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2-Alkyl-2-carboxy-azetidines as scaffolds for the induction of γ-turns

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Abstract—To investigate the ability of 2-alkyl-2-carboxy-azetidines (Azx) to induce reverse turns when incorporated into peptides, RCO-Azx-L-Ala-NHMe dipeptide derivatives were selected as simplified tetrapeptide models, in which the azetidine residue is incorporated at the $i+1$ position. Molecular modelling, ^{1}H NMR and FTIR studies showed the high tendency of the model tetrapeptides to adopt γ-turn conformations, indicating that these azetidine-containing amino acids could serve as general γ-turn promoters.

The search for small molecules able to mimic or induce specific aspects of peptide secondary structure is a valuable approach in the search of new chemical entities able to interfere with peptide–protein and protein–protein interactions.[1,2] An approach to induce secondary structure into peptides is the replacement of proteinogenic amino acids with non-proteinogenic counterparts with secondary structure-promoting effects. In this sense, in our ongoing search for small molecules able to induce secondary structures we have focused our attention on a series of 2-substituted azetidine-2-carboxylic acids (Azx), that combines features of α,α-disubstituted amino acids and a αC^i–αN^i cyclization.[3]

α,α-Disubstituted amino acids have been shown to induce defined secondary structure elements in short peptides, in particular, type III (III′) β-turn, 3_{10}/α-helical structures and fully extended (C_5) conformation, depending upon overall bulkiness and nature (e.g., whether acyclic or αC^i–αC^i cyclized) of their side chains.[4,5]

Among the proteinogenic amino acids, proline is unique as its side chain is bonded to both the α-carbon and its preceding α-amine nitrogen. Due to its cyclic nature Pro influences the protein architecture, and this residue has been found quite often at the $(i+1)$ position of β-turn structures.[6,7] It has been shown that the α-alkylation of Pro, as in α-Me-Pro, provides further stabilization of β-turn conformations in linear peptides.[8] On the other hand, conformational studies have also been carried out on the lower and upper homologues of Pro, the natural occurring amino acids, azetidine-2-carboxylic acid (Azg)[9] and piperidine-2-carboxylic acid (Pip), respectively. In this sense, NOESY experiments on tetrapeptides Ac-Gly-Xaa-Leu-Gly-NMe_2 (Xaa = Azg, Pro or Pip) showed that all formed β-turn conformations, although, the distances between both terminals of the tetrapeptide are larger for Azg and Pip containing peptides in comparison with Pro analogues.[5]

It is worth noting that, to the best of our knowledge, there are no studies on the effect of the α-alkylation of the azetidine ring upon peptide conformation. The 2-alkyl-2-carboxy azetidines possess a ϕ dihedral angle restricted to approximately −70° or 70° depending on the absolute configuration of the asymmetric carbon. These values are similar to those reported for the central residues of the main types of β- and γ-turns, which involve four and three consecutive residues, respectively.[10–13] Quite frequently these turns are stabilized by an intramolecular H-bond between the backbone CO of the first (i) residue and the backbone NH of the fourth $(i+3)$ (β-turn) or the third $(i+2)$ (γ-turns) residues.[10,13,14] Since reverse turns have been shown to be relevant in biomolecular recognition events,[10,15–17] it would be of interest

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to ascertain whether the 2-alkyl-2-carboxy azetidines are able to induce a particular turn conformation upon incorporation into peptides.

As a first step, a simulated annealing molecular dynamic procedure was carried out, to explore the conformational space available to the dipeptide MeCO-Aza-Ala-NHMe using AMBER as the forcefield. This dipeptide may be considered as a simplified tetrapeptide model in which the N-terminal amino acid has been substituted by an acetyl group and the C-terminal by an *N*-methyl moiety.

The analysis of the modeling results showed the presence of cis/trans rotamers around the CO–Aza bond, with the cis conformers having higher energy than the trans ones. It is worth mentioning that in all the conformers the azetidine ring is planar, in agreement with the crystal structure of Boc-L-Azg-OH[18] and the NMR structure of Ac-L-Azg-OH.[19] Then, the characteristic conformational parameters (distances, dihedral and pseudodihedral angles) obtained for conformers with trans amide bond were compared to those expected for the main types of β- and γ-turns. The analysis of the parameters revealed that around 30% of the conformers presented values of the distance between the α-carbon of the first residue (in our model the CH_3 from the N-terminal acetyl group) and the fourth residue (C-terminal CH_3), as well as of the pseudodihedral angle τ[20] corresponding to the atomic sequence αC^{i}–αC^{i+1}–αC^{i+2}–αC^{i+3}, within those required for the formation of β-turns (αC^{i}–$\alpha C^{i+3} < 7$ Å, $-90 \leqslant \tau \leqslant 90$).[10,13,14,20] However, less than 10% of conformers showed the characteristic H-bond of this type of conformation (CO^{i}–$NH^{i+3} \leqslant 2.5$ Å) (Fig. 1A).

On the other hand, an increased percentage of around 40% of the total conformers was able to form the H-bond characteristic of γ-turns (CO^{i}–NH^{i+2} and/or CO^{i+1}–$NH^{i+3} \leqslant 2.5$ Å). The global minimum is included in a family of conformers characterized by the coexistence of two γ-turns (Fig. 1B). It is worth mentioning that most of the lower energy conformers display γ-turn arrangements between i and $i+2$ residues, and that it corresponds to an inverse γ-turn, as it was expected for azetidine derivatives of *S* configuration at the stereogenic centre. These theoretical data seem to indicate a tendency of the 2,2-disubstituted azetidines to preferentially induce γ-turns, although β-turn-like conformations are also possible.

To ascertain experimentally the conformational preferences in solution, we prepared a series of model dipeptide derivatives that incorporate 2-methyl or 2-benzyl substituted azetidine-2-carboxylic acid. The synthesis of the designed dipeptides was performed following classical procedures of peptide synthesis in solution, starting from the appropriately protected azetidine derivatives, **1a** and **2ab**. The enantiomerically pure 2-methyl-azetidine derivative **1a** was prepared from **3a** (4*S* configuration), following a enantioselective route, previously developed by us, based on the use of the chiral auxiliary (+)-10-(*N*,*N*-dicyclohexylsulfamoyl)-iso-

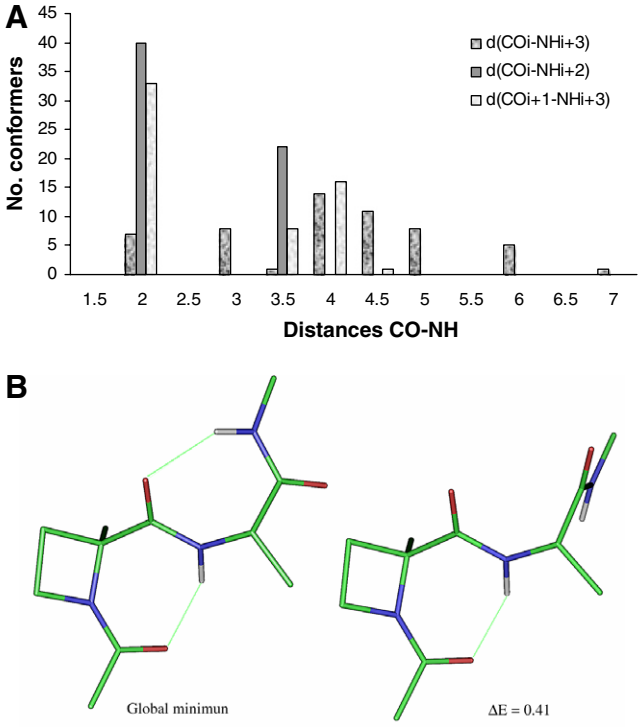
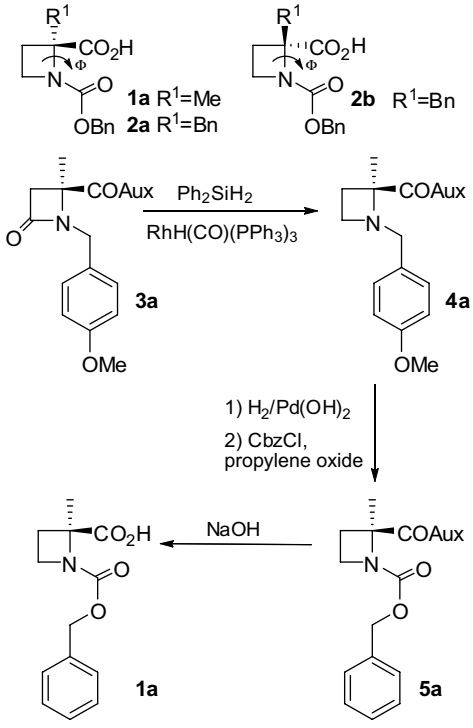


Figure 1. (A) Distance distribution (Å) corresponding to the intramolecular H-bonds for the trans conformers within a +3 Kcal/mol window of the global minimum. (B) Representative minimal energy conformers for the model tetrapeptide MeCO-Aza-Ala-NHMe.



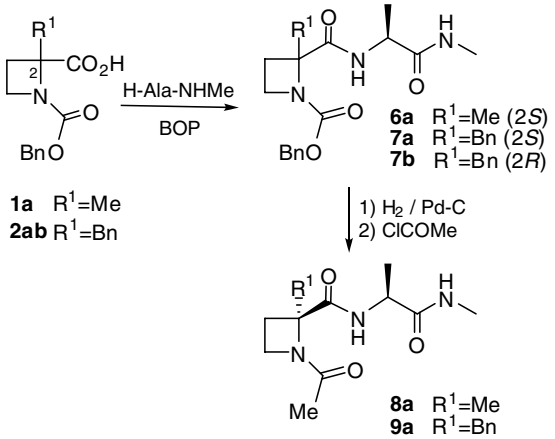
Scheme 1. Synthesis of enantiomerically pure azetidine **1a**. Yields: **4a** (42%), **5a** (49%), **1a** (83%), Aux = (+)-10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol.

borneol (Scheme 1).[21,22] The chemoselective reduction of azetidinone **3a** afforded azetidine **4a** in moderate yield. Subsequent catalytic hydrogenation of the *p*-(methoxybenzyl) group, followed by reaction with benzyl chloroformate led to azetidine **5a**. Finally, removal of the isoborneol ester by saponification provided optically pure (*S*)-*Z*-Aza-OH (**1a**).[23] Azetidines **2ab** (2:1, *S*:*R* ratio) were prepared following a procedure previously developed in our laboratory.[24]

The coupling between azetidine **1a** or **2ab** and H-Ala-NHMe, using BOP as the coupling reagent, led to dipeptides **6a**, **7ab**, respectively, in good yield (Scheme 2). Diastereoisomeric mixture **7ab** was chromatographically resolved into diastereoisomers **7a** and **7b**. Subsequent catalytic hydrogenation of 2(*S*)-azetidines **6a** and 7**a**, using Pd–C as the catalyst, followed by treatment with acetyl chloride in the presence of TEA, resulted in the isolation of products **8a** and **9a**.[25]

The structural features of dipeptides **6**–**9** in solution were analyzed by FTIR and ^{1}H NMR. The IR spectra of these compounds in chloroform showed, for all derivatives except for dipeptide **6a**, the presence of hydrogen-bonded (3380–3360 cm^{-1}) and non-hydrogen-bonded (3456 cm^{-1}) stretching NH bands,[26–28] suggesting the existence of hydrogen-bonding interactions for compounds **7**–**9**. In Figure 2 it is shown the data for compound **8a** and **9a**.

As it has been previously observed for peptides that incorporate proline and azetidine residues,[26,29–32] the ^{1}H NMR spectra of all dipeptide derivatives showed the presence of two set of homologous signals, which indicated the existence of cis/trans isomers around the amide bond CO–Azx. There is a higher population of CO–Azx cis conformers when the polarity of the solvent increases (Table 1), in agreement with the previous reports on related Pro derivatives.[33] On the other hand, the ratio of the trans isomer increases with the volume of the substituent attached to position 2 of the azetidine ring, likely due to steric hindrance between the alkyl group at this position in the azetidine ring and the corresponding residue at the N-terminus, that destabilize the cis isomer.



Scheme 2. Synthesis of the model tetrapeptide derivatives. Yields: **6a** (90%), **7a** (48%), **7b** (12%), **8a** (21%), **9a** (23%).

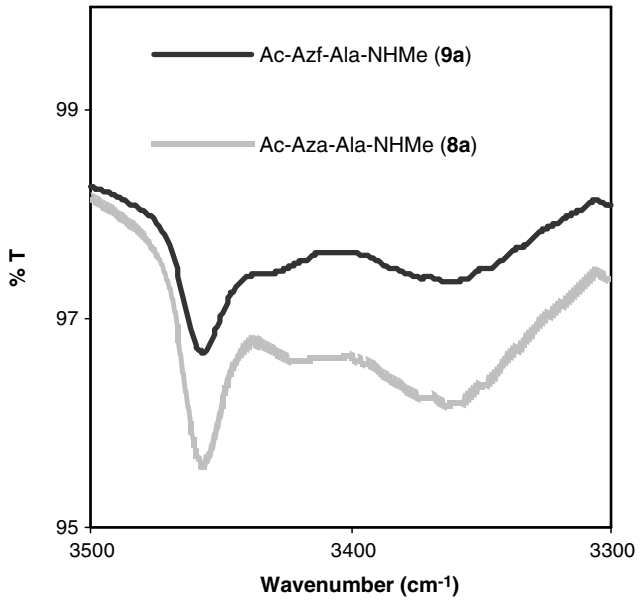


Figure 2. NH stretch region of FTIR spectra for Ac-Aza-Ala-NHMe (**8a**) and Ac-Azf-Ala-NHMe (**9a**) in $CHCl_3$ at room temperature.

Table 1. Percentage of cis rotamers in compounds **6**–**9**

Compound	RCO	R^1	% *cis*-$CDCl_3$	% *cis*-DMSO
6a	Z	CH_3	17	43
7a	Z	CH_2Ph	<5	31
7b	Z	CH_2Ph	<5	26
8a	Ac	CH_3	0	23
9a	Ac	CH_2Ph	0	0

The ^{1}H NMR studies also provide further evidence supporting the presence of intramolecular H-bonds in the trans isomers of compounds **7**–**9**. In particular, the solvent dependence of NH chemical shifts and the temperature coefficients were analyzed. The values of these parameters for the NH proton of the NH–Me moiety, namely $\Delta\delta/\Delta T > 4$ ppb/K, the chemical shift below 7 ppm in $CDCl_3$, and variations of >1 ppm between $CDCl_3$ and DMSO-d_6, indicated that this proton is accessible to the solvent, and thus not involved in the formation of an H-bond. On the contrary, it was observed that the chemical shifts of the NH proton of the Ala residue in compounds **7**–**9**, were above 7 ppm in $CDCl_3$ and that there were small variations (<0.2 ppm) when the solvent was change to DMSO-d_6 (Table 2), which suggested the participation of these protons in H-bonded conformations.[15,27] Moreover, the temperature coefficients of the NH proton of Ala residue in 2-benzyl azetidine derivatives **7a**, **7b** and **9a** are equal or lower than 3 ppb/K, in absolute value, indicative of the existence of an intramolecular H-bond ($CO^{i}\cdots NH^{i+2}$). A similar behaviour is observed for compound Ac-Aza-Ala-NHMe (**8a**), although with a value of NH–Ala $\Delta\delta/\Delta T$ in the uncertainty range (3 ppb/K > $\Delta\delta/\Delta T$ < 4 ppb/K). However, taking into account the small variation of the chemical shift of this

Table 2. Chemical shifts and temperature coefficients for the NH protons of dipeptides **6**–**9**

	δNH–Ala (ppm)		δNH–Me (ppm)		Δδ/ΔT[a] NH–Ala	Δδ/ΔT[a] NH–Me
	$CDCl_3$	DMSO	$CDCl_3$	DMSO		
6a	7.74	7.99	6.38	7.75	−4.9	−4.9
7a	8.18	8.22	6.36	7.81	−3.0	−5.0
7b	8.22	8.11	6.31	7.89	−2.7	−5.4
8a	8.51	8.35	6.44	7.72	−3.3	−4.4
9a	8.78	8.67	6.37	7.78	−2.8	−4.8

[a] Values in ppb/K. Δδ measured in DMSO-d_6, 30–60 °C (each 5 °C for a total of 7 points).

NH upon solvent change in **8a** we might consider that this proton is also involved in the formation of an intramolecular H-bond. Thus with the exception of **6a**, all the other dipeptide derivatives adopt H-bonded γ-turn-like conformation with a H-bond between $CO^{i}\cdots NH^{i+2}$, similar to the second conformer in Figure 1B, which would imply that this is the most stable conformer in solution.

In conclusion, the results of theoretical, IR and NMR conformational studies support that the 2-alkyl-2-carboxy azetidines represent an effective way for inducing γ-turns conformations in short peptides. It is worth mentioning that, so far, there have been described less scaffolds able to induce γ-turns rather than β-turns. Therefore, these constrained amino acids could be useful as scaffolds for γ-turn scan in higher peptides, through the replacement of individual amino acids of the peptide by the azetidine functionalized with the appropriate side chain at position 2. This could provide valuable information regarding the bioactive conformation of peptides of biological interest, which in fact is critical in the design of peptidomimetics.

Acknowledgements

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25. Analytical and spectroscopic data of selected compounds: 2(*S*)-Ac-Aza-L-Ala-NHMe (**8a**): $[\alpha]_D$ −127.74 (*c* 1.01, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.51 (d, 1H, *J* = 7.2, NH–Ala), 6.44 (br s, 1H, NH–CH_3), 4.36 (q, 1H, *J* = 7.2, α-H, Ala), 3.98 (m, 2H, H-4), 2.78 (d, 3H, *J* = 4.9, CH_3–NH), 2.76 (m, 1H, H-3), 2.05 (m, 1H, H-3), 1.90 (s, 3H, CH_3–CO), 1.73 (s, 3H, 2-CH_3), 1.37 (d, 3H, *J* = 7.2, β-H, Ala). ^1H NMR (DMSO-d_6): cis/trans isomers ratio 1:3.3. Trans isomer: δ 8.35 (d, 1H, *J* = 7.3, NH–Ala), 7.72 (m, 1H, NH–CH_3), 4.21 (q, 1H, *J* = 7.3, α-H, Ala), 4.05 (m, 1H, H-4), 3.93 (m, 1H, H-4), 2.56 (d, 3H, *J* = 4.4, CH_3–NH), 2.42 (m, 1H, H-3), 1.94 (m, 1H, H-3), 1.79 (s, 3H, CH_3–CO), 1.54 (s, 3H, 2-CH_3), 1.19 (d, 3H, *J* = 7.3, β-H, Ala), cis isomer: δ 7.99 (d, 1H, *J* = 7.5, NH–Ala), 7.82 (m, 1H, NH–CH_3), 4.21 (m, 1H, α-H, Ala), 4.05 (m, 1H, H-4), 3.93 (m, 1H, H-4), 2.56 (d, 3H, CH_3–NH), 2.42 (m, 1H, H-3), 1.94 (m, 1H, H-3), 1.71 (s, 3H, CH_3–CO), 1.62 (s, 3H, 2-CH_3), 1.21 (d, 3H, *J* = 7.3, β-H, Ala). ^{13}C NMR ($CDCl_3$): δ 174.1 (2-CO), 172.5 (CO–Ala), 172.0 (CO–

CH_3), 71.1 (2-C), 49.1 (α-C, Ala), 45.9 (4-C), 26.4 (3-C), 26.3 (CH_3–NH), 23.0 (2-CH_3), 19.7 (CH_3–CO), 17.1 (β-C, Ala). ES-MS: 242.1 $[M+1]^+$, 264.0 $[M+Na]^+$, 505.2 $[2M+Na]^+$. Anal. Calcd for $C_{11}H_{19}N_3O_3$: C, 54.76; H, 7.94; N, 17.41. Found: C, 54.58; H, 8.20; N, 17.46. 2(*S*)-Ac-Azf-L-Ala-NHMe (**9a**): $[\alpha]_D$ −5.62 (*c* 0.64, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.78 (d, 1H, $J = 7.1$, NH–Ala), 7.28–7.14 (m, 5H, Ph), 6.37 (m, 1H, NH–CH_3), 4.33 (q, 1H, $J = 7.1$, α-H, Ala), 3.56 (m, 1H, H-4), 3.53 (d, 1H, $J = 13.8$, 2-CH_2), 2.95 (d, 1H, $J = 13.8$, 2-CH_2), 2.92 (m, 1H, H-4), 2.72 (d, 3H, $J = 4.9$, CH_3–NH), 2.60 (m, 1H, H-3), 2.16 (m, 1H, H-3), 1.77 (s, 3H, CH_3–CO), 1.35 (d, 3H, $J = 7.1$, β-H, Ala). ^1H NMR (DMSO-d_6): δ 8.67 (d, 1H, $J = 7.3$, NH–Ala), 7.78 (m, 1H, NH–CH_3), 7.35–7.19 (m, 5H, Ph), 4.26 (q, 1H, $J = 7.3$, α-H, Ala), 3.69 (m, 1H, H-4), 3.37 (d, 1H, $J = 13.4$, 2-CH_2), 2.99 (d, 1H, $J = 13.4$, 2-CH_2), 2.91 (m, 1H, H-4), 2.60 (d, 3H, $J = 4.6$, CH_3–NH), 2.34 (m, 1H, H-3), 2.04 (m, 1H, H-3), 1.74 (s, 3H, CH_3–CO), 1.22 (d, 3H, $J = 7.3$, β-H, Ala). ^{13}C NMR ($CDCl_3$): δ 173.7, 172.6, 172.5 (CO–Ala, 2-CO, CO–CH_3), 134.7 (C–Ph), 130.4, 130.3, 128.4 (CH–Ph), 74.8 (2-C), 49.3 (α-C, Ala), 46.2 (4-C), 39.3 (2-CH_2), 26.3 (CH_3–NH), 22.4 (3-C), 19.7 (CH_3–CO), 17.1 (β-C, Ala). ES-MS: 318.0 $[M+1]^+$, 240.0 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.26; H, 7.42; N, 13.36.

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