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# Synthesis of conformationally constrained β-turn thiazolidine mimetic

Paolo Grieco,* Pietro Campiglia, Isabel Gomez-Monterrey and Ettore Novellino

*Dipartimento di Chimica Farmaceutica e Tossicologia, Università di Napoli 'Federico II', Via D. Montesano, 49-80131 Napoli, Italy*

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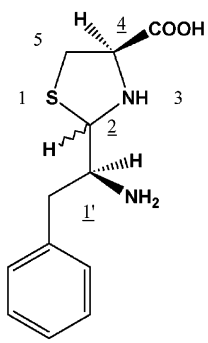
**Abstract**—A dipeptide analog β-turn mimetic with fixed configuration at α-carbons of two amino acid residues in structure type β-turn has been synthesized starting from *L*-phenilalanine and *L*-cysteine in short steps. 

β-Turns are one of three major secondary structural elements of peptides and proteins and play an important role in many of the molecular recognition events in biological systems.[1] A great effort has therefore focused on design and synthesis of small constrained mimetics of turn structure to provide a better understanding of the molecular basis of peptides and proteins interactions with aim to provide potent and selective therapeutic agents.[2,3] Retention of the orientation of the amino acid side chains with simultaneous replacement of the peptide backbone by nonpeptide structures, so-called β-turn mimetics, has become an established topic in the structural design of peptide mimetics. Turn mimetics can be categorized in two distinct groups, internal and external, as displayed by structure of Kahn and Olson.[4,5] A external β-turn mimic structure usually consist of a conformationally restricted dipeptide. We wish to report a new β-turn mimetic based on thiazolidine moiety, as shown in Fig. 1.

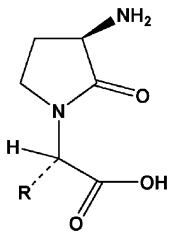
Modeling study using the SYBYL 6.0 molecular modeling program was performed on structure **1** to determine its propensity to adopt a β-turn. The results suggest that the absolute configuration of C-2, C-4 and, C-1′ can affect the conformation of the backbone which will ultimately influence the overall structure. We found that the better β-turn mimetic model is obtained with C-4 and C-1′ in configuration *L*. Also, the modeling indicates that the stereochemistry of C-2 does not influence the conformation of thiazolidine ring and the overall structure to adopt a β-turn motif. Thus, both diasteroimers could be used as β-turn mimetics, Fig. 2.

The synthesis of compound **1** was accomplished by a modified Schmidt[6] procedure from commercially available amino acids (Scheme 1). In our case, the starting Fmoc-*L*-Phe-H was prepared from Fmoc-*L*-Phe-OH by reduction of its *N*,*O*-dimethylhydroxamate derivative with $LiAlH_4$ in dry THF, according to the methods developed by Fehrentz and Castro and reported by Hruby.[7,8]

Subsequently, cysteine hydrochloride was dissolved in water and potassium hydrogen carbonate was added following the addition of solution of aldehyde dissolved in aqueous ethanol.[9] Although our focus was on phenylalanine in this work, it is expected that this procedure will be useful to get differents β-turn structures starting from others amino acids.




Compound **1**




External turn mimetic

**Figure 1.**

* Corresponding author. Fax: +39-081-678630; e-mail: pagrieco@unina.it

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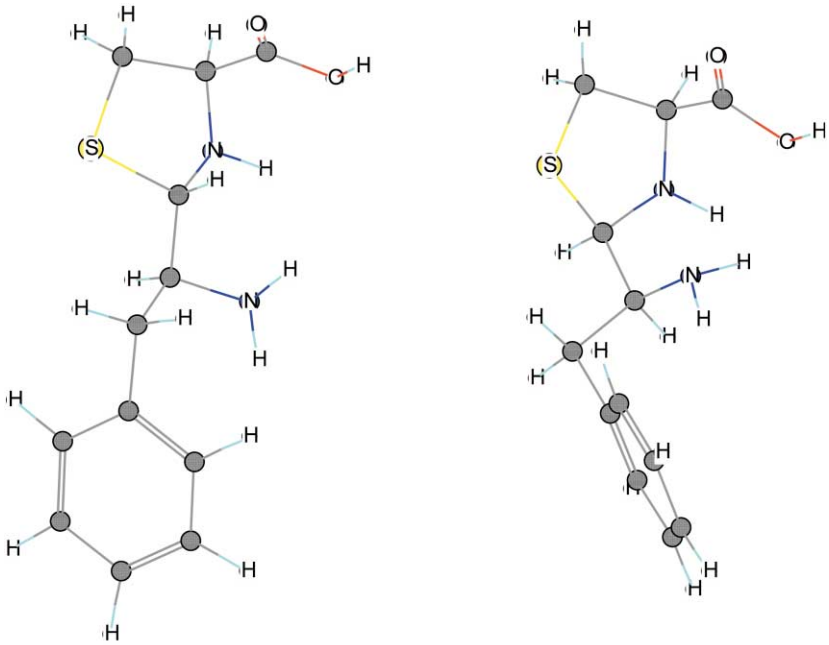
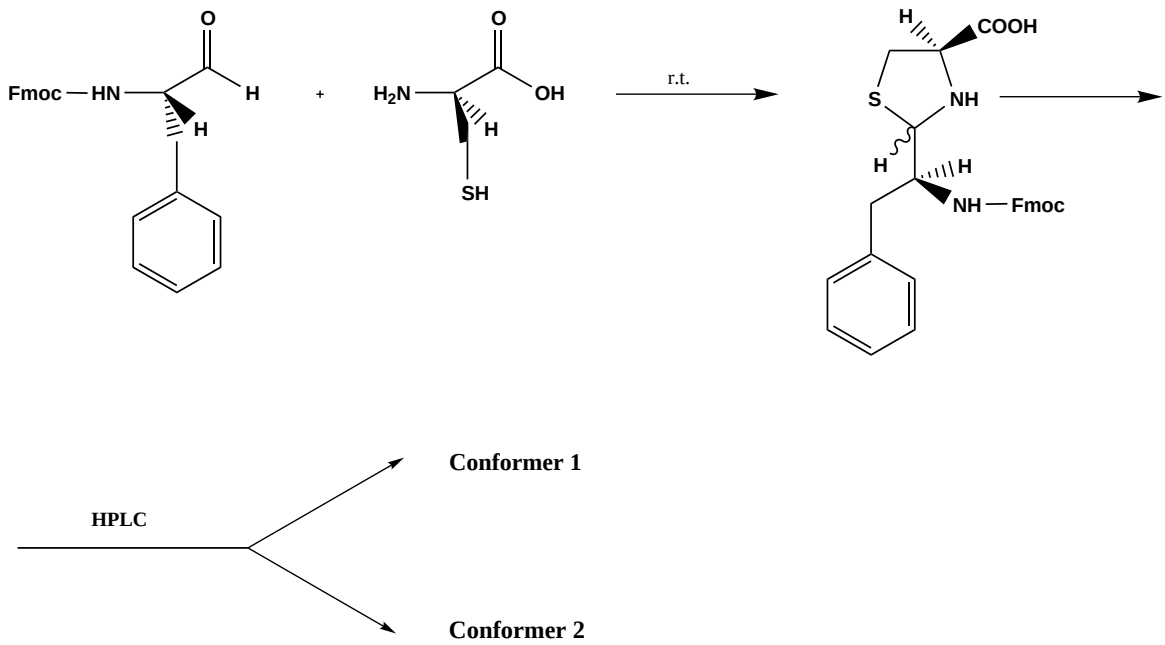


Structure **1a** Structure **1b**

**Figure 2.**




**Scheme 1.**

Compound **1** was obtained as epimeric mixture (1:1, **1a**,**b**) and was resolved by reversed-phase HPLC technique. In fact, the compound **1** has three asymmetric carbons, two of which derives from α-carbons of *L*-phenylalanine and *L*-cysteine of known configuration, while the third one formed by thiazolidine cyclization is epimeric. The determination of the absolute configuration at the asymmetric center C-2 was performed by $^{1}$H NMR.[10] Thus, the diastereoisomer **1a** showed a $J_{2,1'}$ value of 3.2 Hz, consistent with a *cis* disposition of H-2 and H-1′ protons, while in **1b** this coupling constant was 9.0 Hz, indicating a *trans* relationship between protons at the 2- and 1′- positions. As the absolute configuration at C-1′ is *S*, due to the starting *L*-Phe, the configuration at C-2 is *R* in compound **1a** and *S* in its epimer **1b**. In summary we have developed a new β-turn mimetic obtained in high yield and good purity. However, our structure could also be considered as analogue of proline substitued in the 5-position.

Incorporation of this new constrained scaffold **1** into biologically active peptides, such as opioids, substance P and melanocortins, where reverse-turn motif is important for activity, is currently underway in our laboratory and will be reported elsewhere.

## References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9. Synthesis of 2-(*S*,*R*)-[*N*-Fmoc-1′(*S*)-benzylmethylamine] thiazolidine-4*S*-carboxylic acid (**1**): Fmoc-Phe-H (1 nM) was added to a solution of cysteine hydrochloride (1 mM) and potassium hydrogen carbonate (1 mM) in ethanol/$H_2O$ (4/1, 50 mL), and the mixture was stirred at room temperature for 1 h. Then, the mixture was concentrated in vacuo and dichloromethane was added. The organic layer was washed successively with 1N HCl, 10% $NaHCO_3$, $H_2O$, dried over $Na_2SO_4$, and evaporated (yield: 70%).
10. Significant analytical and $^1H$ NMR data of **1a**: white crystalline solid, mp: 271–272°C; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 4.44–4.43 (d, 1H, H-2, $J_{2,1'}=3.2$ Hz), 4.18–4.16 (m, 1H, H-4), 4.15–4.13 (m, 1H, H-1′), 3.45–3.42 and 3.14–3.11 (2m, 2H, H-5); **1b**: white crystalline solid, mp 262–264°C; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 4.58–4.56 (d, 1H, H-2, $J_{2,1'}=9.0$ Hz), 4.30–4.27 (m, 1H, H-4), 4.24–4.22 (m, 1H, H-1′), 3.40–3.38 and 3.11–3.09 (2m, 2H, H-5).