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REVIEW ARTICLE

β-AMINO ACIDS AND THEIR NATURAL BIOLOGICALLY ACTIVE DERIVATIVES. 5. DERIVATIVES OF UNUSUAL ALICYCLIC AND HETEROCYCLIC β-AMIMO ACIDS

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Summary

α-Amino carboxylic acids are one of five major classes of natural products and play a crucial role in diverse biological functions. Historically, the amino acids have been subdivided into proteinogenic and non-proteinogenic respresentatives. β-Amino acids are similar to alfa-amino acids in that they contain an amino terminus and a carboxyl terminus. However, in β-amino acids two carbon atoms separate these functional termini. β-Amino acids, with a specific side chain, can exist as the R or S isomers at either the α(C2) carbon or the β(C3) carbon. This results in a total of 4 possible diastereoisomers for any given side chain. β-Amino acids are not proteinogenic amino acids, but some of them are constituents of soma natural and biologically active compounds.

Unusual β-amino acids are alicyclic β-amino acids and heterocyclic β-amino acids. Alicyclic β-amino acids, in which both the β-amino and the acids functionality are vicinally attached to an aliphatic ring, still represent a demanding challenge to the synthetic chemist. One reason for this lies in the intriguing difficulty associated with controlling the absolute and relative stereochemistry of two adjacent stereocenters. In heterocyclic β-amino acids the nitrogen of amino group is a part of nitrogen heterocycles.

Some natural derivatives of alicyclic β-amino acids and heterocyclic β-amino acids, their chemical structures and biological activities are discussed in this mini-review.

Key words: unusual amino acids; alicyclic β-amino acids; heterocyclic β-amino acids; alkaloids; peptides

INTRODUCTION

β-Amino acids are not as common in nature as their α-analogues. Some β-amino acids are found in more complex structures like peptides, depsipeptides, lactones, alkaloids, and other natural products, and in free form they show interesting pharmacological effects. β-Amino acids are currently of growing interest, not only because of their natural roles, but also because of their use in the synthesis of peptide mimetics and in the synthesis of certain quite new biologically active substances (44). β-Amino acids are a constituent of some toxins and a special class of pore-forming lipopeptides which exhibit antibacterial and antifungal activity (5). Peptidomimetics containing β–amino acids represent one of the strategies in developing therapeutic candidates with increased

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oral bioavailability and resistance to metabolic degradation (67). Consequently, β-amino acids have potential as inducers of secondary structure and even single β-amino acid residues stabilize discrete conformations in cyclic peptides. Natural derivatives of β-amino acids are often characterized by potent pharmacological and toxicological activities that are often crucially based on their β–amino acid substructures. The most important β–amino acids are β-alanine (55), β-leucine (48), β-lysine, β-arginine (49), β-glutamate, β-phenylalanine and β-tyrosine (50). Furthermore, a lot of others unusual β-amino acids exist and these are also components of natural products (51). Like these compounds, alicyclic and heterocyclic amino acids, are the aim of this article.

ALICYCLIC β-AMINO ACIDS (Fig. 1)

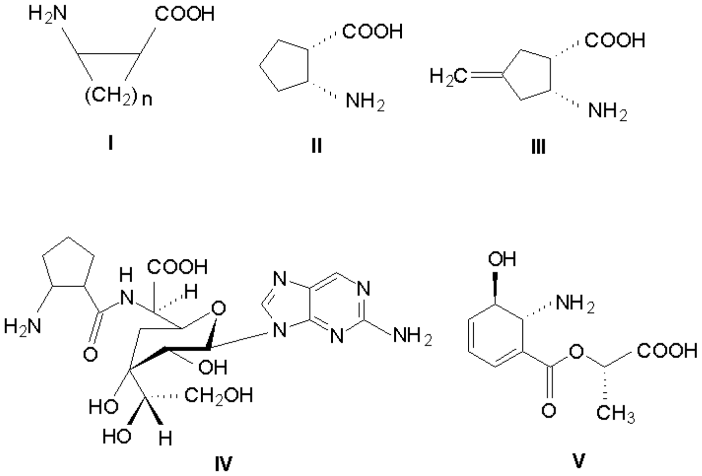


Fig. 1. Alicyclic β-amino acids. 2-Aminocyclopropane-1-carboxylic acid (I, n = 1), 2-aminocyclobutane-1-carboxylic acid (I, n = 2), cispentacin (II), PLD-118 (III), amipurimycin (IV) and oryzoxymycin (V).

Alicyclic β-amino acids of the general formula **I**, in which both the β-amino and the acids functionality are vicinally attached to an aliphatic ring represent interesting group of compounds which alone or installed to bigger molecule show some remarkable biological effects (35). Alicyclic β-amino acids are important synthons in drug research (17). The 3- and 4-membered β-amino acids and its derivatives are rare in nature and usualy are toxic. For some 5- and 6-membered β-amino acids a unique anti fungal activity has been observed, 7-membered β-amino acid derivatives have been investigated for neurological disorders (35). Alicyclic β-amino acids are one class of potent antifungals that have a dual mode of action: These compounds inhibit protein synthesis after concentrative uptake and interfere with self-regulatory mechanisms of amino acid metabolism (64). Alicyclic β-amino acids and their residues are amino acids with two chiral centers resulting in four possible configurations; two configurational *cis* (R,S and S,R) and two configurational *trans* (R,R and S,S) forms.

2-Aminocyclopropane-1-carboxylic acid (**I**, n = 1) and **2-aminocyclobutane-1-carboxylic acid** (**I**, n = 2) are known practically only as synthetically prepared compounds (18) and may be used to prepare peptides and pseudopeptides which represent a group of compounds with conformationally constrained β-amino acid residues (29, 39, 62, 70). The predominance of eight-membered hydrogen-bonded rings has been manifested for (trans,trans)- and (trans,cis)-beta-dipeptides while the formation of six-membered rings is preferred for the (cis,trans) beta-dipeptide similarly to the previously described **(cis,cis)-diastereomer** (71)**.** Likewise **2-aminocyclobutene-1-carboxylic acid** was prepared (3) and incorporated to some small peptides (40, 62) as well as unsaturated derivative, 2-aminocyclobutene-1-carbocylic acid (40).

2-aminocyclopentane-1-carboxylic acid and derivatives

Stereoisomer (1R,2S) of 2-aminocyclopentane-1-carboxylic acid is known as natural product named FR-109615 or cispentacin. Cispentacin was isolated from the culture broth of a *Bacillus cereus* strain, L450-B2.

Cispentacin (II), water-soluble and amphoteric compound, exhibits a strong antifungal *in vitro* activity against various *Candida* strains, e.g. *Candida albicans*, *Candida krusei* and *Candida utilis*. It showed weak *in vitro* activity against *Trichophyton mentagrophytes*, while no activity was observed against *Cryptococcus* and *Aspergillus* species. In addition, cispentacin displayed a potent therapeutic efficacy against a lethal lung *Candida albicans* infection in immuno-compromised mice (32). The 50% inhibitory concentration (IC_{50}) and IC_{100} values of cispentacin against clinical isolates of *Candida albicans* were in the ranges 6.3-12.5 and 6.3-50 µg/ml, respectively. This antibiotic demonstrated good therapeutic efficacy against a systemic *Candida* infection in mice by both parenteral and p. o. administrations. The 50% protection dose (PD_{50}) values after single i.v. and p.o. administrations were 10 and 30 mg/kg, respectively. It was also effective in a systemic infection with *Cryptococcus neoformans* and in both lung and vaginal infections with *C. albicans* in mice. Cispentacin did not induce acute lethal toxicity at 1.000 mg/kg by i.v. injection and 1,500 mg/kg by i.p. and p.o. administrations in mice (45). I.v. administration of 50 mg/kg cispentacin led to a 100 % survival rate. Interesting cispentacin-derived bicyclic β-amino acid has been synthesized and incorporated into the 6-position of GnRH (36).

Cispentacin and its stereoisomers, i.e. (1S,2R)-antipode and trans-diastereomer were tested for their antifungal activity against *C. albicans*. Only cispentacin showed antifungal activity. Both, its (1S,2R)-antipode and its trans-diastereomer were inactive *in vitro* against *C. albicans* and *C. tropicalis*. To explore the structure activity retionship (SAR) of antifungal cispentacin β-amino acids Ohki et al. (43) synthesized several derivatives of this amino acid and described their antifungal activity against *C. albicans*. Among the derivatives modified at the carboxyl and amino group, most derivatives were inactive. From these results, Ohki et al. (43) concluded that both functional groups, the carboxylic acid and the primary amino group, were necessary for potent antifungal activity (28).

One novel derivative of cispentacin is **PLD-118** (**III**) (Bay-10-8888) which competitively inhibits isoleucyl-tRNA synthetase. PLD-118 disrupts fungal protein biosynthesis and cell growth (59). Because of its potent specific activity observed against *Candida* spp. including azole-resistant strains *in vitro* and *in vivo*, in addition to its excellent pharmacokinetics, solubility and safety, PLD-118 was chosen for further development for systemic treatment of *Candida* infections (64). In 2000, PLD-118 was licensed to the Croatian pharmaceutical company PLIVA, where it is now named icofungipen (PLD-118) (58). Based on the very promising results in preclinical and phase I clinical studies, a phase II clinical study was initiated with this compound being the only new compound in development for oral treatment of yeast infection.

Amipurimycin (**IV**), a member of the complex peptidyl nucleoside family of antibiotics, is a *Streptomyces*-derived potent antifungal agent. Amipurimycin was isolated from the culture filtrate of *Streptomyces novoguineensis*. It contains 2–aminopurine, cis-2-aminocyclopentane-1-carboxylic acid and a sugar moiety (21). Amipurimycin is strongly active against *Pyricularia oryzae* (24), the microorganism that causes rice blast disease.

2-aminocyclohexane-1-carboxylic acid and derivatives

Enantiomerically pure, cis- and trans-2-aminocyclohexane-1-carboxylic acids were prepared synthetically (11, 60) as well as some higher 2-amino-cycloalkane-1-carboxylic acids (15) but in nature these amino acids were not found and their natural derivatives are rare.

Oryzoxymycin (**V**) is antibiotic (26) with unusual structure (25) with dihydro-3-hydroxyanthranilic acid moiety. Oryzoxymycin was isolated from a soil sample of *Streptomyces venezuelae*, var. *oryzoxymyceticus*, and this compounds was shown to exhibit moderate activity against *Xanthomonas oryzae*, gram-positive bacteria that attack the leaves of rice plant (6).

HETEROCYCLIC β-AMINO ACIDS

Heterocyclic β-amino acids are of two types. 1-Aza-polycyclo-2-acetic acids (Type 1) or 1-aza-polycyclo-3-carboxylic acids (Type 2). Heterocyclic β-amino acids and their derivatives are not very common in nature. Nevertheless, some examples such as homoproline, capreomycidine, tubulysine or streptolidine are known.

Type 1 Heterocyclic β-Amino Acids (Fig. 2)

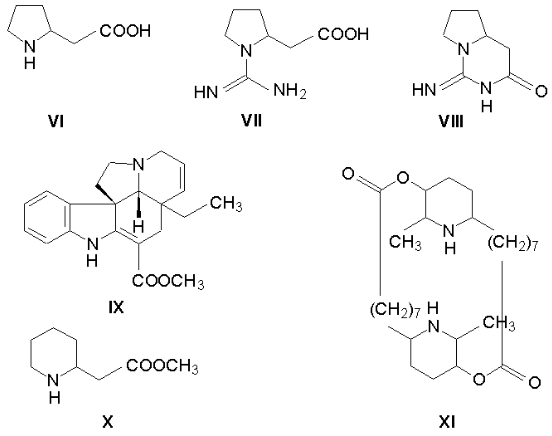


Fig. 2. Heterocyclic β-amino acids of Type 1. Pyrrolidine-2-acetic acid (homoproline) (VI), cimipronidine (VII), cyclocimipronidine (VIII), tabersonine (IX), pelletierine (X) and carpaine (XI).

Simplest representants of these amino acids are aziridine-2-acetic acid and azetidine-2-acetic acid. However, only **pyrrolidine-2-acetic acid** (**homoproline**) (**VI**) is known in nature in the form of guanidine alkaloids **cimipronidine** (**VII**) and **cyclocimipronidine** (**VIII**) that have been isolated and characterized from *Cimicifuga racemosa* roots (16, 23).

(2S,3R) Antipode of homoproline has been isolated in free form from some plants such as *Nicotiana tabacum*, *Tussilago farfara*, *Neurolaena lobata*, *Eupatorium semialatum*, *Melampodium divaricatum and Arnica* sp. (47). Homoproline was found in neamphamide A, depsipeptide from the Papua New Guinea marine sponge *Neamphixus huxleyi*. Neamphamide A contains 11 amino acid residues and an amide-linked 3-hydroxy-2,4,6-trimethylheptanoic acid moiety. The amino acid constituents were identified as L-Leu, L-NMeGln, D-Arg, D- and L-Asn, two residues of D-allo-Thr, L-homoproline, (3S,4R)-3,4-dimethyl-L-glutamine, β-methoxytyrosine, and 4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (46).

Tabersonine (**IX**) is also formal derivative of homoproline. It is a tertiary indole alkaloid isolated from the seeds of *Tabernaemontana dichotoma* (57).

Pelletierine (**X**), formal derivative of piperidine-2-acetic acid, is an alkaloid with anthelminthic activity (73).

Carpaine (**XI**), bis-piperidine alkaloid (53) is a cardioactive principle from the leaves of papaya tree *Carica papaya* (22). It induces bradycardia, depresses the central nervous system and is a potent ameobicide (27).

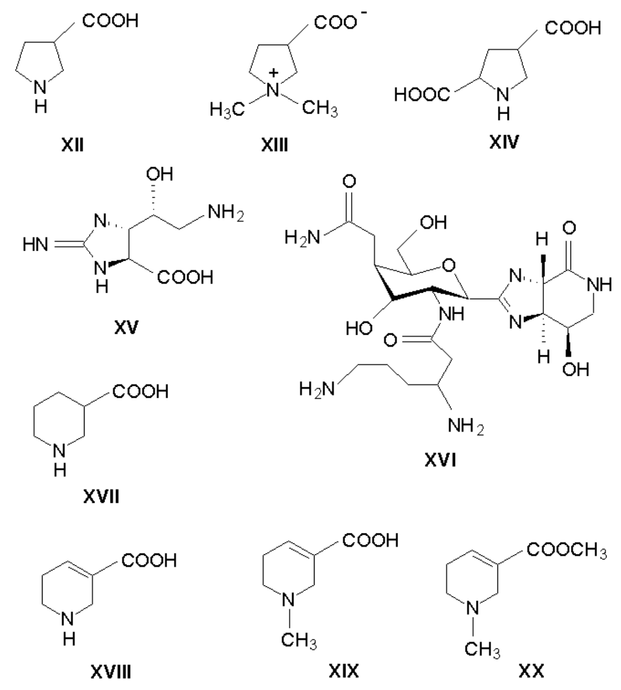
Type 2 Heterocyclic β-Amino Acids (Fig. 3 and Fig. 4)

The most known heterocyclic β-amino acids are derived from 5-membered ring of pyrrolidine or 6-membered ring of piperidine. Their derivatives are contained in some alkaloids, peptides and other biologically active compounds.

3-pyrrolidine carboxylic acid (**β-proline**) (**XII**) exists in two enantiomers. Its (R)-enantiomer was found to act as selective inhibitor of gamma-aminobutyric acid (GABA) uptake in astrocytes (37). Some β-proline analogues was found to bind to strychnine-sensitive glycine receptor (30).

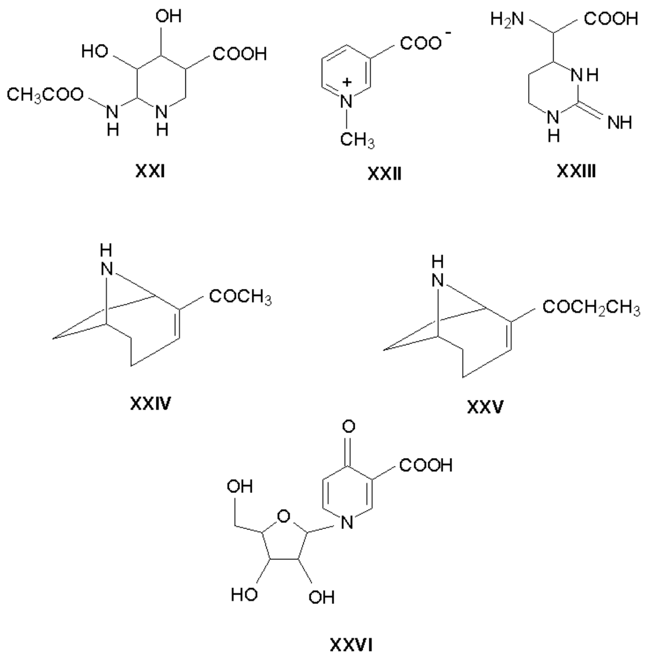
β-Prolinebetaine (**β-stachydrine**) (**XIII**) and its hydroxy-derivative (trans-4-hydroxy-β-prolinebetaine) have been found in many species of marina algae (4).

Pyrrolidine-2,4-dicarboxylic acid (**XIV**) is natural amino acid that reverses plasma mebrane



XII XIII XIV XV XVI XVII XVIII XIX XX

Fig. 3. Heterocyclic β-amino acids of Type 2. β-Proline (XII), β-prolinebetaine (β-stachydrine) (XIII), pyrrolidine-2,4-dicarboxylic acid (XIV), streptolidine (XV), streptothricin (XVI), nipecotic (nipecotinic) acid (XVII), guvacine (XVIII), arecaidine (XIX), arecoline (XX).



XXI XXII XXIII XXIV XXV XXVI

Fig. 4. Heterocyclic β-amino acids of Type 2. Siastatin B (A-72363 B) (XXI), trigonelline (XXII), capreomycidine (XXIII), anatoxin a (XXIV), homoanatoxin a (XXV), clitidine (XXVI).

glutamate transporters and elevates extracellular glutamate levels in vivo (61). Some its synthetic derivatives are potent dipeptidyl peptidase IV inhibitors (72) with promissing approach for the treatment of type-II diabetes (12).

Streptolidine (**XV**) is the only outside derivative of β-amino acids. This aminoacid also known as roseonine is important moiety in aminoglycoside antibiotic **streptothricin** (**XVI**) (74).

Nipecotic or likewise **nipecotinic acid** (**piperidine-3-carboxylic acid**) (**XVII**) is the most important natural heterocyclic β-amino acid. Their simple derivatives are known as alkaloids **guvacine** (**XVIII**), **arecaidine** (**XIX**) and **arecoline** (**XX**).

Nipecotic acid is a powerful non-competitive inhibitor of GABA uptake (34). Nipecotic acid bind to GABA uptake recognition site in the hippocampus of rats and the same binding site is involved in the regulation of ethanol intake (10). Synthetically prepared derivative of nipecotinic acid (e.g. tiagabine), used in the therapy of partial seizures, partial seizures with secondary generalization, stress disorder, psychosis and cocaine dependence (20, 76).

Guvacine (**XVIII**), **arecaidine** (**XIX**) and **arecoline** (**XX**) are constituents of the nut *Areca catachu*, important component of betel (54). Betel has been used extensively as a mild stimulant since antiquity. It also uses in Ayurveda as an aid for phobias and nervousness. Arecaidine and guvacine inhibited the uptake of GABA and β-alanine, but not that of glycine, by slices of cat spinal cord. In cats anaesthetised with pentobarbitone, electrophoretic arecaidine enhanced the inhibitory actions of GABA and β-alanine, but not those of glycine or taurine, on the firing of spinal neurones. Similarly, electrophoretic guvacine enhanced the inhibition of spinal neurones by GABA but not that by glycine (38). Large doses of arecaidine (1 g/kg s.c.) marginally reduced the lethal effects of bicuculline in mice but appeared to have little or no anticonvulsant activity (38).

Arecoline is the main alkaloid of the Areca nut. Owing to its muscarinic and nicotinic agonist properties, arecoline has shown improvement in the learning ability in animal (41). Since one of the hallmarks of Alzheimer's disease is a cognitive decline, arecoline was suggested as a treatment to slow down this process. Arecoline administered via i.v. route did indeed show modest verbal and spatial memory improvement in Alzheimer's patients, though due to arecoline's possible carcinogenic properties (63), it is not the first drug of choice for this degenerative disease (9).

Arecoline was used in veterinary medicine in the treatment of cestodes in dogs. Oral administration causes paralysis of the worms and catharsis, so the worms are expelled alive and intact (19).

A more complex class of β-amino acids derived from nipecotic acid has been isolated from the culture filtrate of the bacterium *Streptomyces nobilis* SANK 60192 (68). They have been designated A-72363 A1, A2, B, and C and have been shown to inhibit several glycosidases. A-72363 B, i.e., (**siastatin B**) (**XXI**) is selective for neuraminidase and β-glucoronidase and A-72363 C for β-glucoronidase and heparanase, with the remaining two compounds exhibiting a weak inhibitory effect on the glycosidases tested (31).

Trigonelline (**XXII**) is an alkaloid occurs in many plants and firstly was isolated from fenugreek seeds (*Trigenella foenum-graecum*), thus the name. Trigonelline, a niacin-related compound, is also a natural constituent of coffee accounting for ~1% dry matter in roasted beans. Recents research has shown that trigonelline is a novel phytoestrogen (2).

Capreomycidine (**XXIII**) is a cyclic guanidine-amino acid ocurring as a constituent of the capreomycins (13), tuberactinomycins (69) and viomycin (77). The capreomycins are tuberculostatic cyclic peptide antibiotics isolated from *Streptomyces capreolus* (42), while the tuberactinomycins have been isolated from *Streptomyces griseoverticillatus* var. *tuberacticus* (75). Due to their strong anti-tuberculostatic activity, syntheses of capreomycins and tuberactinomycins have been performed. Their biological activity is caused by an inhibition of the prokaryotic protein biosynthesis. Both the translocation of the peptidyl-tRNA and the dissociation of the ribosomal subunits are inhibited and misreading is induced (66). Capreomycins and tuberactinomycins are used specifically for the treatment of multidrug-resistant tuberculosis infections in which therapy with other drugs has failed (7). Unfortunately, these antituberculostatics are ototoxic and nephrotoxic (1).

Anatoxin a (**XXIV**) and **homoanatoxin a** (**XXV**) are derivatives of 2-amino-2-cyclooctane-1-carboxylic acid. These toxic alkaloids were found in toxic strains of the filamentous blue-green alga, *Anabaena flos-aquae* (Lyngb.) which have been obtained from a freshwater cyanophyte that had poisoned cattle (14). Anatoxin a and homoanatoxin a are phycotoxins (56). They are postsynaptic depolarizing neuromuscular blocking agents (8) that bind strongly to the nicotinic acetylcholine receptor (65). These compounds are potent neurotoxins which cause rapid death in mammals by respiratory arrest (the mouse LD_{50} is approximately 250 µg/kg, i.p.) (14). Both anatoxins are deadly and their military potential as a toxin weapon is very high (56).

Clitidine (**XXVI**) was isolated as a toxic principle from a poisonous muschroom, *Clitocybe acromelalga* (33). This β-amino acid is a pyridine nucleoside with neurotoxix effect. It appears that poisonous properties of *Clitocybe* mushrooms are caused by complex effect of numerous poisonous substances, but clitidine is the most significant of them (52).

CONCLUSION

On contrary to proteinogenic α-amino acids that are constituents of all proteins and enzymes which control the metabolism in living matter, most β-amino acids only occur as constituents of distinct natural compounds. Apparently, bacteria, cyanobacteria, fungi, and plants often incorporate β-amino acids into secondary metabolites. Natural compounds with incorporated β-amino acids represent substances of interest to both academic and industrial chemists, pharmacologists and toxicologists. Exceedingly important are these compounds for all who are interested in bioorganic and biological chemistry. Many natural compounds characterized by potent biological activities are active thanks to the presence of β-amino acid substructure.

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