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Sulfonyl-γ-AAs as Turn Templates Inducing β-Sheet Conformation in Macrocyclic Peptides

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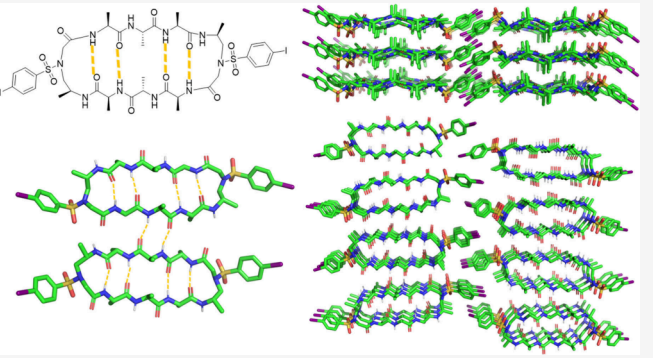
ABSTRACT: β-hairpins are minimal antiparallel β-sheets and essential protein secondary structures, critical for diverse biological functions, yet designing synthetic β-sheet mimics remains challenging due to sequence-dependent folding. Here, we report sulfonyl-γ-AAs (γ-substituted-N-sulfonyl-N-aminoethyl amino acids) as artificial β-turn inducers that drive stable β-sheet conformations in macrocyclic peptides, leading to a class of protein antiparallel β-sheet mimetics. Single-crystal X-ray diffraction of sulfonyl-γ-AAs B1 and a macrocyclic peptide BS-1 containing sulfonyl-γ-AA residues reveals that sulfonyl-γ-AAs adopt a β-turn-like conformation stabilized by both intramolecular hydrogen bonding and intrinsic curvature of the sulfonamido moiety, thereby facilitating the formation of a folded β-sheet structure with defined amino acid residues. To the best of our knowledge, this is also the first report of the crystallographic validation of a polyalanine β-sheet structure enforced by a β-turn mimic. Additionally, circular dichroism (CD) spectroscopy displayed characteristic minima between 208−214 nm in BS-6 to BS-9, consistent with robust β-sheet signatures. 2D-NMR studies revealed the well-folded solution structures consistent with X-ray crystal structures. These results establish sulfonyl-γ-AAs as a versatile class of β-turn templates that drive β-sheet formation, enabling the creation of novel macrocyclic antiparallel β-sheet mimics with broad potential in therapeutic development and biomaterials design.



INTRODUCTION

β-hairpins, characterized by two antiparallel β-strands connected by a short loop or turn, are fundamental protein structural motifs within proteins,[1] noted for their compact architecture and diverse functional roles in biological systems.[2,3] These motifs are stabilized by a network of hydrogen bonds between the backbone carbonyl and amide groups of adjacent strands, resulting in a generally planar conformation with a characteristic subtle twist that enhances both structural integrity and functional adaptability.[3] The loop region, typically comprising two to five amino acid residues, often adopts defined conformations such as type I or II β-turns, which are critical for hairpin folding dynamics and thermodynamic stability. The alternating orientation of side chains, projecting above and below the β-sheet plane, facilitates hydrophobic interactions within protein cores or polar contacts at solvent-exposed interfaces, thereby supporting functions such as molecular recognition and structural stabilization. β-hairpins serve as pivotal structural elements in a wide array of biological processes, underpinning their significance in both natural and engineered systems.[4] These motifs act as critical nucleation points for β-sheet formation in globular proteins such as immunoglobulins and enzymes, thereby stabilizing compact and functionally essential three-dimensional architectures that ensure structural robustness.[5] In molecular recognition, the loops of β-hairpins precisely orient catalytic or binding residues, as exemplified by histidine's role in mediating proton transfer in protease active sites or the specific interactions in antibody−antigen complexes.[6] Furthermore, β-hairpins orchestrate self-assembly in fibrous proteins, contributing to the formation of physiological structures like silk, as well as pathological amyloid fibrils implicated in neurodegenerative disorders,[7] including Alzheimer's, Parkinson's,[8] and Huntington's diseases.[9] Owing to their compactness and versatility, β-hairpins render themselves valuable scaffolds for investigating protein folding mechanisms and for designing synthetic β-turn-mimicking peptides, particularly macrocyclic peptides, where precise conformational control is essential for enhancing bioactivity and therapeutic potential.

Achieving β-sheet conformations necessitates meticulous control over the turn geometry, interstrand interactions, and external factors such as pH and ionic strength, which

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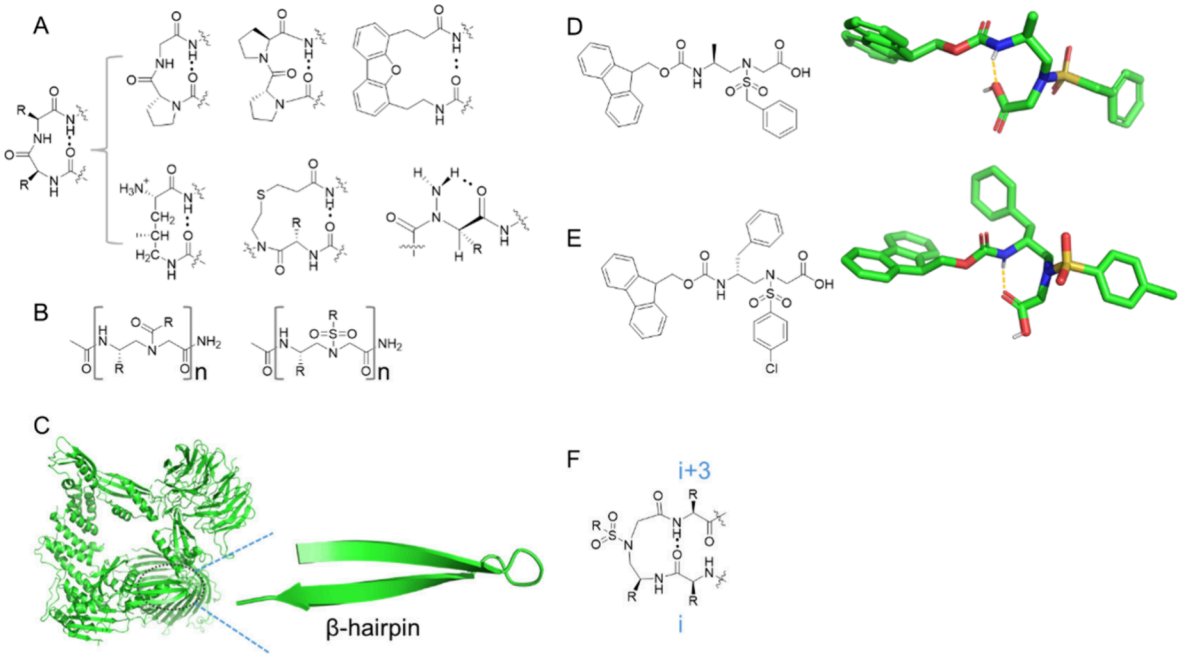

Figure 1. Various strategies for β-sheets mimics. A) The previous reported β-turn mimics, including examples of D-Pro-Gly, D-Pro-L-Pro, dibenzofuran, γ(R)-methyl-ornithine, HBS. B) The structure of γ-AApeptides and sulfonyl-γ-AApeptides. C) One of the natural membrane proteins and the β-hairpin composition (PDB: 7NRI). D) Chemical and X-ray crystal structure of Fmoc-(L)-alanine sulfonyl-γ-AA. E) Chemical and X-ray crystal structure of Fmoc-(D)-phenylalanine sulfonyl-γ-AA **B1** (CCDC: 2537404). F) Proposed β-turn conformation and hydrogen bonding model between i → i + 3 introduced by sulfonyl-γ-AAs.

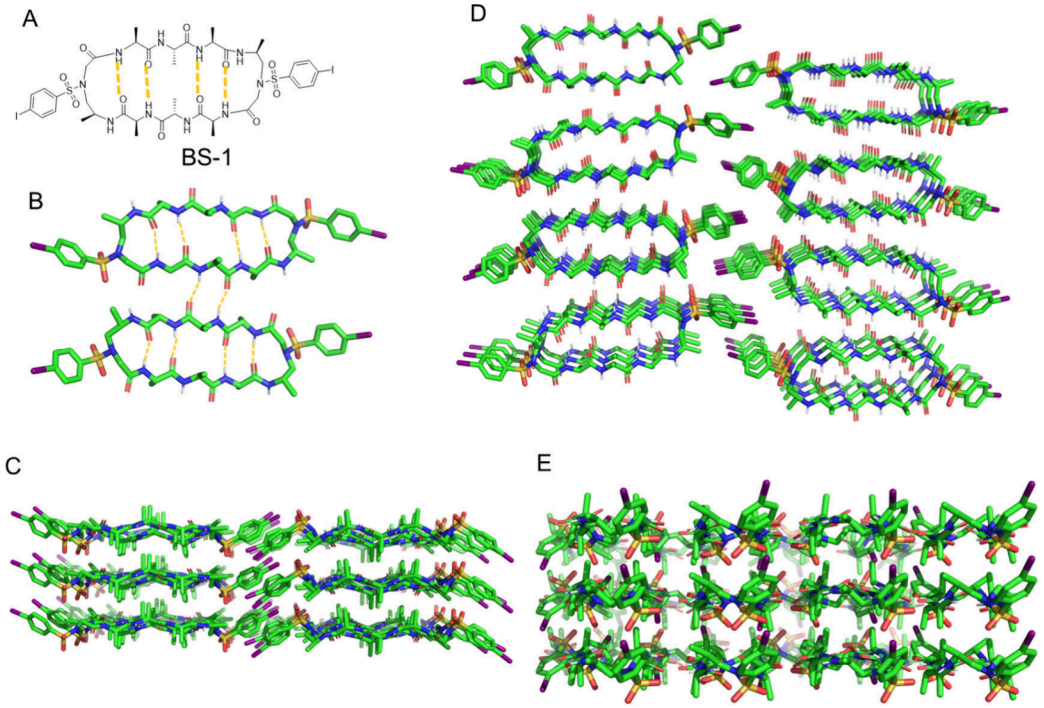

Figure 2. L-Sulfonyl-γ-AA-templated β-sheet crystal structure. A) The primary structure of **BS-1** (CCDC: 2536918). B) The view of the crystal structure of **BS-1** and the intra- and intermolecular hydrogen bond. C-E) Crystal packing of **BS-1** from the front, top, and side view.

collectively dictate folding propensity and stability.[10] To date, a number of turn-inducing linkers with lengths comparable to a dipeptide, such as D-Pro-Gly,[11] D-Pro-L-Pro,[12] dibenzofuran,[13] γ(R)-methyl-ornithine,[14] N-amination,[15] and HBS,[16] have been employed to design β-sheet mimics exhibiting therapeutic and material innovations (Figure 1A). These strategies enhance β-sheet stability by substituting the loop region with turn-inducing templates that enforce proximity, hydrogen bonding, and antiparallel alignment between β-strands, thereby stabilizing the desired conformation.[17,18] Despite their potential as β-sheet inducers, the design of stable β-sheets, particularly within macrocyclic peptides, still presents formidable challenges,[19] primarily due to the intricate dependence of folding on specific sequence compositions and environ-

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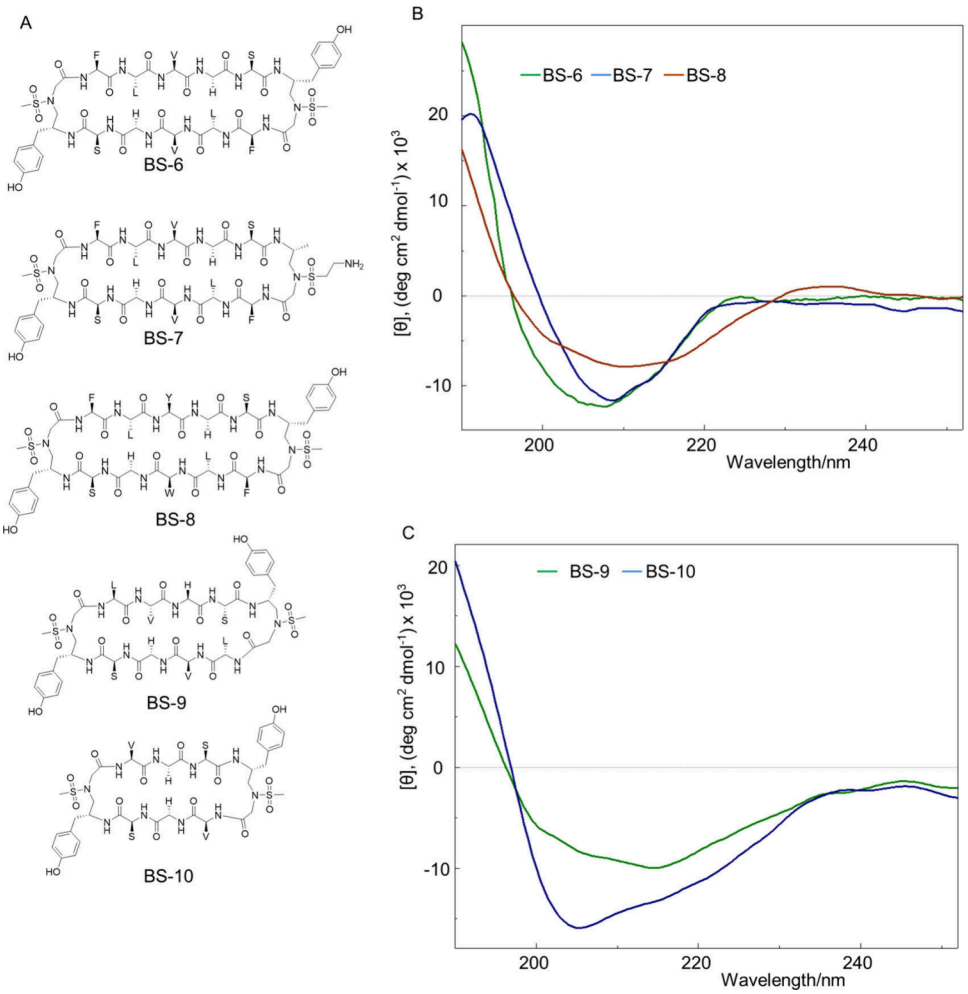

Figure 3. D-sulfonyl-γ-AA-templated β-sheets. A) The primary structure of **BS-6**, **BS-7**, **BS-8**, **BS-9**, and **BS-10**. B, C) The CD spectra of peptides mentioned above at 50 μM in 10 mM KF (pH 7.3) solution at 25 °C.

mental conditions.[20] Thus, we sought to explore the new molecular scaffold, aiming to provide new classes of β-turn mimics.

Our group has explored γ-AApeptides as versatile scaffolds for biomedical and materials science applications (Figure 1B).[21] As a subclass of γ-AApeptides,[22] sulfonyl-γ-AApeptides feature sulfonamido moieties that induce a curved backbone,[23] enabling well-defined three-dimensional folding structures (Figure 1B).[24] Each sulfonyl-γ-AA (N-sulfonyl-γ-N-aminoethyl amino acid) is comparable to two conventional amino acids, offering a compact yet tunable framework.[25] Inspired by established β-turn mimics (Figure 1A), we speculated that sulfonyl-γ-AAs could serve as novel β-turn inducers, attributable to the intrinsic curvature conferred by the sulfonamido moiety.[26] As an alternative scaffold to other moieties used to generate β-sheet mimics, sulfonyl-γ-AAs could offer additional diverse side-chain functionality when incorporated into macrocyclic peptides, simultaneously enabling β-turn formation and providing additional interactions with protein surfaces or a handling group for post modification. To this end, we synthesized a series of sulfonyl-γ-AA-templated macrocyclic β-sheets and used X-ray crystallography, NMR, and CD spectroscopy to assess their β-sheet conformation in solid state and in solution. Our findings establish sulfonyl-γ-AAs as robust β-turn mimics that induce β-sheet structures in macrocyclic peptides, highlighting their potential for therapeutic and material applications.

RESULTS

We previously reported the crystal structure of a L-sulfonyl-γ-AA (Figure 1D),[27] which adopts a folded turn conformation by a hydrogen bond between the C-terminal carboxyl C═O and the N-terminal NH, strongly supporting our design hypothesis. We thus posited that D-sulfonyl-γ-AAs may also be capable of acting as β-turn inducers by folding into a mirror-image conformation. Fortunately, our hypothesis was confirmed after we successfully determined the crystal structure of a D-sulfonyl-γ-AA **B1** (Figure 1E), which exhibits a folded turn stabilized by intramolecular hydrogen bonding similar to the L-sulfonyl-γ-AA. Inspired by the findings, we next investigated whether L-sulfonyl-γ-AA or D-sulfonyl-γ-AA could induce β-turn motifs in macrocyclic peptides to yield antiparallel β-sheet mimics. We first studied the potential of L-sulfonyl-γ-AA as the β-turn mimic in cyclic peptides. To our delight, single-crystal X-ray diffraction of a macrocyclic peptide **BS-1**, comprising two trialanine strands linked by a sulfonyl-γ-AA turn (Figure 2A), was obtained. As depicted in Figure 2B, a robust hydrogen bond between the amide proton of the top strand and the carbonyl group of the bottom strand was detected, revealing an i to i + 3 hydrogen bonding pattern characteristic of a β-turn

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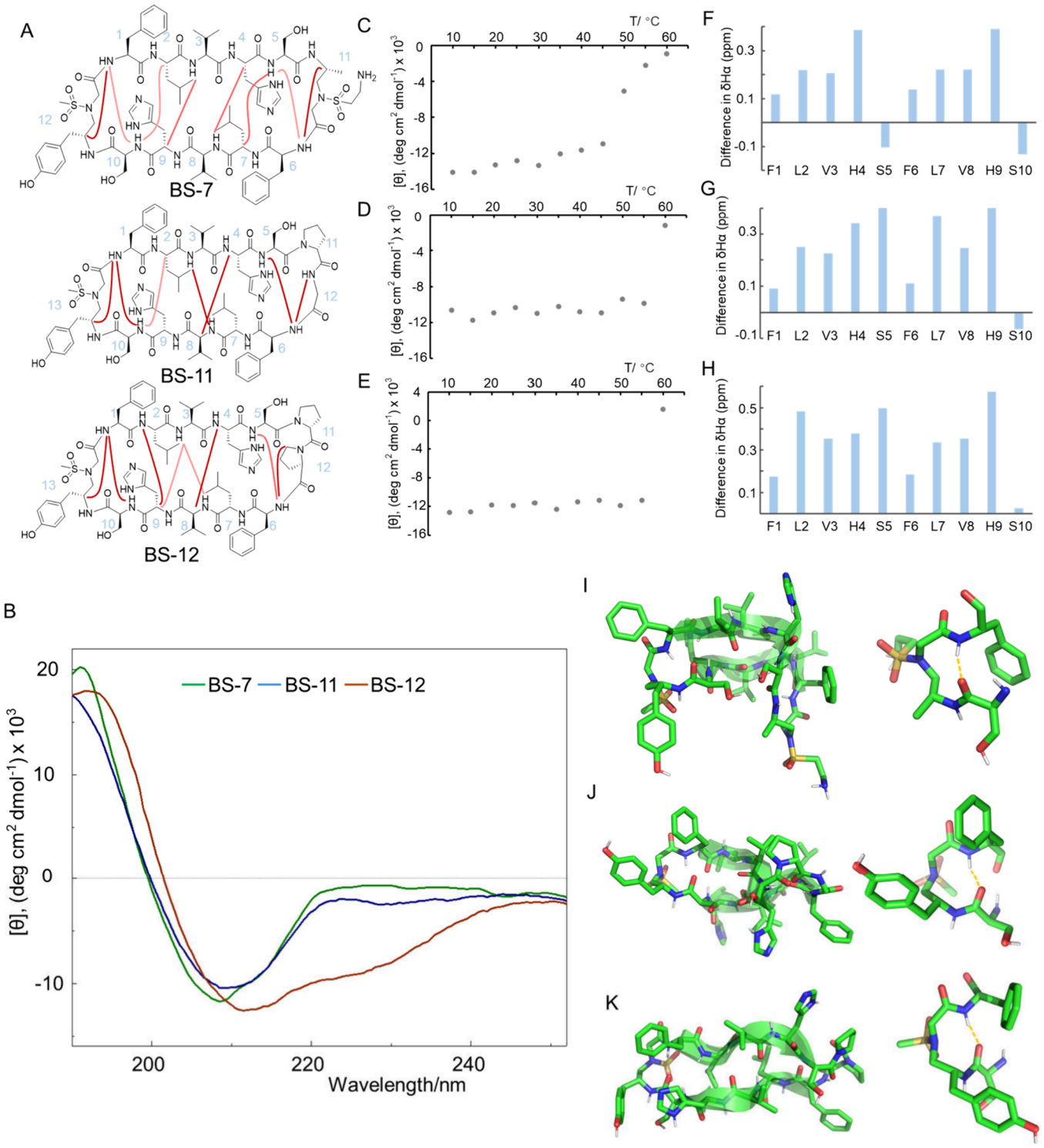

Figure 4. β-Sheets with incorporation of D-Pro-Gly and D-Pro-L-Pro. A) Primary structure of **BS-7**, **BS-11**, and **BS-12**, and their NOE cross peaks observed in NMR spectrum. B) CD spectrum of **BS-7**, **BS-11**, and **BS-12** at 50 μM in 10 mM KF (pH 7.3) solution at 25 °C. C-E) CD thermal denaturation studies on **BS-6** (207.5 nm), **BS-11** (209.5 nm), and **BS-12** (211.5 nm). F) Chemical shift difference $\Delta\delta H_\alpha$ of α-protons of residues between **BS-7** and random coil.[32] G) Chemical shift difference $\Delta\delta H_\alpha$ of α-protons of residues between **BS-11** and random coil. H) Chemical shift difference $\Delta\delta H_\alpha$ of α-protons of residues between **BS-12** and random coils. All these NMR data were acquired of 1.5−2 mM solution of cyclic peptides in 9:1 H_2O:D_2O with 1 mM KF solution (pH 7.3) at 25 °C. I, J and K) The NMR-derived β-sheet conformation of cyclic peptides in solution and the zoom-in view of the sulfonyl-γ-AA-promoted hydrogen bonding at the turn region of **BS-7**, **BS-11**, and **BS-12**.

motif. In addition, the hydrogen bonds formed between the upper strand and bottom strand further stabilize the β-sheet conformation. It is noteworthy that the hydrogen bonds exhibit an alternating pattern of closely spaced and widely separated distances, consistent with the theoretical arrangement of antiparallel β-sheets. In addition, as seen in Figure 2B, the intermolecular hydrogen bonding was detected. The structure confirmed that the sulfonyl-γ-AA enforces the β-turn

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conformation in this cyclic sequence. It is widely known that a β-sheet composed solely of alanine strands is known to be unstable and challenging to crystallize;[14] our success underscores the potential of sulfonyl-γ-AAs as β-turn inducers. However, attempts to use a couple of different L-sulfonyl-γ-AA residues (**BS-2** − **BS-5**) did not yield strong β-sheets in solution based on CD data (Figure S1).

Since D-sulfonyl-γ-AA could potentially act as the turn inducer (Figure 1E), to elucidate the role of the stereochemistry of sulfonyl-γ-AA in β-sheet formation, we synthesized the peptide **BS-6**, incorporating D-sulfonyl-γ-AA as a turn template. The CD spectroscopy revealed a maximum at ∼190 nm and a minimum at 208 nm (Figure 3B), indicative of a better folded β-sheet conformation in solution compared with **BS-2** to **BS-5**. In peptide **BS-7**, one D-sulfonyl-γ-AA turn was substituted with an alanine-based D-sulfonyl-γ-AA. Interestingly, **BS-7** exhibited a minimum at ∼209 nm with intensity comparable to **BS-6**, suggesting that side-chain modifications on the sulfonyl-γ-AA turn do not significantly alter β-sheet stability. Given the prevalence of tryptophan pairing in β-sheet structures, driven by aromatic cross-strand interactions,[28] we synthesized BS-8, by introducing tyrosine and tryptophan residues on the upper and lower strands, respectively. The CD spectrum of **BS-8** displayed a broad minimum between 209−214 nm (Figure 3C), confirming enhanced β-sheet folding.[29] Recognizing that peptide length influences β-sheet stability through effects on hydrogen bonding and conformational entropy,[30] we synthesized peptides **BS-9** and **BS-10**, derived from **BS-6**, with four and three residues per strand, respectively. **BS-9** exhibited a minimum at 215 nm, comparable to **BS-8**, indicating that reducing strand length from five to four residues minimally impacts β-sheet conformation. **BS-10**, with three-residue strands, showed a broad minimum between 203−215 nm (Figure 3C), with a minimum peak near 205 nm, suggesting less population of β-sheet structures, which may be due to reduced interstrand hydrogen bonding. These results demonstrate that D-sulfonyl-γ-AA is highly effective in inducing stable β-sheet conformation in macrocyclic peptides, with folding resilience across varied strand lengths and side-chain compositions, highlighting its potential as a versatile β-turn mimic for therapeutic and material applications.

To evaluate the efficiency of D-sulfonyl-γ-AA as a β-turn mimic, we synthesized macrocyclic peptides **BS-11** and **BS-12**, each incorporating one D-sulfonyl-γ-AA turn template paired with either D-Pro-Gly or D-Pro-L-Pro at the second turn position (Figure 4A). D-Pro-Gly is a well-established β-turn motif, known for inducing β-sheet conformations in 12-residue linear peptides.[31] CD spectroscopy of **BS-11** revealed a minimum between 208−212 nm, while **BS-12** exhibited a broader minimum between 209−214 nm (Figure 4B), both indicative of robust β-sheet folding in solution. To assess thermal stability, we conducted CD thermal denaturation studies on **BS-6** (containing two D-sulfonyl-γ-AA turns), **BS-11**, and **BS-12** (Figure 4C−E). For **BS-6**, a strong β-sheet conformation was maintained below 45 °C, but folding diminished rapidly above this temperature, with minimal ordered structure observed at higher temperatures. In contrast, **BS-11** and **BS-12** retained stable β-sheet conformations up to 55 °C, with their CD minima approaching zero only at ∼60 °C. The CD thermal denaturation results indicated that the D-sulfonyl-γ-AA used in the study could be weaker than D-Pro-Gly or D-Pro-L-Pro as the β-turn inducer. These findings also suggest that D-sulfonyl-γ-AA, alone or in combination with D-Pro-Gly or D-Pro-L-Pro, induces stable β-sheet conformation at physiological temperatures.

To further confirm the formation of β-sheets induced by D-sulfonyl-γ-AA turn templates, we employed 2D-NMR spectroscopy to study macrocyclic peptides **BS-7**, **BS-11**, and **BS-12**, which incorporate D-sulfonyl-γ-AA, or paired with D-Pro-Gly or D-Pro-L-Pro as turn templates, respectively. Using TOCSY and ROESY or NOESY experiments, we assigned key nuclear Overhauser effect (NOE) cross-peaks associated with β-sheet folding (Figure 4A). For **BS-7**, strong NOE cross peaks were observed in F1 NH and Y12 CαH and S10 NH as well as F6 NH and Y11 CαH and S5 NH. These observations indicated the strong potential of the β-turn mimic conformation of D-sulfonyl-γ-AA. For **BS-11** and **BS-12**, NOE cross-peaks in Figure 4A confirmed folded β-sheet conformations in solution, with additional cross-peaks indicating turn formation, notably between the F1 NH and Y13 CαH and S10 NH protons in **BS-12**. These 2D NMR data of BS-7, BS-11, and BS-12, along with their CD spectrum, suggested partial β-sheet formation, in coexistence with non-β-sheet structures. These observations also indicated that the sulfonyl-γ-AA turn may not be as strong as D-Pro-Gly or D-Pro-L-Pro. NOEs between a backbone NH proton and side chain proton as well as a side chain proton and side chain proton were also detected. But for clear view of the backbone interaction, those interactions were not shown. It is noted that in **BS-11** and **BS-12**, the NOEs were observed between the His4 NH proton and Val8 CαH, which may be due to the possibility that those molecules were adopting multiple conformations, including the β-sheet and non-β-sheet structures, leading to conformationally averaged NOEs. We ran the PFG NMR diffusion experiments for **BS-7**, **BS-11**, and **BS-12** at two concentrations, the low concentration (0.3 mM) and the high concentration that we used to run the TOCSY and NOESY (1.5 − 2 mM). For all the three peptides, the diffusion coefficients of low concentration are very close to the value of high concentration, which indicated there were no obvious aggregates at the concentration of 1.5 − 2 mM. Therefore, the NOEs should be intramolecular interactions. To probe secondary structure, we analyzed α-proton chemical shifts, which are a hallmark of β-sheet formation due to their downfield shift relative to random coil or α-helical conformations.[33] As shown in Figure 4F, the α-proton chemical shifts for residues 1−4 and 6−9 in **BS-7** exhibited significant downfield shifts, consistent with β-sheet folding. Notably, residues S5 and S10 in **BS-7** showed an upfield shift (∼0.1 ppm), which may result from the magnetic anisotropy of the phenylalanine side chain at the cross-strand residues F1 and F6.[34] The chemical shift profiles of **BS-11** and **BS-12** were highly similar, with most of the residues at the top and bottom strands downfield shifted significantly, reinforcing the consistent efficacy of D-sulfonyl-γ-AA amino acid in inducing stable β-sheet conformations. We then calculated the high-resolution NMR-derived solution structures of these cyclic peptides, which suggests all the peptides adopt antiparallel β-sheet structures. More intriguingly, hydrogen bonding within the turn induced by the sulfonyl-γ-AA was present in all peptides (Figure 4I-J). Such consistent conformation suggested the effectiveness of sulfonyl-γ-AA's conformation in inducing β-turn formation in various cyclic peptides. These NMR results validate D-sulfonyl-γ-AA as a highly effective β-turn mimic for macrocyclic peptides.

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DISCUSSION

The β-sheet, integral to protein architecture, orchestrates essential biological functions, yet crafting these motifs in small peptides, such as polyalanine, poses significant challenges due to the intricate interplay of sequence-specific folding propensities. In this report, we present sulfonyl-γ-AA as an innovative β-turn mimic designed to elicit robust β-sheet conformations within macrocyclic peptides. Single-crystal X-ray diffraction analysis of the previously reported L-sulfonyl-γ-AA, as well as the currently reported D-sulfonyl-γ-AA **B1** and the peptide **BS-1**, elucidated the capability of sulfonyl-γ-AAs as effective β-turn inducers. **BS-1**, comprising trialanine strands bridged by L-sulfonyl-γ-AA, revealed a definitive i to i + 3 hydrogen-bonded β-turn (Figure 2A), to the best of our knowledge, representing the first crystallographic validation of a polyalanine β-sheet structure.[35] In addition, D-sulfonyl-γ-AA in peptides **BS-6** to **BS-8** showed partial β-sheet conformation, displaying broad minima between 208−214 nm (Figure 3B, C), indicating these modular β-sheets are well folded. Remarkably, shortening strand lengths from five to four residues in **BS-9** had minimal impact on folding,[36] highlighting the exceptional resilience of D-sulfonyl-γ-AA as a turn template.[37] When further shortening the residues from four to three in **BS-10**, the CD minima peaks shifted to around 205 nm, and the spectra are broadened, suggesting although the molecule was less well folded as **BS-9**, there is still a partial β-sheet character. The poorer folding of **BS-10** might be due to the reduced intramolecular hydrogen bonding between and top and bottom strands. Comparative experiments with established turn motifs, D-Pro-Gly and D-Pro-L-Pro, in peptides **BS-11** and **BS-12**, demonstrated equivalent β-sheet stability, with CD minima at 208−214 nm and thermal denaturation studies confirming conformational integrity up to 55 °C (Figure 4D−E). In peptide **BS-6**, the minimum peak stays consistent before the temperature reaches 45 °C, which indicates the β-sheet folding was stable (Figure 4C). The minimum peak weakened when the temperature is above 45 °C, with the minimum peak diminished at 60 °C. Although the result suggested that the sulfonyl-γ-AA unit used may not be as strong as D-Pro-Gly or D-Pro-L-Pro, future exploration of other sulfonyl-γ-AA units could lead to a much enhanced β-turn inducer, due to their enormous chemodiversity of side chains. In addition, the NMR structural studies suggest that one of the D-sulfonyl-γ-AA-mediated β-hairpins **BS-7** shows well-folded β-sheet conformation, with large $\Delta\delta H_\alpha$ (>0.1 ppm) and strong key NOE cross peaks. It should be noted that there were strong NOE cross peaks between the D-sulfonyl-γ-AA C terminal NH-CγH, well indicative of a turn motif by D-sulfonyl-γ-AA. By replacing one of the turn templates with either D-Pro-Gly or D-Pro-L-Pro while keeping another turn template as D-sulfonyl-γ-AA, **BS-11** and **BS-12** both showed strong NOE cross peaks and large $\Delta\delta H_\alpha$. The high-resolution NMR-derived structures supported the consistent conformation of the sulfonyl-γ-AA as the turn-promoter. These findings position sulfonyl-γ-AA as a strong β-turn mimic, capable of inducing relatively stable β-sheet conformations in challenging sequences like polyalanine.

CONCLUSION

We have established sulfonyl-γ-AAs as robust β-turn mimics that induce stable β-sheet structures in macrocyclic peptides. As an alternative scaffold to other moieties used to generate β-sheet mimics, sulfonyl-γ-AAs offer additional diverse side-chain functionality when incorporated into macrocyclic peptides, simultaneously enabling β-turn formation and providing additional interactions with protein surfaces or handling group for post modification. Looking ahead, we envision leveraging a sulfonyl-γ-AA-mediated β-sheet to target critical protein−protein interactions. Additionally, the robust folding properties of these β-sheets inspire their application in designing environmentally responsive biomaterials, such as pH-sensitive hydrogels, which could self-assemble into nanostructured matrices under physiological conditions, facilitating controlled drug release or supporting tissue regeneration in biomedical engineering contexts. These expanded applications underscore the transformative potential of sulfonyl-γ-AA-based β-sheets in advancing therapeutic development and biomaterial innovation.[18,38]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.6c05451.

Experimental section, details about the chemical synthesis procedure, HRMS, HPLC, L-sulfonyl-γ-AA-templated β-sheet conformation discussion, circular dichroism spectroscopy procedure, X-ray crystallography procedure, NMR spectroscopy procedure and NMR peaks assignments, and molecular dynamics calculations based on NOEs (PDF)

Accession Codes

Deposition Numbers 2536918 and 2537404 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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