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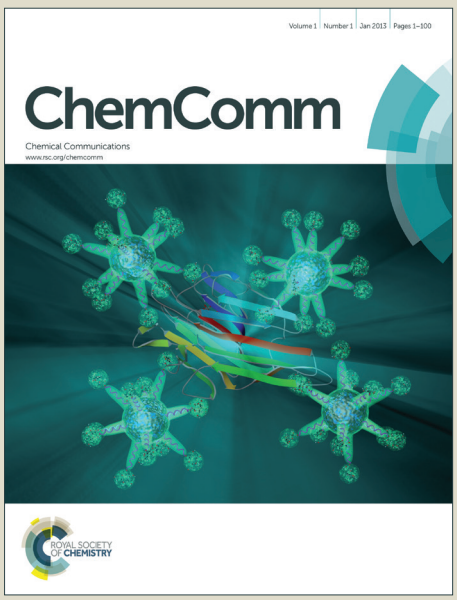

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ARTICLE TYPE

Synthetic Turn Mimetics and Hairpin Nucleators: Quo Vadimus?‡

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Structural mimicry of peptides has witnessed perceptible progress in the last three decades. Reverse turn and β-hairpin units are the smallest secondary structural motifs that are some of the most scrutinized functional cores of peptides and proteins. The practise of mimicking, without altering the function of the bioactive core, ranges from conformational locking of the basic skeleton to total replacement of structural architecture using synthetic analogues. Development of heterogeneous backbones - using unnatural residues in place of natural ones - has broadened further opportunities for efficient structural rigidification. This feature article endeavours to trail the path of progress achieved hitherto and envisage the possibilities that lie ahead in the development of synthetic turn mimetics and hairpin nucleators.

1. Introduction

Amongst different biopolymers, proteins perform key functions in cellular communication, biocatalysis, molecular transportation *etc*., in addition to being a major component in structural organization. In polypeptides/proteins, spatial arrangement of its building blocks/amino acids are decidedly crucial for their properties, and thus their overt functions.

The current trend is the introduction of competent unnatural moieties into the natural backbones and consequently, considerable success has been attained in the area of peptidomimetics. Thus, to identify their structure-led-function, constructing followed by comprehending the conformational features of their synthetic analogues (*i.e.* mimics) in solid- and solution-state becomes highly indespensable. In these grounds, 3D-pharmacokinetic profiling the synthetic candidates has laid tricky challenge to future drug development.

Last two decades have witnessed a sharp rise in peptides as preferred drug candidates with the increasing demand for bio-compatible drugs. However, their poor bioavailability and limited shelf-life necessitate the development of efficient methods for the construction of bio-compatible robust molecules. Conformationally constrained motifs/scaffolds featuring natural/unnatural residues often satisfactorily emulate the secondary structural architecture of the target molecules, especially bioactive peptide entities.[1] The combinations that arise by the virtue of the heterogeneous backbones are quite successful in duplicating the structure and function of native functional entities and also increase stability.[2] They are exceedingly beneficial as they can be effortlessly tethered into natural peptide backbones, without varying much of its structural resemblance.

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‡ Dedicated to mark the 65th birth anniversary of Prof. P. Balaram.

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Although hassled by his (late) father to join Indian Administrative Service (IAS), and serve the nation better, Gangadhar J. Sanjayan, fascinated by colour chemistry in his early days of laboratory encounters, chose chemistry as a career – with a sole dream of doing "something big in science". After completing his advanced studies in chemistry, Sanjayan joined the group of Prof. K. N. Ganesh, for his first stint of post-doctoral studies. Later, he moved to the University of Oxford, UK, to work with Prof. George. W. J. Fleet. Currently, he is leading a group of researchers at NCL, Pune, pondering upon various research problems involving non-covalent interactions.

2. Reverse Turn and Hairpin units in biology

Turns in proteins are the sites, where the polypeptide chain totally folds back on itself, directing proteins to adopt a globular shape.[3] Folding of the peptide chains are largely caused by amino acids like Asn, Gly and Pro (*ca*. 50% of turns found in proteins) *etc*., because of their torsional characteristics. Turn units in peptides are commonly located at the surface of proteins, providing means for the interaction with receptors, thus are involved in various biological events and pathways.[4] Their multi-faceted functions include acting as recognition sites for initiation of complex immunological, metabolic, hematological, and endocrinological reactions. More than a hundred peptide-activated GPCR ligands are identified for their recognition of turn structures.[5] Unlike α-helices or β-sheet secondary structures, turns are termed as irregular structures due to lack of clearly defined torsion angle preferences. In proteins, reverse turns are generally classified into different types on a virtual basis of the number of residues that participate in the formation of *intra*-turn hydrogen bond between the main-chain carbonyl group from the first residue and the main-chain amide group from the last residue of the turn. A peptide turn may be categorized by 7-, 10-, and 13-membered hydrogen bonded rings formed by participation of 3 residues (*γ*-turn), 4 residues (*β*-turn), and 5 residues (α-turn), respectively (Fig. 1a). The other family of turns also exists - characterized by a hydrogen bond between the main-chain amide group of the first residue and the main-chain carbonyl group of the last residue. These are often termed as 'forward turns' possessing reverse hydrogen bonding in turn segments, but they are seldom found in native proteins. Such turn motifs consisting of 2-amino acids (δ-turn) or 3-amino acid residues (ε-turns) have been theoretically established.[6] In the current perception, turns also include 'open' turn conformation lacking a hydrogen bond, whose C_α-C_α distance between the first and last residue may be <10 Å.[7]

β-hairpin structure forms the smallest structural unit conducive for the augmentation of a *β*-sheet secondary structure in proteins (Fig. 1b).[8] They are one of the most preferred motifs/candidates for 'protein epitope mimetic' design due to their involvement in various molecular recognition events.[9]

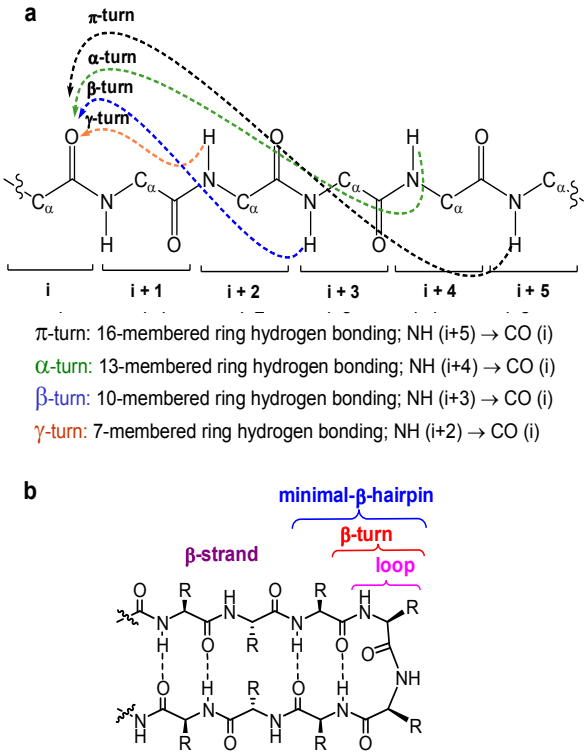

Fig. 1 Types of reverse turns (a) and schematic representation of a typical *β*-hairpin secondary structure detailing the components of its structure such as *β*-strand, *β*-turn, and loop, *etc*. (b).

Incorporation of unnatural residues into the peptide backbone and designed reverse-turn analogues can be extended further to nucleate hairpin formation - often assisted by sidechain-sidechain interactions.[10] Various such mimics have been found to exhibit a wide range of applications in the area of peptide based drugs to catalysis. Reverse turns are common motifs in proteins and a range of bioactive peptide sequences mediate their function through the interaction of the side chains of amino acids situated at the turn units with different receptor sites.[11]

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3. Reverse turn mimics

Various synthetic 3-dimensionally ordered reverse turn mimics lucratively imitate the structural topology/recognition motifs of such peptides, but interfere and disrupt their biological pathways.[12] Their incorporation into functional bioactive core increasingly meliorates the understanding of interactions of small molecules with biological targets such as enzymes or receptors, besides tackling the common 'peptides-as-drugs'-related concerns. The major problem with reverse turn mimetics is their tethering into the agonist active site of peptide hormone/neurotransmitter ligands, owing to the lack of suitable positioning of the side chain groups. Thus, there is always a need for scaffolds with suitable orientation of side chains critical for the event of molecular recognition.

Rigidification or stabilisation of reverse turn can be accomplished using various backbone modifications. The broad purview includes a classification either based on the restriction of the reverse turn loop region or by local/remote locking or by replacement of the core by unnatural constraint inducers. Reverse turn mimetics are classified into two main groups; internal and external, where internal turn mimetics are constructed *via* locking the basic skeleton *i.e.* by linking the termini using intramolecular cycloaddition.[13] External turn mimetics, on the other hand, do not consider the side chains specifically for the construction of dipeptide isosteres. The regular practises employed in creating reverse turn mimics are discussed categorically in subsequent sections (*vide infra*).

3.1 Cyclisation-mediated reverse turn mimics

To retain the conformational feature of reverse turn units, one of the best methods is to bring in a cyclisation-mediated restraint. In order to retain biological activity, cyclic constraints must influence the backbone conformation without compromising crucial side chain interactions with the receptor. There are different modes to achieve the conformation locking like using various synthetic non-peptidic analogues that retain the sites of terminal interactions or fasten the sticky sites using head-to-tail covalent or non-covalent linking.[14]

3.1.1 Cyclisation at local site

In order to obtain selective protein inhibition, Freidinger introduced the idea of local backbone cyclization in order to limit the local mobility of an oligopeptide.[15] Freidinger employed a size-dependent lactam-based lock between the (i + 2) and (i + 3) residues, fixing the *trans* peptide with the constraints that limit the conformation by non-covalent interactions like H-bonding (Fig. 2a).[16] Following this strategy, several scaffolds employing chimeric amino acids-based reverse-turn mimics were formulated in the past three decades.[17] Different strategies include covalent linking/cyclization through bicyclic dipeptide formation (Fig. 2c),[18] peptide coupling (Fig. 2d,e),[19] ethylene bridge formation (Fig. 2k),[20] cyclic ($\alpha_2\beta$)-tripeptides,[21] aminopiperidinone-carboxylate scaffolds,[22] coupling ynamides,[23] coupling thioenamino group,[24] cycloaddition reaction,[25] ring-closing olefin metathesis,[26] *etc.* to render conformational rigidification. Taking the dihedral parameters into consideration, this method was aimed at bringing the four residues into proximity *i.e.* the carbonyl oxygen atom of the first residue (i) and the amide NH proton of the fourth residue (i + 3).

The practice of applying bicyclic conformational constraints at the central i + 1st and i + 2nd residues, led to the origin of the β-turn-dipeptide (BTD) scaffold as a very important class in β-turn mimetics.[27] This strategy was commenced by Nagai and Sato in the early 1980s (Fig. 2b),[28] which was followed by development of an array of β-turn mimetics. A variety of bicyclic lactams,[29] (5,5-, 6,5-, and 7,5-fused)-1-aza-2-oxobicycloalkane amino acids[30] and pyrroloisoquinoline-based tetrapeptide analogues[31] were then created by Scolastico and co-workers. Distinct units to restrict torsional constraints led to the advent of spirocyclic γ-lactam bridge, led by Robinson and co-workers (Fig. 2f). [32] In due course, a range of spirolactam bicyclic and tricyclic systems based on proline were created with promising applications (Fig. 2m).[33]

3.1.2 Remote cyclisation methods

In certain cases, the remote termini were joined together in order to retain the reverse turn structure - mainly the hairpin architecture. It is synthetically feasible, if there are cysteine (Cys) residues present in the peptide backbone, which is very amenable to disulphide brigding.[34] Interstrand triazole bridging[35] and macrocyclization[36] are examples of other approaches meant for remote linking. Kessler and co-workers demonstrated the use of cyclic peptides as conformationally constrained scaffolds, where a recognition motif (such as RGD) was mimicked by cyclic peptide backbone to spatially sample various conformations.[37] This class turned out to be promising in interacting with surface-exposed loops of several proteins where it was seen to adapt to diverse local structural environments like HIV-protease, Zn-finger, and WW domains.[38] Several other azabicyclo[X.Y.0]alkanone amino acid analogs successfully exhibited activities as Caspase 1/ICE, ACE/NEP and thrombin inhibitors.[39]

3.2 Non-peptidic residues as mimics

An additional means for conformational restriction for preparation of reverse turn mimetics is the use of non-peptidic residues, which has been explored well in the past decades. Evidently, this series usually comprises a single entity tethered into peptide backbone to effectively stabilize a reverse turn architecture. Inception of this structural rigidification concept took place in the mid 1980s when Feigel and co-workers used units like phenoxathin-4,6-dicarboxylic acid and 2,8-dimethyl-4,6-bis(aminomethyl)phenoxathiin-10,10-dioxide, to support a cyclic parallel β-sheet (Fig. 2c).[40] Another closer analogue was developed by Kelly and group, featuring functionalized dibenzofuran in the functional core (Fig. 2g).[41] Newer modifications showed use of click chemistry to create 1,4-diphenyl-1,2,3-triazole-incorporated amide derivatives[42] and substitution by dehydroamino acids.[43] Few other candidates generated include benzodiazepines (Fig. 2h), [44] diketopiperazines (Fig. 2i),[45] hydroxyproline-derived diketopiperazine template,[46] tetrahydro-β-carboline-diketopiperazine-based peptidomimetic scaffold,[47] sugars (Fig. 2j),[48] and hydroxypyrrolizidinone,[49] to

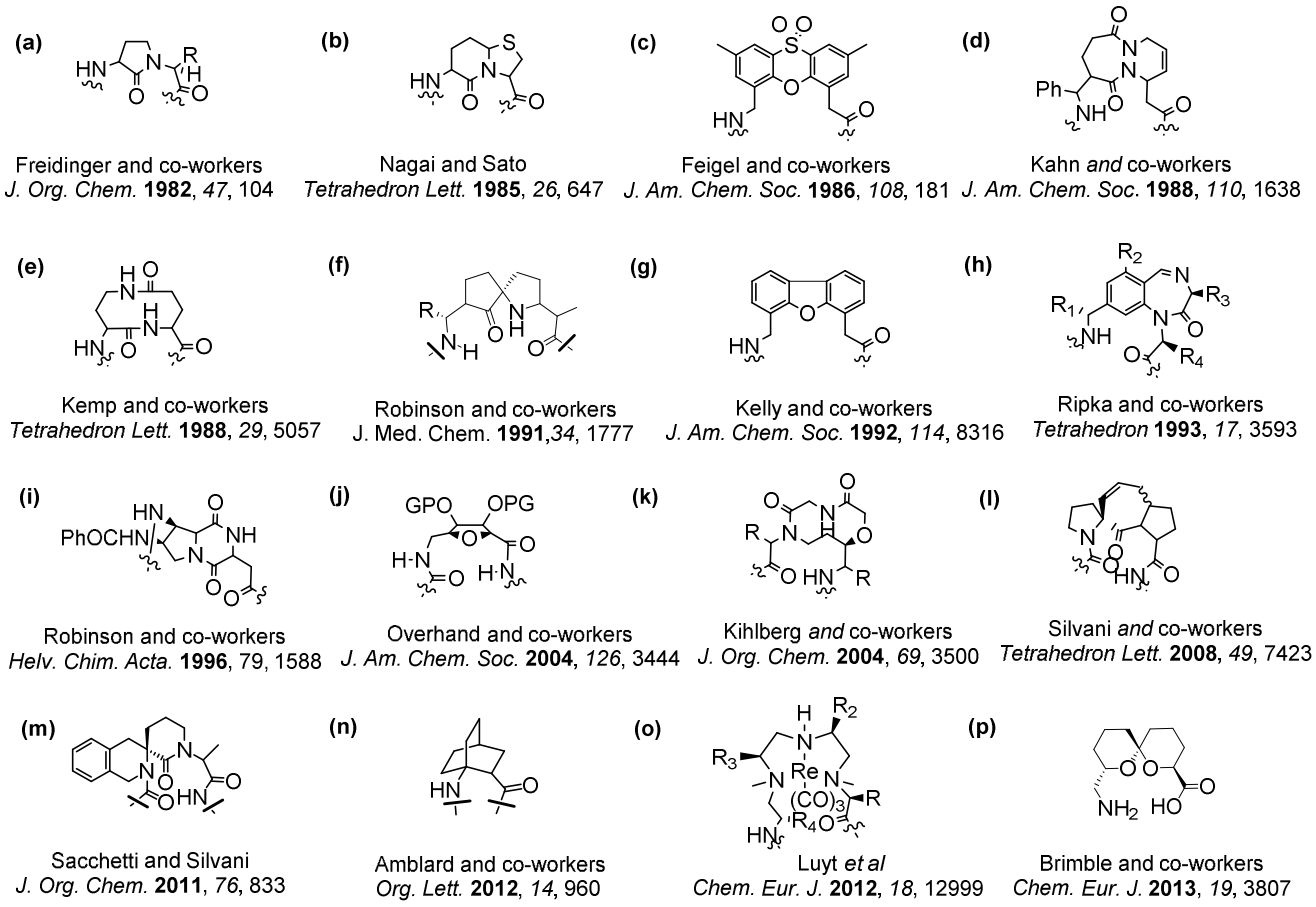

Fig. 2 Selected examples of *β*-turn mimetics.

name a few. Bridging is another means to attain efficient conformational restraint, as evident from the use of (S)-aminobicyclo- [2.2.2]octane-2-carboxylic acid (ABOC) (Fig. 2n).[50] Latest development in this series is the addition of 6,6-spiroketal amino acid (Fig. 2p).[51]

3.3 Metal chelation-based mimics

Marshall and co-workers explored metal-centered chiral pentaazacrowns, which they described to be "glue to keep the pharmacophore groups oriented together in their desired directions".[52] Metals can very well chelate with the amide NHs and efficaciously limit conformational flexibility. Latest developments in this direction have witnessed the use of rhenium to arrest reverse turn conformation (Fig. 2o).[53] Another interesting case is that of 1'-aminoferrocene-1-carboxylic acid, which has been used as turn inducer.[54] Even, self-assembled metal-induced template held by independent phosphane ligands were shown to mimic β-turn effectively.[55]

3.4 Heterogeneous peptide motifs in reverse turn design

The field of foldamers[56]- a branch of peptidomimetics – deals with the thorough analyses of the structural aspects of *de novo* generated secondary structural motifs and exploits this understanding in the development of peptide-derived therapeutics. Foldamer-based mimics maintain stable 3-dimensional compact architecture in both solid and solution-state.

The area of peptidomimetic design has been fast flourishing ever since the discovery of unnatural amino acids (Fig. 3).[57] It has been successful to a larger extent in imitating the topology of natural peptide components with improved binding and selectivity.

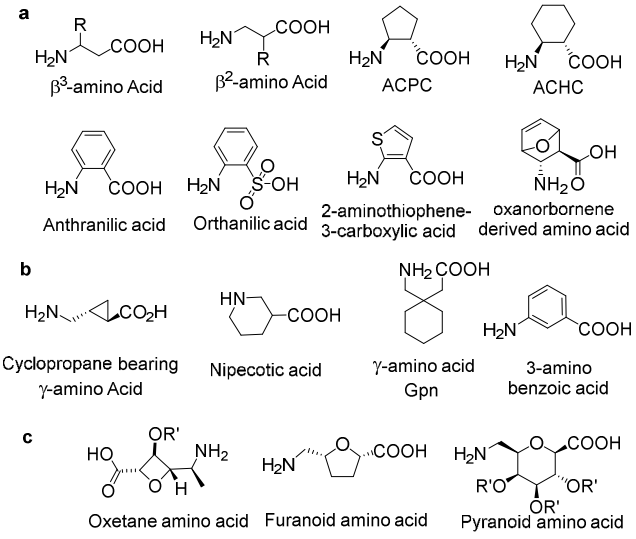

Fig. 3 Selected examples peptide building blocks: *β*-amino acids (a), γ-amino acids (b) and δ–amino acids (c).

Integrating constrained moieties witnessed the use of proline derivatives,[58] α-aminoxy acids,[59] γ-turn inducing 2-alkyl-2-carboxyazetidines,[60] β-lactam-derived amino acid,[61] and so on. To restrict the reverse turn architecture, one of the easiest ways is to integrate torsionally constrained amino acids into the peptide backbone. The common choices include germinal constraints as in α - amino acids like α-amino butyric acid (Aib) (gem-dimethyl substituted open amino acid)[62] and *N*-aminoproline (cyclically constrained).[63] Another important category is the insertion of modified *homo*- analogues *i.e.* β-amino acids like 2-aminocyclopropanecarboxylic acid (ACC),[64] 2-aminocyclopentanecarboxylic acid (ACPC),[65] 2-aminocyclohexanecarboxylic acid (ACHC),[66] and 2-aminobenzoic acid (anthranilic acid, Ant) [67] or γ- amino acids like nipecotic acid (heterochiral dinipecotic acid segment that promotes antiparallel sheet secondary structure),[68] 1-aminomethylcyclohexaneacetic acid (gabapentin, Gpn),[69] *etc*. Research groups of Fleet, Chakraborty, Fuchs and others have introduced diverse class of sugar amino acids (SAAs) with varying preferences for secondary structure formation.[70] SAAs have been extensively used in peptidomimetics exploiting their ready availability, defined stereochemistry and easily convertible substituents attached to constrained cyclic rings. Few other examples of reverse turn architectures involving the above-mentioned amino acids are described as follows. They can be sub-divided into aliphatic-aliphatic and aliphatic-aromatic heterogeneous peptides, based on their composition.

3.4.1 Aliphatic-aliphatic heterogeneous peptides

Pro-Xaa with Xaa = Pro/Gly/Asn is the prominent combination for a reverse turn found in natural proteins. Turn inducing characteristic was unambiguously perceived from the solid-sate conformation of tetrapeptide Piv-^{D}Pro-^{L}Pro-^{L}Ala-NHMe, reported in 1979 from the Balaram group (Fig. 4a).[71] Stereochemistry also provides an excellent tool to tune secondary structures.[72] Modulation of chirality and substitution pattern of the amino acid residues in secondary structure mimics affect their hydrogen-bonding interactions and hence the stability of the structure, which has been illustrated in a number of cases.[73] Balaram's group studied extensively the effect of alternating chirality and confirmed that heterochirality strengthens turn induction capability, which was reiterated by Gellman and group while comparing (D)Pro-Xxx and (L)Pro-Xxx containing sequences.[74] Several such studies have been undertaken by different research groups that highlight the importance of stereochemical patterning approach in the design of peptide-based foldamers, wherein controlling geometry of building blocks is shown to direct the periodic secondary structure formation.[75]

The Balaram group also contributed towards developing hairpin nucleating combinations using simple α-amino acid conjugated with cyclic α,α-disubstituted amino acids (Gabapentin, Gpn) or 1-aminocycloalkane-1-carboxylic acid (Ac_6c) (Fig. 4c).[76] On the other hand, the Gellman group came up with the concept of heterochiral β-amino acid like dinipecotic acid segment to generate a stable reverse turn that promoted antiparallel sheet (Fig. 4b).[77]

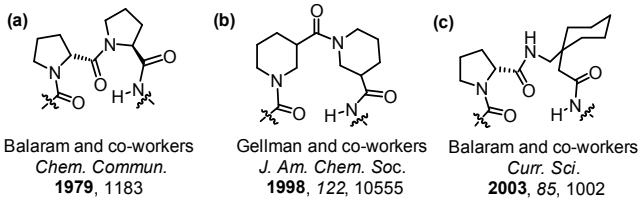

Fig. 4 Molecular structures of reverse turn mimics based on conjugation of aliphatic-aliphatic building blocks.

Turn structures consisting of two amino acid residues (δ-peptides) also has been practically realized by the use of unnatural amino acids like C-linked carbo-γ(4)-amino acids and γ-aminobutyric acid as reported by Sharma *et al.*[78] Even, turns have been achieved with the use of merely one amino acid residue that mimicked reverse turn conformation fairly well. Tomasini and group reported efficient hairpin rendering combinations using Gly at (i+1) position and L-pyroglutamic acid (L-pGlu), (4*R*,5*S*)- / (4*S*,5*R*)-4-methyl-5-carboxybenzyloxazolidin-2-one (L/D-Oxd) at (i+1) position.[79] Strange alterations in conformational features arise by structural modulation using different units like ethylene diammine (EDA) next to Pro-Gly turn motif. Such sequences with R_1-^{L}Pro-Gly-NH-EDA-R_2 were shown to stabilize concurrent α- and β-turns within a single molecule (Fig. 6c, *vide infra*).[80]

3.4.2 Aliphatic-aromatic heterogeneous peptides

The use of aliphatic-aromatic hybrids is comparatively a recent practice in the locale of heterogeneous peptide design. They also often deliver turn structures, owing to the combined local conformational preferences of the α-amino acid and rigidity of the conjoining aromatic residue, as their constrained torsions enforce linear structural design on the plane.

Different designs include reverse turn motif by Smith *et al.,* involving amino acid derived-alcohol conjoined to an aromatic amine that promoted parallel sheet structure (Fig. 5a).[81] Another aliphatic-aromatic amino acid-based reverse turn motif reported from our group is the anthranilic acid-proline conjugated robust *pseudo*-β-turn mimic - highly insensitive towards structural modifications in-and-around the turn motif (Fig. 5b).[82]

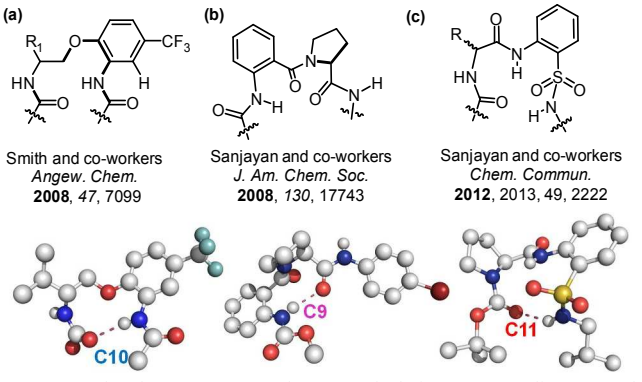

Fig. 5 Molecular structures (above) and their corresponding crystal structures (below) of reverse turn mimics based on aliphatic-aromatic building blocks. Some atoms have been removed for clarity.

The effect of the steric and dihedral angle constraints offered by proline (Pro) on the anthranilic acid (Ant) residue causes formation 9-membered H-bonding pattern between Ant-NH and Pro-CO. Another sequence Xaa-^{S}Ant-Yaa featuring orthanilic acid (2-aminobenzenesulfonic acid, ^{S}Ant), displayed robust C11-hydrogen bonding network (Fig. 5c), which was shown to be insensitive towards various structural perturbations.[83]

With slight substitutional variation using unconventional amino acid like γ-amino acid 3-amino-5-bromo-2-methoxy benzoic acid (Amb) in combination with Pro units *i.e.* Pro-Amb motif, displayed well-defined, compact, three-dimensional folds featuring strong S(7)-type 7-membered periodic γ-turn conformation (Fig. 6a).[84] In another case, the *hetero* foldamer Aib-Pro-Adb sequential repeats featuring γ-aromatic amino acid 3-amino-4,5-dimethoxy-benzoic acid (Adb) exhibited a compact, three-dimensional spiral β-bend ribbon conformation supported by three-centered H-bonding present in the aromatic residue (Fig. 6b).[85] Such cases ascertain how the distinct non-covalent interactions co-operatively assist in stabilizing secondary structural architectures.

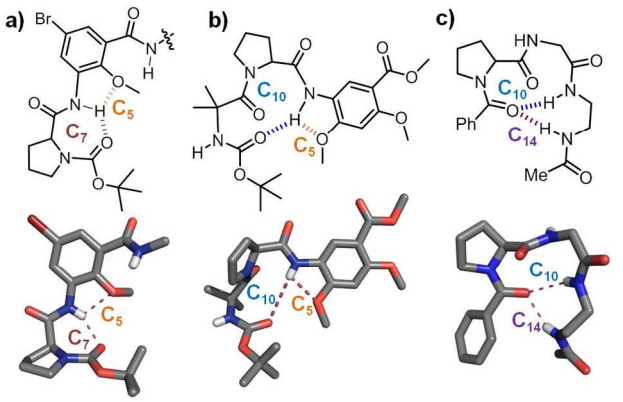

Fig. 6. Molecular structure (above) and crystal structure (below) of -(Pro-Amb)- dipeptide unit (a), Boc-Aib-Pro-Adb-OMe (b), and Bz-^{L}Pro-Gly-NH-EDA-Ac, respectively, reported from Sanjayan's group. Some atoms have been removed for clarity.

In certain other cases, if sheet promoting amino acid residues were incorporated around the *pseudo*-β-turn Ant-Pro motif (Fig. 7, middle), formation of *pseudo*-β-hairpin motif (Fig. 7, bottom) was observed featuring a C9- and C17- H-bonding networks, unlike the C10- and C14- H-bonding found in native β-hairpin secondary structure.[86] On the other hand, even swapping of carboxamide with sulphonamide bond was seen to preserve the pseudo-β-turn (Fig. 7, top).[87] In a curious case, coupling of γ-amino acid 2-aminomethyl benzoic acid (2-Amb) with Pro led to the formation of reverse turn unit with a characteristic C12- H-bonding (Fig. 7, right).[88] Other alterations, however, did seem to affect the structural assembly, such as amide to ester mutation at the C-terminus of Ant-Pro turn,[89] substitution of another Ant residue at the N-terminus,[90] or replacement of Ant unit with five-membered heterocycle-derived amino acid,[91] or constitutional ratio variation.[92] Constitutional variation of the residues brings about drastic changes in the conformational architecture of the peptide motifs occasionally.

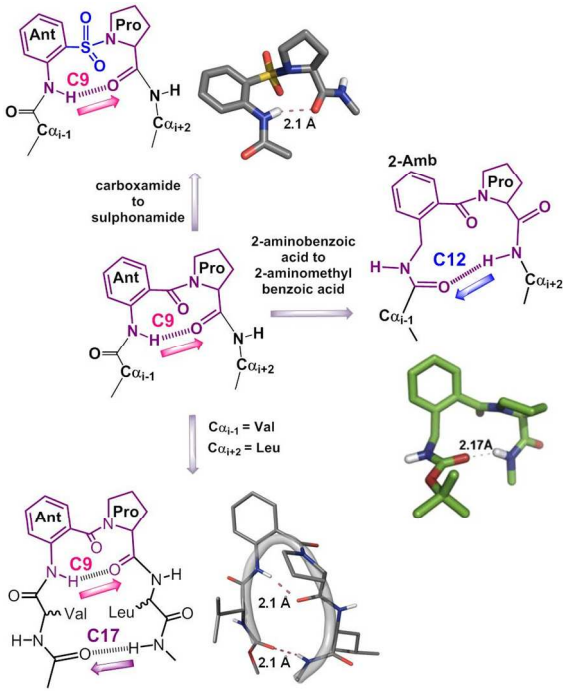

Fig. 7 Schematic representation of effect of linkage modification and substitution modulation about *Ant-Pro* motifs; Comparison of effect of linkages *via* carboxamide (middle) and sulphonamide (top), respectively, formation of *pseudo*-β-hairpin (below), and 2-Amb-Pro dipeptide motif featuring C12- H-bonding network (right).

The typical case of synthetic zipper peptide motif formation with sequence $\alpha\beta_n$ (n=2, α = $^{L/D}$Pro, β = Ant) is highly noteworthy in this regard, which could stabilize as large as 26 atoms-containing H-bonded network (Fig. 8a,b,c).[93] Large sheet-like folded peptide motifs were found to remain unaltered in different solution-state studies and temperature variation experiments. It is also anticipated to stabilize even larger and remote inter-residual interaction with varying residue content, for *example*: 1:4 residue ratios rendered an inter-residual H-bonding network encompassing 42 atoms in its fold (Fig. 8d,e,f). Further extended/higher order architectures are anticipated to preserve the folded architecture and even larger remote inter-residual contacts can be envisioned by the simple induction of fold at the Ant-Pro site, orchestrated by the aromatic-stacking and H-bonding interactions.

4. Applications of reverse turn/β-hairpin

Reverse turn mimics successfully retain the desired conformation for biological receptor recognition by enzymes or peptides. Besides medicinal relevance, it also has established its forte in organic asymmetric synthesis by providing the proper orientation and site selectivity over considerable distances meant to bring reactants closer or activate the functional groups. All the factors that influence and stabilize the β-hairpin mimics have been comprehensively described in a review by Stotz and Topp.[94]

4.1 In therapeutics

Bioactive peptides are ubiquitous in all forms of life and large number of physiological processes in living systems are an outcome of their interactions with the receptor molecules.[95]

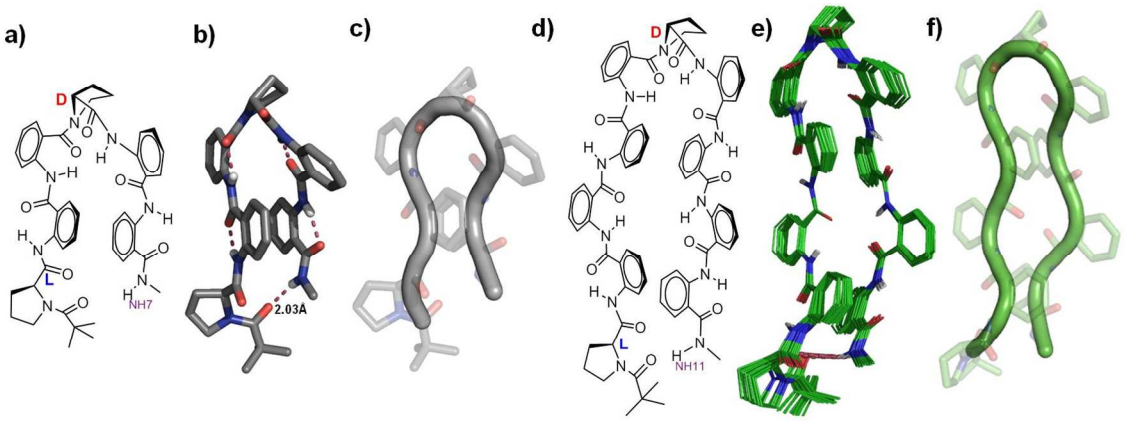

Fig. 8 Synthetic zipper motifs rendered by co-operative effect of stereocontrol and non-covalent interactions like H-bonding and aromatic-stacking.

Several peptides have been identified carrying out specific functions, for instance, octapeptide angiotensin that causes vasoconstrictor effects, vasopressin that brings vasodilator effects, enkephalins and neurotensin that direct central nervous mechanisms like respiratory, cardiovascular, temperature pain and sensory controls. [95] This knowledge significantly stimulated the development of peptide emulating drugs or structural analogs in form of their agonists (which mimic the parent peptide) and antagonists (that occupies peptide receptor) as they are non-toxic. Reverse turns form an integral part in many antibiotics, toxins/antitoxins, ionophores, and metabolic products.

Also, the antimicrobial decapeptide sequences like gramicidin S and tyrocidines A-E, antibiotic viomycin and cyclic dodecadepsipeptide valinomycin, octapeptide amatoxins and the heptapeptide phallotoxins, ferrichromes that show potent growth factor activity and cellular transport factors for iron, all possess turn structures.

Turn mimics have implications in recognition of elements in structure-activity studies of several peptide hormones, angiotensin II, bradykinin, GnRH, somatostatin, and many others. Various groups have worked on incorporating turn mimics into these peptides. Seebach and group replaced (Phe-Trp-Lys-Thr) sequence that binds to somatostatin receptor with a cyclic β-tetrapeptide (Fig. 9).[96] Muniz and co-workers employed constrained dipeptoid analogues containing the hexahydroindolizino[8,7-b]indole for selective and efficient CCK-A receptor antagonism.[97] The cyclic β-peptide showed binding affinity at micromolar concentration (K_D = 3.3 - 186 μM). Pro-Leu-Gly-NH_2 sequence is the one involved in dopaminergic neurotransmission process, which has been investigated using different turn mimetics like bicyclic and spirocyclic ligands for its allosteric modulation effects.[98]

Gramicidin S (GS) is a cyclic decapeptide containing two type II β-turns possessing antibiotic properties. Introduction of azabicycloalkane amino acid-based β-turn dipeptide into GS resulted in an antibiotic analog with similar activity as the parent peptide.[99] Hruby and co-workers also developed a bicyclic leu-enkephalin analogue incorporating 4-phenyl indolizidinone.[100] Similarly, Jurzak and group used (2*S*,6*S*,8*S*)-Indolidin-9-one amino ester as β-turn dipeptide scaffold.[101]

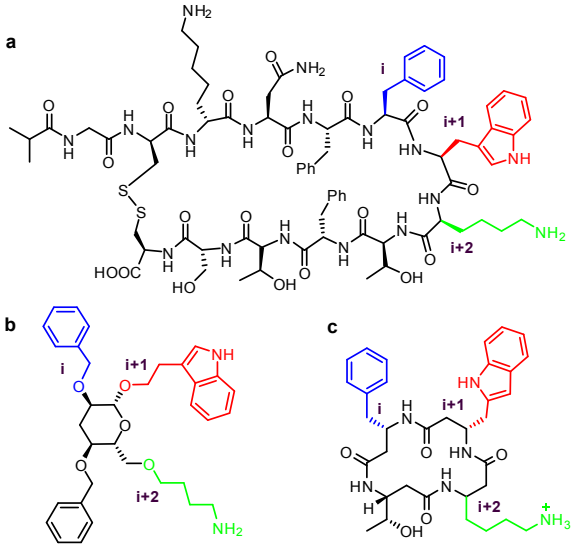

Fig. 9 Somatostatin (a), sugar-based mimic (b) and a cyclic peptide analog of somatostatin reported by Seebach *et al*. (c).

Overhand and group successfully exploited sugar-based reverse turn mimetic, which has been able to mimic GS structure (Fig. 10).[102] Latest development in GS mimicry has seen the use of heterocyclic γ-amino acid ATCs (4-amino(methyl)- 1,3-thiazole-5-carboxylic acid, which exhibited reduced haemotoxicity, but retaining the antibacterial activity.[103]

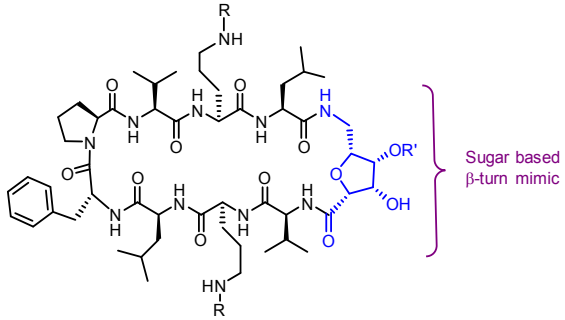

Fig. 10 Sugar-based β-turn mimic of Gramicidin S designed by Overhand *et al.*[103]

Furthermore, Overhand's sugar mimic was shown to successfully stabilize Gramicidin S cyclic hairpin architecture.[104] Several reviews earlier illustrated the principles behind the design and application of *β*-sheet templates and *β*-turn mimics.[105] Most of the β-hairpin templates were designed spanning four peptide residues like dibenzofuran-based and *cis* azobenzene-based templates reported by Kelly and co-workers.[106]

In comparison to the commercialised Angiotensin II (Ang II) receptor antagonists losartan (Cozaar) and valsartan (Diovan), several analogs comprising turn mimics replacing Tyr^4-Ile^5 residues have been synthesized and studied in order to avoid the biocompatibility issues. Ang II is a linear octapeptide with sequence Asp-Arg-Val-Tyr-Ile-His-Pro-Phe and it is the active component of rennin-angiotensin system, which plays important role in regulation of blood pressure, body fluid and electrolyte homeostasis. Replacement of Tyr^4-Ile^5 residues with benzodiazepine-derived β-turn mimic revealed high binding affinity towards AT_2 receptor at (K_i = 1.8 nM) concentration (Fig. 11).[107]

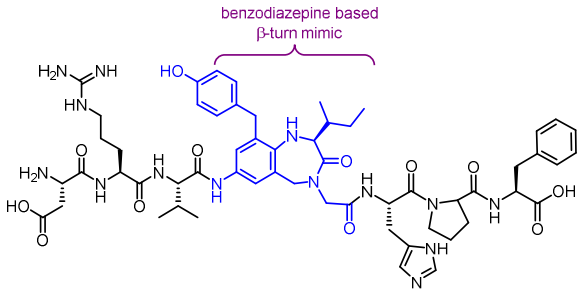

Fig. 11 Angiotensin II analog featuring benzodiazepine as reverse turn mimic designed by Hallberg *et al.*[107]

Further development in this area witnessed rather rigidified strands that stabilize hairpin structures like 1,6-dehydro-3(2H) pyridinone ring (@-tides) developed by Bartlett and coworkers,[108] Nowick's Hao units,[109] alkene isosteres reported by Kelly's group,[110] triazole units reported by Chakraborthy's group[111] and others.[112]

4.2 In catalysis

General points usually considered for the development of catalysts include economy, availability, moisture sensitivity (serious issue for chiral metal complexes), better enantioselectivity and conversion, catalyst loading, and so on. Peptides as catalysts fulfil many of these criteria and thus have found great applications in organocatalytic chemistry as they offer high chemoselectivity, wide substrate scope, chemical robustness and catalyst reusability. One of the very crucial factors involved in governing enantio-selectivity is the stabilization of transition-state for the formation of a single enantiomer. Synthetic turns and hairpin architectures assume rigid conformations, offering specific site orientation and non-covalent contacts helping to achieve high enantio-selectivity.[113] In the early 1980s, simple peptide like poly-alanine (upto >10 residues) was succefully utilised for Julia-Colonna epoxidation. Later, Berkessel *et al.* employed poly-leucine (upto >4 residues) for epoxidation with low catalyst loading and better enantioselectivity.[114]

Peptide mimics possessing β-turn conformations have been exploited greatly in asymmetric catalysis for instance in acylation reactions, oxidations, hydrolytic reactions, and C–C bond formations.[113b,c] Miller's group extensively explored N-methyl-histidine-containing peptides for group transfer chemistry. Previous work from the Miller group has accomplished selective transfer of groups like acyl, phosphoryl, sulfinyl and thiocarbonyl to alcohols,[115] enantioselective mono(sulfonylation)-mediated desymmetrization of meso-1,3-diols,[116] site- and enantioselective oxidation of certain positions of various isoprenols- polyene epoxidation,[117] kinetic resolution of alcohols[118] - amongst various other reactions. Qu *et al.* modified amides into thioamide and utilised the modified tetrapeptide analogue synthesised by Miller and group successfully for acyl transfer reactions (Fig. 12a).[119] The studies carried out by this group reaffirms the requirement of β-hairpin conformation of the peptide sequence for better enatio-selectivity. Wennemer's group introduced peptides of the category Pro-Pro-Xaa for enamine catalysis, where Xaa is an acidic amino acid (Fig. 12b). They utilized tripeptide H-Pro-Pro-Asp-NH_2 with a well-defined turn conformation that was found to be crucial for the high catalytic activity and selectivity of direct asymmetric aldol reactions and asymmetric catalysts for 1,4-addition reactions of aldehydes to nitroolefins.[120] In an elegant example, thiourea catalyst with an aliphatic-aromatic hybrid backbone featuring ten-membered β-turn-like structure that catalyzes Mukaiyama–Mannich reaction with high enantioselectivity (Fig. 12d)[81] was reported by Smith *et al.*

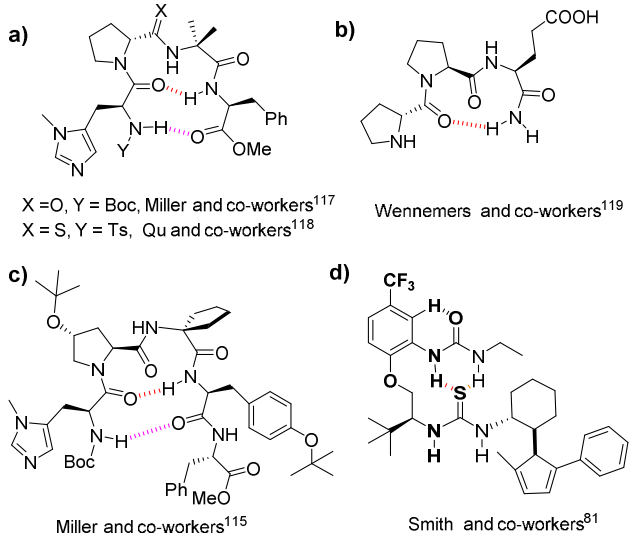

Fig. 12 Selected few examples of peptides used as organocatalysts comprising turn conformation.

5. Conclusions

Tracing the steps in synthetic turn and hairpin mimicry - in stages, reveals how the understanding about secondary structural stabilization/modification has shifted its paradigm from utilization of covalent linkage towards an efficient alternative *i.e.* non-covalent association for their structural stabilization. This strategy has not only helped understanding various non-covalent forces Nature utilizes for the stabilization of biopolymer structures, but also in mimicking

their function and property. The knowledge that bio-organic chemists have gained through the incessant analysis of various non-covalent interactions displayed by reverse turns and hairpins would greatly benefit the development of bio-compatible therapeutics. In addition, these rigidified cores would provide a strong support to the development of green catalysts to facilitate eco-friendly reactions. The spurt of exciting recent developments in the field of "organo catalysis" is an excellent example to substantiate this conjecture.

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Graphical Abstract:

This feature article endeavours to trail the path of progress achieved hitherto and envisage the enormous possibilities that lie ahead in the development of synthetic turn mimetics and hairpin nucleators.