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Understanding the Conformational Analysis of Gababutin Based Hybrid Peptides†

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Abstract: A constrained γ-amino acid gababutin (Gbn) based peptides have been synthesized that form different conformations. In a strive to rationalize the impact of side chain orientations framing tetrapeptide-based supramolecular organic frameworks and morphological entities, Gbn incorporated hybrid peptides Boc-Gbn-Aib-Aaa-Aib-OMe (where Aaa = Phe(F) for peptide **1**, Leu(L) for peptide **2** and Tyr(Y) for peptide **3**) were synthesized by a change in amino acid at third position. The solution state dual folded conformation (C_{12}/C_{10} H-bonded) is probed by 2D NMR studies in support of DMSO-d_6 titration and VT NMR experiments. Peptides **1-3** adopt C_{12}/C_{10} type H-bonded dual folded conformation in crystal state. In addition, distinct supramolecular frameworks are resulting from the modification and orientations of the third residue side chain of peptides **1-3**. A solvent induced morphological diversity of peptides **1-3** is attained by modifying the side chain backbone of tetrapeptides, which are investigated by various microscopic (SEM and AFM) studies. Gbn-based peptides **1-3** show significant morphological and supramolecular packing properties which are fairly different from their gabapentin (Gpn) based analogue peptides.

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Introduction

Design and synthesis of synthetic building blocks to mimic naturally occurring biomolecules is an emerging field of bio-organic and medicinal chemistry.[1-2] Proteolytically stable β- and γ-amino acids are considered as higher homologues to the natural counterparts which are utilized to construct folded peptide structures (peptide foldamers) with the aim of numerous applications in biomedical and material sciences.[3-5] To study the influence on the secondary structures of hybrid peptides, β- and γ-amino acids provide an opportunity to engineer the available backbone through the incorporation of $–(CH_2)_n–$ functionalization method.[6-7] In fact, most of these amino acids are designed to restrict the available conformational freedoms as well as to achieve stable structural propensities both in solid and solution states.[8] Another building block γ-aminobutyric acid (GABA) is a neurotransmitter, which shows various conformational projections about C-C bonds. Thus, structural modifications of GABA render various modified γ-residues and show significant impact on folding and functional properties at atomic and supramolecular level.[7a,g-i] Various constrained synthetic γ-amino acids *via* backbone cyclization at C^{β}—C^{α} (θ_2) were reported to study the folding preferences of peptides (Fig. 1). The backbone of γ-amino acid is restricted through gauche-gauche conformation in αγ-polypeptides to fold into C═O(i)···H─N(i+3) and C═O(i)···H─N(i−1) H-bonded C_{12}/C_{10} folded structure.[9] A new rigid aromatic thiazole-based γ-amino acid based oligomers were synthesized to construct highly stable C_9 folded structure both in organic and aqueous media.[10] Extensive study has been done on achiral β,β-disubstituted γ-amino acid gabapentin based peptides that showed a tendency to form different C_7 to C_{14} hydrogen-bonded folded structures.[11] A chiral α,γ cyclized rigid γ-building block has been utilized to construct several cyclic oligomers.[12] Surprisingly, these cyclic residues adopt anti-conformation and hierarchically form higher order self-assembled peptide nanotubes (SPN) and peptide ion channels rather than forming intramolecular H-bonded turns.

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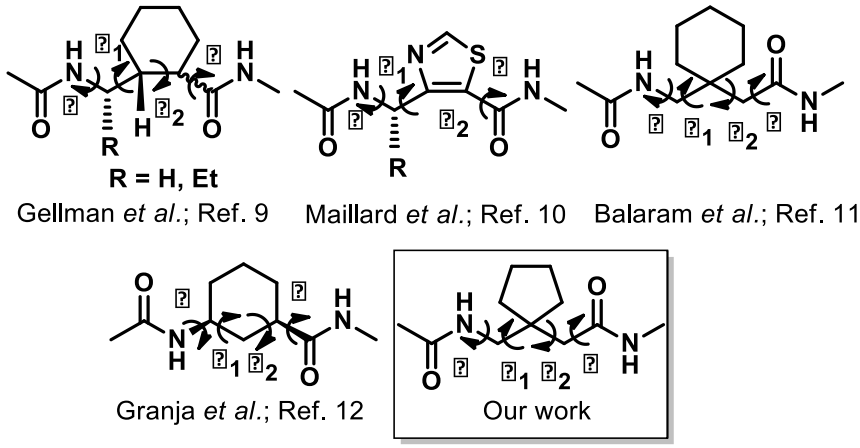

Fig. 1 Chemical structures of various backbone constrained γ-amino acids with backbone torsion angles parameters.

Molecular self-assembly plays a pivotal role to construct complex three-dimensional structures from monomeric bio-molecules.[13] In fact, functional properties of materials are concomitant to their structural ingenuity of self-assembling entities. The nanostructured assemblies have demonstrated a wide range of applications including gas storage, catalysis, antimicrobial, drug delivery.[14-16] Thus, there is an increasing demand for the development of synthetic/ non-protein amino acids based functional peptide materials to execute unique features and potential applications in various disciplines.[17] Over the past few years, we have designed and explored stimuli-responsive self-assembled peptide nanostructures for potential applications in oil spill recovery, templates for the synthesis and catalysis of nanoparticles, development of native chemical ligation strategies and dynamic combinatorial libraries, tissue engineering, and nanoelectronics.[18] Recently, we have reported structural and morphological investigation on Gpn-based hybrid tetrapeptides (Boc-Gpn-Aib-Aaa-Aib-OMe; Gpn = gabapentin, Aaa = Phe/Leu/Tyr), which adopted C_{12}/C_{10} H-bonded dual folded structures and showed diverse supramolecular propensities both in solid and solution states.[18a] To study the role of side chain of γ-amino acid on structural and morphological propensities of hybrid tetrapeptides, one of our major objective was to replace six-membered cyclic ring at β-position (Gpn) with five membered

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cyclic ring at β-position (Gbn). In this study, our objectives include (i) development of a synthetic route to access a building block 1-(aminomethyl)cyclopentylacetic acid hydrochloride (gababutin; abbreviated as Gbn), (ii) to synthesize a series of Gbn incorporated hybrid peptides including Boc-Gbn-Aib-Aaa-Aib-OMe (where Aaa = Phe(F) for peptide **1**, Leu(L) for peptide **2** and Tyr(Y) for peptide **3**) by varying at side chain of third amino acid residue, (iii) to explore the structural aspects of these hybrid peptides **1**, **2** and **3** by means of switch over at the third amino acid position both in crystal and solution states (Scheme 1) and (iv) to investigate nanostructural morphological topographies of peptides in various solvents. In this work, we report the synthesis, structural studies and diverse supramolecular propensities of gababutin based hybrid peptides. A C_{12}/C_{10} hydrogen-bonded double turn folded conformation, formation of self-assembled supramolecular organic frameworks and self-assembled morphological diversity are also reported.

Results and Discussion

To investigate the role of five membered cyclic ring at β-position of γ-amino acid (Gbn) in conformational and morphological propensities of hybrid tetrapeptides, a series of tetrapeptides Boc-Gbn-Aib-Phe-Aib-OMe (**1**), Boc-Gbn-Aib-Leu-Aib-OMe (**2**), Boc-Gbn-Aib-Tyr-Aib-OMe (**3**) were synthesized (Scheme 1). All the tetrapeptides were synthesized by employing fragment condensation solution-phase strategy. A facile and efficient synthetic route was optimized to prepare Gbn (Scheme 1) as a foldamer building block.[19] α,β-Unsaturated ester **5** was easily accomplished by employing a mild base (K_2CO_3) mediated Horner-Emmons modification from cyclopentanone **4** with triethyl phosphonoacetate in THF solvent.[20] Subsequently, compound **5** was subjected to Na_2CO_3 mediated Michael addition at 100-105 °C which yielded compound **6** with good yield in DMSO solvent.[19,21] Hydrogenation of nitro functionality of compound **6** by

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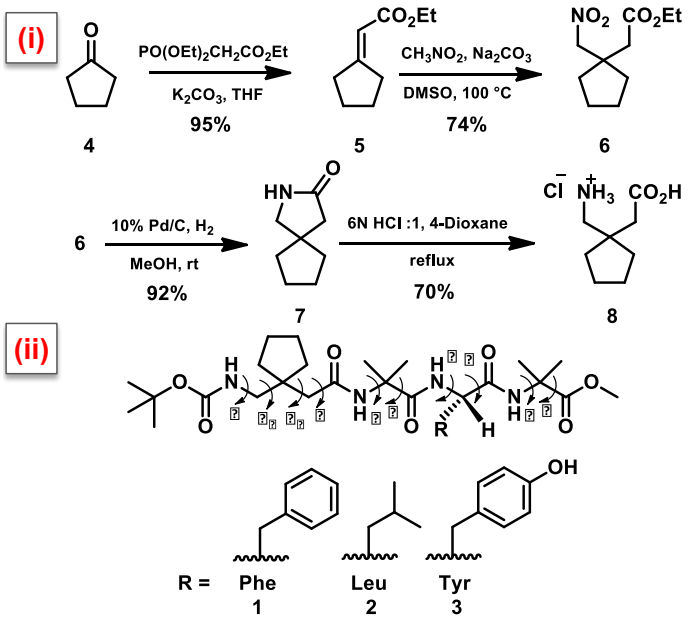
activated Pd/C and hydrogen gas affords lactam **7**, which is a cyclized form of Gbn.[21] Eventually, acid hydrolysis (6N HCl) of compound **7** gives the precursor amino acid **8** Gbn.HCl. The precursor **8** was used as a synthetic foldameric unit to construct terminally protected peptide scaffolds **1**, **2** and **3** (Scheme S1†).



Scheme 1. (i) Synthetic outline of Gbn.HCl precursor. (ii) Chemical structures of peptide **1**, peptide **2**, peptide **3** with backbone torsion angle parameters.

Solution state conformations of peptides

NMR studies of peptides **1-3** were performed to elucidate the peptide conformation in $CDCl_3$ at 298 K. The ROESY spectra (Fig. 2, S1 and S2) display a set of typical strong and medium intra and inter residual NOE correlations which draw a doubly folded stable structure in solution. Peptides **1**, **2** and **3** show characteristic $d_{NN[(i)\leftrightarrow(i+1)]}$ NOEs (between the amide NHs of peptide residues) and $d_{\alpha N[(i)\leftrightarrow(i+1)]}$ NOEs (between Aaa(3) $C^{\alpha}H$ ↔ Aib(4) NH) over the peptide backbone. More essentially, long-range NOEs along Gbn(1) $C^{\gamma}H$ ↔ Aaa(3) NH clearly explain the observation of doubly folded conformation in solution (C_{12}/C_{10} H-bonded fold). The inter-proton d_{NN} distances observed in the crystal state between $d_{NN[(i)\leftrightarrow(i+1)]}$ correlations and

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Gbn(1) $C^{\gamma}H \leftrightarrow$ Aaa(3) NH (Aaa = Phe; peptide **1**, Leu; peptide **2**, Tyr; peptide **3**) are in the limit of NOE range, which supports the above conformation (Fig. S1-S8).[7a,9] The strength of H-bonding interactions and relative solvent-shielded/exposed nature of the amide protons were investigated by DMSO-d_6 titration and variable temperature experiments in $CDCl_3$ (Fig. 2, S9-S11). All the NHs except Gbn(1) NH display negligible shift, signifying their engagement in intramolecular H-bonding (Table S1-S3) interactions.[7a,f] The variable temperature NMR studies further support the involvement of intramolecular H-bonding showing coefficient values $\Delta\delta/\Delta T$ > -4 ppb/K for NH of Aib(2) and $\Delta\delta/\Delta T$ > -3 ppb/K for NH and $C^{\alpha}H$ of Aaa(3). Thus, the observed NMR results suggest a dual folded turn structure of peptides **1-3** in solution.

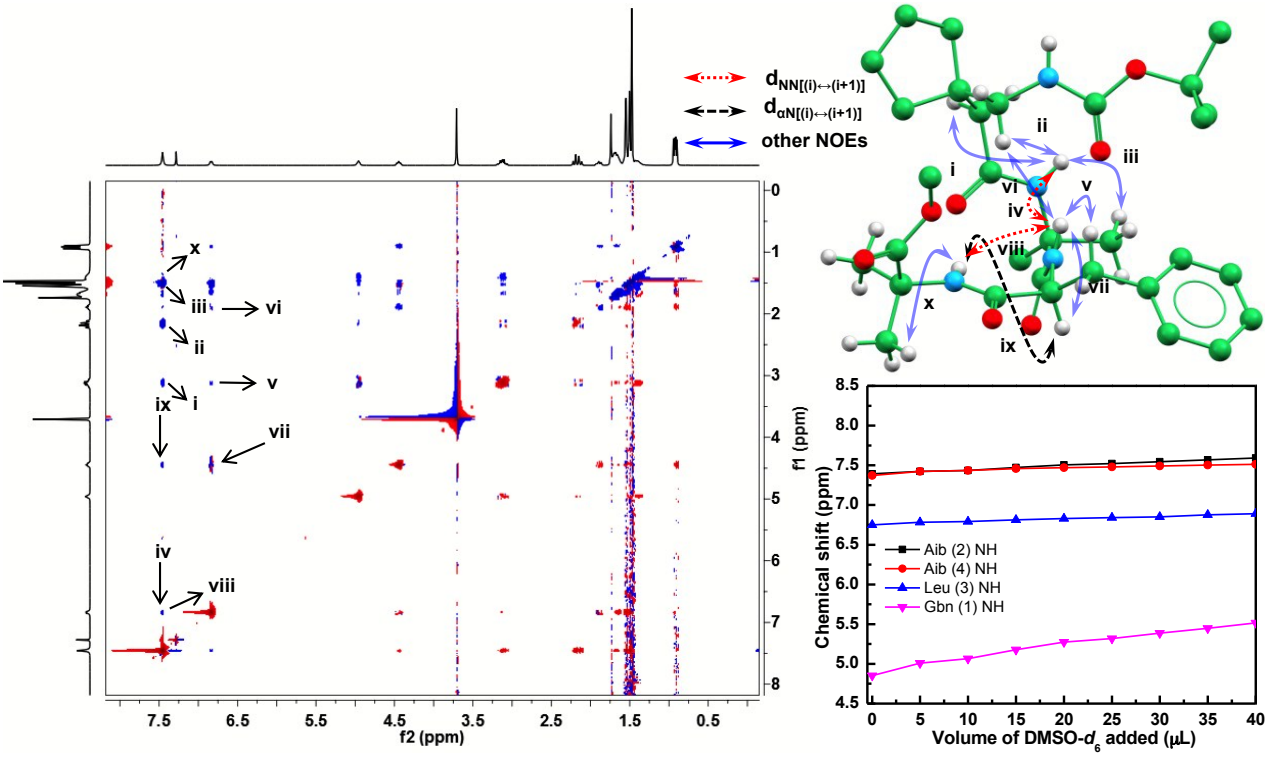

Fig. 2 ^{1}H-^{1}H ROESY spectrum of peptide **1** (400 MHz, $CDCl_3$ at 298 K, mixing time = 200 ms), showing several representative NOEs over the peptide backbone, suggesting a double turn conformation. DMSO-d_6 solvent titrations plot for peptide **1** in $CDCl_3$ supports the presence of hydrogen-bonded folded structure.

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Crystal state structural analysis of peptide motifs

Local accessible conformations (C^{γ}—C^{β} (θ_1) and C^{β}—C^{α} (θ_2)) of Gbn residue are restricted due to geminal substituents at central β-carbon atom. Thus, Gbn based hybrid peptides **1-3** are expected to display gauche-gauche conformations of C^{γ}—C^{β} and C^{β}—C^{α} ($\theta_1 \approx \theta_2 \approx \pm 60°$). Single crystal X-ray diffraction studies (Table S4) reveal that all tetrapeptides **1**, **2** and **3** adopt C_{12}/C_{10} helical double turn conformation with two 1←4 type successive intramolecular H-bonds (Fig. 3). The inter-residual intramolecular hydrogen-bonding pattern for C_{12} and C_{10} are arranged as C═O(i)···H─N(i+3).

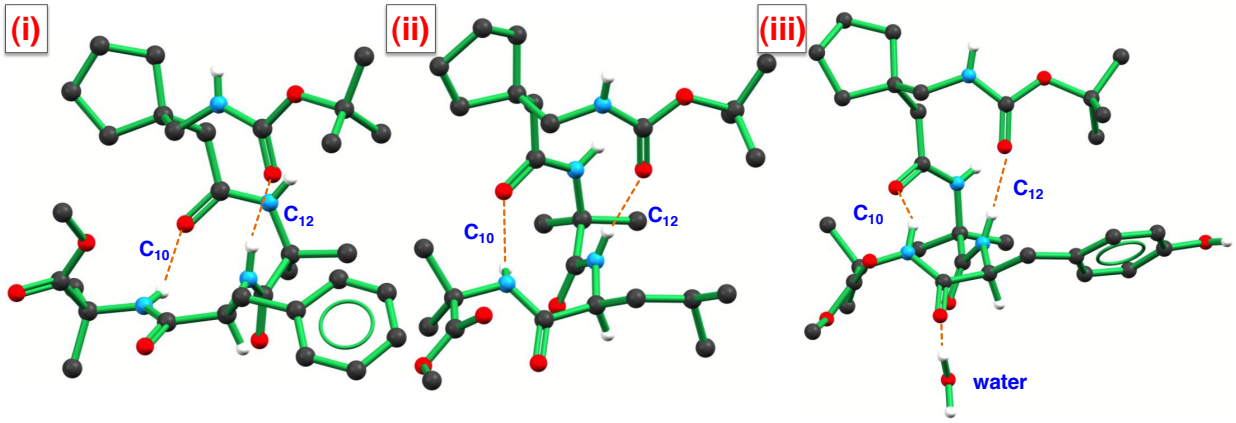

Fig. 3 Molecular conformations observed in crystal of (i) peptide **1**, (ii) peptide **2** and (iii) peptide **3** displaying C_{12}/C_{10} hydrogen-bonded double turn conformation and hydrogen atoms are removed for clarity (except heteroatom and chiral centre attached). Hydrogen bonds are shown in dotted line.

Despite the third amino acid residue varied in reporting tetrapeptide sequences, all three peptides (**1-3**) fold into C_{12}/C_{10} helical double turn conformation across γααα backbone in the crystal state (Fig. S12-S14). A small switch of the side chain of gamma-amino acid residue from six member ring (in gabapentin-based peptides) to five member ring in all reported gababutin-based tetrapeptides (**1-3**), peptides **1-3** display a similar type of conformations (C_{12}/C_{10} double turn) and remarkably result in stable double turn signatures. The molecular conformations and the hydrogen bonding patterns are moreover similar to our previously reported Gpn-tetrapeptides.[18a]

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An unusual 12-membered 1→4 type hydrogen-bonding interaction (Table S5) is formed between C═O (Boc, i) and H-N (3, i+3) of Aaa (Aaa = Phe for peptide **1**, Aaa = Leu for peptide **2** and Aaa = Tyr for peptide **3**). The relevant torsion angles about C^{γ}─C^{β} (θ_1) and C^{β}─C^{α} (θ_2) bonds (Table S6) of Gbn residue in peptides **1-3** are found to be almost ±60° (gauche-gauche conformations). These associated torsions of Gbn residues (in peptides **1-3**) are comparatively overlapped with reported Gpn-based peptides. Moreover, Gbn residues adopt more-rigid conformations (Table S7). Thus, gem dialkyl substitution at C^{β} position of Gbn confines the allowed conformations about C^{γ}─C^{β} (θ_1) and C^{β}─C^{α} (θ_2) bonds to restrict into gauche-gauche conformations which induce the formation of C_{12} hydrogen-bonded turn. Aib(2) [$\phi \cong$ 48-60°, $\psi \cong$ 27-39°] residues in peptides **1-3** adopt a helical propensity, however Aib(4) [$\phi \cong$ 41-60°, $\psi \cong$ 141-146°] residues adopt a semi extended conformation.[11]

A C_{10} hydrogen-bonded β-turn is also observed next to the C_{12} hydrogen-bonded turn in peptides **1-3**, which is originated due to Gbn(1)C═O···H─NAib(4) interaction across the ααα segment (Table S5). A closer inspection of torsion angles of peptides **1-3** demonstrates that molecules A and B of peptide **1** form a Type I β-turn conformation. In peptide **2**, molecules A, C and B, D form Type I β-turn and Type III′ β-turn respectively. Moreover, molecules A and B of peptide **3** feature a Type III and Type III′ β-turn conformation respectively.[18a] The cyclopentane ring of peptides **1-3** adopts an envelope conformation and the amino methyl and carboxyl methyl backbones found to be orientated with an angle of 110.02°. More importantly, the average interior angle for the ring about $_{ring}C^{1}$─C^{β}─$C^{4}{}_{ring}$ is found to 102.247° which marginally deviated from the average interior angle of Gpn residues (Fig. S15). Peptides **1-3** also exhibit well-defined diverse supramolecular organic frameworks (Fig. 4-5 and Table 1).

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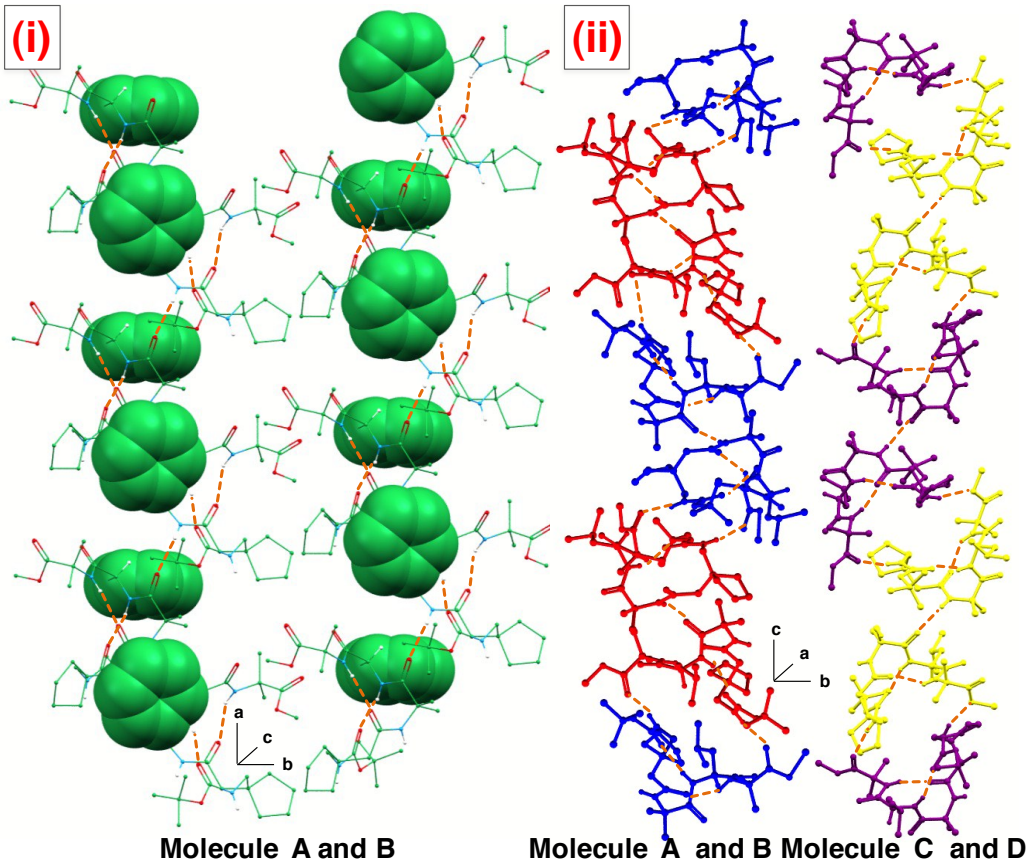

Fig. 4 The packing diagram and supramolecular helical view of peptides **1** and **2** in the crystal structure. (i) Molecules A and B of peptide **1** are aligned and stacked with one on top of the other to form supramolecular helix. (ii) Supramolecular helices resulted from self-association of molecules A (blue) and B (red) and molecules C (purple) and D (yellow). Hydrogen atoms are removed for clarity (except heteroatom and chiral centre attached). Hydrogen bonds are shown as dotted lines.

Peptide **3** is crystallized with two individual molecules (A and B) along with two water molecules in the ASU. Close investigation of supramolecular packing of peptide **3** in crystal state discloses that the peptide subunits along with water molecules are properly aligned and organized to form interesting higher-order supramolecular architectures using various non-covalent interactions.

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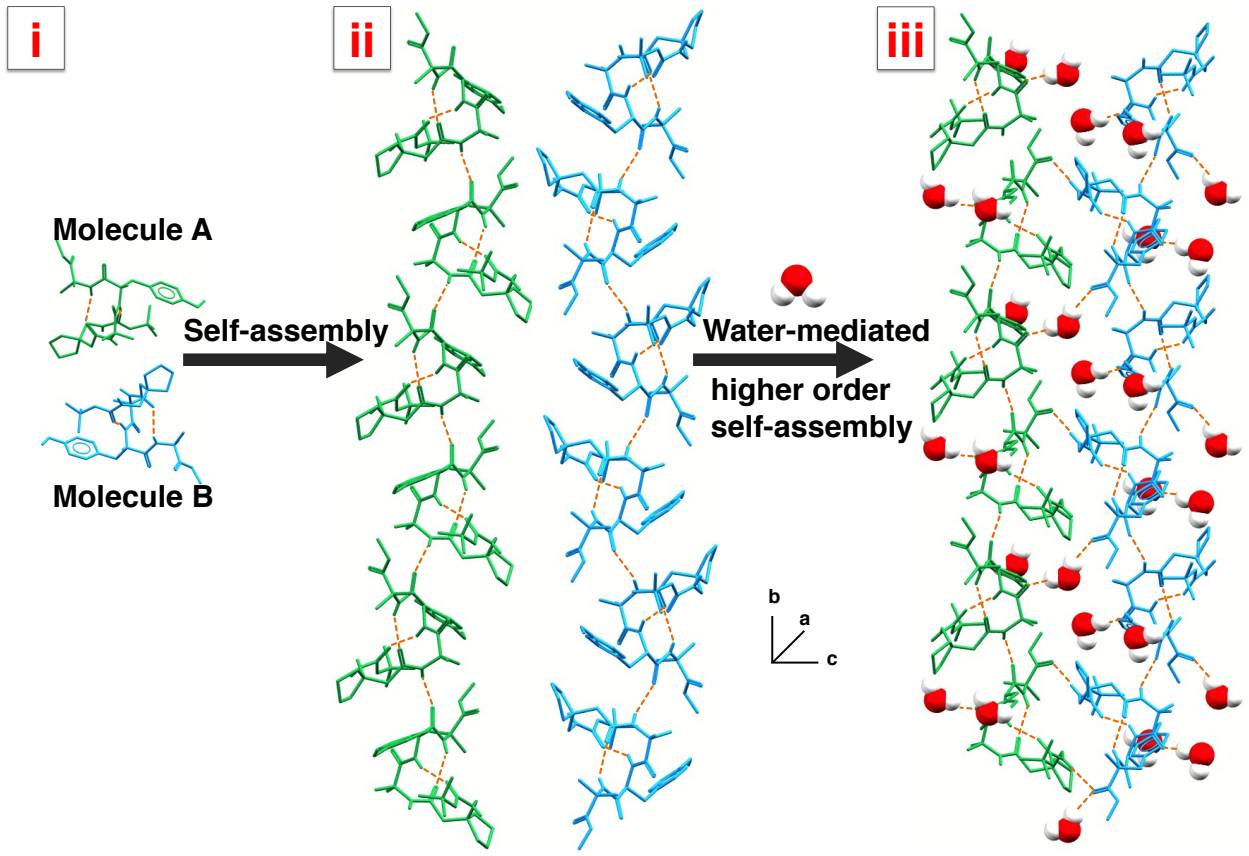

Fig. 5 A higher order-packing diagram of peptide **3** showing formation of supramolecular architectures and the role of the water molecules (red ball-stick representation). (i) Individual linear-association of molecules A (green) and B (blue) results to (ii) supramolecular helices. (iii) Supramolecular helix-helix association into higher order supramolecular architectures with the help of water molecules. Hydrogen atoms are removed for clarity (except heteroatom and chiral centre attached). Hydrogen bonds are shown as dotted lines.

Table 1 List of various hybrid peptides and their supramolecular assemblies in crystal state

S. No.	Compound	Molecular Formulae	Crystal state Conforma-tion	Supramolecular Assembly	Axis[a]	Ref
1	Boc-Gbn-Aib-Phe-Aib-OMe **1**	$C_{31}H_{48}N_4O_7$	C_{12}/C_{10} dual turn	supramolecular single helix	a	Present study
2	Boc-Gbn-Aib-Leu-Aib-OMe **2**	$C_{28}H_{50}N_4O_7$	C_{12}/C_{10} dual turn	supramolecular double helix	c	
3	Boc-Gbn-Aib-Tyr-Aib-OMe **3**	$C_{31}H_{48}N_4O_8$	C_{12}/C_{10} dual turn	solvent mediated supramolecular higher order helices	b	
4	Boc-Gpn-Aib-Phe-Aib-OMe	$C_{32}H_{50}N_4O_7$	C_{12}/C_{10} dual turn	supramolecular helix- helix higher order assembly	b & a	Our previous work [18a]
5	Boc-Gpn-Aib-Leu-Aib-OMe	$C_{29}H_{52}N_4O_7$	C_{12}/C_{10} dual turn	supramolecular single helix	b	
6	Boc-Gpn-Aib-Tyr-Aib-OMe	$C_{32}H_{50}N_4O_8.H_2O$	C_{12}/C_{10} dual turn	solvent mediated supramolecular double helices	b	

[a]axis through which a supramolecular helix formed

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Fig. 5 clearly demonstrates the non-covalent participation of molecule A or B individually via b-axis, of those further stack one on top of the other using intermolecular H-bonds to form supramolecular helical arrays. Moreover, the individual supramolecular helical arrays are connected to form highly packed higher-order supramolecular assembly by using intervening bridged water molecules. Phenolic O─H group of Tyr(3) residue is hydrated with bridged water molecule *via* (water) O···H─O Tyr(3) interaction. This side chain phenolic (O─H) group plays a vital role in the formation of supramolecular arrangement among peptide subunits and water molecules. These supramolecular helical arrangements by peptides **1**, **2** and **3** are formed along crystallographic a-, c- and b-axis respectively. Overall, these higher order diverse supramolecular architectures are formed as a result of the side chain orientations and variable third amino acid residue.[18a,22]

Morphological Features

Tuning the size and shape of the stimuli responsive self-assembled nano/microarchitectures are vital which could be used for a specific application. To know the morphological insights of peptides **1**, **2** and **3** in different solvents, scanning electron microscopy (SEM) and atomic force microscopy (AFM) were performed (Fig. 6-7 and Table 2). Peptides **1-3** show solvent assisted diverse self-assembled morphological structures.[23-26] Evidently, we found that peptides **1-3** produced relatively different morphological features in comparison to their Gpn-based tetrapeptides (Table S8).[18a] SEM image (Fig. 6(i)) of peptide **1** in methanol : water (c = 3.0 mmol L^{-1}) demonstrates the formation of microrods. These microrods are grown from the origin point with width ranging from 0.5 μm to 1 μm which are several micrometers in length. A highly dense bristles type nanofibrous morphology are observed for peptide **2** in methanol : water

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solution (c = 3.0 mmol L^{-1}) (Fig. 6(ii)). The average width of nanofiber structures is found about 15 nm. Peptide **3** in methanol : water self-assembles to render a ribbon type network.[26a-b] These ribbons are interwoven each other with an average width of 300 nm and several micrometers long (Fig. 6(iii)). On the other hand, peptides **1**, **2** and **3** in THF : water (c = 3.0 mmol L^{-1}) self-assemble into diverse micro/nano-architectures as compare to methanol : water system.[25e,26b] As shown in SEM image (Fig. 6(iv)), aligned thick fibrillar structures with diameter ranging from 200 to 1200 nm and length in several micrometers are observed for self-assembled peptide **1** in THF : water solution.

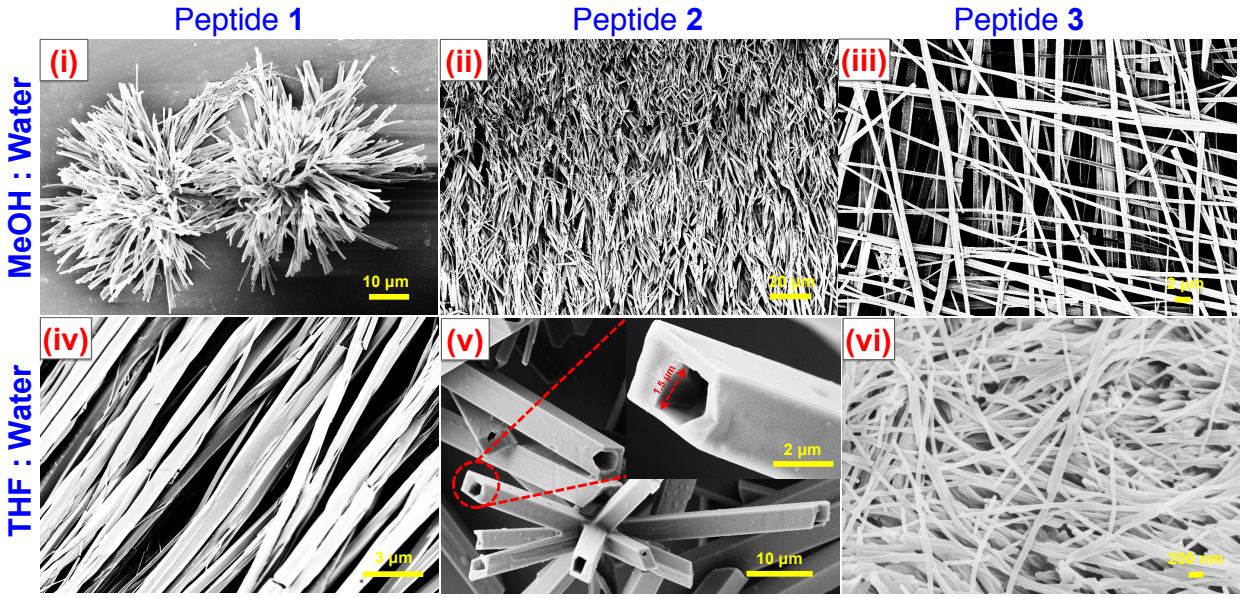

Fig. 6 FE-SEM images showing the evaporation induced microscopic features and solvent-assisted morphological diversity of peptide **1**, peptide **2** and peptide **3** in methanol : water (top row) and in THF : water (bottom row) 1:1 v/v, *c* = 3.0 mmol L^{-1}).

Peptide **2** displays microtubular structures in THF: water. These microtubes exhibit pentagonal cross-sectional shape with a hollow cavity (Fig. 6(v), S16-S17†). Precipitation mass obtained from self-assembly of peptide **3** in THF : water displays dense entangled nanotapes (Fig. 6(vi)) with an average width of 40 nm and several micrometers in length. Atomic force microscopy measurements also reveal the formation of nanostructural features

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(THF : water) which are similar with SEM results (Fig. 7). AFM images of self-assembled peptide **1** (Fig. 7(i)) display aligned flat fiber aggregates with an average height of 72 nm. Fig. 7(ii) shows crystalline type of networks which is formed by self-assembled peptide **2**. These self-assembled structural entities have an average width of 42 nm. AFM analysis of self-assembled peptide **3** exhibits bunch of thin nanotapes. AFM images clearly show nanotape morphology which ensues from the hierarchical assembly of thin fibrils (Fig. 7(iii)). The microscopic analysis demonstrates that the hydrophobicity of the amino acids in peptides as well as solvent polarity play a vital role in supramolecular morphological diversity.[26a-b]

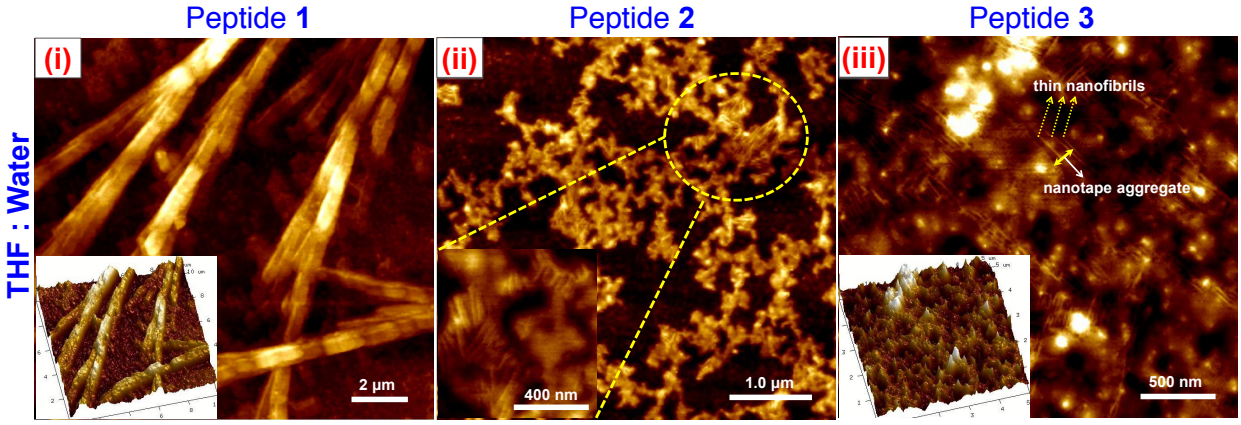

Fig. 7 AFM images depicting the microscopic features of peptides **1**, **2** and **3** in THF : water (1:1 v/v, c = 3.0 mmol L^{-1}). Insets indicating the 3D image of the organization of fiber textures and aggregated nanostructures.

Table 2 Self-assembled morphological diversity of peptides **1-3** in various solvent mixtures[a]

	Self-assembled morphology	
Solvent system	Methanol : water	THF : water
Peptide **1**	Microrods	Aligned thick fibrillar structures
Peptide **2**	Dense bristles type nanofibrous	Rectangular cross-sectioned microtubes
Peptide **3**	Interwoven ribbons	Entangled nanotapes

[a] concentration of peptide solution c = 3.0 mmol L^{-1}

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Conclusion

We have described synthetic route, structural aspects of gababutin precursor and gababutin incorporated hybrid tetrapeptides. The extensive 2D NMR studies revealed the existence of C_{12}/C_{10} dual folded conformation in $CDCl_3$. In crystal state, peptides **1**, **2** and **3** adopted double turn conformations through C_{12} and C_{10} intramolecular hydrogen-bonds, regardless of their third residue. Gbn residue in all the peptides accommodates nicely ±gauche conformations about C^{γ}—C^{β} (θ_1) and C^{β}—C^{α} ($\theta 2$) bonds with backbone parameters of ±60° which are closely overlapped with existing backbone parameters of Gpn residues. Gbn residues formed a more-rigid conformation than Gpn analogue residues due to rigid interior angle. The interior angle of Gbn ring 102.247° fairly deviated from interior angle of Gpn ring. On consideration of these data, we have observed that peptides **1-3** (Gbn-based) showed structural similarity in folding patterns with Gpn based peptides. Remarkably, gababutin-based peptides (**1**-**3**) display relatively different supramolecular packing patterns and morphologies in comparison to the results obtained for gabapentin-based peptides. Several morphological investigations demonstrated solvent dependent evaporation induced morphological diversity of peptides **1**-**3** at ambient conditions. Overall, our study demonstrates the impact of flexible side chain orientations at the third position and the rigidity of Gbn residue in folded structures of reported peptide sequences which could greatly affect their discreet supramolecular structural and functional attributes. It is expected that these interesting gababutin-based peptide scaffolds and corresponding nano/microstructures may find desirable applications in biomedical and material sciences.

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†Electronic supplementary information (ESI) available: ESI Figures, Tables, Crystal and diffraction parameters, microscopic and optical images, *NMR, and HRMS mass spectra of all new compounds. X-ray data for peptides **1-3** have been deposited with the Cambridge Crystallographic Data Centre. CCDC* 1542080 (peptide **1**), 1542088 (peptide **2**), 1542089 and (peptide **3**). *For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x*

Notes and References

1. C Foldamers: Structure, Properties and Applications (Eds. S. Hecht, I. Huc) *Wiley-VCH, Weinheim*, 2007.
2. (a) C. Toniolo, M. Crisma, A. Moretto, C. Peggion, F. Formaggio, C. Alemán, C. Cativiela, C. Ramakrishnan and P. Balaram, *Chem. Eur. J.*, 2015, **21**, 13866; (b) R. V. Nair, S. B. Baravkar, T. S. Ingole and G. J. Sanjayan, *Chem. Commun.*, 2014, **50**, 13874.
3. (a) C. Cabrele, T. A. Martinek, O. Reiser and Ł. Berlicki, *J. Med. Chem.*, 2014, **57**, 9718; (b) B. Legrand, C. André, L. Moulat, C. Didierjean, P. Hermet, J.-L. Bantignies, J. Martinez, M. Amblard and M. Calmès, *Chem. Eur. J.*, 2016, **22**, 11986; (c) C. M. Grison, J. A. Miles, S. Robin, A. J. Wilson and D. J. Aitken, *Angew. Chem., Int. Ed.*, 2016, **55**, 11096.
4. (a) W. S. Horne and S. H. Gellman, *Acc. Chem. Res.*, 2008, **41**, 1399; (b) C. M. Goodman, S. Choi, S. Shandler and W. F. DeGrado, *Nat. Chem. Bio.*, 2007, **3**, 252.

View Article Online
DOI: 10.1039/C8OB00035B

5. (a) Y. Shi, P. Teng, P. Sang, F. She, L. Wei and J. Cai, *Acc. Chem. Res*., 2016, **49**, 428; (b) T. A. Martinek and F. Fulop, *Chem. Soc. Rev.*, 2012, **41**, 687; (c) C. S. Hartley, *Acc. Chem. Res.*, 2016, **49,** 646; (d) G. Guichard and I. Huc, *Chem. Commun.*, 2011, **47**, 5933.

6. (a) I. Avan, C. D. Hall and A. R. Katritzky, *Chem. Soc. Rev*., 2014, **43**, 3575; (b) E. Rémond, C. Martin, J. Martinez and F. Cavelier, *Chem. Rev*., 2016, **116**, 11654; (c) A. F. M. Noisier and M. A. Brimble, *Chem. Rev*., 2014, **114**, 8775; (d) V. Martin, B. Legrand, L. L. Vezenkov, M. Berthet, G. Subra, M. Calmès, J.-L. Bantignies, J. Martinez and M. Amblard, *Angew. Chem., Int. Ed*., 2015, **54**, 13966.

7. (a) B. F. Fisher, L. Guo, B. S. Dolinar, I. A. Guzei and S. H. Gellman, *J. Am. Chem. Soc.*, 2015, **137**, 6484; (b) N. Chandramouli, Y. Ferrand, G. Lautrette, B. Kauffmann, C. D. Mackereth, M. Laguerre, D. Dubreuil and I. Huc, *Nat. Chem*., 2015, **7**, 334; (c) J. Fremaux, L. Mauran, K. Pulka-Ziach, B. Kauffmann, B. Odaert and G. Guichard, *Angew. Chem., Int. Ed.*, 2015, **54**, 9816; (d) J. D. Winkler, E. L. Piatnitski, J. Mehlmann, J. Kasparec and P. H. Axelsen, *Angew. Chem., Int. Ed*., 2001, **40**, 743; (e) C. M. Grison, S. Robin and D. J. Aitken, *Chem. Commun*., 2015, **51**, 16233; (f) S. Chandrasekhar, M. S. Reddy, B. N. Babu, B. Jagadeesh, A. Prabhakar and B. Jagannadh, *J. Am. Chem. Soc*., 2005, **127**, 9664; (g) M. Ganesh Kumar, V. J. Thombare, M. M. Katariya, K. Veeresh, K. M. P. Raja and H. N. Gopi, *Angew. Chem. Int. Ed.*, 2016, **55,** 7847; (h) X.-G. Hu, A. Lawer, M. B. Peterson, H. Iranmanesh, G. E. Ball and L. Hunter, *Org. Lett.*, 2016, **18**, 662; (i) V. V. E. Ramesh, A. Roy, K. N. Vijayadas, A. M. Kendhale, P. Prabhakaran, R. Gonnade, V. G. Puranik and G. J. Sanjayan, *Org. Bio. Chem.,* 2011, **9**, 367; (j) L. Milli, M. Larocca,

View Article Online
DOI: 10.1039/C8OB00035B

M. Tedesco, N. Castellucci, E. Ghibaudi, A. Cornia, M. Calvaresi, F. Zerbetto and C. Tomasini, *J. Org. Chem.*, 2014, **79**, 5958; (k) M. Hosoya, Y. Otani, M. Kawahata, K. Yamaguchi and T. Ohwada, *J. Am. Chem. Soc*., 2010, **132**, 14780.

8. (a) Z. E. Reinerta and W. S. Horne, *Org. Biomol. Chem.*, 2014, **12**, 8796; (b) J. M. Rogers and H. Suga, *Org. Biomol. Chem.*, 2015, **13**, 9353; (c) A. Patgiri, S. T. Joy and P. S. Arora, *J. Am. Chem. Soc.*, 2012, **134**, 11495; (d) G. Lautrette, F. Touti, H. G. Lee, P. Dai and B. L. Pentelute, *J. Am. Chem. Soc.*, 2016, **138**, 8340.
9. M. W. Giuliano, S. J. Maynard, A. M. Almeida, L. Guo, I. A. Guzei, L. C. Spencer and S. H. Gellman, *J. Am. Chem. Soc.*, 2014, **136**, 15046.
10. L. Mathieu, B. Legrand, C. Deng, L. Vezenkov, E. Wenger, C. Didierjean, M. Amblard, M.-C. Averlant-Petit, N. Masurier, V. Lisowski, J. Martinez and L. T. Maillard, *Angew. Chem., Int. Ed*., 2013, **52**, 6006.
11. P. G. Vasudev, S. Chatterjee, N. Shamala and P. Balaram, *Acc. Chem. Res.*, 2009, **42**, 1628.
12. (a) M. Amorin, L. Castedo and J. R. Granja, *J. Am. Chem. Soc*., 2003, **125**, 2844; (b) R. J. Brea, , M. Amorin, L. Castedo and J. R. Granja, *Angew. Chem., Int. Ed*., 2005, **44**, 5710.
13. T. Aida, E. W. Meijer and S. I. Stupp, *Science*, 2012, **335**, 813.
14. (a) V. N. Yadav, A. Comotti, P. Sozzani, S. Bracco, T. Bonge-Hansen, M. Hennum and C. H. Görbitz, *Angew. Chem., Int. Ed*., 2015, **54**, 15684; (b) J. Rabone, Y.-F. Yue, S. Y. Chong, K. C. Stylianou, J. Bacsa, D. Bradshaw, G. R. Darling, N. G. Berry, Y. Z. Khimyak, A. Y. Ganin, P. Wiper, J. B. Claridge and M. J. Rosseinsky, *Science*, 2010, **329**, 1053; (c) G. Distefano, A. Comotti, S. Bracco, M. Beretta and P.

View Article Online
DOI: 10.1039/C8OB00035B

Sozzani, *Angew. Chem., Int. Ed.*, 2012, **51**, 9258; (d) A. Comotti, A. Fraccarollo, S. Bracco, M. Beretta, G. Distefano, M. Cossi, L. Marchese, C. Riccardi and P. Sozzani, *CrystEngComm,* 2013, **15**, 1503.

15. N. Huang, L. Zhai, D. E. Coupry, M. A. Addicoat, K. Okushita, K. Nishimura, T. Heine and D. Jiang, *Nat. Commun*., 2016, **7**, 12325.

16. (a) A. P. Katsoulidis, K. S. Park, D. Antypov, C. Marti-Gastaldo, G. J. Miller, J. E. Warren, C. M. Robertson, F. Blanc, G. R. Darling, N. G. Berry, J. A. Purton, D. J. Adams and M. J. Rosseinsky, *Angew. Chem., Int. Ed.*, 2014, **53**, 193; (b) Y. Ikezoe, J. Fang, T. L. Wasik, M. Shi, T. Uemura, S. Kitagawa and H. Matsui, *Nano Lett.*, 2015, **15**, 4019; (c) J. Bonnefoy, A. Legrand, E. A. Quadrelli, J. Canivet and D. Farrusseng, *J. Am. Chem. Soc.*, 2015, **137**, 9409; (d) B. Li, H.-M. Wen, Y. Cui, W. Zhou, G. Qian and B. Chen, *Adv. Mater*., 2016, **28**, 8819.

17. (a) J. S. Laursen, P. Harris, P. Fristrup and C. A. Olsen, *Nat. Commun*., 2015, **6**, 7013; (b) T. Yamashita, P. C. Knipe, N. Busschaert, S. Thompson and A. D. Hamilton, *Chem. Eur. J.*, 2015, **21**, 14699; (c) L. R. Whitby and D. L. Boger, *Acc. Chem. Res.*, 2012, **45**, 1698; (d) B. Yoo and K. Kirshenbaum, *Curr. Opin. Chem. Bio.*, 2008, **12**, 714.

18. (a) M. Konda, B. Kauffmann, D. B. Rasale and A. K. Das, *Org. Biomol. Chem.*, 2016, **14**, 4089; (b) M. Konda, I. Maity, D. B. Rasale and A. K. Das, *ChemPlusChem*, 2014, **79**, 1482; (c) D. B. Rasale, M. Konda, S. Biswas and A. K. Das, *Chem. -Asian J.*, 2016, **11**, 926; (d) D. B. Rasale, I. Maity, M. Konda and A. K. Das, *Chem. Commun*., 2013, **49**, 4815; (e) A. K. Das, I. Maity, H. S. Parmar, T. O.

View Article Online
DOI: 10.1039/C8OB00035B

McDonald and M. Konda, *Biomacromolecules*, 2015, **16**, 1157; (f) D. B. Rasale, I. Maity and A. K. Das, *Chem. Commun*., 2014, **50**, 8685.

19. D. C. Blakemore, J. S. Bryans, P. Carnell, N. E. A. Chessum, M. J. Field, N. Kinsella, J. K. Kinsora, S. A. Osborne and S. C. Williams, *Bioorganic Med. Chem. Lett.*, 2010, **20**, 362.
20. F. Bonadies, A. Cardilli, A. Lattanzi, L. R. Orelli and A. Scettri, *Tetrahedron Lett.*, 1994, **35**, 3383.
21. (a) M. Yoshida, E. Masaki, H. Ikehara and S. Hara, *Org. Biomol. Chem.* 2012, **10**, 5289; (b) H. Gotoh, H. Ishikawa and Y. Hayashi, *Org. Lett*. 2007, **9**, 5307.
22. (a) H. K. Ganguly, B. Majumder, S. Chattopadhyay, P. Chakrabarti and G. Basu, *J. Am. Chem. Soc*., 2012, **134**, 4661; (b) W. Liyanage and B. L. Nilsson, *Langmuir*, 2016, **32**, 787; (c) Y. Kee Kang and I. K. Yoo, *Biopolymers*, 2014, **101**, 1077; (d) M. J. Stone and R. J. Payne, *Acc. Chem. Res*., 2015, **48**, 2251; (e) J. Shen, C. Ren and H. Zeng, *Chem. Commun*., 2016, **52**, 10361.
23. (a) U. Lewandowska, W. Zajaczkowski, L. Chen, F. Bouilliere, D. Wang, K. Koynov, W. Pisula, K. Müllen and H. Wennemers, *Angew. Chem., Int. Ed.*, 2014, **53,** 12537; (b) E. Schwartz, S. Le Gac, J. J. L. M. Cornelissen, R. J. M. Nolte and A. E. Rowan, *Chem. Soc. Rev.*, 2010, **39,** 1576.
24. (a) G. M. Peters and J. T. Davis, *Chem. Soc. Rev.*, 2016, **45,** 3188; (b) M. Delbianco, P. Bharate, S. Varela-Aramburu and P. H. Seeberger, *Chem. Rev.*, 2016, **116**, 1693; (c) T. G. Barclay, K. Constantopoulos and J. Matisons, *Chem. Rev.*, 2014, **114**, 10217; (d) R. V. Ulijn and A. M. Smith, *Chem. Soc. Rev*., 2008, **37**, 664.

View Article Online
DOI: 10.1039/C8OB00035B

25. (a) J. B. Bale, S. Gonen, Y. Liu, W. Sheffler, D. Ellis, C. Thomas, D. Cascio, T. O. Yeates, T. Gonen, N. P. King and D. Baker, *Science*, 2016, **353**, 389; (b) N. Rodriguez-Vazquez, R. Garcia-Fandino, M. Amorin and J. R. Granja, *Chem. Sci.*, 2016, **7**, 183; (c) J. Kim, S. Kwon, S. H. Kim, C. K. Lee, J. H. Lee, S. J. Cho, H. S. Lee and H. Ihee, *J. Am. Chem. Soc.*, 2012, **134**, 20573; (d) R. K. Spencer, A. G. Kreutzer, P. J. Salveson, H. Li and J. S. Nowick, *J. Am. Chem. Soc.*, 2015, **137**, 6304; (e) Y. Huo and H. Zeng, *Acc. Chem. Res*., 2016, **49**, 922.

26. (a) X. Yan, P. Zhu and J. Li, *Chem. Soc. Rev*., 2010, **39**, 1877; (b) L. Zhang, X. Wang, T. Wang and M. Liu, *Small*, 2015, **11**, 1025; (c) B. D. Wall, Y. Zhou, S. Mei, H. A. M. Ardona, A. L. Ferguson and J. D. Tovar, *Langmuir*, 2014, **30**, 11375; (d) J. D. Brodin, S. J. Smith, J. R. Carr and F. A. Tezcan, *J. Am. Chem. Soc*., 2015, **137**, 10468; (e) A. Bonetti, S. Pellegrino, P. Das, S. Yuran, R. Bucci, N. Ferri, F. Meneghetti, C. Castellano, M. Reches and M. L. Gelmi, *Org. Lett.*, 2015, **17**, 4468; (f) R. D. Gopalan, M. P. Del Borgo, A. I. Mechler, P. Perlmutter and M.-I. Aguilar, *Chem. Biol.*, 2015, **22**, 1417.