and **24** led in this case to a left-handed

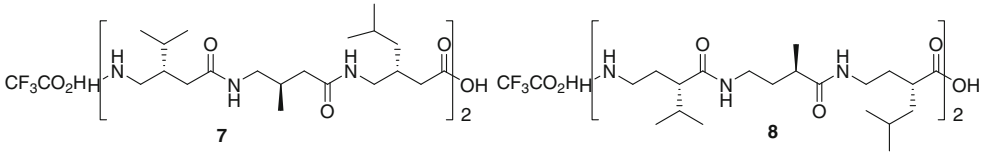
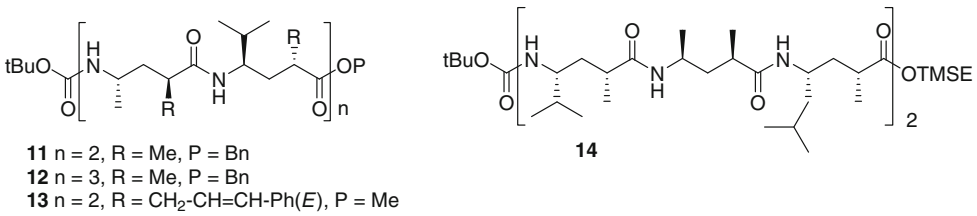


Fig. 4 No secondary structure for monosubstituted hexamers **7** (γ^3-peptide) and **8** (γ^2-peptide)



11 n = 2, R = Me, P = Bn
12 n = 3, R = Me, P = Bn
13 n = 2, R = CH_2-CH=CH-Ph(*E*), P = Me

14

Fig. 6 Structures of $\gamma^{2,4}$-peptides

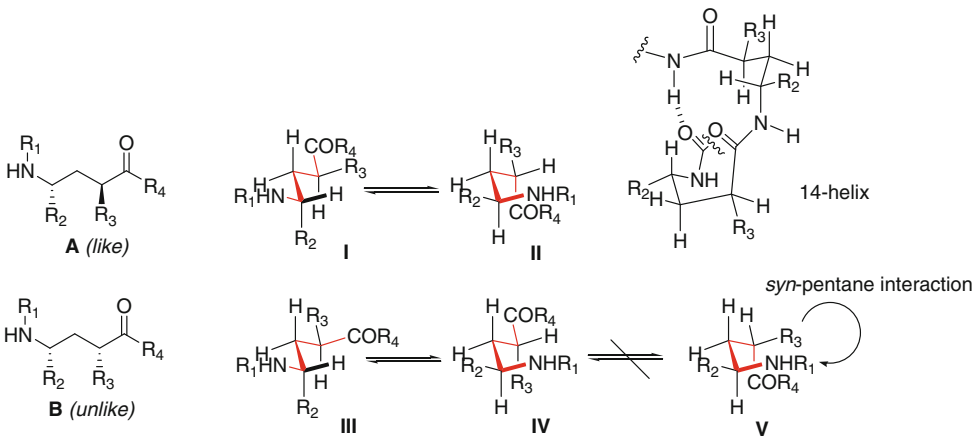
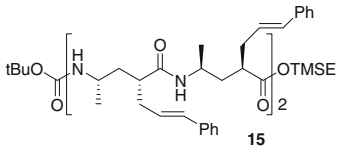
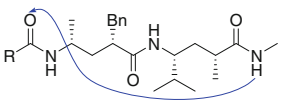


Fig. 7 Conformations of $\gamma^{2,4}$-amino acids and schematic presentation of the 14-membered H-bonded rings

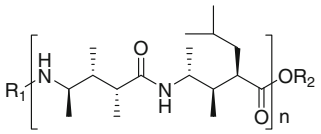


15



16 R = Me
17 R = OtBu

Fig. 8 Structures of $\gamma^{2,4}$-peptides forming a turn conformation with a C_{14} hydrogen bond



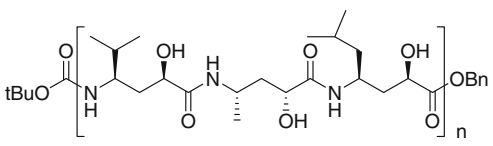
23 n = 2, R_1 = Boc, R_2 = Bn
24 n = 3, R_1 = R_2 = H (TFA salt)

Fig. 10 Structures of $\gamma^{2,3,4}$-peptides: left-handed 14 helix

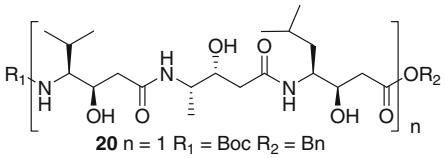
helix, compare Figs. 6 and 10). This means that a supplementary substitution is compatible with this type of secondary structure, there are no steric interferences. To determine this helical structure, the authors obtained a crystallographic structure of tetrapeptide **23**, and they performed extensive NMR studies of hexapeptide **24** in CD_3OH (including temperature-dependence and H/D exchange experiments). Introduction of the extracted NOEs and the dihedral angles derived from coupling constants into a restrained molecular dynamics simulated annealing protocol led to the same helical conformation, with a good superposition of the two secondary structures.

Other conformations are also accessible with γ-peptides containing cyclic monomers. For instance, Royo has synthesized a family of γ-peptides based on *cis*-γ-amino-L-proline (Farrera-Sinfreu et al. 2004). Among these peptides, compound **26** was investigated by NMR spectroscopy. A C_9 ribbon in H_2O has been postulated on the basis of NOE connectivities (Fig. 11).

A C_7 bend-ribbon has also been observed for homochiral and heterochiral tartrate-derived peptidesin benzene-d_6 (Fig. 12). For compounds **27** and **29**, DMSO-d_6 titration experiments were performed and showed the formation of a hydrogen bond between the amide NH group and the carbonyl group of the same residue (in the first residue, this is not true, probably because an ester is a poorer hydrogen-bond acceptor than an amide). This structure was consistent with the observed NOE correlations and with the downfield shift of the chemical shifts of the amide NH in the ^{1}H NMR



18 n = 1
19 n = 2



20 n = 1 R_1 = Boc R_2 = Bn
21 n = 2 R_1 = Boc R_2 = Bn
22 n = 2 R_1 = R_2 = H (TFA salt)

Fig. 9 Structures of $\gamma^{2,4}$- and $\gamma^{3,4}$-peptides with a hydroxyl moiety

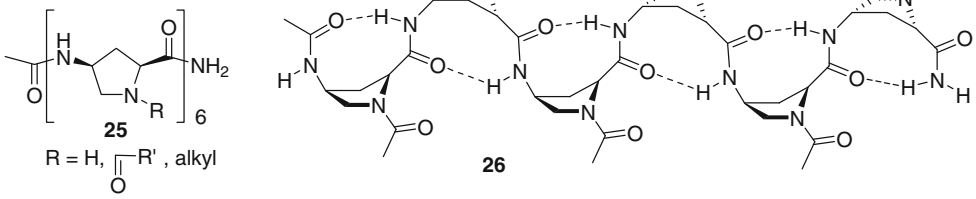


Fig. 11 Oligomers of *cis*-γ-amino-L-proline

spectrum (Kothari et al. 2007). The same pattern was observed for compounds **28** and **30**.

The same type of intraresidue H-bonding has been postulated for the sugar derivative oligomers **31** and **32** (Fig. 13). For dimer **31**, a crystallographic structure revealed a seven-membered ring hydrogen-bonded γ-turn like structure, and for tetramer **32**, a similar high δ_{NH} (observed in benzene-d_6) suggested the same type of structure (Edwards et al. 2006). Oligomers with the opposite configuration for the ether substituent showed no secondary structure. Nevertheless, no further study was described for these compounds.

Cyclopropane γ-peptides have also been studied by Smith. These authors initially synthesized a trimer **33** that adopts an infinite parallel sheet structure in the solid state (Qureshi and Smith 2006). The crystallographic structure shows the formation of a bifurcated hydrogen-bonding pattern: the carbonyl oxygen interacts both with the amide NH group and one CH of the cyclopropane ring (Fig. 14). Subsequently, they use this property to build a hairpin conformation with the help of a nonpeptidic reverse turn (Jones et al. 2008). For compounds **34** and **35**, which are diastereomers, several cross-strand NOE correlations were observed in $CDCl_3$. Variable-temperature and DMSO-d_6 titration experiments were also performed and all these data were indicative of the formation of a hairpin. For compound **35**, a longer extended sheetlike conformation is populated.

The propensity of *trans*-3-ACPC (trans-3-aminocyclopentanecarboxylic acid) to form a parallel sheet secondary structure was studied (Woll et al. 2001). Molecules **36**, **37** and **38** (Fig. 15) composed of *trans*-3-ACPC and D-prolyl-(1,1-dimethyl)-1,2-diaminoethyl units were prepared. Crystal structures of **36** and **37** show that both molecules

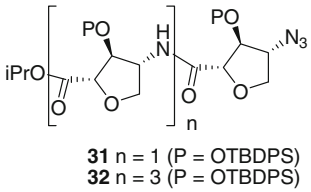


Fig. 13 Sugar derivative oligomers

adopt the hairpin conformation in the solid state. The conformation of compound **37** was confirmed by 2D NMR spectroscopy in CD_2Cl_2. Molecule **38** was synthesized to see if the parallel sheet secondary structure could propagate out from the loop. Analysis by 2D NMR in pyridine-d_5 showed unambiguous evidence of a hairpin conformation, in which the parallel γ-peptide sheet involves the four *trans*-3-ACPC residues.

Table 1 summarizes the conformations stabilized by hydrogen bonds that are observed in the γ-peptide family.

In the α-peptide family, the polyproline helical conformation, stable without any hydrogen bonds, is also present. In the field of β- or γ-peptides, conformations that are stable without hydrogen bonds are rarely observed. In 2000, Guarna described the synthesis of γ-oligomers composed of (1*R*,7*R*)-3-aza-6,8-dioxabicyclo[3.2.1]-octane-7-carboxylic acid, which can be considered either as a γ-amino acid or as a δ-amino acid (BTG, **39**, Machetti et al. 2000). The di-, tri- and tetrapeptides **40**–**42** were studied by NMR and circular dichroism (Fig. 16). The latter spectroscopy, when performed in methanol, showed a positive band (at ca. 210–215 nm), the intensity of which increases with the chain length, indicating an additive contribution of each unit to the ellipticity. This band is preliminary evidence that oligomers composed of BTG can form secondary structures without any hydrogen bonds.

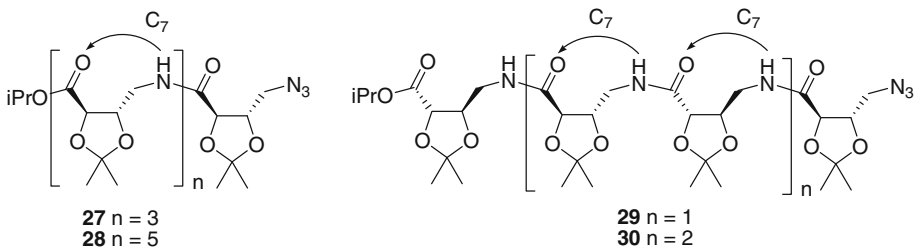
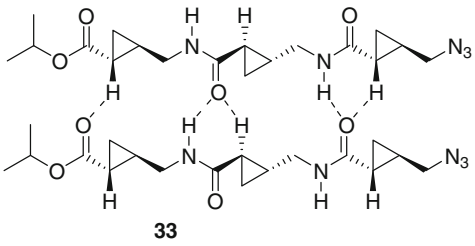
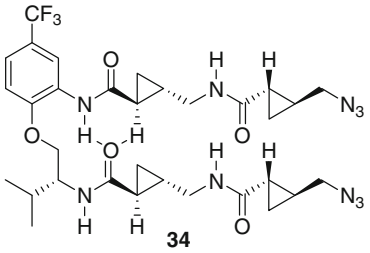


Fig. 12 Oligomers forming a C_7 bend-ribbon





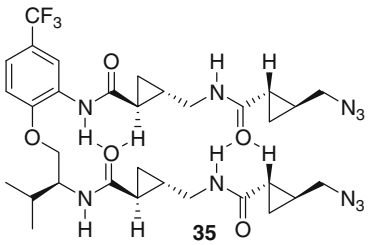


Fig. 14 Hairpin and parallel sheet based on cyclopropane γ-amino acids

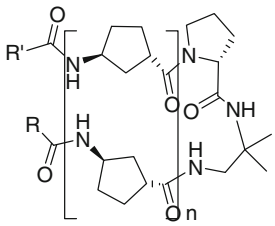


Fig. 15 Hairpin and parallel sheet based on *trans*-3-ACPC

Heterogeneous oligomers containing γ-amino acids

Heterogeneous peptides (alternating with α- or β-residues) considerably increase the number of possible oligomers compared to oligomers composed only of γ-residues. If one considers β- and γ-amino acids, homogeneous backbones generate β- and γ-peptides, respectively. The heterogeneous approach allows different combinations, often with the natural α-amino acids, such as α–γ–α–γ–α, α–α–γ–α–α–γ,

Table 1 Conformations observed in the γ-peptide family

Peptides	Analysis	References	Conformation
1	NMR (Pyr-d_5), RMD	Hintermann et al. (1998)	14 helix
2, **3**, **4**	NMR (Pyr-d_5), RMD	Hanessian et al. (1998)	14 helix
5, **6**	NMR ($CDCl_3$), RMD	Sharma et al. (2006a)	9 helix
Boc-$(Gpn)_2$-NHMe **9**	X-ray	Vasudev et al. (2005)	9 ribbon
Boc-$(Gpn)_4$-NHMe **10**	X-ray	Vasudev et al. (2005)	9 helix
11, **12**	NMR (Pyr-d_5), RMD	Hanessian et al. (1998)	14 helix
13	NMR (Pyr-d_5)	Hannessian et al. (1999)	14 helix
15	NMR (Pyr-d_5)	Hannessian et al. (1999)	Reverse turn
16	X-ray, NMR (CD_3OH)	Brenner and Seebach (2001a)	Reverse turn
17	X-ray	Brenner and Seebach (2001a)	Reverse turn
23	X-ray	Seebach et al. (2001, 2002)	14 helix
24	NMR (CD_3OH), RMD	Seebach et al. (2001, 2002)	14 helix
26	NMR (H_2O)	Farrera-Sinfreu et al. (2004)	C_9 ribbon
27–**30**	NMR (benzene-d_6)	Kothari et al. (2007)	C_7 ribbon
31	X-ray	Edwards et al. (2006)	C_7 turn
32	NMR (benzene-d_6)	Edwards et al. (2006)	C_7 turn
33	X-ray	Qureshi and Smith (2006)	Parallel sheet
34, **35**	NMR ($CDCl_3$)	Jones et al. (2008)	Hairpin
36	X-ray	Woll et al. (2001)	Hairpin
37	X-ray, NMR (CD_2Cl_2)	Woll et al. (2001)	Hairpin
38	NMR (Pyr-d_5)	Woll et al. (2001)	Hairpin

RMD restrained molecular dynamics-simulated annealing protocol

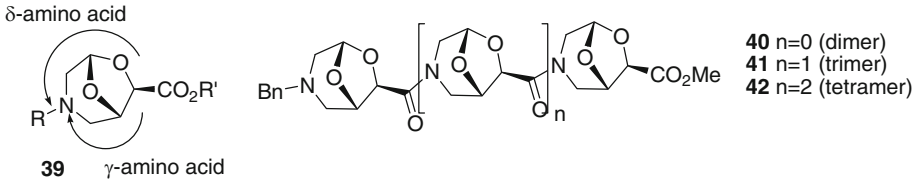


Fig. 16 Oligomers based on BTG

γ–γ–α–γ–γ–α, α–α–γ–γ to name just a few. Several groups have thus studied the conformational analysis of α/γ-peptides and β/γ-peptides.

α/γ hybrid peptides

Introduction of a α-residue in a γ-peptide induces modification of the possible conformations. Concerning the helical accessible conformations, Hofmann performed calculations on unsubstituted hybrid α/γ-peptides (octamers), employing ab initio MO theory at various levels of approximation (Baldauf et al. 2006). He showed that the most stable conformations were the 12-helix conformation and the mixed 12/10 or 18/20 helices (Fig. 17). With a smaller helix dipole, these mixed helices are favored in less polar media.

The 12 helix and the mixed 12/10 helix were observed in several hybrid peptides. For instance, Balaram synthesized many different α/γ hybrid peptides using the constrained γ-residue Gpn (Fig. 5; Vasudev et al. 2009) and observed these helical conformations. The C_{12}/C_{10} mixed hydrogen-bonding pattern was reported in the tetrapeptide Boc-Leu-Gpn-Leu-Aib-OMe **43** crystal structure, composed of three α-amino acids and Gpn (Vasudev et al. 2008). In the Gpn residue, the *gem*-dialkyl unit limits the torsion angles about the Cγ–Cβ and Cβ–Cα bonds to ±60°. The folded conformation of **43** is stabilized by two intramolecular hydrogen bonds: a 12-membered ring is observed between the Boc C=O group and Leu(3) NH groups, while a 10-membered ring is observed between the Gpn(2) NH and Leu(3) C=O groups. The C_{12} hydrogen-bonding pattern was also observed in the tetrapeptides Boc-Aib-Gpn-Aib-Gpn-OMe **44** (Ananda et al. 2005) and Boc-Aib-Gpn-Aib-Gpn-NHMe **45** (Chatterjee et al. 2008b) in the solid state and in chloroform solution. In that case, two successive C_{12} hydrogen-bonded turns [between the Boc C=O group and Gpn(2) N–H group and Aib(1) C=O group and Gpn(4) N–H group] generate a 12 helix. On the contrary, the tetrapeptide Boc-Gpn-Aib-Gpn-Aib-OMe **46** shows (crystallographic structure) two C_7 hydrogen bonds across the Gpn residue, which can be seen as an expansion of the C_5-helix observed in α-peptides (Vasudev et al. 2007).

The 12 helix was also reported in longer peptides in the solid state and in solution. Recently, the octapeptide Boc-$(Gpn\text{-}Aib)_3$-Gpn-Aib-OMe **47** (composed of a succession of Aib and Gpn residues) revealed a continuous 12 helix over the Aib(2)–Aib(6) segment (Chatterjee et al. 2009). The four Aib residues adopt a helical conformation with the sole exception that the terminal residue has the opposite hand. In addition, the N- and C-terminal Gpn residues have a 9-membered hydrogen-bonded ring. The authors also noted the evidence of this 12 helix in longer peptides composed of a succession of Aib- and Gpn-residues (see peptides **48** and **49**; Table 2).

The hybrid αγααγα peptide, Boc-Leu-Gpn-Aib-Leu-Gpn-Aib-OMe **50**, reveals a continuous helical conformation in crystals stabilized by three intramolecular C_{12} hydrogen bonds and one C_{10} hydrogen bond across the central αα residues (Fig. 18; Chatterjee et al. 2008a). This mixed hydrogen-bonding pattern is an extension of the 3_{10} conformation found in the α-peptides.

In the pentamer ααγαα **51**(Boc-Ala-Aib-Gpn-Aib-Ala-OMe) possessing only one Gpn residue, a 12 helix is still observed in the crystallographic structure (Vasudev et al. 2007).

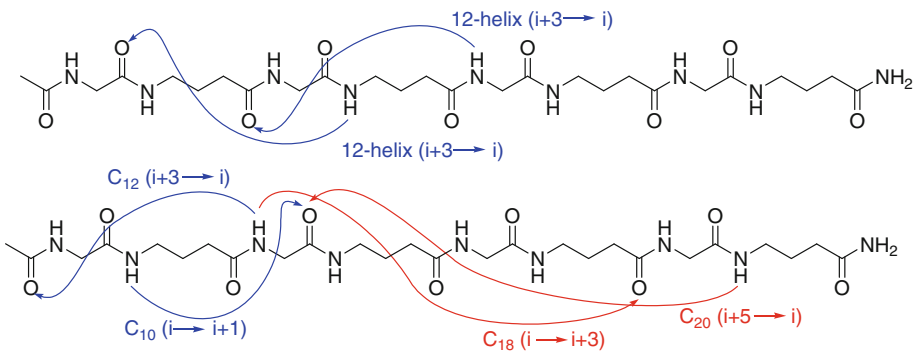


Fig. 17 H-bonding in 12 helix (*top*) and in mixed helices: 12/10 helix or 18/20 helix (*bottom*)

Table 2 Helices observed in the α/γ-peptide family

Peptide	Analysis	Reference	Helix
Boc-Leu-Gpn-Leu-Aib-OMe **43**	X-ray, NMR ($CDCl_3$)	Vasudev et al. (2008)	12/10
Boc-Aib-Gpn-Aib-Gpn-OMe **44**	X-ray, energy minimization	Ananda et al. (2005)	12
Boc-Aib-Gpn-Aib-Gpn-NHMe **45**	X-ray, NMR ($CDCl_3$)	Chatterjee et al. (2008b)	12
Boc-Gpn-Aib-Gpn-Aib-OMe **46**	X-ray	Vasudev et al. (2007)	C_7
Boc-$(GpnAib)_3$-Gpn-Aib-OMe **47**	X-ray, NMR ($CDCl_3$), energy minimization	Chatterjee et al. (2009)	$12 + C_9$
Boc-$(AibGpn)_3$-Aib-Gpn-Aib-OMe **48**	NMR ($CDCl_3$)	Chatterjee et al. (2008b)	12
Boc-$(AibGpn)_3$-Aib-Gpn-Leu-OMe **49**	NMR ($CDCl_3$)	Chatterjee et al. (2008b)	12
Boc-Leu-Gpn-Aib-Leu-Gpn-Aib-OMe **50**	X-ray, NMR ($CDCl_3$)	Chatterjee et al. (2008a)	$12 + C_{10}$
Boc-Ala-Aib-Gpn-Aib-Ala-OMe **51**	X-ray	Vasudev et al. (2007)	12
52	X-ray	Guo et al. (2009)	12
53	X-ray, NMR ($CDCl_3$)	Guo et al. (2009)	12
Boc-Ala-γ$Caa_{(m)}$-OMe **54**, Boc-$(Ala$-γ$Caa_{(m)})_2$-OMe **55**, Boc-$(Ala$-γ$Caa_{(m)})_3$-OMe **56**, Boc-$(γCaa_{(m)}$-Ala-$)_3$-OMe **57**	NMR ($CDCl_3$), RMD	Sharma et al. (2006b)	12/10
Boc-βCaa_4-Ala-βCaa-Ala-$(γ$Caa-Ala$)_2$-OMe **61**	NMR ($CDCl_3$)	Sharma et al. 2009	12/10

RMD restrained molecular dynamics simulated annealing protocol

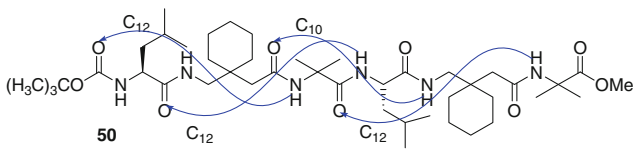


Fig. 18 Structure of peptide **50** with hydrogen bonds

In Gellman's group, a constrained cyclohexyl derivative was used as the γ-amino acid. Linking of this γ-residue and α-residues generated tetra- and hexapeptides **52** and **53**, respectively (Fig. 19). Both adopted a 12-helical conformation, as revealed in the crystal structures and by NMR spectroscopy (Guo et al. 2009). In each case, the maximum number of C=O(i)–H–N(i + 3) H bonds is formed.

Sharma synthesized a family of α/γ-peptides (compounds **54**–**57**) derived from dipeptide repeats with alternating arrays of L-Ala and γ-$Caa_{(m)}$ (C-linked carbo-γ-amino acid from D-mannose, **58**; Fig. 20) and found mixed 12/10-helical conformations for all these compounds by NMR spectroscopy (linked with a restrained molecular dynamics simulated annealing protocol) and CD spectroscopy (Sharma et al. 2006b).

A hybrid sequence composed of βββββαβαγαγα residues [with β = C-linked carbo β-amino acids = β Caa **59** (both configuration at Cβ), α = Ala, γ = C-linked carbo γ-amino acids = γ Caa **60**; Fig. 20] was prepared and consisted of three different foldamer classes: the 12/10 helices of β-peptides and α/γ-hybrid peptides and the 11/9 helix of α/β-hybrid peptides (Sharma et al. 2009). In this peptide **61**, all amide protons [except NH(1) and NH(10)] participate in hydrogen bonding, as suggested by the Δδ values in the solvent titration studies and also by their low field δ values. The authors showed that the 12/10- and 11/9-helical pattern of the first seven residues was identical to that observed in the corresponding βββββαβα peptide. Then, the 11/9 helix smoothly changes into the 12/10 helix of the alternating γ- and α-residues (Fig. 21).

Table 2 summarizes the helical conformations stabilized by hydrogen bonds that are observed in the α/γ-peptide family.

The γ-amino acids have also been used to build hairpin or sheets either by being the turn inducer or by being present in the strands.

Crystallographic studies of Boc-Leu-Phe-Val-Aib-Gpn-Leu-Phe-Val-OMe (**62**; Fig. 22) reveal an almost perfect β-hairpin structure stabilized by four cross-strand hydrogen bonds between the two Leu-Phe-Val tripeptide segments with the Aib-Gpn segment, forming a nonhelical C_{12} turn (Chatterjee et al. 2009). Peptide **62** was also studied in solution, both in methanol and in chloroform. In both solvents, the observation of the interstrand NOEs is consistent with the hairpin conformation similar to that observed in crystals.

It should be noted that crystal structures of dipeptides **63**–**67** (see Table 3) revealed C_7 or C_9 hydrogen bonds, which is adequate to generate an antiparallel sheet (Aravinda et al. 2003; Vasudev et al. 2007). The ^{D}Pro-Gpn-based turn can generate the β-hairpin conformation of peptide Boc-Leu-Phe-Val-^{D}Pro-Gpn-Leu-Phe-Val-OMe **68**, as observed by NMR spectroscopy in methanol according to key NOE contacts (Rai et al. 2007).

This 12-membered pattern has also been observed when γ-aminobutyric acid (named either γAbu or GABA) is used (Maji et al. 2002). Authors observed in peptides

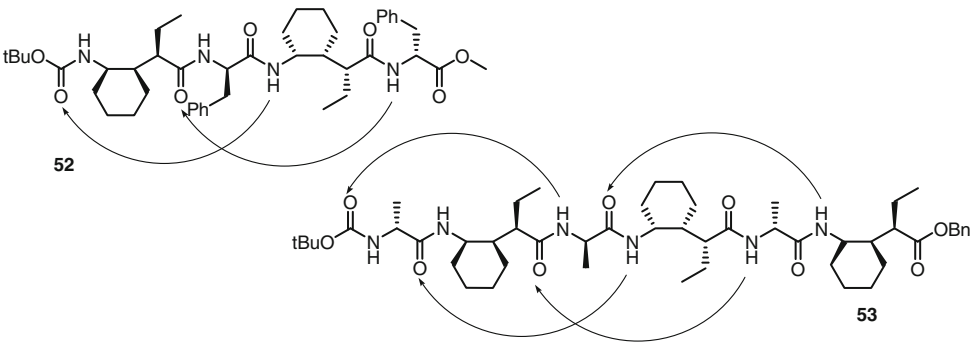


Fig. 19 12 helix of peptides **52** and **53**

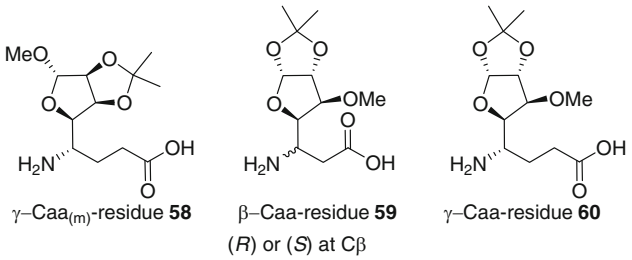


Fig. 20 Structures of β- or γ-amino acids used as monomers

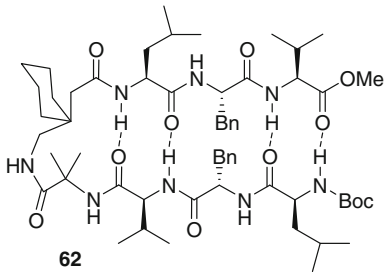


Fig. 22 Hairpin structure of compound **62** induced by the Aib-Gpn residues

Boc-γAbu-Aib-Ala-OMe (**69**) and Boc-γAbu-Aib-Ala-Aib-OMe (**70**) unusual turns composed of 12-membered hydrogen-bonded rings involving the C=O group from the Boc-group and Ala(3) NH group in crystals and in solution. The contiguous location of γAbu and Aib is essential for this conformation (Fig. 23). The crystallographic structure of peptide Boc-Pro-γAbu-OH **71** reveals a folded conformation stabilized by a C–H···O hydrogen bond involving one of the α-methylene hydrogen atoms of the γAbu residue and the C=O group of the Boc group (Fig. 23), characteristic of a β-turn mimetic structure (Sengupta et al. 2006). Curiously, for the same compound **71**, smaller hydrogen-bonded rings (C_5 and C_6) have also been observed in the crystallographic structure by another group (Kumar et al. 2010).

In 2002, Guarna used derivatives of BTG such as compounds **72** and **73** (Fig. 24) and α-amino acids in the synthesis of hybrid peptides Ac-Val-Ala-6-*endo*-BTL-Val-Gly-OMe (**74**) and Ac-Val-Ala-6-*endo*-BtL-Val-Gly-OMe (**75**), respectively (Trabocchi et al. 2002, 2006). The conformations of the corresponding peptides were studied by NMR ($CDCl_3$), IR, and molecular modeling. For peptide **74**, all the NMR analyses provided evidence of a stable β-hairpinlike conformation, which was confirmed by IR and modeling calculations. For peptide **75**, the absence of any cross-strand NOE peaks suggested that the oligomer folded in an open turn probably because of the steric hindrance of the half-chair conformation of the six-membered ring moving the two strands apart from each other.

A β-hairpin conformation in peptide Boc-Leu-Val-γAbu-Val-^{D}Pro-Gly-Leu-γAbu-Val-Val-OMe (**76**) was observed (Roy et al. 2006). In this case, the turn is induced by the ^{D}Pro-Gly residues and the γ-amino acids that are present in the strands (a situation which is similar to peptides in Figs. 14, 15). Although ^{1}H NMR studies in methanol support the formation of the nucleating turn, evidence for cross-strand registry was not detected.

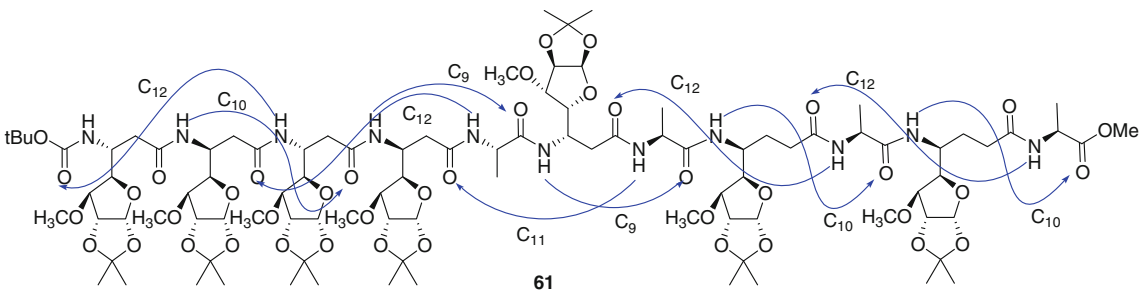


Fig. 21 Structure of peptide **61** with hydrogen bonds

Table 3 Hairpin and turn observed in the α/γ-peptide family

Peptide	Analysis	Reference	Member in the loop
Boc-Leu-Phe-Val-Aib-Gpn-Leu-Phe-Val-OMe **62**	X-ray, NMR (MeOH, $CDCl_3$), energy minimization	Chatterjee et al. (2009)	12
Piv-Pro-Gpn-OH **63**	X-ray, energy minimization	Aravinda et al. (2003)	10 and 9
Boc-Gly-Gpn-OH **64**	X-ray, energy minimization	Aravinda et al. (2003)	7
Boc-Aib-Gpn-OH **65**	X-ray, energy minimization	Aravinda et al. (2003)	9
Boc-Aib-Gpn-OMe **66**	X-ray, energy minimization	Aravinda et al. (2003)	7
Boc-Ac_6c-Gpn-OMe **67**	X-ray	Vasudev et al. (2007)	7
68	NMR (CD_3OH)	Rai et al. (2007)	12
Boc-γAbu-Aib-Ala-OMe **69**	X-ray, NMR ($CDCl_3$)	Maji et al. (2002)	12
Boc-γAbu-Aib-Ala-Aib-OMe **70**	X-ray, NMR ($CDCl_3$)	Maji et al. (2002)	12 and 10
Boc-Pro-γAbu-OH **71**	X-ray	Sengupta et al. (2006)	10
Boc-Pro-γAbu-OH **71**	X-ray, IR	Kumar et al. (2010)	5 and 6
74	NMR ($CDCl_3$), energy minimization	Trabocchi et al. (2002)	13
76	X-ray, NMR (MeOH	Roy et al. (2006)	10

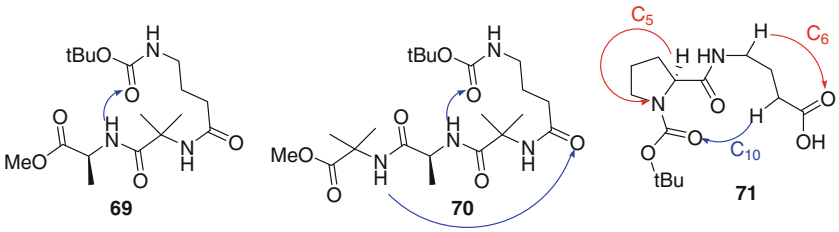
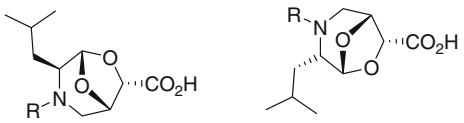


Fig. 23 Turns observed for peptides containing the γAbu residue

However, single crystal X-ray diffraction studies revealed a β-hairpin conformation for both molecules in the crystallographic asymmetric unit, stabilized by four cross-strand hydrogen bonds. The directions of the cross-strand NH···C=O hydrogen bonds alternate in the same manner as in hairpin turns containing α-amino acids in the strands (Fig. 25). The crystal packing has the same features as the packing for an all-α-hairpin peptide except that the α-sheet stacks in **76** have a V-shaped tilt contrasting with the flat arrangement in all α-peptides.

Table 3 summarizes the hairpin and turn conformations stabilized by hydrogen bonds that are observed in the α/γ-peptide family.

The features of (2*S*,1′*R*,3*R*,4*R*)-3,4-(aminomethano)prolinol (γ-Amp_a) and (2*R*,1′*S*,3*S*,4*S*)-3,4-(aminomethano)prolinol (γ-Amp_b) were investigated in the synthesis



72 6-*endo*-BTL **73** 6-*endo*-BtL

Fig. 24 Structures of 6-*endo*-BTL and 6-*endo*-BtL

of alternating α/γ-amino acid sequences (Brackmann et al. 2006). The peptide folding of compounds **77**–**80** (Fig. 26) was examined by CD in water and methanol, and it was shown that the dichroic properties of these oligomers are independent of the solvent. These properties are consistent with γ-Amp residues inducing two different preferred conformations.

An extended sheet has also been observed by Wipf using a γ-amino acid containing a cyclopropane ring. Compound **81** adopts an extended β-sheet conformation in the solid state, crystallizing as an antiparallel dimer (Fig. 27; Wipf and Stephenson 2005). It is noteworthy that for this compound, as for compound **33**, the dihedral angles in the γ-amino acid cyclopropane residue are of the same order of magnitude (all greater than 135°). Thus, both compounds adopt similar geometries dictated by the cyclopropane ring.

Cyclic peptides have also been investigated by the group of Granja (Table 4).

Oligomers composed of (1*R*,3*S*)-3-aminocyclopentanecarboxylic acid (L-γ-Acp, **82**; Fig. 28) or (1*R*,3*S*)-3-aminocyclohexanecarboxylic acid (L-γ-Ach, **83**; Fig. 28) or their enantiomers as γ-amino acid residues mixed with α-amino acids have largely been synthesized in order to study the properties of these artificial nanotubular materials

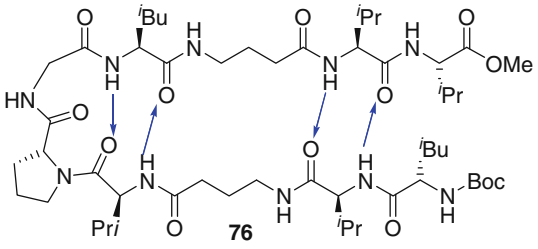


Fig. 25 Hairpin of peptide **76**

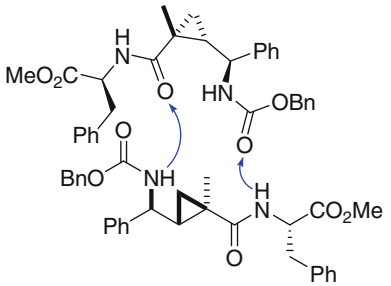


Fig. 27 Extended sheet of dipeptide **81**

(Brea et al. 2009; Garcia-Fandino et al. 2009; Reiriz et al. 2009a). The formation of self-assembling peptide nanotubes (SPNs) can exist with the sole all-*trans*-conformation for the amide bonds (Amorin et al. 2003; Brea et al. 2005). In fact, for peptide **84**, crystallographic and NMR analyses in polar and apolar solvents (CCl_4, $CDCl_3$, MeOH, DMSO) reflect a high degree of symmetry and the all-*trans* conformation required for the flatness of the ring (Amorin et al. 2003). Results observed confirmed the α–α dimerization of flat, antiparallel rings by means of a *β*-sheet-like array. Moreover, such dimers can stack to form nanotubes (Fig. 28; Amorin et al. 2005a).

The same group showed that methylation of either *γ*-residues (**86**–**89**) or α-residues (**90**) has no effect on the dimerization of the flat rings but prevents the self-assembly of the nanotube (Brea et al. 2005; Amorin et al. 2005b). Even the heterodimerization between **86** and **85** or **87** and **90** was observed by NMR and X-ray analysis (Brea et al. 2005). Such heterodimers were used to prepare a bio-inspired nanohybrid dimer system, in which the first cyclopeptide composed of D-*γ*-Acp, D-Leu and decorated with a fullerene as an electron acceptor is coupled by a *β*-sheet-like hydrogen-bond system to a second one composed of D-*γ*-Acp, D-Phe and substituted by an electron donor {2-[9-(1,3-dithiol-2-ylidene)antracen-10(9H)-ylidene]-1,3-dithiole} (Brea et al. 2007; Reiriz et al. 2009a).

A new class of cyclic-peptide foldamers, composed of three α-amino acids and one L-*γ*-Acp (or Ach), was developed (**91**–**95**; Amorin et al. 2008). The authors observed that these peptides can either remain as flat rings that dimerize through arrays of hydrogen bonds of the antiparallel *β*-sheet type (**91**–**92**), or fold into twisted double *γ*-turns, associating in nonpolar solvents to form helical supramolecular structures (**93**–**95**), depending on their backbone *N*-methylation patterns and on the medium.

The same authors prepared cyclic peptides by mixing D-*N*Me-*γ*-Acp residues with Leu and Tyr as α-amino acids and a C2-modified *γ*-amino acid, namely 4-amino-3-hydroxytetrahydrofuran-2-carboxylic acid [*γ*-Ahf-OH (**97**); Fig. 28]. The resulting cyclic peptide **96** can form self-assembling nanotubes, the cavity properties of which can be modulated by the hydroxyl group of residue **97** (Reiriz et al. 2009b).

β/*γ* hybrid peptides

β/*γ*-Peptides have only recently emerged in the literature (an early example was described by Karle et al. 1997), probably because of the lower availability of the *β*-amino acids compared to α-amino acids. These oligomers are nevertheless of particular interest because the backbone of a *β*/*γ*-dipeptide possesses the same number of atoms as an α-tripeptide.

Hofmann performed calculations on unsubstituted hybrid *β*/*γ*-peptides (octamers) (Baldauf et al. 2006). He showed that the most stable conformations were the 11- or 13-helix conformation and the mixed 11/13 or 20/22 helices. As previously stated, these mixed helices are favored in less polar media (Fig. 29). These authors also compared the 13 helix of the hybrid *β*/*γ*-peptides to the secondary structure of the native α-peptides, because a hybrid *β*/*γ*-dipeptide has the same number of atoms as an α-tripeptide. It appears that there are important similarities between these two structures in terms of geometry (good

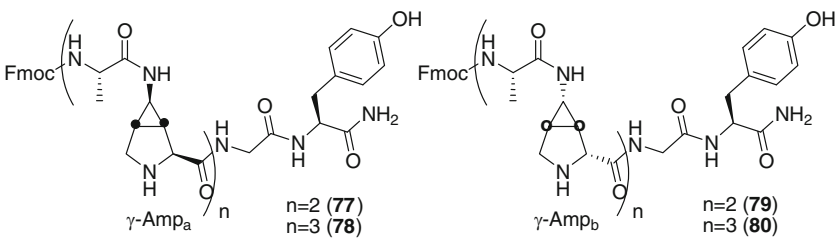


Fig. 26 Structure of α/*γ*-peptides based on *γ*-Amp$_a$ and *γ*-Amp$_b$

Table 4 Structures of the cyclic peptides

Cyclic peptide	Analysis	Reference	Conformation
(L-γ-Acp-D-Ala)$_3$ **84** (L-γ-Ach-D-Phe)$_3$ **85**	X-ray, NMR (CCl_4, $CDCl_3$, MeOH, DMSO)	Amorin et al. (2003)	β-Sheet like
(L-*N*Me-γ-Acp-D-Leu)$_3$ **86** (L-*N*Me-γ-Acp-D-Phe)$_3$ **87**	X-ray, NMR (CCl_4, $CDCl_3$, MeOH, DMSO)	Brea et al. (2005)	β-Sheet like
(D-Phe-L-*N*Me-γ-Ach)$_2$ **88**	NMR (CCl_4, $CDCl_3$, MeOH, DMSO), IR	Amorin et al. (2005b)	β-Sheet like
(L-Leu-D-*N*Me-γ-Acp)$_2$ **89**	X-ray, NMR (CCl_4, $CDCl_3$, MeOH, DMSO, IR	Amorin et al. (2005b)	β-Sheet like
(L-*N*Me-Ala-D-γ-Ach)$_2$ **90**	NMR (CCl_4, $CDCl_3$, MeOH, DMSO), IR	Amorin et al. (2005b)	β-Sheet like
(L-Ser(Bn)-D-*N*Me-γ-Ach-L-Phe-D-Ala)$_2$ **91** (L-γ-Ach-D-Ala-L-Ser(Bn)-D-*N*Me-Ala)$_2$ **92**	X-ray, NMR ($CDCl_3$), IR	Amorin et al. (2008)	β-Sheet like
(L-γ-Ach-D-Phe-L-*N*Me-Ala-D-Phe)$_2$ **93** (L-γ-Ach-D-*N*Me-Ala-L-Ser(Bn)-D-Ala)$_2$ **94** (L-Ser(Bn)-D-γ-Ach-L-Phe-D-*N*Me-Ala)$_2$ **95**	X-ray, NMR ($CDCl_3$), IR	Amorin et al. (2008)	Twist, double reverse turn
(L-γ-Acp-L-Leu-γ-Ahf-OH-L-Phe) **96**	NMR ($CDCl_3$),	Reiriz et al. (2009b)	β-Sheet like

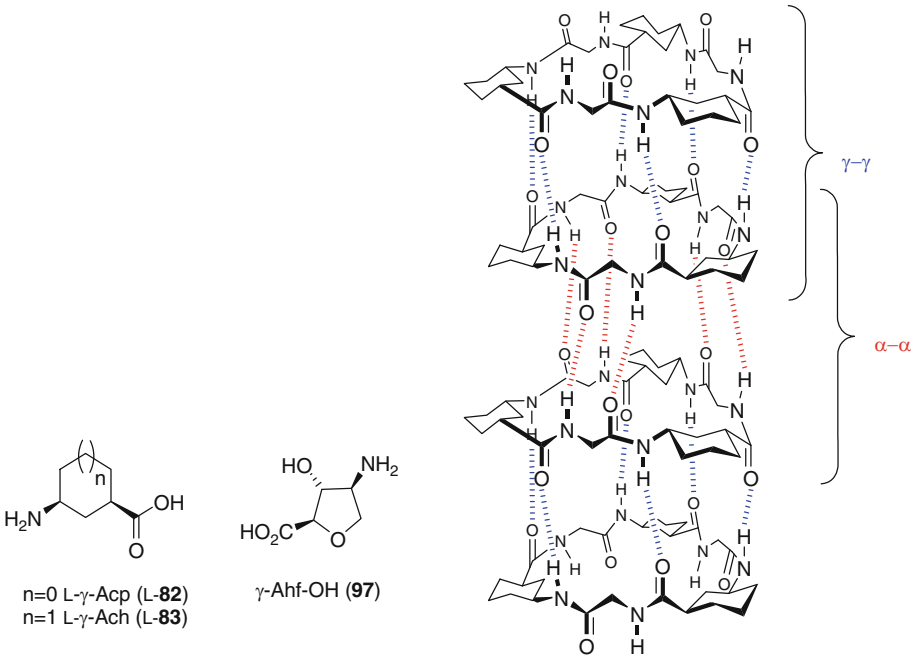


Fig. 28 Structures of the γ-amino acids used for cyclopeptides and representation of nanotubes with hydrogen bond network (amino acid side chains have been omitted for clarity)

superimposition of the two helices), hydrogen bonds and helix dipole orientation.

In order to study these conformations, Kunwar prepared three β/γ-peptides composed of C-linked carbo-β- and γ-amino acids of D-xylose named (*S*)-β-Caa (**59**; Fig. 20) and γ-Caa (**60**; Fig. 20), respectively (Sharma et al. 2006b). These β/γ-peptides {Boc-[(*S*)-β-Caa-γ-Caa]$_2$-OMe (**98**), Boc-[(*S*)-β-Caa-γ-Caa]$_2$-β-Caa-OMe (**99**) and Boc-[(*S*)-β-Caa-γ-Caa]$_3$-OMe (**100**)} were analyzed by NMR ($CDCl_3$) and circular dichroism. For the tetrapeptide **98**, determination of NOEs and coupling constants provided evidence for a 11/13 helix, with an 11/13/11 H-bonded arrangement.

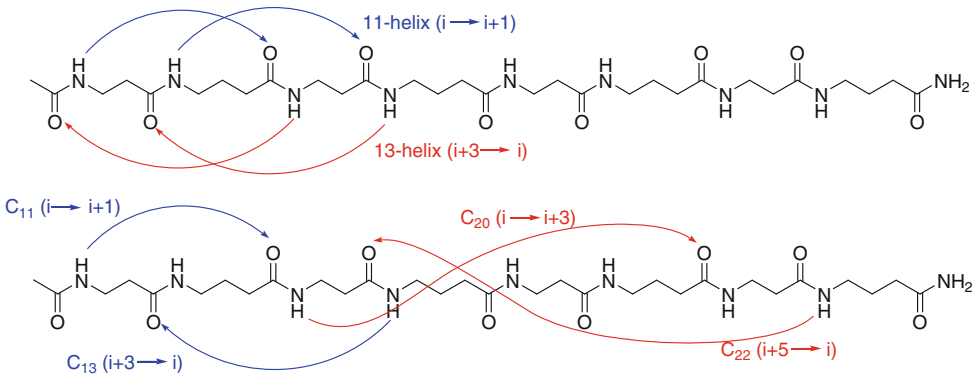


Fig. 29 H-bonding in 11 helix and 13 helix (*top*) and in mixed helices: 11/13 helix or 20/22 helix (*bottom*)

Similar observations were made for the pentapeptide **99** and hexapeptide **100** supporting a 11/13-mixed helix with an 11/13/11 H-bonding pattern (Fig. 30). Restrained molecular dynamics were performed for peptides **98** and **99** and showed 2.7 residues per turn, a 2.2 Å rise per residue and a pitch of 5.9 Å.

The use of a Gpn residue allowed Vasudev to observe and to characterize two C_{13} turns in the solid state for the hybrid sequences Boc-*β*Leu-Gpn-Val-OMe (**101**) and Boc-*β*Phe-Gpn-Phe-OMe (**102**) (Vasudev et al. 2007). In both cases, a C_{13} hydrogen bond between the Boc C=O group and the Val/Phe NH groups is observed (Fig. 31). In peptide **102**, an additional hydrogen bond between the Gpn(2) NH group and the Phe(3) C=O group is observed in the Gpn-Phe segment. This corresponds to a C_{10} hydrogen bond with reversal directionality.

Gellman's group studied the formation of the left-handed *β*/*γ*-peptide 13 helix (Guo et al. 2010). Three peptides composed of *γ*-residues (a aminocyclohexanecarboxylic acid derivative) and of *β*-residues [(*R*,*R*)-2-aminocyclopentanecarboxylic acid *trans*-2-ACPC] were prepared (compounds **103**–**105**; Fig. 32). Both peptides **103** and **104** revealed a 13-atom H-bonded ring in the solid state. In **103**, the 13-membered ring involves the NH group of the second ACPC residue and the C=O group of the N-terminal Boc group. In **104**, the three C=O(*i*)–H–N(*i* + 3) H-bonds are formed. Parameters determined from these crystals are consistent with the predictions for the 13-helical conformations from Hofmann (Baldauf et al. 2006). Peptide **105** gave no high-quality crystals. Nevertheless, 2D ^{1}H NMR spectroscopy in pyridine-d_5 supported a 13-helix conformation. These 13-helical conformations are similar to the α-helix formed by pure α-residues: both have 5.4 Å rise per turn and have similar radii (2.5 vs. 2.3 Å).

Table 5 summarizes the conformations stabilized by hydrogen bonds that are observed in the *β*/*γ*-peptide family.

Araghi used these similarities to mimic α-helical turns in proteins by introducing a *β*/*γ*-pattern (Araghi et al. 2010; Araghi and Koksch 2011). They showed that a heptad of α-amino acids in a protein motif, comprising three 13-atom H-bonded turns of the helix, could be substituted by a pentad repeat of alternating *β*- and *γ*-amino acids with retention of the helix dipole and of the quaternary structure (CD spectra and molecular models).

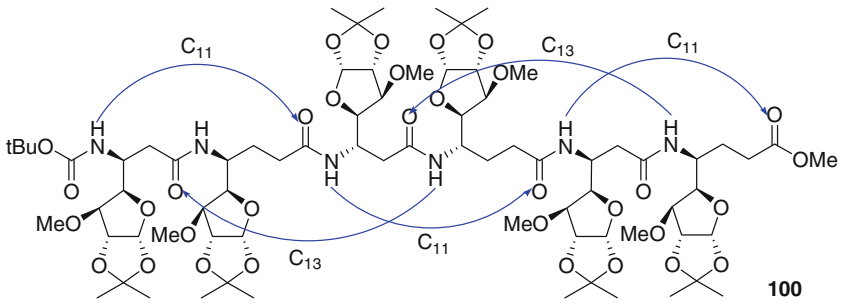


Fig. 30 11/13 helix conformation of hexapeptide **100**

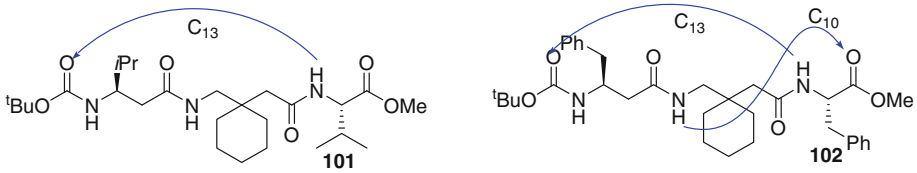


Fig. 31 *β*/*γ* Hybrid peptides with Gpn

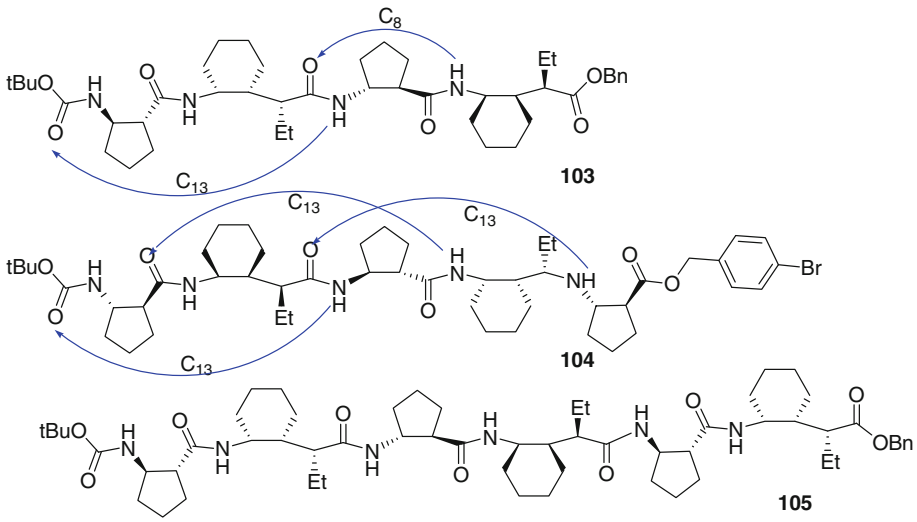


Fig. 32 13 helix based on alternating β and γ-cyclic residues

Table 5 Conformations stabilized by hydrogen bond observed in the β/γ-peptide family

Peptide	Analysis	Reference	Conformation
Boc-[(*S*)-β-Caa-γ-Caa]$_2$-OMe **98**	NMR ($CDCl_3$), CD (MeOH), RMD	Sharma et al. (2006b)	11/13 helix
Boc-[(*S*)-β-Caa-γ-Caa]$_2$-β-Caa-OMe **99**		Sharma et al. (2006b)	11/13 helix
Boc-[(*S*)-β-Caa-γ-Caa]$_3$-OMe **100**		Sharma et al. (2006b)	11/13 helix
Boc-βLeu-Gpn-Val-OMe **101**	X-ray	Vasudev et al. (2007)	C_{13}-turn
Boc-βPhe-Gpn-Phe-OMe **102**	X-ray	Vasudev et al. (2007)	$C_{13} + C_{10}$
Boc-(ACPC-Achc)$_2$-OBn **103**	X-ray	Guo et al. (2010)	13 helix + C_8
Boc-(ACPC-Achc)$_2$-ACPC-OBnBr **104**	X-ray	Guo et al. (2010)	13 helix
Boc-(ACPC-Achc)$_3$-OBn **105**	NMR (Py-d_5)	Guo et al. (2010)	13 helix

RMD restrained molecular dynamics simulated annealing protocol

Foldamers containing analogue of γ-amino acids

One of the first pieces of work demonstrating that chain molecules based on γ-amino acids form defined secondary structure was reported by Schreiber and Clardy (Hagihara et al. 1992). The authors studied protein-like substances in which the repeating unit is a γ-amino acid with an α,β-unsaturation (vinylogous γ-peptides). To restrict the conformational space of the γ-amino acid backbone, an α-methyl substituent was initially examined. For this substitution pattern, allylic strain ($A^{1,3}$) was expected to drive the γ-hydrogen to lie in the amide plane, and would favor sheetlike conformations. The crystal structures of dipeptide **106** revealed that this conformational preference, and a two-stranded, antiparallel sheet was observed in the crystal packing. However, the α-methyl substituent seemed to prevent higher ordered sheets with longer oligomers.

Removal of the α-methyl substituent resulted in vinylogous γ-peptides that are organized in long stacks of parallel sheets. To favor antiparallel alignment, a Pro-Gly dipeptide turn was inserted in two vinylogous γ-amino acids (Fig. 33; **107**). ^{1}H NMR studies in solution revealed the existence of intramolecular hydrogen bonds involving N and C termini. Finally, a tetrapeptide incorporating a vinylogous γ-amino acid, a Pro-Gly turn and a $\gamma^{2,3}$-amino acid showed an helical conformation stabilized by 10- and 12-membered H-bonded rings (Fig. 33; **108**).

Employing ab initio MO theory, Hofmann and coworkers have investigated the folding propensities of the vinylogous γ-peptides by the introduction of an (*E*)-double bond between the Cα and the Cβ atoms of the γ-amino acid constituents (Baldauf et al. 2003). This strategy seems to be an interesting idea to avoid the formation of smaller pseudocycles and to favor helices with larger ones. Conformational analysis showed that structures with nearest-neighbor H-bonds like C_7, C_9 and also C_{12} cannot be formed with α,β-unsaturation. In this case, the most stable conformations proved to be the 19 and 22 helices at HF and DFT levels of ab initio theory.

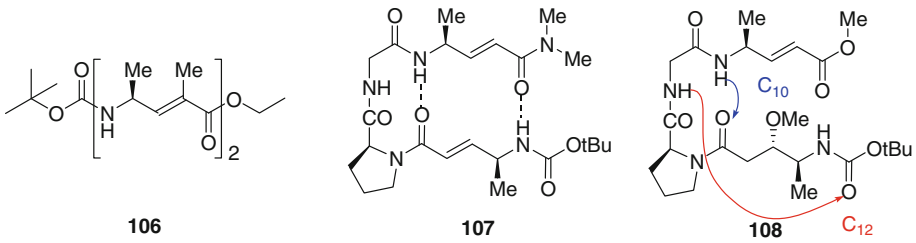


Fig. 33 Schematic structures of vinylogous peptides. Hairpin conformation of **107** and helical secondary structure of **108** with 10- and 12-membered H-bonded rings

In 2003, Chakraborty and Kunwar (2003) produced series of penta- and hexapeptides containing the *E*-vinylogous prolines **109** and **110**. They postulated that since *E*-vinylogous prolines are known to stabilize a *cis* amide bond with the preceding amino acid, such dipeptides might lead to intramolecularly hydrogen-bonded structures when incorporated in the middle of a sequence. As expected, detailed NMR spectroscopy and MD simulation analysis of the major conformer of hexapeptide **111** in $CDCl_3$ revealed a β-hairpin like structure with a well-defined 12-membered H-bonded ring (Fig. 34).

The authors emphasized the similarity between the observed structure and a type VI β-turn (supported by the average φ, ψ angles of central residues).

Grison and et al. (2005) have also studied the insertion of various *cis*- or *trans*-vinylogous residues in short chain peptides using X-ray diffraction in the solid state and ^{1}H NMR and IR spectroscopy in solution. Experimental studies showed that the structural consequences greatly depend on the stereochemistry of the vinylogous residue. The *cis*-vinylogous fragment promotes a folded conformation with an intramolecular NH to CO hydrogen bond closing a C_9 pseudocycle (named "*cis*-vinylog turn"). Compounds containing a *trans*-vinylog fragment accommodated completely different conformations, revealing an open structure and no intramolecular interaction. Further investigation was realized on a *cis–cis*-divinylog dipeptide and experimental data clearly indicated two consecutive *cis*-vinylog turns. Therefore, the authors claimed that an oligo *cis*-vinylog should adopt a helical structure with consecutive *cis*-vinylog turns.

Among the wide variety of unnatural peptidomimetic oligomers, oligoureas can be considered as promising foldamer candidates. In pioneering studies, the Nowick group studied the synthesis of di- and tri-urea derivatives to produce compounds that mimic the structures and hydrogen-bonding patterns of protein β-sheets (Nowick et al. 1992, 1995a). IR and NMR studies revealed that these derivatives are intramolecularly hydrogen bonded and thus suitable for forming rigidified scaffolds (see compound **112**). They next produced compounds such as **113** (Fig. 35), in which a diurea molecular scaffold juxtaposes two dipeptide strands, giving rise to artificial β-sheet-like structures (Nowick et al. 1995b). To create even more robust artificial β-sheets, the Nowick group has also investigated incorporation of a β-strand mimic (derived of 5-amino-2-methoxybenzoïc acid) (Nowick et al. 1996, 1997; Smith et al. 1997).

Although *N,N′*-linked oligoureas have been readily accessible by solid-phase synthesis since 1995 (Burgess and Linthicum 1995; Burgess et al. 1997), their conformational preferences and their folding propensities were only clearly elucidated in 2002 by the Guichard group (Semetey et al. 2002a; Hemmerlin et al. 2002). In the beginning, they postulated that the substitution of NH for C(α) in γ-amino acid residues could stabilize the 14-helical fold by fixing the ψ dihedral angle close to 170°–180°. In fact, in pyridine-d_5 solution, *N,N′*-linked heptaureas containing proteinogenic side chains adopt a well-defined right-handed 12/14 helix, sharing some features with the γ^4-peptide 14 helix. Nevertheless, the structure of heptaurea displayed a more complicated hydrogen-bonding pattern characterized by the presence of both C_{12} and C_{14} pseudocycles as shown below (Fig. 36).

CD spectra recorded in methanol also exhibit a strong positive band at 203 nm suggesting the presence of a defined secondary structure. However, extensive NMR conformational investigations on *N,N′*-linked oligoureas in

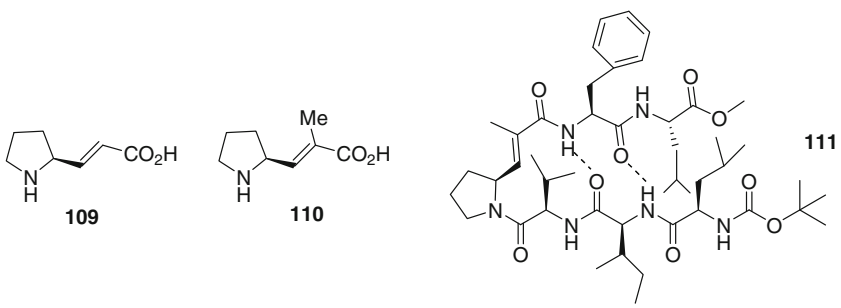


Fig. 34 Structures of *E*-vinylogous prolines **109** and **110**. Schematic representation of β-hairpin structure of **111** with indicated hydrogen bonds

protic solvents revealed that the 12/14-helical fold coexists with other folding conformations with various proportions of urea *cis–trans* rotamers (Violette et al. 2005). The ability of enantiopure *N,N′*-linked oligoureas of various lengths to adopt stable helix conformations was also supported by accurate NMR restrained simulated annealing protocol (Guichard et al. 2008) and X-ray diffraction studies (Fischer et al. 2010). Interestingly, crystallographic data highlight the fact that only four acyclic residues are

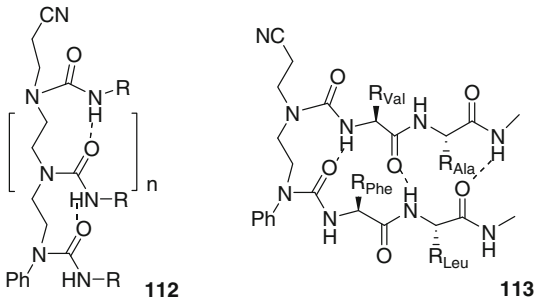


Fig. 35 Triurea molecular scaffold **112**, artificial *β*-sheet **113**

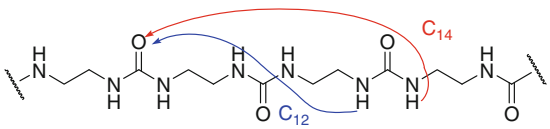


Fig. 36 Schematic representation of the hydrogen-bonding pattern as found in the helix of *N,N′*-linked heptaurea

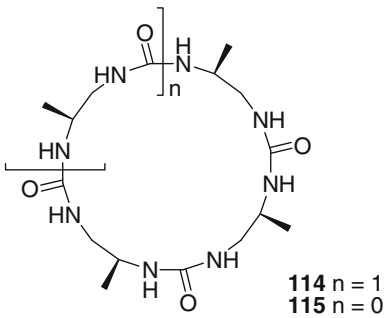


Fig. 37 Structures of macrocyclic oligoureas **114** and **115** forming H-bonded self-assemblies

sufficient to promote complete helix formation with all complementary H-bonding sites being satisfied.

Otherwise, macrocyclic *N,N′*-linked oligoureas such as **114** can represent versatile building blocks for the construction of H-bonded nanostructures (Semetey et al. 2002b).

Enantiopure cyclo-*N,N′*-linked oligoureas can generate robust hydrogen-bonded polar nanotubes in which all urea groups point in the same direction. The dimensions of the cavity in these systems can be controlled by variation of the number of repeat units in the ring (triurea **114** or tetraurea **115**; Fig. 37; Fischer and Guichard 2010.

As previously stated for *N,N′*-linked oligoureas, replacing carbon atoms in a *γ*-peptide backbone by heteroatoms represents a promising opportunity to design new foldamers. *β*-Aminoxy acids are compounds in which an oxygen atom has replaced the *γ*-carbon atom of *γ*-amino acids. Compared to the classical peptide backbone, the "amidoxy" bond induces stiffening of the backbone through the lone pair electron repulsion, which stabilizes the secondary structure.

Several investigations, including FT-IR and NMR spectroscopy in $CDCl_3$, as well as X-ray diffraction studies, have been carried by the group of Yang (Li and Yang 2006) on small *β*-aminoxy peptides with different substitution patterns (Fig. 38).

These studies revealed a clear preference for a nine-membered ring hydrogen bond between the carbonyl -Raygroup of residue $(i - 1)$ and the NH group of residue $(i + 1)$. The so-called "*β* N–O turn" was further stabilized by another six-membered ring hydrogen bond between the NO group of residue *i* and the NH group of residue $(i + 1)$.

Nevertheless, slightly different features have been elucidated for "*β* N–O turn" conformations depending on substitution patterns. In small $\beta^{2,2}$-aminoxy peptides, the N–O bond was positioned *anti* to the Cα–C*β* in the solid state and in $CDCl_3$ solution (Yang et al. 2002). Regarding diamides of β^3-aminoxy acids, the conformation of these two bonds can be *anti* or *gauche* depending on the sizes of their side chains (Yang et al. 2004a). For cyclic $\beta^{2,3}$-aminoxy acids, conformation seems to be independent of the ring size of the side chains with an *anti* arrangement

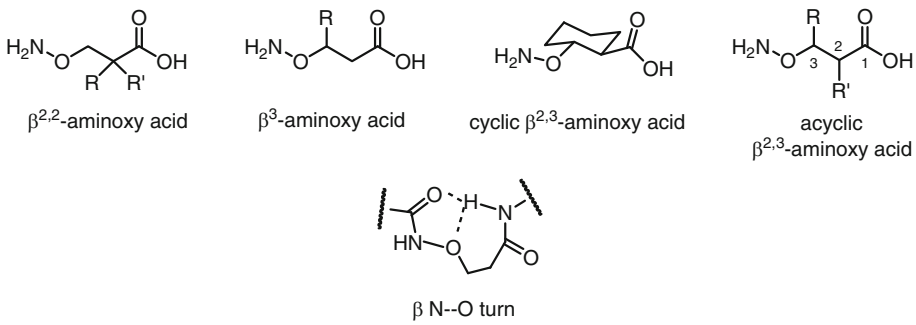


Fig. 38 General formula of different subclasses of *β*-aminoxy acids. Schematic representation of the "*β* N–O turn"

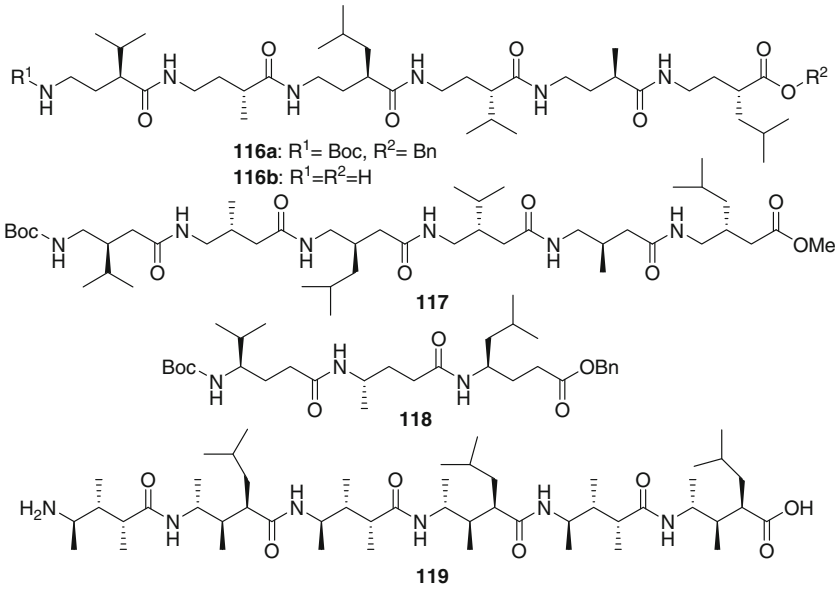


Fig. 39 γ-Peptides tested for stability toward proteolitic enzymes

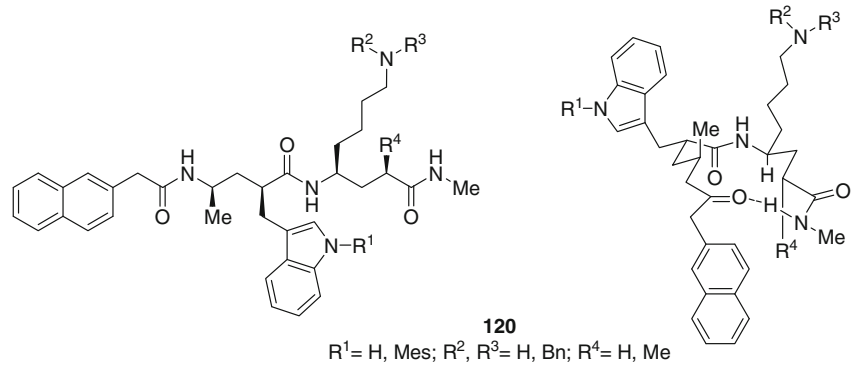


Fig. 40 β-Turn mimic γ-peptides with affinity for human somatostatin receptor

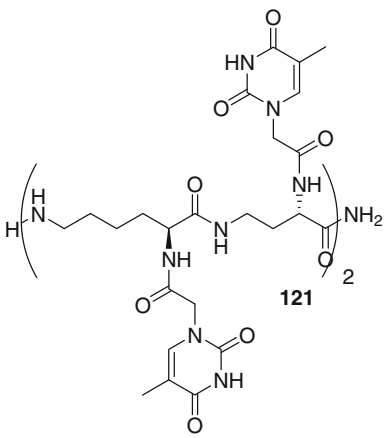


Fig. 41 γ/ε-Hybrid peptide as oligonucleotide analogues

around the Cβ–O bond (Yang et al. 2004b). Finally, in acyclic $\beta^{2,3}$-aminoxy peptides with a *syn* configuration the N–O bond is *gauche* to the Cα–Cβ bonds in both solution and the solid state. In the acyclic $\beta^{2,3}$-aminoxy peptides with an *anti* configuration, an extended strand is found in the solid state, and several conformations including non-hydrogen-bonded and intramolecular hydrogen-bonded states are present simultaneously in nonpolar solvents (Zhang et al. 2010).

Biological properties and applications

Foldamers derived from γ-peptides and analogues show several potential applications, although they have received less attention than those derived from β-peptides. First, γ-peptides display exceptional stability toward proteolytic enzymes: a set of γ^2, γ^3, γ^4 and $\gamma^{2,3,4}$ peptides **116–119** known to adopt an helical conformation were tested with 15 proteolytic enzymes (Fig. 39): no degradation was observed after 48 h, whereas common α-peptides were degraded after 15 min (Frackenpohl et al. 2001).

Some small γ-peptides have been shown to mimic the β-turn of biologically active peptides. For example, the *N*-acyl γ-dipeptide **120**, the conformation of which has been confirmed by NMR spectroscopy (Fig. 40), shows submicromolar affinity for several human somatostatin receptors (Seebach et al. 2003).

Fig. 42 γ-Peptides derived from *cis*-γ-aminoproline

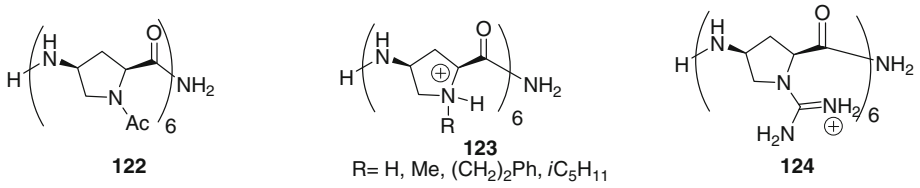
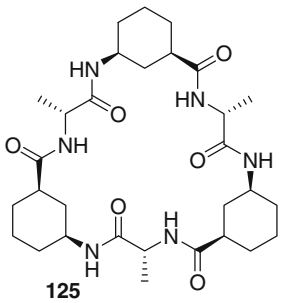


Fig. 43 Hybrid α/γ-cyclopeptide that forms nanotubes in solution



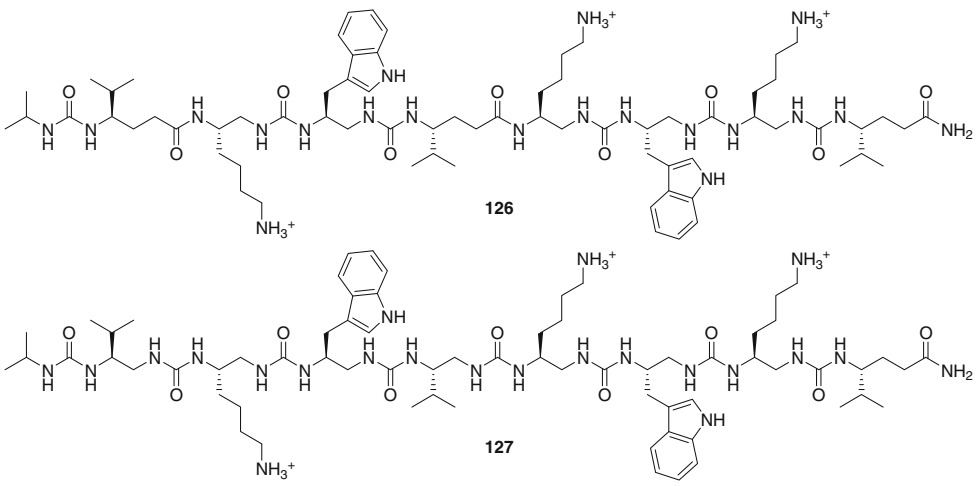
γ-Peptides or γ/ε-hybrid peptides have been used as backbones for the design of oligonucleotide analogues (Roviello et al. 2010). These compounds have been proven to bind to DNA or RNA and are promising substrates for biotechnological applications (Fig. 41). Nevertheless, their structural features have not yet been elucidated.

The cell penetrating ability of natural or synthetic peptides is an important issue for therapeutic applications. This ability is enabled either by the presence of cationic charges (at least 6) or the presence of hydrophobic residues. A series of *N*-functionalized hexamers of *cis*-γ-aminoproline (see Fig. 11) have been synthesized and have proven capacity for cellular uptake (Fig. 42; Farrera-Sinfreu et al. 2005).

The self-assembly of cyclic peptides as nanotubes is an important feature which may find several applications in the field of biosensors or selective transporter systems (Brea et al. 2010; Bong et al. 2001). The cyclic hybrid α/γ-peptide **125** has been shown to form nanotubes in several solvent systems (Fig. 43). These nanotubes possess a hydrophobic inner cavity, which allows the inclusion of nonpolar compounds such as chloroform (Garcia-Fandino et al. 2009).

Antibacterial peptides are helical peptides that contain alternating hydrophobic and cationic side chains. Since these peptides are prone to enzymatic degradation, hydrolysis-resistant analogues have been designed: the oligourea **127** (isosteric to a γ-peptide; Fig. 44) can mimic the helix conformation of the parent peptide and exhibits antimicrobial properties (Violette et al. 2006). Incorporation of γ-aminoacids into the sequence (as for **126**) results in conformational modifications as well as a decrease in the antimicrobial activity (Claudon et al. 2010).

Fig. 44 Antibacterial oligourea and mixed oligourea/γ^4-peptide foldamers



Conclusion

The field of foldamers is still growing. After several years of extensive studies on β-peptides, many foldamers containing γ-amino acids or analogues have been described so far and have shown interesting properties. It is noteworthy that going from α-peptides to β- and γ-peptides, helices of increasing stability are obtained (in the γ-peptide family, helices have been observed with oligomers as short as four residues). Moreover, γ^4-peptide helices have the same screw sense and macrodipole as α-peptide helices, whereas β^3-peptide helices have the opposite. Compared to β-peptides, introduction of a supplementary carbon in the backbone can be a source of structural diversity. Incorporation of γ-amino acid residues in hybrid α/γ- or β/γ-peptides is widening the accessible conformations, leading for the 13 helix of the hybrid β/γ-peptides to a good mimicry of the α-peptide helix. Thus, the easy structuration of γ-peptides, and their high stability and diversity are important assets in the foldamer domain.

All the different types of secondary structures have been observed, ranging from helices, to sheets, turns and extended structures, although there is a lack of good mimics of the polyproline helix conformation. It is likely that other new structural features or properties will emerge by the development of original amino acid building blocks. Potentially interesting results can be expected in the field of wider helices, as they were predicted by Hofmann to be very stable.

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Conflict of interest The authors declare that they have no conflict of interest.

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