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Peptides and peptidomimetics as inhibitors of protein–protein interactions involving β-sheet secondary structures

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Protein–protein interactions involving β-sheet secondary structures have been questioned in many fatal human diseases such as cancer, autoimmune and neurodegenerative diseases. Small selective peptide derivatives and analogues are promising drug candidates for inhibiting this poorly known class of PPIs. In this review, we will highlight the main strategies developed for designing linear and cyclic peptide and peptidomimetic inhibitors of PPIs involving β-sheet structures. These compounds either do not adopt preferred conformations or can mimic protein secondary structures such as β-strands, β-hairpins or α-helices.

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Introduction

The intercommunication between proteins is crucial in both biological and pathological processes. The search for modulators of protein–protein interactions (PPIs) is currently a promising strategy towards next-generation drugs; however, it is still considered as a challenging issue because PPIs generally involve rather flat and large proteins areas [1]. The hot-spot residues (residues involved in the interaction) generally adopt secondary structures and thus using compounds mimicking secondary structures is a relevant strategy to modulate PPIs. Peptide derivatives and analogues have been mainly described to target PPIs involving helix structures and thus those adopting helix conformation have been mainly reported in the published reviews [2,3]. The design of peptides and peptidomimetics targeting PPIs involving β-sheet structures has been much less studied. In this review, we report the strategies developed to design peptide derivatives as inhibitors of this class of PPIs.

The main targeted interactions involving β-sheet rich structures are those found in amyloid proteins aggregates (Table 1). Additionally, also a few other biological targets are discussed in this review, particularly PPIs involving homo and hetero dimerization of proteins through β-strand interactions (Table 1). The review is organized according to the main structure types used for inhibiting PPIs involving β-sheet structures and based on both pure peptide as well as peptidomimetic approaches. In particular, linear peptides adopting β-strand structures or inserting β-sheet breaker elements, cyclic peptides adopting β-hairpin or no preferred structures, acyclic β-hairpins, helix mimics, tweezers and proteins are described (Figure 1).

β-Strand mimics

β-Strands are the simplest peptide structural elements and are rarely isolated. They are known to be the crucial structural elements recognized by specific proteins such as proteolytic enzymes, major histocompatibility complex (MHC) proteins, and transferases [4]. Small peptides are not inclined to spontaneously structure themselves in β-strands. That is why small molecule β-strand mimetics have been designed [5]. However, they show high propensity to self-aggregate and they have mainly been reported as inhibitors of proteases but rarely as inhibitors of PPIs.

A common strategy to inhibit PPIs mediating aggregation of amyloid proteins is to use small peptides based on the amyloidogenic sequence also called sequence recognition element (SRE) of each amyloid protein. These sequences are crucial for the folding of the amyloid protein and constitute the hot-spot of the PPIs involved in the formation of β-sheet structures and thus in the aggregation. These sequences adopt generally a β-strand structure in the misfolded and aggregated amyloid proteins. However the proof that the small and isolated SRE is adopting a β-strand structure alone or in interaction with the amyloid proteins is not or only partially provided. For example, peptide derivatives of β6 and β7 strands of superoxide dismutase 1 (SOD1) have been designed to inhibit the formation of aggregates of SOD1 that is suspected to be an amyotrophic lateral sclerosis (ALS) pathogenic protein, whose misfolding participates to the death of motor neurons [6].

The use of isolated SRE derivatives has been also exploited for inhibiting the aggregation mediated by β-sheet interactions of Amyloid β (Aβ) peptide and of Tau protein in Alzheimer's disease (AD) [7].

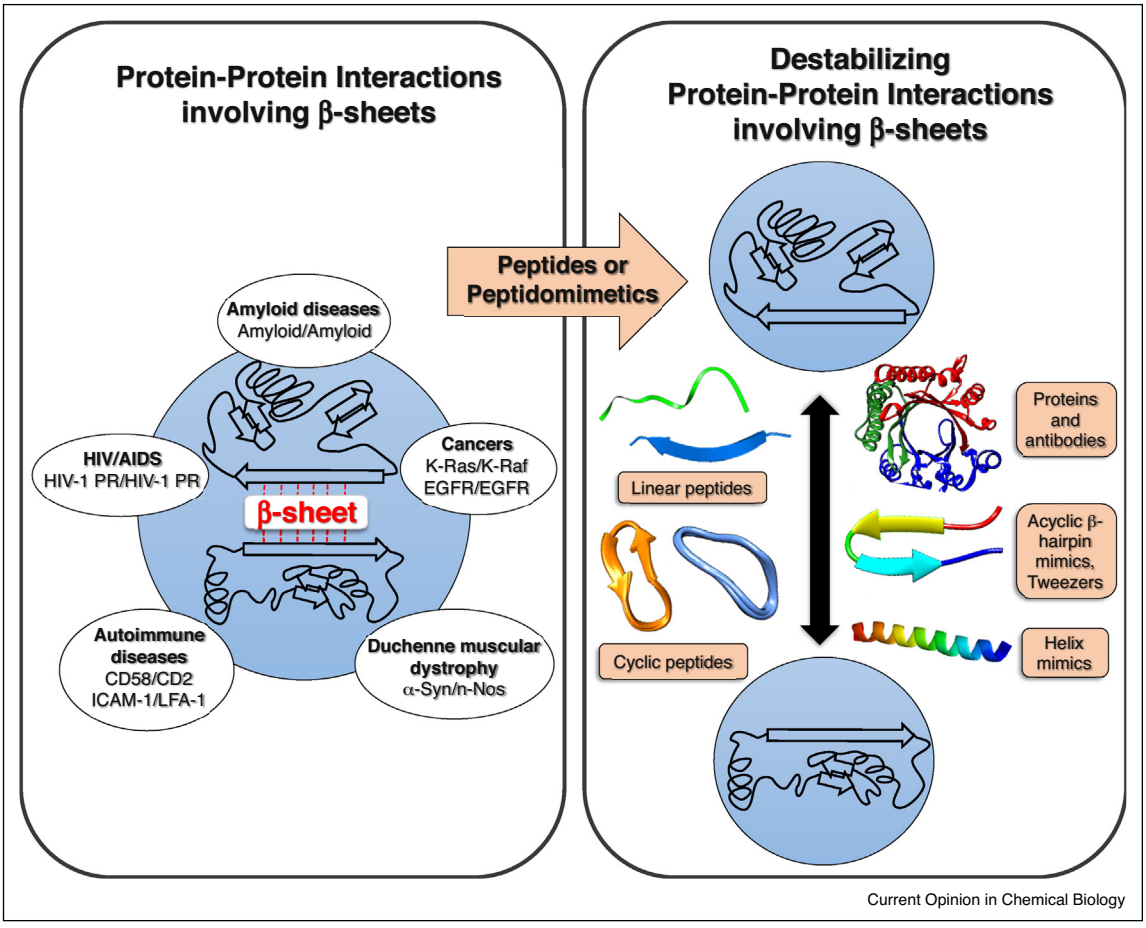
Table 1

Classification of the peptides and peptidomimetics used according to their structures, the PPI partners, and the associated pathologies.

Structural approach	Protein–protein interaction partners	Targeted pathology	Ref.
β strand mimics	Superoxide dismutase 1 (SOD1) aggregation	Amyotrophic lateral sclerosis (ALS)	[6]
	Amyloid β peptide Aβ(1-42) aggregation	Alzheimer's disease (AD)	[7–10]
	Tau protein aggregation	Alzheimer's disease (AD)	[7]
	PDZ[i] domain of α-1 syntrophin/PDZ domain of neuronal nitric oxide synthase (nNOS)	Duchenne muscular dystrophy	[11]
Linear peptide derivatives containing β-sheet breaker element	Human Islet Amyloid PolyPeptide (hIAPP) aggregation	Type 2 Diabetes Mellitus (T2DM)	[12,13,14,16]
	Amyloid β peptide Aβ(1–42) aggregation	Alzheimer's disease (AD)	[15,18–20]
	Insulin aggregation	Impairment in insulin absorption and immune response in insulin injection amyloidosis, autoimmune response in Parkinson's disease	[17]
Cyclic β-hairpin mimics	Intercellular adhesion molecule (ICAM-1)/ lymphocyte associated antigen-1 (LFA-1)	Autoimmune diseases (prevention of allograft rejection, rheumatoid arthritis, Insulin-Dependent Diabetes Mellitus (IDDM), psoriasis)	[23,24]
	PDZ[i] domain of α-1 syntrophin/PDZ domain of neuronal nitric oxide synthase (nNOS)	Duchenne muscular dystrophy	[25]
	Amyloid β peptides Aβ(1-40) et Aβ(1-42) aggregation	Alzheimer's disease (AD)	[26,30,32]
	Human Islet Amyloid PolyPeptide (hIAPP) aggregation	Type 2 Diabetes Mellitus (T2DM)	[26,31]
	T cells glycoprotein CD2 (lymphocyte function-associated antigen-2)/epithelial cells CD58 (lymphocyte function-associated antigen-3)	Autoimmune diseases (rheumatoid arthrisis)	[27,28]
	Epidermal Growth Factor Receptor (EGFR) dimerization	Carcinomas (cell growth and proliferation)	[29]
	Human β2-microglobulin ($H\beta_2M$) aggregation	Dialysis-related amyloidosis (DRA)	[32]
	Human α-synuclein (hαSyn) aggregation	Parkinson's disease	[32]
Other macrocycles	Amyloid β peptide Aβ(1-42) aggregation	Alzheimer's disease (AD)	[35,36]
	PDZ3[i] domain of postsynaptic density-95 kDa protein (PSD-95) with NDMA receptor	Antinociceptive activity in chronic pain	[37,38]
	K-Ras, GTP binding protein (Kirsten Rat Sarcoma Virus)/K-Raf (Rapidly Accelerated Fibrosarcoma)	Solid tumors	[39,40••,41]
Acyclic β-hairpin mimics	Amyloid β peptide Aβ(1-42) aggregation	Alzheimer's disease (AD)	[42,44••,45,46,47•]
	Human Islet Amyloid PolyPeptide (hIAPP) aggregation	Type 2 Diabetes Mellitus (T2DM)	[43]
	Transthyretin (TTR) aggregation	Familial Amyloid Polyneuropathy (FAP), Senile Systemic Amyloidosis (SSA)	[42,47•]
Helix mimics	Human islet amyloid polypeptide (hIAPP) aggregation	Type 2 Diabetes Mellitus	[48,49,50••]
	Amyloid β peptide Aβ(1-42) aggregation	Alzheimer's disease (AD)	[49,51,52••,53]
Tweezer molecules	HIV-1(Human Immunodeficiency Virus type 1) protease (PR) dimerization	Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS)	[54–60]
	Amyloid β peptide Aβ(1-42) aggregation	Alzheimer's disease (AD)	[61]
Proteins, antibodies	Superoxide dismutase 1 (SOD1) aggregation	Amyotrophic lateral sclerosis (ALS)	[62•]
	Amyloid β peptide Aβ(1-40) aggregation	Alzheimer's disease (AD)	[63]
	SUMO-dependent PPI	Tumor development and metastasis, neurodegenerative disorders, metabolic abnormalities, cardiac fibrosis	[64]
	Human Islet Amyloid PolyPeptide (hIAPP) aggregation	Type 2 Diabetes Mellitus (T2DM)	[65]
	Human α-synuclein (hαSyn) aggregation	Parkinson's disease	[66]

[i] The PDZ domain is a protein domain of 80–100 aa mediating a variety of protein–protein interaction in eukaryotic cells, involved in signal transductions pathways. Its name is derived from the initials of the 3 proteins, in which this domain was discovered: *P*SD-95, *D*LG, *Z*O-1.

Figure 1



Peptide and peptidomimetic strategies developed to inhibit PPIs involving β-sheet structures.

A series of β-strand mimics containing unnatural amino acids has been reported to inhibit PPIs mediated via β-sheets. Peptide analogues containing L-amino acids of the SRE alternating with α,α-disubstituted amino acids, were described as able to interact with amyloid proteins through the formation of β-sheet assemblies, in order to inhibit their aggregation [8,9]. Peptidomimetics composed of dipeptides inserted between two 3-amino-pyrazole-5-carboxylic acids as amino acid mimics were designed to match the hydrogen bonds network of a β-sheet and led to water soluble Aβ ligands (compound **1**, Figure 2) [10].

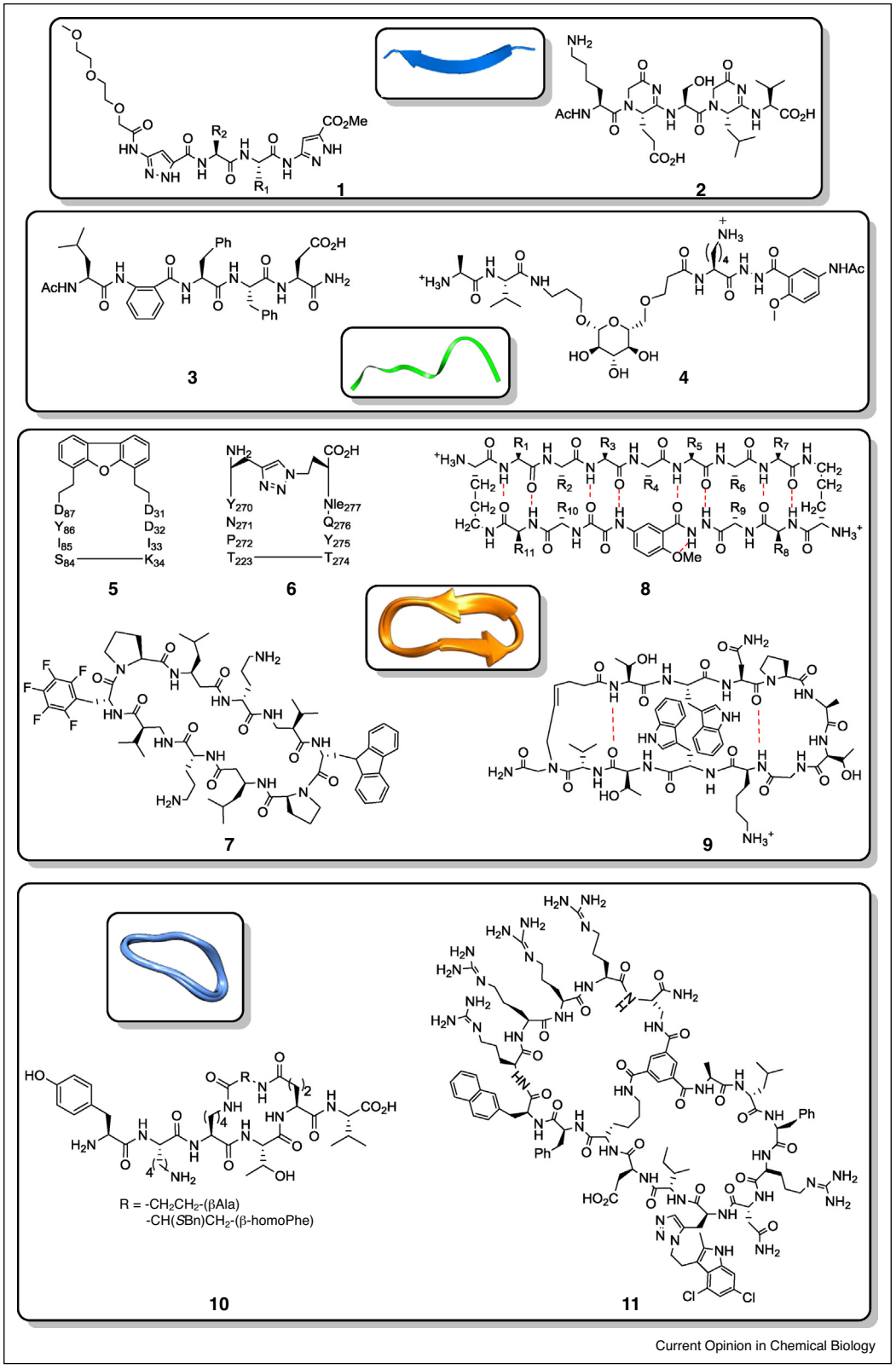
The constrained 4,5-dihydro-2(3H)-pyrazinone moiety was described as favouring an extended β-strand conformation as it was able to reproduce the hydrogen-bonding network and the side-chain functionality of a natural β-strand. Pentapeptide mimics containing two pyrazinone units were designed to inhibit the interaction of the PDZ domain of α-1 syntrophin with nNOS. These compounds bound selectively the PDZ (see the note i of Table 1 for the meaning of PDZ) domain of α-1 syntrophin more tightly than the peptidic analogue and were more stable towards proteolysis (compound **2**, Figure 2) [11].

Unstructured linear peptide derivatives

Small peptides not adopting any preferential conformation have also been described as inhibitors of PPIs involving β-sheet structures. Scanning of peptide combinatorial libraries obtained by phage display allowed the identification of new peptides as inhibitors of Aβ(1–42) aggregation [7].

Small peptides inspired by the amyloidogenic sequence of amyloid proteins but containing a β-sheet breaker element designed to disturb the formation of β-sheet structure have been extensively described. For example, proline, α-aminoisobutyric acid (Aib) and α,β–dehydrophenylalanine have been used [12–14]. More recently, inserting a 2-aminobenzoic or 3-aminobenzoic acid moiety into the amyloidogenic sequence of Aβ(1–40) or of human islet

Figure 2



Examples of β-strand mimetics (**1**,**2**), linear peptide derivatives containing a β-sheet breaker element (**3**,**4**) cyclic β-hairpin mimics (**5**-**9**) and other cyclic peptide derivatives (**10**,**11**).

amyloid polypeptide (hIAPP) allowed the efficient inhibition of Aβ(1–40) and hIAPP aggregation respectively, probably because introduction thereof induced a kink in the peptide that also prevented the self-aggregation of the peptide derivatives (compound **3**, Figure 2) [15,16]. In contrast, inserting 4-aminobenzoic acid maintained the extended structure of the parent peptide and induced self-aggregation of the small peptide and showed no effect in preventing hIAPP aggregation [16].

Small peptides not directly based on the amyloid sequences have been also designed. Trp-Trp-Taurine tripeptide (taurine is 2-aminoethanesulfonic acid) and its dimer were evaluated to consider the electrostatic effect of the sulfonic acid group in a hydrophobic sequence on insulin aggregation. The dimer was an efficient inhibitor of insulin aggregation potentially by binding and stabilizing the α-helix-rich native structure preventing the conformational transition to β-sheet [17].

Inserting sugar moiety in peptides was also proven to increase amyloid aggregation inhibition, particularly of Aβ(1–42) and Tau in AD (Ac-LPFFD-Trehalose) [18,7]. Our group introduced the use of a hydrophilic D-glucopyranosyl scaffold, linked through aminoalkyl and carboxyethyl linkers in the C1 and C6 positions linked to two hydrophobic dipeptides or peptidomimetics based on a 5-amino-2-methoxybenzhydrazide unit (compound **4**, Figure 2) [19,20]. The sugar moiety, acting as the β-sheet breaker element, was essential to prevent the formation of oligomers and fibrils by disrupting soluble oligomers of Aβ(1–42).

Cyclic peptide derivatives

Cyclic β-hairpin mimics

Cyclic peptides have received recent and increasing interest as potential drugs as they offer enhanced pharmacokinetic profiles in terms of oral bioavailability, increased metabolic stability and higher cross membrane properties. Cyclisation reduces the flexibility of the peptide derivatives improving their binding properties and reducing the entropic penalty upon binding [21,22••].

In particular, cyclic peptide derivatives adopting β-hairpin structures can be used to inhibit PPIs involving β-sheet structures. The main reported design of these kind of cyclic peptides was based on peptidic sequences of one partner of the PPIs that were cyclized through natural or mimics of β-turns.

Cyclic dodecapeptide derivatives were shown to inhibit the ICAM-1/LFA-1 interaction mediating T-cell adhesion, involved in autoimmune diseases. They were based on a Pro-Arg-Gly sequence inducing a β-turn structure, and on sequences of the N-terminal region of domain 1 (D1) of ICAM-1 closed by a disulfide bridge. They adopted a similar structure to the β-hairpin formed between D1 and LFA-1. They showed higher inhibition activity than the linear hexapeptides analogues [23,24]. In the context of the interaction of the PDZ domain of α-syntrophin with nNOS, cyclic β-finger peptides (15–23 aa) adopted an anti-parallel β-sheet structure based on C-terminal sequences of nNOS and a D-Pro-Gly β-turn. They prevented the interaction with the PDZ domain of α-syntrophin more efficiently than the linear or retro analogues [25].

17-Residue peptides cyclized through two disulfide-bridged cysteines and containing only four hIAPP-derived side chains inhibited both hIAPP and Aβ more strongly than linear peptides based on hIAPP sequences. Inverting the chirality of certain residues led to a selective inhibitor of Aβ and strongly improved proteolytic stability in human plasma and BBB crossing ability [26].

The interaction between the T-cell glycoprotein CD2 and epithelial cells CD58 plays an important role in autoimmune diseases such as rheumatoid arthritis. The CD58-CD2 interface contains two β-sheets. β-Hairpin mimics using a D-Pro-Pro or dibenzofuran turn mimetic and β-strand sequences of CD2 that bind CD58 were designed (compound **5**, Figure 2) [27,28].

Peptide-based macrocycles using the native sequence of human EGFR and constrained by a triazolyl-bridge of variable length were proteolytically stable and provided the inhibition of EGFR dimerization, that is involved in cell growth and proliferation (compound **6**, Figure 2) [29].

Cyclic β-hairpin mimics not based on the SRE have also been reported. The natural cyclic decapeptide Gramicidin S and analogues alternating β-amino acids and unnatural α-amino acids such as pentafluorophenylalanine (compound **7**, Figure 2), were shown to interfere with the β-sheet structures of Aβ(1–40) to inhibit its fibril formation [30].

A strategy to stabilize β-hairpin structures lies in introducing mimics of β-strands. Macrocyclic β-sheet mimics containing two β-strands and two δ-linked ornithine turns were able to inhibit selectively amyloid protein aggregation. One strand was composed of heptapeptide sequences selected from different amyloid proteins (Aβ, human β2-microglobulin, human α-synuclein, hIAPP). The second strand, designed as the blocking edge, contained an unnatural tripeptide β-strand mimic (Hao, abbreviation of hydrazine, 5-amino-2-methoxybenzoic acid, oxalic acid), flanked by two dipeptides (compound **8**, Figure 2) [31,32].

Other strategies to stabilize β-hairpin structures were found such as the hydrogen bond surrogate (HBS) approach, in which a main chain hydrogen bond was replaced by a covalent linkage (such as the olefin HBS linkage in compound **9**, Figure 2) [33]. However, to our

knowledge no particular use of this methodology has yet been reported to inhibit a specific PPI.

Other macrocycles

In some cases, cyclic peptides designed as inhibitors of PPIs involving β-sheet structures do not adopt any preferential conformation (or the conformation is not specified). In the context of amyloid proteins, cyclic peptides based on SRE have displayed powerful and specific inhibition of amyloid aggregation and have been proven in some cases to be more efficient than their linear peptide parent [34,35]. A library of cyclic hexa-D,L-α-peptides built by alternating D and L α amino acids were screened for their capacity to inhibit Aβ(1–42) aggregation [36]. They could stack to adopt β-sheet-like nanotube structures and to cross-interact with amyloid peptides.

A series of cyclic peptides was developed to target the PDZ-3 domains of PSD-95 with NDMA receptor. The cyclization, performed via a bridge residue of variable lengths between two side chains, increased the binding affinity with PSD-95 and reduced the enzymatic degradation relative to the linear peptide (compound **10**, Figure 2) [37]. Lengthening the linear part of the cyclic peptide with 7 Arginine residues increased the cell permeability [38].

Bifunctional, macrocyclic molecules have been designed to inhibit the PPIs of K-Ras and its effector proteins such as Raf, involved in solid tumours. However, the large and flat interfaces between K-Ras and its effector proteins prevent a small molecule to make sufficient interactions to achieve high affinity and specificity. The rapamycin analogue ('rapalog') concept for inhibition of PPIs has been applied using a bifunctional, macrocyclic molecule that first binds to endogenous FK506-binding protein (FKBP). The rapalog-FKBP complex formed a steric block which prevented the interaction of K-Ras with its effector. A linear peptide sequence of 4–6 amino acid residues linked to the macrocycles aimed at improving the binding affinity and selectivity to K-Ras [39].

Another strategy integrating K-Ras binding and the cell-penetrating peptide (CPP) Arg-Arg-nal-Arg-Fpa (nal for D-β-naphthylalanine, Fpa for L-4-fluorophenylalanine) into a single cyclic peptide allowed membrane permeability but might also play a role in physically blocking K-Ras interaction with its effectors [40••]. By screening a combinatorial library, the same group described bicyclic peptides, which contained an invariant powerful CPP (F-NAL-RRRRQ) in the first cycle and 8 residues in the second cycle leading to a moderately potent and cell-permeable K-Ras inhibitor (compound **11**, Figure 2) [41].

Acyclic β-hairpin mimics

Even if cyclic peptides have received an increasing interest as therapeutics, more specifically to improve the crossing of membranes and the stability towards enzymatic cleavage, it is important to consider that the greater flexibility of acyclic β-hairpin mimics can allow them to adapt to the different shapes of the proteins that engage in PPIs involving β-sheets. However, small and acyclic β-hairpin mimics have been very rarely explored as β-sheet binders and inhibitors of PPIs. This can be due to the difficulty to stabilize linear peptides and analogues in acyclic β-hairpin conformations.

Natural peptides can be stabilized by Trp-Trp non hydrogen bonded cross-strand pairs, also called trpzip peptides. Small β-hairpins based on this strategy were designed to inhibit transthyretin (TTR) and Aβ(1–42) [42] and hIAPP aggregation [43].

Next to natural β-turns also mimics of β-turns have been designed both to stabilize the β-hairpin conformations as well as to increase the stability towards proteolysis. For example, efficient inhibitors of aggregation have been developed in our group, using piperidine-pyrrolidine and 2,5-diketopiperazine β-turn inducers (compounds **12** and **13**, Figure 3) [44••,45,46]. Peptidic strands were progressively replaced by shorter peptides and peptidomimetic arms [45,46].

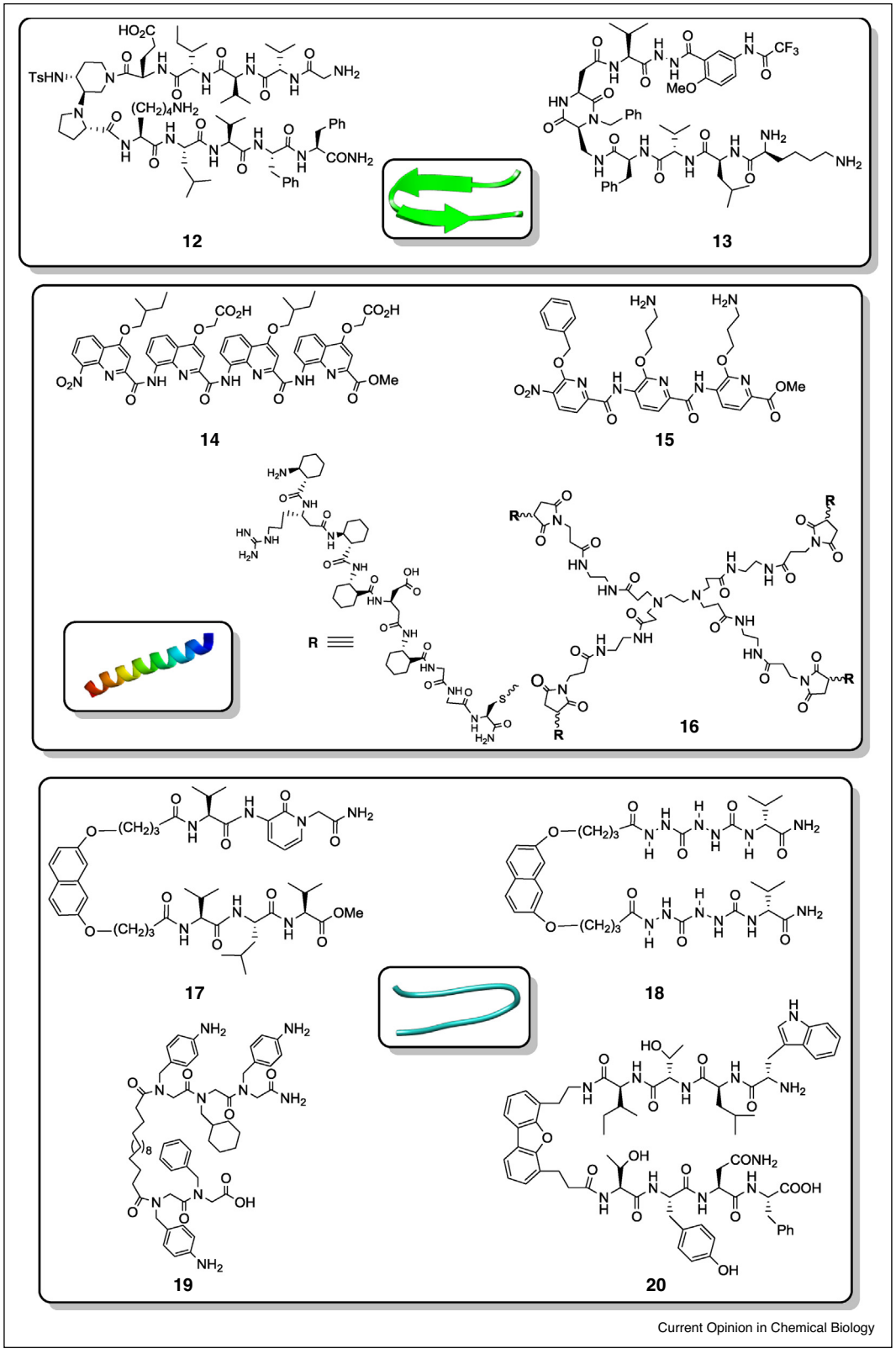
A novel secondary structure called α-sheet has been described as being involved in the structuration of amyloidogenic regions of amyloid proteins. α-Sheets are similar to β-sheets, but while in β-sheet the NH and C=O groups are alternating along the strands, in α-sheets the NH groups are aligned on one side and the C=O on the other. A plane flip can convert the α-sheet into a β-sheet. α-Sheet mimics containing one turn and alternating D-amino and L-amino acids were designed and described as inhibitors of TTR and Aβ(1–42) aggregation [47•].

Helix mimics

A very recent strategy to inhibit PPIs involving β-sheets in an indirect way, is to trap amyloid proteins such as Aβ (1–42) and hIAPP into their non-toxic monomeric forms by targeting their α-helix conformation before they switch to β-sheet conformations that induce the aggregation process. For that purpose, only a few helix mimics, more particularly foldamers, have been reported. Oligoquinoline (compound **14**, Figure 3) [48,49] and oligopyridylamide (compound **15**, Figure 3) [50••,51,52••] showed the ability to induce α-helical conformation of Aβ and hIAPP and to prevent their aggregation.

Foldamer-dendrimers, in which four helices were based on β^3-amino acids with proteinogenic side-chains, alicyclic β-amino acids with 6-membered or 5-membered side chains, and natural amino acids, were developed and could tightly bind Aβ oligomers (compound **16**, Figure 3) [53].

Figure 3



Examples of acyclic β-hairpin mimics (**12**,**13**), helix mimics (**14**-**16**) and tweezer molecules (**17**-**20**).

Tweezer molecules

Tweezer molecules have been described to destabilize PPIs involving protein dimerization, in particular the dimerization interface of the HIV-1 protease (PR), which consists of an interdigitating four stranded antiparallel β-sheet formed by the *N*-termini and *C*-termini of the two PR monomers. The strategy employed was to design molecular tweezers built on a central tether on which two arms derived from the interfacial sequence of PR were linked in order to bind by interdigitation the *N*-termini and *C*-termini of one PR monomer, preventing its dimerization. Our group described tongs based on rigid aromatic tethers (resorcinol, 2.6-pyridinediol, 2.7-naphtalenediol, 2.7-quinolinediol) linked to two tripeptidic strands by a carboxypropyl arm [54]. Peptidic arms were then substituted by β-strand mimics introducing various motifs such as 3-amino-6-methylpyridin2(1*H*)-one (compound **17**, Figure 3) [55], 5-amino-2-methoxy-benzhydrazide [56], and carbonylhydrazide groups (compound **18**, Figure 3) [57], to afford PR dimerization inhibitors showing better efficiency and resistance towards proteolysis. The group of Chmielewski reported inhibitors based on a more flexible aliphatic tether bearing peptidic arms [58] and peptoid arms (compound **19**, Figure 3) [59]. Tongs based on a 4-(2-aminoethyl)-6-dibenzofuranopropionic acid scaffold were further reported to inhibit both PR dimerization and amyloid protein aggregation (compound **20**, Figure 3) [60,61].

Proteins and antibodies

Proteins and antibodies can adopt a variety of secondary structures that can provide high specificity. Their use as inhibitor of PPIs involving misfolding and aggregation has been described. Variants of the protein HBT1 were used to design inhibitors of PPIs in SOD1 aggregation in ALS [62•] and to inhibit Aβ(1–40) aggregation in AD [63]. Artificial binding protein inhibitors of SUMO-dependent PPIs have been reported [64]. Engineered binding protein sequesters of β-hairpin conformation of amyloid proteins have been selected by phage display to specifically inhibit the aggregation of amyloid proteins. Mirecka *et al.* have, for example, selected two β-wrap proteins able to bind the β-hairpin conformation of hIAPP [65] and α-synuclein [66] respectively.

Conclusion

The occurrence of PPIs involving β-sheet secondary structures is probably still underestimated. However, they have been already questioned in many diseases that crucially need therapeutics. This class of PPIs is particularly involved in cancer, autoimmune diseases, viral infections and amyloidoses that concern at least twenty degenerative diseases. The strategy aiming at using peptide derivatives and peptidomimetics is of particular interest because this class of small molecules can adopt proper conformations to block PPIs. Furthermore, they generally offer greater efficacy and selectivity, and a reduced risk of side-effects compared to other small organic molecules. Peptidomimetics show resistance towards proteolysis and can cross cell membranes and the blood-brain barrier. According to the different classes of compounds listed in this review, from small linear peptides to large cyclic peptides and proteins, the use of compounds between 1000 and 2000 Da offers a good compromise between druggability properties and satisfactory interaction with rather large surfaces of the PPI partners. Among the most represented classes, cyclic peptides constitute the most efficient compounds. However, the more recently studied acyclic peptidomimetics, that adopt flexible β-hairpin conformations, are also particularly promising to inhibit PPIs involving a β-sheet structuring of the hot-spot residues. Selectivity can be achieved by mimicking the hot-spot sequence of one protein partner. Of particular interest is the less reported use of helix mimics to stabilize intrinsically disordered proteins in their helical conformation in order to prevent their folding into the β-sheet conformation involved in the pathological PPI processes. According to the state of the art presented in this review, it is probably still too early to establish if inhibitors of PPIs involving β-sheet structures have a real future as therapeutics, because only scarce and preliminary studies have been reported. Nevertheless, the fact that some peptide derivatives and antibodies inhibiting Aβ(1–42) or Tau aggregation in AD have reached clinical trials [7], underscores the potential of this strategy. In addition, *in vivo* validation of the inhibition of the hetero dimerization of proteins through β-strand interactions was obtained in the case of PSD-95/NMDA inhibitors that showed anti-nociceptive effect [38] and activity in the treatment of stroke [67].

To our opinion, four main factors have jeopardized the development of PPI inhibitors involving β-sheet structures as therapeutics. First, the discovery of this kind of PPIs is more recent than in the case of PPIs involving helical structures so less perspective is available. Secondly, this kind of PPIs generally involves hydrophobic residues. Thus, the first studied peptides and peptidomimetics, inspired by the hot-spot residues, were poorly soluble and in addition, by the nature of their structure mimicking β-strands or β-sheets, could aggregate. The introduction of polar groups in inhibitors has proven that hydrophilicity can be increased while activity is maintained. Thirdly, the evaluation of compounds on PPI interference by non-classical biophysical and biochemical techniques is more challenging than the evaluation on more classical targets such as enzymes, receptors, or ion channels. The recent development of robust techniques to study PPIs should help. Finally, the use of peptides in clinics has encountered cost and pharmacokinetic problems. New synthetic strategies to improve productivity and to increase the half-life and bioavailability of peptides and peptidomimetics, along with alternative routes of administration, have allowed a larger number of

peptide-based drugs to be now marketed [68,69]. The next decade should allow us to assess whether the inhibition of β-sheet formation in PPIs by peptides and analogues can offer real therapeutic opportunities.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Ran X, Gestwicki JE: **Inhibitors of protein–protein interactions (PPIs): an analysis of scaffold choices and buried surface area**. *Curr Opin Chem Biol* 2018, **44**:75-86 http://dx.doi.org/10.1016/j.cbpa.2018.06.004.

2. Jesus Perez de Vega M, Martin-Martinez M, Gonzalez-Muniz R: **Modulation of protein-protein interactions by stabilizing/mimicking protein secondary structure elements**. *Curr Top Med Chem* 2007, **7**:33-62 http://dx.doi.org/10.2174/156802607779318325.

3. Pelay-Gimeno M, Glas A, Koch O, Grossmann TN: **Structure-based design of inhibitors of protein-protein interactions: mimicking peptide binding epitopes**. *Angew Chem Int Ed* 2015, **54**:8896-8927 http://dx.doi.org/10.1002/anie.201412070.

4. Watkins AM, Arora PS: **Anatomy of β-strands at protein–protein interfaces**. *ACS Chem Biol* 2014, **9**:1747-1754 http://dx.doi.org/10.1021/cb500241y.

5. Loughlin WA, Tyndall JDA, Glenn MP, Hill TA, Fairlie DP: **Update 1 of: beta-strand mimetics**. *Chem Rev* 2010, **110**:32-69 http://dx.doi.org/10.1021/cr900395y.

6. Banerjee V, Shani T, Katzman B, Vyazmensky M, Papo N, Israelson A, Engel S: **Superoxide Dismutase 1 (SOD1)-derived peptide inhibits amyloid aggregation of familial amyotrophic lateral sclerosis SOD1 mutants**. *ACS Chem Neurosci* 2016, **7**:1595-1606 http://dx.doi.org/10.1021/acschemneuro.6b00227.

7. Ryan P, Patel B, Makwana V, Jadhav HR, Kiefel M, Davey A, Reekie TA, Rudrawar S, Kassiou M: **Peptides, peptidomimetics, and carbohydrate–peptide conjugates as amyloidogenic aggregation inhibitors for Alzheimer's disease**. *ACS Chem Neurosci* 2018, **9**:1530-1551 http://dx.doi.org/10.1021/acschemneuro.8b00185.

8. Etienne MA, Aucoin JP, Fu Y, McCarley RL, Hammer RP: **Stoichiometric inhibition of amyloid β-protein aggregation with peptides containing alternating α,α-disubstituted amino acids**. *J Am Chem Soc* 2006, **128**:3522-3523 http://dx.doi.org/10.1021/ja0600678.

9. Bett CK, Ngunjiri JN, Serem WK, Fontenot KR, Hammer RP, McCarley RL, Garno JC: **Structure–activity relationships in peptide modulators of β-amyloid protein aggregation: variation in α,α-disubstitution results in altered aggregate size and morphology**. *ACS Chem Neurosci* 2010, **1**:608-626 http://dx.doi.org/10.1021/cn100045q.

10. Rzepecki P, Schrader T: **β-sheet ligands in action: KLVFF recognition by aminopyrazole hybrid receptors in water**. *J Am Chem Soc* 2005, **127**:3016-3025 http://dx.doi.org/10.1021/ja045558b.

11. Hammond MC, Harris BZ, Lim WA, Bartlett PA: **Beta strand peptidomimetics as potent PDZ domain ligands**. *Chem Biol* 2006, **13**:1247-1251 http://dx.doi.org/10.1016/j.chembiol.2006.11.010.

12. Abedini A, Meng F, Raleigh DP: **A single-point mutation converts the highly amyloidogenic human islet amyloid polypeptide into a potent fibrillization inhibitor**. *J Am Chem Soc* 2007, **129**:11300-11301 http://dx.doi.org/10.1021/ja072157y.

13. Gilead S, Gazit E: **Inhibition of amyloid fibril formation by peptide analogues modified with α-aminoisobutyric acid**. *Angew Chem Int Ed* 2004, **43**:4041-4044 http://dx.doi.org/10.1002/anie.200353565.

14. Mishra A, Misra A, Sri Vaishnavi T, Thota C, Gupta M, Ramakumar S, Chauhan VS: **Conformationally restricted short peptides inhibit human islet amyloid polypeptide (hIAPP) fibrillization**. *Chem Commun* 2013, **49**:2688 http://dx.doi.org/10.1039/c3cc38982k.

15. Paul A, Chaitanya Nadimpally K, Mondal T, Thalluri K, Mandal B: **Inhibition of Alzheimer's amyloid-β peptide aggregation and its disruption by a conformationally restricted α/β hybrid peptide**. *Chem Commun* 2015, **51**:2245-2248 http://dx.doi.org/10.1039/C4CC09063B.

16. Paul A, Kalita S, Kalita S, Sukumar P, Mandal B: **Disaggregation of amylin aggregate by novel conformationally restricted aminobenzoic acid containing α/β and α/γ hybrid peptidomimetics**. *Sci Rep* 2017, **7** http://dx.doi.org/10.1038/srep40095.

17. Mishra NK, Joshi KB, Verma S: **Inhibition of human and bovine insulin fibril formation by designed peptide conjugates**. *Mol Pharm* 2013, **10**:3903-3912 http://dx.doi.org/10.1021/mp400364w.

18. Sinopoli A, Giuffrida A, Tomasello MF, Giuffrida ML, Leone M, Attanasio F, Caraci F, DeBona P, Naletova I, Saviano M, Copani A, Pappalardo G, Rizzarelli E: **Ac-LPFFD-Th: a trehalose-conjugated peptidomimetic as a strong suppressor of amyloid-β oligomer formation and cytotoxicity**. *ChemBioChem* 2016, **17**:1541-1549 http://dx.doi.org/10.1002/cbic.201600243.

19. Kaffy J, Brinet D, Soulier J-L, Khemtémourian L, Lequin O, Taverna M, Crousse B, Ongeri S: **Structure–activity relationships of sugar-based peptidomimetics as modulators of amyloid β-peptide early oligomerization and fibrillization**. *Eur J Med Chem* 2014, **86**:752-758 http://dx.doi.org/10.1016/j.ejmech.2014.09.031.

20. Kaffy J, Brinet D, Soulier J-L, Correia I, Tonali N, Fera KF, Iacone Y, Hoffmann ARF, Khemtémourian L, Crousse B, Taylor M, Allsop D, Taverna M, Lequin O, Ongeri S: **Designed glycopeptidomimetics disrupt protein–protein interactions mediating amyloid β-peptide aggregation and restore neuroblastoma cell viability**. *J Med Chem* 2016, **59**:2025-2040 http://dx.doi.org/10.1021/acs.jmedchem.5b01629.

21. Nielsen DS, Shepherd NE, Xu W, Lucke AJ, Stoermer MJ, Fairlie DP: **Orally absorbed cyclic peptides**. *Chem Rev* 2017, **117**:8094-8128 http://dx.doi.org/10.1021/acs.chemrev.6b00838.

22. •• Zorzi A, Deyle K, Heinis C: **Cyclic peptide therapeutics: past, present and future**. *Curr Opin Chem Biol* 2017, **38**:24-29 http://dx.doi.org/10.1016/j.cbpa.2017.02.006

A very exhaustive and interesting updating review on cyclic peptides as drugs.

23. Anderson ME, Tejo BA, Yakovleva T, Siahaan TJ: **Characterization of binding properties of ICAM-1 peptides to LFA-1: inhibitors of T-cell adhesion**. *Chem Biol Drug Des* 2006, **68**:20-28 http://dx.doi.org/10.1111/j.1747-0285.2006.00407.x.

24. Anderson ME, Yakovleva T, Hu Y, Siahaan TJ: **Inhibition of ICAM-1/LFA-1-mediated heterotypic T-cell adhesion to epithelial cells: design of ICAM-1 cyclic peptides**. *Bioorg Med Chem Lett* 2004, **14**:1399-1402 http://dx.doi.org/10.1016/j.bmcl.2003.09.100.

25. Seedorff S, Appelt C, Beyermann M, Schmieder P: **Design, synthesis, structure and binding properties of PDZ binding, cyclic β-finger peptides**. *Biochem Biophys Res Commun* 2010, **395**:535-539 http://dx.doi.org/10.1016/j.bbrc.2010.04.060.

26. Spanopoulou A, Heidrich L, Chen H-R, Frost C, Hrle D, Malideli E, Hille K, Grammatikopoulos A, Bernhagen J, Zacharias M, Rammes G, Kapurniotu A: **Designed macrocyclic peptides as nanomolar amyloid inhibitors based on minimal recognition elements**. *Angew Chem Int Ed* 2018, **57**:14503-14508 http://dx.doi.org/10.1002/anie.201802979.

27. Sable R, Durek T, Taneja V, Craik DJ, Pallerla S, Gauthier T, Jois S: **Constrained cyclic peptides as immunomodulatory inhibitors of the CD2:CD58 protein–protein interaction**. *ACS Chem Biol* 2016, **11**:2366-2374 http://dx.doi.org/10.1021/acschembio.6b00486.

28. Gokhale A, Weldeghiorghis TK, Taneja V, Satyanarayanajois SD: **Conformationally constrained peptides from CD2 to modulate protein–protein interactions between CD2 and CD58**. *J Med Chem* 2011, **54**:5307-5319 http://dx.doi.org/10.1021/jm200004e.

29. Hanold LE, Oruganty K, Ton NT, Beedle AM, Kannan N, Kennedy EJ: **Inhibiting EGFR dimerization using triazolyl-bridged dimerization arm mimics**. *PLoS One* 2015, **10**:e0118796 http://dx.doi.org/10.1371/journal.pone.0118796.

30. Luo J, Otero JM, Yu C-H, Wärmländer SKTS, Gräslund A, Overhand M, Abrahams JP: **Inhibiting and reversing amyloid-β peptide (1-40) fibril formation with gramicidin S and engineered analogues**. *Chem—Eur J* 2013, **19**:17338-17348 http://dx.doi.org/10.1002/chem.201301535.

31. Buchanan LE, Dunkelberger EB, Tran HQ, Cheng P-N, Chiu C-C, Cao P, Raleigh DP, de Pablo JJ, Nowick JS, Zanni MT: **Mechanism of IAPP amyloid fibril formation involves an intermediate with a transient -sheet**. *Proc Natl Acad Sci U S A* 2013, **110**:19285-19290 http://dx.doi.org/10.1073/pnas.1314481110.

32. Cheng P-N, Liu C, Zhao M, Eisenberg D, Nowick JS: **Amyloid β-sheet mimics that antagonize protein aggregation and reduce amyloid toxicity**. *Nat Chem* 2012, **4**:927-933 http://dx.doi.org/10.1038/nchem.1433.

33. Sawyer N, Arora PS: **Hydrogen bond surrogate stabilization of β-hairpins**. *ACS Chem Biol* 2018, **13**:2027-2032 http://dx.doi.org/10.1021/acschembio.8b00641.

34. Luo J, Abrahams JP: **Cyclic peptides as inhibitors of amyloid fibrillation**. *Chem—Eur J* 2014, **20**:2410-2419 http://dx.doi.org/10.1002/chem.201304253.

35. Arai T, Araya T, Sasaki D, Taniguchi A, Sato T, Sohma Y, Kanai M: **Rational design and identification of a non-peptidic aggregation inhibitor of amyloid-β based on a pharmacophore motif obtained from *cyclo* [-Lys-Leu-Val-Phe-Phe-]**. *Angew Chem* 2014, **126**:8375-8378 http://dx.doi.org/10.1002/ange.201405109.

36. Richman M, Wilk S, Chemerovski M, Wärmländer SKTS, Wahlström A, Gräslund A, Rahimipour S: **In vitro and mechanistic studies of an antiamyloidogenic self-assembled cyclic d,l-α-peptide architecture**. *J Am Chem Soc* 2013, **135**:3474-3484 http://dx.doi.org/10.1021/ja310064v.

37. Li T, Saro D, Spaller MR: **Thermodynamic profiling of conformationally constrained cyclic ligands for the PDZ domain**. *Bioorg Med Chem Lett* 2004, **14**:1385-1388 http://dx.doi.org/10.1016/j.bmcl.2003.09.103.

38. LeBlanc BW, Iwata M, Mallon AP, Rupasinghe CN, Goebel DJ, Marshall J, Spaller MR, Saab CY: **A cyclic peptide targeted against PSD-95 blocks central sensitization and attenuates thermal hyperalgesia**. *Neuroscience* 2010, **167**:490-500 http://dx.doi.org/10.1016/j.neuroscience.2010.02.031.

39. Wu X, Upadhyaya P, Villalona-Calero MA, Briesewitz R, Pei D: **Inhibition of Ras-effector interaction by cyclic peptides**. *MedChemComm* 2013, **4**:378-382 http://dx.doi.org/10.1039/C2MD20329D.

40. •• Upadhyaya P, Qian Z, Selner NG, Clippinger SR, Wu Z, Briesewitz R, Pei D: **Inhibition of Ras signaling by blocking Ras-effector interactions with cyclic peptides**. *Angew Chem Int Ed Engl* 2015, **54**:7602-7606 http://dx.doi.org/10.1002/anie.201502763
Very smart design of dual bicyclic peptides with one cycle aiming the binding to the protein target and the second cycle used as cell penetrating peptide to increase the crossing of the cell membranes.

41. Trinh TB, Upadhyaya P, Qian Z, Pei D: **Discovery of a direct Ras inhibitor by screening a combinatorial library of cell-permeable bicyclic peptides**. *ACS Comb Sci* 2016, **18**:75-85 http://dx.doi.org/10.1021/acscombsci.5b00164.

42. Hopping G, Kellock J, Caughey B, Daggett V: **Designed Trpzip-3 β-hairpin inhibits amyloid formation in two different amyloid systems**. *ACS Med Chem Lett* 2013, **4**:824-828 http://dx.doi.org/10.1021/ml300478w.

43. Huggins KNL, Bisaglia M, Bubacco L, Tatarek-Nossol M, Kapurniotu A, Andersen NH: **Designed hairpin peptides interfere with amyloidogenesis pathways: fibril formation and cytotoxicity inhibition, interception of the preamyloid state**. *Biochemistry* 2011, **50**:8202-8212 http://dx.doi.org/10.1021/bi200760h.

44. •• Pellegrino S, Tonali N, Erba E, Kaffy J, Taverna M, Contini A, Taylor M, Allsop D, Gelmi ML, Ongeri S: **β-Hairpin mimics containing a piperidine–pyrrolidine scaffold modulate the β-amyloid aggregation process preserving the monomer species**. *Chem Sci* 2017, **8**:1295-1302 http://dx.doi.org/10.1039/C6SC03176E
First proof of concept that flexible acyclic unnatural β-hairpin mimics efficiently inhibit β-amyloid aggregation by preserving the monomer species and by inhibiting β-sheet interactions. They efficiently protect neuroblastoma cells against toxic effects of Aβ even at substoichiometric concentrations.

45. Tonali N, Kaffy J, Soulier J-L, Gelmi ML, Erba E, Taverna M, van Heijenoort C, Ha-Duong T, Ongeri S: **Structure-activity relationships of β-hairpin mimics as modulators of amyloid β-peptide aggregation**. *Eur J Med Chem* 2018, **154**:280-293 http://dx.doi.org/10.1016/j.ejmech.2018.05.018.

46. Vahdati L, Kaffy J, Brinet D, Bernadat G, Correia I, Panzeri S, Fanelli R, Lequin O, Taverna M, Ongeri S, Piarulli U: **Synthesis and characterization of hairpin mimics that modulate the early oligomerization and fibrillization of amyloid β-peptide: synthesis and characterization of hairpin mimics that modulate the early oligomerization and fibrillization of amyloid β-peptide**. *Eur J Org Chem* 2017, **2017**:2971-2980 http://dx.doi.org/10.1002/ejoc.201700010.

47. • Hopping G, Kellock J, Barnwal RP, Law P, Bryers J, Varani G, Caughey B, Daggett V: **Designed α-sheet peptides inhibit amyloid formation by targeting toxic oligomers**. *eLife* 2014, **3** http://dx.doi.org/10.7554/eLife.01681
Only example of α-sheet peptide mimics inhibiting amyloid protein aggregation and thus inhibiting β-sheet interactions.

48. Kumar S, Birol M, Schlamadinger DE, Wojcik SP, Rhoades E, Miranker AD: **Foldamer-mediated manipulation of a pre-amyloid toxin**. *Nat Commun* 2016, **7** http://dx.doi.org/10.1038/ncomms11412.

49. Kumar S, Henning-Knechtel A, Chehade I, Magzoub M, Hamilton AD: **Foldamer-mediated structural rearrangement attenuates Aβ oligomerization and cytotoxicity**. *J Am Chem Soc* 2017, **139**:17098-17108 http://dx.doi.org/10.1021/jacs.7b08259.

50. •• Kumar S, Schlamadinger DE, Brown MA, Dunn JM, Mercado B, Hebda JA, Saraogi I, Rhoades E, Hamilton AD, Miranker AD: **Islet amyloid-induced cell death and bilayer integrity loss share a molecular origin targetable with oligopyridylamide-based α-helical mimetics**. *Chem Biol* 2015, **22**:369-378 http://dx.doi.org/10.1016/j.chembiol.2015.01.006
First convincing proof of concept that α-helix mimics can inhibit amyloid protein aggregation by preventing their initial misfolding in β-sheet structures.

51. Kumar S, Henning-Knechtel A, Magzoub M, Hamilton AD: **Peptidomimetic-based multidomain targeting offers critical evaluation of Aβ structure and toxic function**. *J Am Chem Soc* 2018, **140**:6562-6574 http://dx.doi.org/10.1021/jacs.7b13401.

52. •• Kumar S, Hamilton AD: **α-Helix mimetics as modulators of Aβ self-assembly**. *J Am Chem Soc* 2017, **139**:5744-5755 http://dx.doi.org/10.1021/jacs.6b09734
Rational design library of oligopyridylamide based α-helix foldamers functionalized with negatively and positively charged, alkyl (linear, branched, and cyclic), and benzyl groups in order to mimic side chains of natural amino acids.

53. Fülöp L, Mándity IM, Juhász G, Szegedi V, Hetényi A, Wéber E, Bozsó Z, Simon D, Benkő M, Király Z, Martinek TA, Vertessy BG: **A foldamer-dendrimer conjugate neutralizes synaptotoxic β-amyloid oligomers**. *PLoS One* 2012, **7**:e39485 http://dx.doi.org/10.1371/journal.pone.0039485.

54. Merabet N, Dumond J, Collinet B, Van Baelinghem L, Boggetto N, Ongeri S, Ressad F, Reboud-Ravaux M, Sicsic S: **New constrained "Molecular Tongs" designed to dissociate HIV-1 protease dimer**. *J Med Chem* 2004, **47**:6392-6400 http://dx.doi.org/10.1021/jm040833q.

55. Bannwarth L, Kessler A, Pèthe S, Collinet B, Merabet N, Boggetto N, Sicsic S, Reboud-Ravaux M, Ongeri S: **Molecular tongs containing amino acid mimetic fragments: new inhibitors of wild-type and mutated HIV-1 protease dimerization**. *J Med Chem* 2006, **49**:4657-4664 http://dx.doi.org/10.1021/jm060576k.

56. Vidu A, Dufau L, Bannwarth L, Soulier J-L, Sicsic S, Piarulli U, Reboud-Ravaux M, Ongeri S: **Toward the first nonpeptidic molecular tong inhibitor of wild-type and mutated HIV-1 protease dimerization**. *ChemMedChem* 2010, **5**:1899-1906 http://dx.doi.org/10.1002/cmdc.201000308.

57. Dufau L, Marques Ressurreição AS, Fanelli R, Kihal N, Vidu A, Milcent T, Soulier J-L, Rodrigo J, Desvergne A, Leblanc K, Bernadat G, Crousse B, Reboud-Ravaux M, Ongeri S: **Carbonylhydrazide-based molecular tongs inhibit wild-type and mutated HIV-1 protease dimerization**. *J Med Chem* 2012, **55**:6762-6775 http://dx.doi.org/10.1021/jm300181j.

58. Shultz MD, Bowman MJ, Ham Y-W, Zhao X, Tora G, Chmielewski J: **Small-molecule inhibitors of HIV-1 Protease dimerization derived from cross-linked interfacial peptides**. *Angew Chem Int Ed* 2000, **39**:2710-2713 http://dx.doi.org/10.1002/1521-3773(20000804)39:15<2710::AID-ANIE2710>3.0.CO;2-P.

59. Lee S-G, Chmielewski J: **Cross-linked peptoid-based dimerization inhibitors of HIV-1 protease**. *ChemBioChem* 2010, **11**:1513-1516 http://dx.doi.org/10.1002/cbic.201000248.

60. Song M, Rajesh S, Hayashi Y, Kiso Y: **Design and synthesis of new inhibitors of HIV-1 protease dimerization with conformationally constrained templates**. *Bioorg Med Chem Lett* 2001, **11**:2465-2468 http://dx.doi.org/10.1016/S0960-894X(01)00468-1.

61. Hamada Y, Miyamoto N, Kiso Y: **Novel β-amyloid aggregation inhibitors possessing a turn mimic**. *Bioorg Med Chem Lett* 2015, **25**:1572-1576 http://dx.doi.org/10.1016/j.bmcl.2015.02.016.

62. • Banerjee V, Oren O, Ben-Zeev E, Taube R, Engel S, Papo N: **A computational combinatorial approach identifies a protein inhibitor of superoxide dismutase 1 misfolding, aggregation, and cytotoxicity**. *J Biol Chem* 2017, **292**:15777-15788 http://dx.doi.org/10.1074/jbc.M117.789610
An innovative methodology of computational mapping of the protein–protein interaction potential for designing focused protein libraries.

63. Smith TJ, Stains CI, Meyer SC, Ghosh I: **Inhibition of β-amyloid fibrillization by directed evolution of a β-sheet presenting miniature protein**. *J Am Chem Soc* 2006, **128**:14456-14457 http://dx.doi.org/10.1021/ja065557e.

64. Hughes DJ, Tiede C, Penswick N, Tang AA-S, Trinh CH, Mandal U, Zajac KZ, Gaule T, Howell G, Edwards TA, Duan J, Feyfant E, McPherson MJ, Tomlinson DC, Whitehouse A: **Generation of specific inhibitors of SUMO-1– and SUMO-2/3–mediated protein-protein interactions using affimer (Adhiron) technology**. *Sci Signal* 2017, **10** http://dx.doi.org/10.1126/scisignal.aaj2005 eaaj2005.

65. Mirecka EA, Feuerstein S, Gremer L, Schröder GF, Stoldt M, Willbold D, Hoyer W: **β-Hairpin of islet amyloid polypeptide bound to an aggregation inhibitor**. *Sci Rep* 2016, **6** http://dx.doi.org/10.1038/srep33474.

66. Mirecka EA, Shaykhalishahi H, Gauhar A, Akgül Ş, Lecher J, Willbold D, Stoldt M, Hoyer W: **Sequestration of a β-hairpin for control of α-synuclein aggregation**. *Angew Chem Int Ed* 2014, **53**:4227-4230 http://dx.doi.org/10.1002/anie.201309001.

67. Cook DJ, Teves L, Tymianski M: **Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain**. *Nature* 2012, **483**:213-217 http://dx.doi.org/10.1038/nature10841.

68. Räder AFB, Weinmüller M, Reichart F, Schumacher-Klinger A, Merzbach S, Gilon C, Hoffman A, Kessler H: **Orally active peptides: is there a magic bullet?** *Angew Chem Int Ed Engl* 2018, **57**:14414-14438 http://dx.doi.org/10.1002/anie.201807298.

69. Lau JL, Dunn MK: **Therapeutic peptides: historical perspectives, current development trends, and future directions**. *Bioorg Med Chem* 2018, **26**:2700-2707 http://dx.doi.org/10.1016/j.bmc.2017.06.052.