Fishing in the toolbox of cyclic turn mimics: a literature overview of the last decade

Raffaella Bucci [a] §, Francesca Foschi [b] §, Camilla Loro [b], Emanuela Erba [a], Maria Luisa Gelmi [a]*, Sara Pellegrino[a]

Dedicated to Prof. Franco Cozzi for its 70th birthday.

Abstract: The main goal in developing peptidomimetics is the stabilization of the bioactive conformation of peptides. Among all the secondary structures, turns are of paramount importance. This review highlights the recent advances in the design and synthesis of cyclic turn mimics. Both amino acids, carbo- and hetero-cyclic scaffolds have been considered focusing on their use in the preparation of peptidomimetics and on their ability to induce to induce γ-, β- and α-turns.

1. Introduction

Peptides are versatile tools for scientists: their huge diversity in structure and in biological functions is indeed an endless inspiration source for a wide range of applications, from pharmaceutical chemistry to material science,[1,2] from catalysis to biomedicine.[3] In this context, peptide mimics are a long-standing goal. Among the several strategies to develop peptidomimetics, the simplest one is the insertion of an unnatural amino acid (AA) or a molecular scaffold improving specific features, such as conformational and proteolytic stability, increased bioactivity and new reactivity.[4,5] Conceptually, there are three type of peptidomimetics: **type I** is referred to short peptide chains that replicate the shape of target compounds. These mimics differ from the parent peptides only for the substitution pattern stabilizing the desired secondary structures. **Type II** is referred to functional mimetics that not necessarily possess all the side chain interacting with the parent protein. **Type III** are referred to non-peptide template without atom-by atom analogy with the parent peptides.[6]

The main goal in developing peptidomimetics is the stabilization of the bioactive conformation of the peptides. Among all the secondary structures, turns are of paramount importance. They direct protein globular folding and are usually located at protein surface, where binding normally occurs.[7] The most common turn types are γ-, β- and α-turns (Figure 1). The first one is a pseudo seven-membered ring formed by an H-bond between *i* and *i+2* residues, involving three AA residues. The β–turn is composed by four AAs, forming a pseudo ten-membered ring (*i* → *i+3)*. In the α-turn, the end residues are separated by four peptide bonds (*i* → *i+4*).[8]

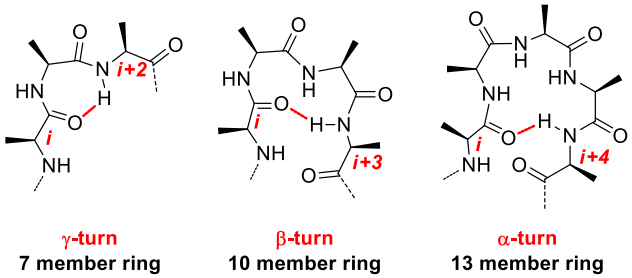
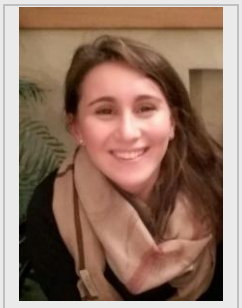


Figure 1. Most frequently occurred turns

In peptidomimetics design, different functional groups beyond the mere AA could be exploited for developing conformationally stabilized compounds. As examples, cyclic diamines[9] can be used in the development of β-hairpin mimics, while peptide bond bioisosteres could be constrained in cyclic structures.[10] This review is a literature survey on the recent advances in the development of cyclic turn mimics. In particular we will focus on both AAs, carbo- and hetero-cyclic scaffolds.

Raffaella Bucci was born in Grottaglie (TA). She graduated in Chemistry at the University of Milan in 2014. She obtained her Ph.D. in Pharmaceutical Science in 2018. During her Ph.D., she completed an internship at ETH Zurich, joining the group of Prof. Helma Wennemers. For the successive two years, she worked as Post-Doc on a project financed by Regione Lombardia, developing new methodologies for the chemical functionalization of cellulose polymers with bioactive molecules. After a Visiting Post-doc in Prof. Zanda's research group in University of Loughborough (UK), focusing on the synthesis of cyclic peptidomimetics through cycloaddition reactions, she is currently working in Prof. Gelmi's research group as a Postdoc on the synthesis and spectroscopic characterization of peptidomimetics with the aim of smart materials preparation.

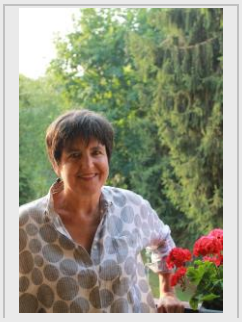
Francesca Foschi was born in Milan (Italy). She received her BS degree in Industrial Chemistry from the University of the Study of Milan in 2007 and her Ph.D. in 2010 at University of the Study of Milan in the field of organic synthesis (in particular synthesis of heterocycle compounds and non natural-amino acids). She is currently a researcher in organic chemistry at the University of the Study of Insubria (Dipartimento di Scienza e Alta Tecnologia – DiSAT).



Camilla Loro, born in 1994, received her Bachelor's degree in Chemistry and Industrial Chemistry in 2017 and the Master's degree in organic chemistry in 2019. She is currently carrying out her PhD program on C-H functionalization reactions applied to the heterocyclic synthesis under the co-supervision of Prof. Gianluigi Broggini of the University of Insubria.

Emanuela Erba was born in Monza (MI) in 1958. She graduated at the University of Milan in Pharmacy in 1982 under the supervision of Prof. Donato Pocar. Her research focuses on the synthesis of heterocyclic systems and preparation of cyclic unnatural amino acids. Moreover, she is interested in the functionalization of polymers with iron chelators to obtain biologically active molecules.

Sara Pellegrino is Associate Professor of Organic Chemistry at the University of Milano, Department of Pharmaceutical Sciences, Italy. Her research focuses on the synthesis of peptides and peptide mimics, and their application in Medicinal Chemistry, Biochemistry and Material Science. Prof Pellegrino is particularly interested in peptide self-assembly and in deciphering molecular interactions at the basis of peptides activities, both as bioactive compounds and as biocomponents for drug delivery. Her studies take advantage on the use of non-standard amino acids as molecular bricks for the stabilization of peptide conformation and activity.



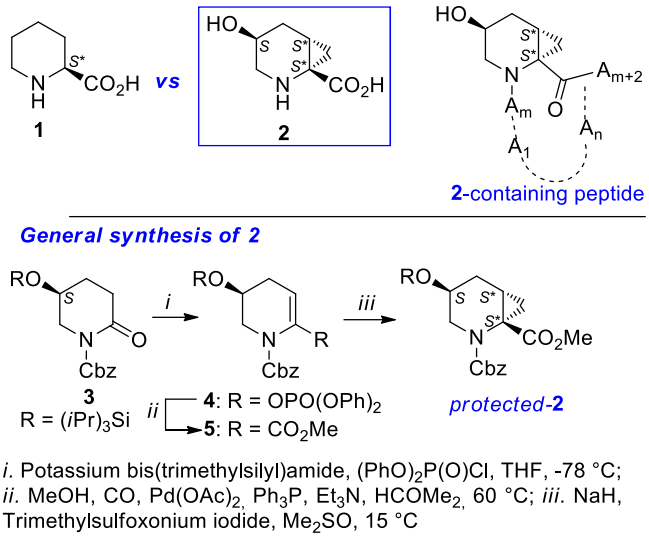
Maria Luisa Gelmi is graduated in Chemistry (1981), obtained her PhD in Organic Chemistry in 1988 and in Pharmaceutical Science in 1990. Currently, she is director of the Department of Pharmaceutical Science, University of Milano. She published more then 130 scientific publications on International Journals dealing with different organic chemistry fields (non proteinogenic amino acids; peptidomimetics synthesis and conformational studies; use of peptidomimetics for biological or nanomaterial applications). She has a long experience in the coordination of research groups and received both international (PI of H2020-MSCA-ITN 2015 EJD-MOGLYNET; member of H2020-MSCA-ITN-2018 EJD-TubInTrain) and national grants.

2. Cyclic AA-based turn mimics

Non coded cyclic AAs are useful intermediates for the synthesis of conformationally constrained peptide analogs able to adopt different type of secondary structural patterns.[11,12] They have been largely studied due to their intrinsic rigid nature and for the network of intramolecular hydrogen bonds that are able of promoting.[13] This section will be focused on cyclic AAs that will be classified among the different AA type, and for each case the induced turn structure will be discussed.

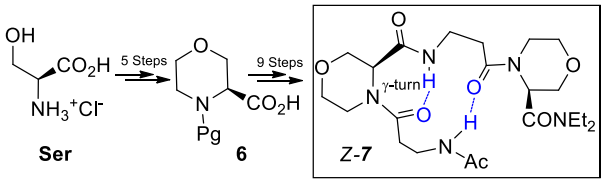
2.1. Alpha AAs

In the wide spreading field of coded-AAs, proline has a peculiar role in biological processes *i.e.* cellular bioenergetics or cell growth. The unique feature of Pro is the *cis-trans* isomerization of peptide bond, when it is inserted into a peptide chain. This peculiarity is at the basis of the protein folding, collagen triple helices formation and many biological processes. [14] Thus, a variety of proline analogues have been developed. Among them, pipecolic acid (**1**, Scheme 1) possesses a predominant role.[15,16] Thus, a number of modifications have been realized on this scaffold to both stabilise specific folding modes and enhance the biological activity of the natural sequences.[17–19] As example, conformational analysis of linear and cyclic peptides incorporating cyclopropane pipecolic acids **2** were reported (Scheme 1).[20]



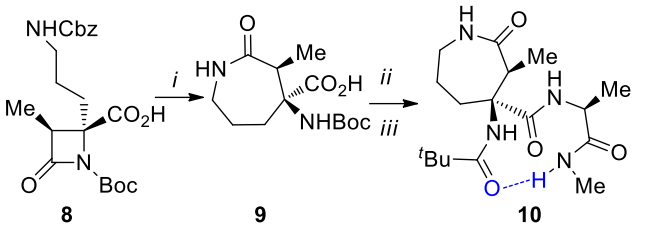
Scheme 1. Synthesis of **2** and its insertion in linear and cyclic peptides.

The general synthesis of **2** involved as the key step a Pd-catalyzed methoxycarbonylation of the optically pure enol phosphate **4** prepared from commercially available protected lactam **3**. Compound **5**, obtained by **4,** was subjected to Corey–Chaykovsky cyclopropanation giving protected **2** as a mixture of diasteroisomers. Incorporation of **2** in peptides follows standard protocols. Conformational analysis of short sequences containing **2** showed a higher rotational barrier around tertiary amide-bond in comparison with those incorporating **1** or proline. In addition, *cis/trans* ratio on **2-**containing peptide depends on the absolute configuration of the Cα atom ($CDCl_3$, NMR). When *S*-**2** was in the *i*+2 position, a type VI β-turn secondary structure was observed.
Another example of Pro-mimic is the α-morpholine-AA **6** (Scheme 2), easily obtained from serine (**Ser**). A γ-turns is present in the related α/β-peptide **7** containing two β-Ala/**6** repeats,[21] characterized by a mixture of *E*- and *Z*- rotamers (NMR analyses; Scheme 2 , only Z-rotamer shown). Furthermore, MM calculations on peptide containing three β-Ala/**6** repeats resulted in a folded structure showing a α-helix stabilized by the presence of γ-turns.



Scheme 2. Morpholine containing peptide **7**.

α,α-Disustituted AAs were also used in the stabilization of turn conformation. In particular, *S,S*-α-quaternary AA with 2-oxoazepane core **9** (Scheme 3) was found to induce a β-turn conformation when incorporated into small peptides.[22] The elegant synthesis proposed by Muniz' research group required, as the key step, the rearrangement of β-lactam **8** to the target AA **9** through a Pd-C catalyzed hydrogenolysis process, which allowed the removal of the *N*-carboxybenzyl (Cbz)-protecting group followed by the in situ intramolecular 7-exotrig cyclization of the free amino function to the carbonyl of the azetidinone ring.



i H_2/Pd-C; *ii* Ala-NHMe, benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate/Et_3N; *iii* *t*BuCOCl

Scheme 3. Synthesis of **9** as β-turn inducer.

The incorporation of **9** into the model dipeptide **10** was accomplished. NMR analysis at variable temperature (both in $CDCl_3$ and DMSO) suggested that NH at *C*-terminus was involved in a H-bond with C=O protecting group at *N*-terminus. These data, in agreement with MM data, indicate the ability of **10** to adopt a β-turn conformation.
β-Turn structures were also found in peptide-analogues of VV-hemorphin-7, modified at position 4 with α,α-disubstituted AAs (**11** and **12**, Figure 2).[23]

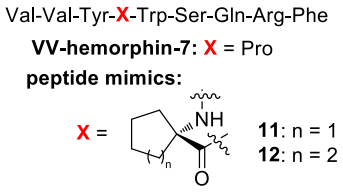


Figure 2. Peptide mimics of VV-hemorphin-7, containing **11** and **12** AAs.

The secondary structure of the synthesized mimetics was determined by IR spectroscopy experiments, suggesting a β-turn conformation due to the proper stretching vibration of the N-H amide bonds. These analogues were tested as potential anticonvulsant agents, showing a drastically decreased activity than VV-hemorphin-7.
Rigid and hindered α,α-disubstituted-AAs can stabilize a γ-turn conformation as reviewed by Crisma et al..[24] As example, homo-dipeptide **14** containing the Adamantane AA **13** folds in a γ-turn (Figure 3), as demonstrated by theoretical analysis, NMR, IR and X-ray data.

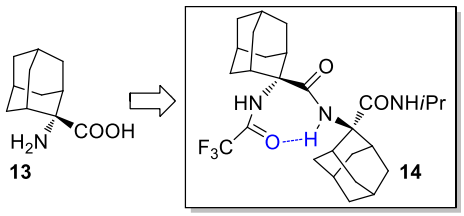
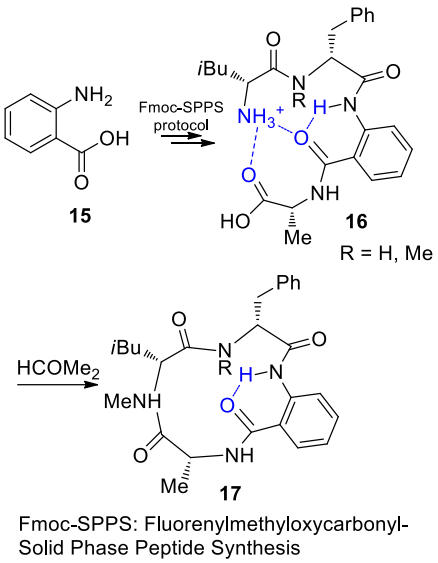


Figure 3. Homo-dipeptide **14** containing **13** AA

2.2. Beta AAs

2-Aminobenzoic acid **15** is a rigid aromatic β-AA that was often employed as turn inducer favouring peptide geometry orientation and their cyclization. In 2017, Sarojini research group found that linear and cyclic tetrapeptides (respectively **16** and **17**; Scheme 4) containing **15** and *L*-AAs, folded in a β-turn conformation.[25]

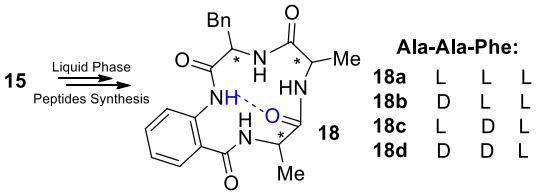


Scheme 4. β-Turn motif induced by **15** in peptide **16** and **17**

X-ray of **16**, in agreement with NMR data, showed a rigid planar β-turn conformation stabilized by three hydrogen bonds. This pre-organized linear framework led an easy cyclization to **17**.

The geometry of cyclic peptides **18** containing compound **15** (Scheme 5) and AAs with *D*- or *L*- stereochemistry was studied by Burgess and coworkers.[26]

NMR analyses indicate that each diastereoisomer exists in one predominant conformation, being the amide protons oriented towards the polar axis, having side-chains in similar orientations to regular and inverse γ-turns and possessing the most common β-turns (types I and II).



Scheme 5. Series of **18** studied by Burgess *et al*.

15 was also recognized essential to generate a pseudo reverse turn motif when linked to a Pro at its carboxylic function (Figure 4) forming a H-bond in the forward direction of the sequence.[27] The reverse β-turn motif was confirmed by NMR and X-ray analyses of a series of tripeptides **19**. The stereochemistry of Pro residue as well as of AAs at *N*-terminus was investigated to reveal possible structural changes of the turn motif. The collected crystallographic data indicated that the conformation of **19** was preserved independently from the tripeptide and stereochemical structural changes.

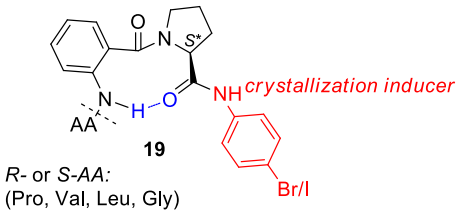
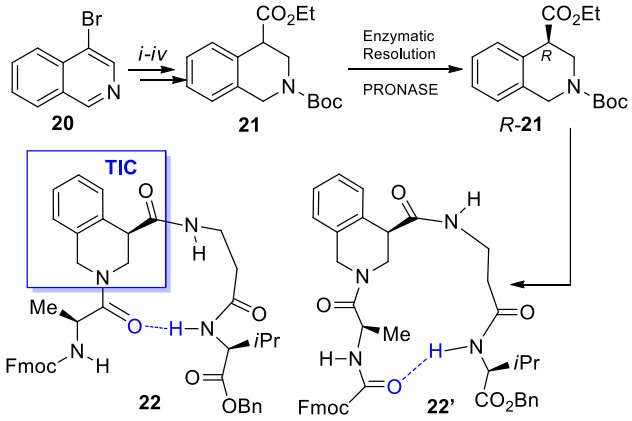


Figure 4. 15 as reverse turn inducer in dipeptide mimics **19** containing Pro

In 2017, Gelmi et al. proposed the synthesis of the constrained enantiopure β[2]-AA **21** (TIC) with a tetrahydroisoquinoline core (Scheme 6) starting from 4-bromoisoquinoline **20**.[28] After a Pd-catalyzed carboxymethylation, reduction of pyridine ring and Boc-protection, compound **21** was obtained. Its enzymatic resolution, using Pronase, gave *R*-**21** (99% *ee*). In the model Fmoc-*L*-Ala-β-TIC-β-Ala-*L*-Val-OBn tetrapeptide **22**, computational and NMR studies demonstrated that the central dipeptide *R*-TIC-β-Ala could act as a flexible turn inducer with formation of two conformers depending on the geometry of tertiary amide bond.



i. CO, Et_3N, $Pd(OAc)_2$, xantphos; *ii*. H_2, PtO_2, AcOH; *iii*. 6N HCl; *iv*. Boc_2O/Et_3N

Scheme 6. Synthesis of non-natural AA **21** as flexible turn inducer.

Periodic γ-turn folding systems were formed in linear peptides based on unnatural-*trans*-β-norborenene amino acid **23**/natural-α-AA (Figure 5).[29]

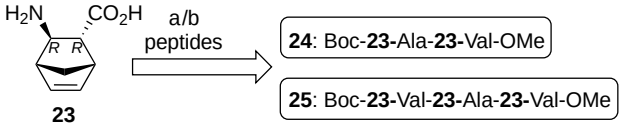
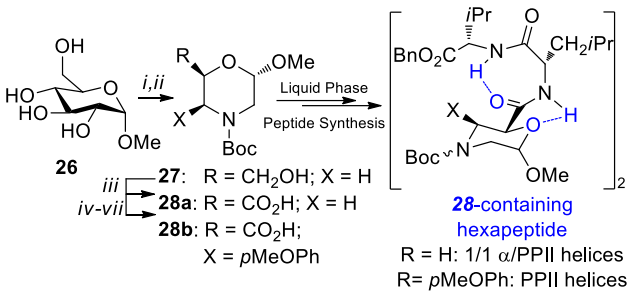


Figure 5. γ-Turn inducer **23** for the preparation of hybrid peptides **24** and **25**

Density functional theory (DFT) calculations, NMR analysis, and Molecular Dynamics (MD) studies indicated that, the α/β hybrid peptides **24** and **25** preferentially adopt periodic 8-membered (inverse-γ-turn)/7-membered (γ-turn) ring hydrogen-bonds. These results did not depend on the nature of the used solvent.

Recently, Bucci et al. reported on the synthesis of two β-AAs with morpholine core, starting from the cheap commercially available α-*D*-glucopyranose **26** (Scheme 7).[30,31] Its oxidation with $NaIO_4$ and the following reductive amination led to the formation of amino alcohol **27**. After the phase-transfer oxidation, AA **28a** was obtained. Finally, a CH-activation allowed the obtainment of the functionalized **28b**, with controlled *cis* relationship between C2 and C3 substituents.



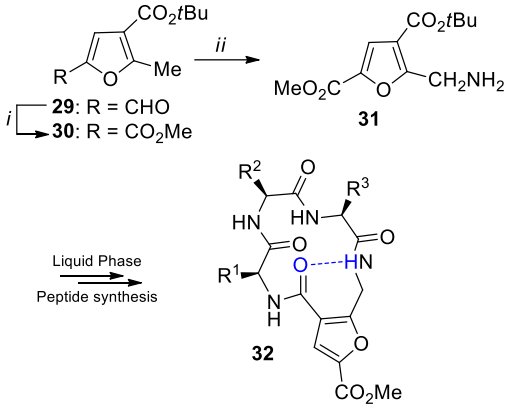
i. 1) $NaIO_4$, MeOH, 2) $BnNH_2$, $NaBH_3CN$; *ii.* H_2, Pd/C, Boc_2O; *iii.* 2,2,6,6-Tetramethylpiperidine 1-oxyl, Bu_4NBr, KBr, NaClO; *iv.* 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 8-Amminoquinoline, 4-Dimethylaminopyridine (DMAP); *v.* Aryl-I, $Pd(OAc)_2$, AgOAc, 110 °C, toluene; *vi.* Boc_2O, DMAP; *vii.* LiOH, H_2O_2, C_4H_8O, H_2O

Scheme 7. Synthesis of **28**-containing hexapeptides

AAs **28a** and **28b** are able to induce a γ-turn when inserted into peptide models (Scheme 7), as proved by bi-dimensional and variable temperature (VT) NMR and computational studies. This conformation was stabilized by the unusual H-bond between the oxygen of morpholine and the NH of the Leucine. This stable turn motif can induce two different helices in hexapeptides (α-helix and PPII-helix). In particular, the insertion of a hindered aryl group at position 3 (*i.e.* **28b**) blocks the rotation on the tertiary amide bond, favouring the *E*-rotamer and thus the polyproline (PPII) helix.

2.3. Gamma AAs

Heterocyclic γ-AAs are able to stabilize α-turn structures, that are quite uncommon, although this structural motif occurred in many biologically active protein sites. Specifically, furan-based γ-AA **31** (Scheme 8) was chosen as tether to organize cyclic tetrapeptides **32** into stable secondary conformations. The synthesis of **31** was accomplished by oxidizing the starting furfural derivative **29** to the correspondent carboxylic acid then transformed into ester **30**. Bromination with N-Bromosuccinimide (NBS) followed and azidation led to the azido derivative then reduced to amine **31**. Its insertion into a tripeptide sequences gave the cyclic peptide **32**.[32]



i. 1) $NaIO_4$, $MeOH/H_2O$, 25 °C, 3 h; 2) $NaClO_2$, NaH_2PO_4, H_2O_2, MeCN, rt, 3 h; 3) CH_2N_2, Et_2O. *ii.* 1) NBS, Azobisisobutyronitrile, CCl_4, 2 h; 2) NaN_3, $HCOMe_2$, 65 °C, 30 min; 3) H_2, Pd/C, AcOEt

Scheme 8. Synthesis of γ-AA **31** and its use in cyclic peptides **32**.

31 brought conformational rigidity in tetrapeptides **32** mimicking an α-turn (type I-αR) through an intra-residual 7-membered hydrogen-bonding. These structures were stable in both aqueous and aprotic solvents, indicating that the secondary geometry depended on the **31** template.

γ-Thiazole based AAs are able to induce pseudo β- or a fused β/α-turn depending on the γ-AA absolute configuration.[33] In particular, a series of sequencies bearing a dipeptide formed from *L*-Phe and *S*- or *R*-γ-thiazoles **33** (Figure 6) were synthesised.

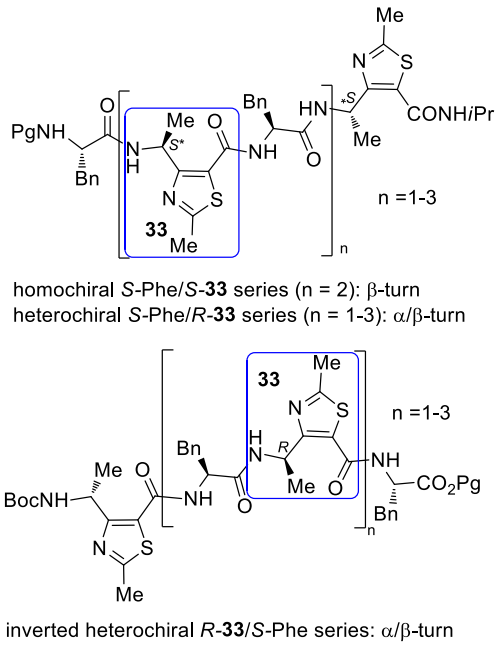
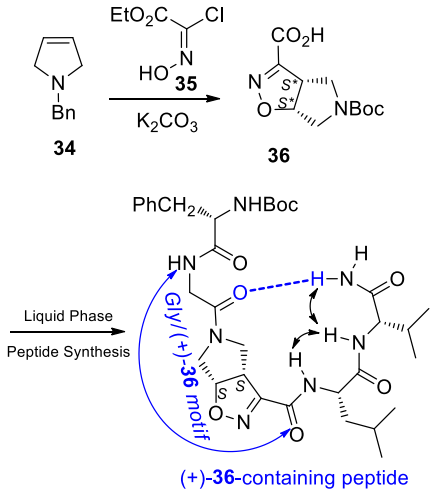


Figure 6. Peptidomimetics containing *S*- or *R*-**33.**

While homochiral *S*-**33**/Phe sequencies adopted pseudo β-turns, the heterochiral homologues *R*-**33**/Phe formed a stable structure, stabilized by C9-12-bifurcated hydrogen bonds in which, *R*-**33** acted as strong turn promoter. The structural behavior and stability of the pseudo β/α-turn induced by *R*-**33** was confirmed for (*R*-**33**/Phe)$_n$ and for (Phe/R-**33**)$_n$ oligomers bearing various number of dipeptide repeats by DFT, X-ray, NMR, CD and FT-IR analysis.

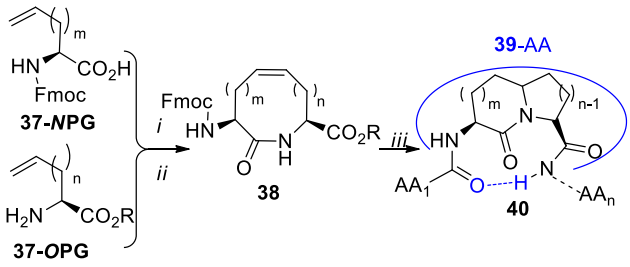
In 2019, Pellegrino et al. described the use of the bicyclic unnatural γ-AA **36** with the pyrrolidine-isoxazoline core, as turn mimic (Scheme 9).[3] This AA was obtained in racemic form by 1,3-dipolar cycloaddition reaction between dipolarophile **34** with nitrile oxide generated *in situ* from chloroxime **35**. The enatiomeric mixture was separated using Chiral Semi-Preparative-HPLC.[34] Each enantiomer was then inserted into model peptides. NMR, FT-IR, CD and molecular modeling studies indicated that the dipeptide Gly/(+)-**36** is able to stabilize a α-turn conformation, due to H-bond between C=O$_{Gly}$ (*i*) and NH of amide protecting group (*i+4)*.



Scheme 9. Synthesis of (+)-**36** and its insertion in model peptides.

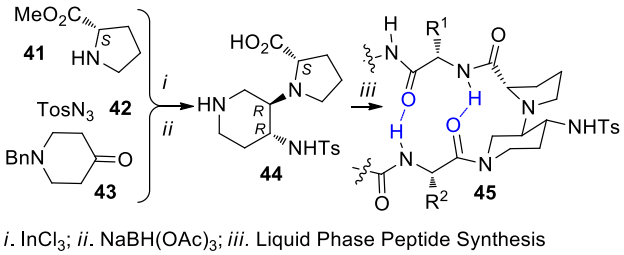
2.4. Delta AAs

Azabicycloalkan-2-one AAs of general formula **39** are a family of dipeptide mimics that can be classified as δ-AAs. Lubell and coworkers developed a selective transannular amidation synthesis of azabicyclo-alkanone scaffold **39** (Scheme 10), starting from unsaturated lactams **38**. The latter was easily obtained by coupling of orthogonally protected allyl-AAs of general formula **37** followed by ring closing metathesis. Iodoacetoxylation in THF of **38** to azacyclo-alkanone scaffold **39** was then performed then used for the preparation of peptidomimetics **40**.[35]



Scheme 10. Peptides **40** containing azabicycloalkan-2-one scaffold **39.**

The combination of NMR spectroscopy and X-ray crystallography showed that peptides **40** could serve as β-turn type mimics.
In 2014, Pellegrino et al. synthesized the δ-AA **44**, as a Gly-Pro analogue (Scheme 11), able to mimic a β-turn.[36] **44** was prepared in one step by a multicomponent reaction and by controlling the stereochemistry of the new strereocenters, starting from the cheap commercially available **41**, tosyl azide **42** and *N*-benzylpiperidone **43**. The optimized multicomponent process consisted in a cascade click cycloaddition and a ring rearrangement reaction, followed by a reductive step.



Scheme 11. Synthesis of **44** and its use for the preparation of antiparallel β-hairpin.

X-Ray and molecular modelling showed that **44** assumed a β-turn-like geometry. To confirm this hypothesis, **44** was inserted into a model peptide, proving that it behaved as Gly-Pro-loop, stabilizing the β-hairpin **45** (Scheme 11). This δ-AA was then used to design small flexible peptidomimetics as inhibitors of β-amyloid-protein aggregation. The obtained compounds were found able to adopt the different hairpin conformations and to adapt to different monomer/oligomer species of β-amyloid, preventing the formation of toxic oligomers while impacting the fibrils formation.[37] Compound **44** was also used as a template for the development of peptide-based catalysts in Henry reactions[38] and asymmetric transfer hydrogenations.[39]
Among δ-AAs, Geyer's research group reported on the synthesis of the bicyclic core-non coded AA **46**, used as β-turn mimic (Figure 7).[40] In particular, they synthesized different peptidomimetics mimicking Foldon β-hairpin protein by using **46** instead of Asp-Gly loop that does not stabilize in a proper way the natural β-hairpin, essential for Foldon protein function. Surprisingly, despite the short sequences and its rigidity, **46** structurally influenced even the long-range part of the molecule, as demonstrated by the dispersion of all the amide signals (^{1}H NMR). After two-dimensional and VT-NMR, it was observed the structural behavior of **46** corresponds a βII turn, compatible with the right-handed hairpin twist.

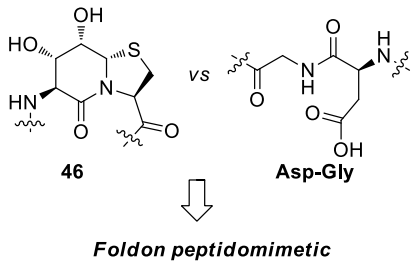


Figure 7. The use of **46** in the synthesis of Foldon mimics.

3. Carbocyclic and heterocyclic scaffold based turn mimics

In this paragraph, cyclic scaffolds able to mimic turns will be reviewed, divided by ring size.

3.1. 3 and 4-Membered rings

Cyclopropane is particularly useful in the development of peptidomimetics, as it can fix its substituents into the *trans*- or *cis*-configuration, due its constrain.[41] This behavior is called 'cyclopropylic strain'.[42]
In 2013, Mizuno et al. reported on the stereoselective synthesis of cyclopropane based tetrapeptide mimics **47-50** (Figure 8), able to stabilize conformations covering β-turn through β -strand, depending on the chirality of the mimic.[43]

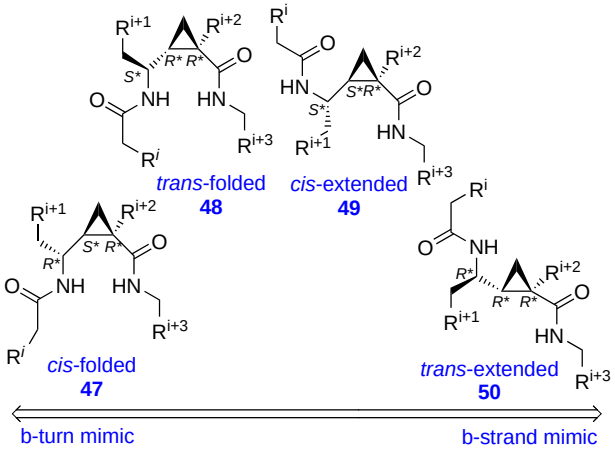
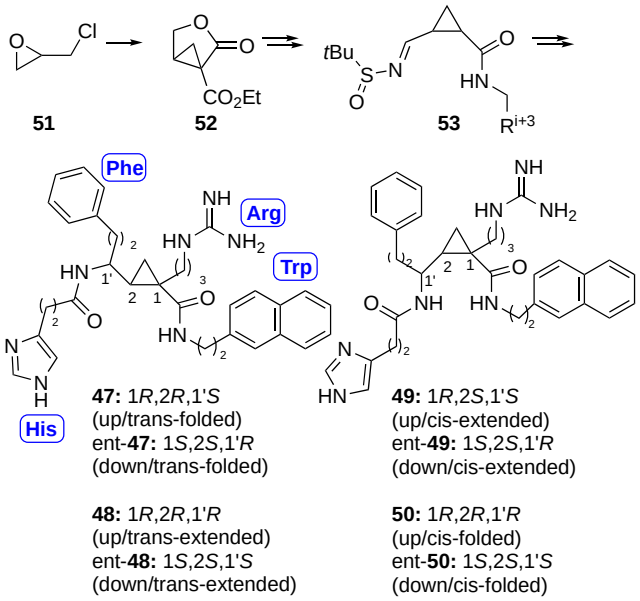


Figure 8. Peptide mimics **47**-**50**

The synthesis of compounds **47-50** is particularly straightforward allowing to build directly the desired tetrapeptide mimics in a few steps. The starting reagent was *R*- or *S*-epichlorohydrin **51** (Scheme 12). R^{i+3} and R^{i+1} containing moieties were regioselectivively inserted starting from ester **52** (or ent-**52**) and the corresponding imine **53**, respectively. In particular, the asymmetric center C1' in the chain was built by a diastereoselective Grignard addition of the R^{i+1} containing moiety to the *R*- or *S*-*N*-tert-butanesulfinyl imine **53**. Eventually, the amino group on the Grignard product was coupled with the R^{i} containing moiety to afford the target peptidomimetics **47**-**50** (Scheme 12).

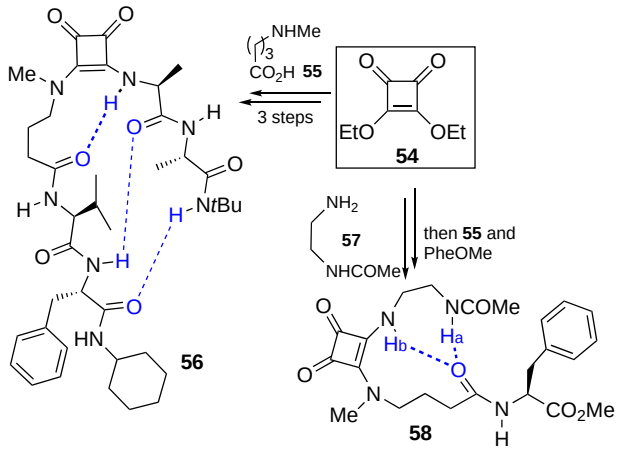


Scheme 12. Synthesis of peptide mimics **47**-**50**.

Compounds **47-50** were used in the development of melanocortin receptor ligands, by insertion of the side chains of His, Phe, Arg and naphtyl moiety, as bioisoster of Trp in the core structure.[44] In particular, submicromolar binding values and their resistance in proteolytic environment made ent-**47** and ent-**48** the best candidates.

Squaramides are 4-member ring able to recognize charged moieties and,[45] thanks to their hydrogen-bonding capability, are able to stabilize the secondary structure of peptidomimetics. In 2018, Rotger et al. investigated the role of the squaramido ring in the stabilization of β-turns for the synthesis of parallel and antiparallel β-hairpins.[46]

Two examples of this class are reported, *i. e.* compounds **56** and **58**. Their synthesis is straightforward, based on the sequential condensations of diethyl squarate **54** with different amino compounds (**55** and **57** in Scheme 13) and AAs condensation.



Scheme 13. Synthesis of **56** and **58** with Squaramide moiety inserted into peptide chain

Conformational features of compounds **56** and **58** were studied in solution. Compound **58** induce the formation of both β- and α-turns, making the folding of the chain very tight. By VT-and NOEsy NMR experiments, it was demonstrated that NH_α and NH_β are involved in stable H-bonds. In compound **56**, the squaramido-based scaffold **54** was inserted into a longer sequence. It was found that, in solution, it exists as an equilibrium between different conformers. Among them, the antiparallel β-hairpin is the most stable one.

3.2. 5 and 6-Membered rings

Lactam building blocks, as Pro analogues, have found application as β-turn inducers. As regard, peptidomimetics **60** with the core sequence of insect kinins (peptide **59**) was studied by Nachman et al. replacing Phe^2-Pro^3 dipeptide block with a 4-aminopyroglutamate linkage (Figure 9).[47] Even though 4-aminopyroglutamate was able to retain a type VI β-turn motif *via* cis-amide bond, the modified analogue showed less potency than the original sequence.

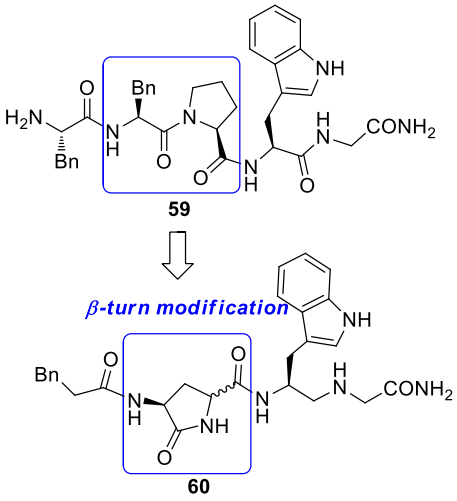
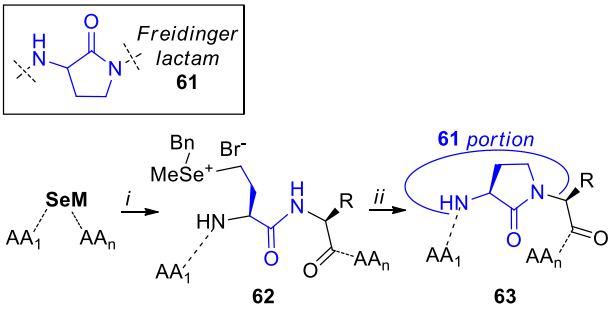


Figure 9. Peptidomimetics **59** and **60** studied by Nachman *et al*.

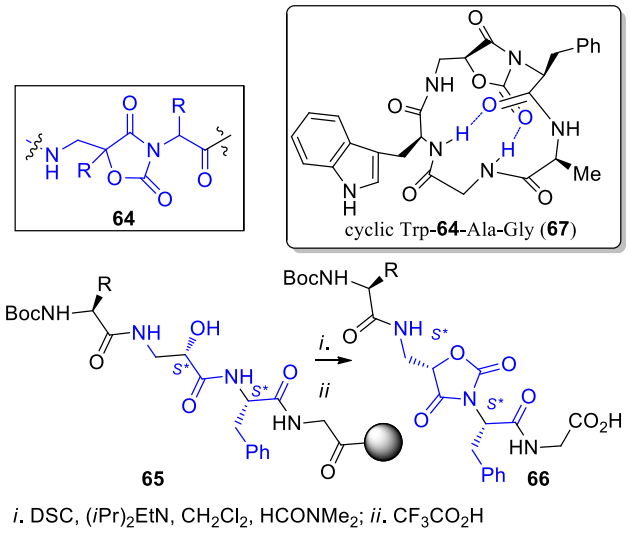
"Freidinger lactam" **61** (Scheme 14) is another widly used scaffold able to force a *trans* peptide bond-conformation inducing γ- or β-turn.[48,49] In its structure we can recognize *i* side-chain cyclized onto the *i+1* nitrogen (Scheme 14).
Dawson and coworkers performed a chemoselective synthesis of peptide **63** containing **61** scaffold that was directly built on the peptide chain **62** containing selenomethionine as key element for the ring synthesis. After the preparation of peptide sequence, a selective Se-alkylation was performed giving peptide **62.** A base-induced cyclization followed affording peptide **63** containing lactame ring.[50]



Scheme 14. Synthesis of **63**.

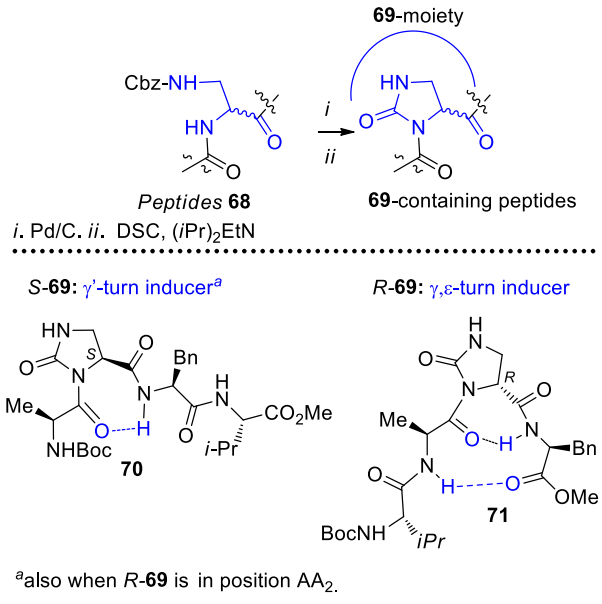
Following this straightforward method, the β-turn inducer was introduced at position 12 of the WW domain of protein Pin 1, a protein model widely studied to evaluate mimics of type II' β-turn systems. CD spectra and thermal denaturation curves implied that **63** did not perturb the protein structure.
In 2016, Gentilucci's research group reported on the synthesis of the turn mimic **64**, which combines a β/α-hybrid dipeptide structure and a Freidinger lactam-like heterocycle (Scheme 15).[49] This scaffold was built directly from the peptide chain, promotes a stable turn conformation, allowing the easy cyclization of the peptidomimetic **66** into the cyclic **67**.
Peptide **66** was obtained, in solution or in solid phase, from peptide **65**. A direct cyclization, mediated by disuccinimidyldicarbonate (DSC) as CO donor, of hydroxy group of isoserine (iSer) on the following AA, gave **64** moiety, already embedded in an oligopeptide sequence (Scheme 15).

A library of cyclic tetra- and pentapeptides were synthesized and characterized by NMR and restrained MD simulations. It was found that the linear peptides containing homochiral scaffolds give cyclic peptides. Tetrapeptides are stabilized by a γ-turn, while pentapeptides by a β- and pseudo β-turn. As an example, compound **67,** *i.e.* cyclic Trp-**64**-Ala-Gly (Scheme 15), showed a stable classical β-turn stabilized by a H-bond between $C{=}O_{Phe}$ and NH_{Trp}. A second β-turn was found, forming a pseudo 10-member ring, by the H-bond between $C{=}O_{64}$ and NH_{Gly}.



Scheme 15. Synthesis of linear **66** and cyclic **67** peptides containing **64** moiety

The same group adopted the above synthetic strategy to build flat structure and trans-restricted geometries in tetrapeptides containing cyclic urea Pro-mimics (scaffold **69**, Scheme 16).[51] Sequences containing **69** scaffolds were reached by easy cyclization of the related linear sequences **68** containing a α,β-diamino propionic acid residue. Peptides bearing both enantiomers of scaffold **69** in their 2- or 3- position were realized (**70** and **71** in Scheme16).



Scheme 16. Peptidomimetics **70** and **71**, containing scaffold **69.**

X-ray analysis indicated a planar disposition of the imidazolidine ring and a *trans*-disposition of the tertiary amide-bond, which resulted to be planar whit the heterocycle. NMR experiments and MD calculations showed that the peptides-like **70,** independently form on the *R* or *S*-stereochemistry of **69**-moiety, adopted a stable reverse γ-turn conformation while **71,** with *R*-**69** in position 3, promoted the additional formation of an atypical ε-turn *via* the formation of a 11-membered ring.
Inspired by the ability of *trans*-pyrrolidine-3,4-dicarboxamide to mimic β-turns developed by Boger's research group,[52] Bellucci et al. evaluated the possibility to introduce some structural complexity to the pyrrolidine scaffold, to improve the stability of the β-turn, increasing in this way the 'druggability' of the mimic.[53] Boger's turn mimic vs Bellucci's peptidomimetics **72** are depicted in Figure 10.

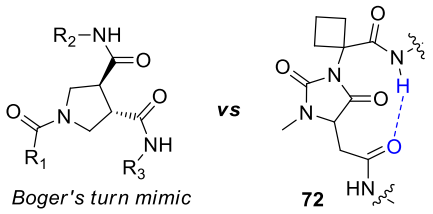
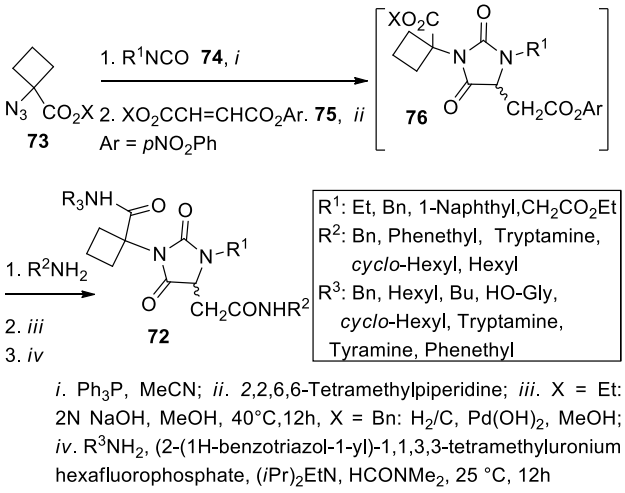


Figure 10. Boger's turn mimic *vs* **72**

The authors synthesized a library of peptides **72**, using a regioselective sequential multicomponent domino process. First, α-azido-cyclo-butyl carboxylic esters **73** and isocyanates **74** were made to react in the presence of Ph_3P affording carbodiimide intermediates that, treated with fumaric acid monoesters **75** produced the 3-cyclo-butylcarbamoyl hydantoin scaffolds **76**. Taking advantage of the different activated carboxylic functions, regioselective amidations were performed using different amines allowing the production of a library of compounds **72** (Scheme 17).



Scheme 17. Synthesis of library of **72**.

Both DFT calculations and X-ray analyses showed a preference for β-turn conformation for all compounds, regardless the nature of the attached residues.
An interesting strategy to stabilize a peptide secondary structure is the substitution of a residue with an aza-AA (*i.e.* an AA with a nitrogen instead of the Cα). Being formed by a semicarbazide scaffold, the aza-AA is able to reinforce β-turn conformations through the combination of lone pair-lone pair repulsion of the adjacent hydrazine nitrogen and urea planarity. During the last decade, different aza-peptides were built and studied for different application such as receptor ligands, enzyme inhibitors, prodrugs, probes, and imaging agents.[54]
Substituted triazole-scaffolds promote specific secondary motifs acting also as *trans*-amidate mimetic. Moreover, triazole unit presents metabolic inertness and tendency to associate with biological targets.[55] In general, this class of compounds was prepared through Cu- or Ru- catalysed click reactions leading to the selective formation of 1,4- or 1,5- substituted triazole, respectively. In particular, the secondary structures inducted by these heterocyclic scaffolds seem to be strictly related to the substitution position.[56] Sewald et al. reported on the synthesis of new class of peptidomimetics containing 1,5-disubstituted-triazole (Figure 11). Having a planar structure,

a strong dipole moment and capability of accepting H-bonds, they behaved as amide bonds.[57] Starting from enantiomerically pure propargylamines and α-azido acids, homo- or heterochiral peptidotriazolamers **77** and **78** were obtained by click reaction between the two reagents followed by the use of classical peptide coupling/deprotection protocols. NMR and MD simulations in Me_2SO or water suggested the formation of a βV_al-turn motif for **77** in which the backbone of the molecule was folded towards the central side of the turn, whereas the side chains were protruding towards the solvent. On the other hands, **78** has similar parameters to polyproline helices.

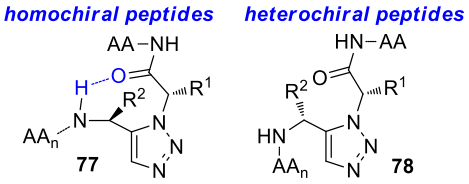
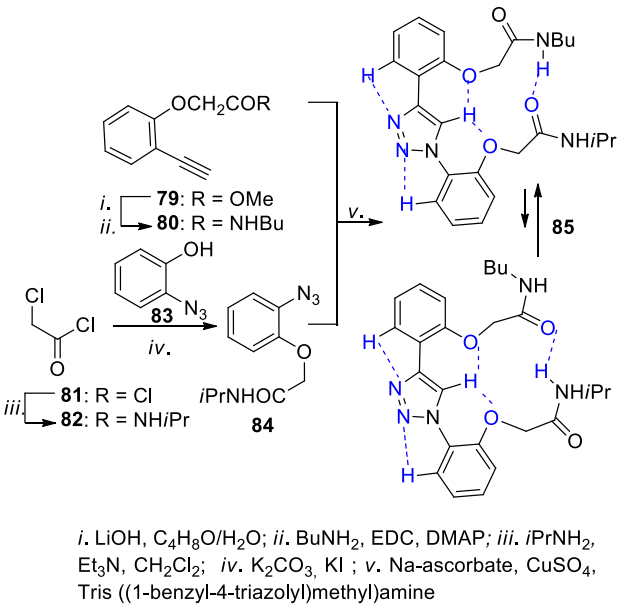


Figure 11. General formula of **77** and **78**.

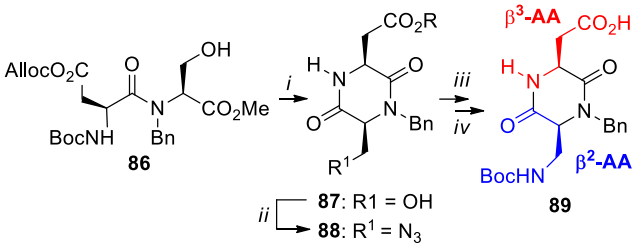
In 2012, Wu et al. published the design of 1,4-diphenyl-1,2,3-triazoles incorporated the amide moiety able to promote the formation of β-hairpin thanks to their stable U-shaped conformation, when inserted into a model peptide.[58] As example, the synthesis and conformational behavior of compound **85** are reported in Scheme 18.
85 was prepared starting from alkyne **79** then converted in **80** into two steps. The azido moiety was prepared by the treatment of chloroacetyl chloride (**81**) with *i*PrNH$_2$ affording compound **82** then reacted with **83**, giving **84**. The key step for the syntheses of **85** is the click reaction between **80** and **84**, for the formation of the triazole core.



i. LiOH, C_4H_8O/H_2O; *ii*. $BuNH_2$, EDC, DMAP; *iii*. *i*PrNH$_2$, Et_3N, CH_2Cl_2; *iv*. K_2CO_3, KI ; *v*. Na-ascorbate, $CuSO_4$, Tris ((1-benzyl-4-triazolyl)methyl)amine

Scheme 18. Synthesis of peptide **85**

VT-NMR and NOESY experiments proved that two conformer are present in solution, both having a β-turn conformation, stabilized by a different H-bond network (Scheme 18).
Diketopiperazine (DKP) scaffold of general formula **89** (Scheme 19) was developed and widely used as β-turn inducer by Gennari's and Piarulli's research groups. DKP-core could be viewed as a combination between a β^3-AA and a β^2-AA. Its synthesis starts from dipeptide **86**, obtained by condensation of *N*-Boc-2*S*-Asp-β-allyl and *S*-*N*-benzylserine methyl ester. After its *N*-terminus deprotection, followed by cyclization, DKP core **87** was obtained. The hydroxy group was transformed into azido one under Mitsounobu conditions giving compound **88**. Finally, Staudinger reaction and allyl-ester hydrolysis led to **89**.



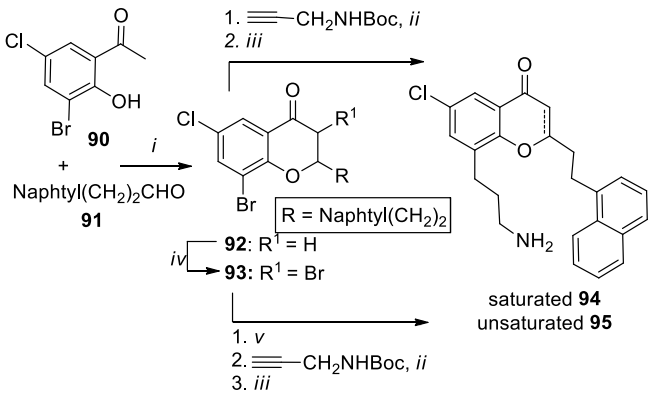
i. 1) CF_3CO_2H, CH_2Cl_2, 2) $NaHCO_3$; *ii*. HN_3, Toluene, -20 °C, PPh_3, Diisopropyl azodicarboxylate; *iii*. Me_3P, Toluene, 2-(Boc-oxyimino)-2-phenylacetonitrile, -20 °C; *iv*. C_4H_9N, $Pd(PPh_3)_4$, 0°C

Scheme 19. Synthesis of **89.**

The scaffold **89** was inserted into a peptide chain to prove, by MD calculation, NMR and CD analyses, its ability as β-turn inducer.[59] The same research groups reported on the synthesis of a DKP library for the preparation of cyclic RGD[60] and iso-DGR[61] peptidomimetics as Integrin Ligands.

3.3. Bicyclic compounds

The chromone-based somatostatin compounds **94** and **95** represent bicyclic heterocycles with remarkable β-turn behavior (Scheme 20). In 2017, Saxin et al. synthesized somatostatin mimics based on chroman-4-one ring system.[62] In its bioactive conformation, the hormone somatostatin adopts a β-turn conformation where the loop is formed by the tetrapeptide Phe7-Trp8-Lys9-Thr10 (numbering refered to somatostatin sequence).[63] 2-Alkyl-chroman-4-one scaffold **92** was built starting from acetophenone derivative **90** and 3-(naphth-1-yl)propanal **91** using a base catalyzed aldol reaction. Compound **94** was obtained from **92** through a Sonogashira cross-coupling, reduction of the alkyne moiety followed by deprotection of nitrogen. The unsaturated compound **95** was prepared in an analogue way but starting from **93**, the brominated compound at C-3 obtained from **92**, then dehydrohalogenated.

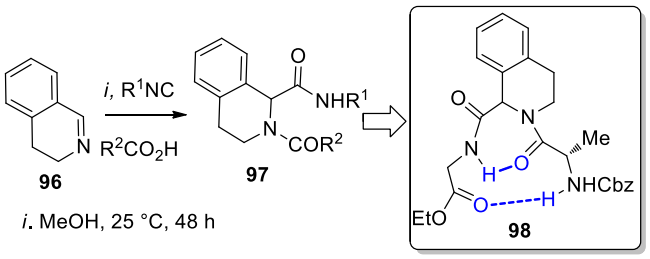


i. iPr_2-NH, 170°C, MW; *ii*. $PdCl_2(PPh_3)_2$; *iii* 1) H_2, Pd/C, 2) HCl
iv. $CuBr_2$, $CHCl_3$, reflux; *v*. $CaCO_3$, $HCONMe_2$, 100°.

Scheme 20. Synthesis of **94** and **95.**

The final compounds **94** and **95** were tested together with sst28 (a natural agonist) for their affinity for the sst2 and sst4 receptor and showed similar affinity at both receptors.

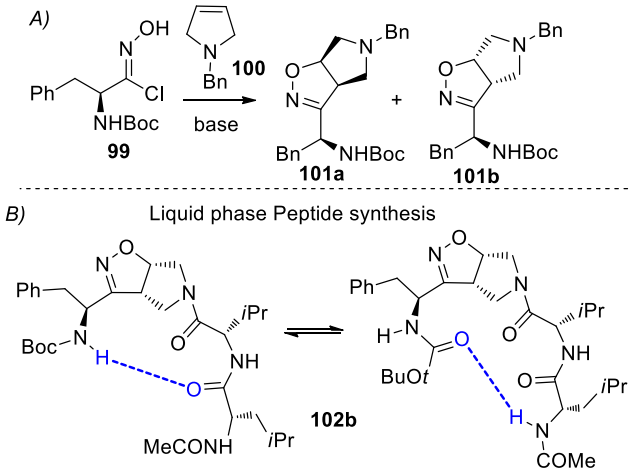
A very straightforward method based on a three-component Ugi reaction (*i.e.* reaction of 3,4-dihydroisoquinoline **96**, isonitriles and carboxylic acids) was published by Rossetti et al. for the preparation of a library of reverse-turn scaffold containing tetrahydroisoquinoline core of general formula **97** (Scheme 21).[64]



Scheme 21. Synthesis of **97**. On the box, an example of the turn mimic **98**

Computational and NMR analyses on the synthesized compounds revealed their tendency to adopt a revers turn with the possibility to stabilize parallel β-hairpin. An example of the turn mimic **98** is shown in Scheme 21.

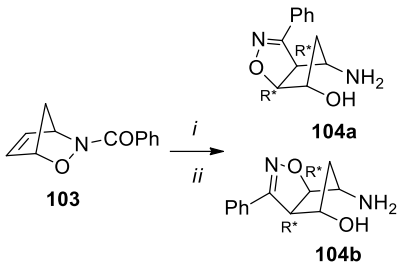
Bucci et al. synthesized a Δ^2-isoxazoline scaffold, fused with a pyrrolidine ring, of general formula **101**, able to stabilize a parallel β-hairpin.[65] Compound **101** was synthesized using a diasteroselective [1,3]-cycloaddition reaction between chloroxime **99** and pyrroline derivative **100** (*A)* in Scheme 22), whose stereochemical outcome is strictly dependent on the base. Computational studies confirmed that π-interactions between the phenyl substituents of the two reagents favor the formation of the 3a*R*,6a*S*-isomer **101b**.



Scheme 22. *A*) Synthesis of the two diasteroisomes **101a** and **101b**; *B*) H-bond network in **102b**

Peptidomimetics containing **101a** or **101b** isomers were prepared by coupling with *N*-Ac-Leu-Val-OH dipeptide. Only scaffold **101b** (NMR studies) was found to stabilize the conformation of model peptide **102b**, that is present in solution as a mixture of two stable parallel β-hairpins, stabilized by two different H-bonds (*B)* in Scheme 22). Scaffold **101b** is indeed characterized by a proper calix conformation directing the two peptide arms, toward a parallel β-hairpin. Moreover, the presence of oxygen and nitrogen atoms in the oxazoline ring, as well as the aromatic part allow intermolecular H-bonds and π-interactions, useful for targeting Protein-Protein interactions.

In 2015, Quadrelli's research group reported on the synthesis of constrained regioisomeric racemic aminols **104a** and **104b**, obtained from oxazanorbornene scaffold, able to induce β-turns when inserted into a pseudo-peptide chain.[66] As depicted in Scheme 23, two different regioisomers were prepared from the highly reactive dipolarophile **103** *via* cycloaddition reaction with a nitrileoxide, followed by amide hydrolysis and *N-O* bond reduction. **104a** and **104b** were functionalized with *N*-Boc-Ala-OH, while the hydroxyl function was derivatized as ester of a desymmetrized malonic acid.



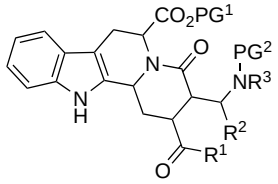
i. NaOH/MeOH, rt; *ii.* H_2, Pd/C, AcOEt, 25 °C, 10 min

Scheme 23. Synthesis of **104a** and **104b**

MD Calculation, NMR titration and VT-NMR demonstrated a β-turn arrangement for all the synthetized compounds. The driving force that makes possible the formation of this motif was found to be the envelope conformation of cyclopentane core fused with the isoxazoline ring. Indeed, cyclopentane adopts a boat-like conformation favouring the turn formation.

3.4. Policyclic scaffolds

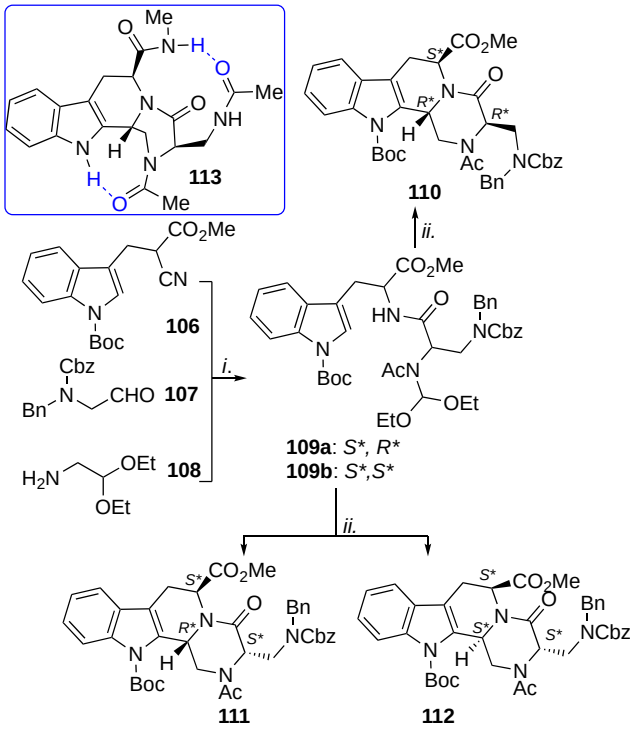
Policyclic compounds containing the indole ring are particularly exploited due to their structural similarity to the tryptophane residue. In 2012, Lesma et al. reported on a Ugi 4-CR/Pictet–Spengler reaction sequence to obtain 1,2,3,4-tetrahydro-β-carboline (THBC)-class peptidomimetics of general formula **105** (Figure 12).[67] The potential of the obtained scaffolds is the possibility of further derivatization with the desired pharmacophoric groups, both on *C*- and *N*-termini for the development of conformationally constrained tryptophan-side chain containing peptidomimetics.



105a: R^1, R^2 = H, Alk; R^3 = H
105b: R^1, R^2 = H, Alk; R^3 = AA side chain

Figure 12. Library of **105.**

The synthesis of tetracyclic **110-112** is shown in Scheme 24. These compounds came from *N*-protected tryptophan derived isocyanide **106**, *N*-protected-2-aminoacetaldehyde **107**, as the carbonyl component, and aminoacetaldehyde diethylacetal **108**, as an amine donor. Diastereoisomers **109a** and **109b** were obtained and separated by chromatography column. The treatment of **109a** with AcOH led only diasteroisomer **110**, while the treatment of **109b** with the same acid gave the diasteroisomers **111** and **112.**



Scheme 24. Synthesis of **105**-like compounds and revers turn stabilized in **113**

To mimic the behavior of additional aminoacidic residues, the *C*- and *N*-termini of these tetracyclic scaffolds were protected respectively as carboxamide and acetyl moieties. After NMR and computational analyses, it was found that the conformational constrained compound **110** is able to mimic a turn conformation (see **113**, Scheme 24).
In 2016, Knuhtsen et al. reported the synthesis of peptidomimetics of general formula **114** (Figure 13) acting as inhibitors of Protein Arginine Methyl Transferases (PRMT).[68] They belong to a family of enzymes that modulate the epigenetic code through modifications of histones.[69] The importance of the tryptophan residue within the inhibitors of PRMT is well documented. Thus, a non-aminoacidic scaffold **114** containing the tryptophan side chain-like core was inserted into a proper peptide sequence.

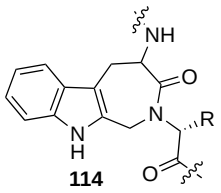
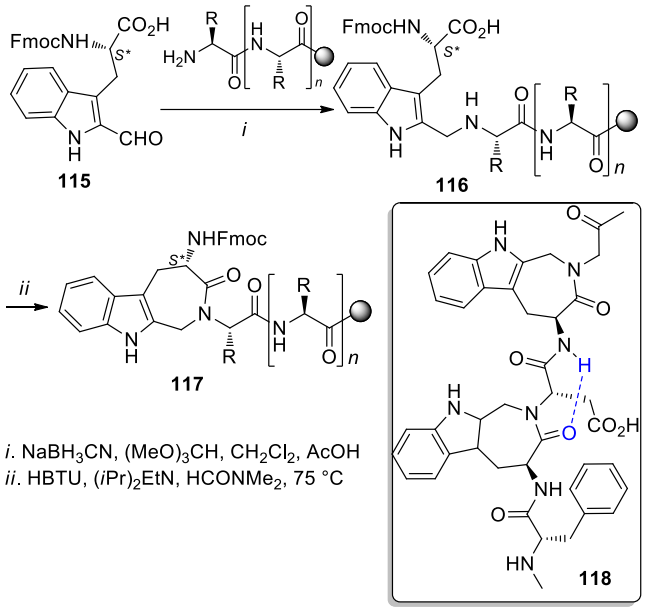


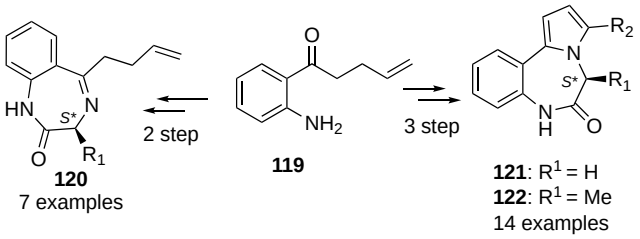
Figure 13. General formula of Knuhtsen's scaffold **114**.

The tricyclic-core **114** in peptide **117** was directly built from **116**, obtained by a reductive amination between the peptide chain linked on a solid support and tryptophan derivative **115**, thanks to an intermolecular cyclization of the free carboxylic acid and the secondary amine (Scheme 25).



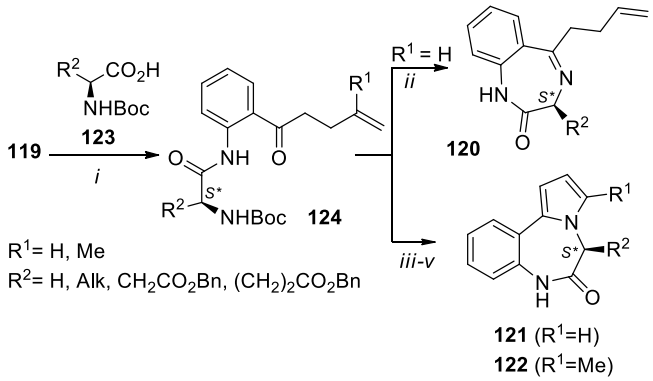
Scheme 25. Synthesis of **118**, an inhibitor of PMRTs

By this way, an analogue of the SHSEFWDWGPGGG PMRTs inhibitor was synthesized by replacing W with the tricyclic scaffold. It was observed that **118** has an increased potency in comparison to the native counterpart. The authors claimed that this behaviour is due to the different conformation of the peptidomimetic, containing a very stable γ-turn, as confirmed by NMR.
Dihydro-benzodiazepinones and pyrrolobenzodiazepinones were also studied in the development of turn mimics. X-Ray and molecular dynamics of different diazepin-2-ones showed indeed dihedral angle values similar to a γ-turn conformation.
In this respect, in 2015 Dorr et al.[70] investigated about diazepin-2-ones conformational behavior producing a library of compounds of general formula **120**-**122** synthesized from a common ketone intermediate **119** (Scheme 26).



Scheme 26. Synthesis of **120-122** from the common intermediate **119**

The synthetic strategy to prepare this library is shown in Scheme 27. Electron-poor aniline **119** was left to react with different α-AAs **123** to afford compounds **124** with small percentage of the racemized product. Benzodiazepinones **120** were synthesized from compounds **124** through Boc protecting group removal, followed by imine formation. Pyrrolo[1,2-d][1,4]benzodiazepinones **121** and **122** were obtained from olefins **124** as starting materials. Their transformation into the corresponding di-carbonyl compounds through oxidation of double bond was first performed, followed by intramolecular reaction of deprotected amino group with the two carbonyl moieties giving pyrrole ring.



i. N,N'-Dicyclohexylcarbodiimide, HOBt, DMAP, 0 °C; *ii*. MW in H_2O;
iii. OsO_4, $NaIO_4$; *iv*. CF_3CO_2H, CH_2Cl_2; *v*. *p*-$MePhSO_3H$

Scheme 27. *a*.) Synthesis of **119**-**122** scaffolds; *b*.) Structures of **121g** as an example of the synthesized library.

From X-Ray analyses it was observed that the ϕ and ψ dihedral angles of the of *S*-**121** [R^2= $(CH_2)_2CO_2Bn$], *S*-**122** and *R*-**120** [R^2= CH_2CO_2Bn] and of those of their enantiomers corresponded to the classical and to the inverse γ-turn, respectively. It has to be pointed out that the obtainment of the two γ-turn type can be interesting for the evaluation of the differences in receptor affinity and activity with respect to of related diazepinone ligands.

4. Conclusion

In the last decade, a huge variety of amino acids and scaffolds have been developed aiming to induce or stabilize different turn types. This field is continuously growing, leading to the obtainment of different peptidomimetics structures particularly useful in drug discovery.[71] There is an undoubted interest in the development of novel drugs derived from bioactive peptides or protein fragments. Peptidomimetics containing stable turn structures are indeed powerful tools encompassing some of the disadvantages in the use of peptides themselves. However, the burgeoning growth of peptide-based nanomaterials could be the next important application of peptidomimetics.[72,73] The possibility to fish in the already available toolbox of turn mimics could thus open new frontiers and perspectives in the development of bio-inspired compounds with smart applications.

Keywords: Peptidomimetics • Non-natural amino acids • Heterocycles • Carbocycles • Secondary Structure Mimics

[1] R. Bucci, A. Contini, F. Clerici, E. M. Beccalli, F. Formaggio, I. Maffucci, S. Pellegrino, M. L. Gelmi, *Front. Chem.* **2019**, *7*, 1–11.

[2] R. Bucci, P. Das, F. Iannuzzi, M. Feligioni, R. Gandolfi, M. L. Gelmi, M. Reches, S. Pellegrino, *Org. Biomol. Chem.* **2017**, 6773–6779.

[3] F. Oliva, R. Bucci, L. Tamborini, S. Pieraccini, A. Pinto, S. Pellegrino, *Front. Chem.* **2019**, *7*, 1–10.

[4] A. Contini, N. Ferri, R. Bucci, M. G. Lupo, E. Erba, M. L. Gelmi, S. Pellegrino, *Pept. Sci.* **2018**, *110*, e23089.

[5] J. Liu, J. Han, K. Izawa, T. Sato, S. White, N. A. Meanwell, V. A. Soloshonok, *Eur. J. Med. Chem.* **2020**, *208*, 112736.

[6] M. Pelay-Gimeno, A. Glas, O. Koch, T. N. Grossmann, *Angew. Chemie - Int. Ed.* **2015**, *54*, 8896–8927.

[7] A. M. C. Marcelino, L. M. Gierasch, *Biopolymers* **2008**, *89*, 380–391.

[8] R. V. Nair, S. B. Baravkar, T. S. Ingole, G. J. Sanjayan, *Chem. Commun.* **2014**, *50*, 13874–13884.

[9] J. M. Langenhan, I. A. Guzei, S. H. Gellman, *Angew. Chem. Int. Ed. Engl.* **2003**, *115*, 2504–2507.

[10] S. Kumari, A. V Carmona, A. K. Tiwari, P. C. Trippier, *J. Med. Chem.* **2020**, *63*, 12290–12358.

[11] F. Fülöp, T. A. Martinek, G. K. Tóth, *Chem. Soc. Rev.* **2006**, *35*, 323–334.

[12] I. V Komarov, A. O. Grigorenko, A. V Turov, V. P. Khilya, *Russ. Chem. Rev.* **2004**, *73*, 785–810.

[13] G. V. M. Sharma, T. Sridhar, P. P. Reddy, A. C. Kunwar, *European J. Org. Chem.* **2013**, 3543–3554.

[14] W. J. Wedemeyer, E. Welker, H. A. Scheraga, *Biochemistry* **2002**, *41*, 14637–14644.

[15] C. Kadouri-Puchot, S. Comesse, *Amino Acids* **2005**, *29*, 101–130.

[16] B. J. V Verkuijl, J. G. de Vries, B. L. Feringa, *Chirality* **2011**, *23*, 34–43.

[17] L. Sernissi, M. Petrovič, D. Scarpi, A. Guarna, A. Trabocchi, F. Bianchini, E. G. Occhiato, *Chem. - A Eur. J.* **2014**, *20*, 11187–11203.

[18] F. Dordoni, D. Scarpi, F. Bianchini, A. Contini, E. G. Occhiato, *European J. Org. Chem.* **2020**, *2020*, 4371–4383.

[19] E. G. Occhiato, A. Casini, A. Guarna, D. Scarpi, *European J. Org. Chem.* **2011**, 6544–6552.

[20] L. Ricci, L. Sernissi, D. Scarpi, F. Bianchini, A. Contini, E. G. Occhiato, *Org. Biomol. Chem.* **2017**, *15*, 6826–6836.

[21] A. Trabocchi, A. Krachmalnicoff, G. Menchi, A. Guarna, *Tetrahedron* **2012**, *68*, 9701–9705.

[22] D. Núñez-Villanueva, M. Á. Bonache, L. Infantes, M. T. García-López, M. Martín-Martínez, R. González-Muñiz, *J. Org. Chem.* **2011**, *76*, 6592–6603.

[23] P. Todorov, P. Peneva, J. Tchekalarova, S. Georgieva, *Amino Acids* **2020**, *52*, 567–585.

[24] M. Crisma, M. De Zotti, A. Moretto, C. Peggion, B. Drouillat, K. Wright, F. Couty, C. Toniolo, F. Formaggio, *New J. Chem.* **2015**, *39*, 3208–3216.

[25] A. J. Cameron, C. J. Squire, P. J. B. Edwards, E. Harjes, V. Sarojini, *Chem. – An Asian J.* **2017**, *12*, 3195–3202.

[26] D. Xin, K. Burgess, *Org. Biomol. Chem.* **2016**, *14*, 5049–5058.

[27] V. H. Thorat, T. S. Ingole, K. N. Vijayadas, R. V Nair, S. S. Kale, V. V. E. Ramesh, H. C. Davis, P. Prabhakaran, R. G. Gonnade, R. L. Gawade, V. G. Puranik, P. R. Rajamohanan, G. J. Sanjayan, *European J. Org. Chem.* **2013**, *2013*, 3529–3542.

[28] R. Bucci, A. Bonetti, F. Clerici, A. Contini, D. Nava, S. Pellegrino, D. Tessaro, M. L. Gelmi, *Chem. - A Eur. J.* **2017**, *23*, 10822–10831.

[29] S. Chandrasekhar, K. V. M. Rao, M. Seenaiah, P. Naresh, A. S. Devi, B. Jagadeesh, *Chem. - An Asian J.* **2014**, *9*, 457–461.

[30] F. Vaghi, R. Bucci, F. Clerici, A. Contini, M. L. Gelmi, *Org. Lett.* **2020**, *22*, 6197–6202.

[31] R. Bucci, A. Contini, F. Clerici, S. Pellegrino, M. L. Gelmi, *Org. Chem. Front.* **2019**, *6*, 972–982.

[32] Y. Krishna, S. Sharma, R. S. Ampapathi, D. Koley, *Org. Lett.* **2014**, *16*, 2084–2087.

[33] C. Bonnel, B. Legrand, M. Simon, J. Martinez, J. L. Bantignies, Y. K. Kang, E. Wenger, F. Hoh, N. Masurier, L. T. Maillard, *Chem. - A Eur. J.* **2017**, *23*, 17584–17591.

[34] L. Tamborini, F. Mastronardi, F. Dall'Oglio, C. De Micheli, B. Nielsen, L. Lo Presti, P. Conti, A. Pinto, *Medchemcomm* **2015**, *6*, 1260–1266.

[35] N. D. P. Atmuri, D. J. Reilley, W. D. Lubell, *Org. Lett.* **2017**, *19*, 5066–5069.

[36] S. Pellegrino, A. Contini, M. L. Gelmi, L. Lo Presti, R. Soave, E. Erba, *J. Org. Chem.* **2014**, *79*, 3094–3102.

[37] S. Pellegrino, N. Tonali, E. Erba, J. Kaffy, M. Taverna, A. Contini, M. Taylor, D. Allsop, M. L. Gelmi, S. Ongeri, *Chem. Sci.* **2017**, *8*, 1295–1302.

[38] S. Pellegrino, G. Facchetti, A. Contini, M. L. Gelmi, E. Erba, R. Gandolfi, I. Rimoldi, *RSC Adv.* **2016**, *6*, 71529–71533.

[39] S. Pellegrino, G. Facchetti, R. Gandolfi, M. Fusè, E. Erba, I. Rimoldi, *Can. J. Chem.* **2017**, *96*, 40–43.

[40] M. Körling, A. Geyer, *European J. Org. Chem.* **2015**, *2015*, 2382–2387.

[41] R. Bucci, N. Sloan, L. Topping, M. Zanda, *European J. Org. Chem.* **2020**, DOI 10.1002/ejoc.202000512.

[42] S. Shuto, S. Ono, Y. Hase, N. Kamiyama, H. Takada, K. Yamasihita, A. Matsuda, *J. Org. Chem.* **1996**, *61*, 915–923.

[43] A. Mizuno, S. Miura, M. Watanabe, Y. Ito, S. Yamada, T. Odagami, Y. Kogami, M. Arisawa, S. Shuto, *Org. Lett.* **2013**, *15*, 1686–1689.

[44] J. E. S. Wikberg, F. Mutulis, *Nat. Rev. Drug Discov.* **2008**, *7*, 307–323.

[45] B. Soberats, L. Martínez, E. Sanna, A. Sampedro, C. Rotger, A. Costa, *Chem. – A Eur. J.* **2012**, *18*, 7533–7542.

[46] L. Martínez-Crespo, E. C. Escudero-Adán, A. Costa, C. Rotger, *Chem. – A Eur. J.* **2018**, *24*, 17802–17813.

[47] R. J. Nachman, K. Kaczmarek, J. Zabrocki, G. M. Coast, *Peptides* **2012**, *34*, 262–265.

[48] L. Belvisi, A. Bernardi, A. Checchia, L. Manzoni, D. Potenza, C. Scolastico, M. Castorina, A. Cupelli, G. Giannini, P. Carminati, C. Pisano, *Org. Lett.* **2001**, *3*, 1001–1004.

[49] L. Gentilucci, F. Gallo, F. Meloni, M. Mastandrea, B. Del Secco, R. de Marco, *European J. Org. Chem.* **2016**, *2016*, 3243–3251.

[50] D. T. Flood, N. L. Yan, P. E. Dawson, *Angew. Chemie - Int. Ed.* **2018**, *57*, 8697–8701.

[51] R. De Marco, J. Zhao, A. Greco, S. Ioannone, L. Gentilucci, *J. Org. Chem.* **2019**, *84*, 4992–5004.

[52] L. R. Whitby, Y. Ando, V. Setola, P. K. Vogt, B. L. Roth, D. L. Boger, *J. Am. Chem. Soc.* **2011**, *133*, 10184–10194.

[53] M. C. Bellucci, M. Frigerio, C. Castellano, F. Meneghetti, A. Sacchetti, A. Volonterio, *Org. Biomol. Chem.* **2018**, *16*, 521–525.

[54] R. Chingle, C. Proulx, W. D. Lubell, *Acc. Chem. Res.* **2017**, *50*, 1541–1556.

[55] P. Prasher, M. Sharma, *Medchemcomm* **2019**, *10*, 1302–1328.

[56] N. Kann, J. R. Johansson, T. Beke-Somfai, *Org. Biomol. Chem.* **2015**, *13*, 2776–2785.

[57] D. C. Schröder, O. Kracker, T. Fröhr, J. Góra, M. Jewginski, A. Nieß, I. Antes, R. Latajka, A. Marion, N. Sewald, *Front. Chem.* **2019**, *7*, 155.

[58] C.-F. Wu, X. Zhao, W.-X. Lan, C. Cao, J.-T. Liu, X.-K. Jiang, Z.-T. Li, *J. Org. Chem.* **2012**, *77*, 4261–4270.

[59] A. S. M. Ressurreição, A. Bordessa, M. Civera, L. Belvisi, C. Gennari, U. Piarulli, *J. Org. Chem.* **2008**, *73*, 652–660.

[60] M. Marchini, M. Mingozzi, R. Colombo, I. Guzzetti, L. Belvisi, F. Vasile, D. Potenza, U. Piarulli, D. Arosio, C. Gennari, *Chem. – A Eur. J.* **2012**, *18*, 6195–6207.

[61] S. Panzeri, S. Zanella, D. Arosio, L. Vahdati, A. Dal Corso, L. Pignataro, M. Paolillo, S. Schinelli, L. Belvisi, C. Gennari, U. Piarulli, *Chem. – A Eur. J.* **2015**, *21*, 6265–6271.

[62] M. Fridén-Saxin, T. Seifert, M. Malo, K. da Silva Andersson, N. Pemberton, C. Dyrager, A. Friberg, K. Dahlén, E. A. A. Wallén, M. Grøtli, K. Luthman, *Eur. J. Med. Chem.* **2016**, *114*, 59–64.

[63] R. M. Freidinger, D. F. Veber, D. S. Perlow, Brooks, R. Saperstein, *Science (80-.).* **1980**, *210*, 656 LP – 658.

[64] A. Rossetti, A. Sacchetti, M. Gatti, A. Pugliese, G. Roda, *Chem. Heterocycl. Compd.* **2017**, *53*, 1214–1219.

[65] R. Bucci, S. Giofré, F. Clerici, A. Contini, A. Pinto, E. Erba, R. Soave, S. Pellegrino, M. L. Gelmi, *J. Org. Chem.* **2018**, *83*, 11493–11501.

[66] M. G. Memeo, M. Mella, V. Montagna, P. Quadrelli, *Chem. – A Eur. J.* **2015**, *21*, 16374–16378.

[67] G. Lesma, R. Cecchi, S. Crippa, P. Giovanelli, F. Meneghetti, M. Musolino, A. Sacchetti, A. Silvani, *Org. Biomol. Chem.* **2012**, *10*, 9004–9012.

[68] A. Knuhtsen, B. Legrand, O. Van der Poorten, M. Amblard, J. Martinez, S. Ballet, J. L. Kristensen, D. S. Pedersen, *Chem. – A Eur. J.* **2016**, *22*, 14022–14028.

[69] J. Fuhrmann, K. W. Clancy, P. R. Thompson, *Chem. Rev.* **2015**, *115*, 5413–5461.

[70] A. A. Dörr, W. D. Lubell, *Org. Lett.* **2015**, *17*, 3592–3595.

[71] E. Lenci, A. Trabocchi, *Chem. Soc. Rev.* **2020**, *49*, 3262–3277.

[72] F. Clerici, E. Erba, M. L. Gelmi, S. Pellegrino, *Tetrahedron Lett.* **2016**, *57*, 5540–5550.

[73] R. Bucci, A. Bossi, E. Erba, F. Vaghi, A. Saha, S. Yuran, D. Maggioni, M. L. Gelmi, M. Reches, S. Pellegrino, *Sci. Rep.* **2020**, *10*, 19331.