Libraries of conformationally restricted and rigid amino acids

ABSTRACT
Library of rigid and conformationally restricted α-amino acids have good perspectives to obtain peptide models and peptidomimetics. Two mini-libraries of α-amino acids have been developed: one consisting of bicyclic proline analogues, another composed of potential glutamate receptor ligands containing spiro [3.3] heptane scaffold. Synthesis of some rigid amino acids using “chiral pool” terpenoids as starting compounds is also described.

Restriction in conformation is an efficient tool in the design of biologically active compounds. The loss in entropy, which is achieved by the restriction, might in some cases be favourable for intermolecular interactions responsible for biological activity. The discovery of such “favourable cases” still relies on “trial and error” method, which requires screening the libraries of structurally similar compounds restricted in conformation in order to find optimal spatial arrangement of the functional groups involved in the intermolecular interactions. Several years ago, Enamine started in-house Projects focused on synthesis of libraries of conformationally restricted α-amino acids. They are very promising for obtaining peptidomimetics – analogues of biologically active peptides (1) – with improved practically important characteristics. Amino acids possessing rigid molecules are of particular interest (2). While the exact definition of the term “conformational rigidity” poses some problems, the difference between molecules restricted in conformation and rigid molecules are easily perceived intuitively. This difference is illustrated in Figure 1. The rigid amino acids, being incorporated in peptides in place of the natural amino acids, can stabilize or destabilize the native structure of the peptides. The stabilization occurs when the torsion angles ϕ, ψ and ω at the rigid amino acid residue are close to the angles characteristic to that peptide secondary structure element, in which the amino acid was introduced. For example, one of the most “abundant” secondary structure elements in peptides is α-helix; its characteristic angles (ϕ = -57°, ψ = -47° and ω = 180°) are shown in Figure 2. If the characteristic angles at a rigid amino acid residue are close to these values, one should expect the stabilization of the α-helix. Otherwise, the amino acid residue can hardly be accommodated by the helix due to the considerable steric strain. The 2,4-methanoproline depicted in Figure 1 with ϕ = -29° will certainly destabilize the α-helix structure. Nevertheless, this amino acid could cause no steric strain at the first position of this secondary structure element. This predictability on the qualitative level is one of the reasons for the popularity of rigid amino acids in peptidomimetic synthesis. Another practically important peculiarity of rigid and conformationally constrained amino acids is that peptidomimetics based on them are usually slowly metabolized in live organisms. This can improve ADME characteristics of potential drug candidates and causes prolongation of their action. One of the libraries synthesized at Enamine consists of bicyclic proline analogues. Proline is often found in those secondary structure elements which are responsible for biological action of peptides, therefore, proline analogues restricted in conformation are of particular interest for peptidomimetic synthesis. Successful literature examples of the peptidomimetic drug design using rigid proline analogues (the residues highlighted in red) are illustrated below:

Enamine’s Rigid Proline Analogues library is composed of bicyclic compounds structurally related to the proline itself. The bicyclic scaffolds in this library are obtained by placing a CH₂ or CH₂CH₂ bridge between different carbon atoms of the S-proline core. All the theoretically possible structures 1–12 are shown in Figure 3. A more flexible molecule with a CH₂CH₂CH₂ bridge (13) is also shown. Variation of the angles ϕ and ψ is very wide over the members of this library, as can be predicted from the available literature data (1).

We have synthesized the amino acids 1-7, 9, 11, 13 (both enantiomers in the case of chiral compounds); synthesis of 8 is now under development. Synthesis of each compound from this library represented a considerable challenge. Despite the simplicity of the molecules, some library members, namely, compounds 7, 8 and 13 were still not described in the literature before our work. We have synthesized compounds 1–3 and 11 using modified literature procedures. An original, stereoselective approach, based on tandem Strecker–intramolecular cyclization reaction of the corresponding chloroketones (5) has been developed for the compounds.
and the amine for the Strecker
The source of the cyanide ion
exemplifying synthesis of
scheme is shown in Figure 4
The characteristic angles ω, ϕ and
are shown.

6, 7, 9 and 13. Our synthetic
scheme is shown in Figure 4
exemplifying synthesis of
starch was the aminonitrile 14,
easily obtained from acetone
cyanohydrine and (S)-α-
phenylethylamine. The use of
optically active 14 was
dictated by the necessity of
chromatographic separation
of the diastereomers 15 and
16 in order to obtain optically
pure final compounds.
Another library we designed
is composed of spirocyclic
analogues of glutamate – an
agonist of excitatory amino
acid receptors. Glutamic acid
analogues of glutamate – an
is composed of spirocyclic
members, we used either separation of stereoisomers or
on the
processes. A novel
Figure 6. Terpenoids (shown in green) used for the
amino acid synthesis, compound 25 and the tricyclic
proline analogue 26 derived from camphor.

Figure 2. A fragment of the α-helix in
proteins or peptidomimetics.
The characteristic angles ω, ϕ and
are shown.

Figure 3. Synthesis of compound 13.

Figure 4. Synthesis of compound 13.

Figure 5. Glutamate analogues restricted in conformation.

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REFERENCES AND NOTES

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