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# Fluorinated Triazole Foldamers: folded or extended conformational preferences

José Laxio Arenas,<sup>[a]</sup> Yaochun Xu,<sup>[a]</sup> Thierry Milcent,<sup>[a]</sup> Carine Van Heijenoort,<sup>[b]</sup> François Giraud,<sup>[b]</sup> Tap Ha-Duong,<sup>[a]</sup> Benoit Crousse,<sup>[a]</sup> Sandrine Onger, <sup>\*[a]</sup>

**Abstract:** While on the one hand the field of peptide-based foldamers capable of providing mimics of secondary structures has aroused growing interest particularly in the field of protein-protein interactions, and on the other hand fluorinated drugs have taken hold in the pharmaceutical market, fluorinated peptidomimetic foldamers are still in their infancy. We report here the easy access to fluorinated triazolamers based on 2-amino-3,3,3-trifluoropropyl-1,4-triazolyl acetic acid (CF<sub>3</sub>-1,4-Tz) and on aminomethyl-1,4-triazolyl-difluoroacetic acid (1,4-Tz-CF<sub>2</sub>). Their conformational analyses by spectroscopic and computational analyses revealed that they are capable to adopt short multi-stranded  $\beta$ -sheet like and elongated  $\beta$ -strand like structures, respectively.

## Introduction

Peptides and proteins can adopt preferential folded structure to ensure their biological functions. Inter- or intramolecular hydrogen bonding between the carbonyl groups and amine protons of the amide bond, and the electrostatic and hydrophobic interactions of side chains are responsible for protein folding. Artificial foldamers are repetitive synthetic building blocks adopting folded molecular architectures able to mimic the structural properties of biomolecules.<sup>[1]</sup> With the current burst of therapeutic peptides,<sup>[2],[3]</sup> the field of peptide-based foldamers able to furnish mimics of secondary structures has gained increasing interest.<sup>[4],[5]</sup> Indeed, peptidomimetic foldamers can offer opportunities to circumvent two major issues of short peptides that are the lack of stability towards proteolysis and their low ability to adopt preferential conformations, preventing their effective use in some therapeutic fields such as the inhibition of protein-protein interactions. In parallel, fluorinated molecules have demonstrated a dramatic interest in medicinal chemistry with about 150 having reached Pharma markets and they constitute almost 30% of all new approved drugs.<sup>[6-8]</sup> Furthermore, the introduction of fluorinated amino-acids into peptides and proteins have increased their biological activity and secondary structure propensity due to the

capacity of fluorine to greatly increase the local hydrophobicity and to strengthen hydrogen bonds.<sup>[9],[10]</sup> Introduction of fluorinated amino acids can also increase chemical and enzymatic stability,<sup>[8,9]</sup> even if in some cases of direct fluorinated analogues of natural amino acids the effect was less noticeable.<sup>[9b]</sup> Furthermore, fluorine “labeling” is a great advantage for studying biological events by <sup>19</sup>F-NMR spectroscopy, such as structure and function of biomolecules, enzymatic mechanisms, ligand-biomolecule interactions, metabolic pathways, as well as for <sup>19</sup>F MRI medical imaging.<sup>[11]</sup> However, to our knowledge, only a very few examples of fluorinated foldamers have been reported.<sup>[12],[13],[14],[15]</sup> Regarding the peptidic ones, fluorinated peptoids,<sup>[13]</sup> and CF<sub>3</sub>- $\beta$ -peptides<sup>[14]</sup> adopt an helical conformation while oligomers of cis-2-amino-1-fluorocyclobutane-1-carboxylic acid and of 2-fluoroaryl substituted  $\alpha,\beta^{2,3}$ -amino acid adopt strand-like secondary structure.<sup>[12]</sup>

We report here the first fluorinated foldamers based on 1,4-disubstituted-1,2,3-triazole (1,4-Tz) amino acids. The 1,4-Tz unit is known as a *trans*-amide surrogate, extremely stable to hydrolysis, and even if its size and dipole moment are larger than its amide surrogate, triazolyl amino acids might replace dipeptides.<sup>[16]</sup> 1,4-Tz dipeptide mimics are classically prepared by the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (also called “click chemistry”) of organic azides and alkynes. However, conformational influence of 1,4-Tz has been only recently studied. In particular, the tendency of  $\beta$ -turn formation for this Tz amino acid system in tri and pentapeptides has been described.<sup>[17],[18]</sup> It has been also shown that a 1,4-Tz amino acid can replace a dipeptide in an  $\alpha$ -helical secondary structure.<sup>[19],[20]</sup> Oligomers of triazole, also called triazolamers have been rarely described. NMR studies of 1,4-Tz trimers (compound **1**, Figure 1) and tetramers, where  $\alpha$ -amino acid residues linked by 1,4-Tz groups, suggest that these oligomers adopt zigzag conformations which closely mimic peptide  $\beta$ -strands.<sup>[21]</sup> Dipole-dipole interactions between neighboring triazole rings appear to play a critical role in stabilizing the observed conformations in polar solvents, such as DMSO and acetone. The anion-induced folding of 1,4-diaryl-Tz oligomers have been reported (compound **2**, Figure 1).<sup>[22]</sup> The group of N. Sewald recently showed by molecular dynamics, the compact folded conformation in DMSO and water, of peptidotriazolamers based on 1,4-Tz in which side chains of natural  $\alpha$ -amino acids were conserved in order to mimic dipeptides (compound **3**, Figure 1).<sup>[23]</sup> Head to tail dimerization has been otherwise reported with similar peptidotriazolamers, mimicking an anti-parallel  $\beta$ -sheet (compound **4**, Figure 1).<sup>[24]</sup>

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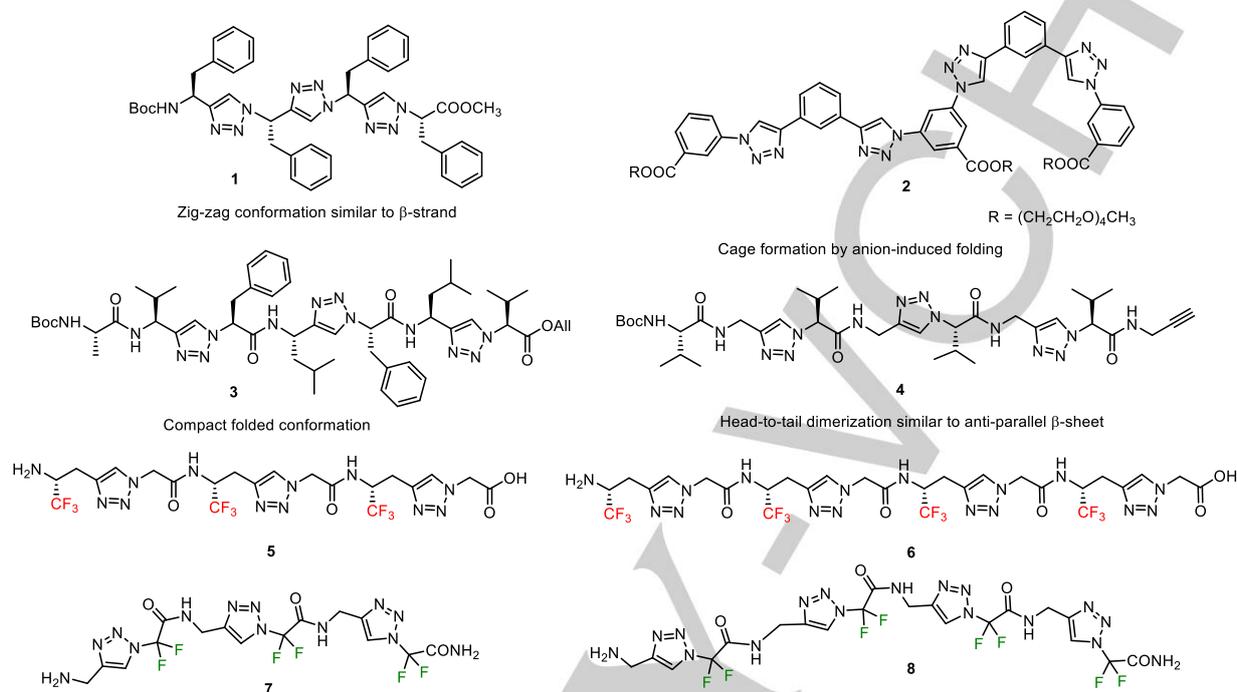
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## FULL PAPER

We have turned our attention here to two different and original classes of fluorinated triazolamers based on (2-amino-trifluoropropyl-1,4-triazolyl)-acetic acid, named also trifluoromethyl homo-1,4-Tz amino acid or CF<sub>3</sub>-1,4-Tz (trimer **5**

and tetramer **6**, Figure 1), and on (aminomethyl-1,4-triazolyl)-difluoroacetic acid named, named *N*-difluoromethyl 1,4-Tz amino acid or 1,4-Tz-CF<sub>2</sub> (trimer **7** and tetramer **8**, Figure 1).



**Figure 1.** Structure of triazolamers based on 1,4-disubstituted-1,2,3-triazole reported in the literature **1-4**, and of the newly designed fluorinated triazole oligomers made of trifluoromethyl homo-1,4-Tz amino acids (CF<sub>3</sub>-1,4-Tz) **5-6** and of *N*-difluoromethyl 1,4-Tz amino acids (1,4-Tz-CF<sub>2</sub>) **7-8**

We anticipated that thanks to the unique properties of fluorine (decrease of the pKa of the neighboring NH, increase of the local hydrophobicity and strength of the hydrogen bonds), the fluorinated groups could promote conformations different from the ones reported for non-fluorinated triazolamers. The trifluoromethyl homo-1,4-Tz amino acid (CF<sub>3</sub>-1,4-Tz) can be considered as a mimic of a  $\beta$ - $\alpha$  dipeptide. Here we describe its asymmetric synthesis by the copper(I)-catalyzed click reaction from one isomer of the trifluoro-pentynamine. This latter was prepared by a Zn-mediated propargylation of the (*R*)-*tert*-butanesulfinyl aldimine. The second scaffold used here to prepare fluorinated foldamers is a *N*-difluoromethyl 1,4-Tz amino acid (1,4-Tz-CF<sub>2</sub>) that can be considered as an analogue of the GlydifluoroGly dipeptide and that was recently prepared by us.<sup>[25]</sup> We demonstrated that the introduction of one monomer 1,4-Tz-CF<sub>2</sub> in short peptides could induce extended structures.<sup>[25]</sup> However, to date we did not have any information about the capacity of oligomers of this novel fluorinated 1,4-Tz scaffold to adopt specific conformations. The syntheses of the trimer **7** and tetramer **8** of both fluorinated 1,4-Tz amino acids are described here. Information on their particular conformation is also provided and showed opposite preferences of CF<sub>3</sub>-1,4-Tz and 1,4-Tz-CF<sub>2</sub> based triazolamers with rather folded or extended conformational aptitude, respectively.

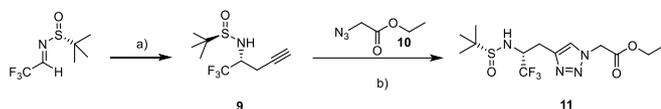
## Results and Discussion

### Synthesis

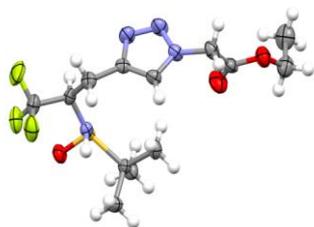
The synthesis of the trimer and tetramer **5** and **6** was based on coupling reactions of the (*R*) isomer of the trifluoromethyl 1,4-Tz monomer **11**. The trifluoromethyl (*R*)-*tert*-butanesulfinyl aldimine<sup>[26]</sup> was first submitted to an asymmetric Zinc-mediated Barbier type propargylation in DMF at room temperature to afford the corresponding (*R,R*<sub>S</sub>)CF<sub>3</sub>-homopropargylic amine **9** in good yield (92%) and good diastereoselectivity (dr 95:5). This stereoselectivity is in accordance with previous results of our group in the Zinc-mediated allylation of the CF<sub>3</sub>-*tert*-butanesulfinyl aldimine in DMF<sup>[27]</sup> and of the group of Fustero et al. who reported recently the addition of propargyl magnesium bromide on the same imine in THF<sup>[28]</sup>. The copper (I) catalyzed azide-alkyne cycloaddition reaction between **9** and ethyl 2-azidoacetate **10**, using CuI (10%) and triethylamine in acetonitrile produced the trifluoromethyl 1,4-Tz monomer **11** in good yield (76%) and as a single regioisomer (Scheme 1).<sup>[29]</sup> Despite the use of a base, no epimerization was observed during the synthesis, as confirmed by <sup>19</sup>F NMR. The absolute configuration of the major (*R,R,S*)-isomer of **11** was unambiguously assigned by X-ray crystallographic analysis (Fig. 2), confirming the stereochemistry assigned in the Barbier type reaction.

## FULL PAPER

The chiral (*R*)-*tert*-butylsulfinyl was preferred to the (*R*)-phenylglycinol chiral auxiliary as it was known to be easily removable under classical acidic conditions, while (*R*)-phenylglycinol was not cleavable under classical hydrogenolysis and required the cleavage of the methyl ether followed by the use of  $\text{Pb}(\text{OAc})_4$ .



**Scheme 1.** Synthesis of the protected trifluoromethyl homo-1,4-Tz amino ester **11**. Conditions: a) Zn (1.5 eq.), propargyl bromide (1.5 eq.), DMF, rt, 2h, yield 92 %, dr 95:5, b) CuI (10%),  $\text{NEt}_3$  (1.0 eq.), ACN, rt, 3h, 76 %



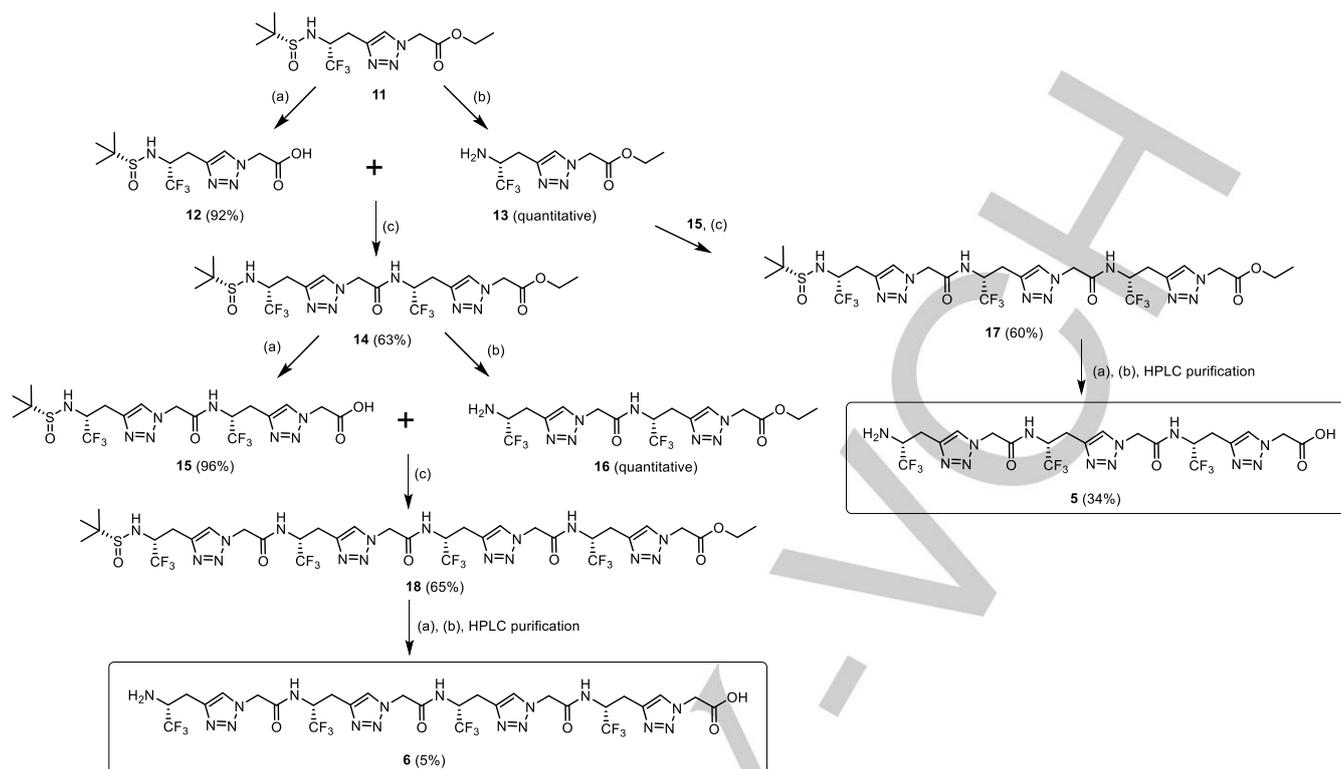
**Figure 2.** X-ray structure of the protected trifluoromethyl homo-1,4-Tz amino acid **11** (CCDC n° 1966743)

Trimer **5** and tetramer **6** were prepared according to Scheme 2. The trifluoromethyl 1,4-Tz monomer **11** was then subjected to a saponification of its C-terminus to give **12** or to an acidic cleavage of its N-protection to give **13**. Due to the strong electron withdrawing nature of  $\text{CF}_3$  group, the acidity of the neighboring proton is relatively strong, and when the saponification reaction occurred at room temperature for 18 hours, epimerization was observed. When the saponification reaction was conducted using LiOH (1M, 2.5 eq.) in THF at 0 °C for 1h, the desired acid **12** was obtained without epimerization in a moderate yield (73%). The best conditions were found using NaOH (2M, 2.5 eq.) in EtOH at 0 °C for 1h, affording **12** without epimerization and in good yield (92%) and no purification needed (Scheme 2). The (*R*)-*tert*-butylsulfinyl group was cleaved at room temperature in the presence of HCl-Dioxane (4M, 30 eq.) for 3h to afford the salt **13** in quantitative yield.

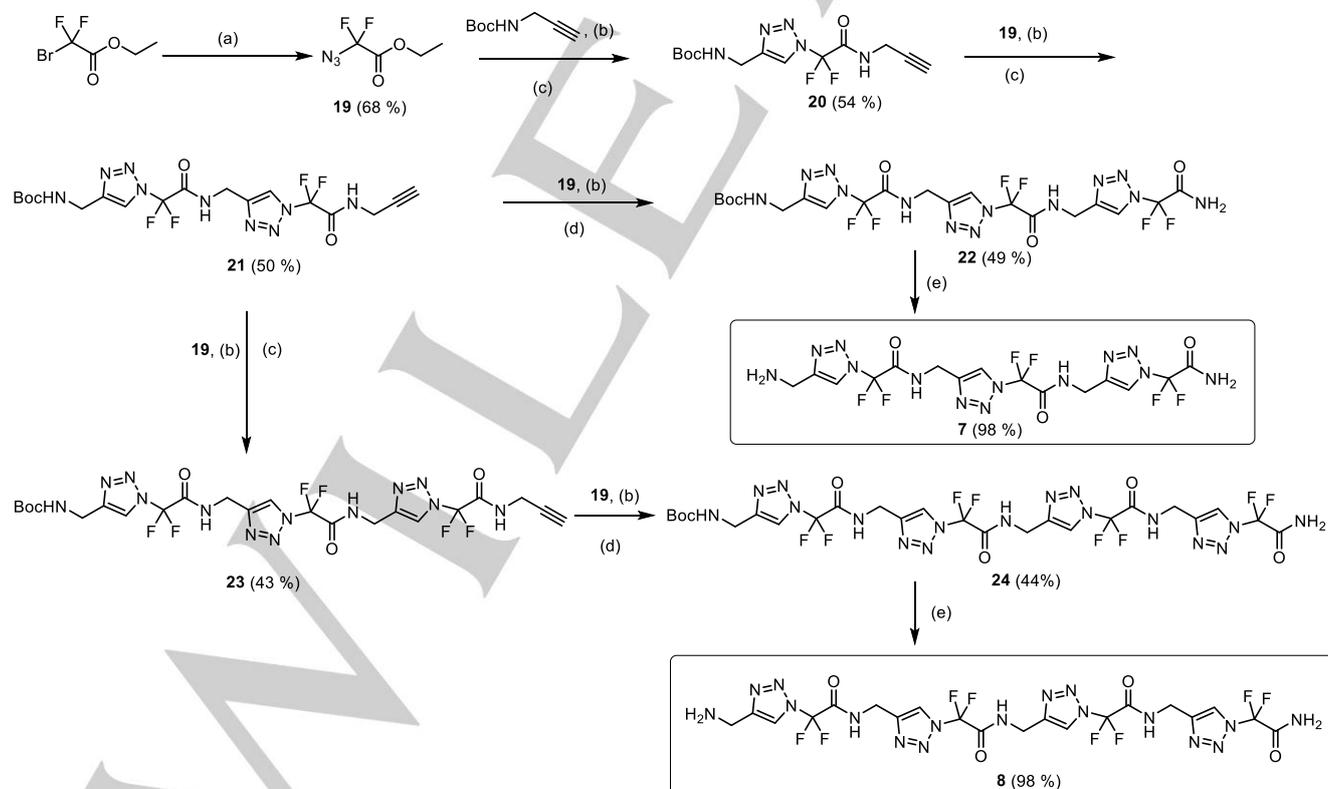
Having in hand the two deprotected monomers **12** and **13**, their coupling was attempted under various conditions. The best results were obtained with the use of HATU/HOAt/DIPEA

(1.5/1.8/3.4 eq.) in DMF for 18 hours affording the dimer **14** in 63% yield (53% using DMTMM/NMM and less than 25% with HBTU/HOBt/DIPEA or EDCI/HOBt/DIPEA). Next, the dimer **14** was successfully and separately deprotected at both sides using the previous procedures described for monomer **11**. Saponification (NaOH 2M, 2.5 eq.) gave the free carboxylic acid dimer **15** in 96% yield and the acidic cleavage of the *tert*-butylsulfinyl group (HCl-Dioxane 4M, 30 eq.) afforded the free amino dimer **16** in quantitative yield. Next, the trimer **17** and the tetramer **18** were synthesized by coupling the free acid dimer **15** with the monomer **13** or the dimer **16** respectively. The reactions occurred smoothly in DMF using HATU/HOAt as a coupling reagent in the presence of DIPEA and afforded both compounds **17** and **18** in satisfactory yields (60 and 65% respectively). Lastly, the fully *N*- and *C*-terminal deprotected trimer **5** and tetramer **6** were obtained via the same previous saponification/acidic cleavage protocols (in 34% and 5% yield respectively, after HPLC purification).

The synthesis of *N*-difluoromethyl 1,4-Tz amino acid scaffold **20** is described in Scheme 3 and starts with the preparation of ethyl 2-azido-2,2-difluoroacetate **19** using ethyl 2-bromo-2,2-difluoroacetate and sodium azide, in dry DMF at 35 °C overnight to provide the volatile corresponding azide **19** (68% of yield).<sup>[30]</sup> Then the triazole derivative in **20** was prepared using conditions similar to the previous synthesis of **11**. Azide **19** and Boc-protected propargylamine were mixed in the presence of CuI (10%) and triethylamine until the disappearance of the starting material (2 h). The intermediate ester which was unstable under purification conditions was subjected to amidification conditions using freshly distilled propargylamine. One to two hours at 0 °C were sufficient to provide the corresponding propargylamide **20** in satisfactory yield (54% for two steps). The same methodology using Huisgen 1,3-dipolar cycloaddition between **20** and azide **19** followed by amidification using propargylamine allowed the preparation of the dimer **21** (50% for two steps). The cycloaddition between **21** and **19** followed by amidification using ammonia in MeOH gave the trimer **22** (49% of yield for two steps). Successive cycloaddition of **21** with **19** and addition of propargylamine led to **23** (43% of yield for two steps), that was subjected to a cycloaddition with **19** and to amidification using ammonia in MeOH to give tetramer **24** (44% of yield for two steps). Hydrochloric acid solution in dioxane was used to cleave the Boc group of **22** and **24** to provide the final trimer **7** and tetramer **8**, respectively, in quantitative yields.



**Scheme 2.** Synthesis of trimer **5** and tetramer **6** based on trifluoromethyl homo-1,4-Tz amino acids (CF<sub>3</sub>-1,4-Tz). (a) NaOH (2M, 2.5 eq.), EtOH, 0 °C, 1-2h; (b) HCl-dioxane (4M, 60 eq.), dioxane or ethanol, rt, 3h; (c) HATU, HOAt, DIPEA, DMF, rt, 18 hours.



**Scheme 3.** Synthesis of trimer **7** and tetramer **8** based on N-difluoromethyl 1,4-Tz amino acids (1,4-Tz-CF<sub>2</sub>). (a) NaN<sub>3</sub> (1.05 eq.), DMF, 35 °C, 18 hours; (b) CuI (10%), NEt<sub>3</sub> (1.0 eq.), THF, rt, 2h; (c) propargylamine, THF, 0 °C, 2h; (d) ammonia in methanol (7N, 5 eq.), 0 °C, 2h; (e) HCl-dioxane (4M, 10 eq.), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 2h;

## Conformational analysis

## NMR

The conformational properties of oligomers **5-7** were conducted by NMR in a protic solvent, which is more challenging for intramolecular folding in comparison with aprotic organic solvents. However, as our attempts to perform these studies in aqueous solutions were hampered by their poor solubility in water, **5-7** were examined in CD<sub>3</sub>OH. Few drops of DMSO (5% DMSO-d<sub>6</sub> in CD<sub>3</sub>OH) were added to solubilize tetramers **6** and **8**. However, tetramer **8** was not enough soluble under these conditions and its characterization was performed in DMF-d<sub>7</sub>, as a compromise between solubility and polarity. The <sup>1</sup>H and <sup>13</sup>C chemical shift assignments of the four compounds are given in Tables S1-S12 (Supporting information, SI). A single set of chemical shifts was observed for all foldamers **5-8**.

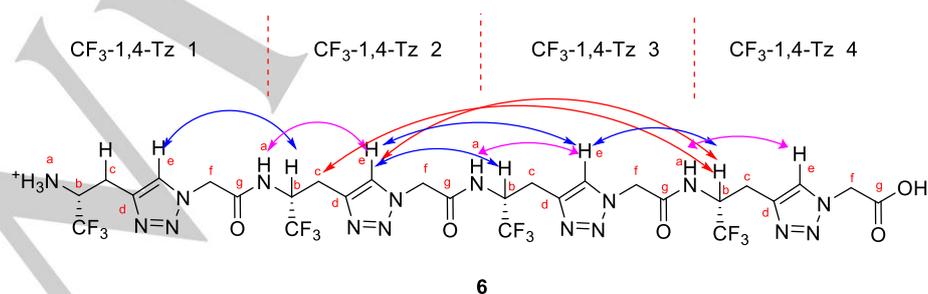
<sup>1</sup>H-<sup>1</sup>H ROE and <sup>1</sup>H-<sup>19</sup>F HOE correlations and the temperature coefficient of the amide bond NH protons temperature coefficient ( $\Delta\delta_{\text{HN}}/\Delta T$ ) were examined to analyze backbone conformational propensities. In aqueous and alcoholic solvents, small negative temperature coefficients ( $\Delta\delta_{\text{HN}}/\Delta T > -4.5$  ppb K<sup>-1</sup>) generally characterize amide protons that are engaged in intra (or inter) molecular hydrogen bonds, while more negative values ( $\Delta\delta_{\text{HN}}/\Delta T < -6$  ppb K<sup>-1</sup>) rather indicate their exposition to solvent. In the trimer of the CF<sub>3</sub>-1,4-Tz **5**, the analysis of  $\Delta\delta_{\text{HN}}/\Delta T$  between 283 and 303K revealed negative values of -6.5 ppb/K (Table 1), indicating that the amide bond NH protons were not engaged in stable intra- (or inter-) molecular hydrogen bonds. The values of temperature coefficients of the amide protons in tetramer **6** were more dispersed (Table 2). The  $\Delta\delta_{\text{HN}}/\Delta T$  value between 278 and 313K of NH<sup>a2</sup> (-2.5 ppb K<sup>-1</sup>) was very different from the other NH

$\Delta\delta_{\text{HN}}/\Delta T$  values (-9.1 and -6.9 ppb K<sup>-1</sup>). The relatively small  $\Delta\delta_{\text{HN}}/\Delta T$  value of NH<sup>a2</sup> (-2.5 ppb K<sup>-1</sup>) indicated that it could be engaged in hydrogen bonding.

The chemical shifts of equivalent protons (NH, CH<sub>Tz</sub>, CH $\alpha$ -CF<sub>3</sub>, CH<sub>2</sub> $\beta$ -CF<sub>3</sub>) as well as <sup>19</sup>F chemical shifts in trimer **5** were very close (Table 1 and experimental section in SI) and it was very challenging to assign ROE correlations. In particular, long range ROE correlations could not be assigned with certainty in the trimer of CF<sub>3</sub>-1,4-Tz **5**, suggesting that either trimer is flexible and does not adopt particular folded conformations or that it may adopt a rather extended conformation (equivalent <sup>1</sup>H are thus subject to a similar solvent environment). In the tetramer of the CF<sub>3</sub>-1,4-Tz **6**, <sup>1</sup>H and <sup>19</sup>F chemical shifts were a little more distinct than in trimer **5**. In particular, <sup>1</sup>H chemical shifts of the third and fourth triazole units were quite different from those of the second triazole unit (Table 2) while the <sup>19</sup>F chemical shifts of CF<sub>3</sub>-1,4-Tz **1** and **4** were rather different and distinct from those of CF<sub>3</sub>-1,4-Tz **2** and **3** (experimental section, SI). This observation can be due to a more stable folded structure leading to different environments of the corresponding proton and fluorine atoms in **6**. Furthermore, some interesting long-range ROE correlations were visible (Fig. 3). Long-range intra-residual NH<sup>a</sup>-CH<sup>e</sup><sub>Tz</sub> ROE correlations in three CF<sub>3</sub>-1,4-Tz units (**2-4**) were visible. Three long-range inter-residual ROEs between CH<sup>e</sup><sub>Tz</sub> of one CF<sub>3</sub>-1,4-Tz unit and CH $\alpha$ -CF<sub>3</sub> (H<sup>b</sup>) of the vicinal unit were present. A ROE correlation between the two CH<sup>e</sup><sub>Tz</sub> of the second and the third CF<sub>3</sub>-1,4-Tz units was also visible. Two long-range ROE correlations between one <sup>1</sup>H of CH<sub>2</sub> $\beta$ -CF<sub>3</sub> (H<sup>c</sup>) and the CH<sup>e</sup><sub>Tz</sub> of the second unit with the CH $\alpha$ -CF<sub>3</sub> (H<sup>b</sup>) of the fourth unit were also remarkable. These distinct long-range ROEs also indicate that tetramer **6** adopts a folded conformation.

**Table 1.** <sup>1</sup>H chemical shifts and <sup>3</sup>JHN-H $\alpha$  for trimer **5** in CD<sub>3</sub>OH at 283K. Temperature coefficients of NH between 283K and 303K.

Residue	a (ppm)	b (ppm)	c (ppm)	e (ppm)	f (ppm)	<sup>3</sup> JHN-H $\alpha$ (Hz)	$\Delta\delta/\Delta T$ (ppb.K <sup>-1</sup> )
CF <sub>3</sub> -1,4-Tz-1	-	4.54	3.16, 3.42	7.87	5.10, 5.26	-	-
CF <sub>3</sub> -1,4-Tz-2	9.13	4.91	3.04, 3.28	7.81	5.08, 5.25	8.8	-6.5
CF <sub>3</sub> -1,4-Tz-3	9.15	4.96	3.06, 3.33	7.90	5.29	9.1	-6.5



**Figure 3.** NMR conformational analysis of tetramer **6**: highlights of the intra-residues ROEs (magenta arrows) and inter-residues ROEs *i/i+1* (blue arrows) and *i/i+2* (red arrows) observed in methanol.

**Table 2.** <sup>1</sup>H chemical shifts and <sup>3</sup>J<sub>NH-H $\alpha$</sub>  for tetramer **6** in CD<sub>3</sub>OH at 283K. Temperature coefficients of NH between 278K and 313K.

Residue	a (ppm)	b (ppm)	c (ppm)	e (ppm)	f (ppm)	<sup>3</sup> J <sub>NH-H<math>\alpha</math></sub> (Hz)	$\Delta\delta/\Delta T$ (ppb.K <sup>-1</sup> )
<b>CF3-1,4-Tz-1</b>	8.97, 9.06	4.15	3.02, 3.27	7.87	4.88, 5.09	-	-
<b>CF3-1,4-Tz-2</b>	8.77	4.80	3.06, 3.28	7.62	5.08, 5.20	9	-2.5
<b>CF3-1,4-Tz-3</b>	9.26	4.79	3.00, 3.23	8.03	5.13, 5.25	9.8	-9.1
<b>CF3-1,4-Tz-4</b>	9.18	4.93	3.02, 3.31	7.83	5.08	10.2	-6.9

In trimer **7** and tetramer **8** of 1,4-Tz-CF<sub>2</sub>amino acid, the analysis of  $\Delta\delta_{\text{NH}}/\Delta T$  revealed negative values around -6.0 ppb/K (Tables 3 and 4), indicating that the amide bond NH protons were not engaged in stable intra- (or inter-) molecular hydrogen bonds. The chemical shifts of similar protons (NH, CH<sub>Tz</sub>, CH<sub>2</sub> $\alpha$ -Tz) were very close (Tables 7S and 10S, SI) and the <sup>19</sup>F chemical shifts were also very similar (with the two fluorines of each N-difluorotriazole unit being equivalent). A full assignment of chemical shifts in tetramer **8** was possible while only assignment by residue was done for trimer **7**. No long-range <sup>1</sup>H-<sup>1</sup>H ROE correlations were visible in both trimer **7** and tetramer **8**. This information suggests that trimer **7** and tetramer **8** could either be flexible and not adopt particular conformations or may rather adopt an extended conformation.

In both trimer **7** and tetramer **8**, 2D <sup>1</sup>H-<sup>19</sup>F HOESY confirmed short range correlations, within each 1,4-Tz-CF<sub>2</sub> unit, between the two fluorine atoms and the protons of the triazole and the NH of the successive unit (see SI, Fig 21S). Thus, as previously observed in our published studies, the rotations on both sides of the CF<sub>2</sub> group seem to be prevented because of either the steric hindrance of the two fluorines or a stabilizing electrostatic interaction between the fluorine atom and the neighbouring protons.<sup>[25]</sup> However, no long-range <sup>19</sup>F-<sup>1</sup>H heteroNOE correlations between different units were observed, confirming an extended conformation.

**Table 3.** <sup>1</sup>H chemical shifts for trimer **7** in CD<sub>3</sub>OH at 313K. Temperature coefficients of NH between 283K and 313K.

Residue	a (ppm)	b (ppm)	d (ppm)	$\Delta\delta/\Delta T$ (ppb.K <sup>-1</sup> )
1,4-Tz-CF <sub>2</sub> 1	-	4.32	8.61	
1,4-Tz-CF <sub>2</sub> 2	10.10	4.69	8.42	-6.0
1,4-Tz-CF <sub>2</sub> 3	10.04	4.69	8.48	-6.0

**Table 4.** <sup>1</sup>H chemical shifts for tetramer **8** in DMF-d<sub>7</sub> at 313K. Temperature coefficients of NH between 283K and 313K.

Residue	a (ppm)	b (ppm)	d (ppm)	$\Delta\delta/\Delta T$ (ppb.K <sup>-1</sup> )
1,4-Tz-CF <sub>2</sub> 1	-	4.52	8.83	
1,4-Tz-CF <sub>2</sub> 2/3/4	10.13	4.74	8.34	-5.3
1,4-Tz-CF <sub>2</sub> 2/3/4	10.25	4.77	8.64	-6.0
1,4-Tz-CF <sub>2</sub> 2/3/4	10.35	4.80	8.52	-6.0

### Molecular modelling

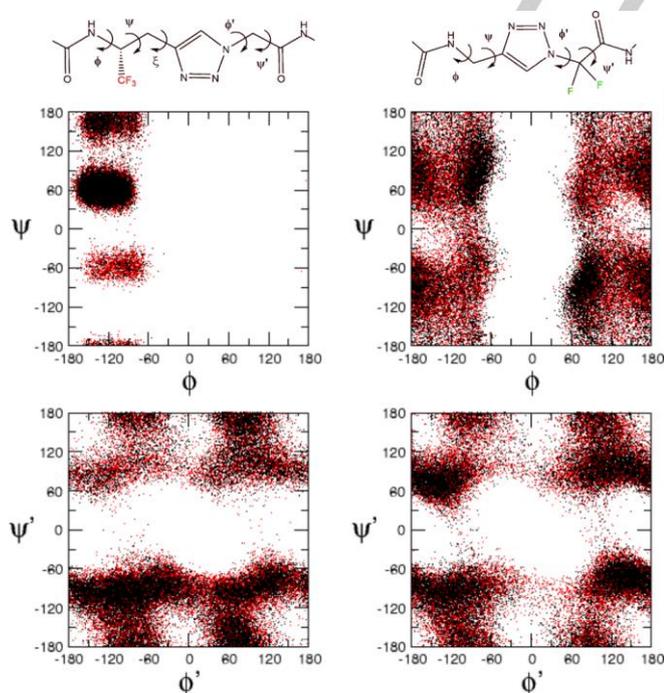
To complement experimental information on the structures of triazolamers **5**, **6**, **7**, and **8**, we conducted a molecular dynamics (MD) study of these compounds. Each molecule was submitted to 200 ns MD simulations in explicit methanol solvent to be as close as possible to NMR conditions (see details of the method in the experimental section). Convergence of our simulations was evaluated first by visually inspecting the time-evolution of RMSD relative to the initial conformation and that of the radius of gyration (Figure 25S, SI), and by comparing distributions of radius of gyration over the three time windows 0-100 ns, 50-150 ns, and 100-200 ns (Figure 26S, SI).

We first examined the local structure and flexibility of triazolamer backbones by plotting Ramachandran diagrams with ( $\phi$ ,  $\psi$ ) values of the first amino acid of the dipeptide unit (at the left of Tz) and the ( $\phi'$ ,  $\psi'$ ) for the second amino acid moieties (at the right of Tz, Fig. 5). In CF<sub>3</sub>-1,4-Tz trimer **5** and tetramer **6**, the ( $\phi$ ,  $\psi$ ) angles of the CF<sub>3</sub>- $\beta$ -amino acids mainly sampled two limited regions centered around (-140°, 60°) and (-140°, 160°), conferring to CF<sub>3</sub>-residues a local conformation either similar to a  $\gamma'$ -turn or extended as in  $\beta$ -strand, respectively.<sup>[31]</sup> Accordingly, the calculated <sup>3</sup>J(<sub>NH</sub>-H $\alpha$ ) couplings for these residues have rather large values in good agreement with the available NMR data (Table 5). In 1,4-Tz-CF<sub>2</sub> triazolamers **7** and **8**, the glycine amino acid ( $\phi$ ,  $\psi$ ) angles explored a much wider region which is approximately twofold-symmetric around the (0°, 0°) point, as expected by the lack of C $\beta$  in their side chain.<sup>[31]</sup>

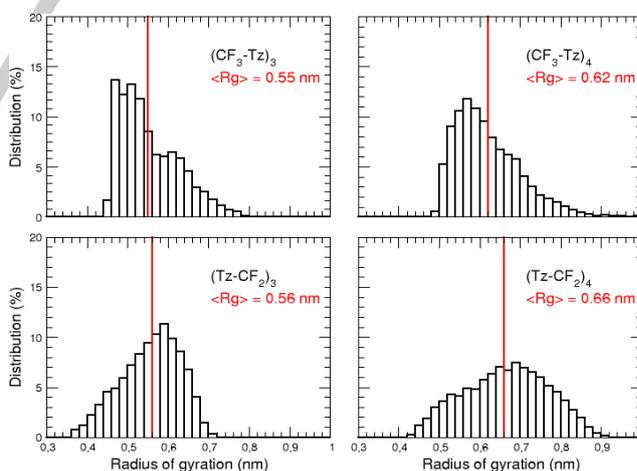
**Table 5.** Trifluoromethyl amino acid  $^3J(\text{H}_\text{N}\text{-H}_\alpha)$  coupling values averaged over MD trajectories or measured in NMR experiments.

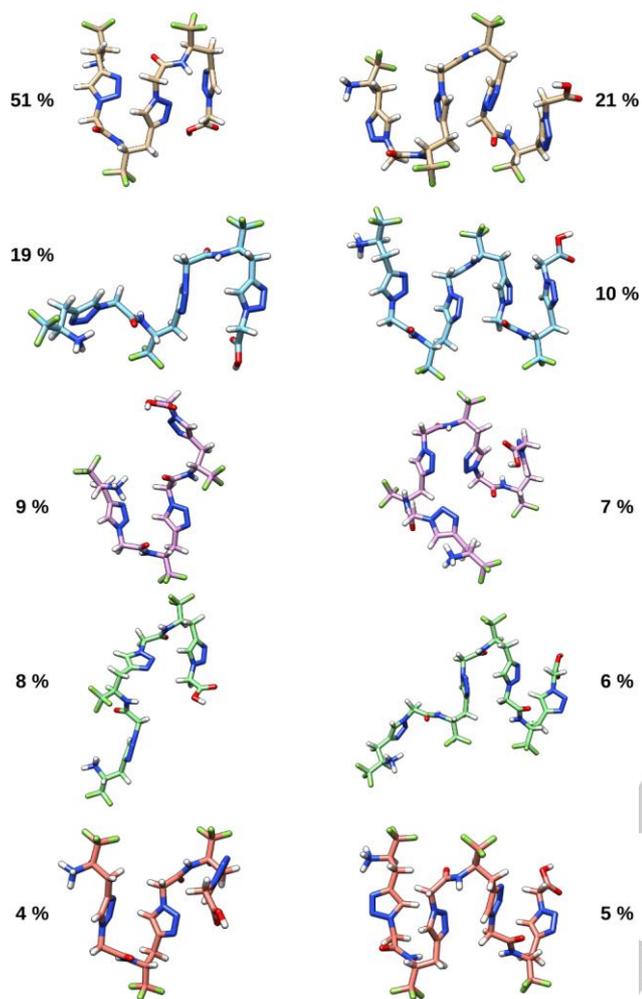
		CF <sub>3</sub> -1,4-Tz 2	CF <sub>3</sub> -1,4-Tz 3	CF <sub>3</sub> -1,4-Tz 4
Trimer <b>5</b>	MD	8.5	8.5	
	NMR	8.8	9.1	
Tetramer <b>6</b>	MD	8.4	8.5	8.5
	NMR	9.0	9.8	10.2

Regarding the ( $\phi$ ,  $\psi$ ) angles, the two hydrogens or fluorines on the C $\alpha$  (right of Tz moieties) also provide Ramachandran plots approximately twofold-symmetric around their central point (Fig. 5), indicating large flexibility at these positions. Nevertheless, it could be noted that, whereas the  $\phi'$  torsion of CF<sub>3</sub>-1,4-Tz triazolamers quasi-equally sampled all values between  $[-180^\circ, 180^\circ]$ , the 1,4-Tz-CF<sub>2</sub>  $\phi'$  angle preferentially adopted large values in the ranges  $[-180^\circ, -90^\circ]$  of  $[90^\circ, 180^\circ]$ . This suggests that the two fluorine atoms preferentially pointed toward the triazole proton and restricted the rotation around the N-C $\alpha$  bond. Altogether, it seems that both CF<sub>3</sub> and CF<sub>2</sub> groups induce a local stiffening of the triazolamer backbone. However, when compared to 1,4-Tz-CF<sub>2</sub>, the CF<sub>3</sub>-1,4-Tz main chain has one additional carbon and one supplementary degree of freedom per building block which allows it to explore compact or folded tertiary structures.

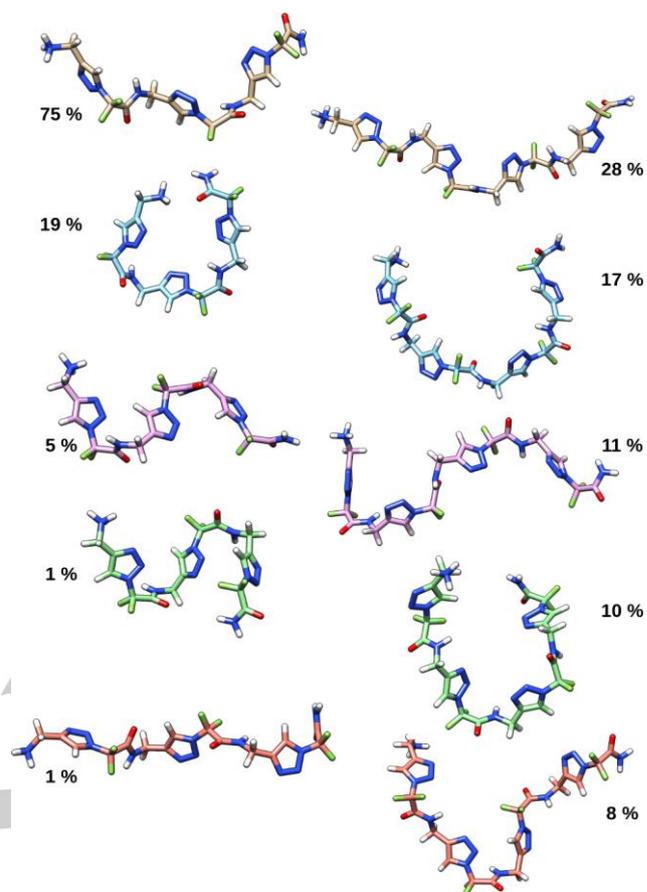
**Figure 5.** Ramachandran plots of the first amino acid of the dipeptide unit (left of Tz) ( $\phi$ ,  $\psi$ ) dihedral angles (top row) and of the second amino acid (right of Tz) ( $\phi'$ ,  $\psi'$ ) torsions (bottom row) in the CF<sub>3</sub>-1,4-Tz trimer **5** and tetramer **6** (left column) and in the 1,4-Tz-CF<sub>2</sub> trimer **7** and tetramer **8** (right column). Black and red points correspond to trimer and tetramer, respectively.

Indeed, despite the additional carbon in their main chain, the distributions of radius of gyration of the CF<sub>3</sub>-1,4-Tz trimer **5** and tetramer **6** are shifted toward lower values than for the 1,4-Tz-CF<sub>2</sub> triazolamers **7** and **8** (Fig. 6). The compact structures sampled by the CF<sub>3</sub>-1,4-Tz triazolamers can be seen in Fig. 7 and compared with the more extended conformations of the 1,4-Tz-CF<sub>2</sub> trimer and tetramer in Fig. 8. The latter illustrates how the local stiffness of the 1,4-Tz-CF<sub>2</sub> main chains prevents them to fold into compact structures and provide to these triazolamers with a worm-like chain behavior. In contrast, the CF<sub>3</sub>-1,4-Tz main chains are sufficiently flexible for allowing the triazole moieties to move closer each other, resulting in transient folded ladder-like structures mimicking short multi-stranded  $\beta$ -sheet. Particularly, in tetramer **6** the central CF<sub>3</sub>-1,4-Tz units 2 and 3 are closed in all the representative structures of the most populated clusters, generated by *gmx cluster* with a RMSD threshold of 0.3 nm (Fig. 7). These folded structures are not maintained by hydrogen bonds between NH and CO nor by hydrophobic CF<sub>3</sub>-CF<sub>3</sub> interactions, but rather by electrostatic interactions between triazole protons He and N2 atom of neighboring subunits. Indeed, as shown in Figure 9, distances between triazole protons He (partially positively charged) and N2 atom (partially negatively charged) of neighboring subunits exhibit bimodal distributions with a close distance around 0.3 nm. These structures might also be favored by  $\pi$ -stacking<sup>[24]</sup> and dipole-dipole interactions<sup>[21]</sup> between triazole units, as previously suggested.

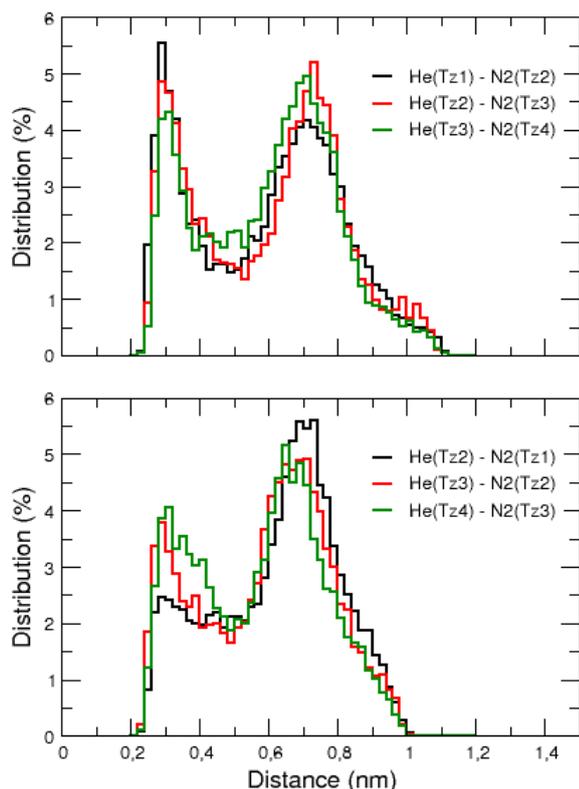
**Figure 6.** Distribution of radius of gyration for the CF<sub>3</sub>-1,4-Tz trimer **5** (top, left) and tetramer **6** (top right) as well as for the 1,4-Tz-CF<sub>2</sub> trimer **7** (bottom left) and tetramer **8** (bottom right), calculated over the 200 ns trajectories.



**Figure 7.** Representative structures of the 5 most populated clusters of the CF<sub>3</sub>-1,4-Tz trimers **5** (left column) and tetramer **6** (right column).

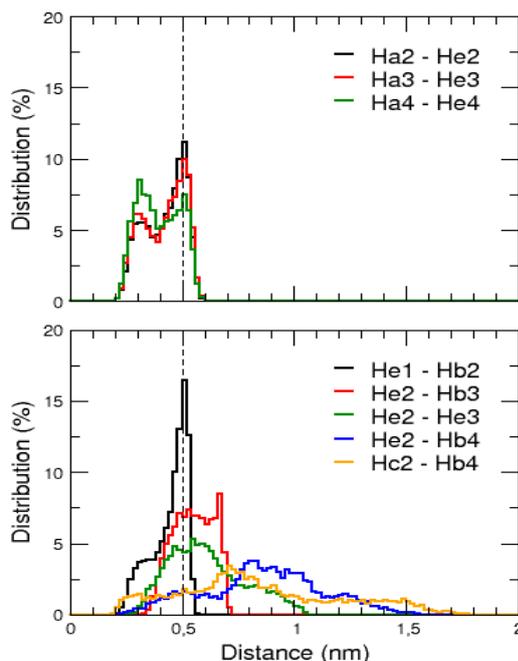


**Figure 8.** Representative structures of the 5 most populated clusters of the 1,4-Tz-CF<sub>2</sub> trimer **7** (left column) and tetramer **8** (right column).



**Figure 9.** Distributions of distance between proton He of triazole *i* and N2 atom of triazole *i*+1 (top) or *i*-1 (bottom) computed from the MD trajectory of tetramer **6**.

The propensity of the CF<sub>3</sub>-1,4-Tz tetramer **6** to form transient ladder-like structure in MD simulations is rather consistent with a few inter-residue NOE detected in NMR experiments (Fig. 3). Indeed, the distances between the involved protons computed from its MD trajectory have significant probabilities to be lower than 5 Å which is the conventional threshold for observing NOE correlations (Fig. 10).



**Figure 10.** Distance distributions of pairs of intra-residue (top) and inter-residue (bottom) protons in the ensemble of structures obtained along the MD trajectory for which NOE can be detected in CF<sub>3</sub>-1,4-Tz tetramer **6**.

## Conclusions

Easily accessible fluorinated triazolamers based on 2-amino-3,3,3-trifluoropropyl-1,4-triazolyl acetic acid (CF<sub>3</sub>-1,4-Tz) and on aminomethyl-1,4-triazolyl-difluoroacetic acid (1,4-Tz-CF<sub>2</sub>) were studied by experimental and computational methods. While many foldamers have been designed and studied, to our knowledge, only three examples of fluorinated peptidomimetic foldamers have been reported to date, two of which are capable of adopting a helical conformation and one which behaves like a strand-like peptide. Triazolamers based on flexible CF<sub>3</sub>-1,4-Tz can adopt folded ladder-like structures mimicking short multi-stranded  $\beta$ -sheet. The driving forces in these structures are rather  $\pi$ -stacking<sup>24</sup> and dipole-dipole interactions<sup>21</sup> of triazole units than NH-CO hydrogen bonding and hydrophobic CF<sub>3</sub>-CF<sub>3</sub> interactions. Very few multi-stranded foldamers have been reported to date.<sup>[32-34]</sup> On the contrary triazolamers built on the less flexible 1,4-Tz-CF<sub>2</sub> adopt rather extended or worm-like chain structures. These two new classes of foldamers could then be explored in different fields and applications, in particular as potential modulators of protein-protein interactions (PPIs) involving  $\beta$ -sheet structures. Indeed while the knowledge of these type of interactions is still in its infancy, they have been already questioned in many fatal human diseases such as cancer, autoimmune and neurodegenerative diseases.<sup>[35]</sup> Pre-organized foldamers adopting extended  $\beta$ -strand like or multi-stranded  $\beta$ -sheet like structures might offer valuable opportunities to study and/or to modulate these PPI.

## Experimental Section

### Synthetic methods

See Supporting Information (SI) for details on the general experimental methods, on the syntheses and characterization of intermediates **9-24** and of final compounds **5-8**.

### Procedure for the Huisgen click reaction to obtain the protected trifluoromethyl homo-1,4-Tz amino ester (CF<sub>3</sub>-1,4-Tz) **11**:

To a solution of azide **10** (1.56 g, 12 mmol) and trifluoromethyl homopropargylamine **9** (2.41 g, 10 mmol) in acetonitrile (10 mL) was added a catalytic amount of CuI (190 mg, 10 mol%) and Et<sub>3</sub>N (1.01 g, 10 mmol). The reaction was stirred at room temperature until completion (3h). The solution was diluted with brine (20 mL) and the aqueous layer was extracted with AcOEt (20 mL x3). The combined organic layers were dried over MgSO<sub>4</sub> and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using cyclohexane/EtOAc (1:2) as eluent. Compound **11** (2.81 g, 7.6 mmol) was obtained as a white solid in 76% yield.

### General procedure for the Huisgen click reaction for 1,4-Tz-CF<sub>2</sub> based oligomers:

To a solution of azide (1.0 equiv.) in dry THF (0.5 M) was added alkyne (1.0 equiv.) under argon. At 0 °C, CuI (10 mol%) and Et<sub>3</sub>N (1.0 equiv.) were added. The mixture was stirred at room temperature for 2 hours. After completion, reaction was quenched using NH<sub>4</sub>Cl sat., extracted with EtOAc (3x 10 mL). The organic layers were washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. Because of the instability of the ester on silica, the product is not isolated and directly put under the following amidification condition. To a solution of difluoroacetylated triazole (1.0 equiv.) in THF (1.0 M) was added freshly distilled propargylamine (1.1 equiv.), or in MeOH (1.0 M) was added a solution of ammonia in methanol (7 N, 5 equiv.) under argon at 0 °C. The mixture was stirred at 0 °C during 1 to 2 hours. After completion, the solution was concentrated under vacuum. The crude was purified by column chromatography using the appropriate solvent (for more details see SI).

### General procedure for the amide bond formation of the CF<sub>3</sub>-1,4-Tz based oligomers:

To the acid derivative (1 equiv.) in solution in dry DMF at 0 °C were added HATU (1.5 equiv.) and HOAt (1.8 equiv.) and the mixture was stirred at 0 °C for 60 min. Then the amine derivative (1.3 equiv.) and DIPEA (3.4 equiv.) were added at 0 °C. The reaction was stirred at room temperature overnight. After completion, the DMF was removed under vacuum. The residue was diluted with EtOAc (10 mL) and washed with 10% aqueous citric acid (10 mL) and 10% NaHCO<sub>3</sub> solution (10 mL), brine (10 mL) and then the organic layer was dried over MgSO<sub>4</sub>. The crude product was purified by column chromatography.

### Trimer (**5**) based on trifluoromethyl homo-1,4-Tz amino acids (CF<sub>3</sub>-1,4-Tz).

Compound **17** (36 mg, 0.045 mmol) was added to a round bottom flask with EtOH (5 mL) at 0 °C. Then an aqueous solution of NaOH 2M (60 µL, 2.5 eq.) was added and the reaction was stirred at 0 °C for 2h and at room temperature for 1h. Then TLC showed the reaction finished completely. EtOH was removed under reduced pressure, then to the residue was added H<sub>2</sub>O (5 mL) and EtOAc (10 mL) and acidified using HCl (1 M, 0.3 mL) at 0 °C to pH 3 (pH Paper). Then quickly extracted with EtOAc (3x10 mL), the organic phase was dried with anhydrous MgSO<sub>4</sub> and the solvent evaporated affording a white solid, which was pure enough for the next reaction.

The resulting acid (34 mg, 0.043 mmol) was dissolved in 2.0 mL dioxane at rt, then HCl-dioxane (4.0 M HCl in dioxane, 330 µL, 1,30 mmol, 30 eq.) was added. The reaction was stirred at r.t. for 3h. After 3h reaction time, the solvent was evaporated under reduced pressure, then the crude residue was subjected to reverse phase preparative HPLC purification and after lyophilization, the salt TFA **5** was obtained as white powder in 34% yield (12 mg, 0.015 mmol).

Preparative HPLC: 44 mg of crude dissolved in 4 mL H<sub>2</sub>O + 1 mL MeCN A: H<sub>2</sub>O + 0.1% TFA, B: MeCN + 0.1% TFA, Column: C18, 150 × 20 mm id, 5 µm, 200 Å, Method Set: 20 min/ 20 mL, Injection Volume: 5.0 mL, Run Time: 30 min, Purification gradients: 20% - 50% MeCN + 0.1% TFA; Analytical HPLC: Sunfire C18 – 2.1 × 150 mm – 3.5 µm; 5% - 95% MeCN + 0.1% TFA in 10 min, UV-Vis wavelength: 220 nm, t<sub>R</sub> = 5.21 min, purity: 100 %. IR (cm<sup>-1</sup>): 3281, 2923, 2852, 1711, 1637, 1557, 1462, 1377, 1260, 1181, 1128, 802; <sup>1</sup>H NMR (800 MHz, CD<sub>3</sub>OH) δ See Tables 1 and 1S, SI; <sup>13</sup>C NMR (200 MHz, CD<sub>3</sub>OH) δ See Table 2S, SI; <sup>19</sup>F NMR (564 MHz, CD<sub>3</sub>OH, decoupled) δ -76.86, -77.20, -77.30, -77.60; ESI-HRMS: m/z calcd for C<sub>21</sub>H<sub>24</sub>F<sub>9</sub>N<sub>12</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 679.1900, found: 679.1912; HPLC analysis: column Xbridge C18 2.1\*150mm – 3.5µm; eluent: H<sub>2</sub>O (0.1% formic acid)/ acetonitrile – gradient : 5-100% in 20 min; t<sub>R</sub> = 9.28 min.

### Tetramer (**6**) based on trifluoromethyl homo-1,4-Tz amino acids (CF<sub>3</sub>-1,4-Tz).

The tetramer **18** (50 mg, 0.085 mmol) was added to a round bottom flask with EtOH (2 mL) at 0 °C. Then an aqueous solution of NaOH 2 M (105 µL, 2.5 equiv.) was added and the reaction was stirred at 0 °C for 2 hours. When TLC showed the reaction finished completely, EtOH was removed under reduced pressure, to the residue was added H<sub>2</sub>O (5 mL) and EtOAc (10 mL) and acidified using HCl (1 M, 0.5 mL) at 0 °C to make the pH was 3 (pH paper). Then quickly extracted with EtOAc (3x10 mL), the organic phase was dried with anhydrous MgSO<sub>4</sub> and the solvent evaporated affording the acid as a white solid in quantitative yield (48 mg), which was pure enough for the next reaction. Then the corresponding acid (48 mg) was dissolved in 2.0 mL DMSO at rt, then HCl-dioxane (4.0 M HCl in dioxane, 640 µL, 2.55 mmol, 30 equiv.) was added. After 3 hours at rt, evaporated all the solvent

as much as possible under reduced pressure, then added diethyl ether to the DMSO solution and compound **6** precipitated. The solvent was removed and **6** was subjected to reverse phase preparative HPLC purification, after lyophilization the salt **6** was obtained as a white powder in 5% yield (4 mg, 0.004 mmol).

Preparative HPLC: 60 mg of crude dissolved in 4 mL H<sub>2</sub>O + 1 mL MeCN; A: H<sub>2</sub>O + 0.1% TFA, B: MeCN + 0.1% TFA, Column: C18, 150 × 20 mm id, 5 μm, 200 Å, Method Set: 20 min/ 20 mL, Injection Volume: 5.0 mL, Run Time: 30 min, Purification gradients: 20% - 50% MeCN + 0.1% TFA; After preparative HPLC: 5% - 95% MeCN + 0.1% TFA in 10 min, UV-Vis wavelength: 220 nm, t<sub>R</sub> = 5.87 min, purity: 100 %; R<sub>f</sub> = 0 (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH: 95/5); IR (cm<sup>-1</sup>): 3232, 2926, 1690, 1561, 1439, 1391, 1251, 1203, 1180, 1124, 800, 721; <sup>1</sup>H NMR (800 MHz, CD<sub>3</sub>OH) δ See Tables 2 and 4S, SI; <sup>13</sup>C NMR (200 MHz, CD<sub>3</sub>OD) δ See Table 5S, SI; <sup>19</sup>F NMR (564 MHz, CD<sub>3</sub>OH, decoupled) δ -76.63, -77.06, -77.11, -77.25; ESI-HRMS: m/z calcd for C<sub>28</sub>H<sub>31</sub>F<sub>12</sub>N<sub>16</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 899.2472, found: 899.2465; m/z calcd for C<sub>28</sub>H<sub>30</sub>F<sub>12</sub>N<sub>16</sub>O<sub>5</sub>Na [M+Na]<sup>+</sup>: 921.2291, found: 921.2292; HPLC analysis: column Xbridge C18 2.1\*150mm – 3.5μm; eluent: H<sub>2</sub>O (0.1% formic acid)/ acetonitrile – gradient: 5-100% in 20 min; t<sub>R</sub> = 10.73 min.; purity: 100 %.

#### Trimer (**7**) based on N-difluoromethyl 1,4-Tz amino acids (1,4-Tz-CF<sub>2</sub>).

The product was obtained from **22** (51 mg, 0.080 mmol) in solution operating in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) to which was added a solution of HCl in dioxane (4.0 M) at 0 °C. The mixture was stirred at room temperature for 2 hours and then concentrated under vacuum to provide **7** as a white solid (45 mg, 98 %) that is pure enough for its characterization.

R<sub>f</sub> = 0.10 (CH<sub>2</sub>Cl<sub>2</sub>/ CH<sub>3</sub>OH : 9/1); IR: 3303, 3149, 1703, 1553, 1437, 1342, 1221, 1181, 1144, 1034; Melting point : 92-94 °C; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ 159.2 (t, <sup>2</sup>J(C,F) = 30.3 Hz), 157.8 (t, <sup>2</sup>J(C,F) = 31.8 Hz), 157.7 (t, <sup>2</sup>J(C,F) = 30.8 Hz), 144.2, 144.1, 141.5, 123.5, 122.2, 122.1, 110.2 (t, <sup>1</sup>J(C,F) = 267.9 Hz), 34.7, 33.5; <sup>19</sup>F NMR (376 MHz, DMSO-d<sub>6</sub>): δ -85.66 (s, 2F), -86.08 (s, 2F), -86.15 (s, 2F); <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OH) δ See Tables 3 and 7S; <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>OH) δ See Table 8S, SI; <sup>19</sup>F NMR (564 MHz, CD<sub>3</sub>OH, decoupled): δ -88.04 (s, 2F), -88.75 (s, 2F), -89.09 (s, 2F); HRMS (ESI-TOF) m/z C<sub>15</sub>H<sub>16</sub>N<sub>13</sub>O<sub>3</sub>F<sub>6</sub> [M+H]<sup>+</sup> cal. 540.1411, found 540.1403; HPLC analysis: column XSelect C18 2.1\*150mm – 3.5μm; eluent: H<sub>2</sub>O (0.1% formic acid)/ acetonitrile – gradient : 5-100% in 20 min; t<sub>R</sub> = 13.07 min. Area% = 100.

#### N-difluoromethyl-triazole Tetramer (**8**).

The product was obtained from **24** (12 mg, 0.015 mmol) in solution operating in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) to which was added a solution of HCl in dioxane (4.0 M) at 0 °C. The mixture was stirred at room temperature for 2 hours and then concentrated under vacuum to provide a white solid (11 mg, 98 %). HPLC purification: column

Pursuit 5 C18 250\*10.0mm; eluent: H<sub>2</sub>O (0.1% formic acid)/ acetonitrile – gradient : 5-50% in 20 min; t<sub>R</sub> = 10.07 min; R<sub>f</sub> = 0.1 (CH<sub>2</sub>Cl<sub>2</sub>/ CH<sub>3</sub>OH: 88/12); IR: 3308, 3135, 2985, 1548, 1437, 1342, 1221, 1181, 1034, 971; <sup>1</sup>H NMR (600 MHz, DMF-d<sub>7</sub>) δ See Tables 4 and 10S, SI; <sup>13</sup>C NMR (150 MHz, DMF-d<sub>7</sub>) δ See Table 11S, SI; <sup>19</sup>F NMR (564 MHz, CD<sub>3</sub>OH): δ -77.08 (TFA), -87.71 (s, 2F), -89.09 (s, 2F), -89.07 (s, 2F), -89.46 (s, 2F). Melting point: 104-106 °C; HRMS (ESI-TOF) m/z C<sub>20</sub>H<sub>20</sub>N<sub>17</sub>O<sub>4</sub>F<sub>8</sub> [M+H]<sup>+</sup> cal. 713.1678, found 713.1687; HPLC analysis: column XSelect C18 2.1\*150mm – 3.5μm; eluent: H<sub>2</sub>O (0.1% formic acid)/ acetonitrile – gradient : 5-100% in 20 min; t<sub>R</sub> = 7.57 min. Area% = 96.

#### Conformational analysis by NMR

See Supporting Information for details.

NMR spectra were recorded on Bruker AVANCE III spectrometers operating at 600MHz (<sup>1</sup>H, 600 MHz, <sup>13</sup>C, 150 MHz, <sup>19</sup>F, 564 MHz) and equipped with a z-gradient TCI or <sup>19</sup>F-QCI cryoprobe, or operating at 800MHz (<sup>1</sup>H, 800 MHz, <sup>13</sup>C, 200 MHz) and equipped with a z-gradient TCI cryoprobe. The <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F chemical shifts of the compounds were assigned using 1D <sup>1</sup>H (with excitation sculpting with gradients for solvent signal suppression), 1D <sup>19</sup>F, 2D <sup>1</sup>H-<sup>1</sup>H TOCSY, 2D <sup>1</sup>H-<sup>1</sup>H ROESY, 2D <sup>1</sup>H-<sup>19</sup>F HOESY, 2D <sup>1</sup>H-<sup>13</sup>C HSQC, and 2D <sup>1</sup>H-<sup>13</sup>C HMBC spectra, recorded at 283 K or 313K.

#### Computational methods

Initial structures of triazolamers **5**, **6**, **7**, and **8** were generated using the 2D to 3D structure conversion program MarvinSketch 6.2.1 from ChemAxon.<sup>[36]</sup> Compound topologies and parameters were generated using the python-based tool ACPYPE.<sup>[37]</sup> Simulations of CF<sub>3</sub>-1,4-Tz and 1,4-Tz-CF<sub>2</sub> compounds were performed with the molecular simulation package GROMACS versions 5.1 and 2016, respectively.<sup>[38]</sup> The Generalized AMBER Force Field (GAFF)<sup>[39]</sup> was used for both solutes and methanol solvent. Each triazolamer was initially placed in a simulation cubic box which dimension is set to the solute largest dimension plus twice 1.4 nm and filled with methanol molecules and one chloride ion to neutralize the systems. Electrostatic interactions were treated using the smooth PME method<sup>[40]</sup> and Lennard-Jones potentials were cut-off at the distance of 1.2 nm. Covalent bond lengths were kept constant using the LINCS procedure,<sup>[41]</sup> allowing a time step of 2 fs. Studied systems were first equilibrated using two short MD simulations of 1 ns each to reach the target temperature T = 300 K and pressure P = 1 bar. Then, each system was simulated during 200 ns in the NPT ensemble using the Nose-Hoover and Parrinello-Rahman coupling methods.<sup>[42–44]</sup> Trajectory coordinates were saved every 20 ps for subsequent analyses using GROMACS tools, including *gmx mindist*, *gmx angle*, and *gmx gyrate* for extracting intramolecular distances, dihedral angles, and radius of gyration, respectively. Conformational ensembles were clustered with a RMSD threshold of 0.3 nm using the *gromos* method<sup>[45]</sup> implemented in the GROMACS program *gmx cluster*.

## Acknowledgements

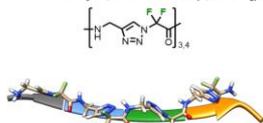
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**Keywords:** peptidomimetics, peptides, amino acids, Fluorine, oligomer, conformation analysis, strand

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## Table of Contents

Trifluoromethyl homo-1,4-Tz amino acid (CF<sub>3</sub>-1,4-Tz)*N*-difluoromethyl 1,4-Tz amino acid (1,4-Tz-CF<sub>2</sub>)

The syntheses and the conformational analyses of the first fluorinated oligomers of triazole, also called triazolamers are reported. Triazolamers based on trifluoromethyl homo-1,4-Tz amino acid, considered as a mimic of a  $\beta,\alpha$ -dipeptide, adopt short multi-stranded  $\beta$ -sheet like structure, while triazolamers based on *N*-difluoromethyl 1,4-Tz amino acid, considered as an analogue of Gly-difluoroGly dipeptide, show elongated  $\beta$ -strand like structure.

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