

$\omega$ -GUANIDINO-SUBSTITUTED- $\alpha$ -AMINO ACIDS

This is a continuation of pending application Ser. No. 607,873, filed May 7, 1984, now abandoned, incorporated herein by reference, which is a continuation-in-part of pending U.S. patent application Ser. No. 451,761 filed Dec. 21, 1982, now U.S. Pat. No. 4,481,190.

## BACKGROUND OF THE INVENTION

This invention relates to  $\alpha$ -amino acids having an  $\omega$ -guanidino group wherein at least one of the guanidino nitrogens are substituted. More specifically, this invention covers arginine-type amino acids wherein one or both of the terminal guanidino nitrogens ( $\text{H}_2\text{N}-\text{C}=\text{NH}$ ) is substituted.

In 1970, Kakimoto and Akazawa reported the isolation and identification of  $\text{N}^G, \text{N}^{G'}$  and  $\text{N}^G, \text{N}^{G'}$ -dimethyl-arginine from urine. This work was reported in *J. Biol. Chem.*, 245, No. 21, 5751-5765 (1970). Subsequently, Patthy A., et al., reported the preparation and characterization of mono-, di-, and tri-methyl related arginines (*Acta. Biochim. Biophys. Acad. Sci. Hung.*, 12 (3), 191-6 (1977)).

It has now been discovered that substituting one or both of the guanidino nitrogens of amino acids such as arginine, homoarginine and related amino acids, provides an amino acyl residue which will increase the activity of a protein into which is incorporated and/or will increase the  $t_{1/2}$  of that peptide.

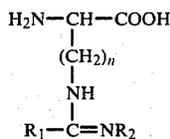
## SUMMARY OF THE INVENTION

This invention refers to novel D- or L- $\omega$ -guanidino-substituted  $\alpha$ -amino acids and amino acyl residues which do not occur in nature. The invention is also directed to various methods of use of these amino acids. A further aspect of the invention involves processes for the preparation of these compounds.

## DETAILED DESCRIPTION OF THE INVENTION

## Description of the Amino Acids

The present invention relates to D- and L- $\alpha$ -amino acids and their corresponding amino acyl radicals which have the formula



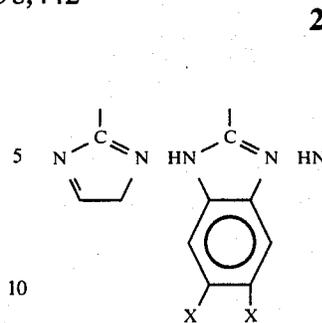
and the pharmaceutically acceptable salts thereof wherein

n is 1 to 5;

$\text{R}_1$  is alkyl of 1-12 carbon atoms, halo lower alkyl or  $-\text{NHR}_3$  wherein  $\text{R}_3$  is alkyl of 1-12 carbon atoms, cycloalkyl, phenyl, benzyl, halo lower alkyl, morpholino or  $-(\text{CH}_2)_n\text{N}(\text{R}_4)_2$  wherein n is 1-5 and  $\text{R}_4$  is lower alkyl;

$\text{R}_2$  is hydrogen or  $\text{R}_3$ ; or

$\text{R}_1$  and  $\text{R}_2$  comprise a ring represented by the following structural formulas:



wherein

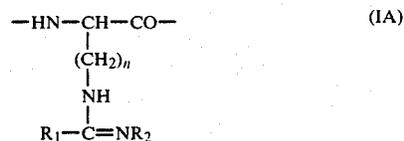
m is 0-6;

A and B are independently hydrogen, alkyl of 1-6 carbon atoms or cycloalkyl; and

X is halo or A and the pharmaceutically acceptable salts thereof. Compounds wherein n is 3 and  $\text{R}_1$  is  $-\text{NHR}_3$  wherein  $\text{R}_3$  is methyl and  $\text{R}_2$  is hydrogen or methyl are excluded from this invention.

These amino acids are useful in the preparation of all peptides, polypeptides and proteins.

This invention covers the amino acyl radicals which are derived from formula I. For example, this invention covers the amino acyl radical represented by the structure



which would be the form in which formula I would exist when incorporated into a peptide, polypeptide or the like; or when present in a compound which is not a polymer based on  $\alpha$ -amino acids. The term "amino acyl radical" also includes the structures derived from formula I wherein either one of the carboxyl or  $\alpha$ -amino groups is a radical as represented by formula (IA), i.e. formula I is the C-terminal or N-terminal amino acid of a polypeptide.

As used herein, the term "pharmaceutically acceptable salts" refers to salts which retain the desired biological activity of the parent compound and do not impart any undesired toxicological effects. These salts may be derived from either acid or base.

Examples of acid addition salts formed with inorganic acids or hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, glucuronic acid, citric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, and the like.

Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylam-