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Il Farmaco 000 (2000) 181–183

IL FARMACO

Alicyclic β-amino acids: useful synthons in drug research

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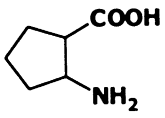
Abstract

The syntheses, transformations and some of the biological features of 2-aminocyclopentanecarboxylic acid and related alicyclic β-amino acids are discussed. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Cispentacin; β-Amino acid; Enantioselective synthesis; Combinatorial chemistry

β-Amino acids, although of less importance than their α-analogues, also occur in peptides and different heterocycles, and their free forms and derivatives exhibit interesting pharmacological effects [1]. A number of syntheses and transformations have been performed on their stereoisomeric alicyclic analogues [2] (e.g. **1**–**3**). Until recently, the investigations [3] were mainly of academic interest, since no naturally occurring compounds were known.

Among the β-amino acid derivatives of cycloalkanes, one of the most exciting is (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin), an antifungal antibiotic, recently isolated from *Bacillus cereus* [4] and *Streptomyces setonii* [5].



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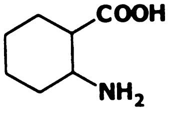

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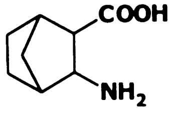

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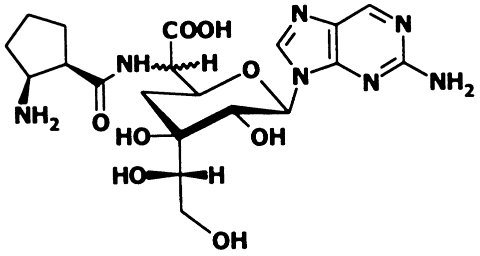

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cis-2-Aminocyclopentanecarboxylic acid (*cis*-2-ACPC) is a component of the antibiotic amipurimycin (**4**) isolated from *Streptomyces novoguineensis*. Compound **4** is strongly active both in vitro and in vivo against *Pyricularia oryzae*, responsible for rice blast disease [6]. Although the absolute configuration of the *cis*-2-ACPC moiety has not been determined, it is probably similar to that of naturally occurring cispentacin.

In consequence of the natural occurrence of cispentacin and its biological activity, interest in investigations of alicyclic β-amino acids has been aroused. Besides their own pharmacological importance, the alicyclic β-amino acids can be used as building blocks for the preparation of modified (unnatural) analogues of biologically active peptides. By substitution of an alicyclic β-amino acid for an α-amino acid in a naturally

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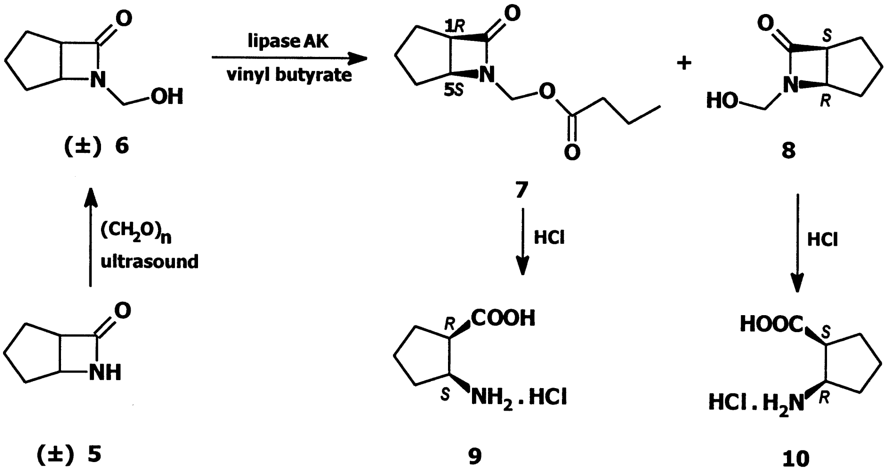
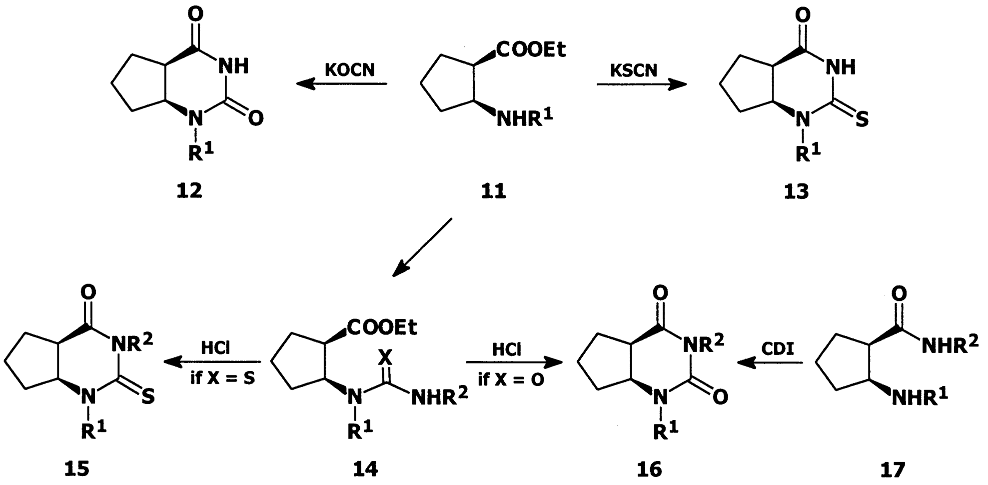
PII: S0014-827X(00)00016-1

occurring pharmacologically active peptide, the activity of the latter can be modified [7]. Moreover, by means of such an exchange, the stability of natural peptides can be increased. The incorporation of β-amino acids with different ring sizes and/or restricted conformations allows modification of the preferred conformation of a peptide. Such investigations should allow more insight into the fine structures of receptors.

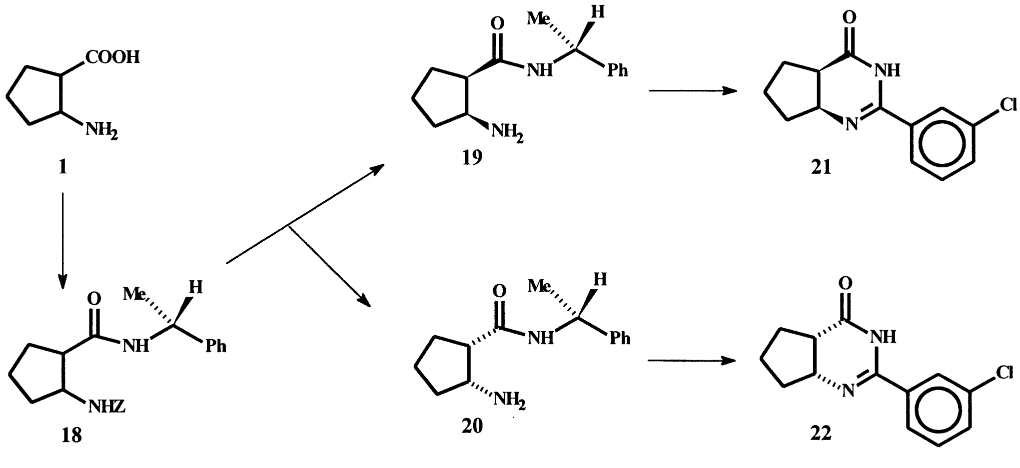
The primary focus of this study is to illustrate the different synthetic strategies and the applicability of



Scheme 1.



Scheme 2.



Scheme 3.

cis-2-ACPC (**1**) in drug research. Besides **1**, other alicyclic β-amino acids, such as *cis*- and *trans*-2-aminocyclohexanecarboxylic acid (**2**), 2,3-*diendo*- and *diexo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acid (**3**) and some of their partially unsaturated analogues, will also be discussed.

Because of the limited space of the abstract, only three examples are presented here. These deal with the synthesis and applications of ACPC in peptide and heterocyclic chemistry (Schemes 1–3).

A number of new enantioselective syntheses have been developed for alicyclic β-amino acids and their analogues [2,8]. A highly enantioselective enzymatic acylation was observed on *N*-hydroxymethylated β-lactam (**6**), which was prepared from racemic **5** with formaldehyde by sonication in THF. Lipase AK-catalyzed butyrylation with vinyl butyrate gave the readily separable azetidinones **7** and **8**. Hydrolysis of **7** and **8** resulted in the enantiomeric 2-ACPC hydrochlorides **9** and **10**, respectively [9] (Scheme 1). Other lipase-catalyzed resolutions were performed on the ethyl esters of a number of alicyclic β-aminocarboxylic acids in organic solvents. The resolutions were based on acylation of the amino group at the *R*-stereogenic center with various 2,2,2-trifluoroethyl esters [10].

The reactions of amino esters **11** ($R^1 = H, CH_2Ph$) with potassium cyanate afforded *cis*-cyclopenta[*d*]pyrimidine-2,4-dione (**12**), while those with potassium thiocyanate led to *cis*-2-thioxocyclopenta[*d*]-pyrimidin-4-one (**13**) (Scheme 2).

When esters **11** ($R^1 = H, CH_2Ph$) were reacted with phenyl or methyl isothiocyanate or isocyanate, adducts **14** were formed in excellent yields. Ring closure of **14** ($R^1 = H$) took place without difficulty when it was refluxed in dilute hydrochloric acid, resulting in pyrimidinones **15** and **16**. *N*-Benzyl-substituted derivatives of **14** could be cyclized to **15** and **16** by refluxing in ethanol containing 22% hydrogen chloride. Further derivatives of **16** were prepared from carboxamide **17** ($R = H$) by cyclization with 1,1′-carbonyldiimidazole [11].

It is noteworthy that the above cyclizations to pyrimidinones were unsuccessful when the starting materials were the *trans* counterparts.

A great number of alicycle-fused 2-substituted pyrimidinones have been synthesized by Bernáth et al. by reaction of the corresponding β-amino acid or its derivatives with ethyl benzimidates, or by reaction of orthoesters with carboxamide [3]. Of this set of compounds, the racemic 2-(*m*-chlorophenyl)-3,4a,-5,6,7,7a-hexahydrocyclopenta[d]pyrimidin-4(3*H*)-one (CHINOIN 143) displayed excellent anti-inflammatory activity. After protection of racemic **1**, the *Z*-amino acid was reacted with (+)-(*R*)-α-methylbenzylamine, followed by deprotection and flash chromatographic separation of the diastereomers, when the enantiomerically pure carboxamides **19** and **20** resulted. When **19** and **20** were reacted with ethyl *m*-chlorobenzimidate, **21** and **22** were obtained, with the loss of the *N*-substituent, in high enantiomeric purity [12] (Scheme 3). The absolute configurations were determined by hydrolysis of **21** and **22** to the corresponding amino acid, which was identified by HPLC [13]. It is interesting to note that the absolute configuration of the eutomer (**21**) corresponds to that of cispentacin.

Whereas α-amino acids have the well-known α-helical motif of proteins, β-peptides constructed from carefully chosen β-amino acids can adopt a different, stable helical conformation defined by hydrogen bonds involving interwoven 14-membered rings. It was reported recently that β-amino acids such as *trans*-2-ACPC and *trans*-2-ACHC can also be used to design β-peptides with a very different secondary structure, a 12-helix [14]. This demonstrates that, by alteration of the nature of the β-peptide residues, rational control can be exerted over the secondary structure.

The pharmacological aspects and use of alicyclic β-amino acids and their derivatives and their applicability in combinatorial chemistry will also be discussed.

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