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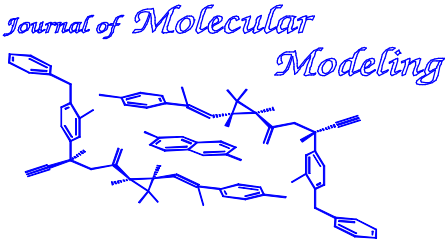

Similarity Study on Peptide γ-turn Conformation Mimetics

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Abstract

The ability of a series of structures to mimic the geometric and electronic properties of an ideal γ-turn has been studied. Initially, an exhaustive conformational analysis was carried out using the molecular dynamics technique at high temperature followed by minimization. Additionally, each minimum was optimized with the semi-ab initio molecular orbital method SAM1. Then, the unique minima found have been superimposed with ideal γ-turns, classic and inverse, using the SEAL program which takes into account steric and electronic parameters for the superpositions and finally, three molecular similarity indices were determined for each superposition. These indices consider the general steric and electronic characteristics of the structures, as well as, the position of the carbon atoms that correspond to the $C\alpha^{i}$ and $C\alpha^{i+2}$ in the peptide chain.

Keywords: γ-turn, peptidomimetics, similarity indices

Introduction

The incorporation of peptide secondary structure mimetics into small bioactive peptides, which leads to restricted analogues, is a well established approach to provide information on the biologically active conformations, and to develop stable, effective and selective receptor ligands [1]. Of special interest are those mimetics which force linear peptide sequences into various defined reverse turn conformations [2].

In recent years, β-turns, as the reverse turns most frequently found in peptides, have been the main focus of attention in the search of conformation mimetics [3]. Little attention has been given, however, to the study of γ-turns. These turns are characterized by a 3->1 hydrogen bond between the CO group of amino acid residue i and the NH group of amino acid residue i+2, as shown in Fig. 1. Two types of γ-turns exist, the classic γ-turn with (ϕ,ψ) values generally in the range (70 to 95, -75 to -45), and the inverse γ-turn (-95 to -70, 45 to 75) [4] . Although these turns are less frequent in proteins than β-turns, a recent analysis of 54 proteins with high resolution X-ray crystal structures has shown the existence of ten classic γ-turns [4], and approximately ten-fold more of inverse γ-turns [5]. On the other hand, it has also been suggested that γ-turns are present in the solution conformation of several peptides, including bradykinin [6], substance P [7], cyclosporin [8, 9], vasopresin [10], and cyclic somatostatin analogues [11]. Additionally, it has been proposed that enkephalins assume a γ-turn conformation when binding to membranes and to the δ-opioid receptor [12-14].

Recently, a few heterocyclic systems have been used to lock three amino acid residues into a γ-turn conformation. Thus, 2-oxo-2,3,6,7-tetrahydro-1H-azepides and 2,4-dioxo-hexahydro-1,5-diazepines have been successfully incorporated into fibrinogen receptor antagonists, inhibitors of platenet aggregation [15, 16], and into a HIV-1 protease substrate [17], respectively. On the other hand, the incorporation of 2-oxo-piperidines, as γ-turn mimetics, into the

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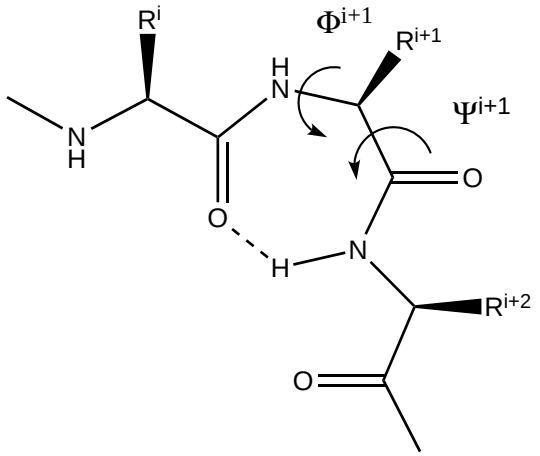
bradykinin sequence support the presence of a reverse turn into the bioactive conformaction of this peptide [18].

Extensive quantum mechanic studies on tripeptide amino acid models (**1**, **2**) in vacuum and aqueous solution [19-21], especially for Ac-Ala-NHMe, have shown that the γ-turn conformation is an energy minimum, being in some cases the absolute minimum [22, 23]. However, when larger peptides have been studied this conformation lost its preponderant role [24]. Molecular modelling studies carried out on γ-turn mimetics have been focused on its structural fitting with specific disposition of a peptide. Thus, the lowest energy conformation of a simplified model of the aforementioned 2-oxo-2,3,6,7-tetrahydro-1H-azepines (**3**) provides a good fit of a cyclic pentapetide fibrinogen antagonist [16]. Likewise, the low energy conformation of simplified 2-oxopi-peridines (**4**) gives a good overlay with the crystal structure of a γ-turn [18].

In this article, the electronic and geometric characteristics of a series of these hetetocyclic systems (**3**, **4**), as well as those corresponding to the model for 2-oxo-piperazines (**5**), previously described as conformationally constrained tripeptide analogues [25], and other seven (**6**-**11**) and six membered systems (**12**-**14**) [26-28] have been compared with those of the ideal inverse and classic γ-turns. For this purpose, three similarity indices have been calculated, the first two compare the generic geometric and electronic behaviour of these structures and the third one, described here for the first time, considers the similarity in the position of the atoms that correspond to $C\alpha^{i}$ and $C\alpha^{i+2}$ in the peptide chain. The aim of this study is to provide a rational basis to analyze the similarity of γ-turn mimetics already described in the literature and to design new structures with the peptide γ-turn conformations.



	Classic	**Inverse**
	Av. Value	Av. value
Φ^{i+1}	75	-79
Ψ^{i+1}	-64	69

Figure 1. *Drawing of γ-turn with their corresponding average angles.*

Methods

The inverse and classic γ-turn conformations for the Ac-Ala-NHMe compound (**1**) have been obtained by fully optimization starting from the characteristic average value angles of these structures (Fig. 1) with the semi-ab initio method SAM1 [29], included in the Ampac 5.0 program [30]. The PRECISE keyword has been used to increase 100 times the geometric and electronic convergency criteria and the atomic charges have been derived to reproduce the molecular electrostatic potential (MEP) generated in four van der Waals layers of the molecule [31].

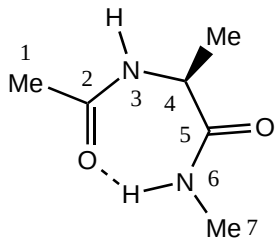
In all the structures (**1**-**14**), a thorough conformational search has been carried out using the molecular dynamics (MD) technique at high temperature and minimization in vacuo (e=1) with the Insight II program [32]. The MD procedures have been carried out heating the molecules at 1500 K increasing the temperature 10 K each 0.15 ps. and equilibrating at this temperature during 20 ps. Finally, 75 ps. of simulation have been carried out, storing 300 structures at equal intervals. Each structure has been minimized with the cff91 [33] force field using initially the steepest descents minimization methods followed by the conjugate gradient until the gradient was bellow 0.0001 kcal/Å. The minima obtained have been compared and the repeated ones eliminated.

The unique minima have been fully optimized with the SAM1 method and their atomic charges have been generated as described above for compound **1**. Again, the new minima obtained have been compared in order to eliminate the repeated ones. In the case of molecules **4** and **13** which have only one chiral center, the conformations of the enantiomeric compound have been automatically generated with an in house program that creates a mirror image of each conformation.

The superposition of the different conformations obtained for each molecule with the classic and inverse γ-turn models have been carried out using the SEAL program [34]. One hundred different starting positions generated using a Monte Carlo algorithm have been used to find the best simultaneous steric and electronic molecular superpositions of the molecules. The best five superpositions have been stored.

The determination of the similarity of the molecules in the superposition disposition has been done using an in house program which calculates three different similarity indices.

Figure 2. *(next page) Compounds used in this study. The asterisks indicate that the two possible enantiomers of this center have been studied.*



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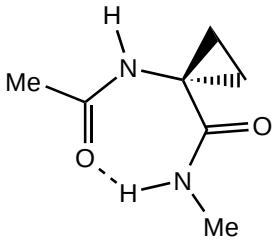

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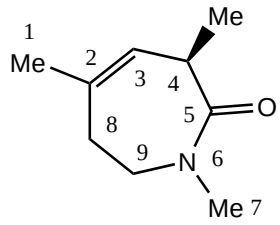

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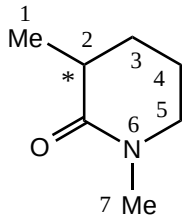

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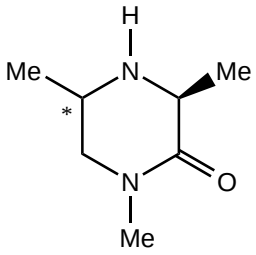

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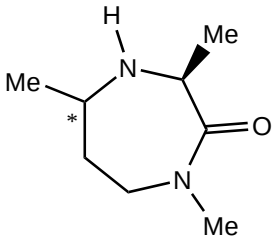

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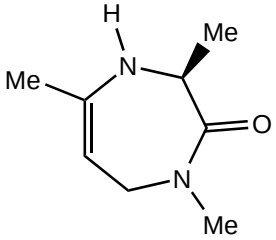

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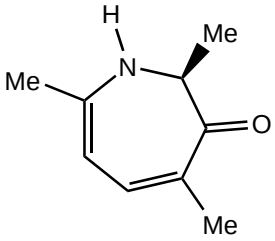

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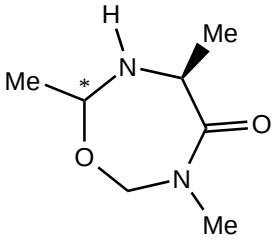

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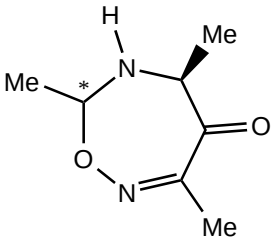

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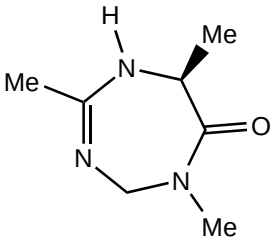

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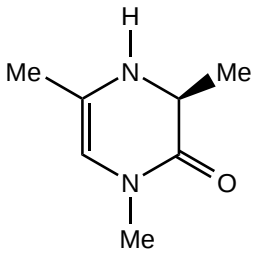

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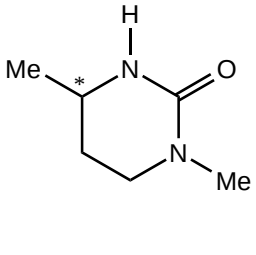

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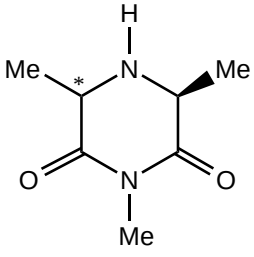

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The first of them indicates the electrostatic similarity on a three dimensional grid that extends 5 Å from the largest molecule in each direction, the density of points considered being 8 per Å^3. The MEP for each molecule was derived from the atomic charges on all the points of the grid except those that are inside the van der Waals volume of any of the two structures assumed in each superposition. The van der Waals volume of the molecules has been defined using the radii values reported by Gavezzotti [35]. Finally, the similarity has been calculated applying a numerical solution of the Carbo index [36]:

$$R_{ab} = \frac{\sum MEP_a^i * MEP_b^i}{\sqrt{\sum MEP_a^{i^2}} * \sqrt{\sum MEP_b^{i^2}}} \quad (1)$$

where MEP_a^i and MEP_b^i indicate the value of the MEP on the same grid point, i, generated for molecules A and B. The maximum value of this index is 1 when the MEPs of two molecules are the same. The minimum value is -1 and corresponds to the hypothetical case when the MEP of one molecule is the negative of the MEP of the other molecule for all the points considered.

A second index, evaluates the shape similarity counting the number of grid points inside the individual and common van der Waals volumes and using the following formula:

$$S_{ab} = \frac{V_{ab}}{Min(V_a, V_b)} \quad (2)$$

where V_a and V_b correspond to the number of points that are inside molecules A and B, respectively, and V_{ab} those which are common to both molecules. The denominator indicates that only the smallest volume of the two molecules is used and thus hypothetical superposition of a subset of a molecule with the whole molecule would provide a maximum value of 1.

The third index evaluates the similar disposition of $C\alpha^i$ and $C\alpha^{i+2}$ atoms of **1** (1 and 7 in Fig. 2), and those corresponding to the peptidomimetic model compounds:

$$D_{ab} = e^{-1/n * \sum_{i=1}^{n} d(C_a^i, C_b^i)} \quad (3)$$

where n corresponds to the number of atom compared, in this case 2, and $d(C_a^i, C_b^i)$ is the distance between each pair of atoms compared. This index may be considered as a measure of the ability of the corresponding structure to keep the correct disposition of the peptide backbone attached to it when it is used as a building block. The value of this parameter is 1 when the atoms compared have the same coordinates and rapidly diminishes as the sum of the distance increases.

The total similarity index of the superposition of molecules A and B can be calculated as the sum of eq. (1)-(3):

$$T_{ab} = R_{ab} + S_{ab} + D_{ab} \quad (4)$$

These indices take into account the similarity of each conformation with a γ-turn. In order to have a similarity value that could be associated to all the conformations of a given molecule, an overall molecular similarity index was developed using the following equation:

$$P_{ab} = \frac{\sum R_{ab}^i * p^i}{\sum p^i} + \frac{\sum S_{ab}^i * p^i}{\sum p^i} + \frac{\sum D_{ab}^i * p^i}{\sum p^i} \quad (5)$$

or

$$P_{ab} = \frac{\sum T_{ab}^i * p^i}{\sum p^i} \quad (6)$$

where p^i is the relative population of conformer i calculated using the Boltzmann distribution equation.

Table 1. *Number of minima found for each compound.*

Comp.	Config. [a]	MD & Minim.	SAM1
1		22	13
2		13	10
3		4	4
4	S	5	4
5	R	4	3
5	S	7	6
6	R	12	11
6	S	15	10
7		6	4
8		5	4
9	R	16	12
9	S	16	12
10	R	14	5
10	S	12	7
11		8	2
12		1	1
13	S	2	2
14	R	4	4
14	S	4	4

[a] Configuration of the center indicated with an asterisk in Figure 2

Results and Discussion

The number of minima found, first in the molecular dynamics/minimization procedure, and then with the SAM1 methods, are included in Table 1. As can be seen, some of the minima found with the molecular mechanics method converge to the same minima with SAM1, reducing the total number of minima found with the last procedure. This tendency has already been described for other semiempirical methods [37]. With respect to the energetic values of the minima, in most of the cases the absolute minimum found with the molecular mechanics method is the same as that found with the SAM1 methods, or corresponds to a minimum of small relative energy. Regarding the number of minima found, as expected, cyclization to a seven membered ring reduces slightly the total number of minima, this reduction being larger in the case of compounds with endocyclic double bonds. The six membered compounds show less degrees of freedom and consequently a smaller number of minima.

The similarity indices of the structures studied have been divided in three tables. The first one (Table 2) includes the best similarity values for each compound compared with the model γ-turns, classic and inverse. Table 3 shows the similarity indices of the absolute minimum of each compound, and in Table 4 are gathered the overall molecular indices, P_{ab}.

In general, the compounds studied can be classified in three different groups: open chain (**1** and **2**), seven membered rings (**3, 6-11**) and six membered rings (**4, 5, 12-14**). The two compounds included in the first group present different capacities to adopt direct and inverse γ-turns, while the in-

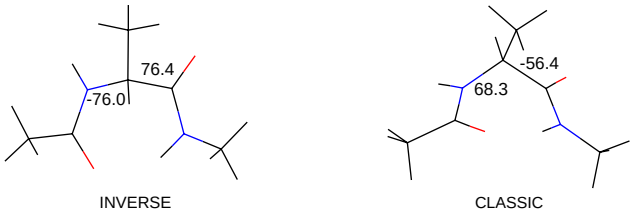

Figure 3. *Structure of **1** used as model of classic and inverse γ-turns.*

Table 2a. *Best similarity indices found for each compound studied when compared with a model of inverse γ-turn.*

Comp.	Conf.[a]	R	S	D	T	E rel.[b]
1		1.00	1.00	1.00	3.00	0.72
2		0.83	0.86	0.78	2.48	0.00
3		0.63	0.92	0.82	2.37	3.38
4	R	0.56	0.76	0.13	1.47	0.82
4	S	0.61	0.77	0.15	1.54	0.00
5	R	0.59	0.82	0.55	1.98	1.06
5	S	0.65	0.74	0.29	1.69	0.77
6	R	0.58	0.90	0.82	2.31	2.35
6	S	0.66	0.88	0.75	2.29	2.12
7		0.76	0.91	0.87	2.55	0.00
8		0.63	0.83	0.64	2.11	0.00
9	R	0.73	0.85	0.72	2.30	5.79
9	S	0.59	0.89	0.68	2.16	0.00
10	R	0.42	0.83	0.71	1.97	0.86
10	S	0.53	0.72	0.11	1.37	2.67
11		0.84	0.89	0.81	2.56	0.00
12		0.28	0.50	0.10	0.89	0.00
13	R	0.44	0.73	0.67	1.84	0.52
13	S	0.45	0.66	0.66	1.78	0.00
14	R	0.45	0.63	0.07	1.16	3.67
14	S	0.46	0.71	0.24	1.42	3.05

[a] Configuration of the center indicated with an asterisk in Figure 2

[b] Relative energy (kcal/mol) of the corresponding conformer.

Table 2b. *Best similarity indices found for each compound studied when compared with a model of classic γ-turn.*

Comp.	Conf.[a]	R	S	D	T	E rel. [b]
1		1.00	1.00	1.00	3.00	1.55
2		0.85	0.87	0.85	2.57	0.01
3		0.70	0.89	0.72	2.32	3.75
4	R	0.71	0.81	0.14	1.67	1.28
4	S	0.69	0.68	0.18	1.55	1.28
5	R	0.66	0.72	0.57	1.96	2.03
5	S	0.65	0.72	0.29	1.67	0.00
6	R	0.72	0.86	0.76	2.35	3.69
6	S	0.60	0.86	0.68	2.16	2.80
7		0.83	0.93	0.83	2.59	1.50
8		0.65	0.84	0.57	2.07	1.35
9	R	0.72	0.80	0.63	2.15	4.97
9	S	0.69	0.84	0.73	2.27	4.84
10	R	0.60	0.73	0.10	1.45	2.35
10	S	0.58	0.82	0.79	2.20	2.67
11		0.90	0.90	0.80	2.61	0.47
12		0.48	0.67	0.31	1.47	0.00
13	R	0.57	0.65	0.58	1.81	0.00
13	S	0.63	0.74	0.63	2.01	0.52
14	R	0.62	0.68	0.50	1.82	3.21
14	S	0.66	0.76	0.45	1.88	3.05

[a] Configuration of the center indicated with an asterisk in Figure 2

[b] Relative energy (kcal/mol) of the corresponding conformer.

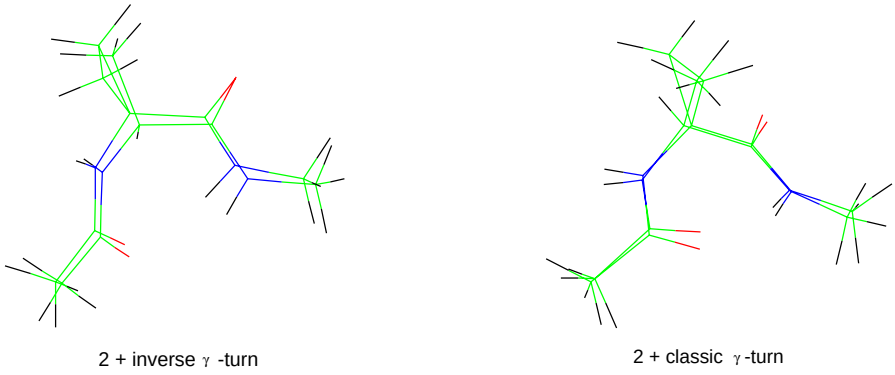

Figure 4. *Superposition of the conformations of* ***2*** *with the models of inverse (left) and classic (right)* γ*-turns that provide the best similarity indices .*

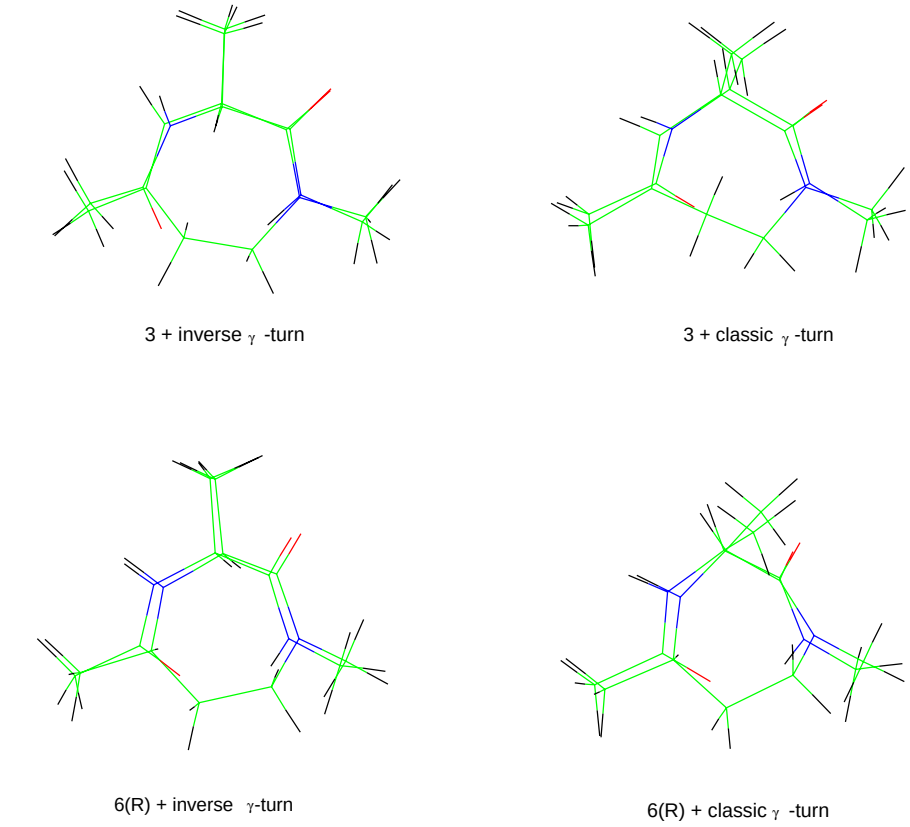

Figure 5. *Superposition of the conformations of* ***3*** *and* ***6****(R) with the models of inverse (left) and classic (right)* γ*-turns that provide the best similarity indices .*

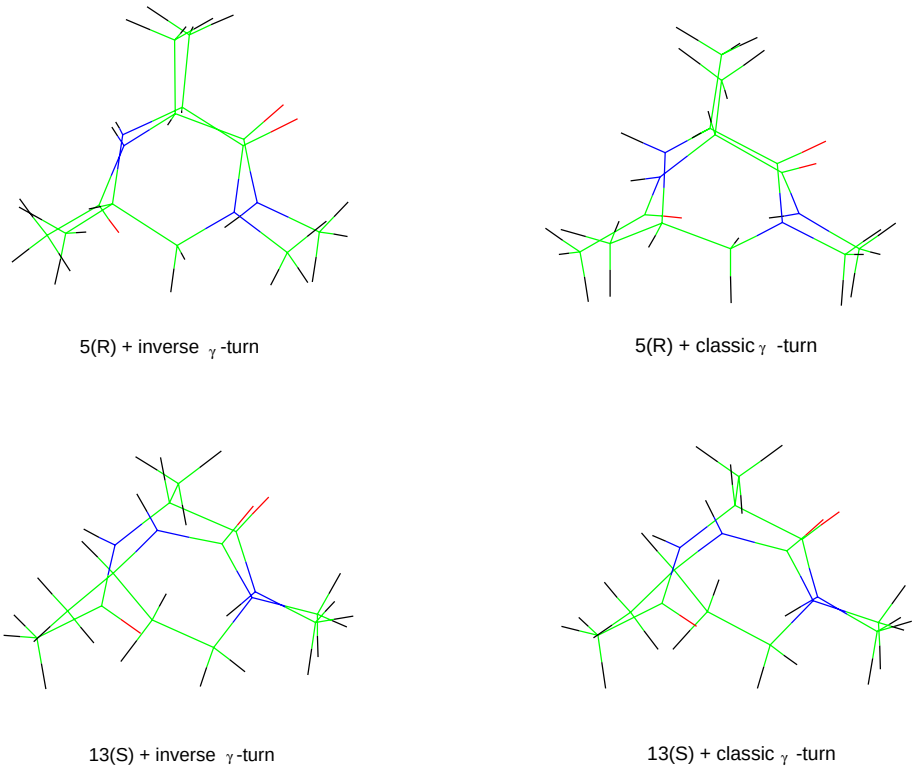

Figure 6. *Superposition of the conformations of **5**(R) and **13**(S) with the models of inverse (left) and classic (right) γ-turns that provide the best similarity indices .*

verse γ-turn conformation of **1** corresponds to a minima with a small relative energy, the classic γ-turn being energetically less favourable. This difference is based on the disposition of the methyl group in position 4, while in the inverse γ-turn conformation it is in equatorial disposition, in the classic one it is axial (Fig. 3). The introduction of larger groups in this position, as is the case of the other amino acids except glycine, should increase its relative energy and consequently diminish its tendency to adopt classic γ-turns. This conclusion is in good agreement with the observed experimental tendency of peptides to adopt classic and inverse γ-turn conformations.

On the other hand, compound **2** shows similar ability to adopt both types of γ-turn, since the presence of the cyclopropane forces the molecule to have one methylene group in equatorial disposition while the other one is in axial orientation. Thus, the conformational study of this compound indicates the presence of two degenerated absolute minima corresponding to both types of γ-turns (Fig. 4).

Compounds which include a seven membered ring (**3, 6-11**) present, in general, conformations with good similarity to both classic and inverse γ-turn (Fig. 5). However, the conformations that better mimic classic γ-turn have larger relative energies due to the axial disposition of the methyl group in position 4, except in the case of **9**(R). This fact, as in the case of **1**, reduces their overall molecular indices.

Regarding stereoisomer in position 2 of the compounds with a seven membered ring (**6**, **9** and **10**), those that allow a simultaneous equatorial disposition of the methyl groups in positions 2 and 4 are the most similar to the inverse γ-turn model. Thus, **6**(R) has a better molecular similarity index than its S isomer, while in the case of **9**, the best index corresponds to the isomer S in agreement with their ability to locate the two methyl groups in equatorial disposition. Structures with double bonds in the 2-8 or 2-3 positions (**7, 8** and **11**) show good similarity indices with inverse γ-turns since the methyl group in position 2 is in a pseudo-equatorial disposition.

The similarity indices shown for these compounds indicate that the atoms involved in the typical hydrogen bond of γ-turns could be substituted by other groups as CH_2, CH and N without an important loss in their ability to mimic these turns. This fact provides a basis to design compounds with limited flexibility maintaining their similarity with γ-turns.

The good results obtained for the similarity of **3** with the inverse γ-turn model are in good agreement with the experimental HIV-1 protease inhibitory activity of compounds that use this structure as building block to induce γ-turn conformation [16].

The compounds containing a six membered ring (**4, 5, 12-14**) show similar values for both classic and inverse g-turns. In general, the similarity indices are, smaller than those

Table 3a. *Similarity indices for the absolute minimum of each compound studied when compared with a model of inverse γ-turn.*

Comp.	Conf. [a]	R	S	D	T
1		0.69	0.80	0.56	2.05
2		0.83	0.86	0.78	2.48
3		0.57	0.90	0.78	2.26
4	R	0.54	0.68	0.13	1.37
4	S	0.61	0.77	0.15	1.54
5	R	0.63	0.76	0.47	1.86
5	S	0.44	0.69	0.38	1.52
6	R	0.52	0.89	0.72	2.15
6	S	0.51	0.65	0.26	1.43
7		0.76	0.91	0.87	2.55
8		0.63	0.83	0.64	2.11
9	R	0.44	0.66	0.28	1.38
9	S	0.59	0.89	0.68	2.16
10	R	0.41	0.62	0.15	1.19
10	S	0.35	0.67	0.09	1.12
11		0.84	0.89	0.81	2.56
12		0.28	0.50	0.10	0.89
13	R	0.43	0.65	0.15	1.25
13	S	0.45	0.66	0.66	1.78
14	R	0.35	0.66	0.12	1.14
14	S	0.24	0.65	0.06	0.95

[a] Configuration of the center indicated with an asterisk in Figure 2

Table 3b. *Similarity indices for the absolute minimum of each compound studied when compared with a model of classic γ-turn.*

Comp.	Conf. [a]	R	S	D	T
1		0.49	0.59	0.18	1.27
2		0.85	0.87	0.85	2.57
3		0.51	0.77	0.13	1.42
4	R	0.66	0.64	0.07	1.38
4	S	0.65	0.64	0.10	1.40
5	R	0.56	0.69	0.31	1.57
5	S	0.65	0.72	0.29	1.67
6	R	0.63	0.65	0.22	1.51
6	S	0.55	0.61	0.05	1.21
7		0.32	0.75	0.34	1.42
8		0.32	0.71	0.33	1.37
9	R	0.62	0.81	0.46	1.89
9	S	0.63	0.62	0.21	1.48
10	R	0.56	0.75	0.07	1.39
10	S	0.47	0.63	0.09	1.20
11		0.43	0.73	0.14	1.31
12		0.48	0.67	0.31	1.47
13	R	0.57	0.65	0.58	1.81
13	S	0.56	0.58	0.13	1.29
14	R	0.71	0.62	0.43	1.77
14	S	0.56	0.67	0.34	1.58

[a] Configuration of the center indicated with an asterisk in Figure 2

obtained in the comparison of the seven membered systems with the inverse γ-turn model but similar to that obtained from its comparison with the classic γ-turn model. An in depth analysis of the results show that the six membered compounds provide, in general, good steric and electronic indices especially in the comparison with the classic γ-turn. However, the results obtained for the similarity index that measure the disposition of atoms 1 and 7 (D) are lower, except for **13** with this similarity index over 0.6 (Fig. 6).

The experimental data showed that only one of the enantiomers of **4** was useful as building block in the synthesis of compounds with affinity for the bradykinin receptor [18]. Even though the authors were not able to identify which enatiomer was the active one, our calculation indicates that if bradykinin adopts an inverse γ-turn the S conformer should be the active one.

Finally, the 2-oxopiperazines (**5**), which have recently been synthesized in our laboratories as conformationally constrained tripeptide analogues, provide the best similarity indices for all studied six membered systems, which indicates that they could be successfully used as building blocks which mimic γ-turn conformations.

Conclusion

The results here reported indicate that in the case of structures with peptidic skeleton, the stability of γ-turn conformations can be modulated with the substituent attached to $C\alpha^{i+1}$.

Compounds with a seven membered ring show good overall molecular similarity indices when compared to an ideal inverse γ-turn; however, their similarity with the classic γ-turn is much smaller. This tendency is due to the different stability of the conformer that better mimics each kind of γ-turn conformation.

The compounds that contain a six membered ring provide good overall steric and electronic similarity with both, classic and inverse γ-turns. However, these compounds are not able to position the atoms which correspond to the $C\alpha^{i}$ and $C\alpha^{i+2}$ in the peptide chain in the same disposition as found in the model γ-turns.

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Table 4a. *Overall molecular similarity index, P, and its components (eq. (5)) of the studied molecules when compared with a model of inverse γ-turn.*

Comp.	Conf. [a]	PR	PS	PD	P
1		0.82	0.75	0.59	2.16
2		0.82	0.66	0.44	1.92
3		0.85	0.51	0.67	2.03
4	R	0.69	0.53	0.13	1.35
4	S	0.76	0.60	0.14	1.51
5	R	0.77	0.62	0.48	1.87
5	S	0.70	0.50	0.35	1.56
6	R	0.88	0.53	0.70	2.12
6	S	0.68	0.53	0.28	1.48
7		0.90	0.73	0.83	2.47
8		0.82	0.60	0.59	2.02
9	R	0.68	0.49	0.26	1.44
9	S	0.87	0.58	0.65	2.09
10	R	0.67	0.41	0.26	1.34
10	S	0.67	0.36	0.10	1.13
11		0.84	0.61	0.65	2.11
12		0.51	0.28	0.10	0.90
13	R	0.68	0.44	0.31	1.43
13	S	0.65	0.48	0.54	1.68
14	R	0.66	0.37	0.12	1.15
14	S	0.59	0.36	0.13	1.08

[a] Configuration of the center indicated with an asterisk in Figure 2

Table 4b. *Overall molecular similarity index, P, and its components (eq. (5)) of the studied molecules when compared with a model of classic γ-turn.*

Comp.	Conf. [a]	PR	PS	PD	P
1		0.62	0.56	0.24	1.41
2		0.79	0.64	0.46	1.90
3		0.75	0.52	0.17	1.44
4	R	0.70	0.68	0.10	1.48
4	S	0.65	0.67	0.12	1.44
5	R	0.69	0.58	0.31	1.58
5	S	0.70	0.63	0.29	1.61
6	R	0.67	0.63	0.27	1.57
6	S	0.63	0.56	0.09	1.28
7		0.77	0.36	0.38	1.52
8		0.73	0.35	0.36	1.44
9	R	0.76	0.62	0.41	1.79
9	S	0.65	0.63	0.26	1.53
10	R	0.73	0.56	0.08	1.37
10	S	0.64	0.48	0.10	1.22
11		0.79	0.58	0.35	1.71
12		0.68	0.48	0.32	1.47
13	R	0.68	0.56	0.45	1.69
13	S	0.63	0.59	0.28	1.51
14	R	0.62	0.69	0.41	1.72
14	S	0.68	0.57	0.20	1.45

[a] Configuration of the center indicated with an asterisk in Figure 2

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