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Design of a turn-linker-turn foldamer by incorporating *meta*-amino benzoic acid in the middle of a helix forming hexapeptide sequence: A helix breaking approach

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ABSTRACT

Single crystal X-ray diffraction studies reveal that the incorporation of *meta*-amino benzoic acid in the middle of a helix forming hexapeptide sequence such as in peptide **I** Boc-Ile(1)-Aib(2)-Val(3)-*m*-ABA(4)-Ile(5)-Aib(6)-Leu(7)-OMe (Aib: α-amino isobutyric acid; *m*-ABA: *meta*-amino benzoic acid) breaks the helix propagation to produce a turn-linker-turn (T-L-T) foldamer in the solid state. In the crystalline state two conformational isomers of peptide **I** self-assemble in antiparallel fashion through intermolecular hydrogen bonds and aromatic π–π interactions to form a molecular duplex. The duplexes are further interconnected through intermolecular hydrogen bonds to form a layer of peptides. The layers are stacked one on top of the other through van der Waals interactions to form hydrophilic channels filled with solvent methanol.

1. Introduction

β-Turns which were first recognized by Venkatachalam in the late 1960s [1], are found to play an important role in stabilizing tertiary structures, initiating folding and facilitating intermolecular recognition [2–4]. Because of their critical importance there has been considerable interest in designing β-turns and β-turn mimetics [5–14]. Although there are several examples of the design and stabilization of isolated β-turns, there are few examples in the literature of small acyclic peptides containing more than one β-turn [15,16]. The peptide turn-linker-turn (T-L-T) foldamer will be useful in designing biologically active peptides. Previously it has been shown that a T-L-T foldamer can be designed and stabilized by connecting two turn inducing tripeptides with a flexible linker such as 1,2-ethylenediamine [15]. The T-L-T foldamers so formed were found to fabricate three-dimensional framework of channel in the solid state through self-assembly.

In this report we explore the possibility of generating T-L-T foldamer by a helix breaking approach. It is known that the 3_{10} helical structures of peptides containing Aib (α-amino isobutyric acid) are stabilized by successive 4 → 1 CO···NH hydrogen bonds, with idealized φ, ψ values of −60°, −30° characteristic of the right handed screw [17–20]. Essentially several turns are connected along the helix axis in a continuous fashion to form the helical structure. Therefore the breaking of helix propagation by inserting a suitable linker in the middle of a helix forming sequence may produce a T-L-T foldamer. Earlier attempts incorporating flexible linkers such as the dipeptide fragments (-β-Ala-γ-amino butyric acid-) and ω-amino acid such as δ-amino valeric acid in the middle of helix forming sequences failed to break the helix propagation [21,22]. The results showed that in spite of losing few hydrogen bonding donors and acceptors in the middle of the sequence the linkers are nicely accommodated into the helical structures. Therefore we thought that instead of using a flexible linker, the incorporation of a rigid linker such as *meta*-amino benzoic acid (*m*-ABA), a substituted γ-amino butyric acid with an all *trans* extended configuration in the middle of a helix forming sequence would help to break the helix propagation. Keeping this in view we chose the peptide **I** Boc-Ile(1)-Aib(2)-Val(3)-*m*-ABA(4)-Ile(5)-Aib(6)-Leu(7)-OMe (Fig. 1) to examine the formation of the T-L-T motif from expected helix breaking. It is important to note that hexa-peptides containing Aib at position 2 and 5 adopt a mixed $3_{10}/\alpha$-helical structure in the solid state and well developed homogeneous 3_{10} helical conformation in the solution phase [23]. Peptide **I** was synthesized by conventional solution phase methods. The solid state structure of the peptide was determined by single-crystal X-ray diffraction studies.

2. Experimental

2.1. Synthesis of the peptide *I*

The peptide was synthesised by conventional solution phase procedures using a racemization free fragment condensation strat-

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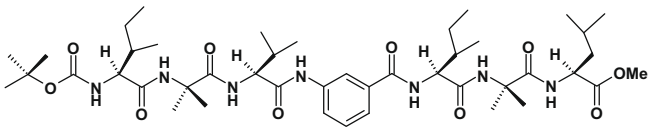

Fig. 1. Schematic diagram of peptide **I**.

egy [24]. The *t*-butyloxycarbonyl and methyl ester group were used for amino and carboxyl protections, respectively, and *N*,*N*′-dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole (HOBT) as coupling agents. Deprotections were performed using trifluoroacetic acid or saponification, respectively. Methyl ester hydrochlorides of Aib, Leu and Val were prepared by the thionyl chloride–methanol procedure. All the intermediates obtained were checked for purity by thin layer chromatography (TLC) on silica gel and used without further purification. The final peptide was purified by column chromatography using silica gel (100–200 mesh) as the stationary phase and ethyl acetate and petroleum ether mixture as the eluent. The reported peptide was fully characterized by NMR studies and X-ray crystallography.

*2.1.1. Boc-Ile-Aib-Val-OMe (**1**)*

The peptide was prepared using the literature method [25].

*2.1.2. Boc-Ile-Aib-Val-OH (**2**)*

Compound **1** (1.4 g, 3.16 mmol) was dissolved in methanol (15 ml) and 2 M NaOH (5 ml) was added. The reaction mixture was stirred at room temperature for 2 days. The progress of the reaction was monitored by TLC. After completion of the reaction the methanol was evaporated. The residue obtained was diluted with water and washed with diethylether. The aqueous layer was cooled in an ice-bath and neutralized with 2 M HCl and then extracted with ethyl acetate. The solvent was evaporated *in vacuo* to give a white solid. Yield: 1.3 g (95.8%).

*2.1.3. Boc-Ile-Aib-Val-m-ABA-OMe (**3**)*

Compound **2** (1.2 g, 2.79 mmol) was dissolved in DMF (5 ml). *m*-ABA-OMe obtained from its hydrochloride (1.05 g, 5.6 mmol) was added, followed by DCC (0.86 g, 4.2 mmol) and HOBT (0.38 g, 2.79 mmol). The reaction mixture was stirred at room temp for 3 days. The precipitated *N*,*N*′-dicyclohexylurea (DCU) was filtered and to the filtrate 20 ml of ethyl acetate was added. The organic layer was washed with 1 N HCl (3 × 30 mL), 1 M Na_2CO_3 solution (3 × 30 mL) and water. The solvent was then dried over anhydrous Na_2SO_4 and evaporated *in vacuo,* giving a light yellow gum. Yield: 1.4 g (91.6%). Purification was carried out using silica gel as the stationary phase and ethyl acetate–petroleum ether mixture as the eluent. Mp = 178–180 °C; IR (KBr): 3420, 3302, 1724, 1665, 1604, 1547, 1511 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$, δ ppm): 9.12 (*m*-ABA NH, 1H, *s*); 8.49 (*m*-ABA (4) H_a, 1H, *s*); 8.17 (*m*-ABA (4) H_d, 1H, *d*, *J* = 6.9 Hz); 7.75(*m*-ABA (4) H_b, 1H, *d*, *J* = 7.8 Hz); 7.36 (*m*-ABA (4) H_c, 1H, *t*, *J* = 8.1 Hz); 6.95 (Val (1) NH, 1H, *d*, *J* = 8.4 Hz); 6.68 Aib(2) NH, 1H, *s*); 5.04 (Ile (3) NH, 1H, *d*, *J* = 3.9 Hz); 4.58–4.54 ($C^{\alpha}H$ of Val (3), 1H, *m*); 3.91 (–OCH_3, 3H, *s*); 3.89–3.84 ($C^{\alpha}H$ of Ile(1), 1H, *m*); 2.70–2.65 ($C^{\beta}Hs$ of Val (3), 1H, *m*); 1.95-1-93 ($C^{\beta}Hs$ of Ile (1), 1H, *m*);1.55 ($C^{\beta}Hs$ of Aib, 6H, *s*);1.44 (Boc–CH_3s, 9H, *s*); 1.29–1.27 ($C^{\gamma}Hs$ of Ile (1) , 5H, *m*); 1.01–0.92 ($C^{\delta}Hs$ of Ile (1) and $C^{\gamma}Hs$ of Val (3), 9H, *m*); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 173.9, 171.9, 170.1, 167.1, 156.5, 138.9, 130.5, 128.6, 124.9, 124.5, 121.1, 81.2, 60.7, 59.3, 57.2, 51.9, 36.4, 29.1, 28.1, 27.5, 25.3, 24.0, 19.5, 16.9, 15.74, 11.52; HR–MS (M^+Na^+) = 571.31, M_{calcd} = 548.67.

*2.1.4. Boc-Ile-Aib-Val-mABA-OH (**4**)*

Compound **3** (1.2 g, 2.19 mmol) was dissolved in methanol (15 ml) and 2 M NaOH (5 ml) was added. The reaction mixture was stirred at room temperature for 2 days. The progress of the reaction was monitored by TLC. After completion of the reaction the methanol was evaporated. The residue obtained was diluted with water and washed with diethylether. The aqueous layer was cooled in an ice-bath and neutralized with 2 M HCl and then extracted with ethyl acetate. The solvent was evaporated *in vacuo* to give a white solid. Yield: 1.1 g (94.1%).

*2.1.5. Boc-Ile-Aib-Leu-OMe (**5**)*

This peptide was prepared following the literature method [25].

Boc-Ile-Aib-Val-m-ABA-*Ile-Aib-Leu-OMe* (Peptide **I**): To *Boc-Ile-Aib-Leu-OMe* (***5***), (0.47 g, 1.07 mmol) trifluoroacetic acid (3 ml) was added at 0 °C and stirred at room temperature. The removal of the Boc-group was monitored by TLC. After 3 h the trifluoroacetic acid was removed under reduced pressure to afford the crude trifluoroacetate salt. The residue was taken up in water and washed with diethyl ether. The pH of the aqueous solution was adjusted to eight with sodium bicarbonate and extracted with ethyl acetate. The extracts were pooled, washed with saturated brine, dried over sodium sulfate, and concentrated to a highly viscous liquid that gave a positive ninhydrin test. This free base of the tripeptide was added to a well ice-cooled solution of compound **4** (0.57 g, 1.07 mmol) in DMF (6 ml) followed by DCC (0.33 g, 1.60 mmol) and HOBt (0.17 g, 1.28 mmol). The reaction mixture was stirred at room temperature for 4 days. The residue was taken up in ethyl acetate and DCU was filtered off and to the filtrate 20 ml of ethyl acetate was added. The organic layer was washed with 2 M HCl (3 × 50 ml), 1 M Na_2CO_3 solution (3 × 50 ml) and brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*, to yield a white solid. Purification was done using silica gel as stationary phase and ethyl acetate–petroleum ether mixture as the eluent. Single crystals were grown from methanol and ethyl acetate mixture by slow evaporation and were stable at room temperature.

Yield: 0.81 g (88.3%). Mp = 150–152 °C; IR (KBr): 3313, 1717, 1674, 1526 cm^{-1}; ^1H NMR 300 MHz (DMSO-d_6, δ ppm): 9.96 (*m*-ABA(4) NH, 1H, *s*); 8.37 (*m*-ABA(4) H_d, 1H, *d*, *J* = 6.6 Hz); 8.34 (*m*-ABA(4) H_a, 1H, *s*); 8.08 (*m*-ABA(4) H_b and Aib (6) NH, 2H, *bs*); 7.74 (Leu(7) NH, 1H, *d*, *J* = 7.8 Hz); 7.57 (Ile(5) NH, 1H, *d*, *J* = 7.8 Hz); 7.33 (*m*-ABA(4) H_c, Aib (2) NH, 2H, *m*); 7.07 (Val(3) NH, 1H, *d*, *J* = 8.4 Hz); 6.76 (Ile(1) NH, 1H, *d*, *J* = 7.5 Hz); 4.26–4.23 ($C^{\alpha}Hs$ of Ile(5) and Leu (7), 2H, *m*); 4.12–4.07 ($C^{\alpha}H$ of Val (3),1H, *m*); 3.80–3.76 ($C^{\alpha}H$ of Ile(1),1H, *m*); 3.57 (–OCH_3, 3H, *s*); 1.59–2.15 ($C^{\beta}Hs$ of Ile(1), Val(3), Ile(4) and Leu(6), 5H, *m*); 1.56 ($C^{\beta}Hs$ of Aib(6), 6H, *s*); 1.53 (Boc-CH_3s, 9H, *s*); 1.45 ($C^{\beta}Hs$ of Aib(2), 6H, *s*); 1.30–1.25 ($C^{\gamma}Hs$ of Ile(1), Ile(5) and Leu(6), 11H, *m*); 1.0–0.87 ($C^{\gamma}Hs$ of Val(3), $C^{\delta}Hs$ of Ile(1), Ile(5) and Leu(7), 18H, *m*); ^{13}C NMR 75 MHz (DMSO-d_6, δ ppm): 173.93, 173.83, 173.02, 171.70, 171.27, 170.08, 167.03, 155.71, 138.80, 134.62, 128.47, 122.47, 122.19, 119.01, 78.19, 56.28, 56.09, 51.79, 50.24, 36.23, 34.97, 30.62, 28.19, 26.94, 25.73, 25.31, 24.69, 24.25, 23.72, 23.08, 22.41, 21.19, 19.21, 17.97, 15.40, 15.12, 11.10, 10.57; HR–MS (M^+Na^+) = 882.03, M_{calcd} = 860.11.

2.2. FTIR spectroscopy

IR spectrum of peptide **I** was examined using Perkin Elmer-782 model spectrophotometer. The solid state FTIR measurements were performed using the KBr disk technique.

2.3. NMR experiments

All ^1H and ^{13}C NMR spectra of peptide **I** were recorded on Bruker Avance 300 model spectrometer operating at 300 and 75 MHz, respectively. The peptide concentrations were 10 mM in $CDCl_3$ for ^1H NMR and 40 mM in $CDCl_3$ for ^{13}C NMR.

2.4. Mass spectrometry

Mass spectrum of peptide **I** was recorded on Voyager-DE MALDI-TOF.

2.5. Single crystal X-ray diffraction study

Peptide **I**, $C_{44.25}H_{75}N_7O_{10.75}$, M = 877.11, monoclinic, spacegroup $P2_1$, Z = 4, a = 16.3030(16), b = 22.092(3), c = 16.440(2) Å, β = 109.414(13)°, U = 5584.4(11) Å^3, dcalc = 1.043 gcm^{-3}. 28232 independent data, respectively, were collected with MoKα radiation at 293K using the Oxford Diffraction X-Calibur CCD System. The crystal was positioned at 50 mm from the CCD. 321 frames were measured with a counting time of 50 s. Data analyses were carried out with the Crysalis program [26]. The structure was solved using direct methods with the Shelxs97 program [27]. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon and nitrogen were included in geometric positions and given thermal parameters equivalent to 1.2 or 1.5 (for methyl hydrogens) times those of the atom to which they were attached. The structure was refined on F^2 using Shelxl97 [27] to R1 0.0805; wR2 0.1873 for 9202 reflections with $I > 2\sigma(I)$. The data have been deposited at Cambridge Crystallographic Data Center with reference number CCDC 723914.

3. Results and discussion

3.1. Peptide conformation in the solid state

Peptide **I** crystallises with two molecules in the crystallographic asymmetric unit designated as **A** and **B**. There are also two solvent water molecules and one solvent methanol, all refined with 50% occupancy. In both molecules, the chiralities at C(2), C(8), C(19) and C(27) are *S* (Figs. 2 and 3). Interestingly as predicted, the rigid linker *m*-ABA is found to break the helix propagation in **A** and **B** to produce T-L-T conformations. Although the Aib containing helices are quite stable, the formation of the T-L-T motif through the breaking of helix propagation was anticipated. In **A** a type II β-turn structure with Ile(1) and Aib(2) occupying the $i+1$ and $i+2$ position is stabilized by an intramolecular hydrogen bond (Fig. 2). The torsion angles at Ile(1) and Aib(2) were found to be φ_1: −64.6(6)°, ψ_1: 136.3(4)° and φ_2: 94.3(5)°, ψ_2: −11.0(5)°, respectively, (Table 1), which are slightly deviated from the ideal values

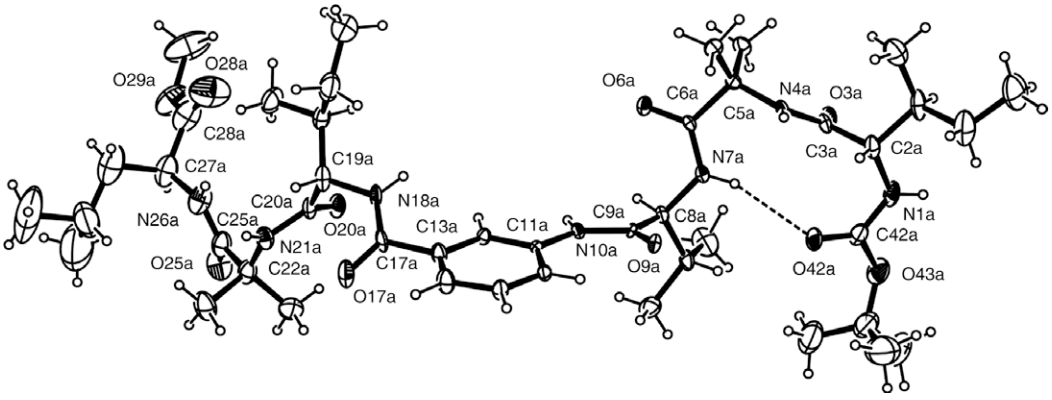

Fig. 2. Structure of conformation **A** of peptide **I** with ellipsoids at 25% probability. Hydrogen bonds are shown as dotted lines.

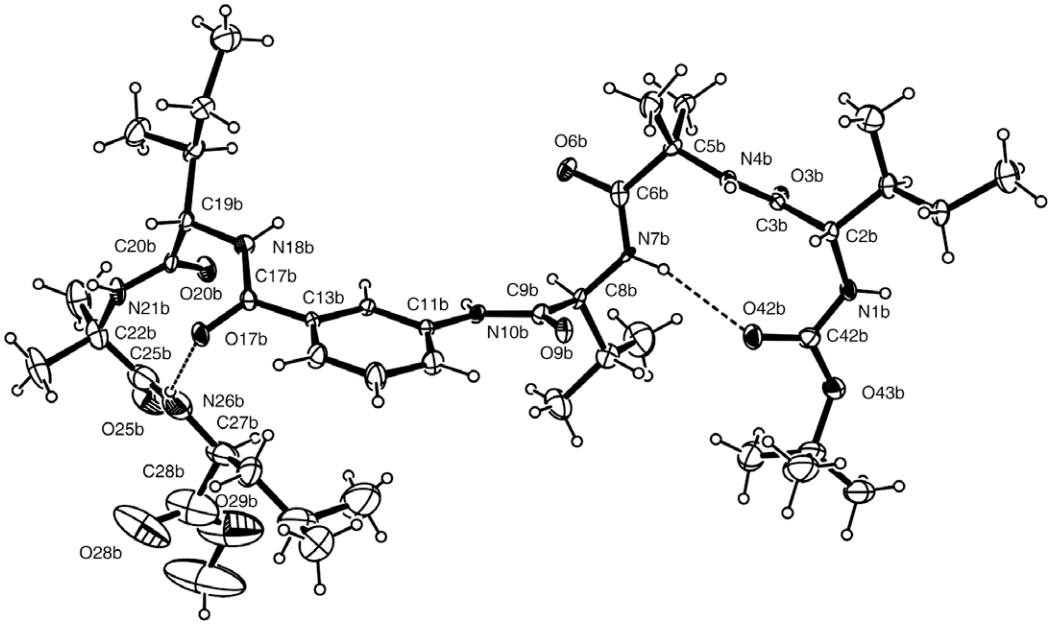

Fig. 3. Structure of conformation **B** of peptide **I** with ellipsoids at 25% probability. Hydrogen bonds are shown as dotted lines.

for a type II β-turn φ_1: −60°, ψ_1: 120° and φ_2: 80°, ψ_2: 0°. As a result a weak intramolecular hydrogen bond between Boc-CO and Val(3)-NH is observed (N7A–H...O42A, 2.47 Å, Table 2). The torsion angles at Ile(5) and Aib(6) were found to be φ_5: −78.0(6)°, ψ_5: 117.9(5)° and φ_6: −75.3(7)°, ψ_6: −27.4(8)°, respectively, (Table 1). The values are deviated significantly from the ideal values for a type II β-turn structure. Therefore the formation of an intramolecular hydrogen bond between N26A–H...O17A to stabilize a β-turn structure is not possible due to large distance between donor and acceptor. However, the structure of **A** shows that the centrally placed *m*-ABA in peptide **I** can disrupt the helix propagation. There is no intramolecular hydrogen bond between the two tripeptide fragments placed before and after the *m*-ABA in peptide **I** (Fig. 2).

Table 1
Selected backbone torsion angles (degrees) of peptide **I**.

	Molecule **A**	Molecule **B**
O43–C42–N1–C2(ω_0)	172.5(4)	−177.6(4)
C42–N1–C2–C3(φ_1)	−64.6(6)	−64.8(5)
N1–C2–C3–N4(ψ_1)	136.3(4)	133.5(4)
C2–C3–N4–C5(ω_1)	174.2(5)	175.8(4)
C3–N4–C5–C6(φ_2)	94.3(5)	89.9(5)
N4–C5–C6–N7(ψ_2)	−11.0(5)	−0.7(6)
C5–C6–N7–C8(ω_2)	179.5(4)	−179.7(4)
C6–N7–C8–C9(φ_3)	−83.6(5)	−91.0(5)
N7–C8–C9–N10(ψ_3)	132.4(4)	136.4(4)
C8–C9–N10–C11(ω_3)	175.7(4)	178.4(4)
C13–C17–N18–C19(ω_4)	−176.4(5)	176.7(4)
C17–N18–C19–C20(φ_5)	−78.0(6)	−67.7(6)
N18–C19–C20–N21(ψ_5)	117.9(5)	119.0(5)
C19–C20–N21–C22(ω_5)	−174.3(5)	−177.9(5)
C20–N21–C22–C25(φ_6)	−75.3(7)	49.5(8)
N21–C22–C25–N26(ψ_6)	−27.4(8)	40.8(8)
C22–C25–N26–C27(ω_6)	−170.2(6)	175.3(6)
C25–N26–C27–C28(φ_7)	−128.9(7)	−58.8(9)
N26–C27–C28–O29(ψ_7)	155.1(6)	137.8(10)

Table 2
Hydrogen bonding parameters of peptide **I**.

D–H···A	H···A/Å	D···A/Å	D–H···A/°
Intramolecular			
N7A–H...O42A	2.47	3.294(5)	162
N7B–H...O42B	2.38	3.207(5)	162
N26B–H...O17B	2.40	3.192(8)	153
Intermolecular			
N1A–H...O17A[a]	2.13	2.918(6)	152
N4A–H...O20B[b]	2.02	2.880(5)	178
N10A–H...O6B[b]	1.96	2.823(5)	177
N18A–H...O9B[b]	2.09	2.911(5)	161
N21A–H...O3A[c]	2.09	2.937(6)	169
N1B–H...O17B[b]	2.11	2.896(4)	152
N4B–H...O20A[d]	2.08	2.939(5)	174
N10B–H...O6A[d]	2.01	2.864(5)	173
N18B–H...O9A[d]	2.05	2.897(5)	168
N21B–H...O3B[d]	2.16	3.013(5)	173

Symmetry elements: [a] $x, y, 1+z$; [b] $x+1, y, z$; [c] $x, y, z-1$; [d] $x-1, y, z$.

The crystal structure of **B** reveals that it adopts a T-L-T conformation corresponding to type II β-turn structures in the (T) regions. In the first tripeptide fragment the type II β-turn structure with Ile(1) and Aib(2) occupying the $i+1$ and $i+2$ positions is stabilized by the intramolecular hydrogen bond N7B–H...O42B, 2.38 Å (Fig. 3, Table 2). The torsion angles at Ile(1) and Aib(2) were found very similar to those in molecule **A** with φ_1: −64.8(5)°, ψ_1: 133.5(4)° and φ_2: 89.9(5)°, ψ_2: −0.7(6)°, respectively, (Table 1). In the second tripeptide fragment the torsion angles at Ile(5) are similar to those in molecule **A** at φ_5: −67.7(6)°, ψ_5: 119.0(5)° but those at Aib(6) are very different at φ_6: 49.5(8)°, ψ_6: 40.8(8)°, respectively, (Table 1) which corresponds to a type II β-turn structure. The intramolecular hydrogen bond N26B–H...O17B (2.40 Å) stabilizes the β-turn structure with Ile(5) and Aib (6) at the corner positions (Fig. 3, Table 2).

3.2. Crystal packing

In the crystalline state molecules **A** and **B** are interconnected in antiparallel fashion through three types of intermolecular hydrogen bonds between Aib(2)–NH...OC–Ile(5), Val(3)–CO...HN–Ile(5) and Aib(2)–CO...HN-*m*-ABA(4) to form a molecular duplex, which is further stabilized by aromatic π–π interaction between two nearly parallel phenyl rings, C(11A)–C(16A) inclusive with C(11B)–C(16B) ($1+x, y, z$) inclusive which intersect at an angle of 24.8(1)°. There are eight contacts less than 4.0 Å with the closest contact is between C(11A) and C(11B) ($1+x, y, z$) at 3.33(1) Å (Fig. 4, Table 2). Eight peptide molecules of **I** from four duplexes are interconnected by two types of intermolecular bonds, between Ile(1)–NH and *m*-ABA(4)–CO and between Ile(1)–CO and Aib(6)–NH to complete each circular subunit. These subunits are further connected in two directions (*a*, *c* axis) to create a two-dimensional layer of peptides. These layers are stacked on top of each other in the *b* direction through van der Waals interactions to create hydrophilic channels with an approximate internal dimension of 9.7 × 4.5 Å in the *c* direction filled with solvent methanol (Fig. 5).

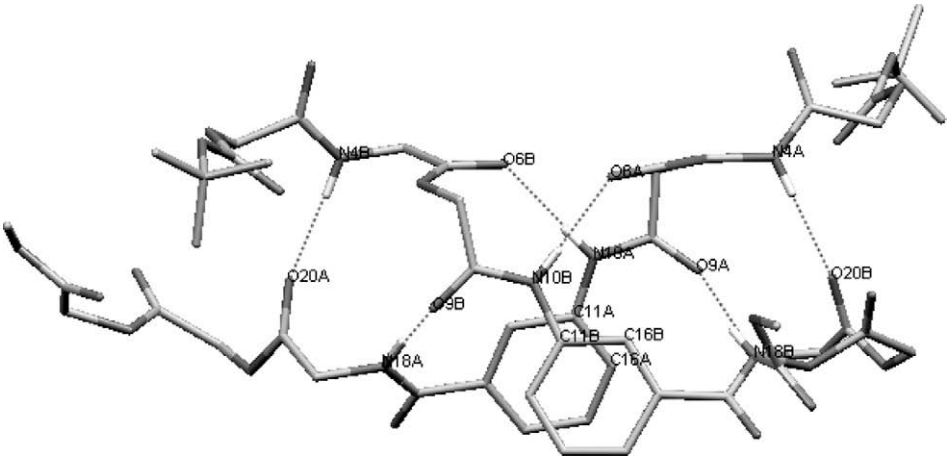

Fig. 4. Showing the formation of molecular duplex with **A** and **B** of peptide **I** (only backbones are shown, no side chains). Hydrogen bonds are shown as dotted lines. Hydrogen atoms only involving in hydrogen bonding are shown.

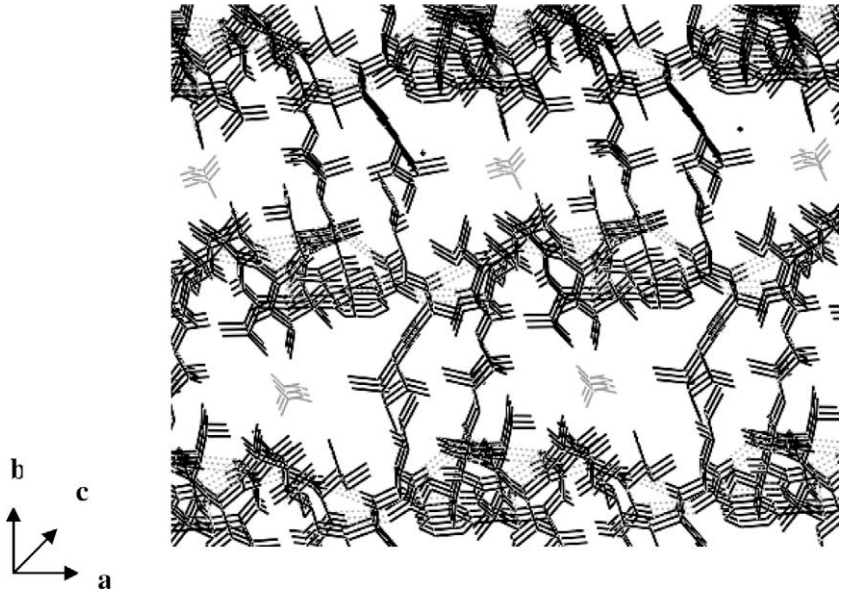

Fig. 5. The layers of peptide **I** are stacked in *b* direction to form the channels. View showing the channels with solvent methanol parallel to *c* axis (hydrogen atoms of peptide **I** are omitted for clarity). Hydrogen bonds are shown as dotted line.

4. Conclusions

In the present study, it has been shown that a turn-linker-turn (T-L-T) foldamer can be generated through the breaking of helix propagation by incorporating a rigid linker like *meta*-amino benzoic acid in the middle of a helix forming peptide sequence. The T-L-T foldamers so formed are found to self-assemble in antiparallel fashion through intermolecular hydrogen bonds and aromatic π–π interactions to form molecular duplexes which are further interconnected in two directions (*a*, *c* axis) to create layers of peptides. The layers are stacked one on top of the other in *b* direction to form hydrophilic channels filled with solvent methanol. The formation of channels through the self-assembly of T-L-T foldamers has been reported previously also [15]. Channels and pores are important for applications in gas storage, selective chiral absorption and catalysis [28].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2009.04.037.

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